

University of Minnesota



National Maternal Nutrition Intensive Course

Paper Presented July 14 2003

Breastfeeding and Risk of Infant Food Allergies



Janice M. Joneja, Ph.D., RD

Breast-feeding and Allergy

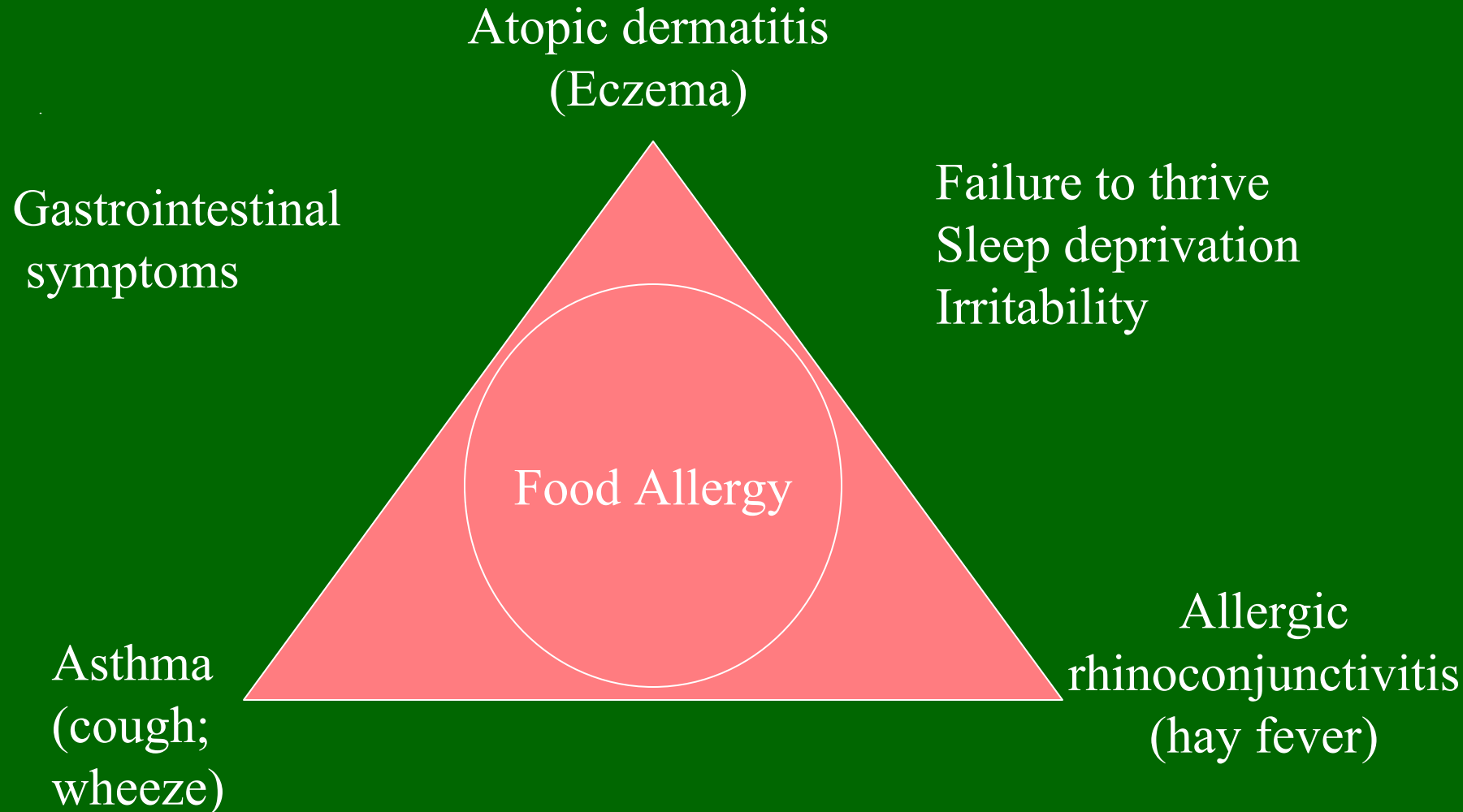
Studies indicating that breast-feeding is protective against allergy report:

