Chapter 7: Genetics
Lesson 7.4: Mutations, Genetic Disorders, and Biotechnology

What causes albinism?

This rare albino alligator must have the specific "instructions," or DNA, to have this quality. The cause of albinism is a mutation in a gene for melanin, a protein found in skin and eyes. Such a mutation may result in no melanin production at all or a significant decline in the amount of melanin. Is this a type of genetic disorder?

What the future holds?

Biotechnology. Gene Therapy. Reality or fiction? During your lifetime, gene therapy is becoming mainstream medicine. In the picture above we see a representation of the insertion of DNA into the nucleus of a cell. Is this possible? Yes. In this chapter, you will learn how human chromosomes and genes are inherited and how they control the traits that make each of us unique, how they can cause disease, and how those diseases can be treated.

Lesson Objectives

- Identify causes of mutation.
- Compare and contrast types of mutations.
- Explain how mutations may affect the organisms in which they occur.
- Describe genetic disorders caused by mutations or abnormal numbers of chromosomes.
- Describe gene cloning and the polymerase chain reaction.
- Explain how DNA technology is applied in medicine and agriculture.
- Identify some of the ethical, legal, and social issues raised by biotechnology.

Vocabulary

- beneficial mutation
- biotechnology
- chromosomal alteration
- frameshift mutation
- gene cloning
- gene therapy
- genetic disorder
- genetic engineering
- germline mutation
- missense mutation
- mutagen
- mutation
- neutral mutation
- nondisjunction
- nonsense mutation
- pharmacogenomics
- point mutation
- polymerase chain reaction (PCR)
- reading frame
- recombinant DNA
- silent mutation
- somatic mutation
- spontaneous mutation
- synthetic biology
- transgenic crop

Introduction

A change in the sequence of bases in DNA or RNA is called a mutation. Does the word mutation make you think of science fiction and bug-eyed monsters? Think again. Everyone has mutations. In fact, most people have dozens or even hundreds of mutations in their DNA. Mutations are essential for evolution to occur. They are the ultimate source of all new genetic material—new alleles in a species. Although most mutations have no effect on the organisms in which they occur, some mutations are beneficial. Even harmful mutations rarely cause drastic changes in organisms or are the cause of genetic disorders.

A relatively new field of biology called biotechnology is addressing genetic disorders and gene mutations in new and innovative ways. Biotechnology is the use of technology to change the genetic makeup of living things for human purposes. Generally, the purpose of biotechnology is to create organisms that are useful to humans or to cure genetic disorders. For example, biotechnology may be used to create crops that resist insect pests or yield more food, or to create new treatments for human diseases.

Biotechnology: The Invisible Revolution can be seen at
http://www.youtube.com/watch?v=OcG9q9cPqm4
‘‘What does biotechnology have to do with me?” is discussed in the following video:
http://www.youtube.com/watch?v=rrT5BT_7HdI&feature=related

Let’s begin by developing an understanding of different types of mutations and what a genetic disorders really is.

Causes of Mutation

Mutations have many possible causes. Some mutations seem to happen spontaneously without any outside influence. They occur when mistakes are made during DNA replication or transcription. Other mutations are caused by environmental factors. Anything in the environment that can cause a mutation is known as a **mutagen**. Examples of mutagens are pictured in **Figure 7.42**.

For a video about mutagens, go the link below.
http://www.youtube.com/watch?v=0wrNxCGKCws&feature=related (0:36)

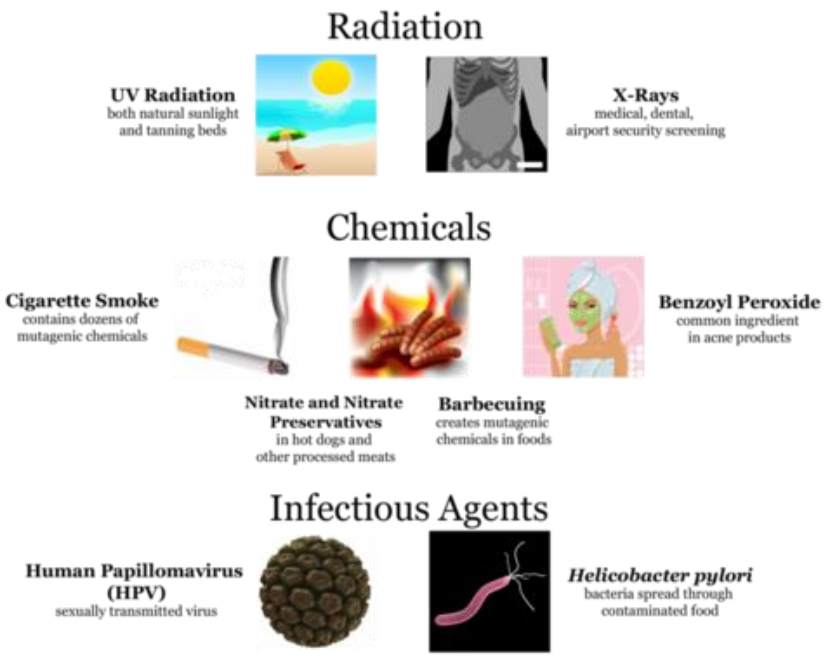

Figure 7.42 Examples of Mutagens. Types of mutagens include radiation, chemicals, and infectious agents. Do you know of other examples of each type of mutagen shown here?

Types of Mutations

There are a variety of types of mutations. Two major categories of mutations are germline mutations and somatic mutations.

- **Germline mutations** occur in gametes. These mutations are especially significant because they can be transmitted to offspring and every cell in the offspring will have the mutation.
- **Somatic mutations** occur in other cells of the body. These mutations may have little effect on the organism because they are confined to just one cell and its daughter cells. Somatic mutations cannot be passed on to offspring.

