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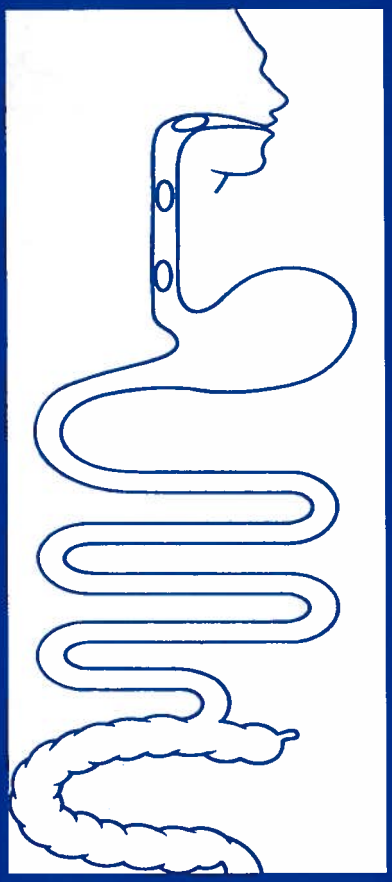

FOOD ALLERGY

AND OTHER ADVERSE REACTIONS TO FOOD

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For more information about its programmes and activities, please contact:

ILSI Europe
Avenue E. Mounier 83, Box 6
B-1200 BRUSSELS
Belgium
Telephone (32) 2 771-0014
Telefax (32) 2 762-0044

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by M. H. Lessof

ILSI Europe

ILSI Press
1126 Sixteenth Street, N.W.
Washington, D.C. 20036 USA
Telephone (202) 659-0074
Telefax (202) 659-8654

ILSI Europe
Avenue E. Mounier 83, Box 6
B-1200 BRUSSELS
Belgium
Telephone (32) 2 771-0014
Telefax (32) 2 762-0044

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FOREWORD

Many foods are capable of eliciting allergic or other adverse reactions, causing a wide range of symptoms in sensitive subjects. Recognising the importance of the topic to public health, the Group of European Nutritionists chose as the subject of its 28th Symposium "Food Allergy and Food Intolerance: Nutritional Aspects and Developments". ILSI Europe was pleased to make a contribution to the conference, which took place at Scheveningen, the Netherlands, in June 1990, and to collaborate in its organisation. The full conference proceedings were published by Karger in 1991 (ISSN 3-8055-5363-3).

This booklet, written by Prof. M. H. Lessof, is based on that conference, with some additional background material to help explain the topic to the non-specialist.

Author: M. H. Lessof
Scientific Editor: R. J. J. Hermus
Series Editor: N. Jardine

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INTRODUCTION

There has been a steady increase in public interest in the importance of diet and its relevance to health. At the same time, however, the public has become concerned that adverse reactions to foods, food additives and drinks may be common and that they can cause a wide range of distressing physical and psychological problems and chronic, disabling diseases.

Adverse reactions to foods certainly do exist, but the label of "food allergy" applied to many of these reactions is often incorrect. Unfounded and inaccurate claims for a diagnosis of food allergy have created unnecessary alarm among the public and have diverted attention from some basic problems.

There are a number of reasons why it is difficult to diagnose and study adverse reactions to food:

- They are caused by a wide range of foods and food additives, many of them common components of the diet.
- They give rise to a wide variety of symptoms, many of which are not specific to adverse food reactions, and which may appear at a variable time after ingestion of a food.
- They are caused by a diverse range of mechanisms.
- Some adverse reactions are psychologically based.
- Diagnostic methods can be cumbersome.

In this monograph, we will put adverse reactions to foods into perspective. These reactions are not as common as popularly thought, and the symptoms are often mild. Excluding psychologically based symptoms, probably no more than one person in 50 is affected. Many foods are capable of provoking a variety of symptoms in susceptible individuals, but the most common reactions are restricted to a few common foods. Demonstrable reactions to food additives are about 10 times less common than to foods themselves.

SYMPTOMS AND SYNDROMES CAUSED BY ADVERSE REACTIONS TO FOODS

The diagnosis of adverse reactions is complicated by the fact that many foods are involved (Table 1), causing a wide range of symptoms by a variety of different mechanisms. A single food may give rise to different symptoms, but likewise the same symptoms may have a number of different causes.

For example, identical symptoms may be elicited by a number of foods: eczema may be caused by milk, egg and many other foods in one and the same person. Asthma can occur as an allergic response to milk, but it can also be triggered by the irritant effects on the air passages of preservatives such as sodium metabisulphite.

Even where a single food is involved and a single part of the body affected, different mechanisms may be responsible in different individuals. For example, diarrhoea in infants receiving soya formulas can be caused by a reaction to the protein in soya, or by an inability to digest disaccharides, especially in formulas containing sucrose.

A single food can give rise to a wide spectrum of adverse reactions. For example, wheat can cause diarrhoea, urticaria and baker's asthma, due to allergic reactions to wheat proteins. In individuals who suffer from coeliac disease, there is a reaction in the intestine against one of the proteins found in wheat, causing diarrhoea and malabsorption. Bread made from wheat can affect intestinal physiology causing effects which may appear abnormal to some individuals (discussed further in Diagnosing Irritable Bowel Syndrome, below).

Symptoms in Children

Many symptoms have been associated with adverse food reactions in children, including diarrhoea, vomiting and blood loss from the digestive tract, eczema, asthma, wheals of the skin (hives or urticaria), swelling of the tissues

(angioedema), migraine and anaphylaxis, as well as some less well-defined conditions especially in severely affected children who are irritable or fail to thrive. An estimated three-quarters of these cases develop by the age of one year.

Some of the conditions which occur in infancy and early childhood are predominantly diseases of early life, but others remain lifelong problems. Recovery rates vary according to the food. Children with an apparent intolerance to cow's milk protein can often tolerate milk within months of diagnosis. However, recovery is least likely to occur in children with allergies to other foods such as peanuts, nuts and fish.

Certain foods are capable of damaging the lining of the small intestine, the best-known example being the damage arising from consumption of wheat products in coeliac disease (discussed in detail in the section on Coeliac Disease, page 16). Coeliac disease affects all ages, but some other, less common, reactions are seen only in children, such as when they are caused by a sensitivity to cow's milk protein or to soy, chicken, rice, fish and egg.

Symptoms in Adults

In adults, the classic allergic symptoms of urticaria, asthma or anaphylaxis may be seen. Some foods provoke

TABLE 1

Adverse Reactions: Causes and Foods Commonly Involved

Type of Reaction	Cause	Foods/food compounds involved
Food allergy	Allergic reaction to a food caused by an over-sensitive reaction of the body's immune system	Eggs, milk, wheat, fish, shellfish, nuts, peanuts, soybean, rice
Pharmacological	Absorption of certain amines from foods containing high amounts	Fermented foods (cheese, red wine, sauerkraut, fermented sausages); fish products
	Other substances with pharmacological type of action	Caffeine
Enzyme defects	Failure of normal enzymatic breakdown after absorption	Alcohol, fructose, amines
	Failure to digest, so that unabsorbed substances reach the lower intestine, where they are fermented	Lactose (in milk), fats
Irritant	Often made worse by acid which refluxes from the top end of the stomach to cause heartburn	Strong spices and flavours; sulphites
Toxic	Toxins	Some shellfish, badly stored food (e.g., green potatoes), and some vegetables, some fungi
Psychological food intolerance	Emotional reaction to a food (reaction does not occur if food is unrecognised)	

gastrointestinal symptoms. Overactive movements of the gastrointestinal tract and increased secretion of mucus seen in allergic reactions often result in nausea, vomiting, abdominal pain and diarrhoea.

Similar but often milder episodes of nausea, bloating, abdominal pain, constipation or diarrhoea occur in patients suffering from the irritable bowel syndrome. Symptoms occur when there is an abnormal response of the intestine after food is consumed, but in some cases there is a strong psychological component to the perception of the symptoms.

It has been suggested that migraine may sometimes result from intolerance to certain foods (cheese, chocolate and red wine have been cited). However, the relationship of food to migraine is poorly understood.

FOOD ALLERGY

Food allergy is not the most common cause of adverse reactions to foods, but it is one of the best understood. There is a wide range of symptoms caused by food allergy, affecting many parts of the body (Table 2), and reactions are sometimes serious. These reactions can occur very quickly, often within minutes, and hence are termed immediate reactions. In the oral allergy syndrome, the lips, cheeks, tongue or throat may swell or itch within minutes of contact with such foods as eggs, nuts or peanuts. Similar reactions can affect the skin, the lungs or the digestive tract, causing symptoms such as skin wheals (urticaria), wheezing (asthma), vomiting and diarrhoea.

Such allergies are more common in children than in adults. Foods commonly involved include eggs, peanuts, cow's milk, soy, wheat, peas, fish, shellfish and nuts, but reactions can also occur to spices such as mustard and sesame or to vegetables, for example, celery and tomato.

