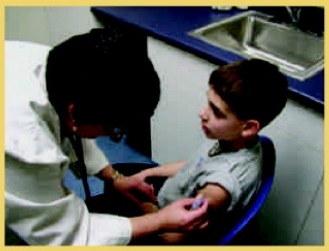
© Yale Science Laboratory

A High Resolution Photo of DNA

CASE A: A Taller Son for Chris



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Chris Crowley is concerned about his 10-year-old son, Mike, who is short—not just short for his age, but very short. Just today Mike came home from school crying. Some kids had made fun of him and pushed him around. This was not the first time.

Chris had gone through this himself. His adult height is only 5 feet 6 inches (1.6 m) tall, which is fairly short for a man. During his teen years, his friends had made fun of him, and he didn't want Mike to go through that.

Chris had recently read an article about human growth hormone (hGH), a drug that might help Mike. hGH is safe and available because now it is made using **recombinant DNA technology**. Children given injections of the drug before puberty sometimes grew 5 to 6 inches (12.7–15.2 cm). Athletes also used it to increase their strength for certain sports. Chris thought that if Mike could grow a few inches and be stronger, it would give him confidence and possibly a better life.

When Chris brought this up with Mike's pediatrician, Dr. Sanchez, he was surprised when she said that Mike wasn't a candidate for hGH treatment. The reason was that Mike was still within the "normal" range of height for his age, and the hormone is used to treat only the shortest 1–2% of all children. She explained that even though Mike was shorter than his friends, he might still grow to be within the normal range of adult height. Moreover, the side effects of this drug are still unknown. Chris left the doctor's office feeling somewhat confused and let down.

Some questions come to mind when reading this case. Before we can address these questions, let's look at what biotechnology and recombinant DNA are, how they are used to create drugs, and their other uses.

7.1 What Is Biotechnology?

Biotechnology couples biological organisms with genetic technology to create products, processes, and services. Many fields contribute to biotechnology, including microbiology, biochemistry, genetics, medicine, environmental sciences, and computer science. The relationships among some of these areas in biotechnology are shown in Figure 7.1, page 148. Underlying biotechnology are several processes, collectively called genetic engineering. These processes include recombinant DNA technology, gene modification, and gene technology. Genetic engineering allows scientists to cut genes out of DNA and to splice or recombine these genes into other DNA molecules. These recombinant DNA molecules can be transferred to organisms, giving them the ability to produce a specifically selected new product (for example, a bacterial cell making a human protein). The ability of a genetically engineered organism to make a product is useful in medicine, agriculture, forensics, industry, and other areas.

Biotechnology has many uses, one of which is making human proteins for medical purposes, including human growth hormone (hGH). As we will see, this application uses several aspects of biotechnology, including recombinant DNA technology, microbiology, and medicine.

Before the development of biotechnology, proteins used to treat disease—such as insulin, hGH, and blood-clotting factors—were collected from many sources, including animals in slaughterhouses, human cadavers, urine, and donated human blood. In some

