DEFINITIONS & TERMINOLOGY

Metals, gases, drugs, Vitamins

Mainly related to Medications

- Toxicology is the study o the adverse effects of chemicals on living organisms.
- **Poisons**: are drugs that have almost exclusively harmful effects
- However, Paracelsus (1493–1541) famously stated that *"THE DOSE MAKES THE POISON"*
- **Toxins??** biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons (lead and iron)
- Toxicology: is the branch of pharmacology that deals with the undesirable effects of chemicals on living systems
- Molecular toxicology: the study of the effects of toxicants at the molecular levels.....cell growth, differentiation, genes, DNA, RNA, proteins

The Mechanism of the adverse reaction

over doses

paracetamol

TOXICOLOGY DISCIPLINES

- Environmental toxicology: we deal with toxins presented in the enviro

  focuses on the impacts of chemical pollutants in the environment on biological organisms, study the effects of chemicals that are contaminants of food, water, soil, or the atmosphere

- Industrial (occupational) toxicology:
  - Toxic exposure in the workplace or during product testing.

- Clinical (medical) toxicology: is concerned with disease caused by or uniquely associated with toxic substances focus on the diagnosis, management and prevention of poisoning or ADEs.

TOXICOLOGY DISCIPLINES

- Forensic toxicology: the use of toxicology to aid medical and legal investigation of death.

نعرف بالمادة الي سببت الـ Toxicity وهل هي مقصودة او لا

is a hybrid of analytic chemistry and fundamental toxicologic principles that focuses primarily on the medicolegal aspects of the harmful effects of chemicals on humans and animals.

What is a Poison??

"All substances are poisons;
there is none that is not a poison.
The right dose
differentiates a poison and a remedy"

Paracelsus (1493-1541)

بنعتبر كل شي، هوه poison وهاد بعتمد على الـ dose

What is a Poison??

- *Poisoning or exposure??*

- Many people consider that poisoning start the moment exposure occurs
- In reality, we are exposed to a wide variety of toxic substances each day from food and water that we ingest, and air that we breath

What is Response?

(protien, DNA, RNA) مستوى الخلية

- ❑ Change from normal state – could be molecular, cellular, organ, or organism level.....the symptoms
- ❑ The degree and spectra of responses depend upon the dose and the organism
  - ✓ Immediate vs. Delayed (carcinogenic) — على السريع response صار Toxicty لل
  - ✓ Reversible vs. Irreversible (liver vs. brain, teratogenic effect) — Can be managed لو تصرفنا اسرع — Irreversible: cells can't be repaired
  - ✓ Local vs. Systemic — at the site of exposer
  - ✓ Graded vs. Quantal.....degrees of the same damage vs. all or none — Graded: انو كل ما زادت ال dose The toxic response will increase
- ❑ Allergic Reactions & Idiosyncratic Reactions....ADRs
  - Allergic Reactions: يعني انا بتحسس من شغلة مثلاً فكل ما اتعرضلها بصير عندي allergic response
  - Idiosyncratic Reactions: *dose independent *frequency independent reaction غير معروف سبب ال

Characteristics of Exposure

1. Dose

- ❑ The amount of chemical entering the body
- ❑ This is usually given as:

mg of chemical / kg of body weight = mg/kg

- ❑ The dose is dependent upon:
  - ➢ The environmental concentration ← مثلاً لو كان في حريق قديم الشخص استنشق CO
  - ➢ The properties of the toxicant
  - ➢ The frequency of exposure
  - ➢ The length of exposure
  - ➢ The exposure pathway (orally - Through the skin, GI)

Characteristics of Exposure

2. Exposure: Pathways

- ☐ Routes and Sites of Exposure:
  - **Ingestion** (GIT), (first pass effect)
    - Ex. Lidocaine and Verapamil (antiarrhythmic drugs)
  - **Inhalation** (Lungs): rapid absorption, because of large alveolar surface area
  - **Dermal/Topical** (Skin), absorption varies with area of application and drug formulation, but usually absorption is slower than other routes
  - **Injection** most commen ، fastest
    - Intravenous, intramuscular, intraperitoneal
- ☐ Typical response of Routes and Sites of Exposure:

