



DrNB Nephrology

Solved Question Bank

Exit examination, 2021–2026. Previous-year questions arranged topic by topic, with model answers referenced to the textbook page.

137 questions | 213 question parts | 66 topics

- | | |
|---|--|
| 1 Renal Anatomy, Development, Physiology & Cell Biology | 6 Chronic Kidney Disease — Progression, Complications & Systemic Effects |
| 2 Fluid, Electrolyte & Volume Disorders | 7 CKD–Mineral and Bone Disorder |
| 3 Acid–Base Disorders | 8 Anaemia of Chronic Kidney Disease |
| 4 Clinical Evaluation, Urinalysis, Biopsy & Diagnostics | 9 Glomerular Disease |
| 5 Acute Kidney Injury & Critical Care Nephrology | |

Written and reviewed by

Dr Akshit Garg

MD, DM (NEPHROLOGY)

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PUBLICATION

DrNB Nephrology

Solved Question Bank

Volume One · Chapters 1–9 of 27

Exit examination, previous-year questions 2021–2026

- | | | | |
|---|---|---|--|
| 1 | Renal Anatomy, Development, Physiology & Cell Biology | 5 | Acute Kidney Injury & Critical Care Nephrology |
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| | | 9 | Glomerular Disease |

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Dr Akshit Garg

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137 questions · 213 question parts · 66 topics · every answer page–cited

Answers written from **Brenner & Rector's The Kidney 12e (2026)**, **Comprehensive Clinical Nephrology 7e (2024)** and the current KDIGO guidelines

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About this book

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To order	www.clinicapublication.com

How to use this book

Questions are grouped by topic, not by paper. Every appearance of a question is listed above its answer with the session and question number, so a topic answered once covers all the years it was asked in. The blueprint under each answer tells you what to write for the marks allotted.

A note on clinical use

Every answer is referenced to the textbook page and to the guidelines current at the time of writing. Drug doses and management decisions should always be confirmed against current guidance and local protocol before they are applied to patient care.

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Sources & How to Read an Answer

Every statement carries a citation. Three classes of source are used, and each is marked differently so you always know where a line came from.

BR (primary)	Brenner & Rector's The Kidney, 12th edition (2026) . Cited as BR §Ch 3, Fig. 3.12, p. 87. Takes precedence over CCN wherever the two disagree.
CCN	Comprehensive Clinical Nephrology, 7th edition (2024) . Cited as CCN §Ch 9, Fig. 9.5, p. 112.
KDIGO	The current guideline, cited by its own year and title in a green panel . Where a newer guideline has superseded what the textbooks report, the guideline governs and the panel says so.
Filled gap	Where neither textbook nor a KDIGO guideline covers the question, the current accepted position is given in a blue panel so it is never mistaken for textbook text.

Topic-wise, not paper-wise. Questions that ask the same thing in different years are answered **once**, under the topic, with every appearance listed above the answer. Where the examiner asked for 3 marks in one year and 7 in another, the answer is written to the larger allocation and the blueprint tells you what to drop for the shorter version.

KDIGO guidelines current at the time of writing

GUIDELINE	CURRENT EDITION	STATUS
Anemia in CKD	KDIGO 2026 — <i>Kidney Int</i> 2026;109(1S):S1-S99	Published — supersedes KDIGO 2012
IgA nephropathy / IgA vasculitis	KDIGO 2025 — <i>Kidney Int</i> 2025;108(4S):S1-S71	Published
Nephrotic syndrome in children	KDIGO 2025 — <i>Kidney Int</i> 2025;107(5S):S241-S289	Published
ADPKD	KDIGO 2025 — <i>Kidney Int</i> 2025;107(2S):S1-S239	Published — first ADPKD guideline
CKD evaluation and management	KDIGO 2024 — <i>Kidney Int</i> 2024;105(4S):S117-S314	Published — supersedes KDIGO 2012
Lupus nephritis	KDIGO 2024 — <i>Kidney Int</i> 2024;105(1S):S1-S69	Published — split out of the 2021 GN guideline

GUIDELINE	CURRENT EDITION	STATUS
Diabetes management in CKD	KDIGO 2022 — <i>Kidney Int</i> 2022;102(5S):S1–S127	Published; a 2026 update is in public review
Hepatitis C in CKD	KDIGO 2022 — <i>Kidney Int</i> 2022;102(6S):S129–S205	Published
Glomerular diseases	KDIGO 2021 — <i>Kidney Int</i> 2021;100(4S):S1–S276	Published (IgAN and lupus chapters since superseded)
Blood pressure in CKD	KDIGO 2021 — <i>Kidney Int</i> 2021;99(3S):S1–S87	Published
Transplant candidate	KDIGO 2020 — <i>Transplantation</i> 2020;104:S1–S103	Published
CKD-MBD	KDIGO 2017 update — <i>Kidney Int Suppl</i> 2017;7:1–59	Published
Living kidney donor	KDIGO 2017 — <i>Transplantation</i> 2017;101(Suppl 8S):S1–S109	Published
Lipids in CKD	KDIGO 2013 — <i>Kidney Int Suppl</i> 2013;3:259–305	Published
AKI / AKD	KDIGO 2012 — <i>Kidney Int Suppl</i> 2012;2:1–138	Published; a 2026 update is in public review
Kidney transplant recipient	KDIGO 2009 — <i>Am J Transplant</i> 2009;9(Suppl 3):S1–S157	Published
Heart failure in CKD	—	In development

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CHAPTER 1

Renal Anatomy, Development, Physiology & Cell Biology

25

QUESTIONS

34

QUESTION PARTS

17

TOPICS

6.3%

OF THE EXAMINATION

Basic-science questions are the most reliably scoring part of the paper: the answers do not change from year to year, and a good diagram earns marks faster than any amount of prose. Fifteen topics account for all twenty-five question parts asked between 2021 and 2026. Countercurrent multiplication, the glomerular filtration barrier, autoregulation with tubuloglomerular feedback, and podocyte biology are the four that recur.

#	TOPIC	ASKED	YEARS
1.1	Structure of the Nephron	1×	2022·Dec
1.2	The Glomerular Filtration Barrier	2×	2022·Dec
1.3	The Renal Interstitium	1×	2024
1.4	Uromodulin in Health and Disease	2×	2021, Jan 2025
1.5	Renal Autoregulation and Tubuloglomerular Feedback	3×	2022·Jun, 2022·Dec
1.6	Determinants of GFR and Renal Functional Reserve	2×	2022·Dec, 2023·Apr
1.7	Urine Concentration and Dilution — the Countercurrent Multiplier	3×	2022·Jun, 2022·Dec, Jan 2025
1.8	Aquaporins	2×	2022·Dec, 2023·Oct
1.9	Kidney Development and Nephrogenesis	2×	2022·B, 2023·Apr
1.10	Nephron Endowment	3×	2023·Oct, 2025–26
1.11	Podocyte Structure, the Slit Diaphragm, and Podocyte Injury and Repair	3×	2023·Oct, 2024
1.12	NETosis, Autophagy and Regulated Cell Death in Kidney Injury	1×	2021
1.13	Transforming Growth Factor- β and the Mediators of Fibrosis	1×	2022·B
1.14	Renin-Angiotensin-Aldosterone Physiology	2×	2022·Jun, 2023·Apr

#	TOPIC	ASKED	YEARS
1.15	The Ageing Kidney	1×	2023-Oct
1.16	Endocrine Functions of the Kidney	2×	2025-26
1.17	Experimental Models of Kidney Disease	3×	Jan 2025

Chapter sources. Brenner & Rector 12e §Ch 1 (Embryology, pp. 3–35), §Ch 2 (Anatomy, pp. 39–77), §Ch 3 (Renal Circulation and Glomerular Filtration, pp. 79–111), §Ch 4 (Glomerular Cell Biology and Podocytopathies, pp. 115–133), §Ch 10 (Urine Concentration and Dilution, pp. 267–287), §Ch 11 (Vasoactive Molecules, pp. 289–319), §Ch 20 (Early Life Origins, pp. 599–639), §Ch 21 (Kidneys in Aging, pp. 643–661), §Ch 27 (Pathophysiology of AKI, pp. 779–813), §Ch 50 (Mechanisms of Progression, pp. 1471–1513). Comprehensive Clinical Nephrology 7e §Ch 1 (Renal Anatomy, pp. 1–11), §Ch 2 (Renal Physiology, pp. 13–25), §Ch 9 (Disorders of Water Metabolism, pp. 108–123).

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.1 Structure of the Nephron

2022-Dec P1 Q4(a)

Structure of Nephron.

5

EXAMINER'S BLUEPRINT

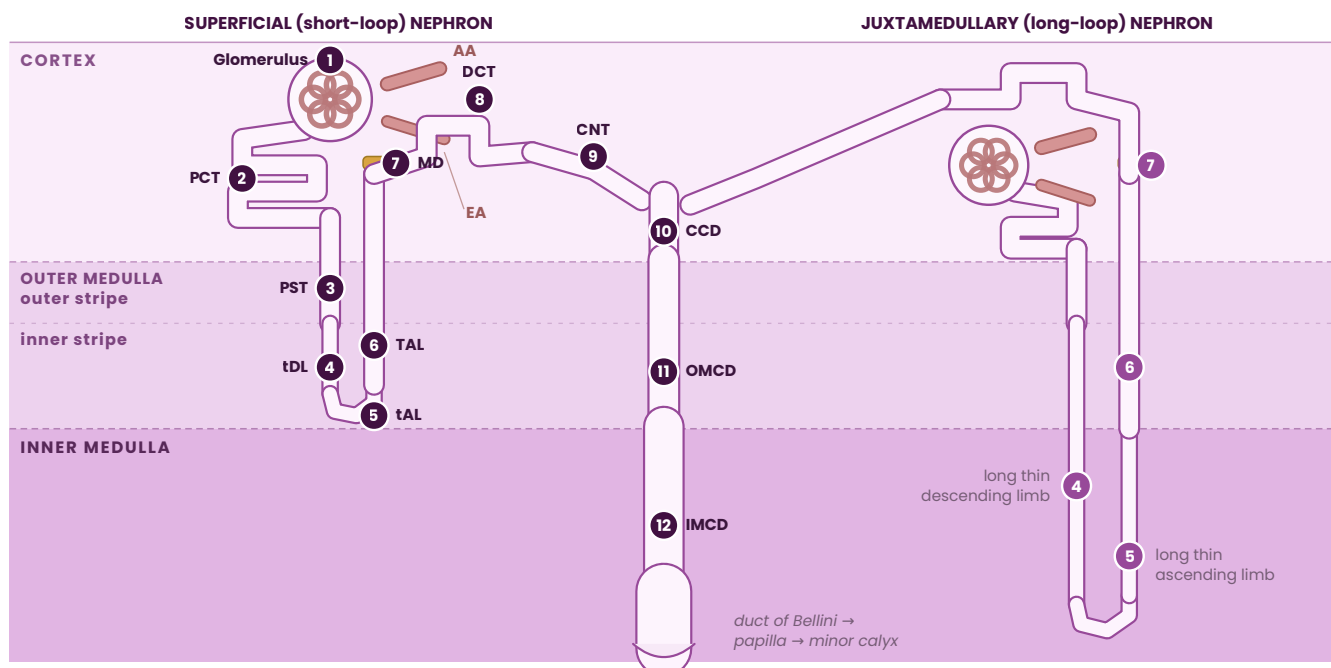
5 marks — define the nephron and state the two populations (1) + a labelled diagram of the segments from corpuscle to collecting duct (2) + one line of function and the defining transporter for each segment (2). Do not spend marks on ultrastructure; that belongs to the GFB answer.

Definition

The nephron is the functional unit of the kidney — the **renal corpuscle** (glomerulus plus Bowman capsule) together with its **tubule** (proximal tubule, loop of Henle, distal tubule and connecting tubule). The **collecting duct is not part of the nephron**: it is derived from the ureteric bud, whereas the nephron is derived from the metanephric mesenchyme.

BR §Ch 1, p. 3; BR §Ch 2, pp. 39–60

Segments of the nephron and collecting duct — position, transport job and key transporters



Short loops turn in the inner stripe and have little or no thin ascending limb; long loops of juxtamedullary nephrons reach the papilla. ≈ 1 million nephrons per kidney (range 250 000 – <2.5 million). BR Ch 2, Fig. 2.5, p. 39.

Segment	Zone	Reabsorptive / transport job	Key transporters, channels & targets	% filtered Na^+
① Glomerulus & Bowman capsule	Cortex	Size- and charge-selective ultrafiltration of ≈ 180 L/day; filtration pressure ≈ 50 mm Hg	Slit diaphragm (nephrin-NEPH1); fenestrated endothelium; GBM HSPG	— (filtration site)
② PCT (S1–S2)	Cortex	Isosmotic bulk reabsorption: Na^+ , HCO_3^- , glucose, amino acids, P_i , Ca^{2+} , water	NHE3 · SGLT2 ($\approx 97\%$ of glucose) NaPi-IIa · AQP1 · NBCe1 · Na^+ - K^+ -ATPase	$\approx 65\%$ (PCT + PST)
③ PST / pars recta (S3)	Cortex $\rightarrow$ outer stripe	Completes glucose uptake; secretes organic anions and cations; vulnerable to ischaemia	SGLT1 ($\approx 3\%$) · OAT1/OAT3 · OCT2 MRP2/MRP4 · MATE1	(within the 65%)
④ Thin descending limb	Inner stripe $\rightarrow$ inner medulla	Water abstraction only — water-permeable, no active NaCl transport; fluid concentrated	AQP1 · UT-A2 (long loops) · no NKCC2	0 (water only)
⑤ Thin ascending limb	Inner medulla (long loops)	Passive NaCl exit, water-impermeable — the “single effect” of the passive model	CIC-K1 + barttin · no aquaporin	passive
⑥ Thick ascending limb (MTAL $\rightarrow$ CTAL)	Inner stripe $\rightarrow$ cortex	Active NaCl uptake without water; dilutes the fluid, builds medullary tonicity; $\text{Ca}^{2+}/\text{Mg}^{2+}$	NKCC2 (loop diuretics) · ROMK · CIC-Kb + barttin · claudin-16/19 — Bartter syndrome	20–25% ($\approx 30\%$ of NaCl)
⑦ Macula densa (end of CTAL)	Cortex, vascular pole	20–30 cells sense luminal NaCl and flow $\rightarrow$ tubuloglomerular feedback and renin control	NKCC2 as sensor · maxi-anion ATP channel A_1 receptor · COX-2 · nNOS · primary cilium	— (sensor)
⑧ Distal convoluted tubule	Cortex	Further dilution; main site of Ca^{2+} and Mg^{2+} regulation; thiazide-sensitive	NCC (thiazides) · TRPM6 · TRPV5 · NCX1 calbindin-D28k — Gitelman syndrome	5–7%
⑨ Connecting tubule	Cortex	Aldosterone-driven Na^+ uptake, K^+ secretion, PTH-dependent Ca^{2+} ; arcades join the CCD	ENaC · ROMK + BK · TRPV5 · AQP2	(within 3–5%)
⑩ Cortical collecting duct	Cortex	Fine Na^+/K^+ control (principal cell); acid-base by α - and β -intercalated cells	ENaC + ROMK + AQP2/AQP3; H^+ -ATPase + AE1 (α); pendrin + H^+ -ATPase (β)	3–5% (CNT + CD)
⑪ Outer medullary collecting duct	Outer medulla	H^+ secretion against a steep gradient; urea-impermeable, so water loss concentrates urea	H^+ -ATPase · H^+/K^+ -ATPase · AQP2/AQP3	<1%
⑫ Inner medullary CD $\rightarrow$ duct of Bellini	Inner medulla	Final osmotic equilibration; urea exit traps urea in the inner medulla (recycling)	AQP2 (apical, AVP/ $\text{V}_{2\text{R}}$) · AQP3 + AQP4 UT-A1 & UT-A3 · ENaC	<1%

$\approx 99.4\%$ of filtered Na^+ is reabsorbed. Drug sites: SGLT2 inhibitors and acetazolamide at ②, loop diuretics at ⑥, thiazides at ⑧, amiloride and mineralocorticoid-receptor antagonists at ⑩–⑫, vaptans at ⑪–⑫. Bartter $\equiv$ ⑥, Gitelman $\equiv$ ⑧, Liddle $\equiv$ ⑩–⑫.

Segments of the nephron and collecting duct, with their positions in cortex and medulla.

Original schematic based on BR §Ch 2, pp. 39–60 and CCN §Ch 1, pp. 3–11.

1 • Two populations of nephrons

- **Superficial / cortical nephrons** — glomeruli in the outer cortex, **short loops** that turn at the outer-inner medullary junction; about 85% of nephrons in humans. Efferent arterioles supply the peritubular capillary network.
- **Juxtamedullary nephrons** — glomeruli near the corticomedullary junction, **long loops** reaching deep into the inner medulla and papilla. Efferent arterioles give rise to the **vasa recta**; these are the nephrons that generate and sustain the medullary osmotic gradient.
- Each human kidney has 8–10 papillae, each draining into a minor calyx, with several minor calyces draining into major calyces.

↳ BR §Ch 1, p. 6; BR §Ch 3, pp. 79–83

2 • Segment-by-segment structure and function

The nephron from corpuscle to collecting duct · BR §Ch 2, pp. 39–63; CCN §Ch 2, pp. 15–25

SEGMENT	STRUCTURE	PRINCIPAL FUNCTION / DEFINING TRANSPORTER
Renal corpuscle	Fenestrated capillary tuft, GBM, podocytes, mesangium, Bowman capsule lined by parietal epithelial cells	Ultrafiltration — ~180 L/day of nearly protein-free filtrate
Proximal convoluted tubule (pars convoluta, S1–S2)	Tall cuboidal cells, dense brush border , abundant mitochondria, extensive basolateral interdigitation, prominent endocytic apparatus	Bulk isosmotic reabsorption — ~65% of Na ⁺ and water, ~90% of HCO ₃ [−] , virtually all glucose and amino acids. NHE3 is the main Na ⁺ entry route; SGLT2 (S1–S2) and SGLT1 (S3); megalín-cubilin retrieve filtered low-molecular-weight proteins and albumin
Proximal straight tubule (pars recta, S3)	Lower brush border, fewer mitochondria; descends into the outer stripe	Continued reabsorption; the segment most vulnerable to ischaemic and toxic injury (outer stripe is relatively hypoxic)
Thin descending limb	Flat epithelium, few organelles; AQP1 in long loops only	Water-permeable, solute-impermeable — water withdrawal concentrates the tubular fluid
Thin ascending limb	Flat epithelium, no AQP1	Water-impermeable , passively NaCl-permeable; no active NaCl transport
Thick ascending limb	Cuboidal, numerous mitochondria, deep basolateral infoldings	The diluting segment — active NaCl reabsorption by NKCC2 with ROMK recycling and basolateral ClC-Kb; water-impermeable. Generates the lumen-positive voltage that drives paracellular Ca ²⁺ and Mg ²⁺ reabsorption. Secretes uromodulin

SEGMENT	STRUCTURE	PRINCIPAL FUNCTION / DEFINING TRANSPORTER
Macula densa	Specialised plaque of ~20-30 closely packed TAL cells at the vascular pole of its own glomerulus	Chemosensor of luminal NaCl; with the extraglomerular mesangium and the granular (juxtaglomerular) cells forms the juxtaglomerular apparatus — see Topic 1.5
Distal convoluted tubule	Begins a variable distance after the macula densa; abrupt transition from NKCC2 ⁺ cortical TAL to NCC ⁺ cells. Highest mitochondrial density in the nephron	Thiazide-sensitive NaCl reabsorption via NCC (regulated by the WNK-SPAK/OSR1 cascade); DCT2 also reabsorbs Ca ²⁺ through TRPV5
Connecting tubule	Functional intermediate between DCT and cortical collecting duct; in apposition to its own afferent arteriole	ENaC-mediated Na ⁺ reabsorption; site of connecting tubule glomerular feedback
Collecting duct (ureteric bud derivative)	Principal cells and intercalated cells (types A, B and non-A non-B)	Principal cells: ENaC, ROMK and AQP2 under aldosterone and vasopressin. Type A intercalated cells: H ⁺ -ATPase and H ⁺ /K ⁺ -ATPase with basolateral AE1 (acid secretion); type B: apical pendrin for HCO ₃ ⁻ secretion. Inner medullary collecting duct adds UT-A1/UT-A3 for urea

3 · Points examiners look for

- Proximal tubule fluid is **always isosmotic** with plasma, whether the kidney is concentrating or diluting.
- The **loop of Henle always dilutes**; the collecting duct concentrates only when vasopressin is present.
- Segment-specific vulnerability: S3 to ischaemia and toxins, TAL to hypoxia, podocyte to haemodynamic and immune injury, DCT to thiazides and calcineurin inhibitors.
- Rabbit kidneys show a clean axial demarcation of DCT, connecting tubule and cortical collecting duct; in humans and rodents the boundaries are far less absolute — quote this if asked about species differences.

↳ BR §Ch 6, p. 177

HIGH-YIELD · CLINICAL PEARLS

- ◆ **The cortex receives about 90% of renal blood flow; the medulla works at a PO_2 of only 10-20 mmHg, which is why the S3 segment and the thick ascending limb are the first to infarct in ischaemia.**
- ◆ The **collecting duct is not part of the nephron** — different embryological origin (ureteric bud). Say this in the first line.
- ◆ 85% short-looped cortical, 15% long-looped juxtamedullary — only the long loops make the medullary gradient.
- ◆ One transporter per segment wins marks: PCT = NHE3, TAL = NKCC2, DCT = NCC, CNT/CD = ENaC, IMCD = AQP2 + UT-A1.
- ◆ The macula densa belongs to the **thick ascending limb**, not the distal convoluted tubule.
- ◆ Draw the diagram first, then annotate — a labelled figure earns more than a paragraph.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.2 The Glomerular Filtration Barrier**2022-Dec P1 Q10(a)**

Components of Glomerular filtration barrier.

3

2022-Dec P1 Q10(b)

Physical characteristic of each component.

7

EXAMINER'S BLUEPRINT

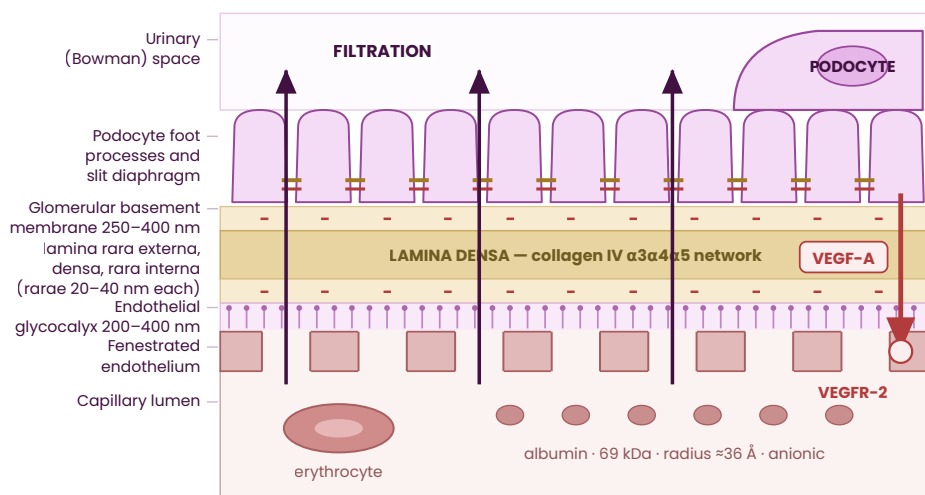
10 marks as a single 3+7 question — name all five layers with a diagram (3) + for each layer give thickness/pore size, charge, composition and what is lost in disease (5) + size- and charge-selectivity data and the Starling determinants of filtration (2).

(a) Components of the glomerular filtration barrier

3

The classical description is three-layered, but the modern composite barrier described in the primary source has **five** elements. Name all five — the two glycocalyx layers are what separate a 3-mark answer from a full one.

The composite glomerular filtration barrier and the podocyte VEGF-A → VEGFR-2 axis



THE PODOCYTE-ENDOTHELIAL VEGF AXIS

VEGF-A is released by the podocyte and crosses the GBM in the direction **OPPOSITE to filtration** to reach VEGFR-2 on the endothelial cell. It maintains the fenestrae — which in the adult have no diaphragms — and the glycocalyx, and so maintains the barrier.

VEGF BLOCKADE

Bevacizumab, ramucirumab, aflibercept; VEGFR-2 tyrosine-kinase inhibitors (sunitinib, pazopanib); soluble FLT-1 in pre-eclampsia → loss of fenestrae and glycocalyx → hypertension, proteinuria, thrombotic microangiopathy.