- A definite improvement in infant eczema and associated gastrointestinal complaints when:
 - Baby is exclusively breast-fed
 - Mother eliminates food allergens from her diet
- Reduced risk of asthma in the first 24 months of life

Breast-feeding and Allergy

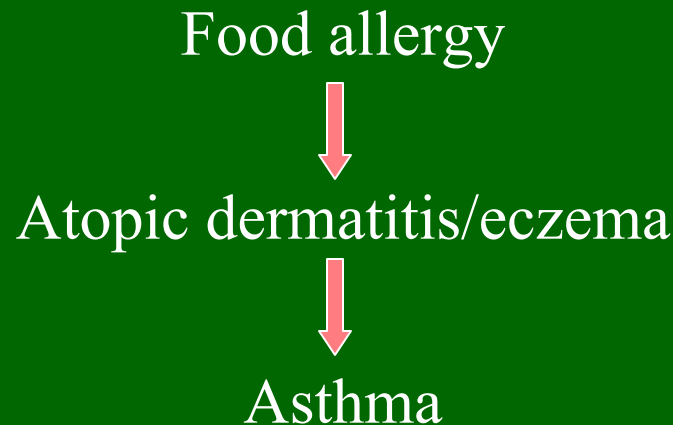
- Other studies are in conflict with these conclusions:
 - Some report no improvement in symptoms
 - Some suggest symptoms get worse with breast-feeding and improve with feeding of hydrolysate formulae
 - Japanese study suggests that breast-feeding increases the risk of asthma at adolescence
- What is the real story?

The Allergic Diasthesis




Perceived Risks Associated with Infant Food Allergy

- Anaphylaxis – may be life-threatening
- Nutritional insufficiency and failure to thrive
- Promotion of the “allergic march”:



Possible Confounding Variables in Studies and Subjects

- Variability in genetic predisposition of infant to allergy
- Mother's allergic history 
- Role of in utero environment and exposure to allergens
- Exclusivity of breast-feeding
- Inclusion of infant's allergens in mother's diet
- Dietary exposure not recognized in infant or mother
- Exposure to inhalant and contact allergens

Immune Response in Allergy

The Hypersensitivity Reactions:

Antigen Recognition

- The first stage of an immune response is recognition of a “foreign antigen”
- T cell lymphocytes are the “controllers” of the immune response
- T helper cells (CD4+ subclass) identify the foreign protein as a “potential threat”
- Cytokines are released
- The types of cytokines produced control the resulting immune response


T-helper Cell Subclasses


- There are two subclasses of T-helper cells, differentiated according to the cytokines they release:
 - Th1
 - Th2
 - Each subclass produces a different set of cytokines

T-helper cell subtypes

- Th1 triggers the *protective response* to a pathogen such as a virus or bacterium
 - IgM, IgG, IgA antibodies are produced ←
- Th2 is responsible for the *Type I hypersensitivity reaction (allergy)*
 - IgE antibodies are produced ←

Cytokines of the T-Cell Subclasses

- TH1 subclass produces:
 - » Interferon-gamma (IFN- γ) 
 - » Interleukin-2 (IL-2)
 - » Tumor necrosis factor alpha (TNF α)

- TH2 subclass produces:
 - » Interleukin-4 (IL-4) 
 - » Interleukin-5 (IL-5)
 - » Interleukin-6 (IL-6)
 - » Interleukin-8 (IL-8)
 - » Interleukin-10 (IL-10)
 - » Interleukin-13 (IL-13)

Does Atopic Disease Start in Fetal Life?

