Glomerular Filtration

1. Describe the structure and function of the glomerular membrane.

Glomerular filtration occurs across glomerular membrane – 3 layers.

Fenestrated endothelium	Fenestrations allow more bulk flow of water and solutes than normal capillary membranes.	Fixed negative charges → repel proteins.
Basement membrane	Large spaced meshwork of collagen and proteoglycan fibrils.	
Epithelium	Inner wall of Bowman's capsule formed from podocytes. Filtrate moves through slit pores between foot processes.	

- Albumin diameter slightly < glomerular pore diameter
  - Minimal change nephropathy → loss of fixed –ve charge → albuminuria.
- Certain low molecular weight substances bound to plasma proteins → conc. in filtrate < total plasma conc.

2. Describe net filtration pressure as a vector sum of hydrostatic and osmotic pressure differences.

Filtration fraction: Proportion of renal plasma flow which is filtered.

$$filtration\ fraction = \frac{GFR}{renal\ plasma\ flow} = \frac{125ml/min}{625ml/min} = 20\%$$

Net filtration pressure = hydrostatic pressure difference + osmotic pressure difference

Bowman's capsular colloid osmotic pressure (π_G) – ~0mmHg.

Bowman's capsular pressure (P_B)

- Not a normal control variable.
- Obstruction of urinary outflow (e.g. by stones) can raise Bowman's capsular pressure → ↓GFR.

Glomerular capillary colloid osmotic pressure (π_G)

- ↑[plasma protein] → nonlinear shift in Donnan* distribution for diffusible ions → disproportionately ↑π_G.
- ↑renal plasma flow + no initial increase in GFR → ↓filtration fraction, ↓end-glomerular π_G → ↑net filtration pressure → ↑GFR
  - Raise renal plasma flow induce increase in GFR, independent of any effect on hydrostatic pressure.

* The Donnan effect is extra osmotic pressure attributable to cations attached to dissolved plasma proteins.

Glomerular capillary hydrostatic pressure (P_G)

- Determined by 3 physiologically controlled variables.
- Arterial pressure
  - Mean arterial pressure → ↑P_G → ↑GFR.
  - Effect subject to autoregulation of renal blood flow and GFR → effect is slight.

Glomerular Filtration

- Afferent arteriolar resistance
  - Constrict → ↑resistance → ↑pressure drop across arteriole → ↓P_G → ↓GFR.
- Efferent arteriolar resistance
  - Moderate constriction → ↑P_G → ↑filtration fraction → ↑GFR.
  - Severe constriction → ↓renal blood flow → ↑filtration fraction → ↑π_G nonlinearly (Donnan effect) → GFR declines after reaching a peak.

Determinant	**Possible causes**
↓K_f	renal disease, diabetes mellitus, hypertension
↑P_B	urinary tract obstruction
↑ π_G	↓renal blood flow, ↑plasma proteins
↓P_G	
• ↓MAP	↓arterial pressure
• ↑afferent arteriolar resistance	↑sympathetic activity, vasoconstrictors
• ↓efferent arteriolar resistance	↓angiotensin II

3. Compare glomerular filtration with formation of interstitial fluid at general systemic capillaries.

		Glomerular capillary value	**Mean systemic capillary value**
Net filtration pressure	Hydrostatic pressure difference + colloid osmotic pressure difference	~10mmHg	~0.3mmHg
Filtration coefficient, K_f	$\frac{filtration\ rate}{net\ filtration\ pressure}$	*60ml/(g.day.mmHg)	1.42ml/(g.day.mmHg)

*g: K_f adjusted for per unit mass of kidneys and systemic capillaries.

Disease states → basement membrane thickened → filtration coefficient↓

- Examples: chronic hypertension, diabetes mellitus.

4. Describe the neural, hormonal and autocoid control of glomerular filtration and renal blood flow.

Renal blood vessels have rich sympathetic innervation

- Strong sympathetic stimulation → renal vasoconstriction → ↓RBF → ↓GFR.
- Mild sympathetic stimulation → little effect.
- Main role – respond to brain ischaemia, severe haemorrhage and ‘fight or flight’.

Glomerular Filtration

Hormone and autocoid control of RBF and GFR

Vasoconstrictors	Sites of synthesis/secretion	Action
Adrenaline	adrenal medulla	↓RBF → ↓GFR
Noradrenaline		
Endothelin	endothelium in damaged vasculature	
Angiotensin II	kidneys, systemic circulation	Preferentially constricts efferent arterioles → ↑P_G, ↓RBF → maintains or ↑GFR and excretion of wastes. Promotes increased reabsorption of Na^+ and water in distal tubules.

Vasodilators	Sites of synthesis/secretion	Action
Nitric oxide	vascular endothelium throughout body	Basal NO level maintains normal renal vasodilation. Impaired NO production → ↑renal vascular resistance → ↓GFR, ↓Na^+ excretion → hypertension.
Prostaglandins		Powerful vasodilators – may oppose vasoconstrictor effects of sympathetic neural and hormonal input under stressful conditions.
Bradykinin		

5. Explain autoregulatory and tubuloglomerular feedback mechanisms in the kidney.

Relatively constancy of RBF and GFR over wide range of arterial pressure (75mmHg – 160mmHg).

Urine output is small difference between large amounts of filtration and reabsorption – increased blood pressure → small increase in RBF and GFR → pressure diuresis/pressure natriuresis.

Autoregulation mostly via tubuloglomerular feedback

- Feedback loop links changes in [NaCl] at macula densa with control of renal arteriolar resistance → Prevents spurious fluctuations in renal excretion.
  - GFR autoregulated at the expense of changes in RBF.
- Macula densa: specialised distal tubular epithelial cells containing secretory organelles directed toward afferent and efferent arterioles.
- Output – delivery of NaCl to distal tubule.
- Juxtaglomerula complex
  - Macula densa cells in initial portion of distal tubules
  - Juxtaglomerular cells in walls of afferent and efferent arterioles.
- ↓NaCl
  - ↓afferent arteriolar resistance → ↑P_G → ↑GFR → ↑flow through loop oh Henle → proportionally less active reabsorption of NaCl.
  - ↑renin secretion by juxtaglomerular cells → renin-angiotensin cascade → ↑angiotensin II → preferentially constricts efferent arterioles → ↑P_G → ↑GFR.

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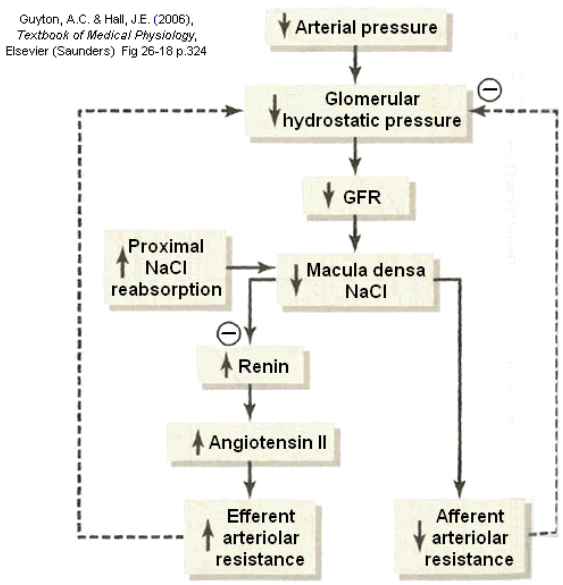

Myogenic autoregulatory mechanism

- ↑arterial pressure → blood vessels stretched → ↑influx of extracellular Ca^{2+} into smooth muscles → blood vessels contract to resist stretch.
- Lack sensory feedback concerning RBF and GFR.