Introduction to Medical Genetics

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Background

- Medical genetics involves any application of genetics to medical practice.

- It includes

- studies of the inheritance of diseases in families,
- analyses of the molecular mechanisms through which genes cause disease, and
- the diagnosis and treatment of genetic disease.

- gene therapy- the insertion of normal genes into patients in order to correct genetic disease-is now possible.

- Medical genetics also includes genetic counseling, which involves the communication of information regarding risks, prognoses, and treatments to patients and their families.

WHY IS A KNOWLEDGE OF MEDICAL GENETICS IMPORTANT FOR TODAY'S Health CARE- PRACTITIONER?

TABLE 1-1 A Partial List of Some Important Genetic Diseases

DISEASE	APPROXIMATE PREVALENCE
Chromosome Abnormalities	
Down syndrome	1/700 to 1/1000
Klinefelter syndrome	1/1000 males
Trisomy 13	1/10,000
Trisomy 18	1/6000
Turner syndrome	1/2500 to 1/10,000 females
Single-Gene Disorders	
Adenomatous polyposis coli	1/6000
Adult polycystic kidney disease	1/1000
α_1-Antitrypsin deficiency	1/2500 to 1/10,000 (whites)*
Cystic fibrosis	1/2000 to 1/4000 (whites)
Duchenne muscular dystrophy	1/3500 males
Familial hypercholesterolemia	1/500
Fragile X syndrome	1/4000 males; 1/8000 females
Hemochromatosis (hereditary)	1/300 whites are homozygotes; approximately 1/1000 to 1/2000 are affected
Hemophilia A	1/5000 to 1/10,000 males
Hereditary nonpolyposis colorectal cancer	Up to 1/200
Huntington disease	1/20,000 (whites)
Marfan syndrome	1/10,000 to 1/20,000
Myotonic dystrophy	1/7000 to 1/20,000 (whites)
Neurofibromatosis type 1	1/3000 to 1/5000
Osteogenesis imperfecta	1/5000 to 1/10,000
Phenylketonuria	1/10,000 to 1/15,000 (whites)
Retinoblastoma	1/20,000
Sickle cell disease	1/400 to 1/600 blacks* in America; up to 1/50 in central Africa
Tay-Sachs disease	1/3000 Ashkenazi Jews
Thalassemia	1/50 to 1/100 (South Asian and circum-Mediterranean populations)

Multifactorial Disorders	
Congenital Malformations	
Cleft lip with or without cleft palate	1/500 to 1/1000
Club foot (talipes equinovarus)	1/1000
Congenital heart defects	1/200 to 1/500
Neural tube defects (spina bifida, anencephaly)	1/200 to 1/1000
Pyloric stenosis	1/300
Adult Diseases	
Alcoholism	1/10 to 1/20
Alzheimer disease	1/10 (Americans older than 65 years)
Bipolar disorder	1/100 to 1/200
Cancer (all types)	1/3
Diabetes (types 1 and 2)	1/10
Heart disease or stroke	1/3 to 1/5
Schizophrenia	1/100
Mitochondrial Diseases	
Kaerns-Sayre syndrome	Rare
Leber hereditary optic neuropathy (LHON)	Rare
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Rare
Myoclonic epilepsy and ragged red fiber disease (MERRF)	Rare

*The term "white" refers to individuals of predominantly European descent; the term "black" refers to individuals of predominantly sub-Saharan African descent. These terms are used for convenience; some of the challenges in accurately describing human populations are discussed in Chapter 14.

A BRIEF HISTORY

- Gregor Mendel, an Austrian monk who is usually considered to be the "father" of genetics, advanced the field significantly by

- performing a series of cleverly designed experiments on garden peas.
- He then used the experimental information to formulate a series of fundamental principles of heredity.

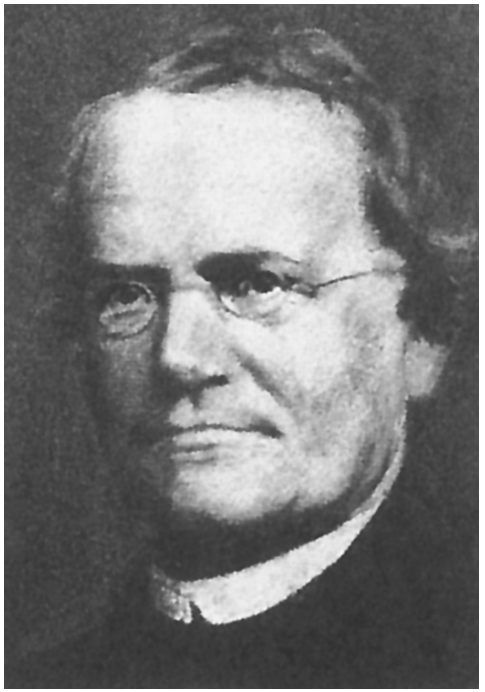

FIG 1-1 Gregor Johann Mendel. (From Raven PH, Johnson GB. *Biology.* 3rd ed. St Louis: Mosby; 1992.)

History

- Genetics as it is known today is largely the result of research performed during the 20th century.

- Mendel's principles were independently rediscovered in 1900 by three different scientists working in three different countries.

- This was also the year in which Landsteiner discovered the ABO blood group.
- In 1902, Archibald Garrod described alkaptonuria as the first "inborn error of metabolism."

- In 1909, Johannsen coined the term gene to denote the basic unit of heredity.

History

- The next several decades were a period of considerable experimental and theoretical work.

- In 1944, Oswald Avery showed that genes are composed of deoxyribonucleic acid (DNA).

- The most significant achievement of the 1950s was the specification of the physical structure of DNA by James Watson and Francis Crick in 1953.

- The basis for what is now known as molecular genetics (the study of the structure and function of genes at the molecular level)

History

- Since the early 1920s, it had been thought that humans had 48 chromosomes in each cell. Only in 1956 was the correct number, 46, finally determined.

- The ability to count and identify chromosomes led to a flurry of new findings in cytogenetics, including the discovery in 1959 that Down syndrome is caused by an extra copy of chromosome 21.

History

- During the past three decades, thousands of genes have been mapped to specific chromosome locations.

- The Human Genome Project, a large collaborative venture begun in 1990, provided the complete human DNA sequence in the year 2003.

- The term **genome** refers to all of the DNA in an organism.

TYPES OF GENETIC DISEASES

- **Chromosome disorders**, in which entire chromosomes (or large segments of them) are missing, duplicated, or otherwise altered. These disorders include diseases such as Down syndrome and Turner syndrome.

- Disorders in which single genes are altered; these are often termed "mendelian" conditions, or **single-gene disorders**. Well-known examples include cystic fibrosis, sickle cell disease, and hemophilia.

- **Multifactorial disorders,** which result from a combination of multiple genetic and environmental causes. Many birth defects, such as cleft lip and/or cleft palate, as well as many adult disorders, including heart disease and diabetes, belong in this category.

- **Mitochondrial disorders,** a relatively small number of diseases caused by alterations in the small cytoplasmic mitochondrial chromosome.

- The first edition of McKusick's *Mendelian Inheritance in Man*, published in 1966, listed only 1,368 autosomal traits and 119 X-linked traits.

- Today, the online version of McKusick's compendium lists more than 23,000 genes and traits, of which almost 21,000 are autosomal, more than 1200 are X-linked, 59 are Y-linked, and 65 are in the mitochondrial genome.

- DNA variants responsible for more than 4000 of these traits, most of which are inherited diseases, have been identified. With continued advances, these numbers are certain to increase.

Fig. 1-2. Continuum of disease causation. Some diseases (e.g., cystic fibrosis) are strongly determined by genes, whereas others (e.g., infectious diseases) are strongly determined by environment.

Structure and function of genes and chromosomes

Dr. Zaid Aburubaiha

- All genetic diseases involve defects at the level of the cell. For this reason, one must understand basic cell biology to understand genetic disease.

→ **Errors** may occur in the replication of genetic material or in the translation of genes into proteins. These errors commonly produce **single-gene disorders**

→ **errors** occurring during cell division can lead to disorders involving entire chromosomes.

- **The process through which genes are replicated and translated into proteins**

- **The process of cell division**

- Microscopic studies of cells led scientists to suspect that the **nucleus** of the cell contained the important mechanisms of inheritance.

- **Chromatin**
- **Chromosomes**

- **Genes**: are transmitted from parent to offspring and are considered to be the basic unit of inheritance.

- genes are composed of deoxyribonucleic acid **(DNA**). DNA provides the genetic "blue-print" for all proteins in the body.

- An error (or **mutation**) in one of these genes often leads to a recognizable genetic disease.

- Each human **somatic cell** (cells other than the **gametes**, or sperm and egg cells) contains 23 pairs of different chromosomes

- **Sex Chromosomes**
- **Autosomes**---Homologous

- Somatic cells, having two of each chromosome, are termed **diploid** cells. Human gametes have the **haploid** number of chromosomes, 23.

- **Mitosis---Meiosis**

Composition and Structure of DNA

- Three basic components: the pentose sugar, **deoxyribose**; a **phosphate** group; and four types of nitrogenous **bases**.

- cytosine and thymine, are single carbon-nitrogen rings called **pyrimidines**
- adenine and guanine, are double carbon- nitrogen rings called **purines**

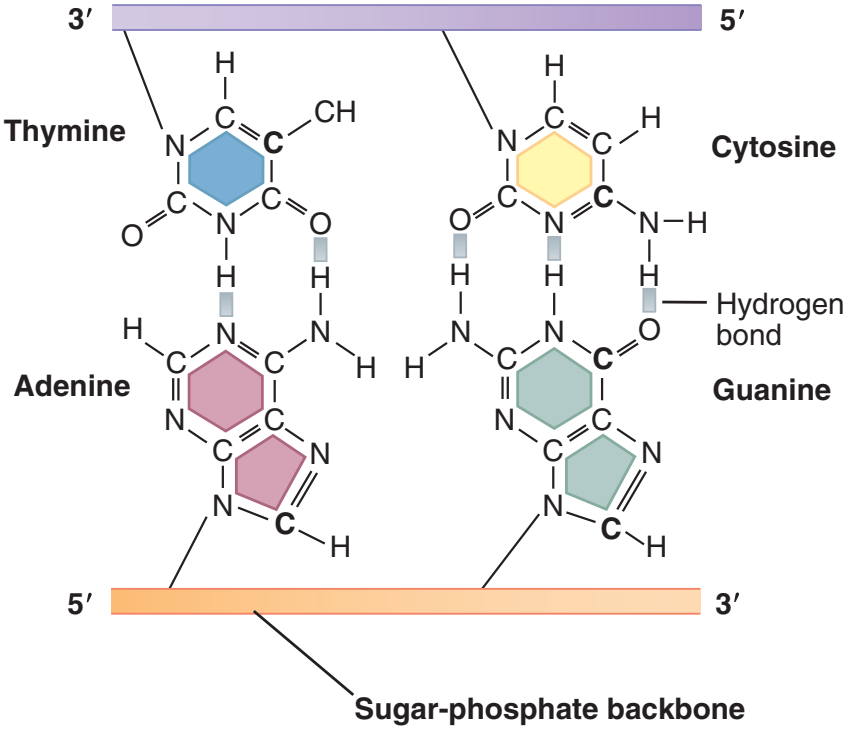

FIG 2-2 Chemical structure of the four bases, which shows hydrogen bonds between base pairs. Three hydrogen bonds are formed between cytosine–guanine pairs, and two bonds are formed between adenine–thymine pairs.

