

November 2005

HST 121
Gastrointestinal Pathophysiology
Midterm Review Topics (5.0)

Section 1: Overview of Embryology (Glickman)

Important embryologic abnormalities:

- Esophageal atresias
- Congenital pyloric stenosis: non-bilious, projectile vomiting in month-old infant
- Duodenal atresia (affects premature & Trisomy 21 infants more than normal)
- Annular pancreas (duodenal obstruction in infancy, pancreatitis/malignancy in adulthood)
- Omphaloceles/umbilical hernias/gastroschisis (MIDgut abn)
- *Ileal diverticulum (Meckel's)*; A portion of the bowel along the Ileum that may be left over from development. More common in males, the rule of 2's – 2'' in length, 2 ' from ileocecal valve, 2% of population, most Sx before 2 years old.
- Volvulus
- Anorectal anomalies
- *Hirschsprung's disease* (dilation of proximal colon due to narrowing/increased luminal pressure in distal colon); due to absence of autonomic ganglion cells in distal colon; the most common cause of neonatal colonic obstruction.

Remember your pathology/anatomy:

- Layers of digestive tract wall (epithelium, lamina propria, muscularis mucosae, submucosa, muscularis propria, adventitia/serosa)
- Extrinsic nervous systems:
 - Parasympathetic: usually EXCITATORY, leads to smooth muscle contraction, vasodilation, secretion of enzymes (pepsin, etc.). SLUDGE (salivation, lacrimation, urination, defecation, GI upset and emesis) symptoms if parasympathetic over-stimulation. Vagus nerve (to upper large intestine)+pelvic nerve
 - Sympathetic: usually INHIBITARY. Inhibits smooth muscle contraction and causes vasoconstriction.
- Enteric/Intrinsic nervous systems:
 - Auerbach's (aka "myenteric plexus" between two layers of muscularis propria): primarily controls motility of GI smooth muscle
 - Meissner's (in submucosa): primarily controls secretion and blood flow
- Blood supply: in via celiac to duodenum, SMA from duodenum to proximal 1/3 of transverse colon, IMA from there to the rectum; out via portal vein to liver.

Section 2: Overview of Physiology (Glickman)

How is the function of the GI tract reflected in its structure?

A simple understanding of the overall structure/function specialization of the GI tract will help you reason through some of the pathophysiological derangements encountered later in the course.

Things to know, and that underlie much of your understanding of the later material

- What are the four layers of the prototypical wall of the GI tract
- Do know the four major GI hormones: Gastrin, CCK, Secretin (think of it as the counter-hormone of Gastrin) and GIP
- Think about the functions of the GI tract, and how they are necessary for organismal survival.

Section 3: Gastrointestinal Pathophysiology (Strate)

Acid Secretion/The Parietal Cell

Why do we need acid in our stomachs?

→to convert pepsinogens to pepsins (which digest 15% of dietary protein), prepare iron for absorption, prevent bacterial overgrowth, activate gastric lipase.

What happens if there too much/too little acid production? How can the former be treated pharmacologically and what is its role in peptic and duodenal ulcer disease?

How does the parietal cell secrete acid?

→Increased cAMP and Ca^{++} stimulate the parietal cell: tubulovesicles fuse with secretory canaliculus and H^+/K^+ ATPase (proton pump) is activated to secrete H^+ into lumen.

→secreted in circadian pattern, higher in evening

→basal level regulated by vagal tone and local histamine

Parietal cell regulation from inside out, and the pharmacologic targets in treating PUD:

1. How to ↑ acid secretion:
 - a. Histamine (paracrine stimulation): H_2 receptor is linked to G_s , which stimulates adenylate cyclase, increasing cAMP. Histamine release also stimulated by acetylcholine.
 - b. Gastrin (endocrine stimulation) and acetylcholine: receptor and acetylcholine receptor (M3) are linked to G_p , which stimulates phospholipase C (PLC), leading to increased Ca^{++} .
2. How to ↓ acid secretion:
 - a. Somatostatin and prostaglandins E are linked to G_i , which inhibits adenylate cyclase, decreasing cAMP.
 - b. Secretin also decreases acid production through not entirely clear mechanism
3. Histamine is the dominant controller of acid secretion.

