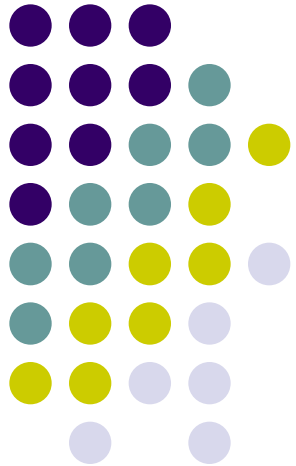
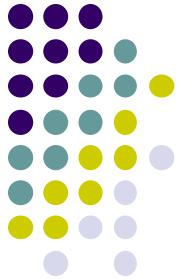
Factors influencing drug effects



Basic factors influencing the action of agent



- **dose**
- **way (route) of administration**

Dose

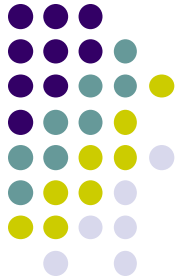
- Measured amount of an agent given in international weight or volume units.

Types of doses

- **subliminal** dose– no effect
- „**liminal**“ (threshold) dose– evaluable effect
- **therapeutic** dose– supraliminal dose suitable for therapy
- **maximal** dose– highest therapeutic dose without toxic effects

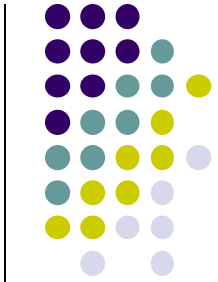
- **Single** or **daily** therapeutic and maximal dose

Types of doses



- **One bout** dose – in bolus, aggressive dose – enables quick reaching of desired concentration
- **Saturant** dose – saturates binding sites and enables reaching of desired plasmatic concentration of free agent
- **Maintaining** dose – maintains desired plasmatic levels after saturation

Types of doses



- **Effective** dose (ED) – is equal to therapeutic dose
- **Lethal** dose (LD) – dose leading to death of experimental animals
- **Toxic** dose (TD) – dose evoking toxic effects

Other characteristics

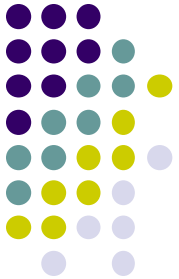
- **Threapeutic range** – difference between LD_{50} and ED_{50} (in animals) or TD_{50} and ED_{50} in humans

- **Therapeutic index** – ratio between LD_{50} and ED_{50} (or TD_{50} and LD_{50}) – expresses ratio between effectivness and risk of drug administration – higher ration, better safety

Way (route) of administration

- Peroral
- Rectal
- Intravesical
- Intranasal
- Into eye
- Into ear
- Superficially (transdermal)
- Intravenous
- Intramuscular
- Subcutaneous
- Intracutaneous
- Intraosseal
- Intracardial

Classification of factors

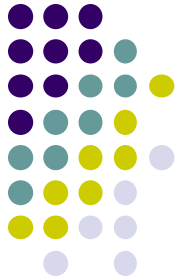


- External factors
- Internal factors

External (exogenous) factors

- Food
- Medicinal form
- Alcohol
- Smoking
- Environmental factors
- Ionizing radiation

Internal (endogenous) factors



- Age
- Sex
- Pathological state of patient
- Genetic factors
- Types of neural function
- Others

Food

- Volume, quality
- Drug absorption
- ↑ bile secretion - ↑ absorption of lipophilic agents (waxed)
  - ↓ absorption of kanamycin
- ↑ enzyme secretion – proteolytic enzymes – peptide degradation

Food

- The drug effect depends on duration of stay in GIT
- ↓ stomach emptying:
  - anticholinergics (NACTON)
  - antihistamines (H_1, H_2, H_3 blokátory)
  - antidepresssants (MELIPRAMIN)
  - neurolpetics (PLEGOMAZIN)
  - analgesics (MORFIN)
  - antacids (ANACID)

- All of them ↑ absorption from stomach (but not intestine), prolong the stay and ↑ drug effects

Food

- ↑ emptying of stomach: metoclopramid, syntostigmin, prostigmin - ↓ effect of drug absorbed from stomach

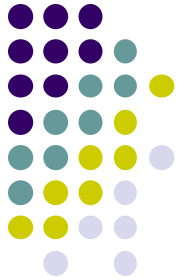
Expressions:

- With meal
- During eating
- On an empty stomach (not before meal)

Food and drugs

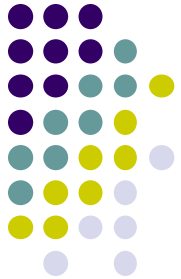
- Fasting
  - barbiturates
  - celafolosporines
  - penicillin – 1 h. before meal
- Not on an empty stomach
  - acetylsalicylic acid
  - antihelmintics
  - doxycyclin
- With meal
  - cimetidin
  - diazepam
  - digoxin
  - ketason
  - hydrochlorotiazid
  - carbamazepine
  - furantoin
  - tetracyclin – 2 h. after meal

Food and drugs



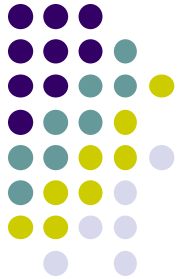
- Acids (ACIPEPSOL) – before meal for ameliorating the taste
- Antacids (ANACID) – between two meals
- Antiulcer drugs (pirenzepin) – with meal
- Digestives – 20-30 min before meal
- Enzymes (PANKREOLAN) – with or after meal
- Laxatives
  - salinic – on an empty stomach dissolved in water
  - chemical – after meal
- Choleretics – with or after meal

Food and drug biotransformation



- first-pass-effect – **liver**
- insufficient protein or lipid supply
- lack of vitamins B1, C, E
- smoking

