Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Adverse Reactions to Food and Food Ingredients

Chairman
Professor H F Woods

Chairman of the Working Group on Food Intolerance:
Professor P J Aggett

Contents

1. Executive Summary

1.1   This report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment considers adverse reactions to food both of immune origin (food allergy) and non-immune origin (food intolerance). The report was drafted by a specially constituted Working Group of the Committee, with the following terms of reference:

- to consider whether the incidence and prevalence of adverse reactions to foods and ingredients are changing;

- to consider those foods identified as commonly causing adverse reactions and rank them separately for prevalence, potency, and severity of reaction;

- to consider the underlying mechanisms;

- to identify factors, both genetic and environmental, which may increase the risk to health.

1.2   A draft report prepared by the Working Group was submitted to the Committee in September 1999. A further draft was the subject of consultation at an open meeting of the Committee in February 2000. Additional changes were made to the report after that meeting.

1.3   There is considerable interest in food safety because of concerns that many people react adversely to foods and food ingredients. Although data on the incidence and prevalence of these reactions are limited, a considerable proportion of the population consider themselves to be subject to such reactions. Therefore it is important that health care professionals are aware of these reactions.

Structure of the report

1.4   Throughout this report adverse reactions to foods and food ingredients are classified in accordance with the system adopted by the European Academy of Allergology and Clinical Immunology. Chapter 2 (the introduction) discusses the division of adverse reactions to food and food ingredients into reactions of immune origin (food allergy) and those of definitely non-immune origin, including adverse reactions where the mechanisms are unknown (food intolerance). This Chapter also describes the composition of the Working Group and its methods of working. Of particular interest was the uneven nature of the information that was available to the Working Group and prevalence data, in particular, were considered inadequate.

1.5   Chapters 3 to 8 are concerned with the clinical features of adverse reactions to foods and food ingredients. Chapter 3 deals with dermal symptoms, Chapter 4 considers gastrointestinal effects, while Chapter 5 considers symptomatology referable to the

respiratory tract. Chapter 6 discusses anaphylaxis, a severe immunologically-mediated condition, which is sometimes fatal. Chapter 7 considers adverse reactions to food that affect the central nervous system, including the possible role of food in behavioural abnormalities such as attention deficit-hyperactivity disorder and in the aetiology of headache and migraine headache. Chapter 8 considers a number of other conditions that have been linked with food, including cystitis, vaginitis and arthritis.

1.6   Chapter 9 discusses the mechanisms that underlie adverse reactions to foods and food ingredients. The mechanisms that underlie IgE-mediated reactions are reviewed and the types of food that may give rise to such reactions are listed. The mechanisms responsible for non-IgE-mediated immune reactions such as the enteropathies including coeliac disease, are considered. The heterogeneous nature of the aetiology of non-immune-mediated adverse reactions to food is discussed in the last part of Chapter 9.

1.7   Chapter 10 discusses diagnosis, investigation and management of adverse reactions to food and food ingredients. As well as history and clinical examination, standard diagnostic techniques and non-validated tests are reviewed. This chapter discusses evidence for the role of breast-feeding in the prevention of food allergy in infants. The diagnosis and management of non-immune-mediated adverse reactions to food are briefly considered.

The Committee's conclusions

1.8   Chapter 11 discusses the Committee's conclusions drawn from the evidence available to the Working Group. The Committee concluded that it could not answer many of the questions posed in its terms of reference because there are no systematic data which would enable the accurate calculation of the incidence and prevalence of adverse reactions to food and food ingredients in the United Kingdom or elsewhere.

1.9   The Committee concluded that adverse reactions to foods can be mediated either through immunological or non-immunological mechanisms. In the case of the former, such reactions are defined as food allergy and the practice of calling all adverse reactions to food "allergies" is inappropriate and misleading. Food allergy is commonly mediated by IgE antibodies although other immunological mechanisms are important in some circumstances. Most adverse reactions to foods are due to intolerances which are either clearly non-immunological or are of unknown or unproven immune pathogenesis. Food aversion of psychological origin was not considered by the Committee.

Prevalence

1.10   There is clear evidence that the prevalence of atopy is increasing in the developed countries of the Western World. Although definitive evidence is lacking, the assumption is that this increased prevalence extends to food allergy. There are no systematic data which would enable the accurate calculation of the incidence and prevalence of adverse reactions to food and food ingredients in the United Kingdom or elsewhere. As many as 20-30% of the UK population think that they have a "food allergy" or some adverse reaction to a food. However when these beliefs are assessed using objective tests, the calculated prevalence of adverse

reactions to food and food ingredients was 1.4-1.8%. Most adverse reactions to foodstuffs are to natural foods rather than to synthetic additives and contaminants, the prevalence of which is about 0.03%. The prevalence of adverse reactions to food and food ingredients is estimated to be up to 8% in infants and young children.

Clinical features

1.11   Clinical features of adverse reactions to food and food ingredients include disorders of the skin, the respiratory tract, and the gastrointestinal tract. Clinical features related to the central nervous system (headaches) and the cardiovascular system may be related to food. Anaphylaxis is a life-threatening, severe, immunologically-mediated reaction involving all these systems. There is limited evidence that other structures, including the joints and genitourinary tract, may also be affected by adverse reactions to food and food ingredients but this is not well-established. It has been hypothesised that foods may be implicated in the aetiology of behavioural abnormalities including autism, attention deficit-hyperactivity disorder, and other less well-defined behavioural abnormalities including delinquency, but the relationships have not been established.

Foods responsible

1.12   Most immunological adverse reactions to foods and food ingredients are caused by a limited number of foods. In children, 90% of reactions are caused by cows' milk, chickens' eggs, wheat, peanuts, tree nuts (walnuts, brazil nuts, hazel nuts) and soya protein. In some instances these reactions, for example that to milk, occur only during early childhood. In adults, the majority of allergic reactions are caused by peanuts, tree nuts, fish and shellfish. Different early feeding practices and the age at which particular items are introduced into the diet may be responsible for observed geographical variation in patterns of food allergy. For example, in Japan rice allergy is common and in Scandinavia reactions to cod are frequent. Patients can react to more than one allergen and cross-reactions to related allergens can occur. The allergens involved in cross-reactions are not necessarily phylogenetically closely related, for example cross-reactions involving sensitivity of an individual to latex and various fruits are being recognised more frequently.

Mechanisms

Immunologically-mediated reactions

1.13 Most allergic adverse reactions to food are mediated by antibody-dependent mechanisms. The Committee considered that the mechanisms whereby adverse immune reactions develop, or oral tolerance of foodstuffs is acquired, are not clear. Similarly, the reasons why some reactions are transient and usually restricted to childhood are unknown. The taking of aspirin and other nonsteroidal anti-inflammatory drugs, exercise, or changes in temperature, particularly increased ambient temperature after exposure to a potential allergen, can precipitate or exacerbate immunological reactions to foods such as urticaria, asthma and anaphylaxis. The perception that the prevalence of food allergy is increasing was mentioned earlier: this increase may be part of a generalised rise in the frequency of atopy in

the population. It is now considered likely that one factor that influences the acquisition of atopy is programming of the developing immune system and there is some evidence to suggest that increased protection of infants from pathogens is associated with an increased prevalence of atopy.

1.14 Immunologically-mediated adverse reactions to foods and food ingredients may aggravate asthma and atopic dermatitis. However, the role of immunological adverse reactions in the pathogenesis of such disorders is unclear because many other factors are also involved in their aetiology. Thus the place for dietary restriction in the management of these conditions, particularly in adults, is uncertain.

1.15 Some adverse reactions to foods and food ingredients are mediated by immunological mechanisms not involving IgE antibodies. The best-characterised of these conditions are the enteropathies, of which coeliac disease, a reaction to gluten in some cereals, is the most widely-known.

1.16 There is a strong heritable component in all classes of immunologically-mediated adverse reactions to foods. The manifestation of the genetic trait depends on an interaction with other environmental factors and on the nature and timing of exposure to the potentially sensitising protein.

Non-immunologically-mediated adverse reactions
1.17 Non-immunologically-mediated adverse reactions are reproducible, idiosyncratic adverse reactions to foods and food ingredients which may be caused by inherited or acquired defects in intestinal transport, digestion and absorption or metabolism of food components or unusual sensitivity to pharmacologically active food components. In many instances the mechanisms are unknown.

1.18 High intakes of fibre or of complex carbohydrates which are not digested in the small intestine can result in fermentation in the large bowel which, particularly in children, can lead to abdominal pain, distension, wind and increased frequency and looseness of stools. Similar features may be caused by novel ingredients which have been designed to retain the organoleptic qualities of foods and, simultaneously, reduce their available energy content.

Effect of diet on delinquent behaviour
1.19 The Committee considered a number of reports suggesting that nutritional changes in the diet of delinquents reduce the number of disciplinary offences committed when in custody. The design of these studies was flawed by problems such as lack of randomisation and the use of inappropriate controls and few studies employed double-blind, placebo-controlled food challenges. Accordingly, in the absence of independent confirmation of these results, it was not possible to assess the significance of such reports.

Attention deficit-hyperactivity disorder
1.20 The Committee considered a number of studies on the effects of diet on attention deficit-hyperactivity disorder. There is evidence from double-blind placebo-controlled food challenges that some patients will respond to the exclusion of some specific dietary

components. Attention deficit-hyperactivity disorder may represent a number of independent but clinically similar conditions. The diagnostic criteria for the disorder are evolving and this confuses both the interpretation and comparison of aetiological studies as well as the detection of any temporal change in prevalence of attention deficit-hyperactivity disorder. Attention deficit-hyperactivity disorder is associated with many factors, including inherited abnormalities relating to dopaminergic systems in the central nervous system. Information concerning this is new and it is likely that its expansion will enable better characterisation, investigation and treatment of the disorder.

1.21   Studies in unselected populations with headache and migraine headaches, attention deficit-hyperactivity disorder, arthritis and similar heterogeneous conditions might overlook the small subgroups of the population who react to dietary components. It is probable that studies in well-characterised subgroups will be more informative about the role of dietary precipitants in these disorders than are studies on large unselected groups. There is currently no means of identifying the small cohorts of patients with these disorders, who might be responsive to exclusion of one or more dietary components.

1.22   The quality of evidence supporting claims of adverse reactions of all types is varied. Whereas specific metabolic abnormalities can be demonstrated in some individuals who suffer non-immunological adverse reactions to food, overall there are few reliable, simple diagnostic tests which will identify actual or potential sufferers of adverse reactions to food and food intolerance.

Diagnosis and management

1.23   The diagnosis of adverse reactions to food and food intolerance requires a high degree of clinical insight, and can be founded on the loss of symptoms when possible precipitants are eliminated from the diet. The 'gold standard' diagnostic test is the double-blind placebo-controlled food challenge. In the case of allergic reactions, ancilliary tests such as skin prick tests and tests based on detecting serum IgE antibodies are insufficiently predictive to displace the double-blind placebo-controlled food challenge as the definitive means of diagnosis. There are a number of procedures used to 'diagnose' and treat adverse reaction to food and food ingredients which do not have a sound evidential base. Misdiagnosis of adverse reactions to food and the imposition of inappropriate exclusion diets can seriously compromise a patient's nutrition and health.

1.24   Health professionals may not be sufficiently well informed about, and alert to, adverse reactions to foods and food ingredients and this may cause patients to seek non-validated means of diagnosis and management. Therefore it is important that there is, amongst health professionals, an improved awareness of adverse reactions to food and food ingredients.

1.25   Successful avoidance of precipitants depends on being able to identify them in foodstuffs. This depends on accurate labelling and the availability of appropriately sensitive tests to detect allergens and other precipitants of adverse reactions. It is not always evident or expected that foods might contain allergens. Such hidden allergens might arise from contamination of the principal food during processing, preparation and cooking, or the allergenic protein might be present at levels which do not need to be declared on food labels. Breast-fed babies might react to allergens, e.g. cows' milk proteins, excreted in their mothers' milk.

Adverse reactions to food and food ingredients

1.26   Food processing and biotechnology can alter the allergenicity of component proteins. Biotechnological and plant breeding techniques have been or are being developed to eliminate some allergenic proteins in cereal grains such as rice and wheat. Procedures are being developed to screen novel foods for the presence of allergens that are identical or closely related to known allergens. Where this is not possible procedures are being developed to identify potential allergens but no definitive process has, as yet, been established.

1.27   The role of breast feeding in preventing or postponing allergic sensitisation in infants is unclear other than its preventative effect in infants with a high risk of developing atopy. There is no good evidence that maternal avoidance of potential allergens, e.g. peanuts and cows' milk, during pregnancy is protective. Nevertheless, in its consideration of peanut allergy the Committee advised previously that, if there is a family history of atopy, pregnant women may wish to avoid the consumption of peanuts and peanut products.

1.28   Adverse reactions to food and food ingredients may have extensive implications for public and emergency health services, the food and catering industries, consumer choice and expenditure, food safety, food labelling policy, and social and educational services. Adverse reactions to food and food ingredients also have major implications for the National Health Service in terms of resources and for the education and training of health professionals.

Recommendations

1.29   Chapter 12 comprises the Committee's recommendations on public health issues and research. These are listed below. In view of the rather different nature of the problem, the Committee's recommendations in relation to attention deficit-hyperactivity disorder and other behavioural disturbances are given separately.

Recomendations on areas other than behavioural disturbance

Epidemiology

- There is a need for better prevalence and incidence data for the UK, based on appropriate objective criteria such as double-blind placebo-controlled food challenge, for both food allergy and food intolerance, using large and representative population samples.

- There needs to be an improvement in case definition, in databases and in other systems for reporting adverse reactions to food and food ingredients. In the case of anaphylaxis use of diagnostic codes needs improvement.

- There is a requirement for better diagnostic criteria to support systematic study of the role of foods and food ingredients in the pathogenesis of conditions such as headache and migraine headache.

- An improved understanding of genetic variation and of the resultant variations in both protein expression and metabolism should be used to explore the basis for adverse reactions to food and food ingredients. This might aid the development of predictive markers for those at risk of such adverse reactions.

Mechanistic research – Immune-mediated adverse reactions to food and food ingredients
1.30   Mechanisms need to be elucidated to enable:

● the development of markers to identify those at risk of adverse reactions to food and food ingredients,

● the improvement of prophylaxis and clinical management,

● the improvement of prevention by modifying the allergen content of foods.

1.31   In particular, mechanisms of oral tolerance and sensitisation need further investigation and this should extend to studies on the effects of early feeding (and diet of the pregnant woman) on the development of allergy. The role of exposure to antigens in utero or via breast milk, and of breast feeding and early feeding in the prevention or postponement of allergic reactions needs investigation.

1.32   Those factors which determine the allergenicity of proteins need to be characterised by studies on the nature, stability and other relevant properties of allergens and their epitopes.

1.33   Factors which exacerbate immune reactions need to be investigated.

1.34   The effects of biotechnology on the hazard deserve study, as does the nature of clinical cross-reactions and co-sensitisation.

1.35   The long-term effects of IgE-mediated adverse reactions to food on those who are symptom free, having outgrown childhood allergies, but who remain skin prick test or radioallergosorbent test positive need to be studied.

Mechanistic research – Non-immune-mediated adverse reactions to food and food ingredients
1.36   Inherited differences in the metabolism of food ingredients need further study.

Clinical research
1.37   For both management and for research purposes, accurate objective tests are needed for both food allergy and food intolerance. Harmonised and generally applicable criteria for the objective assessment of double-blind placebo-controlled food challenges need to be developed.

1.38   Improved standardised test reagents for radioallergosorbent tests and skin prick tests are required.

1.39   The establishment of an accreditation scheme for laboratories involved in the diagnosis and management of adverse reactions to food and food intolerance should be considered.

1.40   There is a requirement for rigorous studies to establish the value of non-validated diagnostic tests.

1.41   There is a need for investigation of the requirement for routine serological screening for coeliac disease in families at risk and populations.

Public health issues

1.42   The awareness of health professionals, especially general practitioners and those in hospital casualty departments, to the diversity, hazards and risks of adverse reactions to food and food ingredients should be increased. Moreover the food industry, including caterers and retailers, and the general public need education about the problem of adverse reactions to food and food ingredients.

1.43   There is a need for improvement in the information the general public and health professionals can obtain on food composition, especially with respect to hidden allergens. The adequacy of current composition tables for the content of precipitants of food intolerance (non-immunological adverse reactions to food and food ingredients) should be reviewed.

1.44   The practice of some companies in making data on the composition of their products available to consumers and health professionals should be encouraged.

1.45   Consideration should be given to establishing a system to enable consumers and health professionals to report adverse reactions to food and food ingredients.

1.46   There needs to be better understanding of social impact and economic cost of adverse reactions to food and food ingredients; the socio-economic consequences for patients and their families of following exclusion diets needs to be evaluated.

Recommendations for research on attention deficit-hyperactivity disorder and delinquent behaviour and diet

Epidemiology

1.47   For both management purposes and for research needs, attention deficit-hyperactivity disorder patients should be rigorously characterised and inheritance patterns and other aetiological factors should be identified.

1.48   The prevalence of food intolerance in children with attention deficit-hyperactivity disorder needs to be further investigated using double-blind challenge designs. The means of identifying a subgroup of attention deficit-hyperactivity disorder patients who respond beneficially to dietary intervention need to be addressed.

Mechanistic research

1.49   If a group of food-responders is identified, the responsible mechanisms should then be explored (immune responsiveness, neurotransmitter metabolite changes, localised changes of brain function, and psychological measures of attention). The preceeding characterisation would help to establish if this might be a single syndrome or a continuum of conditions.

Clinical research

1.50 Objective diagnostic tests for attention deficit-hyperactivity disorder need to be developed for management and for research purposes.

1.51 Trials of alterations in diet should include comparisons with established therapy (behavioural therapies and stimulant drugs).

1.52 Studies of any proposed role of adverse reactions to food and food ingredients in criminal and delinquent behaviour should be performed using suitable randomised and blind protocols.

2. Introduction

2.1   Consumer interest in food safety includes concerns that many individuals react adversely to food and food ingredients. These are not concerns about the long-term sequelae of dietary habits that may influence, for example, obesity, heart disease, cardiovascular disease and cancer. Rather, individuals are concerned about early onset reactions such as skin rashes (eczema, hives or nettle rash), diarrhoea, abdominal pain, hay fever, asthma, headaches, or life-threatening reactions which can occur in some people after they have ingested a particular food or food ingredient.

2.2   Unfortunately the occurrence and nature of such adverse reactions have not been well-characterised or systematically quantified. In the adult population as many as 20-30% believe that they have a "food allergy" or some adverse reaction to a food. However, in a community survey, with double-blind placebo-controlled food challenge (DBPCFC) of positive respondents, the calculated prevalence of adverse reactions to food was 1.4-1.8%. This is most probably an underestimate as the eight test foods selected for study accounted for only about half of those reported as causing problems.[1] Furthermore, many reactions are shown not to be due to an allergy and such misattributions illustrate the confusion in this field. Nonetheless, in the context of consumer interest and clinical and public health services, this is a large number of people.

2.3   Of particular concern to many parents and carers is the possibility that behavioural abnormalities such as attention deficit-hyperactivity disorder (ADHD) in children might be associated with some dietary components. It has also been claimed that criminal behaviour in some individuals might be responsive to the elimination of certain food and food ingredients from their diet or to the correction of deficiencies in their diets.

2.4   The quality of the evidence supporting these and other claims of adverse reactions is varied. An important reason for this is that there are few, if any, reliable simple diagnostic tests which will identify actual or potential sufferers of adverse reactions. Nonetheless, even without such criteria, there is a perception that adverse reactions to foods and food ingredients are increasing in frequency.

2.5   Health professionals may not be sufficiently well informed about, and alert to, adverse reactions to foods. In the absence of such insight, they might be less than sympathetic to the suspicions and claims of their patients. Patients themselves might have false perceptions and expectations of their possible adverse reactions. As a result of these tensions, patients and, in the case of children, their carers can become particularly anxious and more likely to seek non-validated means of diagnosis and management.

2.6   Adverse reactions to food may have wide implications for public and emergency health services, the food and catering industries, consumer choice and expenditure, for health and labelling policy, as well as for public safety.

Terms of Reference of the COT Working Group

2.7   With these considerations in mind, the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) established a Working Group on Food Intolerance with the following terms of reference:

- to consider whether the incidence and prevalence of adverse reactions to foods and ingredients are changing;

- to consider those foods identified as commonly causing adverse reactions and rank them separately for prevalence, potency, and severity of reaction;

- to consider the underlying mechanisms;

- to identify factors, both genetic and environmental, which may increase the risk to health.

Membership of the Working Group and its methods of working

2.8   The membership of the COT Working Group is given at Appendix 7. The Working Group was chaired by Professor Peter Aggett and included individuals with expertise in the areas of clinical and experimental immunology, nutrition, paediatrics, psychiatry, toxicology and epidemiology. It has met on seven occasions. A draft report was submitted to the COT at its meeting on 7th September, 1999.

2.9   The information that the Working Group considered comprised papers, books and reviews in the open scientific literature as well as reviews by official bodies and expert bodies. Information was also supplied by interested parties in response to the announcement of the formation of the Working Group and to advertisements placed in medical journals. In addition the draft report was the subject of an open consultation by being placed on the COT website and being discussed at an open meeting on 23rd February, 2000. A list of the submissions received by the Working Group is given at Appendix 6.

2.10   The Working Group was supported by a Secretariat comprising officials of the Department of Health and, subsequently, the Joint Food Safety and Standards Group and then the Food Standards Agency. The conclusions set out in this report are those of the members of the Working Group and have been endorsed by the COT. The opinions expressed in the report are independent of those of any other body.

2.11   The information and evidence available on adverse reactions are very varied in quality and can be categorised as described in paragraphs 2.13 to 2.18. Each category provides different information; progression from one category to another further characterises the condition, better defining the requirements for research and the applicability of the information.

2.12   The report describes the symptoms and signs of adverse reactions to foods and food   *Introduction*
ingredients, according to the body systems involved. Chapters 3 to 8 demonstrate the
difficulty of establishing causal relationships between adverse reactions and food, and of
identifying the mechanisms involved. In Chapter 9, the underlying mechanisms are
themselves discussed, although it should be appreciated that in many instances the
responsible mechanisms have not been clarified. Diagnosis and management are briefly
reviewed in Chapter 10. Conclusions and recommendations for further research are given in
Chapters 11 and 12 respectively.

Types of evidence considered by the Working Group

Descriptive studies

2.13   Much of the available literature on adverse reactions comes from case reports and case
series. These identify potential hazards and adverse reactions in small numbers of cases.
Descriptive epidemiological studies take this a stage further: they describe the burden, nature
and distribution of disease in terms of personal characteristics, place and time. Those may
alert health professionals to a particular problem and provide suggestions about causality and
possible mechanisms to be tested in analytical studies.

Analytical studies

Cross-sectional studies

2.14   Information on a population or representative sample is collected at a particular point
in time enabling the prevalence or incidence of a specific adverse health effect to be
estimated. Data on potential exposures and other factors thought to be influencing the health
outcome are also collected. As much of the information gathered relates to a single period of
time, it may not be possible to infer causation from this type of study.

Cohort studies

2.15   These studies use a defined group or cohort, which is assumed to be disease-free, the
group being followed to ascertain disease occurrence prospectively. The cohort may all be
potentially exposed to a particular hazard and rates of disease occurrence are then compared
with that of a second group free from the condition of interest. Alternatively, comparisons
may be made within the cohort between subgroups defined by different levels of exposure.
This study design enables population risks to be estimated. However, it may be necessary to
follow up a large cohort for a long time in order to achieve sufficient numbers of adverse
health occurrences, particularly for unusual conditions or those having a long latent period
between exposure and events.

Case-control studies

2.16   These studies compare the characteristics of a group of individuals with a particular
adverse health outcome (cases) against a group of healthy individuals (controls). Data on past
exposures to potential hazards and other characteristics are collected. The retrospective

nature of this study design may lead to inaccuracy and bias. Care is also needed in ascertainment of the cases and selection of an appropriate control group.

Intervention studies

2.17   In this type of study an intervention, for example a drug therapy, or in the case of adverse reactions to food, an elimination diet, is compared with one or more alternatives which can include no intervention or the administration of an inert material (a placebo). Random allocation of the different interventions is an essential element in studies of this type. In the area of adverse reactions to food, the DBPCFC is often used. In this design the response to a food challenge is compared with the response to placebo and the trial participants receive each in random order. This is the cornerstone of the diagnosis of adverse reactions to food and food ingredients. Although the DBPCFC design is crucial for sound studies, this is expensive to carry out in large populations. Additionally, compliance with such procedures may be poor in individuals with established and potentially severe reactions, for example those with certain allergic reactions (see Chapter 10). If previous reactions have been severe, e.g. anaphylaxis, then such challenges would not be ethical. These issues highlight the need for alternative markers for the diagnosis of adverse reactions.

2.18   Most of the evidence available to the Working Group came from case reports and descriptive epidemiology, although in some instances intervention studies were available. In assessing studies for evidence of causality, study designs were categorised as in Table 2.1, intervention studies being the most persuasive of causality.

Table 2.1: Types of evidence of causality

Type of study
Case reports and case series, descriptive studies
Analytical studies
Intervention studies

2.19   The Working Group was not asked to comment on the clinical management of adverse reactions, but this is given some consideration in relation to the recommendations.

Adverse reactions to food

2.20   The popular practice of calling all adverse reactions "allergies" is inaccurate and has created confusion both in the health professions and among the lay public. The term allergy, by definition, denotes an immunological reaction. Reproducible adverse reactions to foods may be mediated by immunological or by non-immunological mechanisms. Classifications for reactions based on these mechanisms have been developed. Although there are various similar classification systems in use, this report uses the categorisation and the definitions of the European Academy of Allergy and Clinical Immunology (EAACI), with the addition of an "unknown" category, see Figure 2.1.[2] Other classifications used and summarised in Appendix

2 include, in the UK, that adopted by the Royal College of Physicians of London and the British *Introduction* Nutrition Foundation in their report on food intolerance and food aversion[3] and, in the USA, that of the American Academy of Allergy and Clinical Immunology.[4]

2.21   In this classification, adverse reactions are divided into toxic and non-toxic reactions. Food aversion of psychological origin is not regarded as an adverse reaction to food for the purposes of this report.

2.22   Toxic reactions, which can affect any individual, are dose-related and are due to exposure to compounds which may be naturally-occurring or produced or acquired at any stage during food preparation. In making a differential diagnosis, it is important to distinguish toxic reactions from food allergy or food intolerance and, for this reason, some examples of toxic reactions are given in Table 2.2.