[i.v > inhalation > i.p > i.m > oral > topical]

GI بال ← absorption بصير فممكن انا استفيد منها اني اعمل للشخص decontamination للمادة او الدوا من ال GI * وبكان او بعض ال Chemical بتصير first pass effect بال راح يبدأ يصيرلهم elemination form systemic circ عبر ازا صار ال Metabolite تحول لـ More toxic Metabolite

Characteristics of Exposure

More toxic تحول لـ Metabolite

Characteristics of Exposure

3. Duration and frequency of exposure → * what is the response هيه اللي بيحدد

كل ما كان Longer time exposure more بكون severe response

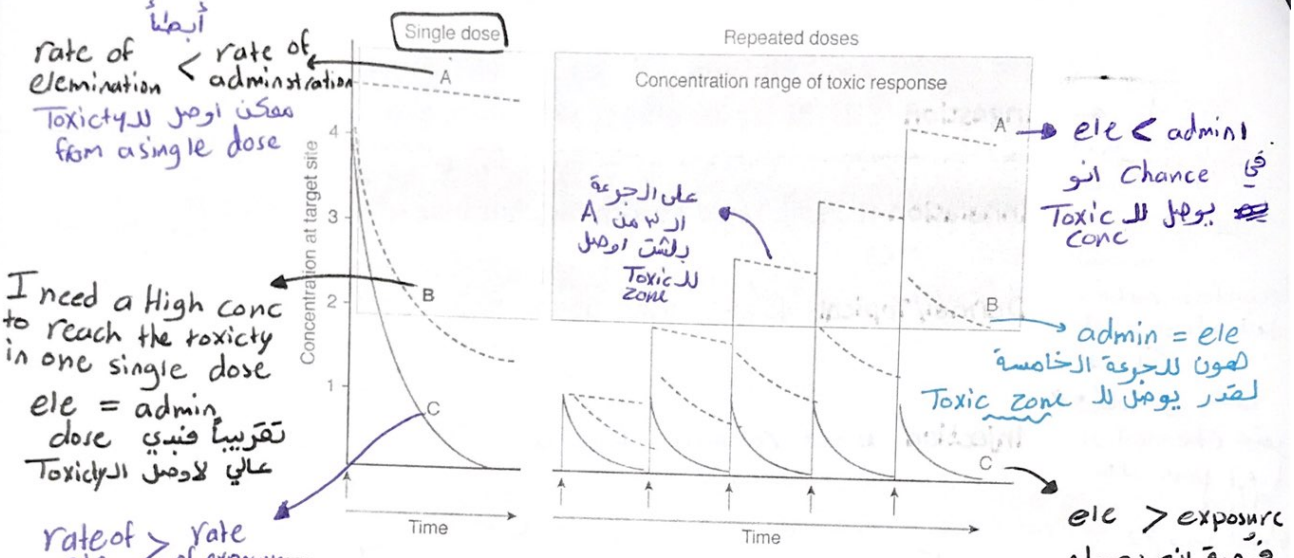
- Toxicologists usually divide the exposure of experimental animals to chemicals into 4 categories.....:

Acute	< 24hr	Usually 1 exposure
Sub-acute	1 month	Repeated exposure → اكتر من 24 ساعة واقل من شهر
Sub-chronic	1-3 months	Repeated exposure
Chronic	> 3 months	Repeated exposure

- Over time, the amount of chemical in the body can build up, it can redistribute, or it can overcome repair and removal mechanisms

* بس برضوا كان في ادوية Single exposure is more toxic than ~~chronic~~ chronic exposure

The other time-related factor that is important in the temporal characterization of repeated exposures is the **frequency** of exposure



The relationship between elimination rate and frequency of exposure

Dose Response Relationship

- The magnitude of drug effect depends on the drug concentration at the receptor site, which is in turn determined by the dose of drug administered and by factors of the drug pharmacokinetic profile
- There is a *graded dose-response relationship* in each individual and a *quantal dose-response relationship* in a population

Graded-dose response relationship

- ❑ The response to a drug is a graded effect, meaning that the the measured effect is continuous over a range of doses

