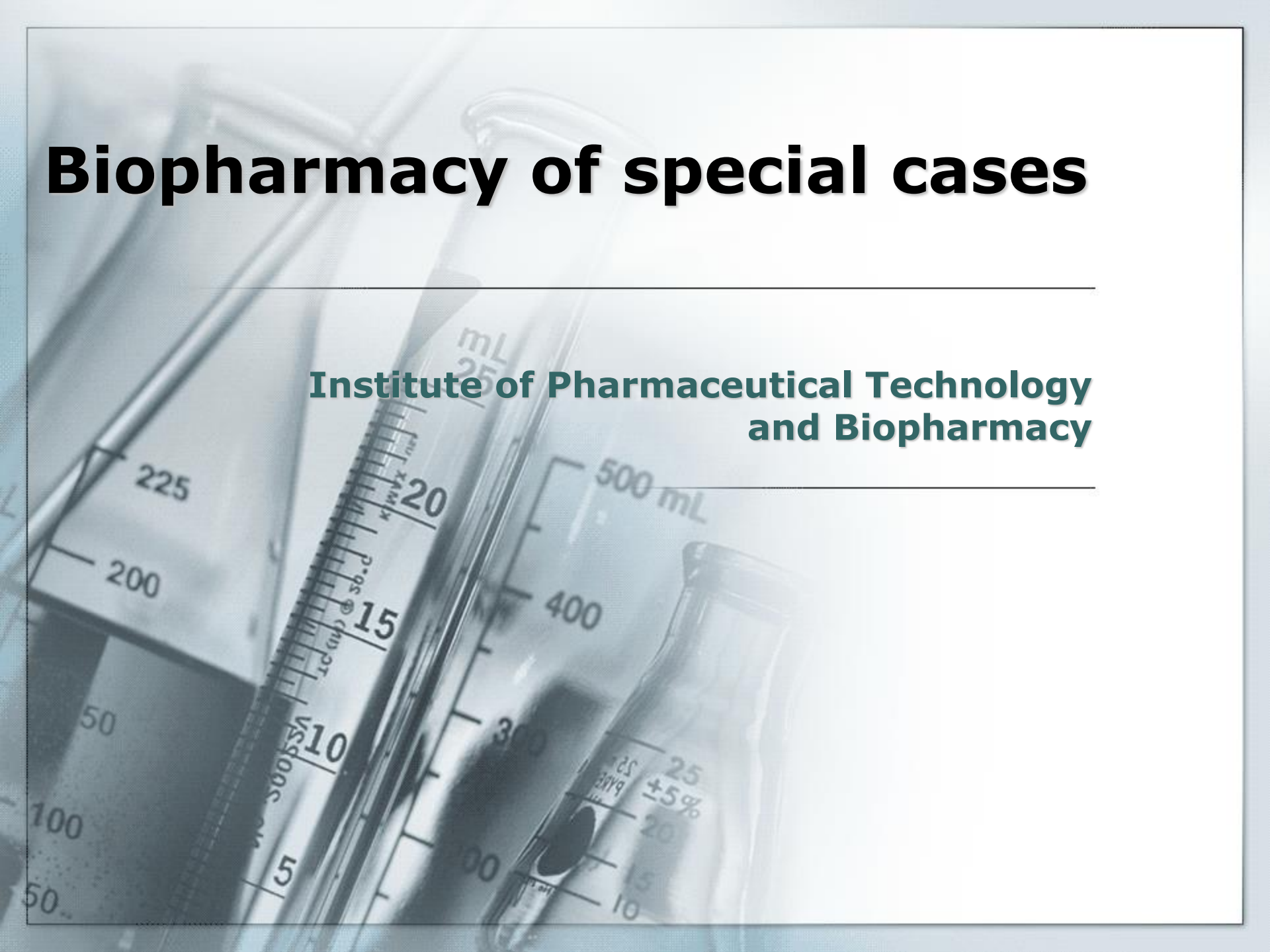
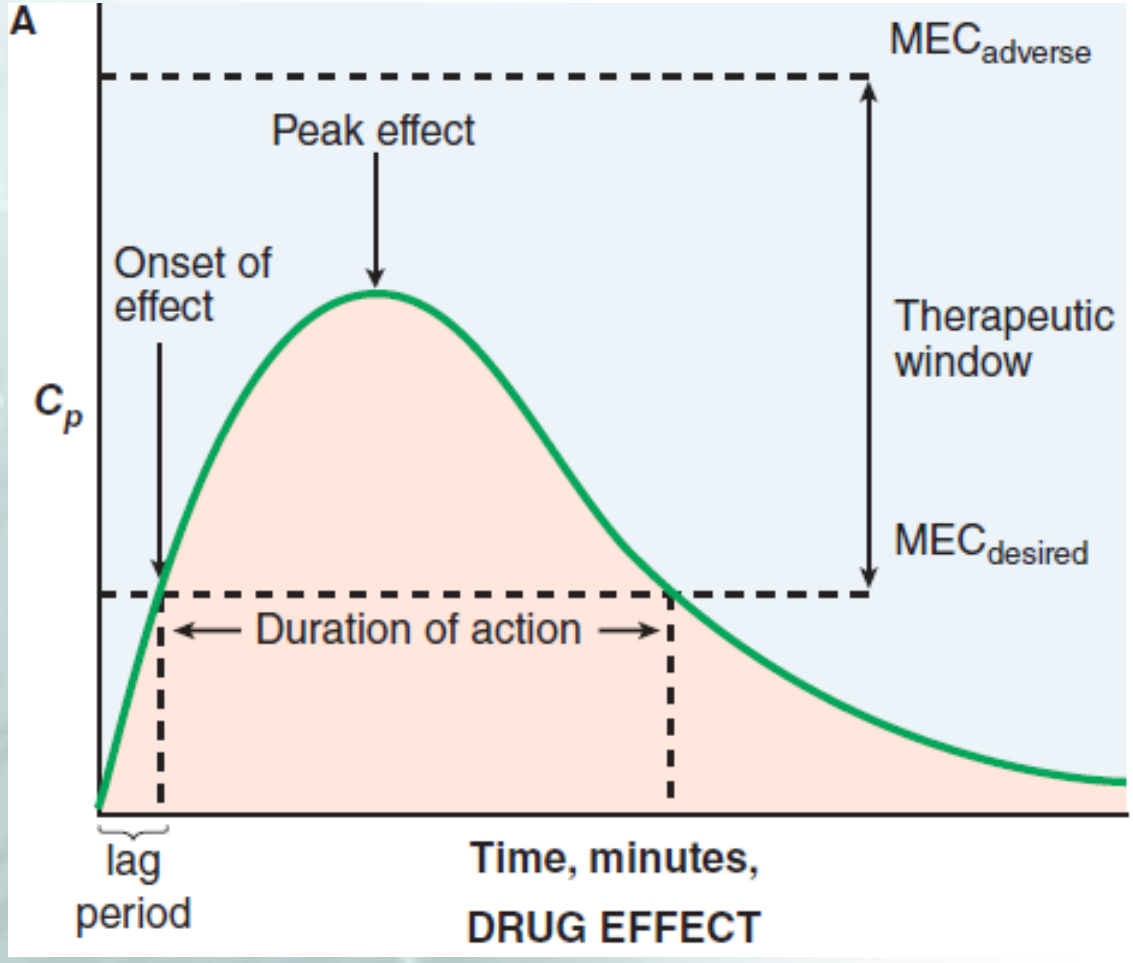
Biopharmacy of special cases

