



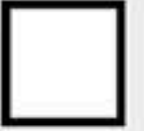
Medical Committee
The University of Jordan



PHARMACOLOGY

Slide # : 6
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SHEET



SLIDES



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Drug efficacy is questioned..

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Drugs 'don't work on many people'

A senior executive at Europe's largest drug maker has admitted most prescription medicines don't work for most people, it is reported.

Allen Roses, of GlaxoSmithKline, is quoted in a national newspaper as saying more than 90% of drugs only work in 30-50% of people.

He said: "Drugs on the market work, but they don't work in everybody."

Mr Roses, an expert in genetics, said new developments should help tailor drugs more specifically.

At present, pharmaceutical companies adopt a "one-drug-fits-all" policy.

But Mr Roses said refinements in genetic technology should make it possible to identify more precisely those people who were likely to benefit from a drug.



Drugs may be more specifically targeted

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PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE

HYPERTENSION DRUGS
ACE Inhibitors

10-30%



HEART FAILURE DRUGS
Beta Blockers

15-25%



ANTI-DEPRESSANTS

20-50%



CHOLESTEROL DRUGS
Statins

30-70%



ASTHMA DRUGS
Beta-2-agonists

40-70%



Percentage of the patient population for which any particular drug is ineffective

Variation in drug responses

Sources of individual variation

Each patient is unique in ability to respond and to how they each respond, but formation of "IDEAL DRUG" will lessen this variation

- Age- very important factor
- Sex- due to hormonal differences
- Weight- less effective and longer lasting in obese individuals (storage in fat)
- Kidney & liver functions - elimination of drug
- Genetic variables- tolerance, allergy (though not always genetic)

Geriatrics

Adults >65 years old

- Fastest growing population in US
- 20% of hospitalizations for those >65 are due to medications they're taking

Pharmacokinetics

- **Decrease in total body water and increase in total body fat affects volume of distribution**
- **Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin**
 - **Serum levels may go up due to decreased volume of distribution**
- **Fat soluble: diazepam, thiopental, trazadone**
 - **Half life increased with increase in body fat**

Metabolism

- Oxidative metabolism through cytochrome P450 system does decrease with aging,
- resulting in a decreased clearance of drugs

Excretion and Elimination

- GFR generally declines with aging, but is extremely variable
 - 30% have little change
 - 30% have moderate decrease
 - 30% have severe decrease
- Serum creatinine is an unreliable marker, why????
- If accuracy needed, do Cr Cl

