تفريغ فارما ١

اسم الموضوع: Distribution

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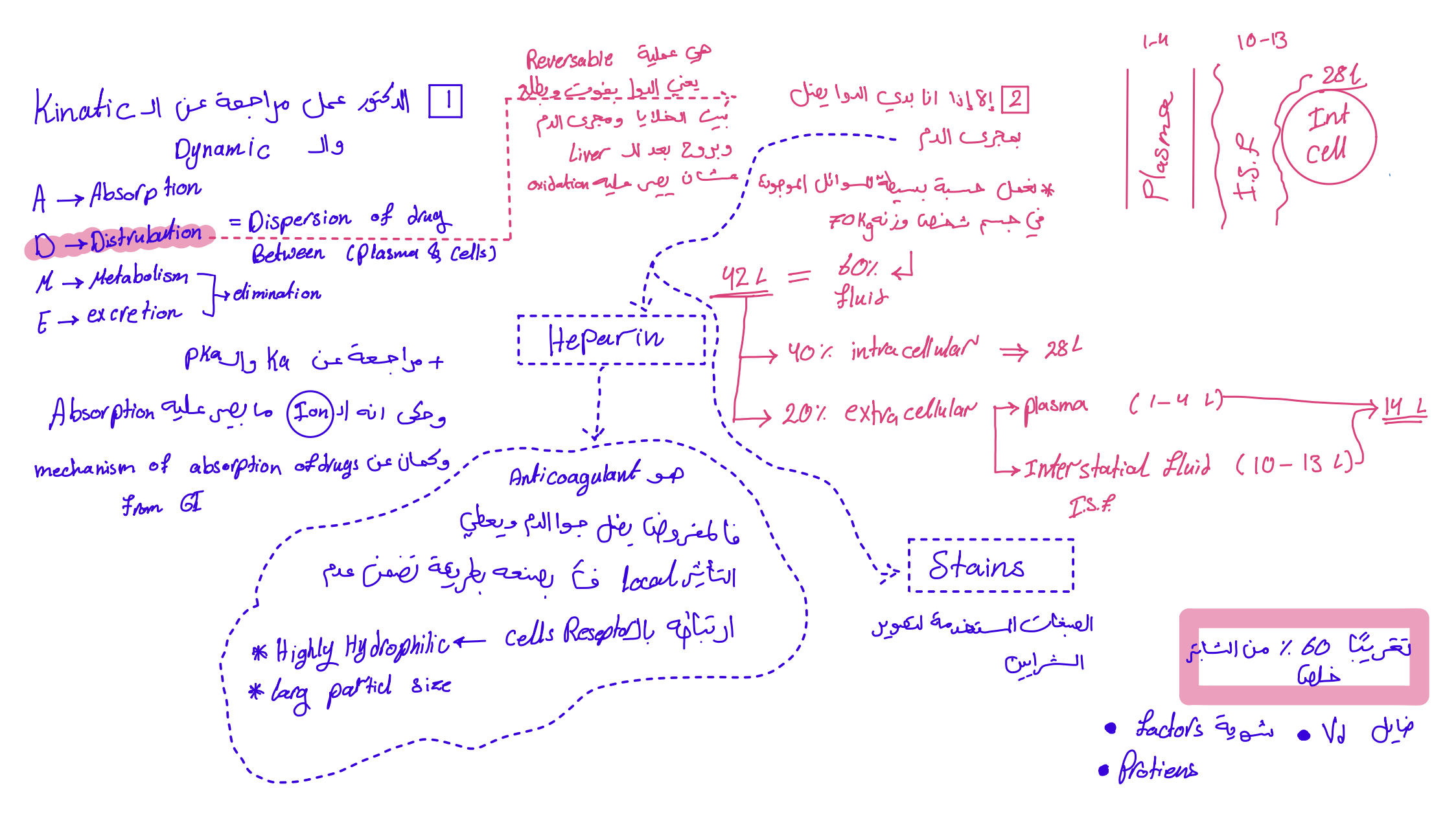
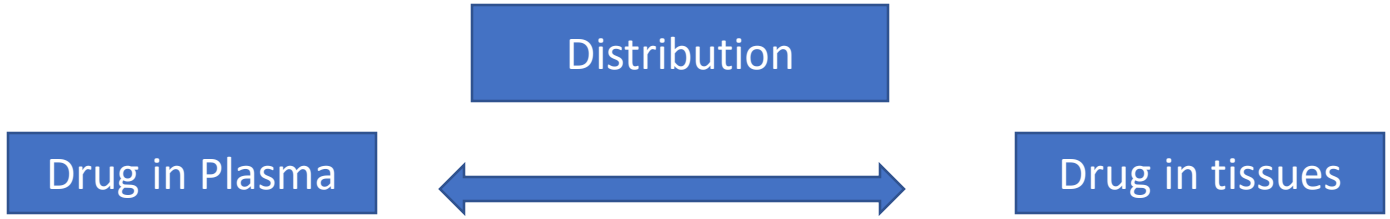
لجان الدفعات


