The Ties That Bind

The Microbiome, Immunity, and Child Development

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How Does this Neonate Survive its Birth?

Gastrointestinal Tract

Immune system

Brain and CNS

Lungs

Kidneys

Vascular flow

Endocrine signaling

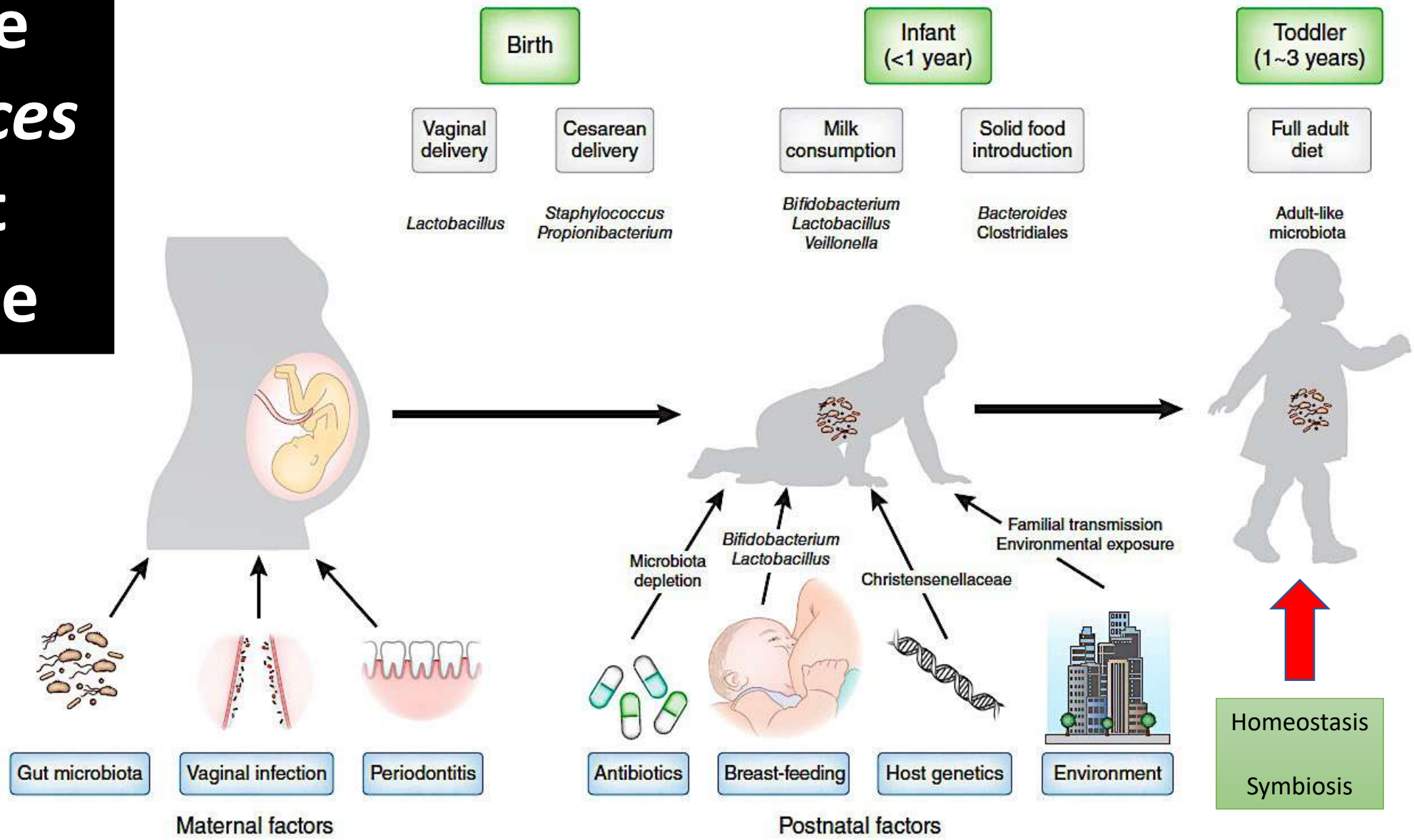
Nervous coordination

The Neonate is still very immature

GI Development Post-birth:

Swallowing
Gastric acidity
Pancreatic function
Epithelial digestion & absorption
Gut motility & nervous system
Bacterial colonization of the microflora
Gut & systemic immunity

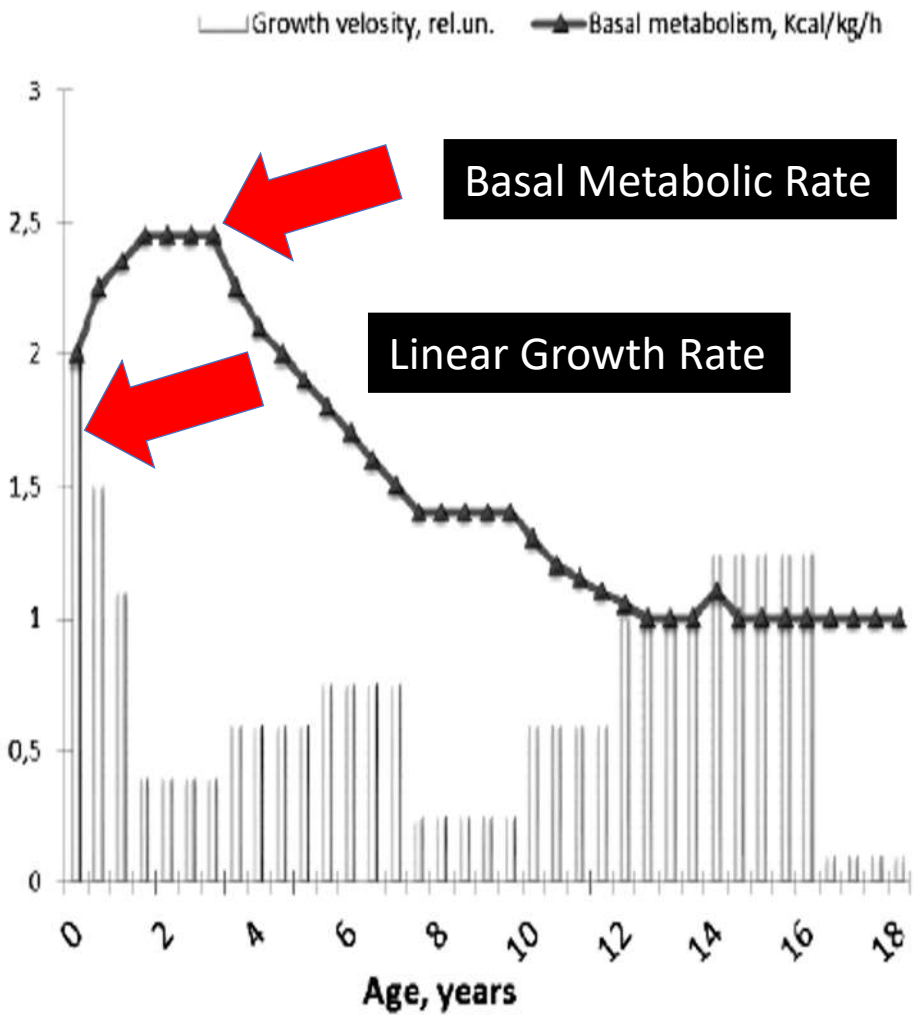
Early life *experiences* are not the same



Tamburini et al. Nat Med, 2016: 22:71e3-22

1. Refinement of organ systems
2. Skeletal growth
3. Muscle mass growth
4. Expansion of the brain

Growth Velocity and Basal Metabolic Rate X Age

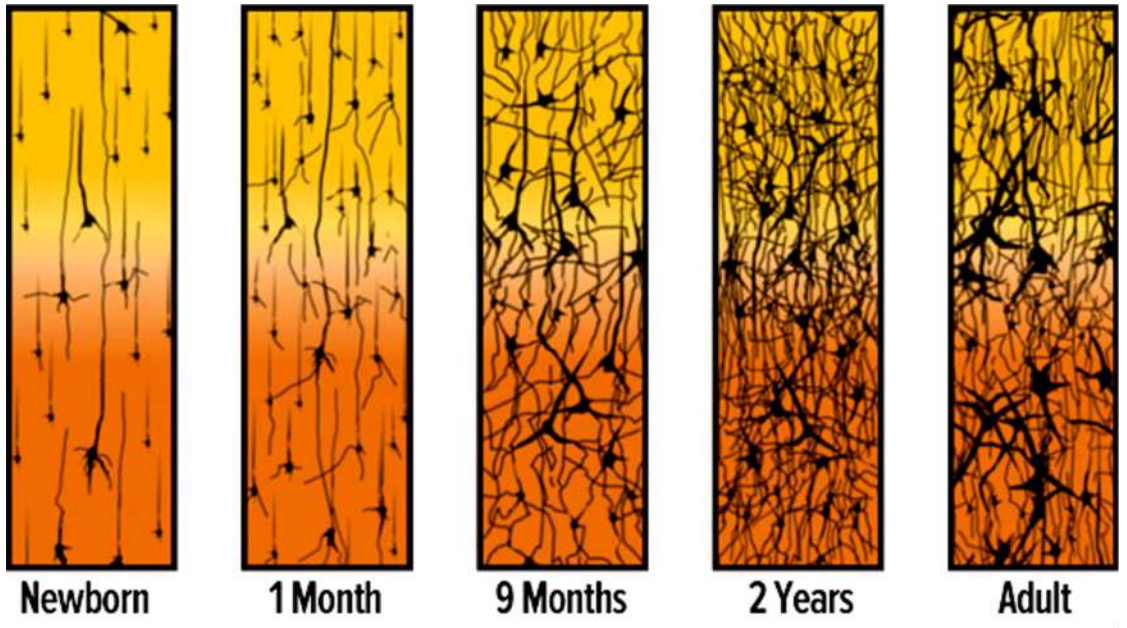


Son'kin V, Tambovtseva R. In, *Bioenergetics,* 2012. Chapter 5: 121-142

4.

Brain Expansion: 0-36 months

Synaptogenesis
&
Myelination



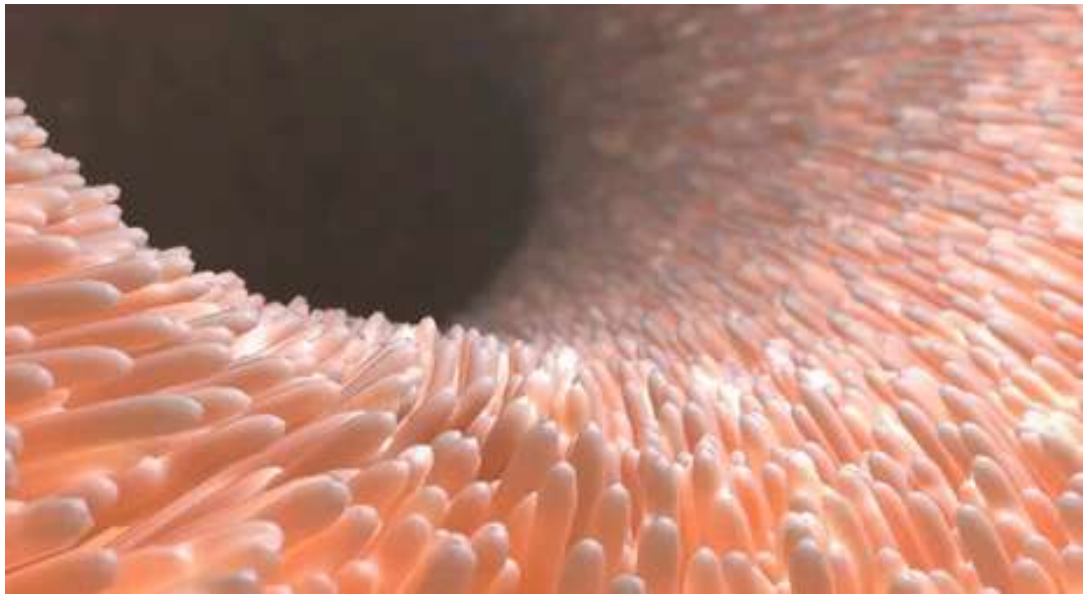
Brain Expansion Requires *Complete Nutrition*

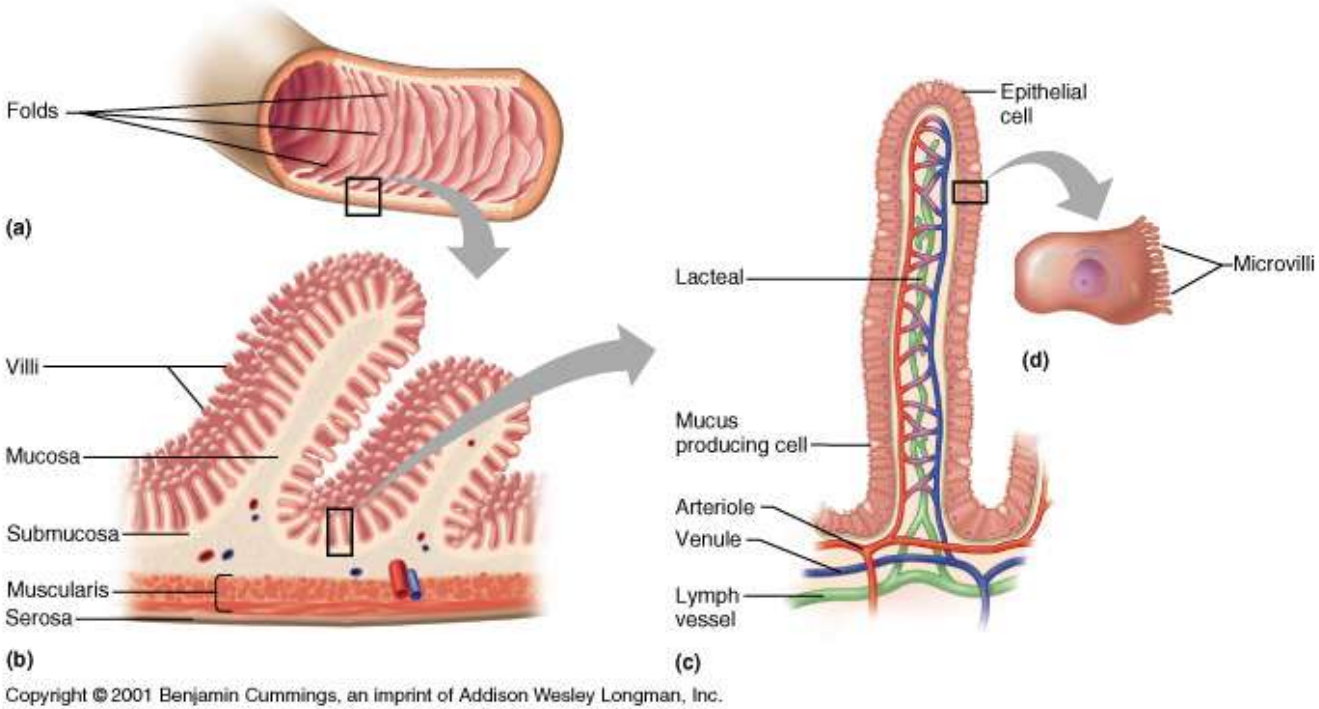
- **Vit B1** – utilize glucose, modulate cognition, language development
- **Vit B1, B6, B12, and choline, tryptophan, tyrosine, histidine, threonine** – synthesis of neurotransmitters
- **Vit B12** – cognition, language
- **Vit C** – concentrated in nerve endings
- **Vit D** – prevents neurodegenerative disease
- **Vit E** – membrane protection
- **Flavonoids** – protect, enhance neuronal function

Bourre. J Nutr Health Aging, 2006: 377
Gonzalez et al, Arch Argent Pediatr 2016. 114:570
Georgieff et al. Acta Paediatr 2018; 107:1310-1321

