**CARDIOVASCULAR PATHOLOGY**

### Pathophysiology of Ischaemic Injury

Lower ATP production as aerobic respiration ceases leads to cessation of myocyte contraction. Cell membrane function is maintained by anaerobic glycolysis until irreversible ischaemic injury occurs.

1. Subendocardial tissue is most susceptible to ischaemia, leading to a transmural (wavefront) progression of injury across the ventricular wall:
   a. Infarction occurs after 1hr at the endocardium, after 12hrs at the epicardium
   b. This provides a therapeutic opportunity:
      i. Thrombolytic therapy – streptokinase, tissue plasminogen activator
      ii. Surgical by-pass – coronary artery bypass graft

2. **Myocardial stunning** – sub-lethal ischaemic injury (<15min) doesn’t affect long-term viability, but recovery of normal myocyte function can take up to 24 hrs

3. **Ischaemic preconditioning** – several brief intervals of ischaemia increases tolerance of the myocardium to a subsequent longer episode by reducing energy demand:
   a. Adenosine metabolism may be altered by activation of receptors and protein kinase C
   b. Long-term effects may be due to the expression of stress or heat-shock proteins that associate with ‘chaperone’ proteins to preserve 3° structure of myocyte components

Despite the effects of vasodilatation, hyperaemia and capillary recruitment, reperfusion is associated with diminished blood flow as a consequence of microvascular injury

1. **No-reflow phenomenon** – it is virtually impossible to reperfuse an infarct when irreversible ischaemic injury develops. This may be to prevent haemorrhage.

2. **Microvascular stunning** (capillary no-reflow) is the reduction in the proportion of capillaries able to distribute restored blood supply after brief ischaemic injury.
   a. Caused by ischaemia to some extent, but mainly by free radical generation

The restoration of blood flow (necessary to salvage reversibly injured tissue) may cause further reperfusion injury by the generation of oxygen-derived free radicals.

1. Normally free radicals are eliminated enzymatically (superoxide dismutase, catalase) or by free radical scavengers (antioxidants e.g. vitamin E, glutathione)

2. The hydroxyl radical is extremely reactive and can initiate a chain reaction of lipid peroxidation by forming lipid free radicals, then lipid peroxides
   a. Resulting loss of unsaturated lipids → irreversible membrane failure

3. Prior to reperfusion:
   a. Natural antioxidants are utilised
   b. Xanthine dehydrogenase is converted to xanthine oxidase by proteases
   c. pH falls due to the accumulation of H⁺ ions with anaerobic glycolysis

4. Reperfusion adds O₂ and rapidly generates reactive oxygen species leading to:
   a. Massive cell swelling
   b. Severe hypercontraction (contraction band necrosis → margins of infarct)
   c. Bleb formation

5. It is not known whether reperfusion injury produces irreversible injury in cells not already in that state. If so, clinical reoxygenation should be preceded by anoxic perfusion to remove accumulated substrates, or by the administration of free radical scavengers to avoid injury.

### Ischaemic Heart Disease

Ischaemic heart disease is the most common type of cardiac disease and the leading cause of death in the West (♀ 23%, ♂ 30%). It is due primarily to coronary atherosclerosis and its complications, and is more common in the left heart due to greater workload.

Low flow in coronary arteries due to atherosclerosis causes angina pectoris when there is increased myocardial demand, and is associated with >50% stenosis of a main vessel.

1. Eccentric plaque – vasodilator drugs may relax the remainder of the vessel
2. Circumferential plaque – angioplasty (PCTA) or CABG is required
3. Myocardium has the capacity to develop collateral vessels over time, but as the atheroma develops individual myocytes die leading to diffuse fibrosis
Acute ischaemic heart disease usually arises from complications of atherosclerosis:
1. 25% – ulceration of the plaque → alteration of flow, collagen exposure
2. 75% – plaque fissures → bleeding into the lesion → balloons into the lumen
3. It is important to identify the lesions likely to complicate and treat appropriately
4. Unstable (crescendo) angina – sudden onset with increasing frequency and severity, with risk of death from regional myocardial infarction or ventricular arrhythmia

Myocardial infarction:
1. 90% are regional due to coronary thrombosis (→ transmural ischaemia/infarction)
   a. Lysis (spontaneous or by thrombolytic therapy) → subepicardial sparing
2. 10% are circumferential subendocardial infarction due to generalised hypoperfusion
3. Response to infarction – necrosis leads to an inflammatory response
   a. 12 hrs – neutrophil infiltration, loss of oxidative enzymes
   b. 12-24 hrs – infarct becomes pale
   c. 24-72 hrs – infarct softens
   d. 3-10 days – hyperaemic border (granulation tissue)
   e. Necrotic tissue replaced by collagenous scar tissue

Most cases of sudden cardiac death are due to infarction or arrhythmias (usually a consequence of ventricular fibrillation) leading to pump failure. Patients with previous symptoms can develop arrhythmias in muscle adjacent to a scar, or from regions of new ischaemic myocardium.

Subsequent complications of myocardial infarction:
1. Cardiac arrhythmia
2. Left ventricular failure with infarction and cardiac dilatation (paradoxic wall movement)
3. Myocardial rupture following autolytic softening
4. Papillary muscle dysfunction → mitral incompetence
5. Mural thrombosis from inflammation and altered flow
6. Acute pericarditis due to inflammation
7. Chronic left heart failure
8. Aneurysm due to scar dilatation – laminated thrombosis → embolism
9. Recurrent MI

Valvular Heart Disease

The incidence of rheumatic fever is high in New Zealand (particularly in Maori). It is an immune disorder that follows a primary streptococcal infection, typically tonsillitis or pharyngitis.
1. Some strains of group A β-haemolytic streptococci induce the production of antibodies that can cross-react with 2° antigens in connective tissue (including heart)
2. RF presents as a flu-like illness with fever, malaise, muscle and joint pain
   a. Aschoff’s nodules – inflammatory lesions composed of degenerate collagen (fibrinoid necrosis) and activated macrophages, lymphocytes and fibroblasts
   b. Similar lesions are cause manifestations in brain (Sydenham’s chorea), skin (subcutaneous necrotic rashes, erythema) and arteries (fibrinoid arteritis)
2. Heart complications due to the formation of Aschoff nodules include:
   a. Rheumatic myocarditis – usually mild
   b. Rheumatic pericarditis → pericardial effusion, fibrinous pericarditis, adhesions
   c. Rheumatic endocarditis → aortic and mitral valves more commonly affected due to the higher pressures in the left side of the heart

Rheumatic heart disease is a common sequel of RF. Aschoff nodules produce ulceration of heart valves, particularly along lines of closure. Platelets and fibrin accumulate, forming vegetations of thrombus. Chronic/repeated damage leads to progressive distortion, eventually leading to stenosis or incompetence. Antibiotics can be used prophylactically in patients susceptible to rheumatic fever.

Endocarditis
1. Non-infective endocarditis – structural abnormalities (or replacement) of the heart valves can be associated with abnormal blood flow and the formation of vegetations
2. Infective endocarditis
Bacteraemias are common during mastication if oral hygiene is poor, from oral/ENT/GI/GU surgical procedures, or from IV drug use. If thrombosis occurs during a bacteraemia, organisms can lodge into vegetations:
   i. Proliferation, invasion, inflammation, destruction of valve tissue
   ii. Scarring, distortion, thrombosis
   iii. Organism-carrying embolism formation leads to downstream infarcts (septicaemia, metastatic abscess formation)

Species infecting the heart valves with low virulence and typically members of the resident flora of their site of origin → subacute bacterial endocarditis.

Species with high virulence derived from sites of infection elsewhere in the body can directly infect normal valves → acute endocarditis.

Clinical sequelae – surgical replacement with allografts or xenografts can improve function, but thrombosis and risk of recurrent bacterial endocarditis will persist.

Infection and toxemia – weight loss, anaemia, café au lait skin, splenomegaly.

Large emboli – infarcts (brain, kidney, spleen), splinter haemorrhages, metastatic abscesses, mycotic aneurysms.

Microemboli – petechial skin rash, Osler’s nodules, retinal haemorrhages.

Immune complex deposition – glomerulonephritis, focal encephalitis, cerebral arteritis.

Causes of death from bacterial endocarditis:
   a. Acute valve perforation
   b. Embolism
   c. Ruptured mycotic aneurysm
   d. Renal failure due to diffuse glomerulonephritis

Mechanical disturbances of valve function may be due to a number of causes – congenital abnormality, post-inflammatory scarring, age-related degeneration, dilation of the valve ring, or destruction by inflammatory necrosis (e.g. subacute bacterial endocarditis).

1. Mitral stenosis is generally caused by post-inflammatory scarring, with thickened and fused valve cusps and chordae tendineae.
   a. Left atrium fails to empty, hypertrophies and dilates
   b. Pulmonary hypertension and vascular congestion leading to haemoptysis
   c. Left heart failure, with atrial fibrillation and thrombosis

2. Mitral incompetence is caused by post-inflammatory scarring, acute post-MI papillary muscle dysfunction, LV dilatation, cusp destruction or floppy valve syndrome (excessive glycoprotein)
   a. Acute pulmonary oedema if the incompetence is acute
   b. Slow development with regurgitation, atrial enlargement and left heart failure

3. Aortic stenosis may be caused by calcification of a congenital bicuspid valve, post-inflammatory scarring or senile calcific degeneration.
   a. LV hypertrophy
   b. Angina pectoris (if severe, syncope)
   c. Sudden cardiac death due to arrhythmia

4. Aortic incompetence can be due to post inflammatory scarring (shortening cusps), infective endocarditis, senile calcification (retraction) or dilation of aortic wall and valve ring (syphilis)
   a. LV hypertrophy
   b. Left heart failure

**Hypertension**

Definitions of hypertension vary, but generally 160/95 is used – with this criterion, around 20% of adults suffer from hypertension. Classification of hypertension should consider:

1. **Aetiology**
   a. Primary (90%)
   b. Secondary
      i. Renal – vascular, renal failure
      ii. Endocrine – Cushing’s, Conn’s, phaeochromocytoma, acromegaly, myxoedema, thyrotoxicosis
      iii. Neurogenic – increased intracranial pressure
      iv. Other – coarctation, polycythaemia

2. **Severity**
   a. Benign
Normal regulation of blood pressure:
1. Baroreceptors in arteries
2. Kidney secretes renin \( \rightarrow \) angiotensin I \( \rightarrow \) angiotensin II (by ACE in the lung)
   a. Constrict arterioles
   b. Aldosterone from adrenal cortex \( \rightarrow \) renal sodium retention, blood volume expansion

Pathogenesis of hypertension
1. Primary hypertension – mechanism not known
   a. Hereditary – familial tendency
   b. Environmental – stress, obesity, smoking, inactivity, salt intake, oestrogens
   c. Possible – renin, \( \text{Na}^+, \text{Cl}^-, \text{Ca}^{2+} \), cell membrane defects, insulin resistance
2. Renal (secondary) hypertension
   a. Renovascular disease (e.g. renal artery dysplasia) – decreased blood flow \( \rightarrow \) increased renin secretion
   b. Renal parenchymal disease – decreased function \( \rightarrow \) salt and water retention

Features of hypertension:
1. Pathological features:
   a. Hyaline arteriolosclerosis in many organs, particularly the kidneys
   b. Kidneys – slightly small, fine surface granularity (benign nephrosclerosis)
   c. Heart – LV hypertrophy, may cause ventricular failure, myocardial infarct
   d. Eye changes show a progression from benign to malignant
      i. Arteriolosclerosis – obscuring of veins by arteries
      ii. Flame-shaped haemorrhages
      iii. Cotton wool ‘exudates’ (swollen nerve fibres)
      iv. Papilloedema of the fundi (indicates malignant hypertension)
2. Clinical features:
   a. Benign (asymptomatic) – raised incidence of MI, heart failure, cerebral haemorrhage
   b. Malignant – high intracranial pressure \( \rightarrow \) headache, confusion, convulsions, visual blurring, scotomata. May lead to heart or renal failure.

Heart Failure

Heart failure is a complication of all forms of heart disease – the heart is unable to pump blood at the rate required for normal metabolism, although the CVS is able to compensate somewhat. Prognosis is generally poor, and median survival rate is 3 years.

1. Acute and chronic – depends on cause (e.g. MI Vs valve incompetence) and the capacity to adapt. Note that chronic failure may follow a period of acute failure
2. Right and left – heart failure will eventually affect both, but symptoms of one will appear first
   a. Left heart failure \( \rightarrow \) poor systemic perfusion, pulmonary congestion
   b. Right heart failure \( \rightarrow \) poor pulmonary perfusion, systemic congestion
   c. 15% of patients present initially with pure right side failure
      i. Right side failure 2” to lung disease is cor pulmonale
      ii. Mitral stenosis is a common cause of right heart failure
3. Low output failure – most cases
   a. Cardiac output fails to increase, and may decrease on exercise - the heart is unable to pump adequately due to one or more of the following:
      i. Intrinsic muscle disease (ischaemia, infarction, myocarditis)
      ii. Increased afterload (mitral incompetence)
      iii. Restricted filling
      iv. Inadequate heart rate
      v. Fluid overload
4. High output failure
   a. Pulmonary congestion and oedema when cardiac output and ejection fraction is normal or elevated, but is unable to oxygenate tissues:
      i. Elevated blood volume (pregnancy, salt/water retention, renal failure)
      ii. Increased venous return
      iii. Decreased peripheral resistance (hyperthyroid, anaemia, cirrhosis)
iv. Congenital heart disease (e.g. AV shunt)

5. Symptoms include:
   a. Dyspnoea
   b. Pulmonary oedema
   c. Systemic venous congestion (oedema, ascites, portal hypertension)

Clinicopathological correlation:

1. Dyspnoea
   a. Subjective symptoms of shortness of breath due to increased blood/water content in the lungs at the expense of air volume
   b. Pulmonary congestion → capillary transudate → crackles on auscultation
   c. Orthopnea due to increased venous return while prone, paroxysmal nocturnal dyspnoea due to progressive pulmonary congestion while asleep
   d. Haemosiderin-laden macrophages in alveoli give rusty sputum

2. Systemic venous congestion and oedema
   a. Kidney tries to compensate by fluid retention → fluid volume overload
   b. Increased JVP indicates increased blood volume
   c. Hepatomegaly with engorged central veins – ischaemic centrilobular regions undergo fatty change (‘nutmeg liver’)
   d. Dilatation of the left ventricle may be apparent on radiograph
   e. Fluid leaks to subcutaneous tissues, and pleural and peritoneal cavities

Myocardial hypertrophy and heart failure – note that inflammatory angiogenesis can occur in the adult heart, but this occurs extensively only after ischaemic necrosis. If this could be induced earlier, functional myocardium could be preserved.