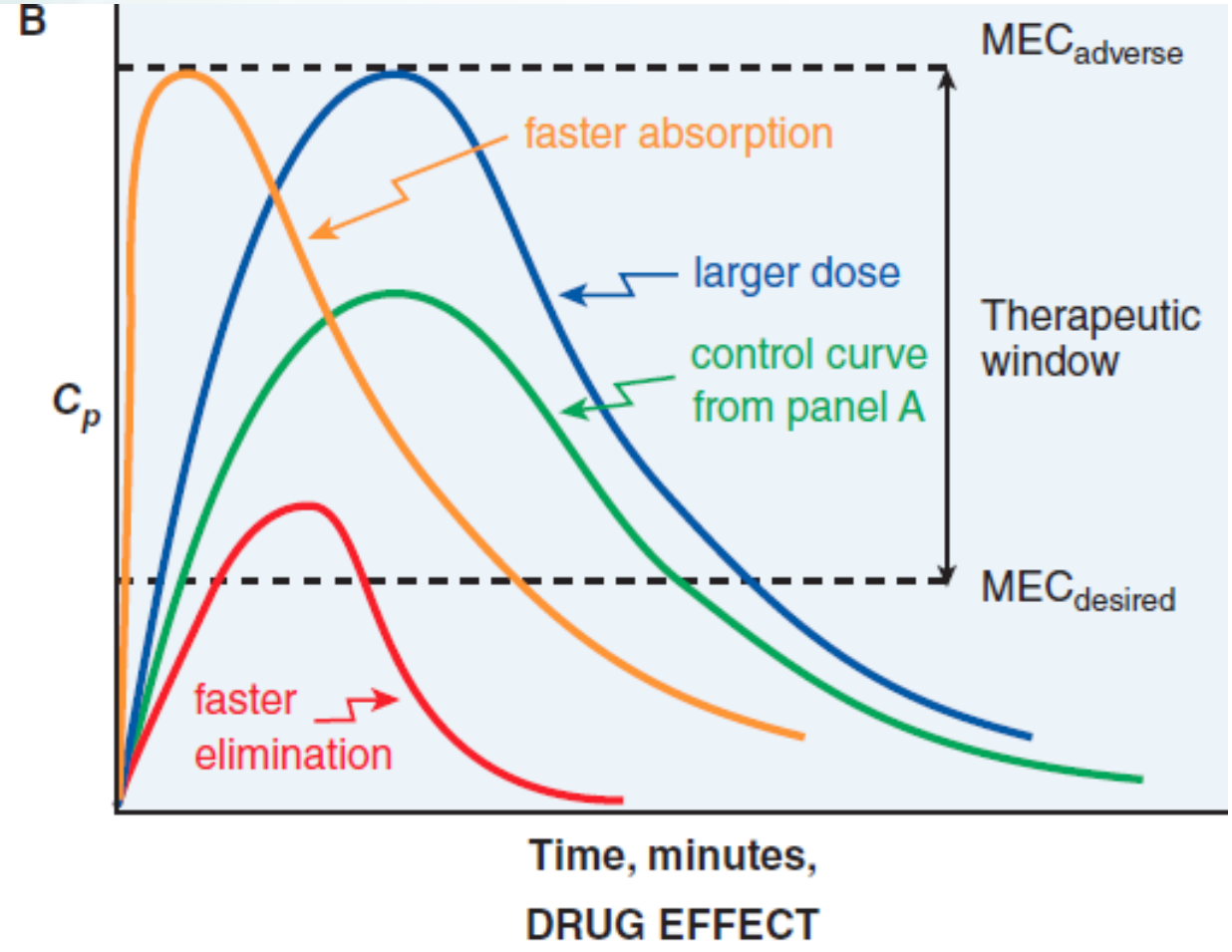


Institute of Pharmaceutical Technology
and Biopharmacy

„Ideal" kinetic



„Changed" kinetic



Pharmacokinetic's Changes may be caused by:

- **Kidney clearence's changes**
- **pH of urine**
- **Liver function**
- **Enzyme induction**
- **Enzyme inhibition**

Pharmacokinetic changes may be caused by:

- **Pregnancy**
- **Early childhood**
- **Old age**

Pregnancy

- Drug use during pregnancy and lactation **requires special consideration** because both the mother and the child are affected.
- Few drugs are considered safe, and drug use is generally contraindicated.
- Many pregnant or lactating women **take drugs for acute or chronic disorders** or habitual use of alcohol and tobacco.

Physiologic – Pharmacokinetic's Changes

- In the pregnant woman, **physiologic changes alter drug pharmacokinetics**.
- Drug effects are **less predictable** than in the nonpregnant state.
- The physiologic and related pharmacologic changes are as follows:

Physiologic – Pharmacokinetic's Changes

Physiologic Change:

- 50% Increase in **plasma volume** and **body water**.

Pharmacokinetic Change:

- Water soluble drugs are distributed and "diluted" more than in the nonpregnant state.
- Drug dosage requirements may increase.
- This effect may be offset by other pharmacokinetic changes of pregnancy.