Mutations also differ in the way that the genetic material is changed. Mutations may change the structure of a chromosome or just change a single nucleotide.

What does radiation contamination do?

It mutates DNA. The Chernobyl disaster was a nuclear accident that occurred on April 26, 1986. It is considered the worst nuclear power plant accident in history. A Russian publication concludes that 985,000 excess cancers occurred between 1986 and 2004 as a result of radioactive contamination. The 2011 report of the European Committee on Radiation Risk calculates a total of 1.4 million excess cancers occurred as a result of this contamination.

Chromosomal Alterations

Chromosomal alterations are mutations that change chromosome structure. They occur when a section of a chromosome breaks off and rejoins incorrectly or does not rejoin at all. Possible ways these mutations can occur are illustrated in **Figure 7.43.** Go to this link for a video about chromosomal alterations: http://www.youtube.com/watch?v=OrXRSqa_3IU&feature=related (2:18).

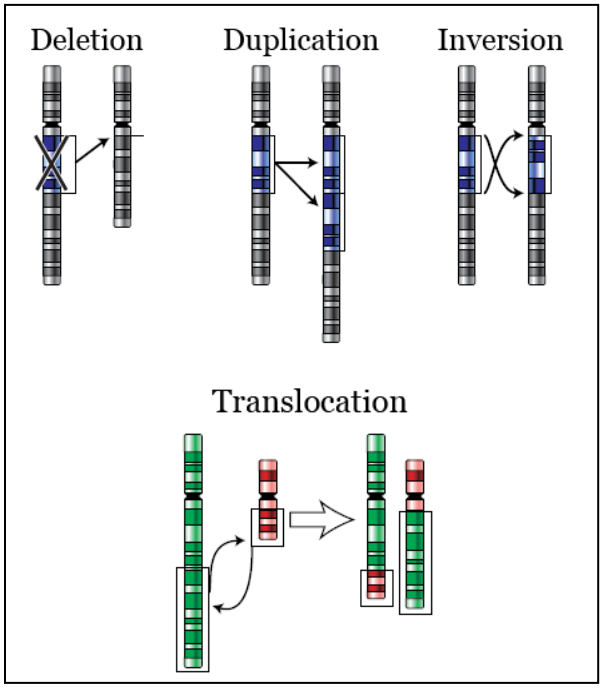

Figure 7.43 Chromosomal Alterations. Chromosomal alterations are major changes in the genetic material.

Chromosomal alterations are very serious. They often result in the death of the organism in which they occur. If the organism survives, it may be affected in multiple ways. An example of a human chromosomal alteration is the mutation that causes Down Syndrome. It is a duplication mutation that leads to developmental delays and other abnormalities.

Point Mutations

A point mutation is a change in a single nucleotide in DNA. This type of mutation is usually less serious than a chromosomal alteration. An example of a point mutation is a mutation that changes the codon UUU to the codon UCU. Point mutations can be silent, missense, or nonsense mutations, as shown in **Table 7.4**. The effects of point mutations depend on how they change the genetic code. You can watch an animation about nonsense mutations at this link: http://www.biostudio.com/d_%20Nonsense%20Suppression%20I%20Nonsense%20Mutation.htm

Table 7.4: **Point Mutations and Their Effects**

Type	Description	Example	Effect
Silent	mutated codon codes for the same amino acid	CAA (glutamine) → CAG (glutamine)	none
Missense	mutated codon codes for a different amino acid	CAA (glutamine) → CCA (proline)	variable
Nonsense	mutated codon is a premature stop codon	CAA (glutamine) → UAA (stop)	usually serious

Frameshift Mutations

A frameshift mutation is a deletion or insertion of one or more nucleotides that changes the reading frame of the base sequence. Deletions remove nucleotides, and insertions add nucleotides. Consider the following sequence of bases in RNA: **AUG-AAU-ACG-GCU = start-asparagine-threonine-alanine.** Now, assume an insertion occurs in this sequence. Let's say an '**A'** nucleotide is inserted after the start codon **AUG**: **AUG-AAA-UAC-GGC-U = start-lysine-tyrosine-glycine.**

Even though the rest of the sequence is unchanged, this insertion changes the reading frame and thus all of the codons that follow it. As this example shows, a frameshift mutation can dramatically change how the codons in mRNA are read. This can have a drastic effect on the protein product.

Spontaneous Mutations

There are five common types of spontaneous mutations. These are described in the **Table 7.5** below.

Table 7.5: **Spontaneous Mutations Described**

Mutation	Description
Tautomerism	a base is changed by the repositioning of a hydrogen atom
Depurination	loss of a purine base (A or G)
Deamination	the removal of an amino group from an amino acid
Transition	a purine to purine (A to G, G to A), or a pyrimidine to pyrimidine (C to T, T to C) change
Transversion	a purine becomes a pyrimidine, or vice versa

Effects of Mutations

The majority of mutations have neither negative nor positive effects on the organism in which they occur. These mutations are called neutral mutations. Examples include silent point mutations. They are neutral because they do not change the amino acids in the proteins they encode. Many other mutations have no effect on the organism because they are repaired before protein synthesis occurs. Cells have multiple repair mechanisms to fix mutations in DNA. One way DNA can be repaired is illustrated in **Figure 7.44**. If a cell's DNA is permanently damaged and cannot be repaired, the cell is likely to be prevented from dividing.

