

Physiology of the Colon

Key Concepts

- Colonic innervation is supplied by both **extrinsic and intrinsic pathways**.
 - **The extrinsic pathways:** are derived from the autonomic nervous system.

The **parasympathetic** input is **excitatory**.

The **sympathetic** input is **inhibitory**.

- **The intrinsic** consists of the myenteric plexus.
- **The interstitial cells of Cajal (ICC)** are the **primary pacemaker cells** of the enteric nervous system.
- **The short-chain fatty acid (SCFA) butyrate** is the primary energy source of the colon.
 - It is produced by the colon as a result of fermentation of complex carbohydrates by colonic flora.

• The colon **absorbs sodium and water** and **secretes bicarbonate** and potassium.

Aldosterone mediates the process of **active sodium absorption** in the colon.

- Colonic contractile events are divided into

1. Segmental contractions.

2. Propagated contractions:

- a. low-amplitude propagating contractions (LAPC).
- b. high-amplitude propagating contractions (HAPC).

The main function of HAPC is to propagate colonic contents toward the anus.

- Functions of the large intestine:
 1. Reabsorb water and compact material into feces.
 2. Electrolyte absorption.
 3. Absorb vitamins produced by bacteria
 4. Store fecal matter prior to defecation.
- Proximal half of the colon (absorbing colon)
- Distal colon (storage colon).

Introduction

- Human fecal production is approximately **128 g/day**, increased by high dietary fiber intake.
- The chemical composition and pH of the fecal output are influenced by diet.
- **Composition of feces:**
 - 75% water
 - 25% solid matter:
 1. Undigested fiber and solidified components of digestive juices (30%).
 2. Bacteria (30%).
 3. Fat (10%-20%).
 4. Inorganic matter (10%-20%).
 5. Protein (2%-3%).
- **Color:**

Brown: largely due to bilirubin which is converted to urobilin and stercobilin.
- **Odor:**
 - Differs among people.
 - Largely influenced by the food eaten.
 - Due to bacteria action.
 - The actual odoriferous products are: indole, skatole, mercaptans, and hydrogen sulfide.
- **Absorption and secretion:**
 - The colonic epithelium is highly efficient at **absorbing sodium, chloride, water, and short-chain fatty acids.**

- In addition, the colonic epithelium **secretes bicarbonate, potassium chloride, and mucus.**
- Under normal conditions, the colon receives approximately **1500 to 2000 mL** of fluid material from the ileum over a 24-hour period.
- Absorbing all but **100 mL of fluid and 1 mEq of sodium and chloride.**
- Resulting in excretion of feces with a **sodium concentration of approximately 30 mmol/l and potassium concentration of 75 mmol/l.**

- Colonic absorptive capacity **can increase up to 5 or 6 liters and 800–1000 mEq of sodium and chloride daily** when challenged by larger fluid loads entering the cecum, a feature that allows the large bowel **to compensate for impaired absorption in the small intestine.**

- **Factors determine colonic absorption ability:**
 1. Volume of fluid.
 2. Composition of fluid.
 3. Rate of flow of luminal fluid.

- Since the work of Cannon in 1902, the **proximal colon** has been recognized to be the primary site responsible for **storage, mixing, and absorption of water and electrolytes.**
- While the **rectosigmoid colon** functions primarily as a **conduit**, it **can also participate in this compensatory absorptive response.**

Colonic Wall Anatomy

There are four layers to the colonic wall:

1. Mucosa:

consists of epithelium, lamina propria, and muscularis mucosae.

2. Submucosa:

- Is just deep to the epithelium and contains vasculature, lymphatics, and Meissner's nerve plexus.
- Consists largely of loose connective tissue with collagen and elastin fibrils.

3. Muscularis propria:

- The muscular layers of the large intestine are composed of both **longitudinally and circularly arranged fibers.**
- **Longitudinal muscle** fibers are concentrated into **three flat bands called the taenia coli.**
- These run from the cecum to the rectum, where the fibers fan out to form a more continuous longitudinal coat.
- **The circular layer of muscle fibers is continuous** from the cecum to the anal canal, where it increases in thickness to form the **internal anal sphincter.**
- **Auerbach's myenteric plexus** is found between the circular and longitudinal smooth muscle layers.

4. Serosa:

The serosa is the outermost layer of the colon and is surrounded by visceral peritoneum.

- **The interstitial cells of Cajal (ICC):**
 - Are specialized mesenchymal, c-kit-positive cells.
 - Primarily serve as **the pacemaker cell of the enteric nervous system**, linking the colonic submucosa electrochemically with the myenteric plexus.
 - There are multiple subtypes of ICC dispersed throughout the musculature of the colon, and controversy exists surrounding their distribution.
 - The ICC are the cells of origin of **GI stromal tumors (GISTs)** which arise from the colonic wall rather than the mucosa.

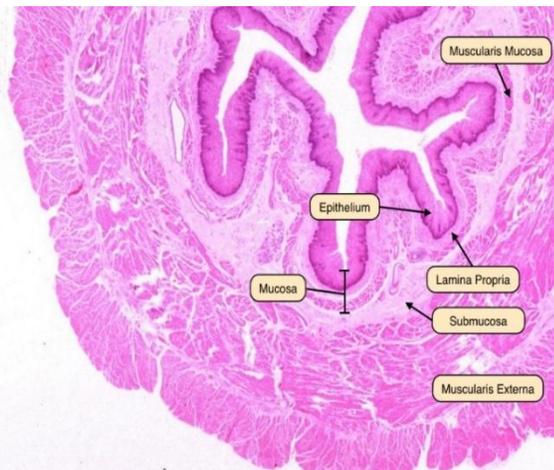
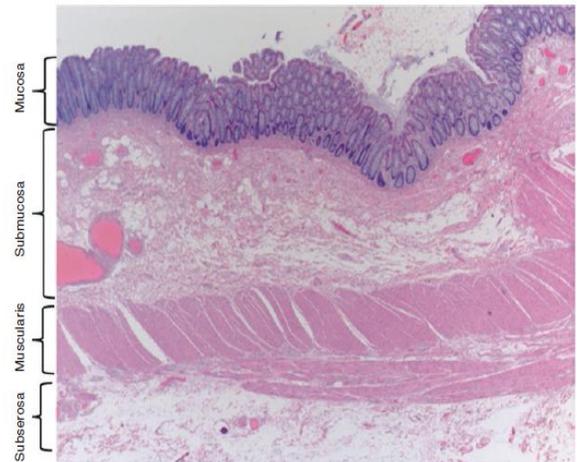
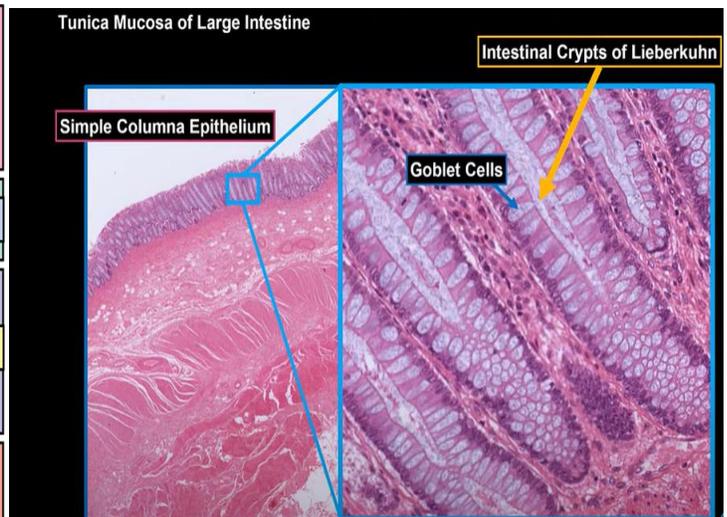
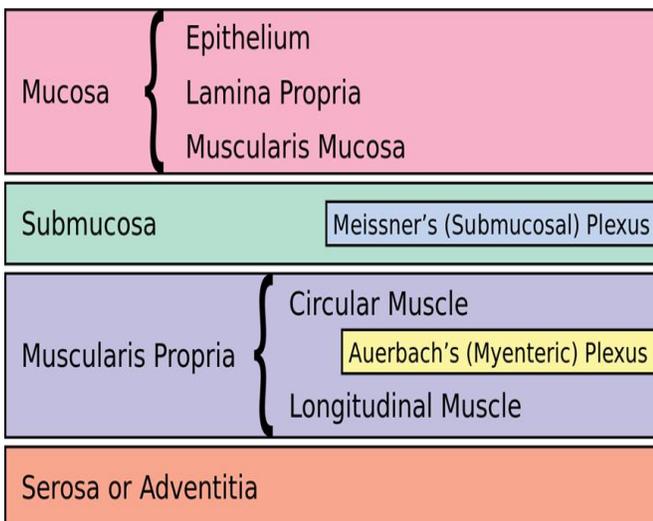


