Gastrointestinal Physiology
Digestion and Absorption
Carbohydrates, proteins, and lipids are digested and absorbed in the small intestine. The surface area for absorption in the small intestine is greatly increased by the presence of the many folds called valvulae conniventes (or folds of Kerckring), which increase the surface area of the absorptive mucosa about threefold. Located on the epithelial surface of the small intestine all the way down to the ileocecal valve are millions of small villi. These villi project about 1 millimeter from the surface of the mucosa brush border consisting of as many as 1000 microvilli that are 1 micrometer in length and 0.1 micrometer in diameter and protrude into the intestinal chyme. The total absorptive area of the mucosa perhaps 1000-fold, making a tremendous total area of 250 or more square meters for the entire small intestine—about the surface area of a tennis court.

Absorption from the small intestine each day consists of several hundred grams of carbohydrates, 100 or more grams of fat, 50 to 100 grams of amino acids, 50 to 100 grams of ions, and 7 to 8 liters of water. The absorptive capacity of the normal small intestine is far greater than this; each day as much as several kilograms of carbohydrates, 500 grams of fat, 500 to 700 grams of proteins, and 20 or more liters of water can be absorbed. The large intestine can absorb still more water and ions, although it can absorb very few nutrients.
A. Carbohydrates

1. Digestion of carbohydrates

We can classify carbohydrates into three main groups:

1. Simple sugars (mono- and disaccharides),

   Mono-saccharides: glucose, galactose and fructose

   Di-saccharides:
   - maltose: glucose + glucose,
   - sucrose (cane sugar): fructose and glucose,
   - Lactose (milk sugar) glucose and galactose,
   - trehalose: glucose + glucose

2. Oligosaccharides (polymers of 3 - 10 monosaccharide units): few
   - maltotriose (three glucose molecules), and α-limit dextrins (five glucose molecules).

3. Polysaccharides (polymers of several hundred monosaccharide units): many
   - Glycogen (animal starch): the glucose molecules are mostly in long chains (glucose molecules in 1:4α linkage), but there is some chain-branching ((produced by 1:6α linkages).
   - Starch (plant starch) and their derivatives are only polysaccharides that are digested to any degree in the human GIT.
   - Amylopectin, which constitutes 80 to 90% of dietary starch, is similar to glycogen but less branched, Amylose is a straight chain with only 1:4α linkages. Also we have cellulose, dextrin, inulin
Stages of Carbohydrate digestion:
In the mouth, starch is attacked by salivary α-amylase. However, the optimal pH for this enzyme is 6.7, and its action is inhibited by the acidic gastric juice when food enters the stomach. The food remains in the mouth only a short time, so probably not more than 5 percent of all the starches will have become hydrolyzed by the time the food is swallowed. Starch digestion sometimes continues in the body and fundus of the stomach for as long as 1 hour before the food becomes mixed with the stomach secretions. Activity of the salivary amylase is then blocked by acid of the gastric secretions because the amylase is essentially inactive as an enzyme once the pH of the medium falls below about 4.0. Nevertheless, on average, before food and its accompanying saliva become completely mixed with the gastric secretions, as much as 30 to 40 percent of the starches will have been hydrolyzed, mainly to form maltose.

In the small intestine, both the salivary and pancreatic α-amylase also acts on the ingested polysaccharides. They hydrolyze 1:4α linkages but spare 1:6α linkages, terminal 1:4α linkages, and the 1:4α linkages next to branching points. Consequently, the end products of α-amylase digestion are oligosaccharides yielding maltose, maltotriose, and α-limit dextrins. Therefore, within 15 to 30 minutes after the chyme empties from the stomach into the duodenum and mixes with pancreatic juice, virtually all the carbohydrates will have become digested.

