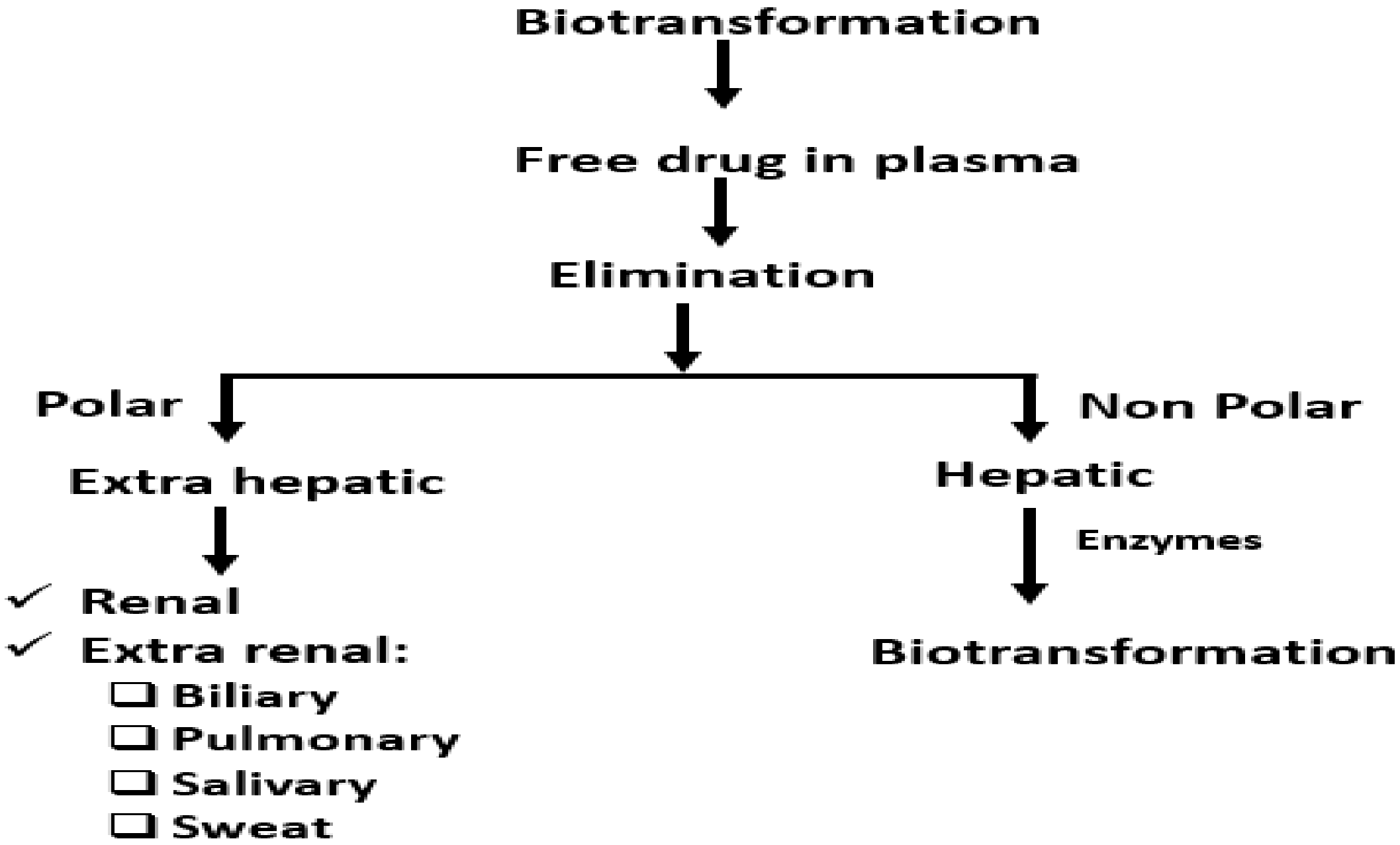

Biotransformation
Free drug in plasma
Elimination
Polar
Non Polar
Extra hepatic
Hepatic
Enzymes
✓ Renal
✓ Extra renal:
❑ Biliary
❑ Pulmonary
❑ Salivary
❑ Sweat
Biotransformation

- Aim of biotransformation

1- Transform the drug from non polar to polar to be excreted by kidney.