SIZE & CHARGE SELECTIVITY

Radius < 20 Å — freely filtered
Radius > 50 Å (≈ 4 nm) — largely excluded
Cationic · neutral · anionic at equal size
Albumin sieving coefficient: classically ≈ 0.0006, but 2-photon imaging suggests 0.02–0.04 (debated); filtered albumin is retrieved by proximal megalin / cubilin

Layer (lumen → urine)	Structure and dimensions	Molecular composition	Contribution to selectivity
Endothelial glycocalyx + endothelial coat	200–400 nm thick gel bridging and overlying the fenestrae	Heparan sulfate, hyaluronan, sialoproteins — strongly anionic	First, coarse macromolecular sieve; repels anionic albumin
Fenestrated glomerular endothelium	Circular pores 60–100 nm across, hourglass profile, 20–50% of the surface; NO diaphragms in the adult	VEGFR-2, TIE2, thrombomodulin, eNOS, PECAM-1	Excludes cells and platelets; the fenestra itself is not size-selective
Glomerular basement membrane (GBM)	250–400 nm in humans (≈ 326 nm ♀, ≈ 373 nm ♂; 132 nm in rat); three laminae, anionic sites every ≈ 60 nm	Collagen IV α3α4α5 (podocyte-derived), laminin-521 (α5β2γ1), nidogen-1, agrin and perlecan HS	Main size barrier at IgG and albumin radius; charge barrier COL4A3/4/5 → Alport
Podocyte foot processes and slit diaphragm	Interdigitating foot processes; slit 30–40 nm wide; SD strands ≈ 25 nm (NEPH1) and ≈ 40 nm (nephrin)	Nephrin-NEPH1 fishnet, podocin, CD2AP, TRPC6, ZO-1, P-cadherin, FAT1/2; apical podocalyxin	Final and most size-selective layer; effacement → nephrotic proteinuria (NPHS1/2, ACTN4)

A specialised glycocalyx also lies between the base of the foot processes and the GBM. The lamina rara interna faces the endothelium and the lamina rara externa the podocyte, each 20–40 nm thick. BR Ch 3 Fig. 3.12 p. 87 · Ch 4 Fig. 4.2 p. 116 · Ch 2 pp. 42–45 · Ch 24.

The composite glomerular filtration barrier.

Original schematic of the elements listed in BR §Ch 3, Fig. 3.12, p. 87 and BR §Ch 4, Fig. 4.2, p. 116.

- 1. Endothelial glycocalyx** — a fine meshwork of glycosaminoglycans covering the luminal endothelium and bridging the fenestrations.
- 2. Fenestrated glomerular endothelium.**
- 3. Glomerular basement membrane**, in three laminae.
- 4. Specialised sub-podocyte glycocalyx** between the base of the foot processes and the GBM.
- 5. Podocyte foot processes and the slit diaphragm** covering the filtration slits.

↳ BR §Ch 3, Fig. 3.12, p. 87

(b) Physical characteristics of each component

7

Layer-by-layer physical characteristics · BR §Ch 3, pp. 86–87; BR §Ch 4, pp. 115–117

LAYER	PHYSICAL CHARACTERISTICS	COMPOSITION	RELEVANCE IN DISEASE
Endothelial glycocalyx	Gel-like, thick, strongly anionic ; forms the <i>initial coarse barrier</i> to macromolecules	Glycosaminoglycans, proteoglycans, sialoproteins, adsorbed plasma proteins	Degraded in sepsis, diabetes and pre-eclampsia — early albuminuria before any structural change
Fenestrated endothelium	Fenestrae 60–100 nm, without diaphragms (unlike most other fenestrated capillaries); occupies a large fraction of the surface	Glomerular endothelial cells; maintained by podocyte-derived VEGF-A and angiopoietin-1	VEGF withdrawal (anti-VEGF drugs, pre-eclampsia) → loss of fenestrae, endotheliosis, thrombotic microangiopathy
Glomerular basement membrane	250–400 nm thick — much thicker than ordinary basement membrane because it is a fusion of the endothelial and podocyte membranes. Three laminae: <i>rara interna</i> , densa , <i>rara externa</i> . Strongly negatively charged. Provides the principal size-selective restriction together with the slit diaphragm	Mature GBM: laminin 521 , type IV collagen α3α4α5 (secreted only by podocytes), the heparan sulfate proteoglycan agrin , and nidogen. The immature GBM contains laminin 111 and collagen α1α2α1	Alport syndrome — mutation of COL4A3/4/5 → lamellation and splitting. Thin basement membrane nephropathy — including loss of podocyte prolyl-3-hydroxylase-2 (P3H2), which is required for GBM remodelling. Negative charge loss → albuminuria
Sub-podocyte glycocalyx	A specialised, highly charged layer between foot-process base and GBM; gold-nanoparticle studies show smaller particles permeate into the lamina densa and accumulate upstream at the base of the foot processes	Podocalyxin-rich anionic coat	Loss of podocalyxin reduces negative surface charge, foot processes lose mutual repulsion → effacement and proteinuria

LAYER	PHYSICAL CHARACTERISTICS	COMPOSITION	RELEVANCE IN DISEASE
Slit diaphragm	A modified adherens junction bridging a slit of about 40 nm ; cryo-electron tomography shows it is built of nephrin-neph1 heterodimers forming a flexible fishnet rather than a rigid zipper. Current evidence suggests the nephrin/neph1 layer is not itself the sieve but a context-dependent, dynamically regulated structure	Nephrin (NPHS1), neph1, podocin (NPHS2), FAT1/2, P-cadherin, TRPC6, CD2AP, ZO-1, MAGI-1, JAM4, MERTK, ITM2B	Congenital nephrotic syndrome of the Finnish type (NPHS1), steroid-resistant nephrotic syndrome (NPHS2, TRPC6, CD2AP). Effacement is the common final morphology of podocyte injury
Mesangium (supporting, not a filtering layer)	Pericyte-like contractile cells; no basement membrane between mesangium and endothelium	Actin, myosin, α -actinin; PDGFR α and ITGA8 markers	Contraction alters filtration surface area and therefore K_f ; expansion is the hallmark of diabetic and IgA nephropathy

Size and charge selectivity – the numbers

- Molecules with a radius **<20 Å** (inulin and smaller) are **freely filtered**; molecules larger than about **50 Å** are restricted.
- The albumin sieving coefficient is **≤ 0.001** — less than one-hundredth of one percent crosses under normal conditions. Filtered albumin is then reclaimed by the proximal **megalín/cubilín** pathway.
- **Size selectivity** resides mainly in the slit diaphragm and the GBM; **charge selectivity** resides in the negatively charged heparan sulfate proteoglycans of the GBM and the two glycocalyx layers. The lamina densa excludes molecules the size of IgG and albumin.
- Proteinuria in disease occurs when barrier integrity is lost and the filtered protein load **overwhelms the proximal reabsorptive transporters**.
- A labyrinthine **sub-podocyte space** beneath the cell body may modulate permeability and participate in glomerulosclerosis.

↳ BR §Ch 3, pp. 86–87

Forces governing filtration across the barrier

The Starling relationship at the glomerulus

$$J_v = L_p[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$$

Because the filtrate is nearly protein-free, $\pi_{BS} \approx 0$ and can be ignored. With $K_f = L_p \times S_f$ (hydraulic conductivity $\times$ filtration surface area):

$$\text{SNGFR} = K_f \times [(P_{GC} - P_{BS}) - \pi_{GC}] = K_f \times P_{UF}$$

BR §Ch 3, Eqs. 5–7, p. 87

HIGH-YIELD · CLINICAL PEARLS

- ◆ Name **five** layers, not three — the two glycocalyx layers are the modern additions and the examiner is looking for them.
- ◆ GBM **250–400 nm**; endothelial fenestrae **60–100 nm and undiaphragmed**; filtration slit **~40 nm**.
- ◆ Only podocytes make type IV collagen **$\alpha3\alpha4\alpha5$** — that is why Alport is a podocyte-GBM disease.
- ◆ Freely filtered $<20 \text{ \AA}$, restricted $>50 \text{ \AA}$, albumin sieving coefficient ≤ 0.001 .
- ◆ The slit diaphragm is a **nephrin-neph1 fishnet**, and current evidence says it is not itself the sieve.
- ◆ Mesangial contraction changes K_f — that is how mesangium influences GFR without being part of the barrier.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.3 The Renal Interstitium**2024 P1 Q10**

Structure & function of renal interstitium.

4+6

EXAMINER'S BLUEPRINT

10 marks — compartment anatomy and how it differs cortex versus medulla (2) + the resident cell populations with their markers (3) + functions: EPO, vitamin D, lymphatic drainage, medullary hyaluronan (3) + the interstitium in disease — fibrosis, IFTA as the strongest prognostic lesion (2).

Structure

4

Definition

The renal interstitium is the space between the basement membranes of the tubular epithelium and the peritubular capillaries — a **reactive compartment** containing resident cells, extracellular matrix and interstitial fluid.

BR §Ch 27, p. 790

- **Volume** — a small fraction of cortical volume (roughly 5–10%) but progressively larger through the medulla, reaching its greatest proportion at the papilla.
- **Cortical interstitium** — narrow, with a fine collagen network; contains the **peritubular capillaries** and the renal **lymphatics**.
- **Medullary interstitium** — expansive, containing the vasa recta, loops of Henle and collecting ducts embedded in a **hyaluronan-rich viscoelastic matrix** produced by type 1 interstitial cells, which form characteristic "bridges" between thin limbs and vasa recta.
- **Lymphatics** — begin as blind-ended initial capillaries, abundant in the **cortex rather than the medulla**; they either follow the main arteries and veins to the hilum or penetrate the capsule. They drain cortical interstitial fluid, which is largely capillary filtrate with a contribution reabsorbed from the tubules.

↳ BR §Ch 3, p. 81; BR §Ch 10, p. 285

Resident cell populations of the interstitium · BR §Ch 1, p. 7; BR §Ch 4, p. 120; BR §Ch 27, pp. 790–793

CELL	ORIGIN / MARKER	ROLE
Cortical and medullary interstitial fibroblasts	Foxd1 ⁺ stromal progenitor of the metanephric mesenchyme	Matrix production and turnover; the cortical peritubular fibroblast is the erythropoietin-producing cell

CELL	ORIGIN / MARKER	ROLE
Pericytes	Foxd1 ⁺ stromal progenitor	Capillary stabilisation; detach and transdifferentiate into myofibroblasts in injury
Type 1 medullary interstitial cells	Stromal progenitor	Secrete hyaluronan ; form bridges between thin limbs and vasa recta delimiting the nodal compartments
Renin-expressing cells	Foxd1 ⁺ stromal progenitor; metaplastic transformation of afferent arteriolar smooth muscle	Renin synthesis and release
Mesangial cells	Foxd1 ⁺ stromal progenitor	Intraglomerular support — a hybrid of pericyte/vascular smooth muscle and fibroblast
Resident mononuclear cells — dendritic cells and macrophages	Bone marrow derived	Immune surveillance; dendritic cells are the earliest producers of IL-6, TNF- α , MCP-1 and RANTES after ischaemia, and also mediate recovery through IL-10 and tolerance induction

Function

6

1. **Mechanical scaffold** — supports tubules and microvasculature and maintains the three-dimensional architecture on which countercurrent exchange depends.
2. **Endocrine** — the peritubular fibroblast produces **erythropoietin** under hypoxia-inducible factor control; this is the cell that fails in the anaemia of CKD and the cell that HIF prolyl-hydroxylase inhibitors target.
3. **Vitamin D activation** — 1 α -hydroxylation occurs in the proximal tubule, but interstitial injury and loss of functioning parenchyma are what translate into deficient calcitriol in CKD.
4. **Solute and fluid transit** — every reabsorbed solute and every secreted solute crosses the interstitium; interstitial composition sets the driving force for water reabsorption from the collecting duct.
5. **Osmotic gradient maintenance** — the medullary interstitium holds the NaCl and urea gradient; the hyaluronan matrix has been proposed as a **mechano-osmotic transducer**, storing energy from peristaltic compression of the papilla and releasing it to promote water absorption (see Topic 1.7).
6. **Lymphatic clearance** — interstitial fluid volume, intrarenal venous pressure and capillary permeability determine lymph formation; elevation of any of these causes **interstitial oedema and falling kidney function**, which is the mechanism of venous

congestion in cardiorenal syndrome. Kidney lymphangiogenesis is strongly associated with injury, inflammation and progression of fibrosis.

7. **Immune sentinel** — the resident dendritic cell/macrophage network initiates and then resolves the innate response; M1 macrophages drive injury, M2 macrophages drive repair.

↳ BR §Ch 3, p. 81; BR §Ch 27, pp. 790–793; BR §Ch 10, p. 285

The interstitium in disease

- **Interstitial fibrosis and tubular atrophy (IFTA)** is the final common pathway of all progressive kidney disease and the **single best histological predictor of outcome**, whatever the primary glomerular lesion.
- Sources of the myofibroblast: resident fibroblasts and pericytes (the dominant source), with contributions debated from epithelial-mesenchymal transition, endothelial-mesenchymal transition and bone-marrow-derived fibrocytes.
- Peritubular capillary rarefaction produces chronic hypoxia, which is itself profibrotic — the **chronic hypoxia hypothesis** of CKD progression.
- Dysregulated autophagy in tubular cells leads to progressive degeneration characterised by interstitial fibrosis.
- In transplantation, **i-IFTA** (inflammation in areas of fibrosis and atrophy) became a formal Banff lesion in the 2017/2019 updates and is required for the diagnosis of chronic active T cell-mediated rejection.

↳ BR §Ch 27, p. 790; BR §Ch 69, Table 69.4, p. 2028

HIGH-YIELD · CLINICAL PEARLS

- ◆ One-line definition: the space between tubular and capillary basement membranes — small in the cortex, expansive in the medulla.
- ◆ The **cortical peritubular fibroblast makes erythropoietin**. Name the cell, not just the kidney.
- ◆ Medullary hyaluronan comes from **type 1 interstitial cells** and may act as a mechano-osmotic transducer.
- ◆ Lymphatics are **cortical**, not medullary.
- ◆ **IFTA is the strongest histological predictor of outcome** in every glomerular disease — always say this.
- ◆ Peritubular capillary rarefaction → chronic hypoxia → fibrosis: the mechanism linking any injury to progression.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.4 Uromodulin in Health and Disease**2021 P1 Q7** Uromodulin in health and disease.

5+5

Jan 2025 P3 Q8(b) Role of uromodulin in health and kidney disease.

4

EXAMINER'S BLUEPRINT

10 marks as 5+5 — health: where it is made, its structure and its four physiological roles (5) + disease: ADTKD-UMOD, the GWAS link to CKD and blood pressure, stones and UTI, uromodulin as a biomarker of tubular mass (5).

(a) Uromodulin in health

5

What it is

Uromodulin, originally described as **Tamm-Horsfall protein**, is a GPI-anchored glycoprotein synthesised exclusively by the **thick ascending limb** of the loop of Henle (and the early distal convoluted tubule). It is cleaved from the apical membrane and is the **most abundant protein in normal human urine**, excreted at roughly 20–100 mg/day.

CCN §Ch 2, p. 18; BR §Ch 6, p. 177 (consensus for the excretion figure)

Physiological roles

- 1. Regulation of tubular sodium transport.** Studies in mice show uromodulin **activates $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransport (NKCC2)** to promote sodium reabsorption in the thick ascending limb. Locally synthesised uromodulin in the DCT, or shed uromodulin delivered from the TAL, also **activates NCC in DCT1**. It therefore sits alongside angiotensin II, aldosterone, vasopressin and potassium as a regulator of distal NaCl handling.
- 2. Defence against ascending urinary tract infection.** Uromodulin binds type 1 fimbriated *E. coli* and is voided in the urine, acting as a soluble decoy receptor.
- 3. Constitutive inhibition of calcium stone formation.** Polymerised uromodulin inhibits calcium oxalate crystal aggregation.
- 4. Maintenance of the water-impermeable TAL barrier** and a proposed immunomodulatory role in the interstitium.

↳ CCN §Ch 2, p. 18; BR §Ch 6, pp. 177, 181

BEYOND THE TWO TEXTBOOKS — CURRENT ACCEPTED POSITION

The textbooks state explicitly that "the role of uromodulin is not fully understood". Two further points are now standard teaching and are included here so the answer is complete: urinary uromodulin concentration is a **surrogate for functioning tubular mass and tubular health**, and **serum** uromodulin has emerged as a marker that falls early in CKD and predicts progression, whereas most tubular biomarkers rise. Present these as emerging rather than established.

(b) Uromodulin in disease

5

Uromodulin in disease · CCN §Ch 2, p. 18; CCN §Ch 50, p. 610; BR §Ch 6, p. 177

SETTING	MECHANISM	CLINICAL PICTURE
ADTKD-UMOD (autosomal dominant tubulointerstitial kidney disease, formerly familial juvenile hyperuricaemic nephropathy / medullary cystic kidney disease type 2)	Missense <i>UMOD</i> mutations, mostly affecting cysteine residues → misfolded uromodulin retained in the endoplasmic reticulum → ER stress and TAL cell injury	Autosomal dominant. Early-onset hyperuricaemia and gout , bland urine sediment, minimal proteinuria, normal or small kidneys with no or few cysts, slowly progressive CKD reaching kidney failure typically in the third to fifth decade. Family history is the clue
Common variants and CKD	Promoter variants raising <i>UMOD</i> expression	Genome-wide association studies have causally linked uromodulin to CKD and to increased blood pressure — one of the strongest and most reproducible loci in kidney genetics. Higher expression → more NKCC2 activity → salt-sensitive hypertension and CKD risk
Nephrolithiasis	Reduced or dysfunctional uromodulin removes a constitutive crystallisation inhibitor	Calcium oxalate stone formation
Urinary tract infection	Loss of the decoy-receptor effect	Increased susceptibility to ascending UTI
Cast nephropathy	Uromodulin is the matrix protein of urinary casts; monoclonal free light chains bind uromodulin in the distal nephron	Obstructing casts of myeloma kidney — the reason light-chain cast nephropathy is a distal lesion
AKI	Uromodulin released into the interstitium after injury modulates the innate response	Uromodulin-deficient mice show worse ischaemic injury; urinary uromodulin falls in AKI

HIGH-YIELD · CLINICAL PEARLS

- ◆ Made **only** by the thick ascending limb; the most abundant protein in normal urine.
- ◆ Four functions: activates **NKCC2** (and NCC), decoy receptor against type 1 fimbriated *E. coli*, inhibits calcium stone formation, maintains the TAL barrier.
- ◆ **ADTKD-UMOD** = dominant inheritance + early gout + bland sediment + minimal proteinuria + small kidneys. Do not miss the family history.
- ◆ GWAS has **causally** linked UMOD to CKD and to blood pressure — quote this; it is the modern part of the answer.
- ◆ Uromodulin is the matrix of casts — including the obstructing casts of myeloma kidney.
- ◆ Unlike most tubular biomarkers, uromodulin **falls** with disease because it reflects surviving tubular mass.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.5 Renal Autoregulation and Tubuloglomerular Feedback**2022-Jun P1 Q2(a)***Regulation of Renal Hemodynamics:* Describe briefly renal autoregulation.

5

2022-Jun P1 Q2(b)*Regulation of Renal Hemodynamics:* Applied aspect of tubuloglomerular feedback.

5

2022-Dec P1 Q2(a)

Renal auto-regulation.

5

EXAMINER'S BLUEPRINT

For a 5-mark “autoregulation” answer: definition and range (1) + the two mechanisms with their time constants (2) + what actually changes — afferent resistance, not efferent (1) + clinical correlates (1). For the 5-mark “applied aspect of TGF” answer, spend the marks on the applications listed in the last section, not on re-describing the mechanism.

(a) Renal autoregulation

5

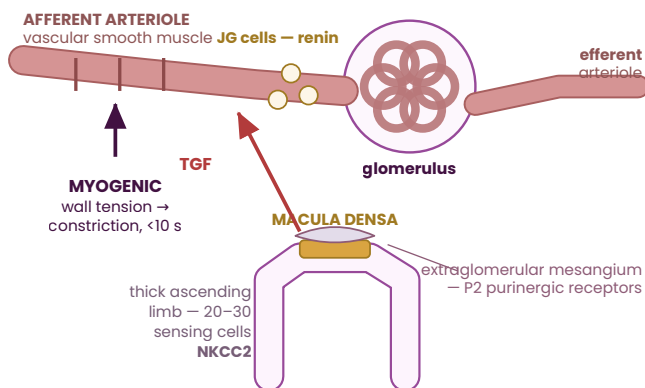
Definition

Renal autoregulation is the **intrinsic ability of the kidney** to respond to a perturbation by altering renal vascular resistance in the direction that minimises disruption of renal blood flow and GFR. It operates over a perfusion pressure range of roughly **80-180 mmHg** and requires no nerves or circulating hormones — it persists in the denervated and isolated perfused kidney.

BR §Ch 3, p. 94

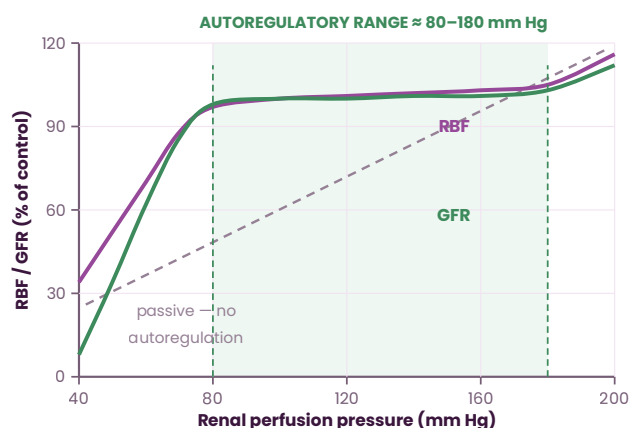
Renal autoregulation — the myogenic response and tubuloglomerular feedback

A · THE TWO EFFECTORS MEET AT THE AFFERENT ARTERIOLE



Efferent arterioles do NOT autoregulate. With sustained hypotension they may constrict through locally generated angiotensin II, which is why GFR is autoregulated more efficiently than renal blood flow.

B · RBF AND GFR ACROSS RENAL PERFUSION PRESSURE



BR Figs. 3.17 and 3.18: lowering perfusion pressure from 120 to 80 mm Hg causes only modest falls in glomerular blood flow and in P^c_c ; below ≈60 mm Hg both decline steeply. Afferent resistance falls as pressure falls (R_a is the autoregulating element) while efferent resistance is essentially unchanged.

C · THE TUBULOGLOMERULAR FEEDBACK SIGNALLING CHAIN



Furosemide blocks NKCC2 and abolishes TGF; A_1 -receptor knockout mice autoregulate poorly — both observations prove the chain.

	MYOGENIC MECHANISM	TUBULOGLOMERULAR FEEDBACK	MODULATORS OF TGF SENSITIVITY
Stimulus	Rise in vascular wall tension (stretch of the afferent arteriole)	Rise in luminal [NaCl] and flow at the macula densa	↑ SENSITIVITY
Sensor → effector	Mechanosensitive cation channels → L-type Ca^{2+} channels open	NKCC2 in macula densa → ATP / adenosine → A_1 R on the arteriole	Angiotensin II · NOS blockade · thromboxane · 20-HETE · volume contraction, dehydration, hypotension
Speed	3–10 s, first-order kinetics	30–60 s; oscillates at 0.025–0.033 Hz (≈3 cycles per minute)	↓ SENSITIVITY
Contribution	Carries the rapid component and is present in all organs (vasomotion); survives furosemide, which kills TGF	Carries the slower component and explains the high efficiency of RBF and GFR autoregulation	Nitric oxide · PGI_2 and PGE_2 · Ca^{2+} channel blockers · AT_1 blockade · P450 epoxigenase (EETs) · volume expansion

Both mechanisms act on the same effector — the afferent arteriole and the whole preglomerular tree — so they interact and are not simply additive. BR states that the two together account for most of the autoregulatory response and that a third mechanism has been proposed (uncertain). Autoregulation is blunted in diabetes (hyperfiltration), in the remnant kidney (prostaglandin-dependent) and in Dahl salt-sensitive hypertension. BR Ch 3, Figs. 3.17–3.21, pp. 94–99.

The two autoregulatory mechanisms and their modulators.

Original schematic based on BR §Ch 3, pp. 94–100 (Figs. 3.17–3.21).

1 · The two mechanisms

Myogenic reflex versus tubuloglomerular feedback · BR §Ch 3, pp. 94–100

	MYOGENIC MECHANISM	TUBULOGLOMERULAR FEEDBACK
Sensor	Afferent arteriolar vascular smooth muscle — stretch	Macula densa — luminal NaCl concentration and flow

	MYOGENIC MECHANISM	TUBULOGLOMERULAR FEEDBACK
Signal	Stretch → depolarisation → opening of voltage-gated Ca^{2+} channels → constriction	NaCl uptake through NKCC2 → membrane depolarisation → release of ATP (through large-conductance anion channels at the basolateral membrane) and, after degradation by 5'-nucleotidase, adenosine acting on the A1 receptor
Effector	Afferent arteriole	Afferent arteriole (same effector — the two mechanisms therefore interact)
Speed	<10 seconds , first-order kinetics, no rate-sensitive component	30-60 seconds ; spontaneous oscillations at 0.025-0.033 Hz (~3 cycles/min)
Specificity	Present in all organs (vasomotion)	Kidney-specific
Evidence	Rapid response component on sinusoidal pressure variation	Furosemide perfused into the macula densa segment abolishes the afferent constrictor response; deletion of the adenosine A1 receptor gene makes autoregulation less efficient

2 · What actually changes

- Autoregulation of glomerular blood flow and of P_{GC} is due **almost entirely to changes in afferent arteriolar resistance (R_A)**, with little or no change in efferent resistance (R_E).
- At **lower** perfusion pressures R_E may contribute to maintaining GFR — this is the physiological basis of angiotensin II-dependent efferent tone, and of the fall in GFR when a RAS inhibitor is given in renal artery stenosis or severe volume depletion.
- The mean glomerular transcapillary hydraulic pressure difference (ΔP) shows **almost perfect autoregulation** across the entire pressure range.
- Graded reduction of perfusion pressure from 120 to 80 mmHg causes only modest falls in P_{GC} and blood flow; below about **60-80 mmHg** the declines become pronounced — autoregulation is exhausted.
- Because both RBF and GFR autoregulate efficiently, the principal resistance changes must be **preglomerular**.

