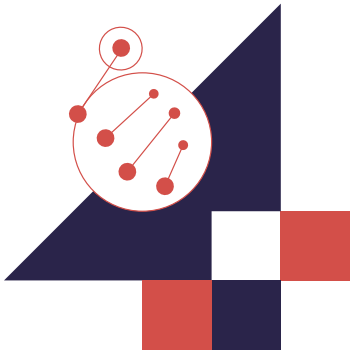
وزارة التعليم
Ministry of Education

موهبة
Mawhiba

نسمو
NSMO

National Science and Mathematics Olympiad

Learning Materials for the Fourth Stage Finals of "NSMO"2026



Biology

Dear Student

The King Abdulaziz and His Companions Foundation for Giftedness and Creativity (Mawhiba) is a pioneering non-profit civil institution, established by the Custodian of the Two Holy Mosques, King Abdullah bin Abdulaziz Al Saud — may Allah have mercy on him — in 1419 AH / 1999 AD. Mawhiba seeks to create a stimulating environment for giftedness and creativity, foster a passion for science and knowledge, and build the leaders of the future through a systematic approach based on the latest scientific methods and best global practices in gifted education. This approach aims to invest in and empower gifted individuals, recognizing them as a fundamental driver of humanity's prosperity.

Mawhiba is committed to supporting a long-term national vision for nurturing creativity and giftedness in the Kingdom, in alignment with the aspirations and objectives of Saudi Vision 2030, particularly in developing human capabilities and preparing a new generation that will serve as the cornerstone of achievement and the hope of the future. Accordingly, Mawhiba believes that investing in the education of gifted students is neither a luxury nor an elitist endeavor; rather, it is a necessity to elevate quality standards, enhance their capabilities, and enable them to contribute meaningfully to their society as future leaders.

Mawhiba also possesses extensive experience in implementing numerous programs for gifted and creative students and plays a central role within the current institutional ecosystem supporting gifted education in the Kingdom. It integrates closely with the national education system through comprehensive identification and care programs for gifted learners, as well as through the exchange of expertise related to planning and high-quality implementation with relevant stakeholders, including the Ministry of Education and leading international academic institutions. This collaboration focuses on the design and delivery of programs and initiatives through advanced educational practices.

Given that scientific competitions are no longer a dispensable luxury but have become an objective measure of excellence and progress in scientific fields and considering the intense competition to reach podiums of achievement, it has become essential for aspiring participants not only to reach these platforms, but also to secure a lasting presence upon them.

In your hands now is the Foundational Training Package, through which you will gain an initial understanding of the nature of competition topics and questions, as well as the essential fundamentals required to progress toward mastery — a stage that places you at the beginning of the competitive path toward the honor of representing the nation in international competitions.

In preparing this training package, we have been keen to present the scientific content in a clear, engaging, and accessible manner that fuels your curiosity and drives your passion toward broader horizons and new realms of challenge and enjoyment in learning. It is therefore fitting to present below the journey you have begun with us through the Mawhoob Competition, and which, God willing, will continue until we achieve your aspirations together.

General Objectives

1. To build foundational biological concepts that prepare students for participation in competitions.
2. To establish a strong base enabling students to continue studying Olympiad-level biology.
3. To enrich the field with scientific content that supports the passion of those interested in Biology Olympiad studies.
4. To promote and spread the culture of the Olympiad.

Specific Objectives

1. The student infers how offspring acquire inherited traits.
2. The student recalls Mendel's laws (law of segregation and law of independent assortment).
3. The student applies Mendel's laws to solve genetic problems.
4. The student identifies non-Mendelian patterns of inheritance.
5. The student compares linked and unlinked genes.
6. The student explains the results of a test cross.
7. The student analyzes pedigree charts to predict inheritance patterns.
8. The student connects chromosome behavior to Mendel's laws.
9. The student interprets unique inheritance patterns of sex-linked genes.
10. The student explains how genetic crossing over leads to recombination of linked genes.
11. The student lists human disorders resulting from changes in chromosome number or structure (e.g., Down syndrome).
12. The student distinguishes between dominant, recessive, and sex-linked inheritance.
13. The student describes experiments that proved DNA is the genetic material.
14. The student explains the structural model of DNA (according to Watson and Crick) and its relationship to function.
15. The student explains the semi-conservative mechanism of DNA replication.

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Chapter One

Mendel and the gene idea

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Mendel and the Gene Idea

Modern genetics was born in a monastery garden, where a monk named Gregor Mendel documented the mechanism of inheritance through discrete particles. Mendel developed his theory of inheritance several decades before chromosomes were observed under the microscope and their behavior was understood.

Using the scientific method, Mendel identified two fundamental laws of inheritance.

Mendel discovered the basic principles of heredity by carefully planned experiments on pea plants (Pisum sativum). One of the main reasons Mendel chose peas was their availability in multiple varieties. For example, one variety bore purple flowers, while another had white flowers.

A heritable feature that varies among individuals, such as flower color, is called a character, while each variant of that character-such as purple or white flower color-is referred to as a trait.

Other advantages of using peas included their short generation time and the large number of offspring produced from each mating. Moreover, Mendel was able to strictly control the mating between plants.

The reproductive organs of pea plants are contained within their flowers. Each flower possesses stamens, the pollen-producing organs, and a carpel, the egg-bearing organ.

In nature, pea plants usually undergo self-fertilization-pollen grains are transferred from the stamens to the carpel of the same flower, and the male nucleus from the pollen grain fertilizes the egg within the carpel.

To perform cross-pollination (fertilization between different plants), Mendel removed the immature stamens of a plant before they produced pollen, then brushed pollen from another plant onto that flower. Each resulting zygote developed into a plant embryo within a seed, allowing Mendel to be certain of the parental origin of each new seed.

example, a plant that produces only purple flowers generation after generation through self-fertilization is said to be true breeding. In a typical experiment, Mendel crossed two true-breeding pea varieties—for instance, one with purple flowers and another with white flowers (as illustrated in Figure 1). This type of mating between two contrasting, true-breeding varieties is called hybridization. The true-breeding parents are referred to as the P generation (Parental generation), and their hybrid offspring constitute the F_1 generation (first filial generation).

When the F_1 hybrids self-pollinate or cross with one another, their offspring make up the F_2 generation (second filial generation). Through quantitative analysis of thousands of F_2 plants from many such genetic crosses, Mendel deduced two fundamental principles of inheritance, now known as the Law of Segregation and the Law of Independent Assortment.

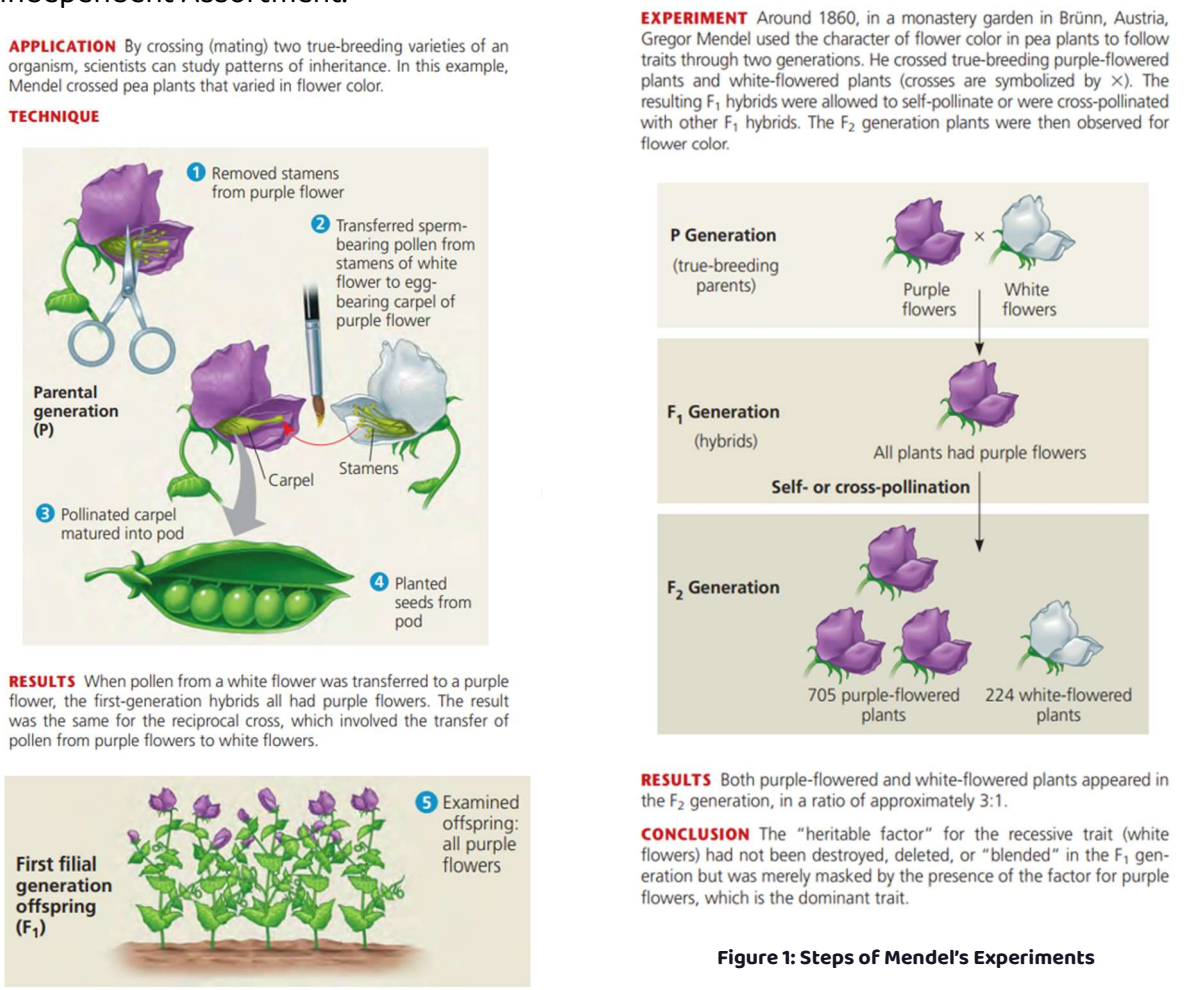


Figure 1: Steps of Mendel's Experiments

The Law of Segregation

As shown in the previous figure (Figure 1), the experiment yielded a completely different result: all F_1 offspring had purple flowers, identical to one of the parental plants bearing purple blossoms.

What happened to the white-flower trait that participated in the original cross? If it had been lost, the F_1 plants would have produced only purple-flowered offspring in the F_2 generation. However, when Mendel allowed the F_1 plants to self-pollinate and grew the resulting seeds, the white-flower trait reappeared in the F_2 generation.

Mendel concluded that the hereditary factor responsible for white flowers was not altered or destroyed in the F_1 plants but was somehow segregated when the purple-flower factor was present.

In Mendel's terminology, the purple-flower color is a dominant trait, while the white-flower color is a recessive trait.

Mendel observed the same pattern of inheritance in six other characteristics, each represented by two distinctly contrasting traits (see Figure 2).

To explain the consistent 3:1 inheritance pattern he observed among the F_2 offspring in his pea-plant experiments, Mendel developed a model consisting of four

Character	Dominant Trait	×	Recessive Trait	F_2 Generation Dominant: Recessive	Ratio
Flower color	Purple	×	White	705:224	3.15:1
Flower position	Axial	×	Terminal	651:207	3.14:1
Seed color	Yellow	×	Green	6,022:2,001	3.01:1
Seed shape	Round	×	Wrinkled	5,474:1,850	2.96:1
Pod shape	Inflated	×	Constricted	882:299	2.95:1
Pod color	Green	×	Yellow	428:152	2.82:1
Stem length	Tall	×	Dwarf	787:277	2.84:1

Figure 2: Results of Mendel's Crosses for Seven Pea Plant Characteristics

interrelated concepts, the fourth of which is the Law of Segregation.

First, alternative versions of genes account for variations in inherited characters. For example, the gene for flower color in pea plants exists in two versions-one for purple flowers and another for white flowers. These different versions of a gene are called alleles.

Today, we can relate this concept to chromosomes and DNA. Each gene corresponds to a specific sequence of nucleotides located at a particular place, or locus, on a chromosome. However, the DNA sequence at that locus can vary slightly in its nucleotide order and thus in the information it encodes. The purple-flower allele and the white-flower allele represent two distinct DNA sequence variants at the flower-color locus on one of the pea plant's chromosomes.

Secondly, for each character, an organism inherits two copies of a gene-one from each parent. (These are also referred to as alleles of that gene.) (Figure 3)

The two alleles at a specific locus may be identical, as in the true-breeding parental (P) generation of Mendel's experiments, or they may be different, as in the hybrid F_1 plants.

Thirdly, if the two alleles at a locus differ, one the dominant allele determines the organism's appearance, while the other-the recessive allele-has no noticeable effect on the organism's appearance.

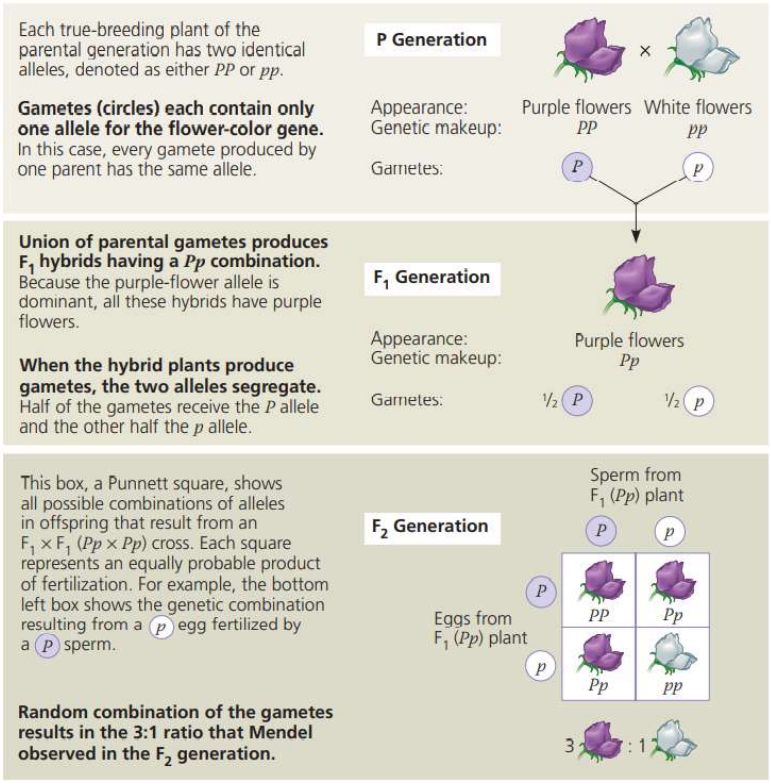


Figure 3: Results of Mendel's Experiments Illustrated with a Punnett Square

Accordingly, the F_1 pea plants in Mendel's experiment had purple flowers because the allele for purple color is dominant, while the allele for white flowers is recessive.

The fourth and final component of Mendel's model, the Law of Segregation, states that the two alleles for a heritable character segregate (separate from each other) during gamete formation and end up in different gametes.

Thus, each egg or sperm cell receives only one of the two alleles present in the organism's somatic cells that produce the gametes.

Note that if an organism has identical alleles for a particular character that is, it is true breeding then all gametes will carry that allele.

However, if the organism has different alleles, as in hybrid plants, then 50% of the gametes will receive the dominant allele, and 50% will receive the recessive allele.

The following figure (Figure 3) illustrates these combinations using a Punnett square, a useful diagram for predicting the allelic composition of offspring from a cross between individuals of known genetic makeup.

We use an uppercase letter to denote a dominant allele and a lowercase letter to denote a recessive allele.

In the F_2 generation,

- ¼ of the plants inherit two purple-flower alleles; these plants clearly exhibit purple flowers.
- ½ of the plants inherit one purple-flower allele and one white-flower allele; these plants also have purple flowers, since the trait is dominant.
- Finally, ¼ of the plants inherit two white-flower alleles, and in these individuals, the recessive trait appears.

Thus, Mendel's model accurately explains the 3:1 phenotypic ratio observed in the F_2 generation.

Useful Genetic Vocabulary

An organism that carries a pair of identical alleles for a particular trait is said to be homozygous. In the parental generation shown in the previous figure (Figure 3), the purple-flowered pea plant is homozygous for the dominant allele (PP), while the white-flowered plant is homozygous for the recessive allele (pp).

An organism that carries two different alleles for a given gene is said to be heterozygous. For example, the hybrid F_1 plants produce gametes containing both P and p alleles. Thus, self-pollination of the F_1 hybrids yields offspring with both purple and white flowers. Because dominant and recessive alleles exert different effects, an organism's observable traits do not always reveal its genetic composition. Therefore, we distinguish between:

- The **phenotype**, referring to the organism's observable traits, and
- The **genotype**, referring to the organism's genetic makeup.

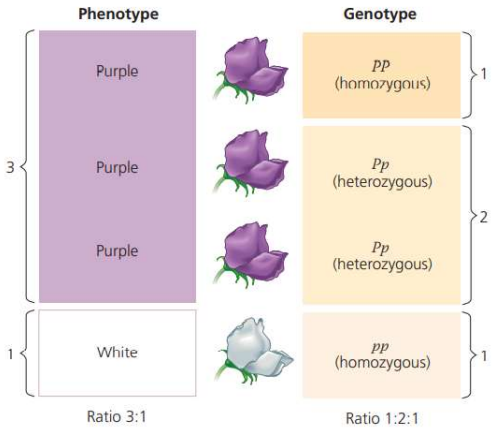


Figure 4. Phenotypes and Genotypes of F_2 Generation Pea Plants

In the case of flower color in pea plants, individuals with **PP** and **Pp** genotypes share the same **phenotype** (purple flowers) but differ in their **genotype**. (Figure 4 illustrates several phenotypes and genotypes of F_2 pea plants.)

The Testcross

Suppose we have a "mystery" pea plant with purple flowers. From its appearance alone, we cannot tell whether it is homozygous (PP) or heterozygous (Pp), since both genotypes produce the same purple phenotype.

To determine its genotype, we can cross this plant with a white-flowered plant (pp), which produces only gametes carrying the recessive allele (p). (Figure 5)

This procedure crossing an individual of unknown genotype with a homozygous recessive individual is called a testcross, because it can reveal the genotype of the mystery organism. Mendel developed the testcross, and it remains a fundamental tool in genetics. (Figure 5)

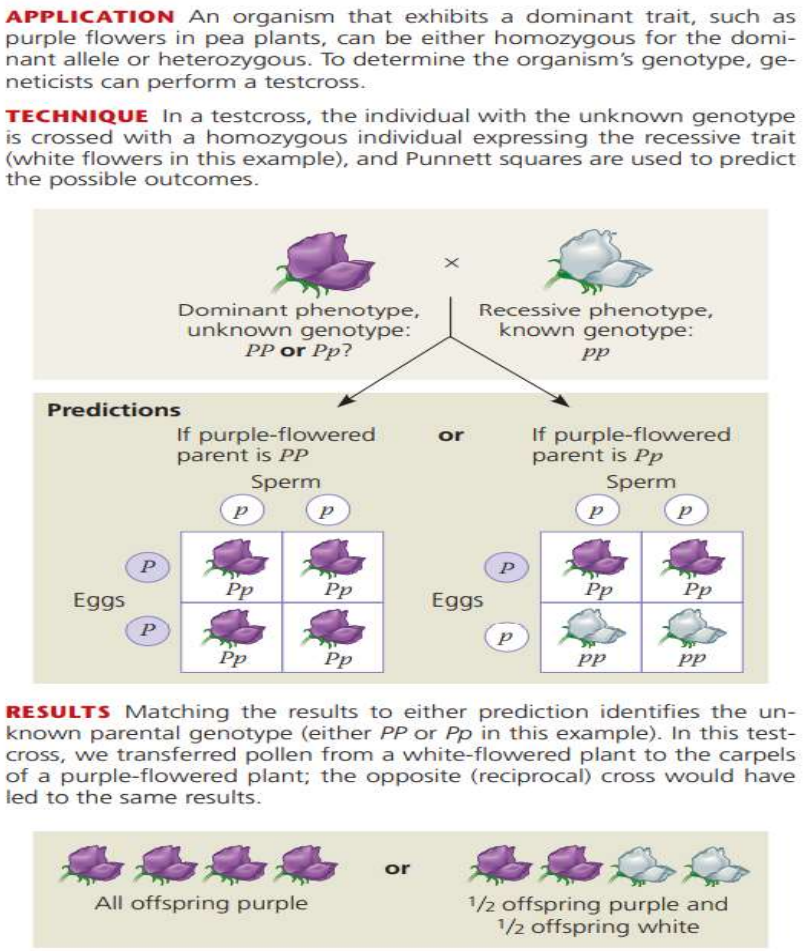


Figure 5. Application of the Testcross Between a Plant of Unknown Genotype and a Recessive Plant, and the Possible Outcomes

The Law of Independent Assortment

Mendel identified his second law of inheritance by tracking two traits simultaneously such as seed color and seed shape. Mendel's experiments with dihybrid pea plants formed the basis of what is now known as the Law of Independent Assortment, which states that

"Each pair of alleles segregates independently of every other pair of alleles during gamete formation."

This law applies only to genes (allele pairs) located on different chromosomes—that is, on non-homologous chromosomes—or to genes that are very far apart on the same chromosome.

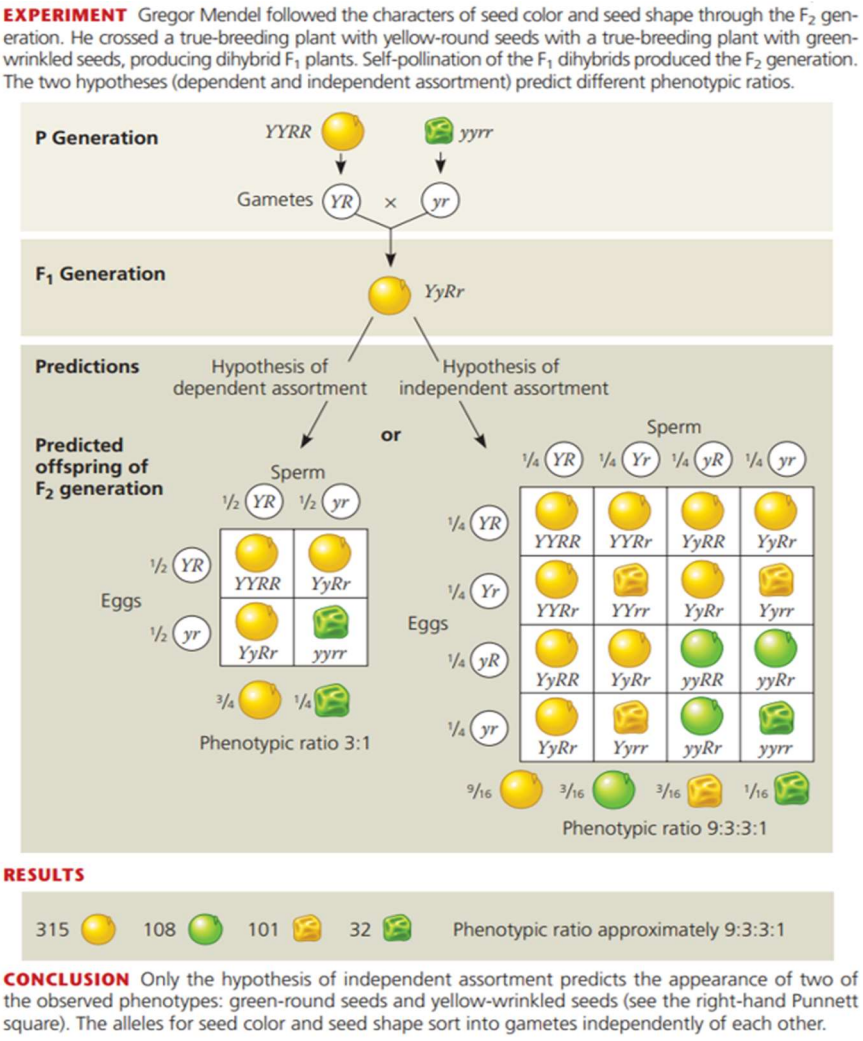


Figure 6. Mendel's Experiments with Dihybrid Pea Plants Demonstrating the Law of Independent Assortment

The Laws of Probability Govern Mendelian Inheritance:

Mendel's Laws of Segregation and Independent Assortment reflect the same rules of probability that apply to flipping coins or rolling dice. The probability scale ranges from 0 to 1: an event that is certain to occur has a probability of 1, whereas an event that cannot occur has a probability of 0. For example, with a coin that has heads on both sides, the probability of getting heads when flipped is 1, and the probability of getting tails is 0. With

a normal coin, however, the chance of landing on heads is ½, and the chance of landing on tails is ½.

Flipping a coin demonstrates an important lesson about probability: for each flip, the probability of getting heads is ½, and the outcome of any given flip is independent of previous results.

We refer to such phenomena like coin tossing as independent events. Each flip of a coin, whether performed sequentially with one coin or simultaneously with multiple coins, is independent of every other flip.

In the same way, during gamete formation, the alleles of one gene segregate independently of the alleles of another gene, which is the essence of the Law of Independent Assortment.

Two fundamental rules of probability help predict the outcomes of gamete combinations in monohybrid and more complex crosses:

1. The Multiplication and Addition Rules Applied to Monohybrid Crosses

To determine the probability of two or more independent events occurring together in a specific combination—for instance, the probability of getting heads when tossing two coins simultaneously—we use the multiplication rule.

According to this rule, the combined probability equals the product of the probabilities of each independent event. Thus,

$$P(\text{heads on both coins}) = \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

We can apply the same reasoning to a monohybrid cross in pea plants. For seed shape, the F_1 plants have the genotype Rr. In a heterozygous (Rr) plant, segregation of alleles functions like flipping a coin: each egg has a ½ chance of carrying the dominant allele (R) and a ½ chance of carrying the recessive allele (r). The same applies to each pollen grain.

To produce a wrinkled seed, both gametes (egg and pollen) must carry the recessive allele (r). The probability of receiving allele r from both gametes equals

½ (from the egg) × ½ (from the pollen) = ¼

Thus, the multiplication rule tells us that the probability of an F_2 plant being rr (wrinkled seeds) is ¼, while the probability of it being RR (round seeds) is also ¼. To determine the probability that an F_2 plant is heterozygous (Rr) rather than homozygous, we use the addition rule.

As shown in the previous figure, the dominant allele can come from the egg while the recessive allele comes from the pollen or vice versa.

Therefore, the F_1 gametes can combine to produce Rr offspring in two distinct ways. According to the addition rule, the probability of any one of several mutually exclusive events is obtained by adding their individual probabilities.

As we have just seen, the multiplication rule gives the individual probabilities for the genotypes of the offspring with respect to seed shape:

¼ RR, ½ Rr, and ¼ rr

Knowing these probabilities, we can apply the same principle to predict the probabilities of different F_2 genotypes, such as YYRR and YyRR, in more complex crosses illustrated below.

- Probability of YYRR = ¼ (probability of YY) × ¼ (RR) = 1/16
- Probability of YyRR = ½ (Yy) × ¼ (RR) = 1/8

The **genotype YYRR** in the Punnett square occupies **one of the sixteen cells**, giving a probability of ***1/16***.

Meanwhile, the **genotype YyRR** occupies **two of the sixteen cells**, corresponding to ***2/16 = 1/8***.

Now, let us see how the multiplication and addition rules can be combined to solve more complex problems in Mendelian genetics.

Imagine a cross between two pea plants in which we track the inheritance of three different traits.

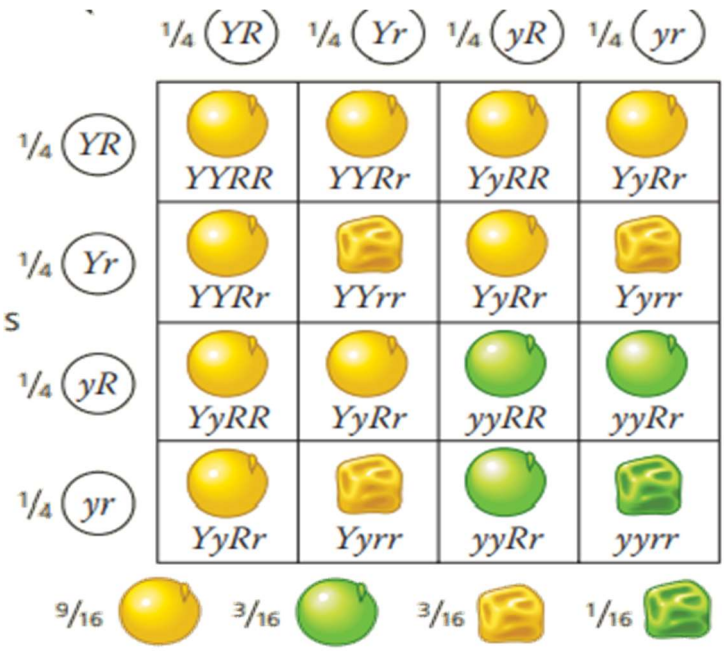


Figure 7. Illustrates a dihybrid Punnett square showing the possible combinations of alleles for seed color (Y/y) and seed shape (R/r) in pea plants, resulting in a 9:3:3:1 phenotypic ratio of yellow-round, yellow-wrinkled, green-round, and green-wrinkled seeds.

We will cross a trihybrid pea plant with purple flowers and yellow, round seeds (heterozygous for all three traits) with another plant that has purple flowers and green, wrinkled seeds (heterozygous for flower color but homozygous recessive for the other two traits). Using Mendel's notation, the cross is: PpYyRr × Ppyyrr.

What fraction of the offspring from this cross is expected to show recessive phenotypes for at least two of the three traits? To answer this, we first list all the possible genotypes that meet this condition:

ppyyRr, **ppYyrr**, **Ppyyrr**, **PPyyrr**, and **ppyyrr**.

(Since the condition requires at least two recessive traits, this includes the last genotype, which expresses all three recessive traits.) Next, we calculate the probability of obtaining each of these genotypes from the PpYyRr × Ppyyrr cross by multiplying the individual probabilities for each pair of alleles.

ppyyRr	¼ (probability of *pp*) × ½ (*yy*) × ½ (*Rr*)	= 1/16
ppYyrr	¼ × ½ × ½	= 1/16
Ppyyrr	½ × ½ × ½	= 2/16
PPyyrr	¼ × ½ × ½	= 1/16
ppyyrr	¼ × ½ × ½	= 1/16
Chance of *at least two* recessive traits		= 6/16 or 3/8

Figure 8. Calculates the probabilities of all possible

Inheritance Patterns are often more Complex than Predicted by simple Mendelian Genetics:

Extending Mendelian Genetics for a Single Gene

The inheritance of traits determined by a single gene may deviate from simple Mendelian patterns when the alleles are not completely dominant or recessive, when a gene has more than two alleles, or when a single gene produces multiple phenotypic effects. Each of these cases is illustrated below.

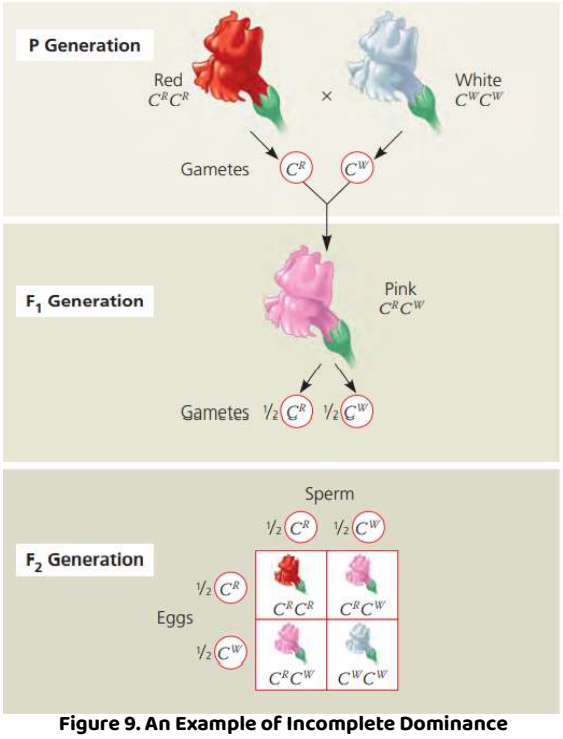


Figure 9. An Example of Incomplete Dominance

1. Degrees of Dominance

Alleles can exhibit varying degrees of dominance and recessiveness relative to each other.

For some genes, neither allele is completely dominant, and the F_1 hybrid shows a phenotype intermediate between those of the two parental varieties.

This phenomenon is known as incomplete dominance, as shown in the following example (Figure 9).

2. Codominance

Another variation in allele relationships is called codominance, in which both alleles affect the phenotype in distinct and separate ways. A well-known example is the determination of human blood groups.

3. Multiple Alleles

Although Mendel studied traits in peas that were controlled by only two alleles, most genes exist in multiple allelic forms.

For example, the ABO blood group system in humans is determined by three alleles of a single gene: I^A, I^B, and i (Figure 10).

An individual's blood type (phenotype) may be one of four: A, B, AB, or O.

These letters refer to two different carbohydrate antigens (A and B) that may be present on the surface of red blood cells (Figure 10A).

A person's red blood cells may carry A carbohydrates (type A), B carbohydrates (type B), both (type AB), or neither (type O), as illustrated in (Figure 10B).

4. Pleiotropy

So far, Mendelian inheritance has been discussed as if each gene affects only one phenotypic trait. Most genes influence multiple phenotypic characters, a property known as pleiotropy.

In humans, pleiotropic alleles are responsible for the multiple symptoms associated with certain genetic disorders, such as cystic fibrosis and sickle-cell disease, which will be discussed later.

In peas, for example, the gene that determines flower color also affects the color of the seed coat, which can be gray or white.

Given the complex molecular and cellular interactions underlying development and physiology, it is not surprising that a single gene can influence multiple traits within an organism.

(a) The three alleles for the ABO blood groups and their carbohydrates. Each allele codes for an enzyme that may add a specific carbohydrate (designated by the superscript on the allele and shown as a triangle or circle) to red blood cells.

Allele	I^A	I^B	i
Carbohydrate	A △	B ○	none

(b) Blood group genotypes and phenotypes. There are six possible genotypes, resulting in four different phenotypes.

Genotype	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB	O

Figure 10. The ABO Blood Groups as an Example of Multiple Alleles

Extending Mendelian Genetics for Two or More Genes

All the previously mentioned cases involve the effects of **alleles of a single gene**. However, there are also cases in which **two or more genes** interact to determine a single phenotypic trait.

1. Epistasis

In epistasis, the phenotypic expression of one gene alters or masks the expression of another gene at a different locus. An example can help illustrate this concept (Figure 11).

In Labrador retriever dogs, the allele for black coat color is dominant over the allele for brown. Let B and b represent the two alleles for this character. For a dog to have brown fur, its genotype must be bb; such dogs are referred to as chocolate Labradors.

A second gene determines whether pigment is deposited in the hair. The dominant allele (E) allows pigment either black or brown, depending on the genotype at the first locus to be expressed.

However, if the dog is homozygous recessive (ee) at this second locus, no pigment is deposited, and the coat appears yellow, regardless of the genotype at the black/brown locus.

In this case, we say that the gene controlling pigment deposition (E/e) is epistatic to the gene that determines pigment color (B/b).

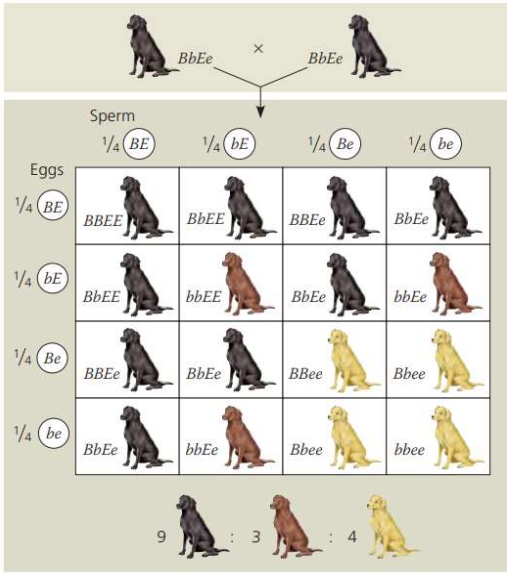


Figure 11. An Example of Epistasis in Dog Coat Color Involving Two Genes That Determine the Phenotypic Expression

2. Polygenic Inheritance

Mendel studied traits that could be classified in an "either or" manner, such as purple versus white flowers. However, many traits such as human skin color and height do not fall into distinct categories because they exhibit continuous variation. These traits are called quantitative characters. Quantitative variation usually indicates polygenic inheritance, the additive effect of two or more genes on a single phenotypic trait. (Note that polygenic inheritance is the opposite of pleiotropy: in pleiotropy, one gene affects multiple phenotypic traits, whereas in polygenic inheritance, multiple genes influence a single trait.) There is evidence that human skin pigmentation is controlled by at least three separately inherited genes.

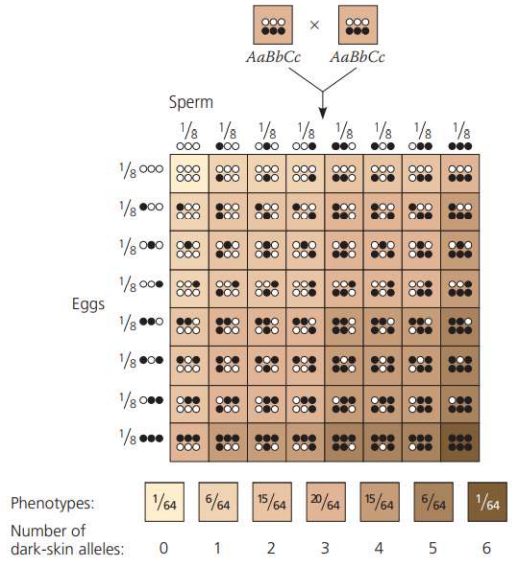


Figure 12. Human Skin Color Genes as an Example of Polygenic Traits

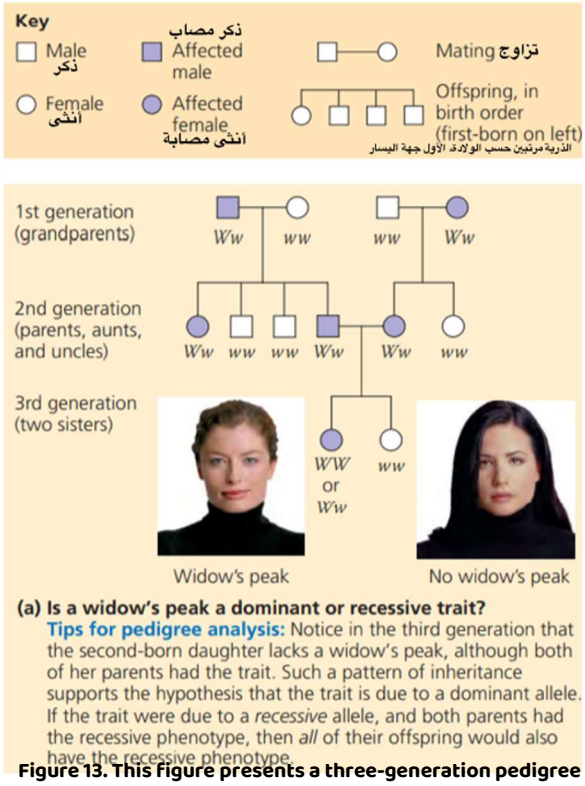
In addition, environmental factors such as sun exposure also influence the phenotypic expression of skin color.

Many Human Traits Follow Mendelian Patters of Inheritance:

Pea plants are convenient subjects for genetic research, but humans are not. A human generation spans a long period about 20 years and parents produce fewer offspring than pea plants or most other species.

The effect of environment on phenotype.
The outcome of a genotype lies within its norm of reaction, a phenotypic range that depends on the environment in which the genotype is expressed. For example, hydrangea flowers of the same genetic variety range in color from blue-violet to pink, with the shade and intensity of color depending on the acidity and aluminum content of the soil.

More importantly, it would be unethical to ask human couples to reproduce solely so that the phenotypes of their offspring could be analyzed! Despite these limitations, the study of human genetics continues, driven by our desire to understand our own inheritance. Although modern molecular biology techniques have led to many groundbreaking discoveries, Mendel's fundamental laws remain the cornerstone of human genetics.



(a) Is a widow's peak a dominant or recessive trait?
Tips for pedigree analysis: Notice in the third generation that the second-born daughter lacks a widow's peak, although both of her parents had the trait. Such a pattern of inheritance supports the hypothesis that the trait is due to a dominant allele. If the trait were due to a *recessive* allele, and both parents had the recessive phenotype, then *all* of their offspring would also have the recessive phenotype.

Figure 13. This figure presents a three-generation pedigree chart tracing the inheritance of the Widow's peak trait, a V-shaped hairline caused by the dominant allele (W).

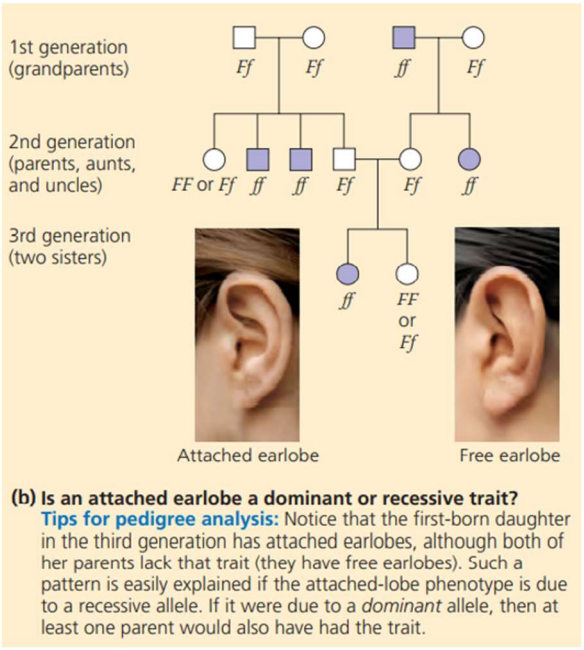
Pedigree Analysis

We cannot manipulate mating patterns among humans, but geneticists can analyze the results of matings that have already occurred. They do this by collecting information about the family history of a particular trait and organizing it into a family

tree, known as a pedigree, which describes the traits of parents and children across generations.

The following figure (Figure 13) shows a three-generation pedigree chart that traces the occurrence of a V-shaped hairline, a trait known as the Widow's peak, which is determined by a dominant allele (W).

The following figure (Figure 14) shows a pedigree chart of the same family, but this time it focuses on a recessive trait attached earlobes. Here, f represents the recessive allele, and F represents the dominant allele, which produces free earlobes. An important application of pedigree charts is their ability to help us calculate the probability that a future child will have a particular genotype or phenotype. Suppose the couple in the second generation of (Figure 13) decides to have another child.



(b) Is an attached earlobe a dominant or recessive trait?
Tips for pedigree analysis: Notice that the first-born daughter in the third generation has attached earlobes, although both of her parents lack that trait (they have free earlobes). Such a pattern is easily explained if the attached-lobe phenotype is due to a recessive allele. If it were due to a *dominant* allele, then at least one parent would also have had the trait.

Figure14. A Three-Generation Pedigree Chart Tracing the Inheritance of Attached Earlobes

What is the probability that the child will have a Widow's peak?

This situation is similar to a monohybrid cross in Mendel's F_1 generation (Ww × Ww).

Therefore, the probability that the child will inherit at least one dominant allele (W) and have a Widow's peak is ¾ (½ Ww + ¼ WW).

What is the probability that the child will have attached earlobes?

Again, this can be treated as a monohybrid cross (Ff × Ff), but this time we are looking for the chance that the offspring will be homozygous recessive (ff). That probability is ¼.

Finally, what is the probability that the child will have both a Widow's peak and attached earlobes?

Assuming that the genes for these two traits are located on different chromosomes, the two pairs of alleles will assort independently in this dihybrid cross (WwFf × WwFf). Therefore, we can apply the multiplication rule:

¾ (chance of Widow's peak) × ¼ (chance of attached earlobes) = 3⁄16 (chance of having both traits).

Pedigree analysis becomes even more crucial when the alleles involved cause debilitating or lethal diseases.

Recessively Inherited Disorders

Thousands of genetic disorders are known to be inherited as recessive traits. Their severity ranges from relatively mild conditions, such as albinism, to life-threatening diseases like cystic fibrosis.

The Behavior of Recessive Alleles

How can we explain the behavior of alleles that cause recessive genetic disorders?

Remember that genes encode proteins with specific functions.

An allele that causes a genetic disorder typically encodes either a nonfunctional protein or no protein at all.

In recessive disorders, **heterozygous** individuals (Aa) are phenotypically normal, because one copy of the normal (dominant) allele (A) produces enough of the required protein. Thus, the recessive genetic disorder appears only in **homozygous** individuals (aa) who inherit one recessive allele from each parent.

