1. **Cell Injury**
   
   Rob Goldin  
   
   - MCD Cell Pathology  
   - Alexandra Burke-Smith

1. To list the causes of cell injury
2. To list the mechanisms of cell injury.
3. To define (and give examples of) hyperplasia, hypertrophy, atrophy, metaplasia and dysplasia
4. To describe the morphological changes associated with reversible and irreversible injury.
5. To describe the differences between apoptosis and necrosis.

   - A normal cell is in homeostatic equilibrium
   - Stress/increased demand on the cell \( \rightarrow \) adaptation of the cell
   - Injury/stimulus with an inability to adapt \( \rightarrow \) cell injury/death

### Causes of cell injury

- Oxygen deprivation
- Chemical agents
- Infectious agents
- Immunological reactions
- Genetic defects
- Nutritional imbalances
- Physical agents
- Aging

**Example**

- Oxygen deprivation \( \rightarrow \) MI (blockage in coronary artery – oxygen supply decrease – cell death)
- Normal myocyte – increased oxygen demand – HYPERTROPHY (increased cell size) = adaptation
- Normal myocyte – increased oxygen demand – cell injury – cell death (MI)

### Injurious Stimuli

<table>
<thead>
<tr>
<th><strong>Cellular Response</strong></th>
<th><strong>Consequence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depends on:</td>
<td>Depends on:</td>
</tr>
<tr>
<td></td>
<td>Type of injury</td>
</tr>
<tr>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td></td>
<td>severity</td>
</tr>
<tr>
<td></td>
<td>Type of cell</td>
</tr>
<tr>
<td></td>
<td>Cell status</td>
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<tr>
<td></td>
<td>Adaptability</td>
</tr>
<tr>
<td></td>
<td>Genetic make up</td>
</tr>
</tbody>
</table>

- Four intracellular systems are particularly vulnerable and often interlinked:
  - Cell membrane integrity
  - ATP generation
  - Protein synthesis
  - Integrity of genetic apparatus
- structural and biochemical components of a cell very integrally related
- multiple secondary effects rapidly occur
- cellular function is lost before cell death which in turn is before morphological changes are seen
Mechanisms of Cell Injury

Adaptation- reversible injury

- **Atrophy**
  - Shrinkage in the size of the cell (or organ) by the loss of cell substance
  - Same number of cells
  - E.g. pernicious anemia is associated with gastric atrophy
  - Dementia is associated with brain atrophy

- **Hypertrophy**
  - Increase in size of cells and consequently an increase in the size of the organ
  - Can be physiological e.g. athletes, or pathological e.g. hypertension
  - Caused by increased functional demand or hormone stimulation

- **Hyperplasia**
  - An increase in the number of cells in an organ
  - Can be physiological or pathological
  - Physiological hyperplasia can be either hormonal or compensatory
  - Pathological hyperplasia is usually due to excessive hormonal or growth factor stimulation
  - E.g. proliferative endometrium, carcinoma

- **Metaplasia**
  - A reversible change in which one adult cell type is replaced by another
  - E.g. physiological change in cervix during puberty
  - Pathological- acid reflux through oesophagus (Barrett’s columnar lined oesophagus)

- **Dysplasia**
  - One meaning: abnormal in form e.g. retinal dysplasia (not what we are talking about)
  - Precancerous cells which show the genetic and cytological features or malignancy but not invading the underlying tissue
  - Screening programmes try to diagnose cancer at this stage, as leads to much more successful treatment
  - Associated with Barrett’s oesophagus

Associated Light Microscope changes:
- fatty change- e.g. alcoholic fatty change during excess consumption
- cellular swelling- e.g. ballooning degeneration due to damage of cell membrane

Cell Death- irreversible injury

<table>
<thead>
<tr>
<th>Apoptosis</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Programmed cell death</td>
<td>• Programmed cell death</td>
</tr>
<tr>
<td>• Usually single/small number of cells</td>
<td>• Sheets of cells</td>
</tr>
<tr>
<td>• No leakage of intracellular components- therefore no associated inflammation</td>
<td>• Marked inflammatory infiltrate- damage to surrounding tissue</td>
</tr>
<tr>
<td>• Physiological</td>
<td>• Enzymatic digestion and leakage of cellular components- lack of energy maintaining cell membrane</td>
</tr>
<tr>
<td>• Active energy dependent</td>
<td></td>
</tr>
</tbody>
</table>

Causes:
1. Embryogenesis
2. Deletion of auto-reactive T cells in the thymus
3. Hormone-dependent physiological involution
4. Cell deletion in proliferating populations
5. A variety of mild injurious stimuli that
cause irreparable DNA damage that triggers cell suicide pathways

**Associated Nuclear Changes:**
- Karyolysis
- Pyknosis
- Karyohexis

**Associated Light Microscope Changes:**
- **Coagulative necrosis**
  - Nuclei disappears, but cell appears normal
  - E.g. myocardial infarct
- **Liquefactive necrosis**
  - Normal cell structure disappears
  - E.g. old cerebral infarct
- **Caseous necrosis**
  - “cheesy” necrosis- normal cell structure gone but granular material remains
  - E.g. pulmonary TB
- **Fat Necrosis**
  - Lipids autodigested by lipases
  - E.g. acute pancreatitis
2. Haemodynamic Disorders

Dr James Carton ([j.carton@ic.ac.uk](mailto:j.carton@ic.ac.uk))

1. Describe the causes and consequences of oedema at different sites.
2. Define thrombosis & give causes and potential consequences of such an event.
3. Define embolism & know the importance of pulmonary embolism in clinical practice.
4. Describe possible causes of haemorrhage and potential outcomes.
5. Define shock and identify the possible causes and mechanisms.
6. Define infarction and describe possible causes, including atherosclerosis.