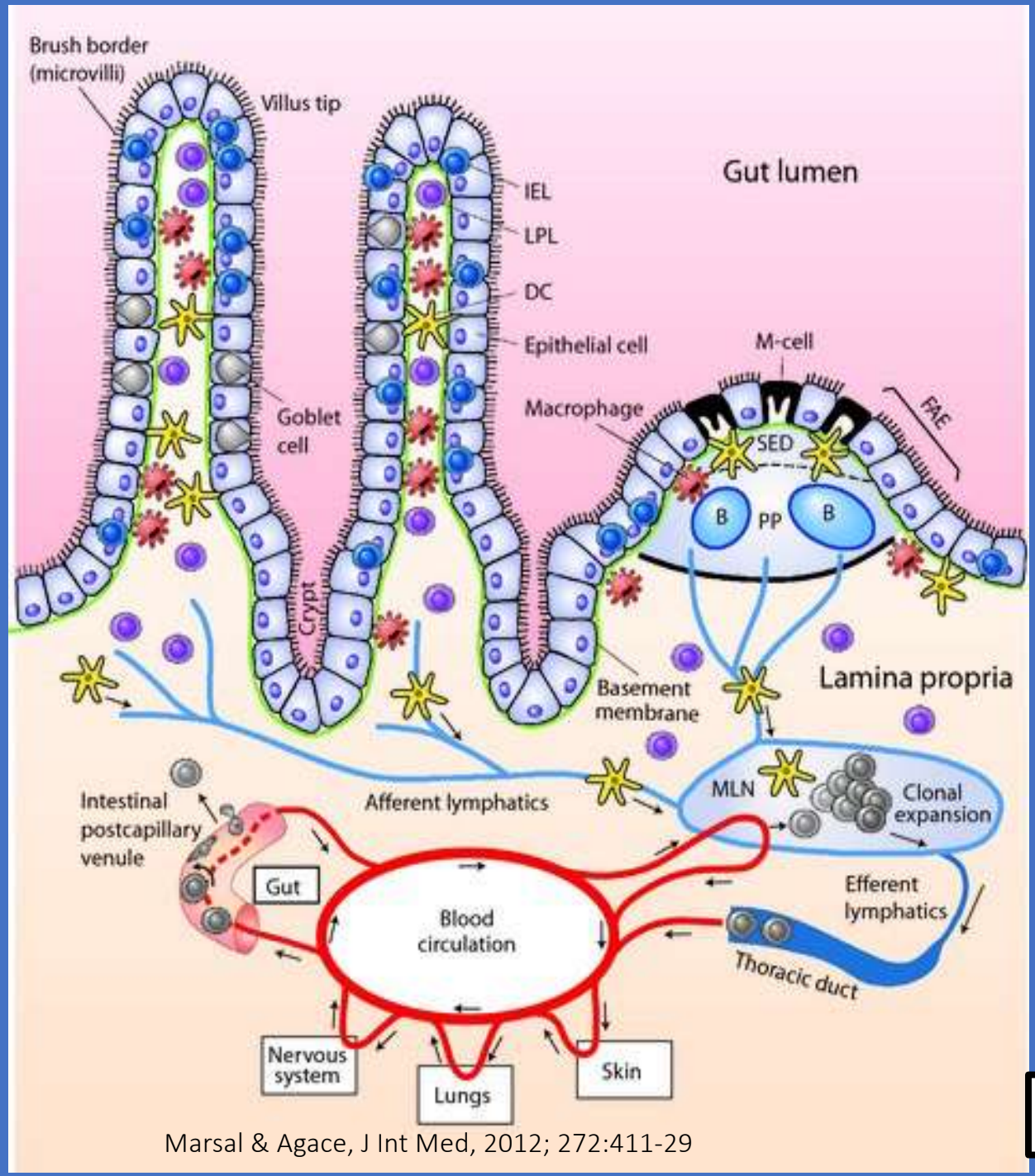
- **Iron** – oxygenation, synthesis of myelin & neurotransmitters, brain development, IQ
- **Magnesium** – energy and ion regulation
- **Zinc** – taste perception, attention
- **Iodine** – (via thyroid) cellular energy metabolism
- **Omega 3 PUFA** – cognition, visual development
- **Lutein** – macular protection

The Intestine





Small Intestine



Marsal & Agace, J Int Med, 2012; 272:411-29

Lumen
bacteria
antigens
nutrients
chemicals
hormones

1

LP- lamina propria
IEL- intraepithelial lymphocytes
LPL- lamina propria lymphocytes
DC- dendritic cells
MLN- mesenteric lymph nodes
PP- Peyer's patch
SED- subepithelial dome
FAE- follicle associated epithelium

Epithelial Cell Layer

2

Immune
Dendritic cells
T regs
B cells

3

Nervous
Sensory axons
Submucosal ganglia
Adrenergic nerves

Vascular/ Lymphatic

Coordination

Immune Tolerance

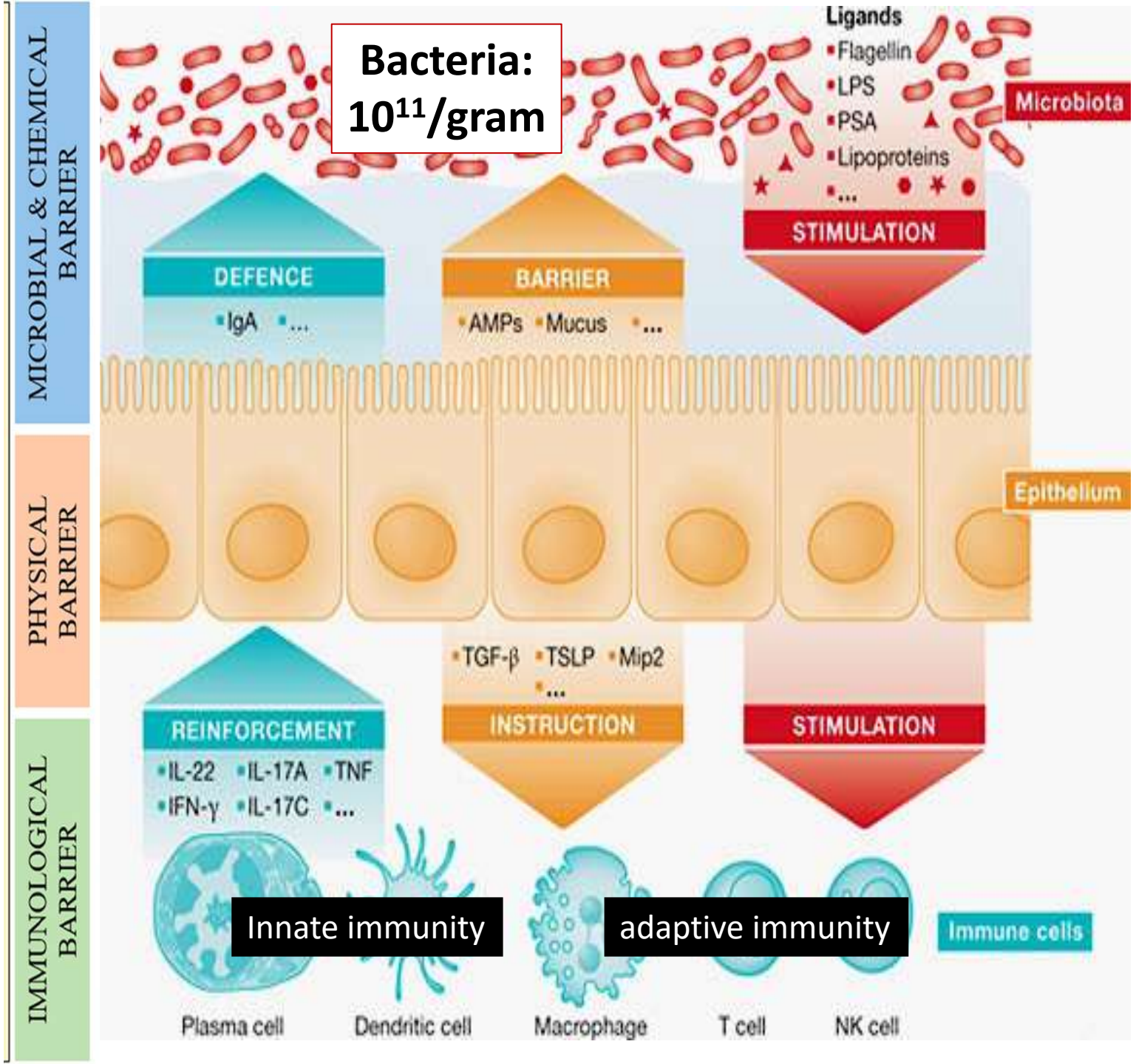
Homeostasis

1 **Lumen**

Mucus

2 **Epithelial Barrier**

3 **Lamina Propria**

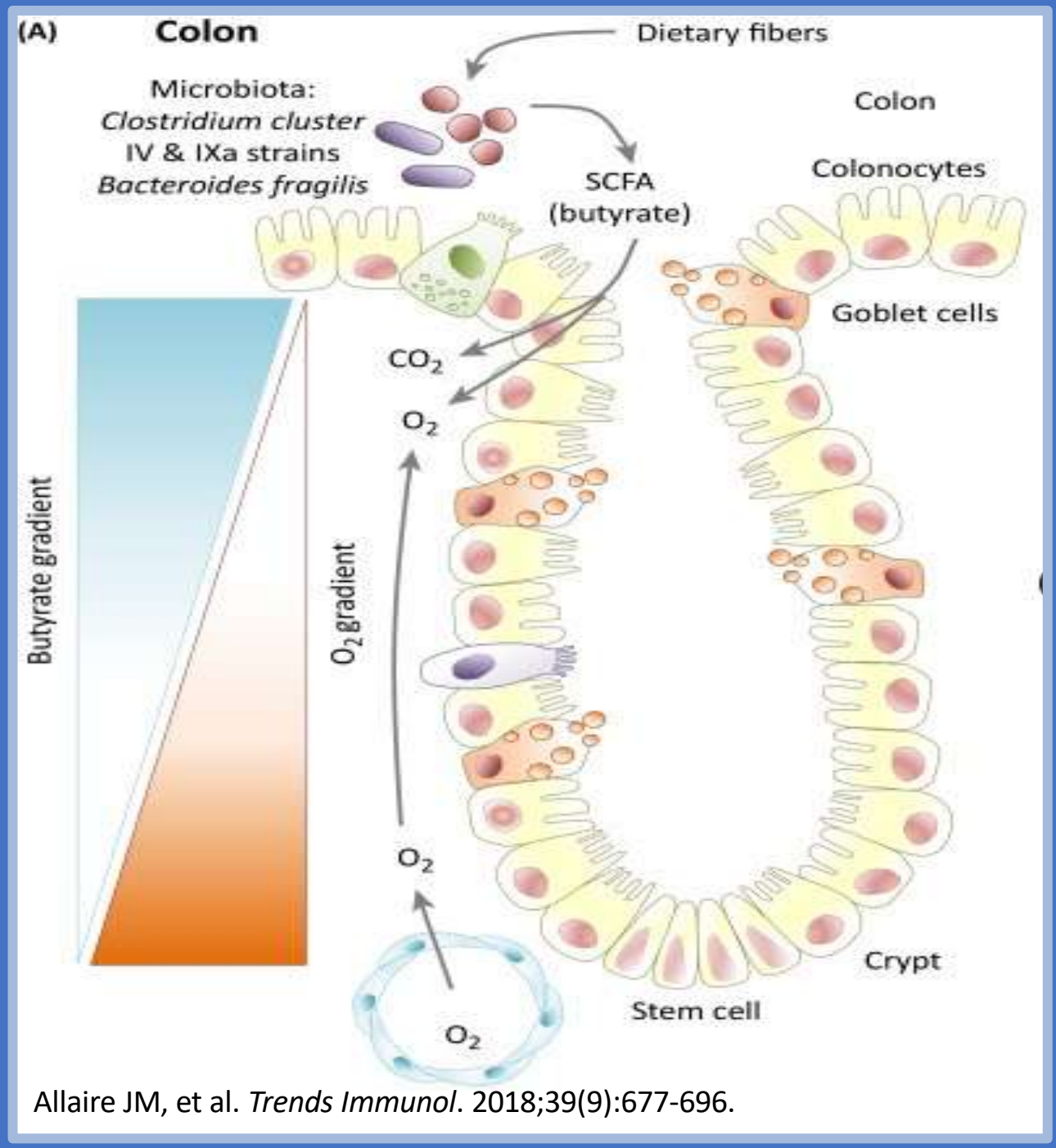


Pott J, Hornef M. *EMBO Rep*. 2012;13(8):684-698.

LPS- Lipopolysaccharide ; PSA- Polysaccharide antigen; AMP- Adenosine Monophosphate; TGF-β- Transforming growth factor beta ; TSLP- thymic stromal lymphopoietin ; Mip2- macrophage inflammatory protein 2 ; IL- interleukin; TNF-Tumor Necrosis Factor ; IFN-γ- *Interferon* gamma; NK- Natural Killer cells

Microbial Metabolic Products: *Short-chain fatty acids –*

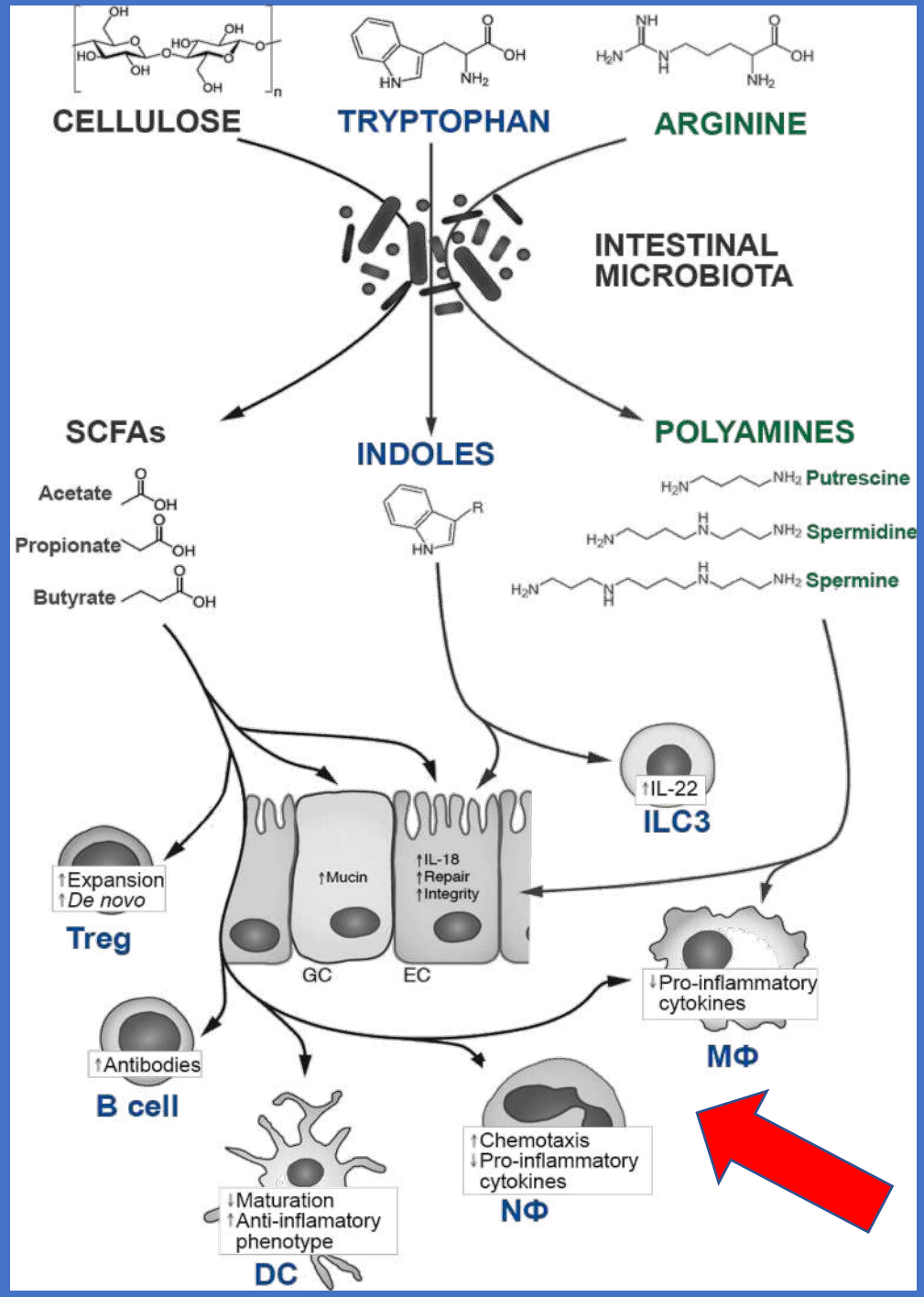
Provide Fuel to Maintain Epithelial Integrity



Allaire JM, et al. *Trends Immunol*. 2018;39(9):677-696.