1. Weber (1987) defines three phases:
   a. Evolutionary phase – structural and biochemical remodelling of the various components of the myocardium each adjust at their own rate
   b. Physiologic phase – remodelling of these compartments is at a balanced rate
   c. Pathologic phase – balance is lost → abnormal function, impaired O₂ delivery

2. Structural changes do occur in the microvasculature during hypertrophy and failure, but the degree to which the patient can compensate is dependent on age, the experimental model and the cause of the hypertrophy

3. Some of these abnormalities may be prevented or therapeutically reversed:
   a. Nifedipine, manoxidine in hypertensive rats can reduce myocardial fibrosis and arteriolar changes
   b. Antihypertensive agents may reduce myocardial interstitial collagen in hypertensive patients
   c. Further developments – angiogenic factors (VEGF, bFGF), dipyridamole

PULMONARY PATHOLOGY

• Pneumonia

Pneumonia is a general term indicating inflammation of the gas exchange regions of the lung, and usually indicates parenchymal lung inflammation due to infection. Classification can be based on:

1. Location of the lesion – alveolar, interstitial
2. Extent of the lesion – lobar, lobular, bronchopneumonia
3. Aetiology – bacteria/fungi (intra-alveolar exudates), viruses (interstitial)
4. Duration – acute, chronic
5. Clinical features:
   a. Age of the patient
      i. < 2yrs – viruses (respiratory syncytial virus, adenovirus, influenza, parainfluenza, Chlamydia trachomatis from maternal UG tract)
      ii. Older children and adults – Streptococcus pneumoniae
      iii. Incidence and mortality (note chronic disease) is higher in the elderly
   b. Community acquired pneumonia – gram negative organisms are rare, and most organisms are treated at home with only 25% requiring hospitalisation
c. **Nosocomial pneumonia** – develops after two days following hospital admission, associated with use of broad spectrum antibiotics, impaired host defences, endotracheal intubation and impaired cough

d. **Concurrent disease**
   i. Alcohol, malnutrition, diabetes, cardiorespiratory disease predispose
   ii. COPD → impaired mucociliary clearance, allowing low virulence organisms (e.g. *Haemophilus influenzae*) → bronchopneumonia
   iii. Influenza infection (1st or 2nd to bacterial pneumonia) has highest mortality in the elderly

e. **Severity of the disease** – note that severity and/or occurrence with concomitant illness is a good indication for treatment in hospital/ICU

### Lobar pneumonia

1. **Aetiology** – usually *Streptococcus pneumoniae* (80%), also *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*

2. **Predisposing factors** – may be nothing except impaired respiratory defence systems
   a. 60% of people carry *Streptococcus pneumoniae* as a commensal in the nasopharynx and it is spread by airborne droplets
   b. May occur in association with airway obstruction (tumours)
   c. Debilitated, immunocompromised, alcoholics and vagrants may be predisposed to *Klebsiella* lobar pneumonia → bulging of interlobar fissures

3. **Pathology** – inhalation of micro-organism → inflammation (large bronchi) → spreads
   a. **Acute congestion** (1 day)
      i. Local vasodilatation → outpouring of exudate → congestion
      ii. Capillaries engorged, alveoli oedematous (eosinophils, bacteria, few neutrophils)
      iii. Macroscopically – heavy, red, dark, firm
   b. **Red hepatisation** (1 day)
      i. Capillary engorgement persists
      ii. Exudate has fibrin, rbcs, neutrophils (→ phagocytosis of bacteria)
      iii. Macroscopically – brick red, dry, firm, airless (feels like liver)
   c. **Grey hepatisation** (8 days)
      i. Decreased vasodilatation and congestion
      ii. Macrophages recruited to alveoli, which are distended and consolidated (due to fibrin and dead cells)
      iii. Macroscopically – fibrinous pleurisy, cut surface dry, airless, grey
   d. **Resolution after ~3 weeks**
      i. Exudate liquefied by fibrinolysis from plasma and macrophages
      ii. If there is no tissue destruction, parenchyma returns to normal
      iii. Rare with some virulent organisms (*Klebsiella pneumoniae*)

4. **Clinical presentation**
   a. Sudden onset cough, purulent rusty sputum, dyspnoea
   b. Pleuritic pain with localised chest signs (dullness, bronchial breathing)
   c. Rigors, fever, sweating

5. **Complications** – disturbances of ventilation-perfusion ratio, pleurisy with effusion, empyema, septicemia, meningitis, abscess (particularly with *Klebsiella pneumoniae*), carnification (small, fibrotic, shrunken lung)

### Bronchopneumonia

1. **Aetiology** – most common in the old and young, debilitated and immunocompromised
   a. *Streptococcus pneumoniae, Haemophilus influenzae*, viruses
   b. May be destructive (necrotising) and may not resolve completely
   c. Sometimes called hypostatic pneumonia in the elderly, or patients with diseases impairing the normal cough reflex
   d. Preceded by bronchitis and bronchiolitis which may have different causative organisms (i.e. viral infection with secondary bacterial infection)

2. **Pathology**
   a. Histology – acute suppurative bronchitis and bronchiolitis is seen with acute suppurative or acute necrotising peribronchiolitis and alveolitis
   b. Macroscopically – patchy (exudative) consolidation with pus formation
Abscess formation occurs frequently and the basal portions of both lungs are usually the most affected. May extend to involve lobules (lobular pneumonia) and may become confluent, simulating lobar pneumonia.

Other important pulmonary infections

1. Obstructive pneumonitis – physical obstruction to a large airway → inflammation (endogenous lipid pneumonia). 2° bronchopneumonia may occur.
   a. Tumours may be suspected in chronic pneumonias which resolve poorly
2.Organising pneumonia – lungs may show effects of oedema, bronchopneumonia, diffuse alveolar damage, organising pneumonia as well as CORD, emboli etc.
   a. Patchy organisation spreads → large, rubbery, firm areas with loss of function
3. Aspiration pneumonitis – decreased cough reflexes, anaesthesia, coma, sleep
   a. Aspiration of vomit, food, foreign bodies → abscess
   b. Note that agonal aspiration of gastric contents is a common terminal event and should not be mistaken for the cause of death
4. Viral (interstitial) pneumonia – interstitial mononuclear inflammatory infiltrate
   a. Primary – influenza, adenovirus, cytomegalovirus (CMV)
   b. Affects bronchioles and causes damage to type I alveolar lining cells and hyaline membrane. Hyperplasia of type II alveolar lining cells may occur.
   c. Histological diagnosis:
      i. CMV → big nuclear inclusions
      ii. Measles → multinucleated Warthin-Finkeldey giant cells
5. Opportunistic infection – immunosuppressed (AIDS, lymphoma, leukaemia)
   a. Candida albicans, Aspergillus fumigatus, Histoplasma capsulatum, Cryptococcus neoformans, CMV, Pneumocystis carinii, TB, common bacteria
      i. P carinii remain in the alveoli and are surrounded by a bubbly-appearing exudate – the inflammatory response may be weak or non-existent.

• Tuberculosis

Tuberculosis is the inflammation caused by Mycobacterium tuberculosis and other mycobacterium. This bacteria is a slender rod-shaped organism (Ziehl-Neelsen stain, acid fast) that is aerobic, slow growing in culture and extremely resistant to drying.

1. Excites cell-mediated immunity involving T-cells and macrophage derived cells
2. Methods of infection:
   a. Inhalation – main method where local dairy herds are free of infection
   b. Ingestion
   c. Inoculation
3. Entry doesn’t always → illness – this depends on age, resistance and immune status

Pathology – note that mycobacteria do not directly damage tissues, but mediate damage due to the specific altered reactivity of the immune system (enhanced resistance, hypersensitivity)

1. Primary lesion (usually in non-immune children on first contact with tuberculosis)
   a. Ghon focus – localised pulmonary infection, usually near the periphery of the middle or lower lobe of the lung
   b. The essential lesion of tuberculosis is the granuloma – characterised by central caseous necrosis within a circumscribed aggregate of cells
      i. Macrophages → epithelioid cells, Langhans giant cells
      ii. Surrounded by T-lymphocytes (→ lymphokines) and fibroblasts
   c. Infection → bronchial and mediastinal lymph nodes (caseous replacement)
   d. Ghon focus + hilar lymph nodes = Ghon complex, usually asymptomatic
2. Developments:
   a. Healing is the commonest result.
      i. Small Ghon foci may undergo complete fibrosis, while larger foci and hilar lymph nodes may become encapsulated and calcified
      ii. Viable organisms may persist in scarred foci for years
   b. Hilar lymph node involvement
      i. Pressure on the bronchi may lead to obstruction and collapse, retention of secretions, and pneumonia or bronchiectasis
c. Spread
   i. Inflammatory reaction in adjacent lung tissue → pleural effusion
   ii. Lymphatic spread → tuberculous pleurisy or pericarditis

d. Invasion of blood vessels
   i. This leads to dissemination → tuberculous foci in many organs (generalised miliary tuberculosis)
   ii. Invasion of the pulmonary artery → miliary tuberculosis in lungs only

3. Post-primary pulmonary infection is recurrence later in life due to immunosuppression (AIDS, malignancy, diabetes, malnutrition, steroids, debilitation)
   a. May also result from gradual extension of Ghon focus, or reinfection by bacilli
   b. Assmann focus – lesions tend to appear in characteristic sites (e.g. upper lobes, apical lower lobes)
      i. Sensitised T-cells recruit macrophages to form large granulomas with extensive and rapid caseous necrosis
      ii. Cell-mediated immunity kills many bacilli and macrophages
      iii. Extension is slow, and hilar lymph nodes not usually affected
   c. A kind of granulation tissue with lymphocytes and macrophages forms at the periphery of the lesion with laying down of fibrous tissue
   d. Cavitation – increased $O_2$ tension favours growth, infected material is coughed up and a natural pathway of spread is formed in the bronchial tree
   e. At this stage the lesion may:
      i. Heal leaving a dense grey scar with central calcification
      ii. Become an encysted fibrotic mass of caseous material (few bacilli)
      iii. Slowly extend by formation of new tubercles
      iv. Disseminate via blood stream or bronchi

Clinical features:
1. Primary tuberculosis is usually asymptomatic – there may be fever, lassitude, erythema nodosum, cough, sputum, or phlyctenular conjunctivitis
2. Post-primary tuberculosis may cause:
   a. Weight loss, anorexia
   b. Night sweats
   c. Cough, haemoptysis, dyspnoea
   d. Malaise, organ-specific signs and symptoms
3. Complications:
   a. Meningitis – aseptic and insidious with neck stiffness, headache, drowsiness, cranial nerve palsies, choroidal tubercules, papilloedema (inconstant)
   b. Genitourinary TB → dysuria, haematuria, polydipsia
   c. TB bone – vertebral collapse (Pott’s disease) associated with paravertebral abscess. Osteomyelitis may be accompanied by arthritis of adjacent joints.
   d. TB peritonitis/enteritis → abdominal pain, GI upset
   e. TB pericarditis – effusion, tamponade, constrictive pericarditis, calcification
   f. Scrofula – tuberculous lymphadenitis of the cervical nodes → overlying skin

Tuberculin skin testing
1. Infection produces sensitivity to the antigenic components (tuberculins)
2. Injection into the skin → local mild inflammatory reaction
   a. No previous exposure → response subsides
   b. Sensitised individuals → hyperaemia and oedema continue to increase with erythema and induration (due to mononuclear perivascular infiltration)
3. Mantoux, Heaf, Tine tests – positive result indicates infection, prior infection or immunisation

Sarcoidosis is a granulomatous disease of unknown aetiology. Granulomatous lesions are typically non-caseating, sharply defined and show only an inconspicuous mantle of lymphocytes. Multinucleated giant cells often contain star-shaped (asteroid bodies) or laminated (Schaumann bodies) structures.
1. Presentation – diffuse lung lesions, bilateral hilar node enlargement, possibly other organ involvement
2. Regresses spontaneously without treatment – fibrocalcific residues and other tuberculous complications do not occur.
3. Aetiology is not well understood. Possibilities:
   a. Form of mycobacterial infection with altered cell-mediated immunity
   b. Non-specific reaction to a wide range of stimulants
   c. Infection cased by an unknown agent

Other infectious granulomatous diseases include syphilis and leprosy.

*Mycobacterium avium-intracellulare* is an opportunistic infection occurring in immunocompromised (AIDS) patients. Most originate in the GI tract or the lungs, with widespread involvement of lymph nodes, liver and spleen. Large numbers of low virulence organisms are present, and swollen macrophages may colour tissues yellow. Granulomas, lymphocytes and tissue destruction are rare.

- **Chronic Obstructive Airways Disease**

**Chronic bronchitis** (excessive tracheobronchial mucus production → cough, expectoration for at least 3 months of the year, for more than 2 consecutive years) and **emphysema** (distension of air spaces distal to terminal bronchioles with destruction of alveolar septae) are separate diseases, but are often present in combination in COPD.

1. **Definitions**:
   a. Blue bloater – patient with severe chronic bronchitis who is severely hypoxic, hypercapnic and oedematous (RVF). Often has a rate of ventilation less than that suggested by measured blood gases
   b. Pink puffer – thin patient with pure emphysema, has normal blood gases due to sustained high ventilation rates

2. **Prevalence**
   a. 20% of adult males have chronic bronchitis – few are clinical, and females are less affected. Note smoking, occupational and environmental exposures.
   b. 2/3 of adult males and ¼ of females have emphysema, most without clinical symptoms

**Pathology:**

1. **Chronic bronchitis** – hyperplasia and hypertrophy of mucous-secreting glands in the submucosa of large cartilaginous airways. May be squamous metaplasia/dysplasia
   a. Reid index quantitates this change, based on the thickness of glands to the thickness of the bronchial wall (0.44 normal, 0.52 abnormal)
   b. Small airways – goblet cell hyperplasia, inflammatory cells, oedema, peri/bronchial fibrosis, intraluminal mucus plugs, increased smooth muscle

2. **Emphysema**
   a. Classified according to the pattern of involvement of acini:
      i. Centri-acinar – respiratory bronchioles and alveolar ducts involved
         1. Relatively less change peripherally in the acinus
         2. Functional reserve – massive destruction before impairment
      ii. Pan-acinar – entire acinus affected
      iii. Paraseptal – proximal acinus normal, distal portion involved
      iv. Irregular – acinus irregularly involved, scarring associated
   b. Pathogenesis:
      i. Alveolar wall destruction results from an imbalance between proteases (elastase) and antiproteases in the lungs
      ii. Smoking increases elastase levels as well as reducing levels of α1-antitrypsin (antielastase)

3. **Contributing factors**:
   a. Cigarette smoking – correlates with both emphysema and chronic bronchitis
   b. Air pollution – urban industrial areas (exacerbations of bronchitis clearly related to periods of heavy pollution with SO₂ and particulate matter)
   c. Occupation – chronic bronchitis more prevalent in workers dealing with inorganic or organic dust or noxious gases
   d. Infection – associated with aetiology and progression of COPD
   e. Familial/genetic – familial aggregation of clinical bronchitis, some concordance for chronic bronchitis in twin studies
Clinical syndromes

1. Predominant emphysema – exertional dyspnoea, minimal cough with a little mucoid sputum
   a. Examination:
      i. Body build is asthenic with evidence of weight loss
      ii. Distress with accessory muscle use (anterosuperior sternal motion) – while sitting, patients lean forward bracing themselves on their arms
      iii. Tachypnoea with prolonged expiration through pursed lips, and retraction of lower intercostal spaces on inspiration
      iv. Neck veins distended in expiration, collapsed on inspiration
      v. Hyper-resonant percussion note, breath sounds reduced with high-pitched rhonchi towards the end of expiration
   b. Blood gas – Arterial $P_{O2}$ 75mmHg, $P_{CO2}$ is low to normal
   c. Spirometry – total lung capacity and residual volume is increased, VC and FEV decreased, elastic recoil of the lung is severely impaired
   d. Complications – right sided heart failure, respiratory acidosis and coma, massive collapse of lungs secondary to pneumothorax

2. Predominant bronchitis – history of cough and sputum production for many years (initially only winter, then increasing in frequency, duration and severity)
   a. Examination:
      i. Overweight and cyanotic, usually no distress at rest
      ii. Respiratory rate normal or slightly increased (no accessory muscles)
      iii. Percussion is resonant, coarse rhonchi and wheezes
   b. Blood gas – decreased $P_{O2} \rightarrow$ erythropoiesis, hypoxic pulmonary vasoconstriction $\rightarrow$ cyanosis, right-sided heart failure $\rightarrow$ oedema
   c. Spirometry – total lung capacity normal, moderate elevation of residual volume, VC mildly diminished, FEV low, elastic recoil only slightly impaired

3. Principles of management
   a. Emphysema – prevention of progression and avoidance of acute insult (irreversible). Measures include stopping smoking and influenza vaccination.
   b. Bronchodilator drugs (methylxanthines, $\beta$-agonists, anticholinergics) may alleviate symptoms
   c. Additional therapy includes bronchopulmonary drainage, intermittent positive pressure breathing devices and oxygen therapy (severe/persistent hypoxia)

Bronchiectasis (permanent abnormal dilatation of bronchi) is considered a disease of the large airways, as this is where the lesions are most obvious – however, the origin generally lies in the obliteration of peripheral airways.

1. Aetiology
   a. Obstruction – foreign bodies, tumour, mucus, asthma, compressive lymphadenopathy (e.g. tuberculosis, carcinoma)
   b. Bronchopulmonary infections (2/3 of all cases) – measles, necrotizing bacterial pneumonias, adenovirus (most common)
   c. Other causes – cystic fibrosis, ciliary dyskinesia (Kartagener’s syndrome)

2. Pathogenesis
   a. Severe inflammation of bronchi and bronchioles $\rightarrow$ destruction of walls of central bronchi and obliteration of peripheral bronchi/bronchioles
   b. Collapse of lung parenchyma (atelectasis) and dilation of bronchi
   c. Inflammation in central airways $\rightarrow$ hypersecretion of mucus and abnormalities of surface epithelium (increased number of goblet cells)

3. Pathological findings
   a. Bronchial dilatation (saccular, varicose, cylindrical) is most common in the lower lobes, especially on the left
   b. Dilated bronchi have thick mucopurulent secretions
   c. Microscopically – destruction of all components of the bronchial wall, chronic inflammation, increased goblet cells, squamous metaplasia, lymphoid follicles, scarring and obliteration of distal bronchia and bronchioles

4. Clinical symptoms – history of severe recurrent bronchopulmonary infection in childhood $\rightarrow$ chronic productive cough (mucopurulent), dyspnoea, orthopnoea

5. Therapy
   a. Antibiotic therapy for infectious exacerbations
Cor pulmonale is defined as right ventricular hypertrophy that results from a disorder of the lungs – this may be caused by a number of conditions that increase pulmonary vascular resistance (recurrent pulmonary emboli, pulmonary fibrosis, chronic pulmonary emphysema).

