Board Review Series

PATHOLOGY

Arthur S. Schneider
Philip A. Szanto

- Reflects USMLE changes
- 500 Board-type questions with explanations
- Numerous tables
- Easy-to-follow outline covering all Board-tested topics
- A comprehensive examination

Board Review Series

Pathology

Arthur S. Schneider, M.D.

Professor and Chair
Department of Pathology
Finch University of Health Sciences/
The Chicago Medical School
North Chicago, Illinois

Philip A. Szanto, M.D.

Associate Professor of Pathology
Finch University of Health Sciences/
The Chicago Medical School
North Chicago, Illinois

Williams & Wilkins
A WAVERLY COMPANY

BALTIMORE • PHILADELPHIA • LONDON • PARIS • BANGKOK
BUENOS AIRES • HONG KONG • MUNICH • SYDNEY • TOKYO • WROCLAW

Williams & Wilkins
351 West Camden Street
Baltimore, Maryland 21201-2436 USA

Rose Tree Corporate Center
1400 North Providence Road
Building II, Suite 5025
Media, Pennsylvania 19063-2043 USA

Managing Editor: Susan E. Kelly
Manuscript Editor: Mary T. Durkin
Editorial Assistant: Kelly A. Reed
Production Supervisor: Laurie Forsyth
Production Editor: Joan M. Leary

Library of Congress Cataloging-in-Publication Data

Schneider, Arthur S.
Pathology / Arthur S. Schneider, Philip A. Szanto.
p. cm.—(Board review series)
ISBN 0-683-07608-6 (pbk. : alk. paper)
1. Pathology—Outlines, syllabi, etc. 2. Pathology—Examinations, questions, etc. I. Szanto, Philip A. II. Title. III. Series.
[DNLM: 1. Pathology—examination questions. QZ 18 S358p]
RB32.S36 1992
616.07—dc20
DNLM/DLC
for Library of Congress

92-49705
CIP

15 14 13 12 11

Preface

The aphorism of Hippocrates, "Life is short, and the Art long; the occasion fleeting; experience fallacious, and judgment difficult," is clearly proven true during the first years of medical school. The time that the student can devote to a single subject is very limited, and the amount of material to be covered is indeed great. Nowhere is this more true than in pathology, traditionally one of the "big courses" of the first two years. The sheer enormity of the task is problematic for students as they attempt to select significant core items that deserve special emphasis from the large amount of material presented in standard texts. The problem becomes especially acute when it is necessary to review large amounts of material when preparing for tests such as the United States Medical Licensing Examination (USMLE). This book is designed to assist students in meeting these needs.

Organization

This book is divided into 23 chapters organized parallel to most standard texts. The first 8 chapters cover general or basic pathology, presenting the major concepts of disease processes viewed as manifestations of a common set of mechanisms of injury. The succeeding 15 chapters cover systemic pathology, surveying the principal disorders of each organ system.

The text is presented in the tightly outlined format of the ***Board Review Series,*** which facilitates quick comprehension and review. Numerous tables supplement textual information throughout the book. Each chapter is followed by review questions and answers and explanations, and the entire text is followed by a Comprehensive Examination. All questions reflect the style and content of USMLE changes.

How To Use This Book

The book is not designed to be used as a primary text but rather as an aid to identifying key concepts during the initial period of study and as a relatively concise source of material suitable for rapid review. Following completion of a unit during the pathology course, many students will find it helpful to quickly go over the corresponding chapter and its accompanying review questions. Core items not identified will easily become apparent by this technique. To prepare for USMLE Step 1, the Comprehensive Examination can be used both as a pretest and as a post-test to help identify areas that merit further attention in the chapters or in standard texts. Special attention should be directed to the explanatory material following the Comprehensive Examination, where a large proportion of the material that has become standard on national examinations is reviewed.

