# Prevention of Food Allergy: From Pre-conception to Early Post-Natal Life

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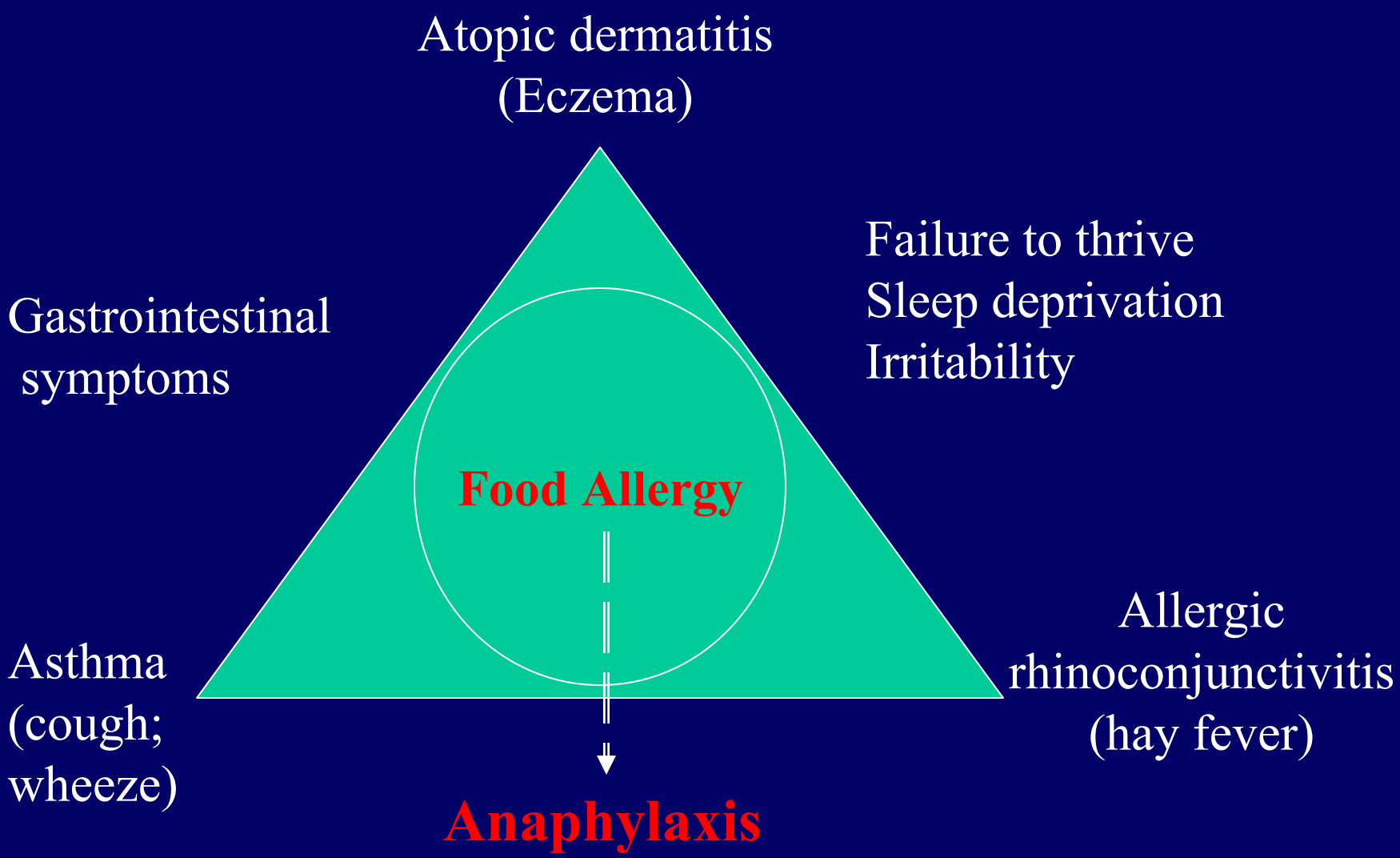
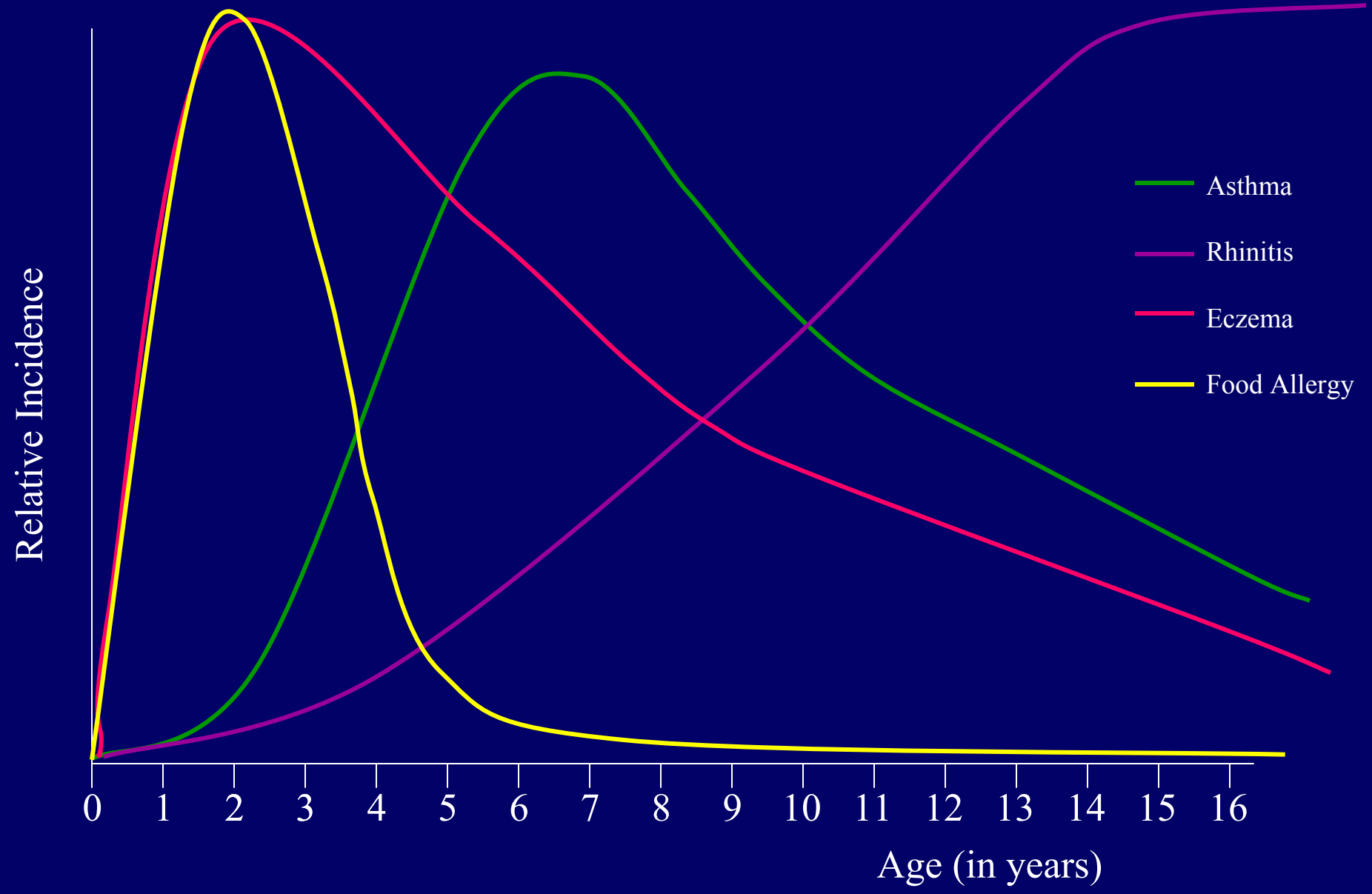
# The Allergic Diasthesis



