Pharmacokinetics 2

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تأثير المدخول الأول

First-Pass Effect

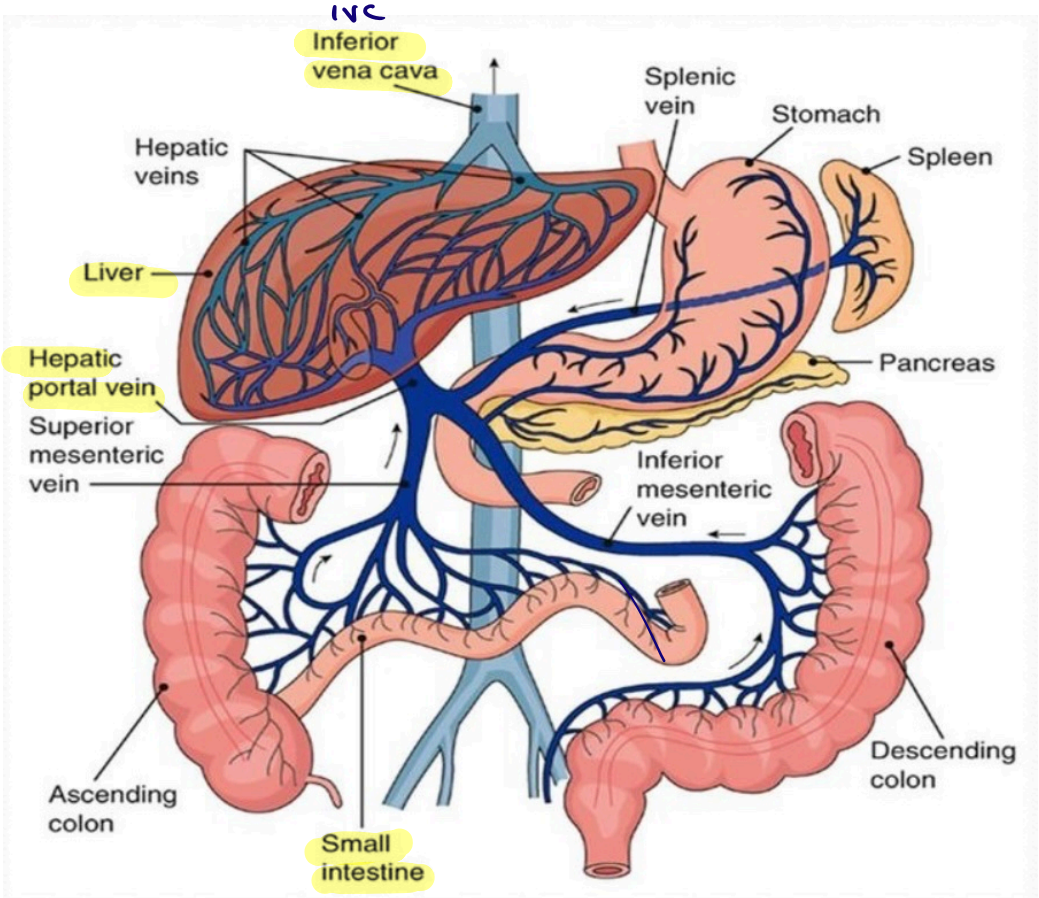
→ The passage of the drug between the lumen of intestine and the systemic circulation

So what happens to the drug passing through them?

- Drugs absorbed from the GIT must pass through the gut wall and portal vein to the liver before reaching the systemic circulation.
- The drug may be metabolized in the gut wall, portal vein, and the liver prior to entry to the systemic circulation. which causes incomplete delivery of the drug
- Or, it may get excreted by the liver through bile.

metabolism of the drug pre-circulation occurs by
- mainly by the liver.
- significantly (for some drugs) by the small intestine.
- Sometimes by endothelial cells of the portal circulation

- Anatomy of the first pass.



The Circulation that carries the drug between the gut and and liver is called "portal Circulation" mediated by the portal vein.