Figure 2.1: Classification of adverse reactions to foods
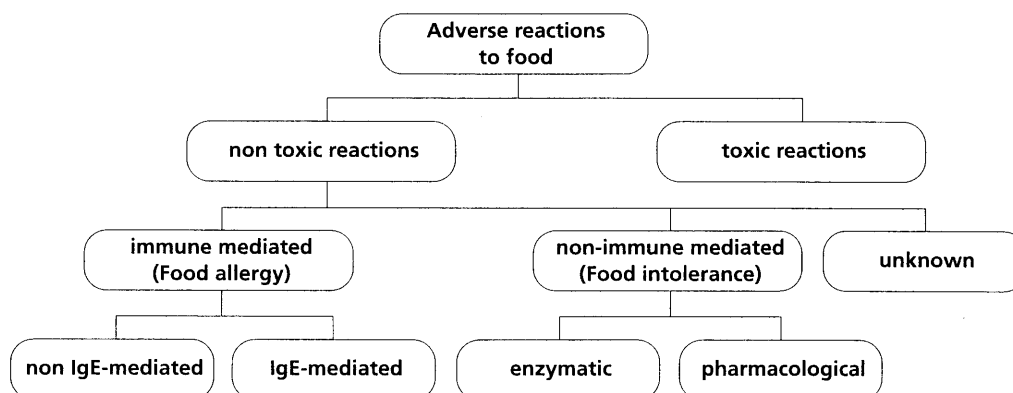
Adapted from Bruijnzeel-Koomen *et al*[2]

2.23   Some non-toxic adverse reactions to food are immunologically-mediated (food allergy). Others are believed not to be mediated via immunological mechanisms (non-immune-mediated; food intolerance) or are of unknown pathogenesis.

Immunologically-mediated reactions

2.24   These reactions are usually induced by proteins (see paragraph 9.12). The immune responses that result in adverse health effects are frequently classified into four main types, designated Types I to IV. Types I, II and III are antibody-mediated. Type I reactions are very rapidly induced and are mediated by IgE antibody. Types II and III reactions are effected by other antibody isotypes (usually IgG), take somewhat longer to develop and are associated, respectively, with direct damage to cells or the deposition of immune complexes. Finally, Type IV reactions are usually delayed, taking one or more days to develop, and T lymphocytes, rather than antibodies, are the important immunological vectors. Most allergic reactions to food are Type I but there is evidence that Type IV reactions are involved in delayed responses to certain foods (see Roitt[16]).

Table 2.2: Examples of naturally-occurring food toxicants

Toxicant		Some food sources	Possible effects	Reference
Cyanogenic glycosides		Kernels of almonds, apricots, cherries, peaches, plums. Cassava	Mental confusion; chronic; cassava has been linked with peripheral neuropathy	Wilson,[5] JECFA,[6] Meredith et al.,[7] Mori et al.[8]
Fungal toxins	Aflatoxins	Peanuts	Liver damage, cirrhosis and cancer	Wang et al.[9] Steyn & Stander[10]
	Trichothecenes	Wheat	Effects in the gut and bone marrow. Toxic alimentary aleukia	Wang et al.[9]
	Fumonisins	Maize	Oesophageal cancer	Wang et al.[9]
	Ochratoxin	Various grains	Nephropathies including Balkan endemic nephropathy	Wang et al.[9]
Glucosinolates		Brassicaceous vegetables	Goitre	Thomas[11]
Pyrrolizidine alkaloids		Comfrey	Liver cancer	Mori et al.[8]
Cycasine		Cycads	Has been causally linked with degenerative neurological disease	Kurland,[12] Mori et al.[8]
Solanine		Potatoes (raw) and related plants	Headache, CNS depression, vomiting	Ellenhorn et al.[13]
Sea food toxins	Histamine	Spoiled fish, especially scombroid fish	Flushing, headache	Slorach,[14] Wedin[15]
	Tetrodotoxin	Puffer fish	Neurotoxicity, often fatal	Wedin[15]
	Saxitoxins	Clams, oysters	Paralytic shellfish poisoning	Wedin[15]
	Domoic acid	Mussels	Memory loss	Wedin[15]

2.25 Immune responses and allergic reactions to proteins are dose-dependent phenomena. *Introduction*
Clinical allergy characteristically develops in two phases. In the first or induction phase a non-sensitised, but nevertheless susceptible, individual is exposed to amounts of the protein sufficient to induce an immune response of magnitude and quality necessary to result in allergic sensitisation. If the sensitised subject is exposed subsequently, *via* an appropriate route, to the same protein then an accelerated and more aggressive secondary immune response will be elicited, resulting in inflammation and the symptoms of allergic disease. Although confirmatory data are not always available, it is the case that for both the induction of allergic sensitisation and for the elicitation of allergic reactions, dose-response relationships exist. The corollary is that in both cases there also exist threshold levels of exposure below which induction or elicitation will fail to develop. There is good evidence that in many cases the level of exposure required for initial sensitisation of a susceptible individual is higher (and sometimes much higher) than that required to elicit an allergic reaction in a subject sensitised previously.

2.26 Food allergy describes the adverse health effects elicited when an individual ingests foods containing one or more proteins to which they have been sensitised. Although other mechanisms may be involved (such as cell-mediated immunity in the pathogenesis of coeliac disease associated with gluten sensitivity) food allergic reactions are most commonly effected by IgE antibodies. Briefly, the protein allergen cross-links specific IgE antibodies bound to mast cell membranes. This in turn causes the degranulation of mast cells and the release of preformed and newly synthesised mediators which together initiate the symptoms of food allergy (see sections 9.1-9.25). Such symptoms can be limited to the gastrointestinal tract (nausea and vomiting, abdominal pain and diarrhoea), the skin (acute urticaria, dermatitis), the respiratory tract (asthma) or, less frequently, may be severe, with systemic manifestations that can result in anaphylactic shock and death.[17]

2.27 In Western European children, 90% of IgE-mediated reactions are caused by cows' milk, wheat, hens' eggs, peanuts, tree nuts (walnuts, brazil nuts, hazel nuts) and soya protein. Four foods, peanuts, tree nuts, fish and shellfish, account for a similar proportion of reactions in adults.[1,17,18]

2.28 The prevalence of immune-mediated adverse reactions to food and food ingredients among children is greater than in adults (reaching approximately 5%) reflecting the fact that some types of childhood food allergies are relatively transient, resolving with time. There is some evidence that the prevalence of food allergy, particularly anaphylaxis, is increasing in developed countries.[19] In France the number of cases of food-induced anaphylaxis increased five-fold over a period of ten years.[20] This increase in reported occurrence may arise from improved diagnosis. However, the same temporal trend certainly applies to allergic rhinitis and asthma and is related to an increase in atopy, which is linked to an increase in serum IgE levels within communities.[21] It has been suggested that environmental factors, including exposure to pollutants in early life may play a role in the increasing prevalence of atopy.[22] However, evidence from studies in Germany has revealed a lower prevalence of atopic disease in the more heavily polluted former East Germany than in West Germany.[23] Interestingly, as standards of living have risen in the former East Germany so has the prevalence of hay fever[23a] and atopy was found to be more prevalent in those of higher social class. Different allergen

load and patterns of exposure may be important.[24] However, on a world-wide basis air pollution and asthma are not strongly correlated.[25] It should be noted that the data cited above relate to asthma and atopy in general and not specifically to food allergy. Nevertheless, such data are relevant because, as is discussed above, rising trends in food allergy may be part of a general increase in the prevalence of atopy in the population.

2.29　It is now considered likely that the way in which the responses of the developing immune system are programmed in neonates and infants is an important determinant of whether or not atopy develops. Indirect evidence suggests that increased protection of infants from viral and bacterial pathogens may cause their developing immune systems to acquire or to retain the characteristics necessary to mount the type of response required for allergic sensitisation.[26] For example the prevalence of atopy is lower in anthroposophic families, who avoid the use of antibiotics and immunisation, other than to tetanus and diphtheria, than in those following other lifestyles.[27]

Food intolerance

2.30　This term is applied to reproducible adverse reactions to foods caused by non-immunological mechanisms. They are idiosyncratic reactions caused by inherited or acquired defects in intestinal transport, digestive and absorptive processes or in the metabolism of some dietary components; pharmacological reactions arising from altered sensitivity to some food ingredients, and often, as yet unidentified mechanisms.

2.31　In some circumstances, food or food ingredients can directly trigger the release of histamine and related mediators from mast cells that are also released by the action of IgE in IgE-mediated food allergy. This is sometimes called pseudoallergy or an allergy-like reaction (see review by Smith[28]). Aspirin and other nonsteroidal anti-inflammatory drugs (e.g. indomethacin, ibuprofen), as well as probably the azo dyes (e.g. the food colour tartrazine), may mimic or potentiate allergic reactions. Thus, it is possible for similar clinical reactions to be caused by immunological and non-immunological mechanisms. Nonetheless, it is important to distinguish true food allergy from other forms of adverse reactions to food because individuals with food intolerance are often able to tolerate small quantities of the relevant food, whereas, for those with immunologically-mediated reactions, a more stringent exclusion of the precipitant from their diet is required. The term pseudoallergy has also been applied to situations in which patients or, in the case of children, their carers believe they react to food in the absence of objective evidence of allergy.[29]

2.32　Pharmacological food intolerance is exemplified by individuals who are abnormally reactive to substances present in some foods, such as the vasoactive amines.

2.33　An example of food intolerance arising from altered enzyme function is absence of the activity of the intestinal enzyme lactase, which breaks down lactose, the natural form of sugar in milk. In the absence of this enzyme in the intestine, lactose is not effectively digested (see paragraphs 9.45-9.46).

2.34　Behavioural problems in children have been attributed to metabolic or nutritional deficiencies or disturbances arising from foods and food ingredients. A variety of nutritional

disturbances has been suggested as being responsible for such behaviour, including   *Introduction*
deficiencies of zinc, essential fatty acids or certain vitamins in addition to adverse reactions
to food and food ingredients, particularly certain food additives.

Clinical features of adverse reactions to food

2.35   Many clinical features can arise from adverse reactions to foods and food ingredients
(Table 2.3). In some cases, adverse reactions may be manifested by symptoms and clinical
signs referable to a single organ system, usually the gastrointestinal tract, the respiratory tract
or the skin. Frequently more than one system is involved. Occasionally, systemic reactions,
such as anaphylaxis, may occur. The following chapters (3-8) deal with the clinical signs and
symptoms of adverse reactions to food and food ingredients.

Table 2.3:   Clinical features of adverse reactions to food and food ingredients

System affected		Clinical features that could be caused by adverse reactions
Skin		Urticaria
		Atopic dermatitis
		Angio-oedema*
Gastrointestinal tract	Oropharynx	Oral allergy syndrome:
		Burning, itching of the lips and mouth and, sometimes, the larynx and pharynx
	Remainder of gastrointestinal tract	Pain, colic
		Nausea
		Vomiting
		Change in stool habit, e.g. looseness, frequency
		Abdominal distension, flatulence
		Heartburn (gastro-oesophageal reflux)
Respiratory tract		Asthma
		Rhinitis
Eyes		Watering eyes
		Conjunctivitis
		Peri-ocular pruritus
Cardiovascular system		Symptoms and signs of hypo- or hypertension
Blood		Symptoms and signs of haemolytic anaemia
Central nervous system		Headache
		Abnormal behaviour (including ADHD)
		Fatigue
		Lassitude
Generalised systemic		Anaphylaxis

* Angio-oedema may also affect the lips and upper respiratory tract

3. Dermal symptoms of adverse reactions to foods

Urticaria and angio-oedema

3.1   Urticaria occurs in acute and chronic forms: acute urticaria being defined as lasting for less than 6 weeks, whereas chronic urticaria lasts for longer periods. In childhood, urticaria is more commonly of the acute type.[30]

Acute urticaria

3.2   Acute urticaria is more common than chronic urticaria. Symptoms generally occur within an hour of contact with, or ingestion of, the precipitant and often fade within 3 hours. Initially there are localised symptoms of itching and burning which progress to erythema and urticaria at the site of contact. Immune-mediated contact urticaria to foods is common and may progress to a more widespread urticaria, angio-oedema (in 50% of cases) and anaphylaxis.[31] Urticaria and angio-oedema occur in 15% of the population at sometime in their lives with an estimated prevalence of 0.05-0.1%.[32,33] Many of these are isolated incidents. Food was implicated as a cause of acute urticaria in 15% of 40 children with acute urticaria.[34] Most acute food-related urticarial reactions occur in atopic subjects. Many different food or food components may cause urticaria (see Table 3.1). Other foods that have been implicated as causing contact urticaria include fish and shellfish, fruits and vegetables, tree nuts, raw beef and chicken, see review by Wilkinson and Shaw.[35]

Table 3.1: Foods and food ingredients implicated as a cause of urticaria and angio-oedema

Food	% of patients who implicated the food item as a causative agent
Milk (cows')	5%
Eggs (hens')	5%
Fish	31%
Nuts (including peanuts)	12%
Non-citrus fruits	10%
Oranges	8%
Tomatoes	5%
Cheese	4%
Wheat	3%
Alcohol	3%
Meat	2%
Food additives (amaranth, Sunset yellow, carmoisine, tartrazine)	9%

Source: E Young, unpublished data; for details of the population studied see paragraph 3.4

Adverse reactions 3.3   In food allergic subjects urticarial wheals develop within minutes of the relevant food
to food and food protein touching the skin: for example, immediate lip swelling may occur in allergic subjects
ingredients on contact with peanuts or peanut butter or after merely being kissed by someone who has
recently eaten peanuts, cows' milk, or egg. Sometimes in severely allergic patients urticaria
may progress to the oral allergy syndrome or to anaphylaxis. This most commonly occurs in
people who are allergic to peanuts, tree nuts and shellfish.[1]

3.4   It is difficult to be sure of the prevalence of urticaria occurring as a response to
exposure to food. In a cross-sectional questionnaire survey of adverse reactions to food, 7500
randomly-selected households in High Wycombe (England) and 7500 households randomly-
selected throughout the UK were approached; 52.7% of households in High Wycombe and
41.6% of those elsewhere responded, comprising 10,522 individuals in High Wycombe and
8328 elsewhere. Of the latter, 6.2% claimed problems with urticaria and 6.3% with angio-
oedema; of these 49% claimed a reaction to foods, suggesting that true prevalence of food-
related urticaria has been underestimated in previous reports.[1]

3.5   Importantly, given the possible progression of urticaria to an anaphylactic episode,
some people were unaware of the potential severity of their reactions. Of those reacting to
peanuts or tree nuts, 61% reported oropharyngeal symptoms. These are potentially severe
because they can precede anaphylactic reactions (see Chapter 6). Thus, although people were
avoiding the precipitants which they had identified, they were placing themselves at risk by
not seeking medical and dietetic help on appropriate avoidance of allergens and by not
obtaining advice on emergency self-medication.[1,19,36]

3.6   Certain drugs, such as aspirin and other non-steroidal anti-inflammatory drugs, can, by
their action on the cyclo-oxygenase pathway of arachidonic acid metabolism, sometimes
exacerbate food-induced urticaria. Rarely, they may do so to the extent of precipitating an
anaphylactic reaction.[37] Vasoactive amines, including histamine, or histamine-releasing agents,
may cause or aggravate urticaria and, on occasion, the condition has been linked with
consumption of azo-dyes, such as tartrazine, and other food additives[38,39] and alcohol (see
paragraph 9.39).

Chronic urticaria

3.7   Early evidence suggested that the incidence of atopic disease was not increased in
patients with chronic urticaria,[40] but a questionnaire-based study of 330 such patients showed
that positive reactions could be induced by food additives in one-third of the subjects.[41] These
reactions, if reproducible, need not be due to food allergy and, in any case, they have not been
confirmed by subsequent studies. In an open challenge study of 94 children with chronic
urticaria 21% reported reactions to food but food was identified, by a combination of history,
skin prick test and elimination diet, as a precipitant in only two subjects.[42] Ortolani and
colleagues, in a review, concluded that IgE-mediated food allergy was demonstrable in only a
small proportion of patients with chronic urticaria.[43] Some individuals react to benzoic acid
(E210), tartrazine (E102) and sunset yellow (E110), as well as other additives (E211, 212, 213,
216, 218), see Appendix 4 and review by Greaves.[44]

Exercise-induced urticaria

3.8   Very rarely, urticaria and angio-oedema can be induced by taking exercise soon after eating a food, such as wheat, shellfish, nuts or celery, whereas neither the food nor exercise alone causes any reaction.[45] Increased ambient or body temperature may also exacerbate urticarial reactions to foods.[46,47]

Dermal symptoms of adverse reactions to foods

Atopic dermatitis

3.9   The prevalence of atopic dermatitis in the UK is increasing. Cohort studies have identified a prevalence of atopic dermatitis of 5.1% of those born in 1946, 7.3% of those born in 1958 and 12.2% of those born in 1970.[48] Another study showed a life time prevalence of atopic eczema of 20% in children aged 3-11 years,[49] however, there is a paucity of information on prevalence in adults. There is some evidence for higher prevalence in certain ethnic groups: for example, the prevalence in black Caribbean children born in the UK was 16.3% compared with 8.7% in white children[50] and was more common in Asians (17.3%) than non-Asians (4.1%) referred to hospital in Leicester.[51]

3.10   The role of food allergy in the aetiology of atopic dermatitis is unclear, because there may be many other factors contributing to the causation of the disease. Although serum concentrations of IgE are usually elevated, in up to 20% of cases they may be within the reference range.[52] However, reactions to food challenges can be demonstrated in a proportion of patients with atopic dermatitis[53] and atopic dermatitis may be exacerbated 24-48 hours after a food allergen is ingested.[54] Usually this is preceded by a reaction with erythema and pruritus occurring within 3 hours of ingestion and an exacerbation of the eczema within 1-2 days. More support for a role of food in atopic dermatitis is provided by the fact that positive immediate skin-test reactions to foods are commonly observed.[52]

3.11   The foods commonly implicated in the causation of atopic dermatitis are shown in Table 3.2 and, in addition to these, some food additives have been reported to aggravate the condition. Although the balance of the evidence is that natural constituents of food are responsible for most cases of food-induced or food-exacerbated atopic dermatitis, there is some evidence for a role of food additives in the disease. DBPCFC studies in 25 children with severe atopic dermatitis identified food additives (tartrazine, sodium benzoate, glutamate and metabisulfite), acetylsalicylic acid and tyramine as causing, within 10 minutes of challenge, pruritus and erythema in the skin of all six of those children challenged with food additives.[55]

3.12   Atopic dermatitis due to cows' milk protein affects up to 7.5% of infants.[56] Sometimes this might arise from exposure to cows' milk protein being excreted in breast milk. Exclusion of cows' milk from the diet of such infants, or that of the mother, would be of benefit.

3.13   Patients under three years of age, as they grow older, may lose atopic dermatitis due to food sensitivity. In one study 75 patients aged 3-18 years with atopic dermatitis and food reactions and who were on elimination diets underwent DBPCFC; after one year 19 had lost all signs of reactions to food; at two years, when 44 of the children with persistent adverse reactions to food were rechallenged, another four had lost their reactivity.[53] In particular,

atopic dermatitis due to cows' milk protein is a transient condition of early childhood and its incidence decreases by 80% before the age of 3 and by over 90% before school age.[56]

3.14 Older patients may have atopic dermatitis as a result of multiple allergies and other factors, therefore the dietary exclusion of single foods does not necessarily assist the management. The role of foods as precipitants of atopic dermatitis is less significant in adults than in children.

Table 3.2: Foods and food ingredients that have been implicated in the causation or exacerbation of atopic dermatitis

Food	References
Cows' milk	Bahna & Heiner,[56] Atherton,[52] Sampson,[17] Van Bever *et al.*,[55] Sampson & Scanlon,[53] Beyer *et al.*,[57] Burks *et al.*[58]
Hens' eggs	Atherton,[52] Sampson,[17] Van Bever *et al.*,[55] Sampson & Scanlon,[53] Beyer *et al.*,[57] Burks *et al.*[58]
Peanuts	Sampson,[17] Sampson & Scanlon,[53] DOH,[59] Burks *et al.*[58]
Tree nuts	Burks *et al.*[58]
Soya	Sampson,[17] Van Bever *et al.*,[55] Sampson & Scanlon,[53] Burks *et al.*[58]
Vegetables (green beans, pea)	Burks *et al.*[58]
Wheat	Sampson,[17] Van Bever *et al.*,[55] Sampson & Scanlon[53]
Fish (cod, catfish)	Sampson,[17] Burks *et al.*[58]
Meat (chicken, beef, pork)	Burks *et al.*[58]
Citrus fruits	Steinman & Potter[60]
Chocolate	Steinman & Potter[60]
Food additives (tartrazine, benzoate, glutamate, metabisulfite)	Van Bever *et al.*[55]

4. Gastrointestinal symptoms of adverse reactions to foods

4.1 The aetiology and symptomatology of adverse reactions affecting the gastrointestinal tract are various (see Table 2.3 above) and the mechanisms involved and the site of the reaction influence the time taken for symptoms and clinical signs to develop after eating the relevant food. Any part of the gastrointestinal tract can be involved and the clinical features may occur alone or together as part of a syndrome.

4.2 The role of foods and food ingredients as precipitants in certain diseases of the gastrointestinal tract, for example Irritable Bowel Syndrome (IBS), remains unresolved.[61] Moreover, the occasional beneficial response to food elimination in patients with IBS does not necessarily imply that particular foods play a role in the aetiology of the disease.

Vomiting and gastro-oesophageal reflux

4.3 Vomiting occurring alone or in combination with acute or chronic diarrhoea is a common feature of adverse reactions to food.[62,63] Vomiting results from irritation or inflammation of the mucosa of the stomach and oesophagus. The inflammatory response may cause bleeding, with blood in the vomit. Gastro-oesophageal reflux can occur as an adverse reaction to food, particularly in infants with allergic gastroenteropathy and an accompanying eosinophilic oesophagitis.[63-65] In infants, objective evidence of gastro-oesophageal reflux as measured by oesophageal pH monitoring can be detected soon after a cows' milk feed although features of an eosinophilic oesophagitis take longer to develop. In adults, drinking coffee and smoking may contribute to reflux by relaxing the gastro-oesophageal sphincter.[66,67] However, the role of adverse reactions to dietary components in the causation of gastro-oesophageal reflux has not been well-characterised.

Diarrhoea

4.4 The passage of frequent loose stools can result from impaired absorption of nutrients and water or from intestinal secretion of fluid as part of an inflammatory response, or from a combination of both.[64] Bacterial overgrowth syndromes and fermentative diarrhoea may arise from functional gastrointestinal disturbances caused by gastroenteritis and surgery (see also paragraph 4.21). Such syndromes are often self-limiting but may occasionally need treatment.

Abdominal pain, distension and flatulence

4.5 Abdominal pain, distension and flatulence sometimes occur, as isolated events, in many instances of adverse reactions to foods and are usually associated with impaired digestion and absorption resulting from damage to the functional integrity of the intestine.

Constipation

4.6   In the lower bowel, inflammatory responses to food may cause constipation. In 65 children (aged 11-72 months) with chronic constipation a double-blind crossover study showed that 68% of the children improved when their customary intake of cows' milk was replaced by soya milk. Many of those who responded had perianal lesions including fissures and chronic rectal inflammation. It was suggested that the resultant painful defaecation induced stool retention and constipation. Only 25% of the children had features of atopy, the majority had no such evidence.[68] The practical relevance of this report is apparent but the findings merit further evaluation because none of the children who benefited was on a strict cows' milk free diet. It needs to be established if the beneficial intervention was the reduction of cows' milk intake or the introduction of soya milk or both of these.

Specific syndromes

4.7   In addition to the clinical features given above, any of which may occur in isolation, there are specific syndromes in which adverse reactions to food or food intolerance may play a part. Some of the more important conditions are discussed below.

Oral allergy syndrome

4.8   Oral allergy syndrome is an IgE-mediated immediate Type 1 allergic reaction characterised by, within several minutes of contact with the food, an initial burning sensation and itching of the lip and oral mucosa, including the palate, followed by oedema. In some instances the clinical features can extend to the larynx and pharynx: laryngeal oedema may cause tightening of the throat, cough, hoarseness and wheezing. These oral effects are associated with rhinoconjunctivitis in about two-thirds of cases.[69] The oral allergy syndrome is frequently associated with relatively labile allergens within fresh fruit and raw vegetables (including peaches, apples, cherries, fennel and celery). There is a strong correlation between oral reactions to some of these foods and sensitisation to pollens.[70-72] However, the oral allergy syndrome is also associated with exposure of sensitised subjects to other foods, including tree nuts, peanuts, eggs, milk and fish.

Cheilitis and oral granulomatosis

4.9   A contact urticarial reaction affecting the skin around the lips can occur, particularly in children, after eating citrus fruits and foods containing benzoic acid. This is not thought to be immunologically mediated and might therefore be independent of the oral-allergy syndrome. More rarely the lips and the adjacent oral mucosa become inflamed and swollen, sometimes chronically as oral granulomatosis and related sensitivity reactions. Reactions such as this have been associated with cinnamic aldehyde as a flavouring agent in toothpastes[73] or chewing gums.[74] Some people with positive cutaneous reactions to spices such as cinnamon, cloves, balsam of Peru and Jamaica pepper may also develop oral and systemic reactions as well as skin reactions when they are exposed to these compounds used in foods, gums or toothpastes or as fragrances.[75-78] Similar reactions may occur to flavours such as L-carvone in mint oils.[79]

Enteropathies

4.10   The major feature of the enteropathies is a loss of the normal structure of the intestinal mucosa which reduces its mucosal digestive and absorptive function.[62,80] Enteropathies have been reported in response to gluten and proteins in other cereals (coeliac disease) and this is the best characterised enteropathy. In young children transient enteropathies to cows' milk, soya, eggs, rice, fish and chicken may occur. The immunological mechanism involved is described later (paragraph 9.26).

Coeliac disease

4.11   Coeliac disease is caused in susceptible subjects by exposure to gluten in wheat. It has a wide range of clinical presentations. The most severe cases may present with diarrhoea, dehydration and shock; less severely affected patients may present with a more insidious malabsorption with weight loss and, in children, failure to thrive. In some childhood cases impaired weight or height gain or delayed puberty are the only clinical evidence of illness.[81] Systematic investigation of older people with anaemia or short stature, or other evidence of under nutrition, has found that coeliac disease can occur without any gastrointestinal symptoms in about 30% of cases,[82] and features as diverse as defective dental enamel, neurological symptoms, mouth ulcers and joint symptoms are associated with the condition.[83,84]

4.12   Increased professional awareness and the availability of serological screening tests have enabled earlier detection of patients with asymptomatic or "silent" coeliac disease, the key diagnostic feature of which is the intestinal villus atrophy which responds to the exclusion of gluten from the diet. On this basis the reported prevalence of coeliac disease in different populations throughout Europe varies considerably, being 0.8% in Northern Ireland, 0.4% in Sweden and 0.3% in Finland.[81,85] These differences may be attributable to factors such as genetic differences or in dietary practice in the timing of introduction and composition of complementary feeds. An increasing incidence of coeliac disease in Sweden has been attributed to the large amount of gluten in the diet of infants in that country, particularly an increase in the content of gluten in proprietary baby foods.[85,86]

4.13   Patients with coeliac disease usually respond to dietary exclusion of gluten. Poor compliance with a gluten-free diet is associated with a deterioration in health and an increased risk of gastrointestinal, particularly small bowel, lymphoma and other malignancies.[87] This risk is higher in patients diagnosed at an older age. This may reflect the duration of dietary exposure to gluten. It is likely that a gluten-free diet reduces the risk of malignancy, but this has not been unequivocally established.

