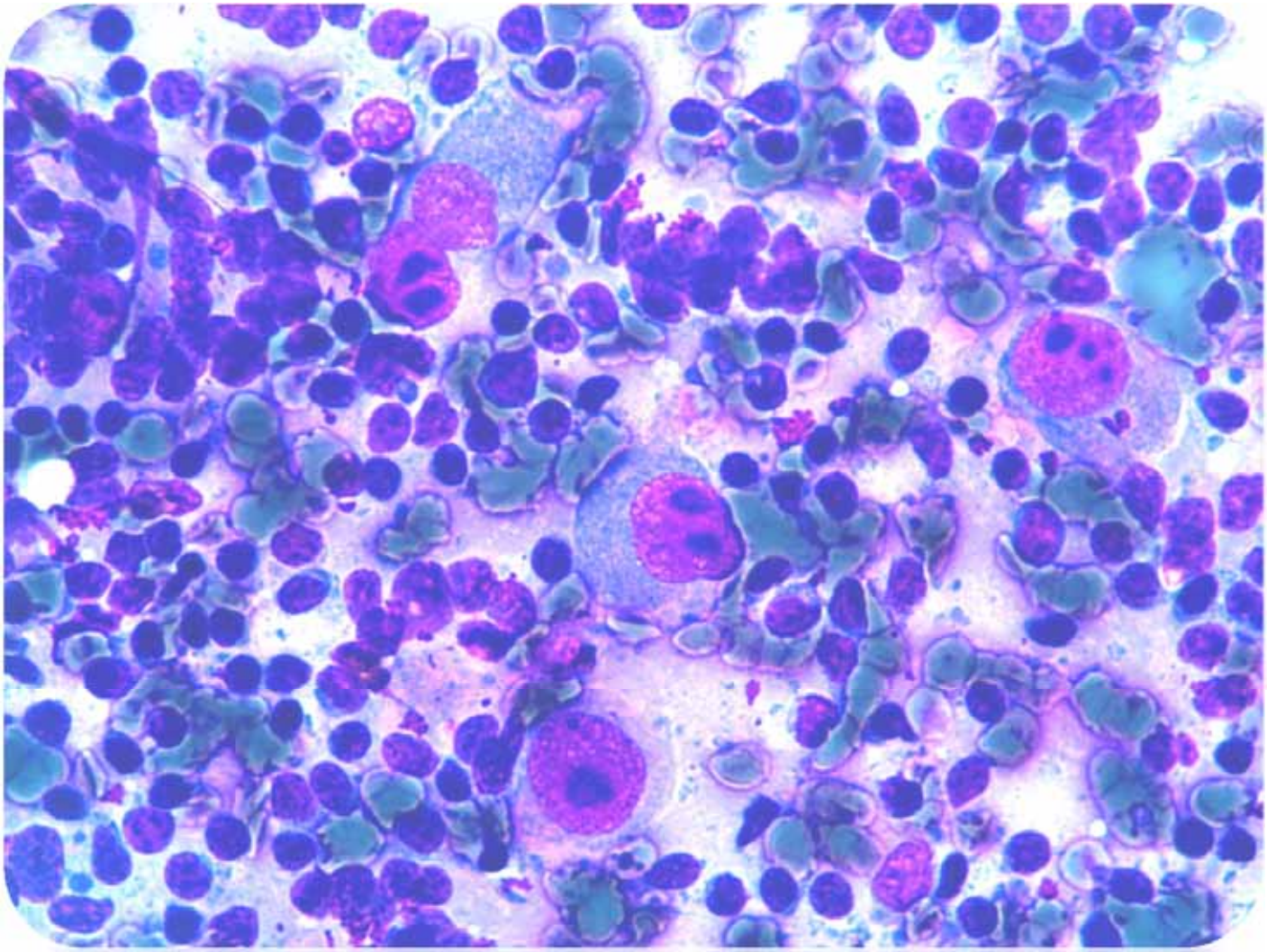
PATHOLOGY 2012



Cell Injury

Summary
1. Stages
2. Causes
3. Mechanism
4. Hypoxia vs Ischaemia
5. Reperfusion
6. Intracellular Accumulations
7. Cellular Aging

Stages of Cell Injury

1. Adaptation
   - Hypertrophy (↑ mass eg skeletal muscle, preg uterus)
   - Hyperplasia (↑ number eg liver, BPH, pubertal breasts, endometrium)
   - Atrophy (↓ mass)
   - Metaplasia (reversible △ mature cell types)
     - Columnar to stratified (except Barrett's)
     - Lungs, gall bladder

1. Reversible
   - Cell swelling & fatty △
   - Morphological changes include swelling: cell, mitochondria, ER

3. Irreversible — Spectrum
   - Membrane damage (mito & cell)
   - *ATP depletion*

4. Death

	Apoptosis	Necrosis
Fcn	Remove old/mutated cells	Remove abnormal material
Morp	● No inflammation ● Shrinkage ● Orchestrated ● Cellular blebbing	● Inflammation ● Swelling ● Protein denat/coag ● Cellular organ breakdown ● Cell Rupture
Nuclear	● Chromatin condensation ● Fragmentation	1. ***Pyknosis*** (small dense nucleus) 2. ***Karylosis*** (faint/dissolved nucleus) 3. ***Karyorrhexis*** (fragmented nucleus)
Causes Or Types	*Physiological* ● Deletion (embryogenesis) ● Involution (prostate, endometrium) ● Turnover (intestinal epi) ● Purpose served (neut post inflam) *Pathological* ● DNA damage ● Protein misfolding ● Viral cytotoxic T cells	a. Coagulative ● Protein denaturation ● Preserved framework ● Occurs with hypoxia in all tissues except brain b. Liquifactive ● Heterolysis/Autolysis > Protein denaturation ● Occurs in brain c. Gangrenous ● Coagulative necrosis of limb ● Wet = liquifactive necrosis of limb d. Caseous (ie TB) e. Fat f. Fibrinoid (immune complex in vessels)

Apoptosis: Mechanism

1. Initiation
   a. Intrinsic (mitochondrial) — Apoptosis ↑
      - ***BCL-2*** & ***BCL-x*** are anti-apoptotic
      - ***Bim, Bid*** & ***Bad*** are receptors that can activate ***Bax*** or ***Bak***
      - Mito damage also forms MPTP → cytochrome C ↓ + *Apaf-1* → ***Caspase-9*** activation

   b. Extrinsic (membrane receptor)
      - Includes ***TNF*** or ***Fas-L*** → ***Caspase-8*** activation
      - FLIP inhibits activation (viruses make FLIP)

2. Execution
   Caspases-8 or -9 → ***Caspase-3 or -6*** activation
   ↓ Cascade of activation
   Cleavage of cytoskeleton & proteins

Causes of Cell Injury

A - anaerobic
B - Bacteria or other infection
C - Chemical insult
D - Drugs
E - Environmental (radiation, temperature, pH, trauma, electricity)
F - Food or nutritional deficit
G - Genetics

Mechanisms of Cell Injury

1. ↓ ATP
   - Caused by toxic or hypoxic △
   - Causes → mitochondrial damage
     → ↑ intracellular calcium
     → rER detachment (↓ protein synth)
     → ↑Glycolysis
     → inhibit Na-K ATPase → ↑ H2O → Swelling

2. Mitochondria Damage
   - Caused by toxic/hypoxic △, ↑Ca, Ox stress, Phos-lip products
   - Causes MPTP → proton leakage → ↓ ATP
     → cytochrome C → apoptosis

MPTP = mitochondrial permeability transition pores

3. Calcium
   - Causes activation of: *phospholipase, proteases, ATPases, Endonucleases, mitochondrial damage*

   ie effects membrane & cytoskeleton

Endonucleases cause chromatin fragmentation

4. ROS (0_2^-, H_2O_2, OH^-, $OHOO^-$)

   Generated by
   - Normal (eg respiration)
   - Radiation
   - Leukocytes (main killing action)
   - Metabolism of exogenous material (eg paracetamol)
   - NO
   - Transition metals

   Inhibited by
   - Inherently unstable
   - Anti-oxidants
   - Scavenging enzymes
   - Catalase (breaks down H_2O_2)

5. Membrane
   - Direct
   - Indirect (ATP, Mitochondria, Ca, ROS)

6. DNA or Protein Damage

Cell Injury

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6. Intracellular Accumulations
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Hypoxia vs Ischemia

- Hypoxia: ↓ O_2 supply Ischaemia
- Ischaemia: ↓ delivery/removal = faster progression of hypoxic △

Reperfusion

- Relevant in MI, ARF, Stroke
- Death can occur post reperfusion
- Causes: ↑ ROS, Inflammatory mediators, Complement (esp IgM) deposition

Intracellular Accumulations

Causes
1. Normal endogenous (↓ destruction)
2. Abnormal endogenous production
3. Normal endogenous (↑ production)
4. Abnormal exogenous

Types
a. Lipids
   - Chol: atherosclerosis, xanthomas, cholesterolosis (GB)
   - TG: liver > kidney, heart, muscle
   - Sequelae: reversible or fibrosis
   - Causes: etoh, nutrition (lack protein), obesity, DM

b. Proteins
   - A1-AT, neurofib tangles in Alzeihmer's

c. Hyaline
d. Glycogen
e. Pigments
   - Lipfuscion, melanin, haemosiderin, homogentistic

f. Calcium
   - Dystrophic calcification = localised calcification
     - Occurs in all necrosis
     - Heart valves
   - Metastatic calcification = hyper ca

Causes	Principle Sites *
• ↑ PTH • ↑ Bone destruction • ↑ Vit D (sarcoid) • Renal Failure	• GIT • Kidneys • Systemic arteries • Pulmonary veins • Lung tissue

*All excrete acid

Cellular Ageing

- *Cellular senescence* implies that each cell has a limited capacity
- Regulated through telomere length (shortens with each replication)
- Telomerase inhibits shortening, used by viruses
- Dysfunction includes accelerated metabolic, genetic damage, DNA repair defects, high calories

Inflammation

Summary
1. Signs of Inflammation
2. Acute vs Chronic
3. Process of Acute Inflammation
4. Process of Chronic Inflammation
5. Mediators of Inflammation
6. Outcomes
7. Types
8. Systemic Effects

Signs of Inflammation

1. Warmth
2. Erythema
3. Oedema
4. Pain
5. Loss of Function

Acute vs Chronic

	Acute	Chronic
Onset	s – min	Days
Duration	min – days	Wks – years
Cells	Neutrophils	Lymphocytes, Macrophages
Morph	Oedema	Angiogenesis, Fibrosis* Tissue destruction

NB neutrophils 6-24hrs / monocytes 24-48hrs
*attempts at tissue repair

Acute

Overview
1. Macrovascular
2. Microvascular
3. Extravasation
4. Chemotaxis
5. Recognition
6. Phagocytosis
7. Termination

1. Macrovascular (↑ blood flow)
- Vasodilation → ↑ hydrostatic pressure → ↑ viscosity
  → erythema
  → cell margination

2. Microvascular (↑ permeability)
- Venule endo contraction (by histamine, bradykinin, leukotrienes)
- Direct
- ↑ Trancytosis
- Leakage of new blood vessels (through angiogenesis)

3. Extravasation

Action	Epi Receptor	Leukocyte Receptor
Transcytosis		
→ Margination	From △ vessel calibre	
→ Rolling	Selectins E, P, L	Oligosaccharides
→ Adhesion	ICAM-1, VCAM-1	Integrins*
Transmigration	PECAM-1	PECAM-1
Migration	CD44	Integrins

*Chemokines & Cytokines modulate surface expression to alter redistribution, induction or avidity

4. Chemotaxis
- Interstitial leukocytes move via chemotaxis stimulation
- Chemotaxis → g-pro/2nd msg → ↑ Ca & GTPase → polymerize actin
- Movement is via pseudopods

5. Recognition
a. Toll-like receptors
b. G-protein R (bacterial peptides)
c. Opsonin R (esp C3b & Fc)
d. Cytokine R (IFN-γ secreted by T cells)

Inflammation

Acute

6. Phagocytosis
   a. Engulfment
      - Phagosome + lysosome → phagolysosome

   b. Killing/Degradation
      - ROS (HOCL) or NO or ONOO or Anaerobic

7. Termination
   - Lipoxins
   - Cytokines
   - Resolvins & Protectin

Mediators of Inflammation

Overview

Origin	Cells	Plasma Proteins
Synth	Preformed or De Novo	Liver (circulating inactively)
Types	1. Vasoactive • Histamine • Serotonin 2. AA[1] Metabolites • Prostaglandins • Leukotrienes • Lipoxins 3. PAF[2] 4. ROS 5. Cytokines	1. Complement 2. Coagulation & Kinin
Commonality	All are short lived due to enzyme inhibition, antioxidants or decay	

[1]Arachadonic acid
[2]Platelet activating factor

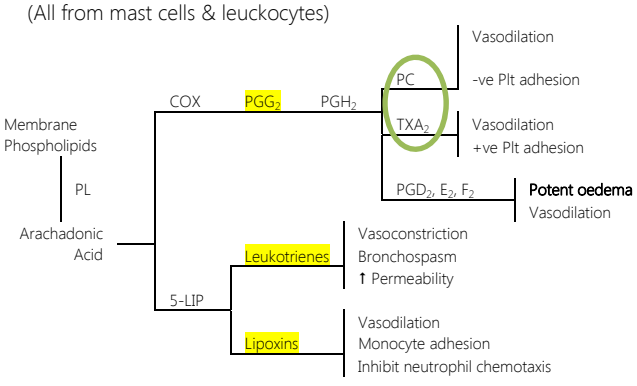
Cell Origin

1. Vasoactive Mediators (dilation + ↑perm)

Histamine	Serotonin
M>>>BP	P only
+ endothelial activation	

M (macrophages) B (basophils) P (platelets)

2. Arachadonic Acid Metabolites
   (All from mast cells & leuckocytes)



3. Platelet Activating Factor
   - From ***Leukocytes & Mast Cells***
   - Derived from phospholipids
   - Causes plt aggregation/leukocyte adhesion, ↑ permeability (x100-1000 histamine), bronchoconstriction, chemotaxis

4. Reactive Oxygen Species
   - From Leuckocytes (NO from endothelium)
   - All cause direct injury via membrane damage
   - NO also inhibits plt adhesion, recruitment

5. Cytokines

	Cell	Cytokine	Action
Chemokines	ML	CXC	Chemotaxis – neutrophils
	ML	CC	Chemotaxis – all other
	ML	C	Chemotaxis – lymphocytes
	M	TNF	Systemic response, Body Mass
	M	IL-1	Systemic response
	M	IL-6	Systemic response
	L (T)	IL-17	Neutrophil recruitment

Local Effects			Systemic Effects
Vascular Endo	leukocytes	Fibroblasts	
• ↑ Adhesion • IL-1 ↑ Coagulation	• Activation • ↑ Cytokines	• ↑ Number • ↑ Collagen	• Fever • Leucocytosis • Proteins • ↑Sleep • ↓ Appetite
Inflammation		Repair	

6. Lysosome Contents
   - From neutrophils or monocytes
   - Neutrophils have 2 types
     1. Primary (large)
        - Myeloperoxidase
        - Bactericidal factors
        - Proteases

     2. Secondary (small)
        - -ases for histamine, collagen, gelatin

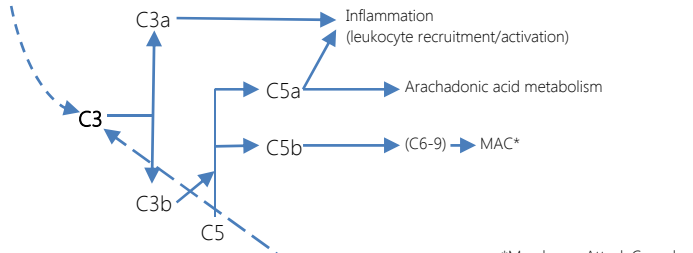
Plasma Origin

1. Complement (C1-9)
   - Liver Synth, autocatalytic activation
   - C3 bridges activation & effect

Activation

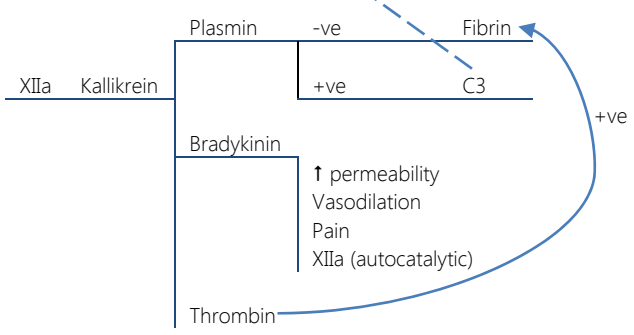
Classic	C1 binds antigen-antibody complexes
Alternative	Complement binds microbial surface molecules
Lectin	Complement binds CHO

Effect
- C3 splits into C3a (breaks off) or C3b (stays bound to microbe)



*Membrane Attack Complex

2. Coagulation & Kinins
   - Inflammation ↑ [clotting factors]
   - Thrombin (factor II) binds to PAR-1 → inflammation



Inflammation

Outcomes of Acute Inflammation

1. Complete Resolution
2. Fibrosis
3. Chronic Inflammation

Types of Acute Inflammation

a. Serous: transudate (eg effusions)
b. Fibrinous: exudate
c. Suppartive: liquifactive necrosis
d. Ulcer: sloughing of inflamed necrotic tissue

Chronic

Causes

- Acute Inflammation
- Persistent stimulus/recurrent acute inflammation
- Low grade response

Due to:

- Microbial
- Immune
- Exogenous toxin

Macrophages

- Circulating ***monocytes*** emigrate to interstitial tissue
- Transform into macrophages
- Role of macrophages differentiated depending on cytokine stimulation (by t cells or microbes) via:
  - IL-4: repair
  - IFN-γ: killing
- Also cause local inflammation through release of ROS incl NO

Other Chronic Inflammatory Cells

- Lymphocytes: activate macs (vice versa)
- Plasma cells: produce antibodies
- Eosinophils: parasitic infections
- Mast cells: binds Fc of Ig eg anaphylaxis

Granulomas

- Type of chronic inflammation with typical morphology
- Focus of macrophages fuse to form giant cell
- Giant cells cause central necrosis (+/- FB)
- Collar of lymphocytes
- Rim of fibrosis around that

Systemic Effects

- Spans "acute phase response" to SIRS
- Due to cytokine release
- Changes include
  1. Pyrexia (mostly via PGE_2 release via COX)
  2. Acute phase proteins (CRP, fibrinogen, ESR)
  3. Leuckocytosis

Repair

Summary

1. Proliferative types
2. Stem Cells
3. Cell Cycle & Regeneration
4. Mechanism of Tissue & Organ Regeneration
5. ECM ↔ CM
6. Healing: Repair, Scar, Fibrosis
7. Cutaneous Wound Healing
8. Local/Systemic Factors in Wound Healing
9. Pathological Aspects of Repair

Proliferative Cell Types

Type	Function	Examples
Labile	Cont dividing	Surface epithelia, marrow
Stable	Quiescent	Liver, kidney, fibroblasts, endothelium
Permanent	Non dividing	Neurons or myocytes

Stem Cells

2 methods of replication/differentiation

	Asymmetric replication	Stochastic
Stem Cell 1	1 Stem + 1 Differentiated	2 stem cells
Stem Cell 2	1 Stem + 1 Differentiated	2 differentiated cells

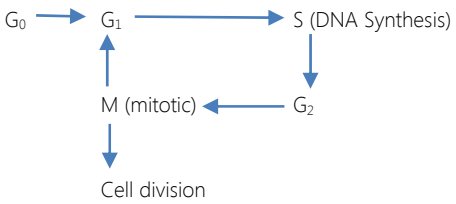
Types

Stem Cell	Function
Embryonic	Pluripotent (multipotent have less differentiating potential)
Induced Pluripotent	Repgrogrammed adult differentiated cells
Adult (Somatic)	Maintain normal tissue homeostasis

Examples of Stem Cells

- Haemopoetic
- Liver (bipotent)
- Brain (unclear fcn)
- Skin
- Intestinal
- Limbal cells in cornea
- Skeletal muscles regeneration via satellite cells

Cell Cycle & Regeneration



Growth Factors

- Stimulate proliferation, cell movement, contractility, differentiation, angiogenesis through ***gene transcription***
- Sources include *macs, plt, mesenchymal cells*

GF		Fcn
EGF	Epidermal	Fibroblasts, hepatocytes, epithelial cells
TGF-α	Transforming	As above
TGF-β	Transforming	Growth inhibitor, anti-inflammatory via nuclear transcription Δ
HGF	Hepatocyte	Mitogenic on epithelial cells and emryogenic
PDGF	Plt derived	Migration/proliferation of fibroblasts, monocytes, smooth musc
VEGF	Vascular Endo	Vasculogenesis, Angiogenesis
FGF	Fibroblast	Angiogenesis, repair, hematopoesis

TTHEPVF

Signalling Mechanisms

- Autocrine: liver, antigen-stimulated lymphocytes, tumours
- Paracrine: wound repair, inflammation, embryonic development
- Endocrine

Types of Receptors/Signalling Pathways

- Receptor-Ligand
- Receptors with intrinsic kinase activity (most GF)
  - IP3/MAP via TK activation on receptor
- Receptors without intrinsic kinase activity (cytokines)
- G-protein/2nd mssenger
- Steroid receptors (nucleic)

Repair

Mechanisms of Regeneration

- Usually compensatory growth through ***hyperplasia*** (liver, pancreas) or ***hypertrophy*** (kidney)
- Usually due to rapid fibroproliferative response

ECM ↔ CM

ECM Functions

- Interstitial matrix
- Basement Membrane
- Cell migration/anchorage, polarity, differentiation, growth
- Depot for growth factors

ECM components

1. Fibrous structural proteins (framework/tensile strength)

   Collagen

Type	Location
I	Skin & Bone
II	Cartilage
III	Hollow or soft tissues
IV	BM

   Elastin, Fibrillin & Elastic Fibers

   - Elastic fibres: elastin core and fibrillin scaffolding
   - Fibrillin defect = Marfan's

2. Adhesive glycoproteins (adheres) (***CAMs***)
   - Usually transmembrane receptors

Location	Type	Function
Cellular	Immunoglobulins	
	Cadherins	Attach to cytoskeleton
	Integrins	Attach to cytoskeleton Binds cell to ECM (Fibronectin)
	Selectins	Sugar Lectin
	Cadherins	Attach to cytoskeleton Cell-cell binding forming zonula adherens or desmosomes
ECM	Fibronectin	Binds to integrins
	Laminin	BM but binds cells or ECM

3. Gel of proteoglycans and hyaluronan (lubricates)
   - Proteoglycans are glycosaminoglycan with a protein core
   - HA bind water to give it turgor but also binds to other ECM elements

Healing: Repair, Scar, Fibrosis

- Scar: fibroproliferative response with deposition of collagen and other ECM components (when unable to regenerate)
- Regeneration: *complete resolution* with new tissue

Dependencies

1. Proliferative capacity of original tissue
2. ECM integrity
3. Duration of insult

Cutaneous Wound Healing: Sequence of Healing

- Similar in other tissues

1. Inflammation (2-6 days)
   - Day 1 Plt adhesion/clot formation
   - Day 1-2 Granulation tissue formation (inflam recruitment)

2. Proliferation (6-12 days)
   - Parenchymal cell migration/expansion
   - Neutrophils replaced by macrophages
   - Granulation → scar (fibroblasts, collagen)

   Angiogenesis
   - Branching of pre-existing vessels & recruitment
   - Vasculogenesis = new vessels from stem cells

   Sequence of Events
   1. Vasodilation with NO
   2. ↑ Permeability (VEGF)
   3. BM breakdown (Metalloproteinase)
   4. Cell-cell breakdown (Plasminogen activator)
   5. EC proliferation/migration
   6. EC maturation
   7. Pericyte recruitment (stabilise new vessels)

   } VEGF+++

3. Maturation (12-16 days)
   - ECM deposition (collagen mostly) / vasculature regression
   - CT Remodelling
   - Wound contraction (by myofibroblast in larger wounds)

Tensile Strength

Time	Strength
1 week	10%
3 months	70-80%

Healing By Intent

Primary	Secondary
Min cell death	Angiogenesis
Min BM damage	fibroblast ingrowth
Min fibrosis	collagen & dense scar formation (contraction)

Local/Systemic Factors in Wound Healing

Local	Systemic
• Size/Location/Type	• Nutrition
• Infection	• Metabolic status
• Trauma	• Circulation
• FB	• Hormones

Pathological Aspects of Repair

- Wound dehiscence
- Keloid
- Contractures

Haemodynamics

Summary
1. Oedema
2. Haemostasis & Thrombosis
3. Thrombosis
4. Embolism
5. Infarct
6. Shock

Oedema (hydrostatic ↔ oncotic ↔ lymphatic drainage)

Mechanism	Cause	
↑ Hydrostatic	Impaired Venous Return • CHF • Constrictive Pericarditis • Ascites • Venous obstruction/compression[1]	Arteriolar Dilation • Heat • Neurohumoral dysregulation
↓ Oncotic	• Protein loss (renal) • Liver cirrhosis	• Malnutrition • Protein-losing gastroenteropathy
Lymphatic obstruction	• Inflammatory • Neoplastic	• Postsurgical • Postirradiation
Na retention	• Excess Na input • Excess reabsorbtion	• Renal hypoperfusion • ↑ renin-angio-ald secretion
Inflammation	• Acute • Chronic	• Angiogenesis

[1]Thrombosis, Mass, Lower extremity inactivity

Clinical Consequences
- Impaired wound healing/gas exchange/cerebral flow/herniation

Hyperaemia vs Congestion
- Hyperaemia: active, due to arteriolar dilation
- Congestion: passive, due to impaired outflow

Haemorrhage
- Petechiae 1-2mm
- Purpure >3mm
- Ecchymosis > 1cm

Haemostasis & Thrombosis (endothelium ↔ plt ↔ coagulation)
- Haemostasis = homeostatic
- Thrombosis = abnormal clotting

Normal Haemostasis
1. Reflex arteriolar vasoconstriction (by endothilin)
2. **Primary haemostasis (platelet activity)**

Endothelial cell damage promotes
- Plt adhesion/activation via vWF → intrinsic cascade
- Tissue Factor release → extrinsic cascade

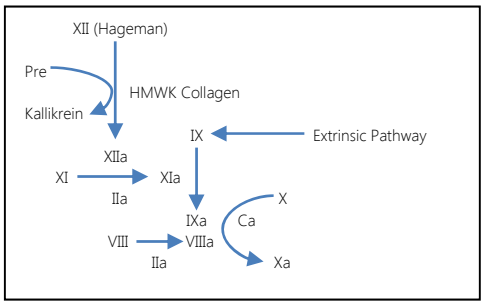
Plt Response

Adhesion	Glycoprotein Ib binds exposed vWF
Degranulation (activation)	α granules = coag & growth factors δ granules = ADP, Ca, Histamine Surface expression of ***phospholipid complex****
Aggregation	ADP = GIIb-IIIa plt receptor binds fibrinogen TXA_2 = vasoconstriction

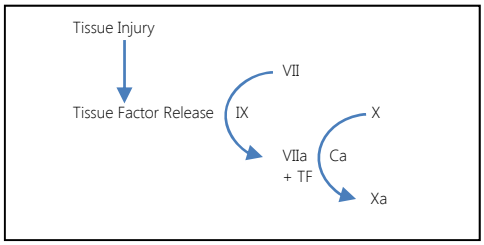
*focus of cascade

3. **Secondary haemostasis (Clotting Cascade)**
- Plt degranulation sets up environment for clotting cascade
- Final step Fibrinogen → Fibrin → Cross link

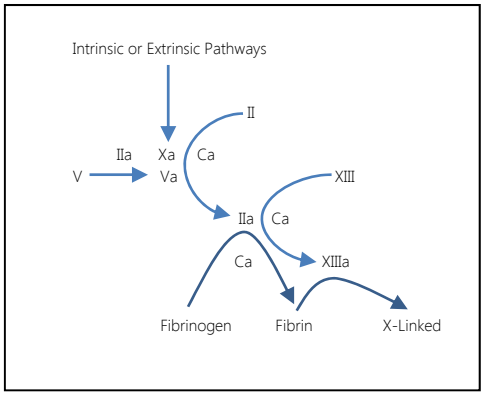
Intrinsic
- More important in inflammation
  (Deficiency doesn't cause bad coagulopathy)
- Initiated by XII activation when in contact with collagen



Extrinsic
- Main pathway in haemostasis
- Faster initiation (less cascades)



Common Pathway
- Starts at Xa
- PT & PTT both measure these factors



Measuring Intrinsic or extrinsic clotting time
- Thromboplastin = TF + Phospholipids
- Partial Thromboplastin = Phospholipids only

∴ aPTT = intrinsic & PT = extrinsic

Control Mechanisms

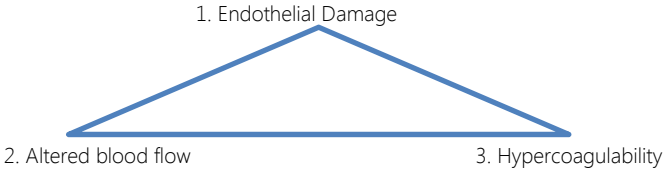
Primary Haemostasis
- Limited to area of ECM exposure
- ADP inhibits plt aggregation
- PGI_2 & NO inhibit plt binding

Secondary Haemostasis
- Limited to area of ECM exposure
- AT complex with heparin-like cofactors from endothelium
- Thrombomodulin cleaves protein C & S → inhibit VIIa
- TFPI inhibit VIIa-TF complex
- IIa induces tPA release → plasmin → cleaves fibrin
- α2 macroglobulin inhibits thrombin

Haemodynamics

Thrombosis

Virchow's Triad



Morphology
- Propagate to the heart (ie ***arterial are retrograde***)

	Venous	Arterial
Cause	Stasis	Endothelial injury or Turbulence
Occlusive?	Yes	Small only
Fatal Event	Embolisation	Occlusion
Morphology	Homogenous	Laminations
Risk Factors	Immobilisation CHF Trauma/Surgery/Burns Puerperal/Postpartum Tumours	Atherosclerosis AF MI Valvular disease

Fate
- Propagation
- Embolisation
- Dissolution
- Organisation/Recanalization
- Mycotic aneurysm

Embolism

Pulmonary
- 95% from DVT (DVT x3 more common – 50% ASx)
- Special types: *Saddle, Paradoxical*

Clinical Outcomes of PE

Clinically	Microscopically
Silent (60-80%)	PE in small arteries = haemorrhage or infarct
Death (≥ 60% obstruction)	PE in medium arteries = haemorrhage
Chronic = PHTN or RHF	

Systemic

Origin	Intracardiac Mural Thrombi (80%) • MI 66% • AF 25% Aortic aneurysm Thrombus Ulcerated plaques Vegetations
Sites of embolisation	Lower limbs 75% Brain 10%
Outcomes	Infarction unless adequate collateral supply

Other

Fat & Marrow	• Long bone fractures • < 10% have clinical findings • Fat embolism syndrome D1-3
Air	• Pulmonary needs > 100cc • Decompression sickness
Amniotic Fluid	• 1 in 40, 000

Infarction
- Ischemic necrosis due to arterial occlusion (97%) or venous occlusion (usually single venous drainage eg gonads)
- Rare causes include *vasospasm* or *extrinsic compression*

Development of Infarct Depends on
- Vascular supply (collaterals eg liver or lung)
- Rate of occlusion
- Vulnerability to hypoxia (eg neurons)
- Oxygen saturation

