MUNI PHARM

INTRODUCTION TO GERIATRICS, PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF GERIATRIC PHARMACOTHERAPY

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Lecture from Geriatric Pharmacotherapy 17.2.2023

Basic terms

Geriatrics

- gerus (old age *gr.*), iatrea (treatment *gr.*)
- branch of the medecine that focuses on health care of old age and aging people

Gerontology

- comprehensive study of aging and common problems related to aged

Old age

- period of life with impairment of physical and mental functions that become increasingly manifestated in comparison to previous years of life

Mean length of life

- **men** – **76** years
- **women** – **82** years

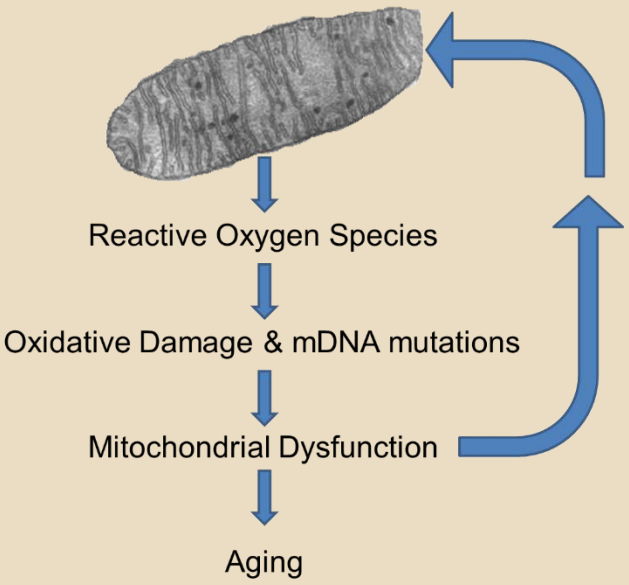
Definition of elderly

- **WHO** – chronological age of 65 years and above
- **UN** – 60+ years will be referred as the older population or elderly

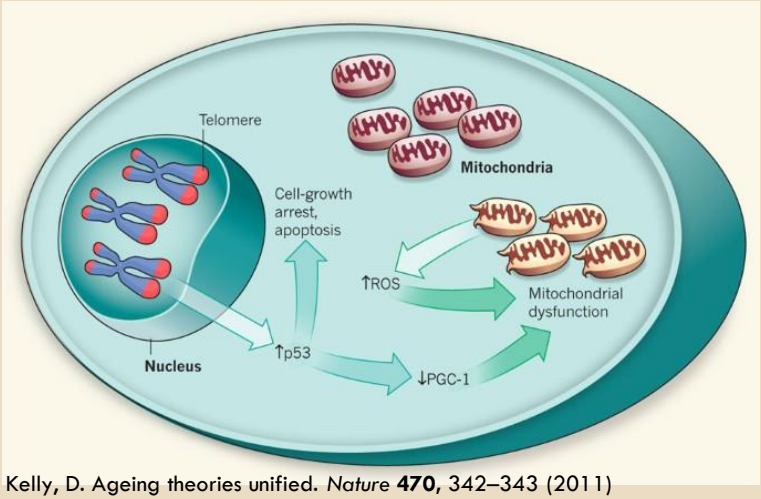
- **young old** – up to 75 years
- **old old** – up to 85 years
- **very old old** – over 85 years

Current theories of aging

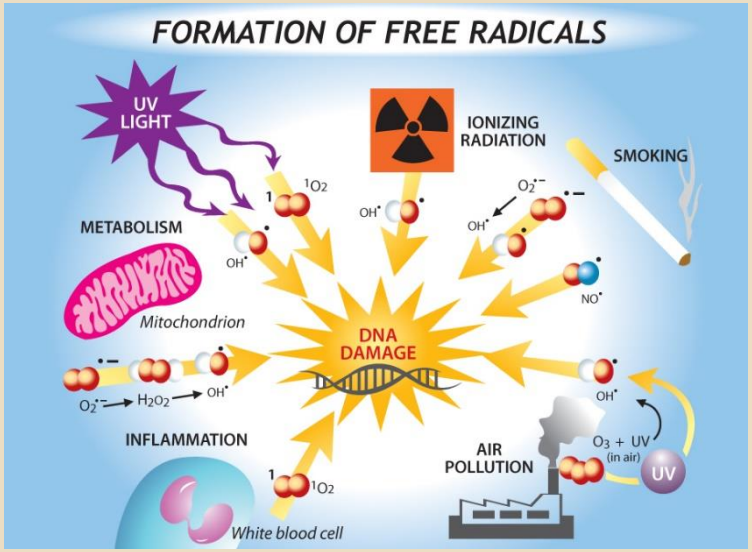
- **free radicals**
  - impairment of enzymes, DNA, cell membranes
- **neuroendocrine**
  - influence on immune system
- **genetic**
  - mutations

