MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture № 16

Digestion and absorption in the gastrointestinal tract. Functions of the liver

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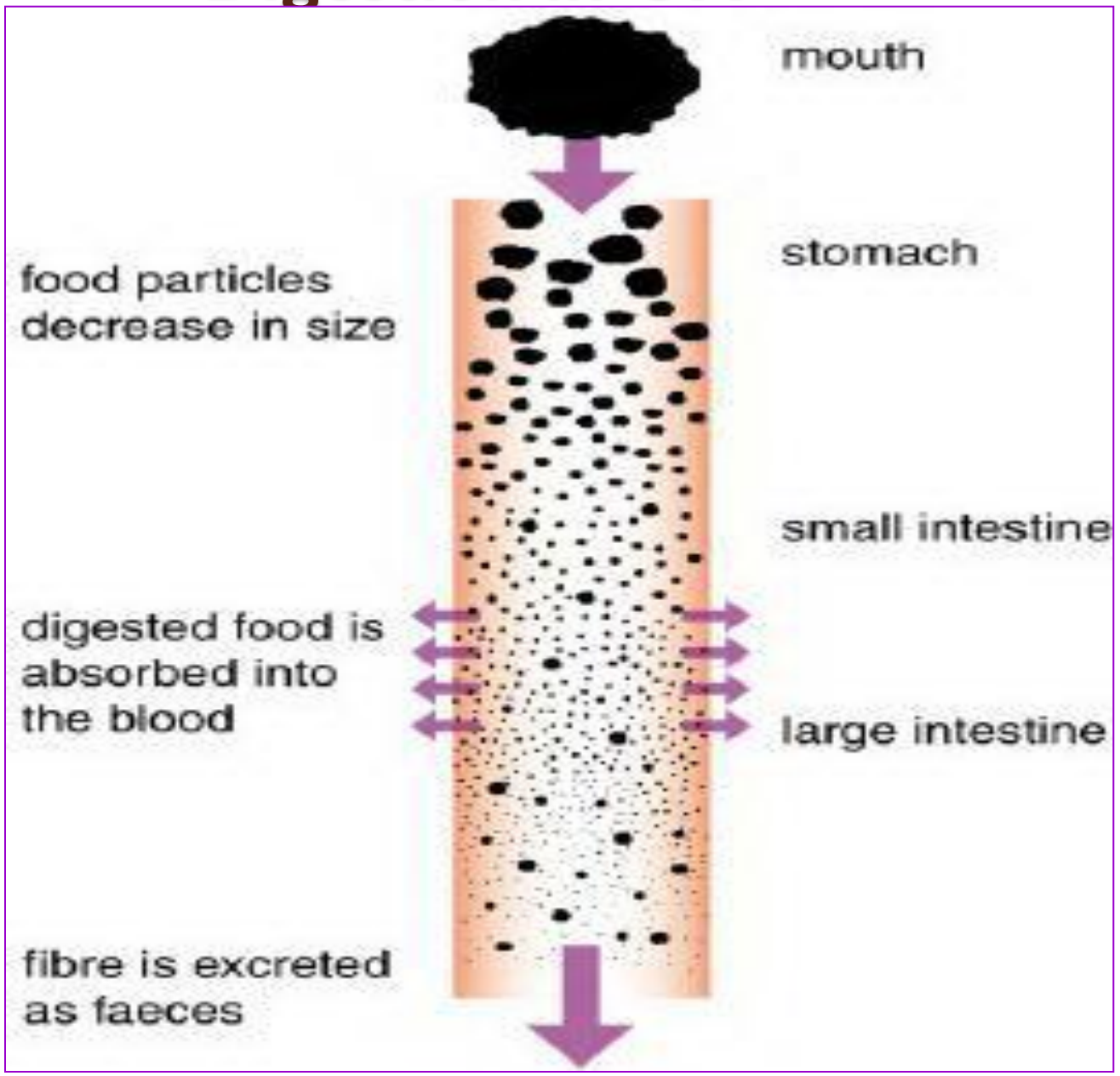
Food stuffs

- **The food** on which the body lives, with the exception of small quantities of substances such as vitamins and minerals, can be classified as **carbohydrates, fats and proteins**.
- **They** generally **can not be absorbed in their natural forms** through the gastrointestinal mucosa and for this reason **have to digested into small enough compounds for absorption**.

Digestion in GIT



Digestion of carbohydrates

- Only 3 major sources of carbohydrates exist in the normal human diet:

  *sucrose (disaccharide, known as cane sugar)

  *lactose (disaccharide in milk)

  *starches (large polysaccharides, present in almost all non animal foods and particularly grains)

Digestion of carbohydrates

Other carbohydrates ingested to a slight extend are: amylose, glycogen, pectins, dextrins etc.

The diet also contains a large amount of cellulose, carbohydrate that can not be considered a food for the human being, because no enzymes secreted in the human digestive tract capable of hydrolyzing cellulose.

Digestion of carbohydrates in the mouth and stomach

- When the food is chewed it is mixed with the **saliva**, which contains the enzyme **ptyalin (α -amylase),** secreted mainly by parotid glands.
- This enzyme **hydrolyzes starch into the disaccharide maltose and other small polymers of glucose (maltotriose and α-limit dextrins).**
- After swallowing, **digestion continues in the body and fundus of the stomach** for as long as one h, **before the food is mixed with the stomach secretion and pH falls bellow 4.0,** because amylase becomes non active.

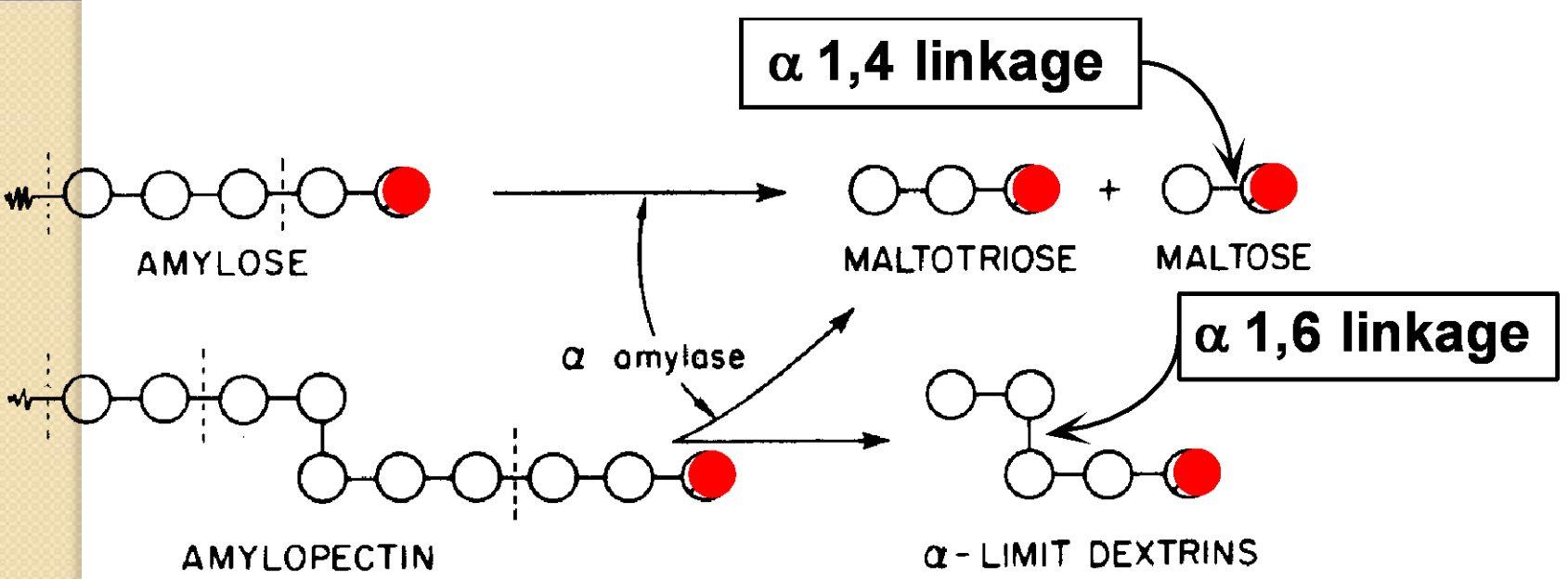
Digestion of carbohydrates in the small intestine

- **Digestion by pancreatic amylase** (identical with salivary α-amylase, but it is several times most powerful --> hydrolysis of α-1,4 bonds between monosaccharides
- **Hydrolysis of disaccharides and small glucose polymers into monosaccharides by the intestinal epithelial enzymes,** located in the membranes of the microvilli brush border of enterocytes

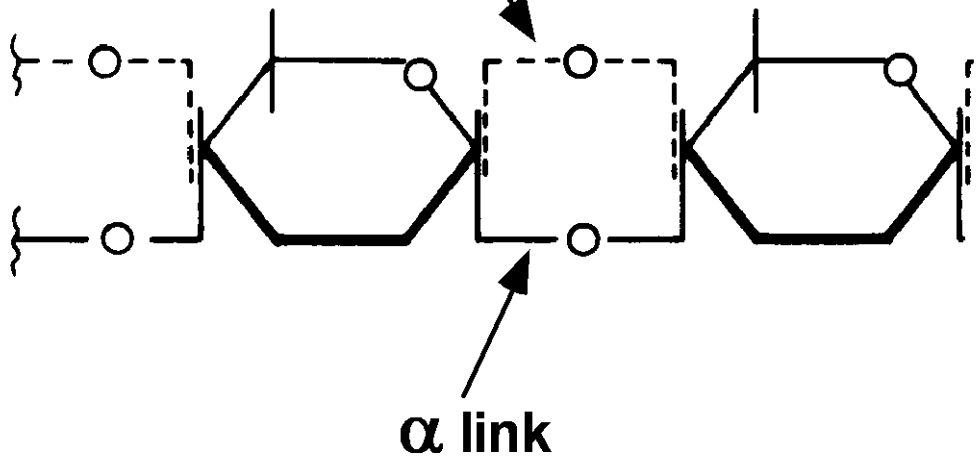
Digestion of carbohydrates in the small intestine

1. **Lactase** splits lactose into
   1mol of galactose + 1mol of glucose
2. **Sucrase** splits sucrose into
   1mol of fructose + 1mol of glucose
3. **Maltase** splits maltose into 2 mol of glucose
4. **α-dextrinase** splits small polymers of glucose into molecules of glucose

- **Thus glucose represents more than 80% of the carbohydrate digestion and galactose and fructose only 20%.**



β link = Cellulose. Digestion requires bacteria in bovine G.I. tract.

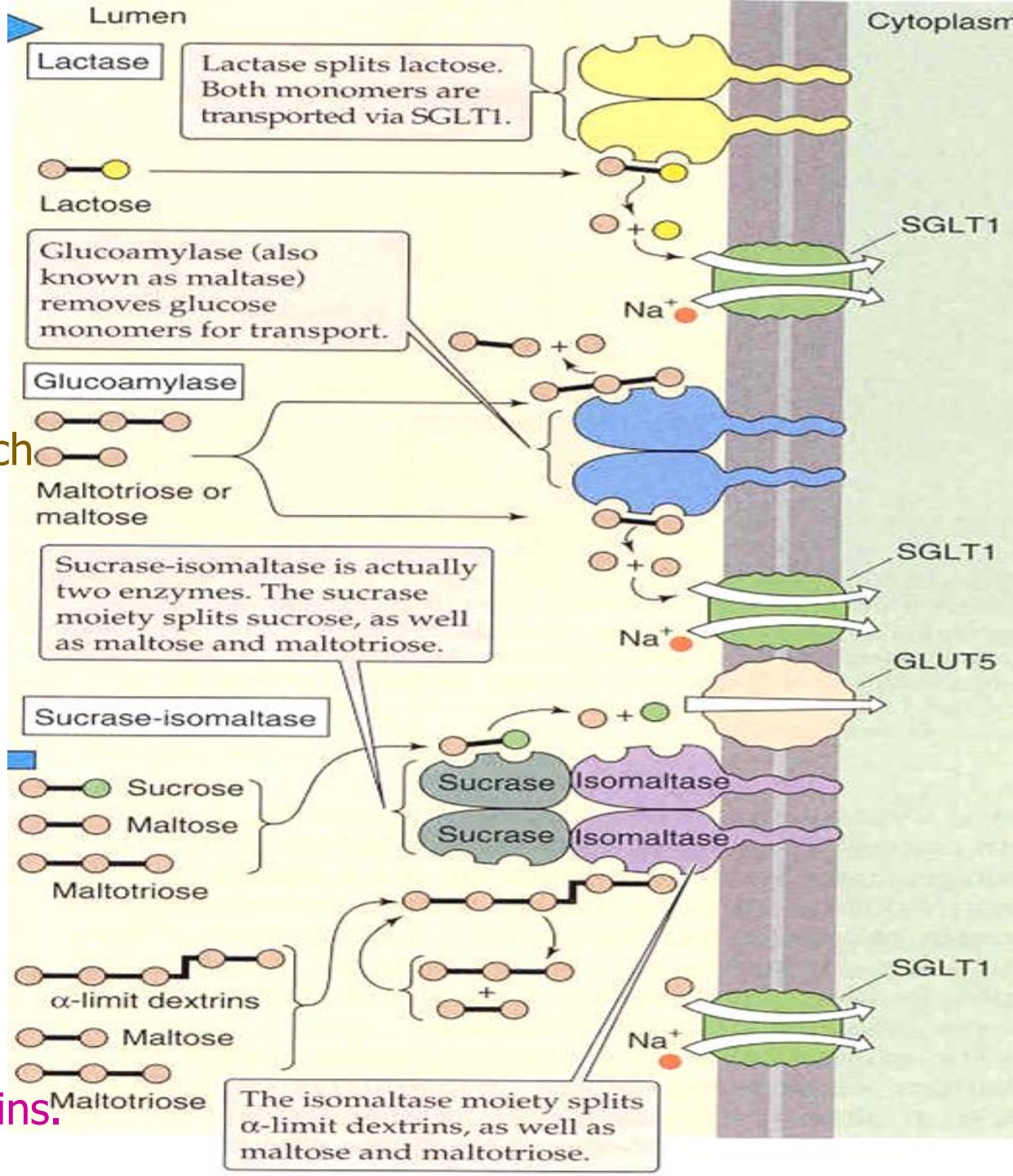


Lactase splits lactose into glucose and galactose.