Acknowledgments

We express our appreciation to our colleagues in the Department of Pathology for their comments and suggestions during the preparation of this text. Special thanks are extended to Dr. Charles McCormack of the Department of Physiology and Biophysics, who critically reviewed the chapter on endocrine disorders, and to Dr. Seymour Ehrenpreis of the Department of Pharmacology and Molecular Biology for his review of the entire manuscript. Special thanks to those who provided illustrations: Dr. Jae O. Ro, a colleague in our department; Dr. Deborah E. Powell of the University of Kentucky; Dr. Juan Rosai of the Memorial-Sloan Kettering Cancer Center; and Dr. John B. Walter of the University of Toronto. We thank our many students who used the manuscript version of this book during their pathology course and during their preparation for examinations, both in the classroom and for USMLE. They provided enthusiastic, encouraging response and constructive feedback.

It is difficult to adequately express our very special debt to Ms. Susan Grimm for her participation in the preparation of the manuscript. She worked side-by-side with us in the detailed writing of the manuscript, typed and retyped successive versions, and labored over every page for countless hours. Her diligence assured that usage was uniform from chapter to chapter, that every verb was properly single or plural, that every "which" or "that" was properly selected, that every comma or semicolon was appropriate, that every word was properly spelled and applied, and that every citation was correct. There is no way that this book could have been completed without her.

We also acknowledge the considerable efforts of the staff at Williams & Wilkins and at Harwal Publishing Company, a division of Williams & Wilkins, who were active in the production of this book. We especially thank Mr. John Gardner, who initiated the *Board Review Series;* the faculty and student reviewers who helped bring the book quality; and most of all Ms. Susan Kelly, Managing Editor of the *Board Review Series,* who, along with her talented staff, forced us (sometimes with great resistance) to do our best to produce a concise, clearly understandable book.

We also thank our respective families for their patience and forbearance during this extended period.

Arthur S. Schneider
Philip A. Szanto

Contents

1

Cellular Reaction to Injury

I. Adaptation to Environmental Stress

A. Hypertrophy

–is an **increase in the size of an organ or tissue due to an increase in the size of cells** and is further characterized by an increase in protein synthesis and an increase in size or number of intracellular organelles.

–results from cellular adaptation to increased workload exemplified by the increase in skeletal muscle mass associated with exercise and the enlargement of the left ventricle in hypertensive heart disease.

B. Hyperplasia

–is an **increase in the size of an organ or tissue due to an increase in the number of cells**.

–is exemplified by glandular proliferation in the breast during pregnancy.

–in some instances, occurs with hypertrophy. Uterine enlargement during pregnancy is caused by both hypertrophy and hyperplasia of uterine smooth muscle cells.

C. Aplasia

–is a **failure of cell production**.

1. During fetal development, aplasia results in **agenesis,** absence of an organ due to failure of production.

2. Later in life, aplasia follows permanent loss of precursor cells in proliferative tissues.

D. Hypoplasia

–is a **decrease in cell production less extreme than aplasia**.

–is seen in the partial lack of growth and maturation of gonadal structures seen in Turner's syndrome and Klinefelter's syndrome.

E. Atrophy

–is a **decrease in the size of an organ or tissue resulting from a decrease in mass of preexisting cells**.

–most often results from disuse, nutritional or oxygen deprivation, diminished endocrine stimulation, aging, and denervation (lack of nerve stimulation in peripheral muscles from injury to motor nerves).
–often is marked by the presence of **autophagic granules,** intracytoplasmic vacuoles containing debris from degraded organelles.

F. Metaplasia

–is the **replacement of one differentiated tissue by another.**

1. Squamous metaplasia

–is exemplified by the replacement of columnar epithelium at the squamocolumnar junction of the cervix by squamous epithelium.
–can also occur in the respiratory epithelium of the bronchus, in the endometrium, and in the pancreatic ducts.
–is associated with chronic irritation and inflammation.
–is also associated with vitamin A deficiency.

2. Osseous metaplasia

–is bone formation at sites of tissue injury. Cartilaginous metaplasia may also occur.

3. Myeloid metaplasia (extramedullary hematopoiesis)

–is proliferation of hematopoietic tissue in sites other than bone marrow, such as the liver or spleen.