In general, the carbohydrates are almost totally converted into maltose and/or other small glucose polymers before passing beyond the duodenum or upper jejunum. Oligo-saccharidases (Maltase, α-dextrinase, and sucrase) responsible for the further digestion of the starch derivatives are located in the outer portion of the brush border, the membrane of the micro-villi of the small intestine. Di-saccharidases (maltase sucrase Lactase trehalase, degrades maltose sucrose Lactose trehalose respectively). Carbohydrates must be digested to glucose, galactose, and fructose for absorption to proceed. Only mono-saccharides are absorbed.
2. Absorption of carbohydrates
   a. Glucose and galactose
      • are transported from the intestinal lumen into the cells by Na+-dependent cotransport
        (SGLT-1: Sodium-GLucose co-Transporter-1) in the luminal membrane. The sugar is
        transported "uphill" and Na+ is transported "downhill."
        This will facilitate the transport of Na and glucose into the enterocytes. This why; the
        transport of most hexose is uniquely affected by the amount of Na in the intestinal lumen.
        There are two kinds of SGLT which are (SGLT-1 and SGLT-2). SGLT-1 and SGLT-2 are also
        responsible for glucose transport out of the renal tubules.
      • are then transported from cell to blood by facilitated diffusion (GLUT 2: GLUcose-
        Transporter-2).
      • The Na+-K+ pump in the basolateral membrane keeps the intracellular [Na+] low, thus
        maintaining the Na+ gradient across the luminal membrane.
        Poisoning the Na+-K+ pump inhibits glucose and galactose absorption by dissipating the
        Na+ gradient.
   b. Fructose
      • is transported exclusively by facilitated diffusion
        (GLUT-5: glucose-transporter-5; therefore, it cannot be absorbed against a concentration gradient.
        GLUT 2 may assist in the absorption of excess luminal fructose GLUT2 also has fructose transport activity
        but with lower affinity than GLUT5 Glucose, galactose, and fructose leave the cell at the basolateral
        membrane by facilitated transport via a common transporter, GLUT2
Absorption of pentose:
Pentoses are absorbed by simple diffusion. **Insulin** has little effect on intestinal transport of sugar. The maximal rate of glucose absorption from the intestine is about (120 gm/hour).

3. Clinical disorders of carbohydrate absorption
   - **Lactose intolerance** results from the absence of brush border lactase and, thus, the inability to hydrolyze lactose to glucose and galactose for absorption. Non-absorbed lactose and H2O remain in the lumen of the GI tract and cause osmotic diarrhea.

**B. Proteins**
**Stomach:**
There are two important protein digestive enzymes which are pepsin and gelatinase (It liquefies gelatin). Pepsin is not essential for protein digestion. One of the important features of **pepsin digestion** is its ability to:
1. **digest the protein collagen**, an
2. **albuminoid type of protein** that is affected little by other digestive enzymes.
   
**Stimulated by:** Acetylcholine and gastrin
Pepsin only initiates the process of protein digestion, usually providing only 10 to 20 percent of the total protein digestion to Pepsin is an endopeptidase responsible for the initial digestion of protein. It hydrolyzes the bonds between aromatic amino acids such as (phenylalanine or tyrosine) and second amino acid, converting the protein to proteoses, peptones, and a few polypeptides. This splitting of proteins occurs as a result of hydrolysis at the peptide linkages between amino acids, so the products of peptic digestion are polypeptides of very diverse sizes.

**Small intestine:**
In the small intestine, the polypeptides formed by digestion in the stomach are further digested by the powerful proteolytic enzymes of the pancreas and intestinal mucosa.

d. Pancreatic proteases
   - include trypsin, chymotrypsin, elastase, carboxypeptidase A, and carboxy-peptidase B. Pancreatic proteases are secreted in inactive forms that are activated in the small intestine as follows:
     1. Trypsinogen is activated to trypsin by a brush border enzyme, entero-kinase.
     2. Trypsin then converts chymo-trypsinoen, pro-elastase, and pro-carboxy-peptidase A and B to their active forms. (Even trypsinogen is converted to more trypsin by trypsin)
Secretion of Trypsin Inhibitor Prevents Digestion of the Pancreas Itself.

It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called trypsin inhibitor. This substance is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. And, because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents activation of the others as well.

When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is often overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called acute pancreatitis. This is sometimes lethal because of accompanying circulatory shock; even if not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.
a. Endo-peptidases
• degrade proteins by hydrolyzing interior peptide bonds.

b. Exo-peptidases
• hydrolyze one amino acid at a time from the C terminus of proteins and peptides.

1. Endo-peptidases: They include trypsin, chymotrypsins, and elastase. They act at interior peptide bonds in the peptide molecules.

