Food Allergy, Hypersensitivity and Intolerance

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Most of the basic clinical features of food allergic states were established by the 1920s. Unfortunately the subject then became bedevilled by extravagant and fanciful claims. As a result, in the UK at least, it languished under an air of quackery for nearly 50 years. It is even more unfortunate that a renewal of interest in the objective study of very real phenomena has been associated with the resurrection of wild unsubstantiated claims of the importance of food allergy in all sorts of conditions in addition to the classical atopic diseases of asthma, eczema, urticaria and gastrointestinal food hypersensitivity.

As May[1] pointed out many misunderstandings about food allergy have arisen because of a failure to appreciate the power of the placebo effect and to take steps to overcome this and the results of observer bias. Also, with modern developments in biochemistry and immunology, it has become clear that a number of different mechanisms can be responsible for syndromes that are superficially identical.

Classification of Adverse Reactions to Food

Adverse reactions to food can be classified both by aetiological mechanism (Fig. 1) and according to the observed symptom pattern. Non-immunological allergomimetic responses have been described as pseudo-allergic reactions (PAR)[2]. Those which resemble IgE-mediated disease can be considered anaphylactoid.

It is becoming increasingly clear that the most common reason for failing to tolerate specific foods is psychological. Therefore the word intolerance should be allowed to revert to its meaning in simple English, namely, any inability to put up with something without ill-effect. Since hypersensitivity was used to describe unusual adverse reactions long before an immunological aetiology was established for any, I suggest it be applied to all unexpected adverse reactions and be defined as: ‘An organic host-damaging reaction which is qualitatively different from, or quantitatively greater than, the effects which the same dose of that substance would have on the generality of the population’.

Food allergy is hypersensitivity in which there is evidence of an immunological aetiology. To date, IgE-mediated reactions in atopy are the only immunological responses to food whose role in the generation of human disease has been demonstrated convincingly, although other allergic processes do seem probable (e.g. in eczema, coeliac disease).

Fig. 1. Aetiological classification of adverse food reactions.
Cultural background has major influences on what is considered desirable and probably most people avoid some foods which are relished by others. Sometimes the exaggeration of simple distaste into food fads and phobias, or the food avoidance of anorexia nervosa, may be justified as being due to an ‘allergy’. However, such patients tend not to present their food avoidance for medical treatment and if seen, rarely present diagnostic problems. Adult Munchausen’s syndrome patients who simulate or deliberately generate genuine anaphylactic emergencies in themselves are rare but well recognised[3]. The allergic form of Meadow’s syndrome (Munchausen’s-by-proxy) is also described[4].

In practice, for those wishing to treat or investigate food-allergic disease, the two most important problems are the psychological processes that can bring about pathophysiological changes identical to those of genuine immunological reactions; this is what we have called ‘pseudo-food allergy’ (PFA). The latter is characterised by the patients’ false conviction that they suffer from food allergy, to which they may attribute symptoms quite dissimilar from those of classical allergic disorders.

Psychologically-Induced Allergomimetic Changes

Relationships between physiological changes, neural and hormonal reflexes, biochemical abnormalities, immunological processes, and mental function are probably more complex in atopic diseases than in any other group of human disorders. Allergy can lead to organic brain syndromes, directly through hypoxaemia, or hypotension or indirectly through the common CNS adverse effects of many anti-allergic drugs[5,6]. The distress associated with the physical effects of disease can lead to anxiety and depressive reactions. Chronic or recurrent problems in childhood, particularly disfiguring conditions such as eczema and physical restrictions due to asthma, have long-term effects on the development of personality, social skills, and choice of work and leisure activities. Conversely, psychological events can also produce many of the physiological changes which follow allergic reactions. On occasion these somatopsychic and psychosomatic influences appear to lead to a vicious circle of self-perpetuating illness.

Both human[7-13] and animal experiments[14,15] indicate the capacity of neural and psychological events to produce allergomimetic physical changes in the lung, nose, skin and gastrointestinal tract. Some may involve neurological modulation of mast cell mediator release. These psychogenic changes are due to one of two possible mechanisms: (1) imbalanced end-organ responsiveness to the normal autonomic nervous system activation of emotional arousal; or (2) specific responses resulting from suggestion or conditioned reflexes.

It must be emphasised that the processes under discussion do not require any psychological abnormality for their generation. Failure to recognise this, and confusion of psychoanalytical with psychophysiological concepts of psychosomatic causation are responsible for the neglect of much important early work. Although psychogenic symptom exacerbations are common, comparative studies show no significant increase in the frequency of psychiatric disorder in atopic patients with mild or moderate disease[16,17]. The slightly increased frequency in the most severely affected individuals is entirely compatible with its being secondary, and is of the same order as that seen in other patients with similar degrees of physical handicap[16-19]. Of course, in atopic patients who independently develop a psychiatric illness, physical function may reflect the mental state through the same processes that operate in the non-psychiatric case.

