Cardiac Injury

- virus
- drugs
- parasite

Inflammation and myocyte damage = MYOCARDITIS

“itis” = inflam. of
Normal

scar (fibrosis)

trichrome stain (collagen—blue)
ruptured atherosclerotic plaque with thrombosis
Cell injury
Repair
bld flow, myocyte death
scar (fibrosis)
heart
dentate line
**Molecular and Cellular Pathophysiology**

**Key Precept:**

Most diseases are manifestations of either:

- inflammation
- repair
- neoplasia
Introduction to Cell Injury

1. A brief illustrated hx of pathology
2. Basic principles of cell injury:
   - agents of injury
   - cellular/tissue adaptive responses
   - prototypes of cell injury
   - cell death: NECROSIS

Pathology:
The Study of Disease

- Anatomic: surgical/autopsy/
  subspecialty (renal/liver)
- Clinical: laboratory tests--blood
  bank--tx med.—microbiology

• What do we do?
  Diagnosis—Teaching--Research
<table>
<thead>
<tr>
<th>HUMORS</th>
<th>QUALITIES</th>
<th>TEMPERAMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>warm-moist</td>
<td>sanguine</td>
</tr>
<tr>
<td>yellow bile</td>
<td>warm-dry</td>
<td>choleric</td>
</tr>
<tr>
<td>black bile</td>
<td>cool-dry</td>
<td>melancholic</td>
</tr>
<tr>
<td>phlegm</td>
<td>cool-moist</td>
<td>phlegmatic</td>
</tr>
</tbody>
</table>

Hippocrates about 400 BC ancient, four winds Galen about 150 AD

Galen 150 A.D.
Giovanni Batista Morgagni:

1760: “The Seats and Causes of Disease”

John Hunter:

• *Gross organ museum* (Royal College of Surgeons, UK)
Marie François Bichat:

- Organs are composed of tissues

- Division of pathology into:
  - General Pathology (pathologic processes which may affect many organ systems)
  - Systemic Pathology (pathologic processes unique to specific organ systems)
Rokitansky:

- Performed 30,000 autopsies
- Observed 60,000 autopsies
- En bloc dissection
1650
Galileo
- first compound microscope

1700
Antoni van Leeuwenhoek
- simple microscope
- observed cell nucleus
Virchow: All disease begins in the cell (Cellularpathologie)
1938

- Berlin
- von Barries
- Ruska
- first electron microscopic pictures

1950's - 1970's

- Freeze fracture
- Scanning electron microscopy
Gene Chip Microarrays
Cell Injury and Response

1. How does a cell become injured?
2. What are the cell’s resources to survive injury?
3. What are the major pathways of cell injury?
4. What cellular changes occur after injury?
5. How does the cell die?
6. How does the tissue react to cell injury & cell death?

Agents of Injury

- Genetic
- Nutritional
- Physical
- Immune
- Infectious
- Chemical
Physical

Free radicals

- \( \text{O}_2 \cdot \)
- \( \text{OH}^- \)
- \( \text{H}_2\text{O}_2 \)
Chemical Agent of Injury

Cell membrane

Vascular compartment

Toll-like receptors
(Toll gene in Drosophila)

---microbe receptors

Phagocytosis

Nuc.
**Cellular resources against injury**

1. Vascular space (delivery of nutrients/cytokines/detox. enz’s/O₂)
2. Extracellular space (collagen + matrix proteins) for restructuring the damaged organ
3. Cell’s structure and differentiation
4. Cell’s capacity to divide
   - postmitotic
   - intermitotic
   - reverting postmitotic

**Postmitotic:** heart, nerve

**Intermitotic:** intestinal epith., skin, bone marrow

**Reverting postmitotic:** hepatocytes, renal tubular epithelium

***Stem cells: b.m.-derived / local organ***
Cellular Physiologic Adaptations To Injury

Prototypes of cell injury

- hypoxia/ischemia
- free radicals
- chemical
- viral
**Free radical injury**

- lipid peroxidation
- protein cross-linking by forming disulfide bonds
- DNA mutations
  - Reactive species (with single unpaired e⁻ in outer orbital) interacts with membrane, lipid, -SH bonds of proteins and DNA nucleotides
  - Superoxide (O₂⁻)
  - Hydroxyl (OH⁻)
  - H₂O₂

**Chemical Injury**

**direct combination** of chemical with molecule or organelle

form reactive metabolite: binds covalently to membr. prot. or lipid
Viral injury

cytopathic
viral replication interferes with cell metabolism--cell damage

immune-mediated damage
against viral Ag's or viral-altered cell Ag's

Ischemic (decreased blood flow) and Hypoxic Injury

- impair cell's aerobic respiration, ATP generation.
- glycolysis produces lactic acid, pH drops, dysfunction of Na-K-ATPase leads to acute cell swelling by influx of Na⁺, efflux of K⁺
- changes in RER/nuclear chromatin/cell surface: REVERSIBLE!
- persistent ischemia: mitochondrial/lysosomal/Ca²⁺/membrane changes: IRREVERSIBLE!
Mechanisms of cell death

- Necrosis
- Apoptosis
Necrosis
Example: coagulative necrosis due to ischemia/hypoxia

- Increased eosinophilia — eosin binds denat. prot.
- Cell swollen — membrane permeability altered
- Cytoplasm glassy — loss of glycogen
- Cytoplasm vacuolated — enzymatic degradation of organelles
- Nuclear pyknosis-karyorrhexis-karyolysis— enzymatic denaturation/degeneration of nucleoprotein
- Necrosis elicits inflammation!!! (vs. apoptosis)

Nuclear changes in necrosis

Viable cell → pyknosis → karyorrhexis → karyolysis

Necrosis
CV

PV

hep. artery

pyknosis

karyorrhexis
Caseous necrosis (e.g., Tuberculosis)

Casein (milk) = white