4.14   There have been reports of gluten-sensitive diarrhoea, without the histopathological and immunological abnormalities typical of coeliac disease.[88]

Dermatitis herpetiformis

4.15   Dermatitis herpetiformis is a papular-vesicular skin disease. In 75% of cases it is associated with an enteropathy which, with the skin lesions, responds well to a gluten-free diet. In the other cases the mucosal damage is less evident. The disease is regarded increasingly as a variant of coeliac disease and 24% of 398 adults with gluten-sensitive enteropathy were found to have dermatitis herpetiformis.[82]

Allergic eosinophilic gastroenteropathy

4.16   Allergic eosinophilic gastroenteropathy comprises a spectrum of conditions, which can occur at any age but which predominantly affect infants and young children, and in which there is eosinophilic inflammation of the gastrointestinal mucosa.[89] Any part of the gastrointestinal tract can be affected and the symptoms and signs reflect the site and extent of the damage. Loss of blood and exudation of serum into the intestinal lumen may result. Involvement of the stomach or oesophagus may present with vomiting. Damage to the small intestine and colon can cause significant loss of endogenous protein and nutrients as well as impaired digestion and absorption. Consequently the range of symptoms include dysphagia, bloody vomit, diarrhoea and impaired increase in both weight and height. In severe cases with protein-losing enteropathy, enterocolitis and a colitis which mimics inflammatory bowel disease may occur. Sometimes children present solely with an anaemia associated with an occult loss of blood in the stools. Some patients are atopic. Most cases present in the first three months of life and resolve spontaneously later, in early childhood.[65,89]

4.17   Eosinophilic gastroenteritis, colitis and proctocolitis can occur in an exclusively breast-fed infant. In such circumstances the mother would be advised in the first instance to adopt a milk exclusion diet.[90,91] However in a study of 95 such infants, 62 responded to maternal dietary elimination of cow's milk, 18 to elimination of egg and 6 and 3 to elimination of maize and soya respectively. Five required elimination from their mothers' diet of two of these protein sources and in 11 the precipitant was not identified. Four responded only to being put on an elimination diet of L-amino acids. All breast-fed infants were able to tolerate a normal diet after 1 year of age and follow-up for up to 10 years has demonstrated neither reoccurrence nor other sequelae.[92]

4.18   The causes and mechanisms of these conditions are not well understood. Some cases are associated with atopic clinical features, an increase in the number of eosinophils in their blood and with positive IgE RAST and skin prick tests to milk allergens, but others do not have these features.[65,93] In some cases without evidence of involvement of IgE-mediated mechanisms, there is evidence for the involvement of other immune mechanisms. Such cases of non-IgE-mediated reactions present similarly to those that are IgE-mediated. They are classified currently as food-protein-induced enterocolitis.[94] Such cases may represent a more severe form of food-induced enteropathy or proctocolitis or they may be a distinct entity mediated by T-cells.[95] These are rare diseases and it is thought that between a third and a half of cases may be caused by food allergy, most frequently to cows' milk or soya.[65,96]

4.19   Eosinophilic colitis can occur in an exclusively breast-fed infant,[97] in such circumstances the mother would be advised in the first instance to adopt a milk exclusion diet.[90,91] If this approach fails, other foods may need to be considered as causative agents (see paragraph 4.17).

Other gastrointestinal conditions in which the role of adverse reactions to food and food ingredients is unclear

Infant colic

4.20 Sometimes known as three-month colic, this is a common problem in babies. However, the actual prevalence is uncertain because the condition is often managed by the parents rather than by a health professional. Its aetiology is probably multifactorial; it is often attributed to adverse reactions to foods such as cows' milk or proteins excreted in maternal breast milk or to a disturbed maternal-infant interaction.[98] A study in babies and older children with allergy to cows' milk proven by challenge found that 75% reacted with colic during a challenge with capsules containing whey protein.[99] Sampson considered that 12-15% of colic was associated with food allergy or intolerance.[100] It has been suggested that bovine IgG in formulas and in maternal breast milk might be responsible for this relationship. However, possible mechanisms have not been fully investigated and the relationship of infant colic to cows' milk and other foods or food components which might be present in maternal breast milk or formulas needs further study. A recent systematic review concluded that infantile colic should initially be managed by reducing the stimulation which their carers might be giving the baby. If this is unsuccessful, then a one week therapeutic trial of cows' milk exclusion, for example using a hypoallergenic formula, might be undertaken.[101]

Irritable bowel syndrome

4.21 IBS is a diagnosis which should be considered in patients either with abdominal pain relieved by defaecation, or with a change in bowel habit, where there are no endoscopic, histopathological or other abnormal findings.[102,103] Intolerances to a variety of foods or food components, including wheat, milk, yeast and maize has been reported.[102,104] There is some evidence that increased colonic fermentation and greater than normal gas production may be involved in the pathogenesis or exacerbation of the symptoms.[105] There is also some evidence, in some cases, of mucosal inflammatory mechanisms involving mast cells, akin to those involved with immunological reactions.[106,107] Thus it is not clear that there is a single cause of IBS, that it is a single entity, or that adverse reactions to food are involved in the pathogenesis.

4.22 Randomised clinical trials to study possible precipitants and the cause of exacerbations in IBS are difficult to conduct and the problems of dealing with the high placebo response rate in this group of patients remains a problem for trial designers. In small, and poorly controlled, studies the elimination of foods, with or without additional oral treatment with sodium cromoglycate, has been effective in some patients.[61,108-110] However, other investigators variously have either failed to find a positive response to dietary manipulation, have found only a poor and non-specific response or have noted features of anxiety or depression in patients with IBS.[111,112] Some patients, particularly those with diarrhoea as their main symptom, may have a reduced pain threshold to normal intestinal distension.[113] Some patients with IBS have improved after starting a wheat free diet.[104]

5. Respiratory effects of adverse reactions to foods

5.1   Foods which have been reported to cause respiratory effects, including asthma and rhinitis, are listed in Table 5.1. Respiratory features are often associated with eczema, urticaria, oral allergy syndrome or other gastrointestinal symptoms.[114-117] However, it has been suggested that 20-40% of children and adults who present with respiratory symptoms have them as the only manifestation of food allergy.[118,119]

Bronchial asthma

5.2   In a study of 107 adults with perennial bronchial asthma, twenty-one of whom had a history of reactions to food, fifteen of the twenty-one (71%) developed bronchial responses to food challenges with a variety of foods.[135] Nevertheless, it is difficult to be sure how many patients with asthma have genuine food-related symptoms.[136]

5.3   In 20 patients who had a history suggestive of food-related asthma with a positive RAST or positive skin prick test or both, a food challenge produced asthma in six patients and other symptoms in five.[114] Studies in children[115,137] and patients of all ages[114] have suggested that 2-8.5% of asthmatics showed bronchospasm on food challenge. In a double-blind study, the condition of 9 out of 21 patients improved when consuming an "allergen-free" diet and none deteriorated.[138] Moreover, in a study of 279 children with a history of food-induced wheezing 24% had positive DBPCFC.[18] However, in another study 38 children with severe chronic asthma showed no evidence that food challenge exacerbated asthma, although the challenges induced other symptoms (abdominal pain, vomiting, and diarrhoea).[139] It is also noteworthy that food-induced respiratory symptoms were produced by DBPCFC in 205 children with atopic dermatitis.[123]

5.4   A questionnaire-based survey of 177 asthmatic children suggested that adverse reactions to food varied according to the season and severity of asthma at the time of ingestion.[140,141] A possible basis for such reactions is that in some patients food allergens may create a background bronchial hyper-reactivity which primes or exacerbates the response to other precipitants of asthma. Thus, although allergens such as egg, milk, soya, wheat or fish identified on the basis of clinical history and positive skin prick test might not in themselves cause symptoms, their elimination from the patient's diet might nonetheless improve the symptoms and the response to standard pharmaceutical agents in some cases.[142]

5.5   It is worth noting that there have been occasional reports of respiratory reactions in people with mite allergies due to contamination of wheat flour with mites.[143] Allergic reactions to honey can be attributed to pollen proteins or to proteins present in the salivary and pharyngeal secretions of bees.[144,145]

Table 5.1: Examples of foods and food ingredients reported to be associated with respiratory symptoms

Food		Examples	References
Milk		Cows'	Heiner & Sears,[120] Lee et al.,[121] Shi & Yang,[122] Bock,[18] Sampson & James,[123] Bernaola et al.,[123a] Oehling et al.[119]
Eggs		Hens'	Hoigné & Scheerer,[124] Sampson & James,[123] Oehling et al.,[119] Bock[18]
Nuts	Tree nuts	Almonds Walnuts Pecan nuts	Hoigné & Scheerer,[124] Shi & Yang,[122] Bock,[18] Sampson & James[123]
	Legumes	Peanuts	Bock,[18] García Ortiz et al.,[125] see also DOH[59]
Seeds		Sesame Sunflower	Shi & Yang[122] Axelsson[126]
Fruit		Apples, apricots, avocados, banana, peaches, pears	Shi & Yang,[122] Blanco et al.,[127] Savonius & Kanerva[128]
Vegetables		Broad beans (fava), chickpeas, green beans (haricot), lentils, peas, soya, Swiss chard	Shi & Yang,[122] García Ortiz et al.,[125] Parra et al.,[129] Bock,[118] Martin et al.[130]
Sea food		Sea fish, shellfish (lobster, shrimp)	Shi & Yang[122] Lemiére et al.[131]
Meat		Beef, mutton, pork, turkey	Shi & Yang,[122] Bock[118]
Cereals		Wheat	Bock[118]
Other food items		Snails	Oehling et al.[119]
Food additives and contaminants		Metabisulfites	Stevenson & Simon,[132] Timberlake et al.[133]
		Monosodium glutamate (MSG)	Allen & Baker[134]

Rhinitis and conjunctivitis (hay fever)

5.6   Rhinitis, with or without conjunctivitis, has been reported in connection with the intake of specific food items, although usually less frequently than asthmatic symptoms.[119,136] Symptoms suggestive of rhinitis were reported in 13% of 206 infants with cows' milk allergy.[146] Some authors have recorded symptoms of rhinitis and conjunctivitis in response to food challenges. Thus, open food challenges of 107 adult patients with asthma caused immediate nasal obstruction in 6% and conjunctivitis in 2% of the patients[135] and open food challenges and DBPCFC on 25 adults with a history of adverse reactions to foods induced rhinitis in four, while none had conjunctivitis on open food challenge and none had rhinitis or conjunctivitis on double-blind food challenge (DBFC).[147,148] Precipitants include cows' milk, peanuts, shellfish and eggs (see Table 5.2).

Table 5.2: Examples of precipitants of rhinitis or conjunctivitis as adverse reactions to food and food ingredients

Precipitant	Reference
Cows' milk	Clein,[146] Bahna & Heiner [56]
Hens' egg	Novembre et al.[115]
Peanut	Atkins et al.[148]
Tree nuts (type not stated)	Oehling et al.[119]
Shrimp	Atkins et al.[148]
Crab	Atkins et al.[148]

Serous otitis media

5.7   Serous otitis media has been reported as an adverse reaction to food, but the relationship is unclear.[149,150] It has been claimed that serous otitis media improves after elimination diets and that recurrence occurs after open food challenge with the relevant food.[151] The foods involved most frequently were cows' milk, wheat and egg white. These authors concluded that food allergy should be considered in all cases of recurrent serous otitis media, but the Working Group found no evidence of a report of a DBPCFC to substantiate this opinion.

Food-induced pulmonary haemosiderosis (Heiner's syndrome)

5.8   This is a very rare multisystem syndrome in children in which there are recurring episodes of pulmonary inflammation with infiltrates of haemosiderin-laden macrophages, peripheral eosinophilia, gastrointestinal blood loss, iron-deficiency anaemia and failure to thrive. The patients have IgG antibodies to cows' milk.[120,152] Reactivity to egg and pork have also been reported.[121] However, the immunological basis of this syndrome is not fully understood.[153,154] The identification of precipitating antibodies to cows' milk (or other allergens involved) may be useful in making the diagnosis. The resolution of symptoms follows the elimination of relevant food proteins.

6. Anaphylaxis

6.1   Anaphylaxis is an acute, potentially life-threatening and sometimes fatal condition, involving the cardiovascular system, the respiratory tract, the mouth and pharynx and the skin, singly or in combination.[123,155,156] The initial symptoms often involve the oropharynx and may include oedema and pruritus of the lips, oral mucosa and pharynx. Effects on the skin include erythema, urticaria and angio-oedema, while vomiting and diarrhoea sometimes occur. Cardiovascular collapse and severe hypotension may ensue, progressing to shock and cardiac arrhythmia. Respiratory symptoms include bronchospasm, cough, stridor, dyspnoea and wheezing. Laryngeal oedema produces cough, dysphonia or dysphagia. Airway obstruction may lead to asphyxia. The symptoms, their sequence and their severity vary from one episode to another and from one individual to another. In some cases the initial manifestation of rapid anaphylaxis may be loss of consciousness. In fatal food-induced anaphylaxis, initial symptoms commonly developed within 3 to 30 minutes and severe respiratory symptoms within 20 to 150 minutes of exposure.[123] A register of all fatal anaphylactic reactions in England and Wales since 1992 suggests there are about 20 deaths annually and that many, possibly most, deaths are due to respiratory arrest rather than cardiovascular shock. About 30% of these reactions are due to foods.[157,158] Many anaphylactic reactions are deceptively mild at their start and, at that time, the potential severity of the reaction too often is underestimated.[19]

6.2   Anaphylaxis is associated with IgE-mediated allergy and the peanut is the most common foodstuff reported to cause the condition in Europe, including the UK[159] (see also SCOOP, unpublished data). Numerous other foods and food ingredients have been associated with anaphylaxis (Table 6.1).

6.3   The precise incidence of anaphylaxis is not known[160,161] (see also SCOOP, unpublished data), but deaths from food induced anaphylaxis are increasing.[19,123,162] This might arise from the use of milk and peanut protein additives in foods and individuals' lack of awareness of this. Food allergy is amongst the most common causes of anaphylaxis,[19] others being bee and wasp stings and drug allergy.[163] There is an increased risk of anaphylaxis occurring in atopic patients with asthma.[72,123,147,148,156]

6.4   Unfortunately there is no national register for this condition and, although in the most recent International Classification of Diseases[164] there is now a code for food-induced anaphylaxis, it is not being used consistently (SCOOP, unpublished data).

6.5   Sometimes anaphylaxis can be provoked if exercise is taken within 24 hours of eating a specific allergen. In this syndrome neither eating the food nor exercise alone cause the reaction independently.[45,47,165-168] Similarly, aspirin and related compounds can exacerbate allergic reactions such as urticaria and cause them to progress to anaphylaxis.[37]

Table 6.1: Examples of precipitants of anaphylaxis

Precipitant	Reference
Peanuts (Legumes)	Gerrard & Perelmutter,[169] Hourihane *et al.*,[159] DOH [59]
Other legumes, e.g. white bean	Yokum & Kahn,[161] Fernández-Anaya *et al.*[170]
Tree nuts (hazelnut, walnut, black walnut, brazil nut, pecan nut, cashew nut)	Stricker *et al.*,[171] Yokum & Kahn[161]
Fish	Golbert *et al.*[172]
Shellfish	Stricker *et al.*,[171] Bock[173]
Cows' milk	Hill *et al.*,[63] Yokum & Kahn,[161] Gerrard & Perelmutter[169]
Hens' eggs	Gerrard & Perelmutter,[169] Yokum & Kahn[161]
Wine	Clayton & Busse[174]
Beer	Fernández-Anaya *et al.*[170]
Banana	Savonius *et al.*[128]
Prunus spp. (cherry, peach, almond)	Bousquet *et al.*[175]
Tomato	Bock[173]
Wheat	Bousquet *et al.*[175]
Oats	Bousquet *et al.*[175]
Millet	Bousquet *et al.*[175]
Seeds (sesame, sunflower)	Axelsson *et al.*,[126] Bousquet *et al.*[175]
Celery	Bousquet *et al.*[175]
Avocado	Blanco *et al.*[127]
	Bousquet *et al.*[175]
Food additives (sulfites)	Prenner & Stevens[176]
Mites (*Dermatophagoides, Thyreophagus* spp in flour)	Blanco *et al.*[143]

7. Effects of adverse reactions to foods on the central nervous system and behaviour

Headache and migraine headache

7.1 Headache is very common and, as in most instances individuals do not seek medical advice, it is difficult to arrive at prevalence rates. The prevalence rates for "migraine" headache (as defined by the International Headache Society, see Table 7.1) or other severe headache are all in a similar range: about 2-9% for males and 4-20% for females.[177-183] In a retrospective study of 847,453 Georgia Medicaid recipients the prevalence of confirmed migraine headache was 1.4% for females, 0.5% for males: after adjustment for factors such as age and race, it was reckoned that the prevalence in the USA was 1.3% for males and 3.8% for females.[183a]

Table 7.1: Classification of migraine headache and tension headache according to the International Headache Society

Classification number	Type of headache
1	Migraine
1.1	Migraine without aura
1.2	Migraine with aura
1.3-1.6	Other migrainous disorders
1.7	Migrainous disorders fulfilling all criteria except one
2	Tension-type headache
2.1	Episodic tension-type headache
2.2	Chronic tension-type headache
2.3	Headache of the tension-type fulfilling all criteria except one

Adapted from Iversen *et al.*[184] and Göbel *et al.*[185]

7.2 There are many types and causes of headaches which, though they are difficult to distinguish, need to be characterised in any discussion of mechanisms and management. Diet is considered by many doctors, as well as patients, to be one of the many factors that can trigger migraine headache and other types of headache and, as a consequence, dietary interventions are widely used and recommended by specialists in the treatment of headache (e.g. Diamond *et al.*[186]). The causal mechanisms are not clear but it is generally agreed amongst practitioners that a group of patients may have migraine headache after ingesting certain foods containing substances with vasoactive properties. The problem is that a large range of factors is associated with the causation of migraine headache[187] and research evaluations of dietary exclusion are sparse.

7.3 Those who suffer with headache often ascribe their symptoms to adverse reactions to food. Of 429 consecutive patients with migraine headache, 16.6% reported that headaches could be precipitated by at least two foods out of cheese, chocolate and citrus fruits.

Additionally, 18.4% reported reactions to all alcoholic drinks, while another 11.8% were sensitive to red wine but not to white wine and 28% reported that beer would precipitate headaches. Individuals who reacted to cheese and chocolate often reacted to red wine and beer but there was no significant relationship between self-reported reactions to diet and those to alcohol in general.[188] In contrast, none of 40 patients with tension headache reported a reaction to food and only one of these was sensitive to alcoholic drinks. The prevalence of sensitivity to cheese and chocolate among 46 patients with some features of migraine headache was intermediate between the prevalence in the migraine and tension headache categories. It was concluded that headaches induced by cheese, chocolate and red wine have causal mechanisms which are more related to migraine headache than to chronic tension headache, and that separate mechanisms contribute to headaches induced by alcoholic drinks in general.[188]

7.4   Patients can keep food and symptom diaries which may provide subjective evidence of foods associated with headache.[189] However, perceptions of medical problems such as headache and associated phenomena, e.g. fatigue, nasal congestion and sinus problems, and abdominal pain are subjective. Ideally, objective criteria would be desirable both for diagnosis and to facilitate management. For example, 38 patients with a history of diet-induced migraine headache were studied, with recording of clinical responses and electroencephalography (EEG) whilst resting, and in response to light stimulation and to hyperventilation. Fasting tests and challenges with chocolate, red wine and cheese were performed randomly over several days after initial baseline recordings. Lateralised headache occurred in sixteen subjects (42%), four of whom also had scintillating scotomata. An EEG abnormality on light stimulation occurred in all 16 individuals who developed headache, compared with 64% of 22 patients who did not.[190] This approach is insufficiently specific to be predictive. However, the absence of predictive tests does not mean that DBPCFC challenges and therapeutic trials of dietary elimination should not be considered in such patients.

7.5   To make significant evidence-based progress in the study of headaches induced by food, methodologies for investigation and for therapeutic trials need to be developed in the light of the following problems:

●   the heterogeneity of migraine headache and its symptomatology,

●   the distinct aetiological subtypes of headache syndromes,

●   the fact that some migraine headache subtypes are sensitive to certain precipitants, others are part of a more generalised constitutional disorder, and some are accompanied by a higher prevalence of migraine headache among family members,

●   the relationship between specific biochemical markers and traits (such as monoamine oxidase deficiency and tyramine sensitivity) claimed in some people with headache.

7.6   Moreover, co-precipitants of headache and migraine headache, and clinical characteristics such as age at onset and gender need to be considered, while a more precise, reliable, and practically useful definition of migraine headache is needed, to enable results to be compared between studies. This is necessary in order to understand the relationship between risk factors and migraine headache subtypes and to understand properly any associations identified in selected clinical populations. A reliable and standardised definition of the disease would improve understanding of the epidemiology of migraine headache.

Effects of adverse reactions to foods on the central nervous system and behaviour

7.7   Assessment of the possible role of adverse reactions to food and food additives in migraine headache has been difficult for some of the same reasons noted below in relation to behavioural reactions. In a controlled provocation trial, involving 88 children with severe frequent migraine headache referred to a specialist centre, 93% recovered on oligoantigenic diets; sequential reintroduction of foods and subsequent DBFC in 40 of the children identified causative foods.[191] Most patients responded to elimination of several foods: cows' milk caused symptoms in most of the children and many deteriorated when egg, chocolate, orange and wheat were reintroduced into the diet.

7.8   Associated symptoms which the children had, including abdominal pain, behavioural disorders, fits, asthma, and eczema, also improved with the elimination diet. Furthermore, dietary exclusions ameliorated the provocation of migraine headache by non-specific factors, such as blows to the head, exercise and flashing lights, suggesting some background food-induced predisposition. However, the degree to which these data can be generalised to the migrainous population is limited because only this highly selected group of subjects was investigated and because of the great difficulty of ensuring that the patients were truly 'blind' to the food challenges being given.

7.9   An open challenge study of 60 adult patients with migraine headache has been reported. They completed a period on elimination diets after a 5-day period of withdrawal from their normal diet and then tested themselves for reactions to common foods.[192] The commonest foods causing reactions were wheat, oranges, eggs, tea, coffee, chocolate, milk and beef. When the foods causing reactions were eliminated, there was a fall in the number of headaches per month, 85% of patients becoming headache-free.

7.10   The causation of migraine headache attacks by a range of foods was evaluated in adults with recurrent migraine headache.[193] The subjects were skin tested with a battery of 83 foods and were put on a diet eliminating those foods for one month or, if no skin test was positive, were put on a diet free of milk, egg, maize and wheat. Of the 43 subjects, 13 experienced a 66% or greater reduction in headache frequency. Eleven of sixteen subjects with positive skin prick tests responded to dietary manipulation, whereas only two of 27 subjects who were skin prick test negative responded. Thus, a positive skin prick test was predictive of response to dietary manipulation in about two thirds of the subjects. DBPCFC with a food or foods found to produce positive skin tests provoked migraine headache in five of seven subjects. In three subjects, plasma histamine rose during migraine headache-provoking challenges. The Working Group found no evidence that this potentially important finding had been confirmed by other workers.

7.11   It is difficult to draw an overall conclusion from these studies, as the foods that have been implicated in migraine headache have been so varied. It remains probable that at least a proportion of migraine headache attacks in some sufferers are provoked by food. It is also probable that the mechanisms vary, so the different precipitants will be considered separately below. In addition, it is noteworthy that natural foods are much more frequently incriminated as causative agents than are additives such as tartrazine and nitrate.

Chocolate

7.12   Chocolate is very widely blamed by patients for causing migraine headache as well as headaches of other types. In a DBPCFC study of headache using chocolate as the active agent and carob as a placebo in 63 women with headache (50% migraine, 37.5% tension-type, 12.5% combined migraine and tension-type), two weeks after starting dietary exclusion of vasoactive amine-rich foods, chocolate was not significantly more likely to provoke headache than was carob in all of the headache diagnostic groups.[194] This result was independent of the subject's perception of the role of chocolate in the instigation of headache. Also, the concomitant consumption of other vasoactive amine-containing foods was not associated with chocolate acting as a headache trigger. Thus this study suggests that there is doubt about whether chocolate can play a major role in triggering headaches for most individuals. However, it is difficult to identify sensitive individuals and it remains possible that a more selected subgroup might show an adverse effect.

Alcoholic drinks

7.13   Many migraine headache sufferers believe that their attacks are provoked by alcoholic beverages and studies have shown that a proportion of patients do react to such drinks (see also paragraph 7.3).[188] If alcoholic drinks can provoke migraine headache a significant but unknown number would benefit from their exclusion. The question then arises of whether the provoking agent is alcohol, in which case all alcoholic drinks should be avoided, or whether some other constituents are responsible (see paragraph 7.3). In a study of 19 subjects who thought that their attacks of migraine headache were provoked by red wine but not other alcoholic drinks, red wine provoked a typical migraine headache attack in 9 out of 11 patients, whereas none of the 8 challenged with vodka had an attack. Neither red wine nor vodka provoked such episodes in other migrainous subjects or controls.[195] The wine used in the study had a low tyramine content. The authors speculated that the phenolic flavonoid content of the wine might be responsible for the migraine headache attacks. Another possibility is that the connection between wine and headache may be mediated by histamine (see paragraph 7.14).

Foods containing vasoactive amines

7.14   Vasoactive amines such as histamine, tyramine and β-phenylethylamine have long been suspected of causing headaches. In an open trial in one hundred patients with adverse reactions to food including headache, a histamine-free diet, avoiding fish, cheese, hard-cured sausage, sauerkraut, wine and beer for four weeks produced improvement in 57 patients, 15 of whom "had total remission", 64% of those with headache were described as improved.[196]

It has been suggested that headache could be induced by histamine in wine in patients suffering from histamine intolerance and that a histamine-free diet was the treatment of choice for histamine-associated chronic headache.[197] However, the application of rigorous trial methodology and detailed metabolic studies have not demonstrated the value of this treatment. Tyramine has been suggested as an aetiological factor in migraine headache.[198] The complicated basis of such findings is suggested by the demonstration that, in a study in which tyramine sulfoconjugation was measured following an oral tyramine load in 30 patients suffering from migraine headache and 14 individuals not regularly suffering from headache, reduced tyramine sulfoconjugation compared with the reference group was found in those patients with a history of major depressive disorder.[199] When the patients with a history of major depression were removed from the analysis, no differences were found between diet-sensitive and non-diet-sensitive migraine headache patients and controls.

Effects of adverse reactions to foods on the central nervous system and behaviour

Coffee and other caffeine-containing drinks

7.15 Not only can the consumption of a food or drink cause adverse effects; it is also possible that ceasing to consume something taken habitually can cause ill-effect. Thus, the excessive consumption of coffee has been reported to cause unpleasant effects akin to anxiety, while those who stop consuming caffeine-containing beverages often report equally unpleasant "withdrawal" effects, which frequently include headaches.[200] In a study of 62 normal adults whose daily intake of caffeine was low to moderate (mean 235 mg, approximately equivalent to 2.5 cups of coffee), the subjects completed questionnaires about symptoms and tests of their mood and performance when consuming their normal diets (baseline period) and at the end of each of two 2-day periods during which they consumed caffeine-free diets and, under double-blind conditions, received capsules containing placebo (placebo period) or caffeine (caffeine period) in amounts equal to their daily caffeine consumption.[201] More subjects had abnormally high depression and anxiety scores, low vigour scores and high fatigue scores on the Profile of Mood States, and moderate or severe headache (52%) during the placebo period than during either the baseline period or the caffeine period. More subjects reported unauthorised use of medications during the placebo period (13%) than during the caffeine period. Performance of a tapping task was slower during the placebo period than during the baseline and caffeine periods. There are therefore some grounds for suggesting that those who regularly consume even low or moderate amounts of caffeine may have a withdrawal syndrome if their daily consumption of caffeine ceases.

