GASTROINTESTINAL PHYSIOLOGY

ENTERIC NERVOUS SYSTEM

Smooth muscle: All smooth muscle is innervated by the autonomic nervous system.

- General Properties:
  - Caveolae: Micro-pits allow for increased surface area on smooth muscle.
  - No Striations: Thin and thick filaments run through in a random order. Smooth muscle has relatively more thin filaments than thick.
  - Plasticity: Smooth muscle is able to stretch to a greater length and compress to a shorter length than skeletal.
  - Calcium supply comes more from outside the cell rather than inside (in the SR), as compared to skeletal.
  - Slow, Sustained contraction as compared to skeletal muscle.

- Multi-unit smooth muscle: Has high innervation density. This is the type of smooth muscle found in Ciliary Muscle and Ductus Deferens.

- UNITARY SMOOTH MUSCLE: The type of smooth muscle found in gut.
  - Sparse innervation compared to multi-unit muscle
  - Functional Syncytium: Gap junctions allow intercellular communication.
  - Shows spontaneous (basal) electrical activity even in the absence of innervation.
    - High basal resting potential (-57 mV vs -80 mV) as compared to skeletal muscle. Smooth muscle is more permeable to Na⁺ which accounts for spontaneous electrical activity.

- SMOOTH MUSCLE CHANNELS:
  - Electromechanical Channels: Channels that transduce electrical activity, in one form or another, to mechanical activity of actin and myosin.
    - Slow-Leaking Ca²⁺-Channels
    - Ligand-Gated Channels
    - Voltage-Gated Na⁺-Channels
  - Pharmaco-mechanical Channels: Channels that employ a second messenger, causing contractility without a change in the cell's electrical potential.

- SMOOTH MUSCLE CONTRACTION:
  - Ca²⁺ enters cell ---> Calmodulin then activates Myosin Light-Chain Kinase (MLCK) ---> MLCK then phosphorylates myosin, turning it on and enabling it to interact with actin ---> contraction occurs.
  - Regulatory step is binding of Ca²⁺ with Calmodulin.

SLOW-WAVES: The basal electrical tone of smooth muscle. No contraction occurs with slow-waves.

- Also called the Basal Electrical Rhythm (BER)
- Magnitude of change is 5 - 15 mV, caused by entrance of Na⁺ into cell. No Ca²⁺ is associated with these waves so no contraction occurs with them.
- Basal Rhythm in Different Regions: Remember these waves are only electrical -- not mechanical.
  - STOMACH: 3 waves per minute
  - DUODENUM: 12 waves per minute. In the duodenum, 30-40% of slow-waves are associated with Ca²⁺ as Ca²⁺ is added to the cells.

ENTERIC NERVOUS SYSTEM: The GI nervous system is independent of the CNS. Activity can go on without any CNS input.

- GI Plexes:
  - MYENTERIC PLEXUS: Outermost plexus located between the two layers of musculature -- between the muscularis circularis and muscularis longitudinalis.
  - SUBMUCOSAL PLEXUS: Located in the submucosa, just outside the Muscularis Mucosae.

- EXTRINSIC REGULATORY INPUT:
  - Chemoreceptors and mechanoreceptors from the GI-Lumen are an important source of input. They are the origin of short reflexes (not involving the CNS) that go through the two GI plexes in the enteric NS.
VAGO-VAGAL (long) REFLEX: Generally stimulatory (increase motility, secretomotor, vasodilatory).
- The Vagus carries both afferents (70%) and efferents. Luminal receptors send afferent signal back to the CNS via the Vagus.

INTESTINO-INTESTINAL (short) REFLEX: Generally inhibitory, involving only the Enteric NS, and completely independent of the Autonomic NS.
- SYMPATHETICS are inhibitory to the GI-Tract. They work primarily by presynaptic inhibition, thus inhibiting release of ACh. In this way we get smooth muscle relaxation.
  - Norepinephrine binds to alpha1-Adrenoreceptors on parasympathetic nerve terminals and thereby inhibit the release of ACh.

NEUROTRANSMITTERS:
- Acetylcholine increases GI-Motility when it acts on smooth muscle.
- Norepinephrine decreases GI-Motility when it acts on smooth muscle.
- Enkephalin (Opoid) decreases GI-motility by inhibiting the release of ACh.
- VASOACTIVE INTESTINAL PEPTIDE (VIP): Acts directly on smooth muscle to cause smooth muscle relaxation.
  - It is localized with ACh in the Vagus Nerve.
  - VIP is in local neurons, and is released when Vagal Fibers excite these inhibitory neurons to cause relaxation: Vagus (Excitatory synapse) ----> Turn on VIP neurons (Inhibitory synapse) ----> Relaxation.

COLOCALIZATION: Enkephalins, VIP, NO, Serotonin, and a whole bunch of other transmitters are localized along with ACh and NorE in the autonomic nervous system. Depending on the nerve, whenever the ACh and NorE are released, so will the other substances be released.

MYOGENIC CONTRACTILITY: The gut has some contractility without any nervous input whatsoever.
- Luminal contents will cause basal contractility without any nervous influence at all.
- Thus there is a constant inhibitory tone of VIP and NO on the gut, to prevent / slow down this contractility.