1-4
10-13
28L
Plasma
T.F.
Int cell
Kinatic الدكتور عمل مراجعة عن الـ 1
Dynamic والـ
A → Absorption
D → Distrubution = Dispersion of drug Between (plasma & cells)
M → Metabolism
E → excretion
→ elimination
Reversable هي عملية
يعني البدا يفوت ويطلع
بين الخلايا ومجرى الدم
ويروح بعد لـ Liver
عشان يصير عليه oxidation
2 إذا انا بدي الدوا يضل
بمجرى الدم
* تضل حسبة بسيطة للسوائل الموجودة
في جسم شخص وزنه 70Kg
42L = 60% Fluid
Heparin
40% intracellular ⇒ 28L
20% extracellular → plasma (1-4 L) → 14 L
→ Interstatial fluid (10-13 L)
I.S.F
Anticoagulant هو
فا مضروفه يضل جوا الدم ويعطي
التأثير local فـ يمنعه بطريقة تضمن عدم
ارتباطه بالـ cells Resepter
* Highly Hydrophilic
* larg partic size
Stains
الصبغات المستخدمة لتلوين
الشرايين
تقريبًا 60 ٪ من الشايتر
خلايا
• Factors شوية • VJ فايل
• Protiens

Distribution

- After reaching plasma, drug has to leave it to be distributed into the interstitial and intracellular fluids



- "Distribution is the dispersion of the drug among the various organs or compartments within the body"

DISTRIBUTION OF DRUGS

- After absorption, drug distributes to
  - Interstetial fluid
  - Intracelluar fluid

Blood flow ↑ ⟶ Distribution ↑

  - liver, kidney, brain, and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin, and fat is slower

Blood flow ↓

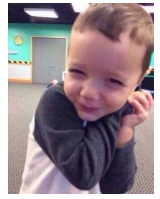
Distribution ↓

➢The **rate** of delivery and potential **amount** of drug distributed into tissues depend on :

- Cardiac output
- Regional blood flow
- Capillary permeability → Brain → Blood Brain Barrier (BBB) → Permeability ↓
- Degree of binding to plasma and tissues protein
- Relative lipophilicity of the drug

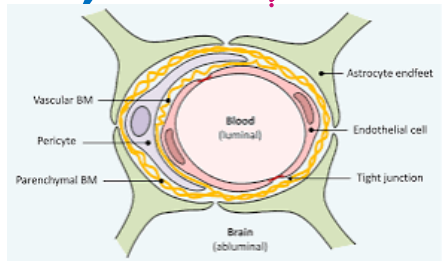
Partion coefficient

Anatomy وحكى تفسيرها من ال
والمفروض انكم متذكرين



➢Well perfused organs **(liver, kidney, brain)** initially receive most of the drug

➢Less perfused organs: (**muscles ,most viscera, skin, and fat)** initially receive less drug



Volume of distribution (V_d)

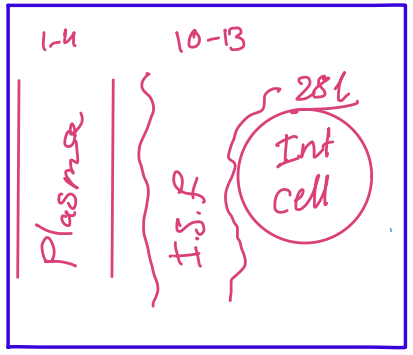
- Fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma at time zero.