The double helix model

- **Watson and Crick's**

→ DNA can be envisioned as a twisted ladder with chemical bonds as its rungs

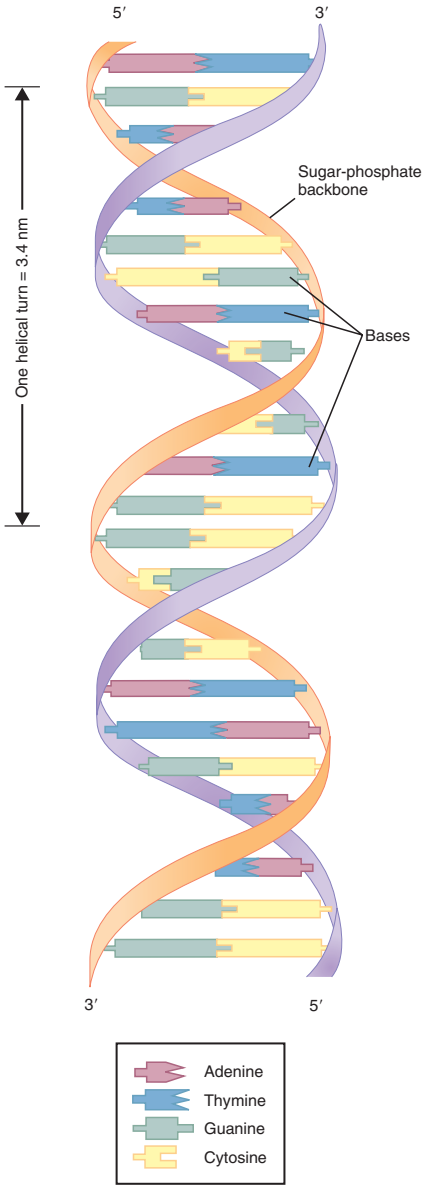

FIG 2-3 The DNA double helix, with sugar-phosphate backbone and nitrogenous bases.

DNA coiling

- The DNA is wound around a histone protein core to form a **nucleosome**
- The nucleosomes form a helical **solenoid**; each turn of the solenoid includes about six nucleosomes.
- The solenoids are organized into **chromatin loops**, which are attached to a protein scaffold.

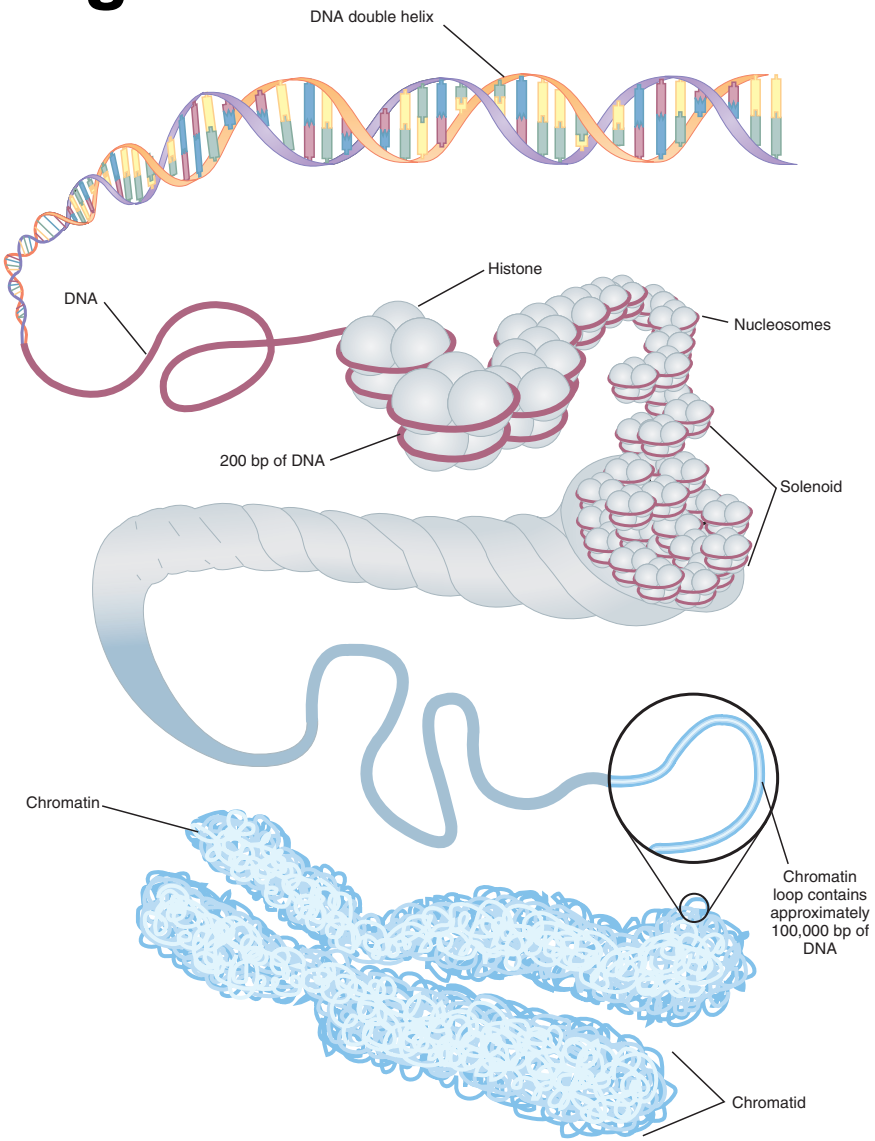

FIG 2-4 Patterns of DNA coiling. DNA is wound around histones to form nucleosomes. These are organized into solenoids, which in turn make up the chromatin loops.

DNA replication

- DNA replication consists basically of the breaking of the weak hydrogen bonds between the bases, leaving a single DNA strand with each base unpaired.

- The consistent pairing of adenine with thymine and guanine with cytosine, known as **complementary base pairing**, is the key to accurate replication

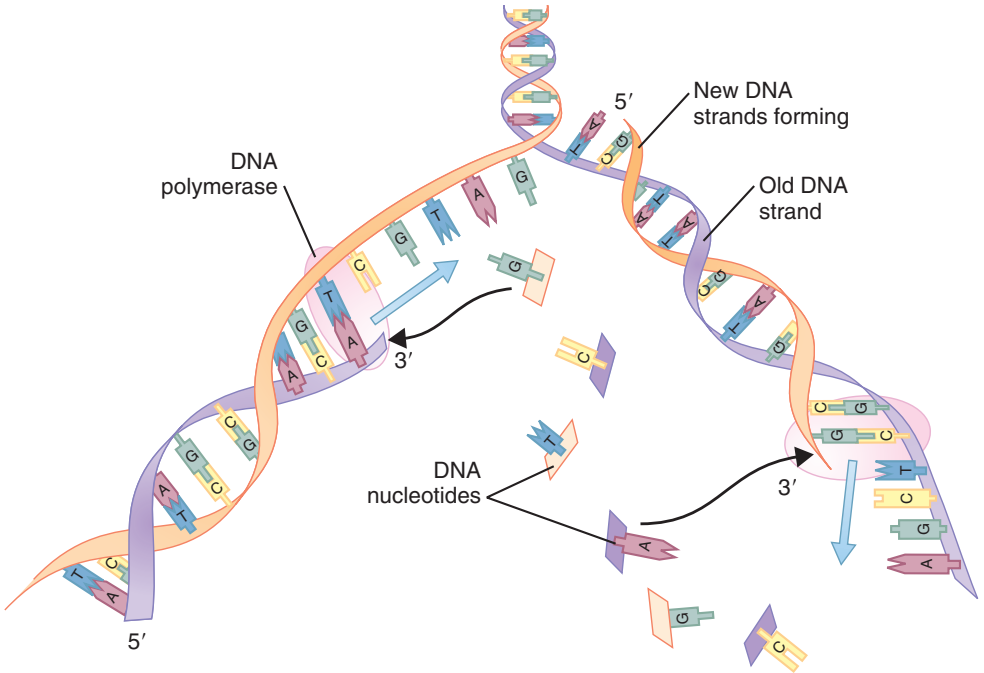

FIG 2-5 DNA replication. The hydrogen bonds between the two original strands are broken, allowing the bases in each strand to undergo complementary base pairing with free bases. This process, which proceeds in the 5′ to 3′ direction on each strand, forms two new double strands of DNA.

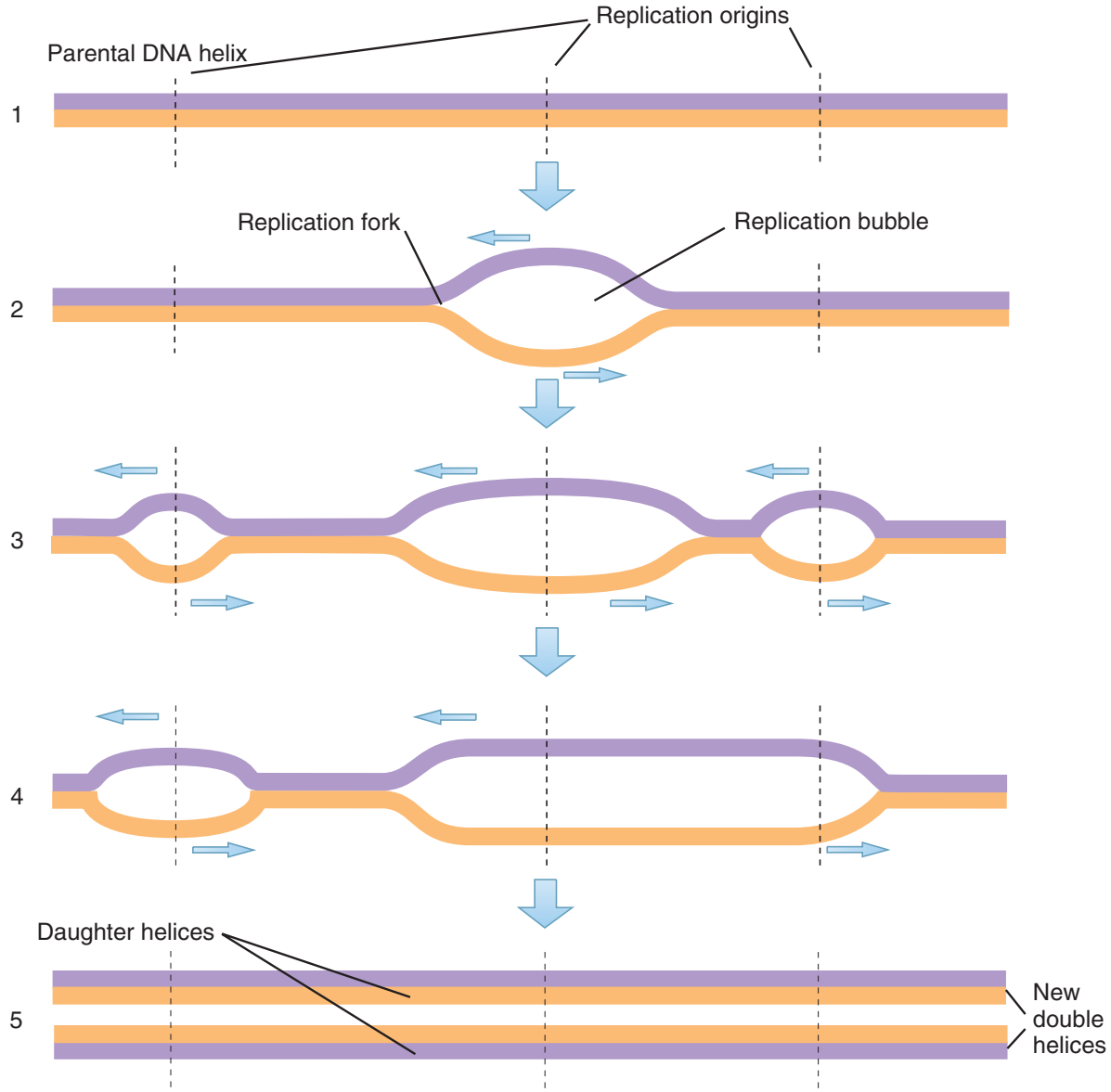

FIG 2-6 Replication bubbles form at multiple points along the DNA strand, allowing replication to proceed more rapidly.