Microbial Metabolic Products

Modulate *Local & Systemic Inflammation*



Postler TS, Ghosh S. *Cell Metab*. 2017;26(1):110-130

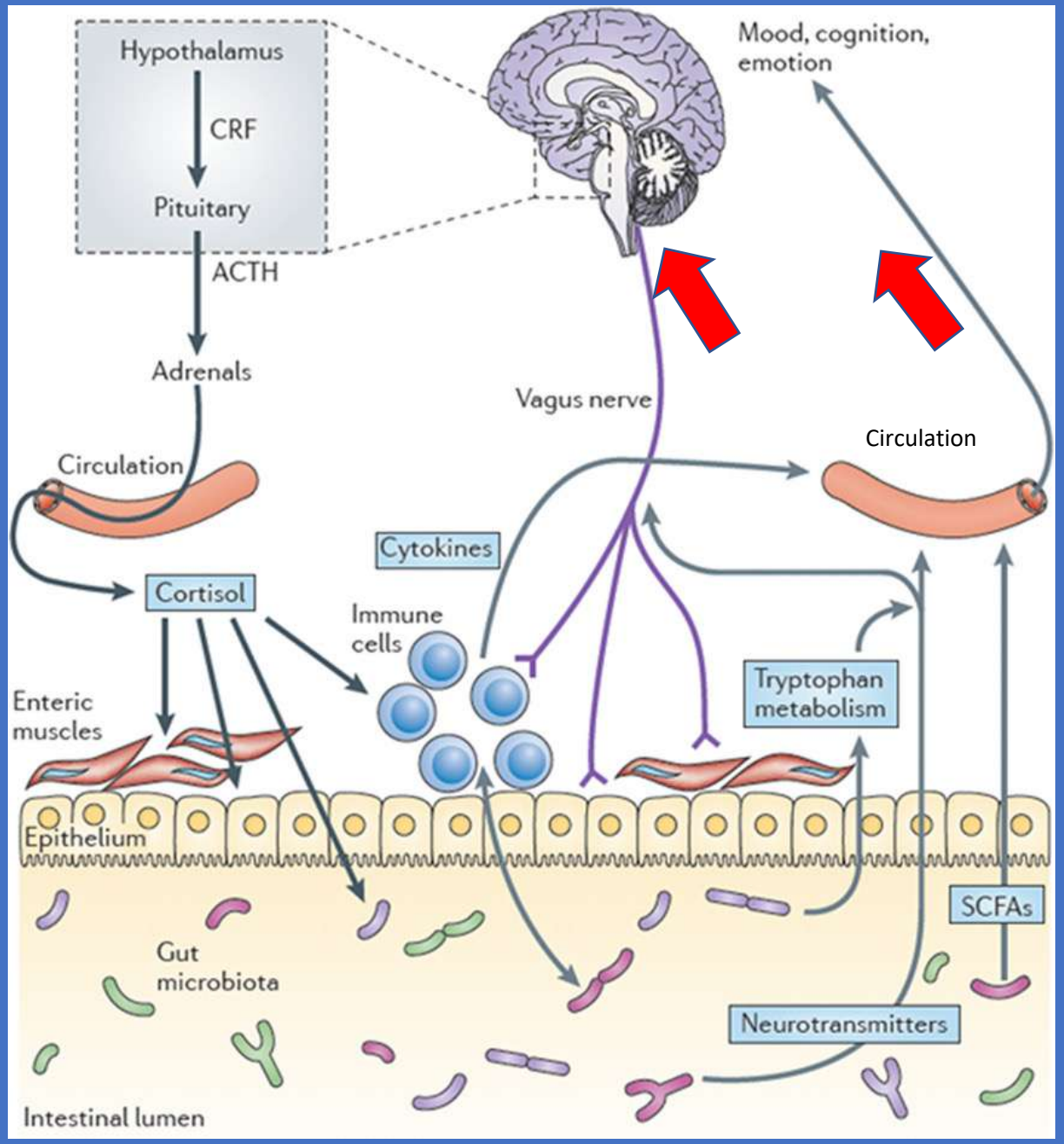
ILC3 – Type 3 innate lymphoid cell
GC – Goblet cell
EC – Epithelial cell
MΦ – Macrophage
NΦ – Neutrophil

Microbial Metabolic Products

also

Signal The Brain

CRF- corticotrophin releasing factor
ACTH- adrenocorticotropic hormone
SCFAs- Short Chain Fatty Acids



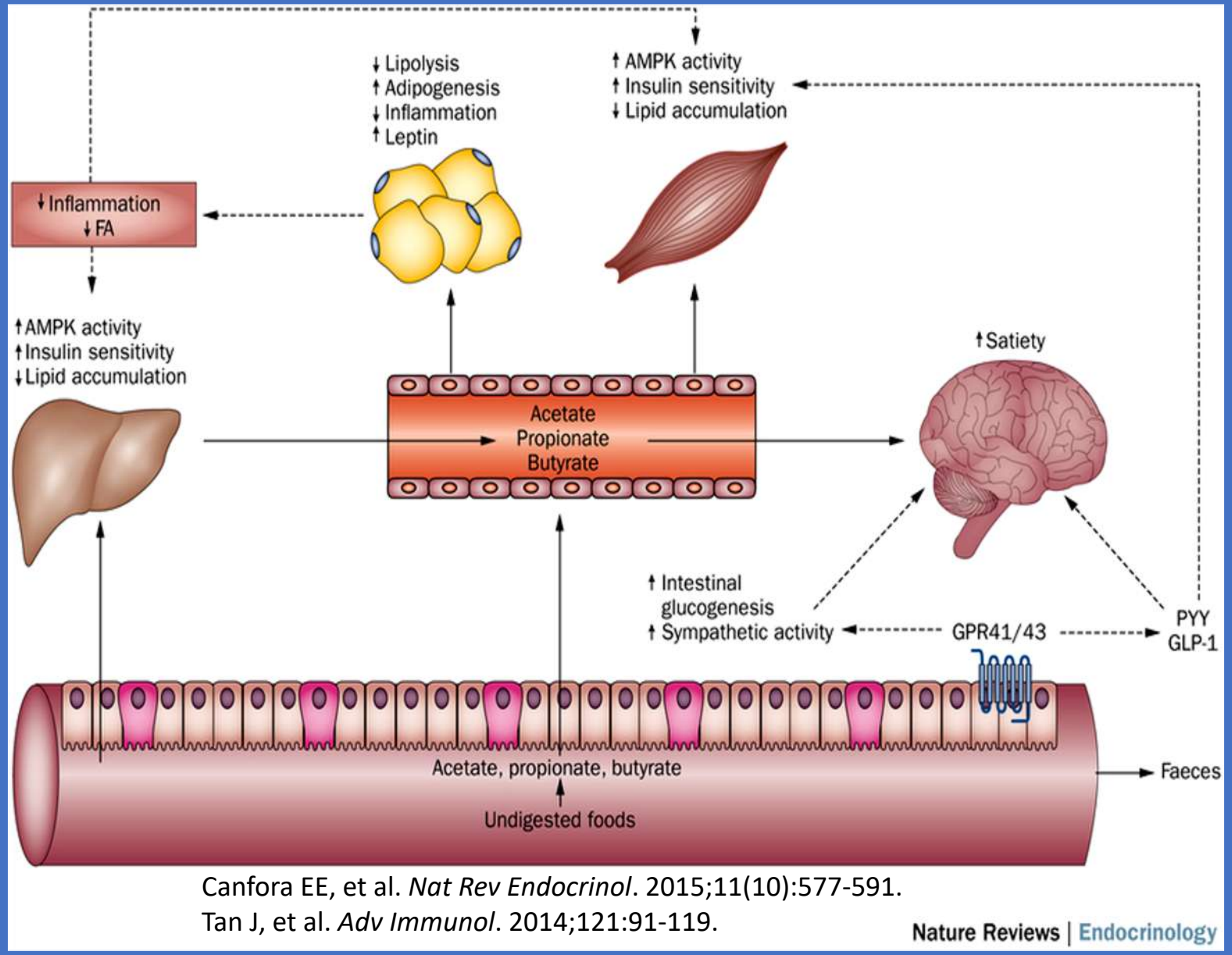
Petschow B, et al. *Ann N Y Acad Sci*. 2013 Dec;1306(1):1-17.

Bacterial Metabolism Affects *Human* Metabolism

Bacterial Metabolic Products

Also

Signal Metabolism

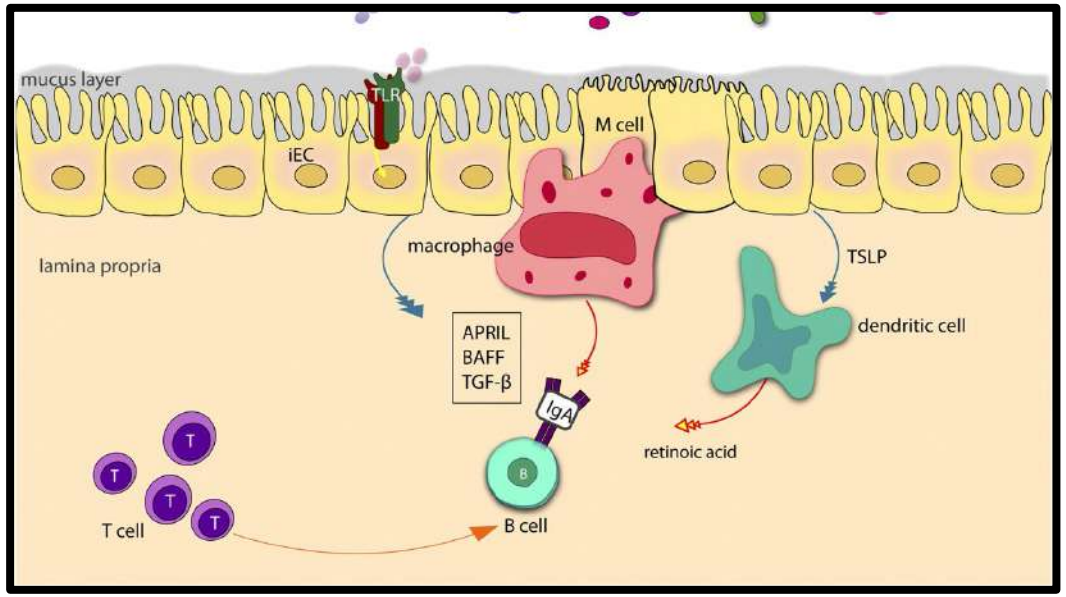


Canfora EE, et al. *Nat Rev Endocrinol*. 2015;11(10):577-591.
Tan J, et al. *Adv Immunol*. 2014;121:91-119.

AMP-activated protein kinase
FA- Fatty acid
GPR- G protein-coupled receptors
PYY- peptide YY
GLP-1- glucagon-like peptide 1

Mandatory Nutrients for Immune Function

Epithelial barriers	Cellular immunity	Antibody production
Vitamin A	Vitamin A	Vitamin A
Vitamin C	Vitamin B_6	Vitamin B_6
Vitamin E	Vitamin B_{12}	Vitamin B_{12}
Zinc	Vitamin C	Vitamin D
	Vitamin D	Vitamin E
	Vitamin E	Folic acid
	Folic acid	Zinc
	Iron	Copper
	Zinc	Selenium
	Copper	
	Selenium	



Complementary Foods

The Most Common Period for

rice

beans

sweet potato

mango

yogurt

spinach

Avocado/ guacamole

carrots

peas

pasta

soy/tofu

pureed beef

IRON

grains

infant cereals

cheese

dates

hummus

scrambled eggs

cucumbers

Growth Faltering

Toddler's Snacks

"Snacks" are mini-meals

- >90% consume snacks
- 33% consume 3 or more snacks/day
- 25% of daily energy
- Averages 288 kcal/ day

Foods	Prevalence	
Any sweet-salty snacks	92%	
Any desserts	82%	
Cakes & Pastries	58%	
Ice cream/frozen treats	21%	
Regular cookies	30%	
Candy	32%	
Salty snacks	53%	
Sweetened beverages	54%	
Muffins, donuts	11%	

Snack Nutrients = 20-35% of total energy

But often include fiber, Vitamins C, D, E, B_{12}, calcium, iron, zinc, & potassium

Deming et al. Pub Health Nutr, 2017; 9: 1584 - 1592

Fibers & Prebiotics

- **Vegetables**
  - Chicory, artichokes, garlic,
  - Onions, shallots, leeks, cabbage
- **Fruits**
  - Bananas, apples, grapefruit, watermelon
- **Legumes**
  - Chickpeas, lentils, red kidney beans, soybeans
- **Nuts, seeds**
  - Almons, pistachio nuts, flax seeds
- **Cereal grain**s
  - Bran, oats, barley

Whole Grains: all 3 parts intact (germ, endosperm, bran)

- amaranth, barley, corn, oats, farro, sorghum, teff, spelt, millet
- bulgur, wheatberries, cracked wheat, quinoa, rye, brown/ wild rice

- **Vegetables**
  - Carrots, beets, broccoli
  - Artichoke, Brussel sprouts
  - Kale, spinach, tomato
- **Fruits**
  - Pears, bananas, strawberries
  - Avocado, apples, raspberries
  - Blueberries, blackberries
- **Legumes**
  - Lentils, kidney beans, chickpeas
- **Fermented Foods**
  - Yogurt, cottage cheese
  - kumbacha, sauerkraut, kefir
- **Nuts, seeds**
  - Almonds, chia & sunflower seeds
- **Grains**
  - Quinoa, oats, popped corn

The Transition to Milk

- Stimulates sIGF-1 release for linear growth
- Maternal intake improves neonatal birth length
- Improves height-for-age Z scores in young children
- Milk's growth stimulation is *stronger than other animal* or *plant protein sources*

But Not Plant "Milks"*

* Soy is the only acceptable substitute

Millward DJ. Nutr Res Rev, 2017; 30: 50–72
doi:10.1017/S0954422416000238

Protein Quality

PDCAAS:
Protein digestibility-corrected amino acid score

Protein Quality
is based on both
amino acid requirements
&
ability to digest the protein*