Fig. 2.2 Normal colonic mucosa. H&E, 250x. The layers of the normal colonic wall are indicated by the brackets. (Courtesy of Julieta E. Barroeta, MD)



General Organization of the Gastrointestinal Tract



Epithelial Types

There are three main types of colonic epithelial cells:

1. Enterocytes:

- **Simple columnar epithelial cells.**
- Major cell type in colonic epithelium, and they play important roles in **nutrient absorption and in secretion.**

2. Goblet cells:

- **Secrete mucus** to lubricate the passage of food through the intestines.
- Enterocytes and goblet cells comprise nearly 95% of the epithelial cells in the colon.

3. Neuroendocrine cells:

- Act as **chemoreceptors, initiating digestive actions, detecting harmful substances, and initiating protective responses.**
- All types of epithelial cells **differentiate from common stem cells, which are located at the bottom of the crypts, and most differentiated cells migrate to the surface epithelium.**

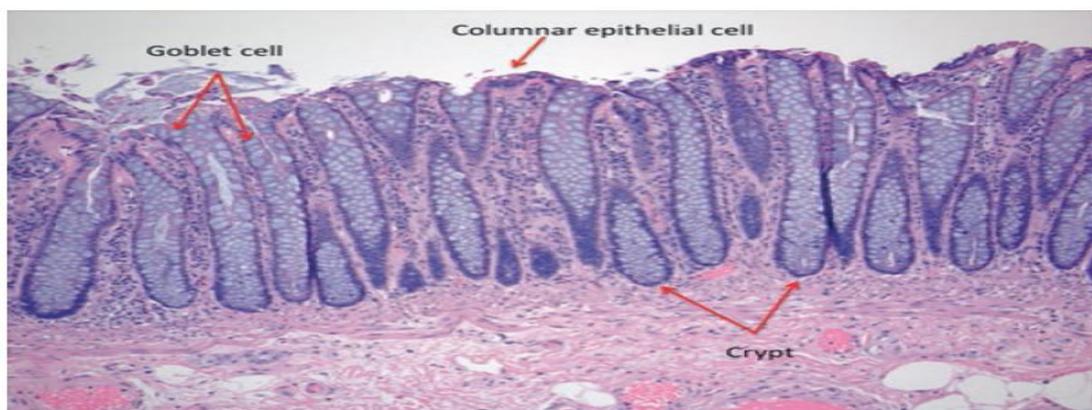


Fig. 2.3 Normal colonic mucosa. H&E, 1000×. Epithelial cell types are clearly visible including goblet cells and columnar epithelial cells. The crypts are the source of the continually regenerating mucosal cells. (Courtesy of Julieta E. Barroeta, MD, used with permission)

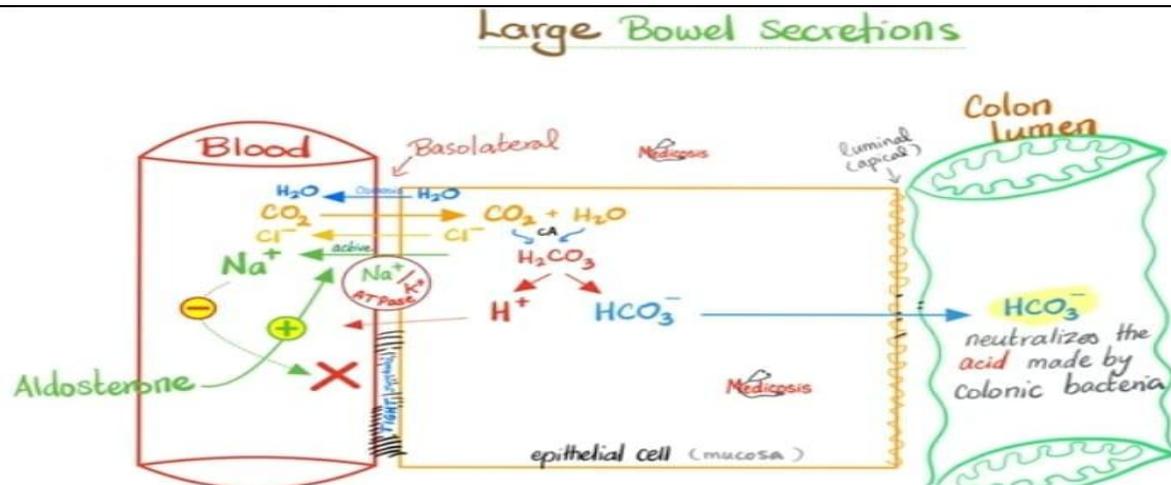
- The epithelium lining is continuously renewed by **dividing cells every 4–5 days.**
- **Crypt** epithelium is **highly proliferative and relatively undifferentiated and secretes chloride.**
- The **surface** epithelium, in contrast, has **low proliferative activity, is well-differentiated, and is highly absorptive.**
- Ion absorption and secretion occur at both the surface and crypt levels.

Secretory Role of Colonic Epithelium

- The colon **absorbs sodium and water** and **secretes bicarbonate and potassium.**
- **Aldosterone** mediates the process of **active sodium absorption in the colon.**
- Vit. K, biotin, B5 and folic acid resulting from bacterial fermentation of CHO are absorbed.
- **Mucus secretion:**
 - The mucosa of the large intestine has many crypts of Lieberkühn.
 - Absence of villi.
 - Contains almost **no enzymes.**
 - Presence of **goblet cells** that **secrete mucus** which provides an **adherent medium for holding fecal matter together.**
 - **Stimulation of the pelvic nerves** from the spinal cord can cause **marked increase in mucus secretion.** This occurs along with increase in peristaltic motility of the colon.