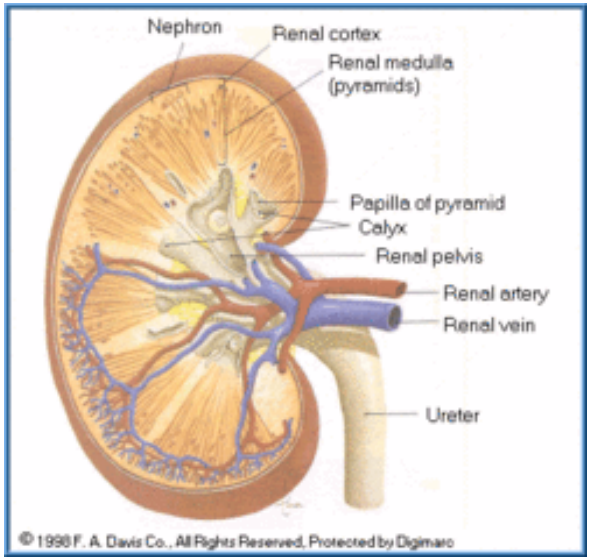
Food and drug distribution



- Differences in serum levels – in higher content of saccharides, proteins and lipids

Food and drug excretion

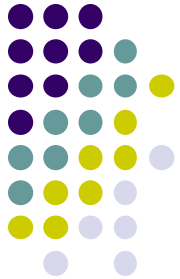
- Urine pH changes
  - ***Acidifying meals:*** meat, bacon, fish, cakes, eggs, cheese
  - ***Base-forming meals:*** butter, vegetables, fruits (except of plums and cranberries)



Food and adverse effects

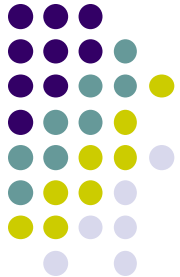
- **Thyrozin** – bananas, pine-apple, lemons, tomatoes, figs, venison (wild animals meat), liver, cheese, caviar, chocolate – if combined with MAO inhibitors (antidepressants) – risk of hypertensive crisis leading to hemorrhagic stroke or death
- **Isoniazid** (antituberculotic) – no Swiss cheese – risk of histamine intoxication.

Food and adverse effects



- **warfarin** – no foods with ↑ content of vitamin K – spinach, cabbage, broccoli – decreasing its effects.
- **diuretics, saluretics, corticosteroids, cardiotonics** – decreasing K^+ - necessary to eat cauliflower, lentil, bananas, apricots, potatoes, plums – natural K^+ supplementation.

Food and adverse effects



- **Barbiturates** for sleep – their effect is increased with simultaneous intake of sugar and decreased with food containing theophylline or caffeine
- **Sweets from licorice** – not to be taken in patients with heart failure – risk of hypokaliemia

Medicinal form

- **Liquid**
- **Solid**
- **Gaseous** (aerosol)

- Liquid – quick absorption, less AEs – important to rinse down some drugs
- Analgesics (ASPIRIN) – in form of **effervescent** tablets

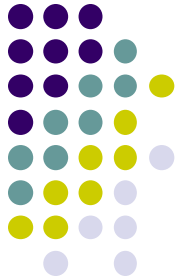
Drugs and „rinsing down“

- **Rinse down with water**: anticholinergics (NACTON), cephalosporins, CURANTYL, doxycyclin – *not with milk – to rinse down with water, sitting or standing, or to swallow solid food – tendency to adhere to esophageal mucous membrane – irritation and inflammation*, erythromycin, sulphonamides (alkalic mineral waters – decreasing adverse effects on kidneys), penicillins, corticosteroids.

- **KCl** – rince down with fruit juice

- **TTC** – solution of citric acid

Drugs and „rinsing down“



- Drugs to be rinsed down **with milk** – phenylbutazon (proptection of stomach), fenytoin, izoniazid, kebuzon, corticosteroids, nitrofurantoin, vitamin D, hormones, hydralazines

- **TTC not with milk** minimum 3 hours before and after meal (neither milk products), no mineral waters like Vincentka, Fatra, Korytnica