Physiologic – Pharmacokinetic's Changes

Physiologic Change:

- Increased **weight** (~14 Kg) and body fat

Pharmacokinetic Change:

- Fat-soluble drugs are distributed more widely.
- Drugs distributed to fatty tissues tend to linger in the body because they are slowly released from storage sites.

Physiologic – Pharmacokinetic's Changes

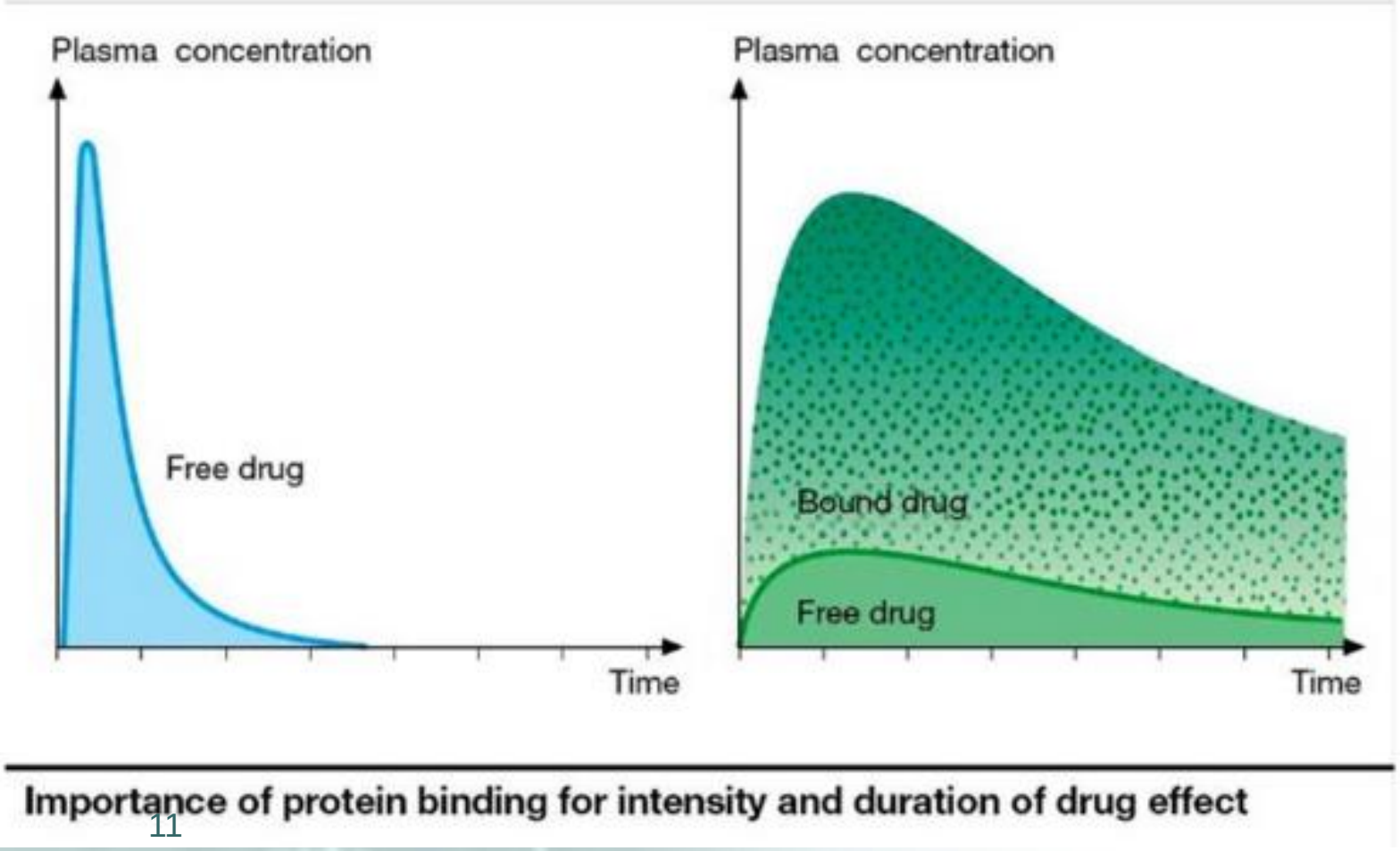
Physiologic Change:

- Decreased **serum albumin**.
- The rate of albumin production is increased. However, serum levels fall because of plasma volume expansion.
- Many **plasma protein-binding sites are occupied** by hormones that increase during pregnancy.

Pharmacokinetic Change:

- **More free drug is available** for therapeutic or adverse effects on the mother and for placental transfer to the fetus.
- A given dose of a drug is likely to produce **greater** effects than it would in the nonpregnant state.

Physiologic – Pharmacokinetic's Changes



Importance of protein binding for intensity and duration of drug effect

Physiologic – Pharmacokinetic's Changes

Physiologic Change:

- Increased **renal blood flow** and **glomerular filtration rate** secondary to increased cardiac output.

Pharmacokinetic Change:

- Increased excretion of drugs by the kidneys, especially those excreted primarily unchanged in the urine (digoxin, lithium).
- In late pregnancy, the increased size of the uterus decreases renal blood flow in supine position.
- This results in decreased excretion and prolonged effects of renally excreted drugs.

Maternal – Fetal Circulation

- On the maternal side, arterial blood pressure carries blood and drugs to the placenta.
- Drugs readily cross the placenta, mainly by **passive diffusion**.
- Placental transfer begins approximately the **fifth week** after conception.
- Drugs given on a regular schedule, **equilibrate with fetal blood which contains 50% - 100% of the maternal blood**.
- After entering the fetal circulation, **large amounts of drugs are active because albumin levels are low** and thus low levels of drug is bound.

Maternal – Fetal Circulation

- Drug molecules are distributed in two ways: **liver** and **kidney**.
- Most are transported to the liver, where they are metabolized.
- Metabolism is slow because **the fetal liver is immature**
- Drugs metabolized by the fetal liver are excreted by fetal kidneys into amniotic fluid.
- Excretion also is inefficient owing to **immature fetal kidneys**.
- The fetus **swallows some amniotic fluid**, and some drug molecules are **recirculated**.

