CELL INJURY, DEATH, AND ADAPTATION

Definitions
Pathology is a discipline bridging clinical practice and basic science.

To render diagnosis and guide therapy
- Identity changes in gross
- Morphology (microscopy) appearance of cell tissues

The scientific focus of pathology is:
- Etiology: on the cause of disease
- Pathogenesis: mechanism of its development and the pathways by which morphologic changes occur

Normal homeostasis if cell adjusting structure and function to accommodate changing demands and extracellular stresses.

Stresses or pathologic stimuli the cell can:
- undergo adaptation
  eg.: atrophy, hypertrophy, hyperplasia and metaplasia
- irreversible injury and ultimately dies

Two principal pattern of cell death:
1. NECROSIS, commonly coagulative necrosis
   - cellular swelling
   - protein denaturation
   - organellar breakdown
2. **APOPTOSIS**, - regulated event
   - programmed death

### CAUSES OF CELL INJURY

1. **Hypoxia** :-Anemia-Ischemia-Intoxication CO2
   - Aerobic oxidative respiration

2. **Physical Agent** :
   - mechanical trauma
   - extreme temperature
   - radiation
   - electric shock
   - atmosphere pressure

3. **Chemical and drugs** :
   - sufficiently concentrated glucose, salt, O2

   - air pollutants
   - insecticides
   - asbestosis
   - ethanol

4. **Microbiology Agents**
   - tape worms
   - rickettsia
   - virus
   - bacteria
   - fungi

5. **Immunologic Reaction**
   - anaphylactic reaction
   - autoimmune diseases
5. Genetic Defects
- congenital Malformation
- sickle cell anemia

6. Nutritional Inbalance
- protein calori insufficiency
- vitamins deficiency
- diabetes

7. Aging

Mechanism of Cell Injury
- Cellular response to injurious stimuli
  - injury type
  - duration
  - severity
- Current Status: ~ nutrional
  ~ hormonal
  ~ adaptibility of the cell
- Intercellular systems
  > cell membrane integrity
  > aerobic respiration
  > protein synthesis
  > integrity genetic apparatus
• Oxygen and oxygen derived free radicals: ischemic and hypoxic injury

**Reversible Injury**
Reduced oxidative phosphorylation in mitochondria. Activity Natrium Pump is reduced
Producing cellular swelling. Loss of microvilli
- Glycogen depleted
- Reduction in protein synthesis
- Formation of cell surface blebs

**Irreversible Injury**
- Severe vacuolization of the mitochondria
- Demage of the mitochondrial matrix
- Demage of plasma membrane
- Swelling of lysosomes
- Accumulation of amorphous calcium
- Rich dentities in mitochondrial matrix
Forms and Morphology of Cell Injury

1. Reversible acute cell injury
2. Necrosis (Cell death after irreversible injury)
3. Cell death by suicide = Apoptosis
4. Subcellular alteration as a respond to chronic or persistent injury stimuli
5. Intracellular accumulations of a number of substances: lipid, carbohidrat, protein, as a result of dearangement in cell metabolism or excessive storage.
**Sublethal Damage**

1. Recoverable – necrosis is not
2. Ultrastructural damage to mitochondria
3. Swelling of cellular organelles (hydroptic deg.)
4. Fatty change is impairment of metabolism

**NECROSIS**

Refers to a sequence of morphologic changes that follow cell death in living tissue

1. Intense eosinophilia of the dead cell is due to loss of RNA and coagulation of protein.
2. Nuclei undergo phase of pyknosis, karyorhexis and karyolysis leaving a shrunken cell devoid of nucleus.
3. Protein may be liberated from the dead cell
The morphologic appearance of necrosis is the result of two essentially processes:

1. Enzymic digestion of the cell
2. Denaturation of protein

**Autolysis** is a dead cell themselves by hydrolitic enzymes

**Heterolysis** from the lysosomes of invading inflammatory cells

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**Morphologic Evidence of Necrosis**

**A. Early Change**
1 – 3 hour before changes of necrosis are recognizable on electron microscopy
6 – 8 hour on light microscopy organelle degeneration

**B. Nuclear Change**
Pyknosis: The chromatine clumps into coarse strands
The nucleus becomes a shrunken dense, basophilic mass
Karyorrhexis: The pyknotic nucleus break up into numerous small basophilic mass

Karyolysis: The nucleus lysis as a result of the action of lysosome deoxy – ribonucleases

C. Cytoplasmic Change
   About 6 hour after cell necrosis
   Cytoplasma becomes homogenous and deeply acidophilic. Enzymatic digestion

D. Biochemical Changes
   Actively transports calcium ions out of the cell

Types of Necrosis
   Depends on:
   1. Cells compositions
   2. Speed of necrosis
   3. Type of injuries
   > Coagulative Necrosis
   Implies preservation of basic structural outline of the coagulated cell or tissue for a span of days.
   The structural protein and the enzymatic protein thus blocking cellular proteolysis
   Coagulation necrosis is characteristic of hypoxic death of cells in all tissue except the brain
   eq. Myocardial Infarction ( occlusion of arterial supply )
Liquefactive or Colliquativa Necrosis
Dead tissue that appears semi liquid as a result of dissolution of tissue by the action of hydrolytic enzymes
   eq.: - cerebral infarction
   - necrosis caused by bacterial inf.

Caseous Necrosis
Dead cell form an amorphous proteinaceaus mass, no original architecture can be seen histologically (soft and white resembling cream cheese)
Most often in fact of tuberculous infection with central necrosis

Gumatous Necrosis
describes dead tissue when it is firm and rubbery like caseous necrosis in the spirochetal infection syphilis.