Allergy is essentially "immunity gone wrong" where a normally harmless substance is perceived as a threat—an allergen—and attacked by the body's immunological defences. Food allergy involves the reaction of a food protein with antibodies produced against it by the immune system. The accompanying symptoms are the result of this inappropriate immune response.

The operation of the immune system is complex and much remains to be learnt about it. The following gives an outline of our knowledge in order to provide an insight into why and how allergic reactions arise.

The Immune System and Its Role in Food Allergy

The body's immune system provides a vital defence

TABLE 2

Symptoms of food allergy

Gastrointestinal
Nausea
Vomiting
Colic
Diarrhoea
Abdominal cramps
Bloating
Respiratory
Rhinitis
Sneezing
Asthma
Recurrent cough
Wheezing
Laryngeal oedema
Dermatological
Angiooedema
Urticaria
Eczema
Pruritis
Erythema (skin inflammation)
Other
Anaphylaxis

FIGURE 1
The structure of IgE antibodies

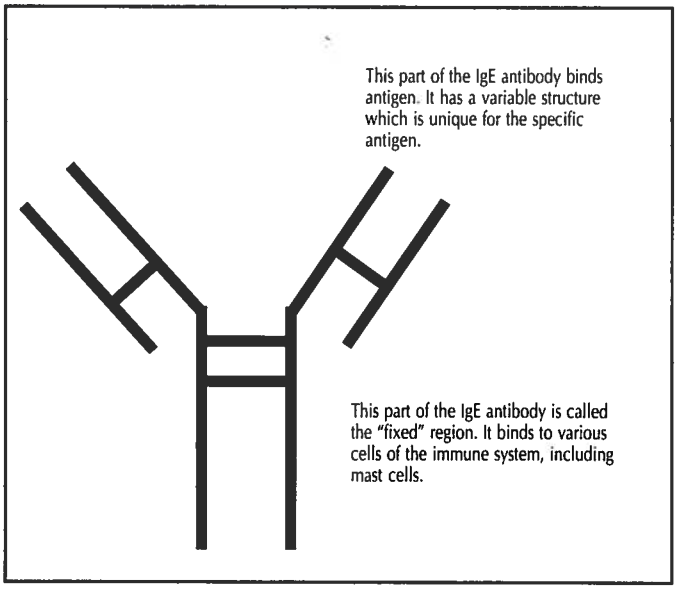
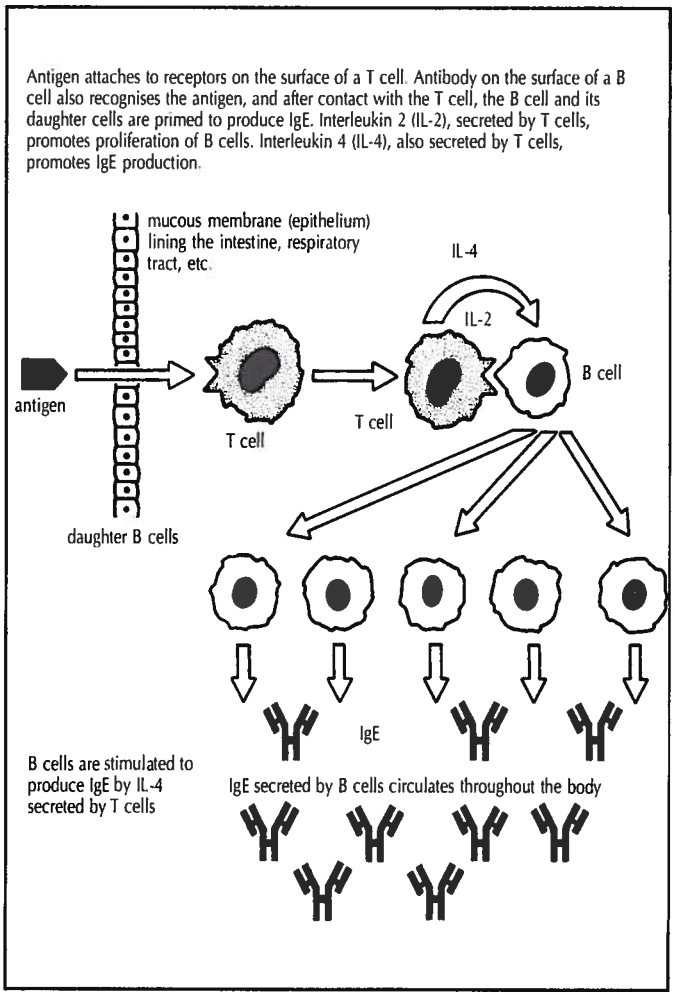


FIGURE 2
Production of IgE antibodies



mechanism against harmful substances and against infection. Immunological reactions to polio vaccine, for example, provide an individual with long-lasting protection against infection with the polio virus.

Defensive cells in the body produce antibodies of different types which react specifically with foreign microorganisms, viruses or foreign substances such as proteins. Antibodies are specific proteins produced by the body which fit onto foreign molecules in a lock-and-key fashion. Although the body's defensive cells can potentially produce a vast variety of immunoglobulins (Ig's), immune reactions trigger the production of specific antibodies in response to particular foreign substances or proteins. Once a particular antibody has been formed (against polio virus, for example), it can be mass-produced by the body whenever it is needed.

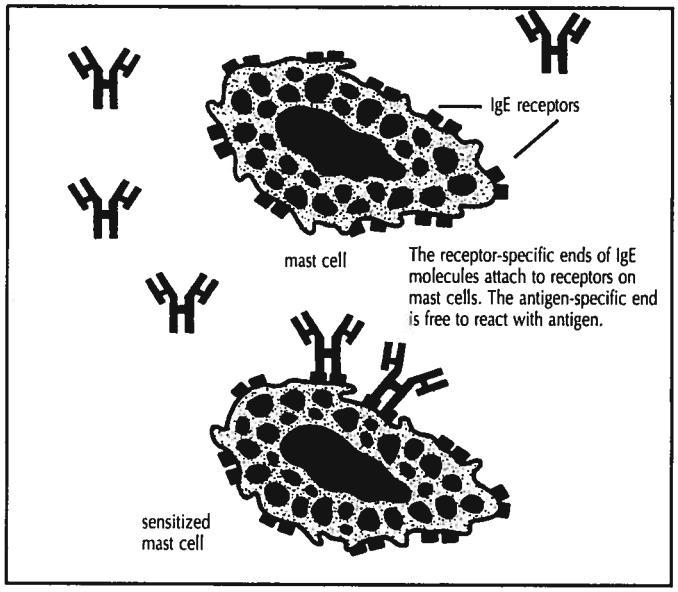
Antibody structures all follow a basically similar pattern (Fig. 1). Although there are other classes of antibodies (IgG, IgA, IgM), it is IgE which is important in immediate allergic reactions. Antibodies bind to foreign proteins or other foreign substances known as antigens, thus neutralising their effect. The antigen may be part of the coat of an invading bacterium or virus or a free molecule, for example, a protein from cow's milk. The antigens in foods which provoke an IgE response are mostly proteins or glycoproteins (proteins with sugar groups attached).

B cells and T cells

B cells and T cells are types of mobile white cells called lymphocytes. They develop and congregate in the organs of the immune system. B cells originate from stem cells in the bone marrow and elsewhere. Each B cell produces one type of antibody which is capable of reacting with one specific antigen in a lock-and-key fashion. Collectively, B cells produce the many thousands of different antibodies needed to counteract the many antigens which may be encountered in a lifetime. (Those clones of B cells which could act against the body's own proteins are eliminated in early life.) When a particular foreign antigen enters the system for the first time, the B cells that produce the antibody against the antigen are primed and activated, so that thereafter they (and their daughter cells) can mass-produce the appropriate antibodies when required. B cells carry samples of their specific antibody on their surfaces, thus permitting their proliferation following interaction with specific antigens. T cells control the activity of B cells (Fig. 2).

T cells also originate from stem cells, notably in the thymus. They do not secrete antibody but like B cells they can recognise a legion of antigens through receptors present on their surfaces—the "T cell receptor". Part of the T cell receptor comprises an antigen-specific molecule related to immunoglobulin. This acts like an antibody, binding to a specific antigen. The combination of an antigen with its specific T cell receptor enables the T cell to control the activity of B cells which recognise the same antigen. "Helper" T cells stimulate the corresponding B cells to secrete antibody against that antigen. "Suppressor" T cells can reduce the activity of corresponding B cells, inhibiting IgE production. T cells also have other regulating effects on the immune response, mainly through the chemical signalling substances—interleukins—which they secrete.

FIGURE 3
Sensitisation of mast cells



IgE is produced by white cells known as B lymphocytes or B cells. Another type of lymphocyte, the "helper" T cell, is also involved in the process. It is a secretion of this cell—interleukin 4 (IL-4)—which influences B cells (see box) to produce IgE rather than another class of antibody (Fig. 2).

The IgE secreted by B cells circulates throughout the body. One part of IgE has a particular affinity for receptors on the surface of mast cells found in body tissues. Mast cells bind the tail of IgE molecules, which thereby sensitise those cells to specific antigens (Fig. 3).

