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Pharmacotherapy Principles

Considerations in Special Populations

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Disclosure

- Lane Nguyen has no relevant financial or personal conflicts of interest to disclose

- Off-label use of medications will be discussed solely for academic purposes by principles of Pharmacodynamics and Pharmacokinetics

Objectives

- Identify the pharmacotherapy principles in special populations
  - Women
  - Obstetrics
  - Pediatrics
  - Geriatrics
- Describe key differences between these cohorts
- Evaluate the potential impact of these differences on clinical trial design

Special Populations



Image source: Shutter Stock

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Pediatric Challenges

- Approximately 25-40% of pediatric trials fail to establish safety or efficacy
  - Moderate improvement through better understanding

- Factors contributing to trial failure
  - Dosing
  - Pharmacokinetic and physiologic differences between adults and pediatrics
  - Feasibility for small populations
  - Appropriate endpoints

Background - Pediatrics

- Food and Drug Administration (FDA) has worked to address the **inadequate pediatric data in drug research**

- FDA Modernization Act of 1997 addressed the need for improved information about drug use in the pediatric population
  - Provides incentives in patent ***exclusivity*** and ***protection***

- Best Pharmaceuticals for Children Act (BPCA) approved in 2002
  - Sponsors of certain applications and supplements can obtain an additional six months of exclusivity

- Pediatric Research Equity Act (PREA) approved in 2003
  - Sponsors of certain applications and supplements are **required** to submit pediatric assessments (unless they receive an applicable waiver or deferral of this requirement)

Food and Drug Administration – Guidance for Industry on Pediatric Study Plans

Comparing BPCA and PREA

Best Pharmaceutical for Children Act

- Drugs and biologics
- **Mandatory** studies
- Requires studies only on indication(s) under review
- Orphan indications exempt from studies
- Pediatric studies must be labeled

Pediatric Research Equity Act

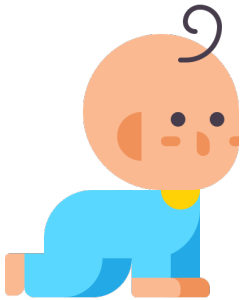
- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and may expand indications
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

- Children mean persons who have not attained the legal age for consent to treatments or procedures in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted

Title 21, Code of Federal Regulations, 50.3(o)

Pediatric Definitions









Neonates	Infants	Children	Adolescents
Birth up to 1 month	1 – 12 months	1 – 11 years	12 – 18 years

As defined by most regulatory bodies including, The American Academy of Pediatrics
Title 21, Code of Federal Regulations, 105.3(e)

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Developmental Pharmacology in Pediatric Patients

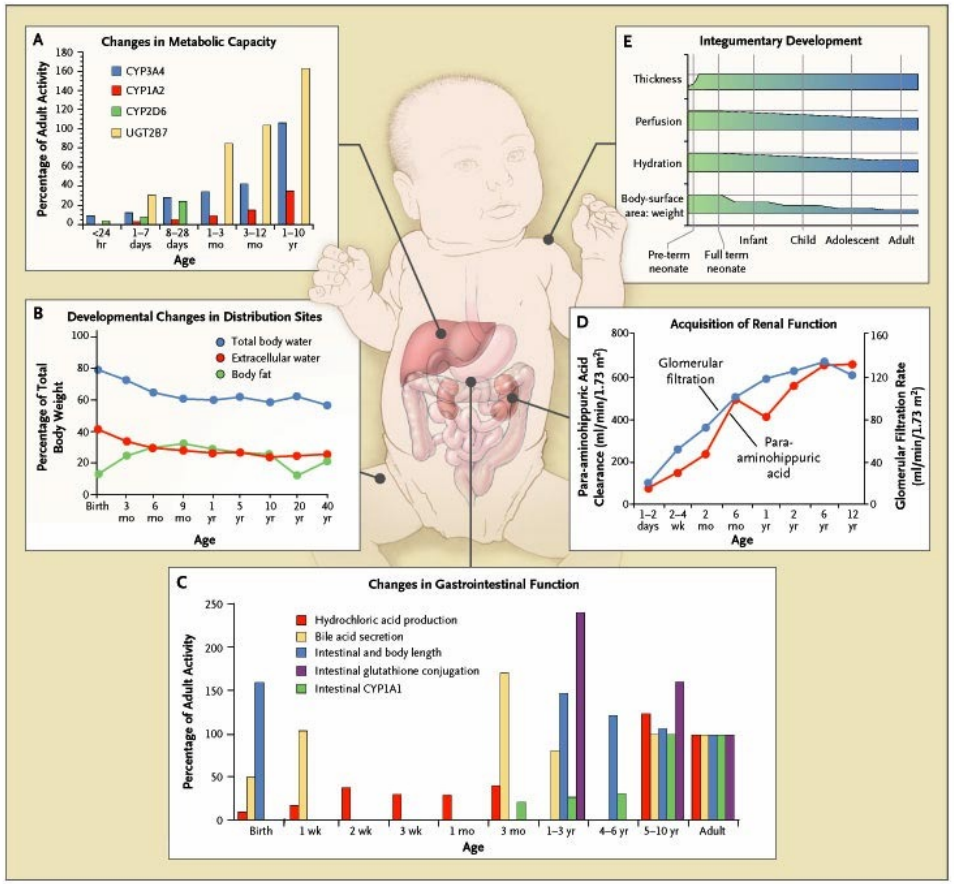


Image source: Kearns GL, et al. *NEJM*. 2003.

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Absorption

- Gastric pH is **neutral at birth** but falls to pH 1 to 3 within 24 to 48 hours after birth
- Gastric pH gradually returns to neutral again by day 8 and subsequently declines reaching adult values only after 2 years of age
- Neonatal and infant pH differences may have a protective effect on acid-labile drugs
  - Partial account for higher bioavailability of beta-lactam antibiotics
  - Reduced bioavailability in weak acids due to increased ionization
    - Acetaminophen
    - Phenobarbital
    - Phenytoin

Kearns GL, et al. *NEJM*. 2003.

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Absorption

- Gastric emptying time in the neonate is prolonged relative to that of an adult

- Delayed absorption of orally administered drugs
  - Phenobarbital
  - Digoxin
  - Sulfonamides

- Reduced intestinal absorption surface area and shorter gut transit time may also be responsible for delayed absorption

Kearns GL, et al. *NEJM*. 2003.

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Absorption

- Age-dependent changes in biliary function and activities of pancreatic enzymes can compromise the body's ability to solubilize and absorb lipophilic drugs
  - Prodrug esters, Erythromycin, absorption is reduced due to the necessity of intraluminal hydrolysis or solubilization

- Percutaneous absorption increased for some drugs due to greater body surface area: body mass ratio
  - Topical applications of drug products

Kearns GL, et al. *NEJM*. 2003.

