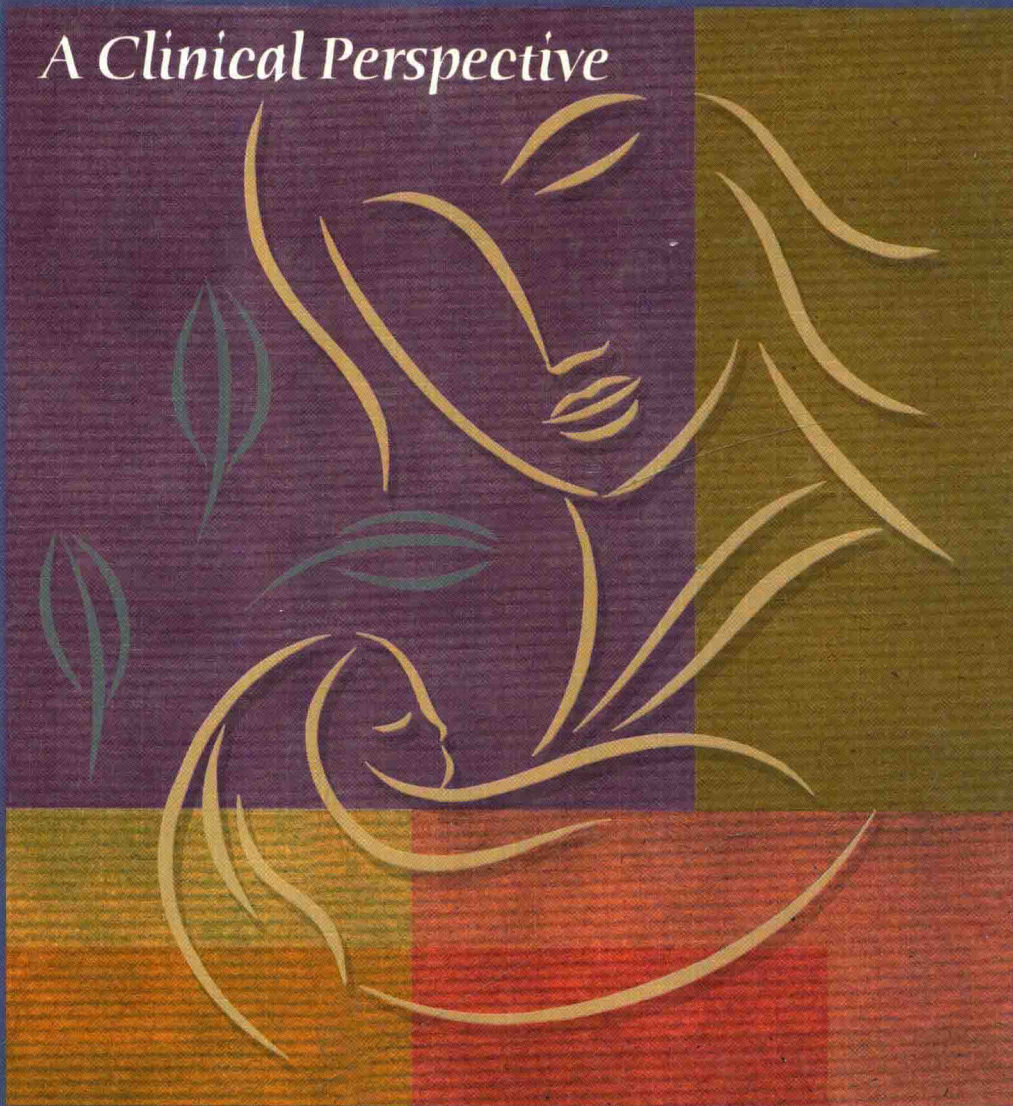


Fourth Edition

Maternal, Fetal, & Neonatal Physiology

A Clinical Perspective



Susan Tucker Blackburn

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Library of Congress Cataloging-in-Publication Data

Blackburn, Susan Tucker.

Maternal, fetal, & neonatal physiology : a clinical perspective / Susan Tucker Blackburn. -- 4th ed.
p. ; cm.

Maternal, fetal, and neonatal physiology

Includes bibliographical references and index.