If, in a subsequent encounter with the sensitised mast cell, the antigen forms a bridge between two adjacent IgE molecules, this acts as the signal for the release of a variety of substances which either have been stored in granules in the mast cell (for example, histamine) or are newly synthesised at the cell surface (such as prostaglandin D_2 and leukotriene C_4) (Fig. 4). Release of these substances causes an inflammatory reaction (see box, page 7) capable of

FIGURE 4
Inflammatory reaction initiated by the mast cell

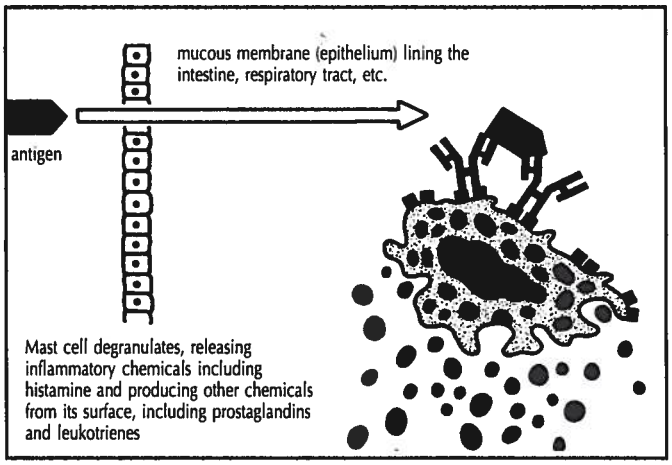
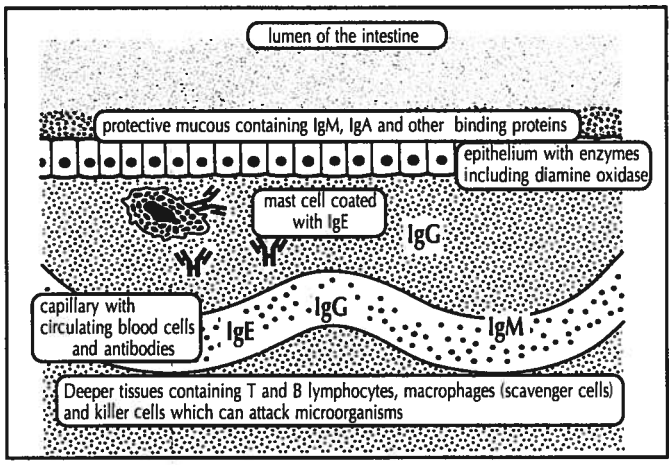


FIGURE 5
The defence barriers of the intestine



damaging, destroying or otherwise facilitating the removal of the foreign material.

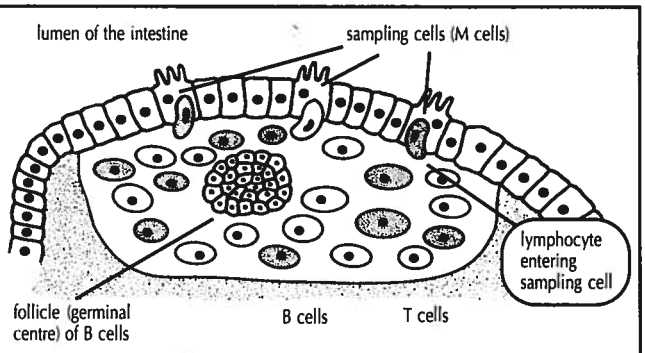
Mast cells are scattered below the skin surface and below the mucous surfaces in eyes, nose, mouth, respiratory tract and intestine. A food-allergic individual can therefore have a widespread reaction when mast cells coated with the appropriate IgE are triggered into activity after encountering the corresponding antigen from the food. On rare occasions, the intensity of the reaction can be extreme, manifested by oedema (swelling), breathing difficulties, a drop in blood pressure and even heart failure. Known as anaphylactic shock, this severe reaction is sometimes fatal.

The presence of sensitised mast cells in the skin can be demonstrated by a simple test in which a small patch of skin is coated with a diluted food solution and then pricked with a needle. The development of a local wheal provides indirect evidence of histamine release and, therefore, of a specific triggering of the local mast cells by a food antigen combining with the IgE on mast cell surfaces.

The Immunological Defences of the Intestine

Many potentially harmful substances and microbial organisms are present in the tonne or so of food eaten by an individual each year, but their penetration is largely prevented by defensive barriers in the intestine (Fig. 5). Viscous mucus, produced by specialised intestinal lining cells forming the mucous membranes, behaves like an antiseptic paint. This "paint" contains various protective substances including s-IgA and s-IgM antibodies, the s-prefix indicating that they are specifically modified to permit their secretion across the intestinal wall. Such secretory antibodies help counteract the entry of soluble antigens, for example, from food residues—a process called immune exclusion. Behind the mucous membrane is the epithelial cell layer. Histamine and other reactive substances are normally bound and destroyed by the mucosa and its enzymes. Substances that penetrate further than this may encounter IgG antibody in the tissues or may trigger mast cells primed with the appropriate IgE.

FIGURE 6
The Peyer's patch of the intestine



Both food antigens and microorganisms can penetrate into the M cells and are brought into contact with migrating lymphocytes. The Peyer's patch can induce either immune tolerance or an immune reaction, depending on the solubility, concentration and other features of the antigen it encounters.

The inflammatory response

The inflammatory reaction, which follows injury to the body, increases the blood supply to the area and brings protective white cells and components of the immune system to the site of the injury. The scale of the reaction can be boosted by a series of enzymes and other blood constituents known as complement. These can also increase the permeability of blood vessels. Prolonged reactions involve T lymphocytes which can infiltrate virtually all tissues. By releasing compounds called lymphokines, T cells can attract yet more cells, leading to a further crescendo of inflammatory activity.

A number of factors, some of which are inherited, determine whether a food antigen causes an allergic rather than another type of immune response. The presence of regulatory molecules is important, for example, IL-4 favours an allergic response. In susceptible people, intestinal allergy can occur when small amounts of antigen penetrate the intestinal wall. Penetration of antigen is increased when there is damage to the intestinal barrier. However, mechanisms in the immune system, both inside and outside the intestine, help to discriminate between those antigens which will be "tolerated" and those which will start an immune reaction.

The importance of the immune system in the intestine is demonstrated by the fact that it contains about 80 billion lymphocytes, compared to a total of approximately 20 billion in the important immune system organs of the bone marrow, spleen and lymph nodes combined. Most lymphocytes in the intestine are found in specialised areas known as Peyer's patches (Fig. 6). Each of these patches contains some 30-40 groups of cells, mostly T and B lymphocytes, clustered in follicles. In addition to these concentrated patches, there are much smaller areas of lymphocyte-rich tissue, and many individual lymphocytes are also scattered along the lining layers of the intestine where they can migrate to areas of inflammation.

Scattered over the surface of Peyer's patches are specialised cells (M cells) through which samples of the antigens present in the intestinal lumen penetrate into the lymphoid tissues of Peyer's patches. Lymphocytes primed to produce antibodies by contact with an antigen through the M cells of the Peyer's patches eventually reach the local lymph nodes and the circulating blood. From there they seed themselves back to the wall of the intestine in many more places, and are also spread to other mucosal sites, notably in the breast and the lung airways. In this way, the local effects of an immune response in the intestine can be spread to all the mucosal surfaces of the body by means of recirculation and distant seeding of T and B lymphocytes.

Why Do Some People Suffer from Food Allergy?

The regulation of the mucosal immune response has to permit reactions against harmful organisms while ensuring tolerance to food antigens as well as to the normal

(harmless) bacteria which reside in the gastrointestinal tract. The soluble antigens of food brought into contact with lymphocytes within the sampling cells of Peyer's patches seem to be able to induce a state of immune unresponsiveness termed oral tolerance. This may be mediated by suppressor T cells which block the activation of specific lymphocytes. Thus, in most circumstances, the antigens present in food are recognised as harmless and do not trigger protective immune mechanisms.

Long-lasting oral tolerance is most easily induced in infancy and childhood when the lymphatic tissues of the intestine first encounter the soluble antigens in new foods. This is also the most common time for defects in the developing immune system to reveal themselves and for allergy to develop, indicating the finely balanced nature of the mechanism.

Food allergy appears to be an excessive response of the immune defences. There are a number of factors which need to be considered to understand why some people suffer from food allergy:

- the patient's genetic predisposition,
- exposure to food and other allergens, and
- the state of the gastrointestinal barrier.

IgE reactions may have originally evolved as a defence against parasites. With improvements in food hygiene, such reactions may be less necessary for health, and those people who inherit a natural tendency to react vigorously may actually be at a disadvantage. In allergic families, it is known that suppression of the IgE response does not occur as readily as in other people, possibly because of an inherited defect which leads to over-production of IL-4 or because of a failure to produce the suppressor substances known as interferons. These defects may explain why those with food allergy have a tendency to suffer from other allergies such as asthma.

