Adverse reactions to food constituents: allergy, intolerance, and autoimmunity

David Kitts, Yvonne Yuan, Janice Joneja, Fraser Scott, Andrew Szilagyi, Jean Amiot, and Marion Zarkadas

Abstract: Food allergies and intolerance represent important health concerns to consumers who are predisposed to these illnesses. Unlike many current food safety issues, food sensitivities are complicated by both complex and multiple individual adverse reactions, which can vary from emotional to pathophysiological ailments. In some instances, the underlying mechanisms that result in the development of food allergies or intolerance have marked differences but produce common symptoms. The present-day diagnosis of these disorders can be impeded by intrinsic limitations in generating accurate information from patient history and biochemical, physicochemical, and immunochemical tests. Oral challenge tests represent effective methods for confirming and testing food allergens and food intolerance; however, these procedures are often restricted to clinical trials. It is important to be able to distinguish among food allergy, intolerance, and autoimmune disease in the management of these disorders. The role of food in the development of autoimmune disease may be exemplified by celiac disease, a food-induced enteropathy, requiring exposure to prolams in wheat, rye, and barley. Various wheat and soy protein sources, including the soy protein isolates used to make infant formulas, have been related to juvenile or insulin-dependent diabetes mellitus (IDDM), a common chronic disease of childhood. Employing food process technologies to eliminate food constituents with potential for intolerance in some individuals is a potentially viable approach for reducing risk to food-related disorders. Finally, the development of food labelling regulations that require the identification of potential food allergens or agents for intolerance in the ingredient declaration on prepackaged food is a positive step toward the prevention of severe adverse reactions in hypersensitive individuals.

Key words: food allergy, intolerance, autoimmunity, process technology, labelling.

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D. Kitts and Y. Yuan. Department of Food Science, The University of British Columbia, 6650 N.W. Marine Drive, Vancouver, BC V6T 1Z4, Canada.

J. Joneja. Allergy Nutrition Research Program, Vancouver Hospital and Health Sciences Centre, Echelon Centre, 605-575 West 8th Ave., Vancouver, BC V5Z 1C9, Canada.

F. Scott. Nutrition Research Division, 2203C, Health Canada, Banting Research Centre, Tunney’s Pasture, Ottawa, ON K1A 0L2, Canada.

A. Szilagyi. Department of Medicine, Division of Gastroenterology, Sir Mortimer B. Davis Jewish General Hospital, McGill University, School of Medicine, 3755 chemin de la Côte Ste-Catherine, Montréal, QC H3T 1E2, Canada.

J. Amiot. Dairy Research Centre, Department of Food Science and Nutrition, Faculté des sciences de l’agriculture et de l’alimentation, Université Laval, Québec, QC G1K 7P4, Canada.

M. Zarkadas. Agriculture and Agri-Food Canada, Food Division/Food Inspection Directorate, Food Production and Inspection Branch, 59 Camelot Drive, Nepean, ON K1A 0X9, Canada.

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2 Author for correspondence.

3 Present address: Department of Nutrition, Faculty of Medicine, University of Toronto, 150 College St., Toronto, ON M5S 3E2, Canada.
confirmé et tester les allergènes et les intolérances alimentaires, mais ils sont souvent limités aux essais cliniques. Il est important de faire la distinction entre allergie, intolérance et maladie auto-immune aux fins du traitement de ces affections. Le rôle des produits alimentaires dans le développement de la maladie auto-immune pourrait être illustré par la maladie coeliaque, une entéropathie provoquée par les produits alimentaires, induite par une exposition aux prolamines contenues dans le blé, le seigle et l’orge. Diverses sources de protéines de soja et de blé, notamment les isolats des protéines de soja utilisés pour fabriquer les aliments lactés pour nourrissons, ont été associées au diabète juvénile ou insulinodépendant (DID), une maladie chronique fréquemment observée dans l’enfance. L’emploi de technologies de traitement des produits alimentaires pour éliminer les composants susceptibles de provoquer une intolérance chez certaines personnes est une approche qui pourrait permettre de réduire les effets indésirables liés aux produits alimentaires. Enfin, l’établissement de règles d’étiquetage exigeant l’identification des allergènes et des agents d’intolérance alimentaires potentiels dans la déclaration d’ingrédients des aliments préemballés est une mesure concrète dans la prévention d’effets indésirables sévères chez les personnes hypersensibles.

Mots clés : allergie alimentaire, intolérance, auto-immunité, technologie des procédés, étiquetage.

[Traduit par la Rédaction]

Introduction

The terms food allergies and food sensitivities define adverse reactions to food constituents, which are often mistakenly interchanged as a result of the similarities in symptoms, which in turn gives rise to confusion and controversy. For example, symptoms of cow’s milk allergy can be confused with lactose intolerance; however, in each case the underlying mechanisms differ. Varying results obtained using the radioallergosorbent test (RAST), skin prick, and titrated oral challenges for assessing allergenicity can further complicate the situation (Wahn et al. 1992). In the case of type 1 hypersensitivity, immediate hypersensitivity to foreign food antigens is initiated by IgE-mediated allergic reactions caused by the breakdown of normal immune tolerance. This is in contrast with metabolic food sensitivities, such as lactose intolerance and favism, where adverse reactions to a food constituent are expressed through the altered metabolism of the individual. Celiac disease, or gluten-sensitive enteropathy, on the other hand is characterized by malabsorption induced by the prolamin fractions of barley, rye, and oats and can result in diarrhea, weight loss, chronic fatigue, and muscle cramps (Scott 1994). In all instances, the susceptibility of an individual to food-induced allergy or intolerance reactions is dependent on genetic susceptibility, age, physiological status, and frequency and extent of exposure to the antigen. In the case of true food allergies, molecular size and conformational structure of component proteins are important for favourable spatial configuration and amino acid sequence, which promotes a positive interaction between antigen and B-cell receptors (Rungkat-Zakaria et al. 1992). The cross-reactivities of allergens from different sources testify to the presence of some common complex structural residues from unrelated proteins (Garcia-Casado et al. 1996). Technologies developed to reduce the probability of antibody–antigen receptor interactions have therefore focused on altering protein structure (Hussein et al. 1996) or glycosylation character (Garcia-Casado et al. 1996). The application of thermal processes to provide this advantage has produced varying results, from the absence of effect associated with pasteurization (e.g., 72°C for 3 min) to a partial effect achieved with ultra high temperature (UHT) processing (e.g., 300°C for 2–3 s) (Jost et al. 1991). Fermentation in low salt zones can result in proteolysis of certain milk proteins only, whereas enzymatic and chemical hydrolysis reduce peptide constituent size and conformation. Recent technologies using enzymatic hydrolysis of food proteins, coupled with ultrafiltration to concentrate low molecular weight hydrolysate material, have produced reasonable results in reducing allergenicity and maintaining nutritional value of otherwise allergenic proteins (Asselin et al. 1988; Boza et al. 1994). Furthermore, biotechnological methods have been developed to selectively remove target proteins from food systems without prior manipulation (Chiancone and Gattoni 1993). Concern about the allergenic potential of new proteins developed from recombinant techniques has also been debated (Lehrer et al. 1996). Regulation of expression of antisense RNA to the allergenic protein gene analogous to recent biotechnologies used to regulate biosynthetic pathways of plants (Oeller et al. 1991) is an example of a potential strategy involving biotechnology.