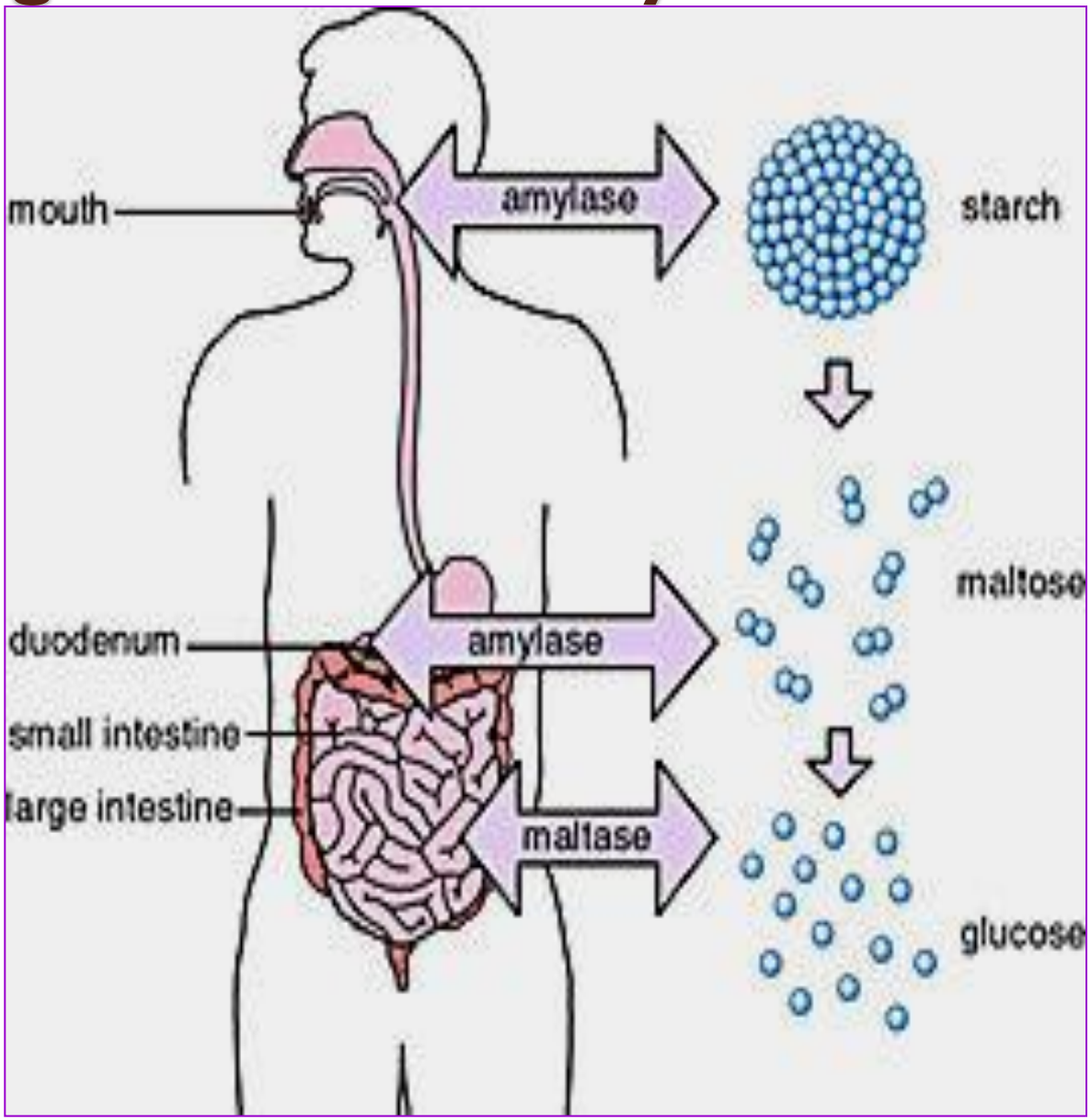
Glucoamylase catalyzes hydrolysis of the α-1,4 bonds of straight starch chains.

Sucrase splits sucrose into glucose and fructose.

Isomaltase (α-limit dextrinase) is the unique enzyme, cleaving α-1,6 bonds of α-limit dextrins.



Digestion of carbohydrates



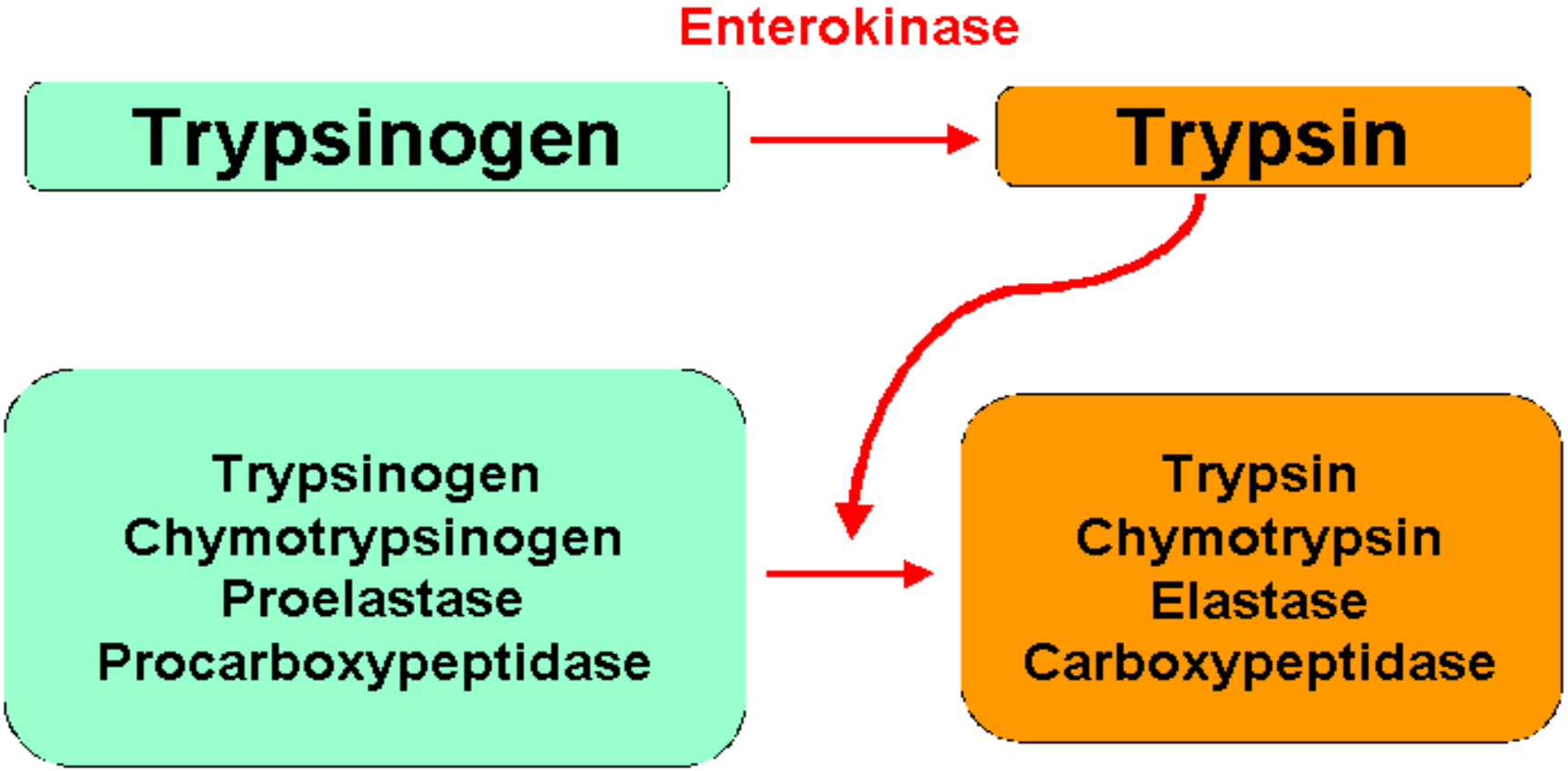
Digestion of proteins in the stomach

- **Proteins** of the diet are formed of long **chains of amino acids bound together by peptide linkages**.
- **Digestion of proteins begins in the stomach under influence of pepsin**. It is **peptidase**, that is most active at a pH of 2.0 to 3.0 and hydrolyses proteins to peptones and polypeptides.
- The important feature of pepsin is its **ability to digest collagen**, a major constituent of connective tissue of meat.

Digestion of proteins by pancreatic secretion in duodenum

- Proteolytic enzymes of pancreatic juice are:
- **trypsin, chymotrypsin** (can split protein molecules into small polypeptides)
- **carboxypolypeptidases A and B** (cleave individual amino acids from the carboxyl ends of the polypeptides)
- **elastase** (digests elastin fibers).
- Only a small percentage of proteins are digested to amino acids by the pancreatic juices. Most remain as dipeptides, tripeptides and some even larger.

Activation of pancreatic proteases



Digestion of peptides by peptidases in the enterocytes

- **The last digestion of the proteins in the intestinal lumen is achieved by the enterocytes** that line the villi of the small intestine,mainly in the duodenum and jejunum.These cells have a brush border that consists of hundreds of microvilli, projecting from the surface of each cell.
- In the cell membrane of these microvilli are multiple peptidases (**aminopolypeptidase and dipeptidases**), that protrude through the membranes to the exterior.

Digestion of peptides by peptidases in the enterocytes

They succeed in **splitting** the remaining **larges polypeptides into tripeptides, dipeptides and a few all the way to amino acids.**

- These products are easily transported through the microvillar membrane to the interior of the enterocyte.
- **Inside the cytosol of the enterocyte are multiple other peptidases that digest them to single amino acids.**

❖ **GI tract contains ingested dietary proteins, proteins of digestive secretions and proteins in exfoliated epithelial cells.**

There are 3 stages of protein digestion in GIT

✓ **In the stomach - pepsins split proteins to oligopeptides and a few amino acids)**

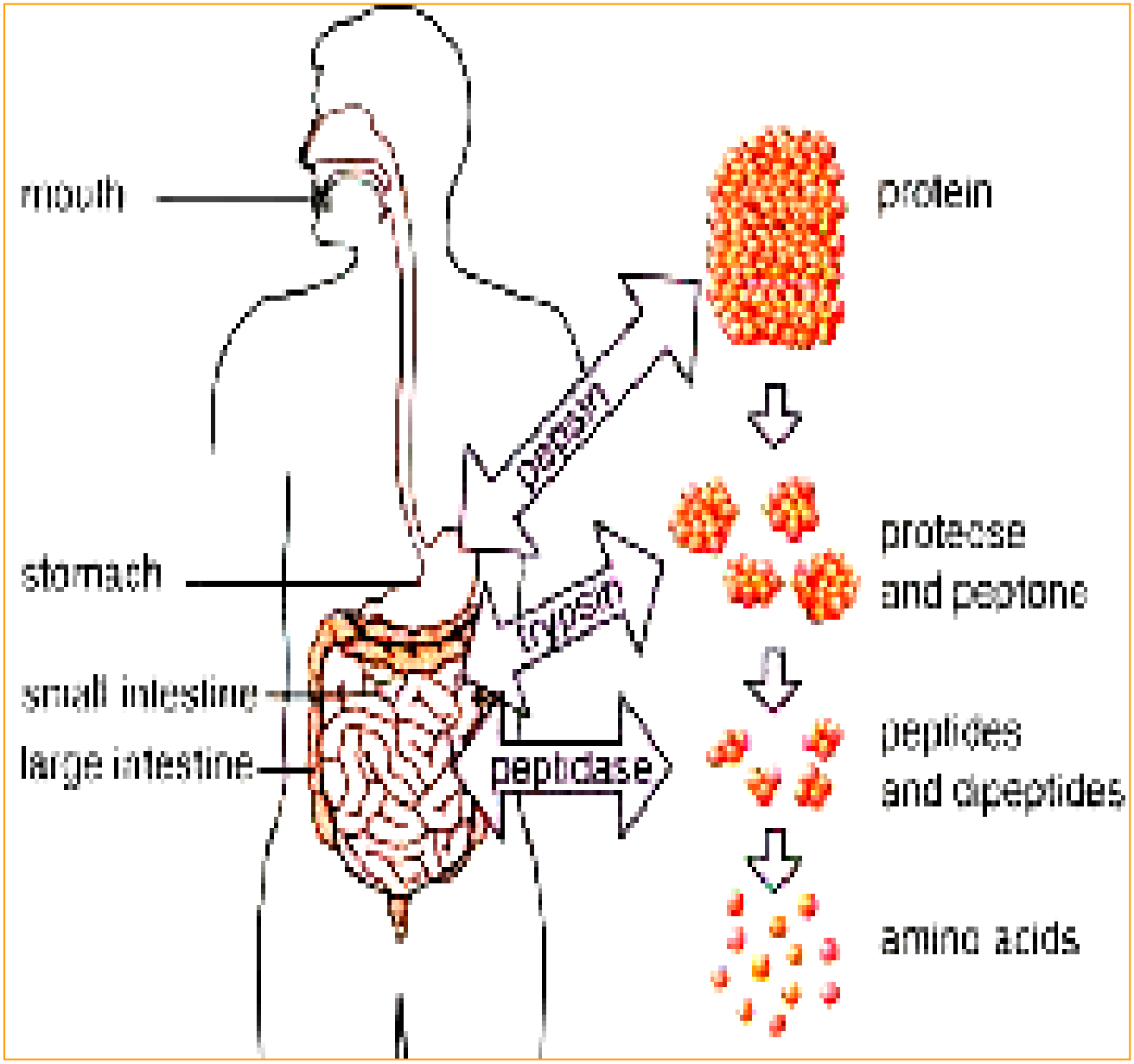
✓ **In the duodenum - trypsin, chymotrypsin, elastase, carboxypeptidase A and B degrade proteins to oligopeptides and in a lesser extent to amino acids.**

