Development of Digestion, Absorption, Intestinal Motor Activity and Mucosal Immune System

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The Versatile Intestine: The intestine is not only a digestive-absorptive organ

- largest immune organ of the body.
- harbors a huge microbial ecosystem.

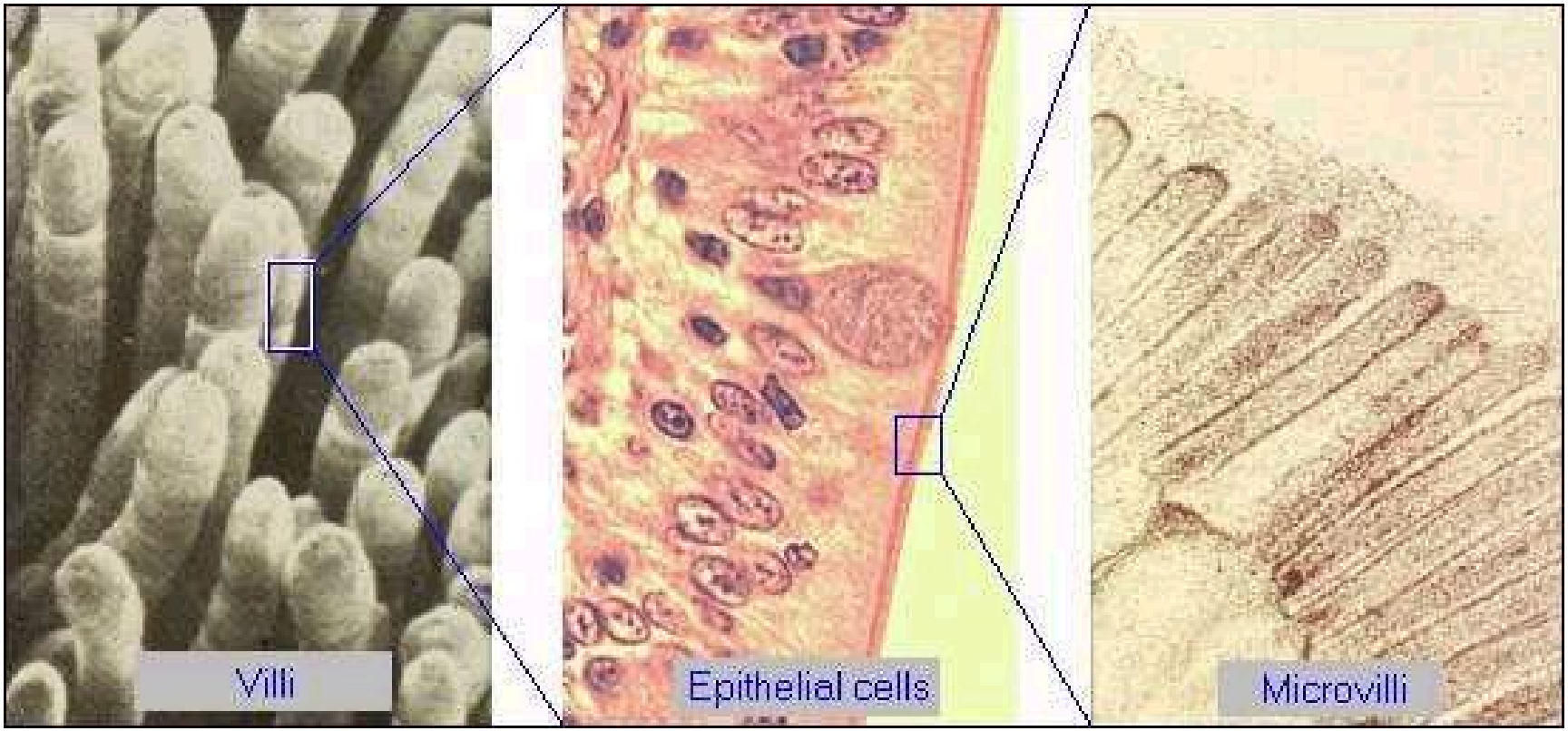
Developmental Anatomy, Physiology And Clinical Applications

- Intestinal growth.
- Quick Overview of the Intestinal Barrier and Immune System
- Swallowing, GE-sphincter function, gastric emptying and intestinal motility.
- Digestion, absorption and assimilation.
- Clinical Implications.

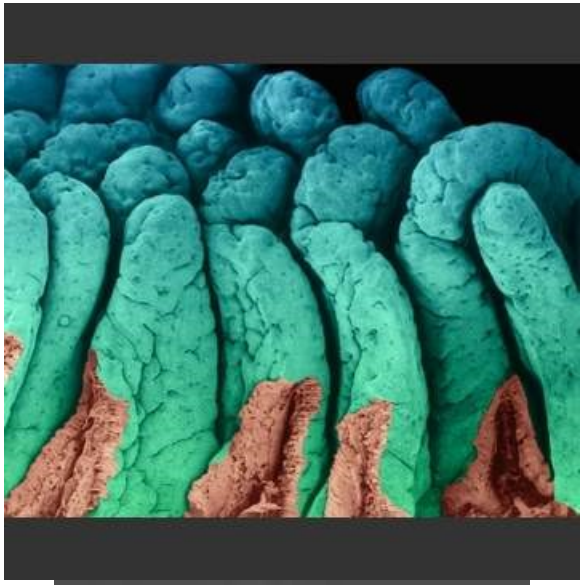
Growth in Length

- Human fetal intestine elongates 1000 fold from 5-40 weeks.
- Length doubles in last 15 weeks of gestation.
- Mean length at birth (term) is 275 cm.

Surface Area: Villi and Microvilli



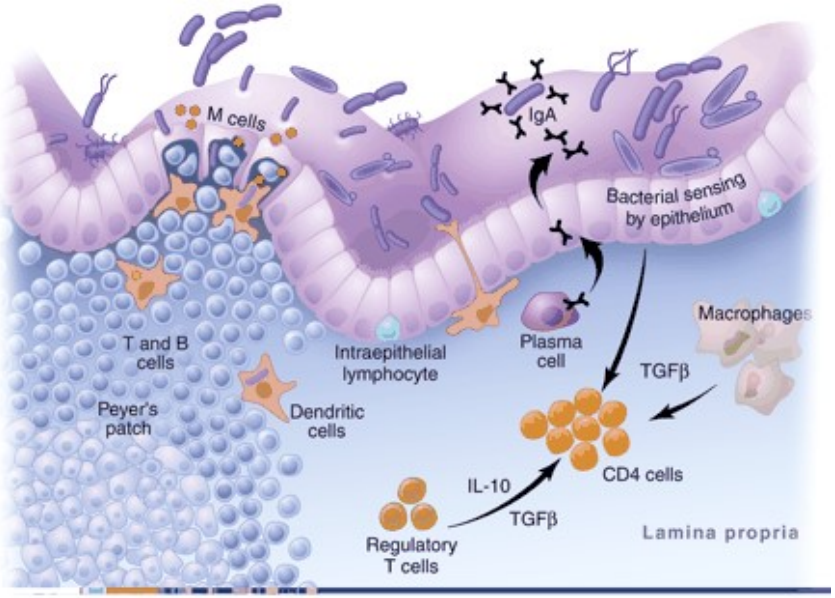
Intestinal Surface Area



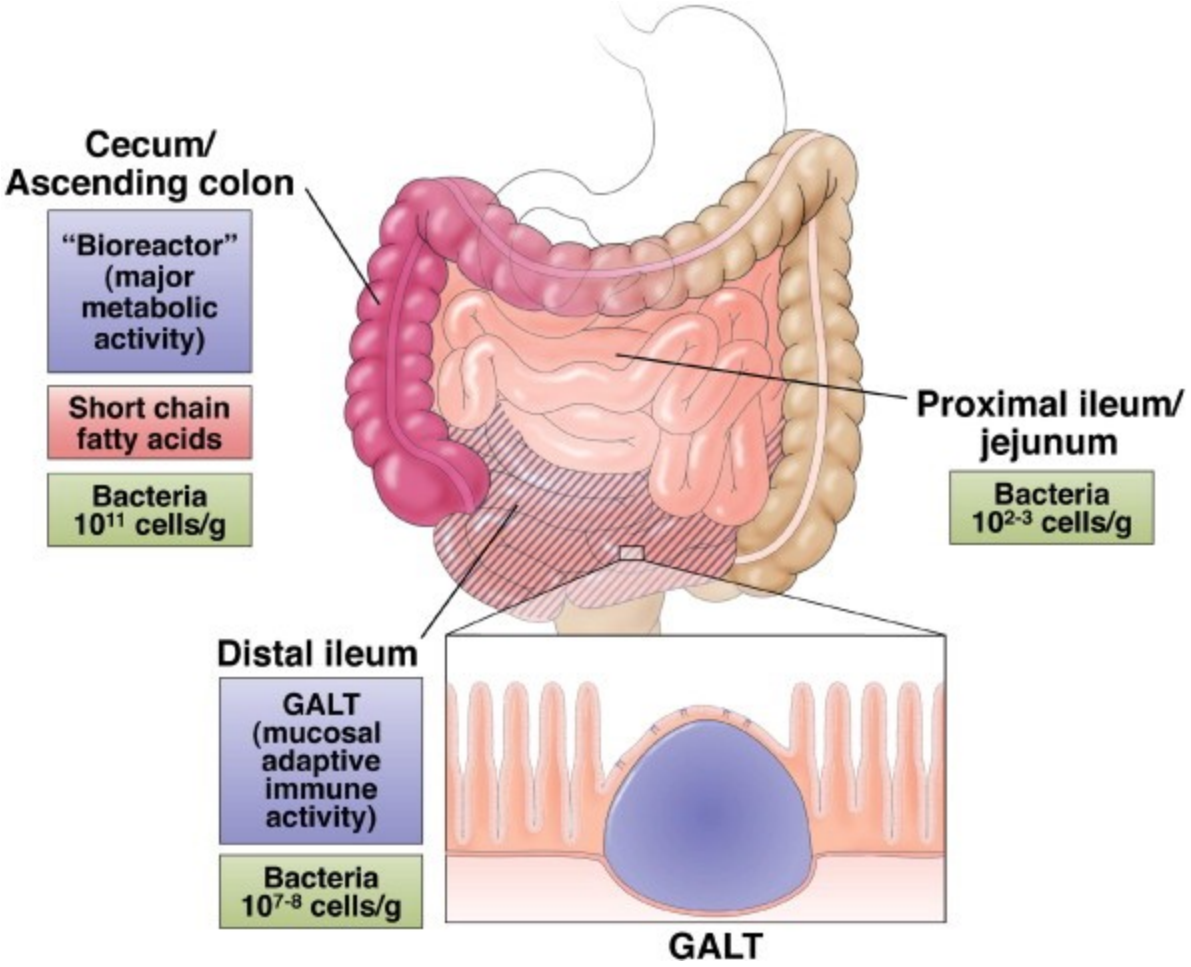
200 m^2

Intestinal Antigenic Load

- Gut content of microbes is ~10^{13} cells.
- An individual consumes at least 2,500 kg. Food antigen during a lifetime.
- A single layer of epithelial cells separates the luminal contents from effector immune cells in the lamina propria.

