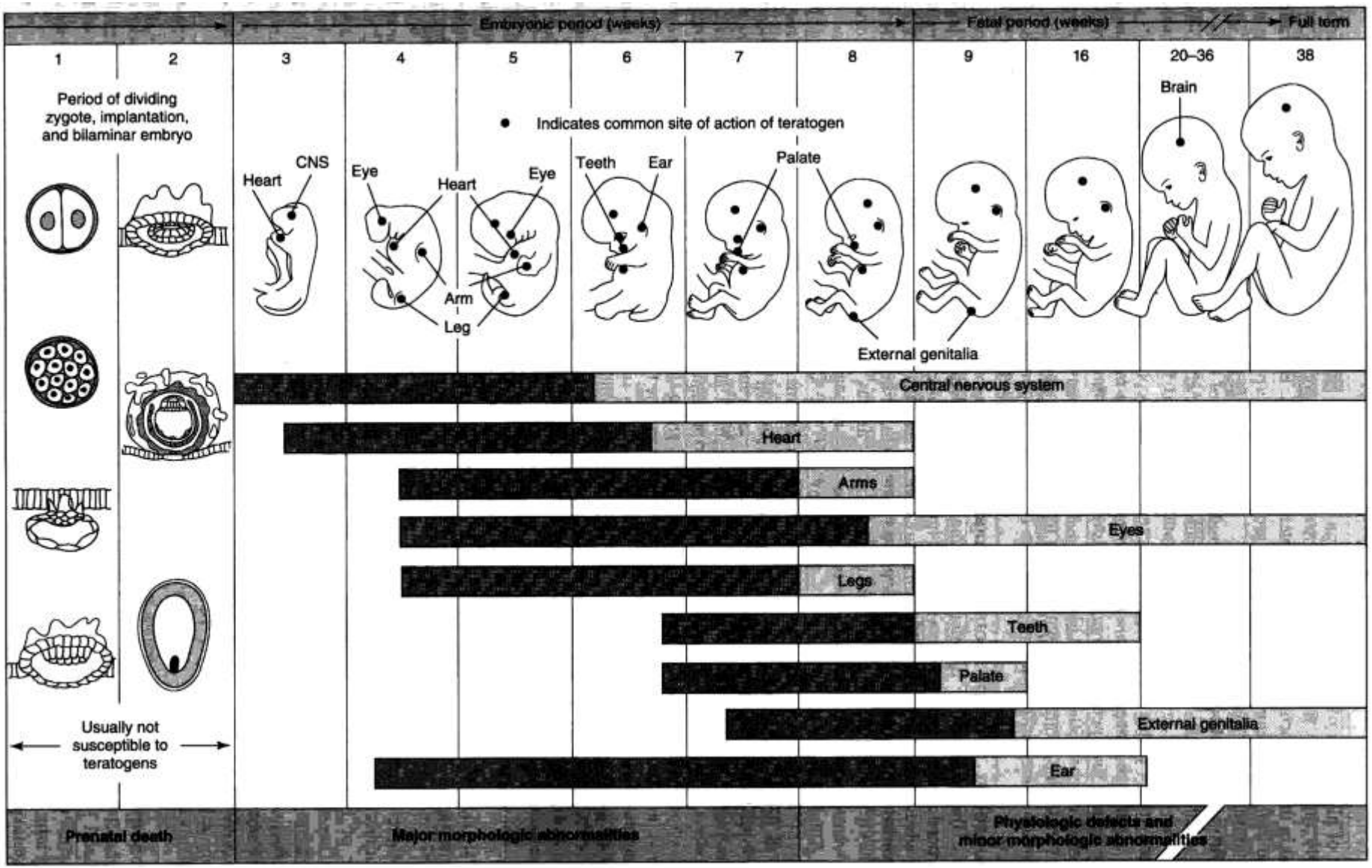
Pharmacokinetics and pharmacodynamics in children and elderly

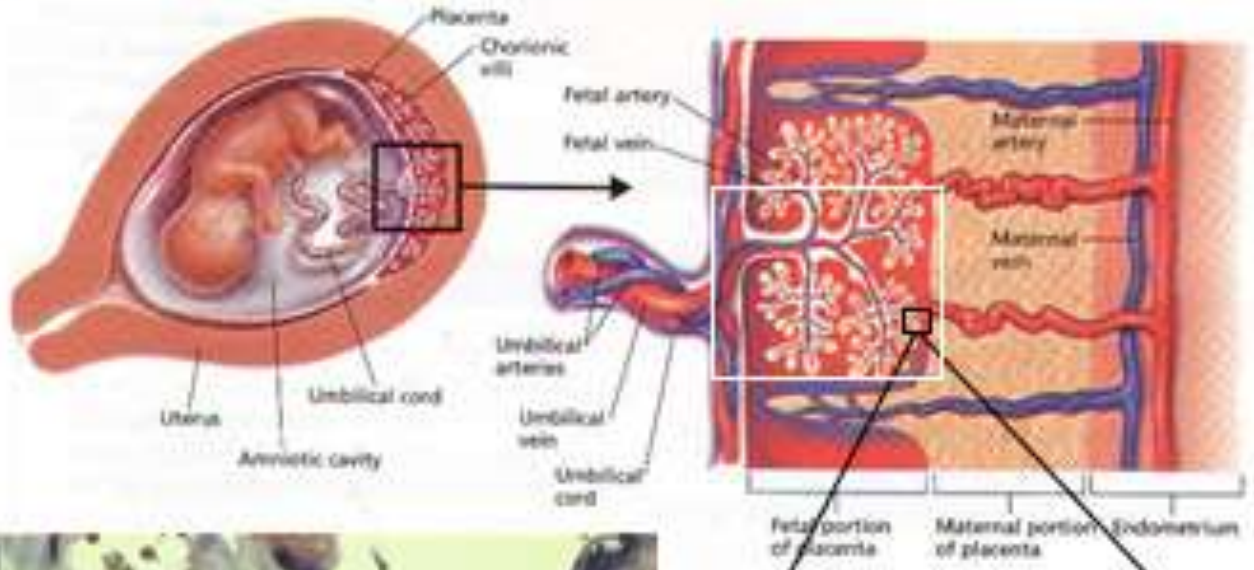
Sándor Kerpel-Fronius, M.D., D.Sc.
Semmelweis University
Department of Pharmacology and Pharmacotherapy
Budapest, Hungary
Email: kerfro@pharma.sote.hu

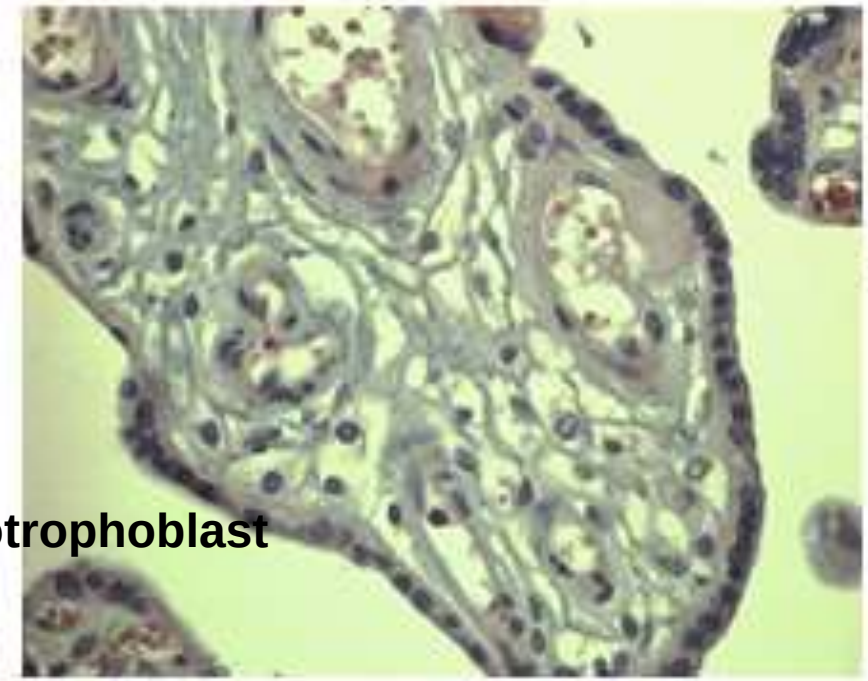
Teratogen effects of drugs, time and place

Moore KL. The developing human . Clinically oriented embryology, 4th ed.Saunders, 1988.

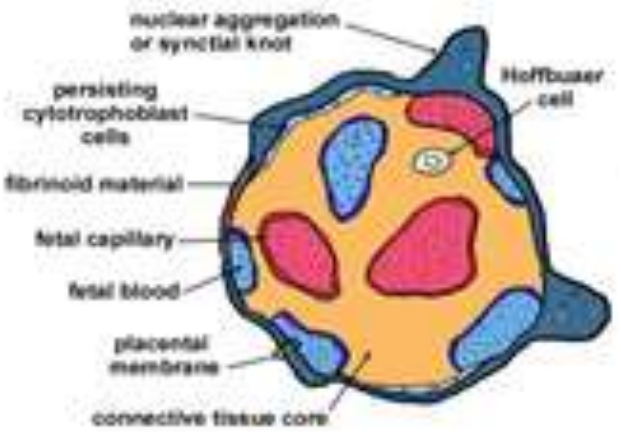


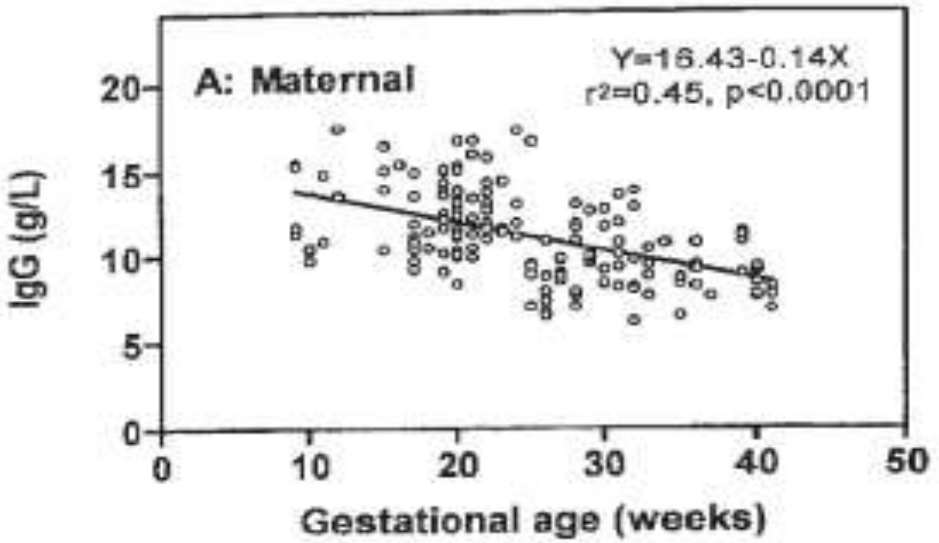
Human Placenta Anatomy

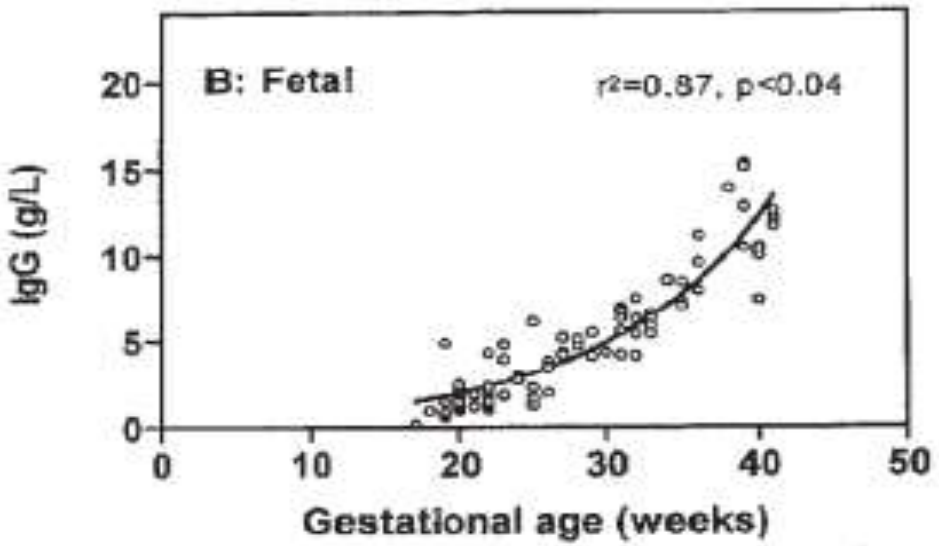




Syncytiotrophoblast







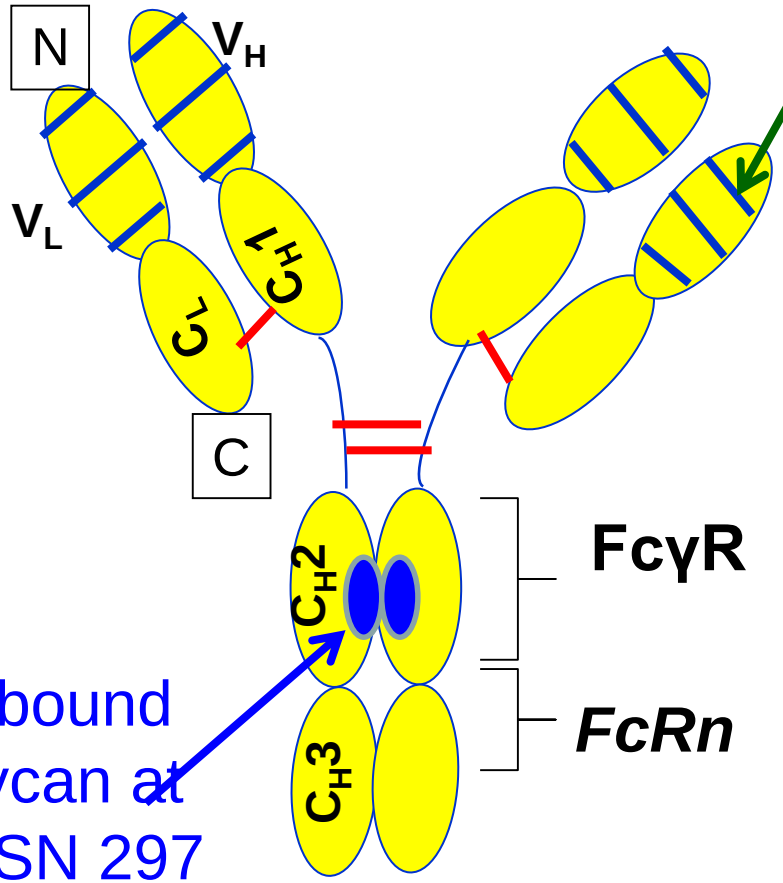
Maternal vein

In vivo maternofetal transport of immunoglobulins during human pregnancy

Malek et al., Am J Reprod Immunol. 1996 Nov;36(5):248-55.