Although heterozygous individuals are phenotypically normal with respect to the disorder, they can still pass the recessive allele to their offspring and are therefore called carriers.

These principles are illustrated in the following figure, using albinism as an example (Figure 15). Most individuals affected by recessive disorders are born to carrier parents who are phenotypically normal.

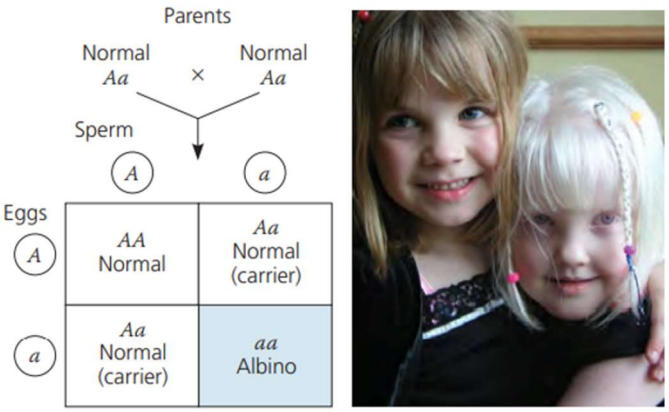


Figure 15. Albinism: a recessive trait. One of the two sisters shown here has normal coloration; the other is albino. Most recessive homozygotes are born to parents who are carriers of the disorder but themselves have a normal phenotype, the case shown in the Punnett square.

A mating between two carriers corresponds to Mendel's F_1 monohybrid cross, with the expected genotypic ratio of 1 AA : 2 Aa : 1 aa. Therefore, each child has a ¼ chance of inheriting two recessive alleles.

In the case of albinism, affected children lack melanin pigment entirely. From this genotypic ratio, we can also infer that among the three children with a normal phenotype (1 AA + 2 Aa), two are expected to be heterozygous carriers, giving a probability of ⅔.

Cystic fibrosis

The most common lethal genetic disease in the United States is cystic fibrosis, which affects about one in every 2,500 individuals of European descent, but is much rarer in other populations.

Question: What are the symptoms of cystic fibrosis?

Sickle-cell Disease: A Genetic Disorder with Evolutionary Implications:

The most common genetic disorder among individuals of African descent is sickle-cell disease, which affects approximately one in every 400 African Americans.

Sickle-cell disease results from the substitution of a single amino acid in the hemoglobin protein of red blood cells (Figure 1-15).

In homozygous individuals, the hemoglobin is entirely of the sickle-cell type, an abnormal form of red blood cells.

In affected individuals, the abnormal hemoglobin molecules aggregate into long fibers that distort red blood cells into a sickle shape. These sickled cells may clump together and block small blood vessels, leading to a variety of symptoms throughout the body, including physical weakness, pain, organ damage, and even paralysis.

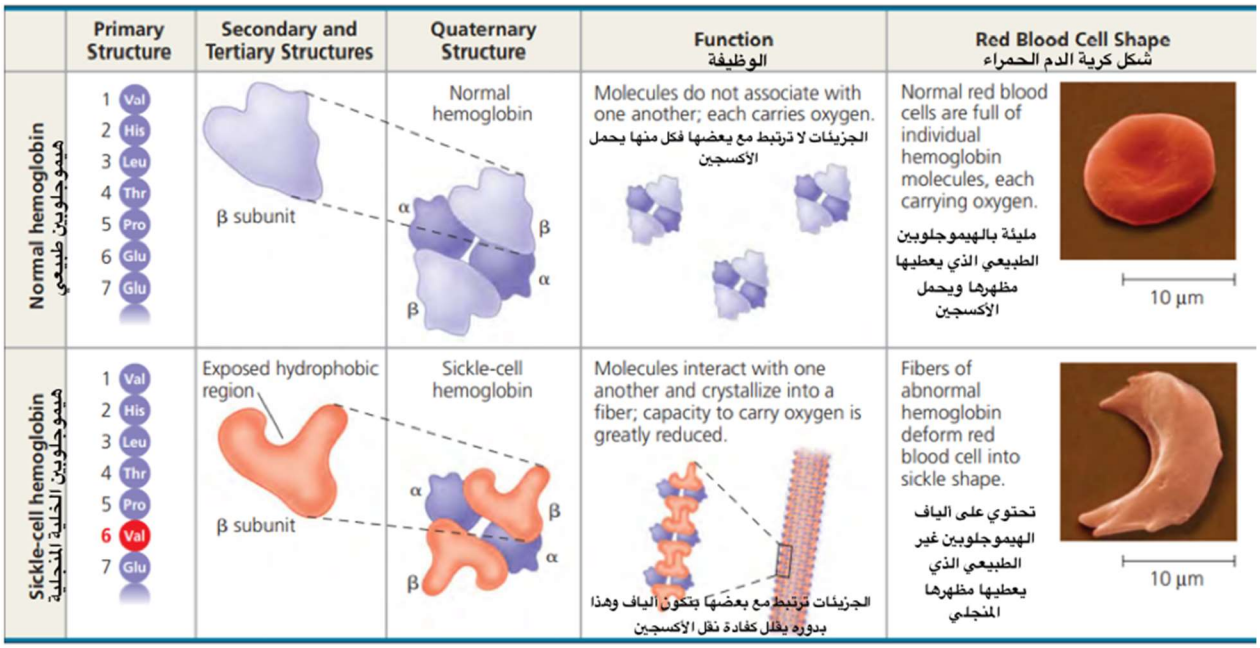


Figure 16. Comparison of normal and sickle-cell hemoglobin and their effects on red blood

Although having two recessive alleles causes the disease, carrying a single sickle-cell allele can still influence the phenotype.

At the organismal level, the normal allele shows incomplete dominance over the sickle-cell allele.

Individuals who are heterozygous carriers often described as having the sickle-cell trait are generally healthy but may experience some sickle-cell symptoms during prolonged periods of low blood oxygen.

At the molecular level, the two alleles are codominant, since both normal and abnormal (sickle-cell) hemoglobins are produced in heterozygotes.

Why hasn't natural selection eliminated the sickle-cell allele from this population?

One explanation is that carrying a single sickle-cell allele reduces the frequency and severity of malaria infections, particularly among young children. The malaria parasite spends part of its life cycle inside red blood cells, and the presence of some sickle hemoglobin in heterozygous individuals reduces parasite density and therefore lessens malaria symptoms.

Dominantly Inherited Disorders

Although many harmful alleles are recessive, several human disorders are caused by dominant alleles.

One example is achondroplasia, a form of dwarfism that occurs in one out of every 25,000 individuals. In this condition, **heterozygous individuals** exhibit the **dwarf phenotype**, as shown in the figure.

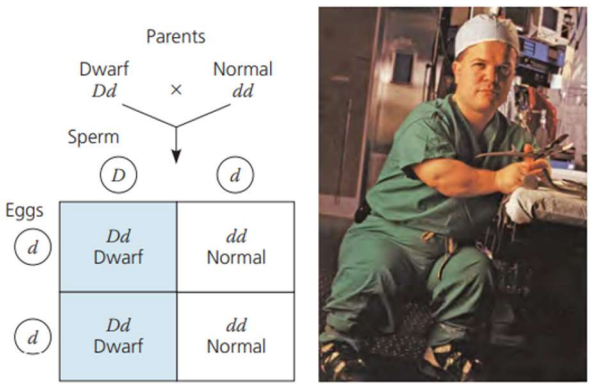


Figure 17. Achondroplasia: a dominant trait.
Dr. Michael C. Ain has achondroplasia, a form of dwarfism caused by a dominant allele. This has inspired his work: He is a specialist in the repair of bone defects caused by achondroplasia and other disorders. The dominant allele (*D*) might have arisen as a mutation in the egg or sperm of a parent or could have been inherited from an affected parent, as shown for an affected father in the Punnett square.

Huntington's Disease: A Late-Onset Lethal Disease

The timing of disease onset greatly influences its inheritance pattern. The effects of a lethal dominant allele may not appear until relatively late in life. By the time symptoms become evident, an affected individual may have already passed the allele to their children. For example, Huntington's disease a degenerative disorder of the nervous system is caused by a lethal dominant allele that shows no obvious phenotypic effects until the individual is about 35 to 45 years old. Once the nervous system deterioration begins, it is irreversible and inevitably fatal.

Counseling Based on Mendelian Genetics and Probability Rules:

Let us consider, for example, the case of a hypothetical couple, John and Carol. Each of them had a sibling who died from the same recessively inherited lethal disease. Before having their first child, John and Carol seek genetic counseling to determine the risk of having an affected child.

From information about their siblings, we know that both of John's parents and both of Carol's parents must have been carriers of the recessive allele. Thus, both John and Carol are the result of a cross Aa × Aa, where a represents the allele causing the disease.

We also know that John and Carol are not homozygous recessive (aa), since neither shows symptoms of the disease. Therefore, their genotypes must be either AA or Aa. Because each is the offspring of an Aa × Aa cross, and the genotypic ratio from such a cross is 1 AA : 2 Aa : 1 aa, each of them (John and Carol) has a 2/3 probability of being a carrier (Aa). According to the multiplication rule, the overall probability that their first child will have the disorder is:

2/3 (John is a carrier) × 2/3 (Carol is a carrier) × 1/4 (two carriers having an affected child) = **1/9**.

Suppose John and Carol decide to have a child after all; there is an 8⁄9 chance that their child will be unaffected. If their child is born with the disease, despite these odds, it would confirm that both John and Carol are carriers (genotype Aa).

Once both parents are confirmed carriers, there is a 1⁄4 probability that any subsequent child will also have the disease. This probability is higher for later children only because the diagnosis of the first child confirms both parents are carriers, not because the genotype of the first child affects the others in any way.

When using Mendel's laws to predict the outcomes of genetic crosses, it is important to remember that each child represents an independent event — meaning that the genetic makeup of one child does not influence that of the next. If John and Carol have three more children, and all three are affected by the genetic disease, the probability of such a result is

$\frac{1}{4} \times \frac{1}{4} \times \frac{1}{4} = \frac{1}{64}$.

Nevertheless, the **chance that another child** born to this couple will have the disease **remains ¼**. Tests for Identifying Carriers

- **Fetal Testing**
- **Newborn Screening**

Chapter Two

The Chromosomal Basis of Inheritance

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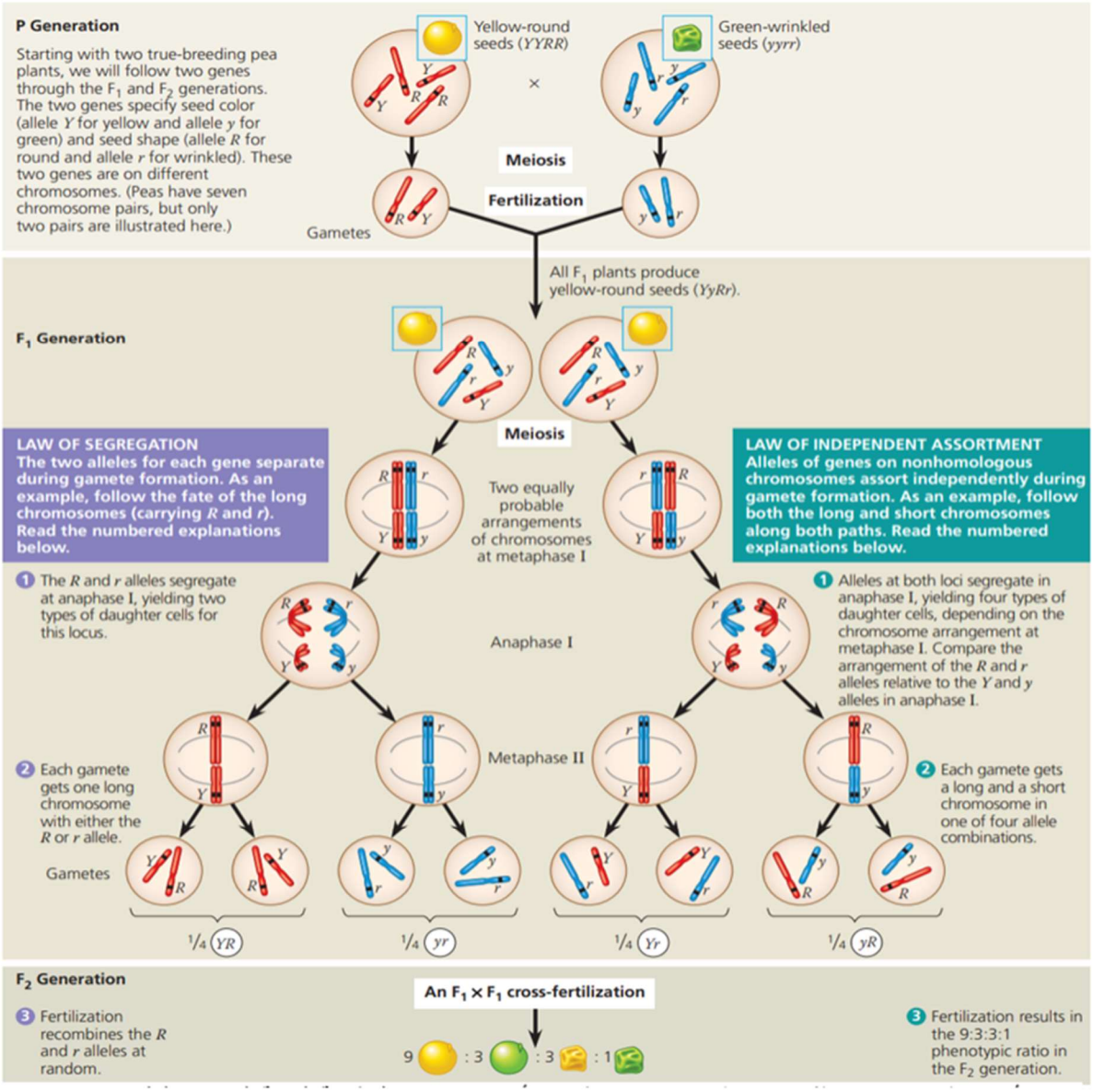
Mendelian Inheritance has its Physical Basis in the Behavior of Chromosomes:



The chromosomal basis of Mendel's laws. Here we correlate the results of one of Mendel's dihybrid crosses. with the behavior of chromosomes during meiosis. The arrangement of chromosomes at metaphase I of meiosis and their movement during anaphase I account for the segregation and independent assortment of the alleles for seec color and shape. Each cell that undergoes meiosis in an F1 plant produces two kinds of gametes. If we count the results for all cells, however, each F1 plant produces equal numbers of all four kinds of gametes because the alternative chromosome arrangements at metaphase I are equally likely.

Morgan's Experimental Evidence

Morgan's Choice of Experimental Organism

Major scientific discoveries are often closely linked to the choice of an appropriate experimental organism for the research problem being investigated. Mendel chose garden peas because they exhibited several easily distinguishable traits. For his experiments, Thomas Hunt Morgan selected a species of fruit fly, *Drosophila melanogaster* a common insect that feeds on the fungi growing on fruit. Fruit flies are prolific breeders; a single mating can produce hundreds of offspring, and a new generation can be reared every two weeks.

Another advantage of *Drosophila* is that it has only four pairs of chromosomes, which can be easily distinguished under a light microscope. Three of these pairs are autosomes, and one pair consists of sex chromosomes.

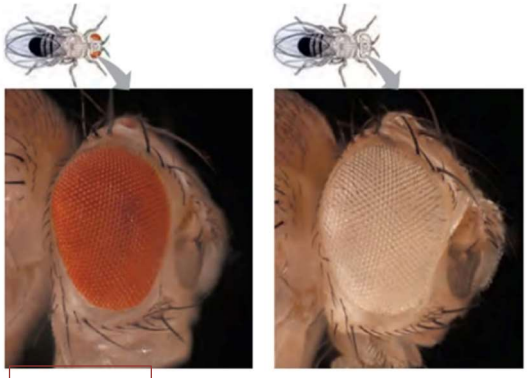


Figure 18. Morgan's first mutant. Wild-type *Drosophila* flies have red eyes (left). Among his flies, Morgan discovered a mutant male with white eyes (right). This variation made it possible for Morgan to trace a gene for eye color to a specific chromosome (LMs).

Females possess two homologous X chromosomes (XX), whereas males have one X and one Y chromosome.

Morgan initially had great difficulty obtaining visible variations in the flies, until he finally discovered a single male with white eyes, instead of the usual red eyes (Figure 18).

The most common phenotype observed in natural populations such as red eyes in fruit flies is called the wild type. Alternative traits, such as white eyes, are referred to as mutant phenotypes, since they result from alleles that are presumed to have arisen by mutation in the wild-type gene.

Morgan and his students developed a notation system for *Drosophila* alleles that is still widely used today. For any given trait, the gene symbol is derived from the first mutant (non-wild type) phenotype discovered. For example, the white-eye allele in fruit flies is represented by w, while the wild-type red-eye allele is designated as w^+.

Correlating Behavior of a Gene's Alleles with Behavior of a Chromosome Pair:

Morgan crossed a white-eyed male fruit fly with a red-eyed female. All F_1 offspring had red eyes, indicating that the wild-type allele is dominant.

When Morgan crossed the F_1 flies with each other, he observed the classic 3:1 phenotypic ratio among the F_2 generation. However, there was an additional and surprising result: the white-eye trait appeared only in males. All F_2 females had red eyes, whereas half of the males had red eyes and the other half had white eyes.

Therefore, Morgan concluded that eye color in fruit flies is somehow linked to sex. Recall that female flies have two X chromosomes (XX), while males have one X and one Y chromosome (XY).

The association between the white-eye trait and male offspring in the F_2 generation led Morgan to propose that the gene responsible for the white-eye mutation is located exclusively on the X chromosome, with no corresponding allele on the Y chromosome. This idea can be visualized in the following figure (Figure 19).

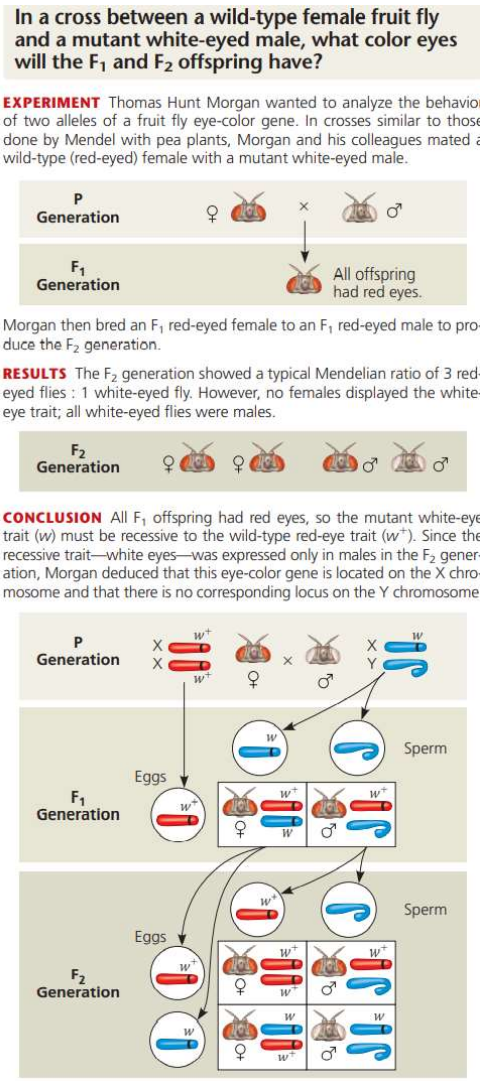


Figure 19. Morgan's Experiments on Fruit Flies Showing the Expected Results for Both the F_1 and F_2 Generations

In males, a single copy of the mutant allele results in white eyes, because males have only one X chromosome and therefore no wild-type allele (W^+) to mask the recessive mutation. In contrast, females can have white eyes only if both of their X chromosomes carry the mutant recessive allele (w). This was impossible for the F_2 females in Morgan's experiment, since all F_1 parents had red eyes.

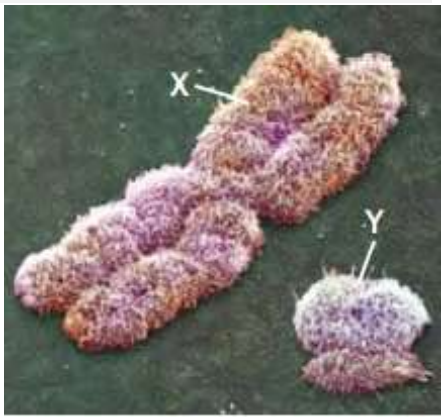
Sex-Linked Genes Exhibit Unique Patterns of Inheritance

Morgan's discovery of the white-eye trait as being linked to sex in fruit flies was a major milestone in the development of the chromosome theory of inheritance. Because an individual's sex chromosomes can be identified simply by observing the sex of the fly, it became possible to relate the behavior of the two sex chromosomes to the behavior of the alleles of the eye-color gene.

In this section, we will examine in more detail the role of sex chromosomes in inheritance, beginning with a review of the chromosomal basis of sex determination in humans and several other animals.

1. The Chromosomal Basis of Sex:

Whether we are male or female is one of the most visually apparent phenotypic traits we possess.



Although the anatomical and physiological differences between males and females are numerous, the chromosomal basis of sex determination is relatively simple.

In humans and other mammals, there are two types of sex chromosomes, known as X and Y. The Y chromosome is much smaller than the X chromosome.

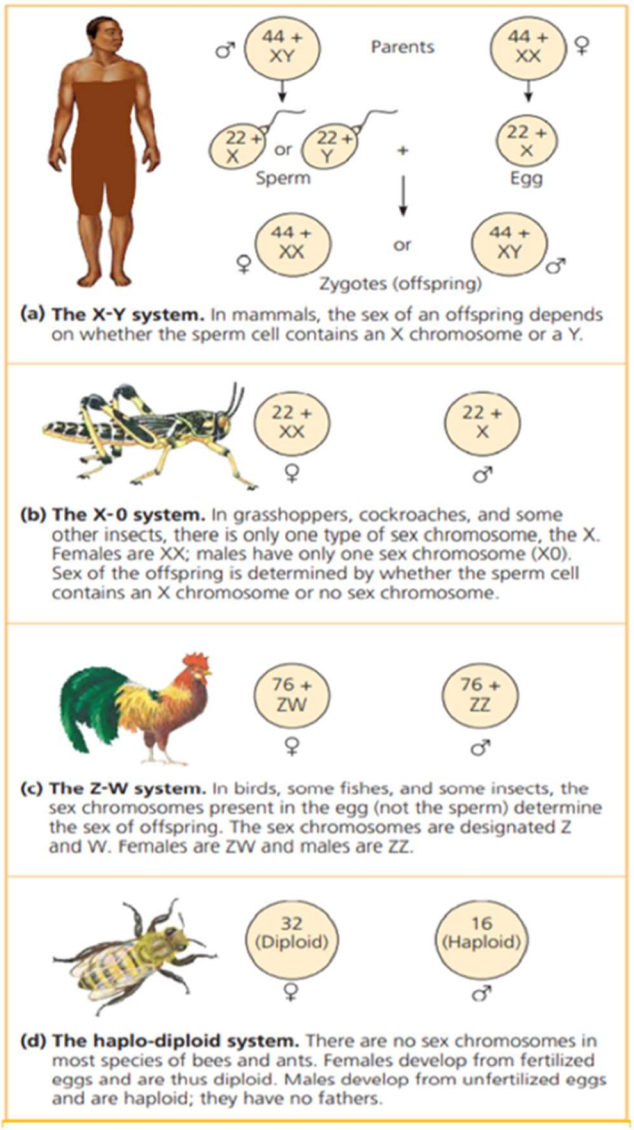
Typically, a female inherits two X chromosomes, one from each parent, while a male possesses one X chromosome and one Y chromosome.

The short regions at either end of the Y chromosome are the only homologous areas shared with corresponding regions of the X chromosome. These homologous regions allow the X and Y chromosomes in males to pair and behave like homologous chromosomes during meiosis in the testes.

In the testes and ovaries of mammals, the sex chromosomes separate during meiosis, ensuring that each gamete receives only one.

Every egg cell carries a single X chromosome, while sperm cells are produced in two categories:

half contain an X chromosome, and the other half contain a Y chromosome. Thus, the sex of each offspring is determined at the moment of fertilization:



Some chromosomal systems of sex determination. Numerals indicate the number of autosomes in the species pictured. In Drosophila, males are XY, but sex depends on the ratio between the number of X chromosomes and the number of autosome sets, not simply on the presence of a Y chromosome. **(Figure 20)**

- If a sperm cell carrying an X chromosome fertilizes the egg, the resulting zygote (XX) develops into a female.
- If a sperm cell carrying a Y chromosome fertilizes the egg, the resulting zygote (XY) develops into a male.

Therefore, sex determination is essentially a matter of chance — a fifty-fifty probability.

As shown in the following figure, the X–Y system used by mammals is not the only chromosomal system for determining sex; the figure illustrates three other sex-determination systems as well.

Researchers have sequenced the human Y chromosome and identified about 78 genes encoding roughly 25 proteins (some genes are duplicated).

A gene located on either sex chromosome is called a sex-linked gene. Those found on the Y chromosome are referred to as Y-linked genes. The Y chromosome is passed from father to all his sons. Because there are very few Y-linked genes, disorders transmitted from father to son via the Y chromosome are extremely rare.

In contrast, the human X chromosome carries approximately 1,100 genes, which are known as X-linked genes.

2. Inheritance of X-Linked Genes

While most Y-linked genes are involved in sex determination, the X chromosomes carry genes that influence many traits unrelated to sex. The X-linked genes in humans follow the same inheritance pattern that Morgan observed for the eye-color locus in Drosophila. Fathers transmit their X-linked alleles to all their daughters, but none to their sons. In contrast, mothers can pass X-linked alleles to both sons and daughters, as illustrated in the following figure (Figure 2-5).

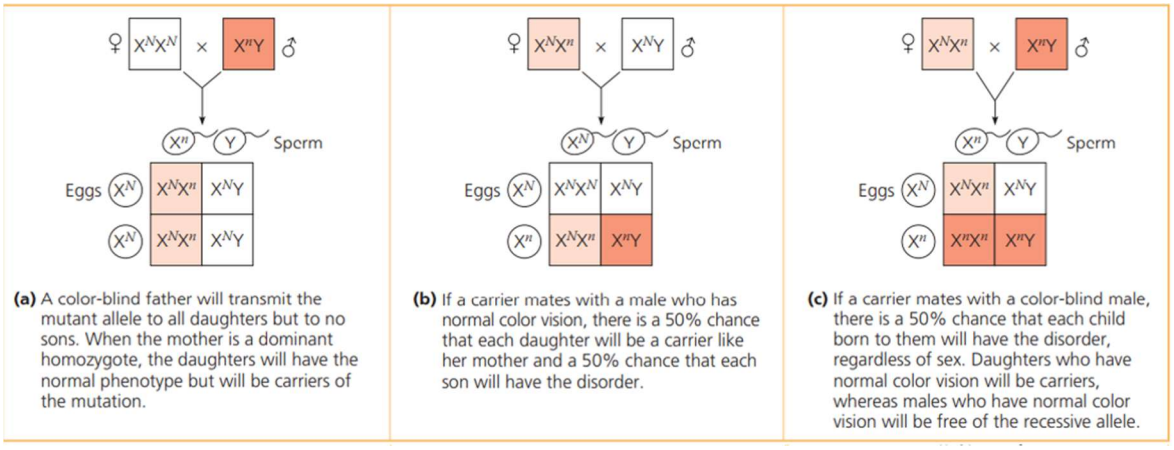


Figure 21. Examples of Inheritance Patterns for X-Linked Genes

If an X-linked trait is caused by a recessive allele, a female will express the trait only if she is homozygous for that allele.

Because males possess only one X chromosome, the terms homozygous and heterozygous are not used to describe their X-linked genes; instead, the term hemizygous is applied in such cases. Any male who inherits the recessive allele from his mother will express the trait. For this reason, X-linked recessive disorders occur much more frequently in males than in females.

However, although the chance of a female inheriting two mutant alleles is much lower than that of a male inheriting one, females can still be affected by X-linked disorders. For example, color blindness is a mild disorder that is always inherited as an X-linked trait.

A daughter who is color-blind may be born to a color-blind father whose wife is a carrier, as shown in the previous figure.

Hemophilia is another X-linked recessive disorder, characterized by the absence of one or more proteins necessary for blood clotting. Individuals with hemophilia experience prolonged bleeding due to delayed clot formation. Minor cuts on the skin usually pose no problem, but bleeding into muscles or joints can be painful and may cause severe damage. Today, people with hemophilia are treated as needed by intravenous injection of the missing clotting protein.

3. X Inactivation in Female Mammals

Female mammals, including humans, inherit two X chromosomes twice the number inherited by males so one might wonder whether females produce twice as many proteins encoded by X-linked genes as males do.

One X chromosome is inactivated in each cell of female mammals during early embryonic development. As a result, female and male cells have the same effective dose one functional copy of most X-linked genes. The inactive X chromosome in each female

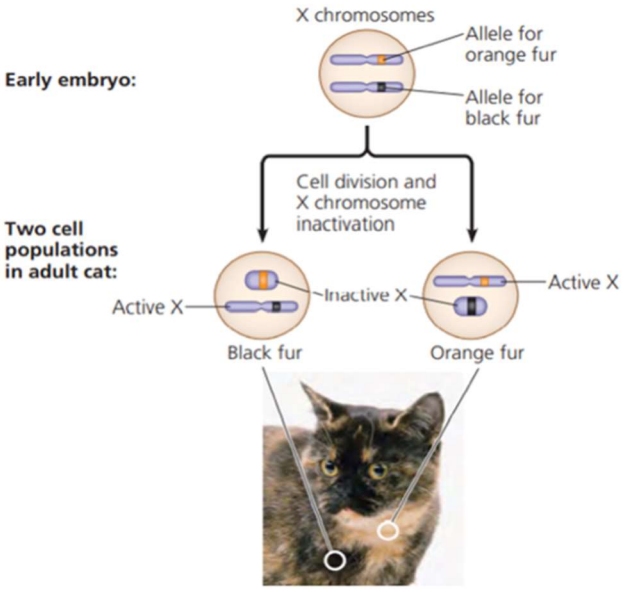


Figure 22. X inactivation and the tortoiseshell cat. The tortoiseshell gene is on the X chromosome, and the tortoiseshell phenotype requires the presence of two different alleles, one for orange fur and one for black fur. Normally, only females can have both alleles, because only they have two X chromosomes. If a female cat is heterozygous for the tortoiseshell gene, she is tortoiseshell. Orange patches are formed by populations of cells in which the X chromosome with the orange allele is active; black patches have cells in which the X chromosome with the black allele is active. ("Calico" cats also have white areas, which are determined by yet another gene.)

cell condenses into a compact structure known as a Barr body. Most of the genes on the X chromosome that becomes a Barr body are not expressed. The following figure (22) illustrates how this mosaic pattern of X-chromosome inactivation produces the spotted coat coloration seen in certain types of cats.

Linked Genes Tend to be Inherited Together because they are Located near each other on the Chromosome:

The number of genes in a cell is far greater than the number of chromosomes. In fact, each chromosome contains hundreds or even thousands of genes (with the Y chromosome being an exception).

Genes located close together on the same chromosome tend to be inherited together during genetic crossing over; such genes are said to be genetically linked and are called linked genes.

(Note the distinction between the terms sex-linked gene, which refers to a single gene on a sex chromosome, and linked genes, which refer to two or more genes located on

the same chromosome that tend to be inherited together.) When geneticists track linked genes in breeding experiments, the results do not follow Mendel's second law of

How Linkage Affects Inheritance

independent assortment.

To understand how gene linkage affects the inheritance of two different traits, let us examine another of Morgan's experiments with the fruit fly *Drosophila*.

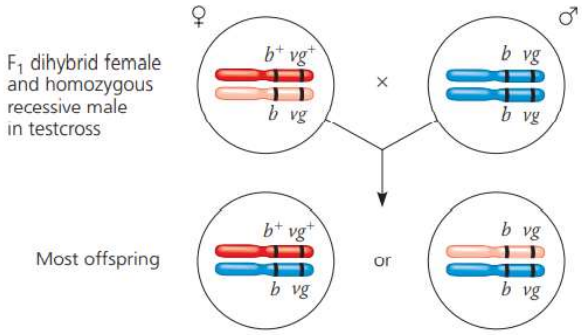


Figure 23. Morgan's Testcross Experiment on the Fruit Fly Drosophila

In this case, the traits studied were body color and wing size, each with two distinct phenotypes. The wild-type flies had gray bodies and normal-sized wings.

In addition to these, Morgan was able through selective breeding to obtain mutant flies that had black bodies and much smaller wings than normal.

The mutant alleles were recessive to the wild-type alleles, and neither of the two genes was located on a sex chromosome. To test the relationship between these genes, Morgan performed the crosses illustrated in the following figures (Figures 23 and 24).

The first cross involved the parental (P) generation to produce dihybrid F_1 flies, and the second was a testcross. From these results, Morgan concluded that body color

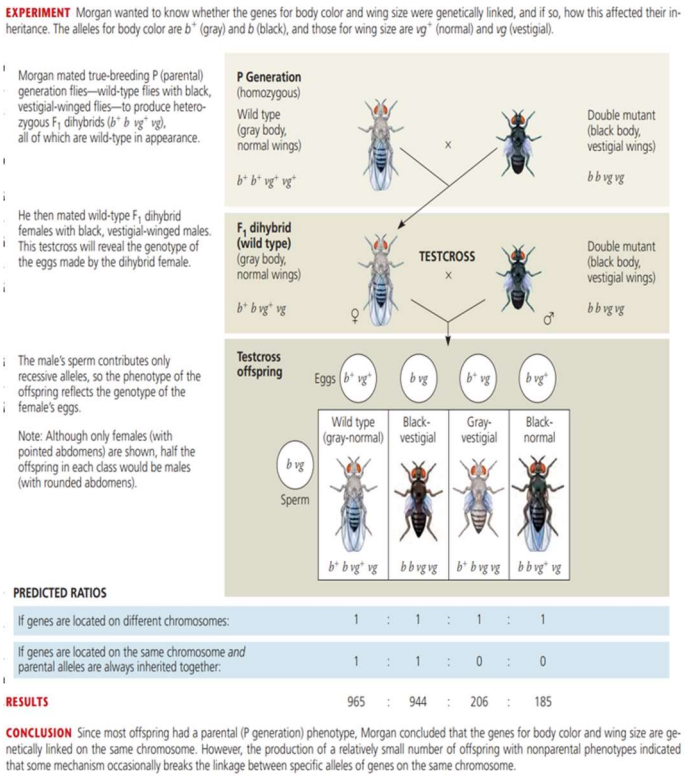


Figure 24.

and wing size are usually inherited together in specific combinations because the genes controlling these traits are located close to each other on the same chromosome.

Genetic Recombination and Linkage

We have learned that meiosis and random fertilization generate genetic variation among the offspring of sexually reproducing organisms. Now, we will examine the chromosomal basis of recombination in relation to the genetic findings of Mendel and Morgan.

Recombination of Unlinked Genes: Independent Assortment of Chromosomes:

From his two-trait crosses, Mendel observed that some offspring displayed combinations of traits that did not match either parent.

For example, consider a cross between a dihybrid pea plant heterozygous for both seed color and seed shape (YyRr) and a plant homozygous recessive for both traits (yyrr). This cross can be represented using a Punnett square as follows:

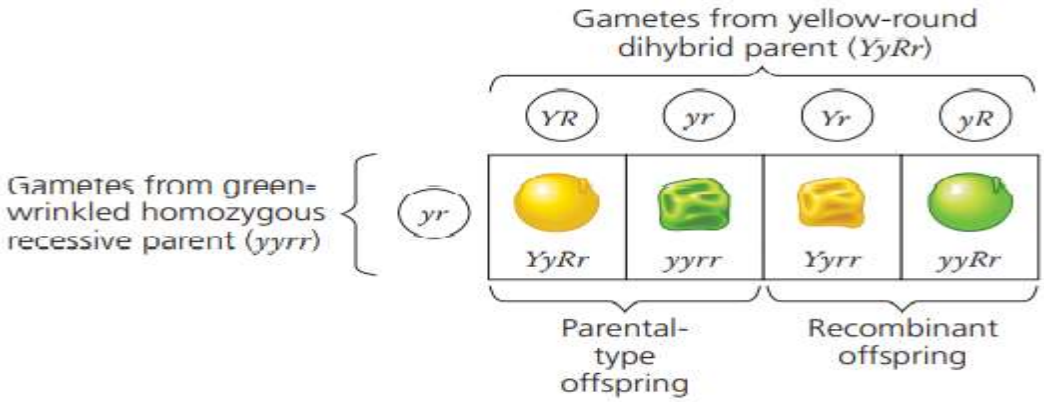
In the Punnett square, it is expected that half of the offspring will exhibit phenotypes matching either parent of the P generation. These offspring are called parental types.

However, two nonparental phenotypes also appear among the offspring. Because these individuals contain new combinations of seed color and seed shape, they are called recombinants.

When 50% of the total offspring are recombinant, as in this example, geneticists say that there is a 50% frequency of recombination. The expected phenotypic ratios among the offspring correspond closely to those that Mendel observed in his YyRr × yyrr crosses.

A 50% recombination frequency is observed in testcrosses for any two genes located on different chromosomes and therefore not linked. The physical basis of recombination between unlinked genes is the random orientation of homologous

chromosomes during metaphase I of meiosis, which leads to the independent assortment of unlinked genes.



Recombination of Linked Genes: Crossing Over:

Now let us return to Morgan's experiments to understand how we can explain the results of his testcrosses with *Drosophila*, shown in (Figure 24). Recall that most of the offspring in the testcross exhibited parental phenotypes for both body color and wing size.

This suggested that the two genes were located on the same chromosome, since the occurrence of parental types at a frequency greater than 50% indicates that the genes are linked. However, about 17% of the offspring were recombinants.

Considering these results, Morgan proposed that some process must occasionally break the physical connection between specific alleles of genes located on the same chromosome. Later experiments confirmed that this process, now known as crossing over, is responsible for the recombination of linked genes.

During crossing over, which occurs while duplicated homologous chromosomes are paired during prophase I of meiosis, a set of proteins orchestrates the exchange of corresponding segments between a maternal chromatid and a paternal chromatid.

In essence, the terminal segments of two nonsister chromatids are exchanged each time crossing over takes place. The following figure (Figure 25) illustrates how crossing over in a dihybrid female fly resulted in recombinant eggs, and consequently, recombinant offspring in Morgan's testcross.

Most eggs contained chromosomes carrying either parental genotypes *(b^+ vg^+)* or *(b vg)* for body color and wing size, but some eggs contained recombinant chromosomes *(b vg^+ or b^+ vg)*. Fertilization of these different classes of eggs by homozygous recessive sperm (b vg) produced a group of offspring in which 17% showed nonparental recombinant phenotypes combinations of alleles not seen in either parent of the P generation.

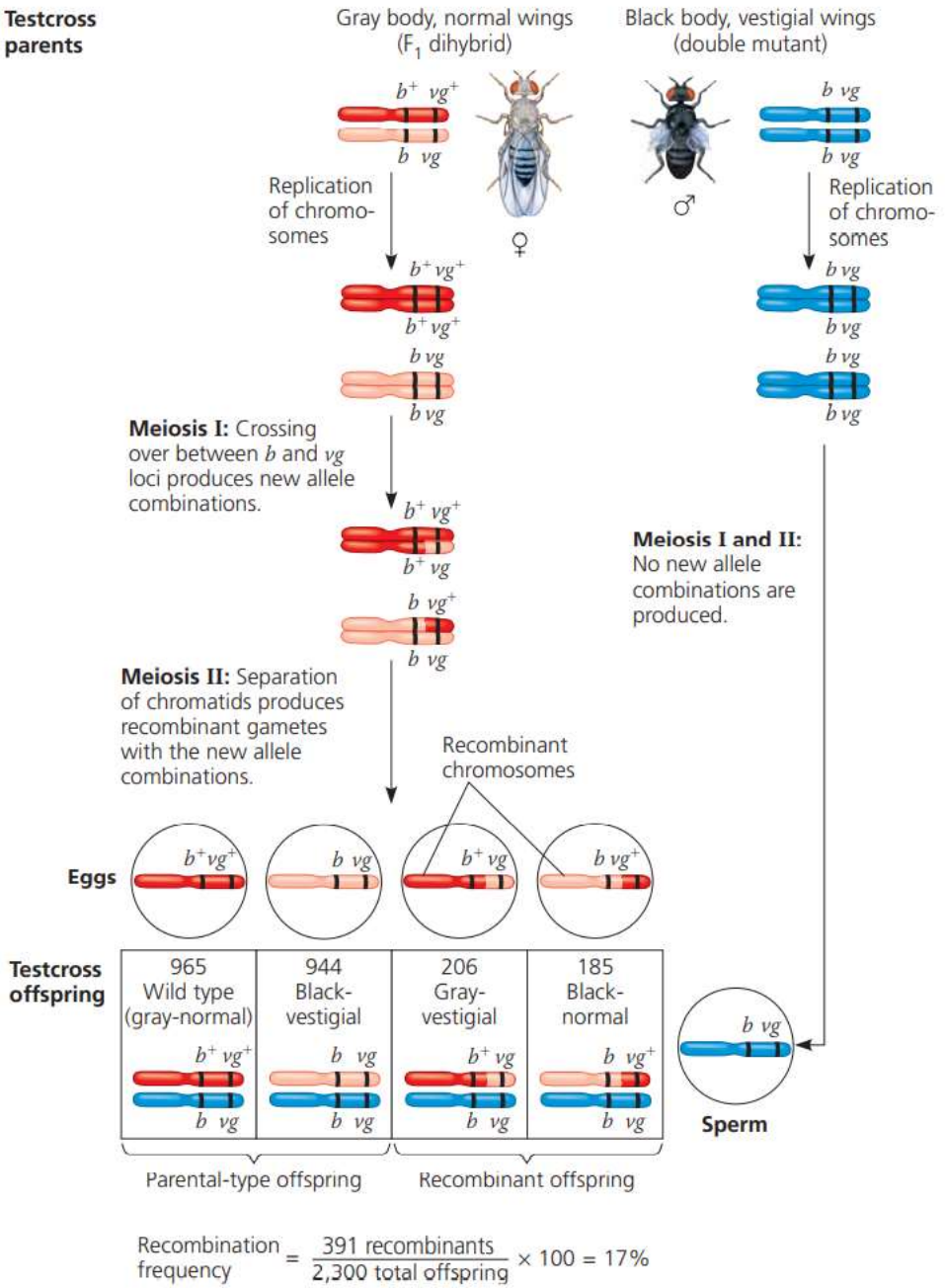


Figure 25. Illustration of How Crossing Over in a Dihybrid Female Fly

Alternations of Chromosome Number or Structure Cause some Genetic Disorders:

Large-scale chromosomal changes can also affect an organism's phenotypic traits. Physical and chemical disturbances, as well as errors during meiosis, can damage chromosomes in major ways or alter their number within a cell. In humans and other mammals, such large-scale chromosomal alterations often lead to spontaneous miscarriage of the embryo, and individuals who are born with these types of genetic abnormalities usually exhibit various developmental disorders.

Abnormal Chromosome Number:

Ideally, the meiotic spindle distributes chromosomes to the daughter cells without error during meiosis.

However, an unfortunate event called nondisjunction may occur, in which a pair of homologous chromosomes fails to move apart properly during meiosis I, or sister chromatids fail to separate during meiosis II (as shown in Figure 26).

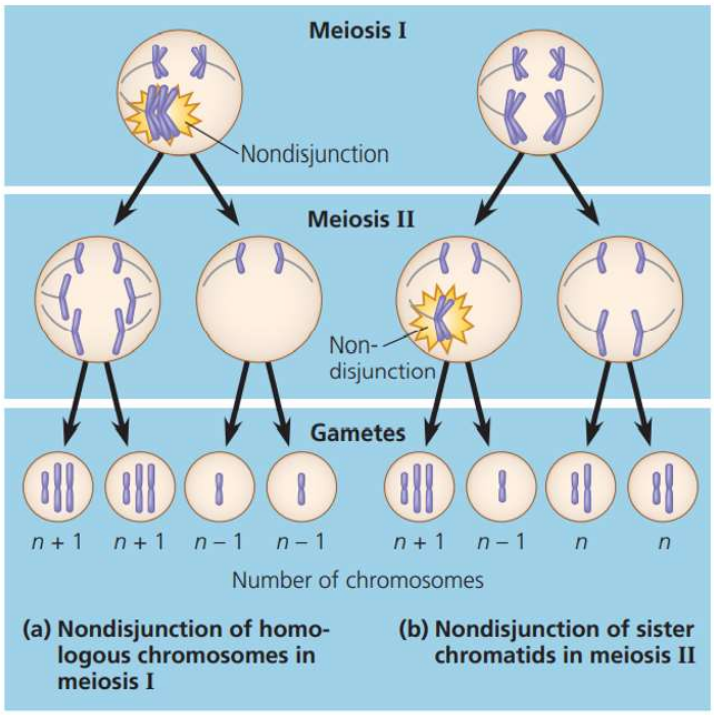


Figure 26. Meiotic nondisjunction. Gametes with an abnormal chromosome number can arise by nondisjunction in either meiosis I or meiosis II. For simplicity,

In such cases, one gamete receives two copies of the same chromosome, while another gamete receives none. The remaining chromosomes are usually distributed normally.