ISBN 978-1-4377-1623-8 (hardback)

I. Title. II. Title: Maternal, fetal, and neonatal physiology.

[DNLM: 1. Pregnancy--physiology. 2. Fetus--physiology. 3. Infant, Newborn--physiology. WQ 205]

612.6'3--dc23

2012002845

Executive Content Strategist: Kristin Geen

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Publishing Services Manager: Deborah L. Vogel

Senior Project Manager: Antony Prince

Design Direction: Karen Pauls

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Preface

Accurate assessment and clinical care appropriate to the developmental and maturational stage of the mother, fetus, and neonate depend on a thorough understanding of normal physiologic processes and the ability of the caregiver to understand the effects of these processes on pathologic alterations. Information on normal pregnancy and perinatal physiology and its clinical implications can be found in various sources, including journal articles, general physiology texts, core nursing texts, and medical references. These sources are often either fragmented, too basic in level, too focused on one phase of the perinatal period (and thus lacking integration within the maternal-fetal-neonatal unit), or lacking in the clinical applications relevant to patient care. Thus they do not adequately meet the needs of nurses in specialty and advanced clinical nursing practice.

Therefore the goal of the first and subsequent editions of this book was to create a single text that brought together detailed information on the physiologic changes that occur throughout pregnancy and the perinatal period, with emphasis on the mother, fetus, and neonate and the interrelationships among them. The purpose of this book is not to provide a manual of specific assessment and intervention strategies or to focus on pathophysiology—it is to present current information on the normal physiologic adaptations and developmental physiology that provides the scientific basis and rationale underlying assessment and management of the low-risk and high-risk pregnant woman, fetus, and neonate. Because the focus of this book is on physiologic adaptations, the psychological aspects of perinatal and neonatal nursing are not addressed. These aspects are certainly equally as important but are not within the realm of this text.

This book provides detailed descriptions of the physiologic processes associated with pregnancy and with the fetus and neonate. The major focus is on the normal physiologic adaptations of the pregnant woman during the antepartum, intrapartum, and postpartum periods; anatomic and functional development of the fetus; transition and adaptation of the infant at birth; developmental physiology of the neonate (term and preterm); and a summary of the maturation of each body system during infancy and childhood. Clinical implications of these physiologic adaptations as they relate to the pregnant woman, maternal-fetal unit, and neonate are also examined. Each chapter describes the effects of

normal physiologic adaptations on clinical assessment and interventions with low-risk and high-risk women and neonates with selected health problems. Of special interest to those seeking quick access to clinical information are tables with recommendations for clinical practice that are included in each chapter, referencing pages with relevant content that provides the rationale underlying each recommendation.

Advanced practice nursing must be based on a sound physiologic base. Thus I hope that this book will be a useful foundation reference for specialty and advanced practice nurses in both primary and acute care settings, as well as for graduate programs in maternal, perinatal, and neonatal nursing and nurse midwifery. This book may also hold appeal for other health care professionals, including physicians, physical and occupational therapists, respiratory therapists, and nutritionists involved in obstetrics and neonatology.

ACKNOWLEDGMENTS

The help and support of many individuals were critical in making this book a reality. These include former and current students, nursing staff, and colleagues who stimulated me to continue to expand my knowledge of perinatal and neonatal physiology and examine the scientific basis for nursing interventions with pregnant women and neonates. The women, neonates, and their families whom I have cared for and from whom I have learned a great deal also stimulated development of this book. Thank you to Ilana Chertok, Robin Webb Corbett, and Tekoa King for sharing their expertise in the chapters they contributed to this edition. Special thanks to Elizabeth Posey, Susan Skinner and Kristie Marbut for their assistance with manuscript preparation. I am grateful for the efforts of the reviewers, whose constructive comments and suggestions helped in refining the content and in making this book more useful for the intended audience. My appreciation and thanks also goes to the staff at Elsevier, particularly Laurie Gower, Content Manager, Sarah Hembree, Associate Content Development Specialist, and Bridget Healy, Project Manager, for their assistance in the development and production of this book. Finally I would like to thank my family for their support, guidance, and encouragement in all of my endeavors.

Susan Tucker Blackburn

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Biologic Basis for Reproduction

The biologic basis for reproduction includes genetic mechanisms and principles, gametogenesis, and embryonic development of the reproductive system. The process of reproduction is influenced by chromosomal and gene structure and function and many mediating and signaling factors including transcription factors, growth factors, and signaling molecules. Reproduction is also influenced by physiologic processes such as hormonal control mechanisms and the hypothalamic-pituitary-ovarian axis, which are described in Chapter 2.

