Physiology

MBBS Recap: high-yield notes for revision

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Revision notes for the MD/MS entrance: the facts and numbers an examiner asks, with the reasoning that lets you rebuild them under pressure.

Cell and general physiology

Body fluid compartments

- **Total body water: about 60% of body weight in an adult man, 50–55% in a woman** (more fat, which is water-poor), about 75% in a newborn, and it falls with age.
- Split: **intracellular fluid (ICF) two thirds (about 40% of weight), extracellular fluid (ECF) one third (about 20%)**. ECF = interstitial fluid (three quarters) + plasma (one quarter, about 5% of weight, 3 L).
- Rule of thumb for a 70 kg man: TBW 42 L, ICF 28 L, ECF 14 L, plasma 3 L, interstitial 11 L.
- For a sodium deficit, TBW is taken as **0.6 × weight in a man and 0.5 × weight in a woman** (0.5 and 0.45 in the elderly): deficit = TBW × (target Na^+ − measured Na^+), in mmol (mEq) in total, not per litre. Example: woman of 60 kg, Na^+ 118 to be raised to 126: 0.5 × 60 × 8 = **240 mmol**.
- Main ECF cation Na^+, anion Cl^- and HCO_3^-. Main ICF cation K^+, anions phosphates and proteins. Plasma differs from interstitial fluid chiefly in its **protein content (oncotic pressure)**.

Measuring volumes: the dilution principle

Volume = amount of marker retained ÷ concentration at equilibrium. **Subtract anything excreted or metabolised before equilibration.** Example: 5 g injected, 0.5 g lost in urine, plasma concentration 0.3 g/L gives 4.5 ÷ 0.3 = 15 L.

Compartment	Marker
Total body water	Deuterium oxide, tritiated water, antipyrine
ECF	Inulin, sucrose, mannitol, radioactive sodium, thiosulphate
Plasma	Evans blue (T-1824), radio-iodinated albumin
Red cell volume, blood volume	^{51}Cr-labelled red cells; or blood volume = plasma volume ÷ (1 − haematocrit)
ICF, interstitial fluid	Cannot be measured directly: ICF = TBW − ECF; interstitial = ECF − plasma

Effect of infusions

- **Isotonic saline (0.9%)**: osmolarity unchanged, so no water enters cells. ECF volume rises; ICF volume and osmolarity unchanged. Of 1 L, about a quarter stays in plasma and three quarters go to interstitium.
- **Hypotonic fluid** (water, 5% dextrose once glucose is metabolised): both ECF and ICF volumes rise, osmolarity falls. **Water intoxication** (a marathon runner drinking litres of plain water; post-operative hypotonic infusions) is this at its extreme: ECF osmolality falls, water moves into cells and **intracellular volume increases**; brain swelling gives headache, confusion and seizures.
- **Hypertonic saline**: ECF volume rises, ICF volume falls (water drawn out), osmolarity rises.
- **Losses work the same way**: diarrhoeal fluid, blood and other isotonic losses come **from the ECF alone**, with no shift out of the cells. Only a loss of pure water (sweating is hypotonic, insensible loss, diabetes insipidus) is shared two thirds ICF, one third ECF. So 500 mL lost in gastroenteritis is 500 mL of ECF, not 333 mL of ICF.
- Normal plasma osmolality about 280–295 mOsm/kg (osmolarity about 285–290 mOsm/L); estimate **2 × Na^+ + glucose/18 + BUN/2.8** (all mg/dL; urea in mg/dL ÷ 6, or in SI units 2 × Na^+ + glucose + urea, all mmol/L). A measured value more than about 10 above the calculated one (osmolar gap) suggests methanol, ethylene glycol or ethanol.

Transport across membranes

Type	Features	Example
Simple diffusion	Down gradient, no carrier, not saturable	O_2, CO_2, lipid-soluble drugs
Facilitated diffusion	Carrier, down gradient, saturable, no ATP	GLUT transporters
Primary active transport	Direct ATP use, against gradient	Na^+–K^+ ATPase (3 Na^+ out, 2 K^+ in), Ca^{2+} ATPase, H^+–K^+ ATPase
Secondary active transport	Energy from the Na^+ gradient the ATPase maintains	SGLT1 and SGLT2 (co-transport); Na^+–Ca^{2+} and Na^+–H^+ exchangers (counter-transport)

- **SGLT1 (enterocyte, apical) takes up glucose and galactose by secondary active transport; GLUT2 (basolateral) lets them out by facilitated diffusion; GLUT5 takes up fructose.** ATP is used only indirectly.
- **Oral rehydration solution**: in cholera the toxin raises cAMP and chloride secretion but leaves SGLT1 untouched, so glucose-coupled sodium uptake continues and water follows osmotically. Reduced-osmolarity ORS (245 mOsm/L, WHO) is the current standard; zinc is added in children.
- **Glucose transporters**: GLUT1 (red cells, blood–brain barrier, basal uptake), GLUT2 (liver, beta cell, kidney, gut basolateral; high capacity, low affinity; the textbook beta-cell transporter, though human beta cells rely more on GLUT1), GLUT3 (neurons), **GLUT4 (skeletal muscle, heart, adipose: insulin-dependent, moves from vesicles to the membrane on insulin signalling; also moved by exercise independently of insulin)**, GLUT5 (fructose).

Membrane potentials

- **Nernst equation at 37 °C: E = (61 mV ÷ z) × $\log_{10}$(outside ÷ inside).** For K^+ (z = +1) a 10-fold gradient gives −61 mV. For chloride (z = −1) with 100 mM outside and 10 mM inside, E = −61 × log 10 = **−61 mV** (the sign flips because the charge is negative).
- Typical equilibrium potentials: K^+ about −90 mV (Guyton −94), Na^+ about +60 mV (+61), Ca^{2+} about +120 mV, Cl^- about −70 to −86 mV depending on the cell.
- **Resting potential of a neuron about −70 mV (about −90 mV in large myelinated fibres, skeletal and ventricular muscle), close to the K^+ equilibrium potential, because the resting membrane is far more permeable to K^+ (leak channels)**. The small Na^+ leak pulls it slightly less negative; the electrogenic Na^+–K^+ pump (3 Na^+ out for 2 K^+ in) makes it **a few mV more negative** (about −4 mV in Guyton's account).
- Goldman equation: potential depends on the permeability-weighted gradients of all ions; the most permeable ion dominates.
- Donnan effect: impermeant intracellular anions (proteins) hold extra K^+ inside.

Cell junctions and membrane lipids

- **Gap junctions** (connexin channels) pass ions and small molecules (a dye injected into one cell spreads to its neighbours), coupling cells electrically: cardiac muscle (at the intercalated discs) and single-unit (visceral) smooth muscle work as a syncytium; multi-unit smooth muscle (iris, vas deferens, piloerector) has few and needs a nerve fibre to each cell. **Tight junctions** seal the space between cells, tight in the collecting duct and bladder, leaky in the proximal tubule; desmosomes give mechanical strength.
- **Cholesterol** buffers membrane fluidity: at body temperature it stiffens the bilayer and makes it less permeable to small water-soluble molecules; at low temperature it stops the fatty acid chains packing tightly, so the membrane does not solidify. Myelin is lipid-rich (about 80% lipid); the inner mitochondrial membrane is the most protein-rich (about 75% protein).

Homeostasis and feedback

- **Negative feedback** restores a regulated variable; **positive feedback** amplifies (labour and oxytocin, LH surge, clotting cascade, the rising phase of the action potential).
- **Gain of a feedback system = correction ÷ remaining error.** A disturbance moves a variable 100 to 130; control brings it to 106: correction 24, error 6, **gain 4**. Guyton writes the gain of a negative feedback system with a minus sign (here **−4**; the baroreceptor system's gain is about −2), so choose −4 if the options carry signs. Perfect control would have infinite gain; the greater the gain, the more precise the control.
- Feedforward control anticipates a change (salivation at the sight of food).
- Cell volume: cells swell in hypotonic and shrink in hypertonic surroundings; the brain adapts to chronic hyponatraemia by losing osmolytes, so correct sodium slowly (risk of osmotic demyelination).

Cell signalling

- G-protein pathways: Gs (↑ cAMP), Gi (↓ cAMP), **Gq (PLC, IP_3, DAG, ↑ Ca^{2+})**. Receptor tyrosine kinases (insulin, growth factors), cytokine receptors (JAK–STAT), intracellular receptors for steroid and thyroid hormones (act on DNA, slow), guanylyl cyclase (ANP, NO).

Nerve and muscle

Action potential

- Stages: resting, depolarisation (voltage-gated Na^+ channels open, positive feedback), repolarisation (Na^+ channel inactivation and delayed K^+ opening), hyperpolarisation (slow K^+ channel closing).
- **Absolute refractory period: no stimulus however strong can fire a second spike, because voltage-gated Na^+ channels are inactivated** (inactivation gate shut until repolarisation). It limits the maximum firing frequency and ensures one-way propagation.
- **Relative refractory period**: a stronger-than-normal stimulus can fire; some Na^+ channels have recovered and K^+ conductance is still raised.
- Threshold about −55 mV in a neuron (about 15–20 mV above the resting level); all-or-none; amplitude does not decay along the axon.
- **Susceptibility of fibres to block** (Ganong): **local anaesthetics C most, A least** (small fibres first; order of loss pain, temperature, touch, pressure, then motor); **pressure A most, C least** (a limb "going to sleep" loses touch and motor before pain); **hypoxia B most**, C least. Local anaesthetics act on voltage-gated Na^+ channels from inside the cell, entering in the uncharged form, and work best on rapidly firing fibres (use-dependent block).

Fibre types

Type	Diameter / speed	Function
Aα	Largest, **70–120 m/s (fastest)**	Motor to extrafusal fibres, proprioception (Ia, Ib)
Aβ	30–70 m/s	Touch, pressure
Aγ	15–30 m/s	Motor to muscle spindle
Aδ	12–30 m/s, thinly myelinated	**Fast, sharp, well-localised 'first' pain**, cold
B	3–15 m/s, myelinated	Preganglionic autonomic
C	0.5–2 m/s, unmyelinated	**Slow, dull, burning 'second' pain**, warmth, postganglionic autonomic

- Sensory (Ia, Ib, II, III, IV) classification is by diameter as well: Ia is the fastest afferent from spindles.
- Conduction velocity rises with diameter; in myelinated fibres roughly 6 × diameter (μm) m/s.
- **Myelin speeds conduction by saltatory conduction: the impulse is regenerated only at nodes of Ranvier**, where Na^+ channels are concentrated, because the myelin raises membrane resistance and lowers capacitance in the internodes. Demyelination (multiple sclerosis, Guillain–Barré) slows or blocks conduction.

Skeletal muscle contraction

- Excitation–contraction coupling: end-plate potential, action potential in sarcolemma and T-tubules, dihydropyridine receptor, ryanodine receptor (RyR1) releases Ca^{2+} from the sarcoplasmic reticulum, **Ca^{2+} binds troponin C**, tropomyosin moves off actin, cross-bridge cycling. Relaxation by SERCA pumping Ca^{2+} back (needs ATP).

- **Smooth muscle**: calcium binds **calmodulin**, activating myosin light-chain kinase, which phosphorylates myosin; no troponin. Cardiac muscle has troponin and relies on Ca^{2+}-induced Ca^{2+} release (RyR2).
- **Sarcomere**: Z line to Z line. **A band = thick (myosin) filaments, constant length during contraction.** I band (thin filaments only), H zone and sarcomere length shorten. Sliding-filament theory: filaments slide, they do not shorten. **Anchors**: **α-actinin cross-links the barbed (plus) ends of thin filaments at the Z disc**; **titin** runs from the Z disc to the M line, holds the thick filament centred and gives passive elasticity; nebulin lies along the thin filament and sets its length; myomesin links thick filaments at the M line; **dystrophin** joins the actin cytoskeleton to the sarcolemma and the extracellular matrix (absent in Duchenne, reduced in Becker muscular dystrophy).
- **Rigor mortis**: ATP is needed to detach myosin heads; when ATP runs out after death, the cross-bridges stay locked. In a South Asian climate it begins 1–2 hours after death and lasts about 24–48 hours in winter, 18–36 hours in summer (Parikh, Reddy); the temperate "rule of twelves" is about 12 hours to develop, 12 to stay and 12 to pass. It passes as the proteins break down, and comes and goes sooner in heat or after exertion; it starts in the myocardium and, among visible muscles, in the eyelids (Nysten's order).
- Length–tension: maximum force at optimal sarcomere length (about 2.0–2.2 µm, full thick–thin overlap); tension falls if overstretched or overshortened.
- Force–velocity: velocity of shortening falls as load rises.

