Secretion and Absorption in the Large Intestine

The large intestine is the last attraction in digestive tube and the location of the terminal phases of digestion. It functions in three processes:

- **Recovery of water and electrolytes from ingesta**: By the time ingesta reaches the terminal ileum, roughly 90% of its water has been absorbed, but considerable water and electrolytes like sodium and chloride remain and must be recovered by absorption in the large gut.
- **Formation and storage of feces**:
- **Microbial fermentation**: The large intestine of all species teems with microbial life. Those microbes produce enzymes capable of digesting many of molecules that to vertebrates are indigestible, cellulose being a premier example. The extent and benefit of fermentation also varies greatly among species.

Absorption, Secretion and Formation of Feces in the Large Intestine

1. **Absorption**: water, sodium ions and chloride ions
2. **Secretion**: bicarbonate ions and mucus

Water, as always, is absorbed in response to an osmotic gradient. The mechanism responsible for generating this osmotic pressure is essentially identical to what was seen in the small intestine - sodium ions are transported from the lumen across the epithelium by virtue of the epithelial cells having very active sodium pumps on their basolateral membranes and a means of absorbing sodium through their luminal membranes. The colonic epithelium is actually more efficient at absorbing water than the small intestine and sodium absorption in the colon is enhanced by the hormone aldosterone.

Chloride is absorbed by exchange with bicarbonate. The resulting secretion of bicarbonate ions into the lumen aids in neutralization of the acids generated by microbial fermentation in the large gut.

Model for electrogenic NaCl absorption in the large intestine

This Na⁺ flux is electrogenic; that is, it is associated with an electrical current, and it can be inhibited by the diuretic drug amiloride at micromolar concentrations.

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Microbial Fermentation
Fermentation is the enzymatic decomposition and utilization of foodstuffs, particularly carbohydrates, by microbes.
The large intestine does not produce its own digestive enzymes, but contains huge numbers of bacteria which have the enzymes to digest and utilize many substrates. In all animals, two processes are attributed to the microbial flora of the large intestine:

1. Digestion of carbohydrates not digested in the small intestine
Cellulose is common constituent in the diet of many animals, including man, but no mammalian cell is known to produce a cellulase. Several species of bacteria in the large intestine synthesize cellulases and digest cellulose. Colonic bacteria rapidly metabolize the saccharides, forming gases, short-chain fatty acids, and lactate. The major short-chain fatty acids formed are acetic acid (two carbon), propionic acid (three carbon), and butyric acid (four carbon). The short-chain fatty acids are absorbed by the colonic mucosal cells and can provide a substantial source of energy for these cells. The major gases formed are hydrogen gas (H₂), carbon dioxide (CO₂), and methane (CH₄). These gases are released through the colon, resulting in flatulence, or in the breath. Incomplete products of digestion in the intestines increase the retention of water in the colon, resulting in diarrhea.

2. Synthesis of vitamin K and certain B vitamins
Synthesis of vitamin K by colonic bacteria provides a valuable supplement to dietary sources and makes clinical vitamin K deficiency rare. Similarly, formation of B vitamins by the microbial flora in the large intestine is useful to many animals. They are not absorbed in the large intestine, but are present in feces.

Q Beans, peas, soybeans, and other leguminous plants contain oligosaccharides with (1,6)-linked galactose residues that cannot be hydrolyzed for absorption, including sucrose with 1, 2, or 3 galactose residues attached. What is the fate of these polysaccharides in the intestine?

A These sugars are not digested well by the human intestine but form good sources of energy for the bacteria of the gut. These bacteria convert the sugars to H₂, lactic acid and short-chain fatty acids. The amount of gas released after a meal containing beans is especially notorious.
Digestive Disorders

1. Stomach and Intestine

Peptic ulcers

Peptic ulcer is a general term that refers to ulcers occurring in the lower esophagus, the stomach, or the duodenum (upper part of the small intestine).

What is the difference between a duodenal ulcer and a gastric ulcer?

A duodenal ulcer is a break in the lining of the upper part of the small intestine (the duodenum); a gastric ulcer is a break in the lining of the stomach.

What causes duodenal and gastric ulcers?

Duodenal ulcers are much more common than gastric ulcers. The primary cause of duodenal ulcers is increased production of acid by the stomach. Gastric ulcers, on the other hand, are thought to be caused by changes in the stomach lining that make it more susceptible to damage by the acid normally produced by the stomach.