Our knowledge of genetics continues to expand at a remarkable rate. The Human Genome Project, an international collaborative effort begun in 1990 and completed in 2003, within days of the 50th anniversary of Watson and Crick's description of the deoxyribonucleic acid (DNA) double helix, accomplished its goal of identifying the human DNA sequence, developing an international database, and developing new investigative tools and methods of analysis.^{3,34,59} An integral part of the Human Genome Project was the identification and analysis of the ethical, legal, and social issues generated by this new knowledge. One of the outcomes of this project was determining that the human genome (DNA sequences containing all of the individual's genetic information) contains approximately 25,000 genes, far fewer than earlier estimates.⁴⁵ The Human Genome Project continues to change our understanding of both human development and the pathogenesis, diagnosis and treatment of diseases.⁵⁹ Although the Human Genome Project has significantly altered our knowledge of genetics, there is still much to learn including exact gene numbers, locations and functions, gene regulation, understanding of noncoding DNA sequences, coordination between gene expression, protein synthesis and conservation, and posttranslational events, complex interaction of proteins, gene therapies, developmental genetics, and better understanding of genes involved in complex traits and multigene disorders.^{15,34,59}

CHROMOSOMES AND GENES

The human genome is the totality of the DNA sequences, containing all of an individual's genetic information. Each human cell, except for the gametes (ovum and sperm),

normally contains 46 chromosomes (diploid number) consisting of 22 pairs of autosomes and 1 pair of sex chromosomes. Autosomal genes are located on the autosomes (chromosomes common to both sexes) and are homologous (a pair of chromosomes with identical gene arrangements). Males have a pair of nonhomologous chromosomes, the X and Y sex chromosomes. In the female, the sex chromosomes (XX) are homologous. One of each chromosome pair comes from the mother and one from the father. The ovum and sperm have only 23 chromosomes (haploid number). This reduction in the number of chromosomes occurs during meiosis. With fertilization and union of the nuclei of the sperm and ovum, the diploid number of 46 chromosomes is restored in the zygote.

Chromosomes

Chromosomes are classified by structure and banding pattern, which varies depending on the stain used or by color if spectral analysis is used. Structural characteristics include the location of the centromere (metacentric, submetacentric, or acrocentric) and the length or size of the chromosomes (Figure 1-1). The upper arm of each chromosome is referred to as the p arm; the lower arm is the q arm. Sections of the p and q arm are numbered according to the banding patterns of mitotic chromosomes so specific loci along each chromosome can be identified. Gismo-trypsin banding (G-banding) has been the most widely used technique, producing up to 300 to 400 metaphase bands. Each band contains many genes. High-resolution banding during late prophase or early metaphase increases the resolution twofold. Newer spectral methods of karyotyping and fluorescent in situ hybridization (FISH) techniques such as chromosome painting, locus-specific mutations FISH, and interphase FISH allow for even greater resolution and specificity of chromosome segments and genes. The karyotype is a pictorial display of chromosomes.

Chromosomes are composed of the DNA double helix and several types of proteins that together are known as *chromatin*. In each chromosome the continuous DNA helix is wound around histone (protein) spools that are coiled around each other to form solenoids. The solenoids are coiled into chromatin threads (Figure 1-2). If unwound, each

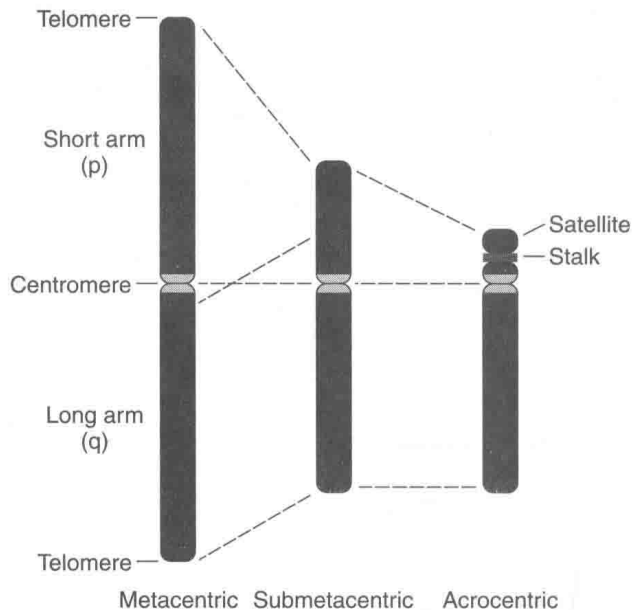


FIGURE 1-1 Schematic diagram of human chromosomes demonstrating metacentric, submetacentric, and acrocentric chromosomes. The location of the centromere, telomere, and short (p) and long (q) arms are indicated. (From Morton, C.C. & Miron, P.M. [2004]. *Cytogenetics in reproduction*. In J.F. Strauss & R. Barbieri [Eds.]. *Yen and Jaffe's reproductive endocrinology: Physiology, pathophysiology, and clinical management* [5th ed.]. Philadelphia: Saunders.)

