Weaning: the Optimal Time for Solid Food Introduction for Allergy Prevention

Attilio Boner

University of Verona, Italy

- ✓ introduction
- ✓ starting point
- ✓ old reccomendations
- ✓ new findings
- ✓ development of tolerance
- ✓ other possible mistakes
- ✓ not only allergy
- ✓ allergy development?
- ✓ what can be done?
- ✓ conclusions

Oral Tolerance

✓Oral tolerance involves the **specific suppression of cellular and humoral immune responses** to ingested antigens.

Chehade M, J ACI 2005,115:3-12.

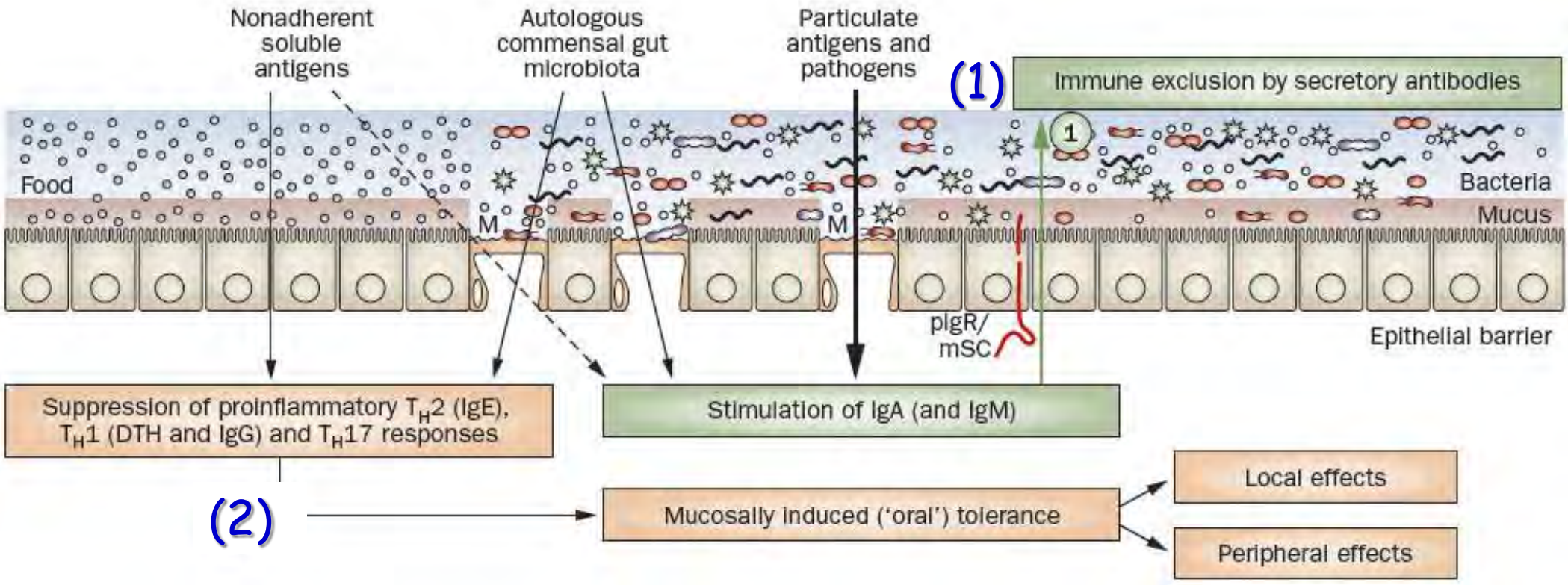
✓Oral tolerance is achieved by a unique gut immune system made up of complex **regulatory networks among immunocompetent cells** (e.g., dendritic cells and T cells)

Faria AM, Immunol Rev 2005,206:232-259

abrogation

Food Allergy

The mucosal immune system has generated two anti-inflammatory strategies: (1) immune exclusion—performed by SIgA to control the epithelial colonization of microorganisms and inhibit the penetration of potentially dangerous agents; and **(2) hyporesponsiveness**—to avoid local and peripheral hypersensitivity against innocuous antigens.

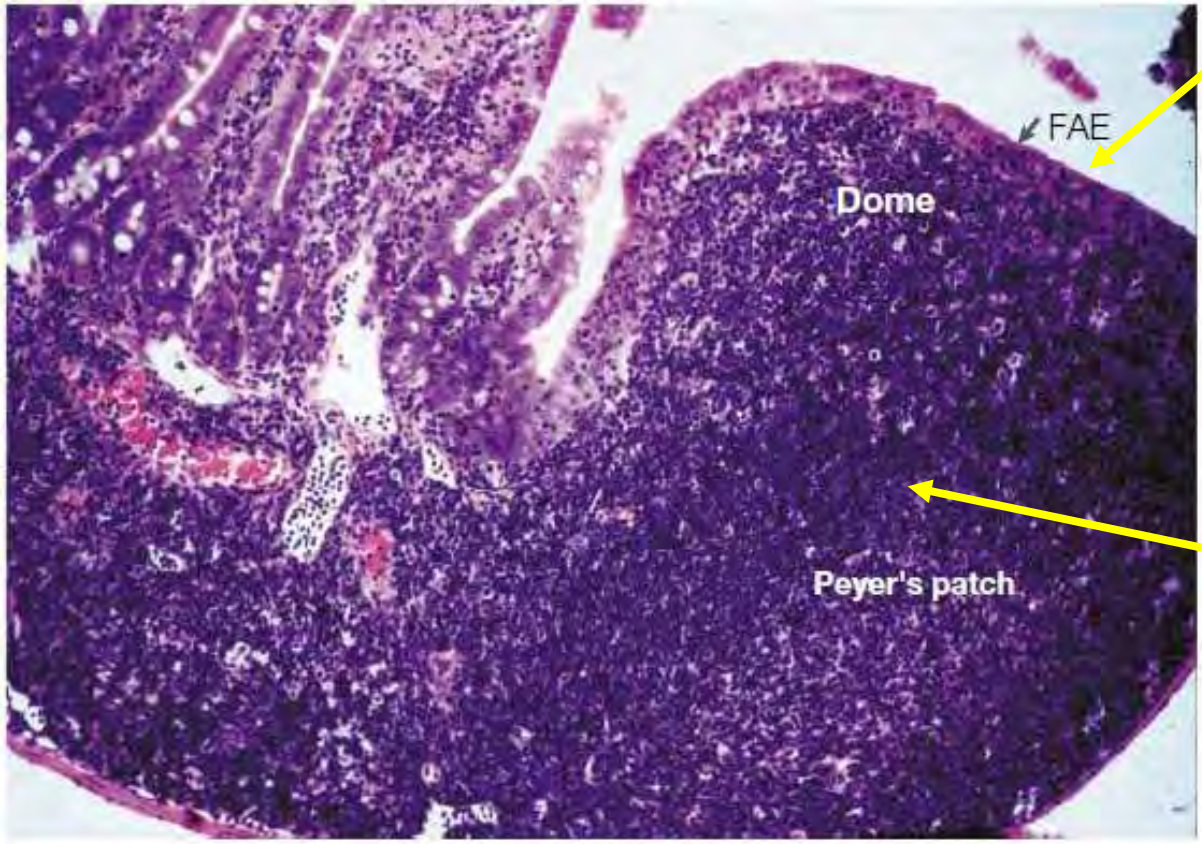


Anti-inflammatory mucosal adaptive immune defense mechanisms.

Brandtzaeg, P. Nat. Rev. Gastroenterol. Hepatol. 2010;7:380-400

Schematic representation of the lymphoid elements of the intestinal immune system. *Mowatt Nat Rev Immunol. 2003;3:331*

inductive sites

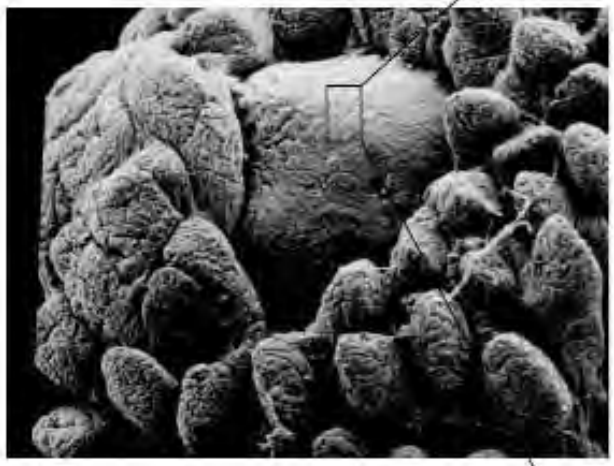


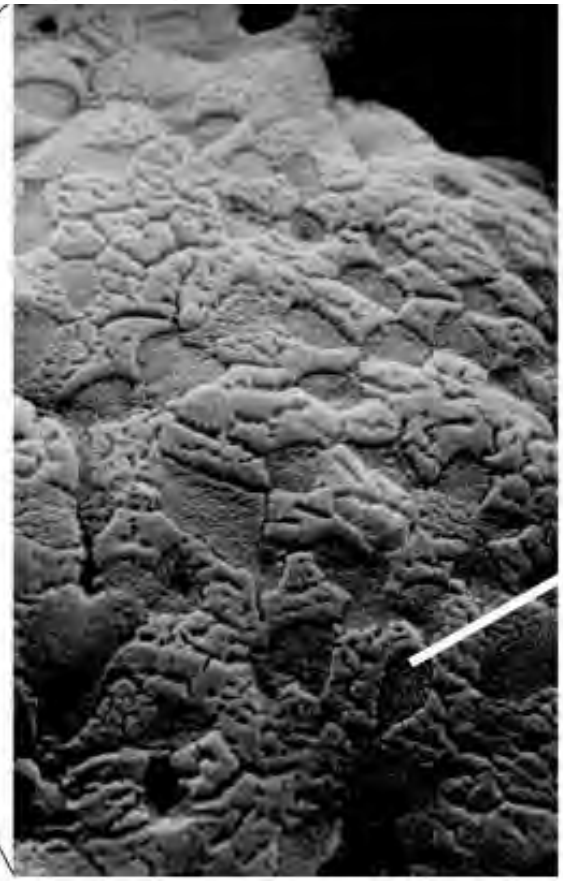
a) The follicle-associated epithelium (FAE), which is comprised of columnar epithelial cells and also contains microfold (M) cells, dendritic cells (DCs), T cells, B cells and macrophages, separates the intestinal lumen from Peyer's patches.