If one of these abnormal gametes unites with a normal gamete during fertilization, the resulting zygote will have an abnormal number of a particular chromosome a condition known as aneuploidy. (Aneuploidy may involve more than one chromosome.) Fertilization involving a gamete that lacks a specific chromosome will result in a missing chromosome

in the zygote (2n − 1); such a zygote is said to be monosomic for that chromosome. If a chromosome is present in three copies in the zygote (2n + 1), the cell is described as trismic for that chromosome.

Mitosis will then transmit this chromosomal abnormality to all embryonic cells.

If the organism survives, it usually exhibits a set of traits caused by the abnormal number of genes associated with the extra or missing chromosome.

Down syndrome is an example of a trisomy in humans, which will be discussed later.

Nondisjunction can also occur during mitosis.

If such an error takes place early in embryonic development, the resulting aneuploid condition may be passed to many cells through subsequent mitotic divisions, potentially having a major effect on the organism.

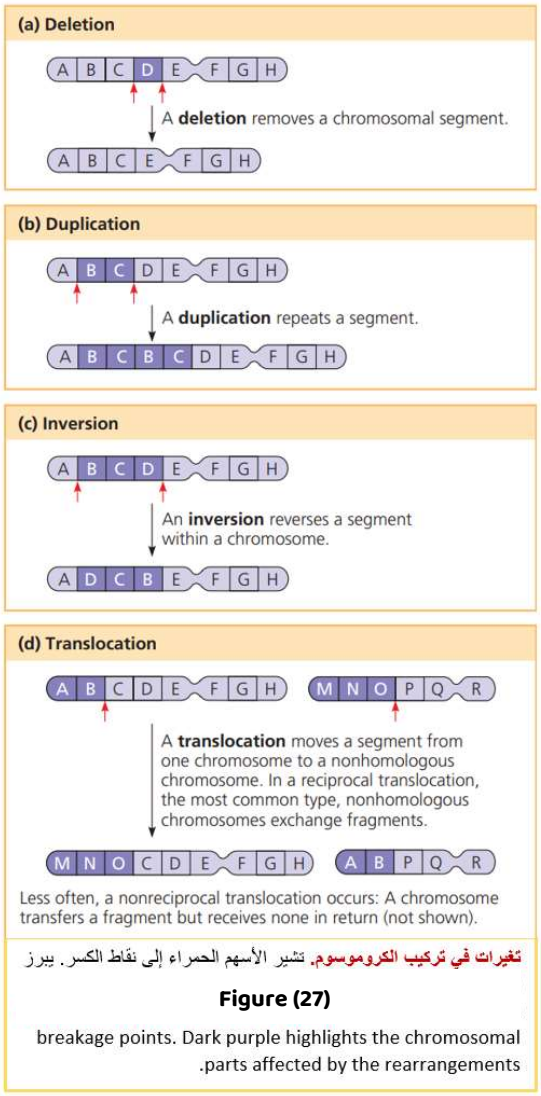
Some organisms have more than two complete sets of chromosomes in all their somatic cells a condition known as polyploidy.

The abbreviations (3n) and (4n) denote triploid and tetraploid, respectively. One way a triploid (3n) cell may arise is through the fertilization of an abnormal diploid (2n) egg, produced by nondisjunction of all chromosomes. A tetraploid (4n) cell can result from the failure of a diploid (2n) zygote to divide after its chromosomes replicate. Subsequent normal mitotic divisions then produce a (4n) embryo.

Polyploidy is relatively common in the plant kingdom. Many of the plants we eat are polyploid for example, bananas (3n), wheat (6n), and strawberries (8n). Polyploid animals are less common, though some species of fish and amphibians exhibit this condition. In general, polyploid organisms tend to appear more normal in structure and function than aneuploid individuals. An extra or missing single chromosome disrupts the genetic balance far more severely than does an entire extra set of chromosomes.

Alterations of Chromosome Structure:

Errors during meiosis or exposure to harmful agents such as radiation can cause chromosomal breakage, leading to four major types of structural alterations in chromosomes, as shown below.



تغيرات في تركيب الكروموسوم. تشير الأسهم الحمراء إلى نقاط الكسر. يبرز

Figure (27)

breakage points. Dark purple highlights the chromosomal parts affected by the rearrangements.

A deletion occurs when a chromosomal fragment is lost, causing the chromosome to lack certain genes. (If the centromere is deleted, the entire chromosome is lost.) The deleted fragment may attach as an extra piece to a sister chromatid, producing a duplication. Alternatively, the fragment may attach to a nonsister chromatid of a homologous chromosome. In this case, the "duplicated" segments may not be identical, since homologous chromosomes can carry different alleles of the same genes.

Sometimes, a chromosomal segment reattaches to its original chromosome but in the reverse orientation, creating an inversion. A fourth possible outcome of chromosomal breakage is when the fragment joins a nonhomologous chromosome, resulting in a rearrangement called a translocation.

Deletions and duplications most often occur during meiosis. During crossing over, nonsister chromatids may exchange unequal portions of DNA, such that one chromatid gives up more genes than it receives. The products of this unequal crossing over are one chromosome with a deletion and another with a duplication.

A diploid embryo carrying a homozygous chromosome with a large deletion (or a single X chromosome with a large deletion in males) loses a significant number of essential genes usually a lethal condition.

Duplications and translocations also tend to be harmful. In reciprocal translocations, where segments are exchanged between nonhomologous chromosomes, and in inversions, the gene balance may remain normal all genes are present in their correct dosage.

However, these rearrangements can alter an organism's phenotype because gene expression may be influenced by the new chromosomal environment; such events can sometimes have severe or deleterious effects.

Human Disorders Due to Chromosomal Alterations:

Changes in chromosome number and structure are associated with a variety of serious human disorders.

As previously discussed, nondisjunction during meiosis can lead to aneuploidy an abnormal number of chromosomes in both gametes and the resulting zygote.

Although the rate of chromosomal abnormalities in human zygotes may be quite high, most of these chromosomal alterations are so severe that the affected embryos are spontaneously aborted long before birth.

However, some types of chromosomal abnormalities cause less disruption to the genetic balance, allowing individuals with certain chromosomal disorders to survive to birth and beyond.

Down Syndrome (Trisomy 21):

One of the most well-known chromosomal abnormalities is Down syndrome, which affects about one in every 700 children born in the United States. Down syndrome is

typically, the result of an extra chromosome 21, so that each cell in the body contains a total of 47 chromosomes instead of the normal 46.

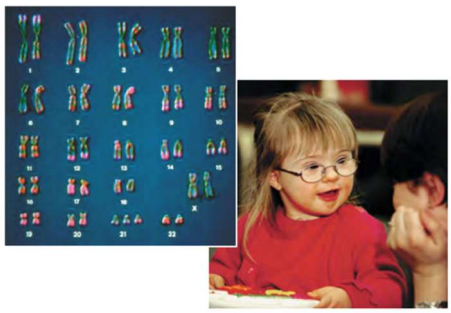


Figure 28. Down syndrome. The karyotype shows trisomy 21, the most common cause of Down syndrome. The child exhibits the facial features characteristic of this disorder.

Aneuploidy of Sex Chromosomes:

Nondisjunction of Sex Chromosomes involving the sex chromosomes can produce a variety of aneuploid conditions.

An extra X chromosome in males, resulting in the XXY genotype, occurs in about one out of every 500 to 1,000 live male births. Individuals with this disorder, known as Klinefelter syndrome, have male sex organs, but the testes are abnormally small, and the individual is sterile.

Females with trisomy X (XXX), which occurs in about one out of every 1,000 live female births, are generally healthy and show no unusual physical features other than being slightly taller than average. They may have a slightly increased risk of learning difficulties but remain fertile.

The monosomy of the X chromosome known as Turner syndrome (Monosomy X) occurs in about one out of every 2,500 female births and is the only known monosomy that is viable in humans.

Individuals with this condition have the genotype XO and are female, but their sex organs do not mature, leaving them sterile. They are typically treated with estrogen replacement therapy, and most have normal intelligence.

Disorders Caused by Structurally Altered Chromosomes:

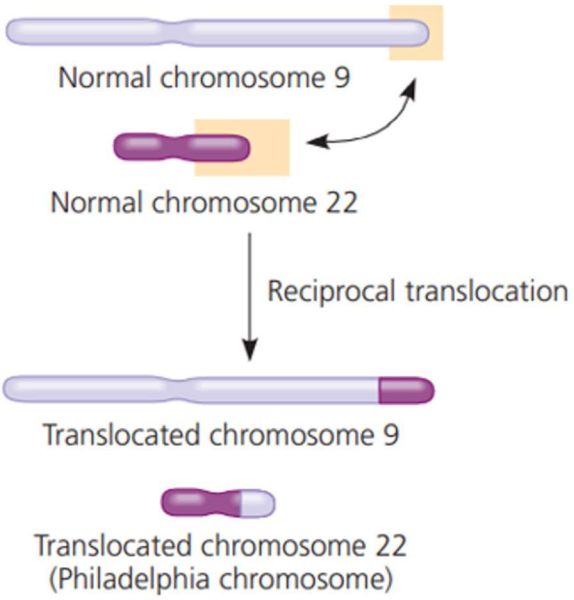


Figure 29. Translocation associated with chronic myelogenous leukemia (CML). The cancerous cells in nearly all CML patients contain an abnormally short chromosome 22, the so-called Philadelphia chromosome, and an abnormally long chromosome 9. These altered chromosomes result from the reciprocal translocation shown here, which presumably occurred in a single white blood cell precursor undergoing mitosis and was then passed along to all descendant cells.

Some Inheritance Patterns are Exceptions to Standard Mendelian Inheritance

We will now describe two natural exceptions to Mendelian inheritance one involving genes located in the nucleus, and the other involving genes found outside the nucleus. In both cases, the sex of the parent contributing the allele plays a significant role in determining the pattern of inheritance.

1. Genomic Imprinting

A difference in phenotypic expression depending on whether an allele is inherited from the male or female parent is called genomic imprinting. (Unlike sex-linked genes, most imprinted genes are located on autosomes.)

Genomic imprinting occurs during gamete formation and results in the silencing of a

specific allele of certain genes. Because these genes are imprinted differently in sperm and eggs, the zygote expresses only one allele of an imprinted gene either the maternal or the paternal allele.

These imprints are maintained and transmitted to all body cells during development.

In each generation, the old imprints are erased in the cells that produce gametes, and the newly forming gametes are imprinted according to the sex of the individual producing them.

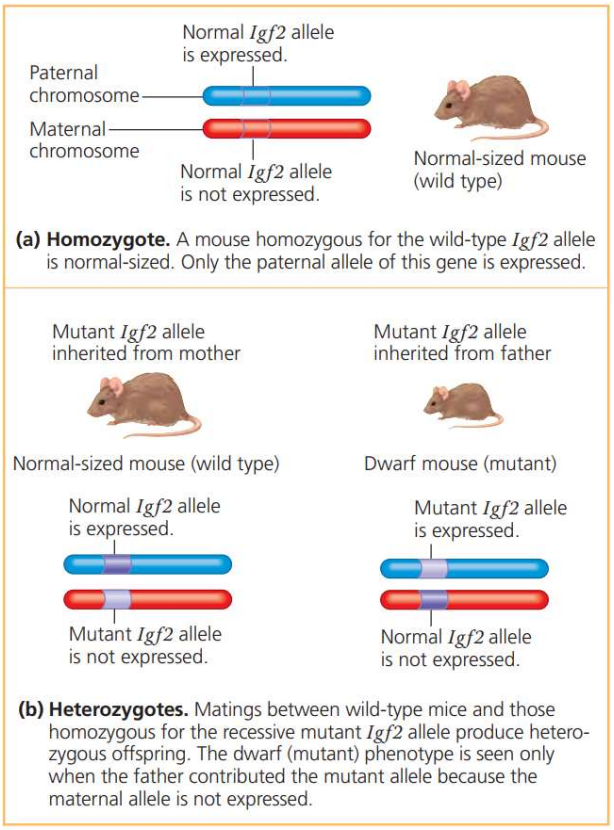


Figure 30. Illustration of Genomic Imprinting During Gamete Formation in Mice, Specifically Involving the Insulin-like Growth Factor 2 (Igf2) Gene

2. Inheritance of Organelle Genes

Not all a eukaryotic cell's genes are located on the chromosomes within the nucleus; some genes reside in organelles within the cytoplasm.

Because they are located outside the nucleus, these genes are referred to as extranuclear genes or cytoplasmic genes.

The mitochondria, as well as chloroplasts and other plant plastids, contain small circular DNA molecules that carry several genes. These organelles replicate independently and transmit their genes to daughter organelles.

The inheritance of organelle genes does not follow Mendelian principles, since their distribution to offspring is not governed by the same mechanisms that control the segregation of nuclear chromosomes during meiosis.

Exercises

Exercise 1	تدريب ١
Which of the following statements defines a genome?	**أي من العبارات التالية يصف الجينوم؟**
A) the complete set of an organism's polypeptides B) the complete set of a species' polypeptides C) a karyotype D) the complete set of an organism's genes and other DNA sequences	A) المجموعة الكاملة من عديد الببتيدات في الكائن الحي B) المجموعة الكاملة من عديد الببتيدات للأنواع C) النمط النووي D) المجموعة الكاملة لجينات الكائن الحي وتسلسلات الحمض النووي الأخرى
Exercise 2	**تدريب ٢**
Quaking aspen trees can send out underground stems for asexual reproduction. Sexual reproduction is not as common, but when it does happen, the haploid gametes have 19 chromosomes. How many chromosomes are in the cells of the underground stems?	**يمكن لأشجار الحور الرجراج المهتزة إرسال سيقان تحت الأرض للتكاثر اللاجنسي. التكاثر الجنسي ليس شائعًا، ولكن عندما يحدث، فإن الأمشاج أحادية العدد تحتوي على ١٩ كروموسومًا. كم عدد الكروموسومات الموجودة في خلايا السيقان تحت الأرض؟**
A) 9 B) 10 C) 19 D) 38	A) ٩ B) ١٠ C) ١٩ D) ٣٨
Exercise 3	**تدريب ٣**

Which of the following statements is true of a species that has a chromosome number of 2n = 16?	أي من العبارات التالية ينطبق على الأنواع التي لها عدد كروموسوم 2n=16؟
A) The species is diploid with 32 chromosomes per cell. B) The species has 16 sets of chromosomes per cell. C) Each diploid cell has eight homologous pairs of chromosomes. D) A gamete from this species has four chromosomes.	A) الأنواع ثنائية الصبغيات مع ٣٢ كروموسوم لكل خلية. B) تحتوي الأنواع على ١٦ مجموعة من الكروموسومات لكل خلية. C) تحتوي كل خلية ثنائية الصبغيات على ثمانية أزواج من الكروموسومات المتماثلة. D) تحتوي الأمشاج من هذا النوع على أربعة كروموسومات.

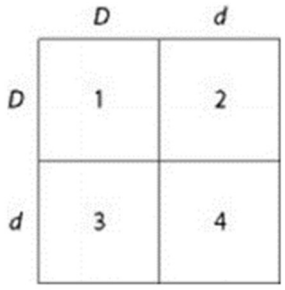
Exercise 4	تدريب ٤
Which of the following characteristics do homologous chromosomes exhibit?	**أي من الخصائص التالية تنطبق على الكروموسومات المتماثلة؟**
A) They carry information for different traits. B) They carry information for the same traits. C) They carry the same alleles. D) They align on the metaphase plate in meiosis II.	A) أنها تحمل معلومات عن صفات مختلفة. B) تحمل معلومات لنفس الصفات. C) أنها تحمل نفس الأليلات. D) تصطف على خط الاستواء في الطور الاستوائي في الانقسام المنصف II.

Exercise 5	تدريب ٥
Somatic cells of roundworms have four individual chromosomes per cell. How many chromosomes would you expect to find in an ovum from a roundworm?	**تحتوي الخلايا الجسدية للديدان المستديرة على أربعة كروموسومات فردية لكل خلية. كم عدد الكروموسومات التي تتوقع أن تجدها في بويضة من دودة أسطوانية؟**
A) four B) two C) eight D) a diploid number	A) أربعة B) اثنان C) ثمانية D) عدد مضاعف

Exercise 6	تدريب ٦
The bulldog ant has a diploid number of two chromosomes. Therefore, following meiosis, each daughter cell will have a single chromosome. In addition to mutations, how might genetic diversity be generated in this species?	**نملة البلدغ لديها عدد ثنائي المجموعة الكروموسومية من اثنين من الكروموسومات. لذلك، بعد الانقسام المنصف، سيكون لكل خلية بنوية كروموسوم واحد. بالإضافة إلى الطفرات، كيف يمكن أن يتولد التنوع الجيني في هذا النوع؟**
A) crossing over only B) independent assortment only C) crossing over and random fertilization	A) العبور الوراثي فقط B) التوزيع الحر فقط C) العبور الوراثي والإخصاب العشوائي
Exercise 7	**تدريب ٧**
Imagine that there are 25 different species of protists living in a tide pool. Some of these species reproduce both sexually and asexually, and some of them can reproduce only asexually. The pool gradually becomes infested with disease-causing viruses and bacteria. Which species are more likely to thrive in the changing environment?	**تخيل أن هناك ٢٥ نوعًا مختلفًا من الطلائعيات تعيش في بركة المد والجزر. تتكاثر بعض هذه الأنواع على حد سواء جنسيًا ولا جنسيًا، ويمكن لبعضها التكاثر اللاجنسي فقط. يصاب البركة تدريجيًا بالفيروسات والبكتيريا المسببة للأمراض. ما هي الأنواع التي من المرجح أن تزدهر في البيئة المتغيرة؟**
A) The sexually reproducing species is likely to thrive. B) The asexually reproducing species is likely to thrive. C) Sexually and asexually reproducing species are equally likely to thrive. D) Neither species will be able to thrive.	A) من المرجح أن تزدهر الأنواع التي تتكاثر جنسيًا. B) من المرجح أن تزدهر الأنواع التي تتكاثر لاجنسيًا. C) من المرجح أن تزدهر الأنواع التي تتكاثر جنسيًا ولاجنسيًا. D) لن يتمكن أي نوع من الازدهار.

تدريب ٨	Exercise 8
أيٌّ من العمليات التالية قد ينتج عنه زيجوت بشري يحتوي على ٤٥ كروموسومًا؟	Which of the following processes might produce a human zygote with 45 chromosomes?
A) خطأ في الطور الانفصالي في الانقسام المتساوي يحدث في البويضة أو الحيوانات المنوية B) فشل نواة البويضة في تخصيب الحيوانات المنوية C فشل البويضة في استكمال الانقسام المنصف II D) انقسام السيتوبلازم غير المكتمل أثناء تكوين الحيوانات المنوية بعد الانقسام المنصف I	A) an error in meiotic anaphase occurring in either an egg or sperm B) failure of the egg nucleus to be fertilized by the sperm C) failure of an egg to complete meiosis II D) incomplete cytokinesis during spermatogenesis after meiosis I

تدريب ٩	Exercise 9
يمكن للفرد ذي النمط الجيني AaBbCCDdEE أن يصنع أنواعًا كثيرة من الأمشاج. أي مما يلي يصف بشكل صحيح سبب احتمال حدوث هذا الموقف؟	The individual with genotype AaBbCCDdEE can make many kinds of gametes. Which of the following correctly describes why this situation is possible?
A) الطفرات المتكررة تشكل أليلات جديدة B) العبور خلال الطور الأول يؤدي إلى التنوع الجيني C) يحدث توزيع مختلف محتمل من الكروموسومات في الأمشاج D) هناك ميل للأليلات السائدة للانفصال معًا	A) recurrent mutations form new alleles B) crossing over during prophase I lead to genetic variety C) different possible assortment of chromosomes into gametes occurs D) there is a tendency for dominant alleles to segregate together
تدريب ١٠	Exercise 10
يحتوي الحيوان الذي يتكاثر جنسيًا على جينين غير مرتبطين، أحدهما لشكل الرأس (H) والآخر لطول الذيل (T). التركيب الوراثي له هو HhTt. أي من الأنماط الجينية التالية ممكن ان تتكون في مشيج من هذا الكائن الحي؟	A sexually reproducing animal has two unlinked genes, one for head shape (H) and one for tail length (T). Its genotype is HhTt. Which of the following genotypes is possible in a gamete from this organism?
Hh (A	A) Hh

B) HhTt C) T D) HT	HhTt (B T (C HT (D
Exercise 11	**تدريب ١١**
Use the figure and the following description to answer the question. In a particular plant, leaf color is controlled by gene locus D. Plants with at least one allele D have dark green leaves, and plants with the homozygous recessive dd genotype have light green leaves. A true-breeding, dark-leaved plant is crossed with a light-leaved one, and the F1 offspring is allowed to self-pollinate. The predicted outcome of the F2 is diagrammed in the Punnett square shown in the figure, where 1, 2, 3, and 4 represent the genotypes corresponding to each box within the square **Which of the boxes in the Punnett square correspond to plants that will be true-breeding?** .	**استخدم الشكل والوصف التالي للإجابة على السؤال. في نبات معين، يتم التحكم في لون الورقة عن طريق موضع الجين D. النباتات ذات الأليل D واحد على الأقل لها أوراق خضراء داكنة، والنباتات ذات التركيب الوراثي المتماثل dd المتماثل لها أوراق خضراء فاتحة. يتم تهجين النبات الحقيقي التكاثر ذو الأوراق الداكنة بنبات فاتح الأوراق، ويسمح للنسل F1 بالتلقيح الذاتي. يتم رسم النتيجة المتوقعة لـ F2 في مربع Punnett الموضح في الشكل، حيث تمثل ١ و٢ و٣ و٤ الأنماط الجينية المقابلة لكل خلية داخل المربع.** **أي من الخلايا في المربع تتوافق مع النباتات التي ستكون نقية؟**
	
A) 1 and 4 only	A) 1 و 4 فقط

B) 2 and 3 only C) 1, 2, 3, and 4 D) 1 only	B) 2 و 3 فقط C) 1 و 2 و 3و 4 D) 1 فقط
Exercise 12	**تدريب ١٢**
Skin color in a certain species of fish is inherited by a single gene with four different alleles. How many different types of gametes would be possible in this organism?	**يُورث لون الجلد في نوع معين من الأسماك بواسطة جين واحد له أربعة أليلات مختلفة. كم عدد الأنواع المختلفة من الأمشاج الممكنة في هذا الكائن الحي؟**
A) 2 B) 4 C) 8 D) 16	A) ٢ B) ٤ C) ٨ D) ١٦
Exercise 13	**تدريب ١٣**
Albinism is a recessive trait. A man and woman both show normal pigmentation, but both have one parent who has albinism (without melanin pigmentation). What is the probability that their first child will have albinism?	**المهاق هو صفة متنحية. يظهر كل من الرجل والمرأة لوناً طبيعيًا، لكن كلاهما لديه أحد الوالدين مصاب بالمهاق (بدون صبغة الميلانين). ما هو احتمال إصابة طفلهم الأول بالمهاق؟**
A) 0 B) 1/2 C) 1/4 D) 1	A) ٠ B) ١/٢ C) ١/٤ D) ١
Exercise 14	**تدريب ١٤**
Black fur in mice (B) is dominant to brown fur (b). Short tails (T) are dominant to long tails (t). What fraction of the progeny of	**فراء الأسود في الفئران (B) هو السائد على الفراء البني (b). الذيول القصيرة (T) هي المسيطرة على ذيول طويلة (t). ما هو الاحتمال من ذرية التزاوج**

crosses BbTt × BBtt will be expected to have black fur and long tails?	BbTt × BBtt المتوقع أن يكون له فرو أسـود وذيول طويلة؟
A) 1/16 B) 3/8 C) 1/2 D) 9/16	A) ١٦/١ B) ٨/٣ C) ٢/١ D) ١٦/٩
Exercise 15	تدريب ١٥
In pea plants, the tall phenotype is dominant to the dwarf phenotype. If a heterozygous pea plant is crossed with a homozygous tall pea plant, what is the probability that the offspring will be dwarf?	في نباتات البازلاء، فإن النمط المظهري الطويل هو السـائد على النمط المظهري القصـير. إذا تم عبور نبات البازلاء متغاير الزيجوت مع نبات البازلاء طويل القامة متماثل الزيجوت، فما هو احتمال أن يكون النسل قصيراً في الحجم؟
A) 1 B) 1/2 C) 1/4 D) 0	A) ١ B) ٢/١ C) ٤/١ D) ٠
Exercise 16	تدريب ١٦
Two true-breeding stocks of pea plants are crossed. One parent has red, axial flowers, and the other has white, terminal flowers; all F1 individuals have red, axial flowers. The genes for flower color and location assort independently. Among the F2 offspring, what is the probability of producing plants with white axial flowers?	تم تهجين اثنين من نباتات البازلاء ذات صـفات نقية. أحد الوالدين لديه أزهار حمراء وجانبية، والآخر لديه أزهار بيضـاء طرفية؛ جميع أفراد F1 لـديهم أزهار حمراء وجانبية. جينات لون الزهرة وموقعها تصـنف بشـكل مسـتقل. من بين النسـل F2، ما هو احتمال إنتاج نباتات ذات أزهار بيضاء جانبية؟
A) 9/16 B) 1/16 C) 3/16 D) 1/4	A) ١٦/٩ B) ١٦/١ C) ١٦/٣ D) ٤/١

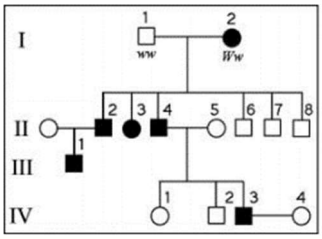
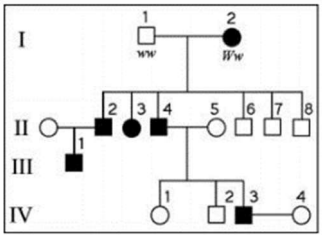
تدريب ١٧	Exercise 17
تزرع نباتات الكوبية التي لها نفس الطراز الجيني في حديقة زهور كبيرة. تنتج بعض النباتات أزهارًا زرقاء وأخرى زهرية وردية. يمكن تفسير ذلك بشكل أفضل من خلال أي مما يلي؟	**Hydrangea plants of the same genotype are planted in a large flower garden. Some of the plants produce blue flowers and others pink flowers. This can be best explained by which of the following?**
A) معرفة أن أليلات عديدة مسؤولة عن ذلك B) أليل الكوبية الزرقاء هو السائد تمامًا على أليل الكوبية الوردية C) الأليلات ذات سيادة مشتركة D) العوامل البيئية مثل درجة حموضة التربة تؤثر على الطراز المظهري	A) the knowledge that multiple alleles are involved B) the allele for blue hydrangea is completely dominant over the allele for pink hydrangea C) the alleles are codominant D) environmental factors such as soil pH affect the phenotype
تدريب ١٨	Exercise 18
قد تكون زهور الفجل حمراء أو أرجوانية أو بيضاء. ينتج عن التهجين بين نبات مزهر باللون الأحمر ونبات أبيض اللون نسلًا أرجوانيًا بالكامل. سمة لون الزهرة في الفجل هي مثال على أي من أنماط الوراثة التالية؟	**Radish flowers may be red, purple, or white. A cross between a red-flowered plant and a white-flowered plant yields all-purple offspring. The flower color trait in radishes is an example of which of the following inheritance patterns?**
A) نظام تعدد الأليلات B) مرتبطة بالجنس C) السيادة المشتركة D) السيادة غير التامة	A) a multiple alleles system B) sex linkage C) codominance D) incomplete dominance

تدريب ١٩	Exercise 19

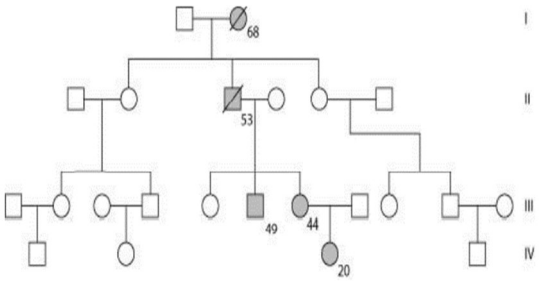
شيخوخة هاتشينسون جيلفورد هو اضطراب وراثي بشري نادر للغاية حيث يوجد شيخوخة مبكرة جدًا وموت، عادةً بسبب مرض الشريان التاجي، بمتوسط عمر ١٣ عامًا. المرضى، الذين يبدون كبارًا جدًا حتى وهم أطفال، لا يعيشون للتكاثر. أي من العبارات التالية يمثل الافتراض الأكثر احتمالًا بخصوص هذا الاضطراب؟	Hutchinson-Gilford progeria is an exceedingly rare human genetic disorder in which there is very early senility and death, usually from coronary artery disease, at an average age of 13 years. Patients, who look very old even as children, do not live to reproduce. Which of the following statements represents the most likely assumption regarding this disorder?
A) المرض سائد و يحمل على الكروموسومات الجسمية. B) سيزداد الاضطراب في التكرار في الأجيال المتعاقبة داخل الأسرة. C) قد يكون الاضطراب ناتجًا عن طفرة في جين واحد لتشفير البروتين. D) سيكون لكل مريض جد أو والد واحد مصاب على الأقل.	A) The disease is autosomal dominant. B) The disorder will increase in frequency in successive generations within a family. C) The disorder may be due to mutation in a single protein-coding gene. D) Each patient will have had at least one affected grandparent or parent
تدريب ٢٠	Exercise 20
تم تحديد لون الريش في الببغاء بواسطة جينين مختلفين، Y للصبغة على السطح الخارجي للريش، وB للصبغة من الداخل من الريش. YYBB أو YyBB أو YYBb أخضر ؛ yyBB أو yyBb أزرق ؛ YYbb أو Yybb أصفر ؛ و yybb أبيض. تم تزاوج اثنين من الببغاء الأزرق. على مر السنين، أنجبوا ٢٢ نسلاً، خمسة منهم من البيض. ما هي الأنماط الجينية الأكثر احتمالا للببغاء الأزرق؟	Feather color in budgies is determined by two different genes, Y for pigment on the outside of the feather, and B for pigment on the inside of the feather. YYBB, YyBB, or YYBb is green; yyBB or yyBb is blue; YYbb or Yybb is yellow; and yybb is white. Two blue budgies were crossed. Over the years, they produced 22 offspring, five of which were white. What are the most likely genotypes for the two blue budgies?
A) yyBB و YyBB B) yyBB و yyBb C) yyBb و yyBb D) yyBb و yybb	A) yyBB and yyBB B) yyBB and yyBb C) yyBb and yyBb D) yyBb and yybb
تدريب ٢١	Exercise 21

تحدث متلازمة مارفان عند البشر بسبب خلل في بروتين النسيج الضام الليفي. عادة ما يكون المرضى طويلين ونحيفين للغاية، وأصابع طويلة مغزلية، وانحناء العمود الفقري، وأحيانًا ضعف جدران الشرايين، وأحيانًا مشاكل في العين، مثل تحرك العدسة. أي مما يلي يمكن أن تستنتجه بشأن متلازمة مارفان من هذه المعلومات؟	Marfan syndrome in humans is caused by an abnormality of the connective tissue protein fibrillin. Patients are usually very tall and thin, with long spindly fingers, curvature of the spine, sometimes weakened arterial walls, and sometimes eye problems, such as lens dislocation. Which of the following would you conclude about Marfan syndrome from this information?
A) إنها متنحية. ب) إنها سائدة. ج) انه متعدد الأشكال. د) إنه تفوق الجينات.	A) It is recessive. B) It is dominant. C) It is pleiotropic. D) It is epistatic.

تدريب ٢٢	Exercise 22
ظهور الفينيل كيتون مع البول (PKU) هي اضطراب بشري متنحي حيث لا يستطيع الفرد استقلاب الحمض الأميني فينيل ألانين بشكل مناسب. لا ينتج الإنسان هذا الحمض الأميني بشكل طبيعي. أي من العلاجات التالية سيكون أكثر فاعلية للأشخاص المصابين بهذا الاضطراب؟	Phenylketonuria (PKU) is a recessive human disorder in which an individual cannot appropriately metabolize the amino acid phenylalanine. This amino acid is not naturally produced by humans. Which of the following treatments would be most effective for people with PKU?
A) إطعامهم الركيزة التي يمكن استقلابها الى فينيل ألانين. B) تنظيم النظام الغذائي للأشخاص المصابين للحد بشدة من امتصاص الفينيل ألانين. C) تغذية المرضى بالأنزيمات المفقودة في دورة منتظمة مثل مرتين في الأسبوع. D) أطعم المرضى كمية زائدة من المنتج المفقود.	A) Feed them the substrate that can be metabolized into phenylalanine. B) Regulate the diet of the affected persons to severely limit the uptake of phenylalanine. C) Feed the patients the missing enzymes in a regular cycle, such as twice per week. D) Feed the patients an excess of the missing product.

تدريب ٢٣	**Exercise 23**
يشير السؤال التالي إلى مخطط النسب في الشكل الخاص بالعائلة، يُظهر بعض أفرادها الصفة السائدة، ويشار إلى الأفراد المتأثرين بمربع أو دائرة داكنة. ما هو النمط الجيني للفرد II-5	The following question refers to the pedigree chart in the figure for a family, some of whose members exhibit the dominant trait, W. Affected individuals are indicated by a dark square or circle. What is the genotype of individual II-5
	
ww (A Ww (B WW (C ww or Ww (D	A) ww B) Ww C) WW D) ww or Ww
تدريب ٢٤	**Exercise 24**
يشير السؤال التالي إلى مخطط النسب في الشكل الخاص بالعائلة، يُظهر بعض أفرادها الصفة السائدة، ويشار إلى الأفراد المتأثرين بمربع أو دائرة داكنة. ما هو احتمال أن يكون الفرد III-1 هو Ww؟	The following question refers to the pedigree chart in the figure for a family, some of whose members exhibit the dominant trait, W. Affected individuals are indicated by a dark square or circle. What is the probability that individual III-1 is Ww?
	
3/4 (A	A) 3/4

1/4 (B	B) 1/4
2/4 (C	C) 2/4
1 (D	D) 1

تدريب ٢٥	Exercise 25
وضح الشكل نسب العائلة. تمثل الرموز المظللة الأشخاص المصابين بأحد النوعين الرئيسيين من سرطان القولون. الأرقام تحت الرموز هي عمر الفرد وقت التشخيص. يتم تمثيل الذكور بالمربعات والإناث بالدوائر. من مخطط السلالة هذا ا، يبدو أن هذه السمة موروثة:	The figure shows the pedigree for a family. Dark-shaded symbols represent individuals with one of the two major types of colon cancer. Numbers under the symbols are the individual's age at the time of diagnosis. Males are represented by squares, females by circles. From this pedigree, this trait seems to be inherited:
	
A) من الأمهات B) صفة متنحية محمولة على الكروموسومات الجسدية C) نتيجة تفوق الجينات D) كصفة سائدة محمولة على الكروموسومات الجسدية	A) from mothers B) as an autosomal recessive C) as a result of epistasis D) as an autosomal dominant

تدريب ٢٦	**Exercise 26**
أي من العبارات التالية يعد تفسيرًا صحيحًا للملاحظة التي تفيد بأن جميع النسل يظهر طراز مظهري لصفة معينة يبدو أنها مزيج من الصنفين الأبويين؟	**Which of the following statements is a correct explanation for the observation that all offspring exhibit a phenotype for a particular trait that appears to be a blend of the two parental varieties?**
A) لا يسود أي من الجينات الأبوية على الآخر. B) تكون جينات السمة سائدة في كلا الوالدين. C) ترتبط الجينات ولا تنفصل أثناء الانقسام المنصف. D) جينات السمة متنحية في كلا الوالدين.	A) Neither of the parental genes is dominant over the other. B) The genes for the trait are dominant in both of the parents. C) The genes are linked and do not separate during meiosis. D) The genes for the trait are recessive in both of the parents.
تدريب ٢٧	**Exercise 27**
عمى الألوان الأحمر والأخضر هو صفة متنحية مرتبطة بالجنس في البشر. شخصان يتمتعان برؤية ألوان طبيعية لديهما ابن مصاب بعمى الألوان. ما هي الطرز الجينية لكل من الأب والأم؟	**Red-green color blindness is a sex-linked recessive trait in humans. Two people with normal color vision have a color-blind son. What are the genotypes of the parents?**
A) X^nY and X^nX^n B) X^nY and X^NX^N C) X^NY and X^NX^N D) X^NY and X^NX^n	A) X^nY and X^nXn B) X^nY and X^NX^N C) X^NY and X^NX^N D) X^NY and X^NX^n

تدريب ٢٨	Exercise 28
بشكل عام، القطط الإناث فقط لديها النمط المظهري للتبقع في لون الفراء. أي من العبارات التالية يفسر هذه الظاهرة؟	**Generally, only female cats have the tortoiseshell phenotype for fur color. Which of the following statements explains this phenomenon?**
A) يرث الذكر أليلًا واحدًا فقط من الجين المرتبط بـ X الذي يتحكم في لون الشعر. B) يحتوي الكروموسوم Y على جين يحجب اللون البرتقالي. C) فقط الذكور يمكنهم الحصول على أجسام بار. D) عمليات الانتقال المتعددة على الكروموسوم Y تمنع إنتاج الصبغة البرتقالية.	A) A male inherits only one allele of the X-linked gene controlling hair color. B) The Y chromosome has a gene blocking orange coloration. C) Only males can have Barr bodies. D) Multiple crossovers on the Y chromosome prevent orange pigment production.
تدريب ٢٩	**Exercise 29**
في البشر، لا يحدث التمايز الواضح بين الجنسين عند الإخصاب، ولكن بعد الشهر الثاني من الحمل. أي من العبارات التالية يصف الحدث الأول لهذا التمايز؟	**In humans, clear gender differentiation occurs not at fertilization, but after the second month of gestation. Which of the following statements describes the first event of this differentiation?**
A) تكوين هرمون التستوستيرون في الأجنة الذكور B) تكوين هرمون الأستروجين في الأجنة الأنثوية C) تفعيل SRY في أجنة الذكور وتذكير الغدد التناسلية D) تفعيل SRY في الإناث وتأنيث الغدد التناسلية	A) formation of testosterone in male embryos B) formation of estrogens in female embryos C) activation of SRY in male embryos and masculinization of the gonads D) activation of SRY in females and feminization of the gonads

تدريب ٣٠	Exercise 30
الضعف العضلي المدمر هو اضطراب بشري يسبب التدهور التدريجي للعضلات. يتأثر الأولاد فقط، وهم يولدون دائمًا لأبوين عاديين ظاهريًا. بسبب شدة المرض يموت الأولاد في سن المراهقة. هل من المحتمل أن يكون سبب هذا الاضطراب هو أليل سائد أو متنحي؟ هل وراثة هذه السمة مرتبطة بالجنس أم الكروموسومات الجسمية؟	Pseudohypertrophic muscular dystrophy is a human disorder that causes gradual deterioration of the muscles. Only boys are affected, and they are always born to phenotypically normal parents. Due to the severity of the disease, the boys die in their teens. Is this disorder likely to be caused by a dominant or recessive allele? Is the inheritance of this trait sex-linked or autosomal?
A) سائد ، مرتبط بالجنس B) متنحية ، على الكروموسومات الجسمية C) متنحية ، مرتبطة بالجنس D) سيادة غير تامة ، المرتبط بالجنس	A) dominant, sex-linked B) recessive, autosomal C) recessive, sex-linked D) incomplete dominant, sex-linked

تدريب ٣١	Exercise 31
أي من الأفراد التاليين سيرث الأليل المرتبط بـ X من رجل يحمله؟	Which of the following individuals will inherit an X-linked allele from a man who carries it?
A) جميع بناته الإناث B) نصف بناته C) جميع أبنائه الذكور D) كل أبنائه الذكور والإناث	A) all of his daughters B) half of his daughters C) all of his sons D) all of his children

تدريب ٣٢	Exercise 32
يُورث نقص انزيم (G6PD) كأليل متنحي مرتبط بالكروموسوم X في البشر. تتزوج امرأة عانى والدها من G6PD برجل عادي. ما هي نسبة أبنائهم المتوقع أن يكونوا G6PD؟	Glucose-6-phosphate dehydrogenase deficiency (G6PD) is inherited as an X-linked recessive allele in humans. A woman whose father suffered from G6PD marries a normal man. What proportion of their sons is expected to be G6PD?

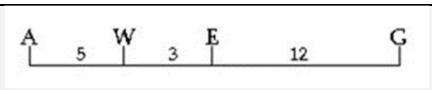
A) ١٠٠٪	A) 100%
B) ١/٤	B) 1/4
C) ١/٢	C) 1/2
D) صفر	D) zero

تدريب ٣٣	Exercise33
استخدم المعلومات التالية للإجابة على السؤال:	Use the following information to answer the question:

Sex	Phenotype	Number
male	wild	123
male	yellow	116
female	wild	240

في تجربة ذبابة الفاكهة، تم عمل تهجين بين إناث متماثلة الجينات من النوع البري والذكور أصفر الجسم. كانت جميع F1s الناتجة من النوع البري المظهر. ومع ذلك، فإن الذباب البالغ من الجيل F2 (الناتج عن تزاوج F1s) كان له الخصائص الموضحة في الشكل. كيف يتم توريث الأليل المتطفر للجسم الأصفر؟	In a Drosophila experiment, a cross was made between homozygous wild-type females and yellow-bodied males. All the resulting F1s were phenotypically wild type. However, adult flies of the F2 generation (resulting from mating of the F1s) had the characteristics shown in the figure. How is the mutant allele for yellow body inherited?
A) إنها متنحية.	A) It is recessive.
B) هو السائد.	B) It is codominant.
C) إنها المهيمنة.	C) It is dominant.
D) أنها مهيمنة بشكل غير كامل.	D) It is incompletely dominant.

تدريب ٣٤	Exercise 34
- استخدم الخريطة التالية لأربعة جينات على الكروموسوم للإجابة على السؤال. بين أي جينين تتوقع أعلى تكرار لإعادة التركيب؟	Use the following map of four genes on a chromosome to answer the question. Between which two genes would you expect the highest frequency of recombination?

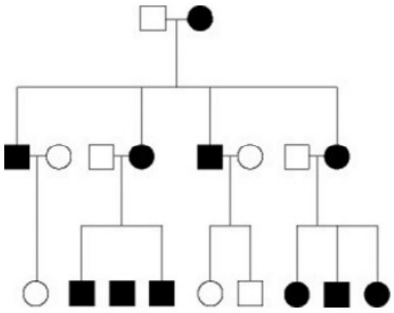


A) A and W B) E and G C) A and E D) A and G	A and W (A E and G (B A and E (C A and G (D
Exercise 35	**تدريب ٣٥**
If cell X enters meiosis, and nondisjunction of one chromosome occurs in one of its daughter cells during meiosis II, how will this affect the gametes at the completion of meiosis?	**إذا دخلت الخلية X في الانقسام المنصف، ولم يحدث انفصال لكروموسوم واحد في إحدى خلاياها الوليدة أثناء الانقسام المنصف II، فكيف سيؤثر ذلك على الأمشاج عند اكتمال الانقسام المنصف؟**
A) All the gametes descended from cell X will be diploid. B) Half of the gametes descended from cell X will be n + 1, and half will be n - 1. C) One-quarter of the gametes descended from cell X will be n + 1, one-quarter will be n - 1, and half will be n. D) Two of the four gametes descended from cell X will be haploid, and two will be diploid.	A) ستكون جميع الأمشاج المنحدرة من الخلية X ثنائية العدد. B) نصف الأمشاج المنحدرة من الخلية X سيكون n + 1 ، والنصف الآخر سيكون n - 1. C) سيكون ربع الأمشاج المنحدرة من الخلية X n + 1 ، والربع سيكون n - 1 ، وسيكون النصف n. D) سيكون اثنان من الأمشاج الأربعة المنحدرة من الخلية X أحادي العدد ، واثنان سيكونان ثنائي العدد.