Monosodium glutamate

7.16 "Chinese restaurant syndrome" was first described in 1968.[202] It was reported as comprising a sensation of burning, warmth, pressure and tingling confined to the face, neck, upper chest and shoulders after eating certain foods. Monosodium glutamate (MSG) was described as an established headache trigger by Scopp[203] but the evidence for this is based on case studies in which the elimination of all food sources of MSG resulted in decreased headache frequency, rather than upon controlled challenge studies. Although still widely reported, the notion of a specific pattern of gastrointestinal and systemic disorders after ingestion of MSG has not been confirmed in a variety of trials, including a DBPCFC study of six subjects who believed themselves to react adversely to MSG.[204] However, a DBPCFC study

Adverse reactions to food and food ingredients

by Yang and colleagues showed headache, numbness, weakness and flushing more frequently after MSG than after the placebo.[205] In both of these studies the challenge doses of MSG used were high (1.25-6 g) compared with usual daily intakes (up to 0.5 g). The weight of evidence does not suggest that MSG in food is likely to be the cause of adverse reactions in the general population. The Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) undertook an evaluation of the toxicity of glutamate salts, including MSG, and declined to assign an acceptable daily intake on the grounds of the low toxicity of this group of compounds [206] (see report by FASEB [207]).

Tryptophan and foods containing tryptophan

7.17 In a study of ten women with recurrent migraine-like headaches, flushing, urticaria and itching, who were put on a protein/tryptophan reduced diet, the migraine-like symptoms and skin manifestations were reduced, compared to when the subjects were on a normal diet.[208] The authors demonstrated impaired uptake of 5-hydroxytryptamine (5-HT) by platelets in the patients when they were on a normal diet. They speculated that impairment of 5-HT uptake was involved in the pathogenesis of migraine headache. It should be noted that L-tryptophan, an essential amino acid, is used as a food supplement and, somewhat in contradiction to the above, dietary supplementation with tryptophan has been suggested for chronic pain management of all types,[209] oral L-tryptophan administration decreasing the perception of pain and appearing to act synergistically with the enkephalins and endorphins. In the UK, because of concerns about the association of eosinophilia-myalgia syndrome[210] with some preparations of L-tryptophan, there are regulations prohibiting the addition of tryptophan to foods intended for human consumption.[211] The use of tryptophan for particular nutritional purposes is currently under discussion by member states of the EU.

Metabolic factors and headache

Sucrose

7.18 Patients with diabetes mellitus sometimes suffer headache during reactive hypoglycaemia and after hypoglycaemic attacks. Therefore it is not surprising that a link between carbohydrate metabolism and headache has been sought. In one study, 74 patients who associated their attacks with the mid-morning or mid-afternoon fasting state underwent a 5-hour glucose tolerance test. Six of the subjects were classified as diabetic, while 56 patients exhibited tests that were consistent with reactive hypoglycaemia. A sucrose-restricted diet brought about some degree of improvement in nearly all the patients with reactive hypoglycaemia.[212] However, this does not mean that such a diet would relieve headache in normal subjects. Nevertheless, in clinical practice, a low-sucrose diet is often recommended for headache but only marginal differences in severity and frequency can be ascribed to such a diet in open trial.

Other factors

7.19 Other metabolic factors have been considered in relation to headache, including migraine headache: Glover and co-workers[213] reviewed endogenous factors, such as phenolsulfotransferase and monoamine oxidase activity and β-phenylethylamine intake, that might be involved in dietary migraine headache. Phenolsulfotransferase activity can be inhibited by a range of dietary constituents, including red wine, and it has been suggested that individuals with low levels of activity of the enzyme may have an increased risk of headache. These effects could include the absorption of toxic phenolic compounds in the food that would normally be broken down by the enzyme. The Working Group could find no evidence that these findings have been replicated.

Evidence of reactions to food or nutrient deficiencies in adults and juveniles with mental disorders

Adults

7.20 Mental illness in adults can be associated with dietary deficiencies. The role of poor nutrition, institutional diets, alcohol abuse and poverty all make it likely that deficiencies often result from mental illness rather than vice versa, although a deficiency will still have harmful effects, including those on mental function. Deficiencies are still reported in spite of advances in the care of the mentally ill. For example, the average plasma vitamin C concentration was lower in 885 psychiatric inpatients (0.51 mg/100 ml) than in a reference group of 110 individuals (0.87 mg/100 ml).[214] Few patients had values as low as those found in clinical scurvy (less than 0.1 mg/100 ml), but 32% had concentrations below the threshold (0.35 mg/100 ml) at which some detrimental effects on health have been reported. Clinically evident deficiencies of other vitamins have also been described. Thus, three patients with Wernicke's encephalopathy and three with wet beri-beri, all accompanied by gross thiamine deficiency, were found during normal psychiatric practice in England.[215] These authors reported two surveys of newly-admitted psychiatric patients in which evidence of thiamine deficiency, with or without minimal clinical manifestations, was found. In the first survey, 38% of patients had biochemical evidence of thiamine deficiency. In the second survey, evidence for deficiency of B group vitamins in addition to thiamine was sought: 30% had evidence of thiamine deficiency, 27% of riboflavin deficiency and 10% of pyridoxine deficiency. Overall, three out of 326 patients surveyed had gross clinical deficiency. Deficiency states can thus both cause psychiatric conditions such as Wernicke's encephalopathy and can also be a secondary feature in mental illness.

7.21 Folic acid deficiency may have a role in the genesis of psychiatric disorders.[216] Folic acid deficiency causes a lowering of brain serotonin in rats, and of cerebrospinal fluid 5-hydroxyindoleacetic acid in humans. Some studies have demonstrated folate deficiency in depression, and there are indications in the literature that some depressed patients who are folate deficient respond to folate administration (see review by Fava *et al.*[217]). Folate deficiency is known to lower levels of *S*-adenosylmethionine which, by raising brain serotonin concentrations, acts as an antidepressant. These data suggest that low levels of serotonin in some depressed patients may be a secondary consequence of low levels of

S-adenosylmethionine. This is not especially controversial, and testing for nutritional deficiencies in high-risk groups is a part of psychiatric practice. Although the exact numbers of cases are not known, surveys suggest that they would account for a small proportion (though obviously an important one) of mental illness, see review by Alpert and Fava.[218] The Committee on the Medical Aspects of Food and Nutrition Policy has recently reviewed the effects of nutritional deficiencies and altered metabolism of folic acid on mental function.[219] Thus, although dietary deficiencies are known to be associated with mental illness, it is probable that the deficiencies that have been observed in psychiatric in-patients result from mental illness rather than vice versa.

Juveniles

7.22 Specific nutritional deficiencies can be caused by a poor diet. It has been hypothesised that poor diet, with a lack of vitamins and minerals or an excess of sugar or a combination of these, might be responsible for delinquent behaviour. Because poor diet can also result from the social adversity known to be associated with offending, studies involving dietary manipulation are most likely to yield results relevant to this hypothesis. In studies such as these, rigorous scientific methodology is needed to ascertain whether changes in the outcomes measured are due to the changes in diet or to other confounding factors which include:

- improvement as a result of all the other interventions that the institution may provide,

- the psychological effects of receiving any intervention,

- selection of a low-risk group for the diet,

- increased adherence to diet by lower-risk subjects.

7.23 The literature on nutritional changes in delinquent youngsters and criminal adults gives much less guidance for clinical practice and is more controversial. The evidence is largely confined to the work of Schoenthaler and his colleagues.[220-227] They have described the results of dietary intervention in a number of institutions for young offenders. Large numbers of young people have been treated in this way and the reports have described decreases, sometimes very large ones, in the frequency of disciplinary infractions in the institutions after the intervention. Interventions used frequently involve diets with reduced sucrose content, elimination of "junk food", vitamin supplementation or a combination of these. Interpretation of the work is difficult because the reports have not supplied the detail required for full scientific evaluation (see Table 7.2), and the scientific requirements outlined in paragraph 7.22 are not met. Moreover, a recent study, albeit questionnaire-based, has found no significant difference in diet between 100 young offenders and 100 matched non-offenders.[228] Accordingly, despite the large numbers involved, it has not been possible to draw conclusions on the validity of the hypothesis. For these reasons we consider that further research is needed before the conclusions of those carrying out the work can be scientifically accepted. It is nevertheless feasible that food and food additives might have pharmacological effects and

that deficiencies of vitamins and other nutrients might influence behaviour. The evidence does not support claims that reactive hypoglycaemia is an important factor in behaviour disturbance, see paragraph 7.18 above.[226,229] Moreover, Wolraich and colleagues[230] who compared children on diets high in sucrose, without artificial sweeteners, with children on diets low in sucrose, but containing aspartame or saccharin found little difference between the groups.

Effects of adverse reactions to foods on the central nervous system and behaviour

Hyperactivity and attention deficit-hyperactivity disorder

7.24   Attention deficit-hyperactivity disorder (ADHD) is a psychiatric disorder, affecting more than 1% of children and perhaps as many as 5% – estimates of prevalence vary according to the exact definition that is used. It is not a disorder with a single cause, but a specific behaviour pattern that may have many causes. The key diagnostic features are summarised below:[231,232]

- **Inattentiveness** – very short attention span, over-frequent changes of activity, distractible,

- **Overactivity** – excessive movements, especially in situations expecting calm such as in the classroom or at mealtimes,

- **Impulsiveness** – will not wait his/her turn, acts without thinking, thoughtless rule-breaking.

7.25   There is a variety of other problems which, although not necessarily due to ADHD, may be associated with it:

- Disorders of executive function, including planning and organisation of cognitive tasks,

- Difficulty responding and recognising social cues,

- Difficulty attending to directions,

- Low frustration tolerance.

Adverse reactions to food and food ingredients

Table 7.2: Studies carried out by Schoenthaler and colleagues on dietary interventions in correctional institutions

Where carried out	Trial type	Number of of subjects	Outcomes	Randomisation	Other Comments	Reference
Virginia	Stated to be double-blind trial of "special diet" (low in sugar, high in vegetables and fruit)	174 test subjects, 102 controls	Unstandardised measures of improved behaviour	Unclear	Probably not truly double-blind	Schoenthaler [220,221]
Alabama	Open trial of improved diet (low in sugar, high in vegetables and fruit)	180 test subjects, 104 controls	Unstandardised measures of improved behaviour	Not randomised	Description of subjects unclear	Schoenthaler [220,222]
Southern California	Open trial of restricted sucrose diet	1382 individuals	Unstandardised measures of improved behaviour	Not randomised	None	Schoenthaler [220,223]
Northern California	Open trial of diet eliminating "junk food"	1121 test subjects, 884 controls	Unstandardised measures of improved behaviour	Not randomised	None	Schoenthaler [220,224]
US east coast	Open trial of adding orange juice to the diet at meals	242 test, 239 controls	Unstandardised measures of improved behaviour	Not randomised	Although the study is described as double-blind, the subjects added orange juice to their diet and no attempt appears to have been made to conceal this	Schoenthaler [220,225]
"A Mid-western state"	Placebo-controlled study of vitamin supple-mentation	32 test, 30 controls	Unstandardised measures of improved behaviour	Randomised		Schoenthaler et al.[227]

7.26   There are also some rather non-specific problems that are often more loosely referred to as "hyperactivity" but are not in fact part of the ADHD symptom complex and are often seen in children who do not show ADHD. These include impairments of learning, memory, sequencing, motor skills, language, modulation of emotional response, compliance with societal demands, sleep patterns, mood and affect.

7.27   In order to diagnose ADHD, the key diagnostic features have to be abnormal as compared with that expected for the developmental level and the age of the child and be present in more than one situation, e.g. at home and at school. Three problems (inattentiveness, overactivity, impulsiveness) have to occur together for the category of hyperkinetic disorders; while ADHD can be diagnosed on the basis of the presence of one of them.[231] Diagnoses made in this way are reliable and predictive of later development.

7.28   The problems start at an early age, are persistent and are a serious risk for later mental health. There is a strong heritability estimated to be about 80-90% on the basis of twin studies.[232-234] However, the exact pattern of inheritance is not known and these studies make it plain that there are also environmental causes. There is plausible evidence for structural and functional abnormalities of the brain underlying ADHD.[235] Thus it has been found that there were global and regional abnormalities in brain glucose metabolism in adults with hyperactivity of childhood onset.[236,237] Several genes coding for neurotransmitter receptors or transporters are known to have variant allelic forms that are more common in ADHD than in the general population and evidence is accumulating for abnormalities in genes related to dopaminergic systems in the CNS. These include the dopamine D4 dopamine receptor,[238] dopamine transporter;[239,240] dopamine-β-hydroxylase[239] and dopamine D5 receptor;[239] these factors in the aetiology of ADHD have been the subject of recent reviews[234,241,242] There is evidence for an association of the D4 receptor gene with other behavioural conditions, including pathological gambling.[243] Several independent research groups have been able to replicate an association between ADHD and a variant allele of the dopamine D4 receptor. However, this allele characterises only a minority of children with ADHD and is also found in more than 10% of children without ADHD: thus it is one contributory factor amongst others.[232,244] Characterising genetic heterogeneity may provide a powerful adjunct when examining the effects of diet in sub-groups of patients with ADHD.

7.29   The broader set of behaviours that are sometimes referred to as "hyperactivity" do not carry the same associations of neurobiological disorder as does the defined diagnosis of ADHD.[245] Nevertheless, they may be very distressing to the child, the family and teachers and deserve attention in their own right. These symptoms are often those that are reported by self-selected members of a parent support group. Researchers have sometimes pointed out, often anecdotally, that the behaviours which change with diet are not necessarily those most clearly associated with ADHD but represent mild levels of irritability.[246] It may therefore be unfortunate that the published research trials to be reviewed are mostly based on children with unequivocal ADHD. It is possible, for instance, that negative results in group trials may be due to the inclusion of more severe and typical cases of ADHD who respond to medication rather than to diet.

7.30   Furthermore, the features of ADHD such as inattentiveness, overactivity and impulsiveness are sometimes associated with distinct inherited conditions such as fragile-X

syndrome, hypothyroidism and phenylketonuria. Other contributory factors include early brain damage, for example before, during or after birth; or arising from infection, maternal alcohol ingestion (foetal alcohol syndrome), substance abuse, pharmaceutical agents, and other toxic agents.

Studies on attention deficit-hyperactivity disorder

7.31 There are reports of more than a hundred randomised controlled trials of specific treatments, as well as a number of meta-analyses that have themselves been quantitatively assessed,[247-249] which show the efficacy of stimulant medication and behaviour therapy in ADHD. In spite of the strong evidence that pharmaceutical treatments are effective, including the Multimodal Treatment study of children with ADHD[250] which showed the benefit of medication compared to community care and behavioural therapy, these are not widely accepted in the UK. One reason for this is that dietary therapies are preferred by many parents, teachers and health visitors.[232,241] Whether diet affects ADHD or is involved in its aetiology is therefore a matter of importance.

7.32 A number of methodological problems, some of which may be unavoidable, make study of the contribution of dietary factors to the aetiology of ADHD difficult. Thus, case identification has often been poor, so that different studies are based on subjects defined by different criteria and it is therefore difficult to draw general conclusions. Studies have often been strongly dependent on subjective ratings of changes to measures of behaviour and susceptible to effects of expectation and suggestion. There has sometimes been difficulty in maintaining the blinding of controlled studies. Difficulties have been created by the multiplicity of possible adverse reactions in the same person and the need for separate testing of behavioural and cognitive effects has not always been fully met. Moreover, in this field there is an unavoidable presence of many potentially confounding and uncontrolled factors in the social environment, fluctuating and context-specific target problems and a mixture of high- and low-frequency target problems, some hard to observe. Furthermore, the possibility that symptomatic change is not necessarily related directly to social adjustment should be considered.

7.33 No single study has been able to overcome all the problems. It is therefore necessary to consider the wide range of studies of dietary manipulation involving exclusion of defined foods and ingredients such as additives, preservatives and salicylates (the "Feingold diet",[251] see paragraphs 7.35-7.36), population surveys and trials of diets that eliminate some of a wide range of foodstuffs and also trials that utilise food challenges.

7.34 It should be noted that there is a number of observations on associations between the effects of dietary differences and ADHD that are not yet fully accepted. These include differences in essential fatty acids in plasma and red blood cells between children with ADHD and healthy controls[252] and the existence of low iron and zinc serum/plasma concentrations in hyperactive children.[253] However, uncontrolled differences between cases and controls in these studies make interpretation of these observations difficult.

Studies on the Feingold diet

7.35   The Feingold diet excludes artificial food colours and flavourings as well as foods containing salicylates (see also paragraph 9.37) which Feingold thought were contributing to hyperactivity in children by a pharmacological rather than an immune mechanism.[251] The diet is also sometimes referred to as the K-P diet, after the Kaiser-Permanente Medical Center in California, where Feingold worked.

7.36   Some studies on groups of children using such an elimination diet, or a variation thereof, and mostly incorporating challenge with food additives such as tartrazine are listed in Table 7.3. Some case studies using similar techniques are tabulated in Table 7.4. These studies have used diets excluding food additives, especially colours, natural and synthetic salicylates, but differ in detail and have been imperfectly characterised, while the subjects have been predominantly hyperactive children. The challenge studies have generally involved controlled exposure to food colours (often in biscuits) in comparison with a placebo. It is difficult to draw overall conclusions. The diet comparison studies suggest that most children with ADHD do not benefit from dietary intervention. Connors[254] suggested that the positive outcomes of the challenge studies, in a small proportion of the subjects, could be explained by a combination of placebo effects and a positive effect of diet. The studies on single cases (see Table 7.4), which allow individual hypotheses to be tested, add some support to this view and it may be concluded that a small number of cases of ADHD may indeed be sensitive to food colours.

Specific dietary precipitants of ADHD

7.37   A number of studies has looked at components of the diet, other than those excluded in the Feingold diet, using a variety of study designs. Most of the comments on the methodology made above also apply to these studies.

7.38   Hyperactive children, on the basis of positive RAST, had a higher prevalence of atopy, in terms of numbers of allergies (but not total allergy score), than groups of learning-disabled or inattentive children.[265] However, removing allergens, particularly those from meat and cereals, from their diets produced a small improvement in behaviour. A controlled trial has been described in which a range of possible dietary precipitants were removed by a radical exclusion diet (known as a "few foods" diet, see Glossary), reintroduced one at a time, and finally compared with a placebo.[266] Statistically significant results were confined to parental ratings. These ratings are the most likely of any to be sensitive to any failure of the maintenance of 'blind' status. In a similar study using a less highly selected series, 78 children started on a few foods diet; of these 59 improved in open trial and 19 were selected because the foods to which they appeared to be intolerant could be successfully disguised for a double-blind crossover challenge. Cows' milk, chocolate, wheat flour, citrus fruits and food colours were among the most commonly implicated foods. Certain foods produced changes in behaviour as assessed by an independent psychologist and on psychological tests, in comparison with a placebo.[267] In a similar study, 19 of 26 children responded in open trial, 16 of the 19 went on to double-blind challenge, and their rated behaviour was worse on challenge days than on "placebo" days.[268]

Studies using diets involving wider food exclusions than the Feingold diet

7.39 Two studies have used a comparison-diet approach to test the hypothesis, sometimes called the multiple intolerance theory, that ADHD could be treated with a diet excluding a greater range of foodstuffs than the Feingold diet. Kaplan and colleagues[272] applied a random-allocation design and found that behaviour ratings of children with ADHD were better during a period of treatment with the exclusion diet than during a period on a comparison diet. The test diet excluded food additives including all artificial colours, preservatives and flavours, as well as chocolate and caffeine-containing foods and drinks and any food that families thought might affect their child. In a random-allocation double-blind trial there was no significant improvement in objectively-assessed behaviour of children in a child psychiatric unit, when they were on a diet that aimed at excluding as many food allergens as possible as opposed to a diet ("provocation diet") that consisted of foods that were rich in potential food allergens, although observed and rated behaviour was somewhat worse on the latter diet.[273]

Table 7.3: Studies involving elimination diets in groups of subjects, including studies which involved challenge with substances suspected of causing ADHD

Design	Test diet and use of control diet	Subjects	Outcome measured	Result	Reference
Double-blind crossover	K-P Control diet used	15 "hyperkinetic" children 6-12 yr	Hyperkinetic symptoms	Reduced symptoms *vs* pretreatment as measured by teachers & parents; reduced symptoms *vs* control diet, teachers only	Conners *et al.*[255]
Double-blind crossover	K-P Control diet used	36 "hyperactive" children 3-13 yr	Classroom and observations; neuropsychological tests	No consistent effects; some on parent rating	Harley *et al.*[256]
DBPCFC crossover	Feingold-type challenge with biscuits containing food additives or placebo biscuit	16 diet-responsive children 4-12 yr	Observations; visual motor tracking test	Reductions in behaviour problems on diet; in general little effect of challenge; some effect on visual motor tracking test	Goyette *et al.*[257]
DBPCFC crossover	Feingold-type challenge with biscuits as above	13 diet-responsive children 3-11 yr	Observation	Reductions in behaviour problems on diet; parent ratings 3 hours after challenge	Goyette *et al.*[257]

Table 7.3: **Studies involving elimination diets in groups of subjects, including studies which involved challenge with substances suspected of causing ADHD –** *continued*

Design	Test diet and use of control diet	Subjects	Outcome measured	Result	Reference
DBPCFC Drug treatment with methyl-phenidate or dextroam-phetamine	Feingold-type challenge with biscuits containing dyes and placebo	26 hyperactive children on stimulants 5-12 yr	Parent, teacher ratings	Parent ratings: inconclusive diet effects, powerful drug effects. Teacher ratings: more diet effects, similar drug effects	Williams et al. [258]
DBPCFC crossover	Feingold-type tartrazine	22 hyperactive children 4-8 yr	Parent, teacher ratings, psychometric tests	Significant challenge effect on report of symptoms in a sub-group only. No effects observed by teachers or using objective tests	Levy et al. [259]
Challenge: placebo-controlled	Feingold-type food dyes 100 or 150 mg in capsules	40 possible hyperactive children. 20 drug-responsive and 20 drug non-responsive average age 10 yr	Comparing tests	Decrement in learning with both doses in drug-responders only	Swanson & Kinsbourne [260]
DBPCFC crossover	Feingold-type diet and biscuits containing mixed food additives 13 or 78 mg	11 hyperactive children 4-13 yr	Observation, psychometric tests	No significant differences	Mattes & Gittelman [261]
DBPCFC crossover	Feingold-type diet. Artificial colourings in cocoa, *in toto* 91.8 mg	10 hyperactive children mean age 11.6 yr	Observation, psychometric tests	Statistically non-significant decrement in performance, colour challenge versus placebo	Thorley [262]
2-Stage: Open trial of diet followed by DBPCFC using tartrazine challenge	Diet "free of colouring": challenge with tartrazine 1-50 mg daily	Open trial: 200 suspected hyperactive children, 54 likely or uncertain reactors in DBPCFC study	Behavioural outcomes	Response in open trial with diet; response in DBPC at doses > 2 mg tartrazine	Rowe & Rowe [263]

Table 7.3: Studies involving elimination diets in groups of subjects, including studies which involved challenge with substances suspected of causing ADHD – *continued*

Design	Test diet and use of control diet	Subjects	Outcome measured	Result	Reference
DBPCFC	Diet that eliminated "food additives"; challenge with tartrazine, sunset yellow, carmoisine, amaranth	19 children who had improved on elimination diet 3-15 yr	Parental observations of behaviour; symptoms of allergy	Improvement in behaviour but not in symptoms of allergy	Pollock & Warner[264]
2 Stage: Open diet study, DBPCFC	Feingold diet; challenge with tartrazine or carmoisine, 50 mg	55 children (open study); 8 DBPCFC 3-15 yr	Parent and teacher observation	73% improved in open study; 2 showed marked response in the DBPCFC	Rowe[246]

Table 7.4: Case studies using challenges in ADHD

Population cases from which drawn	Number of subjects	Nature of challenge	How presented	Outcome measured	Result	Reference
"Community"	2 (apparent responders to the Feingold diet)	Tartrazine (1.2 mg)	Multiple: in biscuits alternating with placebo biscuit: double-blind	Off task behaviour; time out-of-seat; aggression	Increase in off-task behaviour	Rose[269]
Patients referred to clinic	1 reported by parents to respond to the Feingold diet	Additives and placebo	Multiple: in biscuits alternating with placebo biscuit	Observations by mother	Mother judged correctly about 50% of the time	Mattes & Gittelman-Klein[270]
22 patients reported to have responded to the Feingold diet	1 apparent responder	Artificial colourings	Multiple: soft drink containing challenge or placebo	Observation of behaviour	Clear deterioration in behaviour	Weiss *et al.*[271]

Community study

7.40   A community survey has suggested that the great majority of children whose parents believe them to be intolerant of foods do not show any adverse reactions when the food is given under blind challenge conditions.[274] However this approach has been criticised on the grounds that other potentially provoking foods were not excluded while the suspected food was being given. The possible effect of multiple-intolerances can be allowed for by placing patients on few foods diets, to which they do not react, when challenges are being undertaken.[267]

"Immunisation" approach

7.41   An "immunisation" approach has been described in which desensitisation to the putative allergens in food was claimed to lead to a reduced behavioural reaction to a subsequent challenge with the provoking food.[275,276] However, the methodological problems in this study are marked; in particular, the outcome measures were too weak and open to bias to sustain reliable conclusions.

Conclusions

7.42   There is therefore evidence to suggest that some dietary changes, not necessarily the same for all children, can reduce problem behaviour in at least a few children with ADHD. However, there is a need for further replication and elucidation of the findings. What data there are support the above hypothesis as far as effects on subjective findings such as parental or teacher rating scales is concerned. While this is reasonably clear, the effects on more objective measures have received only limited attention. Moreover, it is important to know how far these results can be generalised to less specialised treatment settings, because this therapy is difficult and troublesome.