Factors in the development of peptic ulcers include:

- **Helicobacter pylori**
  Research shows that most ulcers develop as a result of infection with bacterium called Helicobacter pylori (H. pylori).

- **Smoking**
  Studies show smoking increases the chances of getting an ulcer, slows the healing process of existing ulcers, and contributes to ulcer recurrence.

- **Caffeine**
  Caffeine seems to stimulate acid secretion in the stomach, which can aggravate the pain of an existing ulcer. However, the stimulation of stomach acid cannot be attributed solely to caffeine.

- **Alcohol**
  Although no proven link has been found between alcohol consumption and peptic ulcers, ulcers are more common in people who have cirrhosis of the liver, a disease often linked to heavy alcohol consumption.

- **Stress**
  Mucos HCO₃ content creates a "micro-environment" around surface cells to prevent acid damage, but its secretion is inhibited by adrenergic input (prominent in stress!)

- **Acid and pepsin**
It is believed that the stomach's inability to defend itself against the powerful digestive fluids, hydrochloric acid and pepsin, contributes to ulcer formation.

- **nonsteroidal anti-inflammatory drugs (NSAIDs)**
These drugs (such as aspirin, ibuprofen, and naproxen sodium) make the stomach vulnerable to the harmful effects of acid and pepsin.

### 2. Bile and the Biliary System
**Gallstones (Cholelithiasis)**
There are two major types of gallstones, which form due to distinctly different pathogenetic mechanisms.

1. **Cholesterol Stones**
About 90% of gallstones are of this type. These stones can be almost pure cholesterol or mixtures of cholesterol and substances such as mucin.

The key event leading to formation and progression of cholesterol stones is precipitation of cholesterol in bile. There are clearly important genetic determinants for cholesterol stone formation. There is also an important gender bias in development of stones - the prevalence in adult females is two to three times that seen in males and use of contraceptive steroids is a risk factor for development of gallstones.

2. **Pigment Stones**
Roughly 10% of human gallstones are pigment stones composed of large quantities of bile pigments, along with lesser amounts of cholesterol and calcium salts. The most important risk factor for development of these stones is chronic hemolysis from almost any cause - bilirubin is a major constituent of these stones. Additionally, some forms of pigment stones are associated with bacterial infections. Apparently, some bacteria release deconjugate bilirubin, leading to precipitation as calcium salts.

**b. Jaundice**
Jaundice, is yellowing of the skin, sclera (the white of the eyes) and mucous membranes caused by increased levels of bilirubin in the human body. Usually the concentration of bilirubin in the blood must exceed 2-3mg/dL for the coloration to be easily visible. Jaundice comes from the French word jaune, meaning yellow.

**Causes of jaundice**
When red blood cells die, the heme in their hemoglobin is converted to bilirubin in the spleen. The bilirubin is processed by the liver, enters bile and is eventually excreted through faeces.

Consequently, there are three different classes of causes for jaundice. **Pre-hepatic** or hemolytic causes, where too many red blood cells are broken down, **hepatic** causes where the processing of bilirubin in the liver does not function correctly, and **post-hepatic** or extrahepatic causes, where the removal of bile is disturbed.

1. **Pre-hepatic**
Pre-hepatic (or hemolytic) jaundice is caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells). Malaria can cause jaundice. Certain genetic
diseases, such as glucose 6-phosphate dehydrogenase deficiency can lead to increase red cell lysis and therefore hemolytic jaundice. Defects in bilirubin metabolism also present as jaundice.

2. Hepatic
Hepatic causes include acute hepatitis, hepatotoxicity and alcoholic liver disease. Jaundice commonly seen in the newborn baby is another example of hepatic jaundice.

   • Neonatal jaundice
Neonatal jaundice is usually harmless: this condition is often seen in infants around the second day after birth, lasting till day 8 in normal births, or to around day 14 in premature births. Serum bilirubin normally drops to a low level without any intervention required: the jaundice is presumably a consequence of metabolic and physiological adjustments after birth. Infants with neonatal jaundice are typically treated by exposing them to high levels of colored light to break down the bilirubin. This works due to a photo oxidation process occurring on the bilirubin in the subcutaneous tissues of the neonate. Light energy creates isomerization of the bilirubin and consequently transformation into compounds that the new born can excrete via urine and stools.

