Allergic and Immunologic Reactions to Foods

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- BASIC CONCEPTS -

Introduction

Although clinically meaningful reactions to foods were described in the ancient literature, they continue to be mired in controversy despite the explosion of science during the last 50 years. Indeed, the last quarter century since the biochemical description and characterization of the reaginic antibody (IgE) by Kimishige and Teruko Ishizaka has seen a disturbing proliferation of unsubstantiated clinical management strategies that have taken advantage of the complexity of this field and the naivete of the public. The purpose of this grand rounds is to provide an overview of the known, emerging, speculative and unproven concepts that are very much alive in 1994. Although inflammatory bowel disease and a variety of other immunologic illnesses might also be considered within this intellectual domain, they will not be addressed to any significant degree.

Definitions

The definitions provided below provide an operational basis for the following discussions. Different terms are often used in other parts of the world and by practitioners with different perspectives and training; a situation that requires a clear knowledge of this information before proceeding.

Adverse food reaction	Any untoward reaction to consuming a food.
Food allergy	Responsiveness to consuming a food that is mediated by one or more immunologic mechanism.
Food intolerance	Responsiveness to consuming a food that is mediated by non-immunologic mechanisms.

Classification strategies in food allergy

Because of the absence of full knowledge regarding the extent to which a variety of pathophysiologic processes participate in the genesis of clinically diverse syndromes, the ability to classify and, indeed, to diagnose the full range of apparent food-induced reactions is limited. For simplicity I've chosen to present the classical IgE-mediated processes that have been extensively studied and rigorously subjected to clinical testing as a starting point and will introduce other

mechanisms as their consideration warrants.

Fundamental Mechanisms Involved in IgE-mediated Food Allergy

The details of the molecular mechanisms that are brought to bear upon the genesis of humoral immune responses are beyond the scope of the current discussions. Nevertheless, an overview of the immunologic processes that contribute to this process are relevant.

Sensitization and IgE synthesis - Food antigens that escape the negative impact of oral tolerance mechanisms (vide infra) may result in the induction of food antigen-specific IgE as the result of isotype switching from IgM to IgE in B lymphocyte lineage cells. This is an exciting area of active investigation, but fundamentally important is an impact of IL-4 and the CD-40/CD-40L system in order that IgE switching take place. Antigen-specific IgE produced by plasma cells is systemically distributed through the intravascular compartment and subserves its effector function only after binding to high affinity receptors for IgE (FcϵRI) that are primarily represented upon the surface of mast cells and basophils. The IgE-FcϵRI interaction is an extremely tight one; one reason for the very low levels of circulating IgE.

Role of mast cells and mast cell mediators in IgE-mediated immediate food reactions - Tissue mast cells are richly represented in the perivascular areas of barrier tissues; mucosal surfaces and the skin. Surface FcϵRI on mast cells bear IgE with many different immunologic specificities reflecting the current status of allergic sensitization of the host. When a mast cell bearing IgE antibodies that recognize two or more epitopes on a food antigen that has penetrated the epithelial barrier, their associated FcϵRI become physically approximated ("crosslinked" or "ligated" are other terms often used) initiating a complex series of biochemical events that result in the release and/or synthesis of a diverse array of inflammatory mediators capable of inducing profound clinical responses. Preformed and newly synthesized mediators that are released from mast cells upon immunologic activation include histamine, PGD_2, LTC_4, PAF, kinins, TNFα, T_{H2} pattern cytokines, neutral proteases and acidic proteoglycans. The existence of two (or perhaps more) mast cell phenotypes with a subtle, but importantly different pattern of mediators and triggering mechanisms was reviewed by Dr. Gruchalla in her recent grand rounds and will not be repeated here although a summary is provided

in Figure 1.

	Cell type				
	Rodent			Human	
Mediator	CTMC	IMMC	BMMC	SKIN[b]	UC[b]
Preformed					
Amines					
Histamine	+	+	+	+	+
Serotonin	+	+	+	−?	−?
Chemotactic peptides					
ECF	+			+?	+?
NCF	+			+?	+?
Enzymes					
Chymase	RMCPI	RMCPII	+	+	−
Cathepsin G				+	−
Tryptase	+	+	+	+	+
Carboxypeptidase	+		+	+	+
Lysosomal	+	+?	+	+	+
Proteoglycans					
Heparin	+	−	−	+	
Chrondroitin sulfates					
diB		+			
E		+	+	−	+
Newly synthesized					
PAF	+	+	+	+	+
Nitric oxide	+	+			
Arachidonic acid metabolites					
PGD_2	+	+	+	+	+
LTB_4	−	+	+		
LTC_4 (and metabolites)	−	+	+	+	+
Cytokines					
TNFα (stored and newly made)	+	+	+	+ (little stored)	+
IL-1,3,4,6	+		+		
IL-10,IFNγ, etc.			+		

Figure 1 - Phenotypic Differences of Mast Cells. Taken from AD Befus in Handbook of Mucosal Immunology (1994). Eds. Ogra, Lamm, McGhee, Mestecky, Strober and Bienenstock.

A listing of the physiologic effects of the major mediators released by mast cells is provided in Figure 2. These agents are able to cause a diversity of responses in the GI mucosa. As a general rule of thumb, these changes relate to a teleologically cohesive view that these responses seek to rid the GI tract of the offending antigen to which the host has been exposed. This is in keeping with the widely held hypothesis that the IgE immune effector system probably evolved in response

to parasitic infection and hence one can reasonably view the physiologic responses shown below as protective responses gone awry.

Mast Cell-Derived Mediators

- Roles in Food Allergy -

- **Mucosal erythema, edema & permeability**
- **↑ Mucus production, ↓ fluid/electrolyte absorption**
- **SM contraction (↓ gastric emptying, cramps, diarrhea)**
- **PMN & eosinophil chemotaxis & activation**
- **Autocrine / paracrine functions**

Figure 2: Role of mast cell mediators in food-induced allergic reactions

The specific clinical syndromes that constitute the spectrum of IgE-mediated food allergy will be discussed subsequently.

The immunologist's view of the GI tract

Scope of the challenge - In large part the immune system can be viewed as serving to maintain the boundary between self and non-self (typically the environment). In the skin, it is easy to see why its physical characteristics provide nonspecific barrier protection from substantial environmental assault. There the specific immune effector mechanisms are not overly taxed except when the skin is breached by trauma. In striking contrast to this situation, the GI tract contains large amounts of foreign proteins (food or microbial) in a constantly moist environment with an enormous mucosal/environment interfacial area. In order to avoid harmful chronic inflammation in the GI mucosa, it must exclude approximately 99.99% of the intact form of each food protein. How then can it so successfully admit protein-derived nutrients, but exclude from absorption larger proteins given this constant assault?

Nonspecific mucosal barriers - Figure 3 outlines elements that provide protection from food antigens. As one moves craniocaudad a clever potpourri of mechanisms are variably engaged to fulfill this functional goal. In the oropharynx and esophagus the relatively impervious squamous epithelium functions effectively except in highly sensitive allergic individuals. Within the stomach, the GI tract first employs degradation as a mechanism to limit the potential intrusion of food

antigens. In addition, the generation of an effective mucus blanket that serves not only to protect the gastric mucosa, but also limit passage of macromolecules to the epithelial surface. Indeed, this barrier serves a primary role in its ability to effectively exclude molecules of >20kDa and to minimally pass those in the 10-20kDa range. The modest absorptive surface of the stomach compared to the small bowel makes the ability of the latter -- particularly of the jejunum where only partially digested and still antigenically intact proteins are in abundance -- to maintain itself without overt inflammation very impressive in the eyes of an immunologist. It is here, however, that a variety of immunologic processes contribute to the maintenance of relative quiescence with regard to inflammation. Although this will be dealt with more extensively in the following section, it is worth mentioning at this juncture that the GI epithelium itself, of course, represents an additional effective barrier to absorption of intact proteins. An exception to this is the epithelium overlying the Peyer's Patch that has, as one of its functions, the capacity to purposely sample the antigenic content of the GI lumen.

Host Defenses Against Antigen Uptake

Gastric acid
Intestinal proteolysis
Peristalsis
Protective mucus barrier
Intestinal cell membrane composition
Immunologic components
Secretory IgA
Access to lymphoid elements of Peyer's patch
Clearance of immune complexes by Kupffer cells

Figure 3: Host defenses against enteral mucosal penetration of foreign proteins

Elements of the GI mucosal immune system: An overview

The GI tract is a site of an immunologically highly active and complex system that finds itself seeking to bring appropriately powerful forces to bear upon unwanted viral, bacterial and parasitic invasion. But at the same time it must avoid unproductive effector responses against food proteins that are quantitatively equivalently or more greatly represented in the GI lumen. Figure 4 illustrates both the afferent and efferent "arms" of the gut associated lymphoid system (GALT) that involves a variety of cells and the simplified structure shown. Although a full discussion of the diverse immunologic mechanisms in the GALT is not realistic in the context of this review, a few comments are in order related to certain elements

of this system that have become better known during the past decade.