✓ ***Digestion on the luminal surface of the luminal membrane of enterocytes*** **- endopeptidases and exopeptidases degrade peptides to di- or tripeptides and amino acids.**

➢ ***Digestion in the cytosol of the enterocytes*** **- cytosol peptidases degrade di- and tripeptides to amino acids.**

Phase of Protein Digestion	Location	Agents	Outcome
1. Gastric Digestion	stomach	stomach acid pepsin	denaturation large peptide fragments + some free amino acids
2. Pancreatic Proteases	lumen of small intestine	trypsin, chymotrypsin elastase; carboxypeptidases	free amino acids; oligopeptides-2 to 8 amino acids
3. Brush Border Surface	brush border surface of intestine	endopeptidases aminopeptidases	free amino acids di- and tripeptides
4. Absorption	intestinal epithelial cell brush border membrane	five transport systems neutral; basic; acidic; imino; di-/tri- peptides	uptake into epithelial cell
5. Cleavage of Di- and Tripeptides; Transport to Capillaries	epithelial cell — cytoplasm & contraluminal membrane	dipeptidases/tripeptidases facilitated diffusion transporters	free amino acids from di- and tri-peptides amino acids transported into capillaries

Digestion of proteins



Digestion of fats

- **Fats** of the diet are also known as **triglycerides,** each molecule of which is composed of a glycerol nucleus and three fatty acids. In the usual diet are also small quantities of **phospholipids, cholesterol and cholesterol esters.**
- Small amount of digestion of the fats (less than 10%) occurs by **lingual lipase** in the stomach.

Digestion of fats in the small intestine

- **The lipases are water-soluble compounds** and can attack the fat globules only on their surfaces.
- **The most important enzyme for the digestion of triglycerides is pancreatic lipase**. It can digest all triglycerides that it can reach within a few minutes.
- The enterocytes of the small intestine contain a minute quantity of lipase that is usually unimportant.

Digestion of fats in the small intestine

- The first step is **emulsification of the fat** under the influence of bile, that contains **bile salts and phospholipid lecithin.**
- Their polar parts of molecules are highly soluble in water, whereas most the remaining portions of their molecules are highly soluble in fat.
- The fat soluble portions dissolve in the surface layer of the fat globule with the polar portions projecting outward and soluble in the surrounding fluids.
- **This effect decreases the interfacial tension of the fat globules and makes them fragmentable in the small bowels.**

❖Lipids of a normal diet are:

- ✓ tryglycerides - above 90%
- ✓ phospholipids - 5%
- ✓ Cholesterol and sterol esters
- ✓ Fat-soluble vitamins and provitamins

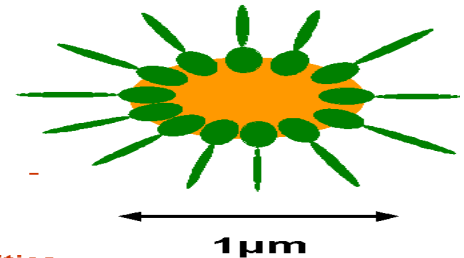
- ❑ Lipids are emulsified by:

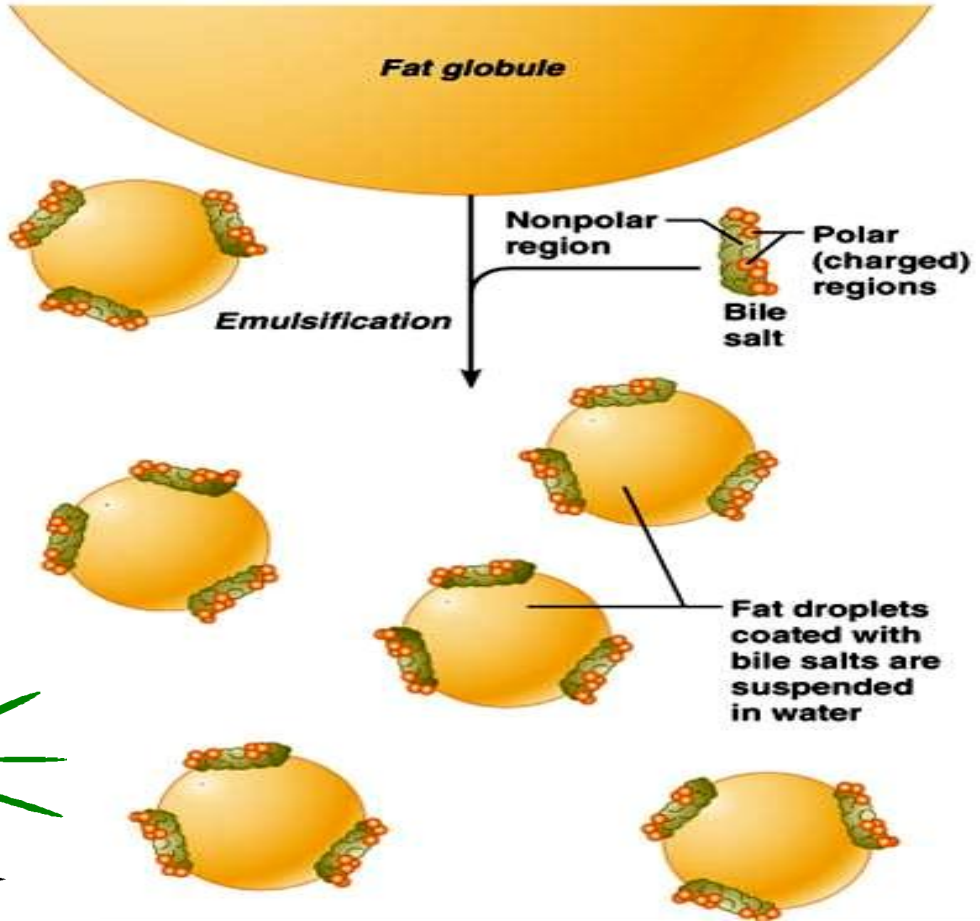
✓ **Cooking**

✓ **Motility of the GI tract**

✓ **Bile salts and phospholipids**

- **Emulsion droplets (1µm in diameter) are covered with bile salts and phospholipids.**





❖ *Pancreatic lipase* catalyzes hydrolysis of triacylglycerols

➢ The activity of the pancreatic lipase depends on the presence of colipase, bile salts, monogycerides, and alkaline pH.

❑ Pancreatic lipase acts only on the surface of oil droplets. The end products of triacylglycerol hydrolysis are fatty acids and 2-monoglycerides.

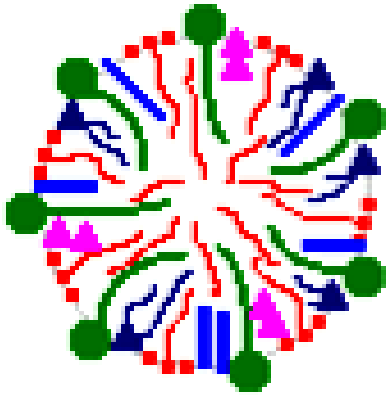
❖ *Cholesterol esterase* degrades cholesterol esters and esters of fat-soluble vitamins.

❖ *Phospholipase A_2* degrades phospholipids to fatty acids and lysophosphatides.

✓ Phospholipase A_2 is secreted as inactive. It is activated by trypsin

❑ The end products of hydrolisis of lipids are: *free fatty acids, cholesterol, 2-monoglycerides, lysophosphatides.* They form (with bile salts and with bile phospholipids) mixed micelles.

▪ Mixed micelles are multimolecular aggregates, about 5 nm in diameter and they contain about 20 to 30 lipid molecules.

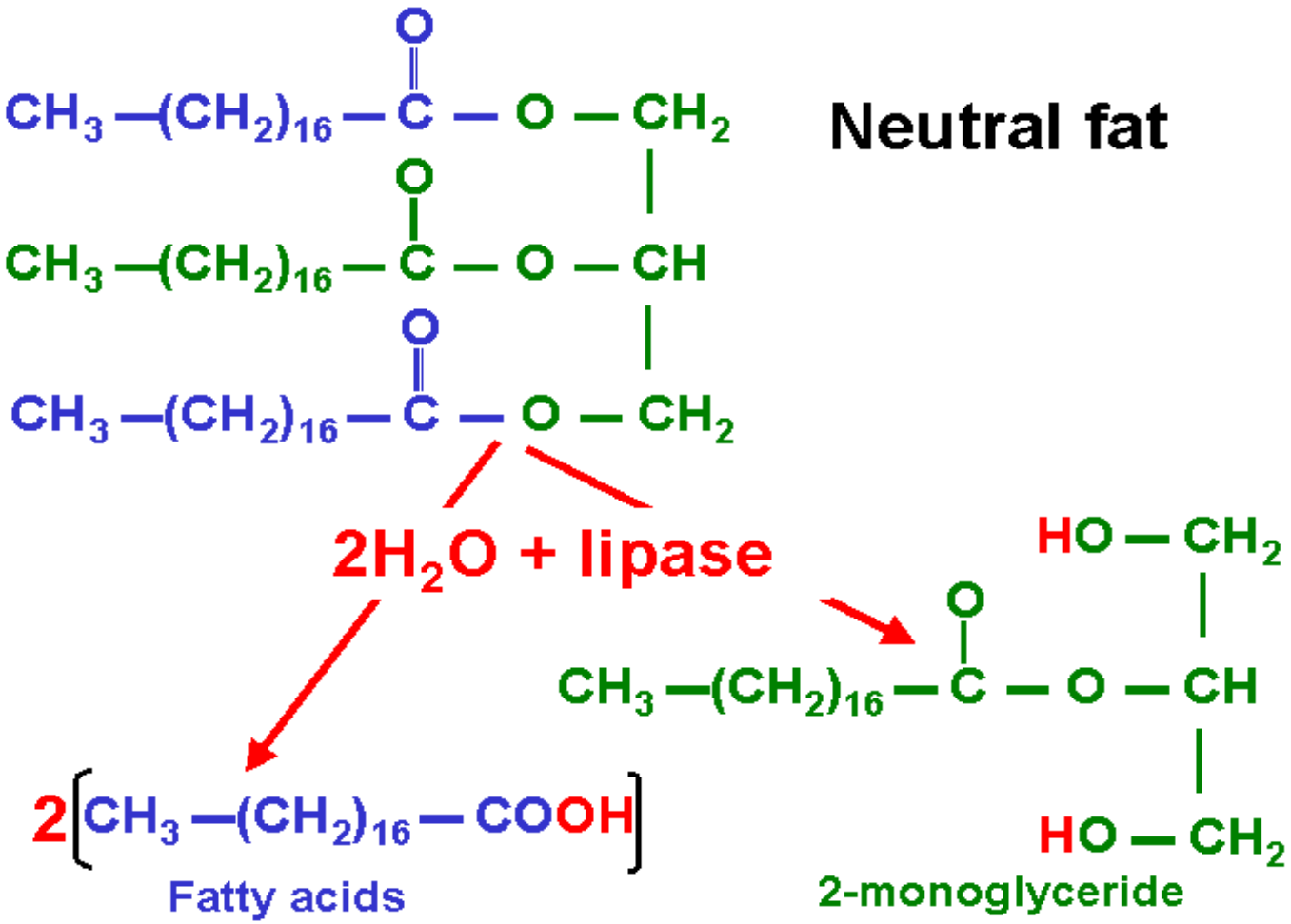


Digestion of fats in the small intestine

- **Bile salts form micelles** – small spherical globules, composed of 20 to 40 molecules of bile salt. Each bile salt molecule is composed of a sterol nucleus (highly fat-soluble) and a polar group (highly water-soluble). Monoglycerids and free fatty acids are dissolved in the central fatty portion of the micelles.
- The bile salts micelles also act as a transport medium to carry the monoglycerids and free fatty acids to the brush borders of the intestinal epithelial cells.
- On delivery of these substances they are released back into the chyme to be used again for this "ferrying" process.