Mental illness and gluten sensitivity

Schizophrenia

7.43   There has been speculation in the literature that schizophrenia might be exacerbated or even caused by an abnormal sensitivity to gluten. One such hypothesis proposes genetic abnormalities that would permit exorphins (the opioid peptides derived from food proteins such as gluten) to reach the cerebrospinal fluid in harmful amounts and/or to interact abnormally with brain opioid receptors, thereby influencing dopaminergic and other neurons.[277] High opioid-like activity in rat brain tissue of isolated peptides from wheat gluten hydrolysates, detected by competitive binding to opioid receptor sites, has been reported. This, by itself, does not prove the hypothesis.[278] The gastrointestinal permeability to ^{51}Cr-labelled ethylenediaminetetra-acetate (EDTA) in patients with schizophrenia (12 in relapse and 12 in remission) was not different to that of a healthy reference group.[279] Challenge studies using gluten have been carried out in schizophrenic patients. One provides some support for gluten as an aetiological factor in schizophrenia.[280] However, the results of several

randomised controlled trials do not confirm this. These randomised controlled trials are limited by their small size and the possible existence of subgroups of responders remains an unanswered question. In a study in which 13 schizophrenics were given gluten-free peanut-flour supplementary cookies and 13 others were given virtually identical biscuits with gluten added, tests and rating scales before and after the 10-day study period showed no greater improvement for those receiving the gluten-free cookies than for those receiving the gluten-added cookies.[281] A double-blind placebo-controlled 5-week challenge with 30 g gluten daily in eight schizophrenic patients who were maintained on a diet free of gluten, cereal grains, and milk (CM-F diet) found no deterioration in clinical status on gluten challenge.[282] Serum α-1-acid glycoprotein measurement demonstrated no evidence of inflammatory response to gluten challenge. The data suggest that sensitivity to dietary gluten is not characteristic of young chronic schizophrenic patients. A double-blind trial of a gluten-free versus a gluten-containing diet was carried out in a ward of a maximum security hospital, 24 patients being studied for 14 weeks. Most suffered from psychotic disorders, particularly schizophrenia. Various aspects of behaviour were rated on the Psychotic In-Patient profile (PIP) at different stages. There were beneficial changes in five parameters of the PIP in the whole group of patients between the pre-trial and the gluten-free period. The changes, however, were maintained during the gluten challenge period and they could possibly be attributed to the attention the patients received.[283]

Autism

7.44   A simple trial was undertaken on 7 patients with infantile autism who were given a gluten-free diet and 3 of whom were then provoked with gluten/placebo in a double-blind study. No beneficial results of the gluten-free diet were seen; rather, it was one more negative factor leading to further social isolation in this group of highly socially handicapped patients and families.[284] In contrast, Lucarelli and colleagues[285] found evidence of an improvement in behaviour in 36 autistic children on diets in which cows' milk, or other foods giving a positive skin test, were eliminated for 8 weeks. Moreover, in these children there were high levels of IgA antibodies against casein, lactalbumin and β-lactoglobulin as well as IgG and IgM for casein as compared to 20 healthy children.

8. Other clinical effects that may be related to adverse reactions to foods

Enuresis and cystitis

8.1   Claims that enuresis in children may respond to dietary elimination of cows' milk, chocolate, citrus fruits and cola have not been systematically evaluated. There have been case reports of eosinophilic cystitis accompanied by dysuria and enuresis. In this disorder the bladder mucosa has an eosinophilic infiltrate which responds to antihistamines, steroids and dietary manipulation.[286] A 10-year old girl with this condition who was reported to have positive skin tests and food-specific IgE antibodies had positive open challenges and clinically improved on an elimination diet.[287]

8.2   Interstitial cystitis is a non-bacterial cystitis which is commoner in women. It has been claimed to be possibly an autoimmune disorder which is aggravated by certain foods on a non-specific basis. Thus, the Interstitial Cystitis Support Group advises sufferers to avoid certain drinks (including alcohol, carbonated beverages and drinks containing caffeine) and foods such as all fruits (except melon and pears), all spicy foods, vinegar, tomatoes, cheese, chocolate, mayonnaise, all tree nuts (except almonds), onions and yoghurt.[288] The relationship of this condition to eosinophilic cystitis is not clear and neither is the basis for the dietary advice described above (see review by Erickson[289]). Systematic DBPCFCs are needed to demonstrate a rationale for interstitial cystitis and for the further definition of this condition and its features.

Vaginitis and vaginal discharge

8.3   IgE-mediated allergic vaginitis in susceptible women has been reported as being caused by oral medications and also possibly by foods.[290] In a study on headache and elimination diets in children, ten of eleven girls had a vaginal discharge which resolved while they were on an elimination diet.[191] Systematic studies would be needed to elucidate whether or not adverse reactions to foods or food ingredients could contribute to the pathogenesis of this problem.

Arthropathy and arthritis

8.4   There has long been speculation on an association between diet and arthropathies and reports that relief from arthritis (probably rheumatoid) could be obtained by the use of exclusion diets.[291-298] Some of these case reports and series suggest a link between foods, particularly milk, other dairy products or eggs, and arthropathy.[299-305] However, although there are reports of arthritis occurring in children with adverse reactions to cows' milk, there is little unequivocal evidence of a link between diet and arthritis, perhaps because of a relative paucity of controlled studies.[306]

Adverse reactions to food and food ingredients

8.5   In one of the larger studies,[307] three hundred patients with rheumatoid arthritis were asked to complete a questionnaire reporting any adverse reactions from food. Of the 159 replies received 52 gave a positive history. Thirty-five were further evaluated. Six patients, who gave the most typical history of food intolerance, were investigated clinically and there was no sign of an immunological reaction to foods. The other patients were interviewed a second time with an extensive allergy questionnaire and none of their reported food intolerances could be substantiated.

8.6   There have been few randomised controlled trials of arthropathy and arthritis. An exception is the study by van der Laar and van der Korst,[302] in which 116 patients who fulfilled at least six American Rheumatology Association criteria, including a positive rheumatoid factor test for the diagnosis of rheumatoid arthritis, were randomly assigned to one of the two groups. During the first 4 weeks of the study the subjects followed their normal diet, then one group received a commercial diet which was "allergen-free" (see paragraph 10.39 *et seq.*) while the other group received a diet which was allergen-restricted, containing only lactoproteins and azo dyes for four weeks, after which they returned to their original diet. Seventy-eight patients completed the study according to the protocol. No differences were seen between the clinical effects of the two diets but there was some clinical evidence of improvement with both diets. Nine patients, three in the allergen-restricted group, six in the allergen-free group, showed favourable responses, followed by marked disease exacerbation during re-challenge. Dietary manipulation also induced some changes in objective measures of disease activity in these patients. Of the nine patients who showed signs of improvement, six participated in a further study. Placebo-controlled re-challenges showed adverse reactions to specific foods in four of these six patients. In three of these patients biopsies of both the synovial membrane and of the proximal small intestine were carried out before and during allergen-free feeding. In two patients, both with raised serum IgE concentrations and specific IgE antibodies to certain foods, marked reductions of mast cells in the synovial membrane and the proximal small intestine were demonstrated.[308]

8.7   It can be concluded from these data, that food intolerance may exist in a minority of patients with rheumatoid arthritis. The demonstration of food intolerance in rheumatoid arthritis is laborious: long-term therapeutic effects are rare and dietary manipulation in the treatment of rheumatoid arthritis must still be considered experimental, until means are discovered to identify those patients who might benefit from dietary exclusion.

9. Mechanisms

Immune-mediated mechanisms

Types of immune reaction to food

9.1   The term allergy describes the adverse health effects that result from the stimulation of a specific immune response. In the case of food allergy it is usually IgE-mediated immune responses that are relevant.

Immediate-type immunological reactions (allergy)

9.2   Most common food allergies are mediated by IgE antibodies, this being the class of antibody responsible for immediate-type (Type I) allergic reactions.[2,309] In susceptible individuals, exposure to the food allergen in sufficient quantity and via a relevant route will stimulate production of specific IgE antibody. The most common and effective route of exposure is believed to be oral ingestion, although sensitisation could occur also by cutaneous or inhalation exposure. Specific IgE antibodies are distributed systemically and will bind, via specialised membrane receptors, to mast cells and basophils, the former being found in vascularised tissues, whereas the latter are found in blood. At this point the individual will become sensitised so that a subsequent encounter with the inducing allergen will provoke an allergic reaction. The allergen will crosslink mast cell membrane-bound IgE antibodies and this in turn causes mast cell degranulation and the release of both preformed and newly-synthesised inflammatory mediators, including histamine and leukotrienes. These together provoke an acute allergic reaction. The process, from exposure of a sensitised individual to the elicitation of an allergic reaction, may take only minutes.

9.3   The initiation and maintenance of the IgE antibody responses are subject to tight immunoregulatory control and are dependent upon the local cytokine microenvironment at the site of entry of the allergen into the body.

9.4   The production of IgE antibody is dependent on T lymphocytes. Cognate interactions between T and B lymphocytes and certain regulatory cytokines influence both the initiation and maintenance of IgE responses. Of particular importance is interleukin 4 (IL-4), a cytokine that has been shown, in mice, to be necessary for normal IgE responses.[310] Mice that lack a functional gene for IL-4 fail to display IgE responses,[311] whereas mice that have a transgene for this cytokine have increased serum concentrations of IgE and mount more vigorous IgE responses.[312] A balance is provided by interferon γ (IFN-γ), a cytokine that antagonises the production of IgE antibody.[313] The same cytokines serve to regulate reciprocally the stimulation of IgE responses in humans.[314] Another cytokine, interleukin 13 (IL-13), which shares some homology with IL-4, also plays a part as a promoter of IgE production and immediate-type hypersensitivity reactions.[315] Although it is the cytokines cited above that, in normal circumstances, have the most profound influence on the initiation and vigour of IgE

responses, there are other cytokines and other cellular interactions which affect the production of IgE by human lymphocytes and the stimulation of IgE responses in mice. There is evidence that other physiological processes may have some effect, notably interactions between the neuroendocrine and immune systems, involving neuropeptide release.[316]
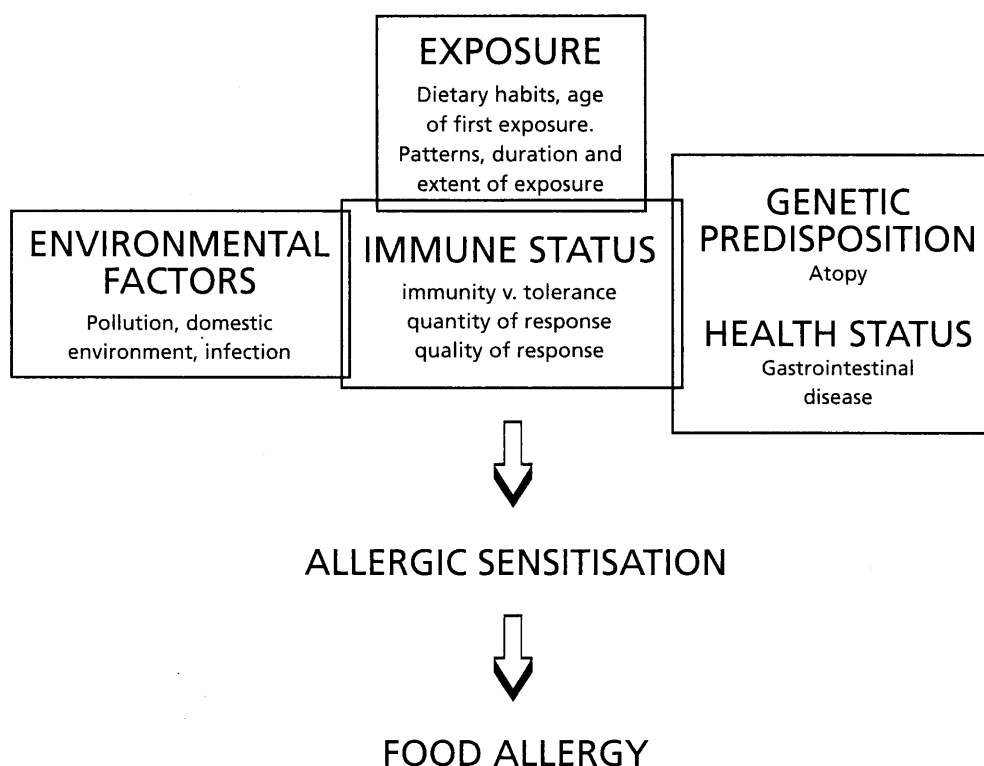
9.5   While cytokines are produced by a wide variety of immunologically-competent cells, it is the T lymphocyte cytokine environment that is probably of greatest importance for IgE antibody production and the regulation of allergic responses. Of particular relevance to the stimulation of qualitatively distinct immune responses are functional subpopulations of T lymphocytes and their cytokine products. More than ten years ago, it was reported that mouse T helper (Th) cells, characterised by expression of the CD4 determinant, display functional heterogeneity.[317] Two main populations are recognised, designated Th1 and Th2: these differ with respect to their cytokine secretion patterns. Some cytokines, such as interleukin 3 (IL-3) and granulocyte/macrophage colony-stimulating factor (GM-CSF), are produced by both cell types. In mice, however, only Th1 cells produce IFN-γ, interleukin 2 (IL-2) and tumour necrosis factor-β (TNF-γ), whereas only Th2 cells produce interleukins 4, 5, 6, 10 and 13.[318] Heterogeneity amongst CD4 T lymphocytes of a similar, although not necessarily identical type, has also been described in man.[319] The significance of this functional diversity among T lymphocytes with respect to allergic disease is that, under conditions where Th2 type responses predominate, then IgE production will be favoured, whereas selective Th1 type responses will serve to inhibit IgE production. The relationship between various cell types and their cytokine products in the regulation of IgE antibody responses and the pathogenesis of allergic reactions are summarised in diagrammatic form in Figure 9.1.

9.6   In addition to promoting IgE responses, cytokines produced by Th2 cells augment the development, localization and activation of mast cells and eosinophils, cells that play pivotal roles in immediate-type allergic hypersensitivity reactions and the more chronic inflammatory responses associated with such reactions.[320]

9.7   Differentiated populations of CD4 T lymphocytes are believed to originate from a common precursor during the evolution of an immune response. It is now clear that a variety of factors can influence the preferential development of functional sub-populations of T lymphocytes, including the nature of the inducing antigen itself, the co-stimulatory molecules that they express and the context within which the antigen is displayed to responsive T lymphocytes. One of the major determinants of selective Th cell development appears to be the local cytokine microenvironment, in association with other co-stimulatory factors produced by antigen-presenting cells. Broadly speaking, it is Th1-type cytokines that drive the development of Th1 cells, while IL-4, IL-10 and other products of Th2 cells favour Th2 responses. Indeed, Th2-type responses fail to develop in IL-4 gene knockout mice.[321] The same cytokines are reciprocally antagonistic insofar as IL-10 inhibits cytokine synthesis by Th1 cells and IFN-γ inhibits the proliferation of Th2 cells. The cytokines that appear to be of greatest importance as determinants of selective Th2 cell development are IL-10 and interleukin 12 (IL-12), the latter being a product of dendritic cells, macrophages and B lymphocytes. IL-12 promotes Th1 cell development and also inhibits Th2-type immune responses.[320]