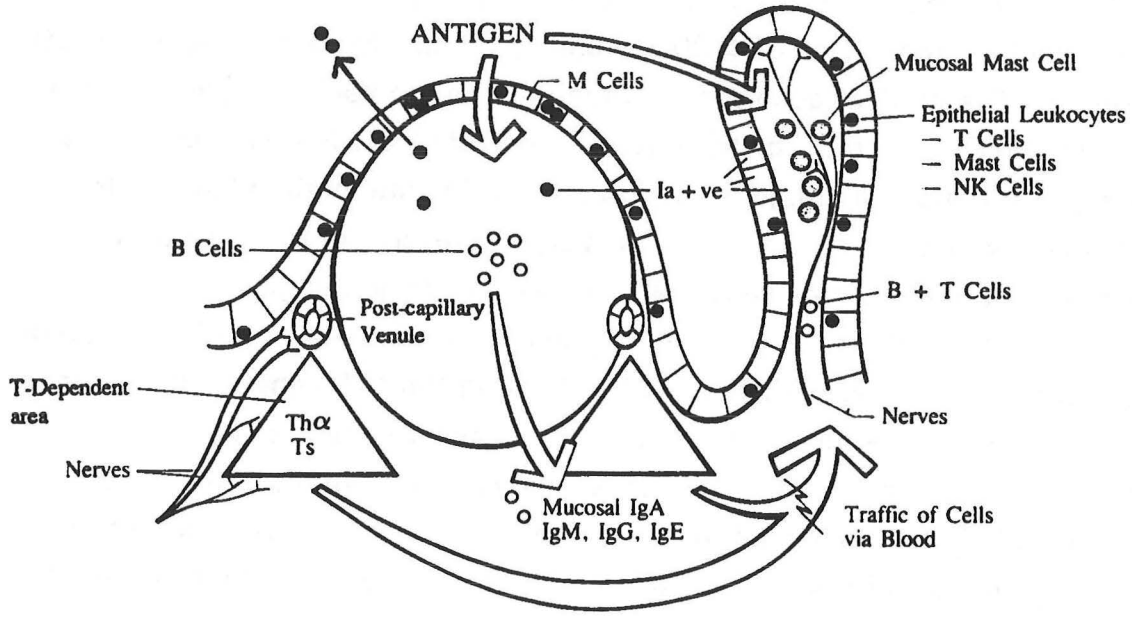

Figure 4: Gut associated lymphoid tissue (GALT) - From Croitoru and Bienenstock in *Handbook of Mucosal Immunology* (1994). Eds. Ogra, Lamm, McGhee, Mestecky, Strober and Bienenstock.

IgA - This isotype is not of recent phylogenetic genesis inasmuch as reptiles and birds possess similar antibody molecules, although there is great diversity even within mammals with regard to the number and structural diversity of IgA subclasses. As does IgM, IgA has the capacity to form polymeric structures $(IgA)_2$ in association with a J (joining) chain that is disulfide linked at the carboxy terminal region of the IgA antibody's constant regions. Circulating IgA is monomeric while that present in secretions (sIgA) is dimeric (Figure 5). Although IgA and IgM are

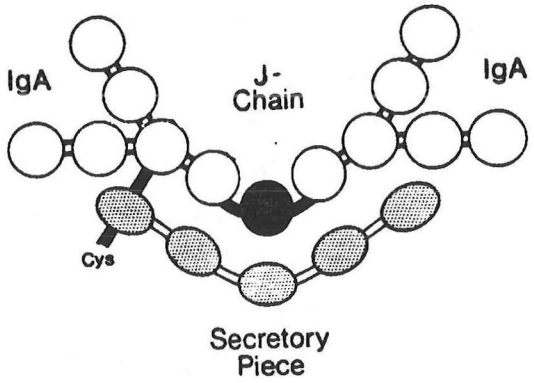

Figure 5: Schematic structure of sIgA [$(IgA2)_2$-J-SC]. SC = secretory component.

actively secreted, other immunoglobulin isotypes are found in a variety of secreted human fluids (Figure 6)

Isotype Distribution of Immunoglobulin and Cells in Selected Human Fluids and Tissue[a]

	Immunoglobulin concentration (mg/ml)				Distribution of Ig+ cells[b]		
Fluid	IgG	IgA	IgM	Tissue	IgG	IgA	IgM
Serum	12.0	3.0	1.5	Bone marrow	55	30	15
Milk	0.1	1.5	0.4	Mammary gland	4	86	10
Parotid saliva	0.004	0.04	0.006	Parotid gland	5	87	6
Jejunal fluid[c]	0.005	0.05	0.002	Jejunum	3	79	18
Hepatic bile	0.09	0.07	0.02	Lacrimal gland	6	77	7
Tears	0.007	0.19	0.006				

Figure 6: Presence of immunoglobulins and Ig-producing B cells in human fluids and secretory sites.

In the GI tract IgA is produced by plasma cells in the lamina propria. It appears that the particular ability of the GI tract to preferentially synthesize the IgA isotype is currently felt to primarily relate to the ability of TGFβ to exert less inhibition of IgA synthesis than it does upon the other immunoglobulin isotypes (IgG in particular). This cytokine has been shown to be an important anti-inflammatory cytokine inasmuch as knockout mice lacking the ability to make it die of overwhelming GI inflammation early in life. Other cytokines that contribute to the formation of IgA include IL-2, IL-6 and IL-10 in addition to the mandatory requirement for activity of the CD40/CD40L system. While IgA receptors exist on eosinophils and other cells, IgA appears relatively (at least compared to IgG_1, for example) incompetent in engaging inflammatory effector mechanisms, particularly complement.

IgA's role in food antigen clearance - IgA binds to a poly-Ig receptor on the epithelial cell's basolateral surface that allows its uptake in specific vesicles and its transport across the cell. Cleavage of this receptor as it and its bound sIgA are transported not only liberates secretory IgA (sIgA) at the luminal surface, but leaves a fragment (the secretory piece or component) disulfide linked to sIgA that serves to protect it from bacterial proteolysis in the intestinal lumen. Figure 7 illustrates schematically several roles that IgA might serve in limiting engagement of potentially adverse inflammation. First, the preferential generation of food antigen-specific IgA in the GI mucosa results in the delivery of food-specific sIgA into the mucus blanket. This allows binding of a large fraction of incompletely digested food antigens to lumenal sIgA within the mucus blanket. Mucus blanket

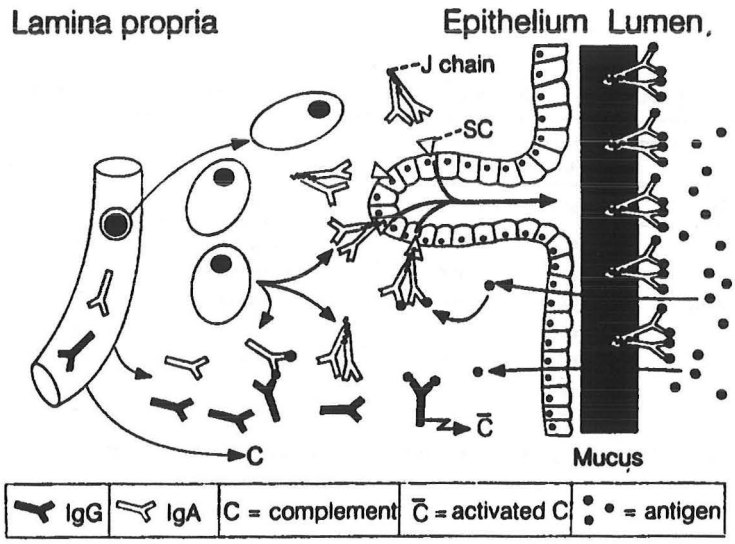

Figure 7: Roles of mucosal IgA interaction in food antigen clearance.

sIgA delays or prevents food antigen penetration, enhances the chances of hydrolysis and markedly attenuates absorption of this antigen. If a food antigen is present in sufficient quantity to penetrate the mucus blanket, avoid luminal sIgA and penetrate the intestinal epithelium, a second IgA-dependent mechanism exists to eliminate food antigens. Specifically, locally synthesized subepithelial sIgA can bind to penetrating antigens, subsequently bind to the poly-Ig receptor and carry bound antigens back to the gut lumen. Moreover, recent evidence indicates that transepithelial passage of sIgA may play a role in neutralization of pathogens in virally-infected epithelial cells.

Intraepithelial T cells - This is an important lymphoid compartment and while there has been a substantial proliferation of knowledge about these cells, there is considerable uncertainty as the normal physiologic role of cells residing within the epithelium of the GI mucosa. Indeed, it is estimated that the since T lymphocytes represent approximately 10% of the total number of cells in the epithelium in the small bowel, the total number of intraepithelial lymphocytes (IELs) exceeds that found in the spleen! These cells are virtually all $CD8^+$ T cells that additionally bear the $\alpha_4\beta_7$ integrin identified by the HML-1 monoclonal antibody. It is of interest and uncertain importance that while murine IELs demonstrate T cell receptor (TCR) usage largely of the $\gamma\delta$ isoform, human IELs reflect either $\alpha\beta$ or $\gamma\delta$ TCR usage in

similar proportions.

It is felt that these cells may contribute importantly in several important immune events in the GI mucosa. First, IELs may recognize and destroy virally-infected epithelial cells and so constrain proliferation of enteric viruses. Second, IELs may serve in the genesis of cytokines that are able to attenuate counterproductive immune reactions to food antigens [as suppressor cells that help to effect oral tolerance (*vide infra*)]. IELs are felt to contribute importantly to the pathologic development of gluten-sensitive enteropathy inasmuch as the frequency and activation state of IELs is substantively elevated.