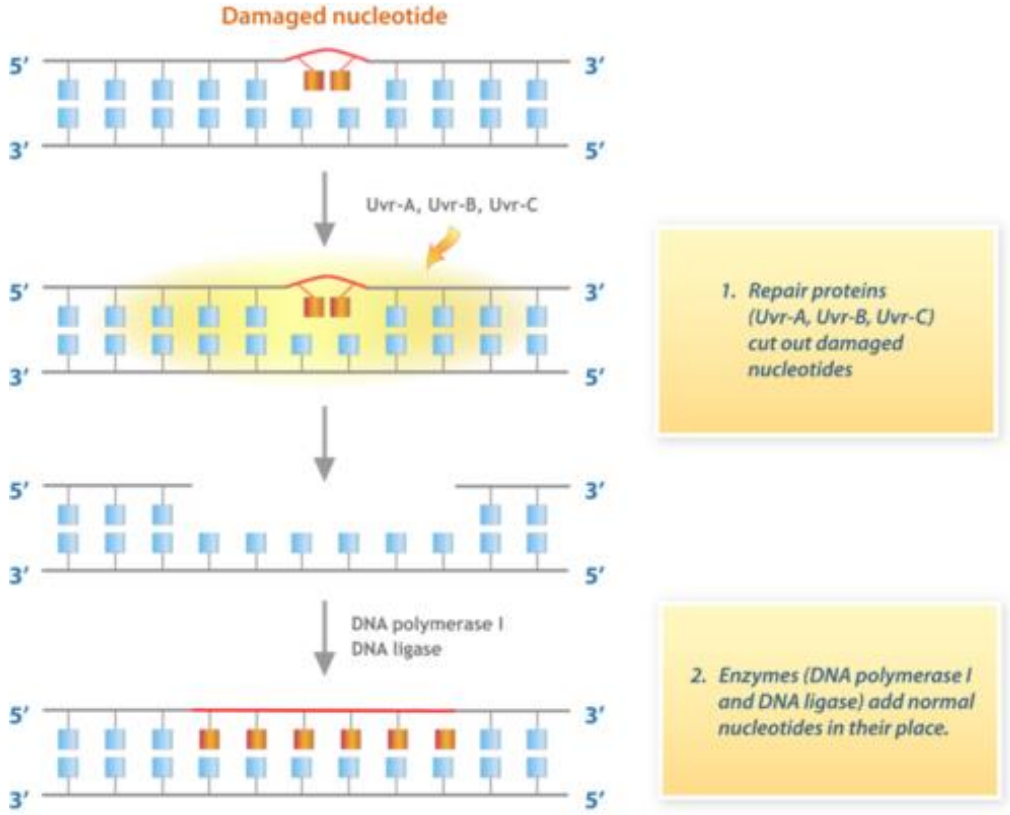

Figure 7.44: DNA Repair Pathway. This flow chart shows one way that damaged DNA is repaired in *E. coli* bacteria.

Is this rat hairless?

Yes. Why? The result of a mutation, a change in the DNA sequence. The effects of mutations can vary widely, from being beneficial, to having no effect, to having lethal consequences, and every possibility in between.

Beneficial Mutations

Some mutations have a positive effect on the organism in which they occur. They are called beneficial mutations. They lead to new versions of proteins that help organisms adapt to changes in their environment. Beneficial mutations are essential for evolution to occur. They increase an organism's changes of surviving or reproducing, so they are likely to become more common over time. There are several well-known examples of beneficial mutations. Here are just two:

1. Mutations in many bacteria that allow them to survive in the presence of antibiotic drugs. The mutations lead to antibiotic-resistant strains of bacteria.
2. A unique mutation is found in people in a small town in Italy. The mutation protects them from developing atherosclerosis, which is the dangerous buildup of fatty materials in blood vessels. The individual in which the mutation first appeared has even been identified.

Harmful Mutations

Imagine making a random change in a complicated machine such as a car engine. The chance that the random change would improve the functioning of the car is very small. The change is far more likely to result in a car that does not run well or perhaps does not run at all. By the same token, any random change in a gene's DNA is likely to result in a protein that does not function normally or may not function at all. Such mutations are likely to be harmful. Harmful mutations may cause genetic disorders or cancer.

- A genetic disorder is a disease caused by a mutation in one or a few genes. A human example is cystic fibrosis. A mutation in a single gene causes the body to produce thick, sticky mucus that clogs lungs and blocks ducts in digestive organs. You can watch a video about cystic fibrosis and other genetic disorders at this link:
http://www.youtube.com/watch?v=8s4he3wLgkM&feature=PlayList&p=397710758E9BCB24&playnext_from=PL&playnext=1&index=17 (9:31).

- Cancer is a disease in which cells grow out of control and form abnormal masses of cells. It is generally caused by mutations in genes that regulate the cell cycle. Because of the mutations, cells with damaged DNA are allowed to divide without limits. Cancer genes can be inherited. You can learn more about hereditary cancer by watching the video at the following link:
http://www.youtube.com/watch?v=LWk5FplsKwMhttp:// (4:29)

Genetic Disorders

Many genetic disorders are caused by mutations in one or a few genes. Other genetic disorders are caused by abnormal numbers of chromosomes. A genetic disorder that is caused by a mutation can be inherited. Therefore, people with a genetic disorder in their family may be concerned about having children with the disorder. Professionals known as genetic counselors can help them understand the risks of their children being affected. If they decide to have children, they may be advised to have prenatal (''before birth") testing to see if the fetus has any genetic abnormalities. One method of prenatal testing is amniocentesis. In this procedure, a few fetal cells are extracted from the fluid surrounding the fetus, and the fetal chromosomes are examined.

Genetic Disorders Caused by Mutations

Table 7.6, on the next page, lists several genetic disorders caused by mutations in just one gene. Some of the disorders are caused by mutations in autosomal genes, others by mutations in X-linked genes. Which disorder would you expect to be more common in males than females?

Few genetic disorders are controlled by dominant alleles. A mutant dominant allele is expressed in every individual who inherits even one copy of it. If it causes a serious disorder, affected people may die young and fail to reproduce. Therefore, the mutant dominant allele is likely to die out of the population.