The tendency to develop allergy may be especially marked in children if both parents are affected. Many patients with food allergy have large quantities of IgE on the surfaces of their mucosal mast cells, and their children sometimes have high blood levels of IgE at birth. Furthermore, the intestinal mucosa of some (but not all) of these children contains a reduced number of IgA-producing cells. It is possible that this IgA deficiency either allows intestinal infections to occur or permits food antigens to penetrate the intestinal wall more easily and thus stimulate IgE production as part of a "second line defence".

In the newborn, the risk of developing an allergy is 40–60% if both parents are allergic, 20–40% if one parent is allergic, and 5–15% if nobody in the immediate family is affected.

Exposure to a potential food allergen can to some extent determine the likelihood of developing sensitivity. For example, allergy to fish is more common in Scandinavia, as is rice allergy in Japan and allergy to peanuts in the United States.

The reaction to food antigens passing through the intestinal wall is affected by the state of the wall, whose permeability may be greater when immature or increased by inflammation following intestinal infection, allowing more antigens to pass through. Passage of antigens is affected by such diverse factors as degree of digestion (for example, lack of stomach acid will reduce digestion); selective IgA deficiency; amount of antigen consumed and whether it is ingested alone or with other foods; and the degree to which food is cooked.

Delayed Reactions of Food Allergy

There is another type of allergic reaction to food where the onset of symptoms of inflammation is delayed. In the large majority of such delayed reactions, IgE is not in evidence. This type of food allergy is less well understood and characterised than "immediate" IgE-mediated reactions. Delayed reactions involve other components of the immune system including migrating cells of the T cell type and various types of scavenger cells.

Delayed reactions may account for the occasional cases of children with symptoms of a similar pattern which appear to be provoked by cow's milk, soya, fish, chicken or rice, and for some of the reactions which occur in babies

sensitive to cow's milk. Such reactions of delayed hypersensitivity also account for at least some of the intestinal problems which occur in coeliac disease (see page 15).

NON-ALLERGIC REACTIONS TO FOODS

The symptoms of a number of adverse reactions to foods mimic allergic reactions but nevertheless do not have an immunological basis. These include certain urticarial skin reactions and other manifestations similar to the symptoms of true allergy. Many of these patients also have abdominal complaints, including abdominal pain and intermittent diarrhoea. Such reactions are due to a variety of mechanisms (see Table 1). For example, it has been estimated that food allergy is demonstrable in fewer than 3% of cases of chronic urticaria but some of the remainder are due to non-allergic reactions to food.

Food Constituents with Pharmacological Effects: Adverse Reactions Involving Amines

In many cases of non-allergic reactions to food, substances known as amines are responsible. Such amines are often termed biogenic amines owing to their physiologically powerful effects and are the same or similar to those released by mast cells as a result of an IgE-mediated reaction. This may explain the similarity of the symptoms to those found in food allergy.

There are at least four major mechanisms where amines are involved in adverse reactions to foods:

- Absorption of biogenic amines such as histamine and tyramine from the intestine, due to either abnormally high levels in food or, more controversially, resulting from synthesis of amines in the intestine by bacteria.
- The enzymes that normally degrade the amines present in food may be absent or partially inactivated.
- The nervous system may regulate the release of histamine from, for example, mucosal mast cells. Some irritants like alcohol or spices may affect nerve endings, thus stimulating histamine release in the mucosa.
- Components in food may directly stimulate the release of histamine and other chemical mediators from mast cells.

Biogenic amines are normal constituents of many foods, but they can also develop during cooking and storage. The largest amounts of histamine and tyramine are found in fermented foods such as cheese, alcoholic drinks, tinned fish and fish products, sauerkraut, pork and fermented sausage products. Scombroid fish (tuna or mackerel) is sometimes stored at temperatures high enough to allow the generation of histamine and other physiologically active amines.

The bacteria normally present in the intestine may synthesize histamine from foods rich in the amino acid histidine. Histamine may be absorbed from the intestine, especially where inflammation or other damage has increased the permeability of the intestine. If histamine penetrates as far as the bloodstream, it can cause flushing by dilating the blood vessels, increasing capillary permeability and causing constriction of the smooth muscle of bronchi and intestine. Experimental infusion of histamine into the bloodstream has been shown to stimulate gastric secretion, and above certain levels there are adverse effects on blood pressure, the pulse rate rises and headache occurs. Still higher levels can lead to asthma and the danger of heart failure.

Besides being absorbed from the intestine, histamine may also be released directly from mast cells and basophils (white blood cells which contribute to symptoms of allergy) by constituents of certain foods. The mechanism is poorly understood but does not involve IgE. Foods involved may include include strawberries, fish and shellfish, but this requires confirmation.

Tyramine also has a number of significant effects. It makes the arteries constrict, raises the blood pressure and can cause migraine headaches.

Other types of amines in food have also been implicated in adverse reactions. Diamines such as putrescine and cadaverine are present in wines, and spermidine occurs in pork and in cereal grains. Other active substances include catecholamines present in various vegetables, tryptamine in tomatoes, and 5-hydroxytryptamine in bananas and avocados.

How does the body defend against amines in foods? Specific types of proteins present in the mucus of the stomach and intestine (Fig. 5) normally bind and inactivate histamine. This protective effect can be lost. For example, the amines putrescine and cadaverine bind strongly to these proteins, leaving fewer binding sites for histamine. Nevertheless, most of the histamine which passes through the epithelium is degraded by the enzyme diamine oxidase which is located in the wall of the intestine. However, putrescine and cadaverine also have a high affinity for diamine oxidase and can inhibit this breakdown of histamine.

Histamine is also inactivated by another enzyme, histamine methyltransferase. Although present in the intestine, especially the colon and rectum, its activity is greatest in the liver. Liver disease (for example, acute hepatitis) can interfere with the activity of the enzyme.

As a result of these defence mechanisms, the amount of free histamine absorbed from food and reaching the blood is normally very low. There is evidence, however, that recurrent reactions to food rich in histamine may be due to a number of mechanisms. These include increased intestinal permeability to histamine, or a defect in the mechanism which breaks down histamine.

Other Food Constituents with Pharmacological Effects

Excessive drinking of coffee or tea has been associated in some individuals with side effects such as heartburn, gastrointestinal disturbances, anxiety, tremor, irregular heartbeats and sleeplessness. Some of these effects can be ascribed to the effects of caffeine. Pharmacological effects can also be caused by unusually high quantities of sodium nitrite, an antioxidant used as a bactericidal agent in cured meats. Nitrites dilate the blood vessels and cause flushing and headache, urticaria or intestinal symptoms.

Enzyme Defects as a Cause of Adverse Reactions

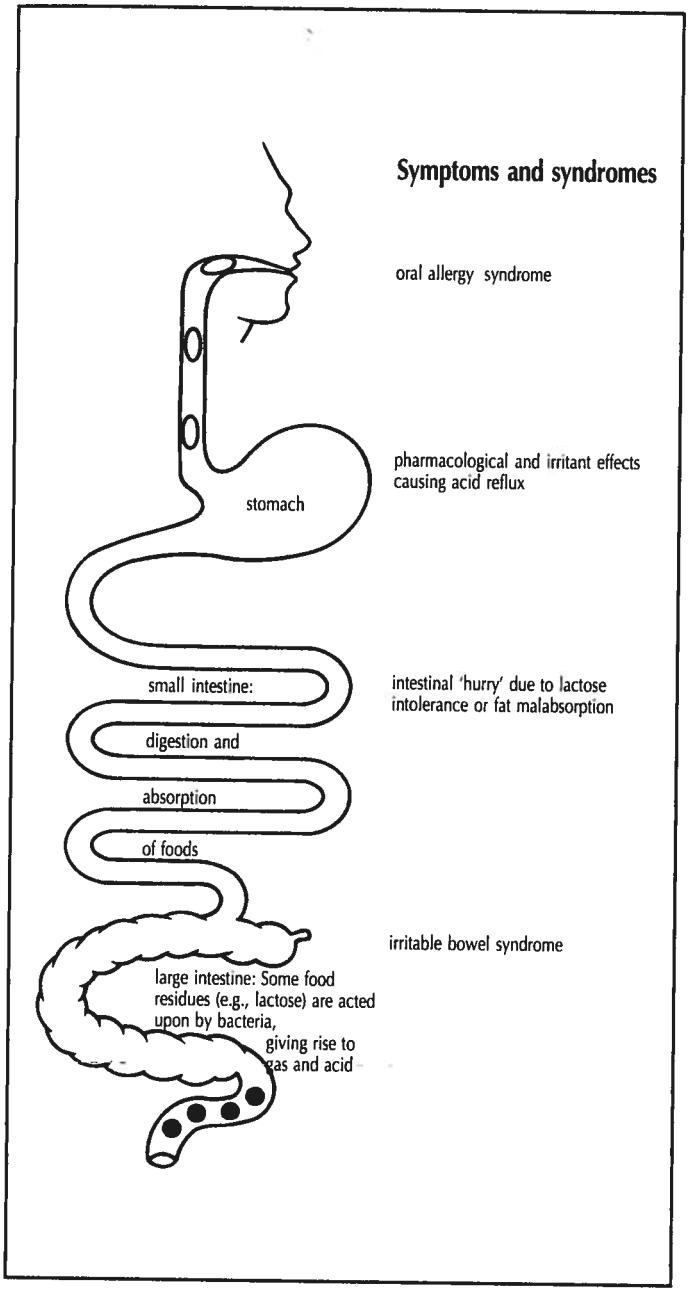
Enzyme defects have a genetic origin. The best-known example is alactasia, a common form of intolerance to cow's milk found in people who have a partial or more seldom a total deficiency of the enzyme lactase, which digests the milk sugar lactose. Alactasia affects up to 80% of the adult population in many parts of the world where a normal and progressive loss of lactase is experienced during childhood as milk consumption declines. In individuals with alactasia, most of the undigested, unabsorbed lactose that reaches the large intestine is fermented by bacteria there, forming carbon dioxide and lactic and propionic acids. The resulting gaseous distension and irritation may cause considerable symptoms (Fig. 7). The symptoms of alactasia mimic those seen in cases of the irritable bowel syndrome, which may also be due to the fermentation of unabsorbed food residues. Alactasia is also sometimes found as a genetic defect in babies where it has serious implications as milk is such an important part of the infant diet.