Morphology
- Wedge shaped (occluding vessel at apex
- Coagulative necrosis (except brain)

Red	White
Haemorrhagic • Venous occlusion • Loose tissue (lungs) • Dual circulation • Previous congestion • Previous occlusion/necrosis	Pale, Anaemic • Solid organs

Shock
- Systemic hypoperfusion

- Cardiogenic
- Hypovolemic
- Septic
- Neurogenic
- Anaphylactic

Septic Shock
- GPB

Pathogenesis
- Inflammation
- Endothelial cell activation = DIC
- Metabolic derangement = hyperglycaemia/insulin resistance
- Immune suppression (heavy response mechanism)
- End organ dysfunction

Stages
- Non progressive
- Progressive
- Irreversible

Immunity

Innate vs Adaptive

Innate

- Epithelium
- Phagocytes: mainly neutrophils & macrophages
  but also monocytes, dendritic cells, NK cells and mast cells (**MMND**)
- Reactions: 1. Inflammation
  2. Anti-viral defence (NK & dendritic cells)

Adaptive

- Humeral (B cells) vs Cellular (T cells)

Lymphocyte	%
T Cells	60-70
B Cells	10-20
NK cells	10-15

Humeral

- B for bone marrow derived
- Antigen stimulation → turn into plasma cells (secrete antibodies)
- BCR (Ig) have IgM and IgD (both membrane bound) to help identify antigen
- IgG T ½ = 3 weeks

Follicular dendritic cells (not 'normal' follicular cells)
- Found in germinal centre of lymphoid follicles (spleen, nodes)
- Have Fc receptors for IgG & C3b
- Trap antigen bound to Antibodies or complement proteins
- Present to B cells

Macrophages
- Phagocytose opsinised (IgG or C3b) microbes

Cellular

T Cells
- T for thymus derived
- T cell receptors (TCR) are antigen specific
- Proliferation is polyclonal (recognises many antigens ∴ monoclonal = neoplastic)
- Antigens are presented to TCR by MHC on APCs (or peptide frag from macs)

TCR		MHC	Function
CD4+	60%	Class II	Secrete cytokines for enhances mac or b-cell killing
CD8+	30%	Class I	Kill host cells harbouring microbe

Dendritic Cells
- Under epithelia, in interstitia & spleen (Langerhans cells refer to immature epithelial cells)
- Receptors include TLR (toll like receptors), and other antigen receptors
- Mobilise to lymphoid aggregates for T cell recognition
  NB follicular dendritic cells occur in humeral immunity

Macrophages
- Phagocytose and present peptide fragments to T cells for recognition
- T cells also increase macrophage proliferation

Natural Killer Cells
- No receptors (TCR or Ig)
- Early defence in absence of prior exposure or activation by microbes or tumours
- ***Antibody cell mediated cytotoxicity***
  CD16 is an Fc receptor on IgG and recognise/lyse IgG coated targets
- Recognise self-class I MHC (down regulated in infected cells)
- NKG2D recognise surface molecules expressed in stress etc
- Secrete cytokines to activate macrophages

Tissues of the Immune System

Primary (generative)
- Mature lymphocytes
- Bone marrow (B cells) & Thymus (T cells)

Secondary (peripheral)
- Lymph nodes, spleen, epithelial and mucosal aggregates
- Concentrate antigen, APC and lymphocytes

Structure: Nodes
- Cortex: B cells (as follicles) – germinal centres if activated
- Paracortex: T cells
- Follicular edge – B cell & T_H cell interaction → B cell activation

Structure: Spleen
- Peri arteriolar: T cells
- Follicles: B cells

Lymphocyte Recirculation

- T cells migrate to tissues
  - Naïve T cells migrate to lymph nodes
  - Activated by Antigen recognition
  - Migrate to site of infection
- B cells turn into plasma cells. Stay in lymph tissue and release antibodies into circulation

Major Histocompatibility Complex

Class	I	II
Expression	All nucleated cells and platelets	Phagocytes with microbes[1]
Encoding	HLA-A, B & C	HLA-D
Action	Intracellular foreign proteins → ER & binds MHC I → Presented on surface to CD8+	Extracellular microbes internalised → endosome or lysosome proteolysis → MHC II binds peptide →presented on surface to CD 4+

[1] Macs, b cells, dendritic cells

HLA dysfunction
(HLA-B* = inflammatory, HLA-D* = autoimmune, HLA-* = inherited errors of met)

Type	Dysfunction	Examples
HLA-A	Inherited errors of metabolism	hemochromatosis
HLA-B	Inflammatory	27 Ank spondylitis
HLA-D	Autoimmune	R3 Sjogrens R4 Rh Arthritis R3,4,3/4 IDDM

Lymphocyte Activation

Display & Recognition

- Requires co-stimulation of both innate (signal 2) and humoral (signal 1)

- Dendritic cells capture microbes & deliver to lymphatic tissue
- Phagocytic cells complex with MHC internally and display on cell surface
- B cells have antigen receptors

- Innate system is activated in parallel with humeral system
- Activated APCs to express costimulators → cytokines → t cell proliferation/differentiation
- Costimulators include CD80 & 86 (recognised by CD28 – naïve T cells)

Activation & Elimination (cellular)

- Phagocytes present antigen to CD4+ → CD40 expression → phagocyte expression
- CD4+ initially secrete AND express IL-2 → self-proliferation
- CD4+ also differentiate into effector cells:

TH1: Secrete IFN-γ → potent macrophage activator
TH2: Secrete IL-4 → B cell stimulation → Plasma cell differentiation →IgE secretion
Secrete IL-5 → eosinophil activation
TH17: Secrete IL-17 → potent neutrophil & monocyte recruitment

Activation & Elimination (humoral)

- Full B cell response to antigen requires CD4+
- B cells ingest protein antigens into vesicles → degrade → display MHC complexed peptides → CD4+ recognition → CD40 expression → B cell activation

Elimination
→ Neutralise microbe
→ Opsonise via IgG & IgM cell surface expression
→ Activation of classical complement pathway → phagocytosis
} TH1 stimulates
Eg IgG crosses placenta for immunity cover

Decline in Response/Formation of Memory

- Apoptosis or Memory Cells

Memory Cells
- Increase pool of antigen-specific lymphocytes
- Faster response (than naïve T lymphocytes)

Hypersensitivity & Immunity

Hypersensitivity

Type 1: IgE mediated

Mechanism	**Initial Exposure** → allergen introduced → allergen presented to naïve T cells by dendritic cells → T cells differentiate to CD4+ → CD4+ secrete IL-4 and other cytokines → B cells class switch to IgE / additional CD4+ activation → Memory cells **Re-exposure** → allergen binds to Memory cells → IgE secreted → Mast cell activation through IgE binding Fc region → Degranulation → Vasoactive amines (immediate reaction) → Membrane phospholipid breakdown (Leukotrienes, PG, PAF) → Cytokines (late phase)
Pathological Lesions	1. Immediate Reaction (5-30 min) • Vascular dilation • Oedema • Smooth muscle contraction • Mucus production 2. Late Phase Reaction (2-24 hrs lasting up to several days) • Eosinophils important (IL-5 potent activator) • Tissue injury • Inflammation
Prototypical	anaphylaxis, bronchial asthma
Other	Atopy = predisposition for Type I hypersensitivity – genetically predetermined

Mediators of Type I

Primary (preformed)
- Vasoactive amines: histamine
- Enzymes: neutral proteases (chymase & tryptase), acid hydrolases
- Proteoglycans: heparin, chondroitin sulphate

Lipids
- Leukotrienes
- Prostaglandins
- PAF

Mast Cells
- Bone marrow derived
- Near blood vessels and nerves in subepithelial plane
- Bind IgE F receptors or Complement (C5a, 3a), physical, Drugs

Basophils
- Also have IgE Fc receptors
- Circulating in low numbers (not in tissues)

Type 2: Antibody-mediated

Mechanism	**1. Opsonisation/Phagocytosis** → Opsonisation by complement (C3b & C4b) & antibodies (IgG) → Ingested by phagocytes **2. Complement & Fc receptor mediated inflammation** → Antibody binds to Fc on leuckocytes → Inflammation **3. Anti-receptor antibody** → Antibody binds to receptor to inhibit function Dysfunction without cell injury or inflammation
Pathological Lesions	• Phagocytosis +/- functional derangement without cell or tissue injury • Inflammation
Prototypical	**1. Opsonisation:** Transfusion, Haemolytic disease of the newborn, autoimmune haemolytic anaemia, thrombocytopenic purpure, **2. Inflammation:** Goodpastures, rhematic fever, vasculitis (from ANCA) **3. Anti-receptor:** Myasthenia, Graves, IDDM

Type 3: Immune complex mediated

Mechanism	**Systemic Immune Complex Disease** 1. Antibody-antigen complex formation in circulation (B cell binds antigen and releases antibody) 2. Deposit in tissues, leukocyte recruitment/activation 3. Inflammation of complex deposition (esp neut & monocytes)
Pathological Lesions	• Inflammation • Necrotizing vasculitis (Fibrinoid necrosis)
Examples	SLE, some GN, serum sickness, Arthurs reaction, polyarthritis nodosa, reactive arthritis, Farmer's lung, Henoch-Schonlein

Type 4: Cell-mediated

Mechanism	**1. CD4+ Proliferation & Differentiation** • Dendritic cells present antigen to Naïve CD4+ (also secrete IL-12 → TH1) • CD4+ secrete IL-2 → Proliferation of self IFN-γ → Proliferation of TH1, Mac activation **2. Response** • Repeated exposure: IFN-γ → Proliferation of TH1, Mac activation • TH17 sometime activated → IL17, 22 → neutrophils & monocytes Or CD8+ activation → perforins & granzymes
Pathological Lesions	• Perivascular cellular infiltrates • Oedema • Granuloma formation • Cell destruction
Prototypical	Contact dermatitis, IDDM (CD8+), Graft rejection (CD8+), Rheumatoid Arthritis, IBD, TB (and tuberculin reaction), MS, Guilain-Barre, Graft versus Host
Other	Sequelae include granuloma formation

Autoimmune Disease

SLE

- Female > Male
- Rash: malar & discoid
- Photosensitivity
- Ulcers (oral)
- Arthritis
- Serositis (pleuritis)
- Renal failure
- Seizures or Psychosis
- Heam: anaemia, leukopenia, lypmphopenia, thrombocytopenia
- Immunological disorder: Anti-DNA, Anti-Sm, Anti-phospholipid
- Antinuclear antibody

Tissue Rejection
- Type 4 > 2 Hypersensitivity

Type 4
- APCs present foreign HLA to CD4 & 8 to produce rejection
- Direct: CD8+ or CD4+ releasing inflammatory mediators (IFN-γ)
- Indirect: CD4+ activate B lymphocytes to release antibodies (chronic rejection)

Type 2 (humeral rejection)

Type of Rejection	Mechanism
Hyperacute	Antidonor antibodies in circulation • Previously rejected transplant • Multiparous women who develop anti-HLA antibodies against paternal antigens • Previous blood transfusions First target is donor vasculature ie Rejection vasculitis
Acute	• Days (or suddenly months or years later) • Humeral rejection: vasculitis • Cellular rejection: interstitial mononuclear infiltrate – responds well to immunosuppressant
Chronic	Vascular changes: dense intimal fibrosis → Ischaemia Interstitial fibrosis Atrophy

AIDs

At Risk Group	%	At Risk Group	%
Homo/Bisexual males	50	Blood transfusions	1
IV drug abuse	20	Haemophiliacs[1]	0.5
Heterosexual contacts	10	Needle stick[2]	0.3
Unknown	5		

[1]Esp Factor VIII or IX before 1985
[2]Prophylaxis reduces x8
NB 2% of all AIDs are < 13yo (ie vertical transmission)

Routes
Sexual contact (> 75%) via direct inoculation or infection of dendritic or CD4+
- Most common route of spread: heterosexual sexual contact
- Usually Male > Male or Male > female (female > male 20x less potent)

Mother-to-infant
- Transplacental
- Delivery (most common = 7 – 49%)
- Breast milk
- Risk factors: high maternal viral load, low CD4+, chorioamnionitis

Parenteral inoculation
- Now less than 1 in 2 million

HIV
- Retrovirus
- HIV-1: US, Europe, Central Africa
- HIV-2: West Africa, India
- Standard RNA genes: gag, pol, env
- Main target: cell mediated immunity = Low CD4+ and impaired function of TH
- Main target organs: lymphoid, CNS also (microglial – macrophage lineage)
  - CNS: normal neurons, abnormal microglia
  - Severe symptoms despite limited histological change
  - Probably due to glial secretions

Life Cycle

Infection:
Main targets are memory CD4+ or dendritic cells and migrate to lymph nodes
→ gp120 (on virus) binds CD4
→ gp120/CD4 requires CCR-5 (on virus) to complete activation
→ gp120/(CD4/CCR-5) causes conformational change to gp41 (on virus)
→ Membrane penetration
→ Membrane fusion

Replication:
→ Reverse transcription → dsDNA (c & proviral) ----------can remain for months/years
→ Target Memory and active T cells (not naïve T cells)
→ Activation by antigen (as per normal CD4+ cells)
→ Cell replication & lysis

Major Abnormalities of Immune Function
- Lypmphopenia: mostly CD4+
- ↓ T cell function (memory), ↓ Type IV hypersensitivity, opportunistic infections, neoplasm
- Altered T cell function: ↓ response, cytotoxicity, helper function
- Polyclonal B cell activation: unable to mount normal antibody response
- Monocyte/Macs: ↓ chemotaxis/phagocytosis, ↓ MHC II expression, ↓ APC function

Natural History
1. Acute Phase

- Mainly CD4+ deficiency
- Replication in lymph nodes → viraemia (days)
- Dissemination
- Seroconversion (3 to 7 weeks)
- Initial containment of HIV by CD8+ cells

Acute viral syndrome:
- week 3-6
- spont resolves after 2 to 4 weeks
- Sx: sore throat, myalgia, fever, weight loss, fatigue

Stable
- Occurs when virus↔ humoral/cellular immunity = viral set point (HIV-1 RNA level)
- Can be stable for years
- Viral set point predicts HIV progression
- CDC categories: 1 = > 500 | 2 = 200-499 | 3 = < 200

2. Middle (chronic) phase
- 7-10 years (early progresses = 2-3 years, long term progresses = 10 yrs)
- No/few clinical manifestations
- Replication in spleen and nodes (almost none peripherally)
- To start with amount destroyed < amount synthesised
- Gradually reverses

3. Clinical AIDs
- Breakdown of host defence
- Starts with long lasting non-specific sx eg fever, weight loss, diarrhoea
- Opportunistic infection

AIDS defining Opportunistic Infections

Infection	Type
Bacterial	• Mycobacteriosis • Nocardiosis (pneumonia, meningitis, disseminated) • Salmonella (recurrent)
Viral	• CMV (pneumonia, intestinal, retinitis, CNS) • HSV (resp & oesph) • VZV • Leukoencephalopathy
Fungal	• Pneumocystis • Candidiasis (resp & oesph) • Cryptococcus (meningitis) • Coccidoidomycosis • Histoplasmosis
Protozoa/Helminths	• Cryptococcus • Toxoplasmosis (CNS)

AIDS defining Tumours

Kaposi Sarcoma
- Most common (up to 30% at time of dx) 5 per 1000
- From HHV8 (human herpes virus 8)
- Spindle shaped cells that express endothelial and smooth muscle
- Chronic inflammatory infiltrates & angiogenic recruitment
- HHV8 + HIV also → rare b cell lymphomas, castleman disease
- Can have normal CD4+ counts

Non Hodgkin B cell lymphoma
- 6% of all AIDs patients
- Systemic (80%), Primary CNS (20%) or Body cavity
- Almost all have EBV as well
- Always have low CD4+ counts
- Including Burkett's

Cervical Cancer Invasive
- From HPV

NEOPLASIA

Nomenclature

- Neoplasia: new growth = neoplasm = tumour
- Tumours are clonal – come from single cell
- Some are mixed eg salivary gland tumours (pleomorphic adenomas)
- Teratoma – all 3 germ layers involved (all other neoplasms are single germ layer derived)

- **Benign**: remain localised
- **Malignant**: can invade and destroy structures and spread to distant sites

All tumours have 2 basic components
- Clonal neoplastic cells – make up the parenchyma
- Reactive stroma – CT, BV, macs, lymphocytes – framework and nutrition

- **Desmoplasia** – excess collagenous stroma
- **Hamartoma** – disorganised mass of cells of indigenous origin – benign
- **Choristoma** – normal cells in abnormal location eg pancreatic cells in stomach

Benign
- End in –oma
- Adenoma – benign epithelial neoplasm derived from glands (not necessary to form glands)
- Papilloma – finger like projections from epithelial surface
- Cystadenoma – benign cyst forming adenomas
- Papillary cystadenoma – benign cyst forming adenoma that protrudes
- Polyp – grossly visible projection above mucosal surface

Malignant
- Sarcoma – malignant from mesenchyme (very little CT)
- Carcinoma – epithelial malignancy
  - Squ cell carcinoma (based on appearance of stratsified squamous epithelium)
  - Adenocarcinoma (glandular pattern)
- Can be differentiated → undifferentiated
- Others not called sarcoma or carcinoma: ***mesothelioma, leukaemia, lymphoma, seminoma, melanoma, wilms tumour***

Characteristics of Tumours

Differentiation and Anaplasia
- Anaplasia = poorly differentiation
- Benign = well differentiated
- Malignant = well → moderately → anaplastic

Morphological changes of Anaplasia
- Pleomorphism: variable size & shape of cell and nuclei
- Polarity: disorganised cell growth
- Other: tumour giant cells, focal necrosis common

Nuclear morphology:
- Hyperchromia from lots of chromatin coarsely clumped along nuclear membrane
- Large nucleus & nucleoli
- Nuclear : cytoplasmic = 1:1 (normally 1:4-6)
- Mitosis: bizarre shapes (eg tri-spindle), also large number (but not pathognomic of malignancy) eg bone marrow, bizarre shapes eg tri-polar spindles

Metaplasia
- Reversible replacement of 1 cell type to another
- Normally columnar → stratsified (apart from resp epithelium)

Dysplasia
- Disorderd growth: Loss of uniformity & loss of architecture
- Seen in metaplastic epithelium (not all)
- Nuclear morphology same as anaplasia
- Carcinoma in situ – dysplasia confined by BM
- Does not always progress to cancer & reversible process when full thickness

Rates of Growth

- Clinically detectable size = 10^9 cells = 1g
- By the time tumour is detectable it has already completed a major portion of its life span

Factors:
1. **Doubling time** (∝ level of undifferentiation – exceptions include uterine fibroids)
2. **Fraction** that can replicate (Growth fraction – size ↓with each replication) chemotherapy targets the growth fraction, reason for debulking tumours – as this will boost growth fraction
3. **Rate of shed** or death

Cancer Stem Cells & Lineage
- Concept of cancer stem cells for targeted therapy
- Low rate of cell division
- Tumour initiating cells (T-IC) have been identified – able to replicate tumour in mouse
- Variable populations between cancers

Local Invasion
- Benign tumours usually have fibrous capsule as a result of pushing and compressing surrounding CT
- Some do not have such discrete planes eg Haemangiomas – can erode skin
- Carcinoma in situ has anaplastic change without BM penetration

Metastasis
- Neoplasm distant to site
- Most malignant cells have mets potential (except gliomas and BCCs)

Routes

Direct body cavity/surface
- Penetrates into natural opening eg peritoneal cavity
- Seen in ovaries

Lymphatic
- Most common
- Sentinel node: first node to receive lymph

Haematogenous
- Typical of sarcomas
- Veins > arteries
- Liver and lung most common recipients
- Thyroid & prostate → vertebral
- RCC → venous spread
- HCC → portal vein
- Mets not always in series eg Breast → bone

Clinical Features

Local & Hormonal Effects
- Obstruction has variable consequences depending on location
- Local erosions → blood loss, infection
- Hormonal effects seen more often with benign (differentiated) lesions
- Paraneoplastic syndrome

Cancer Cachexia
- Loss of body fat/lean body mass & profound weakness, anorexia, anaemia
- Due to ↑ basal metabolic rate (vs starvation)

Paraneoplastic syndrome
- 10% of malignant disease

Syndrome	Cancer	Mechanism
Endocrine		
Cushing's Syndrome (most common endocrine)	Small cell lung (50%) Pancreatic Neural	ACTH or ACTH-like substance
SIADH	Small cell lung Intracranial	ADH or Atrial Natriuretic hormone
Hypercalcaemia (most common syndrome)	Squamous of lung Breast Renal Adult T cell leuk/lymph NB NOT bone cancer	PTH related protein TGF-α TNF IL-1 → Osteolysis
Hypoglycaemia	Ovarian Fibrosarcoma Sarcoma	Insulin/like
Carcinoid	HCC Bronchial adenoma Pancreatic	5HT Bradykinin
Polycythaemia	Gastric Renal Cerebellar HCC	EPO
Nerve & Muscle		
Myasthenia	Bronchogenic	Immunological
CNS/PNS	Breast	Unknown
Dermatological		
Acanthosis Nigricans	Gastric Lung Uterine	Epidermal GF
Dermatomyositis	Bronchogenic Breast	Immunological
Osseous		
hypertrophic osteoarthropathy and clubbing	Bronchogenic	Unknown
Vascular/Haem		
Trousseau (VTE)	Pancreatic Bronchogenic Most others	Tumour products
Thrombotic endocarditis (non bacterial)	Advanced cancers	
Red Cell Aplasia	Thymic tumours	
Other		
Nephrotic Syndrome	Variety	
DIC	Myeloid leukaemia, prostate	

Grading and Staging

- Grade = level of differentiation
  - Histologic grading
  - Doesn't always correlate with clinical
- Stage = extent od spread
  - Size of lesion and spread
  - TNM (Tumour, Nodes, Mets)
  - T0 = in situ, T0-4
  - N0-3
  - M0-2

Laboratory Diagnosis of Cancer

- FNA
- Pap Smear
- Immunohistochemistry
- Flow cytometry
- Molecular diagnosis
- Gene expression

Tumour markers

Marker	Cancer
Hormone	
HCG	Trophoblastic Nonseminomatous testicular tumours
Calcitonin	Medullary carcinoma
Catecholamines and metabolites	Pheo
Ectopic	Paraneoplastic
Oncofetal Antigens	
α-fetoprotein	HCC Nonseminamatous…
CEA	Colon Pancreas Lung Stomach Heart
Isoenzymes	
Prostic Acid Phosphate	Prostate
Neuron-specific enolase	Small cell lung Neurobalstoma
Specific Proteins	
Ig	MM Gammopathies
PSA	Prostate
Mucins/Glycoproteins	
CA-125	Ovarian
CA-19-9	Colonc Pancreas
CA-15-3	Breast

Epidemiology

- Men: Lung, Colon, Prostate
- Women: Lung, colon, Breast
- Geographical: eg gastric ca x6 japan vs US
- Environment: radiation, occupational, obesity, alcohol
- Age

Genetic predisposition

- 10% of malignancies
- Autosomal dominant
  - Dominant inheritance with incomplete penetrance and expression
  - Retinoblastoma
  - Melanoma
  - FAP/Non-polyposis colon cancer
  - Neurofibromatosis 1 or 2
  - Breast & ovarian
  - MEN 1 and 2
  - Nevoid BCC
  - Cowden syndrome
  - Peutz Jaegher syndrome
  - RCC
- Defective DNA-repair
  - Recessive
- Familial
  - Breast, ovary, pancreatic
  - Familial clustering noted without clear inherited predisposition

- Precancerous lesions
  - Leukoplakia
  - Colonic villous adenoma
  - NB most arise de novo

Molecular Basis of Cancer

- Non-lethal genetic damage
- Clonal progeny (heterogeneous end point)
- Multistep
- Targets genes include: growth promoting oncogenes, growth inhibiting tumour suppressor genes, apoptosis regulatory genes, DNA repair genes
- Oncogenes promote autonomous growth (they are mutations of proto-oncogenes)

Invasion and metastasis: Steps

- Clonal expansion/growth/diversification/angiogenesis
- Metastatic subclone
- Adhesion to and invasion of BM
- Passage through ECM
- Intravasation
- Interaction with host lymphocyte
- Tumour cell embolus
- Adhesion to distant BM
- Extravasation
- Metastatic deposit
- Angiogenesis
- Growth

The Warburg Effect

- Cancers use anaerobic glycolysis as first line of energy generation
- Basis to PET scans

Carcinogenic Agents and Their Cellular Interactions

Chemical Carcinogens

- Initiation
  - Direct-acting agents
    - No metabolic conversion to become carcinogenic
    - Unrepaired DNA → replication (to become permanent)
    - Replication by promoters
  - Indirect-acting agents
    - Need metabolic conversion (usually CYP450)
- Promotion
  - Tumour indication in previously initiated cells
  - NB initiated cells are short lived and reversible change and not in themselves tumorigenic

Radiation Carcinogenesis

UV light

- Esp UVB (280-320 nm)

Ionizing Radiation

- Induces DNA mutation through generation of free radicals
- Cell sensitivity to radiation
  - Children: myeloid leukaemia then thyroid cancer
  - Breast and lung less so
  - Skin, bone, gut lease susceptible

Microbial Carcinogenesis

- H Pylori
- Human T cell lymphotropic virus Type 1 → t cell leukaemia/lymphoma
- HPV → cervical carcinoma
- EBV → Burkett's lymphoma (in central Africa and new guinea)
  → b cell lymphoma
  → Hodgkin's lymphoma
  → nasopharyngeal carcinoma
- Hep B & C → HCC

Tumour Immunity

Tumour Antigens

- Tumour specific and tumour associated (eg CEA for diagnosis)

Antitumour Mechanisms

- CD8+ main mechanism
- NK & Macs have a smaller role

INFECTIOUS DISEASES

GENERAL PRINCIPLES

Classes of pathogens

- Bacteria
- Viruses
- Fungi
- Prions
- Protozoa
- Helminths

Prions
- Abnormal host protein (PrP) resistant to protease
- Causes spongiform encephalopathies: CJS, BSE, Kuru
- Can be iatrogenic (CJD) or transmissible (vCJD)

Viruses
- Obligate intracellular parasite
- Structure: nucleic acid genome (DNA or RNA) and protein coat (capsid) +/- lipid membrane
- 20-300nm ∴ seen with electron mic – sometimes inclusion bodies seen eg CMV, HSV not EBV

Bacteria
- Prokaryotes – cell membrane without membrane bound nuclei or other organelles
- Extracellular or intracellular (obligate or facultative)
  - Obligate = chlamydia, rickettsia
  - Extracellular = mycoplasma
- Gram +ve or gram –ve
- Movement: flagella or pili
- Normal intestinal flora: 395 species

Fungi
- Eukaryotes
- Chol cell wall

Protozoa
- Single celled eukaryotes
- Replicate intracellularly (plasmodium) or extracellularly (trichomas)
- Entamoeba: motile or immobile cyst forms

Helminths
- Multicellular organisms
- Produce eggs (schistosomiasis inflammation due to eggs)

Ectoporasites
- Insects or arachnids

Special Techniques for Diagnosing Infection

Technique	Infectious Agent
Gram	Most bacteria
Acid-fast	Mycobacteria
Silver	Fungi, Legionella, Pneumocystis
Periodic Acid-Schiff	Fungi, Amoebae
Mucicarmine	Cryptococci
Giemsa	Campylobacter, Leishmaniasis, malaria
Culture/DNA/Antibodies	All

New & Emerging Infections

Agents of Bioterrorism

Cat	Risk	Agent
A	**High**	Anthrax (bacillus anthracis) Botulism (clostridium botulinum) Plague (Yersinia pestis) Smallpox (Variola major) Tularaemia (Francisella) Viral Haemorrhagic fever (eg Ebola, Lassa)
B	**Mod**	Brucellosis Epsilon (clostridium perfringens) Food (salmonella, e coli) Water (vibrio) Psittacosis (chlamydia psittaci) Q fever (Coxiella burnetti) Typhus (Rickettsia)
C	**Var**	Emerging & engineered

Transmission & Dissemination of Microbes

Skin
- Low virulence through broken, sometimes unbroken (schistosomiasis)
- If not through skin then likely virulent pathogen
- Can go through skin with insect/animal vector

GIT
- Acid protects – not against shigella or giardia
- Mucous, pancreatic enzymes, normal flora, IgA AB in MALT are all defences

Mechanisms of disease
- **Enterotoxins** in food without pathogen
- **Endotoxins** from ingested pathogens eg v. cholera and e coli
- **Invasion** of intestinal mucosa and lamina propria → Ulceration, inflammation, haemorrhage (dysentery) eg shigella, salmonella, campylobacter
- **Sepsis** eg salmonella typhi: damaged mucosa → Peyers patches → mesenteric nodes → blood

Other Pathogens
- Fungal: Immunocompromised patients only
- Protozoa need cysts to overcome acid stomach
  - Giardia attaches to brush border
  - Cryptosporidium internalised by cells
  - Enteromeba histolytica causes contact cytolysis by forming pores in cell mem

Respiratory Tract
- < 5μm → alveoli
- Alveolar macrophages and mucociliary defence
- Mucociliary impairment via
  - Ciliary paralysis: Haemophilus, bordatella
  - Ciliostasis: pseudomonas, mycoplasma

Sexually Transmitted Infections

Pathogen	Disease		
	Both	Male	Female
Virus			
HSV	Herpes		
Hep B	Hepatitis		
HPV	Condyloma cuminatum	Ca	Cervical △ Vulvar Ca
HIV	AIDs		
Chlamydia			
C Trachomatis	Lymphogranuloma venereum	Ure/epidim/proct-it is	Urethral syndrome Cervici/Bartholini/salpingi-tis
Mycoplasma			
Ureaplasma urealyticum		Urethritis	
Bacteria			
N gonorrhoea	Dissemination	Ure/epidim/proct-it is	Urethral syndrome Cervici/Bartholini/salpingi-tis
Treponema	Syphilis	"	"
Haemophilus ducreyi	Chancroid	"	"
Klebsiella	Donovanosis	"	"
Protozoa			
Trichomas		Urethritis, Balanitis	Vaginitis

Mechanisms of Injury
- Direct
- Release toxins
- Induce host immune response

Viral

Tropism = affinity for some host cells, dependant on
- Expression of host receptors
- Cellular transcription factors
- Anatomic barriers
- Environment: temp, pH, host defence

Mechanisms of Injury
- Direct cytopathic effect: induce apoptosis or degredative enzymes
- Antiviral immune response from viral proteins expressed on host cell surface
- Transformation into tumour

Bacterial

Virulence = bacterial properties of adherence, invasion, toxins and effect on host immunity

Adherence
- Adhesions eg strep pyogenes
- Pili eg e coli, Neisseria

Intracellular damage
- Epithelial cells: shigella and e coli (both inhibit protein synth → cell lysis < 6 hrs)
- Macs: mycoplasma tuberculosis and leprae (prevent formation of phagolysosome)
- Both: salmonella
- Intracellular = evades immune response & migration (macs)

Toxins

Endotoxins: part of cell
- From LPS (binds CD14)
- Low levels initiate host immune response
- High levels → septic shock/DIC/ARDs via induction of excess cytokines

Exotoxin: secreted by cell
- Enzymes
- Toxins that alter intracellular signalling
- Neurotoxins eg clostridium botulinum or tetani inhibit NT release
- Super antigens stimulate large number of T cells (toxic shock is an example extreme)

Host immunity
- Granuloma in TB
- Cirrhosis from HBV or HCB
- Rhematic heart disease (s pyogenes)
- Post strep GN

Immune Evasion

Niche growth
- Clostridium or salmonella in intestinal lumen
- Intracellular migration before initiation of host cell response
- Cystic formation eg tapeworm larvae
- Viral latency