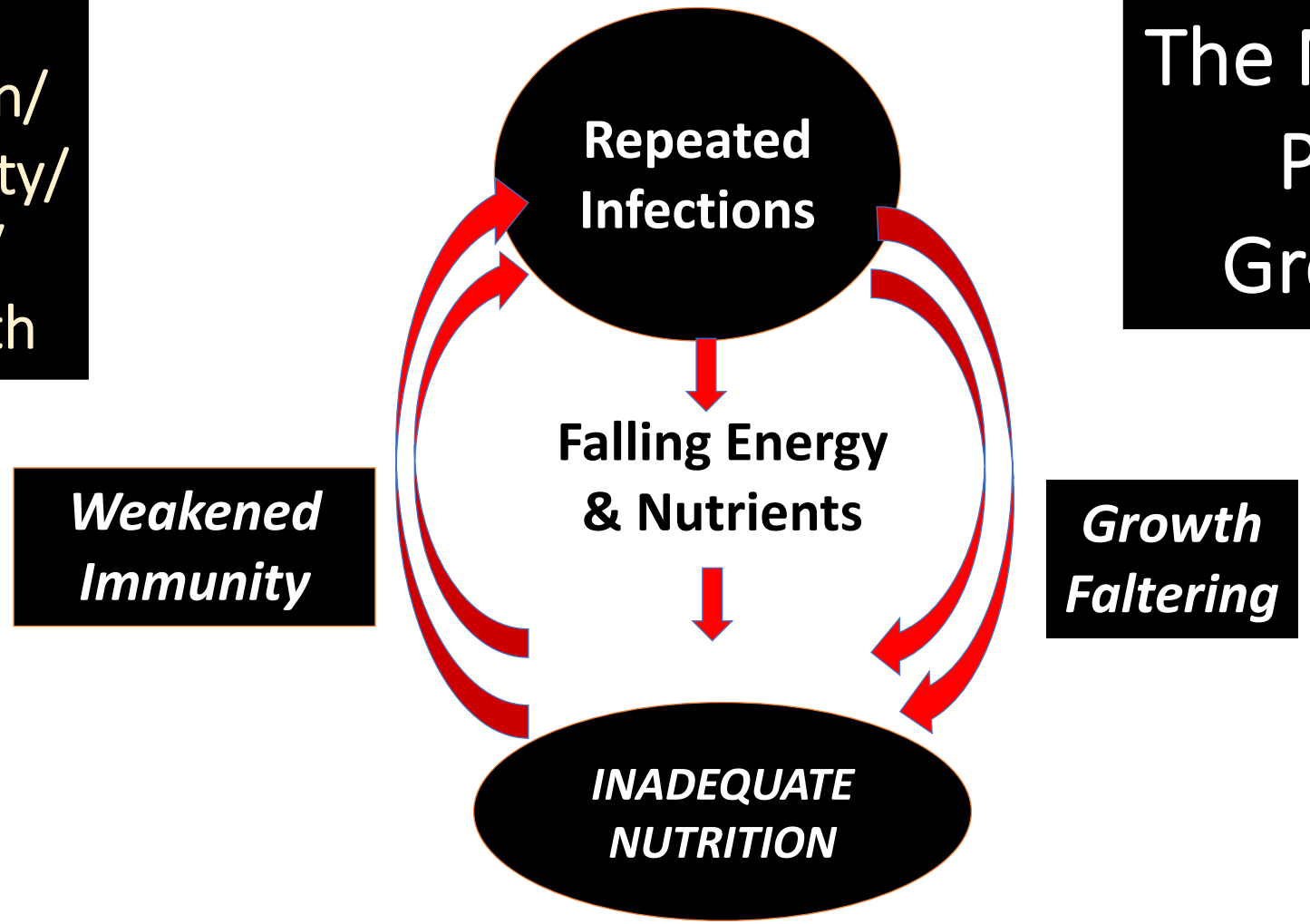
PDCAAS Ranked Values

Protein Sources	Value
Egg	1
Cow's Milk	1
Casein	1
Whey	1
Beef	0.92
Soy	0.91
Chickpeas	0.78
Black beans	0.75
Vegetables	0.73

*WHO has proposed a new ***Digestibility of Indispensible Amino Acid Score (DIAAS)***
http://www.who.int/nutrition/publications/nutrientrequirements/WHO_TRS_935/en/

The Most Common Pathway to Growth Failure

The Cycle: Malnutrition/ Low Immunity/ Infections/ Poor Growth

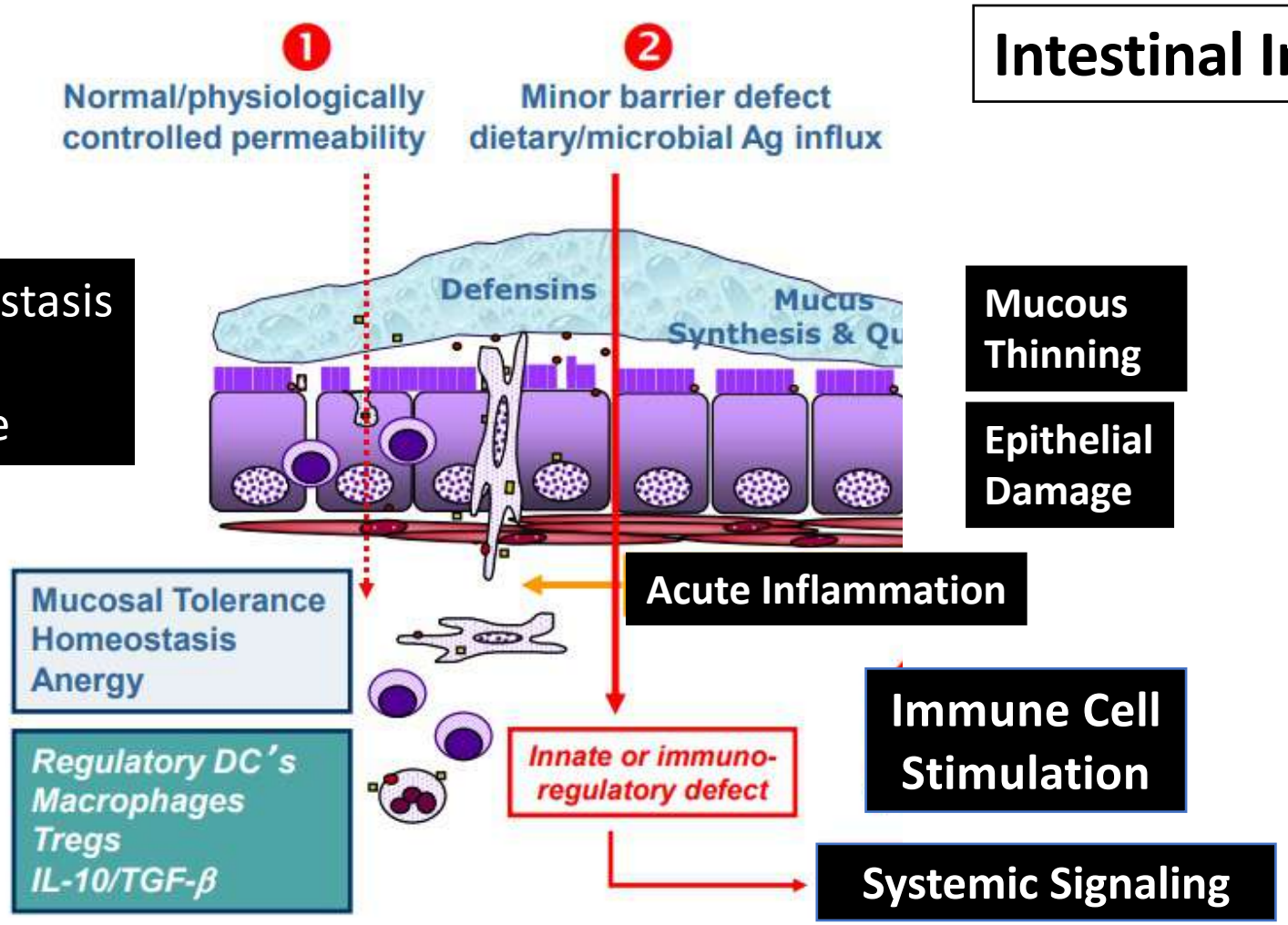


Guerrant RL, et al. *Nat Rev Gastroenterol Hepatol*. 2013;10(4):220-229.

Red Flags: Threats to Growth

Maternal nutritional deficits
Prematurity/ Small for Gestation
Repeated infections*
Food insecurity
Hospitalizations*
Chronic diseases
Neuro-physical disabilities
Stress / mental illness in the family
Fad diet/ Picky eaters/ Food Allergic
Maternal nutritional deficits

Injury to the Epithelial Protective Barrier

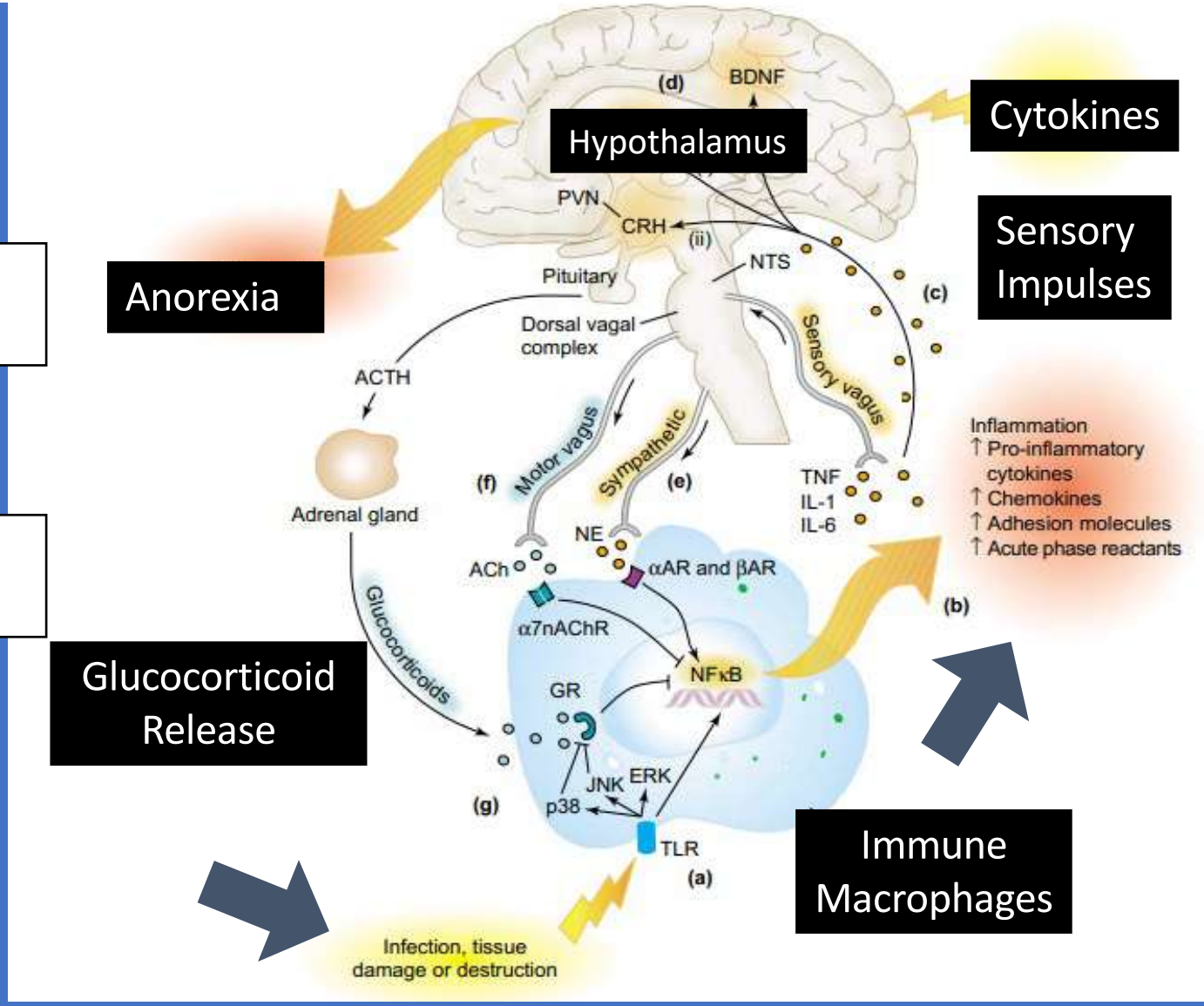


Fasano A. *F1000Res*. 2020;9:F1000 Faculty Rev-69. Published 2020 Jan 31.

Infection, Epithelial Damage, Inflammation, Anorexia

Blocks
Hunger, Food Seeking, Food Reward

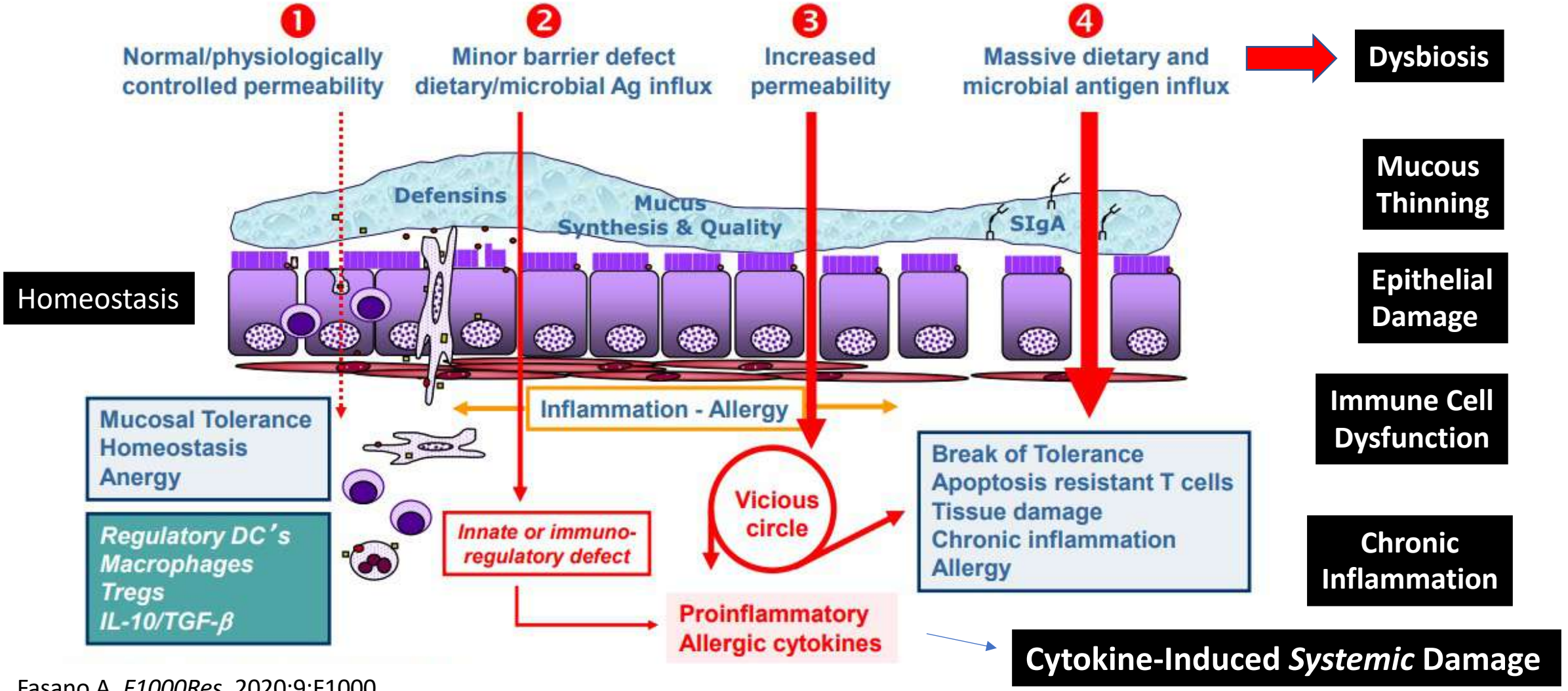
Blocks
Growth Plate and Growth Factors



BDNF- Brain-derived neurotrophic factor; PVN- paraventricular nucleus; NTS- nucleus tractus solitarius; ACH- acetylcholine; NE- norepinephrine; AR- adrenoceptors; a7nAChR- a7 subunit of the nicotinic acetylcholine receptor; ERK- Extracellular Signal-Regulated Kinase; JNK- Jun amino-terminal kinase; TLR- Toll-like receptor