Oedema

Definition: abnormal increase in interstitial fluid. The volume of IF carefully controlled by osmotic pressure, hydrostatic pressure and lymphatic drainage

- **Pulmonary oedema**
  - Caused by raised hydrostatic pressure in the pulmonary capillary bed.
  - Most common cause = left ventricular failure.
  - Fluid accumulates first in the interstitial space and then eventually spills into the alveolar spaces.
  - Breathlessness (dyspnoea) is the main symptom.
  - Breathlessness is typically worse on lying flat (orthopnoea).
  - Fluid in the alveolar spaces predisposes to bacterial infection in the lung (pneumonia)

- **Cerebral oedema**
  - Usually caused by disruption to the cerebral capillaries (and the blood brain barrier)
  - Seen in brain tissue surrounding intracranial lesions such as contusions, haemorrhages, infarcts and tumours.
  - Cerebral oedema contributes to a rise in intracranial pressure (ICP).
  - High ICP risks brain herniation and death.
  - Strategies to reduce ICP include raising the head, infusing isotonic fluids, steroids and osmotic diuretics such as mannitol.

- **Generalised Oedema**
  - Widespread accumulation of fluid in subcutaneous tissues and serous cavities.
  - Complex and multifactorial pathophysiology.
  - Activation of renin-angiotensin-aldosterone pathway thought to be a key factor.
  - Common causes include left ventricular failure, nephrotic syndrome, hepatic failure.

Thrombosis

Definition: abnormal blood clot formation in the circulatory system

3 contributing factors:
- stasis of blood
- injury to vessel wall
- hypercoagulability

- **Venous thrombosis**
  - Stasis and hypercoagulability key factors.
  - Most form in deep leg veins (deep venous thrombosis or DVT).
Pulmonary embolism is the most important potential complication

Arterial thrombosis
- Almost always related to vessel wall injury caused by atherosclerotic plaques.
- Narrowing (stenosis) of the artery by thrombus causes ischaemia of the tissue supplied by the artery.
- Complete blockage (occlusion) of the artery by thrombus causes infarction of the tissue supplied by the artery.

Cardiac thrombosis
- Stasis is the key factor.
- Left atrial thrombosis usually related to atrial fibrillation.
- Left ventricular thrombosis usually related to prior myocardial infarction.
- Systemic embolisation is the most important potential complication.

Emboli
- An embolus is a detached mass within the circulatory system that is carried in the blood to a site distant from its point of origin.
- Most emboli are fragments of dislodged thrombus (thromboemboli).
- Emboli are important because they can lodge in vessels and block them off.

Venous Thromboemboli
- Blood clot forms in vein, breaks free, and travels to the heart
- Embolus travels through the heart and blocks a blood vessel in the lung
- Emboli lodging in a major pulmonary artery cause instantaneous death.
- Emboli lodging in medium sized arteries present with breathlessness.
- Emboli lodging in small arteries cause subtle symptoms of breathlessness, chest pain, and dizziness — these are the hardest to diagnose.
- ~30% of patients with pulmonary embolism will die from it.
- The risk of death increases the longer it takes to make the diagnosis.

Arterial thromboemboli
- Most originate in the heart or carotid arteries.
- May impact in cerebral arteries (stroke), mesenteric arteries (bowel infarction) or the lower limbs (acute lower limb ischaemia).

Haemorrhage

Definition: Extravasation of blood due to vessel rupture.

- May be due to trauma or an intrinsic disease of the vessel.
- Rupture of a major vessel causes acute haemorrhage with risk of hypovolaemia, shock and death e.g. ruptured abdominal aortic aneurysm.
- Rupture of a small vessel can still be rapidly fatal if it occurs at a vital site e.g. brainstem haemorrhage.
- Formation of a solid haematoma within the enclosed cranial cavity can also be fatal by causing a rise in intracranial pressure and tonsillar herniation.
- Chronic low grade haemorrhage may present with iron deficiency anaemia e.g. bleeding from a colonic carcinoma.
Shock

Definition: A generalised failure of tissue perfusion.

- Caused by pump failure (e.g. acute myocardial infarction) or peripheral circulation failure (e.g. hypovolaemia, sepsis, anaphylaxis).
- Circulatory collapse ensues leading to ischaemia of multiple organs.
- Most vulnerable organs are kidneys, bowel, brain, lungs, heart.
- Rapid treatment is required to restore circulatory status and prevent multiple organ failure - patients often in ICU

Infarction

Definition: Tissue necrosis due to ischaemia.

- Most infarcts are due to obstruction of an artery.
- Infarction may also occur due to venous obstruction.
- Infarcts heal by repair. Although structural integrity is maintained, there is permanent loss of functional tissue.

- Myocardial infarction
  - Obstruction in coronary artery
  - Area of infarct represents occluded area
  - Common in left anterior descending artery
  - Large MI = lots of scar tissue – often leads to other infarctions
- Cerebral Infarction
  - Emboli from heart or carotid artery
  - Area of brain undergoes infarction - most common is the middle cerebral artery
  - Right MCA → left hemiplegia (paralysis)
- Small Bowell Infarction
  - Emboli often from heart, migrate through aorta into superior mesenteric artery
  - Gives intestines plum-brown colour

Atherosclerosis

Definition: An inflammatory disease of large and medium sized systemic arteries characterised by the formation of lipid-rich plaques in the vessel wall.