Other enzyme deficiencies can have more generalised effects. For example, people of Asian origin commonly have a deficiency of the enzyme aldehyde dehydrogenase and cannot metabolise alcohol as readily without the accumulation of toxic aldehydes.

Adverse Reactions Due to Toxins in Foods

Toxic effects are to blame in some cases where allergic reactions are suspected. For example, reactions to shellfish can be caused by poisonous dinoflagellates on which the shellfish fed. Toxins can occur naturally in some common foods, for example, glycoalkaloids in badly stored or green potatoes. Toxins may also be present in lima beans and

FIGURE 7
Digestive tract and adverse reactions to foods



millet sprouts. Cassava roots need careful processing to prevent toxicity arising from the cyanide-generating glycosides. Toxins capable of causing illness also arise from fungal or bacterial contamination of food or by degenerative changes in poorly stored food.

DIAGNOSIS OF ADVERSE REACTIONS TO FOODS

Doctors who are aware of the dangers of overdiagnosis of food allergy and the consequent use of inappropriate dietary restriction are sometimes sceptical that a genuine problem exists. By the same token, patients with adverse reactions to foods may be unaware of the relevance of food to their symptoms. Greater awareness is therefore needed by doctors about the symptoms of adverse reactions to foods and the diagnosis and management of the many related conditions.

There is a wide range of both clinical and laboratory tests for the diagnosis of food intolerance, but they vary in their validity and interpretation. In patients with an immediate type of allergic reaction, skin prick tests or laboratory tests for IgE against food antigens are useful. Biopsies of the small intestinal mucosa in patients with coeliac disease can also aid diagnosis. The value of other laboratory tests and diagnostic procedures is limited.

An adverse reaction to a food can only be confirmed if the symptoms disappear after elimination of the suspect food from the diet and reappear following a challenge test, where the food is reintroduced into the diet. Such tests should always be used to confirm an adverse reaction except in those people whose reactions are so severe that a challenge could be dangerous. If the test is to be convincing, the reintroduction of the suspected food should be in a form unrecognised by the patient.

The most convincing form of challenge test is the double-blind, placebo-controlled food challenge. The first step is to control the patient's symptoms by eliminating one or more suspect foods from the diet. "Challenges" are then performed by administering to the patient either a

Controversies Surrounding the Diagnosis of Adverse Reactions to Foods

An entire repertoire of diagnoses and treatments is based on unsubstantiated theories concerning food reactions. These include the placement of food drops under the tongue, either for diagnosis or treatment, and tests where different dilutions of a suspect material are applied to the skin, looking for a "neutralisation point". The so-called cytotoxic test depends on exposing the patient's blood to different food solutions to assess, for example, how quickly the blood cells die. Hair analysis and a variety of electrical tests are other examples of tests offered to the public which have not been objectively validated.

Commercial laboratories which advertise "allergy" diagnosis may fail to distinguish between adverse reactions with an immunological mechanism, for which useful tests are available, and those which have other causes. In one study, nine fish-allergic and ten healthy individuals provided blood samples which, after coding, were sent to five commercial laboratories and to a hospital laboratory. One of the commercial laboratories required specimens of hair. Widely discrepant results were reported by the commercial laboratories between pairs of blood or hair samples taken from the same individual. Non-existent allergies were also diagnosed in virtually all the normal subjects. The hospital laboratory tested for IgE antibodies and obtained 37 correct results out of the 38 samples sent for testing (19 coded pairs).

suspected food or a placebo so that neither the patient nor the clinical observer knows what is being received. The object of such a "double-blind" procedure is to avoid a biased perception of symptoms. Reactions are frequently reported when a challenge contains no food but only placebo, so challenge tests carried out in this way are essential in order to eliminate the possibility of psychologically based symptoms. Many early studies of adverse reactions to foods did not employ this technique, and the results are consequently questionable.

Diagnosing Irritable Bowel Syndrome

Symptoms of the irritable bowel syndrome include nausea, bloating, abdominal pain, constipation and diarrhoea. These features are thought to result from abnormal motility of the gastrointestinal tract, and it is now accepted that in some cases there is an adverse reaction to a food. There have been several reports that the exclusion of specific foods can abolish symptoms of the irritable bowel syndrome, especially in cases associated with diarrhoea. The association between these symptoms and consumption of milk is clear in patients with alactasia, but in other cases of the syndrome the cause is not known.

Diagnosis of the irritable bowel syndrome is complicated by the fact that some individuals are unduly sensitive to the feelings associated with the normal contraction or distension of the intestine. Changes in diet, for example a change from white to wholemeal bread, can speed up mouth-to-anus transit rate, influence intestinal movement, increase stool weight, produce a softer stool, increase frequency of defecation and increase the quantity of flatus. Likewise, some food residues, for example, starch from wheat flour, may not be fully broken down by the digestive process. In the large intestine it can act as a substrate for bacterial metabolism and thereby produce gas. These normal effects are considerably more obvious to the patient than to the outside observer and may even coincide with the symptoms of the irritable bowel syndrome.

It is therefore difficult to evaluate these symptoms and to distinguish those which have a psychological origin.

Diagnosing Psychological Reactions to Foods

People's attitudes to food vary widely and can result in dieting, overeating and food fads. Adults with eating disorders such as anorexia nervosa may seize on the suggestion that their problem could be "allergic" in order to avoid the stigma of a primarily psychiatric diagnosis. Many people who go to the doctor complaining of adverse reactions to food are undoubtedly over-anxious, but this does not necessarily mean that the symptoms are imagined. For example, apprehensive patients may overbreathe (hyper-ventilate) and thereby develop giddiness, a rapid pulse, nausea, weakness, tingling of the hands and feet, and thought disturbances. Once they have been shown that hyper-ventilation reproduces their symptoms, these patients will generally respond to appropriate treatment.

Patients who have psychologically based symptoms without organic disease may diagnose themselves as suffering from any one of a number of "fad" diagnoses, which may include food "allergy," leading to the use of inappropriately restricted diets. Parents who describe their child's adverse reaction to a food may be reflecting their own psychological state rather than the illness of the child. In a well-recognised form of child abuse, the so-called Münchausen's disease by proxy, such parents invent stories about a child's symptoms or physical abnormalities as a reason for imposing dietary or other restrictions on the child.

Even when carefully conducted tests give negative results, many patients with symptoms may still refuse to accept that organic disease is absent. Because such diagnoses fail to address the patient's problem, many such individuals lead limited, disabled lives while denying the possibility of a psychiatric component to their ill health. These patients are in need of a sympathetic hearing, appropriate investigation and much patience and support from their physicians. Without this, many will seek therapy from unorthodox practitioners.

ALLERGY TO COW'S MILK

More than 2000 years ago Hippocrates observed that cow's milk could cause both stomach upset and urticaria. Cow's milk can cause an allergic response in infants as well as other adverse reactions by a variety of mechanisms, including lactose intolerance due to alactasia. Allergy to cow's milk occurs in 0.5–4% of infants and is the most frequent allergy seen in newborn babies, perhaps because cow's milk proteins are among the first foreign antigens they encounter. The infant is usually sensitised by being bottle fed and develops symptoms at any time between a week and six months after birth. Less commonly, the sensitising protein comes from the mother during pregnancy and the child is already sensitive at birth. Sensitisation can also occur through breast-feeding, when traces of cow's milk protein ingested by the mother find their way into breast milk.

The diagnosis of cow's milk allergy is based on the history of milk-related symptoms, sometimes supported by laboratory tests. An allergic cause is particularly likely if the symptoms include eczema or urticaria, or if the milk has been well tolerated for a period before the symptoms began. As in other types of adverse reactions to foods, the results of an oral challenge test can be conclusive. The condition is often found in children with atopy, that is, where there is a genetic predisposition to allergic reactions as shown by a family history of allergy.

