18

Food intolerance

Robert H. LOBLAY and Anne R. SWAIN
Clinical Immunology Research Centre, University of Sydney, NSW 2006; and Department of Dietetics, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia.

Introduction

Food intolerance has aroused increasing public interest as well as professional controversy in recent years. Many patients present with the conviction that a variety of vague symptoms they experience are due to 'food allergies', but their beliefs often cannot be substantiated by objective testing and their physicians are apt to attribute the symptoms to psychological factors[1]. On the other hand many fringe and 'alternative' practitioners believe that food allergy can cause almost any known disease, and their exaggerated claims often appear in popular books or capture the attention of the media. It is our belief that much of the confusion and controversy surrounding the subject has arisen in part from a failure to distinguish clearly between true food allergy, mediated by immunological mechanisms, and the very much more common reactions to food caused by pharmacological idiosyncracies.

We prefer to reserve the term *food allergy* for IgE mediated reactions, which are generally confined to young children with an atopic background; most are sensitive to only one or two specific foods (commonly milk, eggs, wheat, fish or peanuts) which provoke reproducible symptoms, often within an hour or less. By contrast *pharmacological* food intolerance is seen amongst predominantly non-atopic people of all ages; symptoms may involve the skin, gastrointestinal tract, upper respiratory tract or central nervous system, and can be provoked by a variety of chemical substances, both natural and artificial, common to many different foods. The effects of these compounds are dose-related and in susceptible people they exhibit pharmacological properties such as withdrawal, supersensitivity, tachyphylaxis and tolerance. Thus, for each chemical the dose threshold for triggering symptoms varies depending on the individual's recent intake from a variety of food sources, so that a particular food need not necessarily produce the same reaction on different occasions. This, together with the fact that reactions may be delayed by many hours (or even a day or two), means that patients can become easily confused or mistaken about which foods cause symptoms, if

indeed they are able to recognize the relationship at all. Similarly, the physician may be misled by negative challenge tests with individual foods which contain only small doses of the relevant chemicals, particularly if the latter have not been adequately eliminated from the diet beforehand.

Food chemicals

Although much attention has been paid in recent years to the adverse effects of food additives, reactions to natural food chemicals are a more frequent and insidious problem. All plants and lower organisms synthesize an enormous range of secondary metabolites which possess important physiological, ecological and protective properties. Herbivorous animals including humans have developed the capacity to detoxify and excrete many of these xenobiotics, as well as learning to avoid the ingestion of toxic plants by sensing noxious substances. Nevertheless, many commonly eaten foods still contain chemicals capable of provoking adverse reactions if eaten in sufficient quantities by sensitive individuals. This is particularly true of phenolic derivatives, some of which are responsible for endowing foods with flavour and aroma.

The most widely distributed of the natural chemicals capable of provoking symptoms is the salicylate family. Aspirin intolerance was first reported around the turn of the century, and its association with allergic diseases, including food 'allergy', and cross-reactions with tartrazine and benzoic acid are now well recognized[2,3]. However, it is not widely appreciated that significant amounts of benzoates and salicylates occur naturally in many different foods such as fruits (including their juices), vegetables, herbs, spices, nuts, wines, tea and coffee. There is little published information about the distribution of these substances, and this led one of us (ARS) to undertake an extensive analysis of the salicylate content of a range of commonly eaten foods and drinks[4]. This has proved extremely valuable in the design of an effective elimination diet, and in the management of patients with salicylate intolerance. We have estimated that an average Australian diet may contain up to 100 mg of natural salicylate per day, amounts which may readily precipitate symptoms when consumed on a daily basis by sensitive individuals.

Other naturally occurring substances which commonly cause adverse reactions, and which cross-react extensively with additives and salicylates in our experience, are the biogenic amines[5] and monosodium glutamate[6]; less commonly yeast and gluten can produce similar reactions in sensitive people[7]. It should be noted that classification of foods into botanical 'families' bears no relationship to their chemical content, and is of little relevance in the management of patients with food intolerance.