Abnormal responsiveness to chemical transmitters is one of the hallmarks of atopic disease. In the lung this is characterised by bronchial hyper-reactivity. However, the basic abnormality is systemic. In vivo gluconeogenic, cardiovascular and cAMP responses to exogenous β-adrenergic agents are decreased in atopic groups[20-22]. Unusual dermal responses to cholinergic agonists in eczema were one of the earliest physiological peculiarities ever described in atopy[23]. The generation of these abnormalities is the subject of a number of hypotheses, but these are immaterial to the present discussion. It is an empirical observation that atopic individuals behave as if they have an unbalanced autonomic system in which parasympathetic and α-adrenergic actions predominate over the normally counterbalancing effects of β-adrenergic activity[22] (Fig. 2).

The results of this autonomic imbalance vary between tissues, depending on their innervation and distribution of receptors. In the lung it leads to bronchospastic responses to stimuli producing effenter vagal or sympathetic activity, including local reflexes and generalised responses such as those to exercise and the intense emotions of anger and fear which have been recognised as significant inducers of asthma since Hippocrates’ time. It is probable that every asthmatic will experience some degree of bronchoconstriction if stressed intensely enough. As any examination candidate will attest, gastrointestinal motility changes are a common response to fear, but it is not known whether these are any different in atopics. However, functional bladder outlet obstruction may be more frequent in patients with allergic problems.

Studies attempting to assess the relative importance of psychological, allergic and infective processes have concluded that all are involved at some time in most asthmatics[24,25]. Some psychogenic attacks have characteristics suggesting conditioned responses[26-28]. The literature records many cases who have developed asthma, rhinitis, itching or skin lesions when exposed to artificial flowers, or when shown pictures of allergens. Sometimes these responses may initially be due to simple anxiety associated with circumstances that have previously induced severe allergic reactions (e.g. anaphylaxis related to a particular food). Such reactions are clearly self-reinforcing. However, animal experiments show that conditioned asthma can occur without the biochemical abnormalities that characterise human atopy[14,15]. Atropine inhibition of psychogenic asthma in both humans and animals suggests that it is vagally mediated[9,11,12,15].

Experimental observations imply that suggestion can induce physical changes without necessarily requiring
previous conditioning[8–13]. However, clinically and in most experiments purporting to demonstrate the role of suggestion in humans, it is virtually impossible to dissect the effects of simple suggestion, conditioned reflexes and anxiety. The crucial point is that about half of all asthmatics will produce measurable bronchoconstriction if they falsely believe they have received an allergen or pulmonary irritant. Skin lesions can be produced in 20 per cent of patients with urticaria purely by discussing events associated with previous attacks[7]. The classical studies of Graham, Wolf and Wolf[7] demonstrated that a wide range of other changes, including local eosinophilia, nausea and abdominal pain associated with measurable changes in duodenal motility or diarrhoea, can also be induced by telling patients that they have been given a food to which they believe themselves allergic.

It is clear that any objective investigation of hypersensitivity must take account of the possibility of psychogenic changes. Even physiological measurements associated with histological changes or evidence of inflammatory mediator release do not prove the nature of the initiating event, although they may indicate common final pathways. There is no form of blood or skin test which accurately predicts the response to ingestion. We are left with double-blind administration as the only absolute proof of the organic basis of any triggering event, but also with the question of how such tests should be performed and interpreted.

Double-blind Provocation Tests

Several techniques of food administration have been used for double-blind tests. Nasogastric intubation is uncomfortable for the patient and it can be difficult to hide the nature of the injected substance from the administrator. Disguising foods does allow normally ingested quantities to be taken with relative ease and in a natural manner, but it can be difficult to produce preparations whose taste is truly indistinguishable. Encapsulation of dried foods avoids many of these disadvantages. Many commonly incriminated foods are available in ready-dried form from ordinary supermarkets and health food stores.

In practice it is best to take an eclectic approach. Encapsulated food provocation is reproducible in children and adults[29,30] and is the simplest and easiest technique. Most patients with genuine IgE-mediated hypersensitivity react to small, easily encapsulated doses of food. Milk is an exception. The amount of milk powder needed for provocation in many adult patients would require at least 30 capsules. The same dose is easily disguised in a soy-milk ‘shake’. The performance of double-blind provocations with adequate doses of food to disprove the contentions of some pseudo-allergy patients can tax the ingenuity of the researcher, but is rarely required as a routine.

It is simple to decide on the absence of an organic basis when doses of food, which repeatedly induce reactions on open challenge, fail to produce the same response when given in an identical manner apart from their identity being obscured. High placebo response rates in the demonstrable absence of hypersensitivity to the placebo substances, or reactions purely to the suggestion that a particular food has been given, reinforce the presumption that the responses to open administration were psychogenic. Unfortunately, it is not valid to be quite so confident about drawing the converse conclusions. There is a real possibility that apparent positive responses to double-blind provocation could occur purely by chance. Regrettably, the criteria which need to be applied before one can accept the results of such tests as indicating organic sensitivity have received inadequate attention.