↳ BR §Ch 3, pp. 94–95

3 · Is there a third mechanism?

- The myogenic and TGF mechanisms account for most of the response, but a **third, slower system has been proposed**, and the interaction between the two known mechanisms is not simply additive — TGF appears primarily to modulate the **sensitivity** of the myogenic mechanism.

- **Connecting tubule glomerular feedback** is a second feedback loop: the connecting tubule lies in apposition to its own afferent arteriole, and perfusion of the connecting tubule with increased luminal NaCl causes afferent **vasodilatation** — the opposite of macula densa TGF.
- **Glomerulotubular balance** (proximal reabsorption rises as GFR rises) blunts the effect of GFR changes on distal delivery and so interacts with both.

↳ BR §Ch 3, pp. 99–100

(b) Applied aspects of tubuloglomerular feedback

5

1 • The physiological purpose

- TGF **stabilises the delivery of volume and solute to the distal nephron**. Early distal tubular fluid is hypotonic (~120 mOsm/kg); increases in flow raise its osmolality and NaCl concentration at the macula densa, which triggers afferent vasoconstriction.
- It is TGF that explains the **high efficiency** of RBF and GFR autoregulation: ↑ arterial pressure → ↑ RBF and P_{GC} → ↑ GFR → ↑ distal delivery → macula densa sensing → ↑ preglomerular resistance → GFR returns to normal.
- Over the long term, renin secretion controlled by the juxtaglomerular apparatus **resets TGF to a new sodium delivery rate** in accordance with sodium balance.

↳ BR §Ch 3, pp. 96–100

2 • Modulation of TGF sensitivity — the clinically useful part

- **Angiotensin II is the major regulator of TGF sensitivity** (through AT1), although it is **not the mediator** of TGF. Sensitivity is **enhanced** in dehydration, hypotension and hypovolaemia; **diminished** in volume expansion and salt loading, which allows greater distal delivery and corrects the expansion.
- Volume contraction enhances TGF sensitivity and, together with augmented proximal reabsorption, conserves fluid and electrolytes.
- **Neuronal NOS (NOS1) in the macula densa** generates NO, which vasodilates and **blunts** TGF; increased distal NaCl stimulates both nNOS and **COX-2**-derived PGE₂, which counteract TGF-mediated constriction.
- Sensitivity is **increased** by: angiotensin II, NOS blockade, thromboxane, 20-HETE. Sensitivity is **decreased** by: calcium-channel blockade, angiotensin blockade, cytochrome P450 blockade, NO and PGI₂.

↳ BR §Ch 3, pp. 98–100

Applied aspects — where TGF explains clinical phenomena · BR §Ch 3, pp. 96–100; BR §Ch 41, pp. 1186–1187 (hyperfiltration); BR §Ch 49 (diuretics)

CLINICAL PHENOMENON	TGF EXPLANATION
Loop diuretics do not lower GFR	Furosemide blocks NKCC2 at the macula densa, so the macula densa cannot sense the increased distal NaCl. TGF is abolished, the afferent arteriole does not constrict, and GFR is maintained despite a massive natriuresis. The same experiment is the classic proof of the mechanism
Thiazides and the "NCC brake"	Blockade downstream of the macula densa does not abolish TGF; distal delivery rises without the compensatory constriction being lost
Glomerular hyperfiltration in early diabetes	Increased proximal SGLT2-mediated sodium and glucose reabsorption reduces NaCl delivery to the macula densa. TGF interprets this as low GFR and vasodilates the afferent arteriole — raising P_{GC} and single-nephron GFR
How SGLT2 inhibitors protect the kidney	By blocking proximal sodium-glucose reabsorption they restore distal NaCl delivery , reactivate TGF, constrict the afferent arteriole and lower intraglomerular pressure. This is the accepted explanation for the acute "eGFR dip" and for the long-term benefit seen in CREDENCE, DAPA-CKD and EMPA-KIDNEY
The initial creatinine rise on RAS blockade	Efferent dilatation reduces P_{GC} ; a fall of up to 30% within 4 weeks is expected and is not a reason to stop the drug (KDIGO)
Hyperfiltration after uninephrectomy or in obesity	Reduced nephron number → increased single-nephron delivery and resetting of TGF at a higher flow → sustained hyperfiltration → adaptive FSGS
Preserved GFR in early AKI	TGF-mediated afferent constriction in response to increased distal delivery from injured proximal tubules contributes to the fall in GFR — "tubuloglomerular feedback-mediated" AKI
Calcineurin inhibitor nephrotoxicity	Afferent vasoconstriction with enhanced TGF sensitivity; calcium-channel blockers, which reduce TGF sensitivity, are protective
Adenosine antagonists	A1 receptor blockade reduces afferent resistance and raises ΔP ; pre-treatment with an AT1 antagonist prevents this — showing the angiotensin dependence of the response

KDIGO 2024 CKD — THE PRACTICAL READ-OUT

The acute decline in eGFR after starting an SGLT2 inhibitor or a RAS inhibitor is a **haemodynamic, TGF-mediated** effect and is **not** an indication to stop the drug. KDIGO 2024 advises continuing unless the fall exceeds about 30% and advises re-checking creatinine and potassium 2–4 weeks after initiation or dose increase. *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, Kidney Int 2024;105(4S):S117–S314* — as reported in BR §Ch 41, Table 41.5, p. 1194.

HIGH-YIELD · CLINICAL PEARLS

- ◆ Autoregulation range **80-180 mmHg**; the resistance that changes is the **afferent**, not the efferent.
- ◆ Myogenic **<10 s**, TGF **30-60 s** oscillating at 0.025-0.033 Hz. Quote the time constants — few candidates do.
- ◆ TGF mediator = **ATP and adenosine acting on the A1 receptor**. Angiotensin II is the **modulator**, not the mediator.
- ◆ **Furosemide abolishes TGF** — that is both the proof of the mechanism and the reason loop diuretics do not drop GFR.
- ◆ The SGLT2-inhibitor story is the highest-yield applied answer: proximal reabsorption ↓ → distal NaCl ↑ → TGF restored → afferent constriction → lower P_{GC} → the eGFR dip and the long-term protection.
- ◆ Connecting tubule glomerular feedback causes afferent **vasodilatation** — the mirror image of macula densa TGF.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.6 Determinants of GFR and Renal Functional Reserve**2023-Apr P1 Q8(α)**

What are the determinants of glomerular filtration rate?

5

2022-Dec P3 Q2(α)

Renal function reserve.

5

EXAMINER'S BLUEPRINT

Determinants (5): write the Starling equation, then take each of its four terms in turn and name the clinical condition that alters it. Renal functional reserve (5): definition, how it is measured, the normal value, and why it matters — donors, AKI risk, low nephron endowment.

(α) Determinants of glomerular filtration rate

5

The governing equation

$$\text{SNGFR} = K_f \times [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})] = K_f \times P_{UF}$$

where $K_f = L_p \times S_f$ (hydraulic conductivity $\times$ filtration surface area). Because the filtrate is nearly protein-free, $\pi_{BS} \approx 0$. Whole-kidney GFR = SNGFR $\times$ number of functioning nephrons.

BR §Ch 3, Eqs. 5–7, p. 87

The five determinants and what changes each one · BR §Ch 3, pp. 86–95

DETERMINANT	PHYSIOLOGY	RAISED BY	LOWERED BY
1. Glomerular capillary hydraulic pressure (P_{GC})	The principal driving force; set by the balance of afferent and efferent arteriolar resistance	Afferent dilatation (prostaglandins, NO, hyperglycaemia/SGLT2 activity, high protein load), efferent constriction (angiotensin II)	Afferent constriction (NSAIDs, calcineurin inhibitors, adenosine, endothelin, noradrenaline, hypercalcaemia), efferent dilatation (ACE inhibitor/ARB), systemic hypotension below the autoregulatory range

DETERMINANT	PHYSIOLOGY	RAISED BY	LOWERED BY
2. Bowman space hydraulic pressure (P_{BS})	Opposes filtration; normally low	—	Rises in urinary tract obstruction, intratubular obstruction (cast nephropathy, crystal nephropathy, tubular debris in ATN) and abdominal compartment syndrome — each lowers GFR
3. Glomerular capillary oncotic pressure (π_{GC})	Rises along the capillary as protein-free filtrate leaves; opposes filtration and may reach filtration equilibrium	Hypergammaglobulinaemia, haemoconcentration, low plasma flow (more time to equilibrate)	Hypoalbuminaemia; high renal plasma flow delays equilibrium and thereby raises GFR
4. Renal plasma flow (Q_A)	Determines how quickly π_{GC} rises along the capillary — a major determinant whenever filtration equilibrium is approached	Volume expansion, vasodilatation, pregnancy, high protein intake	Volume depletion, heart failure, hepatorenal physiology, renal artery stenosis
5. Ultrafiltration coefficient ($K_f = L_p \times S_f$)	Hydraulic conductivity of the barrier $\times$ filtration surface area; adjusted physiologically by mesangial cell contraction , which alters surface area	Mesangial relaxation (ANP, dopamine, PGE_2)	Mesangial contraction (angiotensin II, endothelin, vasopressin), podocyte loss and foot-process effacement, mesangial expansion, glomerulosclerosis, crescents, membrane thickening

- A sixth, often forgotten determinant at the whole-kidney level is the **number of functioning nephrons** — see Topic 1.10.
- Filtration is driven by the exquisite differential regulation of **preglomerular and postglomerular resistance**: the glomerulus is the only capillary bed nestled between two arterioles, which is what allows independent control of flow and pressure.
- A rise in protein intake raises GFR — the basis of the renal functional reserve test below.

↳ BR §Ch 3, pp. 86, 94; BR §Ch 3, Fig. 3.4, p. 81

(b) Renal functional reserve

5

DEFINITION — STANDARD ACCEPTED TEACHING, NOT VERBATIM IN EITHER TEXTBOOK

Renal functional reserve (RFR) is the capacity of the kidney to increase GFR above its resting baseline in response to a physiological stimulus. It is calculated as **$\text{RFR} = \text{stress GFR} - \text{baseline GFR}$** . In a healthy young adult it is of the order of **20–35 mL/min/1.73 m²** (roughly a 20–30% rise), and it is recruited by increasing filtration in already-perfused nephrons and by recruiting reserve filtration capacity, not by making new nephrons. Both textbooks describe the underlying physiology and use the term (BR §Ch 20, Fig. 20.2, p. 601) but neither gives a formal definition, so the accepted definition is supplied here.

1 · The physiological basis

- A **protein load** raises GFR: creatinine clearance rises measurably across the range of protein intake in healthy people, and the effect is **blunted in the elderly** — the classic demonstration that reserve declines with age.
- Mechanism: an amino acid or protein load reduces proximal NaCl reabsorption and resets tubuloglomerular feedback, causing afferent vasodilatation, a rise in P_{GC} and glomerular plasma flow, and therefore a rise in GFR.
- Vasodilatory mediators implicated include glucagon, NO and prostaglandins.

↳ BR §Ch 3, Fig. 3.4, p. 81

2 · How it is measured

- Measure baseline GFR after an overnight fast.
- Apply the stress: an **oral protein load** (1–1.2 g/kg of cooked red meat) or an **intravenous amino acid infusion**; dopamine has also been used.
- Re-measure GFR at intervals over the next 1–3 hours and take the peak value.
- Report RFR as the absolute increment. **Absent or low reserve in a person with a normal resting GFR is the abnormality** — the resting value can be entirely normal because surviving nephrons are already hyperfiltrating.

↳ Consensus methodology; the protein-load principle is from BR §Ch 3, p. 81

3 · Why it matters clinically

Renal functional reserve across the nephron-number spectrum · BR §Ch 20, Fig. 20.2 and Table, p. 601

	LOW NEPHRON NUMBER	AVERAGE	HIGH NEPHRON NUMBER
Renal functional reserve	None or poor	Sufficient	Excellent
Pre-eclampsia risk	High	Low	Low
Onset of hypertension	Early in life	Late in life	None or very late

	LOW NEPHRON NUMBER	AVERAGE	HIGH NEPHRON NUMBER
Proteinuria for disease stage	High	Adequate	Low
Trigger for sudden creatinine rise or AKI	Mild insult	Modest insult	Severe insult
CKD progression	Fast	Slow	Minimal
Obesity	High risk of adaptive FSGS	Low risk	No adaptive FSGS
Diabetes	Early nephropathy	Late nephropathy	No nephropathy
Glomerulonephritis	Fast progression	Slow	Minimal
Post-donation kidney failure risk	High	Low	No risk

- **Living kidney donor evaluation** — a normal resting GFR with poor reserve identifies the donor whose kidney is already working at capacity.
- **Prediction of AKI** — reduced reserve before cardiac surgery or contrast exposure identifies the patient in whom a modest insult will produce a large fall in GFR.
- **Unmasking subclinical CKD** — reserve is lost before resting GFR falls, so it detects nephron loss that creatinine cannot.
- **Follow-up after AKI** — apparent "complete recovery" of creatinine with loss of reserve identifies residual nephron loss and future CKD risk.
- Reserve is reduced physiologically in **pregnancy** (because GFR is already elevated) and in **ageing**.

↳ BR §Ch 20, p. 601; BR §Ch 3, p. 81

HIGH-YIELD · CLINICAL PEARLS

- ◆ Write the Starling equation first. Every mark in the “determinants” question hangs off it.
- ◆ The glomerulus is the **only capillary bed between two arterioles** — that is what allows flow and pressure to be set independently.
- ◆ K_f is physiologically regulated by **mesangial contraction**, pathologically destroyed by podocyte loss and sclerosis.
- ◆ Raised P_{BS} is the mechanism of obstruction, cast nephropathy and abdominal compartment syndrome.
- ◆ $RFR = \text{stress GFR} - \text{baseline GFR}$; normal $\approx 20\text{--}35 \text{ mL/min/1.73 m}^2$. **Lost reserve with a normal resting GFR is the abnormal finding.**
- ◆ Low nephron endowment = no reserve = mild insult causes AKI, early hypertension, adaptive FSGS with obesity, and high post-donation risk.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.7 Urine Concentration and Dilution — the Countercurrent Multiplier**2022-Jun P1 Q3** Countercurrent multiplier mechanism in the kidney.

10

2022-Dec P1 Q4(b) Concentration & dilution mechanism of urine.

5

Jan 2025 P1 Q9(a) Water handling by the normal kidney.

5

EXAMINER'S BLUEPRINT

10 marks — anatomical substrate (2) + single effect and multiplication with a diagram (3) + solute composition and urea recycling (2) + the unresolved inner-medullary problem (1.5) + determinants and clinical correlates (1.5). For the 5-mark version drop the three inner-medullary hypotheses to one line each and keep the diagram.

The principle

Countercurrent multiplication (Kuhn and Ryffel, 1942) states that osmotic pressure is raised along **parallel but opposing flows in nearby tubes joined by a hairpin turn**. A small transverse transfer of solute between the limbs — the **single effect** — is repeated at every level and is thereby *multiplied* into a large gradient along the axis of flow. Hargitay and Kuhn identified the loop of Henle as exactly such a hairpin in 1951; Kuhn and Ramel then showed mathematically that active NaCl transport from the thick ascending limb could serve as the single effect.

BR §Ch 10, pp. 283–284

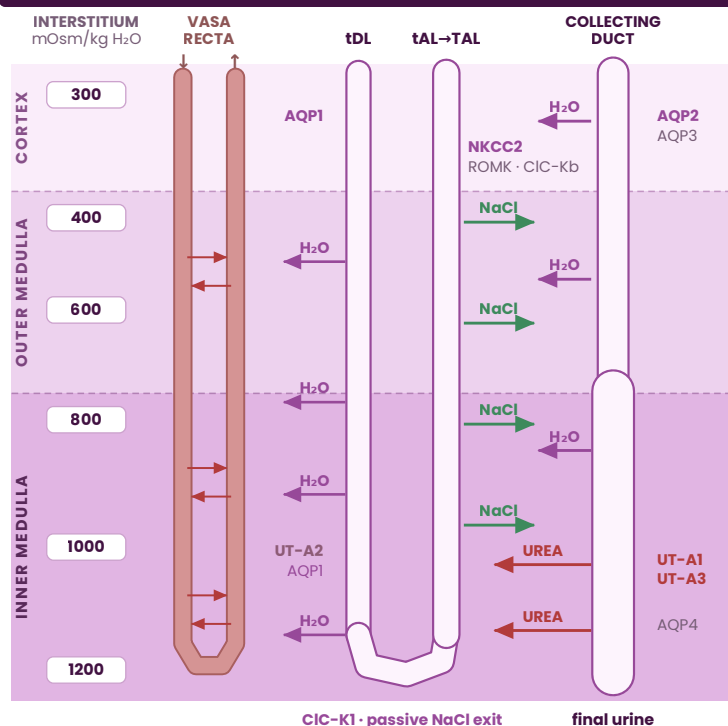
1 · Where dilution and concentration actually happen

- **Proximal tubule fluid is always isosmotic** with plasma, whether the kidney is diluting or concentrating.
- The **loop of Henle is the major site of dilution**, and dilution occurs there *regardless* of whether the final urine is dilute or concentrated.
- During water diuresis, further dilution occurs in the collecting duct by active NaCl reabsorption; early distal fluid is hypotonic (~120 mOsm/kg) and stays hypotonic when AVP is low.
- During antidiuresis the **collecting duct system is the chief site of concentration**, purely by osmotic equilibration with the hypertonic interstitium — **concentration is achieved by water absorption, not by solute addition**.

- Typical osmolalities: proximal tubule 290 whether AVP is high or low; early distal 140; late distal 290 (high AVP) or 100 (low AVP); loop tip 1200 (high AVP) or 600 (low AVP); terminal IMCD 1150 with high AVP.

↳ BR §Ch 10, pp. 274, 283

Countercurrent multiplication in the loop of Henle and osmotic equilibration in the collecting duct



THE SINGLE EFFECT, MULTIPLIED

- SINGLE EFFECT** — the water-impermeable thick ascending limb pumps NaCl into the interstitium through NKCC2. At any one level this creates a transverse gradient of only ≈200 mOsm/kg — the limit of what the pump can sustain.
- MULTIPLICATION** — the hairpin countercurrent geometry converts that small transverse difference into a large axial gradient: 300 mOsm/kg in the cortex rising to 1200 mOsm/kg at the papillary tip.
- EQUILIBRATION** — with vasopressin, AQP2 is inserted into the apical membrane of the collecting duct and water leaves down the gradient until duct fluid equals the interstitium. Without vasopressin the duct stays impermeable and dilute urine is excreted.

UREA RECYCLING — UT-A1 / UT-A3 / UT-A2 / UT-B

Urea supplies a large share of inner medullary osmolality. UT-A1 and UT-A3 (AVP- and hypertonicity-stimulated) let urea out of the terminal IMCD; UT-A2 returns it to the thin descending limb; UT-B in the descending vasa recta and in red cells completes the recycle. The cortical, outer medullary and initial inner medullary duct are urea-impermeable, so water removal there concentrates urea in the lumen first. A low-protein diet lowers maximal urine osmolality.

VASA RECTA — COUNTERCURRENT EXCHANGE

Hairpin vasa recta run alongside the loops. Solute enters and water leaves the descending vessel; the reverse happens in the ascending vessel, so the axial gradient is preserved rather than washed out. AQP1 and UT-B carry the exchange. High medullary blood flow — in volume expansion, for example — washes it out.

Site	High AVP (antidiuresis)	Low AVP (water diuresis)	Why
Plasma / cortical interstitium	290	290	Isosmotic reference
End of proximal tubule	290	290	Proximal fluid is ALWAYS isosmotic — water follows solute
Bend of the loop of Henle	1200	600	Water abstraction in the thin descending limb
Early distal tubule	140	140	ALWAYS hypotonic — the TAL dilutes regardless of AVP
Late distal tubule	290	100	Reaches plasma level only during antidiuresis
Terminal IMCD / final urine	1150	65	Hypertonic with AVP, maximally dilute without it
Vasa recta at the papilla	1200	attenuated	Blood equilibrates with the interstitium it perfuses

Values from BR Ch 10, Fig. 10.7, p. 274 (rat, mOsm/kg H₂O); mechanism from Figs. 10.13–10.19, pp. 279–285. The mechanism of the inner medullary gradient is still unresolved — a passive (Kokko–Rector) model, an external-solute model and a hyaluronan model are all proposed.

Countercurrent multiplication in the loop of Henle and osmotic equilibration in the collecting duct.

Original schematic based on BR §Ch 10, pp. 283–286 (Figs. 10.17–10.19).

2 · The single effect and its multiplication

1. NaCl is **actively reabsorbed from the thick ascending limb** by NKCC2. Because the limb is water-impermeable, luminal osmolality falls below that of the peritubular fluid and interstitial osmolality rises. This is the single effect and the energy source of the whole system.
2. The hypertonic interstitium **withdraws water from the water-permeable descending limb** (AQP1 in long loops), concentrating the fluid travelling towards the bend.
3. That more concentrated fluid enters the ascending limb, where NaCl is extracted again — and the cycle repeats at every level.
4. Because the flows are opposed and continuous, a small transverse difference becomes a large axial gradient: ~290 mOsm/kg in the cortex to ~1200 mOsm/kg at the papillary tip.
5. Two theoretical modes are illustrated (BR Fig. 10.18): **(A) solute addition** from ascending to descending flow, and **(B) water withdrawal** from the descending flow. Current evidence favours NaCl addition to the interstitium with water withdrawal from long descending limbs and collecting ducts, *without* obligatory water absorption from short descending limbs (Fig. 10.19).
6. The increasing gradient with depth requires greater and faster NaCl absorption deeper in the outer medulla, supported by higher Na⁺-K⁺-ATPase activity, and is helped by the water already removed higher up.

↳ BR §Ch 10, pp. 283–286

3 · What the gradient is made of, and urea recycling

- The two principal solutes are **NaCl and urea**. The rise in NaCl occurs predominantly in the **outer medulla**; the rise in urea occurs predominantly in the **inner medulla**.
- The axial gradient is steeper in the outer medulla and papilla than in the outer part of the inner medulla, and is steepest in the papilla where it rises almost exponentially.
- AVP up-regulates **UT-A1 and UT-A3** in the terminal inner medullary collecting duct, delivering urea to the interstitium; UT-A2 in the descending limb returns it to the tubule. The urea-permeable loops act as an effective **countercurrent urea exchanger**.
- Clinical corollary: **low protein intake reduces urea generation and therefore maximal urine osmolality** — the malnourished patient cannot concentrate.

↳ BR §Ch 10, Fig. 10.17 p. 284; pp. 279–285

4 · The unresolved problem of the inner medulla

Thin ascending limbs in the inner medulla are thin-walled and **do not actively transport NaCl**, yet a substantial axial gradient is generated there in antidiuresis. The primary source states explicitly that this is unresolved and sets out three hypotheses.

Three hypotheses for the inner medullary gradient · BR §Ch 10, pp. 284–285

HYPOTHESIS	MECHANISM	EVIDENCE AGAINST
1. Passive mechanism (Kokko & Rector; Stephenson)	Rapid urea reabsorption from the IMCD raises interstitial urea → osmotic water withdrawal from the thin descending limb → high luminal NaCl at the bend → passive NaCl exit from the thin ascending limb = a single effect that is then multiplied	Requires thin descending limbs permeable to water but not urea, yet high urea permeability is measured in both thin limbs ; little or no osmotic water permeability in the lower thin descending limb; in UT-A1/A3 knockout mice inner medullary urea accumulation is lost but NaCl accumulation is preserved. Layton and colleagues re-evaluated the model with measured permeabilities and three-dimensional architecture and concluded that water absorption from descending limbs is not necessary
2. External solute (Jen & Stephenson)	Continuous addition of another osmotically active solute generated in the inner medulla — proposed as lactate from anaerobic glycolysis, two lactate ions per glucose consumed	Modelling by Zhang & Edwards and by Chen et al. predicts that vascular countercurrent exchange restricts glucose delivery to the deep inner medulla, limiting lactate generation exactly where osmolality is highest
3. Hyaluronan as a mechano-osmotic transducer (Schmidt-Nielsen; Knepper)	The inner medullary interstitium is a compressible, viscoelastic hyaluronan matrix made by type 1 interstitial cells. Peristaltic compression of the papilla stores mechanical energy; elastic recoil on decompression promotes water absorption from thin descending limbs and collecting ducts. Consistent with the nodal compartments of Pannabecker and Dantzler	In the rat, the lower 60% of inner medullary descending limbs are water-impermeable, so water is unlikely to be absorbed where osmolality is highest

5 · Countercurrent exchange by the vasa recta

- Ascending vasa recta collect the NaCl absorbed from the loops and the water absorbed from long descending limbs and collecting ducts.
- As ascending vasa recta fluid moves cortically its osmolality exceeds that of adjacent descending limbs and collecting ducts, so it is **progressively diluted** while giving up NaCl to and taking water from the interstitium.
- Loops of Henle **multiply** (generate); vasa recta **exchange** (preserve). Increased medullary blood flow washes the gradient out.

↳ BR §Ch 10, p. 284, Fig. 10.19 p. 286

6 · Determinants of concentrating ability

- **Delivery of NaCl and water to the loop** — sets the ceiling on TAL transport.
- **Volume of tubular fluid delivered to the medullary collecting duct** — an under-appreciated determinant: too much saturates water reabsorption and dilutes the interstitium; too little permits sustained equilibration.
- AVP and collecting-duct water permeability (AQP2); integrity of the medulla; medullary blood flow.
- **Sex** — urine osmolality is generally higher in men, suggesting differences in thirst and AVP action.
- **Age** — maximal concentrating ability declines; older healthy men have *higher* AVP but *lower* urine osmolality, indicating reduced sensitivity; aged rats show reduced aquaporins, urea transporters and V2 receptor.