Exercise 36	**تدريب ٣٦**
Of the following human aneuploidies, which is the one that generally has the most severe impact on the health of the individual?	**من بين حالات اختلال الصيغة الصبغية البشرية التالية، ما هي تلك التي لها عمومًا التأثير الأشد على صحة الفرد؟**
A) 47, trisomy 21 B) 47, XXY	A) ٤٧ ، ثلاثة كروموسومات في الموقع ٢١ ب) ٤٧ ، XXY

ج) ٤٧ ، XXX	C) 47, XXX
د) ٤٥ ، X	D) 45, X
تدريب ٣٧	**Exercise 37**
كثيرا ما توجد الكروموسومات غير الطبيعية في الأورام الخبيثة. قد تؤدي أخطاء مثل عمليات النقل إلى وضع الجين بالقرب من مناطق التحكم الغير مناسبة له. أي من الأحداث التالية قد يحدث بعد ذلك لجعل السرطان أسوأ؟	**Abnormal chromosomes are frequently found in malignant tumors. Errors such as translocation may place a gene in close proximity to different control regions. Which of the following events might then occur to make the cancer worse?**
A) زيادة عدم الانفصال B) التعبير عن المنتجات الجينية غير الملائمة C) انخفاض في التردد الانقسامي D) فشل الخلايا السرطانية في التكاثر	A) an increase in nondisjunction B) expression of inappropriate gene products C) a decrease in mitotic frequency D) failure of the cancer cells to multiply
تدريب ٣٨	**Exercise 38**
تم العثور على امرأة لديها ٤٧ كروموسوم، تتضمن ثلاثة كروموسومات X. أي من العبارات التالية يصف الطراز المظهري المتوقع لها؟	**A woman is found to have 47 chromosomes, including three X chromosomes. Which of the following statements describes her expected phenotype?**
A) الأنثى ذات خصائص ذكورية مثل شعر الوجه B) ظاهر الذكر وهو عقيم C) أنثى صحية ذات طول أعلى بقليل من المتوسط D) انثى عقيمة	A) a female with masculine characteristics such as facial hair B) an apparent male who is sterile C) healthy female of slightly above-average height D) a sterile female

تدريب ٣٩	**Exercise 39**
استخدم الشكل التالي للإجابة على السؤال:	**Use the following figure to answer the question:**



يوضح مخطط السلالة في الشكل انتقال صفة في عائلة معينة. بناءً على نمط الانتقال هذا، تكون الصفة على الأرجح:	The pedigree in the figure shows the transmission of a trait in a particular family. Based on this pattern of transmission, the trait is most likely:
A) من جينات الميتوكندريا	A) mitochondrial
B) سائدة مرتبطة بالجنس	B) sex-linked dominant
C) متنحية مرتبطة بالجنس	C) sex-linked recessive
D) سائدة على الكروموسومات الجسمية	D) autosomal dominant
تدريب ٤٠	Exercise 40
يشارك الحمض النووي للميتوكندريا بشكل أساسي في تشفير البروتينات اللازمة لمعقد البروتين في سلسلة نقل الإلكترون وتصنيع ATP. لذلك، فإن الطفرات في جينات الميتوكندريا من شأنها أن تؤثر بشكل كبير على أي من العمليات التالية؟	Mitochondrial DNA is primarily involved in coding for proteins needed for protein complexes of the electron transport chain and ATP synthase. Therefore, mutations in mitochondrial genes would most affect which of the following processes?
A) تخليق الحمض النووي في خلايا جهاز المناعة	A) DNA synthesis in cells of the immune system
B) حركة الأكسجين إلى كريات الدم الحمراء	B) the movement of oxygen into erythrocytes
C) توليد ATP في خلايا العضلات	C) generation of ATP in muscle cells
D) تخزين البول في المثانة البولية	D) the storage of urine in the urinary bladder

Chapter Three

The Molecular Basic of Inheritance

نسمو NSMO
أولمبيـــاد العلوم والرياضيات الوطني

The Molecular Basic of Inheritance

DNA is the Genetic Material

Today, DNA has become familiar even to school students, and scientists routinely manipulate DNA in the laboratory. However, in the early twentieth century, identifying the molecules of inheritance posed a major challenge for biologists.

Evidence that DNA can Transform Bacteria

In 1928, a British medical officer named Frederick Griffith was attempting to develop a vaccine against pneumonia. He was studying *Streptococcus pneumoniae*, a bacterium that causes pneumonia in mammals. Griffith worked with two strains of the bacterium one pathogenic and the other nonpathogenic (harmless).

He was surprised to find that when he killed the pathogenic bacteria by heating and then mixed the remains with living cells of the nonpathogenic strain, some of the living cells became pathogenic (see figure). Moreover, this newly acquired trait the ability to cause disease was inherited by all the descendants of the transformed bacteria.

Apparently, some chemical component from the dead pathogenic cells caused this heritable change, although the identity of the substance was unknown. Griffith called this phenomenon **transformation**, which is now defined as a change in genotype and phenotype due to the assimilation of external DNA by a cell.

Later, scientists **Oswald Avery, Maclyn McCarty, and Colin MacLeod** identified the transforming substance as **DNA**. However, many scientists at the time remained skeptical because little was known about DNA.

Evidence that Viral DNA can Program Cells:

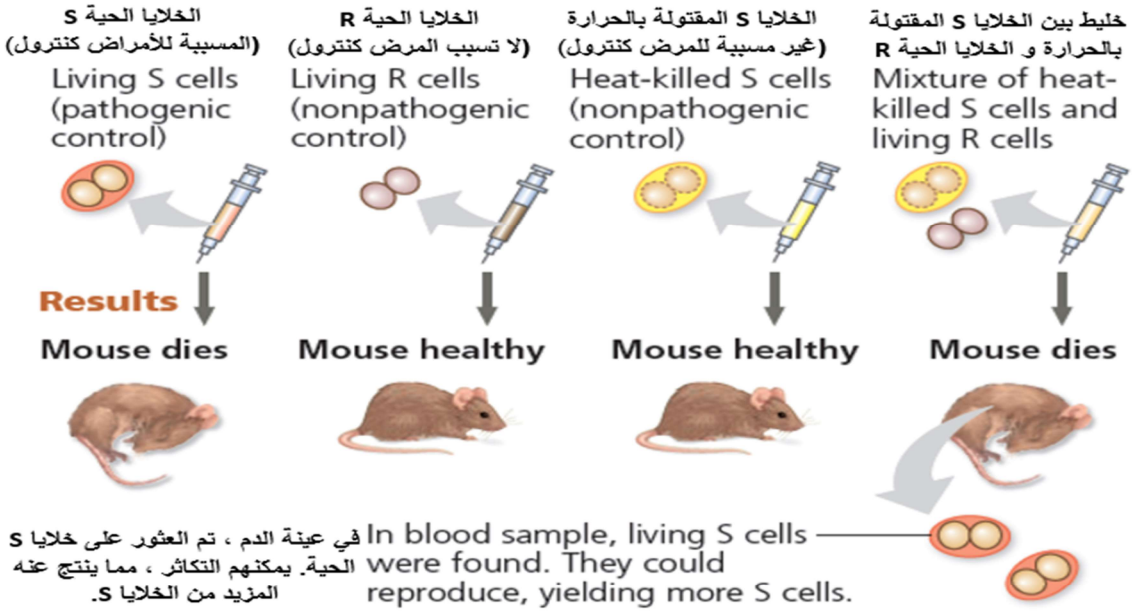
Additional evidence that DNA is the genetic material came from studies of viruses that infect bacteria (as shown in the figure).

استفسار: هل يمكن نقل صفة وراثية بين سلالات بكتيرية مختلفة؟

inquiry: Can a genetic trait be transferred between different bacterial strains?

التجربة: درس فريدريك جريفيث سلالتين من البكتيريا ***Streptococcus pneumoniae***. يمكن أن تسبب سلالة S (الملساء) الالتهاب الرئوي في الفئران ؛ وهي مسببة للأمراض لأن الخلايا لها كبسولة خارجية تحميها من الجهاز المناعي للحيوان. تفتقر خلايا السلالة R (الخشنة) إلى كبسولة وهي غير مسببة للأمراض. لاختبار سمة الإمراضية ، حقن جريفيث الفئران بالسلالتين.

Experiment: Frederick Griffith studied two strains of the bacterium ***Streptococcus pneumoniae***. The S (smooth) strain can cause pneumonia in mice; it is pathogenic because the cells have an outer capsule that protects them from an animal's immune system. Cells of the R (rough) strain lack a capsule and are nonpathogenic. To test for the trait of pathogenicity, Griffith injected mice with the two strains.



الخلاصة: تم تحويل بكتيريا R الحية إلى بكتيريا S ممرضة بواسطة مادة غير معروفة قابلة للتوريث من الخلايا S الميتة التي مكنت الخلايا R من صنع كبسولات.

Conclusion: The living R bacteria had been transformed into pathogenic S bacteria by an unknown, heritable substance from the dead S cells that enabled the R cells to make capsules. **(Figure 31)**

Additional Evidence that DNA is the Genetic Material

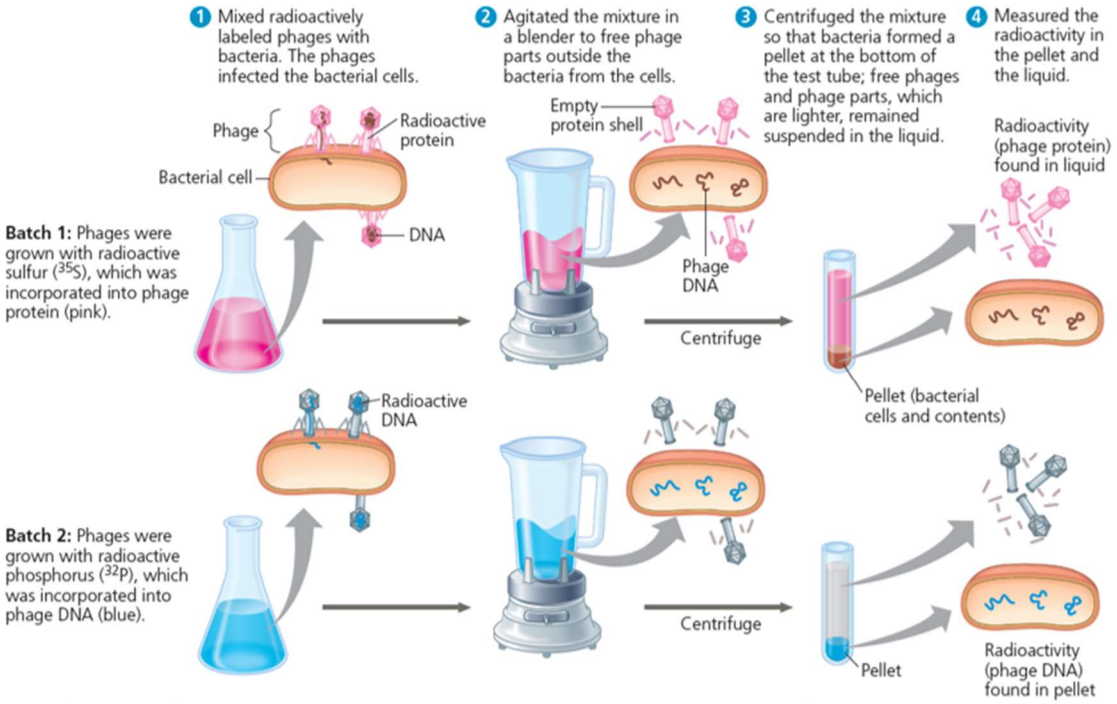
These viruses are called **bacteriophages** a term meaning "bacteria eaters" or simply

الاستفسار: هل البروتين أو الحمض النووي هو المادة الوراثية للفاج T2؟

inquiry: is protein or DNA the genetic material of phage T2?

التجربة: استخدم ألفريد هرشي ومارثا تشيس الكبريت المشع والفوسفور لتتبع مصير البروتين وDNA ، على التوالي ، لفاجات T2 التي أصابت الخلايا البكتيرية. لقد أرادوا معرفة أي من هذه الجزيئات يدخل الخلايا ويمكنهم إعادة برمجتها لإنتاج المزيد من الفاجات.

Experiment : Alfred Hershey and Martha Chase used radioactive sulfur and phosphorus to trace the fates of protein and DNA, respectively, of T2 phages that infected bacterial cells. They wanted to see which of these molecules entered the cells and could reprogram them to make more phages



النتائج: عندما تم تعليم البروتينات (العينة 1) ، ظل النشاط الإشعاعي خارج الخلايا ، ولكن عندما تم تعليم DNA (العينة 2) ، تم العثور على نشاط إشعاعي داخل الخلايا. أطلقت الخلايا التي تحتوي على DNA للفاجات المشعة فاجات جديدة مع بعض الفوسفور المشع.

Results: When proteins were labeled (batch 1), radioactivity remained outside the cells, but when DNA was labeled (batch 2), radioactivity was found inside the cells. Cells containing radioactive phage DNA released new phages with some radioactive phosphorus.

الخلاصة: دخلت DNA Phage الخلايا البكتيرية ، لكن بروتينات الفاجات لم تدخل. خلص هرشي وتشيس إلى أن DNA ، وليس البروتين ، يعمل كمادة وراثية للفاج T2..

Conclusion: Phage DNA entered bacterial cells, but phage proteins did not. Hershey and Chase concluded that DNA, not protein, functions as the genetic material of phage T2. (Figure 32)

phages for short.

Another line of evidence that DNA is the genetic material came from the laboratory of the biochemist Erwin Chargaff.

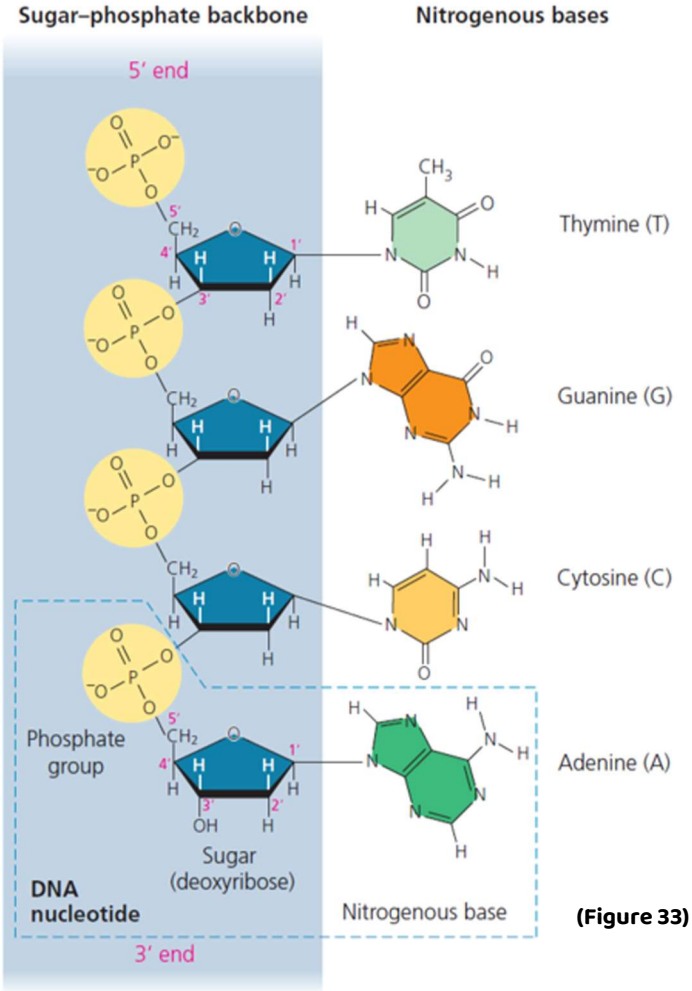
It was already known that DNA is a **polymer of nucleotides**, each consisting of three components: a **nitrogenous base**, a **pentose sugar called deoxyribose**, and a **phosphate group** (see figure).

The nitrogenous base can be **adenine (A)**, **thymine (T)**, **guanine (G)**, or **cytosine (C)**.

Chargaff analyzed the **base composition** of DNA from several different species and, in 1950, reported that the base composition of DNA varies from one species to another.

For example, he found that **32.8%** of the nucleotides in sea urchin DNA have base **A**, whereas **30.4%** of human DNA nucleotides have base **A**, and only **24.7%** of *E. coli* DNA nucleotides have base **A**.

The structure of a DNA strand. Each DNA nucleotide monomer consists of a nitrogenous base (T, A, C, or G), the sugar deoxyribose (blue), and a phosphate group (yellow). The phosphate group of one nucleotide is attached to the sugar of the next by a covalent bond, forming a "backbone" of alternating phosphates and sugars from which the bases project. A polynucleotide strand has directionality, from the 5′ end (with the phosphate group) to the 3′ end (with the ¬OH group of the sugar). 5′ and 3′ refer to the numbers assigned to the carbons in the sugar ring.



(Figure 33)

Chargaff's evidence for **molecular diversity among species** made DNA a strong candidate for the genetic material.

He also noted a remarkable regularity in the **ratios of nucleotide bases**: in the DNA of each species he studied, the number of **A** units equaled **T**, and the number of **G** units equaled **C**.

These two findings became known as **Chargaff's rules**:

1. The base composition of DNA varies between species.
2. Within a species, the percentages of **A** and **T** bases are roughly equal, as are those of **G** and **C**.

Building a structural model of DNA: Scientific Inquiry

Once most biologists were convinced that DNA is the genetic material, the challenge was to determine **how the structure of DNA could explain its role in inheritance**.

The helical nature of DNA was confirmed by the scientists **James Watson and Francis Crick**.

The pattern seen in this image indicated that the **helix consists of two strands**. DNA is shown in several of its various representations in the following figure.

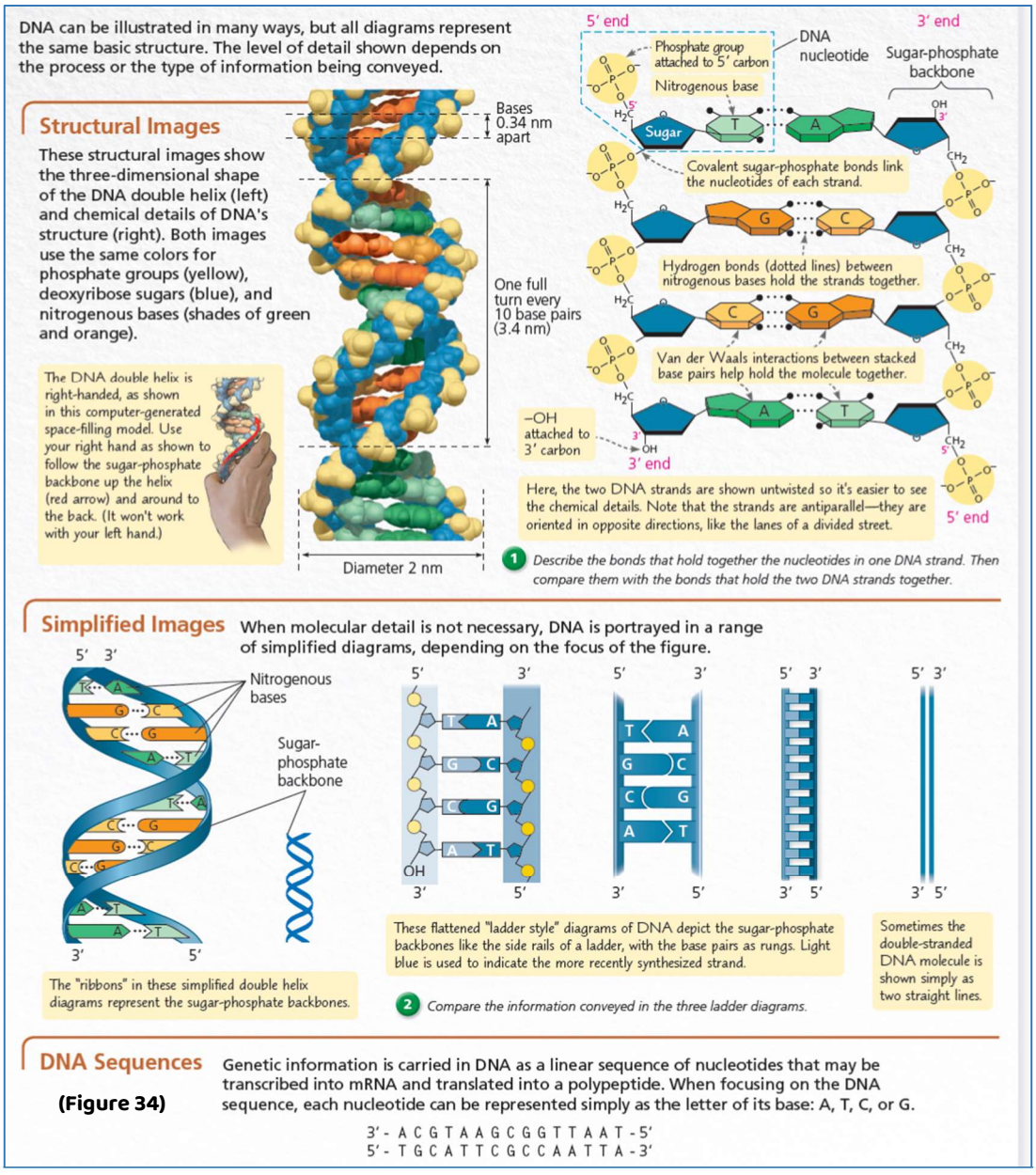
Franklin's arrangement was appealing because it placed the **negatively charged phosphate groups** facing the aqueous surroundings, while the **relatively hydrophobic nitrogenous bases** were tucked safely inside.

In this model, the two **sugar-phosphate backbones** are **antiparallel**, meaning their subunits run in **opposite directions**. You can picture the overall structure as a **rope ladder with rigid rungs**. The side ropes represent the sugar-phosphate backbones, and the rungs represent **pairs of nitrogenous bases**. Now imagine **twisting** the ladder to form a **helix**.

The nitrogenous bases in the double helix pair in specific combinations:

adenine (A) with **thymine (T)**, and **guanine (G)** with **cytosine (C)**.

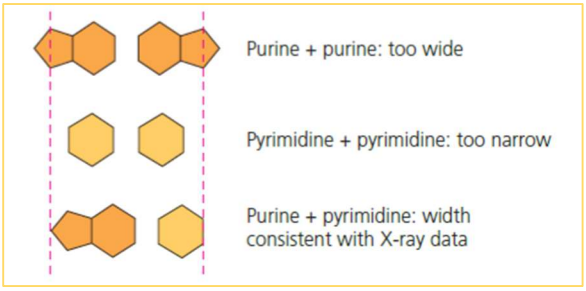
At first, Watson imagined that like paired with like for example, A with A and C with C but this model did not fit the **X-ray data**, which indicated that the double helix has a **uniform diameter**.



Why doesn't this requirement fit with like-with-like base pairing?

A and **G** are **purines**, nitrogenous bases with **two organic rings**, whereas **C** and **T** are **pyrimidines**, bases with **a single ring**. Pairing a purine with a pyrimidine is the only

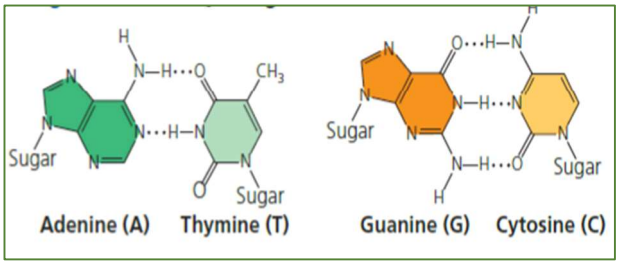
combination that produces a **uniform diameter** for the **DNA double helix**.



Watson and Crick deduced that there must be an additional level of **specificity in base pairing**, dictated by the **structure of the bases** themselves. Each base contains **chemical side groups** capable of forming **hydrogen bonds** with its appropriate partner:

- **A** forms **two hydrogen bonds** with **T**, and only with **T**;
- **G** forms **three hydrogen bonds** with **C**, and only with **C**.
- In short: **A pair with T, and G pairs with C.**

The **Watson-Crick model** accounted for and ultimately explained **Chargaff's ratios**. Wherever one strand of a DNA molecule has an **A**, the partner strand must have a **T**; likewise, a **G** on one strand always pairs with a **C** on the complementary strand.



Therefore, in the DNA of any organism, the **amount of A equals the amount of T**, and the **amount of G equals the amount of C**.

There is **no restriction** on the **sequence of nucleotides** along each DNA strand-the linear order of the four bases can vary in **countless combinations**, giving each gene its **unique base sequence**.

Many Proteins Work Together in DNA Replication and Repair:

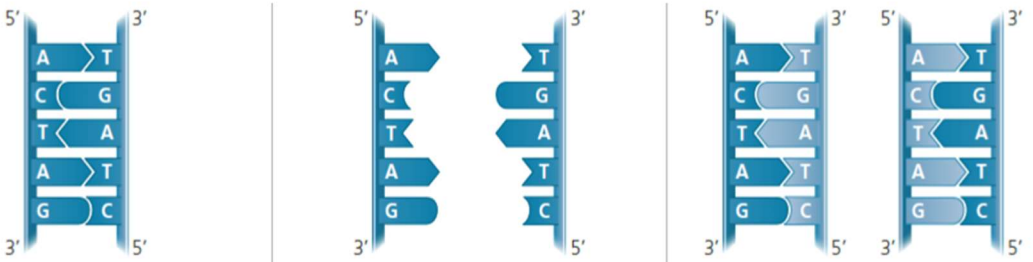
The relationship between structure and function is beautifully illustrated in the **DNA double helix**. The idea of **specific base pairing** in DNA was the flash of insight that led **Watson and Crick** to the discovery of the double helix. At the same time, they recognized the **functional significance** of this base-pairing principle.

The Basic Principle: Base Pairing to a Template Strand

In a second paper, **Watson and Crick** explained their hypothesis on how DNA **replicates**: "Now our model for DNA is, in fact, a pair of templates, each complementary to the other. We imagine that prior to replication, the hydrogen bonds break, and the two chains unwind and separate. Each chain then serves as a template for the formation of a new companion strand, so that eventually we shall have two pairs of chains where we originally had one. Moreover, the sequence of base pairs will be exactly duplicated."

The **following figure (35)** illustrates **Watson and Crick's central idea**.

A model for DNA replication: the basic concept. In this simplified illustration, a short segment of DNA has been untwisted. Simple shapes symbolize the four kinds of bases. Dark blue represents DNA strands present in the parental molecule; light blue represents newly synthesized DNA. (Figure 35)



(a) The parental molecule has two complementary strands of DNA. Each base is paired by hydrogen bonding with its specific partner, A with T and G with C.

(b) First, the two DNA strands are separated. Each parental strand can now serve as a template for a new, complementary strand.

(c) Nucleotides complementary to the parental (dark blue) strand are connected to form the sugar-phosphate backbones of the new "daughter" (light blue) strands.

The **Watson–Crick model** predicts that when the **double helix replicates**, each of the **two daughter molecules** will have **one old strand** derived from the **parental molecule** and **one newly made strand**. This model is called the **semiconservative model** of DNA replication.

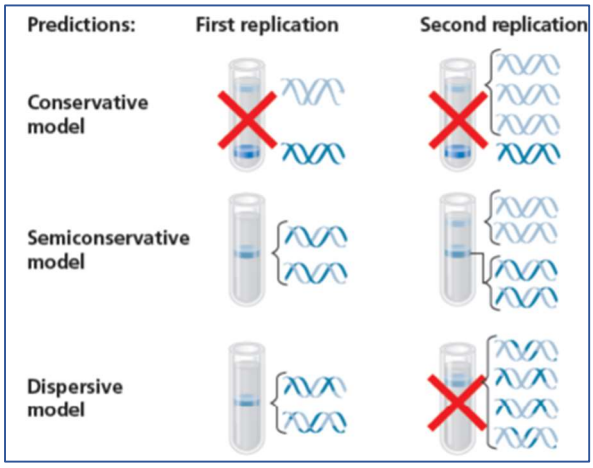
In contrast, the **conservative model** proposes that the **parental strands reassociate** after replication—meaning the **parental molecule is fully conserved**.

A third model, known as the **dispersive model**, suggests that **all four strands** following replication contain a **mixture of old and newly synthesized DNA** (figure 36).

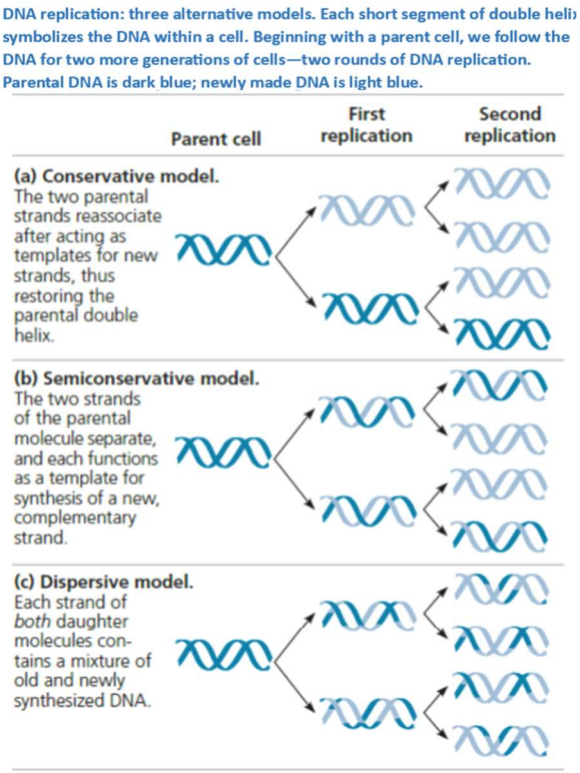
After two years of preliminary work at the **California Institute of Technology** in the late 1950s, **Matthew Meselson and Franklin Stahl** designed an ingenious experiment that

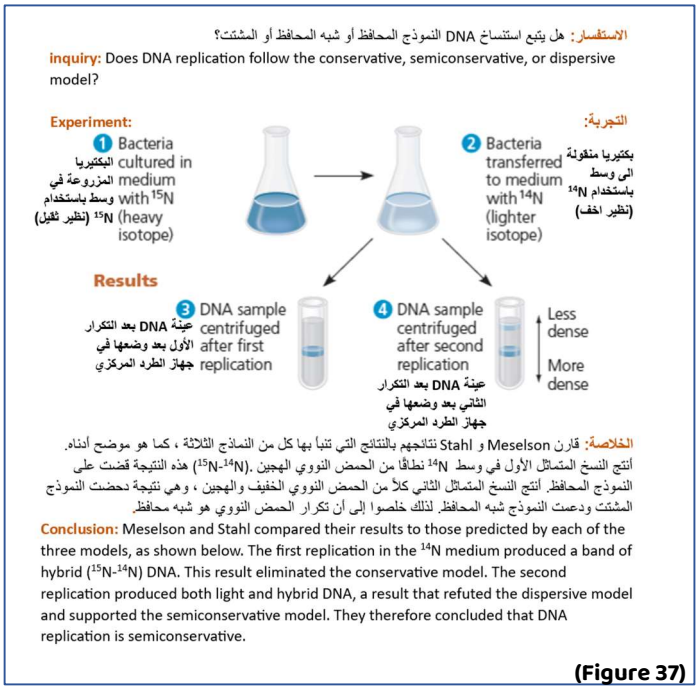
distinguished among the three models illustrated in the following figure (37).

Their results **supported the semiconservative model** of DNA replication, just as **Watson and Crick** had predicted.



(Figure 36)





(Figure 37)

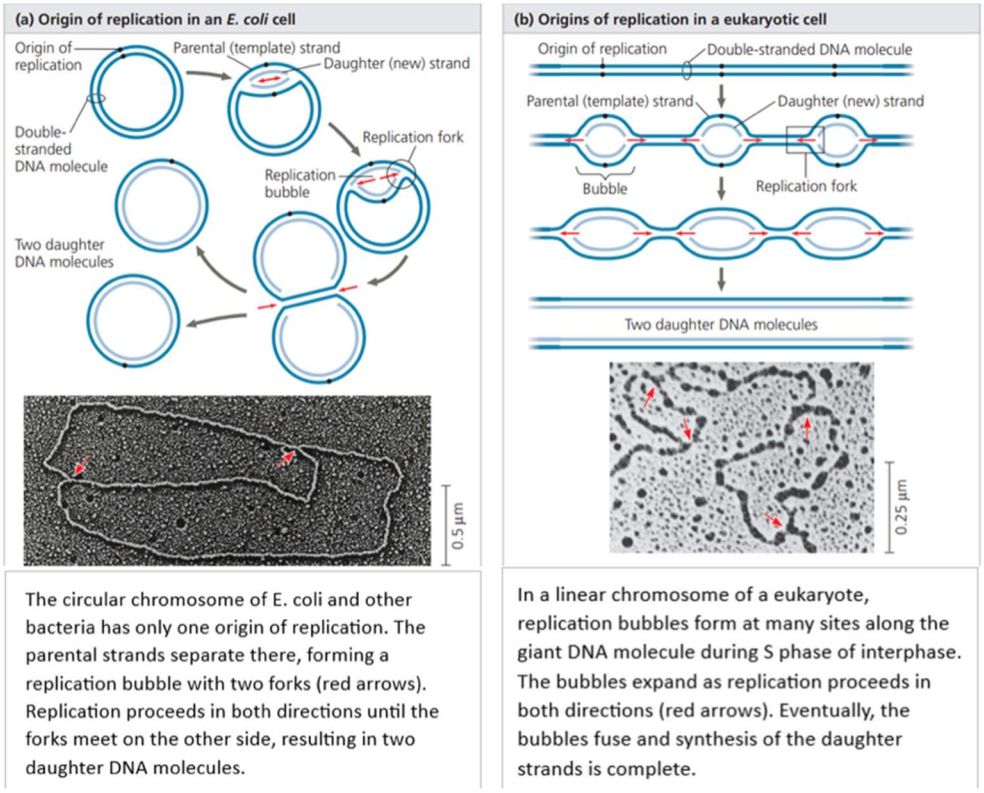
DNA Replication:

- More than ten **enzymes** and other **proteins** participate in the **replication of DNA**.
- Studies indicate that the process of DNA replication is **fundamentally similar** in both **prokaryotes** and **eukaryotes**.

Getting Started

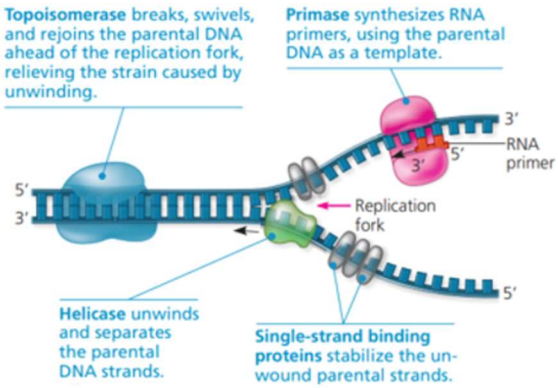
- DNA replication of chromosomes begins at specific sites called **origins of replication** short stretches of DNA that have a **specific sequence of nucleotides**.
- The **E. coli chromosome**, like many bacterial chromosomes, is **circular** and has a **single origin** of replication.
- Proteins that **initiate DNA replication** recognize this sequence, **attach to the DNA**, and **separate the two strands**, opening a **replication "bubble"** (Figure 38a).
- DNA replication then proceeds in **both directions** until the entire molecule has been copied.
- In contrast, a **eukaryotic chromosome** may have **hundreds or even a few thousand** replication origins.
- Multiple **replication bubbles** form and eventually **fuse**, greatly **speeding up the copying** of very long DNA molecules (Figure 38 b).
- As in bacteria, **eukaryotic DNA replication** proceeds in **both directions** from each origin.
- At each end of a replication bubble is a **replication fork**, a **Y-shaped region** where the **parental DNA strands** are being **unwound** (Figure 38 c).
- Several types of proteins are involved in this **unwinding process**:
    - **Helicases** are enzymes that **untwist the double helix** at the replication forks, **separating the two parental strands** and making them available as **template strands**.
    - Once the parental strands are separated, **single-strand binding proteins** attach to the **unpaired DNA strands**, preventing them from **re-pairing**.

- The **untwisting** of the double helix causes **tighter twisting and strain** ahead of the replication fork.
- **Topoisomerase** is an enzyme that helps **relieve this strain** by **breaking, swiveling, and rejoining** segments of the DNA strands.



The circular chromosome of E. coli and other bacteria has only one origin of replication. The parental strands separate there, forming a replication bubble with two forks (red arrows). Replication proceeds in both directions until the forks meet on the other side, resulting in two daughter DNA molecules.

In a linear chromosome of a eukaryote, replication bubbles form at many sites along the giant DNA molecule during S phase of interphase. The bubbles expand as replication proceeds in both directions (red arrows). Eventually, the bubbles fuse and synthesis of the daughter strands is complete.



(Figure 38)

(c)

Some of the proteins involved in the initiation of DNA replication. The same proteins function at both replication forks in a replication bubble. For simplicity, only the left-hand fork is shown, and the DNA bases are drawn much larger in relation to the proteins than they are in reality

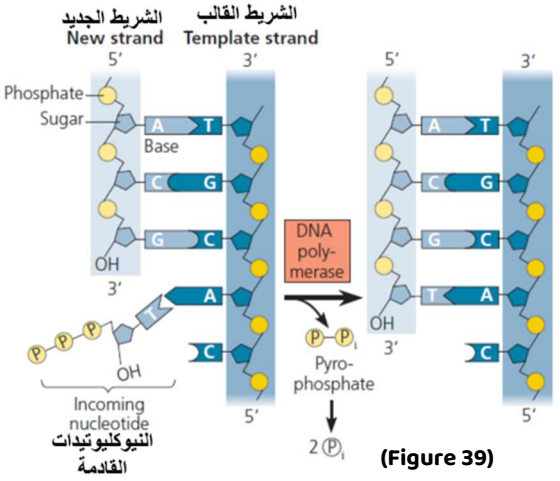
Synthesizing a New DNA Strand

- The **unwound sections** of the parental DNA strands are now available to serve as **templates** for the synthesis of new **complementary DNA strands**.
- However, the enzymes that synthesize DNA **cannot initiate** the synthesis of a polynucleotide; they can only **add DNA nucleotides** to the end of an **existing strand** that is already **base paired** with the template strand.
- The **initial nucleotide chain** produced during DNA synthesis is a short stretch of **RNA**, not DNA. This **RNA strand**, called a **primer**, is synthesized by the enzyme **primase**.
- **Primase** starts a complementary RNA chain with a single RNA nucleotide and then adds RNA nucleotides one by one, using the **parental DNA strand** as a **template**.
- The **completed primer**, usually **5-10 nucleotides long**, is thus base paired to the template strand. The **new DNA strand** will start from the **3' end** of the RNA primer.
- Enzymes called **DNA polymerases catalyze** the synthesis of new DNA by adding nucleotides to the **3' end** of a preexisting strand.
- In *E. coli*, there are several DNA polymerases, but **DNA polymerase III** and **DNA polymerase I** play the **major roles** in DNA replication.
- The situation in **eukaryotes** is more complex at least **11 different DNA polymerases** have been discovered so far.
- Most DNA polymerases require **a primer** and a **template DNA strand**, along which complementary DNA nucleotides are aligned.
- In *E. coli*, **DNA polymerase III (DNA pol III)** adds a DNA nucleotide to the RNA primer and then continues to add DNA nucleotides that are **complementary to the parental DNA template strand** at the **growing end** of the new DNA strand.
- Each **nucleotide** added to the growing DNA strand consists of a **sugar attached to a base and to three phosphate groups** the same basic structure as in **ATP**.
- The only difference between **ATP**, used in **energy metabolism**, and **dATP**, the **adenine nucleotide** used in DNA synthesis, is the **sugar component**: **deoxyribose** in DNA and **ribose** in ATP.
- Like ATP, the nucleotides used for DNA synthesis are **chemically reactive**, partly because their **triphosphate tails** contain an **unstable cluster of negative charges**.

- **DNA polymerase** catalyzes the addition of each monomer via a **dehydration reaction**.
- When a nucleotide monomer is joined to the **growing end** of a DNA strand, **two phosphate groups** are lost as a molecule of **pyrophosphate** (Ⓟ-Ⓟ$_i$).
- The subsequent **hydrolysis of pyrophosphate** into **two molecules of inorganic phosphate (P_i)** is an **exergonic reaction** that helps **drive the polymerization process** (see figure 39).

إضافة نيوكليوتيد إلى شريط DNA. يحفز DNA polymerase إضافة نيوكليوتيد إلى الطرف 3′ من شريط DNA المتنامي ، مع إطلاق اثنين من الفوسفات

Addition of a nucleotide to a DNA strand. DNA polymerase catalyzes the addition of a nucleotide to the 3′ end of a growing DNA strand, with the release of two phosphates



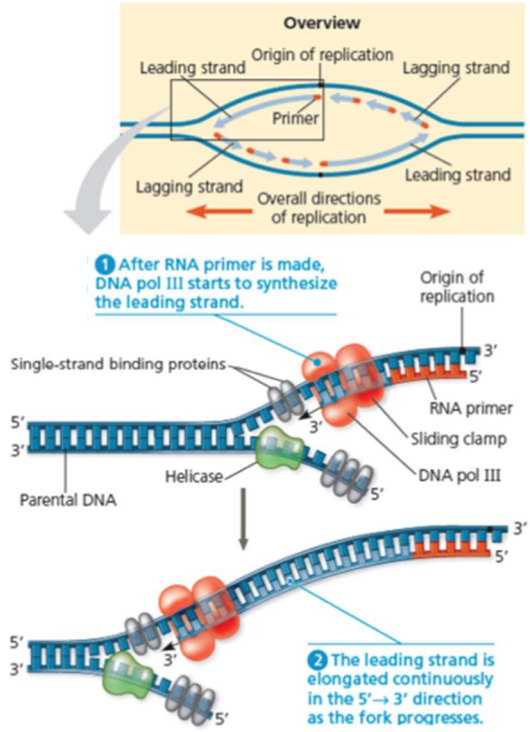
(Figure 39)

Antiparallel Elongation:

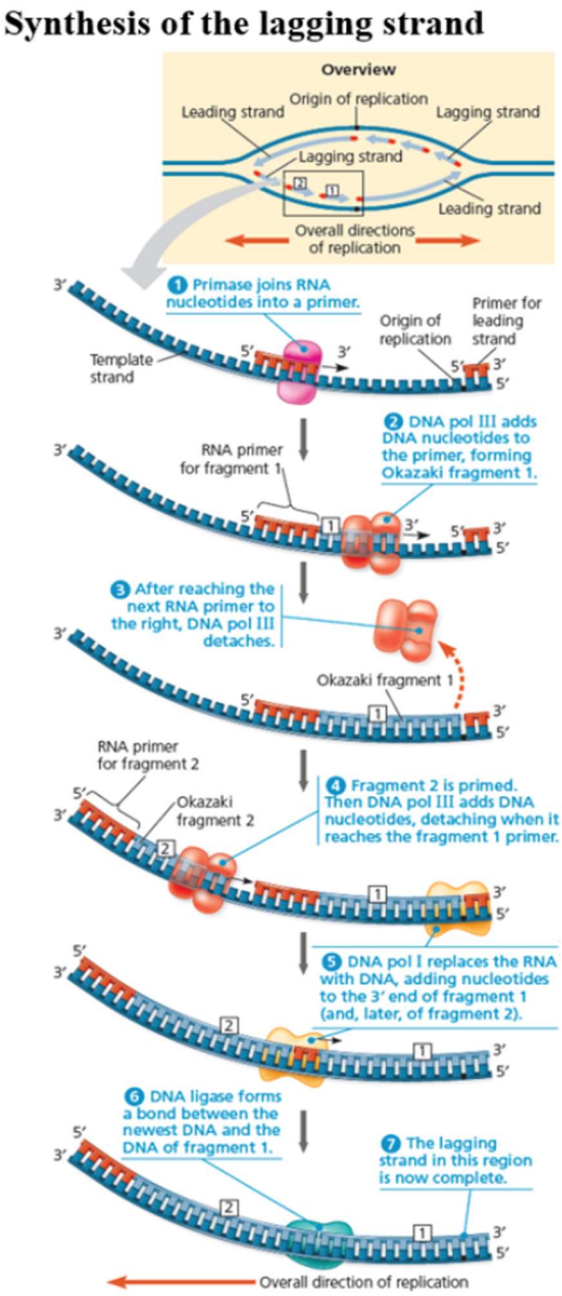
- As noted earlier, the two **ends** of a DNA strand are **different**, giving each strand a distinct **directionality**.
- Furthermore, the two strands of DNA in the **double helix** are **antiparallel**, meaning they are oriented in **opposite directions** relative to each other.
- Therefore, the **two new strands** formed during DNA replication must also be **antiparallel** to their respective **template strands**.
- This **antiparallel arrangement** of the double helix, combined with the properties of **DNA polymerases**, has a crucial impact on how replication occurs.
- Because of their structure, **DNA polymerases** can **add nucleotides only to the free 3' end** of a primer or growing DNA strand **never to the 5' end**.
- Thus, a new DNA strand can **elongate only in the 5' → 3' direction** (see the following figure 40).
- Along one template strand, **DNA polymerase III** can synthesize a **complementary strand continuously**, elongating the new DNA in the **mandatory 5' → 3' direction**.
- **DNA pol III** remains at the **replication fork** on this template strand, continuously adding nucleotides to the new complementary strand as the fork progresses.

