Introduction to Pathology (W2)

Introduction to Pathology (L1)

Cycle

- Health care: helping people: compassion, caring, community, improve quality of life, culture, society, etc
- What went wrong?
- Biological sciences: anatomy, physiology, biochemistry, molecular biology etc…
- Pathology:
  - 1 - guide and provide specific treatments
  - 2 - testing to make diagnoses
  - 3 - screening for disease

Pathology is…

- An academic discipline involving the **study and understanding of disease**
- A medical speciality consisting of experts in particular pathology sub-disciplines
- A group of clinical disciplines related to the application of knowledge of disease in medicine, including **performing and interpreting tests**

Is pathology really necessary for doctors to know?

- Nearly every hospital presentation, including >99% of admissions, involve pathology testing
- 100% of clinical interactions require you to think what could be the cause of this problem
- Around half of all GP interactions will generate at least one pathology test
  - Rational use of pathology testing has been shown to improve patient outcomes

Disease and its cause (L2)

What is pathology?

- The scientific study of disease and its underlying causes
- A medical speciality that utilises knowledge about disease in order to:
  - Diagnose
  - Classify
  - Predict
  - Guide treatment
- From Greek Pathos = experience/suffering and —logia = “study of”

Why are the causes of disease important clinically?

- Clinical/medical model of health care
  - **Diagnosis**/assessment
  - **Management**/treatment
- This requires evidence that diseases are real, that treatments are safe and effective
- We need ways of consistently **defining and classifying** disease to decide:
  - **Treatment** — which will work for our patients?
  - **Prognosis** — what will happen next?
  - **Research** — evaluating current treatment and designing testing new treatments

Disease and its causes

- A disease is an **abnormal condition** that affects part or all of an organism and that consists of a **disorder of structure or function**
  - A problem with a tissue/organ/organ system/whole organism
  - That we can reproducible identify
    - Diagnostic criteria (clinical or pathological or both)
      - Signs, symptoms, morphological changes, biochemical changes, genetic variations, etc
  - Out understanding changes over time

Defining disease

- We need to use **consistent and reproducible criteria** for diseases to ensure we are talking about the same entity, same severity and that it is a ‘real’ disease
- **Patterns of disease vary** between populations and over time
  - **New** and emerging diseases

    - **Changes** in incidence
    - Different **genetic and environmental conditions** influencing underlying risk
- Our **understanding** of disease **changes** over time:
    - New causes may be recognised (e.g. Helicobacter)
    - New subtypes may be recognised
    - New names (usually more appropriate/more correct)
    - Medical vs 'casual' terminology
- The relative importance of **classification changes over time**:
    - If **new treatments** become available the distinction becomes more important
    - **Rare diseases** ("Common things occur commonly" and "when you hear food beats, think of horses, not zebras")

When definitions change
- **Diagnostic drift**: the **parameters that define a disease change over time**
    - e.g. **classification** of cancers, autoimmune diseases, hypertension definition
    - Definition of hypertension changed from 140/90 to 130/80 - **small changes**

When definitions change
- **Diagnostic shift**: new knowledge requires a **complete redefinition** of the problem, resulting in change in name, treatment or understanding - **major changes**
    - Germ theory of disease
    - Knudson/Two-hit hypothesis for carcinogenesis
    - Helicobacter pylori and gastric ulcer
    - HPV and cervical/oropharyngeal cancer
    - Molecular pathological classification of cancer gradually replacing or augmenting morphological classification
- e.g. "Our data demonstrates that most of the tumours diagnosed as IDH wild-type astrocytomas can be allocated to other tumour entities on a molecular basis

Aetiology - the cause
- The 'study of the causes'
- From Greek = 'giving a reason for'
- **Pathology** is the **disease process present** (e.g. blood clot in the lung)
- **Aetiology** is the **underlying causes of disease** (in this example, inactivity, recent surgery, cancer, heart failure, sepsis, drugs (smoking, OCP), older age, obesity
    - Not everyone who is exposed will suffer the same pathology