Umbilical vein

IgG: complex and multifunctional molecule



Complementarity determining regions (CDR)

Antigen binding

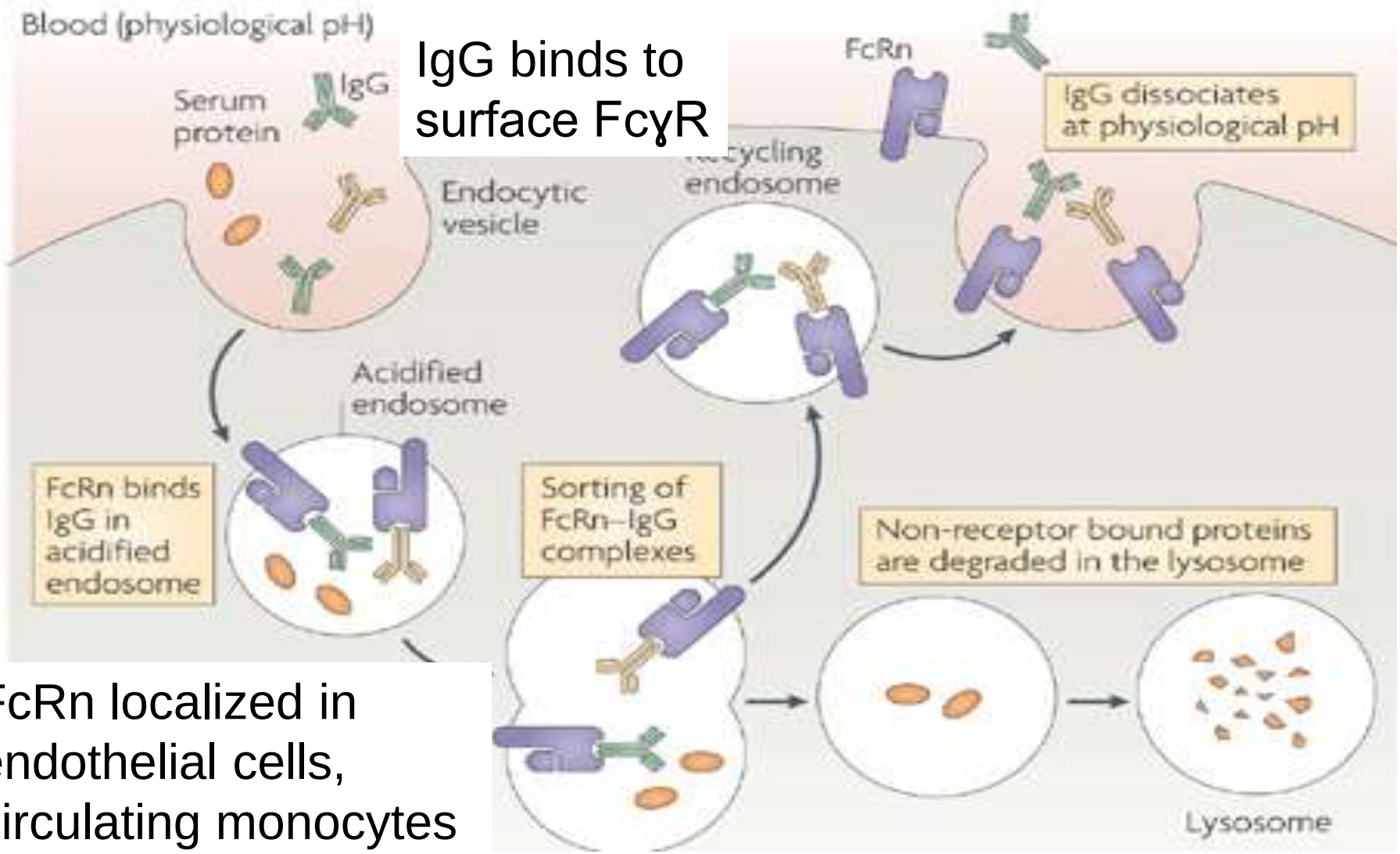
Direct effects due to Fab (eg. apoptosis)

ADCC
CDC
ADCP
functions

Pharmacokinetical characteristics

The physiological role of the neonatal Fc receptor (FcRn)

Roopenian DC & Shreeram A. Nature Rev Immunol. 7:715-725, 2007



FcRn localized in endothelial cells, circulating monocytes in CV system

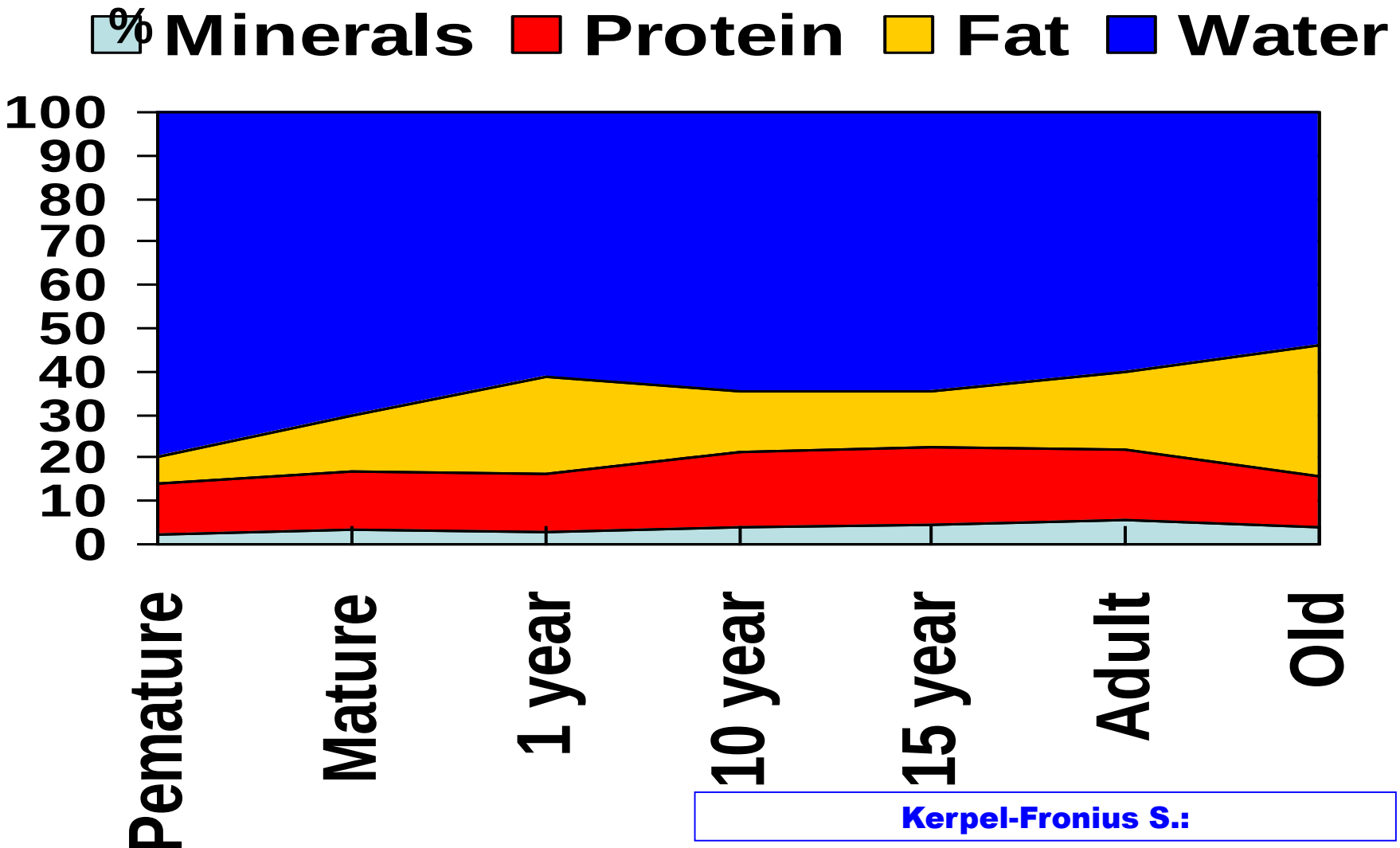
FDA Category definition

Category	Definition
A	Controlled human studies did not demonstrate a risk to the fetus in 1st trimester and later trimesters
B	Animal reproduction studies did not show a risk for the fetus. No human controlled studies, or animal studies were not conducted. Benefit for pregnant women may be acceptable despite potential risks
C	Animal studies have adverse effect to the fetus, no human controlled studies. Benefit for pregnant women may be acceptable despite potential risks
D	There are positive evidences for human fetal risk from clinical experience, but the potential benefit for pregnant women may be acceptable despite potential risks in case of life-threatening serious disease for which no other drugs are avaialble
X	Animal or human studies or clinical experience indicate have demonstrated fetal abnormalities. The use of the drug clearly outweights any possible benefit.

Drugs contraindicated or problematic for use in pregnancy

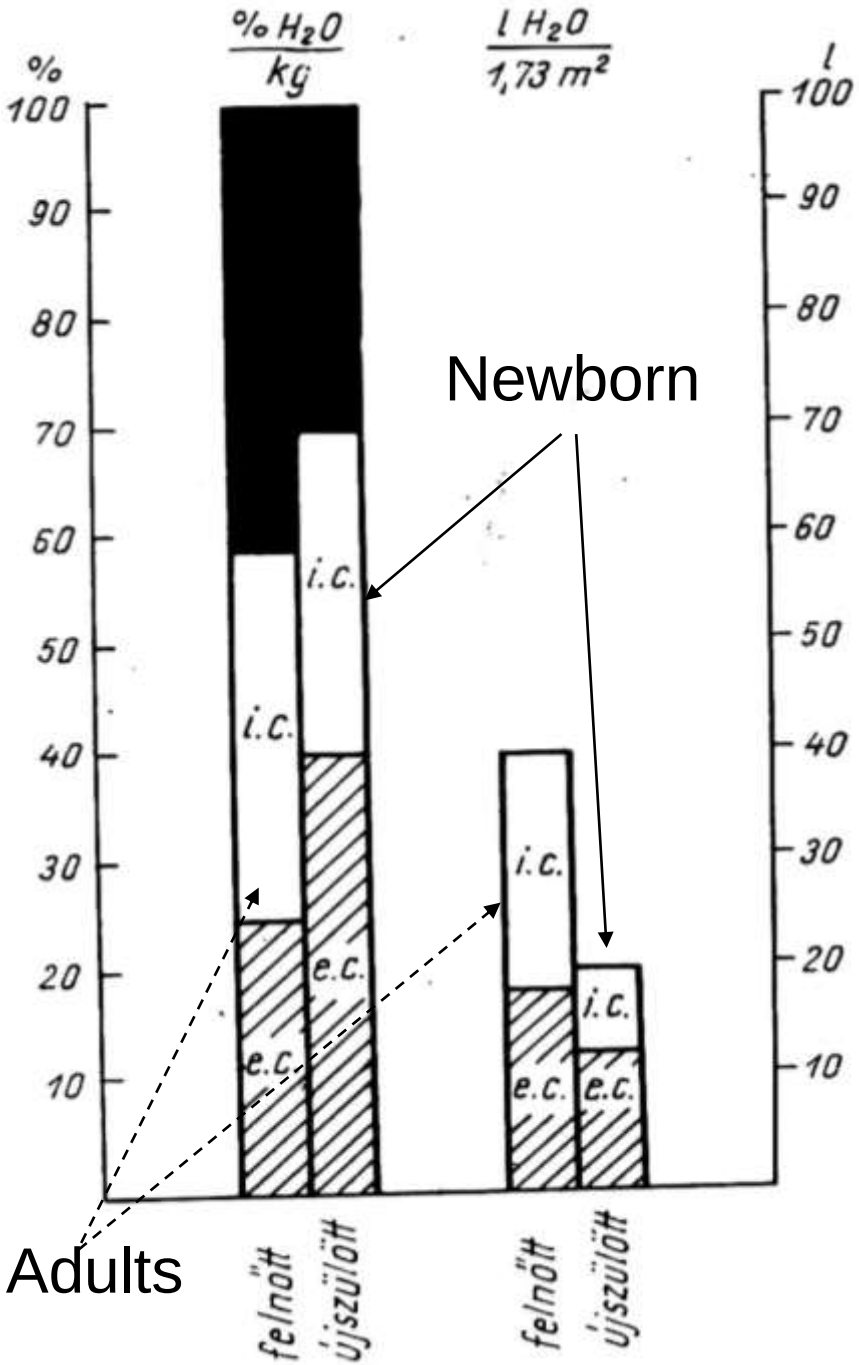
Category	Medicines
X Strongly teratogenic drugs	Contraindicated in pregnancy, risk overweights possible benefits: Cytotoxic, azathioprin, thalidomide, isotretinoin dervatives, cumarin derivatives
D and C Moderately teratogenic drugs.	Their use is indicated in life-threastening, serious diseases: Diethylstilboestrol, androgen hormones, penicillamine
D and C Weakly teratogenic drugs	Their use is indicated if benefit for pregnant women may be acceptable despite potential risks: Antieplieptics, phenytoin derivatives, valproic acid, carbamazepin, lithium, NSAIDs (primarily in late pregnancy), misoprostol, aminoglycosydes, ACEIs, ARBs, ketoconazol, fluconazol, miconazol,azathiopr

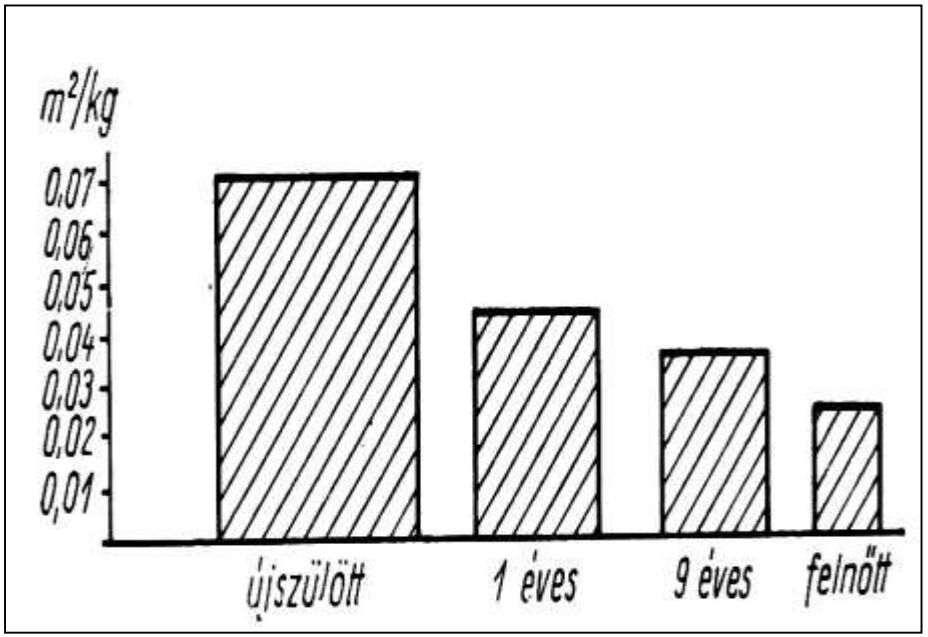
The alteration of body composition with age



Changes in body surface area and water spaces with age

Kerpel-Fronius, Ö, Gyermekgyógyászat, Medicina, 1969



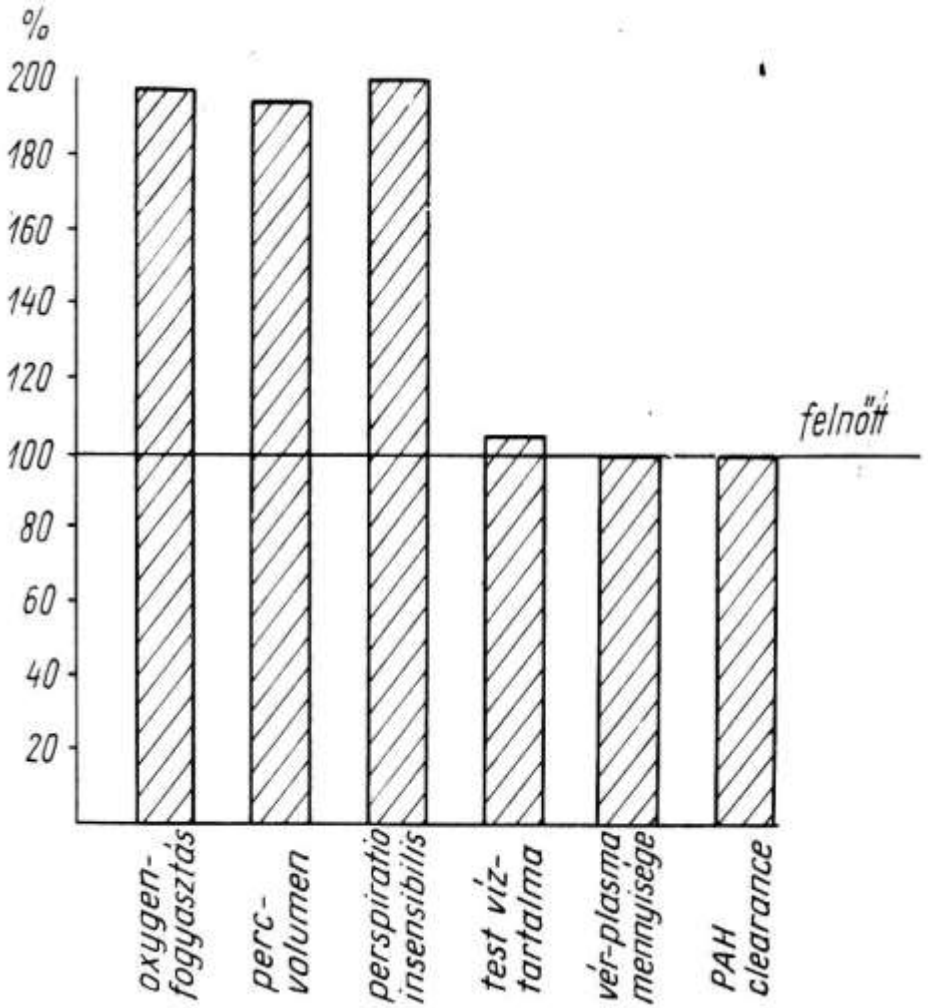


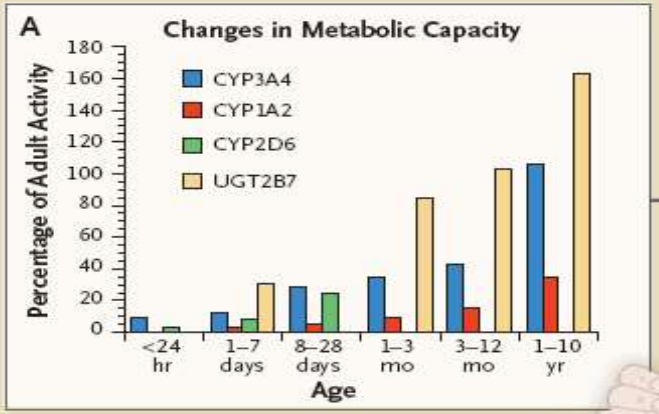
Newborn 1yr 9yr adult

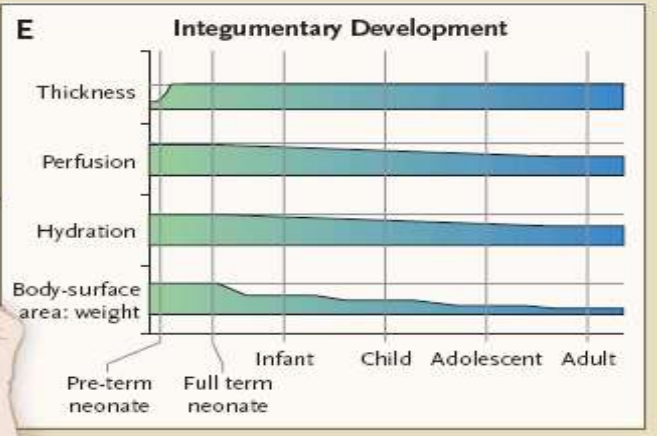
The relation of drug action and blood circulation in children