$$V = \frac{Mass}{C_0}$$

- Importance : it can be useful to compare the distribution of a drug within the volumes of the water compartments in the body

Ex :- Dose = 100, C_0 = 20

$$V = \frac{100}{20} = 5\ L$$



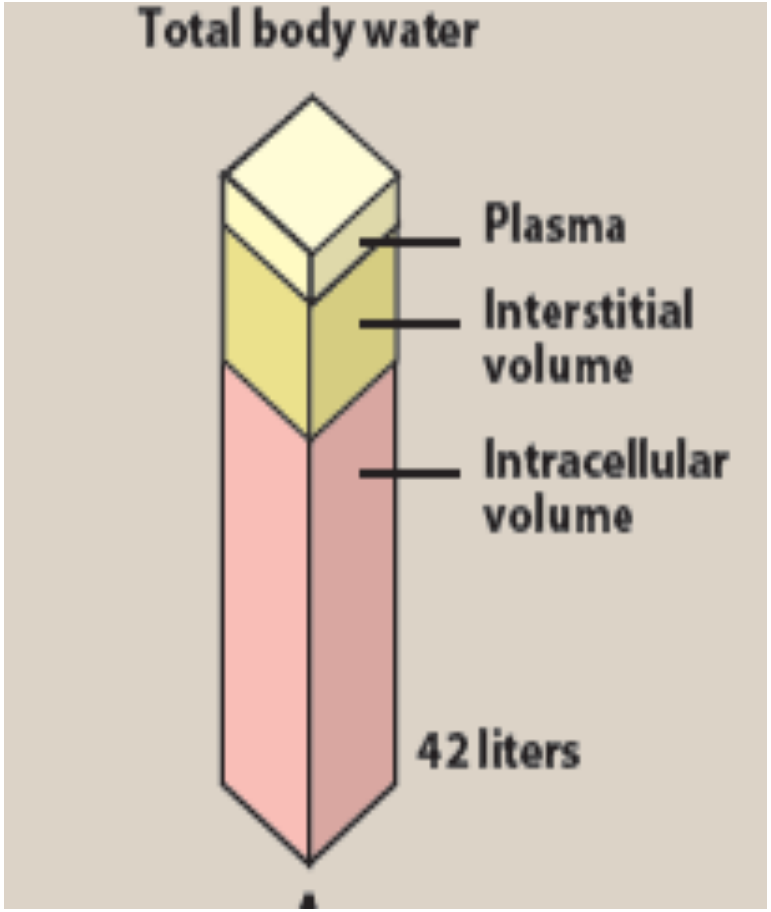
Ex :- Dose = 100, C_0 = 0.1

$$V_d = \frac{100}{0.1} = 1000\ L$$

lipophilic
plasma وعبر الـــ
ISF
Int cell

Water presence in various body compartments :

Schematic representation of body water in a 70kg adult. A total of 42 L. Intracellular volume 28L, Interstetial 13 L and plasma about 4L



V_d

- V_d= Dose/ C_p
- Water soluble drugs will reside in the blood, and fat soluble drugs will reside in cell membranes, adipose tissue and other fat-rich areas.
- Drugs distributed mainly in plasma will have lower Vd values compared to drugs distributed mainly in tissues

مثال :-
إدوية الدسمات
بتتخزن بالدهون
فبعد قطع الدواء
بتضل الـ Side effect
للدوا موجودة

Free drug ⇒ الجزء اللي بستفيد منه

Plasma protein binding ↓ Vd

- Volume of Distribution also relates to whether a drug is Free / protein bound
- Drugs that are charged tend to bind to serum proteins.
- Protein bound drugs form macromolecular complexes that cannot cross biological membranes and remain confined to the bloodstream.