II. Ischemic Cell Injury

A. Causes—ischemic cell injury

–results from cellular **anoxia** or **hypoxia,** which, in turn, results from a variety of mechanisms, including:

1. **Obstruction of arterial blood flow** (the most common cause)
2. **Anemia,** a reduction in the number of oxygen-carrying red blood cells
3. **Carbon monoxide poisoning,** which results in diminution in the oxygen-carrying capacity of red blood cells by chemical alteration of hemoglobin
4. **Decreased perfusion of tissues by oxygen-carrying blood,** as occurs in cardiac failure, hypotension, and shock
5. **Poor oxygenation of blood,** secondary to pulmonary disease

B. Early stage of ischemic cell injury

–affects mitochondria, with resultant decreased oxidative phosphorylation and adenosine triphosphate (ATP) synthesis. Consequences of **decreased ATP** availability include:

1. **Failure of the cell membrane pump** (ouabain-sensitive Na^+K^+-ATPase) results in increased intracellular Na^+ and water and decreased intracellular K^+, which cause cellular swelling and swelling of organelles.
   a. Cellular swelling, or **hydropic change,** is characterized by the presence of large vacuoles in the cytoplasm.
   b. **Swelling of the endoplasmic reticulum** is one of the first ultrastructural changes evident in reversible injury.

c. **Swelling of the mitochondria** progresses from reversible, low-amplitude swelling to irreversible high-amplitude swelling, which is characterized by marked dilatation of the inner mitochondrial space.

2. **Disaggregation of ribosomes and failure of protein synthesis;** ribosomal disaggregation also is promoted by membrane damage.

3. **Stimulation of phosphofructokinase activity** results in increased glycolysis, lactate accumulation, and decreased intracellular pH. Acidification causes reversible clumping of nuclear chromatin.

C. Late stage of ischemic cell injury

–results in **membrane damage** to plasma and lysosomal and other organellar membranes.

–reversible morphologic signs of damage include the formation of:

1. **Myelin figures,** whorl-like structures probably originating from damaged membranes

2. **Cell blebs,** a cell surface deformity most likely caused by disorderly function of the cellular cytoskeleton

D. Cell death

–is caused by severe or prolonged injury.

1. The **point of no return** is marked by **irreversible damage to mitochondria and cell membranes,** leading to **massive calcium influx** and cell death. Release of aspartate aminotransferase (AST), creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) into the blood is an important indicator of irreversible injury to heart muscle following interruption of myocardial blood supply by occlusion of coronary artery blood flow.

2. **The vulnerability of cells to ischemic injury** varies with the tissue or cell type. Ischemic injury becomes irreversible after:

   a. **3–5 minutes for neurons.** Purkinje cells of the cerebellum and neurons of the hippocampus are more susceptible to ischemic injury than other neurons.

   b. **1–2 hours for myocardial cells and hepatocytes**

   c. **Many hours for skeletal muscle cells**

III. Free Radical Injury

A. Free radicals

–are any molecule with a single unpaired electron in the outer orbital.

–are exemplified by activated products of oxygen reduction, which include the superoxide ($O_2^{\bullet -}$) and the hydroxyl ($OH^{\bullet}$) radicals.

B. Generation of free radicals

–occurs by the following mechanisms:

1. **Normal metabolism**

2. **Oxygen toxicity,** as in the alveolar damage that can cause adult respiratory distress syndrome and retrolental fibroplasia, an ocular disorder of premature infants

3. **Ionizing radiation**

4. **Drugs and chemicals,** many of which promote both proliferation of the smooth endoplasmic reticulum (SER) and induction of the P-450 system of mixed function oxidases of the SER. Proliferation and hypertrophy of the SER of the hepatocyte is a classic ultrastructural marker of barbiturate intoxication.
5. **Reperfusion after ischemic injury**

C. Free radical degradation

–occurs by:

1. **Intracellular enzymes,** such as glutathione peroxidase, catalase, or superoxide dismutase
2. **Endogenous substances,** such as ceruloplasmin or transferrin
3. **Spontaneous decay**

IV. Chemical Cell Injury

–is illustrated by the **model of liver cell membrane damage induced by carbon tetrachloride** (CCl_4).

