PHARMACOKINETICS

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LECTURE 1: INTRODUCTION, CONCEPTS, & THE USES OF PHARMACOKINETICS

General definitions

- **Biopharmaceutics** is a major branch in pharmaceutical sciences which relates between the physicochemical properties of a drug in dosage form and the pharmacology, toxicology, or clinical response observed after its administration.

- **Pharmacology** is a branch of medicine and pharmaceutical sciences which is concerned with the study of drug or medication action, where **a drug** can be broadly or narrowly defined as any man-made, natural, or endogenous molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism.

- **Toxicology** is the scientific study of adverse effects that occur in living organisms due to chemicals. It involves observing and reporting symptoms, mechanisms, detection and treatments of toxic substances, in particular relation to the poisoning of humans

General definitions

- **Toxicokinetics** which is the study of kinetics of absorption, distribution, metabolism, and excretion of a xenobiotic under the conditions of toxicity evaluation (is pharmacokinetics studied at high doses (toxic?).

- **Clinical Pharmacokinetics** is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

- **Traditional pharmacokinetic** studies usually involve multiple samples taken at fixed intervals from healthy volunteers. In contrast, **population pharmacokinetic** data are obtained from patients being treated with a drug. These patients are often taking different doses and have blood samples at different times.

What is pharmacokinetics?

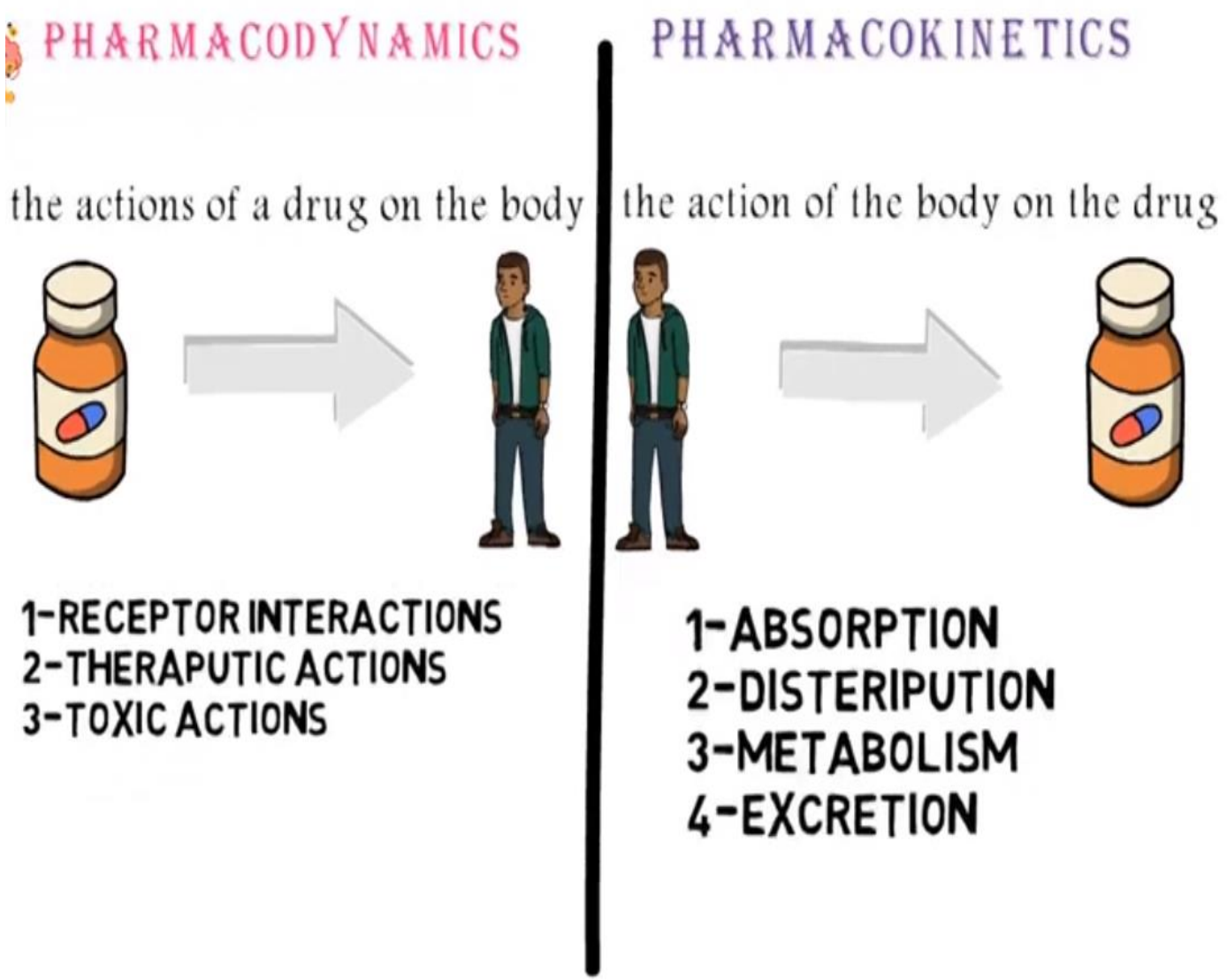
- **Pharmacokinetics describes the movement (Greek– kinesis) of a drug (Greek – pharmakon) around the body.**

- **Pharmacokinetics is the branch of pharmacology** dedicated to determining the fate of chemical substances administered to a living organism – 'what the body does to the drug'.