Clinical evaluation

Food allergy

This most commonly occurs in atopic children with a history of eczema, the major allergens being eggs, milk, wheat, fish and peanuts. Immediate

reactions may cause swelling, itch or burning around the mouth and throat, as well as vomiting, abdominal cramps and diarrhoea. Sensitivity can sometimes be exquisite, such that even the smell of a peanut or fish may produce facial urticaria, angioedema or asthma, and rarely systemic anaphylaxis may occur. In children presenting with chronic eczema the problem is often more insidious, and the relationship between diet and the rash may only be recognized after the relevant foods have been withdrawn and subsequently reintroduced. Most children tend to improve spontaneously as they grow older or else learn to avoid the particular food involved[8], so that it is rare to see an adult presenting for the first time with symptomatic food allergy.

Screening tests are of little value in the diagnosis of food allergy. When symptoms only occur in relation to a specific food the diagnosis can be made from the history, and further investigation may be unnecessary. Skin prick tests or RAST tests are usually only helpful to confirm the diagnosis in doubtful or difficult cases; since positive tests are common in normal individuals[9] they are of no significance in the absence of clinical symptoms. If the diagnosis is suspected the most reliable approach is withdrawal of the major food allergens for at least two weeks, followed by cautious reintroduction one at a time. This should be done under close supervision in very sensitive children.

Pharmacological

This form of food intolerance may present with symptoms affecting the skin, gastrointestinal tract (GIT), respiratory tract or central nervous system (CNS), either individually or in any combination[7]. The best recognized syndromes are recurrent urticaria (and/or angioedema), migraine, and irritable bowel syndrome, but it should be emphasized that food intolerance is not the only cause of these disorders. Respiratory tract symptoms may include nasal congestion, 'sinusitis', pharyngeal irritation and asthma, and GIT symptoms such as mouth ulceration, nausea, abdominal cramps and diarrhoea are common. CNS symptoms can be bizarre at times, resulting in patients being labelled as neurotic or hysterical if food intolerance is not recognized. Headache, lethargy and myalgia are common and may be accompanied by impairment of memory and concentration, mental agitation or depression, dysphasia, visual disturbances, tinnitus, dizziness, autonomic disturbances, paraesthesias and neuralgias. Such patients sometimes mistakenly attribute their symptoms to 'hypoglycaemia', particularly if they occur two to three hours after meals. In individual patients symptoms may affect one or more organ systems simultaneously, or may change from one system to another with time. A family history of related symptoms is very common, women being affected about twice as frequently as men. In children headaches, recurrent abdominal cramps and limb pains are common, and may be accompanied by sleep and behaviour disturbances.

The diet history is generally unreliable in patients with pharmacological reactions, since many patients do not recognize the relationship between foods and symptoms, and those who do are usually unaware that a variety of

apparently tolerated foods can have cumulative effects. Nevertheless, useful clues can sometimes be obtained. For example, a patient who reacts to apples, citrus fruits, tomatoes, strawberries and wine is likely to be salicylate sensitive; alternatively, reactions to cheese, chocolate, bananas, avocado, tomatoes and wine point towards amines as the culprit. Most patients are in fact sensitive to several chemicals and adverse reactions are most likely to occur when these are eaten in combination. It should be noted that failure to react to aspirin whilst on a normal diet does not exclude salicylate intolerance, since many patients will only react to a challenge after dietary salicylates have first been completely eliminated for a week or more. The incidence of salicylate intolerance is therefore likely to have been seriously underestimated in studies published to date[2].

Psychological reactions

Suspicion should be aroused if symptoms occur either at the sight of food, instantaneously on ingestion, or in response to all food and water. Anxiety syndromes associated with hyperventilation can be identified by careful clinical observation, but some patients hyperventilate as a consequence of food reactions which may at times be alarming. Transient depression can also occur as part of a food reaction, and is sometimes sufficiently intense to provoke suicidal thoughts, but delusions, hallucinations or thought disorders are not typical and require independent psychiatric assessment.

Dietary investigation and management

In the investigation and management of pharmacological food intolerance, the first step should be to identify the substances responsible for provoking symptoms in each individual. Allergy testing is obviously inappropriate, and to our knowledge there is as yet no accurate means of diagnosis other than systematic elimination and blind challenge. The strategy we have followed is as follows. (1) We seek to determine whether symptoms are diet-related by assessing their response to stringent elimination of dietary chemicals over a minimum period of two weeks. If symptoms have not remitted after 6–8 weeks the patient is allowed to resume a normal diet. (2) We administer double-blind challenges with purified chemicals (and placebos) in order to identify the range of food components to which each individual is sensitive. (3) We prescribe an individualized diet for each patient depending on their reactions to challenges. (4) We encourage gradual and systematic liberalization by grouping foods according to chemical composition, in an attempt to raise the dose threshold for reactions and thus re-establish tolerance of as many foods as possible.

