Effect of Malnutrition on Resistance to Infection

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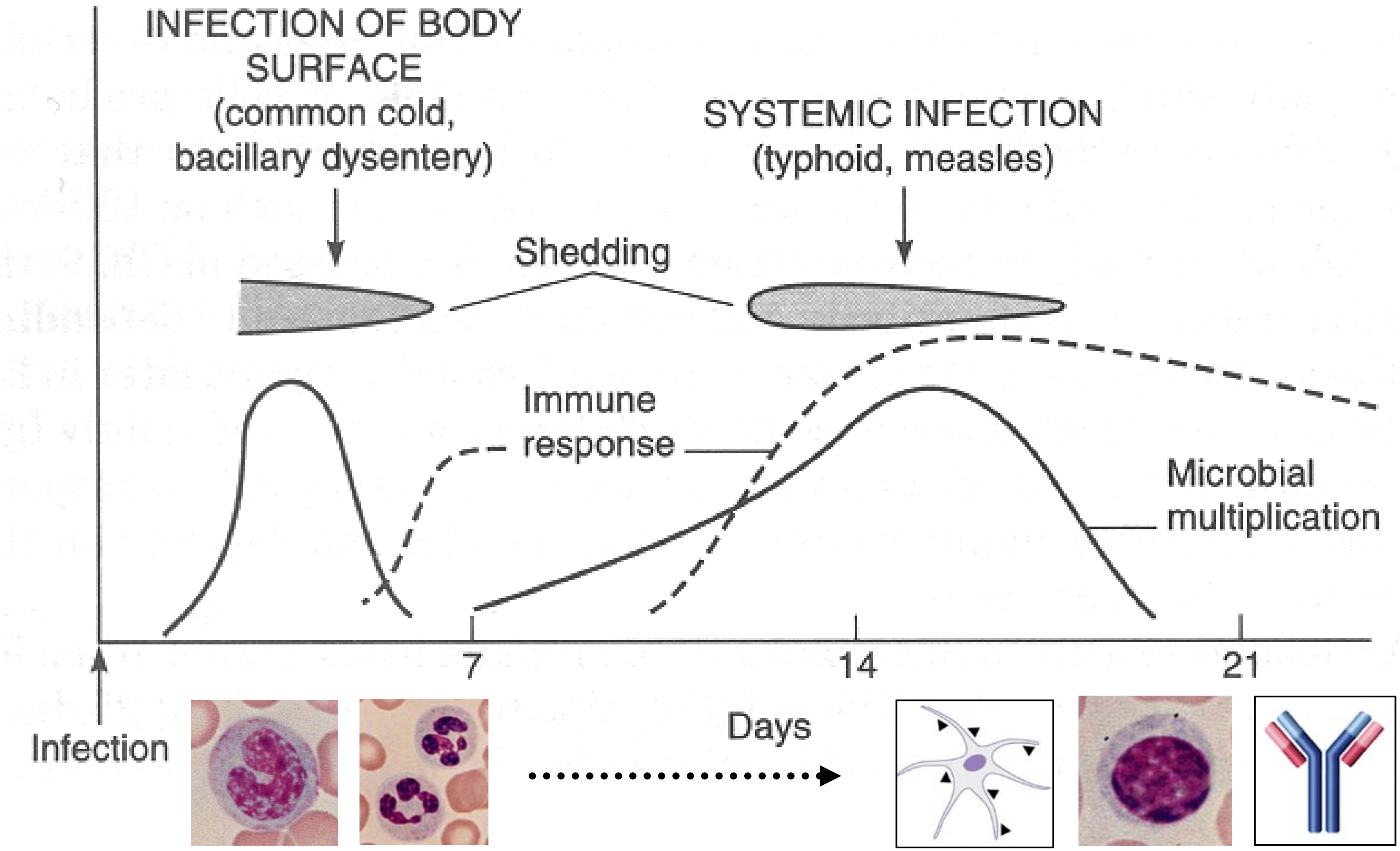
The Immune Response to Infection

Pathogenesis of Infectious Disease. Cedric Mims.



Innate Immunity …….. Adaptive Immunity

Chapter 3: Effect of Malnutrition on Resistance to Infection

1968

- Synergism & antagonism of nutrition and infection
  - Little mechanistic data
- Observational clinical & community studies
- Animal studies
  - Many species
  - Clinical, pathological, & microbiological endpoints

2008

- A focus on mechanisms
  - Some nutrients "modulate" immune response (vitamin A, $\omega 3/\omega 6$ fatty acids)
- Randomized, controlled trials
- Animal studies
  - Mice (± gene of interest)
  - Immunologic endpoints

Chapter 4: Determinants of the Effects of Nutrition on Infection

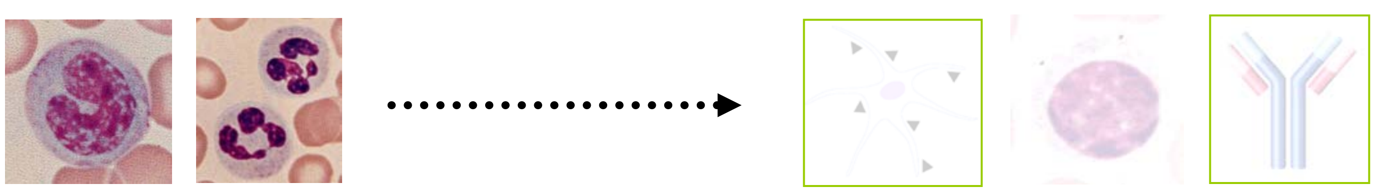
1968

- Immune mechanisms
  - Antibody formation
  - Phagocytic activity
- Protein energy malnutrition impairs protective immunity
- Infectious disease

2008

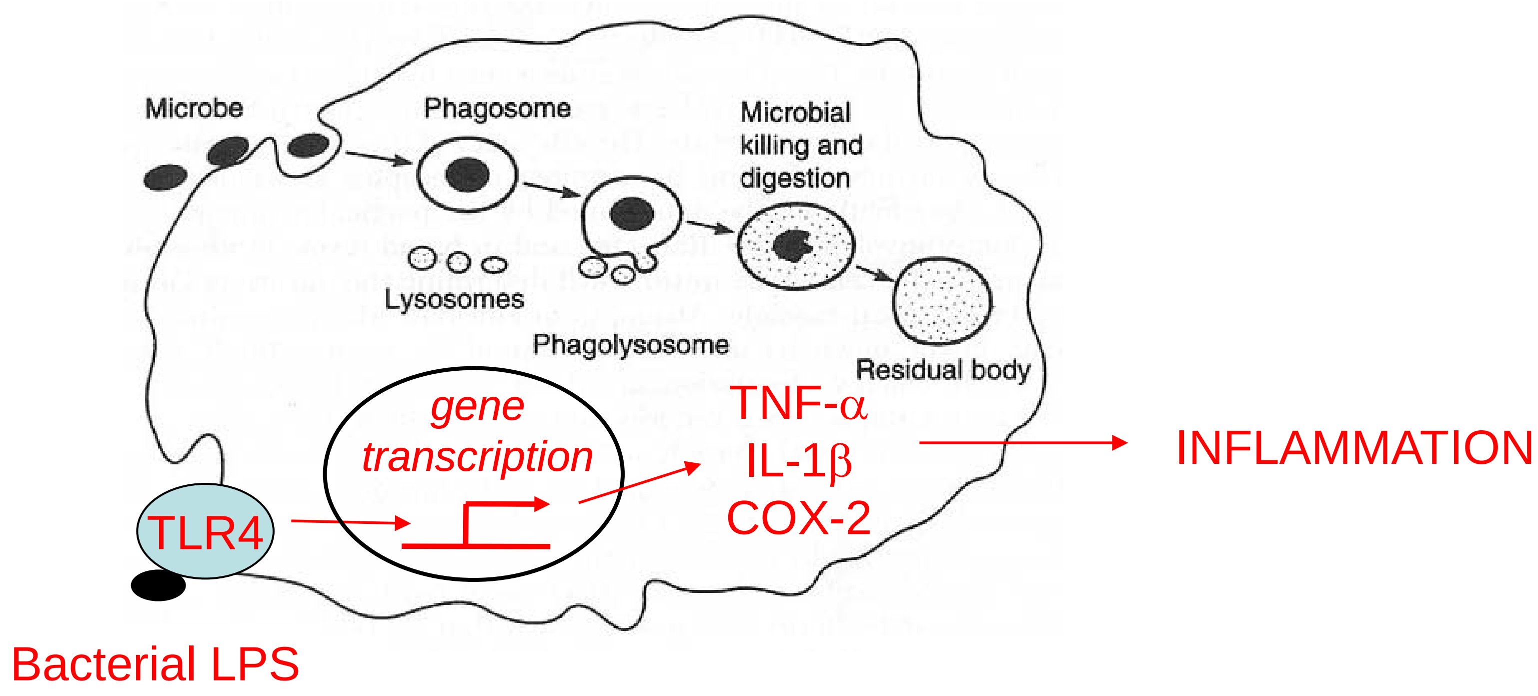
- Adaptive immune system
  - B cells, CTL, Th1, Th2, Th17, Treg, γ/δT, NK, NKT
- Innate immune system
  - Pattern-recognition receptors, anti-bacterial peptides, antigen-presenting cells
- Dietary restriction in a “calorie rich” environment enhances immunity
- Inflammatory disease