Figure 9.1: Interaction of factors that lead to the development of allergy

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                    ┌─────────────────┐
                    │    EXPOSURE     │
                    │  Dietary habits, age
                    │  of first exposure.
                    │  Patterns, duration and
                    │  extent of exposure
┌──────────────────┐├─────────────────┤┌─────────────────┐
│  ENVIRONMENTAL   ││ IMMUNE STATUS   ││    GENETIC      │
│    FACTORS       ││                 ││ PREDISPOSITION  │
│                  ││ immunity v. tolerance
│ Pollution, domestic│ quantity of response
│ environment, infection│ quality of response
```

EXPOSURE

Dietary habits, age
of first exposure.
Patterns, duration and
extent of exposure

ENVIRONMENTAL
FACTORS

Pollution, domestic
environment, infection

IMMUNE STATUS

immunity v. tolerance
quantity of response
quality of response

GENETIC
PREDISPOSITION
Atopy

HEALTH STATUS
Gastrointestinal
disease

⇩

ALLERGIC SENSITISATION

⇩

FOOD ALLERGY

The acquisition of allergic sensitisation requires that an immune response of sufficient magnitude and of an appropriate quality is provoked by the inducing protein antigen. The ability of a protein antigen to induce such a response is determined by a number of factors. The exposed individual must be susceptible. Such inherent susceptibility is governed by both **heritable factors** and by **environmental factors** which influence the characteristics of the immune system. Perhaps the most important is **atopy**, this being a predisposition to mount IgE antibody responses. It is likely also that general **health status** and in particular pre-existing **gastrointestinal disease** will affect the induction of **allergic sensitisation** and/or the elicitation of **food allergic reactions**. For the effective sensitisation of an inherently susceptible subject there must be appropriate exposure to the inducing protein antigen. The **route, extent and duration of exposure** are important variables that will together determine whether an immune response is induced and whether that immune response is of the magnitude and quality necessary to cause allergic sensitisation.

9.8   More recently, it has been found that there is also functional heterogeneity within another population of T lymphocytes, namely the cytotoxic T cells (Tc). These cells are characterised by their expression of the CD8 membrane determinant. Two populations, designated Tc1 and Tc2 have been described: these display selective cytokine secretion patterns comparable respectively with Th1 and Th2 cells. Tc1-type cells may play a particularly important role in the negative regulation of IgE responses.[322] The evidence suggests that an important determinant of allergy is the development with time of discrete

functional sub-populations of Tlymphocytes and the production by these of cytokines that direct the quality of specific immune responses (Figure 9.1).

9.9   An important issue when defining the characteristics of immune responses to food allergens is immunological tolerance and the role this may play in preventing sensitisation to ingested allergens (see paragraph 9.21).

Allergens

9.10   Proteins causing IgE-mediated immunological reactions are called allergens and may be present as major components of food, typically comprising between 1% and 80% of the available protein. Thus, the body is exposed in any normal diet to many foreign proteins that are potentially allergenic. Some of the more important foods which give rise to adverse reactions that appear to be mediated by the immunological mechanisms are listed in Table 9.1.

Table 9.1: Important food items that give rise to adverse reactions mediated by the immune system

Food	Subgroup	References
Milk	Cows', goats', sheep, mares', buffalo	Clein,[146] Buisseret,[323] Ford & Fergusson,[324] Bock & Atkins,[155] Esteban,[325] Bock,[18,173] Burks et al.[58]
Eggs	Hens', ducks' and other birds	Ford & Fergusson,[324] Ford & Taylor,[326] Bock & Atkins,[155] Esteban,[325] Bock,[18,173] Burks et al.[58]
Legumes	Peanuts, lentils, lupin, peas, soya	Bock & Atkins,[155] Esteban,[325] Bock,[18,173] Hefle et al.,[327] Burks et al.[58]
Tree nuts	Walnuts, pecan nuts, almonds, cashew nuts	Bock,[18] Burks et al.[58]
Cereals	Wheat, rye, barley, oats, maize	Wraith et al.,[136] Bock[18]
Fruit	Apples, peaches, plums, cherries, bananas, citrus fruits	Amlot et al.,[69] Bock & Atkins[155]
Fish	Cod	Amlot et al.,[69] Bock & Atkins,[155] Esteban [325]
Shellfish	Shrimps, lobster, crabs	Amlot et al.,[69] Burks et al.[58]
Seeds	Sesame	Shi & Yang[122]
Herbs and spices	Mustard, paprika, coriander, caraway	Niinimäki et al.[328]

9.11 It is not clear why only some food proteins have the potential to induce allergic sensitisation in susceptible individuals. The characteristics which enable proteins to cause allergic disease have not been well-identified. It is noteworthy that the course of food allergic disease is variable and the variability is, at least partially, a characteristic of the antigen; thus not all food allergens are equally capable of inducing an allergic reaction. The reasons for the differing immunological properties of food allergens are unclear. However, changes in allergenicity can arise from processing, cooking and digestion and it is not always clear or predictable whether such changes will increase or decrease reactivity.

Mechanisms

Characteristics of allergens

9.12 Allergens are usually glycoproteins of relative molecular mass 10,000-70,000 Da and are relatively resistant to denaturation by heat and to digestion in the gastrointestinal tract. They are thought to be absorbed intact but this is not necessarily why they cause allergies. In general terms, food allergens are relatively stable proteins but this is not universally the case.[329] Many foods causing allergies have more than one allergen, for example cows' milk has at least twenty. Table 9.2 gives examples of characterised allergens in foods.

9.13 The part of the protein associated with allergenicity is called the epitope and this is characterised by a particular amino acid sequence and the three dimensional structure of the protein. Similar amino acid sequences and structures occur in other proteins which may be from both related and unrelated foods or derived from related or unrelated plant or animal species. Such similar sequences are called homologues and they crossreact with IgE binding sites to one another. Often however serological cross-reactivity between epitopes from different foods is not matched by clinical reactivity to the foods, but some homologues can cause cross-reactivity (e.g. various milks and eggs from different species and particularly the cod allergen Gad c 1 and allergens from other fish).

9.14 Changes in allergens can arise during food processing, cooking and digestion but it is not always known whether such changes will increase or decrease allergenicity or reactivity. For example, pasteurisation at 75°C for 15 seconds does not alter the allergenicity of cows' milk protein in general, whereas treatment at 121°C for 20 minutes reduces the allergenicity of whey proteins but has little effect on that of casein proteins. Sterilisation of milk may enhance its allergenicity. A reduction in allergenicity can be produced by a combination of heat treatment and enzymatic degradation which may break down or change the structure of the epitope, followed by ultrafiltration to remove any residual large molecules which may have escaped the first two steps. Cooked eggs remain allergenic, but foods containing processed egg may not produce reactions. Cooking reduces the allergenicity of fish but cooking cannot be relied upon to eliminate any fish allergenicity. Furthermore, cooking and processing can create neoallergens, as has been noted with pecan nuts.[330]

9.15 Doses of allergens which precipitate reactions in sensitised subjects have not been systematically assessed using DBPCFC. The amounts are small, for example in adults 50 mg of fresh egg induced a reaction[331] whereas 10 mg of freeze-dried ovalbumin produced a reaction in infants.[332] Generally, egg white is more allergenic than egg yolk. With peanuts, quantities as low as 100 µg may cause symptoms in sensitised individuals.[175] In the case of fish, 6 mg of fish

Adverse reactions to food and food ingredients was shown to induce oropharyngeal symptoms and 10 g caused anaphylaxis.[333] That small amounts of allergens can produce reactions was demonstrated in a subject allergic to fish who reacted to potatoes prepared in the same oil as had been used to cook fish.[156]

Table 9.2: Antigens associated with disorders linked to specific foods and groups of foods

Source	Systematic name (non-systematic names in brackets)
Cows' milk	Bos d 4 (α-lactalbumin)
	Bos d 5 (β-lactoglobulin)
	Bos d 6 (serum albumin)
	Bos d 7 (immunoglobulin)
	Bos d 8 (caseins)
Hens' eggs	Gal d 1 (ovomucoid)
	Gal d 2 (ovalbumin)
	Gal d 3 (conalbumin)
	Gal d 4 (lysozyme)
Peanut	Ara h 1 (vicilin)
	Ara h 2 (conglutinin)
Soya bean	Gly m 1A (HPS)
	Gly m 1B (UPS)
Apple	Mal d 1
Sweet cherry	Pru a 1
Kiwi fruit	Act c 1 (cysteine protease)
Celery	Api g 1
Oriental mustard	Bra j 1 (2S albumin)
Yellow mustard	Sin a 1 (2S albumin)
Baltic cod	Gad c 1 (allergen M)
Atlantic salmon	Sal s 1 (parvalbumin)
Various genera of shrimp	Met e 1 (tropomyosin)
	Pen a 1 (tropomyosin)
	Pen i 1 (tropomyosin)
Barley	Hor v 1 (BMAI-1)
Rice	Ory s 1

Modified from Bousquet *et al.*[175]

9.16 Predisposing factors include a genetic propensity as evidenced in the family history. The chance of a child having an allergy is up to 60% if both its parents (or a sibling) are allergic, 20-40% if one parent is allergic, and 15% if no first degree relative is affected. Another factor is the age at which the child was first exposed to the protein as well as the amount and frequency of subsequent exposure.

9.17 Cultural variability in these factors are thought to underlie the geographical variability in the prevalence and nature of allergic food reactions. The influence of early exposure is shown by the high level of fish allergy in Scandinavia, of peanut allergy in the USA, and of rice allergy in Japan; the last of these being particularly rare in the UK. Furthermore, altered immune status, changes in gastrointestinal function, and exacerbating agents such as infection and exposure to cigarette smoke may influence the development of food allergy.[175]

Cross-reactions

9.18   Allergens in a number of foods cross-react (see paragraph 9.13 and Table 9.3). Notable families of cross-reacting allergens are those associated with latex allergy, *vide infra*,[334] and with fruits from the genus Prunus (plums, apricots, peaches, cherries). In some cases cross-reacting allergens are known to have similar epitopes. A number of workers have reported cross-reactions, usually on the basis of RAST testings, and in some cases these appear to parallel taxonomic relationships, for example amongst plants of the Graminae family, where cross-reaction is often shown amongst the foods derived from Hordeae (barley, rye and wheat) but less often with oats, a member of the Festuceae family.[136] In contrast, there have been reports of cross-reactions between plants that are not closely related; such as that between Swiss chard and green beans.[129] On the basis of skin prick testing a proportion of peanut allergic subjects cross-reacted with tree nuts such as Brazil nuts, hazel nuts and walnuts.[159] However, Bock and Atkins[335] found no convincing evidence of clinical cross-reactions between peanuts and botanically-unrelated tree nuts. It should be noted that multiple positive skin tests, for example, to Leguminosae, do not always correlate well with clinically-relevant cross-reactivity.[336] However, adverse reactions to sweet lupin flour has been reported [327,337] and there is evidence using DBPCFC for cross-reactivity between peanut allergens and allergens in sweet lupin.[338-340] Subjects allergic to pollen, especially that of grass, mugwort or birch, may react to certain food items such as pears and walnuts and develop the oral allergy syndrome (see paragraph 4.8).

Latex

9.19   Reactions to latex are of particular interest because they demonstrate that reactions between dietary and non-dietary allergens may have implications for both public and occupational health. Natural rubber latex contains several allergens which vary quantitatively according to growing conditions (e.g. climate, season, soil).[341,342] The major allergens are rubber elongation factor (REF, Hev b 1) and hevein (Hev b 6.02). Traditionally these proteins would have been eluted from the latex during processing, however, with the increased demand for rubber goods created by AIDS, manufacturing processes have changed and more of these allergenic molecules remain in the latex used for surgical gloves, condoms and other products.[343,344] Type I reactions to natural rubber latex cause urticaria, conjunctivitis, rhinitis, asthma and anaphylaxis.[345] Those at risk are health-care workers, especially those with atopy[346] and also, on the basis of studies of children with neural tube defects, patients undergoing repeated surgery who are frequently in contact with rubber gloves. The major allergen for healthcare workers seems to be hevein and for spina bifida patients to be REF. The prevalence in health care workers is 7-10%, while in the general population the prevalence of latex sensitisation is less than 1%.[347] The same epitopes are also present in other plants including banana, kiwi, avocado, mango and chestnuts. Individuals allergic to latex may also react to foods containing these items. Conversely, it is also possible that patients first sensitised to the fruits develop an allergy to latex. Reactions to food were found in 33 of 47 latex allergic patients; positive skin tests to avocado were seen in 53%, potatoes in 40%, banana in 38%, tomatoes in 28%, chestnuts in 28% and kiwi fruit in 17%.[334] However, only 25% of individuals with positive skin reactions had clinical symptoms to latex. Nevertheless, all patients with identified Type I latex allergy should be assessed for possible reactions to foods, and patients allergic to foods reported to cross-react with latex should be seen as being at risk of having latex allergy.

Adverse reactions to food and food ingredients

Table 9.3: Groups of cross-reacting foods

Food	Reported cross-reactions*	Reference(s)
Milk	Goats' milk, sheep milk, buffalo milk, mares' milk	Bahna & Heiner,[56] Sampson & Burk[348]
Peanut	Other legumes (e.g. soya beans, chick peas, green beans, lupins, lentils, peas)	Martin et al.,[130] MAFF,[340] DOH,[59] Moneret-Vautrin et al.[338]
Cereals	Barley, rye, wheat, [various wild grasses]	Wraith et al.,[136] Reese & Lehrer[336]
Apples	Pears, hazelnuts, walnuts, celery [birch, mugwort and grass pollen]	Vieths et al.[349, 350] Ortolani et al.[43] Pauli et al.[70]
Latex and cross-reactions	Bananas, chestnuts, kiwifruit, potatoes, tomatoes, avocado [latex]	Blanco et al.[127] Beezhold et al.[334]
Fruits of Prunus spp.	Almond, apricot, cherry, peach, plum	Pastorello et al.[351]
Fish	Cod, bass, eel, herring, plaice, mackerel	Bernhisel-Broadbent et al.[352]
Shellfish	Shrimp, lobster, crab, crawfish	Musmand et al.,[353] Lemière et al.[131]

* cross-reacting non-food items are shown in brackets [ ]

Unresolved considerations

9.20 There are a number of important considerations in food allergy which remain unresolved. It is not understood why only a proportion of the exposed population develops allergy to common food proteins. It is likely that both genetic and environmental factors are important (Figure 9.1). Predisposition to allergic disease is partly heritable, but the associations are complicated and polygenic in nature. A predisposition not to develop food allergy may also be genetically determined but, in addition, the nature and timing of first exposure to the relevant food may be important, particularly in determining whether sensitisation or immunological tolerance will develop. It is likely that environmental factors, particularly those which pertain during the perinatal period, infancy and early childhood, will impact on susceptibility to allergic disease in general. In developed countries, an increased prevalence of many types of allergic disease has been reported, and this increase is believed to extend to food allergy. While the reasons for this have not been elucidated fully, it is likely that the domestic and social environment during infancy, especially infections, influence susceptibility to allergic disease, particularly that with a respiratory component (see paragraphs 2.28-2.29 above).[354, 355]

Oral tolerance

9.21 Oral tolerance describes a state of antigen-specific hyporesponsiveness or unresponsiveness after prior mucosal exposure. Breakdown of this homeostatic process is

considered to be one cause of food hypersensitivity. There is clinical and experimental   *Mechanisms*
evidence that oral tolerance exists in man.[356] The mechanisms by which tolerance is mediated
include T cell deletion, anergy and suppression. Cell-mediated delayed hypersensitivity
reactions (Th1-type), which are implicated as pathogenetic mechanisms in the development
of food-related gastrointestinal inflammation, are particularly well suppressed (reviewed by
Strobel[357]). Regulatory events during the induction of tolerance are not well-characterised and
remain poorly understood. The balance between tolerance (suppression) and sensitisation
(priming) is dependent on diverse factors,[358,359] including:

- genetic background,

- nature of antigen,

- frequency and extent of administration,

- maturity of the immune system,

- immunological status of the host (virus infections),

- maternal dietary exposure, and

- antigen transmission via breast milk.

9.22   Antigen administration during the postnatal period is thought to have sensitising
effects on animals and infants.[358,360] Larger antigen doses have been shown to cause T cell
deletion in transgenic mice together with anergy, whereas smaller doses lead to suppression
through induction of IL4/IL10-secreting Th2 cells and cells secreting TGF-β.[361]

Sensitisation

9.23   Sensitisation to food allergens is achieved when an IgE response of sufficient
magnitude to permit the subsequent elicitation of an allergic reaction has been generated. IgE
antibody binds to high affinity receptors on the surface of mast cells and basophils,[362] in such
a manner that contact between only a few membrane-associated molecules and the inducing
antigen will trigger the release of highly active mediators of inflammation, including
histamine, proteolytic enzymes, leukotrienes and prostaglandins, from the granules of these
cells.[363] Together, these mediators cause urticaria, angio-oedema, hypotension and sometimes
acute anaphylaxis. In addition to this immediate response to allergens, a more chronic
response may be induced, with the influx of eosinophils, neutrophils and other cell types. The
pathogenetic role of intestinal eosinophils in acute or chronic intestinal reactions is not clear
and the relationship of food allergy to the hyper-eosinophilic syndrome needs
clarification.[91,364,365]

9.24   Sensitisation to some food proteins such as occurs in allergy to cows' milk is much more
common among children, with most individuals losing their sensitivity with time. In contrast,
peanut allergy is long-lasting (and frequently, but not always, lifelong) and the reactions to Ara
h 1 and Ara h 2 tend to be more vigorous and more severe than those induced by milk proteins.

9.25 In immune-mediated adverse reactions to food involving respiratory symptoms the route of sensitisation is not clear. Thus it is possible that sensitisation may be induced via the respiratory route, but once sensitised an individual might react when exposed through another route and with different symptoms. Conversely, onset of symptoms may occur when sensitised individuals are exposed to the relevant allergens by inhalation rather than by ingesting the food.[366-368] Unfortunately, it is not usually known whether such individuals were initially sensitised via inhaling or swallowing the foods, although there are some case reports that are suggestive that inhalation was the route of sensitisation.[126,131,369,370]

Non-IgE-mediated immune adverse reactions to foods

Enteropathies

9.26 The enteropathy of which the pathogenesis has been most extensively studied is gluten-sensitive enteropathy, coeliac disease (see paragraphs 4.11-4.14). Coeliac disease is most often caused by the alcohol-soluble fractions called gliadins in gluten, a protein present in wheat.[81] Analogous proteins in rye (secalins) and barley (hordeins) may cause the same effects. The severity of the disease is very variable. The enteropathy is characterised (Figure 9.2) by an excessive rate of loss of cells from the villi of the small intestine resulting in loss of villi and mucosal flattening, and by mucosal infiltration with plasma cells, lymphocytes and mast cells, i.e. chronic inflammatory change. The plasma cells are predominantly IgA-producing. The only treatment is a gluten-free diet, to which patients generally respond well. Autoimmune elements may be involved in the pathogenesis[371] and, although the precise cause of the disease is not known, a gluten-triggered autoimmune reaction against the tissue enzyme transglutaminase is currently suggested as being involved. There is a hereditary component;[372,373] the evidence for this is based upon a genetic HLA linkage,[374] as with other autoimmune diseases.[81,87,375] In coeliac disease, the DR and DQ HLA genes most frequently involved are DR3 and DQA1*0501-DQB1*0201 (DQ2). Dermatitis herpetiformis seems to share this linkage.[375] Convincing experimental evidence that direct cytotoxicity mechanisms play an important role in damaging the mucosa is lacking and it is tempting to speculate that immunological mediated damage is triggered by systemic and/or local release of mediators (cytokines). These "enteropathic" cytokines may affect intestinal effector cells including fibroblasts and intestinal crypt stem cells. Although the effects of activated T cells on gut morphology are less well understood, cell mediated immune reactions can clearly lead to mucosal destruction in animals and man.[376,377]

Non-immune-mediated adverse reactions

9.27 There are a number of mechanisms whereby adverse reactions to food can occur that are not mediated through the immune system and such reactions have been ascribed to a wide variety of foods and food ingredients. In some cases the connection between the food and the reaction is clear, while with others the connection is much less clear. Some of these foods and food ingredients are listed in Table 9.4. It is important to note that this section is concerned solely with the responses and disorders of otherwise normal individuals. This section is not concerned with those suffering from generalised diseases that affect the ability to ingest, digest

and enjoy a meal, e.g. someone whose stomach or intestines are diseased or have been partly removed for surgical reasons, or who have abnormal functioning of the liver or biliary system.

Mechanisms

9.28   This report does not discuss the consequences of eating food that is decomposed or contaminated with harmful micro-organisms, e.g. botulism, tetanus and Salmonella infection, or the consequences of accumulation of fungal toxins, such as patulin (in apple juice), vomitoxin, or the various toxins that accumulate in shellfish (see Table 2.2 above).

Figure 9.2
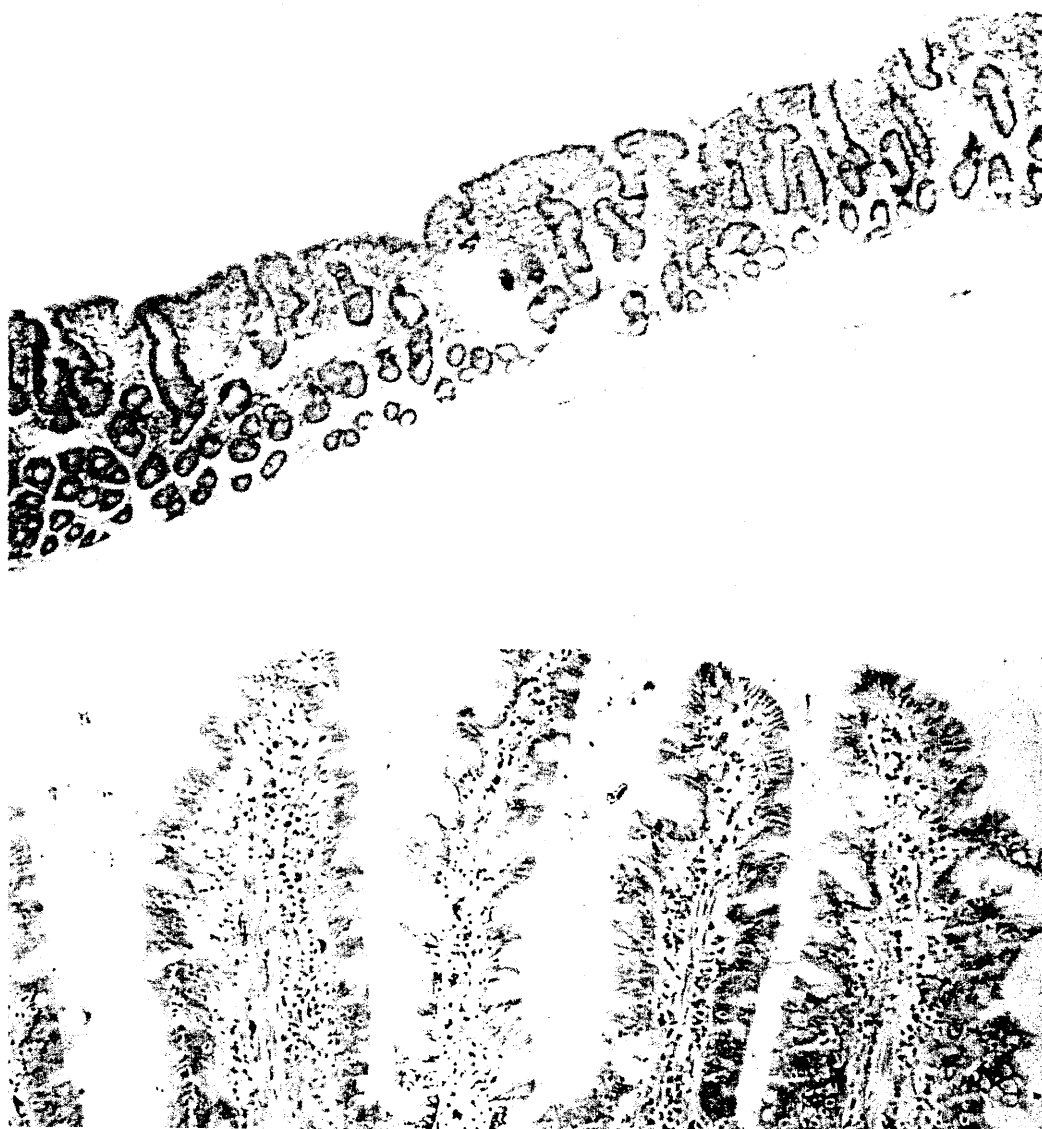
Top: Histological appearance of an intestinal (jejunal) biopsy of a patient with coeliac disease. There is severe shortening and blunting of the villi with a marked increase in inflammatory cell infiltration. The villus to crypt ratio is reduced to 1:1 or below (normally between 2:1 and 3:1). Occasionally patients with a food sensitivity enteropathy other than coeliac disease can show a similar picture.

Below: Normal mucosa showing leaf and finger shaped villi with a villus to crypt ratio of 3:1.

(Courtesy of and © Professor Stephan Strobel, Institute of Child Health)

Table 9.4: Types of food components that are claimed to cause food intolerance by non-immunological mechanisms

Type of material	Examples	Paragraph in the text where discussed or reference
Phytochemicals	Lectins and other haemagglutinins	9.50
	Glucosinolates	Conning[378]
	Protease (including trypsin) inhibitors	Birk[379]
	Saponins	Mori et al.[8]
Bioactive amines	Histamine	9.38-9.42
	Tyramine	9.38-9.42
	β-Phenylethylamine	9.38-9.42
	Octopamine	9.38-9.42
	Serotonin (5-Hydroxytryptamine)	9.38-9.42
Preservatives	Benzoic acid	9.40
	EDTA	Whittaker et al.[380]
	Nitrates and nitrites	9.48
	Sulfites	9.43
	Metabisulfites	9.43
	Sulfur dioxide	9.43
	Butylated hydroxytoluene (BHT)	9.40
	Butylated hydroxyanisole (BHA)	9.40
Colouring agents	Azo dyes e.g. tartrazine	9.40
Flavour enhancers	Monosodium glutamate (MSG)	7.16
Others	Acetylsalicylic acid	9.37
	Caffeine, theobromine	7.15, 9.35
	Sucrose	7.18, 9.46

9.29 By definition, the aetiology of non-immune-mediated adverse reactions of food is independent of the immune system. Even so, some reactions may mimic some of the disorders associated with allergic phenomena because they depend on the actions of the same mediators (e.g. histamine), so that there are similar final pathways. These mediators may even be released from the same cells that would be involved in an immunological reaction, albeit in response to a fundamentally different type of trigger mechanism. Some of these effects merge into toxic effects of food (see Figure 2.1). Some non-immune adverse reactions to food are biochemical in origin and are due to inherited variation in the enzymatic capacity of the gastrointestinal tract or other organs in the metabolism of particular food ingredients (genetic polymorphisms, see paragraphs 9.44-9.49), while others may be due to the inhibitory effects of medicines on enzymes. Other non-allergic adverse reactions to food, perhaps better recognised, are due to an excess of pharmacologically-active compounds in a food, and this type of effect will affect anyone consuming a sufficient quantity of the foodstuff.

Enzymatic abnormalities

9.30   There are a number of inborn errors of metabolism that cause intolerance of particular foods. They are due to an abnormality of genetic origin that effects metabolism of a specific substrate; in the case of carbohydrate metabolism examples include galactosaemia and hereditary fructose intolerance and with amino acids, phenylketonuria and maple syrup urine disease. They are usually diagnosed soon after birth and often respond to dietary manipulation. Although some inborn errors of metabolism are important causes of adverse reaction to food, they are not further discussed here and the reader is referred to specialised texts such as Scriver *et al*.[381] However these conditions illustrate the impact of genotype and associated enzyme polymorphisms on the metabolism of dietary components, which in turn can lead to variations in the susceptibility to the development of adverse effects such as favism (see paragraph 9.47). Conditions of this sort can often be ameliorated by altering the diet.

Excess of normal food

9.31   Food in excess can cause discomfort by physicochemical mechanisms: over-consumption is reputedly more common amongst children but over-consumption can occur in adults. The sheer volume of food consumed over a brief period can lead to unpleasant effects, especially if it is hypertonic and the volume expands further in the intestines as water is drawn into the gut lumen. An increase in complex carbohydrate intake leads to excessive fermentation in the colon, resulting in distension, eructation and flatus: fermentative diarrhoea may occur. Fermentative diarrhoea is an important differential diagnosis of diarrhoea in young children who are on high intakes of refined as well as unrefined carbohydrates. The consequences of overeating various types of beans are a common example of this type of self-limiting reaction, as is the diarrhoea which occurs in children who drink large amounts of apple or pear juice. The latter reaction is induced by sorbitol which is a non-digestible polyhydric alcohol. This and similar compounds may be present in diabetic and other low sugar products, the excessive consumption of which has similar gastrointestinal effects. It is possible that novel non-digestable ingredients being used in reduced-calorie products as fat replacers may cause symptoms as a result of fermentation by colonic bacteria.

Physical factors

9.32   In addition to bulk and tonicity, eating foodstuffs at the extremes of temperature can also lead to discomfort, e.g. as after a large amount of ice cream or a very hot stew. Although not considered here, the effects of excessive alcohol consumption could be considered to fall in this category. Consuming more oily food than usual can cause upset, leading to abdominal pain and loose stools, even though those accustomed to heavily-dressed food items do not suffer any ill effects. Reactive hypoglycaemia is hypoglycaemia occurring after food; it was formerly very common in those who had undergone partial gastrectomy and also may occur in incipient diabetes mellitus. Idiopathic reactive hypoglycaemia is diagnosed on the basis of history and a glucose tolerance test. Some cases may be due to an abnormal insulin response to meals[382] (see also paragraphs 7.18 and 7.23).

Pharmacologically-active substances in foodstuffs

9.33 This category of adverse reaction covers items in the diet which only occasionally contain an active agent at a concentration sufficient for it to affect anyone eating a normal-sized portion. Most represent pharmacological actions of food ingredients. These adverse reactions to food are due either to inherited or acquired variation in the capacity of the body to metabolise some of the many highly pharmacologically active ingredients in foodstuffs, or to an excess of such substances in foods. Pharmacological effects commonly occur soon after eating the responsible food. These non-immune-mediated adverse effects of food tend to be rapidly reversible. They will occur reproducibly after challenge. Their nature varies little and their incidence and intensity are directly related to dose.

Unfamiliar foods

9.34 This category of adverse reaction to food is almost impossible to define because it depends on the diet 'normally' eaten by the affected individual. Nevertheless, the category is intended to cover foods with known pharmacologically active ingredients to which the habitual consumer may become tolerant, or at least relatively indifferent. As examples, the consumption of very hot curries, peppers and spices offers pleasure to habitués but may discomfort the novice. This and the other pharmacological effects of sweating and tachycardia, due to stimulation of certain sensory nerve endings, is primarily caused by capsaicin, a constituent of such foods.[383,384] Furthermore, spices stimulate release of vasoactive amines and other transmitter substances from the gut mucosa, an additional means whereby "hot" food may produce adverse effects. A similar mechanism may account for reactions occurring in response to the practice of eating certain types of mushroom and other plants because of their psychedelic and hallucinogenic effects.

Xanthine-containing foods and beverages

9.35 Many foodstuffs contain and indeed are consumed in part for their content of pharmacologically-active substances, notably the methylxanthines (caffeine, theobromine and related substances) which are present in tea, coffee, cocoa, chocolate and certain soft drinks.[385] Excessive consumption of these compounds will have various effects, which are sometimes experienced as 'adverse', depending on the personality and behaviour of the individual, e.g. there is a range from heightened alertness and tremor to agitation, anxiety and sleeplessness after drinking a lot of strong coffee (see paragraph 7.15 above).[200]

Nutmeg

9.36 Nutmeg can have a hallucinatory action and may even cause a psychotic reaction some hours after eating a large quantity of the grated fruit, probably of the order of several spoonfuls[386-388] Nutmeg may also cause flushing, tachycardia, miosis and fever, such effects probably being due to the content of myristicin. This reaction appears to be rare.

Salicylates

9.37 It has been suggested that salicylate-containing foodstuffs, such as tomatoes and strawberries, should be avoided in food intolerance, however, it should be noted that salicylate in food is not acetylated (see above paragraph 7.35), and that the salicylate content of food is not well-characterised. The daily intake approximates to 1-2 mg, recent analyses have shown that compositional data such as that available to Feingold when he devised his diet

(paragraphs 7.35 and 7.36) was inaccurate, values for the salicylate content of foods were too high. Furthermore, the salicylate present in foods is not well absorbed,[389] in contrast to that in pharmaceutical preparations.

Histamine

9.38 The best example of an adverse reaction to a pharmacologically-active substance is probably scombroid poisoning, which is due to the occurrence of an excessive amount of free histamine in certain species of fish[390,391] such as tuna and mackerel. This effect should, perhaps, more properly be described as a toxic effect of food (see Figure 2.1), except that there may be some individual variation in tolerance of histamine and therefore of the dose needed to produce an effect. Scombroid poisoning can also occur after eating certain other species of fish, for example bluefish, sardines and anchovies. When fish of these types are inadequately refrigerated, commensal marine bacteria decarboxylate the normal amino acid histidine to form histamine in a concentration that surpasses the body's normal capacity to metabolise it to inactive and harmless by-products; clinical effects have been noted after consuming fish containing from 2.5-250 mg histamine per 100 g fish.[392] Ingestion of such fish, even after cooking, may then result in the full spectrum of histamine effects, including flushing, nausea, sweating, colic, diarrhoea and vomiting and urticaria.[8,388] The effects occur within about an hour of eating the fish and last for several hours. A comprehensive account of the causes and clinical features of scombroid poisoning are given by Slorach.[14]

9.39 Many other foods contain histamine derived from bacterial action, for example cheeses such as Parmesan and Blue Roquefort, hard cured sausages, e.g. salami, and certain other foods including spinach.[43,390,392,393] Although the quantity ingested in a normal portion will probably not have a detectable clinical effect in a normal individual, eating a large quantity of several of these items might suffice to produce certain symptoms, such as headache and abdominal discomfort.[394] There have been reports of urticaria provoked by alcoholic beverages. Vasoactive amines including histamine are present in red wines and alcohol-induced urticaria, although rare, does exist and may be mediated by non-allergic means (as noted above in paragraph 3.6).[395] Although many reported cases of alcohol-induced urticaria are due to wine (for example the case of urticaria and anaphylaxis reported by Clayton and Busse[174]) other drinks have been reported to be associated with urticaria. As an example, urticaria and angio-oedema have been reported after drinking beer,[170] however, in this instance the mechanism appeared to be a reaction to proteins in the beer.

9.40 Adverse reactions to other substances in the diet may be mediated via histamine through a non-immune process. Significant rises in plasma and urinary histamine were recorded in two subjects who developed urticaria after azo-dye challenge.[38] It was suggested that an immunological explanation was less likely than a pharmacological explanation to account for the findings and it is noteworthy that tartrazine, but not carmoisine, also provoked histamine release, at high doses, in normal subjects.[39] It should be noted that, in addition to the azo-dyes, certain other food additives, including the benzoate preservatives and the antioxidants BHA and BHT, may release histamine under certain circumstances.

Adverse reactions to food and food ingredients

Amines other than histamine

9.41   A number of foods contain monoamines other than, or in addition to, histamine. In some cases these amines are formed by microbiological decarboxylation of aminoacids: thus many fermented foods, including pickles and some wines, contain tyramine, from tyrosine, or dopamine, from phenylalanine or dihydroxyphenylalanine.[396-398] Other foods also contain monoamines including chocolate (tyramine),[399] citrus fruit (synephrine)[400] and bananas including plantains (serotonin).[401] Cheese, depending on the type, may contain more than one of these amines.[402] Tyramine exerts a sympathomimetic effect by bringing about the release of noradenaline[403] and its administration to rats increases the blood pressure.[404] (β-Phenylethylamine and synephrine appear to act in a similar way to tyramine, while dopamine has an additional direct sympathomimetic effect. The effects of serotonin are more complex than those of the other monoamines, producing intracranial vasoconstriction and skeletal muscle vasodilatation, reviewed by Moneret-Vautrin and Baldwin.[388,405] In the context of adverse reactions to food the importance of these compounds is that they may trigger headaches including migraine headaches (see paragraph 7.14). Although it is biologically plausible that there is a link between amines of this type and headache in certain individuals, the clinical and experimental evidence for this is conflicting and it seems clear that, in normal dietary amounts, these amines do not have clinical effects on most individuals.[406-408] Indeed, there are manifold metabolic and permeability barriers to the uptake of amines.