Maternal – Fetal Circulation

- Drug molecules are also distributed to the brain.
- Drugs enter the brain easily because the **blood–brain barrier is poorly developed** in the fetus.
- Umbilical arteries transport half of the drug- containing blood to the placenta where **reenters the maternal circulation.**
- Thus, the mother can metabolize and excrete some drug molecules for the fetus.

Teratogens

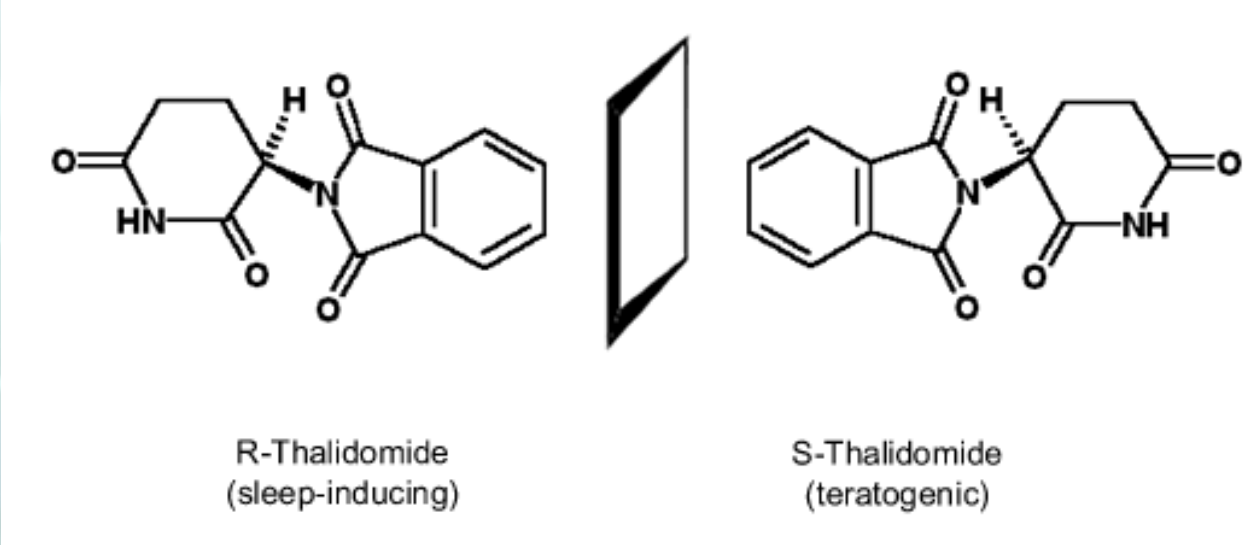
Definition:

A teratogenic, fetotoxic or embryotoxic agent is one that has the possibility to do harm to a developing embryo or fetus as a result of prenatal exposure.

The most dramatic of these effects are:

- the alteration in growth,
- the functional abnormalities,
- and structural malformation trait of teratogens.

Drug effects on the fetus



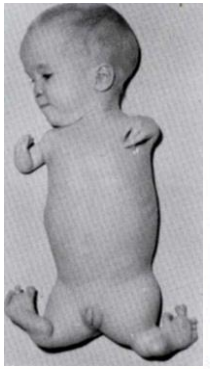
- Approved about 60 years ago in West-Germany
- Pain killer, sedative
- Pregnancy discomfort

Drug effects on the fetus

Medication in pregnancy History

- Beginning of 20th century: the fetus in utero is safe and cannot be harmed by anything (misbelief)

- 3 disasters → the opinions changed:
  - X-ray radiation may cause mental retardation (1920. USA)
  - Cataracts may caused by rubella (1941. Australia)
  - Contergan® (thalidomid): phocomelia (1961. Europe)



Medicinal effects on the fetus

Determinants:

- Nature and dose of the medicinal product and the route of administration
- Length of time of effect
- Level of fetal development (gestation time)

Nature of the drug

Importance of charge, lipid solubility, molecular size

- High **lipid solubility** agents pass more **easily** through the placenta than are water soluble
- The degree of ionization is also significant as the **placenta is more difficult for charged molecules to pass through** (pK)
- **Under 500 Da**, drugs pass into the fetus via **passive transport** (diffusion of maternal blood)

Application mode

Parenteral route:

- high dose, immediate effect, unchanged form

Oral route:

- first pass effect, metabolites, slowly rising blood levels

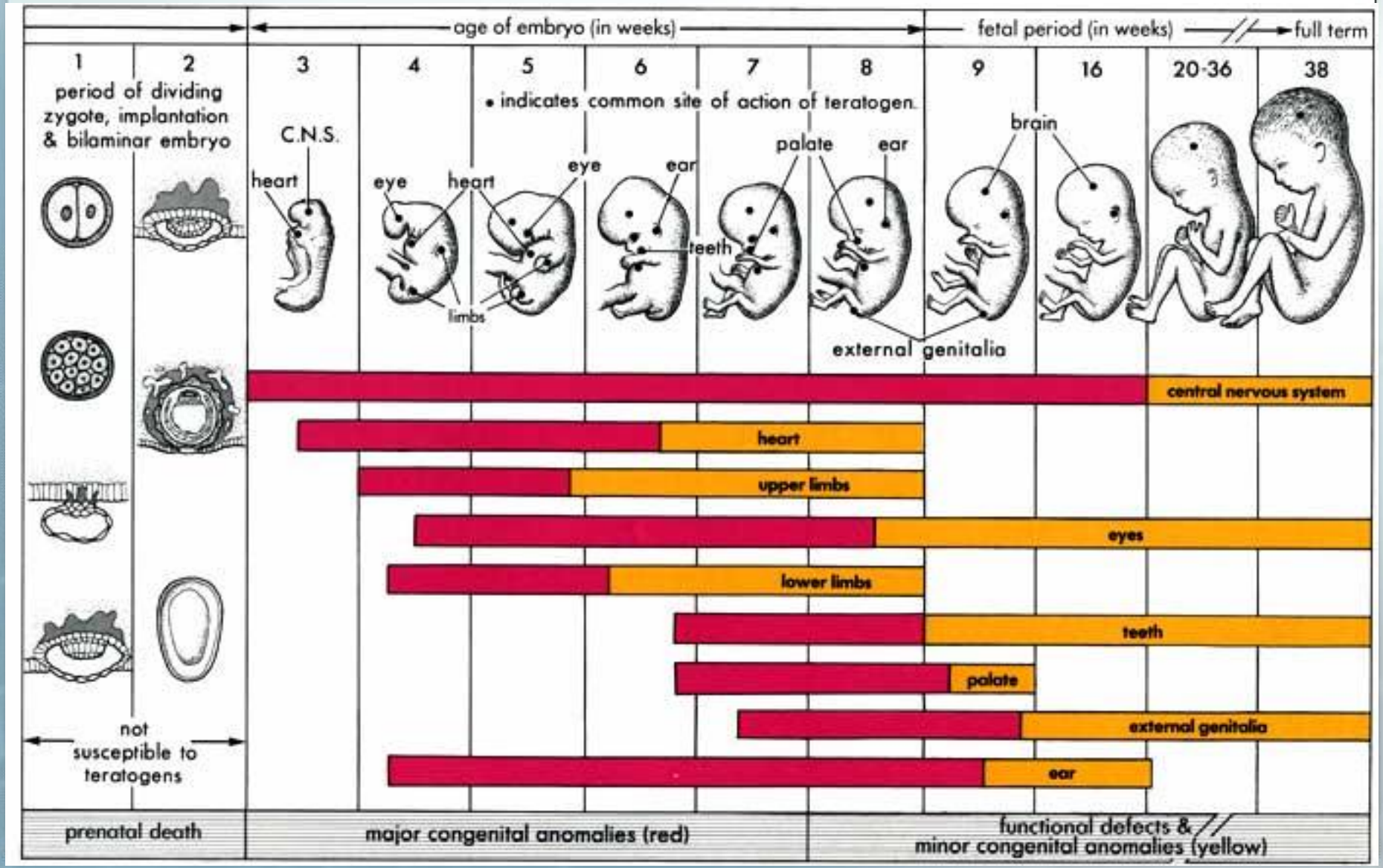
External application (skin, ears, eyes, nose):