Antigenic variation
- High mutation rate: HIV, influenza
- Genetic re-assortment: influenza
- Genetic rearrangement: Borrelia, Neisseria, plasmodium
- Large diversity serotype: rhinovirus, strep pneumonia

Resistance to innate immune
- CHO capsule (in bacteria that cause pneumonia)
- Intracellular movement
- Protease to degrade antibodies

Impairment of T cell response through suppression

Spectrum of Inflammatory Responses to Infection

1. Suppartive
   - Acute tissue damage
   - Mostly extracellular GPC and GNR

2. Mononuclear & Granulomatous
   - Virus, intracellular bacteria, intracellular parasite or chronic inflammation

3. Cytopathic-cytoproliferative Reactions
   - Viruses
   - Cell necrosis and cellular proliferation (sparse inflammatory cells)
   - Proliferation → dysplasia → carcinoma

4. Necrosis
   - Eg clostridium perfringens
   - Damage from toxins not inflammation ∴ sparse inflammatory cells

5. Chronic Inflammation/Scarring
   - Eg constrictive pericarditis

BACTERIAL INFECTIONS

Gram Positive

Staphylococcus
- Skin lesions, Abscesses, Sepsis, OM, Pneumonia, Endocarditis, food poisoning, TSS
- *S epidermidis* common in opportunistic in catheters
- *S saprophyticus* common UTI in young women

Pathogenesis
- Surface receptors for fibrinogen, fibronectin and vitronectin → bridge to host cell
- Polysaccharide capsule helps adhere to prosthesis
- Lipase → skin abscesses
- Superantigens → TSS (*s pyogenes* also causes)

Toxins
α = pore forming → depores host cell
β = sphingomyelinase
δ = detergent
A & B = exfoliative

Morphology
- Pyogenic inflammation → local destruction
- Around hair follicles (except impetigo)
- Lung infections usually due to haematogenous spread
- Scaled skin syndrome (Ritter Disease)

Streptococcus
- Grow in pairs or chains
- Skin, oropharynx, lungs, heart valves,
- Post infective syndromes: RF, GN, Erythema nodosum

β-haemolytic (grouped by surface CHO)

Group A		Group B
S pyogenes		*S agalactiae*
Pharyngitis	Rhematic	colonises female genital tract
Scarlet fever	fever	neonates = sepsis or meningitis chorioamnionitis
Erysipelas	TSS	
Impetigo	GN	

α-haemolytic
- S pneumonia: pneumonia, meningitis
- S viridians = oral flora, endocarditis
- S. Mutans = dental carries

Virulence
- Capsules resist phagocytosis (pyogenes, pneumonia)
- M proteins inhibit phagocytosis (pyogenes)
- Exotoxins → fever & rash (scarlet fever)
- Pneumolysin destroys host cell membrane (pneuomniae)

Morphology
- Diffuse interstitial neutrophilic infiltration
- Minimal host tissue destruction except for necrotizing fasciitis
- Erysipelas
- Strep pharyngitis → GN
- Scarlet Fever (associated with pharyngitis) age 3 – 15, truncal rash
- Lobar pneumonia

Enterococci
- Grow in chains
- Resistant to usual ABx
- UTI & Endocarditis
- Antiphagocytic capsule
- Enzymes degrade host tissue

Diphtheria
- Cornybacterium diphtheriae | Rod
- Transmission: aerosol or skin exudate
- Oropharyngeal fibrino-supprative exudate
- Only one Exotoxin → heart, nerves etc by blocking protein synth
- Diphtheria immunisation prevents effects of toxin (doesn't prevent colonisation)
- Invasion usually local but toxin usually spreads

Listeriosis
- L monocytogenes | Facultative intracellular bacillus
- Severe food borne infection (esp diary, chicken, hot dogs)
- Elderly: meningitis, sepsis or Placental infection
- Internalins expressed promotes phagocytosis → degrades phagolysosome → activated actin polymerisation → propelled to another cell
- exudative inflammation with numerous neutrophils
- NB IFN-γ activated macs can kill listeria

Anthrax
- Large spore forming rod | From soil: exposure from animal or animal products

Major syndromes
- ***Cutaneous*** (95%) pruritic papule → vesicle → surrounding oedema & lymphadenopathy → rupture → black Escher (bacteraemia rare)
- ***Inhalational:*** haemorrhagic mediastinitis (phagocytose and transported to peri-hilar nodes) 2ry meningitis common death within 2 days
- ***Gastrointestinal:*** uncommon, undercooked meat, dysentery with > 50% mortality

Toxin made up of a & B subunits
- B = endocytosis
- A = oedema factor (via ATP conversion to cAMP → H_2O influx) or lethal factor (destroying protein kinase kinases)

Nocardia
- Branched chains like hyphae (similar to moulds)
- Soil
- Opportunistic infections only
- Suppartive response, granulation tissue and fibrosis surrounds

Gram Negative

Neisseria
- Diplococcic aerobic
- Virulence from capsule (inhibits opsonisation) and antigenic variation

Meningitides
- Colonised in oropharynx
- Resp droplets → invade epithelium → haematogenous spread to brain
- Meningitis manifests when serotype is not previously colonised

Gonorrhoea
- 2nd to chlamydia for STI
- PID or urethritis
- Disseminated appears has haemorrhagic rash and septic arthritis
- Neonatal → blindness, sepsis

Whooping Cough
- ***Bordatella Pertussis***
- Coccobacillus
- Invades bronchia epithelium and macs

Virulence
- Haemagglutinin – adheres to CHO on resp epithelium and macs
- Exotoxin similar to e coli – paralyses cilia

Pseudomonas
- Aerobic
- Risk groups: CF, Burns, Neutropenia, contact lens infection, OE
- Pneumonia → thrombosis/necrosis

Virulence factors
- Pili and adherens
- Endotoxin → sepsis and DIC
- Exotoxin → inhibits protein synth (like diphtheria)
- PLC → Red cell lysis, surfactant degradation
- Biofilm
- Fe → direct endothelial toxicity

Plague
- ***Yersinia***
- Facultative intracellular
- Causes massive lymphadenopathy, pneumonia, sepsis
- Marked proliferation

Main species
- Pestis: rats → humans via aerosol or flea bites
- Enterocolitica and pseudotuberculosis → ileitis and mesenteric lymphadenitis

Virulence factors
- Toxin: injected into phagocytes to block phagocytosis and cytokine production
- Biofilm that obstructs flea GIT forcing it to regurgitate prior to feeding

Chancroid
- ***Haemophilus ducreyi***
- Causes acute venereal ulcerative genital infection (most common in Africa and SE Asia)
- Important as a co factor for HIV transmission
- Differs to chancre (syphilis): not indurated or multiple
- Untreated: node enlarge and ulcerate

Granuloma Inguinale (Donovanosis)
- Klebsiella granumolomatis
- Encapsulated Coccobacillus
- Sexually transmitted
- Untreated: extensive scarring + lymphatic obstruction/lymphedema of genetilia
- Dx by smears only
- Nodes spared

Mycobacteria
- Aerobic rods | Grow straight or branching
- Acid fast from way cell wall | Weakly gram +ve

Tuberculosis
- Reservoir: humans, m bovis from cow's milk (removed during pasteurisation)

Epidemiology
- Low hygiene most susceptible
- Primary TB usually asx (maybe fever or effusion)
- Activation of dormant TB → delayed hypersensitivity reaction
- Vaccination is with Bacillus Calmette-Guerin (BCG) – attenuated M Bovis

Pathogenesis

Primary TB (0-3 weeks)
- Mannose capped glycoprotein recognised by macrophages and internalised
- Endosomal manipulation occurs → arrests maturation, ineffective phagolysosome formation
- Unchecked bacillary proliferation occurs and bacteraemia with seeding at multiple sites (Usually asx)
- Virulence on cell wall only

Primary TB (> 3 weeks)
- APCs with bacillary proliferation reach lymphatics and recognised by T cells
- T cells differentiate into TH1 and release γ-IFN (critical mediator)
- Macrophage activated to release ROS, TNF, Chemokines
- Monocyte recruitment → Caseous necrosis with rim of sensitised t cells (aka granuloma)
- Most times this late phase reaction will stop initial infection before severe tissue destruction

Clinical features

Phase	Pathology
Primary TB (weeks)	• Healed lesions: Ghon focus = implantation in airways → Caseous necrosis • Ghon complex = Ghon focus and caseating nodes • Ghon focus → fibrosis (despite seeding in other organs) • Most people are asymptomatic or have nonspecific symptoms
Progressive Primary (more weeks)	• Resembles an acute bacterial pneumonia with lower or middle lobe consolidation, hilar lymphadenopathy and effusion (cavitations rare) • Latent lesions: rarely dissemination → miliary TB esp liver & spleen
-Reinfection/reactivation -	
Progressive Secondary (Years)	• Localised caseating destructive lesions: esp lung & kidney → miliary TB • Apex of lungs • Pre-sensitised cells wall off infection ∴ nodes not as prominent vs primary • Cavitation after walling off • Erosion into airway → secondary infection • Sometimes hematemesis, pleuritic pain

- Isolated TB: meninges, kidneys, adrenals, bone, fallopian tubes, vertebrae (Potts disease), intestinal

M Avium & intracellulare (MAC)
- Found in soil, water, dust, domestic animals
- Uncommon unless immunocompromised
- Primarily in lungs but can disseminate anywhere

Leprosy
- *Mycobacterium leprae*
- Acid fast obligatory intracellular organism propagated in the armadillo
- Skin & peripheral nerves → disabling deformities
- Transmitted through aerosol
- Replicates in cool tissues of skin & extremities (32 – 34 deg)
- Virulence based on cell wall l only (similar to TB ∴ BCG will help)

Clinical manifestations (depends on T helper response)

Tuberculoid (strong TH1 response)
- Dry scaly skin lesions that lack sensation
- Asymmetric involvement of PN from local granuloma destruction → ischaemia
- Prolonged course (decades)
- Sparse bacteria seen

Lepromatous (weak TH1 response)
- Symmetric skin thickening & nodules
- Worse on cooler areas eg ear lobes and feet
- Spreads to Schwann cells
- Late stages appears in blood and sputum
- Abundant bacteria seen

Spirochetes

- Gram –ve slender corkscrew bacteria with axial flagella and coat

Syphilis

- *Treponema palladium*
- Silver stain
- Transmission: Sexual contact > Transplacental

Diagnosis: serology (micro & PCR also available)

- Nontreponemal takes 4-6 weeks and negative in tertiary syphilis
- Treponemal take 4-6 weeks, remain positive in tertiary (even successful tx)
- Immunoflurosceine faster

3 stages of disease

- Proliferative endarteritis occurs in all stages

1. Primary
    - Haematogenous and lymphatic spread occurs before chancre
    - Chancre – firm tender non raised red lesion 3 weeks after contact
    - Heals after 3-6 weeks regardless of intervention
2. Secondary
    - Palmar rash
    - Lymphadenopathy
    - Condyloma latum: broad based elevated plaques in moist areas, painless
    - All lesions contain spirochetes
    - 2-10 weeks after chancre resolves
    - Occurs in 75% of untreated people
3. Tertiary (rare)
    - Neurosyphilis (Asx 33% of time): meningovascular tabes dorsalis, general paresis
    - Aortitis (80% of tertiary): aneurysms, AR – affects vaso vasorum
    - Gummas (nodular rubbery lesions made of Coagulative necrotic centre and palisading border of macs and fibrobalsts and plasma cells): hepatic, skin, bone etc
    - Occurs in 33% untreated patients – after approx. 5 year latent period

Congenital

- During primary or secondary stages ∴ mandatory testing in all patients
- 25% of cases = death

Types: Early (< 2yo)

- Nasal discharge, congestion first few months of life with Bullous rash sometimes
- Sometimes hepatomegaly and skeletal abnormalities

Late (> 2yo)

- Interstitial keratitis, Hutchinson teeth and 8th nerve palsy

Relapsing Fever

- Insect vector (body lice or soft bodied ticks) transmitting Borrelia recurrentis
- Clinically: recurrent fevers with spirochetemia → DIC after 1-2 week incubation
- Blood smears during febrile episodes

Lyme disease

- *Borrelia burgdorferi*
- Rodents to people via ticks
- Pathology inferred through 2ry immune response (no LPS or exotoxin)
  (But it does have antigenic variation)

3 stages

1. Acute illness
    - Tick bite → erythematous papule, erythema chronicum migrans and (disappears after 4-12 wks) lymphadenitis
2. Dissemination
    - CNS: Meningoencephalitis, cranial neuritis
    - Cardiac: Block, Pericarditis, Myocarditis
3. Late chronic form
    - Destructive chronic arthritis, acrodermatitis atrophicans, neuropathy, encephalitis

Anaerobic

Abscess

- Usually mixed anaerobic/facultative aerobic = 1.6:0.9 species totalling 2.5
- Species are usually part of normal flora ∴ minimal toxin effect
- Contents are discoloured and foul smelling, poorly walled off

Clostridium

- GPB anaerobic (dies if exposed to O_2 ∴ necrosis essential for growth)
- Produce spores in soil
- Found by culture, toxin assay (colitis) or both (botulism)

C perfringens, C septicum

- Cellulitis and myonecrosis of traumatic surgical wounds
- Mild food poisoning
- Isch bowel infection
- Neutropenic patients

C tetani

- Releases potent neurotoxin → convulsive contractions of skeletal muscle
- Tetanus toxoid is a formalin fixed neurotoxin

C botulinum

- Canned food not sterilised
- Neurotoxins inhibit Ach release

C difficile

- Pseudomembranous colitis

Obligatory Intracellular Bacteria

Chlamydia

- GN obligate intracellular

Trachomatis has 2 forms during its life cycle

1. Elementary Body (infectious form) – metabolic inactive and spore like
    - Endocytosis
    - Evades fusion with lysosome
    - activates

2. Reticulate Body (active form)
    - Replicates, forms new EB for spread

Variety of infections

- Genitals and eyes: serotype D – K
- Lymphogranuloma L1-3
- Childhood ocular: trachoma (A – C)

Venereal Chlamydia

- X2 gonorrhoea
- Clinical Sx similar to gonorrhoea (except that male urethritis may be asx)
- PCR or culture

Rickettsia Infections

- Vector borne obligate intracellular bacteria
- GN rod
- Epidemic typhus (prowazekii), scrub (orienta tsutsugamushi), or spotted fever (rickettsia)
- Dx usually clinical with serology to confirm
- No sig toxins – pathology
- Target vascular endothelium esp lung and brain
- Proliferate until cell lysis and reinvasion

- Epidemic typhus: body to body via lice
- Scrub – chiggers transmission – milder – vasc necrosis/thrombosis rare
- Spotted fever – ticks

VIRAL INFECTIONS

Acute (Transient) Infections

Paramyxovirus family
- Mumps
- RSV (major LRTI children)
- Parainfluenza
- Human Metapneumovirus

Measles
- ssRNA of paramyxovirus family
- Only 1 serotype without antigenic variation ∴ infection confers lifelong immunity
- Resp droplets
- Proliferates in airway epithelium → lymphoid tissue → vireamia and dissemination
- Warthin-Finkeldey cells is pathognomic (multinucleated giant cells with inclusion bodies)

Clinically
- Croup
- Pneumonia
- Diarrhoea
- Koplik spots[2]
- encephalitis,
- Keratitis
- Haemorrhagic rashes
- Blotchy red-brown rash[1]

[1]On face, trunk, prox limbs due to dilated skin vessels, oedema and mononuclear perivascular invasion
[2]Mucosal ulceration

Mumps
- Resp droplet
- Replicate in lymphocytes (mostly activated T cells) → salivary and other glands
- Mumps parotiditis 70% bilateral
- Can also spread to CN, testis, ovaries, pancreas (aseptic meningitis most common extra salivary complication – 10%)
- Dx clinical or viral cultures
- Mumps orchitis – can cause infarct if swells enough

Poliovirus
- Spherical unencapsulated RNA of enterovirus genus
- Vaccine is live (oral)
- Humans only
- No antigenic variation
- Faecal oral route
- Oropharyngeal infection → intestinal mucosa and nodes → vireamia (transient)
- 1% invades CNS and replicates in motor neurons in spinal cord or brainstem
- Nervous system spread either via vireamia or retrograde axonal spread

Enteroviruses
- *Coxsackie A* (diarrhoea & rash)
- *Coxsackie A* (myopericarditis)
- *Coxsackie* and *echo* (meningitis)

West Nile Virus
- *Arbovirus* (eg dengue or yellow fever)
- Mosquitoes to birds and mammals (birds have a prolonged vireamia)
- Inoculation → replication in skin dendritic cells → nodes → further replication → blood spread incl CNS
- Clinically asx (20% have non-specific Sx)
- Maculopapular rash in ½
- < 1% CNS complications (10% of these are fatal)

Viral haemorrhagic fevers
- Enveloped RNA viruses: *arenavirus, filovirus, bunyavirus, flavivirus*
- All need animal/insect host
- Spectrum of illness: mild to shock
- Not well understood mechanism to haemorrhage

Chronic Latent Infections

- Large encapsulated dsDNA

Group	Viruses	Mechanism
α group	HSV-1, 2, VZV	Latent in neurons
Lymphotropic-β group	CMV, herpesvirus 6 & 7	Latent in a variety of cells
γ-group	EBV, KSHV/HHV8	Latent in lymphoid

HSV
- Oropharyngeal or genital transmission
- Replicate in skin or mucous membrane entry point (vesicular lesions)
- Spread to sensory neurons
- Latent stage: no viral proteins produced
- Reactivation → back to skin
- Other complications: corneal blindness or sporadic encephalopathy
  - Stromal keratitis /Epithelial keratitis
- Neonatal or Genital HSV 2 > 1

VZV
- Chicken pox & shingles
- Replicate in skin or mucous membrane entry point (vesicular lesions)
- Spread to sensory neurons
- Transmission: aerosol, haematogenous, widespread lesions
- Rarely recurs (as shingles)
- Dx: viral culture, viral antigen, cells scraped from lesion
- Shingles occurs when virus reactivated and infects keratinocytes → vesicular lesions associated with burning, sharp pain and itching – trigeminal common
- Ramsay Hunt syndrome = infecting geniculate nucleus → facial paralysis

CMV
- Latent infection includes bone marrow and monocytes
- Asx or mono like infection in healthy but virulent in neonates/immunocompormised
- Histologically: infected cells are both larger with larger nuclei (containing owl's eyes – large inclusion bodies)

Transmission
- **Congenital CMV** (mother new infection, no previous exposure)
- **Perinatal CMV** (mother with active infection)
- **Preschool** – saliva
- **> 15yo venereal > resp or FO**
- Iatrogenic: transplant/transfusion

Clinically
- Transient but severe immunosuppression by infecting dendritic cells to prevent t cell stimulation
- Can also supress NK activity
- Disseminated disease causes focal necrosis without inflammation

Congenital
- 95% Asx
- Cytomegalic inclusion disease: similar to erythroblastosis fetalis IUGR

Perinatal
- Rarely interstitial pneumonitis, FTT. Rash, hepatitis
- Less severe than congenital due to mother antibodies
- Can still transmit disease months to years after

Mononucleosis
- Fever, atypical lymphocytosis, lymphadenopathy, hepatomegaly
- Serology
- Seropositive for life after infection
- 15% of all cases (EBV 85%)

AIDs
- Most common viral pathogen
- Pneumonitis and colitis most common

Chronic Productive Infections

- HPB
- HIV

TRANSFORMING INFECTION (cancer forming)

EBV
- Infectious mononucleosis
- Lymphomas (Burkitt) and nasopharyngeal carcinoma
- Seen in adolescents higher socioeconomics
- Transmitted by close human contact eg saliva
- Starts in nasopharyngeal or oropharyngeal lymphoid tissue (esp tonsils) → submucosal lymphoid

  Either → lysis of infected cells and release of virions
  Or → Itent infection (more common)

Morphology
- Mononucleosis refers to CD8+ and NK cells that are atypical in smears (5-80% are large atypical lymphocytes)
- Mainly lymph spread/replication/damage
- > 60% lymphocytes differential

Clinically
- Fever, sore throat, lymphadenitis
- Atypical Sx common
- Lymphocytosis with large atypical population
- +ve monospot test
- EBV antibodies
- Resolved 4-6 weeks

FUNGAL INFECTIONS

- Eukaryotes with cell walls
- Moulds are multicellular filaments that grow and divide at their tip
- Yeasts are single cells or chains that propagate by budding

Candidiasis
Grows best in warm, moist surfaces
Virulence factors
- Adhesins
- Enzymes
- Biofilms
- Catalase (intracellular survival)
- Adenosine (blocks neutrophil degranulation)

Immune response
- TH17 mostly

Cryptococci's
- Encapsulated yeast

Virulence
- Variable capsule prevent phagocytosis
- Lactase → antioxidant
- Degrade fibronectin and BM
- Healthy: pulmonary granulomas (solitary), rarely Meningoencephalitis

Aspergilliosis
- Mould, septated hyphae branching at acute angles
- Air borne
- Clinical: allergy
- Immune def: chronic sinusitis, necrotizing pneumonia (most common), thrombosis of small vessels
- Host defence: neutrophils & macs

Virulence
- Adhesion to albumin, surfactant and ECM
- Inhibits Antioxidants
- Liver cancer inducible by some toxins

Zygomycosis (mucormycosis)
- Opportunistic
- Mould, non septated with right angled branching
- Primary site; sinus, lung, git and arterial wall on the way

PARASITIC INFECTIONS

Protozoa
- Unicellular eukaryotic organisms
- Transmitted by insect via FO route
- Usually in blood or intestines

Malaria
- Intracellular parasite
- Transmitted by female anopheles mosquitoes

Species
- P. falciparum (most virulent)
- Vivax, Ovale, Malariae (less so)

Life cycle
- Mosquito saliva
- Form sporazoites in blood
- Invade hepatocytes & proliferate
- Hepatocyte rupture
- Merozoite release
- Taken up by erythrocytes
- Hydrolyse red cell HB → hemozoin
- Trophozoite divide to form Merozoite
- Red cell lysis → release of Merozoite → further infection
- Small population develop into sexual form (gametocyte) for mosquito retransmission

Pathogenicity
- Infect erythrocytes at any stage
- Cause infected red cells to clump together and to epithelium → occlusion/ischaemia
- Induce cytokine release to decrease red cell production
- Antigenic variation

Resistance
- Sickle cell (HbS or HbC)
- Absence of Duffy blood group antigen prevents *Vivax* from binding cells
- Antibody and t cell mediated mechanisms after primary infection

Babesiosis
- Transmitted from white footed mice via ixodes ticks
- Invades red cells → haemolytic anaemia

Leishmaniasis
- Chronic inflammatory disease of skin, mm, viscera
- Obligate intracellular parasite
- Transmitted by sand-flies

Lifecycle
- Sand-flies bite infected host and ingest amastigotes → promastigotes in fly intestinal lumen → migrate to salivary gland
- Sand-flies bite 2nd host → promastigotes phagocytosis → amastigotes
- Amastigotes multiply intracellularly in macs of mammalian hosts

Virulence factors
- Lipophosphoglycan (on promastigotes) activate complement and inhibit
- Gp63 binds fibronectin → adhesion
- Proton pump ↓ macrophage intracellular killing

African Trypanosomiasis
- Tsetse flies
- Extracellular parasite
- East African (brucei Rhodesians) = highly virulent
- West Africa (brucei gambiense) = chronic
- Clinical: intermittent fever, lymphadenopathy, sleeping sickness
- Multiply in stomach and salivary glands

Virulence
- Antigenic variation
- Genetic rearrangement

Chagas
- *Trypanosome cruzi*
- Intracellular parasite
- Transmitted by triatomids
- Phagocytose → Activated into amastigotes by low pH → Develop flagella and lyse cell to escape

Acute Chagas
- Mild
- Cardiac damage from direct disease and inflammation/healing
- Rarely severe

Chronic
- 20% 5-15 years later
- MI → myopathy and arrhythmias
- Myenteric plexus damage

Metazoa
- Multicellular eukaryotes

Strongyloidiasis
- Larvae in soil
- Penetrate human skin → Travel to lungs → trachea → swallowed
- Eggs made in small intestines
- Clinical: diarrhoea and malabsorbtion, larvae in duodenal crypts (eosinophilic reaction)
- In immunocompormised hosts invade mucosa → large larvae burden

Cestodes (tapeworm)
- Life cycle requires 2 hosts
  - Definitive host to reach sexual maturity (dogs and fox)
  - Intermediate host (humans and pigs)
- Hydatid from dog or fox stool → invade liver lungs bone → cysts form

Trichinosis
- Undercooked pork
- Larvae mature in git and disseminate haematagenously
- Infect muscle → fever and myalgia, eosinophilia, peri orbital oedema
- Spont die after years

Schistosomiasis
- Freshwater snails
- Penetrate skin → portal vein or pelvis
- Eggs can shed in urine or stool
- Immune response is against eggs → granuloma formation
- Urinary ass with bladder squ cell carcinoma

Lymphatic Filariasis
- Wuchereria bancrofti (90% of cases)
- Mature in lymphatic channels → blood → mosquito
- TH1 mediated response

Clinical
- Asx
- Recurrent
- Chronic → elaphantitis
- Tropical pulmonary eosinophilia

Virulence factors
- Antioxidants
- Impaired antigen presentation
- Neutrophil protease inhibition

INFECTIOUS ENTEROCOLITIS

Bacteria	Reservoir	Site	Symptoms	Complications
Cholera[1]	Human Shellfish Plankton	SI	Diarrhoea	Dehydration
Campylobacter	Chicken Water Milk	LI	Dysentery 15%	Arthritis Guilline Barre
Shigella	Human	L colon Ileum	Dysentery 50%	Reiter HUS
Salmonella	Food	All	+/- Dysentery	Sepsis Abscess
Typhoid	Human	SI	Dysentery Fever	Chronic/Carrier Encephalopathy Myocarditis
Yersinia	Pork Water Milk	Ileum Appendix R colon	Fever Abdo Pain Diarrhoea	Autoimmune[4]
E Coli	Food Water	Colon[2]	+/- Dysentery[3]	Dehydration

[1]Doesnt really cause colitis since it is not invasive
[2]Except ETEC = SI
[3]No dysentery in ETEC & EAEC
[4]Reiters syndrome, myocarditis, GN< thyroiditis sterile arthritis

Key Points
- All gram negative
- The S's are self-limiting (shigella & salmonella – not typhoid) and EIEC

Cholera

Sequence of Events
Attaches to luminal wall by flagella
→ Produces cholera toxin
→ Binds enterocyte surface receptor
→ Toxin a subunit processed in ER
→ Fragment enter cytosol
→ Interacts with ADP
→ G protein activation
→ Adenylyl cyclase activation
→ ↑ cAMP
→ Cl^- released into lumen
→ HCO_3^- & Na secretion (+ H_2O follows)

Campylobacter
- Most common enteric pathogen in developed countries
- **Virulence factors**: flagella, adherence molecules, cytotoxins, cholera-like toxin
- Dx stool culture
- Histo shows nonspecific Neutrophilic colitis

Shigellosis
- Unencapsulated | Facultative anaerobe
- 75% of diarrhoea related deaths
- **Virulence factors**: resistant to stomach acids

Mechanism
Taken up by M cells in intestine
→ Macrophage uptake
→ Apoptosis
→ Inflammation & release of shigella toxin

Salmonellosis
- Typhoid and non-typhoid salmonella
- Virulence factors: type III secretion system facilitating macrophage uptake
- TH_{17} in mucosa limit infection to colon

Typhoid
Pathogenesis
Contaminated food
→ Resistant to low pH
→ Endocytosis by M cells then macrophages
→ Disseminate via lymphatics
→ Systemic lymphatic and macrophage hyperplasia

Morphology
- Enlarged peyers patches and draining nodules
- Lamina propria inflammation → ulceration
- Focal hepatocyte necrosis (typhoid nodules)

Yersinia
- Invade M cells using adhesions

E Coli

Enterotoxigenic e coli (ETEC)
- Food/water
- Main cause of travellers' diarrhoea
- Heat stable toxin → ↑ cGMP
- Heat labile toxin → ↑ cAMP

→ Cl^- & H_2O secretion/inhibit reabsorption

- Non inflammatory

Enterohemorrhagic (EHEC)
- Similar to shigella

Enteroinvasive (EIEC)
- Similar to shigella
- Non toxin producing

Enteroaggregative (EAEC)
- Similar to shigella

Pseudomembranous Colitis
- Overgrowth of c diff
- Pseudomembrane not specific for c diff but is caused by ulceration of mucosa

Whipple Disease
- GP actinomyces
- Diarrhoea, weight loss, malabsorbtion

Viral Gastroenteritis

Virus	Structure	Claim to Fame	Site	Course
Norovirus	ssRNA	50% of all gastro outbreaks	Nonspecific	Self-limiting
Rotavirus	dsDNA	Most common kids diarrhoea	SI	Self-limiting
Adenovirus		2nd most common…	Nonspecific	Self-limiting

Parasitic Enterocolitis

Giardia
- Most common parasite infection
- No invasion – just endotoxin that damages brush border → malabsorbtion, inflammation

Entomaba
- Induce colonic epithelial apoptosis and neutrophil attraction

ENVIRONMENTAL PATHOLOGY

THERAPEUTIC DRUGS

HRT
- Oestrogen & Progesterone
- Oestrogen has risk of uterine cancer
- Used for symptomatic mx of menopause, prevent osteoporosis and MI
- WHI 2002: ↑ risk VTE (first 2 years) & Breast Ca (lobar & ductal-lobar), no change to CV risk
- HRT is useful for CV protection < 60yo

OCP
- VTE: x3 risk
- CVD: in smoking of all ages or non-smoking > 35 (x10 smokers over 35)
- Cancer: ↓ endometrial and ovarian ca, no ↑ breast ca
- Hepatic adenoma

Anabolic Steroids
- Synthetic testosterone
- Stunted growth, acne, gynocamastia, testicular atrophy, facial hair and menstrual changes in women, psychiatric, premature AMI

Paracetamol
- 95% undergo phase II metabolism to harmless metabolites
- 5% metabolised by CYPE to NAPQI which is conjugated by GSH to inactive metabolites
- If GSH is saturated then NAPQI causes liver failure by covalently binding to hepatic proteins
- NAC restores GSH

Aspirin
- Resp alkalosis 2ry to resp centre activation
- Metabolic acidosis follow due to pyruvate and lactate accumulation due to uncoupling of oxidative phosphorylation
- Low pH → salicylates precipitate out of plasma and in brain causes coma
- Chronic ingestion → Salicylism: headache, dizzy, tinnitus, hearing impairment, confusion, drowsiness, nausea, vomiting, diarrhoea
- Other complications: gastritis/ulcers/coagulopathy/nephropathy

Nontherapeutic Agents

Cocaine
- Dopamine antagonist
- CVS: Sympathomimetic, Smoking potentiates coronary vasospasm, Arrhythmias
- CNS
- Foetal hypoxia
- Nasal perforation
- Dilated CM

Heroin
- Opioid
- Resp depression, arrhythmia, cardiac arrest, APO
- Septicaemia, endocarditis, lung abscess
- Amyloidosis and focal glomerulosclerosis

Amphetamines
- 5HT agonist

PHYSICAL INJURY

Thermal Burns
- Factors determining clinical outcome: depth, %SA, internal injuries from inhalation, promptness to therapy

Classification
- Superficial – epidermis
- Partial thickness – dermis
- Full thickness – to subcutaneous tissue