Other processing strategies have been utilized to diminish the effects of adverse metabolic reactions to food components, such as lactose intolerance. For example, fermentation of dairy products with starter cultures of Streptococcus thermophilus and Lactobacillus bulgaricus, producing yoghurt, reduces the lactose content by 20–30% and increases lactic acid content to 50–75% (Renner 1986), as well as contributes to a source of β-galactosidase in unprocessed product. Lactase-deficient individuals tolerate yoghurt better than milk because of the reduced content of lactose and presence of the bacterial enzyme lactase or β-galactosidase. Microbial β-galactosidase activity in yoghurt, however, decreases 10-fold with pasteurization (e.g., 65°C for 3 min; Saviano et al. 1984) and is essentially lost at refrigerated temperatures at pH 4.6 (Kolars et al. 1984). Thus, to be used as dietary adjuncts, these bacteria must survive in large numbers in fermented milk products. Alternatively, if the enzyme is added to yoghurt following pasteurization (e.g., high lactase yoghurt), it must withstand the low pH of human stomach and presence of bile acids in the small intestine. The fact that this may be possible has been shown in hydrogen excretion studies designed to monitor lactose digestion from conventional and high lactase yoghurt (Kotz et al. 1994).

Finally, the accurate labelling of foods identified as potentially causing severe adverse reactions is critically important in assisting individuals with food hypersensitivities to choose from a wide variety of packaged foods. Greater prudence with ingredient labelling of foods that may contribute to potential food sensitivities will require a commitment by industry
to inform the consumer of the presence of ingredients that can cause adverse reactions in susceptible individuals.

This symposium was designed to discuss many of these issues with an overall objective of identifying the sources and underlying mechanisms of common food intolerances, as well as viable methods of reducing the risk of exposure to food constituents that can elicit an allergic or metabolic disorder.

Food allergy and intolerance, defining the difference

Contributed by Janice M. Joneja

The American Academy of Allergy and Immunology Committee on Adverse Reactions to foods defines food allergy as “an immunologic reaction resulting from the ingestion of a food or food additive,” and food intolerance as “a general term describing an abnormal physiological response to an ingested food or food additive that is not proven to be immunogenic” (Bindslev-Jensen et al. 1994). Food allergy, often referred to as well as food hypersensitivity, is a reaction of the immune system to a component of food (almost invariably a protein, or a molecule linked to a protein) that it recognizes as “foreign” (Ferguson 1992). A hypersensitivity reaction of the immune system involves a series of specific events, which result in a clinical symptom. Four distinct hypersensitivity reactions are recognized, each type involving different components of the immune system. Food allergy may be mediated by type I, type II/III, or type IV hypersensitivity, and possibly by a combination of more than one. Traditionally, the term allergy (or atopy) has been reserved for the type I hypersensitivity reaction, while types II, III, and IV may be referred to as “immune-mediated reactions” (Ferguson 1995). Food allergy is more common in children than adults, with an estimated prevalence of 1–3% in children under 5 years of age (Botey et al. 1991). Peanuts, cow’s milk proteins, and egg proteins are frequently the most common foods causing type I hypersensitivity in children. Often early food allergies are outgrown by the age of 5 years, but certain allergies to foods, specifically peanuts, nuts, shellfish, and sometimes fin fish, can last for a lifetime. These are also the foods that are the most frequently implicated in life-threatening anaphylactic reactions (Sampson et al. 1992). In adults, non-immune-mediated intolerance seems to be much more common than food allergy. Inflammatory mediators are released or levels are enhanced by food components or food additives acting through mechanisms that are independent of the immune system. This is presently classified as food intolerance rather than allergy. The most severe allergic response, a life-threatening anaphylactic reaction, mediated primarily by a type I hypersensitivity reaction, is very rare. The immune system mediated reactions causing allergy are summarized in Table 1 (Joneja and Bielory 1990).

Regardless of the hypersensitivity reaction involved, the symptoms of allergy result from the release of inflammatory mediators, which act on body tissues and cause the clinical condition. Thus, allergy is an inflammatory process, and each inflammatory mediator released in the hypersensitivity reaction has its own effect. For example, histamine mediates swelling, itching, effusion, urticaria, angioedema, hypotension, and bronchospasm. Leukotrienes are responsible for the bronchospasm of asthma, whereas bradykinins and prostaglandins mediate pain. Allergy is the result of the combined effect of all of the inflammatory chemicals, and treatment usually involves symptomatic relief with medication designed to combat the local effects of each type of mediator.

An adverse reaction to food that results in clinical symptoms, but which is not caused by a reaction of the immune system, can be classified as a food intolerance. The physiological mechanisms that are responsible for these reactions can be diverse and complex, and many are presently very poorly understood (Furukawa 1991). Examples of non-immune mechanisms of food intolerance are listed in Table 2.

In reviewing the wide range of immunological and physiological mechanisms that are responsible for the clinical symptoms of adverse reactions to foods, it becomes obvious that any single laboratory test could not be expected to identify the specific food components responsible for the reaction. Skin tests are the standard method presently employed by allergists to diagnose allergy. However, when applied for the detection of an adverse reaction to foods, the tests merely determine whether a crude food extract can release histamine from skin mast cells when applied to abraded skin or injected into the dermis. Many of the clinical symptoms triggered by foods are not mediated by this mechanism of response, and the accuracy of the tests has been estimated to be no higher than 30% in most cases (David 1993). A number of tests for the detection of circulating antibodies to food allergens are in use. These include the radioallergosorbent test (RAST) for allergenspecific IgE and the enzyme-linked immunosorbent assay (ELISA) for allergen-specific IgE and IgG, particularly IgG4. However, in practice these tests tend to be even less accurate than skin tests in determining food reactions. Research indicates that everyone has some level of food antibodies in circulation, whether they are atopic or not, and the tests will not determine which specific antibody will lead to clinical symptoms in an individual (Oehling et al. 1981; David 1993). At the present time, the only accurate method available for the detection of the foods, food components, and food additives causing or contributing to the adverse reactions is elimination and challenge. Suspected foods and additives are eliminated from the diet for a specific period of time. The restricted foods are selected on the basis of very careful food intake diaries and medical history. When improvement is achieved (usually within 4 weeks), a sequential incremental dose challenge is instituted to identify the specific food components responsible for the reactions. A final diet is developed that restricts the intake of the “reactive foods” and provides complete, balanced nutrition from alternative sources (Joneja 1995).