2- Transform the pro-drug to Active form.

- # Types of Biotransformation

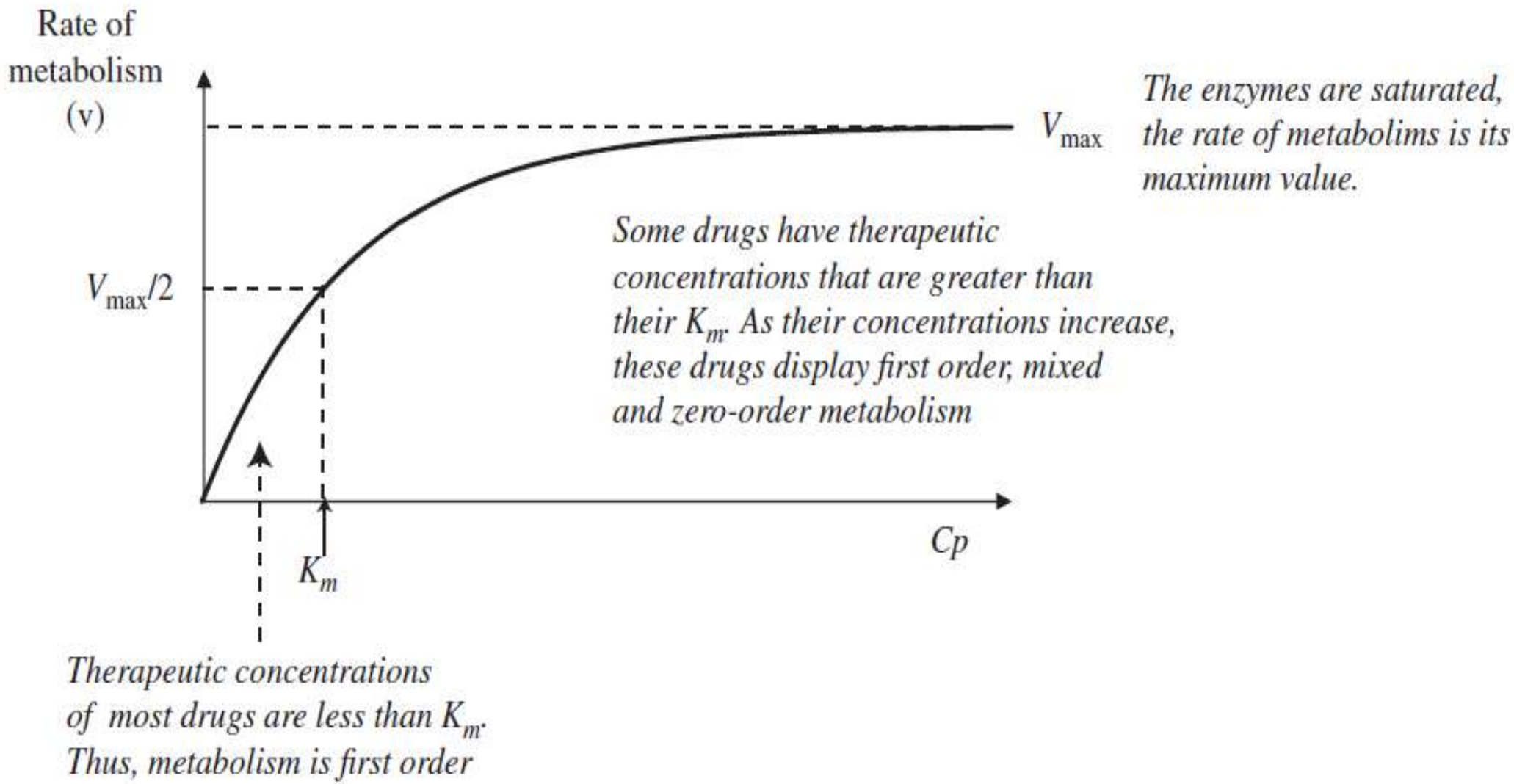
1- Activator Biotransformation

Prontosil→ Sulfanilamide

2- Inactivator Biotransformation

•Adrenaline→Dihydroximandelic acid.

