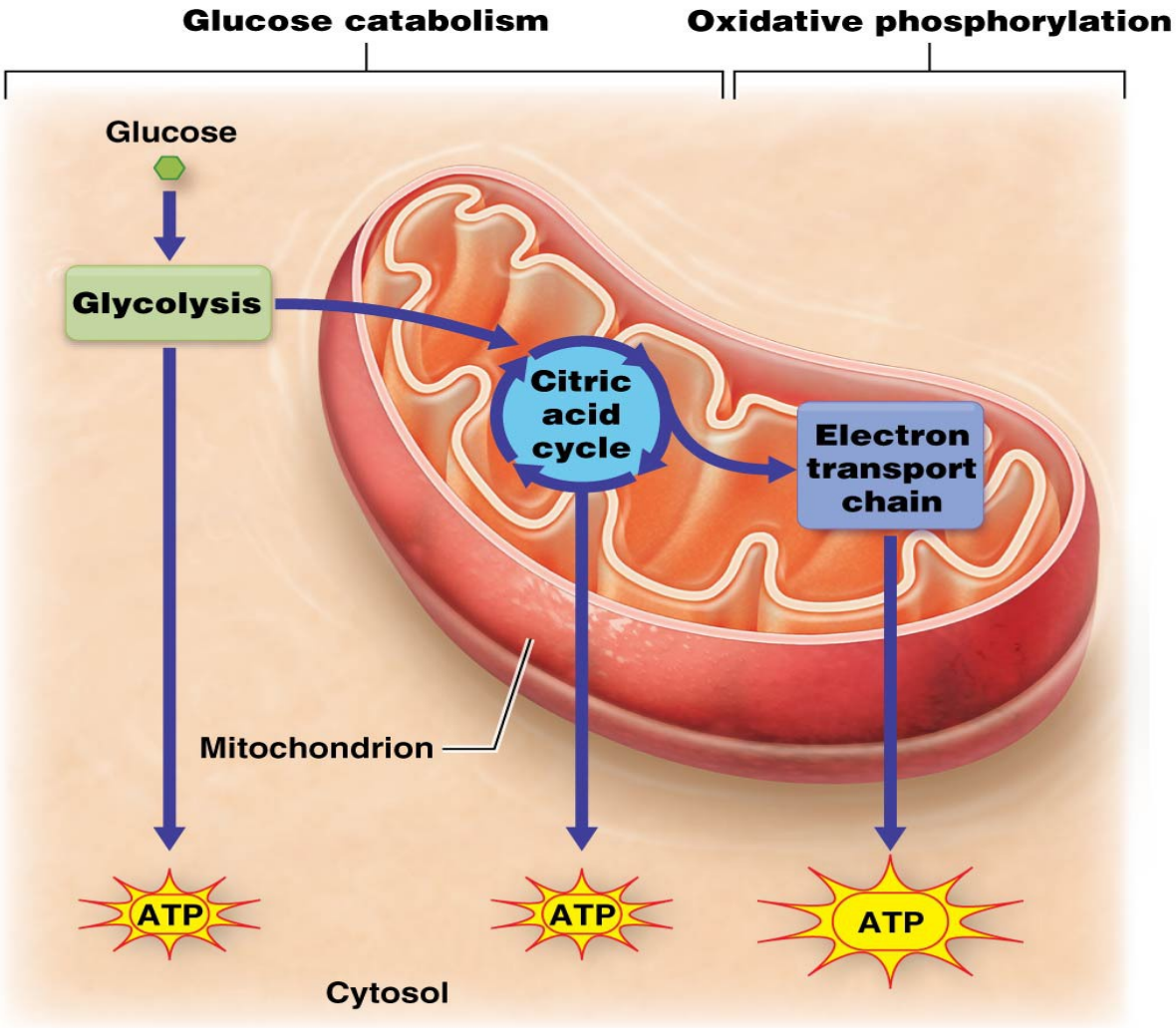
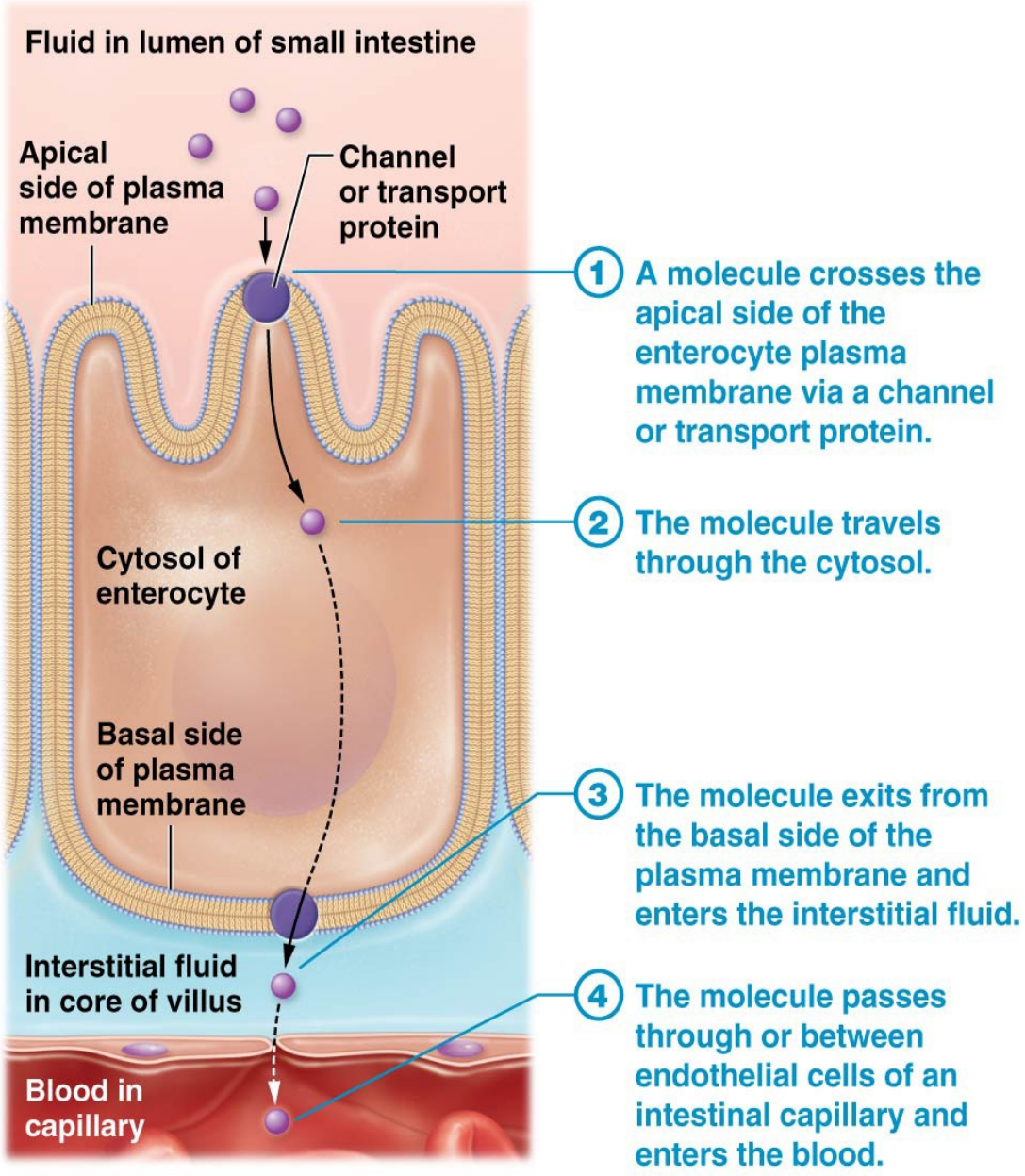
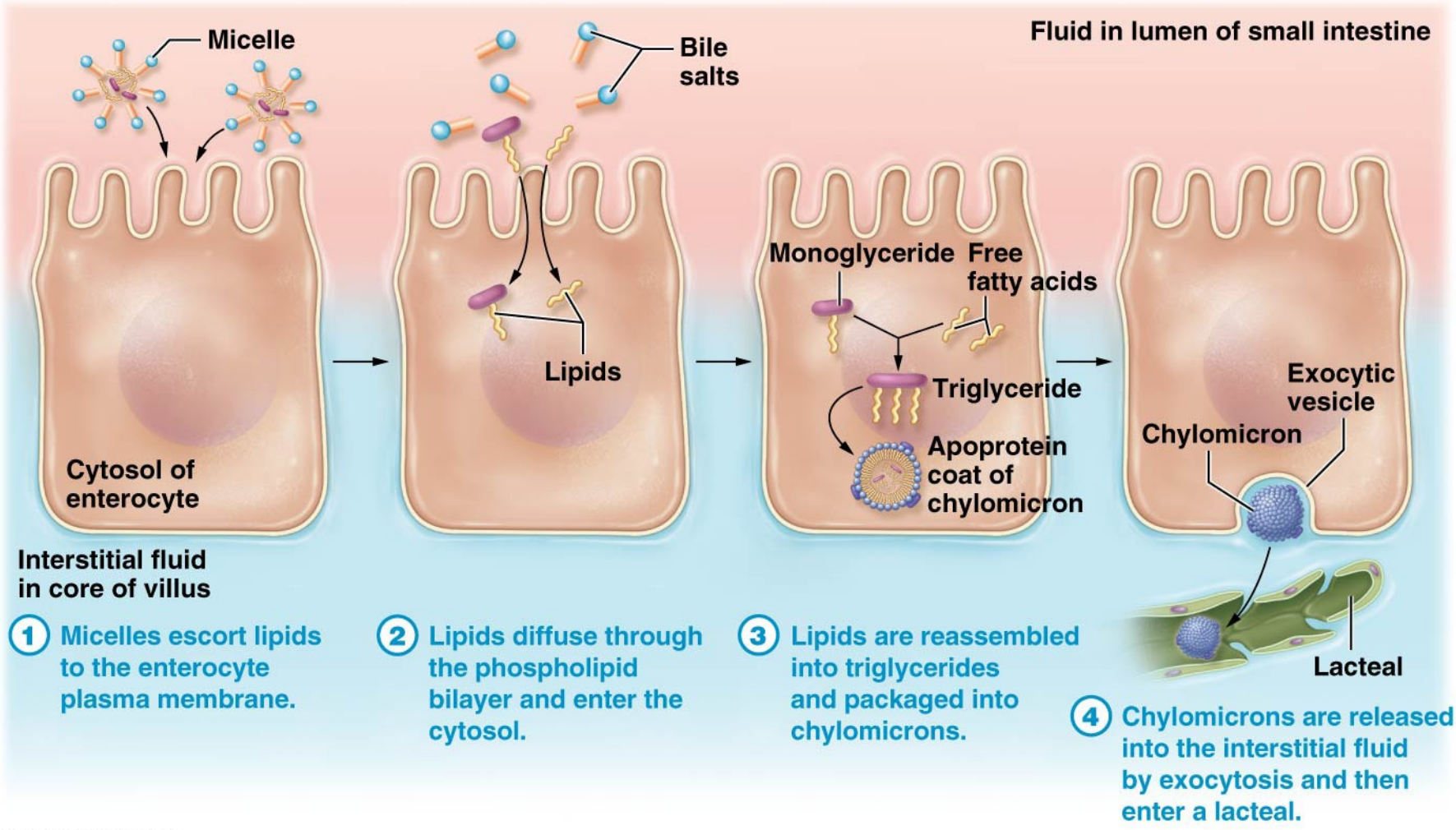
Metabolism (C26)



Path taken by a hydrophilic molecule absorbed into blood through an enterocyte.

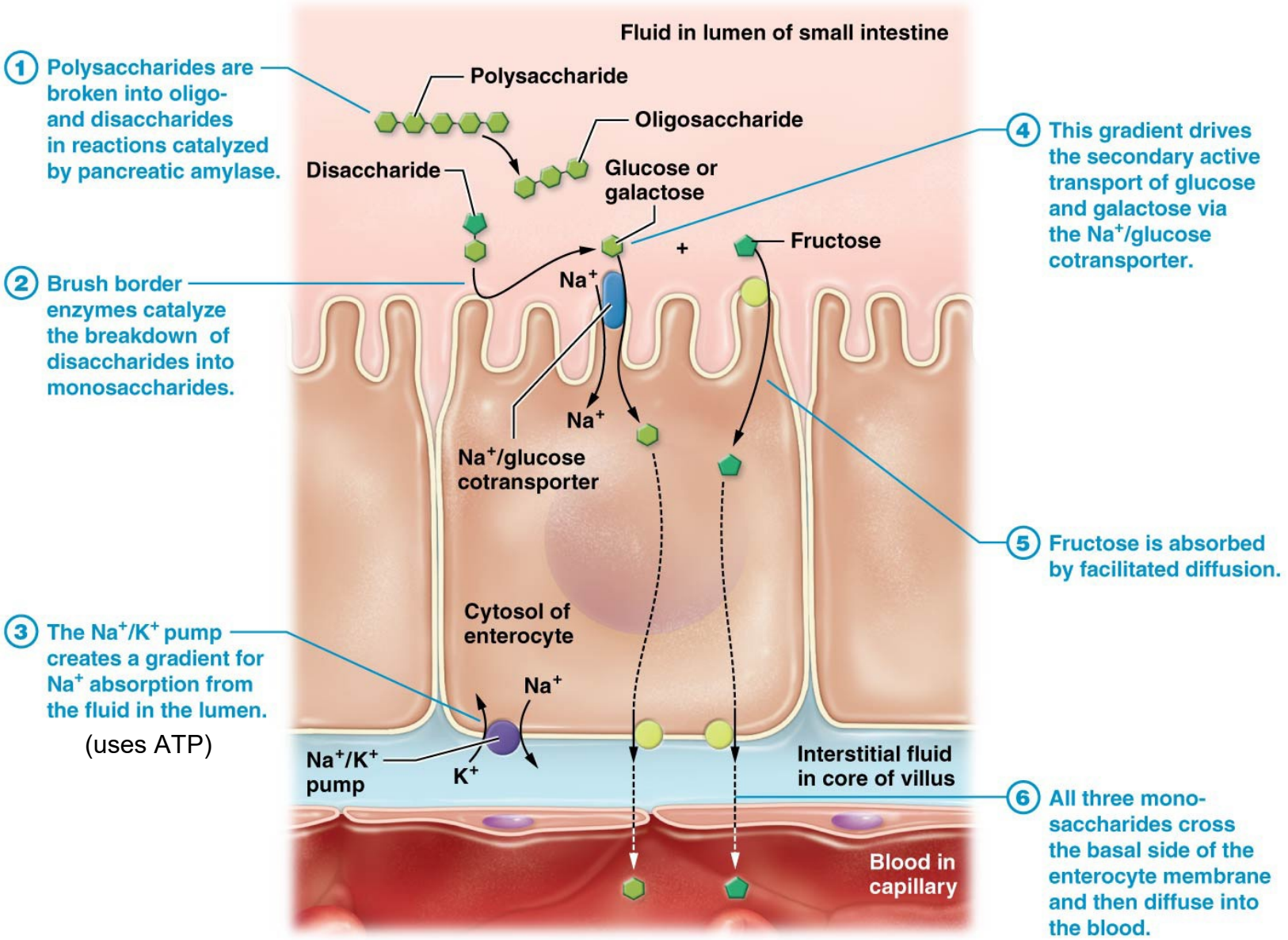


Lipid absorption (hydrophobic molecule) in the small intestine must use a different pathway than hydrophilic molecules. Why?

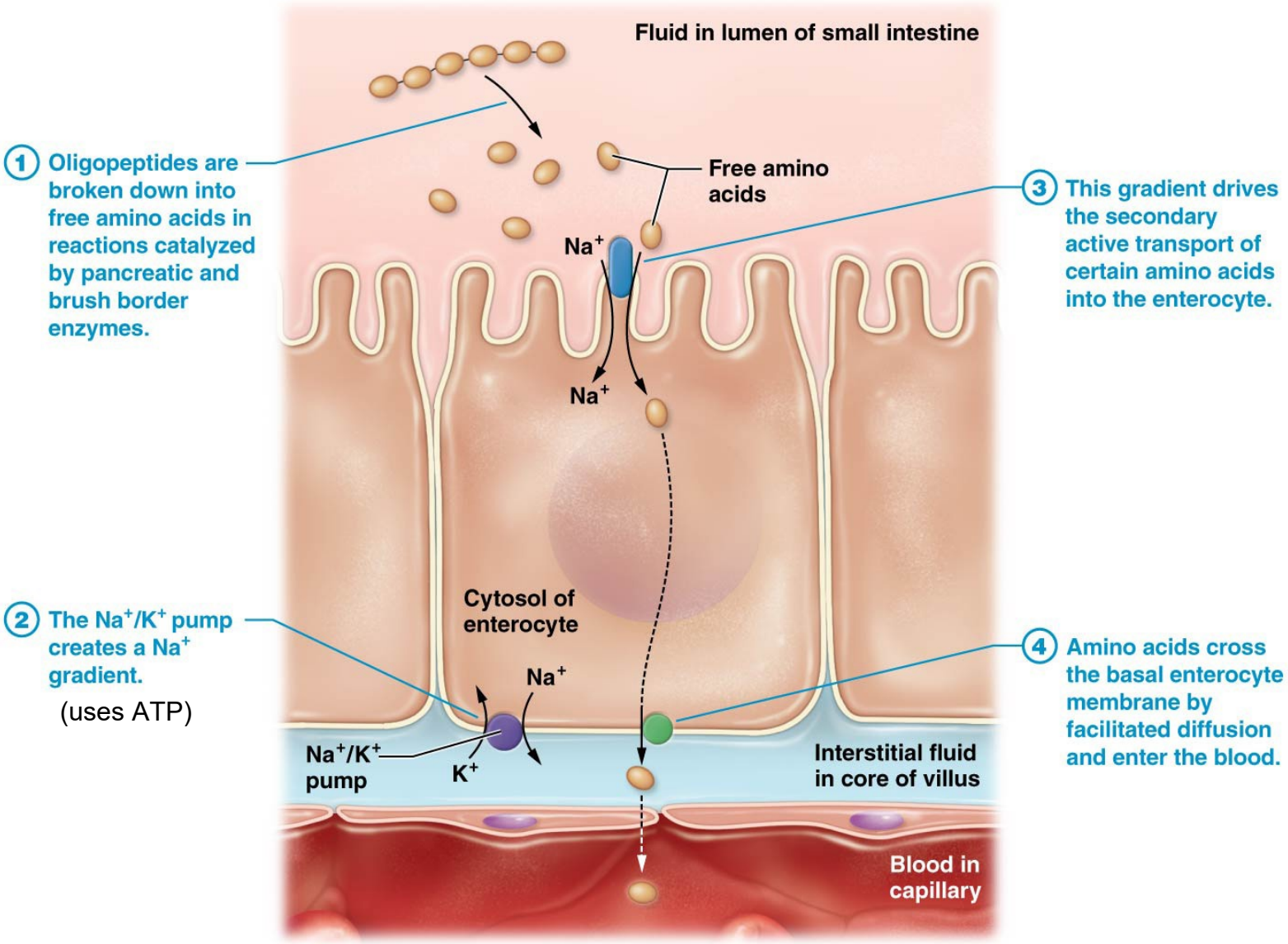


Carbohydrate digestion and absorption in the small intestine.

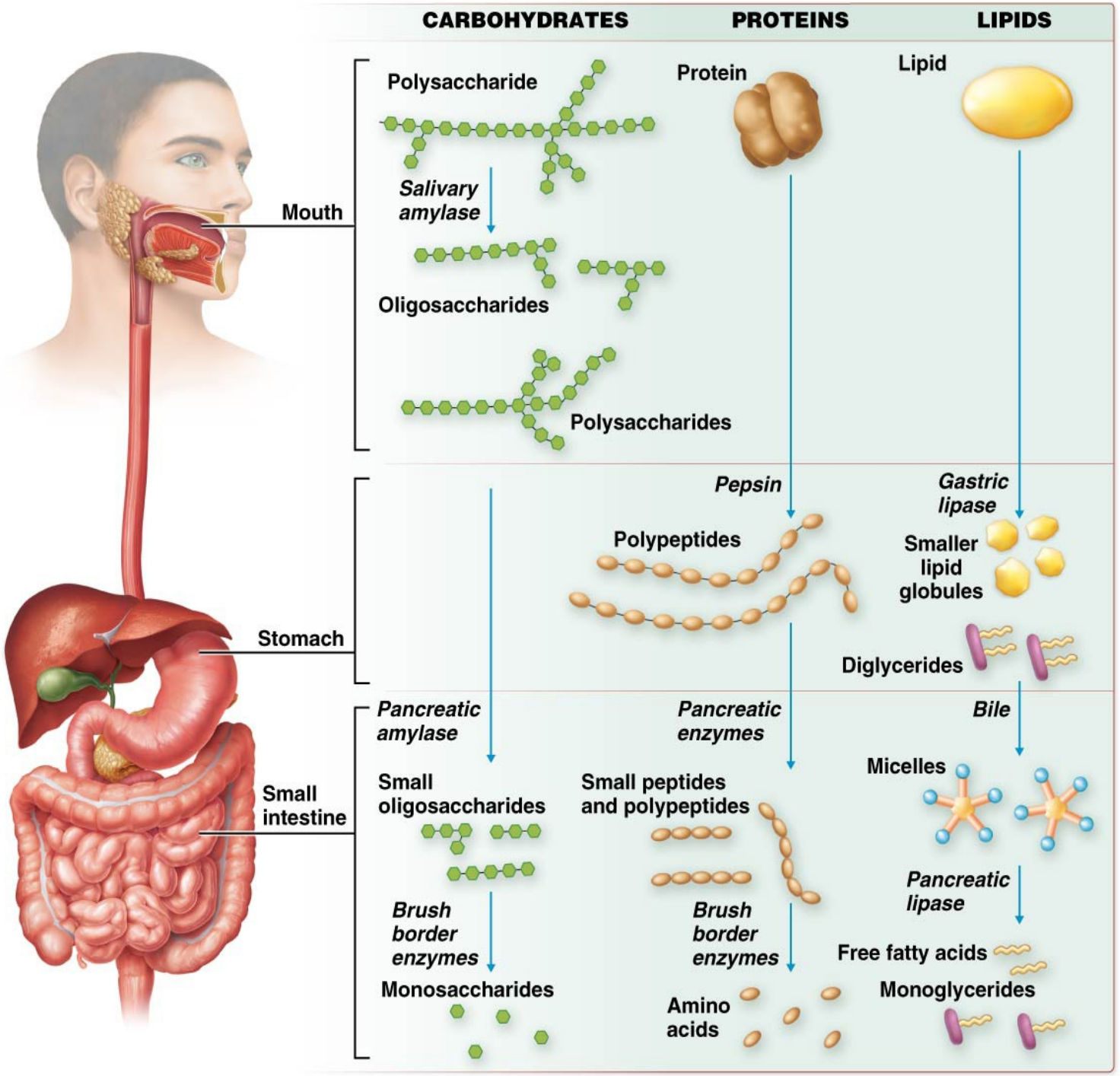
Can you find the symports, antiports, and uniports? Active and passive transporters?



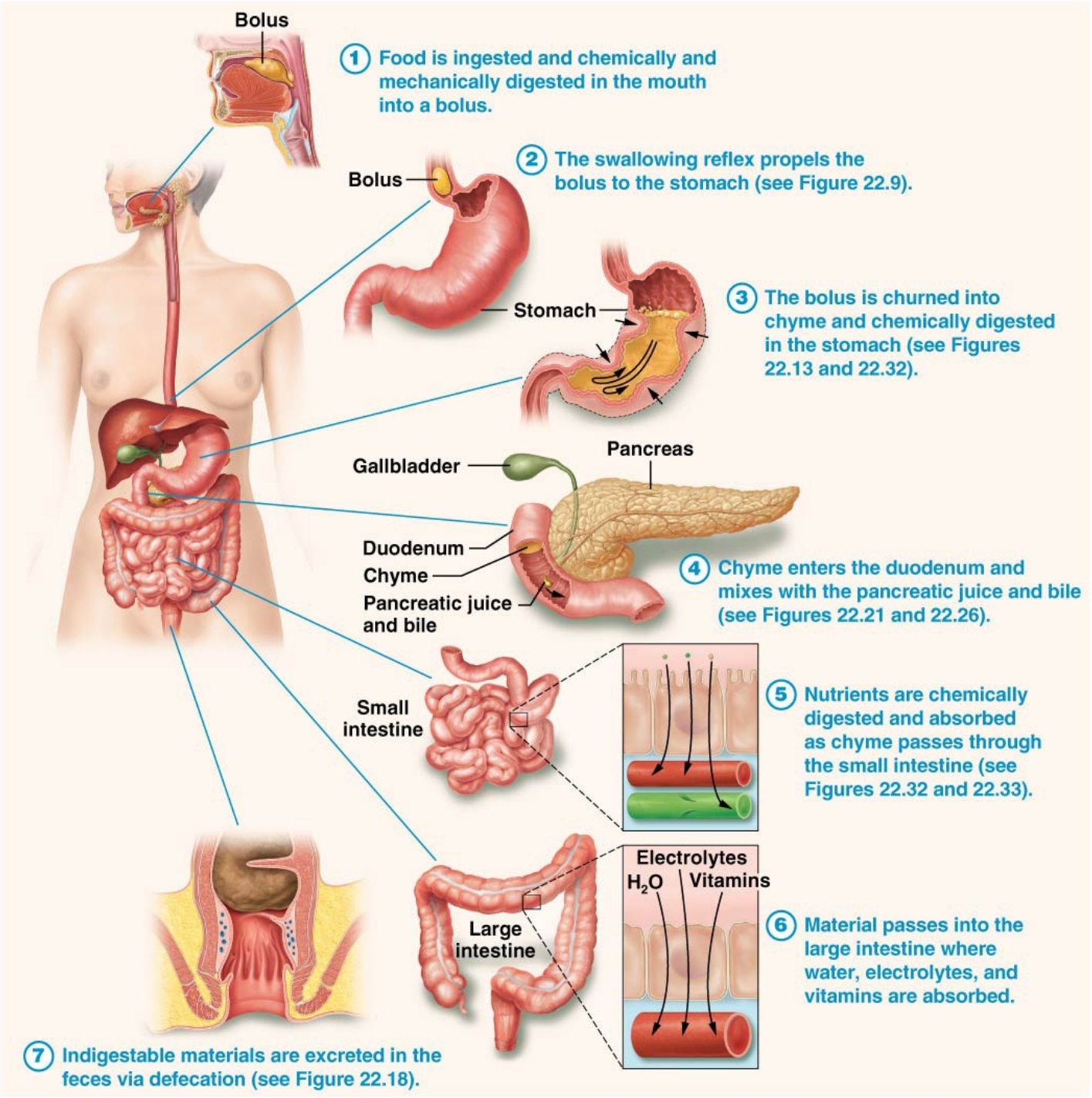
Amino acid digestion and absorption in the small intestine.



What is secondary active transport?

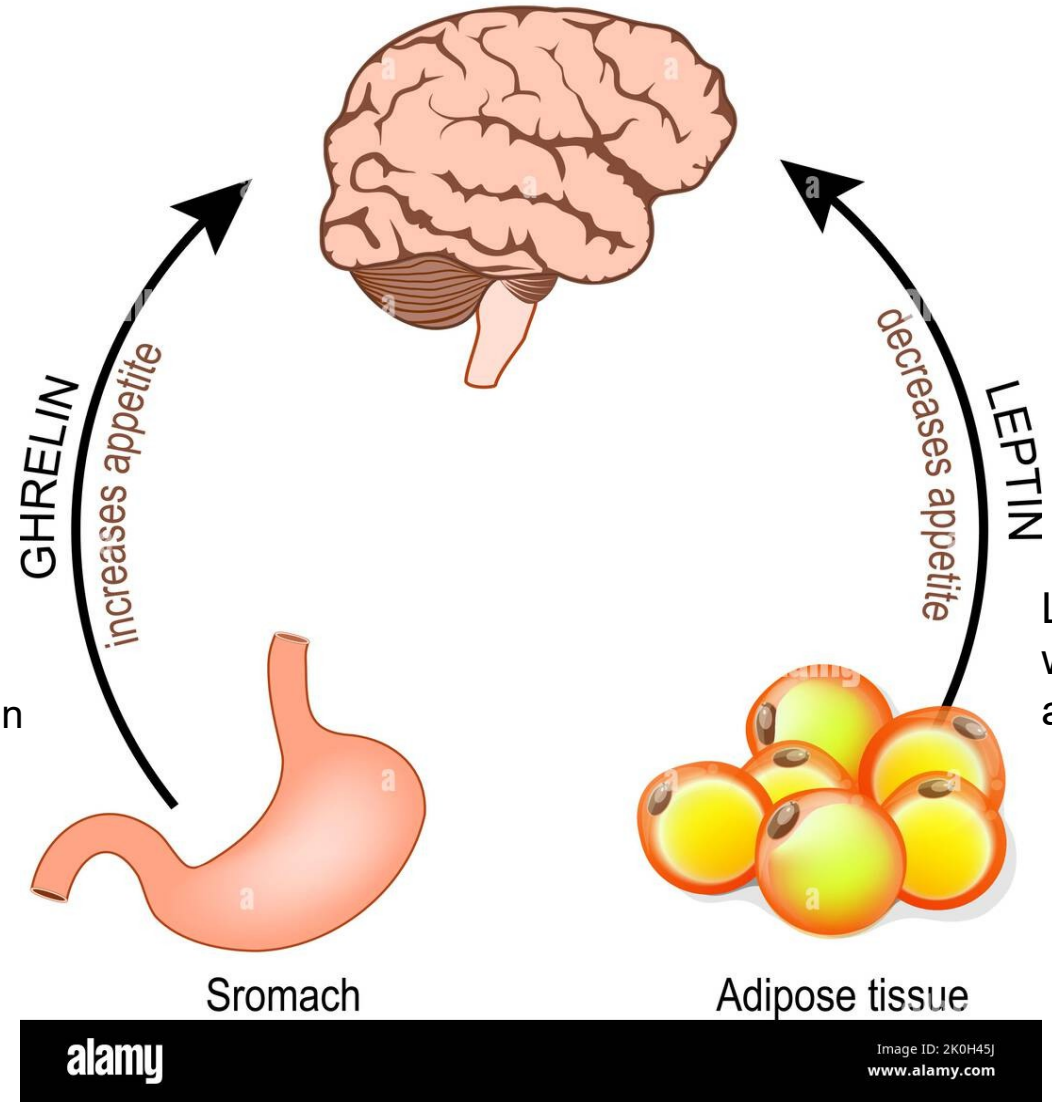


Summary of the digestion of carbohydrates, proteins, and lipids.



The Big Picture of Digestion.

