
Bio Pharma
Saef Dawwas

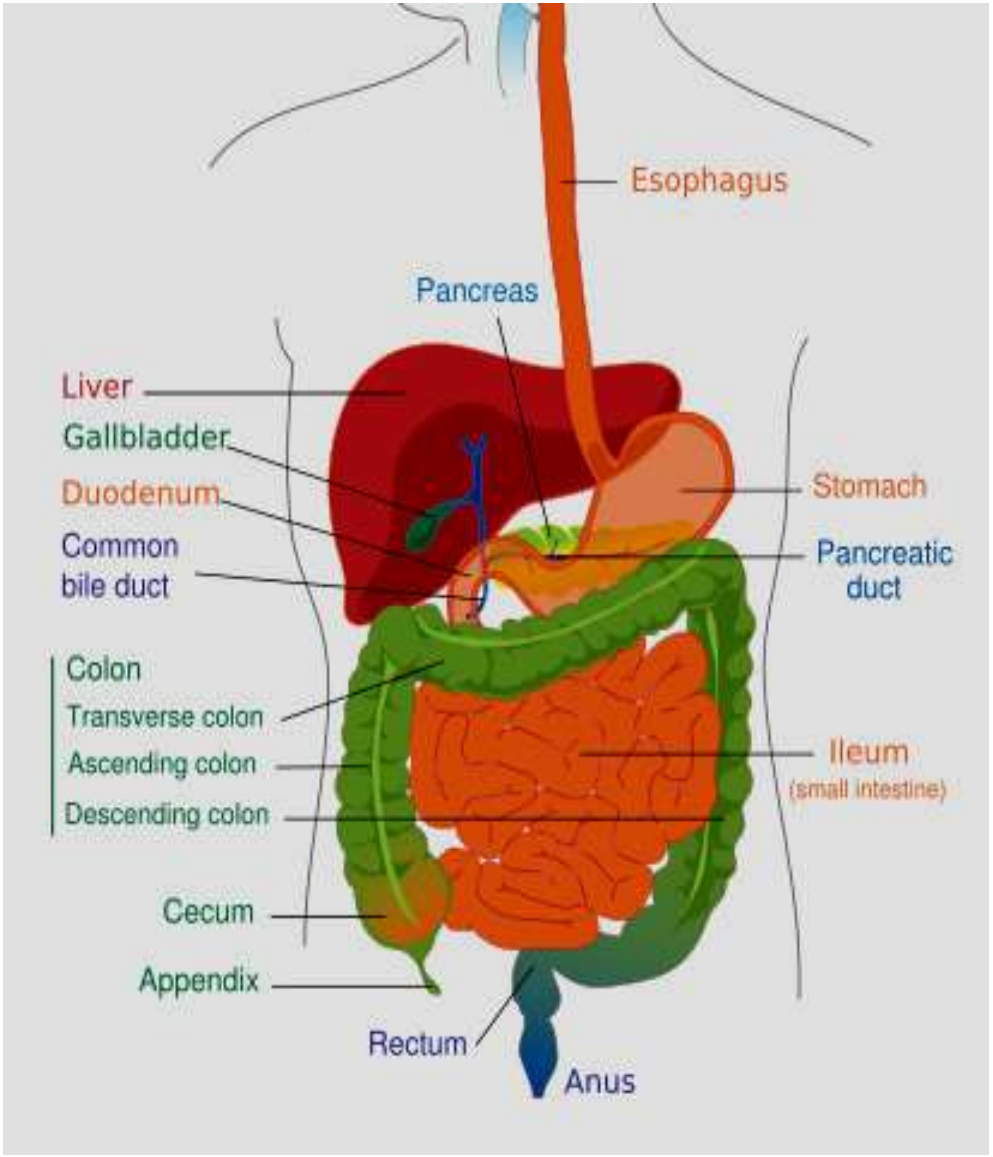
3- Gastrointestinal (GI) Physiology

- 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



اجزاء ال gi بختلفوا عن بعض بأختلاف :