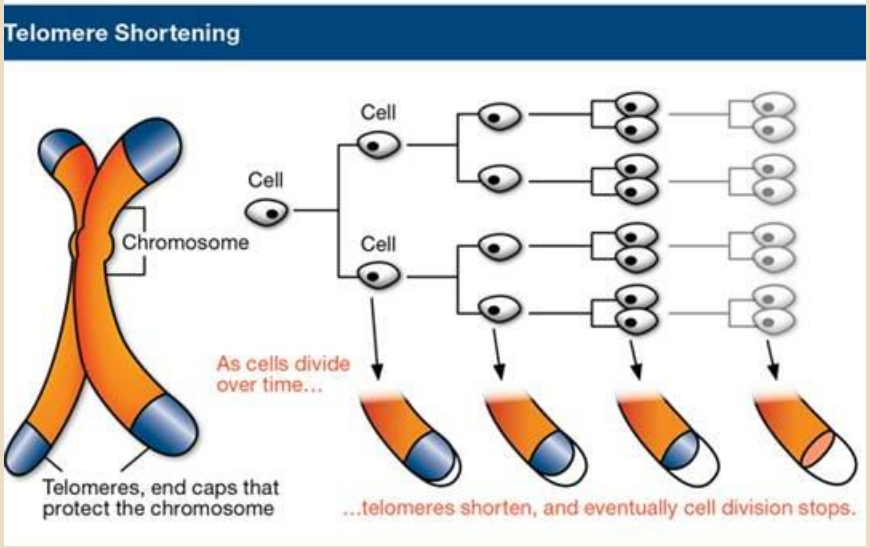


Current theories of aging



Kelly, D. Ageing theories unified. *Nature* **470**, 342–343 (2011)





Theories on Aging, SPH – Boston University, https://sphweb.bumc.bu.edu/otlt/mph-modules/ph/aging/mobile_pages/Aging3.html

Geriatric giants

- the major categories of impairment appearing in old age

- **IMMOBILITY**
- **INSTABILITY**
- **INCONTINENCE**
- **IMPAIRED MEMORY/INTELECT**

- **impairment of hearing and vision**
- **infections**
- **iatrogenic disorders**
- **insomnia**
- **isolation**
- **inanition (malnutrition)**

Diseases in old age

- **polymorbidity**
- **strangenesses in clinical signs**
  - lack of specific symptoms

- importance of interview with the patient
- cooperation with family and family doctor/general practitioner

Cardiovascular system changes

- frequency, ejection fraction and cardiac output increased only during exertion
- changes in the arterial wall
  - thickening of the media, changes in collagen and elastic fibers, deposits of fatty substances (cholesterol) and calcium