Table 7.6: Genetic Disorders Caused by Mutations in One Gene

Genetic Disorder	Direct Effect of Mutation	Signs and Symptoms of the Disorder	Mode of Inheritance
Marfan syndrome	defective protein in connective tissue	heart and bone defects and unusually long, slender limbs and fingers	autosomal dominant
Sickle cell anemia	abnormal hemoglobin protein in red blood cells	sickle-shaped red blood cells that clog tiny blood vessels, causing pain and damaging organs and joints	autosomal recessive
Vitamin D-resistant rickets	lack of a substance needed for bones to absorb minerals	soft bones that easily become deformed, leading to bowed legs and other skeletal deformities	X-linked dominant
Hemophilia A	reduced activity of a protein needed for blood clotting	internal and external bleeding that occurs easily and is difficult to control	X-linked recessive

A mutant recessive allele, such as the allele that causes sickle cell anemia (see **Figure 7.45**), is not expressed in people who inherit just one copy of it. These people are called carriers. They do not have the disorder themselves, but they carry the mutant allele and can pass it to their offspring. Thus, the allele is likely to pass on to the next generation rather than die out.

Watch this link to learn more about sickle cell anemia: http://www.dnalc.org/resources/3d/17-sickle-cell.html

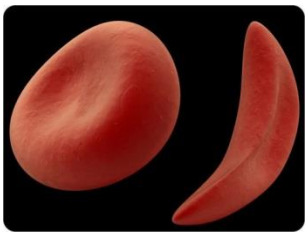

Figure 7.45 Sickle-Shaped and Normal Red Blood Cells. Sickle cell anemia is an autosomal recessive disorder. The mutation that causes the disorder affects just one amino acid in a single protein, but it has serious consequences for the affected person. This photo shows the sickle shape of red blood cells in people with sickle cell anemia.

Cystic Fibrosis and Tay-Sachs disease are two additional severe genetic disorders. They are discussed in the following video: http://www.youtube.com/watch?v=8s4he3wLgkM&feature=related (9:31).

Chromosomal Disorders

Mistakes may occur during meiosis that result in nondisjunction. This is the failure of replicated chromosomes to separate during meiosis (the animation at the link below shows how this happens). Some of the resulting gametes will be missing a chromosome, while others will have an extra copy of the chromosome. If such gametes are fertilized and form zygotes, they usually do not survive. If they do survive, the individuals are likely to have serious genetic disorders. **Table 7.7** lists several chromosomal disorders that are caused by abnormal numbers of chromosomes. Most chromosomal disorders involve the X chromosome. Look back at the X and Y chromosomes and you will see why. The X and Y chromosomes are very different in size, so nondisjunction of the sex chromosomes occurs relatively often.

Table 7.7: Sampling of chromosomal disorders listed along with their genotypes and phenotypic effects.

Chromosomal Disorder	Genotype	Phenotypic Effects
Down syndrome	extra copy (complete or partial) of chromosome 21 (see **Figure 7.44**)	developmental delays, distinctive facial appearance, and other abnormalities (see **Figure 7.44**)
Turner's syndrome	one X chromosome but no other sex chromosome (XO)	female with short height and infertility (inability to reproduce)
Triple X syndrome	three X chromosomes (XXX)	female with mild developmental delays and menstrual irregularities
Klinefelter's syndrome	one Y chromosome and two or more X chromosomes (XXY, XXXY)	male with problems in sexual development and reduced levels of the male hormone testosterone

Treating Genetic Disorders

The symptoms of genetic disorders can sometimes be treated, but cures for genetic disorders are still in the early stages of development. One potential cure that has already been used with some success is gene therapy, a type of biotechnology. This involves inserting normal genes into cells with mutant genes. At the following link, you can watch the video *Sickle Cell Anemia: Hope from Gene Therapy,* to learn how scientists are trying to cure sickle-cell anemia with gene therapy:
http://www.youtube.com/watch?v=6zNj5LdDuTA

If you could learn your risk of getting cancer or another genetic disease, would you? Though this is a personal decision, it is a possibility. A San Francisco company now makes it easy to order medical genetic tests through the Web.