Surface area

Thicknes

Ph

فهذول العوامل بأثروا على ال rate of diffusion

ترتيب حسب ال position

لما ننزل بال gi ال ph وال acidity بتقل

Gastrointestinal (GI) Physiology

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	- الامتصاص قليل	small	short, typically a few seconds, except for some coated tablets	-

العلاقة بين سمك الغشاء (membrain) وال blood supply علاقة عكسية يعني اذا كان الغشاء رقيق بكون مصدر الدم احسن فبمر الدم اكثر للغشاء فبزيد الامتصاص وال bio availability

-في الخد (buccal) الامتصاص بكون احسن لانو المواد الي بتمتص منو ما بتمر بال first metabolism

I. Characteristics of GI physiology and Drug Absorption

لما تزيد ال surface area بزداد امتصاص الدوا والاكل

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 تحتوي microvill	5 - 7	normal	good	Very large	very short,	no

I. Characteristics of GI physiology and Drug Absorption

لما تزيد ال surface area بزداد امتصاص الدوا والاكل

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

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.

-ال ph في ال gi بتختلف باختلاف الموقع
في المعدة بكون اقل اشي وفي الامعاء اعلى اشي

-في ال gi في كثير انزيمات موجودة اهمها :

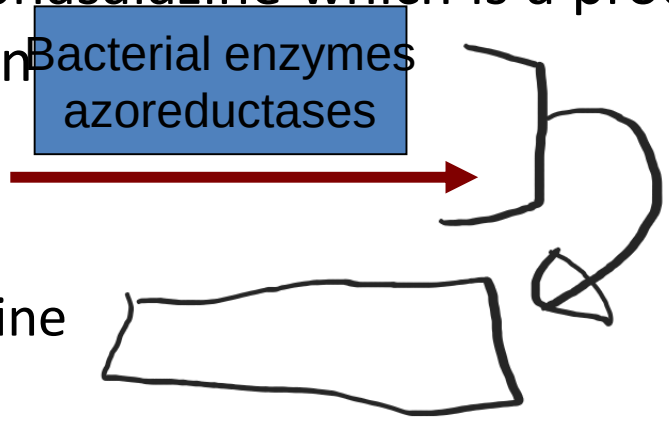
Pepsin
Lipase
Amaylase
Proteases

هذول الانزيمات بتفرزها البنكرياس وبتوديهم للامعاء الدقيقة وظيفتهم تكسير و تحليل وامتصاص البروتين والببتيد وتحويلهم ل simple amino acid

ملاحظة : بآخر السلايد في فقرة صغيرة من سطرين ما كانت مبينة عندي بالسلايد بس شرحها الدكتور انا كتبت شرحها مع شرح السلايد

I. Characteristics of GI physiology and Drug Absorption

- 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



Sulphasalazine → active drug (5-aminosalicylic acid)

Treat inflammintory bowle diseases

-اذا كان الدوا بحتوي في تركيبوا (dosage form تاعتو) على دهون او زيوت فأنو ال lipases رح بتغلبوا بتحليلهم بهاذ بأثر على امتصاص الدوا

-البكتيريا الموجودة بالقولون (زي normal flor)بتفرز بتفرز انزيمات بتحول الادوية من pro to active form

I. Characteristics of GI physiology and Drug Absorption

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.

-قص المعدة اما بكون جزئي اول كلي
كيف بعملوا قص معدة ؟

انو بخلي جزأ من المعدة موجود وبربط ال
esophaguse وال deduniem

هاذ الحكي بأدي انو بتقل مدة بقاء الدوا بالمعدة وبقل تكسيروا وامتصاصوا لانو المعدة المسؤولة عن هاي العملية عن طريق البسين فبقل ال bio availability

-وكمان البروتينات كبيرة الحجم بتتنتقل من غير تكسير فبقل ال bio availability برضو

-اما اذا الدوا موجه للامعاء او كان امتصاصوا هناك فبصير العكس

I. Characteristics of GI physiology and Drug Absorption

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.