Fibre types of skeletal muscle

	Type I	Type IIa	Type IIx (IIb)
Speed	Slow twitch	Fast	Fastest
Metabolism	**Oxidative**, many mitochondria	Oxidative–glycolytic	Glycolytic (anaerobic)
Colour	Red (myoglobin)	Red–pink	White
Fatigue	Resistant	Intermediate	Fatigable
Use	Posture, endurance		Sprint, strength

Neuromuscular junction

- Acetylcholine released by Ca^{2+}-triggered exocytosis binds **nicotinic (N_M) receptors**; acetylcholinesterase ends the signal.
- **Myasthenia gravis**: autoantibodies to postsynaptic nicotinic receptors (fewer functional receptors) give fatigable weakness (ptosis, diplopia worse at evening), a **decremental response to repetitive nerve stimulation**, improvement with edrophonium or pyridostigmine; thymic hyperplasia in about 65%, thymoma in 10–15%. **Anti-AChR antibodies in about 85% of generalised cases**; of the seronegative, many have anti-MuSK (more bulbar and respiratory weakness, poor response to pyridostigmine) or anti-LRP4. Single-fibre EMG (jitter) is the most sensitive test. Current practice adds complement inhibitors (eculizumab) and FcRn blockers (efgartigimod) for refractory AChR-positive disease.
- **Lambert–Eaton syndrome**: antibodies to presynaptic P/Q-type voltage-gated Ca^{2+} channels, so reduced ACh release; low resting compound muscle action potential with an **incremental** response (over 100%) on high-frequency (about 50 Hz) stimulation or after brief exercise; reflexes reduced, autonomic features; about half are paraneoplastic, mostly small cell lung cancer. Treated with amifampridine (3,4-diaminopyridine).
- **Toxins and drugs along the junction**: **botulinum toxin's light chain cleaves SNARE proteins (SNAP-25, synaptobrevin or syntaxin), so vesicles cannot fuse and ACh is not released: flaccid paralysis**; hemicholinium blocks choline uptake into the terminal; curare competes with ACh at the nicotinic receptor; neostigmine and organophosphates inhibit acetylcholinesterase; succinylcholine is a depolarising blocker. On the axon, **tetrodotoxin** and saxitoxin block voltage-gated Na^+ channels from outside, local anaesthetics from inside, and tetraethylammonium blocks K^+ channels.

Other points

- Motor unit recruitment follows the size principle (small, slow units first).
- Tetanus (physiological): fusion of twitches; occurs when stimulus frequency exceeds fusion frequency, because calcium accumulates.
- Isotonic versus isometric contraction; muscle work depends on both force and shortening.

Excitability and nerve injury

- **Rheobase** is the minimum current that excites a nerve given an indefinitely long stimulus; **chronaxie** is the shortest duration needed at twice the rheobase, an index of excitability (shorter in large, fast fibres). **Compound action potential** from a whole nerve is the sum of its fibres' potentials, with several peaks (A, B and C waves) from their differing speeds; amplitude is graded with the number of fibres recruited, though each fibre obeys all-or-none.
- **Wallerian degeneration**: after a nerve is cut, the axon and myelin distal to the injury degenerate within days (the stump's axon swells and breaks up, macrophages clear debris and Schwann cells proliferate in bands of Büngner); proximally there is chromatolysis of the cell body. Regeneration is at **about 1 mm a day** and needs the Schwann cell tube.
- **Neuromuscular blockers**: **non-depolarising** (rocuronium, vecuronium, atracurium; competitive, reversed by neostigmine or sugammadex) versus **depolarising** (suxamethonium: persistent depolarisation, fasciculations first, **phase II block** on prolonged use; not reversed by neostigmine). **Electromyography** shows motor unit potentials: neurogenic lesions give large, long polyphasic units and fibrillations after denervation; myopathies give small, short, polyphasic units.

Blood

Haemoglobin

- **Adult HbA = $\alpha_2\beta_2$ (about 97%), HbA_2 = $\alpha_2\delta_2$ (about 2–3%, raised above 3.5% in β-thalassaemia trait), HbF = $\alpha_2\gamma_2$ (under 1% in the adult).** Embryonic Hb includes ζ and ε chains. Gower and Portland haemoglobins are embryonic.
- HbF binds 2,3-BPG weakly, so it has a **higher oxygen affinity (left-shifted curve, P50 about 19 mmHg against 26–27)**, helping fetal uptake from maternal blood. It is about 70–80% of haemoglobin at birth and falls to adult levels over the first 6–12 months as γ chains give way to β; persistence in β-thalassaemia and sickle cell disease is protective, which is the basis of hydroxyurea.
- HbH is β_4 (α-thalassaemia, three-gene deletion); Hb Barts is γ_4 (four-gene deletion, hydrops fetalis).

- Haem synthesis: glycine + succinyl CoA via ALA synthase (rate-limiting, mitochondria; needs B_6). Iron as Fe^{2+} in haem; methaemoglobin has Fe^{3+} and cannot bind oxygen.

Stored blood

- Red cells stored for weeks lose **2,3-BPG**, so the oxyhaemoglobin curve shifts left and oxygen release to tissues is impaired at first; the transfused cells regain about half their 2,3-BPG within about 6–12 hours and normal levels by about 48–72 hours. They also gain K^+ in the supernatant and lose ATP and pH. Citrate-phosphate-dextrose-adenine (CPDA-1) allows 35 days at 2–6 °C; additive solutions (SAGM) about 42 days; platelets 5 days at 20–24 °C with agitation.

Haemolysis versus marrow failure

- **Haemolysis**: low Hb, **reticulocytosis** (marrow responding), raised indirect bilirubin and LDH, **low or absent haptoglobin**, haemoglobinuria and haemosiderinuria in intravascular haemolysis, spherocytes or schistocytes on smear.
- Low reticulocytes with low Hb suggest marrow failure, deficiency (iron, B_{12}, folate) or chronic disease.
- Reticulocytes mature in the blood in about 1 day (after 1–2 days in the marrow); red cell lifespan 120 days; normal reticulocytes 0.5–2.5% of red cells. Correct for anaemia (reticulocyte index); a corrected value above about 2–3% means the marrow is responding.

Erythropoiesis

- **Erythropoietin in the adult: mainly renal peritubular interstitial (fibroblast-like) cells in the cortex** (about 90%; the liver makes the remaining 10–15% in the adult and is the main source in the fetus). Stimulus: tissue hypoxia, via **hypoxia-inducible factor (HIF-1α)**, stabilised when oxygen is low (degraded by prolyl hydroxylase and VHL in normoxia). Anaemia of chronic kidney disease results from loss of EPO; treated with ESAs; HIF-prolyl hydroxylase inhibitors (roxadustat) are a newer oral option.
- B_{12} and folate needed for DNA synthesis; iron for haem; erythropoiesis sequence: proerythroblast, basophilic, polychromatic, orthochromatic erythroblast, reticulocyte, red cell.
- Sites: yolk sac (from about week 3, mesoblastic stage), liver (from about week 6, the main site in mid-pregnancy) with the spleen, then marrow (from about the fifth month, the only site after birth); in adults the vertebrae, sternum, ribs, pelvis and proximal long bones.

Other high-yield points

- Plasma proteins: albumin (oncotic pressure, about 80% of it), globulins, fibrinogen; **Gibbs–Donnan effect** raises oncotic pressure above that predicted by protein concentration alone.
- Haemoglobin: men 13–17 g/dL, women 12–15 g/dL; anaemia in WHO's terms below 13 in men, 12 in non-pregnant women, 11 in pregnancy. In pregnancy plasma volume rises about 40–50% and red cell mass only about 20–30%, so red cell count, haemoglobin and haematocrit fall (**haemodilution**, the physiological anaemia of pregnancy). Haematocrit: men about 45% (40–50), women about 40% (36–46); **polycythaemia raises viscosity**. ESR (Westergren): up to about 15 mm/h in men, 20 in women.
- Total WBC 4,000–11,000/μL. Differential: neutrophils 40–70%, lymphocytes 20–40%, monocytes 2–8%, eosinophils 1–4%, basophils below 1% ("Never Let Monkeys Eat Bananas").
- Platelets: 150–400 × 10^9/L, lifespan 7–10 days, a third held in the spleen; thrombopoietin made mainly in the liver. Bleeding time 2–7 minutes (Ivy).
- Coagulation: intrinsic (XII, XI, IX, VIII; aPTT), extrinsic (VII; PT), common from X (X, V, II, I); in the body the tissue factor–VIIa complex starts clotting and the cell-based model has replaced the two-cascade picture (factor XII deficiency prolongs the aPTT but does not bleed); vitamin K-dependent factors II, VII, IX, X, protein C and S; heparin potentiates antithrombin; warfarin acts by inhibiting vitamin K epoxide reductase.
- ABO: antigens on red cells, naturally occurring IgM antibodies; group O Rh-negative is the universal red cell donor, AB the universal recipient of red cells and the universal plasma donor. Bombay phenotype (hh) lacks the H antigen and has anti-H, so it accepts only Bombay blood.

Transfusion, Rh disease and leucocyte function

- **Prothrombin time (PT)** tests the extrinsic (factor VII) and common pathways (X, V, II, fibrinogen); it is prolonged first in **warfarin** treatment and in liver disease and vitamin K deficiency because factor VII has the shortest half-life (about 6 hours). Report it as the **INR** (patient PT over control PT, raised to the power of the reagent's sensitivity index); the usual target in warfarin treatment is 2 to 3. The aPTT tests the intrinsic and common pathways and is the one used to monitor unfractionated heparin; bleeding time (platelets) and clotting time are bedside tests.
- **Rh haemolytic disease of the newborn**: an Rh-negative mother sensitised by Rh-positive fetal cells (usually at delivery) makes IgG anti-D that crosses the placenta in later pregnancies and haemolyses the fetal red cells; the first child is spared. **Anti-D immunoglobulin** to the mother at 28 weeks and within 72 hours of delivery or sensitising events prevents it. ABO incompatibility (mother O, baby A or B) can occur in the first pregnancy because anti-A and anti-B IgG are already present.
- **Transfusion reactions**: acute haemolytic (ABO mismatch, preformed IgM antibodies, intravascular haemolysis; stop the transfusion), febrile non-haemolytic (cytokines or antibodies against donor leucocytes, the commonest), allergic or anaphylactic (IgA-deficient recipient with anti-IgA), and TRALI (donor antibodies to recipient leucocytes, non-cardiogenic pulmonary oedema).
- **ESR** rises with fibrinogen and globulins (inflammation, myeloma, anaemia) because they reduce the red cells' negative surface charge and encourage rouleaux; it is lowered by polycythaemia, sickle cells and spherocytes (cells that cannot form rouleaux).
- Leucocyte functions: **neutrophils** are first responders (phagocytosis, 6 to 10 hours in blood); **eosinophils** act against helminths and in allergy; **basophils** and mast cells release histamine and heparin; **monocytes** become tissue macrophages; **T cells** give cell-mediated immunity and **B cells** make antibodies. Innate immunity is immediate and non-specific (barriers, complement, phagocytes, NK cells); adaptive immunity is specific with memory (primary response mostly IgM, secondary mostly IgG; **IgA** in secretions, **IgE** in allergy and helminths, **IgG the only class to cross the placenta**).

Red cell membrane

- **Spectrin** (with actin) forms the submembrane lattice that keeps the red cell biconcave and deformable; it is tethered to the bilayer by ankyrin and band 3 (and protein 4.1). Defects of spectrin, ankyrin or band 3 cause **hereditary spherocytosis**.

Cardiovascular

Conduction system and the cardiac action potential

- Order: SA node (natural pacemaker, 60–100/min, phase 4 "funny" current), internodal pathways, **AV node (slowest conduction, about 0.01–0.05 m/s; gives the roughly 0.1 s nodal delay, about 0.13 s with the penetrating bundle, that lets the atria empty first)**, bundle of His, bundle branches, **Purkinje fibres (fastest, about 1.5–4 m/s)**; atrial and ventricular muscle about 0.3–1 m/s. Intrinsic rates: SA 60–100 (intrinsic rate without vagal tone about 100), AV junction 40–60, ventricle (Purkinje) 15–40.
- Nodal action potential: slow upstroke by **L-type Ca^{2+} current** (no fast Na^+ channels); phase 4 slope set by I_f (HCN channels, blocked by ivabradine), with T-type Ca^{2+} late in phase 4; sympathetic beta-1 steepens it, vagal M2 flattens and hyperpolarises it.
- **Ventricular myocyte**: phase 0 fast Na^+ in; 1 transient K^+ out; **2 plateau: inward L-type Ca^{2+} balanced by outward K^+** (about 200 ms, prolongs refractoriness and prevents tetany); 3 repolarisation by delayed rectifier K^+; 4 resting by I_K1 (about −90 mV). The **absolute refractory period lasts through the plateau** (about 250 ms, nearly as long as the contraction), so heart muscle **cannot be tetanised**; a **relative refractory period** follows (about 50 ms), when a stronger stimulus can fire the cell.
- Calcium-induced calcium release triggers contraction; digoxin inhibits the Na^+–K^+ ATPase, raising intracellular Ca^{2+}.
- ECG: P atrial depolarisation (under 0.12 s), PR interval 0.12–0.20 s (AV delay), QRS ventricular depolarisation (under 0.12 s, usually 0.08–0.10), ST plateau, T repolarisation, QTc under about 0.44 s in men and 0.46 s in women. Atrial repolarisation is hidden in the QRS. At 25 mm/s one small square is 0.04 s; rate = 300 ÷ large squares between R waves.