- This continuously synthesized DNA strand is called the **leading strand**, and it requires **only one primer** for DNA pol III to build it completely.
- To elongate the **other new DNA strand** in the same **mandatory 5' → 3' direction**, **DNA pol III** must work along the **other template strand** in a direction **away from the replication fork**.
- This newly synthesized strand is called the **lagging strand**.
- Unlike the leading strand, which **elongates continuously**, the **lagging strand** is **synthesized discontinuously**, as a **series of short segments**.
- These short segments of the lagging strand are called **Okazaki fragments**, named after the Japanese scientist **Reiji Okazaki**, who discovered them.
- Each fragment is about **1,000–2,000 nucleotides long** in *E. coli* and about **100–200 nucleotides long** in eukaryotes.

Figure 40. Synthesis of the leading strand during DNA replication. This diagram focuses on the left replication fork shown in the overview box. DNA polymerase III (DNA pol III), shaped like a cupped hand, is shown closely associated with a protein called the "sliding clamp" that encircles the newly synthesized double helix like a doughnut. The sliding clamp moves DNA pol III along the DNA template strand.



- The **following figure (41)** illustrates the steps involved in building the **lagging strand** at a single replication fork.
- While **only one primer** is required for synthesis of the **leading strand**, each **Okazaki fragment** on the **lagging strand** must be **individually primed** (steps ① and ④).
- After **DNA polymerase III** synthesizes an **Okazaki fragment** (steps ②–④), another enzyme, **DNA polymerase I**, replaces the **RNA nucleotides** of the adjacent primer with **DNA nucleotides**, one by one (step ⑤).
- However, **DNA pol I** cannot form the final **phosphodiester bond** that joins the newly added DNA to the first nucleotide of the neighboring Okazaki fragment.
- This final joining is carried out by another enzyme, **DNA ligase**, which **seals the sugar–phosphate backbones** of all the Okazaki fragments into a **continuous DNA strand** (step ⑥).



(Figure 41)

- The synthesis of the **leading strand** and the **lagging strand** occurs **concurrently**, proceeding at **the same overall rate**.
- The **lagging strand** is named as such because its synthesis **lags slightly behind** that of the leading strand; each new fragment of the lagging strand **cannot begin** until

enough of the template has been **exposed** at the replication fork.

- The **following figure and table (42)** summarize the process of **DNA replication**.

Summary of Bacterial DNA Replication

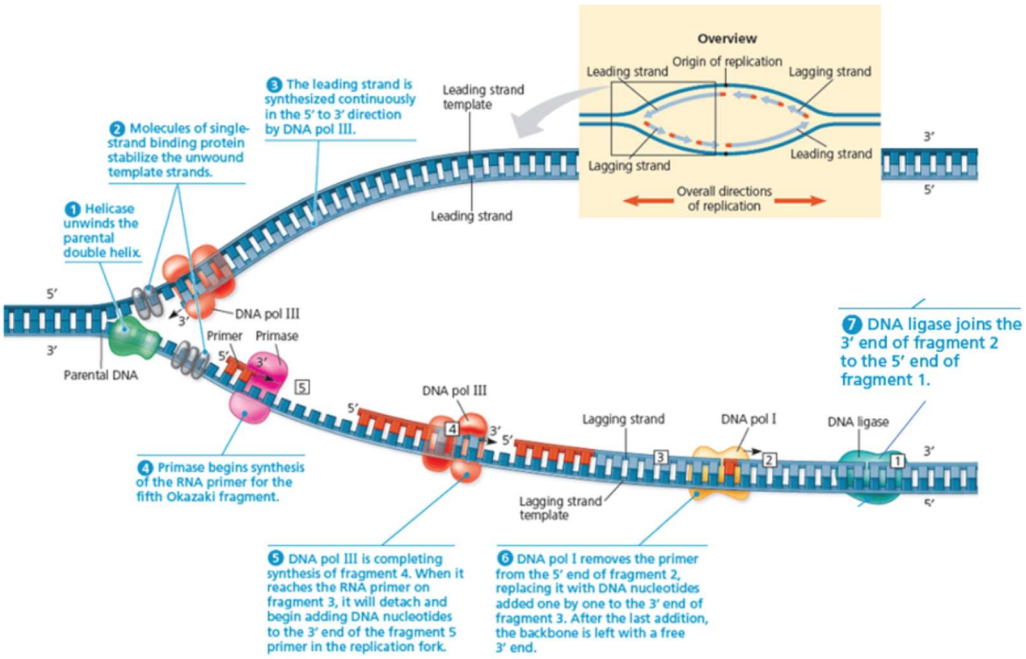
The detailed diagram illustrates the **left replication fork** of the **replication bubble** shown in the upper-right image.

When examining each **daughter strand** in the overall figure, you can observe that **one half** is synthesized **continuously**, forming the **leading strand**, while the **other half** (on the opposite side of the origin) is synthesized **in short segments**, forming the **lagging strand**.

Bacterial DNA replication Proteins and their Functions

Protein	Function
Helicase	Unwinds parental double helix at replication forks
Single-strand binding protein	Binds to and stabilizes single-stranded DNA until it is used as a template
Topoisomerase	Relieves overwinding strain ahead of replication forks by breaking, swiveling, and rejoining DNA strands
Primase	Synthesizes an RNA primer at 5′ end of leading strand and at 5′ end of each Okazaki fragment of lagging strand
DNA pol III	Using parental DNA as a template, synthesizes new DNA strand by adding nucleotides to an RNA primer or a pre-existing DNA strand
DNA pol I	Removes RNA nucleotides of primer from 5′ end and replaces them with DNA nucleotides added to 3′ end of adjacent fragment
DNA ligase	Joins Okazaki fragments of lagging strand; on leading strand, joins 3′ end of DNA that replaces primer to rest of leading strand DNA

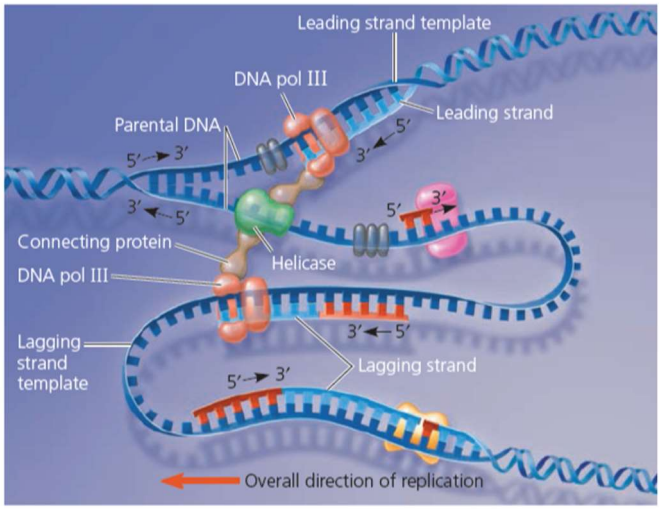
(Figure 42)



The DNA Replication Complex·

- **First**, the various proteins involved in DNA replication form a **single large complex**, often referred to as the **DNA replication machine**. Numerous **protein–protein interactions** enhance the efficiency of this complex. For example, by interacting with other proteins at the replication fork, **primase** appears to act as a **molecular brake**, slowing the progress of the replication fork and coordinating both the **placement of primers** and the **rates of replication** on the **leading and lagging strands**.

"trombone" model of the DNA replication complex. In this proposed model, two molecules of DNA polymerase III work together in a complex, one on each strand, with helicase and other proteins. The lagging strand template DNA loops through the complex, resembling the slide of a trombone.



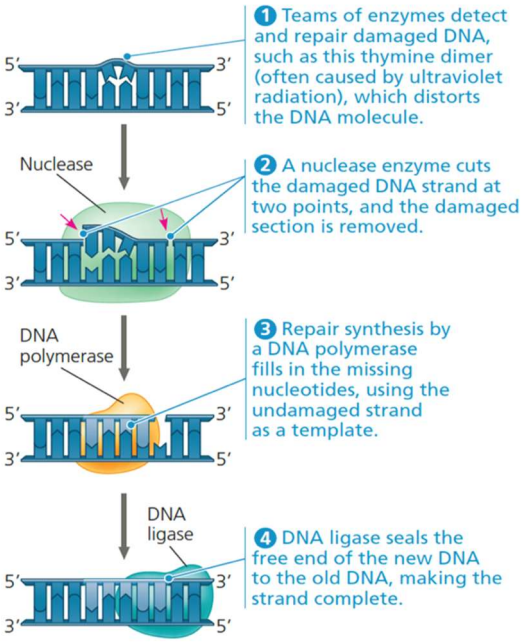
(Figure 43)

- **Second**, the **DNA replication complex** may not move along the DNA; rather, the **DNA itself may be pulled through the stationary complex** during replication.

Proofreading and Repairing DNA

- The process of DNA replication is characterized by a remarkable degree of accuracy, which results from the specificity of base pairing between the incoming nucleotides and those on the template strand.
- Nevertheless, the error rate in the completed DNA molecule is **only about one in 10^{10} nucleotides**, an extremely low frequency. This high fidelity arises because, during DNA replication, **DNA polymerases**

Nucleotide excision repair of DNA damage.



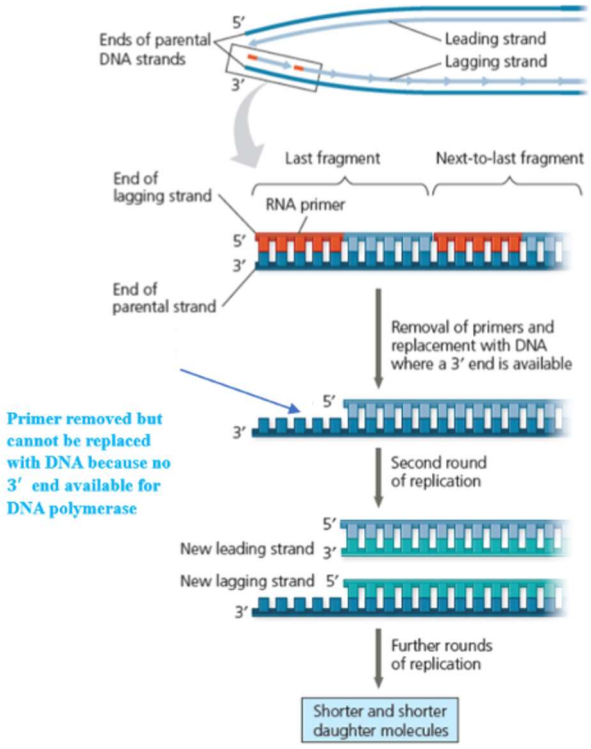
(Figure 44)

proofread each nucleotide against its template **as soon as it forms a covalent bond** with the growing strand. If an **incorrectly paired nucleotide** is detected, the polymerase **removes it** and then **resumes synthesis**.

- Occasionally, however, some **mismatched nucleotides** escape the proofreading activity of DNA polymerases.
- In such cases, the **mismatch repair** system comes into play: **specialized enzymes** remove and replace the incorrectly paired nucleotides that result from replication errors.
- In many instances, a **segment of the damaged DNA strand** is **cut out (excised)** by a **DNA-cutting enzyme**, called a **nuclease**. The resulting **gap** is then **filled in** with nucleotides using the **undamaged strand** as a **template**. The enzymes responsible for filling the gap are **DNA polymerase** and **DNA ligase**.
- One of the most important DNA repair mechanisms is known as **nucleotide excision repair** (as shown in the figure 44).

Replicating the Ends of DNA Molecules

- In the case of **linear DNA**, such as that found in **eukaryotic chromosomes**, the **usual replication machinery** cannot fully complete the **5′ ends** of the **daughter DNA strands**. (This is another consequence of the fact that **DNA polymerase** can only add nucleotides to the **3' end** of a preexisting polynucleotide.) Even if an **Okazaki fragment** could begin with an **RNA primer** hydrogen-bonded near the end of the template strand, once this primer is **removed**, it **cannot be replaced** with DNA because **there is no 3' end**



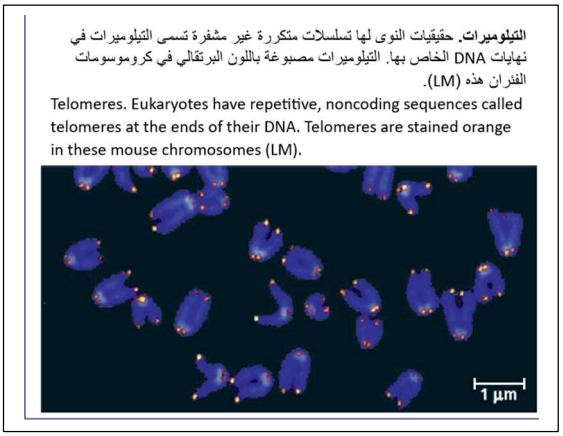
(Figure 45)

available for nucleotide addition (see figure 45).

- As a result, **repeated rounds of replication** produce **progressively shorter DNA molecules**.
- In contrast, most **prokaryotes** have a **circular chromosome** with **no ends**, so this **shortening of DNA** does **not occur**.

But what protects the genes of linear eukaryotic chromosomes from being eroded away during successive rounds of DNA replication?

- **Eukaryotic chromosomal DNA molecules** have special **nucleotide sequences** at their ends called **telomeres** (see figure 46).
- Telomeres **do not contain genes**; instead, the DNA consists of **a specific short sequence repeated many times**.
- For example, in each **human telomere**, the sequence is **TTAGGG**, repeated **100 to 1,000 times**.
- Telomeres serve **two protective functions**:



(Figure 46)

1. **Certain proteins** bound to the telomeric DNA prevent the **staggered ends** of the daughter molecule from **activating the cell's DNA damage monitoring systems**.
2. **Telomeric DNA** acts as a kind of **buffer zone**, providing protection against the **erosion of the organism's genes**, much like the **plastic tips on shoelaces** prevent them from fraying. Telomeres do **not prevent gene erosion entirely**; they simply **postpone it**.

But what about cells whose genome must remain intact and unchanged from one organism to its offspring over many generations?

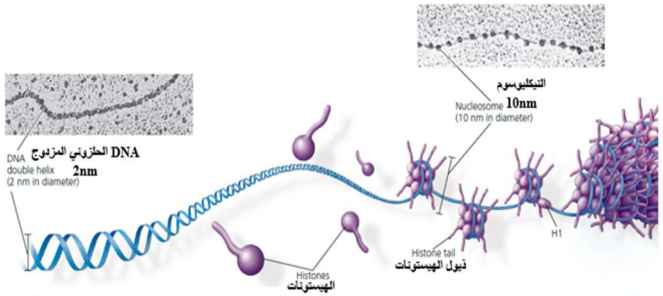
- As shown in the previous figure, **telomeres become shorter** with each round of replication. Accordingly, **telomeric DNA** tends to be **shorter** in the **somatic cells** of older individuals and in **cultured cells** that have **divided many times**.
- If the **chromosomes of germ cells** became shorter with each cell cycle, **essential genes** would eventually be **lost** and thus **absent from the gametes** they produce. However, this does **not** happen because an enzyme called **telomerase catalyzes the lengthening of telomeres** in the **germ cells** of eukaryotes, thereby **restoring their original length** and **compensating** for the shortening that occurs during **DNA replication**.
- This enzyme contains its **own RNA molecule**, which it uses as a **template** to **artificially extend** the **leading strand**, allowing the **lagging strand** to maintain an appropriate length.
- **Telomerase** is **not active** in most **human somatic cells**, but its **activity varies among tissues**. It is **highly active** in **germ cells**, ensuring that **telomeres** reach their **maximum length** in the **zygote**.
- The **natural shortening of telomeres** may protect organisms from **cancer** by **limiting the number of cell divisions** that somatic cells can undergo.
- Cells from **large tumors** often have **abnormally short telomeres**, suggesting they have undergone many rounds of cell division. Further shortening may lead to the **self-destruction** of cancerous cells.
- Conversely, **telomerase activity** is **abnormally high** in many **cancerous somatic cells**, suggesting that their ability to **maintain telomere length** may allow them to **continue dividing indefinitely**. Researchers are currently **studying telomerase inhibition** as a **potential cancer therapy**.

A Chromosome Consists of a DNA Molecule Packed Together with Proteins

- We will now explore how **DNA is packaged** within **chromosomes**, the structures that carry **genetic information**.
- The **main component of the genome** in most **bacteria** is a **double-stranded circular DNA molecule** that is **associated with a small amount of protein**.
- In contrast, in **eukaryotes**, the situation is very different—the genome consists of **linear DNA molecules** associated with a **large amount of protein**.
- In a **eukaryotic cell**, DNA is **precisely combined** with numerous proteins. This complex of **DNA and protein**, known as **chromatin**, fits into the **nucleus** through a **highly organized, multilevel system of packing**.
- The **successive levels of DNA packing** in a chromosome are illustrated in **Figure 47(a)**.
- **Chromatin** undergoes **remarkable changes** in its **degree of packing** during the **cell cycle**.
- In **interphase cells**, chromatin stained for light microscopy typically appears as a **diffuse mass** within the nucleus, indicating that the chromatin is **highly extended**.
- When the cell prepares for **mitosis**, the chromatin **coils and folds**, becoming **highly condensed**. Eventually, it forms the **distinct, short, thick metaphase chromosomes** that can be **individually distinguished** under the light microscope (Figure 47 b).

Figure 47. This illustration, accompanied by transmission electron micrographs, depicts a current model for the progressive levels of DNA coiling and folding. The illustration zooms out from a single molecule of DNA to a metaphase chromosome, which is large enough to be seen with a light microscope.

(الشكل a)



DNA the double helix ، الحلزون المزدوج

الموضح أعلاه هو نموذج شريطي DNA ، حيث يمثل كل شريط أحد خيوط البولي نيوكليوتيد. تذكر أن كل مجموعة فوسفات على طول السلسلة تساهم في شحنة سالبة على طول الجزء الخارجي من كل شريط. يظهر TEM جزيئا من الحمض النووي العاري (الخالي من البروتين) ؛ يبلغ عرض اللولب المزدوج وحده 2nm.

Shown above is a ribbon model of DNA, with each ribbon representing one of the polynucleotide strands. Recall that each phosphate group along the backbone contributes a negative charge along the outside of each strand. The TEM shows a molecule of naked (protein-free) DNA; the double helix alone is 2 nm across.

Histones ، الهيستونات

البروتينات التي تسمى الهيستونات هي المسؤولة عن المستوى الأول من تجميع DNA في الكروماتين. على الرغم من أن كل هيستون صغير - يحتوي فقط على حوالي 100 من الأحماض الأمينية - فإن الكتلة الكلية للهيستون في الكروماتين تساوي تقريبًا كتلة DNA. أكثر من خُمس الأحماض الأمينية الموجودة في الهيستون مشحونة إيجابًا (ليسين أو أرجينين) ، وبالتالي ترتبط بإحكام بـDNA السالب الشحنة. أربعة أنواع من الهيستونات هي الأكثر شيوعًا في الكروماتين. الهيستونات متشابهة جدًا بين حقيقيات النوى. على سبيل المثال ، تختلف الهيستونات من نفس النوع في الأبقار ونباتات البازلاء بحمضين أمينيين فقط. ربما يعكس الحفظ الواضح لجينات الهيستون أثناء التطور الدور المهم للهيستونات في تنظيم DNA داخل الخلايا. هذه الأنواع الأربعة من الهيستونات ضرورية للمستوى التالي من تجميع DNA. (النوع الخامس من الهيستون يدخل في مرحلة أخرى من التجميع).

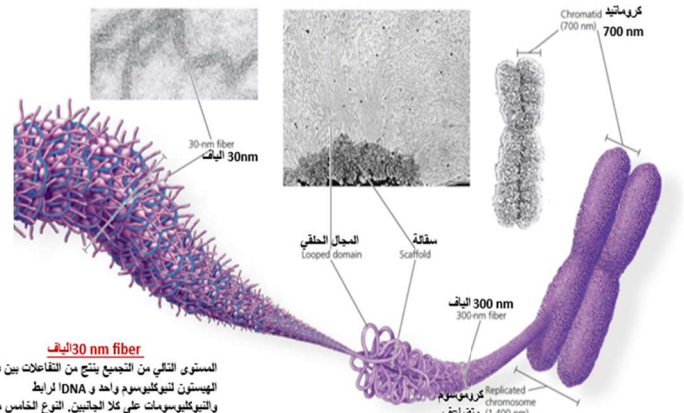
Proteins called histones are responsible for the first level of DNA packing in chromatin. Although each histone is small—containing only about 100 amino acids—the total mass of histone in chromatin roughly equals the mass of DNA. More than a fifth of a histone's amino acids are positively charged (lysine or arginine) and therefore bind tightly to the negatively charged DNA. Four types of histones are most common in chromatin. The histones are very similar among eukaryotes; for example, histones of the same type in cows and pea plants differ by only two amino acids. The apparent conservation of histone genes during evolution probably reflects the important role of histones in organizing DNA within cells. These four types of histones are critical to the next level of DNA packing. (A fifth type of histone is involved in a further stage of packing.)

Nucleosomes, or "beads on a string" (10-nm fiber) ، نيوكليوسومات ، أو "خرز على خيط"

في الصور المجهرية الإلكترونية ، يبلغ قطر الكروماتين غير المطوي 10nm (الألياف 10nm). يشبه هذا الكروماتين الخرز على خيط (انظر TEM). كل "حبة" هي نيكليوسوم ، الوحدة الأساسية لتجميع DNA. يسمى "الخيط" بين الخرزات DNA الرابط. يتكون النيكليوسوم من DNA ملفوف مرتين حول لب بروتين مكون من ثمانية هيستون ، اثنان من كل نوع من أنواع الهيستون الرئيسية. تمنع النهاية الأمينية (الطرف N) لكل هيستون (ذيل هيستون) إلى الخارج من النواة. في دورة الخلية ، تترك الهيستونات DNA لفترة وجيزة فقط أثناء تضاعف DNA. بشكل عام ، يفقدون الشيء نفسه أثناء عملية النسخ ، والتي تتطلب أيضًا الوصول إلى DNA من خلال الآلية الجزيئية للخلية. النيكليوسوم ، ولا سيما ذيولها الهيستونية ، تشارك في تنظيم التعبير الجيني.

In electron micrographs, unfolded chromatin is 10 nm in diameter (the 10-nm fiber). Such chromatin resembles beads on a string (see the TEM). Each "bead" is a nucleosome, the basic unit of DNA packing; the "string" between beads is called linker DNA. A nucleosome consists of DNA wound twice around a protein core of eight histones, two each of the main histone types. The amino end (N-terminus) of each histone (the histone tail) extends outward from the nucleosome. In the cell cycle, the histones leave the DNA only briefly during DNA replication. Generally, they do the same during the process of transcription, which also requires access to the DNA by the cell's molecular machinery. Nucleosomes, and in particular their histone tails, are involved in the regulation of gene expression.

(الشكل b)



30 nm fiber الياف

المستوى التالي من التجميع ينتج من التفاعلات بين ذيول الهيستون لنيوكليوسوم واحد و DNA لرابط والنيوكليوسومات على كلا الجانبين. النوع الخامس من الهيستون يدخل في هذا المستوى ، تتسبب هذه التفاعلات في لف أو ثني الألياف بطول 10nm ، مكونة ألياف كروماتين بسمك 30nm تقريبًا ، ألياف 30nm. على الرغم من أن الألياف ذات 30nm منتشرة تمامًا في نواة الطور البيني ، إلا أن ترتيب التجميع للنيوكليوسومات في هذا الشكل من الكروماتين لا يزال محل نقاش.

The next level of packing results from interactions between the histone tails of one nucleosome and the linker DNA and nucleosomes on either side. The fifth type of histone is involved at this level. These interactions cause the extended 10-nm fiber to coil or fold, forming a chromatin fiber roughly 30 nm in thickness, the 30-nm fiber. Although the 30-nm fiber is quite prevalent in the interphase nucleus, the packing arrangement of nucleosomes in this form of chromatin is still a matter of some debate.

300 nm looped domains المجال الحلقي

تشكل الألياف التي يبلغ قطرها 30nm ، بدورها ، حلقات تسمى المجالات الحلقية المرتبطة بسقالة كروموسوم مكونة من بروتينات ، وبالتالي تشكل ألياف 300nm. السقالة غنية بنوع واحد من topoisomerase.

The 30-nm fiber, in turn, forms loops called looped domains attached to a chromosome scaffold composed of proteins, thus making up a 300-nm fiber. The scaffold is rich in one type of topoisomerase.

Metaphase chromosome كروموسومات الطور الاستوائي

في كروموسوم الانقسام المتساوي ، تلتف المجالات الحلقية نفسها وتطوى بطريقة لم يتم فهمها بالكامل بعد ، مما يؤدي إلى زيادة ضغط كل الكروماتين لإنتاج كروموسوم الطور الاستوائي (كما هو موضح في الرسم المجهري أعلاه). عرض كروماتيد واحد 700nm. تنتهي الجينات المعينة دائمًا في نفس الأماكن في كروموسومات الطور الاستوائي ، مما يشير إلى أن خطوات التعبئة محددة ودقيقة للغاية.

In a mitotic chromosome, the looped domains themselves coil and fold in a manner not yet fully understood, further compacting all the chromatin to produce the characteristic metaphase chromosome (also shown in the micrograph above). The width of one chromatid is 700 nm. Particular genes always end up located at the same places in metaphase chromosomes, indicating that the packing steps are highly specific and precise.

Exercises

Exercise 1 — تدريب ١

Cytosine makes up 42% of the nucleotides in a sample of DNA from an organism. Approximately what percentage of the nucleotides in this sample will be thymine?

يشكل السيتوسين 42% من النيوكليوتيدات في عينة من الحمض النووي للكائن الحي. ما هي نسبة النيوكليوتيدات في هذه العينة تقريبًا التي ستكون الثايمين؟

A	8%	C	42%
B	16	D	58

Exercise 2 — تدريب ٢

In the polymerization of DNA, a phosphodiester bond is formed between a phosphate group of the nucleotide being added and which of the following atoms or molecules of the last nucleotide in the polymer?

في بلمرة الحمض النووي ، تتشكل رابطة فوسفوديستر بين مجموعة فوسفات من النيوكليوتيد المضافة وأي من الذرات أو الجزيئات التالية للنيوكليوتيدات الأخيرة في البوليمر؟

A	the 5' phosphate	C	the 3' OH
B	C6	D	a nitrogen from the nitrogen-containing base

Exercise 3 — تدريب ٣

In *E. coli*, there is a mutation in a gene called *dnaB* that alters the helicase that normally acts at the origin of replication. Which of the following events would you expect to occur because of this mutation?

في *E. coli* ، هناك طفرة في جين يسمى *dnaB* يغير helicase الذي يعمل عادة في التضاعف الاصلي. أي من الأحداث التالية تتوقع حدوثه نتيجة لهذه الطفرة؟

A	Additional proofreading will occur.	سيحدث تصحيح لغوي إضافي.	A
B	No replication fork will be formed.	لن يتم تشكيل شوكة التضاعف.	B
C	Replication will occur via RNA polymerase alone.	سيحدث التضاعف عبر RNA polymerase وحده.	C
D	Replication will require a DNA template from another source.	سيتطلب التضاعف قالب DNA من مصدر آخر.	D

	Exercise 4	تدريب ٤	
	Which of the following characteristics of eukaryotic telomeres cause them to replicate differently than the rest of the chromosome?	أي من الخصـائص التالية للتيلوميرات حقيقية النواة تجعلها تتكاثر بشـكل مختلف عن بقية الكروموسوم؟	
A	the activity of telomerase enzyme.	نشاط إنزيم التيلوميراز	A
B	DNA polymerase that cannot replicate the leading strand template to its 5' end	DNA polymerase الذي لا يمكنه نسخ قالب الشريط القائد إلى 5' end	B
C	Gaps left at the 5' end of the lagging strand template.	الفجوات المتبقية في 5' end من قالب الشريط المتأخر.	C
D	Gaps left at the 3' end of the lagging strand because of the need for a primer.	ترك فجوات في 3' end من الخيط المتأخر بسبب الحاجة إلى التمهيدي.	D
	Exercise 5	تدريب ٥	
	present where the chain opens to form a replication fork:	في منطقة معينة من الكروموسوم ، يوجد تسلسل النيوكليوتيدات أدناه حيث تفتح السلسلة لتشكيل شوكة التضاعف:	
	3' C C T A G G C T G C A A T C C 5'		
	An RNA primer is formed starting at the underlined T (T) of the template. Which of the Following represents the primer ?sequence	يتم تشـكيل RNA التمهيدي بدءًا من T تحتها خط (T) للقالب. أي مما يلي يمثل تسلسل التمهيدي؟	
A	5' G C C T A G G 3'		
B	5' A C G T T A G G 3'		
C	5' A C G U U A G G 3'		
D	5' G C C U A G G 3'		

Exercise 6 — تدريب ٦

You briefly expose bacteria undergoing DNA replication to radioactively labeled nucleotides. When you centrifuge the DNA isolated from the bacteria, the DNA separates into two classes. One class of labeled DNA includes very large molecules (thousands or even millions of nucleotides long), and the other includes short stretches of DNA (several hundred to a few thousand nucleotides in length). Which two classes of DNA do these different samples represent?

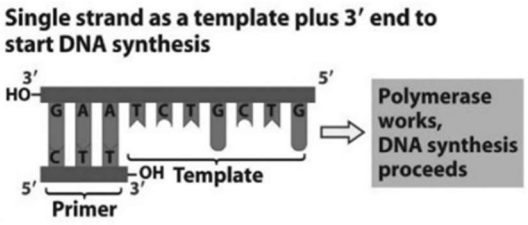
أنت تعرض لفترة وجيزة البكتيريا التي تخضع لتضاعف DNA للنيوكليوتيدات المعلم إشعاعيًا. عندما تقوم بالطرد المركزي لـــDNA المعزول من البكتيريا ، ينقسم DNA إلى فئتين. تتضمن إحدى فئات DNA المعلم جزيئات كبيرة جدًا (آلاف أو حتى ملايين النيوكليوتيدات طويلة) ، والأخرى تشمل امتدادات قصيرة من DNA (من عدة مئات إلى بضعة آلاف من النيوكليوتيدات في الطول). أي فئتين من DNA تمثلهما هذه العينات المختلفة؟

A	leading strands and Okazaki fragments.	شريط قائد وقطع أوكازاكي	A
B	lagging strands and Okazaki fragments	شريط متأخر وقطع أوكازاكي	B
C	Okazaki fragments and RNA primers	قطع أوكازاكي و RNA البادئ	C
D	leading strands and RNA primers.	الشريط القائد و RNA البادئ	D

Exercise 7 — تدريب ٧

Use the figure to answer the following question:

استخدم الشكل للإجابة على السؤال التالي:



Referring to the figure, what bases will be added to the primer as DNA replication proceeds?

بالإشارة إلى الشكل ، ما هي القواعد التي ستُضاف إلى البادئ مع استمرار تضاعف DNA؟

A	5′ C, A, G, C, A, G, A 3′
B	3′ T, C, T, G, C, T, G 5′
C	5′ A, G, A, C, G, A, C 3′

D	3′ G, T, C, G, T, C, T 5′

Exercise 8		تدريب ٨	
Which of the following effects might be caused by reduced or very little active telomerase activity?		**أي من التأثيرات التالية قد يكون ناتجًا عن انخفاض نشاط التيلوميراز النشط أو قلة نشاطه؟**	
A	Cells may become cancerous.	قد تصبح الخلايا سرطانية.	A
B	Telomere lengthens in germ cells	يطيل التيلوميرات في الخلايا الجنسية.	B
C	Cells maintain normal functioning	تحافظ الخلايا على الأداء الطبيعي.	C
D	Cells age and begin to lose function	تشيخ الخلايا وتبدأ في فقدان وظيفتها.	D

Exercise 9		تدريب ٩	
Which of the following statements correctly describes the structure of chromatin?		**أي من العبارات التالية يصف بنية الكروماتين بشكل صحيح؟**	
A	Heterochromatin is composed of DNA, whereas euchromatin is made of DNA and RNA.	يتكون الكروماتين المتغاير من DNA ، بينما يتكون الكروماتين الحقيقي من DNA و RNA	A
B	Heterochromatin is highly condensed, whereas euchromatin is less compact.	الكروماتين المتغاير مكثف للغاية ، في حين أن الكروماتين الحقيقي يكون أقل ضغطًا.	B
C	Both heterochromatin and euchromatin are found in the cytoplasm.	تم العثور على كل من الكروماتين المتغاير و الكروماتين الحقيقي في السيتوبلازم.	C
D	Euchromatin is not transcribed, whereas heterochromatin is transcribed.	لا يتم نسخ الكروماتين الحقيقي ، في حين يتم نسخ الكروماتين المتغاير.	D

Exercise 10		تدريب ١٠	
Researchers found a strain of *E. coli* bacteria that had mutation rates one hundred times higher than normal. Which of the following statements correctly describes the most likely cause of these results?		**وجد الباحثون سلالة من بكتيريا *E. coli* التي لديها معدلات طفرة أعلى مائة مرة من المعدل الطبيعي. أي من العبارات التالية يصف بشكل صحيح السبب الأكثر احتمالية لهذه النتائج؟**	
A	The single-strand binding proteins were malfunctioning during DNA replication..	كانت بروتينات الربط أحادية الشريط معطلة أثناء تضاعف DNA.	A
B	There were one or more base pair mismatches in the RNA primer.	كان هناك عدم تطابق واحد أو أكثر من أزواج القواعد في RNA البادئ.	B
C	The proofreading mechanism of DNA polymerase was not working properly.	لم تكن آلية التدقيق لـــــ DNA polymerase تعمل بشكل صحيح.	C
D	The DNA polymerase was unable to add bases to the 3' end of the growing nucleic acid chain.	كان DNA polymerase غير قادر على إضافة قواعد إلى 3' end لسلسلة DNA المتنامية.	D

Exercise 11		تدريب ١١	
In an analysis of the nucleotide composition of a molecule of DNA, which of the following combinations of base pairs will be found?		**في تحليل التركيبة النوكليوتيدية لجزيء من DNA ، أي من التوليفات التالية من أزواج القواعد سيتم العثور عليها؟**	
A	A = C		
B	A + C = G + T		
C	A = G and C = T		
D	G + C = T + A		

Chapter Four

Gene Expression: From Gene to Protein

نسمو NSMO
أولمبيـــاد العلوم والرياضيات الوطني

Gene Expression: From Gene to Protein

Genes specify proteins via transcription and translation:

Before delving into the details of how genes direct the synthesis of proteins, let us first step back and examine how the fundamental relationship between genes and proteins was discovered.

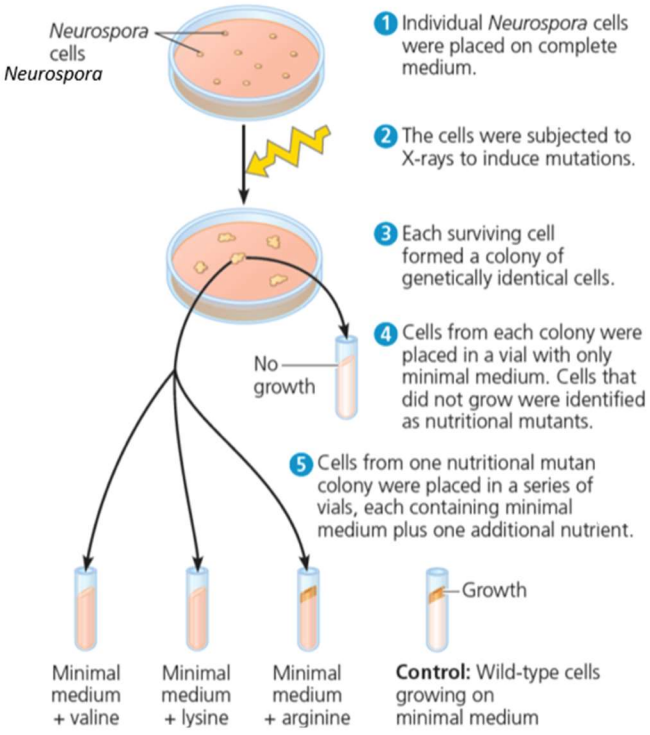
Nutritional Mutants in Neurospora: Scientific Inquiry:

- **Beadle** and **Edward Tatum** began their work using *Neurospora crassa*, a bread mold that is **haploid**. To observe a change in the **mutant's phenotype**, Beadle and Tatum needed to **disable only a single allele** rather than two, as in diploid species of a **protein-coding gene** required for a specific metabolic activity.
- They **bombarded** the *Neurospora* fungus with **X-rays**, known to cause **mutations**, and searched among the survivors for mutants whose **nutritional requirements** differed from those of the **wild-type** bread mold.
- The **wild-type Neurospora** has **modest nutritional requirements**; it can grow in the laboratory on a simple solution containing only the minimal nutrients necessary for growth **inorganic salts, glucose, and the vitamin biotin** incorporated into agar. This simple nutrient mixture is called the **minimal medium**. Wild-type mold cells use their own **metabolic pathways** to synthesize all other molecules they need for growth, dividing repeatedly to form **visible colonies** of genetically identical cells.
- As shown in the **next figure 48**, Beadle and Tatum produced several **nutritional mutants** of *Neurospora*, each unable to synthesize a specific essential nutrient.
- These mutant cells could not grow on **minimal medium**, but they could grow on a **complete medium** containing all the nutrients required for growth.
- For *Neurospora*, the **complete medium** consists of the **minimal medium** supplemented with **all twenty amino acids** and a few other nutrients. Beadle and

Tatum therefore **hypothesized** that in each nutritional mutant, the gene encoding the **enzyme responsible for synthesizing a specific nutrient** had been disabled.

- This experiment produced a valuable **collection of mutant strains** of *Neurospora*, each classified by its defect in a particular metabolic pathway. Two of their colleagues, **Adrian Srb** and **Norman Horowitz**, used a set of **arginine-requiring mutants** to investigate the **biochemical pathway of arginine synthesis** in *Neurospora* (as shown in the following experiment).
- Srb and Horowitz further **pinpointed the specific defect** of each mutant by performing additional tests that distinguished **three classes of arginine-requiring mutants**.
- Mutants in each **class** required a different set of compounds along the **three-step pathway** of arginine synthesis.
- These findings and those from many similar experiments conducted by Beadle and Tatum suggested that **each class was blocked at a different step in the pathway**, because mutations in that class **lacked the enzyme catalyzing the blocked step**.
- Since Beadle and Tatum designed their experiments so that each mutant was **defective in only one gene**, the **combined results** provided strong support for the **working hypothesis** they had previously proposed.
- The **one gene–one enzyme hypothesis**, as they named it, stated that **the function of a gene is to dictate the production of a specific enzyme**.
- Today, we know of **countless examples** in which a **mutation in a gene** leads to a **faulty enzyme**, which in turn results in a **recognizable condition**.

Figure 48. Beadle and Tatum's experimental approach. To obtain nutritional mutants, Beadle and Tatum exposed Neurospora cells to X-rays, inducing mutations, then screened mutants that had new nutritional requirements, such as arginine, as shown here.

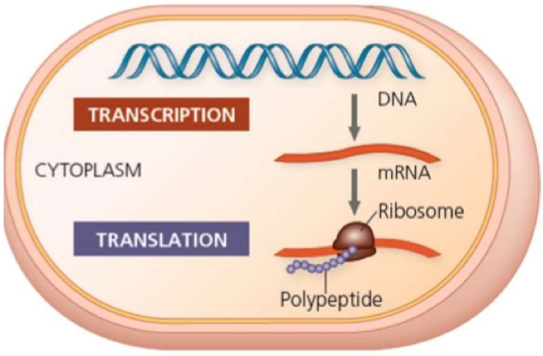


6 The vials were observed for growth. In this example, the mutant cells grew only on minimal medium + arginine, indicating that this mutant was missing the enzyme for the synthesis of arginine.

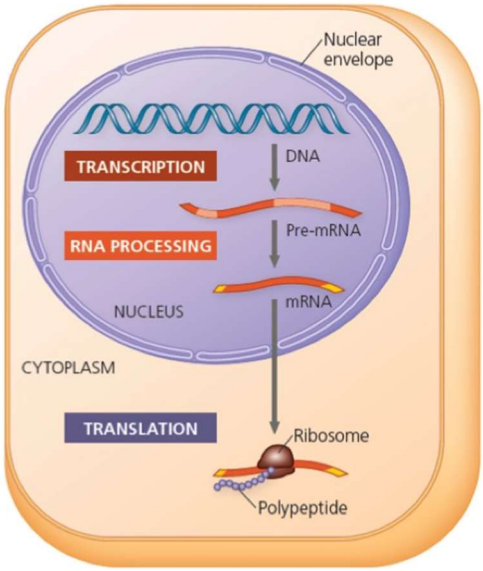
Basic Principles of Transcription and Translation:

- **Genes provide the instructions for making specific proteins**, but a gene does not directly build the protein itself. The **bridge** between DNA and protein synthesis is **RNA**.
- **RNA** is chemically similar to DNA, except that it contains the sugar **ribose** instead of **deoxyribose**, and it has the nitrogenous base **uracil (U)** instead of **thymine (T)**. Thus, while each nucleotide along a DNA strand has a base of **A, G, C, or T**, each nucleotide along an RNA strand has a base of **A, G, C, or U**. An RNA molecule usually consists of a **single strand**.
- Both **nucleic acids** and **proteins** are **polymers** composed of **specific sequences of monomers** that carry information.

- In **DNA** or **RNA**, the **monomers** are the four types of **nucleotides**, which differ in their **nitrogenous bases**.
- **Genes** typically consist of **hundreds or thousands of nucleotides**, each with a unique **nucleotide sequence**.
- Each **polypeptide** in a protein also contains **monomers** arranged in a precise **linear order**—in this case, the monomers are **amino acids**.
- Thus, **nucleic acids** and **proteins** carry information written in **two different chemical languages**, and converting the information from **DNA to protein** requires **two major stages**: **transcription** and **translation**.
- The **basic mechanics** of transcription and translation are similar in **bacteria** and **eukaryotes**, but there is an important difference in the **flow of genetic information** within cells: **bacteria lack nuclei**. Therefore, **no nuclear membranes** separate bacterial DNA and mRNA from the **ribosomes** and other components of the protein-synthesizing machinery (Figure 49a).
- This absence of compartmentalization in bacteria allows **translation of mRNA** to begin **before transcription has finished**. In contrast, **eukaryotic cells** possess a **nucleus**, where the **nuclear envelope** separates **transcription** and **translation** both **spatially and temporally** (Figure 49b).
- In eukaryotes, **transcription** occurs in the **nucleus**, but the **mRNA** must be **transported to the cytoplasm** for **translation**. Before leaving the nucleus, the mRNA is **modified in several ways** to produce the **final, functional form** of mRNA.
- The initial RNA transcript from any gene—including RNA that is not translated into protein—is generally called a **primary transcript**.
- The overall program of **protein synthesis**, in which genetic information is expressed through the **messenger RNA (mRNA)**, can therefore be summarized as follows.



a) Bacterial cell. In a bacterial cell, which lacks a nucleus, mRNA produced by transcription is immediately translated without additional processing.



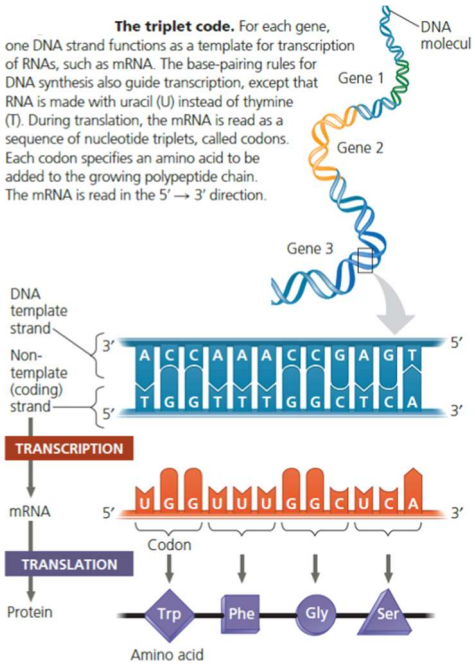
(b) Eukaryotic cell. The nucleus provides a separate compartment for transcription. The original RNA transcript, called pre-mRNA, is processed in various ways before leaving the nucleus as mRNA.

(Figure 49)

The Genetic Code Triplets of Nucleotides

- If each of the four types of **nucleotide bases** were translated into a single amino acid, only **four amino acids** could be specified **one for each base**.
- Likewise, if we assume that each **code word** consisted of **two bases**, with four possible nucleotides in each position, this will yield **16 possible combinations** ($4 \times 4 = 4^2$). However, this is still **insufficient to code** for all **20 amino acids**.
- In contrast, **triplets of nucleotide bases** are the **smallest uniform-length units** capable of encoding all amino acids. If each sequence of **three consecutive nucleotide bases** specifies one amino acid, there can be **64 possible code words** (4^3), which is **more than enough** to code for all 20 amino acids.
- Experimental evidence confirmed that the **flow of information** from **gene to protein** depends on a **triplet code** the genetic instructions for a **polypeptide chain** are written in the DNA as a **series of three-nucleotide words**.
- These **three-nucleotide words** in the gene are **transcribed** into a complementary series of **non-overlapping triplets** in the **mRNA**, which are then **translated** into a sequence of amino acids (as illustrated in the figure 50).