↳ BR §Ch 10, p. 286

Clinical correlates worth one line each: loop diuretics abolish the single effect → isosthenuria; osmotic diuresis and high urine flow → medullary washout; sickle cell disease and medullary interstitial disease → hyposthenuria; lithium and hypercalcaemia → nephrogenic DI through AQP2 down-regulation; low protein intake → reduced urea and reduced maximal osmolality.

Water handling by the normal kidney — the whole sequence in one answer 5

1. **FILTRATION.** About **180 L of water is filtered every day** at a GFR of 125 mL/min. Final urine volume is **1-2 L**, so **more than 99% of filtered water is reabsorbed**. The kidney therefore handles water by deciding how much of an enormous filtered load to return, not by secreting it.
2. **PROXIMAL TUBULE — 65-70%, ISO-OSMOTIC and OBLIGATORY.** Water follows sodium, glucose, amino acids and bicarbonate passively through **AQUAPORIN-1** in both apical and basolateral membranes and by the paracellular route. This fraction is **not regulated** and cannot be varied to defend tonicity.
3. **THIN DESCENDING LIMB — 15%.** Water-permeable (AQP1) but **solute-impermeable**, so fluid entering the hairpin is concentrated by equilibration with the hypertonic medullary interstitium.
4. **THICK ASCENDING LIMB — the DILUTING SEGMENT. Water-IMPERMEABLE,** while **NKCC2** removes sodium, potassium and chloride. Tubular fluid leaves it **HYPO-osmolar (about 100 mOsm/kg)** whatever the state of hydration — this is why the kidney can always make dilute urine, and why a loop diuretic destroys both concentration and dilution.
5. **DISTAL CONVOLUTED TUBULE.** Also water-impermeable; further dilution by **NCC**.

6. **COLLECTING DUCT — the ONLY REGULATED SEGMENT.** Water permeability here is set by **VASOPRESSIN**: V2 receptor → Gs → adenylyl cyclase → cyclic AMP → protein kinase A → phosphorylation of **AQUAPORIN-2** at Ser256 → exocytic insertion of AQP2 into the apical membrane. Water then exits basolaterally through the constitutively expressed **AQP3 and AQP4**. Withdrawal of vasopressin causes AQP2 to be retrieved by endocytosis within minutes.
7. **THE DRIVING FORCE — the COUNTERCURRENT SYSTEM.** Water can only move if there is a gradient to move down: the **countercurrent multiplier** of the loop of Henle generates the corticomedullary gradient (from 300 mOsm/kg in cortex to **1200 mOsm/kg** at the papilla), **UREA RECYCLING** through UT-A1/A3 in the inner medullary collecting duct contributes roughly half of it, and the **vasa recta act as a countercurrent EXCHANGER** that preserves it.

The three requirements for concentrating urine — and the three ways it fails · BR §Ch 10 and §Ch 15; CCN §Ch 9

REQUIREMENT	HOW IT FAILS
1. A hypertonic medullary interstitium	Loop diuretics; osmotic diuresis; medullary interstitial disease; low protein intake reducing urea; high urine flow washing out the gradient
2. Vasopressin secreted in response to osmolality	CENTRAL diabetes insipidus — trauma, surgery, tumour, infiltration, genetic
3. A collecting duct able to respond to it	NEPHROGENIC diabetes insipidus — lithium, hypercalcaemia, hypokalaemia, AVPR2 or AQP2 mutation, post-obstructive, sickle cell

Maximum concentrating capacity is about 1200 mOsm/kg and maximum diluting capacity about 50 mOsm/kg. With an obligatory daily solute load of roughly **600-900 mOsm**, this sets the **minimum obligatory urine volume at about 500 mL** and the **maximum water excretion at roughly 12-18 L/day**. Everything clinical about water — the limit on free-water excretion in beer potomania, the polyuria of osmotic diuresis, the water restriction that treats SIADH — follows from those two limits.

HIGH-YIELD · CLINICAL PEARLS

- ◆ The **single effect** = active, water-impermeable NaCl reabsorption in the TAL. Everything else multiplies or preserves it.
- ◆ NaCl builds the **outer** medullary gradient; urea builds the **inner** medullary gradient.
- ◆ The loop **always** dilutes; the collecting duct concentrates only with AVP — and by water removal, not solute addition.
- ◆ Loops **multiply**, vasa recta **exchange**.
- ◆ Name the three inner-medullary hypotheses — passive, external solute (lactate), hyaluronan — and say the question is unresolved.
- ◆ Two flow determinants: too much fluid to the collecting duct washes out the gradient; too little allows full equilibration.
- ◆ **180 L filtered, 1-2 L excreted — over 99% of filtered water is reabsorbed.**
- ◆ **Proximal tubule 65-70% iso-osmotic and OBLIGATORY; thin descending limb 15%; the collecting duct is the ONLY REGULATED segment.**
- ◆ **The thick ascending limb is the DILUTING SEGMENT — water-impermeable, fluid leaves it at about 100 mOsm/kg whatever the hydration state.**
- ◆ **Vasopressin → V2 → cAMP → PKA → AQP2 phosphorylation at Ser256 → apical insertion. AQP3 and AQP4 are constitutive on the basolateral side.**
- ◆ **Urea recycling supplies roughly half the medullary gradient; the vasa recta preserve it as a countercurrent EXCHANGER.**
- ◆ **Maximum 1200 mOsm/kg, minimum 50 mOsm/kg; obligatory solute load 600-900 mOsm/day gives a minimum urine volume of about 500 mL.**

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.8 Aquaporins**2022-Dec P2 Q10(a)**

Role aquaporins in kidney.

4

2023-Oct P1 Q6(b)

Aquaporins.

4

EXAMINER'S BLUEPRINT

4 marks — a table of the renal aquaporins with site and regulation (2) + the AVP-V2R-AQP2 trafficking cascade (1) + the diseases of each, especially AQP2 and nephrogenic DI (1). A table wins this question outright.

What they are

Aquaporins are integral membrane water channels. **AQP1 was identified in 1991 by Peter Agre** and colleagues, work that won the Nobel Prize in Chemistry in 2003. They allow water to cross membranes at rates far above simple diffusion and give each nephron segment its characteristic water permeability.

BR §Ch 10, p. 273

Aquaporins of the kidney · BR §Ch 10, pp. 273–278

CHANNEL	SITE	MEMBRANE / REGULATION	DISEASE ASSOCIATION
AQP1	Proximal tubule; thin descending limb of long-looped nephrons only (not short loops); descending vasa recta	Constitutive, both apical and basolateral	Proximal tubule fluid absorption is markedly reduced in AQP1-knockout mice. Human AQP1 deficiency (Colton-null) causes an inability to concentrate maximally but is otherwise silent
AQP2	Collecting duct principal cells	Apical — AVP-regulated by shuttling between intracellular vesicles and the plasma membrane. Also basolateral in some regions, increased by AVP and by chronic aldosterone	Autosomal dominant and autosomal recessive nephrogenic diabetes insipidus. Down-regulated in lithium toxicity, hypercalcaemia, hypokalaemia and obstruction; up-regulated in SIADH, cirrhosis, heart failure and pregnancy
AQP3	Collecting duct principal cells	Basolateral, constitutive (AVP increases expression)	Exit pathway for water; knockout causes a concentrating defect

CHANNEL	SITE	MEMBRANE / REGULATION	DISEASE ASSOCIATION
AQP4	Collecting duct principal cells, predominantly inner medullary	Basolateral, constitutive	Exit pathway; also the target antigen in neuromyelitis optica
AQP7	Proximal tubule (S3), apical	Constitutive; also glycerol-permeable (aquaglyceroporin)	Glyceroluria
AQP11	Proximal tubule, intracellular (endoplasmic reticulum)	Constitutive	Knockout produces proximal tubule vacuolisation and polycystic kidneys in mice

The AVP → AQP2 cascade — learn this sequence

1. AVP binds the **V2 receptor on the basolateral membrane** of the principal cell.
2. Gs activation → **adenylyl cyclase 6** → rise in cAMP (mice lacking AC-6 have significant water balance abnormalities).
3. **Protein kinase A** phosphorylates AQP2 (serine 256 is the critical residue) and UT-A1.
4. Phosphorylated AQP2 accumulates in the **apical plasma membrane** by SNARE-mediated exocytosis (VAMP-2, VAMP-3, VAMP-8, syntaxin 3, SNAP23), and water then exits basolaterally through AQP3 and AQP4.
5. **Termination:** β -arrestin binds the phosphorylated V2R → ubiquitylation → clathrin adaptor AP-2 → clathrin-mediated endocytosis. Cytosolic phosphodiesterases destroy cAMP, although the V2R can continue to signal from endosomes after internalisation.
6. Longer-term regulation: AVP raises AQP2 **transcription** through CREB and other factors, with epigenetic control by H3K27 acetylation across the AQP2 promoter and post-transcriptional control by microRNAs. H3K27 acetylation is decreased in hypokalaemia-induced nephrogenic DI, where AQP2 expression is low.

↳ BR §Ch 10, pp. 273–278

Aquaporin-2 expression in disease — the two directions · BR §Ch 10, pp. 273–278; CCN §Ch 9, Fig. 9.6, p. 113

AQP2 DOWN-REGULATED → POLYURIA	AQP2 UP-REGULATED → WATER RETENTION
Nephrogenic diabetes insipidus (congenital and acquired)	Syndrome of inappropriate antidiuresis
Lithium	Congestive cardiac failure
Hypercalcaemia	Cirrhosis with ascites
Hypokalaemia	Pregnancy
Bilateral ureteric obstruction and post-obstructive diuresis	Nephrotic syndrome
Ischaemic and post-ischaemic acute kidney injury	—

TWO POINTS WORTH ADDING

Vaptans (tolvaptan, conivaptan) are V2 receptor antagonists that block this cascade and produce a solute-free water diuresis — the therapeutic mirror image of the pathway above, and the mechanism by which tolvaptan also slows cyst growth in ADPKD (*KDIGO 2025 ADPKD guideline, Kidney Int 2025;107(2S):S1–S239*). **Urinary exosomal AQP2** is being studied as a non-invasive readout of collecting-duct AVP action.

HIGH-YIELD · CLINICAL PEARLS

- ◆ **AQP1 = constitutive, AQP2 = AVP-regulated.** That single contrast answers most of the question.
- ◆ AQP1 is present in the thin descending limb of **long loops only** — a favourite detail.
- ◆ AQP2 apical, AQP3 and AQP4 basolateral. Water must enter *and* leave.
- ◆ PKA phosphorylation at **serine 256** is what drives apical insertion.
- ◆ AQP2 down in lithium, hypercalcaemia, hypokalaemia and obstruction; up in SIADH, cirrhosis, heart failure and pregnancy.
- ◆ Agre, 1991, Nobel Prize 2003 — one line of history is worth writing.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.9 Kidney Development and Nephrogenesis**2022-B P1 Q5(a)**

Congenital abnormalities of kidney and urinary tract (CAKUT):
Describe kidney development (nephrogenesis).

5

2023-Apr P1 Q10(a)

Elaborate on the key steps in the embryological development of the kidney.

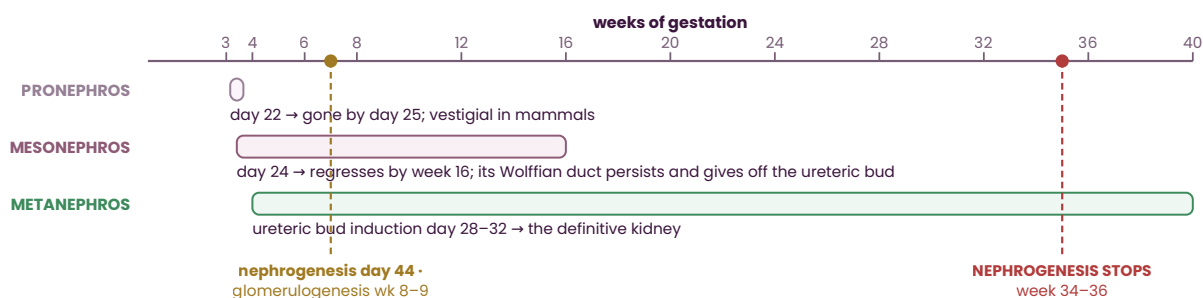
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EXAMINER'S BLUEPRINT

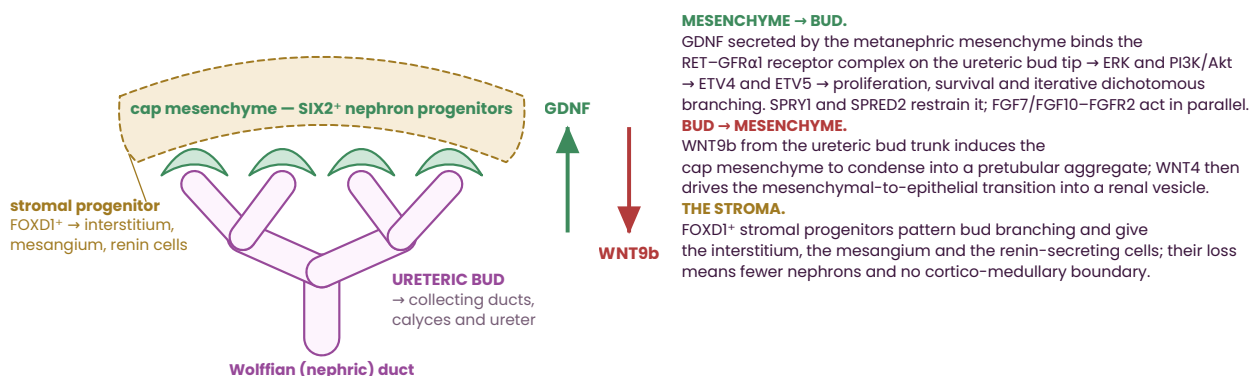
4–5 marks — the three primordia with timing (1) + the triad of progenitors and what each becomes (1.5) + the differentiation sequence from pretubular aggregate to mature glomerulus, as a diagram (1.5) + when nephrogenesis stops and why that matters (1).

Kidney development — from the three primordia to the mature glomerulus

A · THE THREE PRIMORDIA — HUMAN TIMELINE



B · RECIPROCAL INDUCTION IN THE NEPHROGENIC ZONE



C · FROM CAP MESENCHYME TO THE MATURE GLOMERULUS



NEPHROGENESIS CEASES AT 34–36 WEEKS — NO NEW NEPHRONS ARE FORMED AFTER BIRTH

600 000 – 1 000 000 nephrons are made per kidney (≈1 million; range 250 000 to <2.5 million)

Prematurity, low birth weight and intrauterine growth restriction reduce the endowment and raise lifelong risk of hypertension and CKD.

Gene / signal	Expressed in	Role in nephrogenesis	Loss of function
GDNF	Metanephric mesenchyme	Attracts and branches the ureteric bud through RET–GFRα1	Renal agenesis; the commonest node in CAKUT
RET / GFRα1	Ureteric bud tip	Receptor for GDNF → ERK, PI3K/Akt, ETV4 and ETV5	Renal agenesis; association with Hirschsprung disease
WNT9b	Ureteric bud trunk	Induces the cap mesenchyme to aggregate	No nephrons form
WNT4	Pretubular aggregate, renal vesicle	Drives mesenchymal-to-epithelial transition	Arrest at the aggregate stage
SIX2	Cap mesenchyme	Keeps nephron progenitors self-renewing	Premature exhaustion → few nephrons
PAX2 · SALL1 EYA1 · SIX1	Metanephric mesenchyme and nephric duct	Specify the mesenchyme and maintain GDNF	Renal coloboma (PAX2), Townes–Brocks (SALL1), branchio-oto-renal (EYA1/SIX1)
WT1	Metanephric mesenchyme → podocyte	Survival of the mesenchyme; podocyte identity	Mesenchymal apoptosis, no bud outgrowth; Denys–Drash and Frasier syndromes
FOXD1	Stromal progenitor	Patterns bud branching; gives interstitium, mesangium and renin cells	Disrupted cortico-medullary boundary, fewer nephrons
SPRY1	Ureteric bud	Negative regulator of GDNF–RET signalling	Ectopic buds → duplex kidney, reflux
VEGF-A	Presumptive podocyte (S-shaped body)	Attracts VEGFR-2 ⁺ angioblasts into the vascular cleft → capillary loop	Failure of glomerular capillary formation

BR Ch 1, Figs. 1.2–1.5 and Table 1.1, pp. 3–8. Mouse equivalents: pronephros E8.5–E10, mesonephros E10–E14, ureteric bud induction E10.5, nephrogenesis E13, glomerulogenesis E14, cessation at postnatal day 3. The whole sequence is repeated 600 000 to 1 000 000 times per human kidney.

Kidney development from the three primordia to the mature glomerulus.

Original schematic based on BR §Ch 1, pp. 3–8 (Figs. 1.2–1.5).

1 • Three successive primordia

- All three arise from the **intermediate mesoderm / urogenital ridge**, in a rostral-to-caudal sequence.
- **Pronephros** — pronephric tubules and the pronephric duct (precursor of the **Wolffian duct**); appears at **day 22** of human gestation. Vestigial in mammals and regresses; it is the principal excretory organ of larval fish and amphibians.
- **Mesonephros** — develops caudal to the pronephros in the midsection of the urogenital ridge, aligned along the Wolffian duct. Also vestigial in humans and regresses before birth.
- **Metanephros** — the **definitive mammalian kidney**, formed by interaction of the ureteric bud (an outgrowth of the caudal Wolffian duct) with the metanephric mesenchyme, from about week 5 of human gestation.

↳ BR §Ch 1, pp. 3–4

2 • The triad of progenitors

Three progenitor populations and their derivatives · BR §Ch 1, pp. 4–7 (Fig. 1.5)

PROGENITOR	MARKER	GIVES RISE TO
Ureteric bud (UB)	—	Collecting ducts, papillae, calyces, renal pelvis and ureter
Nephron progenitor in the metanephric mesenchyme	Six2⁺ cap mesenchyme	Glomerular podocytes, parietal epithelial cells, proximal tubule, loop of Henle, distal tubule and connecting tubule — <i>the nephron proper</i>
Stromal progenitor	Foxd1⁺	Cortical and medullary interstitial cells, mesangial cells, renin-producing cells and pericytes; also supplies the signals required for UB branching and cortico-medullary patterning

- Loss of stromal cells impairs UB branching, **reduces nephron number**, disrupts nephron patterning with failure of cortico-medullary boundary formation, and causes maldevelopment of the renal vasculature. A reciprocal signal from the UB patterns the stroma in turn.
- The classical signalling axis is **GDNF from the metanephric mesenchyme acting on RET/GFRα1 on the ureteric bud**, with WT1, PAX2, EYA1 and SIX1 upstream and BMP4, Sprouty and FGF modulating branching — mutations in these genes underlie much of human CAKUT.

↳ BR §Ch 1, pp. 4–7; the GDNF–RET axis is standard developmental nephrology

3 • The differentiation sequence

1. **Branching morphogenesis**: rapid, reiterative branching of the ureteric bud. The first several rounds are roughly symmetric; later rounds are asymmetric, with a main trunk extending towards the nephrogenic zone while smaller buds branch and induce new

nephrons. The renal pelvis forms by widening and coalescence of the earliest branches. A human kidney has **8-10 papillae** (the mouse has one).

2. **Condensation:** nephron progenitors aggregate beneath each UB tip as the **cap mesenchyme**.
3. **Pretubular aggregate → mesenchymal-to-epithelial transition → renal vesicle.**
4. **Comma-shaped body → S-shaped body**, with precise proximo-distal patterning that assigns the future glomerulus, proximal tubule, loop and distal tubule.
5. **Capillary loop stage:** endothelial cells migrate into the vascular cleft from E13.5, flatten, and capillary lumens form partly by apoptosis of a subset of endothelial cells; glomerular endothelial cells then develop **fenestrae**.
6. **Mature glomerulus:** podocytes, fenestrated endothelium and the intervening GBM form the size- and charge-selective filtration barrier; mesangial cells provide support and contractility.

↳ BR §Ch 1, pp. 4-7

4 • Vascular development

- A primitive vessel tracks the ureteric bud from E11.5 and elaborates in synchrony with branching and nephrogenesis.
- Capillary networks surround the developing tubules by E13.5; the hilar artery and first-order interlobar branches are identifiable by E14.5, forming the corticomedullary arcades and interlobular arteries, whose further branching produces the **afferent arterioles**.
- Efferent arterioles carry blood to the fenestrated peritubular capillaries and, from juxtamedullary glomeruli, to the vasa recta — the microcirculation on which the countercurrent mechanism depends.

↳ BR §Ch 1, p. 7

The sentence that must appear in every answer: nephrogenesis in humans is complete by **34-36 weeks of gestation**; there is **no post-natal nephrogenesis**. Nephron number is therefore fixed at birth, and every nephron subsequently lost is lost permanently. This is the link between prematurity, intrauterine growth restriction and adult hypertension and CKD — see Topic 1.10.

HIGH-YIELD · CLINICAL PEARLS

- ◆ Pronephros → mesonephros → metanephros. Only the metanephros survives; the pronephric duct becomes the **Wolffian duct**.
- ◆ Three progenitors: **UB** (collecting system), **Six2⁺ nephron progenitor** (nephron), **Foxd1⁺ stroma** (interstitium, mesangium, renin cells).
- ◆ Sequence: cap mesenchyme → pretubular aggregate → renal vesicle → comma → **S-shaped body** → capillary loop → mature glomerulus.
- ◆ The **S-shaped body** is where the glomerular cleft forms and endothelial cells invade — name it.
- ◆ **GDNF-RET** is the branching axis; its disruption is the commonest developmental cause of CAKUT.
- ◆ Nephrogenesis ends at **34-36 weeks**. No new nephrons after birth. Say it in the first or last line.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.10 Nephron Endowment**2023-Oct P1 Q6(c)**

Nephron Endowment.

3

2025-26 P1 Q7(a)

What is nephron endowment?

3

2025-26 P1 Q7(b)

Discuss factors influencing nephron endowment and effect on kidney health.

7

EXAMINER'S BLUEPRINT

3 marks — definition and the true range of human nephron number (1) + what determines it, especially birth weight and prematurity (1) + why it matters clinically, with the Brenner hypothesis and the donor/CKD data (1). Quote the numbers; they are what distinguish this answer.

Definition

Nephron endowment is the **total number of nephrons an individual is born with**. It is fixed at the end of nephrogenesis (34–36 weeks) and follows a **normal distribution across the population**.

BR §Ch 20, Fig. 20.2, p. 601

1 • The numbers

- The old teaching of "about 1 million nephrons per kidney" came from studies prone to bias and small samples, and implied a variability that does not exist.
- Using the gold-standard **disector/fractionator** method on whole autopsy kidneys, an early study of 37 normal Danish adults found a mean of **617,000 nephrons per kidney with a range of 331,000–1,424,000**.
- The widest reported range is a **13-fold variation** in the largest sample studied (159 African American subjects: 210,332 to 2,702,079 per kidney).
- Variability is present from the start: in 15 American infants under 3 months of age the range was **246,181 to 1,106,062** per kidney — reflecting developmental programming rather than post-natal loss.
- An improved in-vivo counting method using CT plus implantation biopsy gives estimates about **27% higher** than previous calculations. Nephron number correlates positively with kidney weight, and papilla/lobe number itself varies from 3 to 22.
- The number of nonsclerotic glomeruli falls with age: an average of 990,661 in donors aged 18–29 years compared with 520,410 in donors aged 70–75 years.

↳ BR §Ch 20, pp. 601–604

2 · What determines endowment

- **Birth weight** — a direct relationship between nephron number and birth weight, and an inverse relationship between nephron number and glomerular volume. Low-birth-weight infants have on average **12% fewer nephrons**; small-for-gestational-age infants in the acid-maceration study had **30% fewer** than appropriate-for-gestational-age infants.
- **Prematurity** — nephrogenesis is incomplete, and there is **no post-natal catch-up** in nephron number.
- **Intrauterine growth restriction** of any cause, maternal malnutrition, maternal diabetes, and nephrotoxin exposure in utero.
- Larger glomeruli are a **surrogate marker of a reduced nephron number**, reflecting compensatory hyperfiltration and hypertrophy.

↳ BR §Ch 20, pp. 604–605

3 · Why it matters — the Brenner hypothesis and the modern evidence

- A low endowment leaves **no renal functional reserve**: a mild insult triggers a rise in creatinine or AKI, hypertension appears early in life, proteinuria is disproportionate to disease stage, obesity causes **adaptive FSGS**, diabetes causes early nephropathy, glomerulonephritis progresses fast, and post-donation kidney failure risk is high (see the table in Topic 1.6).
- **The strongest modern evidence**: in patients undergoing tumour nephrectomy, a nephron number below the 10th percentile for age and sex predicted future CKD (HR 3.15, 95% CI 2.10–4.74) and kidney failure (**HR 7.12, 95% CI 3.47–14.6**) — the first study to correlate nephron number prospectively with outcome.
- Congenital severe nephron deficits — unilateral renal agenesis, bilateral renal hypoplasia, **oligomeganephronia** — produce progressive proteinuria, glomerulosclerosis and kidney dysfunction over time.
- **The counter-argument, which should be stated**: removing one kidney (a 50% reduction in nephron number) does not reliably cause hypertension and kidney disease in animals or humans, although it may be associated with higher blood pressure and low-grade proteinuria. Timing matters — uninephrectomy on postnatal day 1 in rats, or fetal uninephrectomy in sheep, when nephrogenesis is incomplete, does produce adult hypertension.