Cardiac cycle and heart sounds

- Phases: atrial systole, isovolumetric contraction, rapid ejection, reduced ejection, isovolumetric relaxation, rapid then slow filling (diastasis). At 75/min the cycle is 0.8 s: systole about 0.3 s, diastole about 0.5 s; a faster rate shortens diastole most. Atrial contraction adds about 20% of ventricular filling at rest (lost in atrial fibrillation).
- Pressures (mmHg): right atrium 0–5 (mean about 2), right ventricle 25/0–5, pulmonary artery 25/10 (mean about 15), pulmonary capillary wedge 6–12, left atrium about 8, left ventricle 120/0–10, aorta 120/80.
- JVP waves: a (atrial contraction; absent in AF, cannon a in complete heart block), c (tricuspid bulging), x descent, v (atrial filling), y descent (tricuspid opening).
- **S1** closure of mitral and tricuspid; **S2** closure of aortic (A2) then pulmonary (P2); **S3 = rapid passive ventricular filling in early diastole**: normal in children and young adults, in older patients indicates volume overload or heart failure. **S4** = forceful atrial contraction into a stiff ventricle (hypertrophy, ischaemia); absent in atrial fibrillation.
- **Splitting of S2 widens in inspiration**: more venous return to the right heart delays P2 and the left side empties earlier. Fixed split = ASD; paradoxical (reversed) split = LBBB, aortic stenosis; wide split = RBBB, pulmonary stenosis.
- Murmurs: AR is a decrescendo early diastolic murmur with a wide pulse pressure (waterhammer pulse); the **low diastolic pressure in chronic severe AR is from back-flow into the left ventricle in diastole**.

Haemodynamics

- **Stroke volume = EDV − ESV; cardiac output = SV × HR.** EDV 140, ESV 60, HR 75: SV 80 mL, CO **6.0 L/min**. Ejection fraction = SV/EDV = 57% (normal 55–70%; heart failure with reduced EF is 40% or less, mildly reduced 41–49%, preserved 50% or more, in the 2021 universal definition and ESC 2021). Cardiac output about 5 L/min at rest; cardiac index 2.5–4 L/min/m^2.
- **Frank–Starling law**: greater end-diastolic volume (preload) stretches sarcomeres towards optimal length and increases stroke volume. Bowditch (treppe) is the rise in force with heart rate; the Anrep effect is the response to raised afterload.
- **Mean arterial pressure = diastolic + one third of pulse pressure** (130/70: 70 + 20 = 90 mmHg). Pulse pressure = systolic − diastolic.
- **The two circuits are in series, so flow is equal in the pulmonary and systemic circulations**, while pressure and resistance differ: pulmonary vascular resistance is about one tenth of systemic (short, wide, distensible vessels), so a mean pulmonary artery pressure of about 15 mmHg drives the same output that needs about 93 mmHg in the aorta ($\Delta P = Q \times R$).
- **Stroke work** = stroke volume × mean arterial pressure (the area of the pressure–volume loop; plus a small kinetic term); the loop's sides are filling, isovolumetric contraction, ejection and isovolumetric relaxation. The left ventricle does about six to seven times the right's work for the same stroke volume.
- **Poiseuille: flow $\propto r^4$**; resistance $\propto 1/r^4$. Halve the radius: flow falls to 1/16, resistance rises 16-fold. Arterioles are the main site of resistance.
- Laplace: wall tension = pressure × radius (÷ 2 × thickness for stress); explains why a dilated ventricle needs more wall tension.
- Reynolds number above about 2,000 gives turbulence (murmurs, anaemia flow murmurs from low viscosity). **Viscosity** of blood depends mainly on the haematocrit (cells about 45% of volume): it falls in anaemia and rises steeply in polycythaemia, raising resistance (Poiseuille's η).
- Compliance: veins are the capacitance vessels and hold about 60–65% of blood volume (Guyton 64%); systemic arteries about 13%, capillaries 7%, heart 7%, pulmonary vessels 9%. Capillaries have the largest total cross-sectional area and so the slowest velocity of flow.

Regional circulations

- **Heart has the highest oxygen extraction at rest (70–75%)**, so increased demand must be met by raised coronary flow; the kidney extracts only 10–15% (flow far exceeds need). Coronary flow is mostly in diastole, with the left ventricle perfused least during systole. Metabolic (adenosine) vasodilation is the main local control.
- Resting flows: coronary about 225–250 mL/min (4–5% of cardiac output), cerebral about 750 mL/min (15%; 50–55 mL/

100 g/min), renal about 1,100–1,200 mL/min (20–25%; about 360–400 mL/100 g/min, among the highest per gram; the carotid bodies, about 2,000 mL/100 g/min, are the highest), liver about 1,350 mL/min (27%, three quarters of it portal).

- Cerebral: autoregulated between mean pressures of about 60 and 150 mmHg, very sensitive to $PaCO_2$ (↑ CO_2 gives vasodilation; flow changes about 2–4% per mmHg). Pulmonary: hypoxia constricts. Skeletal muscle: metabolic autoregulation at exercise. Skin: sympathetic temperature control.
- Starling forces: capillary hydrostatic pressure opposed by plasma oncotic pressure; oedema from raised venous pressure, low albumin, increased permeability or lymphatic block.

Blood pressure regulation

- **Baroreceptors** (carotid sinus via Hering's nerve, a branch of the **glossopharyngeal (CN IX)**; aortic arch via the aortic nerve of the **vagus (CN X)**; both end in the nucleus tractus solitarius) are tonically active and respond to stretch, most sensitive around a mean pressure of 100 mmHg (range about 60–180); fall in pressure reduces firing, which raises sympathetic outflow and lowers vagal tone. Fast (seconds); they reset within a day or two, so they do not set long-term pressure (the kidney's pressure natriuresis does). **Marey's law**: heart rate varies inversely with arterial pressure, through this reflex.
- **Standing up**: venous pooling lowers venous return, cardiac output and pressure; baroreceptor firing falls and sympathetic outflow rises, with tachycardia and vasoconstriction within seconds. Renin–angiotensin–aldosterone takes minutes to hours.
- **Haemorrhage or severe diarrhoea**: raised plasma renin (from low renal perfusion pressure, beta-1 stimulation and macula densa signals), angiotensin II, aldosterone, ADH, tachycardia.
- Chemoreceptor and ischaemic (Cushing) reflex: raised intracranial pressure causes hypertension with bradycardia.
- Other reflexes: Bainbridge (atrial stretch raises heart rate), Bezold–Jarisch, diving reflex, oculocardiac reflex.
- Valsalva (forced expiration against a closed glottis): phase I pressure rises briefly as intrathoracic pressure is transmitted to the aorta; phase II venous return and pressure fall, with reflex tachycardia; phase III a brief further fall on release; phase IV overshoot of pressure with reflex bradycardia. No overshoot (a square-wave response) in heart failure and autonomic failure. Most murmurs soften in the strain phase; those of hypertrophic cardiomyopathy and mitral valve prolapse grow louder or longer.
- Atrial natriuretic peptide from atrial stretch promotes natriuresis; BNP from ventricles (marker of heart failure).

Exercise

- Cardiac output rises up to 4–6-fold (about 20–25 L/min, more in athletes), mainly through heart rate, with stroke volume rising early; total peripheral resistance falls (muscle vasodilation); systolic pressure rises, diastolic little changed or falls in dynamic exercise; static (isometric) exercise raises both. VO_2 max is the best measure of aerobic fitness. Athletes have a resting bradycardia from high vagal tone and a large stroke volume.

Pressure curves, coronary flow and shock

- **Aortic pressure curve**: ejection raises pressure to the systolic peak; at the end of ejection the ventricle relaxes, blood flows briefly back and the aortic valve shuts, giving the **dicrotic notch (incisura)** followed by a small rebound wave (it separates systole from diastole on the curve and is the site of S2). A wide pulse pressure with the notch lost occurs in aortic regurgitation. Diastolic pressure is held by elastic recoil of the aorta (Windkessel effect).
- **Left coronary flow is greatest in diastole** because systolic contraction squeezes the intramyocardial vessels, nearly stopping subendocardial flow; the right ventricle is less affected because its systolic pressure is low. So tachycardia (short diastole), low diastolic pressure (aortic regurgitation) and raised end-diastolic pressure reduce subendocardial perfusion and cause ischaemia there first; the main local controller is adenosine.
- **Shock**: stages are compensated (baroreflex, vasoconstriction, renin–angiotensin, ADH), progressive (acidosis, precapillary sphincters fail, the vicious circle) and irreversible (cell damage, no response to fluid). Types: hypovolaemic and cardiogenic (cold, low output), distributive (septic, anaphylactic, neurogenic: low resistance), obstructive (tamponade, pulmonary embolus). Capillary refill and the shock index (pulse over systolic pressure above 0.9) are bedside signs.

Respiratory and high altitude

Lung volumes

Measure	Typical value	Note
Tidal volume (TV)	500 mL	
Inspiratory reserve volume	3,000 mL	
Expiratory reserve volume	1,100 mL	
Residual volume (RV)	1,200 mL	Cannot be exhaled
Vital capacity	4,600 mL	IRV + TV + ERV
Functional residual capacity (FRC)	2,300 mL	ERV + RV; resting end-expiration, where lung recoil balances chest wall recoil
Total lung capacity	about 6,000 mL	VC + RV

- **Simple spirometry cannot measure RV, FRC or TLC** (they contain residual volume); use helium dilution, nitrogen washout or body plethysmography (plethysmography also measures trapped gas).
- **Anatomical dead space about 150 mL (about 2 mL/kg)**; physiological dead space = anatomical + alveolar dead space, measured by the Bohr equation: $VD/VT = (PaCO_2 - PECO_2) \div PaCO_2$ (the Enghoff form, using arterial for alveolar PCO_2), normally 0.2–0.35. Anatomical dead space is measured by Fowler's single-breath nitrogen method. **Alveolar ventilation = (TV − dead space) × rate.** Minute ventilation = TV × rate (6 L/min).
- $PaCO_2$ is inversely proportional to alveolar ventilation.

Mechanics

- **Surfactant**: made by type II pneumocytes, mostly **dipalmitoylphosphatidylcholine (DPPC)**, with phosphatidylglycerol and the surfactant proteins A–D (B and C spread the film; A and D are immune collectins); lowers surface tension, which increases compliance and stops small alveoli collapsing (Laplace: P = 2T/r). Made from about 24–28 weeks, adequate after about 34–35 weeks; antenatal corticosteroids hasten it; lecithin:sphingomyelin ratio above 2 in amniotic fluid indicates lung maturity. Deficiency gives neonatal respiratory distress syndrome.
- Compliance falls in fibrosis, pulmonary oedema; rises in emphysema (loss of elastic recoil).
- **Airway resistance: the greatest share lies in the medium-sized bronchi** (about segmental to fourth-to-eighth generation), because the small airways, though narrow, are so many in parallel that their total resistance is low. Resistance falls with lung inflation and rises in asthma and bronchitis.
- Work of breathing; intrapleural pressure is normally negative (about −5 cm H_2O at the end of quiet expiration, about −7.5 at the end of quiet inspiration), more negative at the apex than the base. Total compliance of lungs and chest wall about 100 mL/cm H_2O; lungs alone about 200.
- **Quiet expiration is passive** (elastic recoil); **forced expiration** (exercise, cough, airway obstruction) uses the **internal intercostals** (pull the ribs down) and the **abdominal muscles** (rectus, obliques, transversus: raise abdominal pressure and push the diaphragm up). The diaphragm (the main muscle, about 75% of quiet inspiration) and external intercostals are inspiratory; sternocleidomastoid, scalenes, pectoralis minor and serratus anterior are accessory muscles of inspiration.
- Flow-volume loops: obstructive scooped expiratory curve; fixed upper-airway obstruction flattens both limbs.

Spirometry patterns

	FVC	FEV_1	FEV_1/FVC	TLC	DLCO
Obstructive	Normal or ↓	↓↓	**↓ (below 0.7 after a bronchodilator, GOLD; below the lower limit of normal, ATS/ERS 2022)**	↑ (hyperinflation)	Emphysema ↓; asthma normal or ↑
Restrictive	↓	↓	**Normal or ↑**	↓	↓ in parenchymal, normal in extrapulmonary

- Emphysema: increased TLC, low FEV_1/FVC (for example 0.55), **markedly reduced DLCO** from loss of alveolar surface. Asthma and chronic bronchitis (airway disease) keep DLCO normal.
- DLCO falls in fibrosis, emphysema, pulmonary embolism, anaemia; rises in polycythaemia, pulmonary haemorrhage, asthma, left-to-right shunts.
- **Fick's law**: diffusion rate $\propto$ area × partial pressure difference × solubility ÷ membrane thickness (and $\propto$ solubility ÷ $\sqrt{}$molecular weight, so CO_2 diffuses about 20 times as fast as O_2). Fibrosis and interstitial oedema thicken the membrane; emphysema removes area. Doubling the thickness and halving the area cuts diffusion to a quarter.
- Diffusion-limited gases: CO is diffusion-limited, N_2O perfusion-limited; O_2 is perfusion-limited normally and diffusion-limited in fibrosis and at extremes of exercise or altitude.