Suggestion will produce measurable airway changes in
about 50 per cent of asthmatics. In our own experience, the majority of both atopic and non-atopic adult patients, subjected to double-blind testing, report subjective reactions to about 50 per cent of provocations in series which they believe will contain at least one dose of a food to which they suspect they are allergic. The odds for the correct identification by chance of each test dose are therefore even. In this situation statistical tests on data from a group can only indicate the probability of its having at least one member performing better than chance and do not allow any judgement concerning particular patients. Consequently, for each individual, a decision must be reached for each food on the basis of repeat administrations whose number must be pre-selected according to the level of confidence considered acceptable (Table 1).

### Table 1. Probability of chance identification of blind food provocations.

| Number of provocations in series | Probability P |
|---------------------------------|---------------|
|                                 | All correct demanded | 1 error allowed | all correct or 1 error |
| 2                               | 0.250          | 0.500           | 0.750                  |
| 4                               | 0.063          | 0.250           | 0.313                  |
| 6                               | 0.016          | 0.094           | 0.109                  |
| 8                               | 0.004          | 0.031           | 0.035                  |
| 10                              | 0.001          | 0.010           | 0.011                  |

These tests may be further confounded by two other variables. First, quite independent exacerbations may occur in patients with spontaneously fluctuating symptoms. Second, if the minimal possible dose is employed for provocations (both to minimise risk and to maximise compliance), the reaction induced in a genuinely hypersensitive patient may sometimes be too minor to be detected clinically. The effective level of sensitivity can vary with time. To take these factors into account one may wish to allow one or more errors in the identification of either placebo or active preparation in a provocation series. However, this will affect the total number of administrations required to reach the desired probability for correctly classifying the result (Table 1).

Double-blind feeding tests adjudged by strict criteria are the only acceptable proof of the aetiological role of food hypersensitivity in particular conditions and in individual patients. However, in states in which the role of foods is well established, it may be justifiable to make a presumptive diagnosis without such measures. These include syndromes in which typical histological changes have been shown to be reliable indicators of specific patterns of sensitivity (e.g. coeliac disease) and in infancy prior to the subject’s development of awareness. In our own research we have accepted the presence of hypersensitivity if the subject has identified correctly five or six challenges in a series containing three active and three placebo provocations. In effect this is a working compromise between knowing that just over 1 in 10 such conclusions will be erroneous and the difficulties of larger numbers of tests.

### IgE-Mediated Food Allergy

Patients with evidence of IgE-mediated food sensitivity can present in a variety of ways[31,32] all of which have long been associated with the atopic diathesis: with acute anaphylaxis; less severe reactions in multiple organs; the same allergic responses limited to a single ‘shock organ’ (Table 2) and occasionally in children, with apparent emotional and behavioural changes secondary to the physical changes of allergy which have themselves gone unnoticed (e.g. screaming secondary to abdominal pain, ‘hyperactivity’ due to severe itching). The actual pattern of response produced depends on the level of specific IgE-sensitisation of each organ and on the dose of food ingested. Some patients have different patterns of organ involvement with different foods. Most develop increasingly widespread symptoms as they eat larger amounts. When reactions are limited either by low levels of sensitisation or by small challenges, they are usually confined to the gastrointestinal tract.

Food allergy is quite common in infancy and becomes increasingly infrequent with advancing age. Follow-up provocation studies have confirmed the tendency of young children to outgrow their allergies[33,34]. Food hypersensitivities present in late childhood have a greater tendency to persist[34]. IgE-mediated hypersensitivity to food developing for the first time after childhood has never been demonstrated.

Although there are anecdotal reports of reactions to virtually every type of food, and despite the frequency of positive skin tests and detectable serum IgE antibodies against many, provocation testing indicates that most clinically relevant food allergy is due to a very limited range of foods, particularly milk, eggs, fish and leguminaceae (including soya and peanuts)[29,30,34-36].

### Anaphylactoid Reactions

Much confusion in the literature on food allergy and many present diagnostic difficulties can be traced to the frequency with which non-immunological hypersensitivities produce the features of IgE-mediated reactions. The most important of these are reactions to sulphur dioxide and sulphiting agents, and the syndrome of sensitivity to
salicylates and cross-reacting substances. Failure to recognise the character and origin of these responses to common additives can lead to a wide range of foods being blamed mistakenly, or false classification of reactions as non-organic if provocation is performed with the unadulterated food.

Virtually all asthmatics will respond to inhaled sulphur dioxide with vagally-mediated reflex bronchospasm[37]. SO₂ itself and SO₂-generating sulphites and metabisulphites are used widely in food manufacturing and storage. Quite high concentrations are common in fruit drinks and home-fermented beer and wine. Concentrations sufficient to induce asthma may be released into the air immediately above such products[38], or be absorbed from solution across the buccal mucosa and subsequently enter pulmonary gases[38]. A small number of cases have been described who suffer generalised anaphylactoid reactions to ingested metabisulphites themselves[39,40].

