Pathology

MBBS Recap: high-yield notes for revision

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Revision notes for the MEC PG entrance: general pathology, systemic pathology, haematology and genetics, set out for fast recall after a wrong answer.

Cell injury and adaptation

Adaptations

Adaptation	What changes	Classic examples
Hypertrophy	Bigger cells, no new cells	Heart in hypertension or aortic stenosis, skeletal muscle in training, pregnant uterus (with hyperplasia)
Hyperplasia	More cells (only in cells that can divide)	Endometrium under oestrogen, breast at puberty, **BPH**, regenerating liver after partial hepatectomy; pathological hyperplasia is a soil for cancer (endometrium) but BPH is not premalignant
Atrophy	Smaller cells, fewer organelles	Disuse, denervation, ischaemia, malnutrition, loss of endocrine drive, pressure, ageing (brain); by ubiquitin–proteasome breakdown and autophagy
Metaplasia	One mature cell type replaced by another	See below

- **Metaplasia** is reversible and comes from **reprogramming of stem cells**, never from a change in mature cells.
  - Smoker's bronchus: ciliated columnar to **squamous** (the commonest epithelial metaplasia).
  - **Barrett's oesophagus**: squamous to **intestinal-type columnar epithelium with goblet cells** after long reflux; risk of **adenocarcinoma**.
  - Vitamin A deficiency: squamous change in respiratory and urinary epithelium (and keratomalacia).
  - Stomach in chronic H. pylori gastritis: intestinal metaplasia; bladder in schistosomiasis or stones: squamous.
  - Connective tissue: **myositis ossificans** (bone in muscle after injury).
- Disorders of development, not adaptations: **agenesis** (no organ and no primordium), **aplasia** (the primordium forms but fails to develop), **hypoplasia** (incomplete development, a small organ). **Atrophy** is shrinkage of an organ that had reached its full size.
- **Dysplasia**: disordered growth with nuclear atypia, loss of uniformity and orientation; low grade may regress. **Carcinoma in situ**: full-thickness dysplasia, basement membrane intact.

Mechanisms of reversible and irreversible injury

- **Hypoxia** is too little oxygen in the tissue; **hypoxaemia** is too little in arterial blood (**PaO_2 below 60 mmHg or SaO_2 below 90%**). The cell's components most often damaged, whatever the cause: **mitochondria**, **membranes** (plasma and lysosomal), the **protein-synthesis machinery** (ER, ribosomes), the cytoskeleton and **DNA**.
- First target in hypoxia: **mitochondrial oxidative phosphorylation**, so **ATP falls**. Consequences:
  - Na^+/K^+-ATPase fails, sodium and water enter: **cell swelling**, the **earliest light-microscopic change** of almost every injury ("cloudy swelling", hydropic or vacuolar change), with surface blebs and myelin figures.
  - Anaerobic glycolysis: glycogen depletion, lactic acid, fall in pH, clumping of nuclear chromatin.
  - Ribosomes detach from the rough ER: protein synthesis falls; **fatty change** in liver and heart.
- **Point of no return**: (1) inability to restore mitochondrial function (mitochondrial swelling and vacuolation, with **amorphous flocculent, calcium-rich densities** on EM, the marker of irreversibility) and (2) **profound membrane damage** (plasma membrane, lysosomes). Leaking cell proteins are the serum markers: **troponin** and CK-MB (heart), ALT and AST (liver).
- **Calcium**: cytosolic calcium rises and activates phospholipases, proteases, endonucleases and ATPases, and opens the mitochondrial permeability transition pore.
- **Reperfusion injury**: free radicals from returning oxygen, calcium overload, neutrophils and complement; **contraction band necrosis** in reperfused myocardium (after thrombolysis or PCI).
- **Free radicals**: superoxide, hydrogen peroxide, **hydroxyl radical (the most reactive)**; made by the Fenton reaction (Fe^{2+} with H_2O_2), **xanthine oxidase** (reperfusion), high inspired oxygen (**oxygen toxicity** in premature babies: **retinopathy of prematurity**, **bronchopulmonary dysplasia**), radiation, drugs (paracetamol via NAPQI, carbon tetrachloride via $CCl_3\bullet$). Removed by superoxide dismutase, catalase, glutathione peroxidase and vitamins E, C and β-carotene. Damage: lipid peroxidation of membranes, protein cross-linking, DNA breaks.
- Nuclear changes of necrosis: **pyknosis** (shrinkage and condensation), **karyorrhexis** (fragmentation), **karyolysis** (fading as DNase digests chromatin). Cytoplasm turns eosinophilic.

Necrosis, its patterns

Pattern	Typical setting	Key point
Coagulative (commonest)	Infarcts of solid organs (heart, kidney, spleen); every organ **except the brain**	Proteins denature, architecture kept for days ("tombstone" ghost cells); **Zenker's (waxy) degeneration** of rectus abdominis and diaphragm in typhoid is a form

Pattern	Typical setting	Key point
Liquefactive	**Brain infarct**, abscess, bacterial and fungal infection	Enzymatic digestion; cyst-like cavity weeks after a stroke
Caseous	**Tuberculosis**; also systemic fungi (histoplasmosis), sometimes syphilis	Cheesy, amorphous granular pink debris with no outlines, rimmed by granuloma
Fat necrosis	Acute pancreatitis (enzymatic), breast trauma (traumatic)	Lipase frees fatty acids, which bind calcium: **saponification**, chalky white spots; breast lump mimics carcinoma
Fibrinoid	**Malignant hypertension**, vasculitis (PAN), immune-complex disease, **Aschoff bodies**, base of peptic ulcer	Immune complexes and plasma fibrin in vessel walls, bright pink
Gangrene (clinical term)	Limb ischaemia	**Dry** (coagulative), **wet** (liquefactive from bacteria), **gas** (Clostridium perfringens)

Apoptosis

- Programmed, energy-dependent death of single cells: **no inflammation**, cell shrinks, chromatin condenses at the nuclear membrane, the cell buds into **apoptotic bodies** with intact membranes that macrophages eat (phosphatidylserine flipped to the outer leaflet is the "eat me" signal, detected by **annexin V**).
- Physiological: embryogenesis (interdigital webs), hormone withdrawal (endometrium in menstruation), thymic deletion of self-reactive T cells, involution, cytotoxic T-cell killing. Pathological: DNA damage, misfolded proteins (ER stress), viral hepatitis (**Councilman bodies**), graft-versus-host disease, atrophy of ducts after obstruction. So apoptosis is **not always pathological**.
- **Intrinsic (mitochondrial) pathway**, the main one: DNA damage, growth-factor withdrawal; sensors (BIM, BID, BAD, PUMA, NOXA) activate **BAX and BAK**, which permeabilise the mitochondrial outer membrane; **BCL-2, BCL-XL and MCL-1** block it. **Cytochrome c** leaves, binds **Apaf-1** in the apoptosome and activates initiator **caspase-9**.
- **Extrinsic (death-receptor) pathway**: Fas ligand to Fas (CD95), or TNF to TNFR1; adaptor FADD; initiator **caspase-8**; inhibited by FLIP.
- **Executioner caspases: 3, 6 and 7.** Endonucleases cut DNA between nucleosomes: a **DNA ladder** of multiples of about 180–200 bp on gel electrophoresis (necrosis gives a smear). TUNEL stains the breaks.
- Modern regulated deaths:
  - **Necroptosis**: necrosis-like morphology, programmed mechanism, **caspase-independent**; **RIPK1, RIPK3, MLKL**; blocked by necrostatin-1.
  - **Pyroptosis**: inflammasomes (NLRP3) activate **caspase-1** (and caspase-4/5/11), which cleaves **gasdermin D** into membrane pores and matures **IL-1β and IL-18**: the cell swells, bursts and inflames.
  - **Ferroptosis**: iron-dependent lipid peroxidation, prevented by **glutathione peroxidase 4 (GPX4)**.
  - Autophagy: self-digestion of organelles in nutrient deprivation (Beclin-1, LC3).

Intracellular accumulations and calcification

- **Fatty change (steatosis)**: liver (alcohol, obesity and metabolic dysfunction, diabetes, protein malnutrition, toxins such as CCl_4), heart ("tigered" or thrush-breast heart in severe anaemia). Fat is shown on **frozen sections** with **Oil red O**, Sudan III/IV or **Sudan black** (alcohol processing dissolves it).
- Cholesterol: atherosclerosis, xanthomas, cholesterolosis of the gallbladder (strawberry gallbladder). Proteins: **Russell bodies** (immunoglobulin in plasma cells), **Mallory–Denk bodies** (keratin), reabsorption droplets in proximal tubules in proteinuria. Glycogen: diabetes (Armanni–Ebstein change in tubules), glycogen storage diseases.
- **Hyaline change**: any glassy pink material; hyaline arteriolosclerosis (benign hypertension, diabetes).
- Pigments:
  - **Lipofuscin**: wear-and-tear pigment from lipid peroxidation, yellow-brown, perinuclear; **brown atrophy** of heart and liver in old age and wasting. A marker of free-radical damage, not itself harmful.
  - **Haemosiderin**: golden-brown iron pigment, **Perls' Prussian blue** positive; bruises, heart-failure cells in lung, haemosiderosis, haemochromatosis.
  - Melanin (Fontana–Masson stain), bilirubin, carbon (anthracosis), haematin.
- **Calcification**:

	Dystrophic	Metastatic
Serum calcium	**Normal**	**High** (hyperparathyroidism, vitamin D excess, bone destruction by myeloma or metastases, milk-alkali, sarcoidosis, renal failure with secondary hyperparathyroidism)
Tissue	Dead or damaged: atheroma, damaged valves (calcific aortic stenosis), caseous TB, fat necrosis, dead parasites, psammoma bodies	Normal tissue, mostly where the tissue is alkaline: **lungs, gastric mucosa, kidneys** (acid-secreting organs), blood vessels

- Calcium shows as basophilic deposits on H&E, black with **von Kossa**, red with alizarin red.

Ageing

- Mechanisms: telomere shortening (replicative senescence, the **Hayflick limit** of about 40–60 divisions), accumulated DNA damage, defective protein homeostasis, deregulated nutrient sensing (calorie restriction lengthens life in animals through sirtuins and reduced IGF-1 and mTOR signalling).
- **Telomerase** is an RNA-dependent DNA polymerase (a reverse transcriptase) carrying its own RNA template; it adds TTAGGG repeats. Active in germ cells and stem cells, **reactivated in about 90% of cancers**; it does not repair DNA. Dyskeratosis congenita: telomerase defects (TERC, TERT, DKC1).
- **Werner syndrome** (adult progeria): **WRN, a RecQ DNA helicase**; autosomal recessive; cataracts, grey hair, atherosclerosis and cancers from the 20s. Do not confuse with Wermer syndrome (MEN 1). **Hutchinson–Gilford progeria** (children): **lamin A (LMNA)**, abnormal "progerin"; lonafarnib (farnesyltransferase inhibitor) now treats it (FDA 2020).

Inflammation and repair

Acute inflammation: the vessels

- **Cardinal signs**: rubor, calor, tumor and dolor (Celsus), and **functio laesa**, loss of function (added by Virchow), five in all.
- Sequence: transient arteriolar vasoconstriction (seconds), **vasodilation** (histamine, NO; heat and redness), **increased permeability** (swelling), stasis.
- Permeability mechanisms:
  - **Endothelial contraction** in **venules**: the commonest; immediate transient response (15–30 minutes), by **histamine, bradykinin, leukotrienes C_4, D_4, E_4**, substance P.
  - Direct endothelial injury (burns, toxins): immediate sustained, all vessels.
  - Delayed prolonged leakage (2–12 hours; sunburn, mild thermal injury).
  - Leucocyte-mediated injury; transcytosis (VEGF); leaky new vessels.
- Exudate (protein-rich, specific gravity above 1.020, cells) versus transudate (protein-poor, under 1.012). Pus is a purulent exudate.

Acute inflammation: the cells

Step	Molecules
Margination and **rolling**	**Selectins**: **P-selectin** (from **Weibel–Palade bodies** of endothelium, and platelet granules; histamine, thrombin), **E-selectin** (induced by IL-1 and TNF), L-selectin on leucocytes; ligand **sialyl-Lewis X**
Firm adhesion	**Integrins**: LFA-1 and Mac-1 (β_2, CD11/CD18) bind **ICAM-1**; VLA-4 (β_1) binds **VCAM-1**; chemokines activate the integrins
Transmigration (diapedesis)	**PECAM-1 (CD31)**, mainly in **post-capillary venules**
Chemotaxis	**IL-8 (CXCL8)**, **C5a**, **LTB_4**, bacterial N-formyl-methionyl peptides
Phagocytosis	Opsonins: **IgG Fc, C3b**, collectins; receptors: mannose, scavenger, Fc, complement

- **Neutrophils predominate in the first 6–24 hours; monocytes and macrophages replace them after 24–48 hours.** Exceptions: Pseudomonas (neutrophils persist for days), viral infections (lymphocytes first), allergy and parasites (eosinophils).
- Killing:
  - Oxygen-dependent: **NADPH oxidase** (phagocyte oxidase; the **respiratory burst**) makes superoxide, which becomes H_2O_2; **myeloperoxidase** converts H_2O_2 with chloride into **hypochlorous acid (HOCl)**, the most potent bactericide of the system. iNOS makes nitric oxide and peroxynitrite.
  - Oxygen-independent: lysozyme, **defensins**, lactoferrin, bactericidal permeability-increasing protein, major basic protein of eosinophils.
  - **Neutrophil extracellular traps (NETs)**: chromatin nets that trap microbes; implicated in thrombosis and lupus.

Defects of leucocyte function

Disorder	Defect	Features
LAD type 1	**β_2 integrin (CD18, ITGB2)**, so no firm adhesion	**Delayed separation of the umbilical cord** (over 30 days), omphalitis, recurrent bacterial infection **without pus**, **marked neutrophilia**, periodontitis
LAD type 2	**Absent sialyl-Lewis X** (selectin ligand) from a defect of fucose metabolism; the exam answer is "fucosyl transferase", the gene is the **GDP-fucose transporter (SLC35C1)**	Milder infections, intellectual disability, short stature, **Bombay (hh) blood group** (no fucose, so no H antigen)
LAD type 3	Kindlin-3 (FERMT3): integrins cannot be activated	Infections plus a Glanzmann-like bleeding tendency
Chronic granulomatous disease	**NADPH oxidase**; X-linked **gp91phox (CYBB)** in about two-thirds, the rest autosomal recessive (p47phox commonest)	Abscesses and granulomas with **catalase-positive** organisms: **Staph. aureus, Burkholderia cepacia, Serratia, Nocardia, Aspergillus** (the commonest cause of death); **NBT test negative** (no blue reduction); **dihydrorhodamine (DHR) flow cytometry** is the test of choice; prophylactic co-trimoxazole, itraconazole and interferon-γ; HSCT cures
Myeloperoxidase deficiency	MPO	Commonest inherited phagocyte defect; usually silent, sometimes disseminated **Candida** (especially with diabetes); NBT normal
Chediak–Higashi	**LYST** (lysosomal trafficking), autosomal recessive	**Giant granules** in neutrophils, **partial oculocutaneous albinism**, peripheral neuropathy, bleeding, neutropenia, infections; fatal "accelerated phase" (haemophagocytic lymphohistiocytosis)
Hyper-IgE (Job) syndrome	**STAT3** (autosomal dominant), so few Th17 cells	Cold staphylococcal abscesses, eczema, very high IgE, eosinophilia, retained primary teeth, coarse face

- Why catalase-positive organisms in CGD, the **exam answer**: catalase-positive bugs **destroy their own H_2O_2**, so the phagocyte, unable to make superoxide, has none to borrow for myeloperoxidase; catalase-negative organisms (streptococci, pneumococci) leave theirs, which the phagocyte uses. **Current understanding**: catalase-deficient mutant staphylococci and Aspergillus remain virulent in CGD models, so susceptibility really reflects these organisms' resistance to non-oxidative killing; the catalase rule still predicts the list well.
- Acquired defects: diabetes, corticosteroids (demargination gives neutrophilia but poor emigration), chemotherapy neutropenia, leukaemias, sepsis.

Mediators

Mediator	Source	Main actions
Histamine	Mast cells, basophils, platelets	**Earliest** vasodilation and venular permeability
Serotonin	Platelets	Vasoconstriction, permeability

Mediator	Source	Main actions
Prostaglandins (COX)	Membrane arachidonic acid	**PGE_2**: fever, pain, vasodilation; **PGI_2 (prostacyclin, endothelium)**: vasodilation, **inhibits** platelet aggregation; **TXA_2 (platelets)**: vasoconstriction, **promotes** aggregation; PGD_2 (mast cells)
Leukotrienes (5-lipoxygenase)	Leucocytes, mast cells	**LTB_4**: neutrophil chemotaxis; **LTC_4, D_4, E_4** (formerly SRS-A): bronchoconstriction, permeability; zileuton blocks 5-LOX, montelukast the receptor
Lipoxins, resolvins	Transcellular	**Stop** inflammation (anti-inflammatory; aspirin-triggered lipoxins)
Platelet-activating factor	Many cells	Aggregation, bronchoconstriction, permeability (very potent)
Bradykinin	Kinin system (factor XIIa, kallikrein)	**Pain**, permeability, vasodilation; broken down by ACE (ACE-inhibitor angio-oedema; C1-inhibitor deficiency)
Complement	Liver-made plasma proteins	**C3a, C5a** anaphylatoxins (histamine release); **C5a** chemotaxis; **C3b** opsonin; **MAC (C5b–C9)** lysis
Cytokines	Macrophages, T cells	**TNF, IL-1**: endothelial activation, fever, acute-phase response, cachexia (TNF); **IL-6**: acute-phase proteins; chemokines
Nitric oxide	Endothelium (eNOS), macrophages (iNOS)	Vasodilation, reduced platelet adhesion, microbial killing

- **By effect**, as examiners ask it: **chemotaxis** C5a, LTB_4, IL-8 and bacterial peptides; **vasoconstriction** TXA_2, $LTC_4/D_4/E_4$ and serotonin; **permeability** histamine, bradykinin, $LTC_4/D_4/E_4$, C3a and C5a, PAF; **platelet aggregation** TXA_2 and PAF; **pain** bradykinin and PGE_2; **fever** IL-1, TNF, IL-6 and PGE_2. LTB_4 is chemotactic, not a vasoconstrictor.
- **Fever**: endogenous pyrogens **IL-1, TNF, IL-6** (exogenous: LPS) induce **COX-2** in the hypothalamus (around the organum vasculosum of the lamina terminalis); **prostaglandin E_2 (PGE_2)** raises the set point through cAMP; aspirin and NSAIDs lower it.
- **Acute-phase reactants**: made by the **liver under the drive of IL-6** (and IL-1, TNF): **CRP**, fibrinogen, **serum amyloid A**, **hepcidin**, ferritin, haptoglobin, complement, procalcitonin (bacterial sepsis). Albumin and transferrin fall (negative reactants). **ESR rises mainly through fibrinogen**, which promotes rouleaux.
- Systemic effects: leucocytosis (left shift; leukaemoid reaction above 40,000–50,000/µL), lymphocytosis in viral infection, eosinophilia in allergy and parasites; leucopenia in typhoid, rickettsia and some viruses; sepsis and septic shock (TNF, IL-1, DIC).

Outcomes and morphological patterns

- Outcomes: complete resolution, healing by fibrosis, **abscess**, progression to chronic inflammation.
- Patterns: **serous** (blister, effusion), **fibrinous** (pericarditis: "bread and butter"; may organise into adhesions), **purulent** (abscess), **ulcer**, pseudomembranous (diphtheria, C. difficile).

Chronic inflammation and granulomas

- Infiltrate of **macrophages, lymphocytes and plasma cells**, tissue destruction and attempts at repair (fibrosis, angiogenesis). Causes: persistent infection (TB, syphilis, fungi), immune disease, prolonged toxic exposure (silica, cholesterol).
- **Macrophages**: **M1 (classical)**, activated by IFN-γ and microbial products, kill microbes (NO, ROS) and inflame; **M2 (alternative)**, activated by IL-4 and IL-13, repair and fibrose (TGF-β, PDGF).
- **Granuloma**: a cluster of **epithelioid macrophages** (pink, slipper-shaped nuclei), often **giant cells** (Langhans: nuclei in a horseshoe at the edge; foreign-body: scattered nuclei), rimmed by lymphocytes. **IFN-γ** from Th1 cells keeps macrophages activated; **TNF** maintains the granuloma (hence **TB reactivation with anti-TNF drugs**: screen with IGRA or Mantoux first).

Granuloma	Examples
Caseating	**Tuberculosis**; histoplasmosis, coccidioidomycosis
Non-caseating (immune)	**Sarcoidosis** (asteroid and Schaumann bodies), Crohn's disease, berylliosis, leprosy (tuberculoid), cat-scratch disease (stellate microabscesses), primary biliary cholangitis, syphilis (gumma), granulomatosis with polyangiitis
Foreign-body	Sutures (**suture granuloma**: a firm, painless, non-septic lump at a healed wound, weeks to months after surgery; giant cells with scattered nuclei round refractile, polarisable fragments, no pus), talc (drug injection), silica, cholesterol, keratin
Other named	**Dürck granuloma** (cerebral malaria: glial cells round a small ring haemorrhage); **fibrin-ring (doughnut) granuloma** (Q fever; also Hodgkin lymphoma, CMV, EBV hepatitis, allopurinol)

Repair and wound healing

- **Regeneration** depends on the cell type: **labile** (continuously dividing: surface epithelia, marrow), **stable** (quiescent, divide on demand: **liver**, kidney tubules, pancreas, fibroblasts, smooth muscle), **permanent** (**neurons, cardiac and skeletal muscle**: heal by scar; skeletal muscle has limited regeneration from satellite cells).
- Liver regeneration after partial hepatectomy: hepatocytes re-enter the cycle (IL-6, HGF); oval cells (progenitors) when hepatocytes cannot divide.
- Phases of healing: **haemostasis** (minutes), **inflammation** (neutrophils days 1–2, macrophages from day 2–3), **proliferation** (granulation tissue from day 3–5: new capillaries by **VEGF**, fibroblasts, **type III collagen**; re-epithelialisation), **remodelling** (weeks to months: collagen cross-linked, **type III replaced by type I**; **the mature scar is mainly type I**; matrix metalloproteinases need zinc).
- **Granulation tissue** (pink, granular, bleeds easily) is fibroblasts plus new capillaries plus loose matrix; it is not granuloma.
- **First intention** (primary union: clean, apposed incision; epithelium bridges within 24–48 hours) versus **second intention** (large gap, more inflammation and granulation tissue, **wound contraction by myofibroblasts**, α-smooth-muscle actin).
- **Wound strength**: about **10% of normal at 1 week** (when sutures come out), rising to **70–80% at about 3 months**, and **never back to 100%**.
- Factors impairing healing: **infection (the commonest and most important local factor)**, diabetes, ischaemia, malnutrition (protein; **vitamin C** for hydroxylation of proline

and lysine; **zinc**), **glucocorticoids** (less inflammation, less collagen), radiation, foreign body, movement, poor apposition.

- Too much repair: **hypertrophic scar** (raised, stays within the wound, regresses), **keloid** (grows beyond the wound, does not regress, excess type I and III collagen, more in dark skin, earlobes and over the sternum, recurs after excision), exuberant granulation (**proud flesh**), desmoid (aggressive fibromatosis).
- **Fibrosis** of chronic disease is driven mainly by **TGF-β** (lung, liver, kidney).
- Growth factors: EGF and TGF-α (epithelium), PDGF (fibroblast and smooth-muscle migration), **VEGF** (angiogenesis, the main factor), FGF-2, HGF (liver), **TGF-β** (fibrosis, inhibits inflammation and epithelial proliferation).

Haemodynamics

Normal haemostasis, the frame for everything below

1. **Vasoconstriction**: reflex plus **endothelin** from the injured endothelium (brief).
2. **Primary haemostasis, the platelet plug**: exposed collagen binds **von Willebrand factor**, which binds platelet **GpIb–IX–V (adhesion)**; platelets change shape and release granules (**dense granules: ADP, calcium, serotonin**; **α-granules: fibrinogen, vWF, factor V, PDGF, P-selectin, PF4**); **ADP (via P2Y12) and thromboxane A_2** recruit more platelets; **GpIIb/IIIa** binds **fibrinogen**, bridging platelets (**aggregation**). Phosphatidylserine on the activated platelet is the surface for clotting factors.
3. **Secondary haemostasis**: **tissue factor** (factor III) with factor VIIa starts coagulation in vivo (the extrinsic pathway is the physiological starter; the intrinsic pathway amplifies through IXa–VIIIa and XIa); **thrombin** turns fibrinogen into fibrin, activates platelets (PAR-1), and factors V, VIII, XI and XIII; **factor XIIIa cross-links fibrin**.
4. **Clot stabilisation and resorption**: platelet contraction; **fibrinolysis** by **plasmin** (from plasminogen by **tPA**), giving fibrin degradation products and **D-dimer** (from cross-linked fibrin only).

Endothelium normally prevents clotting	Injured or activated endothelium promotes it
Prostacyclin (PGI_2) and **NO** inhibit platelets; ADPase (CD39) breaks down ADP	**vWF** exposure and release (Weibel–Palade bodies)
Heparin-like molecules activate **antithrombin** (inactivates thrombin, Xa, IXa)	**Tissue factor** induced by TNF, IL-1, endotoxin
Thrombomodulin turns thrombin into an activator of **protein C**, which with **protein S** inactivates **Va and VIIIa**; endothelial protein C receptor	PAI-1 (plasminogen activator inhibitor) reduces fibrinolysis
Tissue factor pathway inhibitor (TFPI); **tPA**	Loss of thrombomodulin

Thrombosis

- **Virchow's triad**: **endothelial injury** (the dominant factor, and on its own enough in the **heart and arteries**: MI, ulcerated atheroma, vasculitis, hypertension, toxins of smoking), **abnormal flow** (**stasis** in veins, atrial fibrillation, aneurysms; **turbulence** in arteries), **hypercoagulability**.
- Arterial and cardiac thrombi start at injury or turbulence, are **platelet-rich ("white")** and **occlusive** or mural (left ventricle after MI, left atrium in AF and mitral stenosis, aneurysms); venous thrombi (**phlebothrombosis**) start in stasis, are **red** (fibrin and red cells), almost always occlusive, and **commonest in the deep veins of the leg** (90%).
- **Which coronary plaque thromboses**: the **vulnerable plaque**, with a **thin fibrous cap over a large lipid (necrotic) core** and many **macrophages** whose metalloproteinases digest the cap's collagen; it often narrowed the lumen only moderately before it ruptured, and causes most acute coronary syndromes. A **stable plaque** (thick collagen-rich cap, small core, often calcified) narrows slowly and gives stable angina.
- Not every hardened artery thromboses: **Mönckeberg medial calcific sclerosis** is calcification of the **media of medium muscular arteries** (radial, ulnar, femoral; usually over 50, and in diabetes and chronic kidney disease), the intima and **lumen spared**, **pipestem** on X-ray, of little clinical effect (it does make arteries hard to compress, falsely raising the ankle–brachial index).
- **Lines of Zahn**: alternating pale (platelets and fibrin) and dark (red-cell) laminations, laid down in **flowing blood**: they mark an **antemortem thrombus**, formed **during life**. Most obvious in thrombi of the heart and aorta; venous thrombi show them less clearly.
- **Postmortem clot**: gelatinous, rubbery, **not attached** to the wall, with a dark red lower "**currant-jelly**" part and a yellow "**chicken-fat**" supernatant; no lines.
- Valve thrombi: infective endocarditis (bulky, friable, with organisms), **non-bacterial thrombotic (marantic) endocarditis** (small, sterile, in cancer and hypercoagulable states, especially mucinous adenocarcinoma), **Libman–Sacks** endocarditis (SLE, both surfaces of the valve), rheumatic **verrucae** along the lines of closure.
- **Fates**: propagation, **embolisation**, dissolution (fibrinolysis, only when fresh), **organisation and recanalisation** (granulation tissue grows in, new channels form), and infection (septic thrombus; **mycotic aneurysm**).
- **Deep vein thrombosis**: half are silent; risks: immobility and bed rest, surgery (orthopaedic hip and knee the highest), trauma and burns, pregnancy and the puerperium, oral contraceptives and HRT, cancer, heart failure, age, obesity, inherited thrombophilia. **Trousseau sign of malignancy**: migratory thrombophlebitis (pancreatic, lung, gastric adenocarcinoma), because tumour cells release **procoagulants**: **tissue factor**, mucins and **cancer procoagulant** (a factor X activator), helped by inflammatory cytokines. Diagnosis: compression **duplex ultrasound**, with D-dimer to exclude (high negative predictive value) in low pre-test probability (Wells score).

Hypercoagulable states

Inherited	Key point
Factor V Leiden (Arg506Gln)	**Commonest inherited thrombophilia in people of European descent** (2–15% carry it); factor Va **resists inactivation by activated protein C** (**APC resistance**); venous thrombosis; **rare in East Asians and Africans** and less common in South Asians (a few per cent); in East Asia **protein S, protein C and antithrombin deficiencies** are the leading inherited causes
Prothrombin G20210A	Second commonest; mutation in the 3′ untranslated region raises the prothrombin level
Antithrombin deficiency	The most thrombogenic of the common ones; **heparin resistance** (heparin works through antithrombin)

Inherited	Key point
Protein C or S deficiency	**Warfarin-induced skin necrosis** (protein C falls before II, IX, X), neonatal **purpura fulminans** in homozygous protein C deficiency
Hyperhomo-cysteinaemia	MTHFR, cystathionine β-synthase; arterial **and** venous thrombosis (acquired: B_{12}, folate, B_6 deficiency)

- Acquired: **antiphospholipid syndrome** (see bleeding disorders), **heparin-induced thrombocytopenia** type II (IgG against **heparin–PF4 complexes** activates platelets: count falls by over 50% **5–10 days** after starting heparin, with **thrombosis**, not bleeding; stop all heparin, give a non-heparin anticoagulant such as argatroban, fondaparinux or a DOAC; no platelet transfusion), cancer, **nephrotic syndrome** (urinary loss of antithrombin; renal vein thrombosis, especially membranous nephropathy), pregnancy, oestrogens, immobilisation, smoking, obesity, myeloproliferative neoplasms, **PNH**, sickle cell disease, COVID-19 (immunothrombosis), and vaccine-induced immune thrombotic thrombocytopenia (anti-PF4, after adenoviral-vector COVID-19 vaccines, 2021).

Disseminated intravascular coagulation

- Systemic activation of coagulation: widespread **microthrombi** (ischaemic damage to kidney, lung, brain, adrenals) with **consumption** of platelets and factors and secondary fibrinolysis, so **bleeding**.
- Triggers: **sepsis** (endotoxin, the commonest cause), **obstetric** (abruptio placentae, amniotic fluid embolism, retained dead fetus, septic abortion, eclampsia), **acute promyelocytic leukaemia**, mucinous adenocarcinomas, massive trauma, burns, snake bite (Russell's viper in South Asia), heat stroke, haemolytic transfusion reaction.
- Laboratory: **low platelets, prolonged PT and aPTT, low fibrinogen, raised D-dimer** and FDPs, **schistocytes** (microangiopathic haemolysis). ISTH score of 5 or more is overt DIC. Treat the cause; platelets, FFP and cryoprecipitate for bleeding.
- Waterhouse–Friderichsen syndrome: haemorrhagic adrenal necrosis in meningococcal sepsis with DIC.

Embolism

- **Pulmonary thromboembolism**: **over 95% from deep leg veins** (popliteal, femoral, iliac; above-knee thrombi embolise most), so pelvic and arm veins are minor sources.
  - **60–80% are clinically silent**; a large embolus at the bifurcation is a **saddle embolus** (sudden death from acute right heart failure, **acute cor pulmonale**, or obstructive shock).
  - **Only about 10% cause infarction**, because the **bronchial circulation** keeps the lung alive; infarction is likelier with left heart failure.
  - Many small emboli over time: **pulmonary hypertension** (chronic thromboembolic).
  - Imaging of choice: **CT pulmonary angiography**; ECG sinus tachycardia (S1Q3T3 is uncommon).
- **Systemic thromboembolism**: about 80% from intracardiac mural thrombi (two-thirds after left ventricular infarction, a quarter from the left atrium in AF); targets: **lower limbs (75%)**, brain (10%), intestines, kidney, spleen.
- **Paradoxical embolism**: a venous thrombus crosses a **patent foramen ovale** or septal defect to the systemic arteries (stroke in a young adult with DVT).
- **Fat embolism**: fat globules after **long-bone fractures** (in about 90% of severe skeletal injuries), soft-tissue trauma, burns, liposuction; **fat embolism syndrome** in under 10%, **1–3 days** after injury: **respiratory distress (hypoxaemia), neurological changes, petechial rash** (axilla, chest, conjunctiva) and thrombocytopenia, anaemia; fat stains (Oil red O) on frozen lung sections. Mechanism: mechanical blockage plus fatty acids injuring endothelium.
- **Amniotic fluid embolism**: about 1 in 40,000 deliveries, at labour or just after; sudden **dyspnoea, cyanosis, shock, seizures, then DIC**; squames, lanugo hair, fat (vernix) and mucin in pulmonary vessels; mortality was classically about 80%, and is lower (about 20–60%) with modern intensive care; survivors often have neurological deficit.
- **Air (gas) embolism**: over **100 mL** usually needed for clinical effect (iatrogenic: central lines, neck and chest surgery, laparoscopy; obstetric). **Decompression sickness (caisson disease)**: nitrogen dissolved at high pressure bubbles out on rapid ascent: "the bends" (joints, muscles), "the chokes" (lungs), and in the chronic form **avascular necrosis** of femoral and humeral heads and tibia. Treatment: **hyperbaric oxygen** recompression.
- Others: tumour, septic, atheromatous (cholesterol clefts in kidney, after catheterisation), foreign body (talc in drug users), bone marrow (after CPR).

Infarction

- Area of ischaemic necrosis, almost always from **arterial occlusion** (99%, mostly thrombosis or embolism); venous occlusion infarcts organs with a single outflow (testis, ovary in torsion; bowel in mesenteric venous thrombosis).
- **Red (haemorrhagic)**: **venous occlusion** (testicular torsion), **loose, spongy tissue** (lung), **dual blood supply** (lung, small intestine, liver), previously congested tissue, and **reperfusion** of a dead area. **White (anaemic)**: **arterial occlusion of solid organs with end-arteries** (**heart, spleen, kidney**).
- Most infarcts are **wedge-shaped** with the apex at the occluded vessel and the base at the organ surface (often with fibrinous exudate on it). Septic infarcts become abscesses.
- Factors deciding the outcome: the anatomy of the blood supply (dual or end-artery), **rate of occlusion** (slow lets collaterals open), **vulnerability to hypoxia** (**neurons die in 3–4 minutes**, myocardium in 20–30 minutes, fibroblasts survive hours), oxygen content of blood (anaemia, heart failure).
- **Myocardial infarction, what is seen when**:
  - **Electron microscope first**: relaxed myofibrils, glycogen loss and swollen mitochondria within minutes (reversible); injury becomes **irreversible at about 20–40 minutes** of severe ischaemia.
  - **Gross change lags**: nothing is visible for hours, but **triphenyltetrazolium chloride (TTC)** leaves dead muscle unstained (pale against brick-red living muscle, which keeps its dehydrogenases) from about **2–3 hours**; dark mottling follows by 12–24 hours.
  - **Light microscope**: **wavy fibres** at the border within the **first 4 hours**; **early coagulative necrosis** with oedema and haemorrhage at **4–12 hours**; **contraction bands** (reperfusion) and the first neutrophils by **12–24 hours**.
  - **Neutrophils dominate at 1–3 days** (and fibrinous pericarditis may appear); **macrophages clear the dead muscle at 3–7 days**, the softest, yellow stage and the **peak time for free-wall, septal and papillary-muscle rupture** (risk continues to about 2 weeks).