Pharmacodynamics (pd)

- **Pharmacodynamics is the science that studies the relationship between the drug concentration at the site of action (receptor) and its pharmacological response.**

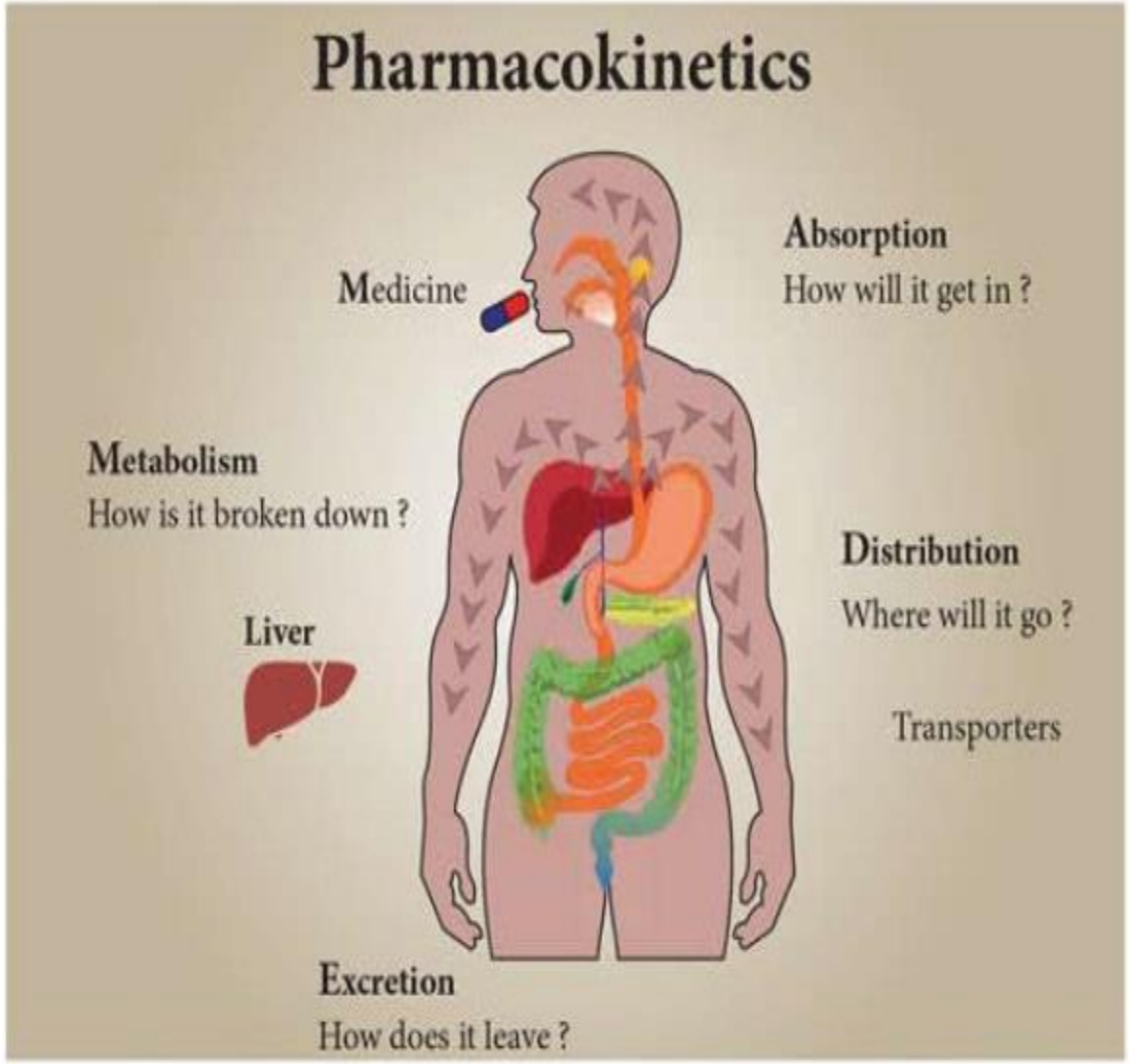
- Drug + receptor → Pharmacological response or toxic response.



PHARMACOKINETICS (PK) Principles

- The science of the kinetics (the study of the rates) of drug absorption, distribution, metabolism and excretion of a drug and its metabolite(s).

- Drug distribution and elimination = Drug disposition.