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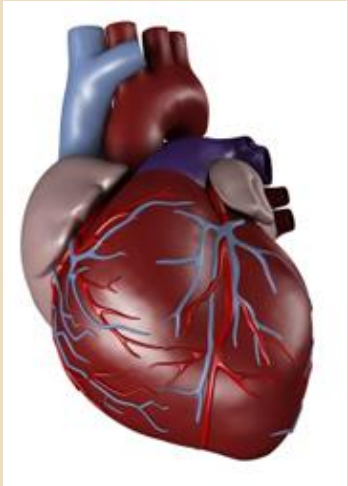
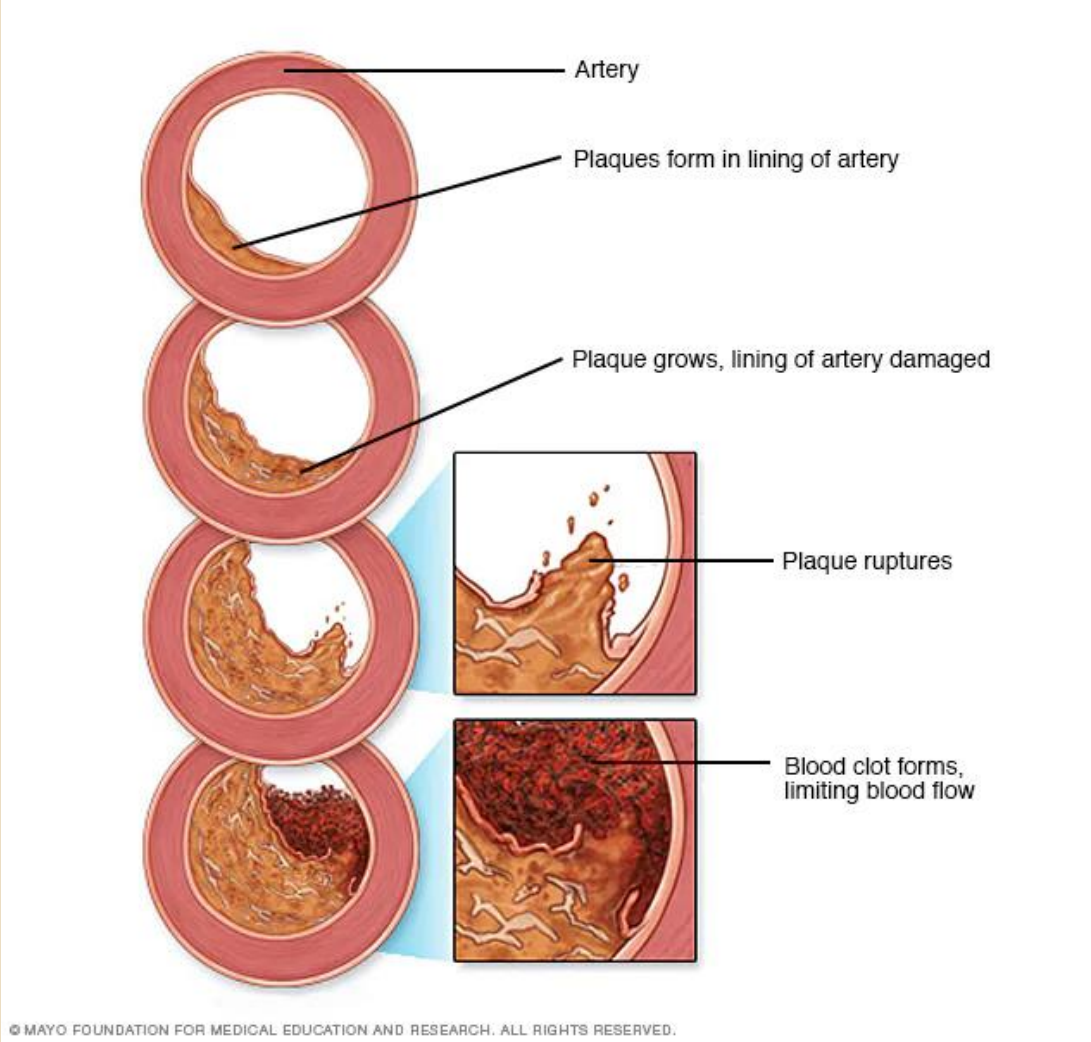
- hypertension
- heart failure
- **ATHEROSCLEROSIS**
  - myocardial infarction
  - brain stroke



Atherosclerosis

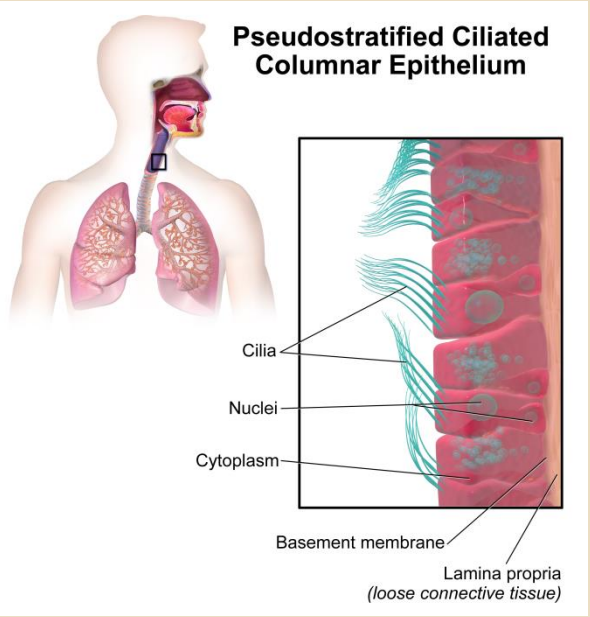


Mayo Clinic, Arteriosclerosis/athrosclerosis, https://www.mayoclinic.org/diseases-conditions/arteriosclerosis-atherosclerosis/symptoms-causes/syc-20350569