Leptin & Ghrelin



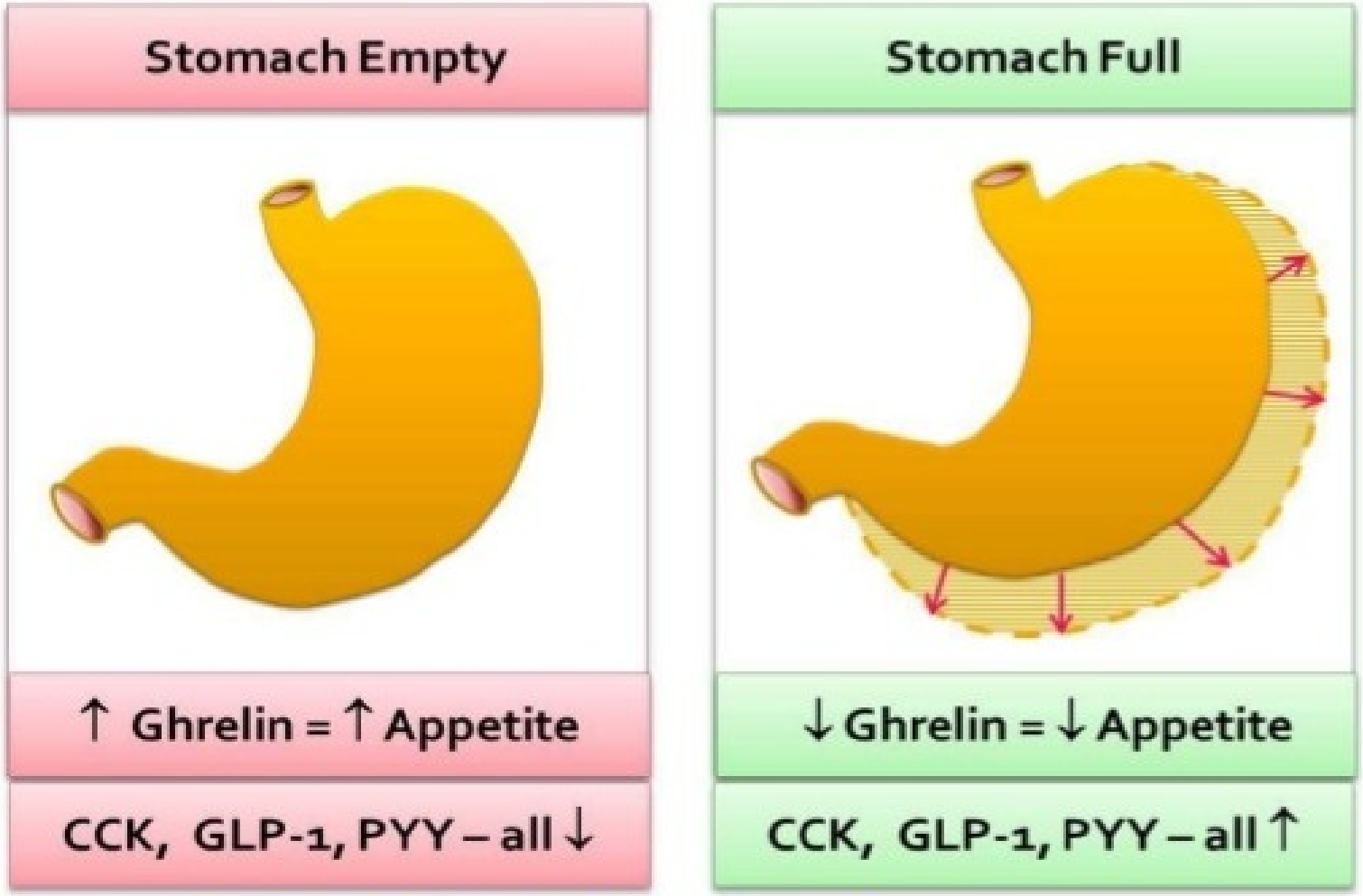
Ghrelin is secreted when the stomach is empty.

Leptin is secreted when adipose cells are full of fat.

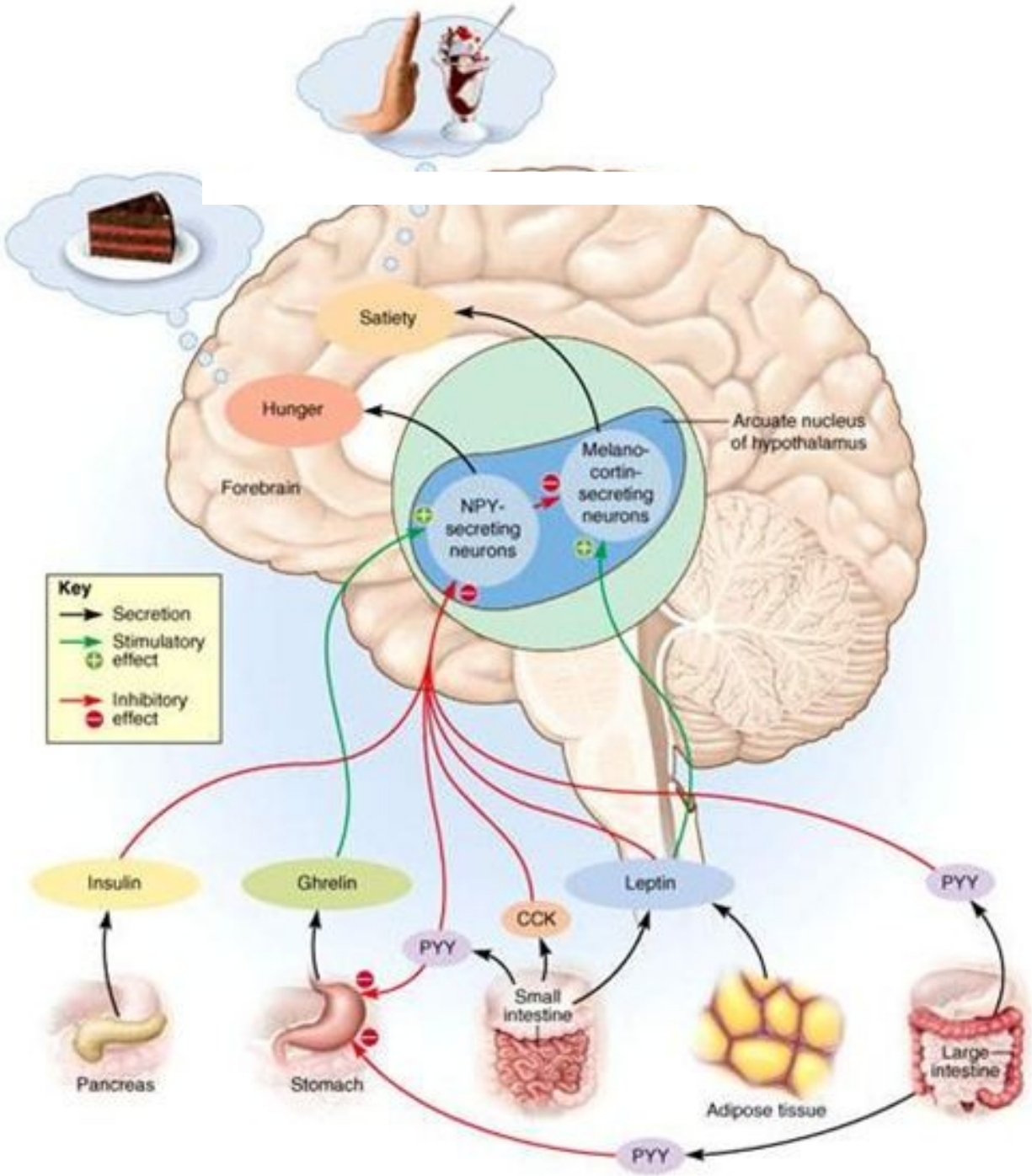
CCK – Cholecystokinin
GLP1 – Glucagon-like peptide 1
PYY – Peptide YY

Primarily regulated by feeding

(Crespo *et al*, 2014)



http://www.nutridesk.com.au/stomach-intestine-ghrelin-cck-glp-1-gut-hormones.phtml


Satiety
Hunger
Forebrain
Arcuate nucleus of hypothalamus
Melano-cortin-secreting neurons
NPY-secreting neurons
Key
Secretion
Stimulatory effect
Inhibitory effect
Insulin
Ghrelin
Leptin
PYY
CCK
PYY
Small intestine
Pancreas
Stomach
Adipose tissue
Large intestine
PYY

Carbohydrate Digestion

- **Starch** – the most digestible carbohydrate
  - starch is first digested to:
    - **oligosaccharides** up to eight glucose residues long
    - then into the **disaccharide maltose**
    - finally to **glucose** which is absorbed by the small intestine
  - process **begins in the mouth**
    - **salivary amylase** hydrolyzes starch into oligosaccharides
    - amylase works best at pH of 6.8 – 7.0 of oral cavity
    - amylase quickly denatured on contact with stomach acid and digested by pepsin
- ***Cellulose*** – *indigestible glucose polymer!*
- ***What is glycogen?***
- ***Do we have enzymes to digest glycogen?***

Carbohydrate Digestion

- salivary amylase stops working in stomach at pH less than 4.5
  - 50% of dietary starch digested before it reaches small intestine
- when reaching the small intestine, pancreatic amylase converts starch to oligosaccharides and maltose within 10 minutes
- oligosaccharides and maltose contact brush border enzymes (dextrinase, glucoamylase, maltase, sucrase, and lactase) /// these act to turn oligosaccharides, maltose, sucrose, lactose, and fructose into glucose
- lactose becomes indigestible after age 4 in many humans due to decline in lactase production (lactose intolerance)

Carbohydrate Absorption

- plasma membrane of the **absorptive cells** has transport proteins that absorb monosaccharides as soon as the brush border enzymes creates monosaccharides

- 80% of absorbed sugar is the monosaccaride glucose

  - Moved from small intestine's lumen across apical enterocyte by **sodium-glucose transport proteins (SGLT) and secondary active transport of the sodium-potasium ATP pump in the basal membrane**

  - then glucose is transported out the base of absorptive cell into ECF by **facilitated diffusion**

  - sugar entering ECF increases its osmolarity /// draws water by osmotic drag from the lumen of the intestine, through **now leaky tight junctions** between epithelial cells

  - water carries additional glucose and other nutrients with it by **solvent drag through leaky junctions**

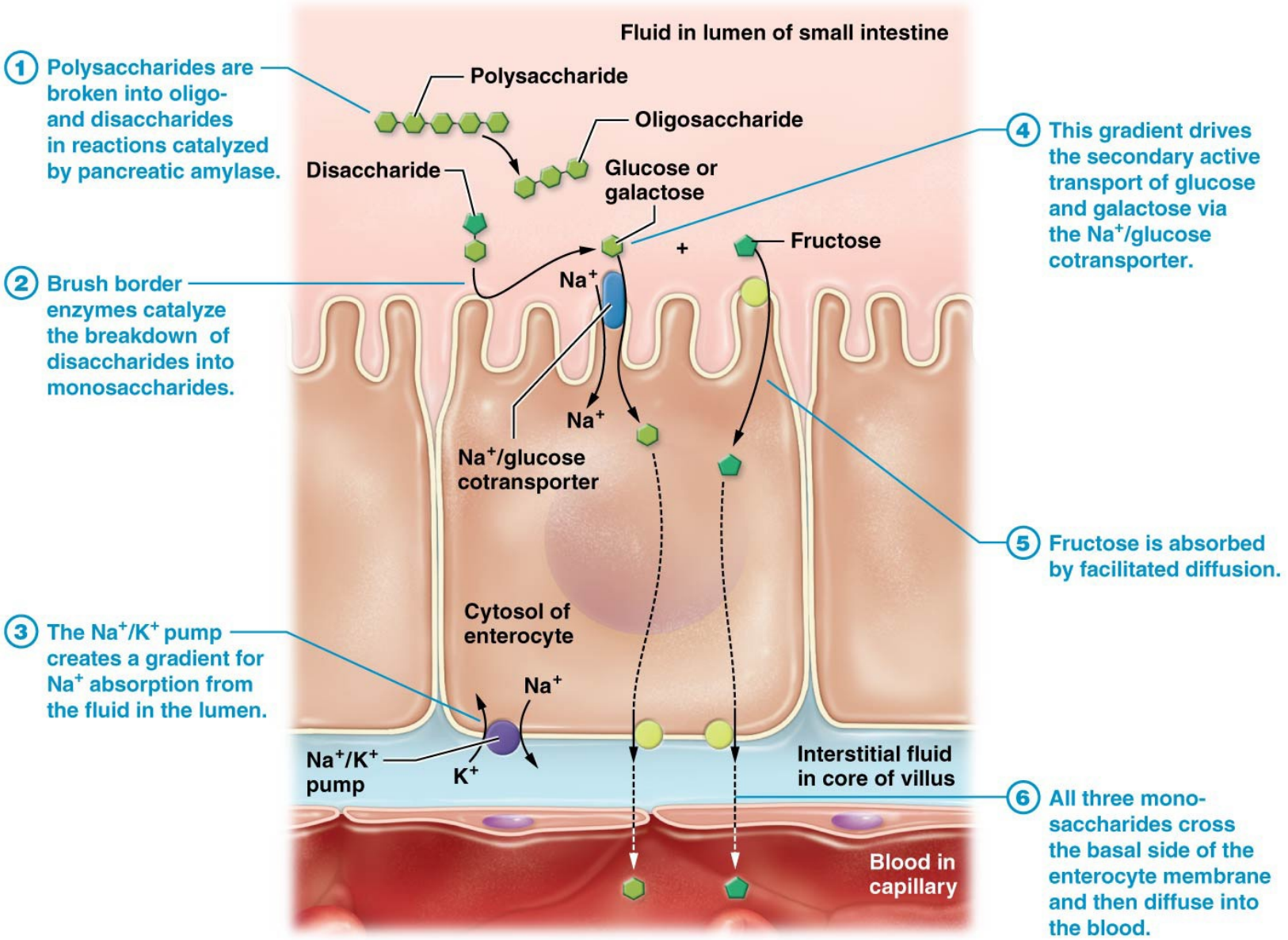
  - **See next slide**

Carbohydrate Absorption

- **sodium-glucose transport proteins** (SGLT) (also transports galactose)
- The SGLT-1 was the first transporter that was studied SGLT. This protein molecule is encoded by SLC5A1 gene (Turk et al., 1994). The SGLT1 protein controls the import of glucose in enterocytes and epithelial cells in the small intestine and proximal convolute tubules in nephrons, respectively.
- fructose is absorbed by facilitated diffusion
- some glucose and galactose may also be transported out of the base of the cell by **facilitated diffusion**
- absorbed by blood capillaries in the **villus**
- hepatic portal system delivers these sugars to the **liver**

Carbohydrate digestion and absorption in the small intestine.

Can you find the symports, antiports, and uniports? Active and passive transporters?



Lactose Intolerance

- At birth, all mammals (including humans) have the enzyme lactase to digest lactose (sugar in milk)

- Many lose lactase as they age. At around age four the transcription factor to make lactase is inhibited. Now unable to digest lactose.

- If lactose passes undigested into large intestine
  - increases osmolarity of intestinal contents
  - causes water retention in the colon and diarrhea
  - gas production by bacterial fermentation of the lactose

- Lactose intolerance occurs in many parts of the population //
  - 15% American whites
  - 90% of American blacks
  - 70% of Mediterranean's
  - nearly all of Asian descent

- May consume dairy products like yogurt and cheese because bacteria in manufacturing process have broken down lactose

Proteins

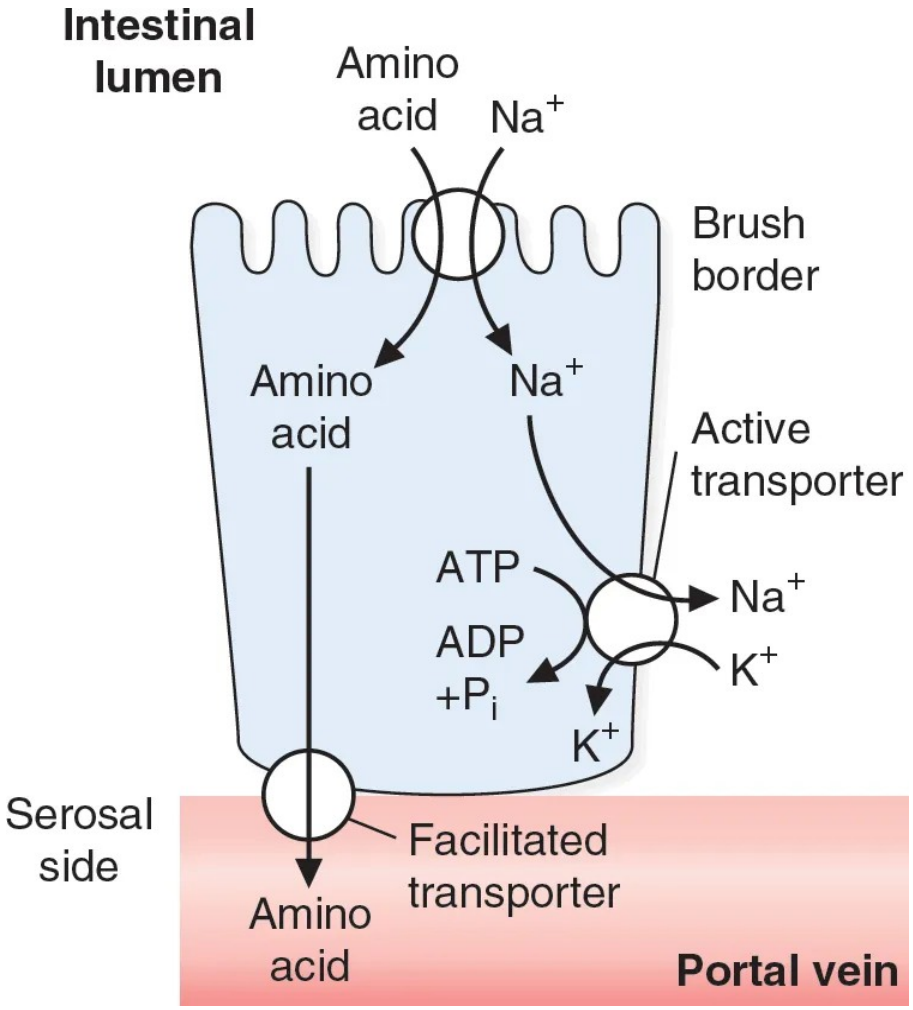
- **amino acids** absorbed by the small intestine come from three sources:
  - **dietary proteins**
  - **digestive enzymes** **digested by each other**
  - **epithelial cells** **sloughed off mucosa and digested by enzymes**
- **endogenous amino acids** from last two sources total about 30g/day
- **exogenous amino acids** from our diet total about 44 to 60 g/day
- **proteases** **(peptidases)**
  - enzymes that digest proteins
  - begin their work in the stomach in optimum pH of 1.5 to 3.5
  - **pepsin** hydrolyzes any peptide bond between tyrosine and phenylalanine
    - **pepsin** digests 10-15% of dietary protein into shorter peptides and some free amino acids

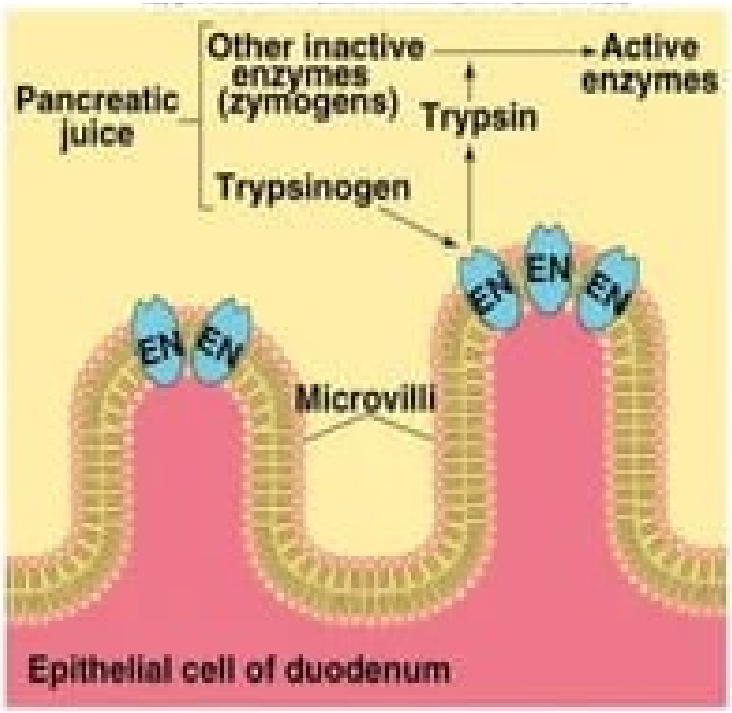
Proteins

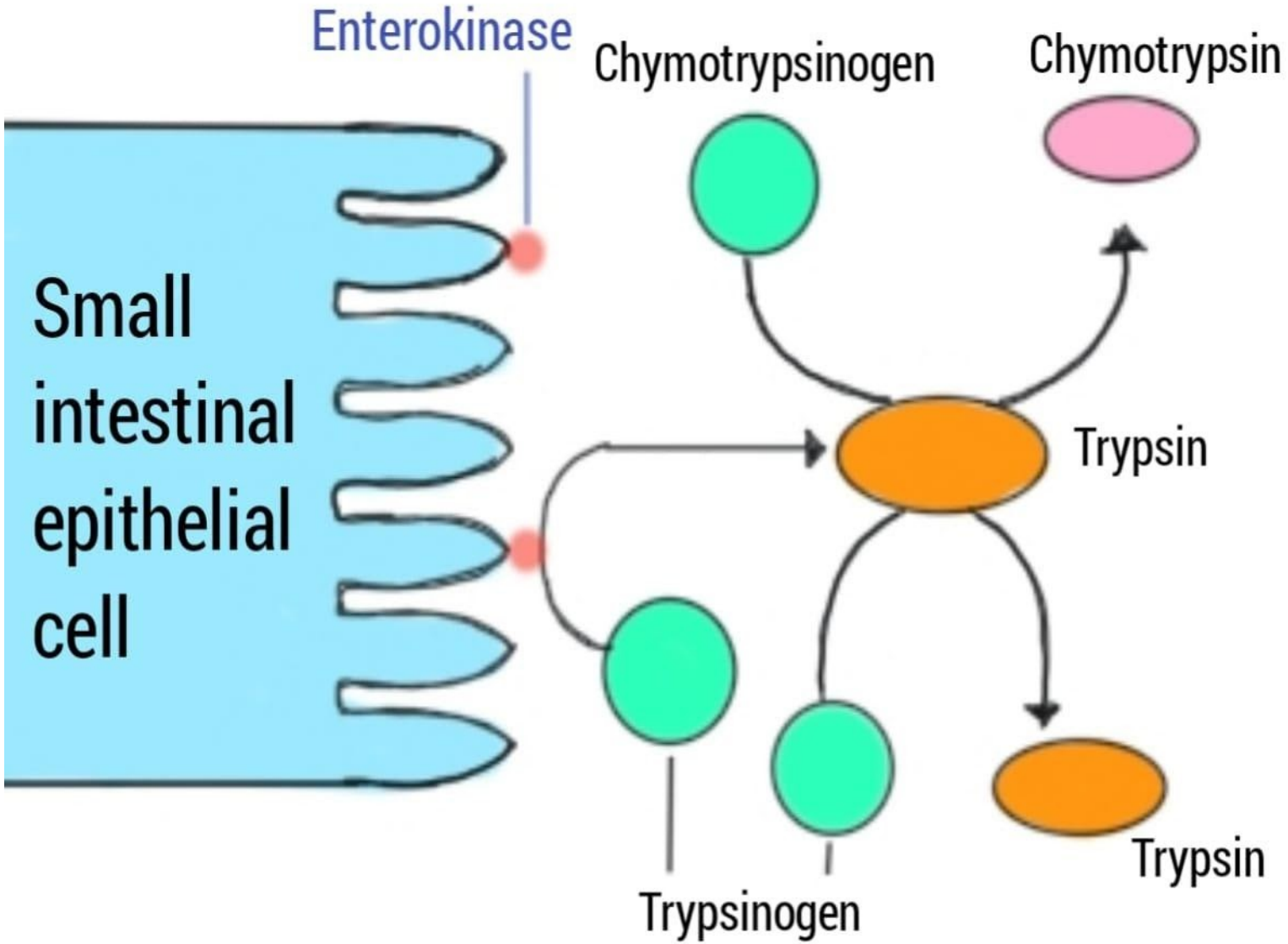
- Protein digestion started in stomach continue in the small intestine
  - Gastric pepsin inactivated when it passes into the duodenum and mixes with the alkaline pancreatic juice (pH 8)
  - pancreatic enzymes trypsin and chymotrypsin take over the process
  - hydrolyzing polypeptides into even shorter oligopeptides
  - oligopeptides taken apart one amino acid at a time by three more enzymes
    - carboxypeptidase – removes amino acids from –COOH end of the chain
    - aminopeptidase – removes them from the $–NH_2$ end
    - dipeptidase – split dipeptides in the middle and release two free amino acids
  - carboxypeptidase is a pancreatic secretion
  - aminopeptidase and dipeptidase are brush border enzymes

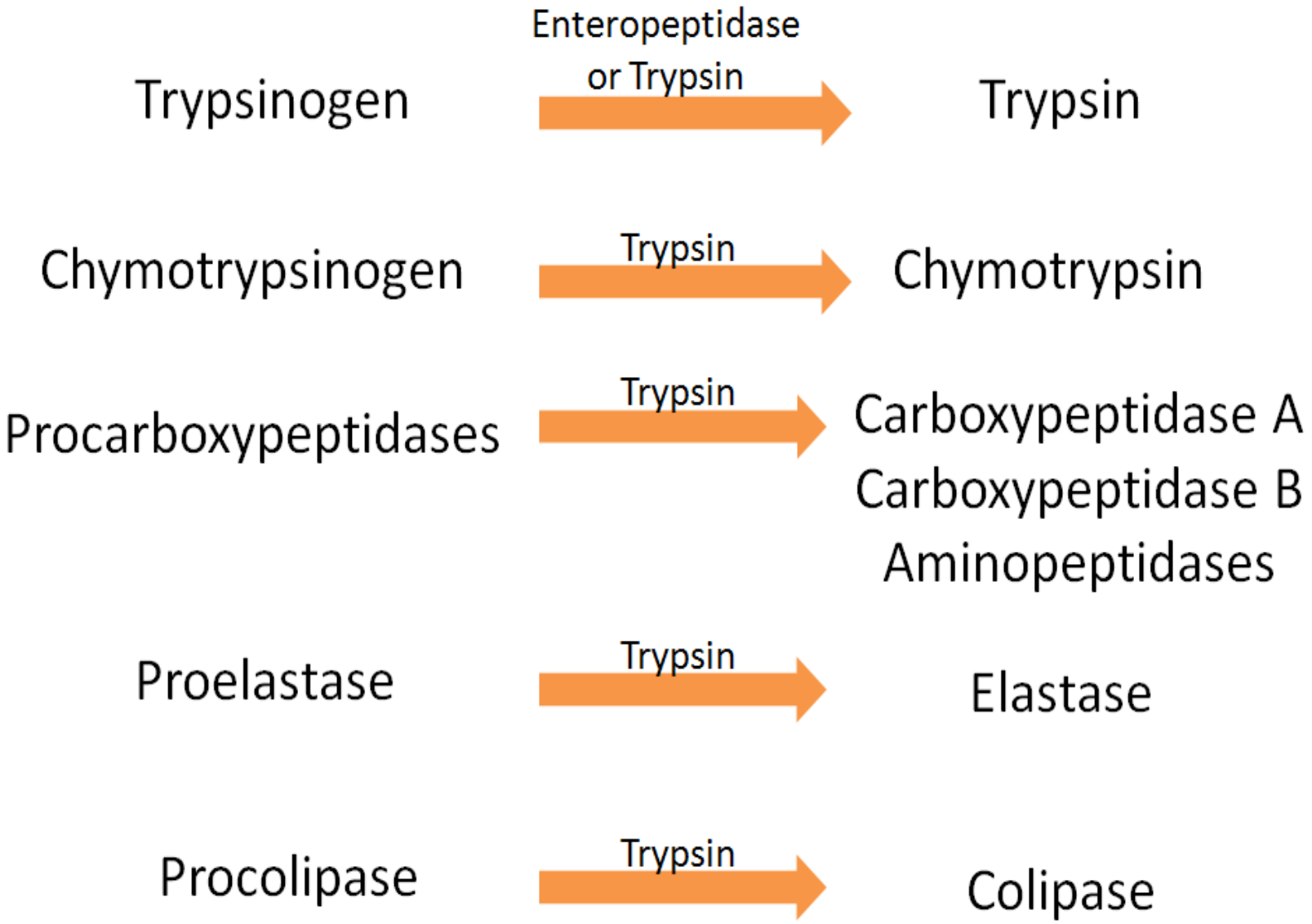
Protein Digestion and Absorption

Pancreatic enzymes take over protein digestion in small intestine by hydrolyzing polypeptides into shorter oligopeptides



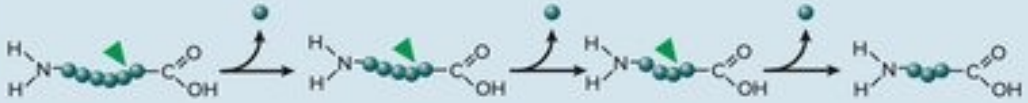

Pancreatic juice
Other inactive enzymes (zymogens)
Active enzymes
Trypsin
Trypsinogen
EN
EN
EN
EN
EN
Microvilli
Epithelial cell of duodenum


Enterokinase
Chymotrypsinogen
Chymotrypsin
Small intestinal epithelial cell
Trypsin
Trypsinogen
Trypsin


Trypsinogen
Enteropeptidase
or Trypsin
Trypsin
Chymotrypsinogen
Trypsin
Chymotrypsin
Procarboxypeptidases
Trypsin
Carboxypeptidase A
Carboxypeptidase B
Aminopeptidases
Proelastase
Trypsin
Elastase
Procolipase
Trypsin
Colipase

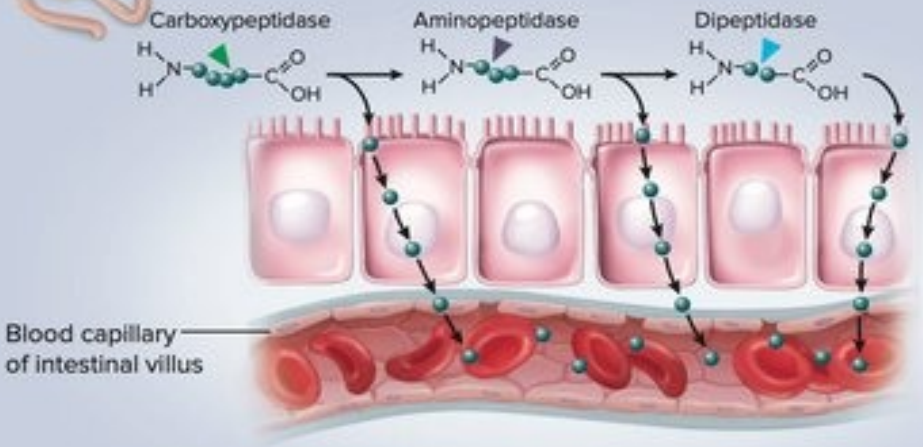
Small intestine
Actions of pancreatic enzymes

Trypsin (▲) and chymotrypsin (▲) hydrolyze other peptide bonds, breaking polypeptides down into smaller oligopeptides.



Carboxypeptidase (▲) removes one amino acid at a time from the carboxyl (—COOH) end of an oligopeptide.

Small intestine
Actions of brush border enzymes (contact digestion)

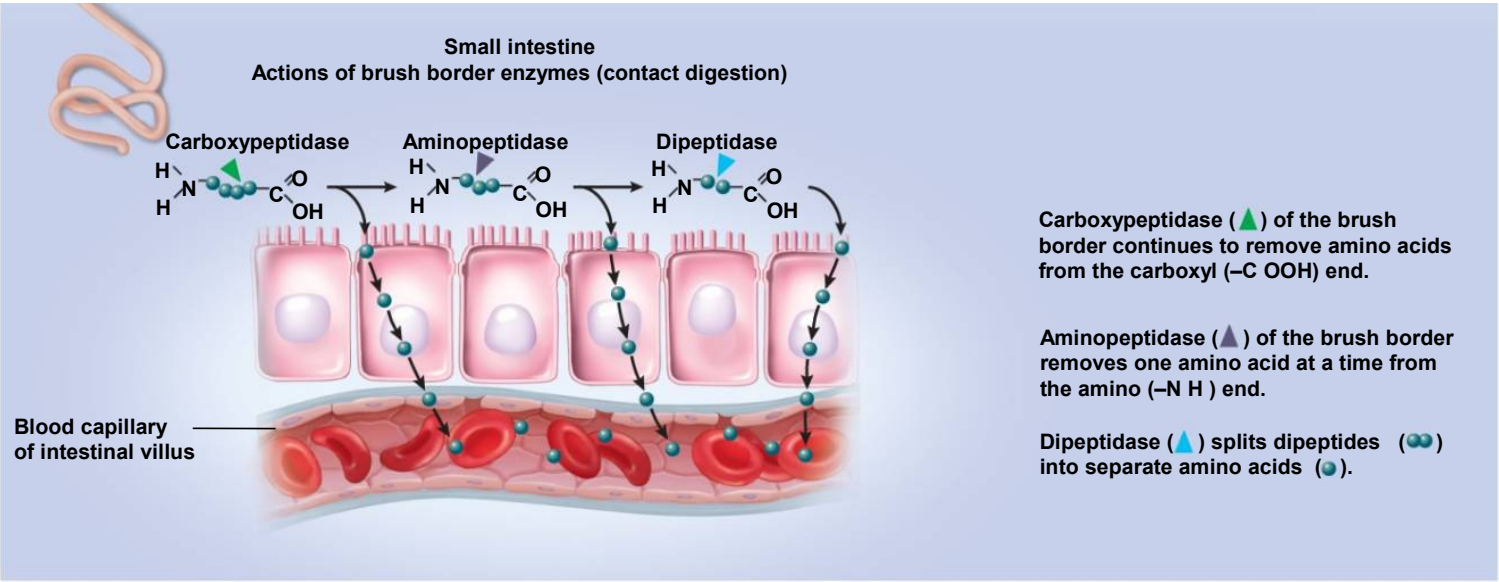


Carboxypeptidase (▲) of the brush border continues to remove amino acids from the carboxyl (—COOH) end.