Plasma Proteins

- ✓Albumin is a major carrier for acidic drugs
- ✓α1- acid glycoprotein binds basic drugs
- ✓Plasma protein acts as a reservoir
- ✓The binding is usually reversible and non specific Therefore many drugs may compete on Albumin binding, resulting in a noticeable displacement of one drug by another (warfarin)
- ✓Protein binding affect drug excretion through the kidneys, its transport and metabolism

نقطة مهمة عن الـ Protien

Protien → Non Selective
← يعني ما بختار الدوا اللي بده يرتبط فيه

Drug → العكس قابلية انها ترتبط بالـ Protien

acid لأنه بحب Base الـ يعني

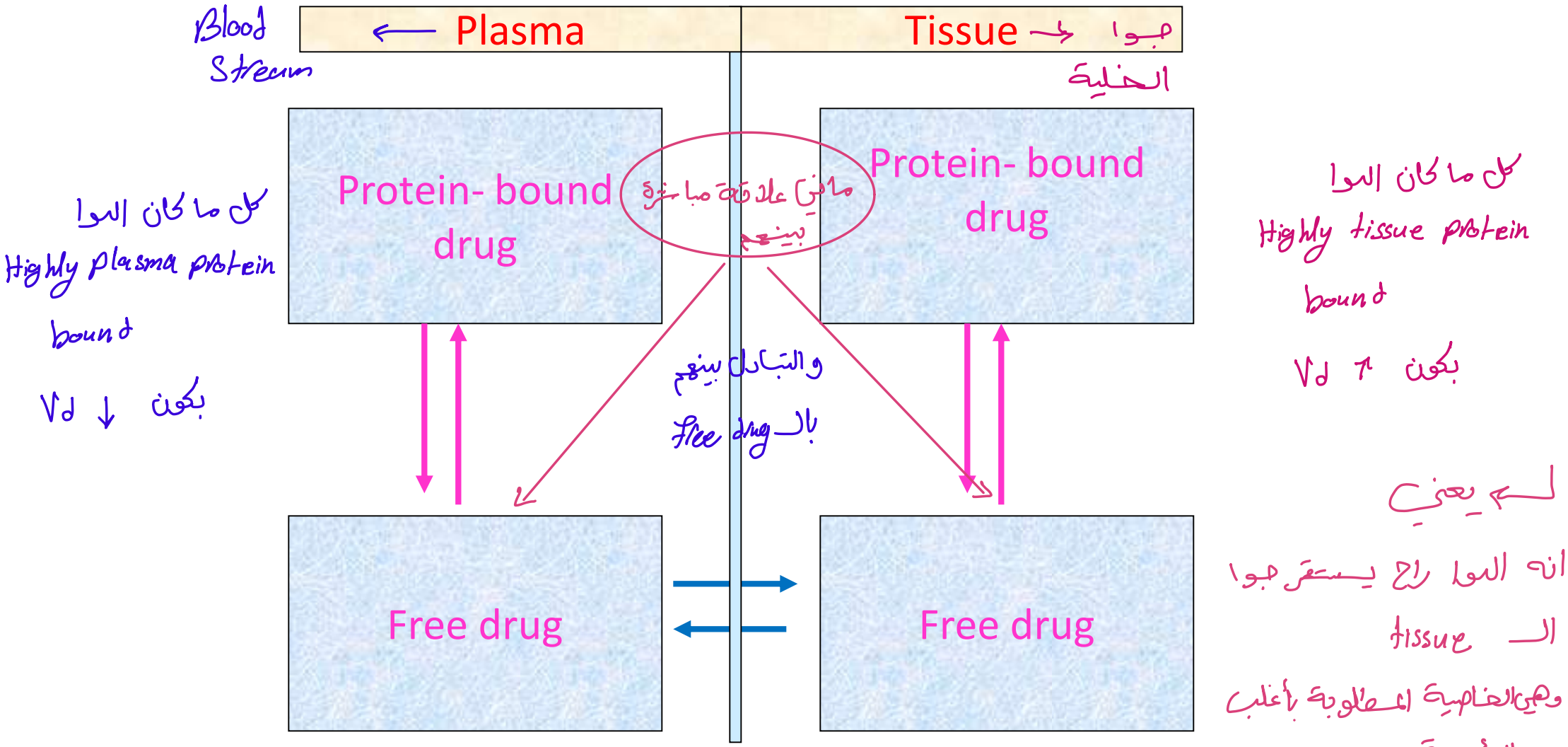
٩٥٪ → ↑plasma protien bind
٥٪ → free drug
هي اللي بتعطي الـ therapeutic effect

امريفنا اللي بوخد warfarin
لازم ليستشي الطبيب والصيدلاني قبل ما يوخداي دوا ← ليش

لأنه ممكن الدوا اللي اخذه يعمل warfarin الـ dispalcement
وبالتالي بزيد تركيزه بالدم عن ٥٪
وبصير Bleeding

هو دوا ← Narow therapeutic index
اقل ← جلطة | ٥٪ | اكثر ← نزيف

Reversable drug binding to albumin is critical to effective drug distribution



The free drug concentration gradient drives transport across the membrane.