Anaphylactoid reactions to aspirin (ASA) are common and vary from severe, acute generalised reactions, through asthma, to chronic urticaria[41-44]. There is often cross-reactivity with other drugs, particularly analgesics, but also with a group of azo-dyes (e.g. tartrazine) and benzoic acid derivatives[42-44]. The latter two groups are frequently added to foods and medicines as colouring agents and preservatives. The syndrome is probably a familial idiosyncrasy inherited independently from atopy even though it may not be expressed until middle life. Major difficulties in identifying it and in estimating its true frequency are the large number of potential precipitants to be tested and the lack of any obvious fixed pattern of cross-reactivity. A significant number of patients with what appears to be an identical syndrome tolerate aspirin itself. For convenience I have used the acronym BAD-sensitivity (Benzoate-Aspirin-Dye) although it must be recognised that individual patients may react to only some of a group containing more than 80 chemical substances[45].

**Review of 250 Allergy Clinic Cases**

To give some idea of the frequency with which different patterns of food intolerance are seen and to compare their importance with that of other allergies, I have reviewed 250 patients assessed by myself in our allergy clinic. These were consecutive cases up to January 1985 and exclude only children under 13 years and patients referred for inclusion in specific research protocols. This clinic provides a general allergy service to South Manchester, but also receives a number of referrals specifically for the investigation of food hypersensitivity from a wider area. Diagnoses of inhalant sensitivities are based on clinical pattern, supported by skin prick test results and confirmed in cases of doubt by appropriate provocation tests. Except in cases of urticaria, food or ingestant hypersensitivity was confirmed by double-blind provocation unless: (a) there were repeatable classical atopic reactions to open provocation that could be blocked by double-blind cromoglycate and which were associated with strong positive skin-prick tests to the food, or (b) in salicylate sensitivity, if there was a history of anaphylaxis.

**Table 3. Reason for referral in 250 consecutive allergy clinic patients.**

| Reason for Referral | No. |
|---------------------|-----|
| Atopic conditions: asthma, rhinitis, eczema | 136 |
| Chronic urticaria without asthma or rhinitis | 48 |
| Wasp anaphylaxis | 3 |
| Non-atopic syndromes attributed to food allergy | 44 |
| Miscellaneous* | 19 |

*Includes referrals for advice concerning future employment in asymptomatic individuals with previous history of allergy, requests for advice concerning prevention of allergy from prospective parents, drug reactions, etc.

The distribution of the patients according to the reason for their referral is shown in Table 3. Urticaria unassociated with asthma or rhinitis is dealt with separately because several forms of urticaria are clearly not related to the atopic syndrome (although they are popularly assumed to be allergic) and because it is our practice only to investigate further those patients who do not respond to exclusion of benzoate food preservatives, salicylates and azo-dyes (BADS).

**Urticaria**

As shown in Table 4, 12 per cent of patients referred with a diagnosis of urticaria actually had some other condition. Of the remainder, 19 per cent had physical urticarias, 14 per cent recurrent attacks of acute urticaria, and 67 per cent chronic urticaria. In 7 per cent of chronic urticaria patients the disease had resolved spontaneously before investigation, 54 per cent responded to a BAD-free diet and 7 per cent to the further exclusion of dietary yeast; half of the latter two groups had a clear history of reactions to analgesics. Only 12 per cent of patients with urticaria had evidence of IgE-mediated allergy as a cause of their problem and in none was this related to food; three cases had episodes of acute urticarial reactions on contact with house dust or grass pollen; two had urticaria associated with either oral or vaginal thrush, immediate positive skin tests to *C. albicans*, and responded to appropriate anti-fungal therapy.

**Asthma, Rhinitis, Eczema**

Of the atopic presentation patients, four had mild eczema alone, 35 rhinitis without asthma and 97 had various degrees of asthma with or without rhinitis, eczema or urticaria. Hypersensitivity to exogenous agents was implicated in at least some symptom exacerbations in 94 per cent of patients; eight had purely reflex non-allergic vasomotor rhinitis or exercise-induced asthma. The frequency of clinically relevant hypersensitivities is shown in Table 5. House-dust mite was considered the predominant allergen responsible for the presenting complaints in 64 patients (48 per cent); 30 (22 per cent) had predominant hay fever/hay asthma and 30 (38 per cent) had two or more clinically important allergens.

Excluding the ubiquitous minor bronchospastic responses to sulphur dioxide and sulphite-containing
Drinks, nine atopic patients (7 per cent) had definite food hypersensitivity which persisted after the age of 16. However, this was incidential in four cases, and food reactions were relevant to the main presenting complaint in only one of the four cases with evidence of food allergy and in the four cases with BAD-sensitivity (i.e., 4 per cent of the atopic group). In comparison, 37 of the atopic patients (28 per cent) had symptomatic animal allergy, which was the presenting complaint in 17 (13 per cent) and the only allergy in 9 (7 per cent). Over the same period we saw three patients with severe anaphylactic reactions to stings.