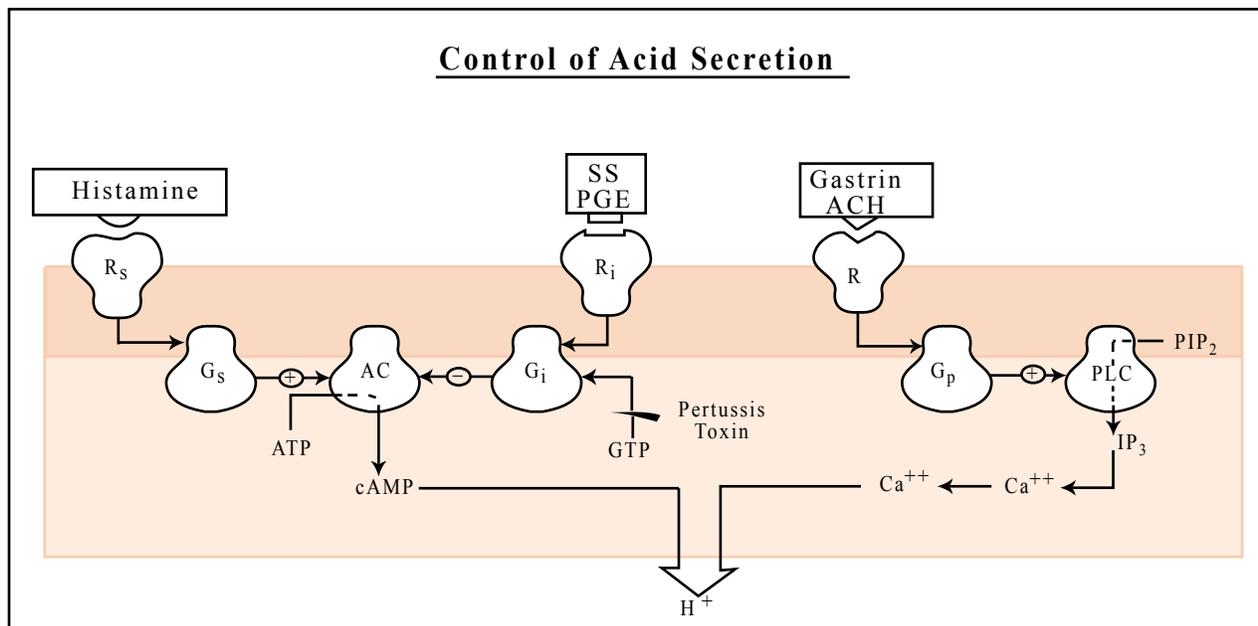


Figure by MIT OCW.

Mucosal Integrity: a balance between protective and damaging factors

Protective factors:

- Bicarbonate & mucus secretion by surface foveolar cells—stimulated by luminal acid, cholinergic (vagal)

stimulation, and prostaglandins. Bicarbonate is decreased by histamine, anoxia, NSAIDs, bile salts. Mucus is decreased by aspirin, NSAIDs, ethanol, bile salts.

- Blood flow (brings bicarbonate, growth hormones like EGF, FGF which help stimulate quick epithelial renewal)
- Prostaglandins and nitric oxide stimulate mucus & bicarbonate secretion, increase blood flow, and inhibit acid secretion.
- Rapid epithelial cell renewal

Injurious factors which damage the protective barrier:

- Main physiological one is acid.
- Pepsin
- Aspirin and other NSAIDs damage cell directly and indirectly by blocking the “good” prostaglandins as well as the “bad” ones responsible for inflammation.
 - Cox-1 (PGHS-1) begins pathway leading from arachidonic acid to cytoprotective prostaglandins.
 - Cox-2 (PGHS-2) leads from AA to inflammatory mediators.
 - Can lead to peptic ulcers; treat by stopping NSAID or by giving misoprostol (synthetic prostaglandin), H₂ blocker (ranitidine), proton pump inhibitor (omeprazole).
- Cigarette smoking.
- Bile acids/activated pancreatic enzymes.

Duodenal physiology (brief discussion)

Main histologic features

- Tall columnar absorptive epithelium with microvilli
- Crypts with stem cells for epithelium and Paneth cells (immunological function) at base
- Mucus secretion by goblet cells and Brunner’s glands (in submucosa)
- I cells (also in jejunum) secrete CCK; S cells secrete secretin

Peptic Ulcer Disease

→ can present in stomach or duodenum

→ Risk factors include the injurious factors listed above plus chronic renal, lung, liver disease. 10% lifetime risk in US population (not all symptomatic)

→ H. pylori is associated with 90% of peptic ulcers.

→ H. pylori causes chronic superficial gastritis, which may progress to chronic atrophic gastritis and gastric adenocarcinoma; chronic infection also associated with MALT lymphoma

1. Drugs to treat H. pylori, use a combination of bismuth+antibiotics+proton pump inhibitor.

Trivia: MALT lymphoma probably the only cancer curable with antibiotics: most cases recede after the eradication of H. pylori. The rest treated with XRT.

2. To reduce acid:

- Antacids that neutralize acid after secretion.
- Sucralfate polymerizes into thick paste at low pH. It adsorbs to ulcers, forms protective layer.
- H₂ blockers are histamine antagonists that stop parietal stimulation & acid secretion. Examples are famotidine, ranitidine, nizatidine, cimetidine.
- Proton pump inhibitors block the H⁺/K⁺ ATPase in parietal cells. Major one is omeprazole.

3. EGD (Esophagogastroduodenoscopy) can be used to clip bleeding ulcers.

Surgery is required after perforation or obstruction occur (distal gastrectomy, vagotomy).