Food-induced autoimmune disease: comparing celiac disease and juvenile diabetes

Contributed by Fraser Scott

Food can play an important role in development of autoimmune disease in susceptible individuals as shown by the classic example of celiac disease (CD), a food-induced (autoimmune-like) enteropathy requiring exposure to prolamins in wheat, rye, and barley. Evidence is accumulating that another autoimmune disease, juvenile or insulin-dependent diabetes mellitus (IDDM), may also be food-induced (Gerstein 1994). We have
suggested that food is the major environmental factor controlling expression of spontaneous diabetes in the BioBreeding (BB) rat. Our approach involves characterizing what we have termed “food autoimmunogens” in mainly plant-based rodent diets that produce the highest diabetes incidence in BB rats and non-obese diabetic (NOD) mice (Scott et al. 1994). These studies show that as in CD, IDDM can be induced by feeding a diet containing wheat gluten. Screening of several foods indicated there are also diabetogenic agents in soybeans (Hoorfar et al. 1991), and this finding was later confirmed in NOD mice (Hoorfar et al. 1993). The diabetogenicity of soybeans remains, albeit reduced, even after the extensive processing used to produce soy protein isolates that are the sole amino acid source in soy-based infant formulas. This information was used to reformulate the American Academy of Pediatrics infant feeding guidelines (Drash et al. 1994; Scott 1995). There appears also

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**Table 1. Hypersensitivity reactions and mechanisms.**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mechanisms involved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I (anaphylactic shock)</strong></td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
</tr>
<tr>
<td>Recognition of foreign Ag and production of specific Abs</td>
<td>Leukocytes act as Ag-presenting cells to recognize and phagocytose the foreign Ag. These cells present Ag fragments on cell surface to T-cells (CD4+ “helper cells”). Activation of T-cell is mediated by T-cell receptor to eventually result in production of an Ag-specific Ab by B-cells.</td>
</tr>
<tr>
<td>T-cells determine class of Ab to be produced</td>
<td>Two subclasses of T-helper cells (CD4+) designated TH₁ and TH₂ are active at this stage. TH₁ cells activate B-cells to secrete IgG antibodies, which initiate immune response to bacteria and viruses. TH₂ cells activate B-cells to secrete IgE antibodies, which initiate immune response to parasitic helminths and allergens such as those involved in food allergies.</td>
</tr>
<tr>
<td>IgE-mediated release of inflammatory mediators</td>
<td>IgE Abs couple with specific receptors on surface of granulocytes (mast cells in tissues or circulating basophils in blood). Degranulation of mast cells occurs when an Ag (10–50 kDa) bridges two adjacent IgE Abs. Degranulation involves cAMP and GMP as well as entry of Ca²⁺ into the cell to result in release of inflammatory mediators. Histamine mediates a number of events including vasodilatation; edema; bronchoconstriction and itching and mucus secretion. Chemotactic factors, which attract other granulocytes in combination with various enzymes and the secondary mediators of inflammation, are responsible for the second phase of the type I hypersensitivity reaction.</td>
</tr>
</tbody>
</table>

Phase 2

Attraction of neutrophils, eosinophils, monocytes and basophils by chemotactic factors

Granulocyte release of inflammatory mediators results in powerful augmentation of allergic reaction

Phase 2 may occur several hours after the initial response, but usually occurs within 4–6 h after phase 1

Type II and III (anaphylactoid reaction)

TH₁-mediated immune response leads to production of Ag-specific IgM and IgG antibodies

Binding of IgG with its homologous Ag results in a complex series of reactions triggering the complement cascade. As a result of the complement cascade, several newly formed proteins are produced, some of which can degranulate mast cells without the necessity for IgE. Other proteins act as chemotactic agents for granulocytes.

Symptoms resemble those of type I hypersensitivity, therefore referred to as an anaphylactoid reaction

Type IV (contact allergy)

Reaction continues as long as in contact with allergen

No Abs are produced; reaction may be mediated by cytokines released from T-cells

Requires cell-to-cell contact between allergen and cytotoxic T-cell lymphocytes

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**Note:** Ag, antigen; Ab, antibody. References for the above table are as follows: Joneja and Bielory 1990; Sampson and Cooke 1990; Sampson et al. 1992; Joneja 1995.
to be a less potent and more variable diabetogenic potential in cow milk (Scott 1996; Scott et al. 1996b). Therefore, as in CD, where there are three major celiac toxic foods, wheat, rye, and barley, IDDM in animal models involves at least three foods, wheat, soy, and cow milk. There are several other remarkable parallels between celiac disease and IDDM (Table 3).

Both CD and IDDM require genetic predisposition related to the major histocompatibility complex class II region, whose proteins are involved in antigen presentation to CD4+ T-cells and have a major role in immune regulation. In the case of CD, the highest genetic risk is associated with HLA-DQ AI*0501 Bl*0201 and HLADR3, whereas the highest risk for IDDM is

<table>
<thead>
<tr>
<th>Food constituent</th>
<th>Physiological mechanism</th>
<th>Symptoms</th>
<th>Food sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Inhibition of or low levels of histamine-metabolizing enzymes (i.e., methyltransferase, diamine oxidase)</td>
<td>Swelling of tissues, rhinitis, urticaria (hives), angioedema (swelling), itching, pain, and headache</td>
<td>Fermented foods (e.g., cheeses, soy products, sauerkraut, alcoholic beverages, vinegars) Microbial contamination, especially fin fish Eggplant and spinach</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Inhibition of or low levels of monoamine oxidase, particularly in those taking antidepressant medication (e.g., Parnate, Nardil)</td>
<td>Tyramine releases norepinephrine from tissue stores, resulting in vasoconstriction, which can cause migraine headaches Response is dose dependent</td>
<td>Fermented foods (e.g., aged cheeses, wines, beer, vinegars, yeast extract) Pickles and relishes containing vinegar Raspberries, bananas, red plums, avocados, eggplant, tomatoes, and chicken liver</td>
</tr>
<tr>
<td>Salicylates (acetylsalicylic acid; ASA)</td>
<td>Sensitivity to ASA is more common among asthmatics than nonasthmatics Inhibition of cyclo-oxygenase pathway of arachidonic acid metabolism to various prostaglandins, resulting in enhanced production of leukotrienes, which mediate bronchospasms of asthma</td>
<td>Urticaria, angioedema, and precipitation of an asthmatic attack in asthmatics</td>
<td>Acetylsalicylic acid in medication, but naturally occurring salicylates are not known to be a problem</td>
</tr>
<tr>
<td>Azo dyes (i.e., tartrazine)</td>
<td>May initiate release of histamine from mast cells</td>
<td>Asthma, urticaria, nausea, migraine headaches, allergic vasculitis, hyperkinesis (hyperactivity), and contact dermatitis</td>
<td>Foods coloured with FD &amp; C No. 5 (tartrazine)</td>
</tr>
<tr>
<td>Benzoates (i.e., benzoic acid, sodium benzoate, benzyl peroxide, parabens)</td>
<td>May affect cyclo-oxygenase pathway of arachidonic acid metabolism, see above</td>
<td>Asthma, urticaria, angioedema, rhinitis, headaches</td>
<td>Benzoic acid and sodium benzoate are used in foods as antimicrobial agents to extend shelf-life Bleaching agent in manufacture of flour, some cheeses Benzyl and benzoil compounds are used as synthetic flavours and perfumes Occur naturally in some foods, e.g., anise, tea, prune, cinnamon, clove</td>
</tr>
<tr>
<td>Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)</td>
<td>Unclear, but those with food allergies appear to be most sensitive</td>
<td>Urticaria, possibly hyperactivity</td>
<td>Used as antioxidant agent in fats and oils and fat foods to prevent rancidity</td>
</tr>
<tr>
<td>Sulphites</td>
<td>When sulphite dissolves, sulphuric acid is formed, which is then converted to sulphur dioxide, a direct irritant to hypersensitive airways Sensitivity is most common in asthmatics, especially steroid-dependent asthmatics; sensitivity is rare in non-asthmatics</td>
<td>Asthmatic attack</td>
<td>Used as an antibrowning agent in beverages, dried fruits and vegetables, white wines, white grape juice Used as dough conditioner in frozen doughs and pie shells Used as bleaching agent in production of maraschino cherries, glace fruits, and citrus peel Antimicrobial agent</td>
</tr>
<tr>
<td>Lactose</td>
<td>Deficiency in intestinal lactase enzyme leaves undigested lactose in gut to result in increased osmotic pressure leading to influx of fluid into bowel lumen Microbial fermentation of lactose will produce short-chain fatty acids and H2 and CO2</td>
<td>Watery diarrhea, abdominal distention and flatulence</td>
<td>Milk, yogurt, ice cream, and cheeses</td>
</tr>
</tbody>
</table>

