On being an OMNIVORE

From an evolutionary perspective, being omnivorous has clearly been advantageous for the human species. The adaptability it brought to our hunter-gatherer ancestors enabled them to spread and survive in almost all terrestrial environments, under a wide range of climatic conditions. After the last ice age ended, the rise of agriculture and domestication of animals enabled them to develop great efficiencies in obtaining food, making possible the division and specialisation of labour, the evolution of complex societies and the emergence of science, technology and industrial development.

Some would argue that, as a species, we have been too successful; that we now infest the planet in plague proportions; that the biosphere has been irreparably damaged by our uncontrolled proliferation; and that we are now causing mass extinctions at a rate comparable to past catastrophes evident from the fossil record. The arguments are well known and do not need elaboration here, except to say that, for the most part, the human consequences of our success — overcrowding, environmental degradation, pollution, famine and war — are largely social and environmental problems shared by whole populations. *Less well recognised is the fact that our omnivorous heritage also carries with it personal health trade-offs, with the costs and benefits distributed unequally amongst* individuals *within the population.*

Eating is an inherently dangerous activity. As carnivores, our immune system must provide protection from a wide range of potentially pathogenic micro-organisms and toxins that can contaminate meat, other foods and water, a task that must be achieved without at the same time provoking immune reactions to food itself. This difficult balancing act works well for most — but not all — people. The cost of immune hyper-vigilance is the propensity to develop food allergies, which can sometimes be fatal.

And as herbivores, we also need to protect ourselves from an enormous number of chemical substances — "secondary metabolites" — that plants produce. To help deal with the daily chemical onslaught in our diet, we have evolved a number of behavioural, metabolic and other non-immunological adaptations that allow most of us to choose plant foods we can eat safely. Some people, however, are more sensitive to the adverse effects of various natural and added food chemicals. Clinically, this problem presents as food intolerance. Though unpleasant, inconvenient, and at times debilitating, this propensity can also have survival advantages for affected individuals and their offspring.

FOOD ALLERGY

In terms of sheer quantity, the greatest immunological challenge we face every day comes from what we eat. In dealing with this the mucosal immune system has a difficult balancing act to perform — it must at once be capable of distinguishing between potentially harmful, harmless and beneficial foreign microorganisms, whilst ignoring the many plant and animal antigens we ingest regularly in kilogram quantities. What is remarkable is that, in most people, most of the time, the immune system manages to do this without provoking either acute allergic reactions or chronic inflammation in the gastrointestinal tract and elsewhere.

This feat is achieved in large part through the selective induction of immunological tolerance, a state of specific unresponsiveness brought about by immunoregulatory mechanisms that are incompletely understood. As with all other biological phenomena, there is individual variation in immune responsiveness within the population. In each person, a complex interplay between genetic, epigenetic and environmental factors tips the scales towards either immunity or tolerance to different classes of antigens. Those individuals with immune responses that are on a hair-trigger may be more secure in their ability to resist certain infections, but this is at the cost of increased susceptibility to allergies and/or autoimmune tissue damage.

Allergies may be defined as immunological over-reactions to otherwise harmless environmental antigens (allergens), most often mediated by **IgE antibodies**. The normal biological function of IgE is to protect us from parasitic infestation. **Mast cells** — 'armed' with IgE bound to surface Fc receptors, packed with inflammatory mediators, and strategically located in the skin, at mucosal surfaces and near blood vessels — are central players in producing the immediate tissue reaction to an invading pathogen. This can begin within minutes of recognition by IgE antibodies.

Initially, the release of **histamine** and other mast cell mediators stimulates a neurogenic **nociceptive** response, with the triggering of defensive reflexes such as scratching, sneezing, coughing, vomiting and/or diarrhoea, which serve to expel would-be invaders. At the same time, an acute inflammatory reaction is initiated. Organisms that manage to penetrate these first lines of defence are attacked and destroyed (or else walled-off and contained) by eosinophils, neutrophils and other cells recruited from the bloodstream in response to chemical signals (**chemokines**) sent out by mast cells.

As with most other antibody responses, IgE antibody production is under the control of **T-lymphocytes**. Sensitisation occurs when Th2 cells — activated by exposure to antigen that has been appropriately processed and presented — stimulate **B-cells** to secrete antibodies into the bloodstream. Circulating IgE antibodies rapidly bind to the surface of tissue mast cells where they lie silently in ambush, awaiting any return of the offending antigen. Meanwhile, T-cells develop long-lasting immunological **memory** for the antigen, such that re-exposure can quickly boost the production of IgE antibodies.

In Australia, about 40-50% of people are atopic, i.e. are genetically predisposed to make exaggerated IgE antibody responses, and about half these individuals will develop clinical allergic disease at some time during their lives. In those who develop food allergies, sensitisation usually occurs very early in life. Contrary to popular belief, exclusive breast-feeding does not prevent this, and indeed many babies become sensitised to foods in the mother's diet while still on the breast. It has been shown that small amounts of intact food protein absorbed from the maternal gastrointestinal tract are excreted in the

breast milk, and can induce IgE antibody responses in highly atopic infants.

