Food Intolerance and Food Aversion

A JOINT REPORT OF THE ROYAL COLLEGE OF PHYSICIANS AND THE BRITISH NUTRITION FOUNDATION

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PREFACE

The concept of allergy to food has attracted a great deal of attention in recent years. Although this condition has not always been very clearly defined, wide publicity is given to the unproven claim that food allergy is becoming more common, that (despite evidence to the contrary) food processing exacerbates the problem, and that the medical profession is not sufficiently well informed to deal with it. It is, however, becoming clear that, if allergy is taken to imply a specific immune reaction of the body, allergic reactions are present only in a minority of cases in which there is an unpleasant reaction to a food. Food intolerance may occur when food contains components which are either generally toxic or toxic to certain individuals, or when the nature of the reaction is as yet unknown. Diagnosis is, however, difficult because it depends on attempts to reproduce a clinical response in a patient who, at different times, may develop symptoms rapidly or more slowly and after smaller or larger quantities of the same food. There is also great uncertainty about the prevalence of this condition in the community at large and particularly about the importance of psychological factors which may lead to food aversion. For these reasons a survey of the present state of knowledge is indicated.

Against this background, the Royal College of Physicians and the British Nutrition Foundation formed a committee to consider these various areas of concern and to make whatever recommendations might be necessary. The terms of reference of the Joint Committee were:

1. To define food intolerance.
2. To assess the frequency of clinical reactions to fresh or stored food preparations.
3. To consider the biological and psychological mechanisms involved in food intolerance, as they affect the public at large and as they affect susceptible groups of individuals who suffer from allergic disorders, enzyme defects, or the effects of other metabolic disorders or drug treatment.
4. To assess the implications of food intolerance for the medical profession, the food industry, the government and the public and to make recommendations for these groups concerning the possible need for further educational, preventive, investigative, therapeutic or research endeavours in this area.

The report of the Joint Committee is presented in the following pages. The Appendix discusses sources of information on food products, and a Glossary has been added in case readers are unfamiliar with some of the terms used.

1. INTRODUCTION

1.1 Definitions

When the body's immune defence mechanism shows an exaggerated response to harmless grains of grass pollen or to articles of food, there can be unpleasant symptoms of 'allergy' without any obvious benefit to the person concerned. Thus, food allergy may be a cause of symptoms but needs to be distinguished from other clinical conditions which are related to food. Two main conditions have been identified, food intolerance and food aversion (Table 1). The following definitions should be used:

Food intolerance itself, which is a reproducible, unpleasant (i.e. adverse) reaction to a specific food or food ingredient and is not psychologically based. This occurs even when the affected person cannot identify the type of food which has been given (for example, when it is disguised by flavouring and given as a purée).

Table 1. Food aversion and intolerance.

Food aversion	Food intolerance
Psychological food intolerance	Enzyme defects
Food avoidance	Pharmacological
	Irritant and toxic
	Allergic
	Fermentation of food residues
	Other

Food allergy, which is a form of food intolerance in which there is also evidence of an abnormal immunological reaction to the food.

Food aversion, which comprises both psychological avoidance—when the subject avoids food for psychological reasons—and psychological intolerance, which is an unpleasant bodily reaction caused by emotions associated with the food rather than the food itself and which does not occur when the food is given in an unrecognisable form.

In those who have reproducible adverse reactions to food due to causes other than food aversion or allergy, various mechanisms may be responsible. These mechanisms include:

(a) A lack of particular enzymes; for example, in people who do not tolerate cow's milk because they cannot digest lactose (alactasia).
(b) A pharmacological effect; for example, due to large amounts of caffeine in strong coffee or tea.
(c) An as yet unexplained histamine-releasing effect in unsensitised individuals; for example, caused by the consumption of foods such as shellfish, strawberries, and pawpaw.
(d) An irritant effect on the mucous membranes of the mouth or bowel, especially when the mucosa is diseased, for example, irritation caused by highly spiced curry or very hot coffee.

(e) An indirect effect caused by the effects of fermentation of unabsorbed food residues in the lower bowel.
(f) Mechanisms as yet unidentified.

1.2 Prevalence of Food Intolerance

A precise assessment of the prevalence of food intolerance is difficult, since diagnosis has depended largely on subjective methods associated with clinical screening tests and the interpretation of a patient's previous history. Thus, widely varying estimates of prevalence may be found in the literature. It is suggested that between 0.3 per cent and 20 per cent of children suffer from, or have suffered from, symptoms caused by some form of dietary intolerance[1]. The wide range of incidence reflects the effects of selective bias and different diagnostic criteria employed in various studies and emphasises the difficulty in establishing a useful estimate of prevalence.

Conditions such as 'cow's milk protein intolerance', the most common food allergy in young children, have been estimated to have a prevalence between 0.2 per cent and 7.5 per cent[2]. In a similar survey involving 400 infants monitored from birth to two years of age, the incidence of milk intolerance was 0.5 per cent[3].

When it comes to assessing the frequency of allergy or intolerance to food additives, the problem is considerably more difficult. This is because a number of colours and additives are often used in combination and appear in a wide variety of foodstuffs. As any one individual may react in a similar way to structurally related colours and additives, it may be difficult to identify which particular food or food component triggers the adverse reaction. Studies concerning reactivity to food additives have therefore been somewhat restricted to selected populations and, in the main, to patients attending hospital for the treatment of 'allergy-like' diseases.

To obtain an approximate figure for the prevalence of additive-induced adverse reactions in the skin, Juhlin[4] reviewed the literature for relevant information and, also using his own data, reached the following conclusions: (a) In patients with chronic urticaria, 33–50 per cent of individuals tested reacted to one or more food additives. (b) Tartrazine produced a reaction in 5–46 per cent of those tested, other azo dyes gave positive reactions in 5–20 per cent of those tested. (c) Among the preservatives tested, benzoate derivatives produced reactions in 3–44 per cent of individuals and the antioxidants, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), were implicated in reactions in 14–15 per cent of individuals. Thus, even in sensitive individuals, there was a very wide range of reactivity to different additives.

These studies cannot provide true estimates of prevalence in the whole population, since an extrapolation from responses obtained in a selected group is based on the assumption that there is no difference in susceptibility among the population at large, which is unlikely to be the case. It is reasonable to assume that the susceptibility of the general population to adverse reactions to additives is likely to be considerably less than that of the special groups studied.

It has been estimated that in every 10 million people about 40,000 will show intolerance to aspirin (0.4 per cent), 6,000 to tartrazine (0.06 per cent) and 5,000 to benzoates (0.05 per cent)[4]. In France, sensitivity to tartrazine was estimated to be between 0.03 per cent[5] and 0.15 per cent[6]. A recent study in Denmark[7] employed a more systematic approach. Initially, the frequency of asthma, chronic rhinitis and chronic urticaria was assessed in the general population over 16 years of age and determined to be in the order of 3.8 per cent, 1.9 per cent and 0.5 per cent respectively. The frequency of adverse reactions to food additives within each group was then determined by reference to previous case histories and previous provocation tests. It was concluded that 0.01–0.1 per cent of the population were sensitive to both tartrazine and benzoates. These figures are in the same order as those suggested by Juhlin[4]. The Commission of the European Communities[8], on the basis of existing evidence, assigned a prevalence of 0.03 per cent to 0.15 per cent for food additive intolerance. When one considers that almost everyone in the population has probably been exposed to tartrazine at some time or another, sensitisation to tartrazine is low.

1.3 Genetic Factors

It would appear that genetic factors can predispose individuals to a number of diseases and this may also hold true for certain types of food intolerance, including those caused by enzyme defects (see Chapter 5.1). It is well established that allergic disorders are more common in the children of atopic parents[9]. The mode of inheritance of susceptibility to allergy is not known but there are suggestive links between the HLA haplotype A1/B8 and atopic eczema[10] and between HLA B8/W3 and gluten sensitivity[11]. Indeed, recent experimental evidence suggests that there may well exist a whole class of non-HLA linked genes that also control immune responses to foreign substances[12]. Genetic factors are of importance in relation to the many types of food intolerance and may be relevant to atopic disease and IgE production. Various types of inherited immune deficiency can also predispose to atopic disease, including deficiencies of complement (C2) or of immunoglobulin A, and defects of T cells or of the mechanisms that stimulate the phagocytic function of leukocytes[13].

Genetic factors may only come into play following the appropriate exposure to the environmental stimulus. Developmental and/or environmental pressures would then be superimposed upon a genetic predisposition before a state of intolerance could appear. A predisposition to dietary intolerance is obviously a real phenomenon, but we remain unclear as to how this operates.

1.4 The Clinical Patterns

Where the affected person develops an immediate swelling of the lips, tingling of the mouth or throat, vomiting or abdominal pain, it may not be difficult to establish the link between a food and the reaction which follows. Even late complications such as diarrhoea, constipation, bloating of the abdomen and fatty stool may be suggestive of

food intolerance, if not allergy. Remote effects are often more difficult to attribute to an identified cause, but food allergy is at least worth considering in people who develop symptoms of hay fever after a particular type of food is eaten or who develop a variety of problems ranging from asthma and eczema to the skin swellings seen in urticaria and angioedema, the state of shock seen in acute anaphylaxis (suggesting hypersensitivity of the 'immediate' type), or the headache and joint pains which occur occasionally. While many of these problems can be shown to have an allergic origin, this is not always the case. It has been suggested that migrainous headaches can occur in people who have difficulty in metabolising tyramine or similar substances which are present in cheese or chocolate and although the matter remains contentious, an enzyme defect may be responsible[14]. The intolerance to rich food which is seen in gouty subjects is an even more clear example of a metabolic cause for food intolerance which, in this case, is associated with a difficulty in metabolising uric acid but has nothing to do with allergy.

In a number of instances it has been claimed, without adequate evidence, that a wide range of symptoms of uncertain origin can be attributed to food intolerance or to a reaction to food additives. Among these are a variety of psychological problems, and a number of so-called hyperactive children in the USA have been given restricted diets in the belief that their hyperactivity is a specific reaction to food additives[15]. There is no good evidence for this belief[16,17], although it has been suggested that behavioural changes may occur in association with a wide range of other symptoms as a result of intolerance to any food[18]. Certainly the psychological aspects of food-associated symptoms deserve further consideration and research.

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2. PHYSIOLOGY OF THE BOWEL AND PROTECTIVE MECHANISMS

There are many classical food related symptoms which will direct the physician's attention to specific diseases. Hot foods, spicy foods and citrus drinks can precipitate heartburn and oesophagitis. Difficulty in swallowing solid foods occurs in oesophageal stricture. Biliary colic may be associated with eating fats. Colicky central abdominal pain will be produced by high residue foods or foods such as sweetcorn when there is a small bowel stricture. Too much food can cause fatty diarrhoea in patients with a failing pancreas. The intake of large quantities of fluid can produce loin pain and nausea in patients with obstructed kidneys (pelvi-ureteric obstruction).

Gastrointestinal Symptoms without Structural or Biochemical Abnormality: 'The Irritable Bowel Syndrome'

The control of bowel activity and the movement of food through the bowel depend on the regulating effects of the nervous system and the endocrine system. Food usually stimulates 'motility' but may inhibit it, for example, a fatty meal slows gastric emptying. The ingestion of food influences not only the upper gastrointestinal tract but may also stimulate the colon by a reflex effect of the autonomic nervous system. Symptoms may arise either because of abnormal motility or because an individual is unduly sensitive to the normal contractions or distentions of the gut. Not surprisingly, these symptoms are often closely related to foods.

The diagnosis of 'irritable bowel syndrome' was first applied to patients with either abdominal pain or a change in bowel habit[1]. However, such patients may have symptoms of abnormal motility affecting any part of the gastrointestinal tract. These include difficulty in swallowing, heartburn, nausea, upper abdominal pain (without ulceration), colicky central or lower abdominal pain, bloating, diarrhoea or constipation. About one-third of patients presenting to a gastrointestinal clinic are given this diagnosis[2].

Many other names have been given to this disorder, including irritable colon, colonic dysfunction, spastic colon, functional bowel disorder, mucous colitis, nervous

diarrhoea, colon neurosis. It has many similarities to the syndrome which Mackarness called 'specific adaptive syndrome'[3]. Appropriate enquiry usually elicits the disclosure of other relevant symptoms in such patients and many complain of fatigue, depression, anxiety, insomnia, or fear of cancer. It is often because of these associated symptoms that it is necessary for all concerned to be reassured that no organic disease is present.

Those with abdominal symptoms self-diagnosed as food allergy may require a more detailed assessment. Many food avoiders with an unsubstantiated self-diagnosis of food allergy do indeed suffer from the irritable bowel syndrome. Self-imposed alterations in diet will influence gut motility, the composition of the stools and the production of gas. In an introspective individual these physiological changes may reinforce the patient's concern.

There is a report in the literature[4] which provides clinical evidence of specific food intolerance in a high proportion of patients with the irritable bowel syndrome subjected to double-blind challenge. However, in another study Bentley and his colleagues[5] were only able to confirm food intolerance in a small proportion of a similar sized sample of patients with irritable bowel syndrome. Further work is being performed by both of these groups and the results, including more details of the gastrointestinal symptoms involved, are awaited with interest.

A distinction must be made between the existence of gastrointestinal symptoms associated with a proven food allergy and with abnormalities elsewhere in the body, and the rather similar gastrointestinal symptoms of irritable bowel syndrome, a condition for which there is no evidence of a true allergic basis. If food intolerance does indeed contribute to the irritable bowel syndrome, even in a small proportion of patients, much further work will be required to elucidate the mechanism.

Even among apparently healthy people symptoms suggesting abnormal intestinal motility or the irritable bowel syndrome are common. Four clinically distinct functional bowel syndromes were found to exist in almost one-third of the 301 healthy British subjects studied by Thompson and Heaton[6]. Abdominal pain, a feeling of incomplete evacuation after defaecation, urgency, hard or runny stools, straining at stool, borborygmi, distension, heartburn and laxative use were all very common. This typical symptom pattern occurred in 13.6 per cent of subjects; 7 per cent suffered non-colonic pain that was commonly associated with heartburn; a further 3.7 per cent had painless diarrhoea; 6 per cent suffered painless constipation. Most of these healthy individuals had not consulted a doctor. Thus, it is factors other than the mere existence of these symptoms which determine whether a patient decides to consult a general practitioner and whether the general practitioner then requests a hospital consultation.

Symptoms of lactose intolerance, in a lactase-deficient individual, are rather similar to those of the irritable bowel syndrome. The two conditions often co-exist. This is, however, unusual in white, British-born adults[7] (see Chapter 5.1).

Local immunological reactions can also influence gastrointestinal motility[8]. Local reactions of immediate hypersensitivity can produce pre-pyloric or pyloric spasm, hypermotility of the small and large intestines, oedema with increased secretion of mucus and spasm of the anal outlet. Again the results may be nausea, vomiting, abdominal pain and diarrhoea, but in this case the basis for these symptoms is truly allergic.

Nature and Properties of Gastrointestinal Defence Mechanisms

The gut wall is protected by its mucous coating, by the tight junctions between the mucosal cells, and by the immunological tissues beneath them. The immunological tissues comprise a major part of the so-called mucosa-associated lymphoid tissues (MALT). The gut-associated lymphoid tissues (GALT) comprise nodular lymphoid tissues (Peyer's patches and the mesenteric lymph nodes), the many single lymphoid cells scattered throughout the mucosa, the phagocytes of the mucosa, the associated lymph nodes and the liver[9].

Immunoglobulins are secreted locally into the mucus[10] which also contains protective enzymes (lysozyme) and protective cells (macrophages). There is a continuous traffic of lymphocytes to and from the gut, the main route being from Peyer's patches via the mesenteric lymph nodes, lymph and blood, back to the mucosa of the small bowel and colon. This allows for widespread distribution of the antibody-producing cells which react with foreign antigens in the gut[11]. Equipped in this way, the MALT can react to antigen in a manner which is quite separate from the body's more general immune system. Thus, antigen administered via the gut tends to induce only local mucosal immune responses, whereas antigen administered by injection or through the bloodstream may produce systemic immunity with little or no mucosal antibody or cellular responses[12]. In both cases, antibody production by B lymphocytes can either be suppressed or increased by the modulating action of various types of T lymphocytes.

Virtually all foods, many partially digested food constituents, food additives, drugs and other swallowed substances (such as dusts and micro-organisms) may act as antigens within the gut, i.e. they have the potential to elicit specific immune responses involving antibodies or cells. It is impossible to separate the digestive functions of the gut from the protective immunological functions, but the nature and amount of digestive secretions, the speed of onward propulsion (or the degree of intestinal stasis), the speed of absorption and elimination will all influence the amount and the physical state of any antigen present in a particular segment of the gut.

An antigen may evoke several types of specific immune response that are not mutually exclusive. Active immunity (for example, the production of protective antitoxins or antibacterial antibodies) may involve both cells and specific antibody. However, immunological tolerance is an equally important specific immune response. This leads to a suppression and downgrading of immune reactions if the same antigen is encountered at a later date[13].

Before immune responses can occur, or immunological

tolerance can be induced, it is necessary for the antigen to gain access to the tissues of the body. Small amounts of any antigen penetrate the normal gastrointestinal surface epithelium at various sites, including the cells overlying the Peyer's patches[9,14]. When this is a first encounter with antigen, there is potential for the induction of specific immune responses. However, there appear to be circumstances when ingestion or enteric exposure to antigen does not lead to clinical or immunological effects, for example if the antigen is rapidly phagocytosed and destroyed within the gut. When the individual is already sensitised or immune, later re-exposure to antigen will produce an interaction with antibody or cells, in the gut or elsewhere in the body, which occasionally leads to clinical manifestations or disease.