PARALYTIC ILEUS: Loss of GI contractility.
- It can occur chronically from overproduction of Sympathetics.
- Post-Operative (Physiologic) Ileus is a very common occurrence with abdominal surgeries

TYPES OF MOTILITY:

PERISTALYSIS: Propulsion of material in the aboral (away from mouth) direction.
- Rate of peristalsis varies in region, but peristaltic generally gets slower as we move down the tract.
- Peristalsis occurs by segmental hyperpolarization followed by depolarization of muscle.
- Mechanism: Bolus of food in a particular location stimulates mechanoreceptors and chemoreceptors in the GI lumen, ultimately resulting in peristalsis:
  - Relaxation of the muscle occurs distal to the bolus, so that the food can go forward. This is mediated by VIP / NO.
  - Contraction of Longitudinal Muscle layer also occurs distal to bolus, because longitudinal contraction causes widening of the GI lumen.
- Contraction of the muscle occurs proximal to the bolus, in order to propel the bolus forward.
- There is a basal level of VIP inhibition in the muscle, and a bolus of food turns off this inhibition: distension of lumen by a bolus will cause inhibition of release of VIP / NO ----> contraction of proximal region.

RHYTHMIC SEGMENTATION: Mixing and churning of materials without propelling them forward in the tract.
- Only involved the circular muscle -- not longitudinal
- Common in small and large intestine

TONIC CONTRACTION: Blocking of the passage of material, as in sphincters.
- Tonic Contraction is myogenic -- it doesn't depend on innervation.
HORMONES, ENZYMES, REGULATORY SUBSTANCES AND STUFF

NEUROENDOCRINE HORMONES: All of below are either exclusively endocrine (glandular secretions into bloodstream), exclusively neural (neurotransmitter) or both. All of below serve regulatory (as opposed to digestive) functions.

- **GASTRIN**: Endocrine.
  - **STRUCTURE**: Active part of peptide is on carboxy-end. It shares the last four residues in common with CCK (Trp-Met-Asp-Phe), and it has a protective \(\text{NH}_2\) on the carboy end to help prevent degradation.
    - **PENTAGASTRIN**: Drug that mimics Gastrin, containing the last four residues in gastrin, and therefore containing similar biological activity.
  - **Distribution**: Gastrin is made by G-CELLS in the ANTRUM of the Stomach.
  - **FXNNS**:
    - It stimulates release of HCl in Parietal Cells.
    - Also stimulates growth of gastric mucosa and proliferation of intestinal enterocytes.
      - Intestinal Resection: If you cut out part of the intestine, higher levels of Gastrin will result.
  - **REGULATION**:
    - *Gastrin release is inhibited by acid in the stomach*. Primary negative feedback mechanism.
    - Gastrin release is stimulated by digested proteins and by Acetylcholine.

- **CHOLECYSTOKININ (CCK)**: Endocrine and neural
  - **STRUCTURE**: Biological activity is contained in last seven residues on carboxy-end, with last four residues in common with Gastrin, and with a protective \(\text{NH}_2\) on the carboxy terminus.
    - Activity on PARIETAL CELLS: CCK in the stomach can bind to Gastrin receptors to BLOCK the effects of Gastrin.
  - **Distribution**: CCK is made from I-CELLS
  - **FXNNS**:
    - Stimulates contraction of the gall bladder
    - Stimulates secretion of pancreatic enzymes.
    - Inhibits gastric emptying as part of the *Entero-Gastric Reflex*. The presence of CCK indicates that the duodenum is currently full and gastric emptying should be slowed.
  - **REGULATION**:
    - CCK-release is stimulated by the presence of peptides in the duodenum.

- **SECRETIN**: Endocrine and neural
  - **Distribution**: Secretin comes from S-CELLS in the duodenum.
  - **FXNNS**: It inhibits stomach motility when released in Duodenum bia the *Entero-Gastric Reflex*.
  - **REGULATION**:
    - Secretin-release is stimulated by acid in the Duodenum.

- **SOMATOSTATIN**: The universal inhibitory substance. It acts in endocrine, neural, and paracrine fashion.
  - **Distribution**: Somatostatin is all over the place.

- **GASTRIC INHIBITORY PEPTIDE (GIP)**: Endocrine.
  - **FXNNS**: Inhibits the release of Gastrin by a pharmacological mechanism. Thus the effect is dose-dependent, and a large (non-physiological) dose is required to elicit a response.
    - Dr. Greenwald thinks this effect is secondary importance because it is only pharmacological.
  - **REGULATION**: Its release stimulated during the Cephalic Phase of gastric secretion.

- **VASOACTIVE INTESTINAL PEPTIDE (VIP)**: Primarily neural

- **MOTILIN**: Endocrine.
  - **FXNNS**: It elicits the *Migrating Motor Complex* in the small intestine, to propel bacteria aborally.

- **GASTRIC RELEASING PEPTIDE (GRP)** (Bombesin): Neural. Involved in the release of Gastrin. Its release is Non-Adrenergic Non-Cholinergic.
  - **REGULATION**: Its release stimulated during the Cephalic Phase of gastric secretion.

- **ENKEPHALIN** (an Opioid):
  - **FXNNS**: Decreases GI-motility by inhibiting the release of ACh.
PREGNANCY:

- Pregnant women tend to gain weight because they have increased levels of CCK (higher fat and protein absorption) and lower levels of Somatostatin.
  - Higher CCK is especially marked during first trimester.
- INFANTS have very high levels of Gastrin to accompany their very high calorie-per-body-weight intake. Gastrin interacts with hypothalamus to somehow promote anabolic growth in infants.