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From Genes to Proteins

- Involves two processes, transcription and translation

- The DNA code is transcribed into messenger RNA, which then leaves the nucleus to be translated into proteins.

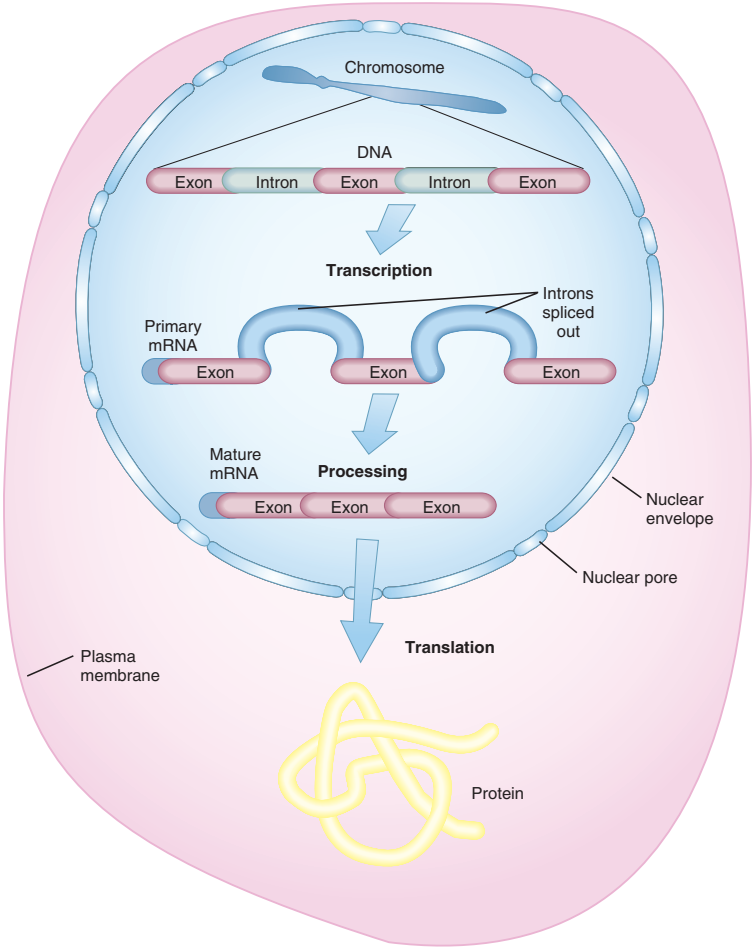

FIG 2-7 A summary of the steps leading from DNA to proteins. Replication and transcription occur in the cell nucleus. The mRNA is then transported to the cytoplasm, where translation of the mRNA into amino acid sequences composing a protein occurs.

Transcription

Transcription is the process by which an RNA sequence is formed from a DNA template.

To initiate mRNA transcription, one of the **RNA polymerase** enzymes (RNA polymerase II) binds to a promoter site on the DNA

The RNA polymerase then pulls a portion of the DNA strands apart from one another, exposing unattached DNA bases.

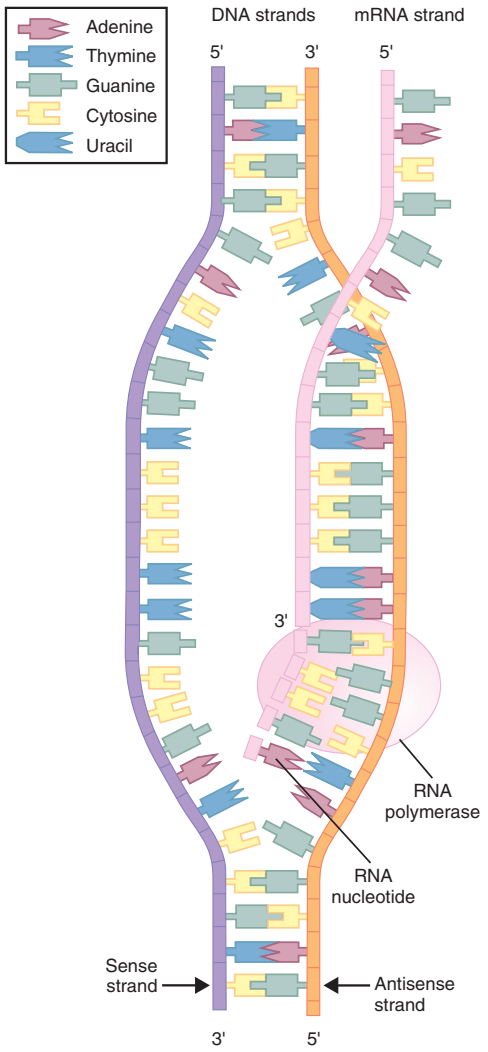

FIG 2-8 Transcription of DNA to mRNA. RNA polymerase II proceeds along the DNA strand in the 3′ to 5′ direction, assembling a strand of mRNA nucleotides that is complementary to the DNA template strand.

Only **one strand** is chosen to serve as a template for mRNA synthesis.

This choice is **determined by the promoter sequence**, which orients the RNA polymerase in a specific direction along the DNA sequence.

mRNA is synthesized only in the **5' to 3' direction**. RNA polymerase moves in the 3' to 5' direction along the DNA template strand.

Because of **complementary base pairing**, the mRNA nucleotide sequence is identical to that of the DNA strand that does not serve as the template.

Dr. Zaid Aburubaiha

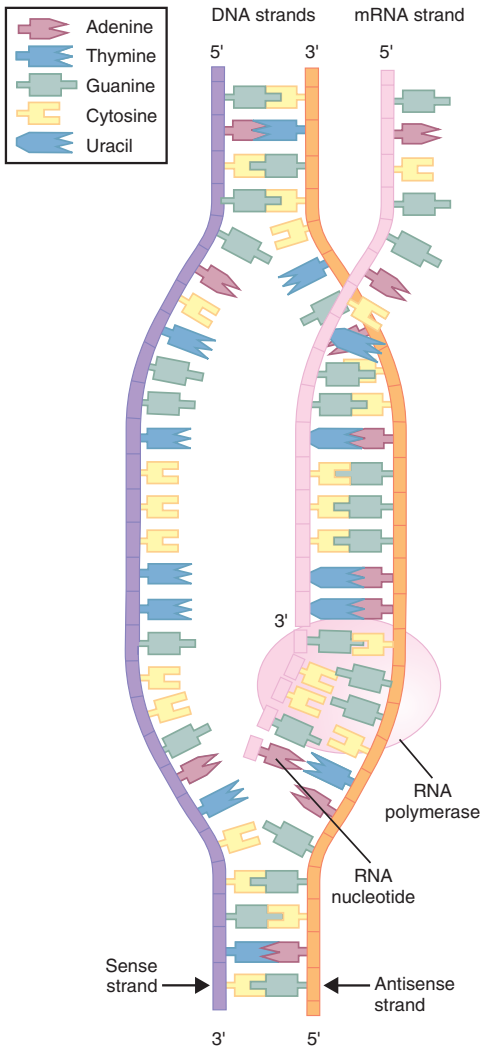

FIG 2-8 Transcription of DNA to mRNA. RNA polymerase II proceeds along the DNA strand in the 3′ to 5′ direction, assembling a strand of mRNA nucleotides that is complementary to the DNA template strand.

Soon after RNA synthesis begins, the 5' end of the growing RNA molecule is "capped" by the addition of a chemically modified guanine nucleotide.

Transcription continues until a group of bases called a termination sequence is reached. Near this point, a series of 100 to 200 adenine bases are added to the 3' end of the RNA molecule (poly-A tail).

Finally, the DNA strands and RNA polymerase separate from the RNA strand, leaving a transcribed single mRNA strand. This mRNA molecule is termed the primary transcript.

Gene Splicing

In **eukaryotes**, Sections of the RNA are removed by nuclear enzymes, and the remaining sections are spliced together to form the functional mRNA that will migrate to the cytoplasm.

The excised sequences are called introns, and the sequences that are left to code for proteins are called exons. Only when gene splicing is completed does the mature transcript move out of the nucleus into the cytoplasm.

Some genes contain alternative splice sites, which allow the same primary transcript to be spliced in different ways, ultimately producing different protein products from the same gene.