The portal vein doesn't drain directly into the systemic circulation, it pass through the liver and drains into the hepatic vein then into inferior vena cava that drains into the heart which pumps the drug to be distributed to all parts of the body.

So Anatomically, the first pass is between the small intestine and the systemic circulation through the portal vein, liver, hepatic vein, IVC, where metabolism of the drug also occurs.

First-Pass Effect

metabolism of the drug before reaching the action site (in the first pass) causes elimination of some of the drug dose, meaning that

- **This will lead to incomplete delivery of the dose given to the systemic circulation.**
- **This process is called "first-pass effect" or "first-pass metabolism" or "pre-systemic elimination".**

elimination before reaching systemic circulation

another thing may happen in the first pass and causes elimination of some of the drug (incomplete delivery) → prior excretion by the liver

First-Pass Effect

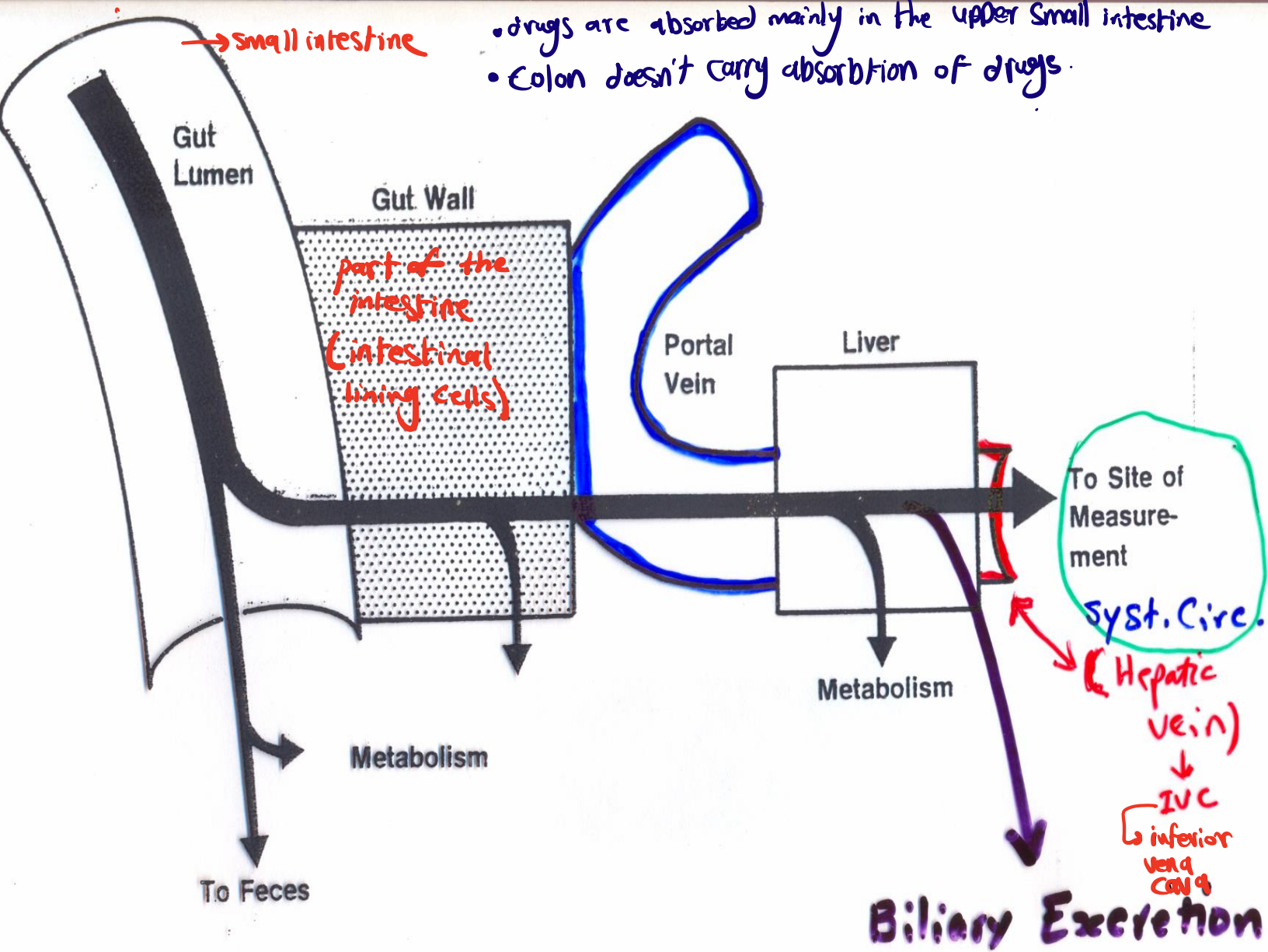
so the first path effect is important clinically, predicting the amount of the dose lost in the first pass, help us choose the right dose given to the patient orally.

