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FOOD INTOLERANCE

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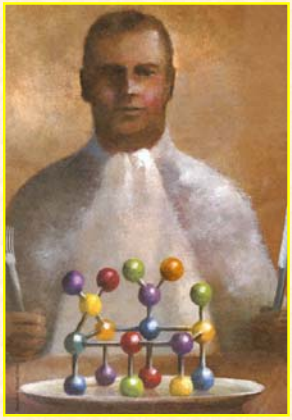
OBJECTIVES

- Understand what is meant by a food intolerance (FI)
- Understand how food additives can lead to a FI response
- Appreciate why gut dysbiosis increases the likelihood of a FI
- Learn how to manage food intolerances



"What is food to one man may be fierce poison to another"

Lucretius circa 75BC
(Roman Poet)

Adverse Food Reactions – a battle of definitions

- **Food allergy (2% of population)**
- **False food allergy**
- **Food intolerance (20%)**
- **Food sensitivity**
- **Food aversion**

A battle of definitions

- **Food allergy** – adverse reaction to food where immune system is involved
- **False food allergy –** Non-immunological mast cell stimulation through foods
- **Food intolerance –** Any adverse reaction to food where the involvement of the immune system is unproven
- **Food sensitivity –** umbrella term for food allergy, food intolerance etc. (non-psychological)
- **Food aversion –** avoidance of food for psychological reasons
- (Brostoff J and Gamlin L. Food allergy and intolerance. 1998; p. 8f)

False Food Allergy

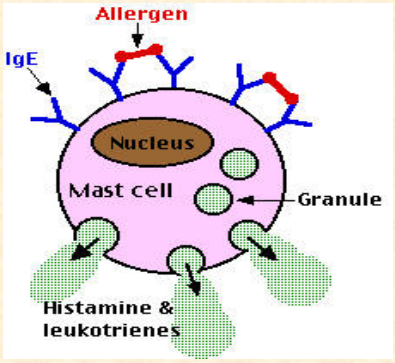
Direct mast cell triggering to release histamine through lectins, peptides etc.

False food allergy

- **Lectins** - Legume family: peanuts, beans, peas and lentils (histamine release through lectins)
- **Peptides** binding to mast cells: in egg white, strawberries, crustacean shellfish such as prawns, shrimp, crabs, lobster, tomatoes, fish, pork, alcohol and chocolate
- **Proteinase:** Pineapple and papaya
- **Unknown mechanism:** Buckwheat, sunflower seeds, mango and mustard

Food Allergy - IgE

- In classical allergy, IgE is produced in response to an otherwise innocuous antigen, such as a food molecule
- IgE antibodies are usually found on the surface of mast cells



Food allergy – anaphylaxis

- Typically:
- Immediate within 15 minutes
- Potentially very severe reaction
- To tiny amounts of a certain food, eg. nuts.

Food Intolerance

Food Intolerance

- Prevalence – very difficult to assess
- Probable range 10-25 % of population
- Any age
- Reaction can occur hours to days later
- Enzyme deficiency (genetic mutation) or immune responses caused by food specific IgG antibodies due to leaky gut.
- Wide range of symptoms affecting many parts of body/organ systems:
- (Brostoff J and Gamlin L. Food allergy and intolerance. 1998)

Food Addiction/Withdrawal Phenomenon

- Balance between food antigen and IgG Ab complexes.
- Less antigen means large complexes therefore more inflammation
- Therefore – food craving => eat and get small complexes, less reaction
- If avoid 4-6 weeks, less antigen and antibody – less craving and reaction gone.