Aminopeptidase (▲) of the brush border removes one amino acid at a time from the amino ($—NH_2$) end.

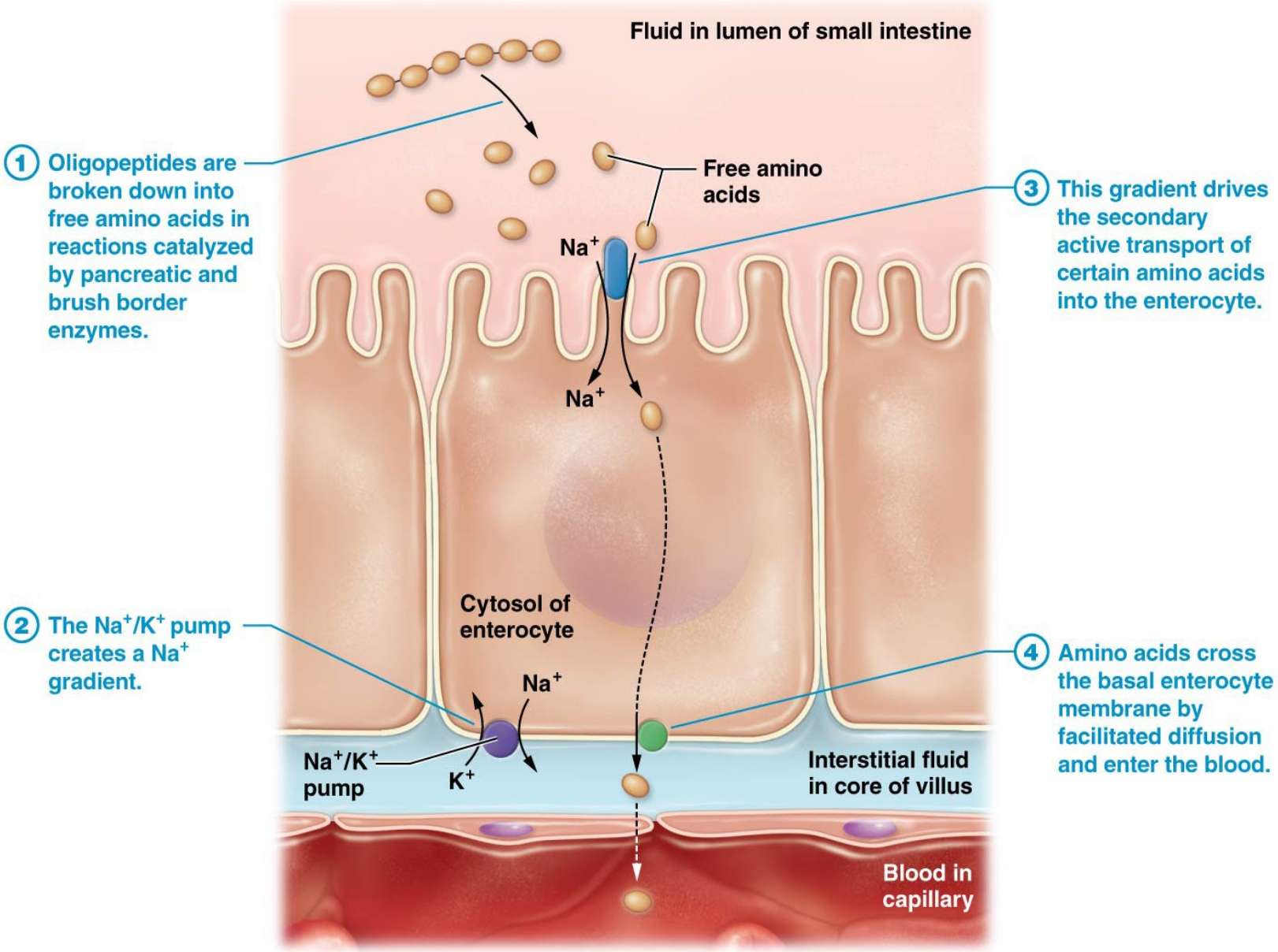
Dipeptidase (▲) splits dipeptides (●●) into separate amino acids (●).

Protein Digestion and Absorption



- brush border enzymes finish task, producing free amino acids that are absorbed into intestinal epithelial cells
  - **sodium-dependent amino acid cotransporters** move amino acids into epithelial cells
  - **facilitated diffusion** moves amino acids into blood stream
- infants absorb proteins by pinocytosis (maternal IgA) and release into the blood by exocytosis

Amino acid digestion and absorption in the small intestine.



What is secondary active transport?

Lipids

- Hydrophobic quality of lipids makes their digestion and absorption more complicated that carbohydrates and proteins

- **Lipases** – fat digesting enzymes

  - **lingual lipase** secreted by the intrinsic salivary glands of the tongue /// generally thought to be inactive in mouth, but activated by stomach acids // acidic enzyme

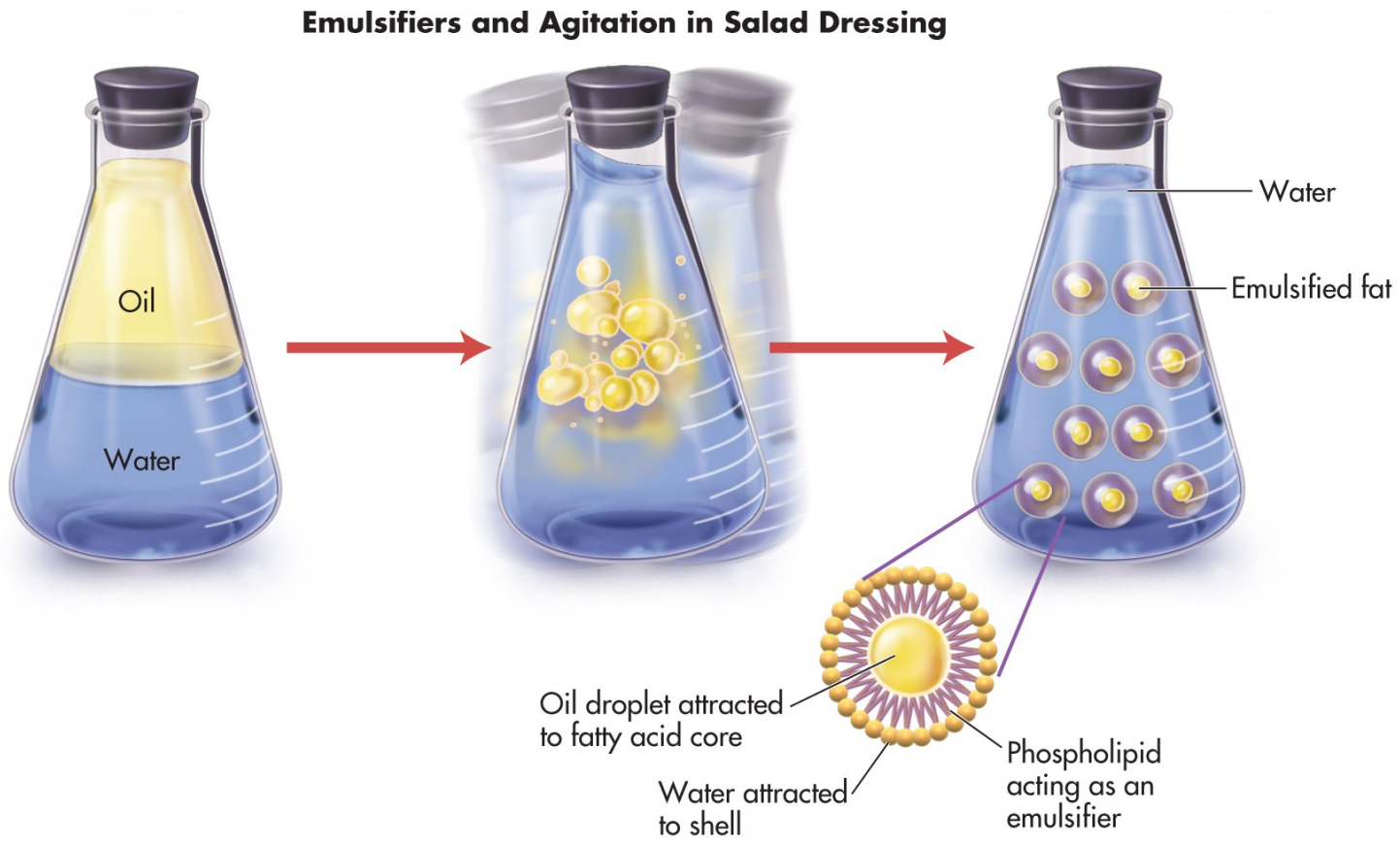
  - stomach's chief cells also produces **gastric lipase ///** 10-15% of lipids digested before reaches duodenum // acidic enzyme // more important for neonates

  - **pancreatic lipase** – in the small intestine digest most of the fats in food

  - fat enters duodenum as large globules exposed to lipase only at their surface

  - globules broken up into smaller **emulsification droplets** by certain components of **bile** // **lecithin** and **bile acids**

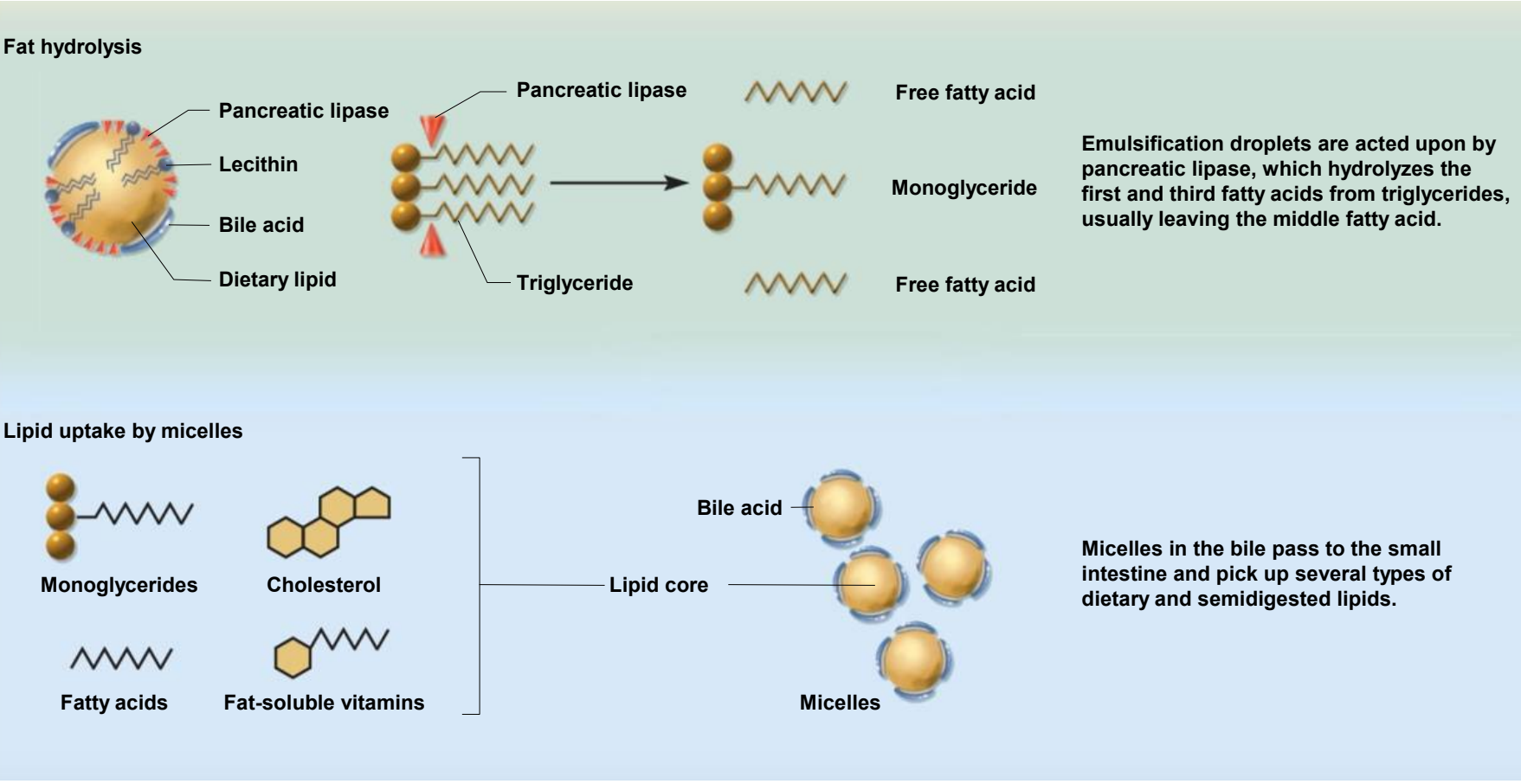
Lipids

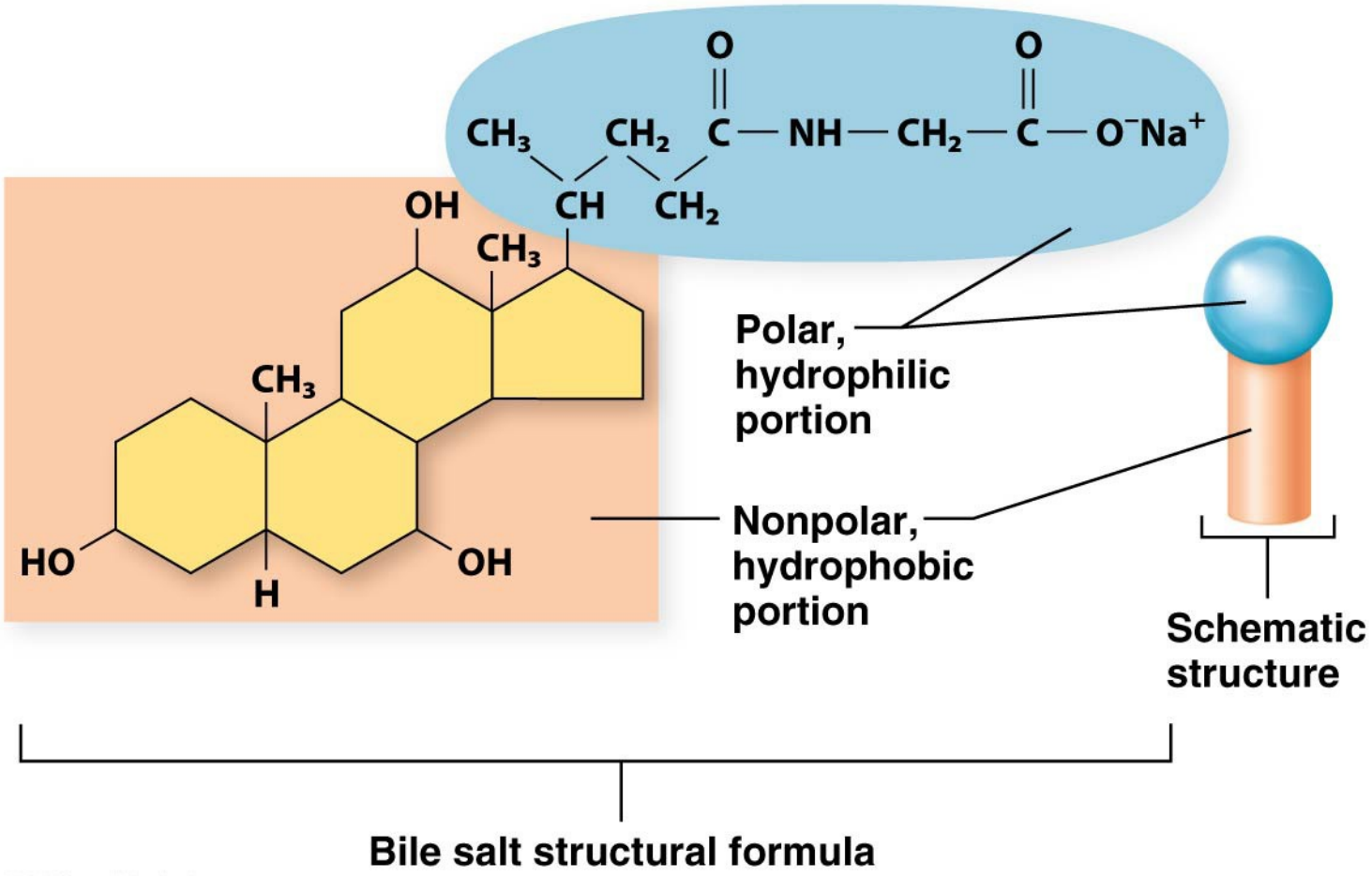

Emulsifiers and Agitation in Salad Dressing
Oil
Water
Water
Emulsified fat
Oil droplet attracted to fatty acid core
Water attracted to shell
Phospholipid acting as an emulsifier

Lipids

- agitation by segmentation breaks up the fats into droplets as small as 1 μm in diameter
- the coating of lecithin and bile acids keep it broken up
- exposing far more of its surface to enzymatic action
- there is enough pancreatic lipase in the small intestine after a meal to digest the average daily fat intake in as little as 1 to 2 minutes
- lipase acts on triglycerides
  - removes the first and third fatty acids from glycerol backbone
  - leaves the middle one
  - the product of lipase action are two free fatty acids (FFAs) and a monoglyceride

Fat Hydrolysis and Micelles




O
O
CH3
CH2
C
NH
CH2
C
O⁻Na⁺
CH
CH2
OH
CH3
CH3
HO
OH
H
Polar, hydrophilic portion
Nonpolar, hydrophobic portion
Schematic structure
Bile salt structural formula

Micelles Role in Lipid Digestion and Absorption

- absorption of free fatty acids, monoglycerides, and other lipids depends on minute droplets in the bile called micelles
  - Micelles are formed in in the liver as well as in the duodenum
  - consist of 20 to 40 bile acid molecules aggregated with their hydrophilic side groups facing outward and their hydrophobic steroid rings facing inward
  - bile phospholipids and cholesterol diffuse into the center of the micelle to form its core

Micelles Role in Lipid Digestion and Absorption

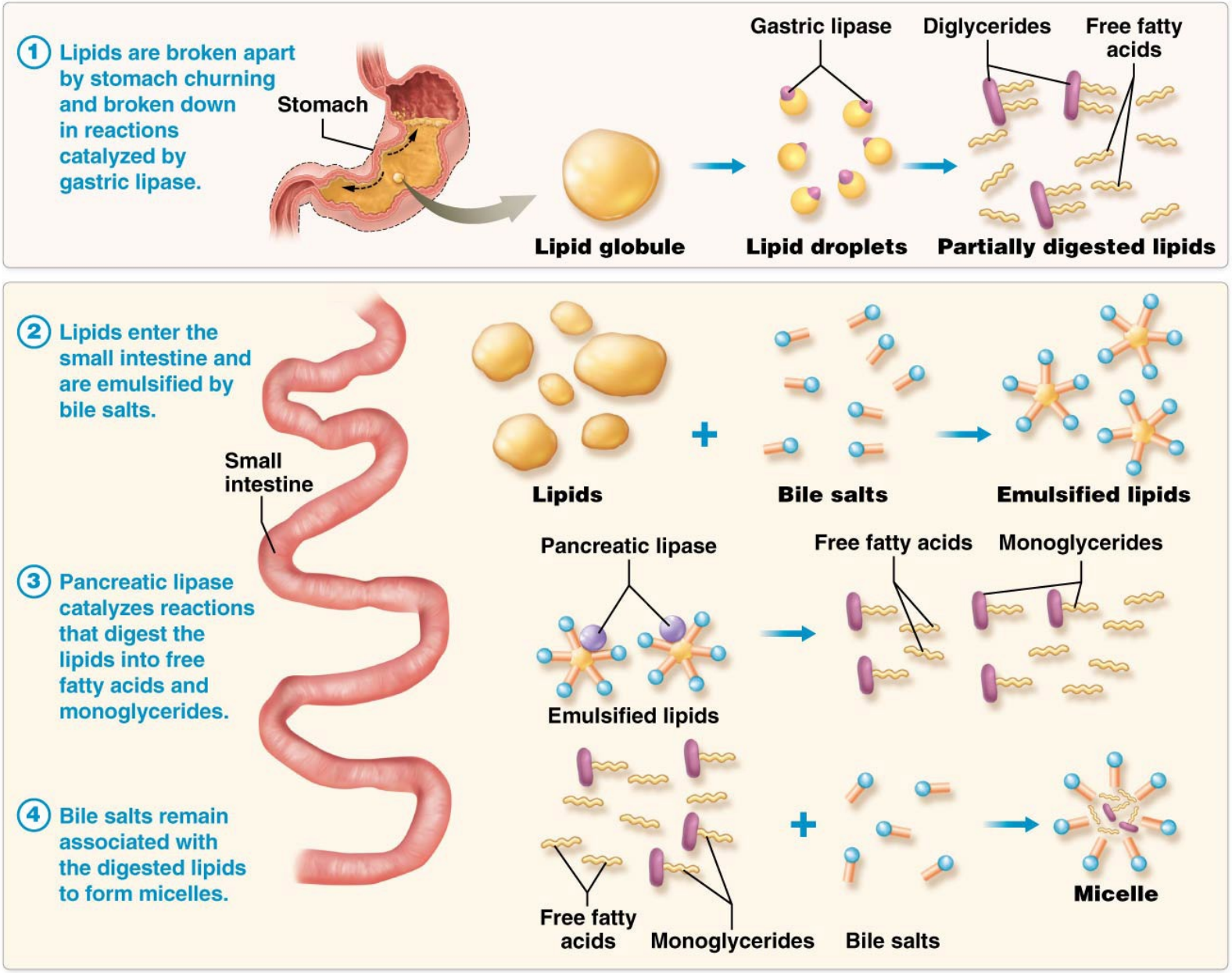
micelles pass down the bile duct into the duodenum /// where they absorb fat soluble vitamins, more cholesterol, and the FFAs and monoglycerides produced by fat digestion

they transport lipids to the surface of the intestinal absorptive cells

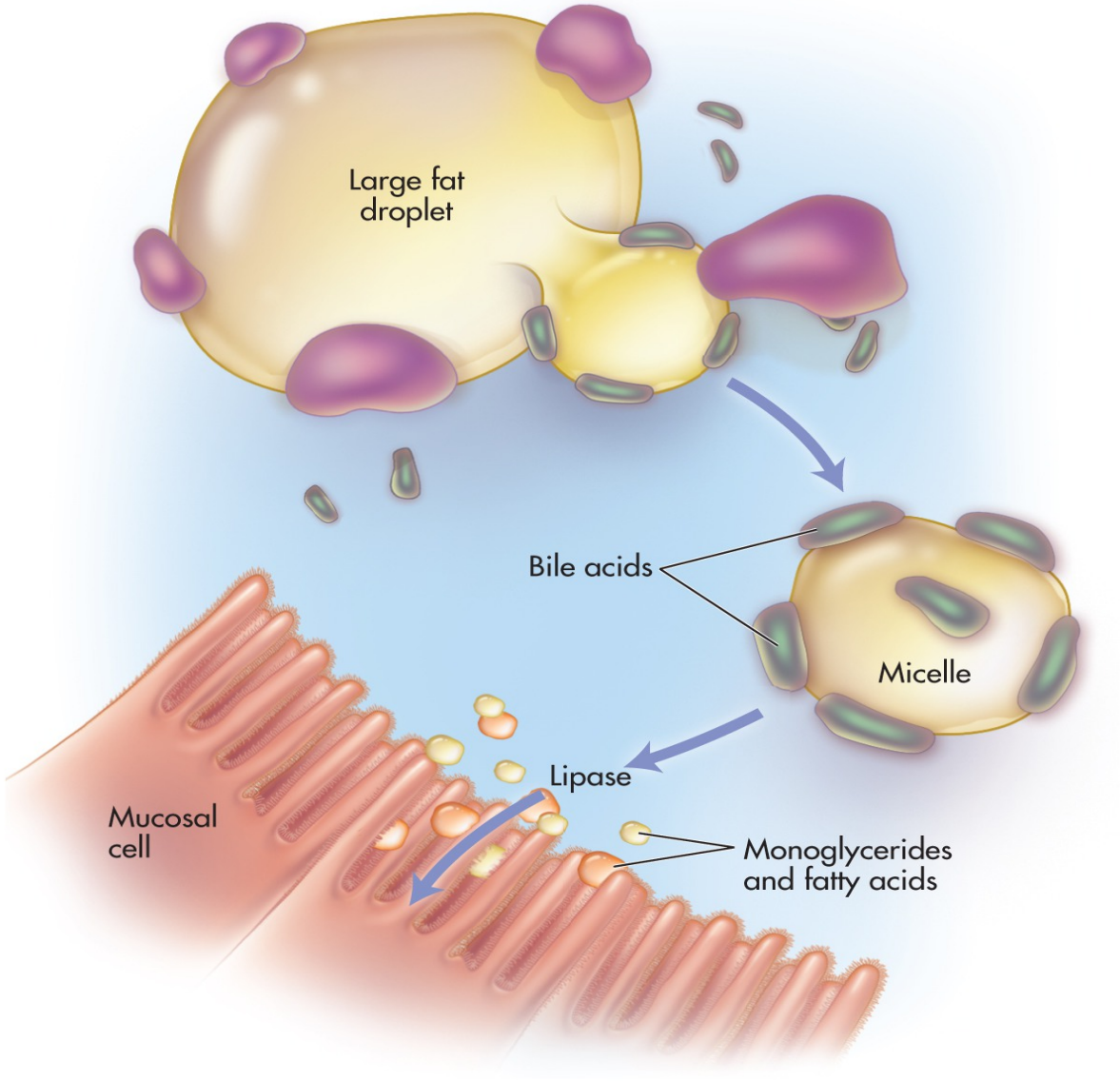
lipids leave the micelles and diffuse through the plasma membrane into the cells

micelles are reused (enterohepatic circulation) /// Reabsorbed in ileum / go back to liver via hepatic portal circulation / returned to bile / secreted back into duodenum

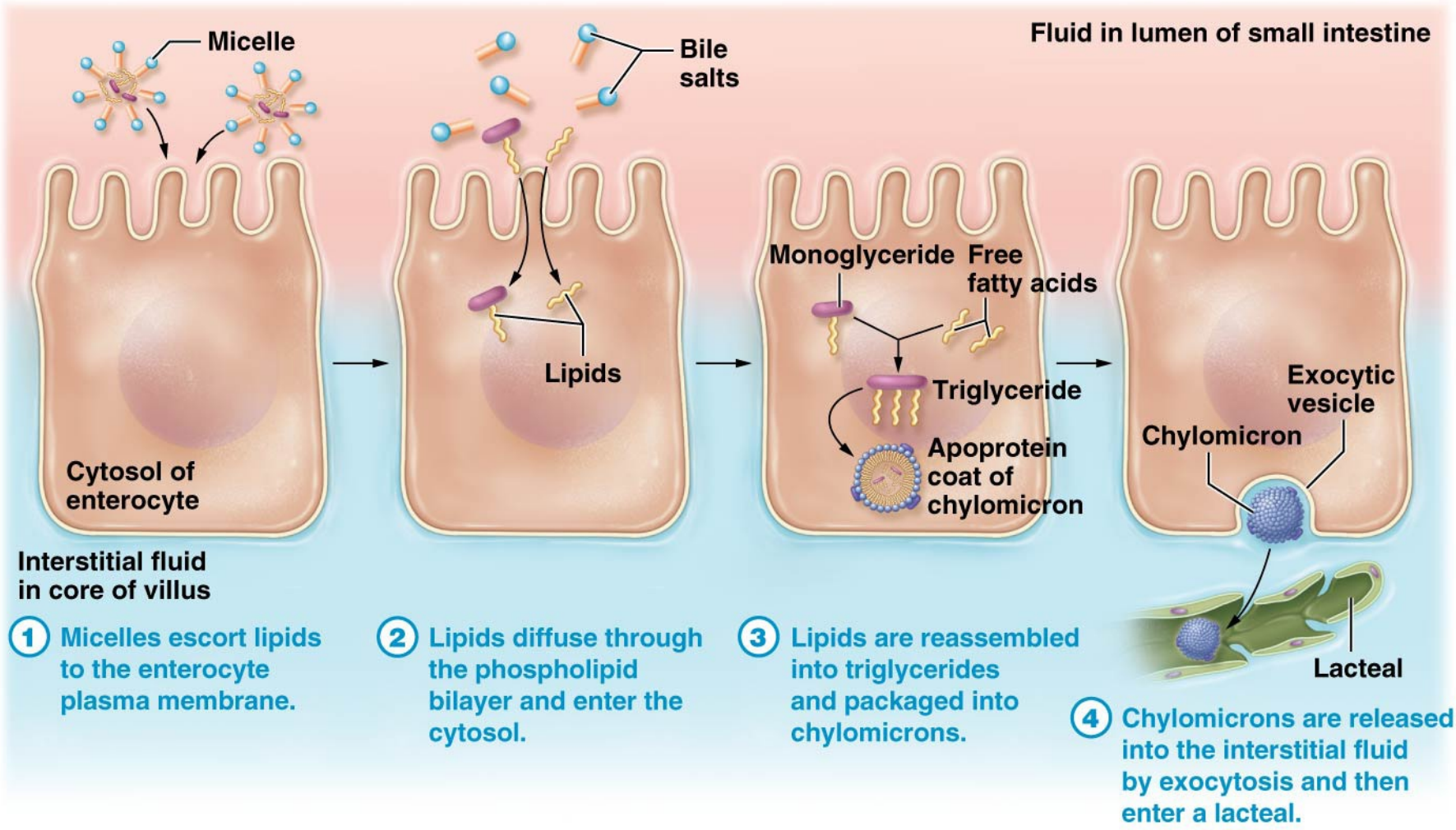
Digestion of lipids.



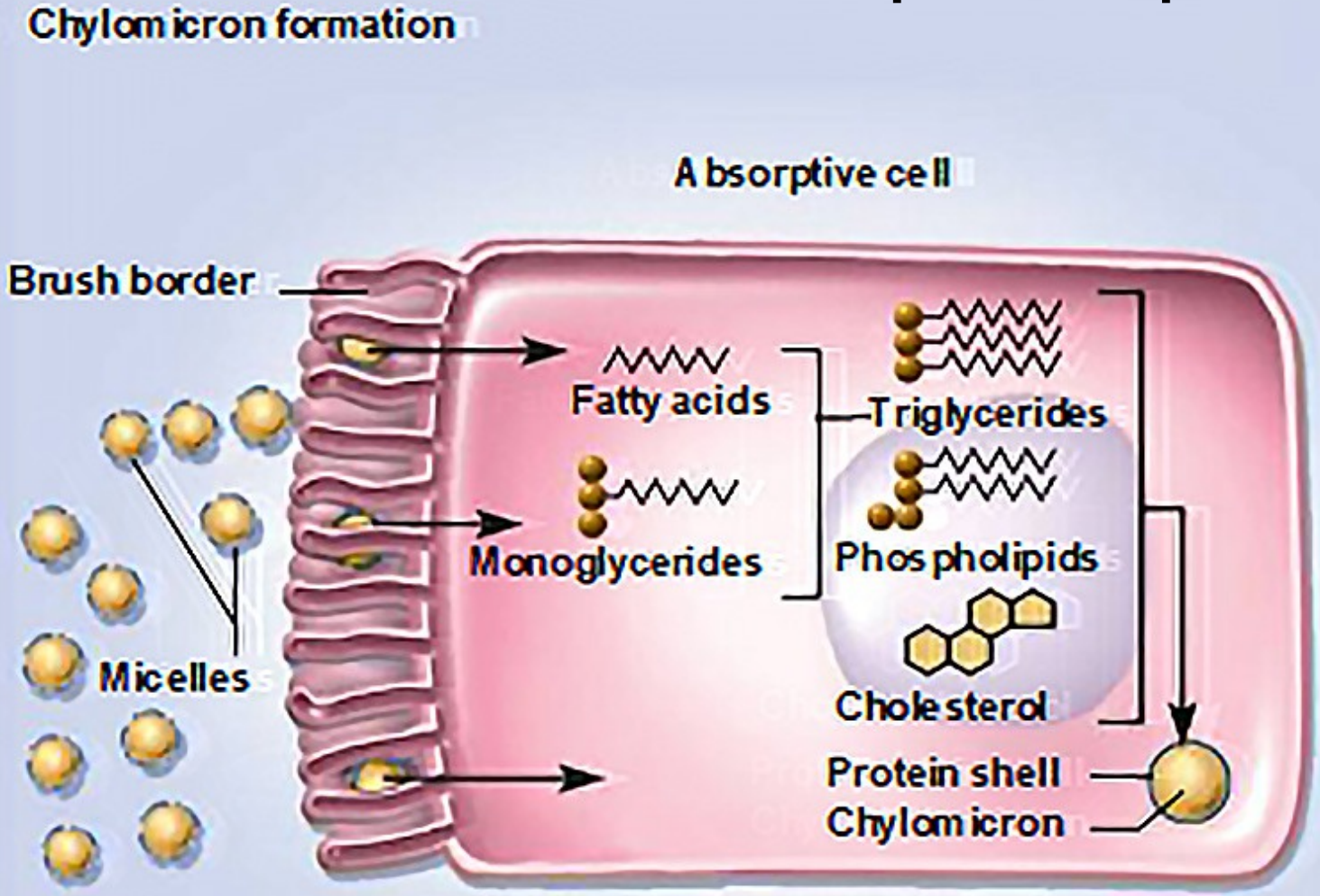
Fat Digestion and Absorption



Lipid absorption in the small intestine.