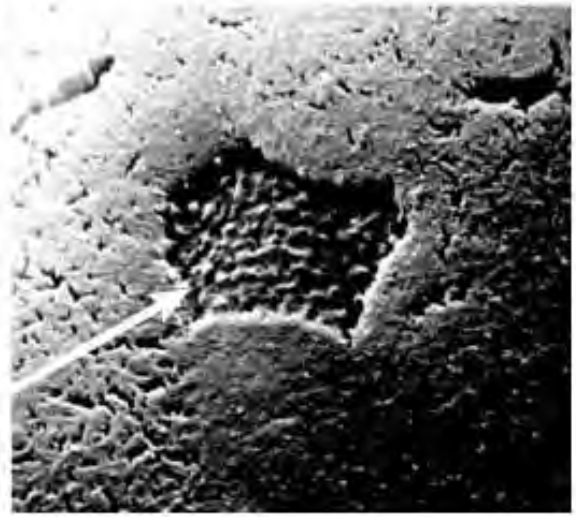
b) Peyer's patches are aggregates of secondary lymphoid tissue present in the submucosa of the small intestine. The area immediately beneath the FAE ('dome') is rich in DCs.

Schematic representation of the lymphoid elements of the intestinal immune system. *Mowatt Nat Rev Immunol. 2003;3:331*

Scanning-electron micrographs of Peyer's patches and follicle-associated epithelium (FAE).







At low magnification (left), the dome shape of the Peyer's patch protrudes between villi into the lumen of the intestine

At higher magnification (centre and right), M cells can be seen as epithelial cells with surface microfolds rather than the microvilli that are seen on the surrounding conventional enterocytes. Antigen is taken up preferentially through M cells (right).

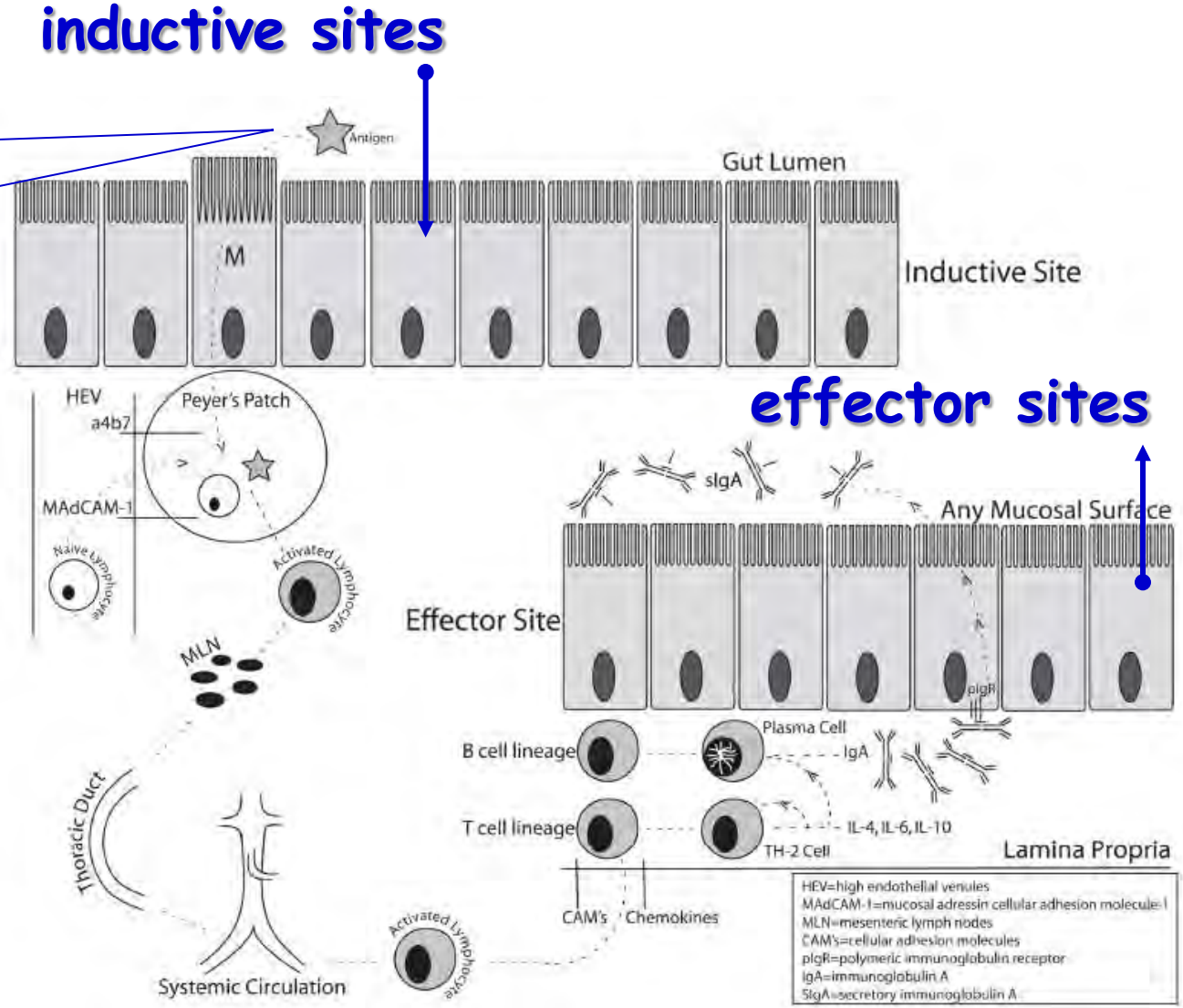
Schematic representation of the lymphoid elements of the intestinal immune system. *Mowatt Nat Rev Immunol. 2003;3:331*

effector sites: villi

a) Normal small intestine showing the characteristic architecture of finger-like villi that are covered by a single layer of columnar epithelial cells, which encloses the **central lamina propria** (LP) (effector sites)

Schematic representation of a typical mucosal immune response. *Hermensen Langenbecks Arch Surg. 2009;394:17-30*

The process begins with **antigen sampling** and recognition at inductive sites

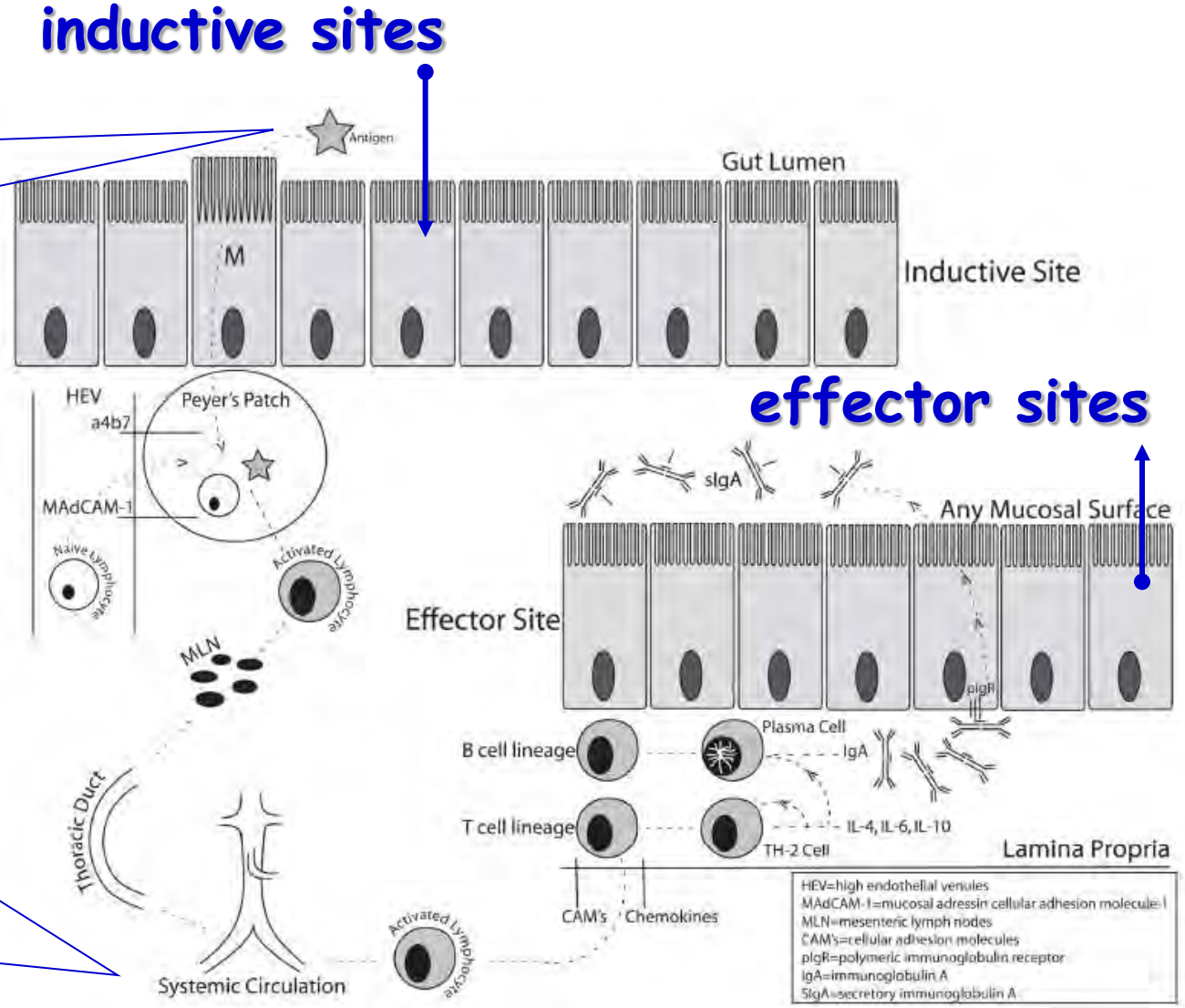


Schematic representation of a typical mucosal immune response. *Hermensen Langenbecks Arch Surg. 2009;394:17-30*