Atopic Symptoms

It is worth considering some clinical features of atopic patients with and without confirmable food hypersensitivity for later comparison with the non-atopic groups. First, patients with objective evidence of IgE-mediated food allergy had recognised their sensitivity since childhood. It only presented a significant problem in a single case and then only because he wished to be able to accept the hospitality of his elderly parishioners so as to avoid giving offence. In contrast, each of the BAD-sensitive patients from this group suffered severe chronic symptoms as a result of their sensitivities and none had previously recognised any consistent food-symptom association. Three of these patients had ‘ulcerative colitis’ associated with asthma or eczema and three had severe, uncontrolled late-onset asthma. The ninth patient from this atopic group had mite-sensitive asthma and questioned whether her own lifelong painless diarrhoea could be due to food when her best friend was found to have coeliac disease. She was sensitive to cow’s milk protein without evidence of IgE-mediated milk hypersensitivity. None of these patients admitted any acute changes in psychological state during food reactions.

Table 4. Forty-eight patients referred for urticaria.

| Physical Urticaria(8) | Recurrent Acute Urticaria (6) | Chronic Urticaria (28) | Non-Urticaria (6) |
|-----------------------|-------------------------------|------------------------|------------------|
| Dermographic          | Allergic                      | BADs syndrome          | Other rashes     |
| Cholinergic           | Idiopathic                    | Other drugs            | 3                |
| Cold-induced          |                               | C. albicans            | 2                |
|                       |                               | Dietary yeast          |                  |
|                       |                               | Spontaneous resolution |                  |
|                       |                               | Idiopathic persistent  |                  |
1 Rare, minor reactions: not investigated
2 Response to dietary exclusion of benzoate preservatives, salicylates and azo-dyes, 8 patients gave histories of analgesic reactions
3 Schorhrooic dermatitis, tinea corporis
4 One case each of pruritis without rash as presentation of haematological disorder, hyperventilation syndrome and acrophobia

Table 5. Clinically relevant hypersensitivities in atopic patients (No. = 132).  

| Hypersensitivity                  | No. of Patients |
|-----------------------------------|-----------------|
| Dermatophagoides pteronyssinus    | 85              |
| Grass pollen                      | 45              |
| Other seasonal allergens          | 4               |
| Animals                           | 37              |
| Food hypersensitivity             | 11              |
| No detectable hypersensitivity    | 8               |
1 Excluding patients presenting with skin problems alone
2 Spontaneous resolution before 17 years in 2 cases

Objective evidence of food hypersensitivity was not found in a further 19 atopic patients referred for its investigation. In seven the question had been raised tentatively by the patient or by their family or physician, but without incrimination of any specific food. Two patients initially suspected several foods which were later tolerated on open reintroduction. Disturbingly, six patients had had confident diagnoses made elsewhere purely on the basis of clinical ecology techniques (2), skin prick tests at NHS clinics (3), or privately performed RAST tests (1). They had been advised to avoid several foods which they could actually eat without any ill-effect. Each was at clear risk of dietary deficiency diseases but none had been offered the advice of a qualified dietitian.

In four patients with ostensibly atopic symptoms and the putative label of food allergy the problem was considered predominantly psychiatric. One 14-year-old boy suffered from Meadow’s syndrome. His diet was severely curtailed by his mother who refused to accept any orthodox explanation or treatment for his very mild allergic rhinitis. She was abetted in this by each of the fringe ‘allergists’ and ‘ecologists’ she consulted. Adolescent food fads and questionable aesthetics seemed more likely than hypersensitivity in a very belligerent 15-year-old girl who would eat only potato crisps. The behaviour of two middle-aged nurses claiming to have multiple allergies prevented any objective investigation but indicated hysterical personality traits. Both had a wide range of non-atopic symptoms in addition to rhinitis and eczema. One was addicted to barbiturates and opiates, and had self-induced Cushing’s syndrome. The other, who had been considered anorexic in her youth, and whose multiple abdominal operations in different cities may have been due to fictitious illness, later admitted that many of her ‘allergies’ were due to distaste.

Non-atopic Symptoms

Forty-one patients whose main symptoms were other than those of classical allergic conditions were referred for the investigation of food hypersensitivity. Five, who had not themselves considered food triggers likely, were referred because physical syndromes such as proctitis and mig-
raine had proved resistant to ordinary treatments. Thirty-six patients considered themselves to be suffering from food allergy at the time they presented to our clinic. In only three cases was there any evidence that any symptoms were related to food and in each these were non-immunological exacerbating factors rather than allergic, or of primary aetiological significance: two had migraine; the third, an epileptic, blamed an increased fit frequency on milk which she was subsequently shown to tolerate. She had probably been suffering from the effects of the large doses of caffeine contained in copious volumes of milky coffee. There was positive evidence of psychological disorder in all the remaining patients. Pseudo-food allergy (PFA) will be considered separately by sex since there were distinct differences in the syndromes presented.

Pseudo-food Allergy (PFA)

Symptoms

There were notable differences between the features observed in young and middle-aged men. Food avoidance was primarily moral and philosophical in four of the five men under 35. Three were adherents of variations of eastern religions, exhibited schizoid features, and described bizarre reactions to foods. For example, one described how fish made his blood cold and his skin 'slimy and slithery'. The fourth was an obsessive body builder who had been surprised by the change in his bowel habit on trying to maintain an adequate calorie intake on his new high-fibre vegetarian diet. The fifth young man had hysterical features and obvious secondary gain in the continuance of 'neurasthenia'. In contrast, the main symptoms of three of the four men over 40 were those of endogenous depression, although each had previously rejected psychiatric explanations and treatments. The fourth was recently bereaved and responded rapidly to support and explanation of his mainly hyperventilatory physical syndromes.