2. Exo-peptidases: They include pancreatic carboxy-peptidase that hydrolyzes the amino acids at the carboxyl and amino ends of the polypeptides. Some free amino acids are liberated in the intestinal lumen, but others are liberated at the cell surface by the amino-peptidase, carboxy-peptidase, endo-peptidase, and di-peptidase in the brush border of the mucosal cells. Some di and tri-peptides are actively transported into the intestinal cells and hydrolyzed by intra-cellular peptidases, with amino acids entering the bloodstream.

Thus, the final digestion to amino acids occurs in three locations: the intestinal lumen, the brush border, and the cytoplasm of the mucosal cells.
2. Absorption of proteins
- Digestive products of protein can be absorbed as amino acids, di-peptides, and tri-peptides (in contrast to carbohydrates, which can only be absorbed as mono-saccharides).
  
a. Free amino acids
  - Na+-dependent amino acid co-transport occurs in the luminal membrane. It is analogous to the co-transporter for glucose and galactose.
  - The amino acids are then transported from cell to blood by facilitated diffusion.
  - There are four separate carriers for neutral, acidic, basic, and imino amino acids, respectively.

b. Dipeptides and tripeptides
- are absorbed faster than free amino acids.
- H+-dependent co-transport of dipeptides and tripeptides occurs in the luminal membrane.
- After the di-peptides and tri-peptides are transported into the intestinal cells, cytoplasmic peptidases hydrolyze them to amino acids. The amino acids are then transported from cell to blood by facilitated diffusion.

Half of the amino acids absorbed in the intestine are from the diet, the remaining part is from digestive secretions and from desquamated mucosal cells.
Absorption of amino acids is rapid in the duodenum and jejunum but slow in ileum.

Approximately 50% of the digested protein comes from ingested food, 25% from proteins in digested juices, and 25% from de-sequestered mucosal cells.

Only 2 to 5% of the protein in the small intestine escapes digestion and absorption. Some of the ingested protein enters the colon and is eventually digested by bacterial action.

The protein in the stool is not of dietary origin but comes from bacteria and cellular debris.

There is evidence that the peptidase activates of the brush border and the mucosal cell cytoplasm are increased by ① resection of part of the ileum and ② they are independent altered in starvation. Thus, these enzymes appear to be subject to homeostatic regulation.

In infants, moderate amount of undigested proteins are also absorbed. The protein antibodies in maternal colostrums are largely secreted immunoglobulin (IgA), the production of which is increased in the breast in late pregnancy. They cross the mammary epithelium by transcytosis and enter the circulation of the infant from the intestine, providing passive immunity against infections. Absorption is by endocytosis and subsequent exocytosis.

Protein absorption decline with age, but adults still absorb small quantities.

Foreign proteins that enter the circulation provoke the formation of antibodies, and the antigen-antibody reaction occurring upon substances entry of more of the same protein may cause allergic symptoms.

Nucleic acids digestion and absorption:

Nucleic acids are split into nucleotides in the intestine by (pancreatic nucleases), and the nucleotides are split into the nucleosides and phosphoric acid by (nucleosidase) enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugars and purine and pyrimidine bases by (nucleosidase) enzyme. The bases are absorbed by active transport.
C. Lipids
1. Digestion of lipids

Mouth and stomach:
- Mouth and stomach secret lingual lipase and gastric lipase respectively.
- Lingual lipase is active in the stomach and can digest as much as 20% of dietary triglyceride.
- The gastric lipase is of little importance except in pancreatic insufficiency.
- In the stomach, mixing breaks lipids into droplets to increase the surface area for digestion by pancreatic enzymes.
- Lingual lipases digest some of the ingested triglycerides to monoglycerides and fatty acids. However, most of the ingested lipids are digested in the intestine by pancreatic lipases.
- CCK slows gastric emptying. Thus, delivery of lipids from the stomach to the duodenum is slowed to allow adequate time for digestion and absorption in the intestine.
Intestine:

1. Pancreatic lipase:

- Pancreatic lipase with molecular weight (100,000 kDa)
- Pancreatic lipase represents about 4% of the total protein in pancreatic juice.
- Pancreatic lipase of the most important enzymes involved in fat digestion (80%)
- Pancreatic lipase hydrolyzes the 1- and 3-bonds of the triglycerides which relative ease but acts on the 2-bonds at a very low rate, so the principle product of its action are free fatty acids and 2-mono-glycerides.
- Pancreatic lipase activity is facilitated when an amphipathic helix that covers the active sites like a lid is bent back.