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Distribution

- Volume of distribution (V_d) determines loading dose and half-life
  - Greater V_d when there is extensive drug distribution to the tissues
  - Lower V_d contributes to higher plasma drug concentrations

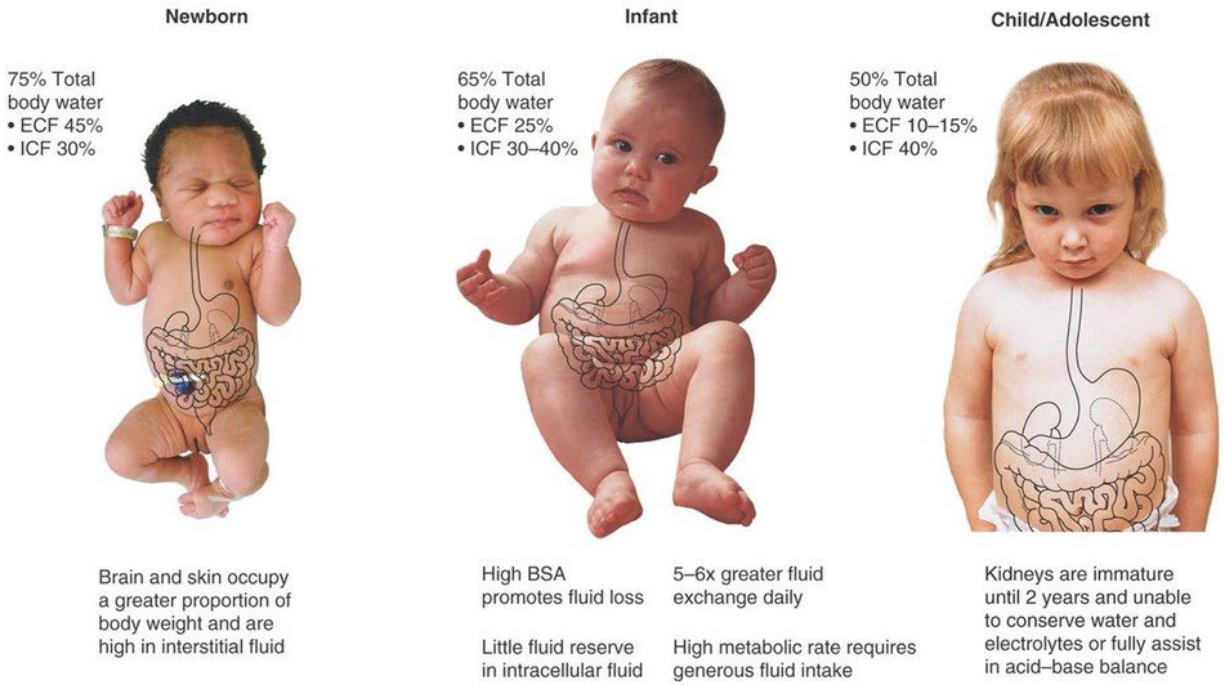


Image source: Pearson Education. 2006.

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Clinical Example of Drug Disposition

- **Ceftriaxone**, broad spectrum 3rd generation cephalosporin, used commonly to treat systemic infections with desirable CNS penetration
- Competitive displacement of bilirubin and increases levels of unconjugated bilirubin in premature neonates
- Hyperbilirubinemia can lead to kernicterus
- **Contraindicated** in neonates 28 days and younger

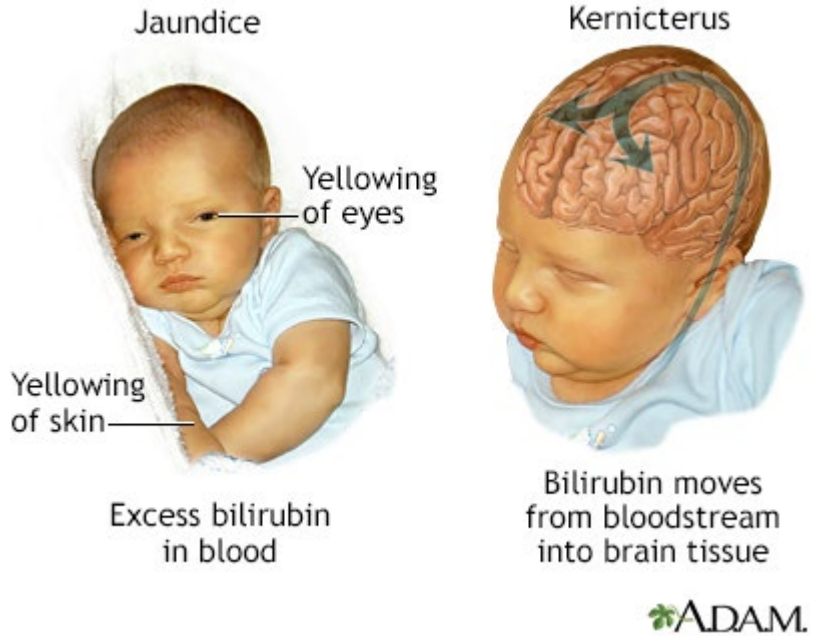
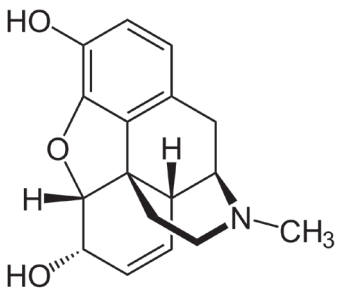


Image source: Adam Health.
Food and Drug Administration – Ceftriaxone Labeling.

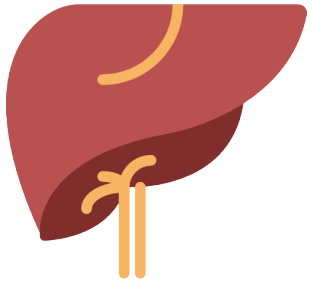
Metabolism – Phase 1 and Phase 2 Reactions

- Drug-metabolizing enzymes, Cytochrome P450 superfamily, are still being investigated to its true effect
  - Suspect immaturity in organ development and function reduces bioactivation



Morphine

UGT2B7



~90% Morphine-3-glucuronide → Minimal analgesia

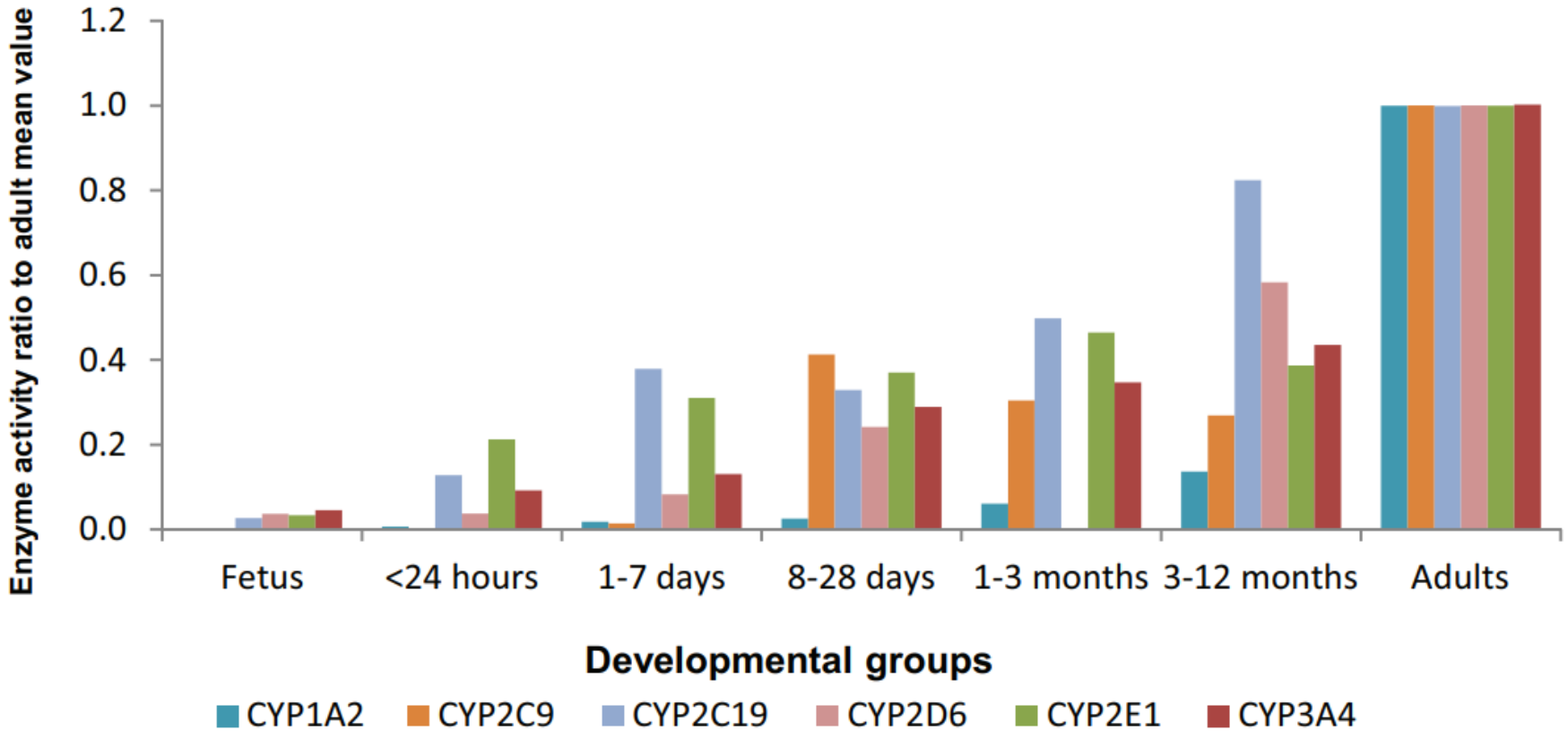
~10% Morphine-6-glucuronide → **Potent analgesia**