Respiratory system changes

- decrease in vital capacity
- dilation of bronchioles and alveoles
- decrease in pO_2, pH
- decreased function of the ciliary epithelium
- impaired mechanics of ventilation

- infections (bronchitis, pneumonia)
- dyspnoea (shortness of breath)
- hypoxia



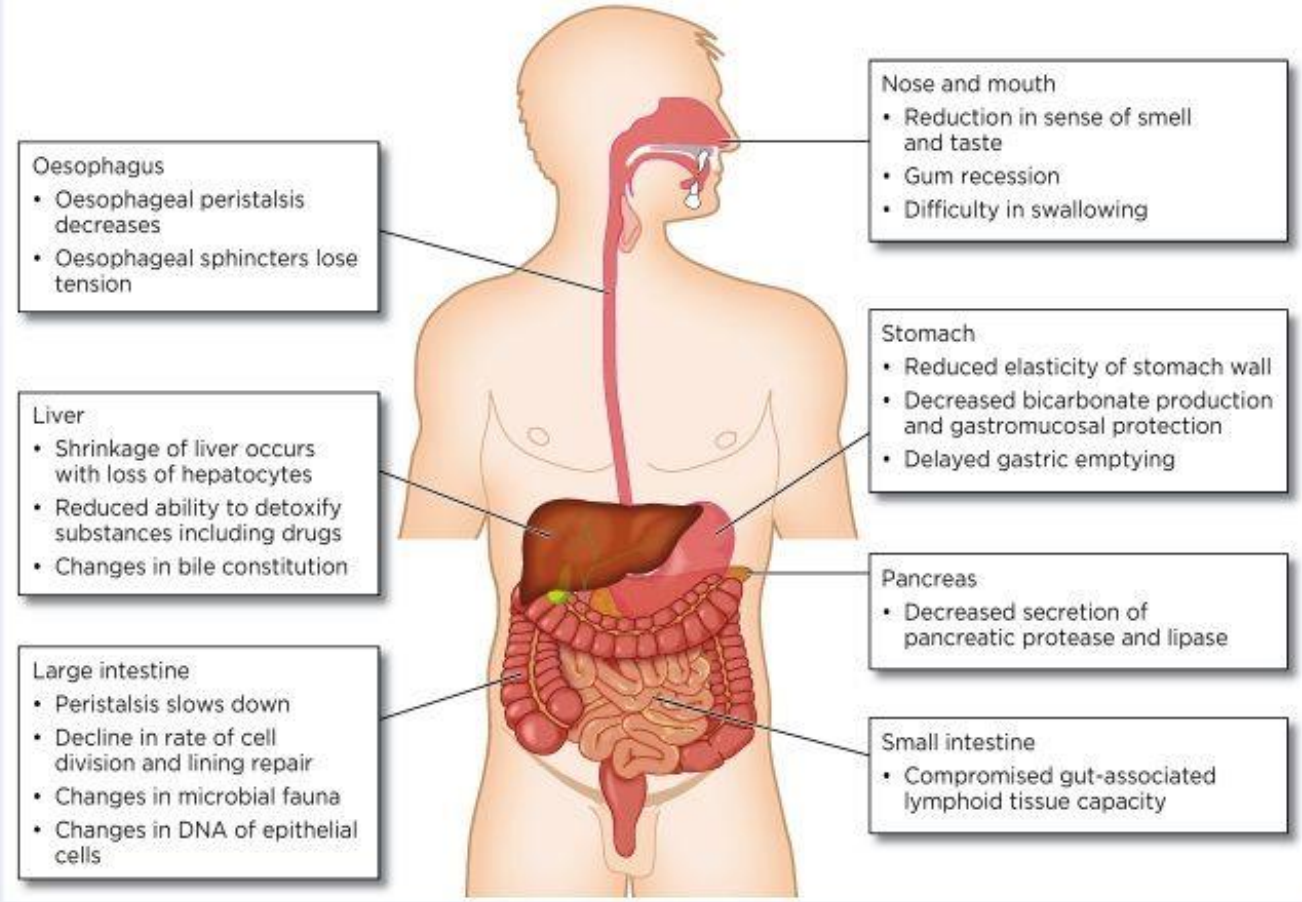
Gastrointestinal system changes

- loss of dentition
- decrease of GIT motility and secretion of digestive juices
- changes in intestinal villi
- bacterial dysbalance in the intestines
- atrophy of pancreas
- decreased activity of microsomal liver enzymes