- minimum systemic concentration

But.... **vaginal** or **rectal** application

- uncertain absorption

Gestational age



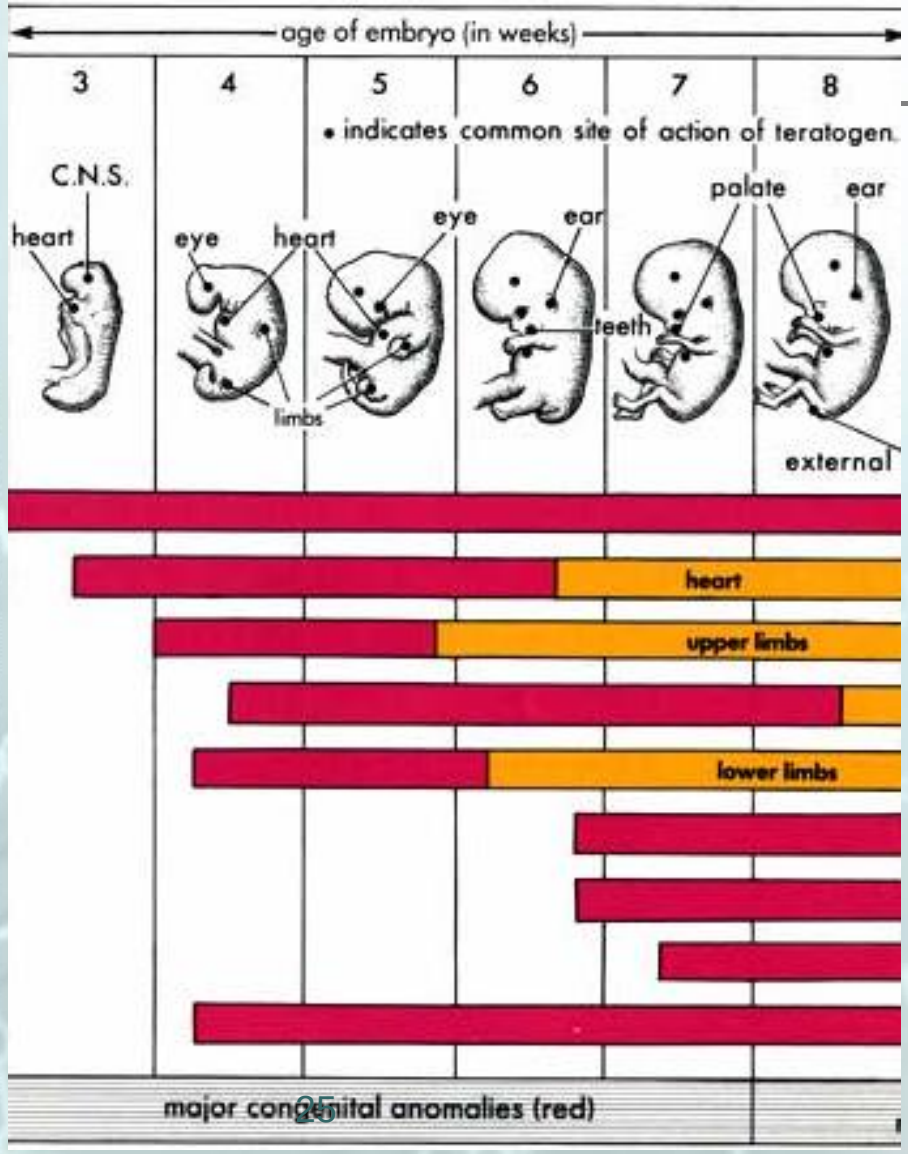
Gestational age

First two week: characterized by an „**all or nothing**” phenomenon.