- During extreme parasympathetic stimulation so much mucus can be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30 minutes this mucus often contains little or no fecal material.
- **Sodium**
 - **Absorption of sodium and secretion of bicarbonate** in the colon are **active processes**, occurring against an electrochemical gradient.
 - This process resides **primarily in the crypt cells** and is responsible for **maintaining a liquid chyme**.
 - Ninety percent of sodium is actively absorbed in exchange for secretion of potassium.
 - The transcellular secretion of chloride accounts for most of the secretory activity.
 - Chloride enters the cell through a sodium carrier located in the basolateral membrane.
 - The majority of **sodium chloride absorption occurs in the proximal colon** and is driven primarily through the electroneutral absorption by tightly coupled luminal **Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchange**.
 - Mucosa of the large intestine has a large capability for Na absorption (active).
 - Electrical $\Delta\psi/\Delta x$ created by this absorption causes Cl absorption as well.
 - Na ions are far **more absorbed than in the small intestine**.
 - **Aldosterone**: increase the expression of basolateral NaK ATPase and luminal Na ion channels.

- Na and Cl absorption creates an osmotic gradient which in turn causes absorption of water.



- The **sodium gradient** is established by **$\text{Na}^+/\text{K}^+ \text{ATPase}$** , and each pump cycle results in the **extrusion of three sodium ions** in exchange for the basolateral **uptake of two potassium ions**, resulting in the **net transfer of one positively charged sodium ion** across the basolateral membrane (Fig. 2.4).
- The resulting secretion of sodium and potassium establishes an **osmotic gradient drawing water into the lumen.**
- **The epithelial Na^+/H^+ exchange** is a pleiotropic membrane transport mechanism that participates in intestinal NaCl transport.
- It also helps to regulate basic cellular functions and the extracellular milieu to facilitate other nutrient absorption and to regulate the gut microbial microenvironment.
- **In the distal colon, the epithelial sodium channel (ENAC) mediates sodium absorption.**
- Sodium is taken up by the ENAC on the luminal side and is excreted on the basolateral surface by the $\text{Na}^+/\text{K}^+ \text{ATPase}$.

- **Chloride is absorbed** through the luminal cystic fibrosis conductance regulator (**CFTR**) and is **then excreted** on the basolateral side via **multiple mechanisms, including KCl cotransporter (KCC1), Cl⁻ channels, and Cl⁻/HCO₃⁻ anion exchangers.**

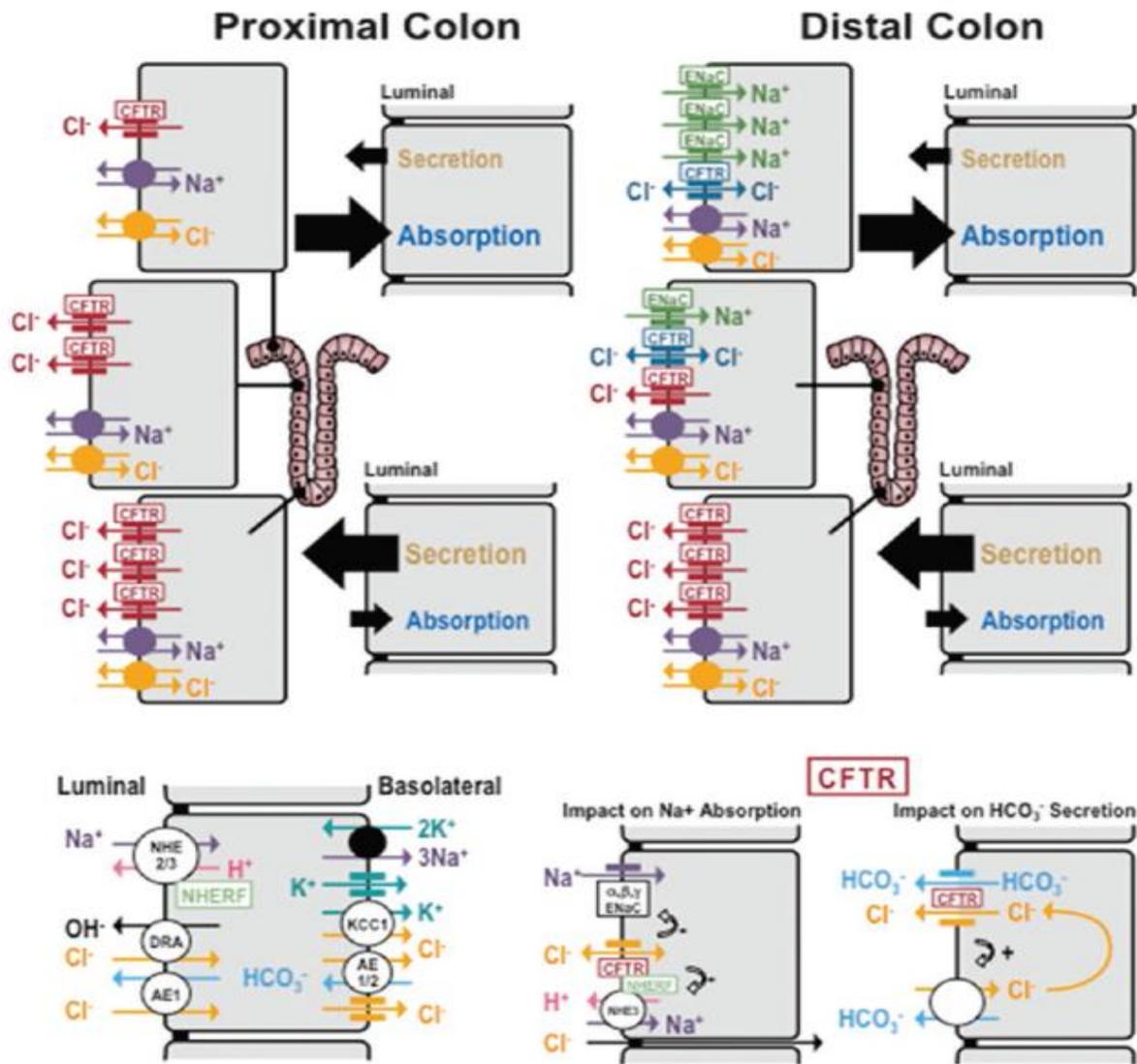
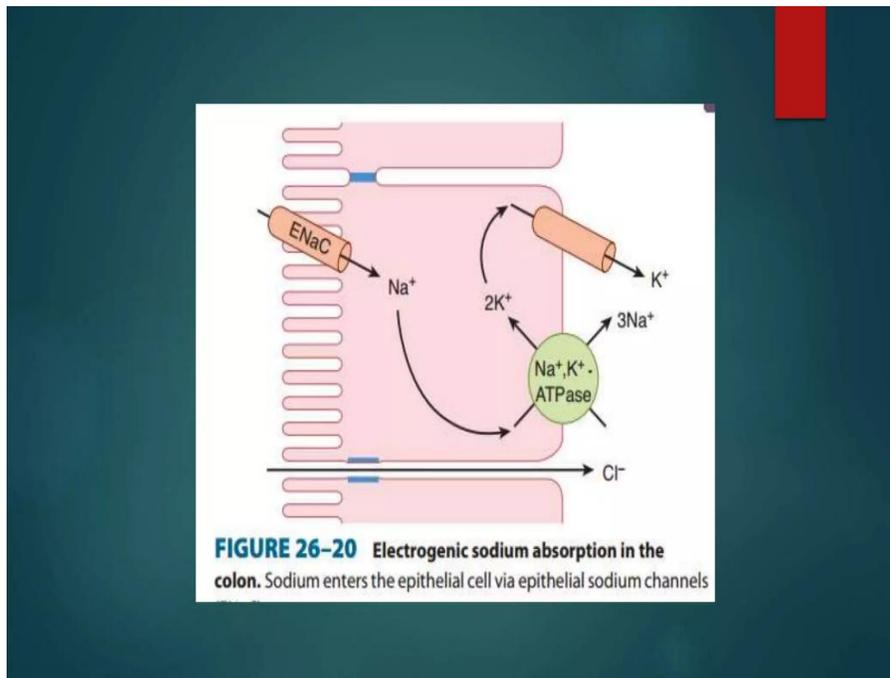


