Assignment Page

Reading
Robbins, Chapter 1
Wheater - Part 1: p2-9

Clinical lab Source: Preface and look over table contents.
Know how to use this book. We will
Being having regular assignments

Slide assignment: Review the “normal” histology
slide set in the path collection.
There are only ten of them.

#6 Myocardial Infarction
#43 Myocardial Infarction
#44 Myocardial Infarction

Look for the nuclear changes we have discussed in class.
Introduction to Pathology

Cellular Adaptation, Cell Injury and Cell Death

I. What is pathology?

A. study of diseases

1. cause

2. mechanism of development

3. structural changes

4. functional consequences

5. intervention and therapeutics

B. categories or groupings

1. congenital

2. acquired (many in this group)

   - infectious, neoplastic, immunologic......
C. cellular and organ consequences

1. Loss of function
   - temporary
   - permanent with cell death

2. repair and restoration of function

II. Adaptation, modifications and response to stress

A. General stuff
   - response to something
   - physiological
   - pathological
   - up and down-regulation
   - induction of new proteins
   - major modifications to altered environment
   - adaptation is generally reversible
B. Hypertrophy - increase in size, not number of cells of an organ

1. Physiological - muscle development

2. Pathological

   - cardiac muscle with high blood pressure and congenital abnormalities
C. Hyperplasia - increase in **numbers** of cells, therefore stimulation of cell division

1. Physiological
   - hormonal mediated - pregnancy and breast growth
   - compensatory - restoration of cells after injury or disease
     - stable, labile and permanent cell populations
     - liver after hepatitis

2. Pathological
   - excessive or unbalanced
     - exogenous estrogens

D. Atrophy - shrinkage in cell **size**, not death of cells of an organ

1. Decreased workload
2. Loss of neural innervation
3. Diminished blood flow (chronically, not acute cessation)
4. Inadequate nutrition
5. Loss of endocrine stimulation
6. Age related

E. Metaplasia - a **reversible** change of one **adult** cell type for another **adult** cell type

1. Response to chronic irritation or low grade injury
   - takes time, not an overnight development
   - generally columnar is converted to squamous (a tougher actor)
     - a form of genetic reprogramming
   - respiratory epithelium of smoker goes to squamous
   - ductal epithelium of salivary glands and pancreas go to squamous with
     chronic obstruction
III. Cell death and injury: the big picture “Bring out your dead...”

A. dead or almost dead “But I’m not dead yet” (i.e. when is it still reversible)?

B. planned or otherwise?

- apoptosis vs. necrosis

C. process or product? What is the purpose?

D. common features

E. types of injury

- hypoxia

- physical agents

- chemical

- infectious

- immunologic reactions
- genetic

- nutritional

- neoplastic transformation

V. Injury and necrosis (unplanned cell death)

A. general features

1. intracellular

   - membrane integrity

   - Changes in intracellular Calcium ion concentrations

   - ATP production and mitochondrial damage

   - protein synthesis

   - nuclear integrity

2. interconnection of all systems, once one is fatally damaged, the rest follow
3. time interval for changes to develop

- death of organism vs death of only a segment of the organism

4. injurious agent

- type
- duration
- magnitude

5. unique aspects of organ involved.

- ability to recover or reproduce lost or damaged members

- RBC’s

- GI epithelium

- neurons

- cardiac muscle
IV. Ischemic and hypoxic injury: REVERSIBLE vs IRREVERSIBLE

(What the heck does **ischemia** mean?)

A. General types

- Oxygen deprivation

- blood flow cessation

- Can you think of others?

B. Reversible

1. oxidative phosphorylation by mitochondria
   - ATP down
   - AMP up

2. anaerobic glycolysis

3. pH drops

4. nuclear changes
5. cellular swelling (volume regulation mechanism impairment)
   - Na and K regulations gets farkled up

6. ribosomes forget what they are suppose to do

7. restore blood flow or oxygen, all is reversible and the cell survives

C. Irreversible injury (you’re going to die)

1. when in the course of the injury and at what level of injury? Who can say?
   - organ sensitivity

2. features
   - membrane damage and loss of volume control are probably most important!!