- **Granulation tissue** starts at the margins at **7–10 days** and is well formed by 10–14 days; **collagen** is laid down over **2–8 weeks**; a **dense, grey-white scar** is complete **after about 2 months** (later: ventricular aneurysm; Dressler syndrome, an autoimmune pericarditis, weeks later).

- Brain infarcts are **liquefactive**; all other solid-organ infarcts **coagulative**.

Oedema

- Starling forces: **raised hydrostatic pressure** (heart failure, venous obstruction, DVT, cirrhosis with portal hypertension), **reduced plasma oncotic pressure** (**nephrotic syndrome**, cirrhosis, protein malnutrition: kwashiorkor), **lymphatic obstruction** (filariasis: elephantiasis; post-mastectomy, radiation; peau d'orange in breast cancer), **sodium and water retention** (renal failure, renin–angiotensin–aldosterone activation in heart failure), **inflammation** (permeability).
- **Transudate**: protein under 2.5–3 g/dL, **specific gravity under 1.012**, few cells (heart failure, cirrhosis, nephrotic syndrome). **Exudate**: protein over 3 g/dL, **specific gravity over 1.020**, cells (inflammation, tumour). For pleural fluid, **Light's criteria** (exudate if fluid/serum protein over 0.5, fluid/serum LDH over 0.6, or fluid LDH over two-thirds of the upper normal serum level).
- Clinical forms: pitting oedema (dependent, cardiac; periorbital first in renal), anasarca (generalised), pulmonary oedema (heart failure, ARDS), cerebral oedema (vasogenic or cytotoxic; herniation).

Hyperaemia, congestion and haemorrhage

- **Hyperaemia** is **active** arteriolar dilation (exercise, inflammation: red); **congestion** is **passive** reduced outflow (heart failure, venous obstruction: blue, cyanotic).
- **Chronic passive congestion**:
  - Lung (left heart failure, mitral stenosis): thickened, fibrotic septa (**brown induration**) and **heart-failure cells** (haemosiderin-laden alveolar macrophages).
  - Liver (right heart failure, Budd–Chiari): **nutmeg liver**, dark congested **centrilobular** (zone 3) areas against pale periportal liver, with centrilobular necrosis; long-standing: cardiac sclerosis ("cardiac cirrhosis").
  - Spleen (portal hypertension): congestive splenomegaly with **Gamna–Gandy bodies** (siderotic nodules).
- Haemorrhage terms: **petechiae** 1–2 mm (platelet disorders, raised capillary pressure), **purpura** 3 mm–1 cm (also vasculitis), **ecchymoses** over 1–2 cm (bruises; colour change red-blue to green (biliverdin) to golden-brown (haemosiderin) as haemoglobin breaks down), haematoma, haemothorax, haemopericardium, haemarthrosis (haemophilia).

Shock

- Systemic hypoperfusion from low cardiac output or low effective circulating volume, leading to cellular hypoxia.

Type	Mechanism	Examples	Cardiac output	SVR	Wedge pressure
Hypovolaemic	Loss of blood or plasma	Haemorrhage, burns, diarrhoea and vomiting	Low	High	Low
Cardiogenic	Pump failure	MI, arrhythmia, myocarditis	Low	High	**High**
Obstructive	Outflow blocked	Massive PE, tamponade, tension pneumothorax	Low	High	Variable
Septic (distributive)	Vasodilation, leaky vessels, DIC	Gram-negative and Gram-positive sepsis, fungi	**High early** ("warm"), low late	**Low**	Low
Neurogenic, anaphylactic (distributive)	Loss of vascular tone; IgE-mediated vasodilation	Spinal cord injury (with **bradycardia**); anaphylaxis	Variable	Low	Low

- **Septic shock mechanisms**: microbial products (LPS, peptidoglycan) on **Toll-like receptors** release **TNF, IL-1, IL-6**, plus complement, **NO** vasodilation, endothelial leak, tissue factor (DIC), immune suppression later, metabolic changes (hyperglycaemia, then insulin resistance), organ failure (**ARDS**, acute kidney injury, adrenal insufficiency).
- **Stages**: **non-progressive** (compensated: tachycardia, vasoconstriction, renal retention of fluid), **progressive** (tissue hypoperfusion, **lactic acidosis**, confusion, oliguria), **irreversible** (lysosomal enzymes, myocardial depression, acute tubular necrosis; recovery impossible even if perfusion is restored).
- Morphology of shock: **acute tubular necrosis** (kidney), diffuse alveolar damage (**shock lung**), **adrenal lipid depletion**, centrilobular hepatic necrosis, haemorrhagic enteropathy, brain watershed infarcts, heart subendocardial necrosis and **contraction bands**.
- **Current definitions (Sepsis-3, JAMA 2016)**: **sepsis** is life-threatening organ dysfunction (a rise in **SOFA score of 2 or more**) from a dysregulated response to infection; **septic shock** needs **vasopressors to keep mean arterial pressure at 65 mmHg or more and lactate over 2 mmol/L despite adequate fluids**. The old SIRS criteria are no longer used to define sepsis. Management (Surviving Sepsis Campaign 2021): cultures, antibiotics within 1 hour, 30 mL/kg crystalloid in hypotension, **noradrenaline** first-line vasopressor.

Immunopathology and amyloid

Cells and cytokines worth knowing

T-helper subset	Driving cytokine	Products	Role, and the disease it drives
Th1	IL-12, IFN-γ	**IFN-γ**, IL-2	Activates macrophages (M1), intracellular microbes; **granulomas, type IV hypersensitivity**, many organ-specific autoimmune diseases
Th2	**IL-4**	**IL-4** (IgE switch), **IL-5** (eosinophils), **IL-13**	Helminths; **allergy, asthma (type I)**
Th17	IL-6, TGF-β, IL-23	**IL-17**, IL-22	Neutrophils, fungi, extracellular bacteria; **psoriasis**, IBD, ankylosing spondylitis (anti-IL-17 and anti-IL-23 drugs)

T-helper subset	Driving cytokine	Products	Role, and the disease it drives
Treg	TGF-β, IL-2	IL-10, TGF-β	**Tolerance**; marker **FOXP3** (mutated in IPEX), CD25

- MHC class I (HLA-A, B, C): **all nucleated cells**, presents cytosolic peptides to **CD8**. Class II (HLA-DP, DQ, DR): antigen-presenting cells, presents endocytosed peptides to **CD4**. HLA genes on **6p21**; **mature red cells have no HLA**. NK cells kill cells that have **lost class I** (virus-infected, tumour), and mediate ADCC (CD16).
- **Immunoglobulins**: **IgG** (four subclasses): the most abundant in serum, the longest half-life (about 21 days), the **only one to cross the placenta**, the main antibody of the **secondary response**, opsonises, warm autoantibodies; **IgM**: a **pentamer**, the first made (**primary response**, and by the fetus: IgM in cord blood means congenital infection), **fixes complement best**, natural ABO antibodies and cold agglutinins; **IgA**: a **dimer** (with J chain and secretory component) in **secretions, colostrum and breast milk**; **IgE**: the least in serum, the shortest half-life, binds mast cells (**type I**, worm immunity); IgD: on naive B cells with IgM. **Papain** cuts above the hinge (two Fab and one Fc), **pepsin** below it ($F(ab')_2$). Class switching needs CD40–CD40L and cytokines (**IL-4 for IgE**).
- **Complement pathways**: **classical** (antigen–antibody, IgM or IgG, through C1q; CH50 tests it), **lectin** (mannose-binding lectin on microbes), **alternative** (spontaneous C3 activation on microbial surfaces; factors B, D, properdin); all meet at **C3**; **C3b** opsonises, **C3a and C5a** are anaphylatoxins, **C5a** is chemotactic, **C5b–C9** forms the membrane attack complex; regulators: C1 inhibitor, **DAF (CD55)**, **CD59**, factor H and I.
- **HLA associations**: **B27** ankylosing spondylitis (over 90%), reactive arthritis, psoriatic and IBD arthritis, anterior uveitis; **DR4** rheumatoid arthritis (shared epitope), with DR3 **type 1 diabetes**; **DQ2/DQ8** coeliac disease (DQ8 also type 1 diabetes); **DR2 (DR15)** multiple sclerosis, Goodpasture; **DR3** SLE, Graves', Sjögren, Addison; **B51 (a split of B5)** Behçet; **HFE (near HLA-A3)** haemochromatosis; DR5 Hashimoto and pernicious anaemia (classical list).
- Pharmacogenetic HLA alleles (modern, examined): **HLA-B*15:02** and **carbamazepine** Stevens–Johnson syndrome (**common in South and Southeast Asians**; test before starting), **HLA-B*57:01 abacavir** hypersensitivity, **HLA-B*58:01 allopurinol** severe skin reactions.

Hypersensitivity (Gell and Coombs)

Type	Mechanism	Timing	Examples
I immediate	Th2 and **IgE** bound to mast cells (FcεRI); cross-linking by antigen releases **histamine** (immediate phase, minutes) then leukotrienes, PAF and cytokines (**late phase**, 2–24 hours, eosinophils)	Minutes	**Anaphylaxis**, allergic asthma, hay fever, urticaria, food allergy, Casoni test (hydatid), **atopy**
II antibody to cell or matrix	IgG or IgM against fixed antigen: **opsonisation and phagocytosis**, **complement and Fc-mediated inflammation**, or **receptor dysfunction**	Hours	**Haemolytic transfusion reaction**, **haemolytic disease of the newborn**, autoimmune haemolytic anaemia, **ITP**, **Goodpasture** (anti-type IV collagen α3), **pemphigus vulgaris** (desmoglein 3), bullous pemphigoid, acute rheumatic fever, ANCA vasculitis; receptor-mediated: **Graves'** (stimulating anti-TSH receptor), **myasthenia gravis** (blocking anti-AChR), pernicious anaemia (anti-intrinsic factor), insulin-resistant diabetes
III immune complex	Antigen–antibody complexes deposit in vessels, joints, glomeruli; **complement activation** recruits neutrophils; **fibrinoid necrosis**, low complement	4–10 days after exposure (serum sickness)	**SLE**, **serum sickness**, **post-streptococcal glomerulonephritis**, **polyarteritis nodosa** (HBV), **Arthus reaction** (local), reactive arthritis, cryoglobulinaemia (HCV), hypersensitivity pneumonitis (partly)
IV T-cell mediated (delayed)	CD4 Th1 and Th17 (cytokine-mediated inflammation, macrophage activation) or **CD8 cytotoxic** killing	**48–72 hours**	**Tuberculin (Mantoux) reaction**, **allergic contact dermatitis** (nickel, poison ivy), **granulomas** (TB, sarcoidosis, leprosy), **type 1 diabetes**, **multiple sclerosis**, Hashimoto's, Crohn's, psoriasis, **acute cellular graft rejection**, SJS/TEN

- **Type V** ("stimulatory", Graves') is a subtype of type II in most current texts.
- **Rheumatoid arthritis**: many review books and past papers class it as **type III** (immune complexes of rheumatoid factor and anti-CCP); **Robbins classes it as T-cell mediated (type IV) with a contribution from antibodies and immune complexes**. Answer type III when only types I–IV appear with a book-style stem; know that both mechanisms act.
- **Irritant** contact dermatitis is **not** immune; allergic contact dermatitis is type IV (patch test).
- Diagnostic tests: type I, skin-prick test and specific IgE; anaphylaxis confirmed by **serum tryptase** (peaks 1–2 hours). Treatment of anaphylaxis: **intramuscular adrenaline 0.5 mg (0.01 mg/kg) of 1 mg/mL into the anterolateral thigh** (WAO and Resuscitation Council UK).

Transplant rejection and graft-versus-host disease

Rejection	Timing	Mechanism	Morphology
Hyperacute	**Minutes to hours**	**Preformed antibodies** (ABO, anti-HLA from transfusion, pregnancy, earlier graft); type II	Thrombosis, fibrinoid necrosis of vessels, cyanotic mottled kidney; prevented by **crossmatch**

Rejection	Timing	Mechanism	Morphology
Acute cellular	Days to weeks (commonest in the first months), or after stopping immunosuppression	**T cells** (CD8 killing, CD4 cytokines); type IV	Interstitial lymphocytes, **tubulitis**, endotheliitis (endarteritis); responds to steroids and calcineurin inhibitors
Acute antibody-mediated	Days to weeks	Donor-specific anti-HLA antibody	Peritubular capillaritis, **C4d deposition** in peritubular capillaries; plasma exchange, IVIG
Chronic	Months to years	T cells and antibodies; the main cause of late graft loss	Kidney: **intimal thickening (transplant arteriopathy)**, interstitial fibrosis, tubular atrophy; heart: **allograft vasculopathy**; lung: **bronchiolitis obliterans**; liver: vanishing bile ducts

- **Graft-versus-host disease**: **immunocompetent donor T cells** attack an immunodeficient host (HSCT, transfusion of non-irradiated blood to an immunocompromised or HLA-similar relative, liver and small-bowel transplants). Acute: **skin rash (palms, soles), liver (cholestatic jaundice), gut (diarrhoea)**; chronic: scleroderma-like skin, sicca, cholestasis. Prevented by **irradiating** cellular blood components (25 Gy).
- Graft best matched by **HLA-DR**, then B, then A; the kidney survives best from an identical twin. Corneal grafts need no matching (avascular).

Autoimmunity

- Tolerance: **central** (negative selection of T cells in the thymus, through **AIRE**, and B cells in the marrow), **peripheral** (**anergy** without co-stimulation through CD28, **Tregs**, deletion by Fas-mediated apoptosis, sequestered antigens).
- Breakdown: susceptibility genes (HLA; **AIRE** in autoimmune polyendocrine syndrome type 1; **FOXP3** in IPEX; **CTLA4**, **PTPN22**, **NOD2** in Crohn's; **FAS** in autoimmune lymphoproliferative syndrome) plus triggers: **molecular mimicry** (rheumatic fever and streptococcal M protein, **Guillain–Barré after Campylobacter**, post-rabies-vaccine encephalitis), **release of sequestered antigen** (**sympathetic ophthalmia**, **mumps orchitis**), polyclonal B-cell activation (EBV) or T-cell activation (superantigens, Kawasaki), epitope spreading. Commoner in women (except ankylosing spondylitis).

Autoantibody	Disease
ANA (immunofluorescence, the screen)	**SLE (over 95%, the most sensitive)**, also other connective tissue diseases, old age
Anti-dsDNA, **anti-Smith**	**SLE, the most specific** (anti-dsDNA follows activity and nephritis)
Anti-histone	**Drug-induced lupus** (procainamide, hydralazine, isoniazid; kidney and CNS spared)
Anti-Ro (SS-A), anti-La (SS-B)	Sjögren's; **neonatal lupus with congenital heart block**
Anti-U1 RNP	Mixed connective tissue disease
Anti-Scl-70 (topoisomerase I)	**Diffuse systemic sclerosis** (lung fibrosis); anti-RNA polymerase III: renal crisis
Anti-centromere	**Limited systemic sclerosis (CREST)**
Anti-Jo-1 (anti-synthetase)	Polymyositis and dermatomyositis with interstitial lung disease; anti-Mi-2 dermatomyositis; anti-TIF1γ cancer-associated dermatomyositis; anti-MDA5 rapid lung disease
Anti-CCP	**Rheumatoid arthritis**, the most specific (about 95%); rheumatoid factor (IgM against IgG Fc) is less specific
c-ANCA (anti-PR3)	**Granulomatosis with polyangiitis**
p-ANCA (anti-MPO)	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, ulcerative colitis, primary sclerosing cholangitis
Anti-mitochondrial	**Primary biliary cholangitis**
Anti-smooth muscle, anti-LKM1	Autoimmune hepatitis types 1 and 2
Anti-tissue transglutaminase IgA, anti-endomysial	**Coeliac disease**
Anti-TPO, anti-thyroglobulin	Hashimoto's thyroiditis
Anti-GAD65, anti-IA-2, anti-ZnT8	Type 1 diabetes
Anti-phospholipase A2 receptor	Primary membranous nephropathy
Anti-AChR, anti-MuSK	Myasthenia gravis; anti-voltage-gated calcium channel: Lambert–Eaton

- **SLE** pathology: type III mostly (with type II cytopenias). **LE cell** (a neutrophil that has eaten a denatured nucleus; obsolete test), **haematoxylin bodies**. Kidney (ISN/RPS classes I–VI): **class IV diffuse proliferative** is the commonest and most severe (**wire-loop** subendothelial deposits). **Libman–Sacks** endocarditis, onion-skin splenic arterioles, low C3 and C4. **2019 EULAR/ACR criteria**: a positive ANA of 1:80 or more is the entry criterion, then weighted clinical and immunological items (10 points).
- **Sjögren's**: lymphocytic sialadenitis (lip biopsy), anti-Ro/La, **about 40-fold risk of B-cell (MALT) lymphoma**.
- **Systemic sclerosis**: fibrosis from TGF-β, small-vessel damage, Raynaud's, oesophageal dysmotility (the commonest gut site), lung fibrosis and pulmonary hypertension (the main causes of death).

Immunodeficiencies

Disorder	Defect	Pointers
X-linked agammaglobulinaemia (Bruton)	**BTK**: no B-cell maturation	Boys after 6 months (maternal IgG gone); **absent B cells**, all immunoglobulins low; no tonsils; pyogenic bacteria, enteroviruses and giardia; **live polio vaccine dangerous**
Selective IgA deficiency	B-cell IgA switch	**Commonest primary immunodeficiency** (about 1 in 600 in Europe); mostly silent; sinopulmonary and giardia infection, coeliac and autoimmunity; **anaphylaxis to blood products** containing IgA (anti-IgA); false-negative IgA tTG test
Common variable immunodeficiency	Mixed, B-cell differentiation	Adults; low IgG, IgA (IgM); B cells present; granulomas, lymphoma, autoimmunity
Hyper-IgM syndrome	**CD40 ligand** (X-linked, commonest) or CD40, AID	No class switching: high IgM, low IgG, IgA, IgE; Pneumocystis, Cryptosporidium

Disorder	Defect	Pointers
DiGeorge syndrome	**22q11.2 deletion**, 3rd and 4th pharyngeal pouches	T-cell deficiency, **hypocalcaemic tetany**, conotruncal heart defects, absent thymic shadow
SCID	**IL2RG (common γ chain; X-linked, commonest)**; **ADA deficiency** (commonest autosomal recessive); RAG1/2	T and B (and in γc, NK) failure; thrush, diarrhoea, failure to thrive, Pneumocystis; **absent thymus**; HSCT; **newborn screening by TREC**
Wiskott–Aldrich	**WAS** (X-linked)	**Eczema, thrombocytopenia with small platelets, recurrent infection** (encapsulated bacteria); low IgM, high IgA and IgE; lymphoma
Ataxia telangiectasia	**ATM** (11q22–23), autosomal recessive, double-strand break repair	Cerebellar ataxia, oculocutaneous telangiectasia, **IgA (and IgG2, IgE) deficiency**, thymic hypoplasia, **raised AFP**, radiosensitivity, **lymphoma and leukaemia** the commonest cancers
C1-inhibitor deficiency	Complement regulator (autosomal dominant)	**Hereditary angio-oedema**: bradykinin-mediated swelling, abdominal pain, laryngeal oedema; **low C4**; no urticaria, **no response to antihistamines or steroids**; C1-INH concentrate, icatibant, lanadelumab
Late complement **C5–C9**	Membrane attack complex	Recurrent **Neisseria** (meningococcal) infection
C3	Central opsonin	Severe recurrent pyogenic infection
C2 (the commonest) and other early components	Classical pathway	**SLE-like disease**, infections
IL-12/IFN-γ axis	IL-12 receptor, IFN-γ receptor	Disseminated **mycobacterial** (BCG) and Salmonella infection
Chronic mucocutaneous candidiasis	Th17 defects (STAT1 gain of function, AIRE)	Candida of skin, nails, mucosa

- **HIV**: **gp120 binds CD4** and a co-receptor, **CCR5** (macrophage-tropic R5 strains, transmission and early disease) or **CXCR4** (T-tropic X4, late); **gp41** mediates fusion. **CCR5-Δ32 homozygotes resist infection**. Reservoirs: macrophages, microglia, **follicular dendritic cells**, latent memory T cells. Lymph nodes: early **follicular hyperplasia**, late involution. **AIDS**: **CD4 under 200/μL** or an AIDS-defining illness (Pneumocystis pneumonia, Kaposi sarcoma, CNS lymphoma, CMV retinitis, cryptococcal meningitis, extrapulmonary TB). Current first-line treatment: **dolutegravir-based** regimens (WHO 2019), treat everyone at diagnosis.

Amyloidosis

- Extracellular deposits of **misfolded protein in cross-β-pleated sheets**, about 90% fibril and 10% non-fibrillar glycoproteins, including **serum amyloid P (SAP) component** in every type (used in SAP scintigraphy) and glycosaminoglycans.
- Appearance: **H&E: amorphous, eosinophilic, hyaline**, causing pressure atrophy of neighbouring cells. **EM: non-branching fibrils 7.5–10 nm wide** (the definitive structure). X-ray crystallography: cross-β pattern.
- Stains:
  - **Congo red**: salmon-pink on light microscopy and **apple-green birefringence under polarised light** (the most specific stain test; current texts call it "anomalous colours").
  - **Thioflavin T or S**: fluorescence. Crystal violet or methyl violet: **metachromasia** (rose-pink). Lugol's iodine on gross tissue turns mahogany brown, then blue with sulphuric acid (the origin of the name "starch-like").
  - **Potassium permanganate** pretreatment abolishes Congo-red staining of **AA** but **not AL**.
  - **Typing**: immunohistochemistry, and now **laser microdissection with mass spectrometry, the gold standard** for the protein.
- **Biopsy**: **abdominal fat-pad aspirate** (the first, least invasive; sensitivity about 70–80% in AL, lower in ATTR), rectal, gingival, salivary gland; biopsy of the affected organ (kidney, heart) is the most sensitive.

Type	Fibril protein	Setting and organs
AL (primary, the commonest systemic type)	**Immunoglobulin light chains (λ more often than κ**, about 3:1)	Plasma cell dyscrasia, **myeloma** (in about 5–15% of patients); heart (**death from cardiac failure and arrhythmia**), kidney, **macroglossia**, **periorbital "pinch" purpura** ("raccoon eyes"), carpal tunnel, neuropathy
AA (secondary, reactive)	**Serum amyloid A** (acute-phase protein from the liver, IL-6 and IL-1 driven)	**Rheumatoid arthritis** (the commonest cause in the West), **tuberculosis**, leprosy, bronchiectasis, chronic osteomyelitis, IBD, **familial Mediterranean fever** (MEFV, pyrin), renal cell carcinoma, Hodgkin lymphoma; **kidney the commonest and most serious organ, renal failure the usual cause of death**; spleen, liver, adrenals
Aβ$_2$m	**β$_2$-microglobulin** (MHC class I light chain, not cleared by dialysis membranes)	**Long-term haemodialysis**: **carpal tunnel syndrome**, joint and tendon deposits, bone cysts
ATTR, wild type (senile systemic)	Normal **transthyretin**	Elderly men: **heart** (heart failure with preserved ejection fraction), carpal tunnel; under-recognised
ATTR, hereditary	Mutant transthyretin (V30M in familial amyloid polyneuropathy; **V122I in about 3–4% of African Americans**)	Autosomal dominant; peripheral and autonomic neuropathy, heart
Aβ	Amyloid β from **amyloid precursor protein (APP, chromosome 21)**	**Alzheimer's disease** plaques and cerebral amyloid angiopathy (lobar haemorrhage); early in **Down syndrome**
AIAPP	Islet amyloid polypeptide (amylin)	Islets in **type 2 diabetes**
ACal	(Pro)calcitonin	**Medullary carcinoma of the thyroid** (amyloid stroma)
AANF	Atrial natriuretic factor	**Isolated atrial amyloid** of old age

Type	Fibril protein	Setting and organs
APrP	Prion protein	Creutzfeldt–Jakob disease, kuru

- Organs: **kidney** (the commonest, glomerular deposits first, **nephrotic syndrome**; kidneys normal-sized or large), **spleen** (**sago spleen**: deposits in the **follicles**, nodular tapioca-like grains; **lardaceous spleen**: diffuse in the **red-pulp sinuses** and walls), **liver** (space of Disse, hepatomegaly with surprisingly normal function), **heart** (subendocardial and interstitial: **restrictive cardiomyopathy**, **low-voltage ECG despite thick walls**, "sparkling" myocardium on echo, late gadolinium enhancement on MRI), tongue (**macroglossia**, AL), adrenals, gut (malabsorption), nerves.
- Modern practice: **technetium-99m pyrophosphate (or DPD) bone scintigraphy** diagnoses cardiac ATTR without biopsy once AL is excluded by serum free light chains and immunofixation; **tafamidis** (transthyretin stabiliser; ATTR-ACT trial 2018) and **RNA-silencing drugs (patisiran, vutrisiran)** or acoramidis treat ATTR; AL is treated as a plasma-cell neoplasm, **daratumumab with bortezomib, cyclophosphamide and dexamethasone** (ANDROMEDA trial 2021), with stem-cell transplant in fit patients.

Neoplasia

Basic terms

Feature	Benign	Malignant
Differentiation	Well differentiated	Ranges to **anaplasia** (pleomorphism, high N:C ratio, hyperchromasia, large nucleoli, atypical mitoses, tumour giant cells, loss of polarity)
Growth	Slow, expansile, often capsulated	Faster, infiltrative
Invasion	None	Present: the next most reliable sign
Metastasis	Never	**The most reliable (unequivocal) sign of malignancy**

- Anaplasia is a hallmark of malignant cells, but only invasion and metastasis prove malignancy. Malignant tumours that **rarely metastasise**: **basal cell carcinoma**, most primary brain tumours (gliomas).
- Naming traps: **lymphoma, melanoma, mesothelioma, seminoma, hepatoma** and **chordoma** (from notochord remnants, at the sacrum and skull base) are malignant despite "-oma". **Hamartoma**: disorganised mass of tissue native to the site (lung hamartoma, now known to be a clonal neoplasm). **Choristoma (heterotopia)**: normal tissue in the wrong place (pancreatic rest in the stomach wall). **Teratoma**: tissues from more than one germ layer, from totipotent cells (mature ovarian cyst benign; testicular teratoma in adults malignant).
- **Spontaneous regression** of a malignant tumour is rare but best known in **neuroblastoma** (stage MS of infancy), **renal cell carcinoma** (metastases), **melanoma** and **choriocarcinoma** (gestational).
- **Carcinoma in situ**: full-thickness dysplasia with the **basement membrane intact**, so it **cannot metastasise**. Invasion through it (even micro-invasion) makes it an invasive carcinoma.
- **Grade** is the degree of differentiation; **stage** (TNM: tumour size or extent, nodes, metastasis; AJCC 8th edition, 2017) is the extent of spread. **Stage predicts outcome better than grade.**

Spread

- **Lymphatic**: carcinomas typically (sentinel node biopsy in breast and melanoma). **Haematogenous**: **sarcomas**, and the carcinomas that invade veins: **renal cell carcinoma (renal vein, IVC)**, **hepatocellular (hepatic and portal veins)**, **follicular thyroid**, **choriocarcinoma**. Liver and lungs are the commonest sites of blood-borne metastases.
- **Sarcomas that spread by lymphatics**: **synovial sarcoma, rhabdomyosarcoma, epithelioid sarcoma, clear-cell sarcoma, angiosarcoma**.
- **Transcoelomic (seeding of body cavities)**: **ovarian** carcinoma (peritoneum), **Krukenberg tumour** (signet-ring carcinoma of stomach to both ovaries), **pseudomyxoma peritonei** (appendiceal mucinous neoplasm). **Perineural**: adenoid cystic carcinoma, pancreatic and prostate cancer.
- Metastasis-free organs: spleen and skeletal muscle are rarely involved. **Bone metastases**: **osteolytic** (most: lung, kidney, thyroid, breast; myeloma), **osteoblastic** (**prostate**; also breast sometimes, carcinoid). Commonest primary of brain metastases: lung; of liver metastases: colon (portal drainage).
- Metastasis steps: loss of **E-cadherin** (epithelial–mesenchymal transition), degradation of matrix (**matrix metalloproteinases**, type IV collagenase), attachment to laminin, migration, intravasation, survival in blood (platelets), extravasation, colonisation; organ tropism by chemokine receptors (CXCR4) and the "seed and soil".

Hallmarks of cancer (Hanahan and Weinberg 2000, 2011, 2022)

- Self-sufficiency in growth signals, insensitivity to growth inhibition, **evasion of apoptosis**, **limitless replication (telomerase)**, sustained **angiogenesis** (VEGF; bevacizumab), **invasion and metastasis**, **reprogrammed metabolism (Warburg effect**: aerobic glycolysis, the basis of FDG-PET), **evasion of immune destruction** (PD-L1, CTLA-4), with enabling **genomic instability** and **tumour-promoting inflammation**. The 2022 update adds phenotypic plasticity, non-mutational epigenetic reprogramming, polymorphic microbiomes and senescent cells.
- Tumours are **clonal**; carcinogenesis is **multistep** (the adenoma–carcinoma sequence: APC, then KRAS, then TP53).

Oncogenes and tumour suppressors

Gene (locus)	Class and mechanism	Tumours
RB1 (13q14)	Suppressor, the **first identified**; hypophosphorylated RB holds **E2F**, blocking the **G1 to S** transition; HPV E7 binds it	**Retinoblastoma** (familial: bilateral, younger), **osteosarcoma**
TP53 (17p13)	Suppressor, "**guardian of the genome**": senses DNA damage (via ATM), arrests cells in **G1 through p21** (CDK inhibitor), drives repair (GADD45), triggers **apoptosis (BAX, PUMA)** or senescence if repair fails; **MDM2** degrades it; HPV E6 targets it	**The commonest mutated gene in human cancer** (over 50%); **Li–Fraumeni syndrome** (germline: sarcomas, breast, brain, adrenocortical, leukaemia)

Gene (locus)	Class and mechanism	Tumours
WT1 (11p13)	Suppressor, transcription factor	**Wilms tumour** (WAGR syndrome, Denys–Drash); WT2 at 11p15 (Beckwith–Wiedemann)
APC (5q21)	Suppressor, degrades **β-catenin** (Wnt pathway)	**Familial adenomatous polyposis** (hundreds of polyps, near-certain colon cancer by 40; Gardner, Turcot); most sporadic colorectal cancers
NF1 (17q11)	Suppressor, **neurofibromin**, a GTPase-activating protein for RAS	Neurofibromatosis type 1: neurofibromas, café-au-lait spots, Lisch nodules, optic glioma
NF2 (22q12)	Suppressor, merlin	**Bilateral vestibular schwannomas**, meningiomas
VHL (3p25)	Suppressor; degrades **HIF-1α**	Von Hippel–Lindau: clear-cell **renal cell carcinoma**, cerebellar haemangioblastoma, phaeochromocytoma; sporadic clear-cell RCC (with 3p loss)
CDKN2A (9p21)	Suppressor, **p16 (INK4a)**, a CDK4 inhibitor	Familial melanoma, pancreas, gliomas, mesothelioma
PTEN (10q23)	Suppressor, opposes PI3K–AKT	Cowden syndrome, endometrial cancer, glioblastoma, prostate
SMAD4 (DPC4, 18q21)	Suppressor, TGF-β signalling	**Pancreatic** and colon cancer, juvenile polyposis
E-cadherin (CDH1)	Cell adhesion	**Hereditary diffuse gastric cancer**, lobular breast cancer
BRCA1 (17q21), **BRCA2 (13q12–13)**	DNA repair (**homologous recombination**)	Breast and ovarian cancer (BRCA1: triple-negative, medullary type; BRCA2: male breast, prostate, pancreas); **PARP inhibitors** (olaparib) exploit the defect (synthetic lethality)
MEN1 (11q13)	Suppressor, menin	MEN 1: parathyroid, pituitary, pancreatic islet tumours
RAS (KRAS, HRAS, NRAS)	GTP-binding signal transducer stuck "on": **the commonest mutated oncogene** (about 30% of cancers)	**Pancreas (over 90%)**, colon, lung adenocarcinoma, follicular thyroid; **KRAS G12C** inhibitors (sotorasib, 2021)
BRAF V600E	Serine-threonine kinase	**Melanoma** (about half), **papillary thyroid**, **hairy cell leukaemia**, Langerhans cell histiocytosis, serrated colon cancers; vemurafenib, dabrafenib
BCR–ABL1, t(9;22)	Fusion **tyrosine kinase**, constitutively active	**CML** (and Ph-positive ALL); **imatinib** blocks its ATP-binding site
MYC (8q24)	Transcription factor	**Burkitt lymphoma, t(8;14)**
MYCN (N-MYC, 2p) amplification	Transcription factor	**Neuroblastoma** (poor prognosis)
BCL2 (18q21)	**Anti-apoptotic**	**Follicular lymphoma, t(14;18)**; venetoclax inhibits it (CLL, AML)
Cyclin D1 (11q13)	Cell-cycle driver	**Mantle cell lymphoma, t(11;14)**; myeloma; breast (amplified)
KIT, PDGFRA	Receptor tyrosine kinases	**GIST**, mastocytosis (KIT D816V), seminoma
HER2 (ERBB2)	Receptor, **amplified**	Breast (about 15–20%), gastric; **trastuzumab**, trastuzumab deruxtecan
EGFR	Receptor, mutated or amplified	**Lung adenocarcinoma in non-smokers and Asians** (about 40–50% in East Asians, lower in South Asians, about 15% in Europeans; **osimertinib**), glioblastoma (amplified), colon (cetuximab works only if RAS is wild type)
RET	Receptor tyrosine kinase	**MEN 2A and 2B** (germline; prophylactic thyroidectomy), **medullary thyroid carcinoma**, **RET/PTC** rearrangement in papillary carcinoma (radiation)
ALK	Fusion kinase (**EML4–ALK**; **NPM–ALK, t(2;5)**)	Lung adenocarcinoma (young non-smokers; crizotinib, alectinib, lorlatinib), **anaplastic large-cell lymphoma**, neuroblastoma (germline)
IDH1, IDH2	Metabolic: make the oncometabolite 2-hydroxyglutarate	Diffuse gliomas (defines astrocytoma and oligodendroglioma, WHO CNS 2021), AML, cholangiocarcinoma
JAK2 V617F	Cytokine-receptor kinase	Polycythaemia vera, essential thrombocythaemia, myelofibrosis

- **Knudson's two-hit hypothesis** (from retinoblastoma): both alleles of a suppressor must be lost; in familial cancer the first hit is inherited (germline), so tumours are earlier and bilateral or multiple. **Oncogenes act dominantly** (one allele), suppressors recessively at the cell level, though the familial syndromes are inherited as autosomal dominant.
- **Mismatch-repair** defects (**MLH1, MSH2, MSH6, PMS2, EPCAM**): **Lynch syndrome (HNPCC)**, colon (right-sided), endometrium (the commonest extracolonic), ovary, stomach, urinary tract; **microsatellite instability**. Sporadic MSI comes from MLH1 promoter methylation (with BRAF V600E). **MSI-high or mismatch-repair-deficient tumours respond to PD-1 inhibitors** (pembrolizumab, the first tissue-agnostic approval, FDA 2017).
- Epigenetic silencing (promoter hypermethylation of suppressors: MLH1, CDKN2A), microRNAs (miR-15/16 deleted in CLL) and long non-coding RNAs also drive tumours.