Oral tolerance: a mechanism of emerging importance

Overview and mechanisms - Administering protein antigens orally has the potential capacity to generate immunologic tolerance to that particular antigen; a process that is active and not simply due to a failure to develop an immune response. Figure 8 illustrates the ability of orally administered ovalbumin to generate tolerance to the subsequent generation of DTH responses (Figure 8a) and circulating IgG antibody (Figure 8b).

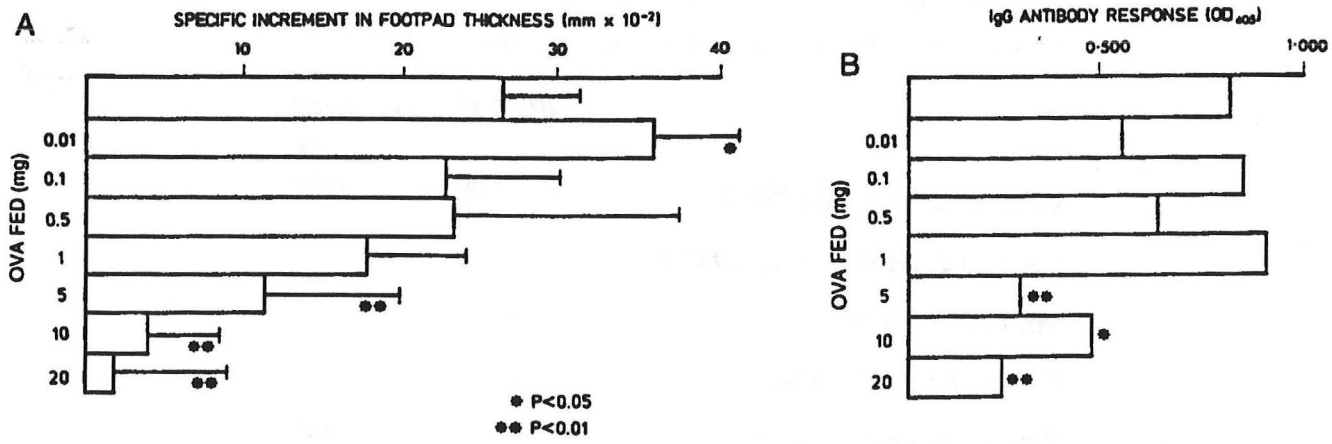

Figure 8: Induction of oral tolerance in mice. The indicated doses of ovalbumin (OVA) were administered to normal mice before SQ administration of OVA. The subsequent development of DTH responsiveness (A) and antibody synthesis (B) was evaluated. From Mowat in *Handbook of Mucosal Immunology* (1994). Eds. Ogra, Lamm, McGhee, Mestecky, Strober and Bienenstock.

Although antagonism of ongoing humoral responses is modest, existing cell-mediated DTH responses can be substantially attenuated by a single oral administration of oral antigen. Soluble antigens, but not particulate ones, are able to cause the development of oral tolerance; an observation suggesting its relevance to soluble food proteins vs. pathogen-associated protein antigens. Although the

mechanisms of tolerance are not fully understood it appears likely that they involve distinctive processing of antigen and the genesis of suppressor T cells. Situations that enhance the activity of the reticuloendothelial system (infection, GVH, recent exposure to an antigen to which an individual has active immunity) tend to increase the likelihood that a reasonable candidate antigen (typically able to generate oral tolerance) will produce active immunization (generation of IgA and/or IgG) instead. For a variety of reasons, this area of investigation has been the subject of increasing investigation. Exposure to multiple new food antigens decreases the likelihood of developing oral tolerance and provides scientific justification for delayed and slow introduction of single foods to infants' diets. These concepts have obvious implications for the development of oral vaccines, a large number of which are in active development.

Implications of oral tolerance for autoimmune diseases - An exciting area of both basic immunologic and clinical research relates to the ability of orally administered antigens to attenuate ongoing autoimmune processes to a clinically significant degree. Figure 9 summarizes the findings of studies exploring the potential therapeutic role of oral tolerance induction upon experimentally-induced (in the animal models) or naturally-occurring autoimmune diseases.

	Effect of Oral Antigen	
Disease / Model System	Animal Models	Human Trials
RA / Exp. Arthritis (collagen II)	+	+
MS / EAE (MBP)	+	±
Experimental Uveitis	+	nd
Diabetes (autoimmune)	+	nd

"Bystander suppression" observed in animal models

Figure 9: Abbreviations used ---> RA = rheumatoid arthritis in humans or its model (collagen- or adjuvant-induced arthritis) in animals; MS = multiple sclerosis in humans or its model (experimental allergic encephalomyelitis) in animals; MBP = myelin basic protein.

In two published reports during the last 12 months, the promise of this strategy has generated a substantial level of enthusiasm. Although each study can justifiably be criticized for some flaws in design, the data argue forcefully for additional studies. In animal models, evidence suggests a central role for a mechanism termed "bystander suppression." This phenomenon centers around the

purposeful generation of suppressor T cells that recognize an antigen that is found in the target area of inflammation (type II collagen in rheumatoid arthritis or myelin basic protein in multiple sclerosis) by administering this antigen orally. These antigen/site-specific suppressor T cells become widely distributed and become activated by their exposure to this antigen at the site of autoimmune inflammation. There, suppressor cell activation antagonizes established immune inflammation. The beauty of this approach is that determination of the responsible auto-antigen for these illnesses is not needed; one need only know what proteins might be preferentially present in the autoimmune inflammatory reaction.

- CLINICAL ASPECTS OF FOOD ALLERGY -

Epidemiology of food allergy

Although convincing food allergy is relatively uncommon, it is a very common perception among the general population that they suffer from food-induced reactions. While survey studies of the perceived incidence of food- or food additive-induced allergy have yielded quite varying figures (13-35%), they all agree that it is vastly out of proportion to the true prevalence of these illnesses (1-2% in adults and 4-8% in young children). A particularly striking example of this concept was demonstrated by a postal survey in the UK that showed that 1372 of 30,000 (4.6%) felt that they suffered from allergic reactions to food additives. When these patients were challenged with a mixture of the commonly perceived offending agents, only 3 (0.2%) had reactions.

The incidence of food allergy in young children is substantially greater than in adults, presumably the result of their "outgrowing" this sensitivity. In the children, 80% of symptoms attributable to food allergy develop within the first year of life. More than 90% of cases can be accounted for by sensitivity to egg, milk, peanut, soy and wheat (and fish in Scandinavian countries). A large study in Denmark indicates that the prevalence of cow mild allergy is 2.2% in children. The natural history of these reactions depends to some degree upon the ability to identify such sensitivity and to avoid offending antigens (diminishing clinical sensitivity to all except peanut), but the spontaneous development of clinical tolerance (distinguished from immunologic tolerance) develops fairly rapidly. For example, of children with documented sensitivity to milk, 56% are able to tolerate it one year later -- a figure that increases to 77% at two years and 87% at three years [Host

and Haken (1990) Allergy 45:587]. Of interest is that while individuals are able to tolerate introduction of previously offending food antigens, they do not stop expressing antigen-specific IgE. That is, skin tests and RAST to these food antigens typically remain positive; a finding that contributes to the difficulty in firmly establishing food-induced allergic disease in adults.

As is discussed below, sensitivity to the foods most often causing clinical findings in children dissipates by the age of 6 to a frequency more typical of adults (~2%). Although immunologically important reactions can develop to any antigen, 90% of such reactions in adults can be attributed to four major foods: peanut, tree nut, fish and shellfish. The natural history of sensitivity to these antigens indicates that sensitivity tends to be quite stable over time.

Nonimmunologic adverse reactions to foods

Figure 10 provided a useful approach for classifying reactions attributed to the consumption of foods. As is indicated by the epidemiologic data discussed above, the vast majority of reactions to foods do not involve immunologic reactions.

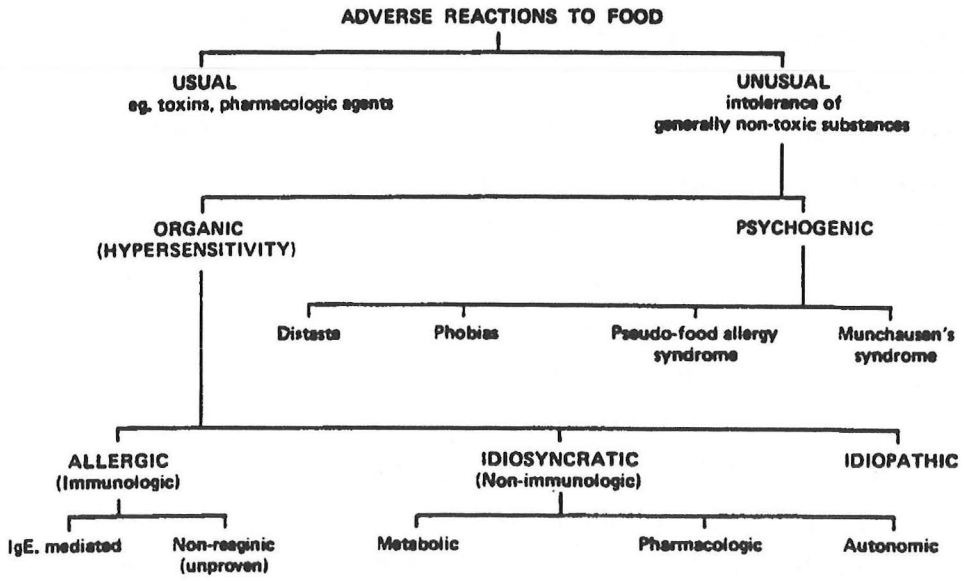

Figure 10: Mechanistic classification of adverse reactions to foods

Psychogenic disorders that are complicated by the perception of food-induced symptoms will not be discussed in greater depth, but at least some attention to the role played by toxic or pharmacologic agents found in foods is in order. Figure 11 illustrates the major differential diagnostic considerations to chronic and acute reactions to the consumption of foods. In addition to the ability of some foods to

