

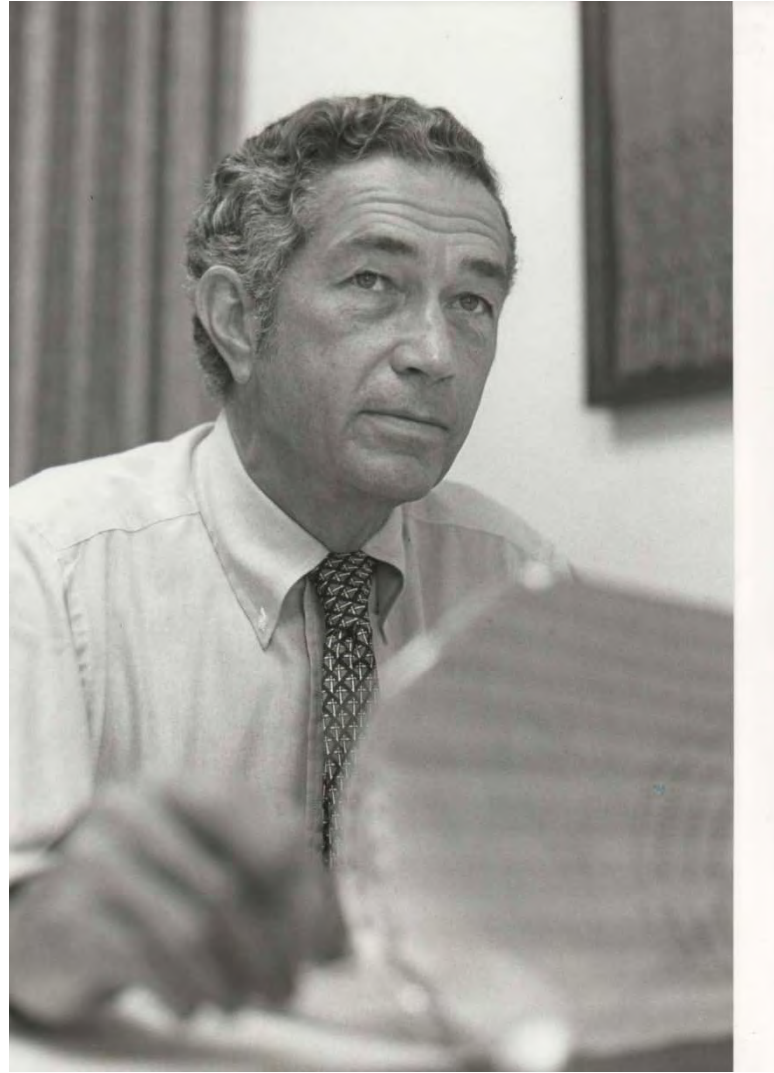
**THIRD GEORGE G. GRAHAM LECTURE
PRESENTED BY THE MIDDENDORF FOUNDATION**

“Interactions of Nutrition and Infection”

***“Effects of Infection on
Nutritional Status”***

**Claudio F. Lanata, MD, MPH,
Instituto de Investigacion Nutricional,
Lima, Peru**

George G Graham, M.D.
1923 - 2007



George's contributions to nutrition... ...and politics!





INSTITUTO DE INVESTIGACION NUTRICIONAL



Thanks to GGG and the course Readings on Nutrition!



N Scrimshaw, C Taylor, & J Gordon

Findings in their 1968 review

- ✓ Effects on nutrition from Typhoid, tuberculosis, Measles and other virus, protozoal and helminthic infections
- ✓ Mostly based on clinical studies on the effect of infections on the metabolism (ie. nitrogen balance) , either on humans or laboratory animals, as well as the effect on some micronutrients
- ✓ No longitudinal studies on children were included, to explore this effect.

N Scrimshaw, C Taylor, & J Gordon

Findings in their 1968 review

- Of particular interest, among many findings, was the description of studies providing daily doses of aureomycin that improved the child's growth only during antibiotic treatment, as compared to placebo.
- No effect on daily Penicillin.
- These studies revealed the problem of bacteria overgrowth in the gut, what has been called “tropical barrier” for delivering good antigens to the gut in the vaccine field.
- Indeed, children in poor countries exposed to unsanitary conditions eat, drink and swallow millions of micro-organisms creating a nutritional burden to the body, due to the immunological and metabolic efforts to keep them under control.

Cryptosporidium infections and growth in “healthy” children

- W Checkley studied the effect of the first infection with *Cryptosporidium parvum* on growth in 207 Peruvian children 0-3 m followed for 2 years:
 - Children with infection and diarrhea gained 342 g less as compared with controls
 - Children infected without diarrhea gained 162 g less than controls
 - Since asymptomatic infections were more common (63%), it had more adverse effect on child growth than symptomatic ones.
- In a separate analysis they also showed that *C. parvum* infections had a long lasting effect on height, especially when they became infected in infancy and were stunted .

Cryptosporidium and growth

- Another study in a birth cohort studied for 5 y in Brazil showed similar results:
 - In the period 0-3 m after infection, both *C. parvum* and *C. hominis* were associated with declines on height
 - But in the period 3-6 m after infection, only *C. hominis* continued to demonstrate declining heights.
 - Effect was greater among asymptomatic children.
- A prospective study in children <3 y in Guinea-Bissau, showed:
 - Cryptosporidium infections were associated with 392 g of weight loss in boys and 294 g in girls.
 - No catch-up growth was observed. Permanent effect.

Cryptosporidium in the gut



What about Giardia infections?

- In a birth cohort studied by weekly stool samples in 220 Peruvian children, showed:
 - Most children became infected and re-infected
 - Giardiasis did not affect growth at 1 or 2 m after infection
 - No effect on diarrhea also
- Similar result in an unpublished birth cohort study done in the 1980s in Lima:
 - No effect on growth and diarrhea
 - No increased malabsorption
- US Travelers in Lima do get severe giardiasis!