- **Therapeutic blood concentration may still be reached by using larger dose. Therefore, the oral dose is usually higher than intravenous dose for such drugs.** (taking into consideration the percentage of elimination pre-circulation)
- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration.**

* assume that the first pass effect reduce the dose to the half, then you need to double the dose to achieve the therapeutic dose and effect.

→ small intestine

- drugs are absorbed mainly in the upper small intestine
- Colon doesn't carry absorption of drugs.



-Summary of the Journey of the drug in the first pass

Small intestines → portal vein → liver → hepatic vein → IVC → heart → **systemic circulation**

But as we mentioned earlier, the full dose of the drug doesn't reach the systemic circulation.

Instead, it may

1) Be not (completely) absorbed by the small intestine. why is that possible?
   taking into account lipid and water solubility, the drug may be not lipid soluble, too lipid soluble, not water soluble, only water soluble

Anyways, in the case of not absorbed drug by intestine:

↳ the drug will be eliminated to feces and some of it will be metabolised by microbial flora (Bacteria in the colon)

2) metabolised in the liver (and the gut wall) OR biliary excreted by the liver
   [first pass effect]

First-Pass Effect

- If the patient is having liver cirrhosis (تليف الكبد) and there is shunting of blood (The blood Bypasses the liver and goes directly to Circulation) by-passing the portal circulation, giving a larger dose orally will lead to substantial increases in concentration of the drug and drug toxicity.

liver Cirrhosis → fibrosis of the liver, causes disturbance of normal anatomy result in shunting of blood.
يعني بتكون في بدل دغري راح لل Circulation بدون ما يمر بالكبد
وبالتالي في نسبة ما ضلت زي ما حسبنا انضارح تضيع
والزيادة بالجرعة ما كانت بمحلها وهاد يؤدي لـ drug toxicity

The portion that is delievered to the systemic circulation is the Bioavailable part of the dose

Bioavailability

- It is the fraction of the unchanged active drug reaching the systemic circulation, following drug administration; irrespective of the route.
- It is equal to "1" or 100% following intravenous drug administration.
- After oral administration, bioavailability may be less than 1, because of:

The value of bioavailability: More than Zero to 100% (percentage) OR between 0-1 (portion)

Example: The bioavailability of the drug is 30% OR 0.3

Bioavailability

1. First-pass effect.
2. Incomplete absorption.
3. Incomplete disintegration and dissolution. of the Dosage form
4. Destruction of drug within GIT lumen by gastric acid, bacteria, ..etc. Not metabolism (Destroying the drug)
5. Faulty manufacturing of the dosage form.
6. Enterhepatic cycling.

Bioavailability

- **The area under the blood concentration *versus* time curve (AUC) is a common measure of the extent of bioavailability.**
- **Causes of reduction of the extent of absorption:**

it also has rate

quantitation of bioavailability → extent of bioavailability
measured by (conc / time) curve

The rate of bioavailability → related to speed of absorption

Both are equally important

Bioavailability

1. **The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.**

water soluble

- **Too hydrophilic drugs can NOT cross lipid membranes easily.**

lipid soluble

- **Too lipophilic drugs are NOT water soluble enough to reach the membrane (to cross the water layer adjacent to the cell).**

Bioavailability

2. Drugs may NOT be absorbed because of the presence of a reverse transporter (P-glycoprotein) that pumps the drug out of the gut wall cells back into the gut lumen.