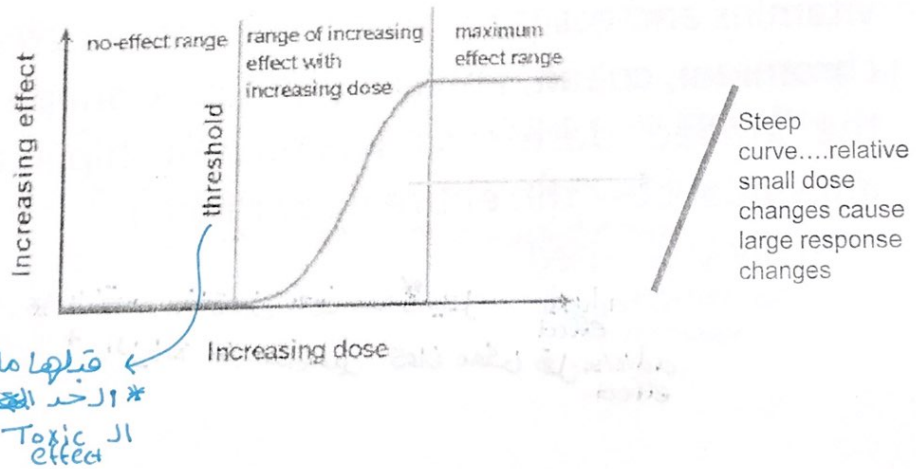
بنحسب الـ effect عن طريق Continuous exposure to a range of doses

- ❑ Graded dose response curves are constructed by plotting the magnitude of the response against increasing doses of a drug (or log dose)

Dose-Response Relationship

- ❑ As the dose of a toxicant increases, so does the response

كل مازدنا الجرعة يتزيد الـ response

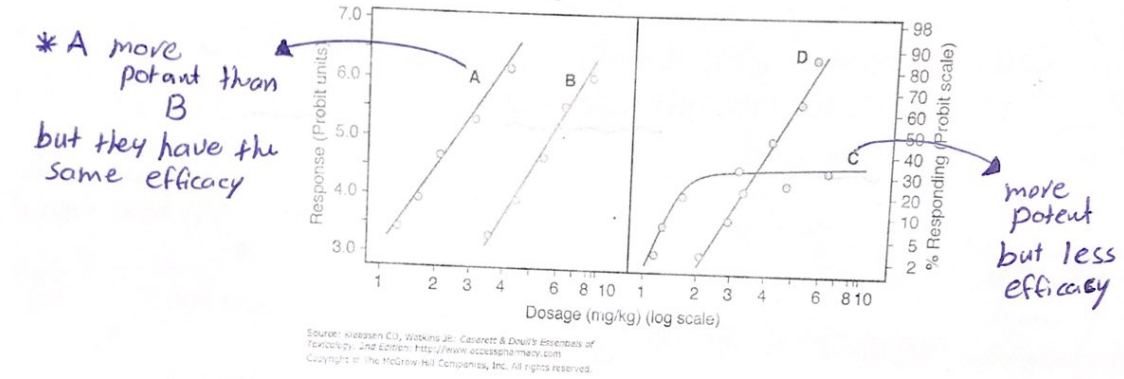


قبلها ما بكون في effect * الحد الفاصل بين non-Toxic / Toxic الـ effect

Graded-dose response relationship

- Two important properties of drugs can be determined by the graded dose response curves:
  - Potency → Matter of the dose needed to produce an effect
  - Maximal toxicity