The most dramatic symptom of allergy to cow's milk is the immediate type of IgE-mediated allergic response resulting in anaphylactic shock. This can be very severe and even result in death if untreated. Other IgE-mediated symptoms may also occur, for example, the so-called oral allergy syndrome characterised by oral irritation, lip and throat tightness, and lip swelling as well as a wide variety of other symptoms typical of food allergy, occurring in any combination.

Mild cases of cow's milk allergy can easily be missed when symptoms occur in an irritable child who does not sleep well or who has relatively mild diarrhoea or eczema, or when milk allergy causes gastrointestinal blood loss leading to anaemia. Differentiating between allergy and a non-allergic reaction to cow's milk can be difficult, as in the child who sometimes vomits and who develops colic after feeding but has no other specific symptoms.

Allergy to cow's milk is not always permanent. Of those who are sensitised before three months, 40% lose their symptoms by three to four years of age. However, of those who are sensitised after three months of age, 80% still have cow's milk allergy when followed to three to four years of age.

The Allergens of Cow's Milk

There are numerous cow's milk proteins, but the major allergens are β-lactoglobulin, α- and β-casein, and α-lactalbumin. Most affected children are sensitised to several proteins of cow's milk, but β-lactoglobulin stimulates the highest antibody levels even though it accounts for only 10% of the total protein. Its potency as an allergen may be because it is the only type of protein in cow's milk which is not present in human milk and because it appears to be somewhat resistant to digestion in the stomach, allowing some to be absorbed undigested.

Several cow's milk proteins including β-lactoglobulin stimulate the production of IgM antibody, and sometimes IgG antibody, in most normal children and adults. But it is not known how or in what circumstances these milk proteins stimulate the production of IgE antibody—and hence allergic reactions.

Making Milk Formula for Infants Less Allergenic

It is vital to find alternative feeds for infants who react against cow's milk. Formulae based on soy protein have been tried extensively, both in the prevention and in the treatment of allergy to cow's milk. However, 7–10% of babies showing allergy to cow's milk protein also have reactions to soy formulae.

An alternative for these allergic babies are infant formulae where the protein has been partially digested with enzymes called proteases. These formulae have been in use for several decades, especially where food allergy is likely to occur in the first few months of life. Trials indicate that newborns babies with a family history of allergy experience a significantly lower incidence of allergy when given milk products treated to produce the smallest size of protein fragments compared with infants fed cow's milk or soya preparations. This benefit continues during the six-month feeding period and beyond.

Allergenicity of Milk and Milk Products

Milk remains an important dietary component beyond infancy, and it is therefore important for those who remain sensitive to milk to know whether processing of milk can reduce its ability to provoke a reaction. Of the standard methods of dairy processing, only heat processing and fermentation are known to affect the allergenicity of milk.

High temperatures reduce the allergenicity of the major whey proteins such as α-lactalbumin and β-lactoglobulin. This reduction of allergenicity may be helpful in some cases of milk allergy but not in others, because heat denaturation does not reduce the allergenic potential of all milk proteins, for example, casein, which is remarkably heat insensitive.

In fermented milk products like yoghurt and kefir, the structure of the milk proteins may remain largely intact after fermentation, thereby maintaining their allergenicity. Although a greater degradation of milk proteins may occur during cheese manufacture, this is not consistent, and it is therefore not safe to assume that all cheeses have low allergenic potential, especially fresh cheese or cheeses with a very short ripening period.

COELIAC DISEASE

Coeliac disease, first described as a clinical entity a century ago, gives insight into how our ideas on adverse reactions to foods have developed. The classical description of patients with coeliac disease is of children under the age of three years who fail to thrive and who have striking fatty diarrhoea, an enlarged abdomen, limp muscles, weakness and a bad temper. In younger children, loss of appetite is a prominent symptom, whereas the older ones mostly eat normally. Infants tend to vomit after feeding and, as they grow, may be so weak that they cannot walk or even stand up. Some have severe malnutrition, anaemia and the swelling of the legs and abdomen that is characteristic of protein deficiency. They fail to gain weight. In older children growth retardation is the most prominent and sometimes the only clinical symptom. Severe and typical cases are now likely to be identified at an early stage, but in many instances the effects of the disease may be relatively mild and the symptoms vague, making diagnosis difficult.

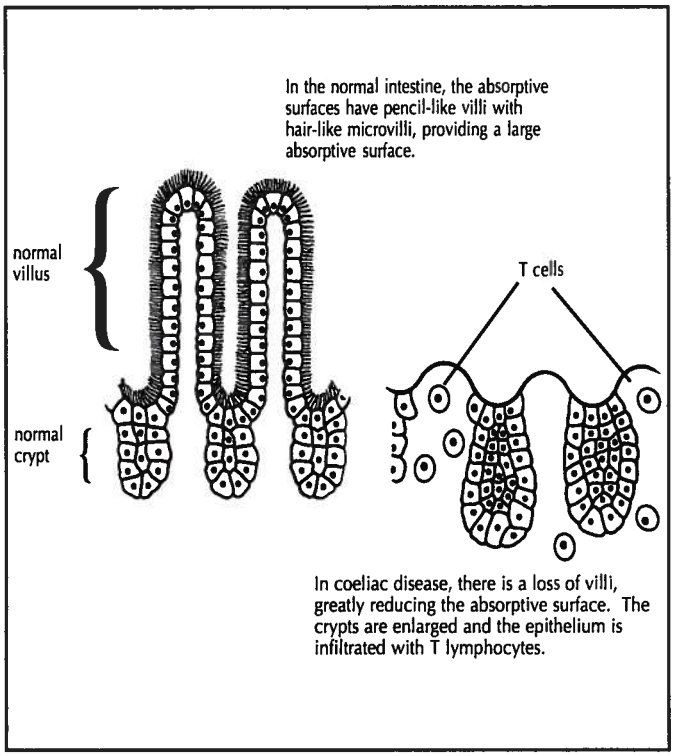
The characteristic feature of coeliac disease is the change in the appearance of the villi of the intestine (Fig. 8). Demonstrating this entails taking a sample of the cells which line the intestine and is now the cornerstone in the diagnosis of coeliac disease. It is not a simple test procedure, and for this reason there may still be delays in reaching a diagnosis. These changes in the villi greatly reduce the ability of the intestine to absorb fat and other nutrients, such as fat-soluble vitamins and calcium, thus causing the characteristic symptoms.

Identifying the Causes of Coeliac Disease

During the Dutch famine at the end of World War II, it was noted that the condition of children with coeliac disease paradoxically improved on the diet of mostly potatoes, tulip bulbs and cabbage, whereas most other children lost weight. This observation together with another one that biscuits, bread and flour-containing meals could cause an exacerbation of symptoms in children with coeliac disease led Dutch investigators to search for a factor in wheat which was toxic to these patients. They identified it as a protein called gliadin, which is an important component of gluten, the major group of proteins found in wheat. Similar proteins from rye, oats and barley, but not those of more distantly related cereals like maize or rice, were also found to be toxic to these children.

Susceptibility to coeliac disease is genetically determined. Between one in 350 and one in 2000 in the European population suffers from the disease. The highest prevalence is seen in closed regions such as the Galway area in Ireland or in Austria, suggesting that genetic susceptibility varies. However, the incidence in North America is much lower

FIGURE 8
Changes in the intestinal absorptive surfaces in coeliac disease



than in Europe among people of the same ethnic origin, so it is believed that environmental factors also influence the development of the disease.

Why Are Coeliac Patients Sensitive to Gluten?

It is still uncertain why sufferers of coeliac disease are sensitive to the gliadin found in gluten. Many abnormalities have been recorded but it is difficult to disentangle those which are of primary importance in causing the disease from those which are simply a result of the disease process.

A leading hypothesis is that an abnormality in the immune system underlies coeliac disease, since increased levels of IgA, IgM and IgG antibodies against gliadin are found together with strikingly increased numbers of B and especially T cells infiltrating the flattened epithelium. It is presumed that there is a defect at some point in the immune mechanism which results in sensitisation to gliadin rather than tolerance. However, the changes that are seen may simply be a reaction to undigested food proteins which seep across the damaged intestinal wall. Even if this is the case, delayed-type immune reactions may still be an important part of the disease process, since a gluten challenge given to patients in remission leads rapidly to the appearance of types of T cells which are involved with cell destruction and to activation of mast cells and B cells.

Other hypotheses not yet completely ruled out postulate that a defect in the structure of the epithelial cell membrane is the primary cause of coeliac disease or that important enzymes in the surface cells of the intestine are lacking.

Dietary Control of Coeliac Disease

Currently the only help for coeliac patients is a gluten-free diet. This is difficult to achieve because gluten is found in many important cereal-based foods but also less obviously in numerous thickeners, emulsifiers and substitutes for animal proteins. By adolescence, the discipline of a gluten-free diet may be difficult to enforce. Many children who do not strictly adhere to their diet experience no symptoms, so it is difficult to assess the long-term effects of this liberalisation of their diet. Some evidence suggests that this non-adherence to a gluten-free diet may increase the risk of bowel cancer in later life.