If PUD is not responsive to medical therapy, consider: Zollinger-Ellison Syndrome and malignancy

Section 4: Pathology/Non-Neoplastic Diseases of Esophagus & Stomach (Glickman)

Esophagus

Anatomy/Histology/Physiology:

- Epithelium is non-keratinized stratified squamous.
- Submucosa contains mucin-producing glands and *venous channels* connecting portal and systemic venous systems (important because of esophageal varices).
- Muscularis propria is under vagal control.
- Adventitia communicates with mediastinum; contains lymph nodes.
- Upper esophageal sphincter (UES): normally contracted, relaxes on swallowing. Loose network of skeletal muscle—mural weakness can allow *Zenker's diverticulum* to form.
- Lower esophageal sphincter (LES): high-pressure area that keeps gastric contents out of esophagus; relaxes on swallowing. Sensitive to hormonal & cholinergic action. Failure to relax leads to *achalasia*.

Disorders:

- Congenital: atresia/fistula (see above), cysts, webs/rings (may cause obstruction)
- Motor-mechanical:
 - Diverticula: Two types are pulsion (eg., Zenker's) from outpouching of weak areas, and traction from pulling out on wall by process like inflammation of lymph nodes (traction, TB, tracheal bifurcation). Diverticula hold food and can lead to stasis/infection/ulceration/obstruction.
 - Fistulae/stenoses from many processes, eg., trauma, tumor, inflammatory strictures.
 - Hiatal hernia: found to some degree in 50% of people. Stomach protrudes up through diaphragm around/near esophagus. Minor forms are benign.
 - Achalasia: narrowed LES leads to chronic obstruction and dilation of esophagus.
 - Scleroderma: fibrosis can involve LES and lead to reflux esophagitis.
- Vascular:
 - *Esophageal varices* due to portal hypertension. These dilated veins can *rupture*, leading to massive bleeding.
 - Ischemia is rare but can occur if dilation leads to pressure on mucosa & venous stasis.
- Inflammatory:
 - *Reflux esophagitis* is most common cause of esophagitis in US (may affect 5% of people). Incompetent LES/faulty esophageal motility leads to gastric reflux/mucosal injury.
 - Acute: neutrophils, eosinophils, necrosis, hyperplasia, longer/more papillae.
 - Chronic: fibrotic stricture, *Barrett's esophagus* (glandular/columnar metaplasia of mucosa), 30-40x risk of *adenocarcinoma* if the metaplasia is *specialized (intestinal-type)*, i.e., contains goblet cells.
 - Also due to infections (in immunosuppressed), corrosive chemicals ingested, radiation

Stomach

Anatomy: cardia, fundus, corpus (body), antrum, pylorus.

Histology & Physiology

Mucosa:

CELL TYPE	WHERE	HOW DEEP	FUNCTION	MISC
Foveolar	everywhere	surface & pits	secrete mucin & bicarbonate	columnar with sparse microvilli

Mucous neck	everywhere	neck/isthmus	stem cells for foveolar, parietal, chief cells	columnar/flask-shaped with sparse microvilli
Cardiac & pyloric mucous	cardia & pylorus	throughout gland	secrete mucin, aid in neutralizing gastric acid	similar to Brunner glands of duodenum
Parietal (Oxyntic)	corpus & fundus	neck/isthmus	secrete HCl & intrinsic factor	pyramidal, eosinophilic (lots of mitochondria), secretory canaliculus
Chief (Zymogenic)	corpus & fundus	base of gland	secrete pepsinogen & gastric lipase	cuboidal, basophilic (lots of ribosomes)
G	Pylorus	deep against basement membrane	secrete gastrin	fried-egg appearance
EC	corpus/pylorus	same as G	secrete 5-HT (serotonin)	fried-egg appearance
D	corpus/pylorus	same as G	secrete somatostatin	same as G & EC
ECL	Corpus	Same	secrete histamine	Same

Muscularis externa has 3 muscle layers. Peristalsis (stimulated by gastrin and vagus) in antrum mixes food, delivering semiliquid chyme to bowel. Pyloric sphincter prevents duodenal reflux.

Disorders:

- Gastritis—can be acute or chronic, diffuse or focal, with or without mucosal atrophy/metaplasia.
 - Acute: caused by stress, salicylates, NSAIDs, ethanol, steroids, bile reflux, *H. pylori*. Damage to mucosa leads to tissue acidosis & injury. Heals upon removal of inciting agent.
 - Chronic:
 - *Helicobacter pylori*-associated is most common type (chronic active gastritis, esp in antrum); increases risk of gastric adenocarcinoma & lymphoma.
 - Atrophic: chronic inflammation leads to atrophy of parietal & chief cells, pyloric/intestinal metaplasia, ↑ adenocarcinoma risk. Loss of parietal cells → ↓ gastric acid & ↓ intrinsic factor → ↑ gastrin production & G cell hyperplasia (may lead to carcinoid tumor) and ↓ B₁₂ absorption → pernicious anemia.
- Acute Stress Ulcer: develop 6-14 days after stress such as extensive burns (Curling's ulcer) or CNS injury (Cushing's ulcer). Commonly multiple erosions/ulcers in stomach. Pathogenesis unclear (hyperacidity, ischemia, drugs?).
- Peptic Ulcer Disease (PUD): 80% duodenum/20% stomach. Strongly associated with *H. pylori* (found in 100% of duodenal ulcers, 70% of gastric ulcers, 45% of people in US). Single, deep, focal ulcers with well-defined margins as compared with ulcerating carcinomas with irregular contours & overhanging margins. Complications are hemorrhage, perforation, obstruction, recurrence.
- Zollinger-Ellison Syndrome: ↑ gastrin production → parietal cell hyperplasia & ↑ gastric acid → multiple erosions/ulcers, malabsorption. Gastrin most often made by a tumor of pancreatic islet cells.
- Menetrier's Disease: Hyperplasia of surface foveolar mucous cells → ↑ mucus, which may lead to protein-losing enteropathy and hypochlorhydria. Also produces hypertrophic rugae.
- Portal hypertension may also lead to varices in the stomach.

Section 5: Mucosal Immunity (Blumberg)

The first part of the section notes is a review of immunology. The focus of the notes is the gut-associated lymphoid tissue (GALT), which is part of the body's mucosa-associated lymphoid tissue (MALT).

Components

Natural intestinal immunity is composed of immunologic & non-immunologic systems. Non-immunologic barriers include: gastric acid, digestive enzymes, bile acids, lysozymes, mucus, peristalsis, indigenous microbial flora, epithelial cell tight junctions.

GALT has one component in the epithelium:

1. Intraepithelial lymphocytes (IELs), which reside between intestinal epithelial cells along their basolateral surface.

- Most IELs are CD8 cells with the α/β T-cell receptor, and CD45RO. Thus, they are memory cells that recognize MHC class I molecules.
 - Especially in the colon, 5-30% of IELs express the γ/δ T-cell receptor, unlike T cells that are not in the epithelium.
- IELs are oligoclonal; thus, they are memory cells with a limited repertoire.

a. Major biologic function is cytokine secretion (IFN- γ), but when activated they become cytolytic that contribute to epithelial death through apoptosis.

b. Thought to be first line of defense against abnormal epithelial cells & mediation of oral tolerance. (large number, cytolytic capability, extremely limited TCR repertoire—suitable for immunosurveillance)

c. Apart from the IELs, absorptive intestinal epithelial cells can function as APCs since they constitutively express MHC class II molecules.

GALT has two components in the lamina propria:

1. Organized compartment, which is the afferent limb of the GALT

- Follicle-associated epithelium, which contains M-cell (derived from intestinal crypt stem cell) samples luminal antigens, transcytosing them to antigen-presenting cells. M cells cover the underlying Peyer's patches. **Selective sampling**
- Peyer's patches (lymphoid aggregates), where naive T and B lymphocytes are activated through DC/macrophage presentation of antigens. They subsequently leave the lymphoid follicles and drain into mesenteric LN—thoracic duct—peripheral blood—homing to original antigenic stimulation and other mucosal sites such as lungs. **Activation**

a. Let's begin in the lamina propria: M-cell associated with a Peyer's patch transports antigen from intestinal lumen,

allowing macrophages & other APCs to present antigen to naive lymphocytes within the Peyer's patch. These lymphocytes home to the Peyer's patch by interacting with molecules on endothelial cells of post-capillary venules in the lamina propria, including

- integrins ($\alpha 4\beta 7$ on lymphocytes)
- L-selectin and LFA1 on lymphocytes
- MadCAM-1 and ICAM on endothelium

b. Activated lymphocytes migrate out of intestines via lymphatics, becoming enriched in IgA B cells. Once in the peripheral blood, these lymphocytes return to the gut.

c. Again, they home to the gut lamina propria through interactions with endothelial cells of post-capillary venules. There they become part of the non-organized compartment.

2. Non-organized compartment, which is the **effluent** limb of the GALT

- loosely distributed through lamina propria: plasma cells, B cells (predominantly IgA producing), T cells natural killer cells, PMNs, mononuclear phagocytes, mast cells.
- In the non-organized compartment, lymphoid cells are 60% T/40% B.
- the T cells:
 - occur in a CD4:CD8 ratio of 2:1, as in the blood
 - express the α/β T-cell receptor
 - express CD45RO, indicating that they are memory cells (probably having seen antigen in the Peyer's patches)