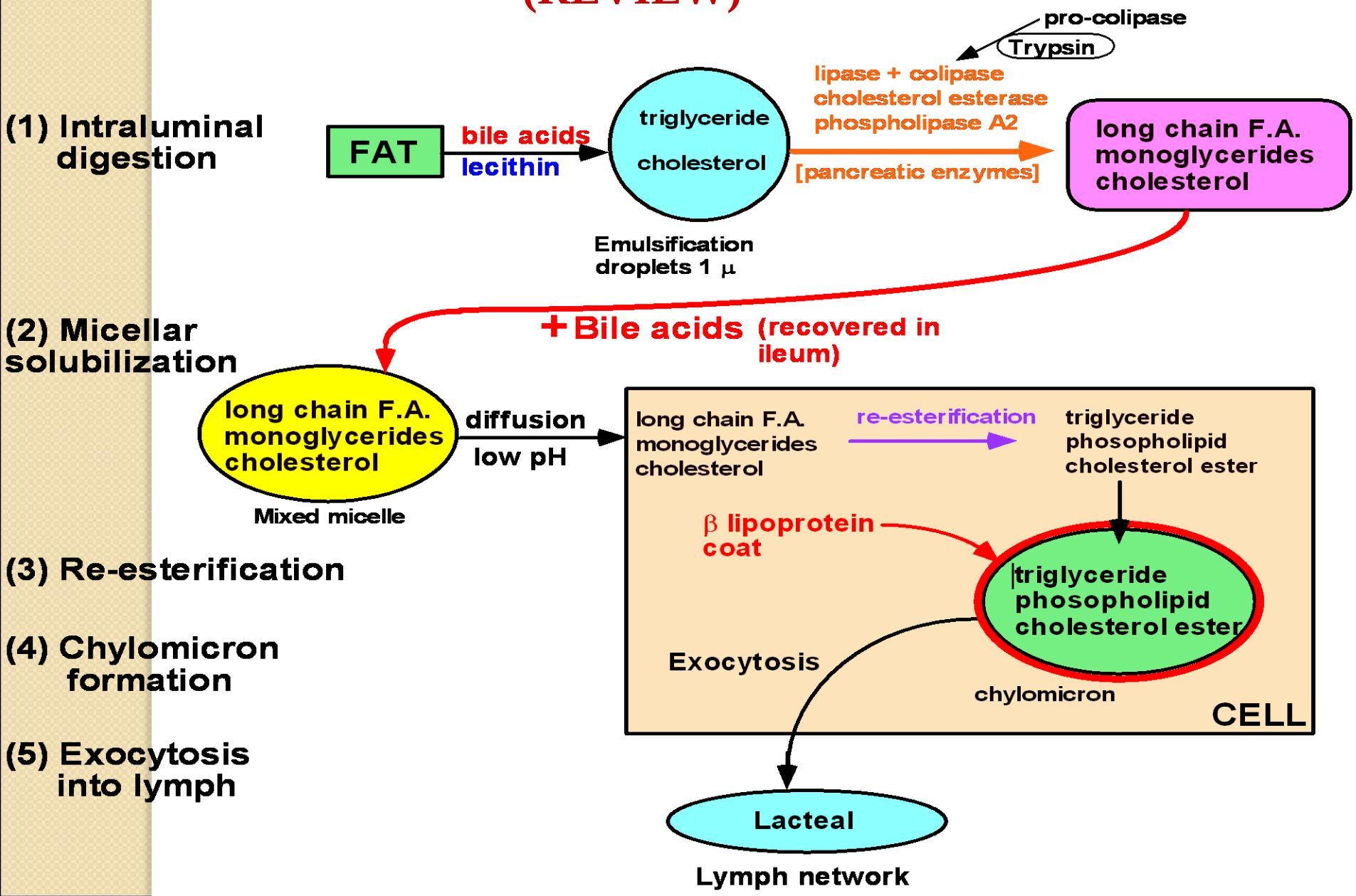
Digestion of fats

- **End products of fat digestion are**: free fatty acids and 2-monoglycerides.
- Digestion of cholesterol esters and phospholipids occurs under influence of pancreatic enzymes cholesterol ester hydrolase and phospholipase A_2 to free cholesterol and digested phospholipids.

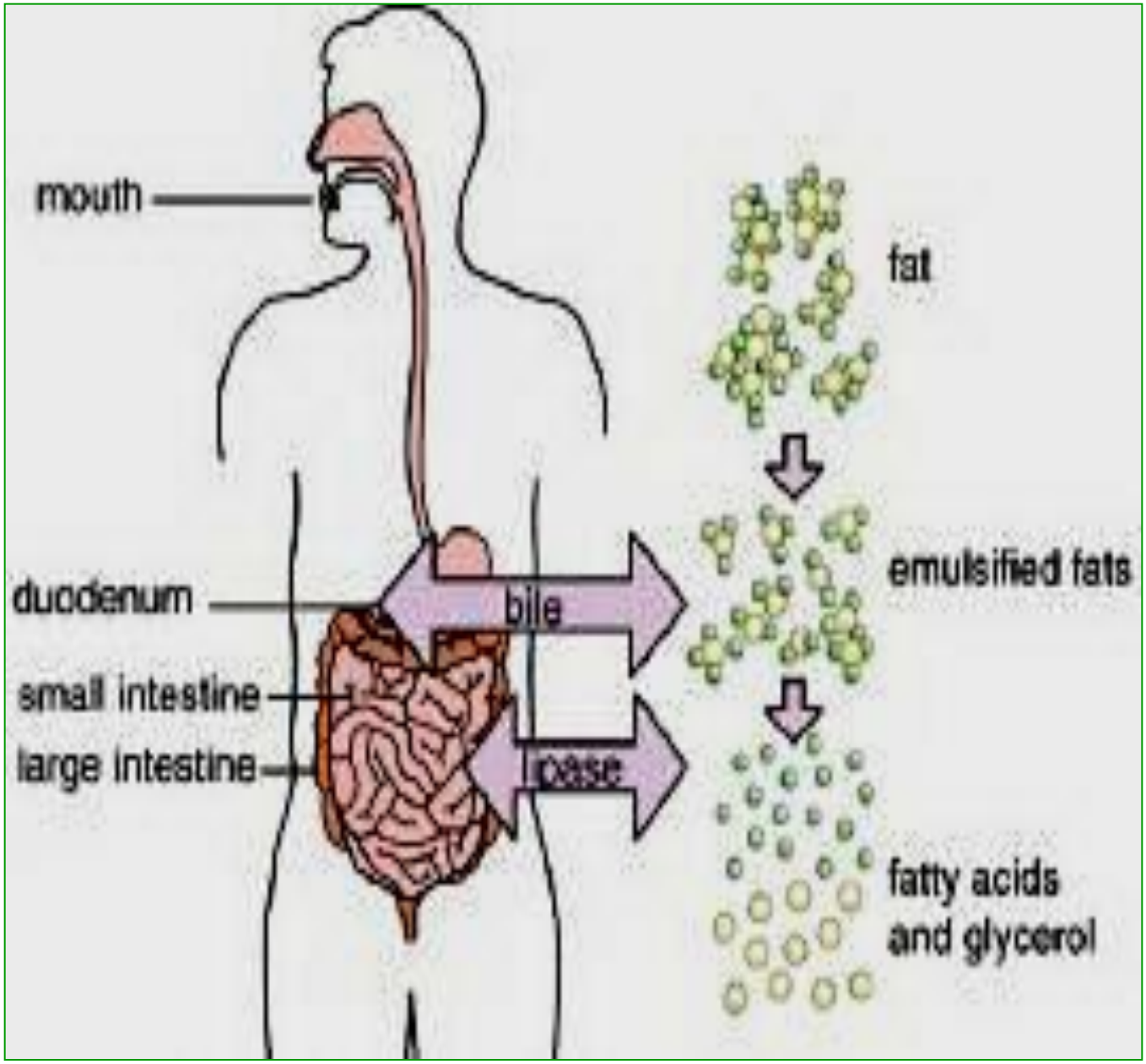

Neutral fat
2H2O + lipase
2
Fatty acids
2-monoglyceride

LIPID DIGESTION

(REVIEW)



Digestion of fats

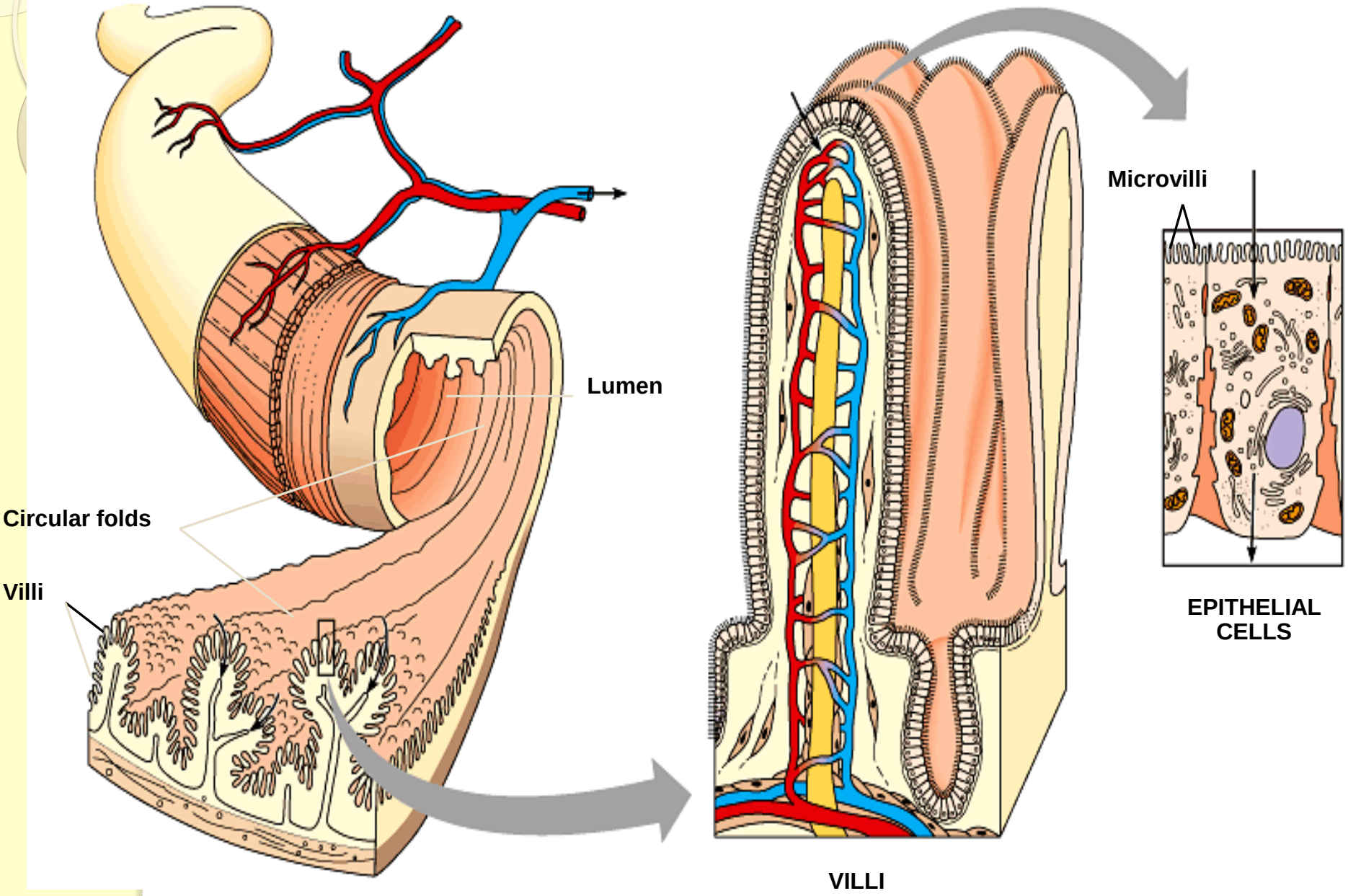


Basic principles of gastrointestinal absorption

- The total quantity of fluid that must be absorbed each day equals to the ingested fluid (1,5 l) + that secreted in GIT (7 l) = 8,5 l.
- **The stomach is a poor absorptive area**, because it lacks the typical villus type of absorptive membrane and because the tight junction between the epithelial cells.
- Only a few highly lipid-soluble substances, such as alcohol and some drugs, like aspirin can be absorbed in stomach.