Basic processes and concepts (general pathology) (important)
1. The **Cell** as unit of health and disease
2. Cell **injury**, cell **death** and adaptations
3. **Inflammation** and repair
4. **Haemodynamic** disorders
5. Diseases of the **immune system**
6. **Neoplasia** (abnormal growth)
7. **Genetic** and **paediatric diseases**
8. **Environmental** and **nutritional diseases**
9. **Infectious** diseases

Pathogenesis
- **Pathogenesis**: The **mechanism** that **leads to development of disease**
- Genesis (Greek) = origin/creation

Term summary (important)
- A **disease** is present when a **specific pathological abnormality** (structural, biochemical, functional, etc) occurs
- **Aetiology** relates to the **underlying causes** of that disease (one or multiple)
- **Pathogenesis** relates to **how that disease developed** (the steps it went through)
- **Pathophysiology** relates to the **functional derangements** that are part of the disease

    - How the disease alters normal physiological functions
- Anything that **increases the likelihood of a disease** occurring is a **risk factor**
- Anything that has **directly led to the development** of a disease is a **cause**
- **Sequelae** are **consequences of the disease** (good, bad and neutral)
- **Complications** are **secondary diseases/problems** that happens as a result of the **disease** or its **treatment** (complication is a type of sequelae)

A disease occurs when a specific pathological abnormality is present (important)
- This results in a **pattern** of findings
- Signs/symptoms/tests allow us to **identify** these patterns
- **Pathogenesis** describes how that process developed
- **Aetiology** considers the underlying cause(s) of that process
- **Classification** allows us to logically group diseases together

Terms (important)
- A **symptom** is something that an **individual experiences** as a result of a disease (e.g. dizziness, pain, flushing) - **subjective**
- A **sign** is **something we can observe/measure** in the patient (e.g. blood pressure, temperature, urine output) - **objective**
- A **test** is something we can **measure or observe** either in the patient or removed from the patient (clinical, radiology, pathology)
- A **syndrome** is a **group of signs, symptoms or abnormalities**

Pathway of disease
- Aetiology: cause of disease
    - Immunologic abnormalities, genetic abnormalities, nutritional imbalances, trauma, structural changes, infections, toxins, biochemical changes
- Pathogenesis: mechanisms of disease
- Molecular, functional, and morphologic abnormalities in cells and tissues
- Clinical manifestations: signs and symptoms of disease

Example
- Pathological diagnosis: **pulmonary embolus** (blood clot in the lung)
    - **DISEASE**
- **Pathogenesis**: **clot forms** due to **abnormalities in flow**, **abnormal coagulation**, endothelial wall damage (Virchow's triad), usually in the deep veins of the lung (DVT in legs is also a disease)
    - Partially detaches and travels through veins until next network of small calibre vessels (lung)
- **Blocks circulation of blood** through pulmonary arterial system (loss of oxygenation, increased strain on heart, possible death
    - **Sequelae/complications**
- **Aetiology**: formation of clot
    - Due to: inactivity, recent surgery, cancer, heart failure, sepsis, drugs (smoking, OCP), older age, obesity
        - Many of these are both **causes** and **risk factors**

What happens in this disease? Large, infiltrating and ulcerated tumour in uterine cervix
1. Human papilloma virus infects cervical epithelial cells
    - **Aetiology**
    - **Risk factors**: anything that increases the likelihood of high risk HPV DNA infection and integration
        - Genetics, environment, behavioural/social
2. Virus integrates into cell, changes protein expression (**pathogenesis**)
3. Can affect p53 and Rb genes (tumour suppressors) and change protein expression (**pathogenesis**)
4. Increased and unregulated proliferation/turnover of cells (**pathogenesis**)
5. Overtime development of further mutations (**pathogenesis**)
6. Dysplasia (pre-cancerous atypia) (**disease 1**)

7. In situ carcinoma (**disease 2**)
8. Locally invasive carcinoma (**disease 3**)
9. Distant metastases (**sequelae**)
   - **Complications**? e.g. spread to other organs - organ dysfunction
   - Local invasion of rectum, urological tract
   - Complications of treatment (surgery, radiotherapy, psychological)
10. Death (**sequelae**)