- During **transcription**, a **gene specifies** the **sequence of nucleotide bases** along the length of the **RNA molecule** that is synthesized.
- For each gene, only **one of the two DNA strands** is **transcribed**; this strand is called the **template strand** because it serves as a **template** for ordering the sequence of nucleotides in the RNA transcript. The **same strand** is used as the template each time the **gene is transcribed**.
- However, along the **same chromosomal DNA molecule**, the **opposite strand** may serve as the template for a **different gene**.



(Figure 50)

- The **choice of which strand** serves as the template depends on the **orientation of the enzyme** that carries out transcription, which in turn is determined by the **specific DNA sequence** associated with that gene.
- The **mRNA molecule** produced is **complementary**, not **identical**, to its **DNA template strand**, because **RNA nucleotides** are assembled according to the **base-pairing rules**.
- The pairing follows the same principle as in **DNA replication**, except that **U** (the RNA substitute for **T**) pairs with **A**, and **mRNA** contains **ribose** instead of **deoxyribose**.
- Just like a newly synthesized strand of DNA, the **RNA molecule** is built in an **antiparallel direction** relative to the **DNA template strand**.
- In the example shown in the figure, the **DNA template triplet** 3'–ACC–5' serves as a model for 5'–UGG–3' in the **mRNA molecule**.
- The **three nucleotides** of the mRNA are called **codons**, and they are conventionally written in the **5'→3' direction**.
- In this example, **UGG** is the **codon** for the amino acid **tryptophan** (abbreviated **Trp** or **W**).
- The term **codon** is also used to refer to the **triplet nucleotide sequence** in the **DNA coding strand**—the strand that is **not used as a template**. These codons are

complementary to the **template strand** and thus **identical in sequence** to the mRNA, except that they contain **T** wherever the mRNA has **U**.

- For this reason, the **non-template DNA strand** is often called the **coding strand**. By convention, when a **gene sequence** is written, the **coding strand sequence** is used.

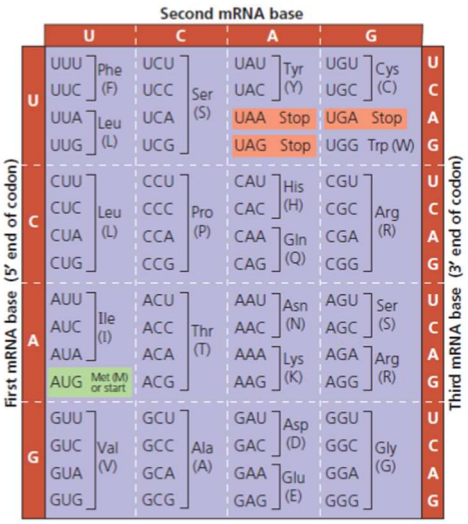
Cracking the Code:

- **Molecular biologists cracked the genetic code** in the early 1960s, when a series of experiments revealed the **amino acid translations** corresponding to each **RNA codon**.
- The **first codon** was deciphered in **1961** by **Marshall Nirenberg** and his colleagues. Nirenberg synthesized an **artificial mRNA** by linking together many identical **RNA nucleotides** containing **uracil (U)** as their base.
- Regardless of where the **genetic message** started or stopped, it could contain only one possible codon **UUU**, repeated continuously.
- Nirenberg added this **poly-U polynucleotide** to a **test-tube mixture** containing **amino acids, ribosomes**, and other components required for **protein synthesis**.
- His **artificial system** translated the **poly-U mRNA** into a **polypeptide** consisting of many units of the amino acid **phenylalanine (Phe or F)** linked together in a long **polyphenylalanine chain**.
- Thus, Nirenberg concluded that the **mRNA codon UUU specifies the amino acid phenylalanine**. Soon afterward, the amino acids specified by the codons **AAA**, **GGG**, and **CCC** were also identified.
- By the **mid-1960s**, the codons for **all 64 triplets** had been deciphered.
- As shown in the **following (table 51)**, **61 of the 64 triplet codons** specify **amino acids**.
- The remaining **three codons** do not specify amino acids; they serve as **"stop" signals**, or **termination codons**, marking the **end of translation**.
- Note that the **codon AUG** has a **dual function**: it codes for the amino acid **methionine (Met or M)** and acts as a **"start" signal** the **initiation codon**.
- Genetic messages typically **begin with the mRNA codon AUG**, which signals the **protein-synthesizing machinery** to start translation at that site. Because **AUG** also

specifies **methionine**, polypeptide chains **begin with methionine** when first synthesized; however, an enzyme may later **remove this initiating amino acid** from the chain.)

- As shown in the table, the **genetic code is redundant** for example, both **GAA** and **GAG** specify **glutamic acid,** but it is **not ambiguous**, meaning that **no codon** specifies **more than one amino acid**.

The codon table for mRNA. The three nucleotide bases of an mRNA codon are designated here as the first, second, and third bases, reading in the 5¿ S 3¿ direction along the mRNA. The codon AUG not only stands for the amino acid methionine (Met, or M) but also functions as a "start" signal for ribosomes to begin translating the mRNA at that point. Three of the 64 codons function as "stop" signals, marking where ribosomes end translation.



(Figure 51)

Transcription is the DNA-Directed Synthesis of RNA: a Closer Look:

We will now **reexamine transcription**, the first stage of **gene expression**, in greater detail.

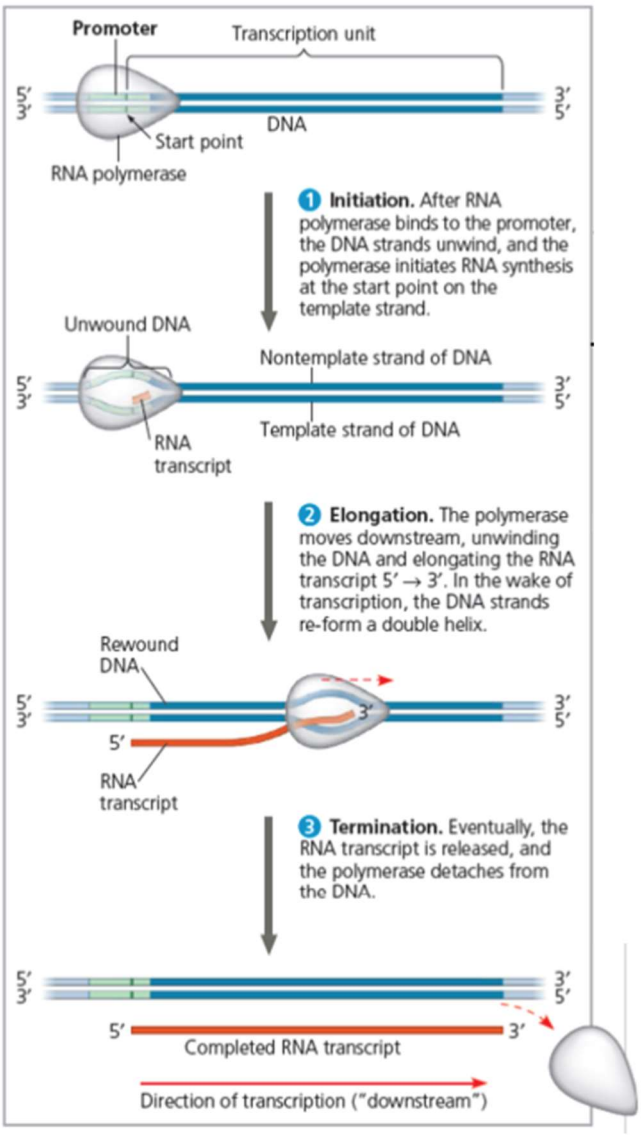
Molecular Components of Transcription:

- **Messenger RNA (mRNA)**, which carries information from DNA to the cell's **protein-synthesizing machinery**, is **transcribed from the template strand** of a gene.
- An enzyme called **RNA polymerase pries apart** the two strands of DNA and **joins** together complementary **RNA nucleotides** along the DNA template strand, thereby **elongating** the RNA polynucleotide (see next figure 52).
- Like **DNA polymerases**, which function in DNA replication, **RNA polymerases** can assemble a polynucleotide **only in the 5'→3' direction**, by adding nucleotides to the **3' end** of the growing chain.
- However, unlike DNA polymerases, **RNA polymerases can start a chain from scratch**; they do **not require a preexisting primer** to add the first nucleotide.
- Specific **nucleotide sequences** along the DNA mark where transcription **begins and ends**. The sequence where **RNA polymerase attaches and initiates transcription** is called the **promoter**.
- In **bacteria**, the sequence that signals the end of transcription is called the **terminator**, while in **eukaryotes** the termination mechanism is **more complex**

and differs.

- Molecular biologists refer to the **direction of transcription** as **"downstream"**, and the opposite direction as **"upstream."** These terms are also used to describe **nucleotide sequence locations** within DNA or RNA.
- Thus, the **promoter sequence** in DNA is said to be **upstream** of the **terminator**. The stretch of DNA **downstream from the promoter** that is **transcribed into an RNA molecule** is called a **transcription unit**.
- **Bacteria** possess a **single type of RNA polymerase** that synthesizes not only **mRNA** but also other forms of RNA involved in protein synthesis, such as **ribosomal RNA (rRNA)**.
- In contrast, **eukaryotes** have **at least three types of RNA polymerase** within their nuclei.

The stages of transcription: initiation, elongation, and termination. This general depiction of transcription applies to both bacteria and eukaryotes, but the details of termination differ, as described in the text. Also, in a bacterium, the RNA transcript is immediately usable as mRNA; in a eukaryote, the RNA transcript must first undergo processing.



(Figure 52)

- The type responsible for the synthesis of **pre-mRNA** is **RNA polymerase II**, while the **other RNA polymerases** transcribe RNA molecules **not translated into protein**.
- In the following discussion, we begin with the **features of mRNA synthesis** common to both **bacteria and eukaryotes** and then describe some of the **key differences** between them.

Synthesis of an RNA transcript:

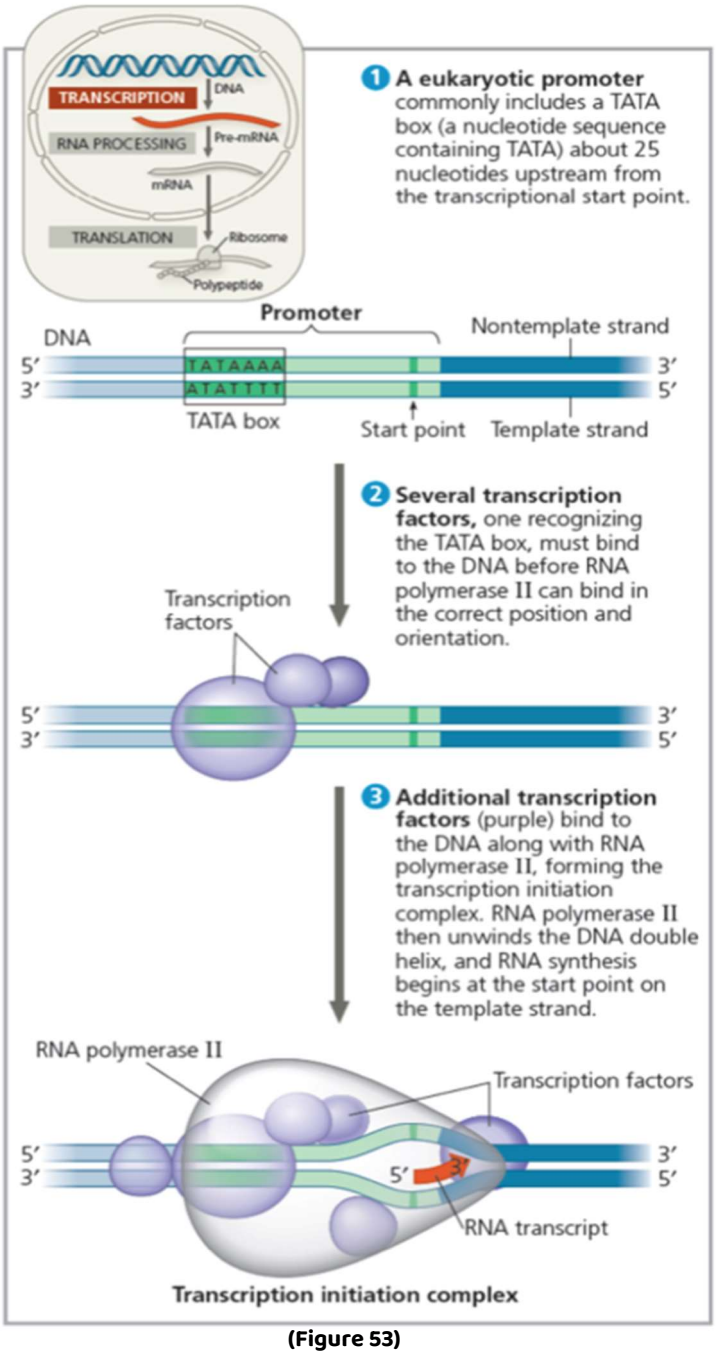
The **three stages of transcription** are **initiation**, **elongation**, and **termination** of the RNA strand. We will now explore these stages in detail and introduce the **key terms** used to describe each process.

RNA Polymerase Binding and Initiation of Transcription:

- The **promoter of a gene** includes within it a **transcription start point** the nucleotide where **RNA polymerase** begins building the **mRNA**. The promoter usually **extends several dozen or so nucleotide pairs upstream** from the start point (as shown in the figure 53).
- Based on interactions with proteins discussed later, **RNA polymerase binds** to the promoter at a **precise location and orientation**. This positioning determines **where transcription begins** and **which strand of the DNA double helix** will serve as the **template**.
- Certain regions of the **promoter** are particularly important for ensuring that **RNA polymerase binds** in a way that guarantees **transcription starts at the correct site**.
- In **bacteria**, a part of the **RNA polymerase molecule itself** recognizes and binds directly to the **promoter**.
- In **eukaryotes**, however, a set of proteins called **transcription factors** mediates the **binding of RNA polymerase** and the **initiation of transcription**.
- Only **after** the transcription factors have bound tightly to the **promoter** does **RNA polymerase II** attach to it. The entire assembly of **transcription factors** and **RNA polymerase II** bound to the promoter is called the **transcription initiation complex**.
- The figure illustrates the **role of transcription factors** and the **crucial DNA promoter sequence** known as the **TATA box** in the formation of the **initiation complex** at a eukaryotic promoter.
- The interaction between **eukaryotic RNA polymerase** and **transcription factors** exemplifies the importance of **protein–protein interactions** in controlling **transcription in eukaryotes**.

- Once the appropriate transcription factors are **firmly bound** to the **promoter DNA**, and the **polymerase** is correctly oriented on the DNA, the enzyme **unwinds the DNA strands** and **begins transcribing** the **template strand** at the **start point**.

The initiation of transcription at a eukaryotic promoter. In eukaryotic cells, proteins called transcription factors mediate the initiation of transcription by RNA polymerase II..

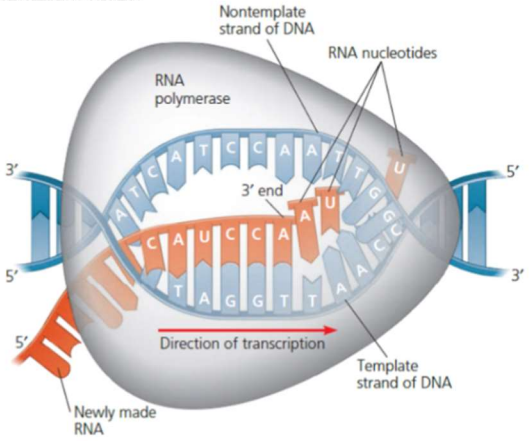


(Figure 53)

Elongation of the RNA Strand:

- As **RNA polymerase** moves along the **DNA**, it **unwinds the double helix**, exposing about **10–20 DNA nucleotides at a time** for **base pairing** with **RNA nucleotides** (as shown in the figure 54).
- The enzyme adds **RNA nucleotides** to the **3' end** of the growing **RNA molecule** as it progresses along the DNA helix.
- Behind this advancing wave of RNA synthesis, the newly formed **RNA strand peels away** from its **DNA template**, and the **DNA double helix reforms**.

Transcription elongation. RNA polymerase moves along the DNA template strand, joining complementary RNA nucleotides to the 3 end of the growing RNA transcript. Behind the polymerase, the new RNA peels away from the template strand, which re-forms a double helix with the nontemplate strand.



(Figure 54)

- A single gene can be **transcribed simultaneously** by **multiple RNA polymerase molecules** following one another like **trucks in a convoy**.
- A **growing RNA strand** emerges from each polymerase, and the **length of each strand** reflects **how far the enzyme has progressed** from the start point along the template.
- The **simultaneous activity** of many polymerase molecules **transcribing the same gene** greatly increases the **amount of mRNA produced**, allowing the cell to **synthesize large quantities** of the **encoded protein** efficiently.

Termination of Transcription:

- **Bacteria** and **eukaryotes** differ in how they **terminate transcription**.
- In **bacteria**, transcription proceeds through a **terminator sequence** in the DNA.
- The **transcribed terminator** (an RNA sequence) functions as a **termination signal**, causing the **polymerase to detach** from the DNA and **release the RNA transcript**, which **requires no further modification**.
- In **eukaryotes**, **RNA polymerase II** transcribes a specific DNA sequence known as the **polyadenylation signal sequence**, which codes for the **polyadenylation signal**

(AAUAAA) in the **pre-mRNA**. This is called a **signal** because, as soon as this six-nucleotide stretch of RNA appears, it is **immediately bound by specific proteins** within the nucleus.

- About **10 to 35 nucleotides downstream** from the **AAUAAA** sequence, these proteins **cleave the RNA transcript** from the polymerase, releasing the **pre-mRNA molecule**. The **pre-mRNA** then undergoes **post-transcriptional processing** before it becomes a **functional mRNA** ready for translation.

Eukaryotic cells modify RNA after transcription:

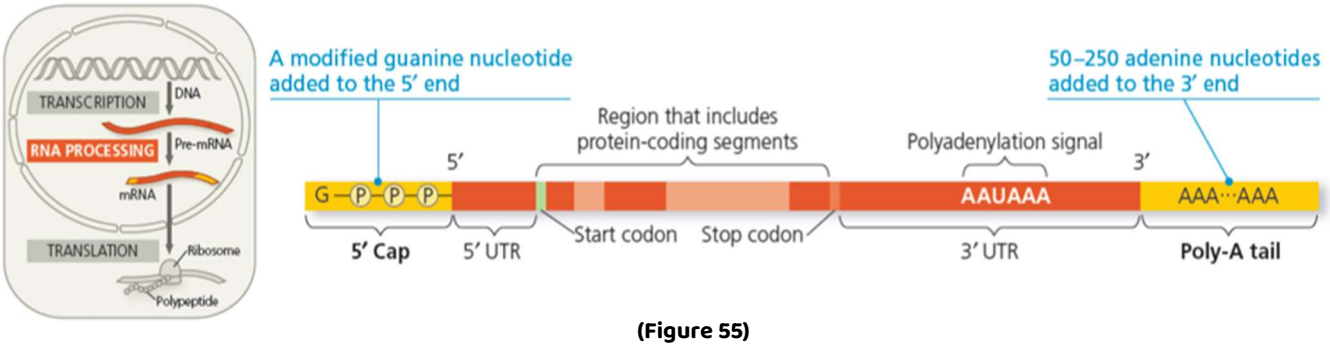
- Within the **nucleus of a eukaryotic cell**, enzymes **modify the pre-mRNA** in specific ways **before the genetic message is sent to the cytoplasm**. During this **RNA processing**, **both ends** of the primary transcript are **altered**.
- In addition, in most cases, **certain interior sections** of the RNA molecule are **cut out**, and the **remaining parts** are **spliced together**. These modifications produce a **mature mRNA molecule** that is **ready for translation** into protein.

Alteration of mRNA Ends:

- Each end of the **pre-mRNA molecule** is **modified in a specific way** (as shown in the figure 55).
- The **5' end**, which is synthesized first, receives a **5' cap** a **modified form of a guanine (G) nucleotide** that is added to the 5' end **after the first 20–40 nucleotides** have been transcribed.
- The **3' end** of the pre-mRNA is also modified **before the mRNA leaves the nucleus**. Recall that the pre-mRNA is **cleaved and released** shortly after the **polyadenylation signal (AAUAAA)** is transcribed.
- At the **3' end**, an enzyme then adds **50 to 250 additional adenine (A) nucleotides**, forming a **poly-A tail**.
- The **5' cap** and the **poly-A tail** share several **important functions**:
    1. They appear to **facilitate the export** of the **mature mRNA** from the **nucleus**.
    2. They **protect the mRNA** from **degradation** by **hydrolytic enzymes**.

3. They help **ribosomes attach** to the **5' end** of the mRNA once it reaches the **cytoplasm**.

- The figure also shows **untranslated regions (UTRs)** at both the **5' and 3' ends** of the mRNA (referred to as the **5' UTR** and **3' UTR**).
- These **UTRs** are parts of the mRNA that are **not translated into protein**, but they have **other essential roles**, such as **ribosome binding** and **regulation of translation efficiency**.



(Figure 55)

Split Genes and RNA Splicing:

- A remarkable stage of **RNA processing** in the **nucleus of a eukaryotic cell** is **RNA splicing** (as shown in the figure 56), during which **large portions of the RNA molecule are removed**, and the **remaining segments are reconnected**.
- The **average length of a transcription unit** along a human DNA molecule is about **27,000 base pairs**, so the **primary RNA transcript** is also quite long. In contrast, an **average protein** consisting of **about 400 amino acids** requires only around **1,200 nucleotides** in the RNA to **code for it**.

(Remember, each amino acid is encoded by a triplet of nucleotides.)

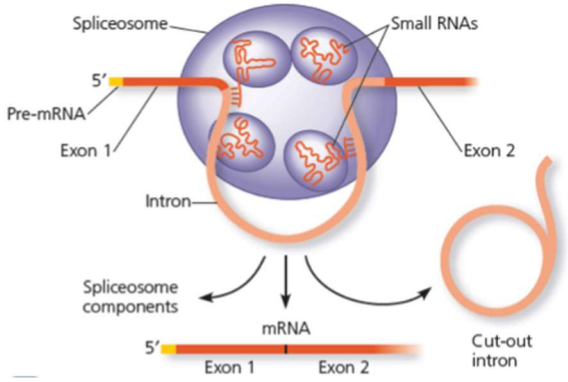
- This is because **most eukaryotic genes** and their **RNA transcripts** contain long **noncoding stretches of nucleotides** regions that are **not translated** into protein.

- Most of these **noncoding sequences** are **interspersed** among the **coding regions** of the gene.
- In other words, the **DNA nucleotide sequence** that encodes a **eukaryotic polypeptide** is usually **not continuous**; it is **divided into segments**.
- The **noncoding segments** of DNA that lie between the **coding regions** are called **intervening sequences**, or **introns**. The **other regions** are called **exons**, because they are **expressed**, usually by being **translated into amino acid sequences**.
- (The exceptions are the **UTRs** untranslated regions of the exons at the RNA ends, which form part of the mRNA but are **not translated** into protein.)
- When a **primary transcript** of a gene is made, **RNA polymerase II** transcribes both the **introns** and the **exons** from the DNA. However, the **mRNA molecule** that eventually enters the **cytoplasm** is a **shortened version**. During **RNA splicing**, the **introns are removed** from the molecule, and the **exons are joined together**, forming an **mRNA molecule** with a **continuous coding sequence**.

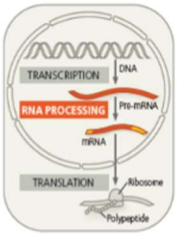
How is pre-mRNA spliced?

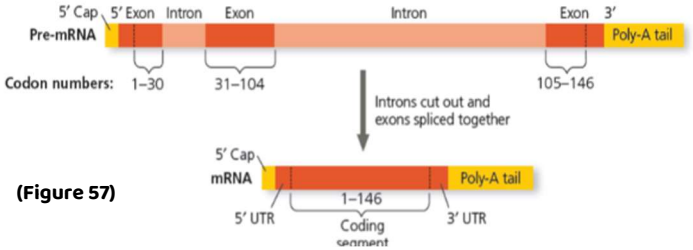
- The **introns are removed** by a large **complex** composed of **proteins** and **small RNAs** called a **spliceosome**.
- This complex **binds to several short nucleotide sequences** along the intron, including **key sequences at each end** (see figure 57).
- The **intron is then released** (and quickly **degraded**), while the **spliceosome joins together** the **exons** that **flanked** the intron.
- It has been found that the **RNAs within the spliceosome** not only participate in **spliceosome assembly** and **recognition of splice sites** but also **catalyze the splicing reaction** itself.

Figure 56. A spliceosome splicing a pre-mRNA. The diagram shows a portion of a pre-mRNA transcript, with an intron (pink) flanked by two exons (red). Small RNAs within the spliceosome base-pair with nucleotides at specific sites along the intron. Next, small spliceosome RNAs catalyze cutting of the pre-mRNA and the splicing together of the exons, releasing the intron for rapid degradation.



RNA processing: RNA splicing. The RNA molecule shown here codes for -globin, one of the polypeptides of hemoglobin. The numbers under the RNA refer to codons; -globin is 146 amino acids long. The -globin gene and its pre-mRNA transcript have three exons, corresponding to sequences that will leave the nucleus as mRNA. (The 5¿ UTR and 3¿ UTR are parts of exons because they are included in the mRNA; however, they do not code for protein.) During RNA processing, the introns are cut out and the exons spliced together. In many genes, the introns are much longer than the exons.





(Figure 57)

Translation is the RNA-Directed Synthesis of a Polypeptide:

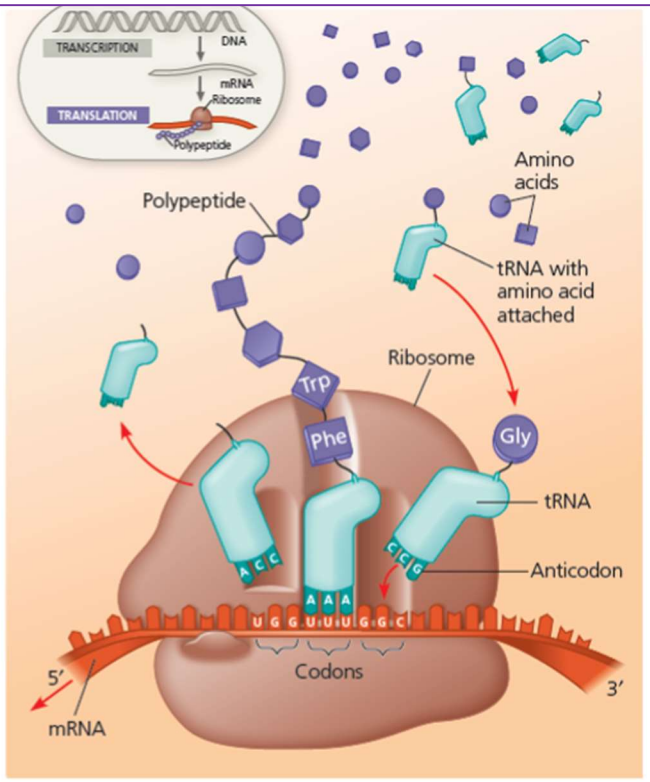
We will now examine how **genetic information flows** from **mRNA to protein**—the process known as **translation** (as shown in the figure 58). Our focus will be on the **basic steps of translation** that occur in both **bacteria** and **eukaryotes**, while also noting the **key differences** between them.

Molecular Components of Translation:

- During **translation**, the cell **"reads" the genetic message** and **builds a polypeptide** accordingly.
- The message consists of a **series of codons** along an **mRNA molecule**, and the **translator** is a molecule called **transfer RNA (tRNA)**.
- The role of **tRNA** is to **transfer amino acids** from the **cytoplasmic pool of amino acids** to a **growing polypeptide** on the **ribosome**.
- The cell keeps its **cytoplasm stocked** with all **20 amino acids**, either by **synthesizing them** from other compounds or by **absorbing them** from the **surrounding solution**.
- The **ribosome**, a structure made of **proteins and RNAs**, **adds each amino acid** brought to it by **tRNA** to the **growing end of the polypeptide chain** (see figure 58).

Translation: the basic concept. As a molecule of mRNA is moved through a ribosome, codons are translated into amino acids, one by one. The translators, or interpreters, are tRNA molecules, each type with a specific anticodon at one end and a corresponding amino acid at the other end. A tRNA adds its amino acid cargo to a growing polypeptide chain when the anticodon hydrogen-bonds to the complementary codon on the mRNA.

(Figure 58)

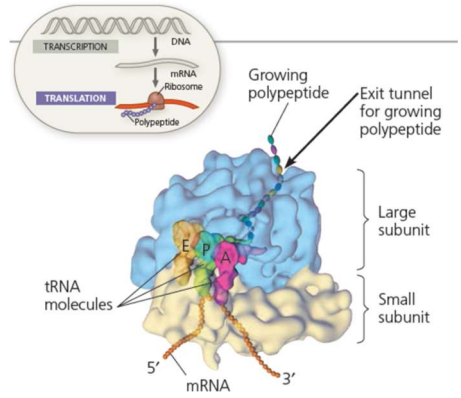
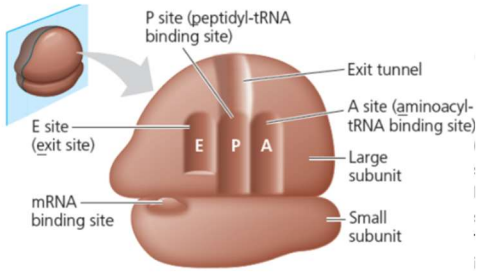


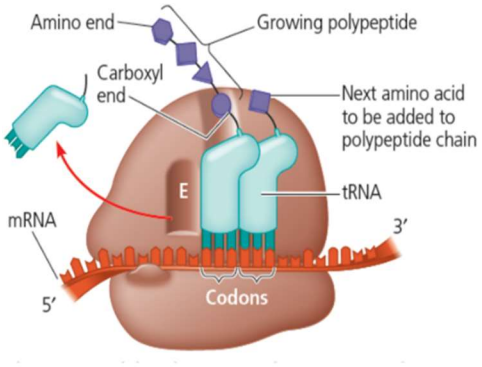
The Structure and Function of Ribosomes:

- **Ribosomes** facilitate the **specific coupling** of **tRNA anticodons** with **mRNA codons** during **protein synthesis**.

- Each ribosome consists of a **large subunit** and a **small subunit**, each made up of **proteins** and one or more molecules of **ribosomal RNA (rRNA)**.

- **Ribosomal RNA** forms the **core** of the **A and P sites** and the **interface** between the two subunits; it also acts as a **catalyst** for **peptide bond formation**. Therefore, the **ribosome** can be regarded as **one colossal ribozyme**.

The anatomy of a functioning ribosome:	
	**(a)** Computer model of functioning ribosome. This is a model of a bacterial ribosome, showing its overall shape. The eukaryotic ribosome is roughly similar. A ribosomal subunit is a complex of ribosomal RNA molecules and proteins.
	**(b)** Schematic model showing binding sites. A ribosome has an mRNA binding site and three tRNA binding sites, known as the A, P, and E sites. This schematic ribosome will appear in later diagrams.

	**(c)** Schematic model with mRNA and tRNA. A tRNA fits into a binding site when its anticodon base-pairs with an mRNA codon. The P site holds the tRNA attached to the growing polypeptide. The A site holds the tRNA carrying the next amino acid to be added to the polypeptide chain. Discharged tRNAs leave from the E site. The polypeptide grows at its carboxyl end.

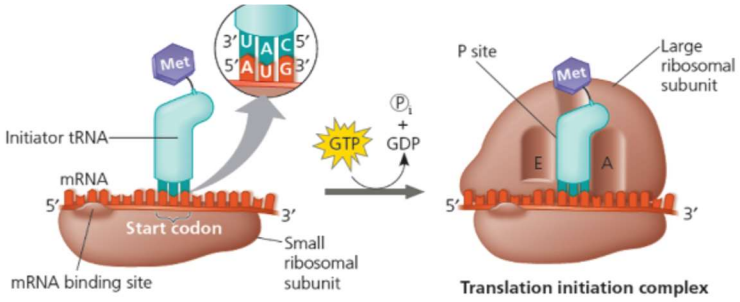
Building a Polypeptide:

We can divide **translation** the **synthesis of a polypeptide** into **three stages**: **initiation**, **elongation**, and **termination**. All three stages require **protein factors** that assist in the process of translation. Some steps in **initiation** and **elongation** also require **energy**, which is supplied by the **hydrolysis of guanosine triphosphate (GTP)**.

Ribosome Association and Initiation of Translation:

- In both **bacteria** and **eukaryotes**, the **start codon (AUG)** marks the **beginning of translation**; this is crucial because it establishes the **reading frame** for the mRNA codons.
- In the **first step of translation**, the **small ribosomal subunit** binds to both the **mRNA** and an **initiator tRNA**, which carries the amino acid **methionine**.
- In **eukaryotes**, the **small subunit–initiator tRNA complex** first binds to the **5' cap** of the mRNA and then **moves downstream** along the mRNA until it reaches the **start codon (AUG)**, where the **initiator tRNA hydrogen-bonds** with the **start codon**.

- Thus, the **first components** that come together during the **initiation stage of translation** are the **mRNA**, the **tRNA carrying the first amino acid of the polypeptide**, and the **small ribosomal subunit** (see figure 59).



❶ A small ribosomal subunit binds to a molecule of mRNA. In a bacterial cell, the mRNA binding site on this subunit recognizes a specific nucleotide sequence on the mRNA just upstream of the start codon. An initiator tRNA, with the anticodon UAC, base-pairs with the start codon, AUG. This tRNA carries the amino acid methionine (Met).

❷ The arrival of a large ribosomal subunit completes the initiation complex. Proteins called initiation factors (not shown) are required to bring all the translation components together. Hydrolysis of GTP provides the energy for the assembly. The initiator tRNA is in the P site; the A site is available to the tRNA bearing the next amino acid.

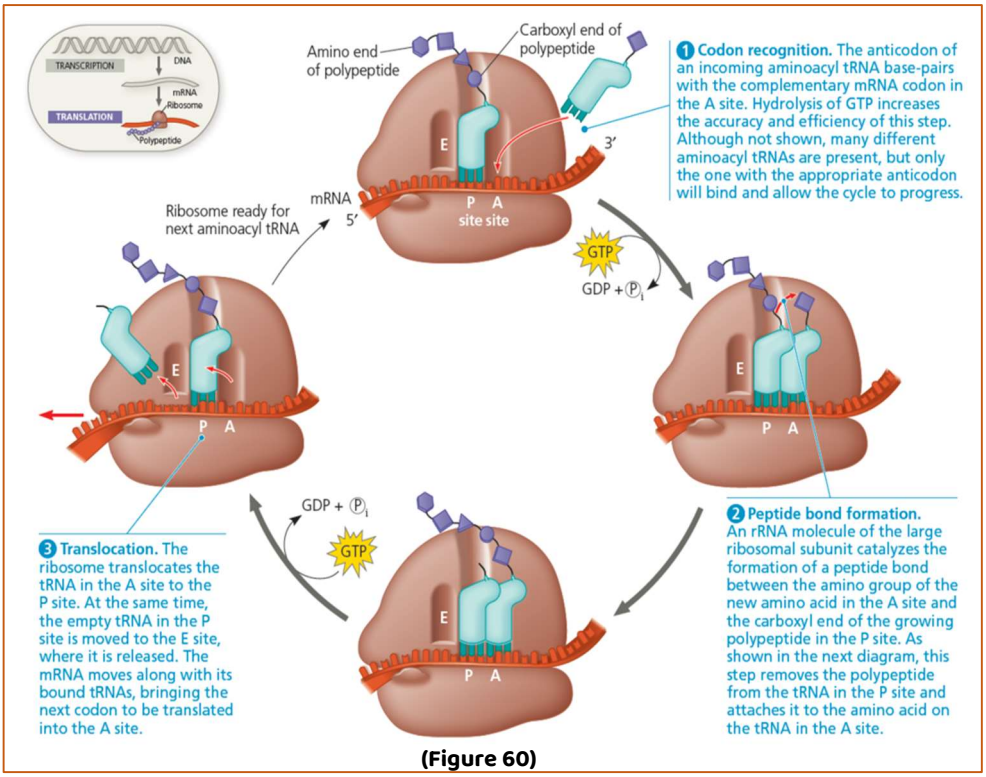
(Figure 59)

- This is followed by the **attachment of the large ribosomal subunit**, completing the **translation initiation complex**. **Proteins called initiation factors** are required to assemble all these components, and the cell also **expends energy** derived from the **hydrolysis of GTP** to form the initiation complex.
- When **initiation** is complete, the **initiator tRNA** sits in the **P site** of the ribosome, and the **A site** is vacant and ready to receive the next **aminoacyl tRNA**.
- Note that the **polypeptide** is always synthesized in **one direction only** from the **initial methionine** at the **amino (N-) terminus** toward the **final amino acid** at the **carboxyl (C-) terminus**.

Elongation of the Polypeptide Chain:

- During the **elongation stage** of translation, **amino acids** are added **one by one** to the preceding amino acid at the **C-terminus** of the **growing polypeptide chain**.

- Each addition involves the participation of several **proteins called elongation factors**, and the process occurs in a **cyclical sequence of three steps**, as illustrated in the following figure 60.



(Figure 60)

Termination of Translation:

- The **final stage** of translation is **termination** (see next figure 61).
- **Elongation** continues until a **stop codon** on the **mRNA** reaches the **A site**. The three **stop codons**-**UAG**, **UAA**, and **UGA** (all written 5'→3')—do **not code for amino acids** but instead serve as **signals to stop translation**.
- A **release factor**, a **protein shaped like an aminoacyl tRNA**, binds **directly to the stop codon** in the **A site**. The release factor causes the **addition of a water molecule** instead of an amino acid to the **polypeptide chain** (water molecules are abundant in the cytosol).
- This reaction **hydrolyzes** the bond between the **completed polypeptide** and the **tRNA** in the **P site**, releasing the polypeptide through the **exit tunnel** of the

ribosome's large subunit. The remaining components of the **translation assembly** are then **disassembled** in a multistep process assisted by **other protein factors**.

- The **breakdown of the translation assembly** requires the **hydrolysis of two additional GTP molecules**.

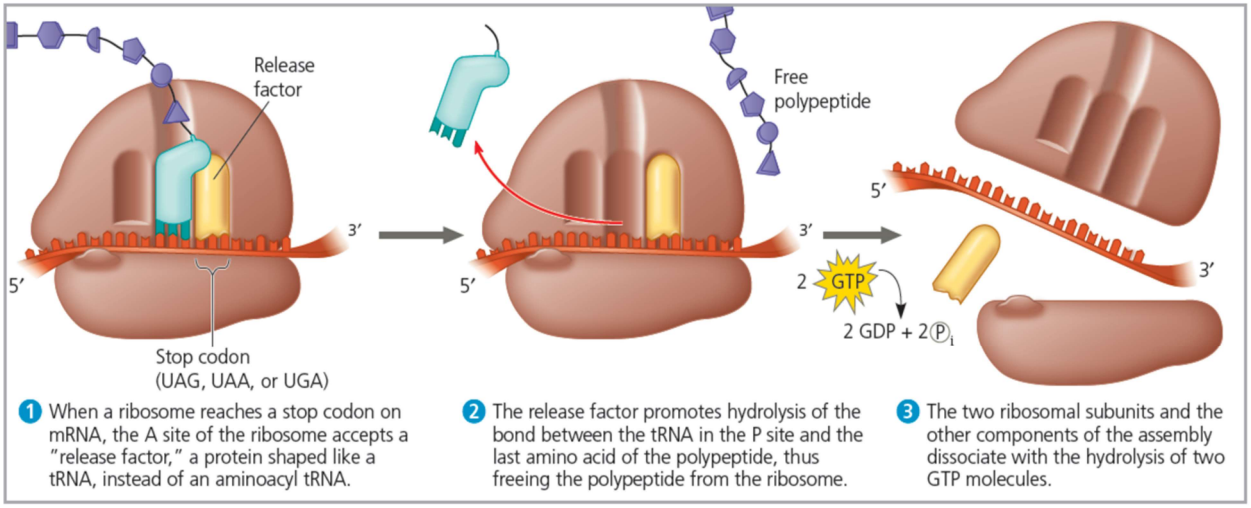


Figure 61. The final stage of translation is termination

Targeting Polypeptides to Specific Locations:

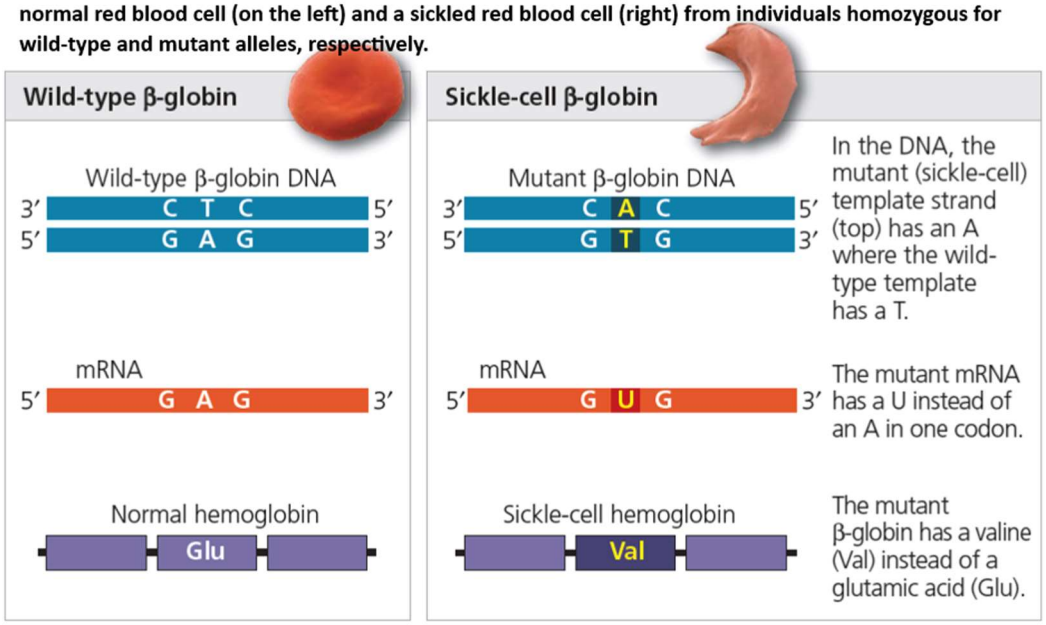
- It is well known that **eukaryotic cells** active in **protein synthesis** possess **two populations of ribosomes**: **free** and **bound**. The **free ribosomes**, which are **suspended in the cytosol**, primarily **synthesize proteins** that remain in the **cytosol** and **function there**.
- In contrast, **bound ribosomes** are attached to the **endoplasmic reticulum (ER)** or the **nuclear envelope**.
- These **bound ribosomes** produce **proteins destined for the endomembrane system** as well as **proteins secreted from the cell**, such as **insulin**.
- It is important to note that the **ribosomes themselves are identical**, and they can **alternate** between being **free** at one time and **bound** the next, depending on the **protein being synthesized**.

Mutations of one or a few Nucleotides can Affect Protein Structure and Function:

- Now that we have explored the process of **gene expression**, we can begin to understand the **effects of changes** on a cell's **genetic information**.
- These changes, called **mutations**, are responsible for the **vast diversity of genes** found among living organisms, as **mutations** are the **ultimate source of new genes**.
- Here, we focus on **small-scale mutations**, involving **one or a few pairs of nucleotides**, including **point mutations**, which are changes in a **single nucleotide pair** within a gene.
- If a **point mutation** occurs in a **gamete** or in a **cell that gives rise to gametes**, it may be **passed on to offspring** and **future generations**.
- When a mutation has an **adverse effect** on an individual's **phenotype**, the resulting condition is referred to as a **genetic disorder** or **hereditary disease**.
- For example, the **genetic basis** of **sickle-cell disease** can be traced to a **single nucleotide-pair substitution** in the gene that encodes the **β-globin polypeptide** of hemoglobin.
- A **change in one nucleotide** of the **template strand DNA** alters the **mRNA** and results in the production of an **abnormal protein** (as shown in the figure 62).
- In individuals who are **homozygous for the mutant allele**, the **sickling** of red blood cells caused by the altered hemoglobin leads to the **multiple symptoms** associated with **sickle-cell disease**, as previously discussed.

- Another **disorder** resulting from a **point mutation** is a **heart condition** known as **familial cardiomyopathy**, which accounts for some of the **tragic cases of sudden death** among young athletes. **Point mutations** have been identified in **several genes encoding muscle proteins**, and any one of these mutations can lead to the development of this disorder.