In babies sensitised to food allergens, atopic eczema is the most common clinical manifestation — around 90% of children with food allergy have a history of infantile eczema. [However, the reverse is not necessarily the case. Across all age groups, only about one third of children with eczema have an identifiable food allergy.] If a sensitised child is unknowingly or accidentally given food containing allergen, there is a risk of developing anaphylaxis — a systemic allergic reaction ("allergic shock") caused by widespread activation of mast cells throughout the body. About 1 in 200 cases of anaphylaxis is fatal.

Although almost any plant or animal food can act as an allergen, in practice just a handful of foods account for over 95% of clinical allergies: cow's milk, egg, peanut and other nuts, fish, crustaceans, and sesame. Beef, rice, soy and wheat can occasionally be involved, but they rarely produce serious or persistent allergic sensitisation. The prevalence of specific food allergies varies around the world, depending on dietary habits — e.g. fish allergies are more common in Scandinavia, and rice allergy is more common in Japan.

With the exception of peanut and fish allergies, which tend to be life-long, most children "grow out" of their food allergies by the time they reach school age. The peak prevalence is 5-8% in the 0-5 year age group, falling to less than 1% in teenagers and adults. The mechanisms underlying this natural acquisition of immunological tolerance are unknown. Nor is it known why peanut and fish allergies usually fail to induce tolerance.

Over the past decade there has been a marked increase in the prevalence of peanut allergy in Australia, the UK, USA, and other developed countries. The reasons for this are unclear. One possibility is that changes in dietary advice in the late 1980s and early 1990s encouraged breast-feeding women to use peanut butter as a good non-animal protein source. This was associated with a trend away from red meat (which had come to be perceived as 'unhealthy') towards vegetarian-style eating with increased consumption of fruit and nuts. In any event, peanut and other nuts now account for more than 90% of fatalities from food anaphylaxis.

In recent decades there has also been an increase in the prevalence of allergic diseases generally. It has been suggested that this may be related to reduced exposure of children to microbes early in life — the 'hygiene' hypothesis. The idea here is that the infant's naïve mucosal immune system, lacking in normal stimulation by microbial 'danger' signals because of an unnaturally hygienic environment, turns its attention to whatever other antigens happen to be around.

Whatever the case, it is tempting to speculate that the change in our primate ancestors from a mainly arboreal vegetarian existence to a ground-based meat-eating hunter-gatherer life-style necessitated the development of more sophisticated — and perhaps, therefore, more error-prone — mucosal defence mechanisms. After all, the microbial world associated with rotting carcasses, decaying flesh and faecal contamination of ground water, is much different from that of fruits, leaves, nuts and berries.

FOOD INTOLERANCE

Food intolerance should be carefully distinguished from food allergy. The term 'intolerance' is applied to non-immunological adverse reactions provoked by natural and/or added chemicals present in commonly eaten foods. Amongst the thousands of naturally occurring food chemicals, salicylates, amines and free glutamate are the ones most frequently implicated. The additives most often involved are preservatives, colourings and flavourings.

Patients may present with a variety of clinical syndromes involving the skin, gastrointestinal tract (GIT), respiratory tract or central nervous system (CNS), either individually or in any combination. Recurrent urticaria and angioedema, migrainous headaches, and irritable bowel syndrome are the most common disorders in which food intolerance can be a major trigger factor. Non-specific constitutional symptoms such as malaise, nausea and fatigue may accompany any of the disorders above, and in some patients, cognitive, mood or behavioural disturbances may also be present.

Although the mechanisms of food intolerance reactions are largely unknown, the clinical manifestations suggest that they are primarily neurogenic. Moreover, their characteristics are typical of pharmacologically active substances, suggesting a receptor-mediated molecular basis:

➢ Reactions are dose-dependent, and can have cumulative effects;

➢ The dose threshold for reaction to a specific food chemical can vary over time, depending on recent intake and other factors;

➢ Cross-reactive substances in the same or different foods can have additive or synergistic effects;

➢ Onset of symptoms can be delayed by 48 hours or more after ingestion;

➢ Acute reactions can be followed by a refractory state (tachyphylaxis) lasting 2-3 days;

➢ When regularly eaten food groups are systematically eliminated from the daily diet, up to 50% of patients experience withdrawal effects, with a transient exacerbation of symptoms occurring during the first week or so.

Specific intolerances, their number, severity and temporal course, and the symptoms provoked by them are highly idiosyncratic. In addition, intolerances exhibit a very strong familial tendency, along with their associated symptom complexes. Taken together, the evidence suggests that the predisposition to food intolerance may be due to genetic polymorphisms at allosteric binding sites in tissue-specific receptor and/or signal transduction systems.

Given the above clinical characteristics, it is not surprising that the diet history is generally unreliable in patients with food intolerances. Many do not recognize the relationship between foods and symptoms, and of those that do, most are unaware that a variety of apparently tolerated foods can have cumulative effects contributing insidiously to chronic symptoms.