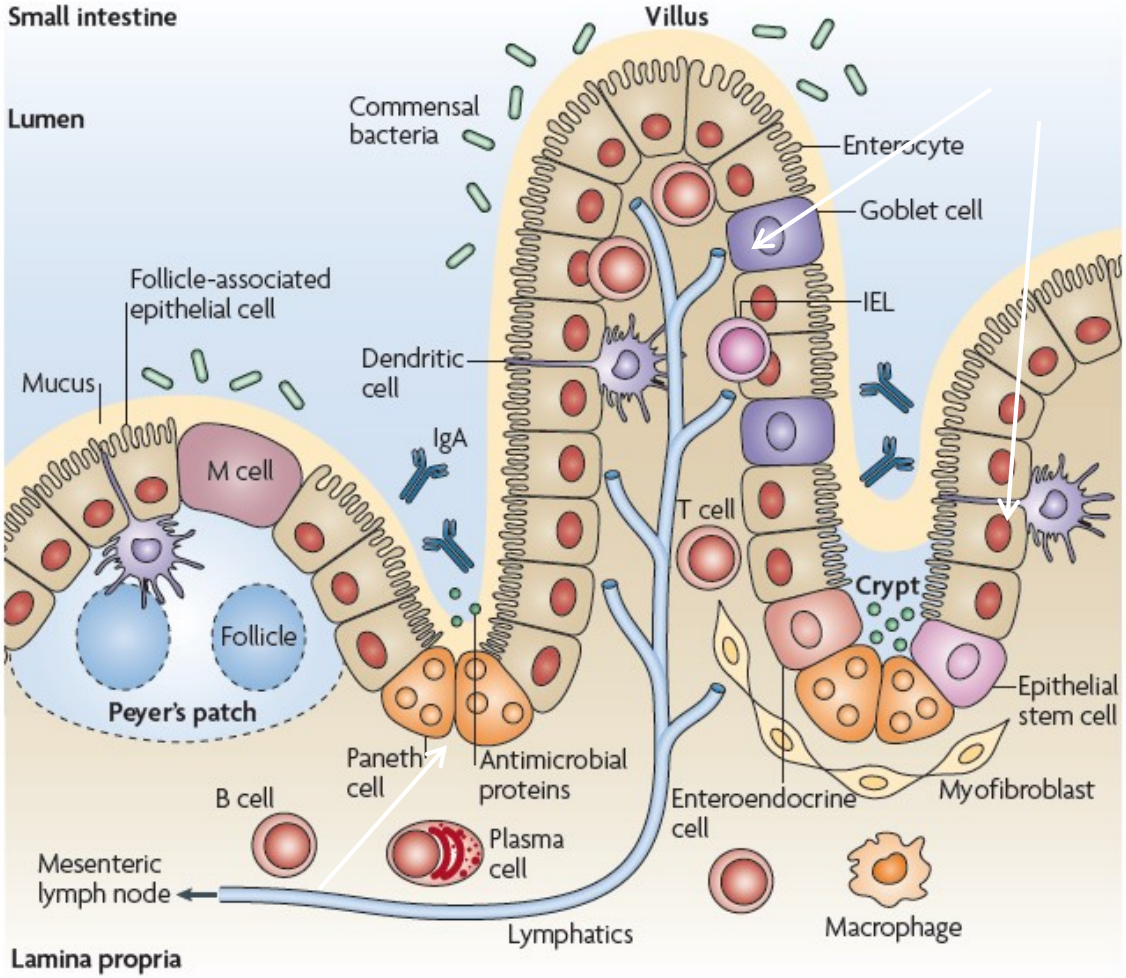


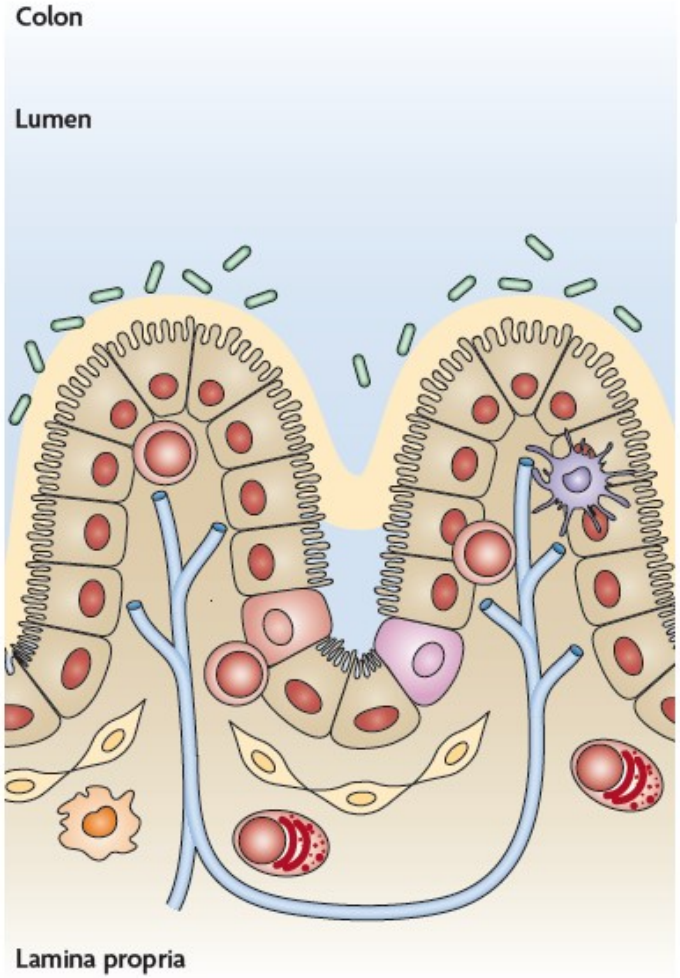
Regional Differences



Neish, A. Gastroenterology vol. 136,No. 1, 2009

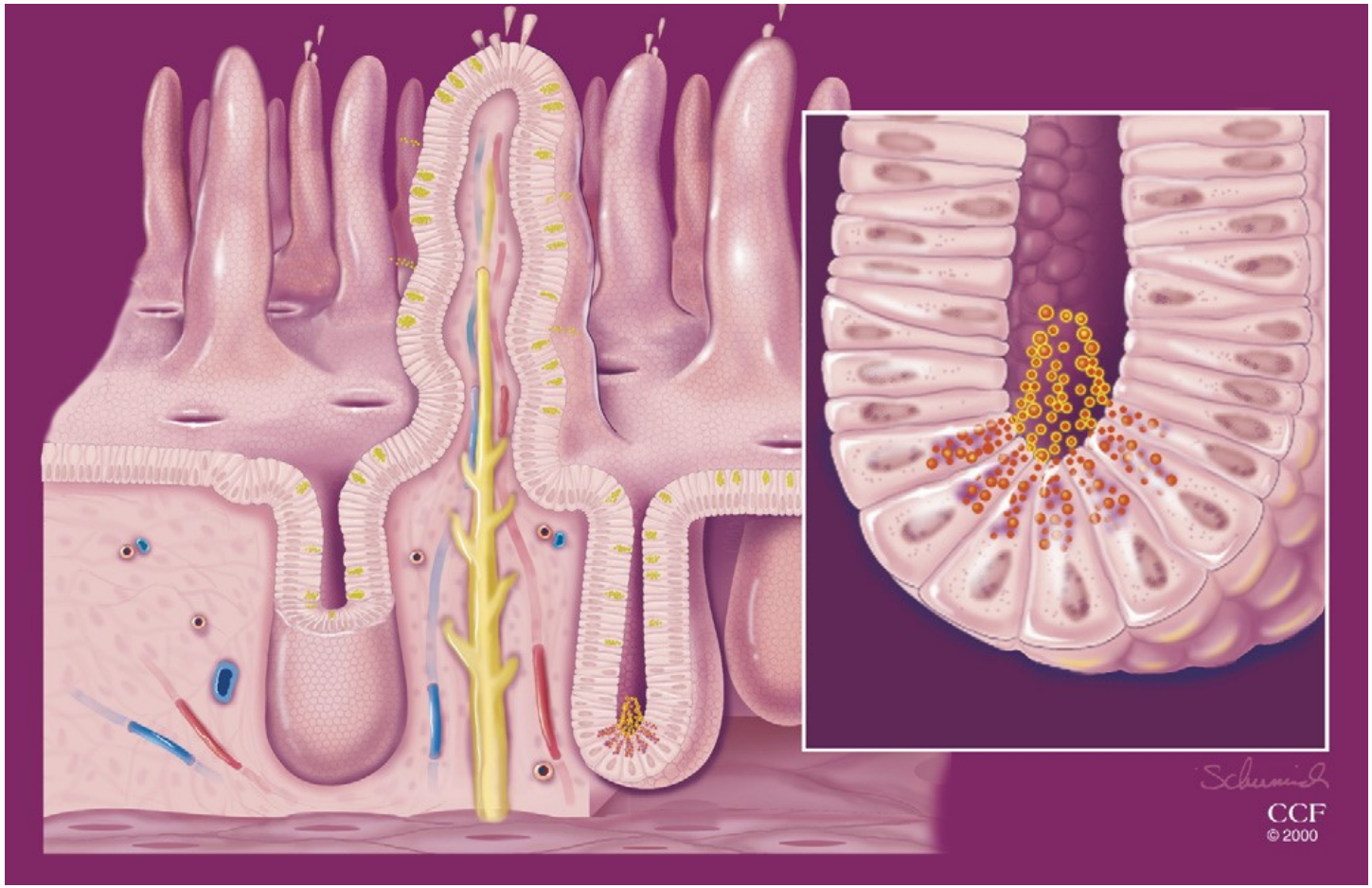
The Intestinal Barrier: Cells



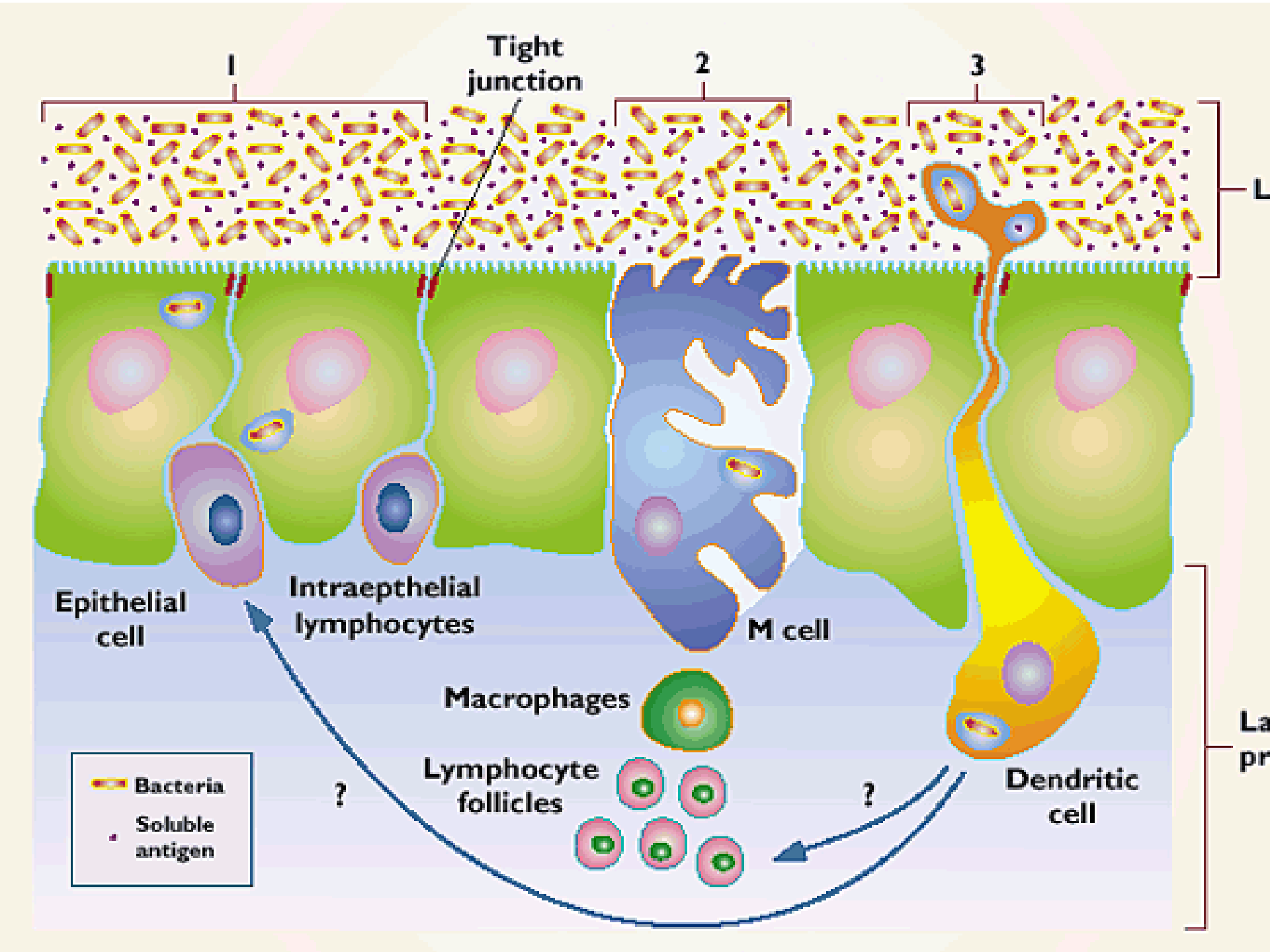


Abreu, M. Nature Immunology Feb. 2010

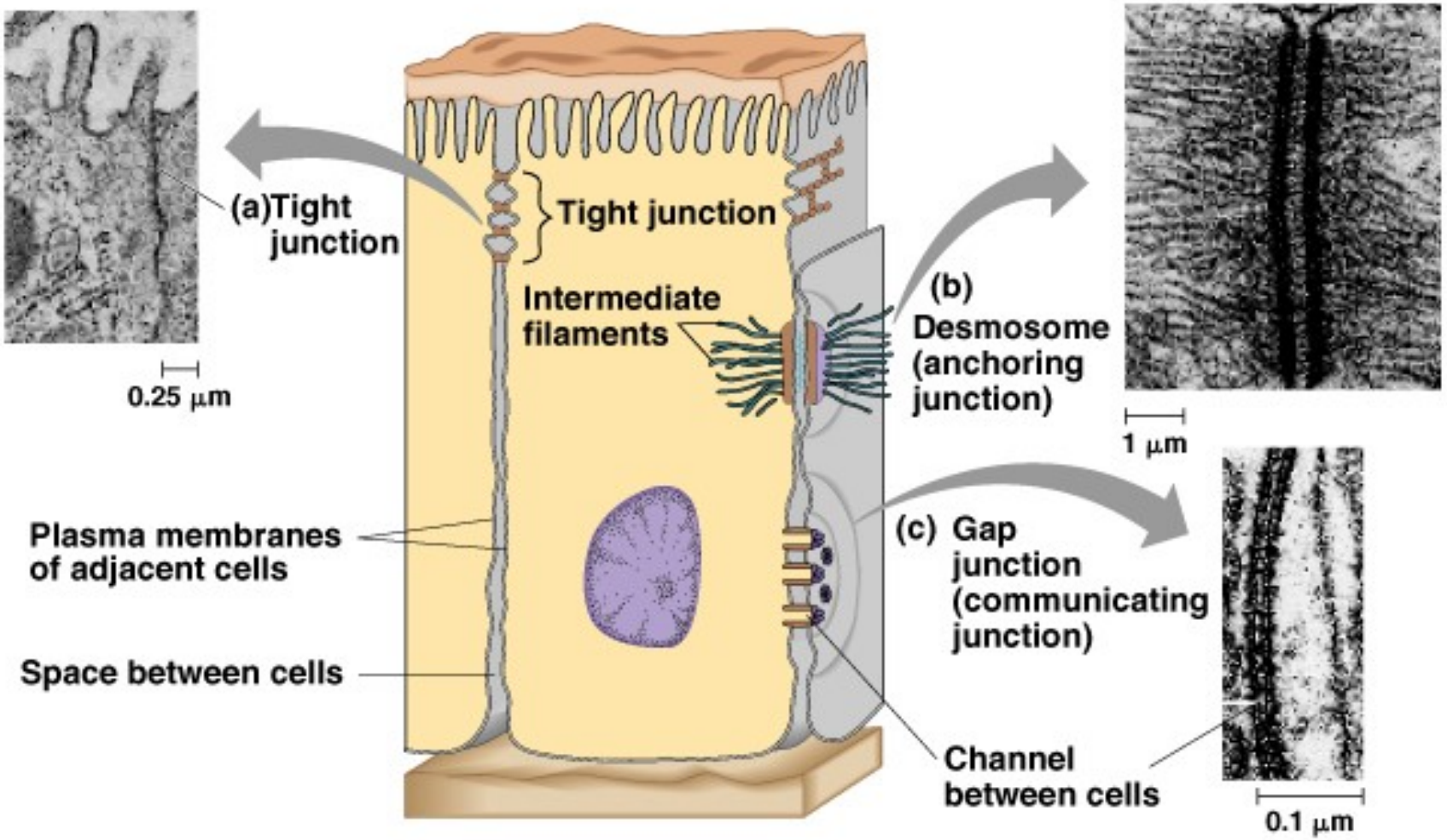
Paneth Cells



Blikslager AT, et al. Physiol Review 87:545-564,2007

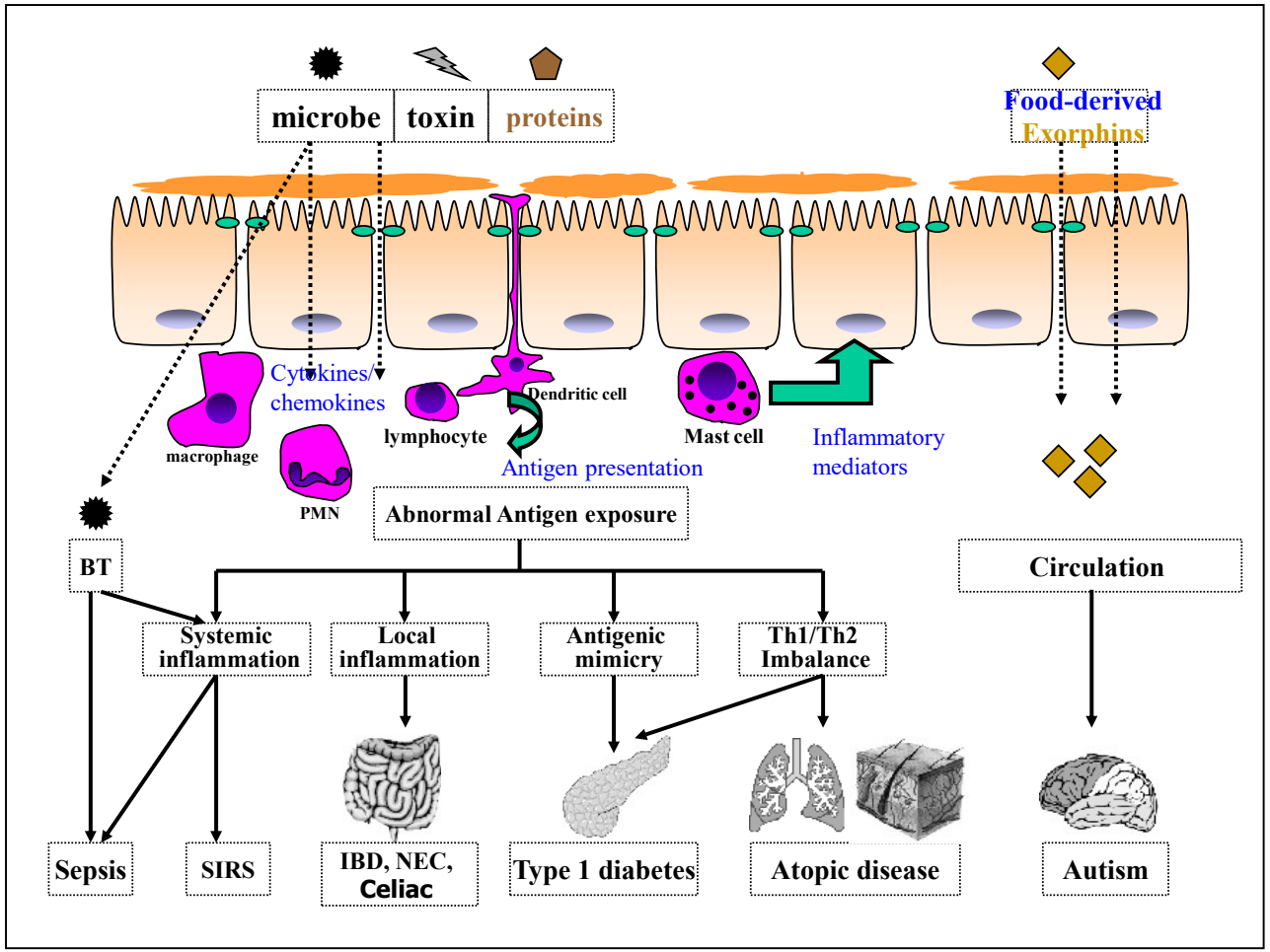

1
Tight junction
2
3
Epithelial cell
Intraepthelial lymphocytes
M cell
Macrophages
Lymphocyte follicles
Dendritic cell
?
?
Bacteria
Soluble antigen

Interepithelial Junction



(b) Courtesy of L. Orci and A. Perrelet, Freeze-Etch Histology (Heidelberg: Springer-Verlag, 1975.) ©1975 Springer-Verlag.

Pediatric Diseases Associated With Barrier Dysfunction



Tight junctions, leaky intestines, and pediatric diseases.
Liu Z, Li N, Neu J. Acta Paediatr. 2005 Apr;94(4):386-93.

Physiological Processes (Fetal Swallowing)

- The fetus swallows 450ml/day of amniotic fluid in the third trimester.
- This is suddenly interrupted at the time of preterm birth.

Mechanical Difficulties

Suck-swallow incoordination-necessitates tube feeding.

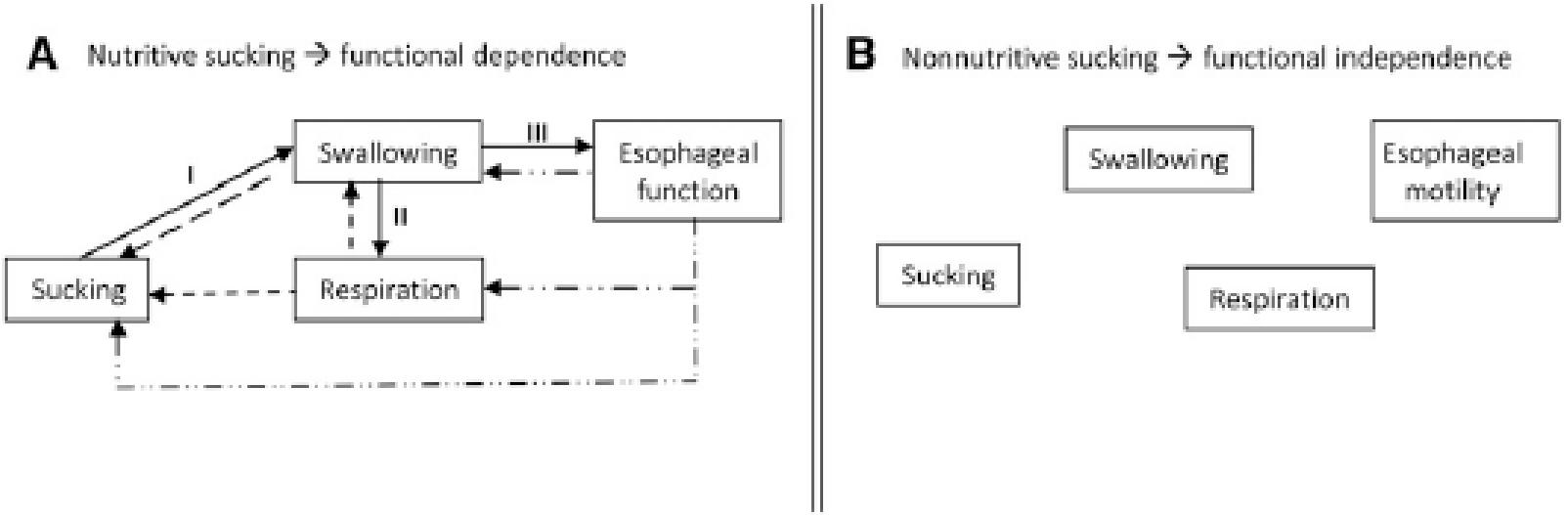
Gastric emptying delayed. Motility disorganized.

Gastroanal transit in ELBW=2-5 days; Term=12-24 hours

Nutritive versus Non-Nutritive Sucking

- Nutritive=1 suck per second; active swallowing
- Non-nutritive=2 sucks per second; minimal swallowing

Nutritive versus Non-Nutritive Sucking

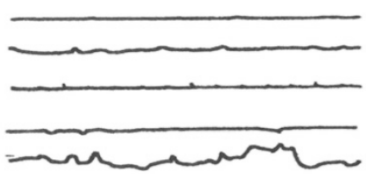
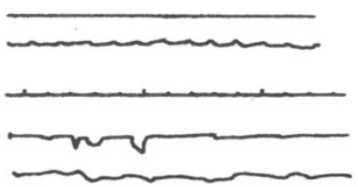
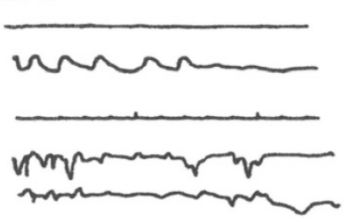
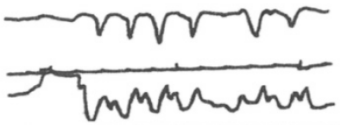