MOTILITY

THE ESOPHAGUS:

- **Anatomy and Pressures:**
  - **Upper Esophageal Sphincter (UES):** Skeletal muscle, essentially comprising the cricopharyngeus muscle.
    - Resting pressure = 50-60 mm Hg to prevent swallowing of air.
    - Muscle tone is **neurogenic** and depends on CNS neural input from swallowing center to remain active.
  - **Body:** Combination of skeletal and smooth muscle.
    - Resting pressure = -5 mm Hg
  - **Lower Esophageal Sphincter:** Smooth muscle, normally closed in order to prevent gastric reflux.
    - Resting pressure = 30 mm Hg
    - LES contractility is **myogenic**. The way we relax the LES is by putting tonal amounts of VIP / NO on the sphincter.
    - VIP inhibition of LES is **Non-Adrenergic, Non-Cholinergic (NANC)**. We know this because **Atropine** does not prevent the inhibition:
      - Give atropine, and the LES will still relax because VIP is not stopped.
      - Give a **VIP-Antibody** and the LES will no longer relax because inhibition has been removed.

- **SWALLOWING REFLEX:** Can be studied with **Manometry** (esophageal pressure) studies.
  - **Oral Phase:** 1 second, voluntary.
  - **Pharyngeal Phase:** 1 second, involuntary. It is stimulated by the presence of the slightest food or liquid (saliva) in the back of the throat.
    - **You cannot swallow if your mouth is absolutely dry.**
    - Aspiration of food is prevented:
      - Respiration is inhibited from this point forward.
      - Epiglottis is NOT important in preventing aspiration. Rather it is **adduction vocal cords** that prevents food getting into trachea.
  - **Esophageal Phase:** 8-10 second, involuntary Esophageal Peristalsis
    - Esophageal Peristalsis is a **Vago-Vagal** (CNS mediated) Reflex.
    - **RELAXATION of Lower Esophageal Sphincter** occurs early in the swallowing reflex -- before the end of peristalsis of the esophagus.
    - At the end of swallowing the LES should tighten up again to prevent reflux of gastric contents.

- **Types of peristalsis:**
  - **PRIMARY PERISTALSIS:** The initial peristalsis, initiated by the swallowing reflex.
  - **SECONDARY PERISTALSIS:** Any subsequent peristalsis, to get any remaining food out of the esophagus. It is initiated by distension of esophagus and mechanoreceptors on smooth muscle.
    - The UES does NOT open with secondary peristalsis. It doesn't need to open.
- **ACHALASIA:** Tonic high pressure at the LES, making it difficult to swallow. Failure of LES to relax due to **lack of VIP** or because enteric system has been knocked out.
  - **ETIOLOGY:** Could be caused by sympathetic over expression (Sympathetics will cause relaxation via stimulation of VIP neurons) or by VIP under expression.
  - **SYMPTOMS:**
    - Distended esophagus because food can't easily get to stomach.
    - Lacking or uncoordinated peristalsis; or no peristalsis at all.
    - Spastic uncoordinated contractions following meal.
**GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD):** Having an incompetent or over-relaxed LES. Heartburn.
- Newborn babies don't have a competent LES, hence they burp up food a lot.
- Secondary peristalsis can help alleviate the symptoms by pushing unwanted chyme back into the stomach.
- **Esophagitis** and **Esophageal Cancer** can result from chronic cases.
- Lying down after a meal (i.e. lack of gravity) worsens the reflux.
- **PROPULSID** = drug that causes contractions of the LES, hence a treatment for GERD. It acts on ACh receptors to amplify the effect of ACh.

**THE STOMACH:**

- **FNXNS:**
  - **RECEPTIVE RELAXATION:** The stomach is a reservoir of food and can accommodate large changes in volume. Pressure increase with more food is gradual.
    - **Mechanism:** Vago-Vagal. More food --------> distend stomach wall and activate mechanoreceptors --------> more VIP on stomach wall --------> relaxation.
  - It converts food to chyme.
  - It controls the rate of Gastric Emptying, so duodenum doesn't get overloaded with bolus.
- **BASAL ELECTRIC RATE:** Stomach BER is about 3 events per minute.
  - This number represents the *maximum* number of contractions that can occur per minute.
- **GASTRIC EMPTYING:** The rate of movement of food from the antrum of the stomach, through the **Pyloric Sphincter** (a true sphincter), and into the duodenum.
  - **General Properties:**
    - **Retropulsion:** Stomach contractions originating at antrum and going backward, to prevent too rapid of gastric emptying.
    - **Liquids empty before solids.**
    - **Fats are slowest** emptying of all substances. CHO's and proteins empty first.
    - **Isotonic contents** empty before hypotonic contents.
    - Stomach acid impedes the rate of gastric emptying.
  - **ENTERO-GASTRIC REFLEX:** Negative feedback from duodenum will slow down the rate of gastric emptying, by multiple mechanisms. Basically, whenever there is food in the duodenum, gastric emptying will be down-regulated.
    - **Acid** in duodenum --------> stimulate **Secretin** release --------> inhibit stomach motility via Gastrin inhibition
    - **Fats** in duodenum --------> stimulate **CCK** and **GIP** --------> inhibit stomach motility
    - **Hypertonicity** in duodenum --------> (unknown hormone) --------> inhibit gastric emptying.
  - **ABNORMAL EMPTYING:** The major role of the duodenum is to restore isotonicity.
    - **Dumping (Gastric Emptying) Syndrome** = TOO RAPID emptying, which can result from resection of part of the stomach
      - **SYMPTOM:** Too rapid emptying --------> hypertonic bolus in duodenum --------> pull fluid in from circulation --------> Severe cardiac problems and **hypovolemia**.
    - **DELAYED EMPTYING** can occur from diabetic neuropathy. It can cause nausea, heartburn, and reflux.