Note: References in this table are as follows: Feldman 1983; McCabe 1986; Sampson et al. 1992; Joneja 1995; Savaiano et al. 1984; Gunnison and Jacobsen 1987; Joneja and Bielory 1990; Schwartz 1992.
related to \( \text{HLADQ B1}^*0302^*0201 \) and \( \text{HLADR3/4} \) (Nepom 1996). It has recently been proposed that CD is underdiagnosed as it may often be present in a silent or latent form (Catassi et al. 1994). The incidence of CD is hard to determine accurately because until recently the only “gold standard” was to examine a biopsy specimen from the jejunum to look for decreased villus height to crypt depth ratio, decreased enterocyte height, and CD3+ intraepithelial lymphocytes. The usual practice is to carry out the biopsy only if one or other CD-related antibodies, anti-endomysial, anti-reticulin, or anti-gliadin antibodies, show abnormal values. Therefore, only recently have studies appeared where screening of the general population has occurred and latent or silent (no overt clinical symptoms, but histologic damage is apparent) forms of CD have been confirmed (Troncone et al. 1996). It has been suggested that the real incidence is closer to 1 in 300 than the often quoted 1 in 1000. Therefore, CD may be more prevalent than previously suspected, an important point because of the increased risk of lymphoma.

The incidence rate for IDDM is increasing in many parts of the world and the frequency has increased 4-fold over the last 30 years (Ellis and Atkinson 1996). The highest incidence is in Finland (42.9 / 100 000) and the lowest in China (0.6 / 100 000). Two centres in Canada have been reported to have a very high incidence of IDDM; these are Prince Edward Island (25.5 / 100 000) and Edmonton (25.7 / 100 000), the latter being the highest in North America (Toth et al. 1996). Considering the high cost in patient suffering, premature death, and increased medical care costs, particularly from complications such as nephropathy, neuropathy, increased cardiovascular disease (2–4 times), blindness, and amputations, it is important to develop means of primary prevention. Removing or inactivating food diabetogens in the diet is an attractive means to obtain this goal.

The link between wheat and CD was first reported in 1950 (Dicke 1950). Although 46 years have elapsed, it is only recently that the structure of certain celiac toxic gliadin peptides was reported (Weiser 1995; Sturgess et al. 1994). The advantage in identifying CD-related dietary peptides is that symptoms, usually reversible, appear within hours of administration to patients. The fact that diet had major effects on spontaneous diabetogenesis was first reported in the early 1980s (Scott et al. 1985; Elliott and Martin 1984). The interaction between food and IDDM is rather different, as we believe this form of diabetes requires frequent and long-term exposure to food diabetogens to induce IDDM, which by the time of appearance of clinical symptoms is not reversible by removing food diabetogens from the diet.

Thus, although it is more difficult to link food and development of IDDM in humans, one positive aspect is the ready availability of two well-described and accepted animal models, the BB rat and NOD mouse. Although some animals (e.g., Irish setter dogs) develop spontaneous CD symptoms, there is no generally accepted animal model for CD. The short time for appearance of symptoms in CD patients eating celiac toxic foods is a major advantage in screening, but the invasiveness of jejunal biopsy limits testing. There is always the question of relevance of animal data to humans at risk, which must make one cautious regarding extrapolations. However, we feel there are sufficient data now to show that diet is a major factor in diabetogenesis in two different species, BB rats and NOD mice. Results from other studies in these animals have formed

### Table 3. Food-induced autoimmune diseases: celiac disease and insulin-dependent diabetes mellitus (IDDM).

<table>
<thead>
<tr>
<th>Genetic susceptibility, multigenic (highest risk shown)</th>
<th>Celiac disease (a food-induced autoimmune like disease)</th>
<th>IDDM (a possible food-induced autoimmune disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Recent data suggest CD is underdiagnosed, generally 1/1000 but may be 1/300 as a result of latent or silent CD; decreasing in children but increasing in adults</td>
<td>Increasing in many geographic locations, Edmonton, Alberta, recently reported highest incidence in North America</td>
</tr>
<tr>
<td>Prodromal period</td>
<td>Months to years</td>
<td>Months to years</td>
</tr>
<tr>
<td>Animal models</td>
<td>Irish setter dogs (not generally available)</td>
<td>Diabetes-prone BB rats and NOD mice</td>
</tr>
<tr>
<td>Food involvement</td>
<td>Yes, 100% food induced in humans</td>
<td>Proposed, major role in diabetes-prone rodents, food role unknown in humans</td>
</tr>
<tr>
<td>Food link first reported</td>
<td>1950</td>
<td>1983</td>
</tr>
<tr>
<td>Foods identified</td>
<td>Wheat gluten, rye, barley, oats (humans)</td>
<td>Wheat gluten, soybean (in diabetes-prone rodents), cow milk (in some human and animal studies)</td>
</tr>
<tr>
<td>Time of exposure required to produce symptoms</td>
<td>Hours, reversible by removing offending foods</td>
<td>Months to years, not reversible</td>
</tr>
<tr>
<td>Identity of food autoimmunogen</td>
<td>Toxic gliadin peptides identified (humans)</td>
<td>Not yet identified</td>
</tr>
<tr>
<td>Effect of hydrolysis</td>
<td>Toxicity can remain after enzymic hydrolysis with pepsin, trypsin, or pancreatin, exhaustive digestion with papain removes toxicity</td>
<td>Partial hydrolysis with papain of soy but not of wheat gluten decreases diabetogenicity in BB rats</td>
</tr>
<tr>
<td>Relation of CD and IDDM</td>
<td>IDDM occurs in up to 6% of CD patients</td>
<td>Overt CD occurs in 2–4% IDDM patients; CD symptoms appear after IDDM is diagnosed; possible causal link of latent or silent CD preceding IDDM has been proposed</td>
</tr>
</tbody>
</table>

**Note:** References for table are as follows: Scott 1994, 1997.
the basis of major clinical interventions such as cyclosporin A, nicotinamide, prophylactic insulin, and other trials. Therefore, the possibility now must be considered that the most common chronic disease of childhood, IDDM, is induced by several food diabetogens (Scott and Kolb 1996).