Lipid Absorption

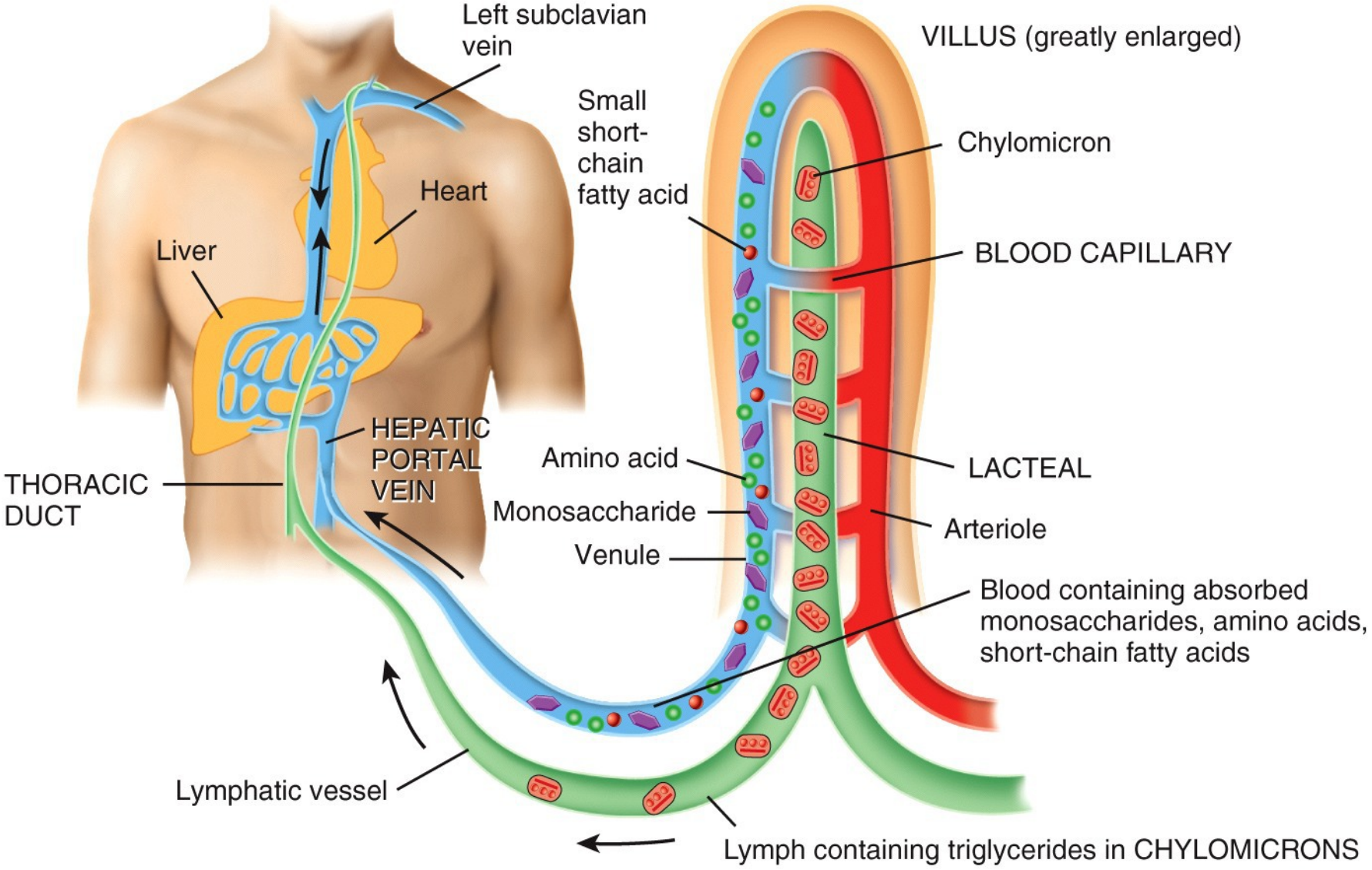


Intestinal cells absorb lipids from micelles, resynthesize triglycerides, and package triglycerides, cholesterol, and phospholipids into 85protein-coated chylomicrons.

Lipid Absorption

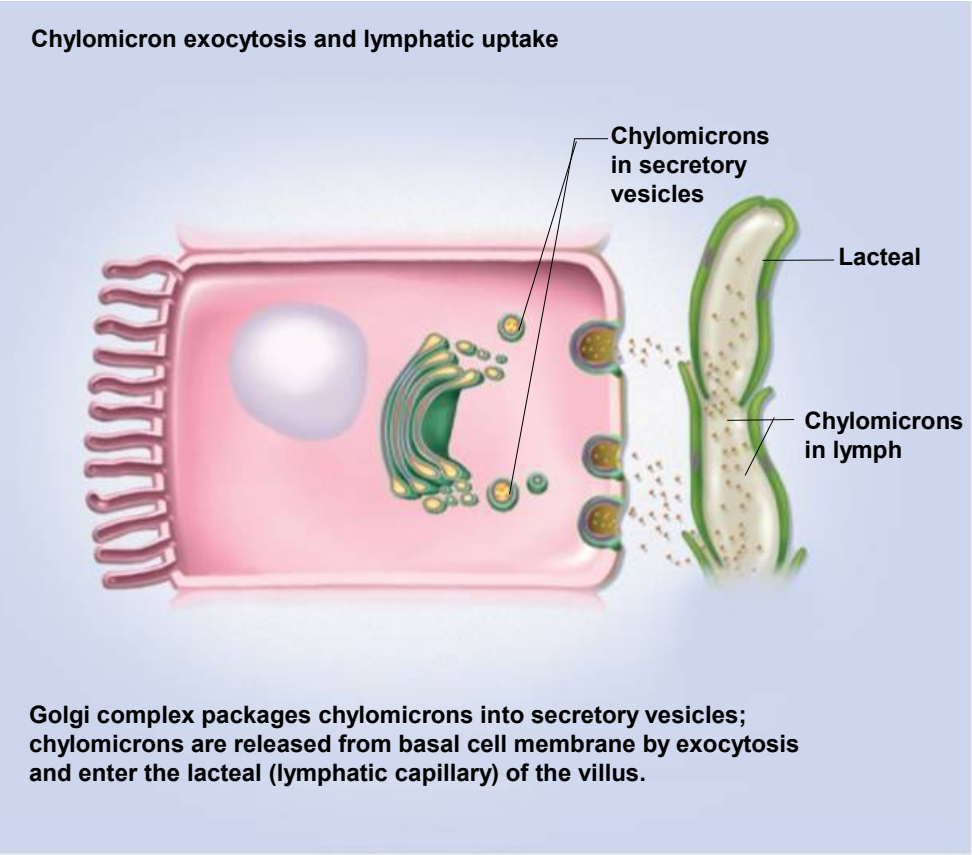
Within the jejunum absorptive cells

- free fatty acids and monoglycerides are transported to the smooth ER
- resynthesized into triglycerides
- golgi complex coats these with phospholipids and protein to form chylomicrons
- Chylomicrons loaded with fat soluble molecules including trigycerides, lecithin, fat soluble vitamins, etc.
  - packaged into secretory vesicles that migrate to basal surface of cell /// release their contents into the core of the villus (lamina propria) /// taken up by more porous lacteal into the lymph /// white, fatty intestinal lymph (chyle) flows into larger and larger lymphatic vessels until they reenter the bloodstream



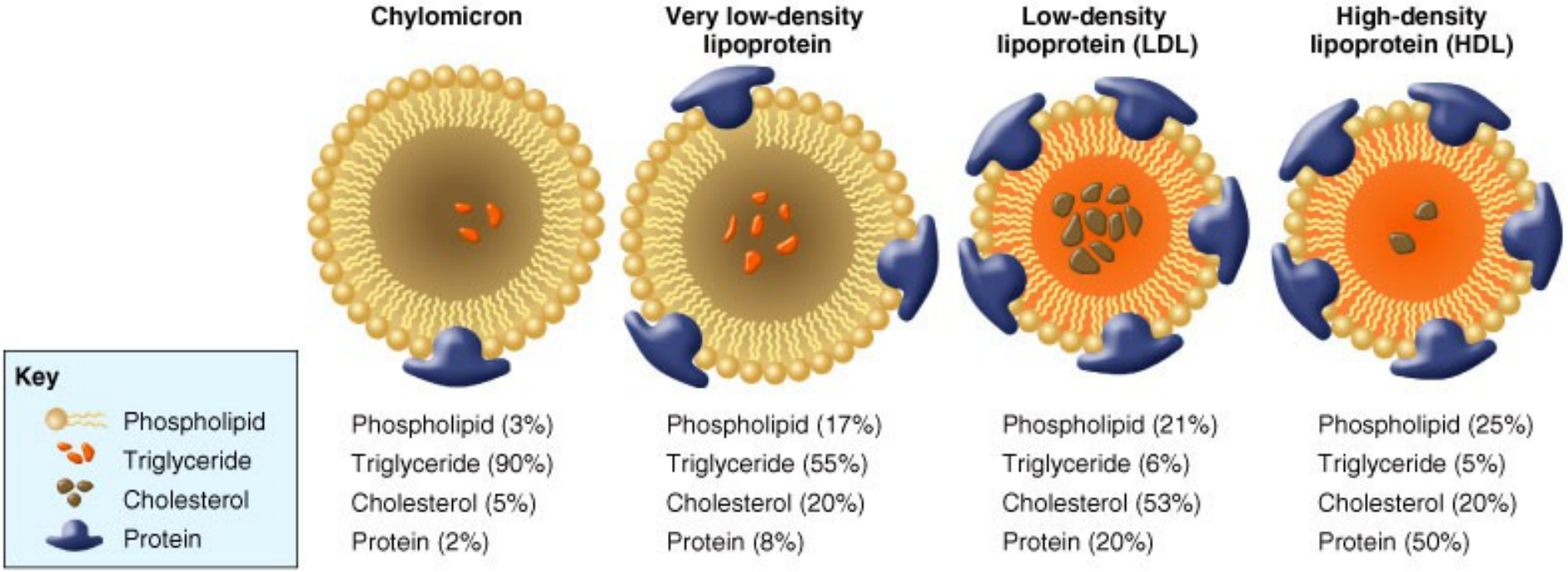
(b) Movement of absorbed nutrients into blood and lymph

Chylomicrons and the Lymphatics



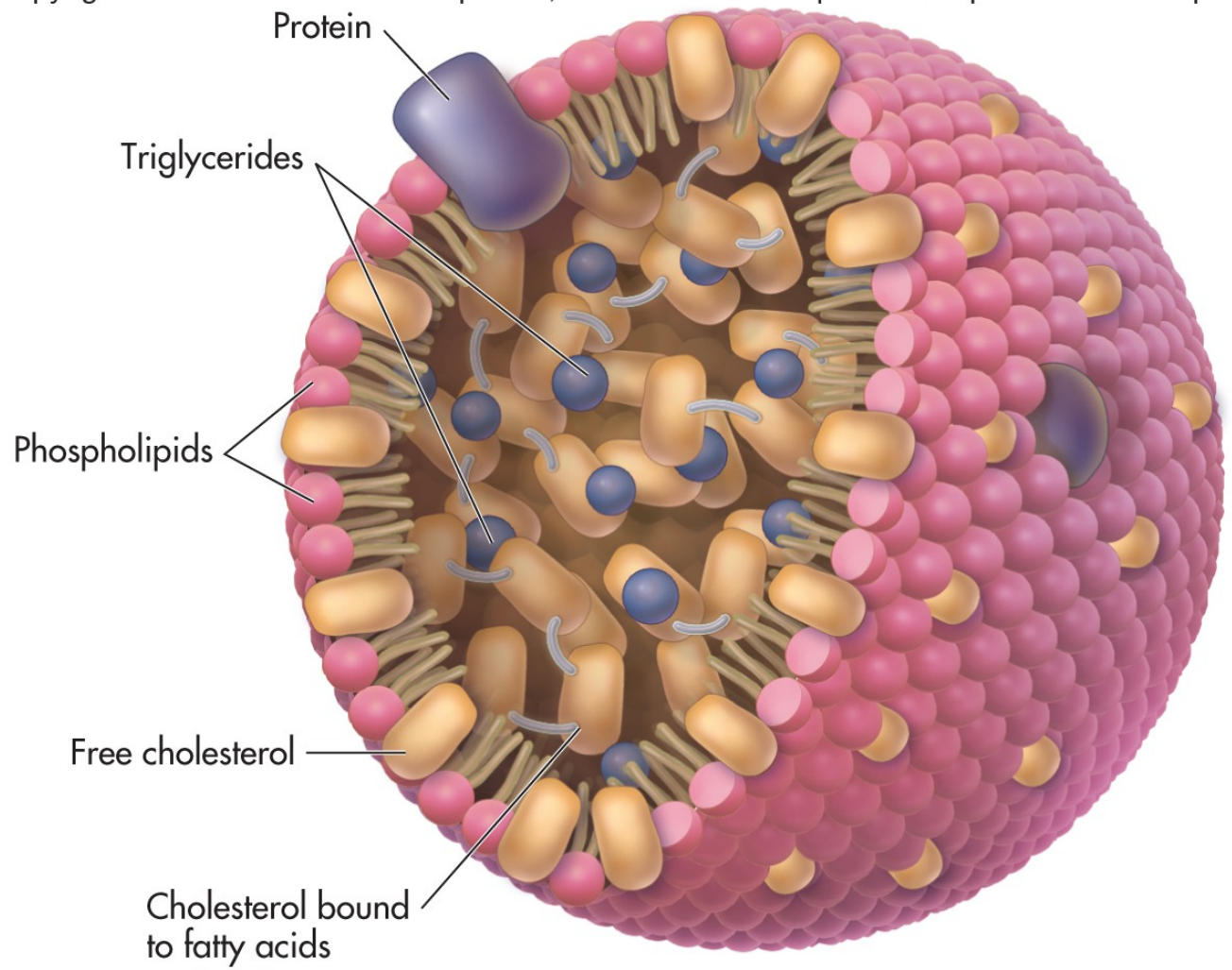
Chylomicrons are released into the lymphatic system in the lacteals of the villi. They enter the bloodstream when lymphatic fluid enters the subclavian vein via the thoracic duct.