- Keflex, V-PNC, Natrium fluoratum, Ferronat, Digoxin – **no milk**

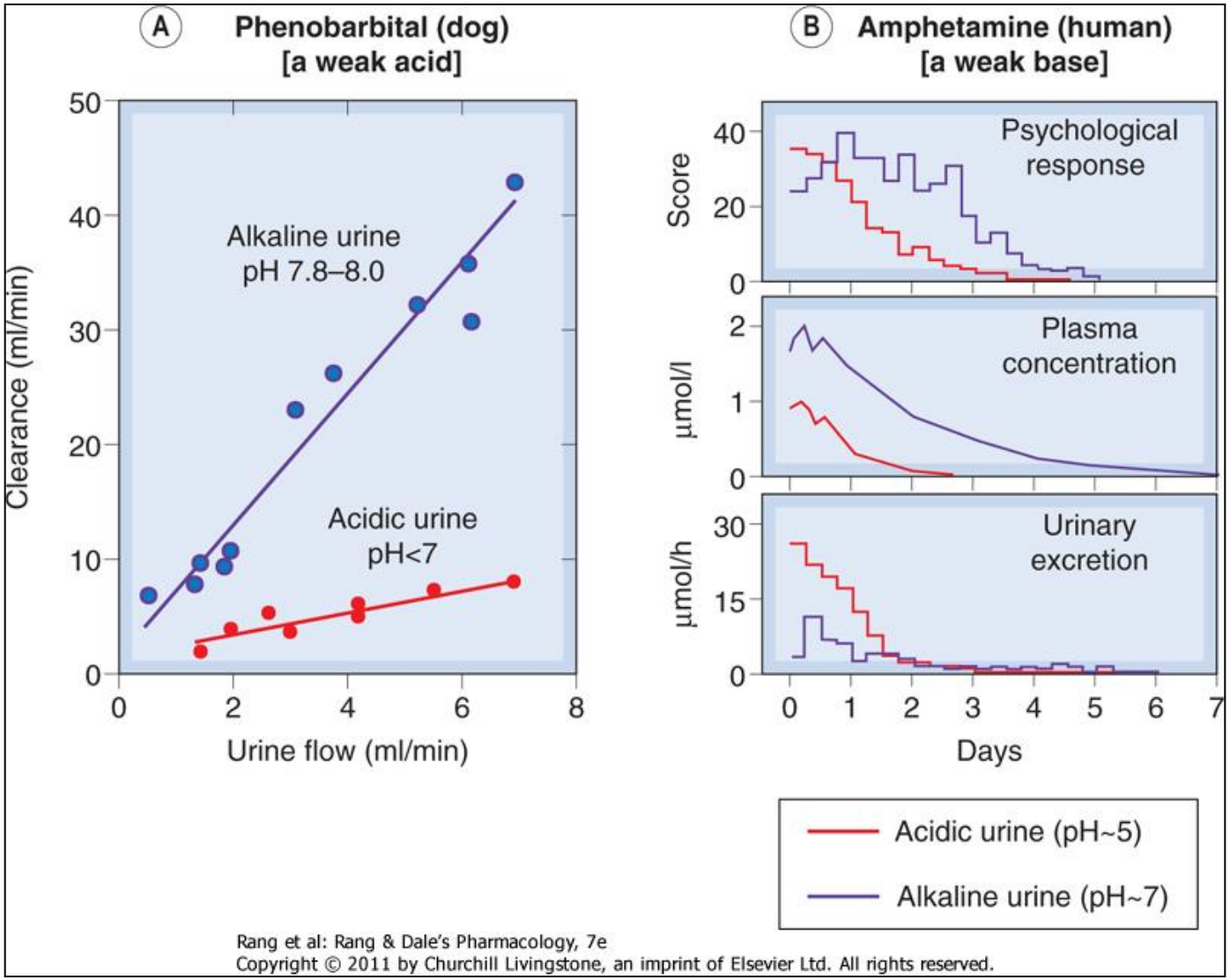
- Acid-labile ATB – ampicillin, erythromycin – no acidic fruit juices, no lemon (tonic, Coca-Cola, fruit ciders)

Drug excretion

- Urine pH - **acidic** – drugs with acidic nature have decreased excretion
- Urine pH - **basic** – drugs with acidic nature have increased excretion

- **Urine alkalinization** ($NaHCO_3$): - used in the therapy of barbiturate intoxication
  - ↑ excretion (barbiturates, Biseptol, Septrin, Sumetrolim, Supristol)
  - ↓ excretion (nalidixin, fenylbutazon, sulphonamides)

The effect of urinary pH on drug excretion



Drug excretion

- **Caffeine** - ↑ secretion of gastric acid, ↑ diuresis, ↑ production of N-nitrosamine – not to combine with neuroleptics (haloperidol, flufenazine) – precipitation

- ↑ content of Na^+ and K^+ in food – edemas
- Na^+ – Vincentka, K^+ – tomatoes, orange, apple juice

- Beer PRAZDROJ 12° - amount of K^+ similar to 1 tablet of Kalium Chloratum SPOFA

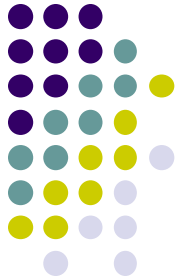
Alcohol and drug absorption

- Low concentration of alcohol - ↑ drug absorption
- High concentration of alcohol - ↓ drug absorption due to pylorospasm
- Do not combine with **Diazepam** – individual susceptibility – misused by drug-addicts – tolerance in the same person may vary – inter- and intra-individual susceptibility.

- The worst effect on drugs (AEs) – white wine, beer, whisky
- Red wine – almost as non-alcoholic drinks (due to tannins)

- Anticholinergics and antidepressants - ↓ absorption of alcohol – hard to get drunken, but prolonged duration

Alcohol and drug biotransformation



- **Acute** intake – prolongs and promotes the effect
- **Chronic** intake – decreases effect of drugs
- **Cimetidin** and **ketotifen** – both increase blood levels of alcohol

Smoking and drug effects

- ↑ metabolic clearance of amitryptilin, diazepam, phenacetin, phenobarbital, insulin, caffeine, paracetamol, pentazocine, theophylline, vitamin C – their effect is lower

- **Nicotine** increases serum levels of cholesterol, TAG and beta-LP

Elderly

- ↓ absorption, ↓ secretion, ↓ acidity, venostasis, ↓ motility, ↓ emptying, changes in bacterial flora
- ↓ active transportation of Ca^{2+} and glucose
- ↑ absorption ability of skin – attention to locally administered corticosteroids

Elderly

Drug biotransformation

- Prolonged biological half-life – fenazon, quinidin, diazepam, paracetamol, phenylbutazon, phenobarbital, lidokaine

- ↓ enzyme activity, ↓ liver blood flow, ↓ activity of kidneys - attention to smoking and alcohol

Children

- ↓ amount of gastric and intestinal secretion
- ↓ acidity
- ↓ proteolytic activity
- ↓ absorption surface
- ↓ muscle mass

Children

Drug biotransformation

- Immature enzymatic systems – glucuronization-transforming system
- Chloramphenicol – **Grey syndrome**
- Sulphonamides, vitamin K – nuclear (cerebral) icterus (kernicterus), death
- ↓ glomerular filtration

Children

- immature CNS and other organs - ↑ susceptibility to morphine – depression of respiratory centre
- ↓ threshold for cramps - amidopyrin, antihistamines
- Children can better tolerate **atropine** and **cardiotonics**

Effect of age on elimination

Table 56.1 Effect of age on plasma elimination half-lives of various drugs

Drug	Mean or range of half-life (h)		
	Term neonate[a]	Adult	Elderly person
Drugs that are mainly excreted unchanged in the urine			
Gentamicin	10	2	4
Lithium	120	24	48
Digoxin	200	40	80
Drugs that are mainly metabolised			
Diazepam	25–100	15–25	50–150
Phenytoin	10–30	10–30	10–30
Sulfamethoxypyridazine	140	60	100

[a]Even greater differences from mean adult values occur in premature babies.
(Data from Reidenberg 1971 Renal function and drug action. Saunders, Philadelphia; and Dollery 1991 Therapeutic drugs. Churchill Livingstone, Edinburgh.)