- In fetal life cytokines are skewed to the Th2 type of response
- Suggested that this may guard against rejection of the “foreign” fetus by the mother’s immune system
- IgE occurs from as early as 11 weeks gestation and can be detected in cord blood
- At birth neonates have low INF- γ and tend to produce the cytokines associated with Th2 response, especially IL-4
- So why do all neonates not have allergy?

Does Atopic Disease Start in Fetal Life? (continued)

- New research indicates that the immune system of the mother may play a very important role
- IgG crosses the placenta; IgE does not
- Certain sub-types of IgG (IgG1; IgG3) can inhibit IgE response
- Suggested that IgG anti-IgE antibodies suppress the Th2 response

Does Atopic Disease Start in Fetal Life? (continued)

- IgG1 and IgG3 are the more “protective” subtypes of IgG
- IgG1 and IgG3 tend to be lower than normal in allergic mothers
- In allergic mothers, IgE and IgG4 are abundant
- In mothers with allergy and asthma, IgE is high at the fetal/maternal interface
- Fetus of allergic mother may thus be primed to respond to antigen with IgE production


Significance in Practice

- Atopic mother's immune system may dictate the response of the fetus to antigens in utero
- Exposure to small quantities of food antigens from mother's diet thought to tolerize the fetus, possibly by means of IgG1 and IgG3, within a "protected environment"
- This is possibly true for the non-allergic mother
- The allergic mother's system may be incapable of this protection
- Current directive: the allergic mother should strictly avoid her own allergens

Example of Interaction of Cytokines

- Under certain circumstances Th2 cytokines (allergy) suppress Th1 cytokines (protection against infection)
 - Results in decrease in the level of immune protection against microorganisms
 - Infection by normally harmless bacteria can occur
- Clinical example:
 - In atopic dermatitis (eczema) the Th2 response in skin tissues suppresses the protective Th1, resulting in high potential for infection by normally harmless bacteria on the skin
- When Th1 predominates, Th2 is suppressed: the “hygiene theory” of allergy

The Neonate: Conditions That May Induce Th2 Response

- Inherited allergic potential (maternal and paternal)
- Intrauterine environment 
- Immaturity of the infant's immune system
- Inflammatory conditions in the infant gut (infection or allergy) that interfere with the normal antigen processing pathway
- Immaturity of the digestive mucosa leading to hyperpermeability (“leaky gut”)
- Increased uptake of antigens