-في ال intestinal wall. في طبقة بتحيط فيه اسمها unstirred water layer (او تسمى stagnant layer) معناها التقريبي طبقة راكدة
بتكون مزيج من المي والمخاط (mocuse) بتعمل كحماية للامعاء وكمان بتعمل حاجز لانتشار الدوا

-بعض الادوية يمكن تعمل complexation مع هاي الطبقة فبأثر على امتصاص الدوا من اي جزأ من اجزاء ال gi لل blood circulation

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

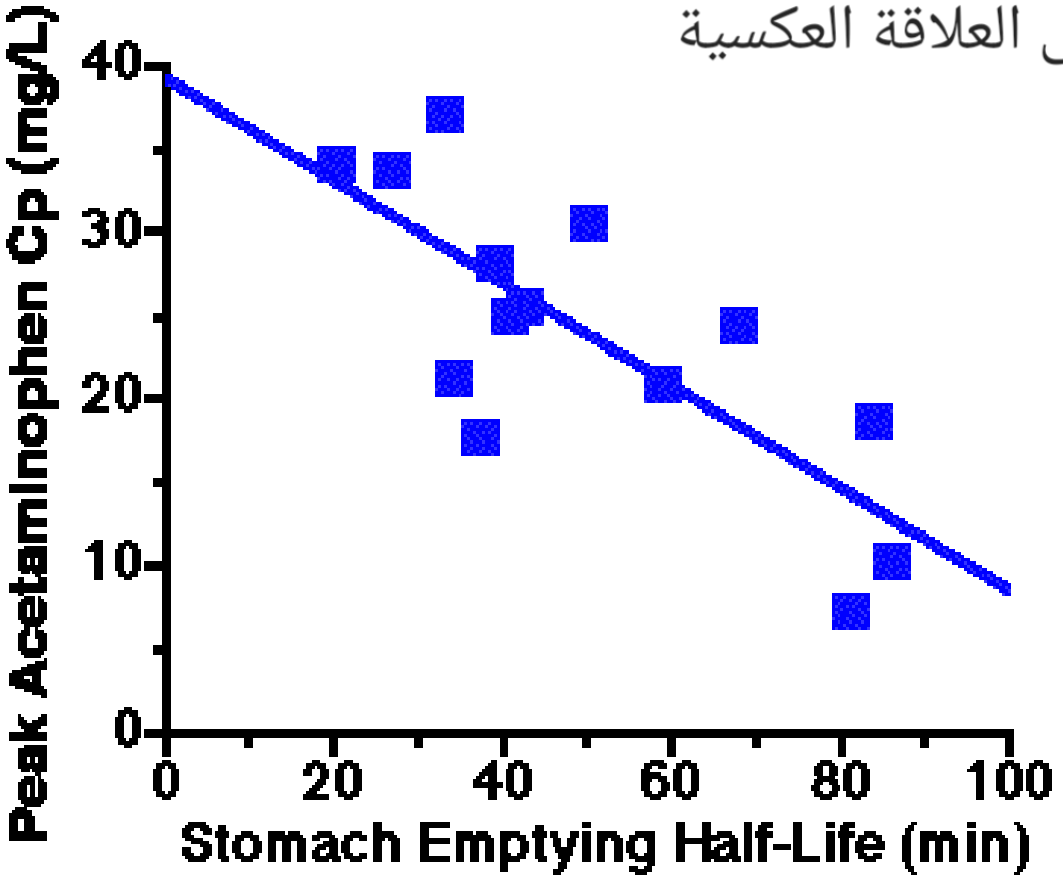
-الوقت الي بحتاجوا المعدة لتفريغ مكوناتها مهما كانت ونقلها للأمعاء الدقيقة
لما يزيد يكون احسن لأنو اغلب امتصاص الأدوية يكون الأمعاء