- constipation
- diverticular disease
- malabsorption
- infectious colitis
- intestinal ischemia

Gastrointestinal system changes

Fig 1. Age-related changes to the gastrointestinal tract



Peter Lamb, from https://www.nursingtimes.net/roles/older-people-nurses-roles/anatomy-and-physiology-of-ageing-3-the-digestive-system-27-03-2017/

Urogenital system changes

- decrease of glomerular filtration rate
- decrease of creatinine clearance, so the serum levels increase
- decrease in the concentration ability of kidneys
  - tendency to dehydration
- weakening of the urinary bladder and urethra smooth muscle, less able to expand and contract
  - decrease of bladder capacity with no full evacuation during urination
- uninhibited contractions

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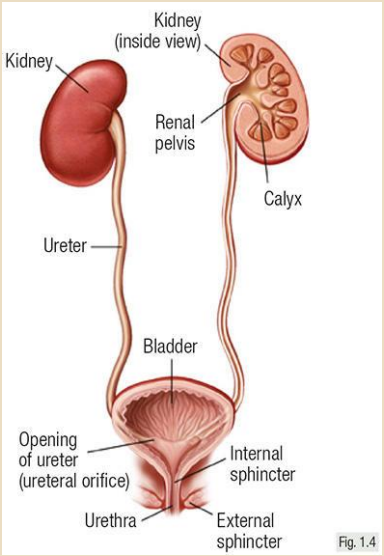
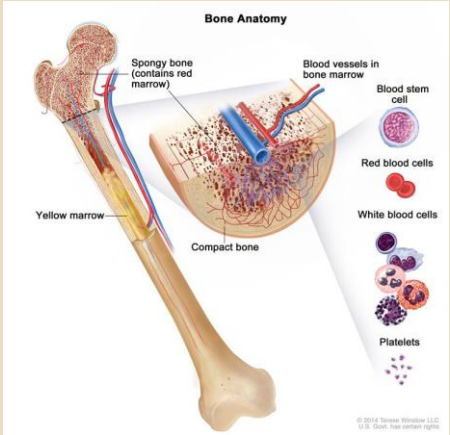
- renal failure
- incontinence
- urinary infections



Hematopoietic system changes

- loss of bone marrow
- decrease in the rate of erythropoiesis
- decrease in phagocytic activity of leukocytes
- platelets more susceptible to aggregation
- loss of fibrinolytic activity – tendency to hypercoagulation

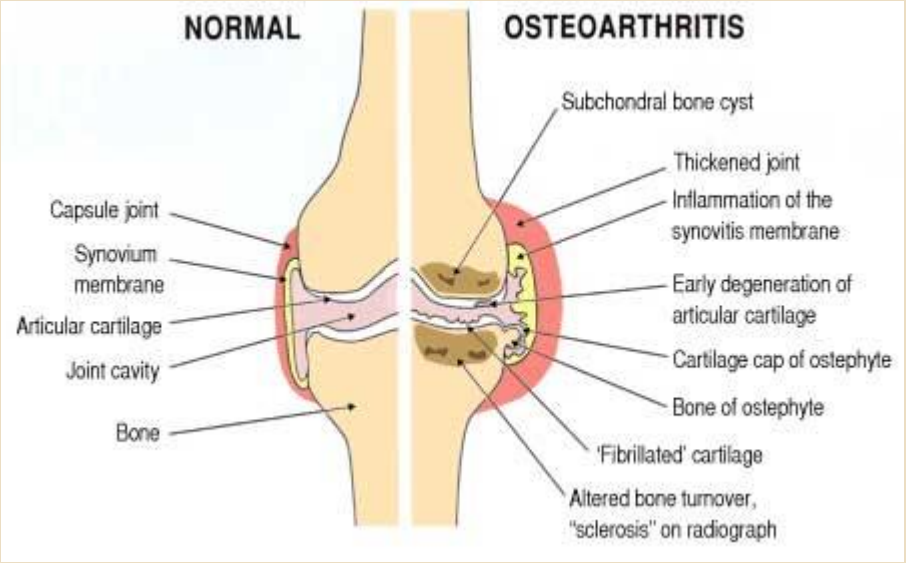
- immune dysfunctions (immunosenescence)
- myeloid malignancies
- anemias



