FUNDAMENTALS OF PATHOLOGY

MEDICAL COURSE AND STEP 1 REVIEW

2018 EDITION

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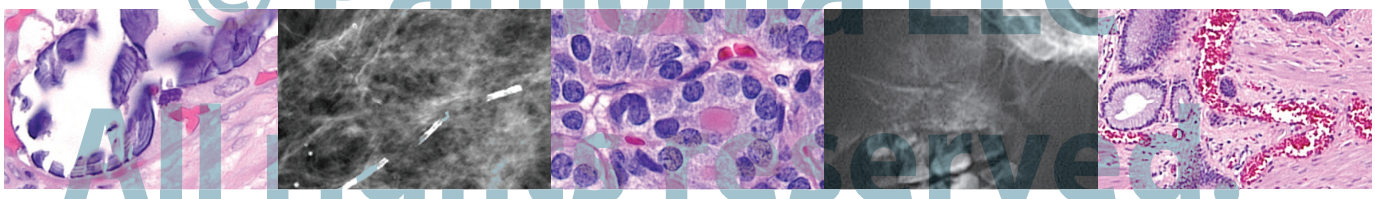

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USING THIS BOOK

This work is intended as a review for students during their preclinical years and while preparing for examinations, such as the USMLE™. To this effect, the organization of this book follows that of most primary texts in the field and parallels the syllabus used in pathophysiology courses in medical schools throughout the United States. Ample space is provided for students to make notes during course study and while viewing the online videos that cover each section of the text (www.pathoma.com).

We recommend that students use *Fundamentals of Pathology* during their medical courses, taking notes in the margin as pertinent topics are covered. When exam time comes around, these notes will likely be invaluable.

For examination preparation, we suggest students read the material first, then listen to the online lecture, and then reread the material to develop a solid grasp of each topic. One should not become disheartened if they are not able to retain all the information contained herein. This deceptively slim volume covers a tremendous amount of material, and repetition will be a key aid as you progress in your studies.

An effort has been made to emphasize concepts and principles over random facts, the forest rather than the trees. Attention to the same by the student will provide a deeper, more meaningful understanding of human disease. We must always remind ourselves that ultimately our goal is to learn, to share, and to serve. *Fundamentals of Pathology* was developed with this goal in mind.

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Growth Adaptations, Cellular Injury, and Cell Death

1

GROWTH ADAPTATIONS

I. BASIC PRINCIPLES

A. An organ is in homeostasis with the physiologic stress placed on it.
B. An increase, decrease, or change in stress on an organ can result in growth adaptations.

II. HYPERPLASIA AND HYPERTROPHY

A. An increase in stress leads to an increase in organ size.
   1. Occurs via an increase in the size (hypertrophy) and/or the number (hyperplasia) of cells
B. Hypertrophy involves gene activation, protein synthesis, and production of organelles.
C. Hyperplasia involves the production of new cells from stem cells.
D. Hyperplasia and hypertrophy generally occur together (e.g., uterus during pregnancy).
   1. Permanent tissues (e.g., cardiac muscle, skeletal muscle, and nerve), however, cannot make new cells and undergo hypertrophy only.
   2. For example, cardiac myocytes undergo hypertrophy, not hyperplasia, in response to systemic hypertension (Fig. 1.1).
E. Pathologic hyperplasia (e.g., endometrial hyperplasia) can progress to dysplasia and, eventually, cancer.
   1. A notable exception is benign prostatic hyperplasia (BPH), which does not increase the risk for prostate cancer.

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III. ATROPHY

A. A decrease in stress (e.g., decreased hormonal stimulation, disuse, or decreased nutrients/blood supply) leads to a decrease in organ size (atrophy).
   1. Occurs via a decrease in the size and number of cells
B. Decrease in cell number occurs via apoptosis.
C. Decrease in cell size occurs via ubiquitin-proteosome degradation of the cytoskeleton and autophagy of cellular components.
   1. In ubiquitin-proteosome degradation, intermediate filaments of the cytoskeleton are "tagged" with ubiquitin and destroyed by proteosomes.
   2. Autophagy of cellular components involves generation of autophagic vacuoles. These vacuoles fuse with lysosomes whose hydrolytic enzymes breakdown cellular components.

IV. METAPLASIA

A. A change in stress on an organ leads to a change in cell type (metaplasia).
   1. Most commonly involves change of one type of surface epithelium (squamous, columnar, or urothelial) to another
   2. Metaplastic cells are better able to handle the new stress.
B. Barrett esophagus is a classic example.

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1. Esophagus is normally lined by nonkeratinizing squamous epithelium (suited to handle friction of a food bolus).
2. Acid reflux from the stomach causes metaplasia to nonciliated, mucin-producing columnar cells (better able to handle the stress of acid, Fig. 1.2).

C. Metaplasia occurs via reprogramming of stem cells, which then produce the new cell type.
1. Metaplasia is reversible, in theory, with removal of the driving stressor.
2. For example, treatment of gastroesophageal reflux may reverse Barrett esophagus.