Fig. 2.4 Schematic of ion-transport channels in proximal and distal colonocytes. (Courtesy of Robin Noel, used with permission)

- **Electrogenic Na⁺ absorption:**
 - Is by epithelial sodium channels (ENaC).
 - Lumen side
 - **Inhibited by amilorides and diuretics.**
 - Na absorption is accompanied by Cl⁻ as well via the CFTR.



Clinical applications of abnormalities associated with sodium

1. ***Clostridium difficile*:**
 - The leading cause of nosocomial diarrhea and pseudomembranous colitis, also exerts **inhibitory effects on epithelial Na⁺/H⁺ exchange mechanism.**
2. **inflammatory bowel disease (IBD):**
 - Both **electrogenic sodium transport** mediated by sodium channels and **electroneutral Na⁺/H⁺ exchange-coupled NaCl absorption** are **reduced.**

- The **Na⁺/H⁺ exchangers** are frequent targets of inhibition in gastrointestinal pathologies, by either **intrinsic factors (e.g., bile acids, inflammatory mediators)** or **infectious agents and associated microbial toxins**.

3. Congenital chloride diarrhea:

- A separate Cl⁻/OH⁻ exchange is represented by a protein called **DRA** (downregulated in colonic adenomas).
- Human DRA mutations are responsible for congenital chloride diarrhea.

4. Infectious diarrhea:

- active and excessive chloride secretion is predominant.

5. Cholera:

- Is a classic example leading to significant **watery diarrhea**.
- If uncontrolled, it can lead to the **loss of large quantities of fluid and electrolytes**, which can result in **dehydration and electrolyte imbalances**, and ultimately **death**.
- In this instance, **cholera toxin binds to the brush border of crypt cells** and increases intracellular adenylyl cyclase activity.
- Adenylyl cyclase **synthesizes cAMP from ATP**.
- The result is a dramatic **increase in intracellular cAMP** that **stimulates active Cl⁻ and HCO₃⁻ secretion into the lumen**.
- **Water follows the osmotic gradient** and **enters the lumen** leading to a **secretory diarrhea**.

- **Potassium**

- The colonic epithelial apical and basolateral membranes are **permeable to potassium**.
- There is a high concentration of intracellular potassium maintained by the Na⁺-K⁺ pump; therefore, some potassium will leak passively across the apical membrane of epithelial cells.
- **The concentration of potassium in the colonic lumen** remains roughly equal to the serum potassium (**4 or 5 mEq/L**).
- In the colon, **net potassium secretion occurs**.
- Because of **potassium secretion and the exchange of chloride for bicarbonate in the colon**, prolonged diarrhea results in **hypokalemic metabolic acidosis**.
- This also contributes to the **alkaline pH of stool water**.

- **Aldosterone**

- Mineralocorticoids can decrease the **sodium** concentration in fecal water **from 30 to 2 mEq/L** and increase the **potassium** concentration from **75 to 150 mEq/L**.
- There is an **increase in sodium permeability of the brush border membrane caused by the activation of new sodium channels**.
- In addition, aldosterone **increases the number of sodium pump molecules in the basolateral membrane**.
- **The influence of aldosterone on sodium transport is exerted at two points:**
 1. In the **distal colon**, **epithelial Na⁺-K⁺-ATPase is activated** by aldosterone.
 2. In the **proximal colon**, the **Na⁺-H⁺ exchange is activated** by aldosterone.

- **Mechanism for Water Absorption**

- **The human colon has a nominal mucosal surface area of about 2000 cm².**
- however, the **total absorptive area is even greater** because **colonic crypt cells are capable of absorption as well as secretion.**
- The continued **production of solutes by colonic bacteria**, together with the **relative impermeability of the colonic membrane to water**, usually causes **stool water to be hypertonic, 350–400 milliosmoles(mOsm)/L**, to plasma.
- The volume of fluid moving from blood to lumen (secretion) is less than that moving from the lumen to the blood (absorption), thus resulting in **net absorption.**
- **Absorption** generally results from the **passive movement of water** across the epithelial membrane **in response to osmotic and hydrostatic pressures.**
- The autonomic nervous system has effects on NaCl transport affecting absorption.
- **Adrenergic (α -receptor) or anticholinergic stimuli** tend to **increase absorption.**

- **Short-Chain Fatty Acid Absorption**

- In the **proximal colon**, bacteria ferment organic carbohydrates to short-chain fatty acids (SCFA), predominantly **acetate, propionate, and butyrate.**
- **Butyrate** is the **main energy substrate for the colonic epithelium.**
- **SCFA** provides approximately **10% of the daily caloric requirements.**

- SCFA are among **the most important microbial metabolites that interact with host cells**, with up to 100 mMols of SCFA produced in the colonic lumen by bacteria.
- Since luminal SCFA are absorbed by colonic epithelial cells into the submucosa and the systemic circulation, a variety of SCFA signaling pathways are likely involved in acute and long-term physiological responses to luminal bacterial activity.
- **SCFA are potent stimuli of sodium and water absorption** in the colon, with **butyrate** being the most effective.
- **SCFA are rapidly absorbed from the colon** which augments sodium, chloride, and water absorption.
- SCFA have several potentially therapeutic effects in vitro:

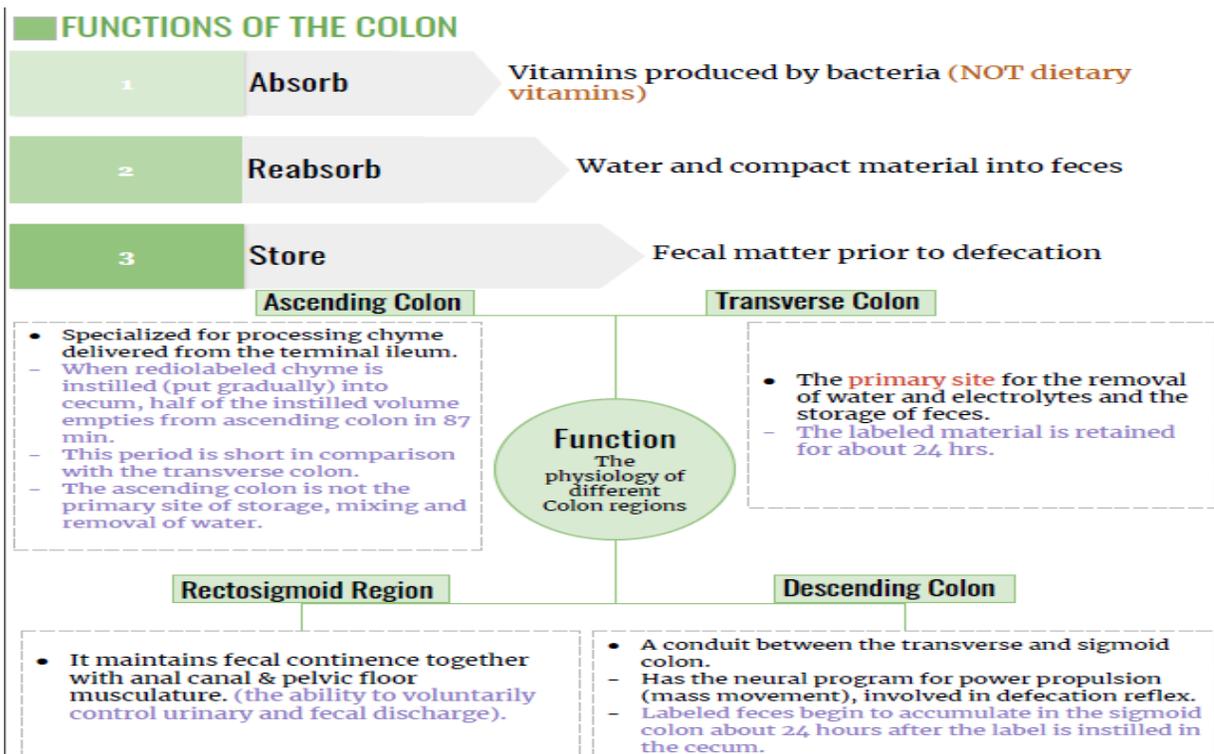
They regulate proliferation, differentiation, gene expression, immune function, and colonic wound healing.

- In **acute diarrhea, fecal SCFA concentrations are reduced**, and this may contribute to **impaired sodium absorption**.
- SCFA potentially **reduce inflammation in ulcerative colitis and diversion colitis**.
- **Butyrate** has also been **hypothesized to reduce the risk of colon cancer**.
- **SCFAs and medium-chain fatty acids** are **primarily absorbed through the portal vein** during lipid digestion.
- **long-chain fatty acids** are **packed into chylomicrons, enter lymphatic capillaries, then transfer to the blood at the subclavian vein**.

- In parallel with the absorption of NaCl, SCFA are absorbed by the colonic epithelium usually by **non-ionic diffusion**.
- An additional SCFA/HCO₃ exchange mechanism:
Cl absorption is stimulated by increased HCO₃ production during SCFA metabolism and stimulation of the apical Cl⁻/HCO₃⁻ exchanger.
- **Importance of SCFA:**
 1. Absorbed SCFA are metabolized and contribute to calories.
 2. Trophic effect on colonic epithelial cells.
 3. Combat inflammation.
 4. Maintain acid-base equilibrium.
 5. Promote absorption of Na⁺.
- **Butyrate:**
 - Least amount produced.
 - Primary energy source for colonocyte.
 - Role in cell proliferation and differentiation.
 - Important in absorption of water and salt.
- **Propionate:**
 - Combines with 3 carbon compounds in liver for gluconeogenesis.
- **Acetate:**
 - Most abundantly produced.
 - Used to synthesize longer-chain FAs by liver.
 - Energy source for muscles.

- **Vitamin K Absorption**

- A lipid-soluble vitamin.
- Plays an essential role in **facilitating blood coagulation** by activating clotting factors.
- Plays a role in **signal transduction, cell proliferation, and bone and cartilage metabolism.**
- Vitamin K is widely distributed in **our diets** and is also **produced by the normal colon microbiota.**
- Humans cannot synthesize vitamin K endogenously and, thus, must obtain it from exogenous sources via intestinal absorption.
- Absorption of dietary vitamin K in the small intestine is carrier-mediated and is an energy-dependent process.
- Absorption in the microbiota-generated vitamin K in the colon is via passive diffusion.



ABSORPTION IN THE LARGE INTESTINE

- Little absorption occurs in the large intestine.
- Most of absorption occurs in the proximal half of the colon (absorptive colon). Whereas the distal colon function for storage (storage colon).
- The large intestine can absorb a maximum of 5 - 8 liters of fluid and electrolytes each day.

Water	<ul style="list-style-type: none"> • About 0.5- 1.5L/day is absorbed. • The net water loss is 100-200 ml/day.
Sodium	<ul style="list-style-type: none"> • In the presence of $\text{Na}^+ - \text{K}^+$ ATPase at the basolateral membrane, Na^+ is actively absorbed and K^+ is secreted into the lumen of colon.
Chloride	<ul style="list-style-type: none"> • Cl^- is absorbed in exchange for HCO_3^- which is secreted.
Vitamins	<ul style="list-style-type: none"> • Vitamins as vit. K, biotin, B5 , folic acid and some amino acids and short chain fatty acids resulting from bacterial fermentation of CHO are absorbed. • It does not absorb vitamin B12.
Others	<ul style="list-style-type: none"> • Certain drugs as steroids and aspirin may be absorbed. • Reabsorption of organic wastes (urobilinogens & Stercobilinogen) and toxins. • Reabsorption of bile salts.

Colonic Innervation

- The gastrointestinal tract is **densely innervated** to provide **information on its luminal contents, processes regulating digestion and absorption, and potential threats.**
- The enteric nervous system is the largest single division of the autonomic nervous system (ANS), containing between 200 and 600 million enteric neurons throughout the GI tract.
- The colon and rectum are innervated by nerves of both **extrinsic and intrinsic origin.**
- The **extrinsic pathways originate from the central and autonomic (sympathetic and para sympathetic) nervous systems.**
- Autonomic pathways run along parasympathetic and sympathetic chains.
- Each of these pathways include afferent (sensory) and efferent (motor) innervation.
- The **intrinsic innervation consists of the enteric nervous system.**
- **Two major sets of ganglia are found in the colon:**
 1. **The myenteric or Auerbach's plexus** is located between the longitudinal and circular smooth muscle layers and plays a **crucial role in colonic smooth muscle function.**
 2. **The submucosal or Meissner's plexus regulates ion transport.**
- **Clinical importance:** The extreme importance of these two plexuses is clear in children with Hirschsprung's disease in which the ganglia of the myenteric and submucosal plexuses are congenitally absent. The aganglionic segments do not relax and peristalsis is disturbed resulting in severe constipation.

MYENTERIC PLEXUS

- Controlling muscle activity along the length of the gut with specific effects:-
 - Increased muscle tone
 - Increased intensity of the rhythmical contractions
 - Slightly increased rate of the rhythm of contraction
 - Increased velocity of conduction of excitatory waves along gut wall, causing more rapid movement of gut peristaltic waves
- Composed of excitatory as well as inhibitory neurons

SUB-MUCOSAL PLEXUS

- Controlling function within the inner wall of each minute segment of intestine such as:-
 - Local intestinal secretion
 - Local absorption
 - Local contraction of sub-mucosal muscleThat causes various degrees of infolding of GI mucosa.
- Composed of mainly excitatory neurons

- **Sympathetic innervation:**
 - Colonic motility is modulated by sympathetic neurons in **prevertebral ganglia**, which has potent effects on colonic function.
 - The **proximal regions** of the large intestine are sympathetically innervated by fibers that originate from the **superior mesenteric ganglion**.
 - **More distal regions** receive input from the **inferior mesenteric ganglion**.
 - There is evidence for **ongoing tonic inhibition of colonic secretion**, since disrupting the pathway causes a substantial increase in secretion.
 - This is largely mediated by a **strong inhibitory drive to secretomotor neurons in submucosal ganglia**, via **α -2-adrenergic receptors**.
 - **Sympathetic activation also directly contracts sphincters via indirect effects (i.e., by reducing acetylcholine release from**

cholinergic neurons) and inhibits activation of enteric neurons, both actions delay GI and colonic transit.