The process begins with **antigen sampling** and recognition at inductive sites

and

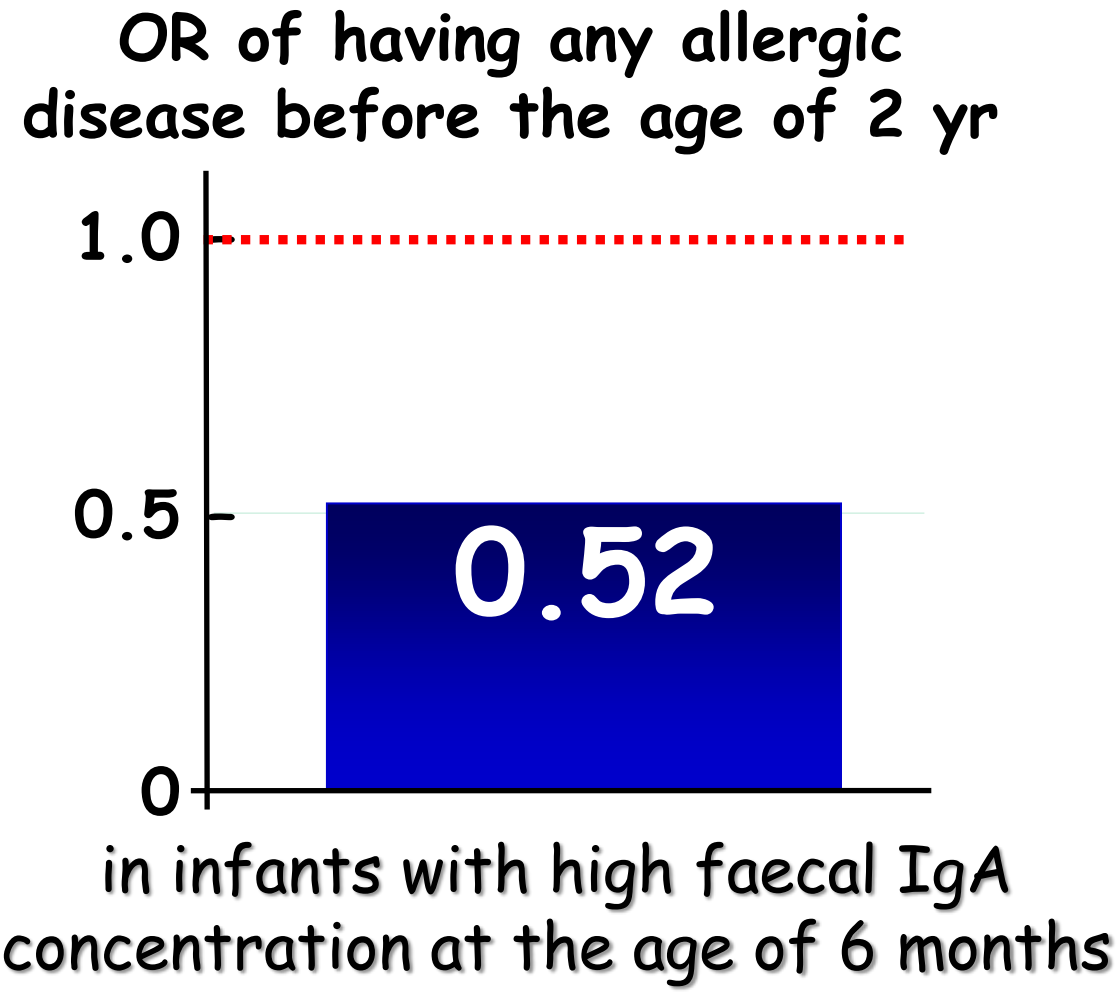
ends with the generation of **antigen specific secretory IgA** at effector sites which is actively transported to the mucosal surface.



High intestinal IgA associates with reduced risk of IgE-associated allergic diseases.

Kukkonen K, Pediatr Allergy Immunol 2010;21:67-73.

- ✓237 infants
- ✓faecal IgA at the age of 3 and 6 months
- ✓by age 2 yr, 124 infants had developed allergic disease or IgE-sensitization (cases) and 113 had not (controls).

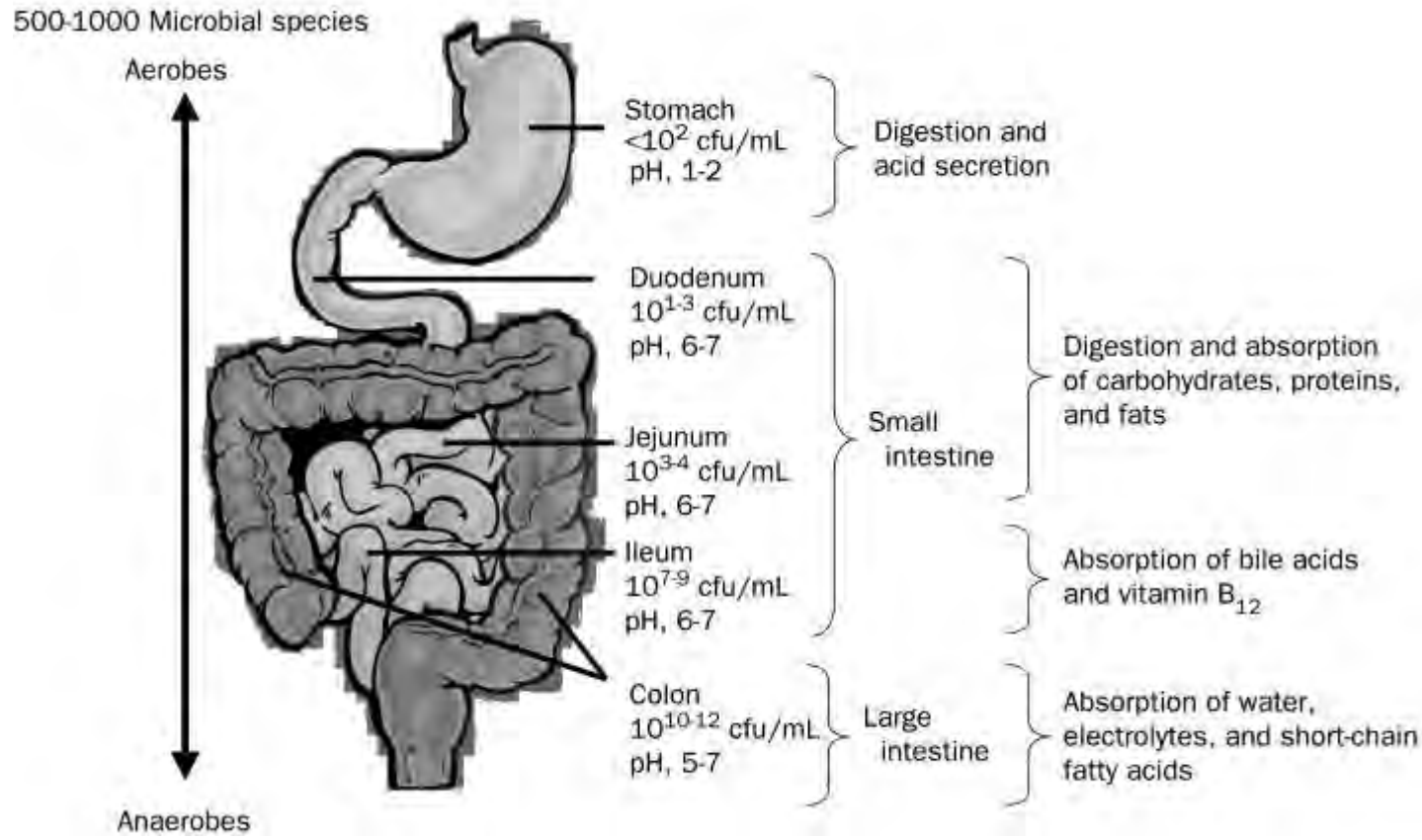


The gut microbiota

- The gut microbiota is estimated to be composed of ~10^{14} bacteria (approximately 10 times the number of body cells) and weighs 1–2 kg.

- The gut microbiome is perhaps 150 times larger than the human genome.

Types, number of bacteria and their function

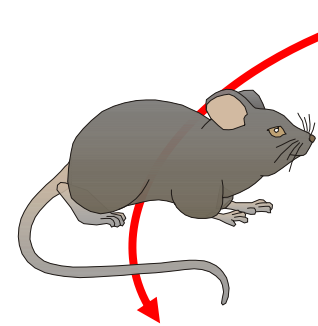


GUT FLORA and TOLERANCE

Burks JACI 2008;121:1344

Inhibition of experimental drug allergy by prior feeding of the sensitizing agent.

Chase MW.
Proc Soc Exp Biol
1946;61:257-9.



immunized and boosted subcutaneously with an antigen

strong in vitro cell-mediated and antibody responses to the antigen.

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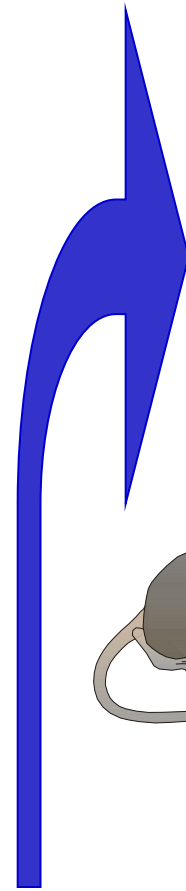

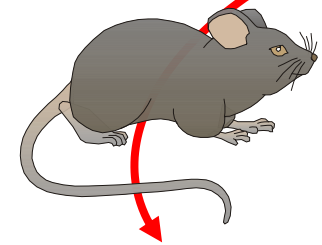

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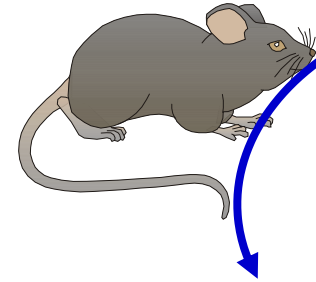
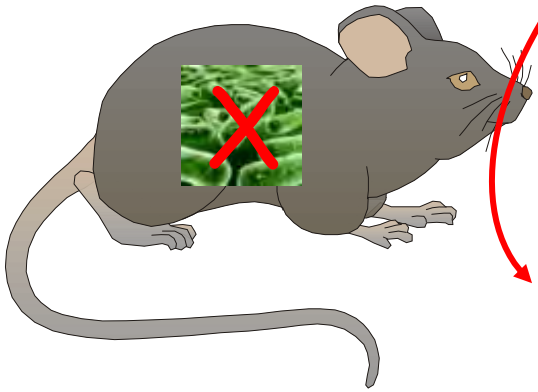


first fed the antigen orally and then immunized subcutaneously

greatly reduced in vitro immune responses to the antigen.

The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction.

Sudo N J Immunol. 1997;159:1739-45.



germfree mice.

orally administered 20 mg of OVA as tolerogen before a systemic challenge with OVA,

1) Th1-mediated responses,
such as the production of IgG2a and IFN-γ,
were abrogated,

2) Th2-mediated immune responses,
such as the production of IgE, IgG1, and IL-4,
were maintained.