A. In this model, CCl_4 is processed by the P-450 system of mixed function oxidases within the SER, producing the **highly reactive free radical CCl_3•**.

B. CCl_3• diffuses throughout the cell, initiating **lipid peroxidation of intracellular membranes**. Widespread injury results, including:

1. **Disaggregation of ribosomes,** resulting in **decreased protein synthesis**. Failure of the cell to synthesize the apoprotein moiety of lipoproteins causes accumulation of intracellular lipids (**fatty change**).
2. **Plasma membrane damage,** caused by products of lipid peroxidation, resulting in **cellular swelling** and **massive influx of calcium,** with resultant mitochondrial damage, denaturation of cell proteins, and cell death

V. Necrosis (Table 1.1)

–is the sum of the intracellular degradative reactions occurring after the death of individual cells within a living organism.

A. General characteristics

1. In pathologic specimens, fixed cells with well-preserved morphology are dead but not necrotic.
2. **Autolysis** refers to degradative reactions in cells caused by intracellular enzymes indigenous to the cell. **Postmortem autolysis** occurs after death of the entire organism and is not necrosis.
3. **Heterolysis** refers to cellular degradation by enzymes derived from sources extrinsic to the cell (e.g., bacteria, leukocytes).

B. Types of necrosis

1. **Coagulation necrosis**
   –most often results from sudden cutoff of blood supply to an organ, particularly the heart and kidney.
   –in early stages, is characterized by general **preservation of tissue architecture**.

Table 1.1. Types of Necrosis

Types	Mechanism	Pathologic Changes
Coagulation necrosis	Most often results from interruption of blood supply, resulting in denaturation of proteins; best seen in organs supplied by end arteries with limited collateral circulation, such as the heart and kidney	General architecture well preserved, except for nuclear changes; increased cytoplasmic binding of acidophilic dyes
Liquefaction necrosis	Enzymatic liquefaction of necrotic tissue, most often in the CNS, where it is caused by interruption of blood supply; also occurs in areas of bacterial infection	Necrotic tissue soft and liquefied
Caseous necrosis	Shares features of both coagulation and liquefaction necrosis; most commonly seen in tuberculous granulomas	Architecture not preserved but tissue not liquefied; gross appearance is soft and cheese-like; histologic appearance is amorphous, with increased affinity for acidophilic dyes
Gangrenous necrosis	Most often results from interruption of blood supply to a lower extremity or the bowel	Changes depend on tissue involved and whether or not gangrene is dry or wet
Fibrinoid necrosis	Characterized by deposition of fibrin-like proteinaceous material in walls of arteries; often observed as part of immune-mediated vasculitis	Smudgy pink appearance in vascular walls; actual necrosis may or may not be present
Fat necrosis	Liberation of pancreatic enzymes with autodigestion of pancreatic parenchyma; trauma to fat cells	Necrotic fat cells, acute inflammation, hemorrhage, calcium soap formation, clustering of lipid-laden macrophages (in the pancreas)
Apoptosis	Cell death affecting solitary cells	Nuclear and cytoplasmic condensation, as seen in Councilman body of viral hepatitis

– **increased cytoplasmic eosinophilia** occurs because of protein denaturation and loss of cytoplasmic RNA.
– is **marked by nuclear changes,** the morphologic hallmark of irreversible cell injury and necrosis. These include:

a. Pyknosis, chromatin clumping and shrinking with increased basophilia

b. Karyorrhexis, fragmentation of chromatin

c. Karyolysis, fading of chromatin material

d. Disappearance of stainable nuclei

2. Liquefaction necrosis

– is characterized by digestion of tissue.
– is marked by softening and liquefaction of tissue.
– characteristically results from **ischemic injury to the central nervous system (CNS).** Following the death of CNS cells, liquefaction is caused by autolysis.

–also occurs in **suppurative infections** characterized by formation of pus, liquefied tissue debris and neutrophils, by heterolytic mechanisms.