كل ما قلت الـdose يزيد الـ potency



* A more potent than B but they have the same efficacy

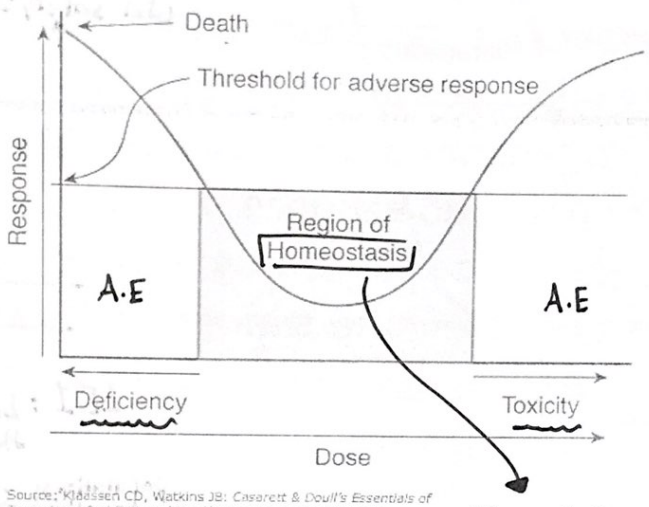
more potent but less efficacy

'U' Shape of the Dose-Response Curve

- For substances that are required for normal physiologic function and survival (e.g., vitamins and essential trace elements such as chromium, cobalt, and selenium), the shape of the "graded" dose–response relationship in an individual over the entire dose range is actually U-shaped.

* النقص بغاية معين ممكن يعمل adverse effect
+ الزيادة من الغاية من كمان ممكن تعمل adverse effect

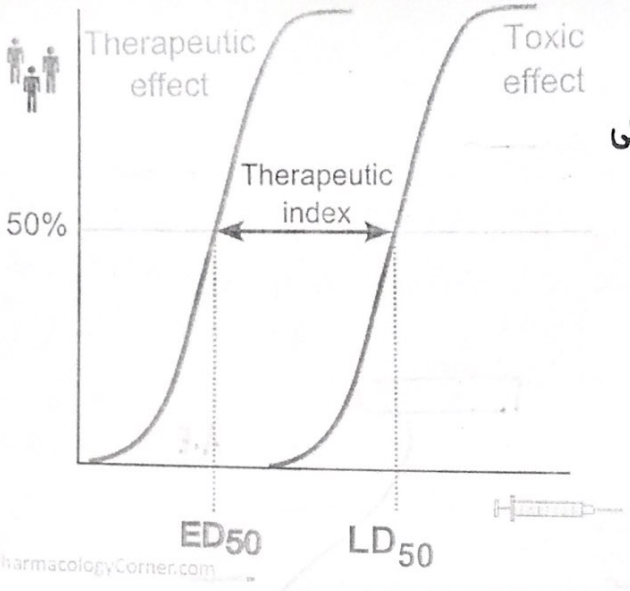
'U' Shape of the Dose-Response Curve



* I need to keep that vitamin in this range in order to save response

Evaluating the Dose Response Relationship

- The quantal (all or none) dose-effect curve is often characterizes the distribution of responses to different doses in a ***population*** of individual organisms
  - Median toxic dose(TD_{50}): the dose at which 50% of individuals/population exhibit a particular toxic effect
  - If the toxic effect is death of the animal, a median lethal dose (LD_{50}) may be experimentally defined
  - Median effective dose (ED_{50}):.....?? effective dose in 50% of the population.



كل ما كانت الكبر بيكون الـ safety اعلى

✓ $TI = TD_{50} / ED_{50}$

✓ For non-drug chemicals: Margin of Safety → بنحسب عندها الـ LD1 مو الـ LD50

LD1 : Lethal dose in 1% of the population

* صون انا بستنى نحس الـ population to die ما

Shift to the left....shift to the right!!!

* يعني لو من 100 ارنب واحد منهم مات صاي صيبه الـ LD 1

* $TI = \frac{LD_1}{ED_{99}}$ ← بنحسب الـ Margin of safety ← بالـ non drug chemicals

!!!.....Molecular Target Concept

Agonist ← bind to the recptor and gives the response

Antagonist → bind to the resptor and blocks the reiponse

Pharmacodynamics

- In the field of pharmacology, an **inverse agonist** is an agent that binds to the same receptor as an **agonist** but induces a pharmacological response opposite to that antagonist. **Antagonist** has no activity in the absence of an **agonist** or **inverse agonist** but can block the activity of either.

* inverse agonist → binds to the resptor but oppesite to the agonist

* يعني لو الـ agonist بزيد الـ H.R ضاد بقلل الـ H.R

Toxicodynamics & Kinetics