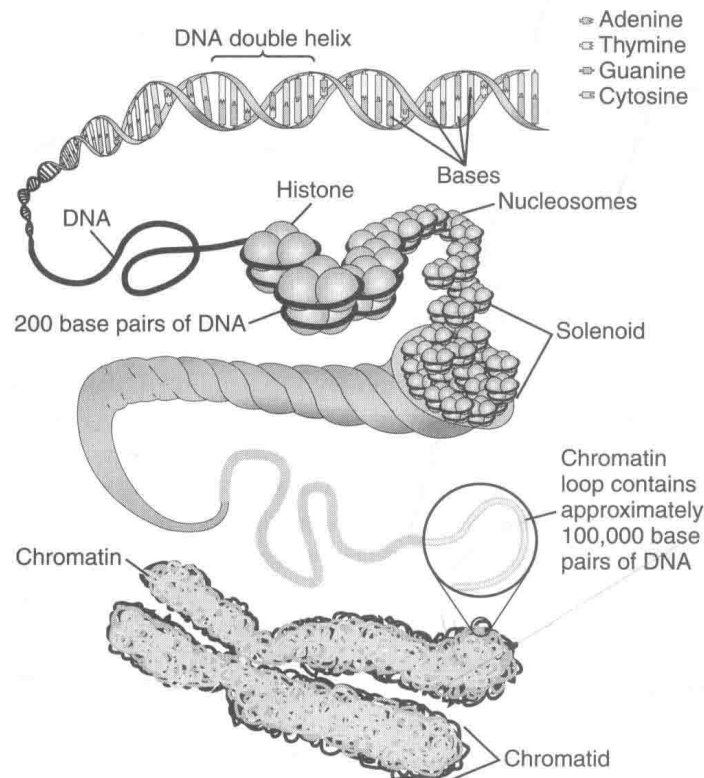


FIGURE 1-2 Structure of DNA and patterns of DNA coiling. DNA is wound around histones to form nucleosomes. These are organized into solenoids that in turn compose chromatin loops. (From Jorde, L.B., et al. [2006]. *Medical genetics* [3rd ed.]. St. Louis: Mosby.)

chromosome would contain approximately 2 m of DNA.³⁵ The DNA double helix is similar to a flexible ladder, with the sides composed of deoxyribose and phosphate and each rung composed of two nitrogen bases connected by hydrogen bonds (see Figure 1-2). The human genome contains approximately 3 million bases, with 50 to 250 million pairs in each chromosome.⁷²

X Chromosomes

Sequencing of the X chromosome identified 1098 genes and 160 million base pairs.⁶³ In comparison, the Y chromosome contains 78 genes and 23 million base pairs.⁶³ There is more variation in gene expression in women than in men.¹² More than 300 X-linked disorders have been identified. The X chromosome contains only about 4% of the genes in the human genome, but these genes are responsible for about 10% of all disorders inherited by Mendelian patterns.⁶³

In all of a woman's somatic cells (but not in her germ cells), one of the two X chromosomes is inactivated (lyonization) and remains condensed. The inactive X is seen in interphase as the Barr body. The number of Barr bodies is one minus the number of X chromosomes. Therefore a normal male has no Barr bodies and neither does a woman with Turner syndrome (XO); a normal female has 1 Barr body, while a male with Klinefelter syndrome (XXY) has one. In the female, both X chromosomes are reactivated during gametogenesis. Thus the woman produces ova with two active X chromosomes which undergo recombination with each other.⁶³ In the female zygote, inactivation begins within 7 to 10 days after fertilization.³⁵ In all cells within the embryo, the inactivated X is random in each cell—it could be the X chromosome the zygote received from its mother or the X chromosome it received from its father—and the same X is inactive in all descendants of that cell. However, in the trophoblast tissue (which is extraembryonic tissue that will become the placenta and chorion) in the preembryonic blastocyst, all the paternally derived X chromosomes are inactivated, whereas all the maternal X chromosomes are active.^{35,41,65}