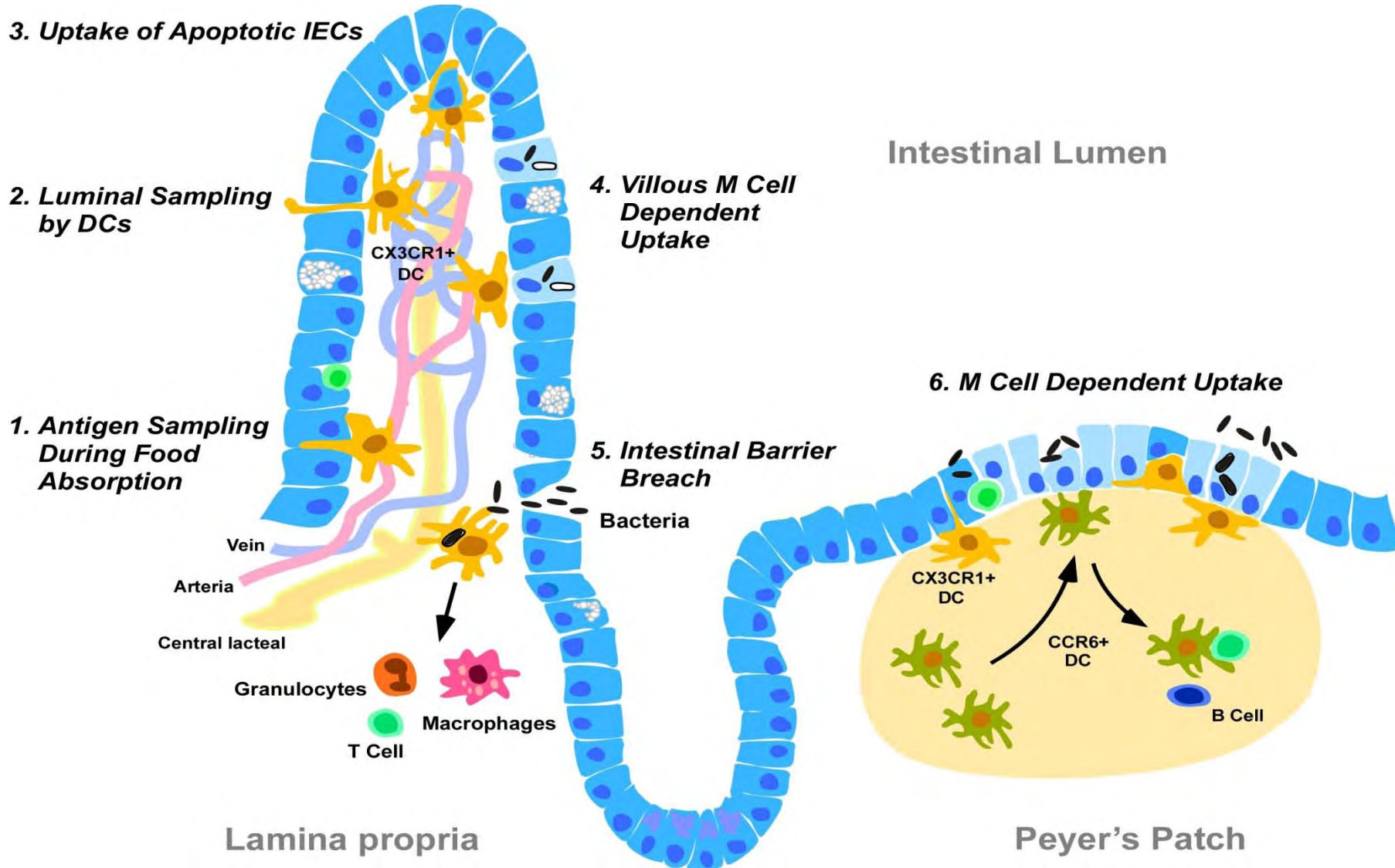
Giardiasis

Possible Explanations:

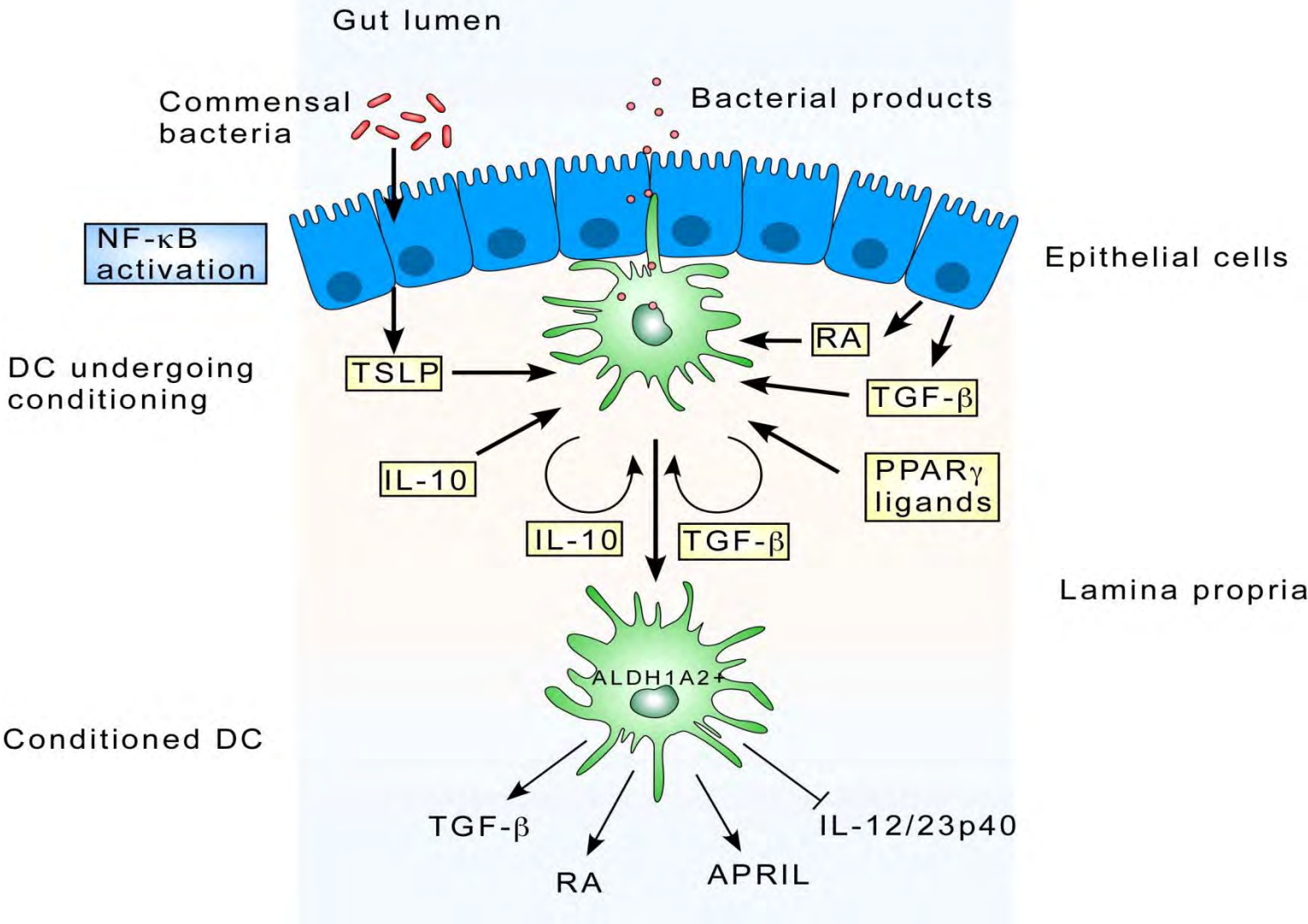
- Early infections may activate the immune system and children became tolerant in endemic areas
- Late infections, however, do cause severe diarrhea
- Animal models supports this theory