Kinetics of reactions



- # Reactions of drug metabolism

✓**Non-Synthetic reactions**

1-Phase I:

- ✓ Oxidation Activation
- ✓Reduction Unchanging
- ✓Hydrolysis Inactivation

Introducing or unmasking polar functional groups (OH, NH2)

✓**Synthetic reactions**

2- Phase II :

Conjugation

- ✓Glucuronic acid
- ✓Sulferic acid
- ✓Acetic acid
- ✓Amino Acids (glycine)

Types of Biotransformation according to position of enzymes in the liver (reactions)

1- Microsomal : in the liver

2- Non Microsomal : outside the liver

Biotransformation reactions

1- Oxidation reactions

- **In microsomal system:**
  1. **Aromatic hydroxylation**
  2. **Aliphatic hydroxylation**
  3. **Epoxidation**
  4. **Deamination**
  5. **N- dealkylation**
  6. **O- dealkylation**
  7. **S- dealkylation**
  8. **N- oxidation and N- hydroxylation**
  9. **Dehalogenation**
  10. **Desulfuration**
  11. **Sulfoxidation**
- **Out microsomal system:**

1. **Amino oxidation: MAO**
2. **Alcohol dehydrogenation: Ethanol Oxidation**

2- *Reduction reactions*

➢In microsomal system:

1. Nitroreduction
2. Azo reduction
3. Dehalogenation reactions

➢Out microsomal system:

1. Reduction of aldehyde
2. Dehydroxylation of catechol

3- Hydrolysis reactions

1. Hydrolysis of esters
2. Hydrolysis of amides

4- Conjugation reactions (phase II)

Addition of :

- ✓Glucuronic acid
- ✓Sulferic acid
- ✓Acetic acid
- ✓Amino Acids (glycine)
- ✓ Methylation

- Biotransformation reactions and pharmacologic activity of the metabolite

1- **Active drug to inactive metabolite**

- Amphetamine by Deamination phenylacetone
- Phenobarbital by hydroxylation hydroxy phenobarbital

2- **Active drug to active metabolite**

- Codeine by demethylation morphine.
- Procainamide by acetylation N-acetylprocainamide
- Phenylbutazone by hydroxylation Oxyphenylbutazone

3-Inactive drug to active metabolite

- Hetacillin by hydrolysis Ampicillin
- Sulfasalazine by azo reduction Sulfapyridine

4-Active drug to reactive intermediate

- Acetaminophen by aromatic hydroxylation reactive metabolite (Hepatic necrosis)
- Benzopyrene by aromatic hydroxylation reactive metabolite (Carcinogenic)

Drugs metabolism
Part 2

❑ Factors affecting the biotransformation

A- The physiological modifications

1. **Species :**
   - ✓ Qualitative differences
   - ✓Quantitative differences
2. **Age**
3. **Race**
4. **Hormonal influences :**
   - ✓ Sexual hormones
   - ✓Suprarenal hormones
   - ✓Thyroid hormones
5. **Nutrition**
6. **Environmental factors**

❑ Factors affecting the biotransformation

B- Pharmacological Modifications:

1- Stimulation of microsomal system enzymes:

A- Classification of enzyme **Inductor substrates:**

- ✓**Phenobarbital type**
- ✓**Polycyclic hydrocarbons types**
- ✓**Steroidal types**

B- Effect of enzyme ***inductors*** *in the hepatic morphology and hepatic biochemistry*

2- Inhibition of microsomal system enzymes

❑ Factors affecting the biotransformation

C- Pathological Modifications

1-Hepatopathy:

- ✓P.K Modifications
- ✓P.D Modifications

2- Hereditary diseases:

- ✓Hereditary methemoglobinemia
- ✓No hemolytic Familial Jaundice:
  - ✓ Crigler- Najjar syndrome
  - ✓ Dubin – Jhonson syndrome
- ✓Mongolism

3- Specific hereditary anomalies:

- ✓ **Rapid and slow metabolizers of isoniazid**
- ✓**Hydrolysis of succinylcholine**

A. The physiological modification affecting the biotransformation

1. Species :

❖ Qualitative Differences

➢ **Cats**: Exogenous substances are not conjugated with glucuronic acid to form glucuronids but endogenous substances as billiribin undergo conjugation with glucuronic acid.

