Life includes Sickness and Death

Pathology is the study of mechanisms and processes of disease.
- Several thousand distinguishable human diseases
- Classified by affected organ/system or by pathological process(es) involved.

Basic medical terms:
- Symptoms (what a patient says), signs (what a doctor detects on exam), lesion (unit of abnormality, usually anatomic), etiology (cause of a disease), pathogenesis (how the etiologic agent causes the disease), prognosis (how the patient can reasonably expect to do).

Basic Mechanisms

- Cellular & molecular aspects of injury & death
  - Types of cell death
  - Oxygenation, blood & free radical injuries

- Cellular response to injury
  - Inflammation and repair
  - Adaptation

- A sampling of important diseases
  - Cancer
  - Infection, sepsis and shock
  - Atherosclerosis and cardiovascular disease
Cell death

- **Necrosis** is abnormal cell death (cf apoptosis)
- **Proximate causes:**
  - Toxins, hypoxia (too little oxygen for cellular respiration)
- **Ultimate causes:**
  - Reduction in blood supply (ischemia), e.g. stroke
  - Too little oxygen in the blood (hypoxemia)
  - Infective agents (producing toxins), trauma, radiation, etc.
- **Consequences:**
  - Cells swell and burst, spilling contents into interstitial fluid
  - Strong inflammatory response, phagocytosis

Necrosis in heart attack

- Heart attack (myocardial infarction) causes ischemic necrosis in cardiac muscle
- Muscle cells die (no nuclei!), infiltrate of small dark inflammatory cells (neutrophils)

Molecular mechanisms

- Lack of oxygen causes:
  - Depletion of ATP:
    - Na/K pump fails: Na\(^+\) influx, followed osmotically by water
  - Reduced synthesis and increased degradation of phospholipids, particularly of cell membrane
    - Increased permeability to Ca\(^{2+}\) (creating calpain & O\(_2\)\(^-\))
  - Mitochondrial membrane leaks calcium (irreversibility)
- Reperfusion injury
  - Creation of free oxygen radicals, O\(_2\)\(^-\), OH\(^-\), H\(_2\)O\(_2\)
    - Very reactive, damaging nearly all biomolecules.
    - Limited detoxification capacity (e.g., superoxide dismutase)
**Cellular response to injury**

*Inflammation*
- Response to many kinds of injury: trauma, heat, chemical
- Sensed as swelling, redness, heat and pain

*Acute inflammation:*
- Lasts minutes to days.
- Fluid and plasma proteins flow in. Capillaries become more permeable. Arteriolar dilatation, venular constriction
- Infiltration of leukocytes, mostly neutrophils at first, then monocytes, then lymphocytes

**Molecular aspects of acute inflammation**

*Circulatory changes:*
- Kinins, particularly bradykinin. Causes vascular dilation & leakage. Also slows heart rate, relaxes smooth muscle

*Leukocyte recruitment:*
- Complex process, requires attraction to site, attaching to and permeating vessels
- Molecular signals include:
  - histamines, prostaglandins, leukotrienes, chemokines
  - The complement cascade (immune response)

**Wound healing**

*Healing occurs with inflammation*
- Removal of debris, repair of tissues
- Keys: angiogenesis & collagen deposition (scarring)

*Formation of new tissue*
- Fibronectin, laminin & integrins help form fibrous extracellular matrix and help new cells attach to it
- Tissue specific growth factors & cytokines influence development of new vasculature, epithelium, etc.
- Fibroblasts produce collagen and elastins

*Need not just cells, but architectural repair*
- Rare in vertebrates...
Cellular adaptation

- **Atrophy**: reduction in cell (and organ) size
  - E.g. in muscles through lack of use or denervation
- **Hypertrophy**: increase in cell size
  - E.g. in cardiac ventricles due to high blood pressure
- **Hyperplasia**: increase in the number of cells
  - E.g. excess estrogen causing endometrial hyperplasia
- **Metaplasia**: change in cell type (to another normal type)
  - E.g. columnar epithelium become squamous in smokers
- **Dysplasia**: change to an abnormal cell type.

Adaptation pictures

- **Atrophy** (in muscle, due to ALS denervation)
  - Atrophied
  - Normal
- **Hypertrophy** (ventricular cardiac muscle)
  - Left is normal, right hypertrophied
  - Fibers are thicker and the nuclei are larger and darker in the hypertrophied myocardium. Clear spaces between cells are processing artifacts

More adaptation

- **Hyperplasia** (often in prostate of older men)
  - Left is normal
  - Middle is hyperplastic
  - Right is high mag hyperplasia
- **Metaplasia**
  - Tracheal epithelium of a smoker shows transition from (normal) columnar epithelium to squamous type normally found in skin.
Cervical dysplasia
- Normal squamous epithelium on left shades into disordered dysplastic cells on the right

Dysplasia is a step toward cancer.

