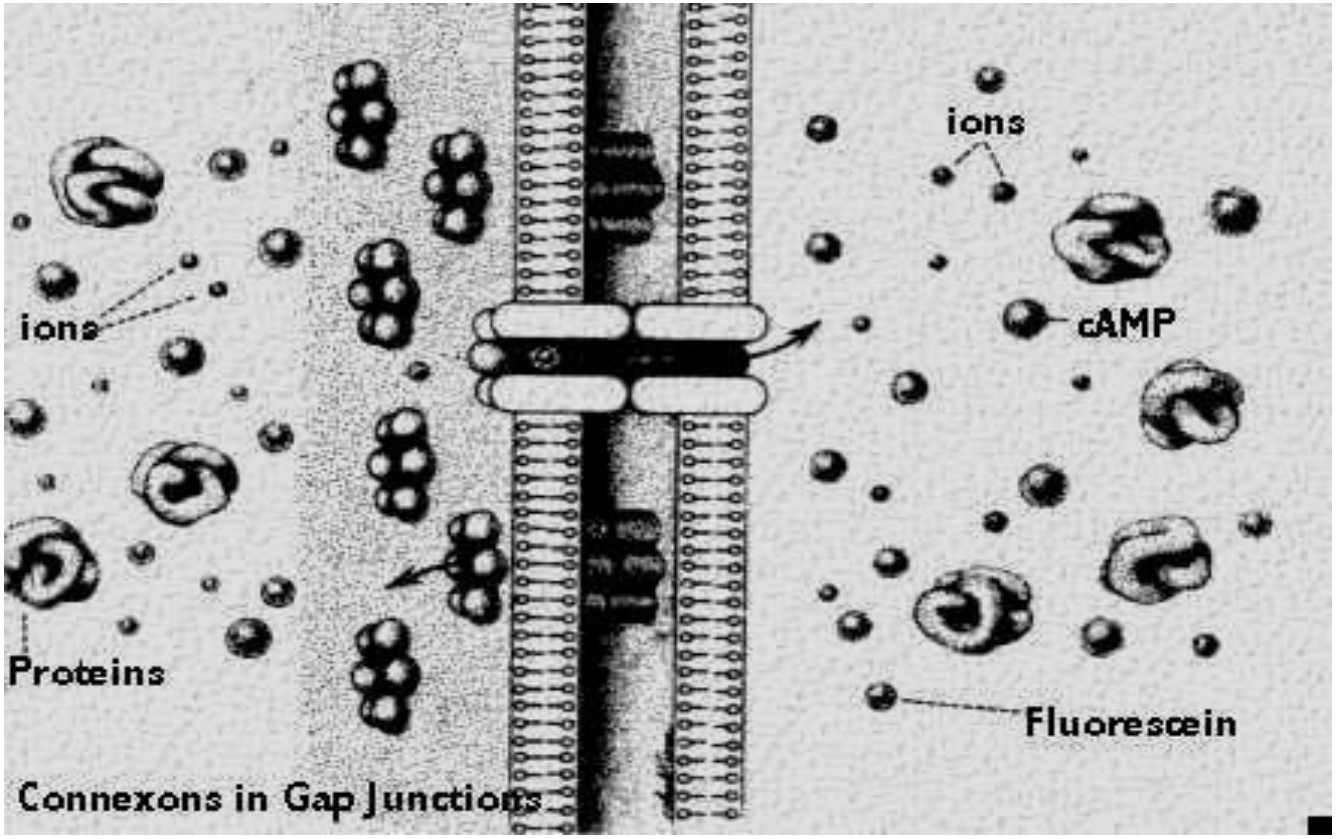
2-Transport across the membranes (Cont.):