Complications (esp SA > 20%)
- Shock (hypovolemic)
- Sepsis (pseudomonas most common)
- Resp insufficiency
- Hypermetabolic state (x2 if 40% burns)
- Hypertrophic scars

Hyperthermia
- Heat cramps – electrolyte imbalance
- Heat exhaustion – poor response to hypovolemic state
- Heat stroke – failure of thermoregulation

Hypothermia
- Predispositions: high humidity, wet clothes, alcohol → vasodilation
- < 32 deg = coma, Bradycardia, AF
- Direct: high salt concentration → crystallise → physical cell trauma
- Indirect: vasoconstriction & ↑ vasc perm → hypoxia & oedema, ↑ blood visc → isch

Electrical
- Burns or VF/Cardiac/Resp Failure
- AC current = tetanic spasm
- Large voltages → paralysis of medullary centres & extensive burns

Radiation

Type	Mechanism	Example
Non-ionising	Can move atoms but not e^-	UV, infrared, microwave, sound wave
Ionising	Can displace electrons	X-ray or γ waves[1]
		α particle[2]

[1]Less focused damage
[2]More focused damage

Dose
- Curie = disintegration per second of radioisotope = 3.7 x 10∧10
- Gray = unit absorbed by target tissue (joules per kg)
- Sievert = equivalent dose = Gray x effect (for x-radiation 1mSv = 1 mGy)
- Rad = 100 Gy
- NB small dose to large area can be lethal (not vice versa)

Effect	Organ	Dose (Sv)
Temp sterility	Testes	0.15
Depression Haematopoiesis	Marrow	0.50
Permanent sterility	Ovaries	2.5-6.0
Temp hair loss	Skin	3.0-5.0
Permanent sterility	Testes	3.5
Cataract	Lens	5.0
Cancer		> 0.050

Modality	Dose (mSv)
AP CXr	0.01
Lateral Cxr	0.15
CT Chest	10

Environmental Pollution

Air Pollution

Outdoor
- UV + O_2 → Ozone
- Skin cancer and smog
- Ozone toxicity through generation of free radicals → alveolar inflammation
- Sulphur dioxide: combustion of coal and oil, paper → burning, airway hypersensitivity
- Particulate matter (soot) → inflammation
- CO → systemic hypoxia (displaces O_2 on Hb)

Indoor
- Wood smoke
- Legionella
- Formaldehyde

Metals

Lead
- Burning of leaded gasoline or lead plumbing
- Lead competes with Ca ions ∴ 80-85% accumulates in bones & teeth

  Toxicity due to
  - Neurotoxicity: altered Ca homeostasis → impaired neurotransmitter releases
  - Peripheral demyelinating neuropathy more common in adults
  - Inhibits heme synthesis → microcytic hypochromic anaemia
  - Altered cartilage remodelling

Mercury
- Mostly fish source
- High binding affinity for cellular thiol in CNS

Arsenic
- Wood preservative, herbicide
- Inhibits mitochondrial oxidative phosphorylation

Cadmium
- Ingesting contaminated food most common
- Alveolar macrophage necrosis → obstructive lung disease
- Renal tubular damage

NUTRITIONAL PATHOLOGY

Anorexia
- Amenorrhoea
- ↓ TH
- ↓ bone density
- Arrhythmias from low PO_4 or K

Bulimia
- Better prognosis
- Mostly electrolyte disturbance

Vitamins
- Fat Soluble: KADE

Vitamin	Fcn	Def
Fat Soluble		
A	Visual pigmentation Specialised epithelial differentiation Immunity	Night blindness Squamous metaplasia Infection (esp measles)
D	Ca & phosphorus absorption and bone mineralisation	Rickets or Osteomalacia
E	Antioxidant	Spinocerebellar degeneration
K	Cofactor for carboxylation of procoagulants	Bleeding
Water Soluble		
B1	Co enzyme in decarboxylase reactions	Beriberi or Wernicke korsakoff
B2,6	Intermediary metabolism	Corneal vascularisation, glossitis
Niacin	Redox reactions	Dementia, dermatitis, diarrhoea
B12	Folate metabolism/DNA synthesis	Pernicious anaemia, degeneration of posterolateral cord tracts
C	Redox & hydroxylation of collagen	Scurvy
Folate	DNA	Megalobalstic anaemia, neural tube defects

CVS

Anatomy

- Weight: 250-300 ♀ 300-350 ♂
- Left vent wall = 1.3 – 1.5cm | Right = 0.3 – 0.5 cm
- Cardiomegaly = ↑ weight OR size

Age related change

Anatomy	Changes
Chambers	↑LA, ↓LV, Sigmoid septum
Valves	Calcific deposits (AV, mitral annular) Fibrous thickening Buckling of MV to LA
Vessels: Epicardial	Tortuous ↑ Cross-sectional luminal area Calcific deposits Plaque
Myocardium	↑ Mass Subepicardial fat Brown atrophy Lipofuscin deposition Basophil degeneration Amyloid
Ao	Dilated & Elongated thoracic Rightward shift Sinotubular junctional calcification Elastic fragmentation Atherosclerosis

HEART FAILURE

- Inability to pump efficiently
- Multiple causes (MI, Valvular disease, HTN)
- Usually **systolic** dysfunction involved
  (**Diastolic** less often – LVH, fibrosis, amyloid, pericarditis)

Homeostatic Mechanisms against CHF

- Frank-starling
- Ventricular remodelling (hypertrophy +/- dilatation)
- Neurohumoral activation: *norepinephrine release, renin-angiotensin activation, ANP release*

Hypertrophy: Cellular Changes (due ↑ work)

Functional Changes

- ↑ Inotropy
- ↑ Chronotropy

Progression to Heart Failure is due to

1. Myocyte metabolism (abnormal)
2. Myocyte apoptosis
3. Ca handling
4. Gene expression

Hypetrophy	
Cellular	• ↑ sER (protein synthesis) → *additional sarcomeres* • ↑ Mitochondria • Enlarged nuclei(↑ DNA replication without division) • Capillary **DO NOT** increase ∝ ∴ ↓ blood supply • Fibrosis is common due to deposition and shift in gene expression
Physiological	• Volume: aerobic exercise (but also has ↑ capillary density ∴ ↓ ino/chrono) • Pressure: isometric – similar to pathological
Pattern	• **Pressure overload** hypertrophy = concentric • **Volume overload** hypertrophy = ventricular dilation*
Severity	• **Mod** hypetrophy (x2-3) common in **HTN, IHD, AS, MR** • **Severe** hypetrophy (x304) common in **AR, HCM**

*∴ Weight more important than weight

Left Sided Failure

- Causes: IHD, HTN, A or MV disease, Myocardial disease
- Sequelae: Pulmonary congestion, LV blood stasis, hypoperfusion

Morphology

- Heart: LV dilatation and hypetrophy, associated LA dilation → ↑ risk AF
- Lung: congestion/oedema esp interlobar septa (Kerley B)

Clinical

- Lungs: dyspnoea → orthopnoea/PND
- AF → thrombosis
- ↓ CO → ARF → ↑ Renin-Angiotensin-Aldosterone & Hypoxic encephalopathy

Types

- Systolic (pump failure)
- Diastolic (stiff LV) ∴ normal @ rest ↓ with effort → APO
  - > 65, women
  - Other RF: HTN, DM, Obesity, Bilateral renal artery stenosis
  - Due to fibrosis (MI, CM), infiltrative disorders (amyloid), restrictive pericarditis, age

Right Sided Failure (Cor Pulmonale)

- Rarely pure (most often due to LHF)
- Pure RHF due to lung path: *pHTN from parenchymal (most common), PE, hypoxia*

Clinical Sequelae

- RV dilation can inhibit LVF
- Liver/Portal: congestive hepatomegaly (nutmeg liver), congestive splenomegaly (2-3x)
- Pleural/Pericardial/Peritoneal effusions (***vs pulmonary only in LHF***)
- Subcut tissue: pitting oedema → anasarca
- Common organs involved: renal (→ further retention, uraemia), brain (same as LHF)

Causes of RHF

Anatomy	Pathology
Parenchyma	COPD, Pulmonary interstitial fibrosis, Pneumoconiosis, CF, Bronchiectasis
Pulmonary Vessels	recurrent PE, pHTN, Arteritis (eg wegners), Drugs, Tumour
Alveoli	metabolic acidosis, hypoxemia, altitude sickness, upper airway obstruction, idiopathic alveolar hypoventilation
Chest Wall	kyphoscoliosis, obesity, neuromuscular

ISCHAEMIC HEART DISEASE

Clinical End Points

- AMI
- Angina
- Chronic IHD → HF
- Sudden death

Causes (demand/anatomy/perfusion)

- **Atherosclerosis** ++++
- Emboli
- Low BP

(+/- ↑ demand)

Pathogenesis

- Atherosclerosis of ***epicardial vessels*** (> 75% obstruction for sx during exercise; > 90% obstruction for sx at rest)
- Collaterals form *over time* to counter
- Clinically significant obstruction: **proximal LAD or LCX or anywhere in RCA**
- Intramural branches are rare
- Plaque △: transition to IHD not fluid due to *plaque rupture, erosion, ulceration, fissure or haemorrhage* +/- thrombosis causing occlusion or inflammation

Angina

- Transient myocardial ischemia
- Stable / Prinzmetal (spasm)→ unstable

Myocardial Infarction

- 10% < 40 | 45% < 65 | Men > Women (protected during reproductive years)

Sequence of events

1. △ Plaque
2. Microthrombi
3. Vasospasm (from plt degranulation)
4. Tissue Factor release → coagulation
5. Thrombotic occlusion

Alternate causes (10% of time)

- *Vasospasm* with/out atherosclerosis
  eg plt aggregation or cocaine
- *Emboli* from LA, mural thrombus, vegetation, prosthesis, paradoxical
- *Vessel* abnormality: vasculitis, sickle cell, amyloid, dissection, shock

Distribution

Artery	Areas	Percentage of all MI
LAD	Apex & Ant 2/3 of vent septum	40-50% incl ant LV, ant vent septum, apex (circ)
LCX	Lateral LV	15-20%
RCA	RV, Posterobasal LV	15-20% incl 15-30% from post free wall of septa 1-3% isolated to RV or RA

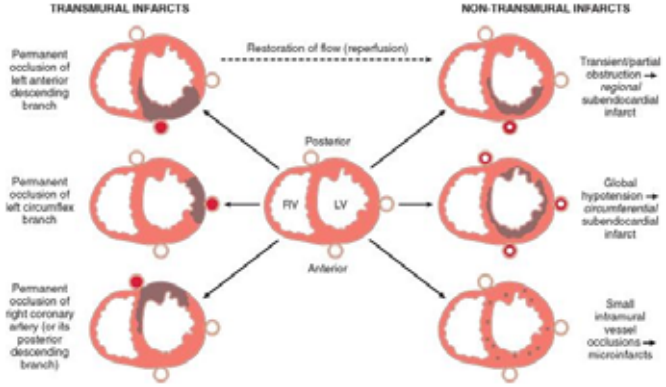
RCA (80%) vs LCX **dominant circulation** = *whichever supplies post 1/3 of ventricular septum*

OTHER COMMON branches

- Left main
- 2ry branches LAD
- Marginal branches of LCx

Transmural vs Subendocardial

- Transmural (STEMI) : full thickness infarct in area of vessel supply
- Subendocardial (NSTEMI): inner 1/3 – ½ ventricular wall due to *resolved thrombosis* or *chronic hypotension* (morphologically diff since circumferential damage)



Key Events

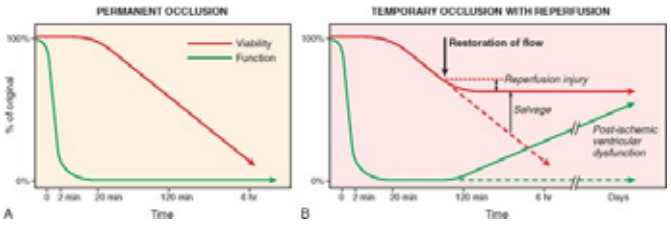
Time	Event
Seconds	ATP depletion
60 seconds	Loss of contractility
10 min	ATP50%
20-40 min	Irreversible injury
40 min	ATP 10%
1 hr	Microvascular injury
6 hr	Necrosis (without collateral flow)

* Early necrosis seen as disruption in sarcolemma membrane

Morphological Changes

Time	Gross	Micro
Reversible		
0 – 30 min	-	-
Irreversible		
30 min – 4 hrs	-	Wavy Fibres[1] at borders
4 hr to 12 hrs	Dark Mottling (occasional)	Early Coag necrosis (6-12 hrs), oedema, haemorrhage
12-24 hrs	Dark mottling (frequent)	Coag necrosis Nuclei pykonsis Myocyte hypereosinophilia, band necrosis, -cytolysis Neutrophilic infiltrates
1-3 days	Mottling & Yellow-tan centre	Cog necrosis Loss of nuclei & striations Neutrophilic infiltrates
3-7 days	Yellow-tan softening & Hyperaemic border	Dead myofibril disintegration Phagocyte removes dead cells
7-10 days	Yellow-tan (max soft) ↓ Red-tan margins	Early granulation Evidence of phagocytosis
10-14 days	↓ Red-grey margins	Granulation tissue/Angiogenesis Collagen deposition
2-8 weeks	Grey-white scar (starting at border)	Collagen deposition ↑ cellularity
> 2 months	Scarring	Dense collagen
Reperfusion	Haemorrhagic Contraction bands (closely packed sarcomeres) Due to exaggerated contractions from high [Ca] from dead cells Endothelial swelling	

[1]Normal contractile myocyte pulling infarcted cells out of shape



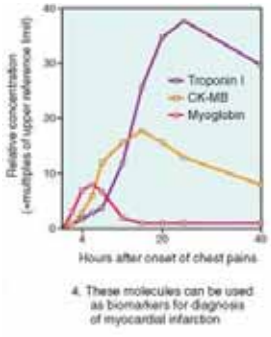
Healing
- Margin to centre
- Healed infarcts have undeterminable age

Extension
- Repetitive necrosis of adjacent regions (appears as centre healing)
- Causes: retrograde thrombus, prox vasospasm, ↓ contractility, micro emboli, arrhythmia

Interventions: Reperfusion
- Types: thrombolysis, angioplasty, stenting, CABG
- Complications: reperfusion injury, stunning, arrhythmias, haemorrhage
- Stunning: reversible heart failure, reversed over a few days
- Hibernating myocardium: self ↓ metabolic activity with potential to restore if supply restored

Clinical Features
- 15% silent
- Overall prognosis:
  Mortality 1st year 30% then 3-4% per year

Lab
- TnI & CK-MB rise within 2-4hrs
- TnI peaks at 20 hrs & persist for 7-10 days
- CK-MB plateaus at 18 hrs but normal after 72 hrs
  - MM: cardiac & skeletal
  - BB brain, lung, others
  - MB cardiac and some in skeletal



Consequences
- Death: 50% in 1 hr of onset
- Poor prognosis: age, female, DM, previous MI

Consequence	Pathology
Contractile dysfunction[1]	10-15% have shock (>40% LV infarct area) 70% mortality
Arrhythmia[1, 3]	Bradycardia, heart block[2], tachycardia PVCs, VT, VF
Myocardial rupture[2]	Either 1. Free wall of ventricle (most common) – ant-lat mid vent 2. Vent septum 3. Papillary muscle rupture RF for free wall rupture: > 60yo, female, HTN, prior MI
Papillary muscle	Particularly MR
Pericarditis or Dressler's	Fevers, chest pain, effusion – autoimmune basis, day 2-3 post MI
RV infarction[3]	Unusual isolated, normally associated with post LV & septum
Extensions	
Expansion[2]	stretching/thinning/dilation of infarcted area due to weak/necrosis
Ventricular Aneurysm[2]	late complication of Transmural MI with early expansion → thrombus, arrhythmia ,failure, NOT rupture
Mural thrombus[2]	
Progressive late CHF[1]	

[1]Large Infarcts
[2]Anterior Transmural Infarcts (LAD)
[3]Posterior (inferior) Transmural Infarcts (RCA or LAD)
} Anterior worse than posterior (inferior)

Ventricular Remodelling
- Hypetrophy & dilation of adjacent non infarcted skin

Chronic IHD
- Due to Infarct healing, remodelling
- Physiologically is the decompensation of remodelling
- Not always previous infarction
- Often thought of as CM

Sudden Cardiac Death
- Without symptoms or with symptoms < 1 hr
- Primarily due to Arrhythmias since only 39% resuscitated have recurrent AMI
- AMI most common trigger (80-90%)

Mechanism
- Damaged myocyte can be electrically unstable ∴ MI can be distant from conduction sys
- Foci due to old scarring
- Non atherosclerotic lesions (10-20%)
  - Congenital abnormality
  - AS
  - MVP
  - Arrhythmias
  - Myocarditis
  - CM or Hypetrophy
  - pHTN
  - Metabolic, Hormonal (catecholamines), drugs (cocaine, methamphetamines)

Arrhythmias:
- Long QT (↑ K conductance)
- Brugada
- Short QT
- Catecholaminergic polymorphic V
- WPW
- SSS
- Isolated disease

VALVULAR DISEASE

Stenosis = block forward flow → pressure overload, usually chronic condition
Insufficiency ++ backwards flow → volume overload, many causes, including insidious onset

Defect	Common Path	Uncommon Path
AS	Calcification of normal/bicuspid valve	rhematic, senile calcification
AR	Dilation of asc (2ry to HTN or age	rhematic, IE, Marfan's Relating to aorta: degen dilation, syphilic aortitis, ank spond, rheumatoid
MS	rhematic	None
MR	MVP	Leaflet: post inflammatory scarring, IE, drugs Tensor apparatus: rupture (muscle > chordae), fibrosis

- Functional regurgitation = due to structural support abnormality (eg LV dilation)
- Congenital vs acquired (66% MV or AV)

Calcification

Calcific AS
- Most common valvular disease – 2% of population
- Bicuspid valves 1% population ie 50% AS due to bicuspid valve
  - Most common congenital cardiovascular malformation
  - Other late complications: AR (from IE, Ao dilation/dissection)
  - *Aortic wall almost always abnormal*
  - Unequal size (larger leaf has *fused raphe – site of calcification*)
  - MV normal
- Sx at 7-9th decade
- Abnormal valve like osteoblasts (vs atherosclerosis – smooth muscle)
- Starts in valvular fibrosa (near margins of attachment)
- No commissural fusion with non-rheumatic AS ie free edges not involved = no fusion
- Normal valve area = 4cm^2, severe stenosis = 0.5 – 1.0 cm^2 (75-100mmHg)
- If symptoms develop: 50% survival 5 year or 2 years if CHF

Mitral Annular Calcification
- Can cause MR, MS, Arrhythmias, Stroke, IE
- Risk factors: female > 60, MVP, high LVP

MVP

- 3% population affected / 3% are complicated: IE, MR, Stroke, Arrhythmias
- TV, AV or PV may be affected
- Midsystolic click
- Most common cause for surgical repair/replacement

	Morphology
Primary	• Leaflets: enlarged, redundant, thick, rubbery, ballooning into LA Histologically: thin collagenous layer & thick spongiosa Mucoid deposition (aka "Myxomatous degeneration")[1] • Tendinous chordae: elongated or ruptured • Annulus dilated
Secondary	• Fibrous leaflet thickening • LV endocardial surface thickening (from chordae friction) • Mural endocardial thickening of the LV or LA (from leaflet friction) • Atrial thrombi • Focal calcification at base of posterior leaflet

[1]Occurs in all forms of MR

Rheumatic

- Acute RF: 10 days to 6 weeks after pharyngitis in 3% of patients (1% of RF die in acute)
- Age 5 to 15 (reactivation in middle age)
- Post group A strep pharyngitis (rarely other sites)
  Cellular immune system targets ***M protein*** on strep then cross react with self in heart
- Valve involvement: MV alone 65-70%, + AV 25% > TV > PV
  Rhematic AS accounts for < 10% of all causes of AS
- Causes myo/epi/endo/pancarditis & valvular disease

Morphology

- **Aschoff bodies** = foci of lymphocytes (mostly T cells), some plasma cells & macs (**Anitschkow cells** – pathognomic of RF)
- Chronic: diffuse fibrosis and neovascularisation (no Aschoff bodies)
- Found in all three layers

Cardinal anatomic changes

- Leaflet thickening
- Commissural fusion/shortening
- Thickening/fusion of chordae tendinae

Clinical Features

- Migratory polyarthritis of large joints
- Pancarditis
- Subcutaneous nodules
- Erythema marginatum of the skin
- Sydenham chorea

Jones criteria for RF

Evidence of group A strep with 2 listed or 1 listed and:

Fever, arthralgia, elevated blood levels of acute phase proteins

Infective Endocarditis

- Microbial colonisation → vegetations, thrombotic debris
- Bacterial endocarditis most common
- Routes of entry: dental, surgery, IVDU, prosthesis
- MV & AV most common

Acute IE

- Highly virulent bacteria on normal valve
- No amendable to conservative Mx = surgery
- Seen in IVDU (skin commensals eg staph epi)

Subacute IE

- Bacteria on abnormal valves (MVP, calcific stenosis, BAV, artificial, congenital)
- Conservative Mx trialled first
- Less destruction: granulation tissue , fibrosis, chronic infiltrates present

Valve Type	Organisms	% overall
Damaged native	*Strep Viridians*	50-60%
Normal	*Staph aeurus*	10-20%
All	Culture negative	15%
Prosthetic	*Staph epidermiditis*	Unknown
All	HACEK[1] & *Enterococci*	Remainder
	GNB , Fungi	

[1]*Haemophalis, Acinobacter, Cardiobacter, Eikenella, Kingella*

	Clinical Features
Splinter Haemorrhages	Nail bed micro infracts from emboli
Janeway lesions	Non tender on palms and soles
Osler Nodes	Tender on pulps of digits
Roth Spots	Retinal haemorrhage

Duke's Criteria for IE **Either pathological criteria or clinical: 2 major or 1 major 3 minor or 5 minor**	
Pathological Criteria	• +ve culture in vegetation, embolus (from veg) or intracardiac abscess • Histo evidence of active endocarditis in a vegetation or abscess

Clinical Criteria	
Major	• +ve BC • Echo evidence of mass, abscess or partial separation of ***artificial valve*** • New valve regurgitation
Minor	• Previous abnormal valves or IVDU • Fever • Vascular lesions1 • Immunological phenomena2 • Micro +ve from unusual organism • Echo with evidence (not diagnostic) of endocarditis/worsening murmur

[1]Petichiae, splinters, emboli, septic infarcts, Mycotic aneurysms, intracranial bleed, Jane way lesions
[2]Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

Non infective Vegetations

- SLE or thrombotic
- Mitral > AV (Regurgitation more common)

Nonbacterial thrombotic endocarditis

- 1-5mm sterile thrombi on leaflets, close to cusp
- Closely attached to underlying valve
- Non invasive/Non inflammatory
- Can cause systemic embolus
- Occurs with DVT, PE, debilitated pt or direct trauma by catheter or swan ganz (common)
- Strong link with mucinous adenocarcinoma
- Trousseau syndrome has some association

SLE aka Libman-sacks endocarditis

- 1-4mm lesions
- Under surface of AV valves, endocardium or chords or mural surface of a or vent
- Fibrinoid necrosis of the valve substance contiguous with vegetation

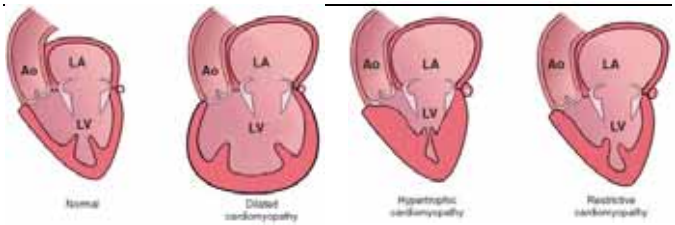
Carcinoid

- Involved right heart valves & endocardium – since mediators are broken down by lungs
- 50% sx: flushing, cramps, nausea, vomiting, diarrhoea
- Plaque like endocardial fibrosis (s muscle, collagen) on inside surface of chambers
- TV and PV involved, sometimes IVC and Pulm Art
- Gastric carcinoid rarely causes (portal breakdown)
- TR most common

Artificial Valves

- 60% 10 yr. complication
- Thromboembolic – most common
- Anticoagulant related haemorrhage
- Endocarditis (*s. epidermidis, aeurus, strep* and fungi)
- Structural deterioration (calcification, healing)
- Inadequate healing
- Exuberant healing
- Disproportion
- Haemolyses

CARDIOMYOPATHY



	Dilated	Hypertrophic[1]	Restrictive
LVEF	< 40%	50 – 80%	45 – 90%
Dysfunction	Systolic	Diastolic	Diastolic
Morphology			
1. Dilation	All chambers	LA	LA
2. Thickening	Nil	LV	LV (mod)
Causes			
Primary	Genetic (20-50%) Alcohol Peri partum Myocarditis Hemochromatosis Chronic anaemia Adriamycin Sarcoidosis Idiopathic	Genetic (100%) Freiderich's ataxia Infants of diabetic mothers	Amyloidosis Radiation Idiopathic
Secondary	IHD Valvular HTN CHD	HTN AS	Pericardial Constriction

[1]Most common cardiac genetic defect

ARVC

Arrythmogenic right ventricular CM occurs when free wall completely replaced by fibrosis

DCM

- Age 20 – 50
- Slowly progressive CHF
- 50% die within 2 years | 25% > 5 yrs

HCM

- Extreme Myocyte hypetrophy – mostly LV septum (3:1)
- Focal ischemia common (ie angina common)
- Common complications: AF, thrombus, CHF, VF, Sudden death (common cause of)

Myocarditis

- Most commonly virus: Coxsackie A or B and other enteroviruses
- Less common CMV, HIV
- Non-viral: tryobisina cruzi (Chagas disease) bacterial (lyme)
- Non-infectious: hypersensitivity from drugs, sle, Sarcoidosis

Amyloidosis of the Heart

- Restrictive CM

PERICARDIAL DISEASE

Effusion & Haemopericardium

- Normally 30-50ml
- Pericardium dilates to prevent cardiac compromise (up to 500ml)
- 200-300ml quickly can cause rupture or dissection

Pericarditis

Causes

- Viral (most common)
- Infection
- Immunological: RF, SLE, Scleroderma, Dressler, Drug
- Misc.: MI, Uraemia, Cancer, Trauma, Radiation
- Most are acute except TB or fungi

Types	
Serous	• **non inflammatory** • examples: RF, SLE, tumours, uraemia, neighbouring infection • rub less frequent due to separation
Fibrinous/Serofibrinous	• most frequent forms • caused by AMI, Dressler's, uraemia, radiation, RF< SLE, trauma • friction rub
Purulent/Suppartive	• direct, blood, lymphatic or cardiotomy • ***constrictive pericarditis*** usually Sequelae
Haemorrhagic	• metastasis in pericardium or bacterial infections (with coagulopathy)
Caseous	• rare, TB (sometimes fungal)

Chronic/Healed	• ranges from plaque-like thickening (Soldier's plaque) to stringy fibrosis causing adhesion (most common)
	  • Adhesive: increased workload
	  • Constrictive pericarditis

TRANSPLANT

- Commonly for DCM & IHD
- Complications: allograft rejection
- Long term: diffuse stenosing intimal proliferation of coronaries (denervated heart feels no pain)
- 1yr survival 70% | 5yr 60%

Congenital

- Major structures occur at weeks 3-8/40
- ½ congenital cardiac diseases dx 1st year of life

Defect	%
VSD	42
ASD	10
PVS	8
PDA	7
Tetrology	5
Coarctation	5
AVSD	4
AS	4
Transposition	4

Left to Right Shunts

VSD

- Usually related (only 20-30% isolated)
- 90% membranous part of IV septum 10% below PV
- Muscular septum defect usually has ***swiss cheese*** like perforations

ASD

- Secundum (90%) foramen ovale near centre of septum
- Primum (5%) Adj to AV valves
- Sinus venosus (5%) entrance of SVC (+/- pulm venous anomaly)

PDA

- Pulm Artery to Ao
- Useful in eg AV atresia

AVSD

- TV & MV malformation always associated
- Partial: primum ASD & cleft ant MV leaflet
- Complete: AV defect and large common AV valve ie all 4 chambers freely communicate
- 33% have down's

Right to Left Shunts = cyanosis

Tetralogy

- Most common
- Degree of shunting depends on severity of sub pulmonary stenosis

1. VSD (usually large)
2. Sub pulmonary stenosis (RVOT obstruction) +/- PVS
3. Overriding Ao (AV forms sup border of VSD)
4. RV hypetrophy

- Right Ao arch 25% of the time

Transposition

- 35% have VSD to compensate
- 65% have PDA or PFO = needs immediate intervention

Obstructive Anomalies

Coarctation

- ♂ x2 ♀
- Turner's syndrome

2 types:

- Infantile: tubular hypoplasia of arch prox to PDA
- Adult: ridgelike infold opposite closed ductus

- Bicuspid AV 50% of time
- Berry aneurysm, ASD, VSD, MR also associated

Pulmonary Stenosis & Atresia
Aortic Stenosis & Atresia

BLOOD VESSELS

VASCULAR RESPONSE TO INJURY

1. Endothelial Cells
- Maintains a non-thrombogenic blood tissue interface
- Endothelial activation = normal homeostasis
- Endothelial dysfunction = pro coagulation

2. Vascular Smooth Muscle
- Migration and proliferation

3. Intimal Thickening
- Due to triggers → smuscle proliferation and ECM proliferation "neointama"
- Once migrated – lose contractibility (not further hyperplasia)

HYPERTENSIVE VASCULAR DISEASE

BP ∝ CO & PVR

Outcomes of Chronic HTN
- Atherosclerosis
- Cardiac hypertrophy & failure
- Multi infarct dementia
- Dissection
- Renal failure
- Stroke

Cause
- 95% Idiopathic/5% causal
- 5% of total → malignant hypertension (SBP > 200 DBP > 120 acutely)
  → Retinal haemorrhage/exudate +/- papilledema. Renal failure

System	Disease	
Renal	CRF RAS or Renal vasculitis Acute GN	Polycystic Renin-producing tumours
Endocrine	Adrenal hyperfunction[1] Exogenous hormone[2] Pheochromocytoma	Acromegaly Hypothyroidism/Hyperthyroidism Pregnancy
CVS	Coarctation ↑ CO ↑ Volume	Polyarteritis Nodosa Aortic rigidity eg vasculitis
Neurological	Psychogenic ↑ ICP	Sleep apnoea Acute stress eg surgery

[1] Cushing's, 1ry aldosteronism, liquorice
[2] glucocorticoids, oestrogen, sympathomimetic, MOAI

ARTERIOSCLEROSIS
- Arterial wall thickening and loss of elasticity

Pattern	Morphology
Arteriosclerosis	Small arteries/arterioles → ischemia
Monckberg medial sclerosis	Calcific deposits in muscular arteries > 50yo Metaplastic → bone but not clinically significant
Atherosclerosis	

ATHEROSCLEROSIS

Atheroma
Components
- Core: necrotic (cell debris, Chol crystals, foam cells, calcium)
- Cover: white fibrous cap (smooth muscle, dense collagen, elastin, proteoglycans)
- Shoulder is rich in cells (macs, t cells, smuscle)
- Periphery: neovascularisation

Complications
- Atherosclerosis (including CAD)
- Mechanical obstruction
- Rupture → thrombosis
- Aneurysm (weakens media)

Risk Factors

Nonmodifiable	Modifiable	Other
↑ Age Male Family History Genetic Abnormality	↑ Chol ↑ BP Smoking Diabetes CRP	↑ homocystine Metabolic syndrome Lipoprotein Lifestyle