3. Caseous necrosis

–combines features of both coagulation necrosis and liquefaction necrosis.
–is marked by a cheese-like (caseous) consistency on gross examination.
–presents an **amorphous eosinophilic appearance** on histologic examination.
–occurs as **part of granulomatous inflammation,** as seen in **tuberculosis**.

4. Gangrenous necrosis

–most often affects the lower extremities or bowel and is secondary to vascular occlusion.
–is termed **wet gangrene** when complicated by infective heterolysis and consequent liquefaction necrosis.
–is termed **dry gangrene** when characterized primarily by coagulation necrosis without liquefaction.

5. Fibrinoid necrosis

–is caused by immune-mediated vascular damage.
–is marked by **deposition of fibrin-like proteinaceous material in arterial walls,** which appears smudgy and acidophilic.

6. Fat necrosis

–occurs in two forms:

a. Traumatic fat necrosis

–occurs following severe injury to tissue with high fat content, such as the breast.

b. Enzymatic fat necrosis

–is a complication of **acute hemorrhagic pancreatitis,** a severe inflammatory disorder of the pancreas.
(1) Proteolytic and lipolytic pancreatic enzymes diffuse into inflamed tissue and literally digest the parenchyma.
(2) Fatty acids liberated by the digestion form calcium salts (saponification, or **soap formation**).
(3) Vessels are eroded, with resultant hemorrhage.

7. Apoptosis

–is the death of single cells within clusters of other cells.
–is marked by shrinkage and increased acidophilic staining, with formation of small round eosinophilic masses often containing chromatin remnants.
–is exemplified by formation of Councilman bodies in viral hepatitis.
–occurs as a physiologic process for removal of cells during embryogenesis and during programmed cell cycling, as in the endometrium during menstruation.

VI. Reversible Cellular Changes and Accumulations

A. Fatty change

–is characterized by the **accumulation of intracellular parenchymal triglycerides**.

–most frequently is observed in the **liver, heart,** or **kidney**. For example, in the liver, fatty change may be secondary to alcoholism, diabetes mellitus, malnutrition, obesity, and poisonings.
–results from an imbalance between the uptake, utilization, and secretion of fat caused by the following mechanisms:

1. **Increased transport of triglycerides or fatty acids** to affected cells
2. **Decreased mobilization of fat from cells,** most often mediated by decreased production of apoproteins required for fat transport. Fatty change is thus linked to the disaggregation of ribosomes and consequent decreased protein synthesis caused by failure of ATP production in CCl_4-injured cells.
3. **Decreased use of fat by cells**
4. **Overproduction of fat in cells**

B. Hyaline change
–describes a characteristic (homogeneous, glassy, eosinophilic) appearance in hematoxylin and eosin sections, most often caused by nonspecific accumulations of proteinaceous material.

C. Accumulations of exogenous pigments

1. **Pulmonary accumulations of carbon, silica, and iron dust**
2. **Plumbism** (lead poisoning)
3. **Argyria** (silver poisoning)
   –may cause a permanent gray discoloration of the skin and conjunctivae.

D. Accumulations of endogenous pigments

1. **Melanin**
   –is **formed** from tyrosine by the action of tyrosinase, **synthesized** in melanosomes of melanocytes within the epidermis, and **transferred** by melanocytes to adjacent clusters of keratinocytes and to macrophages (melanophores) in the subjacent dermis.

   a. Increased melanin pigmentation
   –is associated with suntanning and with a wide variety of disease conditions.

   b. Decreased melanin pigmentation
   –is observed in albinism and vitiligo.

2. **Bilirubin**
   –is a catabolic product of the heme moiety of hemoglobin and, to a minor extent, myoglobin.
   –in various pathologic conditions, accumulates and stains the blood, sclerae, mucosae, and internal organs, producing jaundice. **Jaundice** is most often caused by:

   a. Hemolytic anemia
   –is a decrease in the number of circulating erythrocytes from increased red cell destruction.

   b. Biliary obstruction
   –is an obstruction of intrahepatic or extrahepatic bile ducts.