- Modern practice: tumours are profiled for targets (EGFR, ALK, ROS1, BRAF, KRAS G12C, HER2, NTRK fusions, PD-L1 expression, MSI and tumour mutational burden), often by **next-generation sequencing** and, for monitoring, by **liquid biopsy** (circulating tumour DNA). **Immune-checkpoint inhibitors**: **anti-PD-1** (nivolumab, pembrolizumab), anti-PD-L1 (atezolizumab), **anti-CTLA-4** (ipilimumab); **CAR-T cells** (anti-CD19 in B-cell ALL and lymphoma; anti-BCMA in myeloma).
- **The cell cycle and the cytotoxic drugs**: **p53 holds cells at G1–S** (and G2–M) to repair DNA; tubulin for the spindle is made in G2. **Phase-specific** drugs: **S phase** the antimetabolites (methotrexate, 5-fluorouracil, cytarabine, 6-mercaptopurine, hydroxyurea); **late S and G2** the topoisomerase inhibitors (**etoposide**, topoisomerase II; irinotecan and topotecan, topoisomerase I) and **bleomycin** (G2); **M phase** the microtubule poisons: **taxanes (paclitaxel, docetaxel) bind β-tubulin and stabilise microtubules**, while **vinca alkaloids (vincristine, vinblastine) prevent their assembly** (colchicine and griseofulvin act the same way but are not anticancer drugs). **Phase-non-specific**: alkylating agents, platinum compounds, anthracyclines, dactinomycin.
- **Classic toxicities** asked with them: **busulfan and bleomycin** pulmonary fibrosis; **cyclophosphamide and ifosfamide** haemorrhagic cystitis (acrolein; **mesna** prevents it), ifosfamide also encephalopathy; **cisplatin** nephrotoxicity and ototoxicity; **vincristine** peripheral neuropathy; **doxorubicin** dilated cardiomyopathy (dose-related; dexrazoxane protects); **5-FU and capecitabine** hand–foot syndrome; methotrexate mucositis and marrow suppression (folinic acid rescue).

Carcinogenesis

- **Chemical** (initiation, an irreversible mutation; then promotion, reversible proliferation):
  - Direct-acting (no activation needed): **alkylating agents** (cyclophosphamide: AML, bladder).
  - Indirect (procarcinogens activated by cytochrome P450): **polycyclic hydrocarbons** (tobacco smoke, the soot of Pott's chimney sweeps' scrotal cancer), **aromatic amines and azo dyes** (**β-naphthylamine, aniline dyes: bladder**), **aflatoxin B_1** (Aspergillus flavus on stored grain and groundnuts: **hepatocellular carcinoma**, with a characteristic **TP53 codon 249** mutation), **nitrosamines** (stomach, oesophagus).
  - Occupational: **vinyl chloride** (**angiosarcoma of liver**), **asbestos** (**bronchogenic carcinoma is the commoner asbestos cancer**, with a synergy with smoking; **mesothelioma** is the most specific, with no link to smoking), **benzene** (AML), **arsenic** (skin, lung, liver angiosarcoma), chromium and nickel (lung, nasal sinuses), **cadmium** (lung; IARC Group 1; a link with prostate cancer is suggested, not proven), wood dust (nasal adenocarcinoma), beryllium (lung).
- **Viral**:
  - **HPV 16 and 18** (high-risk): **cervix**, anus, oropharynx; **E6 degrades p53, E7 binds RB**; integration into host DNA. Low-risk 6 and 11: genital warts, laryngeal papillomas.
  - **EBV**: **Burkitt lymphoma** (endemic African), **nasopharyngeal carcinoma** (southern China, North Africa, Arctic), **Hodgkin lymphoma** (mixed cellularity), post-transplant lymphoproliferative disease, primary CNS lymphoma in AIDS, extranodal NK/T-cell lymphoma, gastric carcinoma (about 10%); LMP-1 mimics CD40.
  - **HBV and HCV**: hepatocellular carcinoma (chronic inflammation and regeneration; HBV also integrates; HBx protein).
  - **HTLV-1**: **adult T-cell leukaemia/lymphoma** (Tax protein; southern Japan, the Caribbean), and tropical spastic paraparesis.
  - **HHV-8 (KSHV)**: **Kaposi sarcoma**, primary effusion lymphoma, multicentric Castleman disease. **Merkel cell polyomavirus**: Merkel cell carcinoma.
- **Bacterial and parasitic**: **H. pylori**: gastric adenocarcinoma (intestinal type) and **MALT lymphoma** (eradication cures early MALT lymphoma); **Schistosoma haematobium**: **squamous carcinoma of the bladder**; **Clonorchis and Opisthorchis** (liver flukes): **cholangiocarcinoma**.
- **Radiation**: **UV-B** makes **pyrimidine (thymine) dimers** (repaired by nucleotide excision; defective in **xeroderma pigmentosum**): basal cell carcinoma, squamous carcinoma, melanoma. Ionising: **leukaemia (AML, CML; the shortest latency)**, **papillary thyroid carcinoma** (children; Chernobyl), breast, lung, sarcoma after radiotherapy.
- **Inherited predisposition**: DNA-repair syndromes (xeroderma pigmentosum; **Bloom (BLM helicase)**, Fanconi anaemia (FANC genes, interstrand cross-link repair, AML and squamous cancers), ataxia telangiectasia), the familial cancer genes above.
- **Precursor lesions**: Barrett's oesophagus, chronic atrophic gastritis, ulcerative colitis, leukoplakia (oral **submucous fibrosis** with areca nut chewing, common in South Asia), actinic keratosis, cirrhosis, CIN, atypical endometrial hyperplasia, villous adenoma (the highest malignant potential of colon adenomas).

Paraneoplastic syndromes

Syndrome	Mechanism	Typical tumours
Cushing syndrome	**Ectopic ACTH**	**Small-cell lung carcinoma**, carcinoid, medullary thyroid, pancreatic neuroendocrine tumours
SIADH (hyponatraemia)	ADH	**Small-cell lung carcinoma**, intracranial tumours
Hypercalcaemia (the commonest paraneoplastic syndrome)	**PTHrP** (humoral), or bone destruction, or calcitriol	**Squamous cell lung carcinoma**, breast, renal, ovarian, adult T-cell leukaemia; calcitriol in Hodgkin and other lymphomas
Polycythaemia	**Erythropoietin**	**Renal cell carcinoma**, cerebellar haemangioblastoma, hepatocellular carcinoma, uterine leiomyoma
Hypoglycaemia	IGF-2 or insulin	Fibrosarcoma, mesothelioma, hepatocellular; insulinoma
Lambert–Eaton syndrome	Antibody to presynaptic **voltage-gated calcium channels**	**Small-cell lung carcinoma**
Myasthenia gravis, pure red-cell aplasia	Autoimmune	**Thymoma**
Paraneoplastic cerebellar degeneration, encephalomyelitis	Anti-Yo (anti-Purkinje), anti-Hu	Ovary and breast (anti-Yo); small-cell lung (anti-Hu); anti-NMDA receptor encephalitis with **ovarian teratoma**

Syndrome	Mechanism	Typical tumours
Acanthosis nigricans (adult onset), Leser–Trélat sign (eruptive seborrhoeic keratoses)	Growth factors	**Gastric adenocarcinoma**, other carcinomas
Dermatomyositis	Immune	Ovary, lung, stomach (anti-TIF1γ)
Hypertrophic osteoarthropathy and clubbing	Unknown (PDGF, VEGF)	Lung carcinoma, mesothelioma
Migratory thrombophlebitis (Trousseau), NBTE, DIC	Tumour tissue factor and mucin	**Pancreas**, lung, other mucin-secreting adenocarcinomas; APL (DIC)
Nephrotic syndrome	Immune complexes	Carcinomas (membranous), Hodgkin (minimal change)

Tumour markers

Marker	Tumour, and the catch
AFP	**Hepatocellular carcinoma**, **yolk sac tumour**, embryonal carcinoma (with yolk-sac elements), immature teratoma; raised AFP rules out pure seminoma; also pregnancy (neural tube defects high, Down syndrome low), ataxia telangiectasia
β-hCG	**Choriocarcinoma** and **hydatidiform mole** (very high), embryonal carcinoma, **some seminomas** (about 15%, from syncytiotrophoblastic giant cells)
CA 19-9	**Pancreatic adenocarcinoma** (also cholangiocarcinoma, colon); **not raised in Lewis-antigen-negative people** (about 5–10%); for **monitoring, not screening**
CA 125	**Ovarian epithelial (serous)** carcinoma; also endometriosis, pregnancy, any peritoneal irritation
CEA	**Colorectal** (follow-up after surgery), pancreas, stomach, lung, breast, medullary thyroid; raised in smokers
PSA	**Prostate** (screening is controversial; also raised in BPH, prostatitis, after ejaculation and catheterisation)
Calcitonin	**Medullary carcinoma of the thyroid** (diagnosis, family screening is now by RET testing, follow-up)
Thyroglobulin	Follow-up of **differentiated (papillary and follicular)** thyroid carcinoma after total thyroidectomy
PLAP, LDH	**Seminoma and dysgerminoma** (LDH reflects tumour bulk)
Inhibin	**Granulosa cell tumour** (also used with hCG in Down screening)
CA 15-3, CA 27-29	Breast cancer monitoring
NSE	Small-cell lung carcinoma, neuroblastoma
Chromogranin A, urinary 5-HIAA	Neuroendocrine tumours, **carcinoid syndrome** (5-HIAA)
Urinary VMA and HVA	**Neuroblastoma**; plasma free metanephrines: phaeochromocytoma
Bence Jones protein, serum free light chains, M protein	**Multiple myeloma**
β_2-microglobulin	Myeloma and CLL prognosis

- **Courvoisier's sign** (painless obstructive jaundice with a palpable, non-tender gallbladder) suggests **carcinoma of the head of the pancreas** or the periampullary region, rather than stones; **CA 19-9** is the marker to send.

Specific tumour features

- **Thyroid carcinomas**:
  - **Papillary** (about 85%; the commonest, young women, after radiation): **psammoma bodies**, **Orphan Annie eye (ground-glass) nuclei**, **nuclear grooves**, intranuclear pseudo-inclusions; **diagnosed by the nuclear features**; **lymphatic spread** (cervical nodes), excellent prognosis; **BRAF V600E** (commonest mutation), RET/PTC.
  - **Follicular** (about 10%; iodine-deficient areas): diagnosed only by **capsular or vascular invasion** (so **not on FNAC**: Bethesda category IV), **haematogenous spread** (bone, lung); **RAS**, PAX8–PPARG. An encapsulated follicular lesion with **no capsular or vascular invasion** on well-sampled sections is a **follicular adenoma**, however cellular.
  - **Medullary** (about 5%): from **parafollicular C cells**, **amyloid stroma** (calcitonin-derived), **calcitonin** (and CEA), 20–25% familial (**MEN 2A, 2B, RET**), no radioiodine uptake.
  - **Anaplastic**: elderly, rapid neck mass, TP53, the worst prognosis (all stage IV); BRAF-mutant cases now get dabrafenib with trametinib.
  - Modern: **NIFTP** (non-invasive follicular thyroid neoplasm with papillary-like nuclear features, 2016) was renamed from encapsulated non-invasive follicular-variant papillary carcinoma, and is no longer called cancer (WHO 2022 lists it among low-risk neoplasms).
- **Psammoma bodies**: **papillary thyroid**, **serous** ovarian (and primary peritoneal) carcinoma, **meningioma**, mesothelioma, papillary renal cell carcinoma, prolactinoma (rare).
- **Testicular germ-cell tumours** (95% of testicular tumours; **15–35 years**; cryptorchidism raises risk; precursor germ-cell neoplasia in situ):

Tumour	Histology	Markers and immunohistochemistry
Seminoma (the commonest; peak 30s)	Sheets of uniform cells with **clear cytoplasm** (glycogen) and central nuclei, **fibrous septa with lymphocytes**, granulomas	**AFP normal**; hCG raised in some; **PLAP, OCT3/4, CD117 (KIT), SALL4 positive; CD30 negative**; very **radiosensitive and chemosensitive**, good prognosis
Spermatocytic tumour (WHO 2016 name)	Three cell sizes, no lymphocytes	**Men over 65**; rarely metastasises; not from germ-cell neoplasia in situ
Embryonal carcinoma	Pleomorphic cells in sheets, glands, papillae	**CD30 and OCT3/4 positive**, cytokeratin positive; AFP and hCG variable
Yolk sac tumour	Reticular pattern, **Schiller–Duval bodies**, hyaline globules	**AFP** (and glypican-3); the **commonest testicular tumour in children under 3**
Choriocarcinoma	Cytotrophoblast and syncytiotrophoblast, haemorrhage, no villi	**Very high hCG** (gynaecomastia, hyperthyroidism); early blood-borne spread to lung
Teratoma	Tissues of several germ layers	Malignant in adult men whatever the maturity; benign before puberty

- Testicular lymphoma (diffuse large B-cell) is the commonest testicular tumour **over 60**. Ovarian equivalent of seminoma: **dysgerminoma** (LDH, PLAP).

- **Gastrointestinal stromal tumour (GIST)**: the commonest mesenchymal tumour of the gut; from **interstitial cells of Cajal** (pacemaker cells) or their precursors; **stomach (about 60%)**, small intestine; spindle or epithelioid cells; **CD117 (KIT) and DOG1 positive** (DOG1 also in KIT-negative ones); **activating KIT** (about 75–80%) or **PDGFRA** mutations; risk by size, mitoses and site; **imatinib** (PDGFRA D842V resists it: avapritinib). **Leiomyoma and leiomyosarcoma**: **desmin and SMA positive, KIT negative**; **schwannoma: S100**.
- **Bone tumour clues**: **osteosarcoma** (10–20 years, metaphysis around the knee) makes malignant osteoid and lifts the periosteum where it breaks through the cortex: **Codman triangle**, with a **sunburst** pattern; Ewing sarcoma (diaphysis, onion-skin periosteum) can also lift one; benign lesions (osteoid osteoma, osteochondroma, simple bone cyst) do not. The other bone tumours are in Systemic pathology.
- **Glial tumour clues (WHO 2021)**: **pseudopalisading necrosis and microvascular proliferation mark grade 4 (glioblastoma)**; **Rosenthal fibres** pilocytic astrocytoma; **Homer Wright rosettes** medulloblastoma; **perivascular pseudorosettes** ependymoma.
- Commonest cancers: **worldwide (GLOBOCAN 2022)**, lung leads in incidence and in deaths for both sexes together, then female breast; in women, breast leads. Commonest childhood cancer: **leukaemia (ALL)**, then brain tumours; commonest solid extracranial tumour of childhood: **neuroblastoma**.

Genetics

Chromosomal disorders

- **Down syndrome (trisomy 21)**, the commonest chromosomal cause of intellectual disability (about 1 in 700 live births):
  - **About 95% meiotic nondisjunction** (in **maternal meiosis I** mostly; risk rises with **maternal age**: about 1 in 1,500 under 20, 1 in 350 at 35, 1 in 25 over 45); **about 4% Robertsonian translocation**, usually **t(14;21)**, not age-related and **able to recur** (a balanced-carrier parent: test the parents); **about 1% mosaic** (milder).
  - Features: hypotonia, flat facies, upslanting palpebral fissures, epicanthic folds, Brushfield spots, single palmar crease, sandal gap, **congenital heart disease in about 40%** (**atrioventricular septal (endocardial cushion) defect**, the most characteristic, and VSD), **duodenal atresia**, **Hirschsprung disease**, hypothyroidism, atlanto-axial instability, **early Alzheimer's disease** (APP on chromosome 21, by the 40s), and leukaemia (**ALL** and, under 4 years, **acute megakaryoblastic leukaemia (AML M7)** preceded by **transient abnormal myelopoiesis** with GATA1 mutation; overall risk 10–20-fold).
  - Screening: first trimester **nuchal translucency, low PAPP-A, raised free β-hCG** (combined test); second-trimester **quadruple test: low AFP, low unconjugated oestriol, raised hCG, raised inhibin A**. **Cell-free fetal DNA (NIPT)** is the most accurate screen (detection about 99%); diagnosis needs chorionic villus sampling (10–13 weeks) or amniocentesis (from 15 weeks) with karyotype, QF-PCR or microarray.
- **Edwards (trisomy 18)**: prominent occiput, small jaw, **clenched fists with overlapping fingers**, **rocker-bottom feet**, heart defects; most die within the first year; quad test all markers low.
- **Patau (trisomy 13)**: **holoprosencephaly**, microphthalmia, **cleft lip and palate**, **polydactyly**, cutis aplasia, heart defects.
- **Turner syndrome (45,X)** (about half are 45,X; the rest mosaics or structural X changes): short stature (**SHOX**), **streak ovaries** (primary amenorrhoea, the commonest cause of primary ovarian failure), webbed neck and **cystic hygroma** (in the fetus), lymphoedema of hands and feet in the newborn, shield chest, cubitus valgus, **bicuspid aortic valve (the commonest heart defect)** and **coarctation of the aorta**, **horseshoe kidney**, hypothyroidism; intelligence usually normal; **no Barr body**.
- **Klinefelter syndrome (47,XXY)**: the **commonest cause of male hypogonadism** (about 1 in 600 males); tall, eunuchoid, small firm testes, azoospermia, gynaecomastia (breast cancer risk), high FSH and LH, low testosterone; **one Barr body**.
- The number of **Barr bodies is the number of X chromosomes minus one** (lyonisation: random inactivation of one X in each female cell early in embryonic life, through XIST); hence variable expression in female carriers of X-linked disease.
- **Microdeletion syndromes** (detected by **FISH** or **chromosomal microarray**, not by routine karyotype):

Syndrome	Deletion	Features
DiGeorge / velocardiofacial (the commonest microdeletion, about 1 in 4,000)	**22q11.2** (TBX1)	**CATCH-22**: cardiac (conotruncal: truncus arteriosus, tetralogy, interrupted aortic arch), abnormal facies, **thymic hypoplasia** (T-cell deficiency), cleft palate, **hypocalcaemia** (absent parathyroids; seizures may be the first sign); later psychosis
Williams	**7q11.23** (elastin)	Elfin facies, **supravalvular aortic stenosis**, **hypercalcaemia**, very friendly ("cocktail party") personality
Cri-du-chat	**5p** (5p15)	Cat-like cry, microcephaly, intellectual disability
Wolf–Hirschhorn	**4p**	"Greek helmet" face
WAGR	11p13 (WT1 and PAX6)	Wilms tumour, aniridia, genitourinary anomalies, retardation
Smith–Magenis	17p11.2	Self-harm, sleep disturbance
Miller–Dieker	17p13.3 (LIS1)	Lissencephaly
Prader–Willi, Angelman	15q11–q13	Imprinting, below

- Structural terms: **Robertsonian translocation** (fusion of two acrocentric chromosomes, 13, 14, 15, 21, 22, at the centromere), balanced reciprocal translocation (normal carrier, risk of unbalanced offspring and miscarriage), isochromosome (i(Xq) in Turner), ring chromosome, inversion.

Genomic imprinting and uniparental disomy

- Only one parental allele of an imprinted gene is expressed; the other is silenced by **methylation**.

	Prader–Willi	Angelman
Lost	**Paternal** 15q11–q13	**Maternal** 15q11–q13 (**UBE3A**; the paternal copy is silent in the brain)
Causes	Paternal deletion (about 70%), **maternal uniparental disomy** (about 25%), imprinting defect	Maternal deletion (about 70%), **UBE3A mutation** (about 10%), paternal uniparental disomy (a few)
Features	Neonatal hypotonia and poor feeding, then **hyperphagia and obesity**, hypogonadism, small hands and feet, mild intellectual disability	"**Happy puppet**": inappropriate **laughter**, ataxic jerky gait, **seizures**, severe intellectual disability, absent speech

	Prader–Willi	Angelman
Test	**DNA methylation analysis** detects all three causes; FISH finds deletions only	Methylation, then UBE3A sequencing

- Other imprinting disorders: **Beckwith–Wiedemann** (11p15: macroglossia, omphalocele, hemihypertrophy, Wilms tumour and hepatoblastoma), Russell–Silver.

Trinucleotide repeat disorders

Disorder	Repeat, gene and site	Inheritance and points
Fragile X syndrome	**CGG** in the **5′ untranslated region of FMR1** (Xq27.3); full mutation over 200 repeats leads to **methylation and silencing**; premutation 55–200	X-linked; **the commonest inherited cause of intellectual disability** (Down syndrome is the commonest genetic cause overall); long face, large jaw, large everted ears, **macro-orchidism** (after puberty), autism, mitral prolapse; **anticipation through the mother**; premutation carriers: **fragile X tremor-ataxia** (older men) and **premature ovarian insufficiency**; diagnosis by PCR and Southern blot (cytogenetic fragile site no longer used)
Friedreich ataxia	**GAA** in an **intron of frataxin (FXN)**, chromosome 9q21	**Autosomal recessive** (the only common recessive one); ataxia, loss of reflexes and joint-position sense, extensor plantars, pes cavus, kyphoscoliosis, **hypertrophic cardiomyopathy (the usual cause of death)**, **diabetes**; mitochondrial iron overload; omaveloxolone (FDA 2023)
Huntington disease	**CAG** (poly-glutamine) in **huntingtin (HTT), 4p16**; 40 or more repeats fully penetrant	**Autosomal dominant**; chorea, psychiatric change, dementia, onset 30s–50s; **atrophy of the caudate** (loss of **GABAergic** medium spiny neurons; "boxcar" ventricles); **anticipation through the father** (expansion in spermatogenesis); tetrabenazine
Myotonic dystrophy type 1	**CTG** in the **3′ untranslated region of DMPK**, chromosome 19	Autosomal dominant; myotonia (cannot release grip), distal weakness, frontal balding, **cataracts**, testicular atrophy, cardiac conduction block, insulin resistance; **congenital form through the mother**
Spinocerebellar ataxias (many), **spinobulbar muscular atrophy (Kennedy disease)**	**CAG** (poly-glutamine); Kennedy in the **androgen receptor**	AD; X-linked (Kennedy)

- **Anticipation**: earlier onset and greater severity in successive generations as the repeat expands.

Patterns of inheritance

- **Autosomal dominant**: vertical transmission, males and females equally, **male-to-male transmission possible**; each child of an affected heterozygote has a **50%** risk; **variable expressivity, incomplete penetrance**, new mutations (achondroplasia about 80%, with advanced paternal age), **gonadal mosaicism**. Typical of structural proteins and receptors. Examples: **Huntington**, **Marfan**, **neurofibromatosis 1 and 2**, **familial hypercholesterolaemia** (LDL receptor), **achondroplasia (FGFR3 gain of function)**, **adult polycystic kidney disease** (PKD1 on 16, PKD2 on 4), **hereditary spherocytosis**, **von Willebrand disease (most types)**, osteogenesis imperfecta (most), familial adenomatous polyposis, Lynch syndrome, tuberous sclerosis, von Hippel–Lindau, MEN 1 and 2, myotonic dystrophy, acute intermittent porphyria, hereditary haemorrhagic telangiectasia, Li–Fraumeni, BRCA1/2, Peutz–Jeghers, MODY, otosclerosis.
- **Autosomal recessive**: both parents carriers, **25% of children affected**, 50% carriers (and **two-thirds of unaffected siblings are carriers**); **consanguinity** raises the risk; typical of **enzyme deficiencies (most inborn errors)**. Examples: **cystic fibrosis** (CFTR on 7q31; **F508del** the commonest; commonest lethal AR disease of white people), **sickle cell disease**, **thalassaemias**, **Wilson disease** (ATP7B, 13q), **haemochromatosis** (HFE C282Y), **phenylketonuria**, alkaptonuria, homocystinuria, galactosaemia, **α1-antitrypsin deficiency**, **congenital adrenal hyperplasia** (21-hydroxylase), glycogen and lysosomal storage diseases (except Hunter and Fabry), **Friedreich ataxia**, spinal muscular atrophy (SMN1), albinism, Bernard–Soulier, Glanzmann, ataxia telangiectasia.
- **X-linked recessive**: mostly males affected; **no male-to-male transmission**; **an affected father has all daughters carriers and all sons unaffected**; a **carrier mother** gives each son a 50% risk and each daughter a 50% chance of being a carrier; affected females through lyonisation, Turner or a carrier mother with an affected father. Examples: **haemophilia A and B**, **Duchenne and Becker muscular dystrophy** (dystrophin), **G6PD deficiency**, **Lesch–Nyhan** (HGPRT), **Fabry** (α-galactosidase A), **Hunter** (MPS II), **Wiskott–Aldrich**, **Bruton's agammaglobulinaemia**, **X-linked chronic granulomatous disease**, colour blindness, ocular albinism, X-linked sideroblastic anaemia (ALAS2), nephrogenic diabetes insipidus, Menkes disease, ornithine transcarbamylase deficiency (the only X-linked urea-cycle disorder).
- **X-linked dominant**: an affected father passes it to **all daughters and no sons**; an affected mother to half her children of either sex. Examples: **hypophosphataemic (vitamin D-resistant) rickets** (PHEX), **Rett syndrome** (MECP2, girls; usually lethal in boys), **incontinentia pigmenti**, **Alport syndrome** (mostly X-linked, COL4A5; nephritis, deafness, lens changes). Fragile X is X-linked with an unusual pattern (premutations, anticipation) and is listed as X-linked dominant in some books.
- **Mitochondrial**: transmitted **only through the mother, to all her children**; **heteroplasmy** gives variable severity. Examples: **Leber hereditary optic neuropathy**, **MELAS** (stroke-like episodes, lactic acidosis), **MERRF** (ragged red fibres on Gomori trichrome), Kearns–Sayre (usually a sporadic deletion), mitochondrial myopathy.
- Terms: **pleiotropy** (one gene, many effects: Marfan, PKU), **codominance** (both alleles expressed: AB blood group, HLA), **locus heterogeneity** (one disease from different genes: retinitis pigmentosa), **allelic heterogeneity** (many mutations in one gene: CF), **mosaicism** (two cell lines in one person; gonadal mosaicism explains affected siblings of normal parents).
- **Y-linked**: father to all sons (some azoospermia factor deletions).
- **Multifactorial**: cleft lip and palate, pyloric stenosis (males), neural tube defects (folic acid reduces risk by about 70%),

congenital heart disease, hypertension, diabetes; recurrence risk in a sibling about 2–7%, higher when the index case is of the less often affected sex.

- **Hardy–Weinberg**: $p + q = 1$ and $p^2 + 2pq + q^2 = 1$; for a recessive disease of frequency q^2, **carriers are 2pq, about 2q** when q is small (a disease of 1 in 2,500 gives q = 1/50 and carriers about 1 in 25). Assumes random mating, no selection, mutation or migration, a large population. For an autosomal dominant disease there are no carriers.
- **Consanguinity**: the general-population risk of a serious birth defect is about 2–3%; for children of **first cousins it roughly doubles** (an extra 2–3%), almost all of it **autosomal recessive** disease.

Connective tissue and lysosomal disorders

- **Marfan syndrome**: autosomal dominant; **fibrillin-1 (FBN1, chromosome 15q21)**: weak microfibrils and excess **TGF-β** signalling. **Aortic root dilatation and dissection** (cystic medial degeneration; the cause of death), mitral valve prolapse, **ectopia lentis (upward, superotemporal)**, myopia, tall stature with long limbs (arm span over height), **arachnodactyly**, pectus excavatum, joint laxity, pneumothorax, dural ectasia (revised **Ghent criteria, 2010**). Beta-blockers (and angiotensin-receptor blockers) slow aortic growth; **losartan was hoped to block TGF-β but trials found it no better than atenolol** (Pediatric Heart Network, NEJM 2014). **Homocystinuria** (cystathionine β-synthase, AR) mimics it with **downward (inferonasal) lens dislocation**, intellectual disability and thrombosis. Loeys–Dietz (TGF-β receptor): aggressive aneurysms, bifid uvula, hypertelorism.
- **Ehlers–Danlos syndromes** (2017 classification, 13 types): **classical: type V collagen** (COL5A1/2: skin hyperextensible, atrophic "cigarette-paper" scars); **vascular: type III collagen** (COL3A1: **arterial, bowel and uterine rupture**); **hypermobile** (the commonest; no gene known); kyphoscoliotic: lysyl hydroxylase.
- **Osteogenesis imperfecta**: **type I collagen** (COL1A1, COL1A2), mostly autosomal dominant; multiple fractures with minimal trauma (mistaken for child abuse), **blue sclerae** (thin sclera shows the choroid), dentinogenesis imperfecta, **hearing loss** (otosclerosis-like); type II lethal in the perinatal period; **bisphosphonates** reduce fractures.
- **Mucopolysaccharidoses** (all autosomal recessive **except Hunter, X-linked**; **dysostosis multiplex**, coarse face, hepatosplenomegaly):

Type	Enzyme	Urine GAG	Distinguishing points
Hurler (MPS I H)	**α-L-iduronidase**	**Heparan and dermatan sulphate**	**Corneal clouding**, severe regression, heart disease, death in childhood; HSCT before 2 years; laronidase (enzyme replacement); Scheie (MPS I S) the mild form
Hunter (MPS II)	**Iduronate-2-sulphatase**	Heparan and dermatan sulphate	**X-linked recessive (boys)**, **no corneal clouding**, aggressive behaviour, pebbly skin over the scapulae
Sanfilippo (MPS III)	Heparan-degrading enzymes	**Heparan sulphate** only	**Severe intellectual decline and behaviour problems**, mild somatic signs
Morquio (MPS IV)	Galactose-6-sulphatase (A), β-galactosidase (B)	**Keratan sulphate**	**Normal intelligence**, severe skeletal dysplasia, short-trunk dwarfism, **odontoid hypoplasia** (atlanto-axial instability), corneal clouding
Maroteaux–Lamy (MPS VI)	Arylsulphatase B	Dermatan sulphate	Normal intelligence
Sly (MPS VII)	β-glucuronidase	Several	Hydrops fetalis

- **Sphingolipidoses**:

Disease	Enzyme	Points
Gaucher	**Glucocerebrosidase** (β-glucosidase)	**The commonest lysosomal storage disease** (type 1, adults, no CNS; common in Ashkenazi Jews); hepatosplenomegaly, bone pain and **Erlenmeyer-flask femora**, pancytopenia; **Gaucher cells: "crumpled tissue paper" cytoplasm**; enzyme replacement (imiglucerase) or substrate reduction (eliglustat)
Niemann–Pick A and B	**Sphingomyelinase**	**Foamy macrophages**, **hepatosplenomegaly**, **cherry-red spot** (in about half), neurodegeneration (A); zebra bodies on EM; type C is a cholesterol-trafficking defect (NPC1)
Tay–Sachs	**Hexosaminidase A** (GM2 ganglioside)	**Cherry-red spot**, **no hepatosplenomegaly**, exaggerated startle (hyperacusis), regression from about 6 months; onion-skin lysosomes
Fabry	**α-galactosidase A** (ceramide trihexoside, Gb3)	**X-linked**; burning pain in the hands and feet in childhood, **angiokeratomas**, hypohidrosis, corneal whorls, renal failure, cardiomyopathy and stroke in adults; enzyme replacement, migalastat
Krabbe	Galactocerebrosidase	**Globoid cells**, peripheral neuropathy, optic atrophy
Metachromatic leukodystrophy	**Arylsulphatase A**	Demyelination, metachromatic granules; gene therapy (atidarsagene autotemcel: EU 2020, US 2024)

- **Glycogen storage diseases**: **von Gierke (type I)**: **glucose-6-phosphatase**, severe **fasting hypoglycaemia**, lactic acidosis, hyperuricaemia, hyperlipidaemia, big liver and kidneys; **Pompe (type II)**: **lysosomal acid α-glucosidase (acid maltase)**, **cardiomegaly**, hypotonia, death in infancy without enzyme replacement (alglucosidase alfa); **Cori (type III)**: debranching enzyme, milder; **McArdle (type V)**: **muscle phosphorylase**, exercise cramps and myoglobinuria (burgundy urine), **no rise in lactate on ischaemic exercise**, "second wind"; Andersen (IV, branching enzyme: cirrhosis in infancy), Hers (VI, liver phosphorylase: mild), Tarui (VII, muscle phosphofructokinase: cramps with haemolysis). Sandhoff (hexosaminidase A and B: Tay–Sachs picture with organomegaly), Farber (ceramidase).

DNA repair defects

Repair system	Disorder
Nucleotide excision (bulky lesions, UV thymine dimers)	**Xeroderma pigmentosum**: photosensitivity, skin cancers in childhood
Mismatch repair	**Lynch syndrome (HNPCC)**
Base excision	MUTYH-associated polyposis

Repair system	Disorder
Homologous recombination (double-strand breaks)	**BRCA1/2**, Fanconi anaemia (also cross-link repair), Bloom syndrome
Non-homologous end joining	Some SCID (Artemis, DNA ligase IV), and ataxia telangiectasia (ATM, the damage sensor)
RecQ helicases	**Bloom (BLM)**: short stature, sun-sensitive facial rash, many cancers; **Werner (WRN)**: **adult progeria** (premature ageing from the 20s); Rothmund–Thomson (RECQL4). Child progeria (Hutchinson–Gilford) is **lamin A**, not a helicase
Transcription-coupled repair	Cockayne syndrome

Modern practice

- Tests: karyotype (G-banding, aneuploidy and large rearrangements), **FISH** (microdeletions, rapid aneuploidy), **chromosomal microarray** (first-line for developmental delay and multiple anomalies), **whole-exome and whole-genome sequencing**, PCR with Southern blot or repeat-primed PCR for repeat disorders, methylation tests for imprinting.
- **Newborn screening** by tandem mass spectrometry (amino-acid and fatty-acid oxidation disorders), TREC for SCID; carrier screening; **preimplantation genetic testing** with IVF; **non-invasive prenatal testing** on cell-free DNA.
- Treatments: **enzyme replacement** for lysosomal diseases, **antisense oligonucleotides** (nusinersen) and **gene therapy** (onasemnogene) for spinal muscular atrophy, **CFTR modulators** (elexacaftor–tezacaftor–ivacaftor, 2019) for cystic fibrosis, **CRISPR-edited stem cells (exagamglogene autotemcel, 2023)** for sickle cell disease and β-thalassaemia.

Anaemias

Definitions and approach

- **WHO haemoglobin cut-offs (g/dL)**: men under 13; non-pregnant women under 12; **pregnancy under 11** (the classic answer); children 6–59 months under 11, 5–11 years under 11.5, 12–14 years under 12. **WHO 2024 revision**: children **6–23 months under 10.5**, 24–59 months under 11, and in pregnancy **under 11 in the first and third trimesters but under 10.5 in the second**; adjust for altitude and smoking (relevant in hilly Nepal: Hb rises with elevation).
- Red-cell indices: **MCV 80–100 fL** (microcytic under 80, macrocytic over 100), MCH 27–32 pg, **MCHC 32–36 g/dL** (raised only in **spherocytosis**, and falsely in cold agglutinins), **RDW** (raised in iron deficiency, normal in thalassaemia trait).
- **Reticulocyte count** (normal 0.5–2.5%; supravital stain such as **new methylene blue**): high in haemolysis and bleeding (over 2–3%), low in production failure. **Corrected reticulocyte count = count × (patient's Hb or haematocrit ÷ normal)**: 12% at Hb 5 against a normal 15 corrects to 4%. The reticulocyte production index also allows for early release.
- Commonest anaemia **worldwide and in Nepal: iron deficiency**, most often nutritional (with hookworm, menstrual loss, pregnancy); in high-income countries the commonest cause is chronic blood loss (in men and postmenopausal women, look for gastrointestinal cancer).

Red-cell morphology clues

Finding	Think of
Target cells	Thalassaemia, **HbC**, liver disease, after splenectomy, iron deficiency
Spherocytes	Hereditary spherocytosis, **warm autoimmune haemolysis**, burns, ABO haemolytic disease
Schistocytes (fragments, helmet cells)	**Microangiopathic haemolysis**: DIC, TTP, HUS, HELLP, malignant hypertension; prosthetic valves
Teardrop cells (dacrocytes)	**Myelofibrosis**, marrow infiltration (leucoerythroblastic film)
Bite cells, Heinz bodies (supravital stain)	**G6PD deficiency**, oxidant drugs
Acanthocytes (spur cells)	Severe liver disease, **abetalipoproteinaemia**
Echinocytes (burr cells)	Uraemia, artefact, pyruvate kinase deficiency
Basophilic stippling	**Lead poisoning**, thalassaemia, sideroblastic anaemia (pyrimidine 5′-nucleotidase)
Howell–Jolly bodies (nuclear remnants)	**Hyposplenism**, asplenia (sickle cell, coeliac), megaloblastic anaemia
Pappenheimer bodies (iron)	Sideroblastic anaemia, after splenectomy
Ring sideroblasts (marrow, Perls' stain)	Sideroblastic anaemia: iron-laden mitochondria around the nucleus
Rouleaux	Myeloma, raised fibrinogen or globulins
Hypersegmented neutrophils (5 or more lobes)	**Megaloblastic anaemia** (the earliest blood sign)
Sickle cells	HbSS

Iron deficiency and the iron profile

- Iron metabolism: absorbed as ferrous iron in the **duodenum** (DMT1, after duodenal cytochrome b reduces ferric iron; vitamin C helps, phytates, tea and calcium hinder), exported by **ferroportin** and carried by transferrin. **Hepcidin** (from the liver) **blocks ferroportin**: it rises in **inflammation** and iron overload and falls in iron deficiency and **hereditary haemochromatosis**.