Attempts are being made to identify the exact sequence of amino acids in gliadin which is toxic to coeliac patients. This could lead to improvements in the antibodies used in the analysis of gluten-free food. Furthermore, this knowledge will be essential for the application of biotechnology in the future development of cereal crops containing non-toxic gliadin.

FOOD ADDITIVES: ARE THEY AN IMPORTANT CAUSE OF ADVERSE REACTIONS TO FOODS?

Food additives serve technological functions in many foods. They are used to modify keeping quality, texture, consistency, taste, odour, alkalinity or acidity, or to assist the process of manufacture.

Even traditional food processing involves the use of additives, whether the end product is a loaf of bread or a bottle of wine. About 4000 of these ingredients are now permitted, a large proportion of which are flavourings used in very small quantities. Other food additives ensure the safety of foods or promote convenience, attractiveness and consistent appearance and quality. Additives with "E" numbers have been approved as safe by the European Community. Any new ingredient must be approved by specialist committees which consider whether there is a need for the new material and whether it is safe.

There has been much public concern that additives cause adverse reactions. For example, 7% of a recent population sample in the United Kingdom claimed to react to food additives. In fact, the frequency of intolerance to food additives appears to be low. In the above survey, careful investigation using double-blind challenge tests showed that probably only 0.01-0.23% of the population were actually affected. It is clear from this study that public

concern about food additive intolerance is often based on misconception rather than on identifiable reactions. Adverse reactions to foods appear to be far more common than reactions to food additives.

Many earlier studies of adverse reactions to food additives used unrealistically high challenge doses or were not confirmed with double-blind challenges. However, reactions to food additives can certainly occur. For example, sulphites can provoke asthma in certain asthmatic individuals. This can follow when volatile sulphur dioxide in acidic drinks is inhaled or when sulphite is used to preserve the freshness of fruits and vegetables. More rarely, other food additives have been implicated in asthma. Food colours can cause urticaria in an occasional patient. Hyperactivity in children usually has quite different causes but may perhaps on occasion be caused by food additives (see below).

There is therefore uncertainty about some of the earlier claims of adverse reactions to food additives. Where they have an effect, food additives appear to exacerbate a pre-existing condition rather than induce it. Despite investigation, there is little insight into how additives produce a reaction. Allergic mechanisms are rarely involved, although IgE may be implicated in some sulphite-sensitive asthmatics. It has been suggested that food colours release histamine and prostaglandins in urticaria, most likely because of a direct pharmacological effect in these sensitive individuals rather than by an allergic mechanism. Other additives may act in a pharmacological manner.

In assessing the risks and benefits of food additives, it is worth remembering that food poisoning from microbiological contamination is several thousand times more likely to cause adverse effects due to food than is the occasional asthmatic or urticarial episode provoked by the presence of a preservative or other food additive. Since only a very small minority of people are susceptible to food additives, informative labelling about the ingredients in food products is regarded as the best protection. As long as there is a substantial safety margin for the population in general, no other measures need be taken. In addition, in the Netherlands, the United Kingdom and a few other countries, doctors and dietitians now have access to data banks providing lists of food preparations which are free of certain foods or food additives known to be capable of causing adverse effects in susceptible individuals. It has been suggested that such information could usefully be extended to the additives present in antihistamines and other medicines.

Hyperactivity and Food Additives

It should not be surprising that some foods are capable of affecting behaviour. An example is the effect of caffeine on alertness.

Children with allergic disorders such as asthma and eczema can become restless and irritable after eating foods to which they are sensitive. There is little convincing evidence, however, that behaviour problems are the result of adverse reactions to foods. Nevertheless, in recent years, physicians have seen an increasing number of parents who claim that their children become "hyperactive" as a result of eating foods that contain food additives.

Hyperactivity is characterised by constant restlessness, disorganization and inattention. However, agreed-upon norms for measuring activity levels and attention are lacking, and there is disagreement over whether hyperactivity is a discrete condition or simply a collection of non-specific features present in many behaviour disorders.

Confusion has also arisen because child psychiatrists in North America and Europe use different terminology. Many children diagnosed as hyperactive in some countries may be labelled as having a conduct disorder in others. The following definitions are often used in Europe: *overactivity* implies an excess of physical activity which is nevertheless within the wide boundaries of normal; *hyperactivity* or *attention deficit disorder with hyperactivity* consists of excessive overactivity, short attention span and impulsive behaviour. Young children with severe, intractable restlessness and delayed development are sometimes

considered to be suffering from the hyperkinetic syndrome.

Estimates of the numbers of hyperactive children also vary depending on whether the figures are derived from teacher questionnaire surveys (5–20%) or from clinically diagnosed children attending psychiatric clinics (0.1–1%). There is general agreement that four boys are affected for every girl. Complaints about a child's hyperactive behaviour are common reasons for a child to be referred to a child psychiatrist. Brain damage and brain malfunction, zinc or vitamin deficiency, and sugar intolerance have all been proposed as causes of hyperactivity. However, the only hypothesis that has been systematically tested has been the proposal by B. Feingold in 1975 that hyperactivity in children is caused by food additives and salicylates (aspirin-like chemicals which occur naturally in some vegetables and fruit). Although unsupported by scientific data, Feingold's anecdotal reports led to widespread publicity and uncritical public acceptance, resulting in the formation of numerous support groups advocating additive elimination diets for hyperactive children.

Many of the studies of hyperactivity are open to criticisms which reduce the validity of their findings. It appears that there is a large placebo effect when diets are used to treat hyperactivity, and any significant effect of food additives on behaviour is much more difficult to reproduce in properly conducted studies using double-blind challenges than would be expected from the claims of parents. There have been a number of well-designed trials, from which there is limited evidence suggesting a possible effect on the behaviour of a small minority of young hyperactive children. These studies show that parents who believe that their children are hyperactive because of an effect of food additives are nearly always mistaken.

In conclusion, there is only limited evidence that food additives or any other dietary factor can produce more than a small and possibly transient effect on behaviour in some young children with hyperactivity.

Treatment of Hyperactivity

Often all that is required to allay anxieties is to explain to the parents the many factors which may contribute to hyperactivity and give a reassurance that special diets are not needed. Only in cases when behaviour problems are severe or associated with learning problems will the child require assessment by a clinical psychologist or psychiatrist. In these cases, psychological and sometimes drug treatment may be used.

An additive elimination diet is not usually indicated and should not be used without good reason. Such diets are often socially restricting. Very restricted diets carry the danger of nutritional deficiencies, and the avoidance of fruit and vegetables containing "natural salicylates" as part of the "Feingold diet" is undesirable. Embarking on an inappropriate diet may also neglect other potential methods of treatment.

LIVING WITH ADVERSE REACTIONS TO FOODS

How Widespread Are Adverse Reactions to Foods?

Accurate information on the numbers of people affected by adverse reactions to foods is difficult to obtain. Many people who react to a particular food never see a doctor but simply avoid the food. Questionnaire surveys of representative samples of the general population find that from 4.5% to 33% of the population believe they are affected by adverse reactions to foods. But such questionnaires include all the built-in errors of self-diagnosis. Ideally, questionnaires should be followed up with challenge tests where those who believe they react adversely to foods or food additives are given the appropriate substances in an unidentifiable form and the response compared with that to a placebo. When this is done, a reaction to a food can be confirmed in only about 20% of those who believe they suffer from an adverse reaction to a food. This is in striking contrast to the study on additives mentioned above where 7% of a population believed they reacted to additives: in only one person in 25 of the 7% could a reaction to an additive be confirmed.

Overall, the frequency of adverse reactions to foods including food additives probably lies between the figure recently proposed of at least 1.4% and about 2% (lactose intolerance excluded).

Patient Self-Help Groups

Coeliac societies in various countries have built on the enthusiasm of non-medical people who, from experience, have learned the difficulties of getting good advice on dealing with the health problems and disabilities which arise from coeliac disease. These societies compile and regularly update lists of manufactured foods which are free of gluten. Excellent advice may also be available for patients suffering from other adverse reactions to foods. One group in the Netherlands has a medical board of advisers, invites comments from an "alternative medicine" board and produces its own quarterly publication. It also has support groups which meet regularly, a dietary advice group and a telephone service run by volunteers.

Identifying Allergens in Food

The identification of allergens in purchased foods is greatly helped by food labelling information and by food lists, data banks and advice offered by dietitians, patient self-help groups, government departments and food manufacturers. Such lists of foods that are free of milk, egg or gluten are invaluable, particularly if backed by professional advice on how to avoid mineral and vitamin deficiencies. The role of the dietitian can be crucial. Government requirements for food labelling have also been of great help to those who must face the practical difficulties of keeping to a rigorous diet.