- Risk factors include smoking, diabetes, hypertension, hyperlipidaemia.
- Endothelial injury is thought to be the key initiator (“response to injury hypothesis”).
- Important diseases caused by stable atherosclerotic plaques: stable angina, chronic lower limb ischaemia.
- Important diseases caused by thrombosis overlying an unstable atherosclerotic plaque: unstable angina, myocardial infarction, cerebral infarction, acute lower limb ischaemia.
3. Inflammation

Dr Mary Thompson (m.thompson@imperial.ac.uk)

1. How does understanding basic pathology of acute and chronic inflammation help diagnose and treat the patient?
2. What is the clinical significance of granulomas inflammation?
3. What are the complications and long term effects of inflammation?

What is inflammation?

“Reaction of living vascularised tissue to sub-lethal cellular injury”

- Evolutionary development to protect against infection and trauma
- Many different cell types/soluble mediators
- Generally tightly regulated
- Acute (hrs/days) or chronic (weeks/months)
- Local or systemic effects
- Non-specific (but mediators important)

Unwanted effects

➢ Local
  - Excess local tissue damage and scarring
  - Secondary effects on nearby tissue
➢ Systemic
  - Secondary multi-organ failure e.g. septic shock
  - Amyloid

Importance

- Process underlies many diseases; excessive, deficiency, chronic
- Used to predict sequelae and complications of inflammatory reactions
- Intervene to prevent/reduce adverse effects: drugs, surgery, target malignant cells etc

Examples of diseases

- Infection- common cold, TB
- Autoimmune- rheumatoid arthritis
- Allergic- asthma
- Metabolic- Gout
- Malignant- host reaction
- Inherited- chronic granulomatous disease
- Idiopathic- pulmonary fibrosis, Crohn’s
- Occupational/environmental- silicosis, radiation burns

Components of inflammatory reaction

➢ Cells
  - Neutrophils
  - Macrophages
  - Lymphocytes
  - Eosinophils
  - Mast cells
- ECM
  - Collagen
  - Proteoglycans
  - Fibroblasts

- Soluble factors
  - Antibodies
  - Cytokines
  - Complement system
  - Coagulation system

- Vessels
  - Immediate supply of cells and soluble factors
  - Tissue repair

**Neutrophils**

- Produced in BM
- Circulate in blood, migrate to damaged tissue
- Rapid response - first cell into damaged area
- Kill bacteria and recruit more cells; phagocytosis and degranulation (enzymes, free radicals and soluble mediators)

**Monocyte/Macrophages**

- Kidney shaped nucleus
- Originate in BM
- Circulate in small numbers in blood as monocytes
- Become macrophages in tissues
- Role; phagocytosis, control of other cells using cytokines, viral/atypical bacterial infections

**Other cells**

**Eosinophils**

- Allergic causes
- Parasitic infections

**Mast cells**

- Allergic diseases

**Inflammatory reactions**

- Acute
- Sub-acute
- Chronic

1. **Acute Inflammation**

**Evolution**

- Acute phase – neutrophils (24hrs)
- Chronic phase - monocytes/macrophages (1 week)
- Resolution/repair – macrophages/fibroblasts
**Resolution**

- Architecture returns to normal only if;
- Tissue cells able to regenerate e.g. liver
- There is little structural damage done
- E.g. pneumococcal lobar pneumonia
- Congestion → red hepatisation → grey hepatisation → resolution (during hepatisation, polymorphs and neutrophils fill alveolar spaces)

**Repair**

- Occurs if resolution unable
- Replace normal tissue with fibrous scar tissue
- Fibroblasts- produce collagen
- Collagen
- Remodelling- reorientation of collagen fibres; cross-links over tissue and faces towards stress; maximal tensile strength

**Laboratory Tests**

- **Full blood count (FBC)**
  - Increased neutrophils- bacterial infections, acute episodes of chronic disease e.g. Crohn’s
  - Increased Eosinophils- parasitic infection, drug reactions
  - Increased monocytes- viral infections
- **Monopod test**
  - Atypical monocytes- glandular fever

**Clinical Features**

- **Local**
  - Symptoms- painful and hot
  - Signs- swelling, erythema, heat, exudates
  - Due to release of cytokines
- **Systemic**
  - Symptoms- malaise, loss appetite
  - Signs- fever. shock

**Vascular changes**

- **Vascular calibre and flow increased**
  - Redness and heat
  - Enables rapid delivery of inflammatory cells and mediators
- **Adhesion molecules expressed on endothelium**
  - Inflammatory cells stick to vessel wall
- **Increased vascular permeability**
  - Swelling
  - Leaky capillaries allow cells and mediators to enter tissue- EXUDATE

**Chemotaxis**

- Movement of cells towards injured area
- EXOGENOUS and ENDOGENOUS compounds attract cells
- Breakdown products of bacteria and damaged cells- all chemotactic
Phagocytosis

Kills:
- Free radicals
- Lysozyme
- Lactoferrin
- Major basic protein

EXUDATE

- Fluid, cells and proteins (fibrin, antibodies etc)
- Function: dilutes pathogen, spread of soluble mediators, stops pathogen spreading, gives inflammatory cells substrate to hold and migrate through
- SEROUS—fluid e.g. blister
- FIBRINOUS—fibrin e.g. viral pericarditis
- PURULENT—fibrin + inflammatory cells + debris + fluid (PUS) e.g. peritonitis following bowel perforation