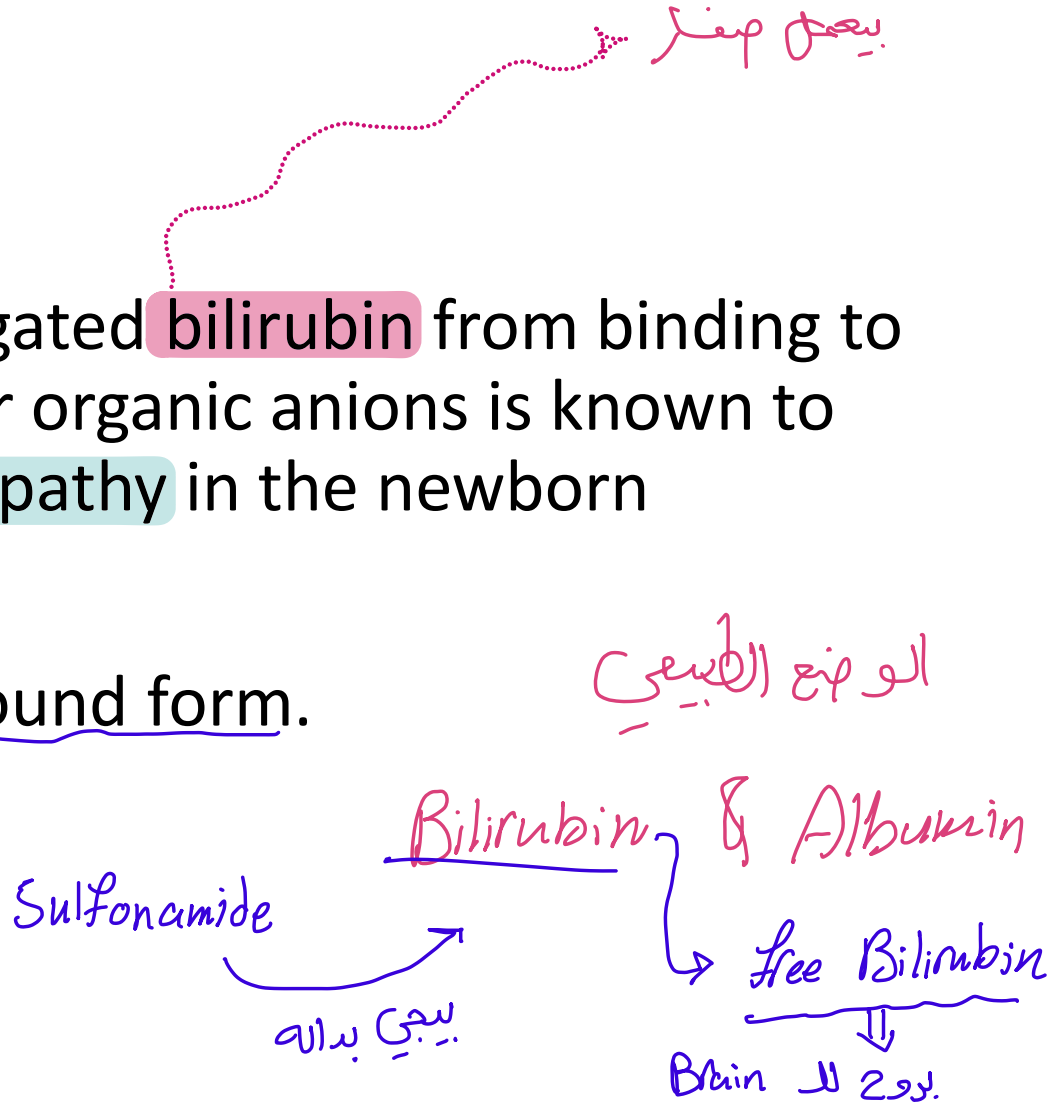
•A large variety of drugs ranging from weak acids and weak bases bind to plasma proteins.