Hemorrhagic Necrosis
describes dead tissue that are suffused with extravasated red cell, when cell death is due to blockage

Fat Necrosis
does not really necrosis. It describes focal areas of fat destruction tipically occuring following pancreatic injury. Or after trauma to fat for example in the breast
Describes foci of hard yellow material seen in dead adipose tissue

> Fibrinoid Necrosis
  when fibrin is deposited in damage necrotic vessel walls in hypertension and vasculitis

> Gangrene
  extensive tissue necrosis; is complicated to a variable degree by secondary bacterial infection

**APOPTOSIS**
is responsible for the programmed cell death in several important physiology processes including:

- The programmed destruction of cells during embryogenesis as in implantation, organogenesis, and developmental involution

- Hormon dependent physiologic involution such as the endometrium, lactating, as in the prostate after castration
Cell deletion in proliferating population such as intestinal crypt epithelium or cell dead in tumor

Deletion of autoreactive T cell in the thymus, cell death of cytokine starved lymphocytes

**CLINICAL EFFECTS OF NECROSIS**

↔ Abnormal function

- Kidney: renal failure
- Cortex in brain: muscle paralysis
- Heart: heart failure
- Lung: hemoptysis

↔ Bacterial infection: gangrene

↔ Release of contents of necrotic cells

- Liver: elevation SGOT
- Heart: creatine kinase

↔ Systemic effects

- Fever
- Inflammatory Reaction

↔ Local effects

- Hemorrhage
- Ulceration
CELLULAR ADAPTATIONS OF GROWTH AND DIFFENTIATION

Environment adaptation of the cell
1. Physiologic Adaptation
   - Hormones
   - Endogenous chemical mediators
2. Pathologic Adaptation
   - Induction of new protein synthesis by target cell

Cell Injury:
- Death of cells (permanent organ injury)
- Sublethal injury (adaptation)

Adaptation of the cell:
1. Atrophy
2. Hypertrophy
3. Hyperplasia
4. Metaplasia
5. Dysplasia
6. Storage

**ATROPHY**
is the decrease in the size and a function of a cell but are not dead

Causes of atrophy:
1. Reduced functional demand
   - Immobilitation in fracture
   - Prolonged bed rest

2. Inadequate supply of oxygen
   - Ischemia

3. Insufficient nutrients
   - Starvation
   - Inadequate nutrition
   - Chronic disease

4. Interruption of trophic signals
   - The functions of many cells depend on signal
     transmitted by chemical mediators

5. Persistent cell injury
   - Caused by chronic inflammation
     - Chronic gastritis
     - Prolonged pressure

6. Aging
   - Particularly in non-replicating cells such as brain,
     heart.
   - Senile Atrophy

- Endocrin system
- Neuromuscular transmission
  - Thyroid
    - Adrenal cortex
    - Ovarium
    - Testis

- Senile Atrophy
The mechanism of atrophy:
• decreased synthesis
• increased catabolism
• influenced by a number of hormones
  eq. Insulin, thyroid stimulating hormone, glucocortiroids

**HYPERTROPHY**

Is an increase in the size of cell accompanied by Augmented functional capacity

Hypertrophy is a response to trophic signals and Commonly a normal processes

I. Physiological (Hormonal) hypertrophy
   - in puberty an increased production of sex hormone
   - hypertrophy breast tissue
   - abnormal hormone production in cancer

II. Increased functional demands
   - exercise
   - pathological conditions
     eq. Myocardial cell
   - kidney hypertrophy on surgical removed
HYPERPLASIA
is an increase in the number of cells in an organ or tissue

Hyperplasia can be:

I. Physiologic hyperplasia
   - hormonal hyperplasia
   - compensatory hyperplasia

II. Pathologic hyperplasia
    excessive hormonal or growth factor stimulation
    eq. Endometrial hyperplasia

1. Hormonal stimulation
   - estrogen increased endometrium (hyperplasia)
   - gynecomastia

2. Increased functional demand
   - secondary polycytemia
   - lymphocyte hyperplasia

3. Persistent Cell Injury
   - chronic inflammation in the skin and the epithelium of viscera
   - hyperplasia of the bladder epithelium
**METAPLASIA**

is a reversible change in which one adult cell type is replaced by another adult cell type. (Metaplasia is the conversion of one differentiated cell type to another)

*It is almost invariably a response to persistent injury and can be thought of as an adaptive mechanism.*

Most common is the replacement of a glandular epithelium by a squamous cell.

- Squamous metaplasia of the bronchial epithelium to tobacco
- Lower oesophagus by reflux acidic gastric
- Endocervical metaplasia

**Metaplasia is usually reversible if the stimulus is removed.**

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**DYSPLASIA**

Cellular dysplasia refers to an alteration in the size, shape and organization of the cellular component of a tissue.

The cells in an epithelium exhibit uniformity of size, shape and nucleus.

Dysplasia means is disturbed by

1. Variation in the size and shape of cells
2. Enlargement, irregularity and hyperchromatism of the nuclei.
3. Disorderly arrangement of the cells within the epithelium
The most common in the cervix and bronchus

It is established that dysplasia is a preneoplastic lesion in the sense that it is a necessary stage in the multistep cellular evolution to cancer.

Dysplasia included in the morphological classification of the stage of intraepithelial neoplasia

**CELLULAR AGING**

Alterations in structure and function that may lead to cell death, or at least diminished capacity of the cell to respond an injury

Reduced cell in:
- pleomorphic vacuolated mitochondria
- repair of chromosomal damage

Morphologic alteration in:
- pleomorphic vacuolated mitochondria
- decreased endoplasmic reticulum
- distorted Golgi Apparatus
- accumulation of lipofuscin pigment
Cellular senescence is multifactorial:

1. The cumulative effects of extrinsic influences: free radical damage

2. Intrinsic molecular program of cellular aging: cell have a finite life span