9.42   There is a well-established association between monoamines in conventional foods eaten in normal portions and marked, even fatal, pharmacological effects in patients being treated with non-specific inhibitors of monoamine oxidases, the principal protective enzymes in the intestinal mucosa. Failure to detoxify the monoamines results in absorption of excessive amounts, causing severe sympathomimetic responses, including tachycardia and hypertension.[409-411] The disorder was first described in patients treated for depression with the older non-selective monoamine oxidase inhibitors, such as the simple hydrazine derivatives, but it has also been reported after isoniazid therapy for tuberculosis.

Sulfites

9.43   A proportion of the population, possibly 1%,[412] is sensitive to sulfites. Sulfites can occur naturally in food while sodium and potassium bisulfites and metabisulfites and sulfur dioxide are widely-used as food additives as preservatives and antimould agents and are found in products such as dried fruits, canned vegetables, maraschino cherries, guacamole and wines,[413] as well as in fresh salads and fruit which have been treated with a "stay fresh" spray. Adverse reactions in non-asthmatics seem to be rare, but a number of case reports indicate that reactions in asthmatics may not be uncommon (e.g. Stephenson & Simon[132]). It has been shown that about 40% of those with a history of sulfite-sensitive asthma respond positively to oral challenge with sodium metabisulfite.[414] It has been suggested that overall 5-10% of asthmatics react to sulfites, but the true incidence is unknown and the mechanism is not understood (see paragraph 5.1).[133,413]

Enzyme polymorphisms

9.44   Effects of enzyme polymorphisms are well known in relation to drugs, where polymorphisms can profoundly affect both the toxicity and efficacy of therapeutic compounds. In relation to other xenobiotics however, little information is available on any effects produced by polymorphisms, presumably because exposure is less well documented and cause-and-effect relationships are more difficult to establish. A variety of enzymes involved in xenobiotic metabolism have been shown to differ in activity between individuals and in many cases these variations have been attributed to genetic polymorphisms. Such enzymes for which there is likely to be an interaction with dietary components include histaminases, sulfotransferases, cytochrome P450 isozymes, glutathione-*S*-transferases, cysteine dioxygenase, flavin monooxygenase and possibly sulfite oxidase. One hypothesis is that failure to catabolise amines in the intestinal wall or liver might permit entry of the active compounds into the circulation in such quantities that the amines could exert their pharmacological actions on the intestinal mucosa, smooth muscle, the heart and elsewhere. Genetic polymorphisms of various enzymes including amine oxidases responsible for the catabolism of these compounds have been reported[197,415-417] but the role of such polymorphisms in adverse reactions to foods remains to be examined. Whilst it is true that the intestinal wall and liver contain highly active enzymes responsible for the inactivation of amines, adenosine derivatives and other pharmacologically active compounds that occur in the diet,[418] there are multiple compensatory metabolic pathways and the barriers to uptake are both selective and efficient. A study by Scadding and colleagues[419] found an association between poor sulfoxidation of *S*-carboxymethyl-L-cysteine and a range of food sensitivities. It was suggested that the metabolic deficiency may alter the metabolism of sulfur-containing food constituents or affect the availability of sulfate for conjugation reactions. A well-defined interindividual difference in metabolism of a food constituent is the N-oxidation of trimethylamine derived from fish. Those individuals with a defective form of flavin monooxygenase have a relatively low ability to oxidase trimethylamine which produces a characteristic odour (fish odour syndrome).[420]

Mucosal disaccharidases

9.45   Disaccharidases are enzymes located in the brush border of the small intestine.[421] Disaccharides are poorly absorbed and oligosaccharides are virtually non-absorbable in the small intestine. Thus the final stage in carbohydrate digestion is hydrolysis of disaccharides by enzymes on the gut mucosa to monosaccharides for absorption (Table 9.5). In the absence of disaccharidase activity the disaccharide passes to the large bowel where it is fermented by the intestinal bacteria to a number of products e.g. carbon dioxide, hydrogen, short chain fatty acids, methane, that can cause a variety of abdominal manifestations, the severity of which depends on the amount of disaccharide consumed.

Table 9.5: Disaccharidase enzymes, their substrates and the resultant monosaccharides

Disaccharidase	Disaccharide hydrolysed	Products of hydrolysis
Lactase	Lactose (milk sugar)	Glucose and galactose
Sucrase-isomaltase:		
Sucrase moiety	Sucrose (cane and beet sugar)	Glucose and fructose
Isomaltase moiety	Isomaltose and α-1,6-bonds in limit dextrins (products of starch digestion)	Glucose
Trehalase	Trehalose (a sugar found in fungi)	Glucose

9.46 In the case of glucose and fructose, their uptake by the mucosa is normally rate-limiting rather than the prior hydrolysis of their combination in sucrose. In the case of lactose, hydrolysis is often the rate-limiting step. Lactase deficiency (alactasia) is the most important disaccharidase deficiency and produces lactose intolerance. Congenital alactasia is rare, but most of the world's population in adult life are unable to digest lactose. This is because most humans, in common with other mammals, have a maturational loss of intestinal lactase activity beyond early childhood, i.e. after they have ceased depending on maternal milk. As a generalisation, lactose can be digested by North Europeans, Punjabis, Mongols and the Fulani and Tussi tribes of Africa. With racial intermixing, the ability of populations to digest lactose increases as European genes, including the (presumably dominant) mutation maintaining lactase activity, enter their gene pool. About 70% of the population worldwide are affected by alactasia: notably Asians and Africans and those of Jewish and Hispanic descent.[422,423] In a Greek population lactose intolerance was present in 7.3% and 8.6% of 5 and 12 year old children and in 75% of adults.[424] The ubiquity of milk and milk products in the typical western diet may therefore cause symptoms in many populations. Nonetheless, there is no need to exclude milk and dairy products unless they cause symptoms, which is not always the case. It is possible for Europeans adults, who normally have lactase activity, to lose it after intestinal disease or surgery and become lactose intolerant either transiently or permanently. Sucrase-isomaltase and trehalase deficiencies are rare. Sucrase-isomaltase deficiency is an inherited disorder, causing intolerance of sucrose.[425] Trehalase deficiency is said to cause intolerance of trehalose present in fungi.[426,427] In all the disaccharidase deficiencies, the effects are dose-related so that, in general, small amounts of the offending disaccharide are tolerated.

Glucose-6-phosphate dehydrogenase deficiency (favism)

9.47 In certain circumstances, deficiency of some of the various enzymes, such as glucose-6-phosphate dehydrogenase (G-6-PD) and methaemoglobin reductase involved in protection of the red cell and haemoglobin against oxidation, can give rise to food intolerance. Of these by far the most important is G-6-PD. G-6-PD is a key enzyme in the pentose phosphate pathway and catalyses the conversion of glucose-6-phosphate and NADP to 6-phosphogluconolactone and NADPH. In individuals with low enzyme activity, acute haemolytic anaemia can occur in response to a number of drugs and also after ingestion of broad (fava) beans, due to their content of two β-glycosides, vicine and convicine. Other foods, e.g. spinach, may have a similar effect. Favism, the disease that results, consists of haemolytic anaemia, accompanied by jaundice, abdominal pain and splenomegaly.[428]

Methaemoglobinaemia

9.48 Low levels of activity of the enzyme methaemoglobin reductase may result in high levels of circulating methaemoglobin and an abnormal response to exposure to oxidant chemicals. In the diet the main components likely to give rise to this phenomenon are the nitrites.[429] It should be noted that methaemoglobinaemia after exposure to nitrites can also be caused by abnormalities of the haemoglobin itself, rather than enzyme deficiency.[430]

Interference with drug metabolism by interaction of food with cytochromes

9.49 An interaction between grapefruit juice and the drug terfenadine can cause fatal cardiac arrhythmias: in these cases grapefruit juice inhibits the presystemic metabolism of that drug, by inhibition of CYP3A4.[431-433] Consumption of preparations of St John's wort (*Hypericum perforatum*), which is available in the UK as a dietary supplement, has been associated with large reductions in plasma concentrations of the HIV-1 protease inhibitor indinavir[434] and acute heart transplant rejection episodes in two patients taking cyclosporin as one component of an immunosuppressive drug regime.[435] In each case induction of the CYP3A4 isoenzyme of cytochrome P450 by St John's wort was implicated as the probable cause (see Breckenridge[435a]).

Action of lectins

9.50 These complex glycoproteins are found in plants such as the castor oil plant, kidney beans, lentils, soya beans, peanuts.[436] They bind tightly to specific carbohydrate groups and, if they become attached to cell surfaces, they may cause pharmacological effects by changing cell permeability and metabolism. Lectins can be cytotoxic or they may force cells to divide. Some lectins are intensely poisonous, whereas others, for example those in tomatoes, are well-tolerated. Many lectins, for example those in wheat, are destroyed in cooking but, with increasing consumption of raw foods, consumption of lectins is almost certainly increasing. If ingested, lectins may cause nausea, vomiting, abdominal pain and diarrhoea within one to seven hours. Recovery occurs within 24 hours and the pattern and timing is often mistaken for food poisoning of microbiological origin. Amongst the commonest causes of illness from lectins is that produced by the phytohaemagglutinin in red kidney beans.[437] Similar disorders can follow consumption of other leguminous seeds including soya beans and lentils. The harmful lectins are often readily removable by washing and cooking but lectins in some foods are resistant to cooking and the precise conditions of cooking can make a considerable difference; thus soaking before cooking greatly decreases the time necessary to inactivate the lectin of red kidney beans.[438]

10. Diagnosis, investigation and management

Diagnosis

10.1   The diagnosis of adverse reactions to food and food intolerance depends on clinical insight, suspicion, and acumen in interpreting the history and examination of the patient being displayed by an appropriately-trained health professional. It is often difficult because of the variable and subjective nature of the symptoms and the lack of objective clinical signs.

History

10.2   The key to clinical diagnosis of immunological and non-immunological adverse reactions to food and food ingredients is the patient's history, particularly the temporal relationships between exposure and reaction. The nature of the reaction should be fully documented, with particular attention being paid to accurate description of the symptoms, to timing relative to ingestion and to the form in which food was eaten, e.g. cooked, raw, fresh, old, processed, and how it was stored. The amount eaten should also be ascertained. The history is most helpful with acute reactions and is less useful with delayed reactions and chronic problems and their exacerbations. Furthermore, if the diet is a limited one and the response is rapid, a cause-and-effect relationship can be easily identified but assessment will be less straightforward when the diet is diversified and the effect is delayed or of slow onset. This is a problem with certain foods, for example cows' milk enteropathy can present insidiously and sometimes asthmatic and skin features develop 2-4 hours after exposure to precipitants. It is helpful to establish if the reaction has been reproducible and to establish if it is associated with exercise or temperature changes.

10.3   Even if a food-related problem is suspected, it is important to avoid preconceptions about the mechanism, particularly by making an assumption that immunological mechanisms are involved. It is equally important to be aware that although adverse and, in particular, allergic reactions to food are common in children, such reactions can occur also in adults.

10.4   The identification of problem foods is not always easy and food and symptom diaries can be used to identify such foods. Thus Kueper and colleagues[189] found that this approach helped 75% of patients when used as a guide for elimination diets. However, subsequent open challenges with the suspected food components only confirmed 47% of the reactions. It should therefore be recognised that, although this approach may help patients in their self-management, it is not sufficiently rigorous to support research-based conclusions and substantiate policy decisions.

10.5   In compiling food diaries, patients, their carers and health professionals need a thorough knowledge of the diets that are consumed by the patients and are reliant on the declared composition of foodstuffs. The information on food labels is not always sufficient for the diagnosis and management of adverse reactions to food. The statutory requirement is that

food labels are required to declare ingredients if they constitute more than 25% of the food stuff (see Appendix 5). Anything below this threshold does not have to be indicated. Consequently it is possible, particularly in the case of allergens, for foods to contain hazards of which the consumer is unaware. For example, a biscuit base or crumble often contains nuts at a level which does not need to be declared. Derivatives of milk, egg and cereals are also very common in processed foods, while nut oils and foods containing them may be a hazard to those who are nut allergic. Such hazards are, understandably, called hidden allergens or hidden hazards, and they represent an important consideration in assessing dietary histories for possible precipitants of reactions, designing elimination diets and in the subsequent avoidance of potential precipitants in the diet.

10.6 Although many manufacturers are willing to release detailed lists of ingredients to patients, carers and appropriate health professionals, manufacturers themselves may not have complete control of the composition of the ingredients which they purchase. Another possible source of uncertainty arises from potential contamination from other production lines during the processing of foods. This is why some products are labelled with a warning to the effect that they cannot be guaranteed not to contain a particular ingredient. From the diagnostic perspective this can sometimes confound analysis of the dietary history and can lead to unexpected variability in the response to elimination diets (see paragraphs 10.11-10.12 below).

10.7 A related problem is the variability of compositional data concerning natural toxicants or other components in natural foodstuffs to which adverse reactions might occur. A variety of test-kits based on immunological analyses are being assessed in the context that they could be used by sufferers or by their carers or professional laboratories to check foodstuffs for specific ingredients.

Family history

10.8 The family history is useful in all types of adverse reaction to food. A family history of atopy will increase the index of suspicion of immune-mediated adverse reaction. If one parent is atopic there is a 20-40% chance of a child developing this type of condition and, if both parents are atopic, a 50-80% chance. A family history of the condition may be present in coeliac disease and in adverse reactions to food of non-immunological origin, such as G-6-PD deficiency and disaccharidase deficiencies. Ethnic origin may be important in these conditions, symptomatic lactase deficiency being classically more common amongst Chinese and Africans than in Caucasians and favism more so in the Eastern Mediterranean peoples.

Occupational and environmental exposure

10.9 An occupational history of exposure, usually by the respiratory route, to allergens present in food is sometimes found in those who work in the food industry and who acquire adverse reactions to the food when it is in the diet.[131,369] Similarly, reactions to certain foods can occur in individuals with occupational exposure to latex, while asthmatic reactions have been reported with occupational exposure to food ingredients.

Investigation

Examination

10.10 Standard physical examinations can provide objective evidence to support patients' histories. They might demonstrate additional clues to the possible basis of an adverse reaction to food. Thus, a child with a skin rash might have other features, for example of the respiratory tract or upper airways, consistent with atopy. There might also be evidence of secondary features of an adverse reaction such as signs of malnutrition. Thus there may be failure to gain weight or height as a result of maldigestion and malabsorption or because of dietary restriction without adequate dietetic advice. If there are behavioural abnormalities or related concerns the examination should pay attention to pyschomotor/neurological development and integrity and efforts should be made to observe the child's behaviour.

Elimination diets

10.11 An important clue to the role of a foodstuff in causing a patient's problems can be derived from the resolution of these problems when an offending foodstuff is eliminated from the diet. A difficulty with this approach arises if the symptoms are caused by more than one foodstuff because then benefits might not be observed if only one precipitant is eliminated from the diet. The strategic planning of an elimination diet needs to be based on a thorough dietary history or food diary coupled with appropriate clinical acumen and an informed insight into the composition of foods to avoid accidental ingestion of precipitants and to ensure the nutritional adequacy of the diet.

10.12 A procedure that is sometimes used is to put the patient on a diet with a limited number of foods and potential precipitants (a "few foods" diet[267]) and then gradually, item by item, at a time interval of about a week, reintroduce the foods that are suspected precipitants. Elimination diets can be very monotonous and demanding and need to be strictly supervised by an appropriate health professional, usually a dietician. Such is the tediousness of elimination diets that often their therapeutic effectiveness can be gauged by the patient's concordance with the diet.

Specific diagnostic tests for immunological adverse reactions to foods and food ingredients

10.13 Diagnostic procedures for allergic disease of the gastrointestinal tract in childhood have been detailed by the European Society for Paediatric Gastroenterology and Nutrition.[438a]

Skin prick tests

10.14 In cases of suspected IgE-mediated immunological reactions to food a skin prick test may be performed. In it a small amount of an allergen in solution is placed on the skin and then introduced into the epidermis by gently pricking the skin surface. A positive reaction is manifested as the development of a wheal the diameter of which can be measured to grade the reaction. A positive test can confirm that the patient is atopic and can strengthen suspicions about probable precipitants: but these tests are not diagnostic. The diagnostic

accuracy of a skin prick test in suspected food allergies varies according to the possible offending food. Negative reactions have a 95% accuracy of there not being an IgE reaction, however, positive tests have only a 50-60% predictive accuracy. Nevertheless, they can be helpful especially in cases where clinical reactions at onset have been severe and would not allow a repeated oral challenge for confirmation of diagnosis.

10.15 The precise composition of the material being tested is important: some test substances are not stable, and there is a need to use locally-produced samples, particularly of fresh fruits and vegetables. There is a need for standardisation of allergens and of derived test materials, as well as protocols to facilitate epidemiological and other multicentre studies of adverse reactions to foods, particularly allergic reactions. Care must be taken during these investigations as severe reactions can be precipitated, and the tests should be done under the supervision of health care professionals (see paragraph 10.26).

Radioallergosorbent test

10.16 The radioallergosorbent test (RAST) demonstrates food-specific serum IgE antibodies but these tests correlate variably with the diagnosis, particularly because the levels of antibody to some extent are exposure-related as has been shown for elevated IgE levels to cows' milk protein.[63,324] Thus, if an individual has already excluded an allergen from her/his diet, the relevant specific RAST test might be negative.

10.17 Thus, RAST and skin prick tests are not in themselves diagnostic. The positive predictive accuracy is insufficient for individual patient management and it also decreases with age.[439] The combined negative predictive accuracy of a negative RAST and skin prick test is around 95%.[58,440] Commonly individuals who have positive IgE RAST and skin tests to food antigens experience no clinical benefits from food exclusion and show no reactions when challenged.

10.18 The wide clinical spectrum of food (cows' milk protein) induced symptoms in childhood helps to illustrate these difficulties.[441] Hill and colleagues[442] assessed the relationship between clinical symptoms and serum antibody levels in children up to five and half years of age, shown by milk challenge to have adverse reactions to cows' milk. They found that the patients could be divided into three groups:

● those children who showed immediate symptoms with small amounts of milk, evidenced by anaphylaxis, angio-oedema, urticaria and diarrhoea,

● those who developed symptoms often up to several hours after intake of moderate amounts of milk (*circa* 200 ml) and in whom the skin test to the offending food was generally negative, and

● those, mostly older children, suffering from a poorly defined multisystem involvement, including e.g. skin, lung, gastrointestinal tract, central nervous system (migraine headache), who often required larger amounts of milk more frequently, and in whom symptoms could take over 24 hours to occur.

10.19 There were higher levels of total IgE and IgE anti-milk antibodies in the first group than in the second, but there was no consistent correlation between acquisition of tolerance and changes in antibody levels in any group.

10.20 The lack of standardisation of tests for the determination of antibodies to dietary antigens, and the lack of discrimination between high and low affinity antibodies with conventional ELISA techniques have made quantitative evaluation of different studies difficult. There is a need for their optimisation to facilitate both the interpretation of published studies and patient management.

Tests for non-IgE-mediated immunological reactions

10.21 In contrast to the situation described later with IgG antibodies to food, the measurement of IgA anti-endomysial and anti-reticulin antibodies in patients with untreated coeliac disease and their relatives has a high specificity and sensitivity, greater than 96%, for gluten-sensitive enteropathy.[87,443] However, it should be noted that these antibodies arise from the pathological process and are not antibodies to gluten or to any other food or food ingredient. Such positive reactions can identify patients in whom intestinal biopsy is merited. The determination of antiglutaminase antibodies, which appear to be closely related to the pathogenesis of coeliac disease may prove to be better diagnostic markers. Similar serological tests are not available for other enteropathies, in these histological examination of biopsies of the intestinal mucosa are necessary for diagnosis.

Endoscopic studies and intestinal biopsy

10.22 Endoscopic biopsy of the small intestine is a relatively simple investigation and is often used in patients with a variety of slow-onset gastrointestinal symptoms such as frequent loose stools or features of unexplained iron deficiency, osteoporosis, weight loss, slow increase in height and other features of malnutrition. Often these features cannot be directly related to food ingestion but in the past the frequency of unexpected coeliac disease was such that this test was an important routine diagnostic tool. The biopsy would be examined for the histopathological changes associated with enteropathies which have been described earlier. Intestinal biopsy is not indicated for the diagnosis of acute IgE-mediated gastrointestinal phenomena. In these conditions a biopsy may show degranulated IgE positive mast cells on conventional histology[444,445] but it is difficult to process the specimen in such a way that the cells can be differentiated with confidence. Gastric, rectal and colonic biopsies are helpful in the evaluation of allergic gastroenteropathies and colitis.

Other tests in immune-mediated adverse reactions to food

10.23 Indicators, such as flow cytometric studies of peripheral blood mononuclear cells and IgE in faecal extracts,[446-449] may identify groups of food allergic patients but their usefulness in the diagnosis of food intolerance in the individual remains to be demonstrated. A more detailed analysis on a cellular level[57] may increase the diagnostic power of *in vitro* tests.

10.24 The measurement of eosinophil inflammatory mediators in stool samples[364] and endoscopic provocation tests[450] in which potential precipitants are applied directly while the intestinal mucosa is observed, are being evaluated. It is hoped that these will improve the possibility of identifying afflicted patients on an objective basis.[61]

Tests of respiratory function

10.25 Tests of respiratory function will be useful where respiratory signs and symptoms are present in immunologically-mediated adverse reactions to food. Such tests may include those for narrowing of the airways and/or inflammation.

Food challenge

10.26 The diagnosis of IgE-mediated and other immunologically-mediated adverse reactions to food can only be confirmed by exclusion of the suspected food substance with amelioration of symptoms and their subsequent recurrence on re-introduction of the offending food. This can be done on an open basis or by single blind challenge when the offending food is given to the subject who is kept unaware of what they are being given. Open challenge is less convincing than a single blind challenge. Ideally the condition should be evidenced by the DBPCFC, which is the "gold standard" because all objective and subjective bias is removed. However DBPCFCs are costly, time consuming and not easy to do: keeping the challenge blind is not always easy. In cases where the placebo and the challenge can be distinguished by taste, capsules can be used and food colours can be disguised in biscuits. Great care is needed. Indeed, in the majority of cases food DBPCFC is impractical as a diagnostic tool and may be dangerous and unethical, as there is a risk that severe reactions may occur. Precautions may be necessary, such as ensuring that emergency treatment facilities are available in the event that a challenge induces an anaphylactic reaction. If a person reacts to more than one food or food ingredient, then dietary exclusion of one of these precipitants may not have any benefit on the patient's clinical features. Similarly any response to a subsequent challenge might not be detected against the background of continuing reactions. Therefore it is often helpful to place such patients on a few foods diet before conducting DBPCFC.

10.27 Objective outcomes which are quantifiable are helpful for the interpretation and standardisation of DBPCFCs. This has been applied to respiratory function and efficiency[114] and to atopic dermatitis (SCORAD)[451] and an overall symptom clinical score has been developed.[1]

10.28 Further attempts to systematise objective scoring of allergic reactions have been based on a scale derived from reactions to Hymenoptera stings.[452]

Non-validated diagnostic tests for immunologically-mediated adverse reactions to food

10.29 There are a number of procedures that have been used to diagnose adverse reactions to food, which have not been fully validated.[440,453] These include:

IgG antibodies

10.30 Early hopes that measuring circulating concentrations of IgG and IgG4 would assist in diagnosis were dispelled by the demonstration that immunological sensitisation and production of IgG and IgG4 antibodies to food proteins were part of a normal immune response which varies according to age and exposure.[454,455] Currently, the determination of IgG antibodies to food has no predictive value for dietary management of patients with food allergic diseases (see also paragraph 10.21).[152,456,457]

Other non-validated tests

10.31 **Cytotoxicity tests.** These are tests in which a food allergen is added to whole blood or white blood cell suspensions *in vitro*. Changes in the appearances of the cells or in their numbers are hypothesised to indicate sensitivity to food containing the allergen. There is little evidence to support the efficacy of these tests in diagnosis[458] and the incidence of false positives is very high.[453]

10.32 **Electroacupuncture including the Vega test.** In this test, the electrical activity of the skin is determined at points considered appropriate for the detection of food allergy and other conditions. There is no scientific or clinical proof of the diagnostic efficacy of the test.[43] The Vega test is a technique that has been developed from electroacupuncture, in which the resistance between the skin in contact with a hand electrode and the skin tested with a measuring stylus is observed, using a galvanometer. Ampoules, containing extract of materials such as Candida are placed in a metal honeycomb which is in series with the circuit. There is no evidence to support the usefulness of this diagnostic method.[459]

10.33 **Sublingual, subcutaneous and intradermal provocation and neutralisation tests.** In these tests, the food extract is given sublingually or injected subcutaneously or intradermally: this provokes symptoms which are neutralised by immediate injection of weaker or stronger solutions of the food extract. The test is not standardised and has been used in the diagnosis of a wide variety of conditions apart from food allergy. Evaluations of the test in relation to food allergy suggest that it has no discriminatory value.[460-462]

10.34 **DRIA test.** This is a variant of the provocation and neutralization test, which relies upon the measurement of the strength of the quadriceps muscle. In sensitive individuals it is said that contact with the allergen brings about a decrease in the strength of the quadriceps. The test does not appear to have been scientifically evaluated.[43]

10.35 **Applied kinesiology.** This is based on the subjective measurement of muscle strength in one hand of the subject, while the other hand holds the suspect food in a glass bottle.[463] There is little information on the value of this test

10.36 **Autologous urine injections.** In this test it is claimed that urine from sensitive individuals will cause positive skin test reactions in subjects with the same sensitivity. There is little information on the value of this test and it may be potentially dangerous.[453]

Non-immune-mediated food intolerance

10.37 In non-immune-mediated food intolerance, the history and examination may have indicated a possible basis for the reaction and tests can be chosen to confirm or test any tentative diagnosis. Because there are many different manifestations and mechanisms involved in these reactions to food, it is not surprising that there is often no specific *in vivo* or *in vitro* test to confirm a clinical diagnosis. However, appropriate food challenges and biochemical tests, e.g. the activity of enzymes such as G-6-PD and methaemoglobin reductase in red blood cells or disaccharidases in intestinal biopsy specimens, can be used to substantiate clinical suspicion and to inform the management of the condition. During an appropriate attack, a raised plasma concentration of histamine may be measured and urinary levels of the metabolites of histamine and catecholamines may be helpful.

Management

10.38 The management of patients with adverse reactions to food depends on the elimination of the suspected precipitants from the diet. Ideally this should be done under the supervision of a competent health professional. This report has already noted that some individuals' perception of their symptoms and of their reaction to possible precipitants are not substantiated by systematic evaluation. Such patients should be discouraged from following self-imposed diets, without medical support, dietary advice or objective monitoring of therapeutic efficacy.[464,465] Otherwise patients are at risk of having an inadequate diet which can cause undernutrition. For similar reasons foods should not be eliminated from the diet solely on the basis of positive skin tests or RAST, in the absence of symptoms and clinical signs suggesting the possibility of adverse reaction to specific foods or ingredients.

Avoidance of the precipitant

10.39 Many prepared or semi-prepared foods contain components that may, at first sight, be unexpected. This means that avoidance is not as easy as it appears and inadvertent exposure may take place. Patients, especially those with severe anaphylaxis-type reactions, need to be suspicious and screening kits may be useful for allergen detection. In immune-mediated food intolerance, patients should be taught that ingestion is not the only route of exposure and that topically applied and inhaled material may be equally dangerous.

10.40 An alternative to patients avoiding allergenic foods is the reduction or eradication of potential allergens from food. This approach is adopted for infant formulas.[466] In these, allergenicity of the cows' milk proteins is reduced by a combination of enzymatic hydrolysis and heat denaturation. This treatment both changes the shape of the proteins and breaks them down to smaller, possibly less allergenic, polypeptides. These products can then be filtered to remove any larger molecules which might remain. Hydrolysed cows' milk formulas are alternatives to soya formulas for infants with cows' milk allergy, as are other types of hydrolysed proteins.[97,101,467] These products are sometimes called "hypoallergenic". Some such formulas are based upon protein sources other than cows' milk. They cannot be regarded as free of potential allergens and some babies react to hydrolysed products. Allergens can be removed in the same way as with cows' milk products. Thus, wheat can be rendered

hypoallergenic by enzyme fractionation.[468] Selective plant breeding and novel techniques such as genetic modification can be used to exclude the antigen causing food allergy (e.g. antisense genetic modification in rice).[469] Furthermore, antibodies can be used to select strains of wheat with low amounts of allergens, such as the 27 kDa wheat albumin.[470]

10.41 Infants with allergy to cows' milk protein should be fed a formula free of cows' milk protein allergens. Thus soya-based formulas may be used in place of milk-based formulas in infants, but since these may also be allergenic, an alternative is to use formulas with reduced allergenicity from different protein sources (such as bovine whey, bovine casein, bovine or porcine collagen, soya or a mixture of these). However, it should be noted that evaluation of the allergenicity of these products by a range of *in vitro* tests of IgE binding and RAST data does not necessarily predict the lack of reaction in sensitised infants. The regulations of the European Union for labelling infant formulas as having reduced allergenicity require that the product's immunoreactive protein content is less than 1% of the total nitrogen-containing substances, but the usefulness of this threshold has not been established. Only pure amino acid mixtures can be regarded as totally non-allergenic. The clinical evaluation of a product for reduced allergenicity and use in the treatment of cows' milk protein allergy is based on the principle that the product should be tolerated by 90% (with 95% confidence) of infants with proven cows' milk protein allergy (reviewed by Høst and colleagues).[466]

10.42 In older patients substitution and alteration of foods can be used. For example, fat spreads that do not contain milk ingredients and soya "milk" can be used by those who are intolerant to cows' milk.