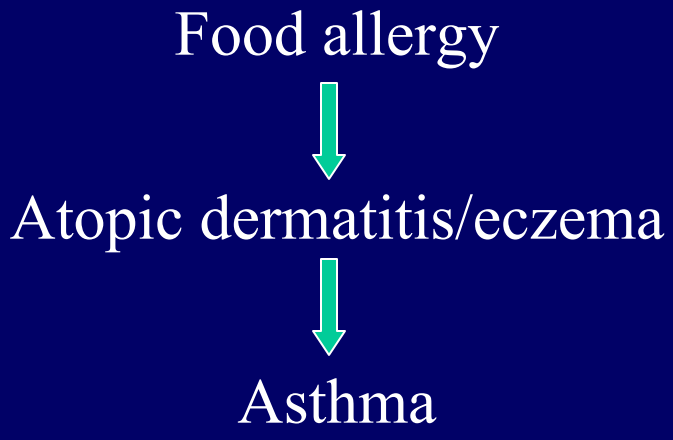
# Age Relationship Between Food Allergy and Atopy

{Adapted from Holgate et al 2001}



# Perceived Risks Associated with Infant Food Allergy

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



# Prevention of Food Allergy in Clinical Practice

Requirement:

- Practice guidelines for:
  - Prevention of sensitization to food allergens
  - Prevention of expression of allergy
- Consensus for practice guidelines using evidence-based research

Current status:

- Lack of consensus

# 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

# Cytokines of the T-Cell Subclasses

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

- 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)

# T-helper cell subtypes

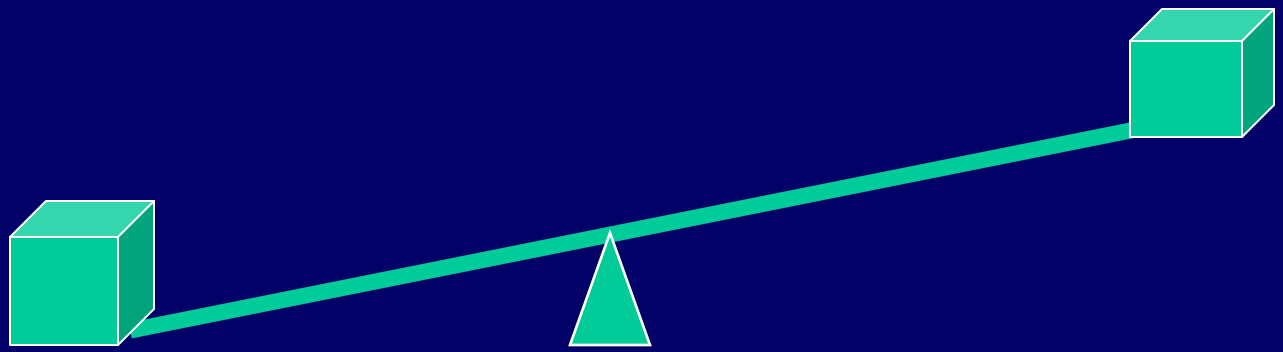
- Th1 triggers the ***protective response*** to a pathogen such as a virus or bacterium
  - IgM, IgG, IgA antibodies are produced
- Th2 is responsible for the ***Type I hypersensitivity reaction (allergy)***
  - IgE antibodies are produced

# TH1 ⟷ TH2 Interactions

Factors promoting:

Th1
- Bacterial and viral infections
- Maturation of the immune system
- Antigen tolerance

Th2
- Parasite infestations
- Immature immune system
- Sensitization to antigen



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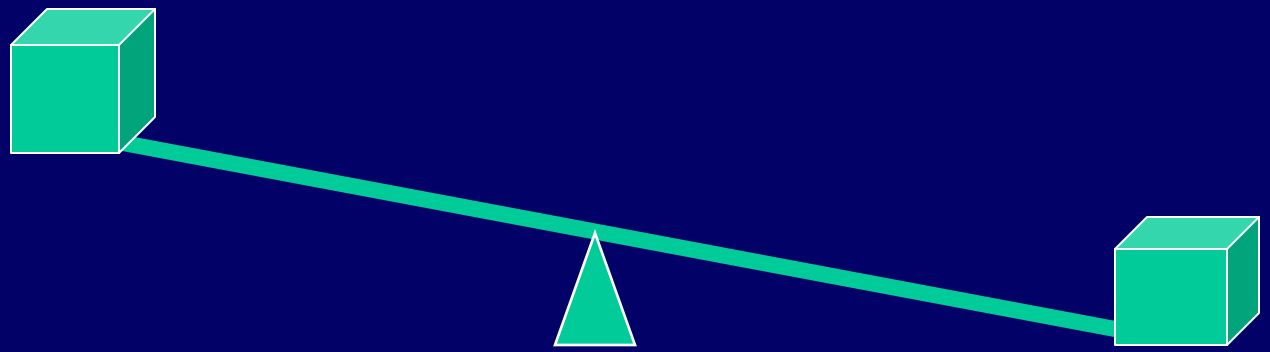


