Fat Digestion

Bile acid physiology

Lipolysis and Micelles

Transport and chylomicron physiology

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NASPGHAN
Physiology Education Series

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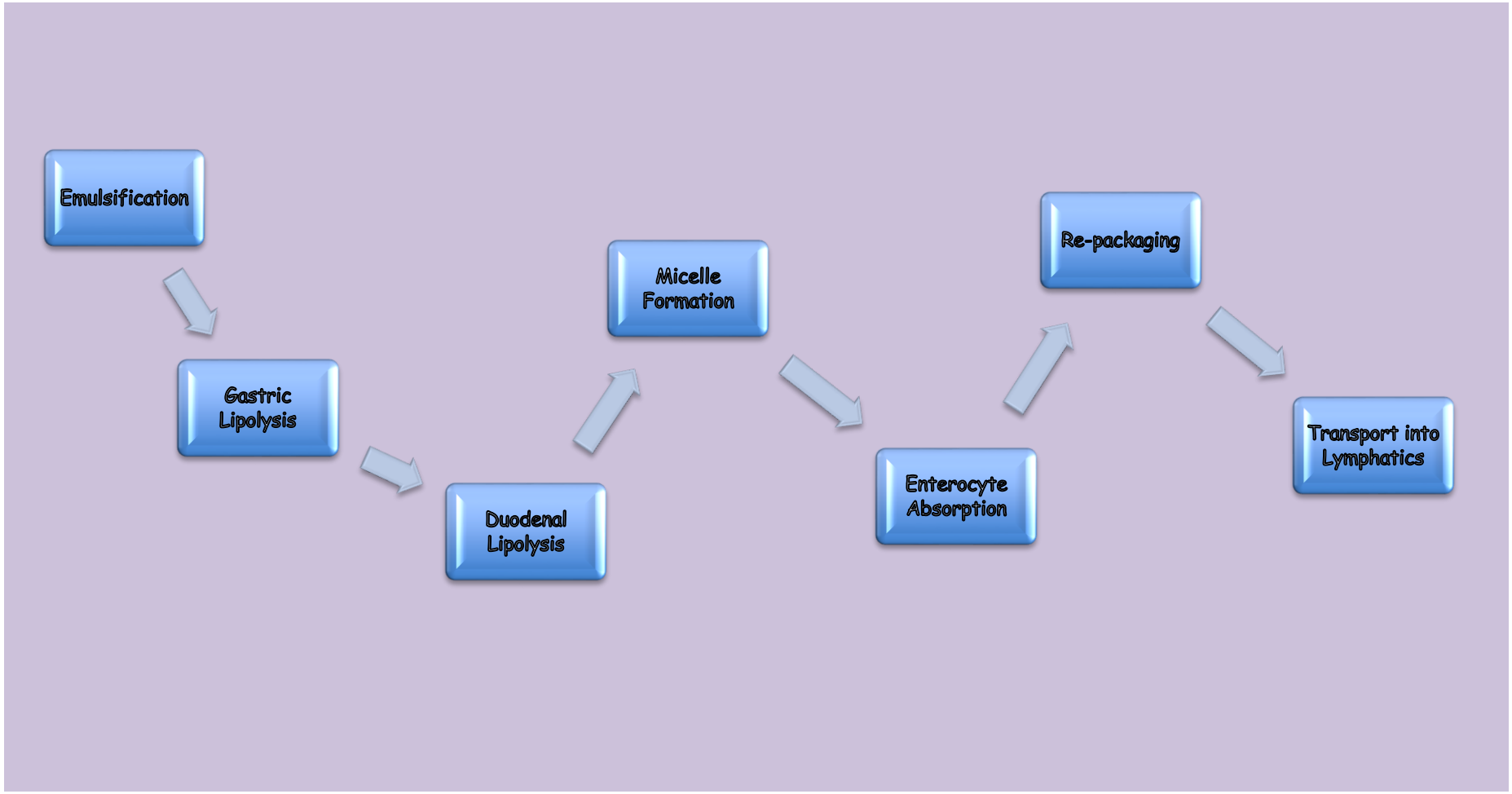
Learning Objectives

- Understand how bile salts are synthesized, secreted, transformed, and conserved
- Describe the composition of micelles and how they function to efficiently move fat-soluble nutrients to the mucosal surface
- Explain how efficient lipolysis proceeds in the intestine
- Understand how long-chain fatty acids, medium chain fatty acids, and fat soluble vitamins gain access to systemic circulation

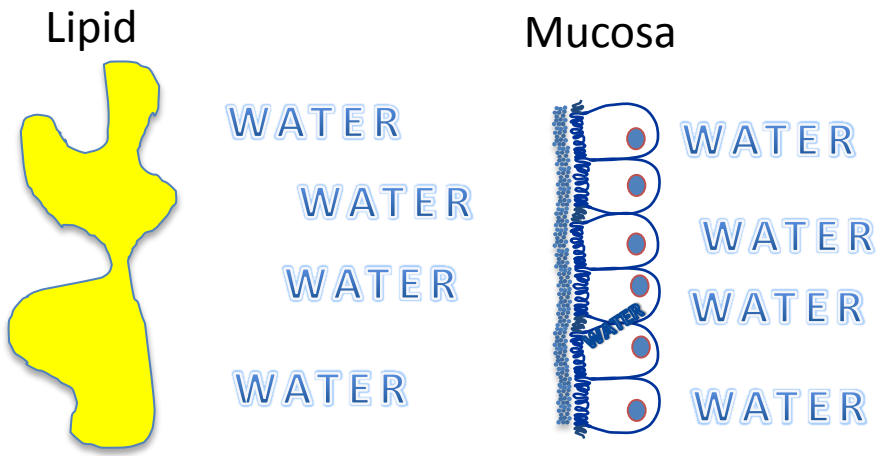
Overview of Fat Digestion



	Input	Output (stool)
Protein:		
Total	~200 g	~1–2 g
	Diet ~100 gm	
	Epithelial Sloughing ~50 g	99.5% abs.
	Secretions: salivary, pancreatic, biliary ~50 gm	
Fat:		
Total	~170 g	~2–6 g
	Diet ~100 g	
	Epithelial Sloughing ~20 g	
	Biliary Lipid ~50 g	97% abs.
Water:		
Total	~10 L	~0.05 L
	Diet ~2 L	
	GI tract secretions ~8 L	99.5% abs.
Ions (Na+, K+, Cl−, Ca+2, Fe+2):		
Total	2.6M	~0.015 M
	Diet ~0.2M	
	Secretions ~2.4 M	99.5% abs.
Total Weight:		
	~22 Kg	~0.2 Kg
	99.1% (re)claimed!	

Fat Digestion- an impressive challenge!

How get nutritionally vital lipid into body through aqueous environment???



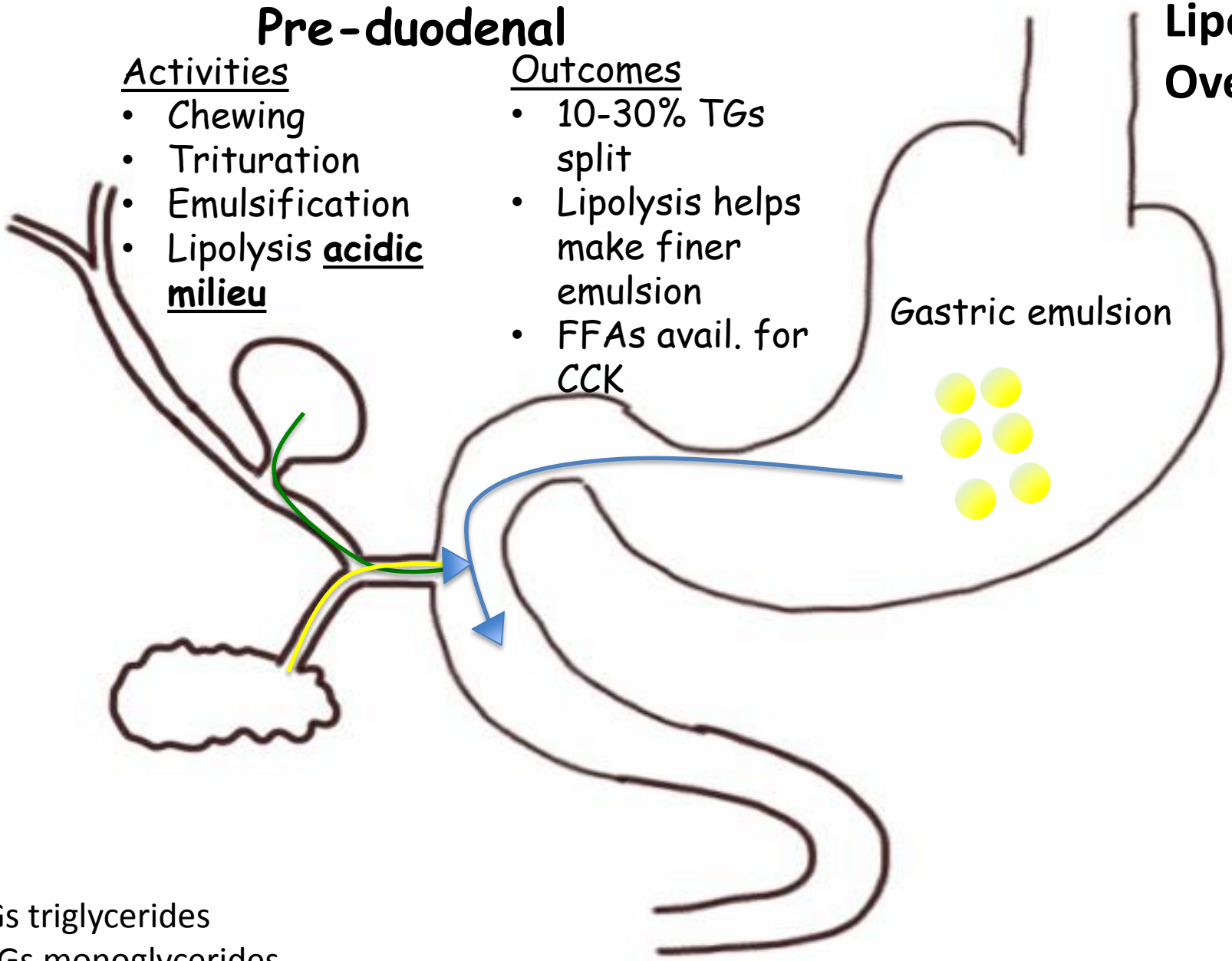
A sequential shuttle system!

Lipolysis-Overview

Pre-duodenal

Activities
- Chewing
- Trituration
- Emulsification
- Lipolysis **acidic milieu**

Outcomes
- 10-30% TGs split
- Lipolysis helps make finer emulsion
- FFAs avail. for CCK



TGs triglycerides
MGs monoglycerides
FFAs free fatty acids
PLs phospholipids

Lipolysis- Overview

Pre-duodenal

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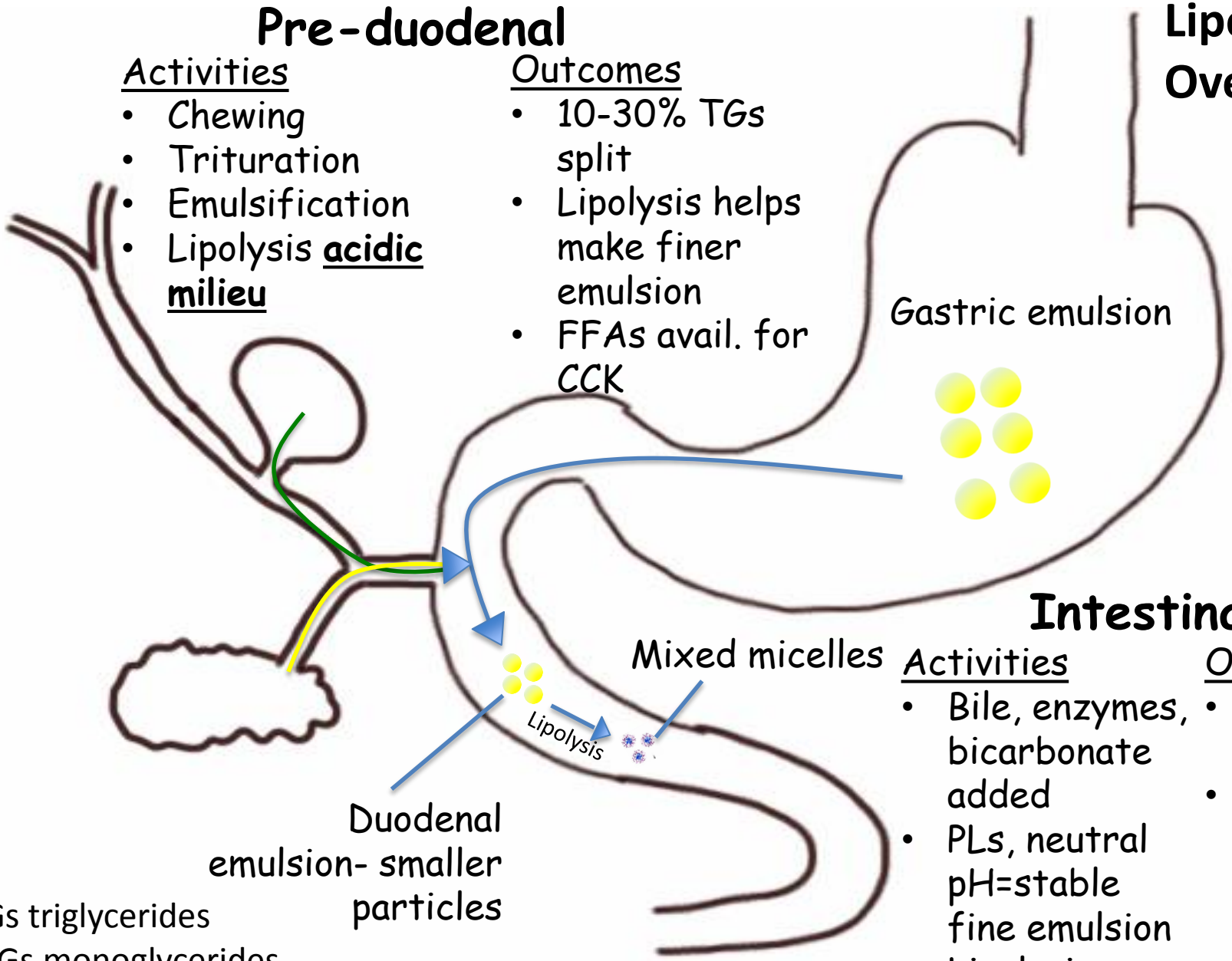


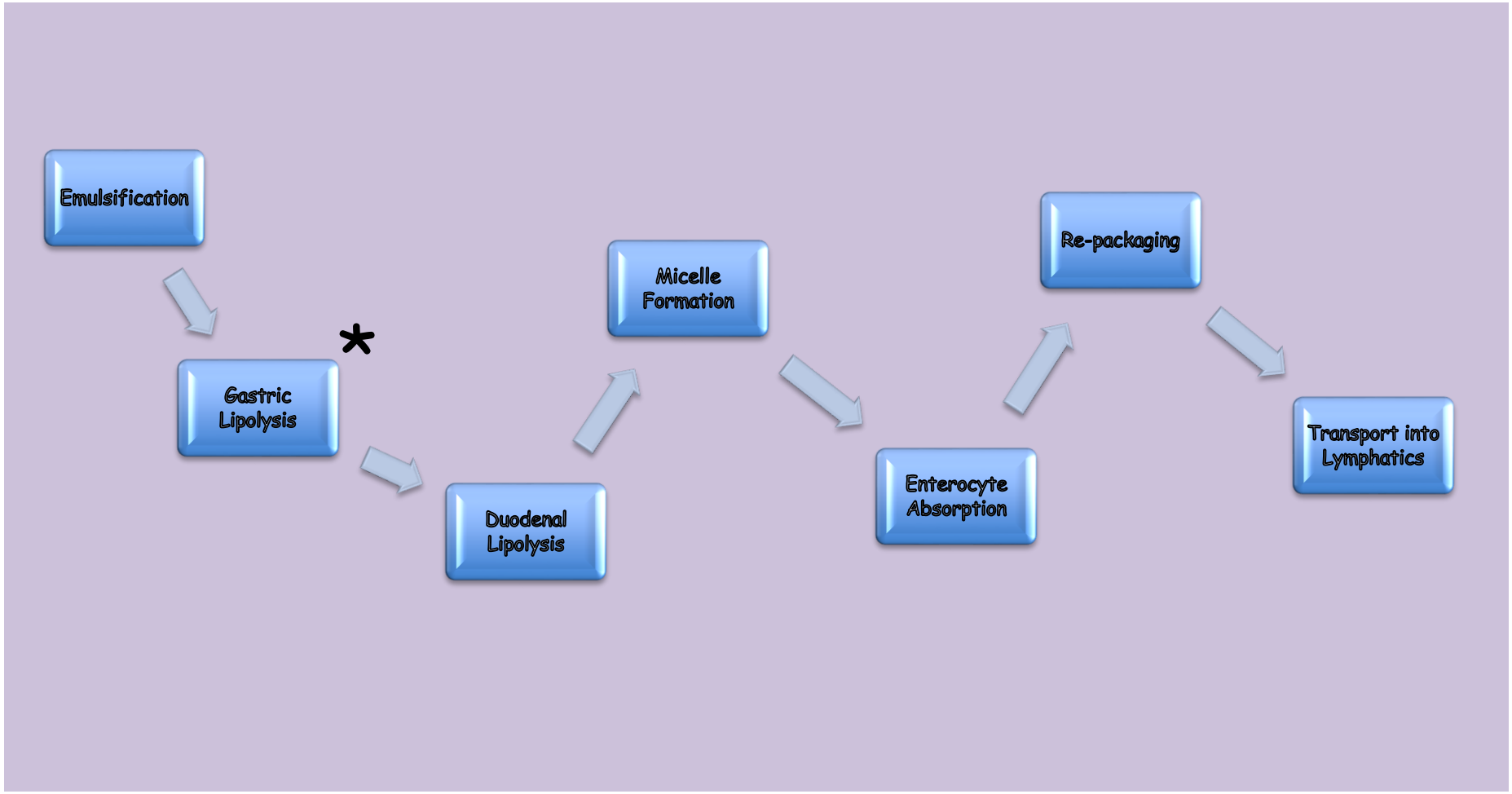
Intestinal

Activities
- Bile, enzymes, bicarbonate added
- PLs, neutral pH=stable fine emulsion
- Lipolysis **neutral milieu**

Outcomes
- FFAs, MGs
- **Mixed micelles**

TGs triglycerides
MGs monoglycerides
FFAs free fatty acids
PLs phospholipids

Overview of Fat Digestion



Gastric lipolysis

- Lingual and gastric lipase very similar
- Species specificity
- Gastric lipase- in fundus
- Enzyme detected in fetus 24 wks gestation
- pH optima 3.5-5.5
- Preference for MCTs
- Prefer to hydrolyze at n-3 position
- Gastric 'pre-digestion'
- Enzyme inhibited by high conc. of BAs and FFAs
- Implications for post-pyloric feeding, or acid-blockade

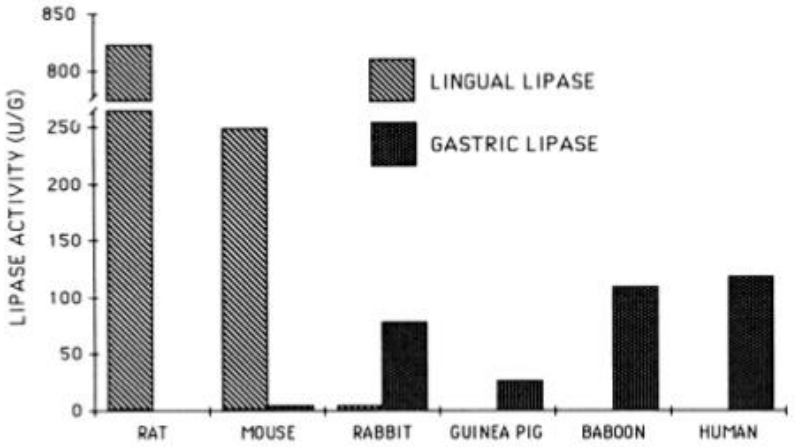


Figure 2. Lingual and gastric lipase activity levels in different species. Data are mean ± SEM of 2 to 3 animals for each species (276). Biochim Biophys Acta 1988 959: 38 (used with permission)

