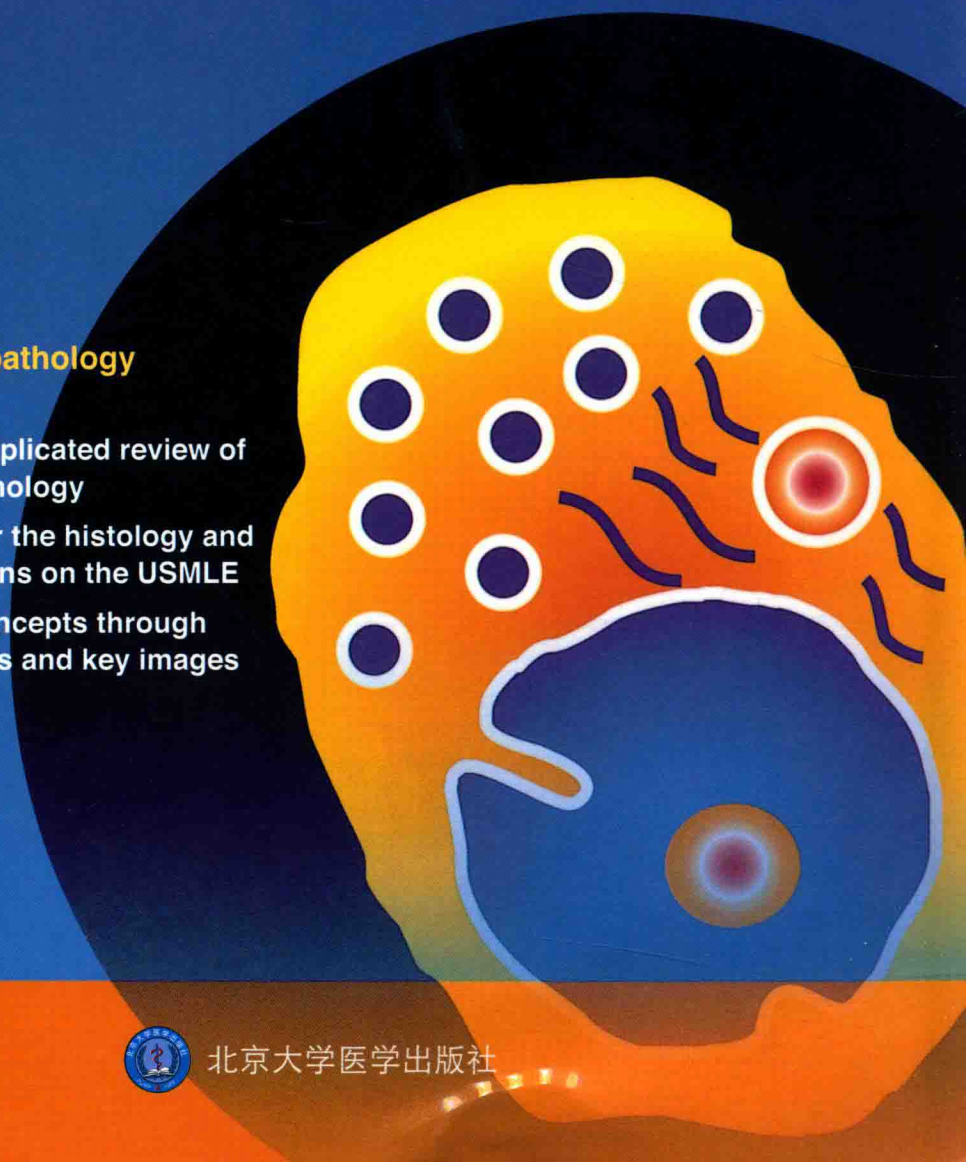
美国医师执照考试

High-Yield™ Histopathology

组织病理学

（第2版）

RONALD W. DUDEK



High-Yield™ Histopathology is designed to:

- Provide an uncomplicated review of histology and pathology
- Help equip you for the histology and pathology questions on the USMLE
- Clarify difficult concepts through simple illustrations and key images

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Histopathology

（第2版）

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出版说明

High-Yield™ 系列丛书是针对美国医师执照考试（United States Medical Licensing Examination, USMLE）的知名品牌图书，受到世界各地读者的欢迎。该系列丛书具有以下特色：

1. 内容高度概括，重点突出，有利于读者快速掌握学科的核心知识。
2. 编排新颖，既有基础知识要点的介绍，又有以疾病为核心的综合归纳，并体现了相关学科的横向联系。
3. 语言规范、地道，既有利于读者快速掌握专业词汇，又有利于医学英语思维的培养。

本系列丛书是参加美国医师执照考试的必备辅导用书，也可作为我国医学院校从事双语教学的教材和参考用书，对教师进行英语授课，学生学习、参加考试具有重要的参考价值。

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I would like to dedicate this book to my mother, Lottie Dudek, who was born on November 11, 1918. Through the years my mother raised her children, maintained a loving marriage, and worked 40 hours per week. In the year 2004, society would describe such a person as a "liberated woman" or "supermom." I would like to acknowledge that my mother was a "supermom" 20 years before the word was fashionable. A son cannot repay a mother. My hope is that "I love you and thank you" will suffice.