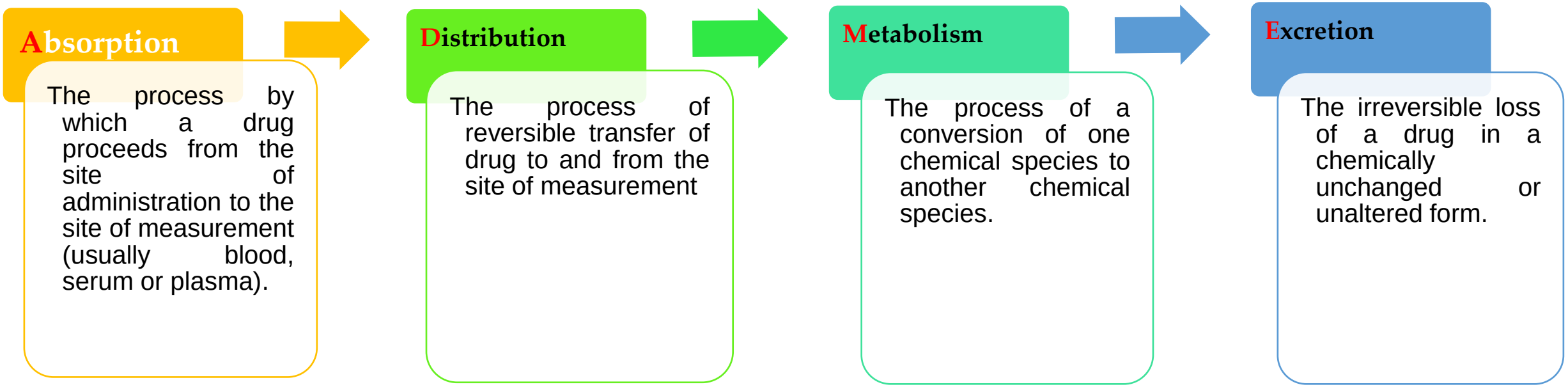


Review of ADME Processes

❑**ADME is an acronym representing the pharmacokinetic processes of:**

✓**A** : Absorption
✓**D** : Distribution
✓**M** : Metabolism
✓**E** : Excretion.

ADME process



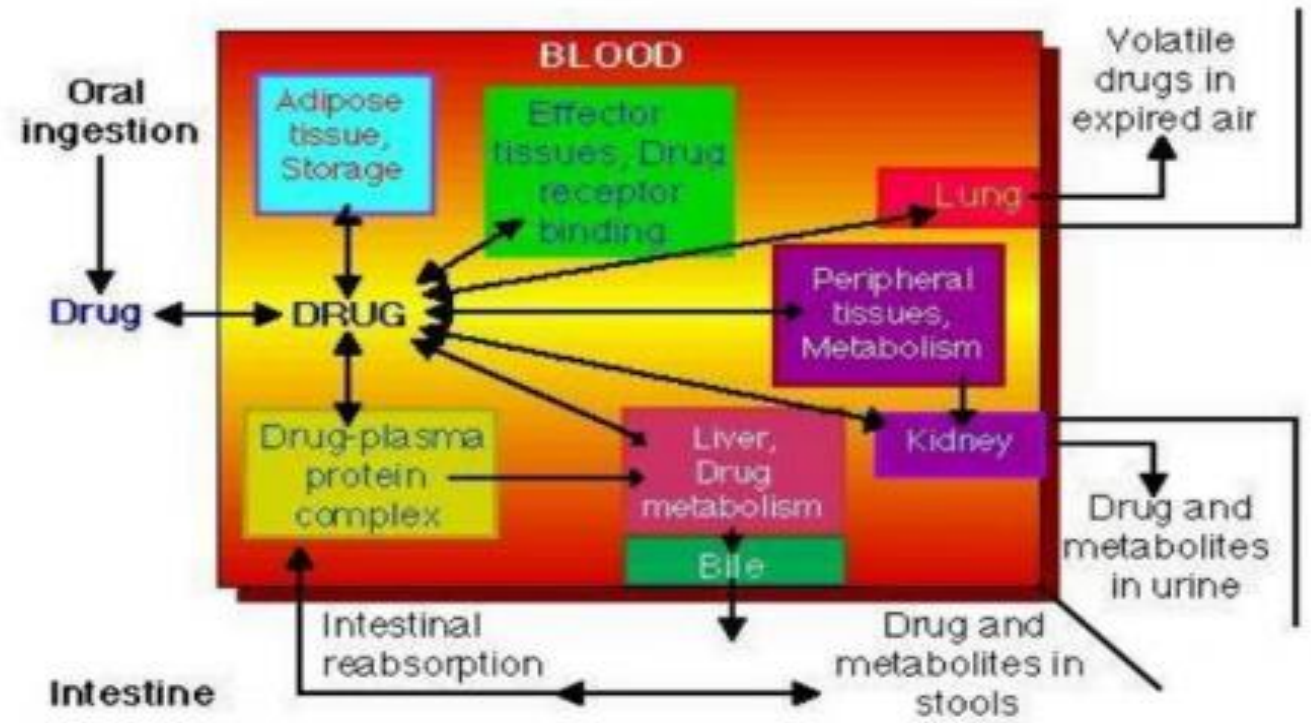
ADME

- Elimination: the irreversible loss of drug from the site of measurement.
- **Metabolism and excretion processes represent the elimination process.**
- Elimination= Metabolism and Excretion.

Pharmacokinetics tries to answer the questions:

- **Why does only a fraction of the total dose reach its target?**
- **How should we dose (route) and how many times (frequency) to maintain drug at target (efficacy)?**

DRUG DISPOSITION



WHY DO WE NEED PK?

PRE-CLINICAL OUTCOMES FROM DOING PK

- Select compounds that have the maximum potential of reaching the target (PK)
- Select the appropriate route of administration to deliver the drug
- Understand how the blood (or plasma) levels relate to efficacy (PK-PD) or toxicity (TK-TD) in order to select safe doses
- Decide on the frequency and duration of dosing in order to sustain drug at target for disease modification
- **Predict Human pharmacokinetics**

How Do We Do PK?