Fat Does More Than Provide Energy: Fatty Acids Modulate Inflammation



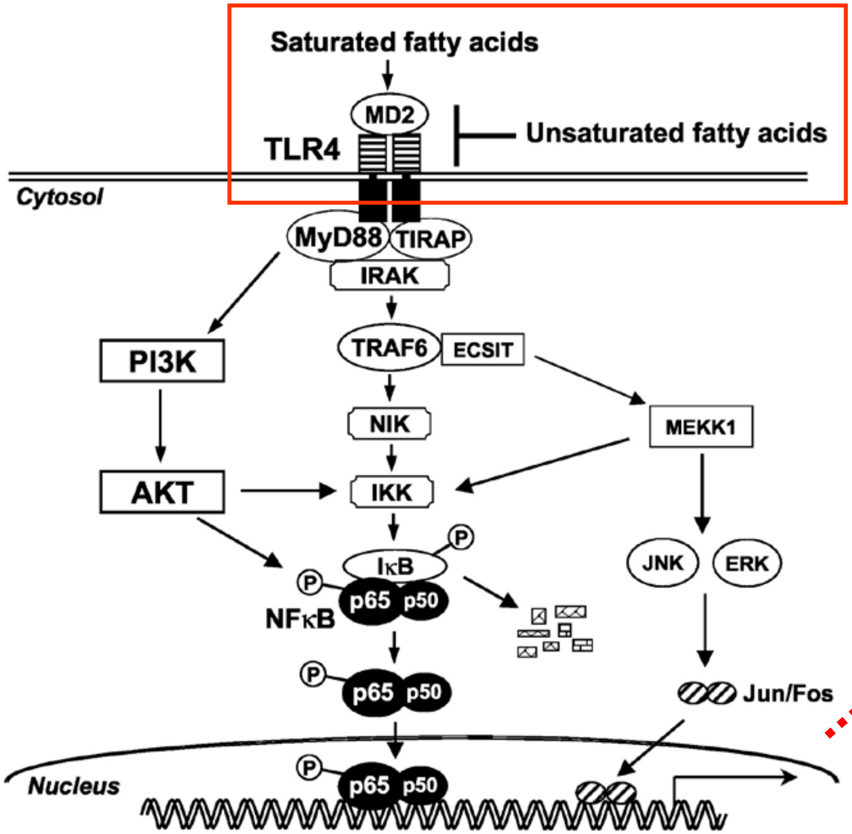
Innate Immunity …...... Adaptive Immunity

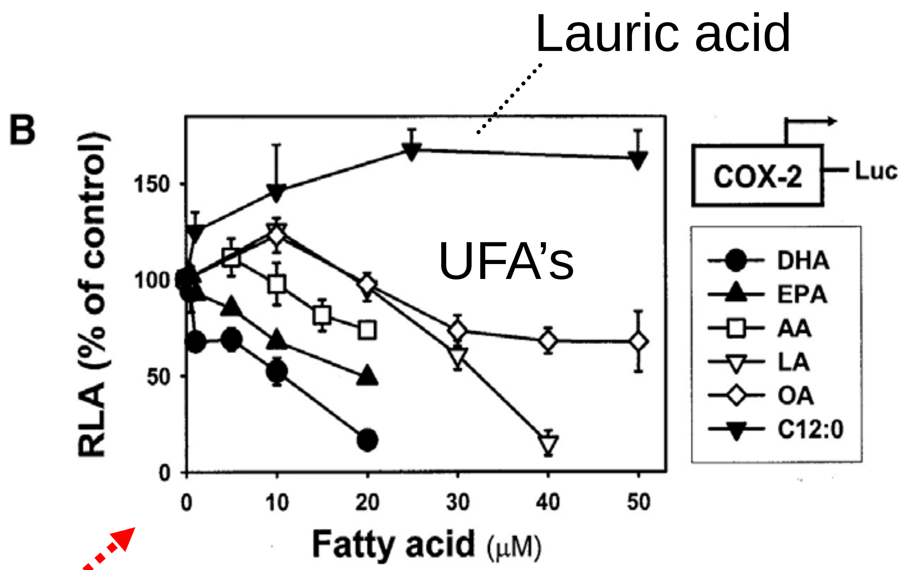
Bacterial LPS stimulates transcription of proinflammatory genes by activation of toll-like receptor 4 (TLR4)



Saturated fatty acids stimulate and unsaturated fatty acids inhibit TLR4 activation

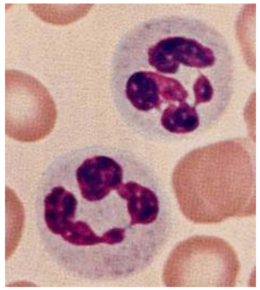
Lee, J. Y. et al. J. Lipid Res. 2003;44:479-486





Cyclooxygenase 2 (COX2) promotes inflammation by metabolizing arachadonic acid (AA) to produce prostaglandins.

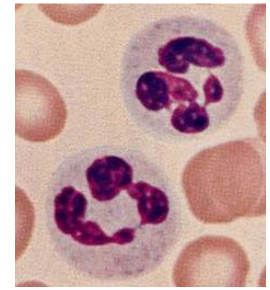
Relative dietary intake of AA and EPA determines membrane AA:EPA ratio



Arachadonic Acid
(AA) 20:4 ω6

COX → 2-series prostaglandins → INFLAMMATION

5LOX → 4-series leukotrienes → INFLAMMATION

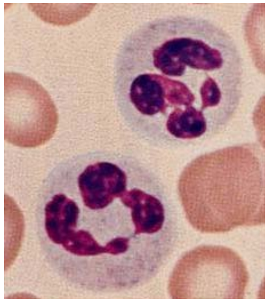


Eicosapentaenoic Acid
(EPA) 20:5 ω3

COX → 3-series prostaglandins → less inflammation

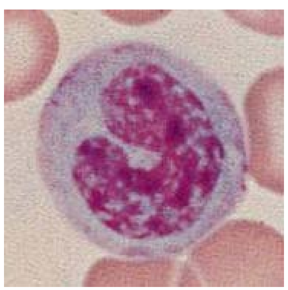
5LOX → 5-series leukotrienes → less inflammation