The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction.

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germfree mice.

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The reconstitution of intestinal flora of GF mice with Bifidobacterium infantis, one of the predominant bacteria in the intestinal flora, **restored** the susceptibility of these Th2 responses to **oral tolerance induction**; however, **this was only effective when such reconstitution was performed in neonates**, but not in mice at an older age.

MECHANISMS OF TOLERANCE

Burks JACI 2008;121:1344

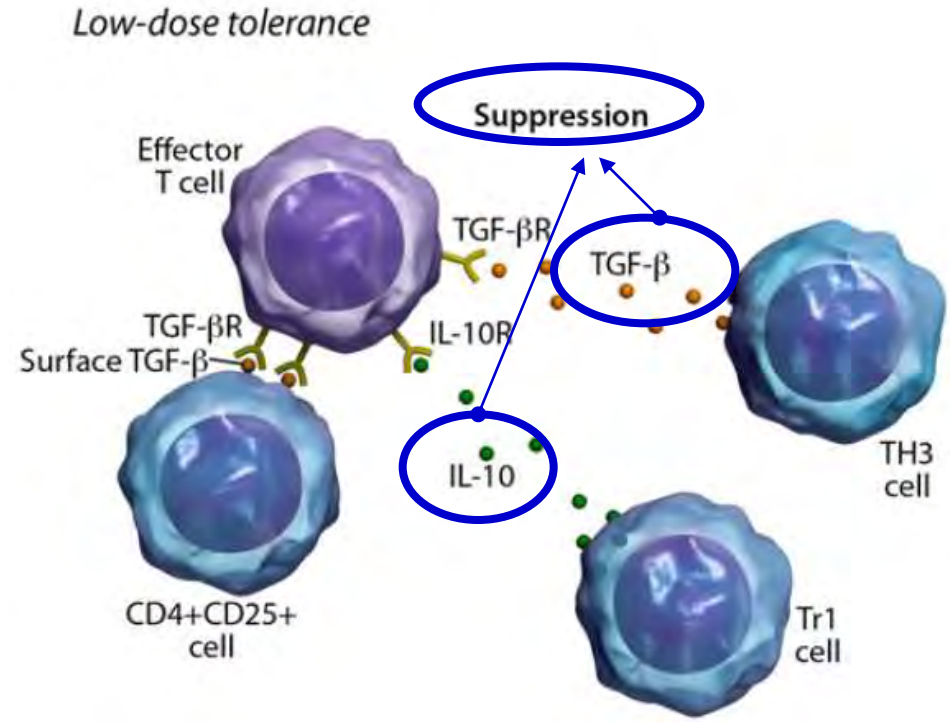
There are 2 primary effector mechanisms for inducing oral tolerance:

1) **Active Suppression** by **regulatory T cells**

or

2) **Deletion or Anergy**

1) Low doses of antigen favor tolerance driven by **regulatory cells**, which suppress immune responses through soluble or cell surface–associated downregulatory cytokines, such as **IL-10**, and **TGF-β (active suppression).**



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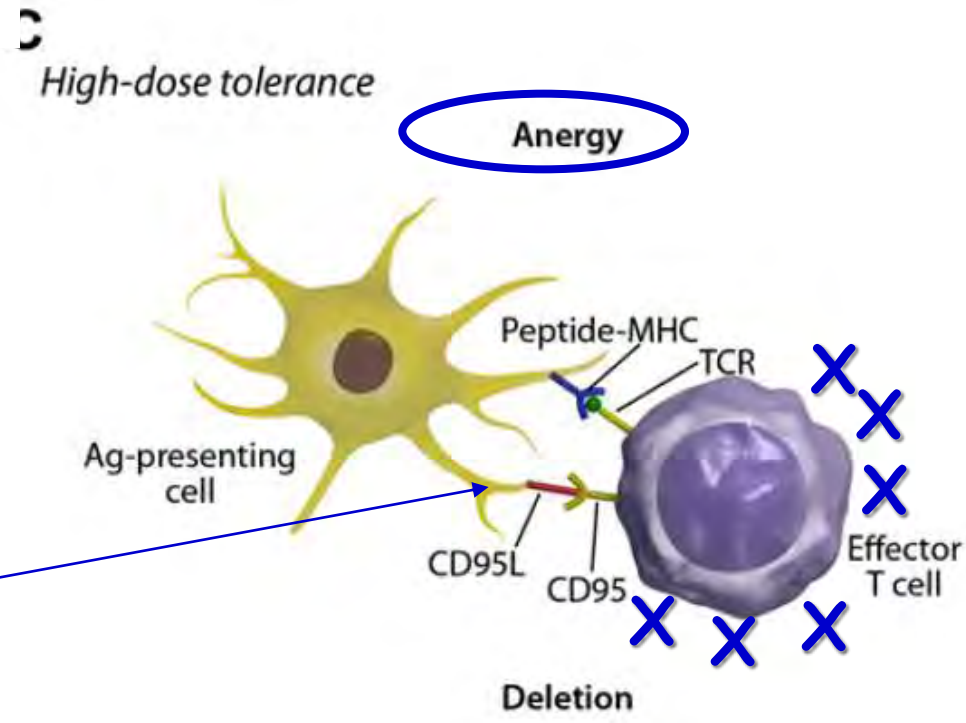
2) **Deletion or Anergy**

2) High-dose tolerance is mediated by lymphocyte **anergy** or clonal deletion.

Anergy can occur through T-cell receptor ligation in the absence of costimulatory signals.



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There are 2 primary effector mechanisms for inducing oral tolerance:

1) Active Suppression by **regulatory T cells**

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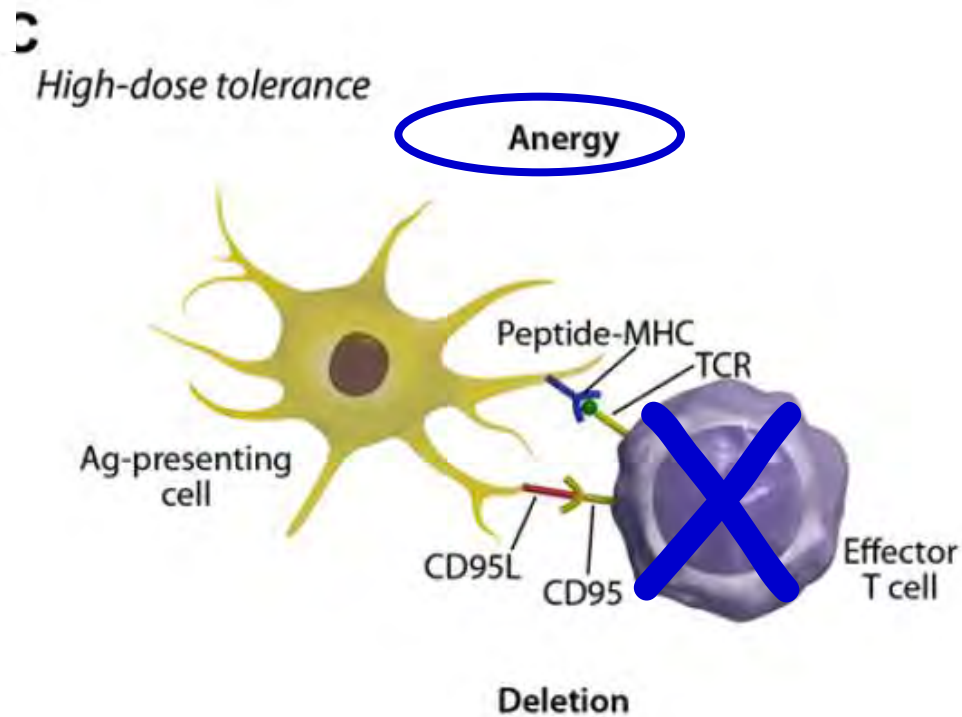
Clonal deletion occurs by means of FAS-mediated apoptosis (CD95).

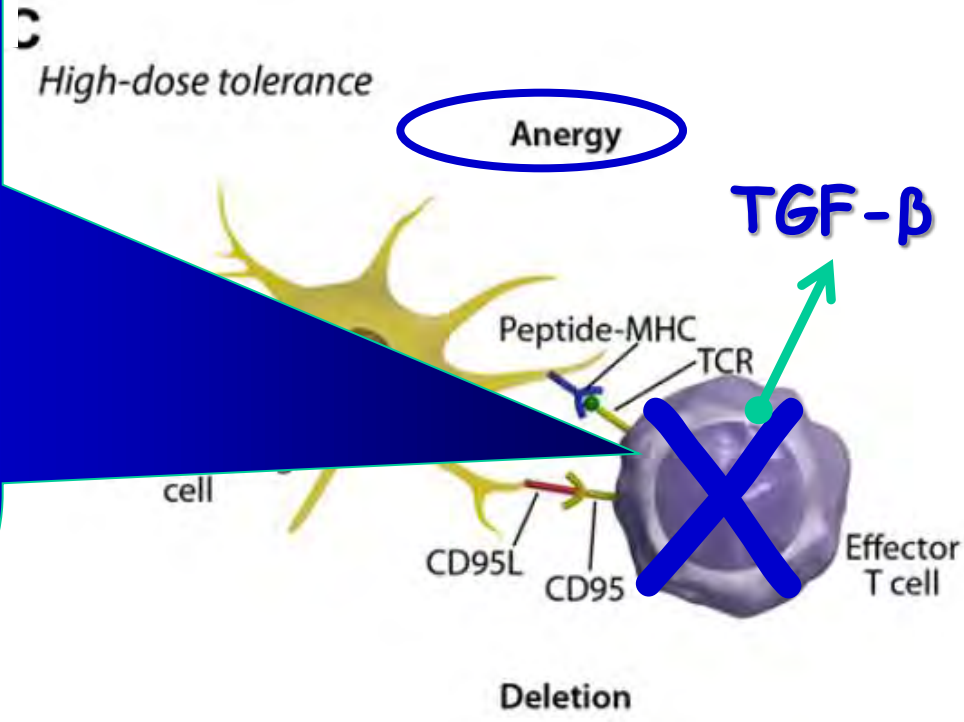


MECHANISMS OF TOLERANCE

Burks JACI 2008;121:1344

Apoptotic T cells release TGF-β in both latent and bioactive forms, and macrophages produce TGF-β on ingesting apoptotic cells. The secretion of TGF-β through the various mechanisms of clonal anergy and deletion can contribute to an immunosuppressive environment in the gut.

ctive Suppression by
egulatory T cells
or
eletion or Anergy



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- ✓ allergy development?
- ✓ what can be done?
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Diet in the allergic child

In an allergic child with mild symptoms does strict avoidance speed recovery?