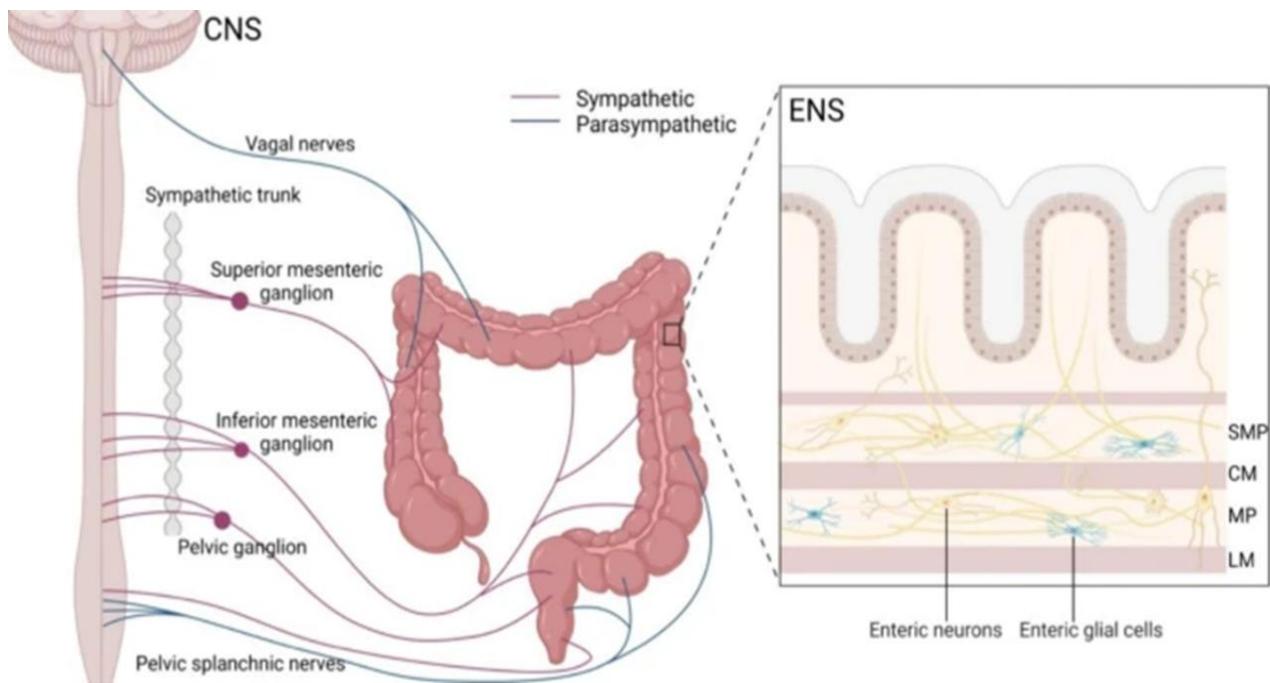
- The **distal rectum and anal canal** are innervated by **sympathetic fibers from the hypogastric plexus.**

- **Parasympathetic innervation:**

There are two pathways of parasympathetic innervation.

- The **cecum and the ascending and transverse** portions of the colon are innervated by the **vagus nerve.**
- **The descending and sigmoid areas of the colon and the rectum** are innervated by **pelvic nerves from the sacral region of the spinal cord.**
- The pelvic nerves enter the colon near the rectosigmoid junction and project orally and aborally within the plane of the myenteric plexus.
- The vagus and pelvic nerves consist primarily of preganglionic efferent fibers and many afferent fibers.
- The efferent fibers synapse with the nerve cell bodies of the myenteric and other intrinsic plexuses.
- **The external anal sphincter**, a striated muscle, is innervated by the **somatic pudendal nerves.**
- Sacral parasympathetic pathways to the colon **primarily synapse onto myenteric neurons.**
- **Excitatory pathways are important for colonic propulsive activity,** especially during defecation; damage to these path ways can cause severe constipation.

- **Chemical mediators:**
 - **Acetylcholine (ACh)** and tachykinins such as **substance P** serve as **major excitatory mediators**.
 - **Nitric oxide (NO)**, vasoactive intestinal peptide (**VIP**), and possibly adenosine triphosphate (**ATP**) serves as **major inhibitory mediators**.
 - Transmission between the **puddal nerves and the external anal sphincter is mediated by ACh**.



Colonic Motility

- Colonic contractile events are divided into:

1. **Segmental contractions (mixing, haustration):** proximal half triggered by stretch (distention) by tenia coli, increase absorption

2. **Propagated contractions (mass movement) :** distal half (stretch, irritation, gastrocolic reflex) over 20 cm

including low-amplitude propagating contractions (LAPC) and high-amplitude propagating contractions (HAPC).

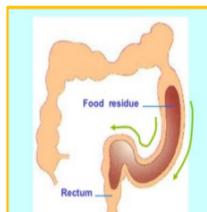
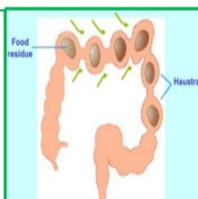
The main function of HAPC is to propagate colonic contents toward the anus.

TYPES OF MOVEMENTS:

1-Mixing movements (Haustrations)

- Ring-like contractions (about 2.5 cm) of the circular muscle divide the colon into pockets³ called **haustra**.
- The contracting segment and receiving segment on either side remain in their respective state for longer periods.
- In addition, there is uniform repetition of the haustra along the colon.
- Net **forward propulsion** occurs when **sequential¹ migration of haustra occurs along the length of the bowel**.

At: Ascending + 1st part of transverse



2-Propulsive movements (Mass Movements)

- The motor events in the **transverse and descending colon**.
- May be **triggered by the increased delivery** of ileal chyme into ascending colon following a meal (**gastrocolic reflex²**).
- Irritants, e.g., castor oil, threatening agents such as parasites and enterotoxins can **initiate mass movement**.
- **Start at the middle of transverse colon** and is preceded by relaxation of the circular muscle and the downstream disappearance of haustral contractions.

At: Descending + rest part of transverse

- **The motor function of the colon includes:**
 - ✓ Propulsion.
 - ✓ Accommodation.
 - ✓ Rapid emptying of a variable portion of the colon during defecation.
 - ✓ The colon must be able to store fecal material until socially acceptable to eliminate.
- Colonic motility is mediated by the **enteric nervous system** in association with **autonomic parasympathetic and sympathetic input** and with input from the **extrinsic nervous system**.
- Colonic motility is characterized by patterns of contraction of longitudinal and circular muscle layers with elimination of feces.
- Motility is integrated with colonic secretion and absorption.

- **Propulsion** is achieved by numerous motor events including **individual contractions, contractile bursts, high-amplitude propagated contractions (HAPCs)**, and possibly **changes in tone**.

- **Accommodation, storage, and distribution** of material within the colon are **mediated by colonic tone**.