Food intolerances and craving

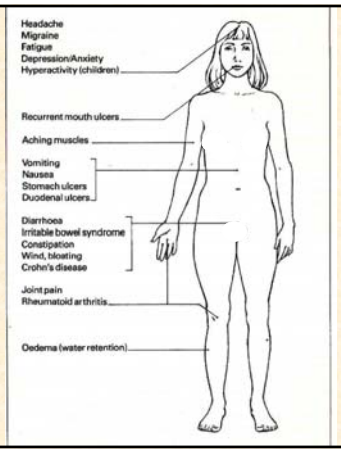
- Somewhat surprising to find that patients with food intolerances often (50%) crave the foods they are intolerant of. → eaten frequently
- Opiates – endorphins
- ***Exorphins:*** foods broken down through digestive enzymes can mimic endorphins.
- In laboratory, these have been produced from milk, wheat, maize and barley, using human digestive enzymes.
- Human effect antagonized by naloxone
- Effects: addictive – euphoric
- Speculate: withdrawal symptoms
- (Brostoff J, Gamlin L, Food allergy and intolerance, 1998; p. 250ff)

Food Intolerance

Majority develop because of:

- Poor digestion
- Dysbiosis
- Candidiasis
- Parasites
- Intestinal infections
- Poorly balanced diet
- alcohol consumption
- Effects of drugs and medications

Symptoms of food intolerance



Symptoms and Signs of Food Intolerance in Children

- asthma, eczema, recurrent otitis media, ADHD +/-, behavioural and learning problems, fatigue, abdominal pain
- Most common offending foods are:

  eggs, milk, nuts, soy, fish, corn and wheat

Common substances involved in non-immune mechanisms of FI

- Lactose and other dissacharides
- Biogenic amines (histamine and tyramine)
- Salicylates
- Preservatives such as sulfites, benzoates, BHT/BHA
- MSG
- Artificial Colouring especially tartrazine
- Janice Vickerstaff Joneja, PhD: Dietary Management of Food Allergies and Intolerances

Plus Common Foods Like:

- Gluten: wheat, oats, barley, rye, triticale

=> gliadinomorphin

- Cow's Milk: protein casein

⇒Casomorphin

- Fish, nuts, seafood, soy

(American College of Allergy, Asthma and Immunology)

Tyramine Intolerance

- Vasoactive amine
- Those sensitive are:
  - taking certain medications,
  - suffer from migraine headaches,
  - suffer from chronic urticaria

Tyramine Intolerance Symptoms

- Pruritis
- Feeling hot
- Flushing of skin
- Sweating
- Chills
- Clamminess
- Lightheadedness
- Hives

Natural Sources of Tyramine

- Aged cheeses, avocado, banana, beer, wine, chicken liver, eggplant, fermented beverages, raspberry, red plum, tomato, vinegar and pickles, wines (esp red), yeast extract, broadbeans, sauerkraut

Migraine – tyramine

- Normally, tyramine ingested in the diet is metabolized by monoamine oxidase in the gut and liver and conjugated by enzymes.
- Patients with dietary migraine have a presumed deficiency in monoamine oxidase and conjugating enzymes, permitting tyramine to be absorbed from the gut into the circulation.
- A vasoconstrictor effect may result, primarily by release of norepinephrine from sympathetic nerve endings.
- (Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003;28:9-15.)

Histamine Intolerance

- Produced by action of histidine decarboxylase (HDC) on aa histidine
- HDC made by bacteria in the large bowel
- Extrinsic histamine: fish and shellfish guts (2x q20min) => not allergy
- Cheese, alcohol, vinegar, sauerkraut, soy sauce, processed meats (all microbial fermentation products).
- Citrus fruits, strawberry, raspberry, tomatoes, apricot, cherry, plums, eggplant, pumpkin all have histamine present naturally.

How much histamine is excessive?

- Threshold depends on:
- Genetic origin – defect in catabolism HMT (histamine methyltransferase) and DAO (diamine oxidase)
- Disease –cirrhosis, viral liver diseases
- Physiological conditions
- Medications – first pass liver

Symptoms of Histamine Excess

- Pruritis (skin, eyes, ears, nose)
- Urticaria
- Angioedema
- Hypotension
- Tachycardia
- "Panic attack"
- Chest pain
- Nasal congestion
- Coryza
- Headache
- Fatigue, confusion, irritability
- Abdominal pain

Management

- Reduce histamine-releasing events
- Avoid consumption of histamine-containing and histamine releasing foods and food additives

Salicylate Intolerance

- 5% of population
- 25% of persons sensitive to ASA also react adversely to azo dye tartrazine.
- Depends on dose
- ? no strong link between ASA sensitivity and salicylate sensitivity
- Found in fruit, veg, herbs, spices and condiments, nuts and seeds.
- Depends on method of farming, type and length of storage.