recombinant DNA technology the process by which recombinant DNA is created

biotechnology scientific process that uses recombinant DNA to make products

Figure 7.1 **The Range of Methods and Uses of Biotechnology**

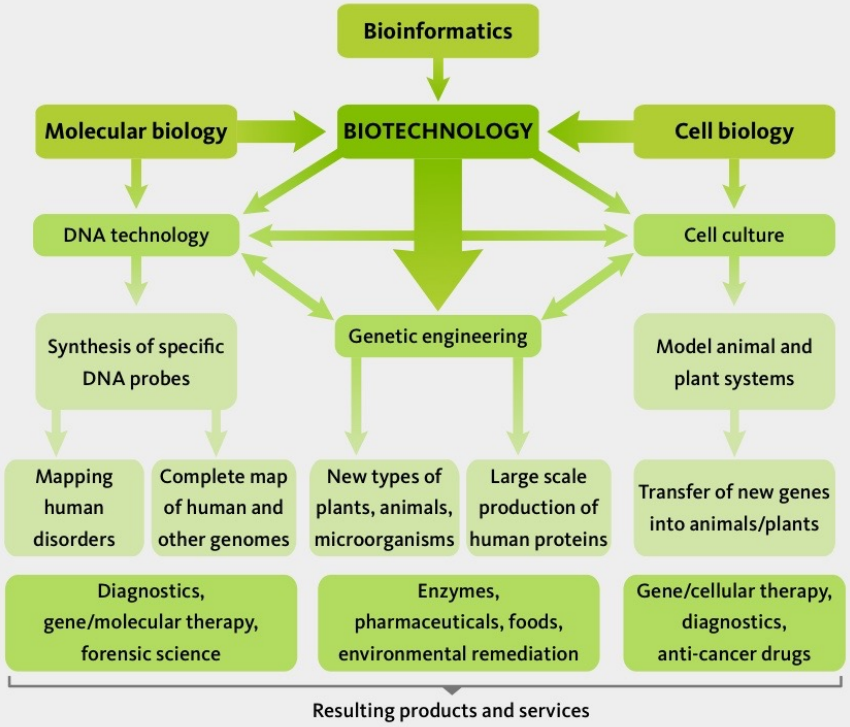


Table 7.1 **FDA-Approved Uses for Human Growth Hormone**

Children
hGH insufficiency or deficiency
Turner syndrome
Prader-Willi syndrome
Chronic renal insufficiency
Infants born small for gestational age
Adults
hGH deficiency
AIDS-associated wasting syndrome

cases, proteins from these sources were contaminated with disease-causing agents that exposed people to serious and potentially fatal risks. For example, before biotechnology was used, some batches of clotting factor made from donated blood were contaminated with HIV (human immunodeficiency virus), the virus associated with AIDS (acquired immunodeficiency syndrome). Many people treated with these contaminated batches of clotting factor became infected with HIV and developed AIDS.

Until 1985, children with growth problems were treated with growth hormone isolated from pituitary glands removed from human cadavers. The available supply was limited, and only a small number of children could be treated. More than two dozen of the 7000 children treated contracted a deadly brain condition because the hGH was contaminated with prions, a disease-causing agent similar to the one that causes mad cow disease.

In 1985, the FDA approved the use of hGH produced using biotechnology and removed the cadaver-derived hGH from the market. Combining technology with genetics allowed human growth hormone to be produced in bacteria, with two immediate benefits: there is no possibility of prion contamination, and unlimited amounts of the hormone can potentially be produced. In fact, partly because of these advantages, the U.S. Food and Drug Administration has expanded the number of conditions that can be treated with this hormone (Table 7.1). hGH can now be used to treat children with very short stature (children shorter than Chris Crowley's son) and not just those with serious growth disorders.

How is biotechnology used to make human growth hormone?

As mentioned above, recombinant DNA technology is one of the methods used in biotechnology. To make human growth hormone, scientists isolated the human gene for hGH from a human cell and transferred it to a bacterial cell, creating a **transgenic organism** (an organism that carries a gene from another species). The transgenic bacterial cell and its descendants synthesize hGH, which is recovered and purified for medical use.

transgenic organism animals, plants, or microbes that have been genetically altered using recombinant DNA techniques

More recently, researchers successfully transferred the gene for hGH into cows, which secrete the hormone into their milk. The milk from these cows is collected, and

the hormone is extracted and purified. It is estimated that a herd of 15 transgenic cows would be able to meet the worldwide demand for hGH. Biotechnology is being used to transfer genes for other medically important human proteins into animals and plants, where these proteins are synthesized in large quantities before extraction and purification for use in treating diseases.

7.1 Essentials

- **Recombinant DNA techniques can be used to transfer genes among species.**
- **Transgenic organisms can produce human proteins that are used in medical treatment.**

7.2 What Is Recombinant DNA Technology?

Recombinant DNA can be defined as the combination of DNA from two or more different organisms. Several steps are required to create human proteins such as hGH in transgenic organisms; these steps are part of recombinant DNA technology. To see how this process works, follow along with Figure 7.2.