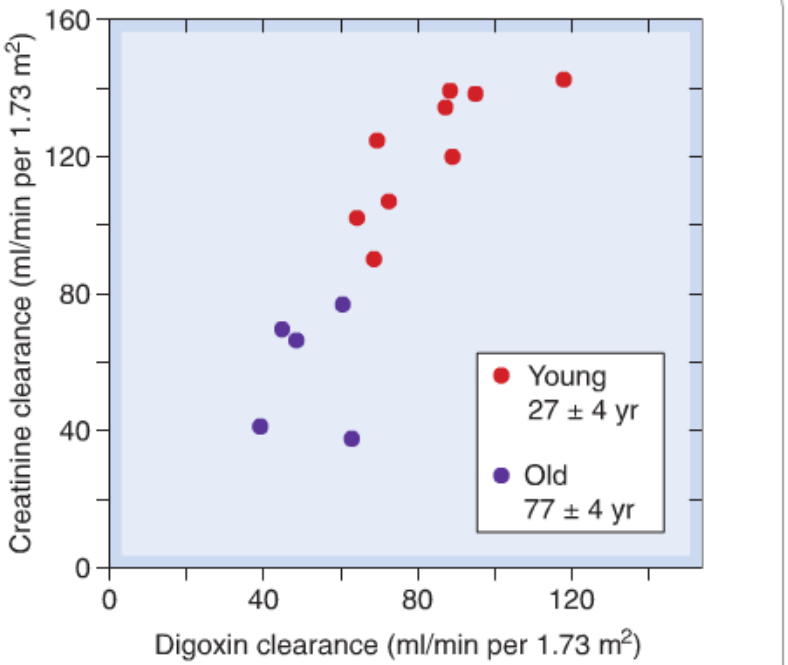


Fig. 56.1 Relationship between renal function (measured as creatinine clearance) and digoxin clearance in young and old subjects. (From Ewy G A et al. 1969 Circulation 34: 452.)

Sex

- periods, gravidity, climacterium - ↑ susceptibility to CNS stimulants and to drugs influencing blood pressure

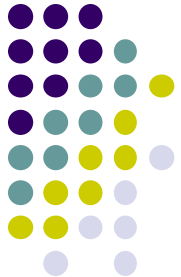
- Women have better toleration for barbiturates

Pathologic state

- ↓ **absorption** – atrophy of intestine epithelia, quick motility (passage – diarrhea, vomiting), GIT tumors ulcerations, surgical interventions

- ↑ **absorption** – GIT inflammation, ↑ congestion

Pathologic state



Drug distribution

- Liver diseases
- Nephrotic syndrome associated with hypoalbuminemia)
- ↓ heart capacity

Drug excretion

- ↓ by kidneys insufficiency, accumulation – risk of AE

Pathologic state

- Drugs excreted with **bile** – attention in cholestatic liver diseases - ↑ effects and AEs (Agofolin, Biogastron, Agolutin, Agovirin, Vinkristin, Regalon)

- Pathological state:
  - **is condition of drug effect** – antipyretics, cardiotonics,
  - **is contraindication of drug administration** – glaucoma and prostate hypertrophy – not atropine

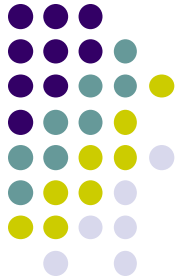
Genetic factors

- Resistance to coumarin anticoagulants (Pelentan)
- Different kinetics – individuals, races (breeds)
- Depends on genetic changes in **cytochrome P-450**
- Slow and fast acetylators – classification of individuals – metaboilism of izoniazid
  - **Slow acetylator** - ↑ plasmatic concentration, ↑ accumulation, ↑ AEs
  - **Fast acetylator** - ↓ plasmatic concentration, ↓ accumulation, ↓ AEs

Genetic factors

- Differences in **acetylation** – sulphonamides, chlorpromazin, prokainamid, izoniazid
- Polymorphism of **hydroxylation** – not completely elucidated yet (captopril, Betaloc, fenacetin, fenytoin, propranolol
- Insufficient biotransformation of succinylcholiniodid - atypical **cholinesterase**
- Deficiency of **glucose-6-phosphatedehydrogenase** – acute hemolysis after administration of dapson, methylene blue, nitrofurantoine, pamaquin, primaquin, quinolones, sulphonamides

Changes in drug effects after repeated administration



Long-term administration

- **continual** – tachyphylaxis, tolerance, drug dependence (addiction), allergy
- **intermittent** – allergy

They belong mostly to AEs

Tachyphylaxis

- occurs after repeated doses (especially with quick repeating) leading to fast and significant decrease in susceptibility of organism to the respective drug.
  - E.g. depletion of mediator – **norepinephrine** after administration of **ephedrine**