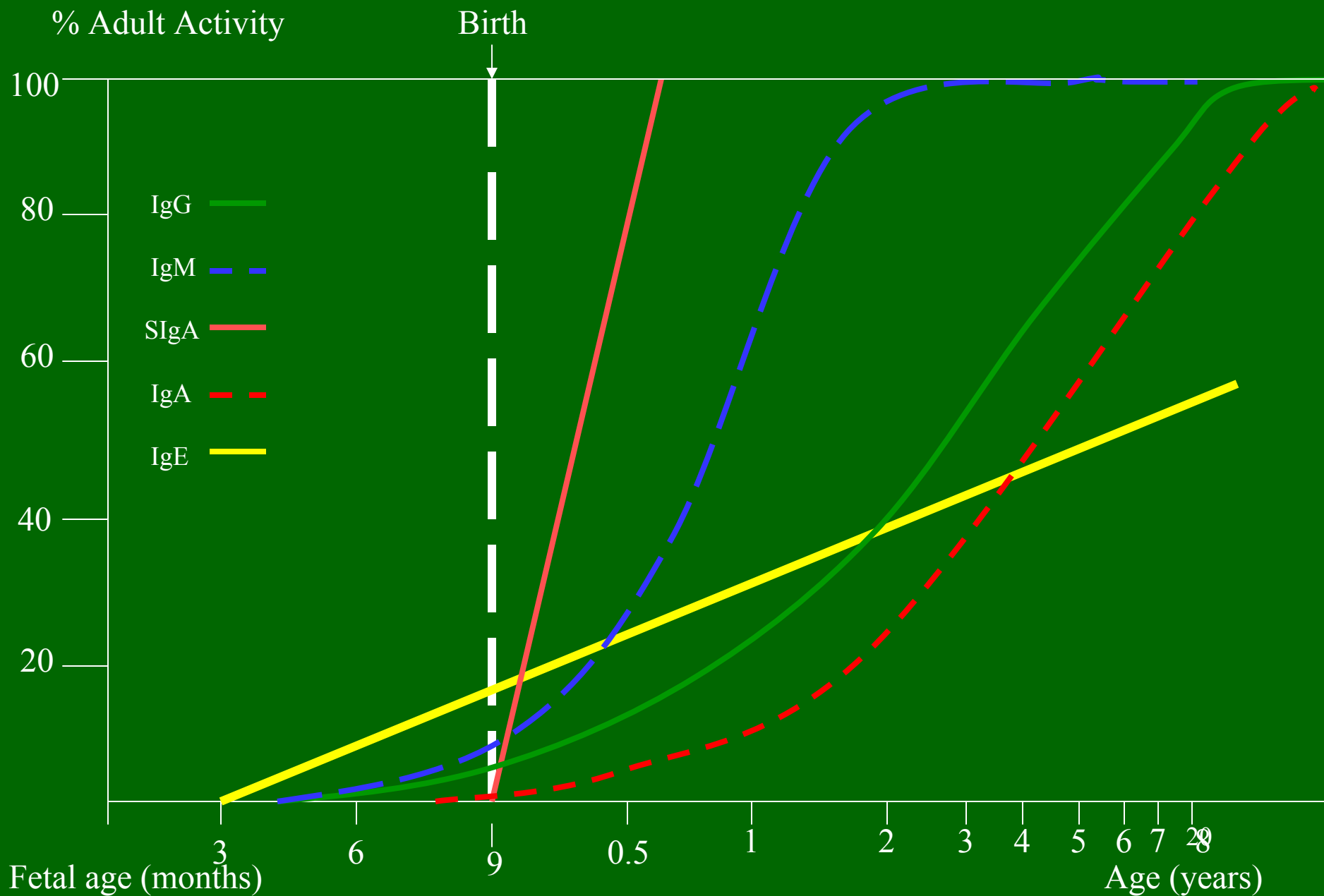
Immune System of the Normal Neonate

- Is immature
- Major elements of the immune system are in place
- But do not function at a level to provide adequate protection against infection
- The level of immunoglobulins (except maternal IgG) is a fraction of that of the adult

Immune System of the Normal Neonate

- Phagocytes can engulf foreign particles
- But their killing capacity is negligible during the first 24 hours of life
- The function of the lymphocytes is not fully developed
- Human milk provides the deficient components

Development of Immunocompetence with Age



Immunological Protection

- Agents in human milk:
 - Provide passive protection of the infant against infection during lactation
 - Mother's system provides the protective factors
 - Stimulate the immune system of the baby to provide active protection
 - Infant's own system makes the protective factors
 - The effects may last long after weaning

Characteristics of Protective Factors Provided by Breastfeeding

- Persist throughout lactation
- Resist digestion in the infant's digestive tract
- Protect by non-inflammatory mechanisms
- Stimulate maturation of the infant's immune system
- Are the same as at mucosal sites (e.g. in the lining of the digestive tract)
- Promote establishment of a protective microbial population in the infant's digestive tract

Immunoglobulins: Secretory IgA (sIgA)

- Antibodies in human milk are predominantly (>90%) secretory IgA (SIgA)
- They reflect mother's immune response to foreign antigens which encounter her body via mucous membranes
- Provide protection against potential pathogens in the environment
- Under “natural conditions” this is also the environment of the infant