Differential Diagnosis of Adverse Food Reactions

- Gastrointestinal disorders (vomiting and/or diarrhea)
  - Structural abnormalities
    - Hiatal hernia
    - Pyloric stenosis
    - Hirschsprung's disease
    - Tracheoesophageal fistula
  - Enzyme deficiencies (primary versus secondary)
    - Disaccharidase deficiency (lactase, sucrase-isomaltase, glucose-galactose)
    - Galactosemia
    - Phenylketonuria
  - Malignancy
  - Other
    - Pancreatic insufficiency (cystic fibrosis, Schwachman-Diamond syndrome)
    - Gallbladder disease
    - Peptic ulcer disease
- Contaminants and additives
  - Flavorings and preservatives
    - Sodium metabisulfite
    - Nitrites/nitrates
    - Monosodium glutamate
- Dyes
  - Tartrazine, ? other azo dyes
- Toxins
  - Bacterial (*Clostridium botulinum, Staphylococcus aureus)*
  - Fungal (aflatoxins, trichothecenes, ergot)
  - Seafood associated
    - Scombroid poisoning (tuna, mackerel)
    - Ciguatera poisoning (grouper, snapper, barracuda)
    - Saxitoxin (shellfish)
  - Infectious organisms
    - Bacteria (*Salmonella, Shigella, Escherichia coli, Yersinia, Campylobacter*)
    - Parasites (*Giardia, Trichinella*)
    - Virus (hepatitis, rotavirus, enterovirus)
  - Mold antigens (?)
  - Accidental contaminants
    - Heavy metals (mercury, copper)
    - Pesticides
    - Antibiotics (penicillin)
- Pharmacologic agents
  - Caffeine (coffee, soft drinks)
  - Histamine (fish, sauerkraut)
  - Serotonin (banana, tomato)
  - Glycosidal alkaloid solanine (potatoes)
  - Alcohol
  - Theobromine (chocolate, tea)
  - Tryptamine (tomato, plum)
  - Phenylethylamine (chocolate)
- Psychologic reactions

Adapted from Sampson HA, *J Allergy Clin Immunol* 1986; 78:212–219.

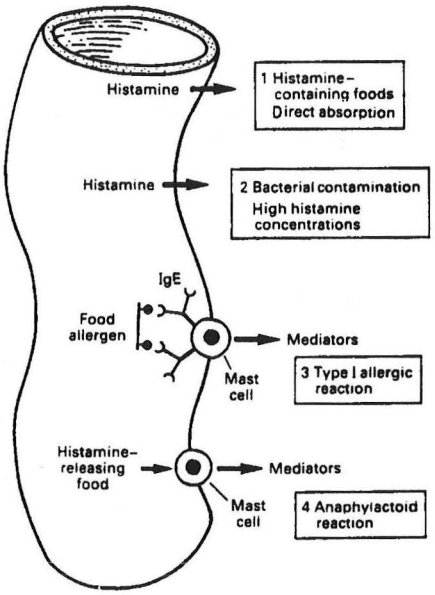

Figure 11: Differential diagnosis of adverse reactions to foods and the mechanisms of some immunologic and nonimmunologic reactions.

contain histamine and tyramine, foods such as strawberries appear to contain agents capable of inducing mast cell degranulation in a nonimmunologic manner that results in urticaria in individuals consuming a large amount at a single sitting. In the appendix, a listing is given to the content of histamine, sulfites and tyramine of a number of commonly ingested foods. Although sulfites are used less frequently now than in the past, they can cause both naso-ocular reactions and worsening of asthma in a way that can mimic food allergy.

Spectrum of clinical syndromes in food allergy

Oral allergy syndrome - This illness is characterized by the rapid development (5-20 minutes) of oropharyngeal symptoms of pruritus, tingling, hoarseness, angioedema or localized areas of edema of the mouth and lips. Studies indicate the association of certain pollen sensitivities in association with sensitivity to certain foods as is indicated in Figure 12.

Pollens and Cross-reacting Foods

RAGWEED	BIRCH	GRASS	MUGWORT
Watermelon	Apple	Buckwheat	Celery
Cantaloupe	Carrot	Potato	Melon*
Honeydew	Potato	Apple*	Apple*
Zucchini	Celery	Carrot*	
Cucumber	Hazelnut	Celery*	
Banana	Orange	Tomato*	
	Parsnips	Melon*	
	Cherry*	Watermelon*	
	Pear*	Orange*	
	Fennel*		
	Walnut*		

*Based on patient reports, allergy to these foods is associated with hay fever.

Figure 12: Associations of pollen sensitivity and the development of food-induced reactions as the result of immunologic cross reactions.

The classical oral allergy syndrome does not involve additional GI symptoms, although it can act as the first symptoms during the development of a more extensive GI allergic response (vide infra). The mechanism of the oral allergy syndrome is felt to be virtually exclusively due to IgE/mast cell responsiveness to the offending food. This can be evaluated and confirmed by epicutaneous (prick) skin testing to suspected food antigens. It is reasonable to consider these reactions to be a form of contact urticaria and are typically of modest severity. Their rapid development after ingesting the offending food usually results in patient self-diagnosis and rarely require physician evaluation. If testing is warranted, freshly prepared extracts of foods (particularly fruits and vegetables) are commonly required as a result of the lability of the responsible food antigens; perhaps explaining the lack of symptoms developing subsequently within the stomach or small bowel.

Rapidly developing allergic reactions limited to the GI tract - Typical symptoms

of the oral allergy syndrome may be present, but reactions more typically involve nausea, abdominal cramping, vomiting, and diarrhea. Like the oral allergy syndrome, these reactions centrally involve an IgE sensitivity to the offending food. As described previously, these symptoms represent a teleologically reasonable protective response seeking both to rid an individual of the offending material and to reduce its absorption. This constellation of findings is often described loosely as "gastrointestinal anaphylaxis."

Common clinically relevant food allergens - The development of double blind placebo controlled food challenges (DBPCFC; described in greater detail subsequently) has allowed identification of the foods that are most commonly involved in food-induced allergic reactions. In Figure 13 below, these foods are listed with their relative tendency to cause anaphylactic reactions and the natural history of sensitivity (when avoidance is practiced). This summary pertains to findings when one considers all ages. The vast majority of reactions to milk, soy, wheat and egg occur in children during the first 12-24 months of life. As indicated below, avoidance results in the dissipation of clinical reactivity usually over a matter of 6 months to a few years. Of interest is that it is not uncommon for antigen-specific IgE to continue to be detected, despite the development of clinical tolerance of the previously offensive food. As described subsequently, the existence of antigen-specific IgE is a necessary, but not a sufficient element in the development of immediate food-induced food allergic reactions.

Food	Anaphylactic Potential	Natural History	Antigen	Size (kDa)
egg	low	brief	ova,ovm	45/28
peanut	very high	many years	Ara h I	63.5
milk	low	brief	casein	19-25
soy	low	brief	SBTI	20.5
tree nuts	high	long term	various	small
crustacea	high	long term	Pen a I	34
fish	moderate	long term	Gad c I	12.3
wheat	low	brief	various	variable

Figure 13: The antigens most commonly associated with IgE-mediated immunologic reactions to foods.

Characteristics of food antigens - Although the antigens involved in the oral allergy syndrome often involve highly labile antigens present in fresh fruits and vegetables, the food antigens causing more extensive GI allergic reactions typically involve very stable proteins. As might be expected, many of these proteins are heat and acid stable and often resistant to proteases. They are typically relatively small glycoproteins (10-70 kDa). Moreover, responsive IgE antibodies more often respond to relatively short sequence-specific linear arrays of amino acids (B cell epitopes) that have little or no conformation-dependence; again, a finding that might be expected of a protein that is able to "run the gauntlet" of the GI tract and penetrate the small bowel epithelium. It is important to point out that all IgE-mediated allergic reactions critically require the existence of an IgE response to two or more epitopes on a penetrating protein or fragment (or the existence of a single epitope on each of two disulfide-linked multimers) in order to activate mast cell surface FcεRI. Some of the false positivity of skin testing and in vitro testing may relate not to inaccuracy in detecting the existence of food-specific IgE, but in the failure of food antigens used in diagnostic tests to accurately reflect the antigens the GI mucosal mast cells might encounter (vide infra) and hence clinical reactivity.

Infantile colic - Although controversial, it is estimated that approximately 15% of infants with colic are attributable to food antigens ingested either as the result of direct consumption or by those eaten by a nursing mother and passed into her breast milk. Regardless of the pathophysiology, the vast majority of these reactions are self-limited and of reasonably short duration and needn't be formally evaluated.