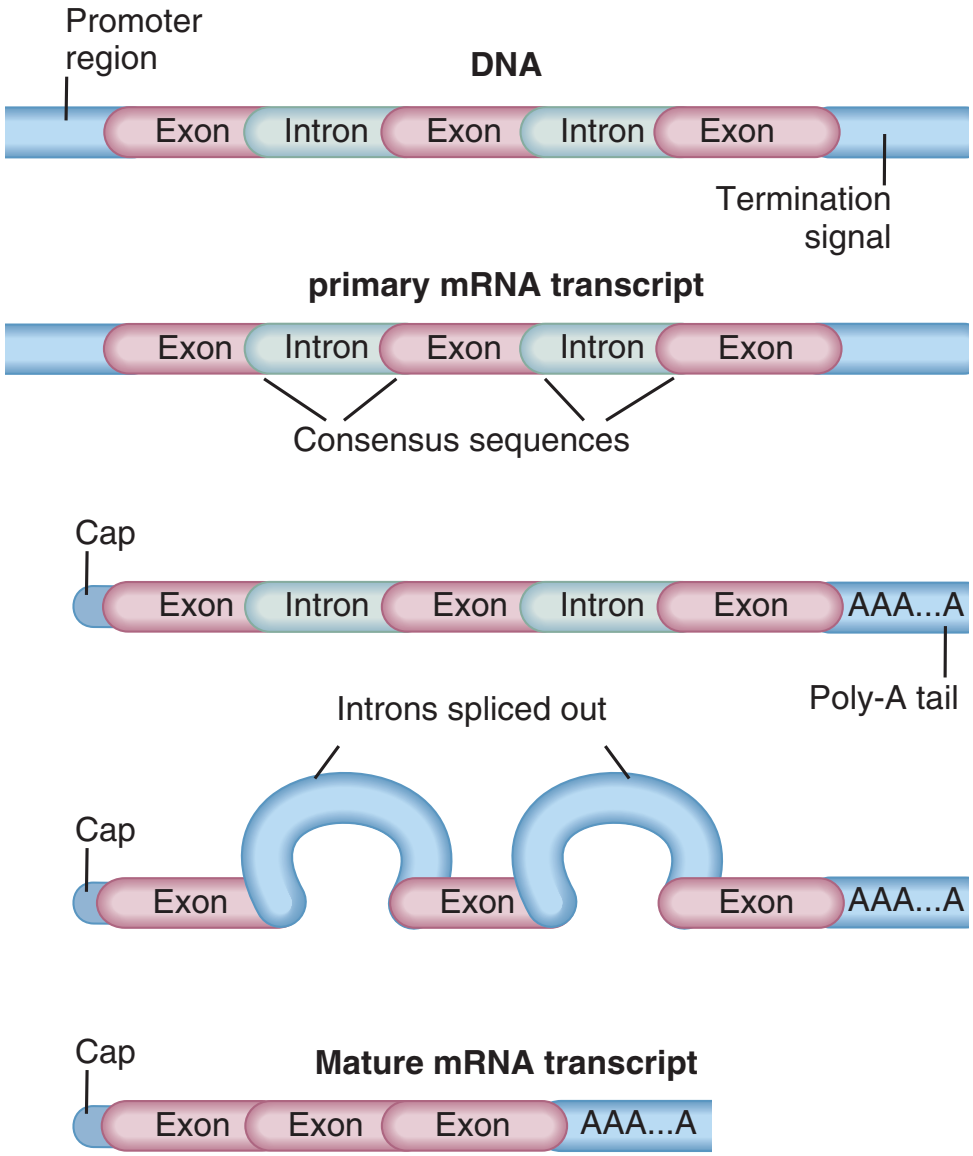

FIG 2-11 Gene splicing. Introns are precisely removed from the primary mRNA transcript to produce a mature mRNA transcript. Consensus sequences mark the sites at which splicing occurs.

The Genetic Code

The body contains **20** different types of amino acids, and the amino acid sequences must in some way be designated by the DNA after transcription into mRNA.

If triplet sets of bases are translated into amino acids, however, 64 (4 X 4 X 4) combinations can be achieved- more than enough to specify each amino acid.

The correspondence between specific codons and amino acids is known as the **genetic code**.

TABLE 2-2 The Genetic Code*

FIRST POSITION (5′ END)	SECOND POSITION				THIRD POSITION (3′ END)
↓	**U**	**C**	**A**	**G**	↓
U	Phe	Ser	Tyr	Cys	U
U	Phe	Ser	Tyr	Cys	C
U	Leu	Ser	STOP	STOP	A
U	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
C	Leu	Pro	His	Arg	C
C	Leu	Pro	Gln	Arg	A
C	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
A	Ile	Thr	Asn	Ser	C
A	Ile	Thr	Lys	Arg	A
A	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
G	Val	Ala	Asp	Gly	C
G	Val	Ala	Glu	Gly	A
G	Val	Ala	Glu	Gly	G

Ala, Alanine; *Arg,* arginine; *Asn,* asparagine; *Asp,* aspartic acid; *Cys,* cysteine; *Gln,* glutamine; *Glu,* glutamic acid; *Gly,* glycine; *His,* histidine; *Ile,* isoleucine; *Leu,* leucine; *Lys,* lysine; *Met,* methionine; *Phe,* phenylalanine; *Pro,* proline; *Ser,* serine; *Thr,* threonine; *Trp,* tryptophan; *Tyr,* tyrosine; *Val,* valine.

*Examples: UUG is translated into leucine; UAA is a stop codon; GGG is translated into glycine. Under some circumstances the UGA codon can specify an amino acid called selenocysteine, which is often called the 21st amino acid.

Of the 64 possible codons, 3 signal the end of a gene and are known as **stop codons**. These are UAA, UGA, and UAG.

The remaining 61 all specify amino acids. This means that most amino acids can be specified by more than one codon.

The genetic code is thus said to be "degenerate." While a given amino acid may be specified by more than one codon, each codon can designate only one amino acid.

Translation

Translation is the process in which mRNA provides a template for the synthesis of a polypeptide.

mRNA cannot bind directly to amino acids. It interacts with transfer RNA (tRNA), a cloverleaf-shaped RNA strand of about 80 nucleotides.

The tRNA molecule has a site at its 3' end for the attachment of an amino acid by a covalent bond. At the opposite end of the cloverleaf is a sequence of three nucleotides called the anticodon.

Dr. Zaid Aburubaiha

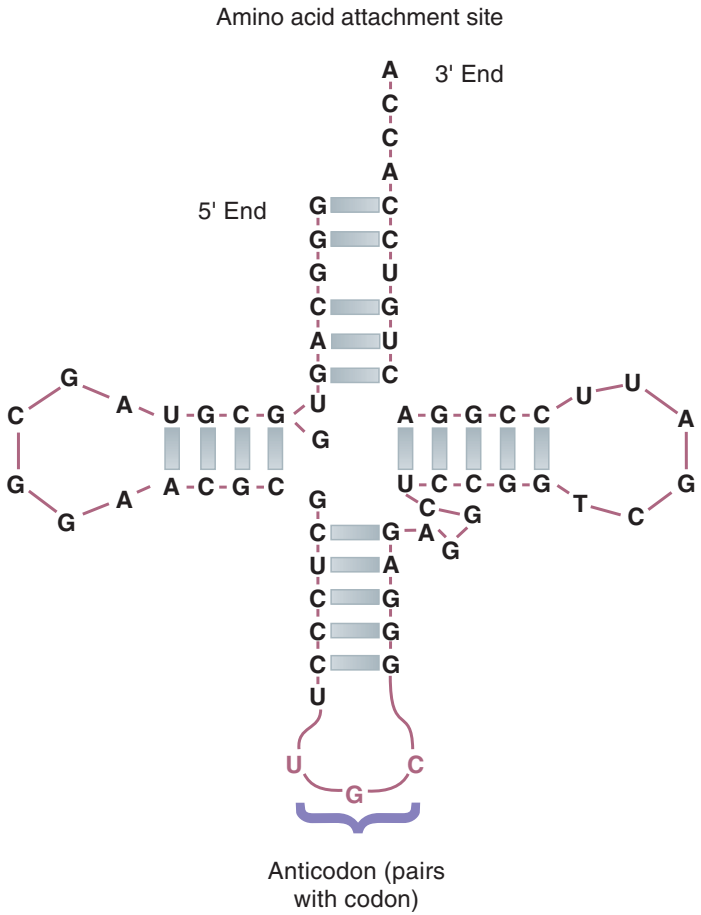

FIG 2-12 The structure of a tRNA molecule. In two dimensions, the tRNA has a cloverleaf shape. Note the 3′ site of attachment for an amino acid. The anticodon pairs with a complementary mRNA codon.

The cytoplasmic site of protein synthesis is the ribosome, which consists of roughly equal parts of enzymatic proteins and ribosomal RNA (rRNA).

During translation, the ribosome first binds to an initiation site on the mRNA sequence, AUG, which specifies the amino acid methionine.

The ribosome then binds the tRNA to its surface so that base pairing can occur between tRNA and mRNA. The ribosome moves along the mRNA sequence, codon by codon, in the usual 5' to 3' direction.

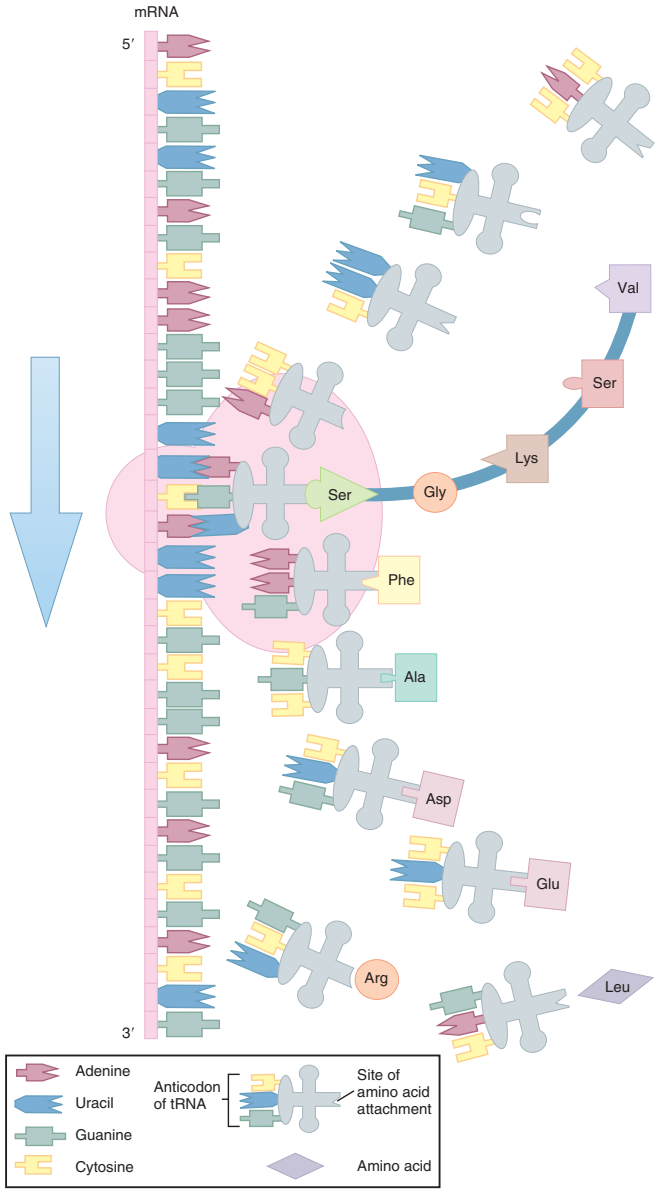

FIG 2-13 Translation of mRNA to amino acids. The ribosome moves along the mRNA strand in the 5′ to 3′ direction, assembling a growing polypeptide chain. In this example, the mRNA sequence GUG AGC AAG GGU UCA has assembled five amino acids (Val, Ser, Lys, Gly, and Ser, respectively) into a polypeptide.

Dr. Zaid Aburubaiha

the ribosome provides an enzyme that catalyzes the formation of covalent peptide bonds between the adjacent amino acids, resulting in a growing polypeptide.

When the ribosome arrives at a stop codon on the mRNA sequence, translation and polypeptide formation cease.

The amino (NH_2) terminus of the polypeptide corresponds to the 5' end of the mRNA strand, and the carboxyl ($COOH$) terminus corresponds to the 3' end.

Before a newly synthesized polypeptide can begin *its* existence as a functional protein, it often undergoes further processing, termed posttranslational modification.

These modifications can take a variety of forms, including cleavage into smaller polypeptide units or combination with other polypeptides to form a larger protein. Other possible modifications include the addition of carbohydrate side chains to the polypeptide.

These modifications are needed, for example, to produce proper folding of the mature protein or to stabilize its structure.

THE STRUCTURE OF GENES AND THE GENOME

- **Introns and Exons**

The intron-exon structure of genes, discovered in 1977, is one attribute that distinguishes eukaryotes from prokaryotes.

Introns form the major portion of most eukaryotic genes. As noted previously, introns are spliced out of the mRNA before it leaves the nucleus.

Splicing is controlled by DNA sequences known as consensus sequences that are located adjacent to each exon.