Protective Action of sIgA

- Secretory piece protects the antibody from the action of digestive enzymes in the infant's intestinal tract
- sIgA remains immunologically active throughout the length of the infant's digestive tract
- Protects the infant from foreign antigens encountered by mother
- As long as mother and infant are together, infant is protected from pathogens in its environment

Immunoglobulins (Antibodies): IgG

- IgG is the only antibody transported across the placenta to protect the fetus in utero
- IgG is produced by the mother's immune system and reflects the exposure of the mother to potentially pathogenic antigens
- In humans there is minimal transportation of IgG to external secretions
- Human milk contains very little IgG

Immunoglobulins: IgG

- Provides protection of the infant for several months after birth
 - This is passive protection
- Maternal IgG is gradually removed from the infant's circulation as infant ages
- Infant produces its own IgG starting immediately after birth:
 - This is active protection

Immunological Factors in Human Milk that may be Associated with Allergy: Cytokines and Chemokines

- Atopic mothers tend to have a higher level of the cytokines and chemokines associated with allergy in their breast milk
- Those identified include:
 - IL-4 - IL-5
 - IL-8 - IL-13
 - Some chemokines (e.g. RANTES)
- Atopic infants do not seem to be protected from allergy by the breast milk of atopic mothers

Immunological Factors in Human Milk that may be Associated with Allergy: TGF- β 1

- Cytokine, transforming growth factor- β 1 (TGF- β 1) promotes tolerance to food components in the intestinal immune response
- TGF- β 1 in mother's colostrum may influence the type and intensity of the infant's response to food allergens
- A normal level of TGF- β 1 is likely to facilitate tolerance to food encountered by the infant in mother's breast milk and later to formulae and solids

Immunological Factors in Human Milk that may be Associated with Allergy: TGF- β 1 (continued)

- TGF- β 1 in mothers of infants who developed IgE-mediated CMA (+challenge; + SPT) *lower* than in:
 - Mothers of infants with non-IgE mediated CMA (+ challenge; - SPT)
 - Mothers of infants without CMA (- challenge; - SPT)

Immunological Factors in Human Milk that may be Associated with Allergy: SIgA

- TGF- β 1 seems to be involved in antibody class-switching to IgA
- Inhibits class switch to IgE
- Lower TGF- β 1 therefore might lead to lower sIgA, and thus less protection at the mucosal surface of the infant's digestive tract
- May result in sensitization to allergens in foods via increased IgE production
- Some studies show no evidence of lower SIgA in allergic infants

Significance in Practice

- Colostrum should be the first fluid encountered by the neonate, regardless of the atopic status of the mother
 - Provides sIgA as well as other protective and maturation factors
- Atopic mothers should avoid:
 - Their own allergens during pregnancy and lactation
 - In addition, the most highly allergenic foods during lactation, starting about 2 weeks prior to delivery

Significance in Practice (continued)

- Non-atopic mothers need not restrict their diet
 - exposure to small quantities of food antigens in breast milk should tolerize infant
- Exclusive breast-feeding for at least 4-6 months for infants with potential for allergy to avoid sensitization from external food allergens
- Non-atopic mother needs to avoid foods only if the infant has already been sensitized to them and demonstrates obvious signs of allergy