Acute gastrointestinal allergic reactions with systemic findings - Extension of allergic responses to foods outside of the GI tract may occur as the result either of dissemination of a food antigen that reacts with mast cells in other tissue sites or of the dissemination of mediators generated by GI mast cells to distant sites in sufficient quantities to cause physiologically meaningful responses. Symptoms and signs can be diverse, from mild brief urticaria to severe protracted cardiovascular collapse and/or respiratory failure. Systemic symptoms often develop quickly, but may evolve more slowly. A reaction that is not immediately severe should not be taken lightly because it may become more severe as the result of continued antigen absorption. Indeed, asthmatic symptoms can appear to become controlled with appropriate intervention only to have respiratory failure ensure. Although it

seems likely that these reactions involve mast cells in a central way, studies using passive transfer of antigen-specific IgE into mast cell deficient rodents indicates the ability to continue to generate cardiopulmonary anaphylaxis with antigen administration. The recent generation of FcεRI knockout mice using two different strategies should provide the opportunity to explore this finding in greater detail.

Food-dependent exercise-induced anaphylaxis - Exercise-induced anaphylaxis (EIA) has been the subject of increased study and recognition during the last decade. Although some patients will develop anaphylaxis with exercise alone, many will require the coexistence of some other condition that itself alone will not cause anaphylaxis for expression of the complete syndrome. While a variety of other "incitants" have been associated with the ability of exercise to cause anaphylaxis (temperature, humidity, aspirin, alcohol, menstrual phase), food ingestion has been felt by patients to be associated with the subsequent development of anaphylaxis in approximately 54% of individuals with EIA although the vast majority of these have not been formally explored. Of note is that sensitivity to celery or cabbage is well out of proportion to its ability to cause other food allergic reactions. Symptoms are typical of anaphylaxis and very commonly include generalized pruritus, urticaria, angioedema or flushing (90%); commonly include upper respiratory symptoms such as cough, hoarseness, dysphagia (~60%); frequently include hypotension with loss of consciousness (~30%); and often include GI symptoms (30%).

Delayed / chronic gastrointestinal symptoms to ingested foods - Although the vast majority of allergic reactions to foods begin within 15-60 minutes, the pattern of their evolution is quite variable. While acute release of IgE-mediated mast cell mediators likely accounts for a substantial fraction of symptoms, the continued evolution of symptoms over 8-12 hours is sufficiently common to suggest the existence of: 1) delayed or late phase reactions on the part of mast cells or cells recruited by initial mast cell release; 2) non-IgE-mediated immunologic reactions or 3) slow elimination and/or large dose of the offending antigen. The vast majority of reactions reported by patients to develop more than 90 minutes after eating, however, are likely not of immunologic origin and typically cannot be recapitulated by double blind placebo controlled food challenges (vide infra). Gluten-induced enteropathy is a non-IgE mediated immunologic reaction that represents an exception to this general rule.

Eosinophilic gastroenteritis is a relatively uncommon illness primarily affecting children that may presents in a variety of ways. Depending upon the extent and area of eosinophilic infiltration in the stomach and/or small bowel, findings may include, diarrhea, malabsorption, failure to thrive, obstructive symptoms or eosinophilic ascites. Diagnosis is made by multiple gastric and small bowel biopsies that demonstrate profound eosinophilic infiltration. A subset of these patients appear to have one or more specific food allergies, although a pathogenic role in the evolution of the underlying eosinophilic gastroenteritis has not been firmly established. Roles for cytokine-producing T cells and/or immune complexes have also been proposed. Systemic steroid therapy is frequently required to gain control of this illness if food allergy is either ruled out or avoiding offensive foods is insufficiently effective.

Delayed / Chronic systemic reactions to foods - As described above, systemic reactions incited by allergic reactions to foods can include delayed components. In protracted anaphylaxis patients may suffer from very slowly resolving cardiopulmonary compromise. Despite lack of continuing exposure to offending antigens and early intervention in anaphylaxis with epinephrine, H1 and H2 histamine antagonists and systemic steroids, some hypotensive reactions have continued for days to several weeks. Candidate pathophysiologic reactions involve IgG antibodies and antigen-specific T cells that might promote reactions of the Type III and Type IV pattern in the Gell and Coombs classification system.

A role for food allergy in the pathogenesis of atopic dermatitis has been debated for some time, but has been clearly demonstrated to occur by the pioneering studies of Dr. Hugh Sampson. Dr. Sampson's data in a tertiary referral setting indicate that approximately one third of children having severe atopic dermatitis have clinically significant food allergy as demonstrated by double blind placebo controlled food challenges (DBPCFC; discussed subsequently). The frequency of food allergy in a less specialized population of children having atopic dermatitis is likely to differ. Not only do these children demonstrate the ability to have cutaneous and other systemic symptoms during DBPCFC, but their leukocytes spontaneously elaborate chemokines and other materials capable of activating basophils. After a period of avoidance of offending foods identified by DBPCFC -- typically associated with improvement of the underlying AD -- patients leukocytes cease their spontaneous formation of these agents.

A small fraction of patients with chronic urticaria without gastrointestinal

symptoms may have underlying food allergy as a cause of their skin disease. Because of the major differences between the nature of the patients evaluated in a primary care, subspecialty or tertiary referral setting, a precise figure for the contribution of food allergy to chronic urticaria is extremely difficult to obtain, but is certainly less than 5% in any setting. Although the yield is small, pursuing an elimination diet not infrequently proves useful during the evaluation of patients with difficult chronic urticaria for both diagnostic and management reasons.

Diagnosis of food allergy

Overview of strategy - Although specific criteria exist for the definition of food allergic patients in a research setting exist, the use of double blind placebo controlled food challenges outside this setting is often not practical even for the allergy and immunology specialist. Hence, criteria for probable and certain diagnoses are less rigorous. Elements that may contribute to the diagnosis of food allergy are listed in Figure 13 and discussed below.

Medical history
Diet history / food diary
Physical examination
Elimination diet
Documentation of food-specific IgE
Challenge testing
    Open
    Double-blind placebo-controlled

Figure 13: Diagnostic information related to the diagnosis of food allergy.

A reasonable (although not universally accepted) flow sheet describing the integration of these elements into a diagnostic plan is illustrated in Figure 14. Of note is that the physical examination participates to very limited degree inasmuch as most patients are not evaluated during brief periods of suspected food-induced symptoms unless they are severe.

Food diary - All symptoms observed and all foods and other foreign materials that are introduced into the mouth should be recorded. The specific foods that are ingested in association with acute or chronic reactions provides useful information as to potentially causative agents that bear closer evaluation.

Testing for the presence of antigen-specific IgE - The use of various *in vivo*

and in vitro tests to demonstrate antigen-specific IgE is complex. A detailed discussion is beyond the scope of this grand rounds discussion, but a summary is essential to provide a working knowledge of the appropriate use of confirmatory testing. Although the frequency of clinical food allergy is relatively uncommon, the presence of antigen-specific IgE to foods is not. As a result, the diagnostic relevance of a positive or negative test for a specific food is largely dependent upon the setting in which is its employed.

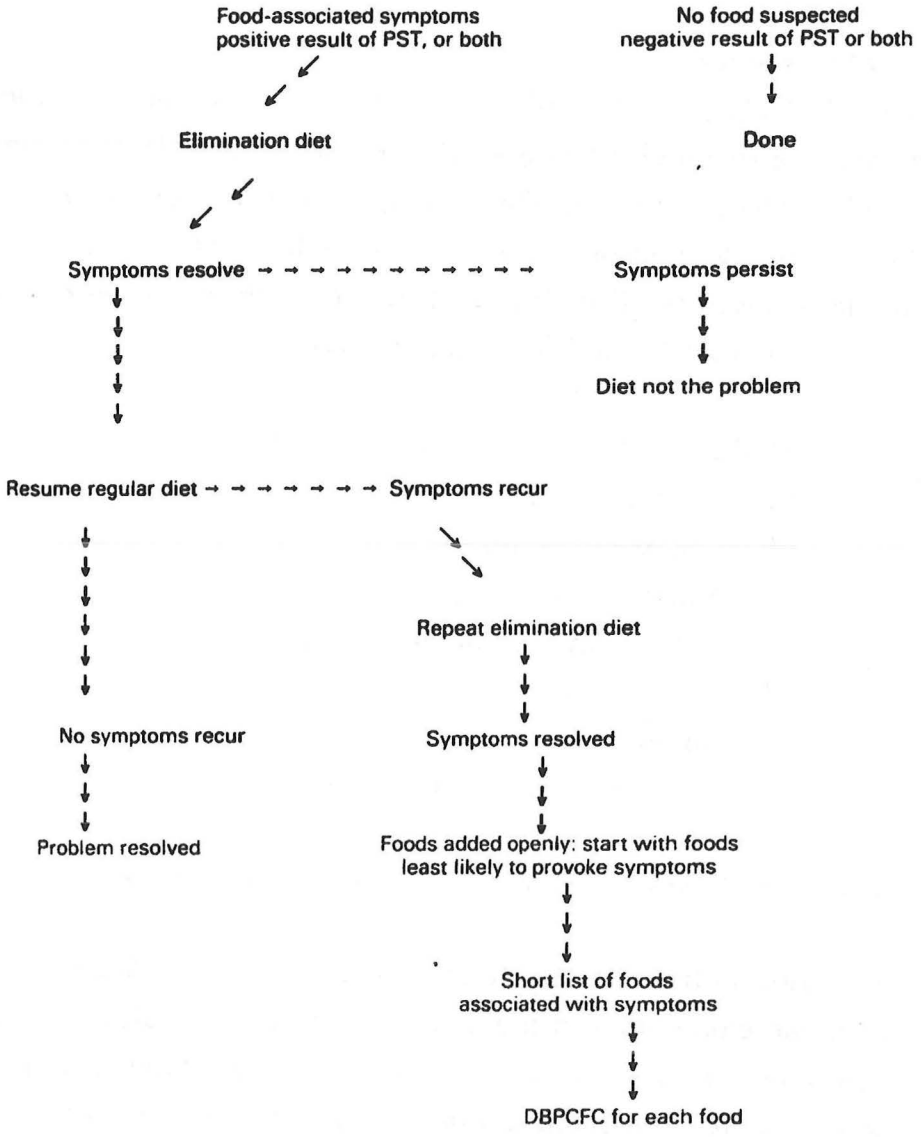

Figure 14: Sample diagnostic plan for evaluating adverse reactions to foods. Adapted from Sampson in *Allergy - Principles and Practice* (1993) Eds. Middleton, Reed, Ellis, Adkinson, Yuninger and Busse.