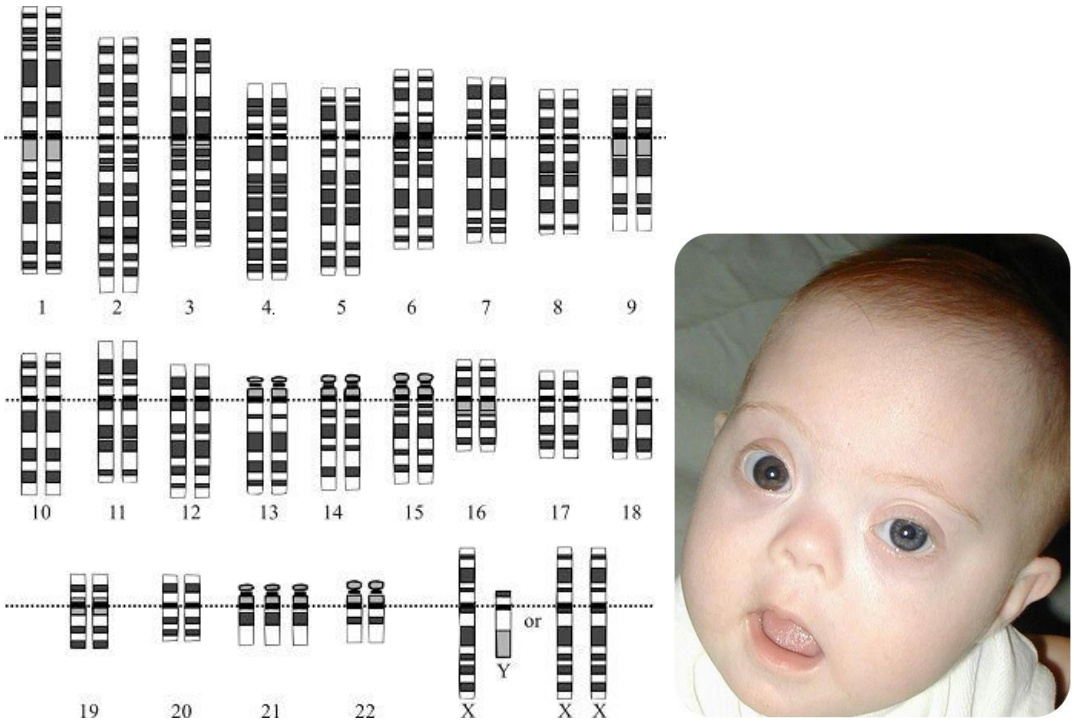

Figure 7.46: Trisomy 21 (Down Syndrome) Karyotype. A karyotype is a picture of a cell's chromosomes. Note the extra chromosome 21. Child with Down syndrome, exhibiting characteristic facial appearance.

Biotechnology Methods

Biotechnology uses a variety of techniques to achieve its aims. Two commonly used techniques are gene cloning and the polymerase chain reaction. Both technologies give researchers the means to make more DNA, but they do so in different ways. In particular, cloning involves the synthesis of DNA from mRNA using an enzyme called reverse transcriptase.

Gene Cloning

Gene cloning is the process of isolating and making copies of a gene. This is useful for many purposes. For example, gene cloning might be used to isolate and make copies of a normal gene for gene therapy. Gene cloning involves four steps: isolation, ligation, transformation, and selection.

1. In isolation, an enzyme is used to break DNA at a specific base sequence. This is done to isolate a gene.
2. During ligation, the enzyme DNA ligase combines the isolated gene with plasmid DNA from bacteria. (Plasmid DNA is circular DNA that is not part of a chromosome and can replicate independently.) Ligation is illustrated in **Figure 7.45**. The DNA that results is called recombinant DNA.
3. In transformation, the recombinant DNA is inserted into a living cell, usually a bacterial cell. Changing an organism in this way is also called genetic engineering.
4. Selection involves growing transformed bacteria to make sure they have the recombinant DNA. This is a necessary step because transformation is not always successful. Only bacteria that contain the recombinant DNA are selected for further use.

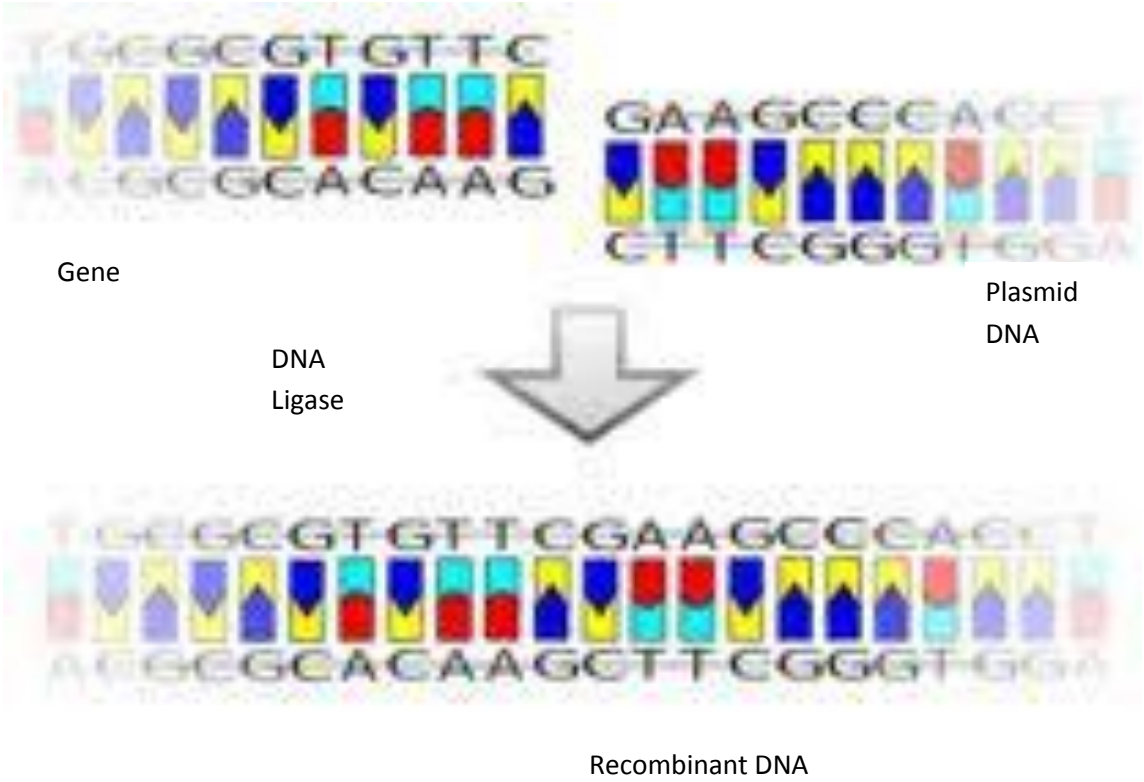

Figure 7.47: Ligation. DNA ligase joins together an isolated gene and plasmid DNA. This produces recombinant DNA.

Recombinant DNA technology is discussed in the following videos and animations: http://www.youtube.com/watch?v=Jy15BWVxTC0 (0.50) and http://www.youtube.com/watch?v=sjwNtQYLKeU&feature=related (7.20).