**SMALL INTESTINE:**

- **Basal Electrical Rate:**
  - Fastest is in duodenum (12 cycles / min). It gets increasingly slower as you move through intestine.
  - **LAW OF THE INTESTINE:** The decreasing electrical rate as you move through tract is ultimately responsible for the movement of food in an **aboral** (i.e. forward) direction. The general movement of food aborally is a result of the basal electrical rate.
  - **MYOGENIC:** Small intestinal motility is myogenic. If you give tetrodotoxin to kill all the nerves, you still get motility.
- **ILEOCECAL SPHINCTER:** Smooth muscle sphincter which acts by short (intestino-intestinal) reflexes. Atropine has no effect on it.
  - Distension on ileal side of sphincter --------> sphincter relaxation --------> bolus can pass through.
Distension on colonic side of sphincter --> sphincteral contraction --> bolus is prevented from moving backward.

COLON:

- Basal Electrical Rate: The colon has the slowest of all BER's.
- HAUSTRATIONS: Slow segmental movements that move food very slowly through colon. This movement is going on continually.
- Mass Movements result from GASTRO-COLIC REFLEX: Food entering into stomach can cause much more rapid and forceful peristalsis in colon, ultimately resulting in defecation.
  - This phenomenon will esp. happen in the morning.
- ANAL SPHINXTER: Internal Anal Sphincter is smooth and external anal sphincter is skeletal.
  - As you increase pressure in rectum (distend it), two things happen:
    - The Internal Anal Sphincter relaxes to accommodate the fecal matter.
    - The External Anal Sphincter contracts to prevent defecation.
    - Pooping is voluntary (usually).
- FIBER is food that is not digested nor digestible. A large constituent of fiber is cellulose which human can't digest.
  - Fiber lowers bowel transit time, especially through the colon.
- MIGRATING MOTOR COMPLEX (MMC): Housekeeping function throughout the small intestine, to sweep bacteria aborally.
  - The MMC occurs post-prandially, after a meal.
  - MMC is caused by Motilin and Acetylcholine -- it is blocked by atropine.

VOMITING:

- VOMITING (EMETIC) CENTER: In the medulla. The following receptors feed into the vomiting center.
  - Chemical Trigger Zone: Floor of the fourth ventricle, controlled by higher centers.
    - Apomorphine is a drug that stimulates the chemical trigger zone.
  - Labyrinthine Receptors in the inner ear, effected by balance.
  - Touch Receptors in throat (as in gagging reflex)
  - Mechanoreceptors and Chemoreceptors in stomach and duodenum.
  - RETCHING AREA: That region of the brain responsible for the act of retching (reverse peristalsis).
- OUTPUT: The vomiting act. Four muscle groups are stimulated in synchronous order to produce vomiting.
  - Four groups of muscles are stimulated: this is the process of retching, which is reverse peristalsis accompanied by relaxation of esophageal sphincters.
    - Inspiratory Muscles: Deep inspiration --> negative thoracic pressure to facilitate upchucking.
    - Abdominal Muscles --> positive intraabdominal pressure to facilitate upchucking.
    - Esophageal, gastric, and duodenal muscles all undergo reverse peristalsis.
    - Esophageal sphincter (LES and UES) must relax for vomiting to occur.
  - Massive Autonomic Discharge occurs with vomiting. combined sympathetic / parasympathetic on salivary glands causes hypersalivation

SECRETIONS and ABSORPTION

SALIVARY SECRETIONS: Average about 1500 mL a day.

- Secreted Substances: Major function of saliva is protection and digestion.
  - Salivary Amylase: Secreted primarily by Parotid gland.
    - Amylase normally operates at pH 7-8 and is therefore inactivated once in the stomach. However, if it is inside a bolus of food and protected on all sides then it can still be active even in stomach.
  - Mucus: Secreted by the other glands (Mandibular and sublingual).
    - FNXX: Lubrication of food and it serves as a buffer.
  - Lactoferrin: Binds Fe in mouth, preventing bacteria from getting it. It thereby serves as an antibacterial role.
**Lingual Lipase**: Released from tongue itself, allows easy movement of fats on the tongue.
- It can serve a backup function in case pancreatic lipase is lacking.

**Secretory IgA**: Antibacterial secretions.

**Lysozymes**: Antibacterial secretions.

- **XEROSTOMIA**: Dry mouth. It can lead to caries (cavities) because the anti-bacterial salivary secretions are lacking. It also leads to impaired speech because saliva is required for speech.

- **HYPOTONICITY**: Salivary secretions are hypotonic and concentrated in HCO$_3^-$ and K$^+$, due to exchangers in the salivary ducts.
  - High in HCO$_3^-$ and low in Cl$^-$, giving basic pH, from a HCO$_3^-$/Cl$^-$ exchanger in salivary ducts.
  - Low in Na$^+$ and higher in K$^+$, as a result of a Na$^+$/K$^+$-ATPase exchanger in salivary ducts.
  - The salivary ducts are impermeable to water, so they retain fluid which results in hypotonicity.

- **Nervous Stimulation of Salivation**: Both sympathetic and parasympathetic cause salivation, but parasympathetic is the primary one. Increased salivation generally results from vasodilation -------> increased blood flow to salivary glands.
  - Parasympathetic: Two pathways
    - **Cholinergic Pathway** causes vasodilation via two mediators: It causes production of kallikrein (a vasodilator) and it causes conversion of Plasma Kininogen -------> Bradykinin (another vasodilator).
    - **VIP Pathway** causes vasodilation directly on the vascular bed.