Basic principles of gastrointestinal absorption

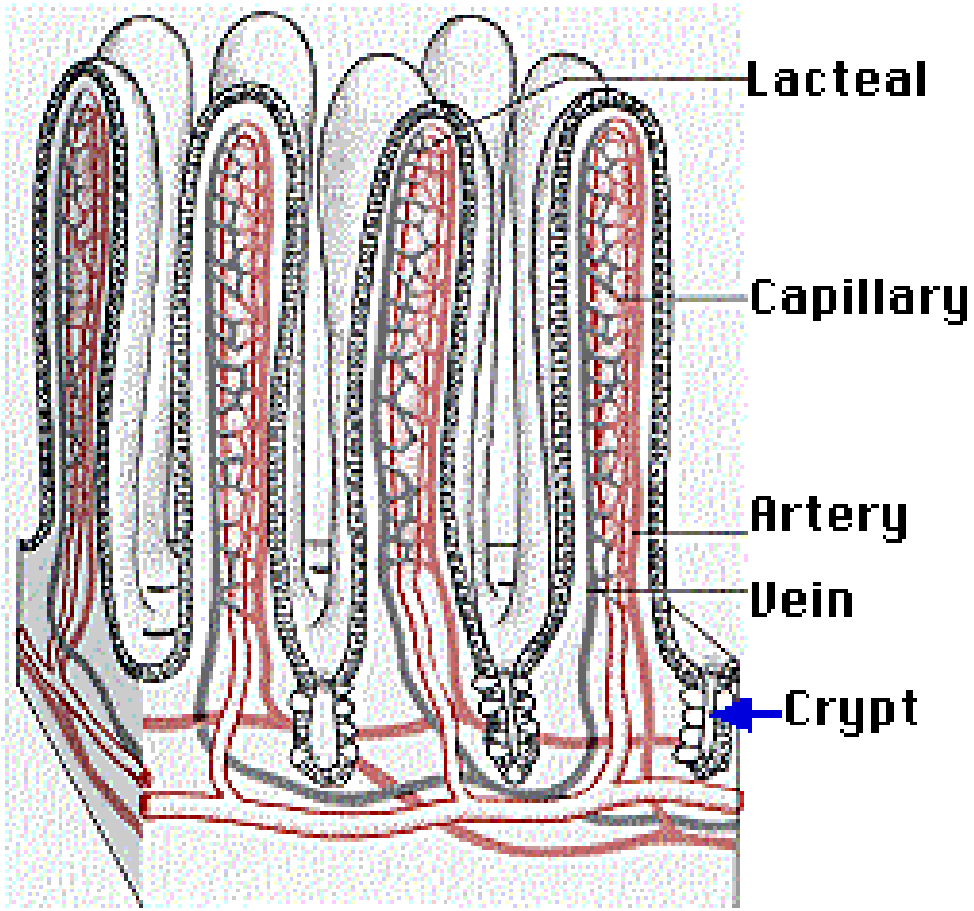
- Absorptive surface of the intestinal mucosa is increased about **3 fold** by valvulae conniventes (**folds of Kerckring**). They extend circularly most of the way around the intestine and are well developed in the duodenum and jejunum.
- These folds are covered by **villi**, which project 1mm from the surface of mucosa and enhances the absorptive area another **10 fold**.
- Each intestinal epithelial cell is characterized by a brush border, consisting of 1000 **microvilli**.
- This increases the surface area exposed to the intestinal materials at least another **20 fold**.


Lumen
Circular folds
Villi
Microvilli
EPITHELIAL CELLS
VILLI

Basic principles of gastrointestinal absorption

- **Thus the combination of these factors increases the absorptive area 1000 fold.**
- General **organization of the villus** shows the advantageous **arrangement of the vascular system and the central lacteal for absorption**. Extending linearly into each microvillus of the brush border are multiple **actin filaments** .

Intestinal villi



Basic principles of gastrointestinal absorption

- They contract intermittently and cause continual movements of the microvilli, keeping them constantly exposed to new quantities of intestinal fluid.
- **Absorption through the gastrointestinal mucosa occurs: by diffusion, by active transport and possibly by solvent drag** (solvent is absorbed because of physical absorptive forces and "drag" dissolved substances along at the same time).

Absorption of monosaccharides

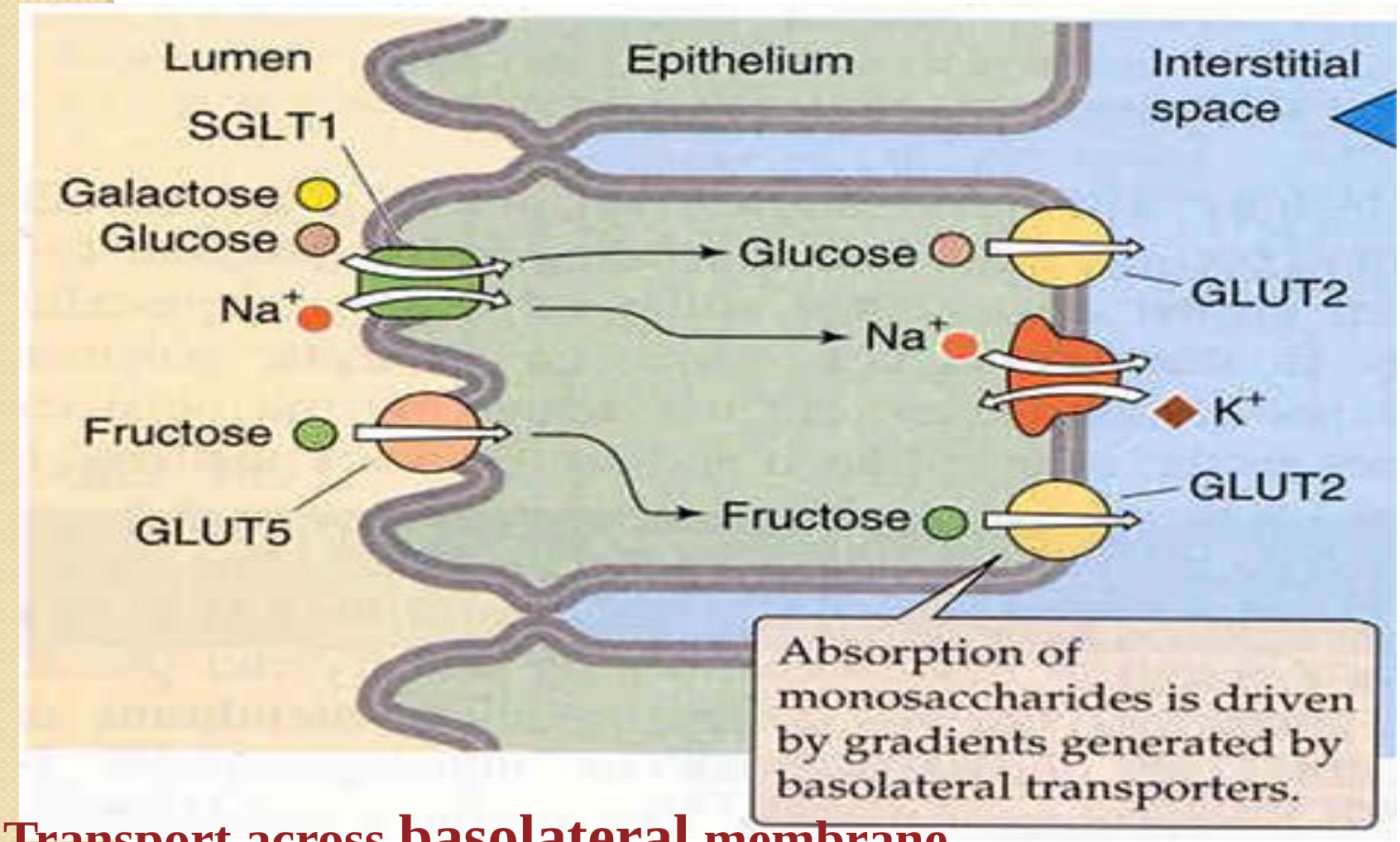
- **Glucose is transported into the cell by a sodium dependent mechanism which transports glucose and sodium ions (secondary active transport).**
- **Galactose is transported by the same mechanism as glucose.**
- **Fructose is transported via facilitated diffusion, and is converted to glucose in the cell.**

➢ ***Glucose is transported out of the enterocytes into the extracellular space by facilitated diffusion.***

➢ Transport across luminal membrane

✓ *Glucose and galactose* are transported by sodium-glucose transport protein (SGLT1) through the apical membrane. The transport is secondary active one.

✓ *Fructose* is transported by GLUT5 - facilitated diffusion.



➢ Transport across basolateral membrane

✓ Glucose, galactose and frucrose are transported by GLUT2.

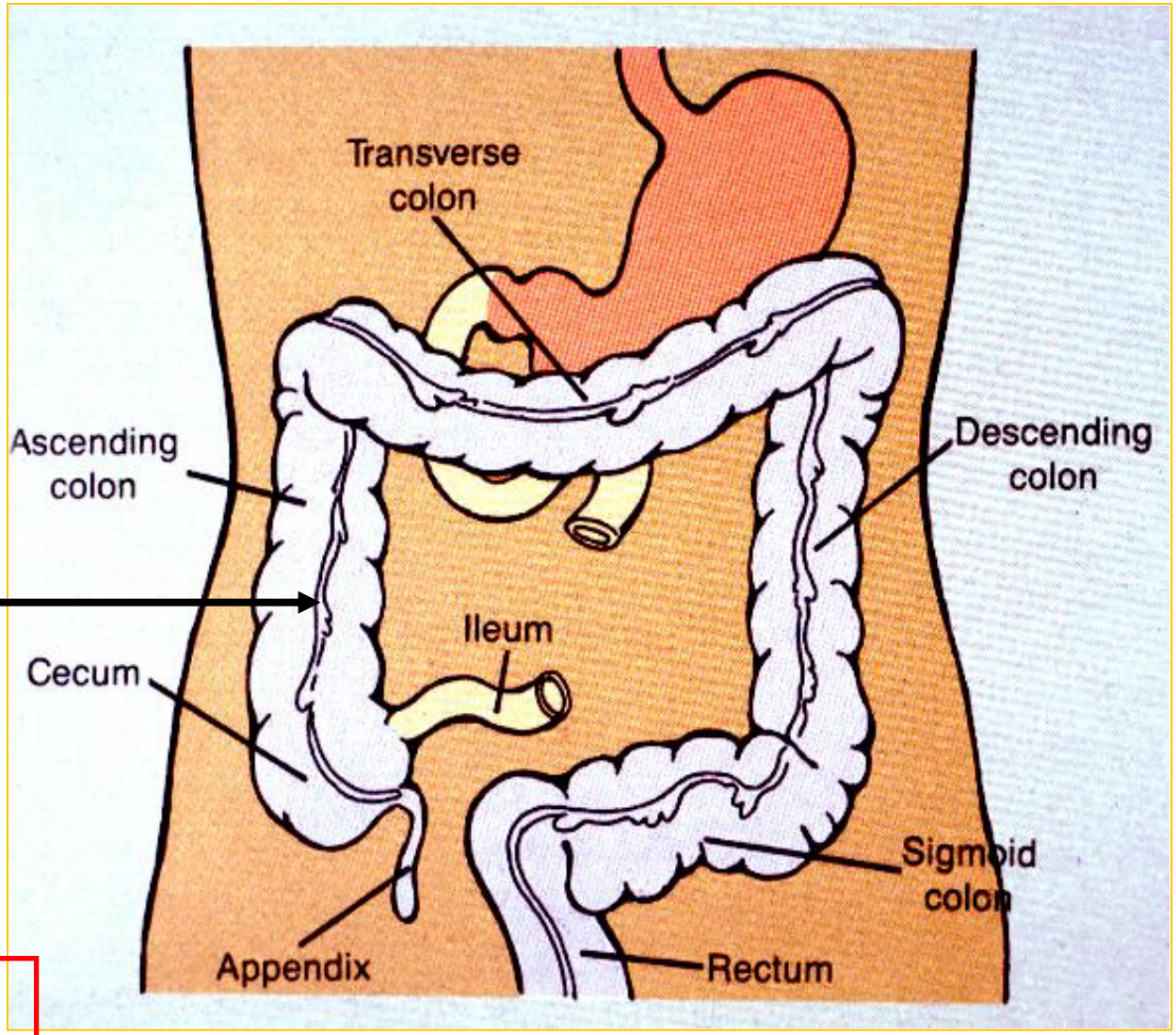
Disorders of carbohydrate absorption

- **If carbohydrate absorption is disrupted**, the high concentration of sugar in the chyme results in osmotic pressure which interrupts the absorption of water. ***This results in diarrhoea***.
- It is not commonly found as **in high sugar concentration glucose can be dragged** with the bulk flow of water through the gap junctions between the cells.

Disorders of carbohydrate absorption

- **If there is a deficiency of carbohydrases** then the complex sugars are not broken down and therefore exert **an osmotic effect**. Additionally if there is gut pathology which results in **villus atrophy** then there is a decreased surface area for absorption and **diarrhea results**.

Undigested Lactose serves as a substrate for colonic flora, which then ferment the lactose, increasing lumen osmolarity, causing retention of fluid in the large intestine.