Inactivation is thought to involve methylation of critical segments of DNA and histone deacetylation initiated by the *XIST* gene on the long arm (q13) of X chromosomes.^{41,58} The inactive X transcribes RNA from this gene so the X chromosome is coated with *XIST* RNA.¹² Not all genes on the inactive X are inactive; 10% of the genes on the inactive X escape inactivation (thus a woman has a double dose of these genes).²⁸ The active genes on the inactive X are generally located on the tip of the short arm, which are homologous with some of the genes on the distal end of the Y chromosome.³⁵

Genes

Genes are the functional units of heredity consisting of DNA sequences that code for specific amino acids and thus for formation of specific proteins. Currently, each human is thought to have approximately 25,000 genes.⁴⁵ Genes make

up only about 10% of the human genome.⁴⁵ Genes are distributed in clusters along the chromosome, so some areas have many genes, others few.³⁵ These protein coding sequences of DNA are called *exons* (expression sequences). Exons have a consistent identifying sequence of nucleotides at each end. Interspersed between these are noncoding sequences, called *introns* (intervening sequences), whose exact role is still not completely clear. Much of the DNA consists of series of repeated nucleotides that may be repeated a thousand or more times.^{35,45} Some of these sequences are needed for DNA transcription factors, RNA translation, chromosome pairing, and other regulatory functions.^{35,45}

Genes are essential in determining and maintaining cell structural integrity and cell function and in regulating biochemical and immunologic processes.²⁸ Some genes control the function of other genes, others regulate the process of embryonic and fetal development. Genes direct protein synthesis and regulate the rate at which proteins are synthesized. The specific proteins synthesized vary depending on the type of cell. For example, a muscle cell synthesizes myosin for muscle contraction, the pancreatic islet cells synthesize insulin, and the liver cells produce γ -globulin. Although the full complement of genes is present in all cells, genes are selectively switched on and off. Therefore all genes are not active at the same time. This activation process is important during development (see "Developmental Genetics" in Chapter 3) and is influenced by age, cell type, and function. In addition, each gene can produce multiple isotypes, each isotype producing a different product. The different isotypes are produced by the splicing and reorganization of exons within a given gene (Figure 1-3).⁴⁴ As a result, a single gene can guide the production of many different forms of messenger ribonucleic acid (mRNA) and thus proteins with individual biologic functions.^{10,16}

Genes are arranged in linear order and in pairs on homologous chromosomes, one chromosome and its genes coming from an individual's mother, the other from the father. Each gene has a specific location, called a *locus*, on the chromosome. One copy of a gene normally occupies any given locus. In somatic cells, the chromosomes are paired so that there are two copies of each gene (alleles). The corresponding genes at a given locus on homologous chromosomes govern the same trait, but not necessarily in the same way. If gene pairs are identical, they are homozygous; if they are different, they are heterozygous. In the heterozygous state, one of the alleles may be expressed over the other. This allele is considered dominant, meaning that the trait is expressed if the dominant allele is present on at least one of the pair of chromosomes. Recessive traits can be expressed only when the allele responsible for that trait is present on both chromosomes or when the dominant allele is not present (as with X-linked genes in the XY male, who is hemizygous for that trait). *Genotype* refers to the genetic makeup of an individual or a particular gene pair. The observable expression of a specific trait is referred to as the *phenotype*. A trait may be a

