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

John Hunter:
• Gross organ museum
  (Royal College of Surgeons, UK)
Marie François Bichat:
- Tissues are composed of organs

Rokitansky:
- Performed 30,000 autopsies
- Observed 60,000 autopsies
- En bloc dissection
Virchow: All disease begins in the cell (Cellularpathologie)
Cesar Milstein  
Nobel Prize 1984  
Monoclonal Ab’s

Gene chip microarray analysis: 2000 — —
- each column represents the data from a microarray hybridized with a complementary RNA pool (Red = high expression; Green = low expression)

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

Genetic

Nutritional

Excess:
- lipid
- carbohydrate
- vitamin

Deficiency:
- vitamin
- protein
- calorie
free radicals

Physical

Chemical
Immune: Autoimmune hepatitis
Attack against host hepatocytes by lymphocytes

Infectious

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

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 (O\(_{2}^{\cdot-}\))
  - Hydroxyl (OH\(^{\cdot}\))

Viral injury
- Cytopathic
  - viral replication interferes with cell metabolism--cell damage
- Immune-mediated damage
  - against viral Ag's or viral-altered cell Ag's

Chemical Injury
- Direct combination of chemical with molecule or organelle
- Form reactive metabolite: binds covalently to membr. prot. or lipid

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 chromatia/cell surface: REVERSIBLE!
- Persistent ischemia: mitochondrial/lysosomal/Ca\(^{++}\)/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

[Diagram of nuclear changes in necrosis]

Viable cell → pyknosis → karyorrhexis → karyolysis