NB Multiplicative effect (eg x3 RF = x7 risk)

PATHOGENESIS
"Response to Injury hypothesis"

Chronic inflammatory ↔ healing cycle

1. **Endothelial Injury**
- Normal epithelium → abnormal gene expression → dysfunction
  → Abnormal adhesion molecules → inflammatory cells binding

  Haemodynamic: Form at branching points
  Lipids: ↑ ROS in endothelial cells
  Chronic Inflammation
  Infection

2. **Response to Injury**
- Lipoproteins (mainly LDL) accumulate in area
- Monocytes adhere to epi → macs & foam cells
  - Platelets adhere

Foam cells
Lipoproteins accumulate in intima
→ Oxidised by ROS from macs
→ Ingested by macs
→ Accumulate

3. **Smooth Muscle Recruitment**
- From platelet products released (and macs and foam cells)

4. **Smooth Muscle Proliferation**
- Produces ECM as well to stabilise atheroma
- Lipid accumulates in cells and in ECM
- Fatty streak → atheroma GF: PDGF. FGF> TGF-α

Morphology
Fatty streaks: earliest lesion
- Start as multiple minute yellow spots of foam cells then coalesce
- Not raised = no flow disturbance
- Seen in children > 10yo

Atherosclerotic plaque
- Intimal thickening & lipid accumulation
- Patchy & Rarely circumferential

Susceptibility (large & medium arteries targeted):
Lower 3rd AA > Coronary > Popliteal > Int Carotids > circle of Willis
NB upper limbs, mesentery and renal arteries spared

Components
- Cells: smooth muscle, macs, t cells
- ECM: collagen, elastic fibres, proteoglycans
- Lipids (intra and extracellular)

Changes
- rupture/ulceration/erosion
- haemorrhage into plaque
- atheroembolism
- aneurysm

Consequences
- Ischaemia and infarction (stenosis or embolisation)
  - Stenosis = 70% = symptomatic
  - Acute plaque change = rupture/fissure or erosion/ulceration or haemorrhage
    - Thin caps and few smuscle more likely to rupture
    - ↑ vascular flow
- Aneurysm
- Thrombosis
- Vasoconstriction

ANEURYSM & DISSECTION

True	intact arterial wall causes: atherosclerosis, syphilis, congenital
False	extravascular haematoma communicating with intravascular space

Classification
- Saccular: outpouching with only part of the circumference, often contain thrombus
- Fusiform: entire circumference
- False
- Dissecting

Pathogenesis

Cause	Mechanism
CT disorder	• Marfan's • Loey-Dietz syndrome • Ehlers-Danlos syndrome • Vit C deficiency
Vascular wall disorders	• Ischaemia → ↓ smooth muscle eg atherosclerosis • HTN also causes ischemia • Degenerative change also causes ischaemia
Inflammation	• Inflammatory cells (from atherosclerosis or vasculitis) produce MMP → degrade ECM
Other	• Trauma • Vasculitis • Congenital defect • Infection (eg Mycotic aneurysms)

AAA
- Men, smokers > 50
- Atherosclerosis main cause with environmental factors
- Mural thrombus common
- Variants: Inflammatory or Mycotic (esp salmonella)

Clinical Features
- Rupture
- Vessel obstruction
- Impingement/erosion of neighbouring structures (ureter or vertebrae)
- Pulsating mass
- Embolism from atheroma or mural thrombus

Risk of rupture
- Related to size
- Rate of expansion = 0.2-0.3cm per year
- < 4cm 0%
- 4-5cm 1%
- 5-6cm 11%
- > 6cm 25%

Thoracic Aortic Aneurysms
- HTN most common but also CT disease
- Clinical features
  - Impinge/erode neighbours
  - Lungs → resp difficulty
  - Oesophagus → difficulty swallowing
  - Cough → recurrent laryngeal nerve
  - Pain → boney erosion
  - Cardiac disease (valvular)
  - Rupture

Aortic Dissection
- Blood splays apart laminar plains of media
- If through adventitia can be fatal (and is a false aneurysm)
- Not always associated with dilation

Risk groups
- Men 40 – 60 with HTN
- Young with CT disorders
- Iatrogenic eg surgery
- Pregnancy

- Not seen with atherosclerosis (since media is fibrosed)

Pathogenesis
- Vaso-vasorum hypetrophy and thinning of medial smooth muscle
- Trigger usually unknown/Cause of weakness usually unknown

Morphology
- Starts with intimal tear – usually asc within 10cm of valve
- Dissects middle and outer thirds of laminar plains

Debakey classification	
I = asc & descending aorta II = asc only	Type A = anything before the left subclavian
III = desc only	Type B = anything after

Complications
- Death due to advential dissection → pericardium, pleural , peritoneum
- Valvular malfunction
- Dissection to any of the arteries

Vasculitis

Causes
- Common: Immune mediated or infection
- Less common: chemical or physical

Non-infectious Vasculitis
Immune Complex-Associated
- Complement activation or recruitment of Fc receptor bearing cells

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)
- Autoantibodies directed against neutrophil constituents
  - p-ANCA (MPO-ANCA): lysosomes = Polyangitis or churg-strauss syndrome
  - c-ANCA (PR3-ANCA): azurophilic granules = Wegners granulomatosis

Anti-Endothelial Cell Antibodies
- Seen in Kawasaki disease

Giant Cell Arteritis
- Most common
- Focal granuloma of medium/small arteries (esp cranial, sometimes aorta)
- T cell mediated response to wall antigen
- Intimal fibrosis
- Skip lesions
- Clinical: headache and facial pain, ophthalmic = 50% blind
- Steroids Tx

Takayasu Arteritis
- Medium/large vessels
- Transmural fibrosis of arch & branches
- Clinically can have poor UL perfusion pressure
- 50% pulmonary artery
- If > 50yo called giant cell aortitis

Polyarteritis Nodosa
- Necrotizing vasculitis of small to medium arteries
- Kidneys > Heart > Liver > GIT (pulmonary spared)
- ANCA negative, 1/3 immune complex mediated
- Disease of young adults

Kawasaki
- Acute febrile illness in children
- Medium to large vessel arteritis
- T cell hypersensitivity to unknown antigen
- 20% develop coronary arteritis → aneurysms → rupture or thrombosis
- ENA positive

Microscopic Polyangitis
- PAN in small vessels
- pANCA commonly +ve
- 90% manifest necrotizing GN or less common pulmonary
- No immune deposition

Churg Strauss
- Small vessel nec vasculitis
- Ass with asthma, allergic rhinitis, peripheral eosinophilia
- ANCA +ve < 50%
- 60% have CM

Wegners

Triad
1. Necrotizing or granulomatous vasculitis of small/med vessels of lungs & upper airways
2. Necrotizing granulomas of upper and lower resp tract
3. GN

- T cell hypersensitivity to inhaled substance
- cANCA +ve 95%

Thromboangiitis Obliterans (Buerger Disease)
- Heavy smokers < 35yo
- Segmenting thrombosing acute and chronic inf of med and small vessels
- T cell response to smoke modified self-antigen

Veins and Lymphatics

Varicose Veins
- Chronically elevated venous pressure → dilation and tortuous → valve incompetence → stasis dermatitis → varicose ulcers
- Men 10-20% or women 25-33% of population
- Causes: pregnancy, hereditary venous defect, obesity, dependent leg position, proximal thrombosis, tumours

Thrombophlebitis and Pleothrombosis
- venous thrombosis eg DVT
- trousseau syndrome = malignancy associated hypercoagulable state
- lower limbs > pelvic plexus

Vena Cava Syndromes
- SVC syndrome due to tumour compressing SVC → dusky head, neck, arms
- IVS syndrome due to external compression or internal (extending hepatic or renal carcinoma)

HAEMOPOIETIC

Normal Development

- Myeloid: bone marrow
- Lymphoid: thymus, nodes, spleen

Development and Maintenance of Hematopoietic Tissues
- Active marrow in axial skeleton only in adults
- HSC have 2 essential properties: self-renewal and pluripotentcy
- In times of stress HSC are released into plasma and differentiate at distant sites eg spleen
- Short term changes via committed progenitors

Normal values

Cell	Population	X10^
White	4.8-10.8	3
Granulocytes	40-70	
Neutrophils	1.4-6.5	3
Lymphocytes	1.2-3.4	3
Monocytes	0.1-0.6	3
Eosinophils	0-0.5	3
Basophils	0-0.2	3
Red cells	4.3-5 (♂) 3.5-5 (♀)	3
Plt	150-450	3

LEUKOPENIA

- Usually neutrophils
- Common causes: Congenital immunodeficiency, HIV, glucocorticoid toxicity, autoimmune, malnutrition, viral infections, cytotoxic drugs
- Infection common < 500

Neutropenia
- Agranulocytosis = clinically significant reduction in neutrophils

Pathogenesis
- Inadequate/ineffective granulopoieses
  - Suppression of stem cells (aplastic anaemia, tumours)
  - Suppression of committed precursors (drugs)
  - Disease eg Megalobalstic anaemia, mylodysplastic syndrome
  - Congenital eg kostmann syndrome

- Accelerated removal
  - Immunological (idiopathic, SLE, drugs)
  - Splenomegaly
  - Peripheral utilisation (ie infection)

Inflammatory White Cell Proliferation

Leucocytosis

Patterns	Examples
↑ Marrow Production	• Chronic infection/inflammation • paraneoplastic • myloproliferative
↑ Marrow release	• endotoxemia • infection • hypoxia
↓ margination	• Exercise • Catecholamines
↓ Extravasation into tissue	• glucocorticoids

Type	Cause	
Neutrophilic	Acute bacterial infection Sterile infection (eg MI, burns)	
Eosinophilic	Allergic, parasitic, drug, malignancy, vasculitis (some)	
Basophilic	Rare | Suggestive of myloproliferative disorder	
Monocytosis	Chronic infections eg TB	Malaria
	Bacterial endocodatitis	IBD
	Rickets	SLE
Lymphocytosis	Usually with low Monocytosis Chronic immune stimulation eg tb, viral (HAV, EBV), pertussis	

Lymphadenitis

Acute Nonspecific Lymphadenitis
- Cervical: infection of teeth, tonsils
- Axillary/Inguinal: limb infections
- Mesenteric: appendicitis
- Generalised: vireamia/bacteraemia

Morphology
- Swollen, grey red, engorged
- Large germinal centres
- Macs have debris
- Central necrosis if from pyogenic organism

Chronic Nonspecific Lymphadenitis
- Follicular hyperplasia
  - From stimuli that activate humoral response
  - Secondary follicle surrounded by mantle zone
    - Follicle is polarized
    - Dark zone = proliferating b cells (centroblasts)
    - Light zone = B cells (centrocytes)
    - Between dark and light = APCs (tingle body macs) & b cell nuclear debris
  - Eg rheumatoid, toxoplasmosis, early HIV
  - Similar to follicular lymphoma but diff because
    - Preserved node architecture
    - Variable size and shape
    - Fq mitotic figures, macs, light/dark zones

- Paracortical hyperplasia
  - T cell mediated immune response eg viral infection
  - T cell region contains immunoblasts, activated t cells
  - Encroach b cell follicles

- Sinus histiocytosis
  - ↑ size and number of cells that line sinusoids
  - Lymph node draining cancer eg breast

SPLENOMEGALY

- 150 g

Function
- Phagocytosis of blood cells and particulate matter
- Antibody production
- Haematopoiesis
- Sequestration of formed blood elements

Causes			
Infection	Mono TB Typhoid Brucellosis CMV	Syphilis Malaria Histoplasmosis Toxoplasmosis	Kala-Azar Schistosomiasis Leishmaniasis Echinococcosis
Congestion (2ry to portal HTN)	Cirrhosis (most common in group) Portal or splenic thrombosis Cardiac failure		
Lymphohaem disease	Non-Hodgkin's lymphoma Multiple myeloma		Myloproliferative disorders Haemolytic anaemia
Immunological-Inflammatory	RA SLE		
Storage	Gaucher disease Niemann-Pick		Mucopolysacchridoses
Misc	Amyloidosis 1ry neoplasms and cysts		Secondary neoplasms

BLEEDING DISORDERS

1. Fragile Vessels
2. Platelet deficiency or dysfunction
3. Coagulation derangement

Lab Test		
Prothrombin Time	Extrinsic & common pathway	V, VII, X, Prothrombin or fibrinogen
Partial Thromboplastin Time	Intrinsic & common pathway	V, VII ,IX, X, XI, XII, Prothrombin, fibrinogen, phospholipid
Platelet count	150-300 x10∧3	
Plt Fcn	none	

Vessel Wall Abnormalities
- Petechiae and purpure
- Causes: infection, drug reaction, poor vascular support, Henoch-Schonlein, hereditary haemorrhagic telenectasia

Thrombocytopenia
- < 100,000 (spont bleeding < 20,000, traumatic haemorrhage 20-50,000)
- Causes Petechiae or purpure (vs clotting factor associated)

Causes
- ↑ consumption eg DIC
- ↓ production eg HIV, aplastic anaemia, bone cancer
- Sequestration eg splenomegaly
- Dilution eg massive transfusion

Chronic ITP
- Normal spleen (but congested)
- Women < 40
- Easy bruising and epistaxis
- Normal PT and PTT
- Antibodies not always detected

Acute ITP
- Usually viral in children but also drugs or HIV
- Self limiting

HITTS
- Type 1: common, heparin causing plt aggregation
- Type 2: less common, autoantibodies to heparin/plt complex → thrombus

HIV related
- ↓ production & ↑ destruction

Thrombotic Microangiopathies: TTP & HUS

TTP
- Due to deficiency in metalloprotease that limits vWF

HUS
- Due to micro-endothelial cell damage usually from toxins by e coli

Symptoms
- Both: thrombocytopenia, microangiopathic haemolytic anaemia, fever,
- TTP: transient neurological deficit
- HUS: renal failure

Defective Platelet Function
- Congenital: ↓ adhesion, defective aggregation, disorders of plt secretion
- Acquired: aspirin, Uraemia

Haemorrhagic Diathesis
- Large ecchymosis or haematomas
- Common sites: gastrointestinal, urinary or joints

Acquired
- multiple clotting factors
- Vit K def: II, VII, IX, X and protein C
- Liver failure
- DIC

Hereditary
- Single clotting factors
- Haemophilia A or B
- Von Willebrands disease

Von Willebrands Disease
- Most common inheritable bleeding disorder
- Type 1 & 3 = ↓ vWF (1 = auto dom, 3 = recessive but severe)
- Type 2 = dominant, vWF dysfunction, mild mod bleeding

Haemophilia A (Factor VIII deficiency)
- Most common fatal inheritable bleeding disorder
- X lined recessive
- ↓ activity and function of VIII
- Severe when < 1% normal
- Moderate when 2-5% normal
- Mild when 6-50% normal

Haemophilia B (Christmas Disease, Factor IX deficiency)
- X linked recessive
- Indistinguishable from A

Disseminated Intravascular Coagulation
- Symptoms: micro thrombi ischaemia or bleeding

Pathogenesis
- Release of tissue factor (or thromboplastic substances in circulation) +
  - Placenta, amniotic fluid
  - Tissue damage eg trauma, burns, surgery
  - Leukemic cells
  - Sepsis (specifically endotoxins → TNF-α release → ↑ TF expression)
- Widespread endothelial injury
  - causes TF release
  - antigen-antibody complexes eg SLE, hypoxia, acidosis, extremes of temp, infection
- Release of TF & Endothelial injury → microthrombi → consumption & occlusion → isch & haemorrhage

Clinical features
- 50% DIC occur in obstetrics setting
- 33% in carcinoma
- Rest: trauma & sepsis

ANAEMIAS

- Reduction of total circulating mass
- Due to blood loss, ↑ rate destruction or ↓ production

	Meaning
MCV	avg volume of rbcs
MCH	average mass of hb per rbc
MCHC	avg concentration
RBC	variation of cell volume

BLOOD LOSS

Acute
- Haemodilution occurs rapidly (movt of water from interstitium)
- Internal bleeding → Fe can be recovered
- Acute loss = normal size and colour
- After 7-10 days reticulocyte count = 10-15%
- Thrombocytosis and leucocytosis also occur

Chronic
- Same anaemia as Fe deficiency

HAEMOLYTIC ANAEMIAS

- ↓ life span
- Accumulation of breakdown products
- ↑ erythropoiesis

Haemolytic Anaemia from Trauma
- Either prosthetic valve or narrowed vessels
- Prosthetic valve
  - Mechanical higher
- Narrowed vessles
  - DIC, SLE, HUS, TTP, malignant HTN
- Haemoylsiss not sevre except for HUS/TTP

Intravascular vs Extravascular

Intravascular
- Less common
- Seen in mechanical (eg prosthetic valves), complement, toxic (eg f. malaria)
- Usually extravascular destruction (mostly spleen)

Sequelae
- Hemoglobineamia/ Methemalbuminemia
- Hemoglobinuria/ hemosiderinuria
- Jaundice

Extravascular
- Removal because they are injured, tagged as foreign or deformed
- Jaundice and Anaemia without the rest seen in intravascular
  (Since no Hb breakdown products in circulation)

Hereditary vs Acquired

Hereditary (intracorpuscular)

Hereditary Spherocytosis
- Spheroidal & less deformable from defective cytoskeleton (mainly spectrin)
  → Splenic sequestration & destruction
- Auto dom (75%) auto rec (25%) – more severe
- Spherocytes also seen in autoimmune haemolytic anaemia

Clinical features
- Splenomegaly (most often and most enlarged of the haemolytic anaemia's)
- Jaundice
- Aplastic crisis occurs when production ↓ (commonly parvo virus) – self limiting
- Haemolytic crisis (↑ destruction) less common and less significant
- 50% have pigment gallstones
- Fixed with splenectomy

G6PD deficiency
- G6PD normally protects against ROS ∴ more significant in stress
- Deficiency is protective against plasmodium falciparum
- X-linked recessive
- Most common enzyme defect, but only 2 sig
  - Class II (A-) = moderate haemolysis
  - Class III = Mediterranean & more severe

Causes
- Anything that ↑ ox stress eg infection (esp typhoid, pneumonia, viral hepatitis)
- Fava beans and drugs

Morphology

Precipitated cross-linked sulfhydryl groups on globin chain due to oxidative stress
- ↑ ox stress → Hb denaturation → Heinz bodies → spleen → consumption
- Haemolysis 2-3 days later
  - Hemoglobineamia/uria.
  - ↓ Haematocrit
  - Since intermittent no chronic signs (eg splenomegaly)
  - Recovery: > reticulocytes

Sickle Cell
- Structurally abnormal Hb (β globin gene)
- Protective against falciparum malaria
- Become sickled during deoxygenation & reversible when oxygenated
- Repeated sickling and reversing → membrane defect and permanent sickling

Determinants of Severity
- % HbS
  - Homozygotes are almost 100% HbS
  - Heterozygotes are 40% HbS
  - HbF inhibits sickling
- [Hb] (ie MCHC) ∴ dehydration ↑ sickling
- Deoxygenation

Sequelae
- Chronic haemolytic anaemia from ↓ lifespan (20 days vs 160)
- Chronic hyperbilirubinaemia
- Small vessel occlusion → ischaemia
  - Due to reversible HbS in late stages (most sticky)
  - Ischemia → further deoxygenation → more late reversible HbS → more occlusion
  - Autosplenectomy: early stages splenomegaly occurs but with micro thrombi and ischaemia → scarring and shrunken spleen
- ↑ Risk of infection
  - Due to malfunctioning spleen (common cause of death in children from sickle cell)

Different Crises
- Vasculo-occlusive (painful crises)
  - Things that ↑ sickling frequency eg infection
  - Common sites: bones, lungs, liver, brain, spleen, penis
- Aplastic crisis (parvovirus)
- Sequestration crisis

Thalassemia Syndromes
- ↓ α or β globin in HbA (α2β2)
- ↓ globin
  → ↑ other globins & Hypochromia (hyper production of α chains → clumping)
  → Premature destruction and mature cell lysis in spleen

β-thalassemia

Deficiency in β globin causes
1. Fe overload: most abnormal Hb die in marrow, reabsorbed in gut
2. Haemolysis: those that are released are removed by the spleen
   → Anaemia→ ↑ EPO → marrow expansions (crew cut skull)

Type	Inheritance	Clinical Manifestations
β thal major	Homozygous	• Transfusion dependant • Smear shows anisocytosis (variable size), hypochromic • Often fatal or early death due to complications
β thal minor	Heterozygous	• Asymptomatic • Protective against f malaria • Smear shows hypochromic, microcytic anaemia (like Fe def)
β thal int	-	• Severe anaemia not requiring frequent transfusion

α-thalassemia

Different excess chains occur
- Newborn = excess γ-chains = Bart Hb
- Adult = excess β-chains = HbH

Both γ and β excess are more soluble than α excess ∴ less severe

Clinical manifestations

Type	Genetics	Clinical Manifestations	β thal equ
Silent carrier	-α/αα	No anaemia	minor
Trait	--/αα	Asians with of severe thalassemia in offspring	minor
	-α/-α	Africans	minor
HbH disease	--/-α	excess β-globin = high affinity for O2 = ↓ O2 offloading = anaemia	int
Hydrops Fetalis	--/--	Excess γ globin → unable to offload O2 → in utero death without transfusion	major

Paroxysmal Nocturnal Hemoglobinuria
- Only acquired cell membrane disease
- GPI-linked proteins unable to attach → lysis by complement
- Occurs in all GPI expressed cells ie plt, agranulocytes
- 75% have chronic intravascular haemolysis
- 25% of nocturnal Hemoglobinuria
- Can arise from aplastic anaemia or acute leukaemia

Clinical outcomes
- Fe def anaemia
- Thrombosis (esp hepatic, portal or cerebral veins) cont 50% deaths
- Chronic

Acquired (extra corpuscular)

Immune mediated Anaemia

- Classified depending on antibody: ***warm antibody, cold agglutinin or cold haemolysin***
- Measured using coombs test (positive) and temp at which agglutination occurs

Type	Ig	Temp[1]	Types
Warm Antibody	G	37	Idiopathic 50% Autoimmune (SLE < drugs) Drugs Lymphoid neoplasms
Cold Agglutinin	M	< 30	Acute: mycoplasma, mono Chronic: idiopathic, lymphoid neoplasm
Cold Haemolysin	G	< 30	Rare: post viral infection in children

[1]For activation of antibodies

Warm antibody haemolytic anaemia

- Most common
- Doesn't fix complement

Drug induced

Hapten Model	Autoantibody Model
• Eg pen or ceph • Bind red cell and induce antibodies • Change shape and removed by spleen	• Eg methyldopa • Generate antibodies to red cell without binding (esp to Rh group)

Cold Agglutinin

- During recovery phase of infection eg mycoplasma or infective mono
- Self limiting

Anaemia of Diminished Erythropoiesis

Megalobalstic Anaemia

- Impaired DNA synth mostly from Vit B12 (pernicious) or Folate def

B12 Deficiency

Normal B12 homeostasis

- Dependant on animal products 100%
- Full saturated stores can last years
- 2-3mg required per day
- IF binds B12 for uptake in ileum
- B12 mobilised in plasma by binding transcobalmain II

Causes of B12 def

- Inadequate intake
- Def of IF (pernicious anaemia)
- Malabsorbtion
- Diffuse intestinal disease
- Ileal resection or ileitis
- Competitive uptake eg tapeworm
- Bacterial overgrowth
- ↑ requirement eg thyrotoxicosis, preg, cancer

Pernicious

- Specifically Vit B12 def due to atrophic gastritis → ↓ production of IF
- Good relationship with Folate def

3 autoantibodies against

Type	Autoantibody blocking mechanism
I	B12 binding IF
II	IF or IF-B12 complex binding mucosa for uptake
III	Proton pumps of gastric cells (not specific for pernicious anaemia)

Clinical Outcomes

- Mod-severe anaemia
- Leukopenia
- Thrombocytopenia
- Achlorhydria
- Neurological: posterolateral spinal tract
- Methylmalonic acid in urine
- Schillings test +ve

Folate def

- Same characteristics as B12 without neurological sequelae
- Entirely dietary; green vegetables
- High reserves – months before seen

Cause	
↓ intake	alcoholism, malnutrition, OCP/anticonvulsants
↑ requirements	pregnancy, infancy, cancer, ↑ haematopoiesis
↑ loss	dialysis
Impaired use	folic acid antagonist

Fe Def Anaemia

Normal Fe metabolism

- Functional: 80% in Hb
- Storage: 15-20% of total body Fe, as ferritin or hemosiderin
  - Readily mobilise during acute need from spleen, liver, marrow, skeletal muscle
  - In either parenchymal (liver, from plasma transferratin) or macrophages (rest from rbc breakdown)
  - Hemosiderin is lysosomal breakdown of Fe into clumps and found only in trace around the body

∴ Ferritin shows state of storage — Fe def: Ferritin < 12micrograms per L; Overload Ferritin > 5000

- Transferrin transports Fe usually 33% saturated
- Most active Fe absorption occurs in duodenum >>> stomach, ileum, colon
- Fe homeostasis usually via amount absorbed (since body loss is limited)

Fe def

- Dietary: malnourished, elderly, poor, infants, children
- Impaired absorption eg Sprue, gastrectomy
- ↑ requirement eg growing, pregnant
- Chronic blood loss – most important

Morphology

- Hypochromic microcytic anaemia

Clinical

- Koilonychias, alopecia, atrophic tongue/gastric mucosa, oesph web
- Plummer-Vinson syndrome: microcytic hypochromic anaemia, atrophic glossitis AND oesph webs

Lab findings

- Serum Fe low
- Serum ferritin low
- Total iron binding capacity high

Anaemia of Chronic Disease

- ↓ erythroid proliferation + impaired Fe utilisation

Causes

1. Chronic microbial infections: OM, endocarditis, lung abscess
2. Chronic immune disorders: RA, enteritis
3. Neoplasms: Hodgkin's disease, lung & breast Ca

Morphology

- ↓ Serum Fe
- ↓ TIBG
- ↑ stored Ferritin (in mononuclear phagocytes)

Pathogenesis

- Probably low erythropoietin response to anaemia
- Inability to transfer stored → plasma
- Marrow hypoproliferation

Aplastic Anaemia

Pancytopenia with

- Anaemia
- Neutropenia
- Thrombocytopenia

Caused by failure/suppression of multipotent myeloid stem cells

- Idiopathic
- Chemical: chloramphenicol, benzene, streptomycin, chlorpromazine, DDT
- Physical: radiation
- Viral: non hep a or b hepatitis, CMV, EBV, VZV
- Inherited: fanconi anaemia

Pure Red Cell Aplasia

- Idiopathic or secondary to mainly Ca (esp thymoma)

Other Marrow Failures

- Space occupying lesions
- Diffuse liver disease
- Chronic renal failure

Polycythaemia

- Relative eg dehydration, prolonged vomiting, diarrhoea
- Absolute eg idiopathic, EPO exogenous, lung disease, high altitude, cyanotic heart disease, EPO secreting tumours

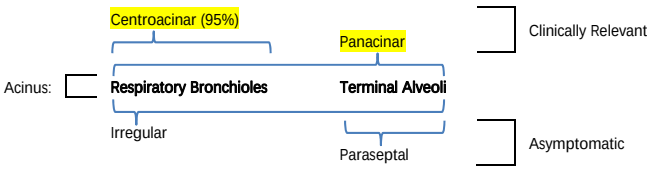
RESPIRATORY

Obstructive Airways Disease

- Asthma, COPD, bronchiectasis
- COPD – 10% non-smoker (most smokers don't get COPD)

Emphysema

- Irreversible enlargement of airspaces distal to terminal bronchioles & wall destruction
- 4th leading cause of M&M, ♀ African America



Type	Lobe	Location	Disease
Centroacinar	Upper Lobes	Proximal Acinus	Smokers
Panacinar	Lower Lobes[1]	Entire Acinus	α-1AT deficiency
Paraseptal	Upper Lobes[2]	Terminal Acinus	Fibrosis, scarring[3]
Irregular	Entire	Entire	Scarring[4]

[1]Anterior Margin
[2]Near Pleura, septa, margins
[3]Probably most common cause of PXT in young people
[4]Probably common

Pathogenesis

- Mild chronic inflammation: ***↑ Macs, CD4 & 8+, Neutrophils***
- Common mediators: ***Leukotriene B4, IL-8, TNF***
- Destruction from protease-antiprotease mechanisms & antioxidants
- Protease-antiprotease hypothesis
  - α1-AT is an anti-protease found in serum, tissue fluid & secreted by neutrophils
  - Antiprotease = ↑ emphysema (1% of all emphysema pt)

Model

- Neutrophils sequestered in peripheral capillaries & Some into alveolar space
- Stimulus (eg smoking)
  → ↑ number/secretions (esp protease from neutrophils)
  → ↑ Elastic tissue destruction
  → Loss of elastic recoil
  → Functional obstruction (ie collapse on expiration)
- Other changes leading to emphysema
  - Goblet cell metaplasia with mucous plugging
  - Inflammatory infiltration +/- follicles
  - Smooth muscle hypetrophy → bronchial thickening → obstruction

Relationship to smoking

- Neutrophils & macs accumulate in alveoli ?nicotine chemotaxis
- ROS in smoke (ie oxidant-antioxidant imbalance)
- Enhances elastase activity in macs (not inhibited by α1-AT)

Morphology

- Upper 2/3 more severely affected
- Apical blebbing/bullae
- Micro: large alveoli, thin septa, loss of alveoli attachment, ↓ capillary beds
- Pores of Kohn (bronchial collaterals)
- Canals of Lambert (broncho-alveolar connections)

Clinical course

- Sx with > 1/3 damage only
- Barrel chested
- Prolonged expiration
- Cor pulmonale = poor prognosis
- Death due to: acidosis, RHF, PXT

Other types of Emphysema

Compensatory Hyperinflation
- Alveoli dilation without destruction eg post partial lung resection

Obstructive Over inflation
- Lung expansion due to obstruction eg tumour or FB
- Due to ball-valve or collateral ventilation

Bullous Emphysema
- Descriptive term for large sub pleural blebs or bullae (ie > 1cm) – usually apex
- Occurs in any emphysema
- Can cause PXT

Interstitial (surgical)
- Air in CT from alveoli tearing

Chronic Bronchitis

- Cough & sputum for > 3 months over 2 consecutive years without other cause found
- Can progress to COPD or cor pulmonale/HF or metaplasia/dysplasia

Pathogenesis

- Long standing irritation – 90% due to smoking
- Early features: hypetrophy of submucosal glands → hypersecretion in trachea and bronchi
- Later: ↑ goblet cell size & number in smaller airways (protective metaplastic reactions)
- Sets up poor innate response to infection

Morphology

- Gross: hyperaemia, swelling, oedema, excess mucous
- Micro: chronic inflammation (ie lymphocytes), enlarged trachea & bronchi glands
- Hypertrophy main change (hyperplasia less so)
- Reid index = ratio of thickness of gland to wall = 0.4 normally
- Progress to squamous metaplasia or dysplasia

Pink Puffers vs Blue Bloaters

	Bronchitis	Emphysema
Age	40-45	50-75
Dyspnoea	Mild; late	Severe; early
Cough	Early; copious	Late; scant
Infections	Common	Occasional
Cor Pulmonale	Common	Rare; terminal
Airway resistance	↑	Normal or slight ↑
Elastic recoil	Normal	↓
Chest film	Prominent vessels large heart	Hyperinflation, small heart
Appearance	Blue bloater	Pink puffer

Asthma

- Chronic inflammation with widespread variable bronchoconstriction
- Reversible

Hallmarks:
- Airway hypersensitivity
- Episodic bronchoconstriction
- Inflammation of bronchioles
- ↑ Mucous secretion