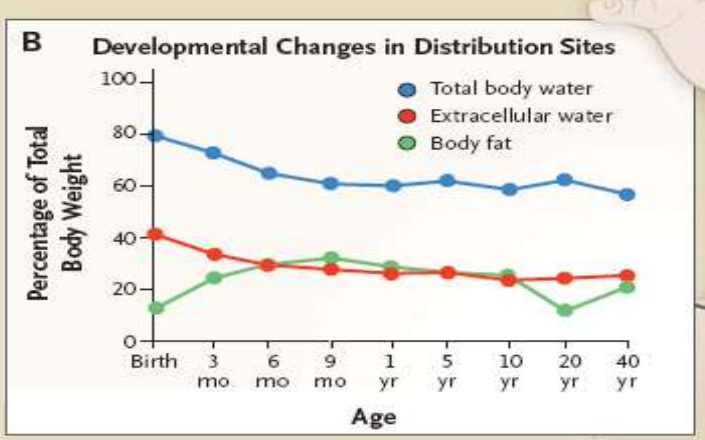
Kerpel-Fronius E, Gyermekgyógyászat. Medicina, 1969

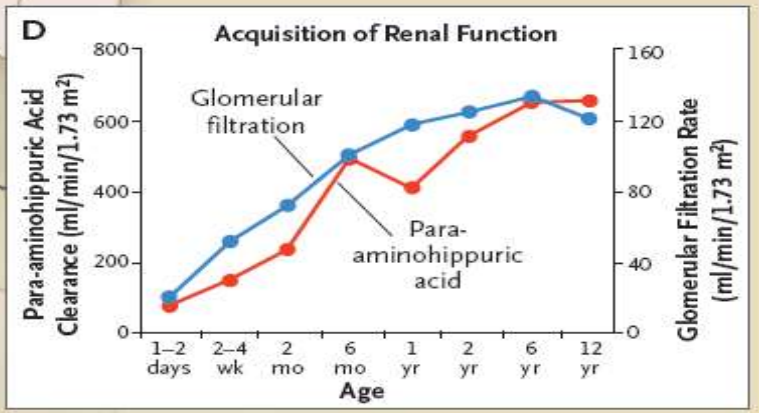
- The minute volume, the oxygen consumption, the perspiration are related to the body surface area and are approximately double of the adult if calculated per kg. Consequently the circulation decompensates more rapidly in babies than in adults.
- The absorbtion and elimination of drugs can be rapidly changed due changes of blood volume perfusing the tissues

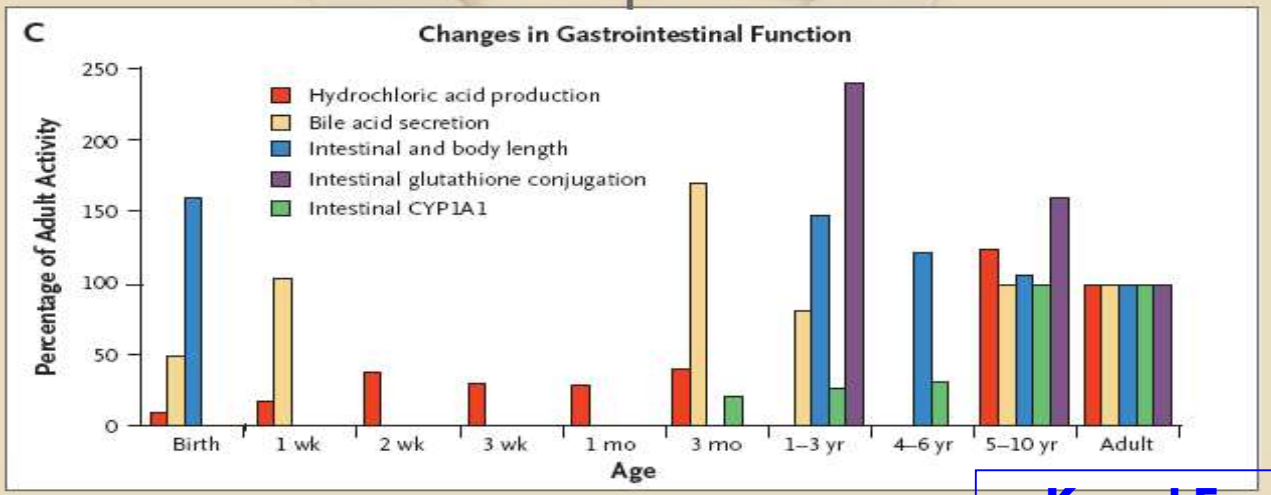



A
Changes in Metabolic Capacity
Percentage of Adult Activity
CYP3A4
CYP1A2
CYP2D6
UGT2B7
<24 hr
1–7 days
8–28 days
1–3 mo
3–12 mo
1–10 yr
Age


E
Integumentary Development
Thickness
Perfusion
Hydration
Body-surface area: weight
Pre-term neonate
Full term neonate
Infant
Child
Adolescent
Adult


B
Developmental Changes in Distribution Sites
Percentage of Total Body Weight
Total body water
Extracellular water
Body fat
Birth
3 mo
6 mo
9 mo
1 yr
5 yr
10 yr
20 yr
40 yr
Age

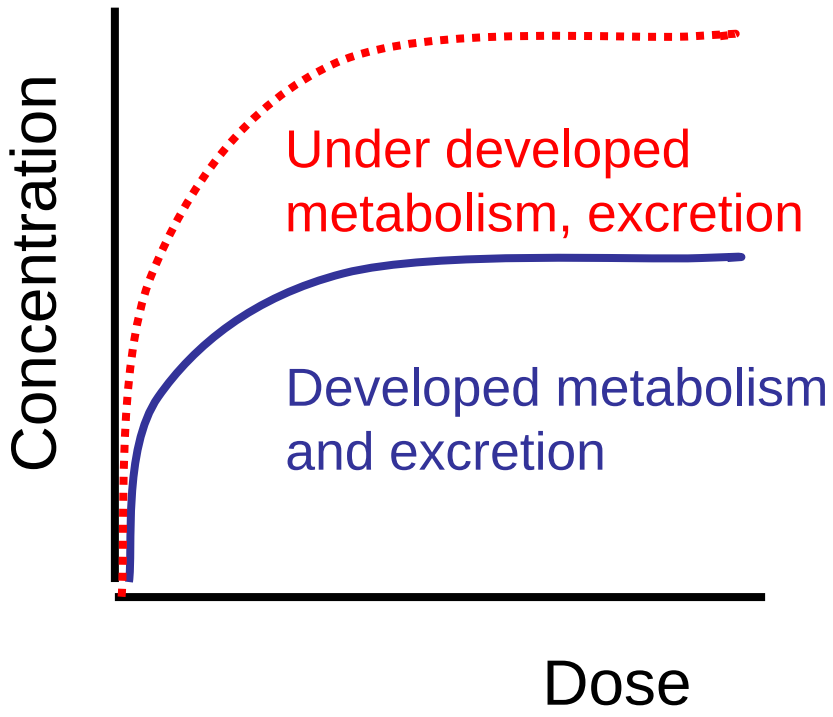

D
Acquisition of Renal Function
Para-aminohippuric Acid Clearance (ml/min/1.73 m²)
Glomerular Filtration Rate (ml/min/1.73 m²)
Glomerular filtration
Para-aminohippuric acid
1–2 days
2–4 wk
2 mo
6 mo
1 yr
2 yr
6 yr
12 yr
Age


C
Changes in Gastrointestinal Function
Percentage of Adult Activity
Hydrochloric acid production
Bile acid secretion
Intestinal and body length
Intestinal glutathione conjugation
Intestinal CYP1A1
Birth
1 wk
2 wk
3 wk
1 mo
3 mo
1–3 yr
4–6 yr
5–10 yr
Adult
Age

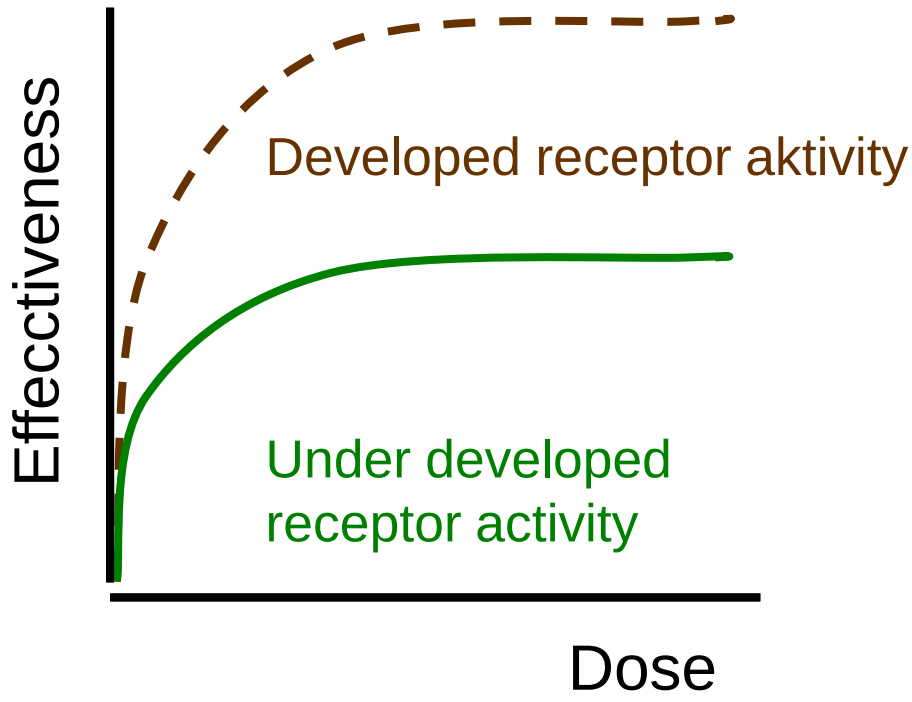
NEJM

The changes of drug metabolism and effectiveness in case of under developed enzyme and/or receptor activities

Drug concentration in the plasma



Drug effect



The changes of drug metabolism and effectiveness in case of under developed enzyme and/or receptor activities

	Developed metabolism and excretion	Under developed metabolism, excretion
Developed receptor activity	Plasma level and drug effectiveness similar to normal adults	Plasma level higher than in normal adults (toxic level!) Drug effectiveness similar to normal adults
Under developed receptor activity	Plasma level similar to normal adults Drug effectiveness less than in normal adults	Plasma level higher than in normal adults (toxic level!) Drug effectiveness less than in normal adults

The calculation of drug dose according to body weight in children (Clark formula)

Basic and Clinical Pharmacology, 7th ed. Katzung BG, Appleton&Lange, 1998.

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Body weight (kg)}}{70}$$

- Due to the higher extracellular water content the drugs are distributed in a larger fluid compartment as compared to adults
- Consequently the calculated dose frequently gives a dose below the therapeutic dose range
- Doses used for babies might result in toxic dose levells in older children
- **The calculated dose cannot replace the dose determined in clinical trials**

The calculation of drug dose based on the body surface area in children

Arzneimitteltherapie, ed. Berthold H, G. Fischer Verlag, 1999.

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Child body surface area}}{1{,}73}$$

- Generally mean body surface area is used. It is more accurate to determine the real body surface area on the basis of body weight and height using nomograms
- The calculated value is closer to the real value especially in children over 3 years
- **The calculated dose cannot replace the dose determined in clinical trials**

Drug absorbtion in children

- Relatively low amount of muscle tissue in babies, especially in prematures, low blood perfusion
- GI tract
  - The production of HCl starts few hours after birth. Adult level is reached within several months
  - Gastric emtying is delayed, 6-8 hours, irregular gut peristaltics
  - Low enzyme activity in the gut epithelium cells, low lipase and bilirubin content. The absorbtion of lipid soluble drugs is low
  - The absorbtion through the delicate skin epithelium is faster than in the adults

Drug distribution in children

- The extracellular water content amounts to 45% of the body weight in babies and only to 16% in adults.
- Water soluble drugs, sulphonamides, aminoglycosides, penicillin derivatives, cephalosporines, digoxin distribute in larger extracellular space, consequently their plasma level become lower than in adults. Higher doses are needed.
- Protein content of the blood is lower, the drug binding capacity of albumine is lower, higher free drug concentration

Drug distribution in children

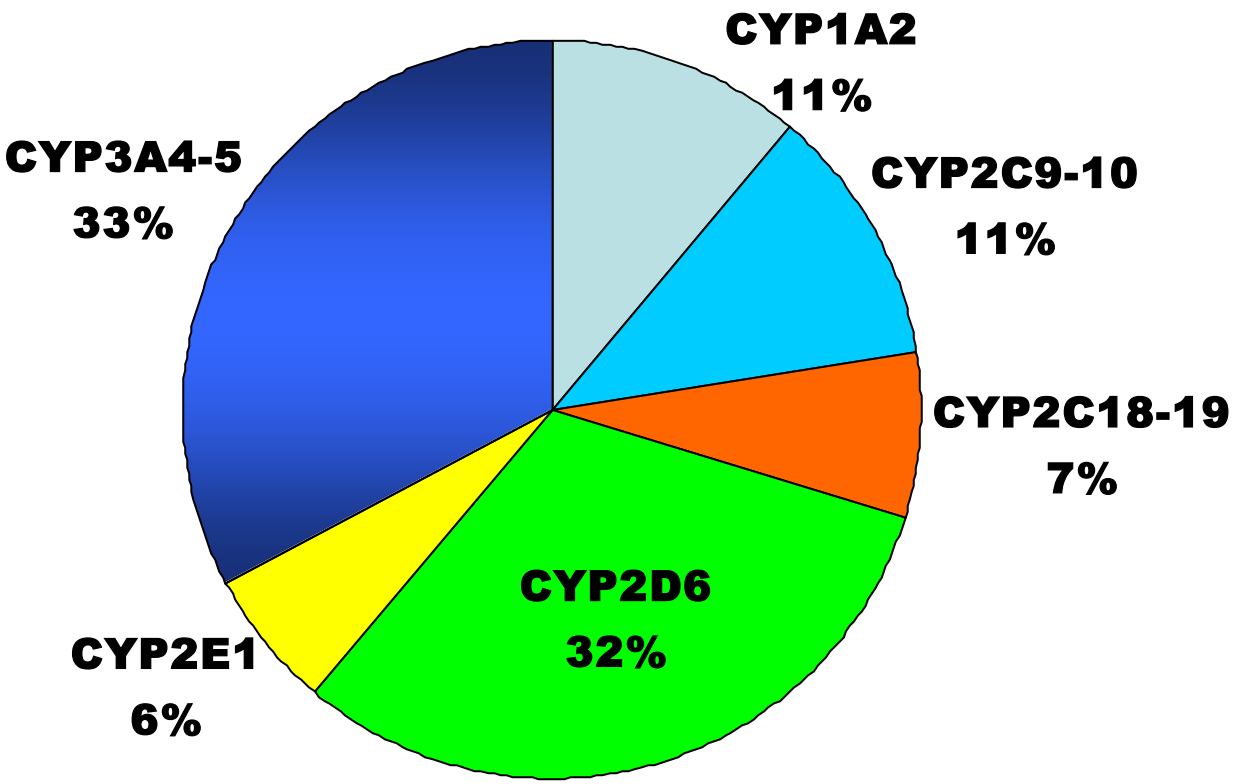
- Bilirubin is more easily displaced from albumine binding
- The fat content of the body is 10-12%, in the adult 18-20%
  - The distribution space of lipid soluble drugs is smaller
  - The permeability of the blood-brain barrier is increased, increased concentration of lipid soluble compounds in the CSF (Primarily premature babies)
  - Anaesthetics, sedatives, morphium

Drug metabolism in children

- The lower concentration of drug metabolizing enzymes result in lower drug metabolism
  - Cytochrome P450 dependent oxydative metabolism
  - Conjugation reactions
  - Lower drug clearance, delayed elimination
  - Adult level of drug metabolism is reached at around 4 years
- The amount of enzymes might be increased by inducers, eg. by antiepileptic therapy during pregnancy

Percentage distribution of drugs metabolized by cytochrome P450 isoenzymes

After Johnson et al.: Orvostd. Sz., 7: 49, 2000.