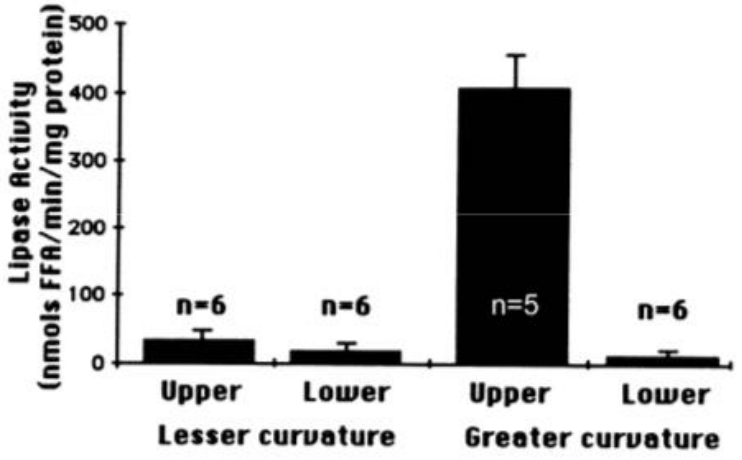


Figure 4. Localization of lipase in the human stomach—the level of lipolytic activity in the gastric mucosa of four sampling sites (33). Gastroenterology 1988 95: 1460 (used with permission)

Clinical correlation- Gastric Lipolysis in Cystic Fibrosis

- Adolescents CF patients and controls
- Given cream to drink
- After 10 min, NG placed and sample taken
- Analysis for products of lipolysis
  - More TG lipolysis in CF group
- Clinical implications?
  - Gastric lipolysis is not trivial
  - ? Especially for patients with developmental or pathologic pancreatic insufficiency

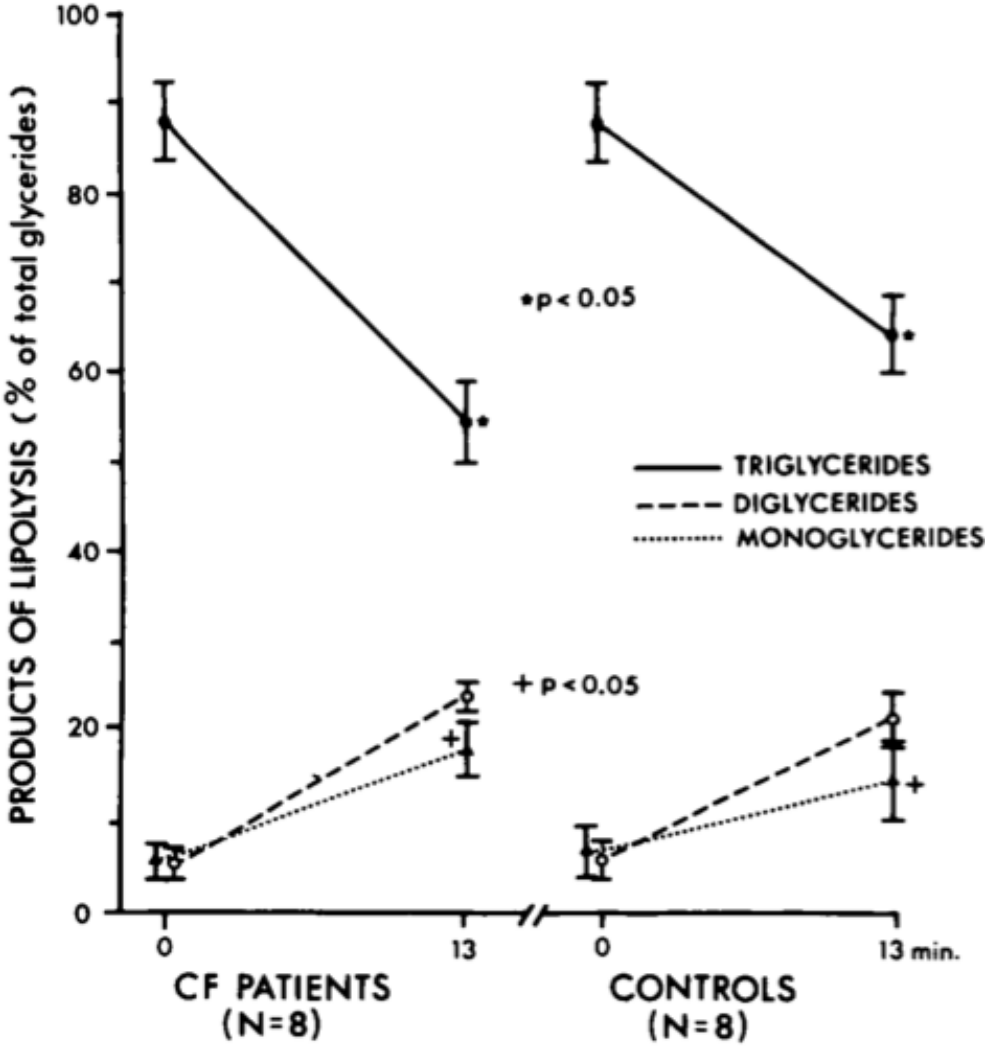
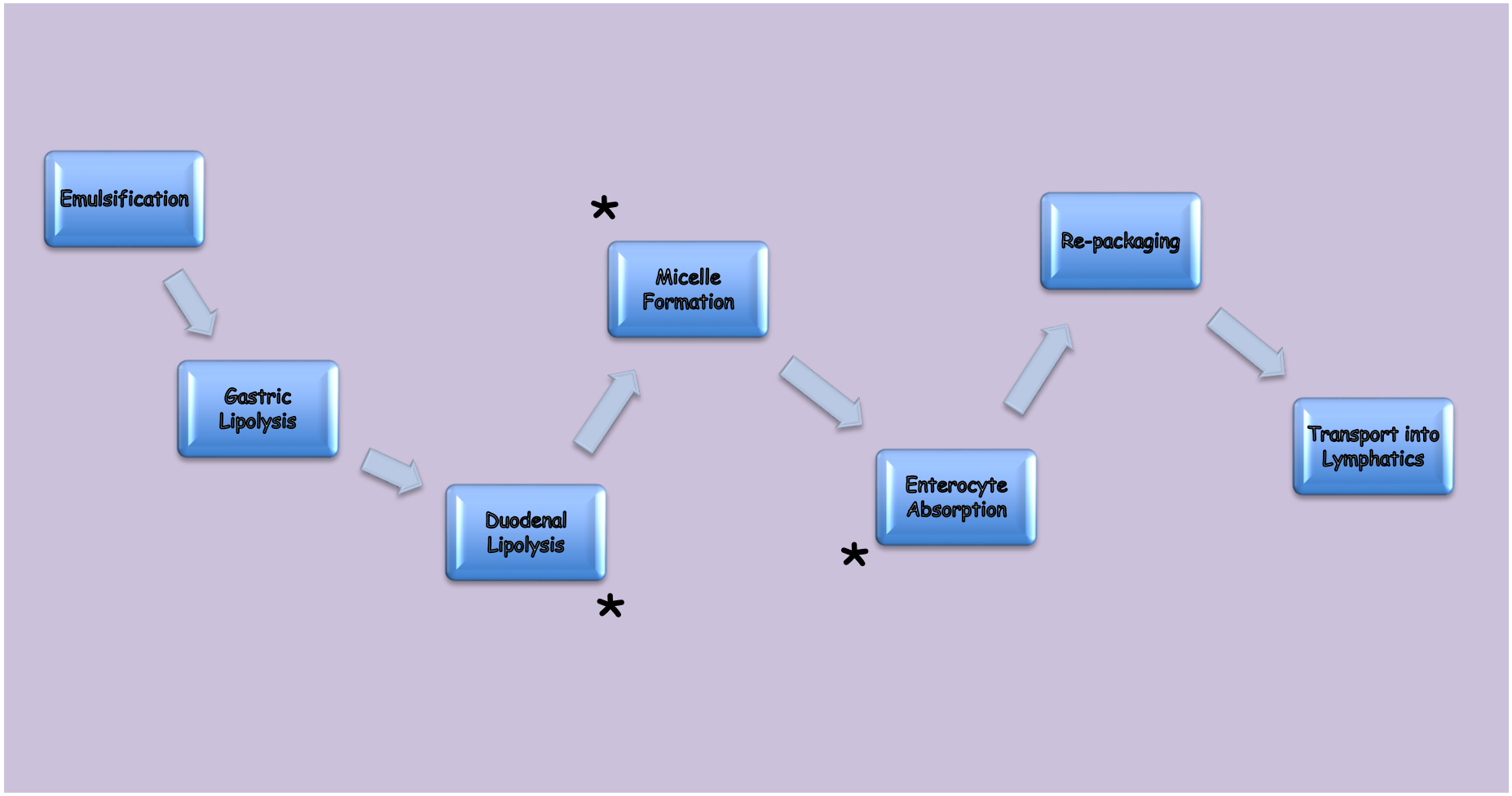


Fig. 3. Rate of intragastric lipolysis of cream (10% butterfat) in CF patients and controls.

Pediatr Res. 1980 Dec;14(12):1360-2 (used with permission)

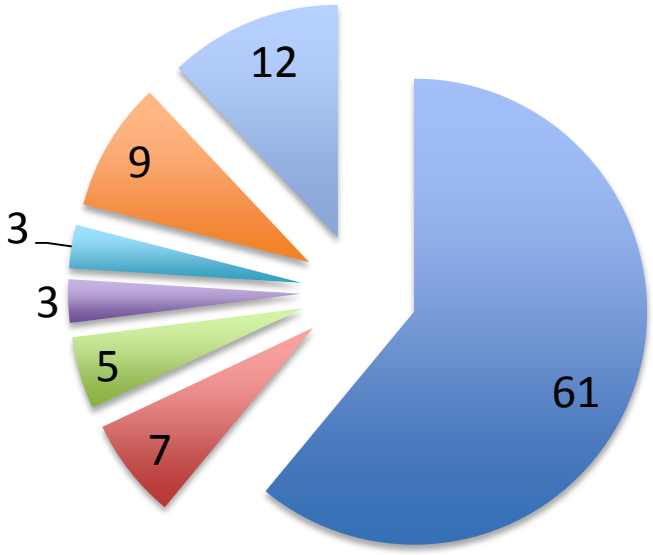
Overview of Fat Digestion



Bile Acid Physiology-- key players in duodenal lipolysis and efficient and complete transfer at mucosal membrane

What is in Bile?

Bile Composition (% of solids)



- **95% Water**

<u>Solids</u>

- **61% bile salts**
- **Extra cholesterol**
- **Lipids to keep bile fluid**
- **Wastes**

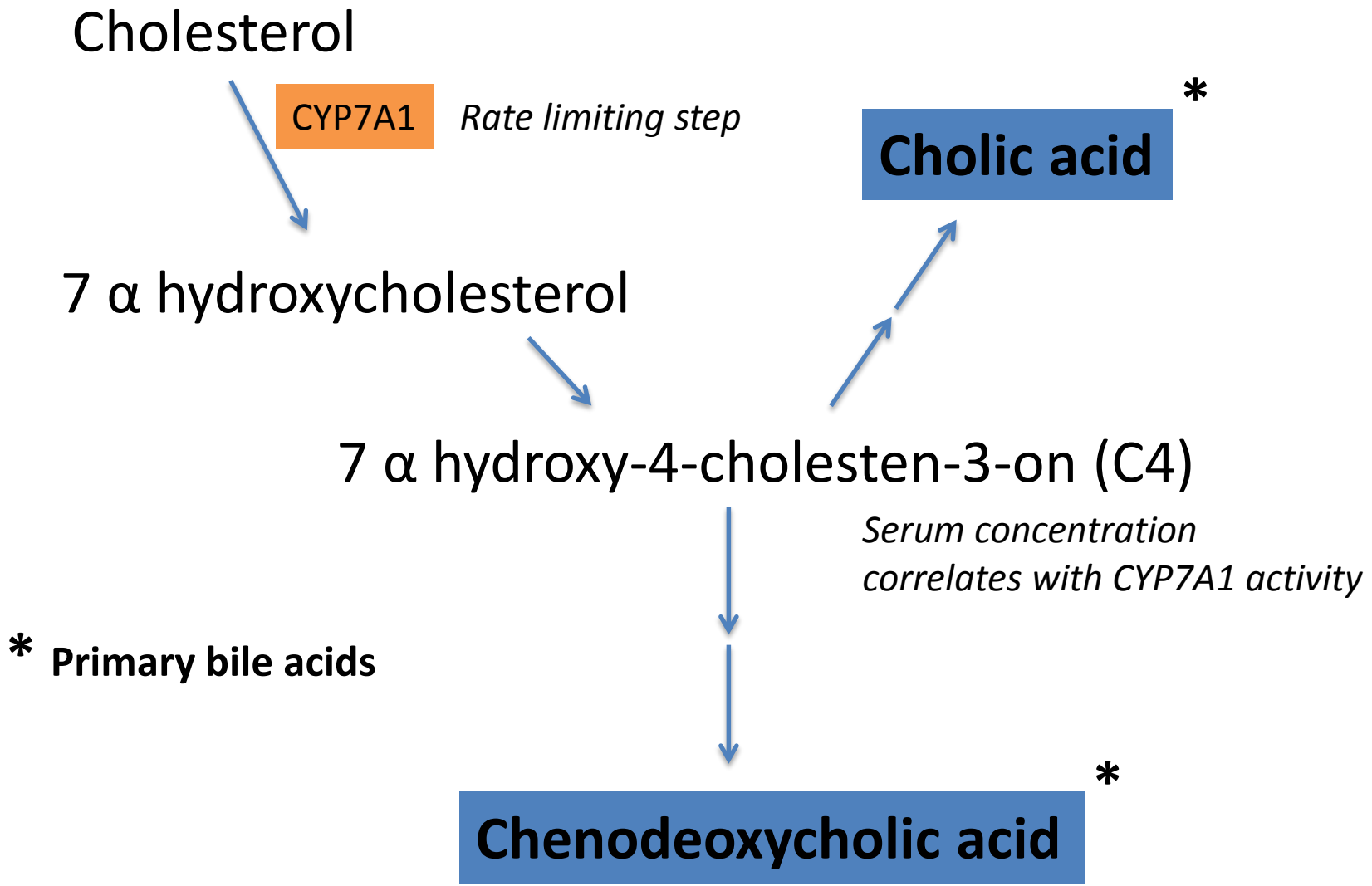
Bile Acids

- **Micellar functions**
  - Intrahepatic
    - Induce canalicular bile flow
    - Xenobiotic and heavy metal 'sink'
    - Solubilize cholesterol
  - Small intestine
    - Solubilize water insoluble fatty acids and FSVs

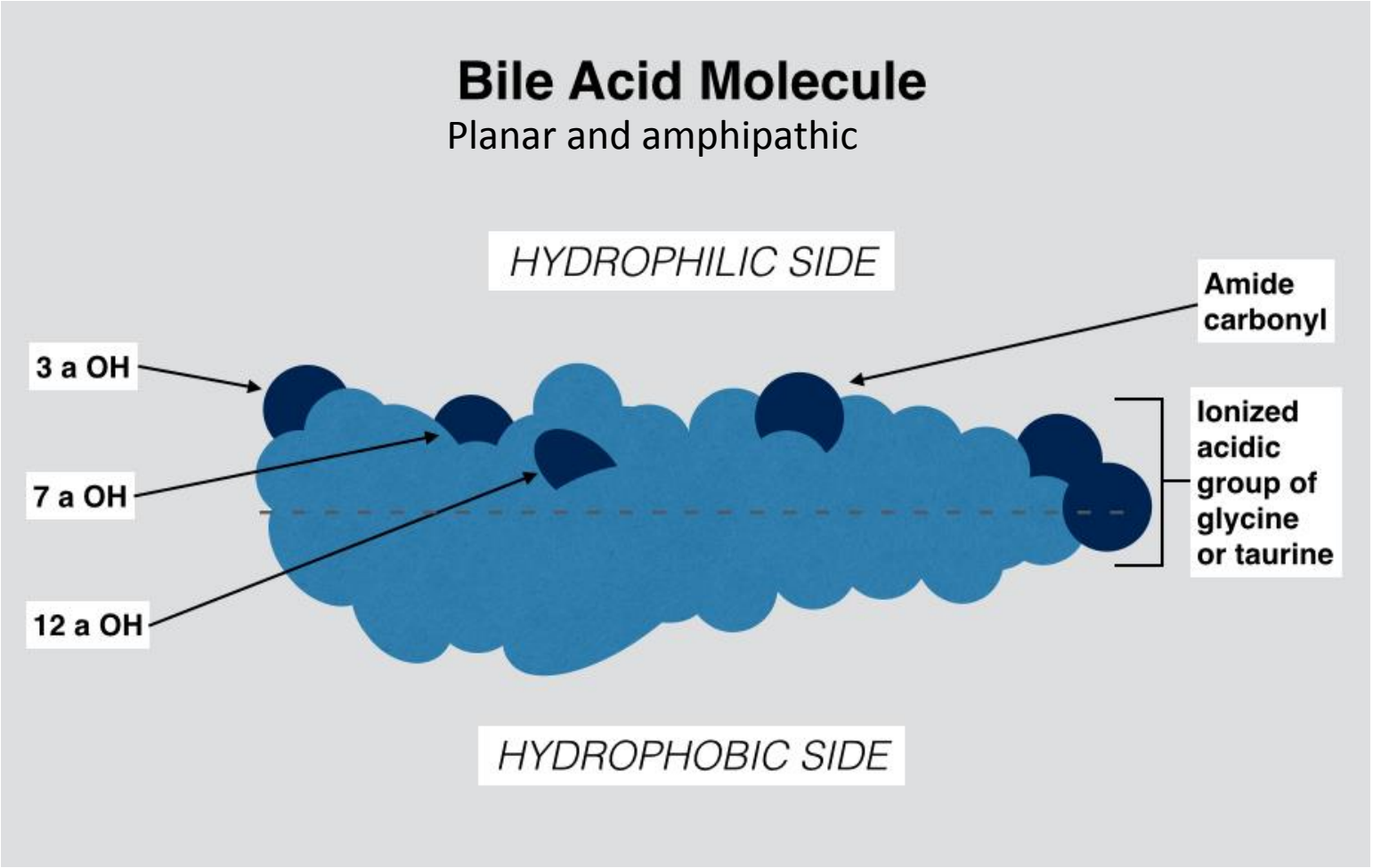
- **Non-micellar functions**
  - Cofactor for bile salt dependent lipases
  - Antimicrobial effect in small intestine
  - Induces secretion of antimicrobial factors (FXR mediated)
  - Promote colonic motility and secretion
  - Promotion of thermogenesis via TGR5 in brown fat

A Hofmann Frontiers in Bioscience 14, 2584-2598, January 1, 2009

Bile Acid Biosynthesis Essentials



Bile Salts are Amphipathic



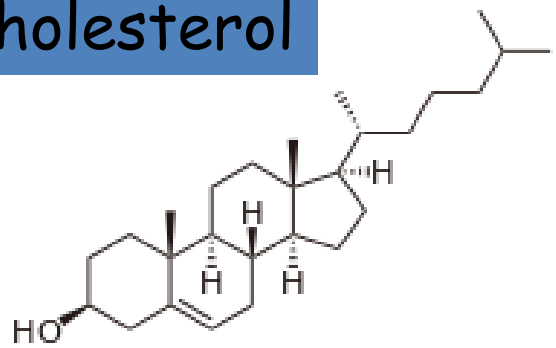
Drawing courtesy of Kate Donovan

Implications?