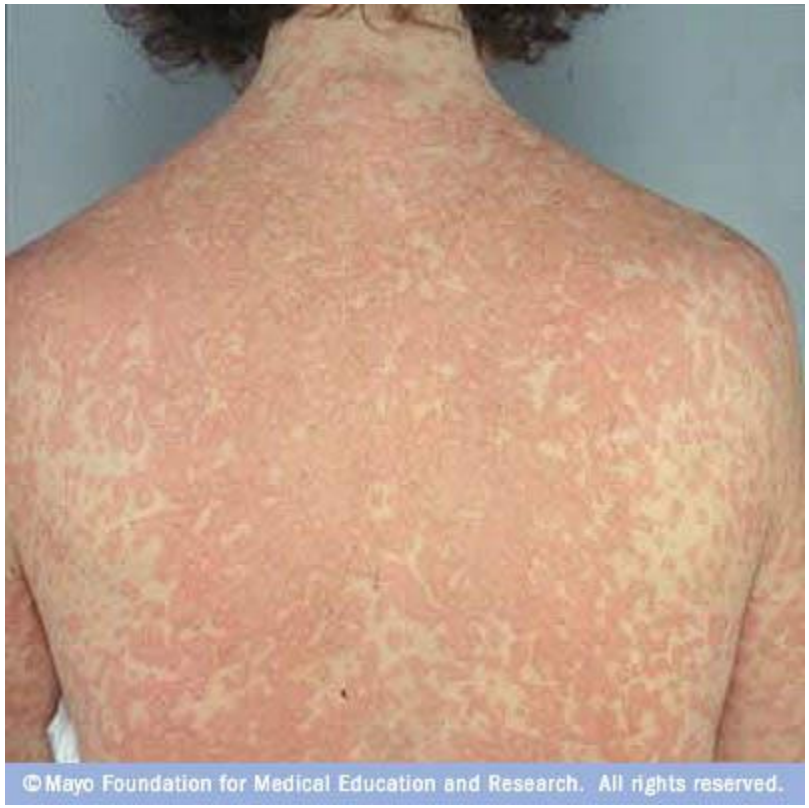
Tolerance

- Occurs after slower decrease of drug effect (during several days or weeks) with necessity of continual increasing the doses to reach the same effect.

  - E.g. in drugs with addiction risk, during long-term administration of **β_2-mimetics**, SH groups by administration of **nitrates**

Allergy

- Unwanted reaction of the body to an agent occurring especially after its repeated administration.



Drug dependence (addiction)

- Unwanted effect occurring especially after repeated administration of some drugs influencing CNS

http://www.councilonalcoholism.net/images/drgsal.jpg

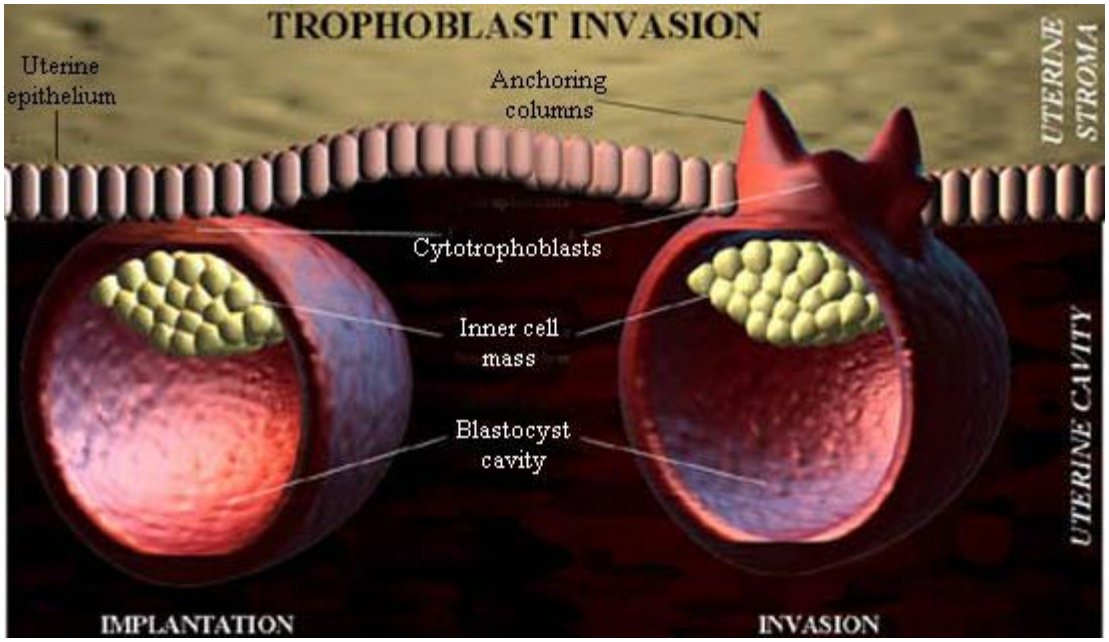
Drugs and gravidity

- Drug for therapy of mother – potential risk of adverse effects for fetus
- Risk of drug adverse effect ↔ *stage of fetal development*

Period before nidation (implantation)

- Relatively safe against teratogenic influences

- „All or nothing“



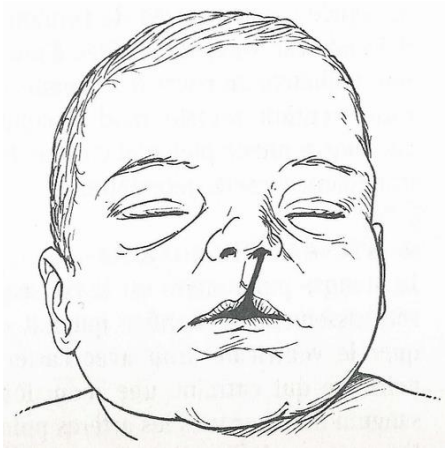
http://www.sgul.ac.uk/depts/immunology/~dash/troph/trophoblast.jpg

Period of embryonic development

- ***Morphological*** development of organs – ↑ susceptibility to teratogens

- 1st trimester (15th – 55th day)

- Specific malformations:
  - Anencephaly – 26th day
  - Transposition of big vessels –34th day,
  - Cleft lip – 36th day,
  - Defect of ventricular septum – 42nd day