![Diagram showing reversible and irreversible injury processes.](image-url)
- globs in mitochondria and mitochondrial dysfunction that cannot be reversed. Very Important

- lysosome break down

- activation of acid hydrolase

- RNAases

- proteases

- phosphatases etc.. etc..

3. self destruction - AUTOLYSIS

4. partially degraded lipids may even calcify and form a soap like material

5. IMPORTANT
- loss of vital constituents from cell through damaged membrane

- amino acids and other things important to cell function

- cellular enzymes may leak from membranes and be measured in blood

These can be of great DIAGNOSTIC IMPORTANCE

- acute myocardial infarction - elevated enzymes
- viral hepatitis - enzymes in blood

6. Cellular enzymes to read about

- CPK, LDH, AST, ALT
- Serum levels in health and disease?
- Organ specificity?
VI. Free radical induced injury; especially “activated oxygen species”

A. unpaired electrons in an “outer orbital”
   - unstable and extremely reactive

B. related to membrane damage

C. Initiation within the cell

   1. radiation

   2. endogenous oxidative reactions

   3. enzyme metabolism of exogenous chemicals

   4. reactive oxygen species ‘ROS’
- superoxide ion \((O_2^-)\), Hydrogen peroxide \((H_2O_2)\) and hydroxyl ions \((OH^-)\)

- P-450 enzyme system

5. interact with both plasma and organelle membranes

- autopropegation of destructive changes

6. degradation of critical enzymes

7. DNA breaks

D. How do you get rid of them? You make them all the time

1. spontaneous decay or use in reactions (termination)

2. inactivation

- sulphhydryl containing compounds

- cysteine, glutathione etc....

- enzyme degradation

- superoxide dysmutase
- catalase
- glutathione peroxidase

E. Balance between formation and termination of the free radicals is the base of it.

F. Many agents that produce what we call “chemical injury” work by the causing the formation of free radicals.

- \( \text{CCl}_4 \)
- Acetaminophen
- others cause direct membrane damage

VII. How can you tell reversible from irreversible cellular changes?

**In other words, injury vs necrosis.**

A. gross and/or microscopic

B. reversible; “I’m not dead yet”

1. gross; not much

2. microscopic:
- cellular swelling: water in cytoplasm as well as organelles
  - “hydropic change” “vacuolar degeneration”
- “fatty change” of cytoplasm
- plasma membrane “blebs” and “myelin figures”
- mitochondrial swelling
- nucleolar disaggregation

C. NECROSIS; OK, this is the biggie, pay attention!

1. Dead tissue but in the living person. Be sure this simple definition is understood!

- enzymatic digestion of the cell proceeds after “death”
- denaturation of proteins

- AUTOLYSIS Enzymatic digestion by enzymes from the cell itself

- HETEROLYSIS Enzymatic digestion from cells sent to clean up the mess or to remove the damage parts. In other words enzymes derived from living inflammatory cells that responded to the site of injury.
2. Recognizable changes of the individual cells in necrosis

- Nuclear changes
  - Pyknosis
  - Karyorrhexis
  - Karyolysis

3. Basic patterns of necrosis involving cytoplasm and extracellular space

- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Enzymatic fat necrosis
- Fibrinoid necrosis

Normal myocardium        Early coagulative necrosis        Lung with TB
VIII. Programmed or planned cell death or removal. This is not necrosis, but the cells die just the same. Be sure you know the difference!!

A. energy dependent process with special “death gene” activation

B. embryogenesis

C. hormone dependent involution

D. cell deletion in proliferating populations

E. tumor cell death

F. death of immune cells and removal of potentially autoreactive cells - Thymus

G. “atrophy” of hormone dependent cells (pathological? or just aging?)

H. loss of neighbors in one organ after the principal element has died. Salivary glands and pancreas after duct obstruction.

I. Graft verses host destruction. We might not want it to happen, but it is cell mediated destruction of a foreign element as far as the immune system is concerned.
J. Some injured cells know they should remove themselves.

- virus infected
- certain toxic agents

K. What does it look like?

1. cell shrinkage

2. chromatin condensation and break down to be recycled

3. formation of cytoplasmic blebs and “apoptotic bodies”
   - round up those enzymes before they can damage the neighbors

4. phagocytosis
5. IN CONTRAST TO NECROSIS, THERE IS NO INFLAMMATORY RESPONSE

Makes hard to see in most cases.
IX. Protective mechanisms. What can a cell do to try to hang on and see if it can survive the insult?