•Binding to other plasma proteins (e.g., lipoproteins and globulins) occurs to a much smaller extent.

Protein Displacement

- For example, displacement of unconjugated bilirubin from binding to albumin by the sulfonamides and other organic anions is known to increase the risk of bilirubin encephalopathy in the newborn

❑ Note that drugs are active in the unbound form.



Tissue Binding → Vd ↑

- Many drugs accumulate in tissues at higher concentrations than those in the extracellular fluids and blood as in (Azithromycin) (10days effect) → 2 Dose (500 , 250) mg على حسب حالة المريض

عنده قدرة على الارتباط ببروتينات الخلية بالتالي يظل فيها لمدة طويلة

- Tissue binding can serve as depot (Reservoir), allowing sustained drug release into the circulation

- Tissue binding of drugs usually occurs with cellular constituents such as proteins, phospholipids, or nuclear proteins and generally is reversible

Fat As a Reservoir

Blood fusion to fat ↓
بتوخد وقت عشان تطلع
الدوا منها وتوصله لمجرى الدم

Ex:
ادوية الاعصاب ←
Highly lipophilic بتكون BBB عشان تعبر الـ
وبتفضل جوه الـ fat لمدة طويلة وبفضل تاثيرها
Side effect يعني

- In obese persons, the fat content of the body may be as high as 50%, however, in lean individuals it constitutes 10% of body weight.

- 70% of the highly lipid-soluble barbiturate *thiopental* may be present in body fat 3 hours after administration
- Fat is a rather stable reservoir because it has a relatively low blood flow

Bone

Blood Flow ↓
Drug Release ↓

- Bone can become a reservoir for the slow release of toxic agents such as radium into the blood

← مثال مش بستخدمه حتى الكانسر

- Tetracycline bone adsorption .

↓
المستخدم في أدوية حب الشباب بحب الكالسيوم
يمسك بالعظم ويعمل Discoloration للأسنان

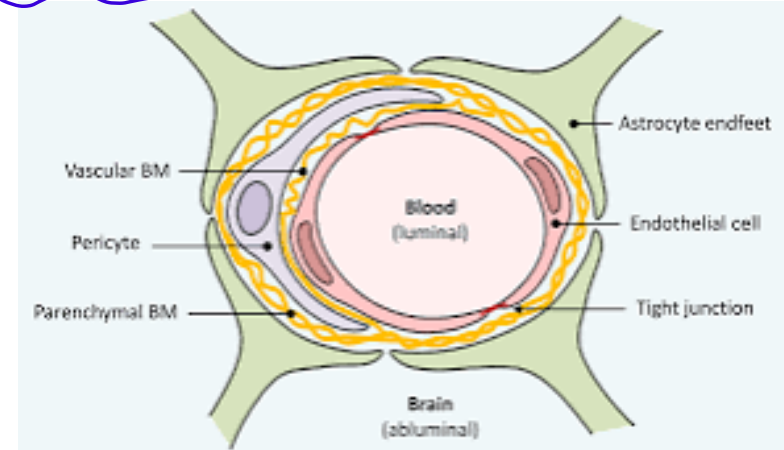
CNS

CSF

Central Nervous System and Cerebrospinal Fluid

لازم الدوا يكون مفلفل تفصيل دحين يعدي يفوت ف ممكن ادخل الدوا عن طريق CSF

- The distribution of drugs into the CNS from the blood is unique
- The unique characteristics of brain capillary endothelial cells which constitute the blood-brain barrier
- the brain capillary endothelial cells have continuous tight junctions