Research continues on the nature and regulation of immune responses to fed antigen. The present state of knowledge, based mainly on work in rodents, is as follows. When an animal which has never previously encountered the substance is fed an antigen, the responses are: (a) secretory antibody response—antibody of IgA class is found within the plasma cells and is secreted into the lumen; (b) there is little or no serum antibody response (antibodies of IgM and IgG classes) and no evidence of immune cell reactions; (c) tolerance to the specific antigen occurs, i.e. there is suppression of subsequent immune responses to the antigen if it is encountered again, and (d) there is little or no production of IgE in the gut or elsewhere.

There are probably several parallel and overlapping mechanisms for regulating the various patterns of immune response to antigen in the gut, involving the regulatory function of T lymphocytes of the 'helper' and 'suppressor' types[15]. The way in which digestion of protein antigen can affect the immunological response has been little studied. It is possible, however, that the digestion of protein generates fragments which are recognised by T suppressor cells and so induce tolerance, whereas the more conventional route for antigen recognition may be through the macrophage, which stimulates T helper cells and leads to a classical immune reaction.

Abnormal Immune Responses to Foods

The diagnosis of food allergy as a cause of food intolerance implies the presence of an abnormal response to one or more foods. The relevant immune responses are by no means fully understood but may include induction of the following[16]: (a) IgE antibodies; (b) mucosal T cell-mediated reactions, and (c) active systemic immunity involving serum antibody of different classes, with the capacity to form large complexes with antigen. Little is known about the part played by other immunological mechanisms or about the role of T cells beyond the mucosal surfaces.

It is important to emphasise that immune responses to foods, without underlying food intolerance, can often be found in normal individuals such as blood donors, and may also follow the disruption of normal physiology in various gastrointestinal and immunological diseases. Some of these immune reactions to foods can be produced in experimental animals, either spontaneously (for example, if a rabbit is regularly fed antigen, a brisk serum antibody response is induced) or by manipulating the immune status of an animal, or its environment, at the time of antigen feeding. For example, a vigorous IgE anti-food antibody response can be induced when antigen and pertussis adjuvant are administered to rats[17].

Mechanisms which probably Protect against Food Allergic Diseases

Research in humans remains restricted, mainly because of ethical considerations and difficulty in reaching the relevant lymphoid tissues within the abdomen. Knowledge about the immune response of healthy infants to foods within the first few months after birth and the mechanisms which protect against the induction of harmful immune responses is limited. Whether such immune responses are different when children are born at term or prematurely is something which needs to be investigated.

The normal functions of the gut, digestive and immunological, are probably quite different at the first encounter with antigen, when oral tolerance can be induced, and later, when the capacity to mount a hypersensitivity reaction is present. Once established, hypersensitivity reactions do not always persist indefinitely. This is evident from the transient nature of cow's milk protein intolerance and other types of food allergy in some children[18,19].

The tendency to develop hypersensitivity reactions may relate partly to the total amount of antigen absorbed, and partly to the nature and quantity of circulating antibody or the number of sensitised lymphocytes and their distribution. Protective factors include (a) normal digestion of antigens, e.g. by gastric acid, pepsin, trypsin, peptidases; (b) an intact gastrointestinal epithelium, free from ulcers; (c) the presence in the lumen of secretory IgA antibodies which are able to bind antigens without causing inflammatory reactions, and (d) the cleansing function of liver phagocytic cells on immune complexes and particulate antigen which are removed from portal blood before they reach the systemic circulation.

To cure food allergy it may be necessary either to identify and re-create the conditions which allow children to recover spontaneously, or to find other ways of recreating immunological suppression or oral tolerance. Apart from the possible effects of dietary exclusion, there are, theoretically, two possible ways of restoring a normal immune tolerance to foods. One is by presenting antigen in a form which will suppress the immune response, perhaps by stimulating suppressor cells; the other is by pharmacological manipulation of suppressor and helper cells, using drugs or other agents which have a selective toxicity for T helper cells (for example cyclosporin A or monoclonal antibodies).

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3. DIAGNOSIS OF FOOD INTOLERANCE AND ALLERGY

A variety of claims have been made both about the clinical features which indicate food intolerance and the tests which can help in the diagnosis. If the complaints are purely subjective it may be difficult to exclude psychological causes. In some cases—especially in people who complain of tingling, giddiness and sweating—a short period of overbreathing is sufficient to reproduce the symptoms, indicating a metabolic disturbance (hypocarbia) which results from hyperventilation. In other cases in which there are objective changes in the skin (urticaria, angioedema, and eczema), the lungs (asthma) or the gastrointestinal tract (vomiting, diarrhoea), support for the diagnosis of food intolerance can be firmly established by giving the food in disguised form and showing that the symptoms recur. Whether objective changes are present or not, the diagnosis of food intolerance can only be established if the symptoms disappear with an elimination diet and if a controlled challenge then leads either to a recurrence of symptoms or to some other clearly identified change—for example, in the microscopic appearance of the jejunum. Although much publicity has been given to a wide range of additional tests, both clinical and laboratory-based, these vary in their validity and interpretation and cannot reduce the importance of the challenge test.

Elimination and Challenge

If there is good reason to suspect a food-induced reaction, a simple diet can be given over a period of at least two and preferably three weeks, eliminating either individually identified foods or, if these cannot be determined, eliminating all those foods which are most closely associated with adverse reactions (see Chapter 6). It should be accepted, however, that improvement on an elimination diet may take up to three weeks, and there may even be withdrawal symptoms in the first week. Only if the symptoms disappear within the period of the diet is the possibility of food intolerance worth pursuing by means of food challenge tests or by challenge with measured amounts of food preservatives and dyes[1].

For those whose symptoms are slow to develop, a disguised purée preparation may have to be given over a period of up to two weeks if the conditions of a double-blind trial are to be achieved. As with any form of challenge testing, some caution is necessary when tests are carried out in highly sensitive subjects in whom severe reactions may be provoked.

One of the disappointing features of the challenge approach is that, even in sensitive subjects, the response is inconstant and may only occur in the presence of potentiating factors such as exercise[2]. Methods have been devised, therefore, for seeking barely detectable, 'sub-clinical' changes after a food challenge, as reflected by the increased intestinal release of prostaglandins[3] or an increased liability to develop asthma after an inhalation of histamine[4]. Other sub-clinical changes of this type are still being explored, including a rise in plasma histamine levels in migraine patients[5] or a fall in platelet-associated serotonin levels in patients with arthritis[6].

Distinguishing Different Types of Food Intolerance

The tests which may identify non-allergic causes of food intolerance are numerous. Of the enzyme defects associated with an intolerance to various foods, the most common is lactase deficiency, a cause of cow's milk intolerance. If this is suspected clinically, it can be confirmed in infants by the testing of stools for reducing substances and also, in both children and adults, by

measuring breath hydrogen after taking lactose by mouth[7].

It is also possible that other enzyme deficiencies are important—for example, the deficiency of aldehyde dehydrogenase isoenzyme 1 which is associated with alcohol-induced flushing[8]. In food-induced migraine it has been suggested that phenolsulphotransferase deficiency may play a part[9], but this requires further study. Further tests for non-allergic causes of food intolerance are still being developed.

In some metabolic disorders, the precise basis of the defect remains uncertain. A reactive fall in blood sugar may sometimes be associated with liver disease, but the tests in current use frequently show a hypoglycaemic response in symptomless people and may therefore exaggerate the importance of this phenomenon (see Chapter 4.1). Aspirin-induced skin reactions (urticaria) provide a further diagnostic difficulty since these, too, are often associated with reactions of intolerance to certain foods[10]. In at least some cases this type of urticaria is more likely to be due to a defect of prostaglandin metabolism without demonstrable evidence of true allergy.

In various bowel disorders, biopsy samples of the bowel mucous membrane can provide further diagnostic information. By far the most well-known of the food-related disorders causing histologically detectable mucosal damage is coeliac disease, in which the microscopic appearances of the mucous membrane are usually regarded as diagnostic. More recently, similar changes have been recognised with increasing frequency in childhood, in association with sensitivity to cow's milk[11] and other foods such as soya, fish, chicken and rice[12,13]. Small bowel biopsy also has a role in excluding other gastrointestinal disorders, e.g. giardiasis, sucrase-isomaltase deficiency and persistent changes following gastroenteritis.

Immunological Tests

The immediate type of allergic response to foods is commonly associated with a raised blood level of immunoglobulin E (IgE) and with the presence of IgE antibodies to food proteins, as demonstrated by skin prick tests or by radioallergosorbent tests (RAST) of the blood.

The usefulness of both types of test is dependent on the extracts used. Skin prick tests remain the more controversial, but the results of such tests, using reasonably pure protein mixtures derived from milk, egg, fish, nuts and some other foods, have been claimed to correlate well with clinical evidence of food allergy[14]. Nevertheless, with either skin tests or RAST, 'clinical false positive' responses are not infrequent. In addition, positive skin tests may be obtained in adult life in individuals whose liability to react in a clinical sense has long disappeared.

The RAST and 'immediate' skin tests have a similar degree of accuracy. The main weakness of both methods lies in their failure to identify those reactions which are delayed by some hours and which do not appear to be associated with IgE antibody. The measurement of histamine release from basophil white blood cells provides a more sophisticated way of detecting IgE reactions, but again, it is no help in diagnosing delayed reactions.

A variety of other immunological tests have been studied[15]. For example, there is an occasional association between coeliac disease and immunoglobulin A deficiency. It is well known also that there is an increased frequency of allergic disorders associated with other abnormalities of the immune system, such as those which occur in people deficient in complement enzymes[16] or whose white blood cells do not function normally.

Nevertheless, none of the many tests in this category have so far proved to be helpful in diagnosis[15]. Included in this criticism are a variety of tests for non-immunoglobulin E antibodies; tests for food-containing immune complexes (food protein combined with antibody); tests which relate to blood enzymes of the complement series; and tests which relate to the behaviour of white blood cells or of the chemical products which they release.

Unorthodox Methods

There are a number of other tests which, in spite of numerous claims, have not been shown to be of value.

The Pulse Test

This was first described in 1942 by Coca[17] and is based on the claim that a rise in pulse rate follows the ingestion of specific foods to which a patient is intolerant. While a rapid pulse rate may develop, especially during severe reactions (anaphylaxis) or as a part of the response to foods containing caffeine, it may also accompany emotional upsets and, by itself, has no diagnostic value.

Sublingual Food Tests

Much attention has been paid to the concept of dropping dilute solutions containing specific foods under the tongue, so that a sufficient amount may be absorbed to provoke general symptoms of allergy or intolerance. While there are instances in which local swelling can follow a brief contact between a particular food (usually nuts or fish) and the lips or tongue, this kind of provocative food testing has not been reliable in practice and has failed to discriminate between control materials and food extracts[18–20]. Thus, although sublingual drops have been claimed to be useful both in diagnosis and in treatment, there is little evidence for such claims.

Rinkel's Intradermal Skin Testing

In this type of skin test the material is injected into the skin rather than pricked into the skin through a drop of dilute solution. Such tests have been shown to be useful in testing for IgE antibodies to pollens or dust mite extracts[21] and have also been used in penicillin allergy, despite the danger of provoking reactions in highly sensitive patients. A similar use of intradermal skin tests, involving injections of food, was described by Rinkel[22–24]. The extracts used have been the subject of considerable criticism. Although intradermal skin tests can give results roughly comparable to those of skin prick tests, they depend on using well-characterised materials and

ensuring that those injected intradermally are one thousand times more dilute[25]. Rinkel's approach has attempted to 'titrate' amounts of poorly characterised material and use this both for diagnosis and for subsequent injection treatment. Whether used in diagnosis or in treatment, any evidence of efficacy has been highly doubtful[26].

Cytotoxic Food Tests

It has been claimed that the white blood cells of food-allergic patients die and disintegrate in the presence of the food to which the patient is sensitive[27]. The results of this test have been shown to fluctuate so much from day to day that they are of no diagnostic value[28]. Furthermore, one British laboratory recently failed to obtain reproducible results on duplicate blood samples taken from the same subjects at the same time[29].

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4. THE CLINICAL PROBLEMS

4.1 Food Intolerance in Childhood

The Dilemma of 'Abnormal' Food-Associated Reactions

Good health in infants is usually judged by measurement of growth which in turn is directly related to nutrition. Thus, a systematic surveillance of infant health has evolved which focuses attention on nutritional intake. The system involves parents, relatives, friends, health visitors, books, 'lay-media', clinic nurses and doctors, and results in much conflicting advice on infant feeding. The confusion of parents and others is compounded by the changing attitudes of the medical profession to infant feeding, for example, to early or late weaning and to breast or bottle feeding[1]. This results in an almost obsessive preoccupation with diet in relation to the infant's performance. The natural parental anxiety about

an infant's progress often leads to the inference that a particular symptom is due to the food. When the food is avoided and improvement follows, this may either be due to a placebo effect, to the resolution of an infection or of parental anxiety, or it may truly represent a food intolerance which can, in some cases, be difficult to identify (see Chapter 5.1).

Weaning, the gradual process of replacing breast or bottle feeding by a mixed diet, coincides with rapid changes in an infant's physical responses and behaviour. Thus, perfectly normal changes, such as occur in the character or frequency of an infant's stool, may be wrongly considered to be abnormal and due to food intolerance.

Paediatricians, general practitioners and health visitors rely heavily on parental observation and interpretation of a child's reactions which are, in turn, modified by the parents' own attitudes and prejudices. There are enormous variations in normal child behaviour which could easily be misinterpreted as due to disease. Conversely, variations in behaviour and mood can occur with any disease. Only when there is a demonstration of a reproducible effect on repeated food challenge and withdrawal, preferably under double-blind conditions, can the diagnosis of food intolerance be established firmly[2]. However, this is difficult to achieve in clinical practice and sometimes may actually be counter-productive. A rigorous programme of investigation and meticulous exclusion diets may not reveal any abnormality. The interest and care shown to the family only serves to convince them that there is a pathological and perhaps allergic basis to the child's symptoms but that the cause of this has not yet been identified. Thus, the diagnosis of food allergy and intolerance is often left in doubt, particularly in the minds of the parents.

Definition of the Problem

Food aversion, intolerance and allergy are as difficult to distinguish in childhood as at any other age. Food aversion is often a reflection of anxiety or other emotional disturbance in the parents rather than in the child. Perhaps 'food intolerance by proxy' would be a more accurate title for such conditions (see Chapter 4.3). Even when there are reproducible adverse reactions to foods, there may be considerable confusion about the terms used. Food intolerance is an appropriate term if no immunological mechanism has been identified; if there is an associated atopic disorder, the symptoms provoked by food are likely to be due to genuine food allergy.

Any clinician dealing with children must have a clear knowledge of normal child development and the variations in normality at different ages[3]. Many of the symptoms listed below can occur in the normal child.

Colic

This is a condition of unknown aetiology, usually occurring in the evening (evening colic or three months' colic) and characterised by rhythmical crying attacks. The infant emits piercing screams, with legs drawn up and face red. The attack lasts for two to 20 minutes and usually ends abruptly. Many infants diagnosed as having colic may be merely crying for attention, or because of hunger, anger or insecurity.

Posseting and Vomiting

These are probably not worth distinguishing. Almost all babies bring up some milk which, providing it does not compromise nutrition and weight gain, may be described as posseting. Severe vomiting that results in failure to thrive has innumerable causes of which food intolerance is but one.

Failure to Thrive

An average baby gains 180-200 g per week after the first 10-14 days of life. An average gain of less than 150g per week in the first three months of life will almost certainly require investigation. Sequential weighing, with the use of standard growth charts, is required to establish that there is failure to thrive.

Diarrhoea

Breast-fed babies commonly have loose and frequent stools (up to 10-12 per day) and in the first few weeks of life explosive stools with mucus may also occur. Thus true diarrhoea without coincident loss of weight, malaise or dehydration may be difficult to diagnose in breast-fed babies. In the bottle-fed baby, the diarrhoea will be more obvious and is more likely to be due to infection.

Nappy Rash

Sooner or later most babies will develop perineal soreness and rash, usually due to ammonia dermatitis, monilial infection or seborrhoeic dermatitis. Atopic dermatitis with the classical lesions of eczema affects 5 per cent of children but rarely before six weeks of age.

Rashes

Maculo-papular rashes occur commonly throughout childhood with many viral infections and are often mistakenly attributed to antibiotic allergy. Transient urticaria also occurs with some infections including β-haemolytic streptococci and may lead to inappropriate investigation for food allergy.

Respiratory Symptoms

Up to six upper respiratory tract infections can be expected per year in children between four and seven years. If associated with transient rashes they may be confused with atopic problems.

Epidemiology

The prevalence of food intolerance was considered in the Introduction. Many paediatricians feel that food allergy

and intolerance is under-diagnosed[4,5], which causes unnecessary suffering. However, the incidence of food allergy is greatest in the first few months of life and decreases with age[6]. Many infants who are initially intolerant of certain foods undergo a complete resolution of their problem as they grow older[7,8]. Resolution of hypersensitivity in infancy may occur in more than 40 per cent of cases within two to two-and-a-half years[8]. There is currently no evidence as to whether children with food intolerance who are treated by diet fare any better in the long term than those continuing to ingest the offending foods. The diet will obviously lead to resolution of current symptoms but may not alter the overall natural history of the condition or the development of new atopic problems.

Prevention

There has been much debate about the suggestion that atopy may be prevented and much attention has been focused on the maternal diet during pregnancy and subsequent methods of infant feeding. It is known that sensitisation can occur *in utero,* especially when mothers eat some foods in excess. One study demonstrated cow's milk IgE antibodies not present in the mother's serum in three out of 200 samples of cord blood sera[9]. While moderation of major food allergens during the last two months of pregnancy would seem sensible, there is as yet no justification for recommending complete avoidance diets. A recent controlled study of a small number of children intolerant to cow's milk suggested that nausea and food aversion were more common in their mothers during pregnancy[10]. However, this study was retrospective and the mother's judgement of a pregnancy may have been coloured by subsequent experience of the child's problems.