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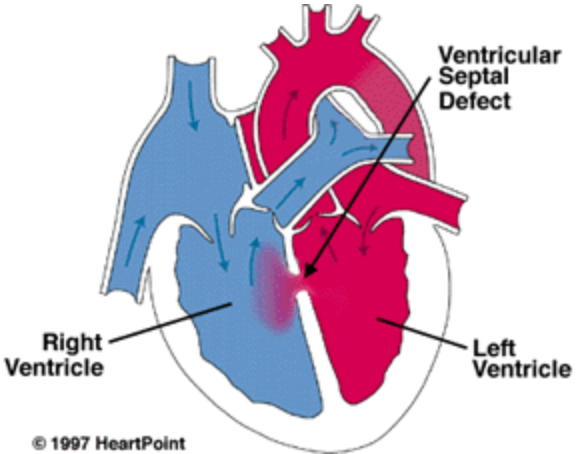


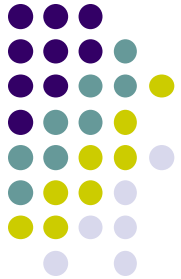
Period of fetal development

- Development of fine tissue ultra-structure, enzymatic and biochemical equipment, receptors, mediators, teeth, genitalia, CNS

- ***Functional changes*** - immediately

  - postnatal (behavioral changes, metabolic diseases….)

Negative drug effects on fetus



- **teratogenic**
- **carcinogenic**

- Genetic factors
- Age
- Alimentation state
- Concomitant diseases
- Physical factors

Teratogenic effects

Drugs evoking fetal malformations

- Morphological, structural changes in growth phase
- Functional changes
- Independent on dose (**thalidomid**)
- Dose-dependent (teratogenic dose - **vitamin A**)

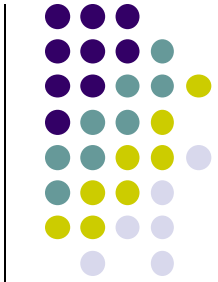
http://www.fda.gov/cder/news/graphics/baby.gif

Carcinogenic effects

Drugs administered to mother evoke cancer in fetus

- **Transplacentar carcinogenesis** (occurs after birth, after latent period) - diethylstilbestrol
- Mostly after administration in second half of pregnancy
- **urethane** – pulmonary adenomas, liver cancer, ovarian cancer

Teratogenic and carcinogenic effects



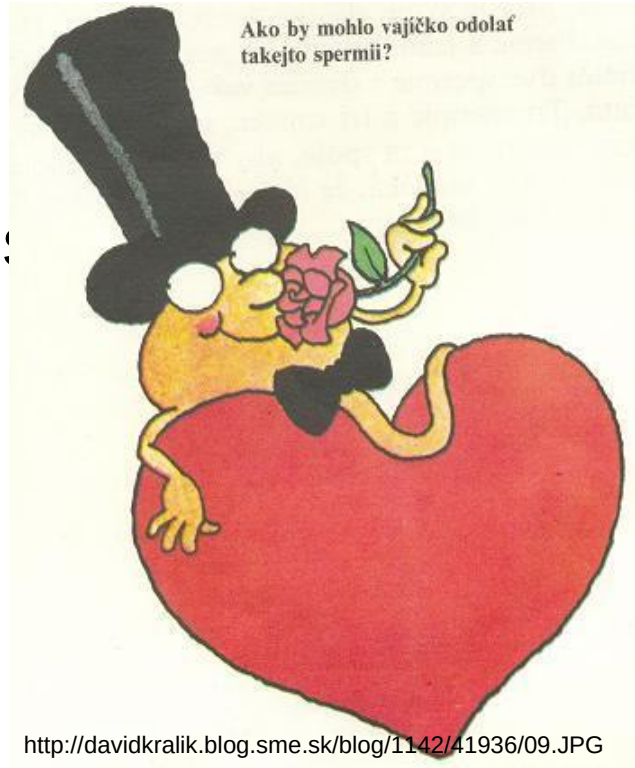
In earlier stage of fetal development is teratogenic, in later phase carcinogenic

- **Ionizing radiation, alcohol, hydantoins, androgens, diethylstilbestrol**

Toxic effects on germ cells

Influence especially on spermiogenesis

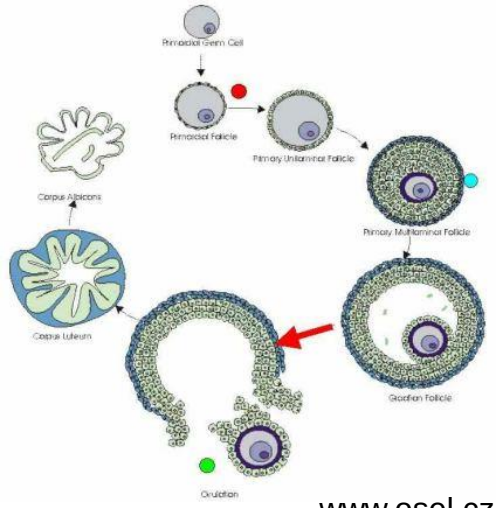
- cytostatics
- hormonal agents – antiandrogens
- antiepileptics
- colchicines
- immunotherapeutics - corticosteroids



http://davidkralik.blog.sme.sk/blog/1142/41936/09.JPG

Effects on egg before fertilization

- **Abstinence symptoms** – addictive agents - opiate analgesics, psychopharmacons
- **Metabolic changes**
  - ***hypoglycemia*** - alcohol, insulin, peroral antidiabetics, propranolol, trimepranol
  - ***hyperglycemia*** - diazoxid
- **Disbalance in electrolytes** - corticosteroids, diuretics
- **Thyroidal dysfunction** - iodine, lithium, anti-thyroidal agents
- **Hematologic changes** **-** bleeding, anemia, platelets disturbances, alcohol, barbiturates, dicoumarol anticoagulants, diuretics, quinine, local anesthetics, nitrofurantoin, salicylates, sulphonamids
- **Icterus-** sulphonamids



www.osel.cz

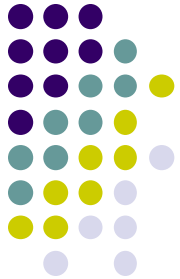
Fetal impairment

- **abortus**

- **morphological**
- **functional**

- **reversible**
- **ireversible**

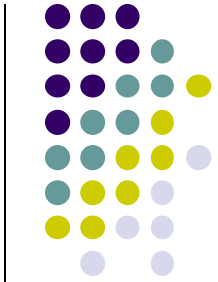
Critical factors influencing drug transport through placental membrane