-العلاقة عكسية بين وقت وجود المادة بالمعدة ومعدل الأمتصاص
لما تزيد بزيد تحلل الدوا عن طريق انزيمات المعدة وبمتص اكثر بالبلازما والعكس صحيح

-بعض الأدوية بتحتاج وجودها اكثر بالأمعاء

II Gastric emptying and motility

منحنى بدل على العلاقة العكسية



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

II Gastric emptying and motility

يحتاجوا
يظلوا مدة
اطول بالمعدة
حتى يتحللوا
لمواد بسيطة

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
امراض بأثروا على ال metabolism	Disease states	-Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in: hyperthyrodism

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

شرح النقطة A

-بعض الادوية يمكن تعمل complexation مع بعض الأغذية والمواد بهاذ الأشي بقلل امتصاص الدوا لانو ما برتبط بالناقل الخاص فيه

e.g.Tetracycline

-المرضى إلى بوخذوا حديد او بوكلوا مشتقات البان بوخذوا الدوا قبل ساعة او بعد ساعتين

III Effect of Food

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.

Bile salts :

برتبط مع الأدوية ضعيفة امتصاص
بسهل امتصاصها
بتفرزوا الكبد
وينتقل للأمعاء
الدقيقة

III Effect of Food

زي ما اخذنا بالبيو كيم

شكل الدوا بشبه شكل الأكل فتنافسوا على نفس الناقل

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.

العلاقة بين dissolution و absorption طردية

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.

زي ما حكينا بأول التفريغ

Hence, there is reduction in drug bioavailability.

III Effect of Food

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.

شرح نقطة G:

-في حالة ال oral druge بكون ال metabolism بال intestine / liver فيها انزيمات بتساعد على ال elemination للدوا فما نستفيد من الدوا بس في مواد بتثبطهم بس مش دايما اشي كويس لأنو احنا محتاج تواجد الدوا بالدم بكمية معينة اذا زاد بصير في عنا سمية وبصير الدوا ضار

-امثلة على المواد الي بتثبط انزيمات الامعاء :

cytochrome P450 (CYP3A)