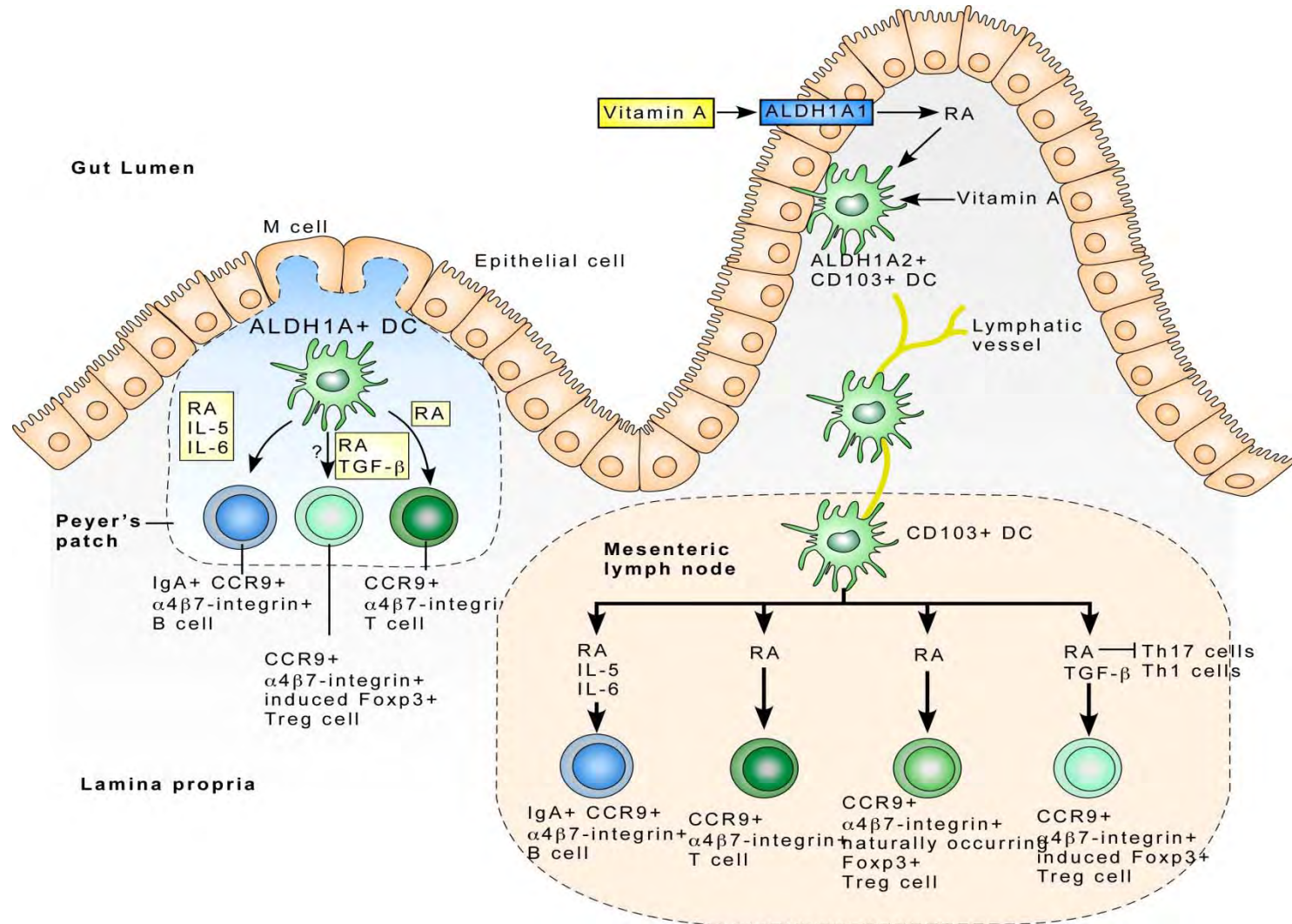
Antigen Uptake in the Intestine



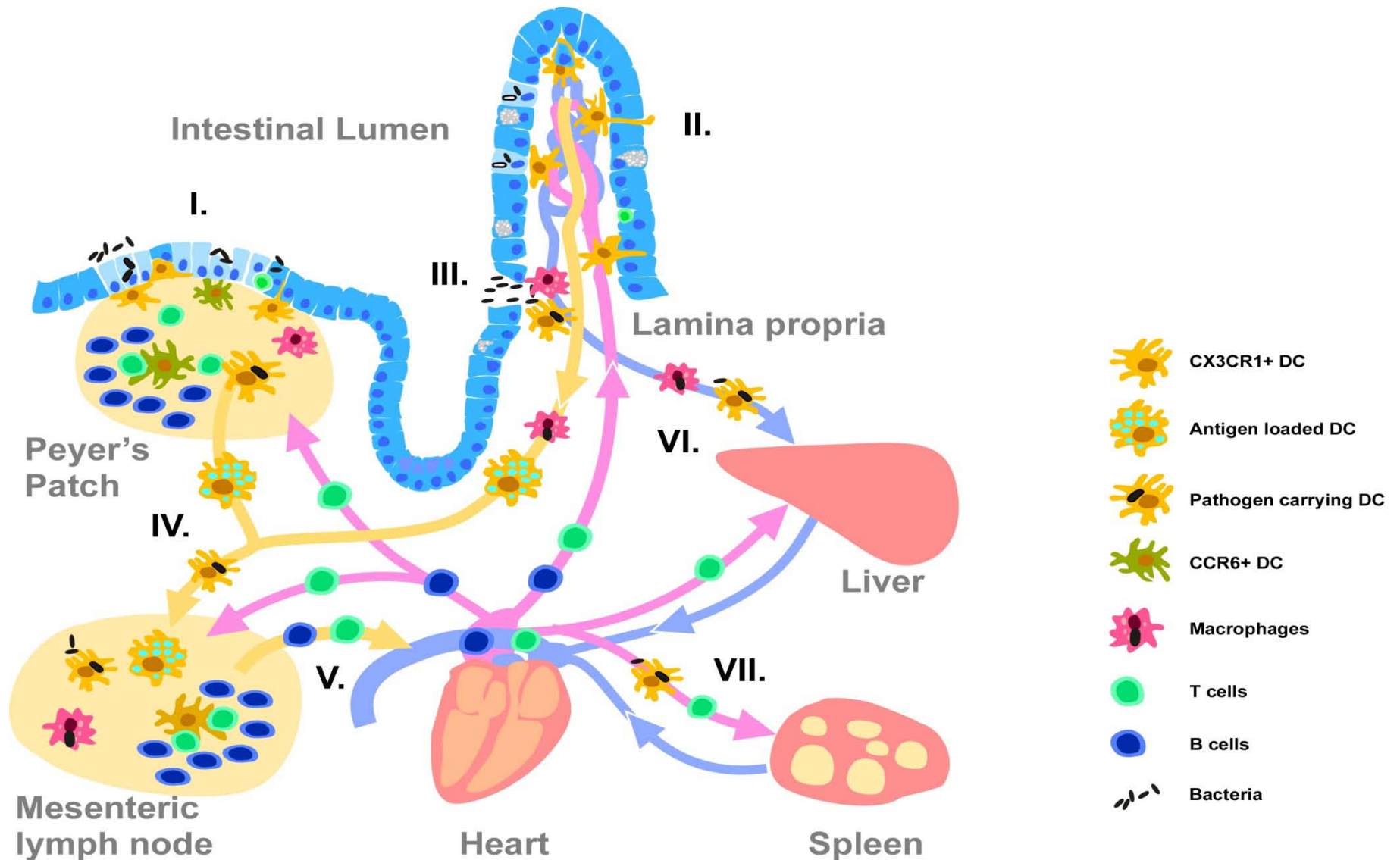
Mucosal Imprinting/Conditioning of Dendritic Cells



Vitamin A is Pivotal for Mucosal DC Function



DC Migration Connects Mucosal Immune Compartments



Nutritional consequences

- The body is actively involved in keeping all these foreign antigens (food, micro-organisms) under control!