Soluble factors in exudate:

➢ Produced locally by cells
  - Preformed:
    o mast cells- histamine
    o neutrophils & macrophages- lysosomal enzymes
  - Newly synthesised
    o Macrophages- nitric oxide
    o Macrophages & lymphocytes- cytokines
    o Prostaglandins
    o Leucotrienes

➢ Circulating plasma proteins
  - Produced by liver
  - Include:
    o KININ system
    o coagulation/fibrinolysis cascade
    o complement system
    o C-reactive protein

➢ Antibodies

Vasoactive Amines

- Released from mast cells, basophils and platelets
- E.g. histamine- allergic responses
- Increases vascular permeability and therefore oedema and swelling e.g. acute asthmatic reactions

Complement System

- Approx 20 proteins
- Activated in cascade sequence
- Important in many diseases
- Effects: chemotaxis, facilitating phagocytosis, lysing of bacterial membranes
- Adverse effects: due to over activation – ANAPHYLAXIS, shock e.g. snake bite
Interleukins

- Proteins
- Proinflammatory or anti-inflammatory
- Procoagulant or anticoagulant
- Induce fever, malaise, weight loss
- Promote cell proliferation e.g. fibroblast proliferation
- Stimulate collagen production → healing/scarring

Prostaglandins and Leukotrienes

- Effects on smooth muscle in walls of blood vessels or bronchi
- Effects on permeability

TARGETING INFLAMMATORY MEDIATORS/STOPPING INFLAMMATION

- Vasoactive amines-- Antihistamines
- Prostaglandins and leukotrienes-- Aspirin etc
- IL-1 and TNF -- Anti-TNF antibodies
- Mediators and neutrophils have a short half life
- Macrophages release anti-inflammatory products
- Mast cells and lymphocytes release anti-inflammatory produces (LIPOXINS)
- Stimulus- e.g. bacterium removed#

2. Chronic Inflammation (CI)

“Inflammation of prolonged duration in which active inflammation, tissue destruction and attempts at repair occur simultaneously”

Causes

- Persistent damage
- Persistent infection
- Prolonged exposure to toxic agent
- Autoimmunity
- Foreign body, e.g. splinter

Cells involved

- Macrophages
- Lymphocytes
- Plasma cells
- NO EXUDATE

NB: special type of chronic inflammation is GRANULOMATOUS

- Macrophages
  - Key cell
  - Longer life than neutrophils
  - Control the inflammatory process

- Lymphocytes and plasma cells
- Part of immune response generated by tissue destruction
- T-cells regulate immune reaction; can be cytotoxic
- Plasma cells produce antibodies

Granulomatous Inflammation

- Particular form of CI showing granuloma formation; cluster of macrophages, involves specific T cells
- Causes:
  - Infection
  - Foreign material
  - Reaction to tumours
  - Immune diseases

Defects in Inflammatory Process

- **Inherited**
  - Chronic granulomatous disease
  - Compliment deficiencies

- **Acquired**
  - Poor adhesion- diabetes
  - Poor phagocytosis and killing- anaemia, diabetes, malnutrition
  - Poor production of soluble factors- poor liver function

Repair

What hinders it?

- **General**
  - Poor nutrition
    - protein for collagen production
    - energy for cell function
  - Vitamin deficiency
    - Vit C needed by fibroblasts to make collagen
    - Vit A required for epithelial regeneration
  - Mineral deficiency
    - E.g. Zinc
  - Suppressed inflammation
    - Steroids
    - Old age
    - Diabetes

- **Local**
  - Poor blood supply
    - E.g. ischaemic leg ulcers
  - Persistent foreign body
    - E.g. splinter
  - Movement
    - E.g. across a fracture site—need for a cast
Complications

- KELOID formation - excess collagen deposition
- CONTRACTURES - fibrous scar tissue contracts as it matures. If scarring occurs across a joint, can cause poor mobility
- Impaired organ function - e.g. fibrous scars in the myocardium after a heart attack

Abnormal Inflammatory Responses

- Excessive unchecked inflammation
  - Local ARDS (Acute respiratory distress syndrome) in lung
  - Systemic — septic shock
  - Tissue damage and MOF (multiple organ failure)

- Deficient inflammatory response
  - Inherited; abnormal neutrophil adhesion and function
  - Acquired; BM suppression
  - Recurrent infections

CASE STUDIES

CASE 1

- 38 yr old
- Overweight
- Female
- C/o (complaining of) right upper quadrant pain
- O/e (on examination) febrile, loss of appetite, tender RUQ
- Blood tests; FBC - raised neutrophil, CRP ESR - both elevated
- DIAGNOSIS: Acute cholecystitis

CASE 2

- 45 yr old
- Repeated episodes of bloating and upper abdominal pain, especially after eating fatty food
- DIAGNOSIS: chronic cholecystitis
1. List four types of death that must be reported to the Coroner
2. List two reasons for conducting Hospital Autopsies
3. Explain how the need for consent from the deceased’s relatives differs between a Coroners’ and Hospital Autopsy
4. List four natural causes of sudden unexpected death in the community
5. What is a bruise? Give an example of a mechanism of injury that would lead to a bruise
6. What is an abrasion? Give an example of a mechanism of injury that would lead to an abrasion
7. What is a laceration? Give an example of a mechanism of injury that would lead to a laceration
8. What is the difference between a cut and a stab? Other than a knife what might cause such a wound?
9. What is the best generic term to use when describing a wound?

