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
400 B.C.
Hippocrates
humoral pathology
disorders of body fluids
Greece
ANTONII BENIVENIT FLOREN. TINI MEDICI ET PHILOSOPHII
DE ABITIS NON NULLOS AC
MIRANDIS MORBÓRVM ET SA-
NATIONVM CAVSIS.

De morbo quam vulgo Gallicus voc.

OVVM MORBI GENVS,
Anno Salutis non eximio fras
sum primum tum Gallum et aeternum.

Hoc ab Hispania incipiens, per Italiam
inciubat enim pulsa
egens diversa in genitalibus membris;
licet interdus, sed raro in capite; & inde
per totum corpus diffusus est.

Aliis aequo
plane minucius ext extincte; sed februe tamet;
in superfcie; & colere sublimate sub quibus
figurascNrabantur; & caro sub
et alia apparent; Aliis urinis similae figurum
rotundas; & ab his figuris levis
resolutis prominentes caro rubesculantes;
Giovanni Batista Morgagni:

1760: “The Seats and Causes of Disease”

John Hunter:

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

• Tissues are composed of organs
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 and Ruska
first electron microscopic pictures
1950's - 1970's

- Freeze fracture
- Scanning electron microscopy

1970's

Immunocyto histochemistry
Cesar Milstein

Nobel Prize 1984
Monoclonal Ab’s
1980's

- new DNA technology
- bacteriophage
- plasmids
- restriction endonucleases
- integrated DNA

PCR
Gene chip microarray analysis: 2000 genes - 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

- $O_2^-$
- $OH^-$
- $H_2O_2$
Chemical
**Immune: Autoimmune hepatitis**  
Attack against host hepatocytes by lymphocytes

**Infectious**

- actinomyces (facial abscess)
- streptococcus (pharyngitis)
- pneumococcus (pneumonia)
- meningococcus (meningococcal meningitis)
- Escherichia coli (pyelonephritis)
- spirochetes (syphilis)
- chlamydiae (lymphogranuloma venereum)
- staphylococcus (osteomyelitis)
- mycobacteria (tuberculosis)
- fungi
  - cryptococcus (meningitis)
  - candida (oral thrush)
  - histoplasma (pulmonary infection)
  - aspergillus (pneumonia)
  - dermatophytes (athlete's foot)
- viruses
  - enterovirus (poliomyelitis)
  - herpes (encephalitis)
  - Herpes simplex (stomatitis)
  - Herpes zoster (shingles)
  - rubella (measles)
  - hepatitis viruses (hepatitis)
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 ($O_2^{-}$)
  - Hydroxyl (OH·)
  - $H_2O_2$

**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
Cell Injury

- Revers
- Irrevers
- Recovery (NL)
- Necrosis

Inflammation
- Vascular
- Cellular
- Cytokine secretion

Coagulation & Fibrinolysis

Extracellular matrix synthesis

Genetic alterations