Lecture 14 (29-Jun-2024)

In this course we will continue talking about

***Metabolism** (Metabolic rxn)

Any chemical rxn done by enzymes (especially liver enzymes) on any chemical structure (endogenous or exogenous)

***Prodrugs**

Medicinal compounds that are inactive and they need to be activated in vivo.

***Theories of Drug Action**

Try to answer why do we have agonists and antagonists

(Both agonists and antagonists have *affinity to their receptors)

***Affinity:-** Drugs tend to bind and form complexes with their receptors

For some chemical structural reasons, some molecules bind with their receptors and they produce response (we call them agonists) while others bind with their receptors and they produce no response (we call them antagonists/blockers/inhibitors (bind to the receptor and prevent agonists to bind to the receptor)).
Why do we have agonists and antagonists?
We have certain structural features in the drug make it agonistic or antagonistic.

Metabolism

What is the most important organ that performs metabolic rxns is The liver

Where? The liver (the main site) (we might see metabolic rxns in other organs (kidney, plasma, skin or brain)

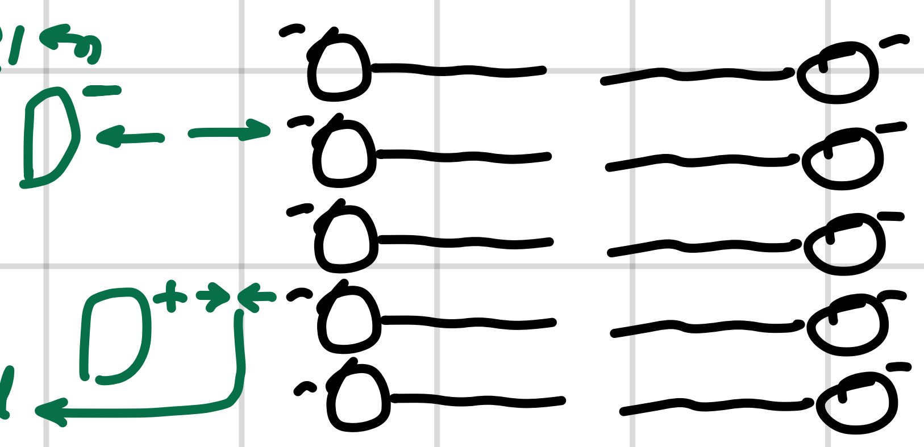
Why? Detoxification (To terminate the biological activity of organic molecules)

How? By enhancing hydrophilicity (↑Hydrophilic → ↓Toxic)

Why does hydrophilicity terminate the biological activity

For any organic molecule to cross the physiological membrane it has to have certain optimum partition coefficient, and has to be unionized

1 Unionized



رح يتنافر مع ال -ve charge الموجودة عال phosphate heads ←

(repulsion)

its adsorbed at phosphate head

(في الحالتين إذا كانوا charged مارح يعبروا ال physiological membrane)

2 has optimum partition coefficient

(must be soluble in water and oil) ذائبية مشتركة

يشبع ال oil بعدين بصير يوزع حاله عالميّ

optimal partition coefficient $P = 100$

$\log P = 2$

$$P = \frac{[S]_o}{[S]_w} = 100$$

must be buffered at pH= 7.4-7.5

for pharmacological use is n-octanol

similar to phospholipid ←

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Golden number

$P \simeq 100$ ($\log P = 2$) will pass through the membranes → very wide volume & distribution

الدم حجمه 5L لو قلنا إنه ال volume of distribution is 5L معناته الدوا تبعنا موزع بالدم فقط مش قادر يطلع برا ال blood vessels.
حجم ال interstitial fluid = 40L لو قلنا إنه ال volume of distribution is 40L معناته الدوا تبعنا well distributed (طلع من الدم ووصل لل interstitial fluid)
إذا كان دوانا عنده p=100 (logP=2) فبنعرف انه قادر يعبر كل ال body compartments من ضمنهم أصعب compartment اللي هو ال brain (إذا الدوا عبره معناته ماضل إشي ما عبره)