- Colipase, a protein with a molecular weight of about (1,000). Colipase is secreted in pancreatic juice, and when Colipase binds to the -COOH-terminal domain (polar) of the pancreatic lipase and activate it, the pancreatic co-lipase displaces the bile acids coating the droplet, thus generating an area where, the pancreatic lipase, can access the triglycerides(non-polar domain: tail). Colipase is secreted in an inactive pro-form and is activated in the terminal lumen by trypsin.

- Pancreatic lipase acts on fats that have been emulsified (bile salt activated lipase)
- Bile salt-activated lipase catalyzes the hydrolysis of 1 cholesterol ester, 2 esters of fat-soluble vitamins, and 3 phospholipids as well as 4 triglycerides.
(2) Other Pancreatic enzymes

1. **cholesterol esterase**: ingested cholesterol ester to cholesterol and fatty acids.

2. **phospholipase A2**
   - Ingested lecithin to lysolecithin (lysophospholipids) and fatty acids. Lysolecithin (lysophospholipids) aid digestion of other lipids by breaking up fat globules into small micelles.
   - Phospholipase A2 is secreted as proenzyme and activated by trypsin and require bile salt for activity.

(3) The hydrophobic products of lipid digestion are solubilized in micelles by bile acids.
2. Absorption of lipids
   a. Micelles bring the products of lipid digestion into contact with the absorptive surface of the intestinal cells. Traditionally, lipids were thought to enter the enterocytes by passive diffusion, but there is some evidence that carriers are involved. Then, fatty acids, monoglycerides, and cholesterol diffuse across the luminal membrane into the cells.
   Glycerol is hydrophilic and is not contained in the micelles.
   b. The fate of the fatty in enterocytes depends on their size:
      First: Fatty acids less than 10 to 12 carbon atoms pass from the mucosal cells directly into the portal blood, where they are transported as free (un-esterified) fatty acids.
      Second: The fatty acids containing more than 10 to 12 carbon atoms are re-esterified to triglycerides in the mucosal cells. In addition, some of the absorbed cholesterol is esterified. The triglycerides and cholesterol esters are then coated with a layer of protein (apoprotein-B), cholesterol, and phospholipids to form chylomicrons maintaining a favorable concentration gradient from the lumen into the cells. These leave the cell and enter the lymphatics.
Lack of apoprotein-B results in the inability to transport chylomicrons out of the intestinal cells and causes a-beta-lipo-protein-emia.

c. Chylomicrons are transported out of the intestinal cells by exocytosis. Because chylomicrons are too large to enter the capillaries, they are transferred to lymph vessels and are added to the bloodstream via the thoracic duct.

Absorption of long-chain fatty acids is greater in the upper part of the small intestine, but appreciable amount are also absorbed in the ileum.

On a moderate fat intake, 95% or more of the ingested fat is absorbed. The processes involved in fat absorption are not fully mature at birth, and infants fail to absorb 10 to 15% of ingested fat. Thus, they are more susceptible to the ill effects of disease processes that reduce fat absorption.

Unlike the ileal mucosa, the rate of uptake of bile salts by the jejunal mucosa is low, and for the most part of the bile salts remains in the intestinal lumen, where they are available for the formation of new
Short-chain fatty acids also referred to as volatile fatty acids:

Short-chain fatty acids are 2 to 5 carbon

Short-chain fatty acids are weak acids.

Short-chain fatty acids have an average normal concentration of about 80 mmol/L in the lumen.

Short-chain fatty acids are produced in the colon by the action of colonic bacteria on complex carbohydrate, resistant starches, and other components of the dietary fiber, i.e., the material that escape digestion in the upper GIT and enter the colon.

Short-chain fatty acids are absorbed in the colon in part by exchange for H⁺; there is a family of anion exchange in the colonic epithelial cells.