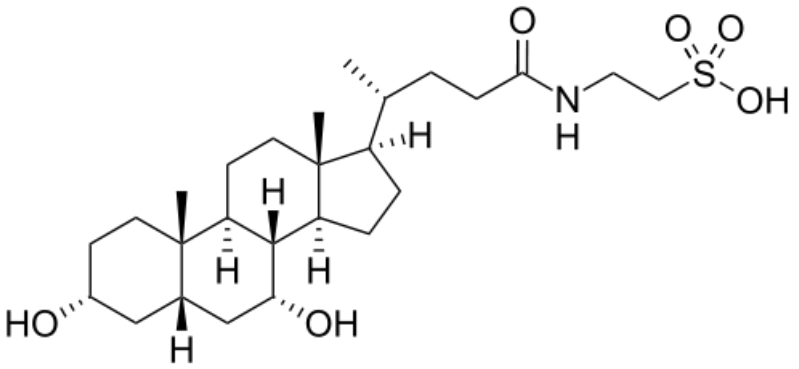
- Emulsion stabilization
- Micelle formation

Bile Acid Structures- A Comparison

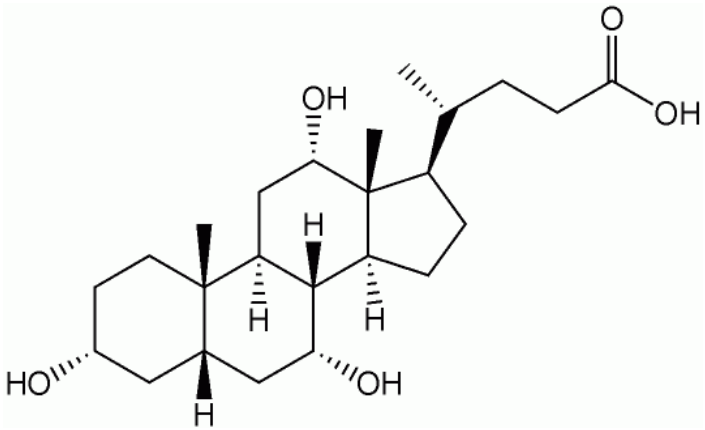
Cholesterol



Taurine



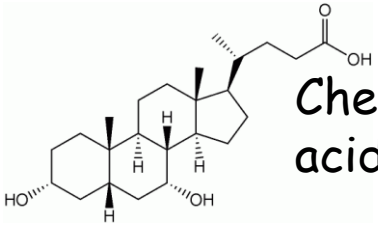
Taurochenodeoxycholic acid- a conjugated bile acid



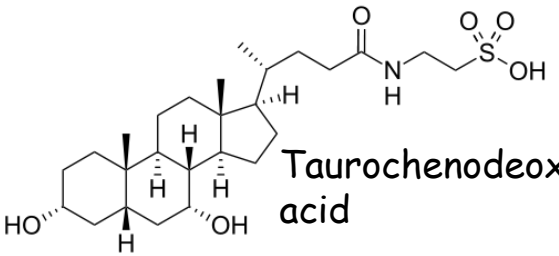
Cholic acid- an unconjugated bile acid

Primary Bile Acids

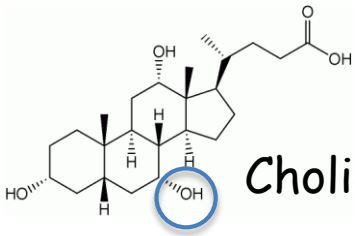
Synthesized in the liver from cholesterol



Chenodeoxycholic acid

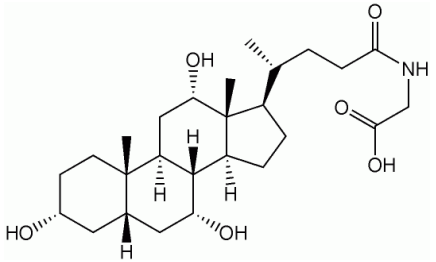


Taurochenodeoxycholic acid



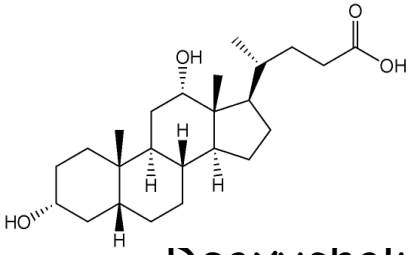
Cholic acid

Conjugation in hepatocytes



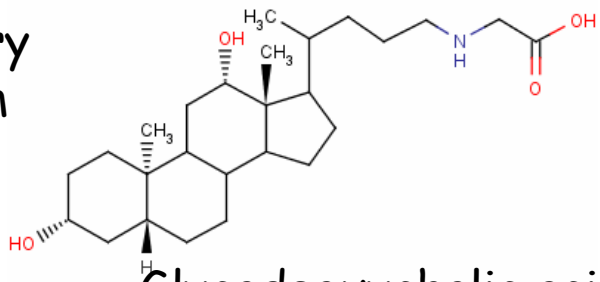
Glycocholic acid

Secondary Bile Acids



Deoxycholic acid

Bacteria can transform primary BAs to secondary in the ileum



Glycodeoxycholic acid

Deconjugation in cecum by bacteria

Unconjugated

Conjugated

Common Bile Acids in Humans

Common Name	Type	Key Characteristic	Pool Size (mg)	Daily Synthesis (mg)
Cholic acid	Primary	Synthesized from cholesterol in the liver	500-1500	180-360
Chenodeoxycholic acid	Primary		500-1400	100-250
Deoxycholic acid	Secondary	Produced in intestine from action of bacteria on primary bile acids	200-1000	NA
Lithocholic acid	Secondary		50-100	NA
Total			1250-4000	280-610

Based on Pattni and Walters *British Medical Bulletin* 2009 92: 79-93

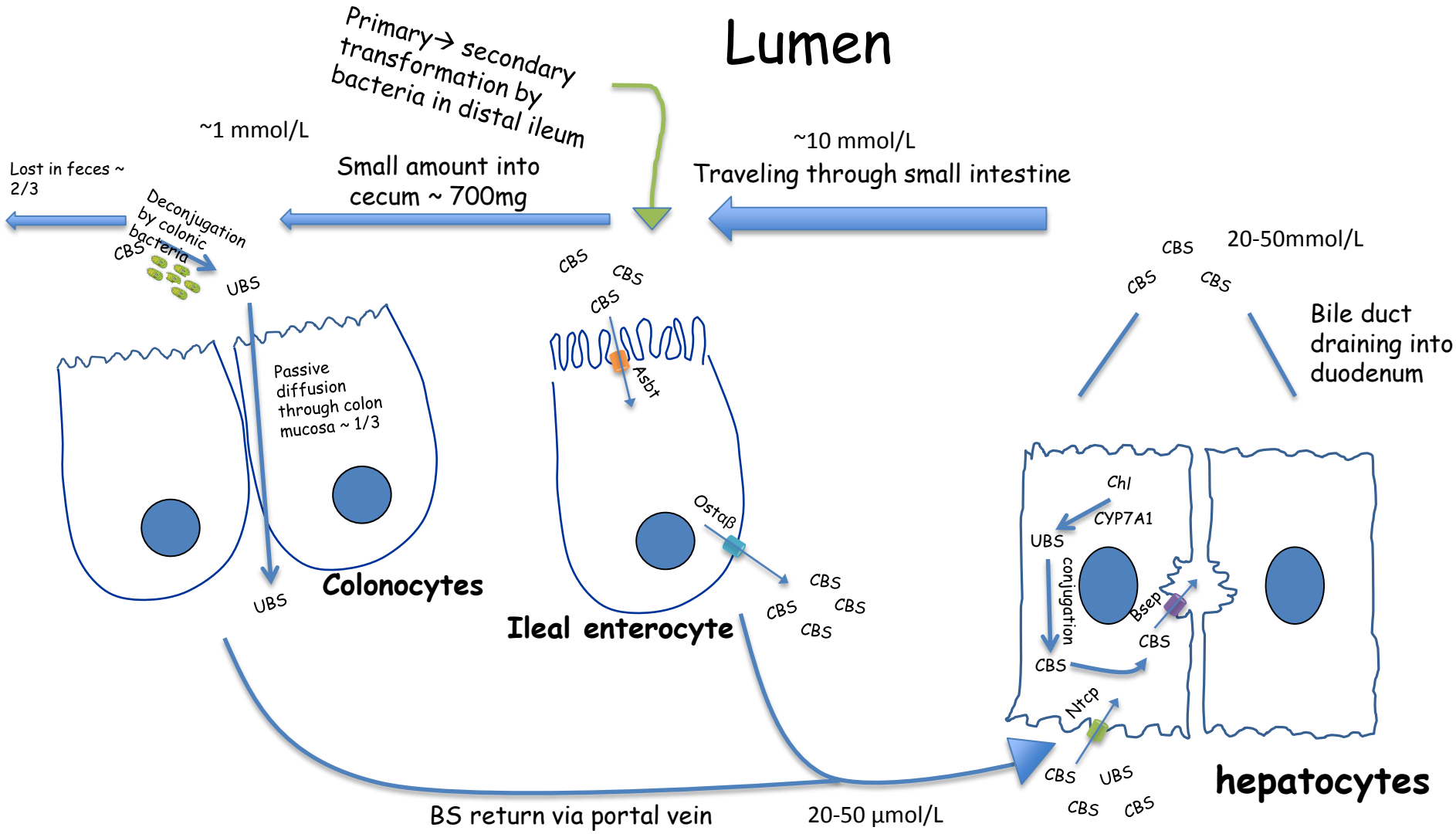
Bile Salt Nomenclature- so no confusion

- **Primary**→ made de novo by liver
- **Secondary**→ altered by intestinal bacteria

- **Unconjugated**→ bile acid without additional polar moieties
- **Conjugated**→ with additional polar moieties (e.g. glycine or taurine) added by hepatocytes before secretion

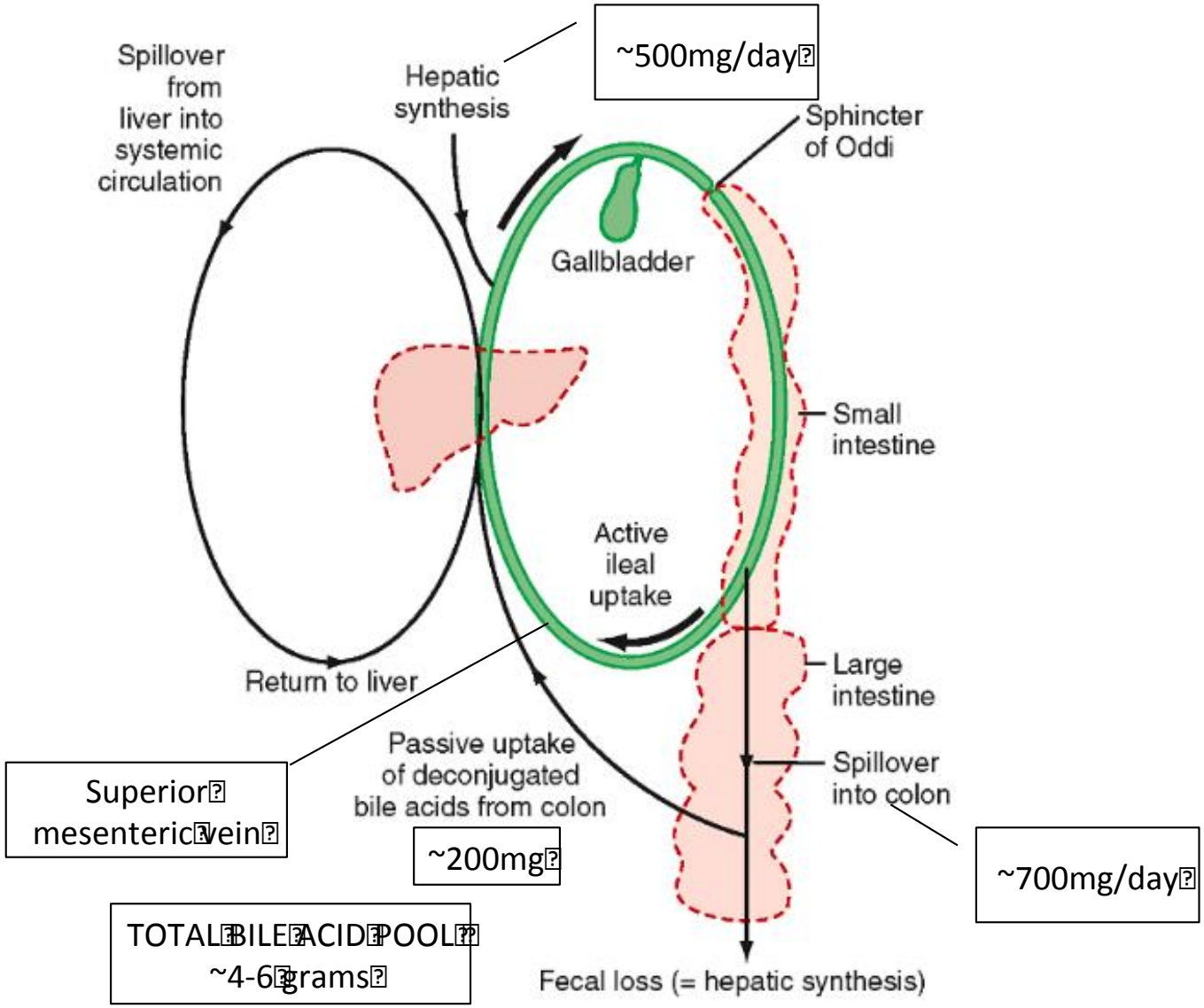
Primary and secondary bile acids can be either conjugated or unconjugated.

Bacteria biotransform primary into secondary Bas in ileum/cecum **AND** they deconjugate CBAs into UBAs in the cecum


Lumen
Primary→ secondary transformation by bacteria in distal ileum
~1 mmol/L
Small amount into cecum ~ 700mg
~10 mmol/L
Traveling through small intestine
Lost in feces ~ 2/3
Deconjugation by colonic bacteria
CBS
UBS
Passive diffusion through colon mucosa ~ 1/3
Colonocytes
Asbt
Ileal enterocyte
Ostαβ
20-50mmol/L
Bile duct draining into duodenum
Chl
CYP7A1
conjugation
Bsep
Ntcp
hepatocytes
BS return via portal vein
20-50 µmol/L
Portal Blood Space/basolateral space

The Enterohepatic Circulation

1. **Not bilirubin**→bili lost to feces
2. Pool recycles ~ 6 times per day
3. Very efficient only 5% lost to stool even with all of this use
4. Secondary active transport in ileum
5. First-pass uptake robust



Berne and Levy Principles of Physiology 6th Edition
Adapted with permission from publisher

Thought Question 1- Idiopathic Bile Acid Diarrhea

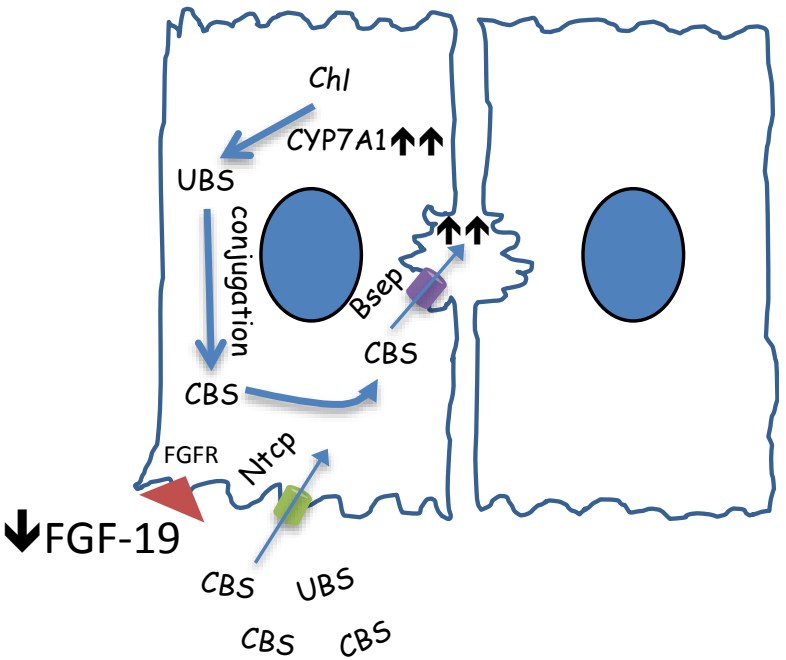
- Walters et al. in 2009 established a reasonable mechanism for bile acid diarrhea, in which excess bile acids gain access to the colon, provoking fluid secretion and diarrhea, while fat soluble vitamin absorption is normal
- Which mechanism seems most plausible, and why?
  1. Microflora alter bile acids, rendering them unabsorbable
  2. The ileal bile acid transporter is defective
  3. A feedback mechanism defect, so that hepatocytes overproduce bile acids
  4. A toxic bile acid, which is highly irritating to the colon

Thought Question 1- Idiopathic Bile Acid Diarrhea

1. Microflora alter bile acids, rendering them unabsorbable-
2. The ileal bile acid transporter is defective
3. **A feedback mechanism defect, so that hepatocytes overproduce bile acids**
4. A toxic bile acid, which is highly irritating to the colon

Clinical Correlation- Bile Acid Malabsorption

- BAM three types
  - 1: ileal dysfunction
  - 2: idiopathic
  - 3: other conditions (e.g. cholecystectomy)
- 2009, describe cause for some patients with type 2→ disordered regulation of CYP7A1



- Ileum fails to make enough FGF-19
- CYP7A1 activity too high because released from inhibition via FGFR binding FGF-19
- Liver makes too much bile acid
- Ileum overwhelmed
- BAs in the colon at high concentrations→diarrhea!