Serum Lipoproteins

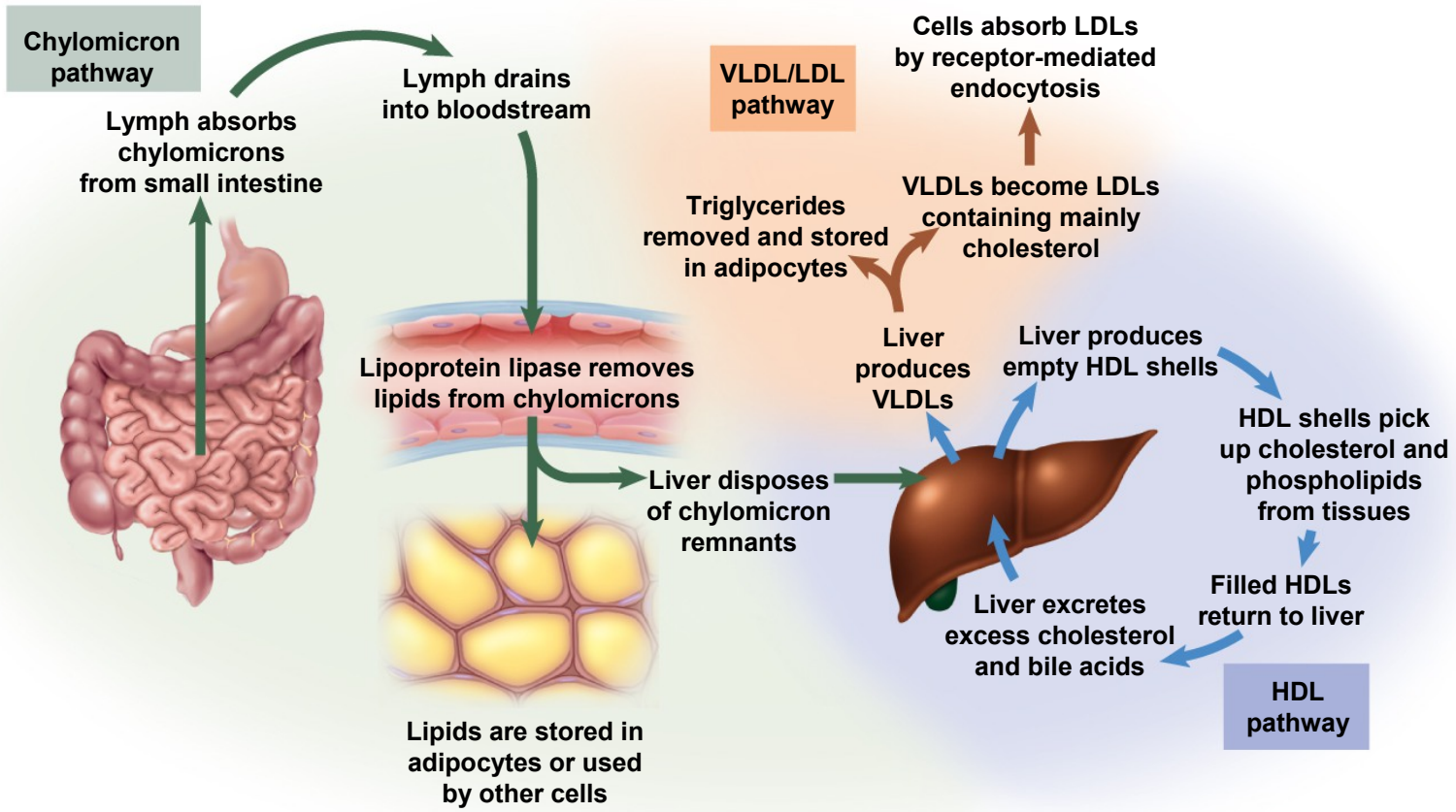


(a) Lipoprotein types

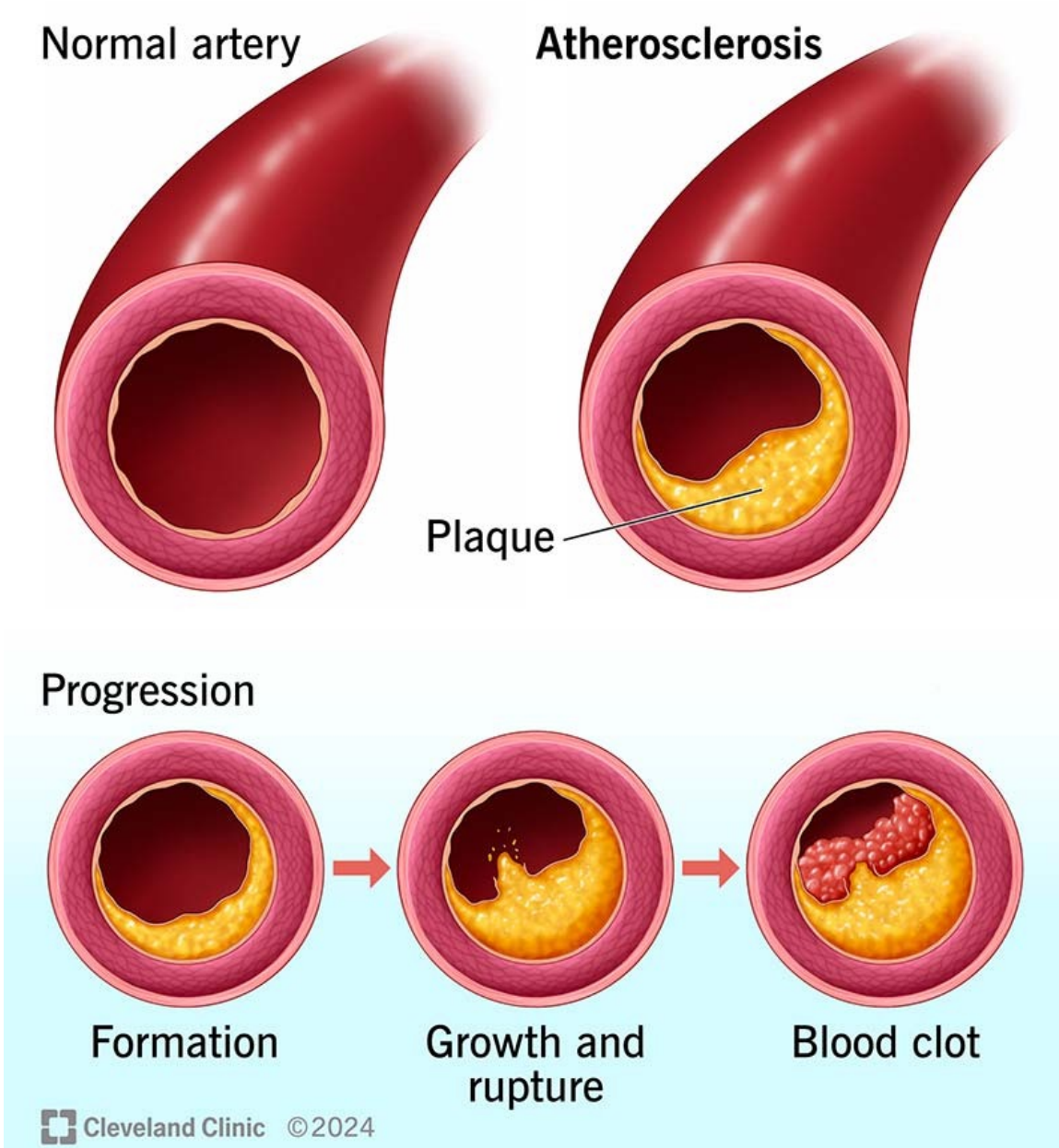
Composition and Roles of Lipoproteins



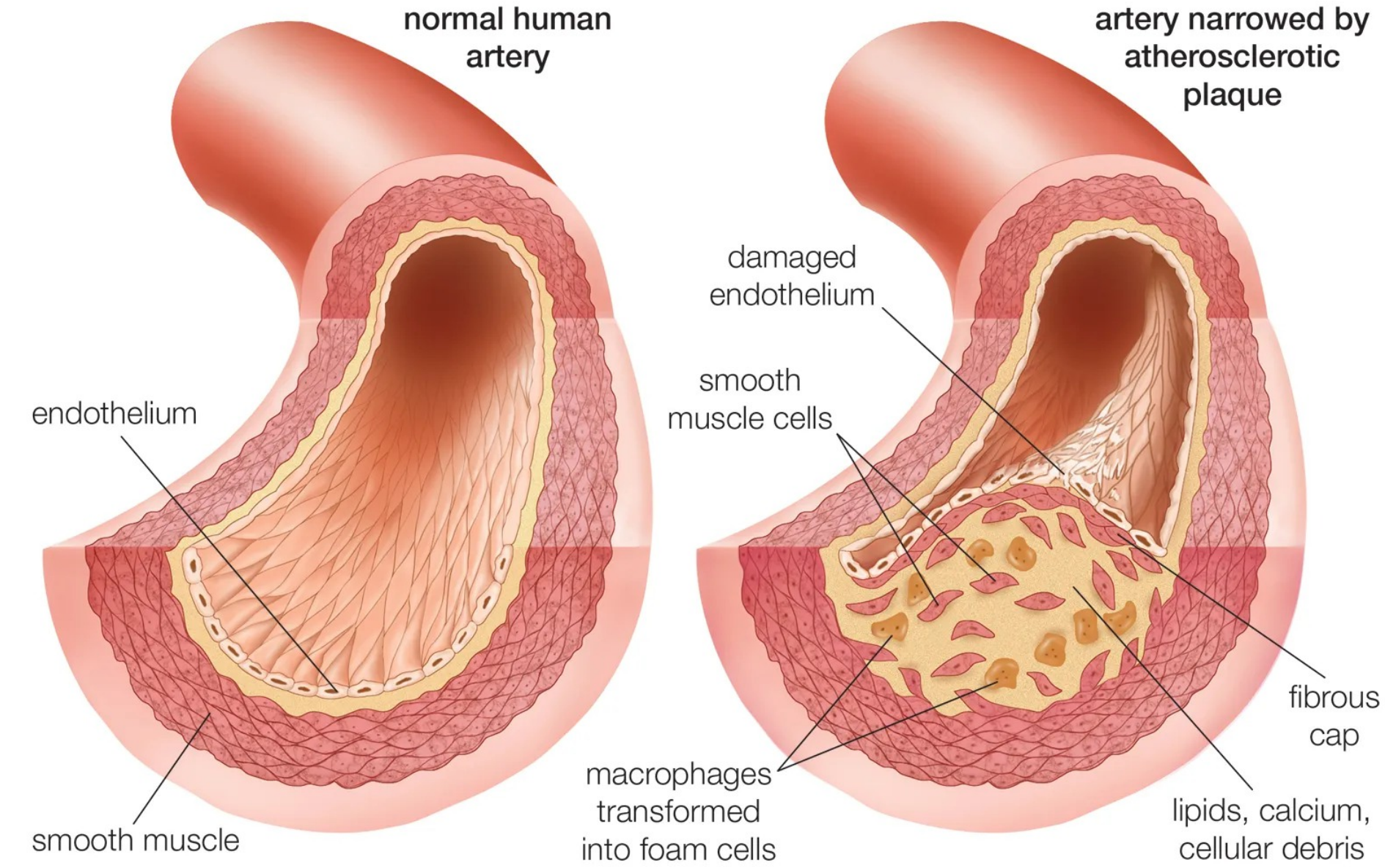
Lipoprotein Processing Pathways

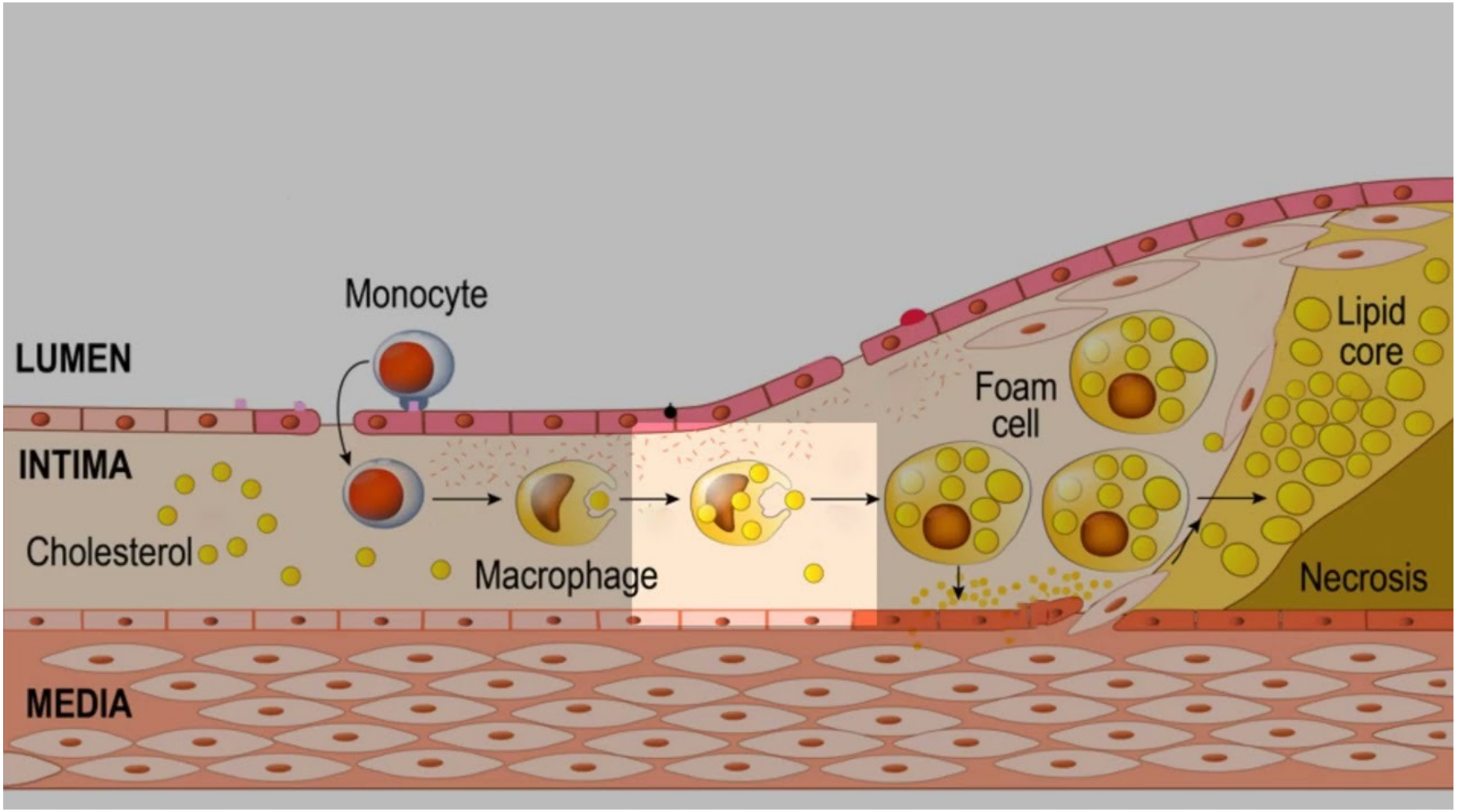


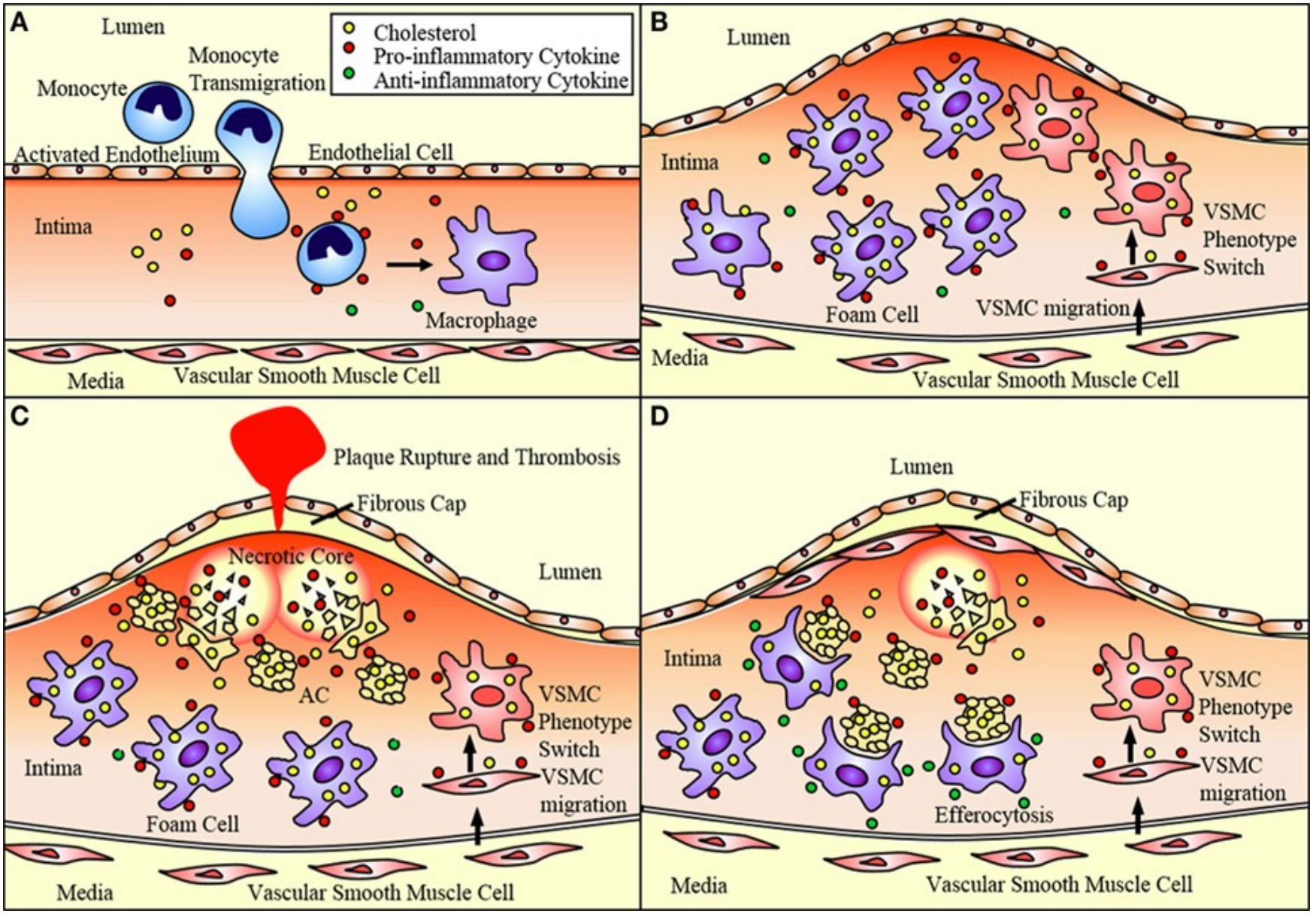
Atherosclerosis

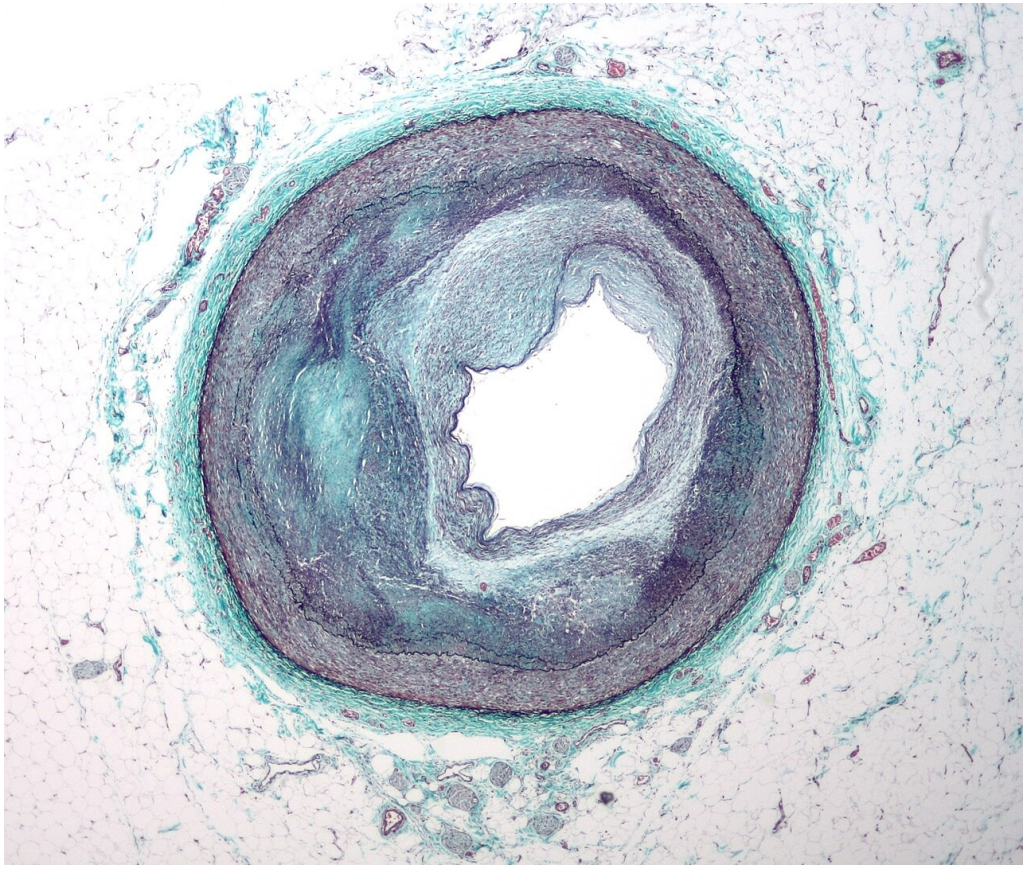


Atherosclerosis



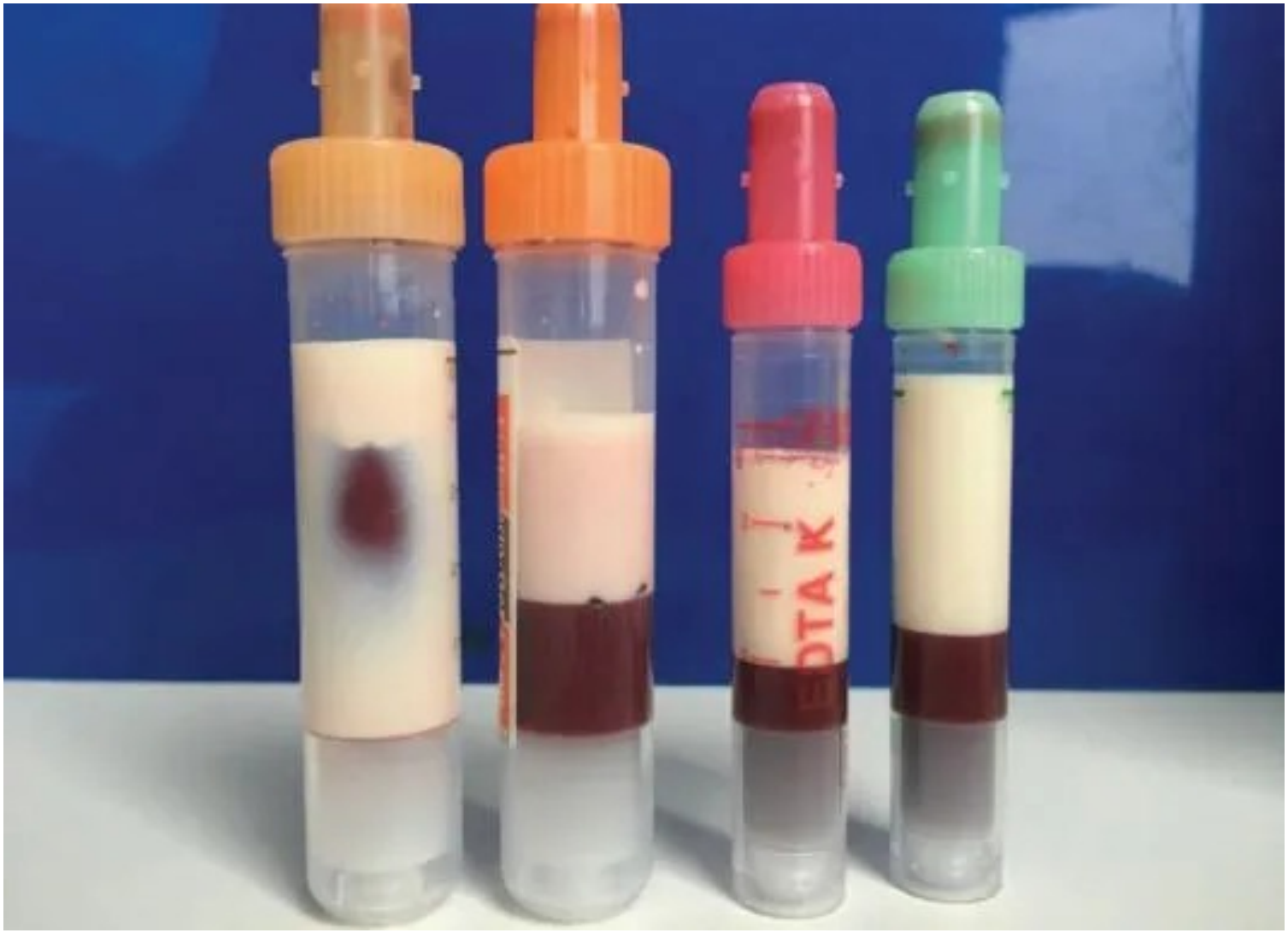

Monocyte
LUMEN
INTIMA
Cholesterol
Macrophage
Foam cell
Lipid core
Necrosis
MEDIA


A
Lumen
Monocyte
Monocyte Transmigration
Cholesterol
Pro-inflammatory Cytokine
Anti-inflammatory Cytokine
Activated Endothelium
Endothelial Cell
Intima
Macrophage
Media
Vascular Smooth Muscle Cell
B
Lumen
Intima
VSMC Phenotype Switch
Foam Cell
VSMC migration
Media
Vascular Smooth Muscle Cell
C
Plaque Rupture and Thrombosis
Fibrous Cap
Necrotic Core
Lumen
AC
VSMC Phenotype Switch
Intima
VSMC migration
Foam Cell
Media
Vascular Smooth Muscle Cell
D
Lumen
Fibrous Cap
Intima
VSMC Phenotype Switch
VSMC migration
Efferocytosis
Media
Vascular Smooth Muscle Cell



What's the difference between arteriosclerosis and atherosclerosis?

Atherosclerosis happens when your arteries become narrow due to a buildup of plaque. It's caused by inflammation in the arteries. Atherosclerosis is a type of arteriosclerosis, a condition in which your arteries become stiff. Arteriosclerosis is caused by elastin fibers in your arteries losing elasticity.Oct 5, 2022



A man in Germany had extraordinarily high levels of triglycerides, a type of fat, in his blood. Above, samples of the man's blood about two hours after they were drawn. The white is the fat.


A-72-37

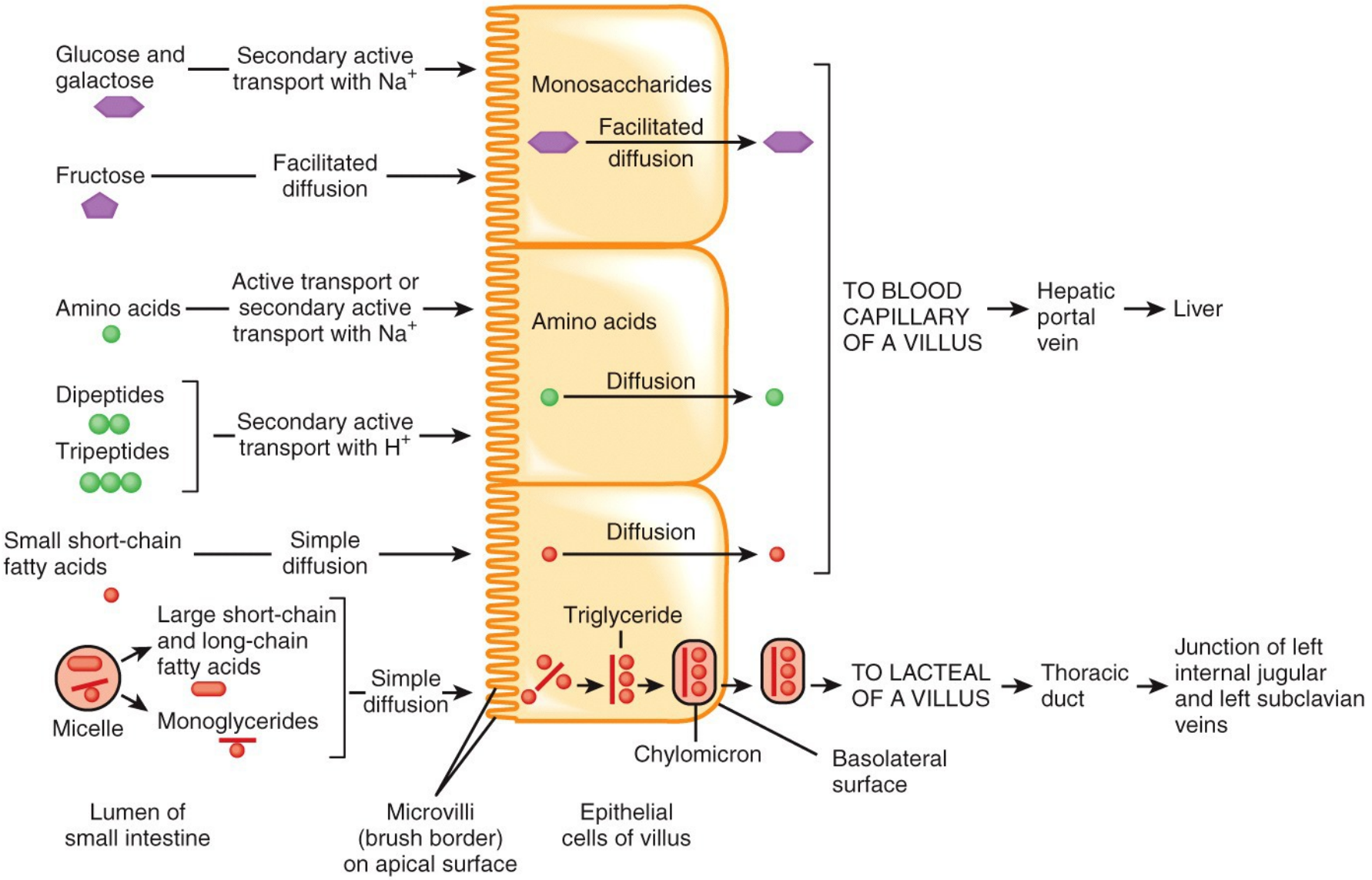
Vitamins

Vitamins are essential nutrients (must come from diet // we can not make them)

absorbed unchanged

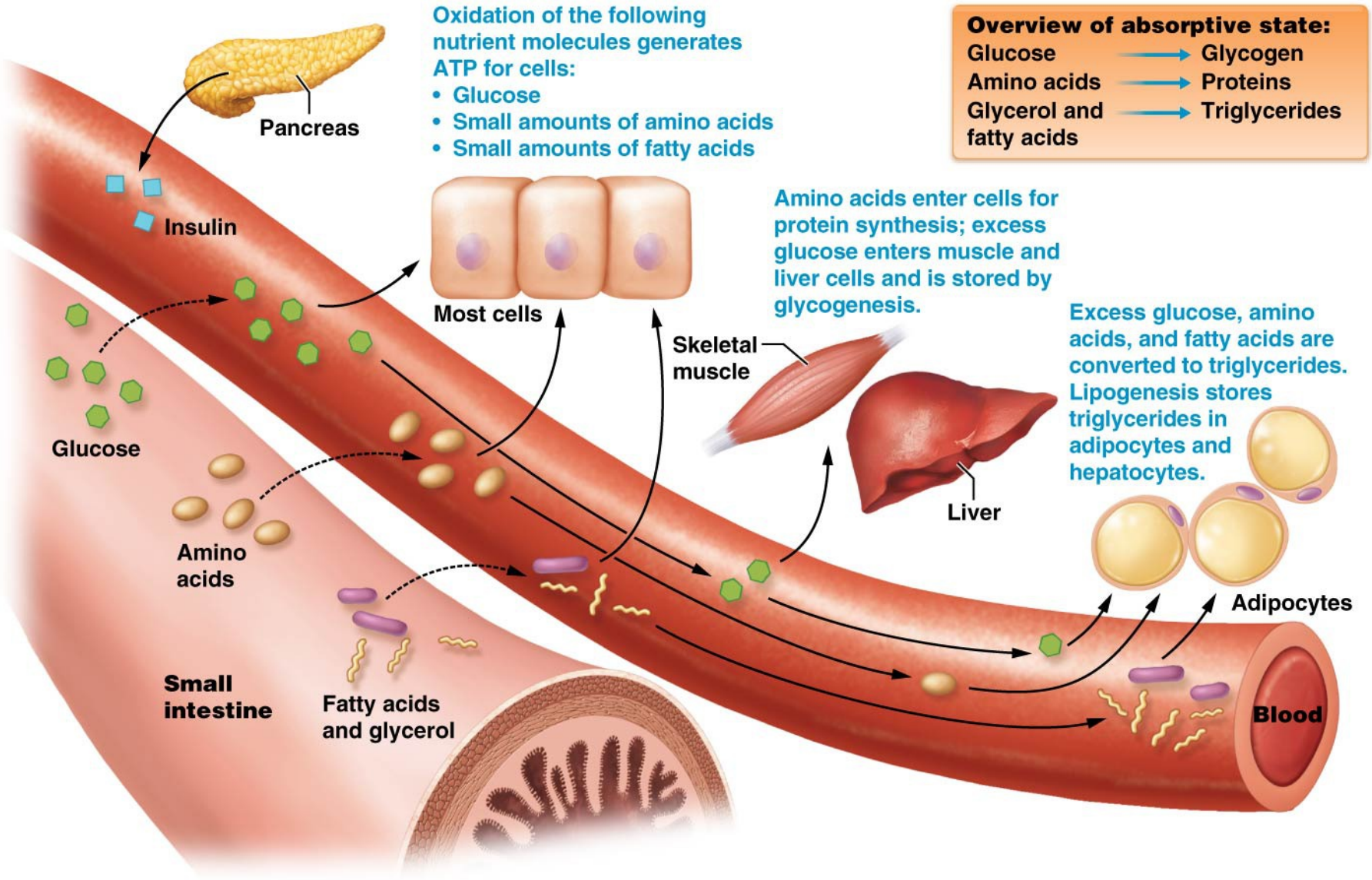
fat-soluble vitamins - A, D, E and K absorbed with other lipids // if they are ingested without fat-containing food, they are not absorbed at all, but are passed in the feces and wasted // Why do we put fatty dressing on our salads?

water-soluble vitamins, like B and C vitamins are absorbed by simple Diffusion /// B_{12} requires gastric intrinsic factor to be absorbed into body



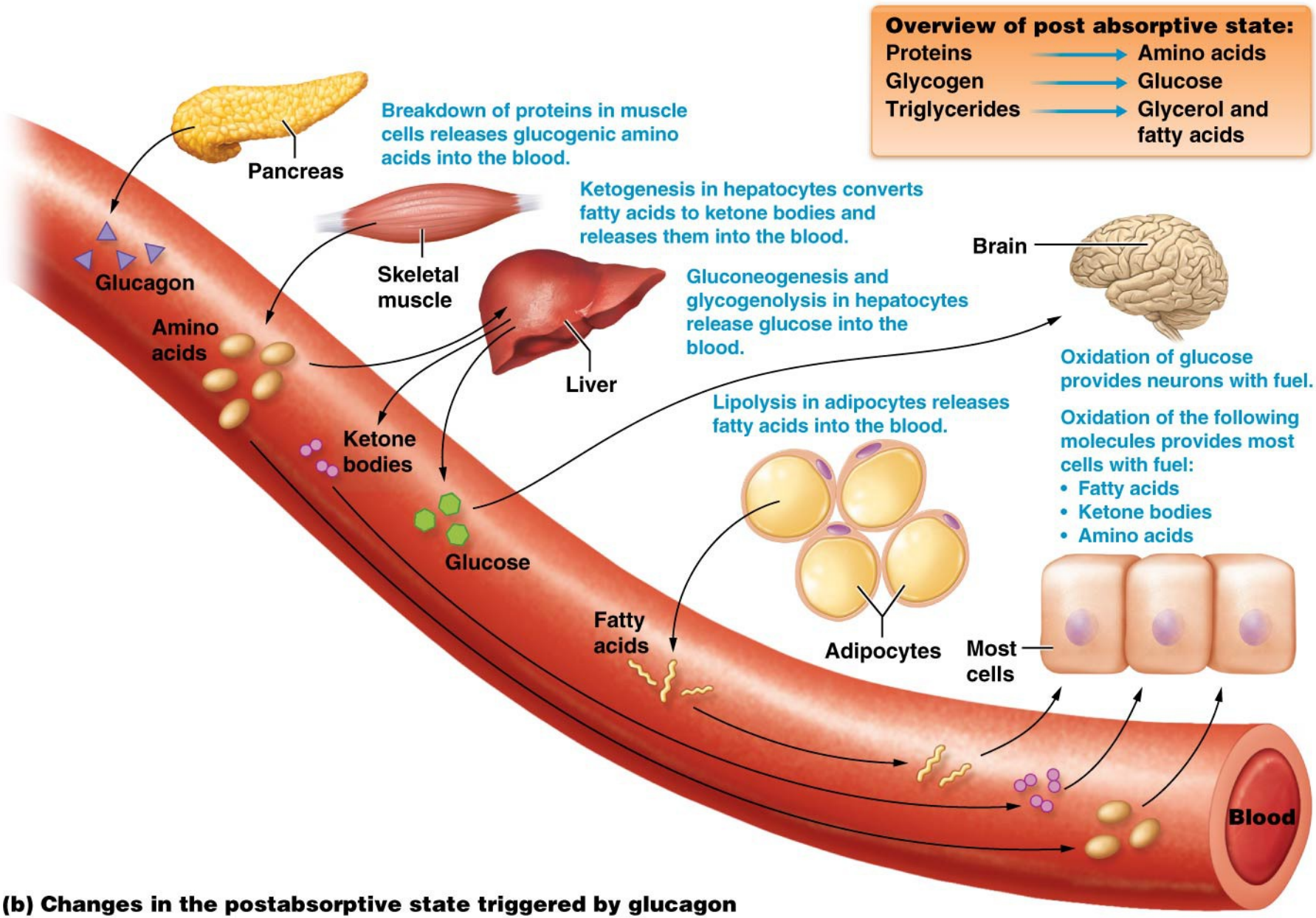
(a) Mechanisms for movement of nutrients through absorptive epithelial cells of villi

The Absorptive State



(a) Changes in the absorptive state triggered by insulin.

The Post Absorptive State



(b) Changes in the postabsorptive state triggered by glucagon

Hormonal Regulation of Digestion (1 of 3)

Gastrin // hormone // produced by G cells of gastric pit

Stimulate gastric secretions

Stimulate lower esophageal sphincter to contract // prevents “heart burn”

Relax pyloric sphincter // allows small amount of chyme to enter duodenum and

By relaxing pyloric sphincter and allowing only small volumes of chyme to enters duodenum it then gives time to process chyme

Hormonal Regulation of Digestion (2 of 3)

- **Chyme leaving stomach stimulates duodeum's enteroendocrine cells to release secretin and cholecystokinin**
  - **These hormones stimulate different types of secretions from the pancreas and gall bladder**
  - **CCK suppress gastric secretion and interacts with hypothalamus to stimulate satiety // stimulate pancreas to produce and release more hormones // stimulate gall bladder to release bile**
  - **Another type of enteroendocrine cells secrete glucose-dependent insulinotropic peptide (GIP) /// this was called gastrin-inhibiting peptide**
    - » **stimulates insulin secretion in preparation for processing nutrients about to be absorbed by the small intestine // reduces gastric contractions**

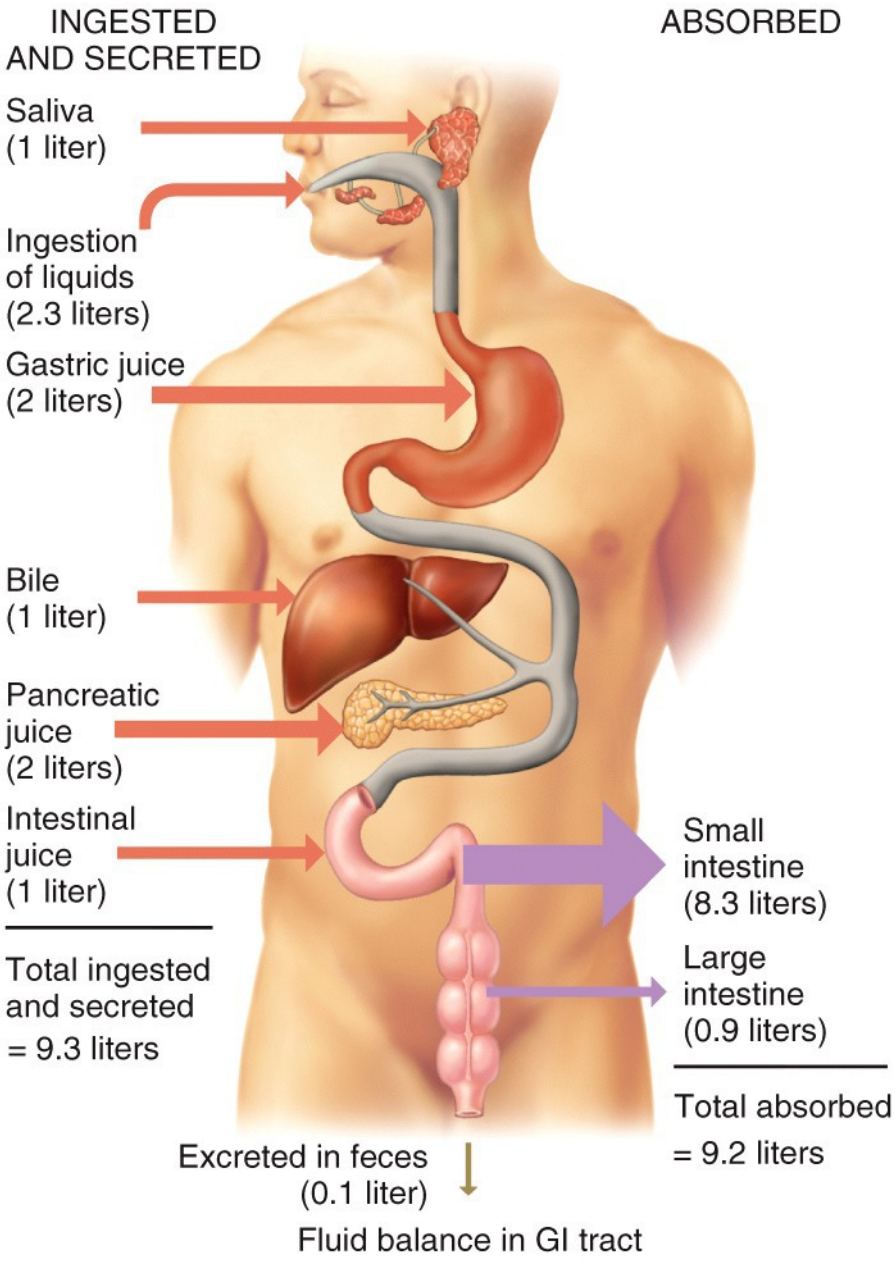
Hormonal Regulation of Digestion (2 of 2)

- **cholecystokinin (CCK) -** secreted by mucosa of duodenum in response to arrival of fats in small intestine
  - stimulate pancreatic acini to **secrete enzymes**
  - strongly stimulates gall bladder
  - induces contractions of the gallbladder and relaxation of hepatopancreatic sphincter causing discharge of bile into the duodenum
- **secretin -** released from duodenum in response to acidic chyme arriving from the stomach
  - stimulates ducts in both liver and pancreas **to secrete more sodium bicarbonate**
  - raising pH to level pancreatic and intestinal digestive enzymes require

Small Intestine VS Large Intestine

- Small intestine functions:
  - Digestion (mechanical and chemical)
  - Absorption of nutrients across mucosa /// active and passive
  - 99.9 percent of nutrients absorbed in small intestine

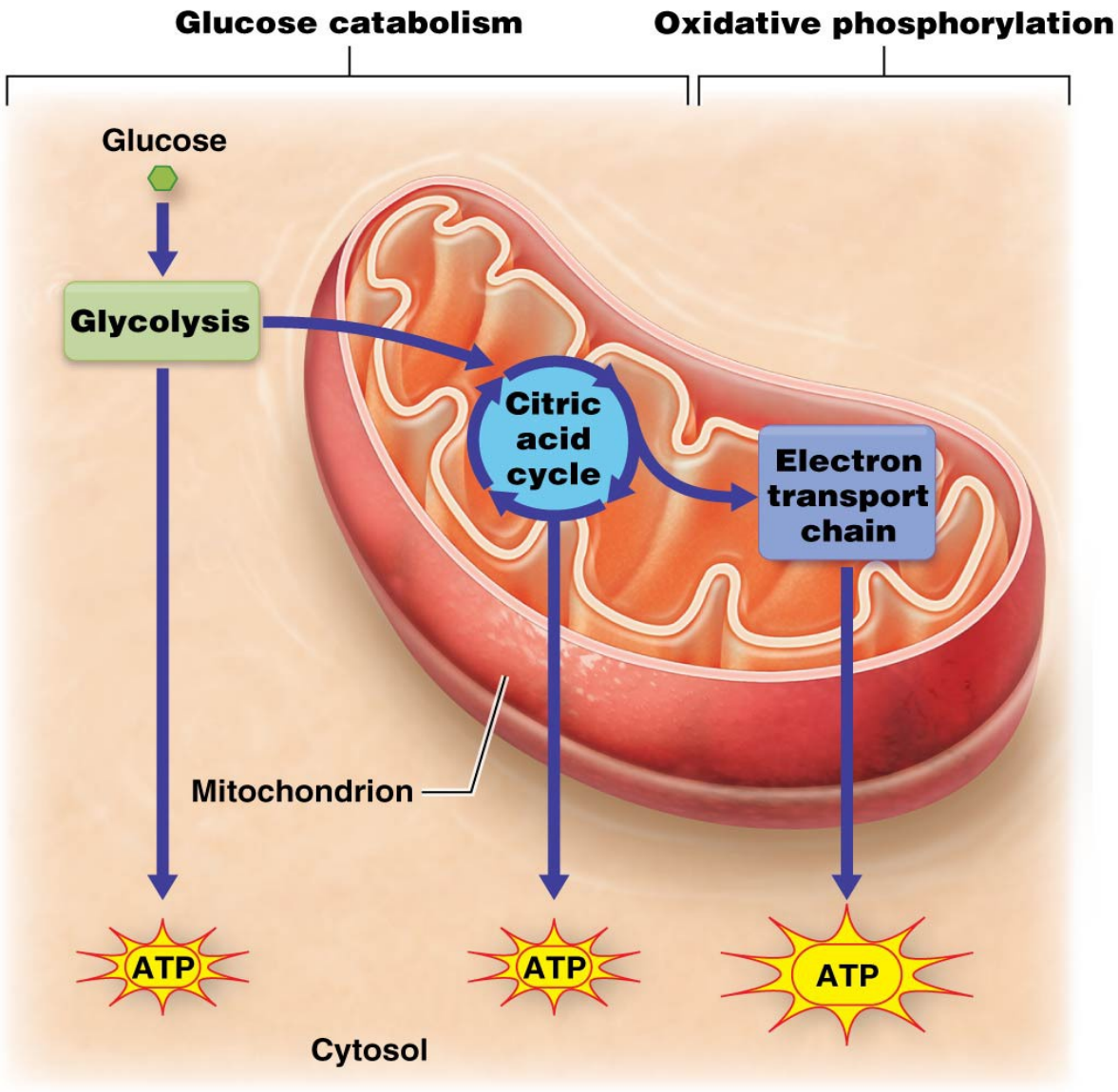
- Large intestine functions:
  - Eliminate food residue
  - Compaction
  - Recover water


INGESTED
AND SECRETED
ABSORBED
Saliva
(1 liter)
Ingestion
of liquids
(2.3 liters)
Gastric juice
(2 liters)
Bile
(1 liter)
Pancreatic
juice
(2 liters)
Intestinal
juice
(1 liter)
Total ingested
and secreted
= 9.3 liters
Small
intestine
(8.3 liters)
Large
intestine
(0.9 liters)
Total absorbed
= 9.2 liters
Excreted in feces
(0.1 liter)
Fluid balance in GI tract