Erroneous interpretation of SPTs e sIgE

Sensitization ≠ allergic disease

Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007.

Mullins RJ, JACI 2009;123:689-693.

- ✓Retrospective study of 778 patients (age 4 mo to 66 years)
- ✓diagnosed with peanut allergy at a community-based specialist allergy practice

a positive IgE test to peanut in childhood

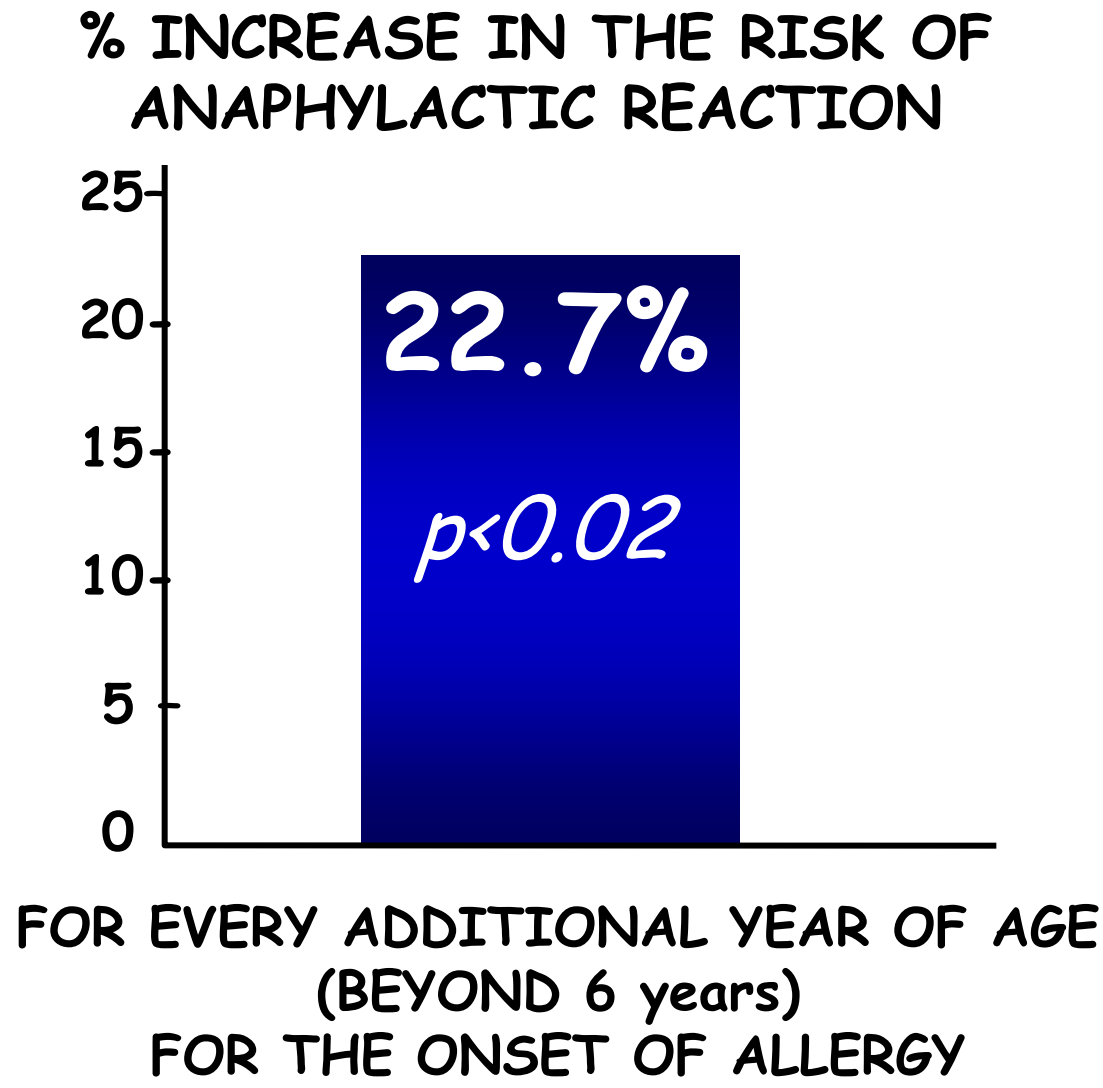
avoidance of peanuts

Late-onset peanut allergy in adults

Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007

Mullins JACI 2009; 123:689

- ✓ 778 patients with peanut allergy.
- ✓ Most peanut allergy (90%) developed by age 72 months (6 yrs).



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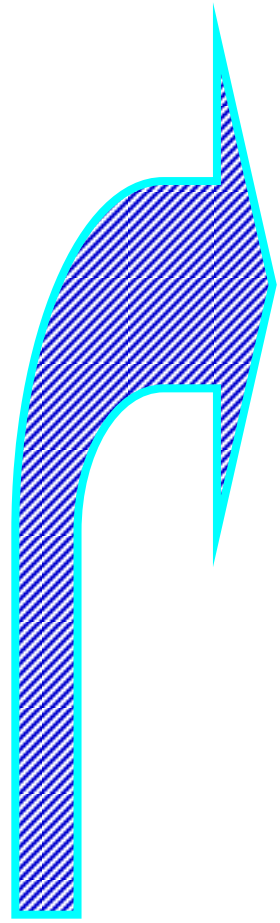
Dose-Response Relationships between Iron Deficiency with or without Anemia and Infant Social-Emotional Behavior *Lozoff, J PED 2008; 152:696*

- ✓ A cohort of 9- to 10-month-old infants.
- ✓ The infants were given oral iron for 3 months.
- ✓ Behavioral coding from videotape at 12 months



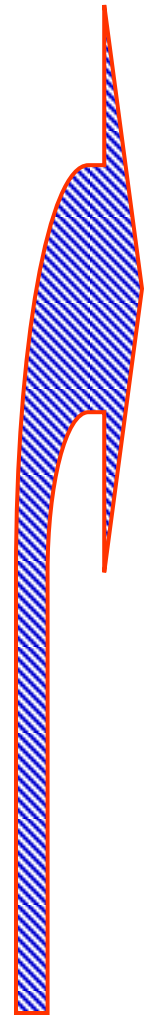
There were significant ($P < 0.05$) linear effects of poorer iron status for:

- increasing shyness,
- decreasing orientation/engagement,
- decreasing soothability, and,
- when an examiner attempted to engage the infants in imitative play, decreasing positive affect and engagement.

Iron Deficiency Anemia and Cognitive Function in Infancy

Carter Pediatrics 2010;126;e427

- ✓ Effects of **iron deficiency anemia (IDA)** on specific domains of infant cognitive function
- ✓ IDA was defined as hemoglobin level<110 g/L with ≥2 abnormal iron deficiency indicators (mean corpuscular volume, red cell distribution width, zinc protoporphyrin, transferrin saturation, and ferritin)
- ✓ **At 9 and 12 months**, the Fagan Test of Infant Intelligence (FTII); A-not-B task; Emotionality, Activity, and Sociability Temperament Survey; and Behavior Rating Scale



- **Infants with IDA showed poorer recognition memory**
- **The Behavior Rating Scale orientation/engagement measure partially mediated these effects**

Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children

Chang Pediatrics 2011;127:e927

- ✓ Children with iron-deficiency anemia (IDA) in infancy whose *anemia* was *not corrected* before 24 months (chronic IDA) *(n=27).*
- ✓ Children with IDA in infancy whose *anemia* was *corrected* before 24 months (corrected IDA) *(n=70).*
- ✓ Children who were *non-anemic* in infancy and at 24 months *(n =64).*

Children who had **chronic IDA** in infancy displayed:

1. less positive affect and frustration tolerance;
2. more passive behavior and physical self-soothing in the stranger approach;
3. delay of gratification.

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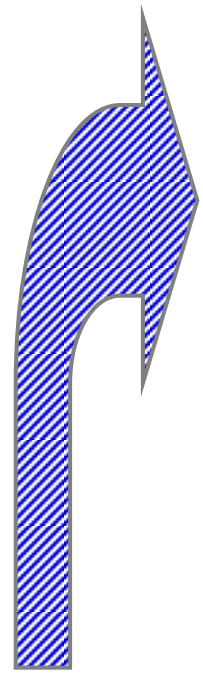

In contrast,
the behavior and affect
of children whose
anemia was **corrected**
before 24 mo of age
were comparable
to those of children who
were non-anemic
throughout infancy.

Infants Perceived as "Fussy" Are More Likely to Receive Complementary Foods Before 4 Months

Wasser Pediatrics 2011;127:229

- The prevalence of overweight among US infants and toddlers has increased by 60% in the past 30 years

- The prevalence is higher among black people (10.3%) than white people (8.7%).

- This disparity in overweight prevalence is concerning in light of research that has linked large infant size and/or rapid postnatal growth with child and adult overweight

Infants Perceived as "Fussy" Are More Likely to Receive Complementary Foods Before 4 Months

Wasser Pediatrics 2011;127:229

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Factors related to such growth patterns include **early complementary feeding** and, conversely, **early discontinuation of exclusive breastfeeding** both of which are disproportionately high among black infants.