Meals eaten outside the home may pose the problem of the "hidden" allergen and cause reactions in highly sensitive people. Problems can arise with sauces of unknown composition, the addition of peanut products in cooking, or cross-contamination of a cooking utensil that contains residual proteins from a food to which an individual is sensitive.

Controlling Adverse Reactions to Foods

The control of adverse reactions to foods can be approached in four main ways: prevention, dietary manipulation, drug treatment, and making foods less allergenic. The first two methods are the main ones in use and are considered in more detail below.

The treatment of adverse reactions to foods with drugs has been largely unsuccessful. For example, disodium cromoglycate has been used in an occasionally successful attempt to prevent reactions, but the results have mostly been disappointing. In severe cases corticosteroids or adrenaline (epinephrine) are useful in giving symptom relief. Administration of adrenaline and an antihistamine in cases of anaphylactic shock can be life-saving.

Preventing and Treating Food Allergy in the Infant

Breast-feeding is commonly recommended as one of the best ways to prevent, or at least delay, the development in infants of allergy, especially to cow's milk. However, because antigens from food eaten by the mother may enter breast milk, breast-feeding can very occasionally provoke food allergy in babies where there is a strong family history of allergy. It has also been suggested that it is beneficial to modify the mother's own diet in the last three months of pregnancy by eliminating or greatly reducing the intake of major food allergens such as milk products, eggs and peanuts. It is highly doubtful if such regimes are worthwhile.

While not uncommon, reactions to cow's milk are not always easy to recognize. The mother of an irritable baby who has a skin rash and diarrhoea and vomits cow's milk may find it hard to decide whether this is normal. Since milk is so vital, there are practical reasons for accepting minor upsets caused by cow's milk if the baby is not vomiting.

Protein hydrolysates or soy preparations can be offered as alternatives in more severe cases of allergy to milk. The development of less allergenic infant formulas is a promising approach.

Social Adjustments

Adverse reactions to foods can be a "hidden handicap" in a child with a perfectly healthy appearance. A family with a food-intolerant child has to surmount a number of difficulties. It may be necessary to convince family members that unpopular measures are necessary for the well-being of the child and that they do not indicate a withdrawal of parental love. The change in eating habits required of the child may be radical, and providing a daily or weekly menu can be a formidable task. Compliance by the child will be assisted if the whole family can eat a similar range of foods, although restrictions on other family members cannot be carried too far. It may be helpful to leave a "forbidden" cake on the table in the hope that this will habituate the child to confrontations with "forbidden" food outside the home. Possession of an emergency kit containing adrenaline may be vital where eating a prohibited food could cause a serious reaction.

Contacts outside the home, such as school personnel or friends' families, should be alerted to the child's allergy and the possible severity of an allergic response. An allergic child out visiting can ease some of the problems by taking along special food and drinks "just in case".

It is never easy to keep rigidly to a diet, but the maintenance of good health is an adequate reward for the trials and tribulations of a restricted food choice. Most children can get used to a diet, however strict. From time to time, new foodstuffs should be tried, preferably under the supervision of a doctor and dietitian.

SUMMARY

"Food allergy" has become almost a cult health preoccupation. Unfounded claims for its diagnosis or self-diagnosis have diverted attention from some very real medical problems and may lead to the omission of nutritious foods from the diet.

Adverse reactions to foods are important in a wide range of conditions, including coeliac disease, cow's milk reactions in infants, various types of food allergy and reactions caused by toxic substances, enzyme deficiencies and the pharmacological effects of some food constituents.

Confirmation of an adverse reaction to a food depends on the demonstration that reintroduction of the food causes symptoms to recur that are not the result of psychological factors. Tests for IgE antibodies to food or for enzyme deficiencies or damage to the intestinal lining can provide strong supporting evidence of an adverse reaction to that food.

The term allergy implies a reaction of the immune system involving among other events an IgE-triggered discharge of histamine from the body's mast cells. In the case of coeliac disease, another form of immune reaction with a delayed response may be involved.

There are various symptoms associated with adverse reactions to foods. They include lip swelling, tightening of the throat, asthma, eczema, urticaria, headache, vomiting, diarrhoea and, in the most severe cases, a state of shock with other features of anaphylaxis. The most common symptoms in infants with cow's milk allergy are vomiting, diarrhoea, eczema and failure to thrive. Children with coeliac disease may have diarrhoea associated with other features such as weakness, a prominent abdomen and bad temper. This results from a reaction against wheat products in the diet which causes damage to the intestinal epithelium.

Adverse reactions which do not have an allergic mechanism may produce symptoms similar to those of food allergy. For example, asthma may result from the effects of the preservative sodium metabisulphite, or

diarrhoea may be caused by lactase deficiency and the consequent fermentation of unabsorbed and undigested lactose in the large intestine.

The overall frequency of food reactions is uncertain, because the majority of people who react to an individual food never see a doctor. Apart from enzyme deficiencies that lead to difficulty metabolising lactose in some populations and alcohol in others, adverse reactions to foods affect only a small percentage of the population—probably less than 2%. Small children are the most commonly affected, and allergy to cow's milk can be particularly troublesome in the children of allergic parents. Reactions caused by food additives are infrequent, and much unnecessary anxiety has been caused by claims that additives are harmful and that they are a frequent cause of allergy or childhood hyperactivity.

It is therefore important that current knowledge about adverse reactions to foods be made widely available and that physicians treat with sympathy and appropriate testing patients who complain of food or additive intolerance. It is unwise to ignore the real or imaginary problems caused by adverse reactions to foods but equally unwise to cause unnecessary alarm. Neither extreme is helpful.

GLOSSARY

Allergen: A substance which provokes an allergic response.

Allergy: An inappropriate and exaggerated immune response.

Amines: Organic compounds, usually derived from amino acids, that contain nitrogen and hydrogen and play a prominent role in biochemical systems.

Anaphylaxis: A generalized inflammatory immune reaction to a foreign protein in a sensitised individual which may be severe enough to be life-threatening.

Angioedema: Swelling of the skin or mucous membrane and underlying tissue.

Antibody: A protein molecule produced and secreted by B cells in response to an antigen, which is capable of binding to that specific antigen.

Antigen: A foreign substance or protein that, when introduced into the body, is recognised by the immune system.

Asthma: Breathing difficulty caused by narrowing of the air passages that is reversible.

Atopy: A genetic predisposition to allergic reaction.

B cells: (B lymphocytes) White blood cells derived from stem cells in bone marrow and elsewhere that produce antibodies.

Basophil: A type of white blood cell that contributes to inflammatory reactions and symptoms of allergy.

Challenge test: Reintroduction of a food previously eliminated from the diet on suspicion that it caused an adverse reaction.

Complement: Blood proteins that amplify the action of antibodies.

Double-blind food challenge: Food challenge test where neither the patient nor the clinical investigator knows the identity of the administered substance.

Eczema: An itching red rash, often on the face, hands or skin folds, which oozes and crusts if scratched.

Enzymes: Proteins that facilitate metabolic reactions. Each enzyme is specific for a given substance.

Epithelium: The surface layer of the skin or the lining layer of the intestinal mucosa or air passages of the lungs.

Fermented foods: Foods that have been subjected to processing involving the action of yeasts or bacteria.

Histamine: An amine found in all tissues of the body. Large amounts are released by mast cells when the body encounters a substance to which it is sensitive, thereby triggering symptoms of inflammation.

Immunoglobulins: Large proteins from which antibodies are formed, and which are then capable of combining with foreign substances (antigens).

Interleukins: Molecules which relay signals between cells of the immune system.

Leukotrienes: Chemical mediators of the inflammatory response, released by various white blood cells and by mast cells.

Lumen: The channel within a tubular organ, for example, the lumen of the intestine.

Lymphocytes: White blood cells crucial to the body's immune defence.

Malabsorption: Failure to absorb nutrients completely.

Mast cells: Granule-containing cells found in tissue whose inflammatory responses contribute to the symptoms of allergy.

Metabolism: The body's highly integrated network of chemical reactions catalysed by enzymes.

Migraine: Recurrent headaches, often mainly one-sided and often preceded by flashing lights, nausea or other warning symptoms.

Mucosa: The lining membrane of tubular organs.

Permeability: Degree of leakiness of membranes.

Pharmacological: Pertains to drug-like actions of chemical substances.

Placebo: A harmless and pharmacologically inactive substance, usually disguised, given to compare its effect with that of an active material.

Prostaglandins: Fatty acids synthesised by various white blood cells and at the surface of mast cells, that can cause either contraction or relaxation of smooth muscles in the airways and in certain blood vessels.

Protease: Enzyme that breaks down proteins.

Stem cell: Precursor cell in various systems which is capable of producing the various functional cells of that system by cell division and differentiation, e.g., stem cells which differentiate into lymphocytes.

Sulphites: Preservatives commonly used in, for example, wine.

T cells (T lymphocytes): White blood cells involved in the immune response.

Toxin: Poisonous substance.

Urticaria: A raised, itching rash, often with well-circumscribed areas (wheals).

Wheal: A well-circumscribed raised area of skin.

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