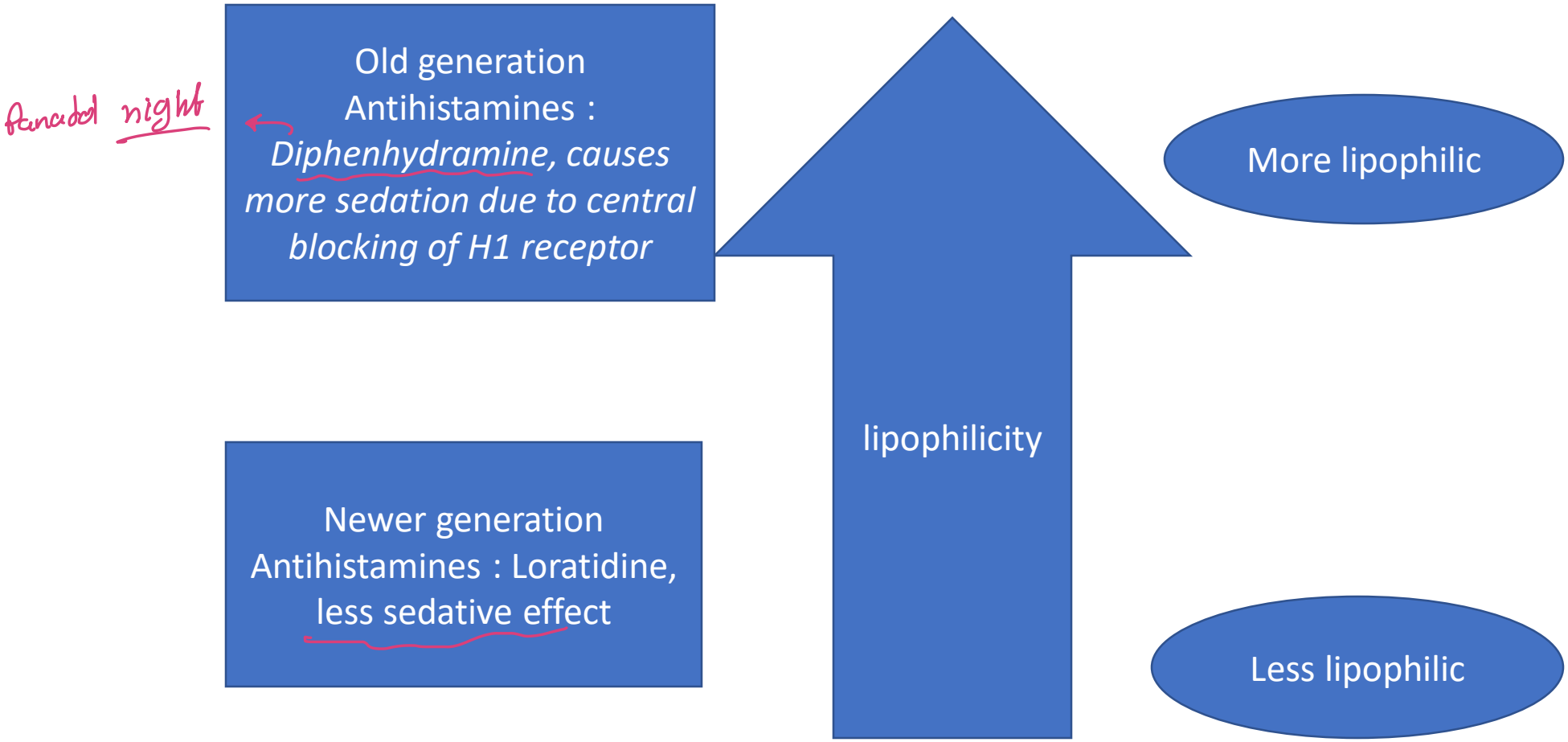


1* Anti-Histamine → يعمل تعاس
لانه يمر على BBB

- The lipid solubility of the nonionized and unbound species of a drug is therefore important factors for BBB penetration

- The more lipophilic, the more Centrally absorbed hence the greater the effect will be.

Example of BBB drug penentration importance

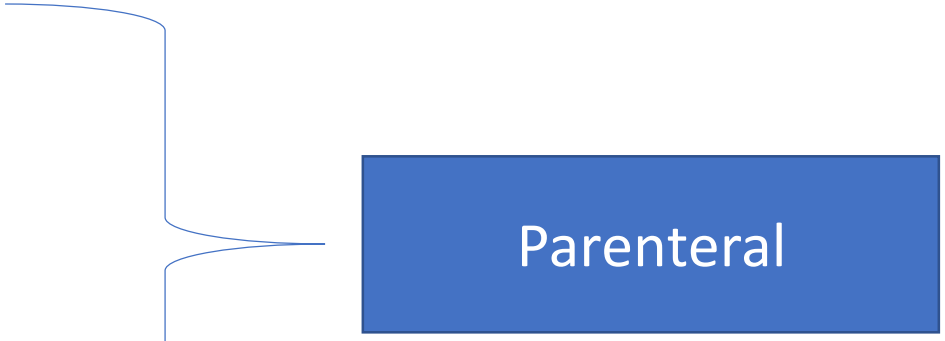


Placental Transfer of Drugs

- Lipid solubility
- Extent of plasma binding
- Degree of ionization of weak acids and bases