Fatty Acids and Allergy

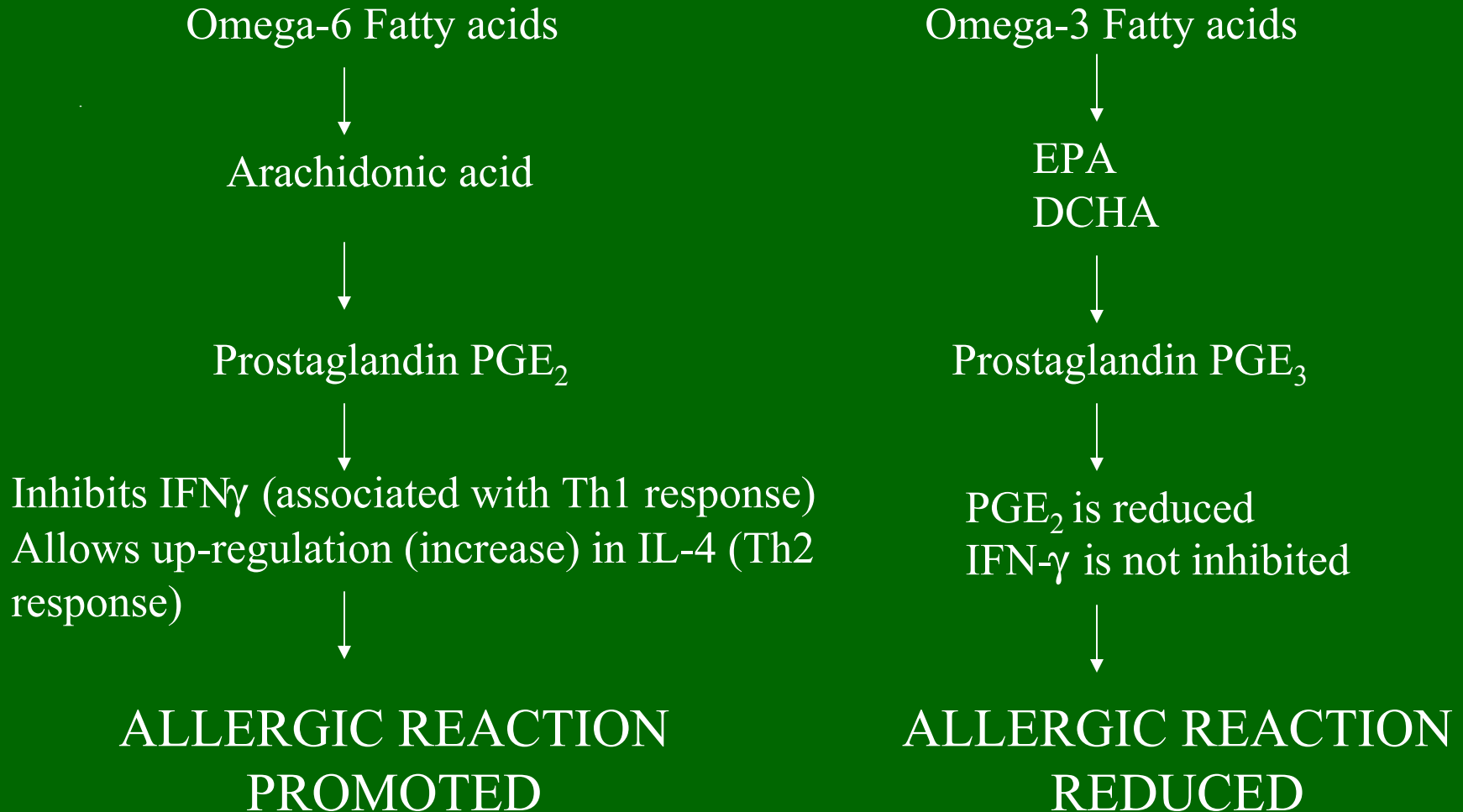


- Theory:
 - Linoleic acid (ω -6 FA) is a precursor of arachidonic acid
 - Arachidonic acid is the precursor of secondary inflammatory mediators, especially of the pro-inflammatory prostaglandin E_2 (PGE_2)
 - PGE_2 has a strong inhibitory effect on $IFN-\gamma$ and increases IL-4; thus promoting the Th2 (allergy) response

Fatty Acids and Allergy

- α -linolenic acid, EPA and DCHA are ω -3 fatty acids
- Are precursors to prostaglandins of the 3 series (PGE₃), which are less inflammatory than the 2 series
- Will tend to inhibit Th2 and thus promote Th1 (protective) activity
- Thus will down-regulate the allergic response
- Increased intake of fish should reduce allergy
- Old-fashioned idea of taking cod liver oil should help prevent allergy