Has Feedback loops

No Feedback loops

Lau, C. et al., AJCN 2016

Development of "Nutritive" Sucking

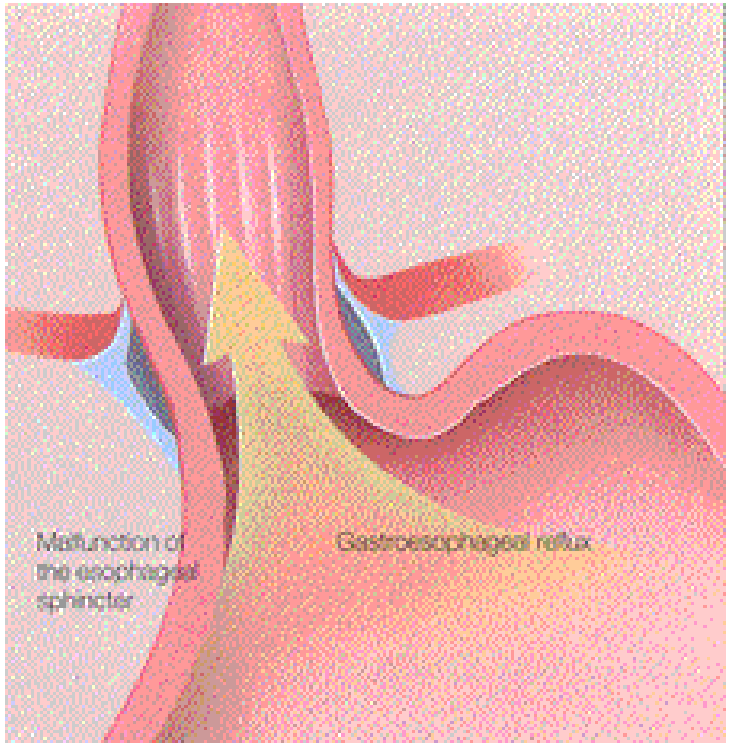
STAGE		SAMPLE TRACINGS	DESCRIPTION
1A and/or 1B	Suction Expression Time (sec) Suction Expression		No Suction Arrhythmic Expression and/or Arrthymic alternation of Suction/Expression
2A and/or 2B	Suction Expression Time (sec) Suction Expression		No Suction Rhythmic Expression and/or Arrthymic alternation of: - Suction/Expression - Presence of sucking bursts
3A and/or 3B	Suction Expression Time (sec) Suction Expression		No Suction Rhythmic Expression and/or Rhythmic Suction/Expression - Suction amplitude increases - Wide amplitude range - Prolonged sucking bursts
4	Suction Time (sec) Expression		Rhythmic Suction/Expression - Suction well defined - Decreased amplitude range
5	Suction Time (sec) Expression		Rhythmic/well defined Suction/Expression - Suction amplitude increases - Sucking pattern similar to that of fullterm infants

Lau, C. et al., AJCN 2016

Readiness to oral feed

- A primary concern of caregivers before weaning patients from tube feeding.
- Current practice includes a trial and error approach usually at 32-34 weeks PMA.
- Some measures such as side-lying feeding position, cheek and chin support and cue based feedings might be helpful.
- Adequate oral feeding often an important criterion for hospital discharge.

Gastro-esophageal Reflux



GERD occurs with stomach content reflux up the esophagus

- **Gastroesophageal Reflux (GER)- a physiologic event** retrograde movement of gastric contents into the esophagus.
- **Gastroesophageal Reflux Disease (GERD)-a pathologic entity** that includes complications derived from GER.