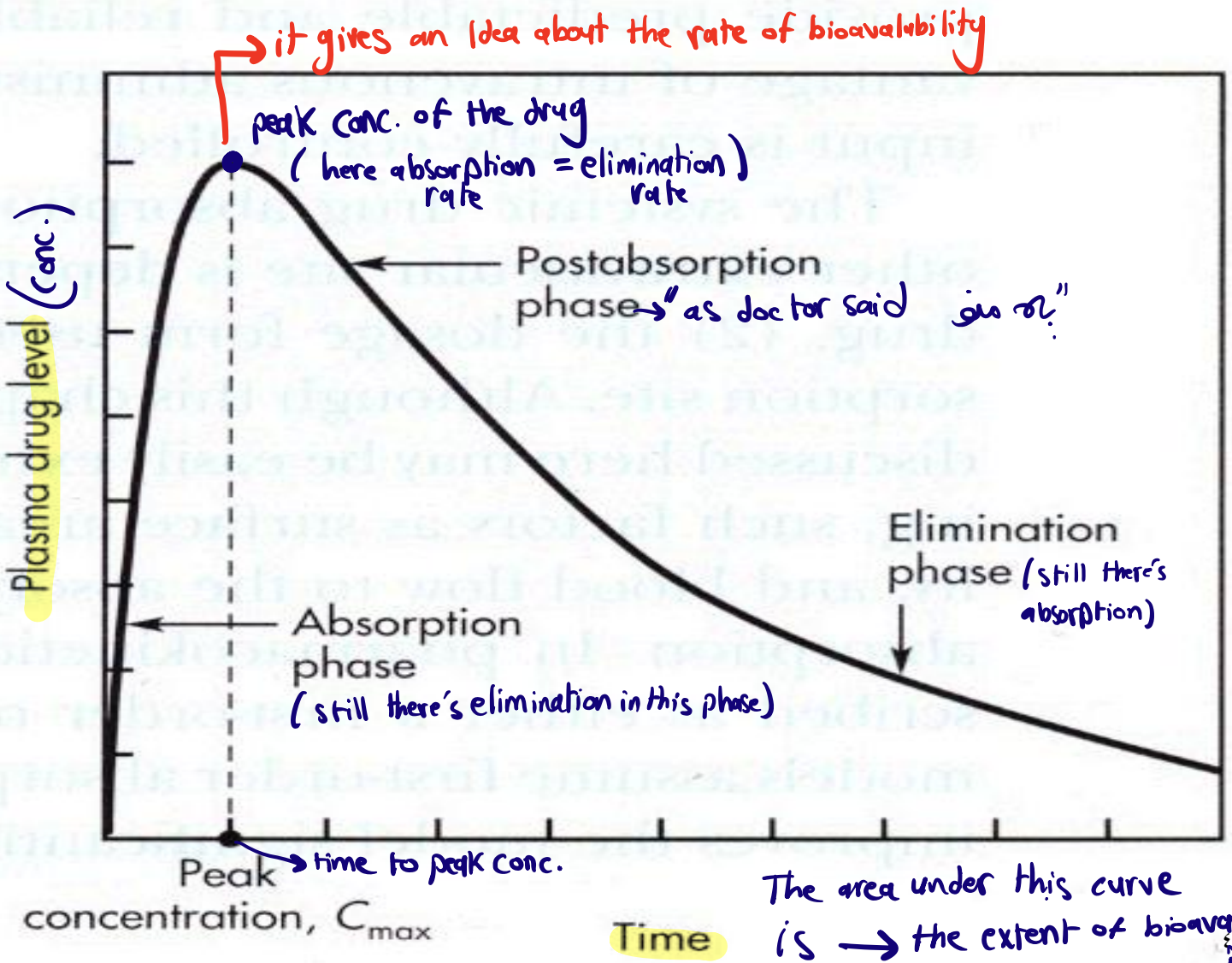
its main duty to protect the body from toxins by preventing those foreign bodies from reaching the circulation