D. Under persistent stress, metaplasia can progress to dysplasia and eventually result in cancer.
1. For example, Barrett esophagus may progress to adenocarcinoma of the esophagus.
2. A notable exception is apocrine metaplasia of breast, which carries no increased risk for cancer.

E. Vitamin A deficiency can also result in metaplasia.
1. Vitamin A is necessary for differentiation of specialized epithelial surfaces such as the conjunctiva covering the eye.
2. In vitamin A deficiency, the thin squamous lining of the conjunctiva undergoes metaplasia into stratified keratinizing squamous epithelium. This change is called keratomalacia (Fig. 1.3).

F. Mesenchymal (connective) tissues can also undergo metaplasia.
1. A classic example is myositis ossificans in which connective tissue within muscle changes to bone during healing after trauma (Fig. 1.4).

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V. DYSPLASIA

A. Disordered cellular growth

B. Most often refers to proliferation of precancerous cells
1. For example, cervical intraepithelial neoplasia (CIN) represents dysplasia and is a precursor to cervical cancer.

C. Often arises from longstanding pathologic hyperplasia (e.g., endometrial hyperplasia) or metaplasia (e.g., Barrett esophagus)

D. Dysplasia is reversible, in theory, with alleviation of inciting stress.
1. If stress persists, dysplasia progresses to carcinoma (irreversible).

VI. APLASIA AND HYPOPLASIA

A. Aplasia is failure of cell production during embryogenesis (e.g., unilateral renal agenesis).

B. Hypoplasia is a decrease in cell production during embryogenesis, resulting in a relatively small organ (e.g., streak ovary in Turner syndrome).

Fig. 1.1 Left ventricular hypertrophy. (Courtesy of Aliya Husain, MD)

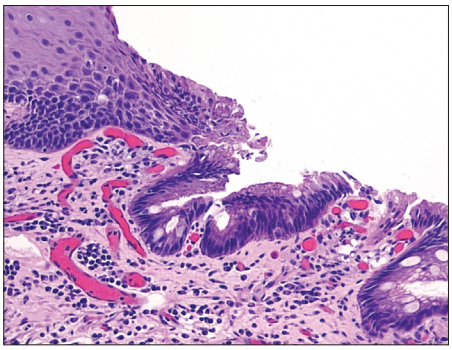

Fig. 1.2 Barrett esophagus.

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CELLULAR INJURY

I. BASIC PRINCIPLES

A. Cellular injury occurs when a stress exceeds the cell's ability to adapt.

B. The likelihood of injury depends on the type of stress, its severity, and the type of cell affected.

1. Neurons are highly susceptible to ischemic injury; whereas, skeletal muscle is relatively more resistant.
2. Slowly developing ischemia (e.g., renal artery atherosclerosis) results in atrophy; whereas, acute ischemia (e.g., renal artery embolus) results in injury.

C. Common causes of cellular injury include inflammation, nutritional deficiency or excess, hypoxia, trauma, and genetic mutations.

II. HYPOXIA

A. Low oxygen delivery to tissue; important cause of cellular injury

1. Oxygen is the final electron acceptor in the electron transport chain of oxidative phosphorylation.
2. Decreased oxygen impairs oxidative phosphorylation, resulting in decreased ATP production.
3. Lack of ATP (essential energy source) leads to cellular injury.

B. Causes of hypoxia include ischemia, hypoxemia, and decreased O_2-carrying capacity of blood.

C. Ischemia is decreased blood flow through an organ. Arises with

1. Decreased arterial perfusion (e.g., atherosclerosis)
2. Decreased venous drainage (e.g., Budd-Chiari syndrome)
3. Shock—generalized hypotension resulting in poor tissue perfusion

D. Hypoxemia is a low partial pressure of oxygen in the blood ($Pao_2 < 60$ mm Hg, $Sao_2 < 90\%$). Arises with

1. High altitude—Decreased barometric pressure results in decreased PAO_2.
2. Hypoventilation—Increased $PACO_2$ results in decreased PAO_2.
3. Diffusion defect—PAO_2 not able to push as much O_2 into the blood due to a thicker diffusion barrier (e.g., interstitial pulmonary fibrosis)
4. V/Q mismatch—Blood bypasses oxygenated lung (circulation problem, e.g., right-to-left shunt), or oxygenated air cannot reach blood (ventilation problem, e.g., atelectasis).