Ventilation–perfusion

- Both ventilation and perfusion rise from apex to base, but perfusion more steeply: **V/Q is highest at the apex (about 3) and lowest at the base (about 0.6); overall about 0.8.** Apex: high alveolar PO_2, low PCO_2 (tuberculosis favours the apex because of the high PO_2). Base: lower PO_2, higher PCO_2.
- **Hypoxaemia from a true shunt (V/Q = 0) is not corrected by 100% oxygen**; that from low V/Q regions, diffusion limitation or hypoventilation is. Hypoventilation alone keeps the A–a gradient normal; shunt, V/Q mismatch and diffusion limitation widen it. Dead space (V/Q = ∞, as in pulmonary embolism) wastes ventilation and raises $PaCO_2$ unless ventilation rises. Normal physiological shunt (bronchial and Thebesian veins) is about 2% of cardiac output.
- West zones: zone 1 (PA > Pa > Pv; not seen normally), zone 2 (arterial > alveolar > venous), zone 3 (arterial > venous > alveolar).
- **Hypoxic pulmonary vasoconstriction** is a local response that diverts blood from poorly ventilated alveoli to better ventilated ones; when it is lung-wide (altitude) it raises pulmonary artery pressure (pulmonary hypertension, right heart strain, HAPE).

Gas transport

- **Oxyhaemoglobin curve**: sigmoid (cooperativity). P50 about 26–27 mmHg. Saturation about 97–98% at a PO_2 of 100, about 90% at 60 (the knee of the curve), 75% at 40 (mixed venous), 50% at 27.
  - **Right shift (lower affinity, easier release):** ↑ CO_2, ↑ H^+ (acidosis), ↑ temperature, ↑ 2,3-BPG, exercise (the Bohr effect), altitude (the exam answer, through 2,3-BPG; at moderate altitude the 2,3-BPG rise and the alkalosis roughly cancel, and at extreme altitude, as on Everest, the alkalosis wins and the curve shifts left, which helps loading in the lung).
  - **Left shift (higher affinity):** ↓ H^+, ↓ CO_2, ↓ temperature, ↓ 2,3-BPG, **HbF, carbon monoxide, methaemoglobin**.
- CO binds haemoglobin with 200–250 times the affinity of O_2, reducing carrying capacity and shifting the curve left; PaO_2 is normal, so peripheral chemoreceptors are not stimulated and the pulse oximeter reads falsely normal (measure carboxyhaemoglobin by CO-oximetry); treat with 100% oxygen, which cuts the COHb half-life from about 4–5 hours on air to about 1–1.5 hours (about 20–30 minutes with hyperbaric oxygen, used if severe).
- O_2 content = 1.34 × Hb × SaO_2 + 0.003 × PaO_2 (mL/dL; 1.34–1.39 mL O_2 per gram of Hb). Arterial content about 20 mL/dL, mixed venous about 15; at rest the tissues take about 5 mL/dL (250 mL/min), an extraction of about 25%.
- **CO_2 transport: about 70% as bicarbonate** (carbonic anhydrase in red cells; HCO_3^- exchanges for Cl^-, the chloride shift), 20–25% as carbaminohaemoglobin, 5–10% dissolved.
- **Bohr effect**: CO_2 and H^+ reduce Hb's affinity for O_2 in tissues. **Haldane effect**: oxygenation of haemoglobin reduces its affinity for CO_2 and H^+, helping CO_2 release in the lungs; deoxygenation in tissues helps CO_2 uptake.
- Partial pressures: inspired (humidified) PO_2 about 150 mmHg at sea level; alveolar PO_2 about 100–104 mmHg, PCO_2 40; mixed venous PO_2 40, PCO_2 45–46; alveolar gas equation $PAO_2 = FiO_2(Patm - 47) - PaCO_2/0.8$ (0.21 × 713 − 50 ≈

100). A–a gradient normally under 10–15 mmHg (rises with age, roughly age/4 + 4).

- **Arterial PaO_2 on room air: normal 80–100 mmHg; hypoxaemia mild 60–79, moderate 40–59, severe below 40.** So 50–60 mmHg is moderate, not mild. The usual exam definition of hypoxaemia severe enough to matter (and of respiratory failure) is a PaO_2 below 60 mmHg. Respiratory failure is a PaO_2 below 60 (type 1, with normal or low $PaCO_2$) or with a $PaCO_2$ above 50 (type 2).

Control of breathing

- Medullary centres: dorsal respiratory group (inspiration; nucleus tractus solitarius), ventral group (both inspiratory and expiratory neurons, used in forced breathing), **pre-Bötzinger complex (the rhythm generator, in the ventral group)**; pontine **pneumotaxic centre** (nucleus parabrachialis in the upper pons, now the pontine respiratory group: **switches off inspiration**, so a strong signal shortens inspiration and raises the rate) and apneustic centre (lesions above it with cut vagi give apneusis).
- **Central chemoreceptors (ventral medulla) respond to H^+ in the CSF**: CO_2 crosses the blood–brain barrier and forms carbonic acid. They give the main drive (about 70–80% of the CO_2 response); they are insensitive to hypoxia, and chronic CO_2 retention resets them.
- **Peripheral chemoreceptors (carotid bodies via CN IX, aortic bodies via CN X) respond to a fall in arterial PO_2 (not content)**, to a rise in $PaCO_2$ and to H^+. They are not stimulated in anaemia, CO poisoning or methaemoglobinaemia because PaO_2 is normal. They respond weakly from about 100 mmHg down and strongly when PaO_2 falls below about 60 mmHg. The sensors are the glomus (type I) cells, whose O_2-sensitive K^+ channels close in hypoxia, depolarising them; the carotid body has the highest blood flow per gram in the body, so it senses arterial, not venous, PO_2. Only the carotid bodies respond appreciably to H^+; they give the whole response to hypoxia.
- Reflexes: Hering–Breuer (stretch receptors prevent overinflation), J receptors (pulmonary oedema), cough.
- **Exercise**: ventilation rises in step with CO_2 production, so in moderate exercise mean arterial PO_2, PCO_2 and pH stay near normal; the drive is neural (feed-forward from the motor cortex, afferents from moving joints and muscles), with a learned component and humoral factors (K^+, temperature, oscillations of PCO_2). Ventilation jumps at the start and falls abruptly at the end, then declines slowly. Only above the anaerobic (lactate) threshold does lactic acidosis add a drive and $PaCO_2$ fall.

High altitude

- Hypobaric hypoxia: barometric pressure falls, inspired PO_2 falls, FiO_2 stays 21%.
- **Acute response: hyperventilation through peripheral chemoreceptors, causing respiratory alkalosis (high pH, low $PaCO_2$, slightly low HCO_3^-)**; example pH 7.50, $PaCO_2$ 27 is respiratory alkalosis. The kidney then excretes bicarbonate (over 2–3 days), which restores pH and lets ventilation rise further.
- **Ventilatory acclimatisation** (ventilation keeps rising over the first days, $PaCO_2$ falls further): the classical answer (Guyton, Ganong) is that the CSF alkalosis first brakes the central chemoreceptors and over days the choroid plexus and kidneys remove bicarbonate from CSF and plasma, releasing the brake. Current physiology (West's *High Altitude Medicine and Physiology*) gives at least as large a part to the carotid bodies becoming **more** sensitive to hypoxia over the same days. Cardiac output rises acutely and returns towards normal over days to weeks as oxygen content recovers.
- **Alkalosis reduces ionised calcium** (more albumin binding), giving perioral tingling and carpopedal spasm with normal total calcium; acetazolamide speeds acclimatisation (a metabolic acidosis that offsets the alkalosis).
- Chronic adaptation: polycythaemia (EPO, within days; red cell mass rises over weeks), raised 2,3-BPG (a right shift that roughly offsets the alkalosis at moderate altitude), more capillaries and mitochondria, pulmonary hypertension and right ventricular hypertrophy.
- Disorders: acute mountain sickness (headache with nausea, fatigue or dizziness, usually 6–12 hours after arrival above about 2,500 m; the 2018 revision of the Lake Louise score dropped the sleep item), HACE (ataxia and confusion; dexamethasone, descent), HAPE (breathlessness at rest, cough; non-cardiogenic oedema from patchy, uneven hypoxic vasoconstriction; descent and oxygen first, nifedipine if they are not available), chronic mountain sickness (Monge disease: excessive polycythaemia, most common in Andean natives). Prevention (Wilderness Medical Society 2019; a 2024 update has since been published): above 3,000 m raise the sleeping altitude by no more than about 500 m a day, with a rest day every 3–4 days; **acetazolamide 125 mg twice daily** for moderate or high risk (dexamethasone if acetazolamide cannot be taken); nifedipine or tadalafil only for those with previous HAPE.
- Highlanders: Tibetans and Sherpas live at altitude with **normal or only slightly raised haemoglobin** (unlike Andeans), blunted hypoxic pulmonary vasoconstriction and higher nitric oxide, linked to variants of **EPAS1** (HIF-2α) and **EGLN1**.

Types of hypoxia

- **Hypoxic hypoxia**: low arterial PO2 (altitude, hypoventilation, V/Q mismatch, shunt, diffusion defect; **pneumonia**, by shunt and V/Q mismatch through consolidated lung, is hypoxic hypoxia whatever the haemoglobin); the only type with a low PaO_2, and the one oxygen helps most. **Anaemic hypoxia**: too little functional haemoglobin (anaemia, carbon monoxide); **PO2 is normal**, and in anaemia so is the saturation of the haemoglobin present, but oxygen content falls and the patient may not be cyanosed. In **carbon monoxide** poisoning the true oxyhaemoglobin saturation is low (co-oximetry) while the pulse oximeter reads falsely normal. **Stagnant (circulatory) hypoxia**: slow flow (heart failure, shock, local ischaemia); arteriovenous oxygen difference is wide. **Histotoxic hypoxia**: tissues cannot use oxygen (**cyanide** blocks cytochrome oxidase); PO2 is normal and venous oxygen is high.
- **Oxygen in other conditions**: in **decompression sickness** breathing oxygen (with recompression) lowers the nitrogen tension in tissue and bubble and washes nitrogen out; hyperbaric oxygen also treats severe carbon monoxide poisoning. A **pulse oximeter** reads falsely normal with carboxyhaemoglobin, tends towards 85% with methaemoglobin, and fails with poor perfusion, motion and dark nail polish; **hyperbilirubinaemia does not disturb it** (it does disturb co-oximetry). Pulse oximeters read high in darker skin (FDA 2021, NEJM 2020), so check an arterial gas when it matters.

- **Compliance in emphysema** is increased because destruction of alveolar walls and elastin reduces recoil (the lung inflates easily but empties poorly), whereas fibrosis and pulmonary oedema reduce it.

Renal and acid–base

Glomerular filtration and renal blood flow

- GFR about 125 mL/min (180 L/day); renal blood flow about 1,200 mL/min (20–25% of cardiac output); renal plasma flow about 600–650 mL/min; filtration fraction = GFR/RPF about 0.2.
- Starling forces (Guyton): glomerular capillary hydrostatic pressure (about 60 mmHg) favours filtration; Bowman's capsule pressure (about 18) and glomerular oncotic pressure (about 32) oppose it, a net of about 10 mmHg. GFR = K_f × net filtration pressure. **The filtration barrier**: fenestrated endothelium (pores 70–100 nm, stops only cells), basement membrane (negatively charged heparan sulphate) and podocyte foot processes joined by **slit diaphragms** (nephrin; not tight junctions). Molecules below about 2 nm radius (about 7 kDa: inulin, glucose) pass freely; filtration falls with size and is nil by about 4 nm; at a given size cations pass more than neutral molecules and neutral more than anions (dextran studies). **Albumin** (69 kDa, radius about 3.6 nm, anionic) is largely held back: the classical answer (Guyton) is **charge repulsion by the negative basement membrane and slit diaphragm**, its loss in minimal change disease giving selective albuminuria; current research gives size selectivity at the slit diaphragm the larger share and debates how much charge adds. Mesangial cells support the tuft and are contractile and phagocytic.
- **Constriction of the efferent arteriole: raises glomerular capillary pressure, so GFR rises (filtration fraction rises), but renal plasma flow falls.** This holds for moderate constriction; severe efferent constriction lowers GFR again, because the plasma oncotic pressure in the glomerulus climbs as more fluid is filtered. Afferent constriction lowers both. Angiotensin II constricts the efferent arteriole preferentially (ACE inhibitors and ARBs lower GFR, particularly in renal artery stenosis or hypovolaemia); prostaglandins dilate the afferent (NSAIDs remove this).
- Autoregulation of GFR between mean arterial pressures of about 75–160 mmHg (Guyton; often quoted as 80–180) (myogenic response and tubuloglomerular feedback).
- **Macula densa** (early distal tubule) **senses NaCl concentration in tubular fluid**; high delivery signals high GFR and constricts the afferent arteriole (adenosine); low delivery dilates it and stimulates renin release from juxtaglomerular cells.
- Clearance = U × V / P. **Inulin clearance equals GFR** (the gold standard); creatinine clearance slightly overestimates (tubular secretion); **PAH clearance estimates effective renal plasma flow** (about 90% of true RPF, since PAH extraction is about 0.9); modern practice uses eGFR (the race-free CKD-EPI 2021 equation from creatinine, with cystatin C when creatinine misleads; KDIGO 2024). A substance with a clearance above the GFR is secreted; below it, reabsorbed.
- Tubular transport: filtered load = GFR × plasma concentration; excretion = filtered − reabsorbed + secreted.