Types of Autopsy, the Coroner, Death Certificates

Coroner: an independent judicial officer of the crown who has a statutory duty to investigate the circumstance of certain categories of death for the protection of the public

Cases that must be reported to the Coroner:

- Cause unknown
- Deceased has not seen doctor recently (14 days before or directly after) e.g. people who live on their own
- COD violent, unnatural or suspicious
- COD accident (even if resulting death is significantly later, e.g. car crash → epilepsy → death years later
- COD due to neglect by self or others, e.g. in nursing homes
- COD due to industrial disease or occupation e.g. asbestos exposure in a factory
- Death due to abortion
- Death during an operation or before/directly after recovery from anaesthetic
- Question of suicide, e.g. hanging
- Death occurred during/shortly after police detention/prison custody
- Death related to poisoning

If any doubt of COD, refer to coroner’s office

Coroners’ Autopsy

- Establishes COD, and once complete his remit is over- regardless of whether natural or unnatural
- Not allowed to use any body parts for research, unlike a hospital autopsy

Hospital Autopsy

Reasons for:

- Very thorough examination of the deceased:
  - Extent of disease
  - Their treatment
  - Effect of treatment and disease
- Audit- major discrepancies between stated COD and actual COD
  - main diagnosis missed in 15% of autopsied cases
- Monitoring effects of new treatments
  - E.g. complex CHD treatments
Teaching
- E.g. unrivalled clinic pathological correlation

Research
- E.g. post mortem brain tissue and variant CJD

Death Certificates
- Data used for epidemiology
- Accurate morbidity and mortality data needed to monitor nations health
- Directs the allocation of resources
- Detects environment risks

<table>
<thead>
<tr>
<th>Hospital Autopsy</th>
<th>Coroners Autopsy</th>
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<tbody>
<tr>
<td>- Consent from Next of Kin (NOK) – person in qualifying relationship - required</td>
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<tr>
<td>- With consent, tissue can be taken and used from the body (see Human Tissue Act) for research etc</td>
<td></td>
</tr>
<tr>
<td>- No consent needed (wishes of NOK considered)</td>
<td></td>
</tr>
<tr>
<td>- Material can only be taken if coroner gives permission - needed to establish COD</td>
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</tbody>
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Conduction of an Autopsy
- In a mortuary
- Dissect through organs systematically
- Look under microscope at specific tissue samples

Death Certification
- Filled in for any death
- Taken to registrar by family
- Scrutinised - must be filled in correctly before registration
  1a) immediate COD (compulsory)
  1b) predisposing factor leading to 1a (not compulsory)
  1c) predisposing factor leading to 1b (not compulsory)
  2) Other contributing factors not directly leading to death

Natural Causes of sudden unexpected death (in the community)

Cardiovascular Disease
- Approx 75% of deaths handled by medical examiners in US
- Cardiac arrhythmia (diagnosis is one of exclusion - full autopsy must be conducted)
- Severe coronary artery atherosclerosis (2 or more vessels)
- Myocardial scarring
- Coronary artery thrombosis
- Acute/sub-acute MI
- Ischaemic Heart disease
- Hypertensive Heart Disease
- Cardiomyopathy
- Myocarditis
- Structural anomalies (eg bridging)
- Floppy mitral valve
- Aortic stenosis (usually calcific)
- Conduction abnormalities (eg long QT syndrome)

**Vascular System**

- Ruptured aortic aneurism - associated with atherosclerosis & hypertension

**Central Nervous System**

- Non traumatic subarachnoid haemorrhage - Berry aneurism (high mortality rate)
- Intracerebral haemorrhage
- Epilepsy

**Respiratory System**

- Pulmonary embolus
- Asthma

**GI tract (not usually unexpected)**

- Bleeding Oesophageal Varices
- Bleeding Ulcers
- Pancreatitis

**Not natural**

- Drugs - approx 1% of all cases reported to coroner
- Alcohol - usually only sudden in alcoholics, often associated with GI problems and often goes with drugs
- Trauma - self induced, accidental, caused by others

**Types of Injury**

- **Bruise/Contusion**
  - Blunt trauma injury
  - Occurs alone (skin intact) or in association with other injury
  - An extravasated collection of blood which has leaked from small arteries, venules and veins but not capillaries
  - Laxity of skin, fragility of vessels and coagulation state etc all effect
  - Takes hours → days to form
  - May be patterned or deep (cannot be seen on epidermal surface)
  - Cannot age a bruise
  - Can bruise after death

- **Abrasion**
  - Graze/scratch - superficial blunt trauma
  - Confined to epidermis
  - May extend to superficial dermis
  - Can occur before and after death
  - Due to TANGENTIAL (distal skin tag occurs) or VERTICAL force (no distal skin tag)
  - E.g. friction burn, car radiator, flooring, whip, stamp

- **Laceration**
  - Split to skin
- Result of blunt force over stretching skin
- Deep (full thickness)
- Bleeds
- Margins ragged and crushed/bruised
- Common where skin can be compressed between force and bone (scalp, elbow, shin)
- Rare over soft fleshy areas (buttocks, breasts)
- Flaying- tangentially applied force → horizontal laceration (difficult to distinguish object causing it)