Types of classifications

- Atopic vs Non atopic
  - Atopic: IgE mediated, most common, environmental triggers
  - Non-atopic (**intrinsic**): usually infectious trigger
- Inflammatory pattern: eosinophilic, neutrophilic, mixed, pauci-granuloylcytic
- Triggers: seasonal, exercise-induced, drug-induced, occupational, smokers
  - Drug: eg NSAIDs
  - Occupational: includes Type I sensitivities

Pathogenesis

- Atopic: genetic – strong T_H2 reactions
- T_H2 secrete IL-4 → B cell IgE release
  IL-5 → activates Eosinophils
  IL-13 → mucous secretion & IgE production

Early phase
- Bronchoconstriction (vagal stim), mucous secretion, variable vascular vasodilation

Late phase
- Inflammation (cytokines released from epithelium)
- Eotaxin = chemo attractant for eosinophils

Alleged Mediators of Asthma

1. *Pharmacological targets*
   - Leukotrienes C4, D4, E4 = constriction and ↑ permeability
   - Ach
2. *Present without antagonist effect*
   - Histamine (bronchoconstriction)
   - PGD2 (bronchoconstriction, vasodilation)
   - PAF (plt, histamine and serotonin release)
3. *Present without known antagonists*
   - Cytokines: IL-1, TNF, IL-6
   - Eotaxin
   - NO
   - Bradykinin
   - Endothilin

Morphological changes: Airway Remodelling

- Epithelial injury
- ↑ airway vascularity
- ↑ smooth muscle hypetrophy/hyperplasia
- ↑ gland hypetrophy & metaplasia
- Collagen deposition → Sub-basement membrane fibrosis (collagen type I & III, normal = IV)

Morphology : Status

- Over distended/inflated alveoli
- Bronchi occlusion & Bronchiole thickening
- Tenacious mucous plugging (Curschman spirals =mucous + shed epithelial cells)
- Charcot-Leyden crystals (made of galaectin-10)

Clinical Course

- Acute attack – hrs
- Difficult expiring
- High eosinophil
- Sputum – Curschman spirals and Charcot-Leyden crystals

Bronchiectasis

- Chronic necrotizing infection
  → Destruction of muscle & elastic tissue
  → Permanent dilation of bronchi/bronchioles

Causes

- Congenital/hereditary: CF. immunodeficiency
- Post-infectious: TB, s aeurus, h influenza, pseudomonas, adeno, influenza, HIV, aspergillus
- Obstruction: tumours, FB, mucous impaction
- Autoimmune: SLE< IBD, transplant, RA

Morphology

- Lower Lobes, Vertical airways, Distal airways
- Histo: metaplasia (columnar → pseudostratisfied → stratsified) or desquamated
- Fibrosis
- Necrotizing ulcerations

Complications

- Common: SOB, Cyanosis
- Less common: cor pulmonale, brain abscess, amyloidosis

Pulmonary Oedema

Microvascular (local) vs Macrovascular (blood flow) vs Undetermined

Macrovascular (haemodynamics)

↑ Hydrostatic Pressure (ie ↑ Pulm v pressure)	↓ Oncotic Pressure (less common)
• LHF – common	• Hypo alb incl liver disease
• Volume overload	• Nephrotic syndrome
• Pulmonary vein obstruction (eg PE)	• Protein losing enteropathies

NB Lymphatic obstruction (eg Ca) rare

Microvascular (alveolar injury)

- Infection incl aspiration
- Shock or trauma
- Drugs incl transfusion
- Chemicals incl inhaled gases (O_2 or smoke) or Radiation

Undetermined

- High altitude
- Neurogenic

Interstitial Disease

(Restrictive disease)

- Inflammatory and interstitial fibrosis
- Causes pHTN & Cor pulmonale
- Histologically seen as honeycomb lung

Fibrosing diseases

Idiopathic Pulmonary Fibrosis

- Progressive interstitial fibrosis
- Unknown cause
- Insidious onset with survival < 3 yrs

Nonspecific interstitial pneumonia

- Better prognosis but less hetrogenicity
- Still unknown cause

Cryptogenic Organizing Pneumonia (BOOP)

- Still unknown cause
- No interstitial fibrosis or honeycomb, but loose fibrous tissue plugs (**Masson bodies**)
- Spont *recovery* or steroids

Pneumoconiosis

- Non-neoplastic lung responses to inhaled substances
- Coal workers: spectrum of ***antracosis*** to ***progressive massive fibrosis***
- Silicosis = nodular fibrosis, highly fibrinogenic
- Asbestos (fibrous silicate)

Granulomatous Disease

Sarcoidosis

- 90% cases involve hilar nodes

Hypersensitivity Pneumonitis

- Farmers lung: from actinomyces spores in hay
- Pigeon breeders lung
- Humidifier/Air con

Pulmonary Eosinophilia

- Acute
- Simple
- Tropical (microfilariae)
- Secondary (infection, hypersensitivity, asthma, allergic aspergilliosis)
- Idiopathic chronic

Disease of Vascular Origin

PE, Haemorrhage, Infraction

- Usually embolic, rarely in situ (associated with pHTN)
- Clinical symptoms lead to electromechanical dissociation or cor pulmonale
- 10% cause infarcts

pHTN

- Occurs when 25% of systemic
- Causes:
  - COPD
  - LHF (congenital, acquired)
  - Recurrent PE
  - OSA
  - CT disease/ Interstitial disease
  - Idiopathic, familial

Diffuse Pulmonary Haemorrhage: Goodpastures

- Antibodies to collagen IV α3 chain (ie BM)
- Male, early adolescence
- PC haemoptysis then GN

Atelectasis

- Incomplete expansion (neonatal)
- Collapse
  - Resportion (obstruction) eg excess secretions
  - Compression eg effusion, pxt
  - Contraction eg fibrosis

Pleura

Effusion

- Transudate or exudate

Factor change	Change	Example
Hydrostatic	↑	HF
Permeability	↑	Pneumonia
Intrapleural pressure	↑	Atelectasis
Oncotic	↓	Nephrotic syndrome
Lymphatic drainage	↓	Carcinoma

Inflammatory

- Serofibrinous
- Suppartive
- Haemorrhagic

Non inflammatory

- Heart, liver or renal failure
- AAA
- Lymphatic obstruction

Tumours

- Malignant mesothelioma – most common in pleura then peritoneum
- Associated with asbestos in 90% (but only 20% have asbestosis)
- Lifetime risk 7-10%
- Latency can be up to 25-46 years

Pulmonary Infections

Innate Defence	Source of Failure
Cough reflex	Coma, paralysis
Mucociliary dysfunction	Smoking, congenital
Secretion accumulation	CF, Obstruction
Phagocytosis inhibition	Alcohol, Smoking, O_2

Clinical Settings		
CA Typical	Strep pneumonia (pneumococcus) (most common) H Influenza Moraxella catarrhalis (2nd most common cause of COPD exac) Staph aeurus Legionella Klebsiella (enterobacter)	
CA Atypical	Mycoplasma (most common) Chlamydia Coxiella Viruses: RSV, parainfluenza, Infl A or B, adeno, SARS	
HA	GN rods Enterobacter (klebsiella, Serratia, E Coli) Pseudomonas Staph Aeurus (resistant)	
Aspiration	Anaerobic flora: Becteroides, prevotella, fusobacterium, peptostreptococcus Aerobic: strep pneumonia, staph aeurus, h influenza, pseudomonas	
Chronic	Nocardia, actinomyces, Granulomatous: TB, histoplasma, blastyomyces	
Necrotizing	Anaerobic (very common) Staph aeurus, klebsiella, strep pyogenes, pneumococcus – type 3	
Immunocompromised	CMV PCP Mycobacterium avium-intracellulare	Invasive aspergilliosis Invasive candidiasis All usual suspects

CA = community acquired
HA = Hospital acquired

Community Typicals

Morphology

Bronchopneumonia	Lobar Pneumonia
• Foci of Suppartive inflammation • Frequently multi-lobar and bilateral (ie patchy consolidation) • Neutrophil rich	1. Congestion: vascular engorgement, intra-alveolar fluid with neutrophils, bacteria 2. Red hepatisation: exudation of neutrophils, red cells, fibrin in alveolar space 3. Grey hepatisation: disintegration of red cells and persistence of fibrosuppartive exudate 4. Resolution

NB Some organisms can display either pattern

Complications
- Tissue destruction/necrosis → abscess (common with pneumococci, klebsiella)
- Empyema; pleural abscess
- Dissemination

Strep Pneumoniae (pneumococcus)
- Most common
- Gram +ve diplococci
- Endogenous in 20% of resp flora
- 20-30% BC +ve
- Pneumococcal vaccine in high risk

Haemophilus Influenza
- Gram –ve
- Most common cause of life threatening LRTI or meningitis in children
- 95% unencapsulated in pharynx
- Encapsulated form secretes haemocin to destroy unencapsulated
- Vaccine for encapsulated
- Unencapsulated spread to cause OM, sinusitis, bronchopneumonia
- Inhibits innate by
  - Pili for adherence
  - Disorganise ciliary beating and degrade IgA

Moraxella
- elderly
- 2nd most common cause of exac COPD
- OM (H influenza, S pneumonia make top 3)

S Aeurus
- High incidence of complications
- IVDU
- Hospital acquired

Klebsiella
- Most common GN pneumonia
- Targets debilitated, malnourished eg chronic alcoholics
- Thick gelatinous sputum

Pseudomonas
- Usually HA or CA CF

Legionella
- Found in artificial aquatic environments
- Inhaled or aerosolised or aspiration
- Common in cardiac, renal, immunological or haematological disease
- Organ transplant common
- Lab: legionella antigen in urine or sputum antibody or culture

Community Atypicals
- Moderate sputum, no consolidation, mildly elevated wcc, lack of alveoli exudate
- Mycoplasma most common – esp in older children/young adults
- Mechanism: organism attaching to upper tract → local inflammation → necrosis
- Common morphology
  - Red-blue congestion
  - Pleural smooth (ie pleuritis, effusions not common)
- Histo: interstitial inflammation, localised within walls of alveoli
  - Main cell types: lymphocytes, macs, sometime plasma cells
  - Neutrophils also if acute

Influenza A, B & C (based on nucleoprotein)
- RNA virus
- Subdivided by viral haemagglutinin and neuraminidase: H1-3, N1-2
- Mechanisms to clear: CD8+ or Mx1 (intracellular anti-influenza protein) induced by macs via IFN-α or β
- A: pandemic or epidemics,
  - ***Epidemics*** via mutation of haemagglutinin/neuraminidase (ie antigenic drift)
  - ***Pandemic*** from antigenic drift (animal RNA recombinant)
- B & C don't have drift or shift, seen in children
- Avian influenza: H5N1 60% mortality – haemagglutinin can be cleaved by other organs = fulminant disease

Human Metapneumovirus (MPV)
- Paramyxovirus
- 5-10% of hospitalised pneumonia

SARS
- Incubation 2-10 days & Spread via resp but also stool
- Coronavirus – LRTI (33% of URTI are coronavirus)
- Diagnosis: viral PCR (peaks day 10), antibodies (variable rise – usually day 28)

Lung Abscess
- Causes other than pneumonia: surgery, dental, bronchiectasis

Aetiology
- Most commonly strep, staph, some GN
- Anaerobic: oral commensals eg becteroides, fusobacterium, peptococcus – all found in 60% of cases
- Entry via: aspiration, antecedent primary lung infection, septic embolism, neoplasia, direct trauma, neighbouring infection, haematogenous seeding
- Idiopathic = primary cryptogenic lung abscess

Morphology
- Aspiration is right sided & single vs Rest = multiple
- Cardinal histo: Suppartive destruction of lung parenchyma within central area of cavitation

Chronic Pneumonia
- Localised in immunocompromised patients
- Granulomatous
- Bacterial (TB) or fungal (histoplasma)

Fungal

Histoplasmosis
- H capsulatum
- Inhalation of dust from soil contaminated by bird/bat droppings
- Intracellular parasite of macs
- Similar morphology to TB
  - Self-limiting & latent primary pulmonary involvement → coin lesions
  - Chronic progressive disease localised to lung apices
  - Localised lesions in extra pulmonary sites
  - Disseminated disease
- Caseous necrosis and sometimes liquifactive

Blastomycosis
- Pulmonary, disseminated or primary cutaneous
- Soil commensal
- Suppartive granulomas form
- Cells difficult to phagocytose

Coccidoidomycosus
- Delayed hypersensitivity reaction
- 10% have lung lesions
- < 1% disseminated disease

Immunocompromised Pneumonia

Causes of infiltrates in the immunocompromised

	Diffuse Infiltrate	Focal Infiltrate
Common	CMV	GN rods
	PCP	Candida
	Drugs	Aspergillus
		Malignancy
Uncommon	Aspergillus	PCP
	Malignancy	Legionella
	Cryptococcus	Cryptococcus
	Other bacteria	Mucor

Pneumonia in HIV
Type depends on CD4+ count
> 200 = bacterial or tubercular
< 200 = PCP
< 50 = CMV or Mycobacterium

Pulmonary Tumours

Carcinomas
- 90-95% of lung tumours
- Most common cause of cancer

Pathogenesis
- 10-20 mutations (at least)
- Tobacco smoking (♀ more susceptible) ↓ risk after 10 yrs cessation, ♂ 87% link
- Environmental exposures eg radiation, pollution, asbestos (x5 – latency 10-30 yrs)
- Genetic
- Precursor lesions (not always develop): squ dysplasia and carcinoma in situ, atypical adenomatous hyperplasia, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Classification
- ***Small cell*** most significant – almost always mets, high initial response to radiation & chemo)
- ***Non-small cell*** – less mets but less response

Type	Subtype	Male%	Female%
Adenocarcinoma[1]	Acinar; papillary, bronchoalveolar. Solid, mixed	37	47
Squamous cell carcinoma*[1]		32	25
Large cell carcinoma	Large cell neuroendocrine carcinoma	18	10
Small cell carcinoma*	Combined small cell carcinoma	14	18
Adenosquamous			
Carcinoid	Typical, Atypical		
Salivary gland			
Unclassified			
Other	Pleomorphic, sarcomatoid or sarcomatous		

*strongest relation to smoking (>98%)
[1]slowest to metastasize

Morphology
- 75% found in 1st to 3rd order bronchi
- 10% mixed

Metastasis (non-small cell)
- All but adrenals: Liver 30-50% | Brain 20% | Bone 20%

Adenocarcinoma
- Glandular differentiation and mucin production in a variety of patterns
- Bronchoalveolar most distinct histologically – peripheral
- ♂ = ♀, not related to smoking
- Slower, Smaller and more peripheral (vs squamous)

Squamous cell carcinoma
- Squ metaplasia → dysplasia → carcinoma in situ → Squamous cell carcinoma
- Invasion locally, along peribronchial tree, intraparenchymal
- Nodal involvement > 50%
- Histo: keratinizing and intercellular bridging

Small cell carcinoma
- Small cells, scant cytoplasm, ill-defined borders, fine granular chromatin with inconspicuous nucleoli
- Probably neuroendocrine progenitor origin (most commonly associated with ectopic hormonal production) ∴ Most commonly cause **paraneoplastic syndrome**

Large cell carcinoma
- Probably poorly differentiated small or adeno

TNM

	T	N	M
0	-	None	-
1	< 3cm	Ipsi hilar/peribronchial	None
2	3-7cm	Ipsi mediastinal/subcarinal	Distant
3	> 7cm	Contralateral	

Grouping

Stage	T	N	M
1a	1	0	
1b	2		
2a	1	1	
2b	2	1	
	3	0	
3a	1-3	2	
3b	3	1	
4			1

Clinical Course
- Cough 75% weight loss 40% chest pain 40% SOB 20%
- 5 yr survival 15%
- Small cell = 6-17 weeks

Paraneoplastic syndrome

Syndrome	Hormone Production
SIADFH	ADH
Cushing's	ACTH
Hypercalcaemia	PTH
Carcinoid	5HT & Bradykinin

- 1-10% (mostly small cell)
- Carcinoid seen in MEN-1

Neuroendocrine Proliferation & Tumours
- Small amounts seen in fibrosis & inflammation
- Tumorlets = small hyperplastic nests of cells – clinically insignificant
- Others include small cell. Large cell and carcinoid

Carcinoid
- 1-5% all lung tumours
- < 40yo, ♂ = ♀
- 60% smoking link
- Low grade malignant neoplasms
- Typical (no p53 mutation or BCL2 or BAX) vs atypical
- Survival: 5 yr 87% & 56%, 10yr 87% & 35% (typical vs atypical)

Misc Tumours
- Harmatoma – seen as coin lesions on cxr (mostly cartilage with some cellular fibrosis)

GASTROINTESTINAL

INFLAMMATORY

Features	CD	UC
Macroscopic		
Region	Ilium (40) ± (30) Colon (30)	Colon
Distribution	Skip	Diffuse
Stricture	Yes	No
Wall Appearance	Thick	Thin
Microscopic		
Inflammation	Transmural	Mucosa only
Pseudopolyps	++	+++
Ulcers	Deep/Thin	Shallow/wide
Lymphoid reaction	+++	++
Fibrosis	+++	+
Serositis	+++	+
Granuloma	Yes	No
Fistula/Sinuses	Yes	No
TH polarity	1	2
Clinical		
Perianal fistula	Yes	No
Malabsorbtion	Yes	No
Malignant potential	Only if in colon	Yes*
Recurrence post resection	Yes	No
Toxic mega colon	No	Yes
Genetic clustering	50%	16%

++ Moderate
+++ marked
*↑ In 8-10 yr with pancolitis, ∝ severity/duration of inflammation

- Both more common in females and present in 20's

MALABSORBTION

Disease	Defect			
	Intraluminal	Terminal	Transepi	Lymph
Celiac*		✓	✓	
Tropical Sprue		✓	✓	
Pancreatitis*	✓			
CF	✓			
1ry Bile acid malab	✓		✓	
Carcinoid			✓	
Autoimmune enteropthy		✓	✓	
Disaccharide Def		✓		
Whipple				✓
Abetaipoproteinemia			✓	
Viral Gastro		✓	✓	
Bacterial Gastro		✓	✓	
Parasitic Gastro		✓	✓	
IBD*	✓	✓	✓	

*most common

Celiac
- Delayed hypersensitivity
- Proximal intestines first
- IgA best test
- Causes Fe & Vit def and sometimes t cell lymphoma, small intestinal adenoma

LIVER

General Features of Hepatic Disease

Lab Correlation

Hepatocyte Injury	Cytosolic hepatocellular enzymes	AST ALT LDH
Biliary	Normal secretions	Bilirubin (serum/urine)
	Damaged epithelium	ALP
Hepatocyte Function	Proteins secreted into plasma	Albumin Prothrombin time
	Metabolism	Ammonia Aminopyrine breath test Galactose elimination (via IV)

Patterns of Hepatic Injury
- Degeneration & intracellular accumulation
- Necrosis & Apoptosis
- Inflammation
- Regeneration
- Fibrosis

Hepatic Failure

Acute Liver Failure
- Fulminant if < 2 weeks of jaundice
- Sub fulminant if < 3 months of jaundice
- Encephalopathy within 6 months of diagnosis
- Hepatic necrosis underlying feature

Causes	%
Paracetamol	50
Autoimmune	15
Industrial Exp	14
HBV	8
HAV	4
HCV	0

Chronic Liver Disease
- Most common route to failure

Hepatic Dysfunction without overt necrosis
- Eg tetracycline toxicity or fatty liver of pregnancy

Clinical Features
- Jaundice
- Hypoalbuminaemia → oedema
- Hyperammonemia → cerebral dysfunction
- Fetor hepaticas = body odour due to portosystemic shunting = systemic exposure of methionine broken down by gut bacteria
- Palmar erythema (local vasodilation) from impaired oestrogen metabolism
- Spider angiomas from oestrogen metabolism too
- Hypogonadism and gynocamastia also

Complications

Hepatic encephalopathy
- Rigidity, hyper-reflexia, asterexis
- Associated with high NH_4
- Histologically only astrocyte swelling and oedema
- Reversible

Hepatorenal syndrome
- 8% of cirrhotic patients
- Failure, Na retention, impaired H_2O excretion
- Due to ↓ renal perfusion, systemic dilation, renin release
- Median survival 2 weeks to 6 months

Hepatopulmonary syndrome
- Chronic liver disease + hypoxemia + intrapulmonary vascular dilation
- NO main mediator

Cirrhosis
- Alcohol, viral, NASH

Morphology
1. Bridging fibrous septa (scars along portal tracts)
2. Parenchymal nodules (hepatocytes surrounded in fibrosis)
3. Disruption of entire architecture

Pathogenesis
- Hepatocyte death + ECM deposition + vascular reorganisation
- Type IV collagen deposits in space of disse causing
  - Fibrotic septal tracts
  - Impaired hepatocyte/plasma exchange
  - Parenchymal vascular shunting
- Proliferation of stellate cells → fibrinogenic cells (expressed through intracellular mechanisms and chemomodulation from kuppfer cells and lymphocytes)
- Contraction of sinusoidal vascular channels → ↑ resistance
- Biliary channel obliteration

Clinical Features
- Initially asx then non-specific
- Cause of death: progressive failure, portal hypertensive complication or hepatocellular carcinoma

Portal Hypertension

Prehaptic
- Obstructive thrombosis
- Narrowing of portal vein
- Massive splenomegaly (↑ splenic vein flow)

Intrahepatic
- Cirrhosis (less so include schistosomiasis, fatty change, Sarcoidosis)

Post hepatic
- RHF
- Constrictive pericarditis
- Hepatic vein outflow obstruction

Pathophysiology

↑ Resistance to portal flow
- At level of sinusoids
- Due to smooth muscle contraction & fibrosis
- Less NO production by sinusoidal cells
- Remodelling → arterio-venous anastomosis → damage to veins from high pressures

↑ Portal flow
- Splanchnic dilation
- Due to NO production 2ry to ↓ clearance of bacterial DNA usually removed by liver

Complications

1. Ascites
   - Due to cirrhosis
   - Clinically detectable at 500ml
   - Serous
   - Serum : ascites gradient > 1.1g/dL
   - Same Glc, Na, K same as blood
   - Erythrocytes suggests Ca vs White cells suggest infection
   - Hydrothorax develops via lymphatics if big enough
   - Pathogenesis
     - Sinusoidal HTN driving fluid into space of disse → removed via lymphatics
     - Percolation of hepatic lymph into peritoneal cavity
     - Splanchnic vasodilation & hyperdynamic circulation
2. Portosystemic venous shunt
   - ↑ portal pressure → reverse flow (through collateral dilation)
   - Sites include oesophageal, rectal and retroperitoneum & falciform ligament of liver
   - Clinically seen as varices, haemorrhoids and caput medusa
   - Varices occur in 40% of cirrhosis (50% die from bleeding)
3. Splenomegaly
   - Up to 1kg
   - Does not correlate with degree of cirrhosis
4. Encephalopathy

Jaundice & Cholestasis
- Obstruction, bilirubin overproduction, hepatitis
- Jaundice & icterus – yellow discolouration of skin & scelra
- Cholestasis – due to bilirubin and bile retention

Bilirubin & Bile formation
- End product of heme degradation
- 85% from red cell breakdown (in spleen, liver and marrow)
- 15% from turnover of hepatic heme or hemoproteins and precursors in marrow
- Erythrocytes → heme release → phagocytose → biliverdin → bilirubin → binds to albumin (insoluble in blood alone)→ liver → processed in ER of hepatocyte → bile → deconjugated in gut lumen by β-glucuronidase → urobilinogen (20% resorbed)
- 2/3 of bile is bile salts – from bile acid conjugation – bile acid from catabolism of chol
  - 95% bile salts reabsorbed
  - Used as detergent

Pathophysiology
- Unconj bili insoluble in H_2O @ physiological pH ∴ binds to albumin (Can't be excreted)
- Unbound unconjugated bili can diffuse into tissues → toxic injury eg **kernicterus**
- Conjugated bili is soluble, non-toxic, weak association with alb, excreted in urine
- Normal bili 0.3-1.2mg/dL
- Jaundice @ 2.0-2.5 mg/dL

Causes

Unconjugated
- Excess production: haemolytic anaemia, int haemorrhage resportion, poor erythropoiesis
- ↓ uptake: drugs prevent albumin binding, gilberts (sometimes)
- Impaired conjugation: breast milk, genetic def of UGT1A1, gilberts, diffuse hepatocellular disease eg viral, cirrhosis, physiological jaundice of newborn
  - Physiological jaundice of newborn: not matured until week 2, worse with breast milk
  - Hereditary

Conjugated
- Canalicular membrane transport deficit
- Impaired bile flow

Disorder	Inheritance	Defect	Clinical course
Unconjugated			
Crigler-Najjar I	Recessive	No UGT1A1	Fatal
Crigler-Najjar II	Dominant*	↓ UGT1A1	Jaundice, some kernicterus
Gilberts	Recessive	↓ UGT1A1	None
Conjugated			
Dubin-Johnson	Recessive	Impaired Glucuronide excretion	None
Rotor	Recessive	↓ uptake	None

*variable penetrance

Cholestasis

- Impaired bile formation or flow
- Obstruction or defect in hepatocyte secretion
- ↑ ALP & GGT

Morphology
Pigment in parenchyma
→ Feathery change (bile pigment in hepatocyte)
→ Fibrosis
→ Cirrhosis

Progressive Familial Intrahepatic Cholestasis

- PFIC-1: infancy, pruritiis
- PFIC-2: impaired bile salt secretion → cirrhosis in first decade of life
- PFIC-3: high GGT, due to detergent effect on un protected apical epithelial surface

Drug & Toxin Induced Liver Disease

Alcoholic Liver Disease

- Steatosis → hepatitis → cirrhosis (10-15% of alcoholics develop)
- Alcohol → mitochondrial dysfunction
- Caloric intake from alcohol displaces other nutrients → malnutrition and vitamin deficiency

Risk factors
- Gender: ♀ > ♂
- African
- Genetic
- Co morbid conditions (esp viral hepatitis)

Steatosis

- Reversible
- Moderate consumption
- Macrovascular globules of lipid accumulation displace hepatocyte nucleus to periphery
- Yellow greasy
- Fibrosis starts at terminal hepatic veins → sinusoids
- Shunting from catabolism to lipid synthesis due to excess NADH due to alc dehydrogenase & acetaldehyde dehydrogenase, impaired lipoprotein assembly and impaired fat metabolism
- Clinical features: hepatomegaly, mild ↑ bili, ALP

Hepatitis

- Reversible
- Hepatocyte swelling & necrosis
- Mallory bodies (clumps in hepatocytes due to tangles cytoskeleton)
- Neutrophilic reaction
- Fibrosis
- Clinical: acute onset, variable lab findings, non-specific symptoms, tender hepatomegaly, ↑ bili, ALP, WCC, progression to cirrhosis, hepatorenal syndrome

Pathogenesis
- Acetaldehyde induced lipid peroxidation → cytoskeletal disruption
- CYP450 (in ER) → ROS
- Causes release of bacterial endotoxins from gut → hepatitis
- Causes release of endothlins in sinusoids → constriction/contraction/hypoperfusion

Cirrhosis

- Irreversible
- Yellow, fatty, enlarged → brown, shrunken, non-fat → tough, pale
- Micro nodules from areas of attempted regeneration
- Fibrosis prominent
- Few Mallory bodies
- Outcomes: bile stasis, irreversible
- Similar to cirrhosis from viral hepatitis
- Clinical: ↑ transaminases, bili and variable alp, anaemia,

Outcomes

- Coma
- Massive bleeding
- Infection
- Hepatorenal syndrome (post hepatitis)
- Hepatocellular carcinoma (1-6% of alcoholic cirrhosis)

Cholelithiasis

- 90% cholesterol – more common west (> 50% Chol monohydrate)
- Remainder pigmented stone

Risk Factors

Chol Stone	Pigmented Stone
• Geography: north Europe, America, Mexico • Old age • Female hormones (gender, OCP, preg) • Obesity & Metabolic syndrome • Rapid weight reduction • Gallbladder stasis • Inborn errors of bile metabolism • Hyperlipidaemia	• Asian, rural • Chronic haemolytic anaemia • Infection • GI disorders (Crohns, resection, CF)

Pathogenesis

Chol

- Chol made soluble in bile by binding bile salts and water insoluble lecithins
- Supersaturation precipitates solid chol monohydrate crystals
- Therefore conditions required include: supersaturation, hypomotility, accelerated nucleation, hypersecretion of mucous to trap nucleated crystals, aggregation of stone

Pigment

- Mix of abnormal calcium salts of unconjugated bilirubin and inorganic calcium salts
- Therefore elevated unconjugated bilirubin diseases puts patient at risk
- Infection causes β-glucuronidase release → unconjugated bilirubin

Morphology

Chol

- Mostly within gallbladder
- Proportions range from 50-100% chol
- **Radiolucent** but 10-20% have enough calcium carbonate = radiopaque

Pigmented

Black = sterile
- Contains oxidised polymers of calcium salts of unconjugated bilirubin
- < 1.5cm
- Crumble to touch
- Spiculated and moulded
- 50-75% radiopaque

Brown = infective, not isolated to gallbladder
- Pure calcium salts, mucin, chol,
- Soft
- Soap like or greasy
- radiolucent

Clinical Features

- Colicky pain
- Complications: empyema, cholycystitis, perforation, fistula, cholangitis
- Increased risk of carcinoma

Cholycystitis

- acute, chronic or acute on chronic
- 90% of the time due to neck or cystic duct obstruction vs 10% are acalculous

Due to chemical irritation
→ Mucosal phospholipases strip away gallbladder epithelium
→ Bile salts irritate exposed gallbladder wall
→ Dysmotility
→ Distension & ↑ pressure & ↓ blood flow

- Infection occurs late in the course
- Diabetes high risk

Acalculous

- Ischaemia due to inflammation, oedema, stasis, biliary sludge (microcrystals of chol), viscous bile, gallbladder mucous
- Risk factors: sepsis, immunosuppression, trauma, diabetes, infection (eg salmonella)

Chronic

- Bouts of mild cholycystitis
- 90% stone related
- 33% have e coli
- Morph: mucosa preserved, rokitasky-aschoff sinuses prominent (outpunching of epithelium)

- **Porcelain gallbladder** = dystrophic calcification, high rate of cancer
- Xanthogranulomatous cholycystitis – very thick walled, shrunken with foci of necrosis and haemorrhage

Infectious Disorders of Liver

Viral Hepatitis

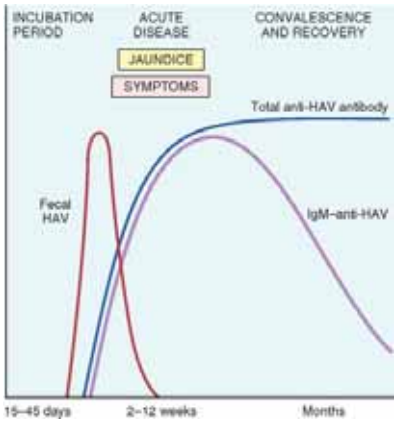
- Mostly by hepatropic virus A – E
- EBV
- CMV
- Yellow fever
- Less common: rubella, adenovirus, herpes, enteroviruses

Virus	A	B	C	D	E
Type	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Family	Hepatovirus	Hepadnavirus	Flavivirus	Deltaviridae	Calcivirus
Route	FO	Parenteral, Sexual, Perinatal	Parenteral, intranasal	Parenteral	FO
Incubation	2-4 weeks	1 – 4 months	7-8 weeks	1-4 months	4-5 weeks
Chronic	Never	10%	80%	5%[1] 70%[2]	Never
Dx	IgM AB	HBsAg or HBcAg AB	PCR HCV RNA	IgM or IgG AB, HDV RNA	PCR HEV RNA