There are reports that IDDM occurs in 4–6% of CD patients and that overt CD occurs in 2–4% of IDDM patients. These rates are 20–30 times those of the general population. It is now apparent that when both diseases occur in the same patient, CD symptoms appear after IDDM is diagnosed (Mäki et al. 1995). One group has proposed a causal link between silent (or latent) preceding CD and IDDM (Pocceco and Ventura 1995). This is an interesting proposal, particularly as wheat gluten can be diabetogenic in BB rats and NOD mice. Higher levels and increased prevalence of anti-gliadin antibodies have been observed in diabetes-prone BB rats compared with control BB rats (Scott et al. 1989).

Most cases of diabetes in BB rats and NOD mice are food related. The development of diabetes represents a continuum that requires long-term, frequent exposure to these dietary agents after infancy with the effect peaking around puberty. Only now are certain mechanisms being revealed. When these animals are fed a protective hydrolyzed casein-based diet, islet mass and the usual low antigenicity of the β-cells are maintained, there are fewer leukocytes invading the islets, and those that are present are predominantly less destructive Th2 instead of pro-inflammatory Th1 cells (Scott et al. 1996a, 1997). T-cells from celiac mucosa also produce Th1 (or Th0) cytokines when stimulated with gluten (Nilsen et al. 1995). Thus, there are remarkable similarities between CD and IDDM. This further supports the proposition that IDDM and CD may soon be described as a food-induced autoimmune disease.

**Lactose malabsorption: physiology and tolerance**

**Contributed by Andrew Szilagyi**

Most of the world’s adult populations are lactose mal digesters, yet evolutionary pressures in man retained the persistence of intestinal lactase as a dominant trait in specific individuals. The teleological explanation of this quirk of nature is not clear. However, man is unique from the standpoint that he continues to ingest dairy products after weaning (Auricchio 1993). Milk represents an important source of both protein and calories, and is a source of nutrition that is most needed, as is the case in developing countries with high malnutrition rates. Perhaps because of this unique feature, intestinal lactase is the best studied carbohydrate enzyme.

The gene for lactase – phlorizin hydrolase (LPH) is located on chromosome 2 (Kruse et al. 1988). Synthesis occurs via precursors mainly in the proximal two-thirds of the small intestine. In lactose mal digesters, the disappearance of LPH begins in childhood in a mosaic pattern along the jejunum (Maiuri et al. 1994) and reaches 10–30% of initial levels. Two phenotypes of deficiency are recognized. In one type, LPH is not synthesized (failure to detect mRNA), whereas in the other example, there is a translational failure (Lloyd 1993). In animals, LPH is under hormonal control.

Corticosteroids (Raul et al. 1983; Malo and Menard 1979), progesterone (Nagpul et al. 1990), and thyroxine (Hodin et al. 1992) exert various effects, however, there is as yet little evidence for hormonal control in man. In fact, control of LPH may be species dependent without a unifying explicative model.

The clinical expression of lactose intolerance is varied. Results from lactose tolerance tests that can be associated with a high frequency of symptoms cannot be used to predict symptoms under natural conditions (Leichter 1973; Lisker et al. 1978). The factors impacting on lactose handling in man include age, ethnicity, and rate of lactase loss, quantity of lactose ingested, quality of lactose form ingested, gastric emptying, intestinal transit, colonic response, bacterial adaptation, and hormonal status (Christopher and Bayless 1971). The classical symptoms of lactose intolerance include flatus, cramps, bloating, and diarrhea. Recently, it was reported that flatus but not bloating is due to intolerance (Levitt et al. 1996). Gas correlates best with measured hydrogen; however, a composite symptom score may also correlate with hydrogen production (Szilagyi et al. 1995). Diarrhea occurs as a colonic response to osmotically active carbohydrate and may be modified by intestinal neurogenic input. Some subjects wrongfully attribute symptoms to increased sensitivity to lactose intolerance and may in fact suffer from irritable bowel syndrome (Suarez et al. 1995). Furthermore, in a number of situations, lactose intolerance will be unmasked or acquired and most include diseases affecting mucosal integrity. Total or subtotal villus atrophy (e.g., gastroenteritis, celiac sprue, nontropical sprue, radiation, chemotherapy, malnutrition, etc.) or anatomical removal of jejunum (e.g., short gut syndrome, jejunal ileal bypass) will certainly aggravate intolerance. However, alterations of intestinal transit as in hyperthyroidism or by removal of antral gastric control (for ulcer therapy) can also induce symptoms and lead to nutritional loss.

Under normal conditions, it has been repeatedly observed that despite initial lactose intolerance, continued milk ingestion can lead to improved symptoms and apparent improvement in tests designed to verify lactose mal digestion (Sadre and Karbarsi 1979; Habte et al. 1973). Because of the potential use of dairy products, it is of interest to evaluate the role of adaptation in man to lactose intolerance. Furthermore, lessons learned from such studies may also apply to other carbohydrate intolerances. In order to continue ingestion of an offending carbohydrate, two conditions should be met. Firstly, from a teleological perspective, the nutrient value should be maintained despite malabsorption of the sugar. Secondly, symptoms from the agent should be minimal or nonexistent. The logical adaptive response, therefore, to continue lactose ingestion is the induction of intestinal lactase. LPH appears to be inducible in certain animal species (Godula et al. 1985); however, in man, despite improved lactase handling, intestinal lactase levels do not change after 1 year of increased dairy ingestion (Gilat et al. 1972). Therefore in man, intestinal enzyme induction is not likely the mechanism of adaptation.

Physiological and endocrine changes occurring with pregnancy offer good examples of potential mechanisms that account for improved handling of lactose. Pregnancy is associated with improved absorption of several nutrients as well as alteration in hormonal and intestinal function. Two studies have shown improved tolerance in the third trimester pregnancy in previously lactose intolerant women. In the first study, 44% of
Guatemalan women, who were initially lactose intolerant, were found to improve their condition in the third trimester (Villar et al. 1988). In the second study, 75% of a small mixed ethnic group were reported to improve their condition in late pregnancy (Szilagyi et al. 1995). Hormonal alterations noted in pregnancy may contribute to better tolerance, but their role is not yet defined.

Symptomatic improvement of lactose intolerance depends on other factors as well. The major putative adaptive response to lactose malabsorption is attributed to bacterial modification of carbohydrate metabolism (Strochchi and Levitt 1992; Perman et al. 1981). In addition to early reports of improved lactose tolerance, Hertzler and Savaiano (1995) showed that lactose breath hydrogen and symptoms can be significantly improved within 2 weeks by lactose feeding in lactose-intolerant subjects. Improvement was accompanied by increased β-galactosidase concentrations in feces, suggesting increased bacterial metabolism. Putative factors that may account for inhibiting H2 concentrations in feces, suggesting increased bacterial metabolism and suggestive evidence of maintenance in retaining calories (Szilagyi et al. 1995). Hormonal alterations noted in pregnancy may contribute to better tolerance, but their role is not yet defined.

Symptomatic improvement of lactose intolerance depends on other factors as well. The major putative adaptive response to lactose malabsorption is attributed to bacterial modification of carbohydrate metabolism (Strochchi and Levitt 1992; Perman et al. 1981). In addition to early reports of improved lactose tolerance, Hertzler and Savaiano (1995) showed that lactose breath hydrogen and symptoms can be significantly improved within 2 weeks by lactose feeding in lactose-intolerant subjects. Improvement was accompanied by increased β-galactosidase concentrations in feces, suggesting increased bacterial metabolism. Putative factors that may account for inhibiting H2 concentrations in feces, suggesting increased bacterial metabolism and suggestive evidence of maintenance in retaining calories (Szilagyi et al. 1995). Hormonal alterations noted in pregnancy may contribute to better tolerance, but their role is not yet defined.