The molecular basis of sickle-cell disease: a point mutation. The allele that causes sickle-cell disease differs from the wild-type (normal) allele by a single DNA nucleotide pair. The micrographs are SEMs of a normal red blood cell (on the left) and a sickled red blood cell (right) from individuals homozygous for wild-type and mutant alleles, respectively.



(Figure 62)

Types of Small-Scale Mutations

Substitutions:

•A **nucleotide-pair substitution** is the **replacement of one nucleotide and its partner** with another pair of nucleotides (Figure 63a).

- Some substitutions have **no effect** on the **encoded protein** because of the **redundancy of the genetic code** more than one codon can specify the same amino acid.
- For example, if a mutation changes the **template strand** from **3'–CCG–5'** to **3'–CCA–5'**, the **mRNA codon** that was originally **GGC** becomes **GGU**, but **glycine** will still be inserted at the correct position in the protein. In other words, a change in a nucleotide

pair may convert one codon into another that is **translated into the same amino acid**. Such a change is an example of a **silent mutation**, which has **no observable effect** on the organism's **phenotype**. Interestingly, evidence suggests that **some silent mutations** can indirectly affect **where or how much a gene is expressed**, even though the resulting protein itself is unchanged.

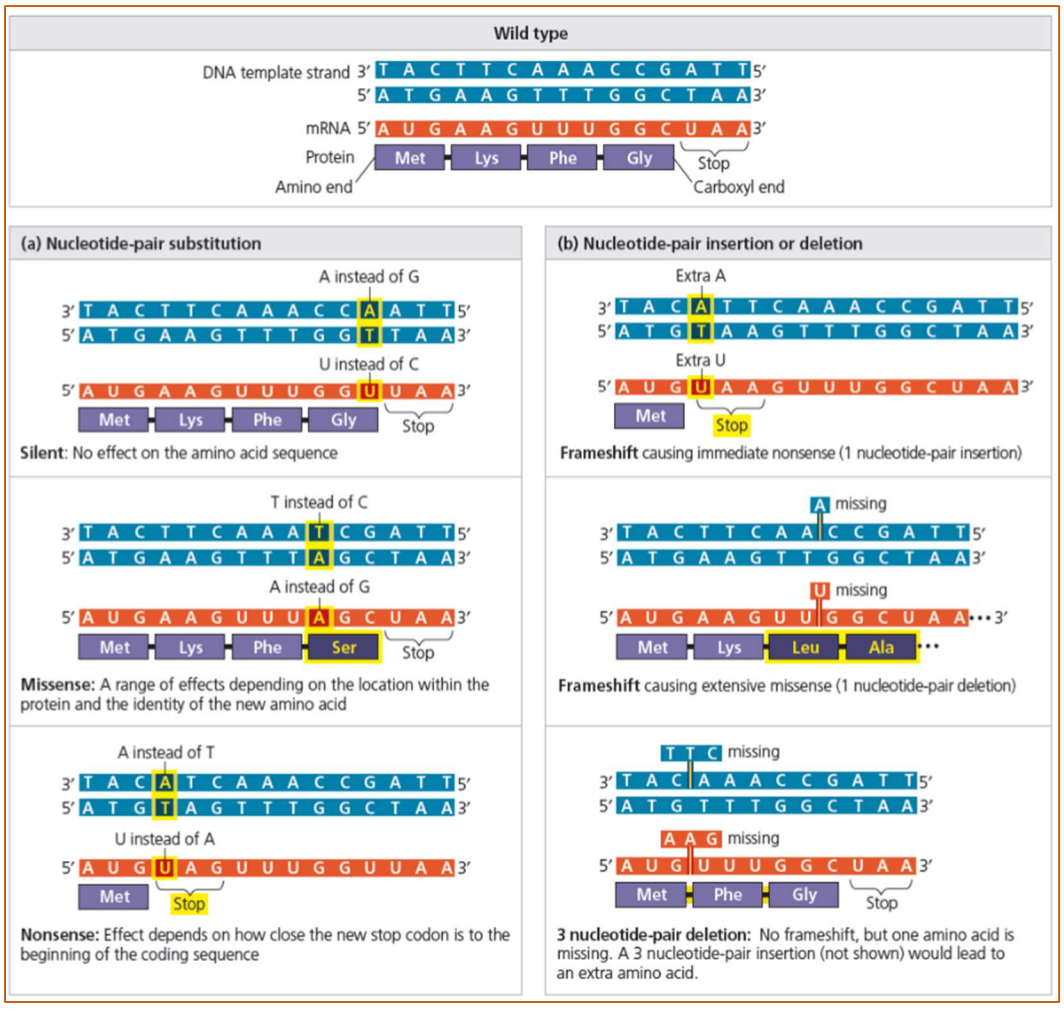
- Substitutions that **change one amino acid** to another are called **missense mutations**.
- Such a mutation may have **little effect** on the protein: the **new amino acid** may have **chemical properties** like those of the one it replaces, or it may occur in a region of the protein where the **precise sequence** of amino acids is **not essential** to the protein's function.
- However, **more significant substitutions** can cause **major changes** in a protein's structure or activity.
- A single amino acid change in a **crucial region** of a protein such as the **β-globin subunit** of hemoglobin shown in the previous figure, or at the **active site** of an enzyme can **drastically alter the protein's activity**.
- Occasionally, such mutations may produce an **improved** or **novel protein**, but more often they are **neutral or detrimental**, leading to a **nonfunctional** or **less active protein** that **impairs cellular function**.
- Most **substitution mutations** are **missense mutations** that is, the altered codon still **codes for an amino acid**, which "makes sense," though **not necessarily the correct one**.
- However, a **point mutation** can also change a codon for an amino acid into a **stop codon**. This is called a **nonsense mutation**, and it causes **premature termination of translation**. The resulting **polypeptide** is therefore **shorter** than the one encoded by the normal gene. Most **nonsense mutations** lead to the production of **nonfunctional proteins**.

Insertions and Deletions:

- **Insertions and deletions** are **additions** or **losses of nucleotide pairs** in a gene (Figure 63b). These mutations often have a **disastrous effect** on the resulting

protein, far greater than that of substitutions. The **insertion or deletion** of nucleotides can **alter the reading frame** of the genetic message the triplet grouping of nucleotides on the mRNA that is read during translation.

- Such a mutation, called a **frameshift mutation**, occurs when the number of nucleotides inserted or deleted is **not a multiple of three**. As a result, all the nucleotides downstream of the insertion or deletion are **improperly grouped into codons**, leading to **extensive missense mutations** that usually end eventually in a **nonsense mutation**, causing **premature termination** of translation and producing a **nonfunctional protein**. **Insertions and deletions** can also occur **outside coding regions**; these are **not called frameshift mutations**, but they can still have **phenotypic effects** for example, by **altering how a gene is expressed**. In such cases, the **protein is still produced**, but it may **confer a different trait**.



(Figure 63)

New Mutations and Mutagens

Mutations can arise in several ways:

1. **Errors during DNA replication or recombination** – Mistakes made by DNA polymerase or during crossing over can introduce changes in the nucleotide sequence.
2. **X-rays** These forms of **ionizing radiation** can cause breaks or structural changes in DNA molecules.
3. **Chemical mutagens** Certain **chemicals** can modify DNA bases, insert themselves into the DNA helix, or disrupt replication, leading to mutations.

Exercises

Exercise 1	تدريب ١
A particular triplet of bases in the template strand of DNA is 5'-AGT-3'. What would be the corresponding codon for the mRNA that is transcribed?	ثلاثية معينة من القواعد في شريط القالب لـــDNA هي 5'-AGT-3' ما هو الكودون المقابل لـ mRNA المنسوخ؟

A	3′-UCA-5′	C	5′-TCA-3′
B	3′-UGA-5′	D	3′-ACU-5′

First Base	Second Base: U	Second Base: C	Second Base: A	Second Base: G	Third Base
U	UUU, UUC — Phe	UCU, UCC, UCA, UCG — Ser	UAU, UAC — Tyr	UGU, UGC — Cys	U
	UUA, UUG — Leu		UAA — Stop; UAG — Stop	UGA — Stop	C
				UGG — Trp	A
					G
C	CUU, CUC, CUA, CUG — Leu	CCU, CCC, CCA, CCG — Pro	CAU, CAC — His	CGU, CGC, CGA, CGG — Arg	U
			CAA, CAG — Gln		C
					A
					G
A	AUU, AUC, AUA — Ile	ACU, ACC, ACA, ACG — Thr	AAU, AAC — Asn	AGU, AGC — Ser	U
	AUG — Met or Start		AAA, AAG — Lys	AGA, AGG — Arg	C
					A
					G
G	GUU, GUC, GUA, GUG — Val	GCU, GCC, GCA, GCG — Ala	GAU, GAC — Asp	GGU, GGC, GGA, GGG — Gly	U
			GAA, GAG — Glu		C
					A
					G

Exercise 2	تدريب ٢
Which of the following sequences of nucleotides are possible in the template	أيٌّ من التســلسـلات التالية للنيوكليوتيدات يكون ممكنًا في الشريط النموذجي للحمض النووي الذي

strand of DNA that would code for the polypeptide sequence Phe-Leu-Ile-Val?		من شأنه أن يرمز إلى تسلسل متعدد الببتيد Phe-Leu-Ile-Val؟	
A	5′-TTG-CTA-CAG-TAG-3′	C	3′-AAA-AAT-ATA-ACA-5′
B	5′-AUG-CTG-CAG-TAT-3′	D	3′-AAA-GAA-TAA-CAA-5′

Exercise 3		تدريب ٣	
What amino acid sequence will be generated, based on the following mRNA codon sequence?		ما هو تسلسل الأحماض الأمينية الذي سيتم إنشاؤه ، بناءً على تسلسل كودون mRNA التالي؟	
5′-AUG-UCU-UCG-UUA-UCC-UUG-3′			
A	Met-Arg-Glu-Arg-Glu-Arg	C	Met-Ser-Leu-Ser-Leu-Ser
B	Met-Glu-Arg-Arg-Glu-Leu	D	Met-Ser-Ser-Leu-Ser-Leu

Exercise 4		تدريب ٤	
According to the central dogma, what is the intermediate molecule involved in the flow of information in a cell that should go in the blank?		وفقًا للفراغ في الوسط، ما هو الجزيء الوسيط المتضمن في تدفق المعلومات في الخلية الذي يجب أن يكون في الفراغ؟	
DNA → _____ → Proteins			
A	mtDNA	C	mRNA
B	rRNA	D	tRNA

Exercise 5		تدريب ٥	
Use this model of a eukaryotic transcript to answer the following question.		استخدم هذا النموذج لنسخة حقيقية النواة للإجابة على السؤال التالي.	
E = exon and I = intron UTR E1 I1 E2 I2 E3 I3 E4 UTR-3′-5′			
Which components of the previous molecule will also be found in mRNA in the cytosol?		ما هي مكونات الجزيء السابق التي سيتم العثور عليها أيضًا في mRNA في العصارة الخلوية؟	
A	5′-UTR I1 I2 I3 UTR-3′	C	5′-UTR E1 E2 E3 E4 UTR-3′
B	5′-E1 E2 E3 E4-3′	D	5′-E1 I1 E2 I2 E3 I3 E4-3′

Exercise 6 — تدريب ٦

A part of an mRNA molecule with the following sequence is being read by a ribosome: 5'-CCG-ACG-3' (mRNA). The following charged transfer RNA molecules (with their anticodons shown in the 3' to 5' direction) are available. Two of them can correctly match the mRNA so that a dipeptide can form..

تتم قراءة جزء من جزيء mRNA بالتسلسل التالي بواسطة الرايبوسوم: 5'-CCG-ACG-3' (mRNA). تتوفر جزيئات RNA للنقل المشحونة التالية (بمضاداتها الموضحة في اتجاه 3' إلى 5'). يمكن أن يتطابق اثنان منهم بشكل صحيح مع mRNA بحيث يمكن تشكيل ثنائي الببتيد.

tRNA Anticodon	Amino Acid
GGC	Proline
CGU	Alanine
UGC	Threonine
CCG	Glycine
ACG	Cysteine
CGG	Alanine

Which of the following anticodons in the first tRNA to bind will complement this mRNA?

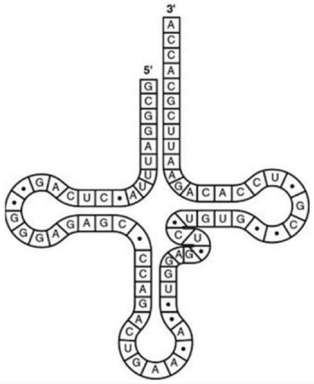
أيٌّ من مضادات الكودونات التالية في الحمض الريبي النووي النقال الأول الذي سيتم ربطه سيكمل هذا الرنا المرسال؟

A	3′-GGC-5′	C	5′-UGC-3′
B	5′-GGC-3′	D	3′-UGC-5′

Exercise 7 — تدريب٧

What type of bonding is responsible for maintaining the shape of the tRNA molecule shown in the figure?

ما نوع الترابط المسؤول عن الحفاظ على شكل جزيء الحمض الريبي النووي النقال الموضح في الشكل؟

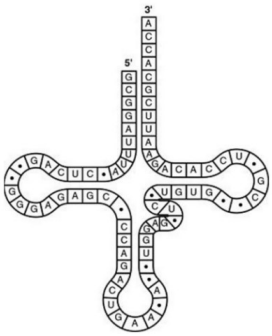


A	ionic bonding between phosphates	الترابط الأيوني بين الفوسفات	A
B	hydrogen bonding between base pairs	الرابطة الهيدروجينية بين أزواج القواعد	B
C	van der Waals interactions beween hydrogen atoms	تفاعلات فان دير فال بين ذرات الهيدروجين	C
D	peptide bonding between amino acids	الرابطة الببتيدية بين الأحماض الأمينية	D

Exercise 8 — تدريب٨

The figure represents tRNA that recognizes and binds a particular amino acid (in this instance, phenylalanine). Which codon on the mRNA strand codes for this amino acid?

يمثل الشكل الحمض الريبي النووي النقال (tRNA) الذي يتعرف على حمض أميني معين ويربطه (في هذه الحالة، فينيل ألانين). ما هو الكودون الموجود على رموز حبلا mRNA لهذا الحمض الأميني؟



A	5′-UGG-3′	C	5′-GUA-3′
B	3′-GUG-5′	D	5′-UUC-3′

Exercise 9 **تدريب٩**

Which of the following types of mutation, resulting in an error in the mRNA just after the AUG start of translation, is likely to have the most serious effect on the polypeptide product?

أي من أنواع الطفرات التالية ، التي تؤدي إلى حدوث خطأ في mRNA بعد بدء الترجمة في AUG مباشرةً ، من المرجح أن يكون لها التأثير الأكثر خطورة على منتج متعدد الببتيد؟

A	a deletion of a codon	حذف كودون	A
B	a deletion of two nucleotides	حذف اثنين من النيوكليوتيدات	B
C	a substitution of the third nucleotide in an ACC codon	استبدال النيوكليوتيدات الثالثة في كودون ACC	C
D	a substitution of the first nucleotide of a GGG codon	استبدال أول نيوكليوتيد لكودون GGG	D

Exercise 10 **تدريب١٠**

Rank the following one-base point mutations with respect to their likelihood of affecting the structure of the corresponding polypeptide (from most likely to least likely).

رتب الطفرات التالية ذات النقطة الأساسية الواحدة فيما يتعلق باحتمالية تأثيرها على بنية البولي ببتيد المقابل (من الأرجح إلى الأقل احتمالًا).

1. insertion mutation deep within an intron

2. substitution mutation at the third position of a codon in an exon

3. substitution mutation at the second position of a codon in an exon

4. deletion mutation within the first exon of the gen

1. إدخال طفرة عميقة داخل intron

2. طفرة استبدال في الموضع الثالث من كودون في الإكسون

3. طفرة استبدال في الموضع الثاني من كودون في الإكسون 4. طفرة حذف داخل الإكسون الأول من الجين	
A 1, 2, 3, 4	C 2, 1, 4, 3
B 4, 3, 2, 1	D 3, 1, 4, 2

Exercise 11	تدريب ١١
Which one of the following structures, if missing, would usually prevent translation from starting?	أي من الهياكل التالية ، إذا كانت مفقودة ، ستمنع عادةً بدء الترجمة؟
A exon	C AUG codon
B 5' cap	D poly-A tail

Exercise 12	تدريب ١٢
Which component is not directly involved in translation?	ما هو المكون الذي لا يدخل مباشرة في الترجمة؟
A GTP	C tRNA
B DNA	D Ribosomes

Chapter Five

Regulation of Gene Expression

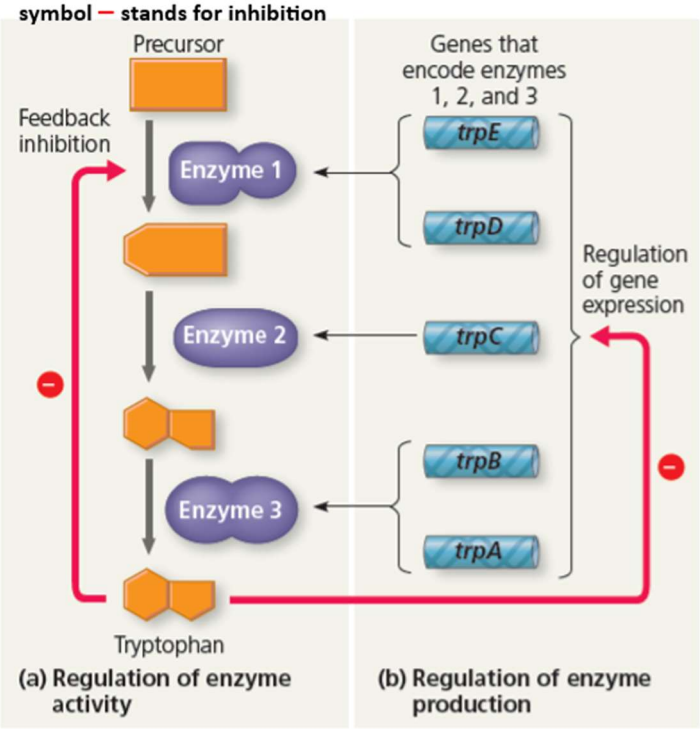
نسمو NSMO
أولمبيـــاد العلوم والرياضيات الوطني

Why is gene expression regulated?

Figure 64. shows E. coli bacteria in two different environments with and without tryptophan.

- Organisms respond to environmental changes by regulating their genes to conserve resources and energy.

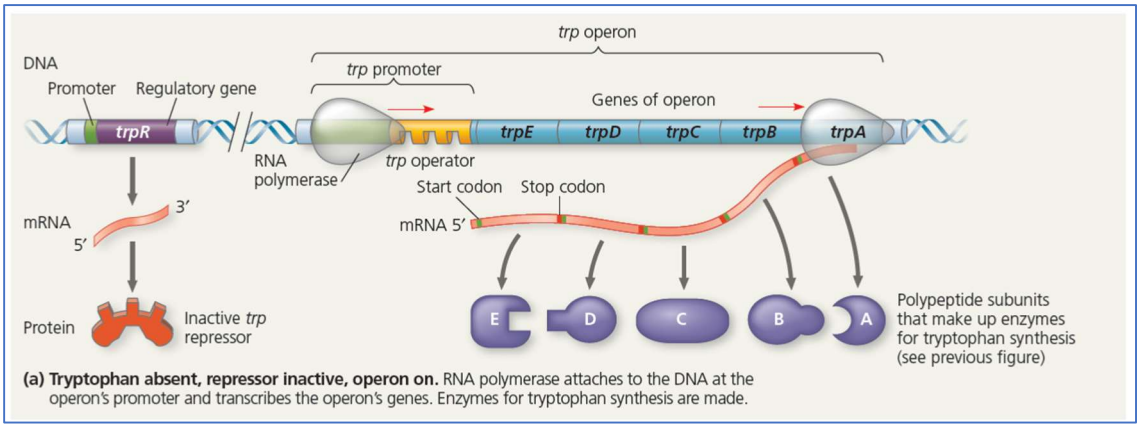
Regulation of a metabolic pathway. In the pathway for tryptophan synthesis, an abundance of tryptophan can both (a) inhibit the activity of the first enzyme in the pathway (feedback inhibition), a rapid response, and (b) repress expression of the genes encoding all subunits of the enzymes in the pathway, a longer-term response. Genes trpE and trpD encode the two subunits of enzyme 1, and genes trpB and trpA encode the two subunits of enzyme 3. (The genes were named before the order in which they functioned in the pathway was determined.) The symbol — stands for inhibition



(Figure 64)

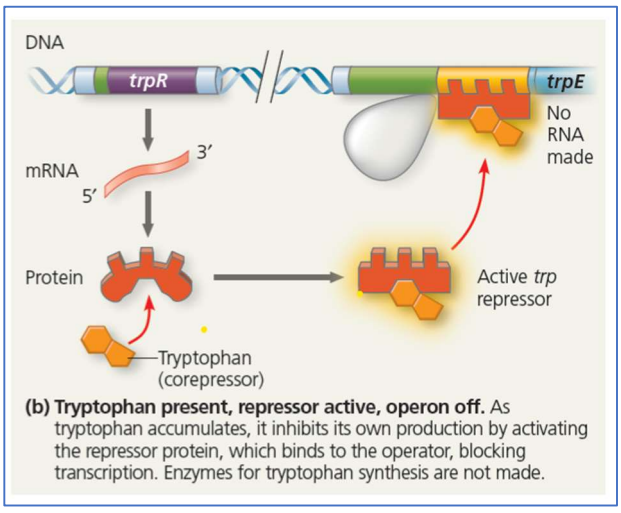
Operon Model – The Fundamental Mechanism in Bacteria

- **Operon:** A cluster of genes controlled together by a single on/off switch.
- **Components of the operon:**
  - **Promoter:** The binding site for the transcription enzyme (RNA polymerase).
  - **Operator:** The binding site for the repressor protein.
  - **Structural genes:** The genes responsible for synthesizing the enzymes.



(Figure 65)

- **Applied Example: Regulation of Tryptophan in Escherichia coli (E. coli)**
  - When **tryptophan levels are low** in the environment, the bacterium **activates the metabolic pathway** to synthesize it.
  - When **tryptophan is abundant**, the bacterium **stops its synthesis** to avoid **wasting resources**.
  - **Mechanisms:**
    - **Feedback Inhibition:** The product (tryptophan) inhibits the activity of enzymes in its own synthesis pathway.
    - **Transcriptional Regulation:** The cell stops producing the enzymes of the pathway by halting **transcription** of the related genes.

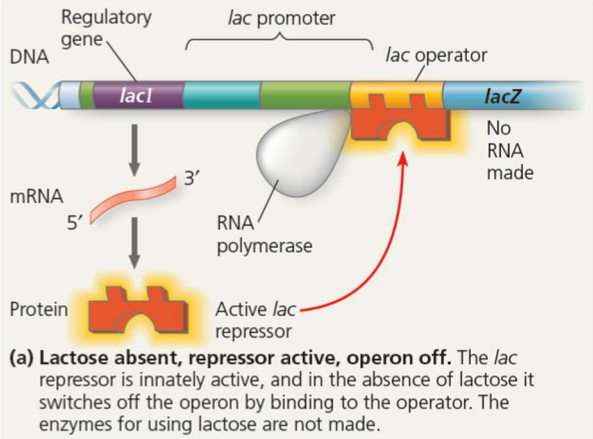


(Figure 66)

Two Main Types of Operons:

A. Repressible Operons – Example: the trp operon:

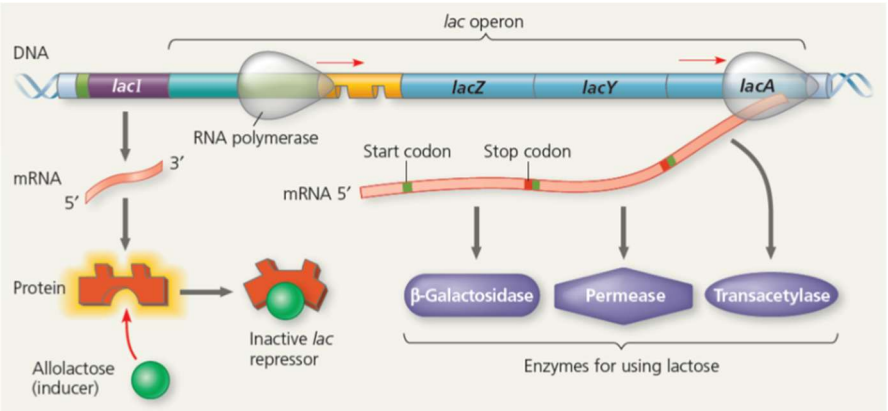
- Usually **active** (producing tryptophan).
- **Repressed** when sufficient tryptophan is present — tryptophan acts as a **corepressor**.



(a) Lactose absent, repressor active, operon off. The *lac* repressor is innately active, and in the absence of lactose it switches off the operon by binding to the operator. The enzymes for using lactose are not made.

(Figure 67)

- **B. Inducible Operons** – Example: the lac operon
  - Usually **inactive** (not producing lactose-digesting enzymes).
  - **Induced** when lactose is present — lactose is converted to **allolactose**, which functions as an **inducer**.

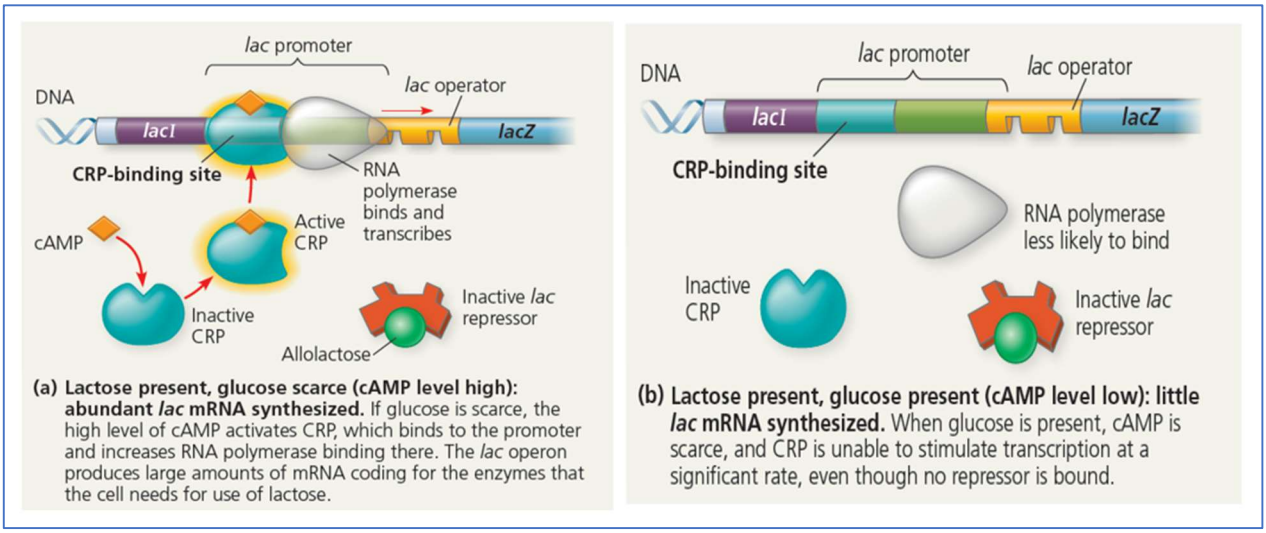


(b) Lactose present, repressor inactive, operon on. Allolactose, an isomer of lactose, binds to the repressor, inactivating it and "derepressing" the operon. The inactive repressor cannot bind to the operator, and so the genes of the *lac* operon are transcribed, and the enzymes for using lactose are made.

(Figure 68)

Positive Regulation – Example: The Effect of Glucose on the lac Operon

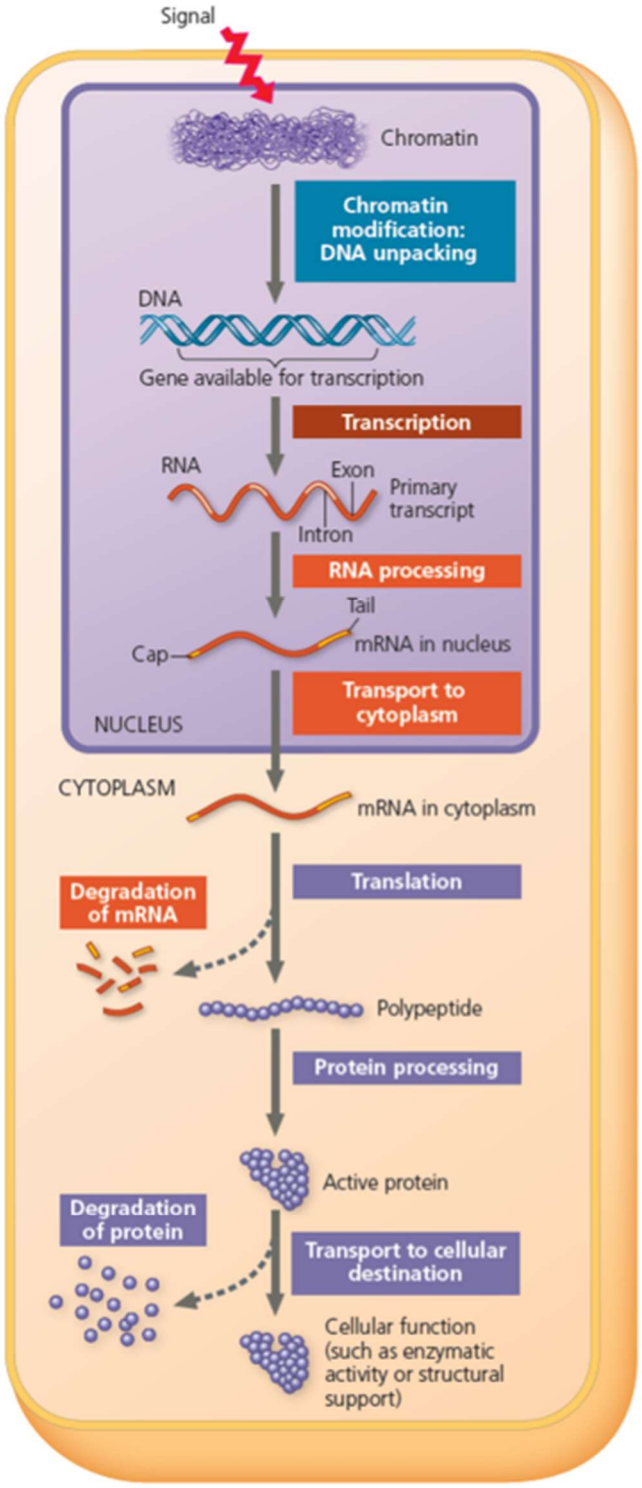
- When **glucose levels are low**, the concentration of **cAMP** increases.
- **cAMP** binds to an **activator protein (CRP – cAMP Receptor Protein)**, activating it.
- The **activated CRP** binds to the **promoter**, enhancing the binding of **RNA polymerase** and **increasing the rate of gene transcription**.



(Figure 69)

Regulation of Gene Expression in Eukaryotes

- It is **more complex** and occurs at **multiple stages**:
    1. **Chromatin Structure Regulation**
    2. **Transcription Initiation Regulation**
    3. **RNA Processing**
    4. **mRNA Stability and Degradation**
    5. **Translation**
    6. **Protein Processing**
- **Goal:** To achieve **cell differentiation** and **differential gene expression** in **multicellular organisms**.



Stages in gene expression that can be regulated in eukaryotic cells. In this diagram, the colored boxes indicate the processes most often regulated; each color indicates the type of molecule that is affected (blue = DNA, red/orange = RNA, purple = protein). The nuclear envelope separating transcription from translation in eukaryotic cells offers an opportunity for post-transcriptional control in the form of RNA processing that is absent in prokaryotes. In addition, eukaryotes have a greater variety of control mechanisms operating before transcription and after translation.

(Figure 70)

Exercises

Exercise 1		تدريب ١	
Which of the following conditions is most likely to cause the lactose operon to be transcribed?		**أي من الحالات التالية من المرجح أن تتسبب في نسخ أوبرون اللاكتوز؟**	
A	There is more glucose in the cell than lactose	يوجد جلوكوز في الخلية أكثر من اللاكتوز.	A
B	There is glucose but no lactose in the cell.	يوجد جلوكوز ولكن لا يوجد لاكتوز في الخلية.	B
C	The cyclic AMP and lactose levels are both high within the cell.	مستويات AMP اللاكتوز الدوري وكلاهما مرتفعان داخل الخلية.	C
D	The cAMP level is high, and the lactose level is low.	مستوى cAMP مرتفع ومستوى اللاكتوز منخفض.	D

Exercise 2		تدريب ٢	
Suppose an experimenter becomes proficient with a technique that allows her to move DNA sequences within a prokaryotic genome. If a researcher moves the operator to the far end of the operon, past the transacetylase (*lacA*) gene, which of the following processes would likely occur when the cell is exposed to lactose?		**لنفترض أن العالمة التي تقوم بالتجربة أصبحت ماهرة بتقنية تسمح لها بتحريك تسلسل DNA داخل جينوم بدائية النواة. إذا قام الباحث بنقل المشغل إلى الطرف البعيد من الأوبرون ، متجاوزًا جين (*lacA*) transacetylase ، أي من العمليات التالية من المحتمل أن تحدث عندما تتعرض الخلية للاكتوز؟**	
A	The inducer will no longer bind to the repressor.	المحرض لن يرتبط بعد الآن بالقمع.	A
B	The repressor will no longer bind to the operator.	القامع لم يعد ملزمًا بالمشغل.	B
C	The operon will never be transcribed.	لن يتم نسخ الأوبرون.	C
D	The genes of the *lac* operon will be transcribed continuously.	سيتم نسخ جينات *lac* operon بشكل مستمر.	D

Exercise 3		تدريب ٣	
Muscle cells differ from nerve cells mainly because they:		**تختلف خلايا العضلات عن الخلايا العصبية أساسًا لأنها:**	
A	express different genes.	التعبير عن جينات مختلفة.	A
B	contain different genes.	تحتوي على جينات مختلفة.	B
C	use different genetic codes.	استخدام رموز وراثية مختلفة.	C
D	have unique ribosomes.	لها رايبوسومات فريدة.	D

Chapter Six

DNA Tools and Biotechnology

نسمو NSMO
أولمبيـــاد العلوم والرياضيات الوطني

DNA Tools and Biotechnology

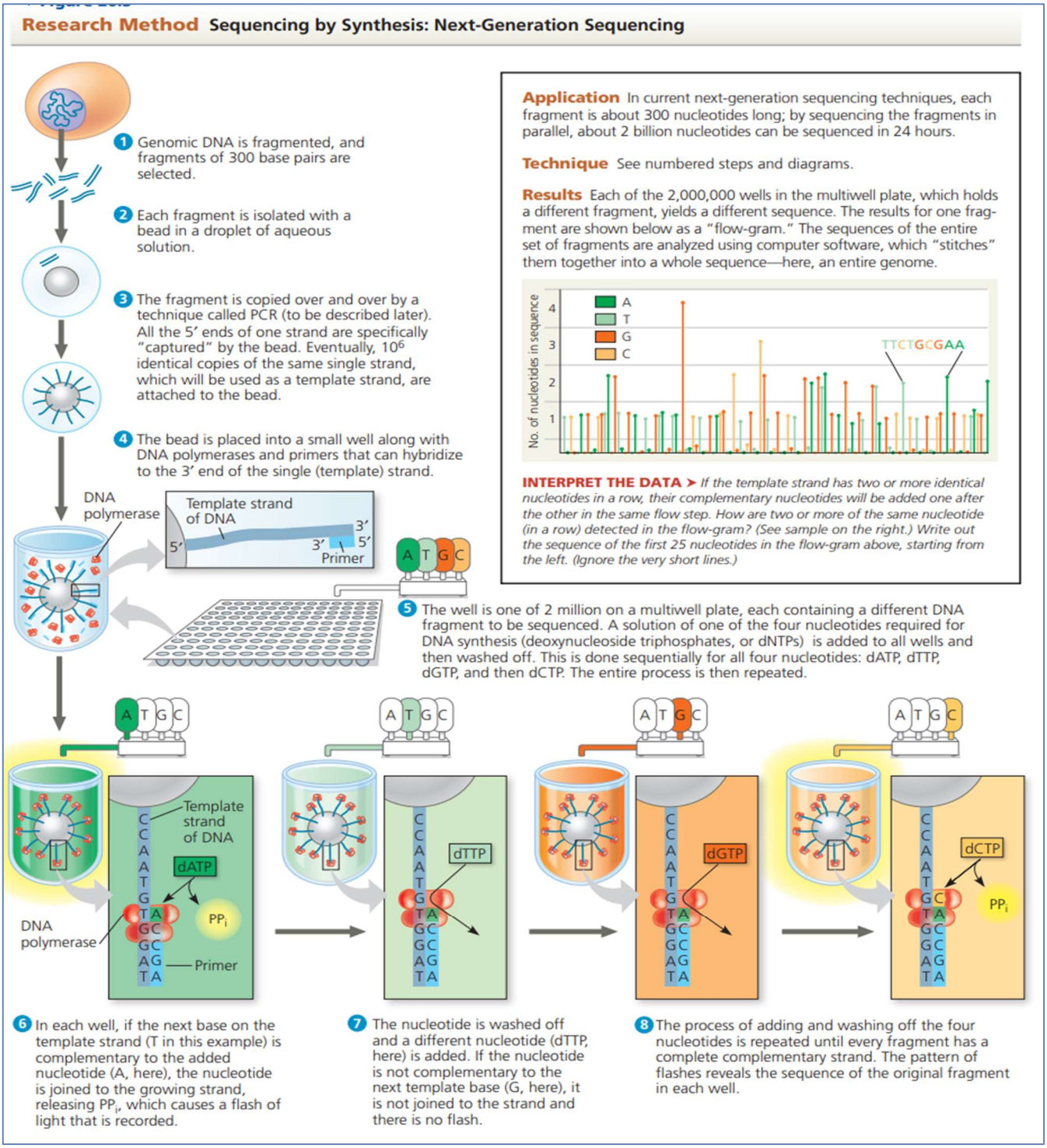
DNA sequencing and DNA cloning are valuable tools for genetic engineering and biological inquiry

The discovery of the **structure of the DNA molecule**, and particularly the recognition that its **strands are complementary** to each other, opened the door to the development of **DNA sequencing** and other techniques now used in biological research. At the heart of these techniques is **nucleic acid hybridization**, the **base pairing** of one strand of nucleic acid to a **complementary sequence** on a strand from a different nucleic acid molecule. In this section, we will first describe **DNA sequencing techniques** and then explore other important methods used in **genetic engineering** the **direct manipulation of genes** for practical purposes.

DNA Sequencing:

- Researchers can exploit the principle of **complementary base pairing** to determine the **complete nucleotide sequence** of a DNA molecule a process known as **DNA sequencing**.
- DNA is first **fragmented into smaller pieces**, and each fragment's sequence is then determined. The first automated sequencing procedure used a technique called **dideoxyribonucleotide (or dideoxy) chain termination sequencing**.
- In this method, **one strand of a DNA fragment** serves as a **template** for synthesizing a set of **complementary fragments** of varying lengths; these are then analyzed to deduce the sequence. **Biochemist Frederick Sanger** received the **1980 Nobel Prize** for developing this technique, which remains in use for small-scale, routine sequencing.
- Over the past fifteen years, **next-generation sequencing** technologies have been developed, offering **much higher speed and throughput**. In these methods, **DNA fragments are amplified** (copied) to produce a **massive number of identical fragments**.

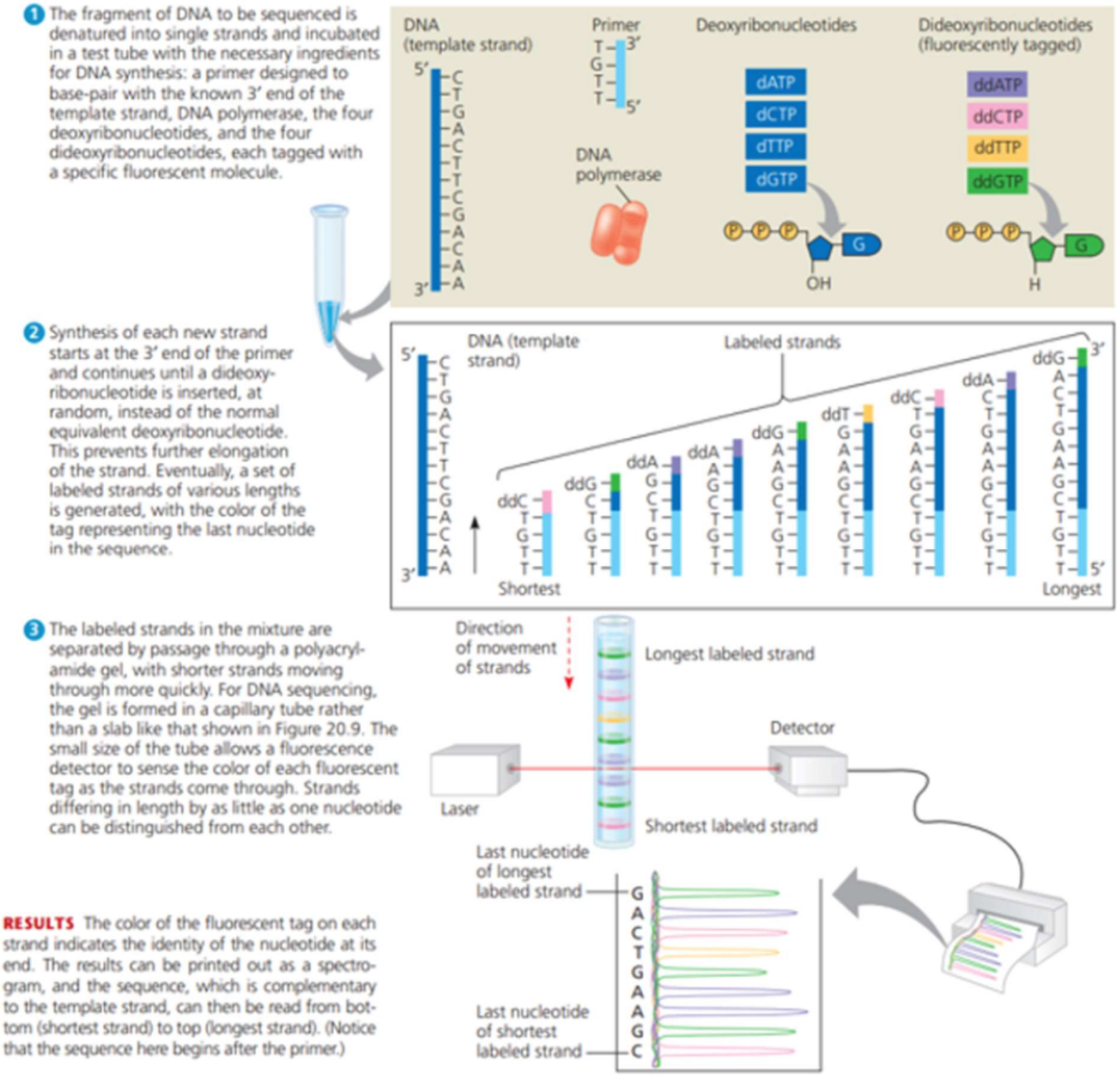
- A single strand of each fragment is **immobilized**, and a **complementary strand** is built **one nucleotide at a time**. A **chemical system** allows electronic sensors to **detect the addition of each of the four nucleotides in real time**; thus, the technique is called **sequencing by synthesis**.
- **Thousands or hundreds of thousands of fragments**, each about **300 nucleotides long**, are sequenced **in parallel** in machines like those shown in the preceding figure accounting for the **high rate of nucleotide sequencing per hour**.
- This is an example of a **high-throughput DNA technology**, now the **method of choice** for studies involving the sequencing of vast numbers of DNA samples even entire genomes composed of many fragments.
- In some newer approaches, DNA is **not fragmented or amplified**. Instead, a **single, very long DNA molecule** is **sequenced directly**.
- Several research groups have developed techniques in which **a single DNA strand** is passed through an extremely tiny pore, or **nanopore**, in a membrane, allowing bases to be identified **one by one** by the **distinct way** each base **interrupts an electrical current**.
- The concept is that each **type of base** interrupts the current for a **slightly different duration**.
- In **2015**, the **first nanopore sequencer** was introduced commercially a **device about the size of a small candy bar**, connecting to a computer via a **USB port**. Its accompanying software enables **real-time sequence detection and analysis**.
- **Improved DNA sequencing technologies** have transformed how we explore **fundamental biological questions** about **evolution** and the **mechanisms of life**.
- In this chapter, you will learn more about how the **rapid acceleration of sequencing technology** has **revolutionized our study of species evolution** and of the **genome itself**.