With one or two exceptions the clinical picture presented by the 24 female PFA patients was remarkably consistent despite variations in the primary underlying psychiatric disorder. They tended to be in their middle to late thirties and early forties, middle class, articulate and either housewives without young children or under-employed for their level of intelligence. All were polysymptomatic and attributed overly psychological symptoms to their allergy, as well as physical symptoms referable to several organ systems (Table 6). Most were adamant that their symptoms were not 'psychological' and many strongly denied being anxious or depressed while at the same time volunteering that food was responsible for panic attacks, agoraphobia, irritability, mood swings, uncontrollable weeping and even suicidal thoughts, etc. Many of the physical symptoms reported by these patients were the recognised somatic concomitants of anxiety or depression, but in most cases at least some of the symptoms were the result of other distinct non-allergic syndromes (Table 7).

Not all of these patients were examined formally by a psychiatrist, but my impressions of these 24 females were entirely in keeping with our earlier comparative study[46] which showed that PFA patients suffer from the same spectrum of psychiatric disorder as unselected new referrals to a psychiatric out-patient department. Four female patients from the present series had features suggestive of a hysterical illness and nine had significant depression. The six who responded to tricyclic anti-depressants covered the entire age range of the female PFA group (32–66 years). Four patients had short-term reactions to social events or to intercurrent physical illness. The remaining five patients, together with the non-tricyclic-responding depressives, gave evidence of life-long neurotic personality traits: they tended to describe themselves as having 'ailed all my life' or of 'never having been what you'd call really well'. Others tended to call them 'odd' or hypochondriacal, although few would fit the formal psychiatric definition of hypochondriasis.

### Table 6. Common symptoms in pseudo-food allergy.

| Type of Symptom       | Pseudo-food allergy |
|-----------------------|---------------------|
| General debility      | Lethargy, tiredness, weakness, 'not well' |
| Affective changes     | Depression, mood swings, irritability, Panic attacks |
| Abnormal sensations   | Paraesthesia, burning, itching, 'swelling' Headaches, head tightness, 'migraine' Aches and pains, 'arthritis' |
| Cardiorespiratory     | Breathlessness, choking, Palpitations, chest pains |
| Abdominal symptoms    | Heartburn, belching, nausea Constipation, diarrhoea |
| Disturbed consciousness| Light-headedness, disorientation, poor concentration or memory Blackouts |

### Table 7. Somatic syndromes in 24 female pseudo-food-allergy patients.

| Syndrome                             | Patients |
|--------------------------------------|----------|
| Chronic hyperventilation syndrome    | 10       |
| Irritable bowel syndrome             | 9        |
| with associated urethral syndrome    | 3        |
| Somatic features of depression       | 7        |
| History of non-food allergies        | 7        |

1Typical symptom pattern associated with evidence of spontaneous hypocarbia or symptoms reproduced on voluntary hyperventilation
2Defined as abdominal pain associated with blotting and distension, and with constipation, diarrhoea or alternating constipation and diarrhoea in the absence of any other organic bowel disorder
3Anxiety-l ethargy, psychomotor retardation, typical disturbances of patterns of sleep, appetite etc. associated with depressed mood
4Includes mild perennial rhinitis, drug rash

The Generation of PFA

There are two main reasons which lead patients to develop the false conviction that they are afflicted by allergies. Regrettably, the first is failure on the part of orthodox medicine, which leaves them vulnerable to the second. Most of our PFA patients had suffered for months...
or years from other well described syndromes which their doctors had failed to recognise, or mismanaged. Once the question had been raised, having failed to find any proper provision for allergy within the National Health Service, they turned to alternatives.

The two most common non-allergic syndromes in PFA were hyperventilation and depression. There seems a remarkable general unawareness of the features and frequency of the chronic hyperventilation syndrome (HVS)[47], of which about half our patients presented obvious features. Four had been treated for 'asthma' without there being evidence of airway obstruction and many had received antihistamines or diuretics for dysaesthesiae such as 'itching' or the subjective feeling of 'swelling'. One was understandably distressed by the diagnosis of hyperventilatory symptoms as multiple sclerosis. Irritable bowel syndrome (IBS), the third common condition in this group, had more often been recognised previously but the ideas the patients had received about it were surprising. In many cases predictable fluctuations in bowel habit related to fibre intake or the ingestion of irritants (e.g. peppers) were taken as confirmation that all their symptoms must be due to food.

There can be little doubt that having become dissatisfied, these patients only turned to allergy as a possible explanation because of recent widespread publicity about the subject; more specifically, by that generated in the marketing of 'clinical ecology'. This recent import from the USA is a mystico-philosophical system of alternative medicine which views illness as maladaptation to the total environment (= allergy). While based on a rejection of the principles and logic of science[48], its pseudo-scientific publicity can seem persuasive to the naïve. Lists of symptoms said to indicate the presence of food allergy in ecology clinic leaflets distributed to health food stores and in paperback books are virtually identical to those of hyperventilation and depressive states. Some ecologists apparently hold that psychiatric disorders are due to the direct cerebral effects of food allergies 'unmasked' by social stress. This is considered justification for the administration of controversial (and expensive) anti-allergic therapy in place of intervention in the factors which led to the stress.