Mechanism of ion pair transport of drugs

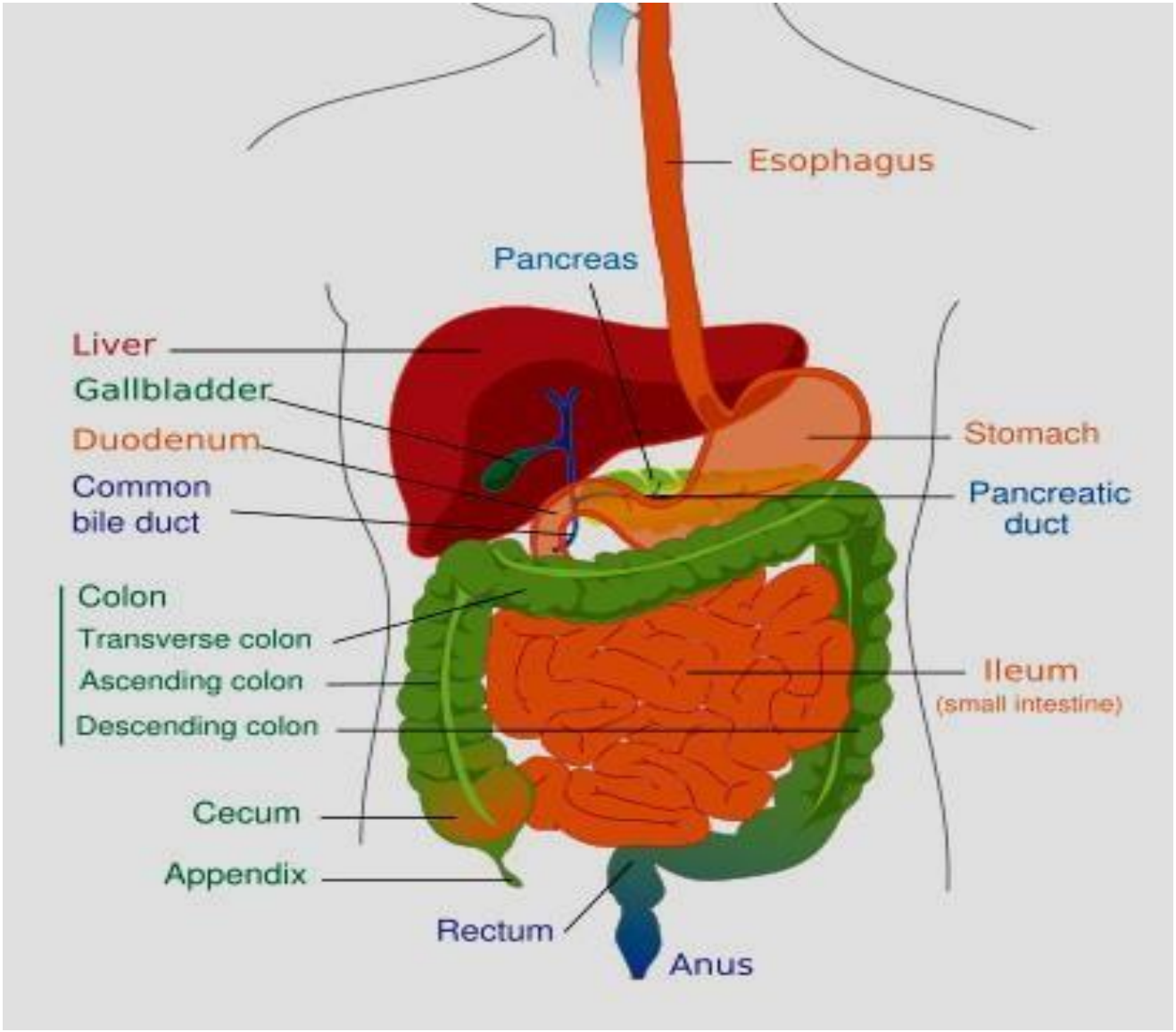
3- Gastrointestinal (GI) Physiology:

- The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters.

- It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon.

- The majority of the gastrointestinal epithelium is covered by a layer of mucous. This is a viscoelastic translucent aqueous gel that is secreted through out the GIT, acting as a protective layer and a mechanical barrier.

Gastrointestinal (GI) Physiology (Cont.):



Gastrointestinal (GI) Physiology (Cont.):

I. Characteristics of GI physiology and Drug Absorption:

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Buccal	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
Oesophagus	5-6	Very thick no absorption	-	small	short, typically a few seconds, except for some coated tablets	-

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Stomach	1.7-3.5	normal	good	small	30 min (liquid) - 120 min (solid food)	no
Duodenum	5 - 7	normal	good	Very large	very short,	no

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Small Intestine	6 – 7.5	normal	good	Very large	About 3 hours	no
Large intestine	6.8 - 7	-	good	Not very large	long, up to 24 hours	Lower colon, rectum yes

I. Characteristics of GI physiology and Drug Absorption (cont.):

The environment within the lumen:

Gastrointestinal pH

- As we observed from the previous tables, the pH of fluids varies along the length of the GIT.
- The gastrointestinal pH may influence the absorption of drugs in a variety of ways:

A- It may affect the chemical stability of the drug in the lumen e.g. penicillin G, erythromycin

