Normal heart

Cardiac Injury
-virus
-drugs
-parasite

Immune system response

Inflammation and myocyte damage = MYOCARDITIS

“itis” = inflam. of

Normal scar (fibrosis)

Cell injury

Repair

Heart

Ruptured atherosclerotic plaque with thrombosis

Blood flow, myocyte death

Scar (fibrosis)
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

**Molecular and Cellular Pathophysiology**

**Key Precept:**
Most diseases are manifestations of either:
- inflammation
- repair
- neoplasia

**A Brief Illustrated History of Pathology**

**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

Edwin Smith Papyrus
Giovanni Batista Morgagni:
1760: “The Seats and Causes of Disease”

John Hunter:
• Gross organ museum (Royal College of Surgeons, UK)

Marie Francois Bichat:
• Organs are composed of tissues
• Division of pathology into:
  - General Pathology (pathologic processes which may affect many organ systems)
  and
  - Systemic Pathology (pathologic processes unique to specific organ systems)

Rokitansky:
• Performed 30,000 autopsies
• Observed 60,000 autopsies
• En bloc dissection
Virchow: All disease begins in the cell (Cellularpathologie)
Gene Chip Microarrays

Agents of Injury
- Genetic
- Nutritional
- Physical
- Immune
- Infectious
- Chemical

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?
Cellular Physiologic Adaptations To Injury

Prototypes of cell injury

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
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⁻)

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!

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

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

Spleen: infarct
Caseous necrosis (e.g., Tuberculosis)

Casein (milk) = white

Cell Injury

- Inflammation
  - vascular
  - cellular
  - cytokine secretion
- Coagulation & Fibrinolysis
- Extracellular matrix synthesis
- Genetic alterations

Lung (apex)