[1]Coinfection FO = faecal oral
[2]Superinfection

Hepatitis A

- Self-limiting | Not chronic, not carrier
- Usually asymptomatic and rare after childhood: sporadic febrile illness +/- jaundice
- 25% of all hepatitis
- Shed in stools 2-3 weeks pre and 1 week post jaundice
- Sometimes from raw or steamed shellfish
- Main mechanism of hepatitis from CD8+ reaction
- IgM antibodies appear with symptoms (in line with drop in faecal shedding)
- IgG anti-HAV AB appears with IgM AB and persists for years
- Vaccine available



Hepatitis B

Outcomes

→ Acute hepatitis with recovery
- → 70% Subclinical disease → 90% Recovery
- → 30% Icteric → < 0.5% Fulminant
- → < 5% Chronic hepatitis → < 2% recovery
  - → 30% carrier
  - → 20% Cirrhosis
    - → 6% HCC

- Carrier state depends on age at which contracted (highest young)

Prevalence	Transmission Type
High	Perinatal
Intermediate	Childhood cut skin
Low	Sexual or IVDU

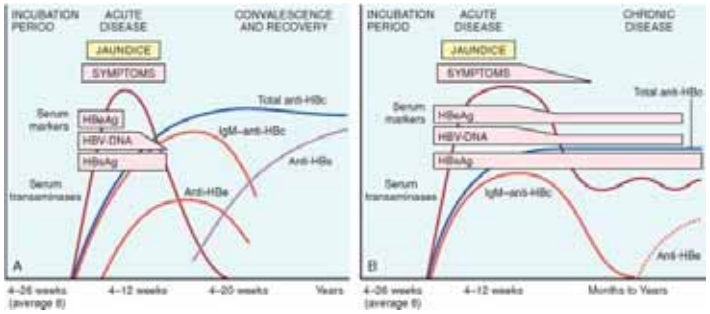
- Remains in blood with active episodes
- Doers not cause hepatitis directly (since carriers have virions in hepatocytes) but from target by CD8+ cells
- Vaccine from purified HbsAg in yeast

Structure

- Dane particle – outer surface envelope with electron dense core
- HBcAG = nucleocapsid core protein – stays in hepatocyte
- HBeAG = longer polypeptide transcript with precore and core regions – into plasma
- HBsAG = envelope glycoprotein (in 3 forms: large, middle, small (most common)
- Polymerase for DNA and reverse transcriptase
- HBx = transcription transactivator – possibly causes liver cancer

Sequence of serological markers

- HbsAg = before sx, peaks during overt disease, declines (undetectable) after 3-6 months
- Anti-HBs AB = after acute disease is over (4 weeks) – persists for life, confers protection
- HBeAg, HBV-DNA, DNA polymerase soon after HbsAg = active viral replication
- Anti-HBe AB = acute infection post climax
- IgM anti-HBc before sx (rises with rise in ALT/AST, replaced by IgG anti-HBc after months
- NB rare mutated strains do not produce HBeAg
- Some vaccine induced escape mutants also occur
- Low levels of HBV DNA can be detected by PCR in some HBV infections



Hepatitis C

- Most common blood borne infection
- Acute infection asx in 85% - more mild vs HAV or HBV

Risk Factor	%
IVDU	54
Multiple Sex Partners	36
Surgery < 6 months	16
Needle stick	10*
Multiple contacts with HCV infected person	10
Occupational	1.5
Unknown	32

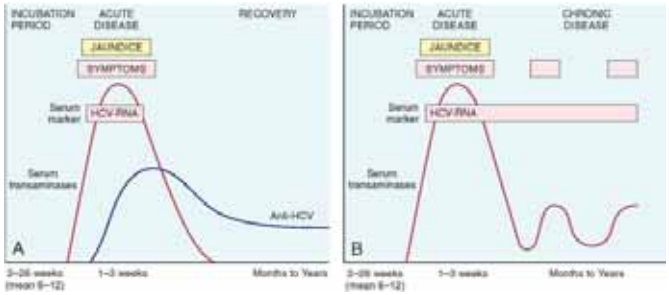
*6x risk vs HIV

Structure: enveloped ssRNA
- Unstable HCV RNA polymerase → multiple genotypes or "quasispecies"
- Makes difficult to make vaccine

Sequence of serological markers
- HCV RNA 1-3 weeks (same as serum aminotransferases)
- If symptomatic can also detect anti-HCV AB in 50-70% otherwise 3-6 weeks later

Chronic hepatitis

- 80-85% with Cirrhosis over 5-20 years in 20-30% of patients
- Evades host immunity via
  - Actively inhibit IFN mediated response via Toll-like signalling cessation & IFN R
- Aminotransferases are fluctuant (sometime normal)
- HCV RNA persists in serum (diagnostic)
- Fulminant hepatitis rare



Hepatitis D

- Requires HBV (needs HbsAg) – 5% of HBV infections
- Co-infection – similar to Hep B infection alone
- Super infection – chronic HbsAg carrier 80-90% of carriers
  - Acute phase: HDV replication with ↓ HBV, ↑ ALT
  - Chronic phase: ↓ HDV ↑ HBV ALT variable → HCC or cirrhosis
- Helper independent latent infection – liver transplant, seen hrs after
  - HBV indolent (with pre-transplant vaccination) but gradually increase in number
- Structure: similar Dane particle to HBV
- HDag is surrounded by HbsAg
- Dx via IgM anti-HDV AB – usually appears later and a short lived marker
- Tx with IFN-α

Hepatitis E

- Self limiting
- Enteric transmission
- Water borne
- Young-middle aged
- 30-60% of hepatitis in India
- High mortality in pregnant women (20%)
- Incubation 6 weeks
- HEV RNA and HEV virions in stool via PCR before symptoms

Syndromes of Viral Hepatitis

Acute asymptomatic infection with recovery (ie serological evidence of infection only)
- HAV, HBV

Acute symptomatic hepatitis with recovery, +/- icteric
- Incubation
- Symptomatic pre-icteric
- Symptomatic icteric
- Convalescence
- NB peak infectivity occurs on last asymptomatic day

Chronic hepatitis with/out progression to cirrhosis
- Symptomatic biochemical or serological continuing or relapsing hepatitis > 6 months
- HCV most common but HBV can do as well
- Clinical: sometimes spider angiomas, palmer erythema, mild hepatomegaly
- Sometimes immune complex disease can precipitate
- HBV: Younger the age at time of infection = more likely chronicity

Fulminant hepatitis
- HBV only
- Encephalopathy within 2-3 weeks without chronic course
- 12% of all fulminate hepatitis (8% HBV 4% HAV)
- Morphology: random areas of necrosis → shrinkage , haemorrhagic appearance

Carrier State
- Either carry without disease, carry with non-progressive disease
- < 1% of acute HBV produce carrier state (common in chronic)
- HCV 10-40% carrier

HIV & Chronic Viral Hepatitis
- 10% have HBV 30% HCV
- Leading causes of mortality and morbidity in HIV patients
- 2nd most common cause of death in AIDs

Morphology
- Mostly similar across different viruses

Acute
- Inflammation
- Apoptosis
- Ballooning degeneration (ie swelling)
- Sometimes cholestasis
- Cell dies, ruptures, sinusoidal collagen collapses, macrophages phagocytose
- Bridging necrosis in severe cases (portal to portal or central to central)
- Kuppfer cells → hypertrophy & hyperplasia (laden with Lipofuscin pigmentation)
- Interface hepatitis: spill over of inflammatory cells into adj parenchyma

Chronic
- Variable: well preserved → destruction
- Early on architecture preserved
- HCV: lymphoid aggregation, bile duct reactive change, mild macrovesicular steatosis with ongoing bridging and interface hepatitis
- HBV: ground glass hepatocytes
- Hallmark is deposition of fibrous tissue – firstly along portal tracts then peri portal septa

Bacteria
- Staph aeurus (TSS)
- Salmonella (typhoid fever)
- T pallidum (syphilis)
- Ascending cholangitis

Parasitic/Helminthic
- Malaria
- Schistosomiasis
- Strongylodis
- Cryptosporidiosis
- Leishmaniasis
- Liver flukes
- Liver abscess: echinococcal or aemobic
  - Usually pyogenic origin via portal vein, arterial, ascending, direct or penetrating

Acute Pancreatitis

- Reversible parenchymal injury with inflammation

80% from biliary tract or alcohol (35 – 60% gallstone)
- 5% of gallstones cause pancreatitis
- Alcohol causes 65% in US to 5% in France
- Gender (M:F) gallstone 1: 3 alcohol 6:1

10-20% no cause
- Idiopathic but probably hereditary

Causes
- Metabolic: alcohol, hyperlipoproteinemia, hypercalcaemia, drugs eg azathioprine
- Genetic: trypsin inhibitor
- Mechanical: gallstones, trauma, iatrogenic (surgery, endoscopy), tumour
- Vascular: shock, embolism, vasculitis
- Infection: mumps, parasites directly

Morphology
- Microvascular leakage → oedema
- Lipolytic enzymes → Fat necrosis & necrotizing pancreatitis & haemorrhagic pancreatitis
  Acute inflammation
- Destruction of blood vessels and interstitial haemorrhage

Pathogenesis
- Auto digestion
- Trypsin (normally inactive in pancreas) can be inappropriately activated → kinin activation and other proteolytic enzyme activation
- Lead to small vessel thrombosis and inflammation

Possible events
1. Duct obstruction
   → ↑ Pressure
   → Accumulation esp lipase (secreted in active form)
   → Local fat necrosis
   → Intracellular release/inflammation/oedema/inhibit blood supply
2. Primary acinar injury (from viruses, drugs, direct trauma, shock)
3. Defective intracellular transport of proenzymes
   - Normal acinar cells transport enzymes and lysosomal hydrolases separately. In damaged cells, enzymes are delivered to lysosomal hydrolases & activated
   - Unknown role

Alcoholic pancreatitis
- Protein rich pancreatic fluid → protein deposition and obstruction of small pancreatic ducts
- ↑ Exocrine secretion & contraction of sphincter of oddi
- Direct toxic effects on acinar cells

Clinical features
- Severe pancreatitis is a medical emergency
- Inflammatory mediators, enzymes into systemic circulation → SIRS
- Tx by resting pancreas and supportive
- 5% die in first week from severe pancreatitis
- Complications include abscess or pancreatic pseudocysts
- 40-60% with necrotizing pancreatitis develop superimposed infection

Chronic Pancreatitis
- Irreversible destruction of exocrine parenchyma, fibrosis, eventual destruction of parenchyma
- Most common = alcohol
- 40% idiopathic, overlap with acute otherwise

Pathogenesis
- Almost all with repeated episodes of acute from chronic (spared islets)
- Ductal obstruction by concretions
  (insult → ↑ protein in secretions → ductal plugs → calcify → obstruction
- Toxic effects – direct effect
- Oxidative stress from toxic agents
- Profibrinogenic chemokines dominate chronic inflammation
  (TGF-β and PDGF → myofibroblast proliferation → collagen deposition)
- Ductal epithelium can be atrophied, hyperplastic or squamous metaplastic
- Late chronic pancreatitis may be burnt out therefore lipase/amylase may not rise

Complications
- 20-25 yr mortality = 50%
- Exocrine insufficiency
- Chronic malabsorbtion
- Diabetes
- Chronic pain
- Pseudocysts in 10%
- Pancreatic cancer (40% risk in hereditary forms)

Renal

Urolithiasis

- Most arise in kidney
- 5-10% of population
- ♂ > ♀
- Onset 20-30 yo
- 80% unilateral
- Usually in renal pelvis, calyx or bladder

	Type	%
Ca Oxalate & Phosphate		
1	Idiopathic	50
2	Hyperuricosuria	20
3	Unknown	15
4	Hypercalciuria & calcemia	10
5	Heperoxaluria	5
6	Enteric	4.5
7	Primary	0.5
	Total	70%
$MgNH_4PO_4$ (struvite)		
	Total	15-20%

Uric Acid		
1	Hyperuricemia	
2	Hyperuricosuria	
3	Idiopathic	50%
	Total	5-10%
Cysteine		
	Total	1-2%

*NB common determinant is **supersaturation** of stone components, **low pH**, **low urine volume** or **bacteria***

Calcium Oxalate
- Radio-opaque
- 5% of hypercalcaemic & hypercalciuric patients (***hyper-para, bone disease, sarcoid***)
- 55% have hypercalciuria without hypercalcaemia due to
  - Absorptive hypercalciuria (from intestines)
  - Renal hypercalciuria (renal)
  - idiopathic
- 20% associated with ↑ uric acid secretion
- 5% associated with hyperoxaluria (intestinal overabsorbtion or primary)
  - More common in vegetarians

Magnesium ammonium phosphate
- After infection (proteus or staph)(converts urea to ammonia = alkaline urine)
- Large stones form eg staghorn calculi
- Radio-opaque

Uric Acid
- Hyperuricemia eg gout, rapid cell turnover
- > 50% don't have hyperuricemia or ↑ uric acid secretion
- Acidic urine
- Radiolucent

Cysteine
- Genetic defect in amino acid resportion (eg cysteine)
- Form at low pH

Obstruction

Level	Cause	
Kidney	Stricture	Calculi Tumour
Ureteric (intrinsic)	Clots Sloughed papillae Inflammation	Calculi Tumour
Ureteric (extrinsic)	Pregnancy Retroperitoneal fibrosis	Tumour
VUJ	Reflux	
Bladder	Functional (eg neurogenic)	Calculi Tumour
Prostate	Hyperplasia Prostatitis	Carcinoma
Urethra	Posterior valve stricture Prolapse Cystocele Meatal stenosis	Tumour

Hydronephrosis
- Renal pelvis dilation with progressive atrophy from outflow obstruction
- Glomerular cont to work for hrs after obstruction
- Renal atrophy from back pressure directly on cortex and vascular compression
- Interstitial fibrosis also occurs later on
- Complete obstruction = mild dilation
- Partial obstruction = progressive dilation
- Post obstructive diuresis is a phenomenon post complete obstruction

Tubular & Interstitial Disease

AKI: ATN
- Most common cause of failure (50% of causes in hospital)
- Reversible since ATN is patchy

Cause	Example
Ischaemia	Trauma, Pancreatitis
Nephrotoxins	Dye, myo or haemoglobin
Tubulointerstitial Nephritis	Hypersensitivity
Obstruction (post renal)	Stone, tumour, clot

Pathogenesis
- Critical event: tubular injury + blood flow disturbance

Tubule cell injury
- Predisposed due to large SA, active transport
- Loss of cell polarity (due in part to Na-K ATPase rearrangement)
  → ↑ Na delivery to DCT
  → Feedback
  → Vasoconstriction
- Detachment of ischemic cells → obstruction
- Irreversible injury
  → ↑ Interstitial pressure
  → Obstruction
- Net effect: ↓ GFR

Vasoconstriction
- Outer medulla sensitive to O_2 (correlates with thick asc limb)
- Due to
  - ↑ renin-angiotensin (from ↑ Na in DCT)
  - ↑ endothilin, NO & PGI_2 (from damaged cells)

Morphology (ischaemic vs toxic)

Casts
- Eosinophilic hyaline and granular
- Common in distal and collecting ducts

Insult	Ischaemic	Toxic
Necrotic distribution	Focal	Uniform
Skip Lesions	Yes	No
Vulnerable areas	Medulla[1]	PCT
Cast occlusion	Common	Uncommon

[1] Sometimes in DCT

Clinical Course
- 95% of nephrotoxic changes are reversible

Phase	Significant Events
Initiation phase	▪ 36hrs ▪ Slight ↑ UO* or ↑ GFR
Maintenance phase	▪ Sustained ↑ UO (40-400ml/day) ▪ ↑ K, ↓ pH, ↑ Na & H2O
Recovery phase	▪ ↑ UO ▪ ↓ K ▪ ↑ risk of infection

*50% of patients have nonoliguric AKI (usually toxins) – more benign course

Tubulointerstitial Nephritis
Infection: Pyelonephritis & Urinary Tract Infections
- Acute (bacterial) vs chronic (bacteria & abnormal anatomy)
- 85% GNB (e coli > proteus > klebsiella)
- Ascending > haematogenous spread (staph & e coli more common in haem spread)

Risk Factors
- Colonisation[1]
- Stasis
- Reflux: vesicoureteral or intrarenal
- Diabetes
- Pregnancy (4-5% of pregnant women)
- Renal lesions
- Immunosuppression/deficiency

[1]instrumentation, females, lack of antibacterial eg prostatic fluid

Acute Pyelonephritis
- Patchy interstitial suppurative inflammation and tubular necrosis
- Glomeruli most resistant to infection

Complications
- Papillary necrosis (mostly obstruction & diabetics)
- Pylonephrosis
- Perinephric abscess

Chronic
- Pelvocalyceal damage uncommon (chronic & analgesic only)
- 10-20% of ESRF
- Chronic obstructive vs chronic reflux (more common)
- Histo hallmark: blunted calyx with overlying scar esp in upper or lower pole
- Some develop FSGS from scars years later (poor prog)

Toxins

3 ways to cause injury

1. Interstitial **immunological** reaction eg methicillin
2. ARF (**nephrotoxic**)
3. **Cumulative** injury eg analgesia abuse

Drugs

- Sulphonamides, synth penicillins, diuretics, NSAIDs
- 15 days after exposure: fever & eosinophilia, rash (25%), △ GFR, haematuria, proteinuria
- Immune related (late phase, dose independent)

Events

Drug administered & act has **haptens**

→ Seed in interstitium (Type IV hypersensitivity)

→ Repeat administration causes IgE mediated response

Analgesic abuse

- ***Papillary necrosis*** → Chronic Tubulointerstitial nephritis
- Caused by antipyretics (usually 2 or more)
- Complicated by renal stones (acidosis) and infection (50%)
- Small % develop transitional papillary carcinoma

NSAIDs

- Inhibit PG → vasoconstriction
- Hypersensitivity → interstitial nephritis & minimal change
- Membranous glomerulonephritis

Causes of papillary necrosis

	DM	Analgesia	Sickle	Obstruction
M:F	1:3	1:5	1:1	9:1
Time	10 yrs	7yrs	Variable	Variable
Infection	80%	25%		90%
Calcification	Rare	Fq	Rare	Fq
# Papillae	Several	Almost all	Few	Variable

Metabolic

Urate Nephropathy

Acute uric acid nephropathy

- Uric acid Crystals in tubules esp CD
- Common in leukaemia, lymphoma during chemo

Chronic uratre nephropathy (gouty)

- Monosodium urate crystals
- Distal tubule and CD & interstitium
- Crystals form tophus*
- Link to lead ingestion

* FB & giant cells surrounding

Nephrolithiasis

- 22% of patients with gout

Hypercalcaemia and Nephrocalcinosis

- Initially mitochondrial distortion in tubular endothelium
  - Calcium deposition in mitochondria, cytoplasm, BM
  - Grossly alternating areas of normal/scarred parenchyma
  - Early clinical signs: unable to concentrate urine

Neoplasm

Multiple Myeloma

- Bence jones proteins and cast nephropathy
  - Light chains are directly toxic
  - Also bind with urinary glycoprotein → casts

Amyloidosis

- Light chain nephropathy – deposition in glomeruli

Physical eg chronic obstruction
Immunological
Vascular
Misc

Hypertensive Renal Disease

Benign Nephrosclerosis

- Sclerosis of renal arterioles and small arteries
- Causes focal ischaemia → glomerulosclerosis & chronic tubulointerstitial injury → ↓ size
- Morphologically: media & intimal thickening and hyaline deposition
- Clinically rarely have proteinuria or ↓ GFR despite mod ↓ renal flow
- At risk groups: HTN, diabetics, African

Malignant HTN

- Rarely starts as normotensive
- 1-5% of HTN, young people, African
- Renal insult → arteriolar Fibrinoid necrosis + hyperplastic arteriolarsclerosis
- ∴ high renin levels
- Clinically BP > 200

Renal Artery Stenosis

- 2-5% of HTN | 70% due to atheroma
- Fibromuscular dysplasia less common

Thrombotic Microangiopathies

- Overlapping findings (thrombocytopenia, microangiopathic haemolytic anaemia, RF)
- Endothelial injury & plt activation common mechanism
- **Haemolytic uremic syndrome** - due to endothelial injury
  - Typical – from food ingested contaminated with shiga-like toxin
  - Atypical – mutation of complement regulatory proteins
- **TTP** – due to plt dysfunction

Glomerular Disease

- Primary GN: kidney is principle organ involved
- Secondary GN: kidney damage from systemic disease
- Clinically & Histologically similar

Pathogenesis

- Immunological deposition + 2ry inflammation
- Intrinsic or in situ antigens eg Goodpastures (anti-GBM antibody)
- Circulating complexes eg SLE or infection

Progression

- When GFR 30-50% progression constant

Focal segmental glomerulosclerosis (FSGS)

- Idiopathic, heroin abuse, HIV, sickle cell, post glomerular necrosis, adaptive
- ↑ flow and permeability in unaffected glomeruli

→ Compensatory hypetrophy

→ Endothelial Injury & Inflammation (proteinuria)

→ Scarring

→ FSGS

→ Nephrotic syndrome

Tubulointerstitial fibrosis

- Isch change/nephrotoxic change
- Due to inflammation

Nephritic Syndrome

- Gross haematuria, mild-mod proteinuria, HTN
- Common in post strep GN
- Due to immune complex deposition either exogenous (strep) or endogenous (SLE)

Post strep GN

- 1-4 weeks post infection of pharynx or skin
- Age 6-10 yo
- Outcomes:
  1. Children 95% recover, 1% rapidly progress 4% chronic failure
  2. Adults: 60% recover quickly

Rapidly Progressive GN (crescentic)

Type I (anti-GBM)	Type II (Immune Complex)	Type III (Pauci-immune)
20%	30%	50%
• Renal limited • Goodpastures	• Idiopathic • Post infectious • SLE • Henoch-Schonlein	• Idiopathic • ANCA associated • Wegners • Polyarteritis • Polyangitis

Clinically

- Haematuria, casts, mod proteinuria, variable HTN & oedema
- Goodpastures also has haemoptysis
- 90% become chronic

Nephrotic Syndrome

- Heavy proteinuria (> 3.5 g/day), hypoalbuminaemia, severe oedema, hyperlipidaemia, lipiduria

Disease	Children	Adults	
Primary			**Secondary**
Minimal change	65	10	DM
Focal segmental	10	35	Drugs
Membranous	5	30	SLE
Memranoproliferative	10	10	Amyloidosis
Other proliferative	10	15	Malignancy
			Misc (eg bee sting)

Membranous

- 85% idiopathic (rest in malignancy, SLE< drugs)
- Chronic immune complex mediated disease
- Clinically: insidious onset of nephrotic syndrome +/- HTN +/- haematuria (15-35%)
- 10yr survival 90%

Minimal change

- Peaks age 2-6yo: usually post infection or routine immunisation
- Normal glomeruli on light micro: diffuse effacement of foot processes
- Tx with steroids = Good prognosis

Memranoproliferative

- Type 1 (common): Antigen-antibody complex deposition
- Type II (dense deposit disease): Alternate compliment pathway activation

Primary Glomerulonephropathies

IgA Nephropathy (Berger's)

- Most common GN
- Mucosal IgA secretion ↑ (immune regulation defect)
- Commonly seen as haematuria for a few days post infection
- Progressive renal failure over years

Alports syndrome

- Hereditary nephritis
- Haematuria → CRF, lens dislocation, nerve deafness, cataracts, corneal dystrophy

Chronic GN

- RPGN 90%
- FSGS (50-80%)
- MPGN (50%)
- IgA 30-50%
- Membranous GN (30-50%)
- Post strep GN (1-2%)

Secondary GN

Henoch-Schonlein Purpura

- 3-8yo
- Good prognosis

Bacterial endocarditis associated

- Immune complex deposition

Diabetic nephropathy

- Proteinuria +/- nephrotic syndrome
- Also causes hyalinising arteriolar sclerosis

MUSCULOSKELETAL

General Principles

Cells	Function
Osteoblasts	Bone matrix synthesis and mineralisation Derive from osteoprogenitor cells
Osteoclasts	Short lived (2 weeks) Multinucleated Bone resportion TNF, M-CSF & IL-1 drive differentiation to this
Osteocytes	From osteoblasts Long lived cells Local bon calcium and PO_4 homeostasis Mechanotransduction

Collagenous Components
- Type I collagen comes from osteoblasts
- **Woven:** Rapid bone formation (eg foetal skeleton and base of growth plate
- **Lamellar:** replaces woven bone gradually, stronger than woven bone

Fractures

- Complete vs incomplete
- Closed vs compound
- Comminuted
- Displaced
- Pathological # due to underlying disease process
- Stress Fracture – slowly developing

Sequence of Events

1. **Anchorage (0-1week)**

   Rupture of blood vessels → haematoma
   - Fills # gap
   - Acts as a fibrin mesh & seals off site
   - Framework for inflammatory influx and fibroblast and new vessels

   At the same time plt & acute inflammatory cells release mediators
   - PDGF, TGF-β, FGF, IL → progenitor cell activation in periosteum, medullary cavity & soft tissue & osteoclastic & blastic activity

   Result
   - Soft-tissue callus – anchors ends together without structural rigidity

2. **Stabilisation (week 2-4)**
   Osteoprogenitor cells deposit subperiosteal trabecular of woven bone perpendicular to cortical axis and in medullary cavity
   - Sometimes activated mesenchymal cells in soft tissue & surrounding bone also differentiate into chondroblasts -? Fibrocartilage and hyaline cartilage
   - Maximal girth at end of week 2-3
   - Endochondral ossification of cartilage deposit along fracture line
   - Bony callus formation
   - Mineralises to allow weight bearing

3. **Early callus formation:** excess fibrous tissue, cartilage, bone
   - Concave portion of # has greatest volume of misaligned fracture
   - During physical activity, unstressed parts reabsorb
   - Medullary cavity also restored

Complications
- Delayed union
- Non-union – cystic degeneration centrally & deposition of synovial like cells to form a false joint (pseudoarthrosis)
- Infection

Abnormalities of Bone Growth & Remodelling

Osteopetrosis
- ↓ Osteoclast activity | Net result: ↑ mass with ↓ strength

Osteoporosis
- Net result: ↓ bone mass & porous
- Normally ↓ bone mass with each resorption/formation cycle – accelerated in osteoporosis
- Cause is multifactorial
  - ↓ oestrogen activity → ↑ osteoclast activity (esp large SA eg vert body)
  - Genetics
  - ↓ physical activity
  - ↓ replicative activity (0.7% per year)
- 30-40% loss before radiologically detectable

Pagets Disease
- Focal ↑ in bone mass which is disordered and structurally poor

3 stages of disease
1. Ostolytic resorption by large clasts (nuclei up to 100 – normally appro x6)_
2. Mixed clast & blast action
   - Disordered woven bone
   - Disordered lamellar bone → mosaic pattern (pathognomic)
3. Burn out
   - Bone sclerosis = Thickened trabeculae & cortices & soft porous bone with little stability

Abnormal Mineral Homeostasis
Rickets & Osateomalacia
- Defective matrix mineralisation
- Usually due to **Vit d deficiency**

Hyperparathyroidism
- High PTH → +++osteoclast activity
- Cortical > cancellous

Osteonecrosis

Causes	
Common	Uncommon
• **Fracture** • **Idiopathic** • **Corticostreroids**	• Radiation • Vasculitis • Sickle cell • Infection • Anaemia • Air embolus (the bends) • CT disorders • Chronic pancreatitis

Morphology
- Medullary only (cortical has collaterals)
- Cancellous and marrow most common
- Cartilage viable from synovial fluid
- Necrotic bone: empty lacunae, ruptured adipocytes +/- saponification
- Creeping substitution from margins
- Can lead to OA

Osteomyelitis

Pyogenic OM
- Via blood (most common in kids), neighbour or direct (more common in adults)
- Staph aeurus 80-90% of cases
  - Receptors for bone matrix components (eg type I collagen)
- E coli, klebsiella, pseudomonas found in IVDU or GUT infection
- Neonatal: h influenza and group B strep
- Sickle cell: salmonella
- 50% no organisms

Location
- Influenced by osseous vascular circulation (varies with age)
- Neonate: metaphyseal vessels penetrate growth plate ∴ met & epiphyses
- Children: metaphysis
- Adult: metaphyseal vessels reunite with epiphyseal vessels after growth plate closure ∴ epiphyses & subchondral regions

Morphology
- Inflammation
- Necrosis within 48hrs
- Spread down shaft of bones and periosteum
- Children: loose periosteum ∴ spreads down bone in this layer
  - Splaying of periosteum inhibits blood supply
  - Both = necrosis
  - Periosteal rupture → sinus
- Sequestrum = dead bone
- Septic arthritis more common in neonates
- 1 week later: New bone deposition around dead bone = **involucrum**

Types of OM
- **Brodie Abscess:** small interosseous abscess mostly confined to cortex and walled off by reactive bone
- **Sclerosing om of Garre:** jaw, extensive new bone formation obscuring most of underlying osseous structure

Clinical Course
- Lytic focus on x-ray
- Complications: #, amyloidosis, endocarditis, sepsis, SCC in sinus tract, sarcoma (rare)

TB OM
- 1-3% of pulmonary TB
- Solitary
- Spine (40% Potts disease) > knees & hips
- More destructive

Arthritis

Osteoarthritis

- Progressive erosion of articular cartilage
- Mostly intrinsic with very small inflammatory component
- 95% idiopathic most common – old age, oligoarticular
- 5% secondary - in young with predisposition (jt injury, deformity, systemic disease)
- Males in hips and women in hands more common

Pathogenesis
- Net impact of multiple genes
- Environmental factors: age, biomechanical stress (obesity, muscle strength, jt stability…)

Phases of injury
- Chondrocyte injury: age and environmental factors
- Early OA: chondrocyte proliferation → remodelling & inflammation
- Late OA: chronic inflammation → chondrocyte drop off

Clinical
- Worse in morning, with use
- Crepitus present
- Osteophytes → root compression
- Hips, knees, C & L spine, PIPJ, DIPJ, 1st CMJ, 1st TMJ (tarsometatarsal)
- Heberden nodes: osteophytes @ DIPJ common in women

Rheumatoid Arthritis

- Systemic inflammatory disorder with principle nonsuppartive proliferative & inflammatory synovitis → cartilage destruction & ankylosis
- Women x3 men

Morphology

Joints
- ↑ vascularity
- Inflammatory soup of CD4+, B cells, plasma cells, dendritic & macs
- Fibrin covering synovium and floating in jt space (as rice bodies)
- Neutrophils in synovial fluid
- Osteoclast activity
- Pannus formation: synovium & synovial stroma with inflammatory cells, granulation tissue, synovial fibroblast
- Pannus bridges apposing bone (with cartilage destruction between) → ankylosis

Skin
- Nodules: 25%
- Pressure areas eg ulnar forearm, elbows, occiput
- Firm, non-tender from subcut tissue
- Central Fibrinoid necrosis with epitheliod histiocyte border and lymphocytes and plasma cells

Blood Vessels
- Vasculitis syndromes
- Medium/small arteries not including kidney (versus PA nodosa)

Clinical
- Symmetrical
- Small jt before large
- Swollen, warm, painful
- Stiff on arising
- Worst damage in year 4 or 5
- Radiographic hallmarks: jt effusion, juxta-articular osteopenia with erosions and narrowing
- Characteristic deformities: radial deviation at wrist, ulnar deviation at fingers, swan neck deformity and boutonniere