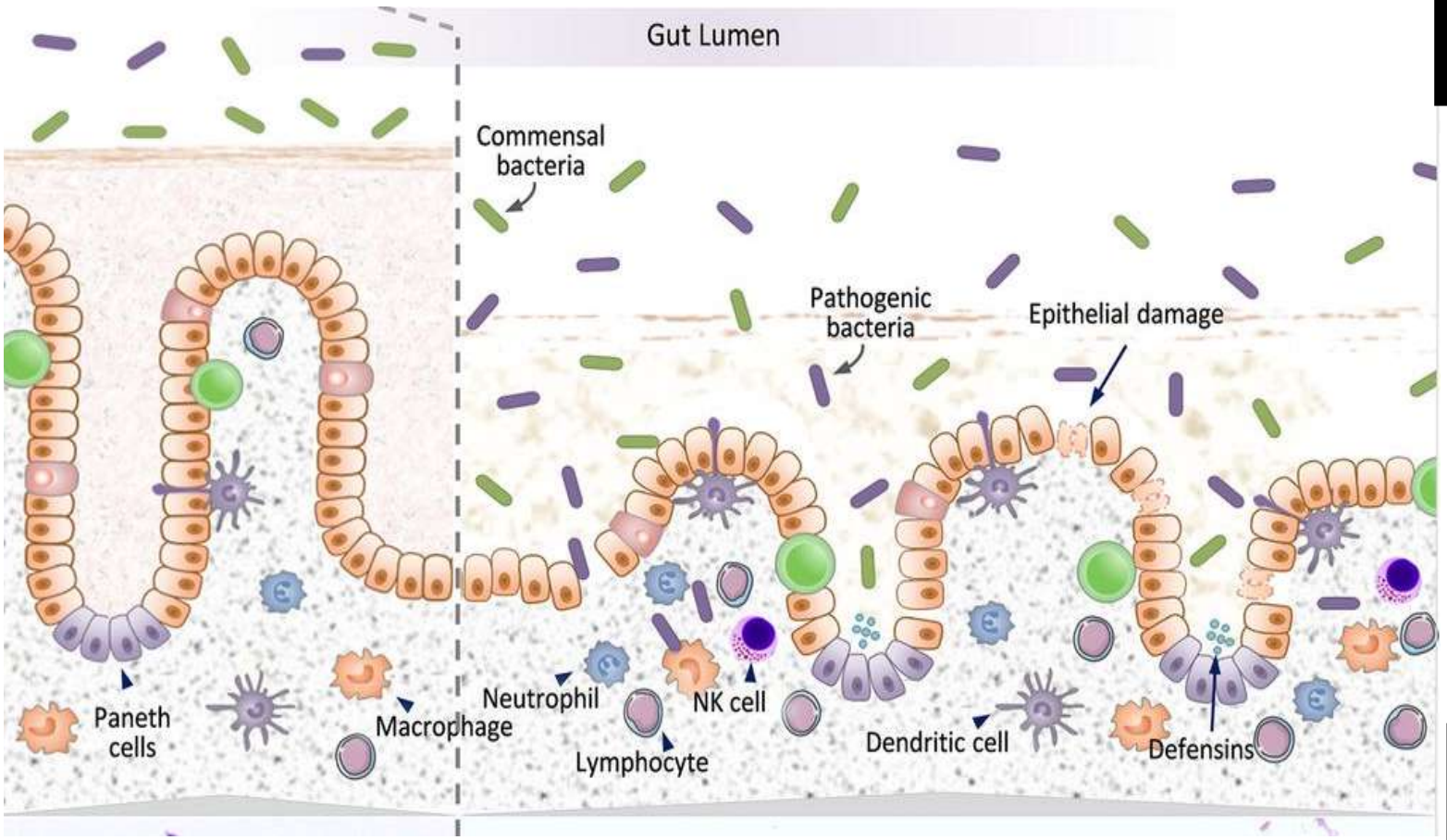
Raison CL, et al. *Trends Immunol*. 2006;27(1):24-31.
Gautron L, Layé S. *Front Neurosci*. 2010;3:59.

Chronic Injury to the Epithelial Protective Barrier



Fasano A. *F1000Res*. 2020;9:F1000 Faculty Rev-69. Published 2020 Jan 31.

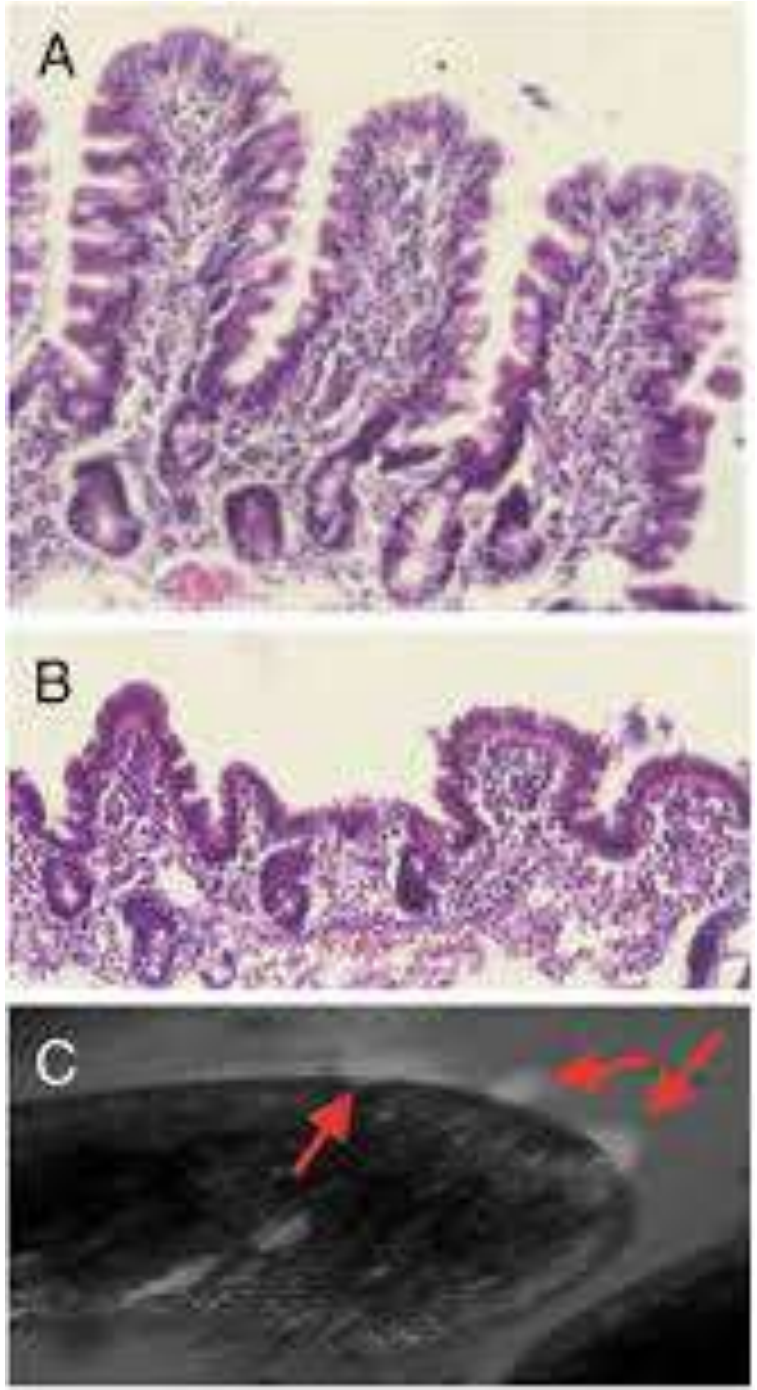
Repeated Injury:
Environmental Enteric Dysfuntion (EED)



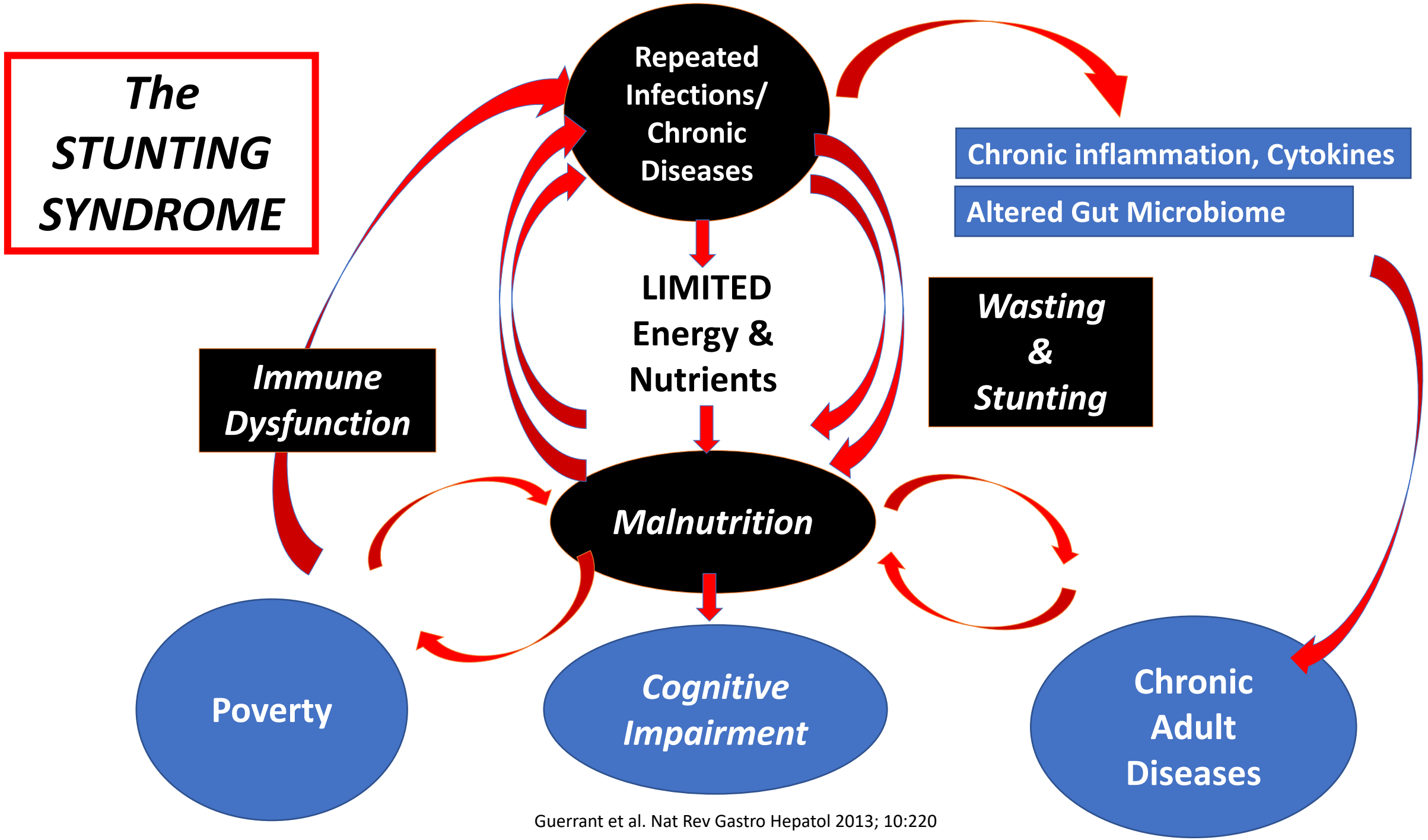
Normal Villi

Blunt Villi

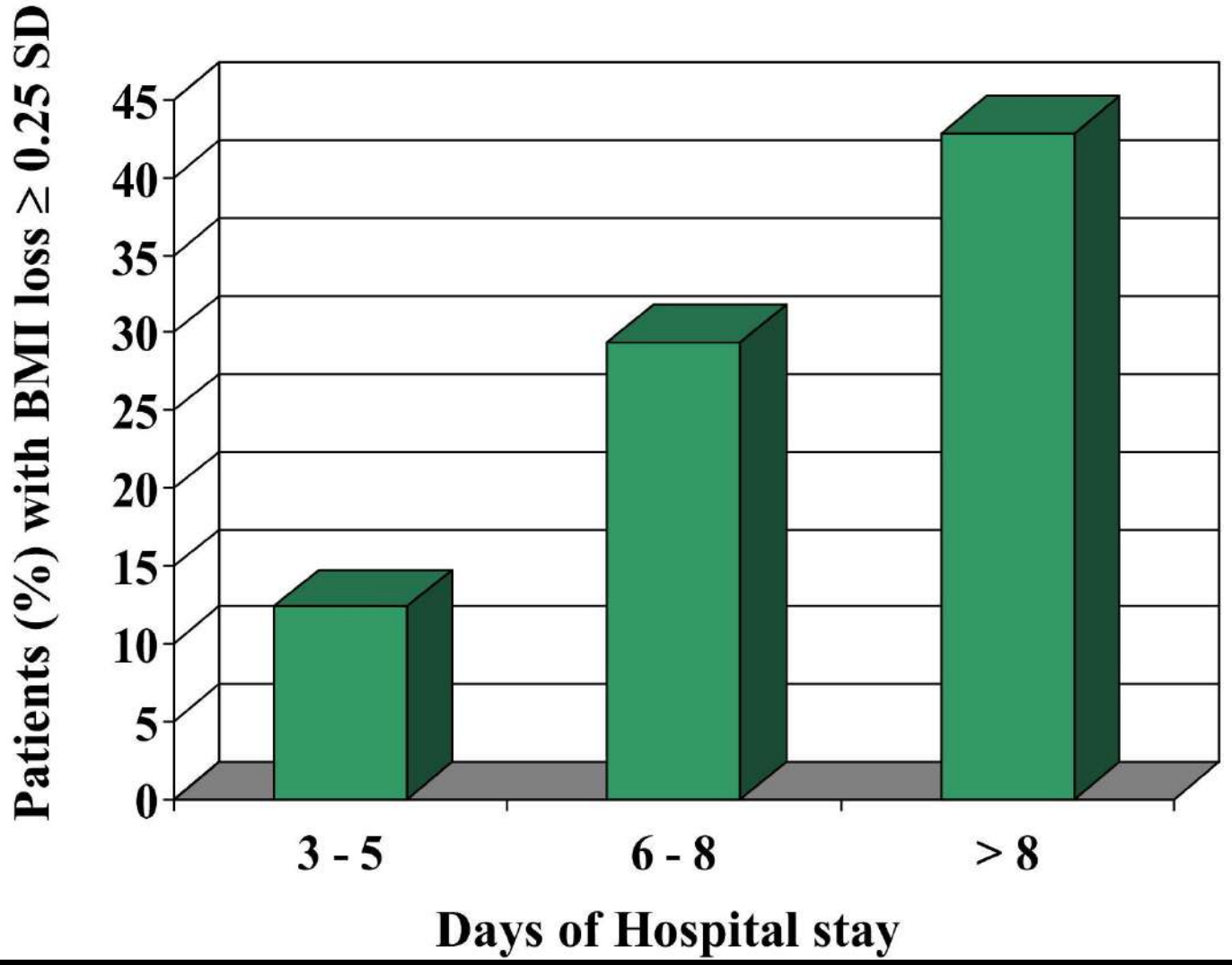
"Leaky" Gut



Owino V, et a. *Pediatrics*.):e20160641
Trehan I, et al. *Arch Dis Child*2016;138(6. 2016;101(8):741-744.



Guerrant et al. Nat Rev Gastro Hepatol 2013; 10:220



Children (percentage) with a BMI decrease ≥0.25 SD
Correlates with their length of hospitalization, *even with mild clinical conditions*

Campanozzi A, Russo M, Catucci A, et al. Nutrition 2009; 25(5):540-547.