Salicylate Intolerance

- Unknown exact mechanism of action
- "drug-like effect" on nasal membranes and skin

Salicylate Intolerance Symptoms

- Puritis, rash, hives
- SOB, cough, wheezing
- HA, fatigue, hyperactivity
- Lack of concentration
- Sinusitis, congestion
- Stomach upset
- Swellings of hands, feet and face
- ?ADHD, ADD (Feingold Association)

Management Suggestions

- Avoid unripened fruit and veg
- All fruit and veg should be ripe and thickly peeled
- Avoid outer leaves of leafy veg
- Food lists

Benzoate Intolerance

- Benzoic acid (BA) and sodium benzoate are used to prevent spoilage by microorganisms
- Occur naturally in foods: most berries, prunes, tea, cinnamon, nutmeg, clove and anise, cherry bark and cassia bark.
- Go to liver => + glycine => excreted 100% as hippuric acid
- Benzoyl peroxide used for bleaching =>BA

Benzoate builds up in the gut lumen

- Occurs when
  - Liver detoxication mech. is compromised,
  - Deficiency in pantothenic acid or glycine

CAUSING: intestinal dysbiosis and weakened mucosal epithelium

Benzoate Intolerance

- Persons sensitive to ASA or suffer from atopic allergies are particularly vulnerable to benzoate sensitivity
- Symptoms: asthma, urticaria, angioedema, headaches, (possible erythema multiforme)

Management

Avoid:

- Natural sources of benzoic acid, processed foods, bleached flour, products containing hydrolysed lecithin: margarine, salad and cooking oils, frozen desserts, chocolate, baked goods.

Sulfite Intolerance

- Sulfur dioxide, sodium bisulfite, sodium (hydrogen) sulphite, sodium metabisulphite, and other sulphites - applied to:
- Dried fruit usually treated with sulphur dioxide – no need for labelling (if no SO2 – 'unsulphured')
- Also used in alcoholic drinks (not labeled), potatoes, apples, coconut, grape juice, some vinegars, frozen pizza dough, fish, glace fruits, restaurant/take-away foods, packaged foods.
- occur naturally
- (Brostoff J, Gamlin L. Food allergy and intolerance. p. 313.)

Sulfite Intolerance

Sulfiting agents are used to:

- Prevent oxidation and browning of light-colored fruits and vegetables such as apples and potatoes
- Prevent black spots on shrimp and lobster
- Control microbial growth in fermenting beverages such as wine
- Prevent decomposition by hindering the growth of bacteria
- Preserve flavor
- Prevent spoilage
- Bleach food starches
- Stabilize and maintain the potency of medications

Sulfite Toxicology (2 pathways)

- 1% of population
- Sulfites + water = SO2 (irritates airways)
- hapten eliciting IgE response
- sulfite oxidase deficiency prevents sulfate formation from sulfite.
- Symptoms of sulfite sensitivity include bronchospasm, wheezing, chest tightness, flushing, hypotension, N/V/D, dysphagia, dizziness, LOC
- urticaria, angioedema, abdominal pain, seizures and anaphylactic shock resulting in death

Sulfite Intolerance

- Sulfites can trigger asthma
- In steroid-dependent asthmatic children, the prevalence has been found to be 20%.
- Reactions to sulfites can vary from mild to severe and even fatal bronchospasm in about 5% to 10% of patients with asthma.
- Sensitivity to sulfites is found more often in women than in men

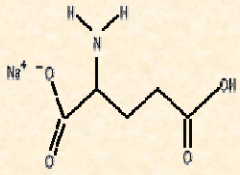
Management

- give asthmatics a food list
- molybdenum deficiency (200 micrograms/d)
- Vit B12 (1-3 grams/day)
- avoid cabbage, garlic, onions, eggs, legumes and brussel spouts.