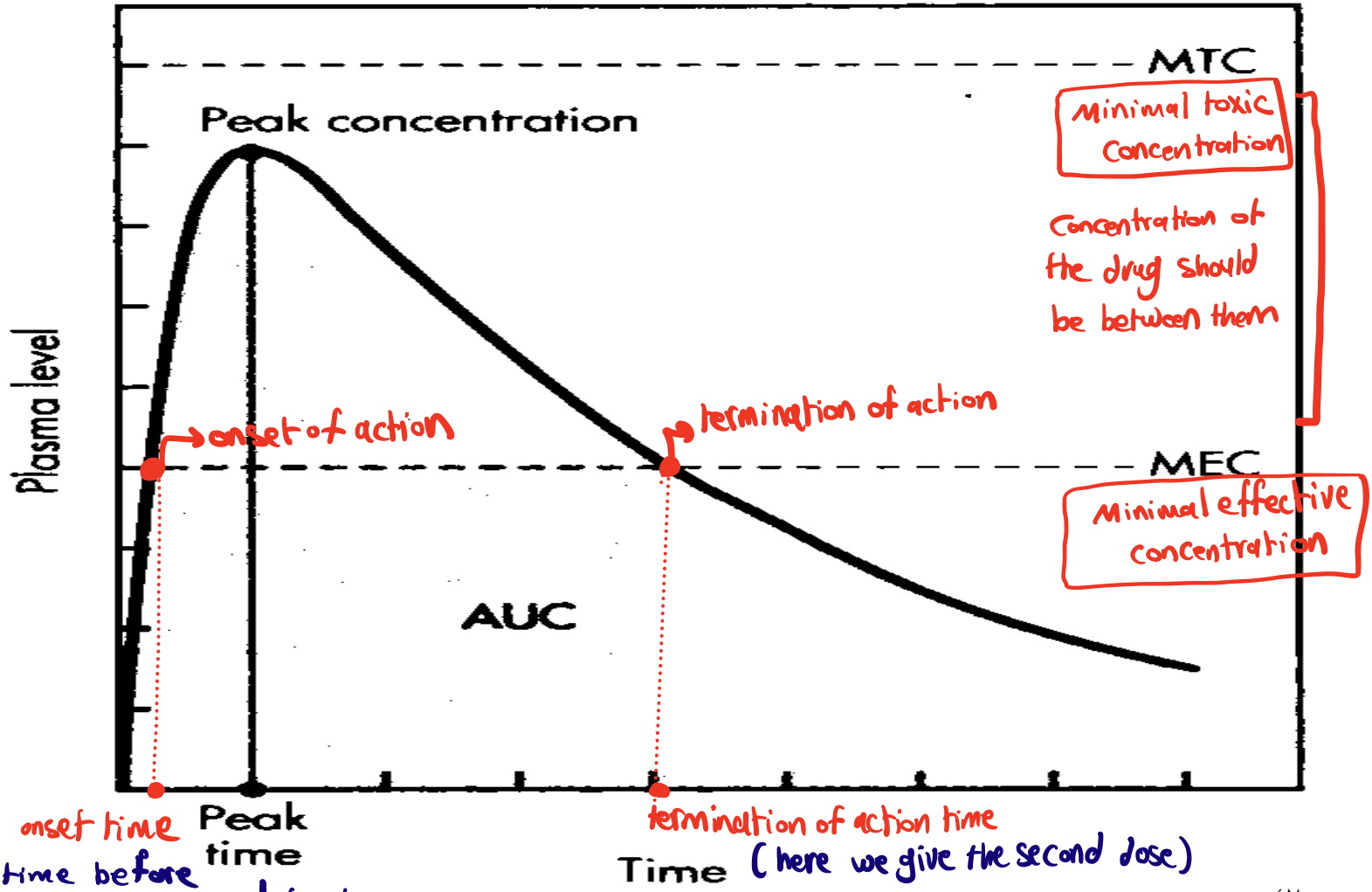
could be a drug

Bioavailability

- **Inhibition of the reverse transporter by the use of some drugs and grapefruit juice, may be associated with substantial increase in drug absorption and thus bioavailability.**
- **Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.**