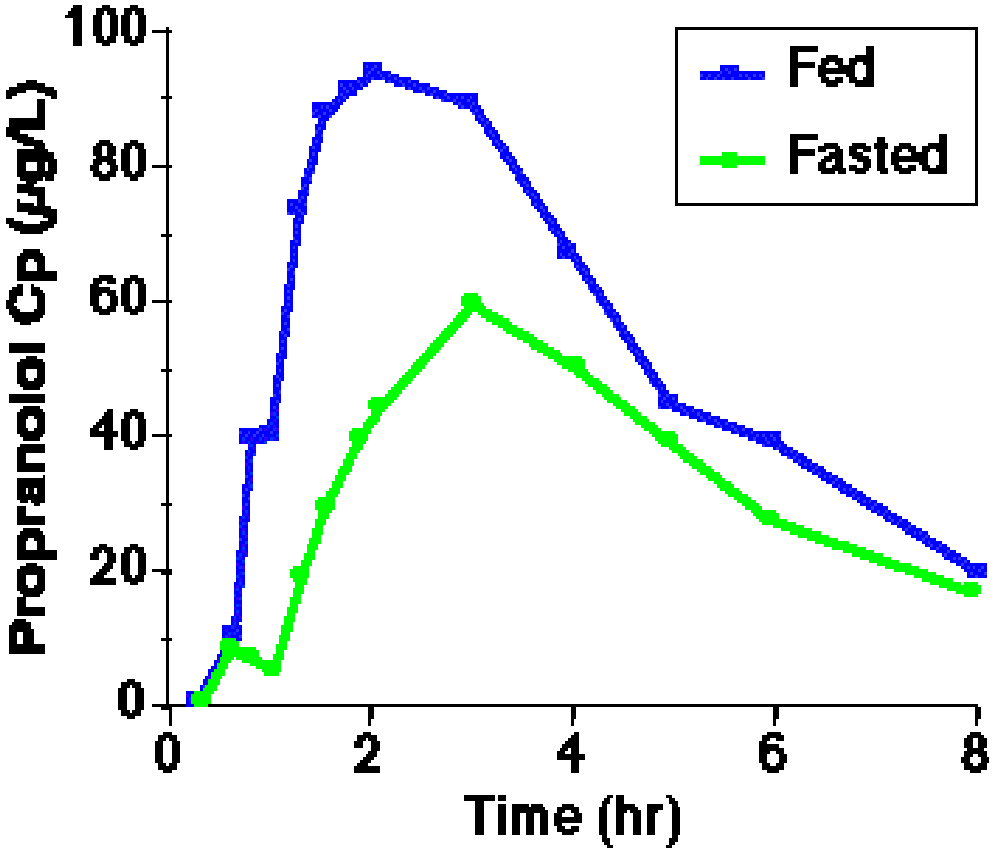
يتم افرازها من الكبد

شرح نقطة H :

-لما توكل بيوصل كمية دم كبيرة للأمعاء فبزيد الامتصاص

-لما تكون كمية الدوا كبيرة بصير saturation اسرع فالمثبطات بالكبد بتعمل بشكل اقل فكمية اكبر متهرب من الـ first metabolism

III Effect of Food



Effect of Fasting *versus* Fed on Propranolol Concentrations

كل دوا وكل اكل بنوخذوا بأثروا على المعدة بطريقة معين فهاذ الي بأثر على وقت اخذ الدوا

Effect of Food

- Timing of drug administration in relation to meals is often important. **Pharmacists** regularly advise patients to take a medication either 1 hour before or 2 hours after meals to avoid any delay in drug absorption.

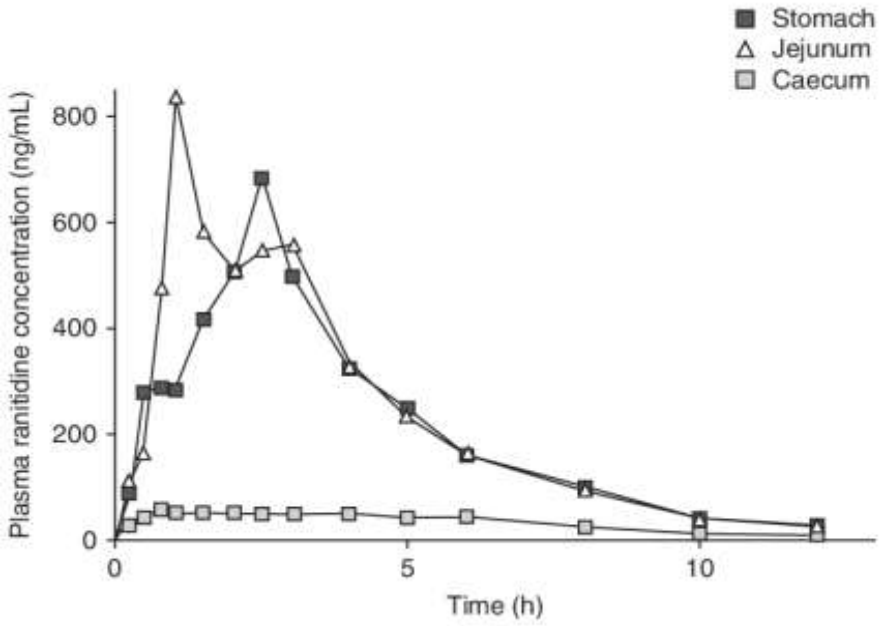
- Since fatty foods may delay stomach emptying time beyond 2 hours, patients who have just eaten a heavy, fatty meal should take these drugs 3 hours or more after the meal, whenever possible.

- Products that are used to curb stomach acid secretion are usually taken before meals, in anticipation of acid secretion stimulated by food. Famotidine (Pepcid), and cimetidine (Tagamet) are taken before meals to curb excessive acid production.