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Infants Perceived as "Fussy" Are More Likely to Receive Complementary Foods Before 4 Months

Wasser Pediatrics 2011;127:229

Prevalence of exclusive breastfeeding through 3 months

likely to delay solid food introduction until 4 months

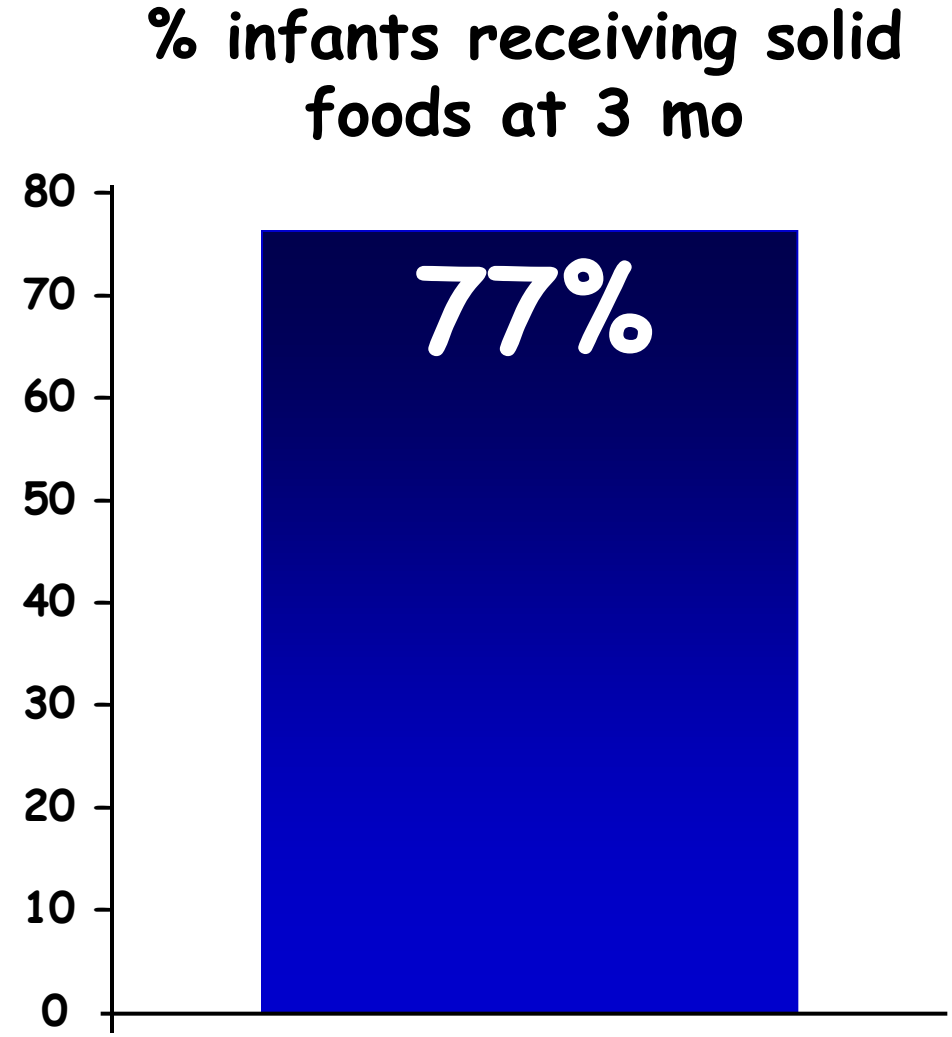
59.5%

37.5%

Infants Perceived as "Fussy" Are More Likely to Receive Complementary Foods Before 4 Months

Wasser Pediatrics 2011;127:229

- ✓ Relationships between early feeding of solids or juice.
- ✓ 6 dimensions of perceived infant temperament.



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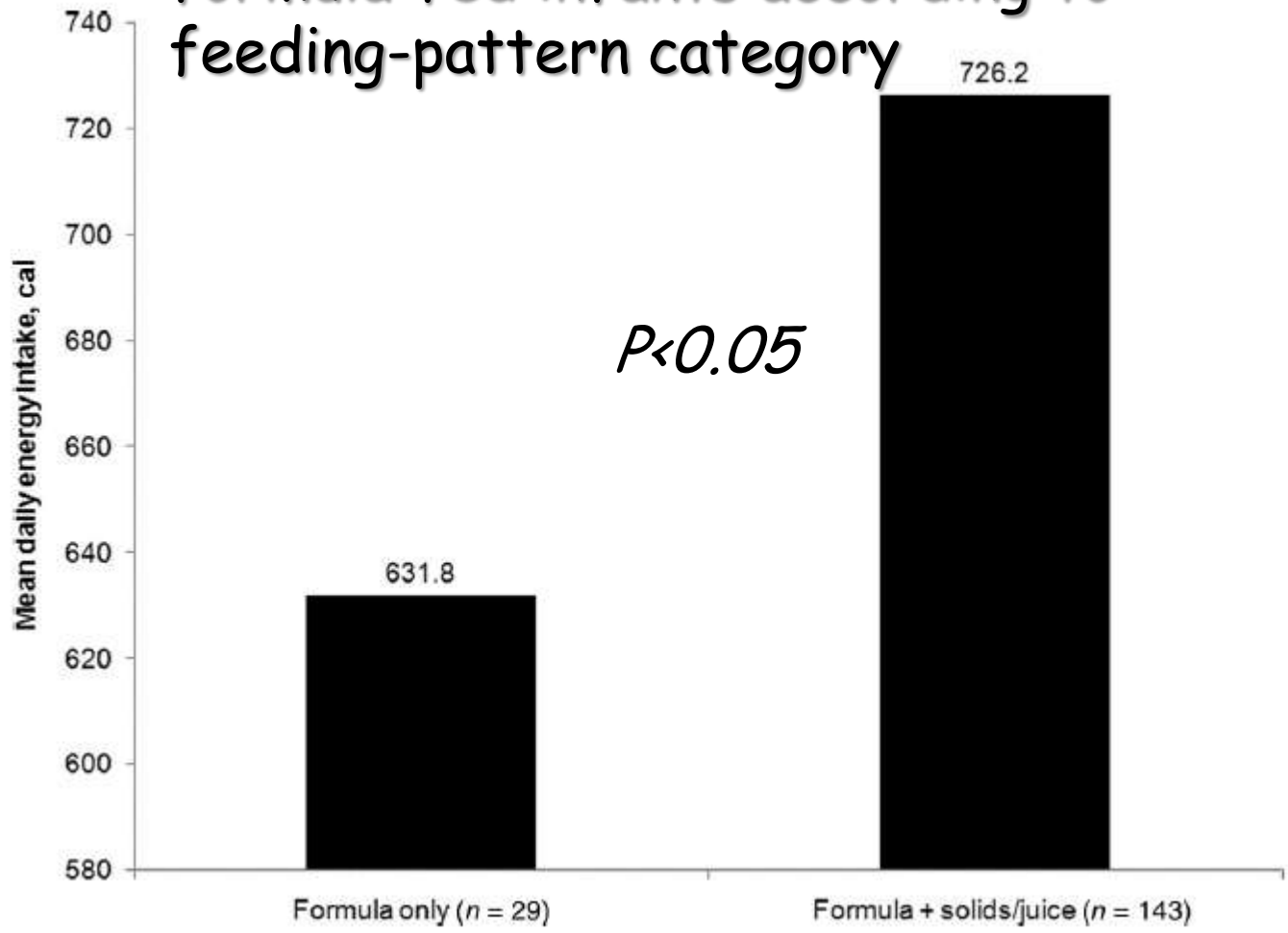
Mean daily energy intake among formula-fed infants according to feeding-pattern category



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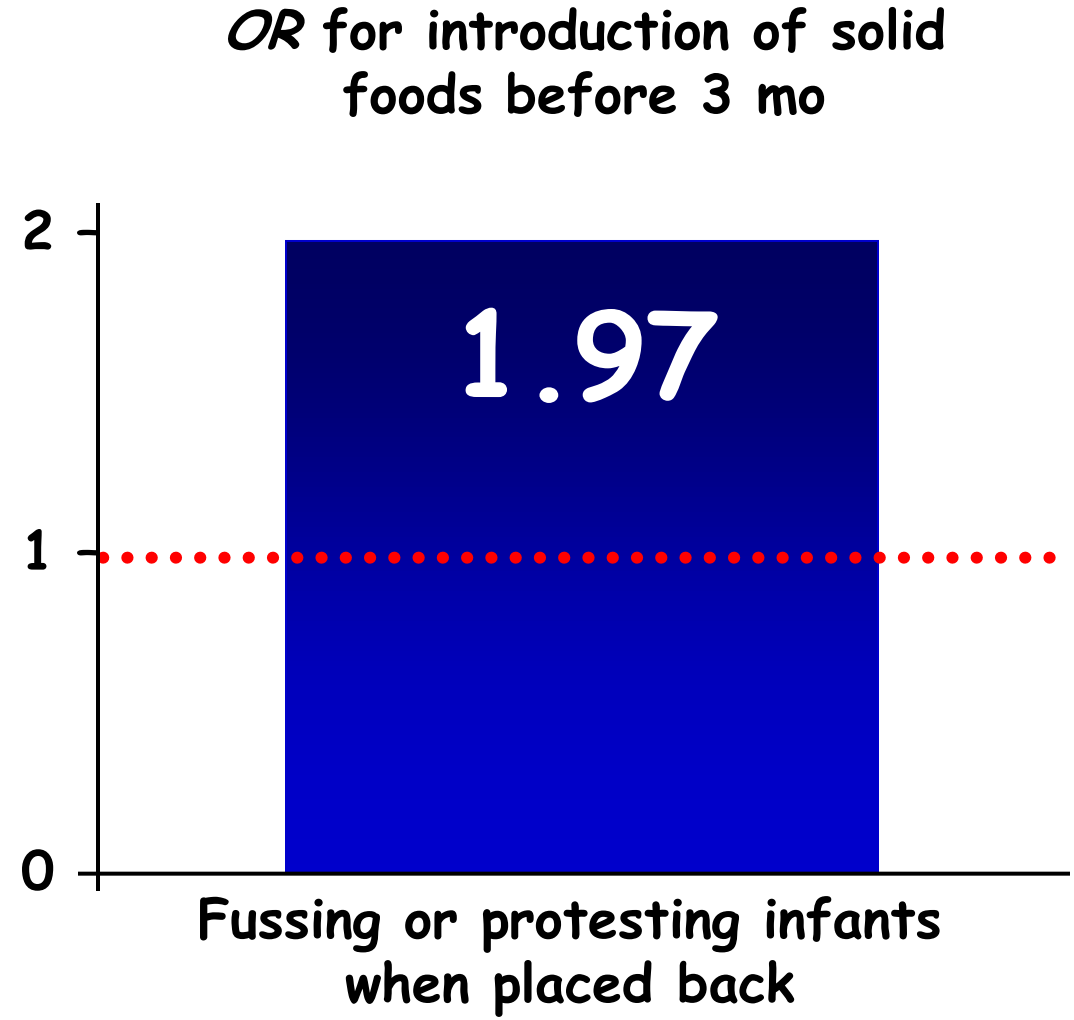