Glucose handling

- Fully filtered; reabsorbed in the proximal tubule by SGLT2 (about 90%) and SGLT1, then exits by GLUT2. Tubular maximum (Tm) about 375 mg/min in men (about 300 in women); **renal threshold about 180–200 mg/dL** of plasma glucose, at which glucose appears in urine (lower in pregnancy, renal glycosuria and with SGLT2 inhibitors); splay is the rounding of the titration curve, because nephrons differ in their Tm and filtered load, so glucose appears before the whole kidney's Tm is reached.
- Worked example: GFR 120, plasma glucose 400 mg/dL (4 mg/mL): filtered load 480 mg/min; Tm 375 mg/min; **excreted 105 mg/min**.
- SGLT2 inhibitors (empagliflozin, dapagliflozin) lower glucose and have cardiorenal benefit; risk of genital infections and euglycaemic ketoacidosis.

Nephron segments

Segment	Key transport
Proximal tubule	**About 65% of filtered Na^+ and water reabsorbed (isosmotic)**; nearly all glucose, amino acids, bicarbonate (80–90%) and phosphate (PTH-inhibited); carbonic anhydrase; secretes organic acids and bases
Thin descending limb	Water out (aquaporin-1), no solute; concentrates tubular fluid
Thick ascending limb	**NKCC2** (Na^+–K^+–$2Cl^-$), **about 25% of filtered Na^+**; impermeable to water; dilutes fluid (the diluting segment); lumen-positive potential drives Ca^{2+} and Mg^{2+} reabsorption paracellularly (the main site for Mg^{2+}, about 60–70%); makes Tamm–Horsfall protein (uromodulin); loop diuretics act here; Bartter syndrome mimics them
Early distal tubule	NCC (Na^+–Cl^-), **about 5% of filtered Na^+**; thiazides (Gitelman syndrome mimics them); Ca^{2+} reabsorption (PTH)
Collecting duct, principal cells	ENaC, a few per cent of filtered Na^+ (aldosterone: Na^+ in, K^+ out; **amiloride and triamterene block ENaC; spironolactone and eplerenone block the mineralocorticoid receptor**; Liddle syndrome is a gain-of-function ENaC); **ADH: V2 receptor, cAMP, aquaporin-2 inserted into the apical membrane** (aquaporin-3 and -4 basolateral)
Intercalated cells	H^+ secretion (alpha type: H^+-ATPase and H^+–K^+ ATPase), HCO_3^- secretion (beta type, through pendrin)

Concentration and dilution

- Countercurrent multiplier in the loop of Henle creates the medullary gradient (from about 300 at the corticomedullary junction to about 1,200–1,400 mOsm/L at the papilla; urine can be concentrated to the same, and diluted to about 50 mOsm/L); obligatory urine volume is about 0.5 L/day (600 mOsm of solute ÷ 1,200); vasa recta (countercurrent exchangers) preserve it; urea recycling in the medullary collecting duct contributes.
- **Loop diuretics block NKCC2 so solute is no longer pumped into the interstitium, abolishing the medullary gradient: urine cannot be concentrated** (and it cannot be diluted either, because the diluting segment is disabled). Thiazides impair dilution but not concentration.
- ADH from the posterior pituitary (made in supraoptic and paraventricular nuclei) is released by raised plasma osmolality (very sensitive, about 1% change) and by large falls in volume (about 10%) through baroreceptors. The volume stimulus is less sensitive but, once reached, the stronger of the two.

- **ADH disorders** (plasma osmolality; urine osmolality; response to desmopressin):
  - **Central DI** (head injury, pituitary surgery, tumour): plasma high, urine dilute, **urine concentrates after desmopressin** (a rise above about 50%).
  - **Nephrogenic DI** (lithium, hypercalcaemia, hypokalaemia, V2 receptor or aquaporin-2 defect): plasma high, urine dilute, **little or no rise** with desmopressin.
  - **Primary polydipsia**: plasma low or low-normal, urine dilute, concentrates on water deprivation; a stimulated copeptin test now separates it from DI best (Fenske, NEJM 2018).
  - **SIADH**: hyponatraemia, plasma osmolality low, urine inappropriately concentrated (above 100 mOsm/kg), urine Na^+ above 30 mmol/L, euvolaemic.

Acid–base

- Henderson–Hasselbalch: pH = 6.1 + log [HCO_3^-] / (0.03 × PCO_2). Normal pH 7.35–7.45, $PaCO_2$ 35–45 mmHg, HCO_3^- 22–26 mmol/L (22–28 in some laboratories). The bicarbonate system is the main extracellular buffer, haemoglobin the main buffer in blood after it, proteins and phosphate inside cells.
- **Anion gap = Na^+ – (Cl^- + HCO_3^-); normal about 8–12 mEq/L** (the exam figure; modern ion-selective analysers read lower, about 3–11, so use the laboratory's range). It is mainly albumin; correct for low albumin: add 2.5 per 1 g/dL fall below 4.
  - **High gap** (added acid): ketoacidosis, lactic acidosis, uraemia, toxic alcohols (methanol, ethylene glycol), salicylates (MUDPILES; the newer GOLDMARK adds 5-oxoproline from paracetamol and D-lactate, and drops iron and isoniazid, which act through lactate).
  - **Normal gap (hyperchloraemic)**: **bicarbonate loss** (diarrhoea, pancreatic fistula, proximal and distal renal tubular acidosis), saline infusion, acetazolamide.
- Example: pH 7.20, $PaCO_2$ 24, HCO_3^- 10, Na^+ 138, Cl^- 100: gap 28 (high); Winter's formula (expected PCO_2 = 1.5 × HCO_3^- + 8 ± 2 = 23) fits, so it is **appropriately compensated** high anion gap metabolic acidosis. Diarrhoea (Na^+ 134, Cl^- 112, HCO_3^- 12): gap 10, normal gap acidosis from stool bicarbonate loss. Delta ratio checks for mixed disorders.
- **Compensation** (expected changes; a value outside them means a second disorder):

Primary disorder	Expected compensation
Metabolic acidosis	$PaCO_2$ = 1.5 × HCO_3^- + 8 ± 2 (Winter), within 12–24 hours
Metabolic alkalosis	$PaCO_2$ rises about 0.7 per 1 mmol/L rise in HCO_3^- (limited by hypoxia)
Acute respiratory acidosis	HCO_3^- rises about 1 per 10 mmHg rise in PCO_2 (cell buffering)
Chronic respiratory acidosis	HCO_3^- rises about 3.5–4 per 10 mmHg; **renal, over 3–5 days, by more H^+ secretion, bicarbonate reabsorption and ammonium excretion (ammoniagenesis)**
Acute respiratory alkalosis	HCO_3^- falls about 2 per 10 mmHg fall in PCO_2 (cell buffering)
Chronic respiratory alkalosis	HCO_3^- falls about 4–5 per 10 mmHg (renal)

- Compensation never brings the pH fully back to normal (except chronic respiratory alkalosis, which may).
- Kidney acid handling: bicarbonate reabsorption (proximal, via carbonic anhydrase), titratable acid (phosphate buffer), **ammonium (NH_4^+) excretion** (the main adaptive response to acidosis); alpha-intercalated H^+-ATPase.
- Respiratory alkalosis: high pH, low $PaCO_2$ (anxiety, altitude, pregnancy, salicylate early).
- Effect on potassium: acidosis moves K^+ out of cells (hyperkalaemia, about 0.6 mmol/L per 0.1 pH fall, less with organic acids); alkalosis the reverse.

Potassium and other electrolytes

- Aldosterone raises K^+ secretion and Na^+ reabsorption in principal cells; flow-dependent K^+ loss with diuretics (hypokalaemia); hypokalaemic metabolic alkalosis in loop and thiazide use.
- Calcium: PTH raises distal reabsorption; loops increase calciuria, thiazides reduce it.
- Normal serum values: Na^+ 135–145, K^+ 3.5–5.0, Cl^- 98–106 mmol/L; total calcium 8.5–10.5 mg/dL (2.2–2.6 mmol/L), about half ionised (1.1–1.3 mmol/L); phosphate 2.5–4.5 mg/dL; magnesium 1.7–2.4 mg/dL; urea 15–40 mg/dL (BUN 7–20); creatinine 0.6–1.2 mg/dL.
- Daily urine about 1–1.5 L; oliguria below 400 mL/day (below 0.5 mL/kg/h), anuria below 100 mL/day, polyuria above 3 L/day.

Tubular handling and micturition

- **Bicarbonate**: about 80 to 85% of filtered bicarbonate is reabsorbed in the **proximal tubule** by Na+–H+ exchange and carbonic anhydrase (the luminal enzyme changes it to CO2 and water); the rest in the thick ascending limb and the alpha-intercalated cells, which secrete H+ by H+-ATPase.
  Potassium: about 65% is reabsorbed in the proximal tubule and 25 to 30% in the thick ascending limb, and the final amount excreted is set by **secretion in the principal cells** (aldosterone, high flow, alkalosis and high plasma K+ increase it).
- **Micturition reflex**: bladder filling (stretch of the detrusor) stimulates pelvic nerve afferents (S2–S4) to the sacral cord and the pontine micturition centre; parasympathetic efferents contract the detrusor and the internal sphincter relaxes; the external sphincter (somatic, pudendal) is voluntarily relaxed. Sympathetic (hypogastric, T11–L2) relaxes the detrusor and closes the internal sphincter, aiding storage.
  Cystometrogram: first desire at about 150 mL, urgency at about 400 to 500 mL; the law of Laplace explains why the pressure rises little at first (a plateau) and then sharply.

Gastrointestinal

Gastric secretion

Cell	Product	Stimulus / note
Chief (peptic) cells	**Pepsinogen** (activated to pepsin by acid; optimal pH 1.8–3.5)	ACh, acid
Parietal (oxyntic) cells	**HCl and intrinsic factor**	ACh (M3), gastrin (CCK-B), histamine (H_2); blocked by PPIs (H^+–K^+ ATPase) and H_2 blockers
G cells (antrum)	**Gastrin**	Peptides and amino acids, distension, vagus (GRP); inhibited by acid (pH below 3)
ECL cells	Histamine	Gastrin

Cell	Product	Stimulus / note
D cells	Somatostatin	Inhibits acid and gastrin
Mucous neck and surface cells	Mucus and bicarbonate	Prostaglandins protect (NSAIDs reduce)

- Phases (Guyton): cephalic (about 30%, vagal), gastric (about 60%, distension and peptides through gastrin), intestinal (about 10% of the acid, through a little duodenal gastrin; mainly it inhibits secretion, through secretin, CCK, GIP and other enterogastrones and the enterogastric reflex).
- Volumes per day: saliva 1–1.5 L, gastric juice about 1.5–2 L, pancreatic juice about 1–1.5 L, bile 0.5–1 L; about 8–9 L enters the small intestine and only 100–200 mL leaves in the stool.
- **Zollinger–Ellison syndrome (gastrinoma)**: autonomous gastrin from a tumour (most in the duodenum, then the pancreas, within the gastrinoma triangle; MEN1 in about 20–25%) causes multiple, atypical ulcers (distal duodenum, jejunum), diarrhoea and a very high fasting gastrin with **strongly acidic gastric fluid (pH 1–2)**. Contrast with atrophic gastritis or PPI use: high gastrin with high gastric pH (low acid). Diagnose by fasting gastrin (above 10 times the upper limit, about 1,000 pg/mL, with gastric pH below 2, is diagnostic), and a secretin stimulation test when the result is equivocal (a paradoxical rise in gastrin, by 120 pg/mL or more); localise with somatostatin-receptor PET-CT (Ga-68 DOTATATE, now preferred to octreotide scintigraphy) and endoscopic ultrasound; treat with high-dose PPIs and resection.
- Alkaline tide: venous blood leaving the stomach is alkaline after a meal.
- **Receptors behind acid secretion**: histamine on H_2 (Gs, cAMP; cimetidine, famotidine block it), ACh on M_3 and gastrin on CCK-B (CCK2) receptors (both Gq, IP_3 and Ca^{2+}; atropine blocks M_3, pirenzepine M_1 on ECL cells and ganglia); all converge on the H^+–K^+ ATPase, which omeprazole blocks irreversibly, so PPIs are the most effective.
- ***Helicobacter pylori*** makes abundant **urease**, splitting urea to ammonia (which buffers acid around the organism) and CO_2; the **^{13}C-urea breath test** measures the labelled CO_2 breathed out (stop PPIs 2 weeks before). Antral infection lowers D-cell somatostatin, so gastrin and acid rise, and reduces duodenal bicarbonate: **duodenal ulcer with high acid**; pangastritis with atrophy gives **gastric ulcer with low or normal acid**.