Arthritic Joint

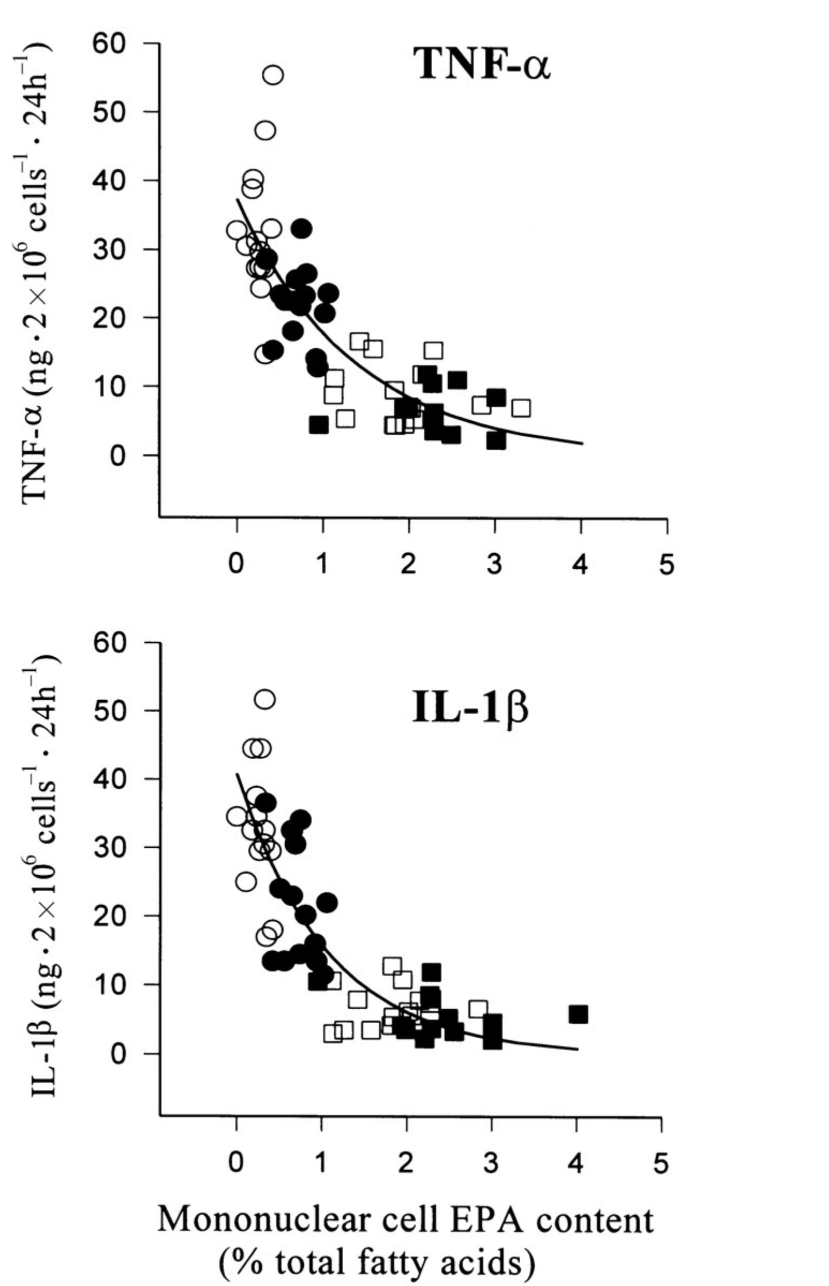


X ← EPA

LTB4
(enhance inflammation)

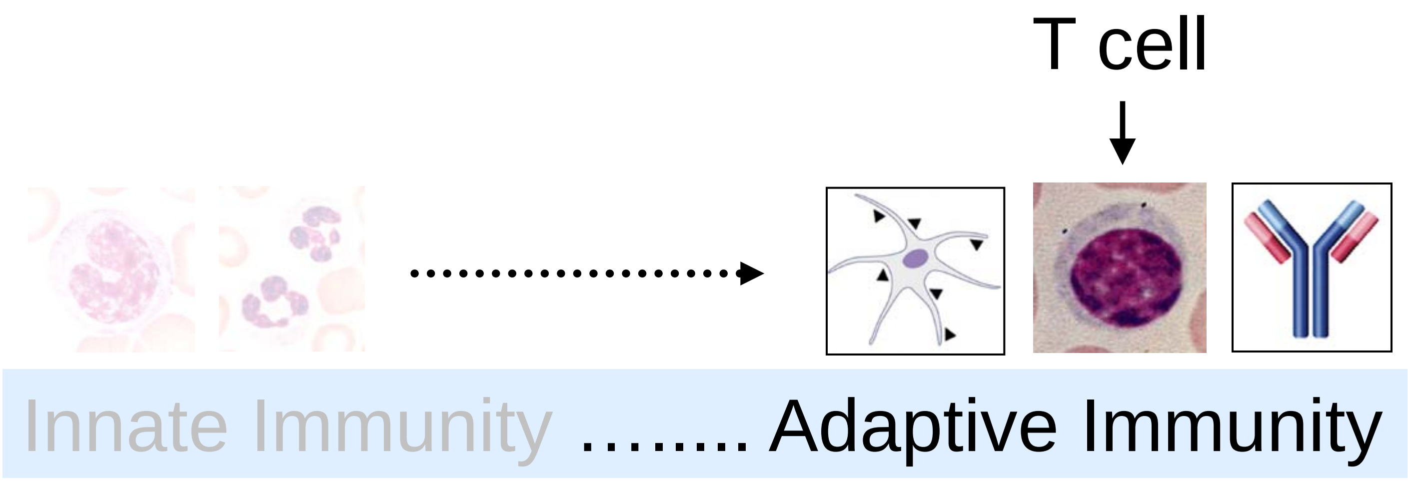


TNF-α, IL-1β



James et al. Am J Clin Nutr 2000;71(suppl):343S–8S.

Protein-Energy Malnutrition, Dietary Restriction and Adaptive Immunity

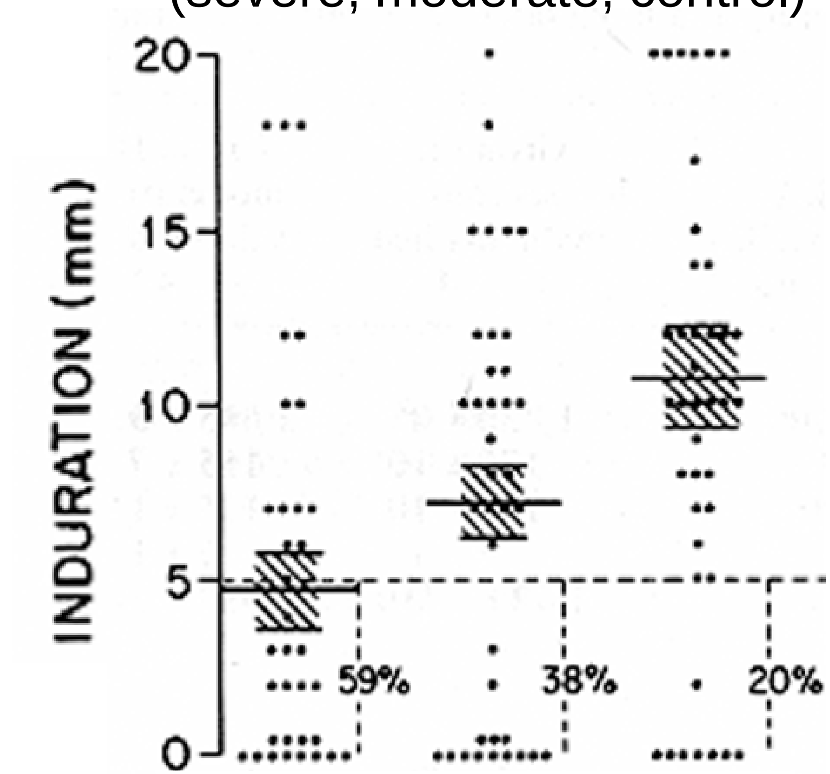


Protein-energy malnutrition impairs thymic function, diminishing T cell-mediated immunity.

Thymic functions recovers rapidly on refeeding.

Mechanism?