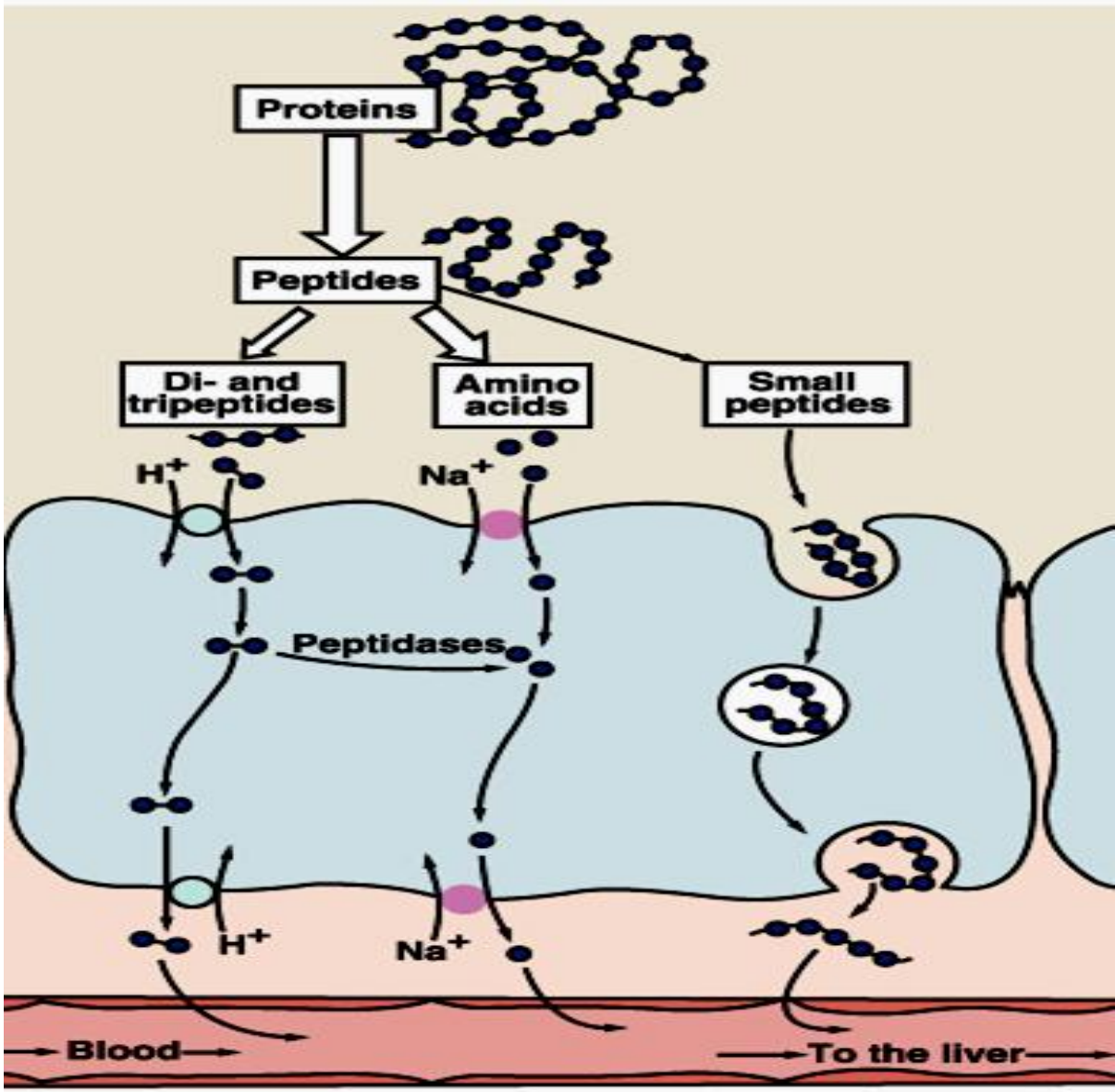
An example of OSMOTIC diarrhea

Absorption of amino acids

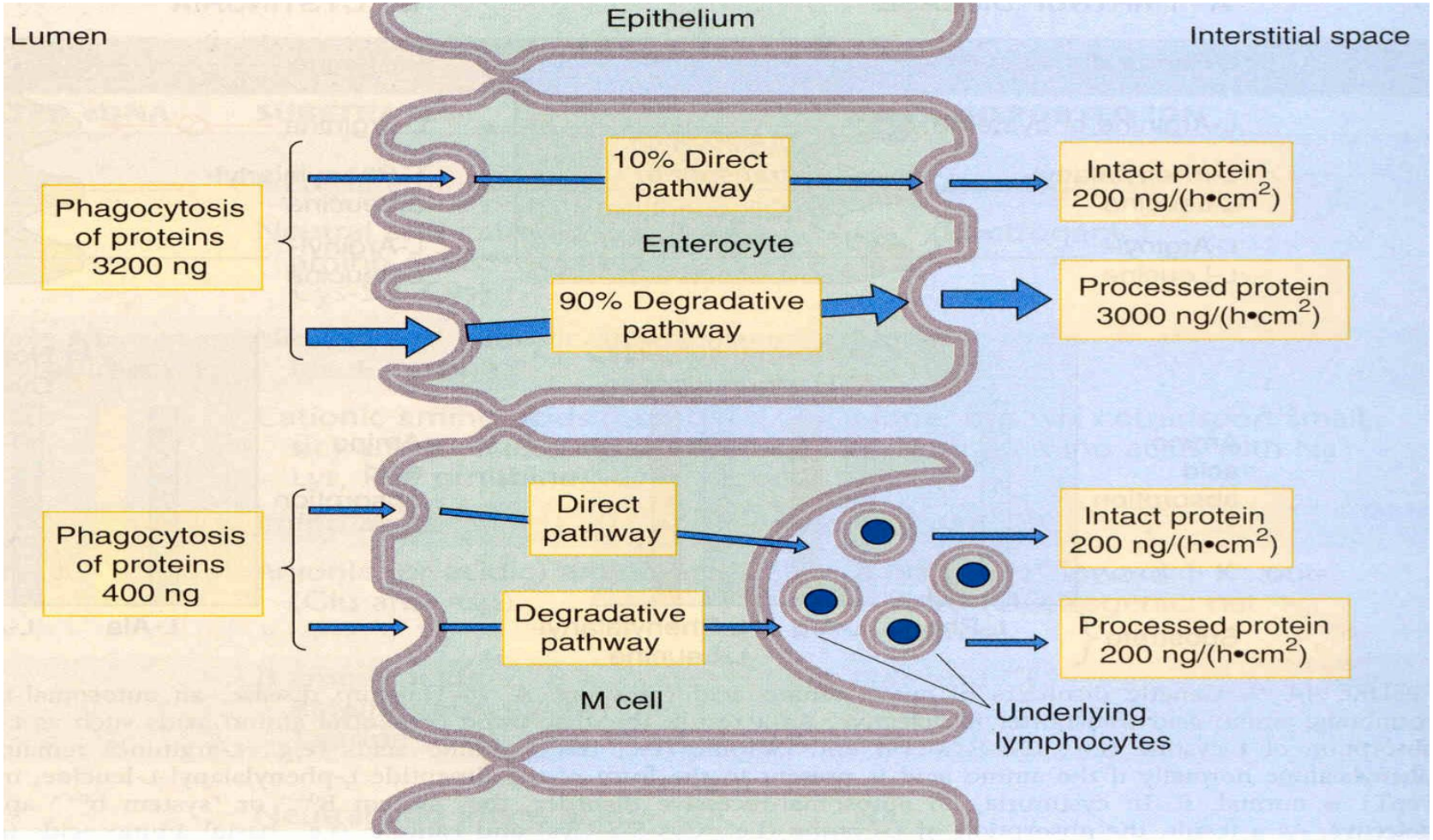
- Amino acids are transported into and out of the enterocyte by sodium dependent transport in a manner similar to glucose.
- A few amino acids are transported by special membrane transport proteins by facilitated diffusion.
- 5 types of amino-acid and peptide transport proteins have been characterized in the luminal membrane of intestinal epithelial cells.

❖GI tract absorbs proteins in form of:

- intact proteins and large peptides
- Oligopeptides - tripeptides and dipeptides
- Amino acids



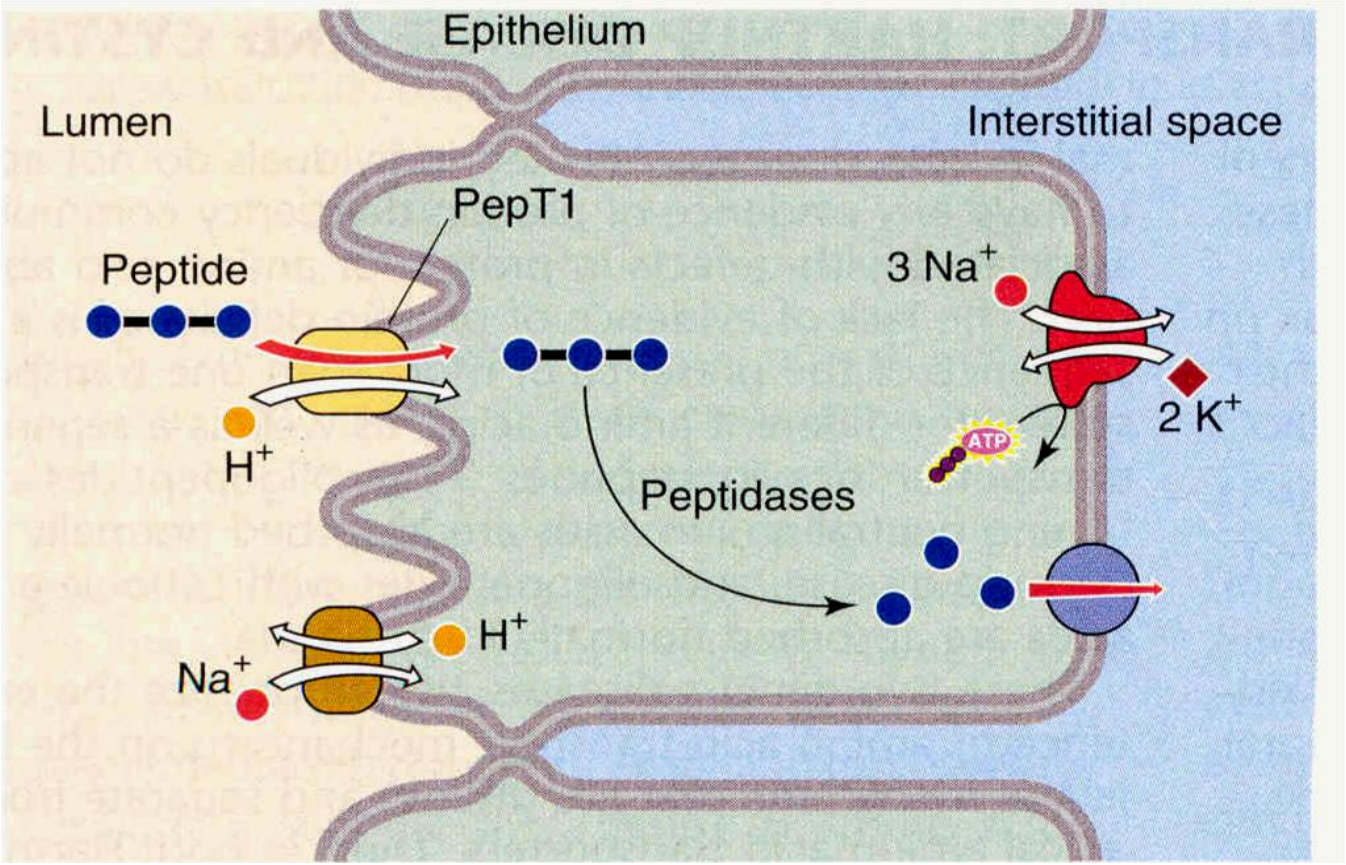
❖ **Small amounts of proteins are taken up by endocytosis from enterocytes and M- cells (M-cells process and present antigens to the other kinds of immune cells in the intestine).**



➢ **The small intestine of newborns has a high capacity for absorption of antibodies present in colostrum.**

❖ **A wide variety of dipeptides and tripeptides is transported acros the plasma membrane by a *single type of transport protein*. It transports peptide together with H+ (peptide/H^+ symport).**

❑ **Transmembrane transport of peptides is *more effective* than that of amino acids.**



▪ **After the peptides become a part of enterocyte, they are degraded to *amino acids* by cytosolic peptidases. Amino acids pass across basolateral membrane by *facilitated diffusion*.**

Absorption of fatty acids and **monoglycerides**

- 1. They **enter epithelial cells** lining small intestine by diffusion.
- 2. They are **reassembled** into triglycerides by epithelial cells.
- 3. They are packaged along with cholesterol and other lipids and released from the cell as fat droplets (**chylomicrons**) by exocytosis.
- 4. They are absorbed into **lymph** vessels (lacteals) → pass to the blood by thoracic lymph.
- 5. Short-chain fatty acids are absorbed directly into the portal blood, from the capillars of the villi.

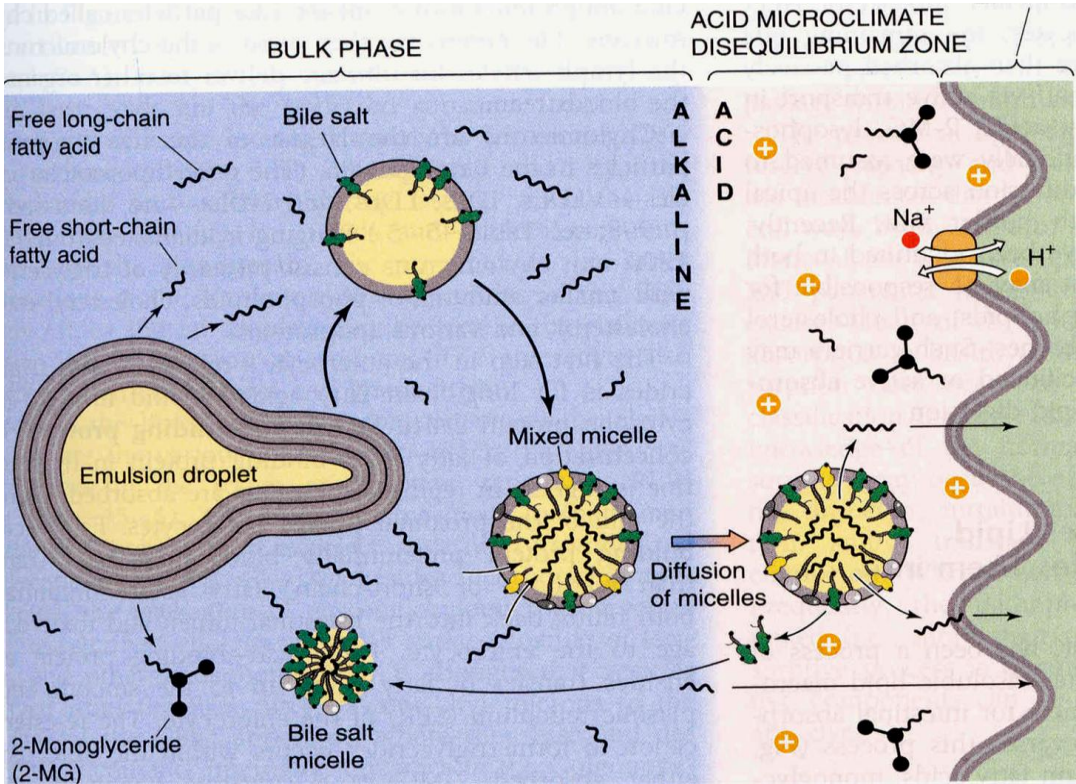
Absorption of lipids

❖ **Mixed micelles are absolutely necessary for absorption of lipids and fat-soluble vitamins.**