Epicutaneous (prick) skin testing for food allergy provides information with the greatest sensitivity and specificity. In vitro tests (such as RAST tests and basophil

histamine release testing) have somewhat less sensitivity (except in children less than a year old who generally have less cutaneous responsiveness). In the setting of food sensitivity confirmed by DBPCFC, the predictive accuracy of prick skin testing is typically 60-90% (Figure 15) while a negative test has a negative predictive accuracy of 75-95% [Sampson (1993) Allergy Proc. 14:259]. When one considers a disease prevalence of approximately 10% in patients being evaluated for suspected food allergy, the positive predictive value is reduced to 40-60%, but the negative predictive value increases to 97-99%. Although intradermal testing has a role in evaluating IgE sensitivity to aeroallergens in allergic rhinitis and allergic asthma, it has no role in the diagnosis of food allergy as a result of its marked sacrifice of specificity for improved sensitivity. The role of skin testing is, therefore, primarily helpful in the setting of negative tests which are capable of strongly ruling out the contribution by a particular food in causing suspected symptoms. The ability to confidently rule out specific IgE-induced food allergy by skin testing requires the use of high potency antigen extracts of foods. This is

Predictive Value of Prick Skin Tests

	PPA		NPA
Food	>3 mm	>1.5 ⊕ ctl	<3 mm
Milk	66%	88%	86%
Egg	78%	88%	74%
Peanut	63%	72%	100%
Soy	28%	33%	85%
Wheat	24%	83%	92%

PPA = positive predictive accuracy.
NPA = negative predictive accuracy.
3 mm = mean wheal diameter compared to negative control.
>1.5 = ratio of food antigen/histamine control mean wheal diameters.

Figure 15: Predictive accuracy of prick skin testing to common food allergens in patients with confirmed positive or negative DBPCFC.

particularly problematic when vegetables and fruits are used inasmuch as commercial extracts of these foods are generally effete and must be freshly prepared by the subspecialist to achieve a reliably result. As mentioned, negative skin testing must be interpreted with caution in infants who are in their first 12-18 months of life.

RAST testing provides less satisfactory screening for the presence of food antigen-specific IgE as described above, but may be required in the setting of dermographism, psychotropic or other medications with H_1 antihistamine effects, diffuse rash or lack of cooperation. If RAST testing must be used, a 3+ reaction should be used as a threshold for positivity. Using a 2+ reaction as a diagnostic threshold only modestly increases sensitivity, but markedly sacrifices specificity. From the perspective of cost, RAST testing is typically 3-5 fold more costly than epicutaneous skin testing.

Testing for possible food intolerance or food allergy: the elimination diet - An extremely useful technique available to all physicians that dramatically assists in clarifying the nature of suspected food intolerance/allergy is the use of an elimination diet. This not only guides further workup, but also often provides reassurance to the patient (and relief to the physician) related to absence of food causation in patients with psychiatric sources of symptoms.

The goal of this procedure is to eliminate from the diet all foods felt to potentially contribute to GI (or other food-induced) symptoms with the expectation that such a maneuver will cause cessation of the patient's symptoms if food intolerance truly exists. For evaluation of rapidly developing clinical reactions (presumed to be IgE-induced), a period of 7-14 days is used (10-14 days preferred). Although a "classic" diet of rice, lamb and water has been recommended, it is more productive to consider the strategy that underlies this approach. It is important to avoid all of the common food allergens (Figure 13), but to restrict intake to foods that are rarely consumed by the patient and, therefore, have little likelihood of causing the suspected food allergic reaction. Spices and flavorings should be avoided (except for noniodized salt) and unprocessed foods should be employed to avoid the potential consumption of a potentially offending food unknowingly present in processed foods. Given the increased consumption of rice by occidental populations and its typical consumption by oriental populations, this food should be carefully considered prior to its use as a permitted food, despite its relative lack of antigenicity.

Employing an elimination strategy can be both simpler and more difficult in infants suspected of suffering from food allergy. Because the number of foods is more limited, the list of candidate "offenders" is substantially restricted. By the same token, the ability to switch to other sources of adequate nutrition that are well tolerated by infants can be problematic. Switching from cow milk formula to

soy-based or casein hydrolysate formulas is rational, but not always tolerated. Extensive hydrolysates such as Neutramigen are reasonably free of intact milk antigens that typically cause allergic reactions, but are often rejected by infants. For infants who are nursing, mothers should be encouraged to limit their own intake of antigens potentially affecting the infant since they can pass into breast milk.

Testing for clinical relevance: challenge testing - The results of skin testing (or RAST testing) for food-specific IgE can be refined by the results of *in vivo* food challenge testing. Negative results can be confirmed by the open administration of a previously suspected food antigen.

Positive *in vitro* tests should, however, be confirmed in a more rigorous and conservative manner by the use of DBPCFC. In the latter, increasing doses of lyophilized antigens (or placebo) are administered q 15-60 minutes until either a clinically significant reaction develops or a dose of 10 grams is reached. This type of testing should be performed only by qualified subspecialists, particularly in the setting of suspected anaphylactic sensitivity. Although the nature of clinical reactions to DBPCFC vary depending upon the clinical situation, Sampson has demonstrated that patients with atopic dermatitis and suspected food allergy demonstrate cutaneous reactions (pruritic morbilliform rashes, 75%), GI symptoms (41%), upper respiratory symptoms (cough, hoarseness; 30%), and wheezing (10%) in children. The rate of false positive reactions to DBPCFC is 0.5-1% while false negative tests are observed at a rate of 2-5%; the latter being identified by the important use of native foods in an open or blinded challenge for foods giving negative DBPCFC results.

While DBPCFC is currently the "gold standard" for rigorously evaluating food allergy, it has several serious drawbacks. It is extremely time consuming and requires substantial expertise to perform. DBPCFC should be performed only by those experienced in the management of anaphylaxis in a setting capable of treating it in an effective manner.

In addition to these readily available testing procedures, the use of other tests has, in investigational situations, demonstrated superiority but are not practical. Mucosal biopsy specimens from a patient suspected of having food allergy can be tested for the ability of a food extract to induce mast cell exocytosis as detected by histamine released from the tissue. Alternatively the gastric mucosa can be tested by introducing food extracts onto the mucosal surface and evaluating the

development of erythema and mucus hypersecretion.

Unproven diagnostic techniques for food allergy - While on rare occasions, IgG-mediated processes may be involved in food allergic reactions, testing for the presence of antigen-specific IgG or of IgG-food antigen immune complexes is of no diagnostic value. While IgG_4 was once felt by some to be pathogenic in some food allergic reactions (protective by others!), a general consensus exists that this is not the case and that the presence or absence of food antigen-specific IgG_4 has no diagnostic value. The existence of food-induced lymphocyte proliferation may be of value in investigational studies, but has no role in the management of individual patients suspected of having food allergy.

While the tests above have at least theoretical value, a number of tests have no rational scientific basis. The most common still in existence include those based upon the concept of "provocation/neutralization." Although no significant scientific underpinning or supportive data exist related to this approach, it involves unblinded challenge (either orally by sublingual drops or parenterally in the skin) with food extracts at a variety of doses in order to elicit any of a variety of typically nonspecific complaints (examples include headache, fatigue, reduced mentation, anxiety) and then adjust the administered dose to determine one (either higher or lower) that is able to "neutralize" the symptoms by the patient's accounting of it. This technique has been subjected to double blind placebo controlled trials and failed to demonstrate efficacy. Another procedure that provides no meaningful diagnostic information is the "cytotoxic test" for foods. This procedure assesses purported changes in the unstained morphology of leukocytes in buffy coat preparations from patients as the result of exposure to food antigens over minutes to hours. The lack of value of the cytotoxic test is in contrast to the experimentally useful assessment of food extract-induced release of histamine from basophils. A third procedure that has been recently marketed seeks to use the sensitivity of ELISA technology to determine the presence of circulating IgG that can bind to immobilized food antigens; a procedure that typically produces many positive results in normal individuals, is extremely costly and lacks documented predictive or therapeutic value.

Treatment of Food Allergy

Overview - At present the mainstay of chronic therapy for individuals suffering from documented food allergy remains avoidance of offending foods that have

been carefully identified as causing symptoms in affected patients. Treatment of acute symptoms developing from known or occult antigen intake is based upon the nature of reaction that ensues. Immunomodulation represents an exciting future therapeutic option, but at present is investigational. The use of a potpourri of unproven techniques by a variety of practitioners is widespread and a source of substantial unnecessary cost expenditure and friction within medicine.