$P < 100$ ($P = 10, 50, 80$) ← إذا عملنا المركب تبعنا very hydrophilic وعنده ذائبية عالية بالمي
كل ما ابتعدنا عن $p = 100$ كل ما حبسنا الدوا أكثر داخل ال plasma ومنعنا عبوره عبر ال membranes

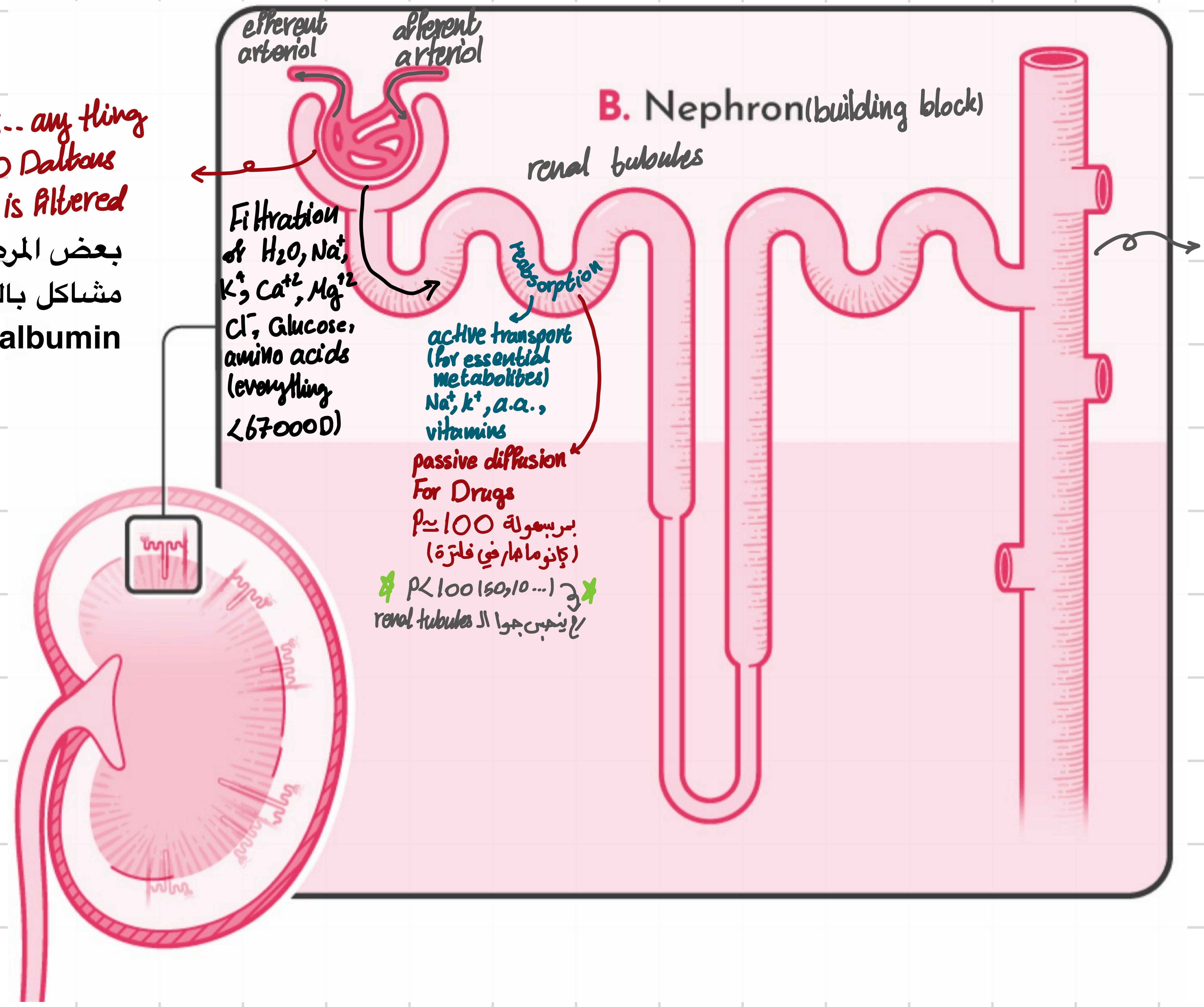
The more hydrophilic a drug is → 1/ The more it gets trapped inside the blood (plasma)
(بيحد من انتشاره)