Disease-Associated Malnutrition in Hospital

- **Critically ill patients (ICU)**
- **Cancer cases**
- **Surgical patients**
- **Cardiovascular disease**
- **“Fragile” (neuro-physical)**
- **Pulmonary disorders**
- **GI disorders**
- **Cystic Fibrosis**
- **Burns**

High risk patients:

- Ventilator time
- Nosocomial infections
- Med/ Surg complications
- Wound healing
- ICU LOS and total LOS
- Long-term prognosis
- Health-care costs

Pelizzo et al. Front Pediatr 2019; 7:86

Factors in Hospital-Acquired Malnutrition

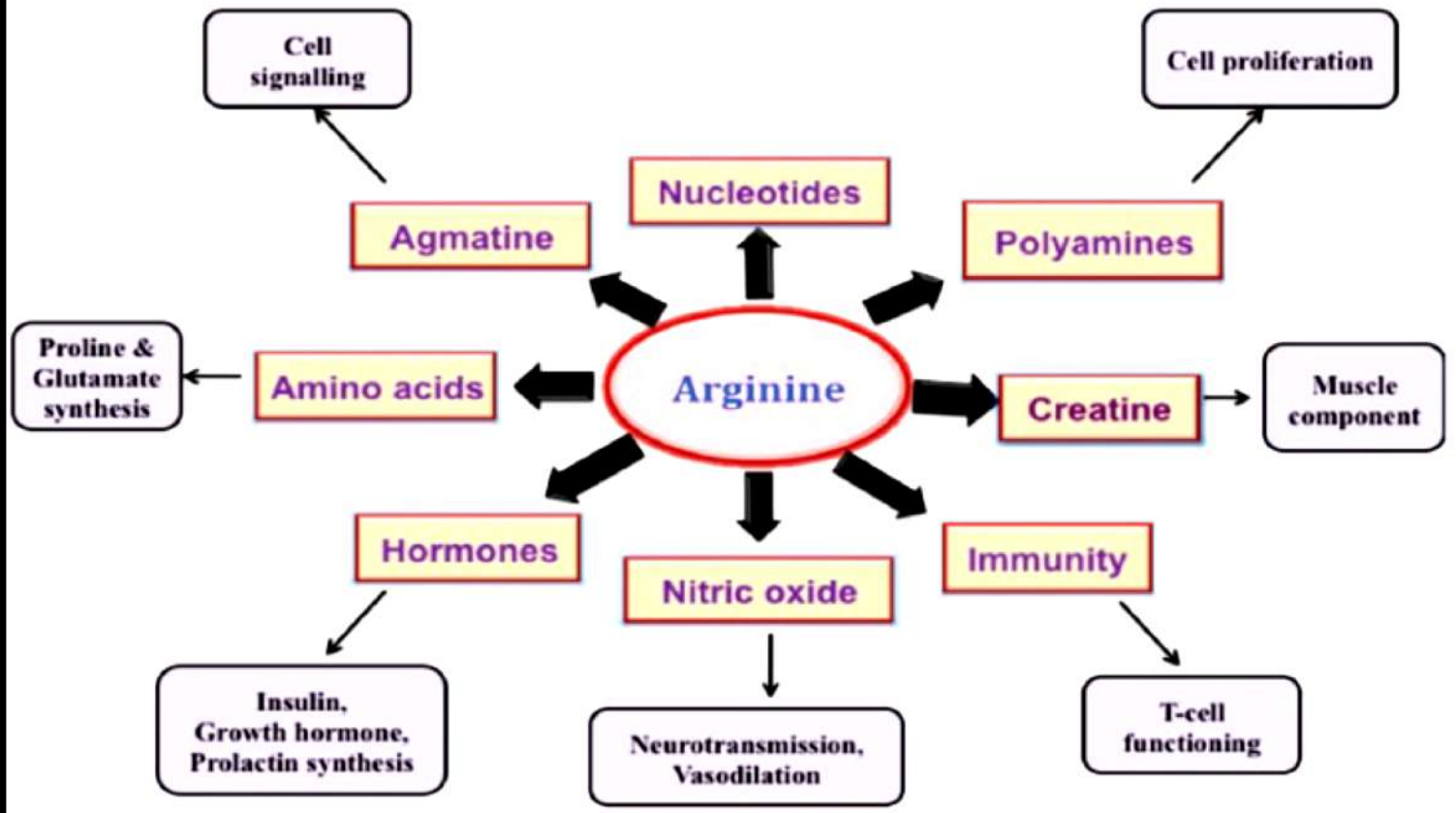
- **Disease-related factors**: malabsorption, anorexia, stress-related catabolism, increased nutritional requirements of fever, inflammation
- **Hospital-related factors**: lack of nutritional assessment, poor food quality, access, medications, testing and procedures
- **Highest risk**: young child, vomiting and diarrhea, constipation, or dysphagia. Esp noted in neurologic and cardiac patients
- **Mechanisms**: poor healing, muscle catabolism, immune dysfunction, GI tract alterations, microbiome changes, fever, respiratory distress, etc

Nutritional Risk Scores (NRS)

Tool	Age Group	Anthropometric measures	Weight Loss	Dietary Intake	Other	Linked to an Action Plan
PYMS: Paediatric Yorkhill Malnutrition Score	1-18 yr	+ BMI	+	+	On admission or for conditions affecting nutrition	Yes
STRONGkids: Screening toolRisk of Nutritional Status & Growth	> 1 mo		+	+	Subjective clinical assessment or high risk case	Yes
STAMP: Screening Tool for the Assessment of Malnutrition in Pediatrics	2-17 yr	+ Height, Weight	+ Compare with growth chart	+	Diagnosis	Yes
SIGNA: Subjective Global Nutritional Assessment (Peds)	1 mo – 17 yr	History from parents	History from parents	History from parents	History of GI illness and functional capacity	Not specified
Pediatric Nutritional Risk Score	> 1 mo		+	+	Pain or pathology	Yes

Arginine

- **Key functions of arginine**
  - Signals lysosomal growth processes
  - Stimulates growth hormone secretion
  - Raises insulin sensitivity
  - Precursor for synthesis of body tissue
  - Supports collagen production (wound healing)
  - Required for immune T-cell function
  - Downregulates cytokine production (lowers inflammation)
  - Is the sole precursor for Nitric Oxide (endothelial function)



Patil et al., 2016 Oncogene. 22:4957-72
Ben-Sahra & Manning, Curr Opin Cell Biol. 2017 Apr; 45: 72–82
Takahara et al. Journal of Biomedical Science (2020) 27:87

Illness
Infections
Inflammation
Trauma
Burns

Lack of Intake

Increased Utilization (arginase)

Serum Arginine Depletion

mTORC-1 *Catabolic* Signal

Skeletal Muscle Degradation (autophagy)

Low Arginine
signals mTORC-1
to switch to a

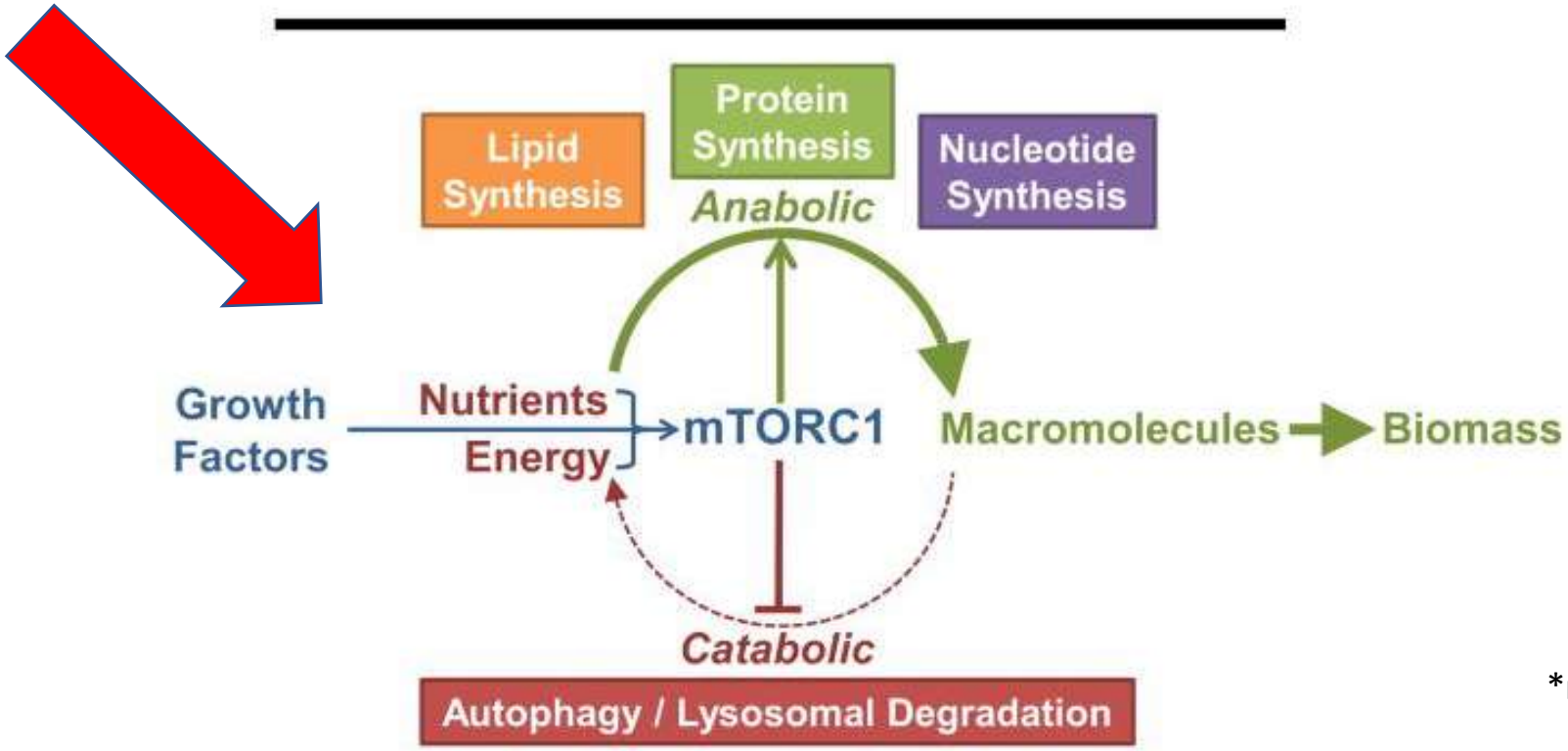
catabolic state
which stimulates

Degradation of muscle mass

Morris et al. Nutr Clin Pract. 2017;32(suppl 1):30S-47S
Bond P. J Int Soc Sports Nutr 2016;13:8 doi: 10.1186/s12970-016-0118-y

mTORC1* Reads Multiple Signals

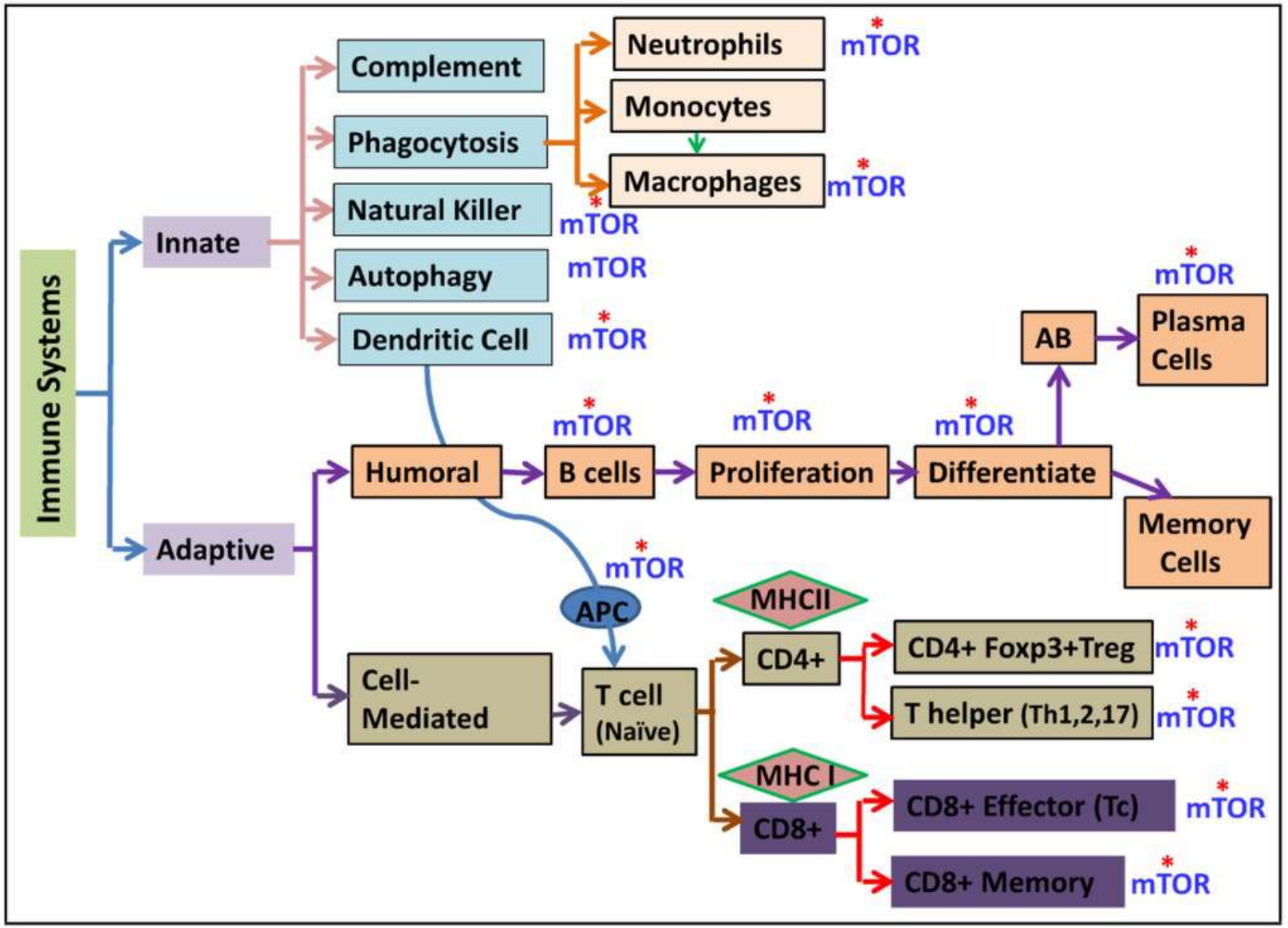
Growth factors: ***insulin, growth factors***
Energy/ Amino acids: ***arginine, leucine & glutamine***



mTORC1 is the cellular switch between **Anabolic & Catabolic** processes

*mTOR- mechanistic target of rapamycin

Tan VP, Miyamoto S. *J Mol Cell Cardiol*. 2016;95:31-41.
Ben-Sahra I, Manning BD. *Curr Opin Cell Biol*. 2017;45:72-82.
He L, et al. *Adv Nutr*. 2018;9(4):493-504.



APC- antigen presenting cell
CD4- cluster of differentiation 4
Foxp3- forkhead box P3

mTOR Signaling affects both *Innate & Adaptive* Immune Response

Soliman GA. *Nutrients*. 2013;5(6):2231-2257.