➢ **Dogs**: The sulfanilamide and/ or sulfathiazole do not convert into acetylated aromatic amines.

Acetylation → Nephrotoxic for man

❖ Quantitative Differences

✓Duration of sleepiness for different species.

✓Relationship between enzymes activity and $t_{1/2}$???

✓Ex: Hexobarbital

Hexobarbital

Species	Effect (Duration) minuts	$t_{1/2}$	Enzyme activity
Mice	12	19	289
Rabbit	49	60	196
Rate	90	140	134

A. The physiological modification affecting the biotransformation

2- Age :

- **Chloramphenicol :**
  - In neonates → Gray's syndrome → Cardiovascular collapse →death.
    (Absence of glucuronyl transferase)
  - In adults: %90 Glucuronization & %10 Deacetylation.

- **Newborn:**

Low microsomal enzyme capacity → Bilirubin increasing but when used with phenobarbital (enzyme inducer)→ Bilirubin decreasing.

- **Elderly patients:**

Generally decreased enzyme activity→ long $t_{1/2}$

A. The physiological modification affecting the biotransformation

3. Race:

- **Black people:**

  Atropine administration → less mydriasis (due to high enzyme activity).

- **5 Rats:**

  Administration of methoxyflurane→ high F in blood → Nephrotoxicity (died)

  Only one rat have rapid biotransformation (Survived).

A. The physiological modification affecting the biotransformation

4. Hormonal influences:

A- Sexual hormones

•More intensive action of drugs in female due to **more adipose tissue** and **less active metabolism** than in male.

•Example: The duration of sleepiness after administration of Hexobarbital in rats

Sex	Duration(min)	Enzyme activity
Female	80	134
Male	22	682

B- Adrenal hormones

•The **adrenalectomy** in rats reduces the biotransformation of hexobarbital and other drugs but when administration cortisone, cortisol or prednisolone the biotransformation increases.

C. Thyroid hormones

(Hypo and hyperthyroidism)

A. The physiological modification affecting the biotransformation

5. Nutrition:

- ✓Diet with less protein and more carbohydrates → Decreases the microsomal enzyme activity.
- ✓Vitamin C→ Increases the enzyme activity.
- ✓Tobacco and alcohol → Enzyme induction.

6. Environmental factors:

- ✓Industrial pollution
- ✓Agriculture pollution

Drugs Metabolism
Part 3

B. The pharmacological modification affecting the biotransformation
Drug – Drug interaction

1. **Stimulation of microsomal enzyme system:**

- Increasing enzyme capacity (activity)→ decreasing t 1/2.
- The stimulants of microsomal enzyme system are called **ENZYME INDUCERS,** and are classified to:

    1. Phenobarbital type.
    2. Polycyclic hydrocarbons type.
    3. Steroidal hormones type (anabolic).

B. The pharmacological modification affecting the biotransformation

1.Phenobarbital type

- Phenobarbital reduces the effect of Hexobarbital, Phenytoin, and bishydroxycumarine (in rats).
- Related Drugs:
    - Phenobarbital
    - Barbital
    - Pentobarbital
    - Meprobamide
    - Phenylbutazone
    - Tolbutamide
    - And others.

1.Phenobarbital type

The mechanism of action:

- Increases the total hepatic mass.
- Increases microsomal enzyme activity (enzyme activity/mg of microsomal proteins).
- Increases NADPH cytochrome -C- Reductase and NADPH cytochrome –P450-oxidase.
- Increases microsomal proteins.