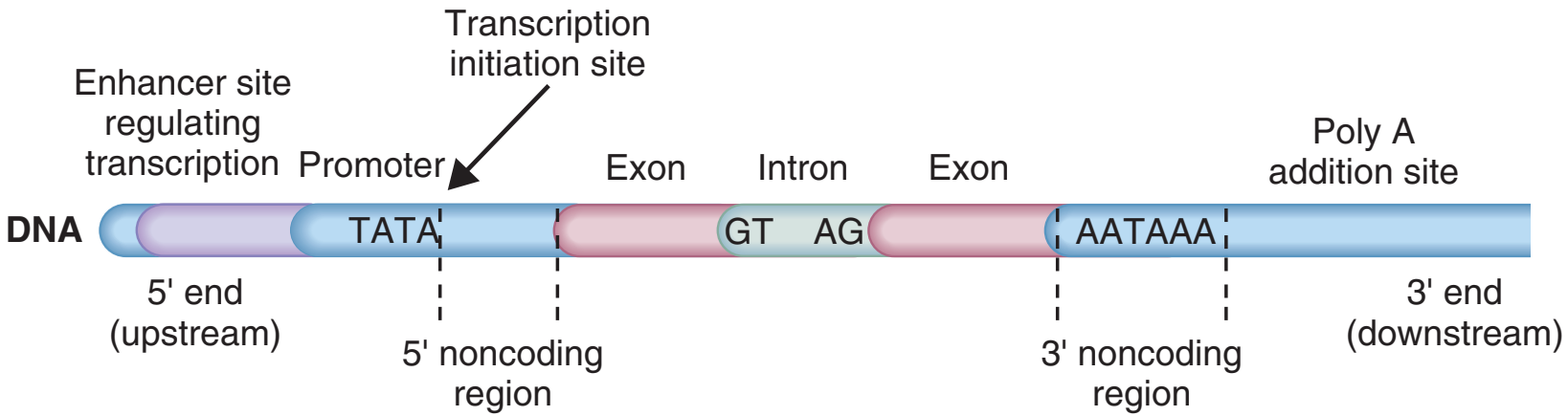

FIG 2-16 Details of gene structure, showing promoter and upstream regulation (enhancer) sequences and a poly-A addition site.

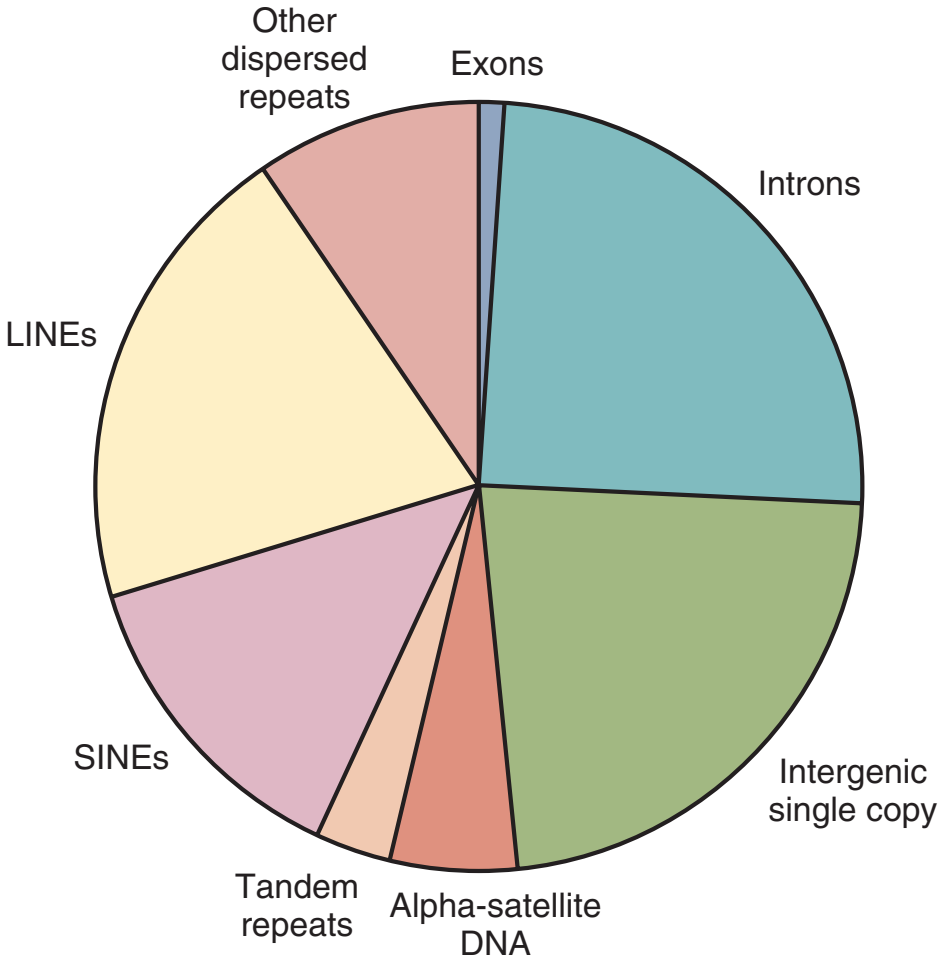

FIG 2-17 Structural composition of the human genome. Because of limitations in mapping repetitive sequences, these figures are approximate. In addition, there is some overlap among categories (e.g., repeat sequences are sometimes found in introns). The category "other dispersed repeats" includes DNA transposons, LTR (long terminal repeat) retrotransposons, and low-copy number duplications.

Introns: by lengthening genes, encourage the shuffling of genes when homologous chromosomes exchange material during meiosis.

It has also been suggested that introns have evolved to modify the amount of time required for DNA replication and transcription.

Types of DNA

The most common, class of DNA is termed single-copy DNA-- are seen only once (or possibly a few times) in the genome.

Single-copy DNA composes about 45% of the genome and includes the protein-coding genes.

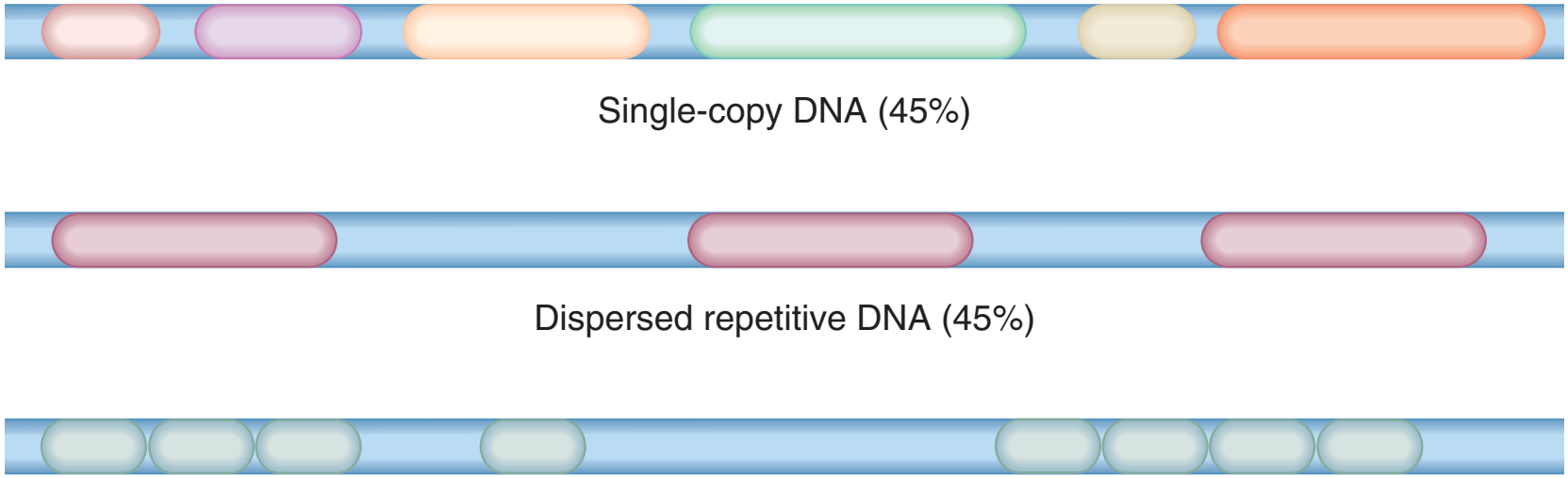

FIG 2-18 Single-copy DNA sequences are unique and are dispersed throughout the genome. Satellite DNA sequences are repetitive elements that occur together in clusters. Dispersed repeats are similar to one another but do not cluster together.

The remaining **55%** of the genome consists of **repetitive DNA,** sequences that are repeated over and over again in the genome, often thousands of times.

There are two major classes of repetitive DNA, **dispersed repetitive DNA** and **satellite DNA.** Satellite repeats are clustered together in certain chromosome locations, where they occur in tandem

Dispersed repeats, as the name implies, tend to be scattered singly throughout the genome (they do not occur in tandem).

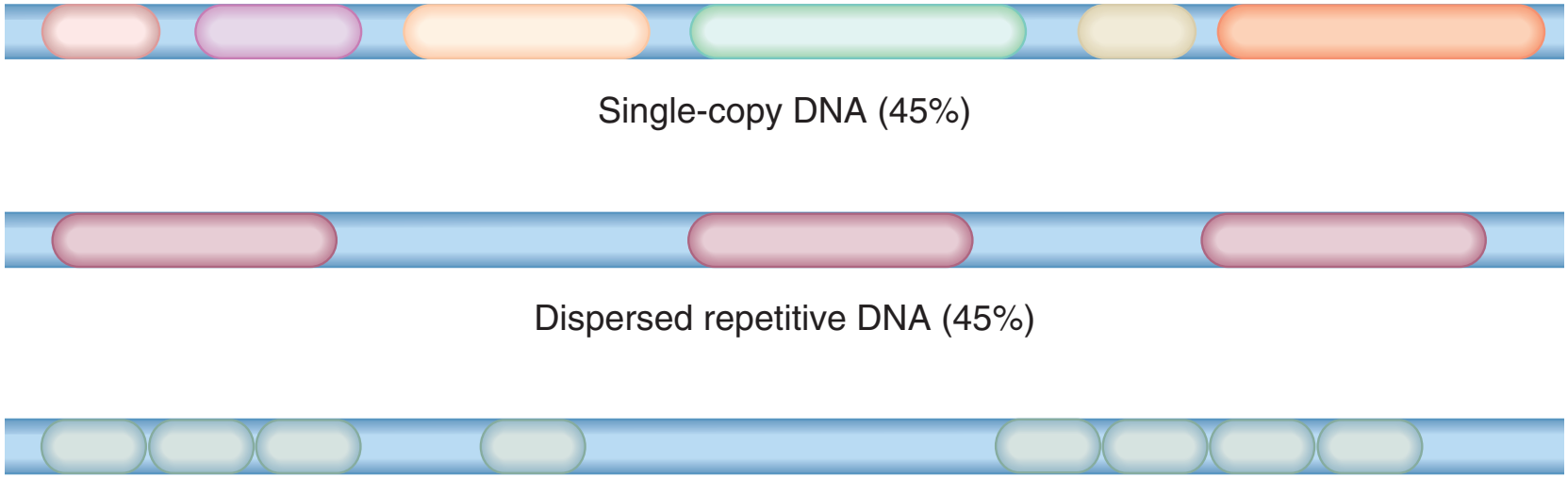

FIG 2-18 Single-copy DNA sequences are unique and are dispersed throughout the genome. Satellite DNA sequences are repetitive elements that occur together in clusters. Dispersed repeats are similar to one another but do not cluster together.