- Velocity of transportation through placental membrane
- Drug amount, reaching the fetus
- Drug distribution in fetal tissue
- Drug effects in combinations
- Autonomic drug use without noticing the physician

- Safe drug for mother ≠ safe drug for fetus
  - Acetylsalicylic acid – impairment of fetal circulation

Velocity of drug transport through placenta



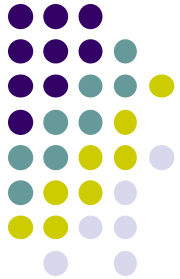
Drug solubility in lipids

- **lipophilic drugs** – quick membrane transportation, entering fetal circulation
- **hydrophilic** – limited placental crossing

Size of drug molecule

- **Low molecular weight (Mr 250-500) – easy transportation**
- **Mr 500-1000 – limited**
- **Mr nad 1000 – not crossing**

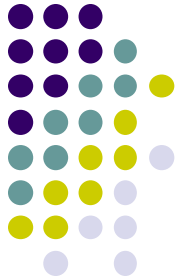
Anticoagulants in pregnancy



- **Heparin** – high-molecular, low solubility in lipids

- **Warfarin** - teratogenic, crosses placental membrane

Drug metabolism in placenta



- Semi-permeable membrane

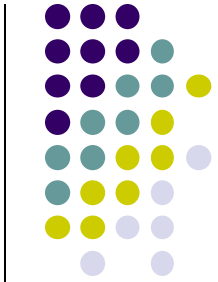
- Metabolic processes in placental tissue leading to degradation of e.g. ethanol, pentobarbital

Drug metabolism in fetus

- placenta - funicle - fetus (60% blood - liver)
- Agents influencing CNS functions
  - ↓ function of fetal blood-brain barrier
  - Progressive maturation of transport mechanisms

- Psychopharmacons administered in the end of gravidity - CNS disturbances in later life of fetus
- Opiate analgesics – breathing disorders – influencing the respiratory centre of newborn
- Therapy of infectious meningitis in newborns - cefuroxim easily penetrates through immature blood-brain barrier

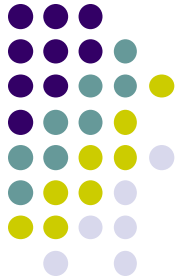
Duration of exposure, distribution of drug in fetus



- Single exposure – may influence structures in phase of quick development (**thalidomide** - extremities)
- Long-term exposure – cumulative effect, impairment of several organs
  - alcohol – **fetal alcoholic syndrome** - FAS, opiates – **opiate dependence**, abstinence syndrome of newborn

- Influencing the transport of oxygen and nutriments through placenta
- Direct influence on fetus

Drug fetal syndromes

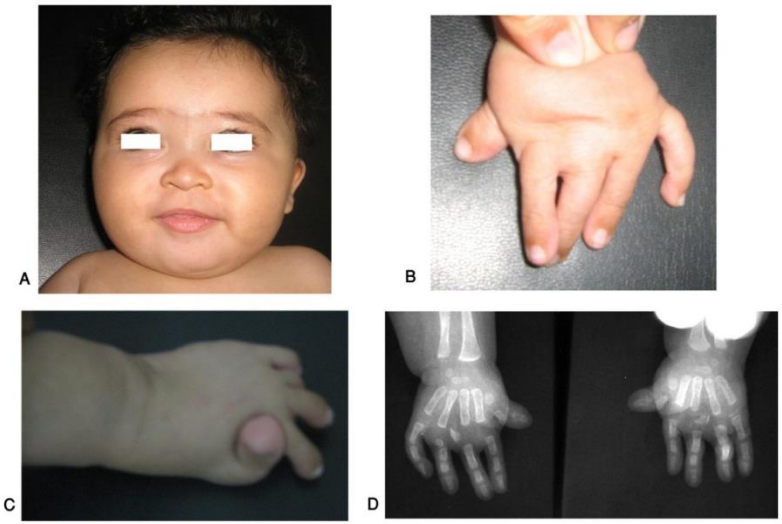


Morphological, functional malformations

- Delayed occurrence:
  - **Alcohol fetal syndrome** – retarded development, skeletal anomalies, CVS defects (daily 100-150 g of alcohol)
  - **Antiepileptics** – hydantoins – fenytoin SODANTON, PHENYTOIN, EPANUTIN, EPILAN, SANEPIL – fetal impairment
  - **Contraceptive pills** - **diethylstilbestrol** – higher incidence of uterine adenocarcinoma in fetus reaching adulthood

Drugs and skeletal development

- Long period of pregnancy
- 6th week to end of 3rd trimester
- Skeletal malformations, impairment of ossification centres – disproportions in growth of extremities, detection of developmental skeletal manomalies – simple, easy to see
- thalidomide, TTC, cytostatics - cyclophosphamid, chlorambucil, busulfan, methotrexate, 5-fluorouracil, acetazolamid, grizeofulvin



Samia A Temtamy, Mona S Aglan. Brachydactyly. Orphanet Journal of Rare Diseases. 3, 15. 2008.