molecular w.t = 300-500 by both mechanisms →

2/ Once it's filtered inside the renal tubules it gets trapped there to be eleminated (شجعت التخلص منه عن طريق ال urine) molecular w.t < 300

3/ Easier to be secreted in the bile molecular w.t > 500 → large molecules
In liver there is active secretion into the bile
Molecules that are hydrophilic and polar they tend to be actively secreted in the bile

ال Bile: هي المادة الصفرا اللي بتطلع من الكبد بتروح عال gallbladder وبعدين بتنزل عال intestine



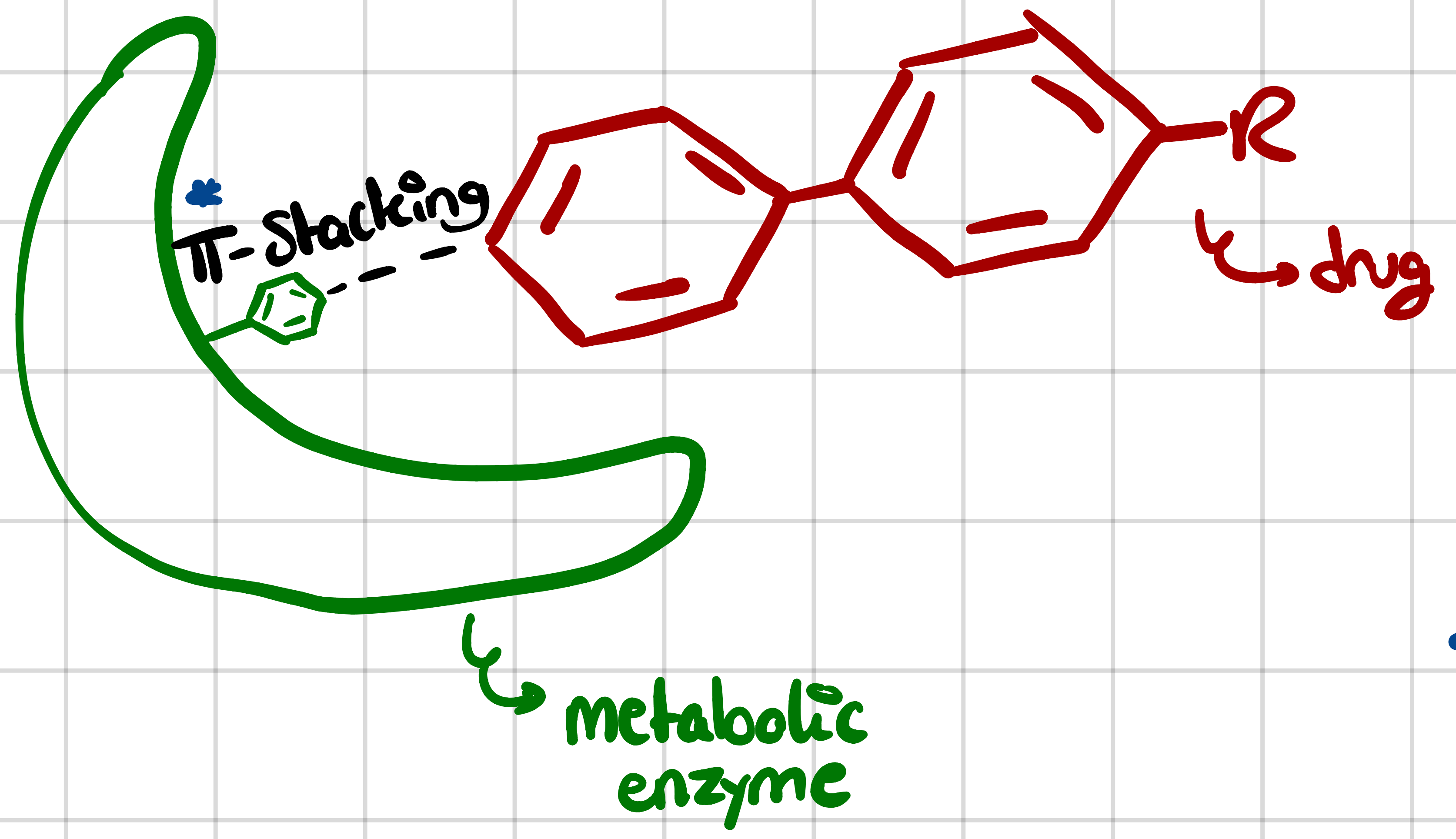
in Glomerulus.. any thing below 67000 Daltons (Albumin size) is filtered
بعض المرضى اللي بكون عندهم مشاكل بالكلى ممكن ال albumin يمر ويطلع بال urine