Kearns GL, et al. *NEJM*. 2003.

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Metabolism – Normalizes by 24 months of age

- Delayed maturation of CYP enzymes contribute to variability in drug clearance under 2 years of age

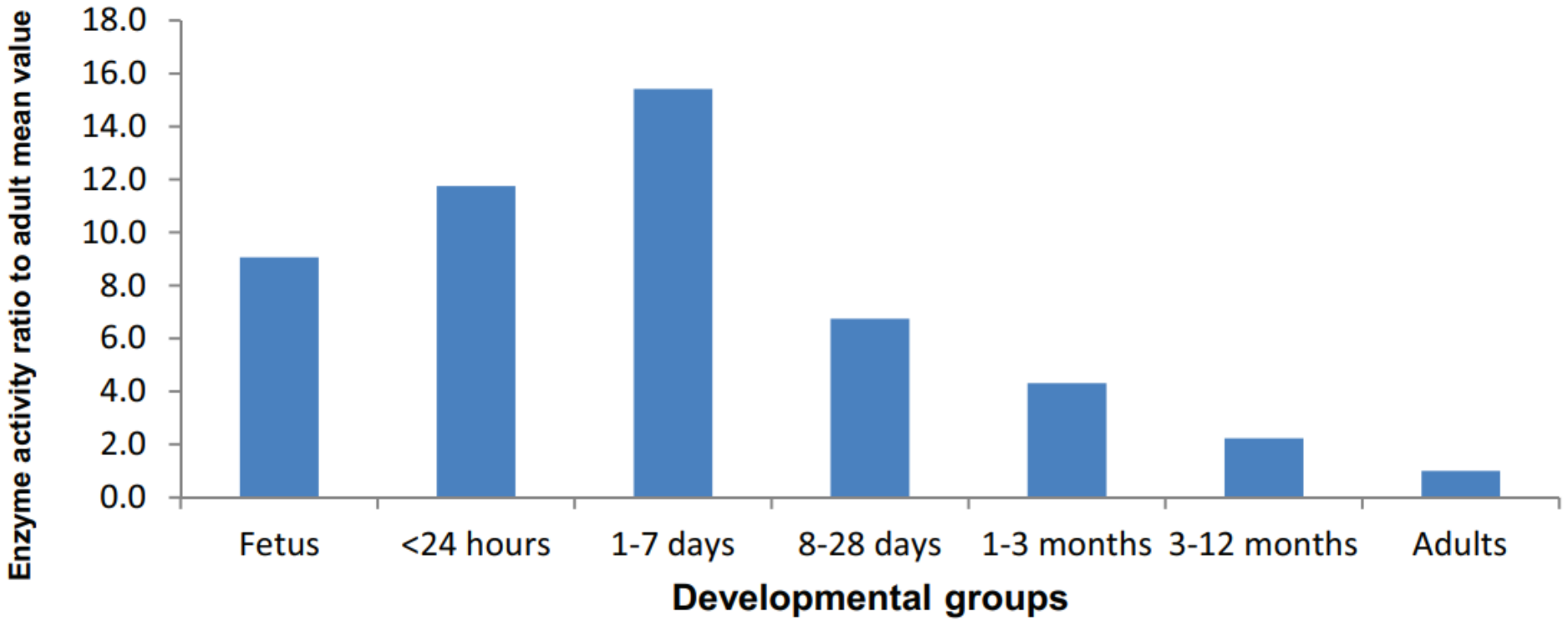


Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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Metabolism – Expression of CYP3A7

- CYP3A7 is primary isoenzyme expressed during the neonatal time period
- Lower metabolic capacity compared to CYP3A4



Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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Metabolism - Transporters

- Limited data on the ontogeny of p-glycoprotein in humans
- Low at birth and increases during first few months of life, reaching adult values by 2 years of age
- Limited data on clinical significance of developmental changes of transporter function

Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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Elimination

- Drug excretion by the kidney is the net result of glomerular filtration, tubular secretion, and tubular reabsorption

$$CL_r = CL_{\text{glomerular filtration}} + CL_{\text{tubular secretion}} - \text{tubular reabsorption}$$