Double peak phenomena

- Some drugs such as cimetidine and ranitidine, 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 f
of a tablet dosage form



Presystemic metabolism

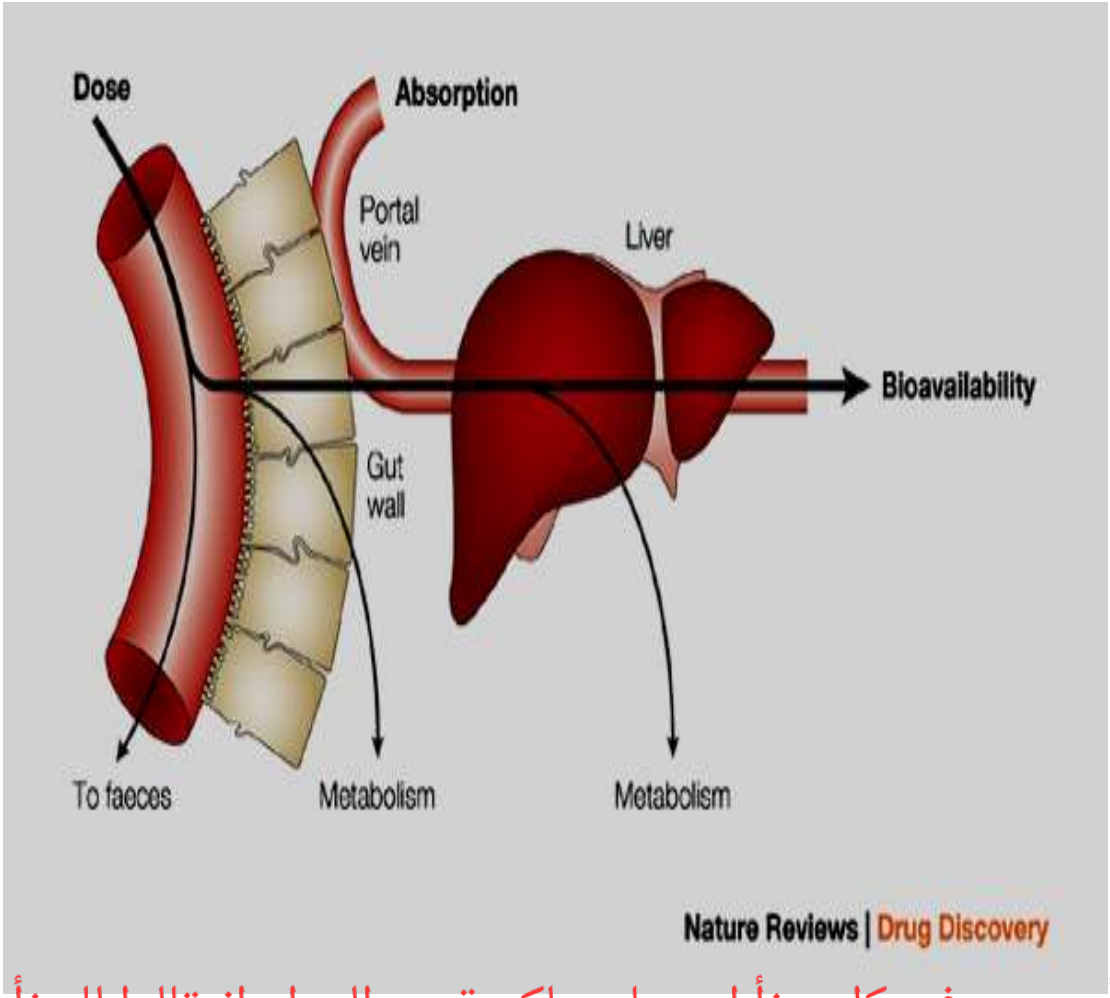
Definition:

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



بمر الدوا بكل جزأ وبصير في كل جزأ امتصاص لكمية من الدوا وانتقالوا للجزأ الي بعدو

Presystemic metabolism

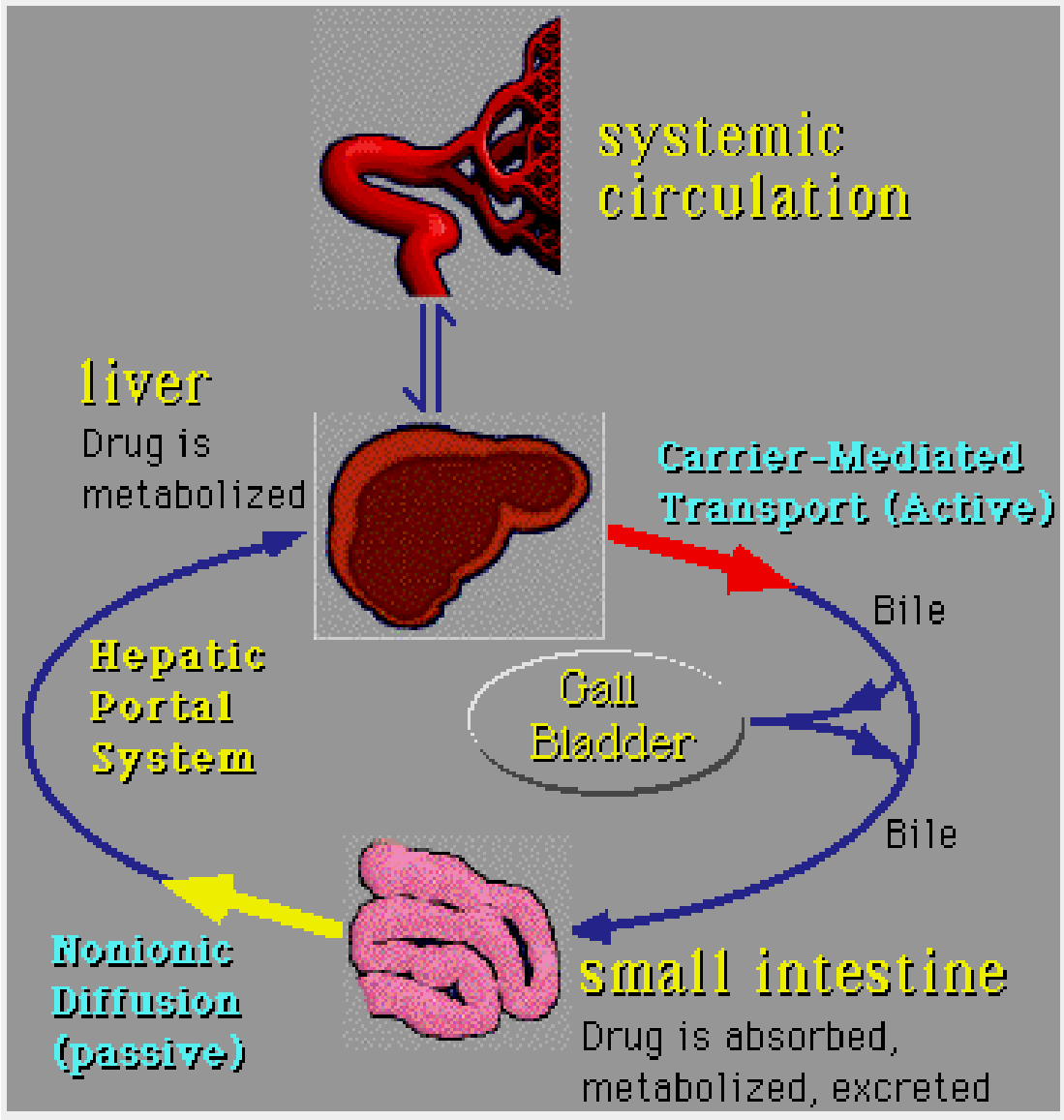
Hepatic metabolism

- 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.

Hepatic metabolism



آخر سلايد بالمحاضرة

اتمنى لكم التوفيق