Is GER(D) a Frequent Problem in Preterm Infants?

- Prior to removal from market 1/5 of preterm infants in US academic centers were treated with cisapride.
- 25% of extremely low birth weight infants admitted to the NICHD network centers were discharged home on medications (e.g. H2 blockers and Reglan) to treat GERD

GERD must be a common problem in the NICU….!!

Ward Rm et al, Pediatrics 1999;103:469-72
Malcolm WE et al, Pediatrics 2008;121:22-7

The nurse reports that this baby is having lots of apneic and bradycardic episodes and is convinced they are caused by reflux.

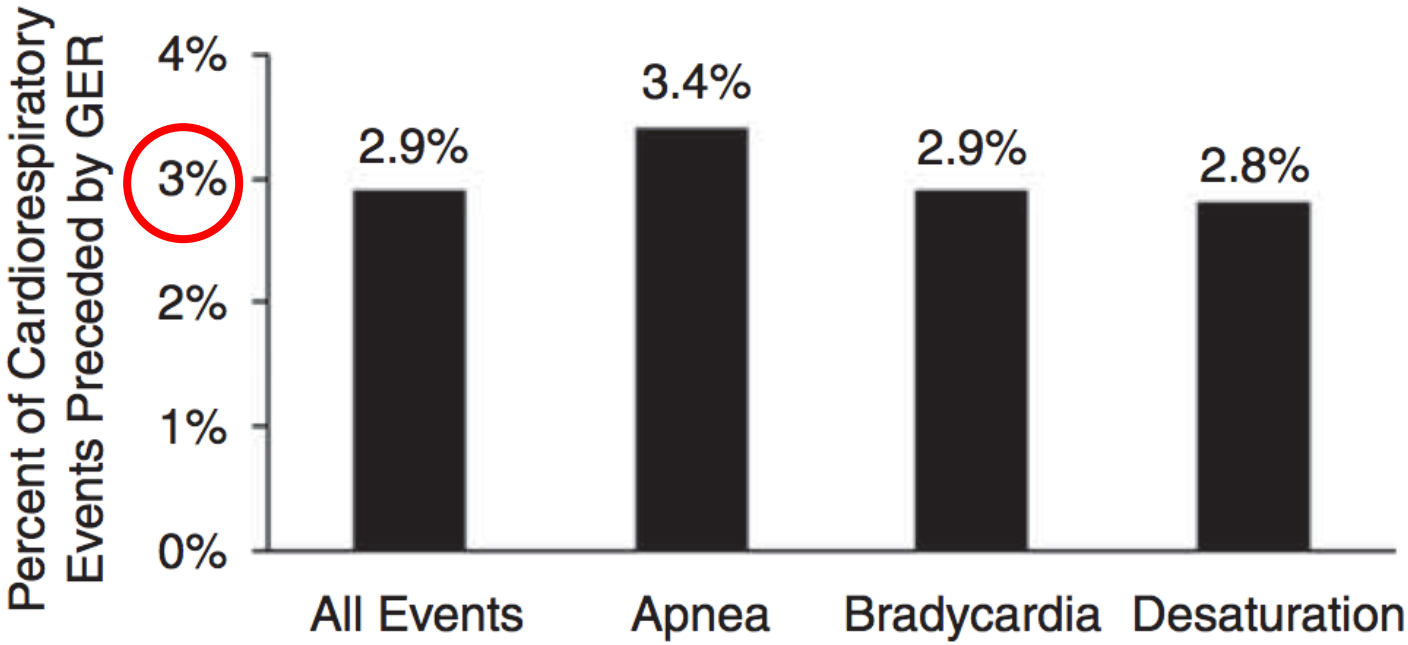
Are Clinical Signs (Behavior) Reliable of GERD in preterm infants?

- **Observers viewed films of these infants: 74% inter-observer agreement in episodes of coughing, hiccoughing, gagging, head retraction, etc.**
- **20 episodes of acid GER recorded (pH<4)**
- **No behavioral pattern was temporally correlated with acid reflux.**

Snel, A., et al. - J Pediatr Gastroenterol Nutr. 2000 Jan;30(1):18-21

Does GER Cause Apnea & Bradycardia in Preterm Infants?

- MII & pH probe in 71 preterm infants (GA 29±3 wks) studied at mean PMA of 37±2.6 wks
- Evaluated timing of GER events vs A&B's



DiFiore J et al J Perinatol 2010;30:683-87

Are GER and Apnea temporally associated in preterm infants?

- GER is **not** associated with the vast majority of episodes of apnea in preterm infants

- In a very small number of infants there is a relationship between GER and apnea.

- There are some preterm, former preterm, and term infants in whom GER may be a contributory factor precipitating episodes of mixed or obstructive apnea

- **Most will outgrow these episodes within the first months of life**

Does Pharmacologic Therapy Decrease Bradycardic Episodes?

- Crossover Trial of preterm infants
- Metoclopramide (0.2mg/kg/dose q 6h)
- Ranitidine (2 mg/kg/dose q8h)

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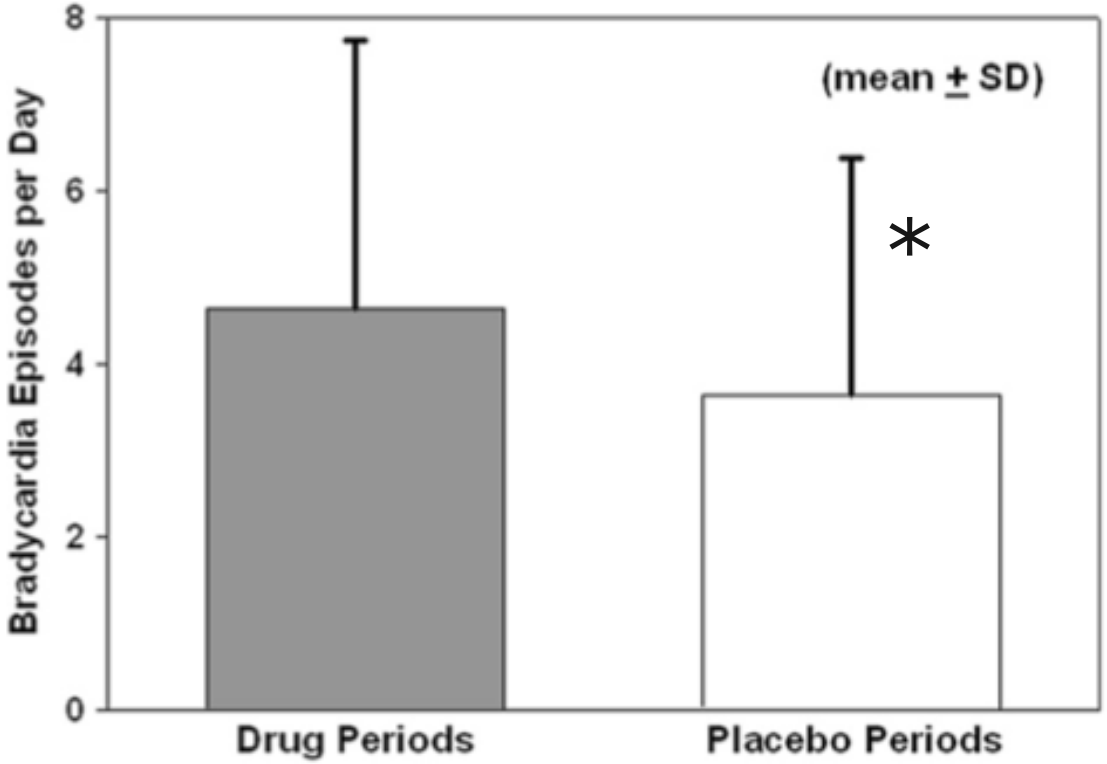


Wheatley DO and Kennedy KA
J Pediatr 2009:155:516-21

GER and Positioning

- **The left side down position showed the lowest esophageal acid exposure (0.8%) in the early postprandial period, and the prone position showed the lowest esophageal acid exposure (5.1%) in the late postprandial period.**
- **CONCLUSION: Placing premature infants in the prone or left lateral position in the postprandial period is a simple intervention to limit GER.**

Covaglia L, J. Pediatrics 2007

Choosing Wisely

TABLE 2 Choosing Wisely Top Five List for Newborn Medicine

1. Avoid routine use of antireflux medications for treatment of symptomatic GERD or for treatment of apnea and desaturation in preterm infants.
2. Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection.
3. Avoid routine use of pneumograms for predischarge assessment of ongoing and/or prolonged apnea of prematurity.
4. Avoid routine daily chest radiographs without an indication for intubated infants.
5. Avoid routine screening term-equivalent or discharge brain MRIs in preterm infants.

GERD, gastroesophageal reflux disease.

Ho, T. et al. **Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value** Pediatrics. 2015 Aug;136(2):e482-

Proprietary Thickener: Used for putative GE reflux/apnea/bradycardia

CLINICAL AND LABORATORY OBSERVATIONS www.jpeds.com • THE JOURNAL OF PEDIATRICS

Late Onset Necrotizing Enterocolitis in Infants following Use of a Xanthan Gum-Containing Thickening Agent

Jennifer Beal, MPH[1], Benson Silverman, MD[1], Jodeanne Bellant, MD[2], Thomas E. Young, MD[3], and Karl Klontz, MD[1]

Adverse event reports submitted to the US Food and Drug Administration suggested a possible association between necrotizing enterocolitis and ingestion of a commercial feed thickener by premature infants. Review in 2011 of 22 cases with exposure revealed a distinct illness pattern. *(J Pediatr 2012;161:354-6)*

Diagnostic Tests for GERD

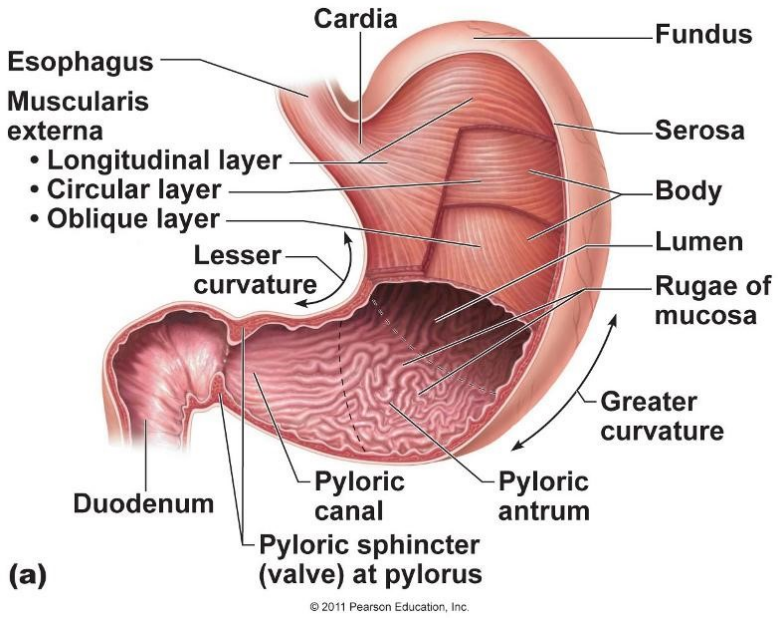
Test	Strengths	Weakness	Ale to Quantify GER Frequency	Able to Diagnose GERD
Upper GI Series	Can identify mimics of GERD such as obstruction	Measured overall brief period so frequency cannot be established Radiation Exposure	No	No. Correlation with symptoms is necessary.
Esophageal pH	12 to 24 hour study allows quantification	Not clear whether acid or non-acid triggers symptoms	Yes	No. Correlation with symptoms is necessary
Multichannel Intraluminal Impedance	12-24 hours allows for quantification of fluid boluses in esophagus	Acidic events not always detected	yes	No. Correlation with symptoms is necessary.

Pharmacologic Therapies

Drug Type	Mechanisms of Action	Proposed Benefit	Examples of Adverse Effects
H-2 receptor antagonists	Suppresses Acid production	Suppression of gastric acidity and mitigation of tissue damage that triggers pain.	NEC, late onset sepsis, Respiratory infections, death, IVH, bradycardia and decreased Ca absorbtion
PPI	More strongly Suppress gastric acidity than H2 receptor antagonists---act through H/K atp pathways.	Similar to above	Similar to above
Metaclopramide	Antagonist of dopamine-2 receptor subtype	Promote esophageal clearance of fluids and enhance lower esophageal sphincter tone.	Tardive Dyskenesia, irritability, drowsiness, apnea, dystonic reaction, oculogyric crisis
Erythromycin	Motilin receptor agonist. Promotes motility throughout GI tract by promoting MMCs		Pyloric Stenosis (antibiotic dosages) and arrythmias

Gastric Motility

- BER---3/minute
- Stimulation of Stomach movement
  - Distension
  - Gastrin
  - Parasympathetics from vagus nerve
  - CCK, secretin, duodenal distension, increased osmolarity and decreased pH inhibit motility



Food Effects on Stomach

- Isotonic solutions---Fast
- Fat---slow

Erythromycin

- The current information favors the use of rescue rather than prophylactic treatment, intermediate to high doses rather than low-dose erythromycin and administering the medication intragastrically rather than intravenously
- oral erythromycin should be used cautiously and selectively in preterm infants with moderately severe functional GI dysmotility and in whom a structural obstructive lesion has been excluded.

Ng, PC Neonatology. 2009;95(2):97-104.