Patients attending our clinic are assessed by both a physician and a dietitian at the outset, and during the elimination and challenge period they are asked to keep a food and symptom diary. The baseline elimination diet itself is critically important: complete exclusion of all relevant substances for at least two weeks is necessary to allow for clearing of residual symptoms, possible withdrawal reactions, and a lowering of the dose threshold which renders patients more sensitive to challenges.

Challenges are administered only when symptoms have cleared (or subsided significantly) for five consecutive days, and although this is usually achieved after two weeks on the elimination diet, up to 6 or 8 weeks may be necessary at times. Open challenges with milk and wheat (as well as eggs in those with eczema) are taken first, and these foods may be added to the baseline diet if there is no obvious reaction. Chemical challenges (in capsules and numbered in an arbitrary order) including placebos are then administered double-blind at 48-h intervals, and if any reaction occurs further challenges are suspended until symptoms have subsided completely. Allowance is made for a 3-day refractory period before recommencing challenges. The dose schedule for challenges has been described in detail previously[7]. At the completion of testing the code for each patient's numbered challenges is broken, and an individualized diet prescribed avoiding only those substances found to provoke a reaction. On some occasions, when there is uncertainty about the result of a particular challenge, it may either be repeated, or foods containing the relevant chemical taken as open challenges.

With certain exceptions, these procedures can be conducted on an outpatient basis. Asthmatics with severe bronchial hyper-reactivity (measured by histamine provocation) and patients with a history of laryngeal oedema or anaphylaxis are routinely hospitalized for graded-dose challenges with salicylate, metabisulphite, MSG and tartrazine.

Successful management requires the involvement of an experienced dietitian with particular knowledge of the chemical composition of all commonly eaten foods. Attention to minor details can be critically important. Withdrawal symptoms are common towards the end of the first week of dietary elimination, and subsequently the dose-threshold for reactions becomes much lower. This means that foods containing small doses of the relevant substances, and which were previously tolerated, may now begin to provoke symptoms, so that apparently minor indiscretions or mistakes with the elimination diet may be responsible for failure of symptoms to resolve. This problem is sometimes compounded by a heightened sensitivity to smells and fumes which often occurs concomitantly when the diet is severely restricted, and which can aggravate symptoms in some patients.

Patients

Using the above approach we have investigated over 2000 patients to date; the most common presenting syndromes, and their response rates are shown in Table 1. Not included are patients presenting with asthma, intractable mouth ulceration, and several other miscellaneous conditions. In the group with recurrent idiopathic urticaria, there was no appreciable difference in the response pattern of subgroups with angioedema or with any of the physical urticarias. Patients with headache consisted predominantly of those with 'common' migraine, with or without a history of classical migraine as well, and a minority with classical migraine alone. Those presenting with 'behavioural' symptoms were mostly children with episodic hyperactivity, irritability or irrational behaviour which was judged by their parents to be

Table 1. Response to elimination diet.

Presenting syndrome	*No. of patients*	*Response rate (%)*
Urticaria	826	70
Eczema	110	47
Irr. bowel	159	43
Migraine	123	60
Behaviour	140	61
Systemic	490	58

uncharacteristic and unpredictable. All children were assessed by a paediatrician attending our clinic, and when psychosocial factors were felt to be the major problem dietary investigation was not recommended.

Patients in the 'systemic' group presented with predominantly neurological symptoms and variable involvement of other target organs as outlined in Table 2. Their average age was 37 and the mean duration of symptoms at presentation was 9.7 years (ranging from 6 months to more than 50 years). In 35 per cent of 200 patients whose records were reviewed, the onset could be clearly dated to a viral infection, most commonly glandular fever. A majority of these patients had symptoms indistinguishable from post-viral myalgia/fatigue syndrome[10,11]; of 60 patients in whom serological studies were performed two-thirds had abnormally elevated IgG antibodies to EBV capsid antigens, but no other consistent laboratory abnormalities were found. Responsiveness to dietary elimination and challenges bore no relationship to a history of infective onset or EBV antibody titres.

Table 2. Systemic symptoms.