Asthma

Asthma is characterised by an increased responsiveness of the tracheobronchial tree to a number of stimuli. It manifests with widespread narrowing of the airways that resolve spontaneously or with therapy, leading to episodic paroxysms of dyspnea, cough and wheezing. Status asthmaticus is a phase of chronic airways obstruction.

Prevalence and aetiology

1. Affects all ages, but predominantly early in life (half of cases occur before the age of 10). More males than females are affected, though this equalises by the age of 30.
2. Atopic (allergic) asthma
   a. Personal and/or family history of allergy – rhinitis, urticaria, eczema
   b. Positive wheel and flare skin reactions to intradermal injection of airborne Ag
   c. Increased IgE in serum, positive response to tests with specific antigens
   d. Frequently seasonal, most often in children and young adults
3. Nonreaginic (idiopathic) asthma – develop symptom complex on contracting upper respiratory tract infection that may last from days to months
4. Other types – pharmacologic, occupational, allergic bronchopulmonary aspergillosis

Stimuli that provoke asthma

1. Allergens
   a. Airborne – must be abundant for a period of time to produce sensitivity, after which minute amounts can lead to exacerbation
   b. Mechanism is unclear, as most airway allergens are too large and are filtered by the nose and mouth – it is also unclear how they get through the epithelium to submucosal mast cells
   c. Mast cells are also present in the mucosa, so interaction may occur at the surface and open tight junctions
2. Aspirin and related substances – usually adults with severe unremitting asthma, nasal polyposis and sinusitis
3. Environmental factors – conditions that promote the concentration of airborne pollutants and antigens e.g. heavy industrial or dense urban areas during thermal inversions or other situations with stagnant air masses
   a. Generally makes all types of asthma worse
   b. May be idiosyncratic or toxic effect, or alter threshold of irritant receptors
4. Occupational factors
   a. In some cases the offending agent is IgE immunogenic
   b. Materials may cause direct liberation of bronchial constrictor substances
   c. Work-related irritant substances may directly or reflexly stimulate airways
5. Infection – most common exacerbating stimulus
   a. Respiratory viruses are of major importance
      i. Children – respiratory syncytial virus, para-influenza virus
      ii. Older children and adults – rhinovirus, influenza
   b. Inflammation may reduce the firing thresholds of sub-epithelial receptors
6. Exercise – especially in cold, dry atmospheres. Related to the degree of cooling of intrathoracic airways, as inspired air must be heated here.
7. Emotional stress – can worsen or ameliorate the disease process
Pathology – gross overdistension of lungs at autopsy, failure to collapse when pleura is opened, and gelatinous plugs in the majority of bronchial branches down to the terminal bronchiole. Histologically there is smooth muscle hypertrophy, mucosal oedema, epithelial degeneration, basement membrane thickening and eosinophilic infiltrates.

1. Immunopathology - concurrence of allergic rhinitis and asthma in patients with a family history, and presence in serum of passive transfer activity towards the antigen
   a. Atopy – tendency to develop an altered state of reactivity after natural exposure to specific antigens
   b. Passive transfer factor is IgE, which fixes to mast cells triggering the release of histamine, serotonin, eosinophil chemotactic factor of anaphylaxis
   c. Leucocytes triggered by the acute response release a second wave of inflammatory mediators that stimulate the late reaction → prolongation

2. Pathophysiology
   a. Decreased airway diameter – bronchial smooth muscle constriction, oedema of bronchial wall and thick tenacious secretions
   b. Increased airway resistance, decreased FEVs and flow rates
   c. Hyperinflation of lungs and thorax, increased work, changes in elastic recoil
   d. Abnormal distribution of ventilation and pulmonary blood flow, mismatched V/Q, altered blood gases – hypoxaemia universal, respiratory failure rare

3. Clinical features
   a. Sense of constriction in the chest, often with non-productive cough and wheezing (inspiration and expiration). Cyanosis is a late sign.
   b. Tachypnoea and prolonged expiration – accessory muscles visibly active
   c. Hyperinflation of the lungs → increased AP diameter of thorax
   d. Termination of episode → cough → thick, stringy mucus with eosinophils, Curschmann spirals and Charcot-Leyden crystals
   e. In extreme cases, there may be no wheezing, an ineffective cough and gasping due to extensive mucus plugging

Therapy
1. Methylxanthines (theophylline) – increase cAMP levels
2. Adrenergic stimulants – β₂ agonists increase adenylate cyclase levels → cAMP
   a. Note that a pure β₂ agonist would dilate airways without cardiac stimulation
3. Glucocorticoids – some controversy over dose and indication, many side effects
   a. Acute illness – obstruction not resolving, or worsening despite therapy
   b. Chronic illness – failure of previous regimes with frequent occurrences of symptoms of progressive severity
4. Sodium cromoglycate – inhibits degranulation of mast cells
5. Anticholinergics (atropine) – sustained side-effects, though recent non-absorbable aerosol agents are effective and relatively free of adverse effects

GASTROINTESTINAL PATHOLOGY

Inflammation of the Colon

Infections/infestations
1. Bacterial enterocolitis
   a. Ingestion of preformed bacterial toxins – effects in hours, pass within days
      i. Explosive diarrhoea and acute abdominal stress (Staph. aureus, salmonella, C. perfringens)
      ii. Systemic toxins (C. botulinum) may → rapid respiratory failure
   b. Infection with enteric pathogens – several hours to days
      i. Diarrhoea, dehydration if secretory enterotoxin (E. coli, Vibrio)
      ii. Cytotoxin → dysentery (Shigella)
      iii. Enteroinvasion – S. typhi
   c. Insidious infection
      i. Yersinia and mycobacteria can present as subacute diarrhoeal illness
      ii. All enteroinvasive organisms can → acute onset of symptoms of idiopathic inflammatory bowel disease
d. Complications – consequences of fluid loss or destruction of intestinal mucosa (dehydration, sepsis, perforation). Death is rapid without treatment

2. **Escherichia coli**
   a. Enterotoxigenic
   b. Enterohaemorrhagic – Shigella-like toxin
   c. Enteropathogenic – effacement of erythrocytes, no invasion
d. Enteroinvasive

3. **Salmonella – typhoid fever**
   a. Can → typhoid fever, food poisoning, septicaemia (no bowel involvement)
   b. Organisms multiply in lymphoid tissue of the small intestine
c. Some enter blood and are taken up by the reticuloendothelial system
d. Headache, prostration, epistaxis, bronchitis, constipation, acute abdomen, high fever
e. After a few days rose spots appear on the skin and the spleen enlarges
f. Ulceration of Peyer’s patches → diarrhoea, haemorrhage, perforation

4. **Clostridium difficile (pseudomembranous colitis)**
   a. Antibiotic-associated diarrhoea due to toxin released from the organism
   b. Disease may be mild and self-limiting, or can present as fulminant colitis
c. Multiple yellow-grey plaques can be seen
d. Subtypes:
   i. Type I – focal epithelial necrosis with underlying fibrin and neutrophil exudate and overlying mucin plug, neutrophils
   ii. Type II – volcano lesions with dilated mucin-filled glands and plaques
   iii. Type III – necrosis of mucosa

5. **Amoebiasis**
   a. Infestation with Entamoeba histolytica
   b. Cysts appear in the faeces – on ingestion they pass unharmed through the stomach and vegetative forms are released in the small intestine
   i. Invade crypts and submucosa in the caecum and ascending colon, but not muscularis mucosae (fan out → flask-shaped ulcer)
   ii. Mucosa between ulcers is normal or slightly inflamed
c. Amoebae are found in the exudate at the base of ulcers and/or mucosal surfaces
d. Complications:
   i. Toxic megacolon
   ii. Perforation
   iii. Amoeboma – superimposed bacterial infection with fibrosis and localisation (sigmoid and caecum). Pass to liver → abscesses

6. **Proctitis in homosexual men**
   a. Pain, per rectal discharge, tenesmus, constipation, diarrhoea, bleeding
   b. Organisms – gonococcus, HSV, syphilis, Giardia, amoeba, Chlamydia, campylobacter, CMV, HPV, cryptosporidiosis, salmonella/shigella
c. Inflamed or ulcerated mucosa – may simulate ulcerative colitis
d. Chlamydia has granulomas – may resemble Crohn’s disease
e. Viral infections – intranuclear inclusions may be seen in epithelial and stromal cells

**Idiopathic inflammatory bowel diseases** including ulcerative colitis and Crohn’s disease

1. **General aspects:**
   a. Aetiology – probably immune. Generally part of a systemic disturbance – chronic liver disease, arthritis, uveitis, ankylosing spondylitis, skin rashes, erythema nodosum
   b. Affect the same type of patients (20-40, ♀♂, Caucasians), and have familial tendency for both. Sometimes there is a histological resemblance, and both carry increased cancer risk.
c. Epidemiology – common in the western world, affect females more than males. Occurs at any age, but peak incidence is 20-30 years.
d. Aetiology:
   i. Infection – mycobacteria, Chlamydia, Yersinia
   ii. Immune – inappropriate exposure to luminal or mucosal antigens – circulating immune complexes may → extracolonic manifestations
   iii. Genetic – familial aggregation, twin concordance

2. **Ulcerative colitis** usually only affects the mucosa, beginning in the rectum and left colon and passing proximally. Skipped areas are generally not seen.
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a. Acute UC – ulceration usually superficial, with surviving islands of mucosa regenerating with oedema and cellular infiltration (inflammatory polyposis)
   i. Deeply congested mucosa with vascular dilation
   ii. Infiltration of lamina propria with plasma cells, lymphocytes, eosinophils, neutrophils
   iii. Cryptitis and crypt abscesses with loss of mucus from goblet cells
   iv. Paneth cell metaplasia
b. Chronic quiescent UC
   i. Recovery of mucus in goblet cells
   ii. Disappearance or reduction of inflammatory cells
   iii. Branching and shortening of crypts

c. Chronic UC with focal activity – focal active cryptitis on top of chronic quiescent UC
d. Complications:
   i. Toxic megacolon (fulminant colitis) usually affects the transverse colon which becomes dilated and thin-walled
      1. Prone to perforation (peritonitis, shock) – deep ulceration may be confused with those of Crohn’s disease
      2. Hyperaemia, inflammation, myocytolysis
      3. Crohn’s disease, ischaemia and amoebiasis can + TM
   ii. Adenocarcinoma (risk of 4-5%)
      1. Increased risk with early onset UC lasting >10yrs
      2. Extensive/pan-colitis
      3. Continuous
      4. Dysplasia especially associated with mass lesion
      5. UC associated cancer is multifocal, invasive and mucoid
   iii. Extraintestinal manifestations
      1. Liver – non-specific fatty change, portal tract inflammation, sclerosing cholangitis, bile duct carcinoma, cirrhosis
      2. Skin – erythema nodosum, pyoderma gangrenosum, papulonecrotic lesions, ulcerating erythematous plaques
      3. Joints – polyarthritis that regresses after colectomy

3. Crohn’s disease is a chronic disease affecting any part of the GI tract at different times (most often small intestine). Colon is affected 20-30%, and intestinal Crohn’s may be preceded by anal disease by many years.
a. Morphology:
   i. Oedema of mucosa and longitudinal fissuring ulcers (cobblestoning)
   ii. Thickening of the entire bowel wall, wrapping fat
   iii. Colon – oedema, patchy lymphoid infiltration, crypt abscesses, preservation of goblet cells
   iv. Small intestine – loss of villi, pyloric metaplasia, thickened submucosa with lymphoid aggregation and epithelioid granulomas
b. Ulcers are aphthous or deep fissures → fistulae
c. Affected segments are hard and narrowed
d. Regional lymph nodes may contain granulomas
e. Complications:
   i. Malabsorption – usually mild, steatorrhoea, B₁₂ if terminal ileum
   ii. Fistulæ – internal, enterocutaneous, anal/rectal
   iii. Toxic megacolon
   iv. Obstruction

Ischaemic colitis
1. Elderly patients with atheroma
2. Segmental, usually affecting the splenic flexure
3. May present as colitis with bleeding
4. Radiology – thumb print sign due to submucosal oedema and haemorrhage
5. Oedema with intervening linear ulcers – mucosa necrotic, wall prone to perforation
6. Chronic ischaemia – strictures (sacculation) due to fibrosis, haemosiderin laden macrophages, fibrotic submucosa, ulcerated and irregularly healed mucosa

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Diverticular disease is a disease of the left side of the colon (especially sigmoid) common in the West with increasing incidence in the last 20 years (10-40% of routine autopsies). It is generally uncommon before age 30, and incidence increases with age.

1. **Morphology:**
   a. Segmental with affected areas having hard, collagenous consistency and prominent taenia coli and circular muscles
   b. Diverticula are folds of mucosa between mesocolon/taenia through slit-like openings

2. **Histology:**
   a. Mucosal invaginations through vessel openings
   b. Attenuated and fibrotic muscle wall

3. **Complications** – usually asymptomatic but can lead to
   a. Abdominal pains, diarrhoea/constipation
   b. Inflammation/fibrosis – may resemble carcinoma
   c. Abscess, perforation, peritonitis – uncommon

4. **Pathogenesis**
   a. Low fibre diet, low stool bulk, abnormal peristalsis → hypertrophied muscle and increased luminal pressure
   b. Focal weakness in colon wall at site of vessel entry

**Diversion colitis** involves inflammatory changes of the mucosa after diversion of the faecal stream. It may be asymptomatic or lead to bleeding and discharge – note that there is a variable severity (may mimic inflammatory bowel disease). Lymphoid hyperplasia is associated with surface degeneration – this may be in response to a change in bacteria flora (loss of epithelial trophic factors)

**Radiation colitis** involves mucosal necrosis with ulceration. Nuclei are atypical, and endarteritis, necrosis and strictures are typical.

**Microscopic colitis** presents as chronic watery diarrhoea with normal bowel on colonoscopy.

1. Several patterns are seen microscopically:
   a. Collagenous – thick layer of collagen beneath epithelium
   b. Lymphocytic – increased intraepithelial lymphocytes, epithelial degeneration

2. Both associated with autoimmunity – different phases of the same disease?

**Drug-induced colitis** (NSAIDS, gold, methyldopa, methotrexate) leads to non-specific inflammation, ulceration, strictures and diaphragm formation in the small intestine.

**Acute appendicitis** is associated with obstruction by a faecalith in most cases. Secretion leads to increased pressure, collapse of draining veins and ischaemia. Consequently mucosal ulceration, inflammation, wall congestion and a serosal exudate develop – this can progress to a suppurative appendicitis prone to rupture.

### Tumours of the Colon

Epithelial tumours of the intestines are a major cause of morbidity/mortality – colorectal cancer is a leading cause of cancer death (15%), and adenocarcinomas comprise most GI tract malignancies (70%). Polyps make up most benign tumours; carcinomas make up most malignant tumours.

**Non-neoplastic (benign) polyps** are formed as a result of abnormal mucosal maturation, inflammation or architecture. They occur sporadically, increasing with frequency with age and may be sessile or pedunculated.

1. **Hyperplastic polyps** – >60yrs, <5mm, non-neoplastic glands ('sawtooth appearance')
2. **Hammartomatous polyps**
   a. Juvenile polyps – single (rectum) or polyposis, inflamed lamina propria with cystically dilated glands
   b. Peutz-Jeghers polyps – lobulated surface, arborizing smooth muscle, non-neoplastic glandular epithelium with abundant goblet cells. Single lesions have no malignant potential, but syndrome carries increased risk of cancers of pancreas, breast, lung

3. **Inflammatory polyps**
4. **Lymphoid polyps**
Neoplastic (adenomatous) polyps are similar to benign polyps but result from proliferation and dysplasia. They are generally precursors to carcinoma.