PERFORMING A PK STUDY

DOSE

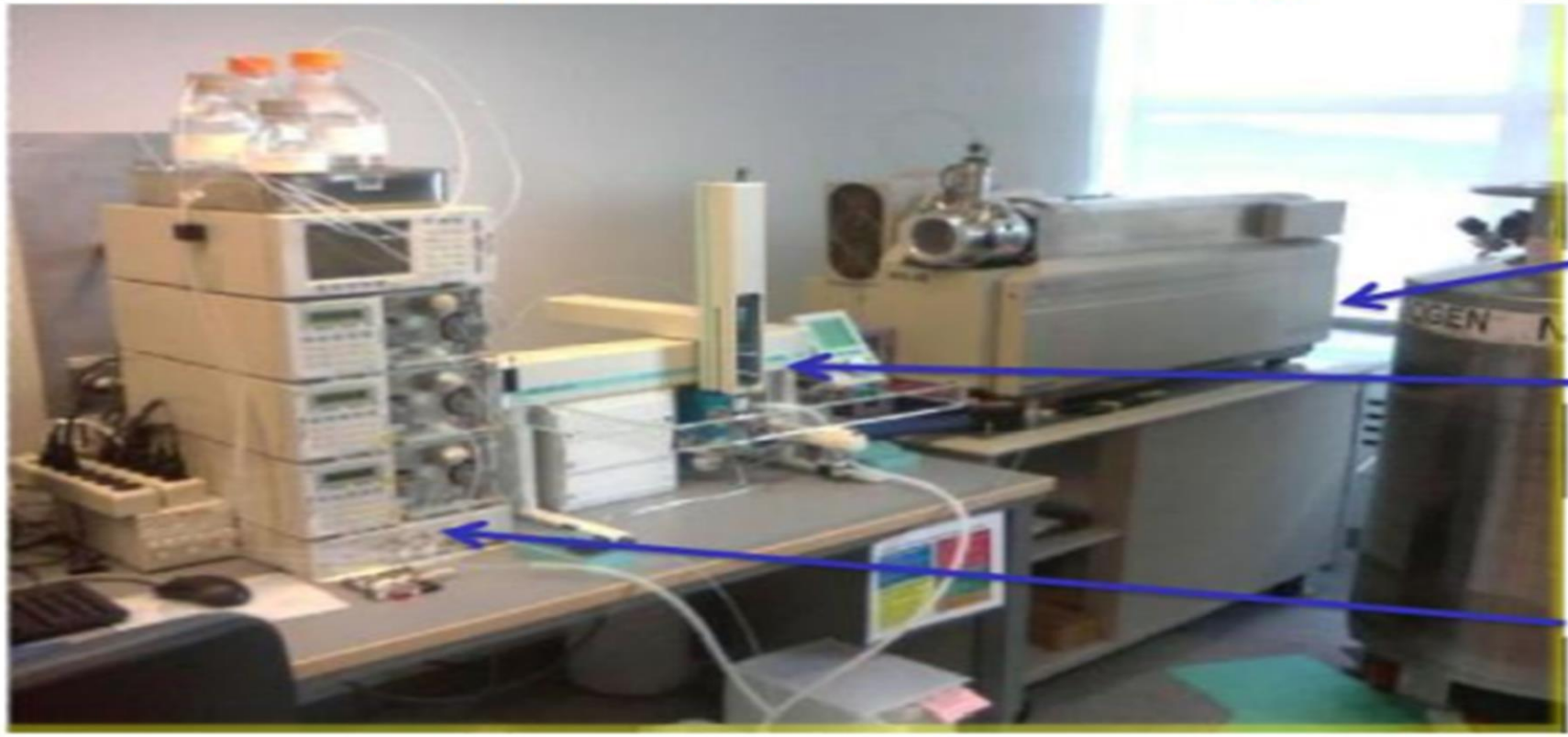
COLLECT SAMPLES (BLOOD, URINE, BILE, FECES)
AT VARIOUS TIMEPOINTS

ANALYZE FOR
DRUG/METABOLITES

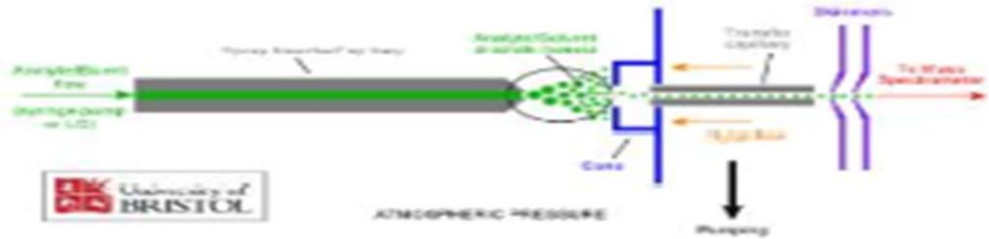
PK DATA ANALYSIS

How is the Data Generated?

Plasma Concentration vs Time Curves



Electrospray ionization MS revolutionized drug discovery! (plasma, urine, bile analysis)



Concept & Uses of Pharmacokinetics

- In practice this involves the measurement and formal interpretation of changes with time of drug and drug metabolite concentrations in plasma, urine and sometimes other accessible regions of the body, in relation to dosing.

- It provides a framework for understanding what happens to a drug when given to an animal or human, where it goes in the body, and how quickly, that enables one to understand the effects that it produces.

Concept & Uses of Pharmacokinetics

- In practice, pharmacokinetics usually focuses on **concentrations of drug in blood plasma**.
- This underpins what is termed the **target concentration strategy**.
- Formal interpretation of pharmacokinetic data consists of fitting **concentration-versus-time data** to a model and determining parameters that describe the observed behaviour.
- **Plasma concentrations (Cp)** are therefore useful in the early stages of drug development, and in the case of a few drugs plasma drug concentrations are also used in routine clinical practice to:

➢ **Individualize dosage**, to achieve the desired therapeutic effect while minimizing adverse effects in each individual patient – an approach known as **therapeutic drug monitoring**, often abbreviated **TDM**.