- Immunotolerance is not immune suppression but more of an activated immune response that creates tolerance.
- The body of a child produces between 3 to 5 mg of IgA daily delivered to the gut lumen
- The gut has strong immunological memory
- Important nutrition burden that needs to be studied and quantified.

Poverty, infections and nutrition in developing countries

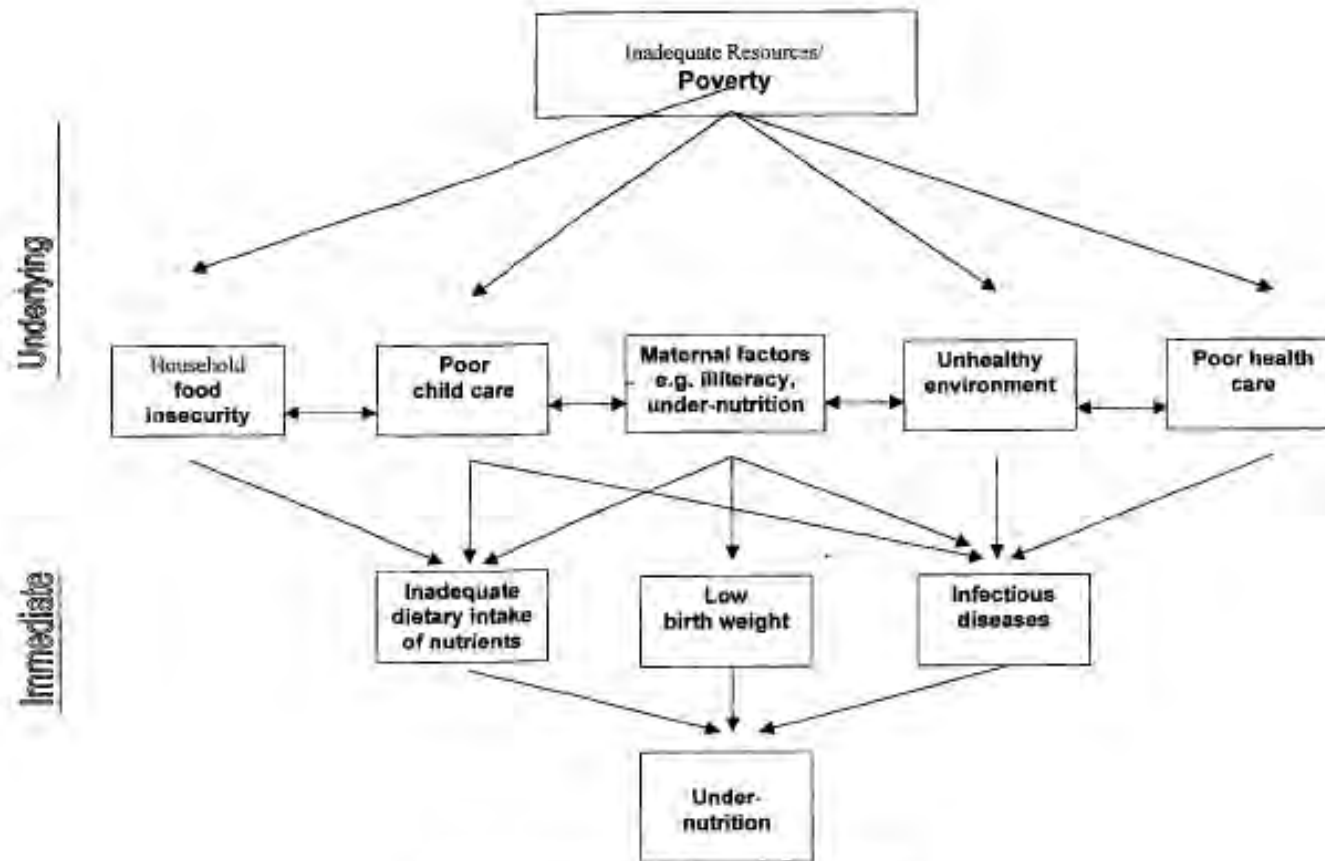
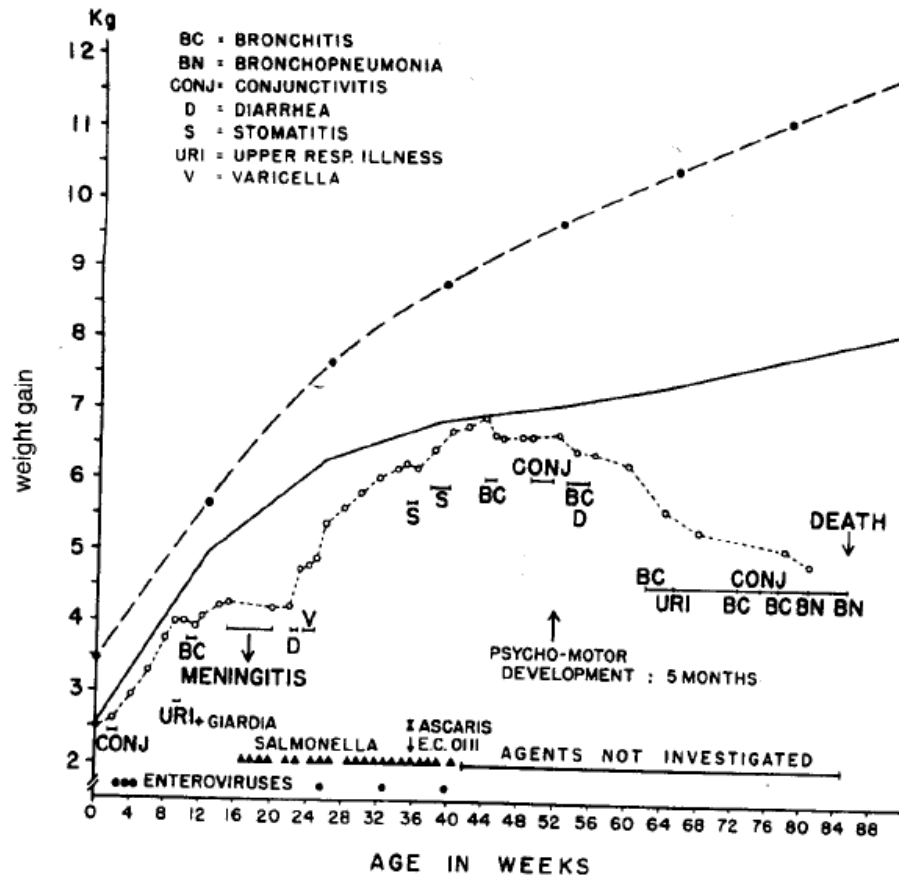