Question :You are on call at 2am. Nurse reports that this baby who is being fed 2 ml breast milk every 3 hours is having 2 cc gastric residuals. What do you do?

- **Tell the nurse not to bother you at 2am?**
- **Stop all feedings?**
- **Ask about the physical exam and perhaps examine baby yourself?**

Checking or Not Checking Gastric Residuals

Table 2. Specific Outcomes Measured. (Mean ± SD)			
Outcomes	Check GR (N=30)	No Check GR (N=31)	P-value
Enteral intake 2 weeks after birth	106.73±53.74	112.20±42.81	0.66
Enteral intake 3 weeks after birth	134.20±39.44	141.00±29.29	0.41
Day of life of full enteral intake at 120 ml/kg/d	16.8±12.4	14.3±12.5	0.29
Day of life of full enteral intake at 150 ml/kg/d	28.1±3.9	22.3±11.7	0.19
Percentage of Change of Growth Parameters:			
Weight at 3 weeks	23.8±19	23.6±21	0.98
Length at 3 weeks	7.1±5	6.4±5.5	0.58
Head circumference at 3 weeks	8.6±5.9	7.8±3.9	0.51
Day of life when PN was discontinued	15.1±11	13.8±5.9	0.57
Day of life when central access was discontinued	**21.3±20.7**	**15.6±5.9**	**0.17**

Murgas Torrazzo, R., J. Perinatology, 2014

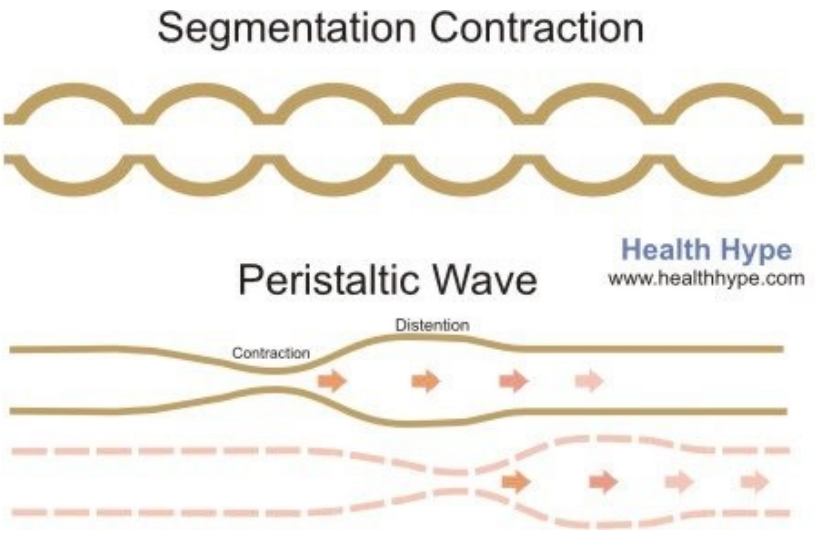
Checking or Not Checking Gastric Residuals

Table 2. Clinical Complications Measured. (%)			
Outcomes	Check GR (N=30)	No Check GR (N=31)	P-value
PNALD	4/30 (13.3)	4/31 (12.9)	1.00
SEPSIS	11/30 (36.7)	9/31 (29)	0.59
NEC	3/30 (10)	1/30 (3.2)	0.35

Murgas Torrazzo, R., et al. J. Perinatology, 2014

Small Intestine

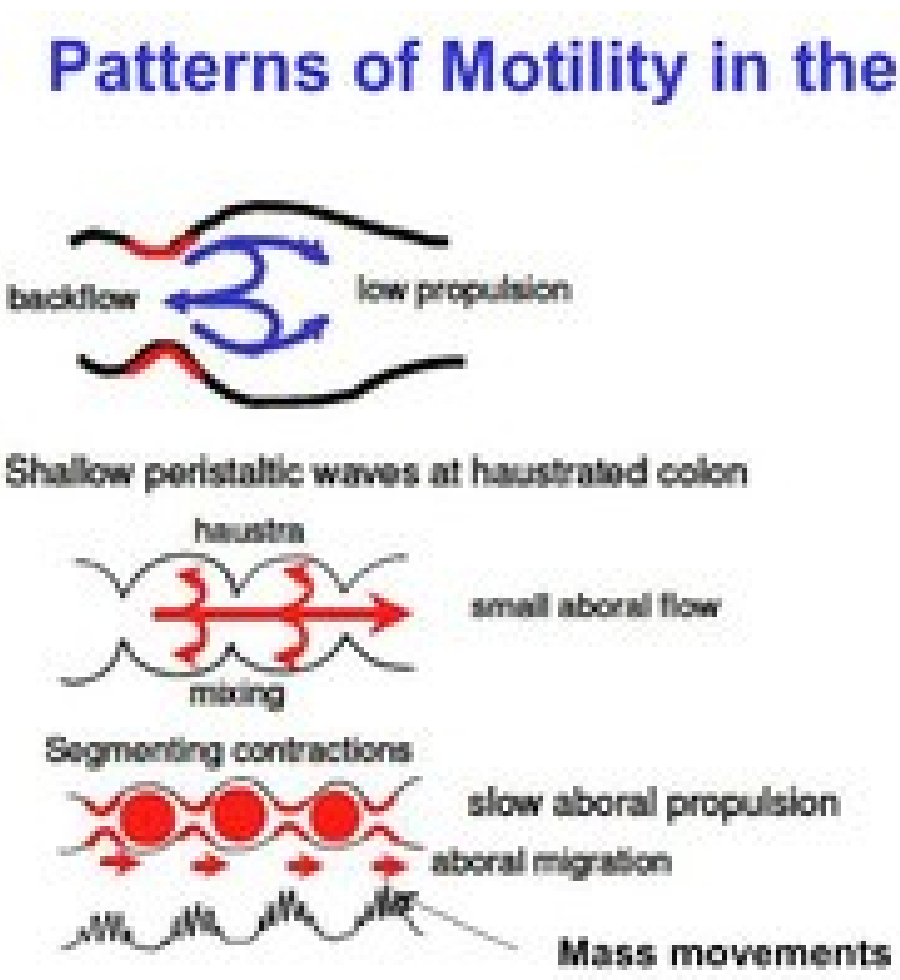
- 12/minute movement
- Segmentation important for mixing
- Peristalsis---forward movement.



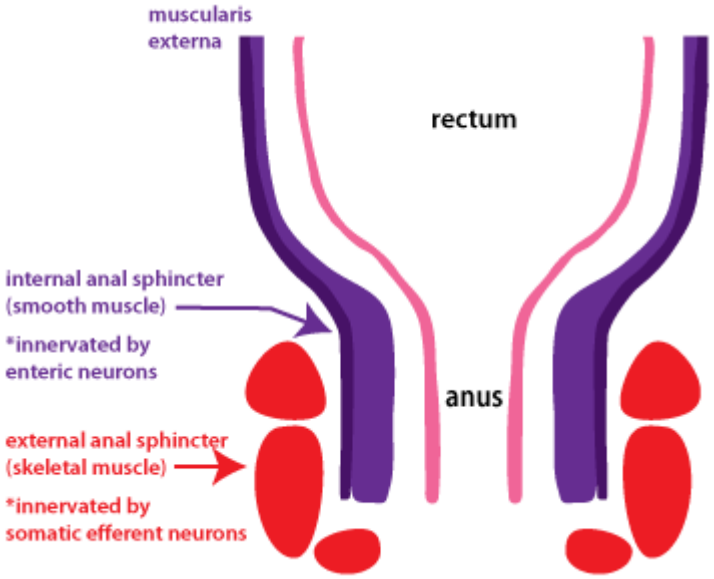
Small Intestine Motor Function in Preterm Infants

- Absence of Migrating Motor Complexes
- Prominence of Clusters
- Absence of mature motor response to feeding.

Colon movements



Mechanisms of Defecation



mass movement

↓

defecation reflex

stimulus:
- distension in rectum

responses:
- contraction in rectum, sigmoid colon
- relaxation of internal anal sphincter
- contraction of external anal sphincter

↓

increased pressure in rectum

delay
- contraction of external anal sphincter
- contraction of puborectalis muscle
- reverse peristalsis in rectum

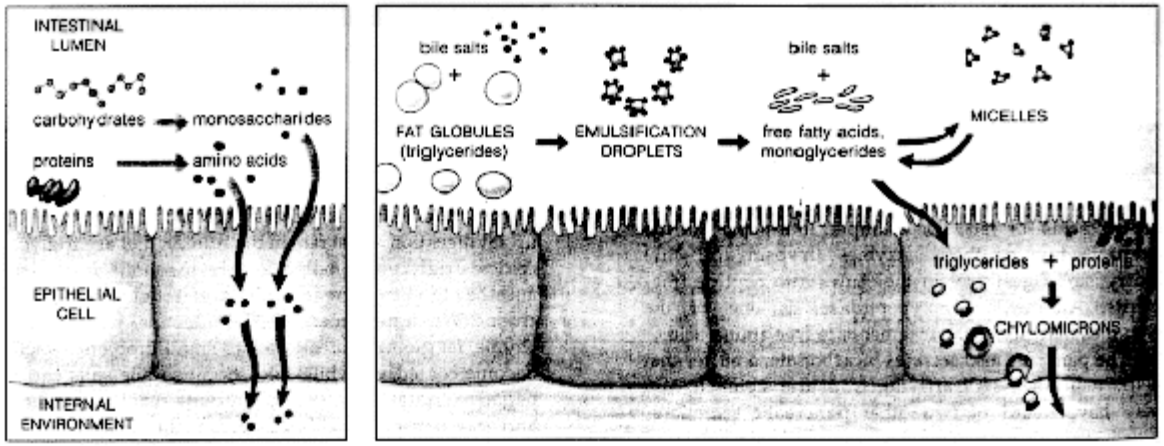
defecation
- relaxation of external anal sphincter
- relaxation of puborectalis muscle
- forward peristalsis in rectum, sigmoid colon
- Valsalva maneuver (increased abdominal pressure)

Passage of Meconium

- Delayed in about 20% of infants with birth weights <1500 grams (Jhaveri, 1987 and Wang, 1994).
- Delayed up to 10 days in infants with birthweights <1250 grams (Meetze, 1993).
- What about suppositories and enemas?

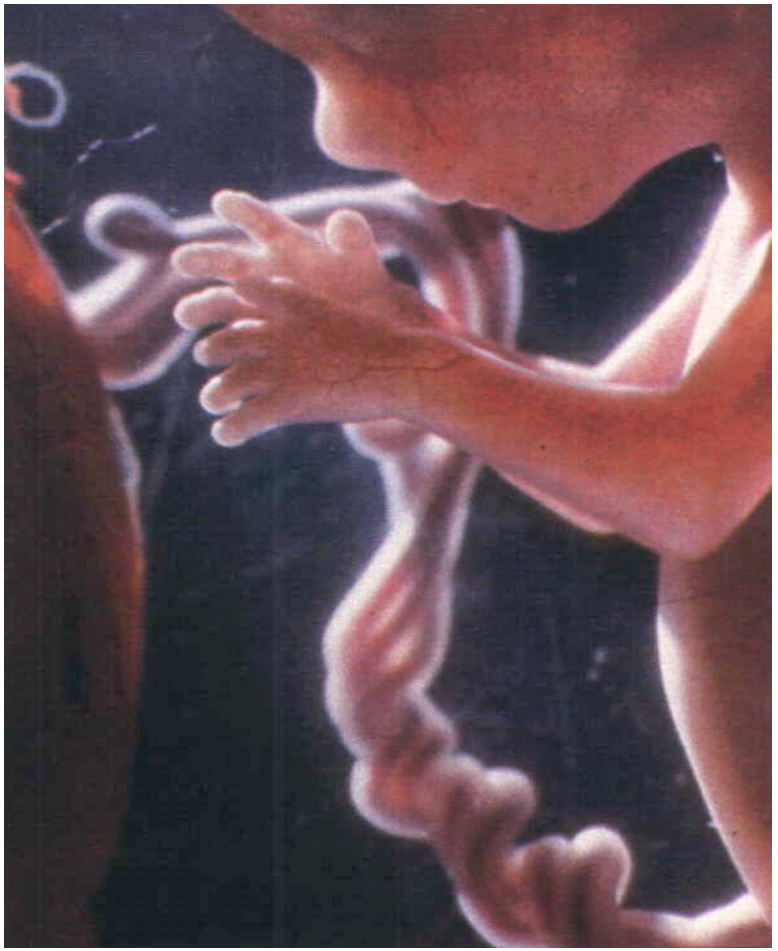
Digestion, Absorption and Assimilation

- Digestion-occurs in lumen.
- Absorption-occurs at the enterocyte interface (microvillus membrane).
- Assimilation-occurs in the enterocyte and beyond.