↳ BR §Ch 20, pp. 601–605

BEYOND THE TWO TEXTBOOKS — CURRENT ACCEPTED POSITION

Public-health corollary worth one line: this is the developmental-origins ("Barker") explanation for the high burden of hypertension and CKD in populations with a high prevalence of low birth weight — including the Indian subcontinent — and the argument for counting maternal and neonatal nutrition as kidney-protective public health policy.

HIGH-YIELD · CLINICAL PEARLS

- ◆ Not "one million" — mean about **600,000-900,000 per kidney** with a **13-fold** range between individuals.
- ◆ Endowment is fixed at **34-36 weeks**; there is no catch-up nephrogenesis.
- ◆ Low birth weight → 12% fewer nephrons; SGA → up to 30% fewer.
- ◆ **Big glomeruli = few nephrons.** Glomerular volume is the surrogate.
- ◆ The Denic nephrectomy data are the number to quote: kidney failure **HR 7.12** for nephron number below the 10th percentile.
- ◆ Give the counter-argument — uninephrectomy in adults does not reliably cause disease. Examiners reward balance.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.11 Podocyte Structure, the Slit Diaphragm, and Podocyte Injury and Repair**2023-Oct P1 Q4(a)** Role of podocytes in renal diseases.

3

2024 P1 Q5(a) Draw the structure of renal podocyte & slit diaphragm.

5

2024 P1 Q5(b) Discuss briefly the podocyte injury & repair mechanism.

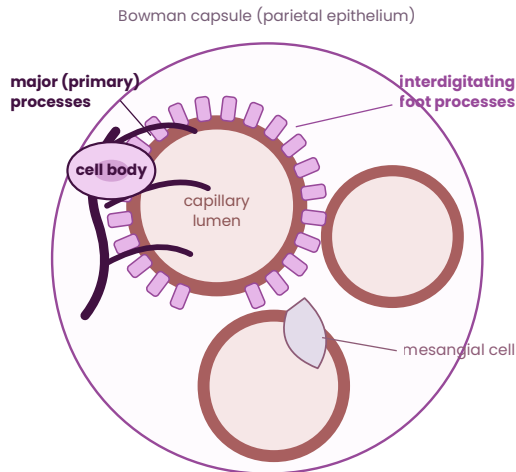
5

EXAMINER'S BLUEPRINT

Structure (5): a labelled drawing is compulsory — cell body, major process, foot processes, slit diaphragm, GBM, endothelium — then the molecular anatomy in three groups (slit diaphragm, adhesion, cytoskeleton). Injury and repair (5): the four functions that can fail (1), the sequence effacement → hypertrophy → detachment (2), the three routes to proteinuria (1), and the limited regenerative options (1).

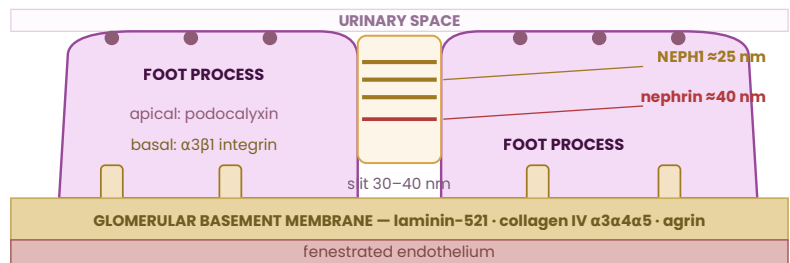
(a) Structure of the podocyte and slit diaphragm

5

Podocyte architecture and the molecular anatomy of the foot process**A · ARCHITECTURE OF THE PODOCYTE**

Podocytes are post-mitotic — lost cells are not replaced.

Foot-process effacement is the common final path of proteinuria, and loss of a large fraction of podocytes leads to irreversible glomerulosclerosis.

C · WHICH PROTEIN, WHICH GENE, WHICH DISEASE**B · MOLECULAR ANATOMY OF THE FOOT PROCESS**

APICAL DOMAIN	SLIT DIAPHRAGM
Podocalyxin — anionic sialomucin, holds the slits apart; linked by NHERF-2/ERM Podoplanin · podoendin · GLEPP-1 (PTPRO) Receptors: AT ₂ R · prostaglandin R · Notch	Transmembrane: nephrin (NPHS1, 9 lg), NEPH1 (5 lg), P-cadherin, FAT1/2, JAM4 Hub: podocin (NPHS2) in a lipid raft CD2AP · ZO-1 · MAGI-1 · Nck · catenins TRPC6 (Ca ²⁺ channel) · Fyn kinase
BASAL (ADHESION) DOMAIN	CYTOSKELETON, SIGNALLING, ANTIGENS
α3β1 integrin binds laminin-521 of the GBM Focal adhesion: FAK · ILK · talin · vinculin · paxillin · EPB41L5 Matrix receptors: dystroglycan, sarcoglycan	Longitudinal actin / myosin-II bundles Synaptopodin (via RhoA) · α-actinin-4 Rho · Rac · CDC42 · INF2 · MYOIE · vimentin mTORC1/2 · MERTK · ANPRs · ITM2B · Notch Antigens: PLA ₂ R1 · THSD7A · NEP · ADAM10

Protein	Gene	Where in the foot process	Function	Mutation / disease
Nephrin	NPHS1	Slit diaphragm, transmembrane; 9 lg repeats, ≈40 nm strands	Core of the SD fishnet; signalling hub to actin	Congenital nephrotic syndrome of the Finnish type (AR)
NEPH1	KIRREL1	Slit diaphragm; 5 lg repeats, ≈25 nm strands, basal layer	Heterodimerises with nephrin to form the SD strands	Proteinuria in experimental models; modifier gene
Podocin	NPHS2	Hairpin in a lipid raft at the SD insertion site	Anchors nephrin; scaffolds TRPC6 and CD2AP	AR steroid-resistant nephrotic syndrome / FSGS
CD2AP	CD2AP	SD cytoplasmic face	Links nephrin/podocin to the actin cytoskeleton	FSGS (haploinsufficiency); susceptibility to CKD
TRPC6	TRPC6	Slit diaphragm, Ca ²⁺ -permeable cation channel	Mechanotransduction → Ca ²⁺ influx, actin remodelling	AD adult-onset FSGS (gain of function)
α-Actinin-4	ACTN4	Actin cross-linker within the foot process	Bundles the contractile actin/myosin system	AD FSGS
Synaptopodin INF2 · MYOIE	SYNPO INF2 MYOIE	Actin-binding protein, formin and motor protein	Stabilise and remodel the actin bundles (via RhoA)	INF2 → AD FSGS ± Charcot-Marie-Tooth; MYOIE → AR FSGS
Podocalyxin	PODXL	Apical membrane; anionic sialomucin, NHERF-2/ERM link	Charge repulsion keeps adjacent slits open	Rare FSGS; lost in minimal change disease
α3β1 integrin	ITGA3 ITGB1	Basal membrane, focal adhesion (FAK, ILK, talin, vinculin)	Binds laminin-521 of the GBM — anchors the podocyte	Congenital nephrotic syndrome + interstitial lung disease
Dystroglycan sarcoglycan	DAG1	Basal membrane matrix receptor	Bind agrin and laminin in the GBM	Lost in minimal change disease (acquired, not inherited)
Laminin β2	LAMB2	GBM, secreted by the podocyte	Ligand for α3β1 integrin	Pierson syndrome — congenital NS with microcoria
WT1	WT1	Nucleus — master transcription factor of the podocyte	Maintains nephrin, podocalyxin and the differentiated state	Denys-Drash (DMS, Wilms); Frasier syndrome (FSGS)
PLA ₂ R1 · THSD7A NEP	PLA2R1 THSD7A MME	Antigens at the base of the foot process	Targets of circulating auto-antibody, not mutated	Primary membranous nephropathy (NEP; antenatal MN)

BR Ch 4, Fig. 4.2 and pp. 114–121. The slit diaphragm is not a simple sieve: nephrin–NEPH1 heterodimers form a flexible, context-dependent fishnet, and its coassembled protein network acts as a signalling hub rather than a static filter.

Podocyte architecture and the molecular anatomy of the foot process.

Original schematic based on BR §Ch 4, Fig. 4.2, p. 116 and pp. 115–117.

- Podocytes are **highly differentiated, mesenchymal-derived, terminally differentiated** visceral epithelial cells with an apicobasal polarity axis between the urinary space and the GBM.
- From a flat cell body they extend long branching **major (primary) processes**, which give rise to **secondary or foot processes** that interdigitate in a **zipper-like fashion** with those of neighbouring podocytes.
- Interdigitating foot processes are connected by **bicellular junctions of uniform width**; areas of **tricellular junctions** (three podocytes meeting) also exist.
- The **slit diaphragm** bridges the ~40 nm filtration slit. Cryo-electron tomography of native murine glomeruli shows it is built of **nephrin-neph1 heterodimers forming a flexible fishnet**, with **neph1 spanning the lower part of the slit close to the GBM** and **nephrin positioned apically** — three layers of ~25 nm strands attributable to neph1 and one layer of ~40 nm strands representing nephrin.
- Current evidence suggests the nephrin/neph1 layer **does not itself operate as the filtration barrier** but is a context-dependent, dynamically regulated structure; native slit-diaphragm proteomics shows it co-assembles with enzymes (MERTK), receptor-signalling components (ANPR) and scaffolds (ITM2B) rather than with classical cell-cell junctional proteins.

↳ BR §Ch 4, pp. 115–116

Molecular anatomy of the foot process — group it this way in the answer · BR §Ch 4, Fig. 4.2D, p. 116

GROUP	MOLECULES
Slit diaphragm — transmembrane	Nephrin (NPHS1) , neph1, FAT1/2, P-cadherin
Slit diaphragm — anchor and signalling hub	Podocin (NPHS2) , a stomatin-family protein that anchors nephrin in lipid-rich membrane compartments; TRPC6 , a Ca ²⁺ -permeable channel that may translate mechanical tension into ion-channel action
Adaptors linking slit diaphragm to actin	CD2AP, Nck, MAGI-1, ZO-1, JAM4
Cytoskeleton	Actin/myosin filaments and longitudinal bundles, synaptopodin , α-actinin-4 ; vimentin-rich intermediate filaments in the cell body and major processes; Rho, Rac and CDC42 regulators
Adhesion to the GBM	Integrin α3β1 connecting laminin 521 to focal adhesions (FAK, ILK, talin, vinculin, paxillin, EPB41L5); α-dystroglycan, sarcoglycan, syndecan-4, integrins α2β1 and αVβ3, type XVII collagen
Apical anionic coat	Podocalyxin (linked to the membrane by NHERF-2 and ezrin/moesin/radixin), podoplanin, podoendin, GLEPP-1
Receptors and signalling	AT1 receptor, prostaglandin receptor, Notch, Wnt, mTORC1/2, Hippo, Fyn

GROUP	MOLECULES
Disease-relevant antigens	PLA ₂ R1, THSD7A, neutral endopeptidase (NEP) — the membranous nephropathy antigens; ADAM10 protease

The five jobs of a podocyte

1. **Build and maintain the GBM** — podocytes and endothelial cells both secrete laminin 111 and collagen $\alpha1\alpha2\alpha1$ during development and laminin 521 after maturation, but **only podocytes secrete type IV collagen $\alpha3\alpha4\alpha5$** of the mature GBM. Podocyte prolyl-3-hydroxylase-2 (P3H2) is required for GBM remodelling; its loss causes **thin basement membrane nephropathy**.
2. **Maintain the barrier by paracrine support** — podocytes secrete angiopoietin-1 (Tie2), normosialylated angiopoietin-like-4 (integrin $\alpha V\beta5$), **VEGF-A** (VEGFR2) and stromal-derived factor 1 (CXCR4), which support endothelial and mesangial migration, differentiation and survival.
3. **Stabilise the barrier** through cell-matrix adhesion receptors, chiefly integrin $\alpha3\beta1$.
4. **Regulate filtration** — by compressing the GBM through adhesion and cytoskeletal tensile force (the "buttress" effect), which reduces macromolecular permeability; by forming the slit diaphragm; and by sensing filtration pressure through a mechanoreceptor complex at the slit diaphragm. **Angiotensin II signalling reduces the buttress force, decompresses the GBM and causes albuminuria.**
5. **Clear the barrier** — foot processes are rich in clathrin-coated pits and multivesicular bodies and are highly endocytic; slit-diaphragm proteins are continuously recycled through endosomes.

↳ BR §Ch 4, p. 117

(b) Podocyte injury and repair

5

1 · Why the podocyte is so vulnerable

- More than **80 pathways** causing podocyte distress have been described, and more than **80 monogenic causes** of podocyte disease are now known.
- Categories of stressor: circulating factors, cell-surface signalling, **mechanical (circumferential and shear) stress**, metabolism, proteostasis, fibrosis, inflammation and the actin cytoskeleton.
- A general theme: podocyte injury involves **reactivation of developmental programmes** — Notch, Wnt, mTOR and Hippo. Overactivation or imbalance of these disrupts cytoskeletal regulation, energy metabolism and protein homeostasis, initiating a **mostly irreversible dedifferentiation**.

↳ BR §Ch 4, p. 117

2 · The histopathological sequence

Effacement → hypertrophy → detachment · BR §Ch 4, pp. 117–119 (Fig. 4.3)

STAGE	WHAT HAPPENS	CONSEQUENCE
Foot process effacement	Reorganisation of the actin cytoskeleton; foot processes retract and spread; slit diaphragms are displaced or lost	The common final morphology of podocyte injury; potentially reversible early
Hypertrophy	Podocytes are terminally differentiated and essentially cannot proliferate, so they respond to GBM distension or podocyte loss by enlarging. mTOR and its target 4E-BP1 are the key regulators, and the timing, extent and duration of mTOR activation decide whether hypertrophy is adaptive or maladaptive . p27 ^{Kip1} mediates hypertrophy in response to hyperglycaemia and stretch	Adaptive in development, growth, and podocyte depletion up to about 20% . Maladaptive with persistent stimuli such as high glucose or subepithelial deposits. Hypertrophic podocytes may be unable to maintain normal foot-process structure, raising local shear stress and triggering detachment
Detachment and loss into the urine	Failure of integrin-mediated adhesion; podocytes are shed live into the urine	Denuded GBM → adhesion to Bowman capsule → synechia → segmental sclerosis. This is the point of no return
Glomerulosclerosis	Disrupted podocyte–endothelial crosstalk and activation of podocyte–parietal epithelial cell interactions	Progressive decline in GFR

3 · The three routes to podocyte-dependent proteinuria

1. **Alteration of the slit diaphragm** — hereditary or acquired defects of one or more structural proteins (nephrin, podocin). Either an absolute fall in protein level or a change in subcellular location produces proteinuria, and because the proteins interact, a change in one cascades to the others.
2. **Alteration of the actin cytoskeletal network** — genetic or acquired, causing either enhanced or decreased actin polymerisation, with loss of the three-dimensional structure and flexibility of the podocyte.
3. **Loss of the anionic surface coat** — loss of podocalyxin reduces the negative surface charge of the foot processes, removing the electrostatic repulsion that keeps them apart, and causes proteinuria. No hereditary podocalyxin mutation is known.

↳ BR §Ch 4, p. 119

4 · Repair and regeneration — what is and is not possible

- Mature podocytes show **virtual absence of mitosis and regeneration**. Their only intrinsic adaptive response is hypertrophy, and that is limited.

- **Parietal epithelial cells** are the leading candidate for podocyte replacement. They derive from the same metanephric mesenchyme and share a phenotype with podocytes at the vesicle and comma stages; single-cell RNA sequencing identifies **five distinct PEC populations** in the mature kidney, and those at the vascular pole retain podocyte features — hence the term "**parietal podocytes**". PEC activation, however, is double-edged: it also drives cellular crescents and the pseudo-crescents of collapsing glomerulopathy.
- **mTOR is the therapeutic fulcrum**: inhibiting mTOR during *adaptive* hypertrophy causes proteinuria and glomerulosclerosis, whereas inhibiting it during *maladaptive* hypertrophy may be beneficial. This explains why sirolimus can precipitate proteinuria in a transplant with reduced nephron mass, yet mTOR inhibition is being explored in diabetic nephropathy.
- Therapeutic implications that follow from the biology: reduce mechanical stress (RAS blockade, SGLT2 inhibition, blood pressure and weight control), remove the injurious stimulus (immunosuppression, glycaemic control), and support the cytoskeleton (the proposed non-immunosuppressive action of calcineurin inhibitors in stabilising synaptopodin).

↳ BR §Ch 4, pp. 118–122; the therapeutic list is standard accepted teaching

5 · Role of podocytes in renal disease — the 3-mark version

Podocytopathies · BR §Ch 4, pp. 115–122; BR §Ch 30, pp. 885–923

CATEGORY	EXAMPLES
Genetic	NPHS1 (congenital nephrotic syndrome, Finnish type), NPHS2/podocin, TRPC6, ACTN4 (α -actinin-4), CD2AP, INF2, WT1 (Denys-Drash, Frasier), LMX1B (nail-patella), COQ2/COQ6 (CoQ10 deficiency)
Immune	Minimal change disease, primary FSGS (circulating permeability factor), membranous nephropathy — where the target antigens PLA ₂ R1, THSD7A and NEP are podocyte proteins
Haemodynamic / adaptive	Obesity-related and reflux-related FSGS, solitary kidney, low nephron endowment, sickle cell disease
Metabolic	Diabetic kidney disease — podocyte hypertrophy, detachment and loss precede albuminuria
Viral and drug	HIV-associated nephropathy and collapsing glomerulopathy (APOL1 risk alleles), interferon, pamidronate, anabolic steroids
Toxic/ischaemic	Pre-eclampsia (anti-VEGF milieu), calcineurin inhibitor toxicity

HIGH-YIELD · CLINICAL PEARLS

- ◆ Draw it. A labelled podocyte with cell body, major process, interdigitating foot processes, slit diaphragm, GBM and fenestrated endothelium earns the structure marks on its own.
- ◆ The slit diaphragm is a **nephrin-neph1 fishnet**: nephrin below near the GBM, nephrin above. Podocin anchors, TRPC6 senses tension.
- ◆ Only podocytes make collagen **$\alpha3\alpha4\alpha5$** and podocyte VEGF-A keeps the endothelium fenestrated — that is why anti-VEGF drugs cause TMA.
- ◆ Sequence: **effacement → hypertrophy → detachment → sclerosis**. Detachment is the point of no return.
- ◆ Hypertrophy compensates for podocyte loss only **up to about 20%**.
- ◆ Three routes to proteinuria: slit diaphragm, cytoskeleton, surface charge.
- ◆ Podocytes essentially cannot divide; **parietal epithelial cells** are the candidate progenitor — and also the source of crescents.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.12 NETosis, Autophagy and Regulated Cell Death in Kidney Injury**2021 P1 Q10**

Netosis and autophagy.

5+5**EXAMINER'S BLUEPRINT**

10 marks as 5+5 — NETosis: what a NET is, how it forms (PAD4), and its role in ischaemic, septic and COVID-associated AKI (5). Autophagy: the three forms with their machinery, the evidence that it is renoprotective in AKI but profibrotic when dysregulated, and the therapeutic angle (5). A table of the regulated cell-death pathways lifts the answer.

(a) NETosis**5****What it is**

NETosis is a form of regulated neutrophil death in which the cell extrudes **neutrophil extracellular traps (NETs)** — webs of decondensed **chromatin and histones** studded with granule proteins that immobilise and kill bacteria. It is a host defence mechanism that becomes injurious when it occurs inside the kidney.

BR §Ch 27, p. 793

- **Mechanism** — neutrophil **peptidyl arginine deiminase-4 (PAD4)** citrullinates histones, allowing chromatin decondensation; the nuclear membrane breaks down and the DNA-histone web is released. PAD4 is the central enzyme and the main pharmacological target.
- **In ischaemic AKI** — infiltrating neutrophils undergo NETosis, releasing cytotoxic **DAMPs such as histones**, which directly injure tubular epithelial cells and amplify interstitial inflammation.
- **In septic AKI** — NETs co-localise with fibroblast growth factor-inducible molecule 14 (Fn14); simultaneous PAD4 deletion and Fn14 inhibition alleviates AKI. Inhibition of gasdermin D with disulfiram, or its genetic deletion, abrogates neutrophil NET formation and reduces multi-organ dysfunction and lethality in sepsis.
- **In COVID-19** — in patients with CKD, SARS-CoV-2 induced a vasculopathy leading to AKI through **greater NETosis and microthrombosis**.
- **Conclusion the source draws:** "NETosis is an important early target for intervention in diverse forms of AKI."

- **Beyond AKI:** NETs are central to ANCA-associated vasculitis — ANCA triggers NETosis, and the NETs display MPO and PR3, perpetuating the autoimmune loop; they also contribute to lupus nephritis and to thrombotic microangiopathy.

↳ BR §Ch 27, p. 793; the vasculitis link is standard accepted teaching

(b) Autophagy

5

What it is

Autophagy is the lysosomal degradation of the cell's own components — a quality-control and nutrient-recycling programme that is constitutively active in the kidney and strongly induced by stress.

BR §Ch 27, Fig. 27.5, p. 789

The three forms of autophagy · BR §Ch 27, Fig. 27.5, p. 789

FORM	MECHANISM	MACHINERY
Macroautophagy	De-novo formation of a cup-shaped double isolation membrane that engulfs a portion of cytoplasm to form an autophagosome, which fuses with the lysosome	Atg1/Atg13/Atg17 initiation complex → Vps34-Vps15-Bec1 nucleation → Atg5-Atg12-Atg16L conjugation → Atg8/LC3-phosphatidylethanolamine lipidation
Microautophagy	Direct engulfment of cytoplasm at the lysosomal membrane by invagination, protrusion and separation	—
Chaperone-mediated autophagy	Direct transport of unfolded proteins into the lysosome	Cytosolic chaperone hsc70 and lysosomal receptor LAMP-2A
Mitophagy (specialised macroautophagy)	Selective removal of damaged mitochondria	PINK1/Parkin; prohibitin-2 (PHB2) — attenuated mitophagy worsens AKI, PHB2 overexpression improves mitochondrial function and reduces NLRP3 activation

The evidence in kidney injury

- **Autophagy is renoprotective in AKI.** Proximal tubule-specific **ATG5** or **ATG7** knockout mice have exaggerated ischaemia-reperfusion injury; **ATG7^{-/-}** mice have worse function and injury with cisplatin; **chloroquine**, an autophagy inhibitor, blocks lysosomal degradation of LC3 and worsens cisplatin AKI; chloroquine or tubular ATG7 ablation worsens LPS-induced septic AKI. In contrast, lack of ATG5 in **distal** tubules causes no significant functional change — the protection is a proximal tubule phenomenon.

- **Ischaemic preconditioning and caloric restriction work through autophagy.** Caloric restriction mimics preconditioning and stimulates the SIRT-SGK1-FOXO3a-HIF1 α axis to preserve PGC1 α . Preconditioning induces tubular autophagy, and its protection is abolished by autophagy inhibitors or proximal-tubule-specific Atg7 deletion. Beclin-1 peptide induces autophagy and protects against ischaemia-reperfusion.
- **But dysregulated autophagy is harmful.** Persistent activation correlates with renal fibrosis; mTOR inhibition can induce persistent autophagy with impaired proliferation. Autophagy is critical for tubular cell survival *early* after AKI, while at *later* stages it regulates fibrosis and productive repair. Dysregulated autophagy results in increased renal degeneration and progressive kidney disease characterised by interstitial fibrosis.
- **Summary sentence for the answer:** autophagy is a dynamic, time-dependent process — protective acutely, potentially profibrotic chronically.

↳ BR §Ch 27, pp. 789–790

The wider family of regulated cell death — worth a short table

Regulated cell death pathways relevant to AKI · BR §Ch 27, pp. 788–793

PATHWAY	DEFINING FEATURE	RELEVANCE
Necroptosis	RIPK1/RIPK3/MLKL-mediated regulated necrosis	Implicated in ischaemia-reperfusion and in TNF- α -induced systemic inflammatory response syndrome; existing drugs may be repurposed to target it
Ferroptosis	Iron-dependent, non-apoptotic death driven by lipid peroxidation when GPX4 (the lipid-repair selenoprotein) fails	Mediates cell death in a non-cell-autonomous and synchronised manner — a potential explanation for nephron loss in AKI. Ferroptosis genes (Ptgs2, Chac1, Acs14, Slc7a11, Hmox1) are enriched in proximal tubule cells after prolonged ischaemia
Pyroptosis	Caspase-1/4/11 activation of gasdermin D → membrane rupture and DAMP release	Intertwined with the NLRP3 inflammasome , AKI and fibrogenesis. Pyroptosis genes (Casp1, Casp3, Casp4, Il1b, Il18, Gsdmd) are enriched after long ischaemia. Disulfiram and dapansutrile are candidate inhibitors; the dsDNA sensor AIM2 also forms an inflammasome and cleaves GSDMD
NETosis	PAD4-driven chromatin extrusion	See part (a)
Apoptosis	Caspase-3/9, non-inflammatory	The classical pathway; membrane integrity is preserved so no DAMPs are released

Why this question is asked. These pathways are the modern mechanistic language of AKI and the reason AKI is no longer described simply as "acute tubular necrosis". Every one of them releases or withholds **DAMPs**, which activate innate immunity and determine

whether repair is adaptive or maladaptive — the link between an episode of AKI and subsequent CKD.

