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Biochemistry and Genetics

生物化学、遗传学

(第4版)

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- Targets what to know for exam success
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Golder N. Wilson

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生物化学、遗传学
Biochemistry and Genetics

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出版说明

美国医师执照考试（United States Medical Licensing Examination，USMLE）是针对全世界各国医学院的学生或毕业生，欲到美国从医的执照考试，考试全部为选择题，采用计算机考试。考试分为：

Step 1（第一阶段）：考察医学基础学科知识，包括解剖学 Anatomy，生理学 Physiology，生物化学 Biochemistry，微生物学 Microbiology，病理学 Pathology，药理学 Pharmacology，遗传学 Genetics，营养学 Nutrition，神经科学 Neuroscience 等。

Step 2（第二阶段）：

（1）临床医学知识（Clinical Knowledge，CK）：包括内科学 Medicine，外科学 Surgery，妇产科学 Obstetrics and Gynecology，儿科学 Pediatrics，神经病学 Neurology，家庭医学 Family Medicine，急诊医学 Emergency Medicine，预防医学 Preventive Medicine 等。

（2）临床技能（Clinical Skill，CS）：要通过 Step 1、Step 2 及 TOEFL 之后才能报考，主要是考察考生的临床实践操作知识。

Step 3（第三阶段）：测试考生的实际工作能力。内容包括采集病史、体格检查、诊断、治疗措施，以及医疗法规等。

USMLE 在北京、上海和广州设有考点，在中国大陆可参加 USMLE Step 1 和 USMLE Step 2 CK 的考试。考试介绍及报名情况可参见 http：//www. ecfmg. com

为了帮助有志于参加 USMLE 的考生更好地复习，北京大学医学出版社全面引进了 McGraw Hill 公司的两个著名 USMLE 复习品牌丛书：PreTest 系列、FIRST AID 系列。这两套丛书经过多次再版，受到世界各地考生的欢迎。本次引进的均为其最新版本。

当前，我国很多医学院校在进行英文授课、考试的改革，本书对国内从事英语授课、考试的教师和学生也有重要的参考价值。为广大的医学生和医务工作者比较中美医学教育和自己掌握的知识提供参考。同时，该书也是学习专业英语的好教材。

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Preface

The new edition of *Biochemistry and Genetics PreTest™: Self-Assessment and Review* is based in part on earlier editions prepared by Golder N. Wilson, MD, PhD, Department of Pediatrics, Texas Tech University Health Sciences Center; Cheryl Ingram-Smith, PhD; Kerry S. Smith, PhD, Department of Genetics, Biochemistry, and Life Science Studies Clemson University Clemson, South Carolina; and by Francis J. Chlapowski, PhD, Department of Biochemistry and Molecular Biology, University of Massachusetts Medical School. All questions are in single-best-answer format and a large number are analogous to those of the United States Medical Licensing Examination (USMLE), Step 1. Questions are updated to the most current editions of leading textbooks in medical biochemistry and medical genetics.

Introduction

Biochemistry and Genetics: PreTest™ Self-Assessment and Review, Fourth Edition, allows medical students to comprehensively and conveniently assess and review their knowledge of microbiology and immunology. The 500 questions provided here have been written with the goal to parallel the topics, format and degree of difficulty of the questions found in the United States Medical Licensing Examination (USMLE) Step 1.

The High-Yield Facts in the beginning of the book are provided to facilitate a rapid review of biochemistry. It is anticipated that the reader will use these High-Yield Facts as a "memory jog" before proceeding through the questions.

Each question in the book is followed by four or more answer options to choose from. In each case, select the one best response to the question. Each answer is accompanied by a specific page reference to a text that provides background to the answer, and a short discussion of issues raised by the question and answer. A bibliography listing all the sources can be found following the last chapter. Over 100 clinical disorders or processes are discussed and related to biochemical and/or genetic mechanisms (see the Appendix for a list of disease examples). For genetic disorders, a McKusick number is included (eg, MIM*154700 for Marfan syndrome) that allows the reader to immediately access information about the disorder using the Online Mendelian Inheritance in Man Internet site *(http://www.ncbi.nlm.nih.gov/omim/)*.

To simulate the time constraints imposed by the licensing exam, an effective way to use this book is to allow yourself 1 minute to answer each question in a given chapter. After you finish going through the questions in the section, spend as much time as you need verifying your answers and carefully reading the explanations provided. Special attention should be given to the explanations for the questions you answered incorrectly; however, you should read every explanation even if you've answered correctly. The explanations are designed to reinforce and supplement the information tested by the questions. For those seeking further information about the material covered, consult the references listed in the bibliography or other standard medical texts.