Polymerase Chain Reaction

The polymerase chain reaction (PCR) makes many copies of a gene or other DNA segment. This might be done in order to make large quantities of a gene for genetic testing. PCR involves three steps: denaturing, annealing, and extension. The three steps are illustrated in **Figure 7.48**. They are repeated many times in a cycle to make large quantities of the gene. You can watch animations of PCR at this link: http://www.dnalc.org/resources/3d/19-polymerase-chain-reaction.html

1. Denaturing involves heating DNA to break the bonds holding together the two DNA strands. This yields two single strands of DNA.
2. Annealing involves cooling the single strands of DNA and mixing them with short DNA segments called primers. Primers have base sequences that are complementary to segments of the single DNA strands. As a result, bonds form between the DNA strands and primers.
3. Extension occurs when an enzyme (Taq polymerase or Taq DNA polymerase) adds nucleotides to the primers. This produces new DNA molecules, each incorporating one of the original DNA strands.

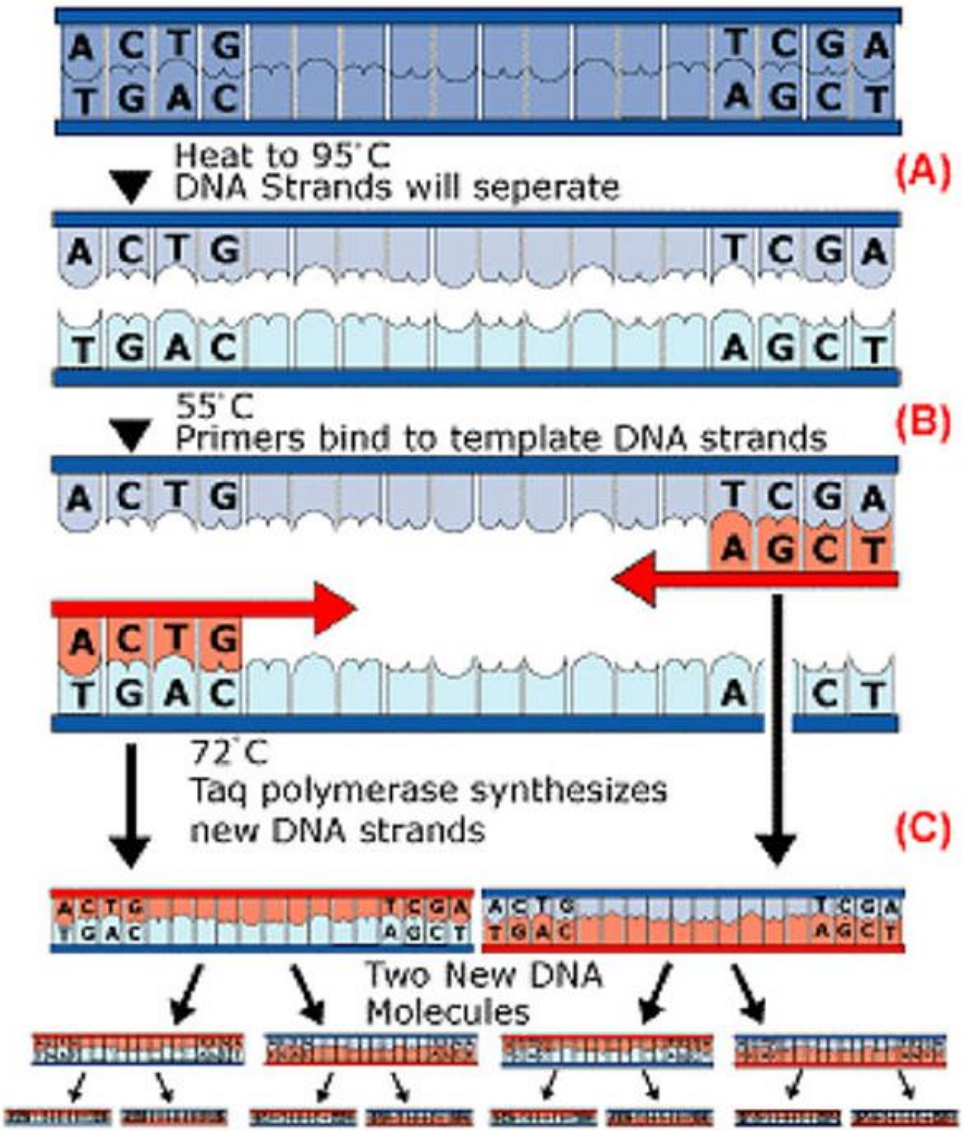

Figure 7.48: The Polymerase Chain Reaction. The polymerase chain reaction involves three steps. High temperatures are needed for the process to work. The enzyme Taq polymerase is used in step 3 because it can withstand high temperatures.

Applications of Biotechnology

Methods of biotechnology can be used for many practical purposes. They are used widely in both medicine and agriculture. To see how biotechnology can be used to solve crimes, watch the video *Justice DNA—Freeing the Innocent* at the following link: http://www.sosq.vcu.edu/

Applications in Medicine

In addition to gene therapy for genetic disorders, biotechnology can be used to transform bacteria so they are able to make human proteins. **Figure 7.49** shows how this is done. Proteins made by the bacteria are injected into people who cannot produce them because of mutations.

Insulin was the first human protein to be produced in this way. Insulin helps cells take up glucose from the blood. People with type 1 diabetes have a mutation in the gene that normally codes for insulin. Without insulin, their blood glucose rises to harmfully high levels. At present, the only treatment for type 1 diabetes is the injection of insulin from outside sources. Until recently, there was no known way to make insulin outside the human body. The problem was solved by gene cloning. The human insulin gene was cloned and used to transform bacterial cells, which could then produce large quantities of human insulin.