Short-chain fatty acids has the following functions:

① are metabolized and make a significant contribution to the total caloric intake.
② exert atrophic effect (has a growth effect) on the colonic epithelial cells.
③ combat inflammation,
④ helping to maintain acid-base equilibrium.
⑤ Short-chain fatty acids also promote the absorption of Na, although the exact mechanism for coupled (Sodium-short-chain fatty acids) absorption is unsettled.
3. Malabsorption of lipids-steatorrhea

Steatorrhea: Passage of fat in large amounts in the feces, due to failure to digest and absorb fat. Stools may be 1 bulky and 2 difficult to flush, 3 have a pale and oily appearance and can be especially 4 foul-smelling.

• can be caused by any of the following:
  a. Pancreatic disease (e.g., pancreatitis, cystic fibrosis), in which the pancreas cannot synthesize adequate amounts of the enzymes needed for lipid digestion
  b. Hyper-secretion of gastrin ► gastric H+ secretion is increased ► the duodenal pH is decreased ► inactivates pancreatic lipase.
  c. Ileal resection, which leads to a depletion of the bile acid pool because the bile acids do not recirculate to the liver
  d. Bacterial overgrowth, which may lead to de-conjugation of bile acids and their "early" absorption in the upper small intestine. In this case, bile acids are not present throughout the small intestine to aid in lipid absorption.
  e. Decreased number of intestinal cells for lipid absorption (tropical sprue)
  f. Failure to synthesize apoprotein B, which leads to the inability to form chylomicrons
Absorption and secretion of electrolytes and H₂O

• Electrolytes and H₂O may cross intestinal epithelial cells by either cellular or para-cellular (between cells) routes.
• Tight junctions attach the epithelial cells to one another at the luminal membrane.
• The permeability of the tight junctions varies with the type of epithelium. A "tight" (impermeable) epithelium is the colon. "Leaky" (permeable) epithelia are the small intestine and gallbladder.

The intestines are presented each day 2000 mL, of ingested fluid plus 7000 mL of secretions from the mucosa of GIT and associated glands. 98% of this fluid is re-absorbed, with a daily fluid loss of only 200 mL in stool.

<table>
<thead>
<tr>
<th>Secretion site</th>
<th>Daily Volume</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>1000</td>
<td>6.0 - 7.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>1500</td>
<td>1.0 - 3.0</td>
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<tr>
<td>Brunners Glands (duodenum)</td>
<td>200</td>
<td>8.0 - 9.0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1000-1500</td>
<td>8.0 - 8.3</td>
</tr>
<tr>
<td>Bile</td>
<td>1000</td>
<td>7.8</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>1800</td>
<td>7.5 - 8.0</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>200</td>
<td>7.5 - 8.0</td>
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Only small amounts of water move across the gastric mucosa, but water moves in both directions across the mucosa of small and large intestines in response to osmotic gradients.

Water moves into or out of the intestine until the osmotic pressure of the intestinal content equals that of the plasma. The osmolality of the duodenal contents may be hypertonic or hypotonic, depending on the meal ingested, but by the time the meal enters the jejunum, its osmolality is close to that of plasma. This osmolality is maintained throughout the rest of the small intestine, the osmotically active particles the osmotic gradient thus generated.

In the colon, Na is pumped out and water moves passively with it, again along the osmotic gradient.
A. Absorption of Na
20 to 30 grams of sodium are secreted in the intestinal secretions each day. In addition, the average person eats 5 to 8 grams of sodium each day. Therefore, to prevent net loss of sodium into the feces, the intestines must absorb 25 to 35 grams of sodium each day, which is equal to about \( \frac{1}{7} \) of all the sodium present in the body.

Whenever significant amounts of intestinal secretions are lost to the exterior, as in extreme diarrhea, the sodium reserves of the body can sometimes be depleted to lethal levels within hours. Normally, however, less than 0.5% of the intestinal sodium is lost in the feces each day because it is rapidly absorbed through the intestinal mucosa. Sodium also plays an important role in helping to absorb sugars and amino acids, as subsequent discussions reveal.

The villous cells absorb Na\(^+\) through the luminal brush border membrane by three mechanisms:

A. An inward diffusion gradient through a Na\(^+\)-channel,

1. Concentration gradient: The \([\text{Na}^+]\) is kept low (14 mM) in the cell, whereas \([\text{Na}^+]\) is 140 mM in the intestinal lumen. This concentration gradient work together with an electrical gradient, 2. Electrical gradient: since the cytosol of the cell is -40 mV with the intestinal content as a reference. Thus Na\(^+\) can easily pass the luminal brush border membrane passively.