Preface

High-Yield Histopathology does more than just review histology. The questions on the USMLE Step 1 cross traditional course boundaries, making it difficult to identify a question that is "strictly histology." Many USMLE Step 1 questions fall into the categories such as histopathology, histophysiology, histomicrobiology, and histopharmacology. To write a review book on basic, traditional histology would not be helpful to the student preparing for the USMLE Step 1 since there are no basic traditional histology questions on the exam. In this regard, *High-Yield Histopathology* reviews important histology concepts as a gateway to the pathology, physiology, microbiology, and pharmacology of clinically relevant topics.

In addition, many students have commented that cell biology topics have been well represented on the USMLE Step 1. To this end, I have included Chapter 1 (Nucleus), Chapter 2 (Cytoplasm and Organelles), and Chapter 3 (Cell Membrane) with up-to-date and clinically relevant information.

I would appreciate any comments or suggestions concerning *High-Yield Histopathology*, especially after you have taken the USMLE Step 1 exam, that you think might improve the book. You may contact me at dudekr@ecu.edu.

Contents

Chapter 1

Nucleus

I Nuclear Envelope.

The nuclear envelope is a two-membrane structure. The **inner membrane** is associated with a network of **intermediate filaments (lamins A, B, C)** called the **nuclear lamina**, which plays a role in the disassembly of the nuclear envelope during prometaphase of mitosis by phosphorylation of the lamins by **lamin kinase** and in the reassembly of the nuclear envelope during telophase. The **outer membrane** is studded with ribosomes and is continuous with the rough endoplasmic reticulum (rER). The inner and outer membranes are separated by a **perinuclear cisterna**. The nuclear envelope contains many pores that allow passage of molecules between the nucleus and cytoplasm (e.g., ions, messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), gene regulatory proteins, DNA polymerases, RNA polymerases). The pores are associated with a **nuclear pore complex** that consists of many different proteins arranged in octagonal symmetry with a central channel.

II Apoptosis.

Apoptosis is a **noninflammatory programmed cell death ("cell suicide")** that is characterized by **DNA fragmentation, a decrease in cell volume, loss of mitochondrial function, cell membrane blebbing**, and **formation of apoptotic bodies**, which are rapidly phagocytosed without an inflammatory response.

A. The chromatin is eventually cleaved by a specific endonuclease into DNA fragments that generate a distinctive **180-bp ladder** that is pathognomonic of apoptotic cell death.

B. Apoptosis is related to a family of proteases called **caspases**, which are found in all cells.

C. Caspases are activated by either extracellular death signals (e.g., killer lymphocytes produce **Fas ligand**, which binds to the **Fas death receptor** on the target cell; **tumor necrosis factor** [TNF] binds to the **TNF death receptor** on the target cell) or intracellular death signals (e.g., mitochondria release **cytochrome c** into the cytoplasm where it activates **Apaf-1 adaptor protein**, which in turn activates caspases).

D. The **Bcl-2** and the **IAP (inhibitor of apoptosis) family of proteins** are the main regulators of apoptosis.

E. Apoptosis occurs in hormone-dependent involution of cells during the menstrual cycle, embryogenesis, toxin-induced injury (e.g., diphtheria), viral cell death (e.g., Councilman bodies in yellow fever), and cell death via cytotoxic T cells or other immune cells.

III Nucleolus

A. The nucleolus consists of portions of five pairs of chromosomes (i.e., 13, 14, 15, 21, and 22) that contain about **200 copies of rRNA** genes per haploid genome that code for **rRNA**.

B. In humans, **RNA polymerase I** catalyzes the formation of **45S rRNA** and **RNA polymerase III** catalyzes the formation of **5S RNA**.

IV Chromatin.

Chromatin is double-helical DNA associated with histones and nonhistone proteins.