E. Decreased O_2-carrying capacity arises with hemoglobin (Hb) loss or dysfunction. Examples include

1. Anemia (decrease in RBC mass)—Pao_2 normal; Sao_2 normal
2. Carbon monoxide poisoning

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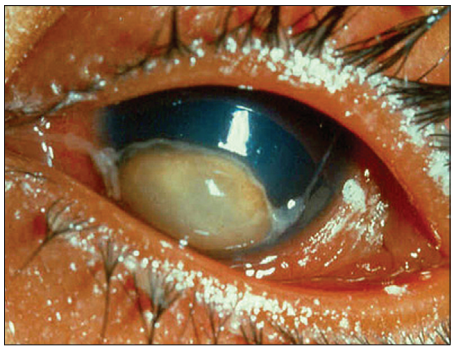

Fig. 1.3 Keratomalacia. (Courtesy of motherchildnutrition.org)

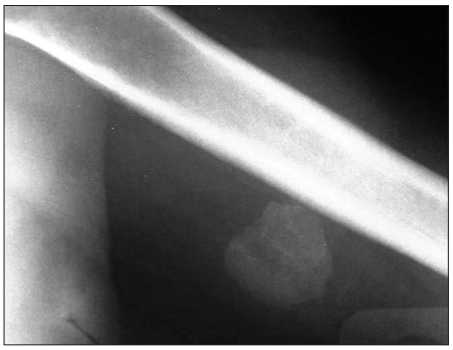

Fig. 1.4 Myositis Ossificans. (Reprinted with permission from orthopaedia.com)

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i. CO binds hemoglobin more avidly than oxygen—Pao_2 normal; Sao_2 decreased
ii. Exposures include smoke from fires and exhaust from cars or gas heaters.
iii. Classic finding is cherry-red appearance of skin.
iv. Early sign of exposure is headache; significant exposure leads to coma and death.

3. Methemoglobinemia
i. Iron in heme is oxidized to Fe^{3+}, which cannot bind oxygen—Pao_2 normal; Sao_2 decreased
ii. Seen with oxidant stress (e.g., sulfa and nitrate drugs) or in newborns
iii. Classic finding is cyanosis with chocolate-colored blood.
iv. Treatment is intravenous methylene blue, which helps reduce Fe^{3+} back to Fe^{2+} state.

III. REVERSIBLE AND IRREVERSIBLE CELLULAR INJURY

A. Hypoxia impairs oxidative phosphorylation resulting in decreased ATP.
B. Low ATP disrupts key cellular functions including
1. Na^+-K^+ pump, resulting in sodium and water buildup in the cell
2. Ca^{2+} pump, resulting in Ca^{2+} buildup in the cytosol of the cell
3. Aerobic glycolysis, resulting in a switch to anaerobic glycolysis. Lactic acid buildup results in low pH, which denatures proteins and precipitates DNA.
C. The initial phase of injury is reversible. The hallmark of reversible injury is cellular swelling.
1. Cytosol swelling results in loss of microvilli and membrane blebbing.
2. Swelling of the rough endoplasmic reticulum (RER) results in dissociation of ribosomes and decreased protein synthesis.
D. Eventually, the damage becomes irreversible. The hallmark of irreversible injury is membrane damage.
1. Plasma membrane damage results in
i. Cytosolic enzymes leaking into the serum (e.g., cardiac troponin)
ii. Additional calcium entering into the cell
2. Mitochondrial membrane damage results in
i. Loss of the electron transport chain (inner mitochondrial membrane)
ii. Cytochrome *c* leaking into cytosol (activates apoptosis)
3. Lysosome membrane damage results in hydrolytic enzymes leaking into the cytosol, which, in turn, are activated by the high intracellular calcium.
E. The end result of irreversible injury is cell death.

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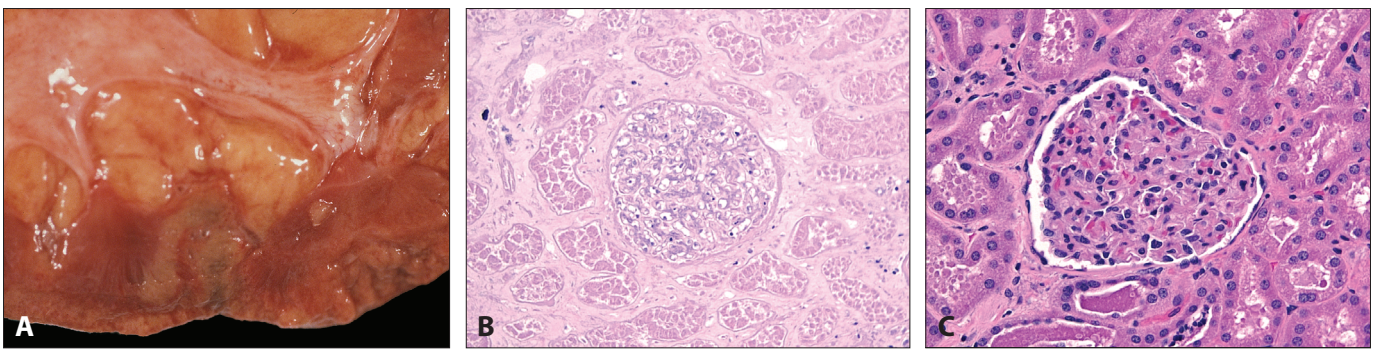

Fig. 1.5 Coagulative necrosis of kidney. **A**, Gross appearance. **B**, Microscopic appearance. **C**, Normal kidney histology for comparison. (A, Courtesy of Aliya Husain, MD)

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