This means that, injury to a **huge number of cells** during the early embryo development will inevitably **cause the loss of the embryo.**

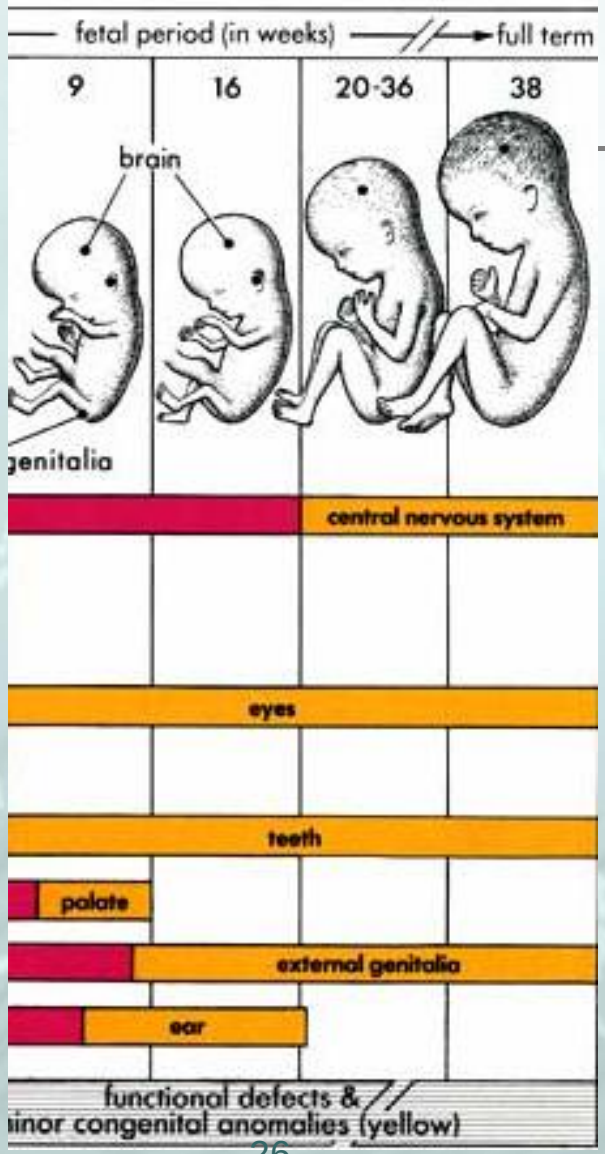
If only **a small number of cells** are damaged, the phenomenon of compensation can defend **the embryo and ensure survival without malformation.**

Gestational age



During **organogenesis** (2-8 weeks), when each system has a specifically vulnerable period, a teratogenic agent can cause severe malformations. However, the fetus can also be disturbed by alterations in structure and function of the organs that have developed in a normal way during embryogenesis.

Gestational age



Embryogenesis (9-40. weeks): Main body forms are developed.

Funcional abnormalities can occur (mental retardation, lower birthweight, kidney disorders etc.)

Pregnancy

Fever, pain, headache:

paracetamol

- Ibuprofen
  - may delays the child-birth or
  - may prolong the child-birth process
- Metamizole Sodium
  - may cause premature blockage of Botallo line

Pregnancy

Diarrhea:

Prevention of dehydration - oral fluid and salt replacement

- Carbo activates
- Smecta (diosmect)

Pregnancy

Constipation:

- Intake of diet rich in fiber
- Enough fluid
- Move
- Lactulose (Duphalac syrup)
- Glycerine suppository
- Clysters

Pregnancy

Hemorrhoids:

- Stool softening
- Zinc Oxide
- Zinc sulphate

Pregnancy

Heartburn:

- Aluminum hydroxide - not in the long run
- Magnesium oxide - not in the long run
- Famotidine - Quamatel mini - **contraindicated!**
- Rennie - Calcium carbonate, magnesium carbonate - **no risk!**

Pregnancy

Nausea:

- Vitamin B_6

Pregnancy

Cough:

Dry cough:

- Dextrometorphan - Robitussin (should be avoided for 1-3 months; administration of the drug during the last 3 months may cause withdrawal symptoms in the newborn; may cause respiratory depression at the end of pregnancy.)
  Prenoxdiazin - Rhinathiol Tusso, Libexin

Cough with mucus production:

- Syrups of natural origin

Pregnancy

Colds, Flu:

- Cough
- Sore throat
- Rhinitis, stuffy nose
- Fever

Pregnancy

Cold sores *(Herpes virus):*

- *Zinc oxyde*
- *Zinc sulphate*

Etiology of malformation

- Causes are unknown in 65-70%
- Genetical factors cause the 20-25% of malformation
- Some kind of intrauterine infections casuse the 3-5%
- Only 1% of malformations are caused by drugs

Drug Effects On The Fetus

Effects are determined mainly by:

- The type and amount of drugs
- Route of administration
- The level of fetal growth and development when exposed to the drugs (gestational age)

Both therapeutic and nontherapeutic drugs may affect the fetus.

The type and amount of drugs

Charge, liposolubility of the drug, and molecular size:

- Agents with high lipid solubility may get across the placental barrier much more easily than water-soluble molecules.
- Ionized drugs are water soluble and are poorly transmitted across the placenta. Ionization of chemicals depends on their pH-pK relationships.
- Drugs, with mass below 500 Da, are transferred by simple diffusion, the rate of which is regulated by the concentration gradients of the medicines

Route of administration

Teratogens can be harmful for the fetus if **the drug level reaches** and exccedes **a certain limit**.

Route of administration can influence the quantity of drug got into the fetus

- Parenteral administration: high dose, immediately, unchanged form
- Per oral administration: bioavailability, first pass effect, metanolized form, drug concentration in the blood increases slowly
- Topical administration (skin, ear, eye, nose): minimal systemic concentration
- **NOTE:** vaginal preparation and suppositories: greater absorbtion surface, close to uterus

Fetal Therapeutics

A few drugs are given to the mother for their therapeutic effects on the fetus:

- Digoxin for fetal tachycardia or heart failure
- Levothyroxine for hypothyroidism
- Penicillin for exposure to maternal syphilis
- Prenatal betamethasone to promote surfactant production in preterm infants.

Principles of Therapy

- Give medications **only when clearly indicated**, weighing benefits to the mother against the risks to the fetus.
- Any drugs used during pregnancy should be given in the **lowest effective doses** and for **the shortest time**.
- The choice of drug should be based on **the stage of pregnancy and drug information.**
- During the first trimester, an **older safe drug is preferred** over a newer drug of unknown teratogenicity.