A. HETEROCHROMATIN is condensed chromatin and is **transcriptionally inactive.** In electron micrographs, heterochromatin is electron dense (i.e., very black). An example of heterochromatin is the **Barr body**, which is found in female cells and represents the inactive X chromosome. Heterochromatin makes up ~10% of the total chromatin.

1. **Constitutive heterochromatin** is always condensed (i.e., transcriptionally inactive) and consists of repetitive DNA found near the centromere and other regions.
2. **Facultative heterochromatin** can be either condensed (i.e., transcriptionally inactive) or dispersed (i.e., transcriptionally active). An example of facultative heterochromatin is the **XY body**, which forms when both the X and Y chromosome are inactivated for ~15 days during male meiosis.

B. EUCHROMATIN is dispersed chromatin and makes up ~90% of the total chromatin. Of this 90%, 10% is transcriptionally active and 80% is transcriptionally inactive. When chromatin is transcriptionally active, there is weak binding to the H1 histone protein and **acetylation** of the H2A, H2B, H3, and H4 histone proteins.

C. NUCLEOSOME

1. The most fundamental unit of packaging of DNA is the nucleosome.
2. A nucleosome consists of a histone protein octamer (two each of **H2A, H2B, H3, and H4 histone proteins**) around which 146 bp of DNA is coiled in 1.75 turns. The nucleosomes are connected by spacer DNA, which results in 10-nm-diameter fiber that resembles a "beads on a string" appearance by electron microscopy.
3. Histones are small proteins containing a high proportion of **lysine** and **arginine** that impart a positive charge to the proteins that enhances their binding to negatively charged DNA. Histones bind to DNA in A-T–rich regions of DNA.
4. Histone proteins have exposed N-terminal amino acid tails that are subject to modification and are crucial in regulating nucleosome structure.
5. **Histone acetylation** reduces the affinity between histones and DNA. An increased acetylation of histone proteins will make a DNA segment more likely to be transcribed into RNA and hence any genes in that DNA segment will be expressed (i.e., **↑ acetylation of histones = expressed genes**).

D. 30-nm CHROMATIN FIBER. The 10-nm nucleosome fiber is joined by **H1 histone protein** to form a **30-nm chromatin fiber.** When the general term "chromatin" is used, it refers specifically to the 30-nm chromatin fiber.

V Chromosomes.

The human genome refers to the total DNA content in the cell, which is divided into two genomes: the very complex **nuclear genome** and the relatively simple **mitochondrial genome.** The human nuclear genome consists of 24 different chromosomes (22 autosomes; X and Y sex chromosomes). The human nuclear genome codes for **≈30,000 genes** (precise number is uncertain), which make up **≈2% of the human nuclear genome.** There are **≈27,000 protein-coding genes** and **≈3000 RNA-coding genes.** The fact that the ≈30,000 genes make up only ≈2% of the human nuclear genome means that **≈2% of the human nuclear genome consists of coding DNA** and **≈98% of the human nuclear genome consists of noncoding DNA.**

A. CENTROMERE

1. A centromere is a specialized nucleotide DNA sequence that binds to the mitotic spindle during cell division.

2. Chromosomes have a single centromere that is observed microscopically as a **primary constriction**, which is the region where sister chromatids are joined.
3. During prometaphase, a pair of protein complexes called **kinetochores** forms at the centromere where one kinetochore is attached to each sister chromatid.
4. Microtubules produced by the **centrosome** of the cell attach to the kinetochore (called **kinetochore microtubules**) and pull the two sister chromatids toward opposite poles of the mitotic cell.

B. THE TELOMERE

1. The human telomere is a 3- to 20-kb repeating nucleotide sequence (**TTAGGG**) located at the end of a chromosome.
2. The telomere allows replication of linear DNA to its full length. Since DNA polymerases *cannot* synthesize in the 3′ → 5′ direction or start synthesis de novo, removal of the RNA primers will always leave the 5′ end of the newly synthesized lagging strand shorter than the lagging strand template. If the 5′ end of the newly synthesized lagging strand is not lengthened, a chromosome would get progressively shorter as the cell goes through a number of cell divisions. This would lead to cell death, which some investigators believe may be related to the aging process in humans.
3. This problem is solved by a special **RNA-directed DNA polymerase or reverse transcriptase** called **telomerase**, which adds many repeats of TTAGGG to the newly synthesized lagging strand.
4. Telomerase is present in **human germline cells** (i.e., spermatogonia, oogonia) and **stem cells** (e.g., in skin, bone marrow, and gut), but is absent from most other somatic cells.

VI Types of DNA Damage and DNA Repair.