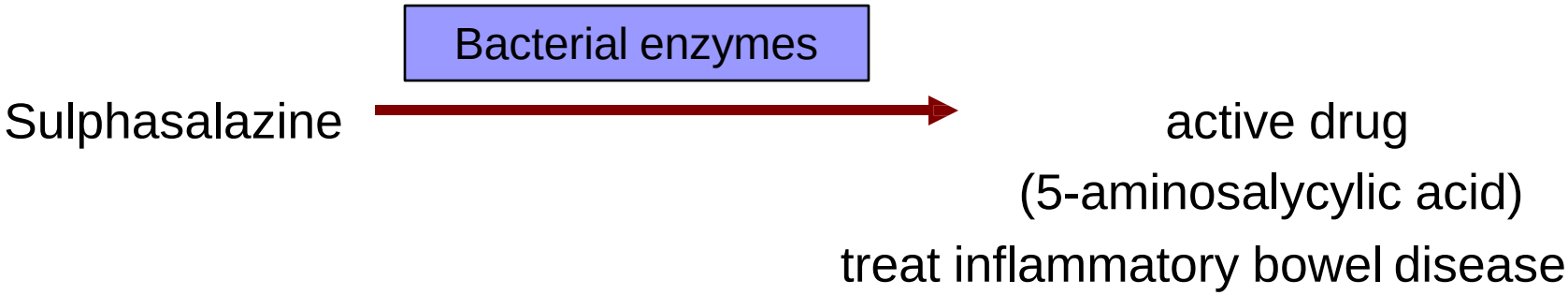
B- affect the drug dissolution or absorption e.g. weak electrolyte drug

Luminal enzymes

- The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine.
- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

I. Characteristics of GI physiology and Drug Absorption (cont.):

- The lipases may affect the release of drugs from fat / oil – containing dosage forms.
- Bacteria which are localized within the colonic region of the GIT secrete enzymes which are capable of a range of reactions.
- e.g. Sulphasalazine which is a prodrug used to target the colon.



I. Characteristics of GI physiology and Drug Absorption (cont.):

Disease state and physiological disorders

- Local diseases can cause alterations in gastric pH that can affect the stability , dissolution and absorption of the drug.
- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This may result in an increased overall rate of absorption of drugs that are absorbed in the small intestine.
- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

I. Characteristics of GI physiology and Drug Absorption (cont.):

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.
- This layer can provide a diffusion barrier to drugs.
- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

II Gastric emptying and motility:

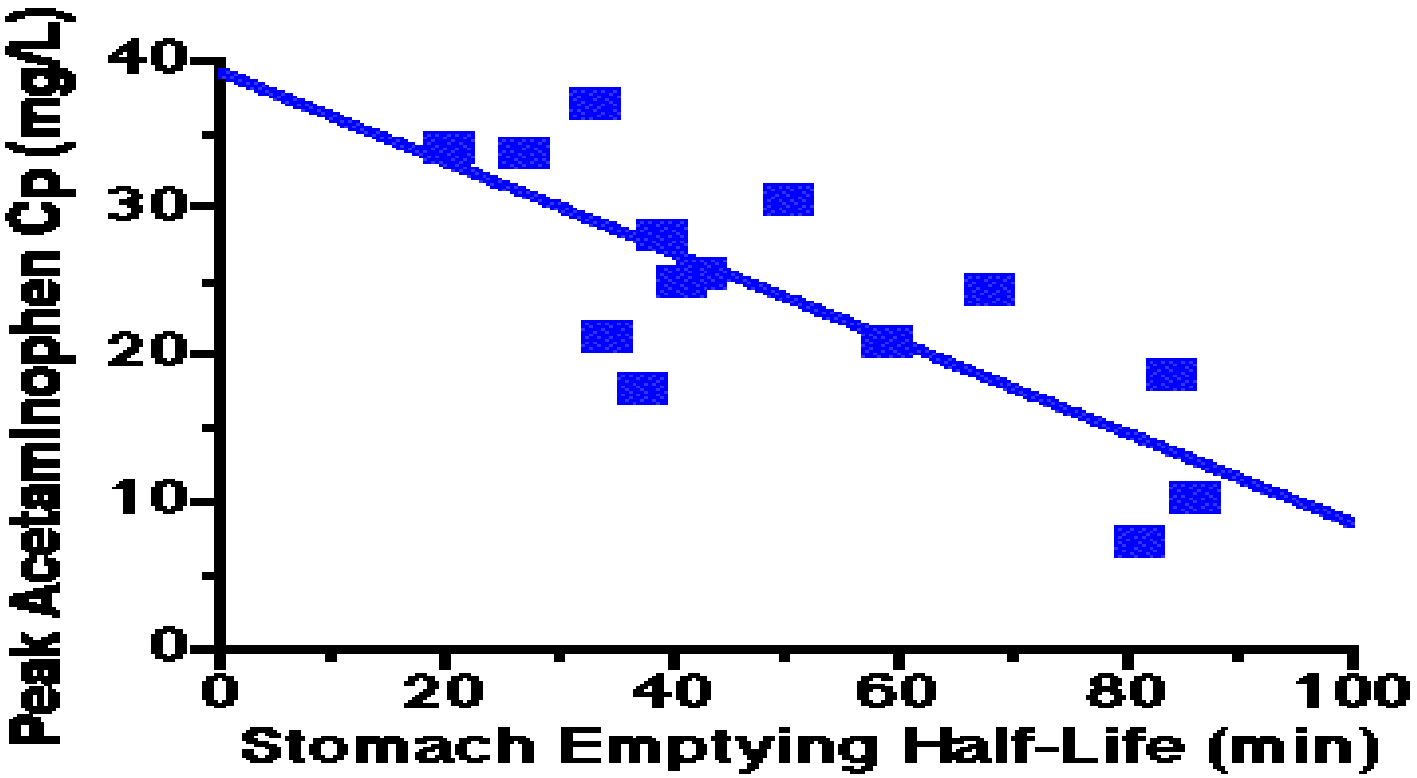
- The time a dosage form takes to traverse the stomach is usually termed: the gastric residence time, gastric emptying time or gastric emptying rate.

- Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption.

-For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration.

- Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

II Gastric emptying and motility:



Dependence of peak acetaminophen plasma concentration as a function of stomach emptying half-life

II Gastric emptying and motility:

Factors Affecting Gastric Emptying

Volume of Ingested Material	As volume increases initially an increase then a dcrease. Bulky material tends to empty more slowly than liquids
Type of Meal	
Fatty food	Decrease
Carbohydrate	Decrease
Temperature of Food	Increase in temperature, increase in empyting rate
Body Position	Lying on the left side decreases emptying rate. Standing versus lying (delayed)
Drugs	
Anticholinergics (e.g. atropine)	Decrease
Narcotic (e.g. morphine)	Decrease
Analgesic (e.g. aspirin)	Decrease

II Gastric emptying and motility:

Factors Affecting Gastric Emptying

Viscosity	Rate of emptying is greater for less viscous solutions
Emotional states	- Stressful emotional states increase stomach contraction and emptying rate -Depression reduces stomach contraction and emptying
Disease states	-Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in: hyperthyrodism
Excercise	Reduce emptying rate

III Effect of Food:

- The presence of food in the GIT can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

A- Complexation of drugs with components in the diet

e.g.Tetracycline forms non-absorable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline.

B- Alteration of pH

Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one.

III Effect of Food (cont.):

C- Alteration of gastric emptying

Fats and some drugs tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

D- Stimulation of gastrointestinal secretions

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability.
- Fats stimulate the secretion of bile. Bile salts are surface active agents which increase the dissolution of poorly soluble drugs (griseofulvin).

  Bile salts can form insoluble and non-absorbable complexes with some drugs, such as neomycin and kanamycin.

III Effect of Food (cont.):

E-Competition between food components and drugs for specialized absorption mechanisms

There is a possibility of competitive inhibition of drug absorption in case of drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist.

F- Increased viscosity of gastrointestinal contents

The presence of food in the GIT provides a viscous environment which may result in:

- Reduction in the rate of drug dissolution
- Reduction in the rate of diffusion of drug in solution from the lumen to the absorbing membrane lining the GIT.

Hence, there is reduction in drug bioavailability.

III Effect of Food (cont.):