DTH skin test (*Candida*) in children with malnutrition (severe, moderate, control)



<60% 60-80% >80%

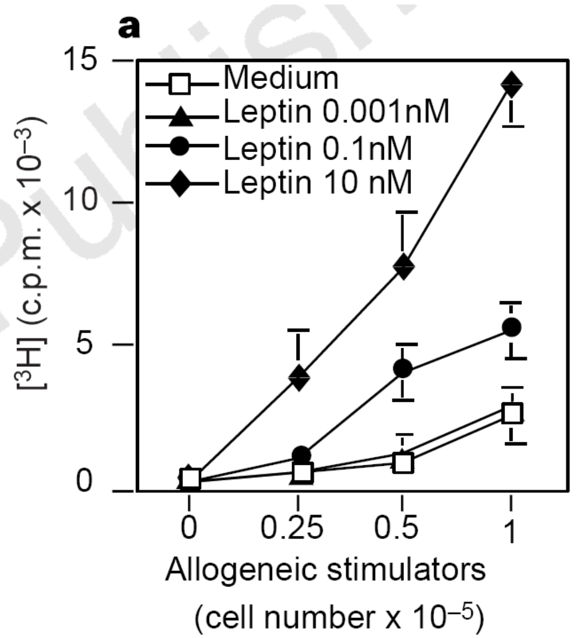
Weight-for-age

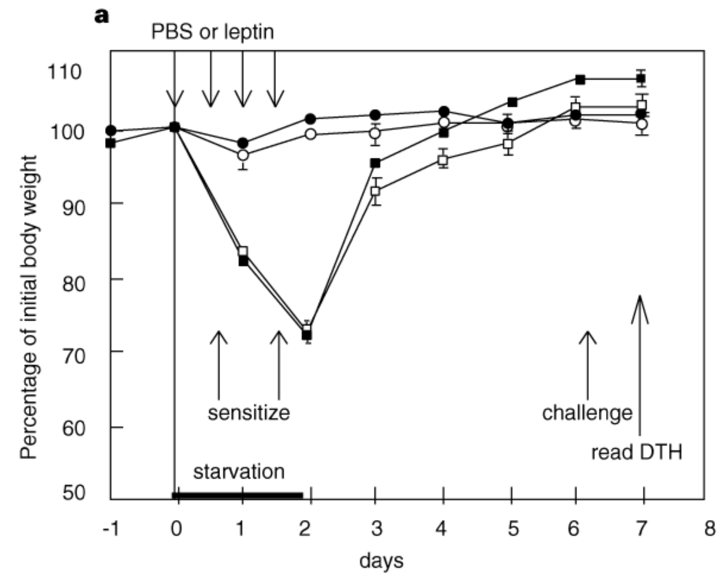
<2.5 >2.5 >2.5

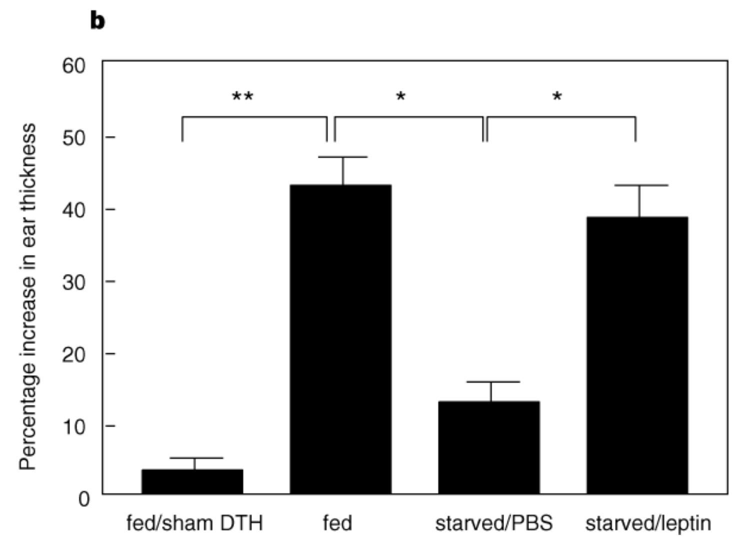
Serum albumin (g/dL)

Neumann et al., Am J Clin Nutr 28:89-104, 1975

T-cell immune deficiency is induced by starvation and reversed by leptin





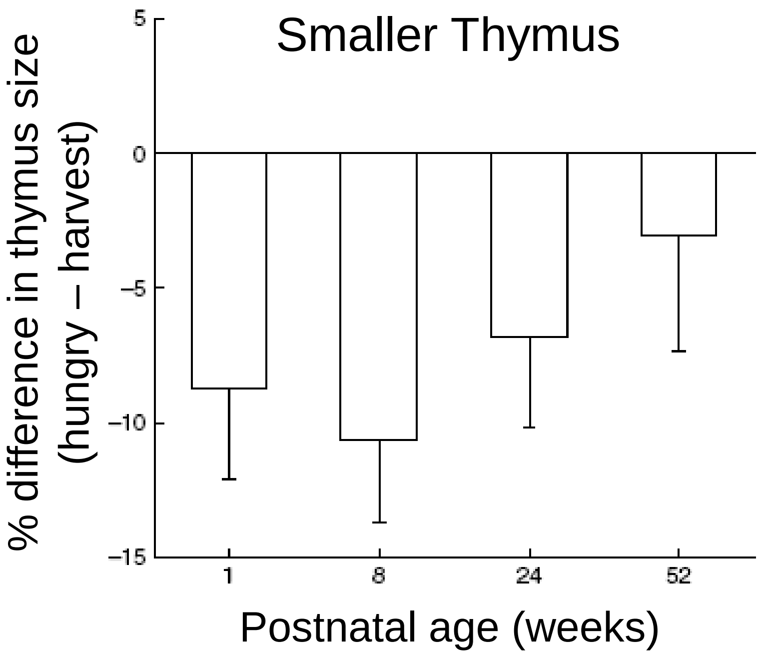


Leptin is produced by adipose tissue, reflects energy reserves and is lower in PEM. Mice without leptin or its receptor have thymic atrophy. T cells have leptin receptors. Leptin promotes T-cell survival, proliferation and differentiation.

Lord et al. Nature 394:897, 1998.

Gambian infants born in hungry season have impaired thymic function and greater mortality as adults than children born during the harvest season