- Glomerular filtration rate in prematurity is dependent on the postnatal age

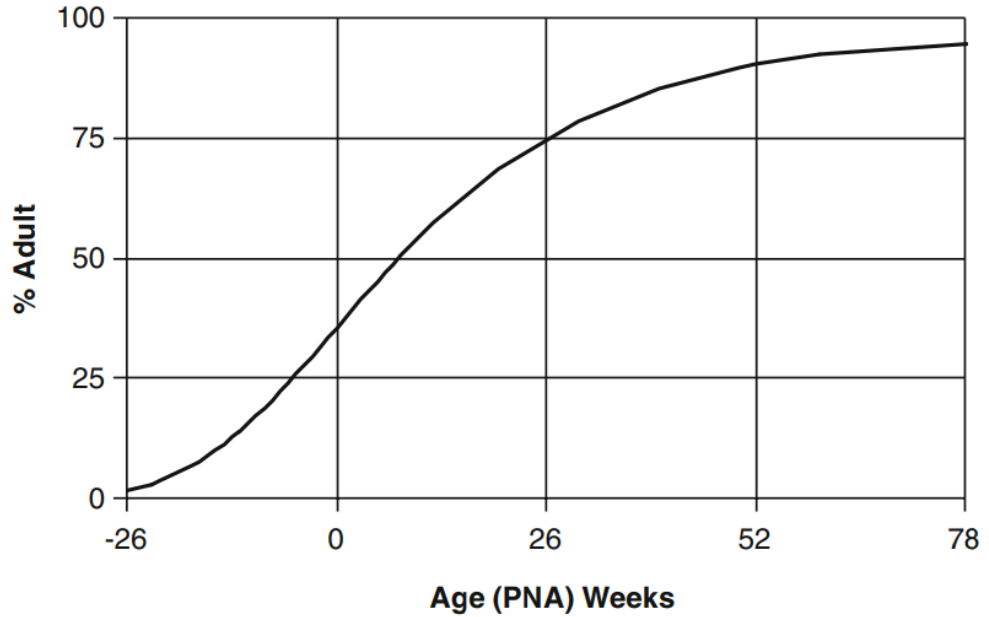


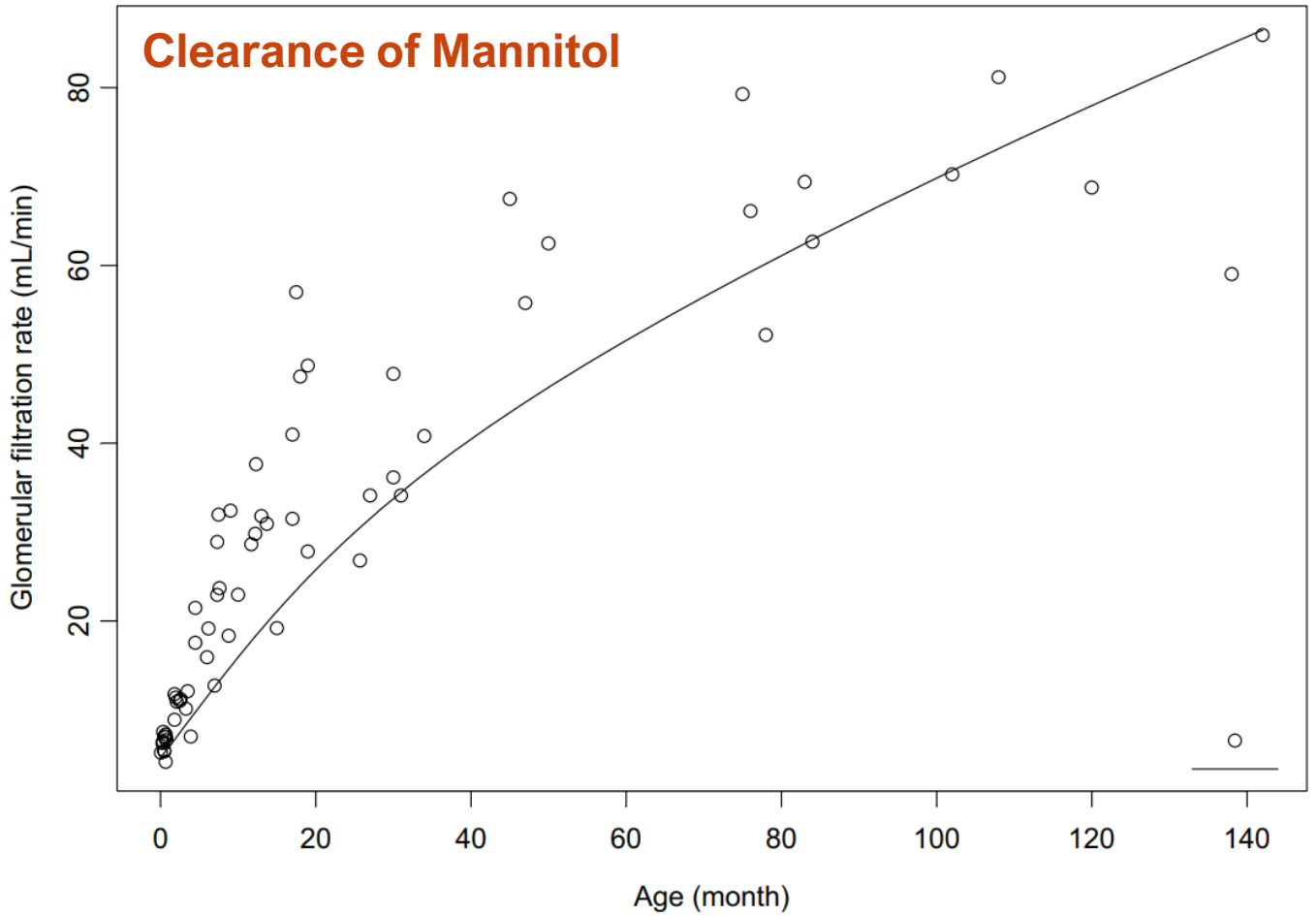
Fig. 4 Maturation of GFR showing the predictions of the sigmoid hyperbolic function. The *abscissa* is expressed as weeks of postnatal age so that 0 would be a full term infant with a PMA of 40 weeks

Rhodin MM, et al. Pediatr Nephrol. 2009.
Kearns GL, et al. NEJM. 2003

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Elimination

- Understanding strengthened by measuring actual drug clearance in PK studies



Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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Pharmacodynamics

- FDA acknowledges limited data available on receptor expression and activity

- Differences can alter exposure response relationships in neonates and impact safety
  - $GABA_A$ receptors with age-dependent function in the brain
    - **Excitatory** effects in neonates/infants
    - **Inhibitory** effects in older children/adults
  - Vitamin K dependent clotting factors (II, VII, IX, and X) only 50% present in neonates
  - Immaturity in innate and adaptive immunity in neonates/infants

- Consider the underlying treatment modalities corresponding to patient care

Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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1884

Pharmacodynamics

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Lu H, et al. *J Pediatr Pharmacol Ther*. 2014.

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Physiological Alterations in the Critically Ill

Variations in V_d

- Fluid balance
- Insensible losses
- Sensible losses

Changes in nonrenal clearance

- Hepatic dysfunction
- Acute respiratory distress
- Elevated intracranial pressures

Residual renal function

- Renal hypoperfusion
- Renal hyperperfusion



Drug-drug interference/interactions

- Competitive antagonism
- Allosteric modulation
- Inhibitors/Inducers

Blood pH

- Acidosis
- Alkalosis
- Mechanical ventilation

Hypoalbuminemia

- Burns
- Systemic capillary leak
- Malnutrition
- Post-operative

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Wildschut ED, et al. *Intensive Care Med*. 2010.

Pharmacotherapy Relationships in External Circuits

- Extracorporeal Membrane Oxygenation (ECMO)
  - Provides cardiopulmonary support in individuals unable to perform adequate gas exchange to sustain life

- Renal Replacement Therapy
  - Provides blood-filtering function of the kidneys under a series of different modalities
    - Intermittent hemodialysis
    - Peritoneal dialysis
    - Continuous renal replacement therapy (CRRT)

Wildschut ED, et al. *Intensive Care Med*. 2010.

