**Lipid transport**

Dietary fat + cholesterol

- Micelles

- Lumen

- Intestinal cell

- Intestinal cell

- Thoracic duct

- Subclavian vein

- Adipocyte

- Adipocyte

- Systemic circulation

- Lumen

- Peripheral cell

- Adipocyte

- LDL receptor

- LDL receptor

- Liver releases VLDL

- VLDL Apo CII activates LPL

- Chylomicron enters lymphatics

- HDL transfers Apo CII and Apo E

- Chylomicron Apo CII activates LPL

- Liver releases VLDL

- VLDL Apo CII activates LPL

- IDL delivers to liver via Apo E

- Endocytosis of LDL

- Lipoprotein lipase

- Hepatocyte

- Cholesterol and TGs

- Bile Canaliculus

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**Erythrocyte sedimentation rate**

Products of inflammation (eg, fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube → ↑ ESR. Often co-tested with CRP levels.

<table>
<thead>
<tr>
<th>† ESR</th>
<th>↓ ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most anemias</td>
<td>Sickle cell anemia (altered shape)</td>
</tr>
<tr>
<td>Infections</td>
<td>Polycythemia († RBCs “dilute” aggregation factors)</td>
</tr>
<tr>
<td>Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)</td>
<td>HF</td>
</tr>
<tr>
<td>Cancer (eg, metastases, multiple myeloma)</td>
<td>Microcytosis</td>
</tr>
<tr>
<td>Renal disease (end-stage or nephrotic syndrome)</td>
<td>Hypofibrinogenemia</td>
</tr>
</tbody>
</table>

**Acute inflammation**

Transient and early response to injury or infection. Characterized by neutrophils in tissue, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

**Stimuli**

Infections, trauma, necrosis, foreign bodies.

**Mediators**

Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

**Inflammasome**—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals) → activation of IL-1 and inflammatory response.

**Components**

- Vascular: vasodilation (↑ blood flow and stasis) and ↑ endothelial permeability
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules and accumulation in the focus of injury followed by leukocyte activation

To bring cells and proteins to site of injury or infection.

Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

**Outcomes**

- Resolution and healing (IL-10, TGF-β)
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs → activation of CD4+ Th cells)
- Scarring

Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence the outcome of acute inflammation by secreting cytokines.
### Congenital heart diseases (continued)

<table>
<thead>
<tr>
<th>Left-to-Right Shunts</th>
<th>Right-to-Left shunts: eaRLy cyanosis. Left-to-Right shunts: “LateR” cyanosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular septal defect</strong></td>
<td>Most common congenital cardiac defect. Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions may lead to LV overload and HF.</td>
</tr>
<tr>
<td><strong>O₂ saturation ↑ in RV and pulmonary artery. Frequency: VSD &gt; ASD &gt; PDA.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Atrial septal defect</strong></td>
<td>Defect in interatrial septum wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.</td>
</tr>
<tr>
<td><strong>O₂ saturation ↑ in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli).</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Patent ductus arteriosus</strong></td>
<td>In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA can eventually result in late cyanosis in the lower extremities (differential cyanosis).</td>
</tr>
<tr>
<td><strong>“Endomethacin” (indomethacin) ends patency of PDA; PGE keeps ductus Going (may be necessary to sustain life in conditions such as transposition of the great vessels). PDA is normal in utero and normally closes only after birth.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Eisenmenger syndrome</strong></td>
<td>Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↓ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left. Causes late cyanosis, clubbing, and polycythemia. Age of onset varies.</td>
</tr>
<tr>
<td><strong>Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Other Anomalies**

- **Coarctation of the aorta**
  - Aortic narrowing near insertion of ductus arteriosus (“juxtaductal”). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs → notched appearance on CXR. Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.
Calcitonin

**SOURCE**  
Parafollicular cells (C cells) of thyroid.

**FUNCTION**  
↓ bone resorption of Ca\(^{2+}\).

**REGULATION**  
↑ serum Ca\(^{2+}\) → calcitonin secretion.

Calcitonin opposes actions of PTH. Not important in normal Ca\(^{2+}\) homeostasis. Calcitonin tones down serum Ca\(^{2+}\) levels and keeps it in bones.