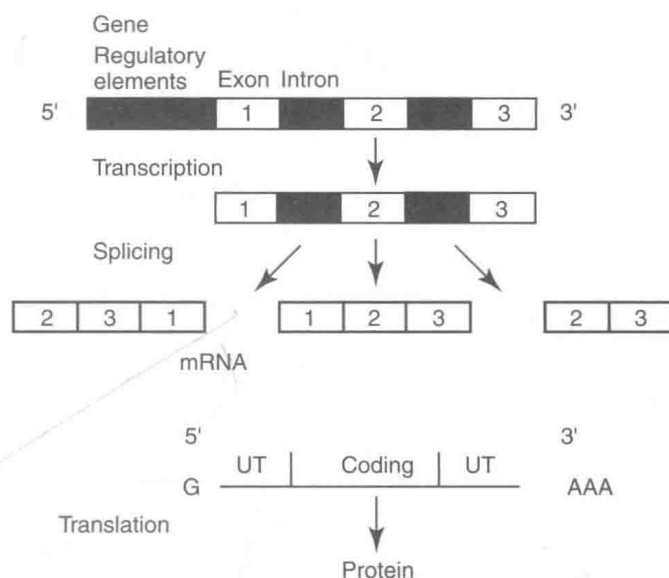


FIGURE 1-3 Scheme for the transcription and translation of a gene within the human genome resulting in multiple gene products using alternative splicing. The gene consists of a 5' promoter sequence containing multiple regulatory elements (e.g., retinoic acid, vitamin D, or steroid/thyroxine hormone-binding elements), multiple exons (indicated as 1, 2, and 3), which contain the sequence encoding the protein, and intervening noncoding DNA sequences (introns). Following transcription, the messenger ribonucleic acid (mRNA) is processed by splicing out the introns and adding a G residue to the 5' end and multiple As to the 3' end. Alternate splicing and rearrangement of exons can produce a number of different mRNAs (transcripts) encoding different proteins (i.e., *transcript 1*, exons 2-3-1; *transcript 2*, exons 1-2-3; *transcript 3*, exons 2-3). The designation UT refers to noncoding untranslated regions in the mature mRNA. The mature mRNA is subsequently transported to the cytoplasm and translated into the primary structure of a protein that then is processed and folded to form the biologic substrate. (From Slavkin, H.C. & Warburton, D. [2004]. *Regulation of embryogenesis*. In R.A. Polin, W.W. Fox, & S.H. Abman [Eds.]. *Fetal and neonatal physiology* [3rd ed.]. Philadelphia: Saunders.)

biochemical property, an anatomic structure, a cell or organ function, or a mental characteristic. Thus traits are derived from the action of the gene and not from the gene itself.^{28,43,71}

DNA and RNA

The transmission of hereditary information from one cell to another is a function of DNA. DNA also contains the instructions for the synthesis of proteins that determine the structure and function of that cell. The nucleus contains DNA; protein assembly occurs within the cytoplasm in the ribosomes. The transfer of information from the nucleus to the site of synthesis is the role of messenger ribonucleic acid (mRNA), which is synthesized on the surface of DNA.

Both DNA and ribonucleic acid (RNA) are nucleic acids made up of a nitrogenous purine (adenine and guanine) or pyrimidine (cytosine and thymine or uracil) base, a sugar (deoxyribose for DNA and ribose for RNA), and a phosphate group (see Figure 1-2). Together these substrates form a structure that is linked in a linear sequence by phosphodiester bonds. DNA is composed of two antiparallel complementary

chains of opposite polarity. These strands form a double helix in which the sides are the phosphate and sugar groups and the crossbars are complementary bases joined by hydrogen bonds. Only complementary bases form stable bonds; therefore adenine (A) always pairs with thymine (T), and guanine (G) always pairs with cytosine (C). Thus the sequence of the bases on one strand determines the sequence of bases on the other.

RNA is a single strand rather than a double helix and contains adenine, cytosine, guanine, and uracil (U), which pairs with adenine, because thymine is not present. There are three major types of RNA: (1) messenger ribonucleic acid (mRNA), (2) ribosomal RNA (rRNA), and (3) transfer RNA (tRNA). Messenger RNA receives information from the DNA and serves as the template for protein synthesis. Transfer RNA brings the amino acids to messenger ribonucleic acid (mRNA) and positions them correctly during protein synthesis. One of the structural components at the protein assemblage site (ribosome) is rRNA. The passage of information from DNA to RNA is called *transcription*; the assemblage of the proper sequence on amino acids is *translation*. Protein synthesis and the sequence of events in transcription and translation are summarized in Box 1-1 below.

The sequence of bases along the DNA makes up the genetic code that specifies the sequence of amino acids in each protein. Each of the 20 amino acids is designated by a specific sequence of three bases (codon). A gene codes for a single protein, which is a series of amino acids. The four bases (A, T or U, C, and G) can be arranged in 64 triplet combinations, of which 61 are used to specify the 20 amino acids. Most amino acids are represented by several codons. For example, AUG codes for methionine, and CAU and CAC both code for histidine. The other three codes are termination codes, which designate the end of a gene (see Box 1-1 below).