➢ **Cut (or slash)**
- Length longer than depth
- Edges clean
- Well defined
- Minimal damage to surrounding tissue

➢ **Stab**
- Depth longer than length
- Edges clean
- Well defined
- Minimal damage to surrounding tissue

Both cut and stab wounds are caused by an object with sharp/cutting edge (Usually knife- can be anything e.g. broken glass, metal)

**NB: EITHER USE THE CORRECT TERM (E.G. LACERATION= BLUNT FORCE INJURY- FULL THICKNESS) OR USE A GENERIC TERM (INJURY/WOUND)** (although technically bruises and abrasions are not covered by these terms as they should involve the full thickness of the skin)
5. Cancer

Dr Rathi Ramakrishnan (r.ramakrishnan@imperial.ac.uk)

1. Define cancer, neoplasia, tumour, metastasis, carcinogen
2. List features which distinguish benign from malignant tumours
3. Give examples of cancers cause by infection, chemical and environmental agents
4. Briefly outline the principals of cancer screening
5. Describe features of pathology which predict the prognosis in cancer

What is cancer?

- Important socio-economic problem
- Significant cause of morbidity and mortality worldwide

**Neoplasm:** new growth- “abnormal mass of tissue, the growth of which is virtually autonomous and exceeds that of normal tissues. The growth is uncoordinated and persists after the cessation of the stimuli that initiated the change”

**Cancer:** from the latin “crab”- the pathological condition characterized by the proliferation of neoplastic cells that tend to invade surrounding tissue and metastasize to new body sites

**Tumour:** swelling, originally for inflammation

**Metastasis:** the development of secondary malignant growths at a distance from a primary site of cancer.

**Carcinogen:** a substance capable of causing cancer in living tissue

**Dysplasia:** disordered growth, limited to epithelium
- Loss of uniformity of individual cells
- Loss of their architectural orientation
- Mild-moderate dysplasia may revert to normal
- Severe dysplasia is permanent e.g. carcinoma in situ

**Metaplasia:** substitution of one mature cell type for another more suited to the environment
- Result of a chronic stimulus, when withdrawn may resolve to normal i.e. adaptive not premalignant
- E.g. smoking causes metaplasia of glandular bronchial epithelium to squamous epithelium

**Nomenclature**

All tumours have two basic components:
- Parenchyma: proliferating neoplastic cells
- Stroma: supportive fluid required for tumour growth

- **Benign Tumours**
  - suffix “oma” to cell of origin
    - **From glandular tissues (epithelial origin)**
      - Adenoma
      - Cystadenoma
      - Papilloma
      - Polyp
    - **From stromal tissues (mesenchymal origin)**
      - Fibroma
      - Lipoma
- Angioma
- Leiomyoma
- Osteoma/chondroma

- **Malignant Tumours**
  - Parenchymal tumours- suffix “carcinoma” (epithelial origin)
  - Stromal tumours- suffix “sarcoma” (mesenchymal origin)

**Benign vs. Malignant**

- **Differentiation and anaplasia**
  - Differentiation refers to the extent to which the parenchymal cells resemble their normal counterparts
  - Anaplasia is a complete lack of differentiation, characterized by marked pleomorphism, hyperchromasia, large nuclei, nucleoliation, irregularity of nuclear membrane, mitotic activity (the cytological features of malignant cells)

- **Rate of growth**
  - Generally the rate of growth of tumours correlates with the level of differentiation

- **Local invasion**

- **Metastasis**
  - Formation of discontinuous tumour implants at a distance from the main tumour mass- unequivocal evidence of malignancy

<table>
<thead>
<tr>
<th>Histological features</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation and anaplasia</td>
<td>Well differentiated</td>
<td>Show various levels of differentiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(well, moderate, poor)</td>
</tr>
<tr>
<td>Rate of growth</td>
<td>Slow growing</td>
<td>Rapid growth- chemotargets</td>
</tr>
<tr>
<td>Local invasion</td>
<td>Grow as cohesive, expansile, encapsulated</td>
<td>Poorly demarcated- infiltrate and destroy the</td>
</tr>
<tr>
<td></td>
<td>masses that remain localised to their site of</td>
<td>surrounding tissue</td>
</tr>
<tr>
<td></td>
<td>origin</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>Seldom metastasize</td>
<td>With 2 exceptions (gliomas and basal cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carcinomas), all metastasize- approx 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients present with metastasis</td>
</tr>
</tbody>
</table>

**Mechanisms of Invasion/metastasis**

- **Lymphatic spread**
  - Along natural lymphatic drainage
  - Most common route for carcinomas initially
  - Regional nodes drain tumours, i.e. axillary then infraclavicular and supraclavicular from UOQ breast carcinomas
  - Nodes may contain the spread locally
  - Tumour evokes immune response which causes NODAL HYPERPLASIA
  - Not every enlarged node in the region of a tumour contains metastatic spread

- **Haematogenous**
  - Through vessel walls
  - Veins are penetrated more frequently than arteries due to thickness of walls
  - Liver and lungs are most common sites due to venous drainage
  - Typical of sarcomas but also by carcinomas later
  - Renal cell carcinoma can grow within the renal vein to the IVC and into the right atrium

- **Body cavities**
  - Peritoneal
  - Pleural
- Pericardial
- Subarachnoid
- Joint
- Most commonly from ovarian carcinomas which may take the peritoneal surface. Also spread of lung carcinoma into pleural cavity.