Collecting duct

Metabolism occurs in two steps:

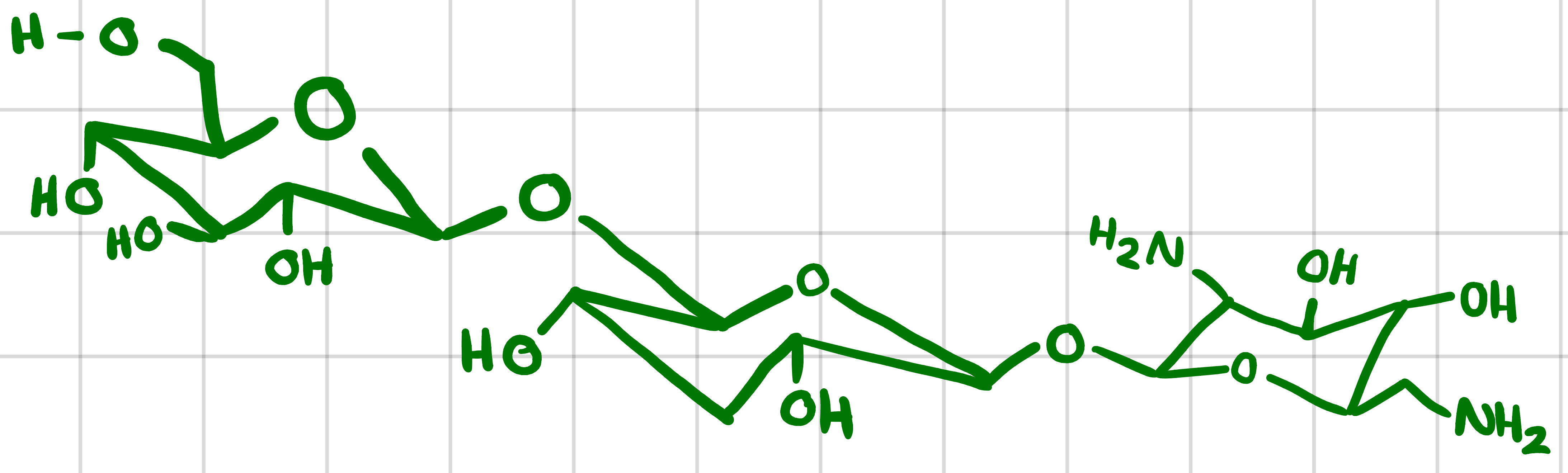
- Phase I metabolic rxns (Functionalization) (add functional group) (most often $-OH$)
- Phase II metabolic rxns (Conjugation) (+ Glucouronic acid)