When acute symptoms occur soon after a meal they are more easily recognised as food-related. However, mistaken attribution is common — meals often involve several possibly relevant foods and ingredients; particular foods can contain several relevant substances; and a given chemical can be present in many different foods. Nevertheless, a clinician armed with detailed knowledge of the chemical composition of foods can sometimes derive useful clues from the history. For example, a patient who reacts to apples, citrus fruits, tomatoes, strawberries and wine is likely to be salicylate sensitive; similarly, reactions to cheese, chocolate, bananas, avocado, tomatoes and wine point towards amines as the culprit.

Because most of the clinical manifestations of food intolerance are non-specific, and the diet history is so unreliable, careful clinical evaluation and systematic dietary testing is necessary to make an accurate diagnosis. Symptoms can be attributed to food intolerance if (1) there is sustained improvement after elimination of the relevant food chemicals, and (2) they

are reproducibly provoked on re-exposure. Ideally, testing should be conducted as formal double-blind, placebo-controlled oral challenges with purified food substances. In routine clinical practice this is not always feasible, but a reasonably reliable assessment can be made with carefully selected open food challenges.

BIOLOGICAL SIGNIFICANCE OF FOOD CHEMICAL INTOLERANCES

When tested rigorously, about two-thirds of patients with food intolerance are found to be sensitive to natural salicylates. These are phenolic substances synthesised (along with numerous other secondary metabolites) by all plants, including those we eat as foods. The principal functions of plant secondary metabolites are regulatory and ecological. Some are 'allelopathic', i.e. they inhibit the growth of competing plant species, helping the plant that produces them to carve out an ecological niche for its own survival and propagation. Some have defensive functions, providing resistance against viruses, bacteria and/or fungi that might threaten the survival of the plant. Others have behavioural effects: they may act as chemoattractants for pollinating insects; they may assist in seed dispersal by taking advantage of an animal's taste for their fruit; or they may be poisonous, hallucinogenic or otherwise noxious in ways that modify the feeding behaviour of herbivorous animals (including humans). It is of interest to note that when Europeans first introduced domesticated animals to the unfamiliar flora in Australia, about one plant species in twenty was found capable of causing death.

Herbivorous animals have developed various biological adaptations to toxic plant substances, including detoxification and excretion, tissue-specific resistance and avoidance behaviours. One of the most important behavioural mechanisms is the sensing of noxious substances by smell and taste, and the induction of conditioned aversions when foods provoke unpleasant reactions.

Amongst plant-derived foods the phenolic (aromatic) chemical content can range from nearly zero (e.g. in refined foods such as table sugar) to 20% or more of the dry weight of the diet of some herbivorous animals. When given a free choice, animals select plant foods with a low phenolic content, e.g. grasses and grains. With the development of agriculture, our ancestors further selected and modified by breeding these and other plants, which we now cultivate as staple foods. For people with a tendency to food intolerance, flavour is a rough guide to phenolic content — the blandest foods are tolerated best.

Carnivores also have problems ensuring that the food they eat is safe. They are exposed to microbial toxins and pathogens in the carcasses they feed on and must also learn to sense danger through smell, taste and nociceptive conditioning. Perhaps human amine/glutamate intolerance is a manifestation of this biological necessity, since amines and glutamate are released by the breakdown of animal proteins in ageing/decaying meat and fish.

There are two well-known rules of survival for a hungry person in an unfamiliar environment:

(1) Eat nothing that tastes unpleasant, particularly if it is bitter or if it smells disgusting;

(2) Eat only a small amount of a novel food, then wait to see if it is agreeable to the stomach.

Perhaps people with a propensity to food intolerances should be thought of as 'canaries', their heightened sensations giving us early warning of hidden dangers lurking in the foods we eat.

Interestingly, too, food intolerances are 3-4 times more common in females, particularly during the reproductive years, and they are often aggravated by hormonal factors (menstrual cycle, pregnancy, oral contraceptives). It is tempting to speculate that this may serve the same biological function as 'morning sickness' and food aversions in pregnancy — protection of the early embryo and developing foetus from exposure to potentially harmful substances in the mother's diet.

Robert H Loblay

Proceedings of the Nature and Society Forum Online Conference: Food for Healthy People and a Healthy Planet, 9-23 September 2001.

SUGGESTED READING

Food allergy: Current knowledge and future directions. Immunology and Allergy Clinics of North America (Ed: Burks AW, James JM), Vol. 19(3), 1999.

Loblay RH, Swain AR. Food intolerance. In: Recent Advances in Clinical Nutrition (Ed: Wahlqvist M, Truswell AS), 1986; 2: 169-177.

Perry CA, Dwyer J, Gelfand JA et al. Health effects of salicylates in foods and drugs. Nutrition Reviews 1996; 54:225-240.

Gordon KD. Evolutionary perspectives on human diet. In: Nutritional Anthropology (Ed: Johnston FE). Alan R. Liss, Inc., NY, 1987.

Johns T. With bitter herbs they shall eat it: Chemical ecology and the origins of human diet and medicine. University of Arizona Press, Tucson, 1990.

Sherman PW, Flaxman SM. Protecting ourselves from food. American Scientist 2001; 89: 142-151. (http://www.americanscientist.org/articles/01articles/sherman.html)

Swain AR, Soutter VL, Loblay RH. *Friendly Food.* Murdoch Books, Sydney, 2004.