Locomotive system changes

- degeneration of articular hyaline cartilage
- reaction of subchondral bone and periarticular soft tissues
- slow loss of total bone mass
  - 3–5 % of cortical bone in decade

- osteoarthritis
- osteoporosis



CNS and sensory system changes

- loss of neurons, degenerative changes
- extracellular deposits of amyloid
- changes in cerebral arteries and neurotransmiters

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- dementia
- trophic changes in auditory pathway
- lack of eye lens elasticity (loss of accomodation to nearby objects)
- opacities in eye lens

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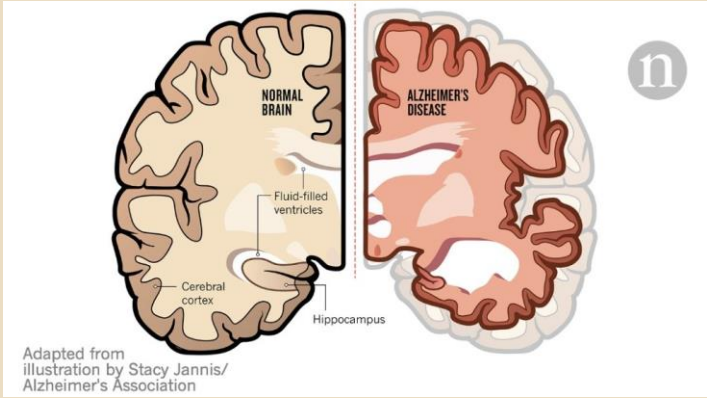
- presbyopia, cataract
- presbyacusis



Pharmacotherapy changes

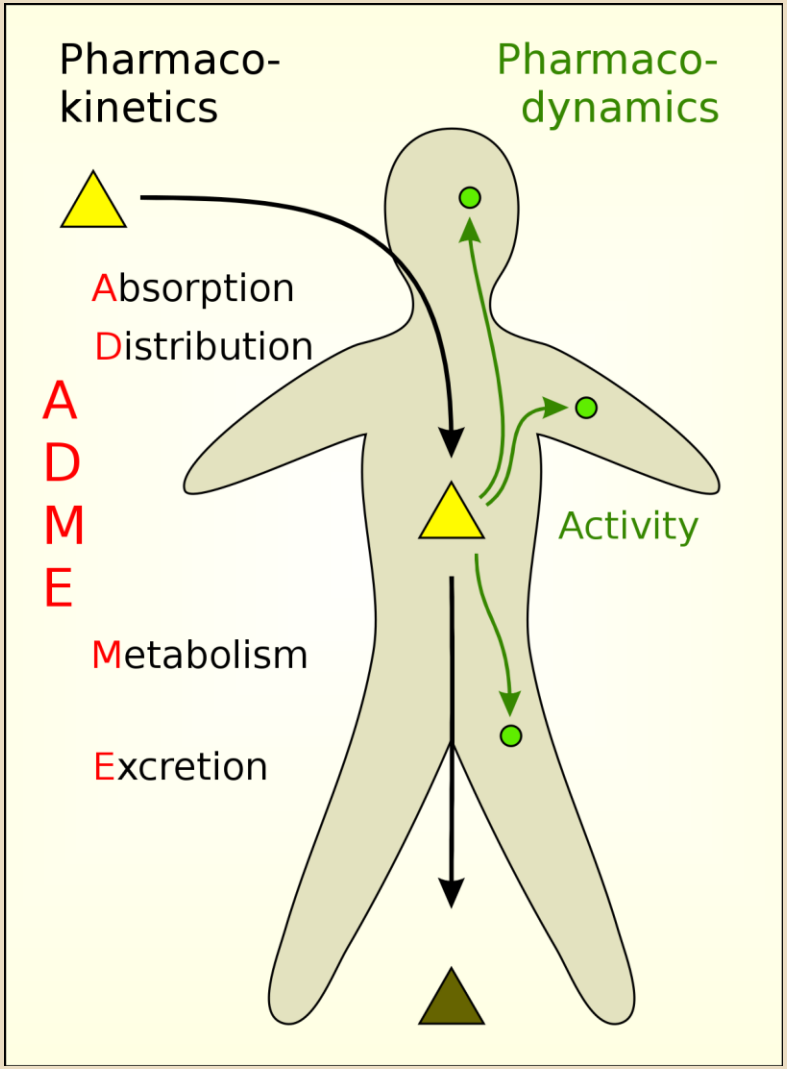
- physiological aging of organs
- age-related changes in pharmacokinetics and pharmacodynamics
- polymorbidity
- limited self-sufficiency
  - visual impairment, impaired mobility, memory and thinking disorders
- influence of social factors
- lower compliance
- polypragmasia
- common side effects of drugs