Lactation

- **Most systemic drugs taken** by the mother **reach the infant in breast milk.**
- For some, the amount of drug is too small for others effects are unknown or potentially adverse.
- Give medications only when **clearly indicated**.
- For contraindicated drugs, the mother should **stop the drug or stop breast feeding.**

Drugs in pediatric

Childhood is divided in

- 0-2 months: newborn
- 3-12 months: infant
- 1-6 years: young child
- 6-15 years: school child
- Above 15 years: adult

Importance of drug handling

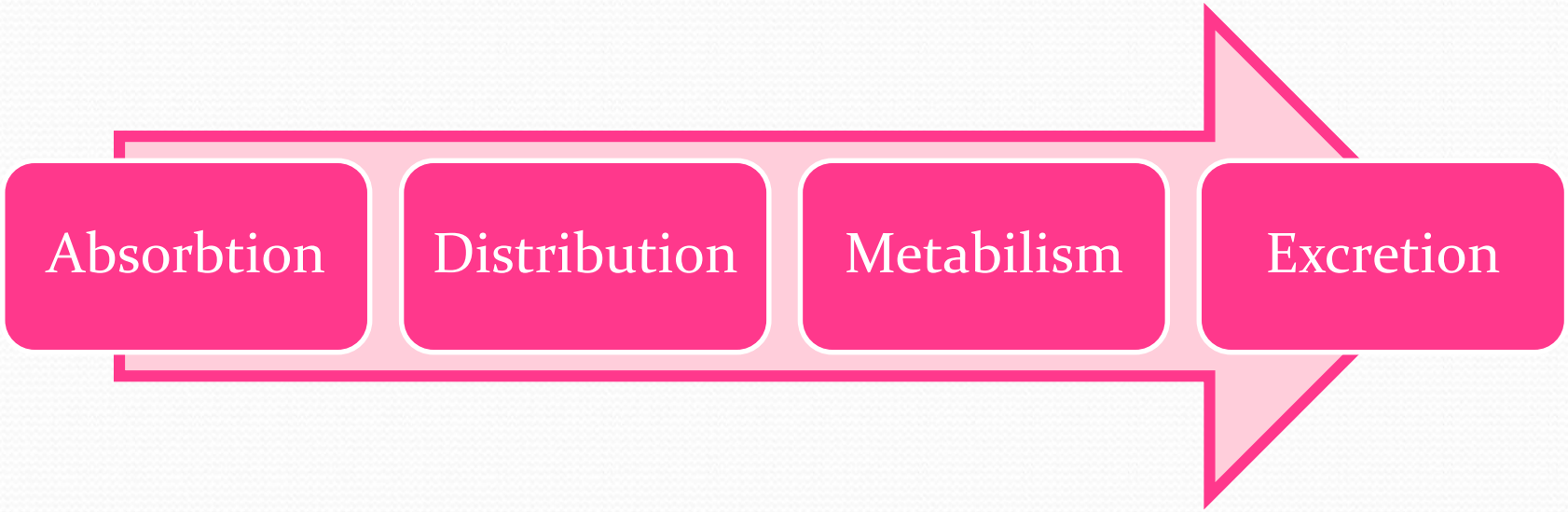
- Lack of data on pharmacokinetic and pharmacodynamic differences has led to several terrible situations in pediatric care:
  - Firstly: the inability to obtain true informed consent.
  - The second obstacle is inherent to children; they grow and change rapidly.
- Infancy and childhood is rapid stage of development and various organs, enzymes and body systems that handle drugs are different in time. Drug studies must be performed on children at each stage of their development to determine appropriate usage.

Highly Critical aspects in child treatment are

- P'kinetic parameters
- Method of drug administration
- Dose & dosage forms

Pharmacokinetics

Drugs that are safe and effective in one group of pediatric patients may be **ineffective or toxic in another**, so an understanding of variability in drug disposition is essential:



Absorbtion

Two factors affecting the absorption of drugs from the G.I. tract:

- pH-dependent **passive diffusion**
- gastric **emptying time**.

pH

Premature Infants- elevated pH

Infant- Range from 6-8

Gastric emptying time

Prolonged gastric emptying time. But lower peristaltic movement than older child and adults.

Absorbtion

Results:

- pH:
  - Higher serum concentrations of acid-labile drugs (penicillin, ampicillin and nafcillin)
  - Lower serum concentrations of a weak acid (phenobarbital)
- Gastric emptying time:
  - Drugs that are absorbed in the stomach may be absorbed more completely than anticipated.
  - In the case of drugs absorbed in the small intestine, therapeutic effect may be delayed.

Absorbtion

Gastrointestinal enzyme activities:

- It is lower in the newborn than in the adult.
- Activities of amylase and lipase, beta- glucuronidase, and glutathione peroxidase enzymes are low in infants up to 4 months of age.
- Neonates also have low concentrations of bile acids and lipase, which may decrease the absorption of lipid-soluble drugs.

Absorbtion

Absorption from Skin:

- Percutaneous absorption may be increased in neonate because of an underdeveloped epidermal barrier (stratum corneum) and increased skin hydration.

Absorption from Rectal route:

- The rectal route of administration can be useful in infants or children who are unable to take oral medication.

Distribution

Drug distribution is determined by :

- Physicochemical properties of the drug itself (pKa, molecular weight, partition coefficient,etc…)
- Physiologic factors specific to the patient. (Total Body Water, Plasma Protein binding of drug, Volume of Distribution)

Distribution

Total Body Water

- 94% in the fetus, 85% in premature infants, 78% in full-term infants, and 60% in adults

Plasma Protein Binding

- Less in newborn and infants, rate of free fraction increases

Volume of Distribution (V_D)

- Generally:
  - In the case of water-soluble APIs the volume of distribution decreases paralell with the age of the patient
  - In the case of fat-soluble APIs the volume of distribution increases paralell with the age of the patient

Metabolism

- Drug metabolism is substantially slower in infants compared with older children and adults.
- Less maturation of various pathways of metabolism within a infant:
  - sulfation pathway is well developed
  - glucuronidation pathway is undeveloped in infants.(chloramphenicol- induced gray baby syndrome)
- doses of some drugs (theophylline, phenobarbital, phenytoin, and diazepam) should be decreased

Excretion

Efficiency of renal excretion is determined by:

- glomerular filtration,
- tubular secretion,
- tububular reabsorption

- These processes may take several weeks to 1 year after birth to develop fully.
- In infants, if possible then avoid Chloramphenicol and Amino glycoside, because their metabolites are accumulated due to immature function of kidney.

Drug therapy in pediatrics

- Dose calculation
- Choice of dosage form
- Disease Condition
- Adverse reaction
- Counseling

Dose calculation

There are two main factors, which influece the dose of API's:

- Body Surface Area (BSA)
- Volume of extracellular space

Dose calculation

During dose calculation body surface should be taken into account instead of body mass.