Not much really.

A. switch to anaerobic glycolysis: detrimental after a short time

B. Stress or heat-shock proteins.
   1. chaperone proteins
      - protein folding and translocation
      - may help to protect proteins not too badly damaged
   2. “ubiquitin” involved in protein degradation; may remove badly damaged proteins before they can cause additional problems.

X. What of non-lethal injury? You know, badly bent but not broken.

A. chronic injury?
   - organelle changes vs. “cellular”

B. adaptive changes?

C. can some of the cellular response actually be detrimental?

D. organelle level - this may be hard to see even with a microscope.
1. Heterophagia - uptake of junk - could be a source of problem as well as “cleaning up after injury.”

- phagocytosis
- primary vs secondary lysosome
- pinocytosis

2. autophagia - internal house cleaning the cell goes through after non-lethal injury

- Lipofuscin pigment - what the heck is this?

- lysosomal storage disorders

3. induction of SER

- chronic drug exposure

4. mitochondrial changes

5. cytoskeletal abnormalities

- failure of fusion and loss of function
- “immotile cilia syndrome”

- accumulation of partially completed structural proteins

E. intracellular accumulation of junk - this may be easier to recognize than the organelle stuff above

1. stockpiling a normal constituent verses

2. altered internal material or

3. exogenous junk (bacteria, pigmentary matter etc...)

F. lipid accumulation **within the cell**

1. triglycerides

   - *fatty change* - hepatocytes especially - ETOH and industrial chemicals

2. cholesterol accumulation

   - arteries - genetic defect - hardening of the arteries - “atheromas”

   - skin - xanthomas - in histiocytes - diabetes and genetic defects of
cholesterol metabolism

- sites of chronic injury - histiocytes - extracellular “slits”

- lipids are removed during processing of tissue, so you actually only see the spaces where the material was. (Does this make any sense?)

G. Stromal infiltration with mature fat cells. Be sure you know how this differs from what is described above.

1. In the situation above, the accumulation is within the cells, either parenchymal or inflammatory.

2. here we have replacement of the organ with adipocytes (fat cells) themselves

H. proteins

1. immunoglobulins in plasma cells

2. Alpha-1-antitrypsin in liver cells (genetic deficiency)
I. glycogen

- diabetes

- “storage disorders”

J. pigments

1. naturally occurring

- lipofuscin

- melanin

- hemosiderin (iron), need Prussian blue stain

- bile

2. not so natural

- coal dust - anthracosis

- silica dust

- tattoo dye

Reference: Robbins: Pathological Basis of Disease
XI. Pathological calcification (more common than you might think)

A. dystrophic calcification

- normal serum levels of calcium
- is a function of pH at the site of chronically injured tissue

B. metastatic calcification

1. generally high serum levels of calcium
   (various reasons, you can probably think of some)

2. occurs where there is a big pH differential
   - stomach
   - lung
   - skin
- kidney

C. both types of calcification may have intracellular or extracellular deposits
   - may even have “heterotopic bone” with bone marrow form at the site

D. unique calcifications associated with specific abnormalities, related to local conditions, not serum levels of calcium.

1. psammoma bodies - little whirls or spiral of calcium seen microscopically
   - some types of tumors, both malignant and benign

E. hyaline change

1. No this is not hyaline like you find in cartilage, rather the term refers to the homogenous and glassy staining property of congealed proteins within a sick or dying cell.

2. typically pink staining, glassy looking snot.
- actually may be intracellular or extracellular, it's the amorphous quality of the congealed proteins that is being addressed here.

XII. Age related

A. wear and tear

B. genetic ? 50 doublings in vitro

- syndromes of premature aging - progeria

- telomere shortening - chromosome stabilizers

C. accumulated free radical damage
D. post-translational modifications

- non-enzymatic glycosylation of proteins

- diabetes and membrane changes

E. loss of induction of heat-shock proteins (at least *in vitro*)
IU senior pays back mom who gave him life

Son back on campus after giving his mother life-saving liver transplant

By Sarah Morton
1-H-T Staff Writer

Indiana University senior Nick Cole is returning classes this week after putting his college career on hold last year. He had good reason for the delay — it was necessary to extend his mother's life.