**Thyroid hormones (T\(_3/T_4\))**  
Iodine-containing hormones that control the body’s metabolic rate.

**SOURCE**  
Follicles of thyroid. 5′-deiodinase converts T\(_4\) (the major thyroid product) to T\(_3\) in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β-blockers and propylthiouracil (PTU). Functions of thyroid peroxidase include oxidation, organification of iodide and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. DIT + DIT = T\(_4\), DIT + MIT = T\(_3\). Wolff-Chaikoff effect—excess iodine temporarily ⊕ thyroid peroxidase → ↓ T\(_3/T_4\) production.

**FUNCTION**  
Only free hormone is active. T\(_3\) binds nuclear receptor with greater affinity than T\(_4\). T\(_3\) functions — 6 B’s:
- Brain maturation
- Bone growth (synergism with GH)
- β-adrenergic effects. ↑ β\(_1\) receptors in heart → ↑ CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate ↑ (via Na\(^+\)/K\(^+\)-ATPase activity → ↑ O\(_2\) consumption, RR, body temperature)
- Blood sugar (↑ glycogenolysis, gluconeogenesis)
- Break down lipids (↑ lipolysis)

**REGULATION**  
TRH ⊕ TSH release → ⊕ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may ⊕ follicular cells in Graves disease. Negative feedback primarily by free T\(_3/T_4\):
- Anterior pituitary → ↓ sensitivity to TRH
- Hypothalamus → ↓ TRH secretion

Thyroxine-binding globulin (TBG) binds most T\(_3/T_4\) in blood. Bound T\(_3/T_4\) = inactive.
- ↑ TBG in pregnancy, OCP use (estrogen → ↑ TBG) → ↑ total T\(_3/T_4\)
- ↓ TBG in hepatic failure, steroids, nephrotic syndrome
Arteries supplying GI structures are single and branch anteriorly. Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

**Superior mesenteric artery syndrome**—characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).

Two areas of the colon have dual blood supply from distal arterial branches (“watershed regions”) susceptible in colonic ischemia:
- Splenic flexure—SMA and IMA
- Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal arteries.

**Gastrointestinal blood supply and innervation**

<table>
<thead>
<tr>
<th>EMBRYONIC GUT REGION</th>
<th>ARTERY</th>
<th>PARASYMPATHETIC INNERVATION</th>
<th>VERTEBRAL LEVEL</th>
<th>STRUCTURES SUPPLIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foregut</td>
<td>Celiac</td>
<td>Vagus</td>
<td>T12/L1</td>
<td>Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)</td>
</tr>
<tr>
<td>Midgut</td>
<td>SMA</td>
<td>Vagus</td>
<td>L1</td>
<td>Distal duodenum to proximal ⅔ of transverse colon</td>
</tr>
<tr>
<td>Hindgut</td>
<td>IMA</td>
<td>Pelvic</td>
<td>L3</td>
<td>Distal ⅓ of transverse colon to upper portion of rectum</td>
</tr>
</tbody>
</table>
**Pectinate (dentate) line**

Formed where endoderm (hindgut) meets ectoderm.

Above pectinate line—internal hemorrhoids, adenocarcinoma. Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

Below pectinate line—external hemorrhoids, anal fissures, squamous cell carcinoma. External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.

**Anal fissure**—tear in the anal mucosa below the Pectinate line. Pain while **Pooping**; blood on toilet **Paper**. Located **Posteriorly** because this area is **Poorly Perfused**. Associated with low-fiber diets and constipation.
Sialolithiasis

Stone(s) in salivary gland duct. Can occur in 3 major salivary glands (parotid, submandibular, sublingual). Single stone more common in submandibular gland (Wharton duct).

Presents as recurrent pre-/periprandial pain and swelling in affected gland.

Caused by dehydration or trauma.

Treat conservatively with NSAIDs, gland massage, warm compresses, sour candies (to promote salivary flow).

Sialadenitis

Inflammation of salivary gland due to obstruction, infection, or immune-mediated mechanisms.