Lethargy	89%	Rhinitis*	39%
Headache	88%	Urticaria*	38%
Gastrointestinal	76%	Mouth ulcers	35%
Myalgia	71%	Asthma/eczema*	16%
Cerebral	65%		

*Past or present history

Amongst adults there was a preponderance of females which was most striking in those with 'systemic' symptoms (Table 3). Patients were drawn from a wide variety of sources with a fairly even distribution of primary, secondary and tertiary referrals, and of those in whom we were able to document food intolerance only about half had previously been able to recognize any relationship between food and symptoms.

Table 3. Sex incidence.

Syndrome	*f(%)*	*m(%)*
Urticaria	65	35
Eczema	64	36
Irr. bowel	71	29
Migraine	72	28
Behaviour	28	72
Systemic	88	12

Challenge results

The frequency of positive challenge reactions in the various patient groups is shown in Table 4. Of the compounds tested the one most frequently incriminated is salicylate but cross-reaction between many of the substances is common and idiosyncratic. Reactions usually begin within a few hours of taking a challenge, but can be delayed by up to 48 hours in some individuals; their duration varies from two or three hours up to several days, and in extreme cases, a week or more. Almost all patients react to more than one substance, averaging three in those presenting with urticaria and six in those with systemic symptoms. The latter behave clinically as the most sensitive group of patients in whom even very minor deviations from their prescribed diet can cause reactions.

Table 4. Reactions to challenges (% positive). Urt - urticaria, Ecz - eczema, IBS - irritable bowel syndrome, Mig - migraine, Beh - behaviour abnormalities, Sys - systemic symptoms.

	Urt	*Ecz*	*IBS*	*Mig*	*Beh*	*Sys*
Salicylates	**62**	**52**	69	62	**74**	**74**
Preservatives	55	50	63	63	67	68
Nitrates	—	43	64	**72**	60	70
Amines	—	36	55	51	40	62
M.S.G.	—	35	**72**	62	39	64
Tartrazine	35	40	53	54	54	59
Antioxidants	—	21	48	36	41	54
Brewers yeast	30	31	54	41	41	48
Gluten	—	—	20	13	0	16
Lactose	7	19	26	12	18	18
Placebos						
Sucrose	—	0	5	8	3	6
Starch	—	8	8	11	3	5
β-carotene	5	—	—	—	—	—

The clinical spectrum of challenge reactions is illustrated for salicylates in Table 5. It is interesting to note that in each group of patients the symptoms provoked were mainly confined to the organ system involved at presentation, and an identical pattern is seen when reactions to any of the other compounds are tabulated in the same way. We have not systematically

Table 5. Salicylate challenge reactions. Urt - urticaria, Ecz - eczema, IBS - irritable bowel syndrome, Mig - migraine, Beh - behaviour abnormalities, Sys - systemic symptoms.

	Presenting syndrome					
	Urt	*Ecz*	*IBS*	*Mig*	*Beh*	*Sys*
Symptoms provoked (%)						
Urticaria	**52**	2	12	1	8	**11**
Eczema	0	**52**	1	0	2	0
Gastrointestinal	13	7	**52**	18	17	**34**
Headache	13	13	10	**47**	9	**28**
Cerebral	2	4	4	6	**60**	**23**
Lethargy	5	0	9	6	7	**30**
Myalgia	2	0	3	1	0	**12**

challenged healthy controls (for ethical reasons), but when each clinical group is compared with our overall patient population it becomes evident that each of the relevant food chemicals can provoke a variety of symptoms, depending on the particular pattern of target organ susceptibility in each individual.

Conclusions

Our experience with the patients described here leads us to conclude that food intolerance is a common problem, causing significant symptoms at some time in perhaps as many as 5-10 per cent of the population, and is frequently unrecognized. However, dietary investigation is not appropriate in all cases, and should only be embarked upon when symptoms are significantly disabling; in patients with minor symptoms, the cure can sometimes be worse than the disease. Patients with urticaria, uncomplicated migraine and irritable bowel can be managed with relative ease, but the most sensitive patients often require a highly restricted diet to control symptoms, and care must be taken to maintain adequate nutrition by appropriate supplementation. In deciding whether to recommend dietary investigation the patient's life-style and attitudes to food should also be taken into account. For example, salicylate exclusion represents a very drastic change for a committed vegetarian, and any form of severe dietary restriction is difficult to manage for a person who leads a very active social life.