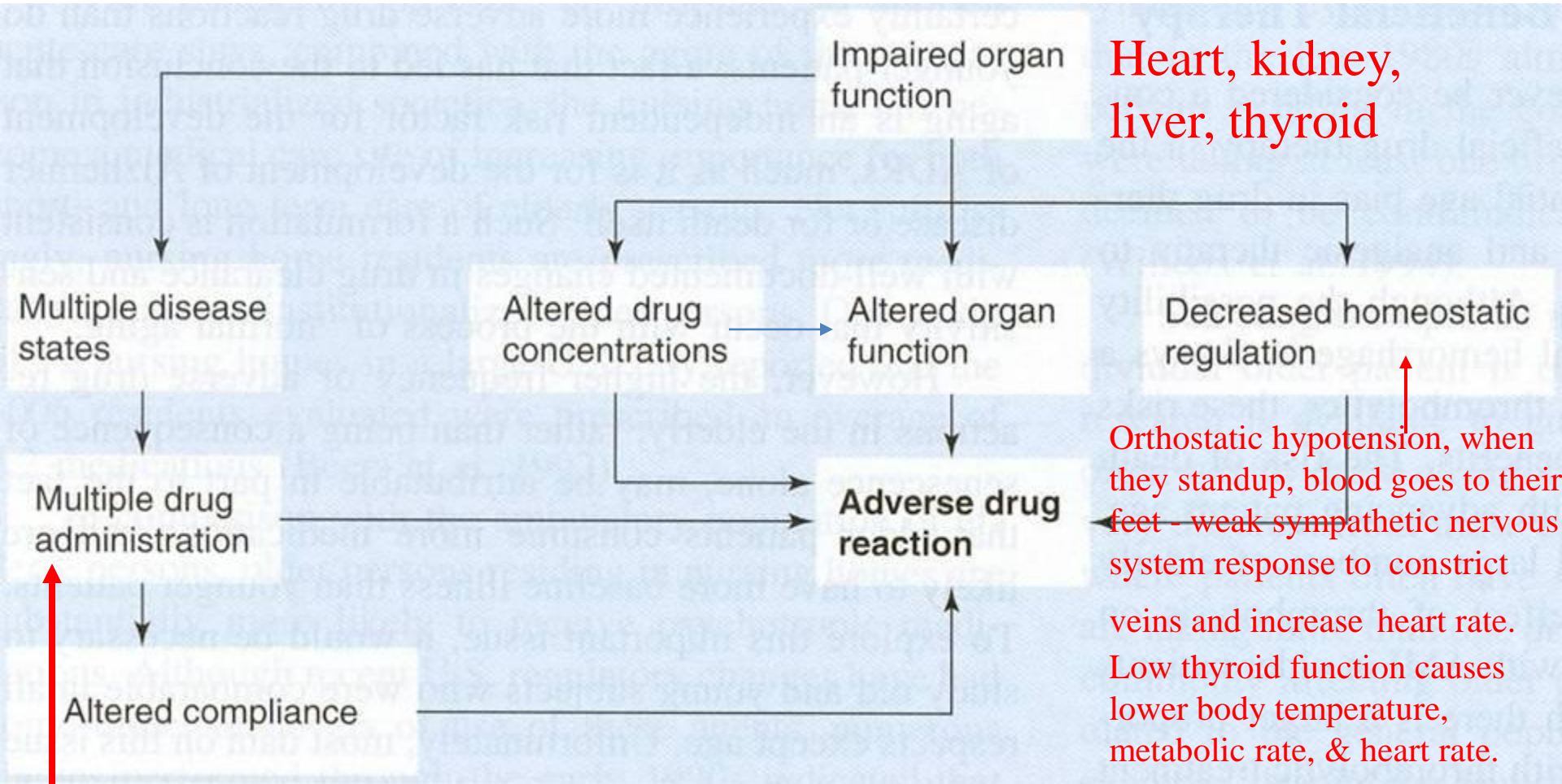
Example: Creatinine Clearance vs. Age

<u>Age</u>	<u>Scr</u>	<u>CrCl</u>
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Pharmacodynamics (PD)

- Age-related changes:
 - ↑↑ sensitivity to sedation and psychomotor impairment with benzodiazepines
 - ↑↑ level and duration of pain relief with narcotic agents
 - ↑↑ drowsiness and lateral sway with alcohol
 - ↓↓ HR response to beta-blockers
 - ↑↑ sensitivity to anti-cholinergic agents
 - ↑↑ cardiac sensitivity to digoxin

Factors contributing to adverse drug reactions in elderly patients



Polypharmacy

How many prescription medications are too many? >4 or >6
Many elderly people receive 12 medications per day

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
 - More available drug
- Immature liver/kidneys
 - Liver often metabolizes more slowly
 - Kidneys may excrete more slowly

Pediatric Dosing

- Traditionally, for less frequently used drugs, extrapolation is done from adult dose on a weight or surface area basis.

Problems

- Absorption may be more or less than adult
- Clearance of some drugs in children is affected by maturation,
 - Cytochrome P450 enzyme system matures over time
 - Glomerular filtration changes over time
- Drug targets may vary with age
- **“Children are not Small Adults”**

Examples

- CYP isoforms vary with age:
For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life
- Carbamazepine (3A4) clearance faster in children than adults
– requires higher doses

SPECIAL CONSIDERATIONS IN PREGNANT AND BREASTFEEDING WOMEN

- IN PREGNANCY, THE DRUG IS REALLY GOING TO TWO PEOPLE, SO YOU MUST CONSIDER HOW THE DRUG MAY AFFECT THE GROWING FETUS.
- IMPORTANT FOR WOMEN TO AVOID AS MANY DRUGS AS POSSIBLE UNLESS ORDERED BY THE PHYSICIAN.
- TERATOGENIC—DRUGS THAT ARE LIKELY TO CAUSE MALFORMATIONS OR DAMAGE IN THE EMBRYO OR FETUS.
- THESE TYPE OF DRUGS SHOULD BE AVOIDED.

Impact of pregnancy on maternal pharmacodynamics ?

- GI absorption

Reduction in gastric motility

Reduction in gastric acid secretions

Increases in gastric pH

N/V of pregnancy

- Resultant decrease in a absorption and relative lower plasma drug concentrations

Definitions

- **Pharmacogenetics** is the study of the effects of a drug in relation to a single or defined set of genes.
- **Pharmacogenomics** is the study of the effect of a drug in relation to the functions and interactions of all the genes in the genome.