Note Concerning Disease Examples

This book provides over 100 disease examples (see Appendix) to illustrate the broad application of biochemistry and genetics to medicine. These include more common chromosomal or multifactorial disorders (Down syndrome, cleft palate, diabetes mellitus) that have incidences ranging from 1 in 200 to 1 in 3000 to less common single gene disorders (cystic fibrosis, glycogen storage diseases) with incidences of 1 in 1600 to 1 per million individuals. Students can ignore clinical information about these rare diseases since such knowledge is not tested in first/second-year biochemistry/genetic courses or USMLE I examinations. The examples are provided to place basic science knowledge in clinical context and to demonstrate the broad range of organ systems and medical specialties that are impacted by genetic/biochemical disease. More relevant to examination are much-used disease prototypes like diabetes, cleft palate, Down/Turner syndromes, sickle cell anemia, phenylketonuria (PKU): students may need to match them with underlying biochemical/genetic mechanisms.

Abbreviations

ACAT	acyl-CoA—cholesterol acyl transferase
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
CDP	cytidine diphosphate
CMP	cytidine monophosphate (cytidylic acid)
CoA	coenzyme A
cyclic AMP	adenosine 3′,5′-cyclic monophosphate (3′,5′-cyclic adenylic acid)
DHAP	dihydroxyacetone phosphate
DNA	deoxyribonucleic acid
DNP	2,4-dinitrophenol
DPG	diphosphoglycerate
dTMP	deoxythymidine monophosphate
dUMP	deoxyuridine monophosphate
EF	elongation factor
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
FAD (FADH)	flavin adenine dinucleotide (reduced form)
FMN	flavin mononucleotide
FSH	follicle-stimulating hormone
GDP	guanosine diphosphate
GMP	guanosine 5′-monophosphate (guanylic acid)
GTP	guanosine triphosphate
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HGPRT	hypoxanthine-guanine phosphoribosyl-transferase
HMGCoA	3-hydroxy-3-methylglutaryl-Coenzyme A
hnRNA	heterogeneous RNA of the nucleus
IDL	intermediate density lipoprotein
IMP	inosine 5′-monophosphate (inosinic acid)
IP_3	inositol 1,4,5-triphosphate
LDH	lactate dehydrogenase

LDL	low density lipoprotein
LH	luteinizing hormone
mRNA	messenger RNA
MSH	melanocyte-stimulating hormone
NAD (NADH)	nicotinamide adenine dinucleotide (reduced form)
NADP (NADPH)	nicotinamide adenine dinucleotide phosphate (reduced form)
PGH	pituitary growth hormone
P_i	inorganic orthophosphate
PP_i	inorganic pyrophosphate
PRPP	5-phosphoribosylpyrophosphate
RNA	ribonucleic acid
RQ	respiratory quotient
rRNA	ribosomal RNA
TMP	thymidine monophosphate
TPP	thymidine pyrophosphate
tRNA	transfer RNA
TSH	thyroid-stimulating hormone
TTP	thymidine triphosphate
UDP	uridine diphosphate
UMP	uridine monophosphate
UTP	uridine triphosphate
VLDL	very low density lipoprotein

Contents

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High-Yield Facts in Biochemistry and Genetics

DNA STRUCTURE, REPLICATION, AND REPAIR

Key concepts: DNA structure (Murray, pp 302-311. Scriver, pp 3-45. Lewis, pp 168-181.)

- Deoxyribonucleic acid (DNA) is the chemical basis of genes and chromosomes, its structure providing information for cell division, embryogenesis, and heredity. Changes in DNA structure cause human variation and genetic disease, providing the basis for DNA diagnosis.
- Each DNA strand is a sequence of the GATC deoxyribonucleotide units shown in Fig. 1A; the DNA strands are directional and are diagrammed with the free triphosphate of the 5′-sugar-carbon (5′-end) at the left and the 3′-end to the right (Fig. 1B). The 2-deoxyribose in DNA contrasts with the 2′ and 3′ hydroxyls of ribose in ribonucleic acid (RNA) that are susceptible to base hydrolysis.
- DNA in eukaryotic cells is a double helix with the strands oriented in opposite directions (antiparallel—Fig. 2A), with sugar-phosphate links on the outside and complementary base pairing on the inside (Fig. 2B). DNA duplex that is not compacted by histone/RNA binding has a length of 3.4 nm per 10 base pairs (bp).
- DNA duplexes can be denatured or "melted" into component single strands at a temperature (T_m) that is proportionate to the fidelity of A-T or G-C base pairing and the percentage of G-C pairs that confer higher melting temperatures due to their three hydrogen bonds (Fig. 2B). The reverse process of renaturation underlies DNA replication, transcription, or repair in that one DNA strand serves as guide or template for its complementary strand.
- The human haploid genome contains 3×10^9 bp of which 70% is unique or low-copy DNA that forms *euchromatin*—less compacted chromatin that is hypersensitive to deoxyribonuclease digestion. Euchromatin contains the estimated 25,000 transcribed genes and stains lightly with standard chromosome banding techniques. The remaining 30% of human