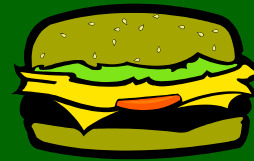
Fatty Acids and Allergy



Sources of ω -6 and ω -3 Fatty Acids

- ω -6 Fatty Acid Sources:

- Meats, especially red meat
- Milk and milk products, including butter, cheese, yogurt



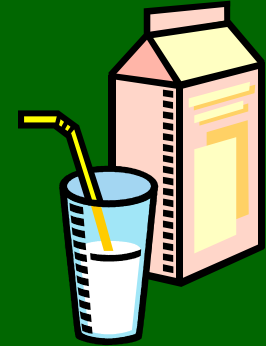
- ω -3 Fatty Acids

- α -linolenic acid:
 - Canola oil; Soy oil; Wheat germ oil;
- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DCHA):
 - Fish, especially oily fish
 - Salmon; Trout; Mackerel; Halibut
 - Cod and Halibut liver oils



Development of Allergy in Breast-Fed Infants:

Cow's Milk Allergy as a Model



- CMA tends to be the first food to elicit symptoms of allergy
- Usually cow's milk antigens are the first foreign proteins encountered by the infant
- Symptoms of CMA commonly appear during the first year of life
- In 75%-90% of allergic infants within the first month
- Symptoms appear within days or weeks after the infant's first exposure to cow's milk
- Incidence of CMA in breast-fed infants who have *never* been given cow's milk is reported 0.4%-0.5%

Diagnosis of Cow's Milk Allergy in the Breast-Fed Infant

- No laboratory tests have proven to be diagnostic of clinical disease
 - Skin prick tests (SPT) are reported as positive in about 45%-47% of infants with immediate-onset symptoms
 - SPT positive in only 17% with delayed-onset symptoms
 - Infants under 6 months may have immediate-onset symptoms on challenge, but SPT negative
 - SPT may become positive in second half of the first year
 - Some practitioners suggest skin-prick test with mother's breast milk as allergen

Diagnosis of Food Allergy in the Breast-Fed Infant

- Reliable diagnosis is based on elimination and challenge:
 - All sources of cow's milk or suspect food allergen protein are eliminated from the infant's and the mother's diet
 - Symptoms of allergy in the infant resolve
 - Identical symptoms occur during food challenge
 - Symptoms again disappear on elimination of all sources of the suspect food
 - In suspected CMA, lactose intolerance must be ruled out

Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Challenge is implemented two to four weeks after elimination of cow's milk or food allergen
 - Before feeding, place drop of the food on outer border of infant's bottom lip
 - Observe for 20 minutes for reddening, irritation
 - If irritation occurs do not give food by mouth

Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Cow's milk and other food challenges can be carried out directly by feeding the food to the infant in incremental doses:
 - Place a drop on the infant's tongue and monitor for symptoms for an hour
 - Feed small quantities at one hour intervals:
 - 2.5 mL ($\frac{1}{2}$ teaspoon)
 - 5 mL (1 teaspoon)
 - 10 mL (2 teaspoons)



Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Challenge via mother's breast milk
 - Mother consumes increasing doses of the suspect allergen at one-hour intervals:
 - 100 mL or ¼ cup
 - 200 mL or ½ cup
 - 400 mL or 1 cup)
 - Ad lib feedings of breast milk by the infant
 - Continues over the next day with free consumption of the food by the mother
- Double-blind Placebo-controlled food challenge (DBPCFC) is usually unnecessary in infants under one year of age

Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Symptoms can be caused by as little as 5mL cow's milk ingested by the mother
- Other foods may be more, or less, allergenic
- More commonly several hundred mLs are needed to elicit symptoms
- Symptoms usually occur 20 minutes to several hours after breast-feeding
- May appear only after accumulated doses on the second day