Thirty years ago, an American study suggested that there was a lower incidence of atopic disease among infants fed on breast or soya milk rather than cow's milk[11]. More recently it has been suggested that atopic individuals sometimes have a temporary defect of immune function early in infancy, when sensitisation may occur[12]. The group that made these observations, and others subsequently, have demonstrated a reduced incidence of allergic disease in breast-fed compared with bottle-fed infants[13-15], but other studies have failed to show this[16-18]. Attention is now focused on the early introduction of diverse solids, which may decrease the incidence of eczema[19] but not of asthma[20].

The allegation that soy milks are less allergenic than cow's milk[11] has not been confirmed[21,22]. There is thus no justification for recommending soy milks instead of cow's milk formulae when breast feeding is not possible. There may even be a contraindication to soy-based formula feeding, in that it results in poor antibody responses to immunisation with poliovirus, diphtheria, pertussis and tetanus vaccines[23]. There is some evidence that the allergenicity of cow's milk may be reduced by heat treatment or hydrolysis, as used in the preparation of infant formulae based on cow's milk[24] (see Chapter 5.3).

Food intolerance and allergy can occur in fully breast-fed infants. The presence of food antigens in breast milk was described many years ago[25]. Several anecdotal and unsubstantiated reports have appeared subsequently, suggesting that these antigens could result in sensitisation and hence, disease[26,27]. Recent in-depth studies have confirmed these observations[28,29] but other factors, such as early inhalant allergen contact and the potentiating effects of intercurrent infection, also facilitate allergen sensitisation[30]. In fact, it would seem that, in allergy prevention, dietary manipulations are less important than the avoidance of heavy allergen exposure by manipulating the month of birth away from the pollen and house dust mite seasons[30,31] and by not possessing household pets[32]. At present the efficacy of any avoidance scheme for the mother remains in doubt.

Disease Spectrum

Food intolerance and allergy in childhood are associated with a wide range of symptoms, including vomiting, diarrhoea, failure to thrive, abdominal pain, eczema, wheezing, urticaria and other rashes, mood alteration, angioedema, flatulence, abdominal distension, steatorrhoea, migraine, epilepsy, enuresis and hyperactivity[5,33]. While classification by system involvement is the usual way to present conditions, this is inappropriate for food intolerance because its manifestations can occur in any combination of systems. The following classification is more appropriate (Table 2).

Table 2. Classification of apparent reactions to food in childhood.

Timing of the reaction to food	Reaction Patterns	Established Relationship
Immediate	Anaphylaxis Angioedema Urticaria	Relationship obvious except when due to azo dyes and preservatives
Immediate and/or late	Vomiting/diarrhoea Failure to thrive Eczema Rhinitis Asthma	Difficult. Often established only by controlled challenge
Not established	Infantile colic Migraine ± epilepsy	Mechanism of association with food intolerance controversial
	Hyperactivity Essential reactive hypoglycaemia	No established association with food intolerance
Non-existent	Food intolerance by proxy	Requires careful assessment by psychiatrist and 'allergist'

Anaphylaxis, Angioedema and Urticaria

These conditions are classically and obviously associated with reactions to food. When the reaction is immediate the offending food can usually be identified by history

alone. Other tests are superfluous, though skin prick testing and IgE antibody tests are usually positive. In such situations intradermal skin tests and food challenge may be dangerous. The foods most commonly involved include eggs, various nuts and fish.

The incidence of urticaria and angioedema is high, more than 20 per cent of the population being affected at some time in their lives[34]. Acute short-duration urticaria is most common in childhood and is usually self-limiting, irrespective of treatment. Chronic symptoms, persisting for more than three months, have identifiable causes in the majority of children but not in adults. Causes include foods, drugs, inhalant allergens, physical agents, hereditary conditions and emotional stress.

Reaction to food additives, such as tartrazine, sunset yellow and benzoates, may not be obvious from the clinical history, as they are regularly imbibed in large quantities by children. When no other cause of chronic urticaria can be identified, it is useful to try a diet which is free of azo dyes and preservatives. In the experience of one paediatric allergy clinic, 50 per cent of such cases improved on a diet, but only 14 of 33 who improved reacted to colouring matter or benzoate in a double-blind challenge. Most of the children who failed to react on challenge were re-established on a normal diet without relapse of symptoms[35].

Gastrointestinal Symptoms

Failure to thrive, diarrhoea, vomiting and gastrointestinal blood loss can sometimes be attributed to food allergy or intolerance. Blood in the stools may be caused by milk-induced colitis, which differs from ulcerative colitis. Of those children who have food allergy or intolerance, only a small number have gastrointestinal symptoms[36]. Many either have, or subsequently develop, other more obvious atopic disorders. Nevertheless, skin tests, total IgE and IgE antibody measurements are of poor diagnostic value in these patients, since both false positive and false negative results can occur[36,37]. Dietary manipulation (see Chapter 6) following the Goldman criteria[2], may be unacceptable to many parents, and, furthermore, the reaction may be misleading because of variations in onset or duration of symptoms. Serial small intestinal biopsies can sometimes provide objective diagnostic evidence. Small intestinal mucosal damage is best documented for cow's milk protein intolerance[37], but can also occur with soy, chicken, rice, fish and egg intolerance[38,39]. This intolerance may occur as a secondary event following acute gastroenteritis[40] and the use of hypoallergenic milk formulae during recovery from gastroenteritis may reduce the incidence of this syndrome[41]. This observation has immense importance world-wide, as demonstrated by studies in Malaysia and Indonesia[42,43].

Coeliac Disease

Coeliac disease is caused by gluten which damages the small intestinal mucosa. Gluten, a mixture of proteins, is a constituent of wheat, oats, rye and barley. Children with coeliac disease most commonly present before the age of two years, with abnormal stools, anorexia, vomiting, abdominal distension, irritability and muscle wasting. However, the condition can present at any age. Symptoms are very varied and may include constipation, acute episodes of diarrhoea, iron deficiency anaemia, rickets and short stature. Coeliac disease is treated with a gluten-free diet, but the diet should not be started until the diagnosis has been confirmed by intestinal biopsy. Intolerance to gluten in coeliac disease is life-long, but transient gluten intolerance is also well described. It is important, therefore, to confirm the diagnosis of coeliac disease by a series of biopsies while on the diet and following gluten challenge. The mechanism by which gluten is toxic to the small intestinal mucosa remains uncertain, but immunological mechanisms are likely. Genetic and environmental factors also play a part.

Eczema

It is becoming increasingly obvious to paediatricians that food intolerance or allergy is an important cause of eczema[44], although the basic mechanisms are still unclear and there are many other factors which may exacerbate the disease. It has recently been suggested that allergens such as house dust mite could cause symptoms by contact sensitivity[45]. Nutritional deficiencies can also be important and supplementation with essential fatty acids may be more appropriate than dietary restrictions[46]. Nevertheless, food intolerance is a common factor and, in the absence of alternative therapy, diet can sometimes be usefully employed[44].

The only controlled cross-over trial of diet in eczema showed a clear advantage in favour of the restricted diet which excluded egg, cow's milk, chicken and beef[47]. Another study utilised elemental diets in children with very severe eczema and demonstrated a dramatic improvement in five out of 10 cases[48]. However, diets are difficult to maintain even with highly motivated patients and parents[49].

Asthma and Rhinitis

The importance of food in causing respiratory disease has not been properly evaluated. Systematic investigation is difficult and consequently a precise diagnosis may be difficult to achieve. At the same time, pharmacological approaches to therapy are relatively simple and efficacious, regardless of allergic status. The only systematic studies carried out have been of aspirin and food colouring sensitivity and these have shown widely discrepant results (see Chapter 5.4).

In devising diagnostic tests it is important to note that challenge tests with foods may not produce a change in lung function but can alter bronchial reactivity as detected by histamine inhalation[50].

Infantile Colic

This common problem affects 16 per cent of infants[51]. It occurs equally in those fed on cow's milk or breast

milk. It is striking how many infants who are subsequently shown to have cow's milk protein intolerance have in the past had persistent screaming and colic[5]. Withdrawal of cow's milk from the diet of breast-feeding mothers was shown to be followed by an improvement in colic in an uncontrolled study[52] but not in a subsequent controlled trial[53]. The association between infantile colic and food intolerance thus remains to be proven but may well be significant in those in whom overt atopic symptoms subsequently develop.

Migraine and Epilepsy

For more than a century it has been accepted that food may provoke migraine but the foods generally implicated have been those containing vasoactive amines (see Chapter 5.1). Claims that allergy may be involved[54] still require confirmation but there is now evidence from the first double-blind placebo controlled trial[55] that children with severe migraine are indeed intolerant of certain foods. The case for believing that many foods in any combination can provoke migraine is a strong one, and although laboratory and skin tests were negative in this trial, some support for an allergic basis comes from the high prevalence of atopy and atopic diseases in the children studied and in their families. However, some of the children who had no evidence of atopy responded to diets in the same way as those who were atopic. Children successfully treated with diet no longer developed migraine when challenged with a variety of recognised non-specific stimuli, and other symptoms such as abdominal pain and eczema also improved. There was also a reduction in fits and hyperkinetic behaviour which occurred in a few of the cases. Evidence obtained in adults suggests (see Chapter 4.2) that there can be several provoking factors for migraine, which are not necessarily the same in all people who have this condition, and there is still doubt as to which of the factors are primary.

Hyperactivity

The terms hyperactivity, hyperkinesis and hyperkinetic syndrome are used very loosely. Many clinical features have been described: over-activity, short attention span, poor concentration, impulsive behaviour and resistance to discipline. Some authorities associate the conditions with defects of neurological function sometimes described as 'minimal brain dysfunction'. The end result is underachievement at school and disruptive behaviour. However, the distinction from any other forms of behaviour disturbance is vague and the evidence linking it to food intolerance is poor.

Estimates of incidence of hyperactivity vary from 3 to 10 per cent in schools in the USA[56] but are much lower in the UK. Feingold[57] suggests an incidence as high as 25 per cent in some schools, which seems hardly credible. It is all too easy to collude with parents, who cannot accept that psychosocial factors are to blame for their child's disruptive behaviour, by accepting that the child is suffering from food intolerance. The use of the Feingold diet[57] (see Chapter 6), which is essentially free from additives and salicylates, has been extensively encouraged by lay organisations representing the parents of so-called hyperactive children. In the experience of a number of paediatricians, mood alteration in relation to food never occurs in isolation, but may be prominently associated with other more obvious reactions such as diarrhoea, migraine, urticaria and eczema[55].

Essential Reactive Hypoglycaemia

Hypoglycaemia is usually defined as a blood glucose concentration of less than 2.2 mmol/litre[58]. This may be associated with a wide variety of symptoms, including hunger, sweating, tachycardia, vague feelings of ill-health, headache, abdominal pain and occasionally bizarre or aggressive behaviour. However, not all individuals will have all the symptoms and most patients with these symptoms do not have hypoglycaemia[59].

Many individuals given a large dose of glucose after fasting will develop rebound (or reactive) hypoglycaemia[58], and the prolonged oral glucose tolerance test has been widely used as a diagnostic investigation for reactive hypoglycaemia. This test is an artificial one, and in only a tiny minority has it been possible to demonstrate that the hypoglycaemia occurs with normal meals and life-styles and that symptoms are related to low blood glucose concentrations and relieved by carbohydrate[60]. Despite this, many writers in the lay press have continued to assert that reactive hypoglycaemia is important, particularly in children, because they eat so-called 'junk' food. It is claimed that the refined carbohydrate in processed foods is responsible for hypoglycaemia and hence symptoms, particularly behavioural ones. However, claims that hypoglycaemia is responsible for much ill-health in adults have not been substantiated by objective evidence [58,60-62], and there have been no systematic studies in children to indicate that hypoglycaemia *per se* is responsible for ill-health.

Non-existent Food Intolerance (Food Intolerance by Proxy)

Inappropriate diets can be dangerous and extensive publicity in the lay media has sometimes resulted in the employment of unnecessary diets with adverse effects[63]. A recent study of 17 healthy children presenting at an allergy clinic[64], showed that the mothers had imposed severe dietary restrictions on the children in the mistaken belief that food allergy was the cause of a variety of vague and unsubstantiated symptoms. The mother's belief had in many cases been reinforced by contact with organisations purporting to be able to diagnose food intolerance by the use of dubious techniques. The characteristics of the maternal involvement have led to the suggestion that through the proxy of their parents, these children manifest a variant of Munchausen's disease, so called after the famous Baron[65].

Management

When the diagnosis of food intolerance is confirmed, children should avoid the offending foods for at least six

months after the last symptomatic contact. It may then be possible to reintroduce small doses of the food under supervision. A spontaneous remission of food intolerance is common, especially in younger children.

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4.2 Food-Induced Reactions in Adults

Foods which cause Reactions

The range of foods which can cause reactions is extensive (Table 3). Evidence of an IgE antibody reaction (i.e. a positive skin or radioallergosorbent test) has been found in approximately three-quarters (73—77 per cent) of patients reacting to egg, nuts and fish. The frequent presence of asthma, eczema, angioedema or urticaria in patients who are intolerant of these foods provides further clinical support for the diagnosis of allergy in such cases[2]. By way of contrast, the foods capable of producing the irritable bowel syndrome have been shown to include wheat (with a normal jejunal biopsy), corn, dairy products, coffee, tea and citrus fruits. Of these, coffee, tea and citrus fruits are not foods which are often associated with clinical evidence of an obvious allergic response.

Table 3. Food allergy and intolerance.

Foods commonly involved		
Cow's milk	Wheat/cereals/flour/yeast	Coffee/tea
Hen's egg	Chocolate	Preservatives
Fish/shellfish	Pork/bacon/tenderised meat	Artificial colours
Other foods reported as causing reactions [1]		
Aniseed	Clove	Pea
Apple	Fennel	Peach
Artichoke	Filbert	Peppers (various)
Banana	Garlic	Potato
Beans (various)	Ginger	Seeds (caraway, dill, poppy, sunflower)
Beet	Herbs (bay, sage, thyme)	Sesame
Berries (various)	Honey	Soya
Celery	Horseradish	Sweet potato
Camomile	Hops	Tapioca
Chestnut	Mango	Vanilla
Chicken	Millet	
Chicory	Mustard	
Cinnamon	Nutmeg	

Milk and dairy products appear to be capable of causing either gastrointestinal or more widespread reactions and may therefore occupy an intermediate position. The same may be true of wheat and yeast products, soya and chocolate[3]. In the study which showed a high incidence of IgE reactions to egg, fish and nuts, only 14 of 46 patients (30 per cent) with milk intolerant or milk allergic symptoms had positive skin or radioallergosorbent tests for IgE antibody[2]. In the remainder, some form of delayed immunological reaction cannot be excluded, but it is also possible that many patients with cow's milk intolerance, including some with the irritable bowel syndrome, have a reaction which is not due to immunological causes of any kind.

A number of non-immunological causes of food intolerance due to enzyme deficiencies or pharmacological problems are discussed in Chapter 5. A relative intolerance to substantial amounts of fatty foods has also been described in otherwise healthy subjects[4]. It is likely that a number of mechanisms which may cause symptoms of food intolerance still remain to be discovered.

Syndromes in Adult Life

Symptoms which occur in the course of food reactions are summarised in Table 4. In adults, food intolerance due to non-immunological causes attracts far more attention than food allergy *per se* but food allergy is by no means rare. Classical allergic symptoms may be present, as in childhood, and the presence of urticaria, asthma, or even anaphylaxis strongly suggests the presence of allergy or some other mechanism which stimulates (or simulates) mast cell activity (see Chapter 5.2). Some less common syndromes also have an immunological component; for example, eosinophilic gastroenteritis is a rare form of bowel disease which is characteristically linked with some form of abnormal immune response to foods[5]. Rectal bleeding in haemorrhagic proctitis has also been proposed

Table 4. Features of food allergy and intolerance.

Gastrointestinal symptoms
Early—
swelling of lips, tingling of mouth or throat, vomiting, pain
Late—
diarrhoea, constipation, bloating, steatorrhoea
Remote symptoms
Rhinorrhoea, urticaria, angioedema, anaphylaxis, asthma, eczema, headache, joint pains

as an allergic response, but there is still insufficient evidence to enable a distinction to be drawn between an allergic form of proctitis and more extensive inflammatory bowel disease[6].

The role of cow's milk in adult food intolerance is poorly understood but it has been claimed that milk can provoke a relapse in patients with kidney disease (causing a steroid-sensitive nephrotic syndrome)[7], and there have been cases in which a low blood platelet count has been reversed on a milk-free diet[8,9].

Other food-provoked symptoms, such as nausea, bloating, abdominal pain, and either constipation or diarrhoea, affect the gastrointestinal tract. These features of the irritable bowel syndrome may be accompanied by allergic symptoms elsewhere but can also occur in isolation, unaccompanied by any evidence of an immunological reaction (see Chapter 2). Two studies, in which double-blind challenges were performed in patients with the irritable bowel syndrome, gave rather discrepant results[10,11]. In one[10], using flavoured purée preparations, food intolerance was reported in as many as two-thirds of cases, sometimes accompanied by objective evidence of an increased release of prostaglandins in the rectum. In the other study[11], which used food in capsules, the only patients (3 of 19) who reacted were patients who had other IgE-mediated reactions. In discussion of these apparently conflicting results it has been emphasised that even psychosomatic reactions may involve the release of chemical mediators and that the finding of raised rectal prostaglandin levels cannot establish the nature of the initiating event[12]. Nevertheless, it may be that relatively small quantities of food in capsules are sufficient to trigger allergic reactions but that larger amounts or repeated challenges are necessary to provoke other types of food intolerance.

It remains to be established whether different quantities of food may provoke symptoms of intolerance due to different mechanisms. For example, the bacterial fermentation of unabsorbed food residues releases hydrogen and carbon dioxide, and the resulting excess of intestinal gas and flatus[13] may be construed as a symptom of food intolerance. Since colonic bacteria can both produce and consume hydrogen[14], it is possible that some adverse reactions to foods may be related to a change in bacterial flora due to infection, the use of antibiotics or some other cause. Such food-induced symptoms may have nothing to do with immunological reactions and may arise solely from bacterial changes.