**GASTRIC SECRETIONS**:

- **GASTRIC EPITHELIAL CELL TYPES**:
  - Parietal Cells: Produce HCl
  - G-Cells: Produce Gastrin.
  - Mucous Neck Cells (along the length of the villus): Produce soluble mucous
  - Chief cells: Produce pepsinogen
  - Surface Mucous Cells: Produces insoluble mucous, which secretes HCO$_3^-$ which serves as a pH-Buffer for the mucosa -- especially in stomach.
  - Stem Cells in crypt

- **PARIETAL (OXYNTIC) CELLS**: Produce gastric acid. Stomach pH 1.3
  - Carbonic Anhydrase: Parietal cell creates carbonic acid via this enzyme: CO$_2$ + H$_2$O $\rightleftharpoons$ H$_2$CO$_3$
    $\rightleftharpoons$ HCO$_3^-$ + H$^+$
    - The H$^+$ is then secreted into the lumen.
    - **ALKALINE TIDE**: The HCO$_3^-$ is transported into the portal circulation and goes to the duodenum. Transport occurs by a HCO$_3^-$/Cl$^-$ antiport.
    - The Cl$^-$ then comes in and goes to the lumen where it joins the H$^+$ to form HCl.
  - PARIETAL CELL STIMULATION: Three things stimulate parietal cells in synergy -- the effects are additive, but the effect of all of them together is greater than the sum of the individual effects.
    - **Histamine**: H2-Receptors are coupled to a G-Protein and act via the beta-adrenergic (cAMP) pathway.
      - H$_2$-Blockers block the histamine receptor.
      - There is an H$_2$-Receptor for histamine in the lungs, which mediates lung mucous secretions.
    - **Acetylcholine**: Muscarinic receptor that acts by the alpha-adrenergic pathway (IP$_3$)
      - Atropine blocks the ACh receptor, duh??
    - **Gastrin**: Gastrin also acts by the alpha-Adrenergic pathway (IP$_3$).
      - Proglutamide blocks the gastrin receptor.
      - CCK will block the gastrin receptor.
  - H$^+$/K$^+$-ATPase symport brings the H$^+$ into the cell. K$^+$ gradient is maintained by the traditional Na$^+$/K$^+$-ATPase.
    - **OMEPRAZOLE** blocks the H$^+$/K$^+$-ATPase. Good drug for antacid.

- **PHASES OF GASTRIC SECRETION**:
  - **BASAL PHASE**: 15% of secretion.
  - **CEPHALIC PHASE**: 30% of secretion, occurs when food is seen, smelled, or tasted. Stimulus originates from higher centers (hence "cephalic").
    - Vagus Nerves releases Acetylcholine during this phase. ACh has two effects:
      - Stimulates release of Gastrin from G-Cells
- Inhibits Somatostatin release from enteroendocrine.
  - **Gastric Releasing Peptide** is also released in stomach. This release is Non-Adrenergic Non-Cholinergic. It also stimulates release of Gastrin.
    - **GASTRIC PHASE:** When food enters stomach, about 50% of secretion.
    - **INTESTINAL PHASE:** Post-gastric-emptying.
- **NEGATIVE FEEDBACK:** **ACID** is the primary inhibitor of Gastric secretions.
  - Acid stimulates the release of **Somatostatin**, which turns off Parietal Cells and G-Cells.
- **GASTRIC MUCOSAL ISCHEMIA:** Ischemia of mucosa causes increased permeability -----> **Gastric Ulcers**
  - **Etiology:** Lots of things; shock, burns, sepsis, trauma.
  - **Treatment:** Use acid-reducers like H2-Blockers
  - **VICIOUS CYCLE:** The excess acid can cause conversion of pepsinogen to pepsin which will stimulate further acid release. That normally only occurs in lumen but with a lesion it can occur in mucosa, and that is not good.
- **HELICOBACTER PYLORI:** Those little critters in the stomach that have been recently proven to cause ulcers.
  - **Urease:** These bacteria can survive in acid because they have high urease which can take urea and create \( \text{HCO}_3^- \) and \( \text{NH}_3 \) out of it, forming a good acid-buffer.
  - **ULCER** treatment should include antibiotics to fight these bacteria, but *H.Pylori is not always found in ulcer patients!* Criteria for determine presence of H-Pylori:
    - Do a biopsy and identify histologically
    - Grow cells in culture
    - Measure the amount of the enzyme urease.
- **INTRINSIC FACTOR (IF):** Produces by parietal cells in stomach, it is necessary for Vit-B12 absorption.
  - **Saliva:** Vit-B12 combines with R-Protein.
  - **Stomach:** Secretes intrinsic factor into bolus.
  - **Intestine:** Vit-B12 lets go of R-Protein and binds to **Intrinsic Factor**
  - **Ileum:** The Vit-B12/IF Complex is absorbed through special transporters. Without the IF, only 20% of B12 is absorbed.
  - **PERNICIOUS ANEMIA:** Autoimmune disease destroys parietal cells, thereby destroying intrinsic factor source and resulting in B12-deficiency.
- **ACHLORHYDIA** is an overgrowth of bacteria in stomach resulting in low HCl secretion which will cause high Gastrin levels.
- **PEPSIN:** Released as pepsinogen in chief cells. Acid converts the proenzyme to pepsin. Pepsin is an **endopeptidase**.
  - Pepsin can continue to **activate itself** once active.
  - **REGULATION:** Following factors stimulate pepsinogen secretion, from most to least prominent.
    - **Acetylcholine**
    - **H^+**
    - **Secretin**
    - **CCK**
  - **Pepsinogen I** found in Chief Cells.
  - **Pepsinogen II** found in duodenum and correlates with duodenal ulcers.