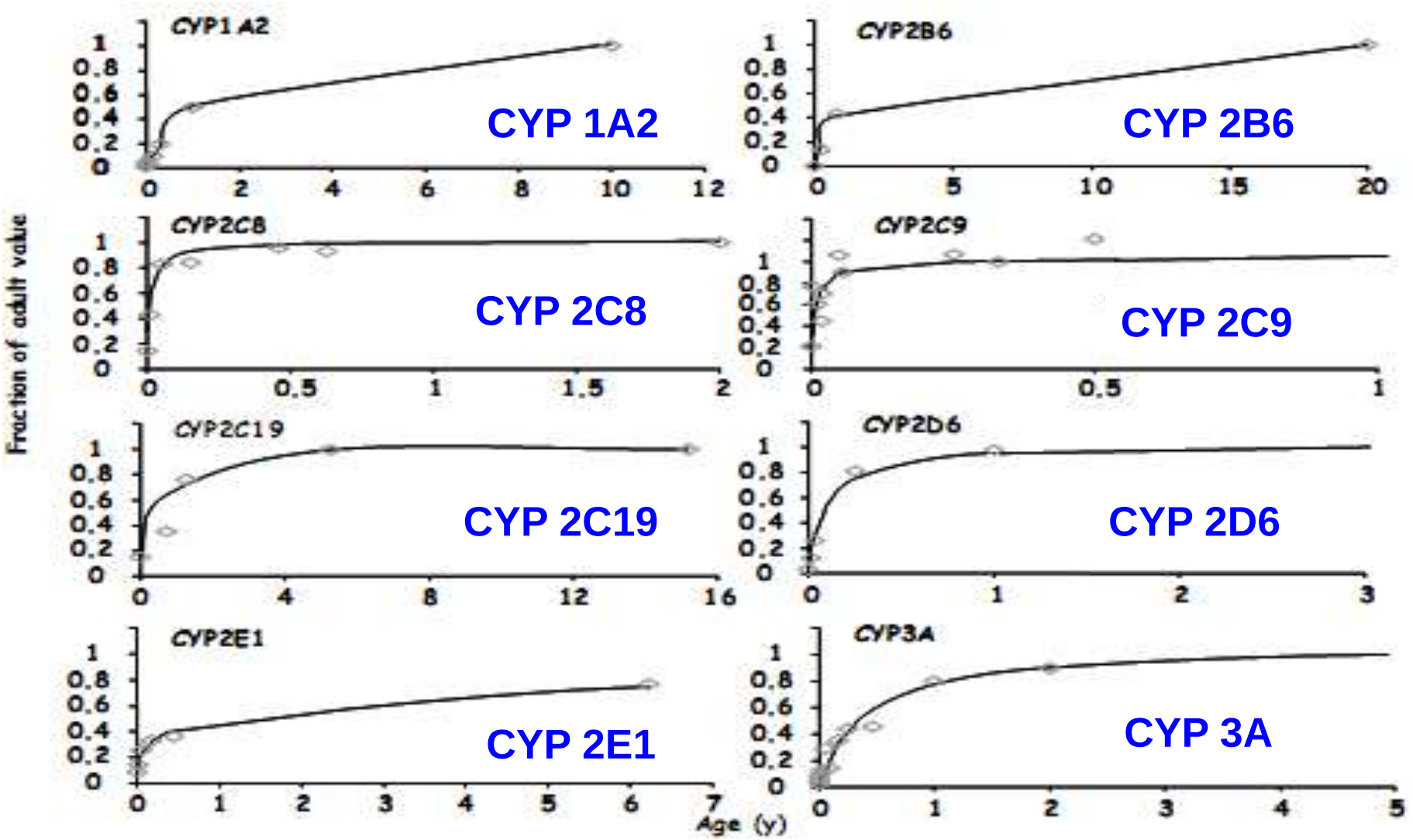


The substrate specificity of the CYP isoenzymes is low, many drugs are metabolized by several CYP species.

CYP3A occurs in a large quantity extrahepatically, e.g. in the gut epithelium

Cytochrome expression/activity as compared to adults, between 0-12 years

Johnson TN et al. Clin Pharmacokin 45:931-56, 2006



- In vitro data, computer simulation

Drug elimination in children

- Decreased elimination via the bile
  - Decreased metabolism and conjugation
  - Decreased production of bile
- Decreased elimination through the kidneys
  - Low filtration rate
  - The tubular functions are less developed than the glomerular filtration (drugs excretion by the tublues might be protracted, e.g. diuretics, penicillin derivatives)

Changing half-life of phenobarbital according to age (CYP2C19)

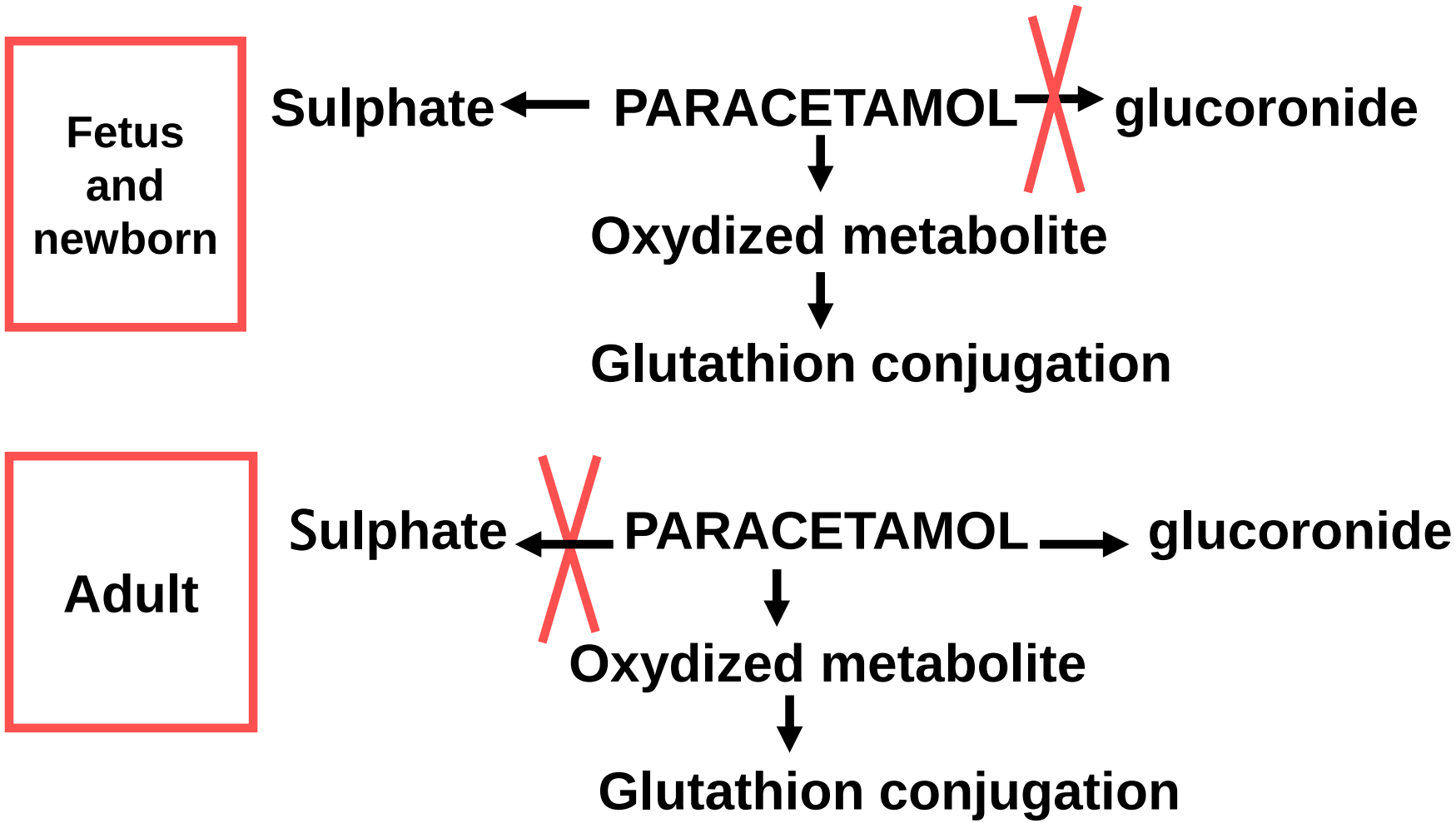
Drug	Age of babies	T1/2 h Babies	T1/2 h Adults
Phenobarbital	0-5 day	200	30 yr 60
Phenobarbital	5-15 day	100	50 yr 80
Phenobarbital	1-30 mo	50	> 70 yr 90 -140

Boreus et al. Acta Paediatr. Scand 1978 Mar;67(2):193-200.l

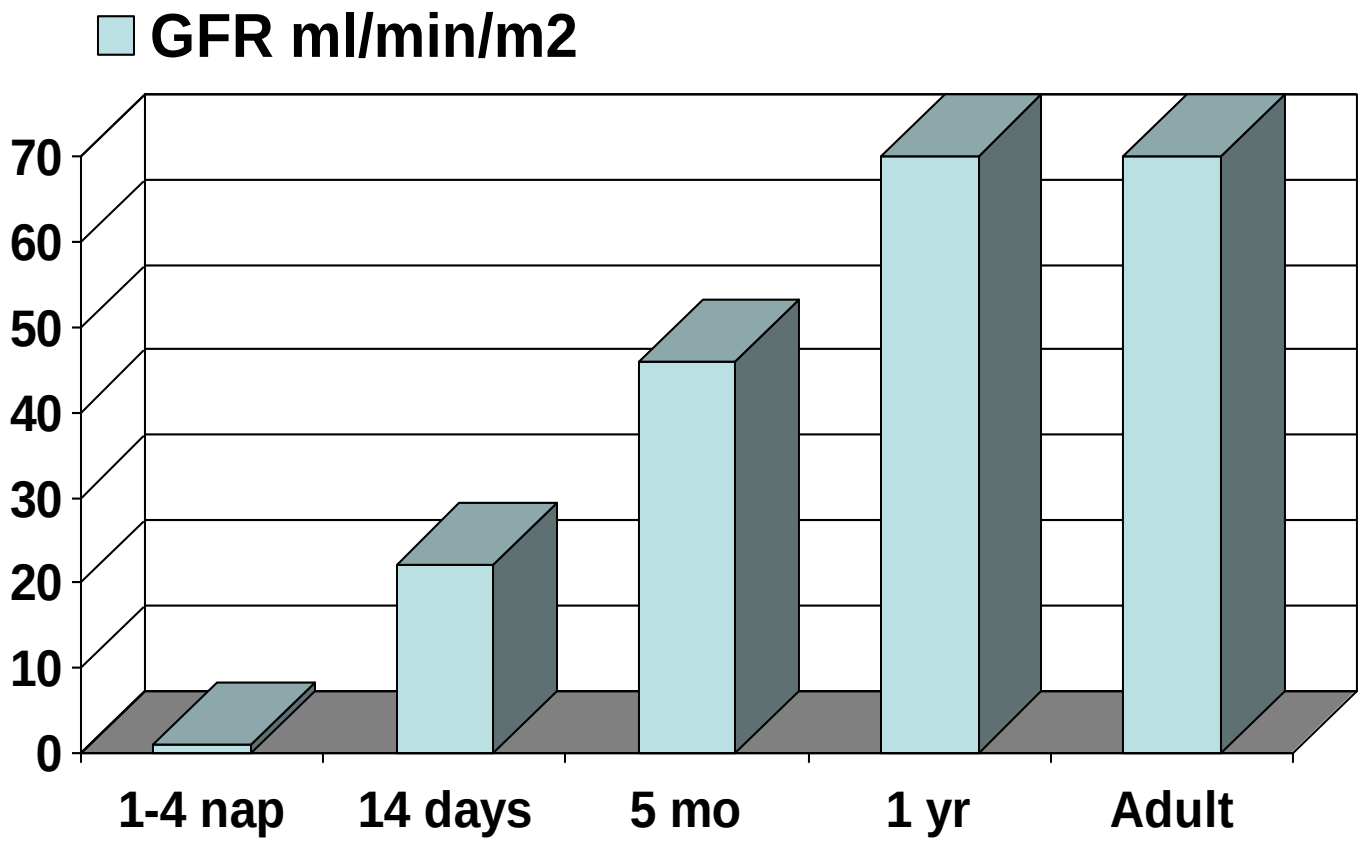
Phenobarbital is first hydroxylated, subsequently glucoronidated and eliminated in the urine and bile. The fraction related to the dose of unchanged and hydroxylated metabolite is similar in the new born and the adults, ~17% and ~10%..The proportion of conjugated metabolite in newborns is 5% (+ sulphated metabilite) and 15% in the adults.

Genetic variation: CYP2C19, in poor metabolizer clearence is 19% lower

Metabolism of paracetamol



The change of glomerular filtration rate with age



Drug application in children

Body composition rapidly changing with age

Changing pharmaco-kinetic properties

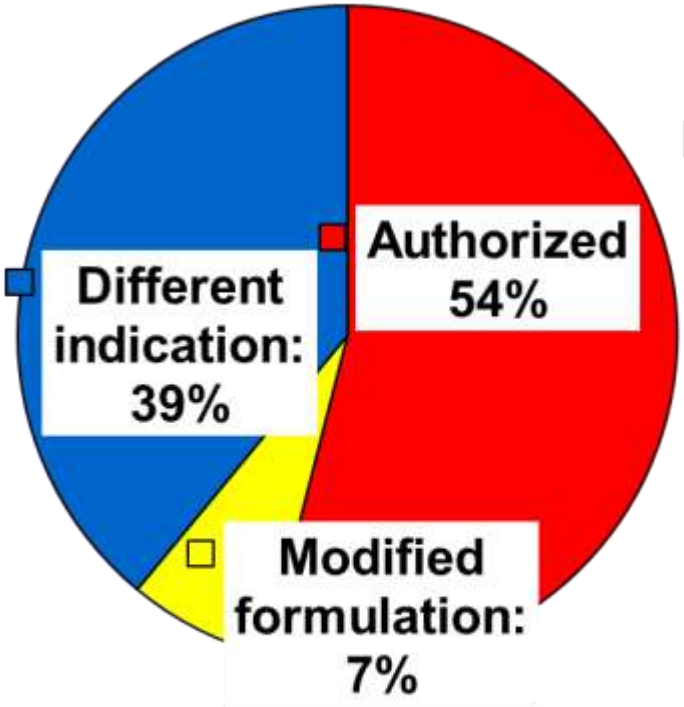
Changing pharmaco-dynamic effects

- Th recommended formulas for calculating drug dose in children give only an approximation because they cannot take into consideration the processes of maturing.
  - The results are doses below or over the optimal
- ***The doses in the various age groups must be determined by pharmacokinetic measurements and clionical dose titration***

Not authorized and and modified drug treatment in 5 EU countries

Conroy et al.: BMJ, 320:79, 2000

Prescription



- ***67% of the pediatric patients receive not authorized drug treatments***
- 624 patients (4 days-16 éyr), 2262 prescriptions

Modified drug treatment

  - Not authorized or specially permitted pharmaceutical formulation, eg. Suspension made from tabletes
  - Imported drugs without local authorization

- **Experimental drugs**
- **Different indication**
- Not authorized indication according to age
- Different administration schedule and administration route

Safe and effectivee drug administration in children

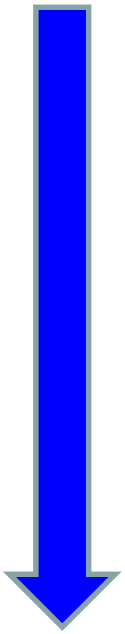
Adequate pharmaceutical formulation

❖ **European Medicine Agency (EMA): Paediatric Regulation**

❖ Paediatric Committee to provides objective scientific opinions on paediatric investigation plans (PIPs), development plans for medicines for use in children.