1. Adenomas – single or polyposis, sessile or pedunculated (~10ys for a polyp to double in size)
   a. Classification – tubular, tubulovillous, villous
   b. Dysplasia ranges from mild to severe, characterised by enlarged, elongated, hyperchromatic nuclei and decreased cytoplasmic mucin
   c. Malignancy – polyp size, architecture (villous bad), and severity of dysplasia
2. Adenocarcinoma

Intestinal polyposis syndromes are characterised by a predisposition to developing numerous intestinal polyps (usually of a certain type). There is either a propensity for polyps to undergo malignant transformation, or a propensity to develop associated malignancies in other organs.

1. Familial adenomatous polyposis – bowel becomes coated with adenomas (500-2500)
   a. Polyps usually occur in the teens to twenties with cancer subsequently developing within 10-15 years.
   b. Genetic defect is in the APC gene on chromosome 5

The development of carcinomas from adenomas is the adenoma-carcinoma sequence

1. Proof of a relationship:
   a. Populations with high rate of adenomas have a high rate of carcinomas
   b. Distribution of adenomas/carcinomas in the colorectum is the same
   c. Early invasive carcinomas often show surrounding adenomatous tissue
   d. Risk of developing cancer is proportional to the number of adenomas present
   e. Peak incidence of adenomas precedes that of colorectal cancer by year
2. Sequence – cumulative effects of a number of molecular/genetic changes
   a. Normal epithelium
   b. Hyperproliferative epithelium
   c. Early → intermediate → late adenoma
   d. Carcinoma

Colorectal carcinomas represent 98% of cancers of the large intestine and 10% of all cancer deaths.

1. Epidemiology and aetiology:
   a. Peak incidence 60-79 years – mainly of a sporadic nature though some may have an underlying genetic component (e.g. HNPCC)
   b. In younger patients there is usually an underlying condition (e.g. ulcerative colitis) or one of the polyposis syndromes
   c. Environmental factors (especially diet) may also play a role in pathogenesis
2. Pathology
   a. Can occur anywhere in the colon, but are much less frequent in the small bowel compared to the large intestine
   b. Proximal large bowel lesions tend to be exophytic, while those in the distal colon tend to be annular and encircling
3. Prognosis – the main indicator is the extent of tumour at the time of operation
   a. Dukes stages:
      i. Dukes A (90% survival) – confined to bowel wall, no nodes involved
      ii. Dukes B (55% survival) – through bowel wall, no nodes involved
      iii. Dukes C (25% survival) – any depth, regional lymph nodes involved
   b. Jass staging may be used for rectal tumours

Other lesions:
1. Carcinoid tumour – derived from endocrine cells along the length of the GI tract
2. Anorectal lesions – mainly squamous cell carcinomas
3. Mesenchymal tumours
   a. Gastrointestinal stromal tumours
   b. Other benign lesions:
      i. Lipoma
      ii. Neuroma
      iii. Angioma
   c. Lymphoma – 1st or 2nd (disseminated, systemic lymphoma)
Hepatitis

Hepatitis refers to inflammation of the hepatic parenchyma and may be caused by infective or non-infective causes. Non-infective causes include:

1. Alcohol
   a. Degree of damage depends on the duration of consumption, quantity consumed and the genetic makeup of the drinker
   b. Fatty change, portal and lobular infiltrates of PMN cells, hepatocellular necrosis with Mallory's hyaline and eventual cirrhosis
2. Drugs/toxins/hyperalimentation
3. Auto-immune hepatitis
   a. Simulates viral hepatitis – often presents acutely and is characterised by large number of plasma cells. Responds well to steroids
4. Primary biliary cirrhosis, primary sclerosing cholangitis and ascending cholangitis
   a. Most of the insult is to the biliary system rather than hepatic parenchyma
   b. Eventual expansion of the portal tracts with piecemeal necrosis and cirrhosis
5. Alpha-1 anti-trypsin deficiency, Wilson's disease, haemochromatosis
   a. Mimic viral hepatitis and progress to cirrhosis, but have major extrahepatic manifestations and characteristic histological features on biopsy
6. Cryptogenic (iatrogenic) hepatitis

Hepatotropic viruses:

1. Hepatitis A “Crappy”
   a. Faecal-oral route, usually self-limited, no chronic stage
   b. Third world countries
2. Hepatitis B “Dopey”
   a. Drug users, sexual transmission
   b. 60% subclinical, 30% acute, 1% fulminant, 4% chronic hepatitis
   c. Increased risk of hepatocellular carcinoma
3. Hepatitis C “Doc”
   a. Transfusion, parenteral transmission
   b. Majority go on to chronic hepatitis
   c. Increased risk of hepatocellular carcinoma
4. Hepatitis D “Lazy”
   a. Defective virus requiring preinfection with Hepatitis B
   b. Frequent fulminant and chronic hepatitis
5. Hepatitis E “Sloppy”
   a. Waterborne epidemics (third world)
6. Hepatitis G “Feeble”
   a. Of questionable significance

Infective hepatitis – the liver is almost always involved in blood-borne infections. The specific hepatotropic viruses cause the same clinicopathological pattern of acute hepatitis, but differ in their ability to produce types of hepatitis:

1. Acute hepatitis – parenchymal changes predominate
   a. Incubation period varies from days to many years (Hepatitis C)
   b. Symptomatic pre-icteric phase
      i. Non-specific symptoms including malaise, fatigue, nausea, anorexia, fever and headaches
      ii. Circulating immune complexes may create a serum sickness-like syndrome consisting of fever, rash and arthralgia
   c. Symptomatic icteric phase
      i. Conjugated hyperbilirubinaemia – urine turns dark, stools turn light (due to cholestasis) and severe itching due to bile salt retention
      ii. Balloon degeneration of hepatocytes, focal necrosis, lobular inflammation, disarray with fatty change, variable portal inflammation
   d. Convalescence
2. Chronic hepatitis – symptomatic, biochemical or serologic evidence of continuing inflammatory hepatic disease for more than 6 months
a. Traditional classification (note that these are really different degrees of severity along a single disease continuum)
   i. Chronic persistent hepatitis – infiltrate limited to portal tracts
   ii. Chronic active hepatitis – evidence of piecemeal and lobular necrosis
b. Characterised by varying levels of hepatocellular necrosis and inflammation
   i. Focal areas of parenchymal necrosis and cell dropout
   ii. Larger lobular areas of confluent necrosis with or without bridging necrosis
   iii. Periportal or perisepal piecemeal necrosis
c. Histological activity index scores the grade of necroinflammatory activity and the stage of fibrosis – aetiology (serology and history), grade (histological assessment of severity) and stage (histological assessment of fibrosis)

3. Fulminant hepatitis – massive or submassive necrosis (25-90% mortality)
   a. 65% due to viruses, 30% to drugs and chemicals
   b. Gross appearance – red/green limp liver with a wrinkled capsule
   c. Histology – lobular necrosis with sparing of periphery and little inflammation
   d. If patient survives, the liver may regenerate completely or may Æ fibrosis

4. Carrier state – an individual without manifest symptoms who harbours and therefore can transmit an organism
   a. Two types – healthy carrier, carrier with chronic hepatitis
   b. Hepatitis B (1-10% adults, 90-95% vertical transmission), Hepatitis C (2-3%), Hepatitis D (low risk)

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<thead>
<tr>
<th>Acute Hepatitis</th>
<th>Chronic Hepatitis</th>
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<tr>
<td>Parenchymal changes predominate</td>
<td>Portal/periportal inflammation predominates</td>
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<tr>
<td>Collapse without fibrosis</td>
<td>Lobular inflammation in flares of activity</td>
</tr>
<tr>
<td>Canalicular cholestasis (bile plugs)</td>
<td>Fibrosis</td>
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• Cirrhosis

Cirrhosis is a diffuse process characterised by fibrosis and nodular regeneration. It is not a specific disease, but the end result of a number of diseases causing chronic liver injury.

1. Fibrosis occurs in response to hepatocyte injury and loss, causing disorganisation of liver architecture.
2. Fibrosis may be in delicate bands (portal-central, portal-portal or both) or may form broad scars replacing multiple adjacent lobules
3. Parenchymal nodules are created by the regenerative activity and network of scars, and lead to vascular reorganisation with haphazard blood flow and abnormal AV connections
4. Classification:
   a. Morphologically – parenchymal nodules can be divided into micronodular (<3mm) and macronodular (>3mm), though this has no bearing on clinical presentation or the course of the disease
   b. Aetologically:
      i. Alcoholic cirrhosis 60-70%
      ii. Viral hepatitis 10%
      iii. Biliary cirrhosis 5-10%
      iv. Haemochromatosis 5%
      v. Wilson’s disease, Alpha-1 antitrypsin deficiency, cardiac cirrhosis, galactosaemia, glycogen IV storage disease and syphilis are rare

Once developed, there is no evidence that the fibrosis can regress. It may be silent or present as anorexia, weight loss, weakness, spider angiomas, gynaecomastia and impaired synthesis (albumin, fibrinogen, prothrombin, clotting factors). Complications include:

1. Liver failure resulting in:
   a. Inadequate synthesis of albumin and clotting factors
   b. Failure to eliminate endogenous products and hormones. When bilirubin levels are elevated, hyperbilirubinaemia occurs (above 2mg/dl Æ jaundice)
2. Portal hypertension occurs mainly due to increased resistance to portal blood flow at the level of the sinusoids (due to perisinusoidal collagen) and compression of central veins (perivenular fibrosis, expansion of parenchymal nodules). AV shunts may also play a role. Complications:
   a. Ascites
b. Porto-systemic venous shunts where blood is diverted from the portal system into lower resistance collateral vessels
c. Congestive splenomegaly, 2° hypersplenism (anaemia, thrombocytopenia)
d. Hepatic encephalopathy from ammonia (2° to diffuse parenchymal damage and porto-systemic shunting)

3. Hepatic cancers – note that most tumours are 2° to neoplasms in the colon, breast, stomach or lung. The most common malignant 1° hepatic tumour is hepatocellular carcinoma, with around 70% of cases arising in cirrhotic livers
   a. Hepatitis B and alcohol-related cirrhosis appear to be the most important predisposing factors
   b. It is theorised that chronic injury leads to sustained hepatocyte hyperplasia, increased susceptibility to various carcinogens and greater risk of chromosomal damage
   c. Proto-oncogenes may be activated, and/or suppressor genes inactivated, leading to a selective growth advantage for a line of cells that may become malignant.

Pancreatic Pathology

The normal pancreas is a ‘hidden’, non-palpable organ with large exocrine and endocrine reserves. Pathologic processes tend to present late when the disease is advanced.

1. Exocrine pancreas – comprised of acinar cells and ducts
   a. Acinar cells contain abundant basal RER and apical zymogen granules
      i. Zymogens – inactive enzyme precursors (trypsin, chymotrypsin, amylase, lipase, nuclease, elastase, phospholipase)
   b. Alkaline fluid secreted by intercalated ducts

2. Endocrine pancreas – islets of Langerhans composed of
   a. Beta cells (insulin) ~70%
   b. Alpha cells (glucagon) 20%
   c. Delta cells (somatostatin) 10%
   d. Pancreatic polypeptide cells 2%

3. Pancreatic protection against self-digestion:
   a. Release of enzymes as inactive forms
   b. Proenzymes activated by trypsinogen → trypsin (by enterokinase produced by duodenal enterocytes – activation should only occur in the duodenum)
   c. Trypsin inhibitors present in pancreatic juices
   d. Acinar cells relatively resistant to proteases

Acute pancreatitis occurs in normal glands with changes/damage that is reversible. It has two forms – mild (70-80%, low mortality) and severe necrotising (20-30%, 25-35% mortality). Overall mortality is 5-10% – severe acute pancreatitis is an emergency.

1. Aetiology
   a. 80% of cases associated with gallstones or alcohol abuse
   b. Other causes include infection, drugs, trauma/ischaemia, hypercalcaemia, hyperlipidaemia and idiopathic (some with biliary sludge)

2. Pathology
   a. Premature activation of pancreatic enzymes within the pancreas itself
      i. Small vessel leakage – oedema
      ii. Fat necrosis 2° to lipase – released fatty acids combine with Ca^{2+} to form chalky/soapy deposits
      iii. Acute inflammation
   b. In the severe necrotising form:
      i. Proteolytic destruction of acini, ducts, islets 2° to proteases
      ii. Blood vessel destruction 2° to elastase
      iii. Pancreas may be blue/black with yellow, chalky foci of fat necrosis
      iv. Fat necrosis may involve other intra- and extra-abdominal sites

3. Pathogenesis
   a. Pancreatic duct obstruction by gallstones and ductal concretions (alcoholics)
      i. Increased intrapancreatic ductal pressure
      ii. Accumulation of enzyme rich interstitial fluid
      iii. Fat necrosis as lipase already active
      iv. Oedema compromises blood flow with 2° acinar cell necrosis
b. Primary acinar cell injury 2° to viruses, drugs, trauma, ischaemia
   i. Activation of released enzymes by lysosomal hydrolases

c. Defective intracellular transport
   i. Delivery of proenzymes to lysosomes instead of zymogen granules
   ii. Activation of proenzymes by lysosomal hydrolases

4. Clinical features
   a. Constant, severe epigastric pain (one cause of acute abdomen)
   b. Nausea and vomiting
   c. Pyrexia, tachycardia
   d. Abdominal distension, ileus
   e. Rarely – shock with DIC and/or ARDS

5. Diagnosis
   a. Serum amylase, lipase – amylase usually, but not specific
   b. Ultrasound to visualise gallstones
   c. CT to indicate necrosis, enlargement, pseudocysts
   d. Laparotomy if diagnosis uncertain

6. Treatment
   a. Pancreas is rested, nasogastric suction, IV fluids and parenteral feeding
   b. Analgesia
   c. Close monitoring in intensive care
   d. Surgical drainage in some patients

7. Complications
   a. Cytokines → systemic inflammatory response (shock, renal failure, respiratory insufficiency)
   b. Pseudocysts – collections of pancreatic secretions without a true epithelial lining. May be associated with 2° haemorrhage, rupture or infection

Chronic pancreatitis occurs due to repeated bouts of mild to moderate pancreatic inflammation with continued loss of pancreatic parenchyma and replacement by fibrous scar tissue.

1. Aetiology
   a. 60-70% have a long history (6-12yrs) of heavy alcohol consumption – these patients develop intraductal plugs and stones (chronic calcifying pancreatitis)
   b. Other causes:
      i. Pancreatic duct obstruction due to strictures, tumours, gallstones, pancreas divisum (obstructive chronic pancreatitis)
      ii. Tropical pancreatitis (possibly 2° to malnutrition or toxins)
      iii. Cystic fibrosis
      iv. Hyperparathyroidism
      v. Autosomal dominant familial pancreatitis (abnormal trypsin)

2. Pathology
   a. Irregular fibrosis – replacement of acinar component but relative islet sparing
   b. Intraductal protein plugs and stones
   c. Mild chronic inflammatory infiltrate
   d. Pancreas rock hard, fibrous appearance – may resemble carcinoma

3. Pathogenesis overlaps with acute pancreatitis to some extent
   a. Ductal obstruction by concretions and stones
   b. Decreased secretion of lithostatine (usually inhibits CaCO₃ precipitation)
   c. Ductal obstruction by fibrosis alters ductal flow
   d. Intraductal hypertension in idiopathic group

4. Clinical features
   a. Repeated pain (mild to severe) – may be 2° to alcohol binges, fatty meals
   b. Malabsorption – treat with low fat diet, enzyme replacement
   c. Diabetes – usually appears later than steatorrhea
   d. Pseudocysts in 10%

5. Diagnosis
   a. Amylase – only slight increase or normal due to loss of exocrine component
   b. Abdominal X-ray – pancreatic calcifications
   c. Ultrasound, CT – duct dilatation, pseudocysts
   d. Impaired pancreatic function tests
   e. Endoscopic retrograde pancreatography – tortuous, obstructed ducts
6. **Prognosis**
   a. Mortality up to 50% over 20-25 years, often due to complications (alcoholism)
   b. 4% develop pancreatic carcinomas over 20 years (may be due to smoking)

**Pancreatic carcinoma** is the 5th most frequent cause of cancer deaths in the US, more common in males over 50 years of age. Most are ductal adenocarcinomas, and prognosis is very poor (5yr survival <2%, 1yr mortality 90%). 15% are operable by a Whipple’s procedure, but even in this group 5yr survival is only 15%.