The 23-year-old donated 60 percent of his liver to her during a live liver transplant earlier this year. Eva Elliott, 43, was suffering from end-stage liver disease spawned by the hepatitis C virus.

The January surgery that gave part of Cole's liver — and new life — to his mother was a success, with his recovery and liver replacement in talking about a month, while his mother's took two months.

It's now been seven months since the surgery.

"Everything has a different meaning now," Elliott said in her Bloomington home last week before returning to San Francisco for continuing treatment at the site of the rare and risky transplant procedure.

"His husband, Peter, will stay here to take care of finances. The surgery has forced them into bankruptcy, he said. But while their vehicles and many other possessions will be gone, they'll keep their house — along with new life and hope."

Mother and son say the Jan. 30 surgery and the recovery following it have changed their lives forever. Each faced fears of dying — for themselves and for their closest kin who lay next to them in the operating room.

The two are now finally busy getting back to routine schedules, though it's been tough for Elliott.

"This week, Cole returned to IU to finish his senior year."

When the microbiology major first heard how sick his mother was in California last year, he dropped his classes and moved there to be near her.

Elliott had gone west to take care of her elderly mother and a week at Stanford University. She moved back to the Bay Area, continuing Saturday, to continue treatments at University of California at San Francisco and to be closer to her daughter and her daughter's family, including a grand son born a day before the surgery.

Her liver was destroyed by the hepatitis virus. The portion of her son's liver she received in the transplant operation has grown to full size, but that does not mean she's cured.

The hepatitis is still present, and she's had two blood transfusions since the surgery.

"The two underwent extensive physical and psychological tests, not only to ensure a match but to determine how their bodies and minds would handle such an intense surgery. Being separated by half a continent will be hard for both of them, but Elliott said she's proud her son is back in school."

Elliott first discovered she had contracted hepatitis C while preparing for surgery in 1987, when tests for the virus came back positive. It's likely she contracted it during a blood transfusion while undergoing gall bladder surgery about a decade earlier.

The virus left Elliott tired and lethargic, unable to spend much time with Cole and her sister. "In a Europe, with whom Elliott now is staying in California."

Cole says his relationship with his mother was not at its best until that point. But during the months leading up to and following the surgery, mother and son shared a bedroom, often talking into the night about topics and faith, death, life and love.

"After the surgery, the discussions also included recovery advice: Cole, whose youth and health - meant a quicker recovery, would often give his mom a heads-up on a particular pain. "In two weeks, you'll be out here," he would say.

While still in the hospital at Valentine's Day approach, they noticed the halls filled with heart decorations. Stuffing a bag together, Cole told his mom he would like to be her Valentine and give her his heart, teasing that, after all, "I've already given you my liver."

Elliott said that relationship has totally changed as a result of the surgery. "I'm overwhelmed. He's my son and my friend," she said.

Physically, there are the scars, of course, tiny ones that stretch across their abdomen. "That's just the exterior reminder, though. ""Inside, we've changed,"" Elliott said.

"Reporter Sarah Morton can be reached at 317-492-25 by e-mail at smorton@herald.com.

IU senior gives mom life-saving transplant

Transplant / from A1

surgery. She also must take 26 pills each day, along with weekly injections and blood tests.

She still has to build up her immune system. But for a woman who was told about a year ago she only had a few left, life moves on — and that's a miracle, she says.

Until the night before their transplant, Elliott pleaded with her son not to undertake the risky procedure — not wanting him to sacrifice his own life for hers.

"She did anything she could to get out of this," Cole said. He jokingly mimics his mother's voice in a high-pitched voice: "Nick, please don't. Nick, you don't have to do this."

But for Cole, there was no alternative. The idea of being a donor had been his, coming during a conversation with the University of California, San Francisco, hospital. All around him were very sick people with yellow nails, long hair and bloodshot eyes — all waiting for a donor liver to receive them.

Elliott's name was behind thousands of others on a cadaver waiting list. Her time was likely too short for her to approach the top of the list.

Now, with part of her son's liver, the doctors have told her she has 30 more years.

Cole said his faith in God and respect for his mother guided him in the decision to donate. "It's weird, giving life to the person that gave you life," Cole said.

Compensatory hyperplasia, how does it work?