Condition	Serum iron	Ferritin	TIBC (transferrin)	Saturation	Other
Iron deficiency	Low	**Low** (the most specific test; under 15 µg/L diagnostic, under 30 likely)	**High**	Low	Microcytic hypochromic, pencil cells, **high RDW**, Mentzer index over 13, raised free erythrocyte protoporphyrin, thrombocytosis
Anaemia of chronic disease (inflammation)	**Low**	**High** (an acute-phase reactant; sometimes only normal)	**Low** (sometimes normal)	Low	**Hepcidin traps iron in macrophages**; normocytic or mildly microcytic; marrow iron present

Condition	Serum iron	Ferritin	TIBC (transferrin)	Saturation	Other
Sideroblastic	High	High	**Normal (or low)**	High	**Ring sideroblasts**; dimorphic film
β-thalassaemia trait	Normal	Normal	Normal	Normal	**High red-cell count, low MCV**, raised HbA_2
Iron overload (haemochromatosis)	High	High	**Low**	**High** (over 45%, the first screening test)	Liver, pancreas ("bronze diabetes"), heart, joints, pituitary

- Iron deficiency stages: depleted stores (ferritin falls first), then iron-deficient erythropoiesis (saturation falls), then anaemia. Clinical: fatigue, **pica** (pagophagia), **koilonychia**, angular cheilitis, glossitis; **Plummer–Vinson (Paterson–Kelly) syndrome**: dysphagia with **post-cricoid web** in middle-aged women, a premalignant state (post-cricoid squamous carcinoma).
- **Treatment**: oral ferrous salts (current practice: **once daily or on alternate days** improves absorption, since each dose raises hepcidin for about a day); response: **reticulocytes rise in 5–10 days**, Hb by about 2 g/dL in 3 weeks; continue 3 months after correction to fill stores. **No response to oral iron** in proven iron deficiency: poor adherence, continuing loss, **malabsorption** (coeliac disease, H. pylori, atrophic gastritis, bariatric surgery), wrong diagnosis. **Intravenous iron** (ferric carboxymaltose, iron sucrose) for intolerance, malabsorption, late pregnancy, CKD, heart failure. Total iron deficit by **Ganzoni**: weight (kg) × (target – actual Hb, g/dL) × 2.4 + stores (500 mg).

Megaloblastic anaemia

- **Defective DNA synthesis** with normal RNA and protein synthesis: **nuclear–cytoplasmic asynchrony** (the nucleus lags), large precursors with open chromatin (**megaloblasts**), **giant metamyelocytes**, ineffective erythropoiesis (intramedullary haemolysis: raised LDH and indirect bilirubin), **pancytopenia**, **raised MCV** (often over 110), oval macrocytes, **hypersegmented neutrophils**.
- **Vitamin B_{12} (cobalamin)**: animal foods only, so **strict vegetarians** (common in South Asia) are at risk; body stores last **3–5 years**; freed by acid and pepsin, bound by R-protein (haptocorrin), then **intrinsic factor** in the duodenum, absorbed in the **terminal ileum** (cubilin).
  - Causes: **pernicious anaemia** (the commonest in the West), gastrectomy, **ileal resection or Crohn's disease**, blind-loop bacterial overgrowth, **Diphyllobothrium latum** (fish tapeworm), **metformin**, proton-pump inhibitors, **nitrous oxide** (oxidises cobalamin), diet.
  - **Pernicious anaemia**: **autoimmune atrophic gastritis of the body and fundus** (antrum spared), **loss of parietal cells, which secrete intrinsic factor and acid**: achlorhydria, **hypergastrinaemia** (G cells unopposed, ECL hyperplasia, gastric carcinoid), risk of gastric adenocarcinoma. **Anti-intrinsic factor antibody is specific** (about 50–70% sensitive); **anti-parietal-cell antibody is sensitive** (about 90%) but not specific. Associated with other autoimmune diseases (thyroid, vitiligo, type 1 diabetes). The **Schilling test** is obsolete.
  - B_{12} alone needed for: **methylmalonyl-CoA mutase** (so **methylmalonic acid is raised**, which explains myelin damage) and methionine synthase (homocysteine raised).
  - **Neurology** (B_{12} only): **subacute combined degeneration** (posterior columns and lateral corticospinal tracts: loss of vibration and position sense, ataxia, extensor plantars with absent ankle jerks), peripheral neuropathy, dementia, optic atrophy; can occur without anaemia. Treat with **intramuscular hydroxocobalamin**; high-dose oral B_{12} also works.
- **Folate**: green vegetables and liver, destroyed by overcooking; stores last only **3–4 months**; absorbed in the **jejunum**. Causes: poor diet, alcohol, pregnancy and lactation, haemolysis, malabsorption (coeliac, tropical sprue), drugs (**methotrexate, trimethoprim, phenytoin**, pyrimethamine, sulfasalazine). **Homocysteine raised, methylmalonic acid normal**; no neuropathy, but folate deficiency in pregnancy causes **neural tube defects** (periconceptional folic acid).
- **Never treat with folate alone until B_{12} deficiency is excluded**: it corrects the blood but lets neurological damage progress.
- Other macrocytosis without megaloblasts: **alcohol (the commonest cause of macrocytosis without anaemia)**, liver disease, hypothyroidism, reticulocytosis, myelodysplasia, pregnancy, drugs (hydroxyurea, zidovudine, azathioprine). Orotic aciduria: megaloblastic anaemia unresponsive to B_{12} and folate, treated with uridine.

Haemolytic anaemias

- Features of haemolysis: **reticulocytosis**, raised **unconjugated bilirubin** (acholuric jaundice), raised **LDH**, **low haptoglobin**, raised urinary urobilinogen; pigment **gallstones**; **aplastic crisis with parvovirus B19**.
- **Extravascular** (spleen and liver macrophages; most haemolysis): splenomegaly. **Intravascular**: **haemoglobinaemia, haemoglobinuria, haemosiderinuria**, very low haptoglobin (mismatched transfusion, PNH, G6PD crisis, falciparum malaria, mechanical valves, clostridial sepsis, march haemoglobinuria).
- **Hereditary spherocytosis**: the commonest inherited haemolytic anaemia in people of northern European descent; **autosomal dominant** in about 75%; defects of **ankyrin (the commonest), spectrin, band 3, protein 4.2**: membrane is lost, cells become **spherocytes** (no central pallor), **MCHC raised**, MCV normal or low.
  - **Osmotic fragility increased**; the **incubated osmotic fragility test** is the more sensitive classical test; **eosin-5′-maleimide (EMA) binding by flow cytometry** is the current screening test of choice (BSH 2011 guideline).
  - **Direct Coombs test negative** (separates it from warm autoimmune haemolysis, which also has spherocytes).
  - **Rigid spherocytes are trapped in the splenic cords and eaten by macrophages**, so **splenectomy cures the anaemia** though spherocytes persist (Howell–Jolly bodies appear). Delay it beyond 6 years of age when possible; **vaccinate** against pneumococcus, Haemophilus and meningococcus first; partial splenectomy and cholecystectomy as needed.
- **G6PD deficiency**: **X-linked recessive**; the commonest enzyme defect of red cells (about 400 million people; common in malaria belts, which it partly protects against); the

hexose monophosphate (pentose phosphate) shunt fails to supply **NADPH**, so **reduced glutathione** cannot be regenerated, and oxidants denature haemoglobin into **Heinz bodies** that splenic macrophages pluck out, leaving **bite cells** (and blister cells).

- Triggers: **infection (the commonest)**, drugs (**primaquine, tafenoquine, dapsone, sulphonamides, nitrofurantoin, rasburicase, methylene blue**, high-dose aspirin, quinolones), **fava beans** (favism, Mediterranean variant), naphthalene (mothballs).
- Episodic **intravascular** haemolysis 2–3 days after the trigger; neonatal jaundice (kernicterus risk).
- **Enzyme assay can be falsely normal during or just after a crisis** (old, deficient cells have gone; reticulocytes have more enzyme): repeat at 2–3 months. **WHO recommends G6PD testing before primaquine or tafenoquine** radical cure of vivax malaria.

- **Pyruvate kinase deficiency**: autosomal recessive, the commonest glycolytic defect; **ATP lack**, rigid cells, echinocytes; raised 2,3-BPG improves oxygen delivery (anaemia well tolerated); mitapivat (2022).
- **Paroxysmal nocturnal haemoglobinuria**: an **acquired** somatic **PIGA** mutation (X-linked gene) in a haematopoietic stem cell, so no **GPI anchor**: loss of **CD55 (decay-accelerating factor)** and **CD59 (membrane inhibitor of reactive lysis)** on red cells, leucocytes and platelets, so **complement lyses the cells**.
  - Triad: **intravascular haemolysis** (dark morning urine: haemolysis occurs all day, overnight urine is concentrated), **thrombosis at unusual sites** (**hepatic veins: Budd–Chiari**, portal, mesenteric, cerebral veins; the commonest cause of death), and **cytopenias** (linked to **aplastic anaemia**; can evolve to AML or MDS).
  - **Iron deficiency** from urinary loss (not iron overload); **leucocyte alkaline phosphatase low**; Coombs negative; smooth-muscle dystonias (dysphagia, erectile dysfunction) from NO consumption.
  - **Diagnosis: flow cytometry for CD55 and CD59, with FLAER** (fluorescent aerolysin, which binds GPI anchors), the gold standard; the **Ham (acidified serum) test** and sucrose lysis test are obsolete.
  - Treatment: **eculizumab or ravulizumab** (anti-C5); proximal complement inhibitors for residual extravascular haemolysis, **pegcetacoplan** (C3, 2021) and oral **iptacopan** (factor B, 2023); allogeneic HSCT is the only cure.
- **Autoimmune haemolytic anaemia** (**direct Coombs (direct antiglobulin) test positive**):

	Warm (commoner, about 80%)	Cold
Antibody	**IgG**, at 37 °C, often against Rh antigens	**IgM** (fixes complement; DAT positive for **C3** only), below 30 °C
Haemolysis	**Extravascular** (spleen): spherocytes	Intravascular and extravascular (liver), agglutination in the cold: acrocyanosis, Raynaud
Causes	Idiopathic, **SLE**, **CLL** and lymphomas, drugs (methyldopa, penicillin as a hapten, cephalosporins, quinidine immune-complex type)	**Mycoplasma pneumoniae** (anti-I), **infectious mononucleosis (anti-i)**, cold agglutinin disease (clonal B cells, older adults), lymphoma
Treatment	**Corticosteroids**, rituximab, splenectomy	Keep warm, rituximab; sutimlimab (C1s inhibitor, 2022); steroids work poorly

- **Paroxysmal cold haemoglobinuria**: the **Donath–Landsteiner antibody** (biphasic IgG against the **P antigen**, binds in the cold and lyses on warming); children after viral infection, historically congenital or tertiary **syphilis**.
- **Microangiopathic haemolytic anaemia**: schistocytes with thrombocytopenia in **TTP, HUS, DIC**, HELLP, malignant hypertension, scleroderma renal crisis; **macroangiopathic**: prosthetic heart valves.
- Other: hypersplenism, burns (spherocytes), **falciparum malaria** (blackwater fever), Clostridium perfringens sepsis, **snake venom**, Wilson disease (copper), drugs.

Haemoglobinopathies

- Normal adult haemoglobin: **HbA (α2β2) about 97%, HbA_2 (α2δ2) 2–3.5%, HbF (α2γ2) under 1%**.
- **β-thalassaemia**: point mutations (not deletions) of the β-globin gene (chromosome 11); excess **α chains precipitate**, causing **ineffective erythropoiesis** and haemolysis.
  - **Trait (minor)**: mild microcytic hypochromic anaemia, **red-cell count high for the degree of anaemia**, **MCV low**, **Mentzer index (MCV ÷ RBC in millions/μL) under 13** (iron deficiency over 13), **RDW normal**, **ferritin normal**, target cells and basophilic stippling, **HbA_2 raised above 3.5%** (the diagnostic test, by **HPLC** or electrophoresis); no treatment; do not give iron; genetic counselling. A worked example: MCV 64 fL with RBC 5.6 × 10^{12}/L gives a Mentzer index of about 11, and an HbA_2 of 5.5% confirms the trait. **Coexisting iron deficiency lowers the HbA_2** and can mask the trait: correct iron first.
  - **Major (Cooley's anaemia)**: presents at **6–12 months** as HbF production falls; severe anaemia, **hepatosplenomegaly**, extramedullary haematopoiesis, marrow expansion (**chipmunk facies**, **"hair-on-end" skull X-ray**, pathological fractures); **HbF raised**, HbA absent or very low; **transfusion-dependent**, with **iron overload** (the main cause of death: heart failure) needing **chelation** (desferrioxamine subcutaneous, **deferasirox** and deferiprone oral); HSCT cures; **luspatercept** reduces transfusion need (2019); **gene therapy** (betibeglogene autotemcel 2022; exagamglogene autotemcel 2023).
  - Thalassaemia intermedia: not transfusion-dependent; HbE/β-thalassaemia (common in South and Southeast Asia, eastern India and Bangladesh).
- **α-thalassaemia**: mostly **gene deletions** (four α genes on chromosome 16): one deleted, silent carrier; two, **trait** (mild microcytosis, **HbA_2 normal**; cis deletion in Southeast Asians gives the risk of hydrops); three, **HbH disease** (**β4 tetramers**, golf-ball inclusions on brilliant cresyl blue); four, **hydrops fetalis** with **Hb Bart's (γ4)**, incompatible with life. In the newborn, Hb Bart's on screening marks α-thalassaemia.
- **Sickle cell disease**: **HbS, β-globin Glu6Val** (glutamic acid to valine at position 6) by a point mutation; **autosomal recessive**; deoxygenated HbS polymerises, cells sickle, become rigid and adhere to endothelium. Trait (HbAS) protects against **falciparum malaria**.
  - Crises: **vaso-occlusive (painful)**, the commonest (dactylitis, hand-foot syndrome, the first sign in infancy; **acute chest syndrome**, the commonest cause of death in

adults; stroke in children; priapism; **papillary necrosis**), **splenic sequestration** (young children), **aplastic (parvovirus B19)**, haemolytic.
  - **Autosplenectomy** by about 5 years (Howell–Jolly bodies), so infection with **encapsulated organisms** (pneumococcus: penicillin prophylaxis and vaccines); **osteomyelitis**: **Salmonella** is the characteristic and often the commonest cause in sickle cell disease, with **Staph. aureus** the other main one; avascular necrosis of the femoral head; **isosthenuria** (concentrating defect, even in trait); leg ulcers; retinopathy (more in HbSC).
  - Diagnosis: sickling test (sodium metabisulphite) and solubility test screen (positive in trait too); **HPLC or haemoglobin electrophoresis** confirms (HbS, no HbA in HbSS); newborn screening.
  - Treatment: **hydroxyurea** (raises **HbF**, the cornerstone), folic acid, transfusion (exchange for stroke, acute chest syndrome), transcranial Doppler screening for stroke risk, L-glutamine, **crizanlizumab** (anti-P-selectin; still licensed in the US, but the EU revoked its licence in 2023 after the STAND trial showed no fewer painful crises than placebo); **voxelotor was withdrawn worldwide in 2024**; HSCT and gene therapy (**exagamglogene autotemcel**, the first CRISPR therapy, 2023; lovotibeglogene).
  - **Nepal**: sickle cell disease is concentrated in the **Tharu population of the western Terai** (studies in Dang, Banke, Bardiya and Kanchanpur), where screening studies have found about 8–12% positive for HbS, most of them carriers.
- **HbE** (β26 Glu to Lys; Southeast Asia, eastern South Asia): mild microcytosis; with β-thalassaemia it gives a thalassaemia major or intermedia picture. **HbC** (Glu6Lys): target cells, crystals.
- **Methaemoglobinaemia**: iron oxidised to the ferric state; chocolate-brown blood, **cyanosis unresponsive to oxygen**, **"saturation gap"** (pulse oximetry about 85%); drugs (dapsone, nitrates, local anaesthetics such as benzocaine and prilocaine, primaquine), congenital cytochrome b5 reductase deficiency; treat with **methylene blue** (not in G6PD deficiency: use ascorbic acid or exchange).

Marrow failure

- **Aplastic anaemia**: **pancytopenia with a hypocellular, fatty marrow** (**trephine biopsy needed**; aspirate is often a "dry tap"), **no splenomegaly**, low reticulocytes. Mostly **idiopathic (autoimmune T-cell attack on stem cells)**; also drugs (**chloramphenicol**, the classic idiosyncratic one; carbamazepine, gold, sulphonamides, felbamate), chemicals (**benzene**), radiation, viruses (**seronegative hepatitis**, EBV, HIV, **parvovirus B19** in haemolytic states), pregnancy, **PNH** clones. Inherited: **Fanconi anaemia** (autosomal recessive, DNA cross-link repair; short stature, absent radii and thumbs, café-au-lait spots, **chromosome breakage with diepoxybutane or mitomycin C**, later AML and squamous cancers); dyskeratosis congenita (telomeres).
  - Severity (Camitta): severe if marrow cellularity under 25% with two of neutrophils under 0.5 × 10^9/L, platelets under 20 × 10^9/L, reticulocytes under 20 × 10^9/L (or corrected count under 1%); very severe if neutrophils under 0.2.
  - Treatment: **HSCT from a matched sibling** (the young), otherwise **immunosuppression with antithymocyte globulin and ciclosporin plus eltrombopag** (RACE trial, 2022).
- **Pure red-cell aplasia**: thymoma, parvovirus B19 (chronic in immunodeficiency), Diamond–Blackfan anaemia (congenital, ribosomal genes, macrocytic, triphalangeal thumbs).
- **Anaemia of chronic kidney disease**: **erythropoietin deficiency**, normocytic, burr cells; erythropoiesis-stimulating agents (target Hb 10–11.5 g/dL, KDIGO), iron; HIF-prolyl hydroxylase inhibitors (roxadustat, daprodustat) are newer oral options.
- **Myelophthisic anaemia**: marrow infiltration (metastatic carcinoma of breast, prostate, lung; myelofibrosis; TB): **leucoerythroblastic film** with **teardrop cells**.
- **Sideroblastic anaemia**: failure of haem synthesis in mitochondria; **ring sideroblasts**; hereditary **X-linked ALAS2** (often **pyridoxine-responsive**); acquired: **myelodysplasia** (SF3B1), **alcohol**, **lead**, **isoniazid** (B_6 antagonist), chloramphenicol, copper deficiency (zinc excess).
- **Lead poisoning**: inhibits **ALA dehydratase and ferrochelatase**: microcytic anaemia, **coarse basophilic stippling**, raised zinc protoporphyrin and urinary ALA, lead lines (gums, metaphyses), wrist and foot drop, encephalopathy in children; chelation with succimer, EDTA, dimercaprol.
- Life spans: **red cells about 120 days** (fetal red cells 60–90 days), **platelets 7–10 days**, **neutrophils about 6–8 hours in the blood** and 1–2 days in the tissues.

Bleeding disorders and blood banking

Coagulation, in tests

- **Vitamin K-dependent factors: II, VII, IX, X, with proteins C and S** (and Z): vitamin K is the cofactor for **γ-carboxylation of glutamate** residues, which lets them bind calcium and phospholipid. **Warfarin blocks vitamin K epoxide reductase (VKORC1)**. **Factor VII has the shortest half-life (about 6 hours)**, so the **PT prolongs first**; **protein C** also falls early (about 8 hours), so **early warfarin is prothrombotic** (heparin overlap; skin necrosis).
- The liver makes all factors except **factor VIII** (endothelium, liver sinusoidal cells) and vWF (endothelium, megakaryocytes); calcium is factor IV, tissue factor III.
- Pathways (classical cascade, the exam frame): **extrinsic** (III, VII), **intrinsic** (XII, XI, IX, VIII, with prekallikrein and HMW kininogen), **common** (X, V, II, I), then **XIII**.

Test	Measures	Normal (approximate)	Monitors
Platelet count	Number	150–400 × 10^9/L	
Bleeding time (Ivy)	**Platelet number and function, vWF** (primary haemostasis)	2–7 minutes	Largely replaced by PFA-100 and aggregometry
Clotting time (Lee–White)	Whole-blood clotting, insensitive	8–15 minutes	Obsolete except as a bedside snake-bite test (20-minute whole-blood clotting test)
Prothrombin time (PT), INR	**Extrinsic and common**: VII, X, V, II, fibrinogen	11–13.5 seconds	**Warfarin (INR)**; liver synthetic function

Test	Measures	Normal (approximate)	Monitors
aPTT	**Intrinsic and common**: XII, XI, IX, VIII, X, V, II, fibrinogen	25–40 seconds	**Unfractionated heparin**
Thrombin time	Fibrinogen to fibrin		Prolonged by heparin, dabigatran, low or abnormal fibrinogen, FDPs
Fibrinogen		2–4 g/L	
D-dimer	Cross-linked fibrin breakdown		Excluding DVT and PE; DIC
Anti-Xa assay			**Low-molecular-weight heparin**, rivaroxaban, apixaban

- **Mixing study**: a prolonged PT or aPTT that **corrects** with normal plasma is a **factor deficiency**; one that does **not correct** is an **inhibitor** (lupus anticoagulant, acquired factor VIII inhibitor, heparin).
- **Sample tubes**: **light blue (sodium citrate, 9:1)** for PT, aPTT and D-dimer; lavender (EDTA) for blood count, blood film and HbA1c; **black (citrate 4:1)** for Westergren ESR; grey (sodium fluoride with oxalate) for glucose; green (heparin) for blood gases, ammonia and osmotic fragility; red (plain) and gold (gel and clot activator) for serum chemistry and serology.

Patterns

Disorder	Platelet count	Bleeding time	PT	aPTT
ITP, other thrombocytopenia	**Low**	Prolonged	Normal	Normal
von Willebrand disease	Normal (low in 2B)	**Prolonged**	Normal	**Prolonged** (often normal in mild type 1)
Haemophilia A or B	Normal	**Normal**	Normal	**Prolonged**
Factor VII deficiency	Normal	Normal	**Prolonged**	Normal
Factor X, V, II deficiency; **vitamin K deficiency, warfarin, liver disease**	Normal	Normal	Prolonged (first)	Prolonged
Heparin	Normal	Normal	Normal or slightly long	**Prolonged**
DIC	**Low**	Prolonged	**Prolonged**	**Prolonged**
Bernard–Soulier	**Low, giant platelets**	Prolonged	Normal	Normal
Glanzmann thrombasthenia	**Normal**	Prolonged	Normal	Normal
Aspirin, uraemia	Normal	Prolonged	Normal	Normal
Factor XIII deficiency	Normal	Normal	**Normal**	**Normal**: **clot dissolves in 5 M urea** (clot solubility test); umbilical stump bleeding, delayed bleeding, intracranial haemorrhage
Factor XII deficiency	Normal	Normal	Normal	**Prolonged, yet no bleeding**
Vascular purpura (scurvy, Henoch–Schönlein purpura, Ehlers–Danlos, steroids, senile purpura)	Normal	Normal or prolonged	Normal	Normal

Inherited bleeding disorders

- **Von Willebrand disease**: **the commonest inherited bleeding disorder** (about 1% by laboratory testing, far fewer with symptoms); vWF mediates **platelet adhesion** (to collagen, through **GpIb**) and **carries and protects factor VIII** (so factor VIII falls and the aPTT lengthens). **Mucocutaneous bleeding**: epistaxis, menorrhagia, gum bleeding, bleeding after dental extraction.
  - **Type 1** (partial quantitative deficiency; **about 70–80%**; **autosomal dominant**; mild): **desmopressin** releases stored vWF.
  - **Type 2** (qualitative): 2A (loss of large multimers), **2B** (gain of function: enhanced binding to GpIb, **thrombocytopenia**, **heightened aggregation with low-dose ristocetin**; **desmopressin contraindicated**), 2M, **2N** (cannot bind factor VIII: mimics mild haemophilia A, autosomal recessive).
  - **Type 3** (virtually absent; autosomal recessive; severe, with joint bleeds): vWF-containing concentrates.
  - Tests: vWF antigen, vWF activity (ristocetin cofactor or GpIb binding), factor VIII, multimers; **ristocetin-induced platelet aggregation reduced** (except 2B), and **corrected by adding normal plasma** (which supplies vWF). Blood group O has about 25% lower vWF levels. **Tranexamic acid** helps mucosal bleeding; acquired vWD in aortic stenosis (Heyde syndrome with angiodysplasia).
- **Haemophilia A (factor VIII)** about 1 in 5,000 male births; **haemophilia B (factor IX, Christmas disease)** about 1 in 25,000–30,000; both **X-linked recessive** (about a third new mutations); severity by factor level (**severe under 1%**: spontaneous haemarthroses; moderate 1–5%; mild 5–40%: bleeding after trauma or surgery). **Haemarthrosis** (knee the commonest; target joints, haemophilic arthropathy), muscle haematomas (iliopsoas), intracranial bleeding, prolonged bleeding after circumcision. **Isolated prolonged aPTT** that corrects on mixing; bleeding time and PT normal.
  - Treatment: factor concentrates (recombinant, extended half-life), prophylaxis in severe disease; **desmopressin for mild haemophilia A** (not B); **inhibitors** (alloantibodies) develop in about 25–30% of severe A (bypassing agents: recombinant VIIa, FEIBA). Modern: **emicizumab** (bispecific antibody bridging IXa and X; weekly to monthly subcutaneous prophylaxis, works with inhibitors; 2017–18), **fitusiran** and concizumab, and **gene therapy** (etranacogene dezaparvovec for B, 2022; valoctocogene roxaparvovec for A, 2022–23).
  - Haemophilia C: **factor XI**, autosomal recessive, Ashkenazi Jews, bleeding after surgery. **Parahaemophilia**: factor V deficiency.
- Acquired haemophilia A: autoantibody against factor VIII in the elderly, postpartum or with autoimmune disease; large bruises; aPTT not corrected on mixing.

Platelet disorders

- **Bernard–Soulier syndrome**: autosomal recessive **GpIb–IX–V deficiency**: **adhesion** defect; **thrombocytopenia with giant platelets**; **ristocetin aggregation absent and not corrected by normal plasma** (the receptor is missing, not vWF); aggregation to **ADP, collagen and adrenaline normal**; flow cytometry: CD42 absent.
- **Glanzmann thrombasthenia**: autosomal recessive **GpIIb/IIIa (integrin αIIbβ3) deficiency**: **aggregation** defect, as fibrinogen cannot bridge platelets; **platelet count and size normal**; **no aggregation with ADP, collagen, thrombin or adrenaline**, **normal ristocetin response** (adhesion intact); no clot retraction; flow cytometry CD41 and CD61 absent.
- **Storage pool disease** (dense granules: Hermansky–Pudlak, Chediak–Higashi; α-granules: **grey platelet syndrome**).
- Drugs: **aspirin irreversibly acetylates COX-1** (no thromboxane A_2 for the platelet's 7–10-day life; antiplatelet at low dose, 75–150 mg daily); **clopidogrel, prasugrel** irreversibly and **ticagrelor** reversibly block **P2Y12** (ADP); **abciximab, eptifibatide, tirofiban** block **GpIIb/IIIa**; dipyridamole and cilostazol raise cAMP. Uraemia (dialysis, desmopressin), cardiopulmonary bypass, myeloproliferative neoplasms impair function.
- **Immune thrombocytopenia (ITP)**: autoantibodies, mostly against **GpIIb/IIIa** (also GpIb), with destruction in the **spleen** and reduced production; **marrow megakaryocytes normal or increased**; **spleen not enlarged**.
  - **Children**: acute, 2–6 weeks **after a viral infection**, sudden petechiae; **self-limiting in about 80%** within 6 months; observation unless bleeding.
  - **Adults**: chronic, insidious, women 20–40 years; secondary to SLE, HIV, HCV, CLL, H. pylori, antiphospholipid syndrome; a **diagnosis of exclusion**. Treat when platelets are under 20–30 × 10^9/L or with bleeding: **corticosteroids** first, **IVIG** for rapid rise (bleeding, surgery, pregnancy), then **thrombopoietin-receptor agonists (eltrombopag, romiplostim, avatrombopag)**, rituximab, fostamatinib, splenectomy (ASH 2019 and the international consensus 2019 now prefer TPO-RAs before splenectomy).
  - Neonatal alloimmune thrombocytopenia (maternal anti-HPA-1a) and neonatal thrombocytopenia from maternal ITP.
- **Thrombotic thrombocytopenic purpura (TTP)**: severe deficiency of **ADAMTS13** (vWF-cleaving protease; **under 10% activity**), acquired autoantibody (most) or congenital (Upshaw–Schulman), so **ultra-large vWF multimers** cause platelet microthrombi. Classic **pentad**: **microangiopathic haemolytic anaemia, thrombocytopenia, fever, neurological signs, renal dysfunction** (fewer than 10% have all five; MAHA with thrombocytopenia is enough to start treatment). Coagulation tests normal (unlike DIC). **Plasma exchange (PEX) urgently**, corticosteroids, rituximab, and **caplacizumab** (anti-vWF nanobody, 2019); **platelet transfusion is avoided**; the **PLASMIC score** predicts severe ADAMTS13 deficiency.
- **Haemolytic uraemic syndrome**: **typical (diarrhoea-associated)**: **Shiga toxin from E. coli O157:H7** (or Shigella dysenteriae type 1) in **children**: bloody diarrhoea, then MAHA, thrombocytopenia and **acute kidney injury**; supportive care, **no antibiotics** (raise toxin release). **Atypical HUS**: inherited or acquired **complement dysregulation** (factor H, I, MCP): **eculizumab or ravulizumab**.
- Heparin-induced thrombocytopenia: see haemodynamics.
- **Gestational thrombocytopenia** (mild, third trimester, benign), **HELLP syndrome** (haemolysis, elevated liver enzymes, low platelets in pre-eclampsia).
- **Dengue**: thrombocytopenia with plasma leak and haemoconcentration (a rising haematocrit is the warning sign); platelet transfusion only for bleeding.

Thrombophilias and antiphospholipid syndrome

- **Antiphospholipid syndrome**: antibodies to phospholipid-binding proteins: **lupus anticoagulant**, **anticardiolipin**, **anti-β_2-glycoprotein I**. Primary or secondary (**SLE**, the commonest association).
  - In the laboratory the antibodies interfere with the phospholipid of the test, so the **aPTT is prolonged and does not correct on mixing** (the dilute Russell's viper venom time is the confirmatory test); the PT is normal. **In the patient they cause thrombosis, not bleeding** ("lupus anticoagulant" is a misnomer).
  - Clinical: **venous** (DVT the commonest) and **arterial thrombosis** (stroke in the young), **pregnancy morbidity** (**three or more unexplained consecutive miscarriages before 10 weeks**, fetal death after 10 weeks, **premature birth before 34 weeks from severe pre-eclampsia or placental insufficiency**), thrombocytopenia, livedo reticularis, valve disease, **false-positive VDRL**. Catastrophic APS: multi-organ thrombosis.
  - **Revised Sapporo (Sydney 2006)** criteria: one clinical plus one laboratory criterion, the antibody **positive twice at least 12 weeks apart**; the **ACR/EULAR 2023** criteria (for research) weight clinical and laboratory domains.
  - Treatment: **heparin then warfarin (INR 2–3), long-term** after thrombosis; **DOACs are avoided, above all in triple-positive patients** (rivaroxaban did worse than warfarin in the TRAPS trial, 2018); in **pregnancy, low-dose aspirin plus low-molecular-weight heparin** (warfarin is teratogenic).
- **Factor V Leiden** (Arg506Gln) is a **thrombophilia, not a bleeding disorder**: the mutant factor Va is functional but **resistant to inactivation (cleavage) by activated protein C**, so thrombin generation goes on (**APC resistance**, screened by a clotting-based APC-resistance test and confirmed by PCR); venous thrombosis. Prothrombin G20210A, antithrombin, protein C and S deficiency: see haemodynamics. Test for inherited thrombophilia only when it would change management, and not during acute thrombosis or on anticoagulants (they lower protein C, S and antithrombin).

Anticoagulant tests, in one line

- **Unfractionated heparin: aPTT** (protamine reverses); **LMWH, fondaparinux, rivaroxaban, apixaban: anti-Xa assay** when needed; **warfarin: PT/INR** (vitamin K and four-factor prothrombin complex concentrate reverse it); **dabigatran** lengthens the thrombin time (idarucizumab reverses); drug details are in Pharmacology.

Blood groups

- **ABO**: gene on **chromosome 9** codes glycosyl transferases that add sugars to the **H antigen** (made by **FUT1** on chromosome 19 from the precursor substance): A adds N-acetylgalactosamine, B adds galactose, O (a non-functional allele) adds nothing, leaving H. Most H on group O cells, least on A_1B.
- **Landsteiner's law**: natural antibodies (**IgM**, from about 3–6 months of age, against gut-bacterial antigens) against the A or

B antigen a person lacks. Group O people also make IgG anti-A,B (so **ABO haemolytic disease of the newborn** affects O mothers' A or B babies, can occur in the **first pregnancy**, and is mild).

- **Group O is the universal red-cell donor (O Rh-negative in emergencies)**; **AB is the universal red-cell recipient and the universal plasma donor**. The commonest group worldwide is **O**.
- **Secretors** (FUT2, about 80%) have A, B and H substances in saliva and body fluids.
- **Bombay phenotype (Oh)**: **homozygous null at FUT1 (h/h)** and usually **non-secretor (se/se at FUT2)**, so **no H antigen**, hence no A or B either: cells type as **O** on forward grouping (and do not react with anti-H lectin, *Ulex europaeus*), but the serum has potent **anti-A, anti-B and anti-H**, which **agglutinates all normal group O cells** and causes severe haemolysis with ordinary O blood. **Only Bombay blood can be given** (rare-donor registries; autologous storage). **Para-Bombay**: no H on red cells but H in secretions (FUT2 active). Autosomal recessive; **first described in Bombay (Mumbai) in 1952** (Bhende and colleagues); about **1 in 10,000 in India**, far commoner than in Europe (about 1 in a million). Seen also with LAD type 2 (fucose defect).
- **Rh**: the **D antigen** (RHD gene, chromosome 1; Rh-negative means the gene is deleted, about 15% of Europeans and about 5% or fewer of South Asians); antibodies are **acquired only after exposure** (transfusion or pregnancy) and are **IgG** (cross the placenta). **Haemolytic disease of the fetus and newborn**: Rh-negative mother sensitised by an earlier Rh-positive pregnancy; **anti-D immunoglobulin** (prophylaxis) at **28 weeks** (routine antenatal) and **within 72 hours of delivery** of an Rh-positive baby, and after any sensitising event (miscarriage, abortion, ectopic, amniocentesis, trauma); the dose for a large bleed is set by the **Kleihauer–Betke** test or flow cytometry (about 500 IU covers 4 mL of fetal red cells). Monitoring: indirect Coombs titres, **middle cerebral artery peak systolic velocity** Doppler for fetal anaemia; intrauterine transfusion.
- Other systems: **Kell** (strongly immunogenic; HDN with suppressed erythropoiesis), **Kidd (Jk)** (antibodies fade and return: **delayed haemolytic reactions**), **Duffy** (Fy(a–b–) cells resist **Plasmodium vivax**; common in West Africans), **Lewis** (not on red cells natively, absorbed from plasma; IgM; rarely matter; Lewis-negative people cannot make CA 19-9), **P** (Donath–Landsteiner antibody), **I/i** (cold agglutinins). **Coombs tests**: **direct** (antibody or complement already on the patient's red cells: AIHA, HDN, haemolytic reactions) and **indirect** (free antibody in serum: antibody screen, **crossmatching**, antenatal screening).
- **Pretransfusion testing**: ABO and Rh grouping (forward and reverse), antibody screen, crossmatch (immediate-spin or full antiglobulin); the commonest cause of acute haemolytic reactions is **clerical error** (wrong patient or sample).