Walters et al. *Clin Gastro Hepatol* 2009 7: 1189-94

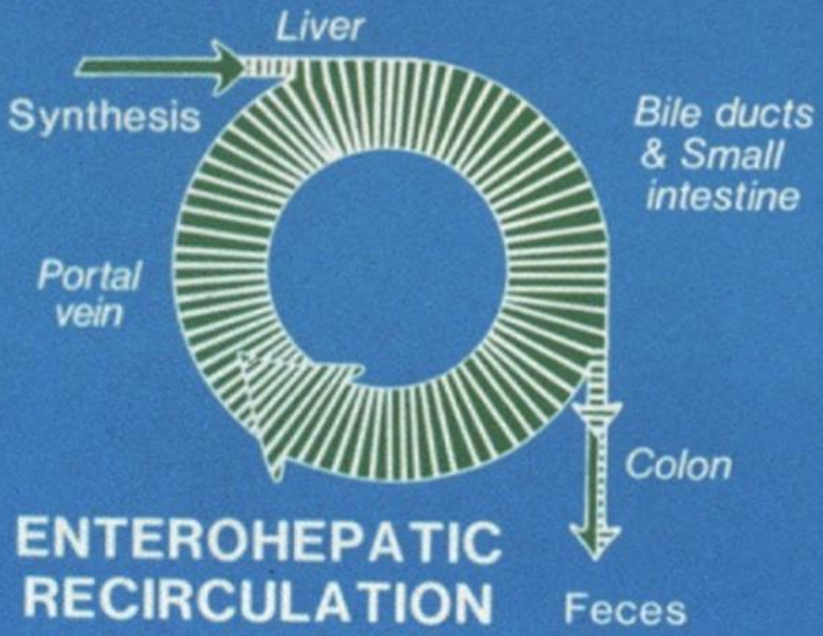
Stating the Obvious, but Easy to Get Confused…

Bilirubin and Bile acids share mechanisms but are handled completely differently in the intestine

CONJUGATES SECRETED INTO BILE ARE NOT REABSORBED UNLESS ACTIVELY TRANSPORTED OR DEGRADED TO LIPOPHILIC PRODUCTS

Conjugated Bile Salts

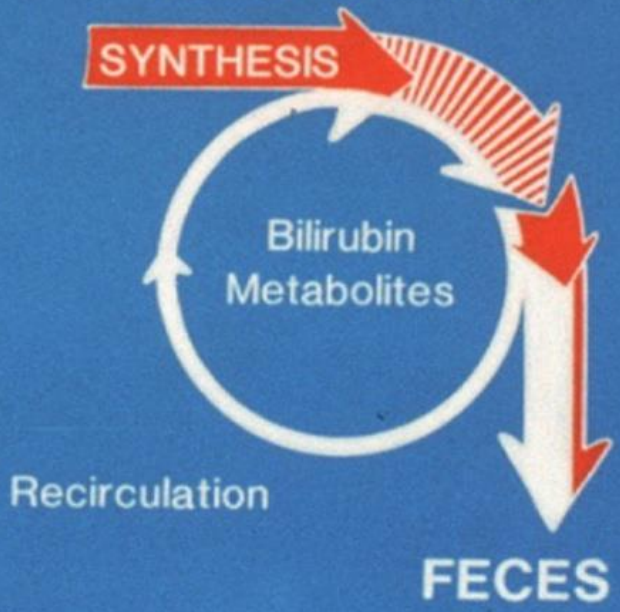
- Actively Transported by Ileum
- Mostly Reabsorbed



ENTEROHEPATIC RECIRCULATION

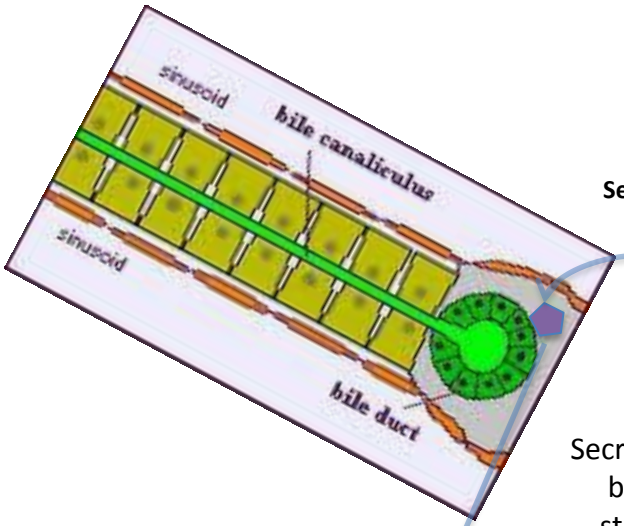
Conjugated Bilirubins

- NOT Actively Transported
- Deconjugated and Reduced
- Mostly Eliminated



Factor	Bilirubin	Bile acids
Synthesis	**Tissue macrophages from senescent red blood cells**	**Hepatocytes from cholesterol**
Hepatocyte Action	Conjugation	Conjugation
Hepatocyte Secretion	Particular transporters into canaliculus	Particular transporters into canaliculus
Bacterial Deconjugation	Yes	Yes
Active GI Transport	**No**	**Yes- Active recovery of nearly ALL bile acids in ileum**
Passive GI Transport	Yes, small amount of de-conjugated molecules	Yes, small amount of de-conjugated molecules
Basolateral transport	Yes – **receive from macrophages**	Yes- **receive from the enterohepatic circulation**

Organ level regulation of Bile Secretion

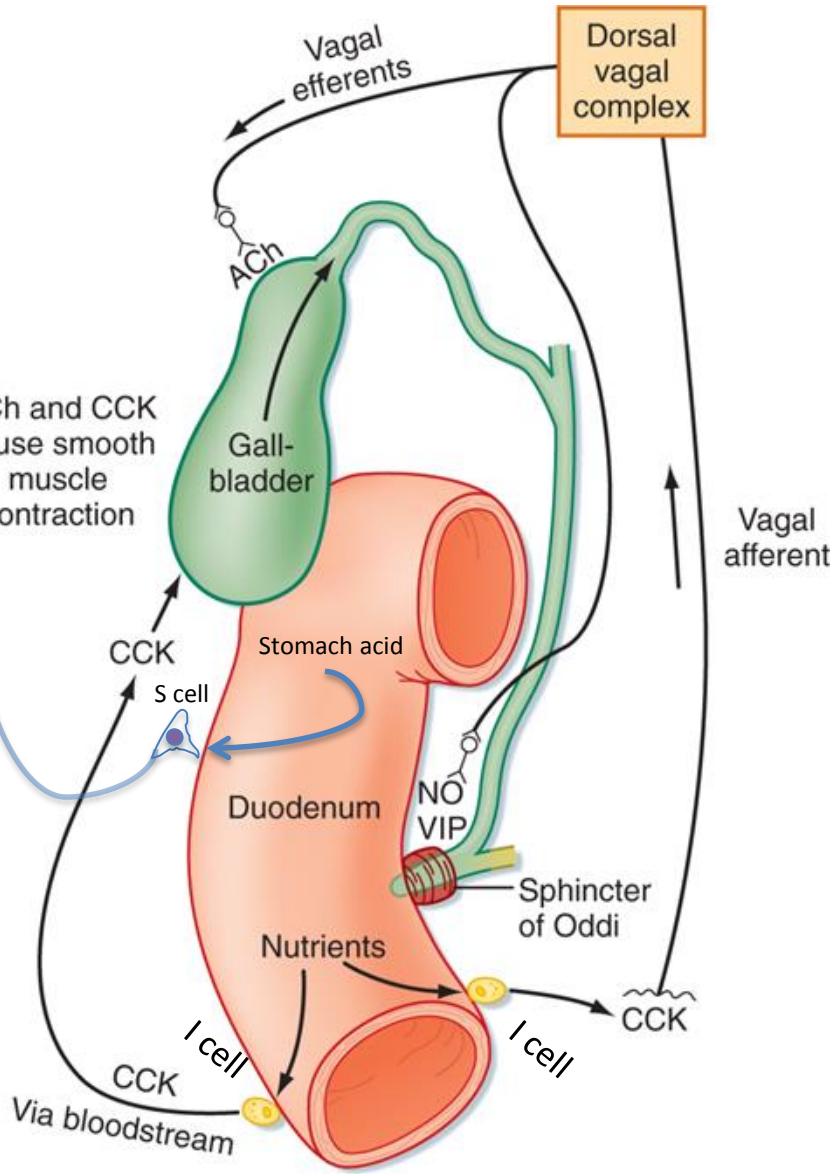


Secretin Rc

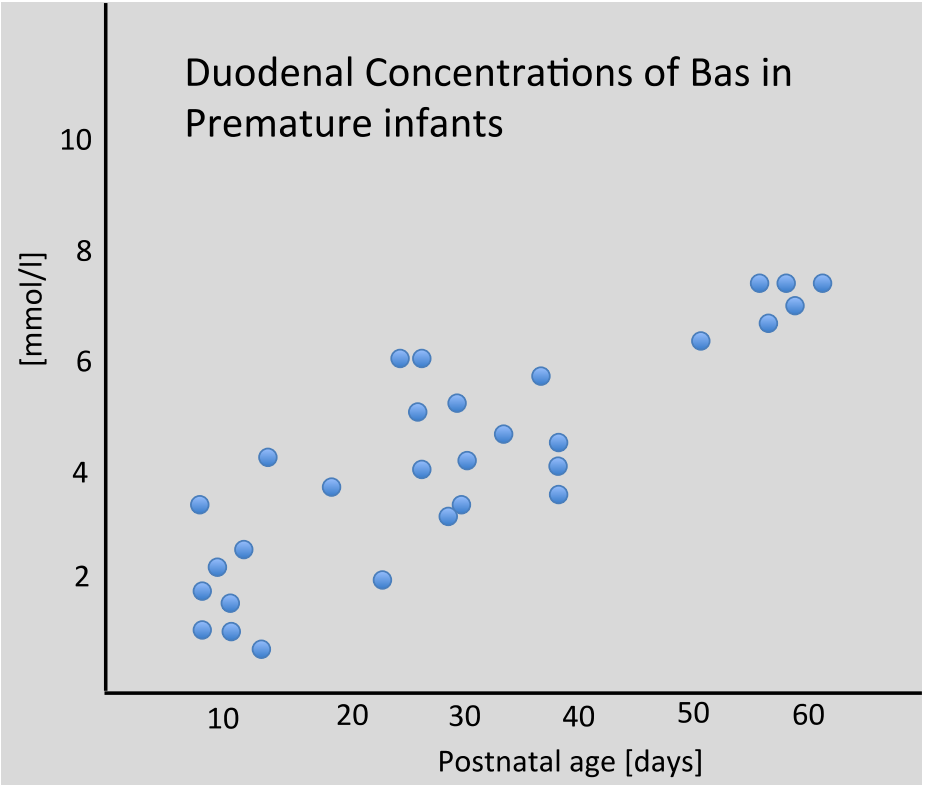
ACh and CCK cause smooth muscle contraction

Secretin via blood stream

↑ Bicarbonate and fluid secretion in bile ducts

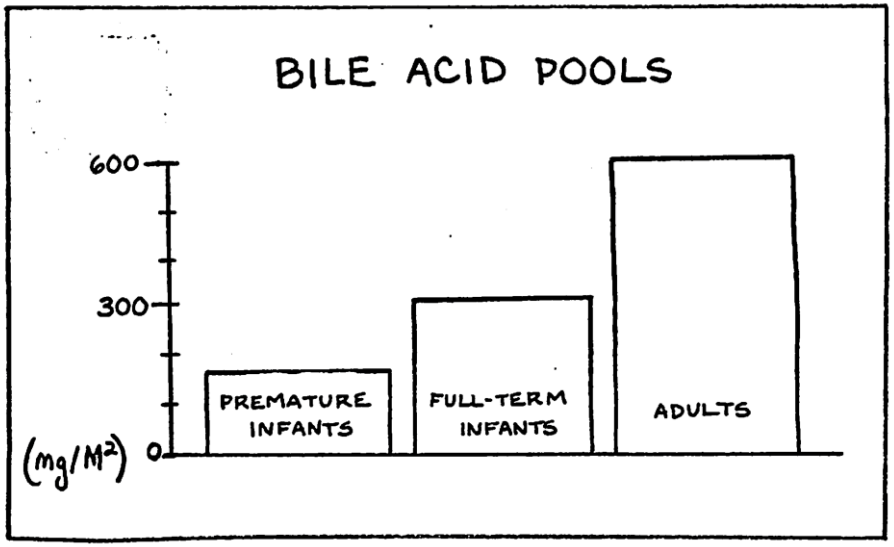


Bile salts- Developmental Note



- Ileal uptake matures in late infancy

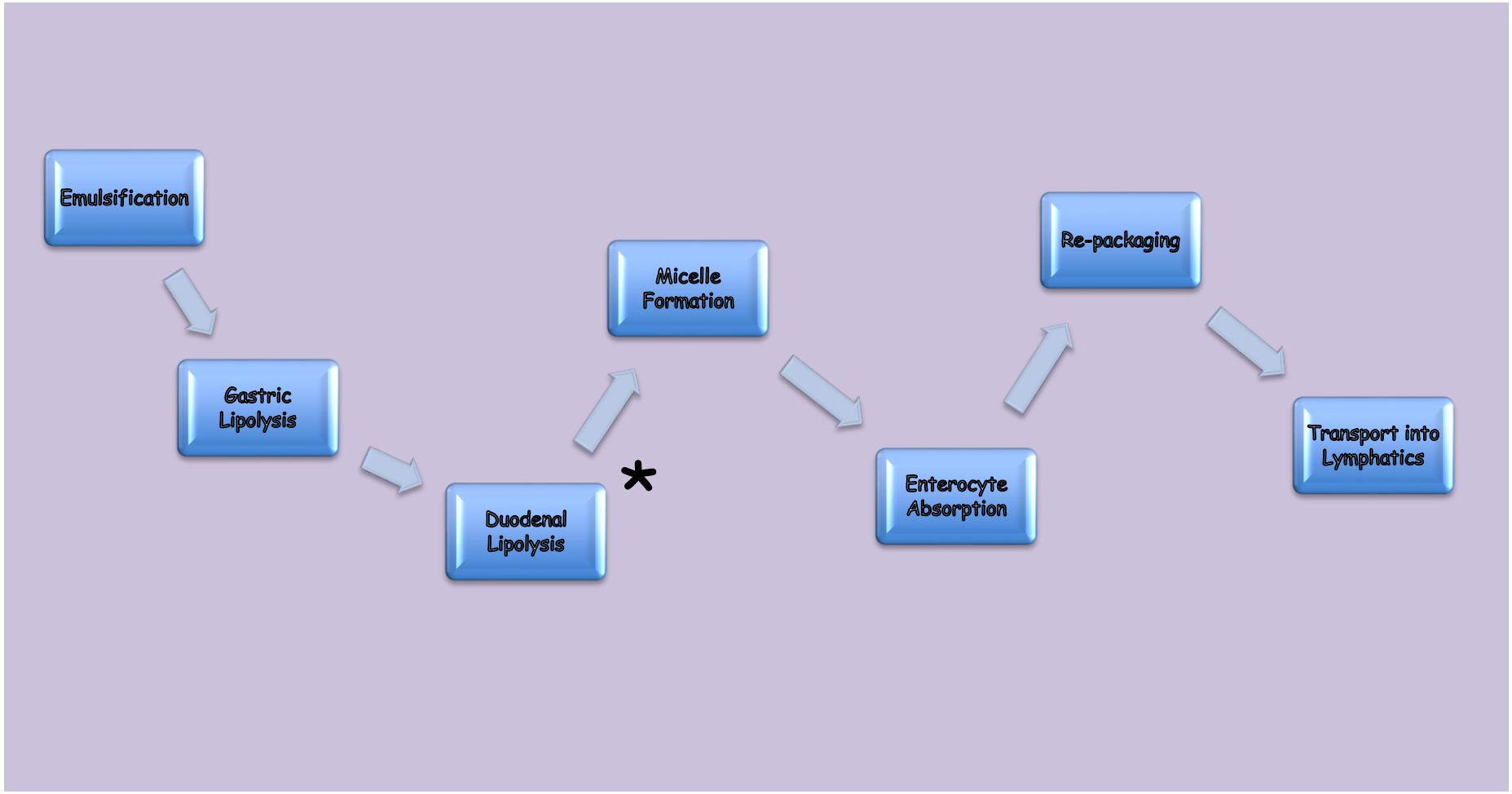
- Liver synthesis and ileal uptake are low at birth



Data from Biol Neonate. 1997;71(4):207-14

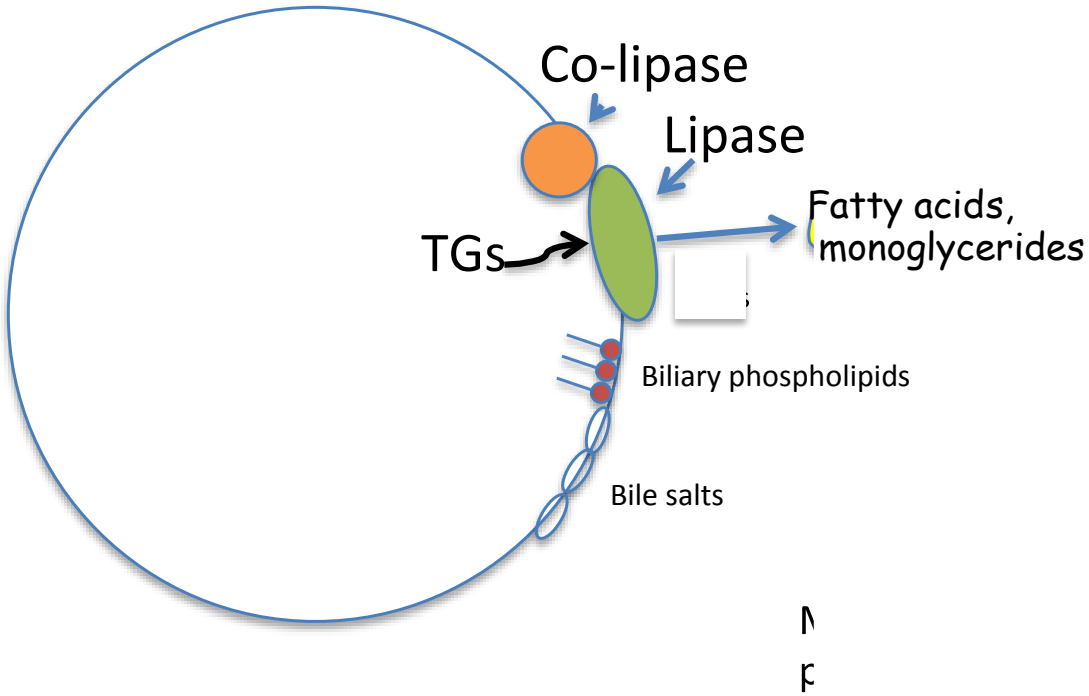
Figure from J Watkins MD

Overview of Fat Digestion



Duodenal Lipolysis

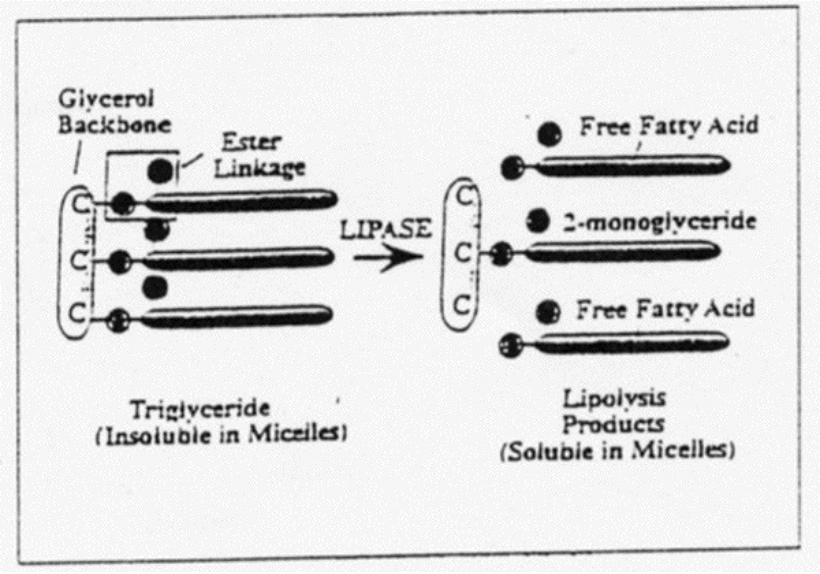
- Pancreatic Lipase attaches to surface of triglyceride globules
- Products are FFAs and 2MGs