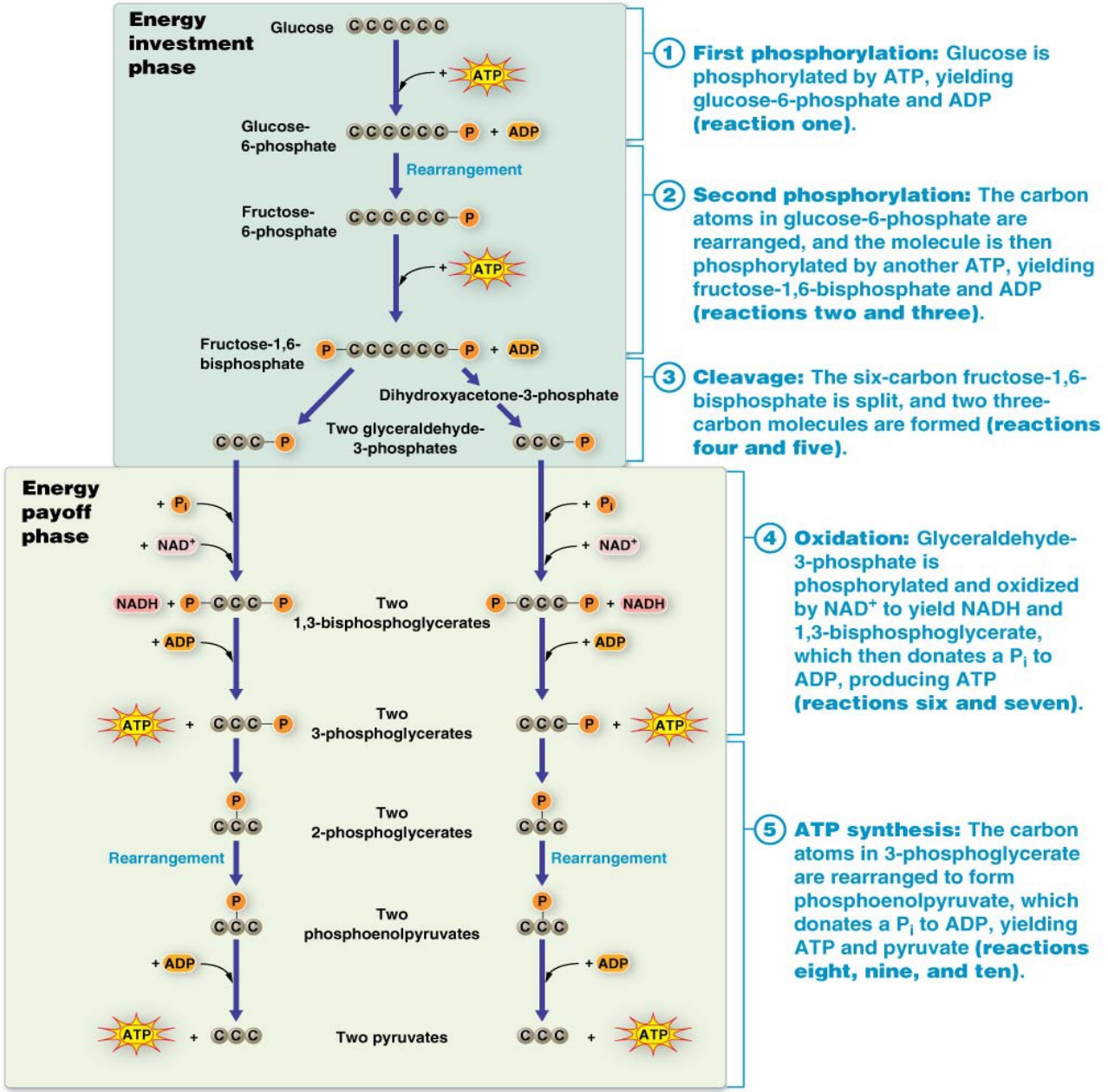
Review of Metabolism

- Gycolysis
- Kreb's Cycle
- Electron Transport Chain
- Anabolism VS Catabolism

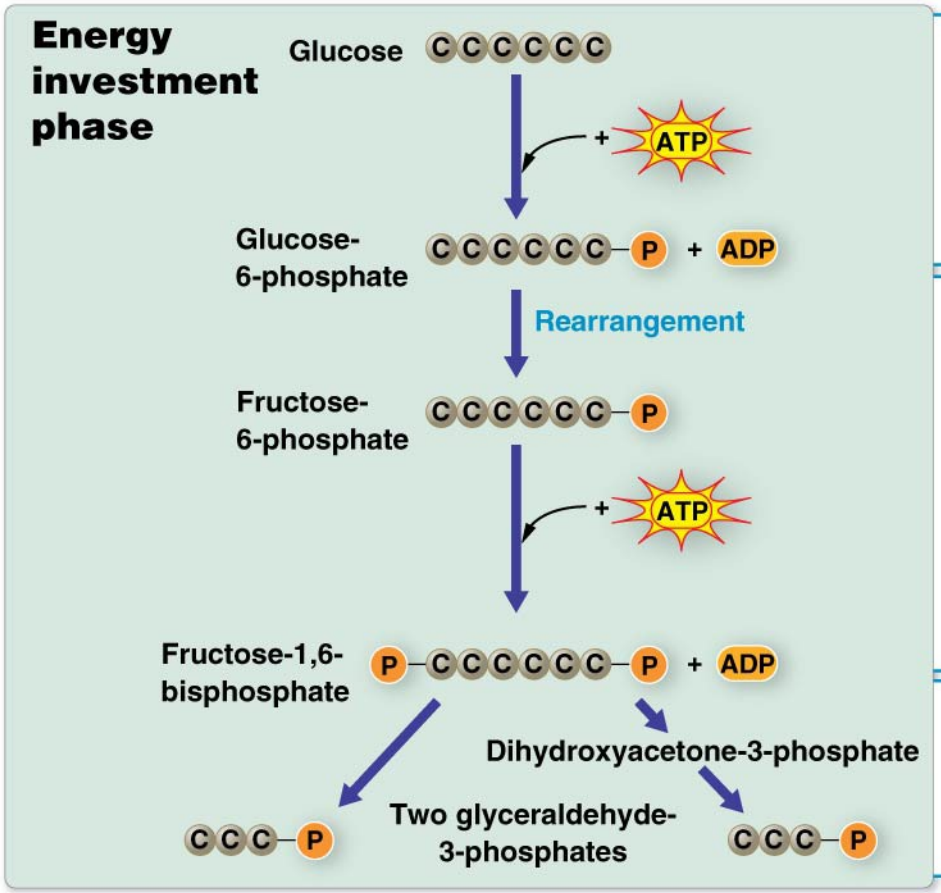
Overview of glucose catabolism and oxidative phosphorylation.



The reactions of glycolysis.



The reactions of glycolysis.

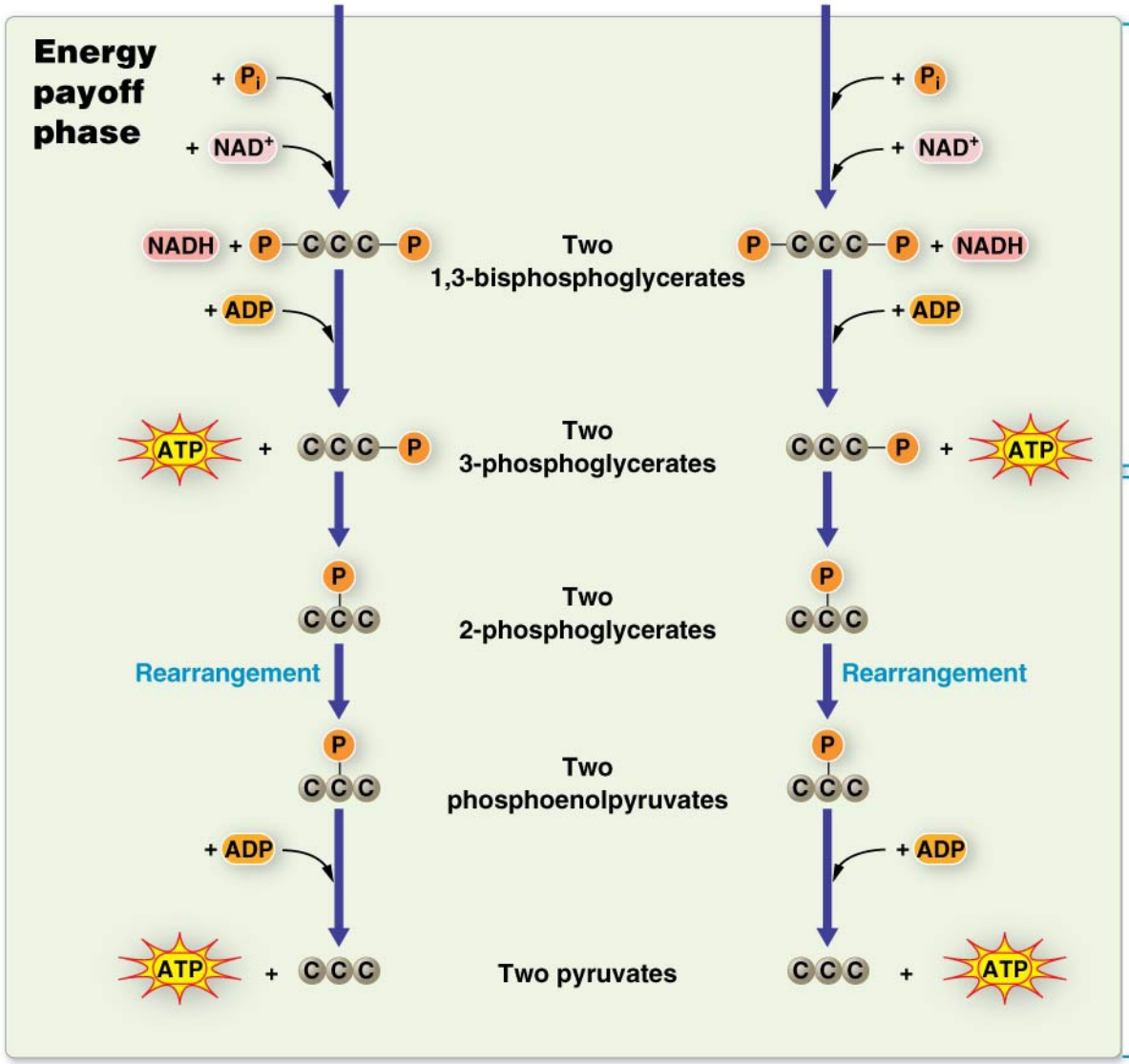


1. **First phosphorylation:** Glucose is phosphorylated by ATP, yielding glucose-6-phosphate and ADP **(reaction one).**

2. **Second phosphorylation:** The carbon atoms in glucose-6-phosphate are rearranged, and the molecule is then phosphorylated by another ATP, yielding fructose-1,6-bisphosphate and ADP **(reactions two and three).**

3. **Cleavage:** The six-carbon fructose-1,6-bisphosphate is split, and two three-carbon molecules are formed **(reactions four and five).**

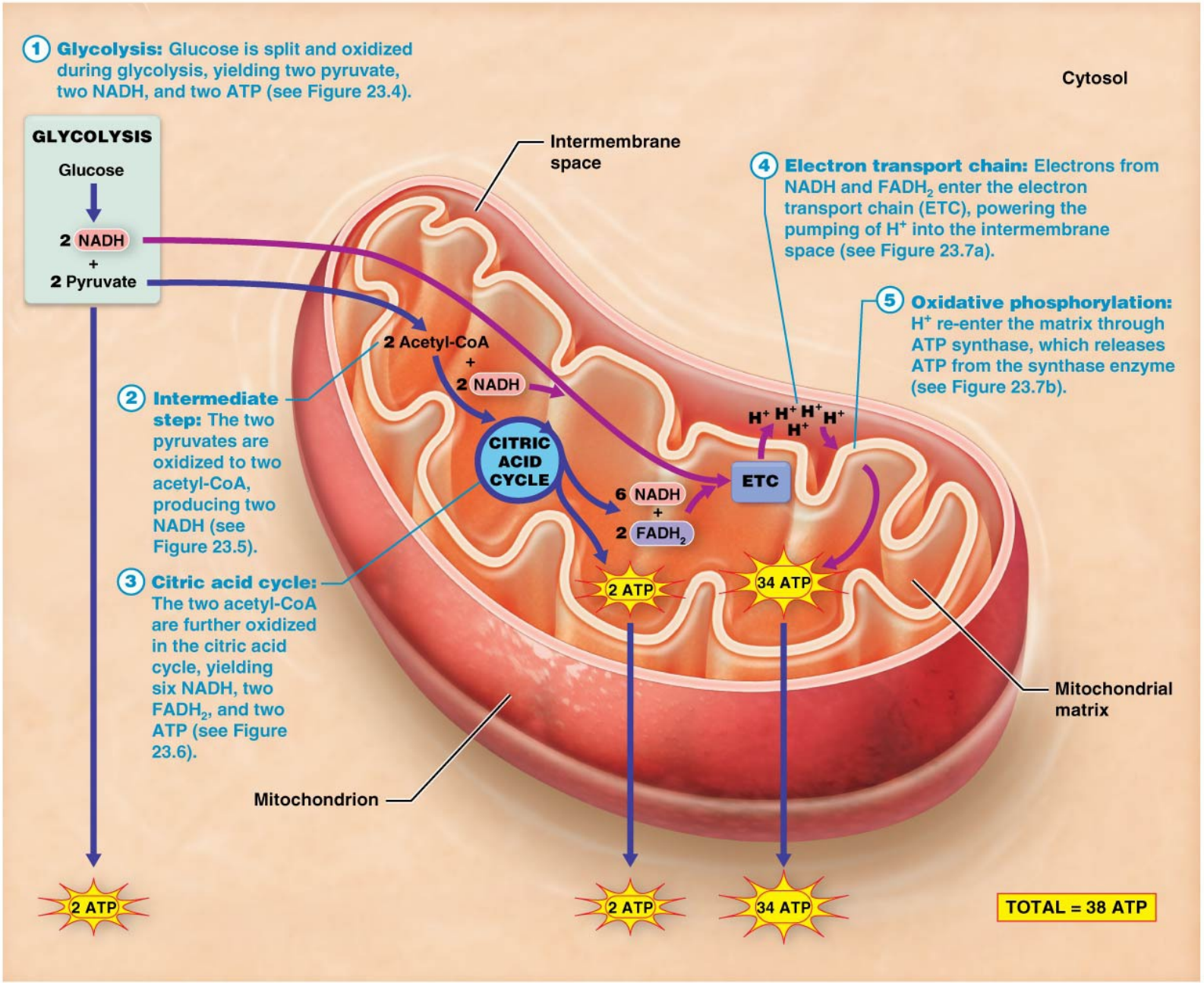
The reactions of glycolysis.



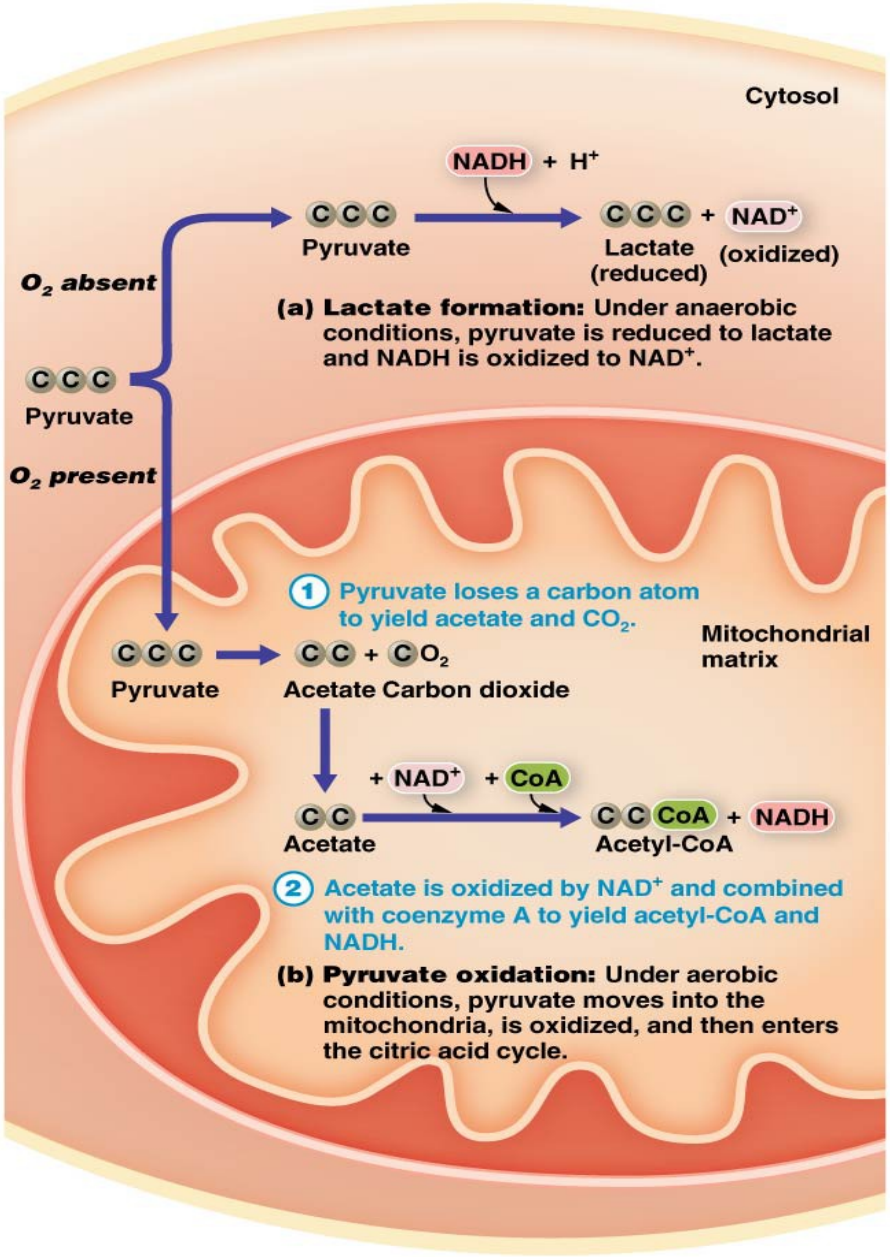
4 **Oxidation:** Glyceraldehyde-3-phosphate is phosphorylated and oxidized by NAD^+ to yield NADH and 1,3-bisphosphoglycerate, which then donates a P_i to ADP, producing ATP **(reactions six and seven).**

5 **ATP synthesis:** The carbon atoms in 3-phosphoglycerate are rearranged to form phosphoenolpyruvate, which donates a P_i to ADP, yielding ATP and pyruvate **(reactions eight, nine, and ten).**

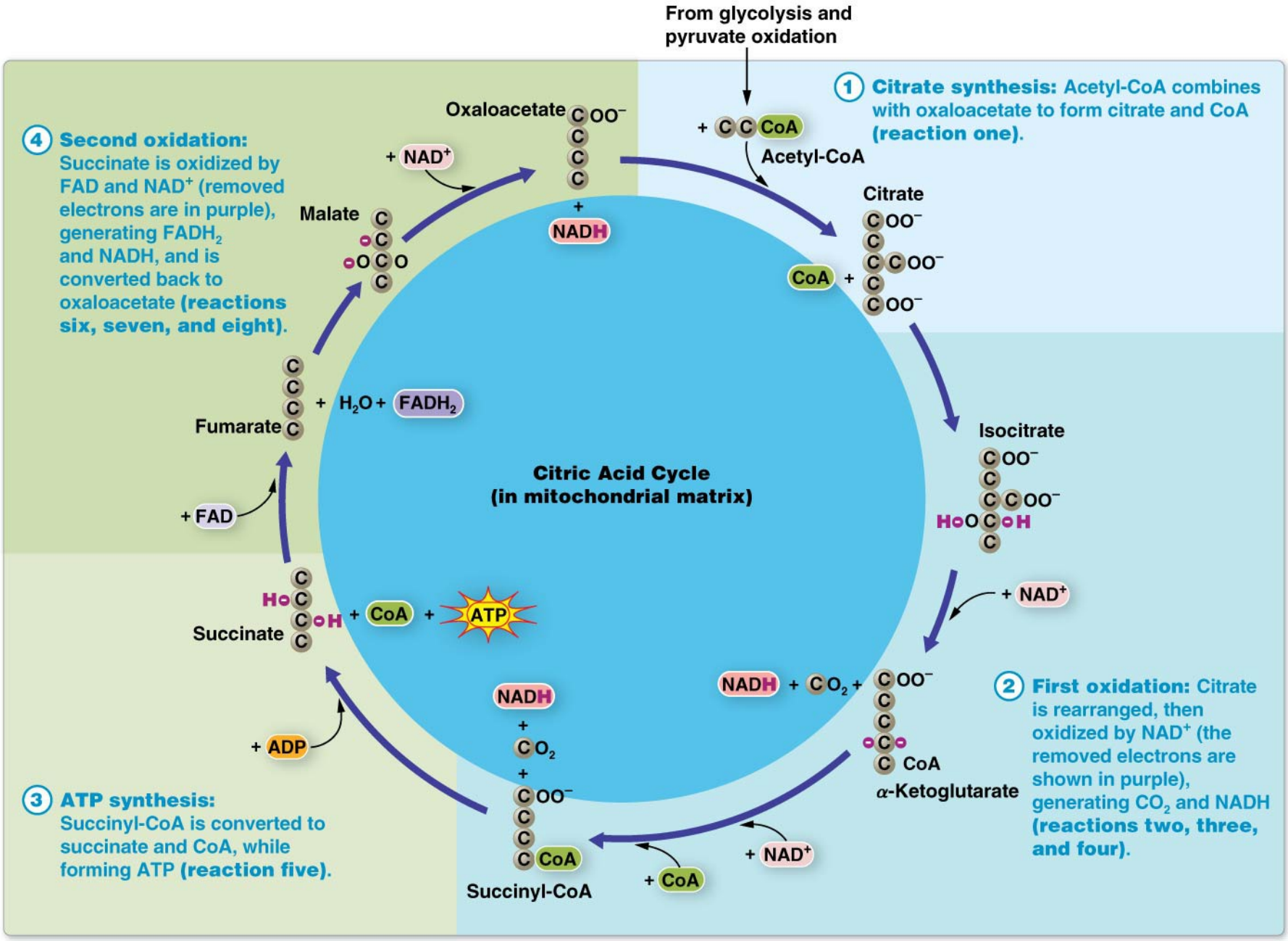
The Big Picture of Glucose Catabolism and Oxidative Phosphorylation



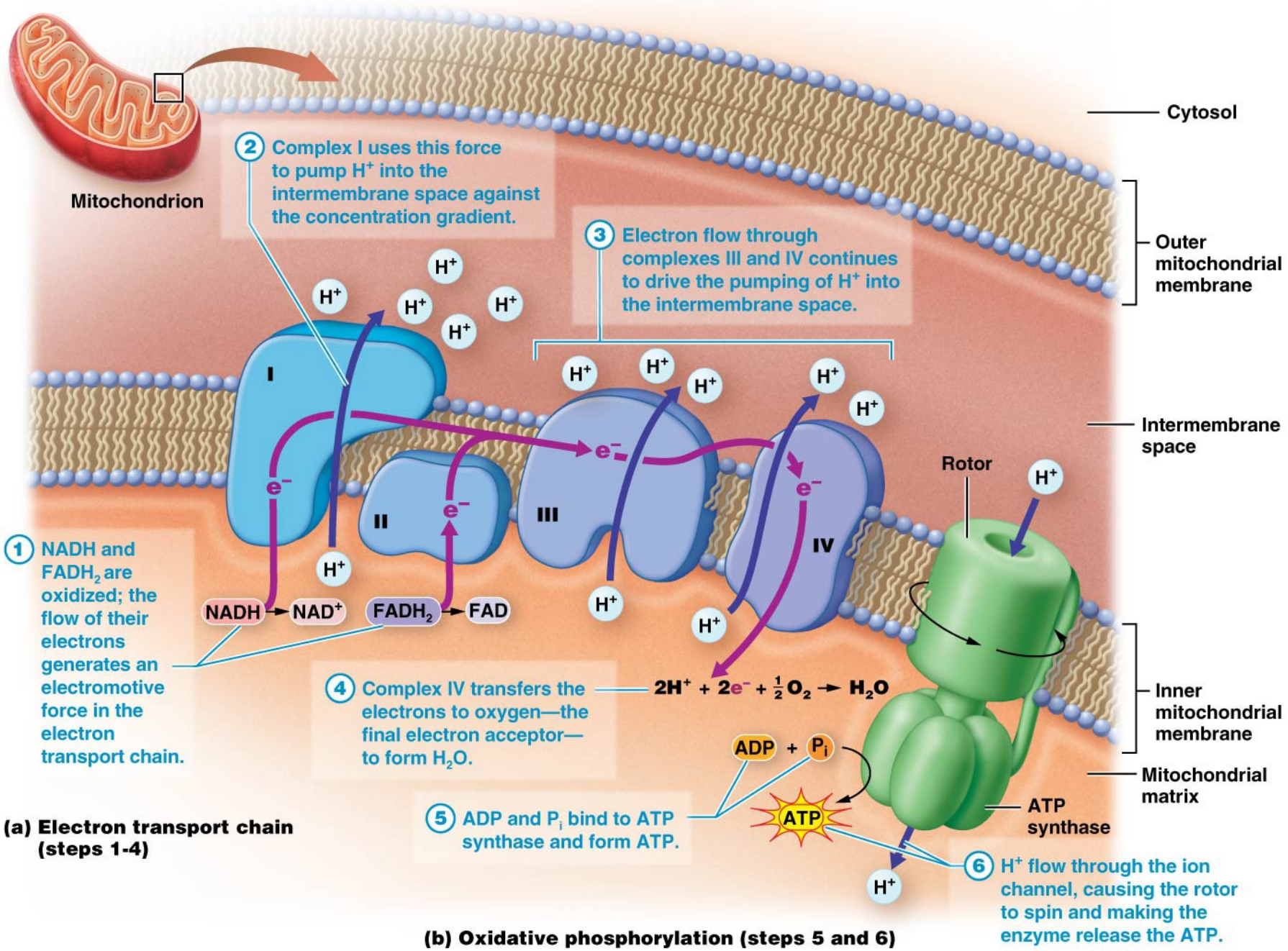
Intermediate step: the fate of pyruvate after glycolysis.



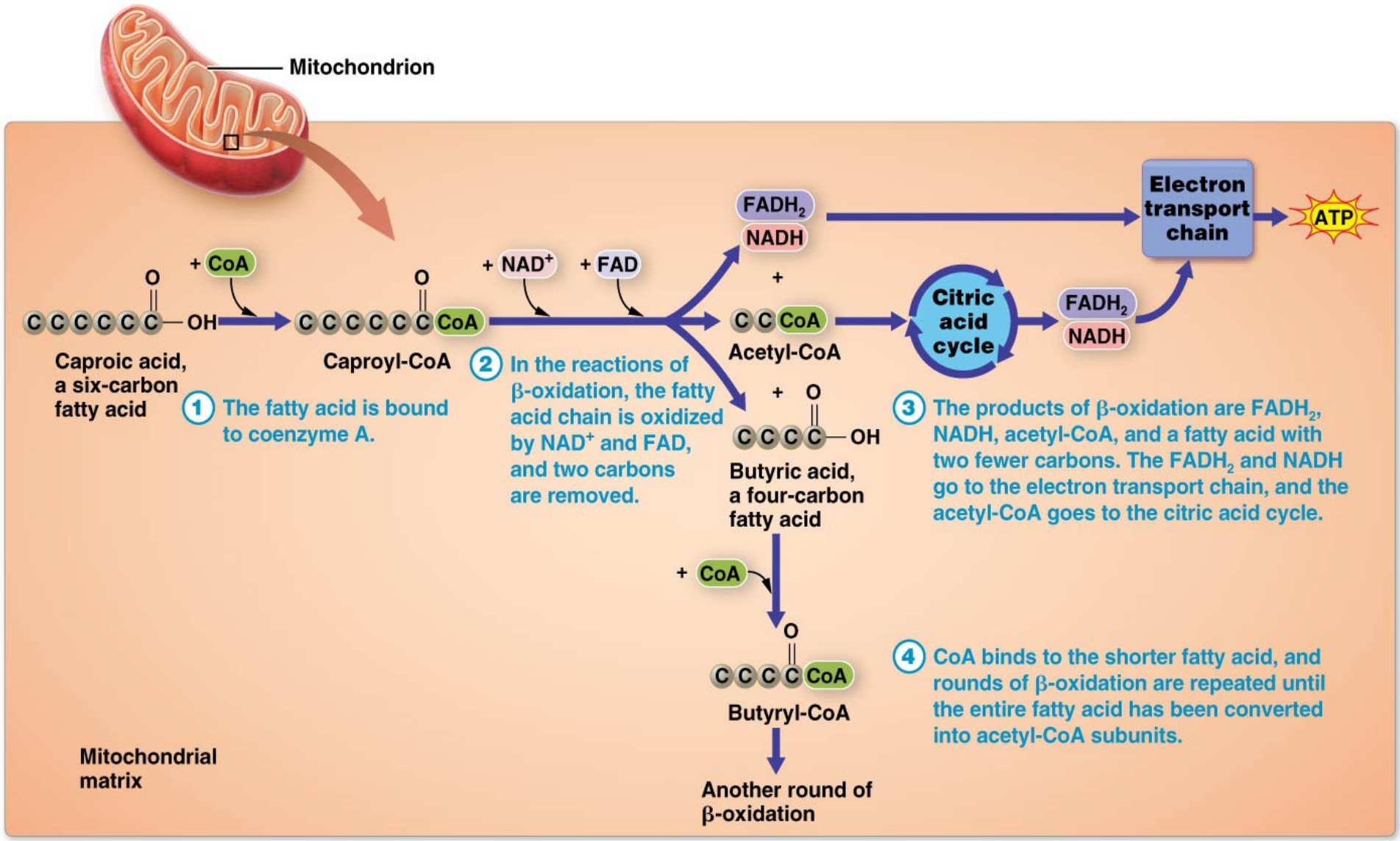
The citric acid cycle.



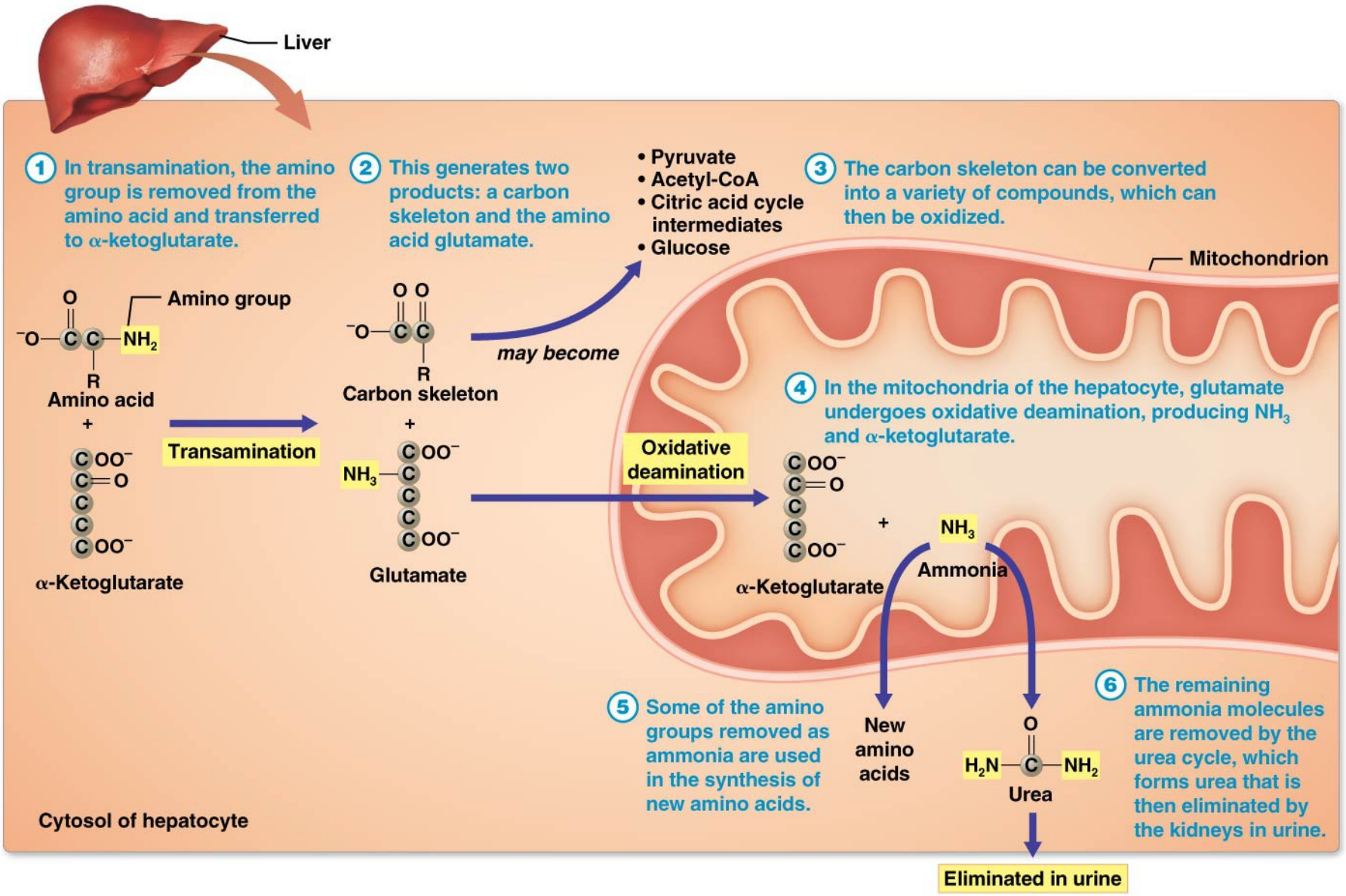
The electron transport chain and oxidative phosphorylation.