Salivary gland tumors

Most commonly benign and in parotid gland. Tumors in smaller glands more likely malignant. Typically present as painless mass/swelling. Facial pain or paralysis suggests malignant involvement of CN VII.

- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.

- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.

- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers. Typically found in smokers. Bilateral in 10%; multifocal in 10%. “Warriors from Germany love smoking.”

Achalasia

Failure of LES to relax due to loss of myenteric (Auerbach) plexus due to loss of postganglionic inhibitory neurons (which contain NO and VIP).

Manometry findings include uncoordinated or absent peristalsis with high LES resting pressure → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis (“bird’s beak”).

Associated with ↑ risk of esophageal cancer.

A-chalasia = absence of relaxation.

Pseudoachalasia (pseudoachalasia) may arise from Chagas disease (T cruzi infection) or extraesophageal malignancies (mass effect or paraneoplastic).
Scaphoid, Lunate, Triquetrum, Pisiform, Hamate, Capitate, Trapezoid, Trapezium (So Long To Pinky, Here Comes The Thumb).

Scaphoid (palpable in anatomic snuff box) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply. Fracture not always seen on initial x-ray. Dislocation of lunate may cause acute carpal tunnel syndrome.

Metacarpal neck fracture

Also called boxer’s fracture. Common fracture caused by direct blow with a closed fist (e.g., from punching a wall or individual). Most commonly seen in 4th and 5th metacarpals.

Carpal tunnel syndrome

Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones); nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Guyon canal syndrome

Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars.

Suggested by Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling). Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use.
Metastatic disease is more common than 1° bone tumors.

<table>
<thead>
<tr>
<th>Primary bone tumors</th>
<th>Benign tumors</th>
<th>Malignant tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR TYPE</td>
<td>EPIDEMIOLOGY</td>
<td>LOCATION</td>
</tr>
<tr>
<td>Osteochondroma</td>
<td>Most common benign bone tumor.</td>
<td>Metaphysis of long bones.</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Middle age.</td>
<td>Surface of facial bones.</td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Adults &lt; 25 years old. Males &gt; females.</td>
<td>Cortex of long bones.</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td></td>
<td>Vertebræ.</td>
</tr>
<tr>
<td>Chondroma</td>
<td></td>
<td>Medulla of small bones of hand and feet.</td>
</tr>
<tr>
<td>Osteosarcoma (osteogenic sarcoma)</td>
<td>Accounts for 20% of 1° bone cancers. Peak incidence of 1° tumor in males &lt; 20 years. Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li–Fraumeni syndrome.</td>
<td>Metaphysis of long bones (often in knee region).</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td></td>
<td>Medulla of pelvis and central skeleton.</td>
</tr>
</tbody>
</table>
### Primary bone tumors (continued)

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EPIDEMIOLOGY</th>
<th>LOCATION</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
</table>
| Ewing sarcoma    | Most common in Caucasians. Generally boys < 15 years old | Diaphysis of long bones (especially femur), pelvic flat bones | Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes)  
Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLI1).  
“Onion skin” periosteal reaction in bone.  
Aggressive with early metastases, but responsive to chemotherapy.  
11 + 22 = 33 (Patrick Ewing’s jersey number). |

---

**Revised Figure**

- **Diaphysis**
  - Round cell lesions
  - Ewing sarcoma
  - Myeloma
  - Fibrous dysplasia
  - Simple bone cyst
  - Osteoid osteoma
  - Osteosarcoma
  - Osteochondroma
  - Physis
  - Giant cell tumor

- **Epihysis**
  - Metaphysis

---

![Image of bone tumors and associated pathology](image-url)
Cerebral perfusion

Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by $\text{PCO}_2$ ($\text{PO}_2$ also modulates perfusion in severe hypoxia). Cerebral perfusion relies on a pressure gradient between mean arterial pressure (MAP) and ICP. ↓ blood pressure or ↑ ICP → ↓ cerebral perfusion pressure (CPP).