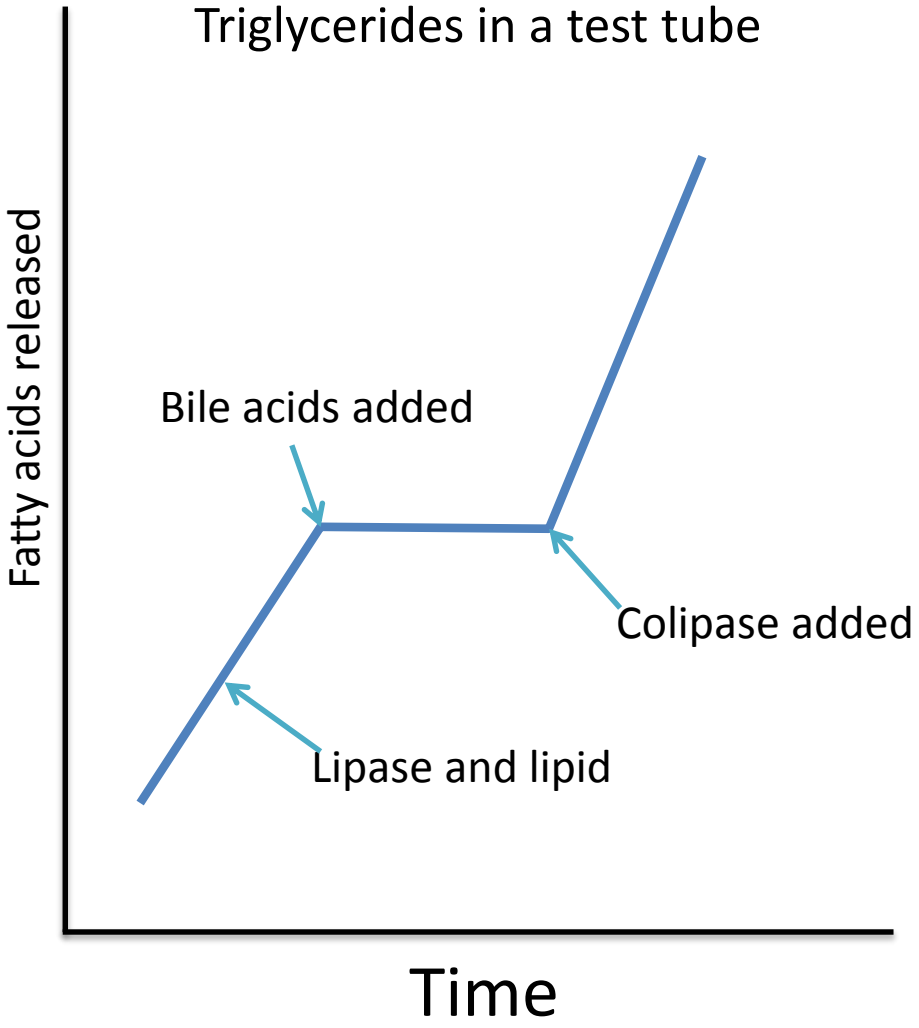


- In the right conditions, pancreatic lipase is very efficient
- 'Right conditions'
  - Neutral pH
  - Mixing
  - Bile salts
  - Co-lipase

Protein	Source	Activity	Requirements	Functionality
Gastric lipase	Chief cells in stomach	Favors hydrolysis of medium chain fatty acids; end product inhibition	pH 4-5; **inhibited by** bile acids > 2-3mM	↑importance infants or PI; difficult to differentiate from lingual lipase
Lingual lipase	Lingual serous glands	Favors hydrolysis of medium chain fatty acids; end product inhibition	pH 4-5; **inhibited by** bile acids > 2-3mM	↑importance infants or PI; difficult to differentiate from gastric lipase
Pancreatic lipase	Pancreatic ascini	Hydrolyzes 1 and 3 positions of TG	pH 7-8; needs co-lipase when bile acids present	Very efficient with colipase; efficiency ↑with gastric 'predigestion'
Colipase	Pancreatic ascini (pro-form)	Co-factor for pancreatic lipase	**Activated by** trypsin	Keeps lipase associated with lipid droplet in presence of bile acids
Secretory phospholipase A_2	Pancreatic ascini (pro-form)	Hydrolyzes phosphatidylcholine and phosphilipids	Calcium; **activated by** trypsin	Reclaims important phospholipids
Cholesterol esterase	Pancreatic ascini	Broad specificity! 1. all three positions on TG 2. Cholesterol esters 3. Vitamin esters	**Requires** bile acids; pH 7-9	Not as efficient as pancreatic lipase
Breast milk lipase	Mammary gland	Similar to cholesterol esterase	**Requires** bile acids; pH7-9	Acid resistant; major role in fat digestion in BF infants

Lipolysis- enzymes and bile salts work together





Pancreatic Lipase:

1. Lipase can work on its own
2. With bile salts + co-lipase, highly efficient
3. Products: FFAs and 2-MGs

Figure from J Watkins MD

Thought Question 2- CF patient missing her enzymes

- An adult with cystic fibrosis has adequate lingual/gastric lipase activity but inability to secrete bicarbonate or pancreatic enzymes.
- She has run out of supplemental pancreatic enzymes.
- She knows to cook with coconut oil (medium chain triglycerides) and try to eat lower fat meals.
- She would like to enhance lipolysis in her GI tract. She therefore chews antacid tablets (sodium bicarbonate) with her meals.

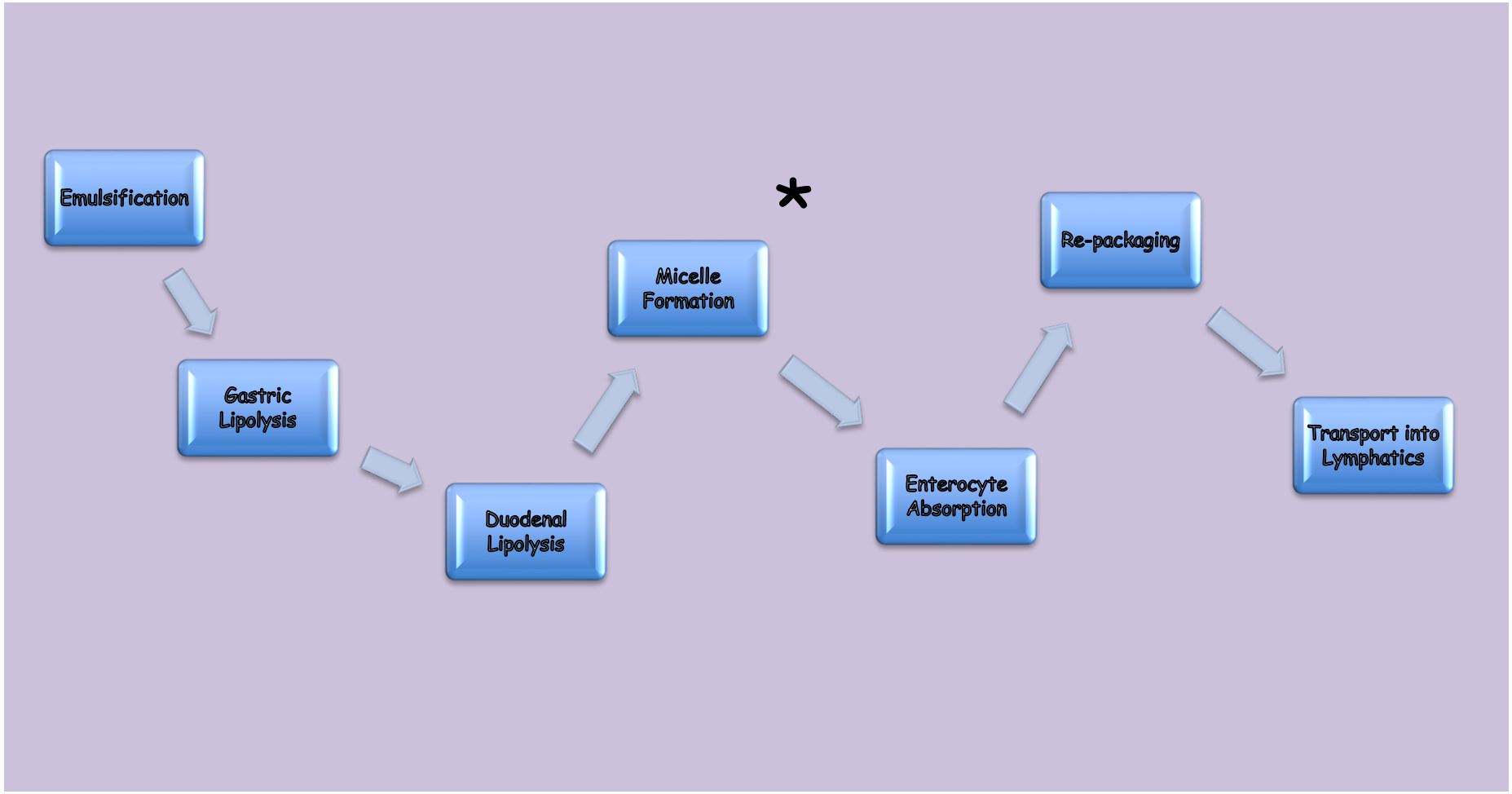
Thought Question 2- which explanation is best?

- An adult with cystic fibrosis has adequate lingual/gastric lipase activity but pancreatic insufficiency--bicarbonate and pancreatic enzyme secretion is very low.
- She has run out of supplemental pancreatic enzymes.
- She knows to cook with coconut oil (medium chain triglycerides) and try to eat lower fat meals.
- She would like to enhance lipolysis in her GI tract. She therefore chews anti-acids tablets (sodium bicarbonate) with her meals.

We would predict that

1. This would help because residual pancreatic lipase would be at pH optima
2. This would help because triglyceride would be more ionized, so emulsion particles would coalesce
3. This would be detrimental because rebound acid secretion would impair downstream bile salt function
4. This would be detrimental because intra-gastric lipolysis would be impaired at more neutral pH

Overview of Fat Digestion



Micelles- recap

- **Challenge**: How to transport a lot of nonpolar molecules in an aqueous environment?
- **Answer**: make them soluble
- **Follow-up**: How?

Answer: coat them with amphipathic molecules in packages that are small enough to move freely in the aqueous phase!

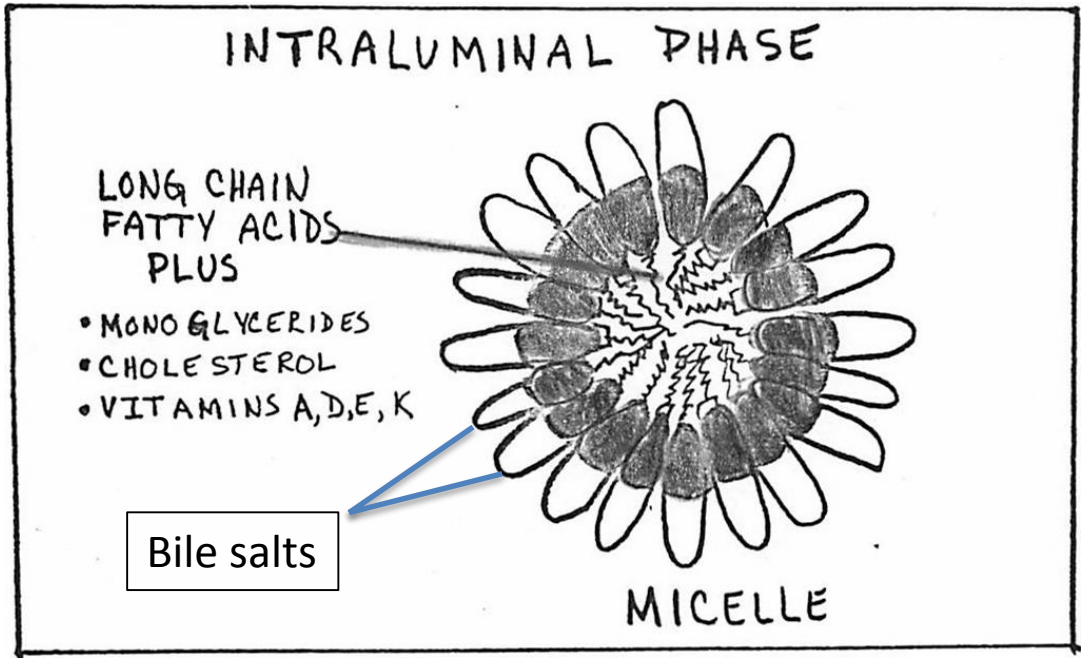
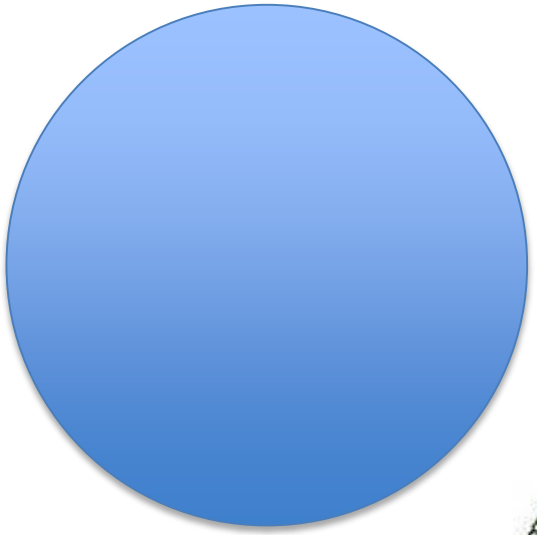


Figure from J Watkins MD

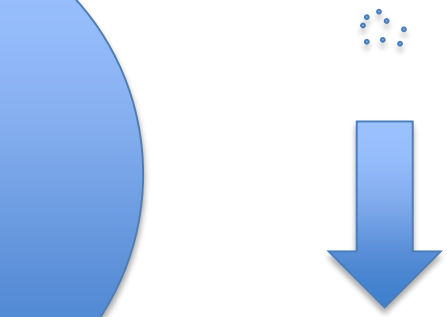
Micelles- size and content

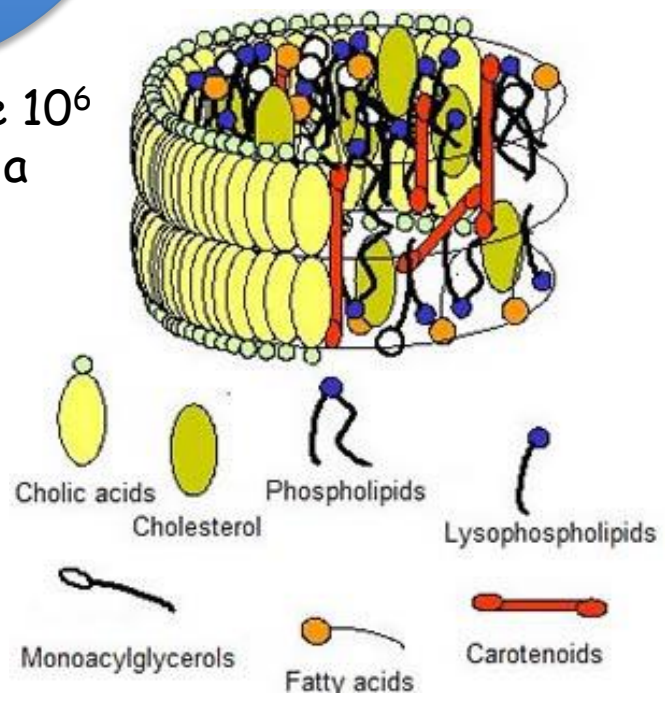
- Stomach makes emulsion particles 2µm in diameter
- Micelles are 20nm in diameter!
- They make transport of fats and vitamins to the enterocyte membrane highly efficient



Emulsion particle 10^6 x bigger than a micelle

Mixed Micelles 1x





https://www.naro.affrc.go.jp/english/nfri/organization/05food_resource_division/05/index.html (used with permission)

Micelles- critical micellar concentration (CMC)

- Micelles won't form unless BA present at high enough concentrations
- 'Critical Micellar Concentration'
- ~1.5mM
- For an adult, this means 2-3grams/hour secreted into duodenum