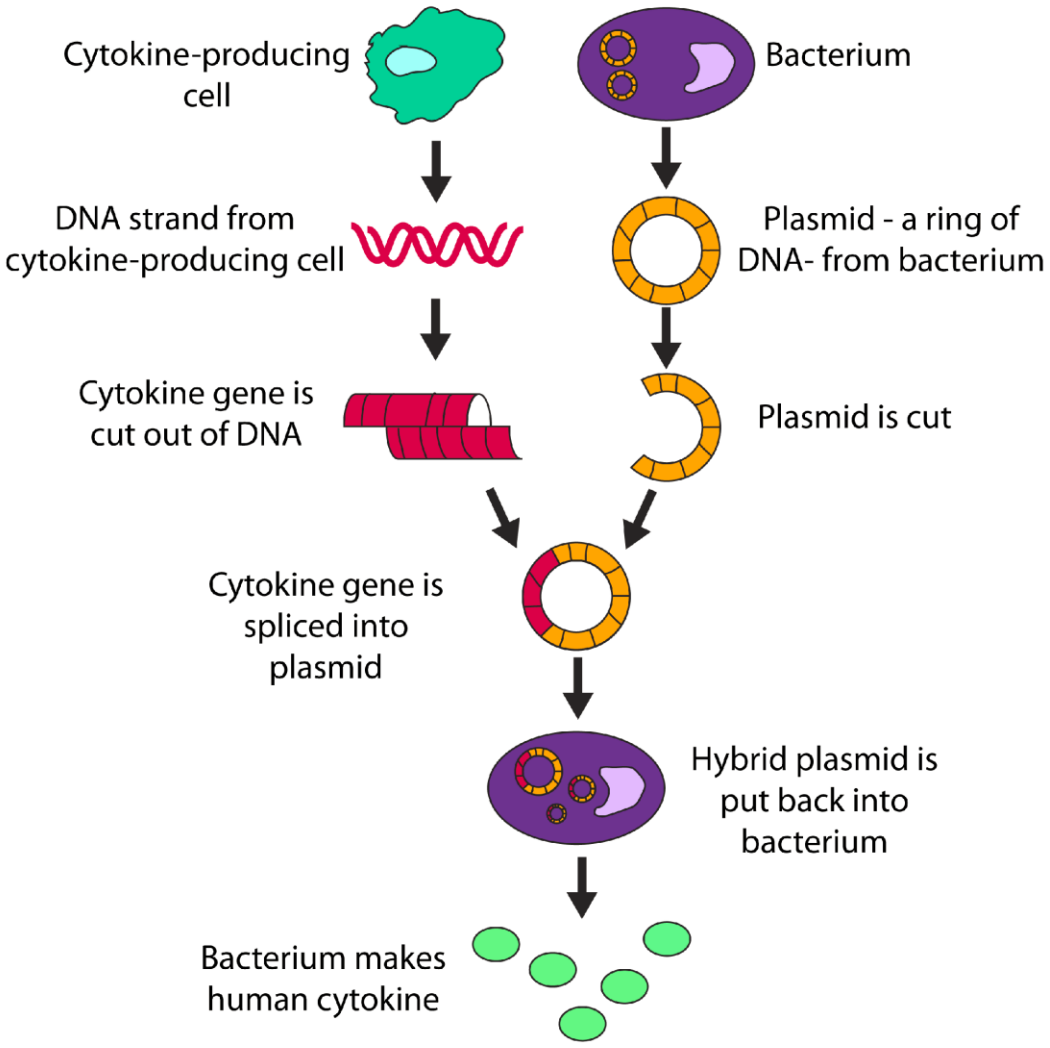

Figure 7.49: Genetically Engineering Bacteria to Produce a Human Protein. Bacteria can be genetically engineered to produce a human protein, such as a cytokine. A cytokine is a small protein that helps fight infections.

KQED: Pharmacogenomics

As we have learned, we know that, thanks to our DNA, each of us is a little bit different. Some of those differences are obvious, like eye and hair color, but others are not so obvious, like how our bodies react to medication. Researchers are beginning to look at how to tailor medical treatments to our genetic profiles, in a relatively new field called Pharmacogenomics**.** Some of the biggest breakthroughs have been in cancer treatment. For additional information on this ‘‘personalized medicine,” listen to http://science.kqed.org/quest/2009/09/11/reporters-notes-personalized-medicine/ .

KQED: Synthetic Biology

Imagine living cells acting as memory devices; biofuels brewing from yeast, or a light receptor taken from algae that makes photographs on a plate of bacteria. The new field of Synthetic Biology is making biology easier to engineer so that new functions can be derived from living systems. Find out the tools that synthetic biologists are using and the exciting things they are building at: https://www.youtube.com/watch?v=rD5uNAMbDaQ .

Applications in Agriculture

Biotechnology has been used to create transgenic crops. Transgenic crops are genetically modified with new genes that code for traits useful to humans. The diagram in **Figure 7.50** shows how a transgenic crop is created. You can learn more about how scientists create transgenic crops with the interactive animation *Engineer a Crop—Transgenic Manipulation* at this link: http://www.pbs.org/wgbh/harvest/engineer/transgen.html .

Transgenic crops have been created with a variety of different traits, such as yielding more food, tasting better, surviving drought, and resisting insect pests. Scientists have even created a transgenic purple tomato that contains a cancer-fighting compound (see **Figure 7.51,** on the next page). To learn how scientists have used biotechnology to create plants that can grow in salty soil, watch the video *Salt of the Earth—Engineering Salt-Tolerant Plants* at this link: http://www.sosq.vcu.edu/ .

Biotechnology in agriculture is discussed at http://www.youtube.com/watch?v=IY3mfgbe-0c (6:40).