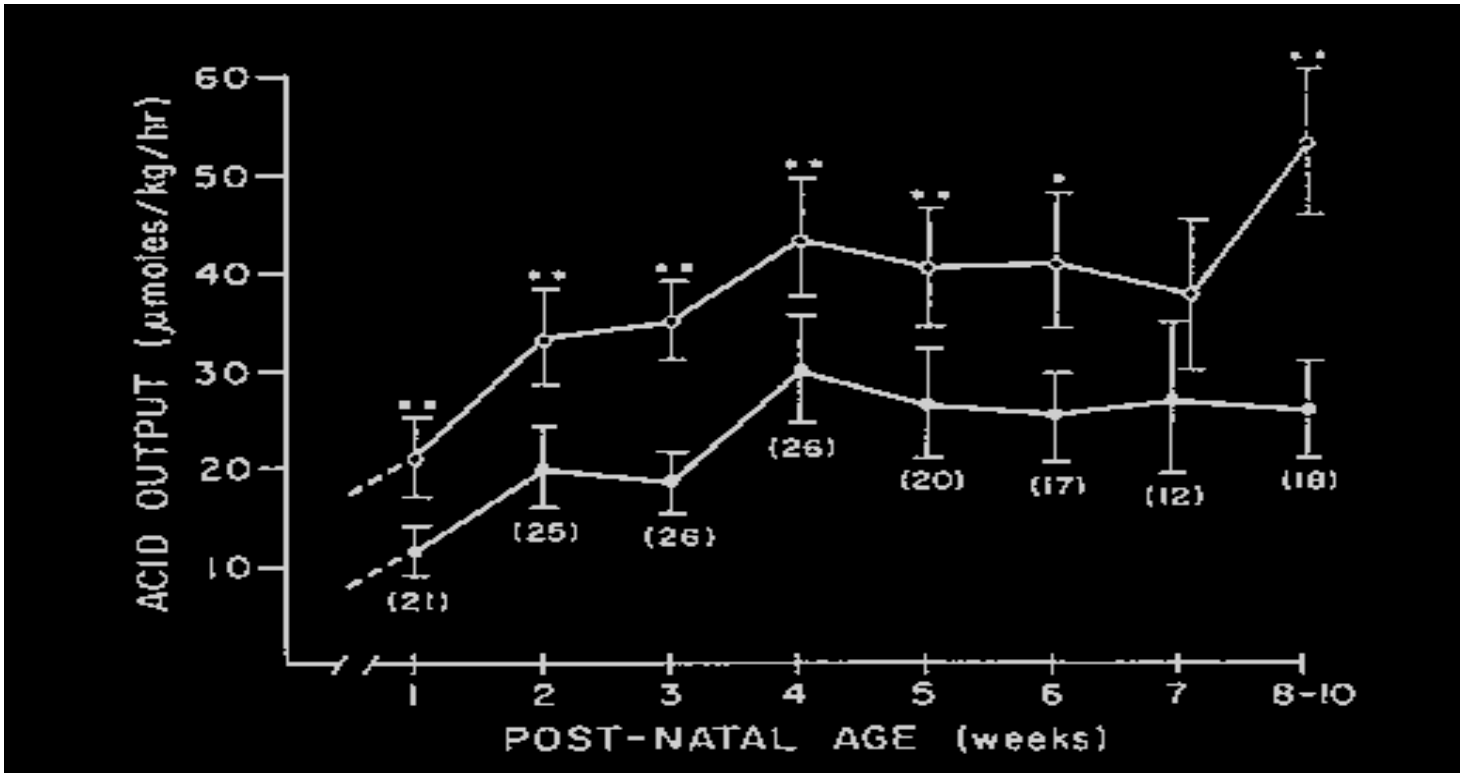


Digestion and Absorption:Protein Requirements

- Accretion rates of reference fetus estimated at 3.5-4.0 g/kg/d.
- ELBW infant would require 330 ml/kg/d of human milk to meet this requirement.



Gastric Acid Secretion



Hyman, PE, et al J Pediatr. 1985 Mar;106(3):467-71.

Acid and NEC

NICHD NRN Case-Control Study
VLBW H2-blocker prophylaxis, not GERD therapy
H2-blocker use associated with NEC.

Gastric acidification RCT N=68, blinded
Decreased NEC in acidification group.

(1) Guillet 2006 (2) Carrion 1990

Protein Absorption

- After luminal hydrolysis, peptides are further hydrolyzed at the microvillus membrane.
- Some amino acids and oligopeptides are absorbed via transporters.
- Some peptides that are absorbed intact are further hydrolyzed by intracellular peptidases.
- MVM and intracellular peptidases are mature early.

Protein Digestion and Absorption: Summary

- Partially and temporarily poor because of low gastric acid and upper GI enzymes.
- Could this immaturity be addressed by the use of hydrolysates?

Protein Hydrolysates

- **Hydrolyzed protein formula versus standard preterm infant formula in babies <1500 grams.*.**
- **Time from initiation of enteral feeds to full feeds was shortened with hydrolyzed protein feeding (10 vs. 12 days).**
- **Didn't have a human milk fed control.**
- **Does it matter?**
- **Very few protein hydrolysate formulas exist for very low birthweight infants that contain adequate protein and minerals----be careful!**

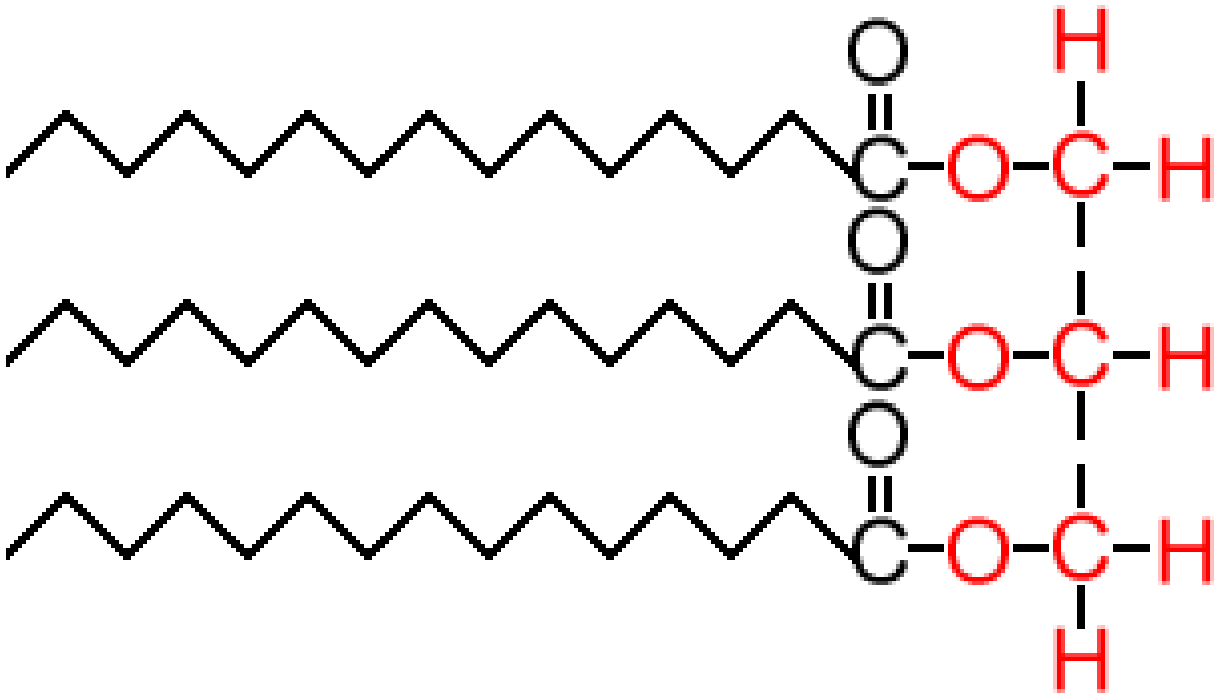
*Mihatsch, et al. Pediatrics, 2002

Essential Fatty Acid Deficiency

FIG. 4. Flaky skin on the foot of patient SW who had received prolonged fat-free intravenous alimentation.

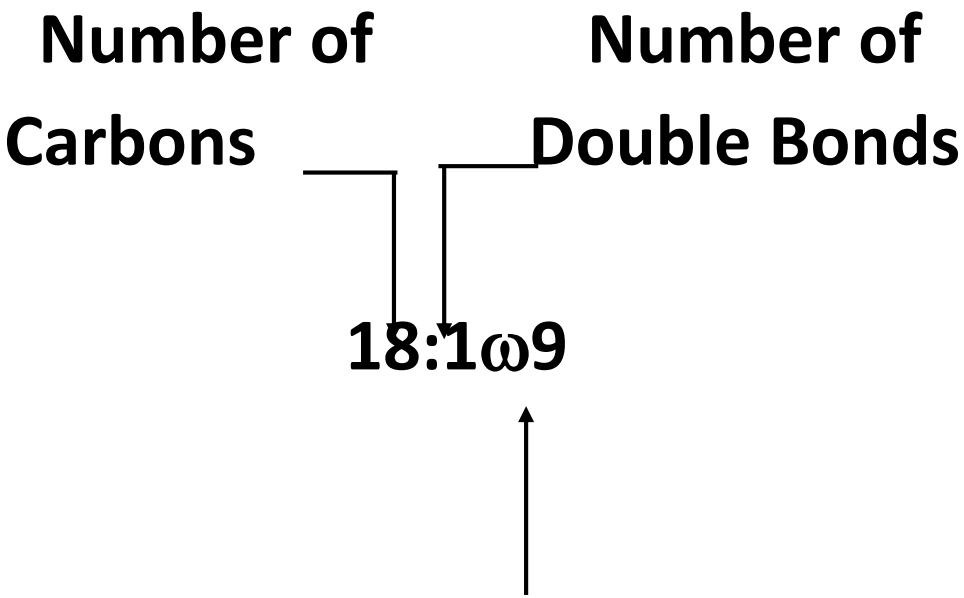
Paulsrud JR

Triglyceride Structure



3 Fatty Acids + Glycerol

Fatty Acid Nomenclature

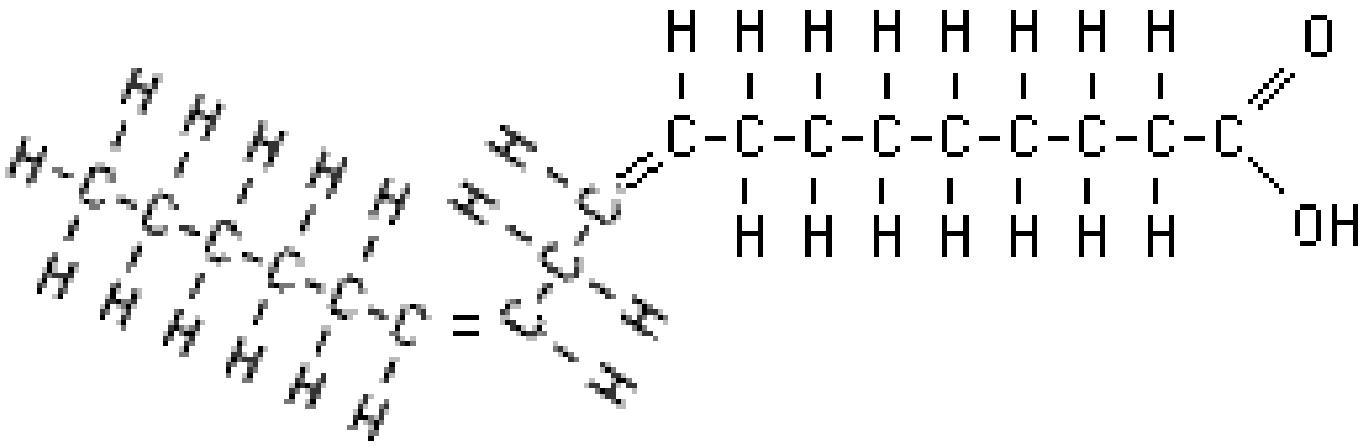


Essential Fatty Acids

Linoleic Acid-C18:2ω-6

Linolenic Acid-C18:3ω-3

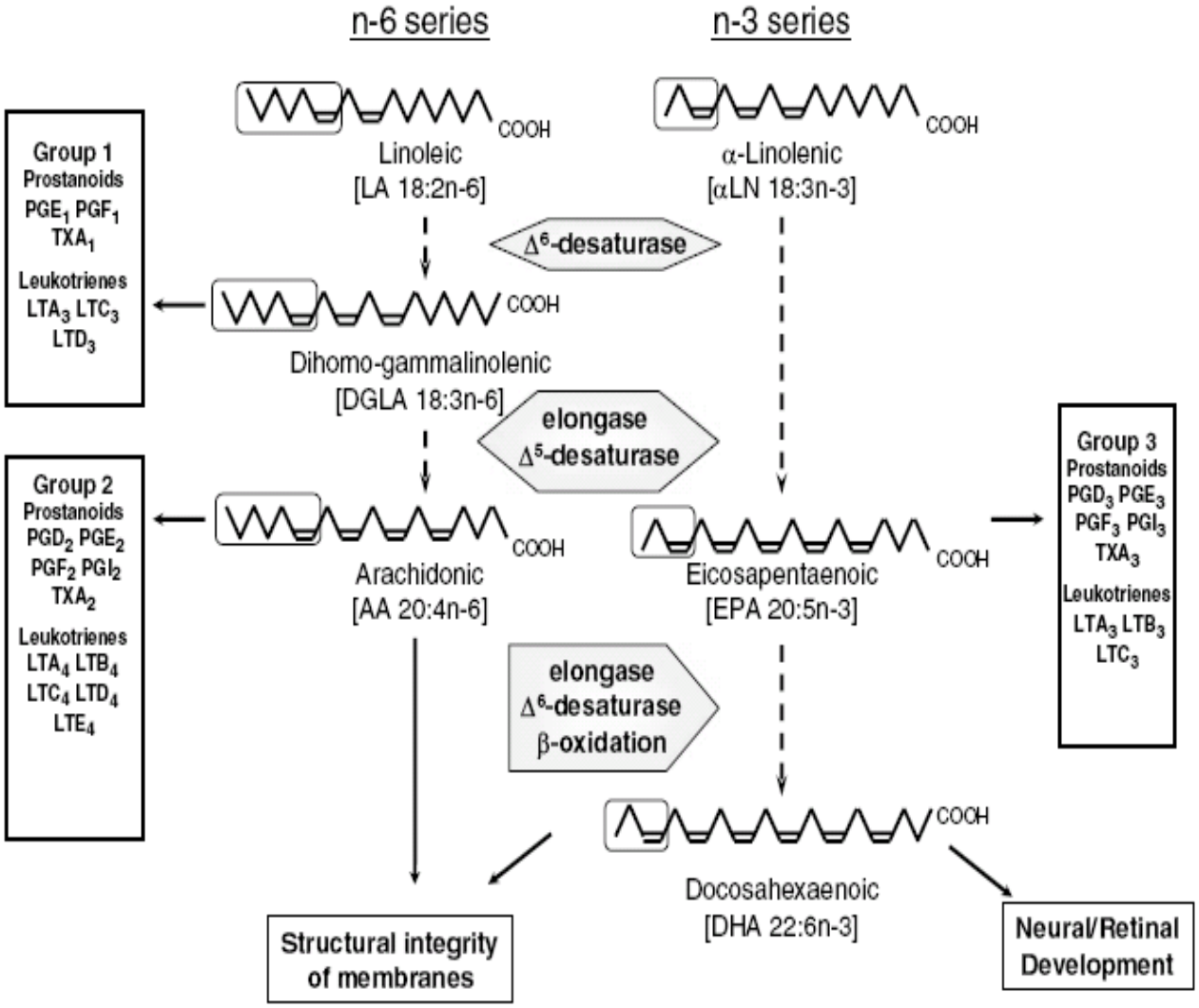
Lipid Nomenclature-Saturation



18: 2

ω6

LCPUFA Synthesis



Haggarty P. EJCN 55:1563,2004

Triene: Tetraene Ratio

Trienes: Derived from
Non Essentials (C18:1n9)