2. Polycyclic hydrocarbons type

(3- methylcolanterene)

- Increases the stimulation of enzymes (selective).
- Increases the amount of cytochrome P-450 but not the NADPH cytochrome reductase.
- Increases the lag time (after administration of 3- methylcolanterene), the lag time is long (hours).
- Related compounds:

  3,4- Benzppyrene

  1,2,5,6- Dibenzatracene

  1,2- Benzatracene

  1,2,3,4- Dibenzopyrene

  Fluorane and others.

3. Steroidal hormones (Anabolic)

- The administration of testosterone and methyl testosterone in rats
  → Increases hepatic metabolism.

- The administration of Phenobarbital + Steroid → Summation effect (induction).

B. The pharmacological modification affecting the biotransformation

➢Effect of enzyme inductors in the hepatic morphology and hepatic biochemistry:

- Increases the hepatic mass due to hypertrophy and hyperplasy.
- Increases synthesis of enzyme proteins and this is related to the synthesis of DNA & RNA.
- The administration of methylcolanterene → Increases DNA in %40.

➢The practical consequences of enzyme inductors:

1. Treatment of pathologies as Kernicterus, Gray Syndrome of newborn.
2. Patients treated with Phenobarbital or any inductor need to increase the dose of other drugs as phenytoin and bis- hydroxyl cumarine.
3. Autoinduction: The chronic administration of inductors (Tolerance).????

B. The pharmacological modification affecting the biotransformation

2. Inhibition of microsomal enzyme system

- **Decreases the biotransformation.**
- **Increases the concentration of drug in blood.**
- **Increases Toxicity.**
- **Increases t1/2.**

Examples:

- **SKF-525A : Administered in rats + Hexobarbital→ increases Sleepiness.**
- **MAO inhibitors → Increases the conc. Of neurotransmittors → Stimulation.**
- **Acetylcholinsteras inhibitors → increases Ach→ Increases cholinomimetic action.**
- **Xanthine oxidase inhibitor (Allopurinol) → Decreases uric acid.**
- **Aldehyde –dehydrogenase → Disulfiran Alcoholic people.**

C. The pathological modification affecting the biotransformation

1. Hepatopathy

A. Pharmacokinetic modifications

Hyperbilirubinemia >2mg/100mL

Decreases enzyme activity→ decreases biotransformation →increases t½ (of sulfamides, isoniazid, lincomycine, rifampicine,and chloramphenicol) →→

Increases concentration of drug in blood .

B. **Pharmacodynamics modifications**

- Encephalopathy → caused by metabolites when are not presented in normal conditions.
- Clofibrate (Antihyperlipidemic) for increased cholesterol because decreased biliary elimination of cholesterol.

C. The pathological modification affecting the biotransformation

2.Hereditary disease

A.Hereditary Methemoglobinemia:

- Caused by nitrits due to oxidation of Fe+2→Fe+3 in hemoglobin molecule by redox system as vit C.
- NADPH and NADH metoglobin reductase.
- NADH not present in patients with Hereditary Methemoglobinemia.
- Related drugs produces Methemoglobinemia.

- Direct oxidation: Nitrites, Nitrates, Chlorats, Purines, Blue methylene.
- Indirect oxidation: Aniline, Sulfonamides, Acetphenitidine, Nitrotuluene,Acetanilide.

B. Non familial Juandice:

Glucuronate formation deficiency → No conjugation → increasing metabolites.

1.Crigler –Najjar Syndrome

2.Dubin- Jhonson Syndrome

C. Monogolasim : Down's syndrome , more sensible for atropine.

C. The pathological modification affecting the biotransformation

3.Specific hereditary anomalies

A.Rapid and slow metabolizers of isoniazid :