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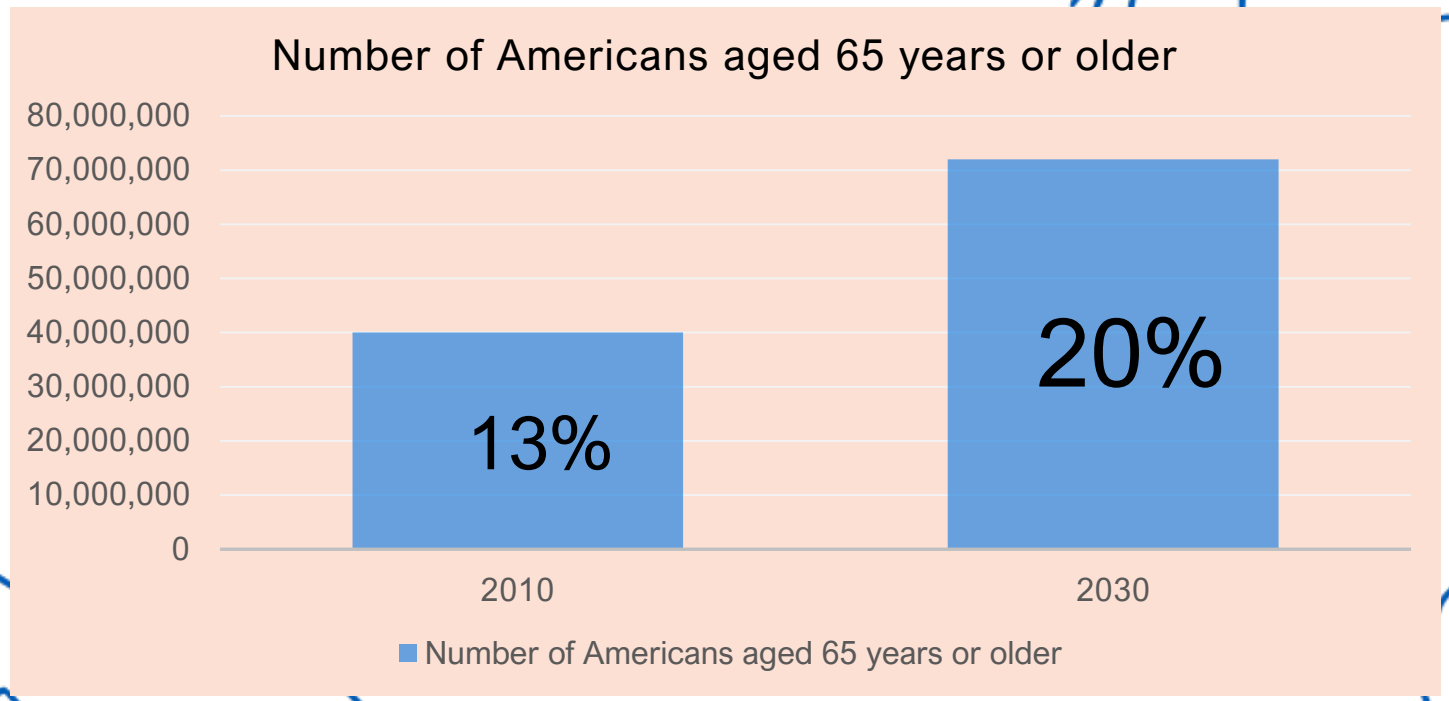




Images source:
CRRT (left) – Washington University of St. Louis.
ECMO (right) - Children's Hospital of Philadelphia.

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A Rising Population



Centers for Disease Control and Prevention.
Department of Health and Human Services. *The State of Aging and Health in America*.

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Prescription Drug Use in Geriatric Patients

- Comorbidities
  - Hypertension
  - Hyperlipidemia
  - Hyperglycemia
  - Autoimmune
- Organ function
- Consequences of adverse effects
  - Anticholinergic
  - Serotoninergic
  - Sympathomimetics
- Concomitant drug therapies
  - Polypharmacy
    - Prospective cohort study of community dwelling adults ages 62 to 85 had concurrent use of ≥ **5 prescription drugs**

Quato D. et al. *JAMA Intern Med*. 2016.

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Geriatric Initiatives from the FDA

- In the 1980s, FDA began several initiatives to increase the quality and quantity of information about the use of drugs in geriatrics patients

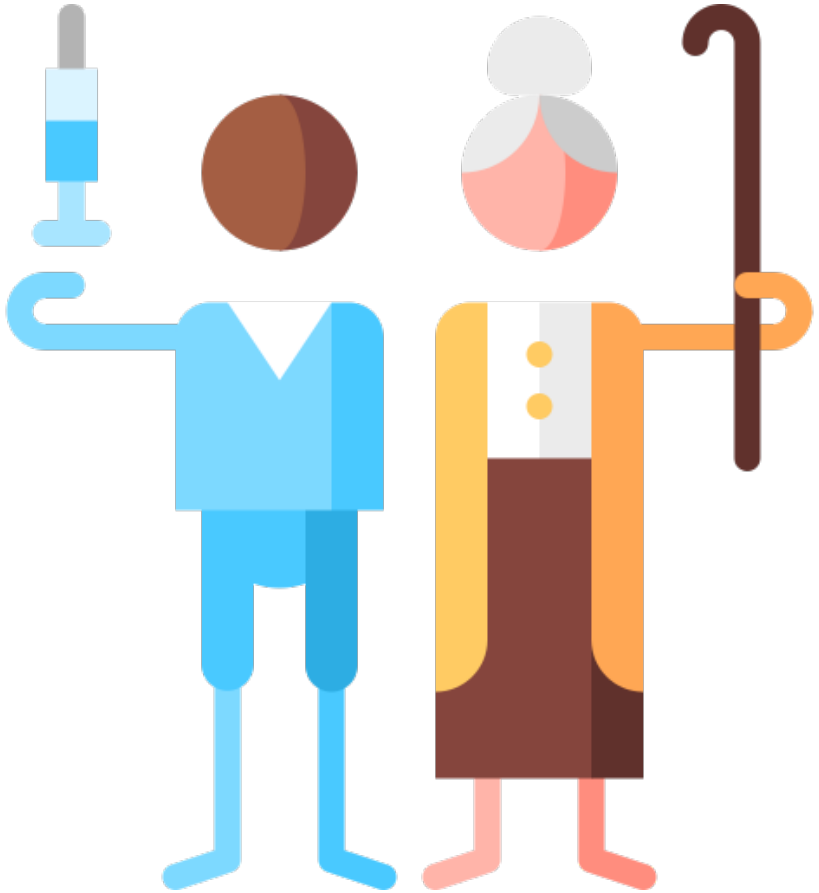
- In 1998, the FDA required new drug application (NDA) holders present in their applications efficacy and safety data based on age
  - Subsequent recommendations for the biologics license application (BLA)

- In 2012 at the International Conference on Harmonisation (ICH) guidance for industry, the FDA reaffirmed the importance of obtaining geriatric data

- In 2012, Food and Drug Administration Safety and Innovation Act (FDASIA) directed the FDA to report on the inclusion of subgroups in clinical studies and the analysis of subgroups in NDAs and BLAs

21 Code Federal Regulations, sections 201.56(d)(4), 201.57, and 210.80

Geriatric Definitions



Generally defined as patients aged 65 years or older

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Geriatric Definitions

- FDA advises that protocols should not ordinarily contain upper age cutoffs
- The ICH guidance suggested that geriatric patients (especially 75 years of age and older) may respond differently to drug therapy than younger adult patients
- Indications approved in ***adults*** include geriatric patients

Example of the ***Geriatric Use*** subsection

Of the total number of DRUG X-treated patients in these studies:

- *n*(x%) were 65 to 74 years of age
- *n*(y%) were 75 to 84 years of age
- *n*(z%) were 85 years of age and older

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Inclusion of Older Adults in Cancer Clinical Trials