None of our PFA patients modified their diets because of a spontaneous association of their symptoms with food. Twenty-three were severely restricting their diet: three because of multiple 'allergies' diagnosed by acupuncturists; five by a clinical ecologist and 15 by self-diagnosis after reading ecology clinic publicity leaflets or Not all in the Mind[49]. At least three of the women were amenorrhoeic as a result of their starvation.

Several of the features of PFA, including its induction simply on reading a book or leaflet, implicate high suggestibility[46]. As a specific illness PFA seems to have several stages of evolution. Patients first become convinced that food allergy must be responsible for physical and/or mental symptoms for which they have received no other explanation that they are able to accept. Symptoms are not associated with specific foods at this stage. Most then start to misattribute coincidental symptom exacerbations to what was last eaten. Subsequently, suggestion leads to psychogenic reactions on re-exposure to foods previously associated with symptoms, and this becomes a self-reinforcing event. In some PFA patients their belief that they suffer from food allergy has the status of an over-valued idea[46]. They may persist in it despite exhaustive investigations failing to reveal any precipitating food or despite receiving rational alternative explanations. The placebo effect of food avoidance often produces initial improvement, but the inevitable symptom recurrence leads, not to a rejection of the first diagnosis, but a search for yet further foods to be avoided.

Reported food-symptom associations are sometimes purely due to misattribution or biased reporting. Comparison of symptom diaries shows no actual change in symptom frequency in some patients describing dramatic relief on particular diets. If drawn to their attention this may be rationalised as proof of the commercial adulteration of the food supply. Some reactions may be due to simple suggestion. The suggestive power of dietary manipulation was demonstrated in one of our earlier studies[50], in which 50 per cent of IBS patients, who had not previously considered themselves allergic, came to consider foods which they later tolerated as being responsible for their symptoms. However, the most common mediator of psychogenic reactions in PFA is demonstrably hyperventilation. In HVS the apprehension associated with ingesting a specific food may be adequate to trigger an attack and the tendency to post-prandial exacerbations exaggerated by the diaphragmatic splitting of gastric distension.

Conclusions

True immunologically-mediated food allergy does occur in adult patients but is uncommon and is a much less important cause of asthma, eczema, urticaria and rhinitis in adults than is sensitivity to house dust, pollens and animals. Non-immunological hypersensitivities to food constituents are both more common and often more difficult to identify. Minor asthmatic reactions to SO2 are extremely frequent, but reactions to metabisulphites and substances cross-reacting with aspirin (BADs) can be dramatic. The latter can also produce severe chronic symptoms and BADs sensitivity should be considered in every patient with poorly controlled asthma, particularly if of late onset or associated with gastrointestinal symptoms.

Subjective psychological and psychogenic somatic adverse responses to food are more common than organic intolerance. The only presently available valid evidence of hypersensitivity is double-blind feeding but even the results of provocation tests require critical appraisal. It is clear that patients on diets for 'food allergy' are at severe risk of developing dietary deficiency diseases. It is therefore crucial that these diets only be embarked upon when justified by objective testing and that suitable dietary supplements be prescribed whenever necessary.

The application of objective investigations to food hypersensitivity has indicated that a number of different allergic and non-allergic reactions are important in several human diseases and also indicated a number of new
directions for future research. In particular, since food hypersensitivity is a common cause of gastrointestinal disease in children and since GI symptoms are frequent in organic food intolerance at all ages, the role of foods in adult human gut disorders should be reassessed.