1. **Associations**
   a. Smoking – strongest risk factor
   b. Familial relapsing pancreatitis has increased risk
   c. Unknown – high fat/low fibre diet, EtOH, coffee, chronic pancreatitis, diabetes

2. **Pathology**
   a. 60% in head, 20% in body, 5% in tail, 20% diffuse
      i. Head – jaundice
      ii. Body and tail – usually widely disseminated at presentation
   b. Spread to nodes, liver, lungs, bone
   c. Histologically – mucin-secreting ductal adenocarcinomas set in dense fibrous stroma

3. **Clinical features**
   a. Jaundice – pruritus, dark urine
   b. Pain – dull, epigastric radiating to the back
   c. Weight loss, diabetes, pancreatitis
   d. Migratory thrombophlebitis (Trousseau's sign) due to procoagulant factors

4. **Diagnosis**
   a. Serology – CEA and CA19.9 are often raised but not reliable
   b. Imaging – ultrasound/CT or MRI, confirmed with fine needle aspiration

**Disorders of the endocrine pancreas**:

1. **Pancreatic endocrine neoplasms** are uncommon. They may be single or multiple, benign or malignant – behaviour is hard to predict. Two worth mentioning:
   a. Insulinomas
      i. Most common islet cell tumour
      ii. 90% benign, usually small, single and encapsulated → surgery
      iii. Presents as hypoglycaemia precipitated by fasting or exercise
   b. Zollinger-Ellison syndrome (gastrinomas) – most malignant, slow growing
      i. G cells usually in antrum not islets, but gastrinomas more often in pancreas or duodenum than stomach
      ii. Presentation:
         1. Hypergastrinaemia stimulates gastric acid → ulcers
         2. May also present with diarrhoea
         3. 20-25% have MEN-1 syndrome (PPP)
      iii. Treatment includes omeprazole, then assessment for surgery

2. **Islets in diabetes**
   a. Type 1 – may see insulitis (infiltration of islets by lymphocytes)
   b. Type 2 – may see replacement of islets by amyloid

**Endocrine Pathology**

Endocrine conditions may be primary (congenital, environmental, inflammation, infarction, isolated organ autoimmune, neoplasia) or secondary (other endocrine abnormality, metabolic, systemic autoimmune). Clinical effects can be hyperfunction, hypofunction, or abnormal mass. It is important to differentiate hyperplasia and neoplasia (benign or malignant).

**Anterior pituitary adenomas** represent 10% of intracranial neoplasms, affect adults aged 30-60yrs.

1. **Functional** – prolactinoma (→ 2° amenorrhoea), GH adenoma (→ acromegaly), corticotroph, thyrotroph
2. **Mass effect** – bilateral homonymous hemianopia, increased ICP
3. **Hypopituitarism:**
   a. Tumours/cysts – adenoma, craniopharyngioma, Rathke cell cyst
   b. Iatrogenic – surgery, radiation
   c. Necrosis – Sheehan syndrome (post-partum complication)
   d. Empty sella syndrome (1°, 2°)
   e. Pituitary apoplexy (haemorrhage)

**Thyroid gland**

1. **Hypothyroidism** – congenital (agenesis, enzyme defects), autoimmune, iatrogenic
2. **Hyperthyroidism** – Graves disease, toxic multinodular goitre (Plummer’s), toxic adenoma, transient thyroiditis, iatrogenic
3. **Hyperplasia**
   a. Multinodular colloid goitre – endemic, sporadic (iodine deficiency) with degenerative changes on histology. Usually euthyroid.
   b. Graves disease – hyperplasia with lymphoid infiltrate, hyperthyroidism with extra-thyroid features. Due to antibody cross-reaction with the TSH receptor
4. **Thyroiditis** (more common in ♀)
   a. Hashimoto’s - autoimmune with diffuse enlargement, often hypothyroid.
      i. Histology – heavy inflammatory infiltrate, Hürthle cell change in follicular cells (more mitochondria)
   b. Subacute (de Quervain) – viral/post-viral with pain, swelling, systemic effects
      i. Histology – follicle disruption, acute and granulomatous inflammation
   c. Reidel (fibrosis) – may be mistaken for high grade neoplasm
5. **Thyroid tumours**
   a. Follicular adenoma
   b. Carcinomas
      i. Papillary (80%) – low grade, slow growing with no capsule. Often multiple (intrathyroid metastasis)
         1. Histology – papillae, psammoma bodies; nuclear clefts, clearing, inclusions and overlapping
         2. Spread to neck nodes, lungs
         3. 10 year survival 98%
      ii. Follicular (15%) – some overtly, some microscopically invasive
         1. Histology – follicles, nuclear features not useful for diagnosis
         2. Spread via blood to bones, lungs
         3. 10 year survival 92%
      iii. Medullary (5%) – parafollicular (C) cells so calcitonin can be used as a marker. 20% familial, including MEN II A, B
         1. Histology – oval tumour cells, amyloid around
         2. Spread via blood
         3. 5 year survival 50%
      iv. Anaplastic (<5%) – older patients, most with multinodular goitre or another tumour
         1. Histology – mainly undifferentiated spindle cells
         2. Most dead within a year due to local invasion
   c. Lymphomas, connective tissue and metastatic tumours

**Parathyroid glands**

1. **Hypoparathyroidism** (rare) – iatrogenic, idiopathic, autoimmune
2. **Hyperparathyroidism**
   a. Primary – 85% adenoma, 10% hyperplasia, <5% carcinoma (MEN syndrome)
   b. Secondary due to low Ca^{2+} – renal failure, vitamin D deficiency

**Adrenal cortex**

1. **Cushing’s syndrome**
   a. Exogenous (iatrogenic)
   b. Endogenous – ACTH-secreting pituitary tumour (Cushing’s disease), adrenal cortical carcinoma/adenoma, paraneoplastic ACTH secretion
2. **Hyperaldosteronism**
   a. Primary – Conn’s syndrome (80%) – adenoma, hypertension, hypokalaemia
b. Secondary (↑renin) – heart failure, renal artery stenosis, hypoalbuminaemia

3. Adrenal insufficiency
   a. Primary (hyperpigmentation)
      i. Acute – crisis, withdrawal of corticosteroid therapy, haemorrhage
      ii. Chronic – Addison’s disease (autoimmune), inflammation, metastasis
   b. Secondary (no hyperpigmentation)
      i. Can be part of panhypopituitarism, no decrease in mineralocorticoids

4. Androgenital syndromes

Adrenal medulla
1. Phaeochromocytoma – may be part of MEN or neurofibromatosis, secreted catecholamines, hypertension (can be episodic)
   a. 10% extra-adrenal, 10% malignant
2. Neuroblastoma – juvenile tumour of primitive cells

Pathophysiology of Diabetes

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism caused by inadequate action of insulin (production or tissue action). It affects 2% of the adult population with an increasing prevalence with age. It also affects 0.2% of the population under 20 yrs.

1. Classification of diabetes
   a. Primary (idiopathic)
      i. Insulin-dependent (type 1) diabetes mellitus
      ii. Non-insulin dependent (type 2) diabetes mellitus
         1. Impaired glucose tolerance – large vessel disease, but not diabetes-specific microvascular problems. 25% → NIDDM
         2. Gestational diabetes mellitus – increased risk of fetal (macrosomia) and maternal (preeclampsia) complications
         3. Maturity onset diabetes of the young – may be associated with molecular abnormalities of the islet form of glucokinase
   b. Secondary (1%)
      i. Pancreatic disease (e.g. pancreatitis, haemochromatosis, CF)
      ii. Hormonal abnormalities (acromegaly, Cushing’s, tumours)
      iii. Drug or chemical-induced diabetes (especially thiazide/loop diuretics)
      iv. Insulin receptor abnormalities
      v. Genetic syndromes (e.g. Prader-Willi syndrome)
      vi. Other causes

2. Aetiology
   a. Genetic – polygenetic
      i. Identical twin concordance in Type 1 (50%) and Type 2 (90%)
      ii. HLA associations in Type 1 (DR3, DR4)
   b. Environment – obesity, pregnancy, stress (including infections – antagonism of insulin by inflammatory mediators)

Clinical presentation:

1. Clinical features:
   a. Uncomplicated diabetes – polyuria, polydipsia, polyphagia, weight loss
   b. Complications
      i. Acute:
         1. Ketoacidosis – lethargy, drowsiness, coma, smell of acetone
         2. Hypoglycaemia (on treatment) – drowsiness, coma
         3. Hyperosmolar non-ketotic coma – type 2
      ii. Chronic – bacterial infections, neuropathy, gangrene

2. Pathogenesis:
   a. Pathogenesis of the diabetic state:
      i. General – increased blood glucose
         1. Breakdown of fat → fatty acids and glycerol → ketone bodies
         2. Protein broken down for energy
      ii. Type 1 – decreased β cells (viruses, HLA type, autoimmune)
      iii. Type 2 – abnormal β cell function, poor insulin sensitivity (amyloid?)
b. Pathogenesis of complications (infections, vascular lesions, neuropathy):
   i. Protein glycosylation → advanced glycosylation end-products → trapping of lipids in arteries, malfunction of cell receptors
      1. Aminoguanidine prevents AGE in clinical trials
   ii. Increased intracellular glucose → sorbitol (neuropathy, cataracts)
   iii. Hyperlipidaemia → increased atheroma

3. Complications:
   a. Cardiovascular system
      i. MI (5x increased risk)
      ii. Mesenteric thrombosis
      iii. Gangrene of legs
   b. Kidneys
      i. Glomerular lesions
      ii. Vascular lesions (renal artery atherosclerosis, hyaline atherosclerosis)
      iii. Pyelonephritis (infections)
   c. Eyes – 25% of acquired blindness in the USA
      i. Retinopathy
         1. Non-proliferative – haemorrhages, exudates, venous dilatation, microaneurysms
         2. Proliferative - vascularisation, fibrosis, macular/vitreous haemorrhage
      ii. Cataracts
      iii. Glaucoma
   d. Nervous system
      i. Peripheral neuropathy – sensory, autonomic
      ii. Brain- infarcts, haemorrhage, generalised neuronal degeneration

GENITOURINARY PATHOLOGY

Kidneys – Vascular and Tubulointerstitial Diseases

The “Zwisus Christ, I can’t believe anyone would classify disease according to the physician who treats it” system for classifying renal disease:

1. Generalised parenchymal diseases
   a. Glomerular
      i. Congenital – congenital nephrotic, Alport’s syndrome
      ii. Immune/Inflammatory – glomerulonephritis, amyloidosis
      iii. Metabolic – diabetic glomerulosclerosis (diffuse and nodular)
   b. Tubulointerstitial
      i. Tubular transport abnormalities – congenital, acquired
      ii. Acute tubular necrosis – vascular, toxic
      iii. Interstitial nephritis – drugs, infection, urate, radiation, myeloma
   c. Vascular
      i. Hypertensive kidney disease – benign/malignant nephrosclerosis
      ii. Renal artery stenosis
      iii. Vasculitis
      iv. Disseminated intravascular coagulation

2. Acquired collecting system abnormalities
   a. Acute pyelonephritis
   b. Chronic pyelonephritis – reflux/obstructive nephropathy
   c. Nephrolithiasis, hydronephrosis

3. Focal lesions
   a. Infarcts, abscesses, scars, cysts (simple, parasitic, neoplastic)
   b. Tumours – Wilm’s (nephroblastoma), RCC, TCC

4. Congenital structural lesions
   a. Agenesis and hypoplasia
   b. Anomalous position, ureters, vessels
   c. Cystic diseases – renal dysplasia, polycystic kidney, medullary cystic disease

5. End stage kidney
Clinical features of generalised parenchymal diseases – note that glomerular filtration rate (total amount of fluid filtered through all functional glomeruli) is the most important measure of renal function. Under normal conditions more than 98% of the glomerular filtrate is resorbed by the tubular system, so urine output does not reflect GFR.

1. **Blocked filter (renal insufficiency)** – note pre-renal and post-renal causes of failure
   a. Arterial blockage
      i. Main renal artery results → decreased blood flow to glomeruli and decreased GFR – if severe and chronic, this leads to tubular atrophy
         1. Bilateral – obstruction results in decreased renal function
         2. Unilateral – ischaemia of JGA releases renin (→ RAAS) causing hypertensive changes in the non-affected kidney
      ii. Small vessel diseases are nearly always diffuse and bilateral
   b. Glomerular blockage
      i. Reversible blockage occurs in types of acute glomerulonephritis
         1. Mechanisms – endothelial swelling, cell proliferation, inflammatory exudates, thrombosis, crescent formation
      ii. Permanent blockage – glomerulosclerosis
         1. Organisation of acute inflammatory/thrombotic lesions
         2. Accumulation of material in mesangium/GBM – nodular diabetic glomerulosclerosis, amyloidosis
   c. Tubulointerstitial blockage
      i. Reversible blockage – acute tubular necrosis, acute interstitial nephritis, intratubular precipitates (uric acid, light chains in myeloma)
      ii. Permanent blockage – tubular atrophy (after interstitial fibrosis)
         1. Tubular atrophy, interstitial fibrosis and glomerulosclerosis are hallmarks of permanent parenchymal damage

2. **Leaky filter**
   a. Haematuria and proteinuria
      i. Haematuria does not necessarily imply glomerular disease except in younger patients or where other manifestations are present
         1. Leakage of RBCs from glomeruli indicates a lesion in the GBM sufficient to allow RBCs to pass through
      ii. Proteinuria almost always implies diffuse parenchymal disease
         1. Normally the glomerulus passes a small amount of protein which is resorbed by the proximal tubule
         2. Tubulointerstitial diseases fail to resorb this (<1g/day)
         3. Immunofluorescence shows extensive loss of heparin sulphate proteoglycan (polyanion which repels albumin)
      iii. Haematuria and proteinuria correlate fairly closely with inflammatory glomerular diseases and non-inflammatory glomerular diseases – a combination of the two is associated with renal insufficiency
   b. Failure of tubular absorption
      i. Generally causes little human disease, but may be important in mediating polyuria with salt wasting and fluid depletion
ii. Causes include:
1. Congenital tubular transport abnormalities
2. Recovery phase of acute tubular necrosis – regenerated tubular cells are immature and incapable of proper function
3. Chronic failure with interstitial fibrosis obstructing movement of fluid and decreasing the number of functional nephrons

3. Blockage and leakage occurring together
   a. Acute nephritic syndrome includes renal insufficiency plus haematuria with varying degrees of proteinuria.
      i. This may be due to partial obstruction of glomeruli, with leakage of blood/protein from inflammatory activity
      ii. Proteinuria may be sufficient to cause the nephrotic syndrome
   b. Renal failure with polyuria cannot be explained on the basis of each nephron responding the same way – while a large number of nephrons have been inactivated, there must be other nephrons that are excessively leaky

• Kidneys – Glomerular Diseases

Nephrotic syndrome is characterised by proteinuria, hypoalbuminaemia, oedema, lipuria, hyperlipidaemia and hypercoagulability. The key feature is proteinuria, which results from altered permeability to the glomerular filtration barrier (GBM and podocytes). The other manifestations are secondary to urine protein loss and can occur with lesser degrees of proteinuria, or may be absent in patients with massive proteinuria.

Acute nephritic syndrome is characterised by sudden onset acute renal failure with oligouria. Extracellular fluid volume expansion, oedema and hypertension develop due to impaired GFR and enhanced tubular reabsorption of salt and water. Glomerular capillary wall damage also leads to characteristic urinalysis – RBC casts, dysmorphic RBCs, leukocytes and subnephrotic proteinuria.