HIGH-YIELD · CLINICAL PEARLS

- ◆ NETs = **chromatin + histones**; the enzyme is **PAD4**; the toxic cargo is **histones as DAMPs**.
- ◆ NETosis in ischaemic AKI, septic AKI (with Fn14), COVID-19 vasculopathy, and ANCA vasculitis.
- ◆ Three forms of autophagy: macro-, micro-, chaperone-mediated. Add **mitophagy** as the fourth and you look current.
- ◆ Key genes: **ATG5, ATG7, Beclin-1, LC3**. Their deletion worsens AKI — the cleanest proof that autophagy protects.
- ◆ **Chloroquine worsens cisplatin AKI** — the pharmacological mirror of the knockout data.
- ◆ Autophagy is protective early and profibrotic late. Say "time-dependent" and you have the examiner.
- ◆ Ferroptosis is **non-cell-autonomous and synchronised** — that is what makes it a candidate for wave-like nephron loss.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.13 Transforming Growth Factor- β and the Mediators of Fibrosis**2022-B P1 Q10(a)**Transforming Growth factor (TGF- β).

3

EXAMINER'S BLUEPRINT

3 marks — what it is and how it is activated (1) + the Smad signalling pathway and its downstream effects (1) + why anti-TGF- β therapy has failed and what is being targeted instead (1). Three crisp paragraphs beat a long list.

What it is

TGF- β is the **master pro-fibrotic cytokine** of the kidney. Three mammalian isoforms exist (TGF- β 1, β 2, β 3); **TGF- β 1** is the dominant one in kidney disease. It is secreted in a **latent** form bound to latency-associated peptide and latent TGF- β binding protein, and must be activated — by integrins (α v β 6, α v β 8), thrombospondin-1, proteases (plasmin, MMP-2/9), reactive oxygen species or low pH — before it can signal.

BR §Ch 50, pp. 1479–1480; the activation mechanisms are standard accepted teaching

1 · Signalling

- **Canonical (Smad) pathway:** active TGF- β binds the type II receptor, which recruits and phosphorylates the type I receptor (ALK5) → phosphorylation of **Smad2 and Smad3** → complex with **Smad4** → nuclear translocation → transcription of matrix genes. **Smad7** is the inhibitory Smad and is reduced in fibrotic kidney.
- **Non-canonical pathways:** MAPK (ERK, p38, JNK), PI3K-Akt-mTOR, Rho GTPases.
- **Upstream drivers in the kidney:** angiotensin II (AT1 receptor signalling induces TGF- β and transactivates the EGF and PDGF receptors through TACE/ADAM17-mediated TNF- α shedding), hyperglycaemia, mechanical stretch, proteinuria, hypoxia and aldosterone.

↳ BR §Ch 11, pp. 289–293; BR §Ch 50, pp. 1479–1480

2 · What it does in the kidney

- **Matrix accumulation** — increases synthesis of type I and IV collagen, fibronectin and laminin, *and* inhibits degradation by inducing PAI-1 and TIMPs.
- **Myofibroblast generation** — activates resident fibroblasts and pericytes; contributes to epithelial- and endothelial-mesenchymal transition.
- **Cell-cycle arrest and hypertrophy** — kidney hypertrophy after nephron loss is achieved by **arrest in late G1** so that cells enlarge instead of dividing. This is driven by CDK4-cyclin D activation without engagement of CDK2-cyclin E, a process regulated by **TGF- β**

and the CDK inhibitors **p21^{Waf1}**, **p27^{Kip1}** and **p57^{Kip2}**. The required increase in RNA and protein synthesis is mediated at least in part by **mTOR**.

- **Mesangial amplification** — after nephron loss, mesangial cells secrete growth factors (angiotensin II, IL-1, IGF-1, EGF) and **activate latent TGF-β**, increasing TGF-β expression and driving compensatory tubular cell hypertrophy (BR Fig. 50.3).
- **Podocyte effects** — apoptosis and detachment; contributes to the podocytopenia of diabetic nephropathy.
- **Immunoregulation** — TGF-β is also essential for regulatory T-cell induction and is immunosuppressive; this dual role is precisely why systemic blockade is hazardous.

↳ BR §Ch 50, pp. 1479–1480 (Fig. 50.3)

3 · Therapeutic status — the point that earns the third mark

BEYOND THE TWO TEXTBOOKS — CURRENT ACCEPTED POSITION

Direct anti-TGF-β strategies have **failed in human trials**: the anti-TGF-β1 monoclonal antibody **fresolimumab** did not meet endpoints in FSGS, and a large trial of fresolimumab in diabetic nephropathy was stopped for futility. Pirfenidone showed only a modest signal. The reasons are instructive — TGF-β is pleiotropic, essential for immune tolerance and epithelial repair, and blocking it wholesale risks autoimmunity and impaired healing. Current strategy is therefore to target TGF-β **indirectly** and **upstream**: RAS blockade, non-steroidal MRA (finerenone), SGLT2 inhibition, endothelin-A antagonism (sparsentan in IgA nephropathy and FSGS), and selective downstream nodes such as Smad3 or the integrin-mediated activation step. Say this explicitly — knowing that anti-TGF-β therapy has failed is more impressive than reciting the pathway.

HIGH-YIELD · CLINICAL PEARLS

- ◆ TGF-β1 is the **master pro-fibrotic cytokine**; it is secreted **latent** and must be activated — integrins, thrombospondin-1, proteases, ROS.
- ◆ Canonical = **Smad2/3 + Smad4**; **Smad7** is the brake and is lost in fibrosis.
- ◆ It both **increases matrix synthesis and blocks matrix degradation** (PAI-1, TIMPs) — say both halves.
- ◆ Compensatory hypertrophy = **late G1 arrest** mediated by TGF-β and p21/p27/p57, with mTOR driving protein synthesis.
- ◆ Angiotensin II induces TGF-β and transactivates EGFR/PDGFR via TACE — the molecular reason RAS blockade is antifibrotic.
- ◆ Direct anti-TGF-β therapy (**fresolimumab**) has failed; the field has moved upstream. This is the modern examiner's point.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.14 Renin–Angiotensin–Aldosterone Physiology**2022-Jun P1 Q8(a)***Renin-Angiotensin System:* Draw a diagrammatic representation of the Renin-Angiotensin System.

5

2023-Apr P1 Q3(a)

Discuss physiology of Renin Angiotensin Aldosterone axis system.

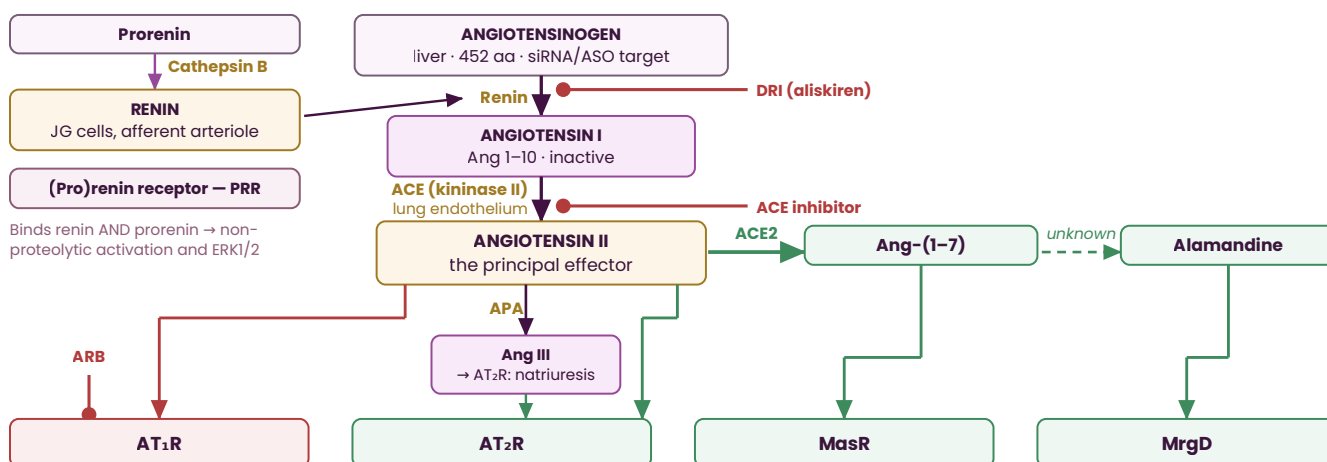
5

EXAMINER'S BLUEPRINT

5 marks — the diagram is compulsory and should include the counter-regulatory ACE2/Ang(1-7)/Mas arm (2) + the three stimuli to renin release (1) + AT₁ versus AT₂ actions (1) + the tissue RAS and one line on why the system is the therapeutic target it is (1).

The renin–angiotensin–aldosterone system, including the counter-regulatory ACE2 / Ang-(1–7) / Mas arm

A · THE CASCADE — ENZYMES IN AMBER, THE COUNTER-REGULATORY ARM IN GREEN, DRUG BLOCKADE IN RED



ALTERNATIVE AND NEWLY DESCRIBED ROUTES

Angiotensinogen → (unknown enzyme) → Ang-(1–12) → (ACE) → Ang I, or (chymase of heart and mast cells) → Ang II directly. Chymase is one reason for “ACE-inhibitor escape”. Ang I → (neprilysin) → Ang-(1–7). Ang III → (aminopeptidase N) → Ang IV → AT₄ / IRAP receptor.

B · WHAT EACH RECEPTOR DOES

AT₁ RECEPTOR — THE CLASSICAL ARM

Vasoconstriction (efferent · afferent) → ↑ intraglomerular pressure
Proximal Na⁺ retention through NHE3; aldosterone release; thirst; ADH
Sympathetic facilitation; NADPH oxidase → reactive oxygen species, NF-κB
TGF-β1 → fibrosis and podocyte injury → proteinuria, glomerulosclerosis
Also drives cardiac and vascular hypertrophy and remodelling

AT₂ RECEPTOR — OPPOSES AT₁

Vasodilation and natriuresis, acting through bradykinin → NO → cGMP
Antiproliferative and antifibrotic
Abundant in fetal tissue; re-expressed after injury
Opposes AT₁R and contributes to the benefit of AT₁ blockade, because unopposed Ang II is then free to act on the AT₂ receptor

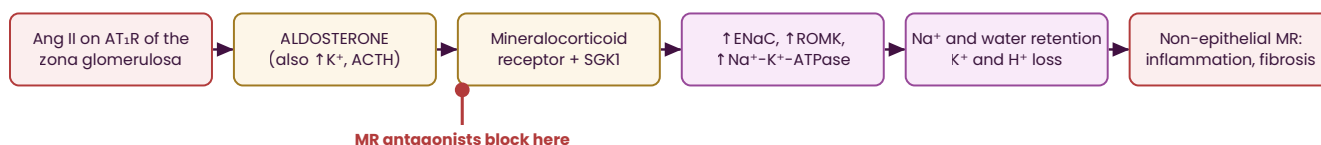
Mas RECEPTOR — ANGIOTENSIN-(1–7)

Vasodilation through NO and prostanoids; natriuresis
Antifibrotic, antiproliferative and anti-inflammatory
Counter-regulates the AT₁ receptor
ACE inhibitors and ARBs raise Ang-(1–7), which is part of their benefit
ACE2, the enzyme that makes it, is also the SARS-CoV-2 receptor

MrgD — ALAMANDINE

Vasodilation and antifibrotic effects, much like the Mas receptor
Formed from Ang-(1–7) by a decarboxylation step that has not yet been characterised, and also directly from Ang A
A newly described limb — its clinical significance in humans is still uncertain

C · THE ALDOSTERONE LIMB AND WHERE EACH DRUG CLASS ACTS



Class	Examples	Site of blockade	Key point
DRI	Aliskiren	Renin — the rate-limiting step	Lowers plasma renin activity; ALTITUDE showed harm when added to an ACEi or ARB — never combine
ACE inhibitor	Ramipril, enalapril, lisinopril	ACE (kininase II): Ang I → Ang II, and bradykinin degradation	Accumulated bradykinin explains cough and angio-oedema; raises Ang-(1–7). Chymase allows escape
ARB	Losartan, valsartan, irbesartan	AT ₁ receptor	Leaves Ang II free to act on AT ₂ R and diverts substrate to the ACE2 / Ang-(1–7) arm; no cough
MRA	Spironolactone, eplerenone, finerenone (non-steroidal)	Mineralocorticoid receptor in the principal cell and in non-epithelial tissue	Blocks aldosterone breakthrough. Finerenone (FIDELIO-DKD, FIGARO-DKD) slows CKD progression in diabetic kidney disease with less hyperkalaemia
ARNI	Sacubitril / valsartan	AT ₁ receptor + neprilysin	Neprilysin inhibition raises ANP and BNP; it must be paired with an ARB because an unopposed RAS would negate it (PARADIGM-HF). Never add an ACEi

BR Ch 11, Fig. 11.1, p. 289 and pp. 288–313. Besides the circulating endocrine system shown here, the kidney has a local tissue-based renin–angiotensin system acting by paracrine, autocrine and possibly intracrine mechanisms, with intrarenal Ang II far above plasma levels.

The renin–angiotensin system including the counter-regulatory ACE2/angiotensin-(1–7)/Mas arm.

Original schematic based on BR §Ch 11, Fig. 11.1, p. 289.

1 • The classical cascade

- **Angiotensinogen** — an α_2 -globulin synthesised by the liver, gene on the long arm of chromosome 1. Its promoter contains an **acute-phase response element binding NF- κ B**, which is why inflammation raises substrate availability.
- **Renin** — an aspartyl protease; the gene is also on chromosome 1 (1q32), with 10 exons and 9 introns. Synthesised as a 406-amino-acid preprohormone; the 23-amino-acid leader is cleaved to give **prorenin**, which is either secreted directly or packaged into dense granules in the juxtaglomerular apparatus. Renin is the **rate-limiting step** and its only substrate is angiotensinogen.
- **Prorenin activation** — the prosegment occupies the catalytic cleft. Acidification of the dense-core granules by vacuolar ATPases provides the optimal pH for the prosegment-cleaving enzymes **proconvertase 1 and cathepsin B**. Non-proteolytic ("open conformation") activation also occurs and is what the **(pro)renin receptor** exploits.
- **Angiotensin I (1-10) → angiotensin-converting enzyme**, a zinc dipeptidyl carboxypeptidase expressed strongly on endothelium, especially pulmonary. ACE is **not substrate-specific** and also **inactivates bradykinin** — the origin of ACE-inhibitor cough and angio-oedema. One gene produces two tissue-specific transcripts: the somatic form (1306 amino acids, 140–160 kDa, **two active sites**) and a shorter testicular form.
- **Angiotensin II (1-8)** — the principal effector octapeptide.

↳ BR §Ch 11, pp. 289–292

2 • Control of renin release — three mechanisms

Regulation of renin secretion · BR §Ch 11, pp. 290–292

MECHANISM	SENSOR	DETAIL
Renal baroreceptor	Juxtaglomerular cells sense afferent arteriolar wall stretch	Changes in perfusion pressure have only a small effect until a threshold of about 90 mmHg is reached, below which renin secretion rises abruptly — doubling for every 2-3 mmHg fall
Macula densa	Luminal NaCl in the thick ascending limb	Reduced NaCl delivery stimulates renin release (COX-2/PGE ₂ and nNOS mediated); this is how loop diuretics and volume depletion activate the system
Sympathetic (β_1-adrenergic)	Renal nerves	cAMP-PKA-CREB pathway raises renin transcription; blocked by β -blockers
Negative feedback	Angiotensin II on JG cells	Short-loop inhibition of further renin release

MECHANISM	SENSOR	DETAIL
Vitamin D	Liganded VDR	1,25(OH)₂D₃ transrepresses the renin gene by blocking CREB binding to the cAMP response element — the molecular basis of the inverse relationship between vitamin D, blood pressure and plasma renin activity. Trials of vitamin D supplementation for blood pressure or kidney protection have given mixed results
Metabolic	Succinate on GPR91	TCA-cycle intermediates accumulate when energy supply and demand are mismatched; succinate stimulates renin release and causes hypertension, an effect abolished in GPR91-deficient mice — a link between the diabetic milieu and RAS activation
Other local factors	—	ANP, kinins, VIP, endothelin, CGRP, dopamine, histamine and arachidonic acid derivatives all modulate renin release

3 · Receptors and actions

AT₁ versus AT₂ — and the counter-regulatory arm · BR §Ch 11, pp. 289, 292–293

RECEPTOR / PEPTIDE	EFFECTS
AT₁ receptor (G protein-coupled, no intrinsic tyrosine kinase)	Vasoconstriction (efferent > afferent), aldosterone release, proximal Na ⁺ -H ⁺ exchange, thirst, ADH release, increased sympathetic outflow, mesangial contraction (↓K _f), enhanced TGF sensitivity. Generates superoxide and hydrogen peroxide through NADPH oxidase — ROS act as second messengers activating p38 MAPK and inflammatory transcription. Transactivates non-receptor tyrosine kinases (Src, Pyk2, FAK, JAK) and the EGF and PDGF receptors : AT ₁ signalling translocates TACE/ADAM17 to the cell surface, where it sheds TNF-α, which then activates the EGF receptor → Erk1/2, PI3K and mTOR → hypertrophy and fibrosis
AT₂ receptor	Vasodilatation through NO/cGMP, antiproliferative and pro-apoptotic, natriuretic — broadly opposes AT ₁ ; up-regulated in injury and in fetal life
ACE2 → angiotensin-(1-7) → Mas receptor	The counter-regulatory arm : vasodilatation, natriuresis, antifibrotic, antiproliferative and anti-inflammatory. ACE2 converts angiotensin II to Ang(1-7) and angiotensin I to Ang(1-9). ACE2 is also the SARS-CoV-2 receptor
Non-classical components	Angiotensin III (via aminopeptidase A), angiotensin IV acting on AT ₄ /IRAP, alamandine acting on MrgD, and the (pro)renin receptor , which both increases catalytic activity of prorenin and signals independently through ERK1/2

4 · Aldosterone — completing the axis

- Angiotensin II and hyperkalaemia stimulate the zona glomerulosa to release **aldosterone**, which binds the cytosolic mineralocorticoid receptor in principal cells.

- Genomic effects: increased **ENaC** and Na⁺-K⁺-ATPase and increased ROMK, through SGK1 and inhibition of Nedd4-2 — net sodium retention with potassium and hydrogen ion secretion.
- **11β-hydroxysteroid dehydrogenase type 2** confers specificity by converting cortisol to inactive cortisone; its congenital deficiency or inhibition by liquorice produces apparent mineralocorticoid excess.
- **Non-epithelial (non-genomic) effects** — cardiac and renal fibrosis, endothelial dysfunction and inflammation. These are the effects that **escape** ACE inhibition and ARBs (aldosterone breakthrough) and are the rationale for mineralocorticoid receptor antagonism, now with the non-steroidal agent **finerenone**.

↳ Standard accepted physiology; the finerenone evidence is in BR §Ch 41, Table 41.8, p. 1197

5 • The tissue RAS

- The classical endocrine view remains valid but has been "considerably augmented" by the recognition of an **independently functioning local tissue-based RAS** acting through paracrine, autocrine and possibly **intracrine** mechanisms.
- Intrarenal angiotensin II concentrations far exceed plasma levels and are locally regulated — which is why RAS blockade has effects out of proportion to its blood-pressure lowering.
- The kidney-protective effect of RAS inhibition was first shown by **Anderson, Meyer, Rennke and Brenner in 1985** in a rodent model of progressive kidney disease, and this observation is the foundation of modern nephroprotection.

↳ BR §Ch 11, p. 289

WHERE THE PHYSIOLOGY BECOMES PRACTICE

KDIGO 2024 CKD and **KDIGO 2022 Diabetes in CKD** both specify: use an ACE inhibitor or ARB at the **maximum tolerated dose** when hypertension and albuminuria coexist; recheck blood pressure, creatinine and potassium at **2-4 weeks**; continue unless creatinine rises by more than **30%** within 4 weeks; manage hyperkalaemia without stopping the drug where possible; and **never use dual RAS blockade** (ACE inhibitor plus ARB, or either with a direct renin inhibitor) because of increased hyperkalaemia and AKI. *As reported in BR §Ch 41, Table 41.5, p. 1194.*

HIGH-YIELD · CLINICAL PEARLS

- ◆ Draw the diagram and **include the ACE2 / Ang(1-7) / Mas arm** — most candidates stop at angiotensin II and lose marks.
- ◆ Renin is the **rate-limiting step**; its only substrate is angiotensinogen. ACE is promiscuous and also degrades **bradykinin**.
- ◆ Three stimuli to renin: **baroreceptor** (threshold ~90 mmHg, doubles per 2–3 mmHg fall), **macula densa**, **β₁-sympathetic**.
- ◆ Angiotensin II constricts the **efferent more than the afferent** arteriole — the whole basis of RAS-blocker haemodynamics.
- ◆ **Vitamin D transrepresses the renin gene** through VDR-CREB interference. A one-line fact that reads as sophisticated.
- ◆ AT₁ transactivates EGFR through **TACE/ADAM17-mediated TNF-α shedding** — the fibrotic limb.
- ◆ Never dual-block. Tolerate a creatinine rise up to 30% in 4 weeks.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.15 The Ageing Kidney

2023-Oct P1 Q7(c)

Change of GFR with aging.

3

EXAMINER'S BLUEPRINT

3 marks — the structural changes with the numbers (1) + what happens to GFR, and the crucial distinction between healthy ageing and CKD (1) + the clinical consequences: drug dosing, donor selection, AKI risk, and how not to over-diagnose CKD in the old (1).

1 · Structural changes with age

The ageing kidney — what the donor studies show · BR §Ch 21, pp. 643–646 (Figs. 21.1–21.3, Table 21.1)

FEATURE	CHANGE WITH AGE
Kidney parenchymal thickness	Falls about 10% per decade on CT
Total kidney volume	Average decline 16.3 cm³ per decade (Framingham MRI study, 1852 subjects), more pronounced beyond age 60 and in men
Cortex versus medulla	Beyond 40 years cortical volume falls while medullary volume rises , so total volume stays relatively constant until about 50; beyond that medullary volume stops rising and total volume falls
Kidney size in women	Diminishes over the whole adult span, whereas in men it begins to fall in the fourth to fifth decade
Nephron number	Average 990,661 nonsclerotic glomeruli in donors aged 18–29 years versus 520,410 in donors aged 70–75 years
Glomerulosclerosis	Increases with age, of the obsolescent (ischaemic) type — Bowman space filled with collagenous material and the tuft retracted. The 95th percentile expected for age rises from 1.7% in donors aged 18–29 to 16% in those aged 70–76
Interstitial fibrosis and tubular atrophy	The "abnormal for age" threshold rises from 0.18% to 6.5% across the same age range
Cysts	Simple cysts of tubular diverticular origin increase in number and size; cortical and medullary cysts ≥ 5 mm are commoner in older men and associate with larger body surface area, albuminuria and hypertension
Arteries	Arteriosclerosis and arteriolar hyalinosis — "age-related nephrosclerosis"; atherosclerosis accelerates the decline in kidney size

The distinction the examiner wants: obsolescent global glomerulosclerosis occurs with normal ageing *and* with disease, but **segmental and solidification forms of glomerulosclerosis occur only with disease and are never simply an age-related finding**. FSGS is not a feature of healthy human ageing. (BR p. 645)

2 · What happens to GFR

- Measured GFR declines from about the fourth decade, conventionally by **0.8–1.0 mL/min/1.73 m² per year**, so that a healthy 80-year-old may have a GFR 30–40% below that of a 30-year-old.
- The decline is **not universal**: in longitudinal cohorts a substantial minority of healthy older people show no significant fall, which argues that much of the "average" decline is driven by accumulated vascular and comorbid disease rather than by ageing itself.
- Renal functional reserve is lost first.** The GFR response to a protein load is clearly blunted in the elderly compared with the young — the resting GFR may still look acceptable while the reserve has gone (see Topic 1.6).
- Concentrating and diluting ability fall.** Older healthy men have *higher* AVP levels but *lower* maximum urine osmolality, indicating reduced sensitivity to AVP; aged rats show reduced aquaporins, urea transporters and V2 receptor. Thirst perception is also blunted — the combination that makes the elderly patient prone to both hypernatraemia and hyponatraemia.
- Sodium conservation and potassium and acid excretion are all slower, so the old kidney handles a salt load, a potassium load or an acid load less well.
- Renal blood flow falls more than GFR, so the **filtration fraction rises** — the surviving nephrons are hyperfiltering.