- **Tone and phasic activity in the colon** show considerable diurnal variation, **increasing slowly after a meal, reducing during sleep,** and **increasing dramatically upon waking**.

- **HAPCs** occur more frequently **during the morning**, during the **postprandial period**, and **preceding defecation**.
- **The colonic motor response to eating** consists of an **increase in phasic (periodic) and tonic contractile (maintained) activity** that begins within several minutes of ingestion of a meal and continues for a period of **up to 3 hours**.
- This response is **influenced by both the caloric content and composition of the meal** with **fat and carbohydrate stimulating colonic motor activity**, while **amino acids and protein inhibit motor activity**.
- **A more prolonged state of contraction, referred to as tone**, is not regulated by slow waves and may be recognized clearly in the colon (response to feeding), as well as in some sphincteric regions.
- **Tone is regulated by actin-myosin interaction mediated by cellular mechanisms** that are modulated by **neurogenic and mechanical stimuli**.
- Phasic contractions, such as those regulating lumen occlusion, may be superimposed on tonic activity.
- Thus, tone can increase the efficiency of phasic contractions by diminishing the diameter of the lumen.
- Tone also modifies wall tension in response to gut filling and is therefore one determinant of perception of distension.

- This motor input interacts with myogenic mechanisms to create regional patterns of contraction and relaxation which mix and propel content.
- It is likely that regular contractile bursts – colonic motor complexes – do occur, each burst occurring once or twice per hour and lasting approximately 6 minutes.
- **Periodic or cyclic motor activity** is evident **more clearly in the rectum**, the **so-called rectal motor complexes**.
- They do not appear to be synchronized with the small intestinal motor migrating complexes, and their precise function and regulation remain unclear.

Modulators of Colonic Motility

CONTROL OF COLONIC MOTILITY

The intramural plexuses directly control the contractile behavior of the colon.

Stimulatory	Inhibitory
acetylcholine & substance P as neurotransmitter	VIP & NO onto colonic smooth muscle cells

Drugs affecting colonic motility:

1. Muscarinic agonists (i.e., hyoscamine) and cholinesterase inhibitors (i.e., neostigmine) increase colonic motility.

1.2. Yohimbine

- ✓ α -2 adrenergic antagonist.
- ✓ Increases colonic motility.
- ✓ promotes fluid and electrolyte absorption.

2.3. Clonidine

- ✓ α -2 agonist reduces motility.
- ✓ Reduces colonic tone and phasic pressure activity, as well as the colonic perception of distention which can **increase colonic compliance**.
- ✓ Can be used to treat **diarrhea predominant IBS**.

3.4. Alosetron

- ✓ Serotonin 5-HT receptors (5-HT₃) **antagonists**
- ✓ Increase colonic compliance.
- ✓ Reduce postprandial rectal motor activity.
- ✓ improve stool consistency
- ✓ delay colon transit
- ✓ reduce rectal sensitivity in IBS.
- ✓ was approved for IBS-diarrhea predominant in women.

A systematic review of published clinical trials through the Food and Drug Administration (FDA) Adverse Events Reporting System documented **the risk of ischemic colitis was higher with alosetron than placebo (0.15% vs. 0.0%)**, and it was subsequently withdrawn from the market.

4.5. Prucalopride

- ✓ A newer high selectivity affinity **5-HT₄ receptor agonist**, has been approved by the FDA.
- ✓ Extensive cardiovascular assessment suggests it does not affect the Q-T interval.

- ✓ For chronic constipation patients, prucalopride can be used to accelerate intestinal and colonic transit.

5.6. Opioids

- ✓ The GI tract contains three opioid receptors (δ , μ , κ), with the gastrointestinal effects mediated primarily by μ receptors.
- ✓ Opioids reduce neuronal excitability and release of neurotransmitters.
- ✓ Morphine increases colonic phasic segmental activity, reduces fasting colonic tone, and attenuates the gastrocolonic response.
- ✓ Opioids also increase fluid absorption partly by delaying transit and increasing mucosal contact time.
- ✓ Opioid-induced constipation or opioid bowel dysfunction is common, affecting 41–81% of patients treated with opioids.

6.7. Lubiprostone

- ✓ a synthetic bicyclic fatty acid derived from prostaglandin E1 that activates apical ClC-2 chloride channels.
- ✓ activates prostaglandin EP receptors and the apical cystic fibrosis transmembrane regulator (CFTR), **causing intestinal fluid secretion.**
- ✓ accelerates small intestinal and colonic transit in healthy subjects.
- ✓ does not affect colonic motor activity in healthy individuals but is approved by the FDA for **treating chronic constipation and female constipation predominant IBS.**

- **Bile acids** infused directly into the human sigmoid and rectum at concentrations of 5 mmol/L stimulated colonic phasic contractions; however, such concentrations are seldom achieved in the colon unless there has been an ileal resection.
- Rectal infusion of **chenodeoxycholic** acid at physiological concentrations stimulates proximal colonic propagated contractions and increases rectal sensitivity.
- Hence, **chenodeoxycholic acid accelerates colonic transit in healthy subjects.**

These effects have pathophysiological and therapeutic consequences.

- When **enterohepatic circulation of bile acids is disrupted** by ileal disease (e.g., Crohn's disease, surgical resection, or radiation ileitis) or idiopathic mechanisms (idiopathic bile-acid malabsorption), **bile acids spill into the colon, causing diarrhea.**
- Idiopathic bile-acid malabsorption may explain diarrhea in some patients with IBS.
- From a therapeutic perspective, **delayed-release chenodeoxycholic acid**, results in **accelerated colonic transit and improved bowel function in females with constipation-predominant IBS.**

Laxatives

1. Osmotic laxatives

- ✓ hypertonic, pull fluid into the intestinal lumen, causing diarrhea.

✓ **Examples:**

- polyethylene glycol-based solutions.
- magnesium citrate-based products.
- sodium phosphate-based products.
- nonabsorbable carbohydrates [lactulose, sorbitol])

2. Stimulant laxatives:

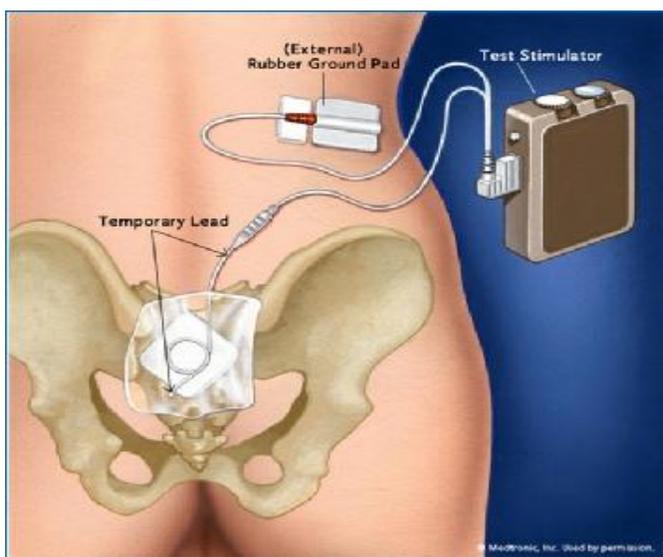
- ✓ by **stimulating** colonic propulsive activity.
- ✓ Stimulant laxatives (e.g., bisacodyl, sodium picosulfate, and glycerol)
- ✓ stimulate **HAPC wave sequences**, thereby leading to **mass movements; bisacodyl and sodium picosulfate also have anti-absorptive plus secretory effects.**
- ✓ Bisacodyl exerts its motor effect through **mucosal afferent nerve fibers**, because the response can be blocked by topical mucosal application of lidocaine.