Pathogenesis of glomerular injury:
1. Immune
   a. Antibody to GBM component – anti-GBM disease
   b. Trapping antigen, fixing antibody – membranous GN
   c. Trapping immune complexes – SLE
   d. Trapping antibody complexes – IgA nephropathy
   e. T-cell or cytokine mediated – minimal change disease
2. Non-immune
   a. Congenital abnormality in GBM components – Alport’s nephropathy
   b. Metabolic change in GBM components – diabetes
   c. Trapping abnormal materials – amyloidosis
   d. Hyperfiltration injury – secondary FSGS

Progressive renal injury:
1. Continued disease activity – persistence of immune complexes e.g. SLE
2. Hypertension – worsens itself, leading to more damage to vessels
3. Hyperfiltration injury – nephrons cannot regenerate, so functional nephrons have an increase GFR but eventually become leaky, deranged or blocked. This is known as focal segmental glomerulosclerosis.
   a. Greater chance of getting renal failure if you have a nephrectomy
   b. ACE inhibitors can save renal function, as decreased efferent pressure → decreased glomerular pressure → decreased GFR

• Genitourinary Pathology

Cervix – the majority of cancers of the cervix are preceded by a precancerous abnormality. The terminology has changed over time – dysplasia/carcinoma in situ, cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SILs – Bethesda system).
1. Not all precancerous lesions progress to cancer as some regress, however the risk of progression increases with the severity of the change.
2. Human Papilloma Virus infection is associated with precancerous lesions, and this has been identified as the primary risk factor for development of cervical cancer
   a. ~100 HPV types are known, divided into low, high and intermediate risk
      i. Low risk found in condylomas (genital warts) – types 6, 1, 42 + 44
      ii. High risk found in high grade lesions and cancer – 16, 18
   b. Pathogenesis is postulated to be:
      i. Sexual activity → HPV exposure
      ii. Squamous intraepithelial lesion →
         1. High risk type 16 + 18 → high grade change, invasive cancer
         2. Low risk type 6 + 11 → regress (rarely progresses)
   c. Other risk factors include early age of first intercourse, multiple sexual partners, smoking and other immunosuppression
3. Cervical intraepithelial neoplasia is graded histologically on an assessment of epithelial maturation, nuclear atypia and mitotic activity. HPV effects (known as koilocytosis) may be superimposed
   a. A significant proportion of women with high-grade untreated CIN will develop cancer (rate of progression 5-15 years)
   b. Treatment – remove all abnormal epithelium (loop excision, laser treatment)
4. Cancer of the cervix
   a. Peak age 40-60yrs, but can span teenage to 80yrs. Majority are squamous carcinomas (85%) – adenocarcinomas and mixed carcinomas less common
   b. Early stage cancers may be asymptomatic
      i. Larger tumours may present with abnormal vaginal bleeding (post-coital), spotting or discharge.
      ii. Smaller tumours may not be visible and hard to see on colposcopy. Some invasive cancers require pathological examination.
      iii. Advanced tumours may be exophytic or ulcerating
   c. Extension occurs initially by local infiltration, but advanced tumours can involve local and distant lymph nodes and organs (lung, bones)
   d. Staging (note the smaller the tumour, the better the prognosis):
      i. Stage 0 – CIN 3
      ii. Stage I (a/b) – cancer is confined to the cervix
      iii. Stage II – carcinoma extends beyond cervix (not pelvic wall or lower vagina)
      iv. Stage III – tumour involves pelvic side wall or lower 1/3 of vagina
      v. Stage IV – carcinoma extends past pelvis or involves bowel/bladder mucosa

Vulva and vagina:
1. Precursor lesions in the vulva and vagina can lead to invasive cancers if untreated. They are classified in the same way as the cervix, and HPV is also implicated.
2. Women who develop an in situ or invasive lesion of the lower genital tract has an increased chance of developing a subsequent lesion in that area
   a. A group of vulvar carcinomas can develop on the basis of skin conditions such as lichen sclerosis (unrelated to HPV and other risk factors)
3. Carcinoma of the vulva is rare (1% of all female and 4% of genital tract malignancies)
   a. Most are squamous carcinomas – patients may be asymptomatic or present with a painless ulcer or nodule
   b. Treatment and prognosis varies with size, but metastasis to inguinal and pelvic lymph nodes occurs relatively early due to the vulva’s rich blood supply

Endometrium:
1. Endometrial hyperplasia – oestrogen in the normal menstrual cycle causes balanced proliferation of both endometrial glands and the stroma
   a. Hyperplasia occurs with abnormally high, prolonged periods of oestrogen stimulation with diminution or absence of progesterone – hence it tends to occur around menopause or in anovulation in young women (PCOS)
   b. Simple hyperplasia is a diffuse response to prolonged unopposed oestrogen. Glands are of varying size and shape – some cystically dilated (‘Swiss cheese’). There is no change in gland to stroma ratio.
c. Complex hyperplasia is usually focal and results in an increased number and size of
glands (increase in gland to stroma ratio)
d. Atypical hyperplasia shows a simple or complex pattern, but the epithelium lining the
glands also shows cytologic atypia – this is strongly associated with adenocarcinoma
of the endometrium

2. Carcinoma of the endometrium
   a. Aetiology – unopposed oestrogen stimulation is a risk factor, though other factors
      (genetic, environmental) are also implicated
      i. Classically patients are diabetic, obese, hypertensive and are infertile
      ii. 250 cases in NZ/year – 75% in postmenopausal women
   b. Presenting symptoms vary
      i. Postmenopausal bleeding is common in the older group, and abnormal
         uterine bleeding in younger patients
      ii. Diagnosis is made by endometrial sampling (pipelle biopsy) or curettage (with
         or without hysteroscopy)
   c. Staging – note that most cancers are endometrioid in type
      i. Stage I – carcinoma is confined to the body of the uterus
      ii. Stage II – carcinoma has extended to the cervix
      iii. Stage III – extended beyond the uterus, but not outside the pelvis
      iv. Stage IV – carcinoma exists outside the pelvis
   d. Most patients (80%) present with Stage I disease and the prognosis is 90% - five year
      survival drops to 10-20% for patients who are stage III/IV
   e. Treatment is mainly surgical with radiation/chemotherapy as adjuvant therapy

Gynaecological Pathology 2

Tumours of the ovary – ~80% are benign and likelihood of malignancy increases with age

1. Primary tumours:
   a. Epithelial tumours represent 60% of ovarian neoplasms
      i. Categorised into 3 major types (serous, mucinous and endometrioid), forming
         a spectrum of abnormality ranging from benign to malignant:
         1. Serous and mucinous cystadenomas
         2. Serous and mucinous tumours of low malignant potential
         3. Carcinomas
      ii. 75% of serous tumours are benign or borderline, while 80-85% of mucinous
          tumours are benign or borderline
      iii. Endometrioid tumours are generally carcinomas and around 15% are found
           in association with endometriosis
      iv. Primary treatment is surgical to determine staging (determines treatment)
          and ‘de-bulk’ tumour, followed by chemotherapy
   b. Germ cell tumours:
      i. Benign cystic teratoma (dermoid cyst)
         1. 90% found in women of reproductive age, 10-15% bilateral
         2. Treatment is surgical attempting to conserve ovarian tissue
      ii. Immature teratoma, endodermal sinus tumours and dysgerminoma
         1. Malignant germ cell tumours found in children and young adults
            similar to tumours found in the testis
         2. Treatment is surgical and by chemotherapy
   c. Sex cord stroma tumours:
      i. Arise from the ovarian stroma – some are hormone-producing resulting in
         oestrogenic or androgenic clinical manifestations
      ii. Demonstrate a range of malignant behaviours

2. Secondary tumours:
   a. Metastatic tumours are most commonly from other sites in the genital tract, though
      10% are from distant sites (breast or GI tract including colon/stomach)
   b. Krukenberg tumours are metastatic tumours (usually from the stomach) with a
      characteristic histological appearance

3. Staging – FIGO staging system
   a. Stage I – growth limited to the ovaries
   b. Stage II – growth involving one or both ovaries with pelvic extension
c. Stage III – growth involving one or both ovaries with intraperitoneal metastases outside the pelvis and/or positive retroperitoneal nodes
d. Stage IV – growth involving one or both ovaries with distant metastases
e. Special category – unexplored cases thought to be ovarian carcinoma

4. Tumour markers – CA-125, CEA (carcinoembryonic antigen), α-fetoprotein, β-HCG

Disorders of early pregnancy:
1. Abortion (definition <20wks) is the result of 10-15% of recognised early pregnancies, though wastage may be up to 40% (occurring before the first missed period)
   a. The most common abnormality in early abortion is an abnormal karyotype – most are cases of autosomal trisomy, triploidy or monosomy X
   b. Maternal causes usually occur late – developmental abnormalities of the female genital tract, cervical incompetence, infection or maternal disease
   c. In approximately 1/3 the fetus and chorionic villi of the placenta are normal
   d. In the remaining 2/3 the fetus is defective and chorionic villi are hydropic – this is the ‘hydropic’ abortion and is the usual finding in 1st trimester abortions

2. Gestational trophoblastic diseases are characterised by proliferation of trophoblast, and can be monitored by measuring serum levels of HCG
   a. Hydatidiform mole – characterised by cystic swelling of chorionic villi accompanied by proliferation of trophoblast. Two types are recognised:
      i. Partial – generally triploid, 69XXY and results from fertilisation of a single egg by 2 sperm (dispermy)
         1. Carries a 5% risk of persistent trophoblastic disease
      ii. Complete – generally diploid, 44XX and results from fertilisation of an ‘empty’ egg (one that has lost its genetic complement)
         1. Carries a 10-15% risk of persistent trophoblastic disease
   b. Choriocarcinoma – highly malignant tumour of trophoblast
      i. 50% follow a molar pregnancy while the remainder follow an abortion or normal pregnancy
      ii. Most arise in the uterus, but they metastasise widely to many sites including lungs, liver and brain
      iii. Very sensitive to chemotherapy, low risk cases have 100% cure rate
   c. Others – invasive hydatidiform mole, placental site trophoblastic tumour, miscellaneous and unclassified trophoblastic lesions

CNS PATHOLOGY

Degenerative brain diseases usually occur in the elderly – there are links with ageing, and both processes have similar morphological changes. They often present with dementia and movement disorders, and are termed degenerative until the underlying pathology is identified (allowing reclassification).

The ageing brain
1. Gross changes
   a. Decreased brain volume with gyral atrophy and ventricular enlargement
   b. Decreased weight (2% per decade after the age of 50)
2. Microscopic
   a. Non-specific:
      i. Minor neuron loss in regions of the cerebral cortex and basal ganglia
      ii. Neuronal atrophy, specifically in large pyramidal neurones
      iii. Expansion of dendritic trees and synaptic plates in surviving neurons to compensate for losses in neural networks
   b. Specific
      i. Amyloid (senile, argyrophilic) plaques form when amyloid precursor protein is modified to form β-pleated sheets in the stroma of grey matter between neurons and glial cells
         1. Diffuse plaques consist of a deposit of soluble amyloid alone
2. Neuritic plaques have a dense core of compacted insoluble amyloid encasing swollen axon endings
   ii. Alzheimer’s neurofibrillary degeneration is seen when abnormal fibrils appear in the cytoplasm of neurons.
   1. Neurofibrillary tangles – neuronal body
      a. Form with age and some brain disease – normally they appear in the hippocampal cortex after age 50
   2. Neuropil threads – axons and dendrites
   3. Neurites – axon endings
      a. Neurites in compact amyloid core \(\rightarrow\) neuritic plaque

Dementia is defined as “a sustained decline in memory, judgement and thinking without a clouding of consciousness”. It is associated with decline in emotional control/motivation and behavioural changes
1. Incidence increases steeply after age 75
2. Common causes include Alzheimer’s disease (60-75%), vascular disease (15%), cortical Lewy body disease (5%) or a combination
3. Differential diagnosis
   a. 1° cerebral cortical degeneration – AD, Pick’s, cortical Lewy body disease
   b. 1° subcortical degeneration – Parkinson’s, multiple systems atrophy, Huntington’s, progressive supranuclear palsy
   c. Cerebrovascular disease
   d. Infection/inflammation (e.g. AIDS)
   e. Prion disease
   f. Toxic and metabolic (alcoholism, hypothyroidism, hypocalcaemia)
   g. Tumours – multifocal
   h. Post-traumatic

Alzheimer’s disease is characterised by generalised brain atrophy (especially temporal).
1. Gross changes
   a. Atrophy – medial temporal and association cortex
   b. Ventricular enlargement
   c. Basal ganglia usually normal
2. Diagnosis is confirmed microscopically – neuritic plaques and neurofibrillary tangles must occur in significantly high numbers in the cortex covering the convex surfaces of the frontal, temporal and posterior parietal lobes.
   a. The state of the hippocampus is irrelevant to diagnosis, but it may become functionally disconnected from other brain circuits
3. Pathophysiology – a major problem is explaining how the laying down of stromal amyloid plaques and the later appearance of neurofibrillary degeneration are related
   a. \(\beta\)-amyloid formation from APP (transmembrane protein)
      i. Initial proteolytic cleavage by \(\alpha >> \beta\)-secretase
      ii. In endosomes/lysosomes – carboxyl-terminal release be \(\gamma\)-secretase
      iii. Transport from cell into stroma
      iv. Aggregation and polymerisation to amyloid fibrils
   b. Substances adhering to amyloid plaques
      i. Complement components
      ii. Growth factor receptors
      iii. Apolipoproteins E and J (E allotypes modify age of onset)
   c. Biochemistry of paired helically-wound filaments
      i. Tau – microtubule-associated protein (MAP)
      ii. Ubiquitin
      iii. Cholinesterases
      iv. MAP 2 and 5
      v. \(\beta\)-amyloid
4. Genetics – familial in about 10% of cases, some dominant
   a. Causative:
      i. AD1 – mutations in the amyloidogenic region of the APP gene \(\rightarrow\) increased A4 production. Note that Down syndrome also shows similar effects due to extra chromosome 21 (AD changes after 50yrs)
ii. AD3 and AD4 code for multi-transmembrane proteins that probably act through the final common path of APP/A4 amyloid

b. Modifying:
   i. AD2 is associated with late-onset familial AD – may encode for the ApoE gene, and e4 allele is known to increase risk of sporadic AD

Pick’s disease is 1/10 as common as Alzheimer’s disease, with onset at age 45-65 (20% autosomal dominant, 80% sporadic). It is characterised by circumscribed and severe (knife-edge) atrophy of frontal and temporal lobes. Microscopically there are Pick’s cells (pale ballooned neurones) and Pick bodies (eosinophilic tau-positive neuronal inclusion bodies).

Movement disorders and systems degenerations

1. Main symptom groups
   a. Akinesic/rigid – Parkinsonism, stiff man syndrome
   b. Hyperkinetic – chorea, myoclonia, dystonia, tics
   c. Ataxic – spinocerebellar degeneration
   d. Motor neuron disease – upper/lower/combined neuron types

2. Parkinsonism is characterised by combined rigidity and bradykinesia, with or without resting tremor. Causes include idiopathic, multiple systems atrophy, progressive supranuclear palsy and others.
   a. Idiopathic Parkinson’s disease
      i. Cerebral hemispheres not atrophic
      ii. Decrease in melanin in the substantia nigra, locus caeruleus (pons), dorsal vagal nucleus (medulla) and autonomic ganglion cells
      iii. Lewy bodies in neurones – laminated eosinophilic bodies stain for ubiquitin
   b. Other Lewy body diseases – neuronal loss and Lewy bodies in other areas may cause prominent symptoms that overshadow Parkinsonism
      i. Autonomic failure – Lewy bodies in sympathetic neurones
      ii. Dysphagia – Lewy bodies in sympathetic neurones
      iii. Dementia – 20% of those over 70 with Parkinson’s develop dementia
         1. Alzheimer changes to cerebral cortex
         2. Lewy bodies diffusely through the cortex
         3. Combination of the two

3. Huntington’s disease is characterised by chorea – non-rhythmic rapid involuntary movements
   a. Autosomal dominant resulting in chorea, rigidity and mental deterioration
   b. Mid or later life onset
   c. Expansion of the CAG trinucleotide repeat in the Huntingtin gene on chromosome 4 (normal 9-37, disease 37-86)
   d. Mild to marked cerebral atrophy and decreased brain weight
   e. Atrophy of caudate nucleus, followed by putamen and globus pallidus
   f. Neurones show simple atrophy and disappear, while astrocytes show reactive proliferation

• Tumours of the Nervous System

Special characteristics of CNS tumours:
1. The anatomic site may have lethal consequences irrespective of histological grade (e.g. a benign meningioma compressing the medulla oblongata → CVS arrest)
2. A slowly growing tumour can infiltrate large regions of the brain → serious clinical deficits
3. Ability to surgically resect infiltrating glial neoplasms without compromising neurologic function is limited
4. Primary CNS tumours rarely metastasise outside of the CNS

Clinical effects of intracranial expanding lesions:
1. Lesions – haematoma, abscess, infarct, granuloma, tumour (benign, malignant)
2. Local effects – weakness, hemiparesis, seizures, ataxia, alteration of behaviour
3. General effects – raised intracranial pressure
Raised intracranial pressure – once the fontanelles have closed, the intracranial contents (brain, CSF and blood) are enclosed in a rigid bony container. Normal upper limit ICP is 20mmHg, and this can increase to about 40mmHg.