Storage and components

Component	Storage	Shelf life	Use
Whole blood	**2–6 °C**	**CPD 21 days; CPDA-1 35 days** (adenine keeps red-cell ATP)	Acute massive blood loss
Packed red cells	2–6 °C	**35 days in CPDA-1; 42 days in additive solution (SAGM)**	Anaemia; 1 unit raises Hb by about **1 g/dL** in an adult
Platelets (random donor from whole blood; single donor by apheresis)	**20–24 °C with constant agitation** (cold makes them cleared)	**5 days** (up to 7 with bacterial testing or pathogen reduction)	Thrombocytopenia: one apheresis unit (or pool of 4–6 random units) raises the count by about **30,000–50,000/µL**; one random unit about 5,000–10,000/µL
Fresh frozen plasma	**–18 °C or colder** (AABB; UK –25 °C; many South Asian blood banks and review books give **–30 °C**)	**1 year** (UK 36 months)	Multiple factor deficiency with bleeding, **DIC**, liver disease, **massive transfusion**, TTP (plasma exchange), warfarin reversal **only when PCC is unavailable**; dose 10–15 mL/kg
Cryoprecipitate (cold-insoluble fraction of FFP thawed at 1–6 °C)	–18 °C or colder	1 year	**Fibrinogen** (the main use: fibrinogen under 1.5 g/L with bleeding), **factor VIII, vWF, factor XIII, fibronectin**, in 10–20 mL per unit; haemophilia A or vWD only when concentrates are unavailable
Granulocytes	20–24 °C, no agitation	**24 hours**	Severe neutropenia with infection
Frozen red cells (glycerol)	–65 °C or colder	**10 years**	Rare groups (Bombay)

- **Storage lesion**: falling **2,3-BPG** (left-shifted oxygen curve; restored within 24 hours of transfusion), ATP and pH; rising **potassium** and free haemoglobin; microaggregates; platelets and labile factors V and VIII lost in stored whole blood.
- **Transfusion thresholds** (AABB 2023 and NICE): restrictive, **Hb under 7 g/dL** in most stable hospitalised adults, **under 7.5** in cardiac surgery, **under 8** in orthopaedic surgery or existing cardiovascular disease; prophylactic platelets under **10,000/µL** (stable), under 20,000 with fever or sepsis, **under 50,000 for surgery or active bleeding**, under 100,000 for neurosurgery or eye surgery.
- **Modifications**: **leucodepletion** (fewer febrile reactions, HLA alloimmunisation and CMV transmission); **irradiation** (25 Gy: prevents transfusion-associated GVHD: in HSCT, Hodgkin lymphoma, purine analogue treatment, intrauterine transfusion, and directed donations from relatives); washing (IgA deficiency, recurrent allergic reactions).
- **Massive transfusion**: replacement of one blood volume in 24 hours (about 10 units) or more than 4 units in an hour; **balanced ratio of plasma, platelets and red cells (1:1:1, PROPPR trial 2015)**, early **tranexamic acid** in trauma (within 3 hours, CRASH-2) and postpartum haemorrhage (WOMAN trial); complications: **hypocalcaemia** (citrate binds calcium), **hyperkalaemia**, **hypothermia**, dilutional coagulopathy and thrombocytopenia, acidosis or later alkalosis (citrate metabolised to bicarbonate).

- **Screening of donated blood** (WHO): **HIV, hepatitis B, hepatitis C, syphilis**, and **malaria** in endemic areas; nucleic-acid testing narrows the window period. Malaria and Chagas can pass in any component.

Transfusion reactions

Reaction	Timing	Mechanism and pointers
Febrile non-haemolytic (the commonest)	During or within 4 hours	**Recipient anti-HLA or anti-leucocyte antibodies**, or **cytokines accumulated in stored components** (platelets); **fever (a rise of 1 °C or more) and chills, no haemolysis, Coombs negative**; paracetamol; **leucodepletion** prevents it
Allergic (urticarial)	Minutes	Recipient IgE against donor plasma proteins; urticaria, itch; antihistamine and resume
Anaphylactic	Seconds to minutes	**IgA-deficient recipient with anti-IgA** (also haptoglobin deficiency): hypotension, bronchospasm, no fever; adrenaline; later give **washed cells or IgA-deficient products**
Acute haemolytic	Minutes to hours	**ABO incompatibility** (usually clerical): fever, rigors, loin and chest pain, hypotension, **haemoglobinuria**, DIC, acute kidney injury; IgM, complement, intravascular; **stop transfusion**, keep the line with saline, recheck identity, **direct Coombs positive**; fatal from as little as 10–50 mL
TRALI	**Within 6 hours**	**Donor anti-HLA or anti-HNA antibodies** (often from **multiparous women**: plasma-rich products) activate recipient neutrophils in the lung: **non-cardiogenic pulmonary oedema**, hypoxaemia, fever, **hypotension**, normal wedge pressure; supportive; male-only plasma donors reduce it
TACO	Within 12 hours	**Circulatory overload** (elderly, heart and renal failure, fast transfusion): **hypertension**, raised JVP, raised BNP; diuretics; **now the leading cause of transfusion-related death in UK haemovigilance (SHOT)**
Delayed haemolytic	**3–14 days**	**Anamnestic** response to a minor antigen (**Kidd**, Rh, Kell, Duffy) after earlier sensitisation: falling Hb, jaundice, positive DAT, extravascular
Transfusion-associated GVHD	4–30 days	**Donor lymphocytes** engraft in an immunocompromised or HLA-sharing recipient: rash, diarrhoea, liver failure, **marrow aplasia**, over 90% fatal; prevented by **irradiation**
Bacterial contamination (septic)	Minutes to hours	**Platelets** (stored warm; skin flora such as Staph. epidermidis) more than red cells (**Yersinia enterocolitica**, cold-loving); high fever, shock
Post-transfusion purpura	About 1 week	Anti-HPA-1a in an HPA-1a-negative woman: severe thrombocytopenia; IVIG
Iron overload	Years	Chronic transfusion (thalassaemia): chelation

Leukaemias and lymphomas

Classification and tools

- Current classifications: **WHO 5th edition (WHO-HAEM5, 2022)** and the **International Consensus Classification (ICC, 2022)**, both genetics-led; the **FAB** classification (M0–M7, L1–L3) is obsolete in practice but still asked.

FAB	Type	Pointers
M0, M1, M2	AML minimally differentiated, without and with maturation	**M2: t(8;21)**, Auer rods, the commonest AML type in children and adults in many series; chloromas
M3	**Acute promyelocytic**	**t(15;17)**, faggot cells (bundles of Auer rods), **DIC**
M4	Myelomonocytic	**inv(16)** with eosinophils (M4Eo)
M5	Monocytic	**Gum hypertrophy, skin and CNS infiltration**, non-specific esterase positive
M6	Erythroid	
M7	**Megakaryoblastic**	**Down syndrome under 4 years**, **myelofibrosis** (dry tap), CD41, CD61

- **Cytochemistry**: **myeloperoxidase** (in 3% or more of blasts) and **Sudan black B** mark **myeloblasts**; specific (chloroacetate) esterase granulocytic; **non-specific esterase (α-naphthyl acetate, inhibited by fluoride) monocytic**; **PAS block positivity** and **TdT** mark **lymphoblasts** (PAS also in erythroleukaemia); **acid phosphatase in T-ALL** (focal); **TRAP** in hairy cell leukaemia. Cytochemistry is now largely replaced by **flow cytometry**.
- Immunophenotype: **myeloid CD13, CD33, CD117**, MPO; **monocytic CD14, CD64**; **stem cell CD34**, HLA-DR (negative in APL); **B CD19, CD20, CD22, CD79a**, PAX5; **T CD2, CD3 (cytoplasmic CD3 is lineage-specific), CD5, CD7**; **TdT** (precursor lymphoid); **CD10 (CALLA)**; megakaryocytic CD41, CD61; erythroid glycophorin A, CD71.

Acute leukaemias

- Clinical: marrow failure (anaemia, infection, bleeding), **bone pain and sternal tenderness**, lymphadenopathy and hepatosplenomegaly (ALL more), gum and skin infiltration (monocytic), CNS and testis (ALL), leucostasis with very high counts, **tumour lysis syndrome**: within hours to days of starting treatment (sometimes before it) in fast-growing, bulky tumours with high counts or LDH (**Burkitt and other high-grade lymphomas, ALL**, AML with high counts), dying cells release **potassium, phosphate and nucleic acids (to urate)**; the phosphate binds calcium, so **hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia**, with acute kidney injury from urate and calcium-phosphate crystals (Cairo–Bishop criteria); prevented by hydration with **allopurinol**, or **rasburicase** in high risk (not in G6PD deficiency).
- **Diagnosis**: **blasts 20% or more** of marrow or blood cells (**WHO**); in **WHO 2022, AML with a defining genetic abnormality is diagnosed at any blast count**, except **BCR::ABL1** and **CEBPA** types, which still need 20%; **ICC 2022** sets 10% for those types and creates MDS/AML for 10–19%. **Auer rods** (fused azurophilic granules, MPO-positive) prove **myeloid** lineage.
- **Acute promyelocytic leukaemia (APL)**: **t(15;17)(q24;q21), PML::RARA**: maturation arrested at the **promyelocyte** (heavily granular, bilobed "butterfly" nuclei, **faggot cells**); **DIC and fibrinolysis** (annexin II): the **early haemorrhagic death** is the main risk (cerebral). A **medical emergency**: start **all-trans retinoic acid (ATRA)** on suspicion, before genetic confirmation; **ATRA with arsenic trioxide** cures most low- and intermediate-risk patients without chemotherapy (APL0406, 2013); watch for **differentiation syndrome** (fever, lung infiltrates, effusions, weight gain: dexamethasone). Usually young adults; CD33+, CD13+, **CD34– and HLA-DR–**.

- **AML** (the commonest acute leukaemia in **adults**, median age about 68):
  - **Favourable**: **t(8;21) RUNX1::RUNX1T1**, **inv(16) or t(16;16) CBFB::MYH11** (the core-binding-factor leukaemias), **mutated NPM1 without FLT3-ITD**, biallelic or bZIP **CEBPA**.
  - **Adverse**: **complex karyotype**, monosomal karyotype, **–5/del(5q), –7**, **TP53** mutation, **KMT2A (MLL)** rearrangements, inv(3), **FLT3-ITD** with high allelic ratio (ELN 2022 now classes FLT3-ITD as intermediate), t(6;9), BCR::ABL1, and AML after MDS or therapy (alkylating agents: 5–7 years, del 5/7; topoisomerase II inhibitors: 1–3 years, KMT2A).
  - Treatment: **"7 + 3" (cytarabine with daunorubicin)**; targeted additions by mutation (FLT3 inhibitors such as midostaurin; IDH inhibitors; anti-CD33 gemtuzumab), **venetoclax with azacitidine** for older or unfit patients (VIALE-A, 2020); allogeneic HSCT for high risk.
  - **Myeloid sarcoma (chloroma)**: extramedullary mass of blasts (orbit, skin), green from MPO; with t(8;21) and monocytic types.
- **ALL** (the **commonest cancer of childhood**, peak **2–5 years**; 80% B-lineage):
  - **B-ALL**: CD19, CD10 (CALLA), CD22, CD79a, **TdT** positive; **PAS block positive**; CNS and **testicular sanctuary** sites (intrathecal methotrexate).
  - **T-ALL**: adolescent **boys**, high count, **anterior mediastinal (thymic) mass** (superior vena cava obstruction, airway compression), cytoplasmic CD3, CD7, TdT, NOTCH1.
  - **Good prognosis**: age **1–10 years**, **WBC under 50,000/μL**, **hyperdiploidy (over 50 chromosomes)**, **t(12;21) ETV6::RUNX1** (the commonest translocation in childhood ALL), girls, rapid early response.
  - **Poor**: **infants under 1 year** (KMT2A rearrangement, **t(4;11)**), **over 10 years** and adults, WBC over 50,000, **t(9;22) BCR::ABL1 (Philadelphia; p190 protein)** (the commonest translocation in adult ALL, about 25%), **hypodiploidy** (under 44), **Ph-like** ALL, iAMP21, T-lineage (historically), CNS disease, poor response; **minimal residual disease after induction is now the strongest prognostic factor**.
  - Treatment: induction (vincristine, steroid, asparaginase, anthracycline), CNS prophylaxis, consolidation, about 2–3 years of maintenance (mercaptopurine, methotrexate); **TKI** (imatinib, dasatinib, ponatinib) for Ph+ ALL; **blinatumomab** (CD19–CD3 bispecific), **inotuzumab ozogamicin** (anti-CD22) and **CAR-T cells (tisagenlecleucel, 2017)** for relapse. **Cure in about 90% of children** in high-income countries.
  - Down syndrome (raised ALL and AML risk), Fanconi, ataxia telangiectasia, Bloom and radiation predispose; Li–Fraumeni (hypodiploid ALL).

Chronic myeloid leukaemia

- **Philadelphia chromosome, t(9;22)(q34;q11)**: **BCR (22) fused with ABL1 (9)**, making a **constitutively active tyrosine kinase** (**p210** in CML; **p190** in Ph+ ALL); present in **over 95% of CML**, in every myeloid lineage and some lymphoid cells (a **stem-cell** disease).
- Adults 40–60; insidious fatigue, weight loss, sweats, **massive splenomegaly** (dragging pain, early satiety); **very high white count** (often over 100,000/μL) with **the whole spectrum of maturing granulocytes** (myelocytes and neutrophils most, the "myelocyte bulge"), **basophilia** (an accelerated-phase sign when 20% or more), eosinophilia, thrombocytosis; **low leucocyte alkaline phosphatase score**; marrow hypercellular, **pseudo-Gaucher cells and sea-blue histiocytes**; high urate and B_{12} (transcobalamin I from granulocytes).
- Phases: **chronic** (most at diagnosis), **accelerated**, **blast crisis** (20% or more blasts, or extramedullary blasts): **myeloid in about 70%, lymphoid in about 30%. WHO 2022 dropped the accelerated phase** (keeps chronic and blast phases, with high-risk features).
- **LAP (NAP) score: low in CML, high in a leukaemoid reaction** (infection, inflammation, pregnancy, steroids, which shows normal mature neutrophils, toxic granulation, Döhle bodies). Also **high in polycythaemia vera**, essential thrombocythaemia, myelofibrosis, Hodgkin; **low in PNH** (and hypophosphatasia). **Diagnosis now by karyotype, FISH or RT-PCR for BCR::ABL1**.
- Treatment: **imatinib** (first-generation TKI, blocks the ATP-binding pocket; IRIS trial), **second-generation dasatinib, nilotinib, bosutinib** (faster responses), **ponatinib** for the **T315I** "gatekeeper" mutation (resistant to the others), **asciminib** (binds the myristoyl pocket: a STAMP inhibitor, 2021); life expectancy now close to normal. Monitoring by **quantitative RT-PCR on the international scale**: **major molecular response is BCR::ABL1 0.1% or less**; treatment-free remission can be tried after sustained deep molecular response. HSCT for resistance or blast crisis.
- **Juvenile myelomonocytic leukaemia (JMML)** (formerly "juvenile CML"): under 4 years, **Philadelphia-negative**, **high HbF**, monocytosis, RAS-pathway mutations (NF1, PTPN11), with neurofibromatosis type 1 and Noonan syndrome. Chronic neutrophilic leukaemia: CSF3R.

Chronic lymphocytic leukaemia and other B-cell neoplasms

- **CLL/small lymphocytic lymphoma**: the **commonest leukaemia of adults in the West** (median age about 70), **much less common in Asia** (including South Asia); clonal small mature **B cells** (5,000/μL or more for CLL; SLL when nodal with fewer cells).
  - Immunophenotype: **CD5 and CD23 positive**, CD19, CD200, **weak CD20 and weak surface immunoglobulin** (light-chain restricted), FMC7 and CD79b weak or negative.
  - Film: **smudge (basket) cells**, fragile cells crushed on smearing.
  - Immune dysregulation: **hypogammaglobulinaemia (infection is the commonest cause of death)**, **warm autoimmune haemolytic anaemia** (Coombs-positive, with **reticulocytosis**), **ITP**, pure red-cell aplasia.
  - Staging: **Rai (0–IV)** and **Binet (A–C)**: anaemia and thrombocytopenia mark advanced disease.
  - Prognosis: **del(17p) and TP53 mutation the worst**, **unmutated IGHV** poor, del(11q) poor; **del(13q) alone favourable** (the commonest abnormality); trisomy 12.
  - **Richter transformation** to diffuse large B-cell lymphoma (sudden nodes, B symptoms, LDH rise).
  - Treatment only when active (watch-and-wait for early stage): **BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib)** and **venetoclax with obinutuzumab** have replaced fludarabine–cyclophosphamide–rituximab and chlorambucil (iwCLL and NCCN, 2023–24).
- **Monoclonal B-cell lymphocytosis**: fewer than 5,000/μL clonal B cells, no nodes; progresses slowly.

- **Hairy cell leukaemia**: middle-aged men; **massive splenomegaly** without lymphadenopathy, **pancytopenia with monocytopenia**, cells with **hair-like cytoplasmic projections**; **TRAP positive** (tartrate-resistant acid phosphatase), **CD11c, CD25, CD103, CD123, annexin A1** (the most specific), **BRAF V600E** (nearly all); **dry tap** (marrow reticulin fibrosis), "fried-egg" cells on trephine; **cladribine** (or pentostatin) with rituximab; vemurafenib in relapse.
- **Follicular lymphoma**: the commonest **indolent** NHL in the West; **t(14;18)(q32;q21)** puts **BCL2** (anti-apoptotic) under the **immunoglobulin heavy-chain enhancer**, so it is **overexpressed** and cells **live too long** rather than divide fast; nodal, nodular pattern of centrocytes and centroblasts; **CD10, BCL6, CD20, BCL2 positive** (reactive follicles are BCL2-negative); graded by centroblasts; transforms to diffuse large B-cell lymphoma.
- **Burkitt lymphoma**: **t(8;14)(q24;q32)** moves **MYC (8)** next to the **heavy-chain locus (14)** (variants t(2;8) κ and t(8;22) λ); **endemic (African)**: children, **jaw** and orbit, **EBV in nearly all**, malaria belt; **sporadic**: abdomen (**ileocaecal**), ovaries, EBV in about 20%; **immunodeficiency-associated** (HIV). Medium-sized cells with lipid vacuoles, **"starry-sky" pattern** (tingible-body macrophages), **Ki-67 near 100%** (the fastest-growing human tumour, doubling about 24 hours); **CD10, CD20, BCL6 positive, BCL2 negative**, TdT negative; **tumour lysis syndrome** on treatment; intensive chemotherapy cures most.
- **Mantle cell lymphoma**: older men, **t(11;14)(q13;q32)**, **cyclin D1 (CCND1) overexpression**, **CD5 positive, CD23 negative**, **SOX11** (also in cyclin-D1-negative cases); lymphomatous polyposis of the gut; aggressive; BTK inhibitors.
- **Marginal-zone (MALT) lymphoma**: **H. pylori** (stomach: **eradication** cures early disease), Sjögren (salivary), Hashimoto (thyroid), **Chlamydia psittaci** (ocular adnexa), **Campylobacter jejuni** (immunoproliferative small-intestinal disease); CD5, CD10, CD23 negative; **t(11;18) API2::MALT1** predicts **no response to H. pylori eradication**.
- **Diffuse large B-cell lymphoma**: **the commonest NHL worldwide** (about 30–40%), aggressive, often extranodal; germinal-centre B-cell type (better) versus activated B-cell type (by gene expression or the Hans algorithm); **double-hit (MYC with BCL2 rearrangement)**: high-grade B-cell lymphoma, poor; **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), or **pola-R-CHP** (polatuzumab vedotin; POLARIX, 2022); CAR-T cells (axicabtagene) in relapse. Primary CNS lymphoma (HIV, EBV; methotrexate-based), primary mediastinal (young women).
- **Lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia)**: **IgM paraprotein**, **hyperviscosity** (visual change, bleeding, headache), cold agglutinins, neuropathy; **MYD88 L265P in over 90%**; **Dutcher bodies** (intranuclear immunoglobulin); BTK inhibitors.
- **Multiple myeloma**: clonal plasma cells (CD38, **CD138**, light-chain restricted) in the marrow; a plasma cell is oval with an **eccentric round nucleus whose chromatin is clumped like a clock face (cartwheel)**, deeply basophilic cytoplasm (rough ER) and a pale perinuclear **hof** (Golgi); older adults (more common in people of African descent).
  - **IMWG 2014 criteria**: **10% or more clonal plasma cells** (or a plasmacytoma) plus a **myeloma-defining event**: **CRAB** (**hyperCalcaemia**, **Renal** failure, **Anaemia**, **Bone** lytic lesions) or a **SLiM** biomarker (**60% or more plasma cells**, involved/uninvolved **free light-chain ratio 100 or more**, more than one focal lesion on MRI).
  - **M protein**: **IgG about 50%**, IgA about 20%, **light-chain only about 20%** (**Bence Jones** protein in urine: precipitates at 40–60 °C and redissolves at 100 °C; not detected by urine dipstick), IgD, non-secretory rare.
  - **Rouleaux**, **very high ESR**, reversed albumin–globulin ratio, low anion gap, hyperviscosity (more with IgA), **infections** (pneumococcus; the commonest cause of death), renal failure from **light-chain cast nephropathy** ("myeloma kidney"; also hypercalcaemia, amyloid AL, light-chain deposition disease), **"punched-out" lytic lesions** (skull, spine, ribs, pelvis; **bone scan is cold**, so use **whole-body low-dose CT, MRI or PET-CT**; skeletal survey is the classic answer), normal alkaline phosphatase. The bone loss and the **hypercalcaemia** come from **osteoclast activation by RANKL**, IL-6 and MIP-1α (CCL3) from the myeloma cells and their marrow stroma, with osteoblasts suppressed (**DKK1**); not from PTHrP, the usual cause in solid tumours.
  - Genetics: **t(11;14)** (standard; venetoclax-sensitive), **t(4;14)**, **t(14;16)**, **del(17p)**, gain 1q: high risk; staging by the **Revised International Staging System** (β_2-microglobulin, albumin, LDH, cytogenetics).
  - Treatment: **proteasome inhibitors (bortezomib)**, **immunomodulators (lenalidomide, thalidomide)**, **anti-CD38 daratumumab** and dexamethasone, then **autologous stem-cell transplant**; bisphosphonates; BCMA-directed CAR-T cells and bispecific antibodies in relapse.
  - **MGUS**: M protein under 3 g/dL, plasma cells under 10%, no end-organ damage; progresses at about **1% a year**. Smouldering myeloma: higher levels without CRAB. Solitary plasmacytoma: radiotherapy.
- Mature **T- and NK-cell** lymphomas: **mycosis fungoides** (cutaneous T-cell lymphoma: patches, plaques, tumours; **Pautrier microabscesses**, cerebriform cells; CD4) and **Sézary syndrome** (erythroderma, nodes, circulating **Sézary cells** with cerebriform nuclei); **adult T-cell leukaemia/lymphoma** (**HTLV-1**, hypercalcaemia, "flower" cells, CD4 and CD25); **anaplastic large-cell lymphoma** (**CD30**, **ALK-positive with t(2;5) NPM1::ALK** in children and young adults with a good prognosis; ALK-negative; breast-implant-associated); **extranodal NK/T-cell lymphoma, nasal type** (EBV, midline destructive lesion, commoner in Asia); peripheral T-cell lymphoma, NOS; enteropathy-associated T-cell lymphoma (coeliac disease).
- **Staging of lymphoma**: **Ann Arbor with the Lugano modification (2014)**: **I** one node region (or one extralymphatic site, IE), **II** two or more regions on the **same side of the diaphragm**, **III** both sides, **IV** diffuse extralymphatic disease (liver, marrow, lung); **A** no symptoms, **B** symptoms; X bulky. **PET-CT** is the staging and response test for FDG-avid lymphomas (Deauville 5-point score), and makes marrow biopsy unnecessary in Hodgkin and most DLBCL.

Hodgkin lymphoma

- **Reed–Sternberg cell**: a large cell with **two mirror-image nuclei or a bilobed nucleus**, each with a large **eosinophilic, inclusion-like nucleolus** ("**owl's eye**"); variants: **lacunar cells** (nodular sclerosis), **mummified cells**, **popcorn (LP) cells** (nodular lymphocyte-predominant). RS cells are **germinal-centre B cells** that have lost their B-cell programme, and are **fewer than 1–2% of the tumour**: the rest is a **reactive** background (lymphocytes, eosinophils, plasma cells, histiocytes) drawn by their cytokines.

- **Classical Hodgkin RS cells: CD15 and CD30 positive**, **PAX5 weakly positive**, **CD45 (LCA) and usually CD20 negative**; EBV (LMP-1) in some; **PD-L1 amplified (9p24.1)**, the reason **PD-1 inhibitors work**.
- Clinical: **bimodal age** (15–35 and over 55), **painless cervical or mediastinal nodes**, **contiguous spread** (predictable, from one node group to the next), **B symptoms** (fever over 38 °C, **drenching night sweats**, **weight loss over 10% in 6 months**), **Pel–Ebstein fever** (cyclical), pruritus, **alcohol-induced nodal pain** (rare, specific), eosinophilia; extranodal spread and leukaemic phase rare (unlike NHL); anergy (cell-mediated immunity impaired).

Subtype	Points
Nodular sclerosis	**The commonest in high-income countries (about 70%)**; **young women**; **mediastinal** mass; **lacunar cells**, collagen bands dividing nodules; EBV rarely; good prognosis
Mixed cellularity	About 20–25% in the West, **relatively commoner in South Asia and other low- and middle-income countries** (the commonest subtype in older Indian series, especially in children); **older men**, **EBV-associated (about 70%)**, **HIV**, advanced stage, **eosinophils**, classic RS cells
Lymphocyte-rich	Older men; **the best prognosis among the classical types**
Lymphocyte-depleted	The rarest; elderly, HIV, low-income countries; abdominal disease, marrow; pleomorphic RS cells; **the worst prognosis**
Nodular lymphocyte-predominant (not classical)	Young men, peripheral nodes; **popcorn (LP, L&H) cells**: **CD20, CD45, BCL6 positive; CD15 and CD30 negative**; **EBV negative**; indolent, late relapses, may transform to DLBCL; **renamed nodular lymphocyte-predominant B-cell lymphoma in ICC 2022** (WHO 2022 keeps the Hodgkin name)

- Treatment: **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine), **PET-adapted**, with radiotherapy in early stages; anti-CD30 **brentuximab vedotin** and **PD-1 inhibitors** (nivolumab) now enter first-line treatment of advanced disease (ECHELON-1, 2018; S1826, 2024). Late effects: second cancers (**breast after mediastinal radiotherapy**, lung, AML), **bleomycin lung fibrosis**, anthracycline cardiomyopathy, hypothyroidism, infertility.
- **Hodgkin against non-Hodgkin**: Hodgkin spreads **contiguously** along axial nodes and is usually localised, rarely involves **mesenteric nodes, Waldeyer's ring** or extranodal sites, has no leukaemic phase, shows a bimodal age curve and is cured in about 85%; non-Hodgkin lymphomas are often **non-contiguous**, involve peripheral and mesenteric nodes, Waldeyer's ring, gut, skin and CNS, can be leukaemic, occur at all ages (Burkitt, lymphoblastic and anaplastic large-cell in children) and vary in prognosis by type. Standard first-line regimens: **ABVD** for Hodgkin, **R-CHOP** for B-cell NHL.

Myeloproliferative neoplasms

- Clonal stem-cell disorders with **increased production of mature cells**, splenomegaly, marrow hypercellularity, thrombosis and haemorrhage, and late **myelofibrosis or AML**. Driver mutations: **JAK2 V617F**, **CALR** (exon 9), **MPL**; CML is defined by BCR::ABL1.
- **Polycythaemia vera**: **JAK2 V617F in about 95%** (exon 12 in most of the rest); raised red-cell mass, often with **raised white cells and platelets** too; **plethoric face, aquagenic pruritus** (itching after a hot bath: mast-cell degranulation), **erythromelalgia** (burning red hands and feet; aspirin responds), splenomegaly, headache, gout, **thrombosis** (**Budd–Chiari**, portal vein, stroke, MI); **serum erythropoietin low** (secondary polycythaemia from hypoxia, smoking, high altitude, EPO-secreting tumours or testosterone has a **high or normal level**); **LAP high**, histamine and B_{12} high.
  - Criteria: the **classic answer**, **Hb over 18.5 g/dL in men and 16.5 in women** (WHO 2008); **current WHO 2016 and 2022: Hb over 16.5 g/dL in men and over 16.0 in women** (or haematocrit over 49% and 48%), with **panmyelosis on marrow biopsy** and **JAK2 mutation**; minor criterion a subnormal EPO.
  - Treatment: **phlebotomy** to a **haematocrit under 45%** (CYTO-PV trial), **low-dose aspirin**, **hydroxyurea** (high risk: age over 60 or previous thrombosis), **ropeginterferon alfa-2b** (2021), **ruxolitinib** (JAK1/2 inhibitor) when hydroxyurea fails.
- **Essential thrombocythaemia**: sustained platelets **450 × 10^9/L or more**, large megakaryocytes; **JAK2 about 55%, CALR about 25%, MPL about 5%**, the rest "triple-negative"; thrombosis and bleeding (acquired von Willebrand syndrome when platelets exceed about 1,500); exclude reactive thrombocytosis (iron deficiency, inflammation, after splenectomy); aspirin, hydroxyurea, anagrelide.
- **Primary myelofibrosis**: **marrow fibrosis** (reticulin and collagen; from megakaryocyte **TGF-β** and PDGF), **dry tap**, **extramedullary haematopoiesis** with **massive splenomegaly**, **leucoerythroblastic** film with **teardrop cells**; JAK2, CALR or MPL; **ruxolitinib**, fedratinib, momelotinib (anaemia), allogeneic HSCT (the only cure).
- **Systemic mastocytosis** (KIT D816V, raised tryptase, urticaria pigmentosa, Darier's sign).

Myelodysplastic neoplasms

- Older adults (median about 70), or after chemotherapy and radiation; **cytopenias with dysplasia** in one or more lineages (**pseudo-Pelger–Huët** bilobed neutrophils, hypogranular neutrophils, **ring sideroblasts**, micromegakaryocytes), **hypercellular marrow with ineffective haematopoiesis**, **blasts under 20%**; risk of AML.
- Genetics (WHO 2022 names groups by them): **MDS with isolated del(5q)** (elderly women, macrocytic anaemia, normal or raised platelets; **lenalidomide** works), **SF3B1-mutated with ring sideroblasts** (**luspatercept**), **TP53** biallelic (poor); monosomy 7, complex karyotype poor; scored by **IPSS-R and IPSS-M**.
- Treatment: transfusion and chelation, ESAs, **hypomethylating agents (azacitidine, decitabine)** for higher risk, allogeneic HSCT.
- **Clonal haematopoiesis of indeterminate potential (CHIP)**: age-related mutations (DNMT3A, TET2) in blood cells without cytopenia; raises the risk of blood cancer and **cardiovascular disease**.

Histiocytic and other disorders

- **Langerhans cell histiocytosis**: clonal Langerhans cells with **Birbeck granules** (**tennis-racket** rods on EM; langerin), **CD1a, CD207 (langerin) and S100** positive; **BRAF V600E** in about half (so it is a myeloid neoplasm; vemurafenib, MEK inhibitors); unifocal (**eosinophilic granuloma** of bone: lytic skull lesion), multifocal (**Hand–Schüller–Christian triad: lytic skull lesions, diabetes insipidus, exophthalmos**),

multisystem infant form (**Letterer–Siwe**: skin rash, hepatosplenomegaly, marrow; poor).

- **Haemophagocytic lymphohistiocytosis**: uncontrolled macrophage and T-cell activation (familial: perforin; secondary to EBV, lymphoma, autoimmune disease): fever, splenomegaly, cytopenias, **very high ferritin**, high triglycerides, low fibrinogen, haemophagocytosis in marrow (HLH-2004 criteria).
- **Leukaemoid reaction** versus CML: a count over 50,000/µL from infection (TB, pertussis: lymphocytic), severe haemolysis, haemorrhage or metastatic cancer; **LAP high**, toxic granulation, no basophilia, no BCR::ABL1. **Leucoerythroblastic reaction**: nucleated red cells and immature granulocytes (marrow infiltration, myelofibrosis, severe sepsis).
- **Infectious mononucleosis** (EBV): **atypical lymphocytes (reactive CD8 T cells, Downey cells)**, heterophile antibody (**Paul–Bunnell, Monospot**), splenic rupture risk, ampicillin rash.

Systemic pathology: named bodies and histology

A high-yield group: an examiner names a body, cell or pattern and asks for the disease.