Chromosomal breakage refers to breaks in chromosomes due to sunlight (or ultraviolet [UV]) irradiation, ionizing irradiation, DNA cross-linking agents, or DNA-damaging agents. These insults may cause **depurination of DNA**, **deamination of cytosine to uracil**, or **pyrimidine dimerization**, which must be repaired by **DNA repair enzymes**. The system that detects and signals DNA damage is a multiprotein complex called **BASC (BRCA1-associated genome surveillance complex)**.

A. DEPURINATION.

About 5000 purines (As or Gs) per day are lost from DNA of each human cell when the *N*-glycosyl bond between the purine and deoxyribose sugar phosphate is broken. This is the most frequent type of lesion and leaves the deoxyribose sugar phosphate with a missing purine base.

B. DEAMINATION OF CYTOSINE TO URACIL.

About 100 cytosines (C) per day are spontaneously deaminated to uracil (U). If the U is not corrected back to a C, then upon replication, instead of the occurrence of a correct C-G base pairing, a U-A base pairing will occur instead.

C. PYRIMIDINE DIMERIZATION.

Sunlight (UV radiation) can cause covalent linkage of adjacent pyrimidines forming, for example, **thymine dimers**.

VII Clinical Importance of DNA Repair (Table 1-1).

The clinical importance of DNA repair enzymes is illustrated by some rare inherited diseases that involve genetic defects in DNA repair enzymes such as xeroderma pigmentosa (XP), ataxia-telangiectasia (AT), Fanconi anemia (FA), and Bloom syndrome (BS), as indicated in Table 1-1.

TABLE 1-1 DNA REPAIR ENZYME PATHOLOGY

Genetic Disorder	Gene Gene Product Chromosome	Clinical Features
Xeroderma pigmentosum (XP) is an autosomal recessive genetic disorder caused by mutations in nucleotide **excision repair enzymes** that results in the inability to remove pyrimidine dimers and individuals who are hypersensitive to **sunlight (ultraviolet [UV] radiation)**	*XPA* gene DNA repair enzyme 9q22.3 *XPC* gene DNA repair enzyme 3p25	Sunlight (UV radiation) hypersensitivity with sunburnlike reaction, severe skin lesions around the eyes and eyelids, and malignant skin cancers (basal and squamous cell carcinomas and melanomas) whereby most individuals die by 30 years of age
Ataxia-telangiectasia (AT) is an autosomal recessive genetic disorder caused by mutations in **DNA recombination repair enzymes** that results in individuals who are hypersensitive to **ionizing radiation**	*ATM* gene PI-3 kinase and a DNA repair enzyme/cell cycle checkpoint protein 11q22-q23	Ionizing radiation hypersensitivity; cerebellar ataxia with depletion of Purkinje cells; progressive nystagmus; slurred speech; oculocutaneous telangiectasia initially in the bulbar conjunctiva followed by ear, eyelid, cheeks, and neck; immunodeficiency; and death in the second decade of life. A high frequency of structural rearrangements of chromosomes 7 and 14 is the cytogenetic observation with this disease.
Fanconi anemia (FA) is an autosomal recessive genetic disorder caused by mutations in **DNA recombination repair** that results in individuals who are hypersensitive to **DNA cross-linking agents**	*FA-A* gene A protein that normalizes cell growth, corrects sensitivity to chromosomal breakage in the presence of mitomycin C, and generally promotes genomic stability 16q24	DNA cross-linking agent hypersensitivity, short stature, hypopigmented spots, café-au-lait spots, hypogonadism, microcephaly, hypoplastic or aplastic thumbs, renal malformation including unilateral aplasia or horseshoe kidney, acute leukemia, progressive aplastic anemia, head and neck tumors, and medulloblastoma; is the most common form of congenital aplastic anemia
Bloom syndrome (BS) is an autosomal recessive genetic disorder caused by mutations in **DNA repair enzymes** that results in individuals who are hypersensitive to **DNA-damaging agents**	*BLM* gene RecQ helicase 15q26	Hypersensitivity to DNA-damaging agents; long, narrow face; erythema with telangiectasias in butterfly distribution over the nose and cheeks; high-pitched voice; small stature; small mandible; protuberant ears; absence of upper lateral incisors; well-demarcated patches of hypopigmentation and hyperpigmentation; immunodeficiency with decreased immunoglobulin A (IgA), IgM, and IgG levels; and predisposition to several types of cancers

Cell Cycle

A. PHASES OF THE CELL CYCLE (TABLE 1-2)

1. **G_0 (Gap) Phase.** The G_0 phase is the resting phase of the cell where the cell cycle is suspended.