Avoidance: the mainstay of treatment - Since it is theoretically possible to eliminate a limited number of offending food allergens from the diet, this approach represents the most important single therapeutic option. Clearly, successful avoidance therapy is dependent upon the correct identification of all of or the principal food allergens responsible for food-induced reactions. The importance of this concept cannot be overstated since making recommendations for avoidance can introduce substantial hardship for patients or their parents. A recommendation to avoid cow milk or wheat or soy or peanut should not be made lightly; these are ubiquitous materials. An inaccurate diagnosis and derivative avoidance recommendation can introduce substantial inconvenience.

Although it may seem relatively simple to accomplish, this form of therapy is fraught with a variety of problems and/or complications. The ubiquity of certain food antigens (milk, soy, wheat, peanut in particular) in processed foods limits the use of these food products for patients with food allergy. Unfortunately, while FDA-mandated changes in labeling have increased information available to consumers, studies have shown the presence of one of more of the food antigens shown in Figure 13 in products that do not list them as ingredients. This can represent a substantial inconvenience and even a danger for adults related to the consumption of processed food and meals prepared by restaurants and cafeterias. More worrisome, however, is the situation in children who are not able to closely monitor the content of the food the consume in day care or school environments.

The existence of anaphylactic sensitivity to foods should motivate the physician to provide an automatic epinephrine injection device for adult patients or adults responsible for a pediatric patient's supervision. Education as to the indications fore its use and the technique to be used is critically important.

In infants, serious food allergy (to milk and soy) can seriously limit the ability to obtain adequate nutrition. Formulas based upon hydrolysates of casein are not entirely free of milk antigens and can pose problems for the highly allergic. Some data suggest that the concomitant use of oral pancreatic enzyme supplementation

may reduce the capacity of formulas to cause food allergic reactions; presumably as the result of enhanced proteolysis of offending food antigens.

The subject of breast feeding and its role in preventing and/or reducing the severity of food allergy in atopic children is controversial. A synthesis of this literature suggests that delayed introduction of cow milk formula in children of atopic parents may be of benefit. Moreover, avoiding ingestion of cow milk and peanut-containing products by nursing mothers reduces the frequency of subsequent development of these food allergies in their children. Nursing per se may be of additional benefit in providing high levels of sIgA directed toward food antigens that can reduce absorption of relatively intact molecules by the immature GI mucosa of the infant. Also along the line of feeding practices of infants, it is noteworthy that the long recommended practice of introducing new foods slowly and singly makes "immunologic sense." Specifically, the ability of a secondarily introduced food to induce oral tolerance is substantially limited -- at least in animal experimental models -- when it comes soon after the introduction of a different food.

As introduced above, the natural history of food allergy in children is such that reintroduction of certain foods after a period of avoidance is rational. Since studies indicate that clinical sensitivity dissipates over 1-2 years in most children related to milk, soy, egg and wheat, these antigens can be judiciously reintroduced at 6-12 month intervals after their elimination from the diet when previous food-induced symptoms are limited to the skin and GI tract. In contrast to these antigens, sensitivity to peanut, tree nuts, crustacea and fish should, in general, be viewed a long term -- lifelong in many patients -- and should be avoided indefinitely.

Management of acute reactions - Management of the various patterns of clinical reactions occurring as the result of antigen exposure are largely self-evident and reflect the typical management of the sequelae of the release and/or genesis of mast cell mediators (histamine, LTC_4, PGD_2, PAF, kinins, proteases and cytokines). Treatment options will be mentioned only briefly.

When it occurs in isolation, the oral allergy syndrome is typically self limited, but can be treated with $H_1 \pm H_2$ histamine antagonists. It is uncommon that the level of oropharyngeal edema would require the use of SQ epinephrine, but it remains a therapeutic option. For medicolegal purposes, it is worth considering prescribing an epinephrine autoinjection device (Epipen^R; and provide education in its use) in the event that airway compromise should take place in an unexpectedly severe future reaction.

More severe GI reactions that involve nausea, vomiting, abdominal cramping and diarrhea also tend to be self limited. Replacement of fluid losses is important and symptoms can, to some degree, be attenuated with the use of H_1 and H_2 histamine antagonists. It can be argued that vomiting and diarrhea serve an important role in removing the offending food antigen and should not be the target of overzealous symptomatic therapy.

Systemic anaphylaxis occurring during severe food allergic reactions must be treated aggressively and followed closely. As with all sources of anaphylaxis, the most important therapeutic agent is epinephrine. Even in situations of substantial cardiovascular compromise, it should be administered SQ and not IV since the latter is often associated with the development of ventricular arrhythmias. In the rare elderly patient with severe food allergy, the existence of known coronary artery disease might reasonably generate caution that motivates the initial use of a reduced dose of epinephrine, but such a dose reduction should be accompanied with an increased frequency of administration (to achieve same total dose/time unit) until cardiopulmonary manifestations are brought under control. H_1 and H_2 histamine antagonists should be promptly administered along with necessary crystalloid and/or colloid to maintain intravascular volume. Potential compromise of the upper airway should be carefully evaluated and followed regularly. Nebulized β_2 agonists should be used with lower airway compromise. Since the food antigen has been ingested, consideration might be given to the use of activated charcoal to attenuate and/or slow further absorption. This strategy has only be evaluated formally in animal models; no human studies have examined this rational approach. Because peak absorption can be slow, food-induced systemic anaphylactic reactions should be carefully followed for intensification after initial improvement with classical pharmacologic intervention ("biphasic anaphylaxis"; a term introduced by Dr. Timothy Sullivan at this institution). While no controlled trials related to the efficacy of systemic glucocorticoids have taken place, their use is rational and may limit and/or shorten the duration of symptoms. To the extent that inflammatory cytokines (TNFα from mast cells, for example) contributes to cardiovascular reactions, limiting its synthesis by the use of glucocorticoids may be important. Although the use of ASA or NSAIDs would appear rational (in being able to antagonize the formation of PGD_2), it appears that some PGD_2 metabolites cause vasoconstriction and anecdotal experience suggests that these agents may worsen a severe reaction. Orally-administered 5-lipoxygenase inhibitors likely will soon be available in the US for the treatment of asthma, but their role in systemic anaphylaxis has not been sufficiently evaluated to make a

recommendation regarding their role in anaphylaxis.

Symptomatic treatment of chronic food allergy - The primary treatment of true food allergy is avoidance. To the extent that this is not realistically achievable *and other GI illnesses have been ruled out*, symptoms of chronic abdominal discomfort and/or diarrhea can be treated symptomatically and/or with anti-allergic medications although little data exists to suggest that this is efficacious. Chronic use of orally administered cromolyn sodium has been the subject of careful study. While it appears that a limited number of patients might benefit from this intervention, no significant change was seen in control vs. treatment groups. The use of oral cromolyn for this indication remains controversial.

In patients in whom skin disease represents the primary or an important target organ for food allergy, treatment appropriate for the condition remains appropriate although efforts at avoidance remain very important. Specifically, attentive local care and topical and systemic pharmacotherapy of atopic dermatitis (typically in children) and suppressive therapy of chronic urticaria with $H_1 \pm H_2$ histamine antagonists (in adults) may quite helpful.

In children, food allergy can in some situations contribute to the severity of allergic rhinitis and asthma on a chronic basis. This is very rarely seen in adults. When it does occur, avoidance of the documented food allergen may prove helpful, but therapy of these respiratory illnesses must center upon their typical management were the putative food allergy not present.

Immunomodulation - While conventional allergen immunotherapy has been shown in rigorous studies to be very helpful in managing allergic sensitivity to aeroallergens in allergic rhinitis and allergic asthma, it has no current routine role in the management of food allergy. Both oral and parenteral immunotherapy trials using food extracts for patients suffering from typical food allergic symptoms have failed to demonstrate efficacy over the years. Recently, the risk of mortality for patients with anaphylactic peanut sensitivity motivated a controlled trial of immunotherapy. An unfortunate medication error led to the death of a study patient and suspension of this trial, although preliminary data appeared somewhat encouraging. Its resumption has involved administration of allergen extracts in an ICU setting.

Although experimental, trials are underway that seek to develop reagents that can achieve antigen-specific T cell tolerance to T cell epitopes on offending food allergens; this would result in the dissipation of B cell-mediated production of

allergen-specific antibodies (including pathophysiologically relevant IgE). A schematic overview of this approach is shown in Figure 16. This technique requires thorough biochemical characterization of all relevant antigens, identification of the most important T cell epitopes and administration of synthetic peptides of these regions. Although this approach appears to have merit in suppressing the expression of antigen-specific IgE in a clinically significant way for aeroallergens, the probable important role of food antigen-specific IgA in reducing antigen penetration in the GI mucosa may limit or preclude a role for this form of immunotherapy related to food allergy.