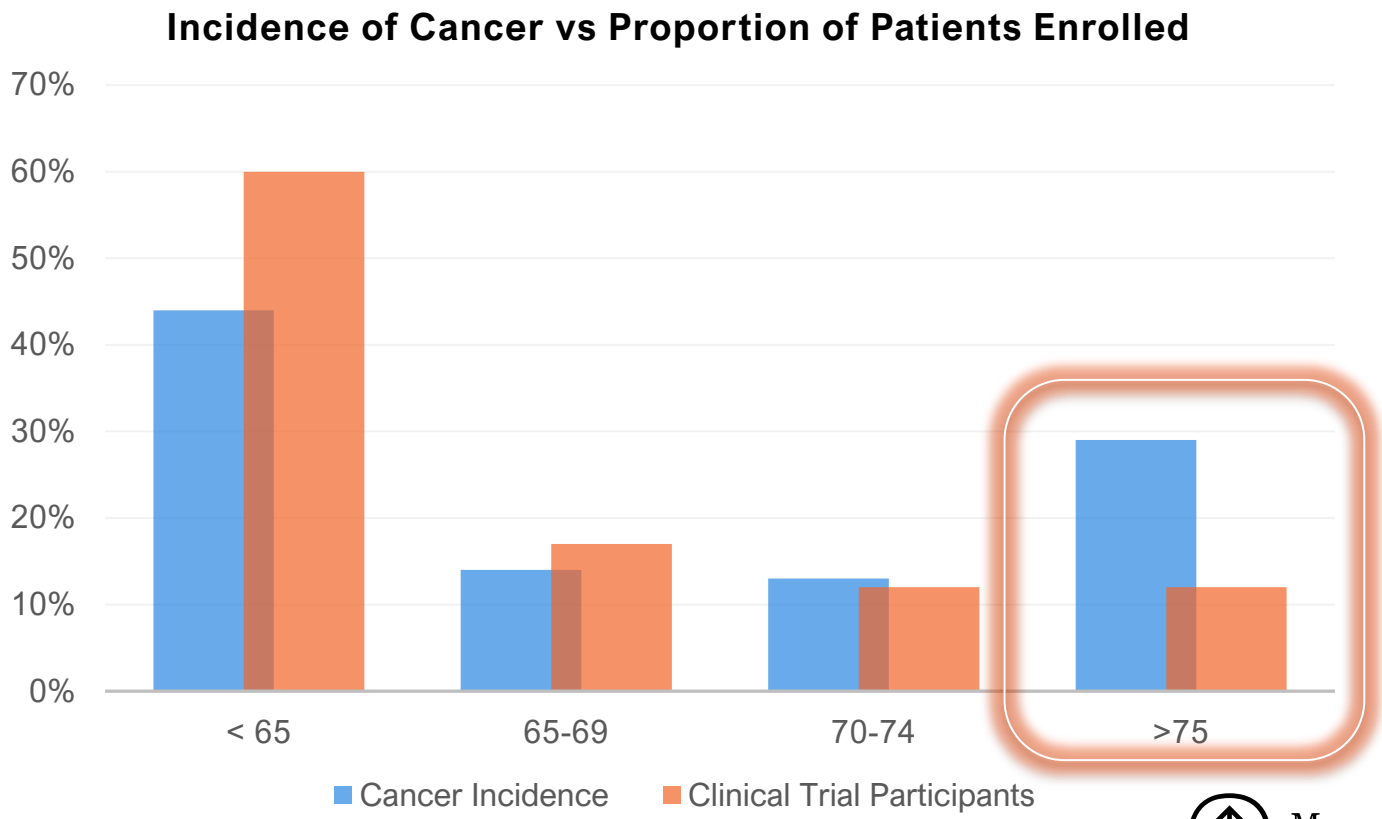
- Guidance document released by the FDA to assist stakeholders, sponsors, and institutional review boards for the inclusivity of older adults in oncology care

- Addresses the follow subsections
  - Trial design
  - Recruitment strategies
  - Additional information needed
  - Adverse event monitoring
  - Report more discrete age subgroups
  - Post-market surveillance

Food and Drug Administration – Inclusion of Older Adults in Cancer Clinical Trials
Levit L, et al. JNCI. 2017.

Inclusion of Older Adults

- 10-year perspective from 2005 to 2015
  - 105 FDA oncology trials evaluated 224,766 patients enrolled
  - **Disparity is greatest in patients ≥ 75 years of age**



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Table adapted from: Singh H, et al. *ASCO*. 2017.

Goals of Geriatric Oncology

What

Improve the quality and quantity of evidence-based medicine for treating older adults with cancer

Improve the quality of care received by older adults with cancer

How

Leverage research designs and infrastructure for generating evidence on older adults with cancer

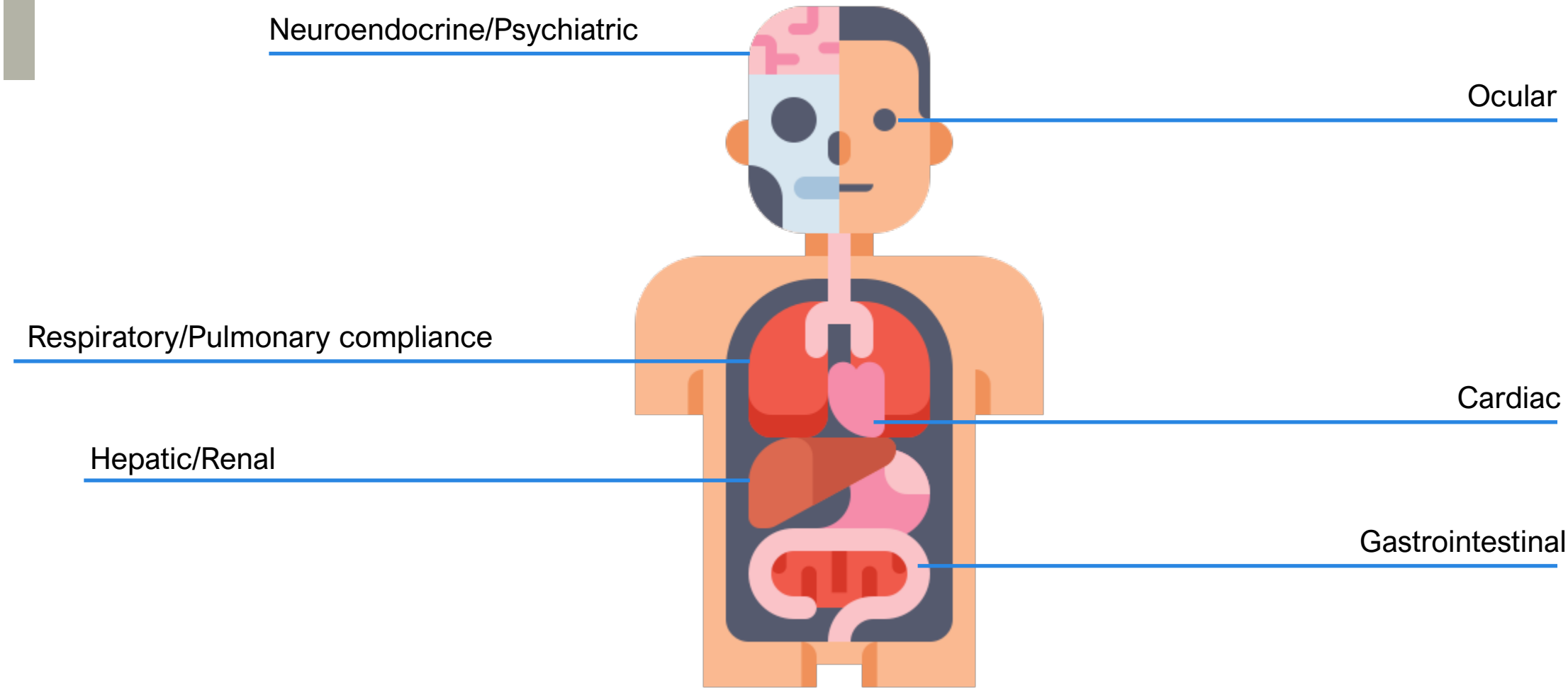
Increase FDA authority to incentivize and require researching involving older adults with cancer

Regulatory changes
Global recruitment and transparency

Hurria A, et al. *J Clin Oncol*. 2016.