FIG. 1. Causes of undernutrition in children.

The Classical “Matagram”



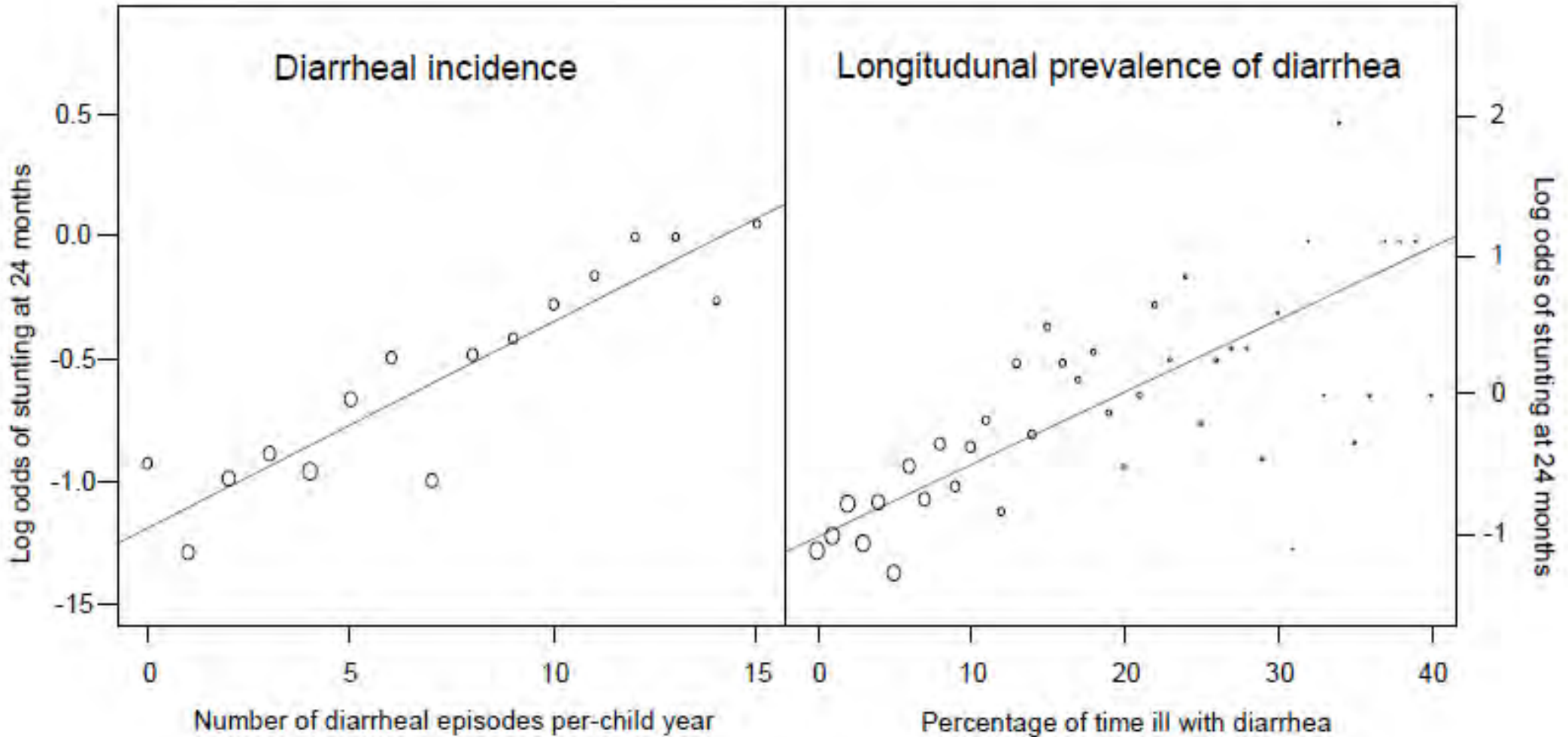
Diarrhea as caused of undernutrition in children