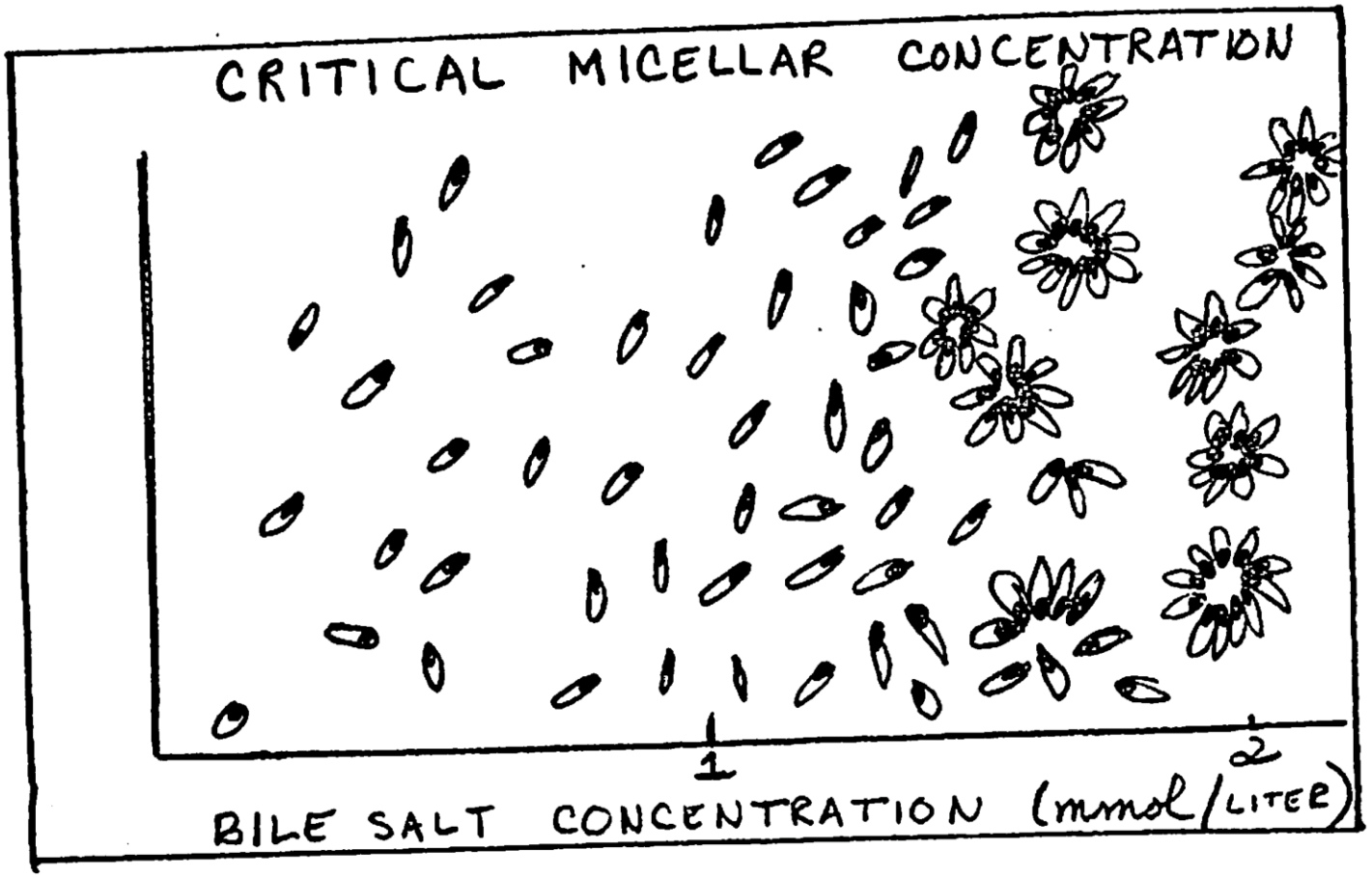
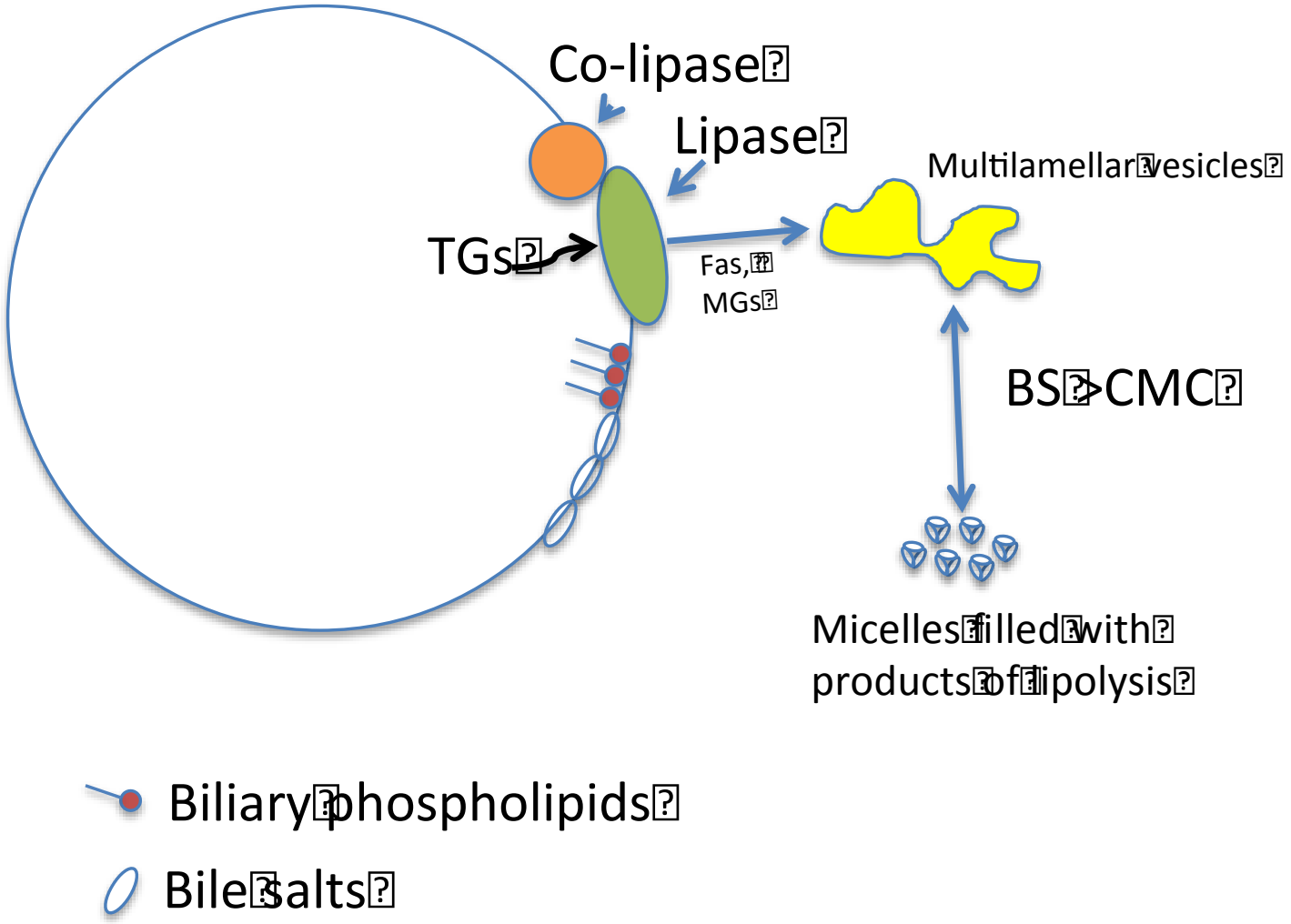
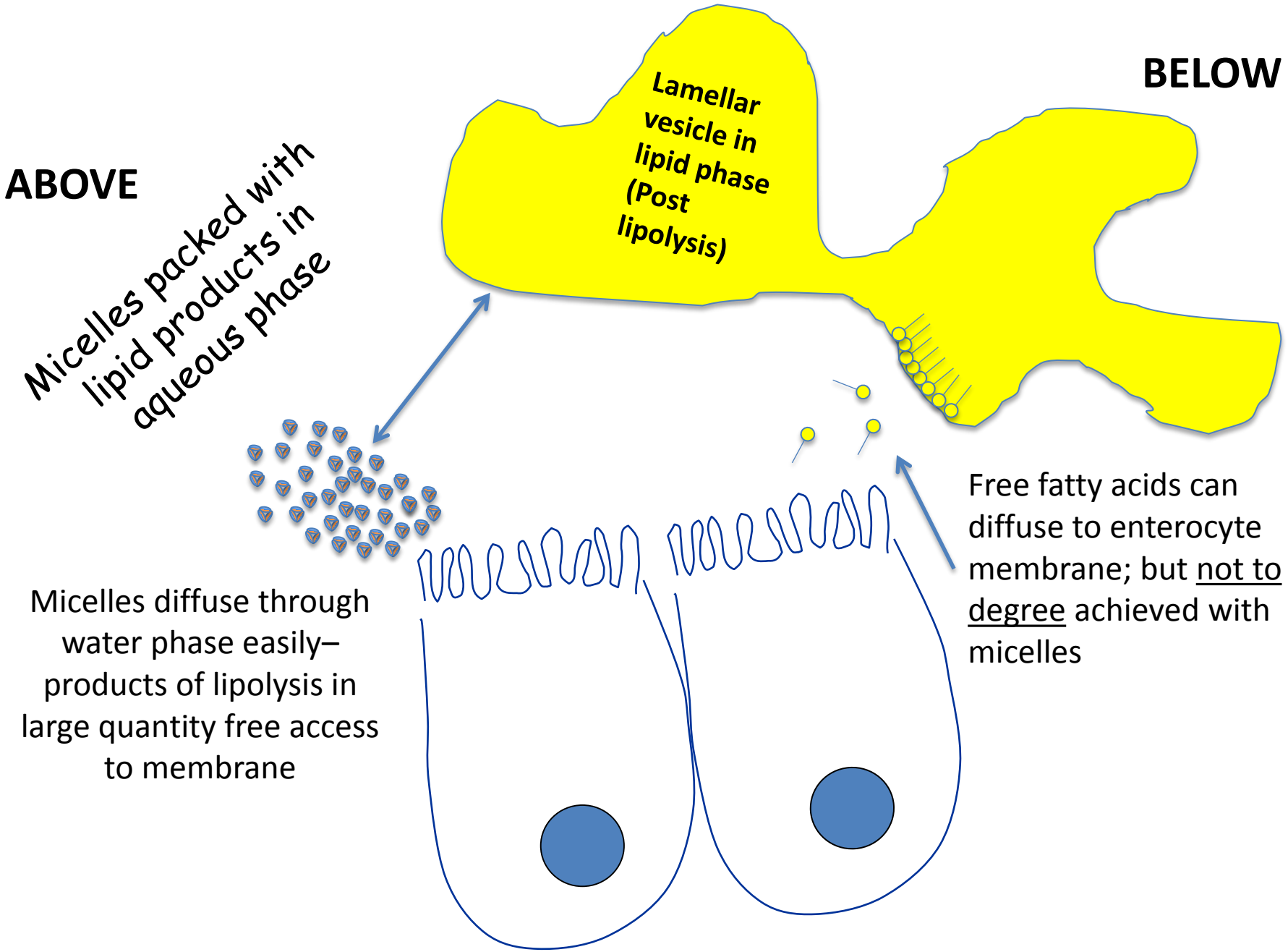


Figure from J Watkins MD

Small intestinal transfer of lipids to Micelles- essentials diagram

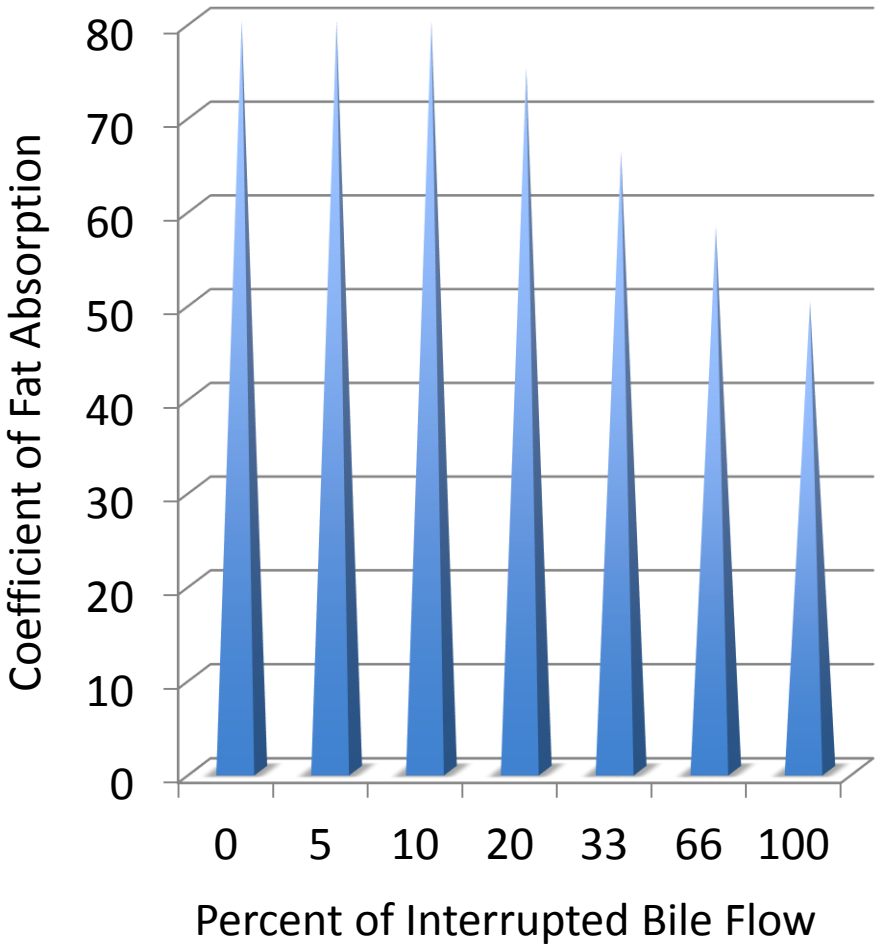


Cartoon Rendition of Being Above or Below the CMC



Fat Absorption is Abnormal But Still Possible Without Bile Salts

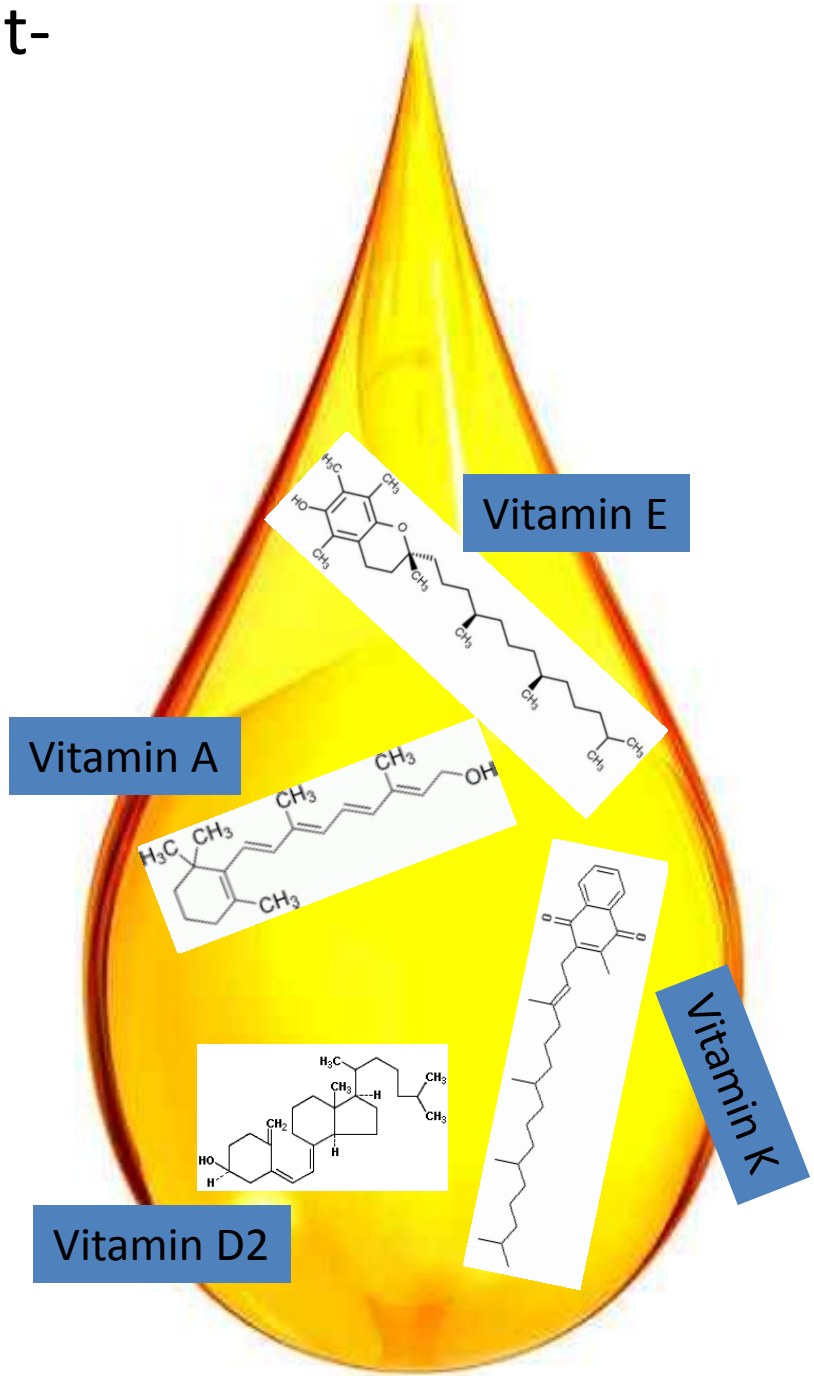
- 16 adult female monkeys
- Controllable interrupted bile flow
- Measured bile production and fecal fat excretion
- Normal monkey chow ~ 12 grams fat/day



From Dowling, Mack, and Small 1970 *JCI* 49: 232-42

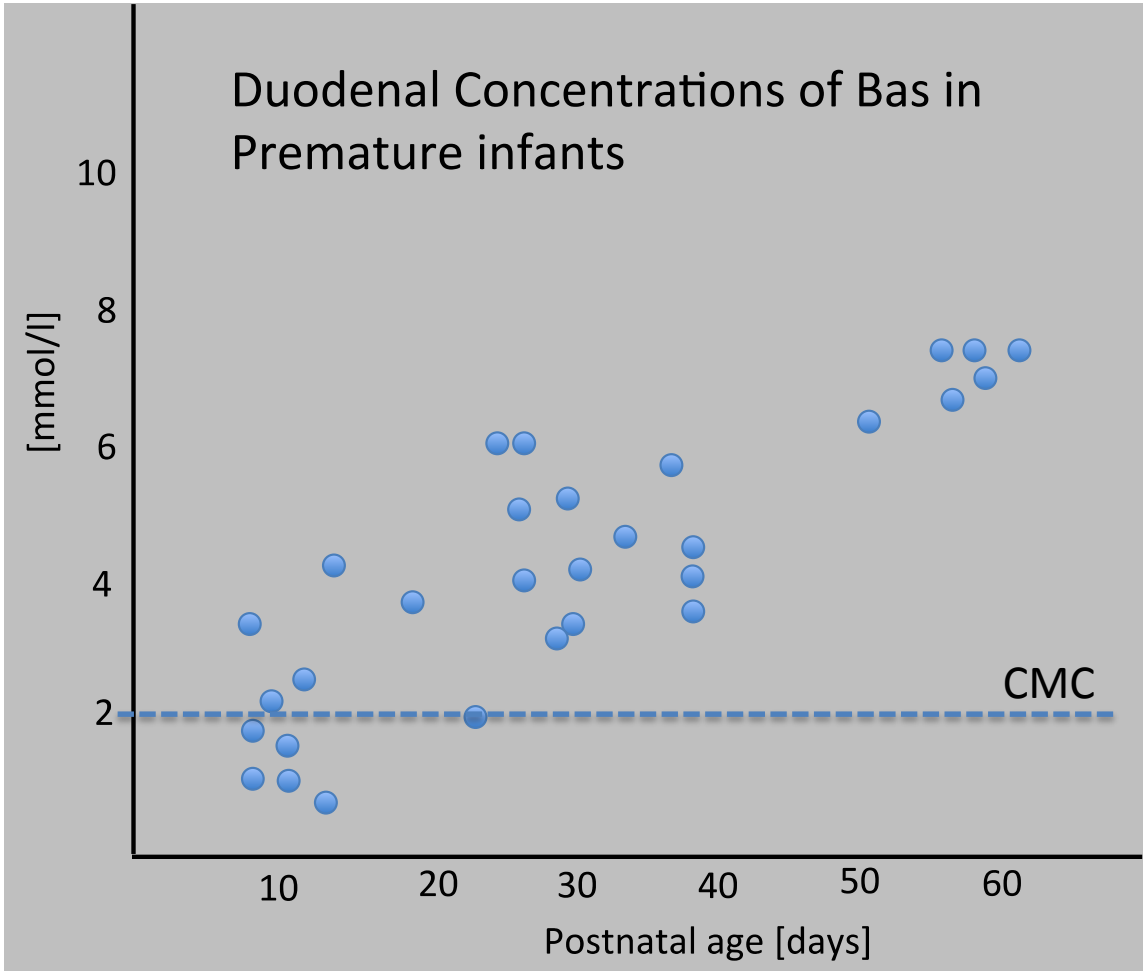
When below the CMC- fat-soluble vitamins?

- **<u>Too nonpolar</u>**→ will stay in the interior of lamellar structures
- **THEREFORE**, vitamin deficiencies **<u>will develop</u>** without special supplementation



CMC and infant fat digestion

- Duodenal BA concentration at CMC in premature infants
- Normally Rises over days- weeks
- Implications for fat and micronutrient absorption



Data from Biol Neonate. 1997;71(4):207-14

In summary, When Below the CMC….

Multi-lamellar structures form from products of lipolysis → Can get up to 70% fat absorption below CMC! → Recruit more intestinal SA; requires pancreas and villi to be working well

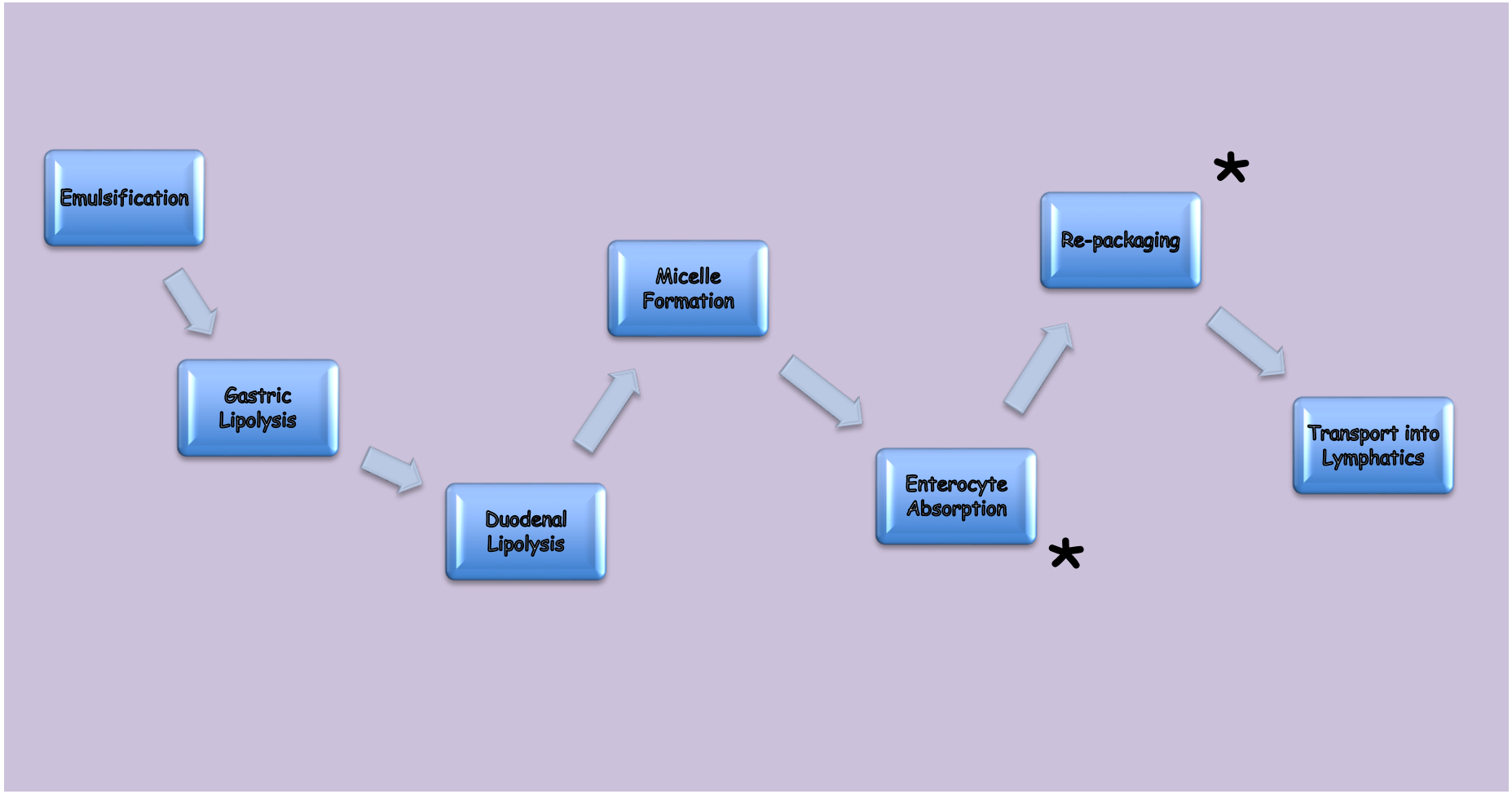
Recruit more intestinal SA; requires pancreas and villi to be working well → Often, pancreas or villi not normal → Some Examples?