Dx of disease
- Morning stiffness
- Arthritis >3 jts
- Arthritis of hands
- Symmetric arthritis
- Nodules
- Serum RF
- X-ray changes

Juvenile Idiopathic Arthritis

- Before 16yo | Min 6 weeks

Subsets
- Systemic arthritis
- Oligoarthritis
- RF –ve polyarthritis
- Rheumatoid factor +ve polyarthritis – teenage girls
- Enthesitis – amles < 6yo
- Psoriatic arthritis
- Undifferentiated arthritis

Differs from adult onset
- Oligoarthritis more common
- Systemic disease more common
- Large joints first
- Nodules & RF absent usually
- ANA +ve common

Seronegative Spondyloarthropathies

- Genetic predisposition with environmental triggers
- Immune mediated
- Extra articular involvement with eyes, skin, CVS

Ankylosing Spondylitis
- Chronic synovitis
- Esp sacroiliac and apophyseal joints
- Squared and fused vert bodies common
- 2nd or 3rd decade of life become sx
- Men x2
- Extra articular: uveitis, aortitis, amyloidosis
- 90% genetic

Reiter Syndrome (reactive arhtirtis)
- Arthritis + nongonococcal urethritis or cervicitis and conjunctivitis
- Men 20-30
- HIV
- Variable outcomes

Enteritis associated arthritis
- Yersinia, salmonella, shigella, Campylobacter
- Out lipopolysaccharide layer stimulates immune response

Infectious Arthritis

Bacterial
- Haematogenous usually
- Gonococcus, staph, strep, h influenza, GNB
- H influenza < 2yo
- S aeurus > 2yo
- Gonococcus in adolescents
- Sickle cell: salmonella

TB
- Mono-articular
- Usually from OM or haem spread
- Insidious
- Granuloma with central Caseous necrosis forms

Lyme
- Borrelia burgdorferi
- 60-80% have arthritis (esp late disease)
- Remitting and migratory pattern
- Large joints: knees > shoulders > elbows > ankles
- Pannus formation → permanent deformity

Crystal induced Arthritis

- Monosodium urate = gout
- Calcium pyrophosphate dehydrate
- Hydroxyapatite

Gout
- Initially monoarhtritic
- Leads to chronic gout with tophi (large aggregates of crystals)
- Urate nephropathy also known complication
- Hyperuricemia doesn't necessarily produce gout

Primary gout (90%)
- Overproduction of uric acid (diet, enzyme defect)

Secondary Gout (10%)
- Overproduction of uric acid with ↑ excretion or ↓ excretion with normal production

Risk factors for gout include
- Age/duration of hyperuricemia
- Genetic
- Alcohol
- Obesity
- Drugs (thiazides)
- Lead toxicity
- Temperature (less soluble in cold)
- Small trauma*

*to release monosodium urate crystals into synovial fluid

Pathogenesis
- Hyperuricemia
  → MSU crystals
  → Complement and kinin activation
  → Phagocytosis of MSU crystals
  → Release during injury or

Clinical Course

Asymptomatic hyperuricemia

Acute gouty arthritis
- Initially monoarticular
- 1st MTP > insteps > ankles > heels > knees > wrist > fingers > elbows

Intercritical gout
- Asymptomatic or polyarticular

Chronic tophacous gout
- 12 years to develop

Pseudo-Gout (Calcium pyrophosphate crystal deposition)
- CPPD over 50
- M = F
- Sporadic vs hereditary vs secondary
- Hereditary: early development, associated with severe osteoarthritis
- Secondary: previous jt damage, ↑ PTH, hemochromatosis, hypo Mg, hypothyroidism, ochronosis, diabetes

Tumours

%	Histo	Benign	Malignant
40	**Hematopoietic**		Myeloma Malignant lymphoma
22	Chondrogenic	Osteochondroma Chondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma[2] Dedifferentiated chondrosarcoma Mesenchymal chondrosarcoma
19	Osteogenic	Osteoid osteoma Osteoblastoma	**Osteosarcoma[1]**
	Fibrogenic	Fibroma Non-ossifying fibroma Fibrous histiocytoma Desmoplastic fibroma	Fibrosarcoma
10	Unknown	Giant cell[3] Unicameral cyst Aneurysmal bone cyst	
	Neuroectodermal		Ewing sarcoma
	Notochordal	Benign notochordal cell	Chordoma

[1] Most common malignant tumour of bone
[2] 2nd most common, 85% idiopathic, remainder from osteochondroma or chondroma
[3] locally aggressive

Metastatic Disease

- 75% from Prostate, Breast, Kidney, Lung
- Children: neurobalstoma, wilms, osteosarcoma, ewings, rhabdomyosarcoma
- Mostly multifocal but kidney & thyroid can produce solitary mets

CNS

Cerebral Oedema & Raised ICP

Cerebral Oedema

Vasogenic	Cytotoxic
• BBB disruption & ↑ vasc permeability • Lack of lymphatics = slow response • Localised or generalised	• Neuronal, glial or endothelial injury • Incl generalised hypoxia or ischemia or metabolic damage

Interstitial Oedema
- Around lateral ventricles → ↓ CSF

Hydrocephalus
- Excess CSF from overproduction or lack of drainage (more common)
- Non communicating hydrocephalus occurs when part of the vent system enlarged
- Hydrocephalus ex vacuo; ↑ CSF volume to fill gap from loss of brain parenchyma

Raised ICP & Herniation
- Cranial vault is rigid: skull, dural folds (falx & tentorium)

Subfalcine Herniation
- Asymmetrical hemisphere expansion
- Cingulate gyrus herniates under falx cerebri
- ACA may be compressed

Transtentorial Herniation
- Medial temporal lobe herniates through the medial (free) part of the tent
- CNIII most often effected → "blown pupil"
- PCA may be compressed
- Kernohan's notch: cerebral peduncle that can herniate to cause hemiparesis
- Duret haemorrhage: haemorrhagic lesions in midbrain that accompany herniation
  Due to shearing of veins penetrating stem

Tonsillar Herniation
- Cerebellar tonsils through foramen magnum
- Compresses cardiac & resp centres

Trauma

Skull Fracture
- Displaced skull # defined as depression > thickness of bone
- BOS # more common with occiput or side of head impact
- Diastatic # cross suture lines

Parenchymal
Concussion
- Altered consciousness with recovery (amnesia surrounding the event often exists)
- Neuropsychiatric syndromes are well recognised

Direct Parenchymal Injury
- Contusion (indirect) vs Laceration (direct)
- Gyri crest are most prone | Common: frontal and temporal
- Coup: contusion direct to point of contact vs contrecoup (diametrically opposite)

Time	Morphology
Early	oedema & haemorrhage (peri capillary)
Hours	blood extends in involved area, into white matter & across cerebral cortex
Day	evidence of neuronal injury (histologically)
Old △	depressed, retracted, yellow-brown patches ie Plaque Jaune

Diffuse Axonal Injury
- Axonal swelling (usually asymmetrical) in deep white matter – seen within hours
- Angular acceleration without impact can cause
- Most vulnerable part of axon is node of Ranvier

Traumatic Vascular Injury
Epidural Haematoma
- Dura normally fused with periosteum
- Dural arteries are vulnerable to trauma
- Blood extravasation → dural separation
- Concave appearance from arterial pressure

Subdural Haematoma
- Bridging veins exist between dura and leptomeninges
- Venous sinuses fixed ↔ brain mobile (even more with old age)
- Self-limiting

Sequence of healing
- 1 week: lysis of clot
- 2 weeks: fibroblast proliferation from dura to haematoma
- 1-3 months: hyalinised CT

ie rpt bleeding greatest in first few months

Sequelae
- PT hydrocephalus (mostly from subarachnoid bleeding
- PT dementia (including Alzheimer's
- PT epilepsy
- Menigiomas
- Infection
- Psychiatric disorders

Cerebrovascular Disease

Impaired Supply: Hypoxia, Ischaemia, Infarction
- Brain requirements: 15% of CO / 20% of O_2 consumption
- Causes include low PaO_2, Low carrying capacity, low flow or low offloading

Factors relating to severity
- Collateral circulation
- Duration
- Magnitude/rapidity of flow reduction

- Inappropriate release of glutamate, high Ca → cascade
- Penumbra = at risk tissue

Global Ischaemia: Hypotension, hypoperfusion, low flow states
- Cell sensitivity: neurons > glial cells
- Watershed infarct = distal parts of arterial supply eg between ACA & MCA supply

Time		Changes
Early	12-24	red neurons, micro vacuolization, eosinophilia, nuclear pyknosis
Subacute	24-2 weeks	necrosis, macs, angiogenesis, reactive gliosis
Repair	> 2 weeks	removal of necrotic tissue, gliosis

Infarction
- Collateral flow: circle of Willis or carotid-ophthalmic pathway
- No collateral flow for thalamus, basal ganglia, deep white matter

Thrombosis
- Carotid bifurcation, origin of MCA, basilar artery ends
- Usually associated with HTN and DM

Embolism
- Cardiac mural thrombi (MI, AF, valvular disease)
- Atheromatous plaques in carotids
- Less common: paradoxical, surgery, other materials
- Most common: MCA (no hemisphere preference)
- Shower embolisation can occur with marrow embolisation post trauma

Vasculitis
- Infection (syphilis or TB – now CMV or aspergilliosis in immunocomp)

Other
- Dissecting aneurysm
- Drug abuse
- Hypercoagulable state

Types of Infarcts
Haemorrhagic (red)
- Petechial haemorrhage
- Embolic events → reperfusion of damaged vessels and tissue → haemorrhage

Non-haemorrhagic
- Thrombosis

Time	Gross	Histological
< 6 hrs	no gross change	
12 hrs		red neurons & oedema
48hrs	pale	↓ neutrophil numbers, replaced by phagocytes
2-10 days	gelatinous/friable	
2-3 weeks	liquefaction	Phagocytes main cell type → Reactive astrocytes
Months		astrocyte response ↓

Hypertensive Cerebrovascular Disease
- Lacunar infarct, slit haemorrhage, encephalopathy

Lacunar Infarct
- Arteriolar stenosis from HTN
- Lenticular nucleus > thalamus > int capsule > deep white matter > caudate nucleus > pons

Slit Haemorrhage
- Rupture of small calibre penetrating vessels

Encephalopathy
- Seen in malignant HTN
- Oedema +/- herniation
- Vascular dementia = multiple small infarcts

Intracranial Haemorrhage
Intracerebral Haemorrhage
- Rupture of small intraparenchymal vessels
- HTN & cerebral amyloid angiopathy are both most common
- HTN = Accelerated atherosclerosis, hyaline arteriosclerosis → micro aneurysms → rupture
- Most commonly originates from putamen (60%)

Subarachnoid Haemorrhage and Ruptured Saccular Aneurysms
- Aneurysms can be Saccular (berry), atherosclerotic, Mycotic, traumatic, dissecting
- Only Saccular aneurysms give rise to SAH

Circulation	Branch	
Anterior 90%	ACom	40%
	PCom	20%
	MCA branches	34%
	Basilar branches	4%

> 1cm = 50% risk of rupture

Vascular Malformations

- AVM- presents as seizures, infarct, MCA (post branches)
- Cavernous – very genetic
- Capillary telenectasia
- Venous angiomas

Infection

Acute Meningitis

- Mostly bacterial, sometimes chemical
- Pyogenic vs aseptic vs chronic

Acute Pyogenic

- Neonates: e coli & GBS | Adult: strep pneumonia, listeria | Adolescent: Neisseria
- Strep pneumonia most common overall

Waterhouse-Friderichsen syndrome: septic meningitis with adrenal infarct and cutaneous Petechiae (seen in meningococcal and pneumococcal)

Morphology

- Distribution depends on pathogen
- H influenza = basal
- Pneumococcal = cerebral convexities near sagittal sinus
- Chronic adhesive arachnoiditis: seen in pneumococcal when capsular proteins produce a gelatinous exudate → arachnoid fibrosis

Acute Viral Meningitis

- CSF: lymphocytic pleocytosis, moderate protein, normal glc
- Rarely viral pathogen found (therefore called aseptic meningitis sometimes)

Acute Focal Suppartive Infections

Brain Abscess

- Direct, local extension (eg sinusitis/mastoiditis) or haematogenous (heart, lung, bone, teeth)
- Predisposing conditions: endocarditis, CHD with L→R shunt, chronic pulmonary sepsis, immunosuppression

Subdural Empyema

- From infection of skull bones or sinuses
- Can cause local thrombophlebitis of bridging veins → infarct

Extradural Abscess

- Associated with OM from adjacent structures

Chronic Bacterial Meningoencephalitis

TB

- Lymphocytes, plasma cells and macs
- Gelatinous or Fibrinous exudate
- Base of the brain most effected
- Tuberculoma sometimes present (Caseous core with granuloma surrounding)
- Arachnoid fibrosis → hydrocephalus

Neurosyphilis

- During tertiary stage of syphilis | 10% of people

Pattern	Morphology
Meningovascular	• Base of brain and sometimes cerebral convexities and leptomeninges • Heubner arteritis (obliterative endarteritis) sometime occurs • Cerebral gummas (plasma cell rich lesions) start in meninges
Paretic	• Treponema palladium • Starts with change in mood (eg delusions of grandeur) → insanity • Frontal lobe damage incl ↓ neuron #, proliferation of microglia, Gliosis, Fe deposits (from small bleeding)
Tabes dorsalis	• Spirochetes → sensory nerves in dorsal root → locomotor ataxia, loss of pain • Charcot joint precipitates

Viral Meningoencephalitis

Arthropod Borne

- Arbovirus
- Generalised neurological deficits
- CSF slight opening pressure, Neutrophilic pleocytosis initially → lymphocytosis, normal glc, ↑ protein

HSV Type 1

- Children & young adults
- 10% have history of prior herpes infection
- Starts as non-specific Sx for 4-6 weeks
- Targets inferior and medial temporal lobes and orbital gyri of frontal lobes

HSV Type 2

- Meningitis in adults, encephalitis in newborns during delivery

VZV

- Cutaneous infection → latent in sensory neurons of dorsal root (or trigeminal ganglia)
- Reactivated as shingles
- Rare to have CNS involvement

CMV

- Foetal and immunosuppressed
- Foetal; periventricular necrosis
- Immunosuppressed; subacute encephalitis in periventricular subependymal region
  → Necrotizing ventriculoencephalitis & choroid plexitis
  Or → lower cord & roots

Poliomyelitis

- Neurophagia of the anterior horn motor neurons

Rabies

- Severe inflammation esp brain stem
- Negri bodies are pathognomic (cytoplasmic round eosinophilic inclusions in pyramids of neurons of hippocampus or purkinje of cerebellum)
- Incubation 1-3 months
- Malaise, headache, fever and local paraesthesia around wound is diagnostic
- CNS excitability → convulsions/flaccid paralysis/fluctuating

HIV

- HIV aseptic meningitis occurs 1-2 weeks after seroconversion in 10% patients
- Microglia main targets

Fungal

- Immunocompromised
- Chronic meningitis vs vasculitis (aspergilliosis) vs parenchymal invasion (candida & Cryptococcus)

Demyelinating Disease

MS

- Autoimmune
- Distinct episodes separated in time, attributable to white matter separated in space
- Women x2
- Peak childhood to 50s
- Initiated by infection (usually unknown)
- CD4 response causes destruction

Morphology: plaques (grey areas of discolouration)

- Active plaques represent myelin breakdown
- Inactive plaques represent gliosis

Clinical features

- Unilateral vision impairment (optic neuritis)
- Brainstem: CN, ataxia, nystagmus, internuclear opthalmoplegia
- Spinal cord lesions: motor or sensory impairment, bladder dysfunction

Neuromyelitis Optica

- Bilateral optic neuritis & spinal cord demyelination
- AB against aquaporin present

Acute Disseminated Encephalomyelitis (ACEM) & Acute Necrotizing Haemorrhagic encephalomyelitis (ANHE)

ADEM post viral (rarely immunisation)

- 20% fatal
- Periventricular demyelination with axon preservation

ANHE

- Following URTI
- Fulminant

Toxic & Acquired Metabolic Diseases

Vitamin Deficiencies

Thiamine (B1)

- Wernicke encephalopathy → Korsakoff syndrome
- Mammillary bodies and haemorrhage and necrosis common

Vit B12

- Ataxia & lower limb paraesthesia → spastic weakness → paraplegia
- Effects both asc and desc tracts through degeneration

Neurological Sequelae of Metabolic Disease

Hypoglycaemia

- Cerebral pyramids, hippocampal pyramid and purkinje cells are sensitive

Hyperglycaemia

- Dehydration from hyperosmolar state → confusion, stupor, coma
- Cerebellar oedema from aggressive rehydration

Toxic Disorders

Carbon Monoxide

- From hypoxia
- Different to other hypoxias: Globus pallidus involvement

Methanol

- Retina (ganglion degeneration)

Ethanol

- Cerebellar dysfunction: truncal ataxia, unsteady gait, nystagmus
- Bergmann gliosis can appear: ant cerebellar atrophy and purkinje cell drop out

Degenerative Diseases

- Common theme is protein accumulation (resistant to proteasome degradation)

Cerebral Cortex (dementia)

Alzheimer's

- 5-10% familial, remainder sporadic
- Neurotic plaques and neurofibrillary tangles and amyloid angiopathy present but not pathognomic

Front temporal Dementia

- Progressive deterioration of language, change in personality
- Many due to Tau inclusions
- FTD with PD linked to Tau mutation: effects Tau association with microtubules

Pick Disease

- Pick cells – large ballooned neurons
- Pick bodies - smooth agryphilic inclusions (made of helical filaments)

Supranuclear Palsy

- Loss of vertical gaze
- Truncal rigidity
- Disequilibrium
- Loss of facial expression
- Mild progressive dementia
- No Tau mutation

Corticobasal degeneration

- Extrapyramidal rigidity
- Asymmetric motor disturbance
- Similar mutation to supranuclear palsy

Vascular Dementia

- Multiple infarcts
- Large infarct
- Vasculitis

Basal Ganglia & Brainstem

Parkinsonism

- Clinical: loss of facial expression, stooped posture, slowed voluntary movt, festinating gait, rigidity, pill rolling tremor
- Due to ↓ nigrostriatial dopaminergic system
  Causes: PD, postencephaltic (eg post influenza 1918), frontotemporal dementia, dopamine antagonists

PD

- Parkinsonism + autonomic and cognitive dysfunction

Lewy Body Dementia

- 10-15% of PD patients

Huntington's disease

- Clinical: Chorea → parkinsonism
- Motor Sx before cognitive
- Atrophy of caudate nucleus & putamen
- Paternal transmission = earlier expression

Peripheral Neuropathies

Inflammatory Neuropathies

Immune mediated Neuropathies (Guillain-Barre syndrome)

- Ascending paralysis
- Demyelinating polyradiculoneuropathy
- 60-70% preceded by vaccination or viral (EBV, CMV) or bacterial (campylobacter, mycoplasma) infection
- Clinical: muscle weakness and loss of deep tendon reflexes (sensory not as bad)

Infectious Polyneuropathies

Leprosy (Hansen's disease)

- Mycobacterium leprae
- Invades Schwann cells to cause segmental demyelination and remylination

Diphtheria

- Due to exotoxin
- Causes paraesthesia and weakness from segmental demyelination

VZV

- Reactivation after dormant in dorsal root ganglia
- Thoracic and trigeminal most common

Acquired Metabolic & Toxic Neuropathies

Diabetes

- Distal symmetric sensory or sensorimotor loss
  - Axonal neuropathy with loss of small fibres (sensory > motor)
- Autonomic neuropathy
  - Postural hypotension
  - Incomplete micturition
  - Sexual dysfunction
- Focal or Multifocal asymmetric neuropathy
  - Eg unilateral ocular nerve palsy
  - 2ry to vascular insufficiency (not directly)

Metabolic/Nutritional

- Renal failure: distal sensorimotor loss
- Chronic liver disease
- Metabolic: Vit B1, 12, 6, E def

Malignancy

- Direct
- Paraneoplastic syndrome
  - More common in lung cancer (esp small cell)

Traumatic

- Lacerations, avulsions, compression, traumatic neuroma

ENDOCRINE

Pancreas

Cell	Secretion
α	glucagon
β	insulin
δ	somatostatin
PP	pancreatic polypeptide → gastric secretions

Other Cells	
D1	VIP → glycolysis and hyperglycaemia
Enterochromaffin	5HT

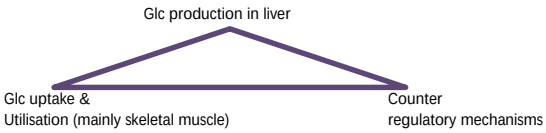
Diabetes

- Defect in insulin secretion, action or both

Diagnosis – either:
- Random Glc > 20 + signs/symptoms
- Fasting Glc > 12,6 (> 10 = impaired)
- Abnormal OGTT (> 20 after 2hrs of challenge) (14-20 = impaired)

Type	Cause	
Type 1	Immune-mediated Idiopathic	
Type 2	Obesity	
Genetic	Defect in β-cells Defect in insulin	Downs Kleinfelters Turners Prada Willi
Exocrine defect	Pancreatitis Trauma Pancractomy Neoplasia	CF Hemochromatosis Fibrocalculous pancreatopathy
Endocrine	Pheochromocytoma Cushing Hyperthyroidism	Glucagonoma Acromegaly
Infection	CMV Coxsackie B Congenital rubella	
Drugs	Phenytoin Glucocorticoids β-agonists Thyroid hormone	IF-α Nicotinic acid
Gestational		

Glucose Homeostasis



Glucose as a regulatory mechanism

Circulating glc enters β cells via GLUT-2 (non-insulin dependent)
→ Glc metabolism
→ ATP
→ Inhibits outwards K channel (also has a sulfonylurea receptor)
→ Polarises membrane
→ Ca influx
→ Insulin release

Site of Insulin Action	Action
Skeletal Muscle	↑ glc uptake, glycogen & protein synth
Adipose	↑ glc uptake, lipogenesis ↓ lipolysis
Liver	↓ GNG, ↑ glycogen synth, ↑ lipogenesis

Pathogenesis of Type 1 DM
- Autoimmune islet cell destruction
- Genetic basis with environmental activation eg infection (usually viral)
- Ketoacidosis occurs after > 90% β cells destroyed

Pathogenesis of Type 2 DM
- Insulin resistance & Inadequate insulin release (first)
- More obvious genetic component (35-60%)

Pathogenesis of Complications

Metabolic pathways leading to complications
- Advanced glycation end products
  - Accelerated in hyperglycaemia → binds RAGE receptors
  - AGE-RAGE complex → ROS, Cytokine & GF, procoagulants, smuscle proliferation
- Activation of protein kinase c
- Intracellular hyperglycaemia and disturbance
  - More important in non-insulin requiring cells eg neurons
  - Intracellular glc accumulation → ↑ ROS

Morphology of late complications

Pancreas
- More common in type 1
- ↓ islet size and number (type 1 > 2) (opposite in neonates of diabetic mothers)
- Insulinitis
- ↓ islet sell mass (type 2)
- Amyloid (type 2)

Macrovascular
- Endothelial dysfunction → atherosclerosis
- MI
- Gangrene
- Stroke

Microvascular
- Thickening of BM
- Retinopathy
- Neuropathy
- Nephropathy
  - Glomerular lesions
    - BM thickening
    - Diffuse mesengial sclerosis
    - Nodular glomerulosclerosis
  - Renal vascular lesions
  - Pyelonephritis

Clinical Features
- Polydipsia, polyuria, polyphagia, ketoacidosis

Ketoacidosis
- ↑ glc = osmotic diuresis = dehydrated
- Adipose breakdown for energy → FFA in plasma
- FFA → liver → ketones (acetoacetic acid or β-hydroxybuteric acid)

- Type 2 have ketosis less often because of higher portal insulin concentration
  - They have hyperosmolar nonketotic coma from hyperglycaemic diuresis

Pituitary
- Anterior: GH, FSH, LH, ACTH, PRL, TSH
- Posterior: oxytocin & ADH (from nucleus in hypothalamus)

Hyperpituitarism

Acidophilic (rest basophilic)

Cell	Hormone	Syndrome
Somatotroph	GH	Gigantism or Acromegaly
Lactotroph	Prolactin	Galactorrhea, amenorrhea, sexual dysfcn, infertility
Mammosomatroph	Prolactin, GH	Combined
Corticotroph	ACTH	Cushing's, Nelson
Thyrotroph	TSH	Hyperthyroidism
Gonadotroph	FSH, LH	Hypogonadism, mass effect, hypootiutarism

NB all tumours are adenomas

Hypopituitarism
- > 75% loss is symptomatic
- IF ant/post sx then hypothalamic origin of pathology
- Tumours
- Brain injury
- Surgery
- Apoplexy
- Sheehan syndrome
- Inflammation/infection

Posterior Pituitary

Diabetes Insipidus
- ADH deficiency (vs nephrogenic – ADH resistance)
- Due to head trauma, tumours, inflammatory states, surgery, idiopathic

SIADH
- Excess ADH
- Due to malignant neoplasms (eg small cell of lung), drugs, infection, trauma

THYROID

Hyperthyroidism

Primary	Secondary
Graves' disease	Distant Adenoma
Multinodular Goitre	
Adenoma	
Neonatal (maternal graves)	

Thyrotoxicosis without hyperthyroidism

De Quervain (painful)
- Thyroiditis from viral trigger, seasonal
- Self-limiting (2-6 weeks)

Subacute lymphocytic (painless)
- Mimics Graves: painless goitre, exophthalmos
- 33% → graves and remainder self-limits

Struma Ovarii (ovarian teratoma)
Exogenous

Graves' disease
- Triad of Hyperthyroidism, infiltrative opthalmopathy, dermopathy (pretibial myxoedema)
- Primarily autoantibodies that activate TSH receptors
- At risk of other autoimmune disease
- High T3 and T4 but low TSH
- Enlarged thyroid

Clinical Manifestations
- Skin: soft, warm, flushed, ↑ sweat
- Heat intolerance
- Weight loss
- Cardiac: ↑ CO, AF, CM, CHF
- Tremor
- Proximal weakness and ↓ muscle mass
- Eyes: exophthalmos, proptosis, lid lag
- Bones: ↑ resorption = ↑ porosity

Thyroid storm
- Abrupt onset of severe hyperthyroidism
- Seen in graves due to catecholamine rise eg surgery or stress
- High chance cardiac arrhythmia

Labs
- TSH – best
- ↑ Free T4 – confirms dx
- T3 hyperthyroidism = ↓ T4

Hypothyroidism

Primary	Secondary
Developmental	Pituitary failure
TH resistance syndrome	Hypothalamic failure
Hashimoto	
Iodine Def*	
Drugs eg lithium	
Post ablative (surgery, XRT)	

Cretinism
- Impaired skeletal or cns → retardation
- Short stature, coarse facial features, protruding tongue
- Umbilical hernia

Myxoedema
- Early: fatigue, apathy, mental sluggishness
- Slow speech & intellectual function
- Listless
- Cold intolerant
- Overweight
- Constipation & decreased sweating
- Cool peripheries
- ↑ Chol and LDL
- Non pitting oedema
- Coarse facial features
- Enlarged tongue
- Deep voice

Goitre
- ↓ thyroid hormone synthesis → ↑ TSH → gland hypetrophy
- Hyperplastic phase: diffuse homogenous enlargement
- Colloid involution phase: occurs if iodine is re established
- Simple = single episode
- Multinodular = recurrent episodes → Mass effect eg superior vena cava syndrome, dysphagia, airway compromise, toxic (uncommon)

Hashimotos
- Women > men
- Autoimmune
- Clinically: painless enlargement, mild hypothyroidism or transient hyperthyroidism (hashitoxicosis = high T3 and T4 but low TSH)
- High risk of developing other autoimmune diseases incl B cell lymphoma

Neoplasms

Risk factors for nodule malignancy
- Single nodule
- Young
- Male
- XRT
- Hot (radioactive)

Carcinomas
- Papillary (85%) > follicular (5 – 15%) > medullary (5%) > anaplastic (< 5%)

Carcinoma	%	Features
Papillary	85	• Asymptomatic • Good prognosis (even with nodal mets)
Follicular	5-15	• Ass with iodine def • Women > men • Haematogenous spread > lymphatic • Painless
Medullary	5	• Neuroendocrine • Secrete calcitonin[1]
Anaplastic	< 5	• Aggressive • Associated with previous carcinoma

[1]But hypercalcaemia not a feature

Parathyroid
- Contain PTH activated by low plasma Ca

PTH
- ↑ renal tubule Ca absorption
- ↑ Vit D → active form in kidneys
- ↑ urinary PO4 (ie ↓ plasma PO4)
- ↑ Gut Ca absorption

Hyperparathyroidism

Primary
- Adenoma 85-90% > hyperplasia (5-10%) > carcinoma

Secondary
- Causes chronic hypocalcaemia
- **Renal failure** most common | Less common: ↓ Ca intake, Vit d def

Clinical Features of both
- Bone disease – osteoporosis l ostitis
- Nephrolithiasis
- GIT disturbance
- CNS alterations eg depression, lethargy, seizures
- NM abnormalities
- Cardiac: Aortic or mitral valve calcification

Hypoparathyroidism
- Surgical
- Autoimmune

Clinical
- Tetany
- Mental change eg anxiety, depression, confusion
- CNS: Calcification of basal ganglia, Parkinson's like movt
- Eyes: lens calcification, cataracts
- CVS: QT prolongation
- Dental: hypoplasia, failure of eruption, defective enamel & root formation

ADRENAL CORTEX

Steroid	Main	Syndrome
Glucocorticoid	Cortisol	Cushing's
Mineralocorticoid	Aldosterone	Hyperaldosteronism
Sex hormones	Oestrogen & Androgen	Androgenital

Cushing's

- Exogenous (idiopathic) vs endogenous (ACTH-dependant or independent)

ACTH Dependant		
Cause	%	M:F
Cushing's Disease	70	4:1
Ectopic Corticotrophin syndrome[2]	10%	1:1

Independent		
Cause	%	M:F
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1

[1]Pituatry adenoma
[2]ACTH secreting pulmonary small cell carcinoma, bronchial carcinoid)

Clinical Features of Cushing's

- Facial plethora
- Round face
- Decreased libido
- Thin skin
- ↓ linear growth
- Menstrual irregularity
- HTN
- Hirsutism
- Depression
- Easy bruising
- Glc intolerance
- Weakness
- Osteopenia
- Nephrolithiasis

Hyperaldosteronism

- Idiopathic (most common)
- Adenoma

Clinical

- HTN
- ↑ stroke & MI through endothelial damage
- Hypokalaemia sometimes

ADRENAL MEDULLA

- Secrete catecholamine's from chromaffin cells

Pheochromocytoma

Rule of 10's

- 10% extra adrenal
- 10% are bilateral
- 10% are malignant
- 10% are without HTN
- 10% → 25% now have germ line mutations

Clinical

- HTN (paroxysmal in 66%)
- Cardiomyopathy
- arrhythmias

CHILDHOOD

SIDS

Risk factors

Parental

- < 20yo
- Maternal smoker
- Drug abuse
- Short intergenstational age
- Late/no prenatal care
- Low socioeconomic

Infant

- Brainstem abnormalities
- Premature/low birth weight
- Male
- Multiple
- Family hx
- Resp infection

Environment

- Prone/side sleeping
- Soft surface
- Hyperthermia
- Co-sleeping first 3 months

Post Mortem

- Infection: viral myocarditis, bronchopneumonia
- Congenital abnormality: AS, LCA from PA
- Traumatic
- Genetic: long QT