Tetraenes: Derived from
Essentials)C18:2n6, C18: 3n3)

Desaturase enzymes prefer the Essentials, but if essentials are not present, Desaturases will act on the non-essentials and increase the ratio. If > 0.2, this Is considered EFA deficiency.

Biochemical EFA Deficiency in Prematures: Holman Index

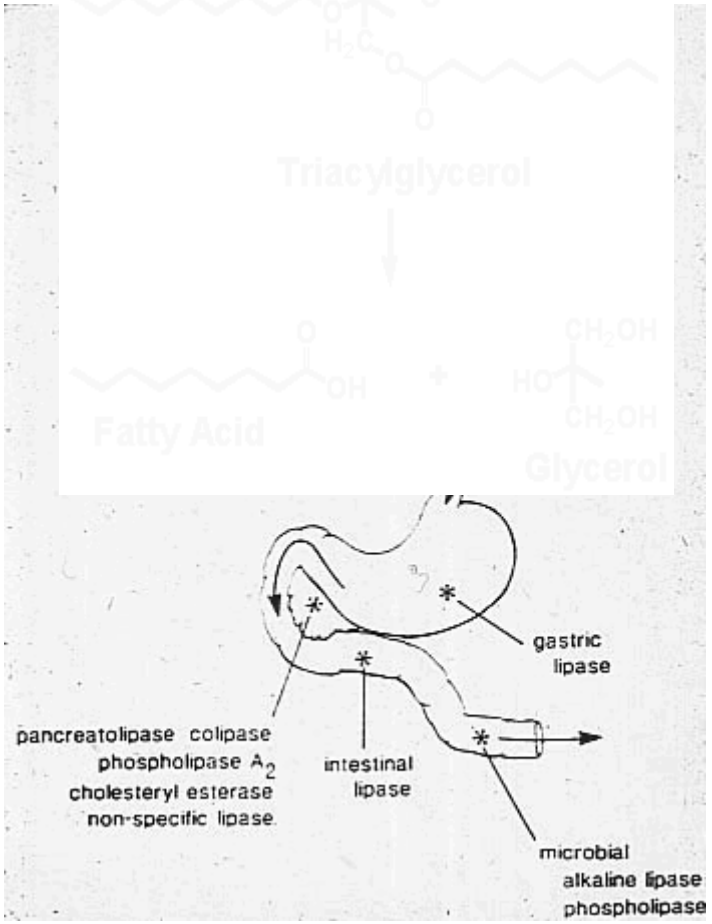
	NO IV Lipid RDS + NO Feed	NO IV Lipid RDS + Feed +	IV Lipid + RDS + NO Feed	NO IV Lipid NO RDS Feed +
Linoleic acid intake (g/kg/d)				
1	0	0.02	0	0.2
3	0	0.20	0.80	1.0
7	0	0.50	1.1	1.7
Triene:Tetraene Ratio > 0.2				
1	1 (5%)	0	0	0
3	3 (15%)	1 (3%)	0	0
7	16 (80%)	4 (13%)	0	0

Birth weight 1.35 kg, gestational age 31 wk; **IV Lipid + = 1 - 3 g/kg/d**

Gutcher, AJCN 1991; 54:1024

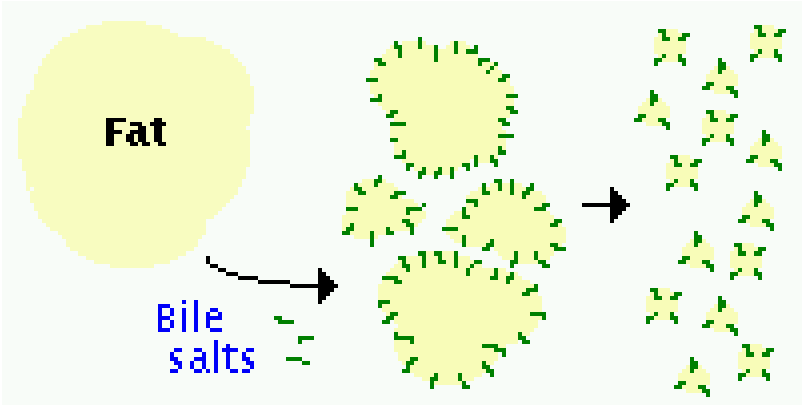
Lipases

- **Lower pancreatic lipases in preterms**
- **Combined with gastric lipase, milk BSSL facilitates lipid hydrolysis and prepares intraluminal lipid for further cleavage by pancreatic enzymes.**
- **BSSL is higher in milk of mothers delivering pre-term than in those delivering at term.**



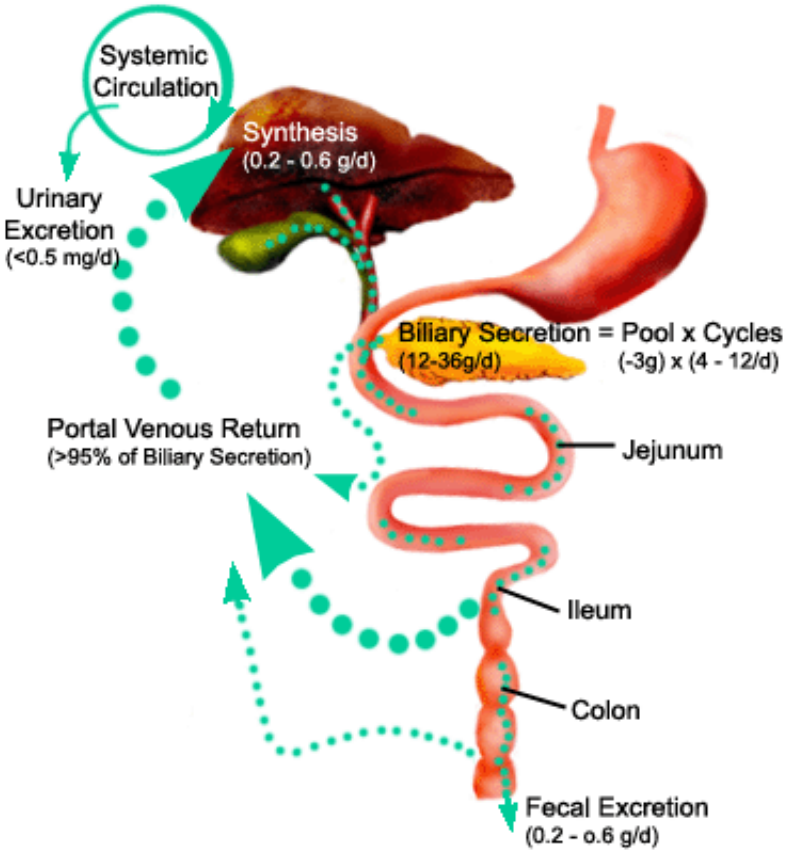
Hamosh, . Biol Neonate 1987;52 (Suppl. 1):50-64