## Predisposing factors:

- Genetic inheritance
- Early exposure to allergen
- Increased antigen uptake

# Example of Interaction of Cytokines

- When Th1 predominates, Th2 is suppressed: the "hygiene theory" of allergy
- Conversely, 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

# Example of Interaction of Cytokines (continued)

- Clinical example:
  - In atopic dermatitis (eczema) the Th2 response in skin tissues suppresses the protective Th1
  - Increase in IL-4; decrease in INF- $\gamma$
  - Results in high potential for infection by normally harmless bacteria on the skin

# Does Atopic Disease Start in Fetal Life?

[Jones et al 2000]

- Fetal 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

# Does Atopic Disease Start in Fetal Life? (continued)

- 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

- Allergenic molecules demonstrated to cross the placenta and sensitize the fetus in utero
- Evidence that low dose exposure to food antigens tolerizes
- Exposure to small quantities of food antigens from mother's diet thought to tolerize the fetus, by means of IgG1 and IgG3, within a "protected environment"

# Significance in Practice continued

- Atopic mother's immune system may dictate the response of the fetus to antigens in utero
- The allergic mother may be incapable of providing sufficient IgG1 and IgG3 to downregulate fetal IgE
- However – there is no convincing evidence that sensitization to specific food allergens is initiated prenatally
- Current directive: the atopic mother should strictly avoid her own allergens