- Identify the gene for growth hormone in humans.
- Extract DNA from human cells that were grown in the laboratory.
- Treat the DNA with a **restriction enzyme**, a protein that cuts the DNA into fragments at specific sites (step 1). Often these cuts leave an overhanging single-stranded region called a "sticky end" (Table 7.2).
- Cut a circular DNA molecule (called a **plasmid**) with the same restriction enzyme (step 2). Many species of bacteria carry these small, circular DNA molecules. Researchers have genetically modified plasmids to create carrier molecules called **vectors** that are used in recombinant DNA technology. This plasmid DNA will be used to carry the inserted human gene into bacterial cells.
- The fragments of human DNA and fragments of plasmid DNA (called vectors) created by restriction enzyme digestion are mixed and spliced together to form **recombinant DNA molecules** (steps 3 and 4).
- The recombinant plasmids carrying human DNA are transferred into bacterial cells (step 5).
- The bacteria that carry the human gene for growth hormone are identified. The process has been engineered so that bacterial cells carrying the growth hormone gene will synthesize the human protein. Once isolated, these bacteria are used to synthesize human growth hormone, which is recovered, purified, and used for medical treatments.

restriction enzyme a protein that, when mixed with DNA, cuts the DNA in a specific place

plasmid circular DNA found in bacteria

vector molecules used for carrying a DNA segment into a host cell, where it is copied

recombinant DNA molecule a DNA molecule that has had a new section added

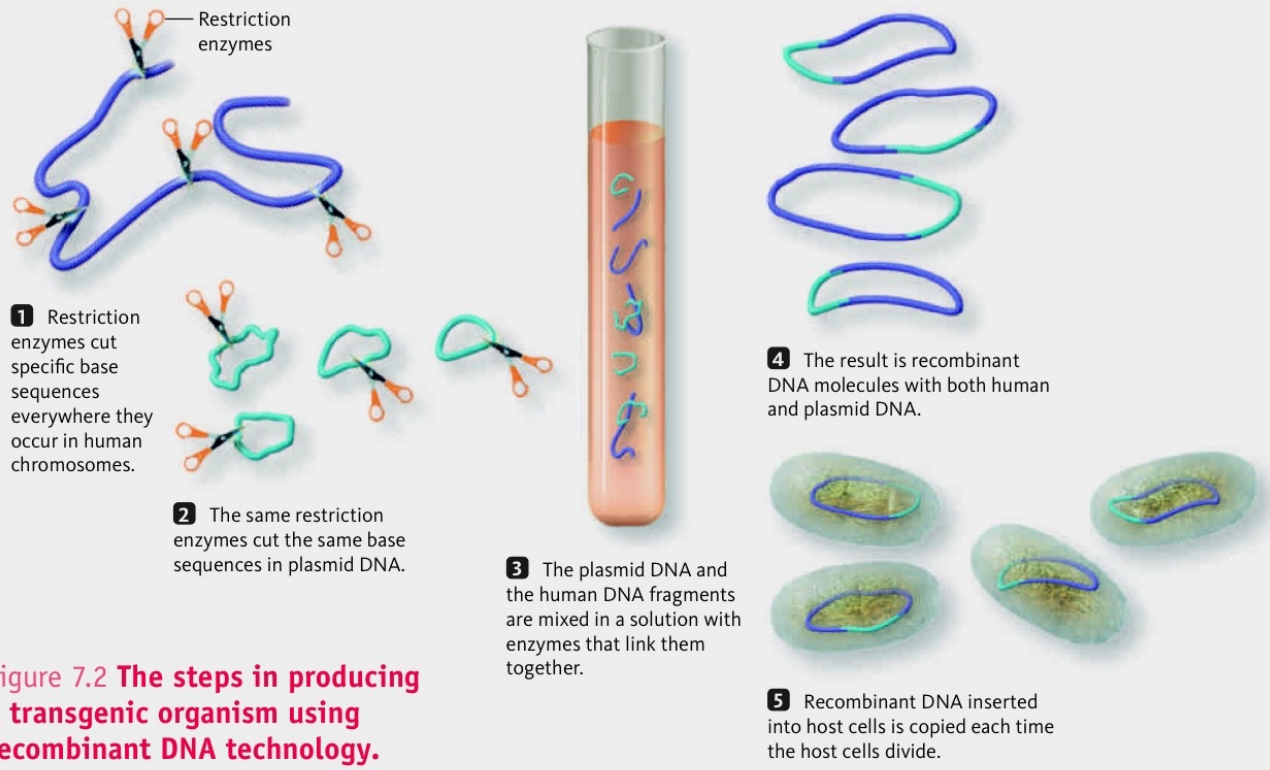


Figure 7.2 **The steps in producing a transgenic organism using recombinant DNA technology.**

Table 7.2 **Restriction Enzymes**

Enzyme	Cutting Sites	Source Organism
*Eco*RI	GAATTC CTTAAG	*Escherichia coli*
*Hind*III	AAGCTT TTCGAA	*Haemophilus influenzae*
*Bam*HI	GGATCC CCTAGG	*Bacillus amyloliquefaciens*

Although we have used the production of human growth hormone as an example, the same process is used to transfer genes from many different organisms into bacteria, yeast, plants, and animals. These transgenic organisms are used to produce a variety of products such as vaccines or proteins for medical use. In agriculture, transgenic plants are used directly as crops with nutritional enhancements or herbicide resistance. Many products we eat, use in our homes, take as medicines, and even wear are or will be produced by biotechnology (Table 7.3).