The value of BSA may be calculated with the next formula:

$BSA(m^2) = BW(kg)^{0,5378} \times height(cm)^{0,3964} \times 0,024265$

BW – body weight

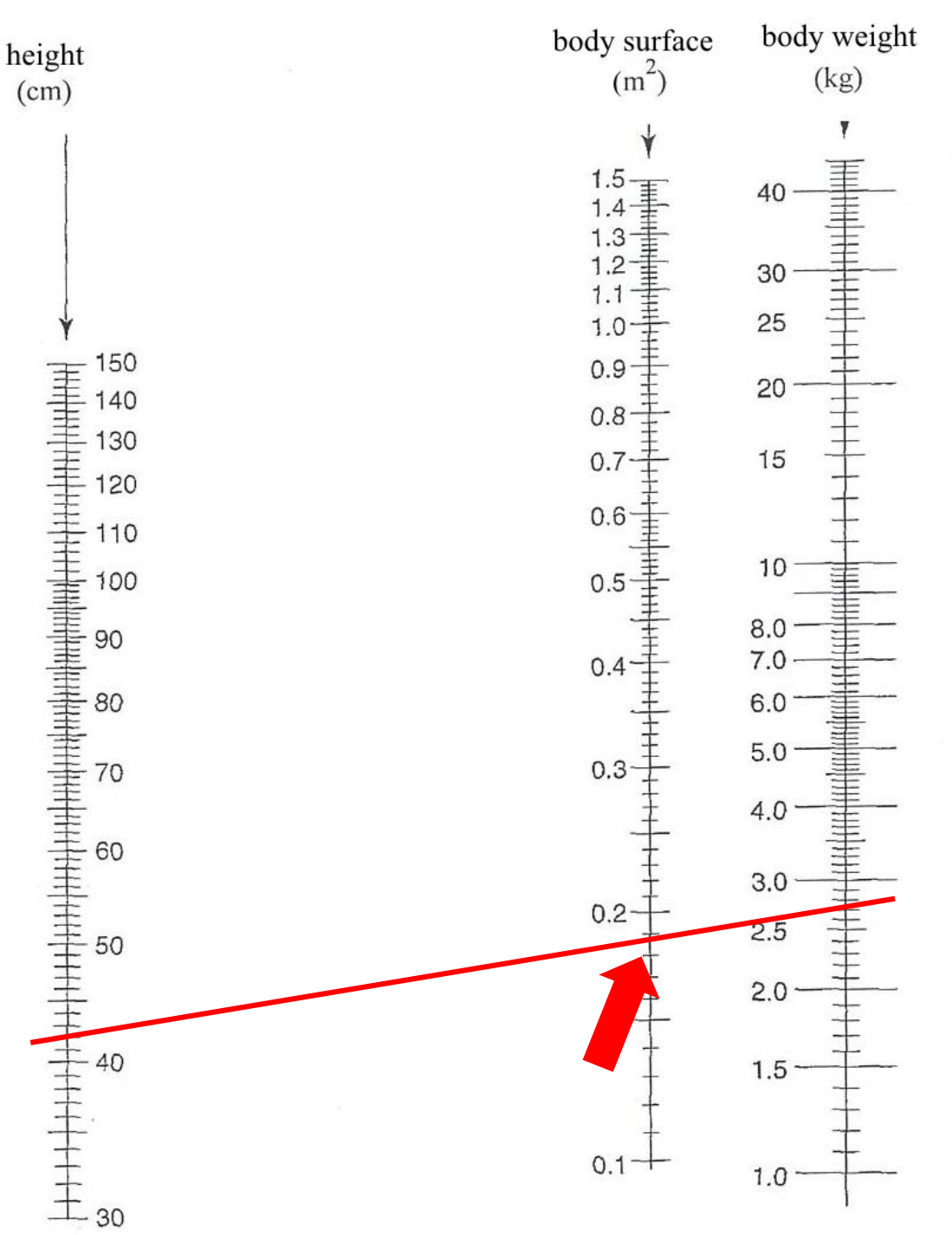
Dose calculation

The simplified formula:

$$BSA(m^2) = \frac{\sqrt{[Height(cm) \times BW(kg)]}}{60}$$

NOTE: These formulas are not suitable to calculate the dose of premature and full-term infants, but they may be used in any other age groups.

Calculating the BSA



Nomogram

Child Dose calculation

$$Child\ dose = \frac{Body\ Surface\ Area\ (m^2) x\ Adult\ dose}{1.73\ m^2}$$

Child Dose calculation

Fried's rule

$$Child\ dose = \frac{Age\ (month)\ x\ Adult\ dose}{150}$$

Young's rule

$$Child\ dose = \frac{Age\ (year)\ x\ Adult\ dose}{Age + 12}$$

from newborn to 15 years

Clark's rule

$$Child\ dose = \frac{Body\ weight\ (kg)\ x\ Adult\ dose}{75}$$

Relationship among age, age-appropriate body weight, height and body surface area and% adult dose

Age	Ideal Body weight (kg)	Height (cm)	Body surface (m^2)	Adult dose %
Newborn	3.5	50	0.23	12.5
1 month	4.2	55	0.26	14.5
3 months	5.6	59	0.32	18.0
6 months	7.7	67	0.40	22.0
1 year	10	76	0.47	25.0
3 years	15	64	0.62	33.0
5 years	18	108	0.73	40.0
7 years	23	120	0.88	50.0
12 years	39	148	1.25	75.0

Choice of Dosage form

Oral Route

- Tablets are less convenient
- Liquid preparation are easy to administer in accurate dose and to form in desirable dose by dilution

Rectal route:

- effective, rapid effect, easy to administer

Topical administration (skin, ear, nose, eye)

Elderly patients

- Clinical and pharmacological testing of drugs is usually performed in younger individuals
- Therapeutic standards developed in this way can be dangerous for elderly patients

Elderly patients

- Absorption varies
- Body fat content increases (distribution)
- Metabolism changes
  - Phase I redox reactions slow down and the rate of hydrolysis reactions increases
  - II. the intensity of the phase reactions does not change
- Excretion changes (decreased kidney function)

Thank you for your attention