Named bodies and inclusions

Body or cell	Disease	Detail
Aschoff body (nodule) with Anitschkow (caterpillar) cells	**Acute rheumatic carditis**	Interstitial granuloma of **fibrinoid necrosis**, T cells, plasma cells and plump activated macrophages with **"caterpillar" chromatin** (Anitschkow cells; multinucleated ones are **Aschoff giant cells**); **pancarditis**; **MacCallum plaques** in the left atrium
Schiller–Duval body	**Yolk sac (endodermal sinus) tumour**	Glomerulus-like: a central vessel in a space lined by tumour cells; AFP, hyaline globules
Call–Exner bodies	**Granulosa cell tumour**	Rosettes around eosinophilic fluid; **coffee-bean nuclei**; oestrogen (endometrial hyperplasia); **inhibin**, FOXL2
Negri bodies	**Rabies**	Eosinophilic **cytoplasmic** inclusions in neurons: **hippocampal pyramidal cells** (Ammon's horn) and **cerebellar Purkinje cells**
Cowdry type A	**Herpes simplex, varicella-zoster**, CMV	**Intranuclear** eosinophilic inclusions with a halo; HSV encephalitis of the **temporal lobes**
Owl's-eye inclusions	**Cytomegalovirus**	Large intranuclear inclusion with halo, plus cytoplasmic inclusions, in **enlarged (cytomegalic) cells**
Cowdry type B	Poliovirus (historically)	Intranuclear, no halo
Guarnieri bodies	**Vaccinia and smallpox**	Cytoplasmic; **Paschen bodies** are the elementary bodies
Molluscum (Henderson–Patterson) bodies	**Molluscum contagiosum**	Large cytoplasmic inclusions
Michaelis–Gutmann bodies	**Malakoplakia**	**Laminated, calcified** (target-like) inclusions in macrophages (**von Hansemann cells**), from defective lysosomal digestion of bacteria, **bladder after E. coli infection**
Councilman (acidophil) bodies	**Yellow fever** (Councilman's original), **acute viral hepatitis**	**Apoptotic hepatocytes**, shrunken and eosinophilic
Mallory–Denk bodies (Mallory hyaline)	**Alcoholic hepatitis**, also MASH (fatty liver disease), Wilson disease, primary biliary cholangitis, hepatocellular carcinoma	Ropy eosinophilic aggregates of **cytokeratins 8 and 18** with ubiquitin in ballooned hepatocytes
Lewy bodies	**Parkinson disease** (substantia nigra), **dementia with Lewy bodies** (cortex)	**α-synuclein**, eosinophilic with a halo
Pick bodies	**Pick disease** (frontotemporal dementia)	Round **tau** inclusions; knife-edge frontal and temporal atrophy
Neurofibrillary tangles, neuritic (senile) plaques	**Alzheimer's disease**	Tangles: hyperphosphorylated **tau**; plaques: **Aβ amyloid** core; **Hirano bodies** (actin) and granulovacuolar degeneration in the hippocampus
Lafora bodies	**Lafora disease** (progressive myoclonic epilepsy)	Polyglucosan, PAS positive
Rosenthal fibres	**Pilocytic astrocytoma** (also Alexander disease, reactive gliosis)	Eosinophilic corkscrew GFAP-rich fibres
Homer Wright rosettes (neuroblastic, around neuropil)	**Neuroblastoma**, medulloblastoma, PNET	
Flexner–Wintersteiner rosettes (true, around a lumen)	**Retinoblastoma**	
Perivascular pseudorosettes	**Ependymoma**	
Verocay bodies	**Schwannoma**	Palisaded nuclei in Antoni A areas
Psammoma bodies	**Papillary thyroid carcinoma, serous ovarian tumours, meningioma**, mesothelioma, papillary RCC	Concentric laminated **dystrophic calcification**
Reed–Sternberg cells	**Hodgkin lymphoma**	CD15, CD30
Russell bodies	Plasma cells (myeloma, chronic inflammation)	Cytoplasmic immunoglobulin; **Dutcher bodies** are intranuclear (Waldenström)
Asteroid and Schaumann bodies	**Sarcoidosis** (not specific)	In giant cells of non-caseating granulomas; Schaumann: laminated calcium
Auer rods	**AML, especially APL (faggot cells)**	MPO-positive fused azurophilic granules
Heinz bodies	**G6PD deficiency**, unstable haemoglobins	Denatured haemoglobin; supravital stain (crystal violet)
Howell–Jolly bodies	**Hyposplenism, asplenia**	DNA remnants
Döhle bodies	Infection (toxic neutrophils), May–Hegglin anomaly	Blue cytoplasmic ER remnants
Donovan bodies	**Granuloma inguinale** (donovanosis)	**Klebsiella granulomatis** inside macrophages: "closed safety-pin" rods

Body or cell	Disease	Detail
Leishman–Donovan bodies	**Visceral leishmaniasis** (kala-azar; in Nepal historically the eastern and central Terai, now spreading into hill districts)	Amastigotes in macrophages of marrow and spleen
Birbeck granules	**Langerhans cell histiocytosis**	**Tennis-racket** rods on EM
Lines of Zahn	**Antemortem thrombus**	
Herring bodies	**Posterior pituitary**	Dilated axon ends of hypothalamic neurons storing ADH and oxytocin with neurophysin
Hofbauer cells	**Placental villi**	Fetal macrophages of the villous stroma; prominent in villitis and hydrops
Orphan Annie eye nuclei	**Papillary thyroid carcinoma**	Clear, ground-glass nuclei with grooves
Civatte (colloid) bodies	**Lichen planus** (also lupus, GVHD)	Apoptotic keratinocytes at the dermo-epidermal junction
Ferruginous (asbestos) bodies	**Asbestosis**	Golden-brown beaded rods, Prussian-blue positive (iron coat)
Curschmann spirals, Charcot–Leyden crystals, Creola bodies	**Bronchial asthma**	Mucus casts; eosinophil galectin-10 crystals; clumps of shed epithelium
Gamna–Gandy bodies	**Congestive splenomegaly** (portal hypertension)	Fibrosis with iron and calcium
Zebra bodies (EM)	**Fabry disease**, Niemann–Pick, metachromatic leukodystrophy	Lamellar lysosomal inclusions
Gaucher cells	Gaucher disease	"Crumpled tissue paper" cytoplasm
Kimmelstiel–Wilson nodules	**Diabetic nephropathy**	Nodular glomerulosclerosis
Crescents	Rapidly progressive glomerulonephritis	Parietal-cell and macrophage proliferation in Bowman's space
Wire loops	**Lupus nephritis** (class IV)	Subendothelial deposits
Reinke crystals	**Leydig cell tumour**	Rod-shaped cytoplasmic crystals
Hürthle (oncocytic) cells	Hashimoto's thyroiditis, Hürthle-cell (oncocytic) neoplasms	Mitochondria-rich pink cells
Signet-ring cells	Diffuse gastric carcinoma (linitis plastica), Krukenberg tumour	Mucin pushes the nucleus aside
Koilocytes	**HPV** infection (CIN, warts)	Perinuclear halo, wrinkled raisin nucleus
Tzanck cells (acantholytic) and multinucleated giant cells	Pemphigus (acantholytic cells); herpes (Tzanck smear giant cells)	
Owl's-eye nucleoli, popcorn cells, lacunar cells	Hodgkin variants	See leukaemias and lymphomas

Special stains

Stain	Shows
Perls' Prussian blue	**Haemosiderin (ferric iron)**: haemochromatosis, ring sideroblasts, marrow iron stores; Turnbull blue for ferrous iron
Congo red	**Amyloid** (apple-green birefringence in polarised light)
PAS (periodic acid–Schiff)	**Glycogen** (diastase-sensitive), **mucin**, **fungal walls**, **basement membranes**; **diastase-resistant PAS-positive granules in Whipple disease macrophages** and **α1-antitrypsin globules**; lymphoblasts (block)
Masson trichrome	**Collagen** (fibrosis, blue or green) and muscle (red)
Ziehl–Neelsen (20% sulphuric acid); modified (1%)	**Acid-fast bacilli** (TB, leprosy with 5%); Nocardia, Cryptosporidium, Isospora (modified); in tissue sections *M. leprae* is shown by the gentler **Fite (Fite–Faraco)** stain
Gomori methenamine silver (GMS)	**Fungi**, **Pneumocystis** cysts
Mucicarmine, India ink	**Cryptococcus** capsule (mucicarmine also epithelial mucin)
Warthin–Starry (silver)	**H. pylori**, spirochaetes, **Bartonella** (cat-scratch disease)
Giemsa	Malaria, Leishmania, H. pylori, blood films
Reticulin (silver)	Reticulin fibres (myelofibrosis grading, liver architecture)
Von Kossa, alizarin red	**Calcium**
Oil red O, Sudan III and IV (**frozen sections**)	**Neutral fat** (fat embolism, fatty liver, liposarcoma); Sudan black B for myeloblasts
Alcian blue	**Acid mucins** (Barrett's goblet cells)
Fontana–Masson	**Melanin**
Toluidine blue	**Mast cells** (metachromasia)
Rhodanine, orcein	**Copper** (Wilson disease); orcein also HBsAg and elastic fibres
Verhoeff–van Gieson	**Elastic fibres**
Luxol fast blue	Myelin
New methylene blue, brilliant cresyl blue	**Reticulocytes** (supravital); HbH inclusions

Immunohistochemistry

Marker	Points to
Cytokeratin (pan-CK)	**Carcinoma**, mesothelioma, synovial sarcoma
Vimentin	**Mesenchymal tumours (sarcomas)**; also melanoma, renal cell carcinoma, endometrial
Desmin	**Muscle** tumours (leiomyoma, leiomyosarcoma, rhabdomyosarcoma)
Myogenin, MyoD1	**Rhabdomyosarcoma** (skeletal muscle)
Smooth-muscle actin, h-caldesmon	Smooth-muscle tumours
S100	**Melanoma**, nerve-sheath tumours (**schwannoma**), **Langerhans cells**, chondroid tumours

Marker	Points to
HMB-45, Melan-A, SOX10	**Melanoma**
CD117 (KIT), DOG1	**GIST**; KIT also mast cells and seminoma
CD45 (leucocyte common antigen)	**Lymphoma** and leukaemia (not RS cells)
CD20, CD3	B and T lymphoma
Synaptophysin, chromogranin, INSM1, CD56	**Neuroendocrine tumours** (carcinoid, small-cell carcinoma, phaeochromocytoma)
GFAP	**Glial tumours** (astrocytoma)
Calretinin, WT1, D2-40	**Mesothelioma** (TTF-1 and CEA negative, against lung adenocarcinoma)
TTF-1	**Lung adenocarcinoma**, small-cell carcinoma, **thyroid**
Napsin A	Lung adenocarcinoma
p63, p40, CK5/6	**Squamous cell carcinoma**
CDX2, CK20 positive with CK7 negative	**Colorectal** adenocarcinoma
CK7 positive with CK20 negative	Lung, breast, ovary, endometrium, thyroid
PAX8	**Kidney, thyroid, Müllerian (ovary, endometrium)**
ER, PR, HER2, GATA3	**Breast** (GATA3 also urothelial)
PSA, NKX3.1	**Prostate**
Thyroglobulin; calcitonin	Follicular-cell thyroid tumours; medullary carcinoma
CD99, FLI1 (NKX2.2)	**Ewing sarcoma** (with t(11;22) EWSR1::FLI1)
CD34, CD31, ERG	Vascular tumours (angiosarcoma); CD34 also GIST, solitary fibrous tumour (STAT6)
CD1a, CD207 (langerin)	**Langerhans cell histiocytosis**
Inhibin, calretinin, SF-1	**Granulosa cell tumour**, sex-cord stromal tumours, adrenocortical tumours
PLAP, OCT3/4, SALL4; CD30	**Germ-cell tumours** (seminoma OCT3/4 and CD117; embryonal CD30)
Glypican-3, HepPar-1, arginase-1	**Hepatocellular carcinoma**
Ki-67 (MIB-1)	Proliferation index (near 100% in Burkitt)

- Common translocations in solid tumours: **Ewing sarcoma t(11;22) EWSR1::FLI1**; **synovial sarcoma t(X;18) SS18::SSX**; alveolar rhabdomyosarcoma t(2;13) PAX3::FOXO1; myxoid liposarcoma t(12;16); clear-cell sarcoma t(12;22); desmoplastic small round-cell tumour t(11;22) EWSR1::WT1; dermatofibrosarcoma protuberans t(17;22) COL1A1::PDGFB.

Related histology

- **Rheumatic fever** follows **group A streptococcal pharyngitis** (not skin infection) by 2–3 weeks; **molecular mimicry** between the **M protein** and cardiac myosin and valve glycoproteins (type II); **Aschoff bodies** are pathognomonic of the acute phase; **mitral valve** the most affected (then aortic): acute small **verrucous vegetations along the lines of closure**; chronic: **fish-mouth or buttonhole stenosis**, fused commissures and short, thick chordae. **Revised Jones criteria (AHA 2015)**, with separate thresholds for low-risk and moderate-to-high-risk populations, and echocardiographic (subclinical) carditis counted as carditis. Rheumatic heart disease remains common in South Asia, unlike the West.
- **Infective endocarditis**: **bulky, friable vegetations containing organisms**, destroying the valve (acute: Staph. aureus on normal valves, tricuspid in injecting drug users; subacute: viridans streptococci on damaged valves; HACEK and Coxiella in culture-negative cases); **modified Duke criteria (2023 ISCVID update)**. Compare **NBTE** (small, sterile, along the lines of closure, in cancer) and **Libman–Sacks** (SLE, both surfaces).
- **Liver acinus zones**: **zone 1 (periportal)**, the best oxygenated, is hit first in **viral hepatitis** (the exam answer, as in First Aid; Robbins notes acute hepatitis injury is often most marked around the central vein) and by phosphorus poisoning and is where portal inflammation starts; **zone 2 (midzonal)** in **yellow fever**; **zone 3 (centrilobular)**, the least oxygenated and richest in cytochrome P450, suffers **ischaemia, chronic passive congestion (nutmeg liver), alcohol, paracetamol and carbon tetrachloride**.
- **Germ-cell histology**: **seminoma** sheets of uniform clear cells with lymphocytes in the septa; **dysgerminoma** is its ovarian twin; **embryonal carcinoma** pleomorphic, CD30-positive, AFP and hCG variable; **choriocarcinoma** cytotrophoblast with syncytiotrophoblast and very high hCG; **yolk sac** Schiller–Duval bodies with AFP.
- **Frozen section**: for intraoperative diagnosis (margins, nodes, nature of a lesion) in about 15–20 minutes; **fat stains need frozen sections**; **10% neutral buffered formalin** (formaldehyde 4%) is the standard fixative; **Bouin's** for testis biopsies; **FNAC** cannot diagnose follicular carcinoma (needs capsular or vascular invasion); thyroid cytology by the **Bethesda system** (2023, third edition), cervical cytology by **Bethesda** (LSIL, HSIL); **liquid-based cytology** and **HPV testing** now lead cervical screening (WHO 2021 recommends HPV DNA testing as the primary screen).

Organ pathology: bone, joint, soft tissue, muscle and skin

- **Fracture healing**: haematoma (days 1–3) → **soft (fibrocartilaginous) callus** (about weeks 1–2) → **hard (woven-bone) callus** (from about weeks 3–4) → **remodelling** into lamellar bone along lines of stress over months. Delay or non-union: movement, infection, poor blood supply, interposed soft tissue, smoking, diabetes.

Bone

Disorder	Key points
Pyogenic osteomyelitis	**Staph. aureus** most often (**Salmonella in sickle-cell disease**; Pseudomonas after a puncture wound through a shoe); haematogenous in children at the **metaphysis** (slow sinusoidal flow); **sequestrum** (dead bone), **involucrum** (new bone sheath), cloaca, **Brodie abscess** (subacute); late: sinus with **squamous carcinoma (Marjolin)**, secondary amyloidosis
Tuberculosis of bone	Spine (**Pott disease**: anterior vertebral collapse, gibbus, **psoas cold abscess**); the **disc space is involved early in pyogenic spondylodiscitis but relatively spared early in TB**
Osteoporosis	Less bone of **normal mineralisation** (osteomalacia: normal amount, unmineralised osteoid); **type I** post-menopausal (trabecular: vertebra, distal radius), **type II** senile (hip); **WHO: T score −2.5 or less**; **calcium, phosphate and ALP normal**

Disorder	Key points
Rickets and osteomalacia	Defective mineralisation (vitamin D lack): **widened, cupped growth plates, rachitic rosary, Harrison groove, bowed legs, frontal bossing**; adults: **Looser zones (pseudofractures)**; calcium low or normal, **phosphate low, ALP high**
Hyperparathyroid bone (osteitis fibrosa cystica)	**Subperiosteal resorption of the radial side of the middle phalanges**, "salt and pepper" skull, **brown tumours** (giant cells with haemosiderin); calcium high, phosphate low, ALP high
Paget disease (osteitis deformans)	Lytic → mixed → sclerotic phases; **mosaic (jigsaw) cement lines**; thick but weak bone (skull, pelvis, spine, femur, tibia), elderly; **ALP very high, calcium and phosphate normal**; *SQSTM1*; deafness, fractures, high-output failure, **osteosarcoma in about 1%**
Fibrous dysplasia	**"Chinese-letter" woven-bone trabeculae without osteoblastic rimming** in fibrous stroma; activating **GNAS** (mosaic); **McCune–Albright**: polyostotic, café-au-lait spots, precocious puberty
Osteopetrosis	Failed osteoclast resorption (carbonic anhydrase II, *CLCN7*): dense brittle "marble" bone, **Erlenmeyer-flask** femora, marrow failure, cranial-nerve palsies

Bone and cartilage tumours

Tumour	Age and site	Clues
Osteoma	Skull, face	Multiple in **Gardner syndrome**
Osteoid osteoma	Teenage boys, cortex of long bones	Nidus under 2 cm; **night pain relieved by aspirin or NSAIDs** (prostaglandin)
Osteosarcoma	**10–20 years, metaphysis around the knee**; second peak in the old with Paget disease or after radiation	**Malignant cells making osteoid**; **Codman triangle and sunburst** periosteal reaction; *RB1* (hereditary retinoblastoma), *TP53* (Li–Fraumeni); spreads to **lung**
Osteochondroma	Metaphysis, teenagers; **the commonest benign bone tumour**	Stalk **capped by cartilage, pointing away from the joint**; *EXT1/EXT2*; malignant change about 1% (higher in hereditary multiple exostoses)
Enchondroma	**Small bones of hands and feet**	Multiple in **Ollier**, with haemangiomas in **Maffucci**; *IDH1/2*
Chondrosarcoma	Adults, **pelvis, shoulder, proximal femur**	Malignant cartilage; behaviour follows grade
Giant cell tumour	**20–40 years, epiphysis** (distal femur, proximal tibia, distal radius)	Osteoclast-like giant cells among neoplastic stromal cells that make **RANKL** (hence **denosumab**); **"soap-bubble"** lytic lesion; *H3F3A* G34W; locally aggressive, rarely to lung
Ewing sarcoma	Children, **diaphysis** of long bones, pelvis	**Small round blue cells** with glycogen (PAS positive, diastase sensitive), **CD99**, **t(11;22) EWSR1::FLI1**; **"onion-skin"** periosteum; fever and high ESR mimic osteomyelitis

Joints

Disease	Pathology
Osteoarthritis	Degenerative cartilage failure: **joint-space loss, subchondral sclerosis and cysts, osteophytes, eburnation**; **Heberden (DIP) and Bouchard (PIP) nodes**; hip, knee, first CMC; spares wrist and MCP
Rheumatoid arthritis	Autoimmune synovitis with lymphoid follicles and plasma cells; **pannus** erodes cartilage and bone; symmetrical small joints, **DIP spared**; **anti-CCP (more specific) and RF**; **HLA-DR4**, *PTPN22*; **rheumatoid nodule: central fibrinoid necrosis ringed by palisading histiocytes**; Felty syndrome, AA amyloid
Tuberculous arthritis	Monoarticular (hip, knee); **Phemister triad**: periarticular osteoporosis, peripheral erosions, slow joint-space loss
Septic arthritis	**Staph. aureus**; **gonococcus** in sexually active young adults; synovial fluid **over 50,000 white cells/μL, mostly neutrophils**
Gout	Monosodium urate: **needle-shaped, negatively birefringent** crystals (**yellow when parallel** to the compensator); **tophus** (urate with a foreign-body giant-cell reaction) in ear helix, tendons; **first MTP (podagra)**
Pseudogout	**Calcium pyrophosphate: rhomboid, weakly positively birefringent**; chondrocalcinosis, knee

Soft tissue and muscle

Tumour	Clues
Lipoma	**The commonest soft-tissue tumour**
Liposarcoma	Adults, **retroperitoneum** and thigh; **lipoblasts**; well-differentiated and dedifferentiated: **MDM2 and CDK4 amplification**; myxoid: t(12;16) FUS::DDIT3
Nodular fasciitis	Fast-growing, self-limited, young adults; *USP6*; benign mimic of sarcoma
Desmoid (fibromatosis)	β-catenin or *APC* (**Gardner**); locally recurrent, never metastasises
Undifferentiated pleomorphic sarcoma	The current name for **malignant fibrous histiocytoma**
Rhabdomyosarcoma	**The commonest soft-tissue sarcoma of children**; **embryonal** (head and neck, genitourinary; **sarcoma botryoides** in the vagina and bladder) and **alveolar** (limbs, **t(2;13) PAX3::FOXO1**, worse); **desmin, myogenin, MyoD1**
Synovial sarcoma	Not from synovium; young adults near large joints; biphasic or monophasic spindle; **t(X;18) SS18::SSX**; cytokeratin, EMA, TLE1

- Sarcomas spread by **blood (lung first)**, rarely to nodes; **grade (FNCLCC: differentiation, mitoses, necrosis)** is the strongest predictor of metastasis, with size and depth.
- **Duchenne dystrophy**: X-linked, **dystrophin (Xp21) absent**, frameshift deletions; onset 3–5 years, **Gowers sign, calf pseudohypertrophy** (fat and fibrosis), CK very high, cardiomyopathy; biopsy: fibre-size variation, necrosis and regeneration, endomysial fibrosis. **Becker**: in-frame mutation, reduced dystrophin, milder. **Myotonic dystrophy**: **CTG repeat in *DMPK***, anticipation, myotonia, cataract, frontal balding, testicular atrophy, conduction block. Others: **limb-girdle** (sarcoglycans, autosomal), **Emery–Dreifuss** (emerin, lamin A/C: early contractures, conduction block), **facioscapulohumeral** (4q35, *DUX4*).
- **Inflammatory myopathies**: **dermatomyositis** (**perifascicular atrophy**, complement-mediated capillary loss, Gottron papules, heliotrope rash, **underlying cancer**); **polymyositis** (**CD8 T cells invading fibres** in the endomysium); **inclusion body myositis** (older men, **rimmed vacuoles**, finger flexors and quadriceps).

Skin

Disease	Pathology
Eczema (dermatitis)	**Spongiosis** (intercellular oedema) with a perivascular lymphocytic infiltrate; chronic: acanthosis, lichenification; allergic contact is type IV (nickel)

Disease	Pathology
Psoriasis	**Parakeratosis, loss of the granular layer, regular acanthosis, thin suprapapillary plates over dilated vessels (Auspitz sign), Munro microabscesses** (neutrophils in the stratum corneum); Koebner; HLA-C*06; IL-23/Th17
Lichen planus	**Purple polygonal pruritic papules, Wickham striae**; **saw-tooth rete ridges, hypergranulosis, band-like lymphocytic infiltrate at the junction, basal vacuolar change, Civatte bodies**; oral lesions, hepatitis C
Pemphigus vulgaris	IgG to **desmoglein 3** (and 1): **suprabasal acantholysis with a "tombstone" row of basal cells**; **intercellular "fishnet" IgG**; flaccid bullae, **Nikolsky positive**, **oral lesions first**; foliaceus: desmoglein 1, subcorneal, no mucosa
Bullous pemphigoid	IgG to **BP180 and BP230 (hemidesmosomes)**: **subepidermal blister with eosinophils, linear IgG and C3 along the basement membrane**; tense bullae, elderly, mucosa usually spared
Dermatitis herpetiformis	**Coeliac disease; granular IgA in dermal papillae**, papillary neutrophil microabscesses; extensor vesicles; dapsone
Lupus (skin)	**Interface dermatitis**, basement-membrane thickening, dermal mucin; **lupus band** (IgG and C3 at the junction); discoid scars with follicular plugging
Basal cell carcinoma	**The commonest skin cancer**; pearly rolled edge, telangiectasia (**rodent ulcer**); **basaloid nests with peripheral palisading and retraction clefts**; **hedgehog (*PTCH1*)**, Gorlin syndrome; **locally invasive, almost never metastasises**
Squamous cell carcinoma	Sun, **actinic keratosis**, scars and chronic ulcers (**Marjolin ulcer**), arsenic, immunosuppression; keratin pearls; may reach nodes
Melanoma	Radial then **vertical growth phase**; **Breslow thickness, the most important prognostic factor**; **BRAF V600E** in about half; S100, SOX10, HMB-45, Melan-A; **acral lentiginous the commonest type in dark-skinned people**
Others	**Naevi**: junctional (at the junction), compound, intradermal (dermis only); **dysplastic naevus** (*CDKN2A*, familial melanoma); seborrhoeic keratosis ("stuck-on", horn cysts; sudden eruption = **Leser–Trélat sign**); Merkel cell carcinoma (polyomavirus, perinuclear dot CK20); mycosis fungoides (**Pautrier microabscesses**)

- **Leprosy**: **tuberculoid** (strong Th1, well-formed granulomas along nerves, few bacilli, **lepromin positive**, few asymmetric anaesthetic patches) versus **lepromatous** (weak cellular immunity, **foamy Virchow (lepra) cells packed with bacilli (globi)**, **clear Grenz zone**, symmetrical nodules, leonine facies, **lepromin negative**); **type 1 (reversal) reaction** is delayed hypersensitivity, **type 2 (erythema nodosum leprosum) is type III (immune complex)**; *M. leprae* does not grow in culture (mouse footpad, armadillo); WHO 2018 uses **three-drug MDT (rifampicin, clofazimine, dapsone) for both forms**, 6 months paucibacillary and 12 months multibacillary. Nepal declared leprosy eliminated as a public-health problem (under 1 per 10,000) in 2010.

Organ pathology: nervous system, eye, ear, nose and throat

CSF in meningitis

	Cells	Protein	Glucose	Other
Bacterial	**Neutrophils**, hundreds to thousands	High	**Low** (under 40% of blood)	Turbid; neonates: group B streptococcus, E. coli, Listeria; older: **pneumococcus, meningococcus** (Waterhouse–Friderichsen)
Viral	**Lymphocytes**	Normal or mildly high	**Normal**	Enteroviruses the commonest
Tuberculous	**Lymphocytes**	**Very high**	**Low**	**Cobweb clot**; **basal exudate**, cranial-nerve palsies (VI), hydrocephalus, endarteritis with infarcts; **tuberculoma** is a ring-enhancing caseous mass
Cryptococcal	Lymphocytes	High	Low	HIV; **India ink, cryptococcal antigen**

- **Encephalitis**: **HSV-1, haemorrhagic necrosis of the temporal lobes**, Cowdry A inclusions; rabies, **Negri bodies**; **Japanese encephalitis** (Culex, pigs and herons; **thalamus and basal ganglia**; endemic in Nepal's Terai; JE vaccine is in Nepal's national schedule); polio, anterior horn cells.
- **Hydrocephalus**: **non-communicating** (aqueduct stenosis, posterior fossa tumours, Chiari II, Dandy–Walker) versus **communicating** (arachnoid granulations scarred after meningitis or subarachnoid bleeding); **normal pressure hydrocephalus: gait, dementia, incontinence**.

Cerebrovascular disease and trauma

- **Infarct evolution**: **red (eosinophilic) neurons at 12–24 hours**, neutrophils over the next days, **macrophages (gitter cells) from about day 3**, then **liquefactive necrosis leaving a cyst** with gliosis. Global hypoperfusion gives **watershed** infarcts and laminar necrosis.
- **Hypertensive haemorrhage**: **Charcot–Bouchard microaneurysms of the lenticulostriate arteries: putamen (commonest), thalamus, pons, cerebellum**; lobar haemorrhage in the elderly: **amyloid angiopathy**; **lacunes** from hyaline arteriolosclerosis.
- **Subarachnoid haemorrhage**: **berry aneurysm**, commonest at the **anterior communicating artery**; adult polycystic kidney disease, Ehlers–Danlos, coarctation; vasospasm at 3–14 days.
- **Extradural**: middle meningeal artery, temporal fracture, **lucid interval, biconvex**; **subdural**: **bridging veins**, elderly and alcoholics, **crescentic**.

CNS tumours (WHO 2021, fifth edition: histology plus molecular markers)

Tumour	Clues
Glioblastoma, IDH-wildtype (grade 4)	**The commonest primary malignant brain tumour of adults**; **pseudopalisading necrosis and microvascular (glomeruloid) proliferation**; "butterfly" across the corpus callosum; **EGFR amplification, TERT promoter mutation, +7/–10** define it even when the histology looks lower grade; **MGMT methylation** predicts temozolomide benefit

Tumour	Clues
Astrocytoma, IDH-mutant (grades 2–4)	Younger adults; *ATRX* loss, *TP53*; the old "secondary glioblastoma" is now astrocytoma, IDH-mutant, grade 4
Oligodendroglioma, IDH-mutant, 1p/19q-codeleted	**"Fried-egg" cells, "chicken-wire" capillaries, calcification**, frontal lobe; chemosensitive
Pilocytic astrocytoma (grade 1)	Children, **cerebellum**, cyst with mural nodule; **Rosenthal fibres, eosinophilic granular bodies**, biphasic; **KIAA1549::BRAF**
Ependymoma	Fourth ventricle in children, spinal cord in adults (NF2); **perivascular pseudorosettes**, true ependymal rosettes; myxopapillary at the filum terminale
Medulloblastoma	**The commonest malignant brain tumour of children; cerebellar vermis**; small round blue cells, **Homer Wright rosettes**; WNT (best), SHH, group 3 (*MYC*, worst), group 4; **drop metastases** through CSF
Meningioma	Adult women, dural-based (**dural tail**), hyperostosis; **whorls and psammoma bodies**, EMA; *NF2*
Schwannoma	**Cerebellopontine angle** (vestibular; bilateral in **NF2**); **Antoni A (Verocay bodies) and Antoni B**; S100 diffusely
Neurofibroma	**"Shredded-carrot" collagen**, mixed cells; **plexiform type is NF1's**, can become MPNST
Others	**Metastases are the commonest brain tumours in adults** (lung, breast, melanoma, kidney; grey–white junction, multiple); **primary CNS lymphoma** (DLBCL, periventricular, HIV and EBV); **haemangioblastoma** (cerebellum, **VHL**, polycythaemia); **craniopharyngioma** (see Endocrine)

- **Neuropathy**: axonal (diabetes, alcohol, B_{12}, vincristine, isoniazid, arsenic) versus demyelinating (**Guillain–Barré**, CIDP, diphtheria, **Charcot–Marie–Tooth 1A: *PMP22* duplication**); **mononeuritis multiplex** in diabetes, vasculitis and leprosy.

Eye

- **Conjunctivitis and keratitis**: bacterial (purulent: Staph. aureus, pneumococcus, H. influenzae), **viral (adenovirus: follicles, epidemic keratoconjunctivitis)**, allergic (**papillae, eosinophils**); keratitis: bacterial, fungal (farm injury), **HSV dendritic ulcer**, **Acanthamoeba** (contact lenses).
- **Trachoma**: *Chlamydia trachomatis* A–C; follicles, conjunctival scarring, trichiasis, corneal opacity; SAFE strategy; **WHO validated Nepal's elimination of trachoma as a public-health problem in 2018**. Ophthalmia neonatorum: gonococcus (hyperacute), chlamydia.
- Uveitis: anterior (HLA-B27, JIA, sarcoidosis, TB, Behçet; keratic precipitates, hypopyon); posterior (toxoplasmosis; CMV retinitis in AIDS).
- **Retinoblastoma**: the commonest intraocular malignancy of children; **leukocoria**; ***RB1* (13q14), two hits; hereditary about 40% (bilateral, early), with later osteosarcoma**; **Flexner–Wintersteiner rosettes**, fleurettes.
- **Uveal melanoma**: the commonest primary intraocular tumour of adults; spreads by blood **to the liver**; *GNAQ/GNA11*, monosomy 3, *BAP1*.

Ear, nose and throat

Lesion	Pathology
Infections	**Acute otitis media** (pneumococcus, H. influenzae, Moraxella); **sinusitis** (ostiomeatal blockage; orbital cellulitis, cavernous sinus thrombosis); **mucormycosis** in diabetic ketoacidosis (vessel invasion, broad non-septate hyphae); tonsillitis (group A streptococcus: quinsy, rheumatic fever, glomerulonephritis); **diphtheria** (grey adherent pseudomembrane; toxin causes myocarditis and neuropathy)
Nasal polyp	Oedematous stroma with **many eosinophils**, respiratory epithelium, thick basement membrane; allergy, **aspirin-exacerbated disease (Samter triad)**; a nasal polyp in a child suggests **cystic fibrosis**
Rhinosporidiosis	*Rhinosporidium seeberi* (an aquatic protist of the Mesomycetozoea; ponds and river sand); **friable, strawberry-like bleeding polyp**; **large sporangia packed with endospores**; India and Sri Lanka, reported in Nepal; excision with cautery of the base, recurrence common
Vocal nodule	Voice abuse; **bilateral, at the junction of the anterior third and posterior two thirds of the cords**; Reinke oedema in smokers
Laryngeal carcinoma	Squamous; smoking and alcohol; **glottic the commonest, hoarseness early, few lymphatics, good prognosis**; supraglottic reaches nodes early. Juvenile laryngeal papillomatosis: **HPV 6 and 11**
Nasopharyngeal carcinoma	**EBV**; southern China and southeast Asia; **non-keratinising undifferentiated carcinoma with a dense lymphoid infiltrate** (lymphoepithelioma); a **neck node is often the first sign**, unilateral serous otitis media, cranial-nerve palsies; plasma EBV DNA for monitoring
Cholesteatoma	**Keratinising squamous epithelium and keratin in the middle ear** (no cholesterol, not a neoplasm); erodes ossicles and bone; marks **atticoantral (unsafe)** chronic otitis media, against tubotympanic (safe)

Organ pathology: respiratory system

- **Atelectasis**: **resorption** (obstruction by mucus or tumour; mediastinum shifts **towards** the collapse), **compression** (effusion, pneumothorax; shifts **away**), **contraction** (fibrosis); neonatal surfactant lack.

	Emphysema	Chronic bronchitis	Asthma	Bronchiectasis
Definition	Permanent enlargement of airspaces distal to the terminal bronchiole with wall destruction, **without obvious fibrosis**	Productive cough **3 months a year for 2 consecutive years**	Episodic reversible obstruction, hyperresponsive airways, **Th2**	Permanent bronchial dilation from infection with obstruction

	Emphysema	Chronic bronchitis	Asthma	Bronchiectasis
Pathology	**Centriacinar** (upper lobes, **smoking**), **panacinar** (**lower lobes**, **α1-antitrypsin deficiency**: PiZZ, unopposed neutrophil elastase, early in life and much worse with smoking; the liver shows **PAS-positive, diastase-resistant globules**), paraseptal (bullae, spontaneous pneumothorax)	**Reid index over 0.4** (mucous gland hypertrophy), goblet-cell metaplasia	**Mucus plugs, Curschmann spirals, Charcot–Leyden crystals**, eosinophils, thick basement membrane, smooth-muscle hypertrophy	Lower lobes; **cystic fibrosis, Kartagener**, TB, ABPA (central); "tram lines", signet-ring sign on CT
Clinical	**Pink puffer**, low DLCO	**Blue bloater**, cor pulmonale	Wheeze, nocturnal cough	Copious purulent sputum, haemoptysis, clubbing

- **Tuberculosis**: **primary**: **Ghon focus** (subpleural, lower upper lobe or upper lower lobe) **with hilar nodes = Ghon complex**, healed and calcified = Ranke complex; **secondary (reactivation)**: **apex** (high oxygen tension), **cavitation**, little nodal disease; **miliary** spread; granuloma of **epithelioid cells, Langhans giant cells (horseshoe nuclei) and caseation**, type IV (Th1, IFN-γ, TNF); **cord factor**; other forms: **tuberculous pleurisy**, laryngeal and **intestinal TB from swallowed sputum**, adrenal (Addison), spine (Pott), **cervical nodes (scrofula)**, meninges; diagnosis by smear, **Xpert MTB/RIF** and liquid culture.
- **Pneumonia**: **lobar** (pneumococcus): **congestion** → **red hepatisation** → **grey hepatisation** → **resolution**; **bronchopneumonia** (patchy, bilateral, basal; Staph. aureus, Klebsiella, H. influenzae); **interstitial (atypical)** (Mycoplasma, viruses; alveolar-wall lymphocytes, hyaline membranes); **aspiration**: right lower lobe (posterior upper-lobe and superior lower-lobe segments when supine), anaerobes, abscess; *Pneumocystis* in AIDS (foamy exudate, silver stain).
- **ARDS (Berlin 2012)**: within a week, bilateral opacities, **PaO_2/FiO_2 300 or less** on PEEP, not cardiac; **diffuse alveolar damage with hyaline membranes** (exudative, proliferative, fibrotic phases).

Pneumoconiosis	Dust	Pathology
Anthracosis	Carbon	Harmless pigment
Coal workers'	Coal	Macules and nodules (upper lobes) → **progressive massive fibrosis**; **Caplan syndrome** with rheumatoid arthritis
Silicosis	Silica (mining, quarrying, stone-crushing, sandblasting)	**Whorled hyalinised nodules with weakly birefringent particles**, upper lobes; **eggshell calcification of hilar nodes**; **raised risk of TB**, lung cancer
Asbestosis	Asbestos (insulation, ship-building, brake linings)	**Lower-lobe interstitial fibrosis; asbestos (ferruginous) bodies: golden-brown beaded rods, Prussian-blue positive**; **parietal pleural plaques** (the commonest lesion); **mesothelioma** and **lung carcinoma** (smoking multiplies the lung-cancer risk, not the mesothelioma risk)
Berylliosis	Beryllium	Non-caseating granulomas, mimics sarcoidosis
Byssinosis	Cotton	"Monday chest tightness"
Hypersensitivity pneumonitis (farmer's lung)	Thermophilic actinomycetes in mouldy hay	Types III and IV; interstitial lymphocytes, **poorly formed non-caseating granulomas**

- **Lung cancer**: smoking (85–90%), radon, asbestos, arsenic; **biomass cooking smoke matters in South Asia, for women who have never smoked**.