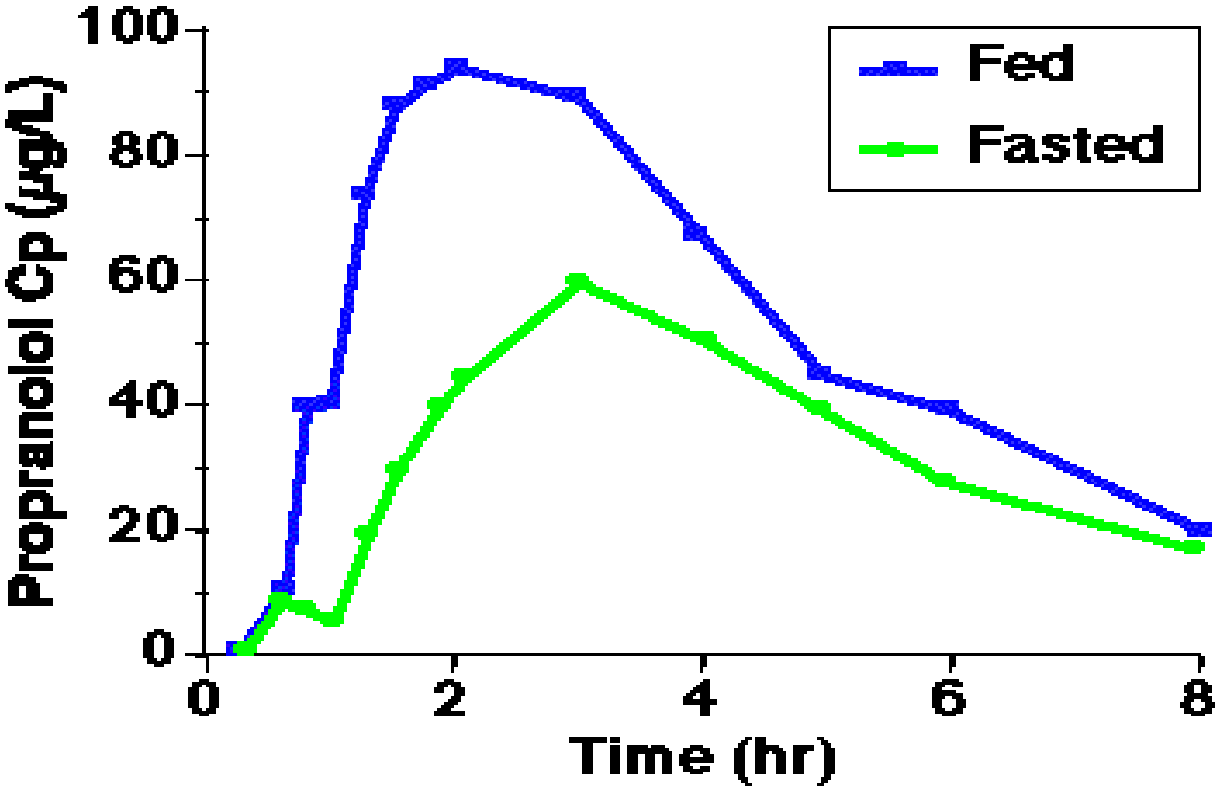
G- Food-induced changes in presystemic metabolism

- Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.
- E.g. Grapefruit juice is capable of inhibiting the intestinal cytochrome P450 (CYP3A) and thus taken with drugs that are susceptible to CYP3A metabolism which result in increase of their bioavailability.

H- Food-induced changes in blood flow

- Food serve to increase the bioavailability of some drugs (e.g. propranolol) that are susceptible to first-pass metaolism.
- Blood flow to the GIT and liver increases after a meal. The faster the rate of drug presentation to the liver; the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems become saturated.

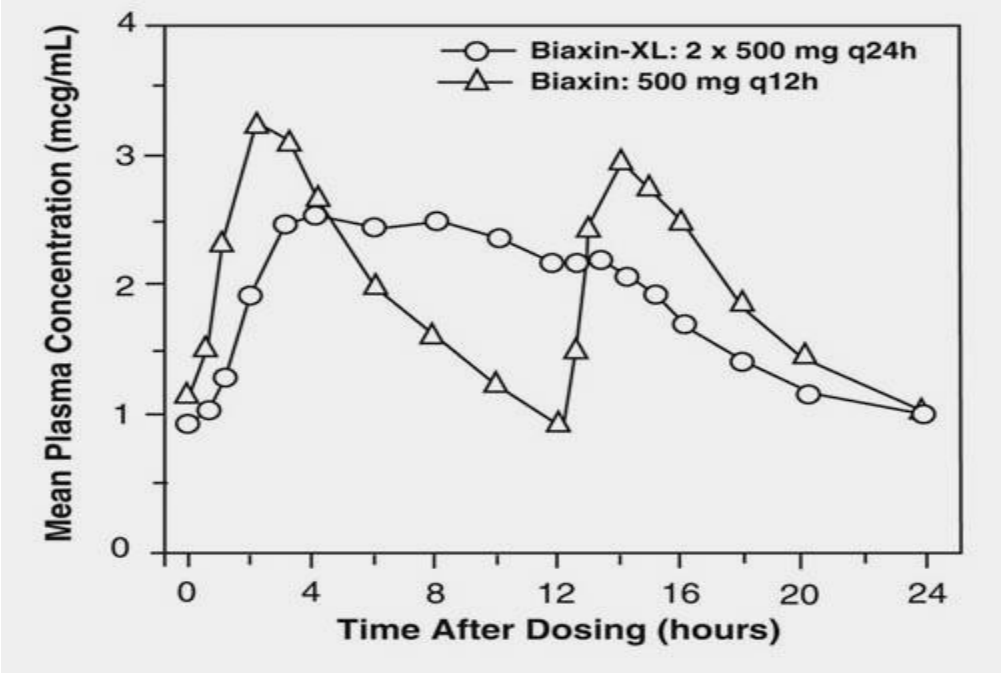
III Effect of Food (cont.):



Effect of Fasting *versus* Fed on Propranolol Concentrations

Double peak phenomena:

- Some drugs such as cimetidine and rantidine, after oral administration produce a blood concentration curve consisting of two peaks.
- The presence of double peaks has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic cycle or failure of a tablet dosage form.