- In a review by A. Baqui of 23 prospective studies that look on the impact of diarrhea on growth:
 - 21 showed an impact on weight
 - 2 studies with no effect were done in Taiwan and Australia
 - From 13 studies with data, the mean (range) weight loss attributable to diarrhea was 14.06 gm/day (1.28-32.0)
 - 13 studies looked for an effect on length/height
 - 4 showed no effect
 - In 8 studies with data, the mean (range) length/height loss attributable to diarrhea was 0.087 mm/day (0.03 – 0.20)
- No meta-analysis has been done

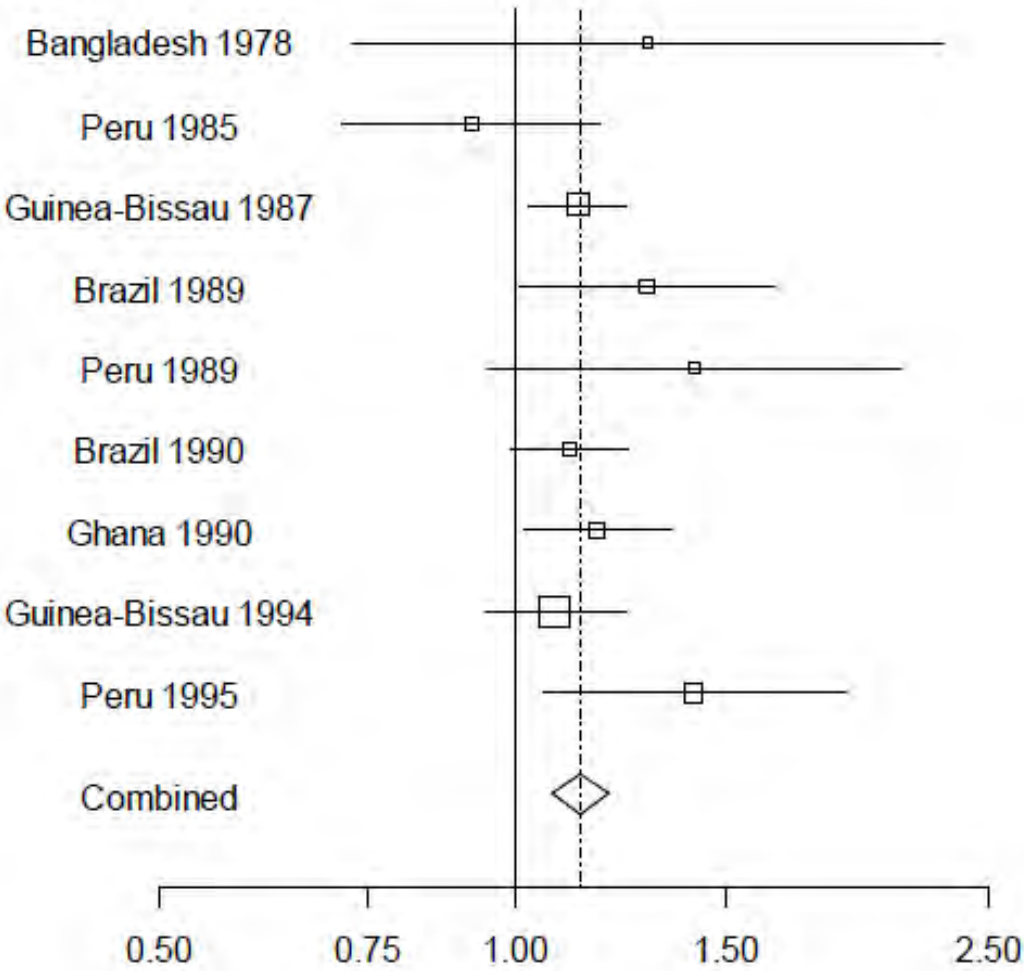
Ref: Baqui AH, Black RE. Nestle Nutrition Workshop Series Vol 48, 2002.

Multi-country analysis of the effect of diarrhea on stunting

- Original data from 9 longitudinal studies done in 5 countries with anthropometric measurements and diarrhea surveillance were analyzed.
- The effect of diarrhea (incidence or prevalence) on stunting at 24 m of age was analyzed, controlling for study location and gender.



Odds of stunting at 24 m when cumulative incidence of diarrhea increased by 5 episodes



Pooled OR = 1.13 (95% CI 1.07 to 1.19)



<10% of children recovered from stunting between 6 and 24 m, beyond regression to the mean