Type	Site and clues
Adenocarcinoma	**The commonest type now; peripheral; women and non-smokers**; TTF-1, napsin A; driver mutations tested (**EGFR, ALK, ROS1, KRAS G12C, BRAF, MET, RET, NTRK**) with PD-L1; **adenocarcinoma in situ and lepidic** replace "bronchioloalveolar"; precursor atypical adenomatous hyperplasia
Squamous cell	**Central**, keratin pearls, p40; **cavitates**; **PTHrP hypercalcaemia**
Small-cell	**Central, strongest smoking link**; small cells, **nuclear moulding, crush artefact**, synaptophysin, chromogranin, TTF-1; early spread; **ACTH, SIADH, Lambert–Eaton**; limited versus extensive stage
Large-cell	Undifferentiated, peripheral

- Local effects: **Pancoast tumour (Horner syndrome, brachial plexus)**, SVC obstruction, recurrent laryngeal palsy; adenocarcinoma gives **hypertrophic pulmonary osteoarthropathy** and migratory thrombophlebitis. Screening: annual **low-dose CT** for heavy smokers 50–80 (USPSTF 2021).
- **Pleura**: fibrinous pleurisy (friction rub), effusions (transudate or exudate by Light's criteria), **empyema** (pus; pleural fluid pH under 7.2 needs drainage), tuberculous pleurisy (lymphocytic exudate, high adenosine deaminase).
- **Mesothelioma**: asbestos, latency 20–40 years; encasing "rind"; epithelioid, sarcomatoid, biphasic; **calretinin, WT1, CK5/6, D2-40 positive; TTF-1 and CEA negative**; *BAP1* loss.
- **Idiopathic pulmonary fibrosis**: **usual interstitial pneumonia**: patchy subpleural basal fibrosis, **fibroblastic foci**, honeycombing; Velcro crackles, clubbing. Sarcoidosis: non-caseating granulomas, bilateral hilar nodes, raised ACE and calcium.

Organ pathology: cardiovascular system

- **Hypertension** (140/90 or more, ESH 2023 and ESC 2024; 130/80 in ACC/AHA 2017): **essential in about 90–95%**; secondary: renal parenchymal disease, renal artery stenosis, primary aldosteronism, phaeochromocytoma, Cushing, coarctation. Vessels: **hyaline arteriolosclerosis** (benign hypertension, diabetes) versus **hyperplastic "onion-skin" arteriolosclerosis with fibrinoid necrosis** (malignant: diastolic usually over 120 mmHg, papilloedema). Kidney: **benign nephrosclerosis** (symmetrically small, finely granular) versus malignant (**"flea-bitten"** petechiae). Heart: **concentric left ventricular hypertrophy**. **Cor pulmonale**: right ventricular

hypertrophy and failure from **pulmonary hypertension** of lung disease (COPD, fibrosis, high altitude).

- **Ischaemic heart disease**: stable angina (fixed stenosis over about 70%), unstable angina (plaque disruption with non-occlusive thrombus, no troponin rise), **Prinzmetal angina** (spasm at rest, transient ST elevation), MI, sudden cardiac death (ventricular fibrillation). **Culprit arteries: LAD 40–50%** (anterior wall, apex, anterior two thirds of the septum), **RCA 30–40%** (inferior and posterior wall, posterior septum, right ventricle), **circumflex 15–20%** (lateral wall). **Subendocardial infarcts** follow global hypoperfusion (the inner layer is the least perfused).
- **Cells in a myocardial infarct** (the full timeline is in Haemodynamics, Infarction): **neutrophils dominate at 1–3 days**, **macrophages at 3–7 days** (the softest stage, when **rupture** peaks), **granulation tissue from 7–10 days**, a dense scar by about 2 months. **Troponin** stays raised 7–10 days; **CK-MB** is normal again by 2–3 days, so it marks **reinfarction**.
- **Complications of MI**: arrhythmia (the commonest cause of early death), cardiogenic shock, **rupture at 3–7 days** (free wall: tamponade; septum: new murmur; papillary muscle: acute mitral regurgitation), **fibrinous pericarditis at 2–3 days** and **Dressler syndrome** weeks later (autoimmune), mural thrombus, **ventricular aneurysm** (late; persistent ST elevation).

Valve disease	Pathology
Rheumatic heart disease (pathology, vegetations and Jones 2015 in Related histology above)	**Pancarditis** with **"bread-and-butter" fibrinous pericarditis**; **Jones major criteria: carditis, migratory polyarthritis, Sydenham chorea, erythema marginatum, subcutaneous nodules**; chronic **mitral stenosis**: left atrial enlargement, atrial fibrillation and mural thrombus, haemoptysis, hoarseness (Ortner)
Infective endocarditis (organisms and Duke criteria in Related histology above)	Vegetations sit on the **low-pressure side** of the jet; **Roth spots, Osler nodes (painful, immune), Janeway lesions (painless, embolic)**, splinter haemorrhages, **focal glomerulonephritis** (immune complexes), septic emboli and mycotic aneurysms
Carcinoid heart	**Right-sided** (tricuspid, pulmonary) plaque-like fibrosis; liver metastases

Myocardium and pericardium	Pathology
Myocarditis	**Coxsackie B** commonest, Chagas, diphtheria toxin, drugs (eosinophilic), giant-cell; **Dallas criteria**: inflammatory infiltrate with adjacent myocyte necrosis
Dilated cardiomyopathy	The commonest; genetic (**titin,** *TTN*), alcohol, myocarditis, **doxorubicin**, peripartum; four-chamber dilation, systolic failure
Hypertrophic cardiomyopathy	Autosomal dominant sarcomere genes (**β-myosin heavy chain, myosin-binding protein C**); **asymmetric septal hypertrophy, myofibre disarray**; dynamic outflow obstruction; **sudden death in young athletes**
Restrictive cardiomyopathy	**Amyloid**, sarcoidosis, haemochromatosis, radiation, **endomyocardial fibrosis** (tropical, children), Loeffler endocarditis
ARVC	Desmosome genes; **fibrofatty replacement of the right ventricle**; sudden death
Takotsubo	Catecholamine surge after stress; **apical ballooning**; reversible

Myocardium and pericardium	Pathology
Pericarditis	**Fibrinous** (uraemia, MI, rheumatic, SLE, viral), purulent, haemorrhagic (TB, cancer), **caseous (TB)** → **constrictive pericarditis** (Kussmaul sign, pericardial knock, calcification)
Cardiac tumours	**Metastases outnumber primaries**; **myxoma** the commonest primary in adults (**left atrium**, ball-valve "tumour plop", fever and IL-6; stellate cells in myxoid stroma; Carney complex); **rhabdomyoma** the commonest in children (**tuberous sclerosis**)

- **Congenital heart disease**: **VSD the commonest**; then ASD (secundum), PDA; **tetralogy of Fallot the commonest cyanotic lesion after infancy** (VSD, overriding aorta, pulmonary stenosis, RVH; **boot-shaped heart**), **transposition the commonest cyanotic lesion in the newborn**; left-to-right shunts can reverse (**Eisenmenger syndrome**); associations: **rubella (PDA, pulmonary artery stenosis)**, **Down syndrome (AV septal defect)**, **Turner (coarctation, bicuspid aortic valve)**, **22q11 deletion (conotruncal defects)**, lithium (Ebstein), maternal diabetes (transposition); most are multifactorial. **Prostaglandin E_1 keeps the duct open; indomethacin closes it**.
- **Atherosclerosis**: endothelial injury → **LDL entry and oxidation** → monocytes become **foam cells** → smooth-muscle migration and **fibrous cap** over a necrotic lipid core with cholesterol clefts; **fatty streaks begin in childhood**; **plaque rupture with thrombosis** causes most acute events (thin caps, many macrophages); **abdominal aorta most affected**, then coronaries, popliteal, internal carotids, circle of Willis; modifiable risks: LDL, smoking, hypertension, diabetes; also lipoprotein(a), hs-CRP.

Vasculitis (Chapel Hill 2012)	Key points
Giant cell (temporal) arteritis	Over 50; **granulomatous inflammation with a fragmented internal elastic lamina**; jaw claudication, **sudden blindness**, high ESR; **skip lesions, so a long biopsy**; steroids at once; polymyalgia rheumatica
Takayasu arteritis	**Young Asian women**; aorta and arch branches ("pulseless disease"); granulomatous
Polyarteritis nodosa	Medium arteries; **segmental transmural fibrinoid necrosis**, lesions of different ages; kidney, gut, nerves, skin; **spares the lungs**; **hepatitis B** in some; **ANCA negative**; microaneurysms
Kawasaki disease	Children under 5; fever 5 days or more, conjunctivitis, strawberry tongue, rash, cervical node, desquamation; **coronary aneurysms**; IVIG and aspirin
Granulomatosis with polyangiitis	**PR3-ANCA (c-ANCA)**; necrotising granulomas of the upper and lower airways, **pauci-immune glomerulonephritis**
Microscopic polyangiitis	**MPO-ANCA (p-ANCA)**; no granulomas; lung haemorrhage and glomerulonephritis
Eosinophilic granulomatosis with polyangiitis	**Asthma, eosinophilia**, MPO-ANCA in about 40%
IgA vasculitis (Henoch–Schönlein)	Children; palpable purpura of buttocks and legs, arthralgia, abdominal pain, **mesangial IgA nephritis**

Vasculitis (Chapel Hill 2012)	Key points
Buerger disease (thromboangiitis obliterans)	**Young heavy smokers** (bidi and hookah included); **segmental thrombosing inflammation of small and medium arteries and veins of the limbs, with microabscesses in the thrombus and a preserved vessel wall**; claudication, gangrene of digits, migratory thrombophlebitis; **stopping smoking is the only effective treatment**

- **Aneurysms**: true (all three layers) versus **false** (haematoma walled by adventitia); **abdominal aortic aneurysm** (atherosclerosis; below the renal arteries, older male smokers; repair at **5.5 cm**); **syphilitic** (**ascending aorta**; **obliterative endarteritis of the vasa vasorum**, "tree-bark" intima, aortic regurgitation, cor bovinum); berry (cerebral); mycotic (infected); **Rasmussen aneurysm** (a pulmonary artery branch in the wall of a tuberculous cavity: haemoptysis); the **splenic artery** is the commonest visceral aneurysm, the **popliteal** the commonest peripheral one.
- **Aortic dissection**: intimal tear with blood tracking in the media; **hypertension** (most), **cystic medial degeneration** (**Marfan, fibrillin-1**; Ehlers–Danlos; bicuspid aortic valve); **Stanford A** (ascending: surgery) versus **B** (descending: medical); tearing pain to the back, **wide mediastinum**, unequal pulses.
- **Heart failure**: reduced ejection fraction (40% or less) versus preserved; **left-sided: pulmonary congestion, "heart failure cells" (haemosiderin-laden alveolar macrophages), brown induration**; **right-sided: nutmeg liver, congestive splenomegaly, ascites, ankle oedema**; high-output: anaemia, thyrotoxicosis, **wet beriberi**, Paget, AV fistula; **BNP and NT-proBNP** raised.

Organ pathology: gastrointestinal tract, liver and pancreas

Mouth, salivary glands and oesophagus

- **Leukoplakia**: a white patch not scraped off and not another disease; dysplasia or worse in a minority (about 5–25%), malignant change in a few per cent; tobacco, **betel quid and areca nut**, alcohol; floor of mouth and ventral tongue carry the highest risk. **Erythroplakia** is rarer and far more dangerous: **most show dysplasia or carcinoma**. **Oral submucous fibrosis** (areca nut; trismus) is premalignant.
- **Oral squamous cell carcinoma**: lateral tongue and floor of mouth; in South Asia, where tobacco and areca are chewed, among the commonest cancers in men (the commonest in Indian men, GLOBOCAN 2022); **depth of invasion** enters the T stage (AJCC 8th).
- **Sialadenitis**: **mumps** (parotid; orchitis, pancreatitis, meningitis); bacterial (Staph. aureus, dehydration, stone); **Sjögren syndrome** (lymphocytic sialadenitis with **lymphoepithelial lesions**, **anti-Ro and anti-La**, **MALT lymphoma** risk). **Stones form most in the submandibular gland** (alkaline, mucous, viscous saliva; uphill duct).
- **Salivary tumours**: about 80% in the parotid, most of them benign; **the smaller the gland, the likelier a tumour is malignant**.

Tumour	Points
Pleomorphic adenoma	**The commonest salivary tumour** (parotid); **epithelial and myoepithelial cells in myxoid and chondroid stroma**; **incomplete capsule with pseudopods, so it recurs after enucleation**; *PLAG1*; carcinoma ex pleomorphic adenoma rarely
Warthin tumour	**Parotid only, older men who smoke**; bilateral or multifocal in about 10%; **double layer of oncocytic epithelium over lymphoid stroma**; **hot on technetium scan**
Mucoepidermoid carcinoma	**The commonest salivary malignancy** (parotid; and in children); mucous, intermediate and epidermoid cells; **CRTC1::MAML2**
Adenoid cystic carcinoma	**The commonest malignancy of the submandibular and minor salivary glands**; **cribriform (Swiss-cheese)**; **perineural invasion** (pain, facial palsy); late lung metastases; *MYB::NFIB*

- **Oesophagus**: **reflux oesophagitis** (basal-zone hyperplasia, long papillae, intraepithelial eosinophils and neutrophils); **eosinophilic oesophagitis** (**15 or more eosinophils per high-power field**, rings and furrows, food bolus impaction, atopy); infections (Candida, HSV punched-out ulcers, CMV deep linear ulcers); **achalasia** (**loss of myenteric ganglion cells**; incomplete LES relaxation; bird's-beak; Chagas disease); **Mallory–Weiss** mucosal tear versus **Boerhaave** full-thickness rupture; **varices** of portal hypertension.
- **Barrett oesophagus**: **intestinal metaplasia (goblet cells) replacing squamous mucosa** of the distal oesophagus after long reflux; male, white, obese; **precursor of adenocarcinoma** through dysplasia (about 0.1–0.5% a year without dysplasia); surveillance biopsies, **ablation for dysplasia**.
- **Oesophageal carcinoma**: **squamous cell carcinoma the commonest worldwide and in Asia** (**middle third**; tobacco, alcohol, **very hot drinks**, achalasia, lye stricture, Plummer–Vinson, tylosis, nitrosamines, poor diet; highest in the "oesophageal cancer belt" from northern Iran to China and in north-east India); **adenocarcinoma** (**lower third**, from Barrett; now the commonest in the West); progressive dysphagia, solids first; poor prognosis.

Stomach

- **Gastritis**: acute (NSAIDs, alcohol, stress, shock: erosions; **uraemia**, where the **ammonia** from urea split by urease impairs the mucosa's defences (bicarbonate secretion) rather than raising acid); **chronic *H. pylori* (type B, the commonest)**: **antrum**, lymphoid follicles, neutrophils in active disease, intestinal metaplasia, atrophy; raises the risk of **peptic ulcer, adenocarcinoma and MALT lymphoma**; organisms in surface mucus (Giemsa, Warthin–Starry); tests: urea breath, stool antigen, rapid urease, histology. **Autoimmune (type A)**: **body and fundus, antrum spared**, antibodies to **parietal cells (H^+/K^+-ATPase) and intrinsic factor**, achlorhydria with **high gastrin**, **pernicious anaemia**, **ECL-cell hyperplasia and neuroendocrine tumours**, adenocarcinoma.
- **Peptic ulcer**: **duodenal (several times commoner; first part; anterior ulcers perforate, posterior ulcers bleed from the gastroduodenal artery; almost never malignant)** versus **gastric (lesser curvature at the antrum–body junction; biopsy to exclude cancer)**; *H. pylori* and NSAIDs; Zollinger–Ellison for multiple or distal ulcers. **Benign ulcer: punched out, flat margins, folds radiating to the edge, clean base**; malignant: heaped-up rolled edge, nodular necrotic base. Layers: necrotic debris, neutrophils, **granulation tissue, scar**. Complications: **bleeding (the commonest)**, perforation, obstruction. **Curling ulcer (burns)**, **Cushing ulcer (head injury)**.
- **Polyps**: hyperplastic (inflammatory) and **fundic gland polyps** (PPI use, FAP; now the commonest in countries where PPIs are widely used); adenomas carry cancer risk.

- **Gastric adenocarcinoma (Lauren)**: **intestinal type** (glands; **Correa cascade**: *H. pylori* gastritis → atrophy → intestinal metaplasia → dysplasia → carcinoma; older men; high-incidence regions such as Japan and Korea; smoked and salted food, nitrites) versus **diffuse type** (**signet-ring cells, loss of E-cadherin (*CDH1*), linitis plastica**, younger, hereditary diffuse gastric cancer: germline *CDH1*); ***TP53*** is the gene **most often mutated** across gastric cancers (about half); **early gastric cancer is confined to mucosa and submucosa, whatever the nodes**; spread: **Virchow node (Troisier sign), Sister Mary Joseph nodule, Krukenberg tumour, Blumer shelf**, peritoneum; **HER2**, **CLDN18.2** and PD-L1 are tested for treatment.
- **Gastric lymphoma** (MALT lymphoma regresses after *H. pylori* eradication; **t(11;18)** predicts no response) and **GIST** (the stomach is its commonest site; see Neoplasia).

Small and large intestine

- **Obstruction**: mechanical versus **paralytic ileus** (after surgery, peritonitis, low potassium); small bowel: **adhesions (the commonest)**, hernias, intussusception, volvulus; large bowel: **carcinoma (the commonest)**, sigmoid volvulus. **Intussusception**: **ileocolic in infants 6–18 months** (hypertrophied Peyer patches after a viral illness), a **lead point (polyp, tumour, Meckel)** in adults; colic, **"redcurrant jelly" stool**, sausage-shaped mass; venous obstruction leads to infarction. **Volvulus**: sigmoid in the elderly ("coffee-bean" film), midgut in malrotation. **Hirschsprung disease**: **no ganglion cells in the submucosal and myenteric plexuses** of a distal segment (*RET*); delayed meconium; **rectal suction biopsy** (no ganglion cells, more acetylcholinesterase-positive nerve fibres, absent calretinin).
- **Coeliac disease**: HLA-DQ2/DQ8, **anti-tTG IgA**; **intraepithelial lymphocytes, crypt hyperplasia, villous atrophy** (Marsh), worst in the duodenum; dermatitis herpetiformis; **enteropathy-associated T-cell lymphoma**. **Whipple disease**: *Tropheryma whipplei*, **PAS-positive foamy macrophages** in the lamina propria.
- **Acute appendicitis**: luminal obstruction (faecolith, lymphoid hyperplasia); **neutrophils in the muscularis propria are the diagnostic criterion**, periappendiceal fibrinopurulent exudate; perforation, abscess, **pylephlebitis**. **Neuroendocrine tumour is the commonest appendiceal tumour** (tip, incidental); appendiceal mucinous neoplasm → **pseudomyxoma peritonei**.
- **Intestinal tuberculosis**: **ileocaecal** region (lymphoid tissue, stasis); **ulcers transverse ("girdle"), healing into strictures**; hypertrophic (mass) form; caseating granulomas; in South Asia **the main mimic of Crohn disease** (in TB the granulomas are large, confluent and caseating, with AFB or a positive PCR or culture).
- **Amoebic colitis**: *Entamoeba histolytica*; caecum and ascending colon, rectosigmoid; **flask-shaped ulcers with undermined edges, trophozoites with ingested red cells**, little inflammation; **amoebic liver abscess** (right lobe, "anchovy-sauce" pus, trophozoites in the wall). **Shigella**: neutrophilic colitis, pseudomembranes.

	Crohn disease	Ulcerative colitis
Site	Mouth to anus, **terminal ileum** most; **skip lesions**	**Rectum always**, continuous proximally; colon only (backwash ileitis)
Depth	**Transmural**	**Mucosa and submucosa**
Gross	**Cobblestone mucosa, creeping fat, linear ulcers, strictures ("string sign"), fistulas, thick wall**	**Broad ulcers, pseudo-polyps, lead-pipe colon** (lost haustra), thin wall
Micro-scopy	**Non-caseating granulomas (about 35%)**, fissures, lymphoid aggregates	**Crypt abscesses, crypt distortion, Paneth cell metaplasia**, goblet-cell depletion; no granulomas
Complic-ations	Fistulae, strictures, malab-sorption (B_{12}, bile salts), **gall-stones and oxalate stones**, perianal disease	**Toxic megacolon**, **colorectal cancer** (duration, extent, PSC), **primary sclerosing cholangitis**
Associ-ations	**Smoking worsens**, *NOD2*, ASCA	**Smoking protects**, p-ANCA
Both	Arthritis, uveitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis	

- **Polyps**: **hyperplastic** (rectosigmoid, no risk); **hamartomatous**: **juvenile (retention) polyp**, the commonest polyp of childhood (mostly under 10; rectum; painless bleeding; may autoamputate): smooth, pedunculated, with **cystically dilated mucus-filled glands in an oedematous, inflamed lamina propria**; a solitary sporadic one has **no malignant potential**, while **juvenile polyposis** (*SMAD4*, *BMPR1A*; usually 5 or more polyps) carries a cancer risk; **Peutz–Jeghers** (*STK11*, lip pigmentation, **arborising smooth muscle**, intussusception, cancers at several sites), Cowden (*PTEN*); **adenomas**: tubular (most), tubulovillous, **villous (highest risk; rectum; hypokalaemia from mucus)**; risk rises with **size over 1 cm, villous change and high-grade dysplasia**; **sessile serrated lesions** (right colon; *BRAF*, CpG methylation).
- **Familial adenomatous polyposis**: ***APC* (5q21)**, autosomal dominant, **hundreds to thousands of adenomas** from adolescence, **cancer nearly certain by about 40** without colectomy; **Gardner** (osteomas, desmoids, epidermoid cysts, CHRPE); **Turcot** (brain tumours). **Lynch syndrome**: **mismatch-repair genes (*MLH1, MSH2, MSH6, PMS2*)**; right-sided, mucinous, **endometrial** and ovarian cancers; lifetime colorectal risk depends on the gene (highest, about 50%, for *MLH1* and *MSH2*); found by **MMR immunohistochemistry or MSI testing** of every colorectal cancer; *MLH1* promoter methylation (with *BRAF* mutation) means a sporadic tumour.
- **Colorectal carcinoma**: **chromosomal-instability pathway (about 85%)**: ***APC*** → ***KRAS*** → **loss of 18q (*SMAD4*)** → ***TP53*** (Vogelstein); **microsatellite-instability pathway** (Lynch, serrated lesions). **Left-sided: annular "napkin-ring", obstruction, altered habit, fresh blood**; **right-sided: polypoid, occult bleeding, iron-deficiency anaemia**. **Stage (TNM, AJCC 8th) is the best prognostic factor** (Dukes is the older system); spreads **first to the liver** (portal vein); **CEA for follow-up, not screening**; ***RAS/BRAF* status decides anti-EGFR treatment; MSI-high tumours respond to checkpoint inhibitors**.
- **Neuroendocrine tumours (carcinoids)**: ileum, appendix, rectum, lung; **carcinoid syndrome (flushing, diarrhoea, wheeze, right-heart valve fibrosis) needs liver metastases**, since the liver inactivates serotonin; **urinary 5-HIAA**, chromogranin A; "salt-and-pepper" chromatin; **WHO grade by Ki-67: G1 under 3%, G2 3–20%, G3 over 20%**.

Pancreas

- **Acute pancreatitis**: **gallstones and alcohol (about 80%)**, hypertriglyceridaemia (over 1,000 mg/dL), hypercalcaemia, ERCP, drugs, mumps, trauma; **intrapancreatic trypsin activation**; **enzymatic fat necrosis (chalky saponification with calcium)**, haemorrhage; **lipase (more specific) or amylase over 3 times normal**; **revised Atlanta (2012)**: mild, moderately severe, severe; **pseudocyst (after 4 weeks; no epithelial lining)**, walled-off necrosis, infected necrosis, ARDS, hypocalcaemia, DIC.
- **Chronic pancreatitis**: alcohol (the commonest); **tropical calcific pancreatitis** (South Asia, young, diabetes, large ductal stones; *SPINK1*); hereditary (*PRSS1*); cystic fibrosis; **autoimmune (IgG4-related, type 1)**; fibrosis, atrophy, **calcification, "chain of lakes" duct**; steatorrhoea, diabetes.
- **Pancreatic ductal adenocarcinoma**: **head in about 60–70%**: **painless obstructive jaundice with a palpable gallbladder (Courvoisier)**; body and tail present late with pain; ***KRAS* (over 90%), *CDKN2A*, *TP53*, *SMAD4***; smoking (the strongest risk), chronic pancreatitis, diabetes, *BRCA2*; precursor **PanIN** and IPMN; **CA 19-9**; **migratory thrombophlebitis (Trousseau)**; about 10% 5-year survival. **Cystic**: serous cystadenoma (older women, benign), **mucinous cystic neoplasm (women, tail, ovarian-type stroma)**, **IPMN** (duct-communicating), **solid pseudopapillary neoplasm** (young women, β-catenin). **Islet tumours**: **insulinoma the commonest functioning** (Whipple triad, mostly benign); gastrinoma (Zollinger–Ellison, **MEN1**).

Gallbladder and bile ducts

- **Gallstones**: **cholesterol** (the commonest in the West; female, fertile, fat, forty; oestrogen, rapid weight loss, ileal disease); **black pigment** (haemolysis, cirrhosis; radiopaque); **brown pigment** (infected bile ducts; East Asia).
- **Cholecystitis**: **acute calculous (about 90%)** after cystic-duct obstruction (empyema, gangrene, perforation; **emphysematous** in diabetics); **acalculous** in the critically ill; **chronic**: **Rokitansky–Aschoff sinuses**, muscle hypertrophy, fibrosis; **porcelain gallbladder**. **Ascending cholangitis**: **Charcot triad** (fever, jaundice, right upper quadrant pain), **Reynolds pentad** (plus shock and confusion).
- **Gallbladder carcinoma**: adenocarcinoma; older women; **gallstones the strongest risk**, porcelain gallbladder, anomalous pancreaticobiliary junction, *Salmonella typhi* carriage; **among the world's highest rates in the Gangetic plain of northern India**; often found after cholecystectomy; invades the liver. **Cholangiocarcinoma**: **PSC, liver flukes (*Opisthorchis, Clonorchis*)**, choledochal cysts, hepatolithiasis; **Klatskin tumour at the hilum**.

Liver

	HAV	HBV	HCV	HDV	HEV
Virus and spread	RNA, faecal–oral	**DNA**, blood, sex, **mother to child**	RNA, blood	Defective RNA, **needs HBsAg**	RNA, **faecal–oral (water)**; zoonotic genotypes
Chronicity	**Never**	**About 90% after neonatal infection**, under 5–10% in adults	**About 70–85%**	Superinfection mostly chronic; coinfection mostly clears	Only in the immunosuppressed
Cancer	No	**HCC, even without cirrhosis**	HCC through cirrhosis	Worsens HBV	No
Vaccine and notes	Vaccine; anti-HAV IgM	**Vaccine** (pentavalent, in Nepal's schedule)	**No vaccine**; direct-acting antivirals cure over 95%	HBV vaccine protects	Vaccine only in China; **fulminant in pregnancy (mortality up to 20–25%)**; water-borne outbreaks in Nepal, Kathmandu valley included

- **HBV serology**: **HBsAg** = infection; **anti-HBc IgM** = acute, and the only marker in the **window period**; **HBeAg and HBV DNA** = replication; **anti-HBs alone** = vaccination; anti-HBs with anti-HBc IgG = past infection.
- **Hepatitis histology**: acute: **ballooning, Councilman (acidophil) bodies, lobular disarray, lymphocytes, Kupffer-cell hyperplasia**, bridging necrosis in severe cases; chronic: **portal inflammation with interface hepatitis**, fibrosis graded and staged (METAVIR, Ishak); **ground-glass hepatocytes in chronic HBV** (finely granular pale-pink cytoplasm: **HBsAg in proliferated smooth ER**, stained by **orcein** or Victoria blue; the core antigen is nuclear); **steatosis and portal lymphoid aggregates in HCV**.
- **Alcohol-related liver disease**: **steatosis (macrovesicular, reversible) → alcoholic hepatitis (ballooning, Mallory–Denk bodies, neutrophils, perivenular and pericellular fibrosis; AST:ALT over 2) → micronodular cirrhosis**. **MASLD (2023)** has replaced NAFLD as the name, and **MASH** replaced NASH; the histology is the same.
- **Cirrhosis**: **diffuse bridging fibrosis with regenerative nodules**; micronodular (under 3 mm: alcohol, biliary obstruction, haemochromatosis) versus macronodular (viral, Wilson, α1-antitrypsin); causes: HBV (the leading one in Asia and Africa), alcohol, HCV, MASLD, autoimmune, PBC, PSC, haemochromatosis, Wilson, α1-antitrypsin, Budd–Chiari, cardiac; **portal hypertension (varices, ascites, splenomegaly, caput medusae), encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis (ascitic neutrophils 250/μL or more), HCC**; Child–Pugh and MELD.
- **Autoimmune liver disease**: **primary biliary cholangitis** (middle-aged women, **anti-mitochondrial antibody**, **florid duct lesion: granulomatous destruction of small interlobular ducts**, high ALP, ursodeoxycholic acid); **primary sclerosing cholangitis** (men, **ulcerative colitis**, **onion-skin periductal fibrosis**, beaded cholangiogram, cholangiocarcinoma risk); **autoimmune hepatitis** (ANA, anti-smooth-muscle, anti-LKM1; high IgG; **interface hepatitis rich in plasma cells**).
- **Liver tumours**: **metastases outnumber primaries**; **haemangioma the commonest benign tumour**; hepatic adenoma (oral contraceptives, bleeding); focal nodular hyperplasia (central stellate scar). **Hepatocellular carcinoma**: **HBV, HCV, cirrhosis, aflatoxin B1 (*TP53* codon 249)**, MASLD, alcohol; **AFP**; **arterial enhancement with washout on multiphase CT or MRI (LI-RADS) diagnoses it in cirrhosis without biopsy**; **invades portal and hepatic veins**; glypican-3, HepPar-1, arginase-1. **Fibrolamellar carcinoma**: young, no cirrhosis, normal AFP, lamellar fibrosis,

DNAJB1::PRKACA. **Hepatoblastoma**: **the commonest liver cancer of children (under 3)**, raised AFP, fetal and embryonal epithelium with mesenchyme, *CTNNB1*, **FAP and Beckwith–Wiedemann**.

Organ pathology: kidney and urinary tract

- **Acute kidney injury**: pre-renal (urea:creatinine over 20, **urine sodium under 20, FeNa under 1%**, concentrated urine), **intrinsic (acute tubular necrosis the commonest; FeNa over 2%, muddy-brown granular casts)**, post-renal; KDIGO stages. **Azotaemia** is raised urea and creatinine; **uraemia** is azotaemia with symptoms (pericarditis, encephalopathy, platelet dysfunction).
- **Chronic kidney disease**: GFR under 60 or damage for over 3 months (KDIGO G1–G5); **diabetes and hypertension the commonest causes**; small kidneys (**not in diabetes, amyloid or polycystic disease**); anaemia (low erythropoietin), **renal osteodystrophy** (high phosphate, low calcitriol, secondary hyperparathyroidism), acidosis, hyperkalaemia.
- **Nephritic syndrome**: haematuria with **red-cell casts**, hypertension, oliguria, proteinuria under 3.5 g/day. **Nephrotic syndrome**: **proteinuria over 3.5 g/day** (children: over 40 mg/m^2/hour), hypoalbuminaemia, oedema, hyperlipidaemia, **lipiduria (oval fat bodies, Maltese crosses)**; infections (IgG loss) and **thrombosis, especially renal vein (antithrombin III loss)**.
- **Mechanisms of glomerular injury**: circulating immune complexes (PSGN, lupus), **in situ complexes** (membranous: **anti-PLA2R**; the **Heymann nephritis** model), **anti-GBM antibody** (α3 chain of type IV collagen), **pauci-immune (ANCA)**, **alternative complement pathway** (C3 glomerulopathy), **podocyte injury** (minimal change, FSGS; nephrin in **congenital nephrotic syndrome of the Finnish type**, *APOL1* risk variants in people of African descent).

Disease	Clinical	Light microscopy	IF and EM
Post-streptococcal GN	Children, **1–3 weeks after pharyngitis, 3–6 weeks after skin infection**; nephritic; **low C3**, ASO or anti-DNase B; over 95% of children recover	**Diffuse hypercellular glomeruli with neutrophils** (endocapillary proliferation)	**Granular IgG and C3; subepithelial "humps"**
Rapidly progressive (crescentic) GN	Renal failure over days to weeks	**Crescents** (parietal cells, macrophages, fibrin) in most glomeruli	**Type I linear IgG** (anti-GBM; with lung haemorrhage = **Goodpasture**); **type II granular** (lupus, IgA, PSGN); **type III pauci-immune** (ANCA)
Minimal change disease	**The commonest nephrotic syndrome of children** (2–6 years); **selective proteinuria**; after infection or allergy; **Hodgkin lymphoma, NSAIDs**	**Normal**	**IF negative; EM: diffuse effacement of podocyte foot processes, the only change**; steroid-responsive, does not progress
FSGS	Adults; **the commonest nephrotic syndrome in people of African descent**; HIV (**collapsing variant**), heroin, obesity, reflux nephropathy, *APOL1*; steroid-resistant	**Sclerosis of parts of some glomeruli**	**IgM and C3 trapped in sclerotic segments**; foot-process effacement; progresses
Membranous nephropathy	**The commonest primary nephrotic syndrome in adults** (white adults); **primary: anti-PLA2R in about 70–80%** (THSD7A a few); secondary: **hepatitis B, SLE, solid cancers, drugs (NSAIDs, penicillamine, gold)**	**Diffusely thickened capillary walls**, no proliferation	**Granular IgG and C3, subepithelial deposits; silver stain "spikes" of new basement membrane between deposits ("spike and dome")**; renal vein thrombosis
Membranoproliferative GN	Nephritic–nephrotic; **hepatitis C with cryoglobulinaemia** (immune-complex type); C3 glomerulopathy (**C3 nephritic factor**; dense deposit disease); **low C3**	Lobular hypercellular glomeruli, **"tram-track" double contours**	Subendothelial deposits (immune-complex type); dense intramembranous deposits (dense deposit disease)
IgA nephropathy (Berger)	**The commonest glomerulonephritis worldwide**; young men; **gross haematuria 1–2 days after a mucosal infection (synpharyngitic)**; normal C3; about 20–40% progress over 20 years; **IgA vasculitis** is its systemic form	Mesangial proliferation	**Mesangial IgA (with C3)**
Alport syndrome	Mostly X-linked (*COL4A5*); **haematuria, sensorineural deafness, eye changes (anterior lenticonus)**	Interstitial foam cells	**EM: thin, then thick, split and laminated ("basket-weave") basement membrane**
Diabetic nephropathy	See Endocrine	**Kimmelstiel–Wilson nodules**, diffuse mesangial sclerosis	GBM thickening
Lupus nephritis	ISN/RPS classes I–VI	**Class IV (diffuse proliferative) the commonest and most severe: "wire loops"**	**"Full house" IF (IgG, IgA, IgM, C3, C1q); subendothelial deposits**; class V is membranous

- **Chronic glomerulonephritis**: symmetrically small, finely granular kidneys; hyalinised glomeruli, tubular atrophy, interstitial fibrosis.
- **Acute tubular necrosis**: **ischaemic** (shock, sepsis; patchy necrosis of the **straight proximal tubule and thick ascending limb**, with **breaks in the basement membrane (tubulorrhexis)**) versus **nephrotoxic** (aminoglycosides, contrast, cisplatin, amphotericin B, heavy metals, **ethylene glycol (oxalate crystals)**, myoglobin and haemoglobin; **proximal tubules, basement membrane intact**); **initiation, maintenance (oliguria), recovery (polyuria, hypokalaemia)**.
- **Acute interstitial nephritis**: drugs (penicillins, NSAIDs, **PPIs**, rifampicin, diuretics) about 2 weeks after starting; fever, rash, **eosinophilia and eosinophiluria**, white-cell casts; interstitial oedema with lymphocytes and eosinophils. **Papillary necrosis**: diabetes, obstruction, **sickle cell**, analgesics, acute pyelonephritis.