Research Method Sequencing by Synthesis: Next-Generation Sequencing
1 Genomic DNA is fragmented, and fragments of 300 base pairs are selected.
2 Each fragment is isolated with a bead in a droplet of aqueous solution.
3 The fragment is copied over and over by a technique called PCR (to be described later). All the 5′ ends of one strand are specifically "captured" by the bead. Eventually, 10^6 identical copies of the same single strand, which will be used as a template strand, are attached to the bead.
4 The bead is placed into a small well along with DNA polymerases and primers that can hybridize to the 3′ end of the single (template) strand.
DNA polymerase
Template strand of DNA
5′
3′
3′
5′
Primer
A T G C
5 The well is one of 2 million on a multiwell plate, each containing a different DNA fragment to be sequenced. A solution of one of the four nucleotides required for DNA synthesis (deoxynucleoside triphosphates, or dNTPs) is added to all wells and then washed off. This is done sequentially for all four nucleotides: dATP, dTTP, dGTP, and then dCTP. The entire process is then repeated.
Template strand of DNA
dATP
DNA polymerase
PPi
Primer
dTTP
dGTP
dCTP
6 In each well, if the next base on the template strand (T in this example) is complementary to the added nucleotide (A, here), the nucleotide is joined to the growing strand, releasing PPi, which causes a flash of light that is recorded.
7 The nucleotide is washed off and a different nucleotide (dTTP, here) is added. If the nucleotide is not complementary to the next template base (G, here), it is not joined to the strand and there is no flash.
8 The process of adding and washing off the four nucleotides is repeated until every fragment has a complete complementary strand. The pattern of flashes reveals the sequence of the original fragment in each well.
Application In current next-generation sequencing techniques, each fragment is about 300 nucleotides long; by sequencing the fragments in parallel, about 2 billion nucleotides can be sequenced in 24 hours.
Technique See numbered steps and diagrams.
Results Each of the 2,000,000 wells in the multiwell plate, which holds a different fragment, yields a different sequence. The results for one fragment are shown below as a "flow-gram." The sequences of the entire set of fragments are analyzed using computer software, which "stitches" them together into a whole sequence—here, an entire genome.
No. of nucleotides in sequence
4
3
2
1
A
T
G
C
TTCTGCGAA
INTERPRET THE DATA > If the template strand has two or more identical nucleotides in a row, their complementary nucleotides will be added one after the other in the same flow step. How are two or more of the same nucleotide (in a row) detected in the flow-gram? (See sample on the right.) Write out the sequence of the first 25 nucleotides in the flow-gram above, starting from the left. (Ignore the very short lines.)

(Figure 71)

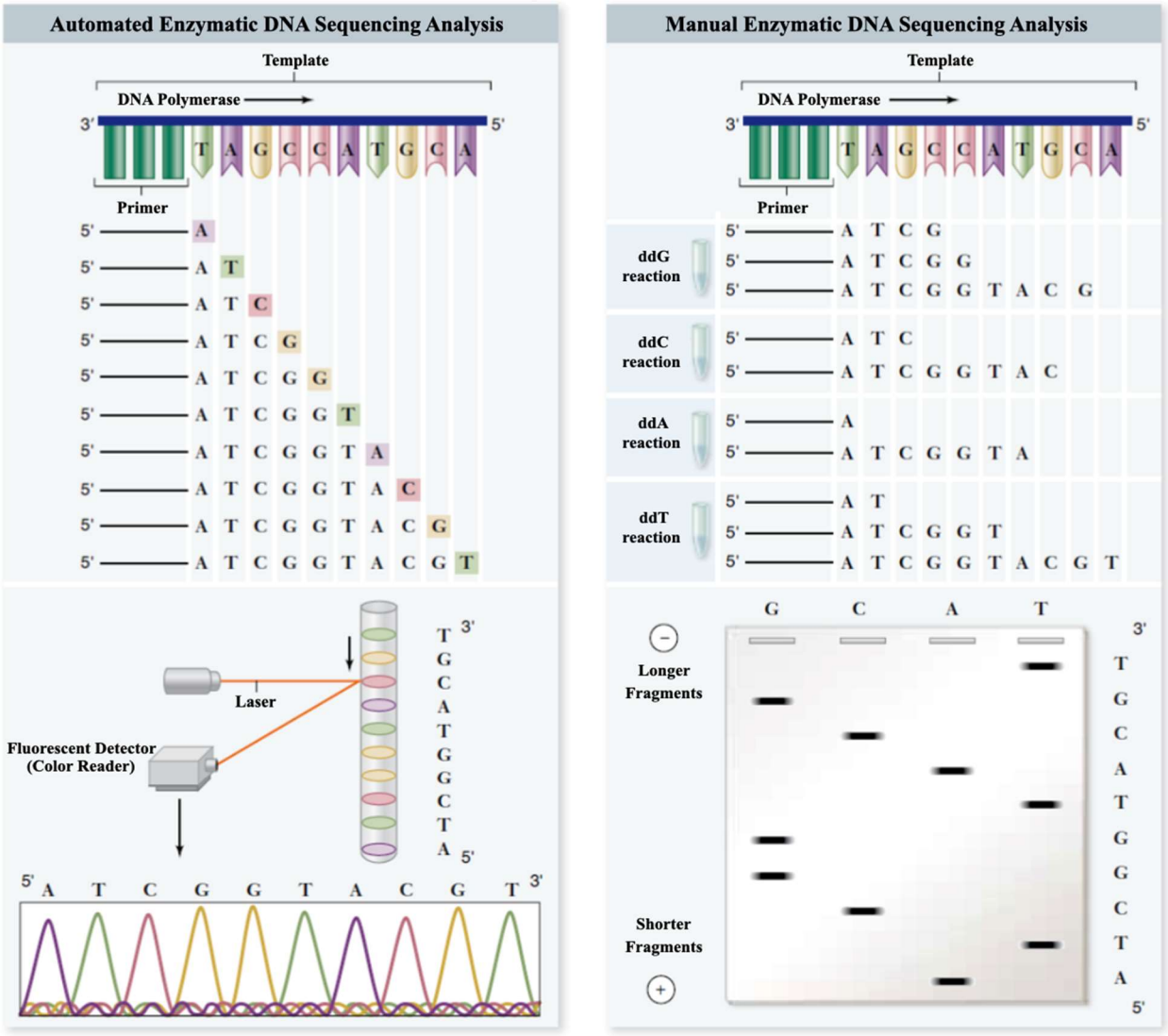
APPLICATION The sequence of nucleotides in any cloned DNA fragment of up to 800–1,000 base pairs in length can be determined rapidly with machines that carry out sequencing reactions and separate the labeled reaction products by length.

TECHNIQUE This method synthesizes a set of DNA strands complementary to the original DNA fragment. Each strand starts with the same primer and ends with a dideoxyribonucleotide (ddNTP), a modified nucleotide. Incorporation of a ddNTP terminates a growing DNA strand because it lacks a 3′ —OH group, the site for attachment of the next nucleotide (see Figure 16.14). In the set of strands synthesized, each nucleotide position along the original sequence is represented by strands ending at that point with the complementary ddNTP. Because each type of ddNTP is tagged with a distinct fluorescent label, the identity of the ending nucleotides of the new strands, and ultimately the entire original sequence, can be determined.



RESULTS The color of the fluorescent tag on each strand indicates the identity of the nucleotide at its end. The results can be printed out as a spectrogram, and the sequence, which is complementary to the template strand, can then be read from bottom (shortest strand) to top (longest strand). (Notice that the sequence here begins after the primer.)

(Figure 72)

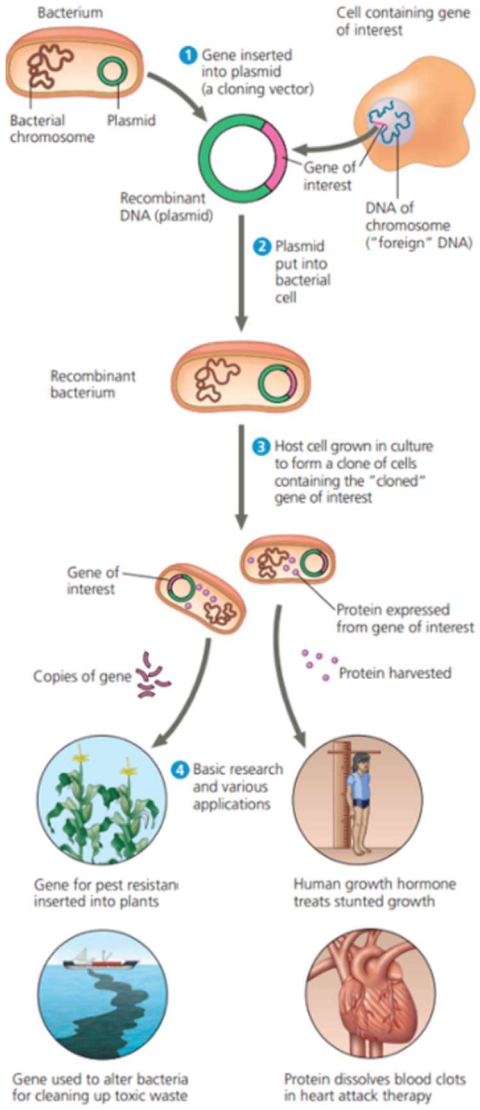


(Figure 73)

Making Multiple Copies of a Gene or other DNA Segment

- A **molecular biologist** studying a specific **gene** or group of genes faces a challenge because **DNA molecules are extremely long**, and a single molecule usually carries **hundreds or even thousands of genes**.
- Moreover, in many **eukaryotic genomes**, the **protein-coding genes** occupy only a **small fraction** of the chromosomal DNA, while the remainder consists of **noncoding nucleotide sequences**.

- To work directly with specific genes, scientists have developed methods for preparing **well-defined segments of DNA** in multiple **identical copies** a process known as **DNA cloning**.
- Most **in vitro DNA cloning** techniques share certain **general features**. One common method involves using **bacteria**, often **Escherichia coli (*E. coli*)**, which contains a large **circular DNA molecule**.
- In addition, **E. coli** and many other bacteria possess **plasmids** small **circular DNA molecules** that are **replicated separately** from the bacterial chromosome.
- A **plasmid** contains only a few genes, which may be **useful under specific environmental conditions** but are **not essential** for survival or reproduction under most circumstances.
- To **clone DNA fragments** using bacteria, researchers first obtain a **plasmid** (originally isolated from a bacterial cell and genetically modified for efficient cloning) and **insert DNA from another source** (foreign DNA) into it (as shown in the figure 74).
- The resulting plasmid is now a **recombinant DNA molecule** a molecule containing **DNA from two different sources**, often from **different species**. The recombinant



Gene cloning and some uses of cloned genes. In this simplified diagram of gene cloning, we start with a plasmid (originally isolated from a bacterial cell) and a gene of interest from another organism. Only one plasmid and one copy of the gene of interest are shown at the top of the figure, but the starting materials would include many of each.

(Figure 74)

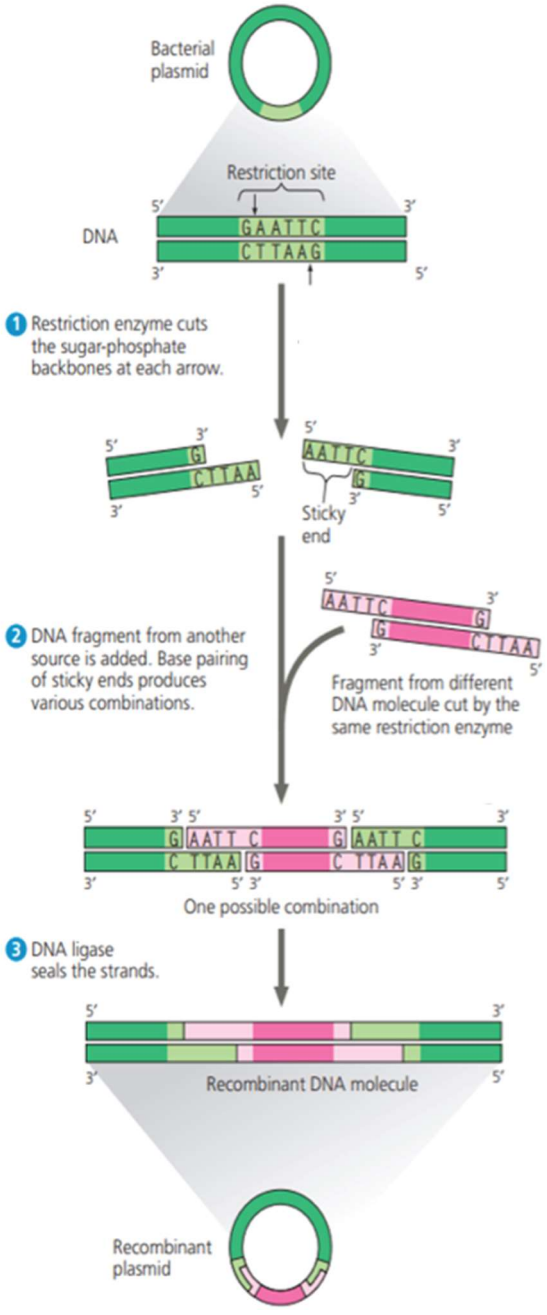
plasmid is then **introduced into a bacterial cell**, producing a **recombinant bacterium**.

- This single recombinant cell **divides repeatedly**, forming a **clone of cells** a population of **genetically identical cells**.
- As the dividing bacteria **replicate the recombinant plasmid** and pass it to their progeny, the **foreign cloned DNA** and any **genes it carries** are **copied simultaneously**. Producing **multiple copies of a specific gene** is a form of **DNA cloning** known as **gene cloning**.
- In the figure, the **plasmid acts as a cloning vector** a **DNA molecule** that can **carry foreign DNA** into a **host cell** and **replicate** there.
- **Bacterial plasmids** are widely used as **cloning vectors** for several reasons: they are **easily obtained**, **manipulated** to form **recombinant plasmids** by inserting foreign DNA in a test tube, and **readily introduced** into bacterial cells.
- **Gene cloning** is useful for two main purposes: to **make many copies** of a particular gene (to **amplify** it) or to **produce its protein product**, as shown in the previous figure.
- Researchers can **isolate copies** of the **cloned gene** from bacteria for use in **basic research** or to give another organism a **new metabolic capability**, such as **pest resistance**.
- For example, a **resistance gene** from one crop species can be **cloned** and **transferred** to another plant species, producing **genetically modified (GM)** organisms.
- Similarly, a **protein with medical applications**, such as **human growth hormone**, can be **mass-produced** from **bacterial cultures** that carry the **cloned gene for the protein**.
- Since an individual gene represents only a **tiny fraction** of a cell's total DNA, the **ability to amplify these rare DNA segments** is crucial for any application involving a **single gene**.

Using Restriction Enzymes to Make a Recombinant DNA Plasmid:

- **Gene cloning** and **genetic engineering** in general rely on the use of **enzymes** that **cut DNA molecules** at a limited number of specific sites.
- **Restriction enzymes** protect a **bacterial cell** by **cutting foreign DNA** from other organisms or infecting **phages**. Hundreds of different **restriction enzymes** have been identified and isolated.
- Each **restriction enzyme** is **highly specific**, recognizing a particular short **DNA sequence** a **restriction site** and cutting both DNA strands at precise points within that site.
- **Figure 75(a)** illustrates how **restriction enzymes** can be used to **clone a foreign DNA fragment** into a **bacterial plasmid**.
- At the top is a **bacterial plasmid** containing a **single restriction site** recognized by a specific restriction enzyme from *E. coli*. As shown in this example, **most restriction sites are symmetrical**, meaning the **nucleotide sequence** reads the same on both strands when read in the **5'→3' direction**.
- The most used **restriction enzymes** recognize sequences containing **four to eight base pairs**.
- Because any short sequence typically occurs **several times by chance** within a long DNA molecule, a restriction enzyme will make **multiple cuts** in such DNA, producing a collection of **restriction fragments**.
- The most **useful restriction enzymes** are those that **cleave the sugar-phosphate backbone** of the DNA strand in a **staggered manner**, as shown in the figure.
- The resulting **double-stranded restriction fragments** have at least one **sticky end** a short single-stranded extension.
- These **short extensions** can form **hydrogen bonds** with **complementary sticky ends** on any other DNA molecules **cut by the same enzyme**.
- The bonds formed in this way are initially **temporary**, but they can be made **permanent** by the enzyme **DNA ligase**, which **catalyzes the formation of covalent bonds** sealing the **sugar-phosphate backbone** of the DNA strand.
- As seen in the lower part of the figure, **ligase-catalyzed joining** of DNA from two different sources produces a **stable recombinant DNA molecule** in this example, a **recombinant plasmid**.

- To **verify recombinant plasmids** after they have been replicated several times in host cells, researchers may **cut the products again** with the **same restriction enzyme**, expecting **two DNA fragments** one the size of the plasmid and the other corresponding to the **inserted DNA**.
- To **separate and visualize** these fragments, researchers use a technique called **gel electrophoresis**.



(Figure 75)

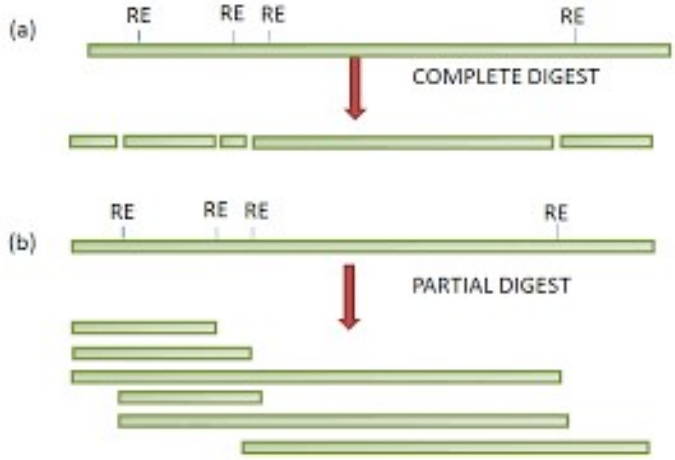
a

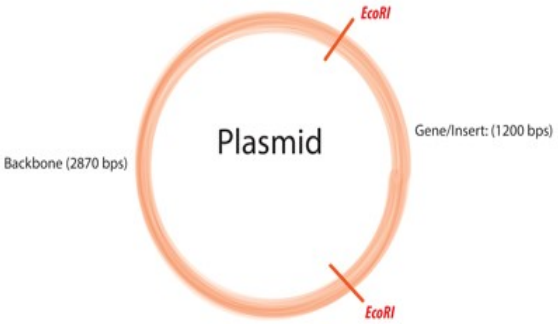
Using a restriction enzyme and DNA ligase to make a recombinant DNA plasmid. The restriction enzyme in this example (called EcoRI) recognizes a single six-base-pair restriction site present in this plasmid. It makes staggered cuts in the sugar-phosphate backbones, producing fragments with "sticky ends." Foreign DNA fragments with complementary sticky ends can base-pair with the plasmid ends; the ligated product is a recombinant plasmid. (If the two plasmid sticky ends base-pair, the original nonrecombinant plasmid is reformed.)

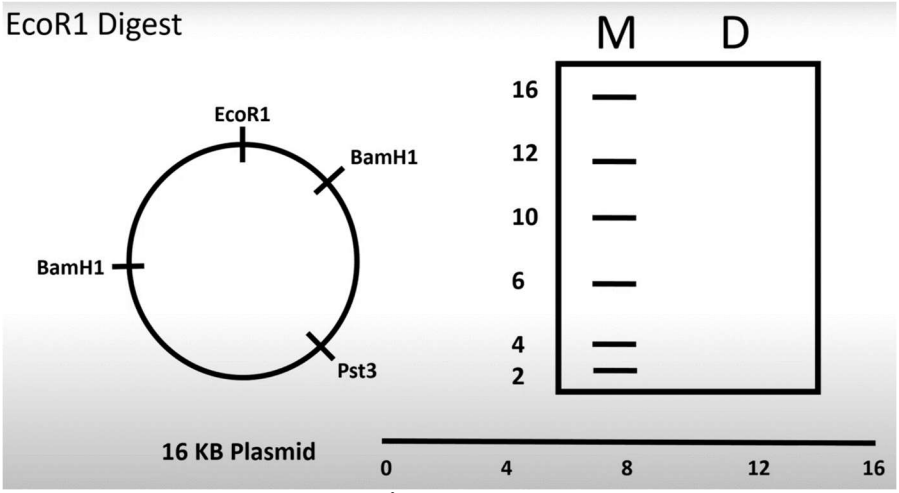
Rules of Restriction Enzymes:

1. They are **highly specific**.
2. In **circular DNA**, the number of fragments produced equals the **number of restriction sites**.
3. In **circular DNA**, the number of fragments produced equals the **number of restriction sites**.
4. In **linear DNA**, the number of fragments equals the **number of restriction sites plus one (+1)**.

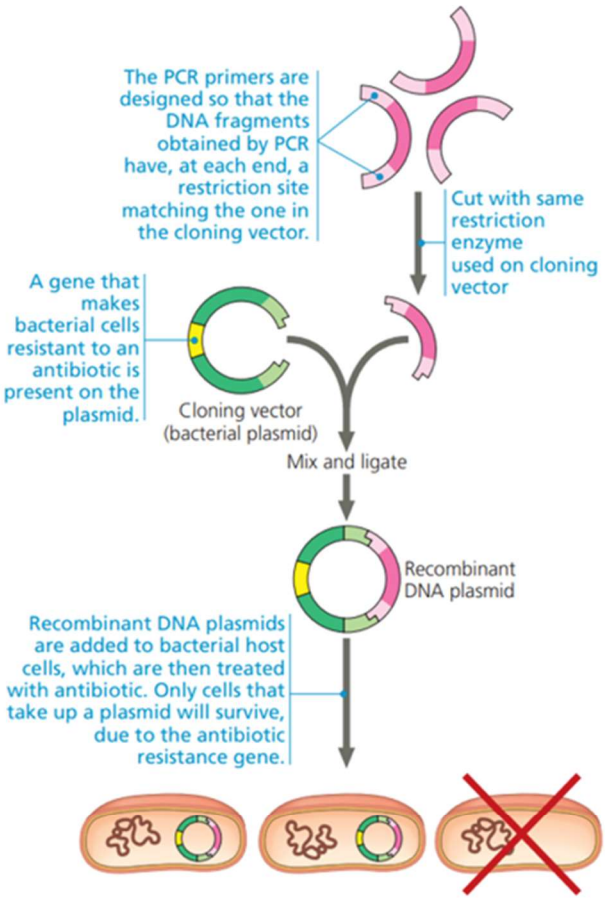
Complete Digestion and Partial Digestion:







(Figure 76)



Use of a restriction enzyme and PCR in gene cloning. In a closer look at the process shown at the top of Figure, PCR is used to produce the DNA fragment or gene of interest that will be ligated into a cloning vector, in this case a bacterial plasmid. The ends of the fragments have the same restriction site as the cloning vector. The plasmid and the DNA fragments are cut with the same restriction enzyme and combined so the sticky ends can hybridize and be ligated together. The resulting plasmids are then introduced into bacterial host cells. The plasmid also contains an antibiotic resistance gene that allows only cells with a plasmid to survive when the antibiotic is present. Other genetic engineering techniques are used to ensure that cells with nonrecombinant plasmids can be eliminated

(Figure 77)

Gel Electrophoresis and Southern Blotting:

- Many methods used to study nucleic acid molecules involve **gel electrophoresis**. This technique employs a **gel made of a polymer**, such as the **polysaccharide agarose**.
- The **gel acts as a molecular sieve**, separating nucleic acids or proteins based on **size, electrical charge,** and other **physical properties** (see next figure).

- Because **DNA molecules carry negative charges** on their **phosphate groups**, they all migrate toward the **positive electrode** in an electric field. As they move, the network of agarose fibers **impedes longer molecules more than shorter ones**, thereby separating them by length.
- Thus, **gel electrophoresis** separates a mixture of linear DNA molecules into **bands**, each consisting of thousands of DNA molecules of the **same length**.
- One historically valuable application of this technique is **restriction fragment analysis**, which rapidly provides information about **DNA sequences**.
- In this type of analysis, the **DNA fragments** produced by **restriction enzyme digestion** of a DNA molecule are **separated by gel electrophoresis**.
- **Restriction fragment analysis** can be used to **compare two different DNA molecules** for example, **two alleles of a gene** if a **nucleotide difference** affects a **restriction site**.
- A change in even **one base pair** within such a site can **prevent a restriction enzyme** from cutting there. Variations in DNA sequence among individuals in a population are called **polymorphisms**; this type is known as a **Restriction Fragment Length Polymorphism (RFLP)**.
- If one allele contains an **RFLP**, cutting the DNA with the enzyme that recognizes the site will yield a **different mixture of fragments** for each allele, producing **distinct banding patterns** in gel electrophoresis.
- For example, **sickle-cell disease** results from a **single-nucleotide mutation** within a **restriction site (RFLP)** in the human **β-globin gene** (see figure).
- To determine whether a person is **heterozygous** for the sickle-cell allele, the individual's DNA can be compared directly with DNA from a **homozygous normal** and a **homozygous sickle-cell** individual.
- As noted earlier, **gel electrophoresis** of DNA fragments cut by a **restriction enzyme** and stained with a **DNA-binding dye** produces too many bands to distinguish individually.
- However, the classic method known as **Southern blotting** developed by British biochemist **Edwin Southern** combines **gel electrophoresis** with **nucleic acid**

hybridization, allowing detection of **bands containing fragments** of the **β-globin gene**.

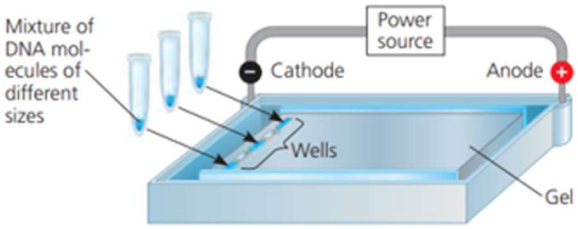
- In **Southern blotting**, the **probe** is typically a **labeled single-stranded DNA molecule** complementary to the gene of interest. The following figure illustrates the entire procedure and how it can **differentiate heterozygous individuals** (in this case, for the sickle-cell allele) from **homozygous normal individuals**.
- Identifying **carriers of mutant alleles** associated with **hereditary diseases** is one major application of **Southern blotting**.
- The technique has also been **adapted for use with RNA and proteins**.
- When **mRNA** is isolated and separated by electrophoresis, the technique is called **Northern blotting**. The procedure is the same, except that **mRNA** is used instead of **DNA**, and there is **no DNA denaturation step**.

Gel Electrophoresis

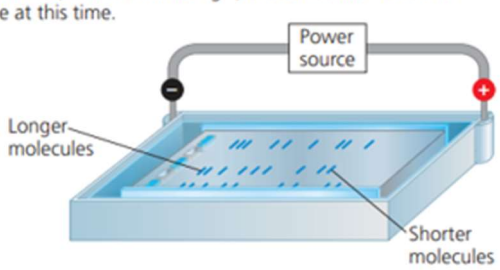
APPLICATION Gel electrophoresis is used for separating nucleic acids or proteins that differ in size, electrical charge, or other physical properties. DNA molecules are separated by gel electrophoresis in restriction fragment analysis of both cloned genes (see Figure 20.10) and genomic DNA (see Figure 20.11).

TECHNIQUE Gel electrophoresis separates macromolecules on the basis of their rate of movement through an agarose gel in an electric field: The distance a DNA molecule travels is inversely proportional to its length. A mixture of DNA molecules, usually fragments produced by restriction enzyme digestion (cutting) or PCR amplification, is separated into bands. Each band contains thousands of molecules of the same length.

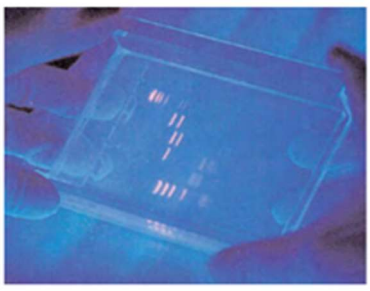
1 Each sample, a mixture of DNA molecules, is placed in a separate well near one end of a thin slab of agarose gel. The gel is set into a small plastic support and immersed in an aqueous, buffered solution in a tray with electrodes at each end.



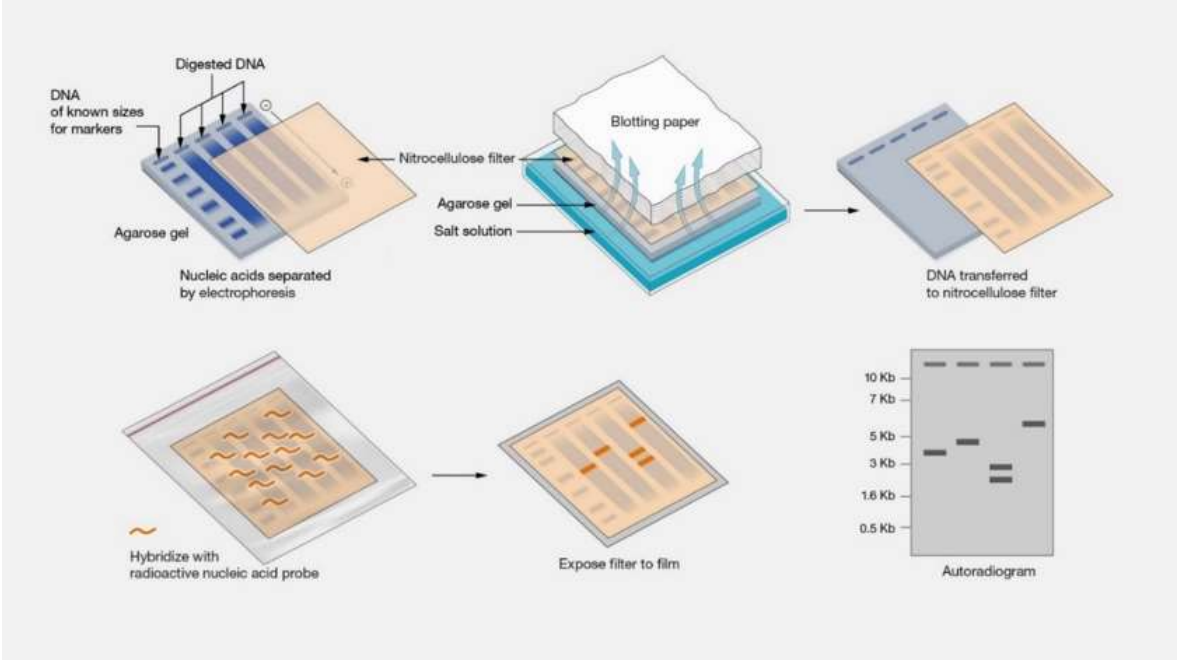
2 When the current is turned on, the negatively charged DNA molecules move toward the positive electrode, with shorter molecules moving faster than longer ones. Bands are shown here in blue, but in an actual gel, the bands would not be visible at this time.

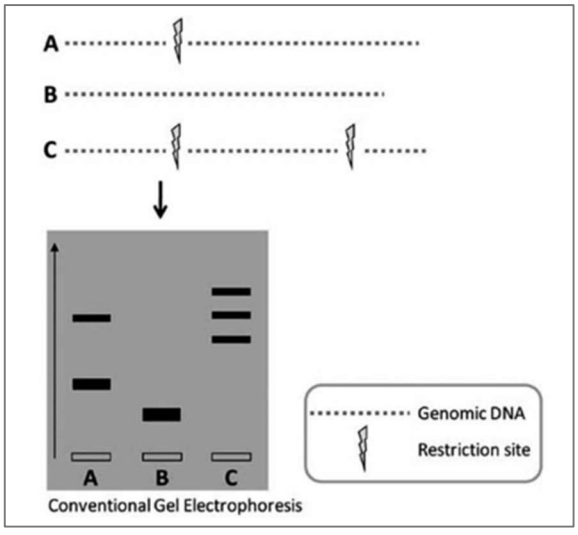


RESULTS After the current is turned off, a DNA-binding dye (ethidium bromide) is added. This dye fluoresces pink in ultraviolet light, revealing the separated bands to which it binds. In the gel below, the pink bands correspond to DNA fragments of different lengths separated by electrophoresis. If all the samples were initially cut with the same restriction enzyme, then the different band patterns indicate that they came from different sources.

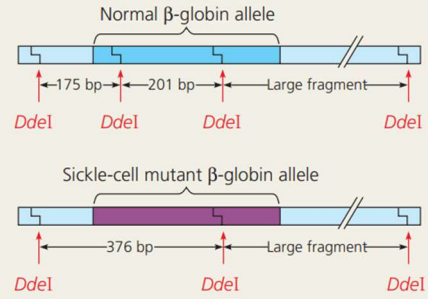


(Figure 77)

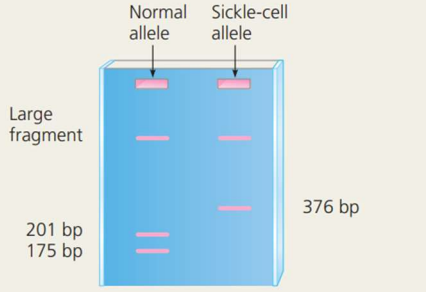




(Figure 78)



(a) *Dde*I restriction sites in normal and sickle-cell alleles of the β-globin gene. Shown here are the cloned alleles, separated from the vector DNA but including some DNA next to the coding sequence. The normal allele contains two sites within the coding sequence recognized by the *Dde*I restriction enzyme. The sickle-cell allele lacks one of these sites.



(b) Electrophoresis of restriction fragments from normal and sickle-cell alleles. Samples of each purified allele were cut with the *Dde*I enzyme and then subjected to gel electrophoresis, resulting in three bands for the normal allele and two bands for the sickle-cell allele. (The tiny fragments on the ends of both initial DNA molecules are identical and are not seen here.)

The Practical Applications of DNA-Based Biotechnology Affect our Lives in Many Ways:

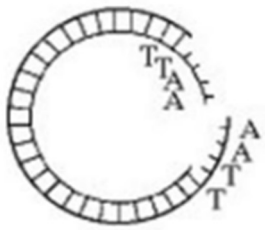
- Diagnosis and Treatment of Diseases
- Human Gene Therapy and Gene Editing
- Pharmaceutical Products
- Forensic Evidence and Genetic Profiles
- Environmental Cleanup
- Agricultural Applications

Exercises

Exercise 1 — تدريب ١

Which of the following enzymes was used to produce the molecule of DNA in the figure?

أي من الإنزيمات التالية تم استخدامه لإنتاج جزيء الحمض النووي في الشكل؟



A	ligase	C	RNA polymerase
B	a restriction enzyme	D	DNA polymerase

Exercise 2 — تدريب ٢

Why are yeast cells frequently used as hosts for cloning ?

لماذا تستخدم خلايا الخميرة بشكل متكرر كمضيف للاستنساخ؟

A	They easily form colonies.	أنها تشكل مستعمرات بسهولة.	A
B	They can remove exons from mRNA.	يمكنهم إزالة exons من mRNA.	B
C	They do not have plasmids.	ليس لديهم بلازميدات.	C
D	They are eukaryotic cells.	هي خلايا حقيقية النواة.	D

Exercise 3 — تدريب ٣

Pax-6 **is a gene that is involved in eye formation in many invertebrates, such as Drosophila.** ***Pax-6*** **is also found in vertebrates. A** ***Pax-6*** **gene from a mouse can be expressed in a fly and the protein (PAX-6) leads to a compound fly eye. This information suggests which of the following characteristics of this gene?**

Pax-6 **هو جين يشارك في تكوين العين في العديد من اللافقاريات ، مثل ذبابة الفاكهة. تم العثور على** ***Pax-6*** **أيضًا في الفقاريات. يمكن التعبير عن جين** ***Pax-6*** **من فأر في ذبابة ويؤدي البروتين (PAX-6) إلى عين ذبابة مركبة. تشير هذه المعلومات إلى أي من الخصائص التالية لهذا الجين؟**

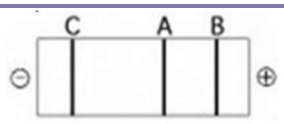
A	Pax-6 genes are identical in nucleotide sequence.	جينات Pax-6 متطابقة في تسلسل النيوكليوتيدات.	A
B	PAX-6 proteins have identical amino acid sequences.	بروتينات PAX-6 لها تسلسلات متطابقة من الأحماض الأمينية.	B
C	Pax-6 is highly conserved and shows shared evolutionary ancestry.	Pax-6 محفوظ للغاية ويظهر أصلًا تطوريًا مشتركًا.	C
D	PAX-6 proteins are different for formation of different kinds of eyes.	تختلف بروتينات PAX-6 في تكوين أنواع مختلفة من العيون.	D

Exercise 4 — تدريب ٤

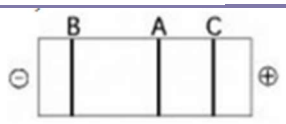
The segment of DNA shown in the figure has restriction sites I and II, which create restriction fragments A, B, and C. Which of the gels produced by electrophoresis best represents the separation and identity of these fragments?

يحتوي جزء الحمض النووي الموضح في الشكل على مواقع تقييد I و II ، والتي تخلق قطع تقييدية A و B و C. أي من المواد الهلامية التي ينتجها الرحلان الكهربي يمثل بشكل أفضل فصل هذه الأجزاء وهويتها؟

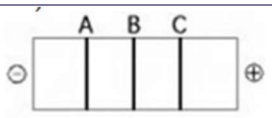
A



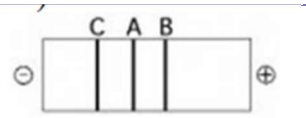
C



B



D



Exercise 5 — تدريب ٥

Which of the following sequences is most likely to be cut by a restriction enzyme?

أي من التسلسلات التالية من المرجح أن يتم قطعه بواسطة إنزيم مقيد؟

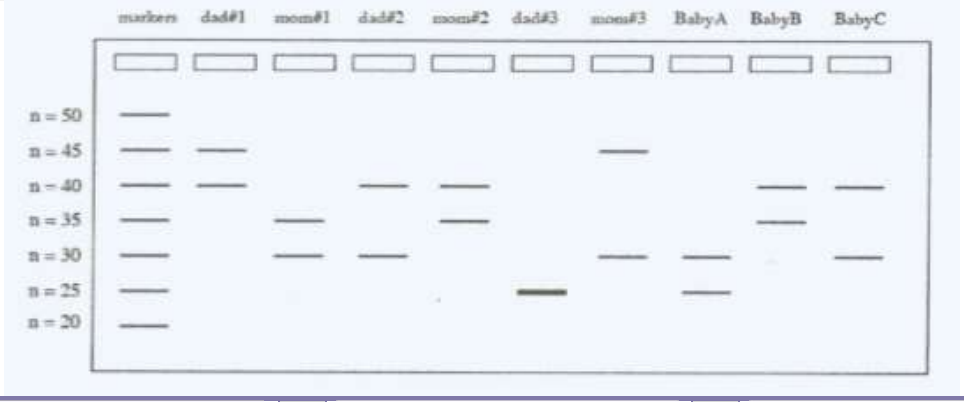
A	5'-AATTCT 3' 3'-TTAAGA-5'	C	5'-AAAATT-3' 3'-TTTTAA-5'
B	5'-AATATT-3' 3'-TTATAA-5'	D	5'-ACTACT-3' 3'-TGATGA-5'

Exercise 6 — تدريب ٦

Select an observation that best describes a correct aspect of the two processes of restriction digest and gel electrophoresis.		حدد الملاحظة التي تصف بشكل أفضل جانبًا صحيحًا من عمليتي هضم التقييد والرحلان الكهربي للهلام.	
A	When separated on a gel, the pattern of DNA bands will be characteristic of those cut with Hind III; different restriction enzymes will not produce these same fragments.	عند فصلها على مادة هلامية ، سيكون نمط حزم الحمض النووي مميزًا لتلك المقطوعة باستخدام Hind III ؛ لن تنتج إنزيمات التقييد المختلفة هذه الأجزاء نفسها.	A
B	The sequence 5'-AAGCTT-3' is found eight times in the Lambda genome, and the restriction enzyme Hind III finds each location.	تم العثور على التسلسل 5'-AAGCTT-3' ثماني مرات في جينوم Lambda ، ويعثر إنزيم التقييد Hind III على كل موقع.	B
C	If an electrical current is not used, eight separate DNA bands would be visible, but they would not be separated as much as when an electrical current is used.	إذا لم يتم استخدام تيار كهربائي ، فستظهر ثمانية نطاقات منفصلة للحمض النووي ، لكن لن يتم فصلها بقدر ما يتم فصلها عند استخدام التيار الكهربائي.	C
D	Only the restriction enzyme Hind III can be used to cut Lambda DNA since restriction enzymes are specific to the type of DNA they can cut.	يمكن استخدام إنزيم التقييد Hind III فقط لقطع DNA Lambda نظرًا لأن إنزيمات التقييد خاصة بنوع الحمض النووي الذي يمكنها قطعه.	D

Exercise 7	تدريب V
The DNA profile of three newborn children (Baby A, Baby B, Baby C) was analyzed, in addition to three married couples (Dad #1 and Mom #1 - Dad #2 and Mom #2 - Dad #3 and Mom #3). . This is to ensure that the children match their parents after the process of sorting them	تم عمل تحليل لملف الـــ DNA لثلاثة أطفال حديثي الولادة (Baby A, Baby B, Baby C)، بالإضافة إلى ثلاثة أزواج (Dad #1 و Mom #1 - Dad #2 و Mom #2 - Dad #3 و Mom #3). وذلك للتأكد من مطابقة الأطفال لآبائهم بعد حدوث عملية فرزهم عن طريق الخطأ بسبب الكادر الطبي. وقد ظهرت نتائج التحليل باستخدام جهاز الفصل الهلامي على النحو التالي:

by mistake because of the medical staff. The results of the analysis using the gel separator appeared as follows:.



A

Baby	Parents
C	Mom #1 و Dad #1
B	Mom #2 و Dad #2
A	Mom #3 و Dad #3

B

Baby	Parents
A	Mom #1 و Dad #1
B	Mom #2 و Dad #2
C	Mom #3 و Dad #3

C

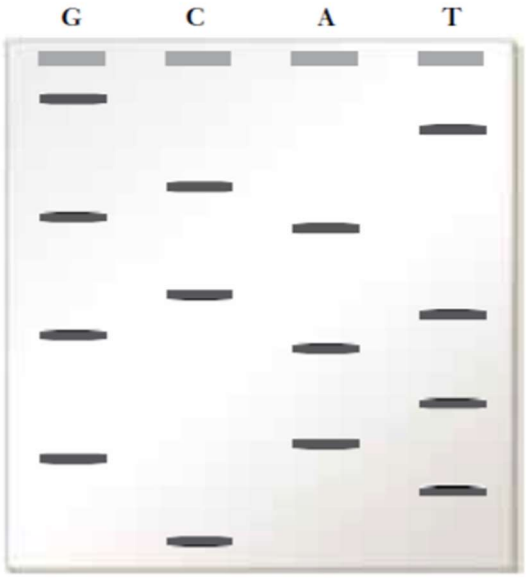
Baby	Parents
C	Mom #1 و Dad #1
A	Mom #2 و Dad #2
B	Mom #3 و Dad #3

Exercise 8

The sequence of a short piece of DNA was analyzed enzymatically using deoxyribonucleotides. Using the gel shown below, Which of the options determines the DNA sequence.

تدريب ٨

حُلل تسلسل قطعة قصيرة من DNA انزيمياً باستعمال نيوكليوتيدات ثنائية منقوصة الاكسجين . باستخدام الهلام المبين ادناه اي من الخيارات يحدد تسلسل DNA .



A	3′_CTGATAGTCAGCTG_5′	C	3′_GGGGCCCAAATTTT_5′
B	5′_GGGGCCCAAATTTT_3′	D	5′_CTGATAGTCAGCTG_3′

Exercise 9 تدريب ٩

What is the most logical sequence of steps for splicing foreign DNA into a plasmid and inserting the plasmid into a bacterium?

ما هو التسلسل الأكثر منطقية لخطوات تلحيم DNA الغريب في بلازميد وإدخال البلازميد في بكتيريا؟

I. Transform bacteria with a recombinant DNA molecule.

II. Cut the plasmid DNA using restriction enzymes (endonucleases).

III. Extract plasmid DNA from bacterial cells.

IV. Hydrogen-bond the plasmid DNA to non-plasmid DNA fragments.

V. Use ligase to seal plasmid DNA to non-plasmid DNA.

I. تحويل البكتيريا مع جزيء DNA المعاد تركيبه.

II. قطع البلازميد DNA باستخدام إنزيمات التقييد (endonucleases).

III. استخراج DNA البلازميد من الخلايا البكتيرية.

IV. يربط الهيدروجين DNA البلازميد بشظايا DNA غير البلازميد.

V. استخدم ligase لإغلاق DNA البلازميد على DNA غير البلازميد.

A	II, III, V, IV, I	C	III, IV, V, I, II
B	III, II, IV, V, I	D	IV, V, I, II, III

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