Satellite DNA composes approximately **10%** of the genome and can be further subdivided into several categories.

Alpha-satellite DNA occurs as tandem repeats of a 171-bp (base pairs) sequence that can extend several million bp or more in length. This type of satellite DNA is found near the centromeres of chromosomes.

Minisatellites are blocks of tandem repeats whose total length is much smaller. These repeats, which are 20 to 70 bp in length, usually have a total length of a few thousand base pairs or so.

Microsatellites, are smaller: the repeat units are usually only 2, 3, or 4 bp in length, and the total length of the array is usually less than a few hundred base pairs.

Dispersed repetitive DNA makes up about 45% of the genome, and these repeats fall into two major categories, **SINEs** (short interspersed elements) and **LINEs** (long interspersed elements).

Individual SINEs range in size from 90 to 500 bp, while individual LINEs can be as large as 7,000 kb.

One of the most important types of SINEs is termed the "***Alu* repeats.**" The term *"Alu"* derives from the fact that these repeat units, which are about 300 bp in size, contain a DNA sequence that can be cut by the *Alu* restriction enzyme.

The *Alu* repeats are a family of genes, meaning that all of them have highly similar DNA sequences. About 300,000 to 500,000 *Alu* repeats are scattered throughout the genome; these repeats thus constitute about 2% to 3% of all human DNA.

THE CELL CYCLE

During the course of development, each human progresses from a single-cell zygote (an egg cell fertilized by a sperm cell) to a marvelously complex organism containing approximately 100 trillion (10^{14}) individual cells.

The cell division processes responsible for the creation of new diploid cells from existing ones are termed mitosis (nuclear division) and cytokinesis (cytoplasmic division).

Before dividing, a cell must duplicate its contents, including its DNA; this occurs during interphase. The alternation of mitosis and interphase is referred to as the cell cycle.

A typical cell spends most of its life in interphase. This portion of the cell cycle is divided into three phases, G1, S, and G2.

During G1 ("gap 1," the interval between mitosis and the onset of DNA replication), synthesis of RNA and proteins takes place. DNA replication occurs during the S (synthesis) phase.

During G2 (the interval between the S phase and the next mitosis), some DNA repair takes place, and the cell prepares for mitosis. By the time G2 has been reached, the cell contains 2 identical copies of each of the 46 chromosomes.

These identical chromosomes are referred to as sister chromatids. Sister chromatids often exchange material during or after the S phase, a process known as sister chromatid exchange.

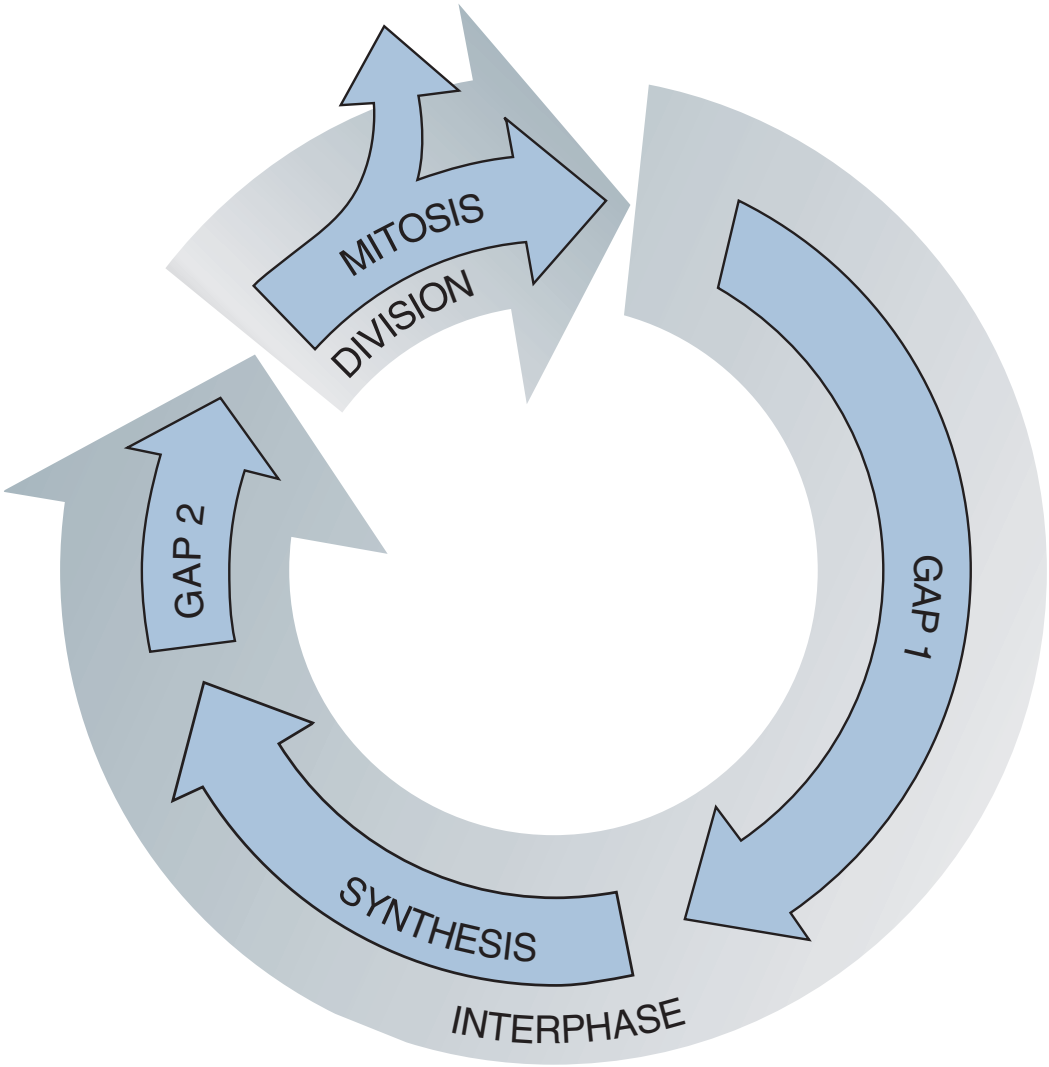

FIG 2-19 Major phases of the mitotic cell cycle, showing the alternation of interphase and mitosis (division).

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The length of the cell cycle varies considerably from one cell type to another.

Some cell types, such as skeletal muscle cells and neurons, completely lose their ability to divide and replicate in adults.

The great majority of this variation is due to differences in the length of the G1 phase. When cells stop dividing for a long period, they are often said to be in the G0 stage.

Before entering mitosis, DNA replication has to be accurate and complete and the cell has to have achieved an appropriate size.

The cell must respond to extracellular stimuli that require increased or decreased rates of division.

Complex molecular interactions mediate this regulation. Among the most important of these molecules are cyclin-dependent kinases (CDKs), a family of kinases that phosphorylate other regulatory proteins at key stages of the cell cycle.

Mitosis

Mitosis is divided into several phases.

During **prophase,** the first mitotic stage, the chromosomes become visible under a light microscope as they condense and coil.

The two sister chromatids of each chromosome lie together, attached at a point called the centromere. The nuclear membrane, which surrounds the nucleus, disappears during this stage.

Spindle fibers begin to form. These radiate from two **centrioles** located on opposite sides of the cell. The spindle fibers become attached to the" centromeres of each chromosome and eventually pull the two sister chromatids in opposite directions.

The chromosomes reach their most highly condensed state during **metaphase**, the next stage of mitosis.

During metaphase the spindle fibers begin to contract and pull the centromeres of the chromosomes, which are now arranged along the middle of the spindle (the **equatorial plane** of the cell).

During **anaphase**, the next mitotic stage, the centromeres of each chromosome split, allowing the sister chromatids to separate. The chromatids are then pulled by the spindle fibers, centromere first, toward opposite sides of the cell.

Telophase, the final stage of mitosis, is characterized by the formation of new nuclear membranes around each of the two sets of 46 chromosomes.

The spindle fibers disappear, and the chromosomes begin to decondense.

Cytokinesis generally occurs after nuclear division and results in a roughly equal division of the cytoplasm into two parts.

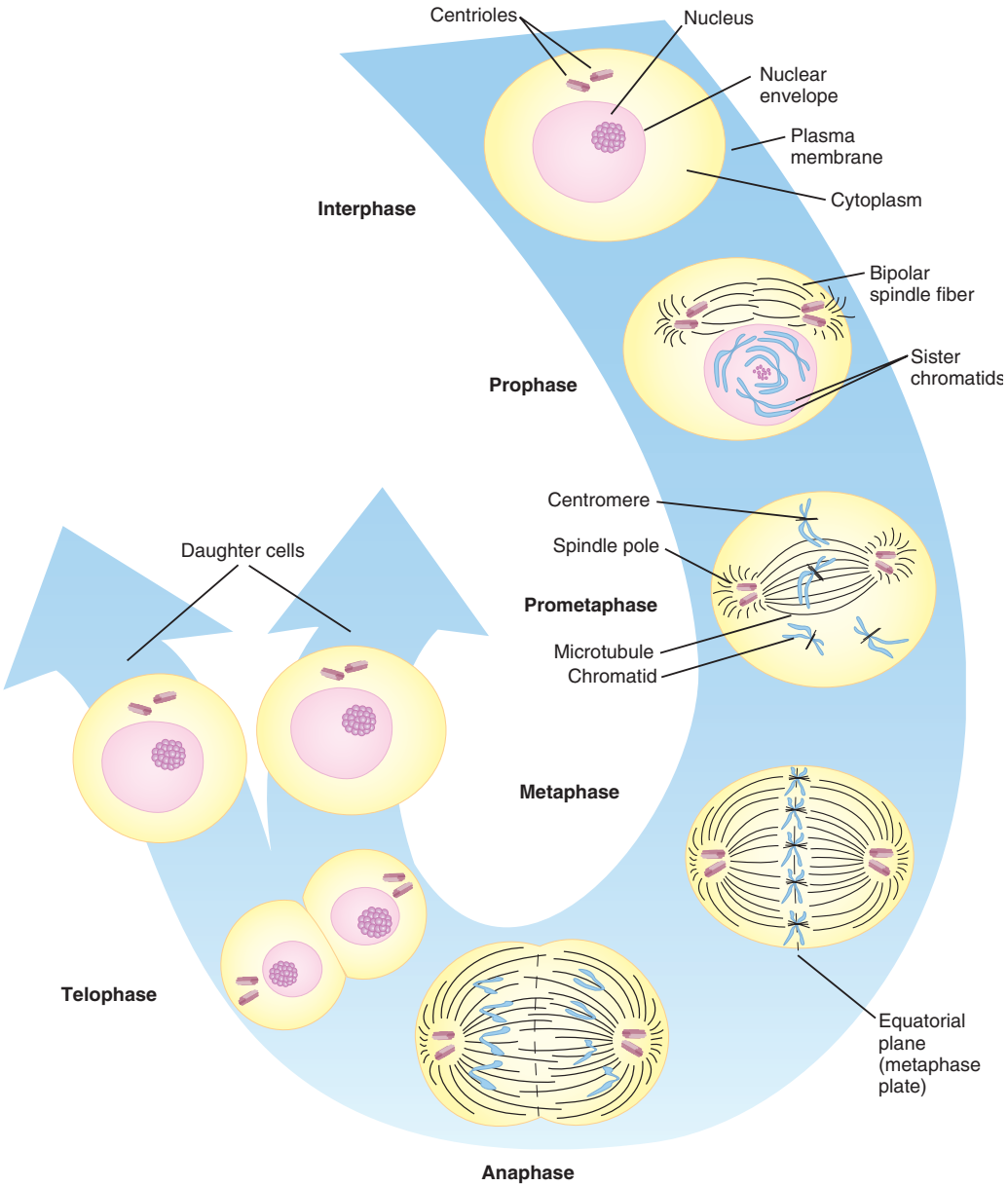

FIG 2-20 The stages of mitosis, during which two identical diploid cells are formed from one original diploid cell.