Urticaria

The itching skin weals (urticaria, nettle-rash, hives) which may follow the ingestion of particular foods are probably caused by more than one mechanism, of which allergy is the most important. In some cases, however, when urticaria is provoked by aspirin or by specific foods (which may or may not contain salicylates) there may be evidence of abnormal prostaglandin release but scant evidence of allergy. In other types of food-induced urticaria, food additives often appear to be responsible and positive provocation tests can be demonstrated in one-third of cases[15] (see Chapter 5.4). The wide range of colouring agents and preservatives in foods (Table 5) may make it almost impossible to identify the individual additives responsible. Furthermore, even the most long-standing urticaria, which subsides on an elimination diet, may fail to recur on re-challenge, in which case the cause remains uncertain.

Table 5. Examples of food additives which have been associated with urticaria.

Antioxidants	
Butylated hydroxyanisole (E320)	
Butylated hydroxytoluene (E321)	
Colourings	
Amaranth (E123)	
Sunset Yellow (E110)	
Tartrazine (E102)	
Preservatives	
Benzoic acid (E210) and its derivatives	
Sodium metabisulphite (E223)	
Sodium nitrite (E250)	
*Flavourings**	
Menthol	
Quinine	
Others	
Papain (used as a meat tenderiser)	
Penicillin, Tetracycline	(As residues from the veterinary treatment of animals)

*No E numbers

The complex nature of urticaria sometimes means that the response to provocation tests is variable. Exercise is a potentiating factor, as shown by a patient with IgE antibodies to shellfish, whose anaphylactic response to a shellfish meal occurred only when the meal was followed by exercise[16]. It should be borne in mind, therefore, that a variable response does not rule out the diagnosis of food-induced urticaria.

Migraine

The relationship of food to migraine has been reviewed elsewhere[17]. Foods which provoke migraine include milk and cheese, fish, chocolate, oranges, alcohol, fatty fried food, vegetables (especially onions), tea and coffee. In many cases it has been suggested that susceptibility to the pharmacological effects of tyramine and other amines

may be a contributory factor but, for the majority of sufferers, the most common precipitating factor is stress. Despite recent evidence in children (see Chapter 4.1), allergy has not been shown to be closely associated with migraine in adults.

It is worth noting that the relationship of food to migraine may also be indirect. Lack of food causes headache and irritability in many people but can precipitate a migraine attack in those who are predisposed[18]. Thus, fasting by Jews and Mohammedans or a low energy intake in those who are slimming can provoke these symptoms. Precipitating factors may also be cumulative: women patients sometimes say they can drink wine but not during the pre-menstrual week, or that their migraine disappears during pregnancy and is exacerbated by the contraceptive pill.

Whatever the precise metabolic cause of an attack of migraine, its development may be followed by a refractory period in which further attacks cannot be elicited. Prodromal symptoms may then occur, however, signalling a susceptibility to further migraine episodes[19]. Cravings for food, in particular sweet or carbohydrate food, may be noted some hours, often the day or evening, before an attack is due[19]. Sleepiness and yawning are another prodrome, as is the symptom of hunger in some people. Some patients become irritable or depressed—others feel elated.

Diet and Joint Disease

The ability of specific foods to provoke joint pain and swelling has been the subject of a number of reports. In some cases there is a well-defined metabolic basis for the symptoms, as in the disturbed uric acid metabolism of gout. In this condition, the effect of alcohol in provoking joint symptoms can be explained by its dual effect of increasing the synthesis of urate[20] and reducing its urinary excretion[21]. The basis for reports that foods containing sodium nitrate or menthol can provoke attacks of palindromic rheumatism[22,23] is less clear.

Despite a number of anecdotal claims that there is an association between food 'allergy' and the more chronic forms of arthritis, there is little evidence for this which could stand up to critical examination[24]. Denman and his colleagues[25] note that joint symptoms can occur as part of a generalised immediate hypersensitivity reaction (for example urticaria) and can be triggered by milk or other readily defined food allergens. Nevertheless, when these investigators gave a basic exclusion diet to 24 rheumatoid arthritis patients for periods of one to six months, there was no evidence that the natural history of the disease was affected, and double-blind food challenges with suspected food allergens caused no significant adverse effects. Neither is there evidence that a lactovegetarian diet can be of benefit in this disease[26].

In a few cases reports that food can exacerbate inflammatory joint disease have been supported by some objective evidence. Parke and Hughes[27] reported the case of a woman with seronegative rheumatoid arthritis who had other features of atopy and had IgE antibodies to milk in her blood. Her symptoms regressed on a milk-free diet and a subsequent milk challenge was followed by an exacerbation of arthritis which could be objectively measured and appeared to be accompanied by an impaired ability to metabolise immune complexes. It is possible that in such patients the food-containing complexes which circulate after a milk feed might be eliminated abnormally slowly and also that these complexes may activate platelets and cause a release of serotonin[28].

The interpretation of these various observations is uncertain. The 'palindromic' rise and fall of joint symptoms in patients with other evidence of food allergic disease is widely known but is seldom a major problem. The more chronic forms of arthritis are another matter. Even if rheumatoid arthritis can be exacerbated by some foods and improved by prolonged fasting[25], this finding may not be specific to the aetiology of the condition. It has been established that absorbed food proteins form circulating immune complexes[29]. An exacerbation of symptoms which follows this type of immune complex 'load' may merely reflect the inability of a patient's reticulo-endothelial system to cope with extra work.

Psychiatric Symptoms

Irritability and depression are among the symptoms which may accompany food intolerance, but it remains to be established whether foods can provoke psychiatric problems alone, unaccompanied by other symptoms which would suggest a tissue reaction elsewhere.

Management

The dietary management of food intolerance has been shown to be effective and is the subject of a later chapter (see Chapter 6). Other approaches to treatment have been unsatisfactory, although aspirin-like drugs can be useful in some subjects to cover dietary lapses and the preventive effects of oral sodium cromoglycate are still being debated. Attempts at desensitisation remain among the unproven remedies for which repeated claims have been made but never substantiated. The fact that spontaneous recovery is not uncommon among food allergic children suggests that some form of suppression of the response is possible. Controlled trial evidence is still needed to prove that any of the available methods of treatment can improve on this spontaneous remission rate.

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4.3 Psychological Aspects and Food Aversion

Attitudes to food vary widely, both in the population at large and in those who have psychological problems. Without an appreciation of these attitudes, a differential diagnosis between food intolerance and psychiatric illness is sometimes difficult, if not impossible. Both normal and abnormal patterns therefore deserve to be considered in more detail.

Food Aversion in General Populations

There is a wide variation in energy and nutrient intake between individuals and between the same individual at different times. This has been shown for children[1], for adults[2] and for adolescents, and it is among the latter that the most marked variation occurs[3].

Adolescence is a time of growth but it is also a time of emotional immaturity and increasing preoccupation with body weight[4]. Many teenage girls think themselves to be fat and this feeling becomes more common with increasing age[5]; remarkably, the feeling has been shown to be seven times more common in teenage girls than boys. Similarly, over-perception of body shape is common among most late teenage girls[6].

'Dieting' is pervasive among young women and it is age-related, being more frequent in older teenagers and, not surprisingly, among those whose weight is above average[5]. In a majority of women 'dieting' is ineffective but a substantial proportion report symptoms such as amenorrhoea connected with their dietary manipulation[5]. Of particular importance is the tendency of such women to have, while 'dieting', a marked and noticeably increased interest in food and food preparation. Carbohydrate abstention and avoidance is often followed by a period of eating in which mainly carbohydrate foods are sought[7]. While this is a feature exhibited by most girls, in some the pattern is more dramatic, and their eating has a 'bingeing' quality (bulimia). This behaviour seems to be associated with the perception these young women have of their bodies and the sociocultural factors which have influenced them. Since the Second World War the desired female shape has become more angular and lean and, as women are responsive to fashion[8], there is pressure on them to conform to a 'slim' image. It follows that society's pressure could lead women, as a whole, to be susceptible to food aversion, faddism and bulimia[9].

Food Fads

Food likes and dislikes are also common. The physician's advice is rarely sought, except when the behaviour is severe. Fads are particularly common in the infant, the adolescent and in those under stress.

Food refusal in infancy is usually part of a more general negativism. The feeding problems of later life can be initiated at this time from the conflict between the parents' need to be sure their child is properly fed and the infant's drive for increasing autonomy[10]. The conflict is

heightened when food becomes an expression of the love that a mother has for her child, and food refusal appears to both recipient and donor as love rejected.

As the infant becomes a child, a particular food can become invested with emotion and be used, with the mother's sanction, to console and comfort. Faddism thus becomes more pathological when love is given less as an intangible and more in the substantial form of food. Normal responses to mood change are not learned, sadness is not appreciated, and discomfort not acted upon except by the passive response of being fed. An unsurprising result is childhood obesity, and the child's shape becomes a reflection of his mother's anxiety, insecurity, or neurotic propensity. The result is to confuse, in the child's mind, the subtle reinforcing experiences concerned with the relationship between hunger and satiety on the one hand and the child's developing autonomy on the other[11].

Adolescence is a time of exploration and enquiry, and food likes and dislikes are part of normal experimentation. However, such normal behaviour can extend to neurotic intensity. The fear of approaching independence from parents, or anger and resentment of dependence on them, especially if heightened by sexual unsureness, may exacerbate previously learned childhood habits. Thus food avoidance, 'dieting', mild bulimia, over-estimation of body shape, and undue preoccupation with body weight are widespread features, particularly in young women.

Food Aversion as an Illness

The difference between a normal attitude to food and an abnormal one is not clear-cut. The degree of food aversion necessary to cause distress will vary widely and depend, in the main, on individual response. In addition, those who develop a phobia which leads them to avoid or reject or over-consume particular foods should be distinguished from those with a psychological intolerance who, by a variety of psychosomatic mechanisms, develop, or occasionally simulate, physical symptoms when particular foods are eaten.

Psychological Food Intolerance

Psychological food intolerance is the clinical manifestation of an adverse physical or psychological reaction caused not by the food itself but by emotions associated with the food or with the eating of that food. Such a reaction may be indistinguishable from those due to food intolerance, but the diagnosis is made by the failure to reproduce an adverse reaction when the patient is unaware that a food has been consumed, i.e. when it is administered by, for example, a nasogastric tube. Thus the avoided food may be a single food, a conceptual series of foods, or unrelated foods which have nothing in common other than subjectively.

The symptoms are vague and fluctuating, and affect different bodily systems, but, as with many psychosomatic illnesses, in any individual patient a particular system will be most responsive. Most commonly, apart from a feeling of being unwell, the patient complains of gastrointestinal symptoms such as abdominal swelling, discomfort or pain, nausea or diarrhoea; or cardiovascular symptoms, palpitations, dizziness or chest pains and migraine or breathlessness. Hyperventilation may be an unrecognised factor (see Chapter 3). Psychological symptoms such as depression, irritability and sleep disturbance are also described but are claimed to be secondary to the worry about 'food allergy'.

In a recent study[12], objective evidence of food hypersensitivity was sought by the use of exclusion diets and provocation tests in 23 patients whose bowel symptoms were suspected of being due to food intolerance. A relationship to food was confirmed in only four patients. A high incidence of psychiatric disorder was found in the remaining 19, which was well within the range of severity seen in new psychiatric out-patient referrals. From the point of view of management, a controlled study of 50 patients with symptoms of the irritable bowel syndrome has shown a significantly greater improvement when psychotherapy was part of the treatment[13].

This and other work suggests that many of the symptoms described by patients claiming 'allergy' can be understood in general psychiatric terms. The marked fluctuations in weight, the bodily swellings, heavy sweating and tachycardia are reminiscent of those described following a bingeing attack in those with 'bulimia nervosa', or the bulimic form of anorexia nervosa, with alternation between episodes of over-eating and more prolonged episodes of food avoidance (see below). The most common psychiatric diagnosis is neurotic depression, although the diagnosis of other types of neurosis and personality disorder may also be made. The patients are usually unduly suggestible and an unsupported diagnosis of allergy has often been suggested first by their medical attendant. On the whole, these patients are hostile to psychiatric diagnosis and can accept an external cause for their symptoms more readily than an internal one. However, a psychiatric diagnosis can usually be made at psychiatric interview.

Neurotic Fads

Neurotic faddism tends to revolve around the active search for a particular food, especially a carbohydrate food. The food is chosen superficially for its availability, sweetness or the sense of fullness it brings. Often the 'choice' reflects the symbolism of the particular food, learned in infancy. The faddism is life-disrupting and persistent and has an obsessional quality to it. The patient recognises that it is a fad and does not try to rationalise this behaviour.

Intolerance of Food by Proxy

Sometimes the intolerance lies not so much with the patient as with his or her family. The family are unable to accept the patient's behaviour or symptoms in terms other than of physical illness. The suggestion, often of medical origin, that the problem could be 'allergic', is seized upon to avoid upsetting an often precarious family equilibrium. The patient gives the impression of being a

passive pawn in a game played by others. When the patient is socially disruptive, the formal diagnosis given is usually psychopathy or 'hyperactivity in childhood', but if the child demonstrates an aversion to food, the diagnosis given may be that of anorexia nervosa.

These cases present certain common features:
(a) there is a positive family history of food allergy or asthma which sensitises the family to the 'danger' of food;
(b) certain members of the nuclear family describe a premorbid interest in food, food preparation or body weight;
(c) at least two members of the family act in concert;
(d) although intelligent, there is a tendency for them to appear very gullible.

In the absence of acceptable help from conventional medical sources, such families often seek out unorthodox methods of treatment and the whole behaviour pattern rapidly becomes entrenched. Such large sums of money can be spent that it becomes increasingly difficult for the family to disengage from their belief that the illness is an allergy, or to recognise that the symptoms stem from family problems.

These families are clearly ill and need to be differentiated from those cases in which the parents of a child with an identifiable disease, such as schizophrenia, have read of the possible role of diet in mental illness and are tempted to give elimination dieting a trial.

'Total Allergy Syndrome'

The 'total allergy syndrome' has received attention in both the medical and the lay press. The term, as currently used, has not been applied to the multiple allergies which occur in highly atopic individuals. Medical responses to the term have been sceptical[14] because, if the title is taken literally, the condition is incompatible with life.

The symptoms of the condition are vague and variable. Weakness, lethargy, convulsions, faintness, fits, asthma-like breathing, migraine, gastrointestinal and urinary symptoms, aches and cutaneous hypersensitivity have been described. Some critics of the allergy theory have suggested that these symptoms closely resemble those of hypocarbia[14] resulting from hyperventilation.

The aetiology, if not allergic, is unclear because few reports have been published and none in great detail. Some descriptions suggest that patients are avoiding food[15], others that psychological intolerance is at the root of the problem[16]. The general impression is that the condition is an example of the abstaining form of anorexia nervosa (see page 105) occurring in an hysterical personality.

The irrational fear of being of normal weight, considered to be a diagnostic feature of anorexia nervosa[17], is usually strenuously denied by both the patient and, usually, her attendants. It is also suggested that it is a personality disorder[16], and in particular a dissociative reaction, whereby the symptoms are unconsciously produced because of an inability to face underlying emotional conflict.

Whether or not the 'total allergy syndrome' exists as a diagnostic entity, a significant number of patients who have been claimed to have the disorder can be diagnosed as having a psychiatric illness. To this may be added the problems of a nutritional disturbance which, in patients treated with an 'elemental diet', can include well-defined biochemical abnormalities[18].

Avoidance of Food and the Eating Disorders

In these disorders, which occur particularly in women, the clinical problem rests not with the food itself but with the avoidance of food, its medical consequences and its psychological aetiology; when the suspected food is knowingly eaten there is no adverse reaction. This differentiates it from physically or psychologically determined food intolerance. Not all patients who present with psychological food avoidance will necessarily complain of an 'allergic' adverse reaction; in fact, perhaps the majority recognise that their symptoms are emotionally determined. However, food avoidance may be consciously or unconsciously masked and then redefined as 'food allergy' (Table 6). The avoidance may be continuous, or interspersed with periods of excess eating, and the patient's body weight may be affected.

Anorexia Nervosa

Perhaps anorexia nervosa is the most malignant form of food aversion to be found. Despite the term, loss of appetite in anorexia is not a feature, and the disorder centres around body weight. While most clinicians would agree with Thoma[19] when he said that the 'most obvious hallmark of anorexia is a physically determined refusal of food', it is the fear of normal adolescent body weight[17] which is the psychological basis of diagnosis of

Table 6. Food intolerance and food aversion.

	Complaint of adverse reaction	Reproducible adverse reaction when Aware of food	Unaware of food	Abnormal immunological reaction
Food avoidance	Maybe	No	No	No
Psychological intolerance	Yes	Yes	No	No
Food intolerance	Yes	Yes	Yes	No
Food allergy	Yes	Yes	Yes	Yes

the condition. Diagnostic criteria have been established for anorexia nervosa[20,21]. Although the condition may not manifest itself until the late teens or twenties, the disorder originates in early adolescence. Adolescent uncertainty and difficulties in accepting the psychological and biological changes associated with adult sexuality are important factors. An endocrine disturbance manifesting as amenorrhoea in women or loss of libido in men is usual.

Anorexia nervosa is divided—on the basis of the persistence of their aversion to food—into two clinical groups. Most commonly, young anorectics maintain their low body weight by avoidance of carbohydrate. A second group of anorectics exhibits bulimia and maintains weight by purgation and psychogenic vomiting.