Subdivision of the pediatric population according to age (ICH 11)

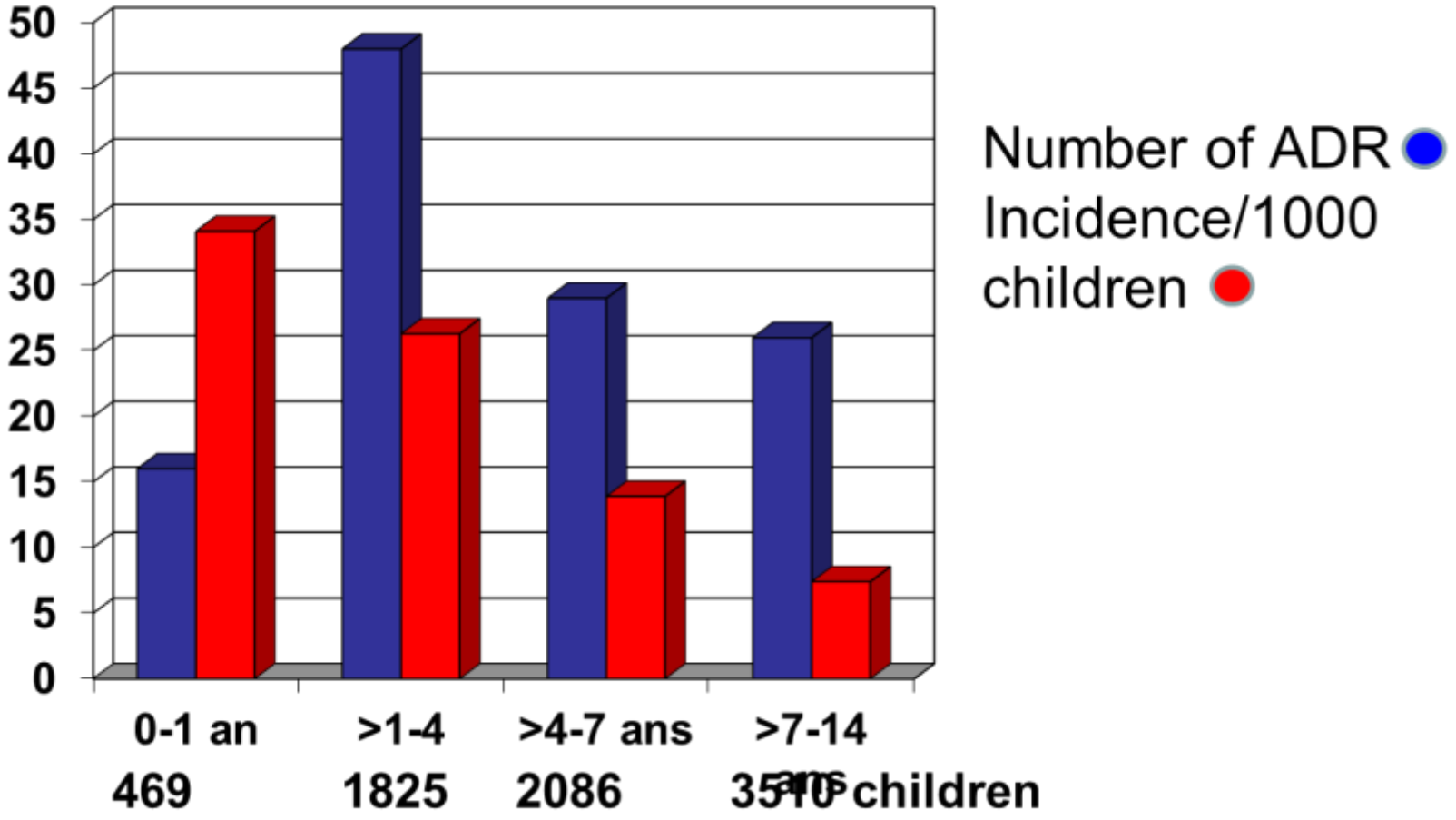
- Premature
- Mature neonate, 0-27 days
- Baby, 1- 23 months
- Infant or child, 2-11 years
- Adolescent, 12-(16)-18 years



Pharmaceutical formulations suitable to treat the specific age groups

Paediatric Network: Number of side effects in children

Menniti-Ippolito, Lancet 2000, vol 355, 1613-14



Senectas ipse morbus

“Every man desires to live long; but no man would be old”

(Jonathan Swift, 1667–1745)

Normal adults

Infants

Different body composition

Activities of physiological functions ***develop*** to various extent at various times

Elderly

Different body composition

Activities of physiological functions ***decrease*** to various extent at various times

United Nations' Definitions

	United Nation's definition 1963	Situation now
3rd Age	60-74	70-84
4th Age	≥75	≥85

The increase in the oldest old will be worldwide enormous

	2010	2050	% increase
Developed countries			
90 y.	8.166	37.774	463%
80-89 y.	46.952	85.849	183%
Developing Countries			
90 y.	12.949	123.526	954%
80-89 y.	74.455	280.741	377%

Essential reserve capacities for interaction with the environment

Campbell AJ & Buchner DM, Age *and Ageing* 1997; 26: 315-318

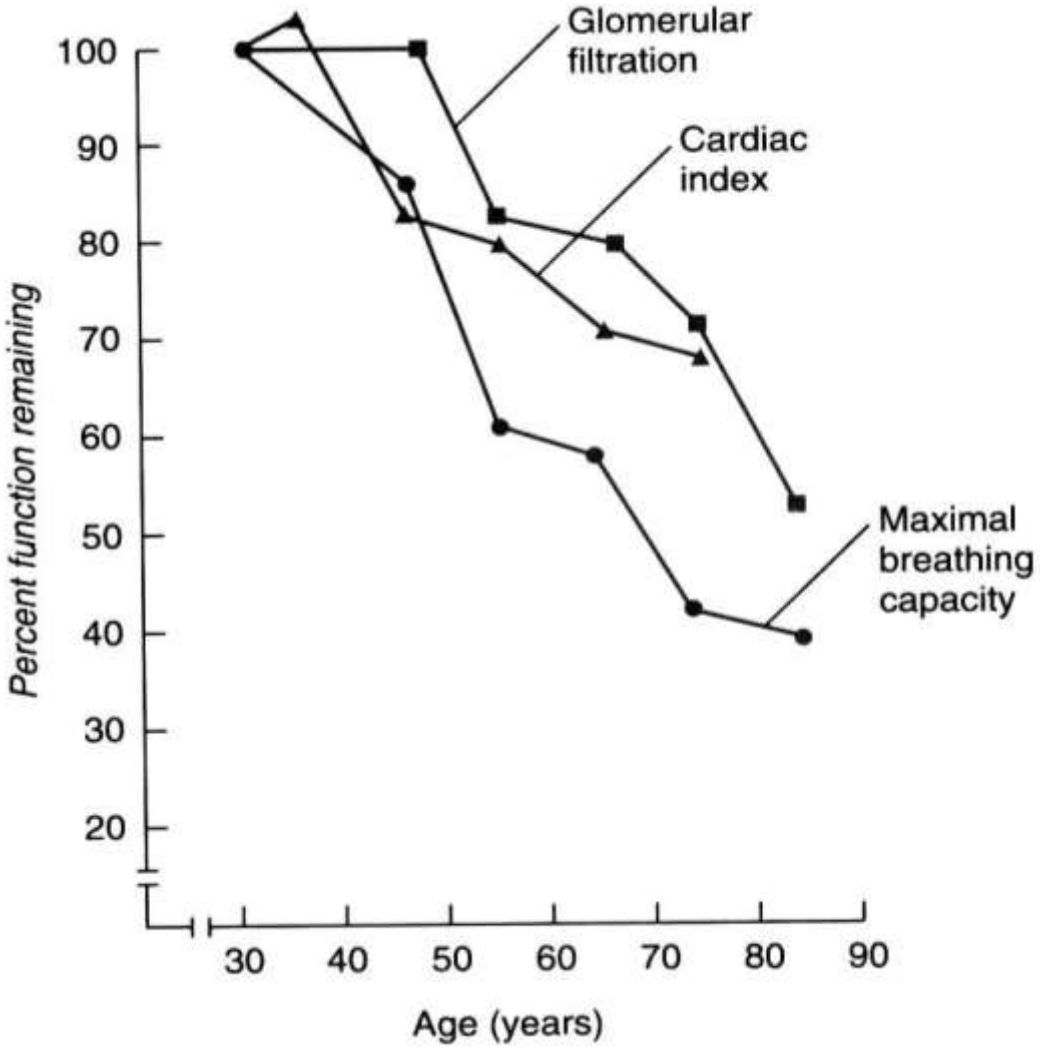
1. Musculosceletal function
2. Aerobic capacity
3. Cognitive and integrative neurological function
4. Nutritional reserve

- ❖ These capacities are commonly reduced by disease, illness and age
- ❖ Severe loss means prediction of death
- ❖ These capacities can be modified by intervention programs

Changes of physiological functions during the life

Kohn RR. Principles of Mammalian Aging. Prentice-Hall, 1978.

- The capacity of physiological functions decreases with age
- These changes might be amplified with pathologic alterations
- These changes effect pharmacokinetic behaviour of drugs



Characteristics of the key components of frailty

Campbell AJ & Buchner DM, Age *and Ageing* 1997; 26: 315-318

Failure of the homeostasis concept in the broader sence

1. Enable interaction with environment
2. Influenced by the interaction with environment
3. Essential for adjustment to stress and damage

x-x-x-x-x

4. *Clinical breakdown may be precipitated by minor physical and psychosocial stresses*
5. *Impairment may be identified prior to clinical manifestation*
6. *Impairment may be corrected*
7. *Components are interdependent*

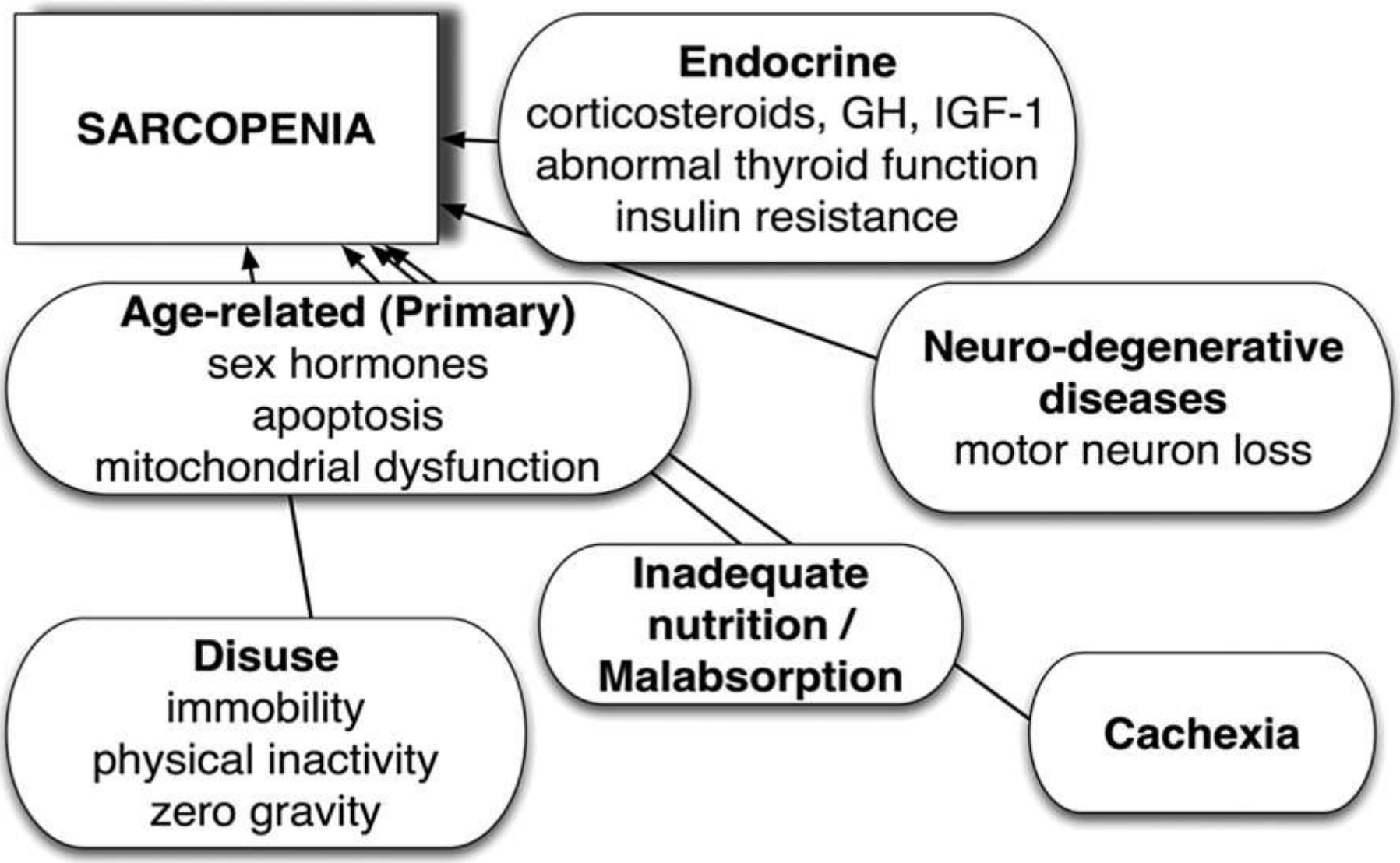
Sarcopenia

Age and Ageing, 39: 412–423, 2010; doi: 10.1093/ageing/afq034

- Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death
- Diagnosing sarcopenia
  - Criterion 1: low muscle mass, low muscle function
  - Criterion 2: strength
  - Criterion 3: performance
- The diagnosis requires documentation of criterion 1 plus documentation of either criterion 2 or criterion 3. (Muscle mass and muscle function are not linearly correlated)
- Fat infiltration of muscle decreases muscle function

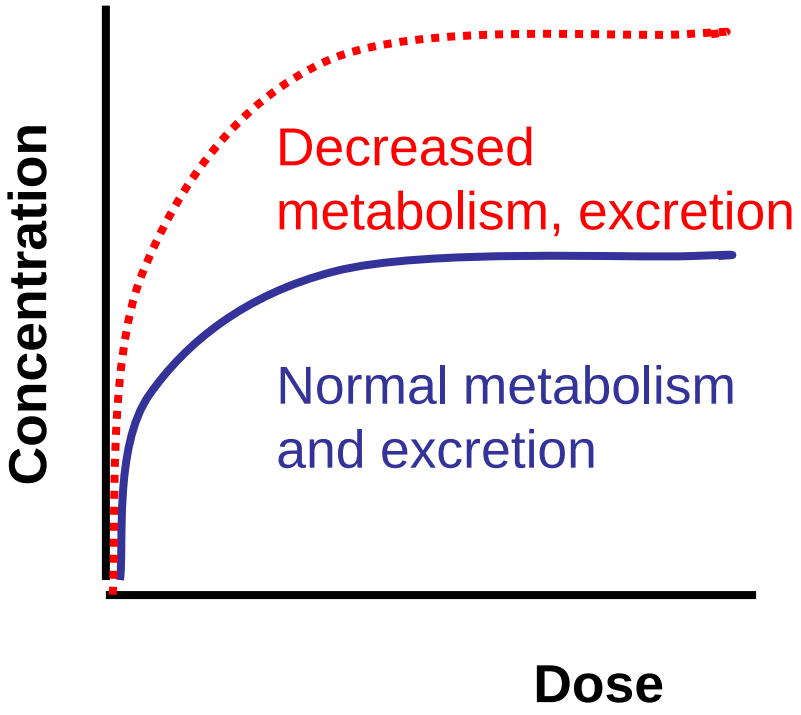
Pathomechanism of sarcopenia

Age and Ageing, 39: 412–423, 2010; doi: 10.1093/ageing/afq034

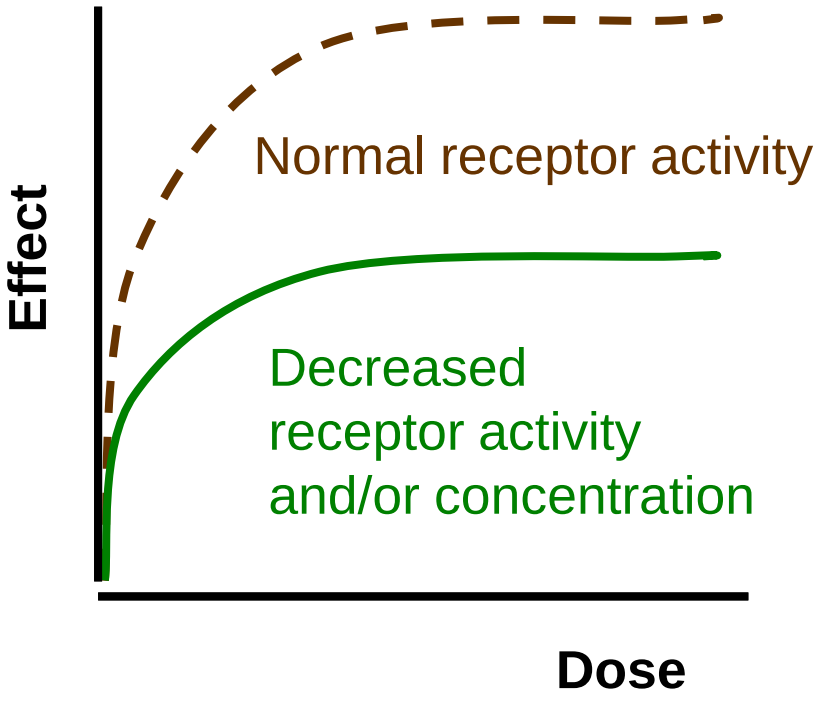


The changes of drug metabolism and effectiveness in case of decreased metabolic and/or receptor activitiescin the elderly