Therapeutic hyperventilation → ↓ $\text{PCO}_2$ → vasoconstriction → ↓ cerebral blood flow → ↓ intracranial pressure (ICP). May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

CPP = MAP – ICP. If CPP = 0, there is no cerebral perfusion → brain death.

Hypoxemia increases CPP only if $\text{PO}_2 < 50$ mm Hg.

CPP is directly proportional to $\text{PCO}_2$ until $\text{PCO}_2 > 90$ mm Hg.

Cerebral arteries—cortical distribution

Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries (cortical border zones) (blue areas in A); or may also occur between the superficial and deep vascular territories of the middle cerebral artery (internal border zones) (red areas in B). Damage by severe hypotension → proximal upper and lower extremity weakness (if internal border zone stroke), higher order visual dysfunction (if posterior cerebral/middle cerebral cortical border zone stroke).
Multiple sclerosis

Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:

- Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)
- Brainstem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO (bilateral > unilateral))
- Pyramidal tract weakness
- Spinal cord syndromes (eg, electric shock-like sensation along spine on neck flexion [Lhermitte phenomenon], neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)

Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects women in their 20s and 30s; more common in Caucasians living farther from equator.

**FINDINGS**

- IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time.

**TREATMENT**

Stop relapses and halt/slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA<sub>B</sub> receptor agonists), pain (TCAs, anticonvulsants).
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic demyelination syndrome</td>
<td>Also known as central pontine myelinolysis. Massive axonal demyelination in pontine white matter due to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause “locked-in syndrome.” Correcting serum Na⁺ too fast: ▪ “From low to high, your pons will die” (osmotic demyelination syndrome). ▪ “From high to low, your brains will blow” (cerebral edema/herniation).</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculopathy</td>
<td>Most common subtype of Guillain-Barré syndrome. Autoimmune condition associated with infections (eg, Campylobacter jejuni, viruses [eg, Zika]) that destroys Schwann cells by inflammation and demyelination of peripheral nerves (including cranial nerves III-XII) and motor fibers likely due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens. Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; majority recover completely after weeks to months. † CSF protein with normal cell count (albuminocytologic dissociation). Respiratory support is critical until recovery. Disease-modifying treatment: plasmapheresis, IV immunoglobulins. No role for steroids.</td>
</tr>
<tr>
<td>Acute disseminated (postinfectious) encephalomyelitis</td>
<td>Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>Also known as hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant inheritance pattern and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits. Most common type, CMT1A, is caused by PMP22 gene duplication.</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Demyelination of CNS due to destruction of oligodendrocytes (2° to reactivation of latent JC virus infection). Seen in 2–4% of patients with AIDS. Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. † Risk associated with natalizumab, rituximab.</td>
</tr>
<tr>
<td>Other disorders</td>
<td>Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy.</td>
</tr>
</tbody>
</table>
**Urethral injury**

- Occurs almost exclusively in men. Suspect if blood seen at urethral meatus. Urethral catheterization is relatively contraindicated.

<table>
<thead>
<tr>
<th>PART OF URETHRA</th>
<th>MECHANISM</th>
<th>LOCATION OF URINE LEAK/BLOOD ACCUMULATION</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior urethral injury</td>
<td>Bulbar (spongy) urethra</td>
<td>Blood accumulates in scrotum</td>
<td>Blood at urethral meatus and scrotal hematoma</td>
</tr>
<tr>
<td>Posterior urethral injury</td>
<td>Membranous urethra</td>
<td>Urine leaks into retropubic space</td>
<td>Blood at urethral meatus and high-riding prostate</td>
</tr>
</tbody>
</table>

**Autonomic innervation of male sexual response**

- **Erection**—Parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):
  - NO → ↑ cGMP → smooth muscle relaxation → vasodilation → proerectile.
  - Norepinephrine → ↑ [Ca²⁺]ᵢ → smooth muscle contraction → vasoconstriction → antierectile.
- **Emission**—Sympathetic nervous system (hypogastric nerve, T11-L2).
- **Ejaculation**—visceral and somatic nerves ( pudendal nerve).

**Point, Squeeze, and Shoot.**
PDE-5 inhibitors (eg, sildenafil) ↓ cGMP breakdown.