- **Pyelonephritis**: **acute** (ascending ***E. coli*** in most; obstruction, reflux, pregnancy, diabetes, catheters; **patchy interstitial suppuration with tubular neutrophil casts, white-cell casts** in urine); **chronic** (**reflux nephropathy** and obstruction: **coarse, irregular, asymmetric corticomedullary scars over blunted, deformed calyces**; **"thyroidisation"** of atrophic tubules); **xanthogranulomatous** (*Proteus*, staghorn stone, foamy macrophages). Significant bacteriuria: **10^5 CFU/mL** (lower counts count in symptomatic women). **Sterile pyuria: renal TB** (caseous papillary destruction, "putty kidney"; three early-morning urines for AFB).
- **Urinary stones**: **calcium oxalate and phosphate (about 75–80%)**; **struvite** (urease-splitting *Proteus*, alkaline urine, **staghorn**); **uric acid** (acid urine, gout, cell turnover; **radiolucent**); **cystine** (cystinuria, **hexagonal crystals**); they form by **supersaturation** (low urine volume, hot climates), **loss of inhibitors (citrate, magnesium)** and a nidus (Randall plaque), helped by stasis and infection; non-contrast CT is the test.
- **Hydronephrosis**: dilated pelvis and calyces with cortical atrophy from obstruction (stones, BPH, pelvi-ureteric junction obstruction in children, tumours, pregnancy); infection, stones, renal failure if bilateral.

Renal tumour	Points
Onco-cytoma	Benign; **mahogany brown, central scar**; oncocytes
Angiomy-olipoma	Vessels, smooth muscle and fat; **tuberous sclerosis**; HMB-45 positive
Clear-cell RCC	**70–80% of RCC;** *VHL* **loss on 3p (sporadic and familial)**, HIF accumulation driving VEGF; golden-yellow, cells clear with lipid and glycogen, delicate vessels; **renal-vein and IVC invasion**; cannonball lung and bone metastases
Papillary RCC	10–15%; *MET*, trisomies 7 and 17; foamy macrophages, psammoma bodies; multiple and bilateral in hereditary forms
Chromo-phobe RCC	About 5%; pale cells with perinuclear halos, loss of whole chromosomes; good prognosis
Wilms tumour	**The commonest renal tumour of children (peak 2–5 years)**; flank mass not crossing the midline; **triphasic: blastema, stroma, epithelium**; **anaplasia (*TP53*) is unfavourable**; *WT1* **(11p13): WAGR, Denys–Drash**; *WT2* **(11p15): Beckwith–Wiedemann**; **nephrogenic rests** are precursors; about 90% cured

- **RCC**: **smoking the leading risk**, obesity, hypertension, acquired cystic disease on dialysis, VHL; **classic triad (haematuria, flank pain, mass) in only about 10%**; paraneoplastic **polycythaemia (EPO), hypercalcaemia (PTHrP)**, hypertension, Cushing, **Stauffer syndrome** (reversible cholestasis).
- **Neuroblastoma against Wilms**: neuroblastoma arises in the adrenal, **crosses the midline**, calcifies, makes catecholamines (VMA, HVA), *MYCN* amplification is unfavourable, opsoclonus–myoclonus.
- **Bladder**: cystitis (*E. coli*; **haemorrhagic with adenovirus and cyclophosphamide (acrolein, prevented by mesna)**; **malakoplakia** with Michaelis–Gutmann bodies; interstitial cystitis with Hunner ulcers); **schistosomal cystitis** (*S. haematobium*, calcified eggs, squamous metaplasia → **squamous carcinoma**; Africa and the Middle East, not Nepal).
- **Bladder carcinoma**: **urothelial in over 90%**; **smoking (the commonest risk)**, **aromatic amines (2-naphthylamine, benzidine: dye, rubber, leather)**, cyclophosphamide, phenacetin, arsenic, radiation; **painless haematuria**; **WHO/ISUP grading: papilloma, PUNLMP, low-grade and high-grade papillary carcinoma**; **flat carcinoma in situ is high grade and progresses**; **field effect: multifocal, recurrent**; **two pathways: low-grade papillary (*FGFR3*, *HRAS*) and high-grade flat or invasive (*TP53*, *RB1*)**; staging turns on **muscularis propria invasion (T2)**; non-muscle-invasive tumours get TURBT with **intravesical BCG**. Adenocarcinoma from a **urachal remnant**; squamous after schistosomiasis or chronic irritation.

Organ pathology: female genital tract, gestational disease, male genital tract and breast

Uterus and tubes

- **Abnormal uterine bleeding** (the term **FIGO 2011, revised 2018, uses instead of "dysfunctional uterine bleeding"**): **PALM** (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia) structural; **COEIN** (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not yet classified) non-structural. **Anovulatory bleeding** (puberty, perimenopause, PCOS): unopposed oestrogen gives **proliferative or disordered proliferative endometrium**, with no secretory phase.
- **Adenomyosis**: endometrial glands and stroma **deep in the myometrium (classically at least one low-power field, about 2.5 mm, below the basalis)**; **diffusely enlarged, globular uterus**; menorrhagia and dysmenorrhoea in parous women in their 40s.
- **Endometriosis**: endometrial glands and stroma outside the uterus: **ovary (chocolate cyst) the commonest site**, uterosacral ligaments, pouch of Douglas, peritoneum ("powder-burn" spots), scars; theories: **retrograde menstruation (Sampson)**, coelomic metaplasia, lymphovascular spread; haemosiderin-laden macrophages; pain, dyspareunia, infertility; CA-125 may rise; **endometrioid and clear-cell ovarian carcinoma** (*ARID1A*).
- **Endometrial hyperplasia**: **two tiers (WHO 2014, kept in 2020): hyperplasia without atypia** (progression about 1–3%) and **atypical hyperplasia / endometrial intraepithelial neoplasia (EIN)** (crowded glands with nuclear atypia; **progression risk many times higher, and carcinoma already present in up to about 40% of hysterectomies**); the old four-tier scheme (simple or complex, with or without atypia; WHO 1994) is still in older texts; **unopposed oestrogen** (anovulation, PCOS, obesity, oestrogen-only therapy, **tamoxifen**, granulosa-cell tumour). **Postmenopausal bleeding**: **endometrial atrophy is the commonest cause**, but carcinoma must be excluded (sample when the endometrium is over 4 mm).
- **Endometrial carcinoma**: the commonest gynaecological cancer in high-income countries.

	Endometrioid (type I)	Serous (type II)
Patient	Perimenopausal, **obesity, nulliparity, diabetes, PCOS, Lynch syndrome**	Older, atrophic endometrium
Precursor	**Atypical hyperplasia / EIN**	Serous endometrial intraepithelial carcinoma
Genes	*PTEN* (commonest), *PIK3CA*, *KRAS*, *CTNNB1*, MMR loss	*TP53*

	Endometrioid (type I)	Serous (type II)
Beha-viour	Usually low grade, good prognosis	Aggressive, peritoneal spread

- Molecular classes (TCGA; in **FIGO 2023** staging): ***POLE*-ultramutated (best)**, **MMR-deficient**, no specific profile, **p53-abnormal (worst)**. Depth of **myometrial invasion** is the key factor in stage.
- **Leiomyoma**: **the commonest benign tumour of women**; monoclonal, oestrogen- and progesterone-driven (grows in pregnancy, shrinks after menopause); *MED12* in about 70%; **whorled white cut surface**; submucosal ones bleed most; degenerations: hyaline (commonest), cystic, **red (carneous) in pregnancy**, calcific. **Leiomyosarcoma** arises on its own, rarely from a fibroid: **two of three: marked atypia, tumour-cell necrosis, 10 or more mitoses per 10 high-power fields**.
- **Pelvic inflammatory disease**: ascending **gonococcus and chlamydia**, then polymicrobial; pyosalpinx, **hydrosalpinx**, tubo-ovarian abscess; **infertility and ectopic pregnancy**; **Fitz-Hugh–Curtis perihepatitis** ("violin-string" adhesions). **Genital tuberculosis**: blood-borne from the lung; **the fallopian tube is involved in nearly all (90–100%)**, the endometrium in about half; **tobacco-pouch fimbriae, beaded tubes**; **a major cause of tubal infertility in South Asia**.
- **Ectopic pregnancy**: **ampulla about 70–80%**, then isthmus, fimbria, interstitial; ovary, cervix, abdomen rarely; **chronic salpingitis (PID) the commonest predisposing condition**, previous ectopic or tubal surgery, IVF, IUCD failure, smoking; **chorionic villi in the tube**; the uterine endometrium shows **decidual change with the Arias-Stella reaction but no villi**.
- **Spontaneous abortion**: loss before 20 weeks (textbook and ACOG) or before 22 weeks or under 500 g (WHO); **chromosomal abnormality in about half of first-trimester losses (trisomy 16 the commonest trisomy, 45,X the commonest single abnormality)**; later: cervical insufficiency, uterine anomaly, **antiphospholipid syndrome**, infection; types and Nepal's law are in the obstetrics notes.

Cervix

- **Cervicitis**: acute (gonococcus, chlamydia, HSV, *Trichomonas*); **chronic non-specific cervicitis the commonest** (lymphocytes, plasma cells, squamous metaplasia, **Nabothian cysts**, ectropion). **Endocervical polyp**: the commonest cervical growth; soft, pedunculated, oedematous fibrovascular stroma with endocervical glands; intermenstrual or postcoital bleeding; almost never malignant.
- **HPV and cervical neoplasia**: **high-risk types 16 (about 50–60% of cancers) and 18 (about 10–15%, more in adenocarcinoma)**, also 31, 33, 45, 52, 58; **E6 degrades p53, E7 binds RB**; the **transformation zone** is the site; **koilocytes** (perinuclear halo, raisinoid nuclei) mark productive infection. **CIN 1 (lower third, LSIL; mostly regresses), CIN 2 and CIN 3 (two thirds to full thickness, HSIL)**; Bethesda cytology: ASC-US, ASC-H, LSIL, HSIL, AGC; p16 block staining marks high-risk HPV transformation. **WHO 2021: HPV DNA testing is the preferred primary screen** (screen-and-treat where needed); VIA where HPV testing is unavailable; **HPV vaccination of girls 9–14 the primary prevention (WHO 2022 accepts a single dose)**.
- **Cervical carcinoma**: **squamous about 80%**, adenocarcinoma about 15–20%; early sexual activity, many partners, smoking, **HIV**, long oral-contraceptive use, high parity; postcoital bleeding; exophytic, ulcerative or **barrel-shaped infiltrative** cervix; **direct spread to the parametria obstructs the ureters, and uraemia is the commonest cause of death**; nodes: paracervical, obturator and internal iliac first, then common iliac and para-aortic. **FIGO 2018**: I confined to the cervix (IB by size: under 2, 2–4, over 4 cm); II beyond the uterus, upper two thirds of the vagina or parametrium, not the pelvic wall; **III lower third of the vagina (IIIA), pelvic wall or hydronephrosis (IIIB), pelvic or para-aortic nodes (IIIC, new in 2018, by imaging or pathology)**; IV bladder or rectal mucosa, or distant. With breast cancer, **one of the two commonest cancers of women in South Asia**.

Ovary

Tumour	Features
Serous tumours	**The commonest ovarian tumours** (benign cystadenoma, borderline, carcinoma); tubal-type epithelium, **psammoma bodies**, often bilateral; **high-grade serous carcinoma, the commonest and deadliest ovarian cancer**: from the **tubal fimbria (serous tubal intraepithelial carcinoma)**, *TP53* **in almost all**, *BRCA1/2* (PARP inhibitors), **CA-125**, WT1 and PAX8; low-grade serous: *KRAS*, *BRAF*
Mucinous tumours	Large multiloculated, usually unilateral; *KRAS*; a bilateral or surface mucinous tumour is probably a **metastasis from the gut**; **pseudomyxoma peritonei usually comes from the appendix**
Endometrioid and clear-cell carcinoma	**Endometriosis**; clear cell with hobnail cells, poor response to chemotherapy
Brenner tumour	Urothelial-type nests with **coffee-bean nuclei**, usually benign
Mature cystic teratoma (dermoid)	**The commonest ovarian germ-cell tumour and the commonest ovarian tumour of young women**; skin, hair, sebum, teeth; **torsion**; **struma ovarii**; malignant change (**squamous carcinoma**) in about 1%, mostly older women; **anti-NMDA-receptor encephalitis**
Immature teratoma	Immature **neuroepithelium** decides the grade
Dysger-minoma	The ovarian seminoma; young women; **LDH**, PLAP, OCT3/4; bilateral in 10–15%; radiosensitive and chemosensitive
Yolk sac tumour	**AFP, Schiller–Duval bodies**; children and young women
Ovarian choriocar-cinoma	hCG; worse prognosis than gestational choriocarcinoma
Granulosa-cell tumour	**Oestrogen** (precocious puberty, endometrial hyperplasia and carcinoma); **Call–Exner bodies, coffee-bean nuclei, inhibin**; adult type *FOXL2*
Sertoli–Leydig cell tumour	**Androgens, virilisation**; *DICER1*
Fibroma and thecoma	**Meigs syndrome: ovarian fibroma, ascites, right pleural effusion**, cleared by removal
Krukenberg tumour	**Bilateral metastases of signet-ring adenocarcinoma, the stomach the commonest source**

Gestational trophoblastic disease

	Complete mole	Partial mole
Karyotype	**46,XX (about 90%, one sperm duplicating in an empty egg)** or 46,XY (two sperms); **all paternal**	**Triploid (69,XXY or 69,XXX), one egg and two sperms**
Fetus	**None**	**Fetal parts often**
Villi	**All swollen (hydropic), circumfer-ential trophoblast proliferation**, no vessels	Some swollen, scalloped; focal trophoblast prolif-eration

	Complete mole	Partial mole
p57 (maternally expressed)	**Negative**	Positive
hCG and scan	**Very high**; **"snowstorm" ultrasound**; uterus large for dates, hyperemesis, early pre-eclampsia, theca-lutein cysts, hyperthyroidism	Lower
Persistent disease	**About 15–20%; choriocarcinoma about 2–3%**	Under 5%; choriocarcinoma rare

- **Choriocarcinoma**: **cytotrophoblast and syncytiotrophoblast with no villi**, haemorrhage and necrosis; **about half after a mole**, a quarter after abortion, the rest after normal pregnancy or ectopic; very high hCG; **early blood spread to lung**, vagina, brain, liver; **cured by chemotherapy (methotrexate, actinomycin D) in most**. **Placental site trophoblastic tumour**: intermediate trophoblast, **hPL positive, hCG low**, chemoresistant (hysterectomy). Invasive mole: villi in the myometrium.

Male genital tract

- **Hydrocele**: fluid in the tunica vaginalis; congenital (patent processus vaginalis) or acquired (infection, trauma, tumour, **filariasis: *Wuchereria bancrofti***, endemic in parts of Nepal); transilluminates, and one can get above it. Varicocele (left, "bag of worms").
- **Testicular germ-cell tumours** (histology and markers are in Neoplasia): **the commonest cancer of men 15–35**; **cryptorchidism the strongest risk** (both testes), Klinefelter (mediastinal), family history, germ-cell neoplasia in situ the precursor; **isochromosome 12p**; **painless mass, removed by inguinal orchidectomy (never a scrotal biopsy)**; **lymph spread to para-aortic nodes** (the testis descends from the L1–L2 level), not inguinal; **raised AFP excludes pure seminoma**; LDH reflects bulk; **mixed tumours are the commonest non-seminomatous form**; cisplatin-based chemotherapy cures over 90%. **Leydig-cell tumour** (Reinke crystals, gynaecomastia or precocious puberty); **lymphoma the commonest testicular tumour over 60**.
- **Penis**: **phimosis** (physiological in young children; pathological after balanitis or **lichen sclerosus (balanitis xerotica obliterans)**); **carcinoma in situ: Bowen disease (shaft), erythroplasia of Queyrat (glans), bowenoid papulosis**; **squamous carcinoma**: uncircumcised men, phimosis and poor hygiene, **HPV 16**, smoking; **rare after neonatal circumcision**; inguinal nodes decide prognosis. Giant condyloma (Buschke–Löwenstein; HPV 6, 11).
- **Prostatitis**: acute bacterial (*E. coli*; tender boggy gland), chronic bacterial (relapsing UTI), **chronic pelvic pain syndrome** (the commonest, no organism), granulomatous (after BCG, TB).
- **Benign prostatic hyperplasia**: **50% of men over 50, about 90% in their 80s**; **dihydrotestosterone (5α-reductase type 2)**; **transition zone** (periurethral); **nodules of glands and stroma**; obstruction, retention, bladder trabeculation and diverticula, hydronephrosis, infection; **not premalignant**; PSA may be mildly raised.
- **Prostate carcinoma**: **acinar adenocarcinoma of the peripheral zone (posterior, felt on rectal examination)**; age, family history, *BRCA2*, African ancestry; **the second commonest cancer of men worldwide (GLOBOCAN 2022)**, less common in South Asia; **small crowded glands with no basal cells (p63 and high-molecular-weight keratin negative), AMACR positive, prominent nucleoli, perineural invasion**; **Gleason score, reported with the ISUP Grade Groups 1–5 (Grade Group 1 = Gleason 6)**; **PSA** (density, free fraction), **PSMA PET** for staging; **osteoblastic** spine metastases (Batson plexus).

Breast

- **Fibrocystic change**: the commonest breast lesion of women 20–50; risk of cancer by category: **non-proliferative (cysts, fibrosis, apocrine metaplasia): none**; **proliferative without atypia** (usual ductal hyperplasia, **sclerosing adenosis**, radial scar, papilloma): about **1.5–2 times**; **atypical ductal or lobular hyperplasia: about 4–5 times**.
- **Fibroadenoma**: **the commonest benign breast tumour, under 30**, mobile "breast mouse"; **intracanalicular and pericanalicular patterns of stroma around benign ducts**; *MED12*; no raised risk (simple). **Phyllodes tumour**: older (40s–50s), large, fast-growing, **leaf-like clefts with hypercellular stroma**; benign, borderline or malignant by **stromal atypia, mitoses and overgrowth**; recurs locally, malignant ones spread by blood (**not to nodes**).
- **Other lesions**: **intraductal papilloma** (bloody nipple discharge, the commonest cause), **duct ectasia**, **fat necrosis** (trauma, mimics cancer), acute mastitis (Staph. aureus, lactation).
- **DCIS**: neoplastic cells confined within ducts; **comedo (high-grade, central necrosis) with calcifications on mammography**; a non-obligate precursor. **LCIS**: **E-cadherin loss**, multifocal, bilateral, no calcification; **both a marker of risk in either breast and a non-obligate precursor of lobular carcinoma** (WHO 2019). **Paget disease of the nipple**: **intraepidermal large clear malignant cells, almost always from an underlying DCIS or invasive carcinoma**; HER2 and CK7 positive, S100 and HMB-45 negative (against melanoma); unilateral eczema-like nipple.

Invasive carcinoma (WHO 2019)	Points
No special type (ductal)	**About 70–80%**; graded by **Nottingham: tubules, nuclear pleomorphism, mitoses**
Lobular	About 10–15%; **E-cadherin (*CDH1*) loss; single-file ("Indian file") cells**, targetoid around ducts; bilateral and multicentric more often; spreads to **peritoneum, gut, meninges and ovaries**
Medullary pattern	Syncytial sheets, pushing border, heavy lymphoid infiltrate; **BRCA1**, triple-negative; now a pattern of NST
Mucinous, tubular	Older women, **good prognosis**
Inflammatory carcinoma	**Clinical: peau d'orange, red swollen breast; tumour emboli in dermal lymphatics**; poor prognosis

- **Risk**: female sex, age, early menarche, late menopause, nulliparity or late first birth, no breastfeeding, postmenopausal obesity, alcohol, combined HRT, chest radiation, **BRCA1** (17q; triple-negative, ovarian cancer), **BRCA2** (13q; ER-positive, **male breast cancer**, pancreas, prostate), *TP53* (Li–Fraumeni), *PTEN* (Cowden), *CDH1*, *PALB2*. **Breast cancer is the commonest cancer of women worldwide (GLOBOCAN 2022)**.
- **Molecular subtypes**: **luminal A** (ER positive, HER2 negative, low Ki-67; best), luminal B (higher Ki-67 or HER2 positive),

HER2-enriched, **basal-like (triple negative: young, BRCA1, visceral and brain spread)**.

- **Prognosis**: **axillary node status the most important factor**, then size, grade, lymphovascular invasion, ER/PR/HER2; spread to **axillary nodes (sentinel node biopsy)**, then bone, lung, liver, brain. ER predicts endocrine response and HER2 predicts anti-HER2 response.
- **Male breast**: **gynaecomastia** (ductal and stromal proliferation, the commonest male breast disorder; neonates, puberty, old age; cirrhosis, Klinefelter, testicular tumours, drugs such as spironolactone, cimetidine, digoxin, ketoconazole); **male breast cancer**: **BRCA2** and **Klinefelter** (about 20–50 times the risk).

Organ pathology: endocrine system and diabetes

- **Pituitary adenoma** (WHO 2022 prefers "pituitary neuroendocrine tumour, PitNET"): **prolactinoma the commonest functioning one** (amenorrhoea–galactorrhoea, impotence; dopamine agonists shrink even macroadenomas); **GH adenoma** (acromegaly, gigantism; *GNAS* in about 40%; IGF-1, failed glucose suppression); **ACTH adenoma** (Cushing disease; **Crooke hyaline change** in the non-tumour corticotrophs; **Nelson syndrome** after adrenalectomy); non-functioning (bitemporal hemianopia, hypopituitarism); **microadenoma under 1 cm**; **a monotonous cell population with lost reticulin** (normal acini keep it); **stalk effect** (mild hyperprolactinaemia); **pituitary apoplexy**. **Craniopharyngioma**: children, **suprasellar, calcified, cystic with "machinery-oil" fluid**, from Rathke pouch remnants (adamantinomatous: *CTNNB1*; papillary in adults: *BRAF* V600E).
- **Sheehan syndrome**: **postpartum anterior pituitary infarction after severe haemorrhage**, the gland being enlarged in pregnancy without a matching rise in supply; **failure of lactation the first sign**, then amenorrhoea, loss of body hair, hypothyroidism, secondary adrenal failure; the posterior pituitary is usually spared.
- **Cushing syndrome**: **exogenous steroids the commonest**; endogenous: **pituitary (Cushing disease, about 70%)**, **ectopic ACTH** (small-cell lung carcinoma, carcinoids), adrenal adenoma or carcinoma; **adrenals: bilateral atrophy with exogenous steroids, bilateral hyperplasia with ACTH, contralateral atrophy with a functioning adenoma**; screen by **overnight dexamethasone suppression, 24-hour urinary free cortisol or late-night salivary cortisol**; high-dose dexamethasone suppresses most pituitary disease but not ectopic or adrenal.
- **Conn syndrome**: adenoma or bilateral hyperplasia; hypertension, hypokalaemia, **high aldosterone with low renin**; spironolactone bodies in the tumour. **Addison disease**: autoimmune in the West, **tuberculosis in South Asia**; hyperpigmentation, hyponatraemia, hyperkalaemia, hypotension. **Waterhouse–Friderichsen**: bilateral adrenal haemorrhage in meningococcal sepsis.
- **Phaeochromocytoma**: chromaffin cells of the medulla; episodic headache, sweating, palpitations, hypertension; **the old "rule of tens" no longer holds: about 30–40% are hereditary** (**MEN 2A and 2B (*RET*), VHL, NF1, *SDHx***); **nests (zellballen) of cells with S100-positive sustentacular cells**, chromaffin reaction (brown with dichromate); **malignancy is defined only by metastasis** (WHO 2022 treats all as potentially metastatic); **plasma free or urinary fractionated metanephrines**; α-blockade before β-blockade before surgery.

Thyroid state	Pathology
Primary hypothyroidism	**Iodine deficiency the commonest cause worldwide; Hashimoto thyroiditis where iodine is sufficient**; surgery, radioiodine, drugs (amiodarone, lithium)
Cretinism	Congenital deficiency: short stature, intellectual disability, coarse face, large tongue, umbilical hernia; **endemic in iodine-deficient Himalayan districts in the past**; prevented by iodised salt; found by newborn TSH screening
Myxoedema	Adult hypothyroidism; **glycosaminoglycan (hyaluronic acid) deposits**: non-pitting oedema, hoarse voice, slow-relaxing reflexes, cold intolerance; high TSH, low free T4
Hyperthyroidism	**Graves disease the commonest (about 60–80%)**, toxic multinodular goitre (Plummer), toxic adenoma; **radioiodine uptake: diffuse high in Graves, patchy in multinodular goitre, one hot nodule in adenoma, low in thyroiditis and exogenous hormone**

Thyroiditis and goitre	Pathology
Hashimoto thyroiditis	Middle-aged women; **anti-TPO and anti-thyroglobulin**; HLA-DR3/DR5, *CTLA4*, *PTPN22*; **dense lymphoplasmacytic infiltrate with germinal centres, atrophic follicles, Hürthle (oxyphil) cells**, fibrosis; painless firm goitre; transient "hashitoxicosis", then hypothyroidism; **raised risk of B-cell (MALT) lymphoma** (and papillary carcinoma)
Subacute granulomatous (de Quervain)	After a viral illness; **painful tender gland, fever, high ESR**; **granulomas with multinucleate giant cells around disrupted follicles**; low uptake; hyper- → hypo- → euthyroid, self-limiting
Subacute lymphocytic (silent, postpartum)	Painless, lymphocytic without germinal centres; anti-TPO
Riedel thyroiditis	**Dense fibrosis spreading into the neck**, rock-hard, mimics carcinoma; **IgG4-related**
Graves disease	**TSH-receptor stimulating antibodies (TRAb)**; **diffuse hyperplasia: tall columnar cells with papillary infoldings, pale scalloped colloid**, lymphoid aggregates; **ophthalmopathy** (orbital fibroblasts and glycosaminoglycans; worse with smoking) and **pretibial myxoedema**
Diffuse and multinodular goitre	**Iodine deficiency** (historically very common in Nepal's hills and mountains; universal salt iodisation prevents it) or goitrogens; hyperplasia then involution → nodules with haemorrhage, fibrosis, calcification; pressure (trachea, retrosternal: Pemberton sign), toxic change; a dominant nodule can hide a cancer

- **Solitary nodule**: most are colloid or dominant nodules of a goitre, or follicular adenomas; about 5–15% are cancers (more in men, the young, and the old, after radiation, and in **"cold"** nodules); **ultrasound (TI-RADS) then FNAC (Bethesda 2023: I–VI)**. **Follicular adenoma**: a **solitary encapsulated nodule of uniform follicles, no capsular or vascular invasion**; carcinoma is told from it only by invasion, so FNAC cannot separate them. The thyroid carcinomas are in Neoplasia: papillary (about 85%; nuclei, lymph spread), follicular (about 10%; invasion, blood spread), medullary (about 5%; C cells, amyloid, *RET*), anaplastic (elderly, rapid, fatal); **thyroid lymphoma arises in Hashimoto thyroiditis**.

Diabetes mellitus

- **Diagnosis (ADA 2024)**: fasting plasma glucose **126 mg/dL (7.0 mmol/L) or more**, 2-hour glucose after 75 g **200 mg/dL or more**, **HbA1c 6.5% or more**, or random glucose 200 or more with symptoms; prediabetes: fasting 100–125 (WHO: 110–125), 2-hour 140–199, HbA1c 5.7–6.4%.
- **Type 1**: autoimmune β-cell destruction, HLA-DR3/DR4 (DQ8); antibodies to **GAD65, IA-2, insulin, ZnT8**; **insulitis (T-cell infiltrate of the islets)**, then loss of β cells; ketosis-prone. **Type 2 (about 90%)**: insulin resistance (obesity, free fatty acids, low adiponectin, inflammation) with failing β cells; **islet amyloid (amylin)**. Others: **MODY** (autosomal dominant: *GCK*, *HNF1A*), pancreatic (chronic and fibrocalculous pancreatitis, haemochromatosis, cystic fibrosis), endocrine (Cushing, acromegaly), drugs (steroids); infants of diabetic mothers have **islet hyperplasia** (neonatal hypoglycaemia).
- **Why tissues are damaged**: **advanced glycation end-products**, protein kinase C activation, **polyol (sorbitol) pathway** (lens, nerves), hexosamine pathway, oxidative stress.
- **Large vessels**: accelerated atherosclerosis; **MI the commonest cause of death**; stroke, **gangrene of the lower limb**.
- **Kidney (the leading cause of end-stage renal disease)**: **GBM thickening (the earliest structural change)**, **diffuse mesangial sclerosis**, **nodular glomerulosclerosis (Kimmelstiel–Wilson)**, **hyaline arteriolosclerosis of both afferent and efferent arterioles** (the efferent is typical of diabetes), **fibrin caps and capsular drops**, papillary necrosis, pyelonephritis; hyperfiltration → **moderately raised albuminuria (30–300 mg/day, the old "microalbuminuria")** → overt proteinuria → falling GFR.
- **Eye**: non-proliferative retinopathy (**microaneurysms the earliest sign**, dot-blot haemorrhages, hard exudates, cotton-wool spots) and proliferative (new vessels, vitreous haemorrhage, tractional detachment); **macular oedema the commonest cause of visual loss**; cataract (sorbitol).
- **Nerves**: distal symmetrical sensory ("glove and stocking"), autonomic, mononeuropathy (**pupil-sparing third-nerve palsy**). Infections: **mucormycosis**, emphysematous pyelonephritis and cholecystitis, malignant otitis externa (*Pseudomonas*). Skin: necrobiosis lipoidica, acanthosis nigricans.

Organ pathology: lymph nodes, blood counts and diagnostic methods

- **Reactive lymphadenitis**: acute (neutrophils, abscess); **follicular hyperplasia** (varied follicles with polarity and **tingible-body macrophages**; against **follicular lymphoma**: crowded uniform follicles without tingible-body macrophages, **BCL2 positive**); **paracortical hyperplasia** (viral infections such as EBV, phenytoin, vaccination); **sinus histiocytosis** (nodes draining cancers). **Granulomatous lymphadenitis**: **tuberculosis the commonest cause in South Asia** (cervical "scrofula", matted nodes, collar-stud abscess, sinuses), sarcoidosis, leprosy, fungi; **stellate necrotising granulomas in cat-scratch disease and lymphogranuloma venereum**. **Kikuchi disease**: young Asian women, necrotising histiocytic lymphadenitis with **karyorrhexis and no neutrophils**. Dermatopathic lymphadenitis (melanin in macrophages). **FNAC is the first test for a node; excision biopsy when lymphoma is suspected**.
- **White-cell changes**: **neutrophilia** (bacterial infection, inflammation, steroids, stress, myeloproliferative disease); **lymphocytosis** (viruses, **pertussis**, TB, CLL); **eosinophilia** (allergy, **helminths**, drugs, Hodgkin, EGPA, hypereosinophilic syndrome, Addison); **basophilia** (CML); **monocytosis** (TB, endocarditis, CMML); **neutropenia under 1,500/μL, severe under 500** (chemotherapy, clozapine, carbimazole, viral infection, aplastic anaemia, **Felty syndrome**, hypersplenism, B_{12} or folate deficiency). The leukaemoid reaction and its difference from CML are in Leukaemias and lymphomas.
- **Pancytopenia**: aplastic anaemia (hypocellular fatty marrow), **marrow infiltration** (leukaemia, myelodysplasia, myelofibrosis, lymphoma, metastases, TB), **megaloblastic anaemia**, **hypersplenism**, PNH, SLE, HIV, sepsis, **kala-azar**; marrow aspiration with **trephine biopsy** decides. Myeloma's findings are in Leukaemias and lymphomas.

Method	What it gives, and its limits
Autopsy	Cause of death and confirmation of diagnoses; **clinical (needs consent) versus medico-legal** (ordered by law)
Exfoliative cytology	Cells shed or scraped from surfaces (**Pap smear**, sputum, urine, effusions, washings, brushings); **wet-fixed in 95% alcohol for Papanicolaou stain**; cheap, good for screening
FNAC	22–25 gauge needle, palpable or image-guided (thyroid, breast, node, salivary gland, liver, lung; **EUS** for pancreas); Giemsa (air-dried) or Pap (wet-fixed); fast and cheap; **no architecture, so it cannot show invasion (follicular carcinoma)** or type all lymphomas; a negative result does not exclude cancer; **core biopsy keeps architecture**
Immuno-histo-chemistry	Antibody to a tissue antigen, shown with a chromogen (DAB); tumour typing, and **predictive markers (ER, PR, HER2, PD-L1, MMR proteins)**
Electron micro-scopy	**Renal biopsy (deposits, foot processes, GBM)**, Birbeck granules, neurosecretory granules, viruses, cilia
Flow cyto-metry	Cell suspensions; **immunophenotype (CD markers) and light-chain restriction** in leukaemia and lymphoma
Karyotype	G-banded metaphases from **cultured dividing cells** (blood, marrow, amniotic fluid); numerical and large structural changes (about 5–10 Mb)
FISH	Fluorescent probes on **interphase cells, no culture needed**: *HER2* and *MYCN* amplification, BCR::ABL1, deletions, aneuploidy; chromogenic ISH for **EBER** (EBV) and HPV
PCR	Denaturation, annealing, extension with Taq polymerase; **RT-PCR** for RNA; **quantitative PCR** for viral load and **minimal residual disease (BCR::ABL1)**; Xpert MTB/RIF; **NGS** panels now profile tumours
Blots	**Southern DNA, Northern RNA, Western protein**

Sources

- Robbins and Cotran Pathologic Basis of Disease (10th edition, 2020); Robbins and Kumar Basic Pathology (11th edition, 2023); Harsh Mohan Textbook of Pathology; Harrison's Principles of Internal Medicine (21st edition); Williams Hematology; Hoffbrand's Essential Haematology; Wintrobe's Clinical Hematology; Nelson Textbook of Pediatrics; Thompson and Thompson Genetics in Medicine; First Aid for the USMLE Step 1 (2022), for checking facts.
- Classifications and guidelines: **WHO 5th edition classification of haematolymphoid tumours (2022)** and the **International Consensus Classification (2022)**; ELN 2022 AML risk; IMWG 2014 myeloma criteria; WHO 2022 endocrine (thyroid) and 2021 CNS tumour classifications; **Sepsis-3 (2016)** and Surviving

Sepsis Campaign (2021); revised Sapporo (Sydney 2006) and ACR/EULAR 2023 antiphospholipid criteria; 2019 EULAR/ACR SLE criteria; AHA 2015 revised Jones criteria; AABB 2023 red-cell transfusion guideline; BSH 2011 spherocytosis guideline; **WHO 2024 haemoglobin cut-offs for anaemia**; ASH and international ITP guidance (2019); GLOBOCAN 2022; Hanahan's Hallmarks of Cancer (2022).

- Blood groups: Bhende and colleagues, The Lancet 1952 (the Bombay phenotype); NCBI Bookshelf, Blood Groups and Red Cell Antigens (H antigen frequencies). Nepal: published screening studies of sickle cell disease among the Tharu of Dang, Banke, Bardiya and Kanchanpur.
- Organ pathology: WHO Classification of Tumours, 5th edition (CNS 2021; Soft Tissue and Bone 2020; Female Genital 2020; Breast 2019; Endocrine 2022; Urinary and Male Genital 2022); Chapel Hill Consensus Conference 2012; KDIGO 2021 glomerular disease and 2024 CKD guidelines; ISN/RPS lupus nephritis classification; FIGO 2011/2018 PALM–COEIN, FIGO 2018 (cervix) and 2023 (endometrium) staging; WHO 2021 cervical screening and 2022 HPV vaccine position; Bethesda systems (cervical; thyroid 2023); ESC/ESH 2023 hypertension; revised Atlanta 2012 (pancreatitis); Berlin ARDS definition 2012; modified Duke criteria (ISCVID 2023); ADA Standards of Care 2024; WHO 2018 leprosy guidelines; WHO trachoma elimination validation for Nepal (2018); USPSTF 2021 lung-cancer screening; AJCC 8th edition staging.