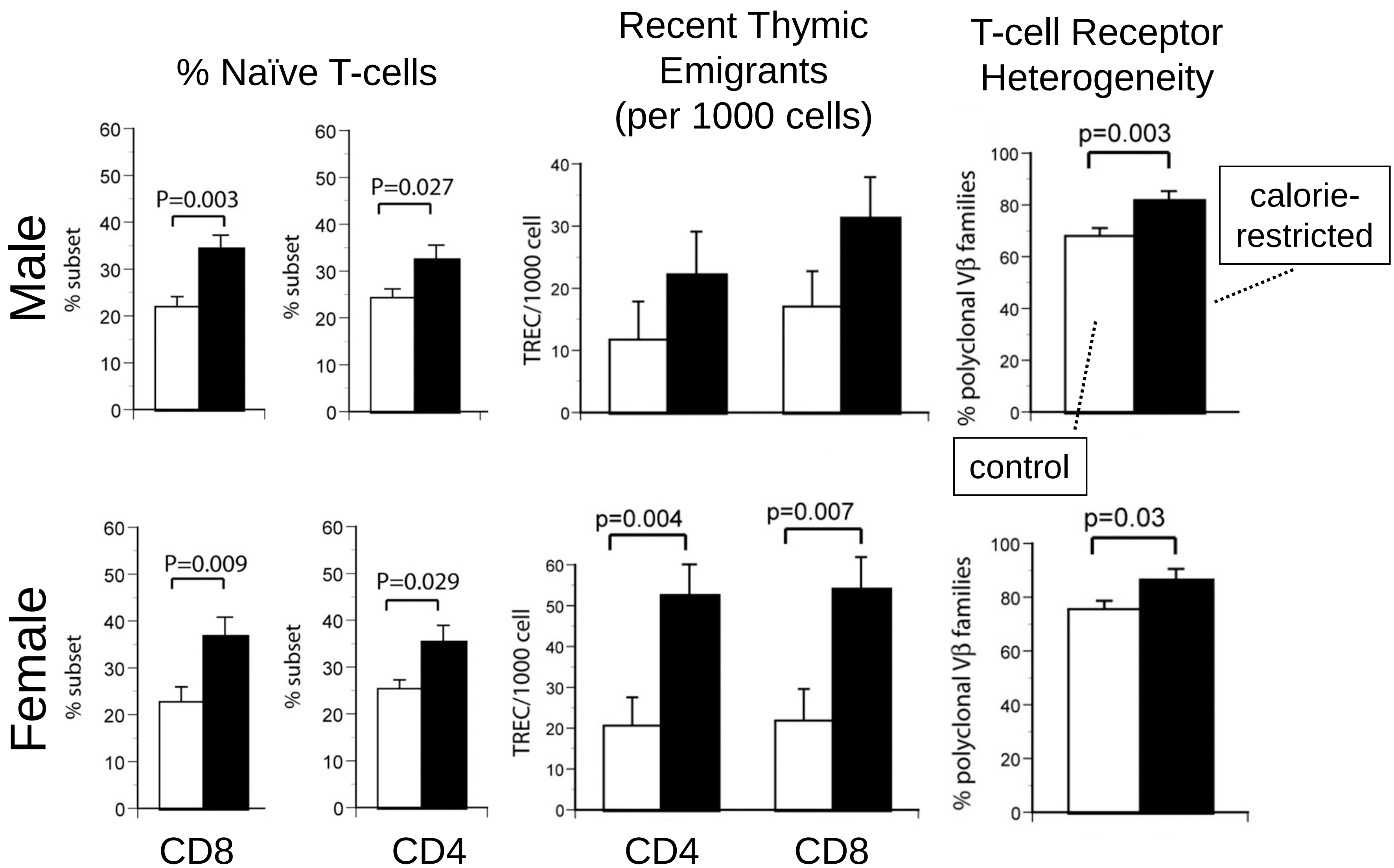
Moore et al. Proc Nutr Soc (2006), 65, 311



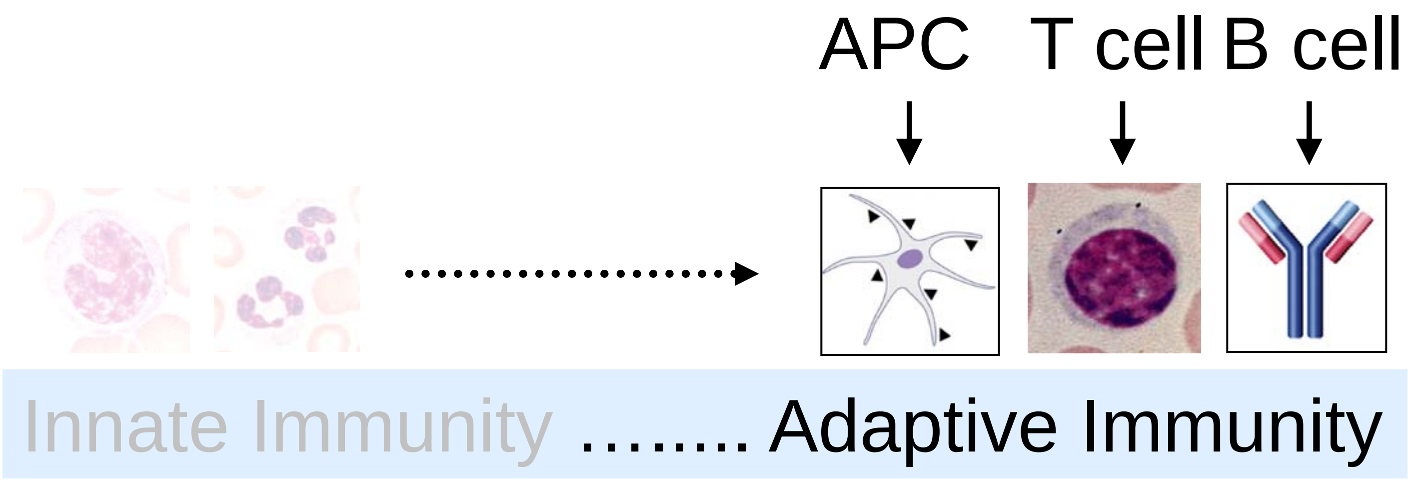
Thymic Function - 8 wk old infants born in harvest season have a significantly higher % of recent thymic emigrant T-cells in their blood than do infants born in the hungry season (2.12 v. 0.92 per 100 T-cells, $P = 0.006$)

T-cell senescence is delayed by caloric restriction in long-lived nonhuman primates

Messaoudi et al. PNAS 103:51 2006



Vitamin A, Community Intervention Trials, Nuclear Receptors and Adaptive Immunity



Vitamin A supplementation decreases early childhood mortality in community-based RCTs

Study	*Relative Risk*	*p-value*
Aceh, Indonesia	0.73	0.024
Ghana	0.82	0.005
Hyderabad, India	0.94	0.817
Jumla, Nepal	0.74	0.058
MSG, Indonesia	0.70	0.001
Sarlahi, Nepal	0.71	0.003
Sudan	1.04	0.756
Tamil Nadu, India	0.50	0.001
Summary	0.775	3×10^{-9}

Vitamin A supplementation decreases mortality from measles

Hussey and Klein NEJM 323:160, 1990

Subjects

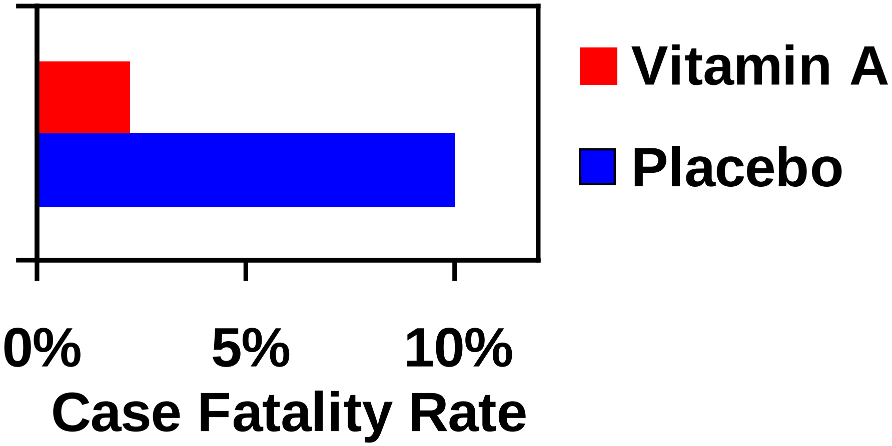
- 189 children < 13 y of age admitted to hospital for measles