GENOMICS

Genetics involves examination of individual genes and their effects. Genomics is “the study of the functions and the interactions of all the genes in the genome.”²⁵ This focus includes gene-environment interactions and will increase our understanding of complex disorders such as diabetes, Alzheimer’s disease, hypertension, and cancer.²⁵ Genomics includes a focus on genetic variations that may alter the risks of disease and on how genes interact with chemical, infectious, environmental, physical, and pharmacologic agents, with an increased emphasis on risk assessment and prevention, development of new diagnostic, treatment, and prognostic techniques and new fields of study such as pharmacogenetics.³⁹ Genomics will raise additional ethical, legal, and social issues.^{14,59}

Genetic polymorphisms are variations in the genome sequence that occur throughout the genome with a frequency of about 1 in 100 basepairs.⁶⁸ Polymorphisms may involve the substitution of a single nucleotide base (single nucleotide polymorphisms, or SNPs) or a group of alleles or alternate gene forms that are inherited together (haplotypes). SNPs are the simplest form of DNA variation among individuals.⁶⁸ The human genome contains more than 10 million SNPs.²⁵ Polymorphisms may be nonfunctional and have no effect on the individual or alter expression of a protein that increases the risk of disease, especially with exposure to specific environmental agents or drugs.³⁸ These variations may be important in altering the effects of exposures to environmental health hazards such as mercury, alcohol, tobacco smoke, air pollutants, and other toxins leading to different levels of risk and susceptibility to disease and to adverse environmental influences within the population.^{18,38} Since SNPs can result in individual differences in responses

BOX 1-1 Sequence of Events in Transcription and Translation

TRANSCRIPTION

1. The two strands of the deoxyribonucleic acid (DNA) double helix separate in the region of the gene to be transcribed. One strand acts as a template.
2. Free nucleotide bases pair with the nucleotide bases in DNA.
3. The nucleotide triphosphates paired with one strand of DNA are linked together by DNA-dependent ribonucleic acid (RNA) polymerase to form messenger ribonucleic acid (mRNA) containing a sequence of bases complementary to the DNA base sequence.
4. Once the (mRNA) has formed, the DNA strand rewinds.
5. mRNA is processed before leaving the nucleus. Introns (non-coding areas of DNA) are removed and promoter and terminator structures are added to promote stability and efficiency of translation.

Translation

6. The processed mRNA passes from the nucleus to the cytoplasm, where one end of the mRNA binds to a ribosome.
7. The ribosome is formed from ribosomal RNA (rRNA) and proteins. The mRNA codons are “read” by the ribosome and translated into amino acids.
8. Free amino acids combine with their corresponding transfer RNA (tRNA) in the presence of specific aminoacyl-tRNA synthetase enzymes in the cytoplasm.
9. Amino acid-tRNA complexes bind to sites on the ribosome and the three base anticodons in tRNA pair with the corresponding codons in mRNA.
10. Each amino acid is then transferred from its tRNA to the growing peptide chain, which is attached to the adjacent tRNA.
11. The tRNA freed of its amino acid is released from the ribosome.
12. A new amino acid-tRNA complex is attached to the vacated site on the ribosome.
13. mRNA moves one codon step along the ribosome.
14. Steps 9 to 13 are repeated over and over until all the codons have been read.
15. The completed protein chain is released from the ribosome when the termination codon in mRNA is reached.

to drugs, understanding these variations can individualize pharmacologic management. Research in this area has also identified polymorphic genes and environmental influences that can alter susceptibility to birth defects.^{18,79} For example, genetic differences in folate metabolism may increase the risk of neural tube defects and pregnancy loss; a rare transforming growth factor- α polymorphism has been linked with orofacial clefts with exposure to cigarette smoke; differences in enzymes needed for metabolizing anticonvulsant drugs may increase the risk of congenital anomalies in women taking these drugs; polymorphisms in alcohol metabolism may increase the risk of fetal alcohol syndrome; polymorphisms in drug metabolizing enzymes may result in impaired pregnancy maintenance with exposure to cigarette smoke or male infertility with exposure to organophosphate pesticides.^{18,79} Study of polymorphisms and gene-environment interactions may lead to better understanding of complex reproductive disorders such as preeclampsia, infertility, and preterm labor as well as disorders such as diabetes, hypertension, infection, coronary artery disease, obesity, and psychiatric disorders.^{28,68,79}

CELL DIVISION

Genetic material is passed to daughter cells in two ways: via mitosis in somatic cells and in germ cells via mitosis (during the initial development of germ cells) or meiosis (during gametogenesis). Before onset of either mitosis or meiosis, DNA replication must occur. Before a cell divides, the accurate replication of the genetic material stored within the DNA of the parent cell is essential. During DNA replication, the strands of the double helix uncoil, relax, and separate. The exposed nucleotide bases pair with complementary free nucleotides. DNA polymerase links the nucleotides together, resulting in two identical molecules of DNA to pass on to daughter cells. Enzymes within the cell nucleus “read” the replicated DNA and repair errors. If errors are not repaired, a mutation results. DNA replication is illustrated in Figure 1-4. Mitosis and meiosis are illustrated in Figure 1-5.