Pharmacotherapy strategy and rules

- help of family members
- written overview of prescription
- reduction in prescribed drugs if possible
- patient compliance

- **amount of drugs as little as possible**
- **doses as low as possible**
- **duration of therapy as long as possible**

Pharmacokinetics and Pharmacodynamics



Absorption changes

- **gastric evacuation is slowed down**
  - delay in drug effect
  - degradation of drug in acid environment
- **slow passage through small intestine**
  - higher drug absorption (digitalis)
- **reduced blood circulation in splanchnic region**
  - decrease in drug absorption
- **decreased absorption area in the small intestine**

Distribution changes

- **decrease in amount of water** (15–20 %)
- **loss of active body mass**
- **increase in fatty tissue**
- **hypoalbuminemia**

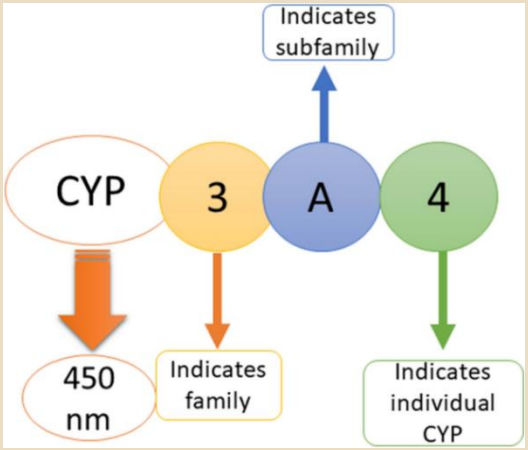
- increase in plasma levels of hydrophilic drugs
- risk of toxicity during accumulation of lipophilic drugs in adipose tissue
- increase in free fraction of albumin-bound drugs (anticoagulants)

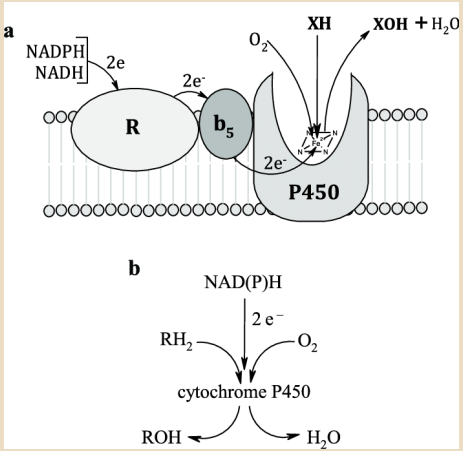
Biotransformation changes

- activity of liver **microsomal cytochrome P450 enzymes** is decreased

- biotransformation of drugs slowed down

- increased risk of drug interactions in polypragmasia





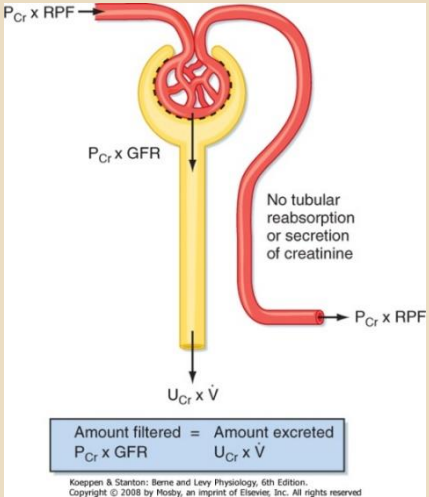
Biotransformation changes

Decrease in biotransformation due to CYP changes

- **CYP3A4**
  - alprazolam, granisetron, fentanyl, lidocaine, amlodipine, isradipin, clarithromycin, verapamil, zolpidem
- **CYP2C9**
  - diclofenac, phenytoin, indomethacin
- **CYP1A2**
  - warfarin, propranolol, imipramine