The goal



rational means to optimize drug therapy and ensure maximum efficacy with minimal side effects.

Example

- African hypertensive

 diuretics

 ACEI and β -blockers.

- Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.

the first race-based prescription drug in the United States.

(FDA) then approved (BiDil)

What is Personalized Medicine?

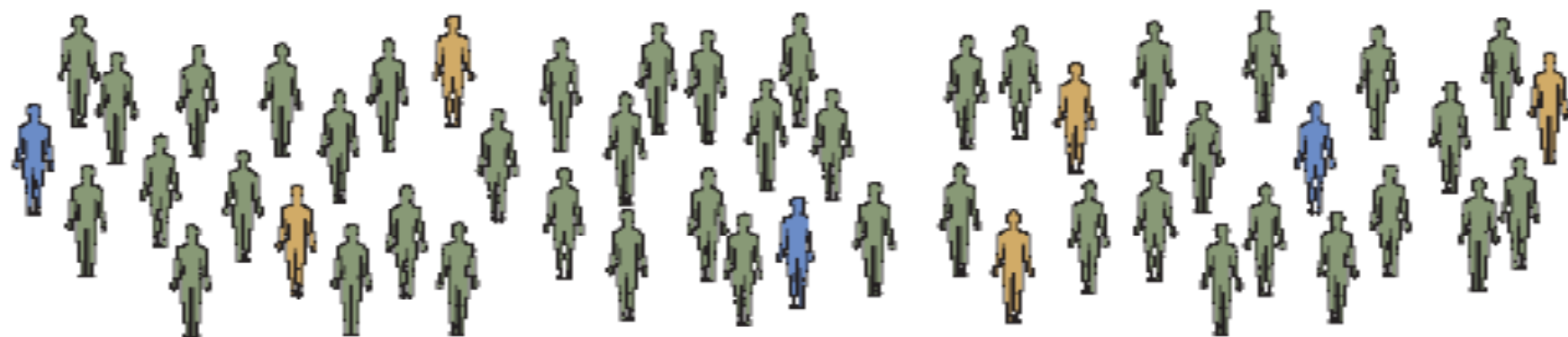
Personalized medicines simply means the prescription of specific treatments and therapeutics best suited for an individual's genetic makeup

Personalized Medicine will enable doctors to:

Use medications and other treatments that would work best for each individual

Avoid medications that would cause an individual to have bad side effects

Different patients receiving the same medicine



GCCCACTC

Treat patients genetically predisposed to respond well.



GCCCGCTC

Screen out patients likely to experience adverse events or lack of efficacy



What are SNPs

- Single Nucleotide Polymorphisms
 - A SNP is a site of the DNA in which a single base-pair varies from person to person
 - They are the most common form of genetic variation in the human genome (frequency of >1%)

The basis of Genetic Diversity...



- Different arrangements of NUCLEOTIDES in a nucleic acid (DNA) provides the key to DIVERSITY among living organisms.