Poor
Dietary Intake

Family Concern

FEEDING PROBLEMS

At-Risk

Energy/
Nutrient
Deficits

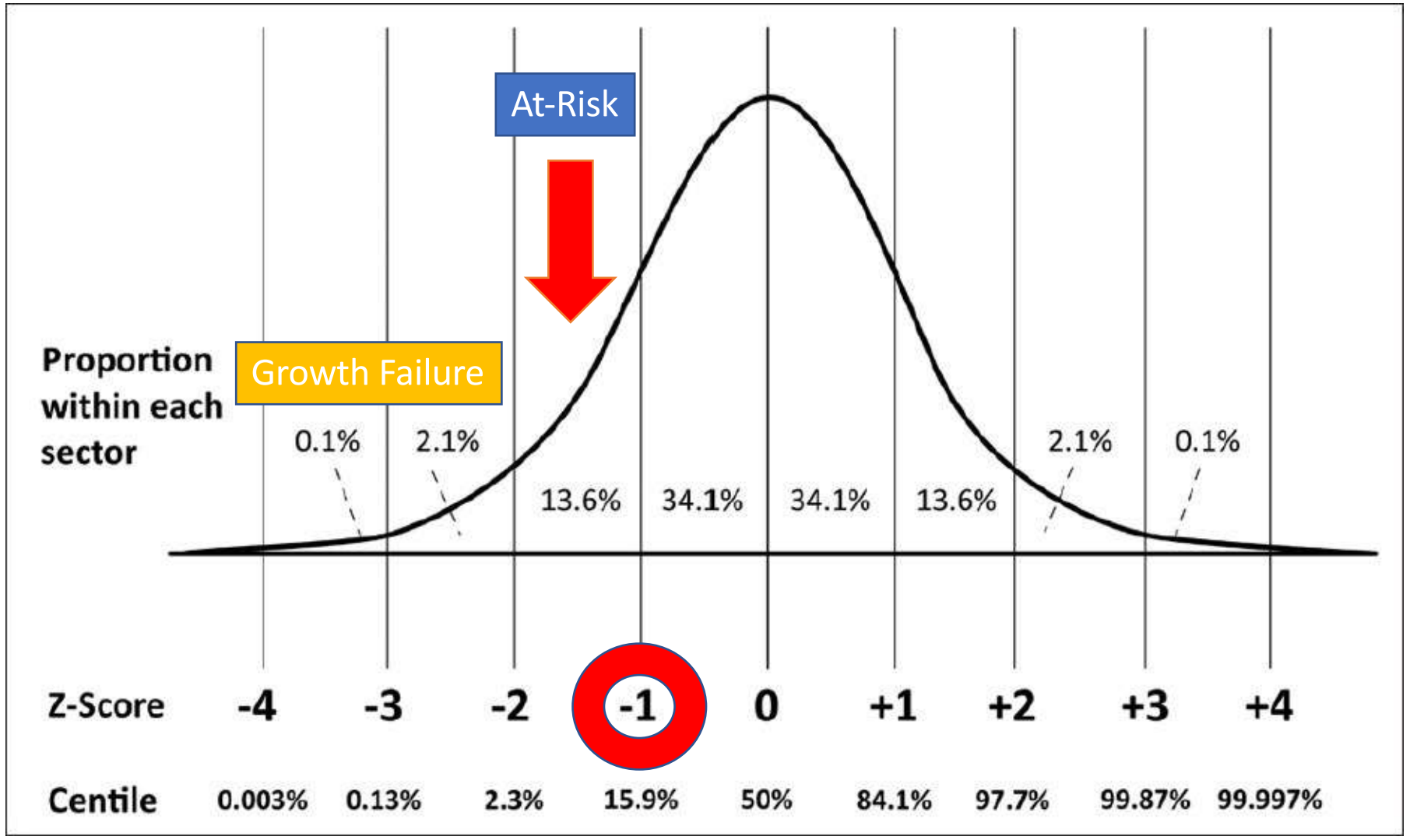
Weight < 5th %

Height Slows

Physician Concern

Serious Complications

Find the At-Risk Child



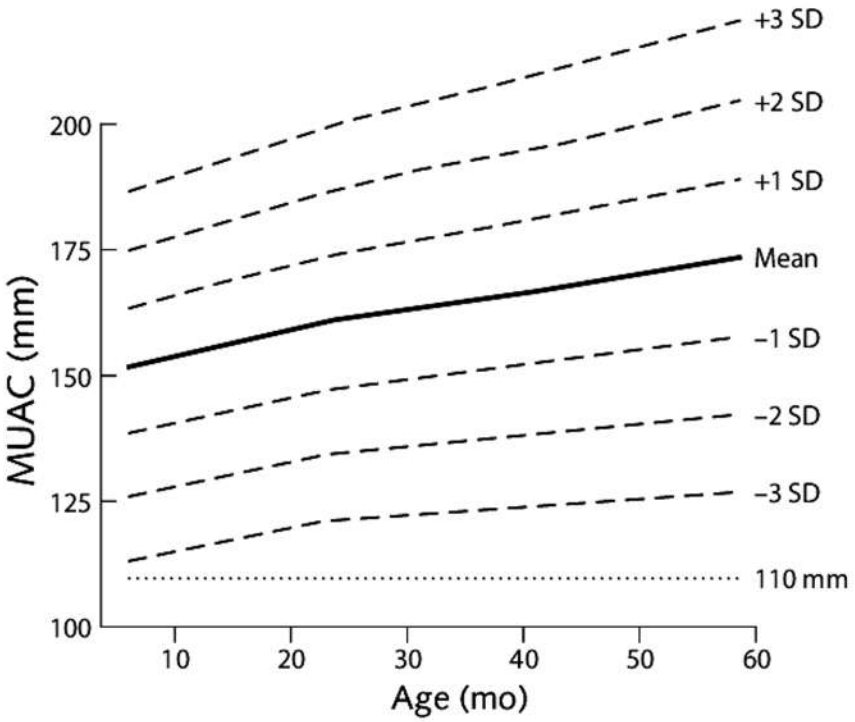
4 Measures of Growth

Measurements
Weight
Height / Length
Skin fold thickness
Mid arm circumference*

Mehta NM et al., ASPEN/ AND, JPEN 2013

Mid-Upper Arm Circumference (MUAC)

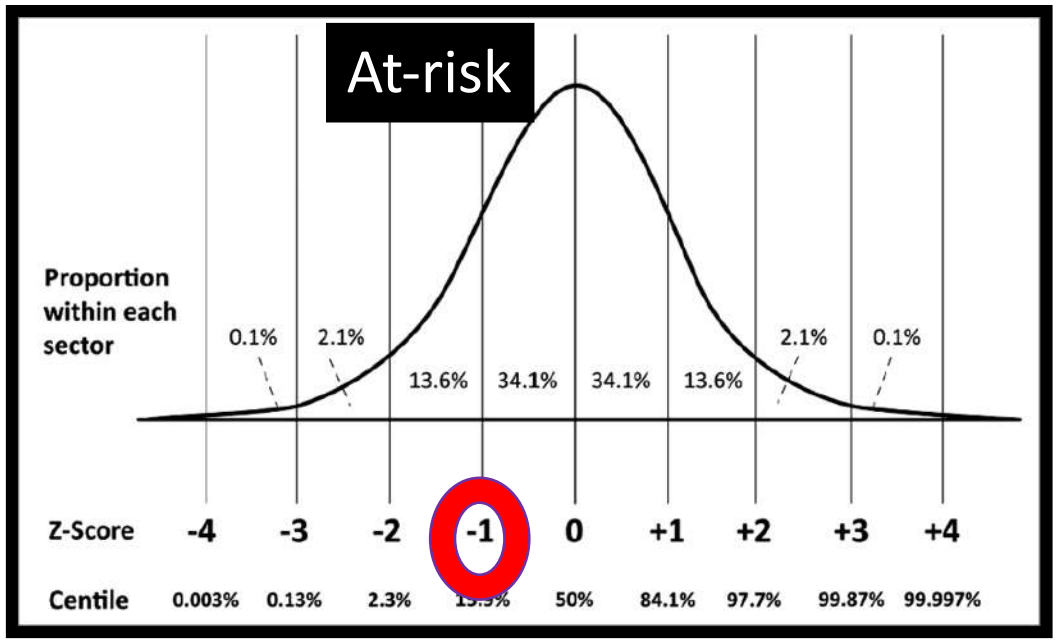
A simple tool to screen for malnutrition in children



For example, among infants in Gambia, a value below 115 mm predicted malnutrition-related deaths

Mwangome et al. Bull WHO, 2012; 90: 887
Aguavoet al. Pub Health Nutr 2015; 18:3244
Isanaka et al. Matern Child Nutr, 2019; 15:e12688

Intervene *Before* Malnutrition



Murray RD. Pediatr Ann 2018;47:e465-e469

* Screen and plot growth
* History of risk factors
* Diet & feeding questionnaire
* Intervene with *balanced* energy & nutrients for growth
* Family feeding counseling & support
* Ensure *complete* catch-up growth
* Close follow-up

Long-Term Use of an ONS for the *At-Risk Child*

- **N=200 3–4 yo Filipinos**
- ***At-risk children*: 5th–25th %-ile BMI (WHO standard)**
- **48 weeks of intervention**

Counseling 3x in 48 weeks
Food groups, protein quality, staple foods, fiber, Portion size, behavioral help

Compared with

Counseling 3x in 48 weeks

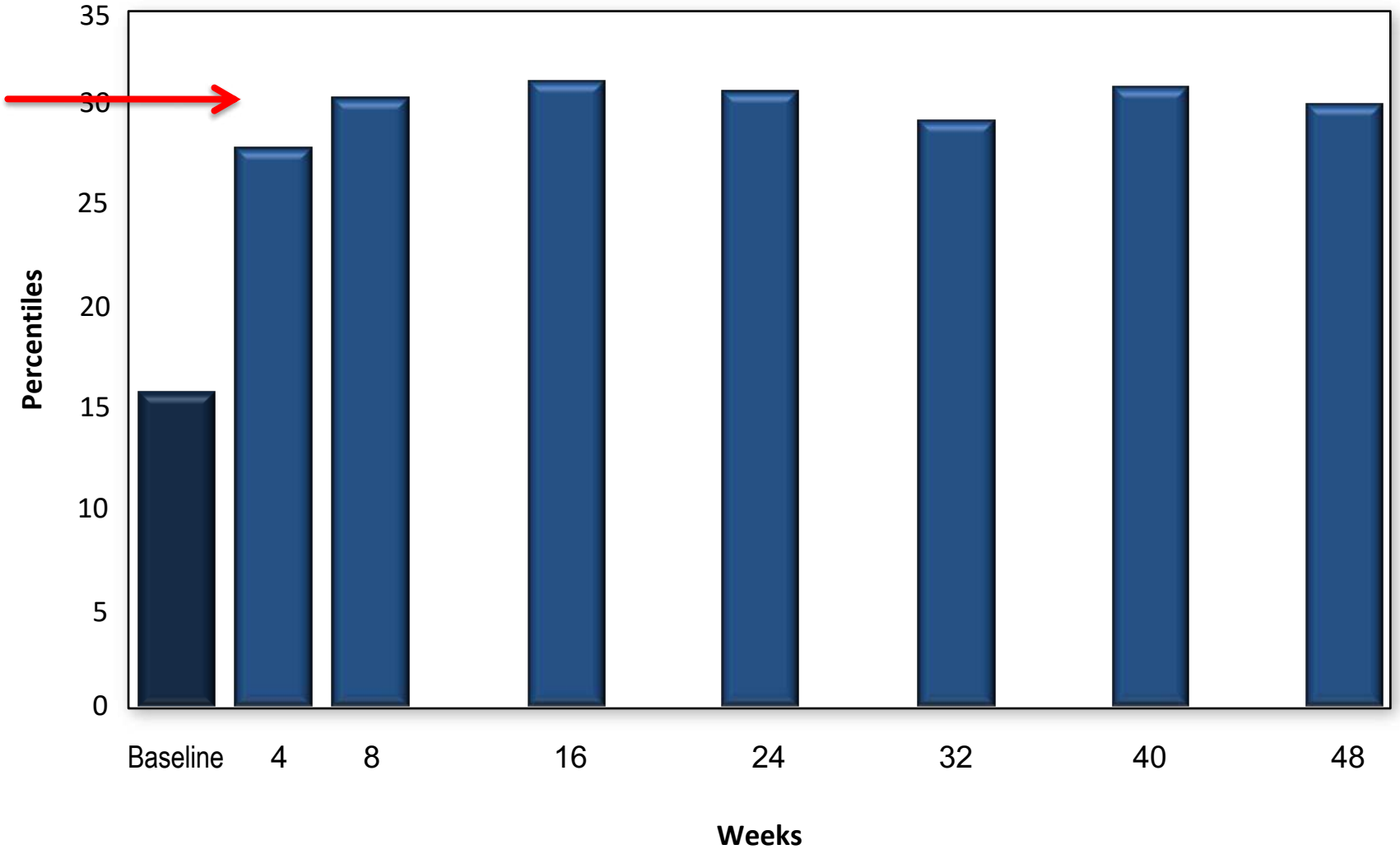
plus

***ONS: twice daily x 48 wks (*450 kcal)**

30-50% of daily nutritional needs
13.5 g protein and 17.7 g fat
59.4 g carbs
28 vitamin/minerals
Pre- and pro-biotics

Huynh *et al*, J Hum Nutr Diet, 2015; 28:623-35
Huynh et al, Nutr Sci. 2016 May 13;5:e20-e31

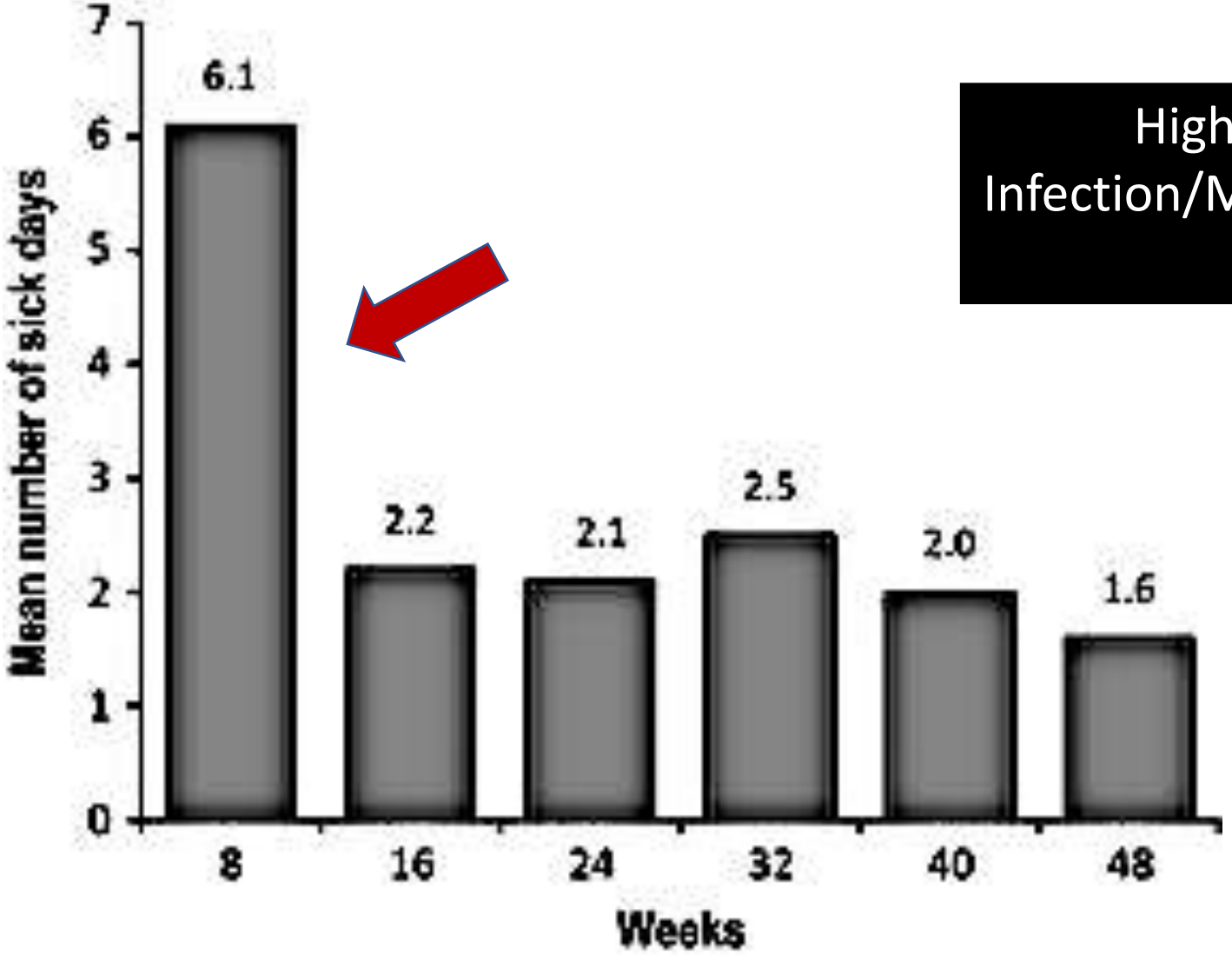
ONS Rapidly Improved Weight-for-Height *without Obesity*



