B. 17 Diuretics

a. Outline the physiological basis of classifying diuretics, related to their site of action.

Site of action
- PCT: osmotic and carbonic anhydrase inhibitors (predominantly)
- loop diuretics (loop diuretics, thiazides, collecting ducts)
- cortical part of loop, DCT: thiazides
- collecting ducts: potassium-sparing diuretics, ADH antagonists (demeclocycline, Li⁺, alcohol)

b. Describe the actions of mannitol, frusemide, thiazides, aldosterone antagonists and carbonic anhydrase inhibitors.

mannotol
- a sugar alcohol
- osmotically active but not metabolized

pharmacokinetics
- not absorbed orally → diarrhoea
- administered IV
- distributed throughout ECF
- not metabolized
- renal excretion by filtration

pharmacodynamics
- expands plasma volume
  - ↑ RBF, GFR
- filtered at glomerulus
- exerts osmotic pressure to prevent PCT reabsorption of Na⁺ and water
- high flow in loop “washes out” countercurrent multiplier
- produces dilute urine

adverse actions
- water loss in excess of Na⁺ loss → hypernatremia
- excess K⁺ loss, particularly if aldosterone is high

clinical use
- rapid diuresis for reduction of intracranial or intraocular pressure

frusemide
- loop diuretic
- sulfonamide derivative

pharmacokinetics
- high oral bioavailability
- 96% protein bound
- \( V_d = 0.1 \) l/kg (circulation)
- \( t^{1/\beta} = 1 \) h
- urinary filtration and secretion
- acts from tubular lumen

Diuretics 2.B.17.1 James Mitchell (December 24, 2003)
pharmacodynamics
- inhibits Na⁺, K⁺, 2Cl⁻ transporter in ascending loop
- ↓ medullary gradient
- ↓ lumen-positive potential
  - Ca²⁺, Mg²⁺, K⁺ loss
- vasodilation of renal vessels and systemic veins (?mechanism)

adverse actions
- cation loss
- dehydration → renal failure, gout
- ↑ aldosterone and DCT flow → K⁺ and H⁺ loss
  - hypokalaemic metabolic alkalosis
- ototoxicity
- sulfonamide allergy

clinical use
- acute pulmonary oedema (venodilation)
- hypercalcaemia
- overdose of anions: Br⁻, F⁻ and I⁻

thiazides
- sulfonamide derivatives
- some have carbonic anhydrase inhibiting activity

pharmacokinetics (chlorothiazide)
- high oral bioavailability
- 95% protein bound
- Vₚ 0.2 l/kg
- t₁/₂β 1.5 h
- renal excretion by organic acid mechanism

pharmacodynamics
- inhibit DCT NaCl uptake
- ↑ Ca²⁺ uptake

adverse actions
- hypokalaemic metabolic alkalosis
- hyponatraemia
- ↓ glucose tolerance, lipids
- sulfonamide allergy

clinical use
- cardiac failure
- hypercalciuria

spironolactone
- synthetic steroid

pharmacokinetics
- hepatic metabolism

pharmacodynamics
- competitive inhibitor at aldosterone receptor
- ↓ Na⁺ reabsorption, ↑ K⁺, H⁺ reabsorption

adverse actions
- steroid effects: gynaecomastia, prostate enlargement
- hyperkalaemia, acidosis (esp. with NSAIDs, ACE inhibitors)

amiloride

pharmacokinetics
- urinary excretion unchanged

pharmacodynamics
- inhibits Na⁺ transport in luminal membrane
- acts in lumen

Diuretics 2.B.17.2 James Mitchell (December 24, 2003)
adverse effects
  hyperkalaemia, acidosis

acetazolamide
  sulfonamide, carbonic anhydrase inhibitor

pharmacokinetics
  well absorbed orally
  not metabolized
  weak acid actively secreted in PCT
  eliminated within 12 h

pharmacodynamics
  prevents secretion of H⁺ in PCT to reabsorb HCO₃⁻
  results in alkaline diuresis
  inhibition of carbonic anhydrase in ciliary body and choroid plexus causes reduced volume and more acidic aqueous humor and CSF

adverse effects
  HCO₃⁻ depletion and acidosis result in reduced diuretic effect
  increased urinary phosphate and Ca²⁺ can cause calculi
  K⁺ depletion due to increased luminal electronegativity
  reduced urinary NH₄⁺ excretion in alkaline urine (reabsorbed as NH₃)
  exacerbates hepatic encephalopathy
  ↓ renal clearance can result in toxic levels in renal impairment
  cross-sensitivity with other sulfonamides

clinical use
  glaucoma (not for diuretic effect)
  acute mountain sickness (alkalosis, ↑ ICP)
  alkalinizing urine in drug overdose (e.g. salicylate)