**ZOLLINGER-ELLISON SYNDROME:**

- **ETIOLOGY:** Pancreatic tumor -----> Under secretion of Pancreatic Enzymes -----> Over secretion of GASTRIN due to no CCK.
- **SYMPTOMS:**
  - **Peptic Ulcer Disease**
    - Increased Gastric Emptying.
  - **Diarrhea** from hypergastrinemia
  - **Steatorrhea** (fat in stool):
    - Denaturation of pancreatic lipase due to acidic environment in the duodenum.
    - Reduced Intrinsic Factor activity.
  - **GERD**
PANCREATIC SECRETIONS:

- **General Properties:**
  - They are basic (pH = 8.2). Higher HCO$_3^-$ at increased flow levels until it plateaus.
  - They are isotonic (unlike salivary hypotonic)
- **REGULATION:** Secretin and CCK both stimulate pancreatic secretions.
  - H$^+$ -------> stimulates S-Cells to secrete Secretin -------> stimulates pancreatic enzymes.
  - Fats in duodenum -------> stimulate I-Cells to secrete CCK -------> stimulates pancreatic enzymes.
  - BOTH CCK and Secretin are required for maximal (or near maximal) pancreatic secretion.
  - Phenylalanine stimulates the release of CCK, and it coupled with Secretin results in maximal HCO$_3^-$ secretion from pancreas.
- **ACID TIDE:** Pancreatic Ductal Cells counter the alkaline tide with an acid tide.
  - Na$^+$/H$^+$ Antiport transports H$^+$ into the blood (which counteracts the HCo$_3^-$ from parietal cells).
  - Carbonic Anhydrase can then make lots of HCO$_3^-$, which it secretes into the lumen.

GALL BLADDER / BILIARY SECRETIONS:

- **Gall Bladder** concentrates Bile from the liver.
  - NaCl is pulled out of gall-bladder cells, and H$_2$O follows, so that bile becomes superconcentrated.
  - CHOLAGOGUE: Any substance that causes contraction of the gall bladder, such as CCK.
  - CHOLERETIC: Any substance that increases the flow of bile down the bile duct, but does not affect bile synthesis. Example = bile salts.
  - HYDROCHOLERETIC: Any compound that promotes the secretion (synthesis) of bile in the liver, such as Secretin.
- **Sphincter of Oddi** keeps the bile in the gall bladder. It is tonically contracted when no food is in the duodenum.
  - CCK causes contraction of the gall bladder and relaxation of the Sphincter of Oddi.
- **MICELLES:** Bile Salts + Cholesterol + Lecithin
  - LECITHIN (PHOSPHATIDYLCHOLINE): MICELLES require lecithin to function at maximum efficiency. It increases threefold the fat-emulsifying capacity of micelles.

SYNTHESIS / STRUCTURE OF BILE ACIDS: Bile acids are synthesized from cholesterol in the liver, stored in the gall bladder, and secreted through the common bile duct.

- **SYNTHESIS** of BILE ACIDS: 7alpha-Hydroxylation of Cholesterol: The key, rate-limiting step in bile-acid synthesis. This hydroxylation destined the product to become a bile-acid.
  - CHOLATE: The major bile acid. It has three OH-groups in the rings, and a carboxylic acid at the end of the side chain.
    - It is more amphipathic than deoxycholate because it has one more hydroxy group.
  - DEOXYCHOLATE: The minor bile acid. It is missing one of the OH-groups (at the 12 carbon)
- **REGULATION** of BILE SYNTHESIS: Negative Feedback from the Bile Acids themselves. They inhibit 7alpha-Hydroxylase.
- **SYNTHESIS** OF BILE SALTS: LIVER -- Bile Acids esterified to Glycine or Taurine. Bile Salts are even more polar than their corresponding acids.
  - Glycocholate: Cholate with glycine added as an amide function.
  - Taurocholate: Cholate with Taurine added as an amide function. Taurine is a modified cysteine.
  - Glycochenodeoxycholate and Taurochenodeoxycholate are the minor bile salts.
- **SECONDARY BILE ACIDS AND SALTS:** Bacteria in the INTESTINE modify bile salts by removing the 7alpha-carbon, to the "secondary" bile salts.
- **ENTEROHEPATIC CIRCULATION:** The circulation of bile between the intestine and liver.
  - New Synthesis: A small of bile acids are newly synthesized every day. This is mixed in with bile acids that are recirculated.
  - Conjugation: Adding the glycine or taurine to the bile acid to form a bile-salt, before secretion. This occurs in the liver.
  - Secretion: We secrete daily about 15-30 grams of bile acids into the GI tract.
  - Deconjugation: Deconjugation and reduction of bile salts often occurs in the intestine, aided by intestinal bacteria.
Reabsorption: 90% of the bile acids are reabsorbed in the intestinal tract -- in the ileum, after most nutrients have already been absorbed.
  - Reabsorption sends the acids through the portal circulation and ultimately back to the liver.
Excretion: Some bile acids are excreted in the feces on a daily basis, about the same as the amount that is newly synthesized every day. This is one way to get rid of cholesterol.
  - **GALLSTONES** occur when bile is composed of more than 15% cholesterol. This makes cholesterol precipitate out of the bile solution and form stones.
    - WOMEN are at higher risk for gall stones because estrogen tends to yield higher cholesterol levels. Women taking BIRTH CONTROL are at even higher risk, relatively, for same reason.