- the CD4 cells are mostly helper/inducer cells for Ig production
 - mostly have an activated phenotype (CD69, high intracellular calcium)
 - thus, the gut is in a state of “physiologic inflammation,” ready to pounce if necessary
 - the B cells:
 - mostly focus on IgA synthesis (& less on IgM, IgG, IgE)
 - are induced to divide and grow by IL-4 and IL-5
 - are induced to differentiate terminally into IgA plasma cells by IL-6
- a. So the T & B cells focus on Ig secretion. How does IgA secretion into the lumen work?
- Epithelial cells synthesize polymeric immunoglobulin receptor (PIgR) in their ER and Golgi and express PIgR on the basolateral membrane, facing the lymphoid cells.
 - Plasma cells secrete dimeric IgA, which binds to PIgR & is endocytosed.
 - The whole PIgR-IgA complex is transported in vesicles to the apical side, where the intact IgA plus a piece of PIgR called secretory component are secreted into the lumen.
 - Secretory component remains bound to IgA in the intestinal lumen, and it may stabilize or protect IgA from proteolysis.
- b. What is the function of IgA?
- In the lumen, IgA inhibits bacterial adherence to epithelia, neutralizes bacterial toxins, binds to and neutralizes viruses, and blocks absorption of antigens from the gut.
 - IgA is secreted into the bile, where it protects the biliary tract & proximal small bowel. IgA-antigen complexes are also secreted into bile, thus possibly ridding the circulation of harmful absorbed antigens.
 - IgA is able to neutralize intracellular pathogens in cells that possess the PIgR pathway.
 - IgA does not activate complement or enhance opsonization.

Section 6: Motility of the Alimentary Tract (Goyal)

Neural Control:

- Skeletal muscle neural control: Lower motor neurons control skeletal muscles of oral cavity and external anal sphincter. Muscles respond to acetylcholine via nicotinic receptors.
- Smooth muscle neural control:
 1. Extrinsic: connector between enteric and CNS. speeds up and slows down activity controlled by enteric system
 Sympathetic nerves act via norepinephrine, inhibiting motor activity except in sphincters
 Parasympathetic nerves stimulate esophageal peristalsis, gastric emptying (vagus nerve), and anorectal activity (sacral nerves) but have little effect on intestines. (Case in point: urinary retention 2/2 BPH can be relieved by a combination of terazosin, an alpha-1 antagonist to relax the bladder sphincter, while Bethanechol, a parasympathomimetic is used to promote bladder smooth muscle contraction.)
 2. Enteric nervous system (myenteric/submucous plexuses): “displaced CNS” coordinates peristalsis, sphincter relaxation, etc. Diverse array of chemical mediators: Ach, GABA, VIP, ATP, serotonin, and most recently NO. Pay particular attention to its function in control of sphincter tone: 1> tonically contracting smooth muscles; 2> The Yin-Yang of sphincter relaxation: balance between NO/VIP releasing enteric neurons and cholinergic enteric neurons

Types of electrical activity:

- Slow waves, or pacemaker potentials, or electrical control activities, are oscillatory changes in membrane potential that may cause a small amount of contraction.
- Spike potentials, or electrical response activity, lead to phasic or tonic muscle contraction.
- Pacemaker cells for spikes are the interstitial cells of Cajal.

Types of muscle activity:

- electromechanical coupling/pharmacomechanical coupling leads to \uparrow intracellular Ca^{++} in muscle cell; can be blocked by calcium channel blockers
- propagated waves: can move intestinal contents forward (aboral, peristaltic) or backward (oral, antiperistaltic)

- nonpropagated contractions (spastic, segmental) mix intestinal contents
- longitudinal muscle contractions slide intestine over the food in the lumen

Movement of Food

Oral Cavity: swallowing is voluntary

Oropharynx: involuntary swallowing reflex leads to beginning of peristaltic wave

Esophagus:

- UES relaxes before bolus of food arrives
- peristalsis initiated in pharynx (*primary peristalsis*) continues
 - secondary peristalsis is what occurs in response to esophageal distention not swallowing
- LES relaxes before food bolus arrives (under influence of VIP and NO)

Stomach:

- stomach relaxes (mediated by vagus) as food reaches it from the esophagus
- after meal, terminal antrum contracts against closed pylorus to grind & mix food
- higher volume of gastric contents → ↑ rate of gastric emptying
- ↑ osmolarity, pH < 3.5, fats → ↓ rate of gastric emptying
- during digestive period, only liquids & small particles leave stomach
- 2-4 hours after meal, stomach is empty

Small Intestine:

- During digestion, *fed pattern* occurs—segmental contractions to mix food with enzymes and aid in absorption. A few aboral contractions gradually move food.
- After digestion/absorption, *interdigestive migrating motor complex* (interdigestive housekeeper) begins in duodenum (initiated by hormone motilin). Segmental and propulsive contractions alternate with inactivity. MMC reaches terminal ileum in 1.5 hours.
- *Giant peristaltic contraction* is high-amplitude contraction of 20-30cm segment of distal small intestine/colon that propagates uninterrupted. Occurs periodically. Associated with diarrhea/abdominal cramps/defecation.

Gallbladder/Sphincter of Oddi: CCK causes gallbladder contraction, Sphincter of Oddi relaxation.