Elimination changes

- manifestations of **mild renal failure** in 30–50 % of patients over the age of 70
  - decrease of renal clearance
- **impairment of tubular functions**
- **risk of toxic effects**
  - aminoglycosides, atenolol, digoxin, NSAIDs, ACEi, fluconazole, metformin, methotrexate



Examples of drug interactions

Drug	Interaction	Effect
warfarin	barbiturates, metronidazole	effect ⇩ effect ⇧
sulphonylurea	cimetidine	hypoglycemia
benzodiazepins	cimetidine	sedation ⇧
prednisone	barbiturates	antiallergic and antiinflammatory eff. ⇩
digoxin	verapamil, spironolactone	toxicity ⇧
teophylline	cimetidine	toxicity ⇧
chinidine	barbiturates	antiarhytmic eff. ⇩

Pharmacodynamic changes

Clinical issue	Changes in elderly	Drugs of interest
Orthostatic hypotension	reduced sensitivity of baroreceptors in the area carotid sinus and in the aortic arch, reduced sensitivity of myocardial beta-receptors	central antihypertensives, diuretics, beta blockers, tricyclic antidepressants, phenothiazine antipsychotics, benzodiazepines, opioids
Postural instability, risk falls and fractures	reduced proprioception and postural stability, decreased skeletal muscle tone	central antihypertensives, diuretics, BB, TCA, phenoth. antipsychotics, BZD, opioids, muscle relaxants
Decrease in cognitive functions, delirium	structural and neurochemical changes in the CNS, decreased acetylcholine transferase, higher permeability of the blood-brain barrier	TCA, neuroleptics, barbiturates, BZD, opioids, antiparkinsonians, H2-block., metoclopramide, theophylline, digoxin, indomethacin

Pharmacodynamic changes

Clinical issue	Changes in elderly	Drugs of interest
Constipation, subileus	decreased smooth muscle tone and GIT motility, higher sensitivity to anticholinergic AEs	opioid analgesics, TCA, antihistamines, antispasmolytics
Urinary incontinence/ retention	decreased smooth muscle tone, higher sensitivity to anticholinergic AEs	diuretics, especially loop (increased diuresis), anticholinergics (urinary retention)
Risk of hyponatremia and dehydration	ADH decrease, renal loss of Na, insufficient thirst	SSRI, diuretics, lithium, digoxin
Increased risk of hypothermia	poor thermoregulatory mechanisms	sedatives and hypnotics, antipsychotics
Erectile dysfunction, gynecomastia	decrease in sex hormone production	α1-sympatholytics, sedatives, urinary spasmolytics, spironolactone, digoxin

Low dose regimens in old age

- **start low, go slow**
  - start treatment with a low dose and only gradual increase

Drug	Usual daily dose	Effective dose in old age
atorvastatin	10 mg/d	5 mg/d
diclofenac	100–200 mg/d	75 mg/d
enalapril	5 mg/d	2,5 mg/d
metoprolol	100 mg/d	50 mg/d
omeprazole	20 mg/d	10 mg/d
ibuprofen (analgesic)	400–800 mg/d	200 mg 3-4x/d
trazodone	150 mg/d	25–100 mg/d

Beers criteria

- list of the potentially inappropriate medications (PIMs) use in older adults
- first developed in 1991 by **Mark H. Beers, MD** to decrease inappropriate prescribing and AEs
- revisions and updates managed the American Geriatrics Society

STOPP and START criteria

- **STOPP** (Screening Tool of Older Person´s potentially inappropriate Prescriptions)
- **START** (Screening Tool to Alert doctors to the Right Treatment)

- divided into the cathegories according to the organ system

Disease – complex condition

- **genetics**
- **external influences**
- **dehydration**
- **malnutrition**
- **polypragmasia x insufficient therapy**

- **social problems** (isolation)
- **psychical problems** (loss of partner, family troubles)