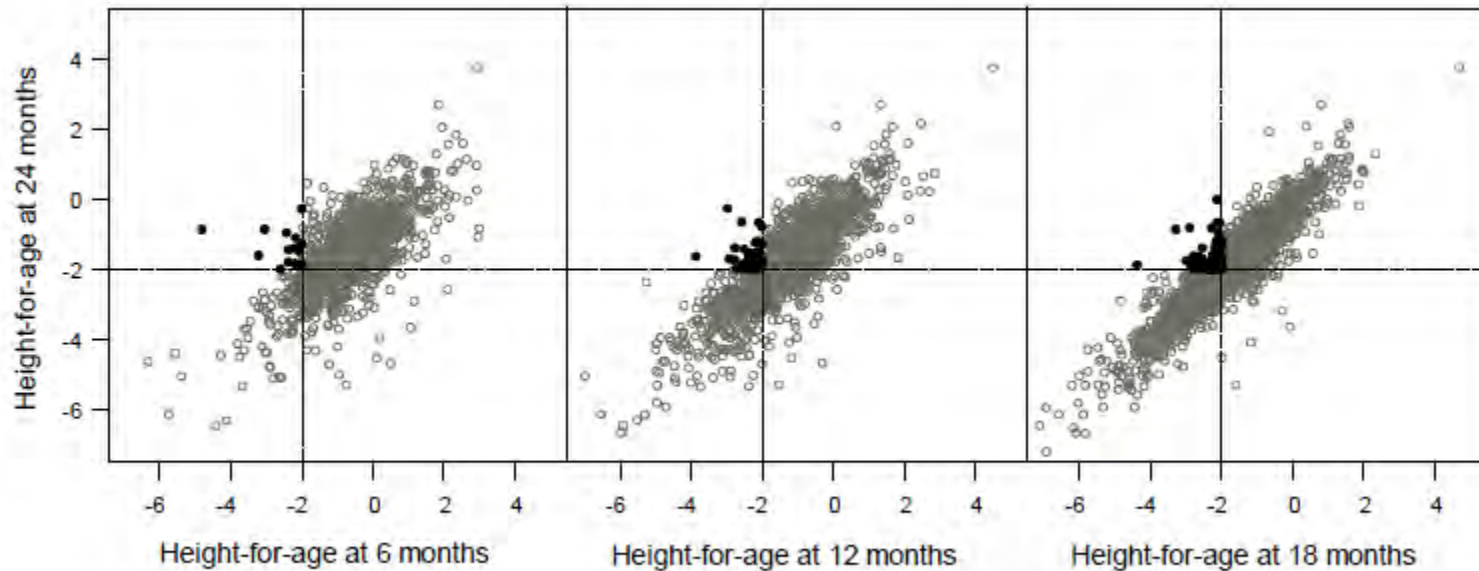
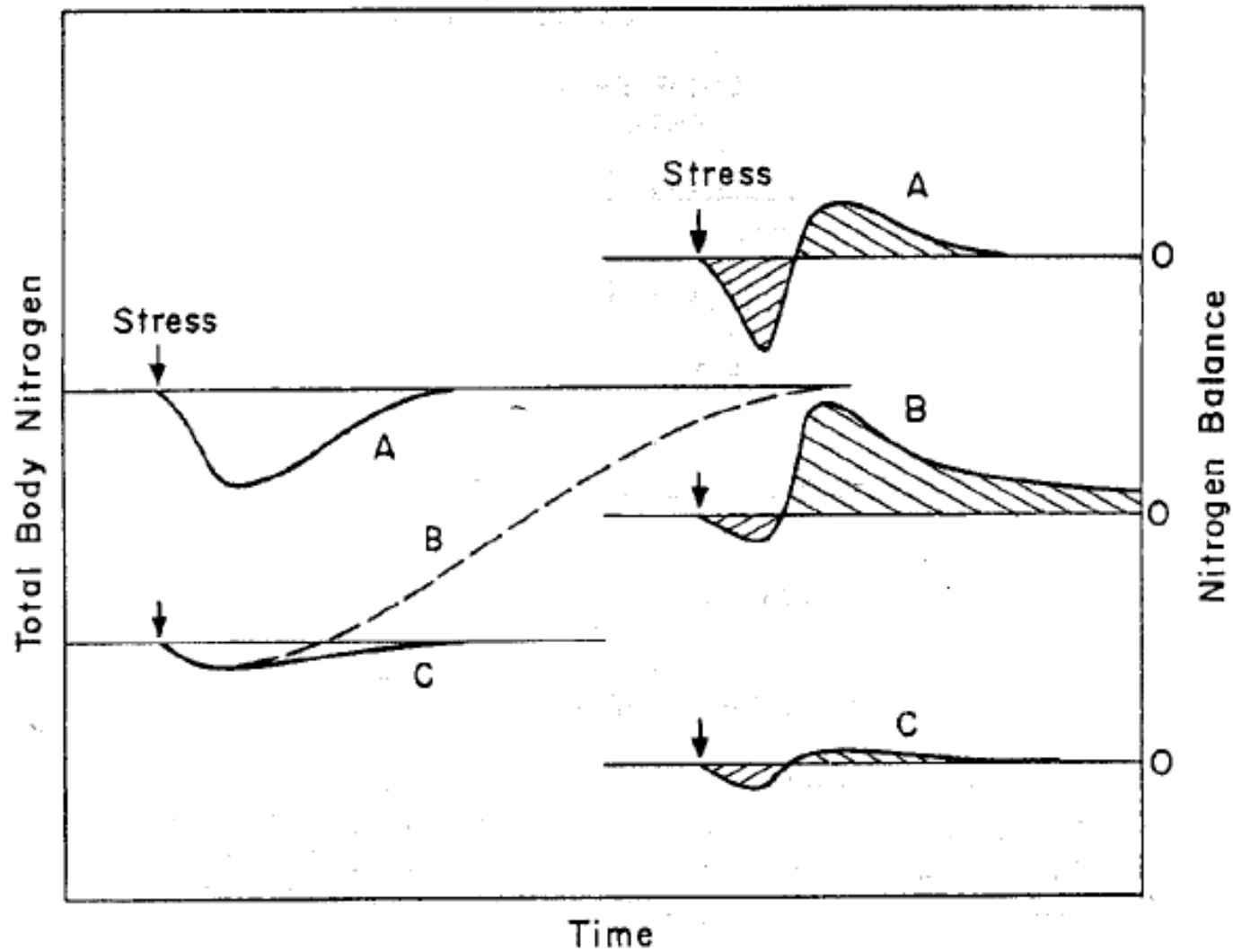
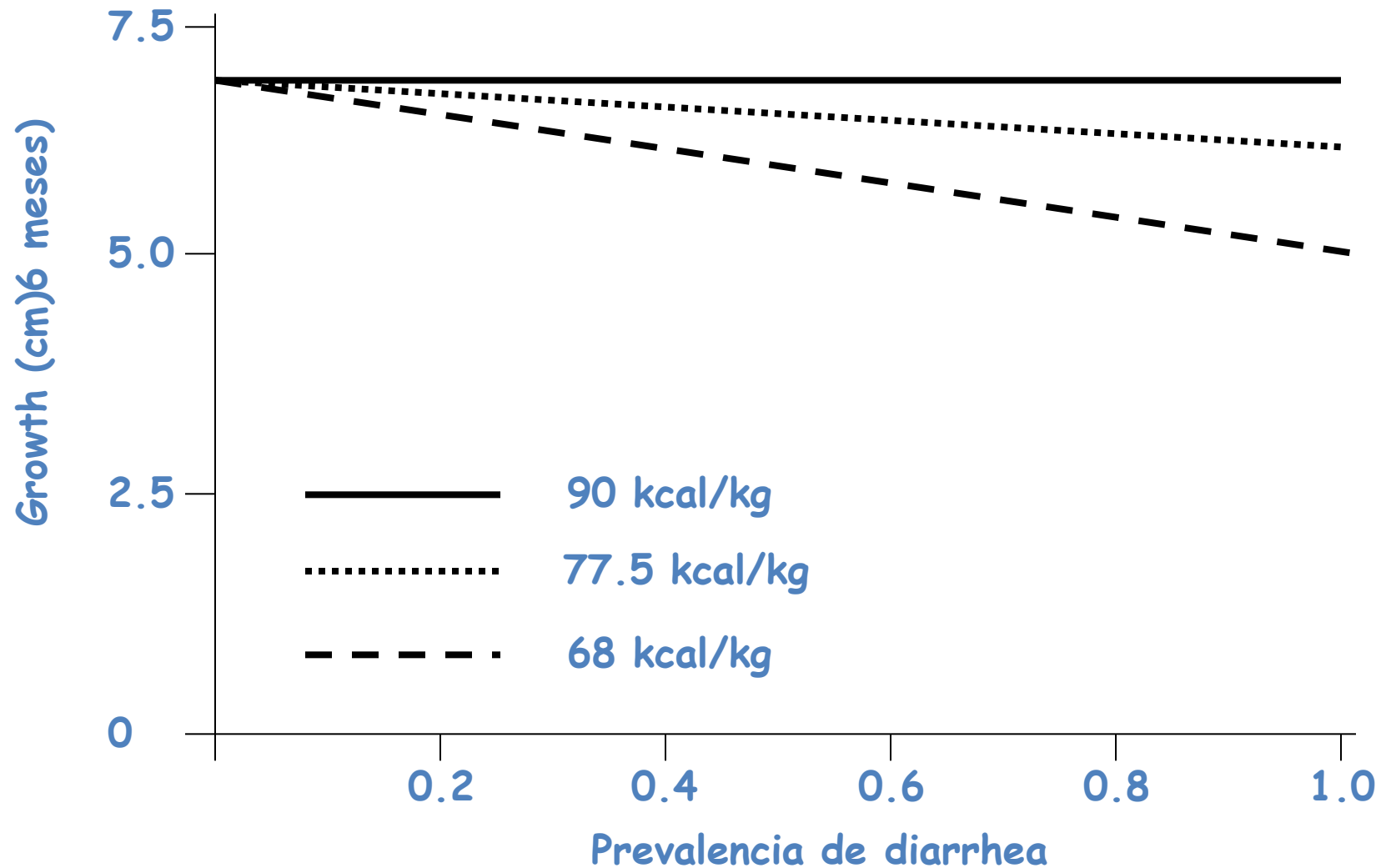