Colon:

- short & long segmental contractions occur in mostly nonpropulsive trains; aid in mixing and storage
- mass movement/giant peristaltic contraction results in rapid shift of large volume towards more distal part of colon
 - gastrocolic reflex & orthocolic reflex
 - can result in defecation

Rectum/Anus: Defecation reflex: stretching of rectum wall initiates reflex—efferent parasympathetic signals sigmoid colon/rectum to contract and internal anal sphincter to relax (involuntary)—if not ready, reflex ends, external sphincter contracts voluntarily—reflex re-initiated until you go

Motility Disorders:

Achalasia: Two features: tonically contracted LES and dysfunctional esophageal peristaltic contractions due to loss of myenteric neurons or selective loss of VIP/NO neurons. Etiology: idiopathic; Chagas; Parkinson's; Herpes infection
 HD-aganglionic megacolon

Section 7: Lipid Digestion, Absorption, Malabsorption (Carey)

We need fat because:

- source of chemical energy and essential fatty acids
- fat soluble vitamins A, D, E, K

Fat digestion occurs best at water-lipid interface where lipases are most active (lid is open). Therefore, *emulsions* of fats in phospholipids are best for digestion. Phospholipids decrease amount of energy needed to emulsify fats.

Lipases produce mixed micelles and unilamellar vesicles from emulsified particles.

- human milk lipase (in human milk) only functions in duodenum/jejunum
- gastric lipase produced by chief cells functions at low pH on triglycerides
 - fatty acids released stimulate CCK to be secreted
 - digests 30% of fat
- pancreatic lipase is active in duodenum/jejunum
 - requires colipase to prevent inactivation by bile salts
 - completes hydrolysis of triglycerides
- pancreatic bile-salt-dependent lipase is active in duodenum/jejunum
 - acts on micelles: fat soluble vitamin esters, steryl esters
- pancreatic phospholipase A₂
 - only lipase requiring activation by trypsin cleavage
 - requires Ca⁺⁺
- microbial lipases are important in malabsorption, where they induce steatorrhea

Cholecystokinin (CCK) secreted in response to fatty acids

Secretin secreted in response to acid in the duodenum.

Remember their actions from above.

Activation of proenzymes:

- bile salts activate enterokinase by solubilizing it
- enterokinase activates trypsin
- trypsin activates colipase and phospholipase A₂

Absorption of Fatty Acids

1. a. Fatty acids and monoglycerides enter enterocytes via passive and facilitated diffusion. Fatty acid binding protein (FABP) in apical membrane transports FA to ER.
b. Cholesterol absorbed passively by NPC1L1 on apical membrane; 50% is returned to lumen via ABCG5/8, which is regulated by the transcription factors LXR/RXR.
2. In ER, re-esterification to reform triglycerides.
3. Apolipoproteins & lecithin added to form *chylomicrons*, which diffuse into lymphatics.
4. Also, unesterified fatty acids enter portal veins, bind albumin, end up in liver (less important).
5. Fats in chylomicra are catabolized by lipoprotein lipase.
6. Fat cells & capillaries take up fatty acids, monoglycerides. Triglycerides resynthesized by tissue lipase.
7. Fats then available for metabolic needs.

Sudan Test for Fecal Fat detects fatty acids after treating stool with acetic acid and heating in the presence of ethanolic Sudan III (dye).

Malabsorption Classification by failure of:

1. digestion (intraluminal); eg., pancreatic insufficiency (such as in chronic pancreatitis)
2. dispersion (intraluminal); eg., bile salt deficiency (such as in liver disease)
3. absorption (mucosal); eg., celiac sprue with loss of villi
4. transport (lamina propria, lymphatics); eg., abetalipoproteinemia

Many malabsorption syndromes are mixed.

Section 8: Intestinal Pathophysiology (Lencer)

Structure

Remember histology: crypts, villi, microvilli, lymphoid follicles.

Surface area amplification: cylinder → folds (3x) → villi (10x) → microvilli (20x)

Function

Barrier

1. Extrinsic barriers: mucus, unstirred aqueous layer adjacent to cells, secreted bicarbonate, hydrophobic layer consisting of phospholipid
2. Intrinsic barriers are the *major* ones:
 - Transcellular: restricts passage of hydrophilic compounds
 - Paracellular: tight junctions (zonulae occludens) are rate-limiting barrier. They allow cations in more than anions. They are more restrictive distally.

Absorption

1. General structure:
 - Villus absorptive cell is columnar with brush border (microvilli) on apical side. Cell is highly polarized, with tight junction belt around cell near apical side.
2. Note efficiency of absorption (input/output table in section notes).