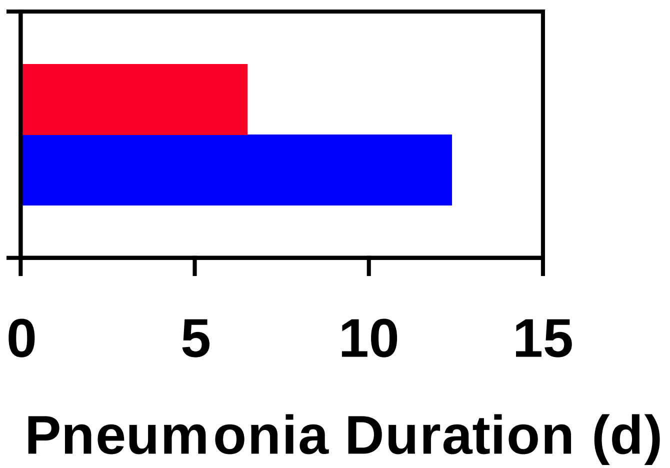
Treatment

- 200,000 IU vit. A on admission and d 2

Results

- Reduced mortality and severity





Vitamin A supplementation slows recovery in children hospitalized with pneumonia

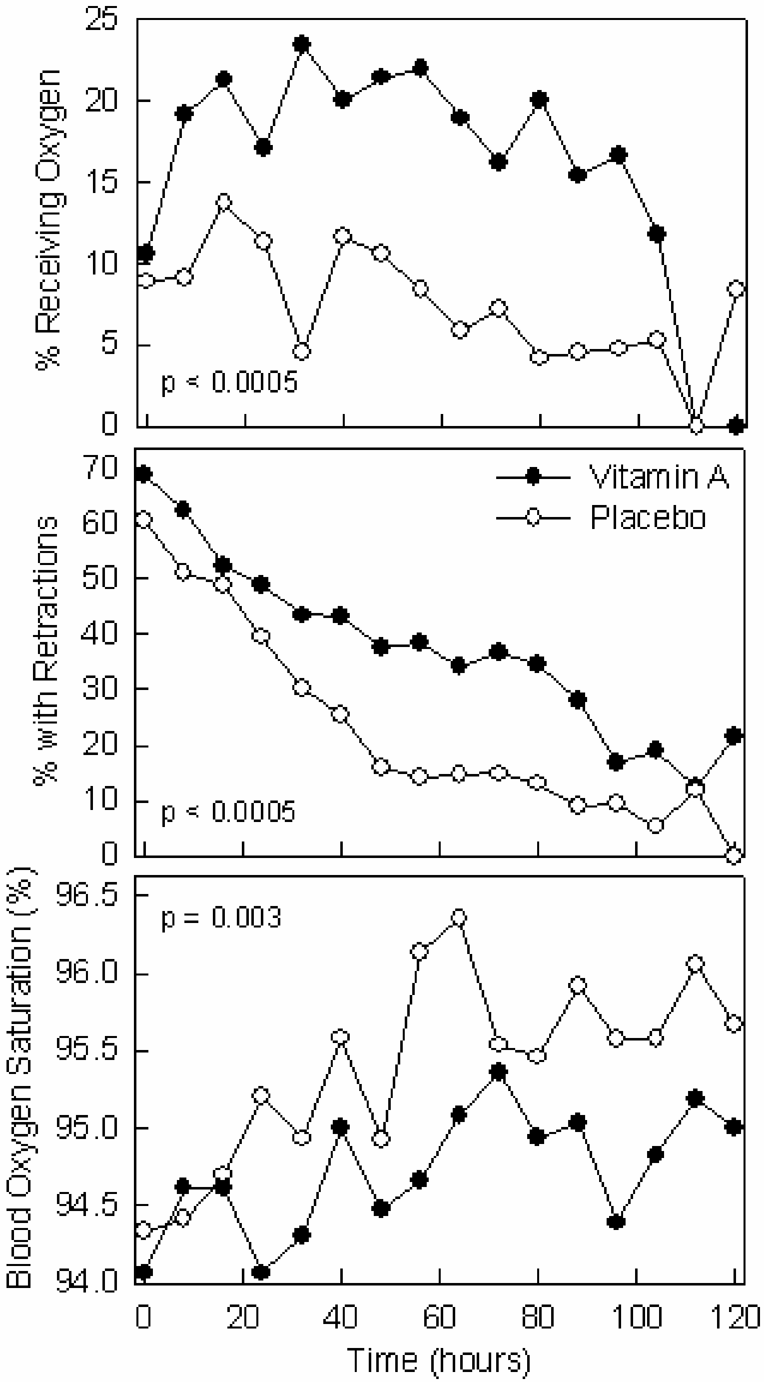
Stephensen et al, Pediatrics 101:e3-10, 1998

Hypothesis

- Vitamin A will decrease duration and severity of pneumonia

Results

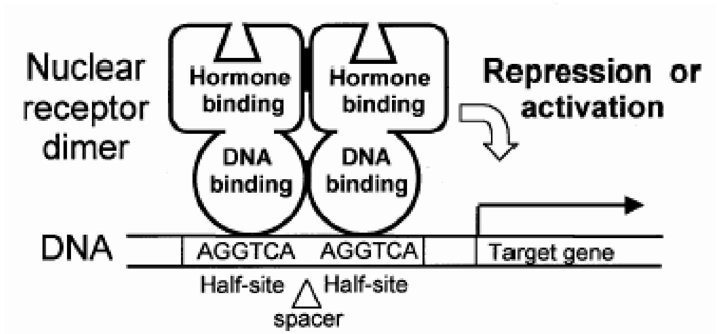
- no change in duration of hospitalization
- Vit. A slowed normalization of clinical indicators of severity
- Vit. A decreased prevalence of subclinical deficiency



1968: What is the active metabolite of vitamin A in the immune system?