Intestinal hormones

Hormone	Cell / site	Stimulus	Actions
Cholecystokinin (CCK)	I cells, duodenum and jejunum	Fat (fatty acids) and amino acids	**Contracts gallbladder**, relaxes sphincter of Oddi, enzyme-rich pancreatic juice, slows gastric emptying, satiety
Secretin	S cells, duodenum	**Acid (pH below 4.5)**	**Bicarbonate-rich pancreatic and biliary secretion**, inhibits gastrin and acid
GIP	K cells, duodenum and jejunum	Glucose, fat	Releases insulin (incretin); tirzepatide acts on both GIP and GLP-1 receptors
GLP-1	L cells, ileum and colon	Nutrients	Incretin, delays gastric emptying, satiety (semaglutide, liraglutide are agonists; DPP-4 inhibitors slow its breakdown)
Motilin	M (Mo) cells, duodenum	Fasting	Migrating motor complex (erythromycin is a motilin agonist)
Ghrelin	Gastric fundus (X/A cells)	Fasting	Hunger; GH release; rises before meals
Somatostatin	D cells	Acid	General inhibitor (octreotide is the analogue)
VIP	Enteric neurons		Relaxes smooth muscle and sphincters, intestinal secretion; VIPoma gives watery diarrhoea, hypokalaemia, achlorhydria (WDHA)

- Pancreatic juice: acinar cells give enzymes (trypsinogen, amylase, lipase), duct cells give bicarbonate (secretin, cAMP): chloride leaves through the apical **CFTR** channel and returns in exchange for bicarbonate (Cl^-/HCO_3^- exchanger, SLC26A6; CFTR also carries some bicarbonate itself). In **cystic fibrosis** the defective CFTR leaves ductal secretion scanty, thick, acidic and protein-rich, so ducts plug, the gland is destroyed and enzymes do not arrive (steatorrhoea, fat-soluble vitamin deficiency); sweat chloride above 60 mmol/L is diagnostic, and CFTR modulators (elexacaftor–tezacaftor–ivacaftor) now treat most patients. Enterokinase (enteropeptidase) in the brush border activates trypsinogen.
- Bile: bile acids (cholic and chenodeoxycholic) conjugated with glycine or taurine; micelles; about 95% reabsorbed in the **terminal ileum** (sodium-dependent transporter, ASBT) by enterohepatic circulation, the pool of 2–4 g cycling about 6–10 times a day (ileal resection or Crohn's disease gives bile acid diarrhoea and fat malabsorption). Returning bile salts are **choleretic** (they stimulate bile secretion) and **inhibit their own synthesis** (7α-hydroxylase, CYP7A1) by negative feedback through the nuclear receptor FXR and intestinal FGF19; CCK contracts the gallbladder.

Motility

- **Slow waves (basic electrical rhythm, BER) are generated by the interstitial cells of Cajal** (between the muscle layers); they set the maximum contraction frequency but do not themselves contract muscle; spikes are superimposed to trigger contraction.
- **Slow-wave frequency: about 3 per minute in the stomach, 12 in the duodenum (highest), falling to 8–9 in the terminal ileum** (duodenum > ileum > stomach); in the colon it rises from about 2 per minute in the caecum to about 6 in the sigmoid (Ganong). The falling gradient along the small intestine aids aboral propulsion.
- Peristalsis (myenteric plexus, ACh and substance P behind the bolus, VIP and NO ahead of it), segmentation, migrating motor complex every 90–120 minutes in fasting (the "housekeeper", driven by motilin; loss of it favours bacterial overgrowth). Law of the gut. Gastrocolic reflex. Hirschsprung disease lacks ganglion cells (RET mutation).
- Enteric nervous system: myenteric (Auerbach) plexus for motility, submucosal (Meissner) plexus for secretion.

- Swallowing: oesophageal peristalsis, lower oesophageal sphincter relaxation by vagal VIP and NO (failed in achalasia).
- Gastric emptying slowed by fat (CCK), acid and hypertonicity.

Absorption

- Carbohydrates: only monosaccharides absorbed (SGLT1 for glucose and galactose, GLUT5 for fructose). Proteins: di- and tripeptides by PepT1. Fats: micelles, chylomicrons into lymph, medium-chain triglycerides go straight to the portal vein.
- **Vitamin B_{12} with intrinsic factor is absorbed in the terminal ileum** (cubam receptor); haem iron and non-haem iron (Fe^{2+}, DMT1) in the duodenum and proximal jejunum; folate in the jejunum; calcium in the duodenum (calbindin, vitamin D); fat-soluble vitamins with fat.
- **After total gastrectomy or in pernicious anaemia, intrinsic factor is no longer made, so B_{12} cannot be absorbed**; megaloblastic anaemia appears after about 3–5 years, because the body's stores (2–5 mg, mostly in the liver) against a need of 1–3 µg a day last that long; folate stores last only about 3–4 months. Terminal ileal resection or Crohn's disease, fish tapeworm and bacterial overgrowth also cause B_{12} deficiency. Schilling test (largely replaced by serum B_{12}, methylmalonic acid and anti-intrinsic factor antibodies).
- Colon: absorbs water and sodium; produces short-chain fatty acids (butyrate) from fibre; secretes K^+ and HCO_3^-.

Liver, bile pigments and others

- Bilirubin: unconjugated (indirect, albumin bound) to conjugated by UDP-glucuronosyltransferase; excreted in bile; converted to urobilinogen in the gut. Normal total bilirubin about 0.3–1.2 mg/dL (conjugated under 0.3); jaundice is visible above about 2–3 mg/dL.
- Saliva: 1–1.5 L/day, pH 6–7, hypotonic, made by the parotid (serous), submandibular (mixed, most of the resting flow) and sublingual (mostly mucous) glands; contains α-amylase (ptyalin), lingual lipase, IgA and lysozyme. The ducts take back Na^+ and Cl^- and add K^+ and HCO_3^-; at high flow there is less time for this, so saliva becomes closer to plasma (more Na^+ and Cl^-, less K^+). Secretion is driven mainly by parasympathetic nerves (atropine dries the mouth); aldosterone lowers salivary Na^+.

Deglutition, vomiting, defecation and the jaundice pattern

- **Swallowing**: voluntary oral phase (tongue pushes the bolus back), pharyngeal phase (reflex, controlled by the swallowing centre in the medulla through V, IX, X; soft palate rises, larynx rises and the epiglottis closes the airway, upper oesophageal sphincter relaxes, respiration inhibited) and oesophageal phase (primary peristalsis, secondary peristalsis if retained, lower oesophageal sphincter relaxation by vagal VIP and NO). Achalasia fails to relax the sphincter and loses myenteric ganglion cells.
- **Vomiting**: coordinated by the medullary vomiting centre, driven by the chemoreceptor trigger zone (area postrema, outside the blood–brain barrier, dopamine D2, 5-HT3, NK1), vestibular, vagal and higher inputs; preceded by nausea, salivation and retrograde peristalsis; antiemetics act on those receptors (ondansetron, metoclopramide, aprepitant).
- **Defecation**: rectal distension relaxes the internal anal sphincter (rectosphincteric reflex), the external sphincter is voluntary (pudendal nerve), and the gastrocolic reflex triggers mass movement after meals; the sacral parasympathetic (S2–S4) drives the defecation reflex, and its loss leads to constipation and overflow incontinence.
- **Obstructive jaundice**: conjugated bilirubin cannot reach the gut, so **stools are pale**, **urine is dark with bilirubin present (conjugated bilirubin is water soluble)** and **urobilinogen is absent**, itching from bile salts, raised alkaline phosphatase. In haemolytic jaundice urine has urobilinogen but **no bilirubin** (acholuric); in hepatocellular jaundice urobilinogen is variable and bilirubin is present. The terminal ileum reabsorbs the bile salts (enterohepatic circulation), so ileal resection lowers the bile salt pool.

Endocrine and reproduction

Hormone mechanisms

- Peptide and catecholamine hormones act at membrane receptors (cAMP, IP_3/Ca^{2+}, tyrosine kinase); steroid and thyroid hormones act at intracellular or nuclear receptors, slowly.
- Hypothalamic–pituitary axes and negative feedback: CRH–ACTH–cortisol, TRH–TSH–T_3/T_4, GnRH–LH/FSH–sex steroids, GHRH/somatostatin–GH–IGF-1; dopamine inhibits prolactin.

Thyroid

- Iodide trapped by the sodium–iodide symporter, oxidised by thyroid peroxidase, organified onto thyroglobulin (MIT, DIT), coupled to T_3 and T_4; peroxidase is blocked by carbimazole and propylthiouracil (PTU also blocks peripheral T_4-to-T_3 conversion by type 1 deiodinase); perchlorate and thiocyanate block the symporter. T_4 is about 90% of what the gland secretes; T_3 is the active hormone, about 80% of it made by peripheral deiodination; reverse T_3 is inactive. In plasma over 99% is protein-bound, mostly to thyroxine-binding globulin; T_4's half-life is about 7 days, T_3's about 1 day. Normal TSH about 0.4–4.0 mIU/L.
- **In primary hypothyroidism, low T_3 and T_4 remove negative feedback on pituitary thyrotrophs and hypothalamic TRH, so TSH is raised** (high TSH with low free T_4). In central hypothyroidism TSH is low or inappropriately normal. Subclinical: high TSH with normal free T_4.
- Wolff–Chaikoff effect (iodide excess transiently inhibits hormone synthesis).

Insulin and glucagon

- Insulin: beta cells (about 60–70% of islet cells; alpha 20%, delta somatostatin about 10%); made as proinsulin, cleaved to insulin and C-peptide in equal amounts (C-peptide tells endogenous from injected insulin); glucose enters via GLUT2, ATP closes K_ATP channels, depolarisation, Ca^{2+} in, release (sulfonylureas close K_ATP). Actions: ↑ glucose uptake in muscle and fat (GLUT4), glycogen, lipid and protein synthesis; ↓ lipolysis, gluconeogenesis, ketogenesis.
- **Insulin drives K^+ into cells by stimulating the Na^+–K^+ ATPase of muscle and liver, so insulin deficiency leaves K^+ in the ECF**; with acidosis, DKA causes hyperkalaemia even though total body K^+ is depleted (K^+ falls when insulin is given, so replace it). Conversely insulin with glucose and nebulised salbutamol treat hyperkalaemia by shifting K^+ into cells (after calcium gluconate to protect the heart); bicarbonate is the classic third, but current guidance (UK Kidney Association 2023) keeps it for those with metabolic acidosis, since it shifts little K^+ on its own. Fasting plasma

glucose normal 70–99 mg/dL; diabetes at 126 or more, 2-hour OGTT 200 or more, HbA1c 6.5% or more (ADA).

- Glucagon: alpha cells; ↑ glycogenolysis and gluconeogenesis, ketogenesis.

Adrenal

- Zona glomerulosa: aldosterone (angiotensin II and K^+); fasciculata: cortisol; reticularis: androgens; medulla: catecholamines.
- **Congenital adrenal hyperplasia**: low cortisol raises ACTH, which drives the precursors toward androgens. **21-hydroxylase deficiency (about 90–95%)**: high 17-hydroxyprogesterone, low cortisol and aldosterone, androgen excess (a virilised girl with ambiguous genitalia; in the salt-wasting form a crisis at 1–4 weeks with vomiting, hyponatraemia, hyperkalaemia and hypotension). **11β-hydroxylase** (high 11-deoxycortisol) and **17α-hydroxylase** deficiencies give **hypertension and hypokalaemia** from excess deoxycorticosterone; 11β is virilising, 17α lowers androgens and oestrogens (sexual infantilism, undervirilised boys).
- **Adrenal insufficiency**: primary (Addison; autoimmune in the West, tuberculosis still important in South Asia) has high ACTH, pigmentation, hyponatraemia, hyperkalaemia and volume loss; secondary (low ACTH) has no pigmentation and no hyperkalaemia, because angiotensin II keeps aldosterone going.
- **Cushing syndrome**: central obesity, purple striae, hypertension, proximal weakness, hyperglycaemia. Raised ACTH means ACTH-dependent: **pituitary corticotroph adenoma (Cushing disease): cortisol suppresses with high-dose dexamethasone** (the adenoma keeps partial sensitivity); **ectopic ACTH (small cell lung cancer, carcinoid) and adrenal tumours do not suppress**. Low ACTH with high cortisol is an adrenal cause. The most common cause overall is exogenous glucocorticoids; of endogenous causes, Cushing disease is about 70%. Screening (Endocrine Society): 24-hour urinary free cortisol, late-night salivary cortisol, 1 mg overnight dexamethasone test (cortisol above 1.8 µg/dL, 50 nmol/L, fails to suppress). High-dose dexamethasone suppression is the exam answer for telling pituitary from ectopic ACTH; **in current practice pituitary MRI and, when it is unclear, inferior petrosal sinus sampling with CRH or desmopressin (a central-to-peripheral ACTH gradient) are the tests of choice**, since the high-dose test misclassifies many.
- Cortisol: permissive for catecholamines, ↑ gluconeogenesis, anti-inflammatory, diurnal peak in the early morning (around waking, about 6–8 a.m.) and lowest around midnight; about 90% bound to cortisol-binding globulin (transcortin) and albumin. Aldosterone escape: in primary hyperaldosteronism, sodium retention stops after a few days (pressure natriuresis, ANP), so oedema is absent. **Conn syndrome**: hypertension, hypokalaemia, metabolic alkalosis, low renin, no oedema; screen with the aldosterone-to-renin ratio, which the Endocrine Society now advises for every adult with hypertension (2025 guideline, replacing 2016's high-risk groups); unilateral adenoma removed, bilateral hyperplasia treated with spironolactone or eplerenone. Endogenous Cushing syndrome not cured by surgery is controlled with steroidogenesis inhibitors (metyrapone, ketoconazole, osilodrostat).
- Adrenal medulla: about 80% adrenaline, 20% noradrenaline (adrenaline needs PNMT, induced by cortisol from the cortex); metabolites metanephrines and vanillylmandelic acid (plasma free metanephrines are the best test for phaeochromocytoma).