➢ Contiguous
- Spread to adjacent organs etc

Cancer Epidemiology

➢ Age
- Incidence increasing due to aging population
- In general, higher incidence >55 yrs
- Certain cancers specifically affect the young

➢ Geography
- Stomach cancer Japan > USA
- Melanoma NZ & Australia > Iceland

➢ Environmental
- UV light
- Occupational agents like asbestos
- Diet and weight
- Alcohol
- Smoking
- Infections- notably viruses (HPV, HBV, EBV etc)

Genetics

For a large number of cancers there exist some hereditary predispositions. There are 3 categories of hereditary forms:

➢ Inherited autosomal dominant cancer syndromes
  - E.g. Familial retinoblastoma
  - FAB (Familial adenomatous polyposis coli)

➢ Familial cancers
  - E.g. breast cancers
  - Ovarian
  - colonic

➢ Autosomal recessive syndromes of defective DNA repair
  - E.g. xeroderma pigmentosa
  - Bloom syndrome

Non-heredity

- Increased risk i.e. liver cirrhosis and HCC
- Inflammation & cytokines with growth of transformed cells, promoting genetic instability and carcinogenesis
The molecular basis of cancer

Carcinogenesis

- Multistep process
- Genetic hypothesis: tumour mass results from the monoclonal expansion of a single progenitor cell
- Accumulation of successive subsequent mutations allows progression and accounts for heterogeneity
- INITIATION
  DNA damage- genetic mutations

  ➔ PROMOTION
  activation of cancer promoting genes
  inhibition of apoptosis
  inactivation of cancer suppressor genes

  ➔ TRANSFORMATION
  expression of altered gene products
  loss of regulatory gene products

  ➔ PROGRESSION
  malignant neoplasm formed

Targets of genetic damage

4 classes of regulatory genes

- Oncogenes— Growth promoting
- Anti-oncogenes— Growth inhibiting/tumour suppressor
- Anti-Apoptosis genes— genes regulating programmed cell death
- DNA repair genes

Oncogenes

- Derived from proto-oncogenes
- Genes regulating normal cellular growth
- Examples associated with tumours
  - Myc → Burkitt lymphoma
  - N-Myc → neuroblastoma
  - CyclinD1 → mantle cell lymphoma

Tumour suppressor genes

- Usually regulate normal cell growth
- Classic e.g. is Rb gene in genetically inherited retinoblastoma- requires two hits; inheritance of mutated copy of one Rb gene followed by acquisition of damage to remaining copy
- 50% of all tumours contain mutations in the P53 gene; housekeeping gene which prevents genetically damaged cells from replicating
- BRCA-1 & BRCA-2 breast cancers are familial and one of these mutations present in 80% of breast cancers

Anti-apoptosis genes

- Genetic defects accumulate causing pro-apoptotic genes (Bax family), which usually cause programmed cell death
- Anti-apoptotic (bcl2) genes prevent this causing unregulated PROLIFERATION
- Over-expression of bcl2 and prevention of apoptosis results in indolent growth of lymphocytes found in many low grade lymphomas and other somatic malignancies
DNA repair genes

- Genomic instability syndromes- inherited mutations of DNA repair proteins
- Not directly oncogenic
- Act by permitting mutations to occur during normal cell cycles

Carcinogens

Definition: agents that cause genetic damage and induce neoplastic transformation of cells. There are different classes:

- Chemicals
- Radiation
- Microbial agents (mainly viruses)
- Hormones
- Miscellaneous

Chemical carcinogens

- No common structural features
- Some chemicals are inducers (permanent DNA damage)
- Others are promoters (reversible DNA damage)
- Direct acting agents do not require metabolism for activation e.g. dimethyl sulphate
- PROCARCINOGENS need metabolic conversion to active peptide e.g. aromatic amines activated in the liver causing UB cancer
- If enzyme is present within tissues, tumour occurs at the site, e.g. skin and lung cancers with aromatic hydrocarbons
- Major classes- hydrocarbons, amines, nitrosamines, azo dyes, alkylating agents
- Promoters include hormones, drugs etc

Microbial Carcinogens

- Oncogenic Viruses
  - Generally in young
  - EBV- Burkitt’s Lymphoma
  - HPV- cervical cancers
  - HBV & HCV - Hepatic cancers
  - HHV8- Kaposi’s sarcoma
  - Oncogenic viral DNA genome directly incorporated into host cell DNA
  - Oncogenic RNA viral genome transcribed into DNA by enzymes prior to incorporation

- Bacterial Carcinogens
  - Helicobacter Pylori- stomach and pancreatic cancer

Radiations

- Ultraviolet- skin cancer
- Ionising EM radiation i.e. X-rays cause an increase in leukaemia and solid tumours
Clinical Practice

Diagnosis

- **Laboratory methods**
  - Cytology FNA (freehand or USS guided)
  - Histology (core biopsy, incisional or excisional biopsy)

- **Other methods**
  - Tumour typing
  - Immunocyto/histochemistry
  - Flow cytometry
  - Molecular methods (PCR, FISH, DNA microarrays, spectral karyotyping)
  - Tumour markers- CEA AFP Ca125 etc

Grading and Staging

- **Staging**
  - Main clinical staging system- TNM (WHO), based on
    - T – Primary Tumour Size (T1-T4)
    - N – Nodal Status (N0, N1-3)
    - P -- Presence of metastases (M0,M1-2)
    - Others include DUKE’s for colorectal, FIGO for ovarian cancer and Ann Arbor for lymphoma