1 cup shuts P-glycoprotein 36 hours


it gives an idea about the rate of bioavalubility
peak conc. of the drug
(here absorption rate = elimination rate)
Postabsorption phase → "as doctor said 🙄"
Elimination phase (still there's absorption)
Absorption phase
(still there's elimination in this phase)
Plasma drug level (conc.)
Peak concentration, C_{max}
time to peak conc.
Time
The area under this curve is → the extent of bioavailability
(How much the drug is absorbed)


MTC
Minimal toxic Concentration
Peak concentration
Concentration of the drug should be between them
Plasma level
onset of action
termination of action
MEC
Minimal effective concentration
AUC
onset time
Peak time
termination of action time
Time (here we give the second dose)
(time before onset time called lag time which is between the time of administration and the onset of action)

Effect of First-Pass Effect on bioavailability

- The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):
- ER = $Clearance_{liver}$/ Blood flow to the liver (90 L/hour in a healthy 70 Kg man).

$$ER = Cl_{liver}/Q$$

- Bioavailability (F) can be predicted from the extent of absorption (f) and ER.

$$F = (f) . (1 - ER)$$

For later

Effect of First-Pass Effect on bioavailability

- **A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%.**
- **Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.**

for later

التكافؤ الحيوي

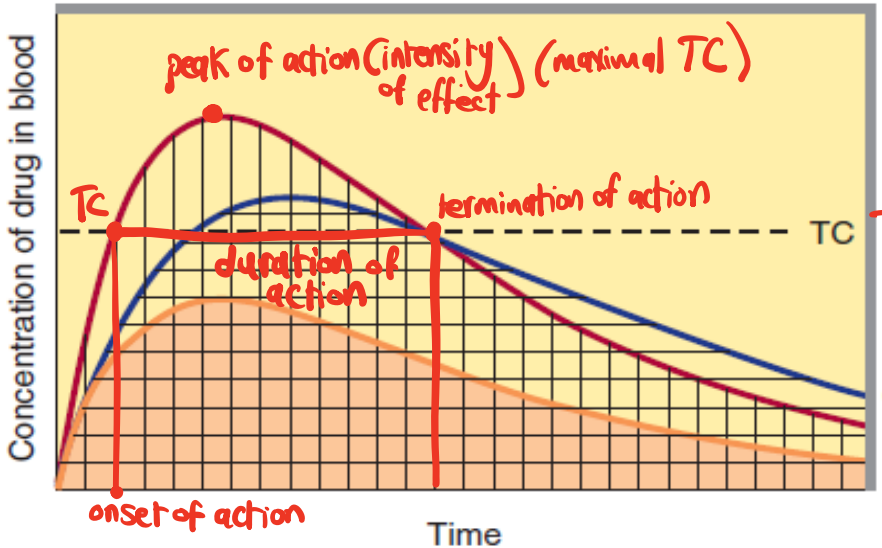
Bioequivalence

نفس الدواء بس التاني تصنيع بلد بوقت بمكان تاني

Comparing two drugs that are made in two different places, is the second one equivalent to the original one in the extent and rate of bioavailability?

- This term is used to compare the rate and extent of absorption of different formulations of the same active drug.
- The extent of absorption is measured by AUC, and the rate is assessed by C_{max} (peak concentration) and T_{max} (time to peak concentration).