Prolactin

- Secreted by lactotrophs under tonic **inhibition by hypothalamic dopamine**; stimulated by TRH, suckling, oestrogens, sleep, stress. Hyperprolactinaemia (prolactinoma, dopamine antagonists such as metoclopramide and antipsychotics, stalk compression, hypothyroidism, renal failure) gives galactorrhoea and amenorrhoea because **it suppresses kisspeptin and pulsatile GnRH**, so LH and FSH fall and follicles do not mature. Cabergoline (a dopamine agonist) is first-line.

Female reproductive physiology

- Menstrual cycle: follicular phase (FSH recruits follicles, oestradiol rises), ovulation, luteal phase (progesterone). Theca cells make androgens (LH), granulosa cells aromatise them to oestrogens (FSH).
- **Ovulation is triggered by the LH surge**, caused by positive feedback of high oestradiol (about 200 pg/mL or more for about 50 hours) on the pituitary and hypothalamus; ovulation follows about 34–36 hours after the surge begins (10–12 hours after the LH peak). FSH rises less.
- The luteal phase is the constant one, about 14 days; differences in cycle length come from the follicular phase. Ovulation is marked by a rise of about 0.3–0.5 °C in basal body temperature (progesterone) and a mid-luteal serum progesterone above about 3 ng/mL (day 21 of a 28-day cycle).
- Corpus luteum makes progesterone, oestrogen and inhibin A; lifespan about 14 days without pregnancy.
- **In early pregnancy hCG from the syncytiotrophoblast acts on the LH receptor to rescue the corpus luteum**, keeping progesterone high until the placenta takes over (luteoplacental shift, 7–10 weeks). hCG doubles about every 48 hours in early pregnancy, peaks at 8–10 weeks (about 100,000 IU/L), is detectable in serum about 8–10 days after conception (soon after implantation) and by urine tests at about the time of the missed period, and is very high in molar pregnancy.
- Placental hormones: hCG, human placental lactogen, oestriol (marker of fetoplacental function), progesterone.
- Oxytocin: milk ejection and uterine contraction (positive feedback); prolactin for milk synthesis.

Male reproductive physiology

- Leydig cells (LH) make testosterone; **Sertoli cells (FSH) support spermatogenesis, form the blood–testis barrier, secrete androgen-binding protein and inhibin B, which feeds back on FSH**, and make anti-Müllerian hormone. Testosterone is converted to dihydrotestosterone by 5α-reductase (finasteride inhibits it) and aromatised to oestradiol.
- Testicular biopsy in azoospermia: **Sertoli-cell-only syndrome** has tubules lined by Sertoli cells with **no germ cells at all** (FSH high); **hypospermatogenesis** has every stage present but fewer; maturation arrest stops at one stage.
- Spermatogenesis takes about 64–74 days (classically 74), plus about 2 weeks in the epididymis, where sperm gain motility; capacitation happens in the female tract. It needs a temperature about 2–3 °C below body temperature. Semen (WHO 2021 lower reference limits): volume 1.4 mL,

concentration 16 million/mL, total 39 million, progressive motility 30%, normal forms 4%.

Calcium, growth and others

- PTH raises calcium (bone, kidney, active vitamin D) and lowers phosphate (inhibits proximal reabsorption); **its secretion is set by ionised (free) calcium**, about half of the total, through the calcium-sensing receptor on chief cells (cinacalcet acts on it); a change of albumin alters total calcium without changing the ionised fraction, so PTH does not respond. The proximal tubule's 1α-hydroxylase (stimulated by PTH, low calcium and low phosphate) makes calcitriol; urinary hydroxyproline marks bone collagen breakdown; FGF23 from bone lowers phosphate and calcitriol. Calcitonin (parafollicular C cells) is minor in humans; vitamin D (calcitriol) increases intestinal calcium uptake.
- **Calcium disorders**:

Disorder	Ca^{2+}	Phosphate	PTH
Primary hyperparathyroidism	High	Low	High
Hypoparathyroidism	Low	High	Low
Pseudohypoparathyroidism (Gs defect, end-organ resistance; no urinary cAMP rise to PTH)	Low	High	High
Humoral hypercalcaemia of malignancy (tumour PTHrP, often squamous)	High	Low	**Low** (suppressed by the calcium)
CKD (secondary hyperparathyroidism)	Low or normal	High	High (low calcitriol)

- Growth hormone acts via IGF-1 from the liver; secreted in pulses, mostly in slow-wave sleep; raised in hypoglycaemia, exercise, stress, fasting and by ghrelin and arginine; inhibited by glucose (the basis of the glucose suppression test for acromegaly), somatostatin and IGF-1.
- Posterior pituitary: ADH and oxytocin are made in the supraoptic and paraventricular nuclei and carried down the axons (with neurophysins) to be stored and released.

Puberty, menopause and contraception

- **Puberty**: pulsatile GnRH secretion rises as the hypothalamus matures (leptin and kisspeptin permissive); the order in girls is thelarche (breast budding), pubarche, growth spurt, then menarche about two years after the breast starts; in boys testicular enlargement (above 4 mL), then pubic hair and the growth spurt late. Adrenarche (DHEA rise) is separate from gonadarche. **Precocious puberty** is before age 8 in girls, 9 in boys.
- **Menopause**: follicles run out at a median age of about 51 (earlier in many South Asian series), oestradiol falls and loses negative feedback, so **FSH and LH rise (FSH above 40 IU/L)**; hot flushes, vaginal atrophy and bone loss follow; oestrone from adipose androgens becomes the main oestrogen.
- **Combined oral contraceptive**: oestrogen and progestogen suppress GnRH, LH and FSH, preventing the LH surge (**no ovulation**), thicken cervical mucus and thin the endometrium; progestogen-only and the levonorgestrel IUS act mainly on mucus and endometrium. **Mid-cycle LH surge** is the one event driven by positive oestradiol feedback.
- **Milk ejection (let-down)**: suckling afferents in the nipple reach the hypothalamus (paraventricular nucleus), which releases **oxytocin** from the posterior pituitary to contract myoepithelial cells; it can be triggered by the baby's cry and inhibited by stress; prolactin is for synthesis.

CNS and special senses

Sensory receptors and adaptation

Receptor	Stimulus	Adaptation
Pacinian corpuscle	**High-frequency vibration (best about 200–300 Hz; range about 30–800)**, deep pressure; onion-like lamellae filter out sustained pressure	Fastest
Meissner corpuscle	Light touch, low-frequency vibration and flutter (about 30–50 Hz; glabrous skin, two-point discrimination)	Rapid
Merkel disc	Sustained pressure, texture, fine detail	Slow
Ruffini ending	Skin stretch	Slow
Free nerve endings	Pain, temperature	**Pain adapts least**

- **Pain shows the least adaptation** (slowly adapting nociceptors, which can even sensitise: hyperalgesia), keeping a warning present while damage continues. Rapidly adapting (phasic) receptors signal change; slowly adapting (tonic) signal maintained stimulus; muscle spindles, Golgi tendon organs, baroreceptors and chemoreceptors are also slowly adapting. Smell and the feel of clothing adapt quickly (smell about half in the first second, then mostly centrally).
- Nociceptor transducers: TRPV1 (heat above about 43 °C and capsaicin), TRPM8 (cold and menthol), TRPA1 (irritants); the transmitters of C fibres are glutamate and substance P. Gate control (Melzack and Wall): Aβ touch input inhibits pain transmission in the substantia gelatinosa (why rubbing helps, and TENS). Endogenous opioids act in the periaqueductal grey, rostral ventromedial medulla and dorsal horn.
- **Weber's law: the just noticeable difference is a constant fraction of the original stimulus.** Detecting 2 g on 100 g is 2%, so on 500 g the smallest detectable addition is 10 g. **Weber–Fechner law**: perceived intensity is proportional to the logarithm of stimulus intensity; Stevens' power law is the modern refinement.
- **Law of specific nerve energies (Müller)**: the sensation depends on which pathway is excited, not on the stimulus; the related law of projection (activity in a pathway is felt at the receptor's original site) explains phantom limb sensations.
- **Bell–Magendie law: dorsal roots carry sensory fibres and ventral roots carry motor fibres.** Pseudounipolar cell bodies lie in the dorsal root ganglion.
- Sensory pathways: dorsal column–medial lemniscus (fine touch, vibration, proprioception; crosses in the medulla), spinothalamic (pain and temperature; crosses at the spinal level), thalamic VPL/VPM, then the primary somatosensory cortex (postcentral gyrus; the homunculus). Brown-Séquard: ipsilateral motor and dorsal column loss below the lesion, contralateral pain and temperature loss starting one or two segments below it.

Spinal reflexes and muscle receptors

- **Muscle spindle: lies in parallel with extrafusal fibres, signals length and its rate of change (Ia and II afferents)**; gamma motor neurons keep it taut during contraction. Stretch

reflex is monosynaptic (knee jerk); inhibits antagonists by reciprocal inhibition.

- **Golgi tendon organ: lies in series with the muscle, signals tension (Ib afferent)**; autogenic (inverse myotatic) inhibition via an interneuron, protecting from excessive force.
- Withdrawal (flexor) reflex, polysynaptic, with the crossed extensor reflex; the plantar response is extensor (Babinski) in upper motor neuron lesions and normally in infants up to about 1 year; clonus and hyperreflexia in upper motor neuron lesions (spinal shock first, then spasticity); lower motor neuron lesions give flaccidity, fasciculation and wasting.
- **Decerebrate rigidity** (intercollicular section, below the red nucleus): cortical and rubrospinal influences are removed and the **vestibulospinal and pontine reticulospinal drive to the antigravity extensors is unopposed**; all four limbs extend. It is a gamma (spindle-driven) rigidity, abolished by cutting the dorsal roots or destroying the lateral vestibular nucleus. **Decorticate** posturing (lesion above the red nucleus): rubrospinal drive flexes the arms, the legs stay extended.
- **Cord transection**: spinal shock (flaccid, areflexic, atonic bladder with retention) for days to weeks, then spasticity and reflex return; a lesion above the sacral segments leaves an **automatic (spastic, reflex) bladder**, a sacral lesion an autonomous (flaccid) one. A lesion above C3 stops breathing (the phrenic nerve, C3–C5, loses its drive from the medulla); a cervical lesion cuts the whole sympathetic outflow (T1–L2) off from the brain, and one above T6 risks autonomic dysreflexia.

Cerebellum and basal ganglia

- Cerebellar cortex: **granule cells are the only excitatory neurons (glutamate, parallel fibres onto Purkinje cells)**; **Purkinje, basket, stellate and Golgi cells are all inhibitory (GABA)**. Purkinje cells are the sole output of the cortex and inhibit the deep nuclei (dentate, interposed, fastigial). Mossy and climbing fibres are the inputs, both excitatory (climbing fibres only from the inferior olive, one to each Purkinje cell; mossy fibres from everywhere else, through granule cells). Cerebellar inputs enter through the inferior and middle peduncles and its output leaves mainly through the superior peduncle. Lesions give ipsilateral ataxia, intention tremor, dysmetria, dysdiadochokinesia and nystagmus. Vermis (trunk), hemispheres (limbs; ipsilateral).
- Basal ganglia: direct pathway (facilitates movement) and indirect pathway (inhibits). **Parkinson disease: loss of dopaminergic neurons of the substantia nigra pars compacta**, so nigrostriatal dopamine falls, the direct pathway weakens and the indirect strengthens (tremor, rigidity, bradykinesia). Symptoms appear after about 60–80% of the nigral neurons are lost; Lewy bodies contain α-synuclein. Treated with levodopa plus carbidopa, dopamine agonists, MAO-B inhibitors; deep brain stimulation of the subthalamic nucleus or globus pallidus internus. Striatal neurons: the direct pathway carries D1 receptors, the indirect D2; the striatum's transmitter is GABA.
- Basal ganglia lesions by site: subthalamic nucleus (hemiballismus), caudate and putamen (chorea; Huntington), substantia nigra (parkinsonism), globus pallidus (athetosis; dystonia).
- **Hemiballismus: lesion of the contralateral subthalamic nucleus** (small stroke; violent flinging movements of the opposite arm and leg). Huntington disease: caudate loss (chorea; CAG repeats in HTT on chromosome 4, autosomal dominant with anticipation). Wilson disease: lenticular nucleus (putamen).