85% Compliance with Consumption of ONS over 48 weeks

Huynh *et al*, 2015; 28:623-35
Huynh et al, 2016; 13;5:e20-e31

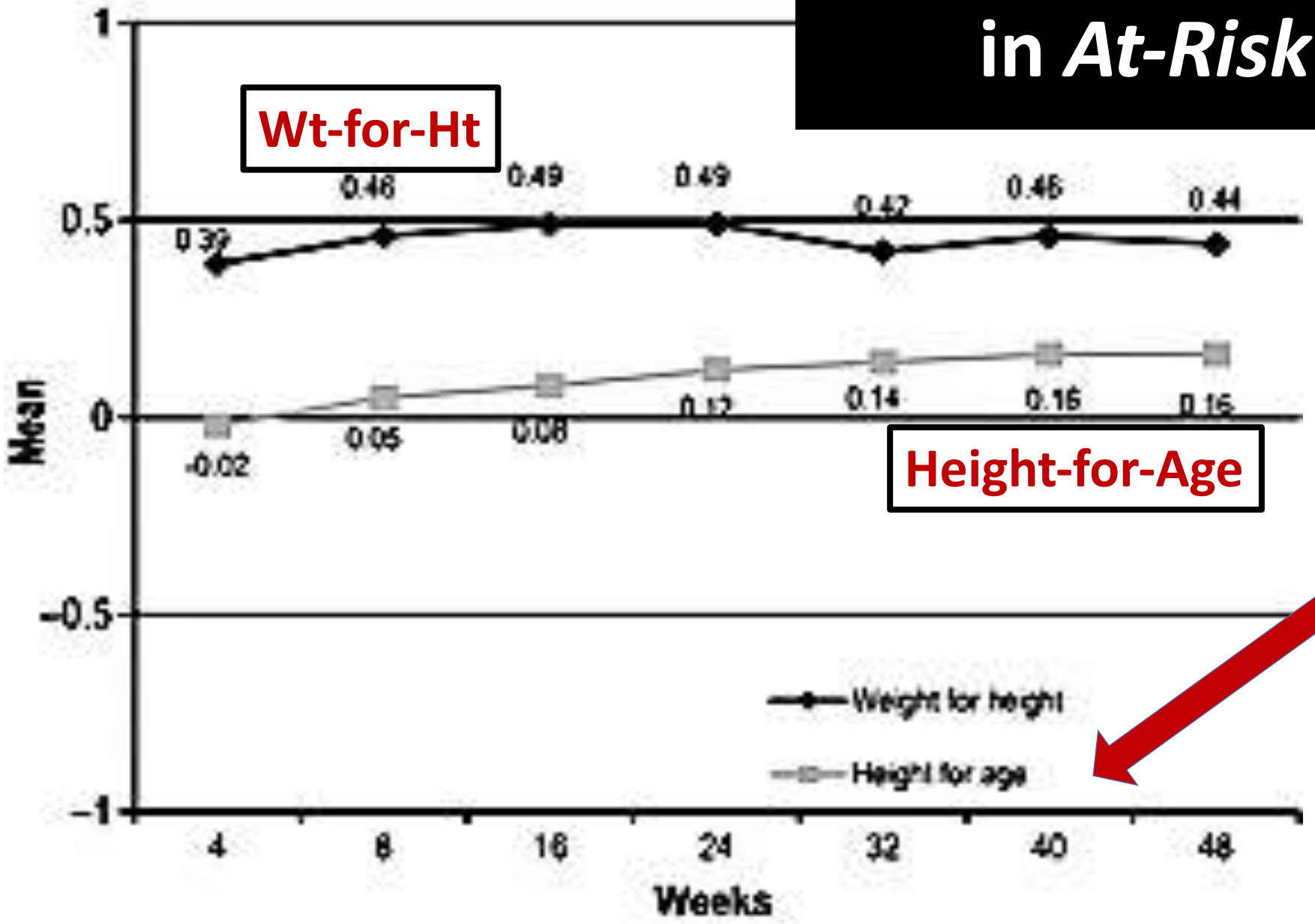
Number of Sick Days Fell on ONS Treatment



High quality nutrition broke the Infection/Malnutrition/ Immune Dysfunction Cycle

Huynh et al. J Hum Nutr Diet, 2015; 28:623-35

Linear Growth Rises in *At-Risk* Children



Growth Plates Respond *Slowly* over Time

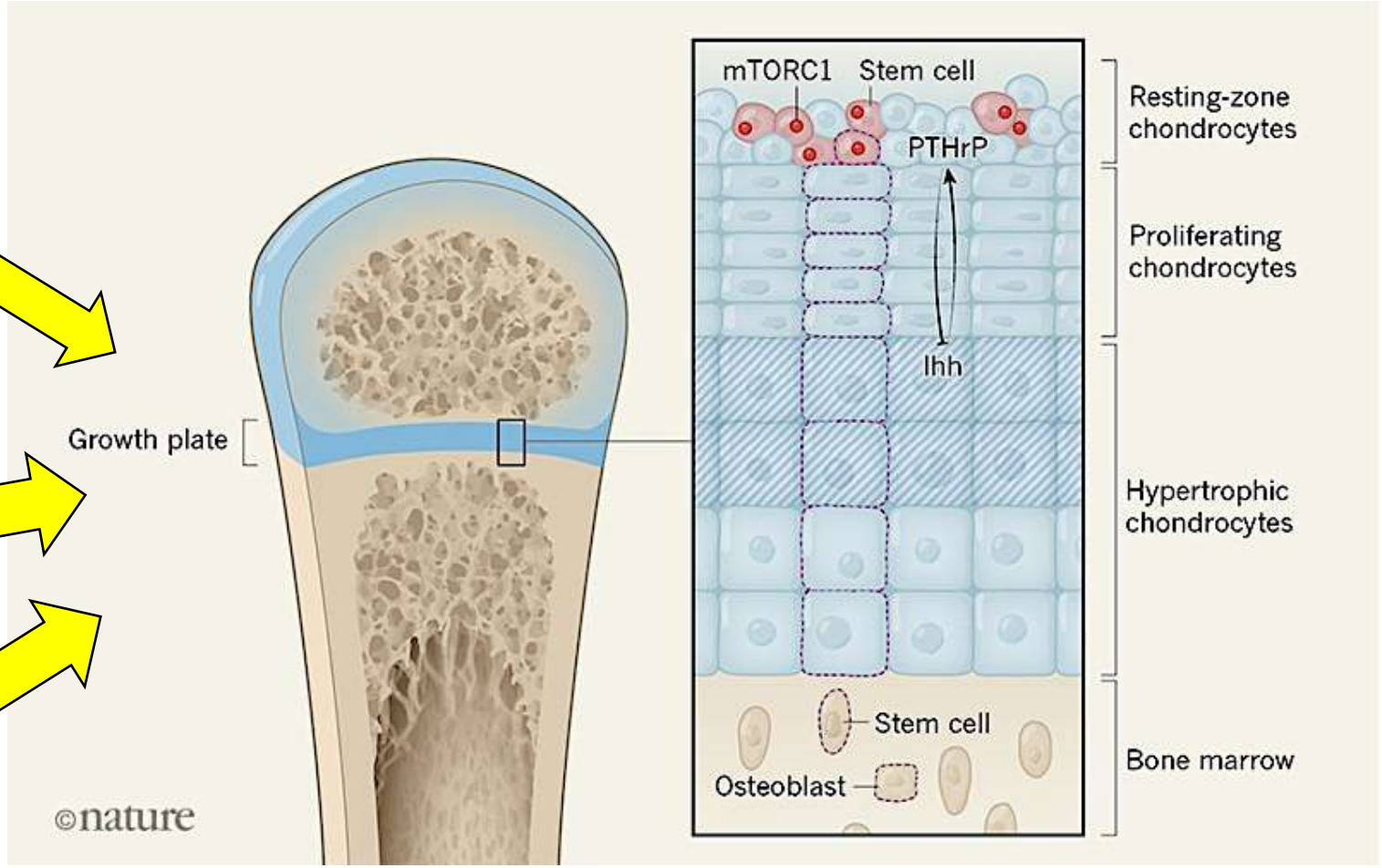
Huynh *et al*, 2015; 28:623-35

Malnutrition Blocks Linear Growth in Many Ways

ENDOCRINE
Lowers IGF-1 (Liver)
Lowers Thyroid Hormone
Low Androgens
Low Estrogens

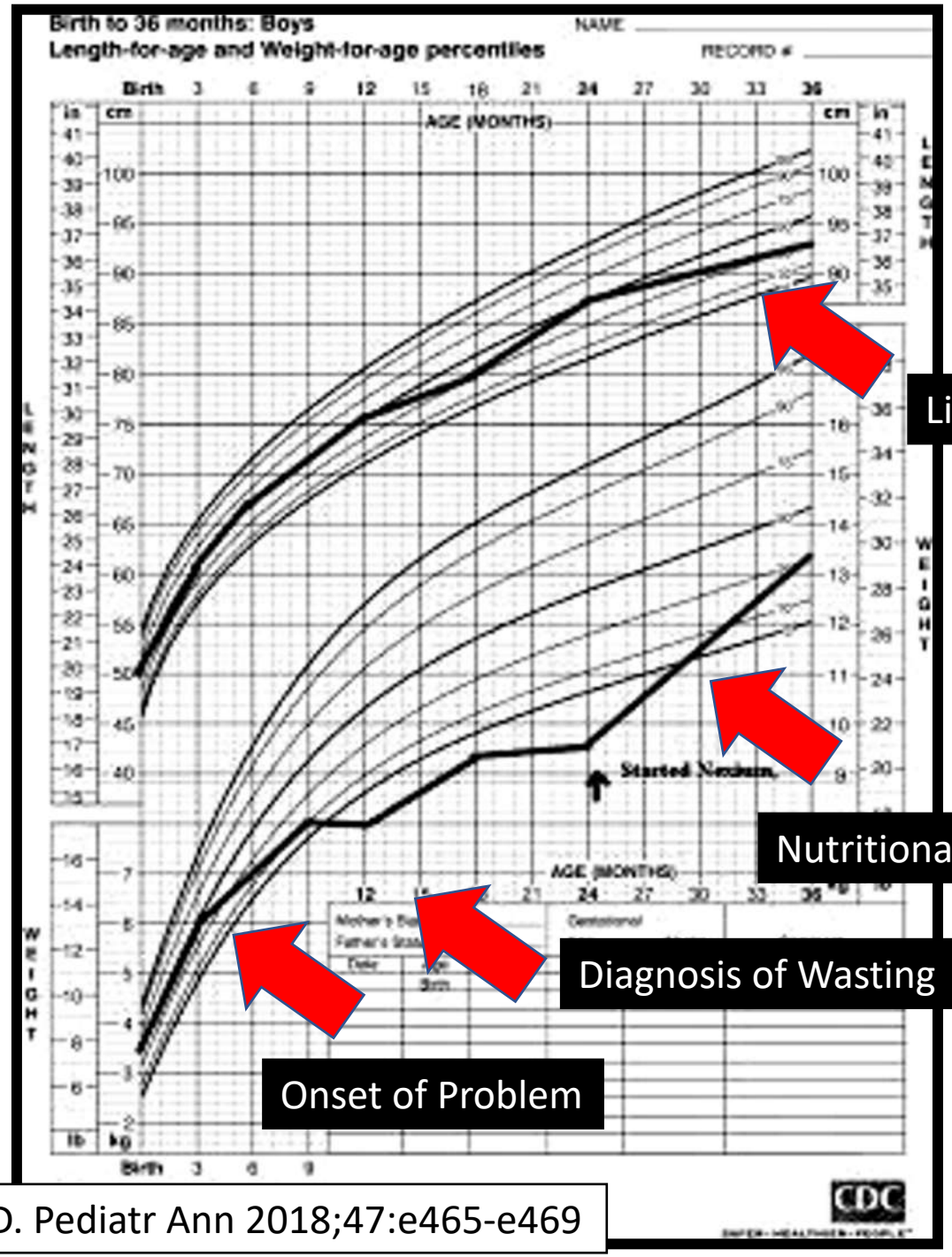
MALNUTRITION
Calories
Protein
Vitamins
Minerals

INFLAMMATION
Raises cytokines
& glucocorticoids
Lowers appetite



Wuelling M, Vortkamp A. Nature, 2019; 567:178-179

Millward JD. *Nutr Res Rev*.2017;30(1):50-72.

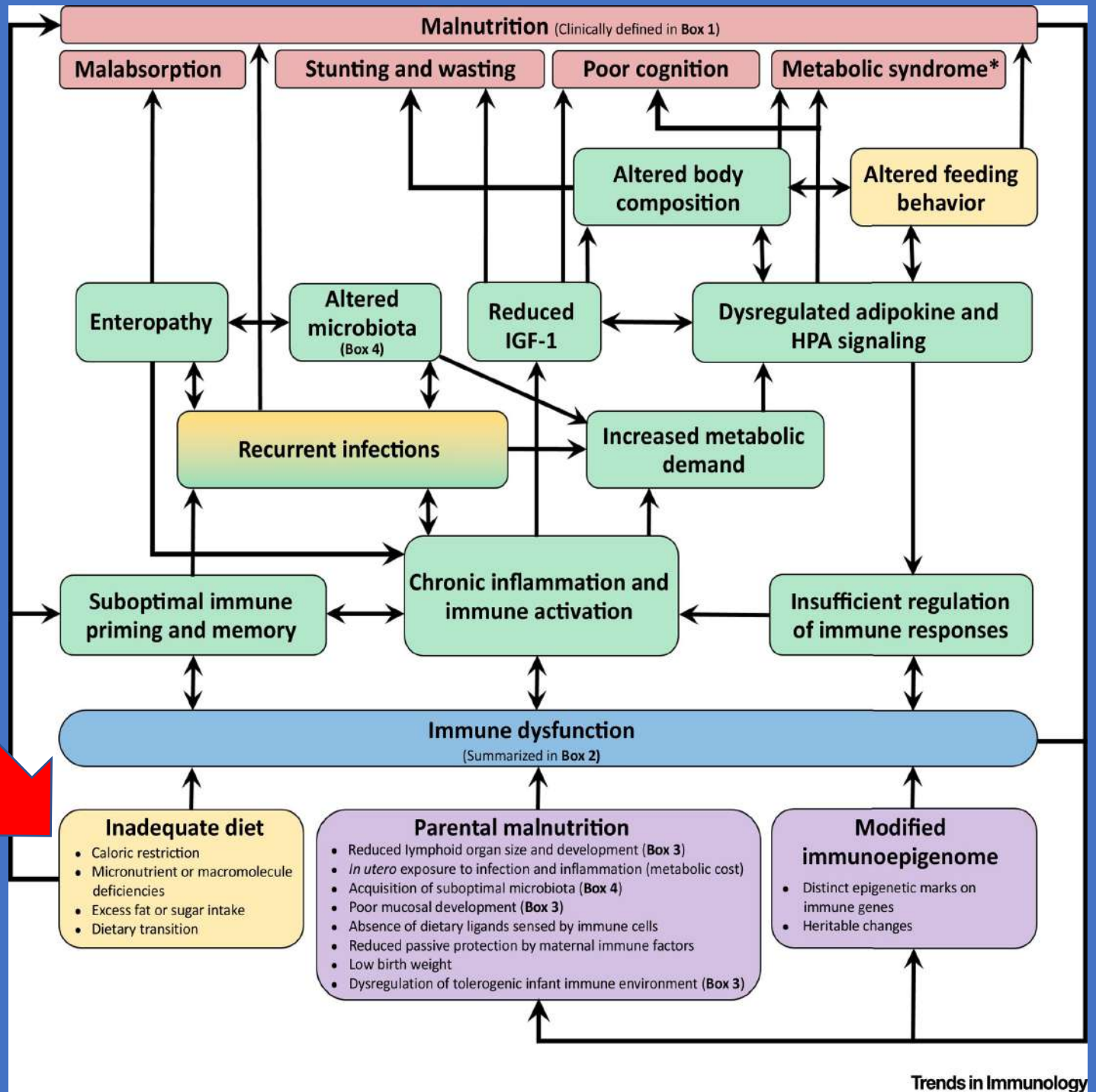


Failure to Respond to "*Risk*"

Wasting
&
Stunting

Murray RD. Pediatr Ann 2018;47:e465-e469

Nutrition Breaks the Cycle



HPA- hypothalamic pituitary adrenal

Bourke CD, et al. *Trends Immunol*. 2016;37(6):386-398.

Key Points

- Extraordinary growth in early life
- Microbiome, epithelium, and immunity
- The Cycle: malnutrition, weak immunity, infection, growth
- Balanced nutrition breaks the cycle
- Early enough, aggressively enough, long enough