FIG. 2. EXPECTED CHANGES IN NITROGEN BALANCE UNDER VARIOUS CONDITIONS



- A = well nourished
 B = poorly nourished before stress, well nourished after
 C = poorly nourished throughout

Effect of Prevalence of Diarrhea on Growth Depends on Level of energy Consumption



Possible mechanisms to explain the effect of Diarrhea on nutrition

- ▶ Reduced dietary intake due to poor appetite or vomiting
 - 15-20% reduction of energy consumption in non-breastfed children.
- ▶ Change of feeding patterns by parents?
- ▶ Reduced absorption of nutrients
 - Enterocyte and crypt cell destruction
 - Increased motility and reduction of transit time
 - Transient malabsorption of protein, fat, carbohydrates.
 - Increased intestinal permeability to test sugars

Possible mechanisms to explain the effect of Diarrhea on nutrition

- ▶ Loss of nutrients:
 - Loss of nutrients: increased fecal excretion of Zn, Cu and other nutrients
 - Increased urinary loss of Vit A
 - Increased utilization of nutrients to fight infection
- ▶ ETEC, Rotavirus and dysenteric illnesses are the best examples of these effects
- ▶ Persistent diarrhea (>14 days duration) has worst prognosis.

Does ARI have a similar effect than diarrhea on nutrition?

- Less number of studies than with diarrhea
- In their review Baqui and Black:
 - 4 of 8 studies found impact of ALRI on weight.
 - In 2 studies: 14.7 g/d and 30 g/d weight loss
 - 3 of 5 studies more severe ALRI had an effect on linear growth
- One study have documented 10-20% reduction of food intake
- Lack of appetite may be the main mechanism, mostly associated with fever or greater severity of illness
- There is a need of more epidemiological studies

Ref: Baqui AH, Black RE. Nestle Nutrition Workshop Series Vol 48, 2002.



Tuberculosis and Nutrition

- Long recognized and included in 1968 review
- TB is associated with severe wasting and negative nitrogen balance.
- Chemotherapy improves nutrition status, more so if good nutritional support is given
- But nutritional effect is long lasting: TB patients have an impaired anabolic response to feeding, due to an “anabolic block” with altered amino acid metabolism, explaining refractory responses to nutrition rehabilitation (Ref: Macallan DC et al Clin Sci 1998;94:321-31.)
- HIV infections make TB patients have less body cell mass

Measles and Nutrition

- Also recognized in the 1968 review, as a cause of kwashiorkor in undernourished children.
- Anorexia, refusal to eat due to stomatitis, catabolic effects, protein-losing enteropathy.
- Acute and persistent diarrhea secondary to measles due occur for a long period after measles
- Persistent immunosuppression
- Interaction with vit A deficiency

Malaria and Nutrition

- Few humans studies in 1968 review
- More definitive studies came from treatment trials:
 - Pyrimethamine or chloroquine prophylaxis vs placebo has shown increased weight in children from Ghana, Gambian and Nigeria.
 - Insecticide-treated bed nets trials have also demonstrated a positive effect on nutrition in Kenya and Tanzania.
 - A long study over 5 years in Vietnam have showed that an integrated malaria control program produced an annual increase of height for age Z score of 0.11 to 0.14 extending into preadolescent age.

HIV/AIDS and Nutrition

- Effect starts in the uterus: high risk of IUGR and LBW
- Important growth (weight and linear) retardation due to asymptomatic HIV infections in children in Africa
- Mechanisms are due to both, direct metabolic effects of HIV infection, as well as HIV-induced secondary infections.
- Severe wasting related to increased inflammatory cytokines, including interleukins 1 and 6 that induces anorexia.
- Several micronutrients are also affected: Vit A, Vit B12, Vit E, C, D, niacin, folate, iron, magnesium, zinc, selenium.

In Conclusion

- Well conducted epidemiological studies and clinical trials have clearly documented the importance of infections on nutrition of children in developing countries.
- However, with few exceptions, these effects may be transient and not long lasting if children are well fed.
- The nutritional cost of living in poor, un-healthy environment with high intake of micro-organisms and asymptomatic infections need further attention
- Thanks Nevin, Carl and John for stimulating 40 years of very exciting research!



Thanks!