Therapeutic Drug Monitoring (TDM)

- Table 1.1 shows examples of some drugs where a therapeutic range of plasma concentrations has been established, enabling TDM. Concentrations of drug in other body fluids (e.g. urine, saliva, cerebrospinal fluid, milk) may add useful information.

Table 1.1: Examples of drugs where therapeutic drug monitoring (TDM) of plasma concentrations is used clinically

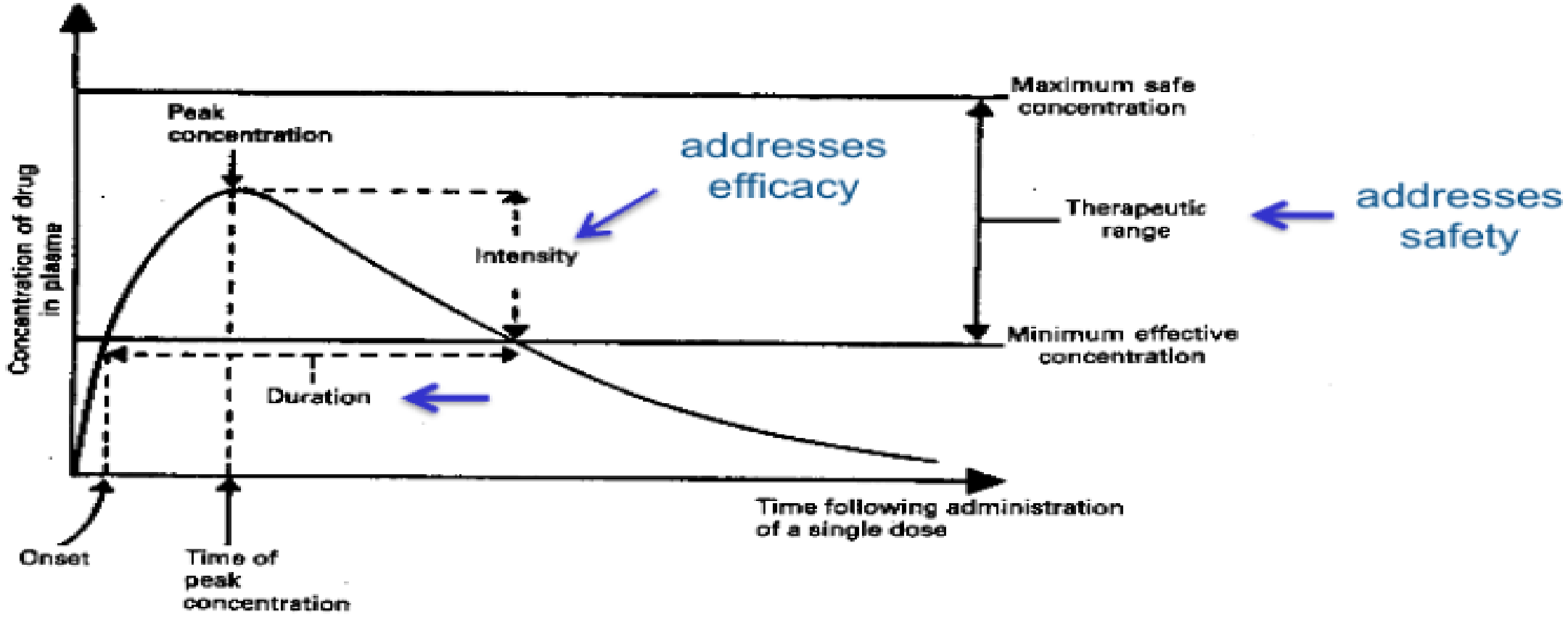
Category	Example(s)
Immunosuppressants	Ciclosporin, tacrolimus
Cardiovascular	Digoxin
Respiratory	Theophylline
CNS	Lithium, phenytoin
Antibacterials	Aminoglycosides
Anticancer drugs	Methotrexate

Concept & Uses of Pharmacokinetics

- Some descriptive pharmacokinetic characteristics can be estimated directly by inspecting the time course of drug concentration in plasma following dosing – important examples, are the maximum plasma concentration following a given dose of a drug administered in a defined dosing form (C_{max}) and the time (Tmax) between drug administration and achieving Cmax.

Descriptive Pharmacokinetic Characteristics

Plasma Concentration vs Time Curves



Relationship between the plasma concentration–time curve obtained following a single extravascular dose of a drug and parameters associated with the therapeutic or pharmacological response