Memory and language

- **Hippocampus consolidates short-term to long-term declarative memory**; bilateral damage gives anterograde amnesia (patient H.M.). Amygdala: emotional memory and fear (bilateral damage: Klüver–Bucy syndrome). Papez circuit: hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nucleus, cingulate gyrus, back to the hippocampus; Korsakoff syndrome (thiamine deficiency) damages the mammillary bodies and dorsomedial thalamus. Procedural memory: basal ganglia and cerebellum. Working memory: prefrontal cortex. Long-term potentiation (NMDA receptors, Ca^{2+} entry) is the cellular basis of hippocampal learning.
- **Wernicke aphasia: fluent but meaningless speech, poor comprehension, with a lesion in the posterior superior temporal gyrus (Brodmann 22) of the dominant hemisphere.** Broca (inferior frontal gyrus, Brodmann 44 and 45): non-fluent, comprehension intact. Conduction aphasia (arcuate fasciculus): poor repetition. Global aphasia: both areas. Transcortical aphasias spare repetition. Language is in the left hemisphere in over 95% of right-handers and about 70% of left-handers.
- Sleep: about 4–6 cycles of 90 minutes a night; N1 (theta), **N2 (sleep spindles and K complexes; about half the night)**, N3 slow-wave sleep (delta; GH release; night terrors and sleepwalking), more in the first half of the night; **REM** (atonia, dreaming, rapid eye movements, a desynchronised, wake-like EEG with sawtooth waves, pontine origin with PGO waves; about 20–25% of sleep in adults, about 50% in newborns), more in the second half. Narcolepsy: loss of hypothalamic orexin (hypocretin) neurons, REM at sleep onset, cataplexy.
- EEG rhythms: **beta above 13 Hz (alert, eyes open), alpha 8–13 Hz (awake, relaxed, eyes closed, occipital; blocked by eye opening or attention: alpha block)**, theta 4–7 Hz (drowsiness, normal in children), delta below 4 Hz (deep sleep, infants; in an awake adult, brain disease).

Hearing and balance

- Sound is transmitted through the tympanic membrane and ossicles to the oval window, with impedance matching of about 22-fold in pressure (area ratio about 17 × ossicular lever about 1.3), about 25–30 dB. The tensor tympani and stapedius damp loud low-frequency sound (the acoustic reflex, latency about 40–80 ms, so it does not protect against sudden noise). Human hearing spans about 20–20,000 Hz, most sensitive at 1,000–4,000 Hz; speech mainly 500–2,000 Hz (noise-induced loss begins at 4,000 Hz, the dip). Basilar membrane tonotopy: **high frequencies at the base (narrow, stiff), low at the apex** (place theory). Inner hair cells (one row) send about 90–95% of afferent fibres; outer hair cells (three rows) amplify by electromotility (prestin) and make otoacoustic emissions.
- **Endolymph is rich in K^+ (about 150 mmol/L) and low in Na^+ (about 1 mmol/L), like intracellular fluid, secreted by the stria vascularis**, and is held at **+80 mV (the endocochlear potential)**; perilymph resembles CSF/extracellular fluid.
- **Brainstem evoked response (BERA) waves**: I cochlear nerve (distal), II cochlear nerve (proximal) or cochlear nucleus, III superior olivary complex, IV lateral lemniscus, **V inferior colliculus** (the exam answer, Dhingra's "E COLI"; current physiology says wave V arises from the lateral lemniscus

where it ends in the inferior colliculus, so take whichever the options offer). Wave V is the largest and the last to disappear as the stimulus is reduced, and is used for threshold and newborn screening. Stereocilia bending opens mechanotransduction channels; K^+ enters from endolymph and depolarises the hair cell (an unusual K^+-driven depolarisation).

- Conductive versus sensorineural loss: Rinne and Weber tests. Vestibular hair cells in the semicircular canals (angular acceleration) and otolith organs (linear acceleration, gravity); vestibulo-ocular reflex.

Vision

- **In darkness the rod is depolarised, cGMP-gated Na^+ channels stay open and it releases glutamate continuously; light activates rhodopsin, transducin and phosphodiesterase, which lowers cGMP, closes the channels, and the rod hyperpolarises and releases less glutamate.** Photoreceptors never fire action potentials.
- Rods (about 120 million): night (scotopic) vision, high sensitivity, rhodopsin (11-cis-retinal, needs vitamin A: night blindness), absent from the fovea, most dense about 20° from it; cones (about 6 million): colour (three opsins, peak about 420, 530 and 560 nm) and acuity, fovea, photopic vision. Dark adaptation: cones adapt in about 5–10 minutes, rods take about 20–30 minutes (near full by 40); light adaptation takes about 5 minutes. Red–green colour blindness is X-linked recessive (about 8% of men of European descent). Purkinje shift: in dim light blue looks brighter than red, as vision passes to rods (peak about 500 nm).
- Visual pathway: retina, optic nerve, chiasm (nasal fibres cross), optic tract, lateral geniculate, optic radiation (Meyer's loop, temporal), occipital cortex. Pupillary light reflex: pretectal nucleus, Edinger–Westphal nucleus.
- Accommodation: ciliary muscle contraction (parasympathetic, CN III) relaxes the zonules and thickens the lens.

Taste and smell

- Taste: anterior two thirds by chorda tympani (CN VII), posterior third by CN IX, epiglottis by CN X; all end in the nucleus tractus solitarius, then VPM thalamus, then the insula and frontal operculum. Five tastes; every region of the tongue senses all of them (the "tongue map" is a myth). Taste cells live about 10 days.

Taste	Receptor	Note
Sweet	**T1R2 + T1R3** (G protein, gustducin)	**Chemical classes that taste sweet (Guyton): sugars, glycols, alcohols, aldehydes, ketones, amides, esters, some amino acids**, saccharin, lead salts
Umami	T1R1 + T1R3, mGluR4	Glutamate (monosodium glutamate)
Bitter	T2R family (about 25 genes)	Alkaloids (quinine, the reference), many poisons; lowest threshold of all tastes
Salty	ENaC (amiloride-sensitive)	Na^+ ions
Sour	OTOP1 proton channel (identified 2018–2019)	H^+; the classic answer is H^+ entry blocking K^+ channels

- Olfaction: bipolar neurons (replaced throughout life, every 1–2 months) with about 400 kinds of G protein-coupled odorant receptor, through the cribriform plate to the olfactory bulb (mitral cells, glomeruli); **the only sense not relayed through the thalamus first** (to the piriform cortex and amygdala). Anosmia with hypogonadism is Kallmann syndrome (failed migration of GnRH neurons).

Autonomic and cerebrospinal fluid points

- Hypothalamus: temperature (anterior, heat loss; posterior, heat conservation; the set point is raised in fever by prostaglandin E_2, which antipyretics block), thirst (osmoreceptors in the organum vasculosum of the lamina terminalis and subfornical organ, outside the blood–brain barrier), circadian rhythm (suprachiasmatic nucleus, driven by melanopsin retinal ganglion cells; melatonin from the pineal at night), satiety (ventromedial; leptin from fat acts on the arcuate nucleus) and hunger (lateral).
- Autonomic: all preganglionic fibres release ACh at nicotinic (N_N) receptors; postganglionic parasympathetic release ACh at muscarinic receptors; postganglionic sympathetic release noradrenaline, except to sweat glands (ACh, muscarinic); the adrenal medulla is a modified sympathetic ganglion.
- **CSF**: about 500 mL made per day (0.35 mL/min; about 70% by the choroid plexus), total volume about 150 mL, renewed 3–4 times a day; reabsorbed through the arachnoid granulations (and lymphatic routes). Opening pressure lying down about 70–180 mm H_2O (5–15 mmHg). Clear, under 5 lymphocytes/µL, protein 15–45 mg/dL, glucose 50–80 mg/dL (about two thirds of blood glucose), chloride higher and K^+ lower than in plasma.

Motor lesions, eye signs and visual field defects

- **UMN versus LMN**: upper motor neuron lesions give spastic weakness, hyperreflexia, clonus, extensor plantar (after an initial spinal shock), little wasting; lower motor neuron lesions give flaccid paralysis, hypotonia, hyporeflexia, fasciculation and marked wasting. **Amyotrophic lateral sclerosis** (motor neuron disease) is the classic disease with **both**: wasting and fasciculations beside brisk reflexes and extensor plantars, with sensation, eye movements and sphincters spared. The **corticospinal tract** is the main voluntary pathway, crossing in the medulla (pyramidal decussation); the **lateral** system (lateral corticospinal and rubrospinal) serves the distal limb muscles, the **medial** system (reticulospinal, vestibulospinal, tectospinal and anterior corticospinal) posture, tone and the axial muscles.
- **Horner syndrome**: ptosis (Müller's muscle), miosis, anhidrosis, enophthalmos from interruption of the sympathetic pathway to the eye (the hypothalamus–T1–superior cervical ganglion pathway: e.g. Pancoast tumour, carotid dissection, lateral medullary syndrome). **Argyll Robertson pupil**: small irregular pupils that **accommodate but do not react to light** (neurosyphilis; also diabetes); the lesion is in the pretectal region of the midbrain, which interrupts the light reflex but spares the separate near-response pathway.
- **Visual field defects**: optic nerve lesion gives monocular blindness; **optic chiasma** (pituitary tumour) gives bitemporal hemianopia; optic tract, LGN or optic radiation give contralateral homonymous hemianopia; **Meyer's loop (temporal lobe)** gives contralateral upper quadrantanopia ("pie in the sky"), the parietal radiation lower quadrantanopia; occipital lesions give homonymous hemianopia with **macular sparing** (dual blood supply to the occipital pole).
- **Limbic system**: hippocampus, amygdala, cingulate and parahippocampal gyri, mammillary bodies and septal area (the Papez circuit and memory above); **Klüver–Bucy**

syndrome from bilateral amygdala (anterior temporal) lesions is placidity, hyperorality, hypersexuality and visual agnosia.

- **Hearing tests**: **Rinne** compares air and bone conduction (normal is air better than bone, positive); **Weber** lateralises to the deaf ear in conductive loss and to the better ear in sensorineural loss. **Otosclerosis** is stapes footplate fixation, a conductive loss that begins in young women and worsens in pregnancy; Rinne is negative on the affected side.
- **Raised intracranial pressure** is highest on waking (recumbency, a rise of $PaCO_2$ in sleep dilating cerebral vessels, less CSF absorption), so its headache is worst in the early morning.
- **Cushing reflex** (raised intracranial pressure compresses the medullary vasomotor centre, the ischaemia drives a rise in systolic pressure, then bradycardia from baroreflex and irregular breathing) is a late sign of herniation.

Sources

The notes rest on standard texts and guidelines: Guyton and Hall's Textbook of Medical Physiology; Ganong's Review of Medical Physiology; Boron and Boulpaep's Medical Physiology; Berne and Levy Physiology; Costanzo's Physiology; Harrison's Principles of Internal Medicine (for clinical correlates, including acid–base, endocrine and neurological disease); Kandel's Principles of Neural Science; Sherwood's Human Physiology; WHO's guidance on oral rehydration (2002, with the reduced-osmolarity solution); the 2018 Lake Louise acute mountain sickness score and the Wilderness Medical Society's guidelines (2019) for altitude illness; GOLD 2025 and the ATS/ERS 2022 interpretation standard for spirometry; KDIGO 2024 and CKD-EPI 2021 for eGFR; the 2021 universal definition of heart failure and ESC 2021; WHO's laboratory manual for semen (6th edition, 2021); the Endocrine Society's guideline on Cushing syndrome; ADA Standards of Care; the UK Kidney Association's hyperkalaemia guideline (2023); Parikh and Reddy for post-mortem changes; Dhingra for the brainstem evoked response; West's Respiratory Physiology for the grading of hypoxaemia; West's High Altitude Medicine and Physiology for ventilatory acclimatisation; the Endocrine Society's guideline on primary aldosteronism (2025, replacing 2016); Fenske and colleagues (NEJM 2018) on copeptin in polyuria; Sjoding and colleagues (NEJM 2020) and the FDA (2021) on pulse oximetry in darker skin; the CF Foundation's diagnostic guidelines (2017) for sweat chloride; First Aid for the USMLE Step 1 (2022) for checking facts.