# The Neonate: Conditions That Predispose to Th2 Response

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

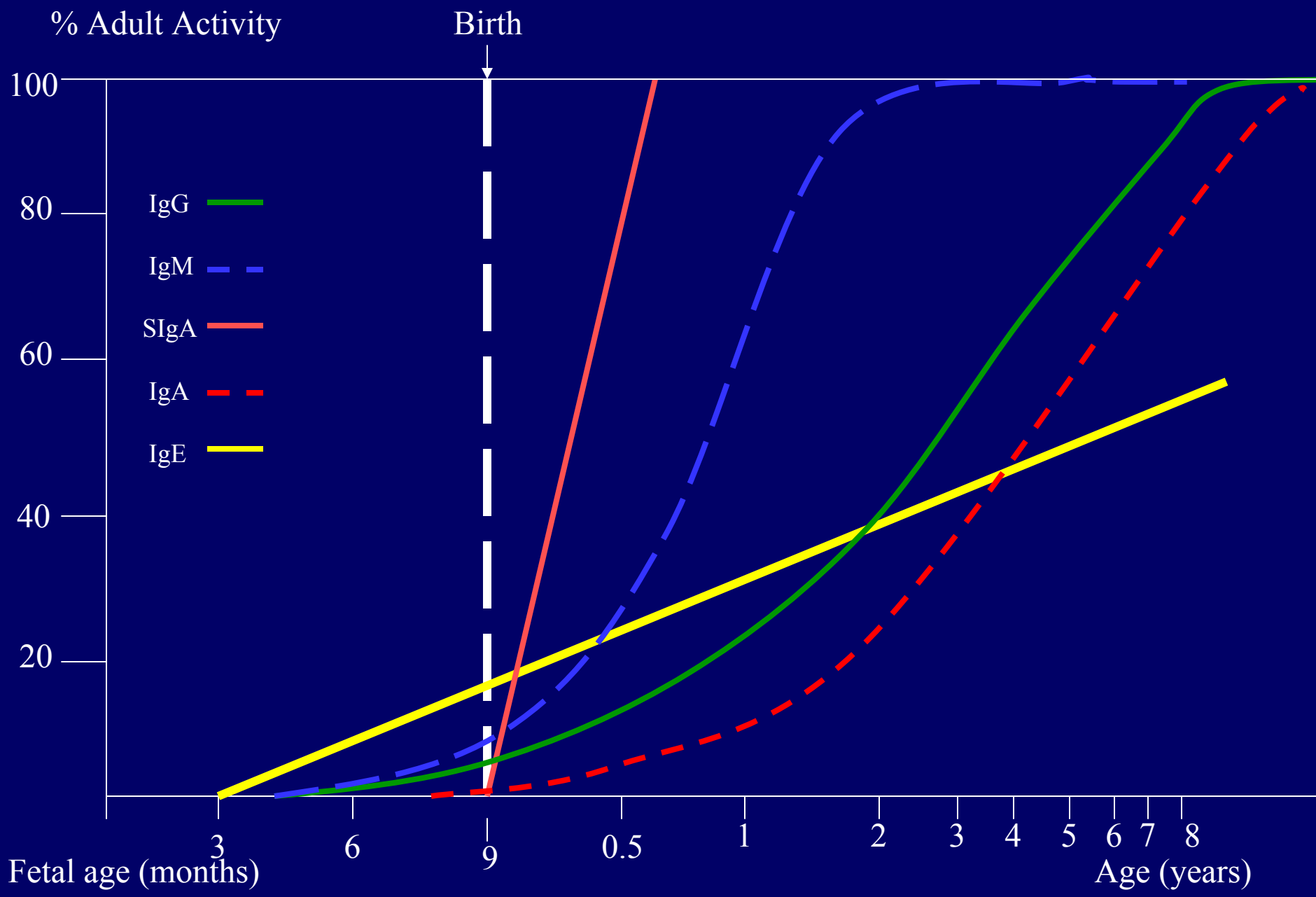
# Immune System of the Normal Neonate

- 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



# 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
  - Why the conflicting results?

# 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

# 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-β1

- Cytokine, transforming growth factor-β1 (TGF-β1) promotes tolerance to food components in the intestinal immune response
- TGF-β1 in mother's colostrum may influence the type and intensity of the infant's response to food allergens
- A normal level of TGF-β1 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-β1 (continued)

- TGF-β1 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)

[Saarinen et al 1999]

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

- TGF-β1 seems to be involved in antibody class-switching to IgA
- Inhibits class switch to IgE
- Lower TGF-β1 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

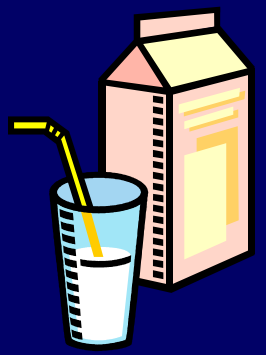
- Colostrum should be the first fluid encountered by the neonate, regardless of the atopic status of the mother
  - Provides sIgA as well as other protective and maturation factors
- Atopic mothers should avoid:
  - Their own allergens during pregnancy and lactation
  - In addition, the most highly allergenic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

# 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

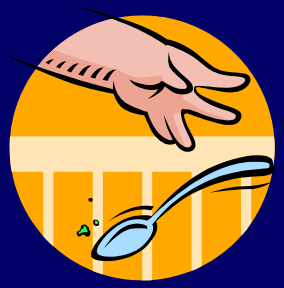
- Reliable diagnosis is based on elimination and challenge:
  - All sources of cow's milk or suspect food allergen protein are eliminated from the infant's and the mother's diet
  - Symptoms of allergy in the infant resolve
  - Identical symptoms occur during food challenge
  - Symptoms again disappear 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 (½ 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

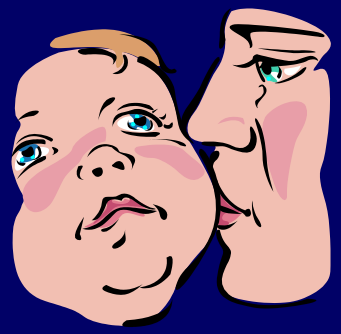
- Present thinking is that sensitization occurs predominantly from external sources
- The antigens in mother's milk then elicit symptoms in the previously sensitized infant
- However, new research suggests that sensitization via breast milk may occur in the atopic mother and baby pair: this remains to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

# Current Areas of Investigation to Reduce Risk of Allergy

Science to Practice

# 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-γ 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 ($PGE_3$), 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

Omega-6 Fatty acids

↓

Arachidonic acid

↓

Prostaglandin $PGE_2$

↓

Inhibits IFNγ (associated with Th1 response)
Allows up-regulation (increase) in IL-4 (Th2 response)