Table 7.3 **Some Drugs Produced by Biotechnology**

Drug	Uses
Abatacept	Rheumatoid arthritis
Alefacept	Psoriasis
ATryn	Anti-thrombin deficiency
Erythropoietin	Anemia
Etanercept	Immune disorders
Factor VIII, X	Blood-clotting disorders
Follicle-stimulating hormone	Fertility treatment
Infliximab	Immune disorders
Interferons	Leukemia
Hepatitis B vaccine	Hepatitis B immunity
Human growth hormone	Growth deficiency
Insulin	Diabetes
Trastuzumab (Herceptin)	Breast cancer

7.2 Essentials

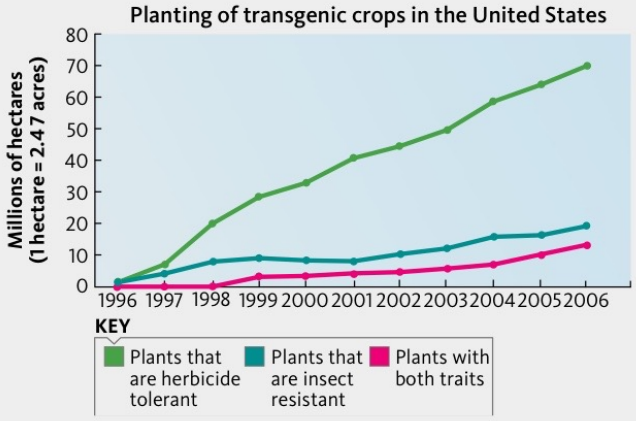
- **Restriction enzymes bind to DNA at specific recognition sequences and cut the DNA at these sequences.**
- **Recombinant DNA is created when DNA from two or more different organisms is joined.**
- **Biotechnology is the commercial use of recombinant DNA techniques to produce drugs, enhanced crop plants and farm animals, industrial chemicals, waste treatment, bioremediation, and many other uses.**

7.3 How Is Biotechnology Used to Make Transgenic Plants?

Transgenic crops have been grown in the United States since 1996. The graph in Figure 7.3 shows the dramatic increase in the production of transgenic crops between 1996 and 2006 in the United States. Products made from corn and soybeans, as well as cottonseed and canola oils, currently account for the majority of foods that contain transgenic ingredients.

Biotechnology is widely used in agriculture to make transgenic crop plants with new characteristics (Figure 7.4). Genes transferred to the crop plant can originate in another plant, an animal, or even fungi or bacteria. One or more new genes are used to give the transgenic plant a unique trait, such as resistance to **herbicides** (chemical weed killers), insects, or viral or fungal diseases.