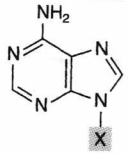
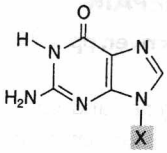
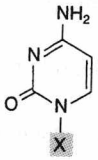
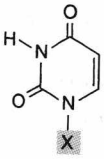
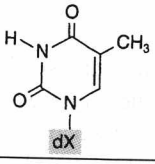
Base Formula	Base X = H	Nucleoside X = ribose or deoxyribose	Nucleotide, where X = ribose phosphate
	Adenine A	Adenosine A	Adenosine monophosphate AMP
	Guanine G	Guanosine G	Guanosine monophosphate GMP
	Cytosine C	Cytidine C	Cytidine monophosphate CMP
	Uracil U	Uridine U	Uridine monophosphate UMP
	Thymine T	Thymidine T	Thymidine monophosphate TMP

Figure 1 (A)

Bases, nucleotides, and nucleosides. *(Reproduced, with permission, from Murray RK, Bender DA, Botham KM, et al.* Harper's Illustrated Biochemistry. *28th ed. New York, NY: McGraw-Hill; 2009:287.)*

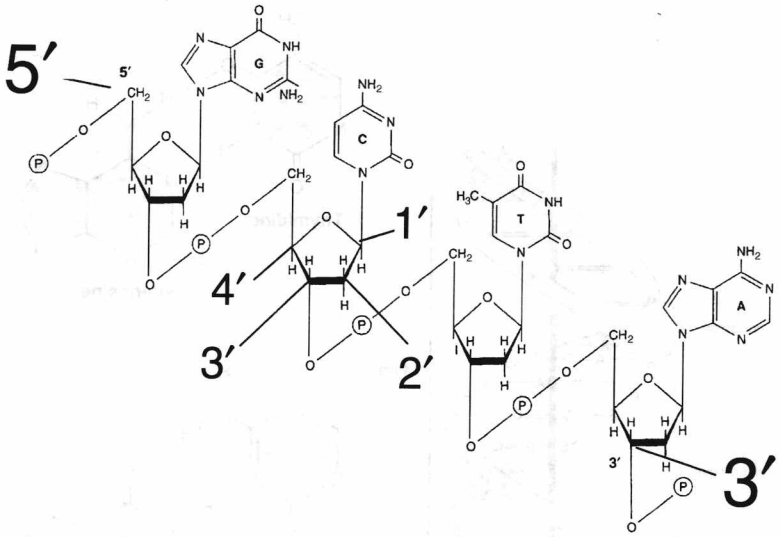


Figure 1 (B)

DNA strand showing 5′ to 3′ direction of phosphodiester linkages. The pictured strand could also be diagramed as pGpCpTpA. ***(Adapted, with permission, from Murray RK, Bender DA, Botham KM, et al.*** **Harper's Illustrated Biochemistry.** ***28th ed. New York, NY: McGraw-Hill; 2009:306.)***

genomic DNA contains repetitive DNA sequences that compose *heterochromatin*. Heterochromatin is more compacted chromatin that is less transcribed but important for the structure of chromosome centromeres, telomeres, and satellites.

- Heterochromatin structures evident in the standard Giemsa (G)-banded, metaphase karyotype include densely stained centromeres that anchor chromosomes to the meiotic/mitotic spindle and separate short (p) from long (q) arms. Satellites are regions of heterochromatin that may extend like snail eyes from the p arms of certain chromosomes, their stalks containing ribosomal RNA genes preferentially stained with silver (nucleolar organizer regions or NOR). Telomeres form the ends of chromosomes and have special replication properties. Telomere lengths shorten with age and expand in some neoplastic cells.