Drug concentration in the plasma



Drug effect



The changes of drug metabolism and effectiveness in case of under developed enzyme and/or receptor activities

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Drug absorption, distribution, metabolism and elimination in elderly patients

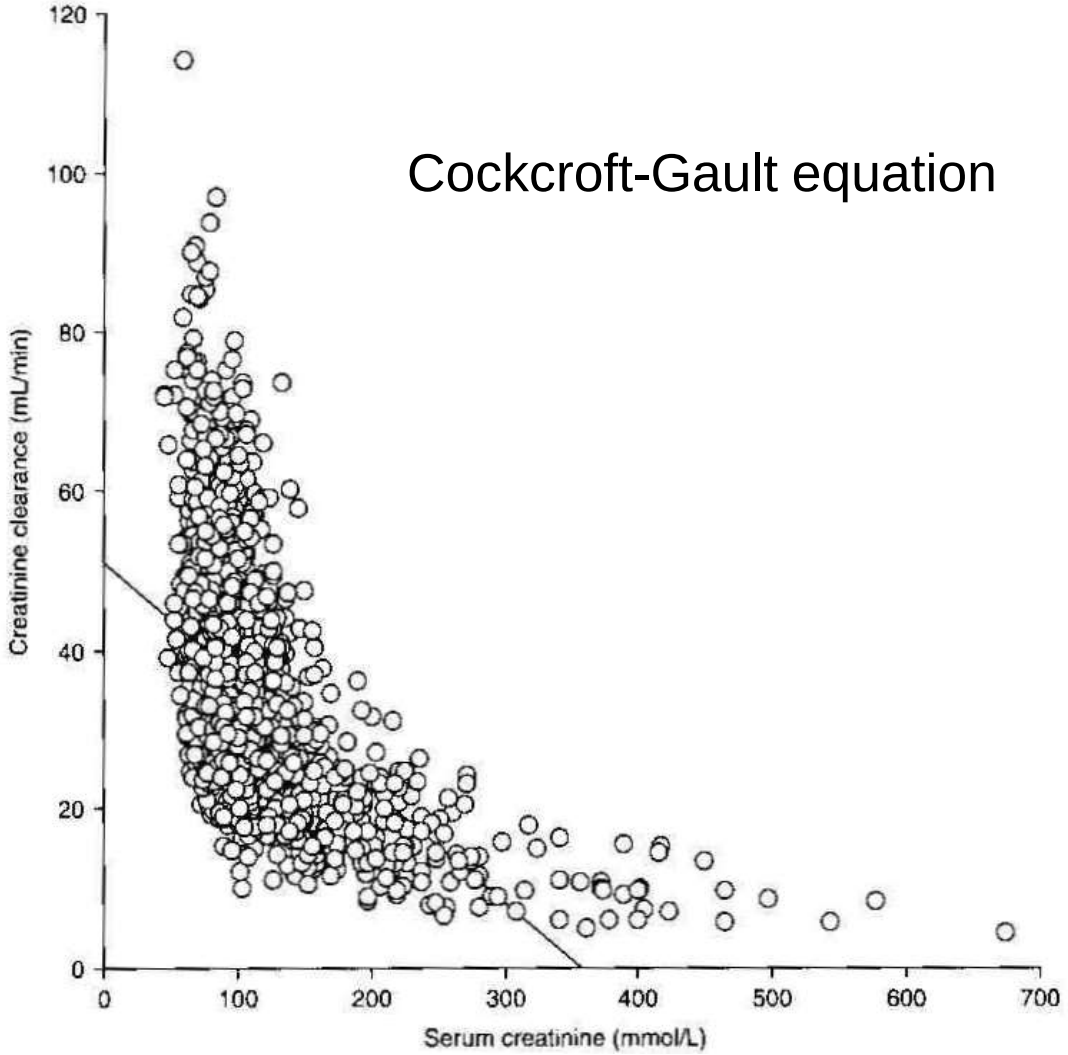
- Absorption: decreased HCl production, higher pH, decreased gut motility
- The alterations in drug absorption rarely have significant clinical implication
- Distribution:
  - Due the higher lipid content of the body the elimination and of lipid soluble drugs is protracted. The duration of drug action increases
  - Due to the lower water content of the body water soluble compounds attain a higher plasma level
  - Due to decreased albumine content the drug binding capacity decreases

Drug absorption, distribution, metabolism and elimination in elderly patients

- Liver metabolism
  - ***Decreased liver blood flow***
  - Decreased activities of the liver drug metabolizing enzymes
- Drug elimination through the kidneys
  - ***Decreased kidney blood flow***
  - Decreased rate of glomerular filtration
    - Attention! endogenous creatinine clearance is not reliable due to decreased production of creatinine in the elderly. Age factor must be used!
  - Deacreased tubular activity

Glomerular filtration rate in patients >70 years

Merle et al. Drug Aging 22:375-392, 2005

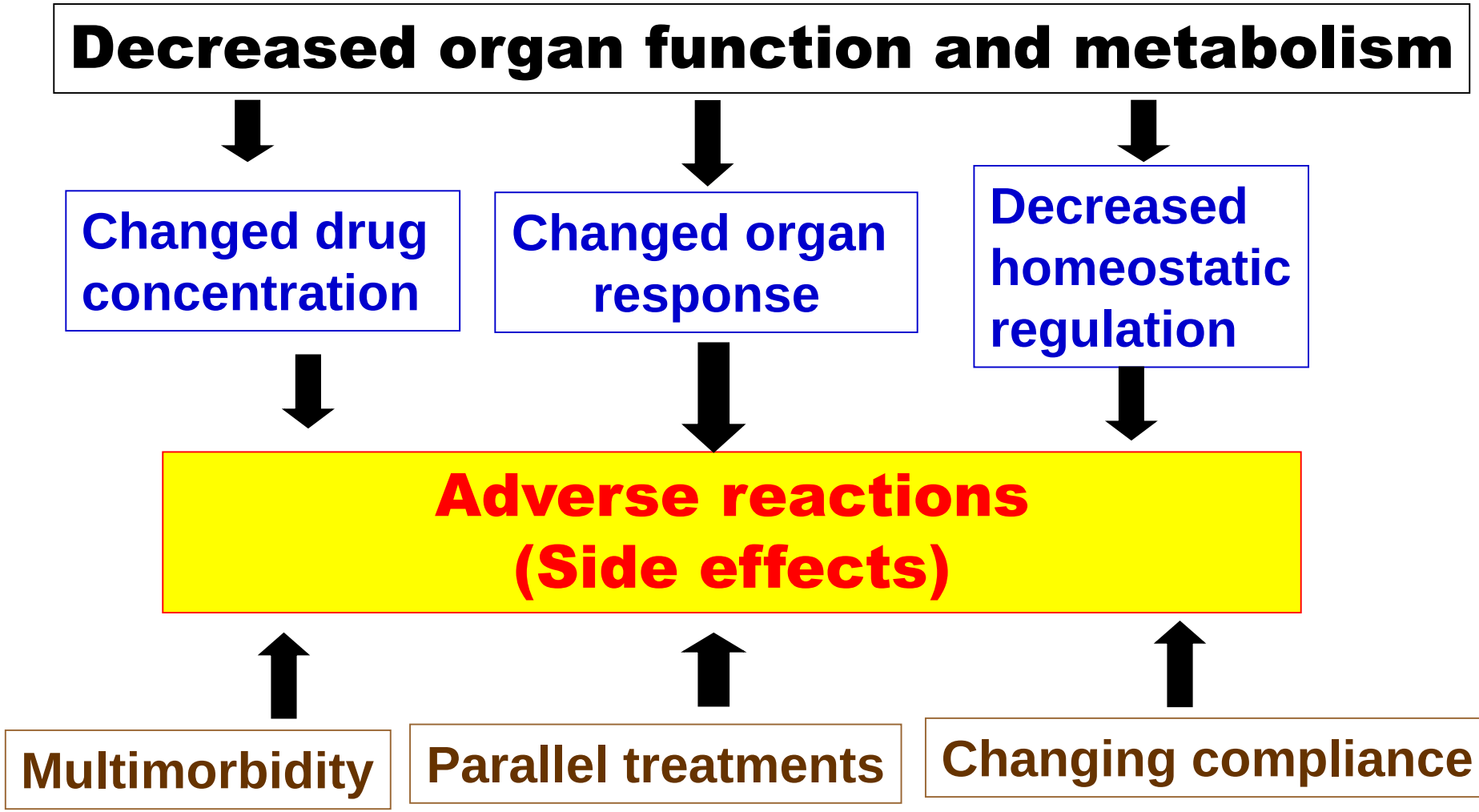


Cockcroft-Gault equation

- 1837 patients hospitalized not for renal failure
- Median age:: 86 (70-103) yr
- Median creatinine clearance: 35 (5-115) ml/min
- Creatinine clearance usually decreases with age, but in some indiviuals it remains normal
- The clearance falls to „pharmacological dangerous" level, below 60 ml/min/1,73 m^2 , around 80 yrs

Causes leading to adverse reactions in the elderly

Wehling M és Peiter A Internist, 44:1003-1009, 2003



Definition of the Geriatric Patient

- Higher age group (mean 85 years)
- Many active pathologies (mean 8)
- Tendency to inactivity and bedridden status; high risk to institutionalisation
- High risk for loss of autonomy
- Many psycho-social problems

General principles of the care of elderly patients

- Philosophy of assessment and care which is multidisciplinary and holistic
- Recognition of subtle and atypical presentations of illness in later life
- Capabilities in recognizing and dealing with multiple illnesses, co-morbidity
- Careful attention to syndromes such as falls, fits, faints, dementia and incontinence which standard medical care frequently ignores and to drugs causing more severe side effects in the elderly

Factors influencing drug therapy in the elderly patients

- **Pharmacodynamic alterations**, increased or decreased sensitivity
- The sensitivity of certain organs, mainly that of the central nervous system, to drugs increases
- The alteration of the immune system results more often allergic drug reactions
- Compensating ability of the homeostatic mechanisms is decreased

Pharmacotherapeutic strategies related to pharmacodynamic changes in the elderly

Decrease of receptor sensitivity

β-adrenoreceptors

- ➢ Decrease of the effectiveness of adrenergic compensatory mechanisms
- ➢ Increased doses of agonists must be used in the elderly

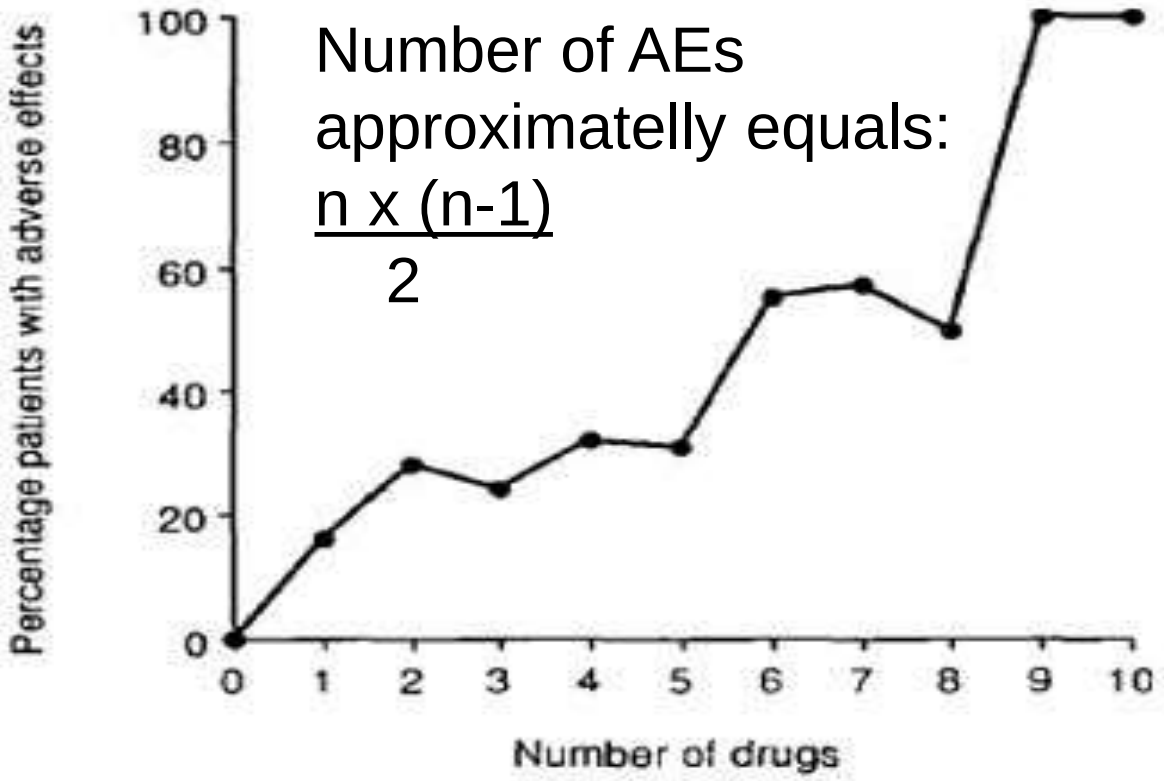
- ❖ The incidence of postural hypotension is increased due to the decreased sensitivity of the pressure sensitive receptors (Bainbridge reflex)
- ❖ The response to decreased intravascular volume is attenuated. The cardiac output is decreased sooner and more extensively following vasodilatator and/or diuretic theapy
- ❖ The sensitivity of the respiratory center is decreased, the respiratoric response to pathologic conditions is attenuated
- ❖ Decreased sensibility to bronchodilatator beta- adrenergic agonists, diminished response to asthma therapy

Central nervous system

- Central Nervous System
  - Decreased cell mass, conduction velocity in nerve cells
  - Agitation at night
  - Delirium occurs more frequently
  - Psychotic reactions
  - Increased sensibility to barbiturates and benzodiazepines
- Sensitivity to cholinergic receptors decreases
  - Problems in the use of anticholinergic medicines.
  - Incontinence
  - More frequent falls