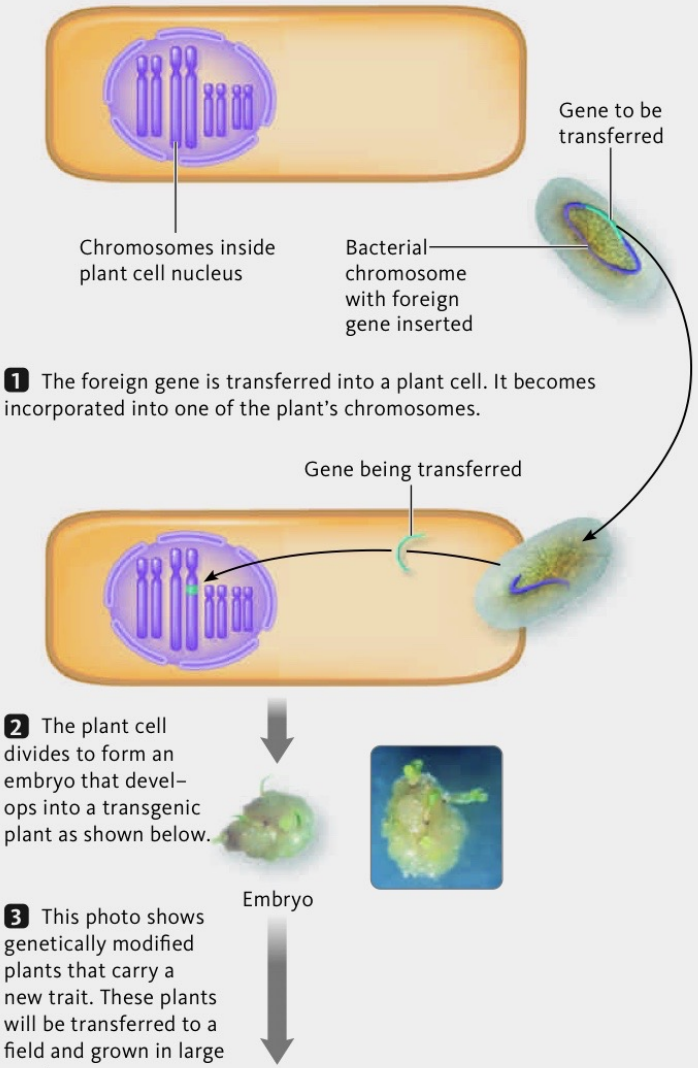
Figure 7.3 **The Use of Transgenic Crops in the United States between 1996 and 2006**



herbicides poisons that kill plants

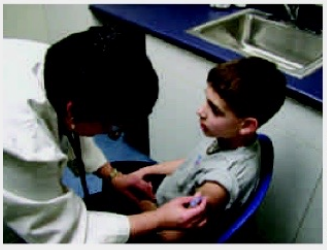
transgenic crops crops that have been altered by introduction of DNA from another organism

Figure 7.4 **The Production of Transgenic Crop Plants** A specific gene is incorporated into a bacterial cell and used to transfer a genetic trait into a plant cell (1). The plant cells are grown in the laboratory (2), and then transferred to a field to form a mature genetically modified organism (3). Traits transferred to crops in this way are herbicide resistance and resistance to insects.



Lowell Georgia/CORBIS

CASE A: QUESTIONS



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Now that we understand how some biotechnology processes work, let's look at some questions related to Mike's short stature.

1. After the doctor's visit, Chris decided he must deal with Mike's short stature without the use of hGH. Suggest four ways that Chris could deal with Mike's stature.
2. What do you think Chris should do?
3. Did Dr. Sanchez do the right thing in denying Mike hGH treatment?
4. Should parents be able to make all medical decisions for their children?
5. If Dr. Sanchez administered hGH to Mike, what might happen?
6. Should Mike be included in the decision whether or not to undergo hGH treatment?
7. Human growth hormone is legal in the United States for treating those with low hGH levels and children who are considered too short. If hGH has other potential uses, should it be used for those purposes? Why or why not?
8. Athletic associations including the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA) have concluded that use of hGH by athletes might give them an advantage over others; therefore, they have banned the use of this hormone. What do you think?

Some other examples of products created with biotechnology are shown in Figure 7.6, page 152.

Figure 7.5 **The use of transgenic crops in 22 countries has increased every year following their introduction.**

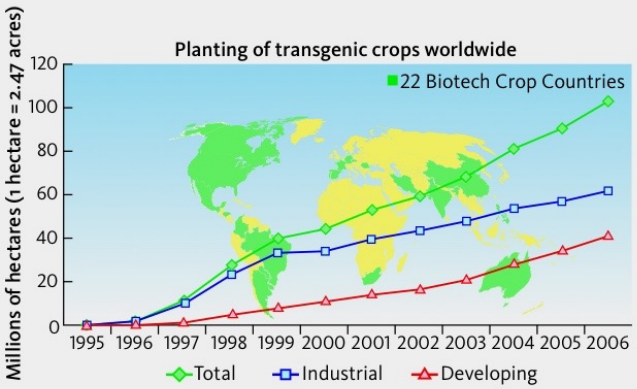
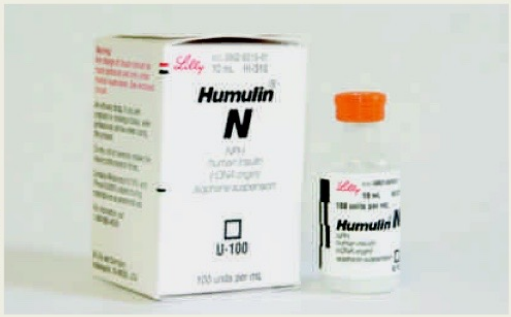