- In enzymology when we loose affinity we loose turnover, what is turnover?
  - if glucokinase has a turnover of 3000, it means that it transforms 3000 glucose molecules to glucose-6-phosphate -high affinity to glucose- (سريع)
- This is not the case in metabolic enzymes
- Why are they called "mixed function enzymes"?
  - because they are not specific (selective), they can oxidize phenytoin, phenobarbital, caffeine, metronidazole…etc = they can deal with numerous substrates
  - This is good for us because we are not exposed to a single polymer, we get in contact with many types of toxins from everything so we need metabolic enzymes that can deal with any toxin
  - This type of enzymes have a large binding pocket (catalytic pocket) and handles the substrates with one or two interactions only (e.g: pi stacking in phenytoin)



- didn't interact with the drug with 5 interactions like glucokinase did, just one interaction -or 2-
- non specific ⇒ binds to any drug with ⌬

- These enzymes also loose the "high turnover" found in glucokinase
  So if u want to find metabolic products in urine you will need to wait for after 6 hours of exposure to drug without renal elimination, but if the drug undergoes quick renal elimination you will not see it in urine.
  An example is gentamicin:



Gentamicin

- Aminoglycoside (سكر) Anti-biotic
- Very Hydrophillic (OH_s)
- Cationic (NH_2) -Positivily charged-
- not active orally, given parentrally
- found in urine ⇒ doesn't get reabsorbed
  - renal tubules بنحبس بال -

- Doesn't get metabolized in urine
- Used for UTI
- its metabolized by bacteria in a form of resistance but the liver doesn't metabolize it

- So metabolism doesnt happen rapidly because mixed function oxidases are non specific (Slow enzymes)
  - مقابل فقدانهم للـ Specificity صاروا بطيئين -

- Other compounds like phenytoin, phenobarbital..etc which are lipophilic, they're reabsorbed when they reach the renal tubules
- فترة تعرضها للـ metabolism طويلة نسبياً (6 hours+)
  بعدها منبلش نشوفها بالـ urine

B) Microsomal Oxidases - Slow, non Specific)

- If you homogenize the liver (طحنته) you will see that the fine particles of the liver are still metabolically active for up to 6 hours provided that you put it in proper conditions (e.g proper buffer, isotonic solution, presence of glucose, bubbled oxygen…etc), these particles that maintain metabolic activity are called microsomes
- So when we say microsomal oxidases we mean liver oxidases (they dont come from anywhere other than the liver) → Phase 1 metabolic reactions only happen in liver