The intestinal mucosa has ion permeable tight junctions - it is leaky. This para-cellular transport is so great that the net absorption of Na\(^+\) and Cl\(^-\) through the cells only amounts to 10% of the total transport through the mucosa.
B. A Na\(^+\)-H\(^+\)-exchange
The transport of Na\(^+\) into the enterocyte is through a co-exchange protein (Na\(^+\)/H\(^+\)). Part of the energy released by Na\(^+\) moving down its gradient is used to extrude H\(^+\) into the intestinal lumen. Here H\(^+\) reacts with bicarbonate from bile and pancreatic juice to produce CO\(_2\) and water, thus reducing the pH of the intestinal fluid.

C. A Na\(^+\) -solute coupled cotransport (the solute being glucose, galactose, bile salts, water-soluble vitamins and amino acids).

The basolateral membrane of the enterocyte contains a Na\(^+\)-K\(^+\)-pump, which maintains the inward directed Na\(^+\)-gradient. The pump is energized by the hydrolysis of ATP, which provides the driving force for Na\(^+\) entry. Thus an active process pumps Na\(^+\) out in the small interstitial space and K\(^+\) is pumped into the cell. The basolateral membrane also contains many K\(^+\)-channel proteins, so K\(^+\) will leak back to the interstitial space almost as soon as it has entered the cell. The K\(^+\) is absorbed by diffusion - a daily net total of 80 mmol.
B. Secretion of Bicarbonate and Absorption of Chloride Ions in the Ileum and Large Intestine.

The epithelial cells on the surfaces of the villi in the ileum, as well as on all surfaces of the large intestine, have a special capability of secreting bicarbonate ions in exchange for absorption of chloride ions. This capability is important because it provides alkaline bicarbonate ions that neutralize acid products formed by bacteria in the large intestine.

2. Absorption of Chloride Ions in the Small Intestine

A. In the upper part of the small intestine, chloride ion absorption is rapid and occurs mainly by diffusion. Absorption of sodium ions through the epithelium creates electronegativity in the chyme and electro-positivity in the para-cellular spaces between the epithelial cells.

Chloride ions then move along this electrical gradient to “follow” the sodium ions.

B. The ileum and large intestine

Chloride is absorbed across the brush border membrane by a brush border membrane chloride-bicarbonate exchanger. Chloride exits the cell on the baso-lateral membrane through chloride channels.

C. Large intestine (colon)

There is a neutral sodium chloride transport mechanism where sodium is exchanged for hydrogen and chloride is exchanged for bicarbonate.
3. Absorption of Bicarbonate Ions in the Duodenum and Jejunum.

Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine because large amounts of bicarbonate ions have been secreted into the duodenum in both pancreatic secretion and bile.

The bicarbonate ion is absorbed in an indirect way as follows:

When sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium.

These hydrogen ions, in turn, combine with the bicarbonate ions to form carbonic acid (H_2CO_3),

carbonic acid (H_2CO_3) then dissociates to form water and carbon dioxide. The water remains as part of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired through the lungs. This process is the so-called “active absorption of bicarbonate ions.” It is the same mechanism that occurs in the tubules of the kidneys.
Potassium, magnesium, phosphate, and probably still other ions can also be actively absorbed through the intestinal mucosa.

In general, the monovalent ions are absorbed with ease and in great quantities. Bivalent ions are normally absorbed in only small amounts; for example, maximum absorption of calcium ions is only 1/50 as great as the normal absorption of sodium ions. Fortunately, only small quantities of the bivalent ions are normally required daily by the body.

- As in the distal tubule, K+ secretion in the colon is stimulated by aldosterone.
- In diarrhea, K+ secretion by the colon is increased because of a flow rate dependent mechanism similar to that in the renal distal tubule. Excessive loss of K+ in diarrheal fluid causes hypokalemia.

Absorption of other substances

1. Vitamins
   a. Fat-soluble vitamins (A, D, E, and K) are incorporated into micelles and absorbed along with other lipids.
   b. Most water-soluble vitamins are absorbed by Na+-dependent cotransport mechanisms.
   c. Vitamin B12 is absorbed in the ileum and requires intrinsic factor.