Mitosis

Mitosis is the process by which growth of the organism occurs and cells repair and replace themselves. This process maintains the diploid number of 46 chromosomes, forming two daughter cells, each with a single strand of DNA, that are exact replicas of the parent (unless a mutation occurs). The cell cycle consists of four stages: gap 1 (G1), synthesis (S), gap 2 (G2), and mitosis (M). G1, S, and G2 comprise interphase. During G1, the longest stage, proteins needed by the cell are synthesized and substances needed for DNA replication are amassed; DNA replication occurs in the S stage. After completion of DNA replication, each chromosome consists of two identical strands of DNA, called *sister chromatids*. G2 is a resting stage, during which errors in DNA are corrected and the cell prepares for the final M stage, in which the cell

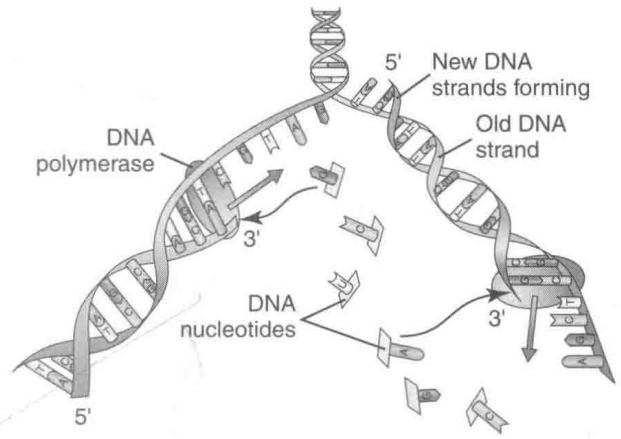


FIGURE 1-4 DNA replication. The hydrogen bonds between the two original strands are broken, allowing the bases in each strand to undergo complementary base pairing with free bases. The process forms two new double strands of DNA. (From Jorde, L.B., et al. [2006]. *Medical genetics* [3rd ed.]. St. Louis: Mosby.)

divides.⁴⁵ The length of time for a cell to complete the entire cycle varies with the type of cell and may last hours (epithelial tissues) to weeks (liver cells).¹⁰ The cell cycle is regulated by enzymes such as cyclin-dependent kinases (CDKs), which are control switches for the cycle (i.e., switching from G1 to S or from S to G2); maturation promoting factor, which triggers progression through the cell cycle; protein 63, which blocks the cycle if the DNA is damaged to allow time for DNA repair; and protein 27, which can also block the cycle by binding to cyclins and blocking entry into S.³⁵ Alterations in these substances can lead to production of mutations and cancerous cells.^{10,35}

Thus before initiation of mitosis, DNA replication has occurred (see Figure 1-5). At this point each cell still has 46 chromosomes, but each chromosome has 2 strands of DNA, which is twice the usual amount of DNA. Just before cell division, the duplicated DNA threads (chromatin) change from a loose, relaxed mass and become condensed and tightly coiled, forming the rod-shaped chromosomes. This condensing process facilitates the transfer of DNA to the daughter cells. This change is the first sign of cell division.

As the cell enters prophase, the chromosomes each consist of two DNA threads (sister chromatids). The two chromatids are joined at a single point called the *centromere*. Late in prophase the nuclear membrane begins to disintegrate. The centrioles (two small cylindric bodies) separate and move to opposite sides of the cell. A number of microtubules are observable at this stage. These are spindle fibers that extend from one side of the cell to the other, between the centrioles.

During metaphase the chromatids line up on the metaphase plate in the center of the cell. Other spindle fibers now extend from the centrioles and are attached to the centromere region of the chromosome. In anaphase, the chromosomes divide at the centromere into sister chromatids that are pulled to opposite poles. As the chromosomes reach their respective poles, they begin to uncoil and elongate. A ring of protein appears around the center of the cell and the cell begins to