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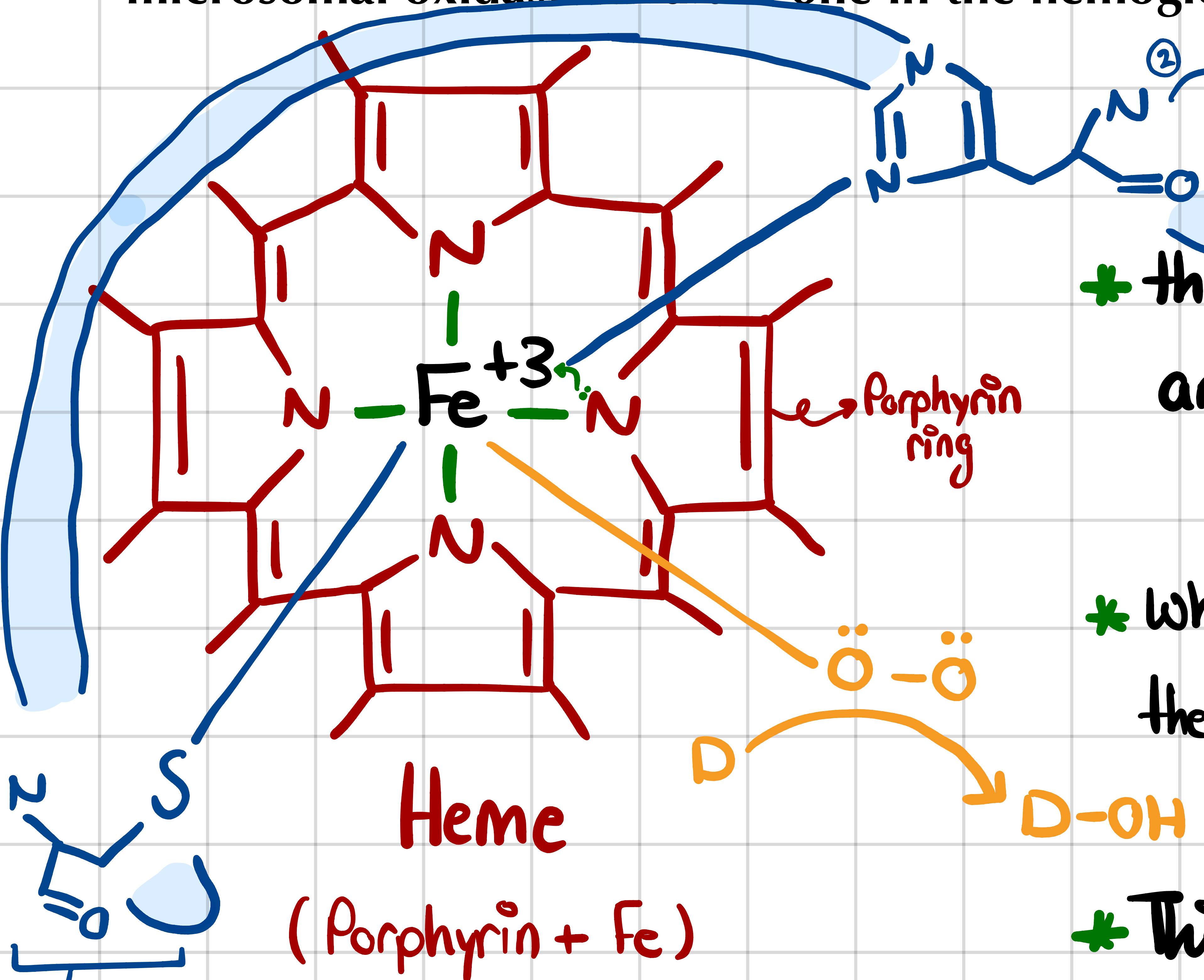
C) Cytochrome P450 isoenzymes

- They all have a protein part and a non protein part (co-factor), and they all differ from each other by their protein parts and they all have the same cofactor which is the heme (similar to the one in hemoglobin)
- The difference between the heme in the cytochrome p450 or mixed function oxidases or microsomal oxidases and the one in the hemoglobin is the iron atom → Ferrous (Fe^{+2}) in hemoglobin → Ferric (Fe^{+3}) in Cyp450



② or it can bind with other A.A (e.g: Histidine) depending on Cyp450

① Amino acid with S group ⇒ Cysteine (from protein structure)

- the bonds joining an e^- donor ($\ddot{N}$) with an e^- acceptor (Fe^{+3}) are Coordinate Bonds (Strong bonds)
- when multiple Coordinate bonds are linked to the same atom its called Chelation

- This Fe^{+3} can form 6 Coordinate bonds - it has 6 empty orbitals - :
  - 4 with the porphyrin
  - the other 2 bonds hold the cofactor (heme) to the protein structure (2 possibilities) (5th)
  - the 6th bond will be with Oxygen gas (which we breathe) its given to the drug when its Oxidized with an OH

- Why is it called Cytochrome p450?
  - Cyto: Cell
  - Chrome: pigment
  - P450: the cellular pigment that absorbs light at $\lambda = 450$ nm (red colored)

inc. in redness when CO is added
bc heme has more affinity to it than O_2
(thats why its toxic bc it binds to heme → Cyp450)