10.43 Those suffering from coeliac disease are usually advised to avoid wheat, rye and barley. Traditionally it has been assumed that oats should also be avoided but it has been shown, in adults with coeliac disease, that a moderate intake (approximately 80 g daily) can be tolerated.[85,471] In adverse reactions not of immune origin, avoidance of the precipitant is often the only measure that can be taken. This can sometimes be done by removal of the precipitant during processing rather than by avoidance of the food (as with red kidney beans). Selective breeding and genetic modification of plants may be used to reduce potential exposure. Sufferers from the non-immune type of adverse reaction to food rarely have very acute symptoms and the offending item(s) rarely constitutes a major proportion of the diet, with the possible exception of lactose in lactose intolerance. Therefore major alteration of the diet is seldom necessary.

10.44 Clearly some consumers and those involved in health care and food processing would benefit from being able to detect potential allergens in food. To this end, enzyme immunoassay techniques have been used successfully for the detection of proteins from soya, gluten and milk in food. Immunoassay kits have also been developed for peanut globular storage protein and egg, and are being developed for whey, casein, soya bean and almond.

Novel foods

10.45 Novel foods, whether they are exotic imports, new breeds, or whether they are the products of genetic modification, other biotechnologies and processing, might be potential

allergens. The risks of allergic or other reactions arising from novel products or from altered exposure and absorption of immunoreactive epitopes are considered in the safety evaluation of products which might be allergenic.[340] If the food is known to be associated with one of the eight well-known food allergens, then it is tested for allergenicity *in vitro* against serum from patients known to react to the related allergen. It has been calculated that fourteen subjects are needed to have a probability of 99% of detecting an allergen with which 50% or more sensitised individuals would react. If there are any positive reactions no further tests are done. Negative results are confirmed by skin prick tests in the same subjects; if these are also negative then the study progresses to a DBPCFC to confirm the lack of any reaction.[472] Recombinant proteins have a similar allergenicity to their native counterpart. This has been demonstrated during the assessment, using the above procedure, of a transgenic soya plant which contained the gene for a Brazil nut protein which had been inserted to improve the methionine content of the soya. The known allergenicity of the Brazil nut protein was found to persist.[473] If the novel product has no strong association with any allergenic food, or none at all, then the above *in vitro* and *in vivo* assessments of allergenicity are not practicable. Indirect methods are then used. These involve structural and amino-acid sequence analysis of the proteins, assessments of other physico-chemical characteristics such as stability to simulated gastrointestinal hydrolysis[329] and studies in animal models. The appropriateness of these approaches and their reliability are not yet established fully.[474,475]

Elimination diets

10.46 In cases of adverse reactions to foods, where the food has been identified the prescription of a diet that will avoid the food or ingredient should in theory be easy but the comments on composition (see paragraph 10.5 and Appendix 5) should be borne in mind. With adverse reactions to ubiquitous food items such as soya and peanut and to a lesser extent some tree nuts, the risk of exposure to hidden allergens should be explained to patients. In severe food allergy the nature and risks of reactions following re-exposure need to be discussed with the patient and potential problems, such as the fact that labelling can often not be relied upon, must be explained.

Other treatment modalities

Drugs - disodium cromoglycate

10.47 Some authors report positive effects of oral disodium cromoglycate and other anti-allergic compounds on clinical symptoms and on intestinal permeability[476-478] Prospective studies examining this form of management are lacking and this therapeutic approach either is only occasionally effective in a minority of patients or is entirely lacking in efficacy.[110,479,480]

Probiotics

10.48 The use of specific probiotics (for example *Lactobacillus* CG) to modify the intestinal microflora of infants is being explored. It is suggested that these ameliorate the symptoms of food allergy by changing the allergenicity of dietary proteins, reducing the intestinal mucosal inflammatory response and permeability and enhancing the gut's IgA response to dietary antigens.[481]

Immunotherapy

10.49 Because of the difficulty of avoiding some precipitants of adverse reactions to food of immune origin, specific immunotherapy has theoretical attractions. However, there are safety issues involved and the use of immunotherapy remains controversial and of uncertain value,[482] although immunoprophylaxis based on the oral administration of nanoparticles containing DNA encoding for peanut allergens is being studied.[483]

Injectable adrenaline

10.50 Subcutaneous injection of adrenaline is beneficial and even life saving for use in the event of severe anaphylaxis of the type associated with immunological adverse reactions to peanut.[59,484,485] The need to continue carrying adrenaline preparations should be assessed regularly by competent health professionals.

Prevention

10.51 Allergen avoidance to avoid sensitisation may be practised: whereas this is hardly practicable with the whole population, advice may be given to groups especially at risk. Thus, the Committee's report on peanut allergy[59] advised that infants in high risk groups (defined as children with atopic parents or siblings) should not eat peanuts or foods containing peanuts. In addition, it was advised that pregnant and nursing mothers whose child might be in a high risk group may wish to avoid peanuts or foods containing peanuts during pregnancy and lactation. This advice, made specifically with respect to peanuts, might be extended to include diets involving the elimination of other allergens during pregnancy and lactation. However, the role of exposure to antigens in breast milk in the aetiology of adverse reactions of immune origin is presently unclear (see paragraphs 10.52-10.55). Moreover, there are obvious problems in restricting the diet during pregnancy. With infants who are not being breast fed, the use of infant formulas based on non-milk protein sources e.g. soya or proteins degraded by heat and enzymatic digestion (hydrolysates), may reduce infants' exposure to allergens (see paragraphs 10.40-10.41). It should be noted that sensitisation can occur via non-food sources (see paragraphs 9.23-9.25).[486,487]

Role of breast feeding in prevention of sensitisation

10.52 Breast feeding is presumed to have an allergy preventative effect when compared with feeding the infants with formulas based on cows' milk, but this is controversial. The ideal study to investigate this would involve randomising babies to formula-fed and breast-fed groups. This would not be regarded as ethical. Studies in this area include: (i) studies of whole populations of children, regardless of family history; (ii) studies confined to children with a family history of atopy; (iii) studies confined to children with a specific atopic disorder. Although the earliest general population study showed a protective effect for breast feeding in relation to development of eczema in the first 9 months,[488] other studies showed no protective relationship.[489,490,491] For asthma and wheezing, no protective effect was found in one study,[492] it was evident in two others.[493,494] In another such study the effect was found only up to one year,[490] while in a further study there was an association which did not achieve statistical significance.[494a]

10.53 Moreover, skin prick testing showed, in one population, that allergic response was significantly more likely in children who had been breast fed.[495] Among the five studies of children with a familial history, one showed no relationship with eczema, wheezing or positive skin test,[496] one showed increased IgE antibodies among those who had been breast fed,[497] one showed no relationship with eczema but a significant reduction in wheezing in the first year of life;[498] only the two studies by Chandra[499] and Chandra and colleagues[500] claimed substantial benefits for breast feeding but it is not clear how comparable the groups were in his studies.

10.54 Some of the confusion in the studies may be due to confusion of diagnoses. For example, in one study breast feeding was significantly associated with a reduced prevalence of wheezing, but this seems to have been entirely due to a reduced prevalence of lower respiratory infection (one of the benefits of breast feeding) rather than of asthma.[498,501,502] Criticisms of studies that fail to find a protective effect have tended to suggest either that the mother did not breast feed for long enough, or introduced non-breast milk supplements too early. Alternatively, it has been suggested that, while breast-feeding, they have failed to avoid ingestion of the likely sensitiser. There are definite advantages in breast-feeding in terms of the avoidance of infection, and it is important not to discourage mothers from breast-feeding. The stress to a mother of restricting her own and her child's diet in the hope of preventing allergy (with consequent guilt if the child develops asthma or eczema) is not justified for major components of the diet on the evidence available.

10.55 In recent prospective studies the allergy preventative effect has only been evident in infants with a high risk of developing atopy who have at least one first degree relative with atopy. In these infants breast feeding for the first four months of life alone or with a cows' milk free diet was associated with a significant reduction of atopic dermatitis and cows' milk allergy during the first 2-4 years of life. There is no good evidence that maternal avoidance of cows' milk during pregnancy is protective. There is some evidence that this practice may enhance the preventative effect on atopic dermatitis of breast feeding but this is disputed.[466]

Prognosis and natural history

Immune-mediated adverse reactions to food

10.56 The duration of clinical symptoms, for example in cow's milk allergy, is very variable both in infancy and childhood.[58,61,155] Thus, 85% of children who had cows' milk allergy in the first two years of life had lost their reaction at three years of age.[503] Similarly 80% of infants with egg allergy could tolerate egg at 5 years of age.[504] Infants who develop allergic symptoms under the age of 3 months appear to have a better prognosis for future clinical tolerance as compared with those with a later onset.[63] The time to clinical recovery may be related to the sensitising food and the age of first exposure or reaction.[53,326,505] For example, peanut allergy has been considered to be a persistent allergy.[335,506] However, in a longitudinal study it was found that 18% of preschool children with a history of a mild reaction to peanuts subsequently lost their reaction,[507] consequently this concept may need to be re-appraised. In contrast, patients with coeliac disease should avoid gluten for life but, for gluten enteropathy of onset in childhood, the need for continued dietary exclusion would usually be reassessed in adolescence.

Non-immune-mediated adverse reactions to food

10.57 In the case of non-immune adverse reactions to food, the prognosis depends on the underlying disease. In many cases, e.g. favism, the biochemical defect is life-long and an appropriate diet will therefore have to be followed for life.

I I. Conclusions

11.1   The remit of the Working Group, as defined in their terms of reference, was:

●   to consider whether the incidence and prevalence of adverse reactions to foods and ingredients are changing;

●   to consider those foods identified as commonly causing adverse reactions and rank them separately for prevalence, potency, and severity of reaction;

●   to consider the underlying mechanisms;

●   to identify factors, both genetic and environmental, which may increase the risk to health.

Classification of adverse reactions

11.2   In order to address the remit the Working Group adopted the classification system for adverse reactions to foods defined by the European Academy of Allergy and Clinical Immunology. In this classification a distinction is made between those reactions which result from a toxic mechanism applicable to any individual and other adverse reactions to food which are not general in the population.

11.3   Adverse reactions to foods can be mediated either through immunological or non-immunological mechanisms. In the case of the former, such reactions are defined as food allergy. The practice of calling all adverse reactions to food "allergies" is inappropriate and misleading and a clear distinction between immunologically-mediated food allergy and non-immunological food intolerance should be made. Food allergy is commonly mediated by IgE antibodies although other immunological mechanisms are important in some circumstances. Most adverse reactions to foods are due to intolerances which are either clearly non-immunological or are of unknown or unproven immune pathogenesis. Food aversion of psychological origin was not considered by the Working Group.

Prevalence

11.4   There are no systematic data which would enable the accurate calculation of the incidence and prevalence of adverse reactions to food and food ingredients in the United Kingdom or elsewhere. As many as 20-30% of the UK population think that they have a "food allergy" or some adverse reaction to a food.[1] However, in a community survey, with DBPCFC of positive respondents, the calculated prevalence of adverse reactions to food was 1.4-1.8%. This is likely to be an underestimate as the eight test foods selected for study accounted for about half of the foods reported as causing problems. Most adverse reactions to foodstuffs are to natural foods rather than to synthetic additives and

contaminants, the prevalence of which is about 0.03%. The prevalence is estimated to be up to 8% in infants and young children.

11.5 There is clear evidence that the prevalence of atopy is increasing in the developed countries of the Western World. Although definitive evidence is lacking, the assumption is that this increased prevalence extends to food allergy. There appears to have been an increase in the numbers of patients with food-induced anaphylaxis in the UK (see paragraphs 2.28 and 6.3).

Clinical features

11.6 Clinical features of adverse reactions to food and food ingredients include disorders of the skin (e.g. atopic dermatitis and urticaria), the respiratory tract (e.g. asthma, allergic rhinitis) and the gastrointestinal tract (e.g. gastro-oesophageal reflux, diarrhoea, abdominal distension and pain and, with severe mucosal damage, features of malabsorption and malnutrition). Clinical features related to the central nervous system (headaches) and the cardiovascular system can occur. Anaphylaxis is a life-threatening, severe, immunologically-mediated reaction involving all these systems.

11.7 There is limited evidence that other structures, including the joints and genitourinary tract, may also be affected by adverse reactions to food and food ingredients but this is not well-established.

11.8 It has been hypothesised that foods may be implicated in the aetiology of behavioural abnormalities including autism, attention deficit-hyperactivity disorder and other less well-defined behavioural abnormalities including delinquency, but the relationships have not been established.

Immunological adverse reactions to food

Foods responsible for adverse reactions

11.9 Most immunological adverse reactions to foods and food ingredients are caused by a limited number of foods. In children 90% of reactions are caused by cows' milk, chickens' eggs, wheat, peanuts, tree nuts (walnuts, brazil nuts, hazel nuts) and soya protein. In some instances these reactions, for example that to milk, occur only during early childhood. In adults, in the UK, the majority of allergic reactions are caused by peanuts, tree nuts, fish and shellfish.

11.10 In other countries, different early feeding practices and the age at which particular items are introduced into the diet may be responsible for observed geographical variation in patterns of food allergy. For example, in Japan rice allergy is common and in Scandinavia reactions to cod are frequent. Patients can react to more than one allergen and cross-reactions to related allergens can occur. The allergens involved in cross-reactions are not necessarily phylogenetically closely related, for example cross-reactions involving sensitivity of an individual to latex and various fruits are being recognised more frequently.

Mechanisms

11.11 The mechanisms whereby adverse immune reactions develop, or oral tolerance of foodstuffs is acquired, are not clear. Similarly, the reasons why some reactions are transient and usually restricted to childhood are unknown. Exercise or changes in temperature, particularly increased ambient temperature after exposure to a potential allergen, can precipitate urticarial, asthmatic and anaphylactic reactions to foods.

11.12 Immunologically-mediated adverse reactions to foods and food ingredients might aggravate asthma and atopic dermatitis. However, the role of immunological adverse reactions in the pathogenesis of such allergic disorders is unclear because many other aetiological factors are also involved. Thus the place for dietary restriction in the management of these conditions, particularly in adults, is uncertain.

11.13 Some adverse reactions to foods and food ingredients are mediated by immunological mechanisms not involving IgE antibodies. The best-characterised of these conditions are the enteropathies, of which coeliac disease, a reaction to proteins, usually gluten in wheat, is the most widely-known. Reactions of this type to cows' milk, soya, chicken eggs, rice, fish and chicken are much rarer.

11.14 The prevalence of coeliac disease varies throughout Europe and has fluctuated over time, with the incidence in the UK having fallen recently. Although some of these features may be attributable to genetic differences, it is more probable that they reflect variations in the timing of introduction and the composition of complementary feeds, and the duration of breast feeding.

11.15 There is a strong heritable component in all classes of immunologically-mediated adverse reactions to foods. The manifestation of the genetic trait depends on an interaction with other environmental factors and on the nature and timing of exposure to the potentially-sensitising protein. This interaction has not been elucidated.

Non-immunological adverse reactions to food

11.16 Non-immunologically-mediated adverse reactions are reproducible, idiosyncratic adverse reactions to foods and food ingredients which may be caused by inherited or acquired defects in intestinal transport, digestion and absorption, abnormal metabolism, or increased sensitivity to pharmacologically-active substances. Some adverse reactions of the gastrointestinal tract result from the bulk of food ingested or from the bacterial fermentation of complex carbohydrates (such as disaccharides in disaccharidase deficiency) and other non-digestible dietary components e.g. some complex carbohydrates which have not been absorbed in the proximal intestine. In some cases the mechanisms are unknown.

11.17 Occasionally food ingredients can cause adverse reactions that resemble allergic reactions, by releasing the same chemical mediators that are involved in allergic reactions. Thus they might also exacerbate and mimic immunologically-mediated reactions such as

asthma and atopic dermatitis. Compounds that may be responsible include tartrazine, sodium benzoate, glutamate, metabisulfite, acetylsalicylic acid, histamine and tyramine.

Adverse reactions affecting the central nervous system and behaviour

11.18 It is probable that in some individuals headache and migraine headache attacks are provoked by food. The mechanisms by which these attacks are caused are various. Possible precipitants include coffee, chocolate and alcoholic drinks. Progress in this area depends on better characterising the patients, the heterogeneity of headache and migraine syndromes, and associated specific metabolic defects.

11.19 There are reports that nutritional changes in the diet of delinquents reduce the number of disciplinary offences committed when in custody. The design of these studies was flawed by problems such as lack of randomisation and the use of inappropriate controls and few studies employed DBPCFCs. Accordingly, in the absence of independent confirmation of these results, it was not possible to assess the significance of such reports.

Attention deficit-hyperactivity disorder

11.20 There is evidence from double-blind placebo-controlled food challenges that some patients will respond to the exclusion of some specific dietary components. Attention deficit-hyperactivity disorder may represent a number of independent but clinically similar conditions. The diagnostic criteria for the disorder are evolving and this confuses both the interpretation and comparison of aetiological studies as well as the detection of any temporal change in prevalence of attention deficit-hyperactivity disorder.

11.21 Attention deficit-hyperactivity disorder is associated with many factors, including inherited abnormalities relating to dopaminergic systems in the central nervous system. Information concerning this is new and it is likely that its expansion will enable better characterisation, investigation and treatment of the disorder.

11.22 Studies in unselected populations with migraine, headaches, attention deficit-hyperactivity disorder, arthritis and similar heterogeneous conditions might overlook the small subgroups of the population who react to dietary components. It is probable that studies in well-characterised subgroups will be more informative about the role of dietary precipitants in these disorders than are studies on large unselected groups. There is currently no means of identifying the small cohorts of patients with these disorders, who might be responsive to exclusion of one or more dietary components.

Genetic variation

11.23 Genetic variation may be expressed as polymorphisms of enzymes affecting the metabolism of dietary components. Such variation may underly the variability, within populations, of responses to dietary components such as histamine, tyramine, β-phenylethylamine, octopamine, certain catecholamines and adenosine derivatives, and sulfites. However, because there are many compensatory alternative metabolic pathways available, the role of such polymorphisms in adverse reactions to foods remains to be confirmed.

11.24 An important enzyme defect is the natural loss after early childhood of the intestinal enzyme lactase, which breaks down the milk sugar lactose. This deficiency is present in about 70% of the world population, notably Asians, Africans and those of Jewish or Hispanic descent. Deficiency of this enzyme causes lactose intolerance. However, most affected individuals tolerate small amounts of milk in their diets and, at low levels of intake, about 200 millilitres per day, there is no need for them to avoid milk and dairy products. Other enzymatic defects affecting the digestion of sugars are much rarer. *Conclusions*

Miscellaneous causes

11.25 A variety of adverse reactions have been attributed to pharmacologically-active substances in foods and beverages, e.g. the methylxanthines: caffeine and theobromine (in tea, chocolate and coffee), vasoactive amines, myrasticin in nutmeg and salicylates. Not all of these reactions have been well characterised.

11.26 Lectins in the diet can cause a variety of gastrointestinal symptoms which can be mistaken for food poisoning.

11.27 Some medications can increase the risk of an adverse reaction to foods. Examples are aspirin and monoamine oxidase inhibitors.

11.28 High intakes of fibre or of carbohydrates which are not digested in the small intestine can result in fermentation in the large bowel which, particularly in children, can lead to abdominal pain, distension, wind and increased frequency and looseness of stools. Similar features may be caused by novel ingredients which have been designed to retain the organoleptic qualities of foods and, simultaneously, to reduce their available energy content.

Diagnosis and management

11.29 The quality of evidence supporting claims of adverse reactions of all types is varied. Whereas specific metabolic abnormalities can be demonstrated in some individuals who suffer non-immunological adverse reactions to food, overall there are few reliable, simple diagnostic tests which will identify actual or potential sufferers of adverse reactions to food and food intolerance.

11.30 The diagnosis of adverse reactions to food and food intolerance requires a high degree of clinical insight and can be founded on the loss of symptoms when possible precipitants are eliminated from the diet. The 'gold standard' diagnostic test is the double-blind placebo-controlled food challenge. It might not be advisable or ethical to undertake such a challenge if the patient has a clear history of a severe adverse reaction such as anaphylaxis.

11.31 In the case of allergic reactions, ancilliary tests such as skin prick tests and tests based on detecting serum IgE antibodies are insufficiently predictive to displace the double-blind placebo-controlled food challenge as the definitive means of diagnosis.

Adverse reactions to food and food ingredients

11.32 There are a number of procedures used to "diagnose" and treat adverse reaction to food and food ingredients which do not have a sound evidential base. Misdiagnosis of adverse reactions to food and the imposition of inappropriate exclusion diets can seriously compromise a patient's nutrition and health.

11.33 Health professionals may not be sufficiently well informed about, and alert to, adverse reactions to foods and food ingredients and this may cause patients to seek non-validated means of diagnosis and management. Therefore it is important that there is, amongst health professionals, an improved awareness of adverse reactions to food and food ingredients.

11.34 Successful avoidance of precipitants depends on being able to identify them in foodstuffs. This depends on accurate labelling and the availability of appropriately sensitive tests to detect allergens and other precipitants of adverse reactions.

11.35 It is not always evident or expected that foods might contain allergens. Such hidden allergens might arise from contamination of the principal food during processing, preparation and cooking, or the allergenic protein might be present at levels which do not need to be declared on food labels. Breast-fed babies might react to allergens, e.g. cows' milk proteins, excreted in their mothers' milk

11.36 Food processing and biotechnology can alter the allergenicity of component proteins. Biotechnological and plant breeding techniques have been or are being developed to eliminate some allergenic proteins in cereal grains such as rice and wheat. Procedures are being developed to screen novel foods for the presence of allergens that are identical or closely related to known allergens. Where this is not possible procedures are being developed to identify potential allergens but no definitive process has, as yet, been established.

11.37 The role of breast feeding in preventing or postponing allergic sensitisation in infants is unclear other than its preventative effect in infants with a high risk of developing atopy. There is no good evidence that maternal avoidance of potential allergens, e.g. peanuts and cows' milk, during pregnancy is protective. Nevertheless, in its consideration of peanut allergy the Committee advised previously that, if there is a family history of atopy, pregnant women may wish to avoid the consumption of peanuts and peanut products.

Implications for public health

11.38 Adverse reactions to food and food ingredients may have extensive implications for public and emergency health services, the food and catering industries, consumer choice and expenditure, food safety, food labelling policy, and social and educational services. Adverse reactions to food and food ingredients also have major implications for the National Health Service in terms of resources, and for the education and training of health professionals.

Conclusions on the terms of reference

11.39 On the basis of the conclusions reached by the Working Group it has not been possible to answer fully all the questions in the terms of reference. Thus:

- *'to consider whether the incidence and prevalence of adverse reactions to foods and ingredients are changing'* would require the comparison of studies that have been done at different points in time, using exactly the same methodology, definitions and outcomes. The results of studies using different methodology, outcomes or diagnoses can not reliably be used to provide this information. Study groups need to be representative of the populations of interest. Moreover, hospital referral or admission statistics are similarly unreliable for comparisons over time. It is essential to develop proper control groups and procedures, random allocation to defined treatments, blind assessment and standard measures of outcome. Probably the most important single requirement is random allocation to comparison treatment groups.

- In considering *'those foods identified as commonly causing adverse reactions and rank them separately for prevalence, potency and severity of reaction'* the conclusions above list those foods which are commonly associated with food allergies. Milk, associated with lactose intolerance, is also a common cause of non-allergic food intolerance, but there are no data available on which to rank the causes of other non-allergic adverse reactions to food. This information would be obtained reliably only if all the members of a large population were studied using the same protocol. Such a study would be demanding and expensive and has not been undertaken for any other disorder, other than routine screening for disorders involving inborn errors of metabolism.

- For the same reasons it is not possible *'to identify factors, both genetic and environmental, which may increase the risk to health'* of adverse reactions to food and food ingredients. To achieve this food intolerant and allergic individuals need to be identified and characterised in relation to the environment to which they are exposed and their genetic susceptibility. Suitable epidemiological studies to develop hypotheses in this context have not been reported.

11.40 Because of the lack of suitable studies which would have allowed the Working Group to answer fully its terms of reference it has made a number of recommendations for research studies that would provide additional information on the topics that it has considered. These recommendations are described in the next chapter. The Committee noted recommendations on standards of care for allergy services recommended by the Royal College of Physicians of London and the Royal College of Pathologists.[508,509]

12. Recommendations for further research

Recommendations on conditions other than attention deficit-hyperactivity disorder

12.1 The Committee has made a number of recommendations in relation to research and other issues on adverse reactions to food and food ingredients: these are listed below. In view of the rather different nature of the problem, the Committee's recommendations in relation to attention deficit-hyperactivity disorder are given separately.

Research

Epidemiology

- There is a need for better prevalence and incidence data for the UK, based on appropriate objective criteria such as double-blind placebo-controlled food challenge, for both food allergy and food intolerance, using large and representative population samples.

- There needs to be an improvement in case definition, in databases and in other systems for reporting adverse reactions to food and food ingredients. In the case of anaphylaxis use of diagnostic codes needs improvement.

- There is a requirement for better diagnostic criteria to support systematic study of the role of foods and food ingredients in the pathogenesis of conditions such as headache and migraine headache.

- An improved understanding of genetic variation and of the resultant variations in both protein expression and metabolism should be used to explore the basis for adverse reactions to food and food ingredients. This might aid the development of predictive markers for those at risk of such adverse reactions.

Mechanistic research

Immune-mediated adverse reactions to food and food ingredients
12.2 Mechanisms need to be elucidated to enable:

- the development of markers to identify those at risk of adverse reactions to food and food ingredients,

- the improvement of prophylaxis and clinical management,

- the improvement of prevention by modifying the allergen content of foods.

Adverse reactions to food and food ingredients

12.3   In particular: mechanisms of oral tolerance and sensitisation need further investigation and this should extend to studies on the effects of early feeding (and diet of the pregnant woman) on the development of allergy. The role of exposure to antigens in utero or via breast milk, and of breast feeding and early feeding in the prevention or postponement of allergic reactions needs investigation.

12.4   Those factors which determine the allergenicity of proteins need to be characterised by studies on the nature, stability and other relevant properties of allergens and their epitopes.

12.5   Factors which exacerbate immune reactions need to be investigated.

12.6   The effects of biotechnology on the hazard deserve study, as does the nature of clinical cross-reactions and co-sensitisation.

12.7   The long-term effects of IgE-mediated adverse reactions to food on those who are symptom free, having outgrown childhood allergies, but who remain skin prick test or radioallergosorbent test positive need to be studied.

Non-immune-mediated
12.8   Inherited differences in the metabolism of food ingredients need further study.

Clinical research

Improved diagnostic techniques
12.9   For both management and for research purposes, accurate objective tests are needed for both food allergy and food intolerance. Harmonised and generally applicable criteria for the objective assessment of double-blind placebo-controlled food challenges need to be developed.

12.10 Improved standardised test reagents for radioallergosorbent tests and skin prick tests are required.

12.11 The establishment of an accreditation scheme for laboratories involved in the diagnosis and management of adverse reactions to food and food intolerance should be considered.

12.12 There is a requirement for rigorous studies to establish the value of non-validated diagnostic tests.

12.13 There is a need for investigation of the requirement for routine serological screening for coeliac disease in families at risk and populations.

Public health issues
12.14 The awareness of health professionals, especially general practitioners and those in hospital casualty departments, to the diversity, hazards and risks of adverse reactions to food and food ingredients should be increased. Moreover the food industry, including caterers and retailers, and the general public need education about the problem of adverse reactions to food and food ingredients.

12.15 There is a need for improvement in the information the general public and health professionals can obtain on food composition, especially with respect to hidden allergens. The adequacy of current composition tables for the content of precipitants of food intolerance (non-immunological adverse reactions to food and food ingredients) should be reviewed.

Recommendations for further research

12.16 The practice of some companies in making data on the composition of their products available to consumers and health professionals should be encouraged.

12.17 Consideration should be given to establishing a system to enable consumers and health professionals to report adverse reactions to foods and food ingredients.

12.18 There needs to be better understanding of social impact and economic cost of adverse reactions to food and food ingredients; the socio-economic consequences for patients and their families, of following exclusion diets needs to be evaluated.

Recommendations for research on attention deficit-hyperactivity disorder and delinquent behaviour and diet

Epidemiology

12.19 For both management purposes and for research needs, ADHD patients should be rigorously characterised and inheritance patterns and other aetiological factors should be identified.

12.20 The prevalence of food intolerance in children with ADHD needs to be further investigated using double-blind challenge designs. The means of identifying a subgroup of ADHD patients who respond beneficially to dietary intervention need to be addressed.

Mechanistic research

12.21 If a group of food-responders is identified, the responsible mechanisms should then be explored (immune responsiveness, neurotransmitter metabolite changes, localised changes of brain function, and psychological measures of attention). The preceeding characterisation would help to establish if this might be a single syndrome or a continuum of conditions.

Clinical research

12.22 Objective diagnostic tests for ADHD need to be developed for management and for research purposes.

12.23 Trials of alterations in diet should include comparisons with established therapy (behavioural therapies and stimulant drugs).

Adverse reactions to food and food ingredients 12.24 Studies of any proposed role of adverse reactions to food and food ingredients in criminal and delinquent behaviour should be performed using suitable randomised and blind protocols.