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Meiosis

When an egg cell and sperm cell unite to form a zygote, their chromosomes are combined into a single cell.

Because humans are diploid organisms, there must be a mechanism to reduce the number of chromosomes in gametes to the haploid state.

The primary mechanism by which haploid gametes are formed from diploid precursor cells is termed **meiosis**.

Two cell divisions occur during meiosis.

During **meiosis I**, often called the reduction division stage, two haploid cells are formed from a diploid cell. These diploid cells are the oogonia in females and the spermatogonia in males.

Following meiosis I, a **second meiosis**, the equational division, takes place, and each haploid cell is replicated.

The first stage of meiosis is interphase I. During this phase, as in mitotic interphase, important processes such as replication of chromosomal DNA take place.

The second phase of meiosis I, prophase I, begins as the chromatin strands coil and condense, causing them to become visible as chromosomes.

During a process called synapsis, the homologous chromosomes pair up, side by side, lying together in perfect alignment.

As prophase I continues, the chromatids of the two chromosomes intertwine. Each pair of intertwined homologous chromosomes is called a bivalent (indicating two chromosomes in the unit) or tetrad (indicating four chromatids in the unit).

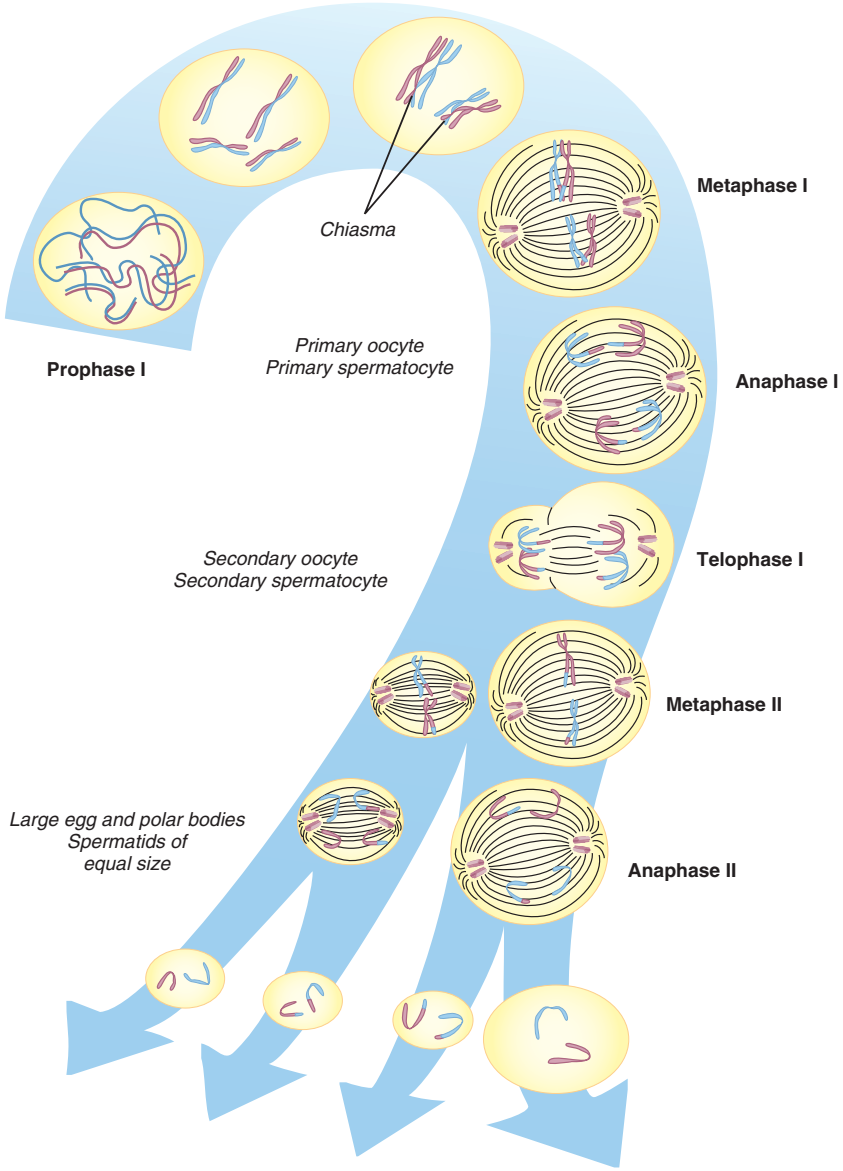

FIG 2-21 The stages of meiosis, during which haploid gametes are formed from a diploid cell. For brevity, prophase II and telophase II are not shown. Note the relationship between meiosis and spermatogenesis and oogenesis.

Dr. Zaid Aburubaiha

A second key feature of prophase I is the formation of chiasmata, cross-shaped structures that mark attachments between the homologous chromosomes.

This process, called crossing over, produces chromosomes consisting of combinations of parts of the original chromosomes.

At the end of prophase I, the bivalents begin to move toward the equatorial plane, a spindle apparatus begins to form in the cytoplasm, and the nuclear membrane dissipates.

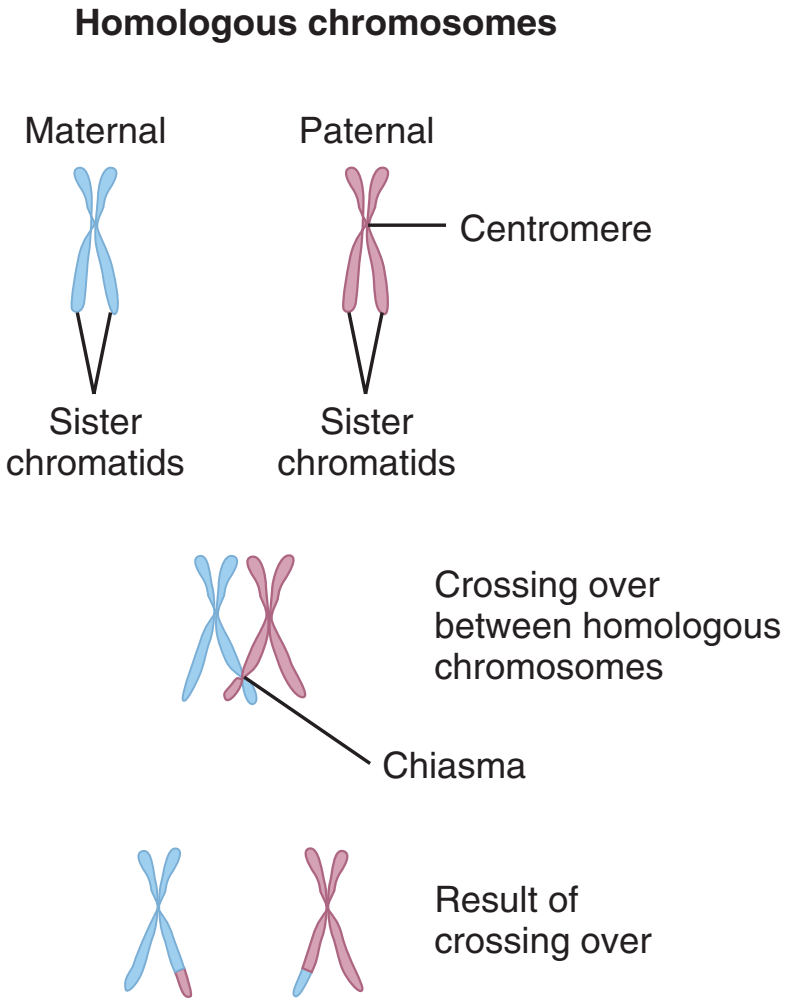

FIG 2-22 The process of chiasma formation and crossing over results in the exchange of genetic material between homologous chromosomes.

Metaphase I is the next phase, this stage is characterized by the completion of spindle formation and the alignment of the bivalents, which are still attached at the chiasmata, in the equatorial plane. The two centromeres of each bivalent now lie on opposite sides of the equatorial plane.

During anaphase I, the next stage, the chiasmata disappear, and the homologous chromosomes are pulled by the spindle fibers toward opposite poles of the cell.

The key feature of this phase is that, unlike the corresponding phase of mitosis, *the centromeres do not duplicate and divide,* so that only half of the original number of chromosomes migrate toward each pole.

The next stage, **telophase** I, begins when the chromosomes reach opposite sides of the cell. The chromosomes uncoil slightly, and a new nuclear membrane begins to form. The two daughter cells each contain the haploid number of chromosomes, each having two sister chromatids.

In humans, cytokinesis also occurs during this phase. The cytoplasm is divided approximately equally between the two daughter cells in the gametes formed in males.

In those formed in females, nearly all of the cytoplasm goes into one daughter cell, which will later form the egg. The other daughter cell becomes a polar body, a small nonfunctional cell that eventually degenerates.

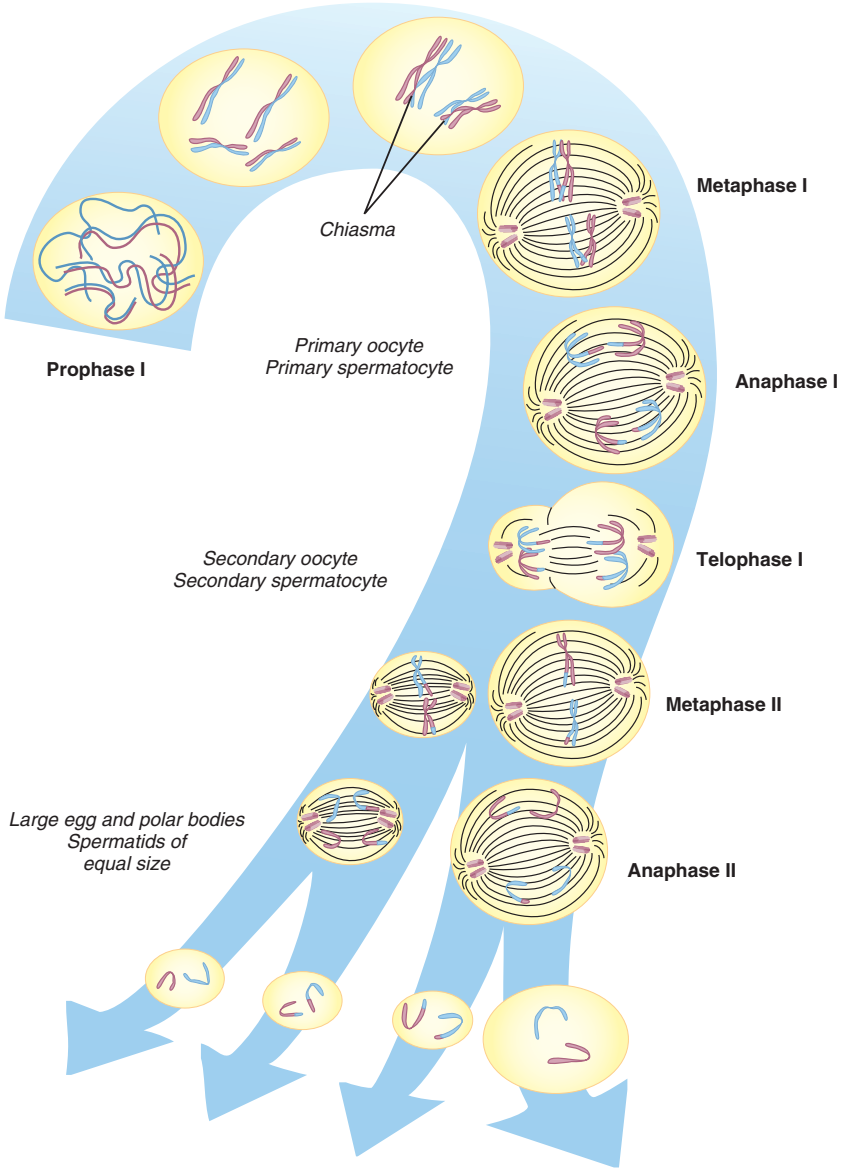

FIG 2-21 The stages of meiosis, during which haploid gametes are formed from a diploid cell. For brevity, prophase II and telophase II are not shown. Note the relationship between meiosis and spermatogenesis and oogenesis.