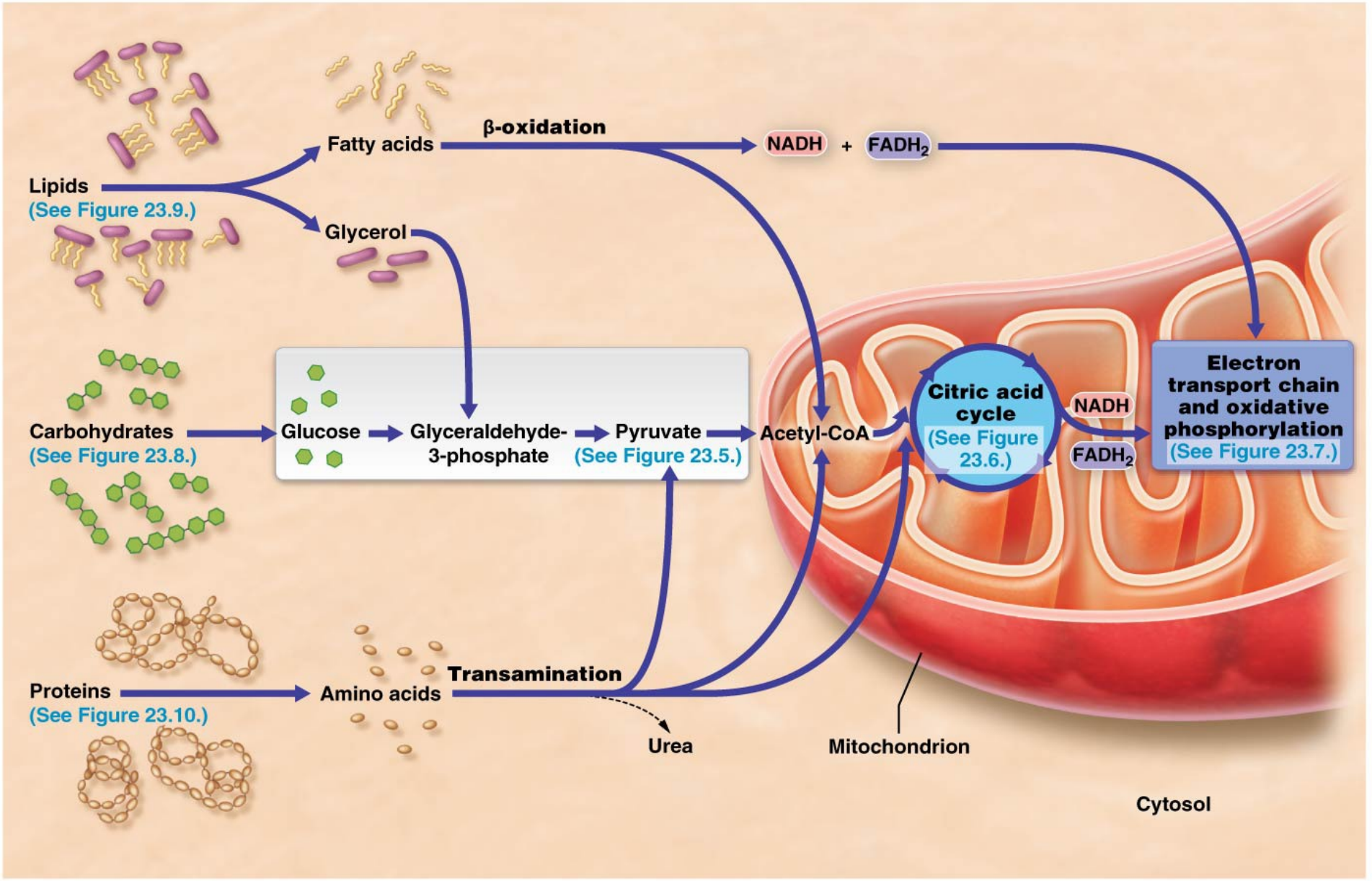
Fatty acid catabolism and β-oxidation.



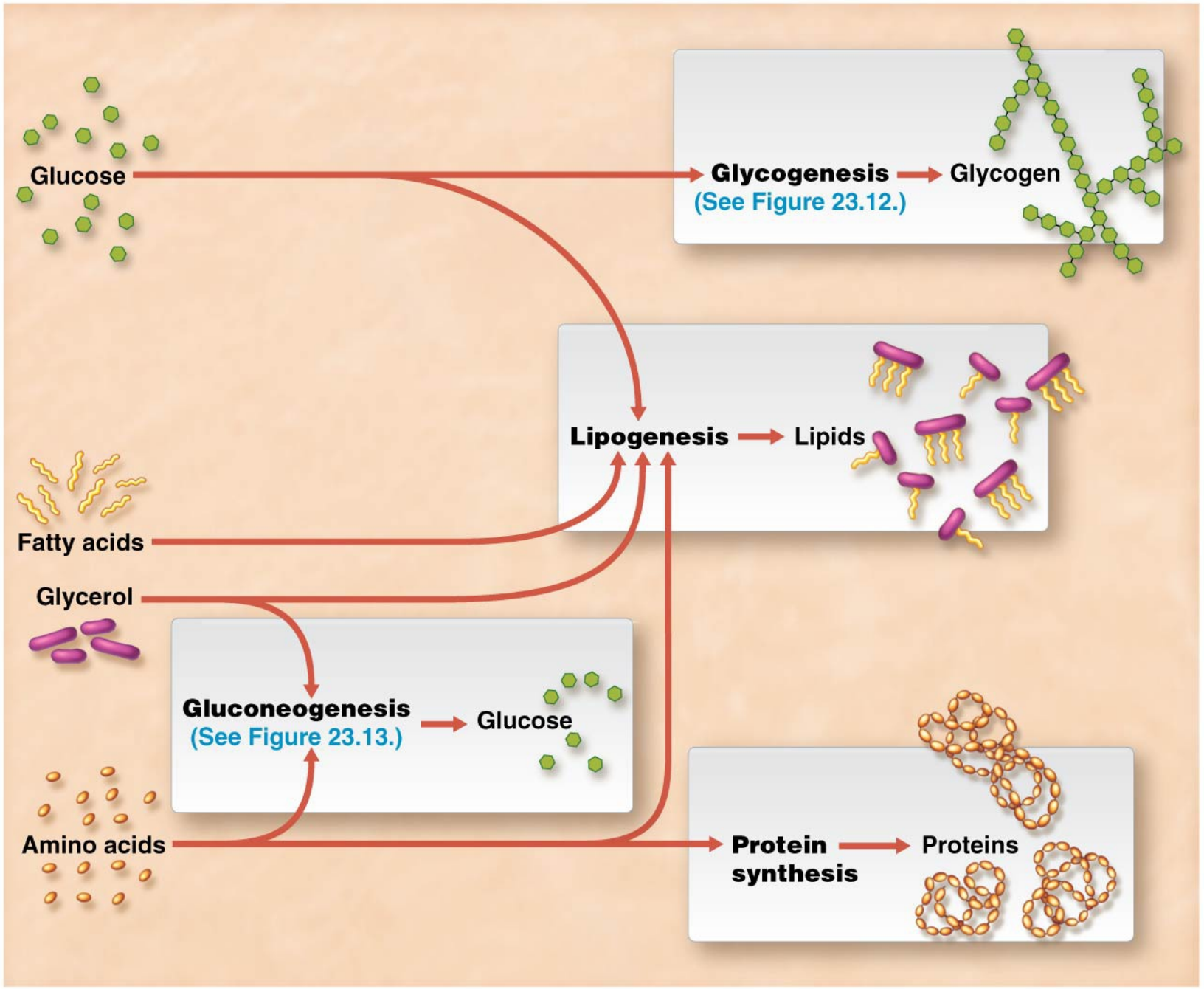
Amino acid catabolism.



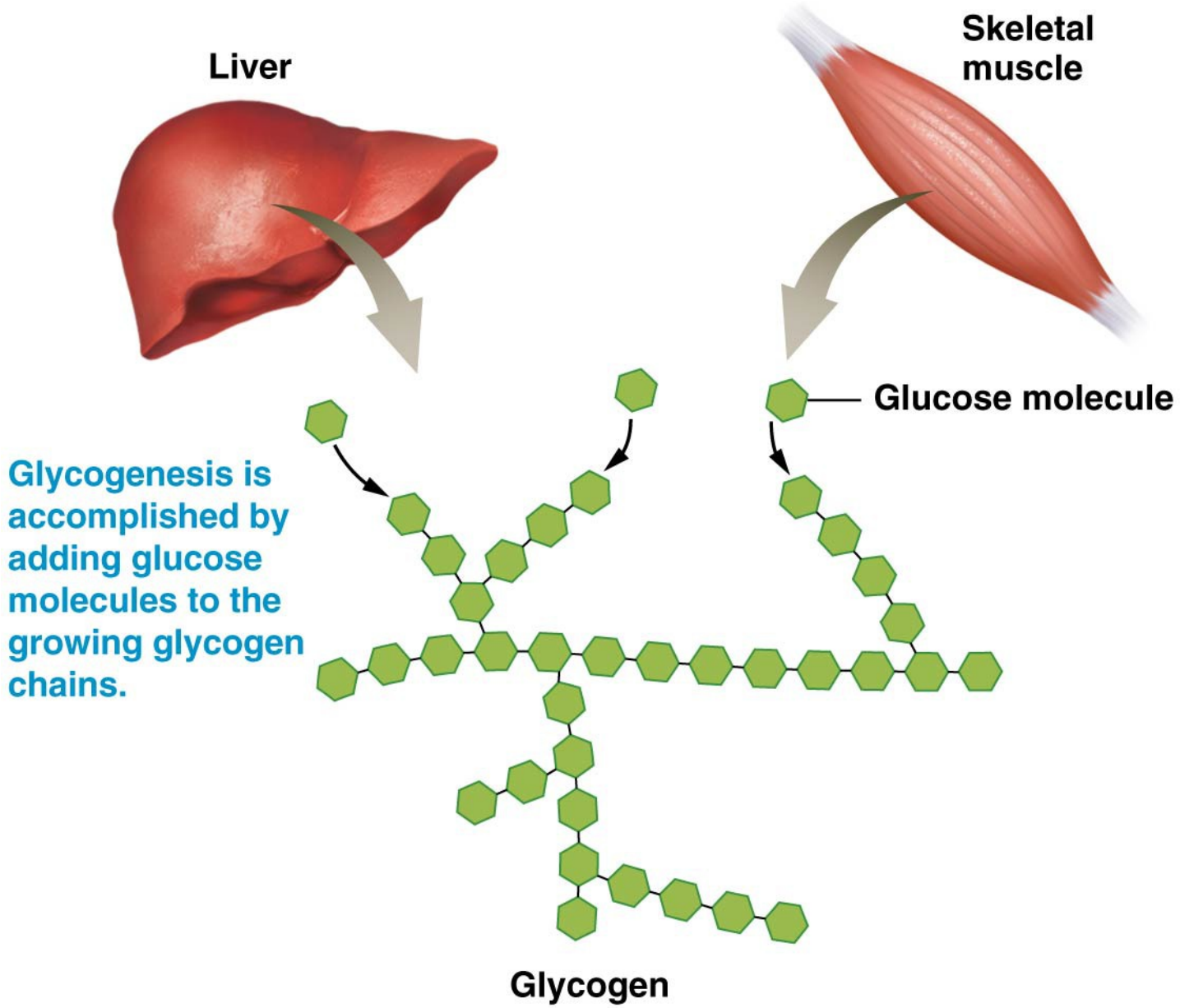
The Big Picture of Nutrient Catabolism



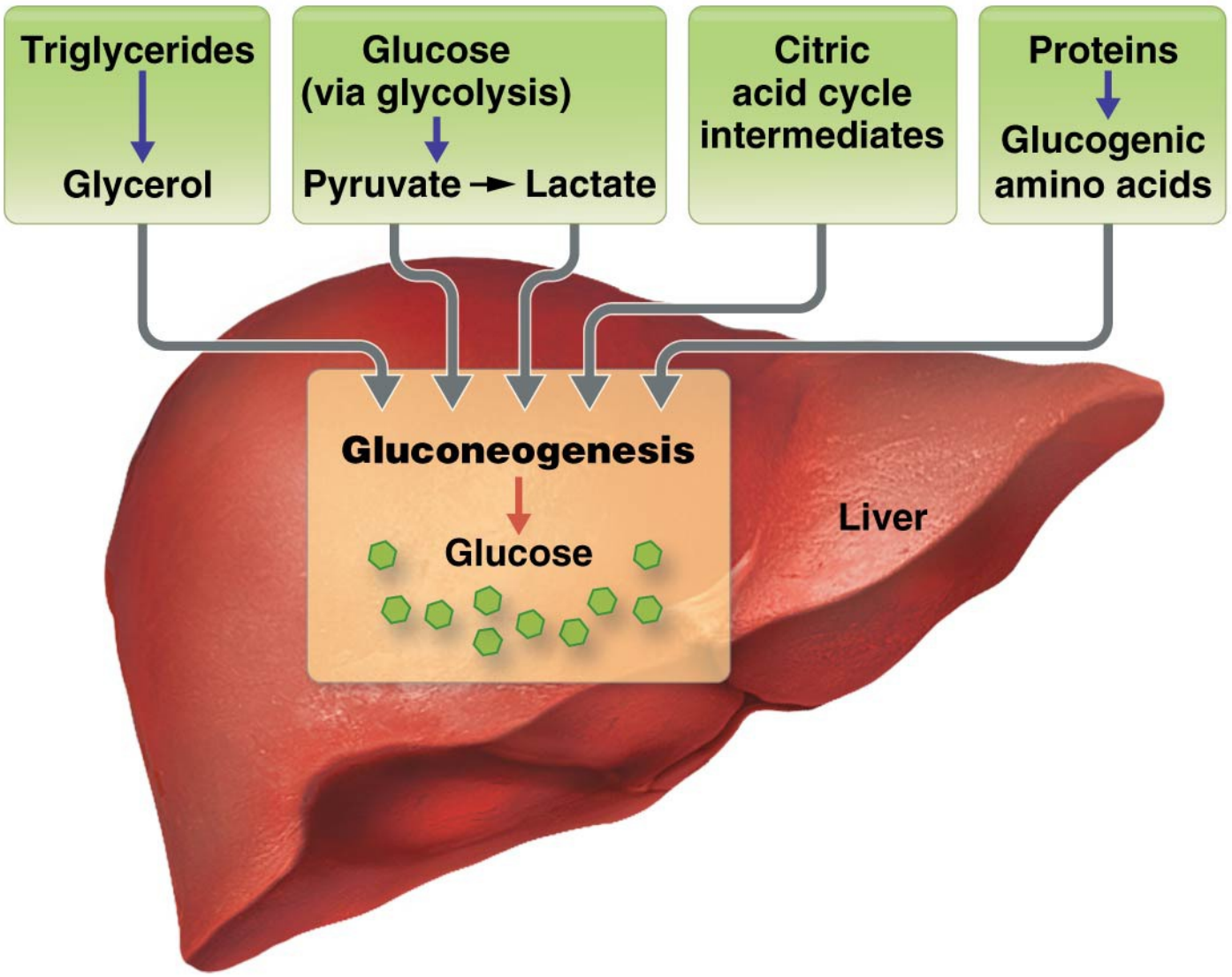
The Big Picture of Nutrient Anabolism



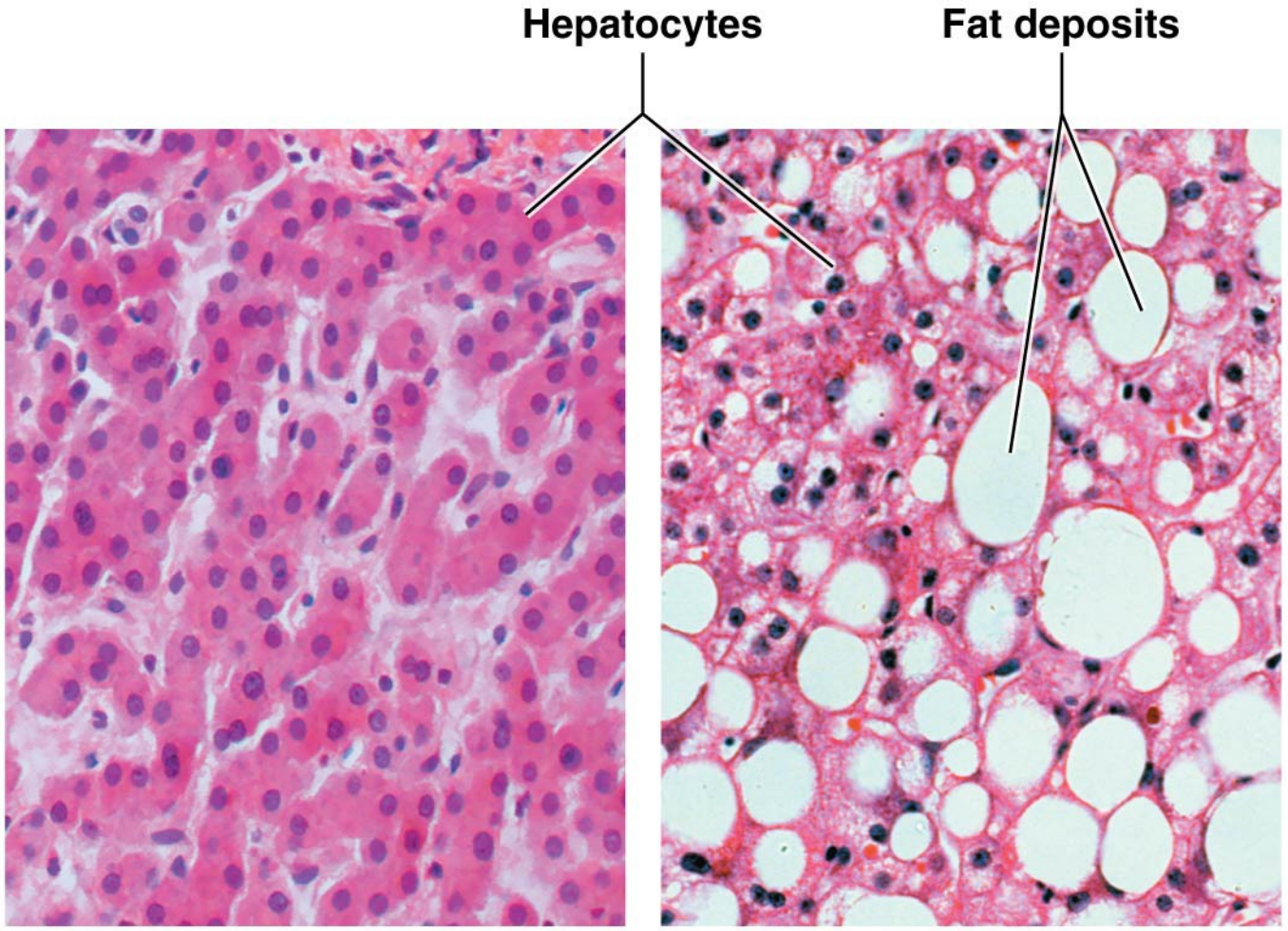
Glycogenesis.



Gluconeogenesis.



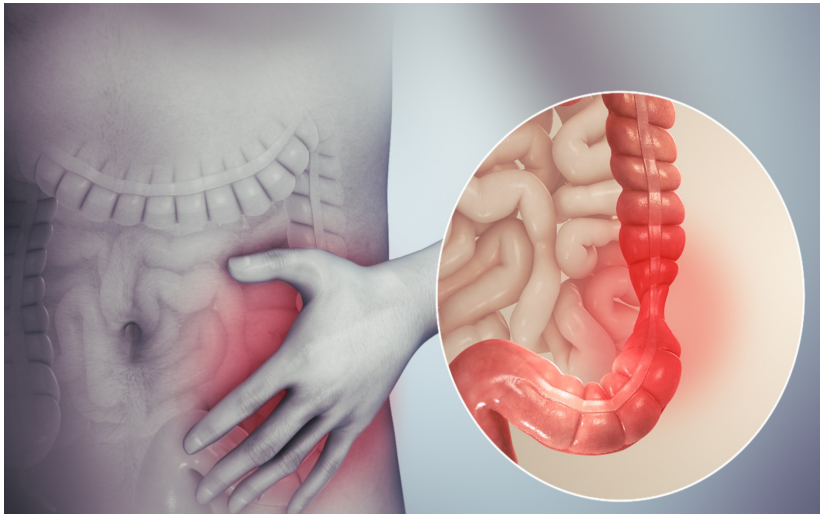
Too Much Lipogenisis in Hepatocytes



GI Tract Diseases

- Irritable Bowel Syndrome
- Crohn Disease
- Ulceratis Colitis
- Celiac Disease

Irritable Bowel Syndrome



Irritable bowel syndrome (IBS) is a common disorder that affects the large intestine. Signs and symptoms include cramping, abdominal pain, bloating, gas, and diarrhea or constipation, or both. IBS is a chronic condition that you'll need to manage long term.

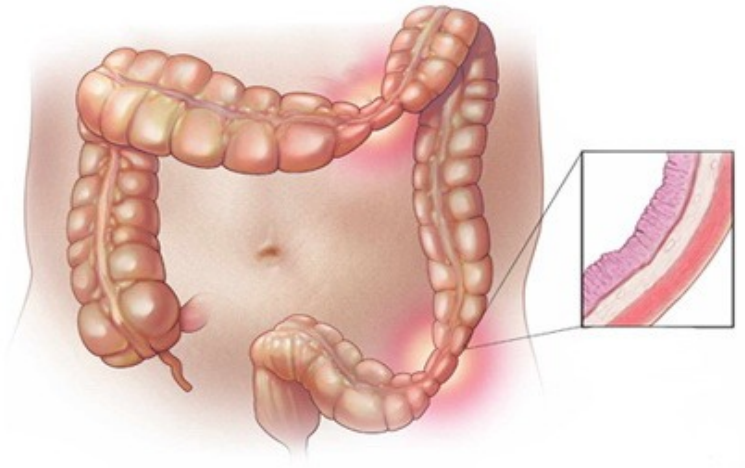
Only a small number of people with IBS have severe signs and symptoms. Some people can control their symptoms by managing diet, lifestyle and stress. More-severe symptoms can be treated with medication and counseling.

IBS doesn't cause changes in bowel tissue or increase your risk of colorectal cancer.

Symptoms - The signs and symptoms of IBS vary. The most common include: abdominal pain, cramping or bloating that is typically relieved or partially relieved by passing a bowel movement /// Excess gas /// Diarrhea or constipation — sometimes alternating bouts of diarrhea and constipation // Mucus in the stool

Most people with IBS experience times when the signs and symptoms are worse and times when they improve or even disappear completely.

WHAT ARE THE SYMPTOMS OF IRRITABLE BOWEL SYNDROME?



- BACK PAIN
- URINARY INCONTINENCE
- PAIN DURING SEXUAL INTERCOURSE
- STOMACH CRAMPS
- ABDOMINAL PAIN
- DIARRHEA
- CONSTIPATION
- BLOATING
- FLATULENCE
- INCONTINENCE
- STOOLS THAT CONTAIN MUCUS
- LETHARGY AND DROWSINESS

Marina Del Rey Hospital
A CEDARS-SINAI AFFILIATE

Crohn's Disease is a chronic, inflammatory disease of the gastrointestinal tract. It is an autoimmune disorder, meaning your body's immune system mistakenly attacks healthy tissue in your body.

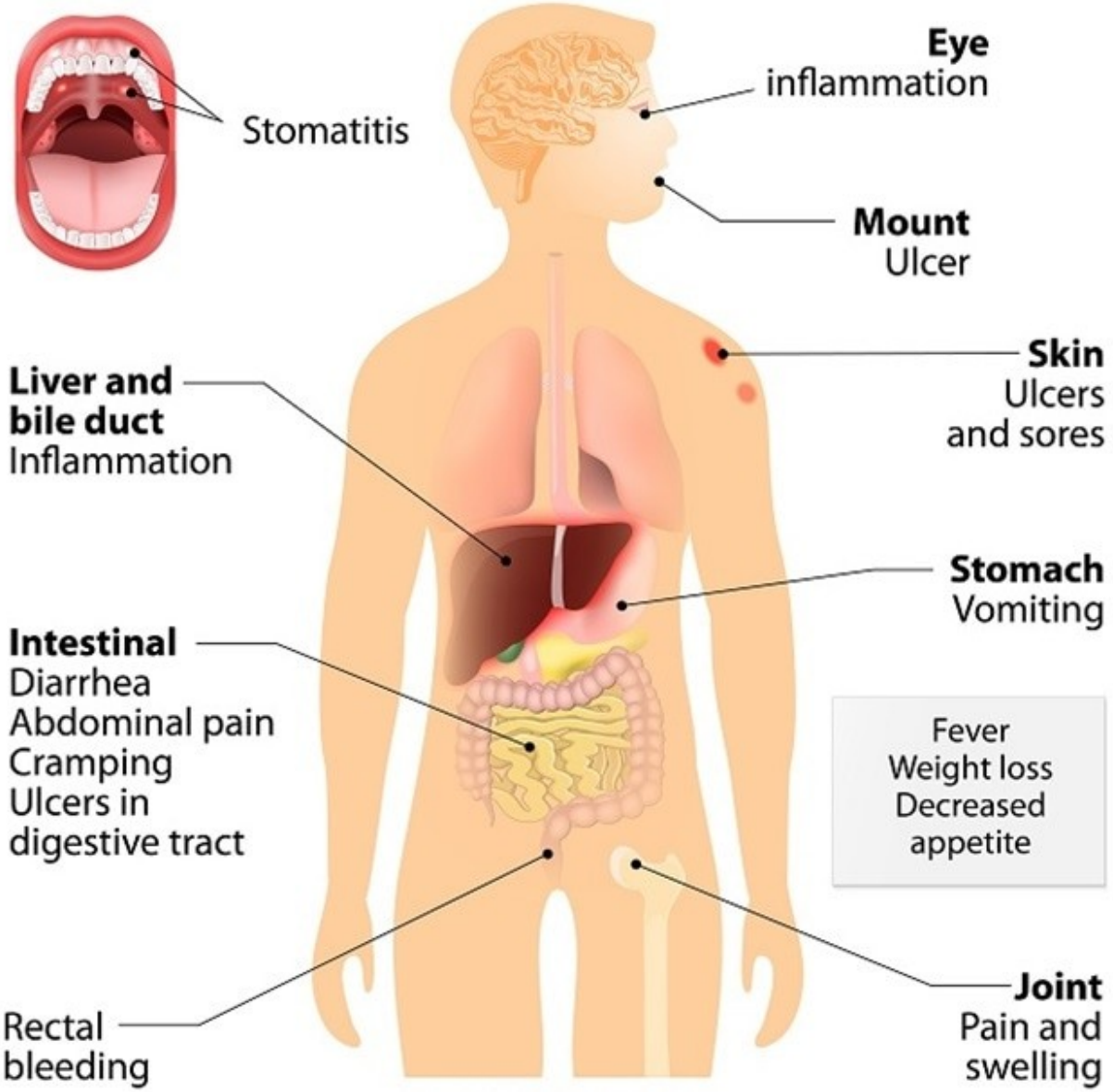
Crohn's disease is chronic (ongoing), and may appear and disappear at various times. Initially, it may affect only a small part of your gastrointestinal tract, but the disease has the potential to progress extensively.

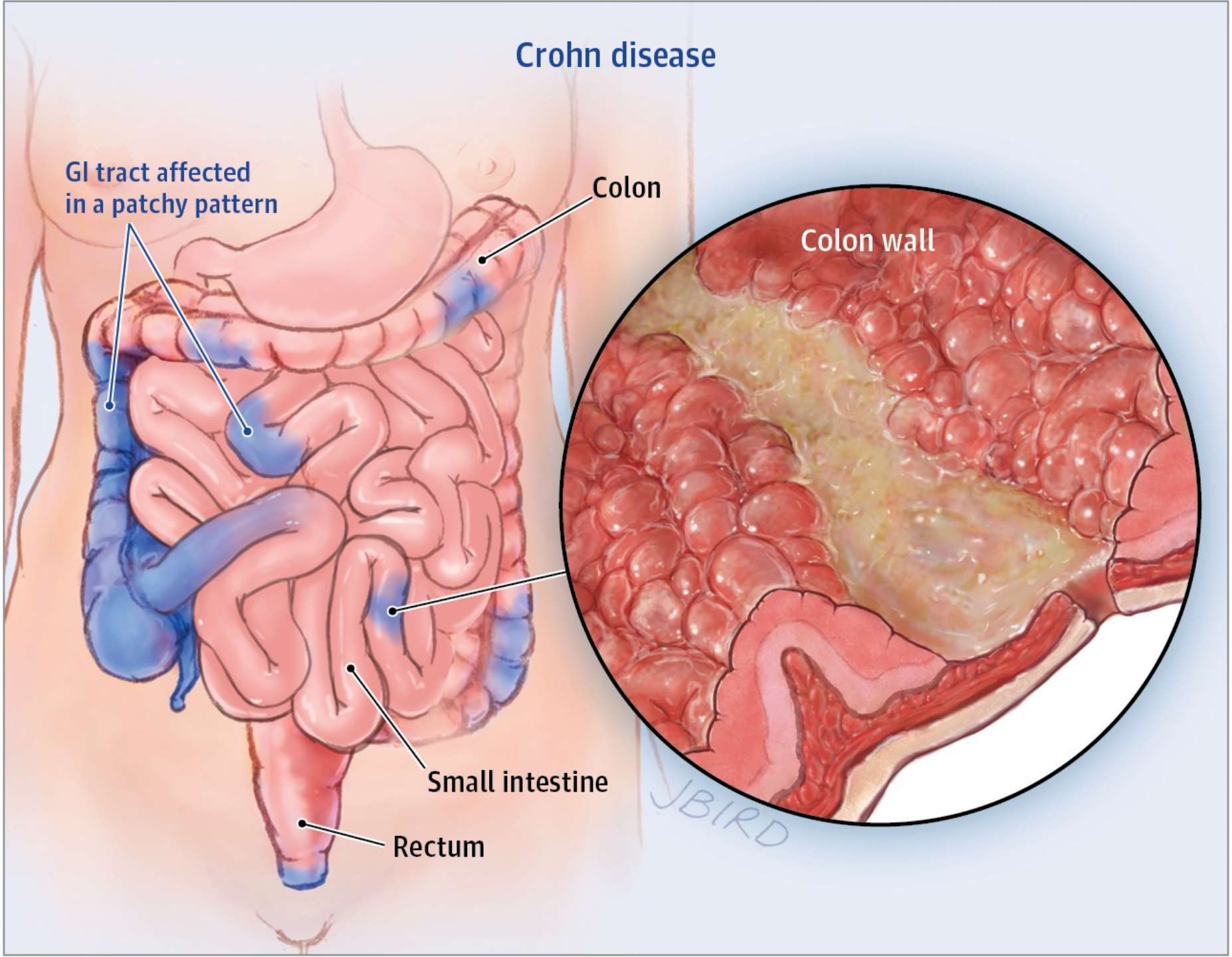
Who Gets Crohn's Disease?

Crohn's disease appears early in life; approximately one-sixth of patients have symptoms before 15 years of age. Although the cause is unknown, doctors suspect a genetic influence, since many members of the same family may be affected. Crohn's disease affects the Jewish population more than the general population.