**BILIRUBIN METABOLISM AND EXCRETION:**

- **Bilirubin** is the normal product of heme-breakdown. It is carried by Albumin in the blood stream, where it goes to liver.
- LIVER: Bilirubin is conjugated to **Bilirubin Glucuronide**, making it water soluble and lipid insoluble.
- Bilirubin Glucuronide is then secreted in bile to intestine.
- INTESTINE: Bilirubin Glucuronide is converted to **Urobilinogen** by stepwise reductions mediated by intestinal bacteria.
- **UROBILINOGEN FATE:**
  - 80% of it is them excreted in feces.
  - 20% is resorbed.
    - Most of that goes back to liver and is re-secreted.
    - Some of that goes to systemic circulation and is then excreted in urine.

**JAUNDICE:** Caused by bilirubin build up, indicating problems with the liver.

- **HEMOLYTIC JAUNDICE:** Greater amount of heme breakdown -----> increased bilirubin in intestine -----> excessive urobilinogen in feces
  - This can be caused by **Pernicious Anemia**.
- **OBSTRUCTIVE JAUNDICE:** Obstruction of bile-duct, preventing Bilirubin Glucuronide from entering intestine; it is therefore diverted to kidneys -----> excessive bilirubin in urine + big drop in fecal urobilinogen

**INTESTINAL ABSORPTION:** Absorption is ultimately dependent on the **Na⁺/K⁺ Pump** to create the gradient.

- **SODIUM:** Na⁺ is transported into the enterocytes by three mechanisms:
  - Electrochemical Channels: (40%) Na⁺ simply moving with its electrochemical gradient.
  - Na⁺/Nutrient Cotransport: (30%) There are several Na⁺-Cotransporters, for glucose and for individual amino acids.
  - Na⁺/Cl⁻ Cotransport: (30%) "Neutral" cotransport of Na⁺ and Cl⁻, bring water in with it.
- **PERICELLULAR:** Recent evidence says that majority of fluid appears to be absorbed between cells rather than through cells (transcellular), although both occur.
- **CHLORIDE:** Cl⁻ is absorbed throughout the intestine.
- **POTASSIUM:** Passively absorbed in small intestine, and secreted in large intestine.

**NEUROGENIC SECRETION:**

- Three secretomotor neurotransmitters for enterocytes:
  - Substance P
  - ACh, both preganglionic and postganglionic
  - VIP, Postganglionic
- Inhibitory neurons act on the preganglionic to prevent secretomotor excitation:
  - Somatostatin
  - Sympathetics
  - Opioids: Patients on opioids can become quite constipated and get a condition called "Narcotic Bowel."
- **VIPOMA:** Cancer causing excess release of VIP -----> excess secretion -----> secretory diarrhea.
DIARRHEA:

- There are two types of Diarrhea: Secretory and Osmotic
- **SECRETORY DIARRHEA:** Diarrhea caused by hypersecretion, via too much secretomotor stimulation or too little inhibition.
  - No Solute Gap -- fecal analysis is osmotically normal or hypoosmotic.
  - The Diarrhea does not go away after the meal is gone.
  - **ETIOLOGY:**
    - **CHOLERA TOXIN:** It causes increased basal levels of cAMP in enterocytes. cAMP is *not normally active ever* in enterocytes. The result is that Cl⁻ channels on luminal membrane are blocked open --------> perpetual secretion.
    - Even worse, the toxin also blocks Na⁺-Cl⁻ Cotransport, reducing absorption of fluid.
  - **Gastric Tumor --------> Over secretion of Gastrin.**
  - **Zollinger-Ellison Syndrome**
- **OSMOTIC DIARRHEA:** Diarrhea caused by hyperosmotic bolus in intestine -- it is *food-dependent.*
  - **SOLUTE GAP:** Fecal analysis shows a large "solute gap," i.e. hyperosmotic feces.
  - The diarrhea goes away when food is out of GI-Tract.
  - LAXATIVES cause osmotic diarrhea because their contents (magnesium) are like fiber in that they are not absorbed --------> higher bolus toxicity.
  - **Gluten Enteropathy:** Intolerance for wheat (gluten), causing blunting of enterocyte brush-border --------> decreased surface area for absorption --------> osmotic diarrhea.
  - **Celiac Sprue** also causes osmotic diarrhea.

PROTEIN DIGESTION:

- **PEPSIN:** Secreted by stomach. Endopeptidase.
  - Pepsinogen ------> Pepsin by the action of H⁺ in the stomach.
  - Mainly splits bonds between Tyr and Phe.
- **TRYPsin:** Endopeptidase
  - It is a Serine-Protease, i.e. it uses Serine as its active site to cleave proteins.
  - Trypsin is activated by **ENTEROKINASE,** which is secreted in the intestinal brush-border.
    - It converts Trypsinogen ------> Trypsin
  - **CLEAVAGE-SPECIFICITY:** Trypsin cuts amino acids that are adjacent to Lysine and Arginine.
  - **Auto-Catalytic:** Activated trypsin acts on trypsinogen to make more of itself.
    - Trypsin also acts on Chymotrypsinogen to make Chymotrypsin!
- **CHYMOTRYPSIN:** Endopeptidase
  - Chymotrypsinogen is activated by **Trypsin.**
  - **CLEAVAGE-SPECIFICITY:** It cleaves aromatic and non-polar side-chains. It is not as specific in its cleavage site as Trypsin. It will cleave any of the following residues: Trp, Phe, Tyr, Met, Leu
- **ELASTASE:** Endopeptidase
  - Elastase is activated by **Trypsin,** too.
    - It converts Proelastase ------> Elastase
  - **CLEAVAGE-SPECIFICITY:** It cleaves residues adjacent to Alanine, Glycine, and Serine residues.
- **CARBOXYPEPTIDASE:** These are *exopeptidases* that cleave at the carboxy-end.
  - They are both activated by **Trypsin** just like above: Procarboxypeptidase ------> Carboxypeptidase
  - They are both *Metalloprotease* which require Zinc for catalysis. This is a different mechanism than the endopeptidases which are serine proteases.
  - These guys are **secreted in the pancreas.**
  - **Carboxypeptidase-A:** Cleaves neutral and acidic side-chains (on the carboxy end), such as Alanine, Valine, Isoleucine, Leucine.
  - **Carboxypeptidase-B:** Cleaves basic residues -- Lysine, Arginine
Every time Trypsin cuts a protein, you are left with a protein piece that has either Lys or Arg at the carboxy-end! Carboxypeptidase can then take over to remove that end-piece. This in effect gives us a free amino acid of Lysine or Arginine which can then be absorbed.

**AMINOPEPTIDASE:** *Exopeptidases* that cut at the amino end of a peptide.
- This is secreted by the intestinal mucosa further along the small intestine (jejunum).
- This is a *metalloprotease* that requires Zinc and Manganese for catalysis.
- This cuts, usually on smaller peptides, one acid at a time off the amino end.

**Dipeptidase:** An *Aminopeptidase*, similar to above, which cuts two acids at a time from the amino end of a peptide.

**Protein Absorption:**
- About 70% of proteins are taken in as dipeptides and tripeptides. They can then be further degraded by intracellular peptidases.
- About 30% are taken in as free amino acids, via *Na⁺*-Cotransport. There are multiple Na⁺ transporters for the different classes (neutral, basic, acidic) of amino acids.

**Carbohydrate Digestion:**

**Salivary Amylase:** Begins breakdown of starch in mouth.

**Pancreatic Amylase:** Breaks down alpha-1,4 (starch) linkages into disaccharide components. Secreted by pancreas into lumen of duodenum.
- **Cellulose = beta-1,4 linkage.** That is not digestible by humans and thus constitutes fiber.
- alpha-1,6 Limit Dextrins branches can also exist in starch. They are broken down by isomaltase.

**Disaccharidases:**
- **Sucrase:** Breaks down Sucrose -----> Glucose + Fructose
  - Located in the intestinal brush-border.
- **Maltase:** Breaks down Maltose -----> Glucose + Glucose
  - Located in the intestinal brush-border.
- **Lactase:** Breaks down Lactose -----> Glucose + Galactose
  - Located in the intestinal brush-border.
  - **Lactose Deficiency** is a very common problem. It results in osmotic diarrhea.
- **Isomaltase:** Breaks down alpha-1,6 LIMIT DEXTRANS Branches in starch.
  - Located in the Intestinal Brush Border

**Sugar Absorption:** Disaccharides go to the enterocytes where they are broken down by disaccharidases (as above). The monosaccharides are then transported as follows:
- **Glucose:** Enters enterocyte via *Na⁺*-Glucose Cotransport, and enters bloodstream via facilitated diffusion on other side.
- **Galactose:** Uses the same Na⁺-Glucose transporter as above, but it has a *lower affinity for the transporter* than glucose. So, if both sugars are present then glucose will preferentially bind.
- **Fructose:** Passes through membrane by *simple diffusion*.
- **Glucose-Galactose Malabsorption** syndrome: Congenital disorder; mutation in Na⁺-/Glucose Cotransporters. The child was successfully raised on a Fructose diet.

**Fat Digestion:**

**General Process of Digestion and Absorption:**
- **Emulsification** by *micelles.* Bile salts facilitate the attachment of Pancreatic Lipase to the lipids.
  - There is an *unstirred water layer* right at the villus border. Due to its detergent properties, micelles can penetrate that border.
- **Digestion:** LIPASE then breaks down the triglyceride -----> monoglyceride + free fatty acids.
- Fatty Acids diffuse through enterocytes by simple diffusion.
- **Re-Esterification:** Fatty acids are re-esterified to triglycerides inside the enterocytes.
- **Chylomicron Formation:** Chylomicrons are formed as protein coats + cholesterol is added to the triglyceride.
- **Lymph:** Chylomicrons enter circulation through *lacteals* -----> lymphatic system.  
  - *Short Chain fats go directly into the portal blood -- not into lymph.*
• LINGUAL LIPASE: In the tongue.
• PANCREATIC LIPASE: The main triglyceride cutter. It attaches to micelles, with aid of bile salts, to facilitate
  Triglyceride -----> 2-Monoglyceride + 2 Fatty Acids
• PHOSPHOLIPASE A₂:
• COLIPASE: Forms a "wedge" in fat globules which facilitates attachment of lipase.
• OVERSUPPLY of Pancreatic Enzymes: 25% intact pancreas is sufficient for adequate fat absorption. There is great
  redundancy in the supply of pancreatic exocrine enzymes.