1. Short bowel syndrome: missing SA and/or ileal bacterial overgrowth
2. Biliary disorders: both pancreatic and biliary pathology
3. Crohn's disease: generalized ileal dysfunction, bacterial overgrowth

Thought Question-3 two patients…

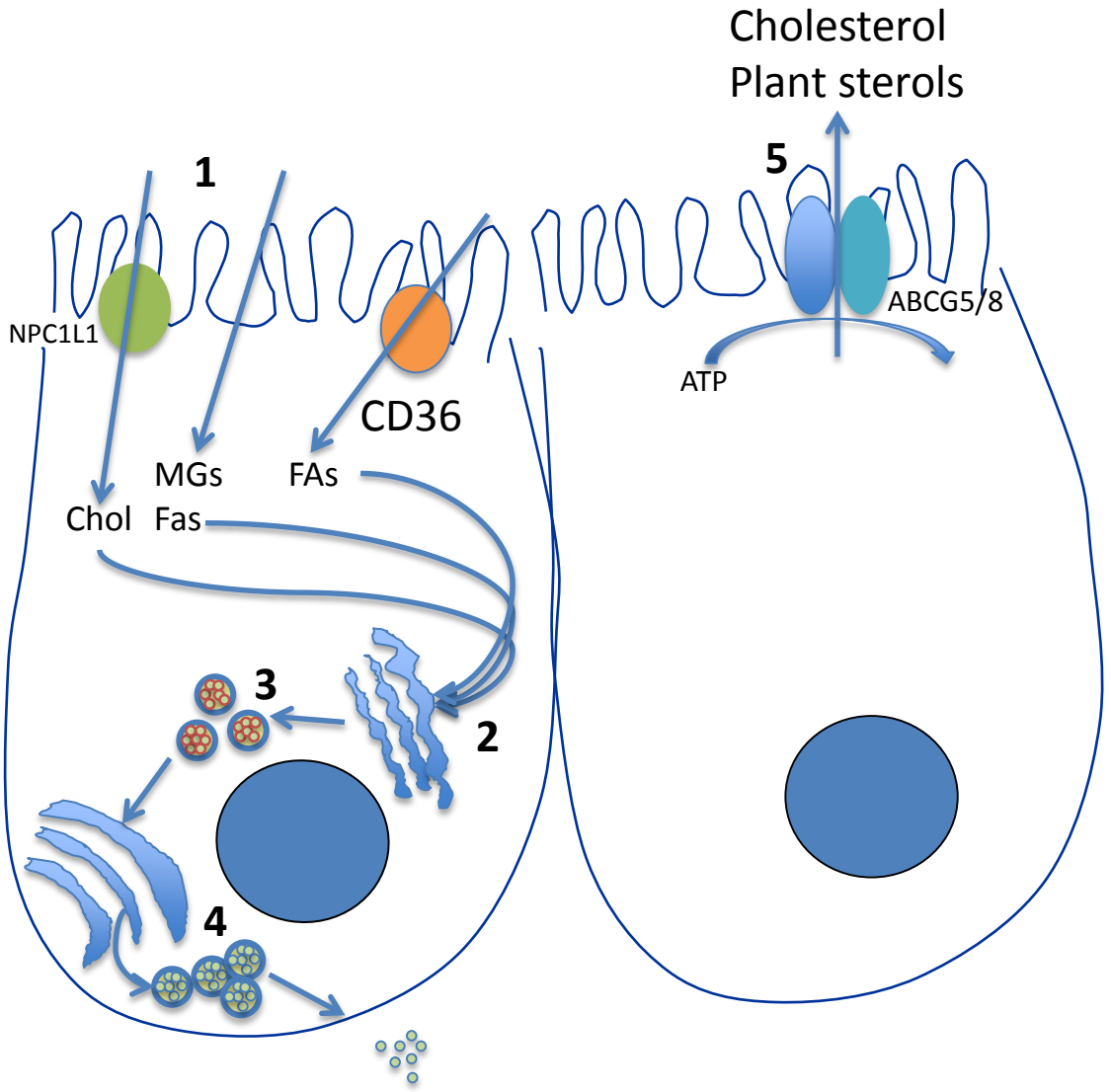
- Q: an infant with cholestasis from biliary atresia and a man with traumatic common bile duct disruption (the bile is diverted into an external bag outside the man's body) from a MVA are in hospital. You are in the lab. True or False, and then give short explanations
  - The infant stool has innumerable lipid droplets of triglyceride, while the adult stool has a modicum of triglyceride droplets.
  - Serum Vitamin E is normal in the adult, but low in the infant.
  - Both infant and adult would have stools containing a modicum of triglyceride droplets and would have normal serum vitamin E levels if they were provided supplemental pancreatic enzymes.

Overview of Fat Digestion



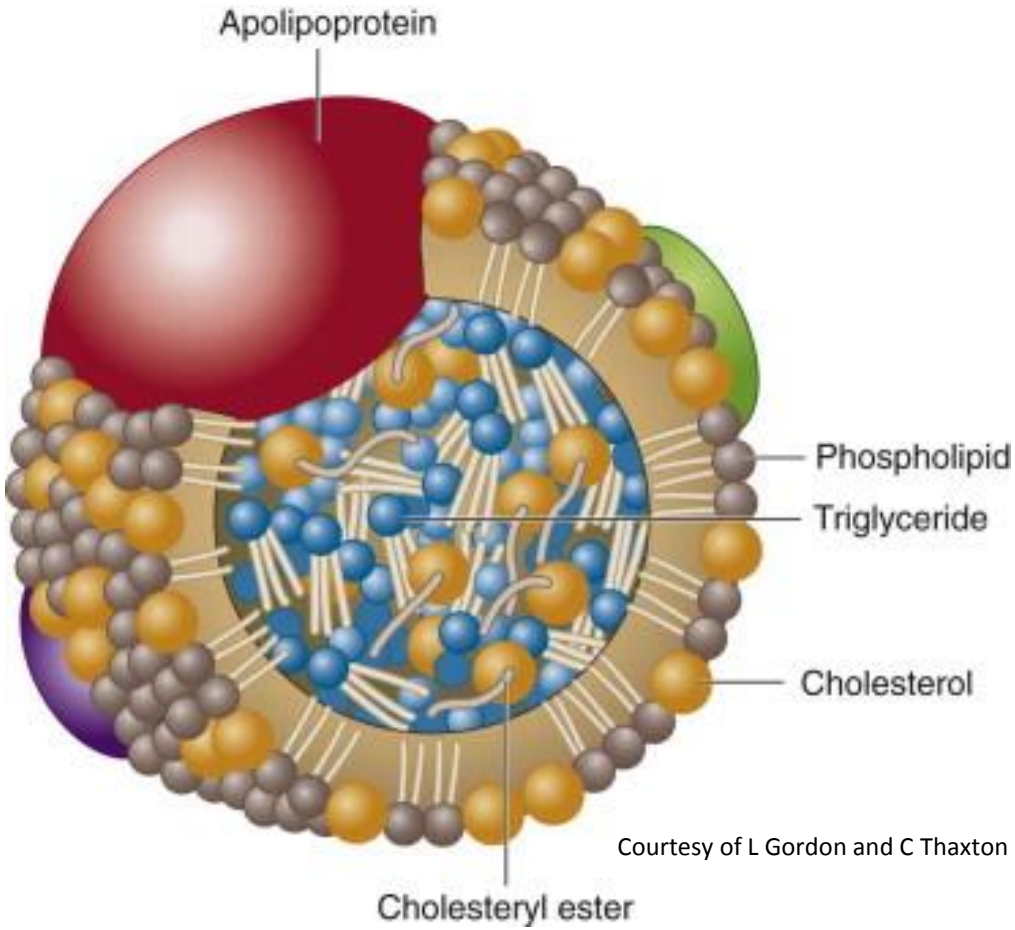
Villus tip lipid transport and processing

1. Lipolytic product transport
2. Re-esterification
3. Pre-chylomicrons ER→ Golgi
4. Chylomicron release
5. Cholesterol and plant sterol efflux



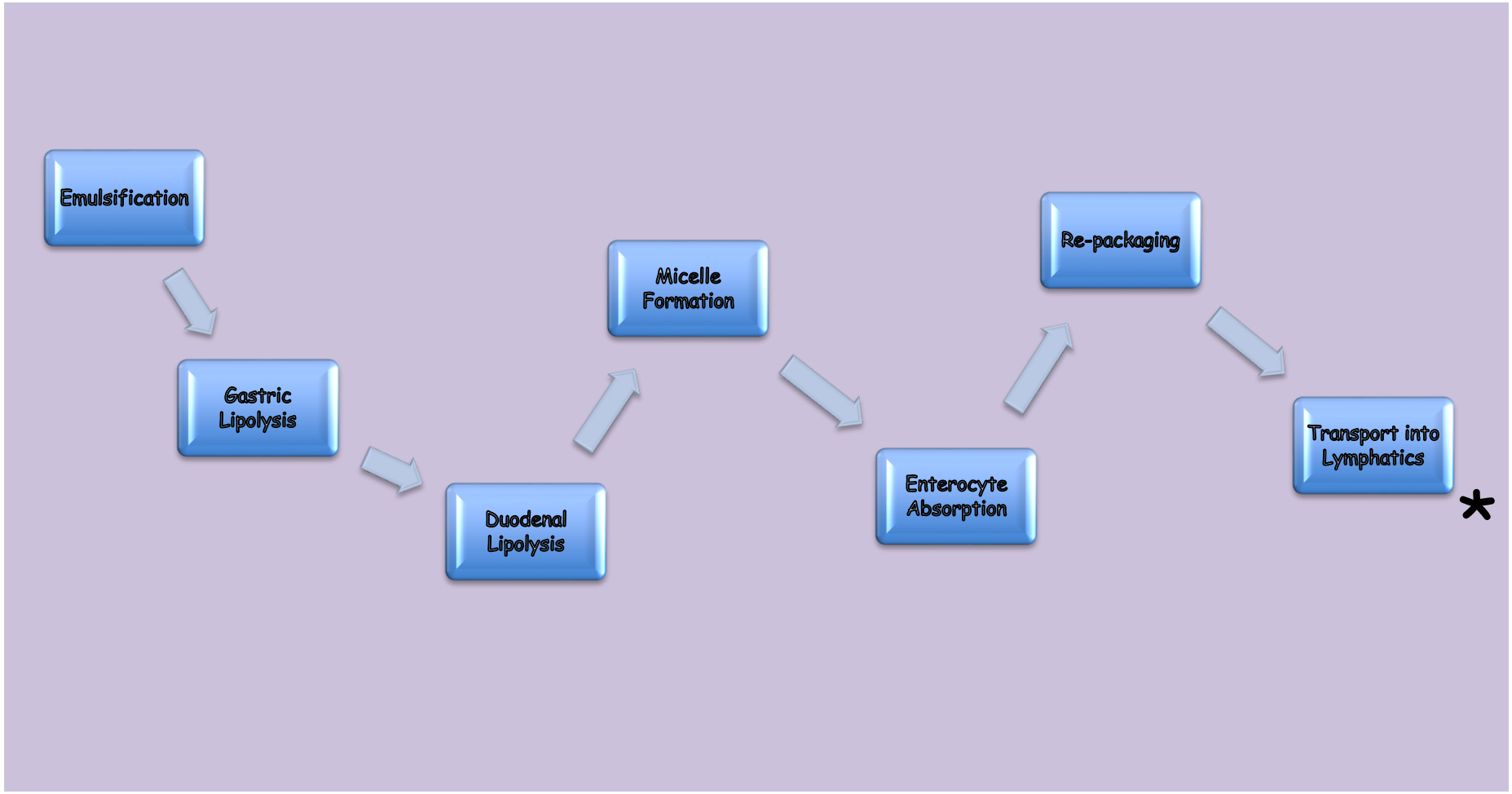
What's in a chylomicron?

- **Apolipoproteins**-act as cofactors for enzymes or ligands
- **Phospholipid and cholesterol coat**
- **Core**- TGs, cholesterol esters, vitamin esters (90% of weight)



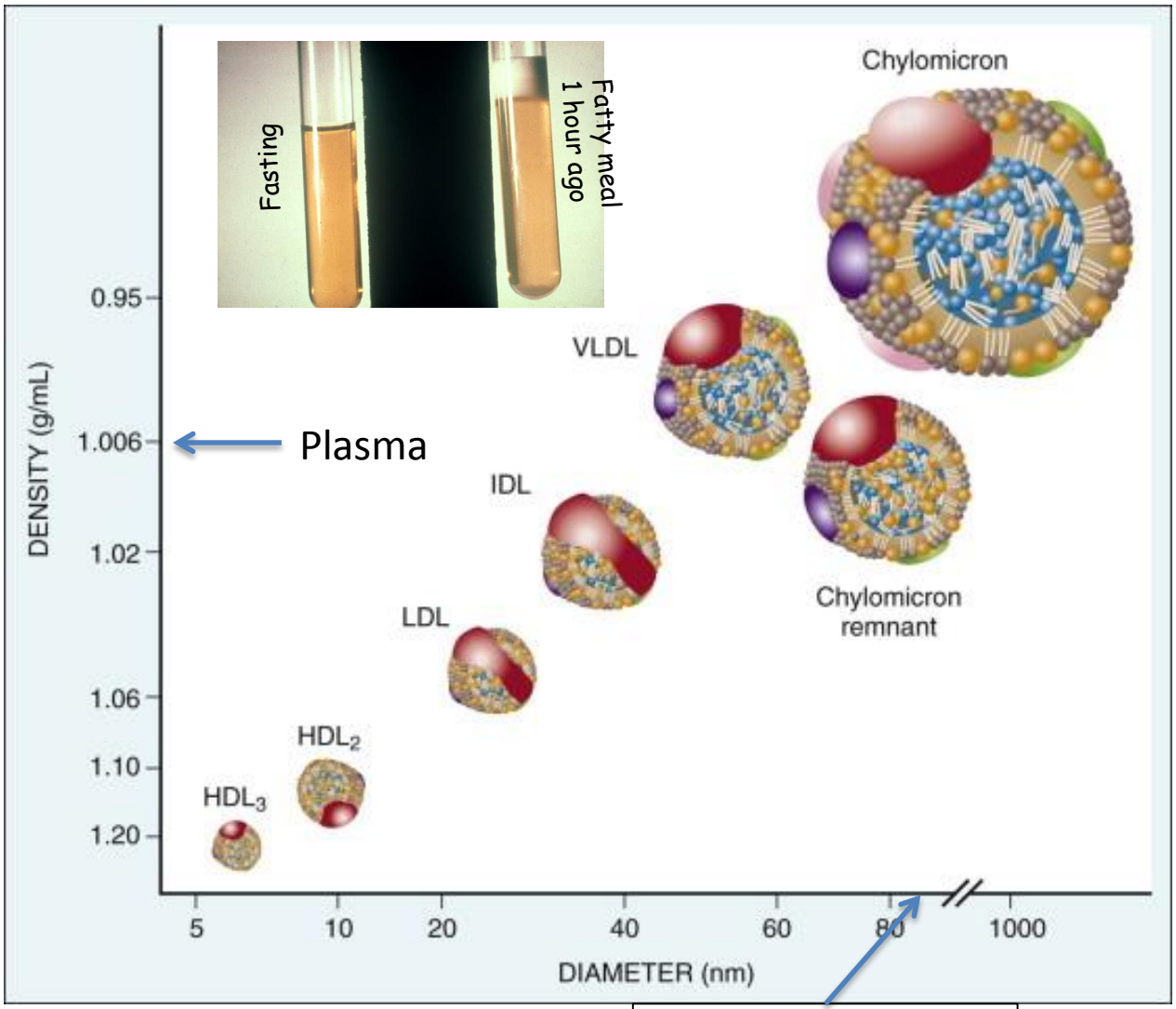
Courtesy of L Gordon and C Thaxton

Overview of Fat Digestion

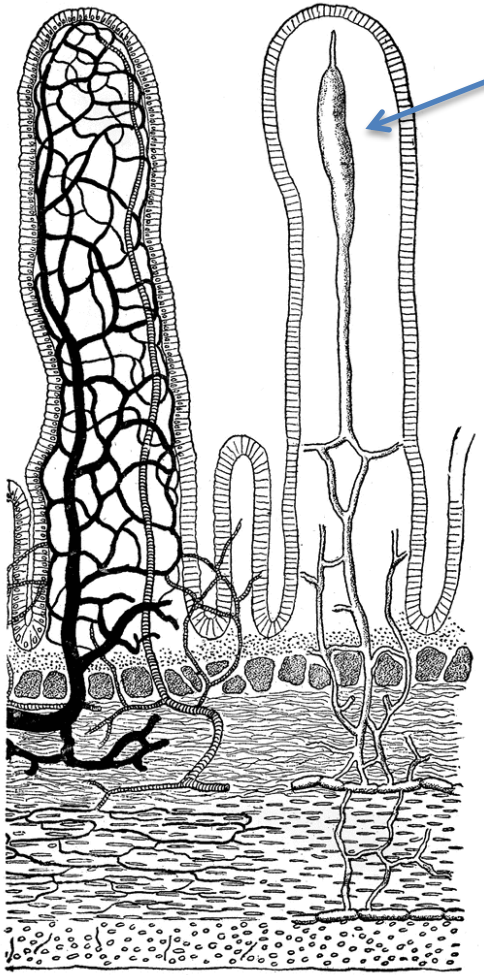


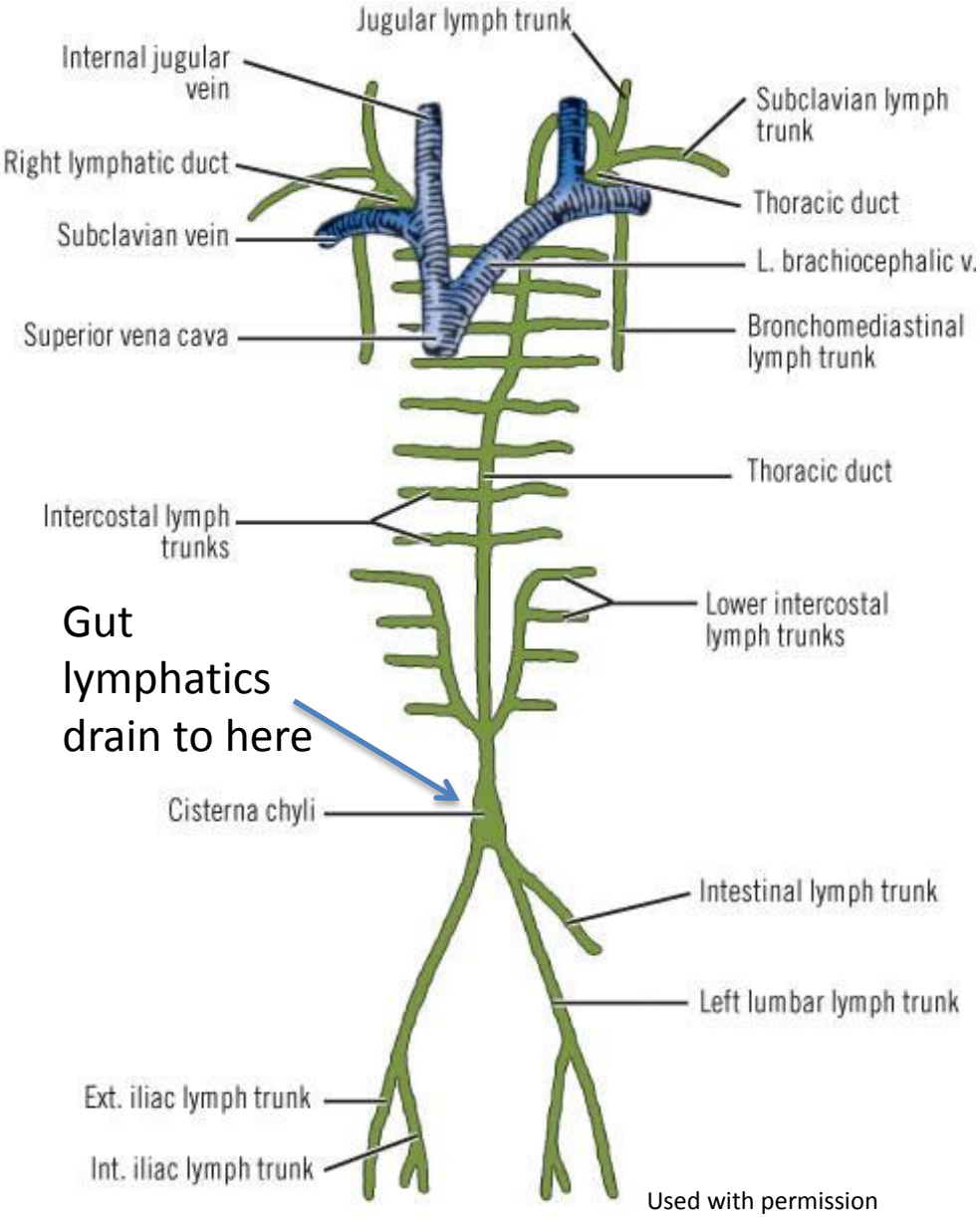
Chylomicrons to Systemic Circulation

- Released basolaterally
- Admission
  - Capillary endothelium-no
  - Lymphatic endothelium-yes
- Peristalsis
- Lymph channel contractility