1. Stages of raised ICP
   a. Spatial compensation – as lesion expands, CSF decreases (ventricles shrink and subarachnoid space is partially obliterated). Compression of venous sinuses reduces blood volume and there is local loss of brain tissue
   b. Compensatory process ineffective – slow ICP rise. Systemic blood pressure rises (preserves cerebral perfusion pressure). Headache, drowsiness
   c. ICP rises rapidly, cerebral perfusion pressure falls. Increasing depression of consciousness, bradycardia, irregular respiration

2. Pathophysiology
   a. Compression of venous sinuses and cortical veins → cerebral oedema
   b. Headache due to distortion of dura mater and pain-sensitive blood vessels – worse on waking up, throbbing. Frontal, occipital or both.
   c. Papilloedema – due to venous compression
   d. Centre dysfunction:
      i. Vomiting – compression/ischaemia of vomiting centre in medulla
      ii. Increased arterial pressure, bradycardia – cardiac centre dysfunction
      iii. Irregular respiration – dysfunction of respiratory centre
   e. Nerve compression:
      i. 6th nerve palsy – compression against petrous temporal bone
      ii. 3rd nerve palsy – compression against tentorial edge
      iii. Bilateral extensor plantar reflex – ventricular dilation
      iv. Unilateral extensor plantar reflex – compression of cerebral peduncle against tentorial edge

Structural changed resulting from brain tumours:

1. Focal changes
   a. Changes within tumour mass – rapid increase in size mediated by increased rate of growth, haemorrhage or cyst formation
   b. Changes involving adjacent neural tissue – compression/displacement, destruction/invasion, reactive gliosis, ischaemia and necrosis

2. Regional changes
   a. Oedema – venous stasis, arteriolar vasodilation, high capillary permeability
   b. Disturbances of CSF circulation → hydrocephalus
   c. Gyri flattened, sulci obliterated
   d. Cerebral herniations

3. Supratentorial tumours
   a. Lateral shift of midline structures, ipsilateral ventricle shrinks, contralateral ventricle dilates
   b. Subfalcine cingulate, uncus and parahippocampal gyri herniation
   c. Midbrain narrowed in transverse axis
   d. Contralateral cerebral peduncle, ipsilateral 3rd nerve and posterior cerebral artery compression against tentorium (peduncle → Kernohan notch)
   e. Posterior inferior displacement of mamillary bodies
   f. Haemorrhage and infarction in midbrain and pons
   g. Cerebellar tonsil herniation (foramen magnum), medulla oblongata compression

4. Infratentorial tumours
   a. Hydrocephalus
   b. Cerebral hemispheres enlarge – gyri flattened, sulci obliterated
   c. Cerebellar tonsillar herniation
   d. Superior cerebellar herniation

There is a list of tumours on the handout, but who the fuck really cares?
**Prostate Cancer**

The normal prostate weights around 20g (up to 3x this in prostatic hyperplasia) and is a conglomerate of glands contributing 15-30% of seminal fluid. It is divided into four zones:

1. Transition zone – 5% of gland volume
   - BPH zone (benign prostatic hypertrophy)
   - Minority of cancers arise here
2. Central zone – 25% glandular tissue, surrounds ejaculatory ducts
3. Peripheral zone – 70% glandular tissue
   - Majority of cancers arise here
   - Also zone of prostatitis
4. Anterior fibromuscular zone
   - Sphincter control zone

**Prostatitis**

1. Bacterial or abacterial (often not identified) → antibiotics
2. Acute inflammation within glands and surrounding stroma

**Benign prostatic hypertrophy** – nodular hyperplasia

1. 70% men by 60yrs, 90% by 70yrs – not a pre-malignant condition
2. **Morphology**
   - Gland weighs 60-200g – enlargement occurs in the transition zone
   - Nodules of glands and stroma, may infarct
3. **Aetiology**
   - DTH (dihydrotestosterone) stimulates proliferation of glands/stroma
   - Increased oestrogen levels in older men increases number of androgen receptors – hence prostate more susceptible to DTH action
4. **Clinical**
   - Urethral compression – frequency, difficulty starting/stopping, dysuria
   - Urinary retention – bladder/renal infections
   - Treatment – TURP (transurethral resection of prostate)

**Prostate adenocarcinoma** is the most common cancer in men (10% cancer mortality) and the 2nd leading cause of cancer death. It is increasing in incidence (possibly due to better public awareness) and increases in incidence after the age of 50.

1. **Aetiology**
   - Largely unknown
   - Suspected factors – age, rare, family history, hormone levels
2. **Diagnosis** – no specific symptoms except late obstruction or metastatic disease
   - DRE (digital rectal exam) – may be a firm area/nodule
   - TRUS (transrectal or transurethral ultrasound biopsy)
     i. Core biopsies
     ii. Prostatic chips
   - Serum PSA (prostatic specific antigen)
   - Microscopically:
     i. Closely packed glands with an infiltrative pattern
     ii. Enlarged dark nuclei, prominent nucleoli
     iii. Absent basal cell layer (HMW cytokeratin stain)
     iv. Neural or vascular invasion
3. **Grade** – Gleason Grading System (1-5)
   - Examine architecture of invasive glands and compare to Gleason standards,
   - Add the highest number to the next highest to get a grade (lower is better)
4. **Staging**
   - T1 – clinically inapparent
   - T2 – palpable within the prostate
   - T3 – extends through capsule
   - T4 – invades adjacent structures other than seminal vesicles
5. **Management** depends on grade and stage of tumour
a. No treatment
b. Radical – prostatectomy (with/without nerves), radiotherapy
c. Palliative care – anti-androgen (castration, drugs), radiotherapy (local/mets)

6. Progression
   a. Local spread – extraprostatic spread, seminal vesicles, other pelvic organs
   b. Lymph nodes – pelvic, aortic (may block ureters)
   c. Distant metastases – especially vertebral bodies

Prostatic intraepithelial neoplasia is presumed to be the premalignant condition for prostatic adenocarcinoma and is often found in association with cancer in the peripheral zone.

1. Histology
   a. Nuclear enlargement and nuclei
   b. Piling up of nuclei (stratification)
   c. Basal cells still present – hence an in situ condition (non-invasive)

2. In men with high grade PIN, likelihood of finding cancer in later biopsy is 33-50%

• Breast Cancer

The breast consists of modified sweat glands in lobes/lobules, separated by adipose and connective tissue. Ducts drain each lobule into a lactiferous duct that drains each lobe. These are lined with epithelium over myoepithelium – neoplasms can arise from epithelium (most), lobules or stroma

1. Incidence – rare before 20, increases to peak around the age of menopause. Breast cancer is the most common malignancy in women (18% of cancer mortality) – 1% occur in men.
   a. Geographic influence
      i. Highest – England and Wales
      ii. Lowest – Thailand, Korean Republic, China
   b. Risk factors
      i. Genetic – family history, especially 1st degree relatives increases risk 3x, 9x if the relative is premenopausal with bilateral cancer (50% risk)
         1. BRCA1/2 genes associated with early onset (1% aetiology)
      ii. Menstrual/reproductive history – early menarche, late menopause
         1. Nulliparous women have 2x risk of women who have had their first child by the age of 20
      iii. Exogenous reproductive steroid hormones – OCP/HRT controversial
   iv. Diet/nutrition – obesity, dietary fat, alcohol intake

2. Classification of breast tumours
   a. Benign – fibroid adenoma, tubular adenoma, benign phyllodes tumour, intraductal papilloma, nipple adenoma
   b. Invasive – infiltrating ductal carcinoma (65%), infiltrating lobular carcinoma, Paget’s disease of the nipple, colloid carcinoma, tubular carcinoma, cribriform carcinoma, malignant phyllodes tumour
   c. Non-invasive – ductal carcinoma in situ, lobular carcinoma in situ, non-invasive papillary carcinoma

3. Infiltrating ductal carcinoma is the most common breast cancer (65%). Diagnosis is generally on the basis of exclusion of other tumour types:
   a. Macroscopic
      i. Stellate or well-circumscribed with invasive or pushing margins
   b. Microscopic
      i. Pushing or infiltrative margin
      ii. Irregular rounded clumps, single, and cords of tumour cells
      iii. Poorly formed tubules and glandular lumens may be present
      iv. Highly variable – may be necrosis, inflammation

Clinical aspects:
1. Detection
   a. Screening – self-examination, clinical examination, mammography
   b. Diagnosis – FNA, needle core biopsy, excision biopsy, frozen section
2. **Grading** – important prognostic indicator, but not used in staging
   a. Graded out of 3 (slight, moderate, marked) for:
      i. Degree of tubule formation
      ii. Regulation of size, shape, staining of nuclei (pleiomorphic)
      iii. Number of mitoses
   b. Add scores → grading (I, II, III) → indication of 5 year risk
3. **Staging** – used to stratify patients for therapy, forms the basis of prognostic assessment and is needed for comparison in research
   a. Based on size and spread (lymphatics → axillary nodes → lung, bone, liver)
   b. May involve any combination of examination, mammography and scans
   c. Note size, mobility, skin changes of primary, lymph nodes and metastases
   d. Pathological staging requires tissue examination from primary, lymph nodes and other parts – TNM system – primary tumour, lymph nodes, metastases
4. **Other prognostic indicators**
   a. Axillary lymph node metastases – most important prognostic indicator
   b. Tumour cells:
      i. Hormone receptor status (positive good) – treatment with tamoxifen
      ii. Cytoplasmic cathepsin D increases risk of metastases
   c. Tumour size – correlates with metastases, though behaviour important
   d. Bilaterality – breast carcinomas increases risk in the other breast (1%/year)
   e. Vascular invasion, ductal carcinoma in situ, margins of resection specimen
5. **Treatment**
   a. Lumpectomy – breast conserving
   b. Mastectomy
   c. Radiation and/or chemotherapy
   d. Tamoxifen – anti-oestrogen → growth inhibition, can be used as prophylactic

### Malignant Melanoma

The incidence and mortality of **malignant melanoma** is on the increase. It is characterised by intense episodic exposure (squamous cell carcinoma and basal cell carcinoma result from cumulative sun exposure) and the benign lesion is the melanocytic naevus.

1. **Clinical risk factors**
   a. Family or personal history (including occupational)
   b. Large number of moles, clinically atypical moles
   c. Sunburn in childhood or adolescence, acute/intermittent exposure to sunlight
   d. Light skin, eyes, hair (North European ancestry)
2. **Clinical warning signs**
   a. Asymmetry or changes in shape, colour, size
   b. Appearance of a new lesion
   c. Borders notched or irregular
   d. Colour variable (blue, white, grey, pink, red)
   e. Diameter exceeds 6mm

### Melanocytic naevi:

1. **Common acquired melanocytic naevi** – pigmented skin lesion composed of benign proliferation of melanocytes in epidermis or dermis following UV exposure
   a. Can lead to melanoma or tan skin tags in old age
   b. Flat or slightly elevated, oval, regular outline (sharply demarcated)
   c. Pathology – melanocytes form nests in rete → dermis → small clusters
      i. Lentigo – basal layer of epidermis
      ii. Junctional naevus – tips of rete ridges
      iii. Compound naevus – nests in epidermis with cells in dermis
      iv. Dermal naevus – intraepidermal melanocytes with cessed growth
      v. Skin tag – dermal component → neuromesenchyme
2. **Melanocytic naevi with dysplasia**
   a. Abnormal growth patterns
   b. Cytological abnormality of melanocytes
   c. Lymphocytic infiltrate with connective tissue changes
   d. Precede most malignant melanomas
Melanoma

1. **Superficial spreading melanoma** (radial growth phase)
   a. Early malignancy - slightly elevated, palpable border, haphazard colour
   b. Large epithelioid melanocytes in nests and single cells throughout dermis
   c. May be restricted to epithelium (in situ) or extend focally into the dermis
   d. Lymphocytes, growth in all directions, no dermal mitoses/metastases

2. **Vertical growth phase melanoma**
   a. Melanocytes have focal mitotic activity → spherical nodules
   b. Cells may have little or no pigment (differs from radial growth phase)
   c. Dominant site of growth → dermis, extends to lower half of reticular dermis
   d. Cellular immune response may be absent, may or may not metastasise

3. **Metastatic melanoma**
   a. Arises from melanocytes of the vertical growth phase
   b. Spread is to regional lymph nodes, but may also spread via blood

Types of malignant melanoma

1. **Nodular melanoma** - all malignant features expressed in the initial lesion
   a. Circumscribed elevated nodule – initially spheroidal (no radial growth phase)
   b. One or more nodules of cells grow in expansile fashion in dermis

2. **Lentigo maligna melanoma** - large pigmented macule on sun-damaged skin
   a. Fair, elderly Caucasians on exposed body parts
   b. Flat, irregular brown/black patch on face or hands
   c. Cells of radial growth phase predominantly in basal layer
   d. In vertical growth phase cells are spindle-shaped
   e. Modest lymphocyte infiltrate and solar degeneration of connective tissue

3. **Acral lentiginous melanoma**
   a. Dark-skinned people on soles, palms and nail beds
   b. Irregular brown/black patch in radial phase – confined to basal epidermis
   c. Vertical phase similar to lentigo maligna melanoma
   d. Brisk lymphocyte response

4. **Variants** – desmoplastic (spindle cell, neurotropic), amelanotic

Clinical aspects:

1. **Clark’s level**
   a. Radial growth phase
      i. In situ – in epidermis only
      ii. Level 2 – in papillary dermis
   b. Vertical growth phase (potentially metastatic)
      i. Level 3 – impinges on reticular dermis
      ii. Level 4 – invade between collagen bundles of reticular dermis

2. **Staging**
   a. I – 1° melanoma less than 0.75mm thick and/or Clark level II, N0, M0
   b. II – 1° melanoma 0.76-1.50mm thick and/or Clark level III, N0, M0
      i. Ila – 1° melanoma 1.51-4.00mm thick and/or Clark level IV, N0, M0
      ii. Iib – 1° melanoma >4.00mm thick and/or Clark level V, N0, M0
   c. III – Regional lymph nodes and/or in-transit metastasis (N1/2, M0)
   d. IV – Systemic metastasis (any N, M1)

3. **Prognostic features**
   a. Thickness, ulceration, excision margins, regression
   b. Mitotic activity, lymphocytic activity
   c. Type (SS and LM better), site (BANS worse), sex (M worse)
   d. Clark’s level

4. **Metastases**
   a. Lymph nodes, skin, lung, brain, liver, other

5. **Treatment**
   a. Excision
   b. Prophylactic lymph node resection is usually not done
   c. Spread → palliation
Carcinoma of the lung

90-95% of all primary lung tumours are carcinomas, and they are the leading cause of cancer deaths in men and women. They account for about 1/3 of all cancer deaths, and 98% of cases occur after the age of 40.