↓

ALLERGIC REACTION PROMOTED

Omega-3 Fatty acids

↓

EPA
DCHA

↓

Prostaglandin $PGE_3$

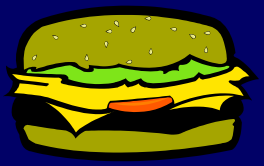
↓

$PGE_2$ is reduced
IFN-γ is not inhibited

↓

ALLERGIC REACTION REDUCED

# 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

# Conflict of Results

[Duchen et al 2000; n=120]

- Lower levels of long-chain ω-3 fatty acids in mature breast milk of mothers of atopic as compared to non-atopic infants (atopy measured during first 18 months)

[Stoney et al 2004 (n=620)]

- Higher levels of long-chain ω-3 fatty acids in colostrum of mothers of infants sensitized to foods (cow's milk; egg; peanut: STP +)) at 6 months of age compared to those of non-sensitized infants
- Breast milk fatty acid profile was the same in atopic and non-atopic mothers

# Vitamin Supplementation and Risk of Allergy

[Milner et al 2004 (n = >8,000)]

- Vitamin supplementation in the first 6 months associated with:
  - Higher risk for asthma in black infants
  - Higher risk for food allergies in formula-fed infants
- Vitamin supplementation at 3 years of age associated with:
  - Increased risk for food allergies but not asthma
  - In both breast-fed and formula-fed children

# Vitamin Supplementation and Risk of Allergy (continued)

[Matheu et al 2003 (murine study)]

- Early vitamin D supplementation augmented allergen-induced Th2 response, with production of:
  - IL-4
  - IL-13
  - IgE
- Vitamin D supplementation tends to downregulate Th1 response, with beneficial effects on development of Th1-mediated conditions such as:
  - Airway eosinophilia
  - Type 1 diabetes mellitus

# Epicutaneous Exposure to Food Allergens

[Hsieh et al 2003 (murine study)]

- Patch administration of ovalbumin induced:
  - High level of ovalbumin-specific IgE
  - Elevated plasma histamine levels
  - Histological changes in intestine and lung tissue
  - Th2-predominant cellular immune response in lungs after oral challenge
- Significance of epicutaneous exposure to allergens as a result of skin testing?

# Role of Micro-organisms in Preventing Food Allergy

- Commensal gut microflora might suppress Th2 response by promoting:
  - Th1 response
  - Protective SIgA production
  - TGF-ß production
- In mouse food anaphylaxis, lactobacillus:
  - Induced IL-12 production
  - Suppressed IgE-response
  - Suppressed anaphylaxis

# Probiotics in Prevention of Food Allergy

Human study [Kalliomaki et al 2001]

- Mothers given lactobacillus GG antenatally
- Infants given oral lactobacillus for 6 months post-natally
- Treated group reduced risk of eczema at 2 years
- No difference in treatment and control groups:
  - Total IgE
  - Specific IgE to food allergens
  - Skin-prick tests

# Summary of Current Research
## 1. Identification of Risk Categories

- High risk:
  - Atopic mother
- Moderate risk:
  - Atopic father
  - Atopic sibling(s)
- Low risk:
  - No family history of allergy

# Summary of Current Research
## 2. Preventive Measures

- High risk:
  - Identify mother's allergens
  - Maternal avoidance of her own allergens from preconception onwards
  - In addition, starting about two weeks prior to delivery mother avoids most highly allergenic foods throughout lactation
    - Peanuts
    - Tree nuts
    - Shellfish
    - Fish
    - Eggs
    - Milk proteins
  - Degree of avoidance of eggs and milk remains controversial

# Summary of Current Research

## 2. Preventive Measures (continued)

- Moderate risk
  - No need to restrict mother's diet prior to, or during most of her pregnancy
  - Starting two weeks prior to delivery, mother avoids the most highly allergenic foods and continues throughout early lactation
    - Peanuts
    - Tree nuts
    - Shellfish
    - Fish
    - Eggs
    - Milk proteins
  - Degree of avoidance of eggs and milk remains controversial

# Summary of Current Research
## 2. Preventive Measures (continued)

- Low Risk:
  - Good nutrition practices for mother from preconception onwards
  - Good nutrition practices for early infant feeding
  - Breast-feeding is the best possible source of nutrition and protection
  - Allergen avoidance is unnecessary unless the infant demonstrates signs of allergy