Presystemic metabolism:

Definition: The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation.

Gut wall metabolism

- This effect is known as first-pass metabolism by the intestine.
- Cytochrome P450 enzyme, CYP3A, that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme e.g. cyclosporin.

-

Presystemic metabolism:

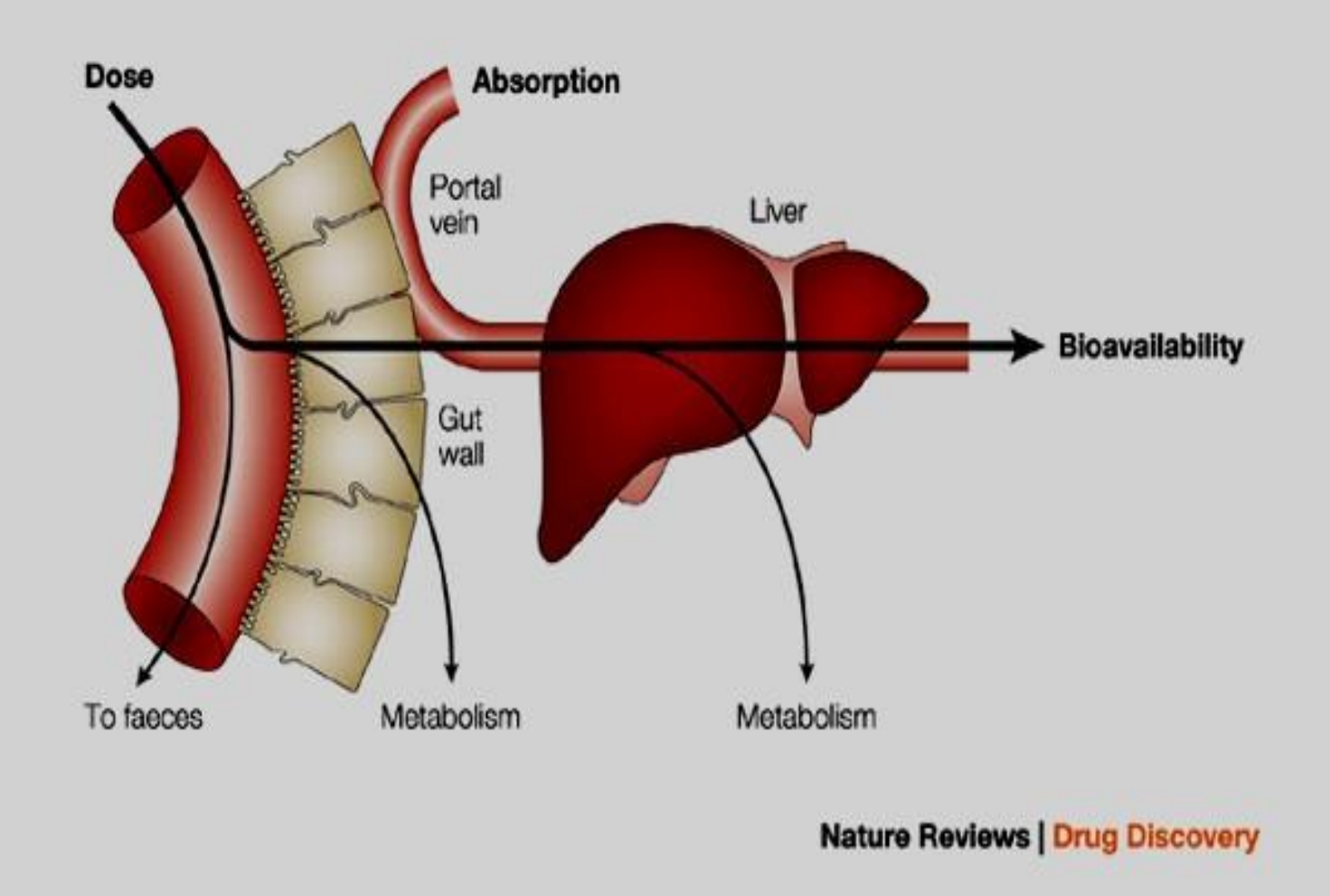
Hepatic metabolism

- After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

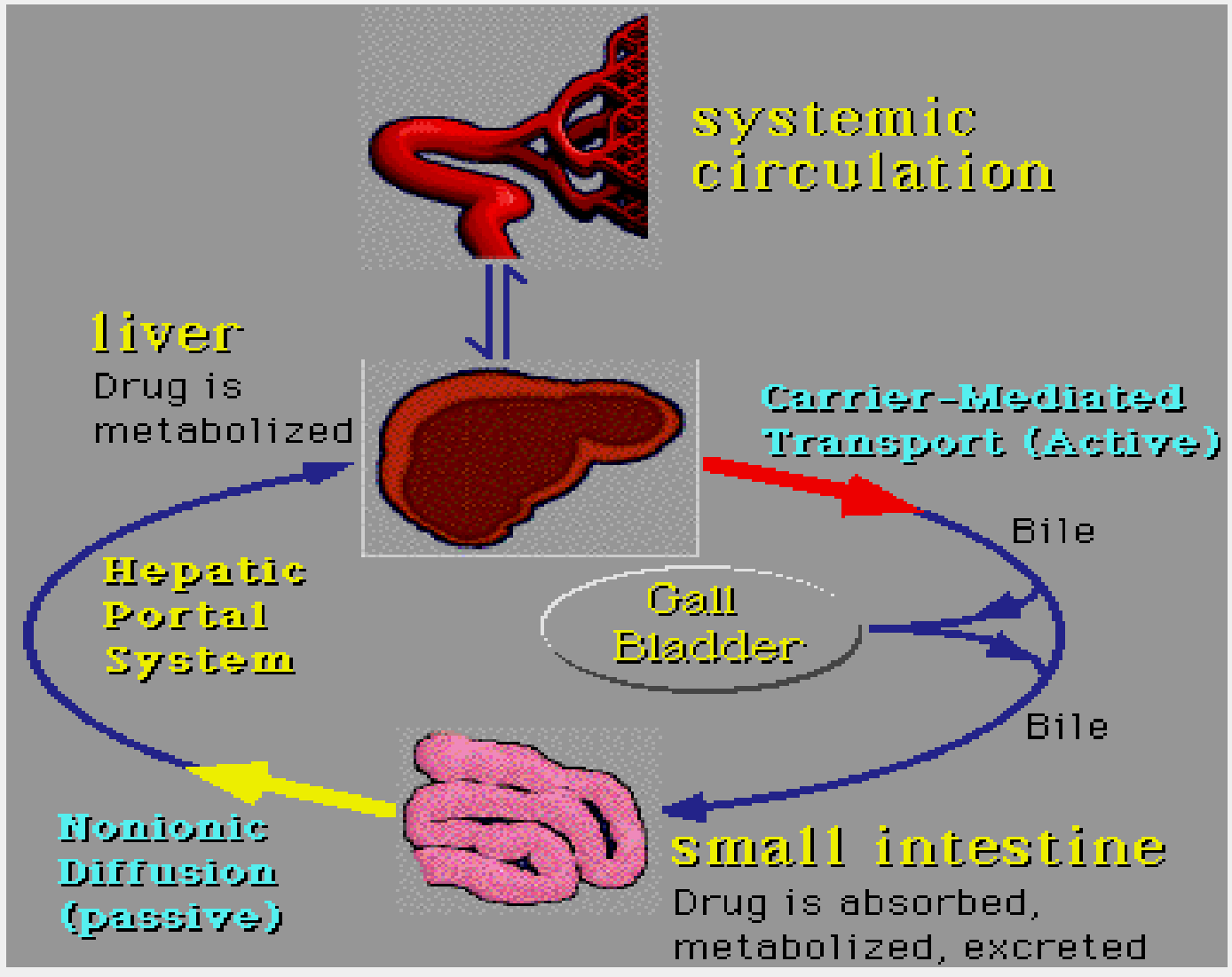
- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system.

- This *first pass* through the liver thus greatly reduces the bioavailability of the drug.

Presystemic metabolism (Cont.)



Hepatic metabolism (Cont.)



II Physical-Chemical Factors Affecting Oral Absorption:

Physical-chemical factors affecting oral absorption include:

A- pH-partition theory
B- Lipid solubility of drugs
C- Dissolution and pH
D- Drug stability and hydrolysis in GIT
E- Complexation
F- Adsorption

A. pH - Partition Theory:

- According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.