There are a number of clinical similarities between those patients who present with anorexia nervosa (particularly when it is associated with an hysterical personality) and those anorectic patients who claim 'allergy' with no supporting evidence of food intolerance. Both groups (a) declare a fear of food, which reaches the intensity of a phobia that they can rationalise and may even extend to environmental chemicals; (b) insist on preparing their own food and tend to eat alone; (c) have a deep-rooted interest in food and food preparation; (d) voluntarily place themselves on exclusion diets even at low body weight; (e) desire to isolate themselves away from food; (f) claim lethargy but show intermittent periods of hyperactivity; (g) claim a plethora of bodily symptoms accompanied by clinical features such as low body weight and amenorrhoea, and (h) tend to be suggestible.

The Bulimic Syndrome

Bulimia nervosa[22] or the bulimic syndrome[23] is a recently described disorder characterised by powerful and intractable urges to over-eat, particularly carbohydrate foods. The fatness, ordinarily the result of such binge-eating, is prevented by psychogenic vomiting, purgation, or intermittent periods of starvation, so that the patient (normally a woman) remains within her normal range for weight. The bulimic episodes are awaited with great distress and marked by feelings of loss of control, self-disgust, anger and depression. Diagnostic criteria have been established by Russell[22] and the American Psychiatric Association[24]. Some patients give a history of having had anorexia nervosa[22] but many do not[7,23]. The prevalence of bulimia in general populations is unknown, but symptoms associated with it are common[25-27] and may be increasing. Treatment can be successful[28].

Bulimia is a private affair: it is not uncommon for spouse and general practitioner to know nothing of the patient's behaviour. The bulimia is periodic but runs a prolonged course. Attacks are initially stimulated by emotional stress or by the taste of carbohydrate, but later, when the bingeing becomes daily, it has the features of a compulsion or habit. Dietary intakes vary, but the 'binge-foods' are usually sweet or starchy. Mean intakes of patients who vomit daily are 7,000 k calories per day[29].

Electrolyte disturbances can occur, particularly if the patient combines the vomiting with the use of laxatives or diuretics. Fits, tetany and fever can lead to misdiagnosis. On examination the patient appears pale, sweaty and tremulous, the teeth may be eroded and the salivary glands swollen but painless. The abdomen is distended, often with marked borborygmi. Menstrual irregularities commonly occur, although the patient is of normal body weight.

The majority of such patients tend to be quiet, shy, hard-working women whose predominant clinical symptom is either depression or anger. However, a minority present with psychopathic or hysterical features. In particular, they are rather gullible and suggestible, emotionally shallow or histrionic[7].

A number of features are common to bulimia nervosa and psychological food intolerance: (a) an unusual preoccupation with food and food preparation which preceded the presentation of the disorder; (b) gastrointestinal symptoms; (c) marked fluctuations in weight; (d) episodes of sweating unrelated to exercise; (e) abdominal distension; (f) bouts of tachycardia; (g) a tendency to affect females, and (h) those affected tend to be psychologically hostile but suggestible.

Food Aversion and other Mood States

Food manipulation and weight fluctuation can occur in association with many psychiatric illnesses. Compensatory eating is common in mild neurotic depression, while reduced appetite is more frequent in the less obviously stress-related endogenous depressions. Food avoidance may also occur in other psychotic disorders.

Conclusion

Food aversion is common and comes in many guises. Among those claiming to have allergic disorders there are significant numbers who can be diagnosed as being psychiatrically ill and who may respond to psychiatric treatment. Systematic research into the aetiology, pathogenesis and clinical features is needed.

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5. DEFINING THE PROBLEM AREAS

5.1 Food Intolerance and Inborn Errors of Metabolism

Although inborn errors of metabolism are generally rare, those who are affected by them are often unable to metabolise one or more of the constituents of foods. Symptoms may arise because of the accumulation of toxic intermediates which cannot be processed through the normal metabolic pathways or else because of a deficiency of essential nutrients[1].

The relationship between the symptoms and the food in those who have acute reactions may be readily apparent. The same relationship is not usually obvious in those in whom the reactions are of a more chronic nature and which may develop only gradually over months or years.

Most of the inborn errors discussed below are very rare. However, adult-onset lactase deficiency may be an important contributor to non-specific symptoms of food intolerance in the UK, especially among non-Caucasian people. Glucose-6-phosphate dehydrogenase deficiency and aldehyde dehydrogenase deficiency also have a prevalence in certain ethnic groups that exceeds 1 per cent of the population.

In this chapter, the inborn errors are divided into two categories which may overlap: those in which the disorder is primarily gastrointestinal, causing defects in digestion or absorption, and those with a systemic defect.

Inborn Errors of Digestion and Absorption

Inborn errors of the gastrointestinal system may affect the digestion and absorption of carbohydrate, fat and protein[2].

Carbohydrate

The most frequent symptom of carbohydrate malabsorption is watery acid diarrhoea following ingestion of a specific sugar. In severe congenital disorders such as glucose-galactose malabsorption, the diarrhoea may be profuse and start in the neonatal period, but in others the symptoms vary considerably. There is always improvement when the offending sugar is withdrawn from the diet.

Lactase Deficiency

Two types of lactase deficiency are recognised, the congenital and the acquired forms[3]. Congenital lactase deficiency presents neonatally with profuse watery diarrhoea and collapse when milk feeds containing lactose are given[4]. The condition is inherited and withdrawal of the lactose can be life-saving.

The acquired type presents later, following a decline in lactase activity which occurs during childhood. In some ethnic groups the prevalence of this type of hypolactasia may reach 90 per cent but in Western European Caucasians it is less than 10 per cent[5,6]. Although in various ethnic groups there appears to be a relationship between the prevalence of hypolactasia and the quantity of milk drunk by that population, it is generally accepted that this condition has a genetic basis and is not determined by environmental influences[3,5].

The diagnosis of hypolactasia may be suspected if diarrhoea, abdominal distension, discomfort and flatulence follow the ingestion of milk, but the symptoms themselves may not differ from those of the irritable bowel syndrome (see Chapter 2). Many lactase-deficient

patients take some milk without any difficulty, and symptoms occurring after a single lactose load differ little from those which occur after a placebo[7,8]. Despite this, the diagnosis of lactase deficiency is usually established by giving a lactose load, observing the clinical response, and measuring stool sugars and the breath hydrogen. This may be confirmed by measurement of lactase activity in mucosa obtained by small intestinal biopsy[5]. Finally, symptoms should improve when lactose has been withdrawn from the diet.

Primary Sucrase-Isomaltase Deficiency

Deficiency of the enzyme sucrase-isomaltase causes a wide spectrum of symptoms, ranging from severe diarrhoea to mild symptoms of loose stools with abdominal discomfort, particularly in the older child[3]. The enzyme is responsible for the hydrolysis of sucrose, maltose and some bonds of dextrins. Investigations follow similar lines to those carried out for lactase deficiency but a sucrose load is used, followed by measurement of the enzyme activity[5].

The diagnosis seems surprisingly easy to miss. Symptoms tend to improve with age and are often mistaken for symptoms of the irritable bowel syndrome or are misconstrued as a reflection of maternal anxiety[9].

Trehalase Deficiency

The difficulty in distinguishing enzyme defects from other causes of food intolerance is well illustrated by trehalase deficiency. Trehalose is a non-reducing sugar which occurs in lower plants, including young mushrooms. One family has been described in which severe symptoms developed after eating mushrooms[10]. The family proved to be trehalase-deficient. Since symptoms which occur after eating mushrooms are commonly attributed to toxins; this condition may be more common than is generally recognised.

Protein

In the inherited disorders of protein digestion, where there is a deficiency of digestive enzyme such as enterokinase and trypsinogen, the clinical features are failure to thrive, the production of offensive stools, hypoproteinaemia and anaemia[11]. The major complications are caused by a deficiency of essential amino acids and other nutrients rather than any toxic effect of the protein.

Absorption of Amino Acids

When amino acids are poorly absorbed, the clinical features may be due to the deficiency of essential nutrients, such as the deficiency of lysine and arginine in lysinuric protein intolerance[12], but other symptoms may be caused by the absorption of breakdown products of the unabsorbed amino acids. It has been suggested, though never proved, that some of the neuropsychiatric features of Hartnup disease are due to the absorption of indoles and free amines[13]. One patient with an isolated defect of the absorption of methionine who had diarrhoea, fits and mental retardation, improved on a low methionine diet[14].

Fat

The malabsorption of fat causes steatorrhoea and failure to thrive and the symptoms are often exacerbated by a high fat intake. This may be due to isolated deficiency of the enzymes lipase and colipase[15], and to pancreatic disease. Cystic fibrosis in particular and Shwachman's syndrome may present solely with gastrointestinal symptoms[16].

In abetalipoproteinaemia there is usually steatorrhoea and failure to thrive[16]. The retinal and neurological complications which develop later are thought to be secondary to malabsorption of fat-soluble vitamins, particularly vitamin E[17].

Systemic Disorders

Disorders of Amino Acid and Intermediary Metabolism

In this section, the disorders of amino acid and intermediary metabolism are divided into those which lead to toxic levels of ammonia in the blood (hyperammonaemia), those which cause an accumulation of organic acids, and those in which there is a defect in the catabolism of one or more amino acids but no acute symptoms.

Hyperammonaemia

Ammonia is a major product of the catabolism of amino acids. Normally it is converted rapidly into urea and rendered harmless. Any disorder (Table 7) affecting the synthesis of urea may therefore cause the accumulation of ammonia, which is highly toxic, particularly to the central nervous system[12].

Table 7. Inborn errors (rare) causing hyperammonaemia.

N-acetyl glutamate synthetase deficiency
Carbamoyl phosphate synthetase deficiency
Ornithine carbamoyl transferase deficiency
Arginosuccinate synthetase deficiency (Citrullinaemia)
Arginosuccinate lyase deficiency (Arginosuccinic aciduria)
Argininaemia
Hyperornithinaemia, hyperammonaemia, homocitrullinaemia syndrome
Lysinuric protein intolerance
Hyperlysinaemia with hyperammonaemia
(Organic acidaemias)

The most severely affected patients present in the neonatal period with a disturbance of brain function (toxic encephalopathy) which is often fatal. Those who are less severely affected may present in the first year of life with failure to thrive, loss of appetite, vomiting and delayed development. Symptoms are commonly made worse by protein and, as a result, mothers may unconsciously select a low-protein diet. Patients may also have episodes of nausea and vomiting, anorexia, lethargy, slurring of speech and ataxia. These attacks which, when severe, may cause loss of consciousness and other neurological abnormalities, are commonly misdiagnosed as

encephalitis, poisoning or as behaviour disorders. Attacks may be precipitated by dietary protein, although the patients commonly have an aversion to high protein foods, and attacks may also be precipitated by infections which cause the resultant breakdown of body protein and hence the accumulation of ammonia.

Disorders of Organic Acid Metabolism

In the organic acidaemias there is an accumulation of acidic metabolites which are mostly derived from the breakdown of essential amino acids[17]. Many disorders have now been described (Table 8) which may present in the neonatal period or later in infancy and which have very varied clinical features. The most severe disorders may be precipitated by milk feeds in the neonatal period. There is an overwhelming illness, usually with a severe metabolic acidosis and toxic encephalopathy. Children with less severe disease may present later in infancy with failure to thrive, vomiting, anorexia, delayed development and neurological symptoms. The symptoms may clearly be exacerbated by protein and may develop with the introduction of cow's milk and mixed feeding, but the relationship between the protein intake and the symptoms is often not clear-cut. Infections, particularly those causing vomiting, may cause endogenous protein breakdown and hence an accumulation of organic acids with an exacerbation of symptoms.

Table 8. Some of the less rare organic acidaemias.

Maple syrup urine disease (branch chain ketoaciduria)
Propionic acidaemia
Methylmalonic acidaemia
Isovaleric acidaemia
β-Ketothiolase deficiency
Glutaric aciduria type 1

Other Amino Acid Disorders

Several disorders of amino acid catabolism cause a chronic illness without acute symptoms[1]. The association between the protein intake and the disorder is not readily apparent. These conditions are listed in Table 9.

Disorders of Carbohydrate Metabolism

Fructosaemia

Patients with this condition cannot break down fructose and as a result they develop nausea, vomiting, abdominal pain, sweating and even convulsions when fructose is given[18]. Children most commonly present with loss of appetite, failure to thrive, and liver disease, the symptoms starting with the introduction of mixed feeding. The cause of the child's illness may not be immediately obvious and a careful dietary history is always necessary. Older patients develop a marked aversion to all foods containing sucrose (which contains fructose) or fructose itself, sometimes developing curious feeding habits or anomalous behaviour. On a fructose-free diet the patients do extremely well.

Table 9. Other amino acid disorders causing chronic illness.

Disorder	Symptoms if Untreated	Response to Diet
Phenylketonuria	Mental retardation, fits	+
Cystathionine synthetase deficiency (classical homocystinuria)	Mental retardation Eye, skeletal and vascular complications	+
Tyrosine aminotransferase deficiency	Eye and skin complications	+
Alkaptonuria	Joint disease	–

Notes

1. Prolinaemia types I and II are now regarded as benign conditions.
2. Histidinaemia is no longer thought to cause mental retardation but may be causally related to speech problems.

Galactosaemia

Most babies receive galactose (as lactose in milk feeds) soon after birth, so patients with galactosaemia usually present in the neonatal period. Symptoms may be very acute, with vomiting and collapse, or acute liver dysfunction may develop. Less frequently, the vomiting is not so severe but there is a failure to thrive, poor developmental progress, and the appearance of cataracts[19]. Patients do not develop an aversion to galactose, so that the toxicity of galactose is not readily discernible. On a galactose-free diet there is a rapid recovery from the acute symptoms, although the long-term results are disappointing[20].

Disorders of Fat Metabolism

Lipoprotein Lipase Deficiency and Apo C II Deficiency

The chylomicra, which are the product of absorption of ingested fat, are broken down by the action of lipoprotein lipase, an enzyme which requires the presence of an apoprotein (Apo C II) before it achieves full activity. Any deficiency of this enzyme or of the apoprotein allows a massive accumulation of fat to occur, mostly as chylomicra, which gives the plasma a milky appearance[21]. The retina has a characteristic milky appearance and skin xanthomata may develop. Infants may fail to thrive and have an enlarged liver and spleen, and in all patients abdominal pain is common, particularly after fatty meals. In adult life approximately one-third will have episodes of pancreatitis, but this is uncommon during childhood. On a very strict low-fat diet the patient's symptoms improve.

Disorders of Alcohol Metabolism

When alcohol is metabolised in the body, acetaldehyde is an intermediate product. A deficiency of aldehyde dehydrogenase isoenzyme I, the enzyme that oxidises acetaldehyde, is common in oriental races; approximately 40 per cent of the Japanese have this disorder[22]. The absence of this enzyme has been blamed for the facial flushing and unpleasant symptoms that orientals commonly develop after alcohol and which are similar to those experienced by alcoholic patients given disulfiram (Antabuse) to reinforce their resolve to avoid alcohol.

Miscellaneous Disorders of Metabolism

Pyruvate Dehydrogenase Deficiency
Patients with the milder variants of pyruvate dehydrogenase deficiency (an enzyme of carbohydrate metabolism) can be very sensitive to carbohydrate-containing foods[23]. These can provoke metabolic acidosis and neurological symptoms.

Fructose 1-6, diphosphatase Deficiency
Patients with fructose 1-6,diphosphatase deficiency cannot synthesise glucose in the liver, i.e. they have a defect of gluconeogenesis[18]. In some patients consumption of fructose may provoke acute illness, with a decrease in blood sugar and acidosis. Fasting or infection may also provoke severe symptoms.

Familial Periodic Paralysis
Carbohydrate loading is one factor which may provoke a flaccid paralysis in the type of familial periodic paralysis which is associated with low blood potassium levels[24]. Other precipitating factors include certain drugs and exertion.

Glucose-6-phosphate Dehydrogenase Deficiency
Broad beans can provoke the sudden breakdown of red blood cells (acute haemolysis) in patients with the severe Mediterranean form of the enzyme deficiency—glucose-6-phosphate dehydrogenase deficiency[25].

Trimethylaminuria
Trimethylamine, formed in the gut from the bacterial breakdown of choline, is normally oxidised and excreted in the urine. In the absence of this oxidase, trimethylamine accumulates in the body fluids[26]. This malodorous and volatile compound is excreted in the breath and sweat, causing the patient to have a most unpleasant body odour (that of decomposing fish). The symptoms are exacerbated by eating fish, or foods with a high choline content such as eggs.

Diagnosis and Management

Despite the extreme rarity of most of the conditions mentioned in this section, it is important that medical advisers are aware of these disorders, since many have a high mortality and morbidity. The diagnosis may often be suspected from the history and examination. Appropriate investigations can almost always lead to a precise diagnosis and often to effective dietary treatment.

There is another reason why enzyme deficiencies require careful documentation. If there is both a mild and a severe form of enzyme deficiency—as in alactasia—the severe form offers a recognisable pattern of symptoms which makes it possible to suspect and then identify milder variants. It is also entirely possible that mild deficiencies of enzymes such as aldehyde dehydrogenase can cause clinical problems due to reduced ability to metabolise certain foods—just as a deficiency of acetylating enzymes can cause problems due to the slow metabolism of drugs. Without further evidence, however, this remains a speculation.

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5.2 Pharmacological Reactions associated with Foods

Many foods are capable of producing pharmacological effects which can be clinically important either if the food is taken in large quantities or the patient tolerates it badly because of an enzyme defect or other biochemical variant. The substance having a pharmacological action may be a component of the food itself or a constituent added in processing (see Chapter 5.3). Small residues of agricultural chemicals or bacterial or fungal contaminants, known to be toxic to everyone in large quantities, may be responsible for clinical symptoms in some sensitive subjects. There is, therefore, some overlap between pharmacological and toxic reactions, but this chapter is restricted to pharmacological actions. Both toxic and pharmacological reactions may be immediate, or may be cumulative with a long incubation period, as in the dietary induction of hypertension. It is, however, considered that food intolerance is restricted to short-term reactions.