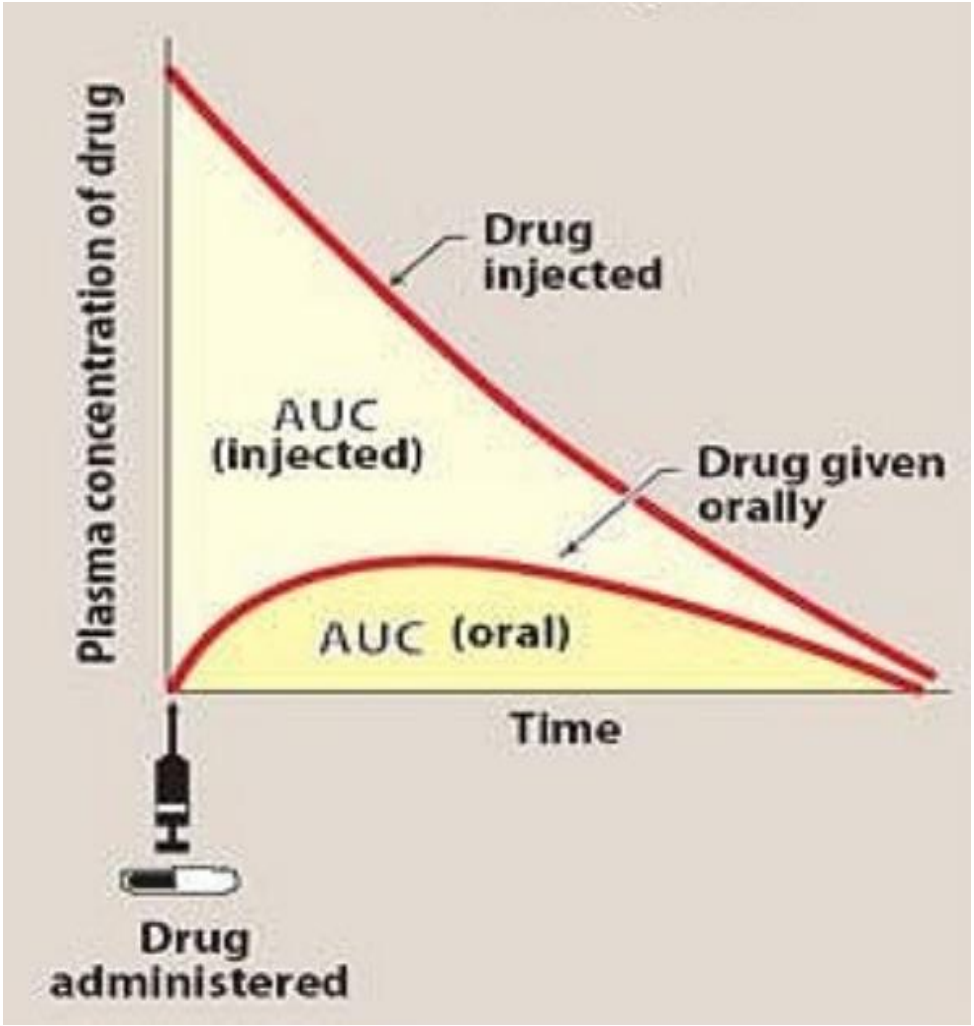
Applications of Pharmacokinetics

- Bioavailability measurements.
- Effects of physiological and pathological conditions on drug disposition and absorption.
- Dosage adjustment of drugs in disease states, if and when necessary.
- Correlation of pharmacological responses with administered doses.
- Evaluation of drug interactions.
- Clinical prediction: using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy.

Bioavailability measurements

- Bioavailability is usually assessed by determining the area under the plasma concentration–time curve (AUC).

- The most reliable measure of a drug's bioavailability is AUC.
- Blood drug concentration in human following the administration of the drug by oral or IV routes. A comparison of the behaviour of orally administered drug with that of IV administered drug in human.