It has not escaped our attention that many of the syndromes which we can now attribute, at least in part, to food intolerance have been traditionally regarded as 'psychosomatic' and, indeed, many of our patients with systemic symptoms could easily satisfy the diagnostic criteria of hysteria (somatization disorder). It is of interest to note that the great majority of patients in whom this diagnosis is made are female, and food intolerance is reported as a symptom in nearly 50 per cent[12].

The mechanism of adverse reactions to food chemicals must remain speculative at present, although available evidence indicates they are not immunologically mediated. Their idiosyncratic nature, the cross-reactivities between apparently unrelated compounds, and the individual variability in target organ responsiveness obviously place certain constraints on the possible mechanisms. We favour the view that reactions represent exaggerated neuropharmacological responses, possibly involving regulatory neuropeptides[13], in genetically susceptible individuals. Consideration of the clinical spectrum suggests that the nociceptor system may be involved[14], and it is interesting to wonder whether a need to protect the foetus might account for the striking female predominance amongst our patients. Salicylates are known to be teratogenic[15,16], as are many other plant chemicals, and natural selection is likely to favour the offspring of women who are more sensitive to the noxious effects of these substances. It also seems reasonable to think that the nausea and unusual food aversions which are so common during early pregnancy might have a similar biological basis.

Acknowledgements — We thank the following colleagues for referral of patients and assistance in their clinical evaluation: Professor A. Basten, Drs. P. Gatenby, R. Kater, W. Selby, V. Soutter, S. van Nunen, H.A.D. White, K. Yan. We also thank Ms G. Boyd and Ms J. McQueen for their assistance in dietary management and Professor A.S. Truswell for his advice in the analysis of food salicylates.

References

1 Pearson, D.J., Rix, K.J.B. & Bently, S.J. (1983): Food Allergy: How much in the mind? A clinical and psychiatric study of suspected food hypersensitivity. *Lancet* **1,** 1259-1261.
2 Settipane, G.A. (1983;: Aspirin and allergic diseases: A review. *Am. J. Med.* **74,** (No. 6A) **85,** 950- 960.
3 Food intolerance and food aversion. (1984): Joint report of the Royal College of Physicians and British Nutrition Foundation. *J. Roy. Coll. Physns* **18,** 83-123.
4 Swain, A., Dutton, S. & Truswell, A.S. (1985): Salicylates in food. *J. Am. Diet. Ass.* **85,** 950-960.
5 Maga, J.A. (1978): Amines in foods. *CRC Crit. Rev. Food Sci. Nutr.* **10,** 373-403.
6 Giacometti, T. (1979): Free and bound glutamate in natural products. In *Glutamic acid: advances in biochemistry and physiology,* ed L.J. Filer *et al.,* pp 25-34. New York: Raven Pres.
7 Allen, D.H., Van Nunen, S.A., Loblay, R.H., Clarke, L. & Swain, A. (1984): Adverse reactions to foods. *Med. J. Aust.* S37-S42 (Suppl.).
8 Bock, S.A. (1982): The natural history of food sensitivity. *J. Allergy Clin. Immunol.* **69,** 173-177.
9 Denman, A.M. (1983): Food Allergy. *Br. Med. J.* **286,** 1164-1166.
10 Anon (1985): EBV and persistent malaise. *Lancet* **1,** 1017-1018.
11 Behan, P.O., Behan, W.M.H. & Bell, E. (1985): The postviral fatigue syndrome — an analysis of the findings in 50 cases. *J. Infection* **10,** 211-222.
12 Woodruff, R.A., Goodwin, D.W. & Guze, S.B. (1982): Hysteria (Briquet's syndrome). In *Hysteria* ed A. Roy, pp. 117-129. New York: John Wiley.
13 Polak, J.M. & Bloom, S.R. (1983): Regulatory peptides: key factors in the control of bodily functions. *Br. Med. J.* **286,** 1261-1466.
14 Lembeck, F. (1983): Sir Thomas Lewis's nocifensor system, histamine and substance-P-containing primary afferent nerves. *Trends in Neurol. Sci.* **6,** 106-108.
15. Rainsford, K.D. (1984): *Aspirin and the salicylates,* pp. 241-243. London: Butterworths.
16 Zierler, S. & Rothman, K.J. (1985): Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. *New Engl. J. Med.* **313,** 347-352.