Caffeine

Caffeine, a methyl xanthine, is a potent pharmacological agent. It is formed in many species of plant, including coffee beans, tea leaves and kola nuts. It is the most popular and widely used stimulant drug in the world. Depending on the length of infusion, a cup of tea contains between 50 and 80 mg caffeine and a cup of coffee between 40 and 150 mg caffeine; lesser amounts are present in cola drinks. The pharmacologically active dose is 200 mg, and hence clinical effects could be produced either by taking large quantities of coffee and tea or, in the more susceptible subjects, by taking only moderate quantities of these drinks.

Caffeine is addictive and has widespread pharmacological actions which include stimulation of the central nervous system and the heart. It also increases the output of gastric acid and urine and, since it dilates the lung airways, it is a bronchodilator.

Clinical Effects

Coffee and tea have been implicated in several clinical syndromes. Caffeine toxicity can produce a clinical picture similar to a chronic anxiety state associated with tremor, sweating, palpitations and rapid breathing[1]. Susceptibility varies, but it can induce a sense of 'palpitations' due to extra heartbeats (extrasystoles) or bouts of rapid heart beating (paroxysmal tachycardia)[2]. As a stimulant it can also cause insomnia.

Caffeine is a vasoactive amine which can cause headache and is a potent inducer of migraine. Stopping caffeine often reduces attacks of migraine, but the effects are complex and sudden withdrawal may lead to a reaction manifested by severe headache, irritability and lassitude[1]. This accounts for some cases of weekend migraine in subjects used to taking large quantities of coffee in the week at work but much reduced amounts at the weekend.

Caffeine stimulates gastric secretion, but decaffeinated coffee is even more active in this respect, indicating that other uncharacterised chemicals in coffee also act on the gut. Large doses of both coffee and tea can produce nausea and vomiting in susceptible subjects. The overall effects on the gut are still not sufficiently clear to allow firm advice to be offered to patients with symptoms of oesophageal reflux, nausea, vomiting or diarrhoea, except to advise avoidance, particularly in subjects who take large quantities, if coffee or tea appears to precipitate them[3].

Coffee first reached Europe via Venice in 1615 and Thomas Willis first described 'restless legs' (Ekbom's syndrome) in 1685. The principal symptom is an unpleasant creeping sensation in the lower legs between the knee and ankle, although the sensation can occur elsewhere. The discomfort only appears at rest, usually in the evening or at night, and is associated with an irresistable need to move the limbs to obtain relief. Hence the term restless or jittery legs. A clinical study by Lutz[4] has shown that excessive caffeine is an aetiological factor. The symptoms often disappear after caffeine withdrawal.

When the clinical picture is suggestive of caffeine intolerance, an estimate of caffeine intake should be obtained and a trial period without caffeine should be considered. Because of the real risk of a withdrawal reaction, the caffeine intake should not, however, be stopped abruptly. Improvement of symptoms following withdrawal of coffee or tea does not prove that caffeine is itself responsible, as at least 300 other organic substances have been identified in coffee.

Vasoactive Amines

Vasoactive amines are present in many foods, including wine, cheese, yeast extracts, bananas and avocados. These chemicals include histamine, tryptamine, tyramine and serotonin, which are discussed in more detail in Chapter 5.3. High concentrations of tyramine (1-2 mg/g) are present in some cheeses and pickled fish. Phenylethylamine is found in chocolate. Citrus fruits contain octopamine and synephrine.

Vasoactive amines act directly on blood vessels and indirectly by the liberation of adrenaline and noradrenaline from nerve endings. These substances can cause facial flushing and urticaria and can precipitate headache, particularly in susceptible subjects. In a controlled study in patients with migraine, 125 mg of tyramine produced headache in 80 of 100 subjects, whereas lactose tablets produced headache in only 6 of 66 controls[5].

Conditions which mimic Food Allergy

Histamine effects can be provoked by non-immunological mechanisms and this has led to the concept that end-organ effects which mimic allergy (pseudo-allergy or 'false food allergy') may be much more common than true allergic reactions[6]. These effects could follow the consumption of foods which are rich in amines or which stimulate histamine release in susceptible individuals. They could also arise from the metabolic action of fermenting flora in the colon, which synthesise histamine (see Chapter 5.3). However, histamine cannot readily penetrate the mucosal barrier, and abnormal gut permeability may act as a contributory factor.

The histamine-induced symptoms produced by these various mechanisms mimic true allergic phenomena involving histamine and other mediators which are released as a consequence of antigen-antibody reactions. Symptoms include flushing, headache, local swellings (oedema), itching, and skin rashes such as urticaria. Abdominal symptoms include pain, flatulence, constipation and diarrhoea. In contrast to true food allergy, which is usually precipitated by even minute quantities of the allergic food, 'false food allergy' occurs only after ingestion of large quantities of the offending substance and, unlike true food allergy, there is no evidence of an immunological reaction, hence skin prick tests, intradermal tests, and RAST studies are all negative.

Miscellaneous Reactions to Food

Monosodium Glutamate

The Chinese Restaurant Syndrome (Kwok's Syndrome) can mimic a myocardial infarction, with tightness or pain in the chest radiating to both arms and back and associated with general weakness and palpitations. It follows the eating of Chinese food rich in monosodium glutamate. The mechanism is unknown but oesophageal irritation has been suggested because orange juice, coffee and spiced tomato juice can provoke oesophageal pain in subjects with oesophagitis[7]. A relative deficiency of vitamin B6 might be an alternative mechanism[8].

There have also been reports of asthma following the ingestion of food containing monosodium glutamate. The relationship of this symptom to glutamate has been established by challenge tests[9].

Salt

A further syndrome associated with Chinese food comprises headache, thirst and a feeling of bloating about one to four hours after eating the food[10]. An average Chinese take-away meal can contain 225 mmol of sodium, including monosodium glutamate, and the plasma sodium can increase by 5 mmol/litre.

Lectins

The seeds of many edible legumes contain variable amounts of proteins, known as lectins, some of which possess the ability to agglutinate red blood cells and hence may be termed 'haemagglutinins'. It has been suggested that, because of these lectins, many raw beans have a poor nutritive quality and certain beans, notably the kidney bean, contain lectins which are toxic when eaten in the raw state. Lectins are heat-labile and hence thorough cooking (boiling) of the bean will eliminate the toxic properties[11].

Diet, Behaviour and Mental Disease

There have been suggestions that diet can affect mental disease. Claims[12] that schizophrenia is influenced by wheat and rye have not been confirmed[13], although there is a high incidence of schizophrenia in patients with coeliac disease[14] and peptides derived from gluten can be detected in brain tissue[15]. There are also claims that hyperactivity in children can be improved by dietary manipulation, including avoidance of additives[16], but this has been the subject of considerable controversy (see Chapters 4.1 and 6).

The possible role of neurotransmitters in such mental disorders has also been examined. Most drugs which modify normal or abnormal behaviour act by altering the amounts of particular neurotransmitters present within the brain. Certain food constituents are known to cause similar changes in the release or actions of neurotransmitters, and they might therefore be expected to influence behaviour[17]. In particular, high-carbohydrate, low-protein meals which elevate brain tryptophan, or the administration of tryptophan itself, accelerate the synthesis of the neurotransmitter serotonin[18], which is associated with an increase in fatigue and reduced activity. However, while this might suggest that fluctuations in dietary composition could be expected to cause minor changes in mood, the available evidence does not suggest that diet is a major aetiological factor in psychiatric disorders. Widely publicised claims to the contrary[19,20] require substantiation. Nevertheless, the patient's attitude to food may play a central role in some psychiatric disorders, as discussed in Chapter 4.3.

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5.3 Food Intolerance Arising from the Storage and Processing of Food

Storage

Many changes occur in foods between harvesting and consumption. Some of these post-harvest changes are deliberate (see below and Chapter 5.4), and others are adventitious.

During the handling of food, storage fungi, mites and their faeces are the main causes of intolerance. Occupational allergies arising from food packaging also occur, some associated with the food itself and some as a result of pyrolysis of packaging materials. The allergies associated with pyrolysis are not considered here. Storage changes fall into two categories, those inherent in the food, i.e. arising from reactions within the food, and those arising from contamination. Many of the substances known to cause food intolerance are stable even when subjected to extreme physical and chemical conditions (see below) and would be unaffected by storage.

An association between food storage and intolerance was noted over a century ago when Salter advised asthmatics to avoid eating cheese, especially if it was old and decayed[1]. However, relatively few cases of food intolerance which can be directly attributed to changes in food during storage have been reported in the literature.

Adverse Response in Food Handlers during Storage and Packaging

Storage Mites and Insects

In the UK, mites, usually species of *Acarus, Tyrophagus* and *Glycyphagus,* infest a wide range of stored commodities, including cereals and cereal products, dried milk powder, cheese, sugar and dried fruit. Some people, when exposed to mites or fragments of their bodies, develop allergic asthma or dermatitis[2]. Grain dust contains many mites and insects which may cause allergic symptoms in grain workers. Weevil dust may be heavily contaminated with the fungus *Penicillium* or bacteria, and it is thought that these contaminants are the cause of respiratory symptoms[3]. Allergy to storage mites is now considered to be more important and widespread than was previously thought[4].

Micro-organisms

Micro-organisms develop on grain during storage, and storage fungi such as *Aspergillus* spp. largely replace harvest fungi. *Erwinia herbicola* and other Gram-negative bacteria also develop. The chief determinants of these storage microflora are the water activity (the amount of available moisture) and temperature of the stored grain[5]. Most of the spores of these microbes are known to be allergenic and the respiratory symptoms in grain workers have been attributed to these[3]. Cheese Washer's Lung has been attributed to the fungus *Penicillium casei,* which grows on the surface of stored cheese[6-8].

Packaging Dusts

Workers exposed to dried mushroom soup dust in the packaging area of a factory have been shown to produce symptoms of rhinorrhoea, dyspnoea and wheezing[9]. Similarly, asthma can be induced by exposure to dust from soya beans and the food additive papain during packaging[1,10].

Adverse Responses after Ingestion of Food

Changes arising from Chemical Reactions within the Food

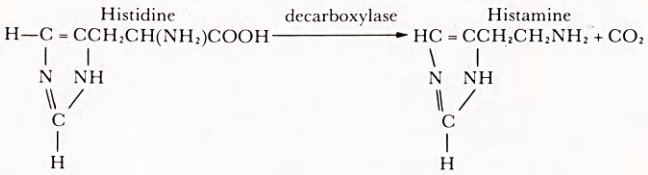
Inherent chemical changes occurring in food during storage have been reported to cause responses of intolerance in some individuals. In other cases, the substances which are involved have a more general toxic effect upon the population as a whole. The distinction between toxicity and intolerance cannot always be clearly drawn.

Bleumink reported intolerance in some people which was produced by ripe or stored tomatoes but not by green ones. Later investigation identified the active component of ripe tomatoes as a glycoprotein produced in the tomato skin by non-enzymatic browning (Maillard) reactions during ripening and storage[11]. This component was resistant to heat and to trypsin and chymotrypsin, so there was a high probability of its reaching the circulation after digestion[12] (see below). Martin briefly noted that

decomposed foods, for example rancid fats, may be a cause of urticaria[13].

Microbial Changes within the Food

Histamine Production. A rise in histamine levels occurs in a number of foods during storage. This results from the conversion of histidine to histamine in the food. Bacterial decarboxylases are commonly implicated in this biochemical change:



Histamine is a normal constituent of fermented foods such as cheese and sauerkraut, although the amounts of histamine present are usually small[14]. When certain microbial species, such as *Proteus morganii,* are allowed to proliferate, the histamine concentration may increase greatly. Large amounts of histamine usually occur only in old, fermented products or those which have undergone spoilage[14,15].

Scombroid fish poisoning (or scombrotoxin illness) is a condition which arises from the consumption of badly stored scombroid fish, such as mackerel, containing high levels of histamine[16]. The symptoms, which cannot be distinguished clinically from an allergic reaction, may be provoked by canned, uncanned and smoked fish. Gilbert and his colleagues reported that the symptoms of scombroid fish poisoning were essentially those of histamine toxicity, and included urticaria, nausea, vomiting, facial flushing, intense headache, epigastric pain, a burning sensation in the throat, dysphagia, thirst and lip swelling. In a study of 196 British cases, the incubation periods for a reaction varied from 10 minutes to two hours, the mean being 1.3 hours. However, many cases recovered within three to six hours and most had no symptoms by the next day[17].

Scombroid fish are normally stored at 0°C and remain edible for about 12 days, having a low histamine level of 3-4 mg/100g. At room temperature, histamine concentrations of the order of 100mg/100g are rapidly reached and the scombroid fish become toxic, even though they may still appear acceptable to the consumer. Non-scombroid fish sometimes contain high concentrations of histamine but do not cause this type of poisoning. Arnold and Brown have suggested, therefore, that histamine cannot be the only substance involved in the reaction[18].

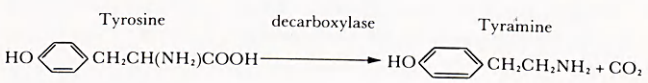
Scombroid fish poisoning can be totally prevented by proper attention to hygiene at all stages of production, distribution and storage. The most important measure of prevention is to keep the fish properly refrigerated[16].

Histamine in other foods may cause problems. A survey of 390 sausage samples of nine different types in the USA revealed higher and more variable levels of histamine in dry fermented sausages such as pepperoni and Italian dry salami than in either cooked or semi-dry sausages. Dry fermented sausages are allowed to ferment naturally for longer periods than semi-dry sausages[15]. Significant brand-specific differences of histamine levels in the dry fermented sausages suggested that proper control of natural fermentations could largely prevent histamine accumulation. It also suggested that different environmental conditions during sausage processing can have a dramatic effect on the histamine content of the product. Storage conditions at the retail level may also allow microbial growth, with resultant histamine formation[15].

Goldstein and Heiner[1] noted that, in 1859, asthmatics were advised to avoid cheese, especially if it was old and decayed. Liberation of amino acids, which occurs in the ripening of cheeses, is one of the factors governing the formation of histamine, in amounts which can reach 260 mg/100g of cheese[14]. There are anecdotal reports that cheeses containing high concentrations of histamine can provoke symptoms of histamine intoxication[19].

It is often difficult to distinguish between reactions to histamine or other toxic components of food and reactions which result from allergy—or some other type of food intolerance. Substances which derive from the dinoflagellate diet of some shellfish can cause toxic effects that are often wrongly interpreted as being 'allergic', and individuals vary in their susceptibility both to toxic effects of this kind and to the effects of histamine. The adverse effects of histamine may be increased, for example, in people who are taking drugs such as isoniazid which interfere with enzyme activity, and impede the destruction of histamine by amine oxidases[17].

Tyramine Intoxication. Tyramine is produced from the amino acid tyrosine by a decarboxylation similar to that of the histidine/histamine conversion:



High concentrations of tyramine have been found in fermented cheeses, such as Blue Stilton and Roquefort. In contrast to the action of histamine, tyramine elevates blood pressure. It acts pharmacologically by releasing noradrenaline from tissue stores which in turn causes the blood pressure to rise[14]. Tyramine is normally rapidly destroyed in the body by monoamine oxidases, but some drugs used in the treatment of depression inhibit monoamine oxidases. If patients taking these drugs consume a large amount of cheese, the tyramine present is not destroyed and may produce alarming reactions. The symptoms of headache, severe nausea and dizziness may occur, with an acute rise in blood pressure followed occasionally by cerebral haemorrhage or cardiac failure[14,20].

Other foods have been implicated in the high blood pressure crisis caused by tyramine, for example chocolate, yeast extract, liver, sausages, broad beans and pickled herrings. Low levels of tyramine are found in

some fruit and vegetables, but it is unlikely that they could precipitate episodes of hypertension unless very large quantities were consumed[14].

Storage Changes arising from Contamination

Chemical. There is little information in the literature on the prevalence of reactions of food intolerance caused by contaminants of food. A number of anecdotal reports can be found of individuals developing allergic-type reactions when exposed to canned food. These suggest that some people may be intolerant to contaminants, such as resins from can linings, or trace metals from the can itself[21,22]. It is also recognised that some substances known to cause intolerance do migrate from plastic packaging, for example formaldehyde, benzoates and sodium bisulphate[23-25]. There is, however, no evidence to suggest that the ingestion of foods containing trace amounts of these migrated substances is responsible for food intolerance.

Additives are widely used in the food industry to prevent inherent microbial and chemical changes, for example, nitrite to inhibit *Clostridium* and antioxidants to prevent rancidity. However, there seems to be a lack of evidence about the interaction between additives and the food itself, reactions which might occur during storage and give rise to substances capable of causing food intolerance.

Microbial. Microbial contamination of food is likely to result in chemical changes in the food itself, as described earlier. Mycotoxins arise from the storage of mould-contaminated foods, but they are generally considered to constitute a toxicological problem rather than one of food intolerance in humans.

Processing

Food is processed domestically and industrially by essentially similar methods differing only in scale. Heat treatment affects protein structure and hence might be expected to influence the capacity of proteins to provoke intolerance. Many of the food 'allergens' studied have been shown to be glycoproteins which are relatively stable both to heat and proteolytic enzymes. Skin reactive components in egg, cod, salmon, haddock and tomatoes appear to be thermostable[12], as are those in peas, beans and peanuts[26]. Bleumink suggested that the active agents which arise from heating fish, and those formed during maturation of peas, beans and peanuts, may also be generated by non-enzymatic browning (Maillard) reactions, which might presumably also occur during processing[12].

Conversely, heat treatment of some foods does reduce their ability to cause adverse responses. Heat appears to inactivate certain components in potatoes which would otherwise cause skin reactions[27], as does solvent dehydration of bananas[28]. Boiled milk or 'long-life' milk can occasionally be shown to be tolerated when raw milk cannot. It is certainly recognised that individuals who experience an acute allergic reaction to boiled egg may tolerate well-cooked eggs in cakes. One report in the literature suggested that orange marmalade could be eaten with impunity by a subject who collapsed after eating raw orange[29]. Chlorogenic acid, an 'allergenic' determinant in oranges and coffee, is destroyed by heat[30]. The results of experimental work with guinea-pigs at the National Institute for Research in Dairying indicated that it may be feasible to produce a non-sensitising formula based on heat-denatured whey proteins[31].