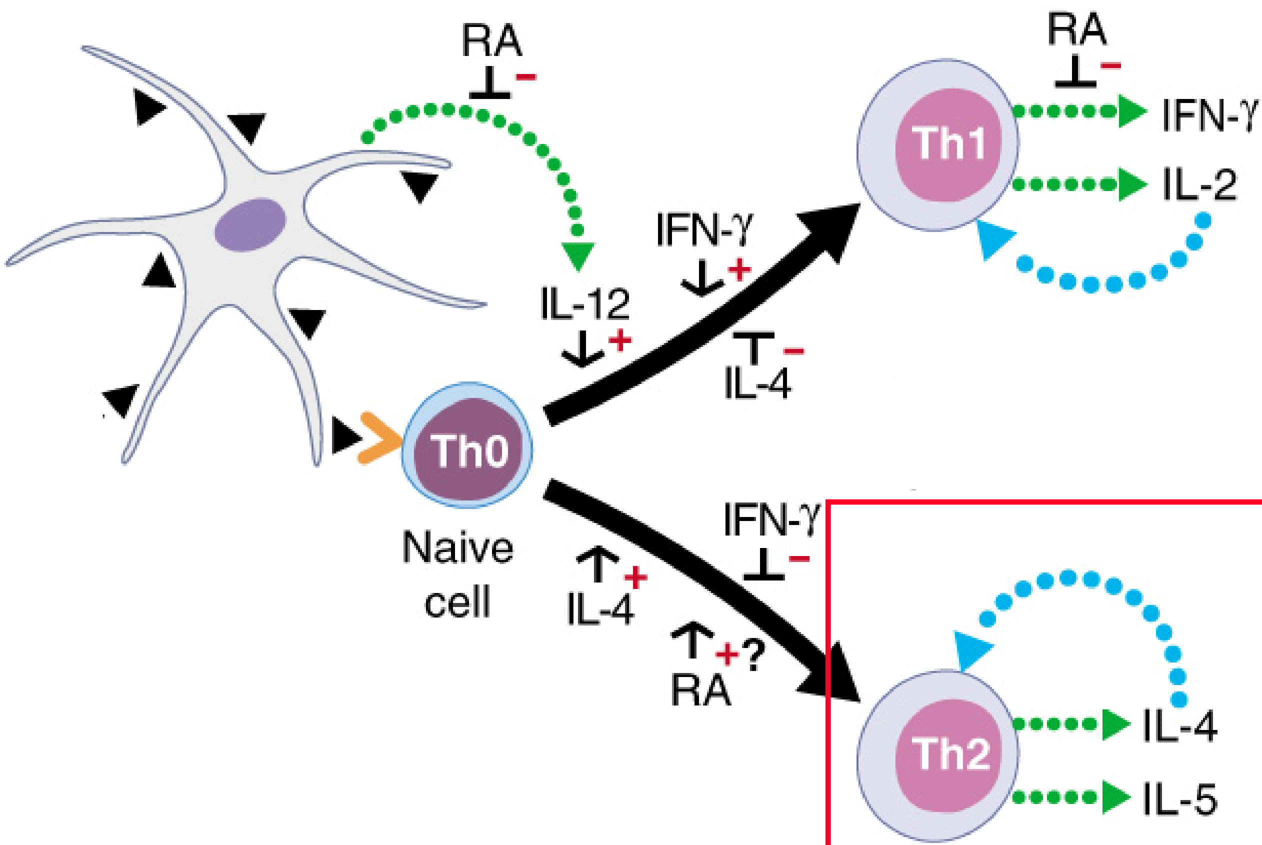
1987: P. Chambon, R. Evans Labs

Retinoic Acid ··························►



RAR:RXR

Vitamin A promotes Th2 responses



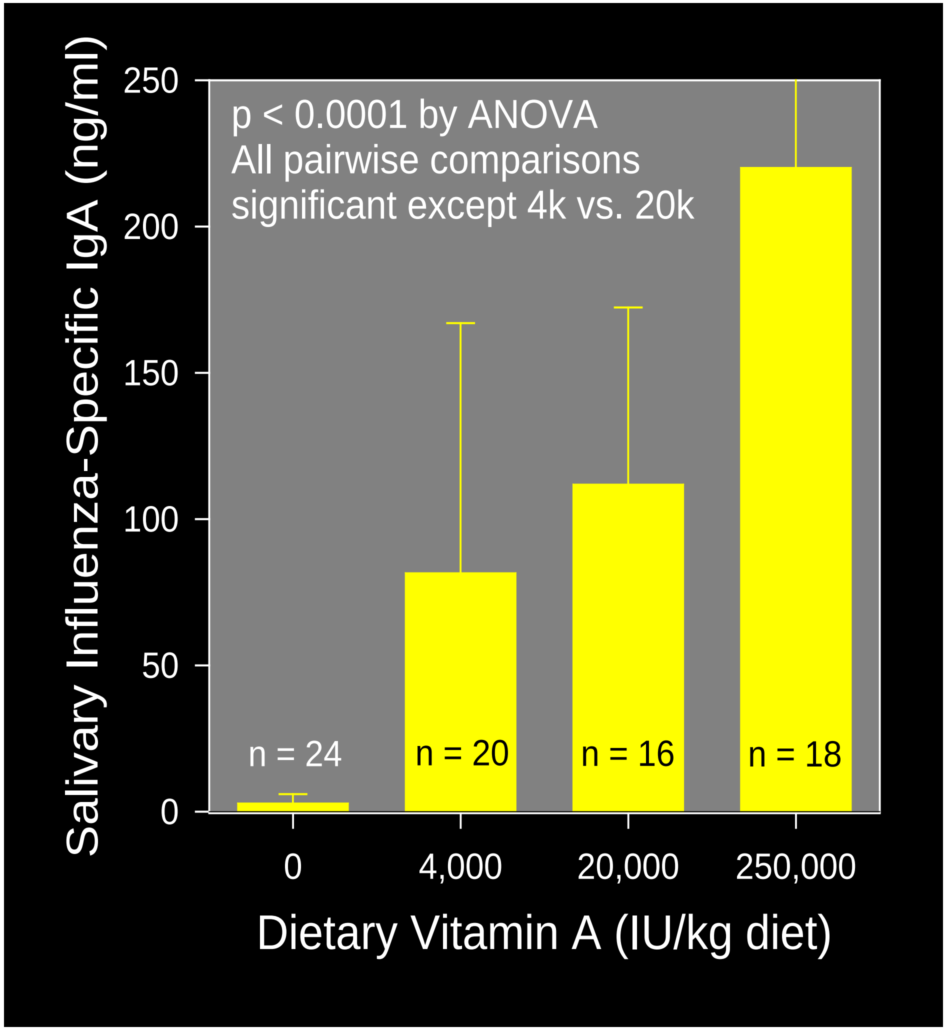
Defense against intracellular pathogens
-cytotoxic T-cells
-IgG2a
-Macrophage activation

Defense against extracellular pathogens
-IgA, IgG1, IgE
–(α4β7 integrin)
-eosinophils

Impaired by vitamin A deficiency

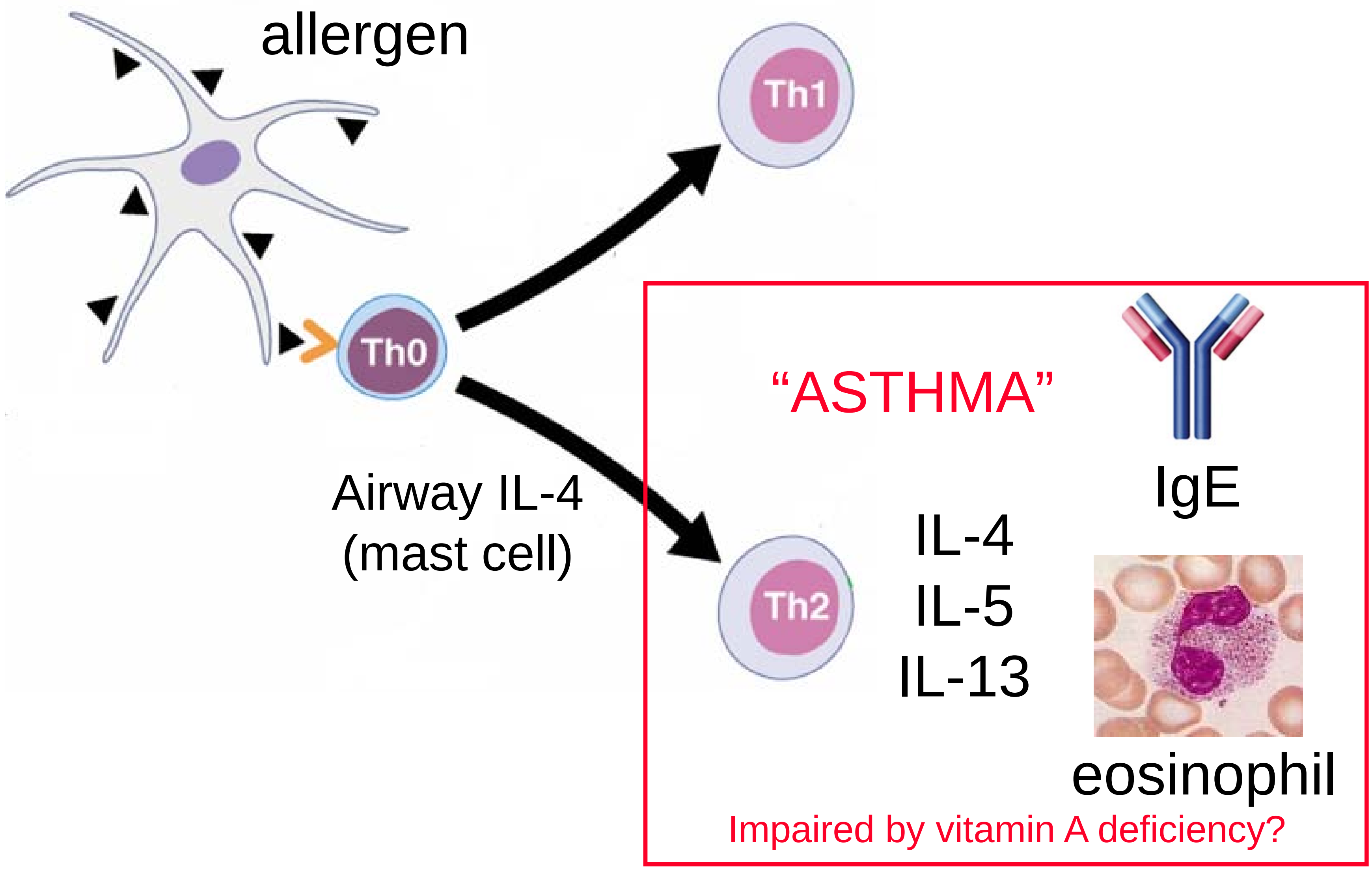
RA = Retinoic Acid

Vitamin A deficiency decreases and high vitamin A increases influenza-specific salivary IgA response by decreasing number of flu-specific plasma cells