- **Grading**
  - Histological
  - low and high grade (Less useful than staging)
  - based on the degree of differentiation and the number of mitoses

Effects on Patient

- Both benign and malignant tumours affect the host
- Anxiety (breast lumps)
- Related to location i.e pressure, ulceration, infection, bleeding (hormonal effects)
- Metabolic cancer cachexia (increased BMR, reduced fat and muscle bulk) TNF alpha
- Paraneoplastic syndromes- endocrinopathies, hypercalcemia, thrombotic diathesis, acanthosis nigricans

Prevention and Screening

- **Screening**
  - Detect cancer either at preinvasive stage/early (stage 1). For successful screening programs:
    - Reliable prediction of tumour behaviour
    - Treatment available
    - Target population has enough people at risk to justify expense
    - Cost-effective and reliable screening tool
  - In UK, cervical cancer and breast cancer screening with piloting for colorectal cancer

- **Prevention**
  - Vaccinations- Human Papilloma virus, Hepatitis B virus to protect against cervical/liver cancers
1. Using the example of Helicobacter Pylori infection of the stomach, discuss the varied outcomes of infection and why these occur, and how inflammation can lead to cancer or lymphoma in this organ.

2. List two major complications of peptic ulcers and describe the consequences of these.

3. Using the example of a case of atherosclerosis, list 3 major outcomes of this arterial disease.

**Helicobacter Pylori**

**Dyspepsia 1**

- Male
- Age 46 yrs
- Dyspepsia for 3 yrs
- Worse recently- abdominal pain after meals
- Episode of melaena (blood in stool)
- Blood test Hb 9.0 (13.0 normal)
- Endoscopy- ulcer in duodenum; when acid and food hits ulcer → pain after eating
- BIOPSY OF GASTIC ANTRUM- helicobacter associated gastritis
  - Chronic inflammation; lymphocytes
  - Acute inflammation; neutrophils

**Helicobacter pylori**

- 20% adults in developed countries by age 50, 80% in UDCs
- Majority (70-80%) asymptomatic
- 2x relative risk for gastric carcinoma

<table>
<thead>
<tr>
<th>Normal Stomach</th>
<th>Helicobacter Pylori Stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lined by gastric mucosa</td>
<td>Glands destroyed by neutrophils</td>
</tr>
<tr>
<td>Columnar epithelium mucin secreting glands</td>
<td>Lamina propria filled with lymphocytes</td>
</tr>
<tr>
<td>Acid/pepsinogen body</td>
<td></td>
</tr>
<tr>
<td>Lamina propria mucularis mucosa</td>
<td></td>
</tr>
</tbody>
</table>

➢ **Topography and Outcome**
- D cells of the antrum (in the stomach) produce somatostatin
- Somatostatin inhibits gastrin
- In ANTRAL GASTRITIS (inflammation of a region of the stomach) D cells are reduced
- Principle cause of duodenitis and duodenal ulcer is acid

➢ **Gastric Ulcers**
- Infection spreads with age
- Pangastritis (inflammation of the entire stomach)
- Atrophy of body mucosa
- Acid decreases
- Increased number of gastric ulcers

➢ **Complications**
- Haemorrhage
- Perforation
Dyspepsia 2

- Female
- Age 76 yrs
- C/o vague abdominal pain and nausea
- Dyspepsia for years
- Blood tests Hb11
- Endoscopy performed
- INTESTINAL METAPLASIA shown in gastric mucosa
  - Response to long term damage
  - H. pylori present in bile
  - Cancer risk
- GASTRIC DYSPLASIA - an abnormal pattern of growth in which some of the histological features of malignancy are present
  - Pre-invasive stage
  - Intact BM
- Risk of progression to cancer; H. Pylori strong risk in presence of intestinal metaplasia and atrophy; increased 8x over long time (>15 yrs)
- GASTRIC CANCER
  - Japan: mass endoscopy programs led to 35% early gastric cancers vs. 10% in US

Dyspepsia 3

- Male
- Age 76 yrs
- Dyspepsia
- Early satiety (feeling full)
- Blood tests Hb 8
- Endoscopy performed
- Liver function tests - abnormal
- Liver CT scan - multiple lesions

Gastric Cancer

- High incidence in Japan, Chile, Italy, China, Portugal, Russia
- 2:3 ratio women to men
- 90% of all malignant tumours are carcinomas
- asymptomatic until late; weight loss, abdominal pain, nausea, vomiting, altered bowel habit
- kills more people worldwide than lung cancer

Dyspepsia 4

- Male
- Age 76 yrs
- Early satiety
- Blood tests Hb 8
- Endoscopy performed
- LYMPHOMA diagnosis
Atherosclerosis

- **Occludes arteries slowly**
  - Angina
  - Myocardial scarring
  - Dementia
  - Claudication

- **Occludes arteries suddenly**
  - Plaque rupture
    - Thrombosis
    - atheroembolization
  - Haemorrhages into plaques
    - MI
    - Stroke
    - Gangrene of the bowel

- **Weakens artery walls**
  - Aneurysms

**Case 1**

- Male
- History of hypertension
- Sudden loss of consciousness
- Died in A&E
- Post mortem (PM) carried out

**Case 2**

- Male
- Died in an RTA (road traffic accident)
- Post mortem- aneurysm found
- Cause of death natural or unnatural?

**Case 3**

- Male
- Central chest pain
- Died 7 days post admission

These show different examples and outcomes of atherosclerosis.