Bile Acids

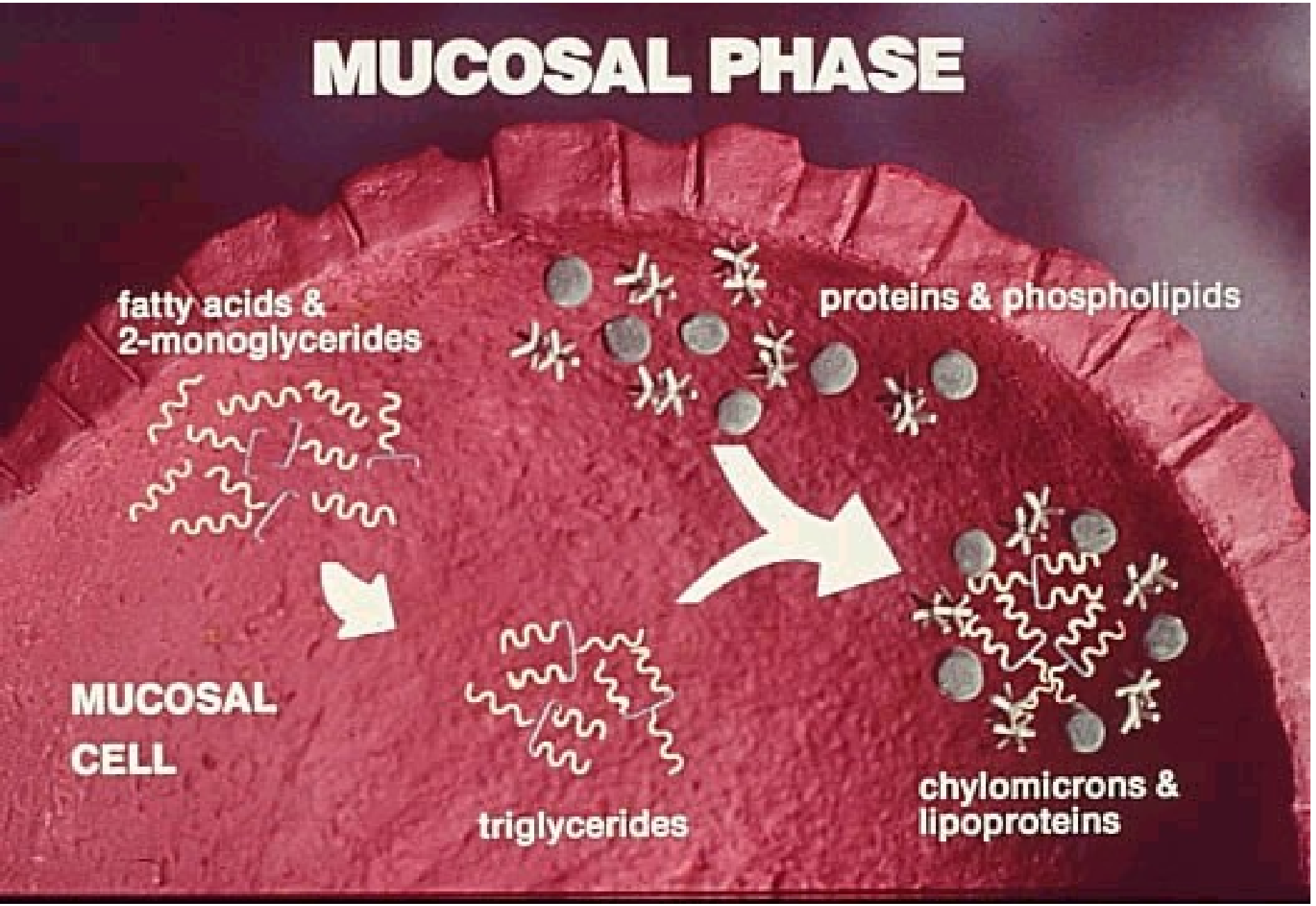


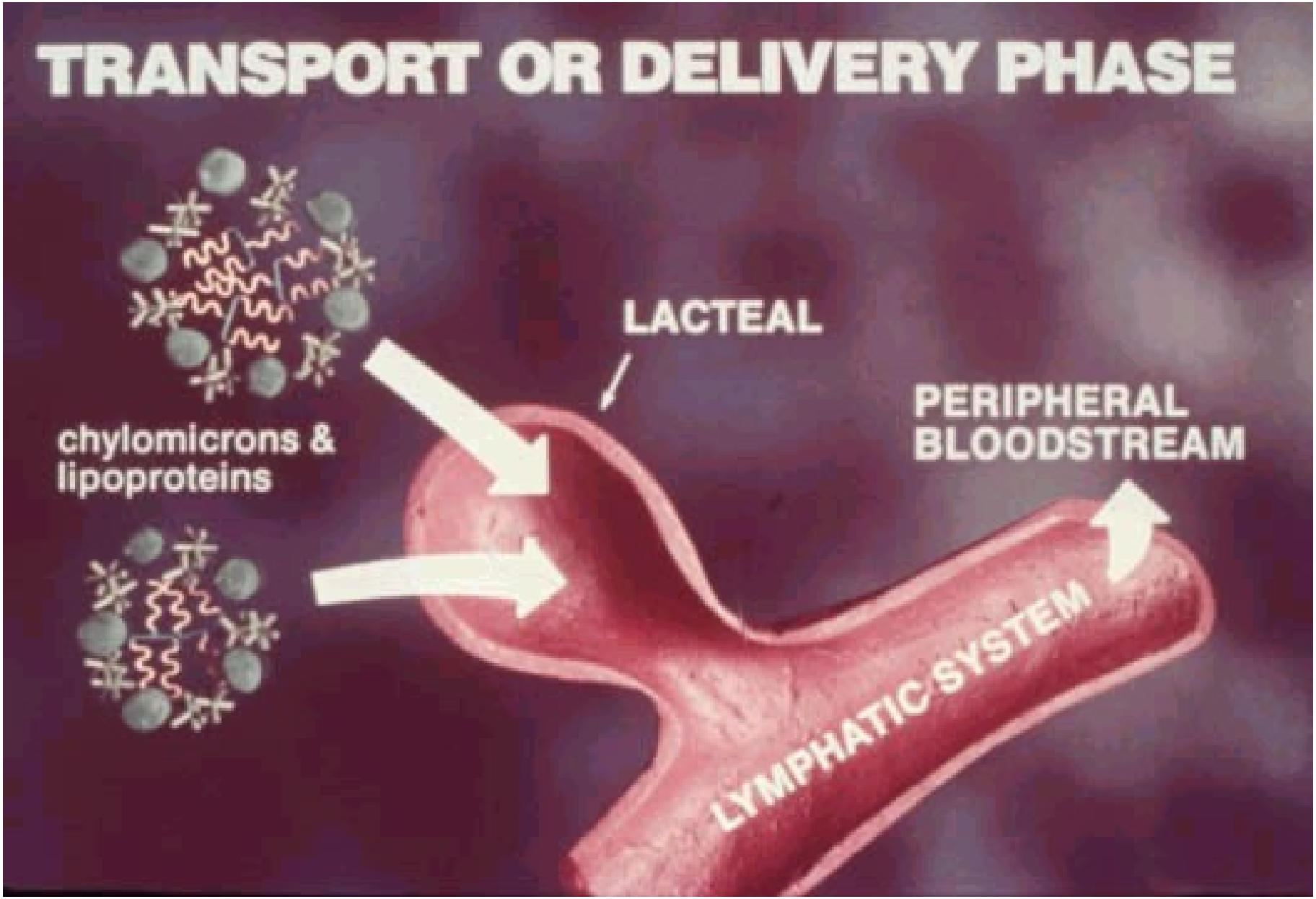
- Emulsify large fat globules.
- Increase fat mucosal interaction.
- Not necessary for short or medium chain

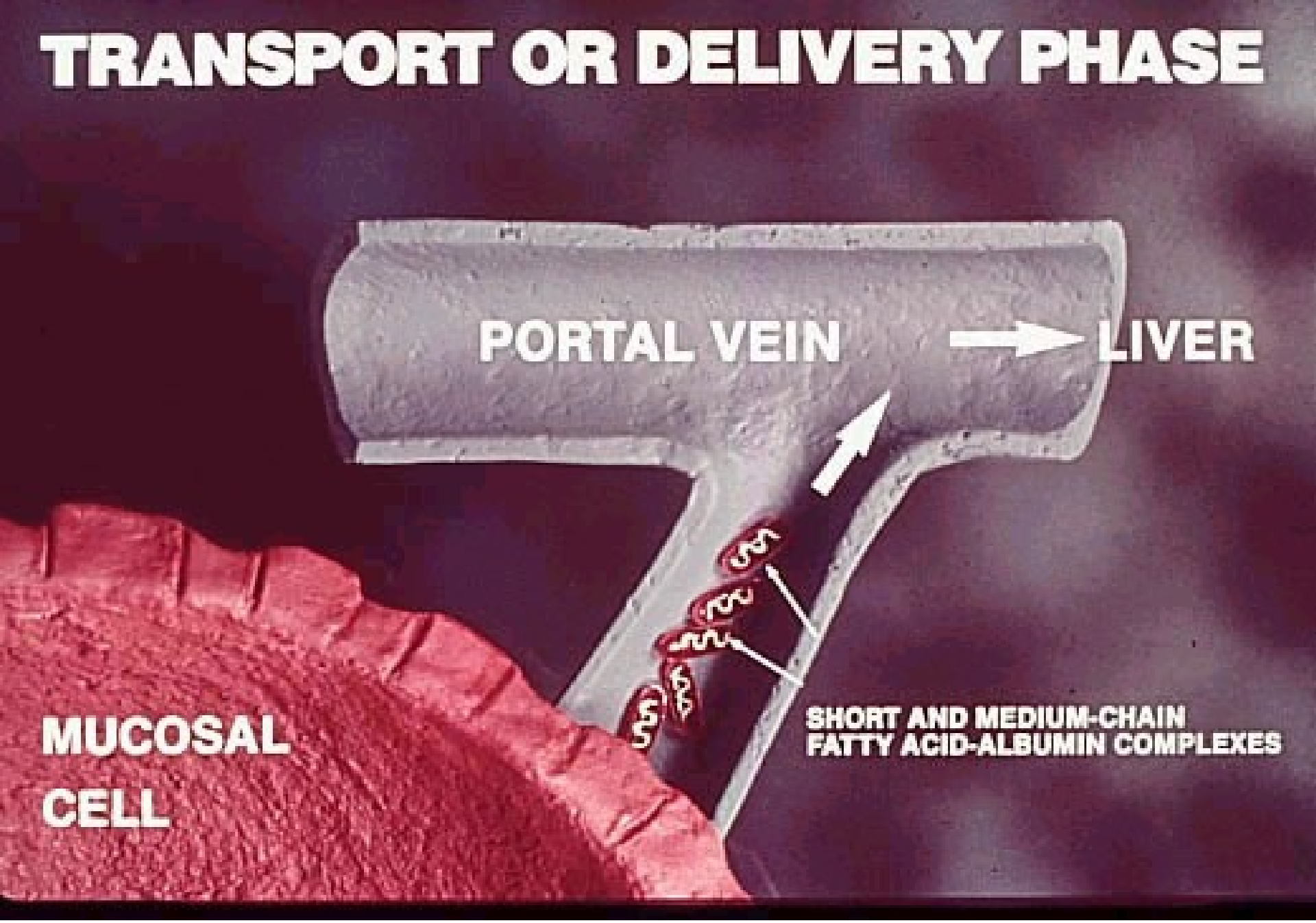
Bile Acids



- Synthesis is lower in preterm.
- Bile acid reabsorption is lower in preterm.
- Duodenal bile acid concentration usually below CMC for a few weeks


MUCOSAL PHASE
fatty acids &
2-monoglycerides
proteins & phospholipids
MUCOSAL
CELL
triglycerides
chylomicrons &
lipoproteins


TRANSPORT OR DELIVERY PHASE
LACTEAL
chylomicrons &
lipoproteins
PERIPHERAL
BLOODSTREAM
LYMPHATIC SYSTEM


TRANSPORT OR DELIVERY PHASE
PORTAL VEIN
LIVER
MUCOSAL CELL
SHORT AND MEDIUM-CHAIN FATTY ACID-ALBUMIN COMPLEXES

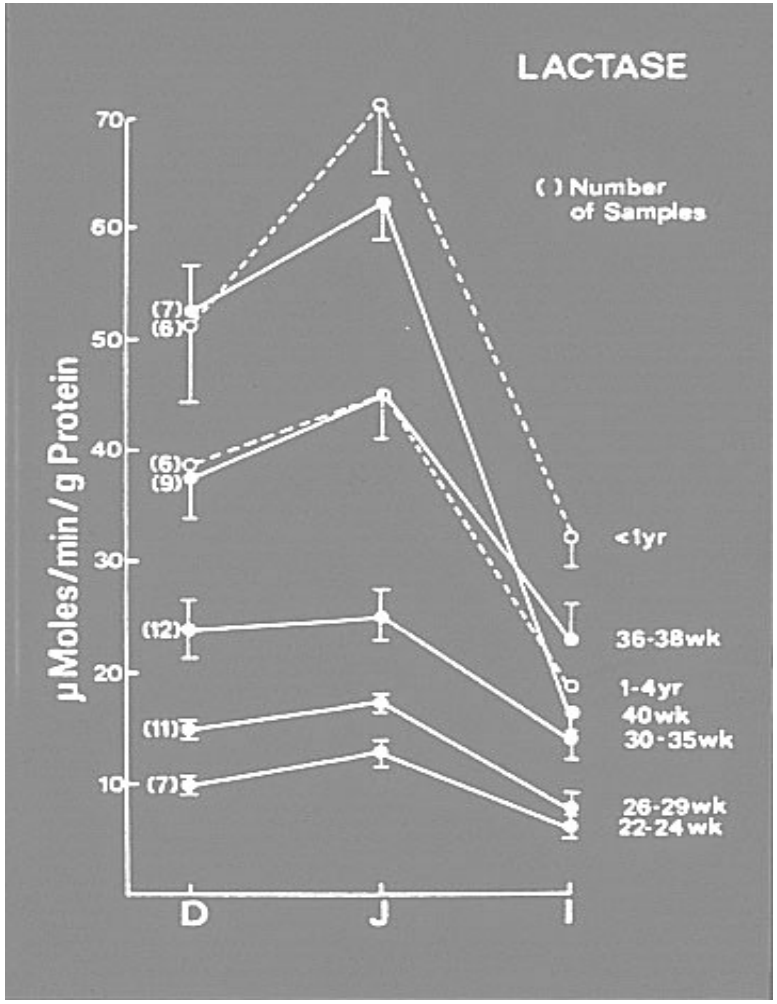
Lipid Digestion and Absorption: Summary

- Human milk contains lipases, which aid in the digestion of lipids.
- Digestion is temporarily poor, especially for long chain lipids because of low bile acid secretion and reabsorption.

The “Myth” of Lactose Intolerance in Preterms?

- Myth: the premature is not able to absorb lactose.
- However: Human milk is well tolerated by premature with lower NEC and better feeding tolerance.
- Should we use other carbohydrate sources?

Lactase in Human Intestine



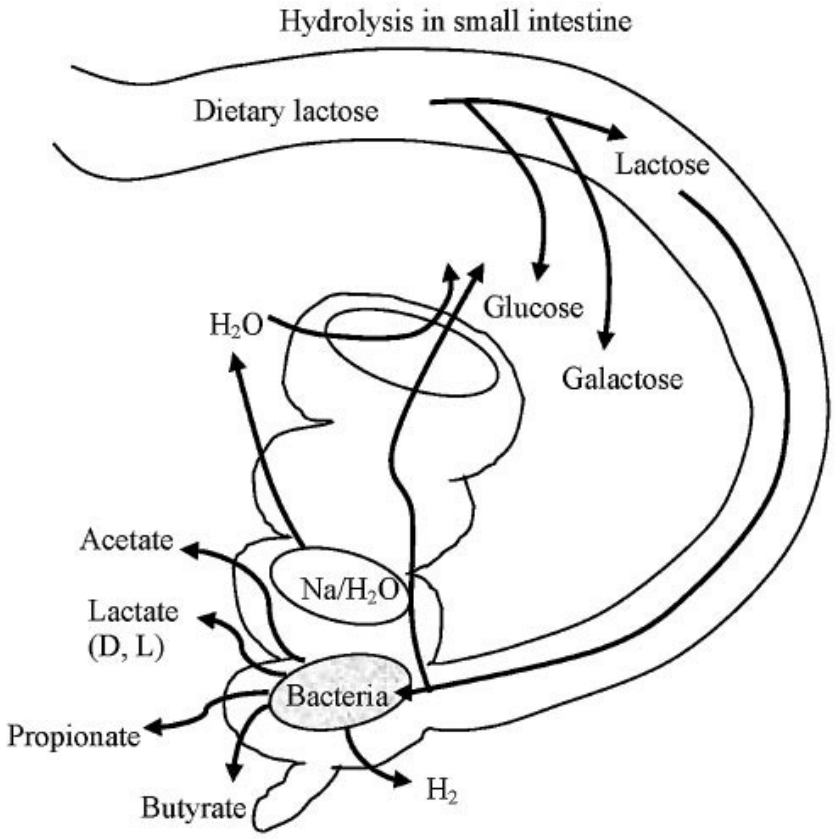
(Antonowitz and Lebenthal, Gastroenterology 1976)

Does Low Lactase Activity Matter for Preterms?

- Preterm infants (26-30 weeks gestation):n=135.
- “Lactase” activity determined using lactulose/lactose in urine.
- Early feeding resulted in greater lactase activity at 10 days of age (by 100%).
- Human milk feeding resulted in higher lactase activities than formula feeding.

What happens to undigested/unabsorbed lactose?

- 20% of dietary lactose may reach the colon in Neonates
- Lowers distal intestinal pH.
- Beneficial effect in that it promotes Bifido and Lactobacillus growth.



Heyman, MB Pediatrics,2006

Butyrate

- Most important fuel for colonocyte
- Increased proliferation
- Increased differentiation
- Tightens interepithelial junctions.

Take Home Messages

- The Developing GI tract is complex and is much more than an organ of digestion and absorption.
- The premature intestine is capable of significant but limited digestion and absorption.
- Motility is be limiting but all of these functions are stimulated with enteral feeding.
- Use it!!