- As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (poorly-lipid soluble) form of such drugs.

- Consequently, the absorption of a weak electrolyte will be determined by the extent to which the drug exists in its unionized form at the site of absorption.

A. pH - Partition Theory (Cont.):

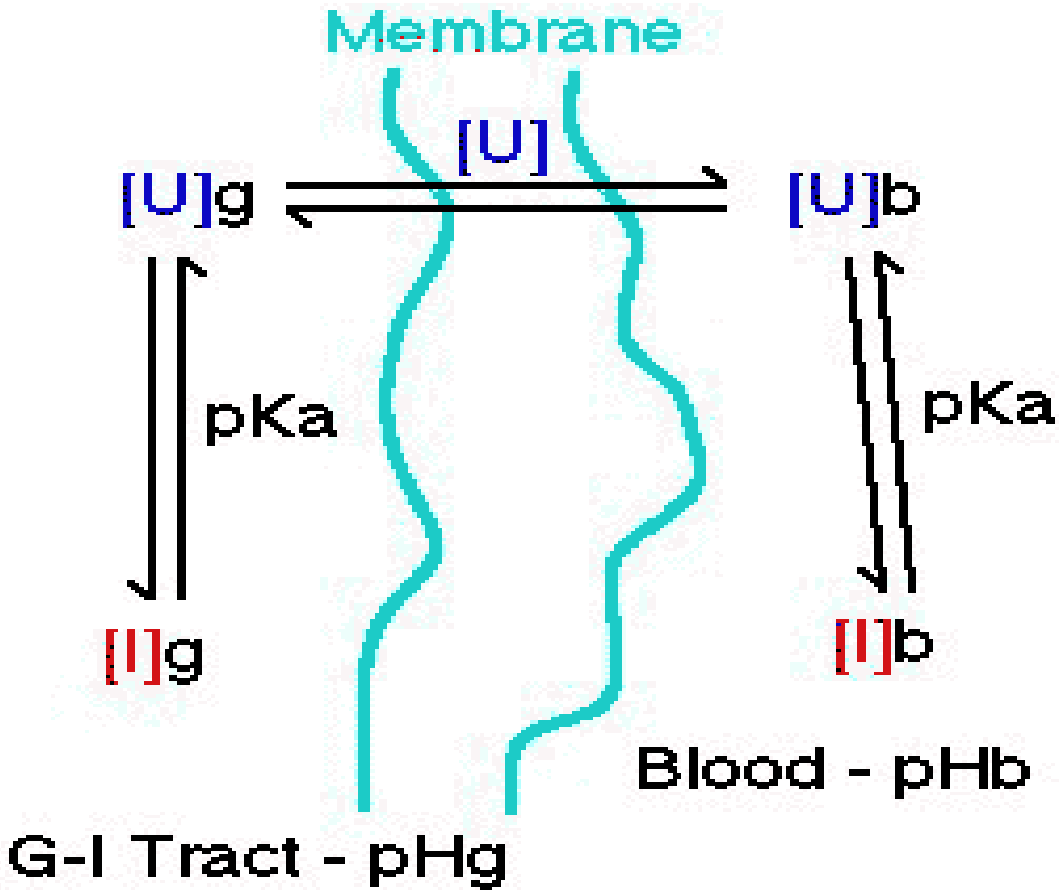


Diagram Showing Transfer Across Membrane

A. pH - Partition Theory (Cont.):

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using ***Henderson - Hasselbach equation.***

**** Weak acids (e.g. aspirin):**

$$HA \rightleftharpoons H^+ + A^-$$

$$Ka = \frac{a_{H^+} \bullet a_{A^-}}{a_{HA}} \approx \frac{[H^+] \bullet [A^-]}{[HA]}$$

Dissociation Constant equation - Weak Acids

taking the negative log of both sides

A. pH - Partition Theory (Cont.):

$$-logKa = -log[H^+] - log\frac{[A^-]}{[HA]}$$

Rearranging gives the following equation:

$$pKa - pH = log\frac{[U]}{[I]} = log\frac{[HA]}{[A^-]}$$

Henderson - Hasselbach Equation - Weak Acids

A. pH - Partition Theory (Cont.):

****Weak Bases:**

$$pKa - pH = log\frac{[I]}{[U]} = log\frac{[HB^+]}{[B]}$$

Henderson - Hasselbach Equation - Weak Bases

Limitations of the pH-partition hypothesis:

-Despite their high degree of ionization, weak acids are highly absorbed from the small intestine and this may be due to:

1- The large surface area that is available for absorption in the small intestine.

2- A longer small intestine residence time.