Lactase deficiency in individuals, which results in an intolerance to lactose, is widespread, being especially marked in populations in Africa, South-East Asia, India, the Middle East and Latin-America (see Chapter 4.1). Commercial lactases from yeast can be used for enzymic hydrolysis of milk or milk products. The addition of lactase to sterilised milk immediately before packing and the use of immobilised enzyme technology to hydrolyse lactose in whole whey[32,33] represent further developments in processing which have been designed to reduce intolerance to milk.

A variety of reactions to many different foods have been reported but many of these are individual occurrences and are not well documented.

Mites and fungi are the main contaminants causing reactions associated with occupational exposure to stored food prior to its ingestion, and asthma is the main response. Reactions at the packaging stage are generally the result of exposure to mite and fungal dusts, or to food dust itself; again, the symptoms are largely respiratory rather than topical, food rarely being touched by hand in the food industry.

Storage changes resulting from microbial action within foods appear more common than changes resulting from chemical reactions *per se.* There is the added problem of microbial contamination, for example in fermented sausage. Attention to hygiene, controlled storage, and the addition of additives, may help to inhibit inherent microbial changes.

Similarly, while evidence linking food intolerance to processing is scarce, it would seem that processing of food may either increase or reduce the prevalence of intolerance. Overall though, the capacity of foods to cause food intolerance would appear to be reduced by methods of processing.

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5.4 Adverse Reactions to Food Additives

A food additive is any substance not commonly regarded or used as food, which is added to, or used in or on, food at any stage to affect its keeping quality, texture, consistency, taste, odour, alkalinity or acidity, or to serve any other technological function in relation to food, and includes processing aids in so far as they are added to, or used in or on food[1].

A steadily increasing number of reports associate intolerance to food additives with clinical disorders usually considered to be allergic in origin, for example urticaria, angioedema and asthma. Substances reported to provoke such reactions include colouring substances, such as tartrazine[2,3]; preservatives such as benzoates[4] or sulphur dioxide[5]; and antioxidants such as butylated hydroxyanisole or butylated hydroxytoluene[6,7].

The most commonly reported manifestations of food intolerance associated with food additives are in the skin (usually urticaria or angioedema) and in the respiratory tract (particularly asthma and rhinitis). Migraine and the irritable bowel syndrome have also been reported. While there are reports of other adverse reactions such as hyperactivity, psychological disturbance, urinary incontinence and arthralgia[8-10], there is no good evidence to implicate intolerance to food additives in hyperactivity[11-13]. Since some additives are chemically similar to substances known to affect the nervous system, it remains possible that they might have some behavioural effects.

General Incidence

It is extremely difficult to ascertain the incidence of clinical responses truly attributable to food additives, or even to tartrazine alone, because much depends upon the clinical history. The diversity of clinical manifestations means that there is no particular diagnostic sign. Elimination diets and 'blind' challenges require much time by clinician and patient, and the interpretation of results may not always be objective.

A further cause for confusion in obtaining evidence of susceptibility is that data are mainly obtained from highly selected groups of patients with skin or respiratory disorders. Food additives, if they have any influence on the condition, may exacerbate a pre-existing intolerance caused by an entirely different agent.

It is a reflection of the difficulties of accurate diagnosis that estimates of incidence of susceptibility are variable and tentative (see Chapter 1.2).

Sensitivity to Tartrazine and Salicylates

Tartrazine (FD & C Yellow No. 5) is the colour most frequently implicated in food intolerance studies. The first report of intolerance to tartrazine appeared in 1959 and described three patients, each of whom reacted to a corticosteroid product containing tartrazine[2]. Tartrazine is added to many pharmaceutical products as well as to foods and soft drinks. Reports of adverse reactions to tartrazine have been more common for pharmaceutical

preparations than for food and drink. This may be because patients taking pharmaceutical preparations are under more regular medical supervision, because the concentration of tartrazine in pharmaceuticals is higher, or because sick people are likely to be more sensitive than the general population.

There is no evidence at present that these reactions are mediated through specific IgE antibodies normally implicated in Type I allergic reactions[10]. However, recent findings have suggested—though as yet without confirmation—that there may be an association between clinically identified intolerance to tartrazine and IgD antibodies to tartrazine[14].

A number of animal studies have been carried out to elucidate the mechanism of tartrazine intolerance. Delayed hypersensitivity (contact dermatitis) can be induced in guinea-pigs[15] but the reported clinical responses in man are of the immediate type, so this finding is unlikely to be relevant to man. Tartrazine itself will not induce antibody formation in animals but if conjugated preparations are used, antibodies can be stimulated[16]; again there is no evidence that this is relevant in the human situation. Finally, the effect of tartrazine on histamine release from mast cells has been examined[16,17]. Safford and Goodwin[16] did not find tartrazine to be a stimulator if it penetrated mast cells but Peterson *et al.*[17] did observe histamine-induced changes in pulmonary flow after guinea-pigs were injected with doses of tartrazine.

Adverse reactions to tartrazine occur most commonly in subjects who are sensitive to acetylsalicylic acid (ASA). Depending on the test protocol followed, 10-40 per cent of aspirin-sensitive patients respond to tartrazine, reactions ranging from severe asthma to urticaria and mild rhinitis[18-20]. The chemical structure of the tartrazine molecule has features similar to those of benzoates, other azo compounds, pyrazole compounds and the hydroxy-aromatic acids, which include salicylates. It is known that the azo group can be reduced in the intestine and liver[21,22], indicating one of the several routes through which these molecules, too small in themselves to act as antigens, could be conjugated to a larger molecule to form an antigenic structure (a hapten)[23,24].

In the majority of subjects, intolerance to ASA also does not seem to involve immunological mechanisms, although there is published evidence to suggest that allergic reactions play a part in some ASA-sensitive patients[25]. Apart from ASA, exposure to salicylates in the diet is a common experience. Salicylates are present in a number of vegetables and fruits (see Chapter 6). Many of the natural salicylates are stable and appear unchanged in food products such as preserves and wine. A range of synthetic salicylates are also used to flavour sweets, ice-cream, soft drinks and cake mixes. The chemical similarity of these materials with aspirin poses a possible explanation for the multiple susceptibility to other substances seen in ASA-sensitive patients.

A major breakthrough in the understanding of the mechanisms involved in ASA intolerance came with the discovery that aspirin can inhibit prostaglandin synthesising enzymes via the cyclo-oxygenase pathway[26]. The inhibition of the prostaglandins is associated with the release of bronchoconstricting mediators from mast cells. Patients with aspirin-sensitive asthma have also been found to have idiosyncratic reactions to other non-steroidal anti-inflammatory drugs which are able to inhibit prostaglandin synthesis[27]. Thus a close correlation between the prostaglandin system and adverse reactions to aspirin appears to exist in certain individuals. Tartrazine has not been shown to inhibit prostaglandin pathways[28,29].

Susceptibility to Adverse Reactions

Because so many chemicals present in the environment contain sulphonated benzene groups, the nature of the sensitising agent is difficult to identify. The majority of the tartrazine-sensitive patients also have high total serum IgE levels which are indicative of allergies to a variety of substances. Whether or not immunological mechanisms other than those commonly involved in drug and food allergy play a role in adverse reactions to food additives, particularly in hypersensitive individuals, can only be clarified by further investigations. The existence of a dose-response and threshold effect for tartrazine and other additives[10] suggests that it is unlikely that the reactions to tartrazine have an immunological basis. On the other hand, individuals who display dermatological and respiratory sensitivity to additives generally appear to belong to a select group that is atopic or exhibits allergic or idiosyncratic responses to a variety of ingested and inhaled material. Whether food colours or other food additives are able to initiate a state of intolerance in susceptible individuals or whether they act only on previously sensitised individuals can only be resolved by research.

The mechanisms for production of adverse reactions to food additives do not appear to be immunological. However, research needs to be carried out on both the epidemiology of, and the basic mechanisms concerned in, adverse reactions to food additives. It must be emphasised that there is no suitable experimental model available to assess the allergic potential of new food additives.

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6. THE PLACE OF DIET IN THE DIAGNOSIS AND TREATMENT OF FOOD INTOLERANCE

The Complementary Roles of the Doctor and the Dietitian

The provisional diagnosis of food intolerance will be made by a clinician on the basis of the medical history, clinical findings and appropriate laboratory investigations. The diagnosis and treatment for certain conditions may be clear-cut, for example in patients with lactose intolerance or food-related angioedema. In these cases, a specific diet will be requested from, and implemented by, the dietitian. In other circumstances, when symptoms are mild, simple symptomatic treatment may be more appropriate initially than diagnostic and therapeutic diets, which tend to be time-consuming and difficult. The clinician must decide, in consultation with the patient, to what extent dietary investigation is necessary.

The dietitian's role is crucial in taking the baseline diet history, in working out the elimination diet as part of the diagnostic process, and in devising the maintenance diet. The dietitian must first ensure that any prescribed elimination and therapeutic diet is nutritionally adequate, planned to meet individual needs, and easy to follow at home. Second, she or he must, with the clinician, review the patient's progress on the diet in the light of the clinical findings, assess the patient's compliance, and update the diet to include new product information. The dietary diagnosis and treatment of food intolerance involves constant consultation between and review by the clinician and dietitian during the initial elimination phase, the secondary food reintroduction phase and the maintenance phase.

The Diet History

When a severe reaction occurs immediately after ingesting a food, the patient is usually aware of the precipitating circumstances; but when reactions are delayed, or if more than one substance provokes symptoms, it can be very difficult to pinpoint the offending food or foods. Hence, an essential part of the diagnostic process will be to take a careful diet history from the patient.

The patient's past and current eating patterns may disclose any abnormal patterns or dietary restrictions which might lead to nutritional problems. The diet history should also highlight any previous therapeutic dietary restrictions and describe the patient's reactions to them.

A useful adjunct to the diet history is the food diary. The patient is asked to keep a record of all food and drinks taken, usually over a period of seven days, and any symptoms that may occur are also recorded. In order to encourage patient compliance, emphasis is placed on the types of food and drink consumed rather than the quantities. If, for whatever reason, a week is considered to be too long, the record should be kept for a minimum of four days. This should include the weekend, since many people alter their eating patterns at this time. To prolong the procedure for more than a week is irksome to the

patient and does not necessarily produce better, or additional, information.

Exclusion, Elimination and Challenge Diets

When it is clear from the initial diet history that only one or two foods appear to be related to the patient's symptoms, a simple exclusion diet may be used. This might entail excluding a very specific component of the diet, for example strawberries. Alternatively, a more general approach may be needed, using either an extremely restricted diet of lamb, pears and rice[1], or a diet which eliminates those foods which are most commonly associated with adverse reactions, such as milk products, eggs, fish, pork, nuts, wheat products, coffee, tea, chocolate, alcohol and artificially coloured or preserved foods. This type of oligo-allergenic (or oligo-antigenic) diet, as it is sometimes termed, is given for one to three weeks (unless severe reactions occur in the meantime). It is only if the symptoms disappear within the period of the diet that the possibility of food intolerance as a diagnosis is worth pursuing.

The choice of foods which a patient may reasonably include in an elimination diet is necessarily arbitrary and may be varied according to the clinical syndrome. For example, on the basis of their experience in treating the irritable bowel syndrome, Hunter and his colleagues use a modified elimination diet which excludes wheat, potato, dairy products, citrus fruits and coffee[2] but does not exclude fish or meat, as these foods are an infrequent cause of symptoms in such patients. Another example is the exclusion diet used by Egger and his colleagues [3] in the investigation of migraine. This includes one meat (lamb or chicken), one carbohydrate food (rice or potatoes), one fruit (banana or apple), one vegetable (brassica), water, and vitamin supplements. Those who do not improve on this diet within three or four weeks are offered a second diet that contains no foods in common with the first.

Whatever the details of the diagnostic diet used, there will be patients who fail to respond, either because they are still consuming foods to which they react or because their illness is not in fact food-related. In these circumstances, a clinical decision has to be taken as to whether food reactions can be excluded from further consideration or whether an even more restricted diet, i.e. an elemental diet, is needed. Elemental diets are unpalatable and few patients can tolerate them for long. Since their use reduces the bulk of intestinal secretions, a dramatic relief of symptoms may result if factors such as intestinal obstruction contribute to the clinical picture, and this must always be borne in mind.

If symptoms disappear on an elimination diet and a provisional diagnosis of food intolerance is made, it is necessary to see if symptoms return when foods are reintroduced slowly, one at a time. Initially, foods will be reintroduced openly and then in disguised form so that they are not identified by the subject[4]. Since adverse reactions to food may sometimes depend on quantity, the newly reintroduced food may need to be taken on two or three successive days before it can be assumed not to cause symptoms. Furthermore, because delayed reactions may sometimes occur, new foods should be added only at intervals of five to six days. If the patient reports that symptoms are recurring, the suspect foods are withdrawn again. Foods which appear to produce symptoms are then given in double-blind challenge tests in which the patient is given, in random sequence, the disguised test food or a specially constituted food which is identical in taste, colour, texture and appearance[2]. Capsules which contain either food or a harmless alternative can also be used but are suitable only if there is a history of reaction to small quantities of the test substance. It is only rarely necessary to introduce the challenge material by stomach or nasogastric tubes, which have the disadvantage that they bypass the lips, mouth and other areas where attacks may be triggered, and also introduce the added unpleasant stimulus of the tube itself.

It can take weeks or even months to reintroduce foods singly to an oligo-allergenic diet. It is essential, therefore, that the basic diet is nutritionally adequate for the individual patient for whom it is devised. The wider the range of excluded foods, the more difficult and demanding this diet becomes. The difficulties experienced by patients should never be under-estimated. Some of the more restricted diets require much time and patience and it is essential that there should be close liaison between the doctor and dietitian to provide adequate support to the patient.

Maintenance Diets

Once a food or variety of foods are established as the cause of intolerance, a diet which avoids the food or foods responsible for the intolerance must be devised. It is important, particularly in the case of children, that the patient's management is planned and supervised by an experienced dietitian. Throughout the UK there are dietitians working in hospitals who have specialised in paediatric dietetics and their expertise should be used. When adults are the patients, it is essential that the diet should be as near to normal as possible, varied enough to ensure the patient's compliance, and not too costly. It should also be reviewed periodically.

The nutritional adequacy or otherwise of an exclusion diet depends largely on the food or foods being excluded. If, for example, nuts or shellfish are the suspected culprits, their exclusion from the daily diet is not likely to cause nutritional problems. However, the practical and nutritional implications of telling patients to avoid eggs, milk or wheat are much greater. Milk substitutes are available if required, but wheat is less easy to replace and many of the substitutes contain wheat starch and are therefore not suitable. Furthermore, eggs, milk and wheat are frequently used in manufactured foods, so it is much more difficult than is generally appreciated to exclude these items from the diet. Inadequate diets abound—either self-selected or prescribed by those without expert nutritional knowledge—and they can be harmful[5]. As an adjunct to the dietary management, symptomatic, anti-allergic or other therapy may be prescribed by the clinician.

Unorthodox Diets

Rotation Diets

One of the more elaborate regimens advocated is the 'rotation diet', in which a cross-section of food from different biological groups is eaten daily on a rotating basis. While it is generally known that some patients can tolerate modest quantities of particular foods if they are taken at spaced intervals but have symptoms if the same food is eaten in large quantities on consecutive days, there is little evidence to justify the obsessional adherence to the detailed food prescriptions contained in many formal 'rotation diets'. There is also a danger that such diets will be nutritionally unsound, particularly when used for children when food intolerance is diagnosed 'by proxy' (see Chapter 4.1).

The Feingold Diet

Another example of a restrictive diet which has gained a considerable following both in the USA and in the UK is the Feingold diet, used in the treatment of hyperactive children (see Chapter 4.1). The basic diet as described by Feingold involves the elimination of two groups of foods, but the basis for their exclusion is not always scientifically justified[6]. The first group consists of various fruits and vegetables containing natural salicylates, for example cucumber, tomatoes, berries, apples, oranges and several other fruits. The second group consists of foods known or thought to contain artificial food colouring matters, preservatives and other additives. However, even where the diet is in frequent use, there is some inconsistency in the foods excluded. In the Feingold regimen the entire family is generally encouraged to follow the diet and it must be adhered to completely. If, after four to six weeks, the child has shown a favourable response, the foods in the first group may be slowly reintroduced but the items in the second group (the food additives) are permanently excluded.

In 1975, the Nutrition Foundation in the USA examined the claims of Feingold[7]. They concluded that, at that stage, the therapeutic claims were based only on incidental reports and they therefore recommended controlled clinical studies of the diet. Double-blind trials of such a diet are difficult to execute, but in the USA between 1975 and 1979 a number of such trials were set up and produced some equivocal results[6]. The Nutrition Foundation reviewed these trials in 1980[6] and concluded that they provided sufficient evidence to refute the claims that artifical colourings, flavourings and salicylates were responsible for hyperactivity.

More recently, both a National Institute of Health Consensus Development Conference[8] and the American Council of Science and Health[9] were unable to find any significant reduction in the incidence of hyperactivity in children on the Feingold diet, which could not be explained by a placebo effect. This conclusion has also been drawn in the UK[10,11].

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CONCLUSIONS AND RECOMMENDATIONS

For the purpose of this report, food intolerance includes only short-term or relatively short-term effects (excluding conditions which involve cholesterol and blood lipid abnormalities, diabetes and coronary artery disease). Food intolerance is a condition in which there are reproducible adverse effects after ingesting a specific food or food ingredient. The mechanisms include a genetically determined inability to cope with a food because of an enzyme deficiency; a pharmacological effect due to substances such as tyramine and caffeine; a histamine-releasing effect in susceptible individuals, due to the consumption of food such as shellfish or strawberries; an irritant effect of food on the mucosa of the gastrointestinal tract, particularly if it is diseased; immunological mechanisms; an indirect result of the fermentation of unabsorbed food residues in the lower bowel; and finally, as yet unidentified mechanisms such as those resulting in adverse reactions to food additives.