Dr. Zaid Aburubaiha

The equational division, **meiosis II**, then begins with interphase II. This is a very brief phase. The important feature of interphase II is that, *no replication of DNA occurs.*

Prophase II, similar to mitotic prophase, except that the cell nucleus contains only the haploid number of chromosomes. During prophase II the chromosomes thicken as they coil, the nuclear membrane disappears, and new spindle fibers are formed.

Following this phase is metaphase II, during which the spindle fibers pull the chromosomes into alignment at the equatorial plane.

Anaphase II then follows. This stage resembles mitotic anaphase in that the centromeres split, each carrying a single chromatid toward a pole of the cell.

Telophase II, like telophase I, begins when the chromosomes reach opposite poles of the cell. There they begin to uncoil. New nuclear membranes are formed around each group of chromosomes, and cytokinesis occurs.

In gametes formed in males, the cytoplasm is again divided equally between the two daughter cells. The end result of male meiosis is thus four functional daughter cells, each of which has an equal amount of cytoplasm.

In female gametes, unequal division of the cytoplasm again occurs, forming the egg cell and another polar body.

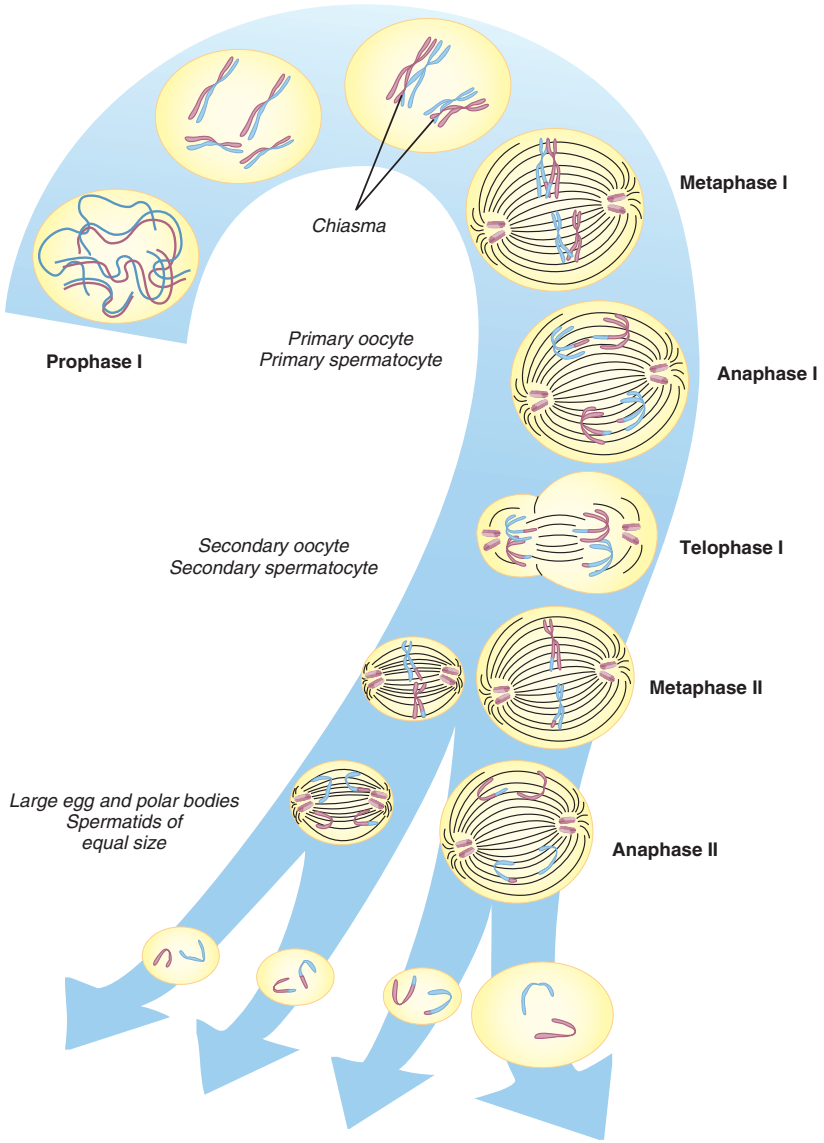

FIG 2-21 The stages of meiosis, during which haploid gametes are formed from a diploid cell. For brevity, prophase II and telophase II are not shown. Note the relationship between meiosis and spermatogenesis and oogenesis.

Dr. Zaid Aburubaiha

The Relationship Between Meiosis and Gametogenesis

In **mature males**, the seminiferous tubules of the testes are populated by spermatogonia, which are diploid cells.

- After going through several mitotic divisions, the spermatogonia produce primary spermatocytes.
- Each primary spermatocyte, which is also diploid, undergoes meiosis I to produce a pair of secondary spermatocytes, each of which contains 23 double stranded chromosomes.
- These undergo meiosis II, and each produces a pair of spermatids that contain 23 single-stranded chromosomes.

The spermatids then lose most of their cytoplasm and develop tails for swimming as they become mature sperm cells. This process, known as **spermatogenesis**, continues throughout the life of the mature male.

Oogenesis, the process in which female gametes are formed, differs in several important ways from spermatogenesis. Whereas the cycle of spermatogenesis is constantly recurring in males, much of female oogenesis is completed before birth.

- Diploid oogonia divide mitotically to produce primary oocytes by the third month of fetal development.
- More than 2 million primary oocytes are formed during gestation, and these are suspended in prophase I by the time the female is born.
- Meiosis continues only when a mature primary oocyte is ovulated.
- In meiosis I, the primary oocyte produces one secondary oocyte (containing the cytoplasm) and one polar body.
- The secondaty oocyte then emerges from the follicle and proceeds down the fallopian tube, with the polar body attached to it.
- Meiosis II begins only if the secondary oocyte is fertilized by a sperm cell. If this occurs, one haploid mature ovum, containing the cytoplasm, and another haploid polar body are produced.

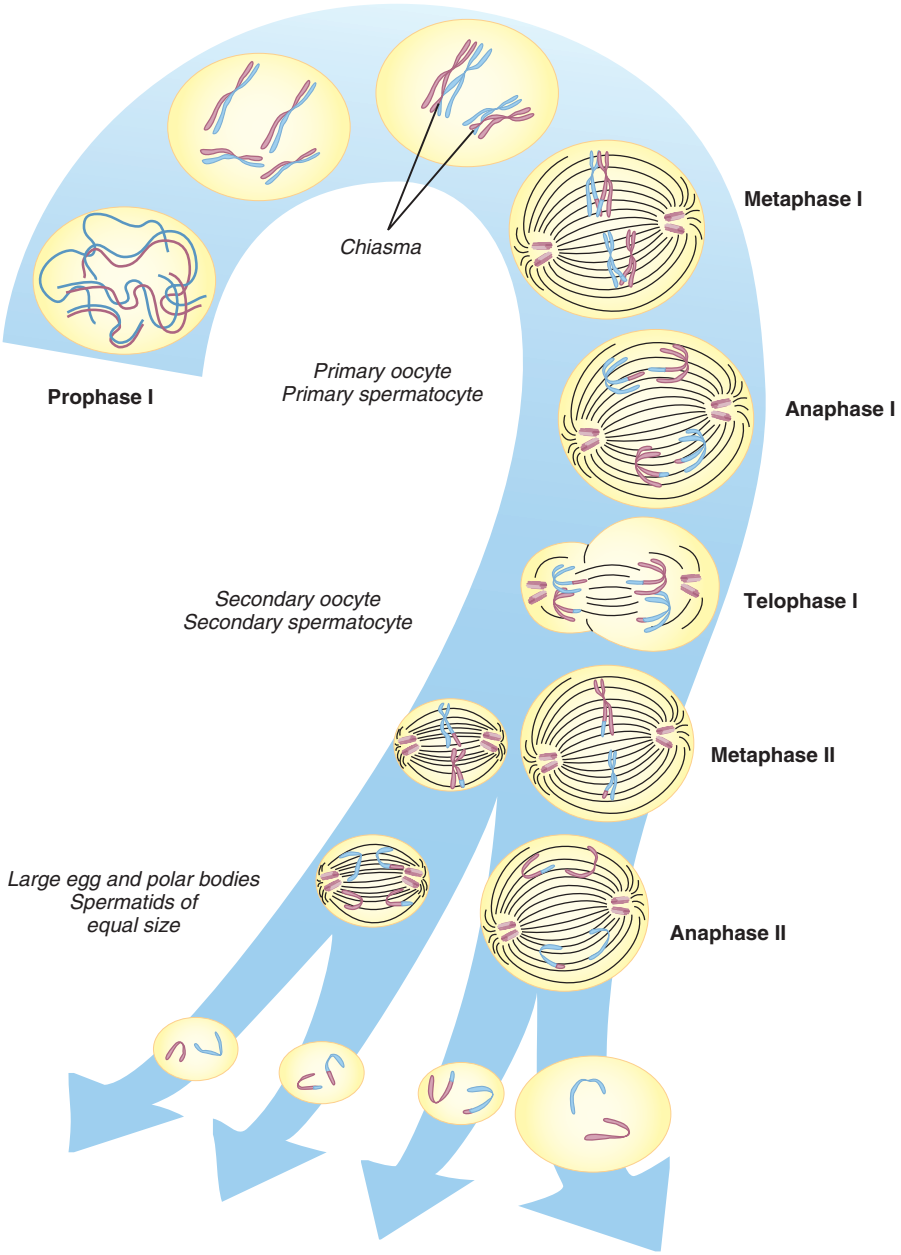

FIG 2-21 The stages of meiosis, during which haploid gametes are formed from a diploid cell. For brevity, prophase II and telophase I are not shown. Note the relationship between meiosis and spermatogenesis and oogenesis.