2. Calcium
   - absorption in the small intestine depends on the presence of adequate amounts of the active form of vitamin D, 1,25-dihydroxycholecalciferol, which is produced in the kidney. 1,25-dihydroxycholecalciferol induces the synthesis of an intestinal Ca2+-binding protein, calbindin D-28K.
   - Vitamin D deficiency or chronic renal failure results in inadequate intestinal Ca2+ absorption, causing rickets in children and osteomalacia in adults.
3. Transport and Storage of Iron.

- In adults, the amount of iron lost from the body is relatively small. The losses are generally un-regulated, and total body stores of iron are regulated by changes in the rate at which it is absorbed form the intestine.

- The female daily loss is more than male.

- Various dietary factors affect the availability of iron for absorption, for example, the phytic acid found in cereals reacts with iron to from insoluble compound in the intestine. So do phosphate and oxalate.

- No more than a trace amount of iron is absorbed in the stomach, but the gastric secretion dissolve the iron and permit it to form soluble complex with ascorbic acid and other substances that aid its reduction to \( \text{Fe}^{2+} \) form. The importance of this function in human is indicated by the fact that iron deficiency anemia is a trouble and relatively frequent complication of partial gastrectomy.

- The small amount of iron that is lost each day (about 1-2 mg) is matched by dietary absorption of iron. Iron is brought into the cell through an active transport process involving the protein DMT-1 (divalent metal transporter-1), which is expressed on the apical surface of enterocytes in the initial part of the duodenum. DMT-1 is not specific to iron, and can transport other metal ions such as zinc, copper, cobalt, manganese, cadmium or lead. Enterocytes also absorb heme iron through a mechanism that has not yet been characterized.
Once inside the enterocyte, there are two fates for iron:

1. It may leave the enterocyte and enter the body via the basolateral transporter known as ferroportin; in which iron is stored in the liver and other tissues.

2. It can be bound to an apoferritin that can bind many atoms of iron per molecule (about 4500 iron atoms) to form ferritin (an intracellular iron-binding protein). This iron will be lost from the body when the enterocyte dies and is sloughed off from the tip of the villus.

When iron is absorbed from the small intestine, it immediately combines in the blood plasma with a beta globulin, apotransferrin, to form transferrin, which is then transported in the plasma.

Normally, the capacity of transferrin to bind iron in the plasma greatly exceeds the amount of circulating iron. The transferrin saturation (percent of transferrin occupied by iron) is measured to determine if an individual has an excessive load of iron in the body. The normal transferrin saturation is in the range of 20-45%.
The iron is loosely bound in the transferrin and, consequently, can be released to any tissue cell at any point in the body. Excess iron in the blood is deposited especially in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow.

In the cell cytoplasm, iron combines mainly with a protein, apoferritin, to form ferritin. Apoferritin has a molecular weight of about 460,000, and varying quantities of iron can combine in clusters of iron radicals with this large molecule; therefore, ferritin may contain only a small amount of iron or a large amount. This iron stored as ferritin is called storage iron.

Smaller quantities of the iron in the storage pool are in an extremely insoluble form called hemosiderin. This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate. Hemosiderin collects in cells in the form of large clusters that can be observed microscopically as large particles. In contrast, ferritin particles are so small and dispersed that they usually can be seen in the cell cytoplasm only with an electron microscope.
When the quantity of iron in the plasma falls low, some of the iron in the ferritin storage pool is removed easily and transported in the form of transferrin in the plasma to the areas of the body where it is needed. A unique characteristic of the transferrin molecule is that it binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow. Then, along with its bound iron, it is ingested into the erythroblasts by endocytosis. There the transferrin delivers the iron directly to the mitochondria, where heme is synthesized. In people who do not have adequate quantities of transferrin in their blood, failure to transport iron to the erythroblasts in this manner can cause severe hypochromic anemia (i.e., RBCs that contain much less hemoglobin than normal).

When RBCs have lived their life span of about 120 days and are destroyed, the hemoglobin released from the cells is ingested by monocyte-macrophage cells. There, iron is liberated and is stored mainly in the ferritin pool to be used as needed for the formation of new hemoglobin.