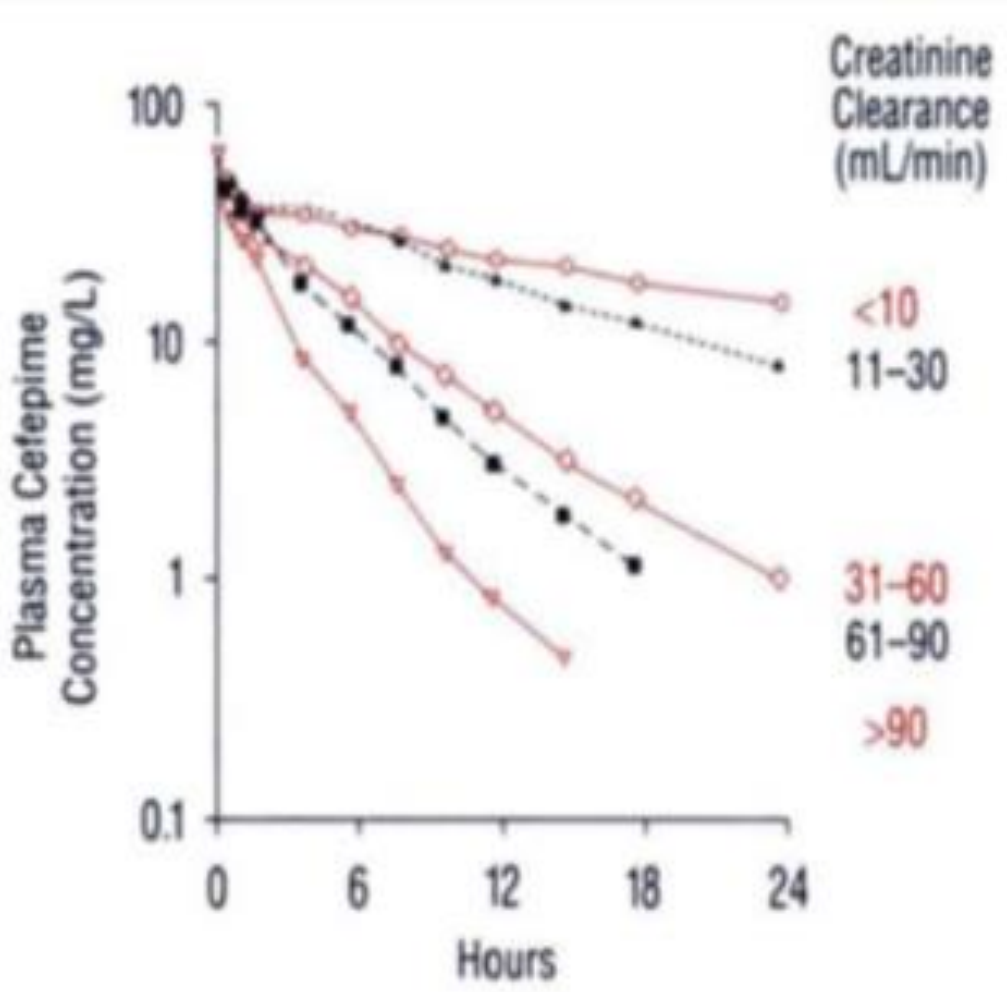


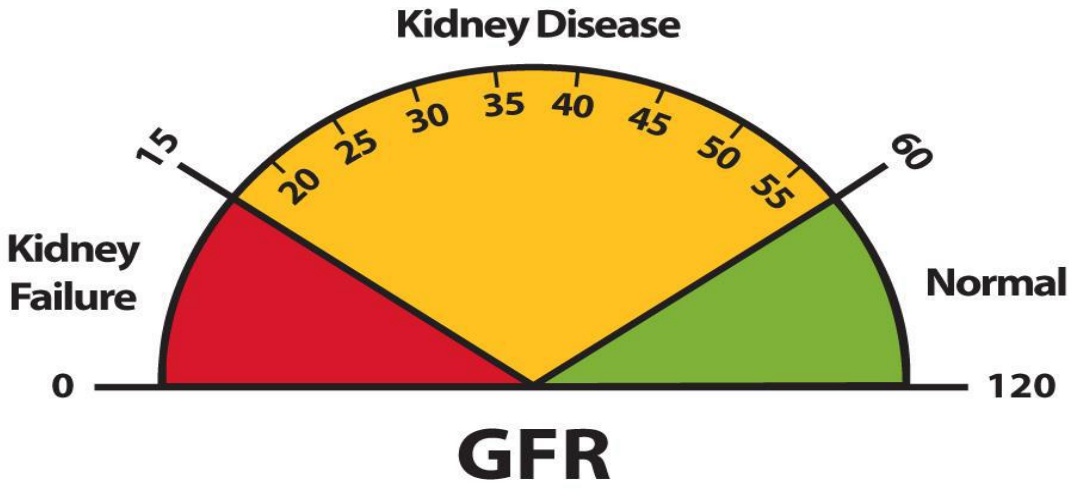
Bioavailability

- Bioavailability: is the fraction of administered drug that reaches the systemic circulation.
- Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form.
- For example: if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, then the bioavailability is 0.7 or 70%.

Effects of physiological and pathological conditions on drug disposition and absorption

- Plasma conc-time profile of cefepime after a 1000 mg IV infusion dose.