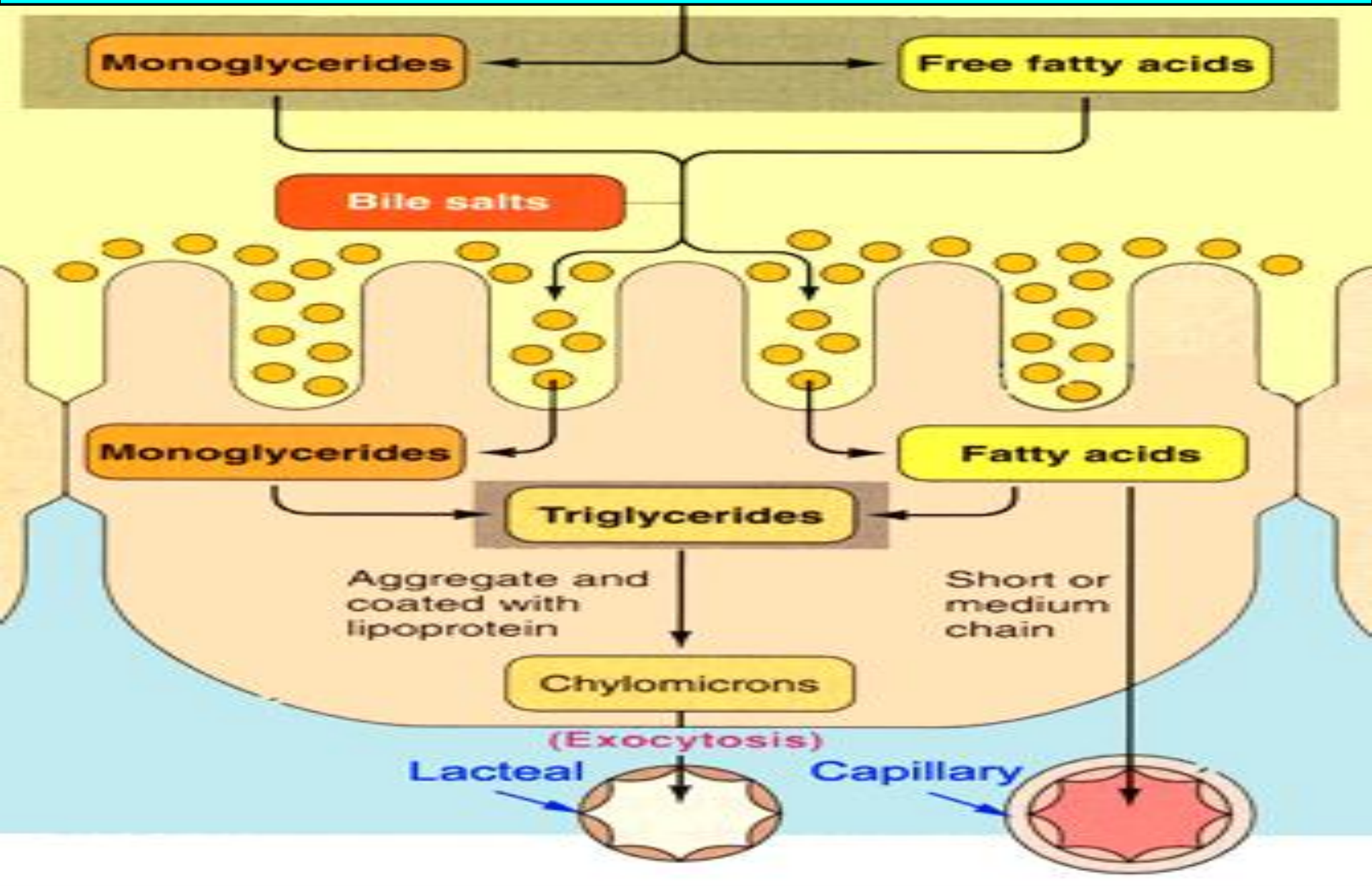
➢ **Hydrophilic surface of the mixed micelles enables them to enter unstirred layer among microvilli and contact with lumenal membrane of the enterocytes. Most lipid molecules pass across membrane of enterocytes by diffusion. Membrane transport proteins mediate the facilitated transport of long-chain fatty acids, cholesterol and lysophospolipids across membrane into the enterocyte.**

➢**ABC transporter removes cholesterol from the membrane and pumps it back into the lumen of the intestine**

❑ **Lipids are fully absorbed in the upper part of small intestine: duodenum and the upper half of ileum.**



❖ **Short-chain fatty acids (<6 C) and middle-chain fatty acids (6-12 C) are not reesterified. They pass directly into blood capillaries of the villi.**



Disorders of fat absorption

- **Excess fat in the stools is termed steatorrhoea**. The stools are pale in color, bulky and highly smelly. They also float. **Steatorrhoea is associated with poor fat absorption**, due, for example to coeliac disease or gluten enteropathy, **when villi are lost and absorption greatly decreased.** Fat absorption can also be affected by **acid hyper secretion** as pancreatic lipase is acid-labile and fats are therefore not digested or **lack of bile salts.**

Water and electrolyte absorption

- **Water is absorbed under influence of osmotic gradient.**
- As we have seen **sodium** can be absorbed in a variety of ways from the gut.
- **It diffuses** into enterocytes **down it's concentration gradient**, but is also actively taken up in co-transport with both glucose and amino acids.
- It is also **co-transported** with other ions such as **chloride**, or **exchanged** such as with **hydrogen ions**.
- Sodium ion absorption drags other ions such as chloride with it - electrical effect.
- Water also passes through the tight junctions by bulk flow, following the movement of ions.

- **Water and ions move across the epithelial layer in two opposite directions; from the lumen to the blood (absorption) and from the blood to the lumen (secretion). The net flow is the difference between the opposite flows.**
- **The transport is transcellular and paracellular.**

small intestine:

- **-** there is a **net absorption of Na^+, Cl^-, K^+** and **water**, and **net secretion of HCO_3^-**

colon:

- **-** there is a **net absorption of Na^+ и Cl^-** and **net secretion of K^+ и HCO_3^-**

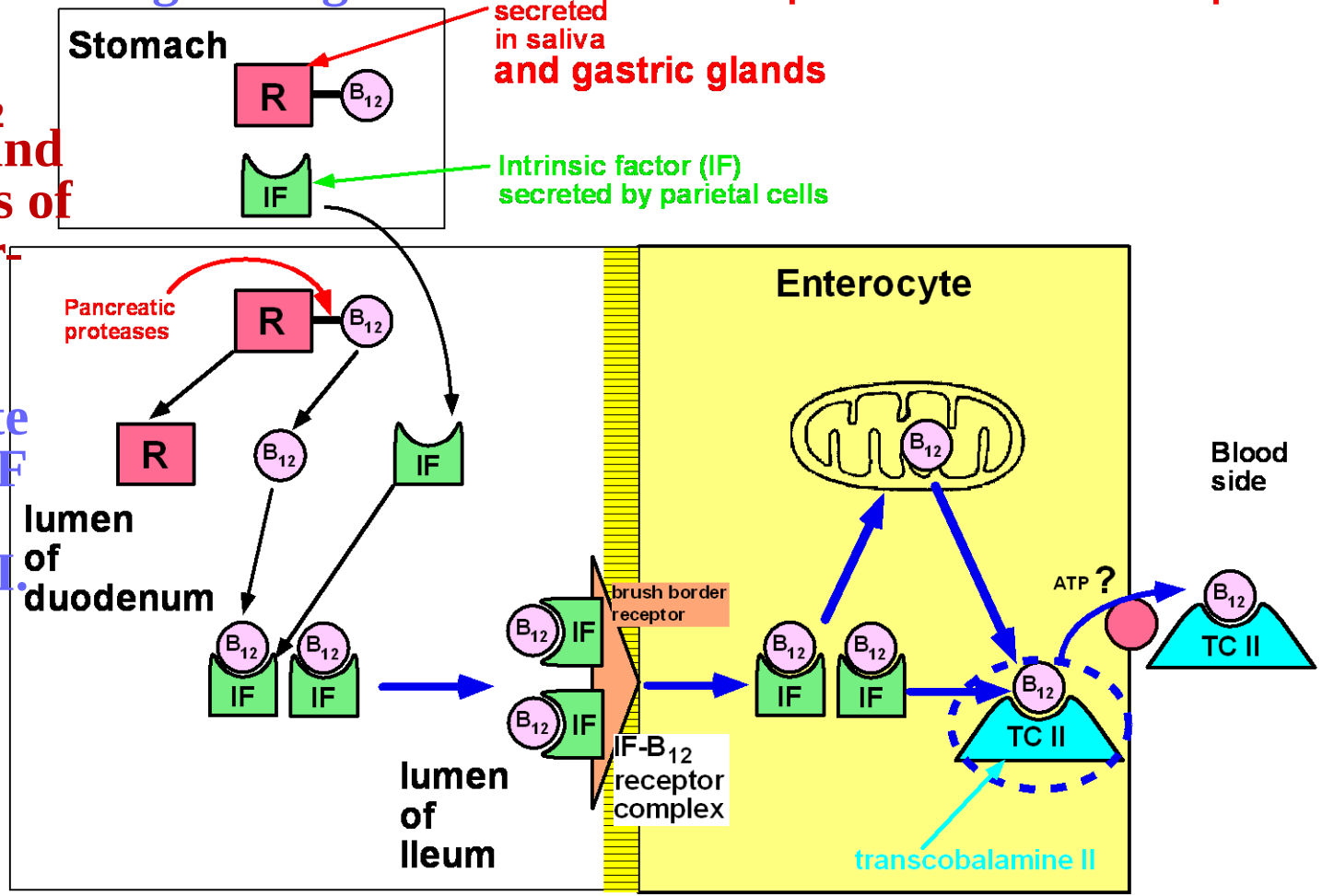
Absorption of Vitamins

- The **vitamins** can be separated into the **fat soluble** (A,D,E,K) and **water soluble** (B,C) classes.
- All the vitamins **are absorbed by secondary active transport** or **by passive or facilitated diffusion**, either in the water soluble or fat soluble compartments.
- VitB_{12} must bound with intrinsing factor, secreted by the stomach to absorpt.

Absorption of vitamin B_{12} (cobalamin)

- Most of the dietary vitamin B_{12} is bound to proteins
- The digestion of proteins by pepsin releases free vitamin B_{12}. The free vitamin B_{12} binds to haptocorrin (R-proteins) secreted by gastric and salivary glands.
- Pancreatic proteases degrade haptocorrin and the free cobalamin is transferred to IF (intrinsic factor), secreted by parietal cells of gastric glands.

- Complex IF-B_{12} resists digestion and enters enterocytes of ileum by receptor-mediated endocytosis.
- In the enterocyte B_{12} is split from IF and is bound to transcobalamin II.
- B_{12}-TCII leaves the enterocyte and enters blood vessels.



Absorption of calcium

- **The absorption of calcium from the gut is dependent upon parathyroid hormone (PTH).**
- PTH stimulates the conversion of 25, hydroxy- vitamin D_3 to 1,25 dihydroxy-vitamin D_3 in the kidney.
- This acts on enterocytes in the gut to directly stimulate the transcription of the gene encoding the **calcium binding protein**.
- This action results in more calcium binding protein being expressed in the membrane of the cell, which promotes calcium absorption thereby returning calcium plasma levels to normal.