The second major adaptive influence toward improved symptoms concerning lactose intolerance may relate to altered intestinal transit. In pregnancy, delayed gastric emptying and intestinal transit have been reported (Lawson et al. 1985; Szilagyi et al. 1996a). In addition, the volume of intestinal contents, fat content, and osmolarity accompanying lactose ingestion will contribute to increased gastric delay both through local factors and as well an eventual activation of jejunal and ileal breaks (Spiller et al. 1984; Lin et al. 1996). Both fat and carbohydrate (Tohno et al. 1995) can activate the breaks through neuronal or hormonal (e.g., peptide YY) mechanisms. Delayed intestinal transit may increase contact time between lactose and lactase, but there is little data on improved absorption per se. There are, however, example models of such an event occurring for other nutrients (Eisenbraun and Ehrlein 1996). The second effect of delayed intestinal transit is to reduce the volume of undigested carbohydrate delivered to the colon per unit time (Read et al. 1985). Both an inverse correlation between H2 concentrations and transit time (Ladas et al. 1982) and a direct correlation between H2 concentration and symptoms of intolerance (Szilagyi et al. 1995) have been reported. There are now a number of publications linking delayed intestinal transit with improved symptoms (Ladas et al. 1992, 1995). Moreover, the findings in pregnant individuals can be mimicked by loperamide therapy prior to lactose ingestion by euthyroid men (Szilagyi et al. 1996b). The improvement is accompanied by delayed intestinal transit.

In summary, lactose-intolerant subjects may improve handling of lactose under certain conditions. Although there is no proof of direct lactose absorption, there are reduced symptoms and suggestive evidence of maintenance in retaining calories and micronutrients for absorption. The main mechanism accounting for improvement with continued lactose ingestion is related to colonic bacterial adaptation. A second helpful effect may also result from delayed intestinal transit. However, this effect applies mainly during pregnancy. With both events, improvement in lactose handling results from a net reduction of gas (mainly H2 production). The measured exhaled H2 (reflecting maldigested carbohydrate reaching the colon) by current tests is a vectorial net sum of H2 production and consumption by bacteria and the amount of lactose delivered to the colon per unit time. In turn, under normal conditions the amount of lactose delivered per unit time is dependent on the inverse relationship between quantity of lactose ingested and intestinal transit time. In this latter relationship both variables may be manipulated to improve lactose handling.

**Food processing strategies and reduced allergenicity of milk**

**Contributed by J. Amiot**

Prevention of allergy is one health issue for which foods have been developed for over 40 years. In general, food allergens are glycoproteins with acidic pHk, having molecular mass ranging from 14 000 to 70 000 daltons (Hefle 1996). Most allergenic foods contain multiple allergens. The eight most common allergenic foods in order of frequency in the United States are egg, peanut, milk, soy, crustaceans, fish, and wheat (Carter 1995). However, milk appears to be the most common allergenic food among the pediatric population. Milk allergy occurs primarily in infants and children below 2 years of age, and estimates of its frequency have been reported to range from 0.3 to 7.5% (Ghosh et al. 1989).

Foods containing small quantities of milk, ranging from 0.04 to 1.1%, were shown to produce allergy (Hefle 1996). Sensitivity to different milk protein constituents in patients has been reported to be, in descending order, β-lactoglobulin (β-Lg), 82%; caseins, 43%; α-lactalbumin (α-Lac), 41%; and serum albumin (BSA), 18% (Ghosh et al. 1989). Antigenic sites of native β-Lg depend upon steric conformation of the protein molecule and are not of the continuous or sequential type (Ghosh et al. 1989).

Avoidance diets are the only reliable means of prevention of allergies from these sources. For babies and children fed on milk, prevention programmes have been developed. Dietary manipulation during pregnancy has not been proven effective. However, dietary manipulation during lactation has been shown to be much more effective because food antigens can be passed to the infant via breast milk (Wolfe 1995). Although breast-feeding has absolute priority, infant formulae based on bovine milk continue to be supplemented or substituted for breast milk whenever required. Various technological approaches have been proposed to eliminate the allergenicity of bovine milk proteins from infant formulae. The first approach is obviously to replace cow milk with milk from other animal species such as goat, sheep, or ass (Isolauri et al. 1995). Such factors as cross-reactivity with cow’s milk, as well as low microbial and nutritive quality of such milks, make these poor alternatives to this approach. A different method is to substitute cow milk proteins with proteins from other animal (collagen, chicken) or vegetable (soybean) species, or a mixture of both (soybean and collagen). Because of the high incidence of soya intolerance in infants who are sensitive to cow’s milk protein, the use of soya-based infant formulae is not recommended (Businco et al. 1992).

Thermal processing treatments have been proposed to modify
milk protein structural properties and related allergenicity. Heat treatments at temperatures higher than those used for evaporation, pasteurization, or drying are required to significantly reduce protein allergenicity. Whey proteins heated at 100 or 115°C for 30 min, and milk heated at 126°C for 9 min can induce a diminished immunogenic response. However, heat treatments of this magnitude also destroy much of the nutritional quality of milk. Moreover, the allergenicity of β-Lg can be enhanced by the Maillard browning reaction with lactose (Taylor 1986). Therefore, heat treatments are not considered to be an adequate alternative to produce hypoallergenic infant formulae.

Most of the hypoallergenic formulae on the market today contain protein in the form of hydrolysates. The selection of appropriate enzymes and the control of technical conditions (e.g., time, pH, temperature) can be used to obtain the required degree of hydrolysis, as well as peptides of required molecular weight (Asselin et al. 1988, 1989). However, too extensive a hydrolysis can produce peptides with an extremely unpleasant and bitter taste; these small peptides can also increase the osmolarity of formulae and reduce the stability of the emulsion. Heat stability of such formulae is also impaired. Nevertheless, partially and extensively hydrolysed formulae containing whey, casein, and soya proteins are available. Most casein formulae are extensively hydrolysed, and some are also lactose free. Extensively hydrolysed whey formulae are also available, as well as mixtures of casein and whey hydrolysates and mixtures of soybean and whey or soybean and collagen hydrolysates.

Partially hydrolysed formulae (PHF) contain a high proportion of peptides with molecular mass greater than 2500 daltons. Extensively hydrolysed formulae (EHF) contain peptides mostly under 1700 daltons and less. Therefore, EHF appear to be hypoallergenic formulae suitable for therapy of sick children, while PHF are considered to be hypoantigenic formulae for prophylaxis in children from atopic families with no cow’s milk allergy (Sawatzki et al. 1994). Trace amounts of intact milk proteins, including β-Lg, have been found in most formulae, including those based on caseins (Görtler et al. 1995; Carter 1995). Other alternatives, including formulae based on mixtures of free amino acids, have been proposed. Girsh (1993) also proposed using milk permeate to prepare such formulae. Extensively hydrolysed formulae or amino acid mixture based formulae are particularly recommended in infants with multiple food allergies.