↳ BR §Ch 21, pp. 643–661; BR §Ch 3, Fig. 3.4, p. 81; BR §Ch 10, p. 286

IS LOW EGFR IN AN OLDER PERSON "CKD"? — KDIGO 2024

KDIGO retains a **single threshold of eGFR <60 mL/min/1.73 m² for more than 3 months** as CKD, irrespective of age, and rejects age-adapted thresholds — because even in older people a reduced eGFR carries excess risk of kidney failure, cardiovascular events and death. What KDIGO 2024 emphasises instead is **risk-based** management using the cause-GFR-albuminuria (CGA) classification and the kidney failure risk equation, so that an 80-year-old with G3a A1 and a stable trajectory is monitored rather than referred. Albuminuria, not eGFR alone, is what separates age-related decline from disease. *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD, Kidney Int 2024;105(4S):S117–S314.*

3 · Clinical consequences

- **Drug dosing** — creatinine generation falls with sarcopenia, so serum creatinine underestimates the true fall in GFR. Use a cystatin C-based or combined equation where the stakes are high, and dose renally cleared drugs accordingly.
- **Susceptibility to AKI** — loss of functional reserve, impaired autoregulation, arteriolar hyalinosis and polypharmacy make the old kidney vulnerable to a mild insult.
- **Living donor selection** — the reference ranges above exist precisely so that an implantation biopsy in a 70-year-old donor is interpreted *for age*: up to 4 globally sclerotic glomeruli in a 16-glomerulus biopsy is within the expected range at 76 years, whereas at 25 years one is the limit.
- **Avoid over-diagnosis and over-treatment** — but also avoid dismissing genuine disease. Albuminuria, an active sediment, a falling trajectory, or segmental sclerosis on biopsy all indicate disease rather than ageing.
- **Electrolyte fragility** — blunted thirst plus reduced concentrating ability makes hypernatraemia common in the dependent elderly, while thiazides and reduced free-water clearance make hyponatraemia the commonest electrolyte abnormality in the older outpatient.

↳ BR §Ch 21, pp. 643–661; BR §Ch 60

HIGH-YIELD · CLINICAL PEARLS

- ◆ Quote numbers: parenchymal thickness **–10% per decade**, volume **–16.3 cm³ per decade**, nephrons **990,661 → 520,410** from the twenties to the seventies.
- ◆ Cortex shrinks while medulla expands until about age 50 — total volume can look deceptively normal.
- ◆ Glomerulosclerosis expected for age: **1.7% at 18–29 years, 16% at 70–76 years**. Interpret a donor biopsy *for age*.
- ◆ **Obsolescent** global sclerosis = ageing or disease. **Segmental and solidification** sclerosis = disease only. Never age.
- ◆ GFR falls **~1 mL/min/1.73 m² per year** after 40 — but not in everyone, and **reserve is lost before resting GFR**.
- ◆ Higher AVP but lower urine osmolality in the old — reduced sensitivity, not reduced hormone.
- ◆ KDIGO 2024 keeps **eGFR <60** as the threshold at every age, and manages by risk rather than by an age-adapted cut-off.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.16 Endocrine Functions of the Kidney**2025–26 P1 Q6(a)**

Mention the endocrine functions of kidneys.

3

2025–26 P1 Q6(b)

Discuss their role in homeostasis.

7

EXAMINER'S BLUEPRINT

Two asks, ten marks, and the split is doing all the work. Part (a) is a **3-mark ENUMERATION** — the examiner wants a list, fast, and the mark is lost by writing prose. Give the two halves: the kidney as an **ENDOCRINE ORGAN** (erythropoietin, renin, calcitriol, klotho, prostaglandins, kallikrein-kinin, endothelin, urodilatin, dopamine, renalase) and the kidney as an **ENDOCRINE TARGET** (PTH, calcitriol, aldosterone, ADH, ANP/BNP, insulin, FGF-23, thyroid hormone). A single sentence naming the kidney as a site of hormone **DEGRADATION** earns its place. Part (b) is 7 marks and must be organised by **HOMEOSTATIC AXIS, not by hormone** — oxygen and erythropoiesis, blood pressure and extracellular volume, calcium-phosphate-bone, acid-base, and sodium and water. Then close the answer where the examiner is heading: **WHAT FAILS IN CKD** — anaemia, secondary hyperparathyroidism, hypertension, acidosis — and the **THERAPEUTIC COROLLARY** of each, because every endocrine function of the kidney has become a drug class. Name the HIF-PHD oxygen sensor and the 2019 Nobel Prize, name klotho, and give numbers.

(a) Enumeration — the kidney as endocrine organ and as endocrine target

3

The frame to open with

The kidney is **BOTH AN ENDOCRINE ORGAN AND AN ENDOCRINE TARGET ORGAN**, and it is also a major site of **HORMONE CATABOLISM**. It **SECRETES** erythropoietin, renin and calcitriol as true circulating hormones, releases **klotho** as a circulating co-factor, and generates a set of **INTRARENAL AUTOCRINE AND PARACRINE MEDIATORS** (prostaglandins, kinins, endothelin, urodilatin, dopamine, nitric oxide, adenosine). It **RESPONDS** to parathyroid hormone, calcitriol, aldosterone, vasopressin, the natriuretic peptides, insulin, FGF-23 and thyroid hormone. And it **DEGRADES** insulin, PTH, glucagon, calcitonin, β 2-microglobulin and most small peptide hormones — which is why insulin requirement falls and PTH fragments accumulate as GFR declines.

BR §Ch 1–3; CCN §Ch 1–5

THE KIDNEY AS AN ENDOCRINE ORGAN — what it makes, where, and why · BR §Ch 1–3 for the anatomy and the erythropoietin and renin cell types; BR §Ch 11 (Vasoactive Molecules and the Kidney) for prostaglandins, kinins,

endothelin, natriuretic peptides and dopamine; CCN §Ch 1–5. The renalase entry is declared as material beyond the two source textbooks

HORMONE / MEDIATOR	SITE OF PRODUCTION	PRINCIPAL STIMULUS	PRINCIPAL ACTION
ERYTHROPOIETIN	PERITUBULAR INTERSTITIAL FIBROBLASTS of the deep cortex and outer medulla (renal EPO-producing cells, REPC), a neural-crest-derived population; NOT tubular cells	Tissue hypoxia sensed by the HIF-PHD system; anaemia, hypoxaemia, high altitude, cobalt, androgens	Binds EPO-R on erythroid colony-forming units, prevents their apoptosis and drives terminal erythroid differentiation. Around 90% of adult EPO is renal; the liver is the fetal source and retains only a minor capacity
RENIN (and prorenin)	JUXTAGLOMERULAR GRANULAR CELLS — modified smooth muscle cells of the terminal afferent arteriole; gene REN on chromosome 1q32	The THREE STIMULI : (1) renal baroreceptor — a fall in afferent arteriolar wall stretch; (2) MACULA Densa — reduced NaCl delivery sensed through NKCC2, signalled by COX-2 / PGE₂ and nNOS (adenosine acting at A1 is the inhibitory arm); (3) β1-ADRENERGIC sympathetic stimulation through cAMP	Aspartyl protease; cleaves hepatic angiotensinogen to angiotensin I. cAMP is the stimulatory second messenger and CALCIUM IS INHIBITORY — the "calcium paradox" of renin release
CALCITRIOL — 1,25-dihydroxyvitamin D	PROXIMAL TUBULE mitochondria , by 1α-HYDROXYLASE (CYP27B1) , acting on 25(OH)D taken up at the brush border as the vitamin-D-binding-protein complex through MEGALIN-CUBILIN	UP : PTH, hypocalcaemia, hypophosphataemia, low FGF-23. DOWN : FGF-23, hyperphosphataemia, and calcitriol itself (which induces the degrading enzyme CYP24A1 , 24-hydroxylase)	The only obligatory site of vitamin D activation. Drives intestinal calcium and phosphate absorption, suppresses the PTH gene, suppresses renin transcription, and regulates bone remodelling

HORMONE / MEDIATOR	SITE OF PRODUCTION	PRINCIPAL STIMULUS	PRINCIPAL ACTION
KLOTHO (α Klotho)	DISTAL CONVOLUTED TUBULE predominantly, also proximal tubule, parathyroid and choroid plexus; gene KL on chromosome 13	Downregulated by uraemia, inflammation, angiotensin II and oxidative stress	DUAL IDENTITY. As a MEMBRANE CO-RECEPTOR it converts FGFR1(IIIc) into a high-affinity receptor for FGF-23 . Shed by ADAM10/17 it circulates as SOLUBLE KLOTHO , a true hormone that stabilises TRPV5 at the surface, modulates ROMK and NaPi-2a, and inhibits Wnt, IGF-1 and TGF- β signalling — anti-senescence and anti-fibrotic
PROSTAGLANDINS — PGE ₂ , PGI ₂ , TXA ₂	COX-1 constitutively in collecting duct and vasculature; COX-2 in the MACULA Densa and medullary interstitial cells. PGE ₂ made by medullary mPGES	Angiotensin II, vasopressin, endothelin, volume depletion, low NaCl at the macula densa	Vasodilatory brake that PRESERVES RENAL BLOOD FLOW IN VOLUME DEPLETION ; stimulates renin; inhibits sodium reabsorption in the TAL and collecting duct and antagonises the action of vasopressin . Blocking them is the entire toxicology of NSAIDs
KALLIKREIN-KININ SYSTEM	CONNECTING TUBULE CELLS secrete tissue kallikrein into the lumen; it cleaves kininogen to bradykinin and kallidin	Aldosterone, PGE ₂ , high potassium intake	Acts on the B2 receptor to release NO and PGE ₂ — vasodilatation and natriuresis . Degraded by ACE (kininase II) , which is why ACE inhibitors potentiate kinins — the mechanism of both the cough/angio-oedema and part of the nephroprotection

HORMONE / MEDIATOR	SITE OF PRODUCTION	PRINCIPAL STIMULUS	PRINCIPAL ACTION
ENDOTHELIN-1	Endothelium, mesangium, and above all the INNER MEDULLARY COLLECTING DUCT — the highest ET-1 -producing tissue in the body	Shear stress, angiotensin II, hyperglycaemia, proteinuria, salt loading	ETA = vasoconstriction, mesangial contraction, fibrosis, podocyte injury. ETB on the collecting duct = NATRIURESIS through NO, with inhibition of ENaC and of vasopressin-driven water reabsorption. Therapeutic target: sparsentan, atrasentan, zibotentan
URODILATIN	DISTAL TUBULE AND COLLECTING DUCT — an ANP-family peptide from the same NPPA gene, differentially processed (ANP 95-126)	Volume expansion, raised central venous pressure	Acts LUMINALLY on inner medullary collecting duct NPR-A, generating cGMP and inhibiting ENaC — a paracrine natriuretic hormone that never enters the circulation . More resistant to neprilysin than ANP. Synthetic form = ularitide
DOPAMINE	PROXIMAL TUBULE , decarboxylated from circulating L-DOPA by AADC — the kidney is a genuine dopamine-synthesising organ independent of nerves	A high-salt diet	Autocrine-paracrine natriuretic hormone. D1-like receptors inhibit NHE3 and basolateral Na⁺-K⁺-ATPase . Defective D1-receptor coupling, from GRK4 polymorphisms , is one of the best-defined mechanisms of SALT-SENSITIVE HYPERTENSION

HORMONE / MEDIATOR	SITE OF PRODUCTION	PRINCIPAL STIMULUS	PRINCIPAL ACTION
RENALASE	PROXIMAL TUBULE , secreted into blood and urine	Catecholamine surge	A secreted FAD-dependent amine oxidase that metabolises circulating catecholamines. Deficient in CKD, and proposed as one mechanism of uraemic sympathetic overactivity. Recent, and declared as filled-gap content
1,25D-independent minor roles	Various	—	The kidney also generates NITRIC OXIDE (nNOS in the macula densa, eNOS in the endothelium), ADENOSINE (the mediator of tubuloglomerular feedback at the A1 receptor), ATP , and angiotensin II locally — an intrarenal RAS that operates at concentrations far above plasma

THE KIDNEY AS AN ENDOCRINE TARGET — the second half of the enumeration, and the half candidates forget · BR §Ch 2–3 and §Ch 11; CCN §Ch 1–5. The thyroid, insulin and sex-hormone entries are standard endocrine physiology assumed by both textbooks and are declared as filled-gap content

HORMONE	RECEPTOR AND NEPHRON SITE	RENAL ACTION
PARATHYROID HORMONE	PTH1R , proximal tubule and distal convoluted tubule	PHOSPHATURIC — retrieves NaPi-2a and NaPi-2c from the brush border. Stimulates CYP27B1 and inhibits CYP24A1. Increases distal calcium reabsorption through TRPV5. Inhibits proximal NHE3, producing a mild proximal bicarbonate leak
CALCITRIOL	VDR , distal convoluted tubule and collecting duct	Increases TRPV5, calbindin-D28k and NCX1 — transcellular calcium reabsorption. Negative transcriptional regulator of the RENIN gene — the mechanistic link between vitamin D deficiency and hypertension. Autoregulates by inducing CYP24A1

HORMONE	RECEPTOR AND NEPHRON SITE	RENAL ACTION
ALDOSTERONE	MINERALOCORTICOID RECEPTOR , principal cells of the connecting tubule and cortical collecting duct; also intercalated cells	Through SGK1 and inhibition of Nedd4-2 : increases ENaC surface expression, Na ⁺ -K ⁺ -ATPase and ROMK. Sodium retention, potassium secretion and distal acidification . Specificity conferred by 11β-HSD2 , which converts cortisol to inactive cortisone
VASOPRESSIN (ADH)	V2 receptor, basolateral principal cell; V1a on vasa recta and mesangium	Gs to cAMP to PKA, phosphorylating AQP2 at Ser256 and trafficking it to the apical membrane. Also upregulates UT-A1/UT-A3 urea transporters, NKCC2 and ENaC — vasopressin builds the medullary gradient as well as using it
ANP AND BNP	NPR-A (guanylyl cyclase A) , glomerulus and inner medullary collecting duct	cGMP-mediated: afferent dilatation with efferent constriction raises GFR; inhibits ENaC and the medullary Na⁺-K⁺-ATPase; suppresses renin and aldosterone . Degraded by NEPRILYSIN — hence sacubitril
INSULIN	Insulin receptor, all nephron segments	ANTINATRIURETIC — stimulates NHE3, NKCC2, NCC and ENaC, and this is a principal mechanism of hypertension in insulin resistance. The kidney also performs 25% of endogenous glucose production in the post-absorptive state and degrades 30-40% of circulating insulin
FGF-23	FGFR1(IIIc) with KLOTHO as obligate co-receptor , proximal and distal tubule	PHOSPHATURIC — internalises NaPi-2a and NaPi-2c. Suppresses CYP27B1 and induces CYP24A1 , so it lowers calcitriol — the opposite of PTH on this axis. In the DCT it increases NCC and TRPV5. Klotho-independent action on cardiac FGFR4 drives left ventricular hypertrophy
THYROID HORMONE	Nuclear thyroid receptors, proximal tubule	Permissive for normal renal growth and nephron maturation; increases renal blood flow, GFR, Na ⁺ -K ⁺ -ATPase and NHE3. Hypothyroidism reduces measured GFR by 20-40% and causes hyponatraemia; treating it raises creatinine-based eGFR without any change in kidney structure

HORMONE	RECEPTOR AND NEPHRON SITE	RENAL ACTION
Others worth naming	—	Glucocorticoids (free water excretion, GFR), catecholamines ($\alpha 1$ on the proximal tubule, $\beta 1$ on the JG cell), growth hormone and IGF-1 (hyperfiltration), oestrogen and testosterone (sex differences in transporter expression), adrenomedullin and PTHrP

(b) The role of these hormones in homeostasis

7

Five axes: **(1) OXYGEN AND ERYTHROPOIESIS · (2) BLOOD PRESSURE AND EXTRACELLULAR VOLUME · (3) CALCIUM, PHOSPHATE AND BONE · (4) ACID-BASE · (5) SODIUM AND WATER.** Give one short block per axis with the mediator, the sensor, the effector and the number. Then a closing block on what happens when the endocrine kidney fails. That structure gets all seven marks; a hormone-by-hormone list gets four.

Axis 1 — Oxygen sensing and erythropoiesis

- **The sensor is the HIF-PROLYL HYDROXYLASE SYSTEM, and this is the single most examinable piece of modern renal endocrinology.** In **NORMOXIA**, **PROLYL HYDROXYLASE DOMAIN enzymes (PHD1-3, genes EGLN1-3)** hydroxylate specific proline residues on the **HIF- α** subunit, using **MOLECULAR OXYGEN, 2-OXOGLUTARATE, FERROUS IRON AND ASCORBATE** as cofactors. Hydroxylated HIF- α is recognised by the **VON HIPPEL-LINDAU (VHL) E3 UBIQUITIN LIGASE** and destroyed in the proteasome within minutes.
- In **HYPOXIA** the hydroxylases stall for want of their substrate oxygen, **HIF- α escapes degradation**, translocates, dimerises with **HIF-1 β (ARNT)** and binds the **hypoxia response element** of the **EPO** gene. **HIF-2 α , not HIF-1 α , is the isoform that drives renal erythropoietin.** A second oxygen-dependent enzyme, **FIH-1**, hydroxylates an asparagine residue and blocks recruitment of p300/CBP — a fine-tuning switch.
- **Because the hydroxylases need iron and 2-oxoglutarate, the oxygen sensor is also an IRON sensor** — which is why HIF stabilisation coordinately raises EPO, lowers **HEPCIDIN**, and upregulates transferrin, transferrin receptor, DMT1 and ferroportin. Erythropoiesis and iron supply are switched on by one signal.
- **The 2019 Nobel Prize in Physiology or Medicine went to Kaelin, Ratcliffe and Semenza for this pathway.** Germline proof of principle: **CHUVASH POLYCYTHAEMIA (VHL R200W)** and gain-of-function **HIF2A** mutations causing erythrocytosis with paraganglioma.

- **Homeostatic logic:** the kidney is the ideal oxygen sensor because renal oxygen consumption is tightly coupled to sodium reabsorption, which is itself coupled to GFR and therefore to renal plasma flow. **A fall in oxygen-carrying capacity changes renal tissue pO_2 without changing renal blood flow** — so the kidney reports on arterial oxygen CONTENT, which is exactly the variable erythropoiesis must defend.

↳ Declared as material beyond the two source textbooks; the erythropoietin cell of origin and the outline of HIF biology are given in BR §Ch 1–3 and in the BR anaemia of CKD chapter

Axis 2 — Blood pressure and extracellular fluid volume

- **Renin is the rate-limiting step of the entire system and the kidney is its only meaningful source.** Angiotensinogen (hepatic α_2 -globulin) is cleaved to the decapeptide **angiotensin I**, then by **ACE** on pulmonary and systemic endothelium to the octapeptide **angiotensin II**.
- **Angiotensin II at the AT1 receptor is the most efficient sodium-retaining signal the body possesses:** it constricts the efferent arteriole to preserve GFR at low perfusion pressure, directly stimulates proximal NHE3, releases **ALDOSTERONE** from the zona glomerulosa, releases vasopressin, stimulates thirst and salt appetite, and augments sympathetic outflow. The **AT2 receptor and the ACE2 / angiotensin-(1-7) / Mas arm are counter-regulatory** — vasodilatory, natriuretic and antifibrotic.
- **Against it stands a natriuretic-vasodilator set that is also renal:** prostaglandins, kinins, medullary endothelin acting at ETB, urodilatin, dopamine and nitric oxide. **Normal blood pressure is the resting position of this tug-of-war.** This is why an NSAID given to a volume-depleted, RAAS-activated patient causes AKI — it removes one side of the balance.
- **PRESSURE NATRIURESIS is the master mechanism, and the endocrine systems set its slope, not its existence.** Guyton demonstrated that the kidney has infinite gain for long-term blood pressure control: any sustained hypertension must involve a rightward shift of the pressure-natriuresis relationship. **Angiotensin II, aldosterone and sympathetic activity shift it right; natriuretic peptides, dopamine, kinins and nitric oxide shift it left.**
- **The clinical corollary:** every antihypertensive that works long-term works by resetting pressure natriuresis, and **a transplanted kidney carries its blood pressure phenotype with it** — the Dahl cross-transplantation experiments and, in humans, the observation that blood pressure follows the donor kidney.

↳ BR §Ch 11; BR §Ch 1–3; CCN §Ch 1–5. Guyton pressure natriuresis and the cross-transplantation data are declared as filled-gap content

Axis 3 — Calcium, phosphate and bone: the kidney as the hub of the bone-kidney-parathyroid-gut axis

- **The kidney is the only organ that both ACTIVATES vitamin D and EXECUTES the phosphaturic response**, so it sits at the centre of the axis rather than at its periphery.
- **Calcium arm:** hypocalcaemia is sensed by the parathyroid **CaSR**, PTH rises, and PTH acts on the proximal tubule to increase **CYP27B1** and on the distal tubule to increase **TRPV5**-mediated calcium reabsorption. Calcitriol then raises intestinal calcium absorption and closes the loop by suppressing the PTH gene. **Roughly 98% of the 10 g of calcium filtered daily is reabsorbed — 65% proximally and paracellularly, 20% in the TAL through the claudin-16/19 pore driven by the lumen-positive voltage, and 10-15% transcellularly in the DCT, which is the only regulated step.**
- **Phosphate arm:** the effector is **FGF-23 from osteocytes**, and the kidney is both its target and, through klotho, the organ that makes the target responsive. FGF-23 internalises **NaPi-2a and NaPi-2c**, so phosphate is excreted, and simultaneously

suppresses calcitriol, so no more phosphate is absorbed from the gut. **PTH is also phosphaturic but RAISES calcitriol; FGF-23 is phosphaturic and LOWERS it. That single contrast is worth a mark.**

- **KLOTHO is the variable that makes the whole axis fail first in CKD.** Klotho is expressed in the DCT and falls very early — before phosphate rises, before PTH rises. **The sequence of CKD-MBD is: KLOTHO DOWN → FGF-23 UP → CALCITRIOL DOWN → PTH UP → and only at the end, PHOSPHATE UP.** Phosphate is the last abnormality to appear and the one most commonly measured — a diagnostic trap.
- Soluble klotho is itself a hormone: it stabilises **TRPV5** at the apical membrane by removing terminal sialic acids, it inhibits **Wnt** and **IGF-1** signalling, and it is anti-fibrotic. **Klotho-null mice develop a premature-ageing syndrome with hyperphosphataemia, vascular calcification, gonadal atrophy and a short lifespan — a phenotype rescued by a low-phosphate diet, which established phosphate as the toxin.**

↳ BR §Ch 1–3 and the BR CKD-MBD chapter; CCN §Ch 1–5 and §Ch 11. The klotho biology and the sequence of CKD-MBD are declared as partly beyond the two source textbooks

The CKD-MBD cascade, in the order in which the abnormalities appear

① PHOSPHATE RETENTION — the first event

Nephron loss reduces the filtered load of phosphate. Serum phosphate stays **NORMAL** at first because FGF-23 and PTH raise fractional excretion — a new steady state is bought at the price of a permanently higher PTH, and the cycle repeats with every further loss of GFR.

Overt hyperphosphataemia (> 4.6 mg/dL, 1.5 mmol/L) is late: about 4% of patients at eGFR 39–30, 17% at 29–20 and 38% below 20 mL/min/ 1.73 m².

② ↑ FGF-23 and ↓ α-KLOTHO — the earliest measurable change

FGF-23 is raised **BEFORE** phosphate and before PTH: > 100 RU/mL in ~31% of patients at eGFR above 70 and in more than 90% below 20 .

It inhibits NaPi-IIa, NaPi-IIc and Pit-1 (phosphaturia) and suppresses CYP27B1 (1α-hydroxylase) while promoting vitamin D catabolism — the opposite of PTH's effect on calcitriol.

Tissue α-klotho, the obligatory co-receptor shed by the distal tubule, is downregulated early, so FGF-23 resistance develops; iron deficiency, inflammation and erythropoietin all raise FGF-23 further.

③ ↓ CALCITRIOL

1,25(OH)₂D falls because FGF-23 and retained phosphate inhibit 1α-hydroxylase, because less 25(OH)D is delivered to the proximal tubule, because 25(OH)D levels themselves fall, and because C-terminal PTH fragments accumulate.

1,25(OH)₂D < 22 pg/mL in 16% at eGFR above 70 , 31% at 49–40, 45% at 39–30, 52% at 29–20 and 67% below 20 .

④ HYPOCALCAEMIA

Low calcitriol reduces intestinal calcium absorption, and the skeleton is resistant to the calcemic action of PTH (low calcitriol, downregulated PTH receptor, phosphate retention, C-terminal fragments).

This is a **LATE** event: calcium < 8.4 mg/dL (2.1 mmol/L) in under 2% until eGFR 39–30, then 6% at 29–20 and 17% below 20 — in practice a CKD G4 finding.

⑤ SECONDARY HYPERPARATHYROIDISM

Driven by hypocalcaemia, by low calcitriol releasing the PTH gene from suppression, and by phosphate acting directly — it blunts the calcium-sensing receptor and stimulates parathyroid growth independently of calcium and calcitriol.

iPTH > 65 pg/mL in 11% at eGFR above 80 , 21% at 69–60, 28% at 59–50, 39% at 49–40, 54% at 39–30, 67% at 29–20 and 84% below 20 .

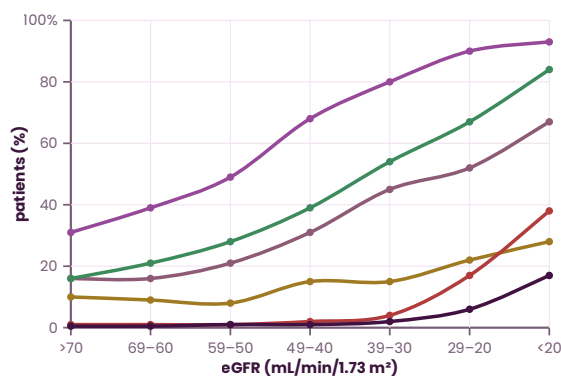
The gland itself changes: hyperplasia begins within days experimentally and progresses from diffuse to nodular, monoclonal expansion, with decreased vitamin D receptor, calcium receptor and α-klotho expression and a raised calcium set-point — which is why advanced disease resists active vitamin D and calcimimetics.