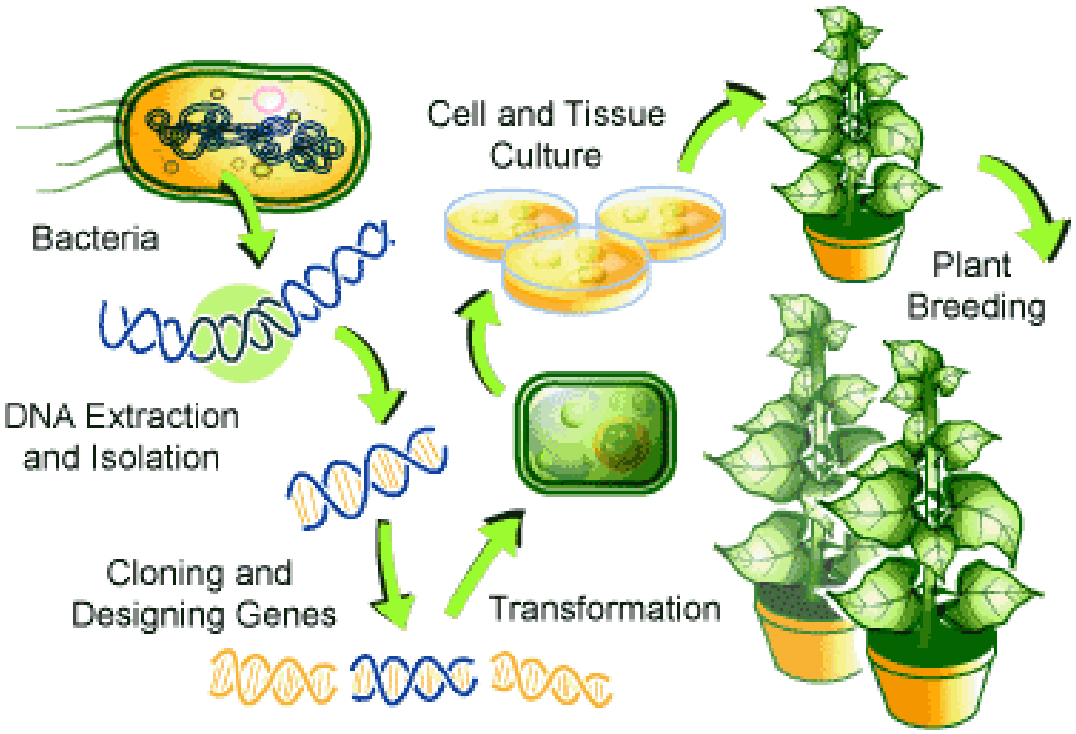

Figure 7.50: Creating a Transgenic Crop. A transgenic crop is genetically modified to be more useful to humans.

Figure 7.51: Transgenic Purple Tomato. A purple tomato is genetically modified to contain a cancer fighting compound. A gene for the compound was transferred into normal red tomatoes.

Ethical, Legal, and Social Issues

The use of biotechnology has raised a number of ethical, legal, and social issues. Here are just a few:

- Who owns genetically modified organisms such as bacteria? Can such organisms be patented like inventions?
- Are genetically modified foods safe to eat? Might they have unknown harmful effects on the people who consume them?
- Are genetically engineered crops safe for the environment? Might they harm other organisms or even entire ecosystems?
- Who controls a person's genetic information? What safeguards ensure that the information is kept private?
- How far should we go to ensure that children are free of mutations? Should a pregnancy be ended if the fetus has a mutation for a serious genetic disorder?

Addressing such issues is beyond the scope of this textbook. The following example shows how complex the issues may be:

A strain of corn has been created with a gene that encodes a natural pesticide. On the positive side, the transgenic corn is not eaten by insects, so there is more corn for people to eat. The corn also doesn't need to be sprayed with chemical pesticides, which can harm people and other living things. On the negative side, the transgenic corn has been shown to cross-pollinate nearby milkweed plants. Offspring of the cross-pollinated milkweed plants are now known to be toxic to monarch butterfly caterpillars that depend on them for food. Scientists are concerned that this may threaten the monarch species as well as other species that normally eat monarchs.

As this example shows, the pros of biotechnology may be obvious, but the cons may not be known until it is too late. Unforeseen harm may be done to people, other species, and entire ecosystems. No doubt the ethical, legal, and social issues raised by biotechnology will be debated for decades to come. For a recent debate about the ethics of applying biotechnology to humans, watch the video at the link below. In the video, a Harvard University professor of government and a Princeton University professor of bioethics debate the science of ''perfecting humans." http://www.youtube.com/watch?v=-BPna-fSNOE .

Lesson Summary

- Mutations are caused by environmental factors known as mutagens. Types of mutagens include radiation, chemicals, and infectious agents.
- Germline mutations occur in gametes. Somatic mutations occur in other body cells. Chromosomal alterations are mutations that change chromosome structure. Point mutations change a single nucleotide. Frameshift mutations are additions or deletions of nucleotides that cause a shift in the reading frame.
- Mutations are essential for evolution to occur because they increase genetic variation and the potential for individuals to differ. The majority of mutations are neutral in their effects on the organisms in which they occur. Beneficial mutations may become more common through natural selection. Harmful mutations may cause genetic disorders or cancer.
- Many genetic disorders are caused by mutations in one or a few genes.
- Other genetic disorders are caused by abnormal numbers of chromosomes.
- Many genetic disorders are caused by mutations in one or a few genes. Other genetic disorders are caused by abnormal numbers of chromosomes.
- Gene cloning is the process of isolating and making copies of a DNA segment such as a gene. The polymerase chain reaction makes many copies of a gene or other DNA segment.
- Biotechnology can be used to transform bacteria so they are able to make human proteins, such as insulin. It can also be used to create transgenic crops, such as crops that yield more food or resist insect pests.
- Biotechnology has raised a number of ethical, legal, and social issues. For example, are genetically modified foods safe to eat, and who controls a person's genetic information?

References/ Multimedia Resources

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