Suggested Sources of Sensitizing Food Allergens

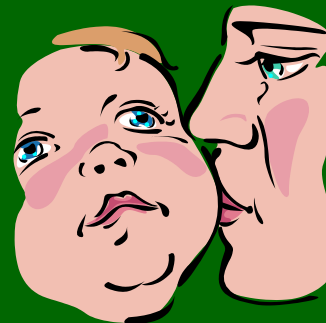
- Present thinking is that sensitization occurs predominantly from external sources
- The antigens in mother's milk then elicit symptoms in the previously sensitized infant
- However, new research suggests that sensitization via breast milk may occur in the atopic mother and baby pair: this remains to be proven

Suggested Sources of Sensitizing Food Allergens (continued)

- Suggested food sources of allergens:
 - Infant formulae, especially in the new-born nursery before first feeding of colostrum
 - Solid foods
 - Covertly by caretakers
 - Accidentally
- Inhalation of allergens

Suggested Non-Fed Sources of Sensitizing Food Allergens

- Through the skin (especially when eczema is present)
 - In eczema creams and ointments (especially peanut protein)
 - Milk proteins in non-food articles e.g. diaper rash ointment; paper coating; cosmetics; pet foods
 - Kissing on cheek after consumption of food e.g. milk; peanut butter
 - Skin prick tests



Summary of the Protective Effect of Breastfeeding on Development of Allergy

- Differing reports on the role of breastmilk in protecting against the development of allergy:
 - Food allergy; Eczema; Asthma; Rhinitis;
- May reflect the combined effect of inheritance and atopy in the mother
- Recent research seems to suggest that when the infant inherits atopy from the father, mother's breastmilk is protective against allergy
- When inherited from the mother, breastmilk is not protective against the development of allergy

Implications of Research Data

- Exclusive breast-feeding with exclusion of infant's known allergens will protect the child against allergy if it is inherited from the father
- Exclusive breast-feeding with exclusion of mother's and baby's allergens will reduce signs of allergy in the first 1-2 years
- Reduction or prevention of early food allergy by breast-feeding does not seem to have long-term effects on the development of asthma and allergic rhinitis

Foods Most Frequently Causing Allergy

1. Egg

» white

»yolk

2. Cow's milk

3. Peanut

4. Nuts

5. Shellfish

6. Fin fish

7. Wheat

8. Soy

9. Beef

10. Chicken

11. Citrus fruits

12. Tomato

Current Recommendations for Practice

- If mother is atopic:
 - Mother eliminates all sources of her own allergens during pregnancy to attempt to reduce IgE and IgG4 in the uterine environment
 - Continues to avoid her own allergens during lactation
 - Mother consumes adequate quantities of ω -3 oils, especially fish
 - if she is allergic to fish substitute soy oil, canola oil
 - Exclusive breast-feeding without exposure of infant to external sources of food allergens for 6 months

Current Recommendations for Practice (continued)

- If father is atopic, but mother is not:
 - No recommendations for mother to restrict her diet during pregnancy
 - No recommendations for mother to restrict her diet during lactation unless the baby shows signs of allergy
 - Exclusive breast-feeding for 4-6 months

Current Recommendations for Practice (continued)

- If infant demonstrates overt signs of allergy (eczema; gastrointestinal complaints; rhinitis; wheeze)
 - Identify specific food trigger by elimination and challenge
 - Exclusive breast-feeding with mother excluding her own and baby's food allergens
- Careful monitoring of mother's diet for nutritional adequacy, especially of vitamins and trace elements

Current Recommendations for Practice (continued)

- Allergic mother may need to avoid the most highly allergenic foods during lactation, even if she is not allergic to them:
 - Peanuts
 - Tree nuts
 - Cow's milk
 - Eggs
 - Shellfish
- Benefits of this remain to be proven, but at present the strategy is indicated and recommended