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Age-Related Changes in Physiology



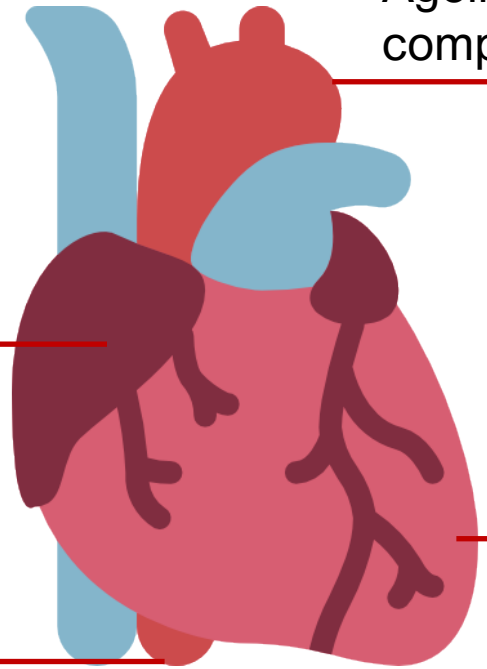
Mangoni AA, et al. Br J Clin Pharmacol. 2004.

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Cardiac Structure and Function

Ageing reduces elasticity and aortic compliance in the greater arteries

Reduction in the intrinsic resting heart rate with delayed conduction time between the sinoatrial node (SA) and atrioventricular (AV) node



Increased systolic arterial pressure impairs left ventricular ejection

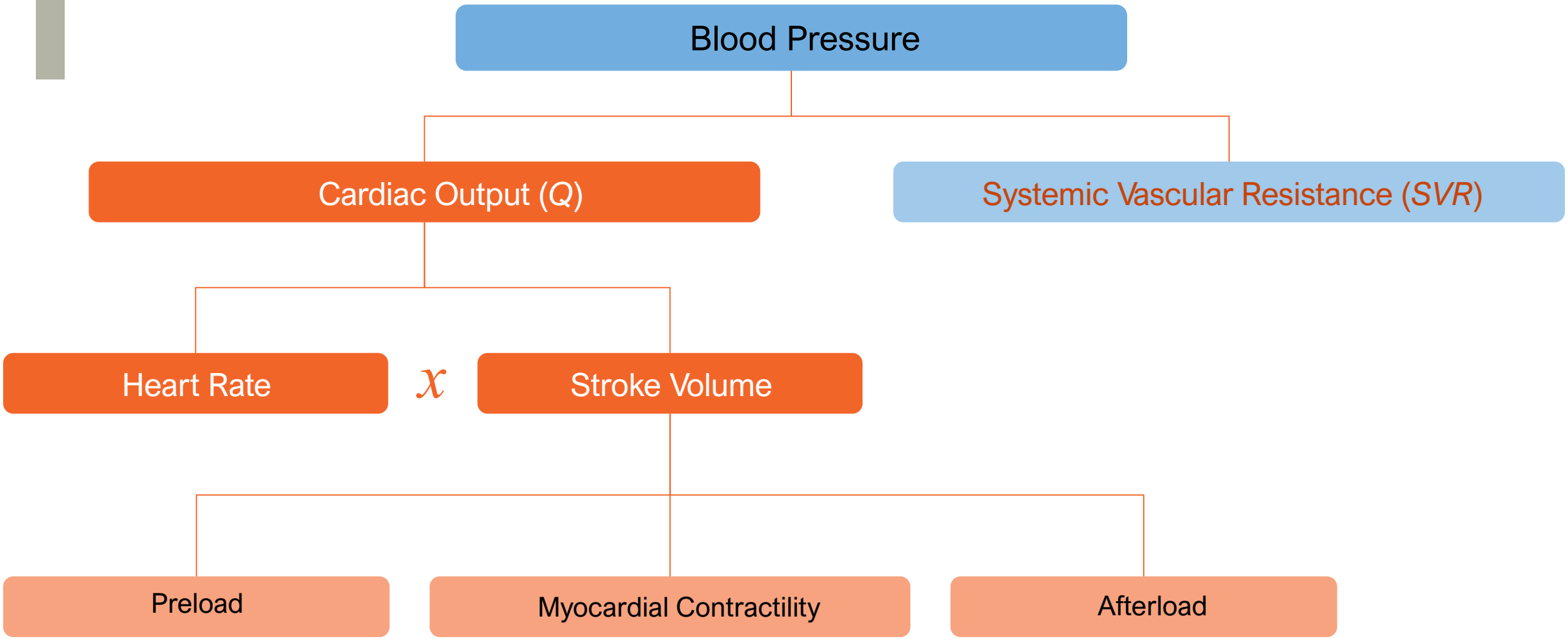
Postural changes resultant in hypotension in the elderly relies on increased stroke volume

Results in ventricular hypertrophy and interstitial fibrosis

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Mangoni AA, et al. Br J Clin Pharmacol. 2004.

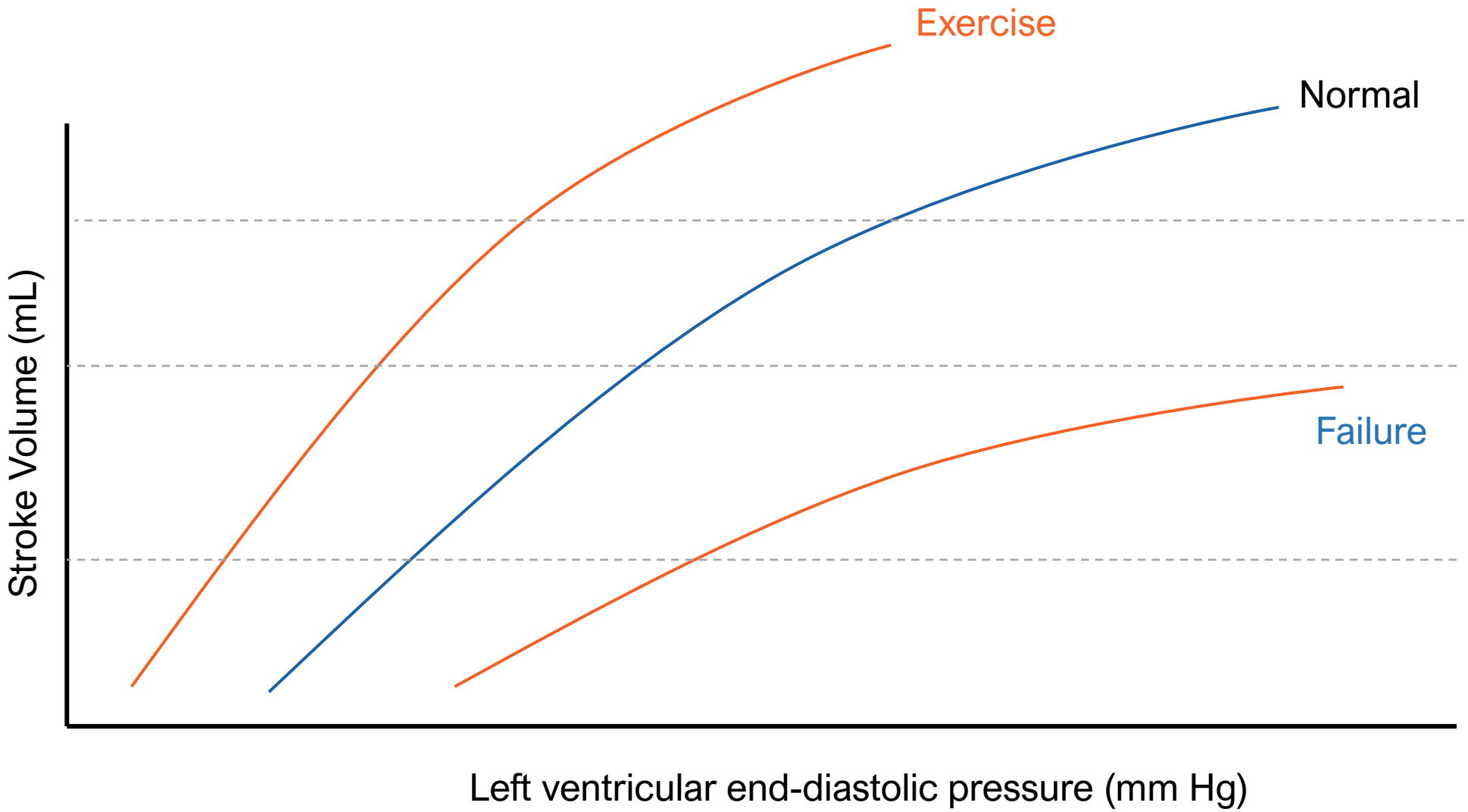
Determinants of Cardiovascular Function



Katz MA et al. *Circulation*. 2002.