Monosodium Glutamate – MSG

Synonyms:

- Sodium glutamate,
- MSG,
- L-glutamic acid,
- monosodium salt
- Hydrolyzed vegetable protein
- Autolyzed yeast
- Whey protein



MSG

- Monosodium glutamate is added to many foods as a flavor enhancer.
- It is ubiquitous in processed foods,
- It is found in frozen foods, canned soups, salad dressings, processed meats, sauces, and snack foods.
- Occurs naturally in tomato, mushrooms and cheese

MSG Intolerance

- Some asthmatics may have serious reactions to MSG
- Headaches generally appear within 15-60 minutes after ingesting relatively large amounts of MSG.
- MSG is a potent vasoconstrictor, and a vascular basis for the symptoms appears most likely.

MSG Symptoms

- The term *Chinese restaurant syndrome* was coined after a report associated Chinese food with headache and a group of symptoms, including flushing, paresthesias, sweating, palpitations, weakness and facial swelling, neck ache, blurred vision, N/V, tachycardia, rigors, asthma, depression, irritability, slurred speech, water retention, paranoia.

Management

- Educate Asthmatics
- Ask, ask, ask
- Trisalts
- Check labels
- Vit B6

Tartrazine Intolerance

- Tartrazine (Yellow No. 5) is an approved azo dye present in many food products and even drugs (!)
- Tartrazine sensitivity is most frequently manifested by urticaria and asthma.
- Mechanism of action unknown

Tartrazine Intolerance

- Cross-sensitivity in aspirin-sensitive and NSAID-sensitive patients may also occur.
- Azo dyes in general have been implicated in accentuating hyperkinetic syndromes in children.

- (Dipalma JR. Tartrazine sensitivity. Am Fam Physician. 1990; 42: 1347-50.)

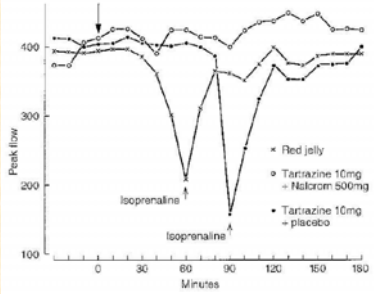


Figure 8.23 **The record of PEF in a woman with late onset asthma.** PEF fell after red jelly containing tartrazine and after tartrazine preceded by placebo, but was prevented by pre-treatment with Nalcrom.

(Reprinted from Wraith DG. Asthma and rhinitis. Clin Immunol Allergy 1982;2:101-12, with permission)

Management

- Hyperactivity in children => 6-week open trial of a diet free of synthetic food coloring. Behavioral improvement with the diet
- Less irritable and restless, corrected sleep disturbance.
- Therefore avoid commercial pre-made foods

Rowe KS, Rowe KJ. Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study. J Pediatr. 1994; 125: 691-8.

Aspartame

- Marketed under the popular names NutraSweet, Equal, Spoonful and Equal-measure.
- Found in many sugar-free candies, gums and soft drinks
- Aspartame is made up of three chemicals, aspartic acid, phenylalanine and methanol
- Digestion: methanol → formaldehyde

Aspartame and migraine

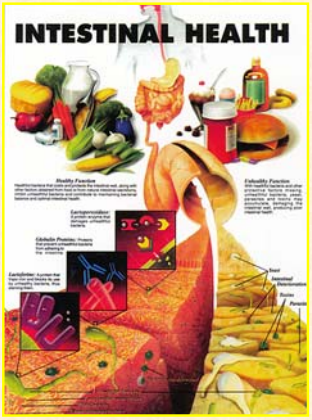
- migraine, epilepsy, and neuropsychiatric problems.
- *'The evidence is in favor of aspartame as a significant trigger of headaches in migraine, especially when the exposure is prolonged.'*

- (Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003; 28: 9-15.)

For food intolerance:

1) Elimination of offending foods.