Genetic Factors Determining Drug Response

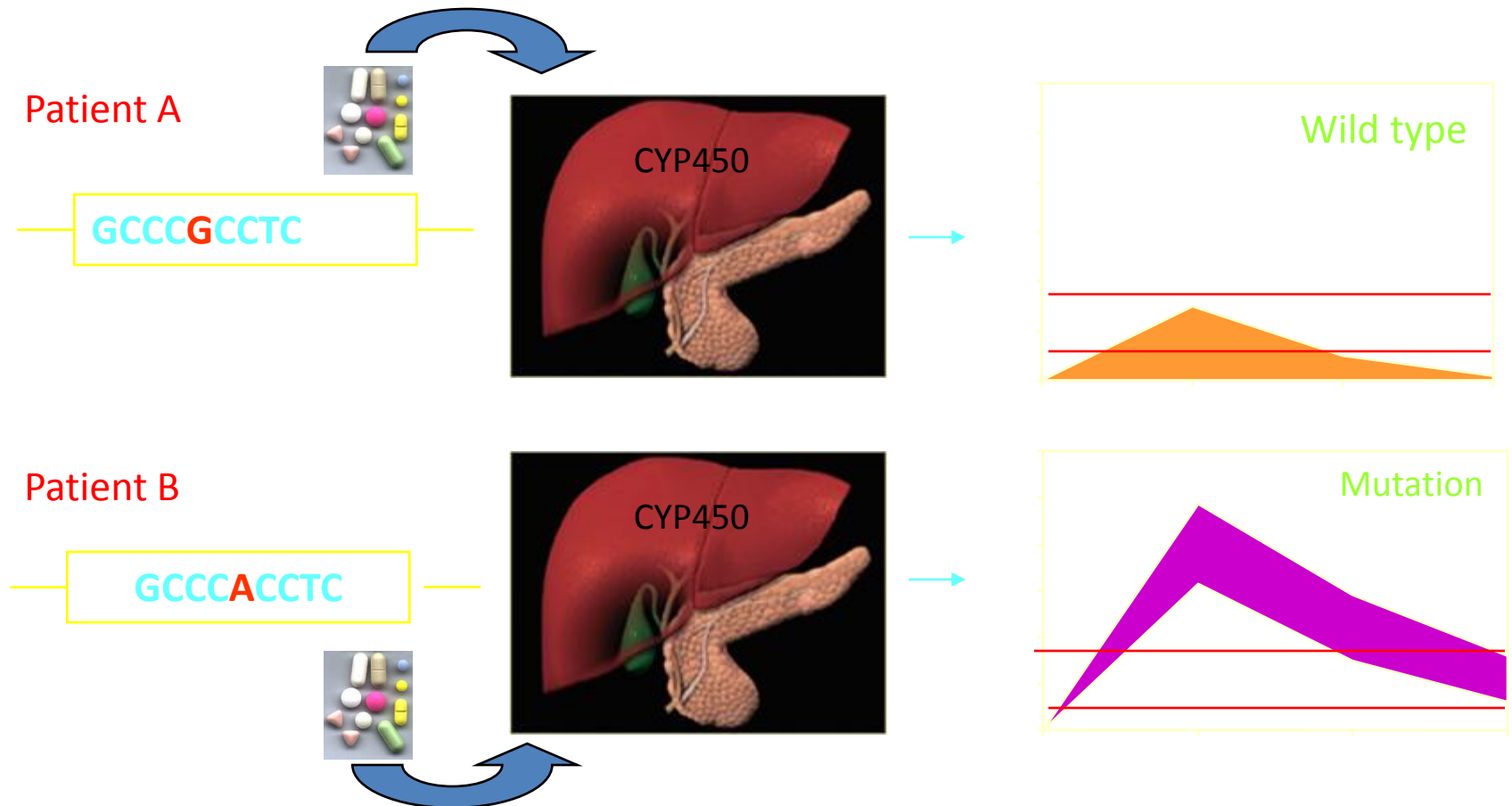
Polymorphisms
in Drug
Receptors
(e.g. β 2AR)

Polymorphisms
in Drug
Transporters
(e.g. MDR1)

Polymorphisms
in Drug
Metabolizing
Enzymes
(e.g. CYP2D6)

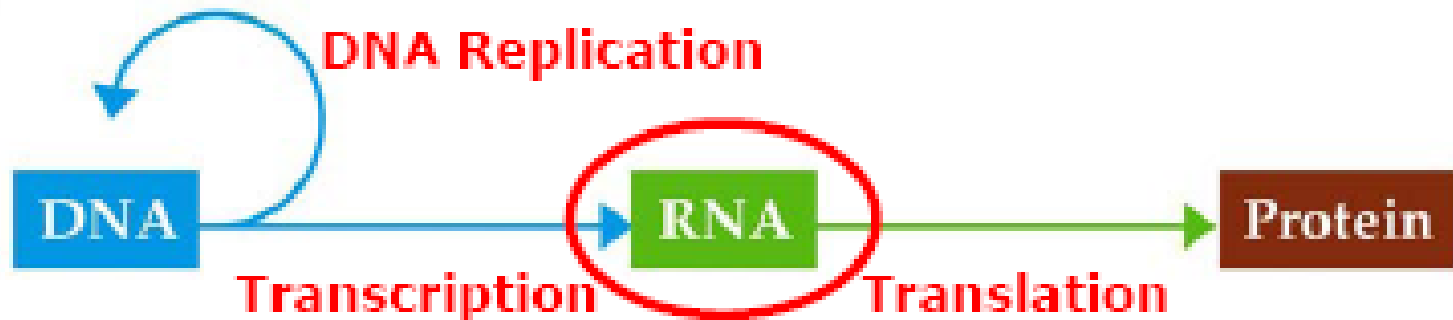
Pharmacogenetics and Drug Metabolism

Same dose but different plasma concentrations



The Central Dogma

The Flow of Information: DNA → RNA → Protein



- A gene is expressed in two steps:
 - DNA is transcribed to RNA
 - Then RNA is translated into protein