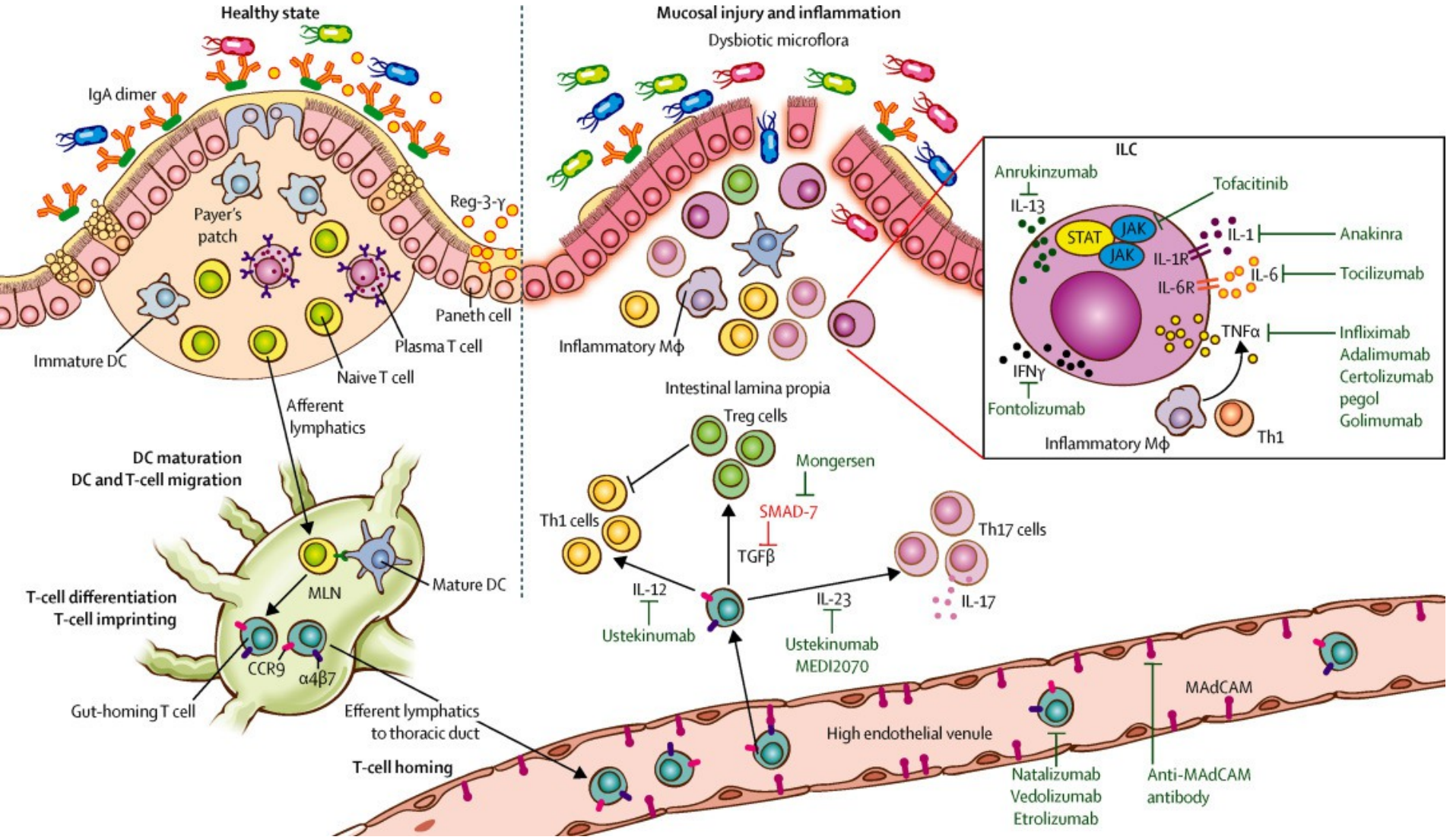
Crohn's disease often begins in a person's teens or twenties, though some patients experience symptoms even earlier. Most common symptoms include (see next slide)

Crohn's disease



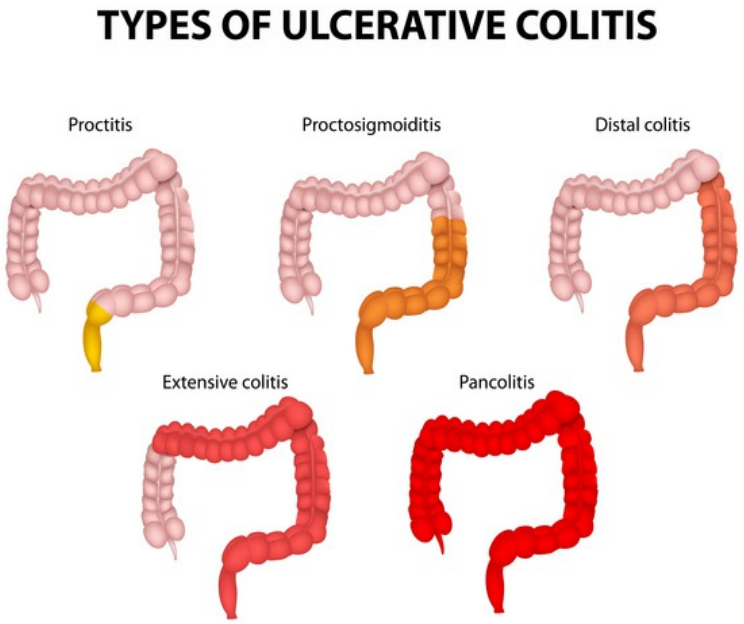

Crohn disease
GI tract affected
in a patchy pattern
Colon
Colon wall
Small intestine
Rectum
JBIRD

Crohn Disease



Ulcerative Colitis (UC) is a disease that affects your large intestine, or colon. It causes irritation and swelling called inflammation. ... UC is a type of inflammatory bowel disease, but it's different from other diseases with similar symptoms, like Crohn's disease or irritable bowel syndrome.

Ulcerative colitis is usually only in the innermost lining of the large intestine (colon) and rectum. Forms range from mild to severe. Having ulcerative colitis puts a patient at increased risk of developing colon cancer. Symptoms include rectal bleeding, bloody diarrhea, abdominal cramps, and pain.



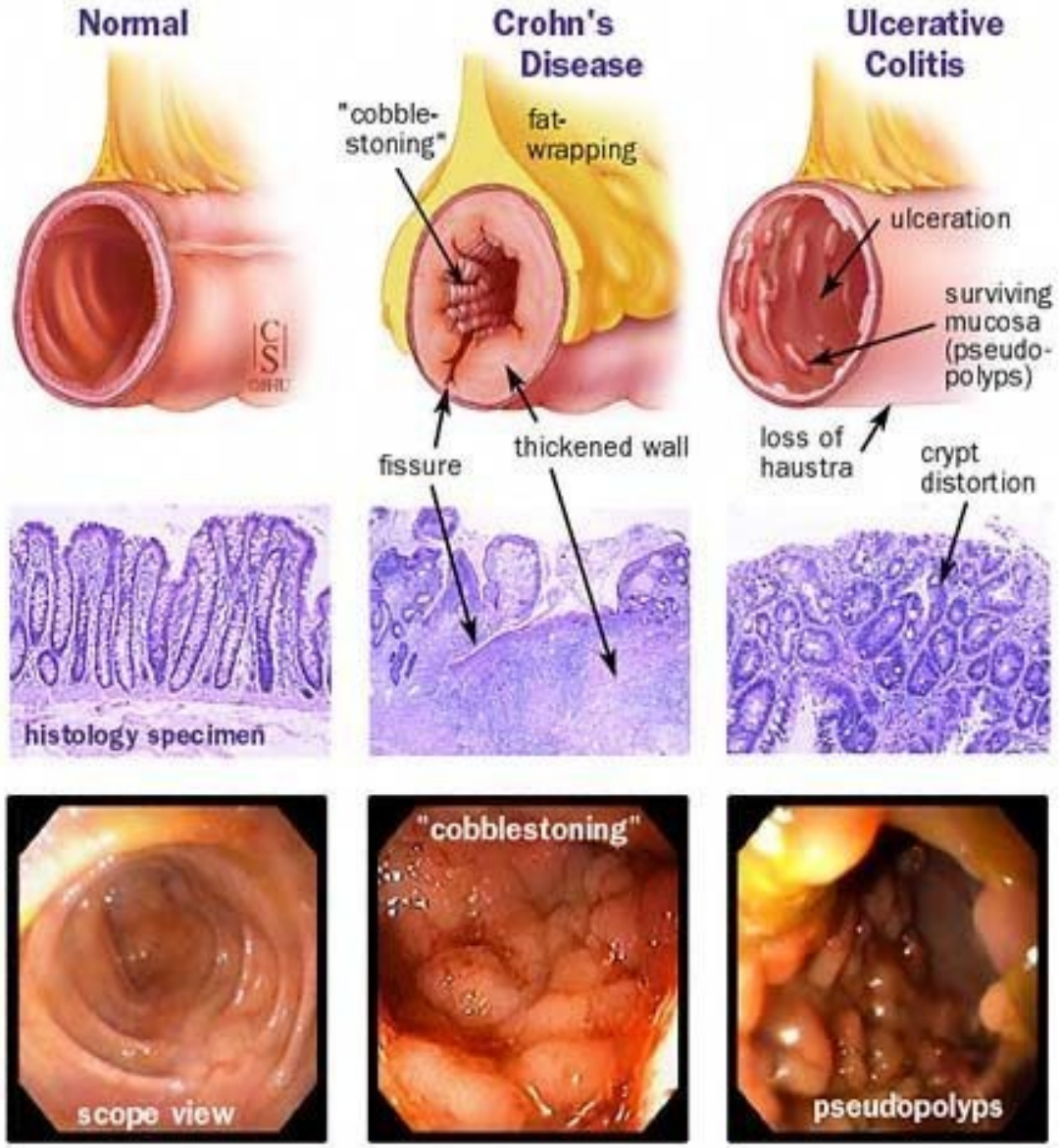
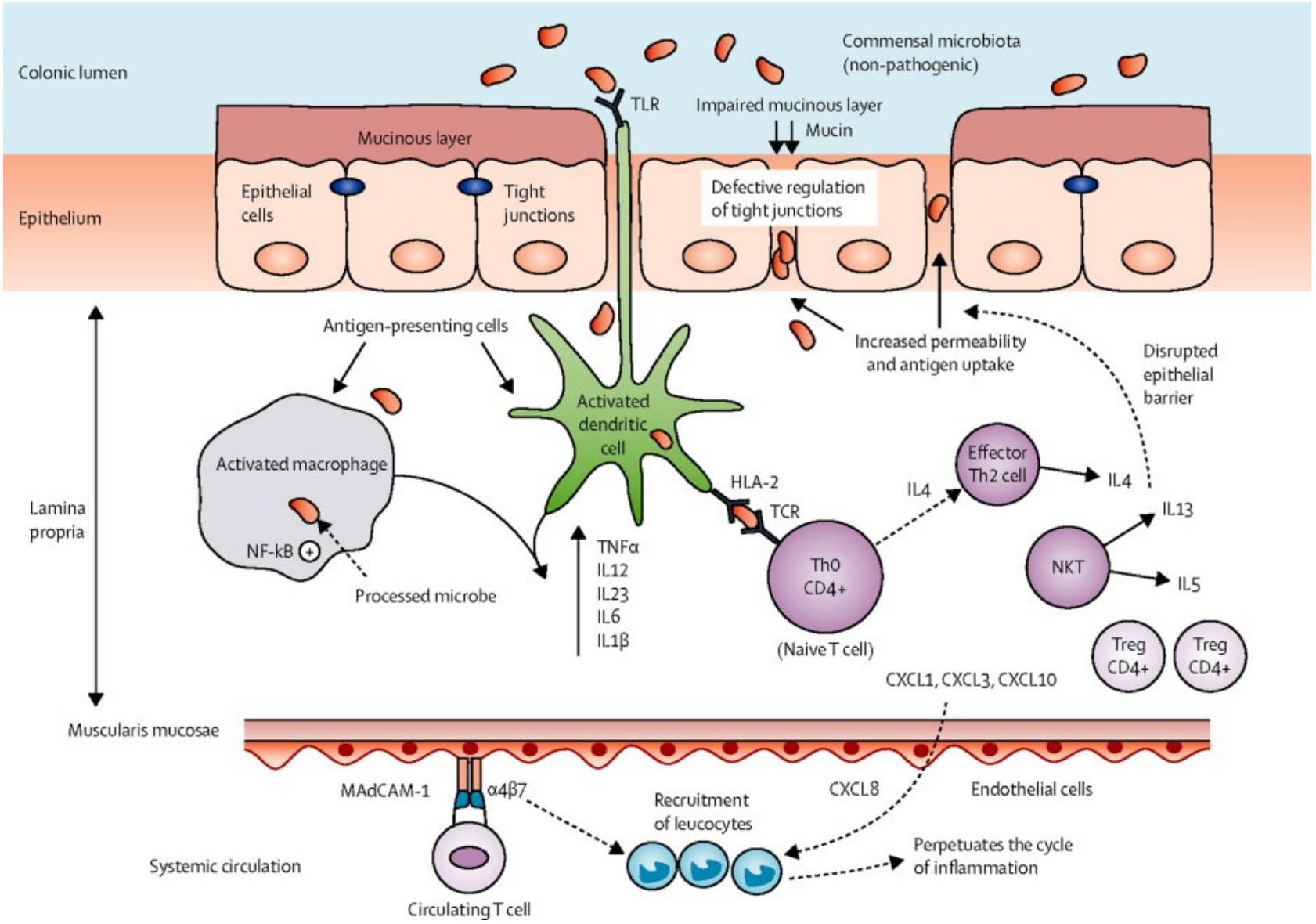


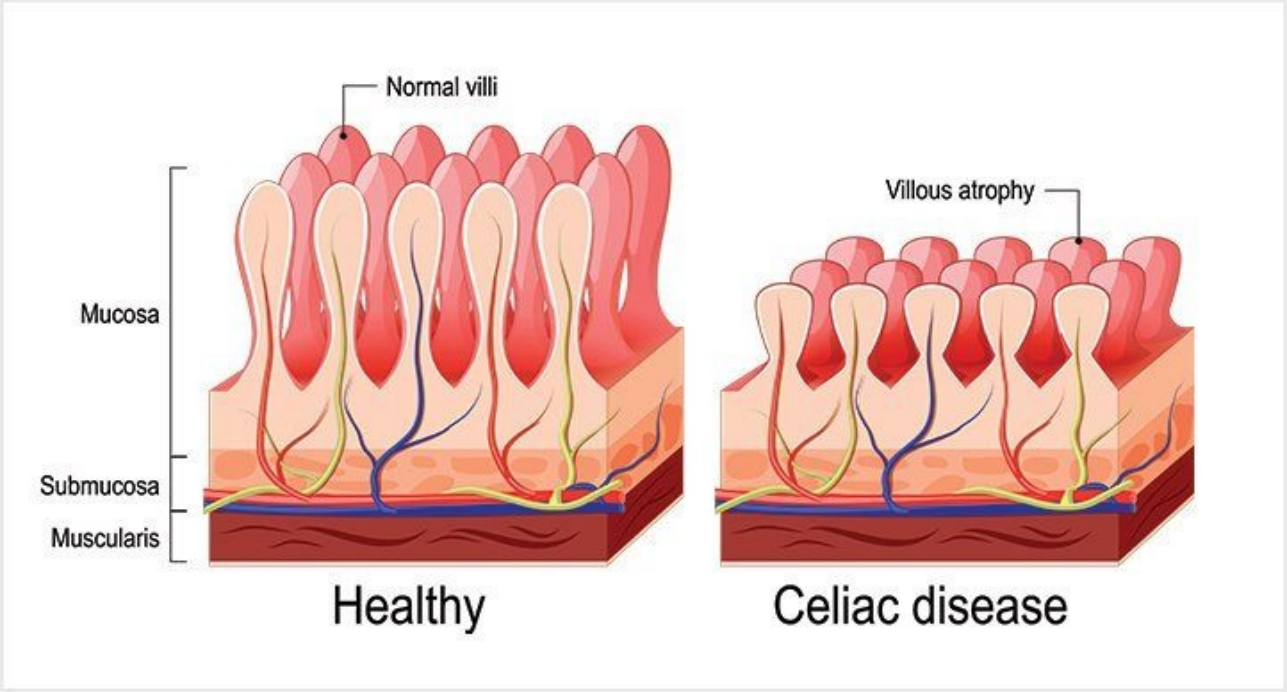
Figure 4. Gross (**top**), histological (**center**), and endoscopic (**bottom**) appearance of normal colon, Crohn's disease, and ulcerative colitis.

Ulcerative Colitis Pathophysiology



Celiac Disease

Celiac disease is an example of hypersensitivity that causes an immune disease condition. The immune response causes damage to their small intestine. People hypersensitive to gluten need to eliminate gluten from their diet. Gluten is a protein found in wheat, rye, and barley.



SYMPTOMS OF CELIAC DISEASE

UNEXPLAINED WEIGHT LOSS

STOMACH & MUSCLE CRAMPS

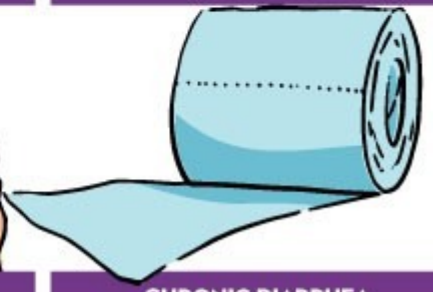
NUMBNESS & TINGLING IN LEGS

TOOTH ENAMEL LOSS

JOINT PAIN

WEAK BONES

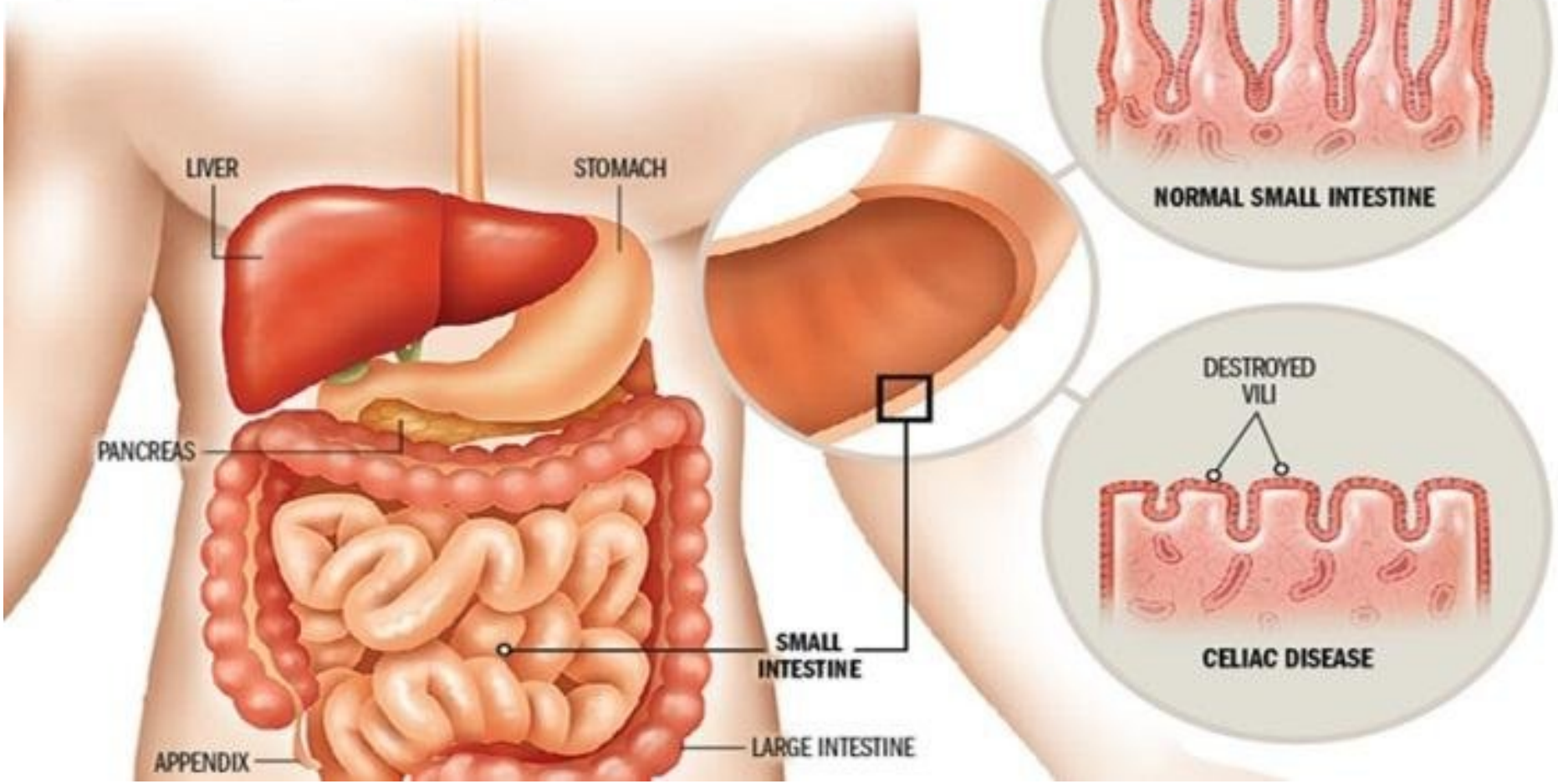
INFERTILITY

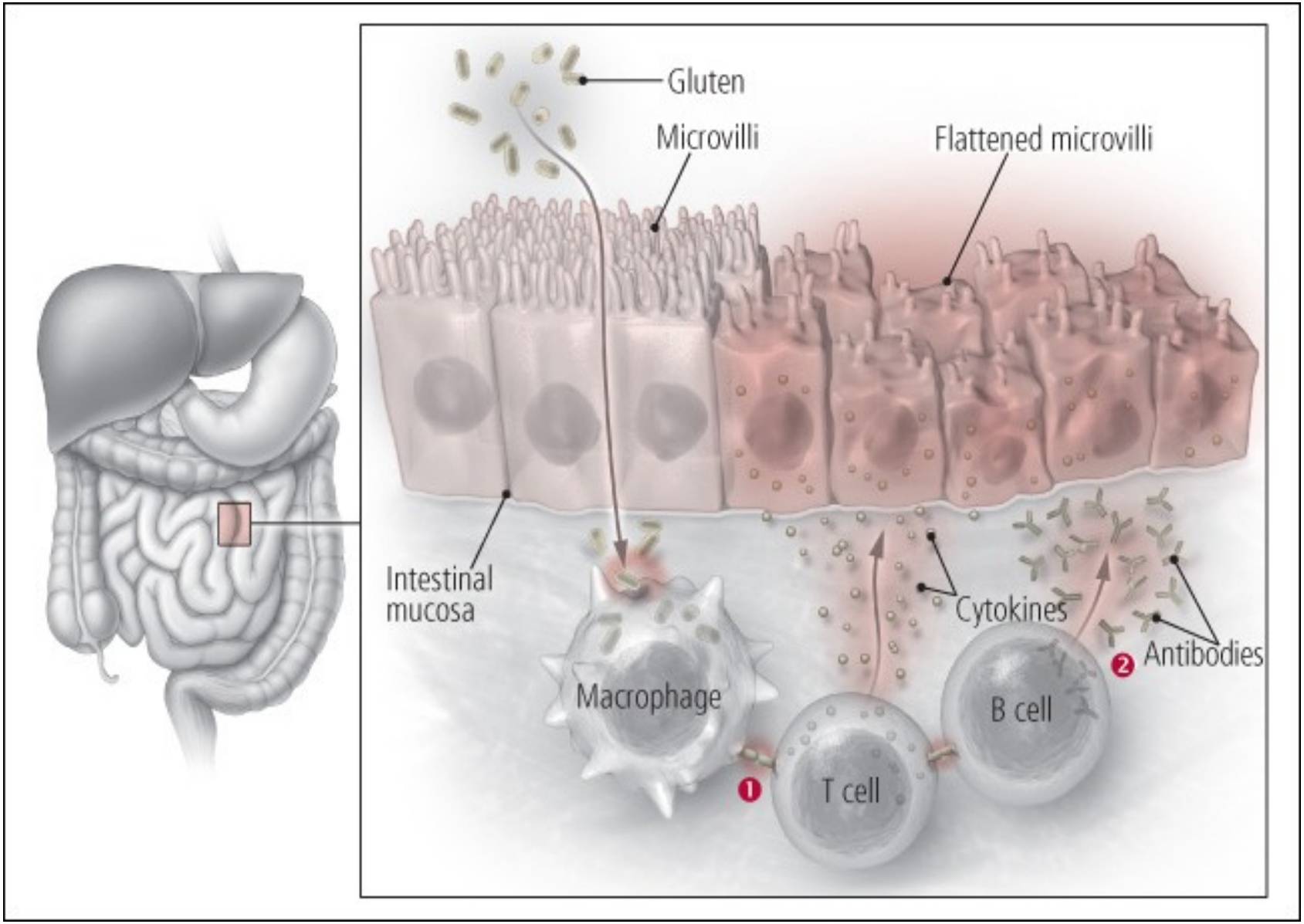


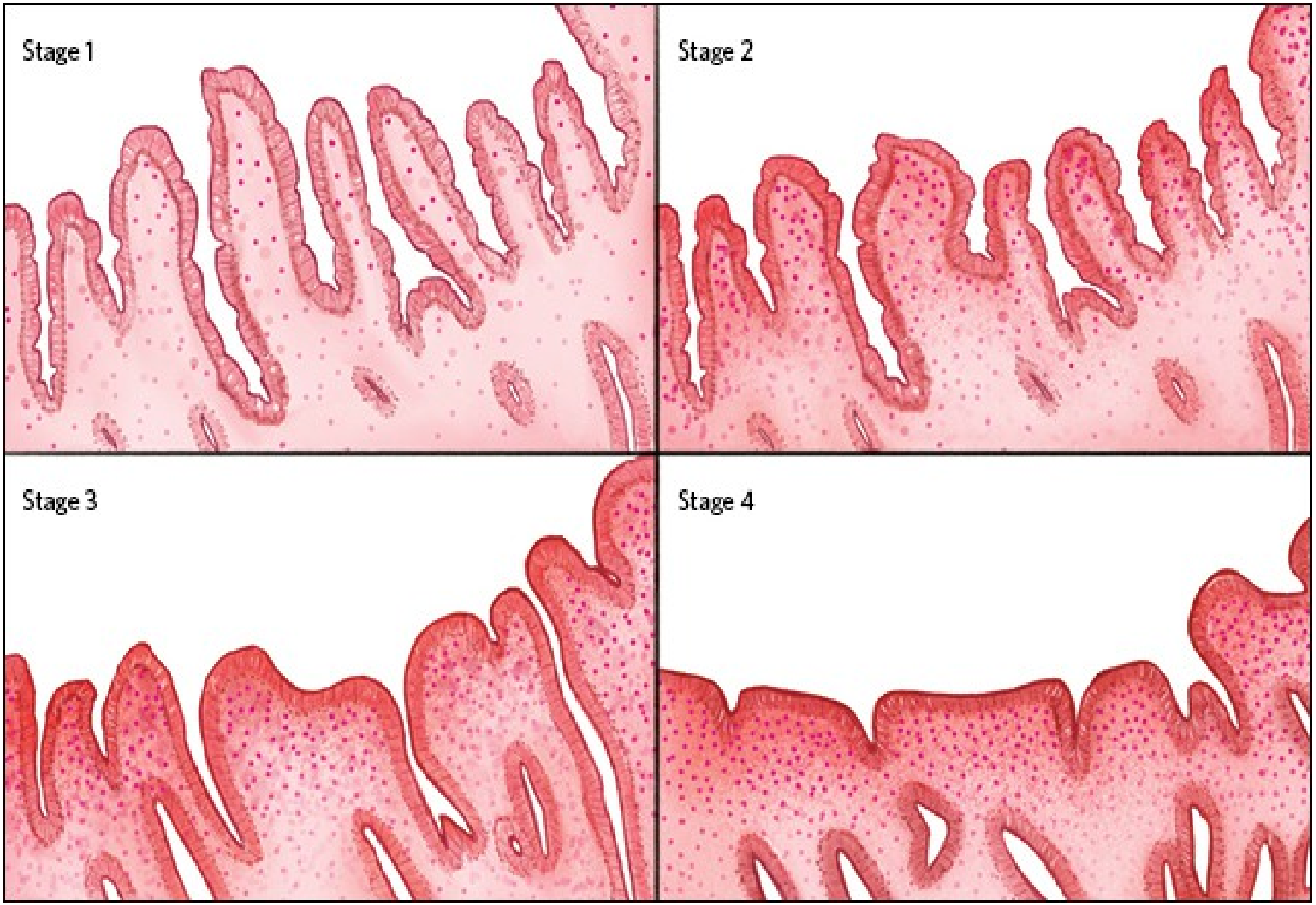
CHRONIC DIARRHEA OR CONSTIPATION

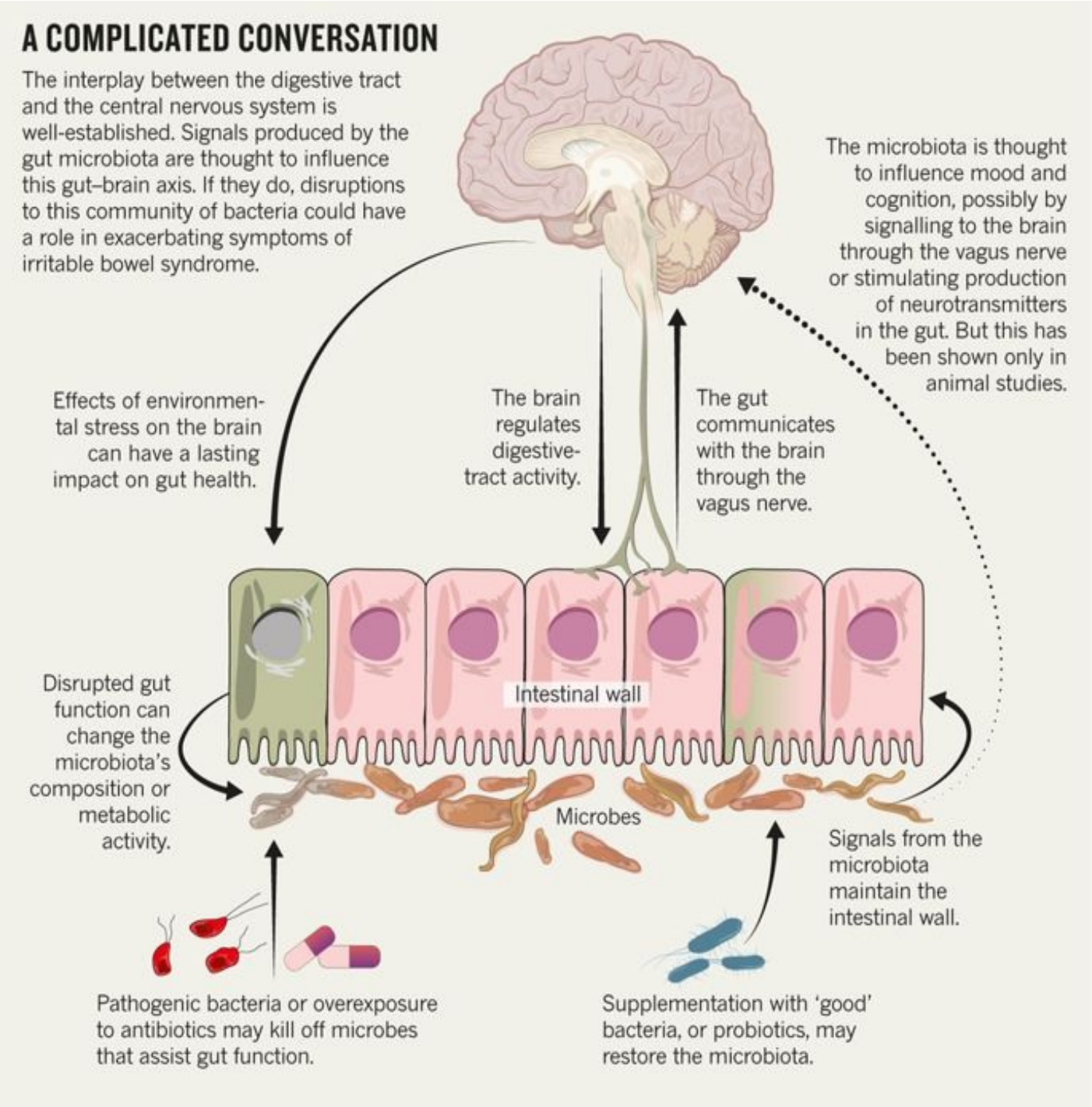
Damage from celiac disease

In a healthy small intestine, tiny hairlike projections called villi absorb nutrients from food. When people with celiac disease eat foods containing wheat, barley, or rye, the body's immune system attacks the gluten proteins. This immune response also destroys the villi, leading to nutritional deficiencies.




Gluten
Microvilli
Flattened microvilli
Intestinal mucosa
Cytokines
Antibodies
Macrophage
B cell
T cell
1
2


Stage 1
Stage 2
Stage 3
Stage 4



See home page link Openbiome.

The Big Picture of Digestion.