Lymphatic Topography





Used with permission

Skandalakis JE, Colborn GL, Weidman TA, et al: *Skandalakis' Surgical Anatomy*: http://www.accesssurgery.com

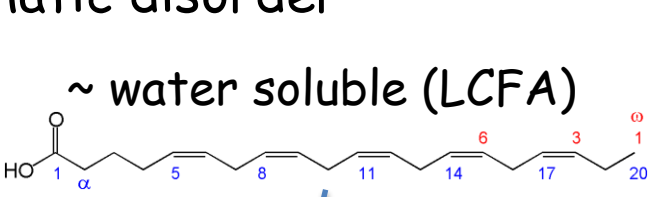
http://etc.usf.edu/clipart/15400/15463/sminttrans_15463.htm

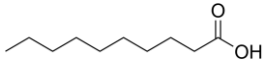
Medium-chain FAs

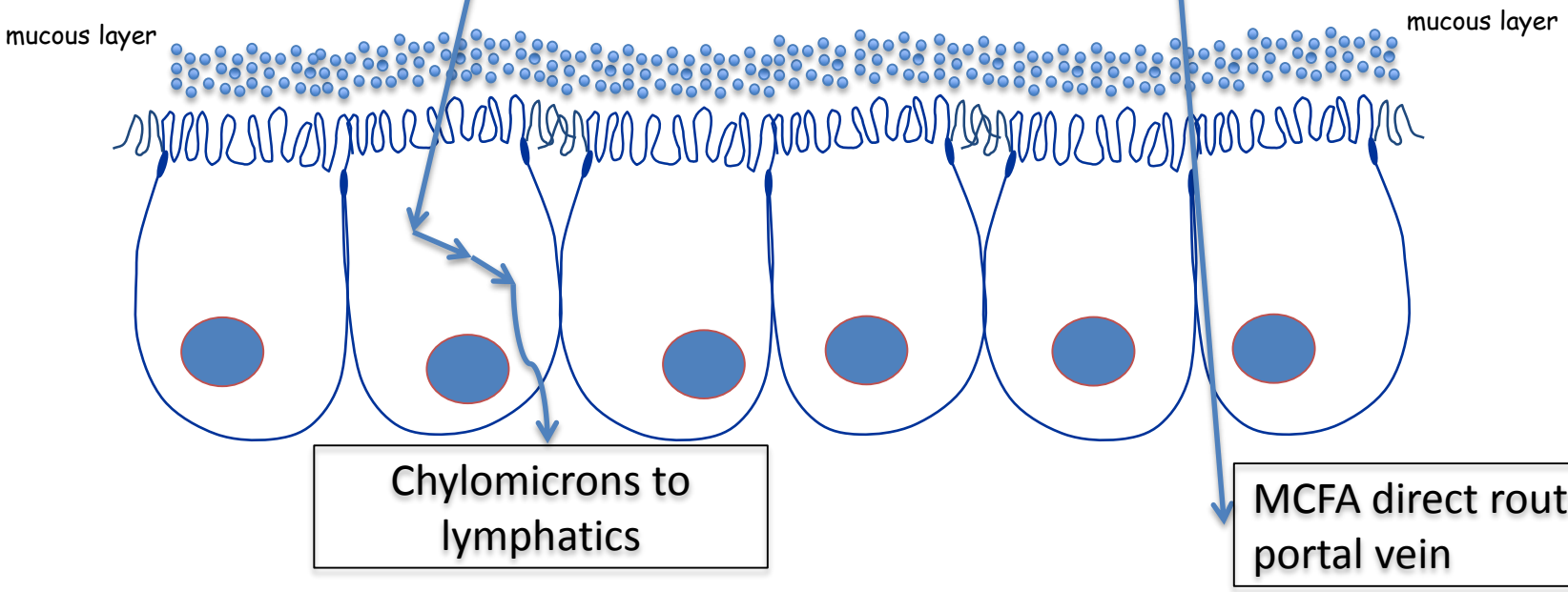
Implications?

- Short bowel syndrome
- Bile salt deficiency
- Lymphatic disorder

- More water soluble (MCFA)
- Hydrolyzed quickly, gastric lipase especially
- May be absorbed in the stomach!
- Paracellular movement

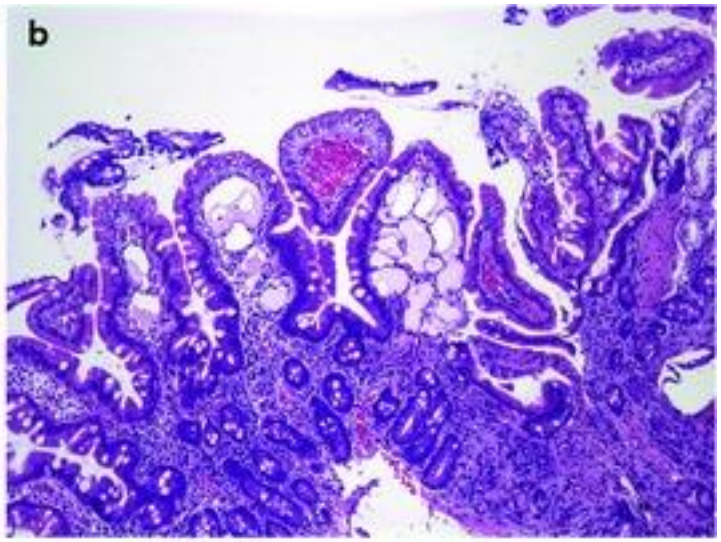


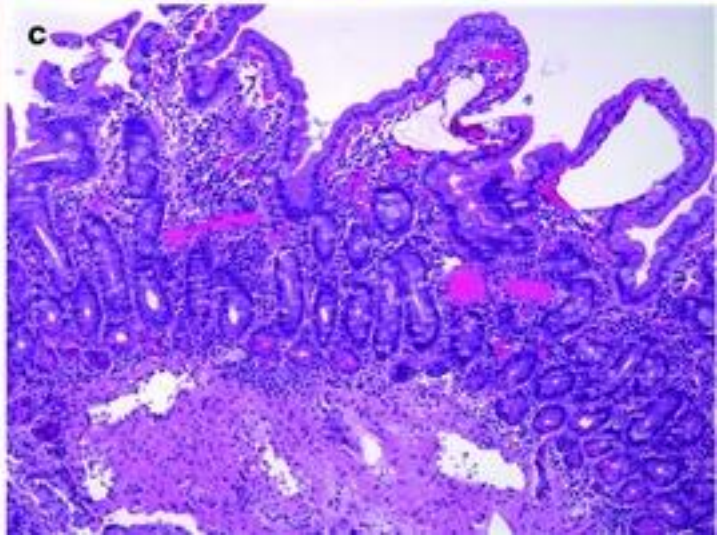




Clinical Correlation- 1º lymphangiectasa

a duodenum- mucosa studded with white nodules characteristic of IL; **b, c** duodenal biopsy from patient with IL-- villi are distorted by dilated lymphatics (H and E x100)



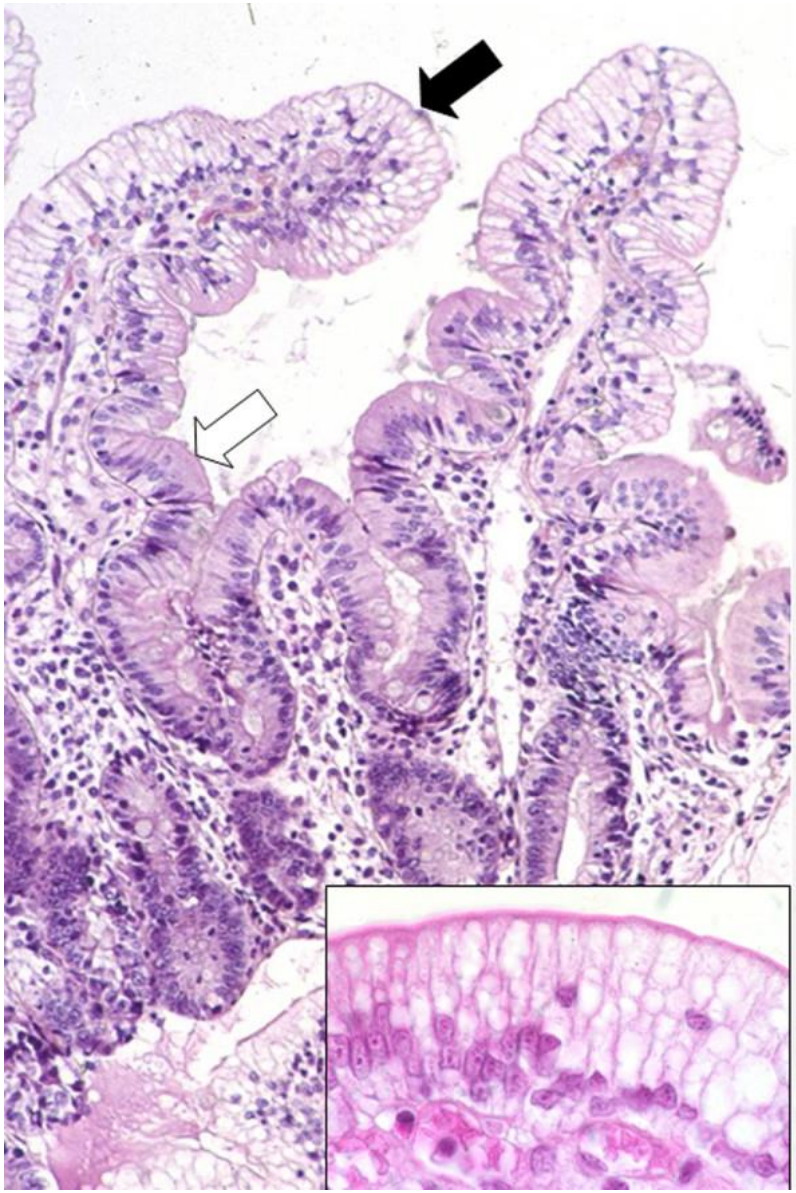


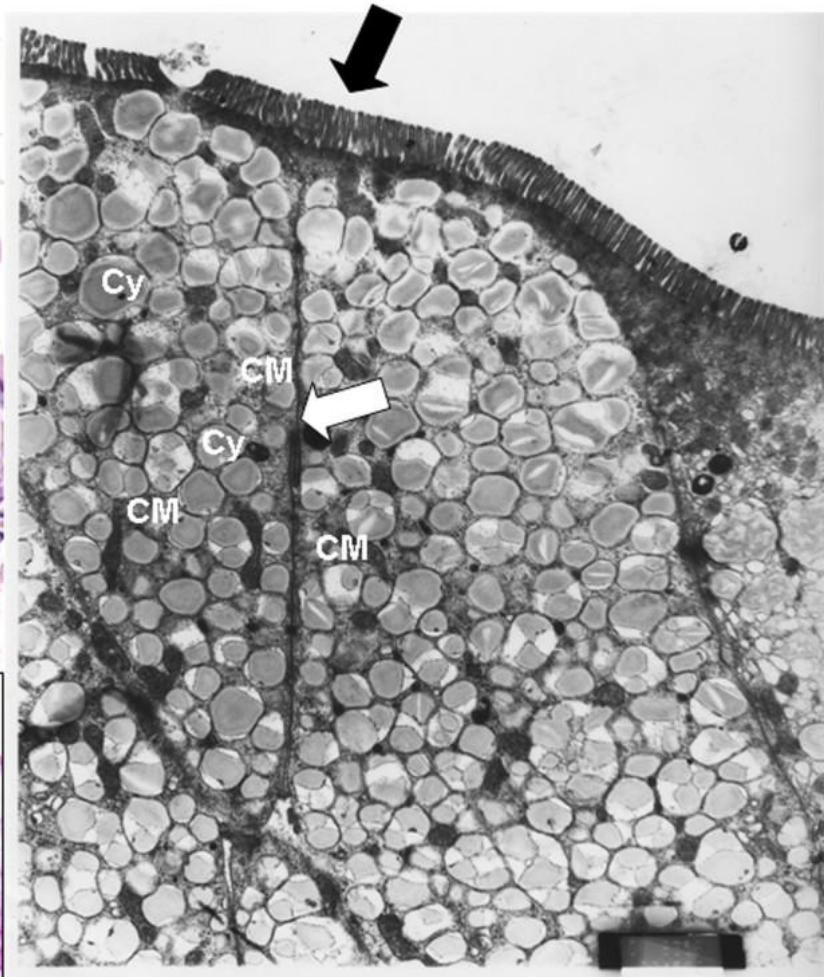
Problems: diarrhea, hypoproteinemia, edema
Physiology: lymph leakage into lumen
Fix: decrease lymph flow
Nutrition script: MCT-based fats, high protein

From SpringerImages library

Hauser et al. JPGN Image of the Month February 2009
http://www.naspghan.org/content/101/en/duodenal

What is going on?





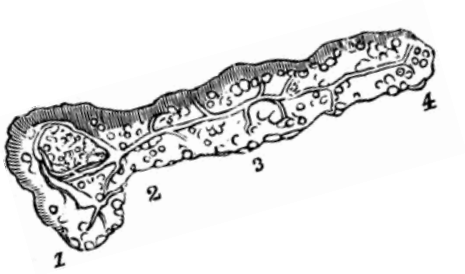
Left: micrograph of enterocytes filled with fat globules; Right: EM of enterocytes filled with vesicles containing chylomicrons

Peretti *et al. Orphanet Journal of Rare Diseases* 2010 **5**:24 doi:10.1186/1750-1172-5-24 (used with permission)

Thought Question-4 chylomicron retention disease

A child has enterocytes that cannot secrete chylomicrons

- Q1: would medium-chain triglycerides in place of long-chain result in less steatorrhea?
- Q2: A colleague proposes giving pancreatic enzymes. Would this be effective?
- Q3: Another colleague proposes giving massive amounts of predigested omega-3 fatty acids. And this?
- Q4: Water-miscible vitamin preparations allow even vitamin E to be easily absorbed without bile salts. Would this work for this child?



Summary Points

1. Fat digestion is most complicated because vital nutrients that are insoluble in water have to transfer efficiently and safely from one aqueous environment to another through a layer of cells.
2. This problem is solved by enzymes that can work on the surface of emulsion particles;
3. AND, by lipolytic break down products which can be solubilized in micelles.

http://etc.usf.edu/clipart/38800/38801/pancreas_38801.htm
http://images4.wikia.nocookie.net/__cb20121217140702/popeye/images/d/d2/Normal3.JPG

Summary Points- 2

3. Critical processes include:
   - mechanical breakdown to form an emulsion
   - enzymatic hydrolysis of triglyceride mostly on account of pancreatic lipases
   - transfer of hydrolysis products into micelles when bile acids are in adequate supply
   - enterocyte transport
   - repackaging into chylomicrons
   - transfer out of enterocytes through lymphatic channels to the blood for systemic delivery

Summary Points-3

4. Pancreatic and biliary secretions are provoked by release of secretin and CCK in the duodenal mucosa.
5. Bile salts are conserved by their entero-hepatic circulation; synthesis of bile acids is tightly controlled.
6. Fatty acids and fat soluble vitamins are delivered to the enterocyte membrane in mixed micelles. Transfer across the membrane occurs passively and by facilitated diffusion.

Summary Points-4

7. Most fats are re-esterified and packaged into chylomicrons and exit basolaterally via exocytosis for transport to lymph channels and then via thoracic duct to systemic circulation.
8. Medium-chain triglycerides are more readily hydrolyzed in the stomach, released fatty acids have greater water solubility that long-chain counterparts, and can reach systemic circulation via the portal vein bound to albumin.

Boards-style Questions-pancreas

- Which explanation seems most plausible in the case of a patient with cystic fibrosis and new GJ feeds who is having worsening oily stool and poor weight gain?
  A. The proton pump inhibitor dose is too high; intense acid suppression is inhibiting duodenal lipolysis.
  B. The pancreatic enzymes are not being given in the GJ tube.
  C. The formula is being delivered beyond the stomach-gastric lipolysis cannot contribute to intraluminal digestion.
  D. A formula switch occurred that contain mostly long-chain triglycerides.

Boards-style Questions- bile salts

- A child with bile salt export pump (BSEP) deficiency received a biliary diversion for intractable pruritus. Stumbling at night occurs six months later. You suspect vitamin A deficiency. Which explanation is most plausible?
  A. Vitamin A is being lost in the bile.
  B. Emulsion particles are no longer stable; vitamin A esters cannot be hydrolyzed.
  C. Unabsorbed fatty acids are forming soaps and the precipitant removes vitamin A from the lumen.
  D. Vitamin A esters are being hydrolyzed but inadequate micelle formation prevents enough Vitamin A from reaching brush border for absorption.

Boards-style Questions- lymph

- A child with neuroblastoma has chylous ascites 4 days after the tumor is resected. The child is made NPO and started on parenteral nutrition. True or False:
  - A. Parenteral nutrition will improve ascites because intravenous fat will get incorporated into chylomicrons in the thoracic duct.
  - B. Exclusive medium-chain triglyceride (MCTs) diets would also work because of MCT's suppressive impact on chylomicron exocytosis.
  - C. Parenteral nutrition will not help because IV fat still will get incorporated into chylomicrons in the interstitium.
  - D. A balance of medium and long-chain triglycerides in the diet would prevent ascites because the medium chain fatty acids would complex with long chain acids and albumin in plasma.

Please send any questions or comments to:

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or

- Daniel.Kamin@childrens.harvard.edu