Aetiology

1. Smoking is the major risk factor in 75% of cases and is increasing in the 3rd world
   a. Risk of death from bronchial carcinoma increases by a factor equal to the number of cigarettes smoked per day (dose-dependent)
   b. Excess risk is approximately halved every 5 years after quitting
   c. Also \( \rightarrow \) larynx, oesophagus, kidney, pancreas and bladder cancer, and COPD, atherosclerosis, gastritis and peptic ulcers
2. Passive smoking
   a. Non-smoking woman has 24% greater risk if she lives with a smoker
   b. Also \( \rightarrow \) SIDS, croup, asthma and glue ear in children
3. Genetic factors may determine susceptibility – e.g. degree of induction of an enzyme that can activate hydrocarbons \( \rightarrow \) carcinogens
4. Ionising radiation – radon gas, uranium mines, atomic bomb survivors
5. Asbestos – more deaths from related lung cancer than mesothelioma
   a. Interaction of asbestos and smoking is multiplicative (53x population risk)
6. Other – air pollution, diffuse pulmonary scarring

Types of carcinoma – over 90% develop in mucosa of large bronchi (bronchogenic)

1. Squamous cell carcinoma (20-45%) is more common in males, 98% smokers
   a. Bronchial irritation \( \rightarrow \) inflammation \( \rightarrow \) hyperplasia \( \rightarrow \) metaplasia \( \rightarrow \) neoplasia
   b. Macroscopic – central necrotic mass, cheesy appearance
   c. Microscopic – pearls, cell keratinisation, intercellular bridging
   d. PTHrP may be released \( \rightarrow \) hypercalcaemia
2. Adenocarcinoma (25-40%) is more common in females, 75% smokers
   a. Glandular differentiation with mucin production
   b. May arise in the periphery of the lung \( \rightarrow \) scar carcinoma
   c. Bronchioalveolar carcinoma – well differentiated, better prognosis
   1. Grossly and on chest X-ray simulates pneumonia
3. Small cell carcinoma (10-25%), very strong relationship with smoking
   a. Arise from neuroendocrine cells of the bronchial tree (Kulchitsky cells)
   b. Highly malignant – grows rapidly, metastasises early (before diagnosis)
   c. Small to intermediate sized cells with little cytoplasm and numerous mitoses
   d. Most commonly gives rise to paraneoplastic syndromes
4. Large cell carcinoma (<10%)
   a. 10% are undifferentiated – most are shown to be poorly differentiated adenocarcinomas or squamous cell carcinomas on staining/EM

Location of carcinoma:

1. Central cancers present as a large, irregular expanding mass (may \( \rightarrow \) compression)
   a. Secondary lung changes occur as a result of bronchial obstruction of intercurrent infection
   b. Chest symptoms are common – cough, haemoptysis
   c. May invade \( \rightarrow \) pericardium, heart, phrenic nerve, recurrent laryngeal nerve
2. Peripheral cancers may grow silently without local symptoms until late disease
   a. Often incidental finding on X-ray, or present as generalised/metastatic effects
3. Paraneoplastic syndromes may result from ectopic production of circulating factors
   a. Elaboration of hormones – ADH (SiADH), ACTH, PTHrP
   b. Non-endocrine effects such as clubbing
4. Metastasis
   a. Lymphatic spread outside of the lung may be extensive (hilar, mediastinal)
   b. Haematogenous spread is common (invasion of pulmonary vein)
   c. 90% show multiple metastases to liver, adrenal, bone, brains, kidneys
   d. Hypercalcaemia may be due to PTHrP or bone metastases
5. Staging is an indication of how far the tumour has spread
530.307 – Pathophysiology Notes

a. Dictated by size of the primary, whether it involves pleura, chest wall or mediastinum, the extent of spread to lymph nodes and distant metastases
b. TMN system – tumour (size, location, invasion), lymph nodes, metastases
c. High stage tumours have a poor outcome and are usually not offered surgery, while low stage non-small cell carcinomas have a better outcome

Clinical aspects

1. Presentation – 85% present with symptoms, while 15% are incidental findings
   a. Common symptoms include cough, weight loss, dyspnoea, chest pain
   b. Other signs/symptoms include haemoptysis, hoarseness, dysphagia
   c. Distended veins and dusky oedema of head/arms due to SVC obstruction
   d. Arm pain and Horner’s syndrome due to tumour in apices (Pancoast tumour)
2. Investigation – diagnosis suspected radiologically, confirmed histologically
   a. Sputum cytology – 40% of cancers positive (particularly central)
   b. Bronchoscopy – biopsy, bronchial brushing and washing
   c. Radiologically guided biopsies
   d. Mediastinoscopy or thoracotomy
3. Treatment
   a. Small cell carcinoma (25%) - highly malignant, disseminated at diagnosis
      i. Untreated ➔ very symptomatic, median survival 3 months
      ii. Chemotherapy ➔ remission in 80%, median survival 11 months
      iii. Monitor blood count, wig (hair loss), antiemetics
   b. Non-small cell cancer (75%)
      i. Surgical resection – best chance if patient is fit and no metastasis
         1. Staging is important – TNM (tumour/nodes/metastases)
         2. Accuracy of staging depends on degree of assessment
      ii. Radiotherapy – mainly for relief of symptoms (SVC obstruction, lobar collapse, haemoptysis, chest wall pain respond well)
      iii. Chemotherapy – used for inoperable tumours (palliation)
4. Prognosis
   a. 5 year survival is 10-11% – average time to death after diagnosis is 5-6mths
   b. Outlook for surgical candidates (20-30%) better – with small tumours (<4cm), 5yr survival is up to 40% for squamous cell, 30% for adenocarcinoma
   c. Some patients are completely cured with lobectomy or pneumonectomy
   d. Mean survival for small cell carcinomas with chemotherapy is 1 year

• Approach to the Patient with Cancer

Cancer in NZ:

1. In 1996, there were 16,056 new cases of cancer and 7,461 people in NZ died of cancer
2. The most common cancers in NZ, accounting for 83.4% of all cases in NZ are:
   a. Males – prostate, large bowel, lung, melanoma, bladder, lymphoma, leukaemia, stomach, kidney, pancreas
   b. Females – breast, large bowel, melanoma, lung, lymphoma, ovary, uterus, cervix, leukaemia, pancreas
3. Prostate cancer, large bowel cancer, breast cancer and melanoma account for 15%, 15%, 12%, 10% and 10% of all new cases respectively

Clinical manifestations of cancer may be due to local effects of the primary tumour, effects produced by metastatic tumours or generalised effects of the presence of malignant disease.

1. Primary tumours – may invade local structures
   a. Expanding mass – swelling
   b. Epithelial breach – bleeding, ulceration
   c. Obstruction of tubes – dysphagia, abdominal pain, venous obstruction
   d. Compression of nervous tissue – pain, neurological deficit, raised ICP
2. Metastatic tumours:
   a. Lymphatic spread – lymphadenopathy, lymphoedema
   b. Organ dysfunction – breathlessness
   c. Loss of structural integrity – bone pain
   d. Obliteration of organ – hepatomegaly
530.307 – Pathophysiology Notes

3. Paraneoplastic syndromes
   a. Hormone production
      i. PTHrP – hypercalcaemia (non-small cell lung cancer)
      ii. ADH – hyponatraemia (small cell lung cancer)
      iii. β-chlorionic gonadotropin – gynaecomastia (testicular cancer)
      iv. TNF – cachexia (various)
   b. Immunological
      i. Anti-neurone Ab – sensory neuropathy (small cell lung cancer)
      ii. Anti-ACh receptor Ab – myasthenia gravis (thymoma)
      iii. Anti-Ca\(^{2+}\) channel Ab – Lambert-Eaton syndrome (small cell lung cancer)
   c. Unknown aetiology – clubbing (non-small cell lung cancer), fever (various)

Family and social history (previous exposures)
1. Familial cancer syndromes
   a. Familial polyposis coli (APC) – multiple polyps and colon cancer
   b. Hereditary non-polyposis colorectal cancer (hMSH2, hMLH1)
   c. Li Fraumeni syndrome (p53) – many tumour types
   d. Retinoblastoma (RB1) – bilateral retinoblastoma and other cancers
   e. Familial breast cancer (BRCA-1, -2) – breast/ovarian and early onset breast cancer
2. Environmental carcinogens
   a. Cigarette smoke – lung, head and neck, oesophagus, bladder cancers
   b. Asbestos – mesothelioma, lung cancers
   c. Radiation – leukaemia, other cancers
   d. Sunlight – melanoma

Diagnosis:
1. Pathology – assessment provides information on whether the cancer is benign or malignant, the cell type from which the tumour has arisen and the degree of differentiation (grade)
   a. In general, biopsy the most accessible suspicious lesion – it is not necessary to biopsy the primary if an accessible metastasis is present elsewhere
      i. FNA – superficial/subcutaneous skin, lymphadenopathy, breast lumps
      ii. Direct biopsy – bronchoscopy, colonoscopy, upper GI endoscopy
   b. Immunohistochemical techniques may help distinguish different histological subtypes
2. Tumour staging – description of the extent of disease \(\rightarrow\) determines treatment
   a. Clinical – physical examination, blood tests, imaging, endoscopy
   b. Pathological – inspection/palpation of organs during surgery, pathology of excised tumour, regional lymph nodes and biopsies
   c. TMN system – size of primary (T), lymph node involvement (N), metastases (M)
3. Functional assessment – functional reserve provides an important indication about how the patient is likely to cope with the stress of the cancer and its treatment
   a. Performance status tables are useful in assessing prognosis and likelihood of benefit and toxicity from cytotoxic chemotherapy e.g. ECOG performance status scale:
      i. PS 0 – asymptomatic, normal activity
      ii. PS 1 – symptomatic but ambulatory
      iii. PS 2 – symptomatic but in bed <50% of day
      iv. PS 3 – symptomatic, in bed >50% of day, requires assistance
      v. PS 4 – bed-ridden, severely disabled
4. Tumour markers – limited use in diagnosis/screening as they are also produced in association with many non-malignant conditions, but are useful for following treatment/remission
   a. Alpha-fetoprotein – germ cell tumour, HCC, (cirrhosis, hepatitis)
   b. β-hCG – gestational trophoblastic disease, germ cell tumour, (pregnancy)
   c. CA-125 – ovarian cancer, (menstruation, peritonitis, pregnancy)
   d. Carcinoembryonic Ag – adenocarcinoma, (pancreatitis, hepatitis, inflammatory bowel)
   e. Prostate specific Ag – prostate cancer, (prostatitis, prostatic hypertrophy)

Principles of cancer treatment
1. Treatment planning – often more than one treatment \(\rightarrow\) assessment, discussion, explanation
   a. Is the disease localised and hence amenable to local surgery/radiotherapy?
   b. Does treatment offer the possibility of cure, or are benefits limited to palliation?
2. Surgery – complete excision of the tumour along with a margin of normal uninvolved tissue
   a. Removal of lymph nodes may provide information on prognosis and further therapy
3. Radiation therapy – EM radiation damages DNA of target cells to induce cell death
   a. Planning involves careful definition of the radiation field and dosing schedule
   b. Usually delivered in daily fractions five times a week
4. Chemotherapy – cytotoxic drugs or endocrine agents for tumours that are no longer localised

Radiotherapy and chemotherapy may be potentially curative in head and neck, lung, breast, large bowel and anal cancer, leukaemia, lymphoma, germ cell tumours and childhood cancers.

**Radiation Therapy**

2800 new patients/year have radiotherapy at Auckland – 45% of cancer patients require radiotherapy

1. Palliative intent – 50% of patients
   a. Indications – bone pain and other pains, brain metastases, compression (spinal cord, dysphagia, dysphonia, haemoptysis), haematuria, bleeding from ulcerated tumours
   b. Fewer and less complex treatments, fewer side effects, less demanding on patient

2. Radical/curative intent – 50% of patients
   a. Definitive (gynaecological, head and neck) – radiotherapy, chemo-radiation
   b. Adjuvant (breast cancer) – pre-/post-operative radiotherapy/chemo-radiation

3. Side effects of radiotherapy may be general (tiredness, nausea), acute (during treatment – skin, mucosa) or late (fibrosis, organ specific).

**Combined surgery and radiotherapy:**

1. Rationale:
   a. Functional/cosmetic – limb preservation (soft tissue sarcoma), breast conservation
   b. Risk reduction of loco-regional recurrence

2. Post-operative radiotherapy – e.g. squamous cell carcinoma oral cavity – indications:
   a. Positive margins or margins <5mm
   b. Bulky primary or invasion of contiguous structures
   c. Lymph/vascular space invasion, perineural invasion
   d. Multiple nodal involvement, extra-nodal spread

3. Pre-operative radiotherapy
   a. T3 adenocarcinoma of the rectum, soft tissue sarcoma, advanced breast cancer
   b. Pre-operative radiotherapy is more ‘dose-effective’ than post-operative radiotherapy:
      i. Treatment-related mortality (radiation enteritis) is less
      ii. Significant tumour down-staging may allow sphincter sparing surgery

4. Multidisciplinary clinics involving radiation oncology at AHSL include breast, lymphoma, upper GI, lower GI, gynaecological, urological, head & neck, brain, chest, skin, paediatric, (sarcoma)

**Radiotherapy theory**

1. Fractionation schedules depend on repair, reoxygenation, redistribution, repopulation (4 Rs)
2. Radiotherapy modalities
   a. External beam
   b. Brachytherapy – intracavity (gynaecological malignancies) or interstitial implantation
   c. Unsealed sources – 131I, strontium
3. Radiotherapy units – examples of radiotherapeutic schedules:
   a. Palliative – 8Gy in 1 F, 20Gy in 5 F over 1 week
   b. Adjuvant post-operative – 60Gy in 30 F over 6 weeks
   c. Definitive radiotherapy – 70Gy in 35 F over 7 weeks
4. Future directions – useful for avoiding radiosensitive organs (e.g. spinal cord)
   a. Conformal radiotherapy, stereotactic radiotherapy
   b. IMRT
   c. New chemo-radiation strategies,
   d. New therapeutic adjuvants (e.g. hypoxic cytotoxins – tirapazamine)

**Principles of Systemic Cancer Therapy**

Surgery and radiotherapy are effective treatment modalities for localised tumours, but more widely disseminated cancers require systemic forms of therapy – cytotoxic drugs and endocrine agents.
1. **Model of tumour growth** – first-order kinetics
   a. Tumour starts with one malignant cell with a constant doubling time – a constant proportion of cells are dividing per unit of time, and numbers increase exponentially
      i. $10^8$ cells – tumour is clinically evident, $10^{12}$ cells – tumour becomes lethal
   b. Chemotherapy also follows first-order kinetics – a given dose kills a constant proportion of cells regardless of the initial tumour size. Repeated doses after the disappearance of clinical disease are therefore required to eradicate tumour cells

2. **Pharmacodynamics** – relationship between drug concentration and effects
   a. The relationship between log drug concentration and tumour cell killing is described by an S-shaped curve for many chemotherapy drugs
   b. Chemotherapy drugs also kill normal cells in a concentration-dependent manner
      i. Concentration-effect curves for normal cells lie to the right of tumour cells
      ii. The margin between the curves defines the tumour selectivity of the drug
   c. The therapeutic index (EC50 for killing of normal cells over EC50 for killing of tumour cells) defines the ability of a drug to kill tumour cells relative to normal cells

3. **Combination chemotherapy**
   a. Chemotherapy with single agents has limited effectiveness (e.g. methotrexate in choriocarcinoma) – multiple drug therapy has more commonly proved effective
   b. To provide different mechanisms of tumour cytotoxicity, drugs with differing modes of action are often combined for cancer treatment – e.g. BEP for testicular cancer
      i. Bleomycin – induces DNA breaks, lung toxicity
      ii. Etoposide – topoisomerase II poison, bone marrow toxicity
      iii. Cisplatin – induces DNA crosslinks, peripheral nerve toxicity

**Clinical aspects of cancer chemotherapy**

1. **Role of cancer chemotherapy**
   a. Cure – potential for eradication is predicted from the pathology of the tumour
      i. Leukaemias, lymphomas, germ cell tumours and many childhood tumours are highly sensitive to chemotherapy
      ii. Other cancers are not so chemo-sensitive and cure is not a realistic goal
   b. Chemotherapy combined with surgery or radiotherapy
      i. Adjuvant chemotherapy – with surgery in treatment of localised tumours
         1. Improves survival via eradication of micro-metastatic disease
         2. Breast cancer, large bowel cancer, osteosarcoma
      ii. Combined modality therapy – combined chemotherapy/radiotherapy
         1. Chemotherapy may potentiate radiotherapy or kill cells beyond the radiation field, radiotherapy may treat areas of residual disease
         2. Anal, cervical, head and neck, oesophageal, lung cancers
   c. Palliation – may improve survival-time and symptoms control, though can contribute to decreased quality of life by causing side effects and requiring clinic visits

2. **Cancer chemotherapy drugs**
   a. Alkylating agents bind covalently to DNA (crosslinks) – e.g. cyclophosphamide
   b. Platinum drugs form bonds with DNA bases (crosslinks) – e.g. cisplatin
   c. Antimetabolites inhibit DNA synthesis (S-phase cells) – e.g. methotrexate
   d. Antimicrotubule drugs disturb mitotic spindle formation (M-phase) – e.g. vincriistine
   e. Topoisomerase interactive drugs inhibit topoisomerases – e.g. doxorubicin
   f. Hormonal agents inhibit effects of sex steroid hormones – e.g. Tamoxifen

3. **Adverse effects of cancer chemotherapy** – generally predictable, reversible and treatable
   a. Neutropenia is the most common side effect with levels lower at 1-2 weeks after chemotherapy, can → sepsis. Therapy with G-CSF reduces severity and duration.
      i. Anaemia and thrombocytopenia are less common, managed with transfusion
   b. Nausea and vomiting – distinguished from causes needing specific management
      i. Chemotherapy drugs stimulate the vomiting reflex at the brain stem or peripheral nerves innervating the gastrointestinal mucosa
      ii. Neurotransmitter antagonists are effective in preventing nausea and vomiting – serotonin type 3 receptor (ondansetron), dopamine (metoclopramide)
   c. Alopecia, mucositis/stomatitis, second tumours, developmental abnormalities, peripheral neurotoxicity, sex-steroid deficiency
   d. Alternatively, adverse effects can be categorised into antiproliferative, mutagenesis, microtubule disturbance and hormone deficiency