Rate of B is also less than that of A



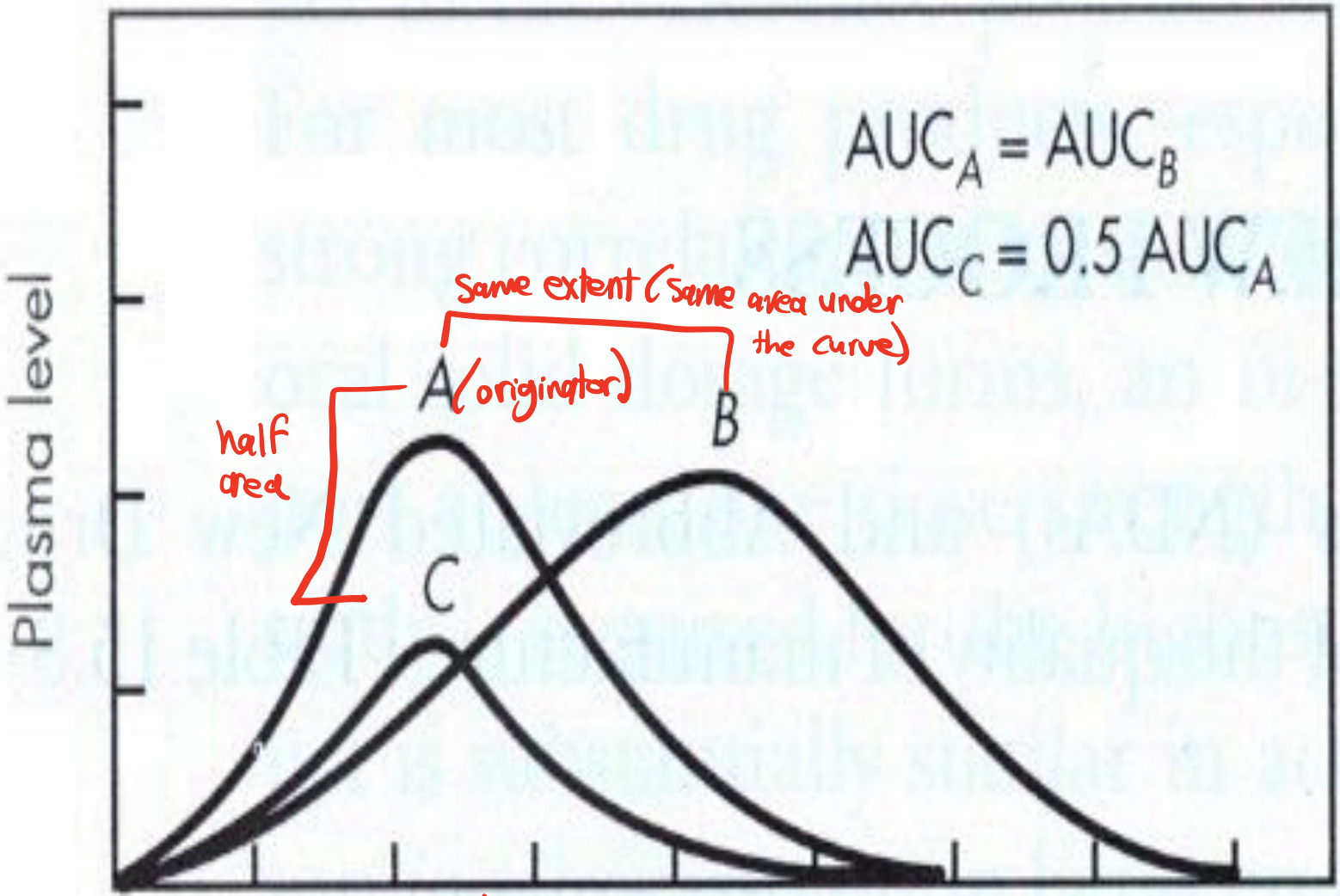
C: peak conc < original
• time to peak delayed
"smaller peak, longer time to peak"

A: Drug rapidly and completely available
B: Only half of availability of A but rate equal to A
C: Drug completely available but rate only half of A

• duration of action

The result: The rate is not equivalent though the extent is the same looking at the area under the two curves

FIGURE 3-4 Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.



* we don't want the second drug to be more bioequivalent than the originator

A is always the originator