2) Intestinal health with optimal detoxication function achieved through an excellent diet and corrective measures where imbalances exist.



The Immune Barrier

- Throughout length of small intestine => GALT or MALT=>sIgA => (?def or high antigenic load)
- Gut is the largest immune organ containing over 60% of the cell mass of the immune system
- Complex relationship between intestinal hyperpermeability and adverse food reactions => increasing IgG1 and 4

Honor thy symbionts

- ability to break down otherwise indigestable plant polysaccharides, biotransformation of conjugated bile acids, degradation of dietary oxalates, and synthesis of certain vitamins.
- so we become tolerant of a wide variety of microbial antigens.
- appears to reduce allergic responses to food or environmental antigens.
- (Jian Xu and Jeffrey I. Gordon; Honor thy symbionts. PNAS; 2003; 10452–10459.)

"Welcome to - the leaky gut"

Contribution to gut dysbiosis - **hypochlorhydria**

- Reduced stomach acid
- ?significance of PPIs/antacids
- Leads to reduced breakdown of proteins in stomach (→ ?allergy/intolerance)
- Failure to inactivate yeast (→ ?fungal type dysbiosis)
- failure to inactivate pathogenic bacteria (→ ? bacterial type dysbiosis – small bowel bacterial overgrowth)

Causes of small intestinal **bacterial** overgrowth (SIBO)

- Hypochlorhydria or drug induced hypoacidity
- Crohn's disease
- Diabetes (20-40% of Diabetics with chronic diarrhoea)
- SLE, Scleroderma
- Chronic pancreatitis
- Giardiasis and other parasitic infections
- Malnutrition
- Reduced motility in elderly patients, weight loss in elderly (significant problem)

Other causes of gut dysbiosis

- Antibiotic use (NB. Single course of antibiotics probably not enough to cause significant gut dysbiosis)
- Radiation treatment
- Surgery
- Stress
- Alcohol

Types of 'gut dysbiosis'

- Bacterial dysbiosis (e.g. bacterial overgrowth in small or large intestine)
- Parasitic infections
- Fungal type dysbiosis (controversial!)

Gut Dysbiosis

Signs and Symptoms

- "IBS-like", bloating, flatulence, D/C, undigested food in stools, food sensitivities, dyspepsia, fatigue, rashes, myalgias, arthralgias
- compromised digestion and absorption
- vit B, iron and calcium deficiencies

Gut Dysbiosis

Treatment and Prevention:

- Look at diet (sugar intake!)
- prescribe probiotics with antibiotics

The 4 R approach

- **Remove:** bacteria, viruses, fungi, parasite, allergens and toxins
- **Replace:** pancreatic enzymes, HCl, intrinsic factor
- **Reinoculate:** probiotics
- **Repair:** prebiotics, diet, supplements

How to diagnose food intolerance?

Complete list of reliable laboratory tests for food intolerance

-
-
-
-
-

Only reliable test for food intolerance

Elimination diet and reintroduction

- Caveat: not for 'true' food allergies, because of the risk of anaphylactic reactions
- Phenomenon of 'masking' and 'unmasking'

Unreliable laboratory tests or investigations for food intolerance

- RAST, Skin prick does not work in food intolerance (non-immunologic)
- 'Alternative blood tests' probably not reliable
- 'Fringe medicine tests' very problematic (kinesiology, VEGA, etc.)
- **BUT – IgG subclasses can be helpful**

Management of Food Intolerance

- Elimination diet – one or multiple foods
- Rotation diet
- Confirm with provocation

Management of Food Intolerance

- Eliminate/avoidance => desensitize the body => withdrawal first
- Abdiction model *(Claudia Miller)*
- 4 -5 day Rotation diet of very unusual foods 30 days later or eliminate longer if reaction still
- **Note**: 1 teaspoon of unbuffered powdered vit C in a glass of water OR Alka Seltzer Gold