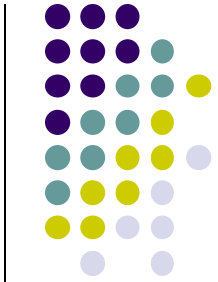
Drugs interaction

Reason of many unclear impairments of fetus

- drug + drug
- drug + additive agents (foods, exhalants, chemical agents of environment)

- Potentiation of effect on fetus
  - **nicotine** - ↑ teratogenic effect of **insulin**
  - **Benzooic acid -** ↑ teratogenic effects of **acetylsalicylic acid**

Fetal (perinatal) pharmacotherapy



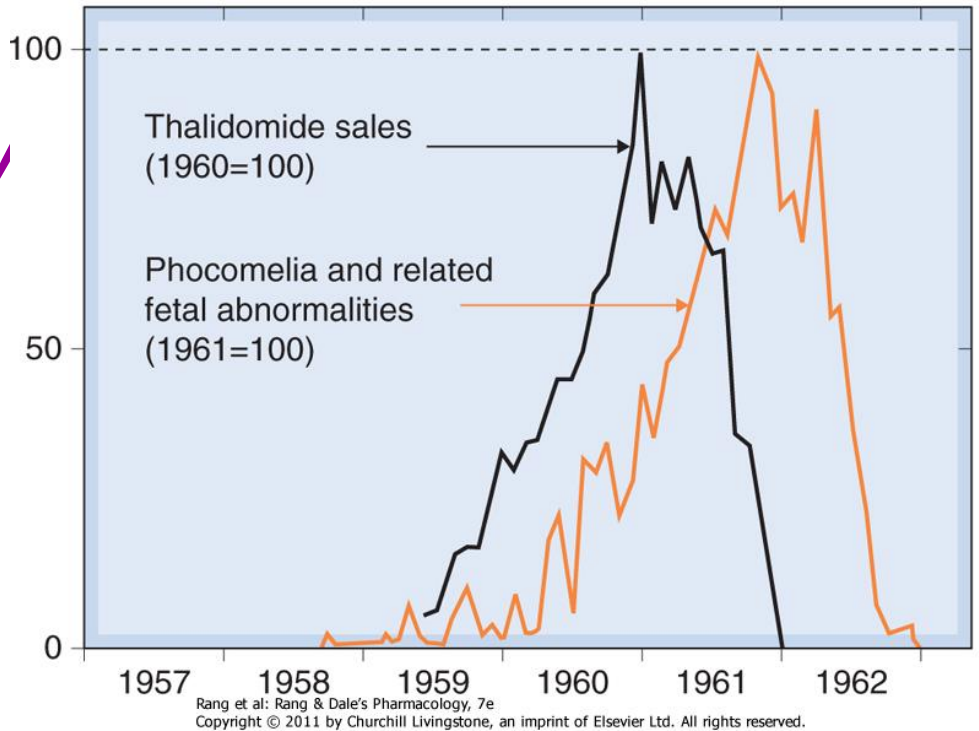
- Administration of drug to pregnant woman aiming to treat fetal disorder
  - **corticosteroids** – stimulation of lungs maturation, in risk of preterm birth and RDS
  - Therapy of heart arrhythmias
  - **fenobarbital** ↑ metabolism of bilirubine

Classification of drugs according to teratogenic effect

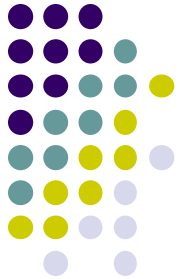
I. group - evident teratogens:

- Thalidomid
- Estrogens
- Cytostatics – inhibitors of folic acid - methotrexate

Interruption of pregnancy



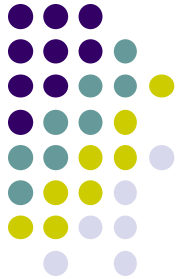
Classification of drugs according to teratogenic effect



II. group – agents suspicious for teratogenic effects:

- Antiepileptics - phenytoin, phenobarbital
- Anticoagulants - warfarin
- Alkylating cytostatics - cyklophosphamid, busulphan, chlorambucil
- Thyreostatics - propylthiouracyl, thiouracyl
- Peroral antidiabetics – tolbutamid
- other - streptomycin, TTC, alcohol

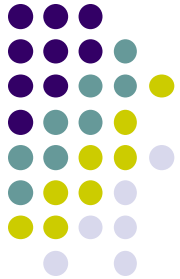
Classification of drugs according to teratogenic effect



III. group – agents potentiated by external factors (without clear evidence):

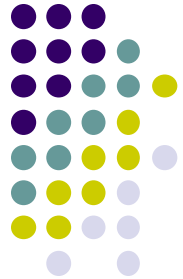
- Peroral contraception pills
- Anxiolytics
- Antiemetics
- Acetylsalicylic acid
- Chemoterapeutics – sulphonamides
- Antimycotics – griseofulvin
- Antimalarial drugs - quinine

Classification of drugs according to teratogenic effect



- Influence of **local and general anesthetics** – healthcare personnel – repeated exposure – last trimester – disturbed physiological function of fetus – respiratory disturbances, ↓ muscular tone in fetus
- **Nicotine** - 10 cigarettes - ↓ birth weight, retardation in further development
- **Addictive agents**

Classification of drugs according to teratogenic effect



IV. group – other drugs

Drugs during lactation

- **Recommendation** – drug administration **immediately after breastfeeding** and 3 hours before another breast feeding

- Most of the drugs occur in maternal milk in very low concentration – they do not reach therapeutic dose

Drugs during lactation

Dangerous

- **Antimicrobial agents, sulphonamides** – compete with bilirubine in binding to plasmatic albumin - ↑ probability of nuclear icterus,
- **TTC** - teeth, bones,
- **Chloramphenicol** - „grey syndrome“ of newborn
- **Isoniazid** - deficit pyridoxine
- **Psychopharmacons - hypnotics** – numbness, ↓ sucking reflex,
  - **Diazepam** – accumulation in the body

Drugs during lactation

- **Analgesics** – morphine, pentazocin, tilidin - addiction – abstinence syndrome – do not stop their administration suddenly! Continual decreasing doses.
- **Alcohol** – low doses, nicotine, caffeine – minimal concentration in milk
- Drugs modifying **endocrine functions** - contraindicated