Psychological factors also play an important part in determining attitudes to food. Recognition should be given to food aversion, which denotes the psychological avoidance of food and includes psychological intolerance, a condition in which symptoms are caused by emotions associated with a food but do not occur when the food is given in a disguised form. Recognisably different are eating disorders, such as anorexia nervosa and the bulimic syndrome, which do not primarily affect appetite but involve an abnormal attitude to body weight and food.

Conclusions

1. Reactions of food intolerance have gained increasing recognition in recent years but the lack of adequate scientifically based research and the lack of medical interest has led to the proliferation of organisations, centres and individuals offering advice which has little scientific basis.
2. A wide variety of symptoms have been incorrectly attributed to the effects of foods; even when the attribution is correct, there has been confusion between conditions caused by allergy, enzyme deficiencies, pharmacological reactions, psychological reactions and other mechanisms. Food intolerance can both mimic other conditions and be mimicked by them.
3. No estimate can be made of the prevalence of food intolerance because of a lack of adequate information. With the exception of rare but specific biochemical defects, diagnostic methods still depend on dietary studies or on a psychiatric assessment and are highly subjective.
4. The dietary approach to the management of food intolerance is particularly complex and may lead to nutritional difficulties and social disruption. There are considerable dangers in the unsupervised use of diets, especially for infants and young children.
5. For those patients who react abnormally to components of various foods, there is a need for better access to information on the ingredients of foods beyond what is given on the label.
6. Emotional difficulties are common and may sometimes be secondary to immunological or other types of food reaction. Whatever the aetiology, these patients are often ill and in need of treatment which takes account of their psychological and emotional needs as well as any physical aspects of their food intolerance.

Recommendations

1. The Committee recommends that further efforts should be made to inform the public, the medical and associated professions, industry and government about the nature and prevalence of food intolerance. In furtherance of this recommendation, the Committee is considering the publication of a version of this report to be aimed at the non-scientific reader.
2. There is a need for dietary diagnostic methods to be carried out and interpreted by strict criteria, especially because placebo responses are common. Potential diagnostic pitfalls should be given more publicity among the medical and dietetic professions and the inadequacy of untested methods should be emphasised.
3. Before suggesting that a patient's symptoms may be 'allergic' in origin or require treatment on this basis, it is recommended that doctors should seek and consider the results of methodical investigation, including provocation tests. Treatments which have not been properly evaluated should not be endorsed.
4. Treatment may involve more than one member of a multi-disciplinary team. Expert medical and dietetic advice should be more widely available for both adults and children, and the dietetic approach to the subject should be further studied and evaluated.
5. It is recommended that the feasibility of setting up a central data bank for food product composition be examined. Products which are free of ingredients known to be responsible for intolerance should be registered in the data bank, and doctors and dietitians should have access to it.
6. It is recommended that efforts should be made to obtain support for research into the epidemiological and scientific aspects of food intolerance, including improvement of the experimental design and analysis of results of controlled trials both for diagnosis and treatment.

Targets for Research

While some advances have been made in the understanding of food intolerance and food aversion in the last ten or twenty years, our knowledge of the aetiology of these conditions, of reliable diagnostic methods, and of satisfactory forms of treatment, is still inadequate. It would be impossible to describe all the gaps in our knowledge, but research into the various areas enumerated below appears to be particularly urgent or timely.
1. To define the mechanisms, immunological or non-immunological, by which foods and food additives cause reactions in susceptible individuals; and to assess the prevalence and relative frequency of the different subcategories of food intolerance and food aversion.
2. To define, where possible, the chemical nature of the substances which provoke reactions, whether present in foods or food additives, and to obtain pure preparations of these substances for diagnostic and research purposes.
3. To examine and improve methods for detecting: immunological responses to foods; the release of pharmacological mediators (often not associated with specific immune reactions); and the biochemical abnormalities to be found, especially in patients with metabolic defects, enzyme deficiencies, and migraine.
4. To determine the similarities and differences in symptomatology between patients with food intolerance and with various psychiatric conditions, particularly depression, personality disorder and the eating disorders.
5. To examine the influence of the maternal diet during pregnancy and lactation and the effects of post-natal environmental influences on the immune responses of the infant and the development of food intolerance.
6. To evaluate treatment methods, including: the use of mediator antagonists and other pharmacological approaches; methods for modulating the immune response, including the development of new drugs acting on the mast cells; psychiatric treatment, including pharmacological approaches and psychotherapy; and unorthodox methods of treatment for which unsubstantiated claims have been made.

APPENDIX: THE PROVISION OF INFORMATION ON FOOD PRODUCTS

When a person is known to be intolerant to identified food(s) or food ingredient(s), these must be avoided. It is relatively easy to avoid such common causes of intolerance as, for example, hen's eggs, cow's milk, fish, chocolate, some cereals, fruits and nuts. However, components of prepared foods cannot be easily avoided unless their presence is made known, and such ingredients as components of cow's milk may be included in prepared foods without being clearly identified.

Most food manufacturers in the UK supply dietitians and clinicians with product composition details on request: some do so routinely. The British Dietetic Association supplies lists of manufactured products which are free from particular components to its members. Label declarations are another source of information, although at present not all components need be specifically declared. It could be argued that the declarations of the content of food additives by reference number rather than by name may also obscure the nature of the additives, but information on these reference numbers is now becoming more widely disseminated[1,2]. As constituents of a food product may change, it is important that those people who are intolerant of certain foods check the label for product composition.

UK Regulations for Labelling Foods

Until 1st January 1983, labelling was controlled through Regulations made in 1970[3] and subsequently amended by a number of Statutory Instruments [4-7]. Since that date 'The Food Labelling Regulations 1980'[8] have largely superseded the Regulations of 1970. They take account of the Food Standards Committee's Second Report on Food Labelling[9] and implement Directives 79/112/EEC on the labelling, presentation and advertising of foodstuffs for sale to the ultimate consumer, and 77/94/EEC on foodstuffs for particular nutritional uses[10].

The general requirements are that all food to which the regulations apply must be marked or labelled with the following information: (a) the name of the food as prescribed by law or its customary name; (b) a list of ingredients in descending order of weight of inclusion; (c) an indication of minimum durability; (d) the name and address of manufacturer, packer or seller within the European Community; (e) particulars of the place of origin of the food if its absence could lead to a purchaser being misled; and (f) instructions for use if their absence could be expected to cause problems.

Additives must be declared within the list of ingredients and in accordance with specific requirements set out in the 1980 Regulations[6].

List of Ingredients

It is permitted to use generic names in accordance with certain provisions; for example, 'cheese' may be used for any type of cheese, hence the product may have come from the milk of cattle, sheep or goats but not be specifically identified as having come from any particular species.

In some cases, origin is also required to be stated, as for example with 'fat'; where descriptive terms 'animal' or 'vegetable' should be added.

Declaration of Additives in the Ingredients List

The declaration of each additive is related to its function as defined by the manufacturer. In some cases, additives have more than one function and then the declaration is made within the category relating to the chief function as determined by the manufacturer. In the UK regulations approximately 270 additives are specifically permitted and the number of names that may appear on the label may be many more if one takes account of synonyms. They include antioxidants, preservatives and colouring agents, among a wide range of ingredients, which, together with other substances such as vitamins and essential nutrients, have as their main roles the maintenance of product quality and the enhancement of the acceptability of the product to the consumer. Depending upon function, some additives need, at present, only be declared by their category and not specifically. These are antioxidants, colours, emulsifiers, emulsifying salts, flavourings, preservatives and stabilisers.

For a second group of additives, the category name must be followed by the specific name or by the EEC number (E number). These are acids, acidity regulators, anti-caking agents, anti-foaming agents, artificial sweeteners, flavour enhancers, flour improvers, gelling agents, glazing agents, raising agents and thickeners. Explanatory information on the E number system is available from the Ministry of Agriculture, Fisheries and Food[1].

Exemptions from Part at least of the Labelling Requirements

Food sold or served in certain conditions need not be labelled as fully as described so far and in particular need not be so specific with respect to additives. Broadly, this refers to foods that are not pre-packed, fancy confectionery products, foods sold at catering establishments, fast foods and small packages where the surface area is less than 10 square centimetres.

Future Regulations on Food Labelling

Further regulations based on the Food Standards *Second Report on Claims and Misleading Descriptions*[11] have been proposed recently, and deal with nutritional claims made for products.

It is proposed that in any ingredients list all additives, except flavourings, should be declared specifically. To facilitate this change, serial numbers have been allotted to many more additives, and these may be used in place of the specific name when a category name is also required to be declared.

References

1. MAFF booklet *Look at the Label.* London: HMSO.
2. Food and Drinks Industries Council (FDIC) booklet *Food Additives.* London: FDIC.
3. The Labelling of Food Regulations 1970 (S.I. 1970 No. 400).
4. Statutory Instrument 1972 No. 1510.
5. Statutory Instrument 1976 No. 859.
6. Statutory Instrument 1978 No. 646.
7. Statutory Instrument 1979 No. 1570.
8. The Food Labelling Regulations 1980 (S.I. 1980 No. 1849).
9. MAFF Food Standards Committee (1980) *Second Report on Food Labelling.* FSC/REP/69. London: HMSO.
10. Directives 79/112/EEC (O.J. No. 133. 8.2.79, p.1) and 77/94/EEC (O.J. No. 126, 31.1.77, p.55).
11. MAFF Food Standards Committee (1980) *Second Report on Claims and Misleading Descriptions.* FSC/REP/71. London: HMSO.

GLOSSARY

This glossary is intended for the general reader.

Abetalipoproteinaemia, characterised by the lack of the β lipoprotein fraction of the blood.
Aflatoxin, a toxic product which may be formed when *Aspergillus* mould grows upon various foodstuffs, particularly cereals and peanuts.
Allergen, a foreign substance which provokes a harmful immune response.
Allergy, an untoward immunological reaction, especially of the type which involves immediate hypersensitivity.
Amenorrhoea, loss of menstrual periods.
Anaphylaxis, an immediate hypersensitivity reaction to a foreign substance, which, in severe cases, can be generalised and life-threatening.
Angioedema, areas of swelling of the skin or mucous membrane together with the underlying tissue.
Anorexia, loss of appetite (adjective = anorectic).
Antibody, protein of the immunoglobulin type which is capable of combining specifically with certain types of foreign substance (antigens).
Antigen, usually a protein, sometimes a polysaccharide, which is capable of provoking an immune response.
Arachidonic acid, a fatty acid from which a number of chemical mediators are synthesised.
Arthralgia, painful joints.
Ataxia, unsteadiness, poor muscle co-ordination.
Atopy, an hereditary disposition to develop allergy.
Basophil, a circulating white blood cell which stains with basic dyes, and is capable of releasing mediators such as histamine.
Borborygmi, intestinal rumbling.
Bronchodilator, causing widening of the airways.
Bulimia, a condition associated with binge eating habits.
Catabolism, the breaking down of substances in the body tissue.
Cell-mediated immunity, specific immunity which depends on the presence of T lymphocytes.
Complement, an enzyme system which is activated by various means, but notably by the combination of antibody and antigen, and which triggers the changes of inflammation and other biological reactions.
Conjugate, two substances coupled together.
Cyclo-oxygenase, an enzyme which synthesises prostaglandins and other mediators from arachidonic acid.
Cystic fibrosis, an inherited disease causing harmful effects upon the digestive tract, the lungs and other organs.
Cytotoxic, harmful to cells.
Dermatitis, inflammation of the skin.
Dinoflagellate, a unicellular organism on which some bivalve shellfish feed.
Dysphagia, difficulty in swallowing.
Eczema, a red, scaling, itching type of skin eruption.
Encephalitis, inflammation of the brain.
Encephalopathy, disease of the brain.
Enuresis, bed-wetting.
Eosinophilic, infiltrated with white cells of the type which stain with eosin and which tend to be associated with either parasitic infection or allergy.
Epithelium, the covering of the skin and mucous membranes.
Familial periodic paralysis, an inherited condition in which there are attacks of weakness and a defective metabolism of potassium.
Gastroenteritis, inflammation of the stomach and bowel.
Gastrointestinal, concerning the stomach and bowel.
Giardiasis, a parasitic infection of the bowel.
Hartnup disorder, a disease in which the intestinal transport of amino acids is impaired.
HLA antigens, substances present on the surface of cells which vary with the individual's tissue type and are important in determining the body's reactions (especially its immunological reactions).
Hydrolysis, breakdown due to the incorporation of the components of water.
Hyperactivity, over-activity.
Hyperammonaemia, excess of ammonia in the blood.
Hypermania, a state of extreme over-activity.
Hypersensitivity, over-sensitivity.
Hypocarbia, a condition in which the carbon dioxide level of the blood is abnormally low because of overbreathing.
Hypoglycaemia, abnormally low levels of glucose in the blood.
Hypolactasia, low levels of the enzyme lactase.
Hypoproteinaemia, low levels of protein in the blood.
Immediate hypersensitivity, an excessively sensitive reaction of the body, often occurring within minutes. Sometimes used as an alternative term for allergy.
Immune response, specific reaction to antigen, e.g. by antibody production, cell-mediated immunity, or immunological tolerance.
Immunoglobulin (Ig), member of a family of proteins from which antibodies are derived. There are five main classes known as IgA, D, E, G and M. IgE antibodies are those which are most closely associated with immediate allergy.
Immunological, concerned with the study of immunity.
Immunological tolerance, a response leaving the

lymphoid tissues specifically unreactive to an antigen (e.g. a food) which is capable in other circumstances of provoking antibody production or cell-mediated immunity.

Immunopathological, due to an abnormal immune response.

In utero, in the womb.

Isoniazid, a drug, derived from nicotinic acid, used to treat tuberculosis.

Jejunum, a part of the small bowel.

Leukocyte, white blood cell.

Lymphocyte, a specialised white cell with a variety of immunological functions, including antibody production (B lymphocytes) and cell-mediated reactions (T lymphocytes). T lymphocytes also have a regulating (suppressor or helper) effect upon antibody production.

Lymphoid tissues, all tissues in which the predominant, active cells are lymphocytes—lymph nodes, Peyer's patches, tonsils, adenoids, spleen and thymus.

Lymphokines, the soluble factors released from lymphocytes which stimulate or modulate the activity of other cells.

Macrophage, a mobile cell which can, among its many activities, ingest foreign particles, transport antigen, and release a number of enzymes.

Maculo-papular, a description of numerous spots of skin rash, which are often both raised and coloured.

Metabolic acidosis, a disorder of metabolism in which body acids accumulate.

Migraine, periodic headache, often one-sided and often accompanied by nausea, visual disturbances and other features.

Monilia *(Candida),* a genus of yeasts which can produce disease (candidiasis).

Monoclonal antibody, an artificially stimulated immunoglobulin reagent derived from cultured cells which are selected to produce only a single, very highly specific antibody.

Mycotoxins, toxins produced by fungi.

Nephrotic, associated with a type of kidney disease in which much protein is lost in the urine.

Neuropeptides, compounds made up of sequences of amino acids which can stimulate or modulate the activity of the nervous system.

Neurotransmitter, chemical substances which stimulate or transmit the passage of impulses in the nervous system.

Oedema, swelling of body tissues due to accumulation of fluid.

Oesophagitis, inflammation of the gullet.

Oligoallergenic, containing few allergens.

Palindromic, recurrent or episodic.

Pancreatitis, inflammation of the pancreas.

Peristalsis, propulsive movements of the bowel.

Phagocyte, a cell which ingests foreign particles or the body's breakdown products (e.g. a macrophage).

Phagocytosed, ingested into a cell.

Pharmacological, concerned with the action of drugs.

Proctitis, inflammation affecting the rectum, i.e. the lower end of the bowel.

Prodrome, a premonitory symptom which heralds others.

Prostaglandins, oxidative products of arachidonic acid which act as chemical mediators, capable of modulating many body functions.

Psychogenic, originating in the mind.

Psychosomatic, depending on the relationship between the mind and the body's functions.

Pyloric, pertaining to the lower opening of the stomach.

Pyrolysis, decomposition which is influenced by heat.

Radioallergosorbent tests. Particles which have been coated with antigen are exposed to the patient's blood. The amount of antibody which attaches to these particles is then estimated with the help of radioactive markers.

Reaginic, mediated by antibody of the type found in allergic subjects.

Refractory period, period in which an event cannot easily be reproduced.

Reticuloendothelial system, a phagocytic 'scavenger' system which is diffusely located in several tissues including liver, spleen and bone marrow.

Rhinitis, inflammation or over-reaction of the nose.

Rhinorrhoea, running of the nose.

Shwachman's syndrome, a condition in which, among other features, there is a failure of pancreatic secretions.

Scombroid, belonging to the mackerel family.

Seborrhoeic, associated with an excessive production of sebum from the sweat glands.

Seronegative arthritis, inflammation of the joints which is unaccompanied by serum changes of the type found in rheumatoid disease.

Serotonin, 5-Hydroxytryptamine. A biologically active amine which is found in the gut, the nervous system, and the dense granules of blood platelets.

Steatorrhoea, fatty diarrhoea.

Tetany, spasm and hyper-excitability of muscle.

Thalassaemia, a hereditary anaemia in which there is a defective mechanism for synthesising globin chains and therefore haemoglobin.

Thromboxane, an oxidative product of arachidonic acid which is related to the prostaglandins.

Thymus, a lymphoid organ which has an important role in the development and maintenance of immunological activity.

Trypsinogen, the parent substance of the protein-digesting enzyme trypsin.

Urticaria, an itching, raised, patchy rash of the skin which is sometimes associated with allergy.

Vasoactive amines, amine substances which affect blood vessels.

Xanthomata, fatty deposits beneath the skin.