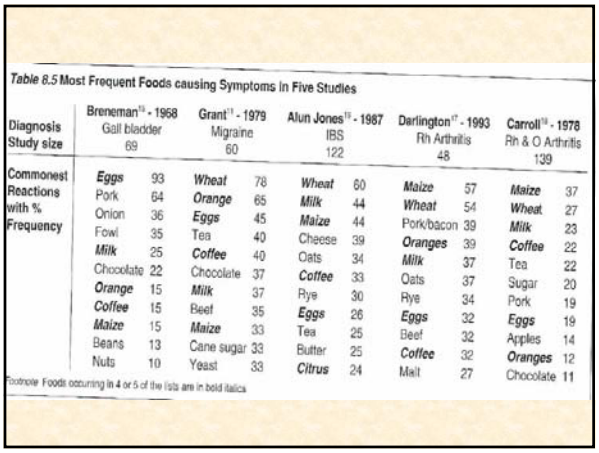


Table 8.5 Most Frequent Foods causing Symptoms in Five Studies

Diagnosis / Study size	Breneman[13] - 1968 Gall bladder 69		Grant[11] - 1979 Migraine 60		Alun Jones[15] - 1987 IBS 122		Darlington[17] - 1993 Rh Arthritis 48		Carroll[18] - 1978 Rh & O Arthritis 139	
Commonest Reactions with % Frequency	***Eggs***	93	***Wheat***	78	***Wheat***	60	***Maize***	57	***Maize***	37
	Pork	64	***Orange***	65	***Milk***	44	***Wheat***	54	***Wheat***	27
	Onion	36	***Eggs***	45	***Maize***	44	Pork/bacon	39	***Milk***	23
	Fowl	35	Tea	40	Cheese	39	***Oranges***	39	***Coffee***	22
	Milk	25	***Coffee***	40	Oats	34	***Milk***	37	Tea	22
	Chocolate	22	Chocolate	37	***Coffee***	33	Oats	37	Sugar	20
	Orange	15	***Milk***	37	Rye	30	Rye	34	Pork	19
	Coffee	15	Beef	35	***Eggs***	26	***Eggs***	32	***Eggs***	19
	Maize	15	***Maize***	33	Tea	25	Beef	32	Apples	14
	Beans	13	Cane sugar	33	Butter	25	***Coffee***	32	***Oranges***	12
	Nuts	10	Yeast	33	***Citrus***	24	Malt	27	Chocolate	11

Footnote Foods occurring in 4 or 5 of the lists are in bold italics

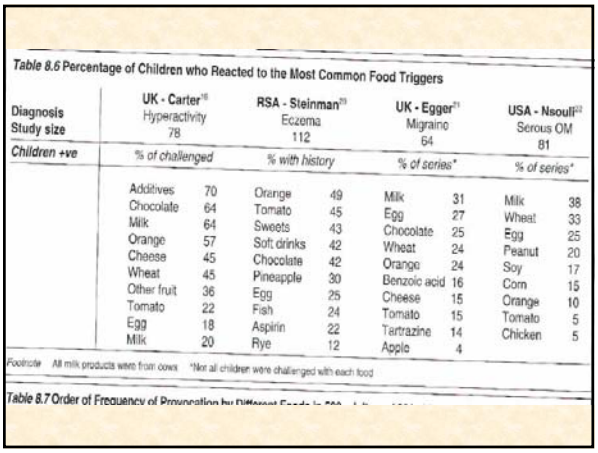


Table 8.6 Percentage of Children who Reacted to the Most Common Food Triggers

Diagnosis / Study size	UK - Carter[16] Hyperactivity 78		RSA - Steinman[20] Eczema 112		UK - Egger[21] Migraine 64		USA - Nsouli[22] Serous OM 81	
Children +ve	*% of challenged*		*% with history*		*% of series**		*% of series**	
	Additives	70	Orange	49	Milk	31	Milk	38
	Chocolate	64	Tomato	45	Egg	27	Wheat	33
	Milk	64	Sweets	43	Chocolate	25	Egg	25
	Orange	57	Soft drinks	42	Wheat	24	Peanut	20
	Cheese	45	Chocolate	42	Orange	24	Soy	17
	Wheat	45	Pineapple	30	Benzoic acid	16	Corn	15
	Other fruit	36	Egg	25	Cheese	15	Orange	10
	Tomato	22	Fish	24	Tomato	15	Tomato	5
	Egg	18	Aspirin	22	Tartrazine	14	Chicken	5
	Milk	20	Rye	12	Apple	4		