The relation of the number drugs and the occurrence of adverse effects

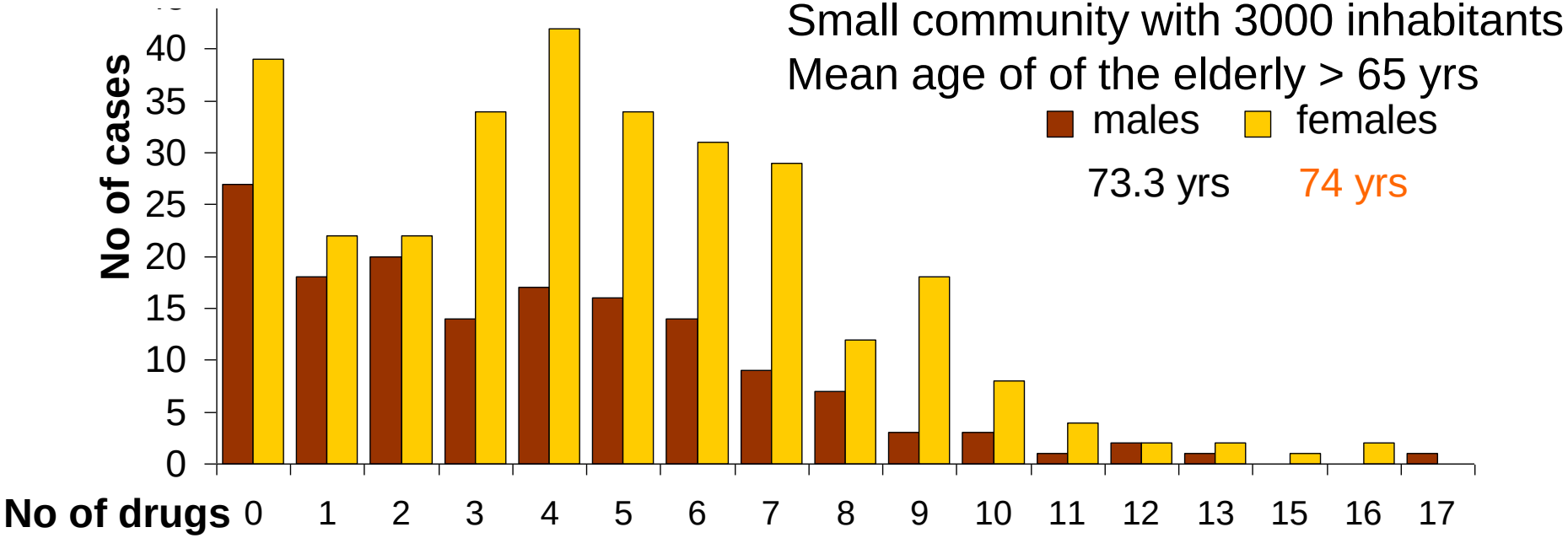
Cresswell et al. Br Med Bull. 83:259-274, 2007



- Patients > 65 years use usually ≥ 5 drugs/day simultaneously
- 1/3 of elderly hospitalisation is due to AE

Number of chronically consumed drugs in elderly patients living in a community

Soós Gy. and coworkers



	Males	Females	Total
No drugs [Cases] (%)	27 (18%)	39 (13%)	66 (15%)
< 5 drugs	69 (45%)	120 (40%)	189 (41%)
≥ 5 drugs	57 (37%)	143 (47%)	200 (44%)
Total	*153(100%)*	*302 (100%)*	*455(100%)*

Mark Howard **Beers** MD
1955-2009

Beers List

Courtesy of Gy. Soós

The Beers Criteria is a list of specific medications that are generally considered inappropriate when given to elderly people

Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Beers MH et al. Arch Intern Med. 1991 Sep;151(9):1825-32.

Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
Fick DM et al. Arch Intern Med. 2003;163:2716-2724.

American Geriatric Society
Beers criteria for potentially inappropriate medication (PIM) use in older adults (2012)

www.americangeriatrics.org

- Originally conceived in 1991
- The recommendations should be viewed as a guide for identifyinfg medications for which the risks of use in older adults outweigh the benefits
  1. Not effective or high risk in elderly patients
  2. The dose, the dose schedule and the duration of the therapy significantly influence the effects in eldrly patiens
  3. Some of the drugs can be used in the elderly but might be inappropriate in case of severe liver and/or kidney damage

Adaptation of Beers criteria to various national drug lists

- France. Laroche ML, Charmes JP, Merle L, Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol, 2007, 63:725-731
- Mann E, Böhmdorfer B, Frühwald t et al. Potentially inappropriate medication in geriatric patients; the Austrian consensus panel list. Wien. Klin Wochenschr, 2012, 124:160-169
- Holt S, Schmiedl S, Thürmqann P, Potentially inappropriate medications in the elderly: The PRISCUS list. Dtsch Artzebl Int, 2010, 107:543-551
- Bor A, Matuz M, Doró P, Viola R and Soós Gy. Az időskori gyógyszeralkalmazás problémái. Orvosi Hetilap, 2012, 153:1926-1936

Association of severe side effects frequently occurring in elderly patients with drugs

Signs and symptoms	Groups of medicines
Anticholinergic side effects (delirium)	Antiemetics, drugs affecting Parkinson-disease, spasmolytics, analgetics, antiarrhythmics, antihistamines, tricyclic antidepressants, sedatives (neuroleptics)
Confusion	Morphine and derivatives, benzodiazepines, antidepressants, classical antipsychotic drugs (neuroleptics), drugs affecting Parkinson-disease, anticholinergic agents, centrally acting antihypertensive agents, corticosteroids > 40 mg daily dose

Association of severe side effects of drugs frequently occurring in elderly patients

Groups of medicines	Increased risk of falls due to various effects of drugs
Benzodiazepines Tricyclic antidepressants	Sedation, confusion, equilibrium disturbance
Antihypertensive agents	Hypotension
Antipsychotics, antidepressants	Parkinson syndrome, bradykinesia, rigor, tremor
Insulin and oral antidiabetics	Hypoglycaemia
Aminoglycoside antibiotics, acetylsalicylic acid, chinidine	Vestibular impairment

Drug groups most commonly associated with side effects in the elderly (%)

Cresswell et al. Br Med Bull. 83:259-274, 2007

	All preventable drug problems (n= 1406)	ADR and overtreatment (n= 98)	Patient adherence problem (n= 98)	Undertreatment (n= 45)
Antiplatelets %	16	17.3	2	8.9
Diuretics %	15.9	16	20.4	2.2
NSAID %	11	12	4.1	0
Anti-coagulants %	8.3	8.9	4.1	0
Opioid analgesics %	4.9	5.4	4.1	0
Beta-blockers %	4.6	4.4	4.1	11.1
ACE inhibitors %	3.5	3.2	9.2	0

Drug groups most commonly associated with side effects in the elderly (%)

Cresswell et al. Br Med Bull. 83:259-274, 2007

	All preven-table drug problems (n= 1406)	ADR and overtreat-ment (n= 98)	Patient adherence problem (n= 98)	Under-treatment (n= 45)
Antidiabetics %	3.5	3.2	9.2	0
+ inotropes %	3.2	3.2	3.1	2.2
Corticoids %	3.1	3.2	1	0
Antidepress. %	3	3.2	1	0
CCB %	2.8	2.7	1	8.9
Antiepilept. %	2.3	0.9	8.2	28.9
Nitrates %	1.7	1.2	5.1	8.9
Inhaled cortic. %	0.6	0	7.1	2.2
TOTAL %	86.1	86.4	83.7	88.9

GI bleeding due to NSAIDs

Pérez-Gutthann S et al. Pharmacotherapy 19:854-859, 1999.

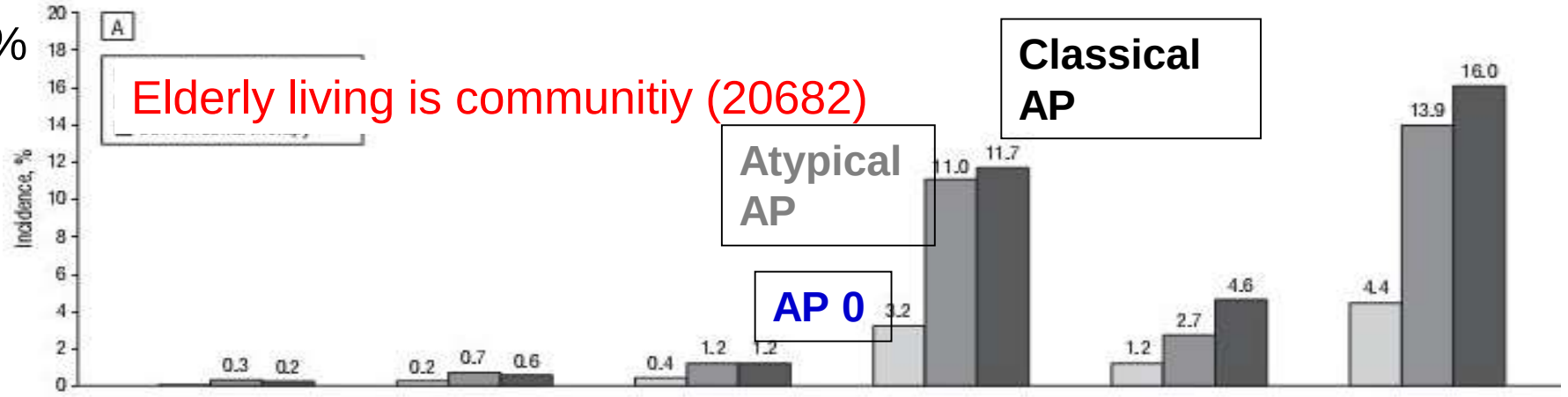
NSAID	Number of users	Incidence rate (CI) per 10^4 users
Diclofenac (≤75 mg)	22,146	1.8 (0.5-4.6)
<70 yr	18,407	1.60 (0.3-4.8)
≥70 yr	3739	2.7 (0.1-14.9)
Naproxen (≤750 mg)	46,919	2.3 (1.2-4.2)
<70 yr	39,720	1.3 (0.4-2.9)
≥70 yr	7199	8.3 (3.1-18.1)
Ibuprofen (≤1200 mg)	54,830	0.4 (0.04-1.3)
<70 yr	47,323	0.2 (0.01-1.2)
≥70 yr	7507	1.3 (0.03-7.4)

Retrospective cohort study on 3 million UK citizens

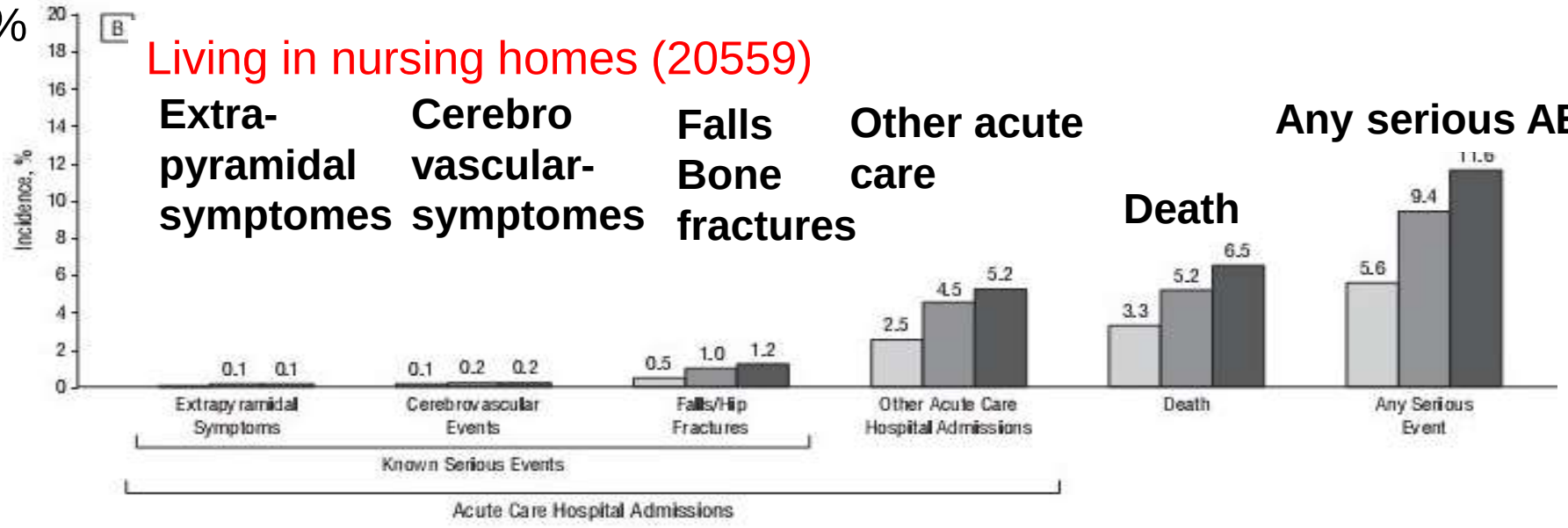
The serious side effects of antipsychotic therapy in elderly patients

Rochon et al., Arch Intern Med, 168:1090-1096, 2008

20%



20%



Acute hospitalization

Different trial endpoints

- For patients ≥ 85 years, the 5-years mortality is not longer relevant
- The quality of life is then more important for the patients
  - Keeping the personal autonomy
  - Motility, self care, mental function
- Special trials for elderly patients are needed with different and/or additional endpoints
  - age adjusted therapy targets
  - primarily important quality of life parameters

Imperial College London

The HYpertension in the Very Elderly Trial

N. Beckett, R. Peters, A. Fletcher, C. Bulpitt on behalf of the HYVET committees and investigators

British Heart Foundation

HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

ClinicalTrials.gov: NCT00122811

The Trial:

International, multi-centre, randomised double-blind placebo controlled

Inclusion Criteria:

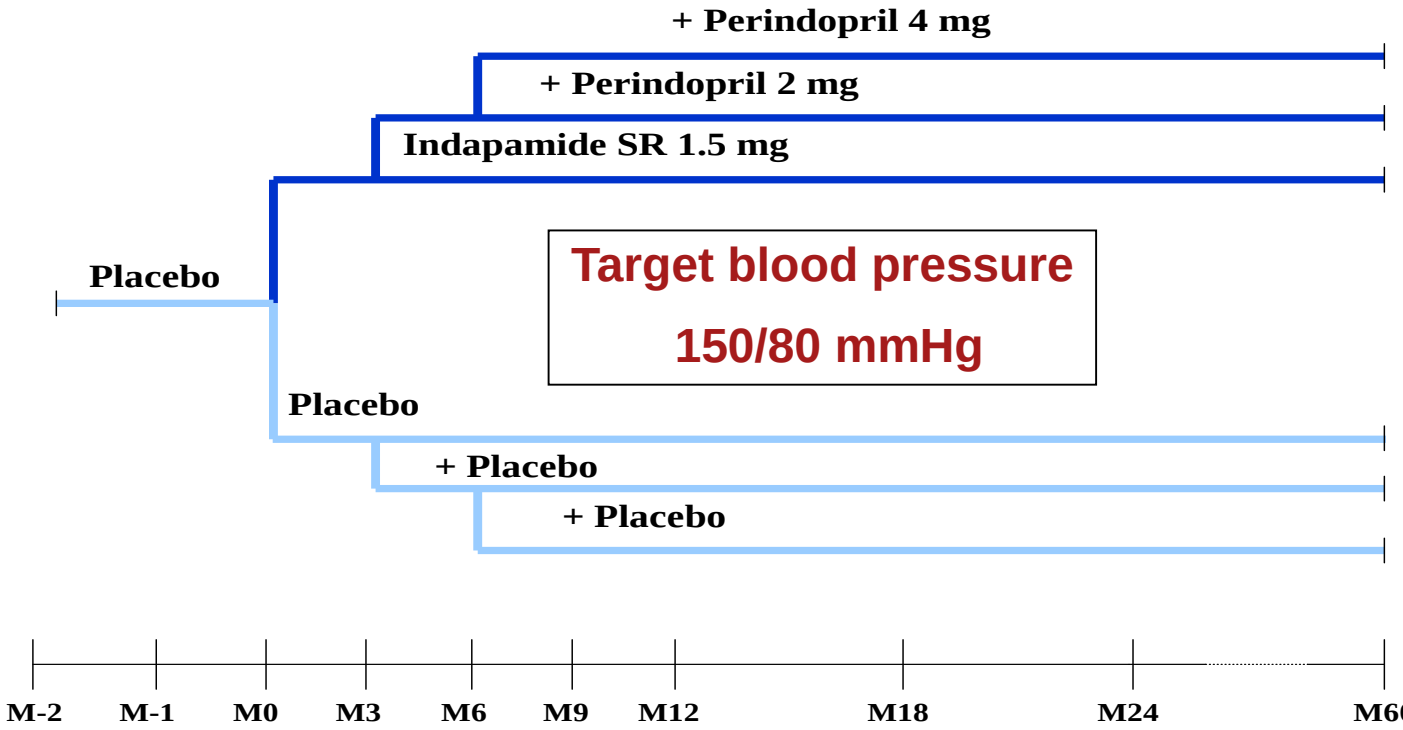
Aged 80 or more,
Systolic BP; 160 -199mmHg
+ diastolic BP; <110 mmHg,
Informed consent

Exclusion Criteria:

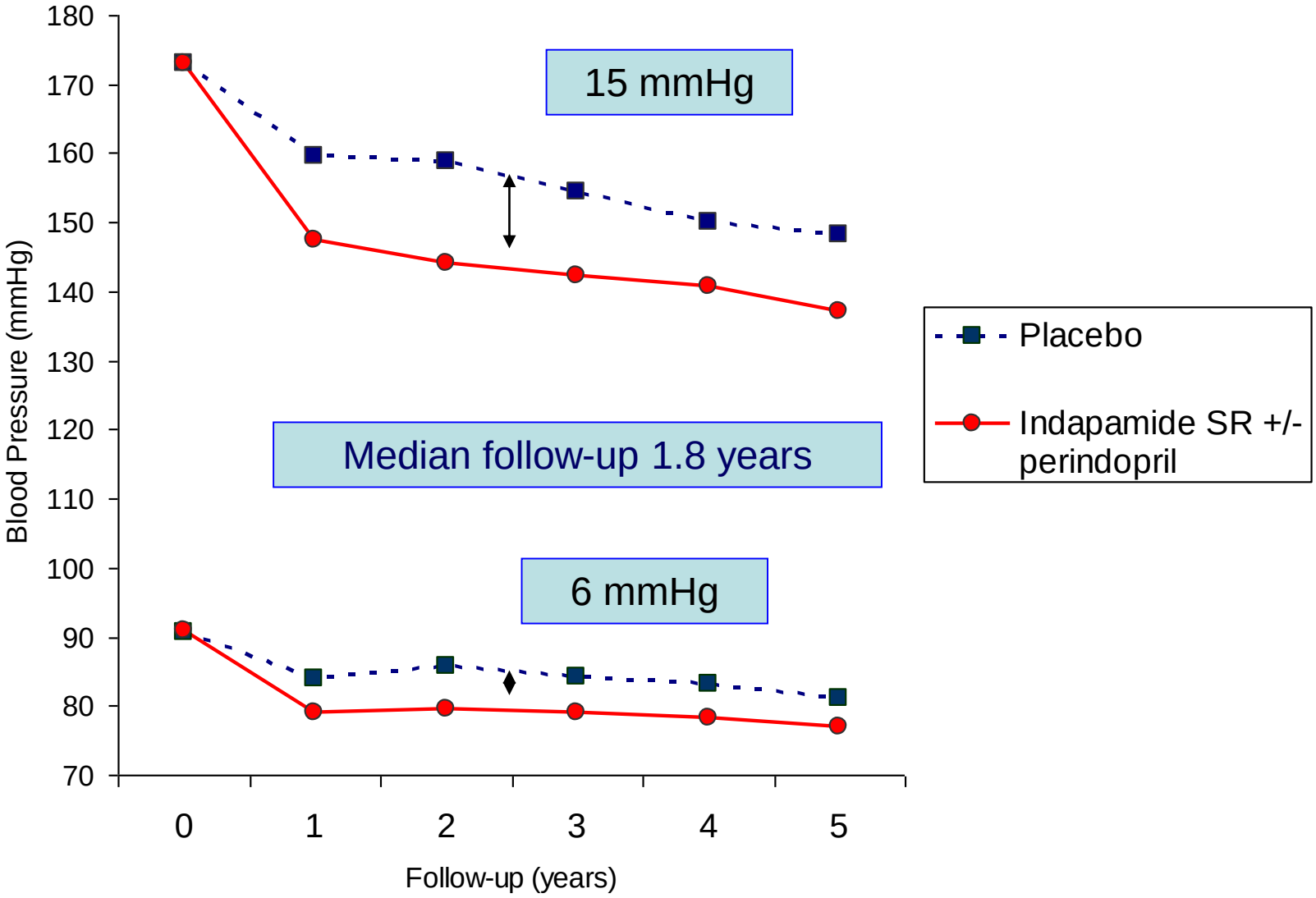
Standing SBP < 140mmHg
Stroke in last 6 months
Dementia
Need daily nursing care

Primary Endpoint:

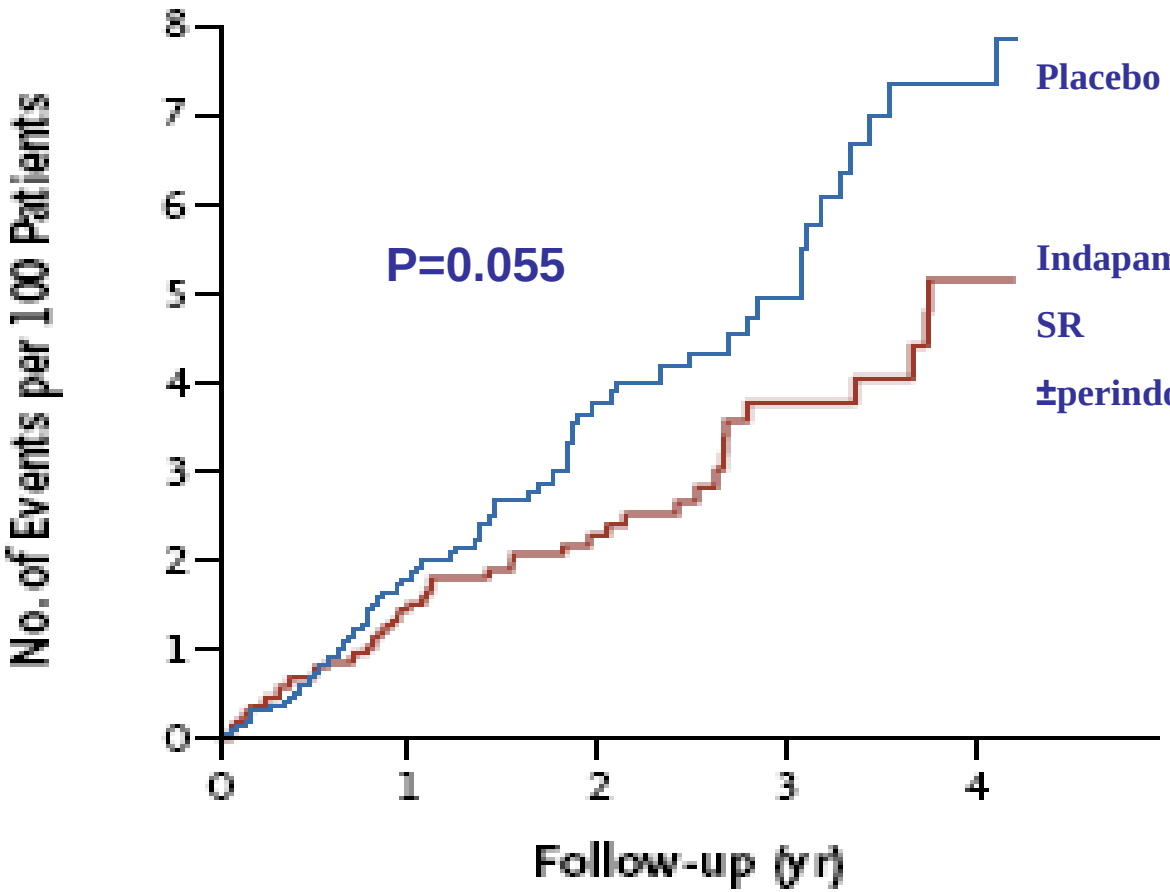
All strokes (fatal and non-fatal)



Blood pressure separation

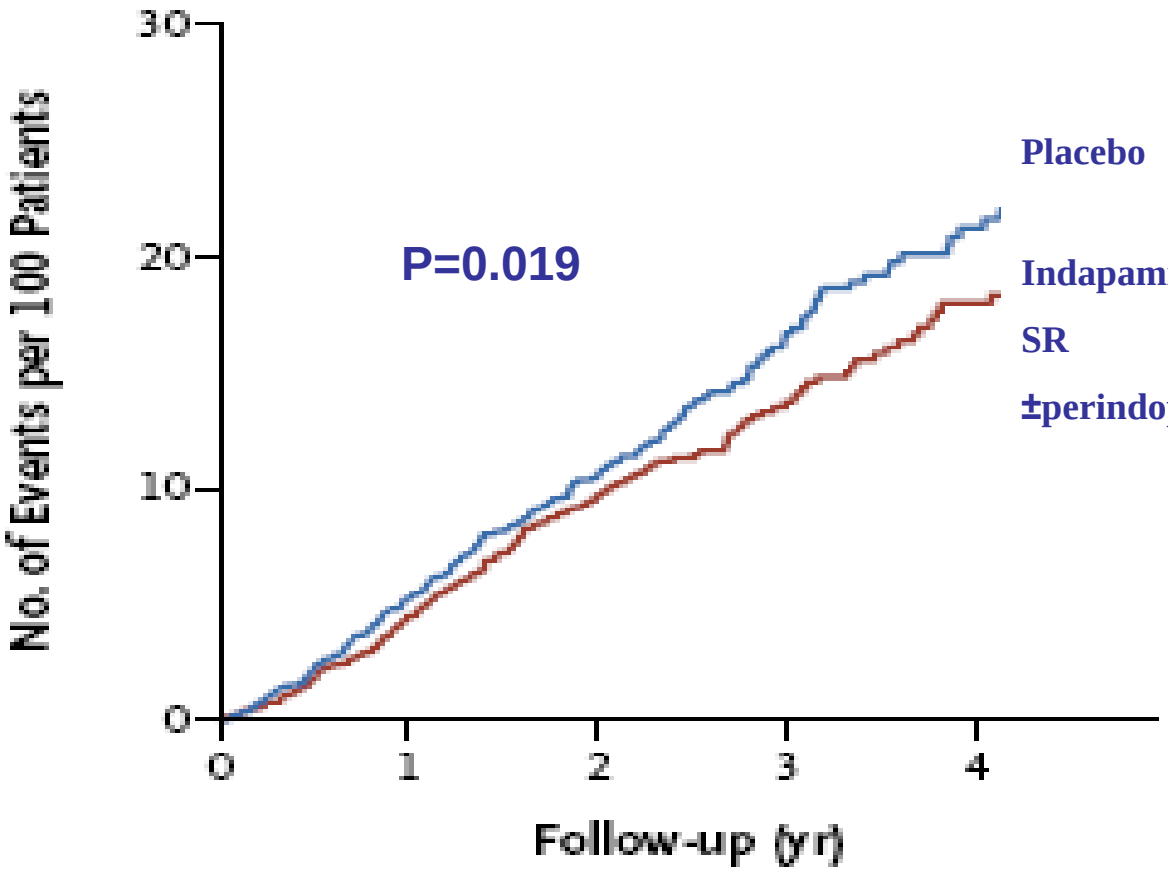


All stroke (30% reduction)



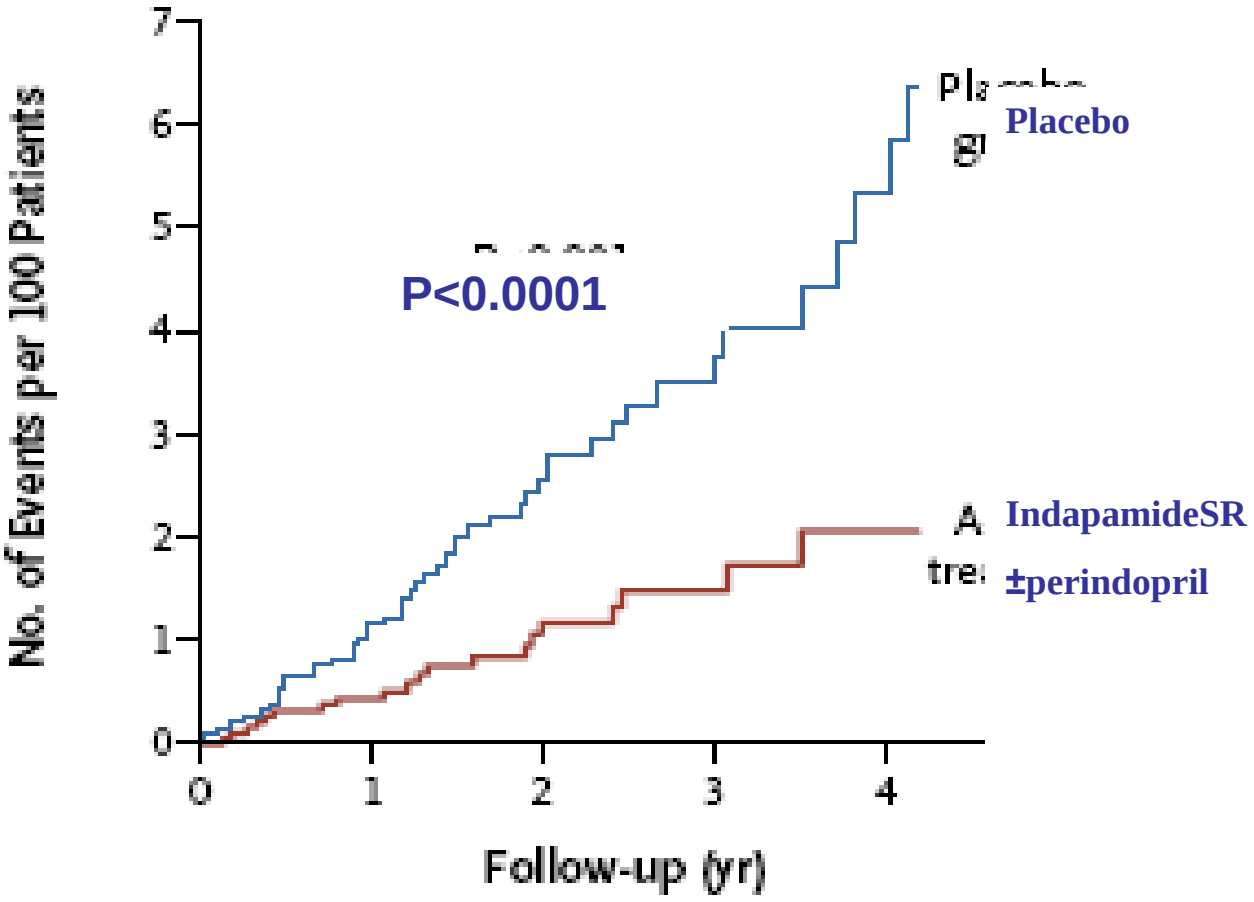
No. at Risk					
Placebo	1912	1484	807	374	194
IndapamideSR ±perindopril	1933	1557	873	417	229

Total Mortality (21% reduction)



No. at Risk					
Placebo	1912	1492	814	379	202
IndapamideSR ±perindopril	1933	1565	877	420	231

Heart Failure (64% reduction)



No. at Risk					
Placebo group	1912	1480	794	367	188
Placebo	33	1559	872	416	228
IndapamideSR ±perindopril					

Cardiac failure in elderly patients

Weir RAP et al. Br J Cardiol, 13: 257-266, 2006

- Framingham study: 34 yr follow-up, 5209 pts, prevalence of CHF based on symptoms:
  - 50–59 yr: 0.8%,
  - 60–69 yr: 2.3%,
  - 70–79 yr: 4.9%
  - > 80 yr: 9.1%
- Leading causes:
  - CA disease and hypertension
  - Age is an independent risk factor
- Physiological changes in the heart of the elderly:
  - Remodeling: disappearance of myocytes, increased amount of connective tissue, increased wall thickness
  - Dying of cells within the heart impulse conductive system
  - Relative increase of the RAAS and sympathetic activities, decreased sensitivity of beta receptors.

Risk of mortality in elderly patients with preserved LVEF

Shah et al. *Am J Cardiol* 2008;101:217-222

- CHF with preserved LVEF > 40%)
- 13 5553 patients, > 65 yr, risk of dying at 1 and 3 yr (RR)
  - Statin: 0.69; 0.73 irrespective of cholesterol level, diabetes, CA disease
  - ACEI: 0.88; 0.93
  - Beta-RB: 0.93; 0.92
- Optimal: triple combination therapy

The administration of ACEIs in elderly patients

Weir RAP et al., Br J Cardiol, 13:257-266, 2006

- In elderly patients (>80 yr) the decrease of death rate is similar to those below 60 yr
- ACE inhibitors are frequently under dosed in the elderly (side effects represent relative contraindication, doctors are afraid treating eldeerly patients aggressively)
- Start low, go slow. Dose increase should be slow and more gradual
- Target dose is similar in young and elderly patients
- Renal function should be monitored tightly

The administration of BRBs in elderly patients

Weir RAP et al., Br J Cardiol, 13:257-266, 2006

Beta blocker	Starting dose	Increments	Target dose
Metoprolol CR/XL	12.5–25 mg once daily	25 mg, 50 mg, 100 mg, 200 mg	200 mg once daily
Bisoprolol	1.25 mg once daily	2.5 mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg	10 mg once daily
Carvedilol	3.125 mg twice daily	6.25 mg, 12.5 mg, 25 mg, 50 mg b.d.	25–50 mg b.d.
Nebivolol	1.25 mg once daily	2.5 mg, 5 mg, 7.5 mg, 10 mg	10 mg once daily

Background and golden rules of geriatric drug therapy

Body composition changing with age

Changing pharmacokinetic properities

- Start low

Changing pharmacodynamic effects

- Go slow
- Slow titration untill the optimal dose is reached

Careful observation and follow-up