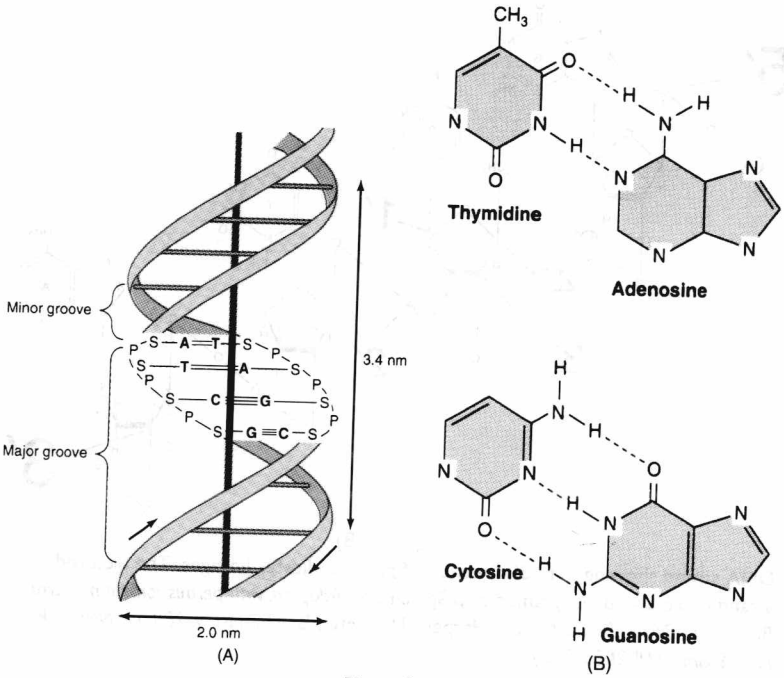


Figure 2

(A) Structure of DNA (B form) showing the double helix with antiparallel strands (arrows). One complete turn (3.4 nm) includes 10 base pairs (bp) A, adenine; C, cytidine; G, guanine; T, thymine; P, phosphate; S, deoxyribose sugar; (B) Base pairing showing two hydrogen bonds (broken lines) between A and T and three bonds between C and G. *(Reproduced, with permission, from Murray RK, Bender DA, Botham KM, et al.* Harper's Illustrated Biochemistry. *28th ed. New York, NY: McGraw-Hill; 2009:304.)*

- DNA is compacted some 8000-fold in eukaryotic cells, associating with histone octamers (two H2A-H2B dimers plus two H3/H4 dimers) and histone H1 to form nucleosomes (10 nm), chromatin fibrils (30 nm), chromosome loops (300 nm), and chromosomes; the average human chromosome (haploid number 23) contains a DNA duplex of 1.3×10^8 bp (4 cm compacted to 1.4 mm) and about 1000 genes.
- DNA can be modified by several chemical reactions including methylation at CpG dinucleotides during genomic imprinting and some types of oncogenesis. The associated histones can also be modified by acetylation,

phosphorylation, methylation, etc, often at basic amino acids like lysine and arginine where cationic ammonium side chains form ionic bonds with DNA phosphate groups. Such modifications together with binding of small RNAs constitute a "second code" of genetic regulation that is known as epigenesis.

Key concepts: DNA replication and repair (Murray, pp 334-347. Scriver, pp 3-45. Lewis, pp 171-184.)

- Copying of DNA is synchronous during cell division (DNA replication) and continuous when needed to replace altered bases or broken strands (DNA repair).
- DNA replication is effected by DNA polymerase I, a complex of helicases and topoisomerases for duplex DNA unwinding, primase for initiating DNA copying with RNA primer, DNA single-strand binding proteins (SSBs) for maintenance or proofreading, and ligase for sealing nicks between nascent strands and Okazaki fragments (Fig. 3).
- DNA synthesis occurs during the synthetic or S phase of the cell cycle, after the growth or gap 1 (G1) phase and before the gap 2 (G2) and mitosis (M) phases. The cycle is coordinated by a protein cascade of cyclin-dependent protein kinases (CDKs), cyclins (cyclin D1 is a product of the *bcl* or B-cell lymphoma oncogene), and transcription factors including E2F and Rb (retinoblastoma protein).
- Maintenance of the primary DNA code responsible for accurate protein synthesis and function requires proofreading at the time of DNA replication and DNA repair. Since there are 10^{16} cell divisions per lifetime with 6×10^9 bp replicated for each cell division, more than 6×10^{25} bp of DNA must be replicated during each human lifetime. Extremely low DNA error or damage rates must be enforced because even one error per 10^{20} bp replicated would yield almost a million mutations per individual lifetime.
- Specific DNA repair processes (Table 1) exist for each of the four types of DNA damage: (1) depurination or other modification of DNA bases (radiation, chemical agents), (2) two-base alterations (thymine-thymine dimers with ultraviolet light), (3) strand breaks (radiation, free radicals), and (4) cross-linkage of DNA with its associated proteins (chemical agents).
- Four checkpoint controls monitor DNA and chromosome integrity during the cell cycle—checks for damaged DNA at G1 and G2, incomplete replication in S, and improper spindle alignment at M. Irreparable damage halts cell cycle progression and initiates cell death (apoptosis). The tumor suppressor gene p53, mutated in Li-Fraumeni tumor syndrome and several human cancers, has a key role in G1/G2 checkpoint controls.

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