Classification of disease
- **Classification** of disease reflects the systems we use to define diseases and group diseases together or separate them
  - There are many different approaches to classification
  - "Lumping" vs "splitting"
- Classification by **process and/or underlying cause** are most common and probably most useful
- Classification by time course and severity is also important
  - Acute (sudden/short term) vs chronic (long term)
  - Relapsing
  - Relapsing/remitting
  - Self-limiting
  - Progressive
- Classification is complex, detailed and can be contentious
  - ICD vs DSM for mental health disorders
- You need a workable method to be able to approach routine clinical problems, learn and retain knowledge (and answer exam questions)

The pathological sieve
- **V**ascular
- **I**nflammatory / Infective
- **T**rauma
- **A**utoimmune
- **M**etabolic
- **I**atrogenic / **I**diopathic
- **N**eoplastic (abnormal growth) (and other growth disorders)
- **C**ongenital / Genetic
- **D**egenerative
- **E**nvironmental
- "**VITAMIN CDE**" mnemonic

Also consider
- There is **overlap** between categories
- Several specific mechanisms are important across systems and may involve multiple different processes:
- **Degeneration**
  - Conditions relating to age-related destruction of tissue, or stress-related destruction of tissue e.g. osteoarthritis, Alzheimer's disease
- **Environmental** (conditions relating to exposures to toxins, pollutants etc) – e.g. asbestos and mesothelioma, smoking and lung cancer
- **Psychological/Neurological** (conditions relating to the nervous system, presenting either with psychological symptoms or physical symptoms or both) – e.g. epilepsy, schizophrenia

Thinking Clinically
- Which **system** is involved?
- Which **process or processes** are involved?
- What might be the **cause**(s)?
- What might be the **short term effects** (**signs** and **symptoms**, impact on patient)?
- What might be the **long term effects** (**sequelae**/**complications**)?
- **Management**/treatment. Priorities? Options? Balancing harm and benefits?

The clinical utility of pathology (L3)

Role of pathology in diagnosis and management in healthcare system

- Knowledge of **normal structure and function**
- **Identification** of **abnormal structure** or function
- Matching with **known entity or define new entity**
- Knowledge of **natural history** of disease
- Plausible and proven **treatments**
- **Monitoring** of disease (cure, recover, progression)

Pathological disciplines

- Anatomical pathology
  - Surgical pathology/histopathology/cytopathology
- Haematology
- Microbiology
- Immunology
- Genetic pathology / genomic medicine
- Chemical pathology (clinical biochemistry)
- Foresnive pathology

Diagnostic tools and techniques

- **Look** (morphology), **Measure** and **React**
- To identify variations from normal (e.g. from normal anatomy/histology, from normal biochemistry values, from normal haematology reference ranges)
- This means you need to know normal

Diagnostic Tools and Techniques

- **Morphology**: underlying cellular processes affect how cells, tissues look - recognition of patterns remains important. Can be qualitative or quantitative
  - **Macroscopic**/gross
  - **Microscopic** (haematoxylin and Eosin/H&E stain, Gram stain, many others)
  - Ultrastructural (electron microscopy)
  - Quantitative (used ins haematology in particular)
- **Biochemistry**/toxicology
  - **Presence** or **absence of cellular products**, molecules or **toxins** can define a disease state, influence treatment or inform further testing
- Immunological
  - Expression of **cell surface markers** or **antigens** can be detected, allowing typing of cells, identifying abnormal protein expression or demonstrating clonality
  - Immunohistochemistry
  - Immunofluorescence
  - Flow cytometry
  - Others
- Genetic
  - **Presence** of **abnormal chromosomal arrangements** of **gene sequences** defines tumour types, may define disease states and may lead to development of disease in the future
  - Cytogenetics, FISH, PCR, sequencing, etc

Look

- Autopsy
- Macroscopic pathology
- Histopathology
- Cytopathology
- Blood films
- Microbial cultures
- e.g. Gram stain for bacteria, Toluidine blue for H. Pylori, Giemsa stain for Giardia, silver stain for fungi, Ziehl Neelsen for mycobacteria