Administration Routes

- Oral
- Sublingual
- Rectal
- Intravenous
- Subcutanous
- Intramuscular
- Intra-arterial
- Intrathecal and epidural
- Pulmonary absorption



Administration routes :Oral route

- Most common method of administration, safest and most convenient and economical
- Disadvantages include limited absorption for some drugs, emesis and GE upset, destruction of some drugs by gastric enzymes and always needs patient cooperation.
- Absorption is governed by :

-Drug factors: pH, ionization, etc..

-Blood flow to the area of absorption

* Entering coating for acid labile drugs → with acid coat

* Controlled release preparations (increase compliance)

↳ long sustain Release ⇒ مش بقدر ألتزم بالدوا
لو كان الكثر من جهة خلال النهار

* بقدر اتحكم بالجرعة
* لو اكتشفنا انه الدوا خطأ لأي سبب
بقدر اعطي مضاد الله او اخرج الدوا من المعدة
قبل مايصير عليه امتصاها
* ما بحتاج شخص متخصص لحتى يعطيه

تحت اللسان

Sublingual route :

Despite the small surface area, however its significant for some medication with high lipid solubility thus ensuring very fast absorption

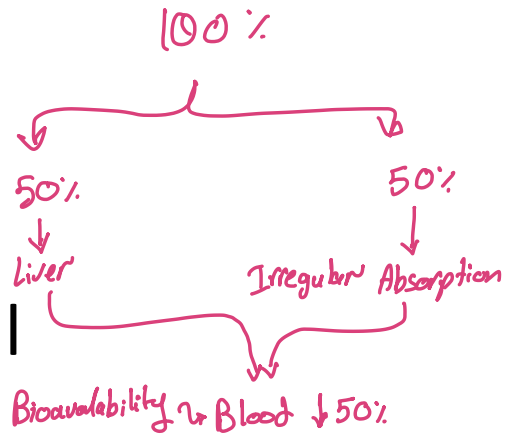
مافي First pass metabolism

(Nitroglycerine in angina)

Rectal route:

Used when oral route is precluded (patient is unconscious).

Mainly used for children . Almost 50% of the dose will bypass liver metabolism , irregular absorption rate, and may cause irritation



Parenteral injection

IV

- **Intravenous** :BA is complete and rapid. Used in cases such as general anesthesia, also used for irritating drugs because they will be diluted in blood. however unpleasant action may happen, so there is a need of slow infusion and clinical supervision when using this route.

- **Intramuscular** :

- Drugs in aqueous solutions have rapid absorption or specialised depots via this route depending on the blood flow rate.
- Absorption in females is slower due to different adipose tissue distribution. Also absorption pattern is unpredictable with obese patients.

- **Intra arterial**:

occasionally some drugs are injected into arteries to localize the effect such as in head and neck cancer.

- **Intrathecal** :

mainly used when drugs cant cross BBB or CSF

- **Pulmonary absorption** :

used for volatile drugs and gases, ensures rapid and high absorption due to the large surface area of lungs. Such as Aerosols as inhalation.

"Advantages are mainly bypass liver , and this route is ideal for lung diseases such as asthma because the site of administration is the site of action".

- **Subcutaneous** :

  Used only for drugs that are not tissue irritating, otherwise it causes severe pain and necrosis .Insulin and heparin administration is a good example of this route .

  Unsuitable for drugs which are administered with large volume.

Topical application

1) **Mucous membranes :**

Drugs applied to such membranes as, conjunctiva.nasopharynx, oropharynx, vagina

2) **Skin** :

few drugs can penetrate intact skin!!! Penetration depends on the surface area of application and on the lipid solubility. However , systemic absorption occurs in cases of wounds and burns.