3. Post-hepatic
Post-hepatic (or obstructive) jaundice, also called cholestasis, is caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones in the common bile duct and pancreatic cancer in the head of the pancreas.

The van den Bergh test:
When a mixture of sulphanic acid, hydrochloric acid and sodium nitrite (diazo reagent) is added to serum containing an excess of bilirubin glucuronide a reddish-violet color results, the maximum color intensity being reached within 30 seconds (direct reaction) (for hepatic and post hepatic jaundice)
When the same above reagents are mixed with serum containing an excess of billirubin itself or bilirubin-protein complex no color develops until alcohol is added, then the reddish-violet color appears. (indirect reaction) (for pre hepatic jaundice)
Note: the addition of alcohol solvent provides the means of solution for the water insoluble bilirubin which is thus enabled to react with the diazo reagent

3. Intestine
Diarrhea is an increase in the volume of stool or frequency of defecation. It is one of the most common clinical signs of gastrointestinal disease, but also can reflect primary disorders outside of the digestive system.
There are numerous causes of diarrhea, but in almost all cases, this disorder is a manifestation of one of the four basic mechanisms described below.

1. Osmotic Diarrhea
Absorption of water in the intestines is dependent on adequate absorption of solutes. If excessive amounts of solutes are retained in the intestinal lumen, water will not be absorbed and diarrhea will result. Osmotic diarrhea typically results from one of two situations:

   • Ingestion of a poorly absorbed substrate: The offending molecule is usually a carbohydrate or divalent ion. Common examples include mannitol or sorbitol, epson salt (MgSO₄) and some antacids (MgOH₂).
   • Malabsorption: Inability to absorb certain carbohydrates is the most common deficit in this category of diarrhea, but it can result virtually any type of malabsorption. A common example is lactose intolerance resulting from a deficiency in the brush border enzyme lactase. In such cases, a moderate quantity of lactose is consumed (usually as milk), but the intestinal epithelium is deficient in lactase, and lactose cannot be effectively hydrolyzed into glucose and galactose for absorption. The osmotically-active lactose is retained in the intestinal lumen, where it "holds" water.

   • A distinguishing feature of osmotic diarrhea is that it stops after the patient is fasted or stops consuming the poorly absorbed solute.

2. Secretory Diarrhea
Large volumes of water are normally secreted into the small intestinal lumen, but a large majority of this water is efficiently absorbed before reaching the large intestine. Diarrhea occurs when secretion of water into the intestinal lumen exceeds absorption. Many millions of people have died of the secretory diarrhea associated with cholera. The responsible organism, Vibrio cholerae, produces cholera toxin, which strongly activates adenyl cyclase, causing a prolonged increase in intracellular concentration of cyclic AMP within crypt enterocytes. This change results in prolonged opening of the chloride channels that are instrumental in secretion of water from the crypts, allowing uncontrolled secretion of water.

Exposure to toxins from several other types of bacteria (e.g. E. coli heat-labile toxin) induce the same series of steps and massive secretory diarrhea that is often lethal unless the person or animal is aggressively treated to maintain hydration. In addition to bacterial toxins, a large number of other agents can induce secretory diarrhea by turning on the intestinal secretory machinery, including:

- some laxatives
- hormones secreted by certain types of tumors (e.g. vasoactive intestinal peptide)
- a broad range of drugs (e.g. some types of asthma medications, antidepressants, cardiac drugs)
- certain metals, organic toxins, and plant products (e.g. arsenic, insecticides, mushroom toxins, caffeine)

In most cases, secretory diarrheas will not resolve during a 2-3 day fast.

3. Inflammatory and Infectious Diarrhea

The epithelium of the digestive tube is protected from insult by a number of mechanisms constituting the gastrointestinal barrier, but like many barriers, it can be breached and often associated with widespread destruction of absorptive epithelium. In such cases, absorption of water occurs very inefficiently and diarrhea results. Examples of pathogens frequently associated with infectious diarrhea include:

- Bacteria: Salmonella, E. coli, Campylobacter
- Viruses: rotaviruses
- Protozoa:

4. Diarrhea Associated with Deranged Motility

In order for nutrients and water to be efficiently absorbed, the intestinal contents must be adequately exposed to the mucosal epithelium and retained long enough to allow absorption. Disorders in motility than accelerate transit time could decrease absorption, resulting in diarrhea even if the absorptive process per se was proceeding properly.