Neoplasm (tumor) is a mass of new tissue
- Develops its own blood supply
- Benign (stay in place) or malignant (invades other tissues)

Dysplasias grow into malignant neoplasms

Dysplasia (and on to Neoplasm)

Breakdown of the deal of multicellularity
- Abnormally proliferating, invasive somatic cells

Cancer cells
- Grow very quickly (although often not as quickly as embryonic or bone marrow or intestinal epithelial cells)
- Tend to de-differentiate, but exhibit some of the characteristics of their cell type of origin, e.g. make glands
- Cancer when cells invade past a basement membrane

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Molecular Biology of Cancer

Large-scale rearrangements of chromosomes common in cancer; sometimes specific

Oncogenes are genes whose mutations or expression (or lack) is associated with cancer
- Bcl2: component of transduction of apoptosis signal. Cells with mutated Bcl-2 do not respond to apoptosis signals.
- p53: inhibits reproduction of cells with damaged DNA. Many human tumors have a p53 defect.
- PTEN: mutation or loss found in many advanced (metastatic) tumors; possible role in cell adhesion
Lung cancer (from tobacco) dominates cancer deaths.
Breast cancer worst killer for women, but lung accelerating
Colorado has lowest incidence in US for all cancers (and 3rd lowest tobacco use)

Cancer Research Directions

- Current regimes based on agents that are toxic to all rapidly dividing cells
  - Horrendous side effects, poor efficacy.
- More specific therapies require finding “molecular signatures” of tumor cells
  - From signatures come diagnostics and drug targets
- Focus on interaction between genes, environment and lifestyle
  - Familial cancer predispositions (e.g. BRCA1) are very rare
- Many disappointments (anti-angiogenesis?)

Infectious disease

- Caused (in part, at least) by an external agent
  - Bacteria (e.g. clymidia, rickettsia, streptococcus, TB)
  - Virus (e.g. AIDS, common cold, smallpox, West Nile, etc.)
  - Fungus (e.g. yeast infections, thrush, athlete's foot)
  - Parasite (e.g. malaria, Giardia, trypanosomes, worms)
  - Prion (e.g. Cutzerfild-Jakob, Kura)
- Infectious diseases are usually opportunistic
  - Malnutrition, alcohol, wound foreign bodies, etc. play a role
- Largely treatable, but kill tens of millions of people a year internationally.
Immunization

- Immunization is tremendously effective
  - Smaller role for antibiotics; Large early role for sanitation.

- Immunization is not universal
  - Poverty, Ideology, Profitability

Multiple organ failure & Sepsis

- Multiple organ failure (shock) can be thought of as “whole body inflammation.”
  - Generally fatal, and a common endpoint to many diseases/injuries. Also, the worst surgical complication.

- Sepsis is when this is caused by a widespread infection (in the bloodstream).
  - May be mediated by the bacterial molecule endotoxin

- No current treatment or effective diagnosis
  - Controversial new drug is recombinant human protein (activated protein C); some modest effect, but not great.
  - Still looking for quickly testable diagnostic markers

Atherosclerosis and Cardiovascular disease

- Atherosclerosis is a stereotyped response of the inner surfaces of large arteries to insults.
  - Cells between the endothelium and the internal elastic membrane take up cholesterol-rich lipid
  - #1 killer in US. Treated with exercise, diet and cholesterol lowering drugs

- Consequences:
  - Slow occlusion: angina, ischemic scarring of heart; atherosclerotic dementia
  - Sudden occlusion (thrombosis, atheroembolization) or hemorrhages into plaques (myocardial infarct, stroke)
Molecular Biology of Atherosclerosis

- Eukaryotic cells regularly ingest regions of membrane by **endocytosis**.
- Process happens at specific regions of membrane, **clathrin-coated pits**.
  - Receptor-mediated endocytosis preferentially takes up particular external molecules.
  - Cells use this to take up cholesterol, a lipid required for membrane synthesis, from the blood.
- Excess cholesterol is deposited on arteries as plaque.

Causes of Death in the US

- **Cardiovascular disease, cancer & trauma**

Economics and Disease

- Many risk factors for disease correlate with economic status
  - Malnutrition with poverty
  - Obesity/inactivity with wealth