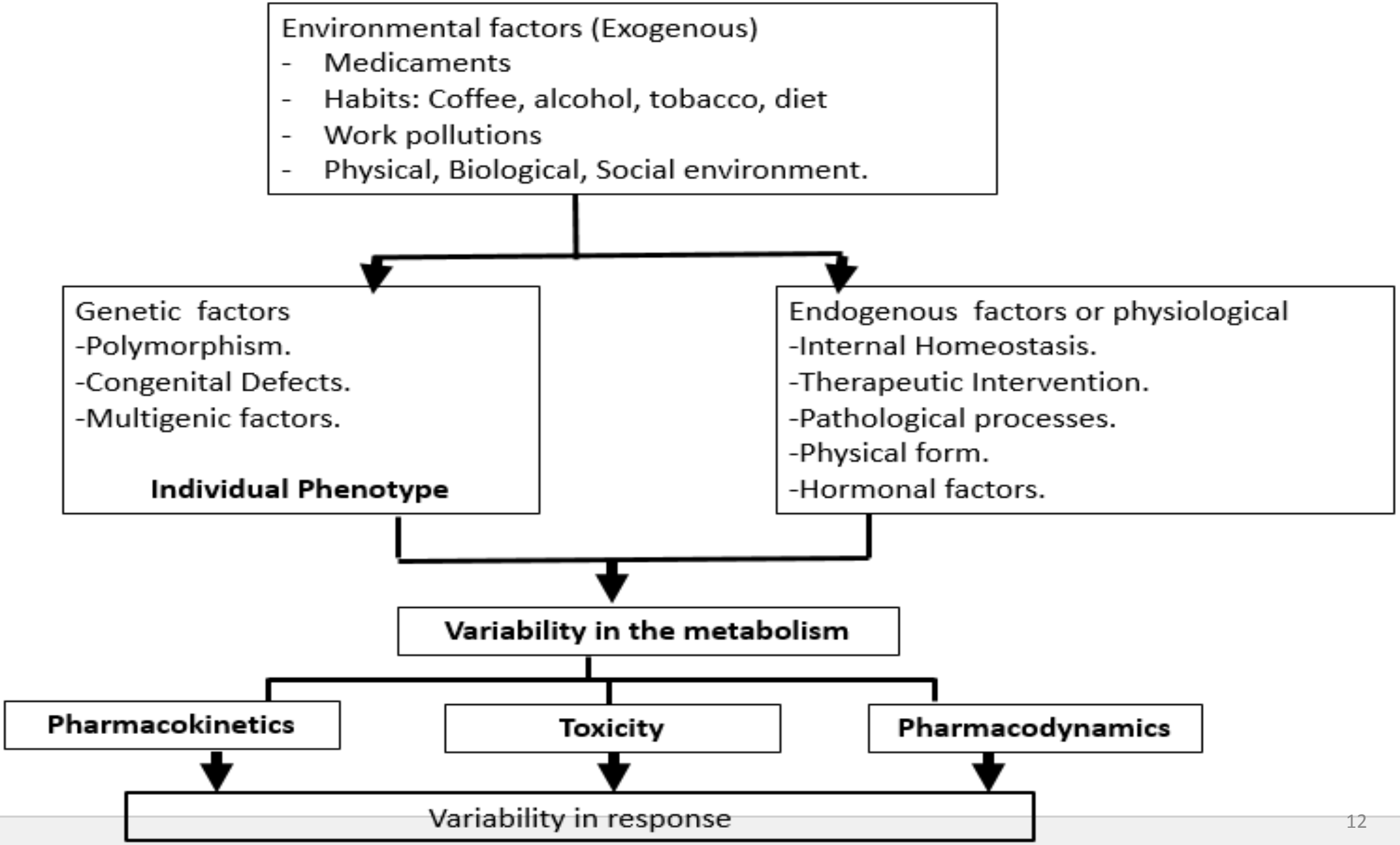
Rapid → Japan %84, Scadinavia %82 → **decreasing t½**.

Slow→ Meditarian area 13 %.

B. Hydrolysis of Succinylcholine →Neuromuscular relaxation

Cholinesterase →(Glycoprotein, pseudo cholinesterase (Atopic).

Factors can modify the metabolism



Molecular basis of polymorphism

- Homozygotic and heterozygotes genes → Stable RNA messenger → Functional metabolic enzyme→ Efficient metabolizers.

- Homozygotic genes with mutation → Unstable or aberrant RNA messenger → less Functional metabolic enzyme → Deficient metabolizers.

In Deficient metabolizers:

- Increased bioavailability.
- Decreased Clearance.
- Increased drug accumulation.
- Increased pharmacological effect (therapeutic and toxic).