Ultrafiltration has been used in combination with protein hydrolysis to eliminate residual proteins and peptides of large molecular weight from partially or extensively hydrolysed whey proteins. This procedure also allows the elimination of aggregates that can be formed between small peptides and native proteins, these aggregates could be allergenic (Chiancone et al. 1995). In combination with hydrolysis, heat treatment was proposed by Jost et al. (1987) to eliminate milk proteins such as BSA that are heat labile but enzyme resistant. As a commercial practice, UHT treatment should be preferred in order to reduce the loss of available lysine that can occur in milk as a result of the formation of the Maillard reaction (Kanhai et al. 1987).

Hussein et al. (1996) proposed attaching free methionine to peptides from milk protein hydrolysates by a plastein reaction using proteolytic enzymes under specific stoichiometric conditions. The modified peptides were shown to have lower antigenicity. A process for lowering the concentration of β-Lg in cheese whey has also been filed for patent by University of British Columbia research group of Dr. Nakai (University of British Columbia 1992). The same group had previously shown that all milk proteins, except β-Lg, precipitate at pH 3.0 in 4 mM ferric chloride solution.

Further improvements in hypoallergenic milk infant formulae require a better understanding of the allergenic properties for milk and whey proteins. Carter (1995) stated that intact proteins are mainly responsible for the formation of IgE–antigen complexes. However, Ball et al. (1994) have shown that the peptide sequence 97–108 of β-Lg is a major continuous allergenic epitope recognized by human IgE binding. We have shown that the lower molecular weight fraction of a β-Lg trypsin hydrolysate, obtained by elution chromatography, contains peptides exhibiting allergenic activity (Pelletier 1990). However, no reaction, measured with two distinctive monoclonal antibodies against bovine β-Lg and sera from patients allergic to β-Lg, was obtained from the individual low molecular weight peptides. Since those peptides were isolated by reverse phase HPLC, it is believed that hydrophobic interactions between peptides are related to observed allergenicity. In addition, we have shown that whey protein hydrolysis with pepsin and chymotryptsin is more effective than with trypsin to reduce β-Lg and α-Lac allergenicity. Pepsin and chymotryptsin are known to mainly hydrolyse proteins where hydrophobic amino acids are located (Asselin et al. 1989).

The hydrophobic areas of β-Lg are mostly located inside its cone-shaped structure. The integrity of this three-dimensional structure is maintained by different chemical bindings, the most important being two disulfide (S—S) bonds. The breakdown of S—S bonds can be achieved with chemical reagents, such as urea and mercaptoethanol, and result in various levels of reduction. Reduction of S—S bond can significantly reduce the allergenicity of β-Lg measured by its reactivity with IgE from patients allergic to β-Lg. Complete reduction of S—S bonds may be the only way to eliminate β-Lg reactivity. Since reagents such as mercaptoethanol are toxic, we have proposed to reduce the whey protein disulfide bonds by electroreduction, which is a modification of the electrodialysis procedure already used to demineralize whey for infant formula. However, the level of S—S bond reduction attained so far (52%) is too low to have a significant effect on protein allergenicity (Bazinet et al. 1997; Bazinet 1993).

Further improvements in milk infant formulae will probably involve genetic engineering, including the production of recombinant human milk and human milk proteins by transgenic animals or microorganisms (Lönnerdal 1996; Prieto et al. 1995), the production of genetically engineered ligands that would bind to milk antigens, and the removal of identified epitopes from milk proteins by genetic manipulation of cows (Wo and Kleinman 1996).

**Food allergy labelling in Canada**

Contributed by Marion Zarkadas

There are relatively few data available on the prevalence of adverse reactions to foods in Canada, the United States, or other countries. Estimates vary because of differences in
Table 4. A comparison of the 1996 draft list endorsed by Codex Alimentarius Commission and the proposed Canadian list of foods known to cause adverse reactions, which should always be declared on food labels.

<table>
<thead>
<tr>
<th>Food group</th>
<th>CODEX(^a) (draft list, endorsed 1996)</th>
<th>HC/AAFC(^b) (proposed 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cereals</td>
<td>Gluten sources: wheat, rye, barley, oats, spelt, or their hybridized strains</td>
<td>Wheat, rye, barley, oats, and hybridized strains</td>
</tr>
<tr>
<td>Legumes, nuts, and seeds</td>
<td>Peanuts, tree nuts, soy</td>
<td>Peanuts, tree nuts, soy, sesame</td>
</tr>
<tr>
<td>Milk</td>
<td>Milk (including lactose)</td>
<td>Milk</td>
</tr>
<tr>
<td>Eggs</td>
<td>Eggs</td>
<td>Eggs</td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>Fish and crustacea</td>
<td>Fish and shellfish</td>
</tr>
<tr>
<td>Sulphites</td>
<td>≥10 ppm</td>
<td>Sulphites</td>
</tr>
</tbody>
</table>

\(^a\)CODEX, Codex Alimentarius Commission Report.
\(^b\)HC/AAFC, Health Canada/Agriculture and Agri-Food Canada.

Inclusion criteria, including reportable causes of death, difficulties in estimating undiagnosed and unreported cases, and in some cases apparent differences from one country to another. Double-blind placebo-controlled food challenge (DBPCFC) data for food allergies in children in the United States indicate that only 7 foods account for nearly 95% of the reactions (Bock and Atkins 1990; Hid 1994). The foods reported most often to cause adverse reactions in children were egg (25%), peanuts (24%), milk (23%), tree nuts (10%), soy (6%), fish (3%), and wheat (2.5%) (Schwartz 1992). The Canadian Paediatric Society, Allergy Section (1994) identified peanuts, tree nuts, eggs, and milk as the common allergens to children in Canada, but added that fish, crustaceans, molluscs, and soy could also be lethal.

Based on an extensive review of the scientific literature, a joint committee identified the major foods causing severe adverse reactions in hypersensitive individuals. A consultation document along with a background paper (Agriculture and Agri-Food Canada / Health Canada 1996) were circulated to interested parties representing the medical community, industry, consumers groups, and government. The proposed list was reviewed and fully endorsed by the Canadian Society of Allergy and Clinical Immunology, and fully endorsed by the Allergy/Asthma Information Association and the Canadian Celiac Association. Concern was expressed by some respondents about the inclusion of sesame seed, because the incidence of allergy did not appear to warrant its inclusion, and rye, barley, oats, and triticale, because they did not cause anaphylaxis. The final decision about the foods that should be included in the list will be made by Health Canada, the department responsible for health hazard analysis.

The proposed list of foods causing adverse reactions in Canadians is compared in Table 4 with the draft list endorsed in 1996 by the Codex Committee on Food Labelling (Codex Alimentarius Commission 1996). The Canadian Food and Drug Regulations, which apply to prepackaged foods at all levels of trade in Canada, require a complete list of ingredients on the labels of almost all foods. However, in these regulations certain food ingredients are exempt from a declaration of some or all components (ingredients of ingredients). For example, margarine when sold must have an ingredient list on the label. However, if margarine is added to another food such as cookies, the ingredients of the margarine, such as vegetable oil, skim milk powder, etc., would not be required to be listed on the cookie label.