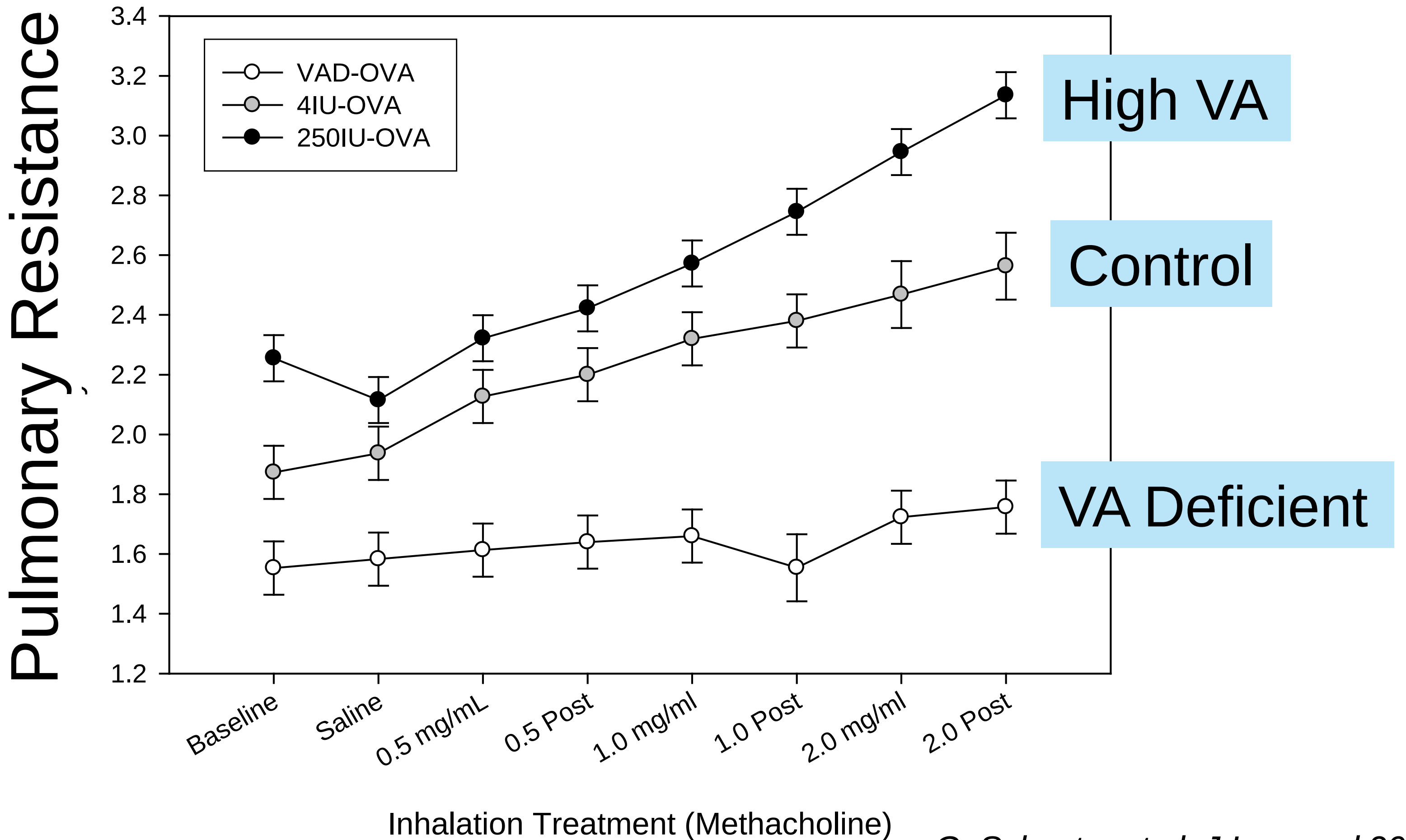


D. Cui et al., J Nutr, 2000

Th2 Response Promotes Asthma Development

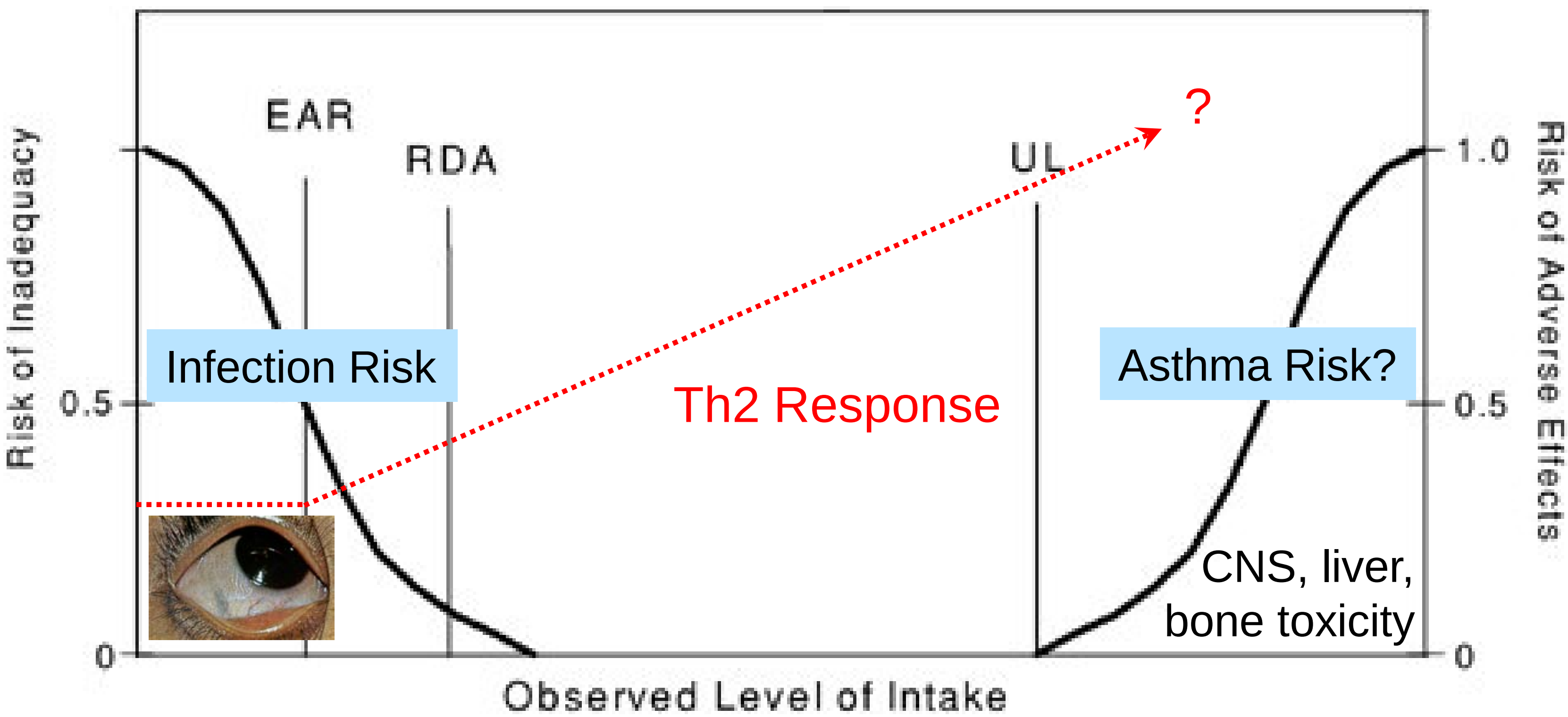


Vitamin A deficiency decreases & high vitamin A increases severity of eosinophilic pulmonary inflammation ("asthma") in mice



G. Schuster et al. J Immunol 2008

Vitamin A Requirements



Summary

1968

- Nutritional deficiencies are definitively associated with increased severity of infectious disease

2008

- Treating micronutrient deficiencies with supplements decreases morbidity and mortality in randomized, controlled trials
- Detailed mechanistic data on impact of some nutrient deficiencies on specific aspects of immunity from mouse models
- MISSING LINK: Mechanistic studies in humans with nutritional deficiencies in appropriate populations and geographic settings