Absorption of calcium

- **There are two ways of Ca^{2+} absorption: active transcellular and passive paracellular**

➢ **Active transcellular transport - in duodenum only**

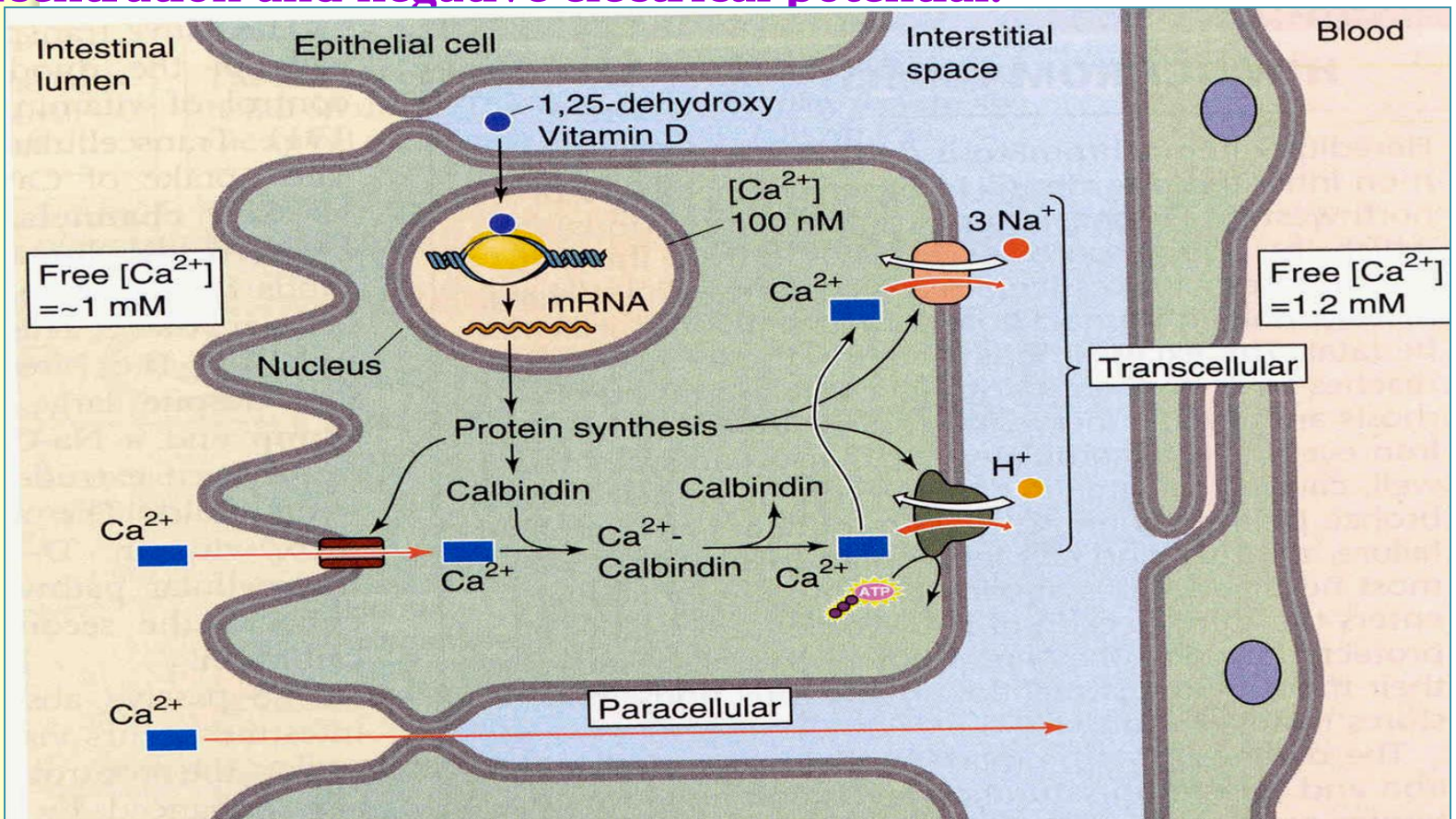
✓ Ca^{2+} enters the enterocyte **across channels and by transport protein**

✓ **In the cytosol Ca^{2+} binds with calbindin**

✓ **Ca^{2+} leaves the enterocyte by Ca pump and Na/Ca exchanger**

- **All the three stages of Ca transport are stimulated by vitamin D**

➢ **Passive paracellular transport - in jejunum and ileum, towards lower concentration and negative electrical potential.**



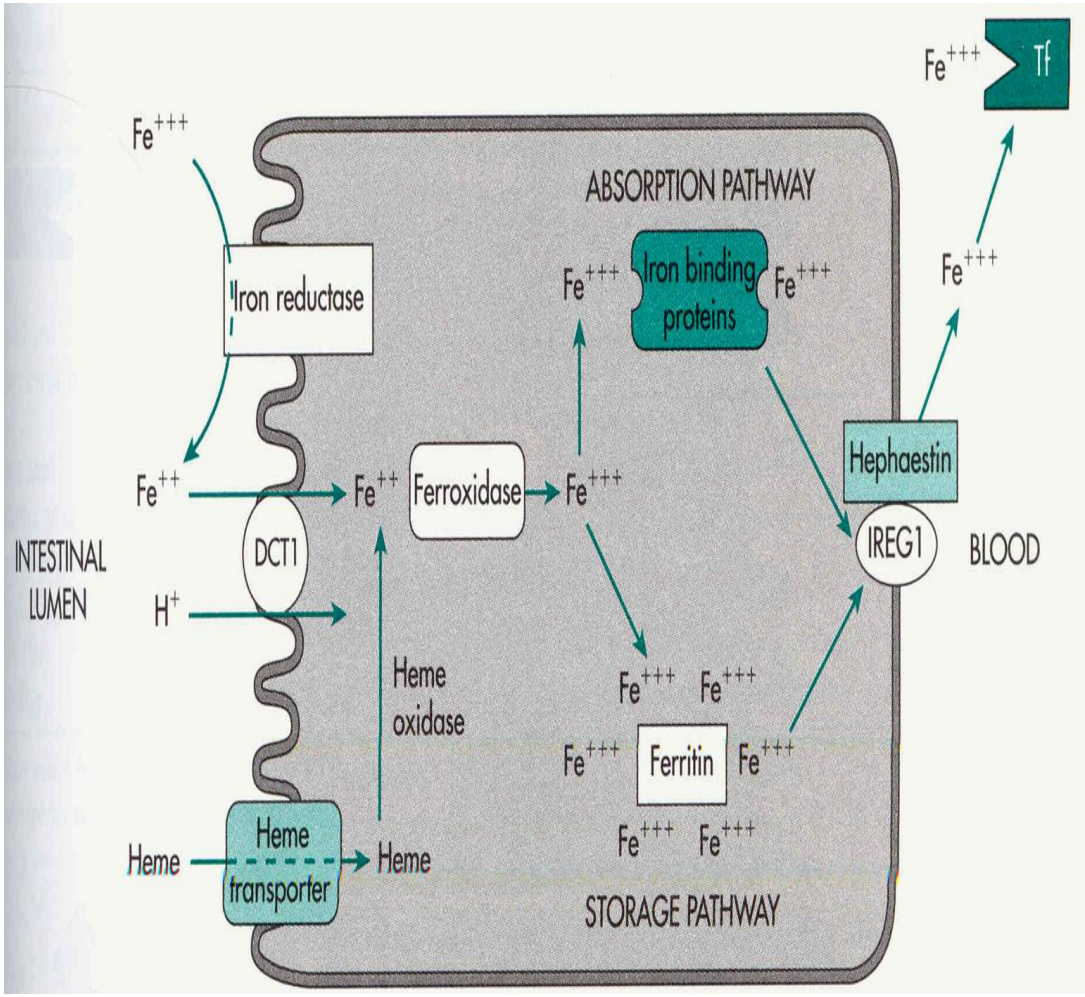
Iron

- **Iron uptake in the gut is mediated by a binding protein, transferrin.**
- This protein binds two molecules of iron and is then taken up into the cell **by receptor mediated pinocytosis**.
- Once in the cell the iron is either stored by binding to an intracellular protein **ferritin**, if plasma iron levels are high, or is transported out of the cell and bound to plasma transferrin for transport around the body.

Absorption of Iron

- Iron in the food enters enterocyte as Fe^{2+} and as heme.
  - Iron reductase and ascorbinic acid reduce Fe^{3+} of the food to Fe^{2+} .
  - Fe^{2+} is absorbed in the duodenum.

- Fe^{2+} enters enterocyte across apical membrane by cotransport with H^+(DCT1)
- **Heme** is transported across apical membrane by endocytosis or facilitated diffusion.
- ✓ In the enterocyte Fe^{2+} is split from the heme.
- Fe^{2+} is oxidized to Fe^{3+} in the cytosol. Fe^{3+} is stored in the enterocyte or tranported to the blood.
- ✓ Fe is transported through cytosol by protein mobilferrin.
- ➢ Fe^{3+} leaves enterocyte across basolateral membrane by transporter (IREG1) associate with hephaestin.



Functions of the liver

- **Reservoir function of the liver**(blood reservoir)
- **The blood cleansing function**(Kupffer cells)
- **Metabolic functions of the liver**

  - **Carbohydrate metabolism (glucose buffer function)**
    - Storage of glycogen
    - Conversion of galactose and fructose to glucose
    - Gluconeogenesis

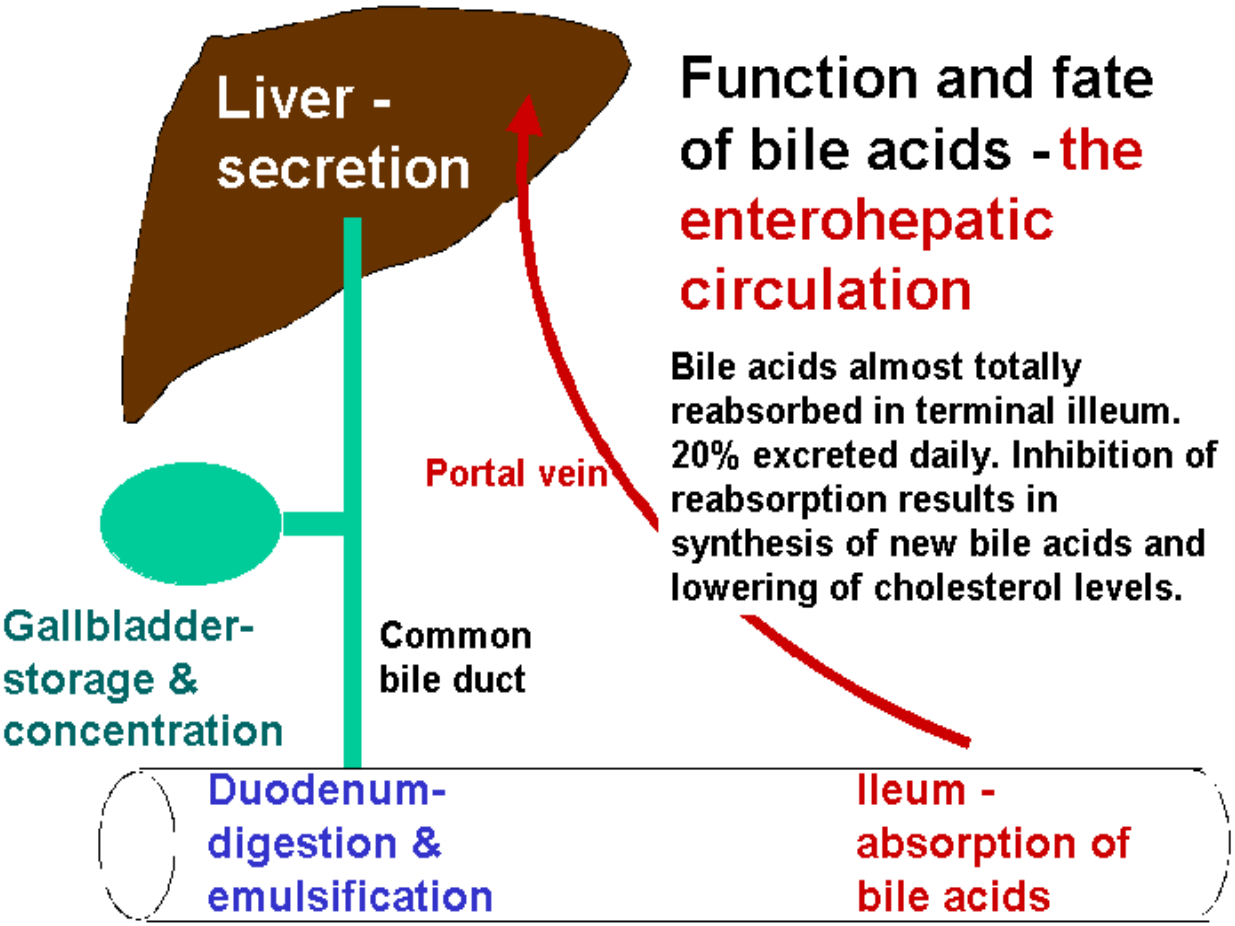
Functions of the liver

- **Protein metabolism**

- Deamination of amino acids
- Formation of urea for removal of ammonia
- Formation of plasma proteins
- Interconvertion among the different amino acids

Functions of the liver

- **Storage of vitamins**(D,B_{12},A)
- **Relation of the liver to blood coagulation** (the liver forms protrombin, fibrinogen, accelerator globulin, factor VII).
- **Storage of iron** (in the form of ferritin)
- **Production of the bile –** effect on the digestion
- **Removal or excretion of drugs, hormones and other substances into the bile**
- **Excretion of the bilirubin into the bile**



Function and fate of bile acids - the enterohepatic circulation

Bile acids almost totally reabsorbed in terminal illeum. 20% excreted daily. Inhibition of reabsorption results in synthesis of new bile acids and lowering of cholesterol levels.

Excretion of the bilirubin in the bile

- The **red blood cells have lived av. 120 days** into the blood and become too fragile to exist longer in the circulation.
- Their cell membranes rupture and the released **hemoglobin is splits into globin and heme, after phagocytosis by the reticuloendothelial system**.
- There is formed **biliverdin,** that is rapidly reduced to **free bilirubin**. It is released from the macrophages into the plasma.

Excretion of the bilirubin in the bile

- The **free bilirubin combines strongly with the plasma albumin** and **is transported** throughout the blood and interstitial fluid.
- It **is absorbed trough the hepatic cell membrane,** after releasing of plasma albumin.
- Into the hepatic cells **free bilirubin is conjugated with glucoronic acid to form bilirubin glucoronide.**

Excretion of the bilirubin in the bile

- In this form bilirubin **is excreted from the hepatocytes by an active transport into the bile and then into the intestines.**
- **There ½ of the conjugated bilirubin is converted** by bacterial action **into the** substance **urobilinogen**, which is highly soluble.
- Some of urobilinogen is reabsorbed through the intestinal mucosa back into the blood.

Excretion of the bilirubin in the bile

- Most of this is once again re-excreted by the liver back into the gut, but about 5% is excreted by the kidneys into the urine.
- After exposure to air in the urine, the **urobilinogen** becomes **oxidized** to **urobilin**, or in the feces, it becomes altered and oxidized to form **stercobilin**.

Thanks for your attention!