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Frank-Starling Law of the Heart



Katz MA et al. *Circulation*. 2002.

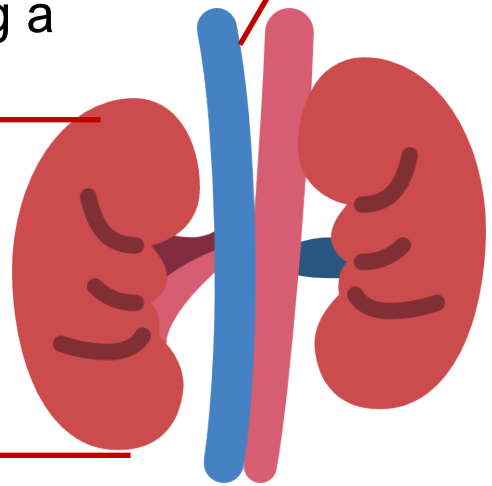
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Renal System

Plasma flow and glomerular filtration decline with age, but uniformity and consistency is difficult to predict

Renal mass decreases with age resulting a direct reduction of nephron activity

Intra-renal vascular changes may also occur



No changes in the medullary vascularity has been reported

Preservation of the autonomic response with catecholamines

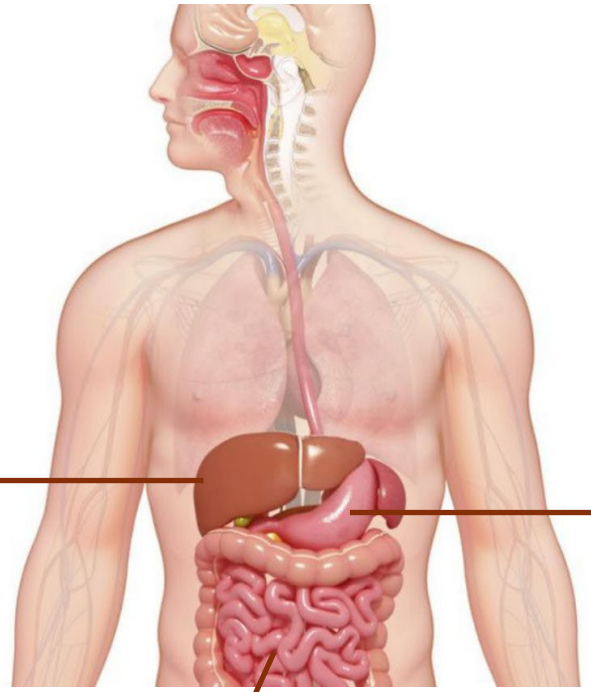
Accurate assessment of renal function is imperative for dose finding studies

Acid-base balance often presents as a challenge with declining renal function

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Mangoni AA, et al. Br J Clin Pharmacol. 2004.

Gastrointestinal System



Volumetric reduction and blood flow reduction is seen with an ageing liver

Hydrochloric acid and pepsin secretion are reduced with age

Gastric emptying time is similar in elderly patients to that of younger adults

Advancing age reduces the absorption of several substances in the small intestine

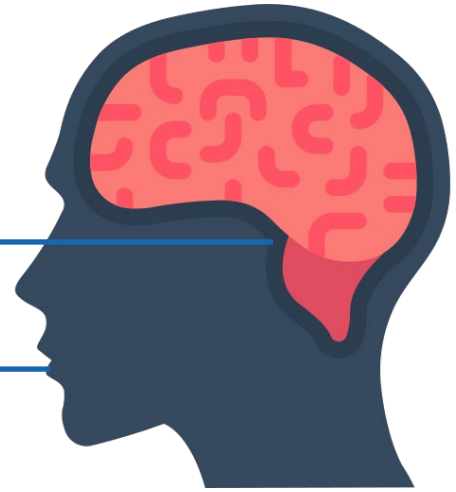
Polysaccharides and monosaccharides
Monovalent and divalent cations

Mangoni AA, et al. *Br J Clin Pharmacol*. 2004.

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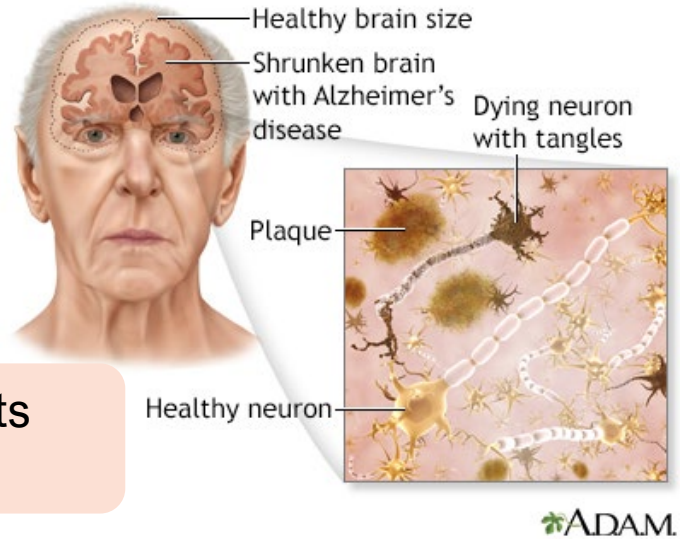
Neuroendocrine

Hypothalamic-pituitary adrenal (HPA) axis function can alter drastically dependent on psychosocial and physical stress over the years



Excessive HPA activation and glucocorticoid release results in dendritic atrophy in the hippocampus

- Impairs memory and learning
- Impairs feedback inhibition



Numerous studies involving neurological and neurochemical effects needed to further understand these changes

Mangoni AA, et al. *Br J Clin Pharmacol*. 2004.
Image source: ADAM Health.

Implications on Pharmacokinetics

- Drug absorption studies in the elderly demonstrate conflicting results
  - Vitamin B12, iron, and calcium absorption is diminished
  - Levodopa absorption in increased
- First-pass metabolism reduction is evident due to volumetric loss of the liver and blood flow
- Body composition changes with advancing age
  - Reduction in total body water
  - Muscle mass reduction
  - Total body fat increases
- Compositional changes results in changes in drug disposition

Mangoni AA, et al. *Br J Clin Pharmacol*. 2004.

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Implications on Pharmacokinetics

- Protein binding changes have not been observed solely due to advancing age
  - Changes are dependent on malnutrition or acute illness
- Reduction in renal function affects the clearance of numerous drugs and investigative drugs
  - Drugs with intrinsic narrow therapeutic index must be cautiously used
  - Toxicity can be exacerbated due to age-related physiologic decline
- Intrinsic and extrinsic factors must be accounted for during drug use

Mangoni AA, et al. *Br J Clin Pharmacol*. 2004.

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Conclusion

- The FDA has since made several important initiatives to improve the transparency, research conduct, and address the disparity of special populations

- Scientists and healthcare providers equipped with the fundamental knowledge of developmental pharmacology and age-related physiology can enhance their role in clinical trial design, recruitment, and research

- Children are not small adults and should be considered accordingly to their age appropriate cognitive and physical development

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Pharmacotherapy Principles

Considerations in Special Populations

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