Footnote All milk products were from cows *Not all children were challenged with each food

Table 8.7 Order of Frequency of Provocation by Different Foods in [illegible]

Common Foods

Food intolerance in **IBS**

- Elimination diet relieved symptoms.
- **Milk, wheat, eggs and coffee** were most frequently identified to cause symptom exacerbation in IBS.

Exclusion diet and **IBS-** Manchester

- Diet excluding all foods to which they had raised IgG antibodies
- Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (p = 0.003).

- (W Atkinson, T A Sheldon, N Shaath, P J Whorwell. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004; 53: 1459–1464.)

Table 2 Frequency of foods excluded from the diet (% of patients)

Food	Treatment group	Sham group
Barley	26.7	9.3
Corn	22.7	14.7
Rice	8	54.7
Rye	8	25.3
Wheat	49.3	8
Milk	84.3	1.3
Beef	24	9.3
Chicken	21.3	13.3
Pork	5.3	36
Cabbage	12	24
Celery	5.3	21.3
Haricot bean	17.3	14.7
Pea	38.6	1.3
Potato	9.3	61.3
Soy bean	22.7	10.7
Tomato	4	44
Apple	1.3	33
Orange	6.7	29.3
Strawberry	0	20
Almond	28	12
Brazil nut	22.7	17.3
Cashew nut	49.3	8
Peanut	10.7	20
Walnut	2.7	29.3
Cocoa bean	1.3	21.3
Shellfish	21.3	10.7
Fish mix	17.3	28
Whole egg	57.3	26.7
Yeast	86.7	0

Food intolerance and **RA**

- elimination diet excluding milk, eggs, cereals and food additives
- Percentage of patients with severe pain decreased from 40% day and 44% night to 14% (day) and 0% (night) after 6 weeks. The number of painful joints was reduced from 20 to 14 after 6 weeks. There was significant decrease in the length of morning stiffness and increase in grip strength.
- ¾ of patients described themselves as 'better' or 'much better'.
- Average weight loss due to the diet was over 4.5 kgs.
- (Darlington, LG, Ramsey NW, Mansfield JR. Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. Lancet, February 1, 1986; 236-8)

Migraine

- Migraine patients reporting a particular food or drink as a precipitant varies from 7% to as high as 44% .
- prevalence of diet-related migraine varied with race: diet-related migraine prevalence was higher in white patients (61%) than in black patients (35%)
- Most commonly implicated foods are chocolate, cheese, citrus fruit, and alcoholic drinks.
- (Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003;28:9-15.)

Migraine – food intolerance

- Double-blind trial of an elimination diet in 88 patients treated with a diet that eliminates all but a few sensitizing food antigens.
- 93% with severe frequent migraine responded and were free of headaches.
- The diet consisted of lamb or chicken, rice or potato, banana or apple, Brassica, water, and vitamin supplements.
- **Cow's milk and cheese** caused headaches in most of the patients in the study, but none of the patients complained of headaches after substituting goat's milk cheese.
- (Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. Lancet 1983;2:865-9. Egger J, Carter CM, Soothill JF, Wilson J. Oligoantigenic diet treatment of children with epilepsy and migraine. J Pediatr 1989;114: 51-8.)

Summary food intolerance

- Probably quite common (?20% of population)
- Multiple symptoms in many organs/organ systems that often are considered 'psychogenic'
- Because of delayed reaction, 'masking', and even food craving, often not clear what the offending foods are
- Difficulties in making the diagnosis (controversial)
- Only reliable test exclusion diet and reintroduction (??but perhaps IgG)
- However: diagnosis and treatment also possible with a rotation diet.