Absorption of specific solutes:

- Carbohydrates: broken down by amylase (see above) and then by enzymes found at brush border (sucrase, lactase, etc.). Glucose, galactose, fructose absorbed by transporters at apical membrane. Glucose/galactose transported by SGLT1, Na⁺/Glucose cotransporter powered by basolateral Na⁺/K⁺ pump; fructose crosses apically through GLUT5. All 3 sugars cross basolateral membrane through GLUT2, via facilitated diffusion.
- Proteins: broken down by proteases & oligopeptidases found at brush border. Oligopeptides enter cells by H⁺/Peptide cotransporter powered by H⁺ gradient. Amino acids enter cells by various cotransporters that mainly use Na⁺ gradient for power. Cross basolateral membrane by facilitated diffusion, except for *L-glutamine*, the preferred metabolic substrate for absorptive cells, which may be absorbed basolaterally.
- Water: absorbed passively secondary to osmotic pressure from solute transport
- Sodium: *very important* for absorption of water, most water-soluble nutrients & ions. Paracellular pathway/solvent drag important (50%) in jejunum/ileum. Driving force for transcellular pathway is produced by basolateral Na⁺/K⁺ pump. Apical transport varies by region: Na⁺ channel in colon, nutrient coupled uptake and Na⁺/H⁺ exchange in small intestine.
- Chloride: Na⁺ coupled uptake; Cl⁻/bicarbonate exchange in ileum & colon
- Potassium: absorbed and secreted passively—paracellularly, powered by Na⁺/K⁺ pump.
- Calcium: solvent drag (vitamin D independent); unknown transporter. Absorbed primarily in duodenum.
- Iron: first oxidized to Fe²⁺ by ferrireductase on villus cell surface; then transported in by DCT1/NRAMP2, which can take up a number of divalent metals but not Ca²⁺. Transport powered by proton gradient. Crosses apical membrane through ferroportin (known previously as IREG). Absorbed primarily in duodenum and proximal jejunum.
- Vitamin B₁₂: Intrinsic factor (secreted in stomach by parietal cells) complexes with B₁₂, allowing receptor-mediated endocytosis by cells in distal ileum.

Secretion

1. Goblet cells secrete mucin, are found in villi and crypts.
- Crypt cells are columnar stem cells which give rise to other epithelial cells.
- *secretory component* receptor on basolateral side binds IgA (made by plasma cells in lamina propria); whole complex translocates across cell and is secreted into lumen
 - secrete chloride electrogenically:
 - Na⁺/K⁺/2Cl⁻ cotransporter on basolateral membrane uses Na⁺ gradient
 - K⁺ can equilibrate through a basolateral channel
 - apical Cl⁻ secretion via CFTR
 - Increased chloride secretion is mechanism of secretory diarrhea (know the distinction between secretive and osmotic diarrhea)

Section 9: Vascular & Inflammatory Diseases/Pathology of Intestines (Glickman)

Vascular Disorders

Vascular Malformations

- Telangiectasias (Sporadic Vascular Ectasias)
 - are acquired abnormalities
 - are clusters of tortuous, thin-walled vessels
 - are most common vascular anomaly of GI tract; most frequent cause of GI bleeding in those over 60 yrs. old
 - usually present with recurrent, low-grade GI bleeding
- Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease
 - is an autosomal dominant, systemic disorder of blood vessels
 - direct connections between arteries & veins via very thin-walled vessels
 - bleeding especially frequent in tissues without stromal support: most frequent presentations are epistaxis and GI bleeding
- Secondary vascular ectasias
 - examples of causes: renal failure, portal hypertension, systemic sclerosis
 - most common is hemorrhoid, due to ↑ venous pressure (constipation, pregnancy, cirrhosis)
- Arteriovenous Malformations
 - focal meshwork of large, thick-walled veins associated with abnormal arteries
 - usually a single lesion
 - bursting can lead to death from hemorrhage in minutes

Vasculitis

- Henoch-Schönlein Purpura
 - due to vascular entrapment of circulating immune complexes containing IgA
 - activation of complement leads to inflammation that targets small vessels
 - clinical picture includes palpable purpura, joint/GI tract/kidney involvement
- Microscopic Polyangiitis (Hypersensitivity Vasculitis)
 - often drug-induced
 - few/no immune deposits
 - involves large & small blood vessels
- Vasculitis Secondary to Multisystem Autoimmune Disease (eg., SLE, RA)
- Polyarteritis Nodosa (PAN)
 - targets mesenteric arteries with fibrinoid necrosis/elastin fragmentation
 - characteristic *beaded* appearance of affected arteries
 - GI/renal involvement go together
- Amyloidosis: can mimic inflammatory bowel disease

Mesenteric Vascular Insufficiency

- Vaso-Occlusive Disease
 - embolism from cardiac mural thrombosis after MI
 - atheroembolism after arterial surgery
 - thrombosis at site of atherosclerotic plaque or anomaly; usually associated with low-flow state
 - venous thrombosis: idiopathic, or in context of hypercoagulable state (cirrhosis, abdominal inflammation, trauma)
 - bowel strangulation leads to mechanical occlusion of vessel
- Nonocclusive Vascular Disease
 - most common cause of bowel ischemia (50% of cases)
 - systemic or local hemodynamic disturbance superimposed on atherosclerotic narrowing of proximal mesenteric vessel
 - can lead to ischemic colitis

Varices

- usually caused by portal hypertension, found in esophagus, stomach, colon
- Esophageal
 - occur in 66% of cirrhotic patients; account for 50% of deaths from cirrhosis
 - asymptomatic until they rupture
 - rupture has mortality rate of 40%