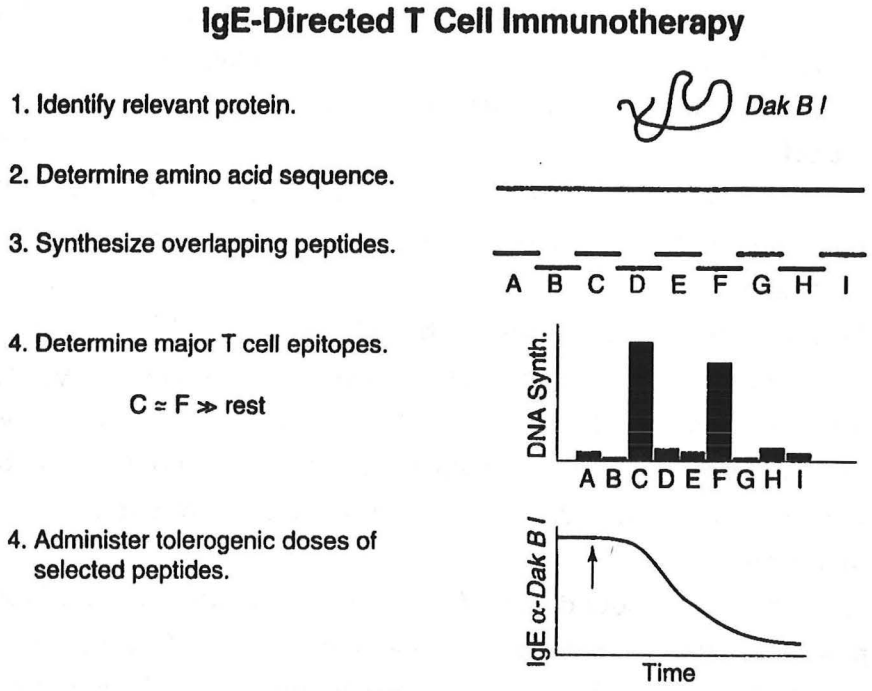

Figure 16: Summary of strategy employed to reduce allergen-specific IgE by administering relevant tolerogenic peptides.

In the future, it seems likely that a variety of less specific approaches will become available either to suppress the synthesis of IgE of all specificities or its ability to interact successfully with its high affinity receptor on mast cells and basophils. To the extent that these treatments are effective, then IgE-mediated food allergic responses may become subject to successful suppression.

Unproven therapies in food allergy - In a previous section of this review, diagnostic procedures that are without documented merit were presented. A number of therapeutic interventions advocated by physicians who use these approaches have

been recommended and have failed to demonstrate efficacy when subjected to rigorously controlled clinical studies by neutral third parties. Several of the more common are listed below:

1. The use of injected or orally administered food antigens (typically at very low dose) in order to "neutralize" the putatively offensive foods present in the diet is without scientific support.
2. The use of high dose vitamin therapy in an effort to reverse typically poorly characterized symptoms attributed to food allergy is similarly without substantial basis.
3. The use of "rotary diversified diets" involving the consumption of foods in a highly stylized rotating program has been advocated to avoid foods that are felt by some practitioners to be "suppressing" the immune system. This cumbersome intervention has not been demonstrated to be of benefit.
4. Similarly, reports related to the ability of salicylates and sucrose to cause attention deficit disorder in children have not stood up to rigorous testing.
5. The consumption of "natural foods" based upon their ability to boost immune responsiveness that has been purportedly suppressed by food additives has no merit. The potential for long term toxicity of additives remains a different issue, but suppression of normal immune function by commercially grown and/or processed foods has not been demonstrated.
6. The administration of low doses of histamine or serotonin to neutralize that produced by food ingestion or "chemical exposure" in routine daily activities lacks a scientifically meritorious foundation and has not been demonstrated to be effective.

Indeed, the majority of patients who are under the care for food allergy by practitioners advocating unproven practices are felt to suffer from psychiatric illnesses. The pattern of symptoms typically encountered is shown below:

Symptoms attributed to food allergy in patients without objectively confirmable organic food hypersensitivity[1]

Lethargy, tiredness, being vaguely 'not well'
Sleep disturbance, daytime or post-prandial drowsiness
Head, abdominal, chest, joint and muscle pains
Nausea, abdominal swelling and/or discomfort; constipation and/or diarrhoea
Breathlessness, palpitations, dizziness, lightheadedness, faints
Parasthesiae, itching or burning skin, peripheral 'swelling'
Poor concentration, disorientation, loss of memory and/or confidence
Depression, irritability, mood swings, panic attacks, agoraphobia
Disturbed sexual function

[1] 19 patients, with an average of more than 6 presenting complaints each.

References

Note: An outstandingly referenced chapter related to food allergy was written in 1993 by Dr. Hugh Sampson. It is chapter 66 of *Allergy - Prinicples and Practice* (eds. Middleton, Reed, Ellis, Adkinson, Yunginger and Busse). What follows recommendations for additional reading in textbooks are Dr. Sampsons categorized references to the pivotal papers representing the body of work that forms the basis this grand rounds.

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Appendices

Foods rich in histamine (μg/g)	
Fermented cheeses	up to 1330
Fermented drinks (wine)	20
Fermented foods	
sauerkraut	160 mg/kg (a portion of 250 g = 40 mg)
Dry pork and beef sausage	225
Pig's liver	25
Tinned tuna	20
Tinned anchovy fillets	33
Tinned smoked herring's eggs	350
Tinned foods	from 10 to 350
Meats	10
Vegetables	traces
Tomato	22
Spinach	37.5
Deep-frozen fish	1
Fish, fresh shellfish	0.2
Fish:	
tuna	5.4
sardine	15.8
salmon	7.35
anchovy fillets	44

Foods rich in tyramine* (μg/g)	
French cheeses:	
Camembert	20–86
Brie	180
Gruyère	516
Cheddar	1466
Roquefort, hung game	High but variable
Brewer's yeast	1500
Soused herrings	3030
Chianti	25

Chocolate contains methyltyramine

Some examples of foodborne toxins or toxin-producing organisms, excluding plant foodstuffs

Pathogen or toxin	Principal symptoms	Common food source	Reference
Bacillus cereus	(a) Diarrhoea	Proteinaceous food vegetables, sauces, puddings	Lund (1990)
	(b) Vomiting	Fried rice	Lund (1990)
Bacillus subtilis	Vomiting, diarrhoea, flushing, sweating	Meat & pastry, meat/seafood with rice	Lund (1990)
Bacillus licheniformis	Diarrhoea	Cooked meat and vegetables	Lund (1990)
Clostridium botulinum	Neuroparalytic disease (botulism)	Meat, fish, vegetables hazelnut conserve	Lund (1990)
Clostridium perfringens	Diarrhoea, abdominal pain	Meat, poultry	Lund (1990)
Salmonella enteridis	Diarrhoea, abdominal pain, fever, vomiting	Poultry, eggs	Coyle *et al.* (1988) Baird-Parker (1990)
Staphylococcus aureus	Vomiting, abdominal pain, diarrhoea	Numerous, but especially cooked high-protein foods	Tranter (1990)
Verotoxin-producing *Escherichia coli*	Haemorrhagic colitis	Ground beef	Sekla *et al.* (1990)
Listeria monocytogenes	Listeriosis	Unpasteurised cheese, undercooked meat	Linnan *et al.* (1988) Schwartz *et al.* (1988)
Dioxins and dibenzofurans	Adverse effects uncertain when consumed in quantities found in food	Fish	Svensson *et al.* (1991)
Cantharidin	Sensitivity to urethra and genitalia; priapism	Frogs which have Meloidae (blister beetles)	Eisner *et al.* (1990)
Methyl mercury	Brain damage	Fish, bread	Clarkson (1990)
Toxic alkaloid (saxitoxin) in dinoflagellates and plankton	Diverse neurological disorders (paralytic shellfish poisoning)	Clams, oysters, scallops and mussels	Morgan & Fenwick (1990) Mills & Passmore (1988)
Brevetoxins	Paraesthesia, abdominal pain, diarrhoea, transient blindness, paralysis, death (neurotoxic shellfish poisoning)	Clams, oysters, scallops and mussels	Scoging (1991)
Ciguatera toxin	Diverse gastrointestinal and neurological disorders	Fish (especially reef predators)	Morgan & Fenwick (1990) Ruff (1989) Hashimoto *et al.* (1969)
Tetrodotoxin	Diverse gastrointestinal and neurological disorders	Puffer fish, certain newts	Scoging (1991) Mills & Passmore (1988)
Domoic acid	Vomiting, diarrhoea, hyperexcitation, seizures, memory loss (amnesic shellfish poisoning)	Mussels	Scoging (1991) Teitelbaum *et al.* (1990) Perl *et al.* (1990)
Okadaic acid, dinophysis toxins, yessotoxin, pectenotoxins	Diarrhoea, vomiting, abdominal pain (diarrhoetic shellfish poisoning)	Mussels, scallops	Scoging (1991)
Scombrotoxin (usually histamine)	Headache, palpitations, gastrointestinal disturbance	Mackerel, tuna and related species	Morrow *et al.* (1991) Morgan & Fenwick (1990) Taylor *et al.* (1989) Gilbert *et al.* (1980) Arnold & Brown (1978)
Tetramine (red whelk poisoning)	Diplopia, dizziness, leg pains	Whelks	Black *et al.* (1991) Reid *et al.* (1988)
Grayanotoxins (in honey from areas of Turkey where Rhododendrons are grown)	Hypotension, bradycardia, vomiting, sweating	Honey	Yavuz *et al.* (1991)
Unknown (? in algae) (turtle flesh poisoning)	Cardiorespiratory failure, death	Turtles	Chandrasiri *et al.* (1988)

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