- **Sacral nerve stimulation**

- While sacral nerve stimulation is **approved by the FDA to treat fecal incontinence**, its role for treating constipation is unclear.
- Sacral nerve stimulation modulates the **extrinsic nerves innervating the pelvic floor and colon**.
- stimulation of the **S3 root also induces propulsive activity throughout the entire colon** and has been shown to **increase stool frequency in patients with slow transit constipation**.

In Kamm's study, colonic transit was assessed in 27 of 45 patients with medically refractory chronic constipation who proceeded to permanent sacral nerve stimulation.

Of these 27 patients, 20 had delayed colonic transit before but only 9 had delayed transit after sacral nerve stimulation.



Microbiome

- A normally functioning GI tract has healthy, well-established colonizing microbiota in its mucosa and lumen, which are major contributors to the maintenance of whole-body homeostasis.
- It is well established that **the species composition and relative abundance of the gut microbiota** are impacted by **the diet, lifestyle, and overall health of an individual.**
- Humans have developed a commensalistic relationship with the gut microbiome.
- Over time, this relationship has evolved to become a mutual and interdependent one, in which the physiologic activity of the microbiota has a significant impact on the host and the activity of the host impacts the general comprising the microbiota.
- In support of life, **gut microbial metabolism supplies the host with short-chain fatty acids and essential vitamins (vitamins B and K) and contributes to the synthesis and absorption of essential amino acids.**
- The adult human intestine contains approximately **110 trillion bacteria.**
- Gas chromatography-mass spectrometry analysis detected more than 700 volatile organic compounds from human feces.
- Our **microbiota is established in the period after birth and although it can be modulated by factors, such as diet, illness, and antibiotic treatment, is relatively resistant to change in later life.**

- The microbial composition **changes along the length of the gut**, in response **to changes in the luminal environment including presence of nutrients, acidity, and oxygen content.**
- Microbial diversity has been used as an index of a “healthy” microbiota, but this is probably a simplistic notion as some beneficial plant foods will decrease diversity yet produce a beneficial host response.
- There is considerable variability that likely depends predominantly on diet and lifestyle.

- The role the human microbiome plays in health and disease is actively under investigation.

- The composition of **feces is altered in diseases** such as IBS, IBD, colorectal cancer, and autism, implicating that **the pathogenesis of these diseases is associated with dysbiosis** (an imbalance in bacterial composition, changes in bacterial metabolic activities, or changes in bacterial distribution within the gut).
- Several studies demonstrate alterations in the fecal and colonic mucosal microbiome in constipation and diarrhea.
- Absent interventional trials, it is unclear whether these associations reflect cause and effect.

However, even after adjusting for demographic features, diet, and colonic transit, the microbiome discriminated between health and constipation with an accuracy of 92%.

- Patients with **IBD** have **altered microbiota**, and they may have changes in their gut microbiota **that precede a diagnosis**.
- IBD is thought to be an **aberrant immune response to luminal content including the microbiota**.
- A shift in the delicate balance (dysbiosis) of “good” bacteria and “bad” pro-inflammatory bacteria may be important for the development and maintenance of IBD.
- For example, ***Roseburia spp.*** Are decreased in those already **diagnosed with IBD**, and as such, the manipulation of the microbiota using antibiotics, probiotics, and prebiotics might be useful in treating IBD.

- **Crohn’s disease (CD)** is associated with **lower overall microbial diversity when compared to healthy controls**.

- The abundance of both the ***Proteobacteria*** and ***Bacteroidetes*** **was significantly higher in CD** when compared to healthy controls and those with ulcerative colitis (UC).

- **Low numbers and the absence of *Faecalibacterium prausnitzii***, a common member of the healthy gut microbial community, have **been associated with UC**.

- Antibiotics have been used to treat IBD with the goal of decreasing concentrations of bacteria in the lumen and altering the community composition.

- The National Institutes of Health (NIH) Human Microbiome Project (NIH HMP) is a roadmap for biomedical research and has three main goals:
 1. Utilize new high-throughput screening technology to characterize the microbiome more completely by studying multiple body sites from 250 “normal” individuals;
 2. Determine if there are associations between changes in the microbiome and health and disease.
 3. Standardize data resources and new technologies for the wider scientific community.

- Phase II of this project has begun, and it aims to examine changes in three microbiome-associated conditions: (1) preterm birth, (2) IBD, and (3) type 2 diabetes.

- The indigenous human microbiome is dominated by two bacterial phyla: ***Firmicutes* and *Bacteroidetes***.
- In many studies, the *Firmicutes* and *Bacteroidetes* account for **greater than 98%** of the bacteria present in the human gut.
- It has long been appreciated that different classes of antibiotics affect the human gut microbial community, both targeted and off-target.

- The use of antibiotics can open niches that were otherwise occupied and allow for new species (good or bad) to take up residency.

For example, changes in human gut microbiome community structure after exposure to the **fluoroquinolone antibiotic, ciprofloxacin**, have **shown that much of the community is altered.**

❖ Dethlefsen et al. reported that all aspects of the gut microbiome community, that is, diversity, richness, and evenness, were decreased and the abundance of approximately one-third of the species present was changed

- **The loss of diversity may cause acute human disease by impacting the role of the microbiome on nutrition, metabolism, and pathogen resistance.**
- After antibiotic treatment was stopped, many of the communities rebounded and closely resembled the original community.
- In some cases, it took nearly **6 months for the microbiome to rebound.**
- It has been suggested that **broad-spectrum antibiotics, especially those with activity against anaerobes**, might **cause longer-lasting changes in the gut microbial community.**

GUT FLORA (GASTROINTESTINAL MICROBIOTA)

it's a complex community of microorganisms that live in GIT. It's established at 1-2 years after birth. They live in symbiosis with human & their effects are beneficial to the body.

FUNCTIONS OF BACTERIAL FLORA

1

Synthesis of vitamin K & some B group vitamins: folic acid, biotin, thiamine, B12.
- The bacteria-formed vitamin K is important since the amount in our daily ingest food isn't sufficient to maintain adequate blood coagulation.

2

Deconjugation and decarboxylation of bile salts.

3

Breakdown of bile pigments to produce stercobilinogen¹.

4

Decarboxylation of amino acids to produce amine & histamine. The amines are excreted in feces and responsible for its smell.

5

Breakdown of urea by bacterial urease to ammonia. Most ammonia is absorbed and converted back into urea by the liver².

6

Fermentation of undigested oligosaccharides producing gases. *Colon bacilli are capable of ingesting small amounts of cellulose.*

Chronic disruption of normal flora in the colon leads to bruising and excessive bleeding.

FOOTNOTES

1. *Stercobilinogen* (fecal urobilinogen) is a chemical created by bacteria in the gut. It is made of broken-down hemoglobin. It is further processed to become the chemical that gives feces its brown color.
2. Ammonia is normally converted to urea in the liver and cleared out of the body through the urine. In individuals with acute or chronic liver disease, there's a buildup of ammonia in the blood which play a role in *hepatic encephalopathy*.