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References

1. May, C. D. (1982) Journal of Allergy and Clinical Immunology, 69, 255.
2. Bukor, P., Kallos, P., Schumberger, H. D. and West, G. B. (eds) (1980) Pseudo-Allergic Reactions: Involvement of Drugs and Chemicals. Basel: Karger.
3. Hendrix, S., Sale, S., Zeiss, R., Uley, J. and Patterson, R. (1981) Journal of Allergy and Clinical Immunology, 67, 8.
4. Warner, J. O. and Hathaway, M. J. (1984) Archives of Disease in Childhood, 59, 151.
5. Sankey, R. J., Nunn, A. J. and Sills, J. A. (1984) British Medical Journal, 288, 1369.
6. Fusukawa, C. T., Shapiro, G. C., DuHamel, T., Weiner, L., Pierson, W. E. and Bierman, C. W. (1984) Lancet, 1, 621.
7. Graham, D. T., Wolf, S. and Wolff, H. G. (1950) Journal of Allergy, 21, 478.
8. Luparello, T., Lyons, H. A., Bleecker, E. R. and McFadden, E. R. (1968) Psychosomatic Medicine, 30, 819.
9. McFadden, E. R., Luparello, T., Lyons, H. A. and Bleecker, E. (1969) Psychosomatic Medicine, 31, 134.
10. Luparello, T. J., Leist, N., Laurie, C. H. and Sweet, P. (1970) Psychosomatic Medicine, 32, 509.
11. Luparello, T. J., McFadden, E. R., Lyons, H. A. and Bleecker, E. R. (1971) New York State Journal of Medicine, 71, 2161.
12. Spector, S., Luparello, T. J., Kopetzky, M. T., Sourdra, J. and Kinsman, R. A. (1976) American Review of Respiratory Disease, 113, 43.
13. Fry, L., Mason, A. A. and Pearson, R. S. (1964) British Medical Journal, 1, 1145.
14. Ottenberg, P., Stein, M., Lewis, J. and Hamilton, C. (1958) Psychosomatic Medicine, 20, 395.
15. Justesen, D. R., Braun, E. W., Garrison, R. G. and Pendleton, R. B. (1970) Science, 170, 864.
16. Graham, P. J., Rutter, M. L., Yule, W. and Pless, I. B. (1967) British Journal of Preventive and Social Medicine, 21, 78.
17. McNicoll, K. N. and Williams, H. B. (1973) British Medical Journal, 4, 16.
18. Neuhaus, E. C. (1958) Psychosomatic Medicine, 20, 181.
19. Oswald, N. C., Waller, R. E. and Drinkwater, J. (1970) British Medical Journal, 2, 14.
20. Middleton, E. and Finke, S. R. (1968) Journal of Allergy, 42, 288.
21. Fireman, P., Palm, G., Frady, G. and Drash, A. (1970) Journal of Allergy, 45, 117.
22. Kaliner, M., Shelhamer, J. H., Davis, P. B., Smith, L. J. and Venter, J. C. (1982) Annals of Internal Medicine, 96, 349.
23. Lobitz, W. C. and Campbell, C. J. (1953) Archives of Dermatology and Syphilology, 67, 575.
24. Williams, D. A., Lewis-Farrig, E., Rees, L., Jacobs, J. and Thomas, A. (1958) Acta allergologica, 12, 376.
25. Rees, L. (1963) Journal of Psychosomatic Research, 7, 253.
26. Herxheimer, H. (1953) International Archives of Allergy, 3, 192.
27. Dekker, E. and Groen, J. (1956) Journal of Psychosomatic Research, 1, 58.
28. Dekker, E., Pelser, H. E. and Groen, J. (1957) Journal of Psychosomatic Research, 2, 97.
29. May, C. D. (1976) Journal of Allergy and Clinical Immunology, 58, 500.
30. Bernstein, M., Day, J. H. and Welsh, A. (1982) Journal of Allergy and Clinical Immunology, 70, 205.
31. Lessof, M. H., Wraith, D. G., Merrett, T. G., Merrett, T. and Buisseret, P. D. (1980) Quarterly Journal of Medicine, 49, 259.
32. Minford, A. M. B., MacDonald, A. and Littlewood, J. M. (1982) Archives of Disease in Childhood, 57, 742.
33. Dannaeus, A. and Inganas, M. (1981) Clinical Allergy, 11, 533.
34. Bock, S. A. (1982) Journal of Allergy and Clinical Immunology, 69, 173.
35. Bock, S. A., Lee, M. Y., Remigio, L., Holst, A. and May, C. D. (1978) Clinical Allergy, 8, 559.
36. Sampson, H. A. and Alvergo, R. (1984) Journal of Allergy and Clinical Immunology, 74, 26.
37. Boushey, H. A. (1982) Journal of Allergy and Clinical Immunology, 69, 335.
38. Freedman, B. J. (1977) Clinical Allergy, 7, 407.
39. Penner, B. M. and Stevens, J. J. (1976) Annals of Allergy, 37, 180.
40. Stevenson, D. D. and Simon, R. A. (1981) Journal of Allergy and Clinical Immunology, 68, 26.
41. Samter, M. and Beers, R. F. (1967) Journal of Allergy, 40, 281.
42. Juhlin, L., Michaelsson, G. and Zetterstrom, O. (1972) Journal of Allergy and Clinical Immunology, 50, 92.
43. Michaelsson, G. and Juhlin, L. (1973) British Journal of Dermatology, 88, 525.
44. Stenius, B. S. and Lemola, M. (1976) Clinical Allergy, 6, 119.
45. Schumberger, H. D. (1980) Drug-induced pseudo-allergic syndrome as exemplified by acetylsalicylic acid intolerance, in PAR. Volume I. (ed. P. Bukor, P. Kallos, H. D. Schumberger and G. B. West.) Basel: Karger.
46. Rix, K. J. B., Pearson, D. J. and Bentley, S. J. (1984) British Journal of Psychiatry, 145, 121.
47. Magarian, G. J. (1982) Medicine (Baltimore), 61, 219.
48. Randolph, T. G. (1976) in Clinical Ecology (ed L. D. Dickey ) pp. 9-17 and 44-66. Springfield: Thomas.
49. Mackarness, R. (1976) Not all in the Mind, London: Pan.
50. Bentley, S. J., Pearson, D. J. and Rix, K. J. B. (1983) Lancet, 2, 295.