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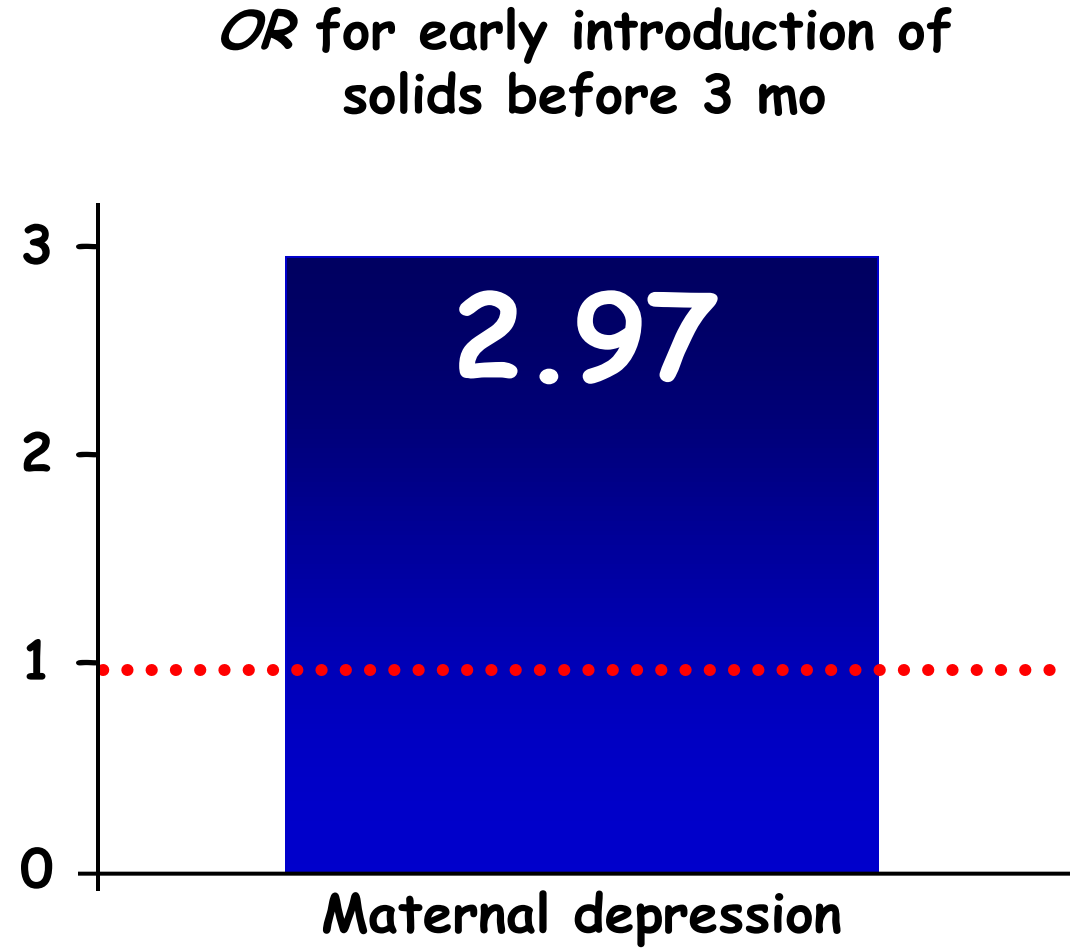
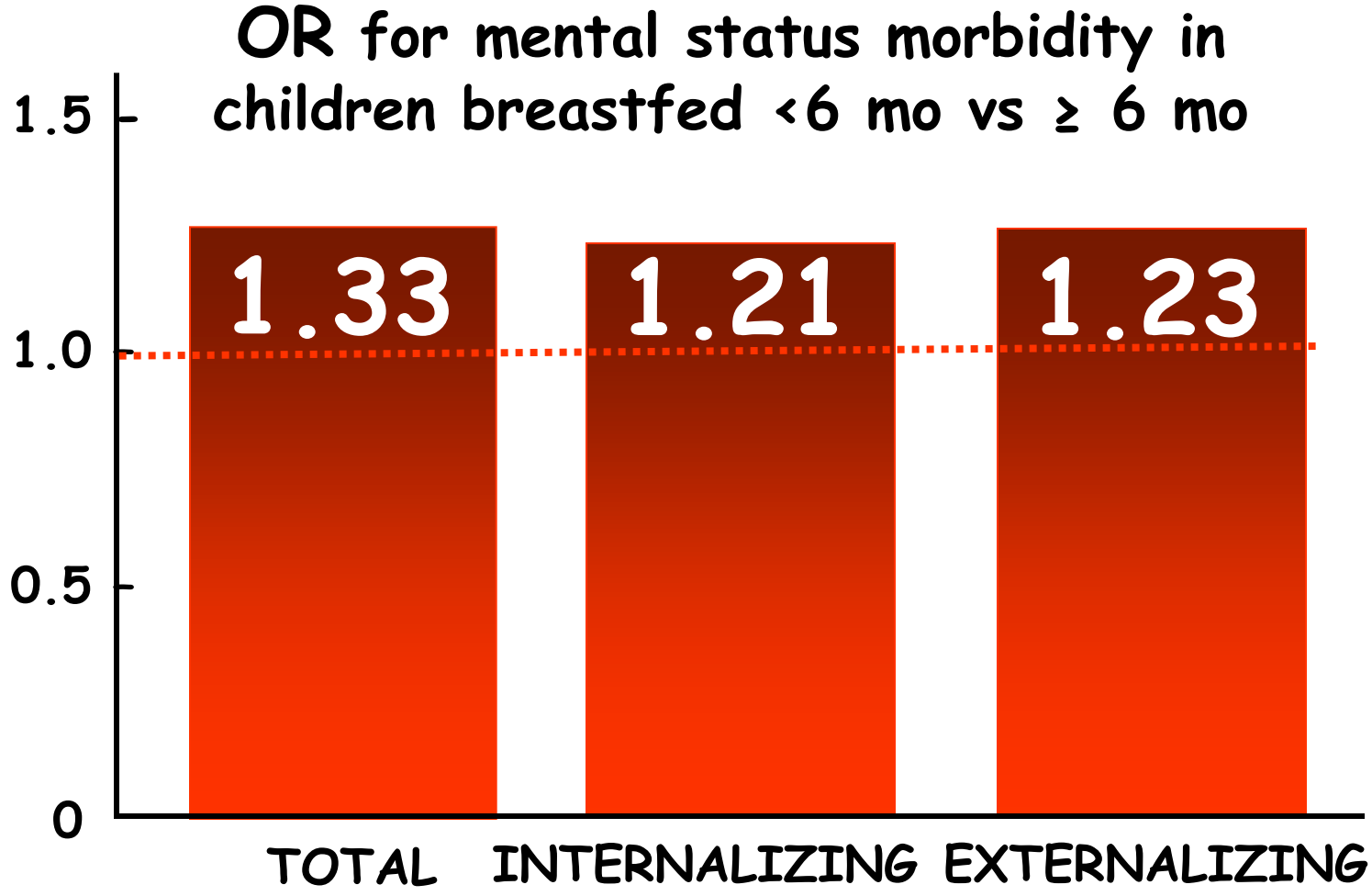


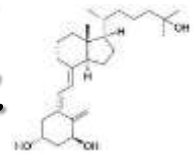
The Long-Term Effects of Breastfeeding on Child and Adolescent Mental Health: A Pregnancy Cohort Study Followed for 14 Years *Oddy J Pediatr 2010;156:568-74*

- ✓ 2900 pregnant women
- ✓ Newborn followed for 14 yrs.
- ✓ Mental health status by the Child Behaviour Checklist (CBCL) at 2, 6, 8, 10, and 14 yrs.

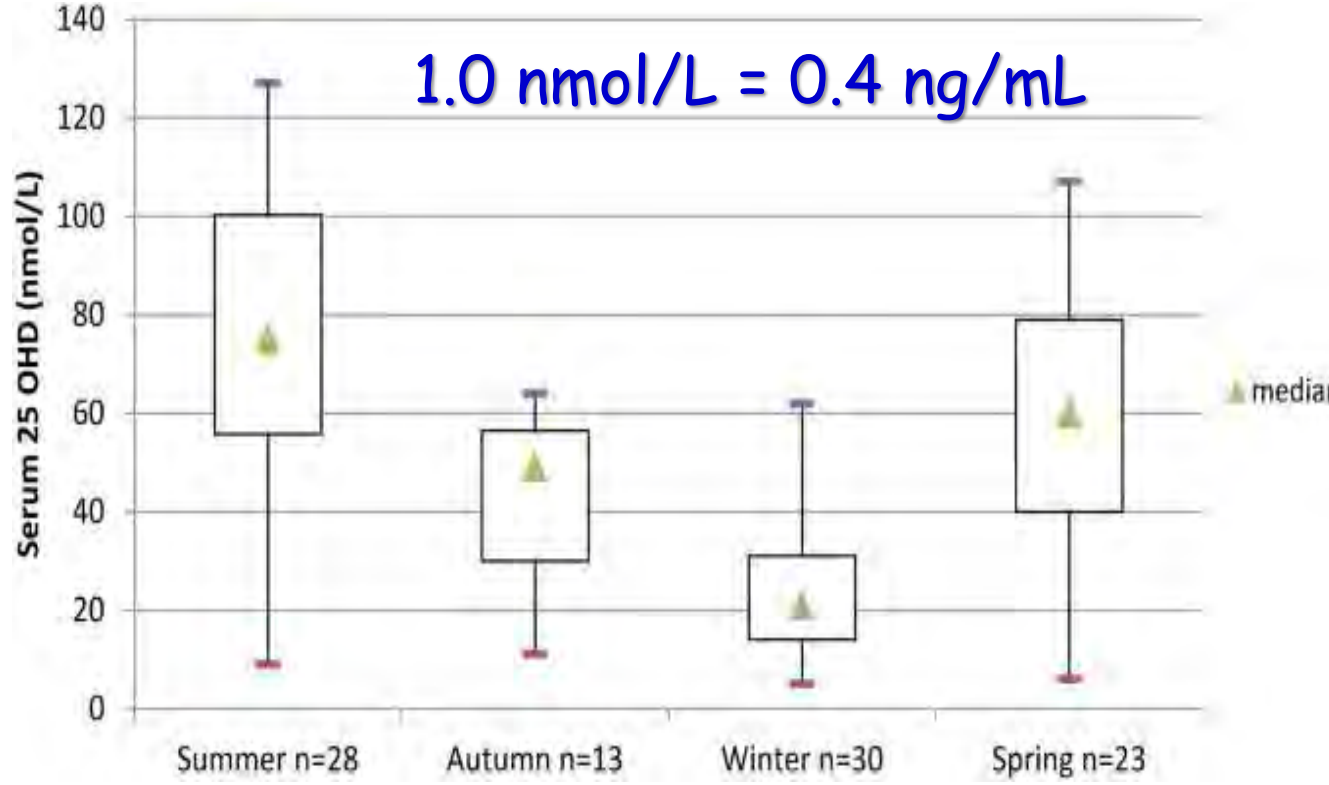


Vitamin D status of exclusively breastfed infants aged 2–3 months *Wall, Arch Dis Child 2013;98:176*

- ✓94 healthy term exclusively *breastfed infants* (mean age 10wks) who were receiving *no vitamin D supplements.*



Box plot of seasonal serum 25-OH vitamin D concentrations in 94 exclusively breastfed infants (aged 2–3 months).