Inflammatory Disorders

Infectious Enteritis: *most common GI problem worldwide*

- viruses, bacteria, protozoa, nematodes, rarely fungi; know examples of each from list in notes
- diarrhea & malabsorption
- toxin production, tissue invasion

Celiac sprue (gluten enteropathy)

- hypersensitivity response to protein in wheat
- complete flattening of the villi → malabsorption
- complications include T-cell lymphoma, adenocarcinoma of small intestine

Various immunodeficiency disorders

Infectious Colitis: similar to infectious enteritis

- some colon-specific pathogens: *Clostridium difficile* (antibiotic-associated pseudomembranous colitis), *Entamoeba histolytica*, *Schistosoma mansoni*, japonicum
- diarrhea (no malabsorption)

1. Diverticulitis:

- inflammation of outpouchings of colon due to fecal impaction/bacterial overgrowth
- cramps, intermittent constipation & diarrhea; treat with high-fiber diet

2. Acute appendicitis: most common cause of abdominal emergency/immediate surgery in US

- luminal obstruction & bacterial overgrowth thought to be main cause
- begins with periumbilical pain (referred from midgut) which then shifts to right lower quadrant once peritoneum is affected
- complications: perforation, peritonitis

3. Inflammatory Bowel Disease (IBD) (know this for the boards).

- idiopathic, chronic, ulcerating disease with periodic exacerbations

Crohn's Disease (CD)	Ulcerative Colitis (UC)
may affect any part of GI tract; primarily terminal ileum targeted	colon only; begins in rectum, progresses retrograde; sometimes backwash ileitis
Focal, patchy distribution	diffuse, confluent distribution
deep/sharp fissuring ulcerations; often leads to scarring, stricture	broad, shallow ulcerations limited to mucosa
Noncaseating granulomas in 50% of cases	none
malabsorption of B ₁₂ and bile salts; steatorrhea	none
2x normal risk of small bowel cancer	increased risk of colon cancer

Section 10: GastroIntestinal Neoplasms (Glickman)

Esophagus

1. Squamous Cell Carcinoma (SCC)

- 6% of GI malignancies in US
- outcome depends on stage: for superficial, 5-year survival is 50-80%
- predisposing factors: alcohol, tobacco, achalasia, corrosive esophagitis

2. Adenocarcinoma

- arise mostly from Barrett's esophagus (95%)

- otherwise similar to SCC

Stomach

1. Polyps: benign must be differentiated from adenomas, which can progress to:
2. Adenocarcinoma
 - most common gastric neoplasm
 - risk factors include: environmental nitrates, dietary carcinogens, genetics, chronic inflammation
 - two types: intestinal (from metaplastic mucosa), diffuse (from surface foveolar cells)
 - intestinal type has well-differentiated glandular cells, and grossly is luminal & fungating
 - diffuse type has poorly differentiated, “signet ring” cells full of mucin, and grossly is mural and ulcerating
 - highly malignant with potential for dissemination
3. Malignant Lymphoma
 - most GI lymphomas are found in stomach and are B-cell derived
4. GI Stromal Tumors (GISTs): usually leiomyomas, usually benign

Intestines

1. Neuroendocrine (Carcinoid) Tumors are relatively uncommon but are the most common malignancy of the small intestine.
 - Carcinoid Syndrome: tumors secrete serotonin, normally metabolized in liver. If there are liver metastases, detoxification of serotonin is impaired. Systemic effects of serotonin/other metabolites: flushing of skin, watery diarrhea, right heart failure, bronchospasm.
2. Non-neoplastic Polyp Syndromes
 - generalized juvenile polyposis (autosomal dominant)
 - Peutz-Jeghers Syndrome: autosomal dominant, increased melanin in face, digits, oral area, hamartomatous GI polyps, increased risk of some cancers
3. Neoplastic Polyps
 - Adenomas that are dysplastic and are an early step in sequence leading to cancer.
 - Once dysplastic epithelium crosses basement membrane, it becomes carcinoma.
 - *Familial Adenomatous Polyposis Coli*: autosomal dominant; hundreds of polyps → 100% risk of progression to carcinoma unless colon is removed.
4. Colorectal Adenocarcinoma
 - 15% of yearly cancer deaths in US
 - highly refined, low-residue diet is risk factor
 - develops from neoplastic polyps
 - Genetics: most common molecular hits occur in APC, MSH2, DCC, K-ras, p53; classic demonstration of multi-step tumorigenesis theory of cancer
 - left colon—usually “napkin-ring” lesions leading to constriction
 - right colon—usually sessile, polypoid masses that outgrow blood supply
5. Other Syndromes:
 - Hereditary Non-Polyposis Colorectal Cancer (HNPCC) has <100 adenomatous (flat) polyps, 100% cancer risk
 - Cowden’s Syndrome: oral cutaneous lesions & GI hamartomas, ↑ GI, thyroid, breast cancer risk
 - Cronkhite-Canada Syndrome: hamartomatous polyps, cutaneous lesions, ↑ colorectal cancer risk.