⑥ BONE AND VESSEL

BONE — renal osteodystrophy, classified by turnover, mineralisation and volume (below). Fractures, bone pain, subperiosteal erosions and resorption of the terminal digits, brown tumours, kyphoscoliosis, slipped epiphysis and growth retardation in children.

VESSELS AND SOFT TISSUE — extraskeletal calcification aggravated by a persistently high calcium-phosphate product: vascular (most common), myocardial, pulmonary and periarticular; acute periartthritis from calcium phosphate crystals; pruritus; and rarely calciphylaxis. Hyperphosphataemia carries a strong independent mortality risk, elevated calcium an intermediate one, and high or low PTH a weak one.

Percentage of patients with the abnormality, by eGFR band (CCN Fig. 88.3 data)



■ FGF-23 > 100 RU/mL
 ■ 1,25(OH)₂D < 22 pg/mL
 ■ iPTH > 65 pg/mL
 ■ 25(OH)D < 15 ng/mL
 ■ phosphate > 4.6 mg/dL
 ■ calcium < 8.4 mg/dL

WHAT THE CURVES SHOW

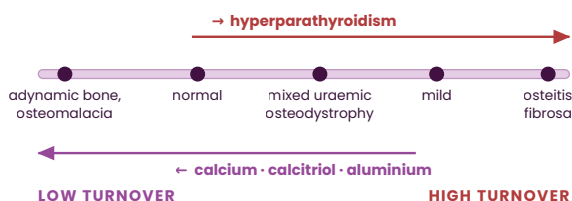
Read the curves from left to right and the **ORDER** of the cascade is obvious: FGF-23 is already abnormal in a third of patients while phosphate and calcium are still normal in almost everyone; calcitriol and PTH follow; hyperphosphataemia and hypocalcaemia appear only in CKD G4–G5.

At the individual level there is wide variability in early CKD — some patients have a raised FGF-23 with a normal iPTH, others a raised iPTH with a normal FGF-23, and others both.

The bone lesion: the KDIGO turnover / mineralisation / volume (TMV) classification

TURNOVER	MINERALISATION	VOLUME
Low	Normal	Low
Normal	Abnormal	Normal
High		High

Any combination of the three descriptors is possible in a given biopsy.



READING THE CLASSIFICATION

TURNOVER is the rate of skeletal remodelling, measured by double-tetracycline labelling (bone formation rate, activation frequency). Tetracycline 500 mg three times daily for 2 days, a 10-day interval, then demeclocycline 300 mg three times daily for 3 days, and biopsy 4 days later.

MINERALISATION is how well collagen is calcified — osteoid volume and thickness, mineralisation lag time. Impaired by vitamin D deficiency, calcium or phosphate deficiency, acidosis and aluminium.

VOLUME is the amount of bone per unit volume of tissue.

The classical lesions map onto it: osteitis fibrosa = high turnover; osteomalacia = a mineralisation defect with excess unmineralised osteoid; adynamic bone disease = a paucity of cells, low turnover, NO excess osteoid; mixed ureaemic osteodystrophy = both high turnover and a mineralisation defect. The spectrum runs from low turnover (driven by calcium, calcitriol and aluminium) to high turnover (driven by hyperparathyroidism).

Low turnover now predominates: 59% of 489 biopsies in one series, and 62% of white but only 32% of black patients in another; a mineralisation defect was found in only 3%. Adynamic bone has largely replaced osteomalacia. Both extremes fracture, and low turnover also predisposes to vascular calcification because bone cannot buffer a calcium load.

Serum PTH is a poor surrogate: it predicts high turnover reliably only above about 500 pg/mL. Biopsy remains the gold standard, and bisphosphonates and denosumab should not be given in CKD unless work-up shows a high-turnover state.

The CKD-MBD cascade, in the order in which the abnormalities appear.

Original schematic based on CCN §Ch 88, Figs. 88.1, 88.4–88.6, pp. 1003–1005.

Axis 4 — Acid-base

- **This axis is more enzymatic than endocrine, but it is hormonally driven and it belongs in the answer.** The kidney defends pH by reclaiming filtered bicarbonate (80–90% proximally through NHE3 and carbonic anhydrases II and IV) and by generating new bicarbonate through **AMMONIAGENESIS from glutamine in the proximal tubule** and titratable acid excretion.
- **The endocrine controls:** **ALDOSTERONE** drives the type A intercalated cell H^+ -ATPase and, indirectly through ENaC-generated lumen negativity, the whole of distal acidification. **ANGIOTENSIN II** stimulates proximal NHE3 and ammoniagenesis. **PTH inhibits proximal bicarbonate reabsorption**, which is the mechanism of the mild proximal acidosis of hyperparathyroidism. **Endothelin** is a key stimulus to proximal acidification in acidosis.
- **Why it fails in CKD:** acidosis of CKD is initially a defect of **AMMONIAGENESIS PER NEPHRON, not of bicarbonate reclamation**. Total ammonium excretion falls because nephron number falls, even though each surviving nephron makes more. **Metabolic acidosis then accelerates muscle proteolysis, bone buffering, insulin resistance, and CKD progression itself** — hence the alkali-therapy trials.
- **The feedback loop that closes the circle:** acidosis suppresses renal 1α -hydroxylase and raises PTH, and hyperaldosteronism worsens metabolic alkalosis. **The acid-base and calcium axes are not independent.**

↳ BR §Ch 1–3 and the BR acid-base chapters; CCN §Ch 1–5

Axis 5 — Sodium, water and tonicity

- **TONICITY is defended by water, VOLUME by sodium, and the kidney runs both circuits with different sensors and different hormones.** Confusing the two is the commonest error in a general nephrology viva.
- **Water / tonicity:** hypothalamic osmoreceptors sense a 1–2% rise in plasma osmolality, vasopressin is released, and the **V2-cAMP-AQP2** axis traffics water channels into the apical membrane of the principal cell. **Urine osmolality can range from 50 to 1200 mOsm/kg — a 24-fold operating range.** The countercurrent multiplier of the loop of Henle, the urea recycling loop and the vasa recta countercurrent exchanger provide the gradient that vasopressin exploits.
- **Sodium / volume:** the sensors are the afferent arteriolar baroreceptor, the macula densa, the cardiopulmonary and arterial baroreceptors. The effectors are **RAAS and the sympathetic nervous system (retaining) against ANP, BNP, urodilatin, dopamine, prostaglandins and kinins (excreting)**. Aldosterone can drive urinary sodium below 10 mmol/L in severe volume depletion and the natriuretic peptides can drive it above 200 mmol/day on a salt load.

- **Where the two circuits interact:** baroreceptor-mediated, NON-OSMOTIC vasopressin release in effective arterial volume depletion overrides the osmostat. **That single fact explains the hyponatraemia of heart failure, cirrhosis and nephrotic syndrome, and explains why the treatment is to correct the volume signal, not to give salt.**

↳ BR §Ch 1–3 and §Ch 11; CCN §Ch 1–5 and §Ch 8–9

The closing paragraph the examiner is waiting for — what fails in CKD

Endocrine failure of the kidney, and the drug class that answers each failure · BR §Ch 1–3 for the physiology; the guideline statements are KDIGO 2012 Anaemia, KDIGO 2017 CKD-MBD and KDIGO 2024 CKD; the trial data are declared as material beyond the two source textbooks

ENDOCRINE FUNCTION LOST	CLINICAL CONSEQUENCE	THERAPEUTIC COROLLARY
ERYTHROPOIETIN — REPC transdifferentiate into myofibroblasts and stop making EPO	NORMOCYTIC NORMOCHROMIC ANAEMIA , typically appearing at eGFR below 30 mL/min/1.73 m² (earlier in diabetes). Compounded by inflammation-driven HEPCIDIN excess causing functional iron deficiency, shortened red cell survival, blood loss on dialysis and uraemic inhibition of erythropoiesis	ESAs — epoetin alfa/beta, darbepoetin, methoxy PEG-epoetin beta — after iron repletion. KDIGO 2012 Anaemia: do not initiate an ESA when Hb is ≥10 g/dL in CKD-ND; in dialysis initiate when Hb is between 9 and 10 g/dL to avoid falling below 9; DO NOT INTENTIONALLY MAINTAIN Hb ABOVE 11.5 g/dL , on the evidence of the NORMAL HEMATOCRIT TRIAL, CHOIR, CREATE and TREAT (in TREAT, darbepoetin to 13 g/dL doubled the risk of stroke, HR 1.92). Plus HIF-PHIs — see below
CALCITRIOL — loss of 1α-hydroxylase with loss of functioning proximal tubular mass, and active suppression by FGF-23	HYPOCALCAEMIA, SECONDARY HYPERPARATHYROIDISM, osteitis fibrosa cystica , and in India a heavy burden of florid disease with brown tumours from late presentation on a background of nutritional vitamin D deficiency	Active vitamin D — calcitriol, alfacalcidol, paricalcitol, doxercalciferol. KDIGO 2017 CKD-MBD reserves calcitriol and analogues for CKD G4-G5 and does not recommend their routine use in G3a-G3b , because they raise calcium and phosphate. CALCIMIMETICS — cinacalcet, etelcalcetide, evocalcet — lower PTH while lowering calcium and phosphate

ENDOCRINE FUNCTION LOST	CLINICAL CONSEQUENCE	THERAPEUTIC COROLLARY
KLOTHO	Resistance to FGF-23 at the parathyroid despite very high levels; loss of anti-fibrotic and anti-senescence signalling; VASCULAR CALCIFICATION	No klotho-replacement therapy exists. Phosphate binders, dietary phosphate restriction and control of hyperparathyroidism are the surrogates. Declared as filled-gap content
APPROPRIATE RENIN REGULATION — renin is inappropriately normal or high for the degree of sodium retention	VOLUME-DEPENDENT AND RENIN-DEPENDENT HYPERTENSION , left ventricular hypertrophy, proteinuria and progression. Aggravated by afferent sympathetic signalling from the diseased kidney	RAAS BLOCKADE — ACE inhibitor or ARB at the maximum tolerated dose plus sodium restriction and a diuretic. Non-steroidal MRA finerenone (FIDELIO-DKD, FIGARO-DKD) and SGLT2 inhibitors (DAPA-CKD, EMPA-KIDNEY) now sit on top of it
AMMONIAGENESIS	METABOLIC ACIDOSIS , muscle wasting, bone buffering, accelerated CKD progression	Oral sodium bicarbonate. KDIGO 2024 CKD suggests treating to maintain serum bicarbonate within the normal range; note that BiCARB in older adults showed no benefit and the evidence is weaker than the physiology suggests. Be honest about this
INSULIN AND PEPTIDE DEGRADATION	Falling insulin requirement and HYPOGLYCAEMIA as GFR declines ; accumulation of PTH fragments confounding immunoassays; β 2-microglobulin amyloidosis in long-term dialysis	Dose reduction of insulin and of renally cleared sulfonylureas; use an intact (second- or third-generation) PTH assay ; high-flux or haemodiafiltration membranes for β 2-microglobulin

HIF-PHIS — THE THERAPEUTIC PAY-OFF OF THE OXYGEN-SENSING STORY, AND THE LINE THAT DATES YOUR ANSWER

HYPOXIA-INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITORS are orally active small molecules that inhibit PHD1-3, stabilise HIF- α and produce a coordinated **physiological** erythropoietic response: a modest rise in endogenous EPO to within or near the physiological range, a **fall in HEPICIDIN**, increased transferrin and duodenal iron absorption, and therefore efficacy **even in the inflamed, ESA-hyporesponsive patient**. Agents: **ROXADUSTAT, DAPRODUSTAT, VADADUSTAT, MOLIDUSTAT, ENARODUSTAT** and **DESIDUSTAT**, the last of which was developed in India and approved by the CDSCO in 2022 — an Indian-context point worth making.

The evidence, stated honestly. All the major programmes met their non-inferiority endpoints for haemoglobin. Cardiovascular safety is where they diverge: **ASCEND-D** (daprodustat, dialysis) met non-inferiority for MACE; **ASCEND-ND** (non-dialysis) also met it;

INNO2VATE (vadadustat, dialysis) met non-inferiority but **PRO2TECT** (non-dialysis) did NOT, with a MACE hazard ratio of 1.17. Pooled roxadustat analyses raised concerns about thrombosis and about MACE in the non-dialysis population, and the **FDA declined approval of roxadustat in 2021** while approving daprodustat in 2023 **for dialysis patients only**. Class concerns: **thrombosis and vascular access loss, a theoretical malignancy risk from HIF-driven VEGF, pulmonary hypertension, and cyst growth in ADPKD**. They are approved and widely used in India, China, Japan and Europe. **The honest summary for the examiner: they work, they are oral, they overcome inflammation, and their cardiovascular safety is probably class- and population-dependent rather than uniform.**

WHAT THE GUIDELINES ACTUALLY SAY

KDIGO 2012 ANAEMIA IN CKD (still the current anaemia guideline): evaluate iron status first, and **"DO NOT USE ESA THERAPY TO INTENTIONALLY INCREASE THE Hb CONCENTRATION ABOVE 13 g/dL"**, with a general target range of 10–11.5 g/dL and individualisation permitted. **KDIGO 2017 CKD-MBD UPDATE**: in CKD G5D, maintain iPTH in the range of **APPROXIMATELY 2 TO 9 TIMES THE UPPER NORMAL LIMIT** of the assay (2C), and for adults requiring PTH-lowering therapy use **calcimimetics, calcitriol, a vitamin D analogue, or a combination** (2B) — the guideline deliberately does not privilege one class. **KDIGO 2024 CKD**: treat metabolic acidosis to maintain serum bicarbonate in the normal range, and continue RAAS inhibition at the maximum tolerated dose rather than stopping it for a modest rise in creatinine or potassium.

HIGH-YIELD · CLINICAL PEARLS

- ◆ **SECRETES:** erythropoietin, renin, calcitriol, klotho (soluble), prostaglandins, kinins, endothelin, urodilatin, dopamine, renalase. **RESPONDS TO:** PTH, calcitriol, aldosterone, ADH, ANP/BNP, insulin, FGF-23, thyroid hormone. **DEGRADES:** insulin, PTH, glucagon, calcitonin, β 2-microglobulin.
- ◆ Erythropoietin comes from **PERITUBULAR INTERSTITIAL FIBROBLASTS**, not tubular cells — and about 90% of adult EPO is renal.
- ◆ Normoxia: PHD1-3 hydroxylate HIF- α using O_2 , 2-oxoglutarate, Fe^{2+} and ascorbate → VHL ubiquitin ligase → proteasome. Hypoxia: HIF- α is stabilised. HIF-2 α is the EPO isoform. Nobel Prize 2019 — Kaelin, Ratcliffe, Semenza.
- ◆ The three stimuli to renin: renal baroreceptor, macula densa NaCl delivery (COX-2/PGE₂ stimulatory, adenosine-A1 inhibitory), and β 1-sympathetic. cAMP stimulates; **CALCIUM INHIBITS** — the calcium paradox.
- ◆ Calcitriol is made by CYP27B1 in **PROXIMAL TUBULE MITOCHONDRIA**; 25(OH)D enters bound to DBP through MEGALIN-CUBILIN. PTH and hypophosphataemia turn it up; FGF-23 and phosphate turn it down.
- ◆ PTH is phosphaturic and **RAISES** calcitriol. FGF-23 is phosphaturic and **LOWERS** calcitriol. That contrast is a whole mark.
- ◆ **KLOTHO** is both a membrane **CO-RECEPTOR** for FGF-23 (with FGFR1-IIIc) and a shed **CIRCULATING HORMONE** that stabilises TRPV5 and inhibits Wnt and IGF-1 signalling.
- ◆ The order of CKD-MBD: **KLOTHO falls first** → FGF-23 rises → calcitriol falls → PTH rises → phosphate rises **LAST**.
- ◆ Renal dopamine is made in the **PROXIMAL TUBULE** from circulating L-DOPA and inhibits NHE3 and Na^+ -K⁺-ATPase; GRK4 polymorphisms uncouple the D1 receptor and cause **SALT-SENSITIVE HYPERTENSION**.
- ◆ The **INNER MEDULLARY COLLECTING DUCT** is the highest endothelin-1-producing tissue in the body, and collecting-duct ET-1 acting at ETB is **NATRIURETIC**.
- ◆ Urodilatin comes from the same NPPA gene as ANP but is processed differently and acts **LUMINALLY** on the inner medullary collecting duct — a paracrine natriuretic hormone that never enters the blood.
- ◆ **KDIGO 2012:** do not intentionally raise Hb above 13 g/dL; target 10-11.5 g/dL. **TREAT** — darbepoetin to 13 g/dL **DOUBLED** stroke risk (HR 1.92).
- ◆ HIF-PHIs raise EPO and **LOWER HEPICIDIN**, so they work in inflammation. **DESIDUSTAT** is Indian-developed and CDSCO-approved (2022). **PRO2TECT** (vadadustat, non-dialysis) **MISSED** non-inferiority for MACE; daprodustat is FDA-approved for dialysis patients only.

CHAPTER 1 · RENAL ANATOMY, DEVELOPMENT, PHYSIOLOGY & CELL BIOLOGY

1.17 Experimental Models of Kidney Disease

Jan 2025 P3 Q3(a)

Heymann nephritis.

3

Jan 2025 P3 Q3(b)

Experimental model for minimal change disease.

3

Jan 2025 P3 Q3(c)

Experimental model for diabetic kidney disease.

4

EXAMINER'S BLUEPRINT

A pure laboratory-nephrology question, and it is answered badly because candidates describe models without saying **WHAT EACH MODEL PROVED**. Every part should end with the translational pay-off. **(a) Heymann nephritis, 3 marks:** active versus passive, the **Fx1A** antigen, **MEGALIN as the rat podocyte antigen**, the discovery that deposits form **IN SITU rather than being trapped circulating complexes**, and **SUBLYTIC C5b-9** as the effector — then the payoff, that this model **PREDICTED the human PLA2R story**. **(b) MCD models, 3 marks:** **PAN**, **ADRIAMYCIN with its strain dependence**, **LPS with podocyte B7-1**, and the transgenic podocyte-depletion models — then the honest statement that **no model reproduces the circulating permeability factor or the steroid responsiveness**, with the new anti-nephrin antibody work as the exception that is beginning to change this. **(c) DKD models, 4 marks:** tabulate **chemical / genetic type 1 / genetic type 2 / accelerated / diet-induced**, give the **AMDCC criteria** verbatim in substance, and explain **WHY rodents do not make nodular glomerulosclerosis or lose GFR**. Declare the whole topic as beyond the two source textbooks where it is.

SOURCE DECLARATION — READ THIS BEFORE YOU WRITE THE ANSWER

Experimental model systems are discussed only in passing in **Brenner & Rector 12e** and **Comprehensive Clinical Nephrology 7e** — both describe the **IN-SITU IMMUNE-COMPLEX MECHANISM established by Heymann nephritis** in their membranous nephropathy chapters, and both outline rodent diabetic models in their diabetic nephropathy chapters, but neither carries a systematic account of model systems. **Everything in this topic that is not explicitly attributed to BR or CCN is declared as material beyond the two source textbooks**. Say this in one line at the top of your answer script — it is honest and it costs nothing.

(a) Heymann nephritis

3

What it is

HEYMANN NEPHRITIS is the rat model of MEMBRANOUS NEPHROPATHY, described by **Walter Heymann in 1959**. Rats are made to produce antibody against an antigen present on the **SOLE OF THE PODOCYTE FOOT PROCESS**. The antibody binds there, immune complexes form **IN THE SUBEPITHELIAL SPACE ITSELF**, complement is activated locally, and the animal develops **heavy non-selective proteinuria with subepithelial deposits, GBM spikes, diffuse foot-process effacement and NO GLOMERULAR HYPERCELLULARITY** — histologically indistinguishable from human membranous nephropathy.

Declared as material beyond the two source textbooks; the in-situ mechanism it established is described in the BR and CCN membranous nephropathy chapters

Active versus passive — the first thing to write · Declared as material beyond the two source textbooks

	ACTIVE HEYMANN NEPHRITIS (AHN)	PASSIVE HEYMANN NEPHRITIS (PHN)
How it is induced	IMMUNISE the rat (classically the LEWIS strain) with crude proximal tubular brush-border extract — FRACTION 1A, "Fx1A" — in complete Freund adjuvant	INJECT heterologous antibody intravenously — sheep or rabbit anti-Fx1A immunoglobulin
Immunology	A genuine AUTOIMMUNE disease: the rat makes its own autoantibody	PASSIVE TRANSFER of preformed antibody; the autologous phase follows when the rat mounts a response against the injected foreign IgG
Time course	Autoantibody at 4-6 weeks , proteinuria from about 8 weeks , progressive	Deposits within 1-5 days ; heterologous-phase proteinuria at about day 5 , autologous phase from day 14
What it is used for	Studying the initiation and the T-cell dependence of the autoimmune response	Dissecting the EFFECTOR mechanism — this is the model in which complement dependence was proved, because the deposit can be created on demand and complement then manipulated
Limitation	Slow, variable, strain-restricted	Requires production of heterologous antiserum; the foreign IgG itself is immunogenic

- **THE ANTIGEN IS MEGALIN (gp330, LRP2)**, a 600-kDa endocytic receptor of the LDL-receptor family, together with its chaperone **RAP (receptor-associated protein)**. In the rat, megalin is expressed both on the proximal tubular brush border — which is why

brush-border extract works as the immunogen — and, crucially, in **CLATHRIN-COATED PITS AT THE BASE OF THE PODOCYTE FOOT PROCESS**.

- **THE DEPOSITS FORM IN SITU. This is the single most important thing the model established.** Before Heymann nephritis, subepithelial deposits were assumed to be circulating immune complexes filtered and trapped in the GBM. **Couser, Salant, Kerjaschki and Farquhar showed that antibody crosses the GBM alone, binds its fixed podocyte antigen, and the complexes are then shed from the coated pits into the subepithelial space where they coalesce.** The proof: the model works in the isolated perfused kidney with no circulating complexes at all.
- **THE EFFECTOR IS COMPLEMENT, ACTING IN SUBLYTIC AMOUNTS.** C5b-9 inserts into the podocyte plasma membrane. Because the quantity is **SUBLYTIC, the podocyte is not killed — it is ACTIVATED:** reactive oxygen species, eicosanoid and protease release, endoplasmic reticulum stress, DNA damage, actin cytoskeletal disassembly with displacement of nephrin and podocin from the slit diaphragm, and TGF- β -driven overproduction of GBM material, which is what makes the **SPIKES. C5b-9 is shed into the urine and urinary C5b-9 tracks disease activity.**
- **THE PROOF OF COMPLEMENT DEPENDENCE:** in **C6-DEFICIENT rats**, or rats depleted of complement with cobra venom factor, **the immune deposits form normally but NO PROTEINURIA OCCURS.** Antibody binding alone is not injurious. Equally, **NEUTROPHILS AND MACROPHAGES ARE NOT REQUIRED** — the subepithelial deposit lies on the far side of the GBM, beyond the reach of circulating leucocytes. **This is precisely why human membranous nephropathy is a NON-INFLAMMATORY glomerulopathy with no hypercellularity, no haematuria of significance and no crescents** — a direct model-to-human read-across.

↳ Declared as material beyond the two source textbooks

HEYMANN NEPHRITIS PREDICTED HUMAN MEMBRANOUS NEPHROPATHY BY FIFTY YEARS. Megalin is **NOT expressed on the human podocyte**, so the human antigen had to be something else — and the model told everyone exactly what to look for: a **PODOCYTE SURFACE PROTEIN recognised by a circulating autoantibody.** **Debiec and Ronco found the first one in 2002 — NEUTRAL ENDOPEPTIDASE, in alloimmune antenatal membranous nephropathy.** **Beck and Salant found the big one in 2009 — the M-TYPE PHOSPHOLIPASE A2 RECEPTOR (PLA2R), positive in 70-80% of primary membranous nephropathy** — followed by **THSD7A (1-5%)** and the expanding list of **EXT1/EXT2 (membranous lupus nephritis), NELL-1, SEMAPHORIN-3B (paediatric), NCAM1, PCDH7, HTRA1, NETRIN G1, CONTACTIN-1, FAT1 and TGFBR3.** Heymann nephritis also supplied the therapeutic logic: **if the disease is antibody-driven, remove the B cell — which is the rationale for RITUXIMAB (GEMRITUX, MENTOR, STARMEN, RI-CYCLO)** — and if the effector is complement, block complement, which is the current clinical-trial frontier.

(b) Experimental models of minimal change disease

The four families of model — tabulate them · Declared as material beyond the two source textbooks

MODEL	HOW IT IS MADE	WHAT IT REPRODUCES	LIMITATIONS
PUROMYCIN AMINONUCLEOSIDE NEPHROSIS (PAN) — the classical model, rat	Single intravenous or subcutaneous injection of puromycin aminonucleoside (of the order of 15 mg per 100 g body weight) into a rat	The most faithful phenocopy of MCD: nephrotic-range proteinuria by day 5-10, diffuse foot-process effacement, NORMAL light microscopy and NO IMMUNE DEPOSITS , with spontaneous remission. REPEATED or high-dose injection converts it into FSGS — which is itself the experimental demonstration of the MCD-to-FSGS continuum	SPECIES-RESTRICTED — rats are susceptible and MICE ARE RESISTANT , which blocks the use of transgenic technology. Injury is DIRECT PODOCYTE TOXICITY mediated by reactive oxygen species (free-radical scavengers are protective) — not immune, so it models the lesion, not the disease

The sample ends here

You have read the opening pages of Volume One. The complete set answers 342 questions and 537 question parts across 182 topics and all 27 chapters of the DrNB Nephrology exit examination, 2021–2026.

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