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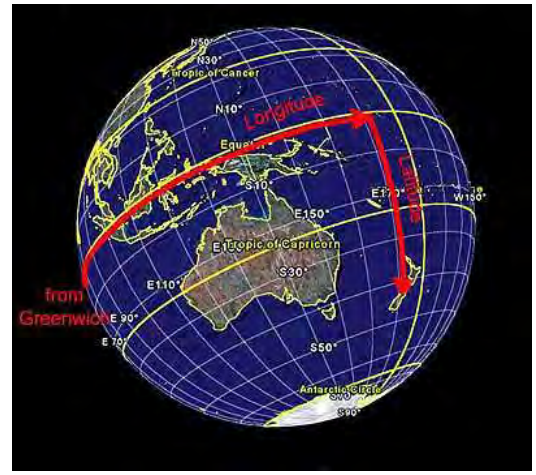
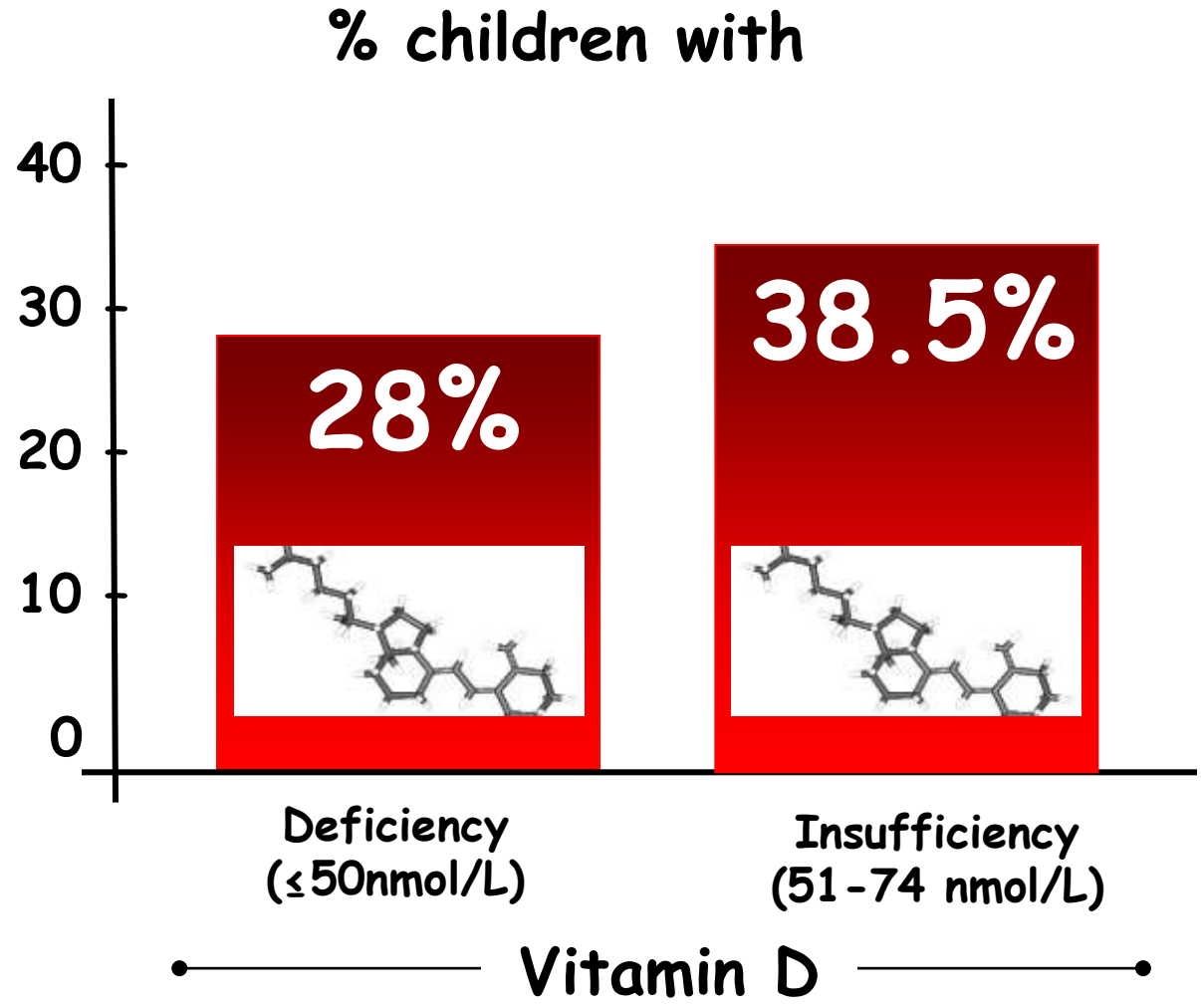
Conclusions



- Vitamin D deficiency is prevalent in exclusively breastfed infants in New Zealand.
- Vitamin D supplementation should be considered as part of New Zealand's child health policy.

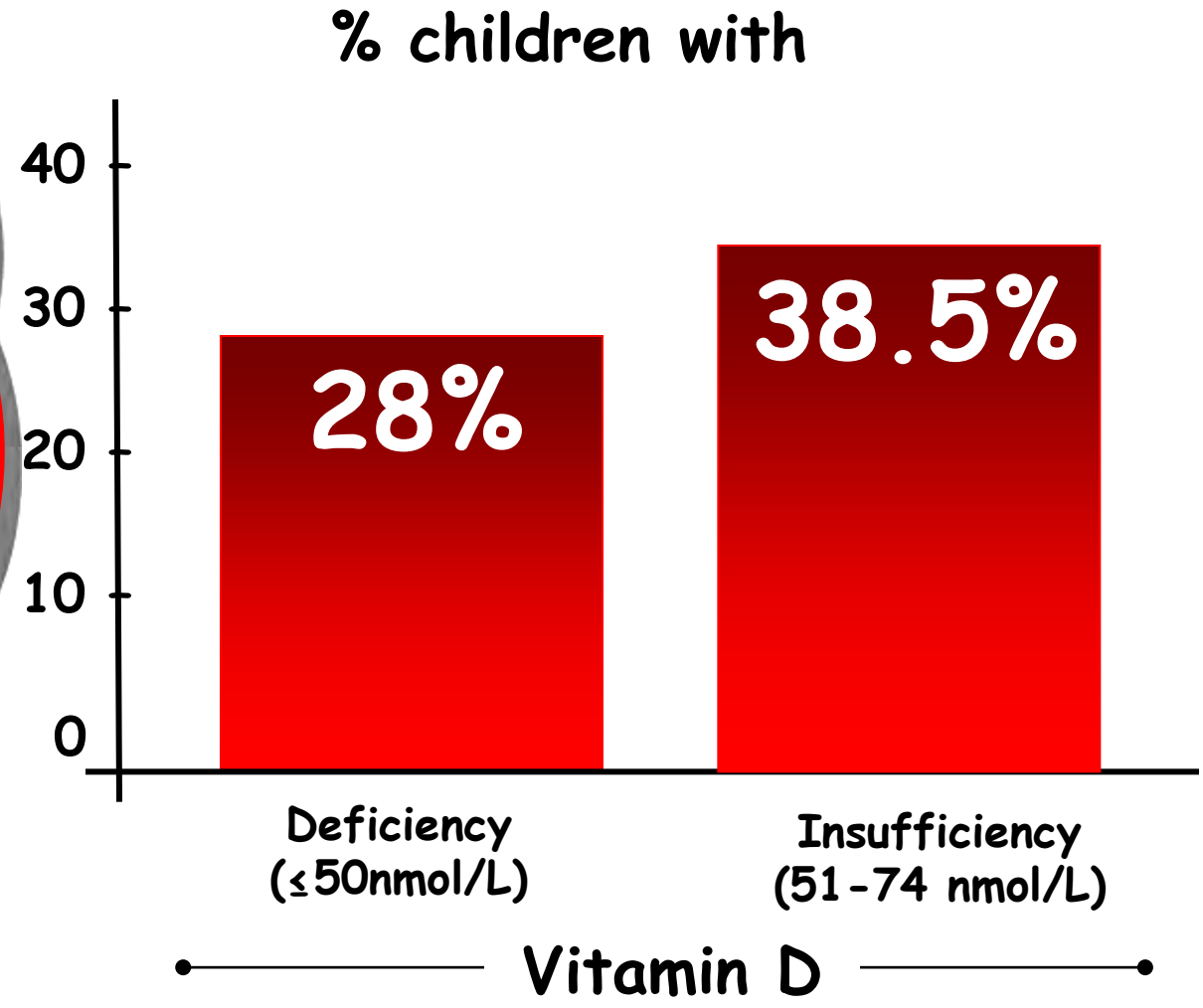
Vitamin D Status of Exclusively Breastfed 4-Month-Old Infants Supplemented During Different Seasons *Halicioglu O., Pediatrics 2012;130:e921*

- ✓ 25(OH) D levels.
- ✓ 143 exclusively brestfed 4-month-old infants supplemented daily with 400 UI of vitamin D, Turkey between May 2008 and April 2009.



Vitamin D Status of Exclusively Breastfed 4-Month-Old Infants Supplemented During Different Seasons *Halicioglu O., Pediatrics 2012;130:e921*

During winter days, serum 25(OH) levels were <20ng/mL in 45.4% of infants and <10 ng/mL in 10.6% of infants.



Vitamin D Status of Exclusively Breastfed 4-Month-Old Infants Supplemented During Different Seasons *Halicioglu O., Pediatrics 2012;130:e921*

CONCLUSIONS:
Despite supplementation with 400 IU of vitamin D daily, the rate of vitamin D deficiency was worryingly high in 4-month-old exclusively breastfed infants living in Izmir, Turkey.

So, additional studies are needed to clarify optimal amount of vitamin D supplementation to the infants, especially during winter days.