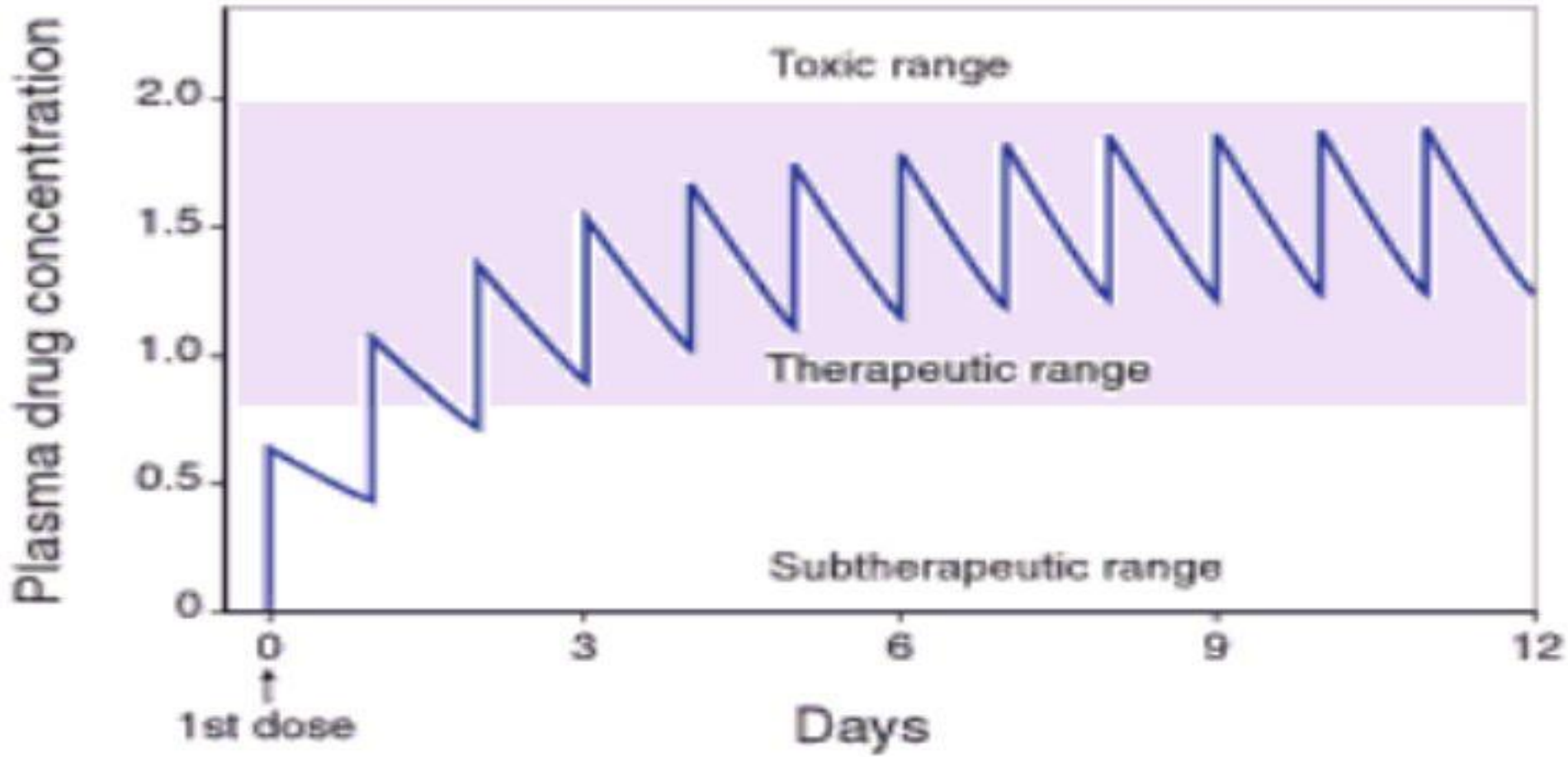




GFR category	GFR (mL/min/1.73 m²)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.
Note: Data from KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1–150.[2]
Abbreviation: GFR, glomerular filtration rate.

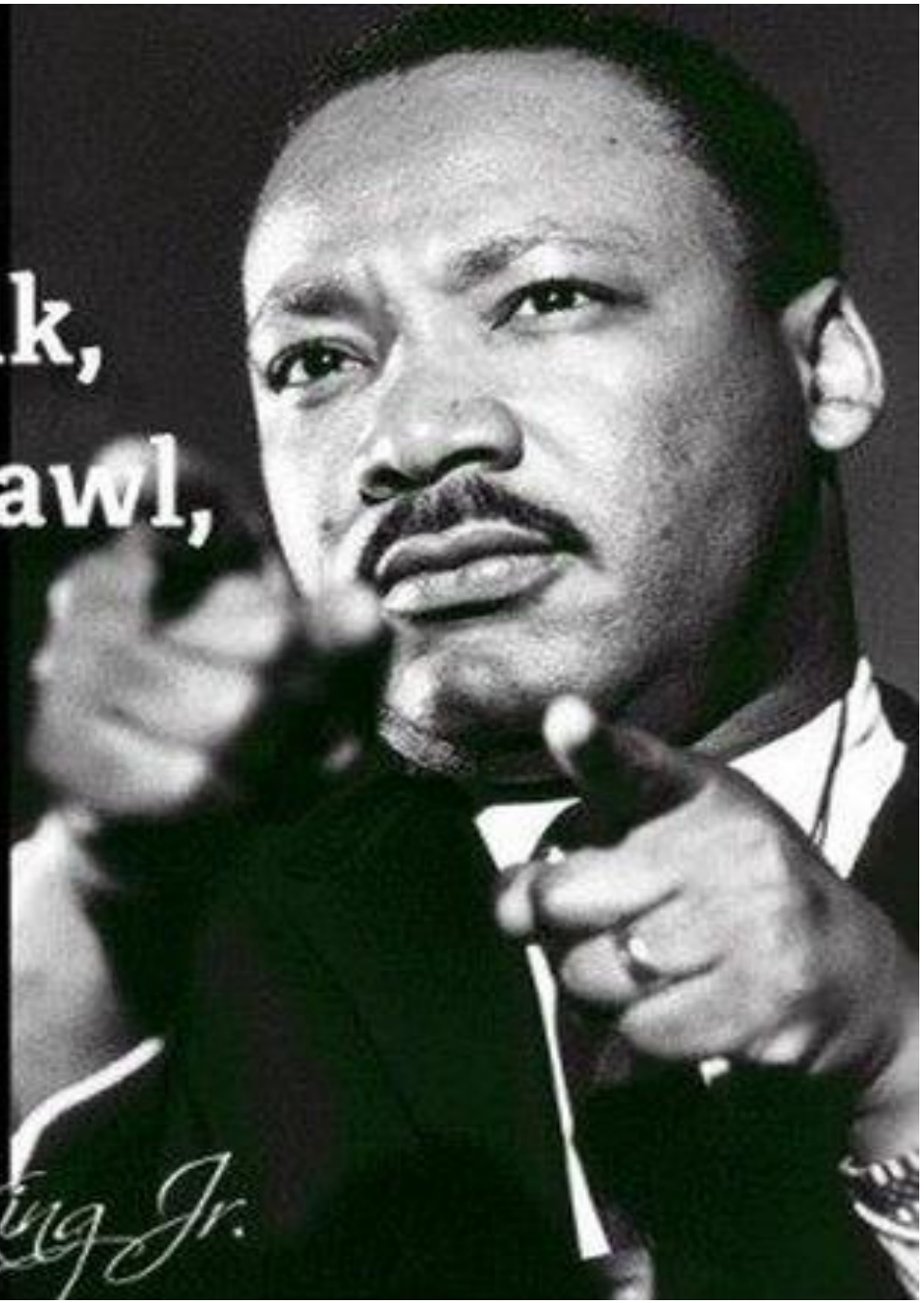
Applications of pharmacokinetics



Using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy

If you can't fly then run,
if you can't run then walk,
if you can't walk then crawl,
but whatever you do
you have to
keep moving forward.

~ Martin Luther King Jr.



THANK YOU

ANY QUESTIONS?