One of the major problems identified in the regulations is the exemption from a component listing of a variety of food mixtures, especially seasonings and flavours. The word “seasoning” can be used as the common name on the food label, if the seasoning constitutes less than 2% of the total weight of the product. At this level, all of the components of these mixtures, with a few exceptions, are not presently required to be declared on the label. These mixtures often contain ingredients such as wheat, milk, and egg and could contain foods such as peanuts and sesame. When such food mixtures are added as ingredients to other foods, listing the ingredients known to cause adverse reactions would overcome this problem.

The Food and Drug Regulations require that plant proteins hydrolysed by enzymes must identify the plant source in the common name. However, plant proteins hydrolysed by other means are not identified by source. This is a concern to many hypersensitive individuals, since these products are made primarily from wheat, soy, and corn and are added to a wide variety of food products. The potential allergenicity of various commercially hydrolysed plant proteins is presently being evaluated, and preliminary results from Health Canada indicate that some hydrolysed soy proteins are antigenic. When hydrolysed proteins from animal sources are present, the protein source must be declared, e.g., hydrolysed casein. Partially hydrolysed plant proteins, which are added to a variety of foods for modifying both flavour and texture, could retain the ability to cause severe adverse reactions in hypersensitive individuals. Therefore, all forms of hydrolysed plant proteins should be identified by plant source. Such a requirement would more closely harmonize Canadian labelling regulations with those of the United States (Federal Register 1993), which require the name of the protein source in the common name of all hydrolysed proteins.

Most forms of starch must now be identified by plant source on food labels. For example, cornstarch is required administratively to be declared by plant source, whereas modified starches are not required to identify the plant source. Most modified starches are made from corn, but they may be from wheat, tapioca, potato, and other starches. Wheat starch contains varying amounts of gluten and is not permitted in gluten-free foods in Canada. A proposal has been made that the plant source of all forms of starch should be identified on food labels. Table 5 gives examples of some food ingredients whose components are exempted from being declared by the Food and Drug Regulations, and examples of typical components that could be present but which under the existing regulations are not required to be declared on the food label.

Although component exemptions and nonspecific common
names impact on label accuracy, even more serious problems sometimes result from (i) cross contamination of foods during manufacture, storage, and at retail; (ii) foods that are packed in the wrong containers; (iii) a mixture of labels in one box provided by a supplier; (iv) old labels being used up after a product formulation change; (v) mixing reworked foods with no change in the label; (vi) imprecise declarations; and (vii) inaccurate terminology. When unidentified allergens are discovered in foods, industry, along with Health Canada and Agriculture and Agri-Food Canada, may be involved in product recalls and allergy alerts. To avoid this, many food manufacturers are now taking an active role to prevent unidentified allergens in foods by training employees about possible adverse reactions to foods and improving quality control in the plant.

In 1993, the Health Protection Branch (HPB) of Health Canada established a precautionary labelling policy allowing a “may contain” statement regarding the possible presence of allergens in foods, to be placed at the end of the list of ingredients on a food label, e.g., “may contain peanuts.” The policy indicates that the use of this statement is voluntary, and is to be used judiciously. It was felt that such statements could serve a useful purpose by warning individuals with food hypersensitivities of the possible presence of allergens in foods. Industry is very supportive of this policy. However, concern has been expressed by some medical and consumer groups that excessive or injudicious use will severely limit food choices for consumers with adverse reactions to foods. It is proposed, therefore, that such statements be used only when it is impossible to assure the absence of the foods identified. Precautionary labelling should not be used in lieu of adherence to Good Manufacturing Practice, and should be used only as a temporary measure until adequate steps can be taken to ensure absence of the identified food ingredient.

### Conclusions

Identifying and characterizing food constituents that produce allergy, intolerance, or autoimmunity is a difficult endeavour. There is no known characteristic chemical structure common to all food allergens, intolerances, or autoimmunogens. Moreover, tests used to indicate histamine release from sensitized cells in response to food constituents, or the presence of circulating antibodies to the foods tested (e.g., RAST, ELISA), are limited in identifying true clinical reactivity to a food constituent(s). Some reports suggest the incidence of several of these conditions or diseases may be increasing. Individuals vary in their susceptibility to these disorders, and the severity of adverse reactions can range from localized discomfort (e.g., lactose intolerance) to more serious consequences, such as death from anaphylaxis following an allergic reaction or increased risk of lymphoma in patients with celiac disease. Clinical expression of these conditions is often dependent on genetic susceptibility and environmental factors (e.g., stress, presence of other allergens, viral or parasitic infections, hormonal status, and exercise), in addition to ingestion of the causative agent. Apart from hypersensitivity reactions, disaccharide intolerances, and celiac disease, the physiological response to many food components is relatively unknown. Celiac disease is a food-induced autoimmune condition, and it has been suggested that food plays an important role in development of another autoimmune disease, IDDM, which is associated with significant morbidity and mortality. It may be possible in some instances that these components are inactivated, removed, or possibly decreased in foods by various food-processing or bioengineering techniques. Notwithstanding this, it is important to consider the potential hazards of food processing or technological advances, which may produce different allergens, or for that matter contribute to increased allergenic potential of the processed food. Where modification of the food is not yet practical, avoidance may be the only means of preventing the adverse reaction. Thus, accurate information must be supplied to the consumer about sources of offending food components such as lactose or protein antigen(s). This is particularly important on food labels, and recent proposed Canadian recommendations requiring disclosure of food constituents in manufactured foods are aimed at addressing this issue. The presentations at this symposium indicated that it is possible to identify foods and some of the food constituents that cause a variety of adverse reactions in susceptible humans. In addition, several current or proposed food-processing techniques and the provision of appropriate information that may reduce the risks to health associated with these components were discussed.

### Acknowledgements

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**Table 5.** Examples of food ingredients presently exempt from a component declaration by the Food and Drug Regulations (B.01.009 (1) and (2)), and examples of typical components.

<table>
<thead>
<tr>
<th>Ingredients exempt from a component declaration</th>
<th>Examples of typical components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margarine</td>
<td>Milk ingredients</td>
</tr>
<tr>
<td>Bread</td>
<td>Up to 5% nonwheat flour (e.g., pea, soy, etc.)</td>
</tr>
<tr>
<td>Baking powder</td>
<td>Starch</td>
</tr>
<tr>
<td>Icing sugar</td>
<td>Starch</td>
</tr>
<tr>
<td>Prepared meat, fish, poultry, if less than 10% of an unstandardized food</td>
<td>“Fillers” may contain flour, starch, gluten, milk, soy, etc.</td>
</tr>
<tr>
<td>“Binders” may contain milk, egg, seasonings, etc.</td>
<td></td>
</tr>
<tr>
<td>Natural and artificial flavouring preparations</td>
<td>Malt</td>
</tr>
<tr>
<td>Wheat starch, wheat flour, wheat gluten Cheese</td>
<td>Peanuts, tree nuts, sesame</td>
</tr>
<tr>
<td>Seasoning, herb mixtures, spice mixtures</td>
<td>If ≤2% of product: HP sauce, Worcestershire sauce, soy sauce, ketchup, mustard Skim milk powder Wheat flour, wheat starch Peanut, almond, sesame</td>
</tr>
</tbody>
</table>
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References


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