Figure 7.6 **Some Products of Biotechnology**

Transgenic Plants and Animals

Photo courtesy of Professor Qing-Hu Ma, Institute of Botany, Chinese Academy of Sciences

Transgenic tobacco plants are also being used to produce hGH. Most work with transgenic plants to make human proteins is still in early stages of development, but soon fields of transgenic plants or small herds of transgenic animals may replace laboratories for making human proteins used in medical treatments.

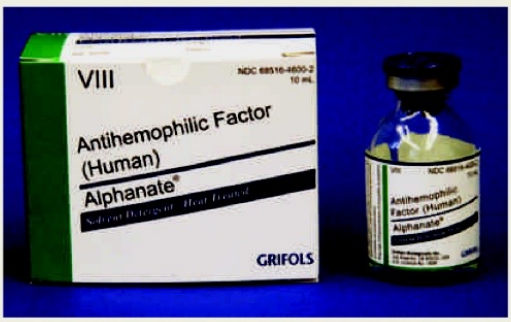


Eric Carr/Alamy

One of the most successful uses of recombinant DNA technology is the synthesis of human insulin. Many people who have diabetes must take the protein insulin because their bodies do not produce it. Before insulin was made using recombinant DNA, it was extracted from the pancreases of pigs and cows. Some people with diabetes had allergic reactions to pig and cow insulin. Now that recombinant human insulin is available, such reactions are rare.

© Golden Rice Humanitarian Board

Golden rice is a transgenic strain of rice that contains two genes from daffodils and one gene from bacteria. With these added genes, the rice plants synthesize beta-carotene, a compound that turns the rice a golden color. When the rice is eaten, beta-carotene is converted into vitamin A. In many Asian countries there is a dietary deficiency of vitamin A. Golden rice strains are now available for planting in Southeast Asia.



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Factor VIII is a protein that helps form blood clots. People with one form of hemophilia need Factor VIII because it is not present in their blood. Recombinant DNA techniques have been used to make human Factor VIII, so people with hemophilia do not have to use blood donors to get this needed protein. In the 1980s, many people with hemophilia contracted HIV from tainted blood products.

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The human tissue-typing gene complex called HLA has been transferred to pig embryos. The adult pigs that result have organs compatible with humans. Transplanting these organs (called *xenotransplantation*) to needy recipients can increase the number of organs available for transplantation.

Transgenic plants resistant to herbicides are now available worldwide and are being used in almost two dozen countries (Figure 7.5, page 151). Transferred genes can also increase the nutritional value of crops, helping eliminate dietary deficiencies that are widespread in many parts of the world.

7.3 Essentials

- **Transgenic bacteria, plants, and animals are created with recombinant DNA techniques.**

7.4 Are Transgenic Organisms Safe?

The development and use of transgenic crops have generated controversy in many regions, including the United States, Europe, and developing African nations. Genetic engineering has been used to make crop plants resistant to herbicides, pests (as shown in the cotton plant photo in Figure 7.7), and disease, and to change nutritional value, chemical content, growing season, and crop yields. Accompanying these advances, many questions have been raised about the safety and environmental impact of transgenic crops, often called *genetically modified (GM) crops* or *genetically modified organisms (GMOs)*, such as the Flavr Savr tomato (Figure 7.8). Several organizations and movements actively oppose the introduction and use of transgenic crops. Controversies about transgenic crops focus on safety and labeling, and the rights of farmers, loss of traditional crops, and biodiversity, among others. As transgenic crops become more common and new ones are developed, we clearly need to identify and monitor any health and environmental risks and resolve the related economic and social issues.

What do we know so far about these risks of transgenic crops? Most food produced from transgenic crops contains one or more proteins encoded by a transferred gene. Standards for evaluating the safety of foods from transgenic crops are in place in many European countries and the United States. In general, transgenic crops are considered safe if the proteins produced by the transplanted genes are not poisonous and do not cause allergies any more than plants crossbred in the normal breeding method.

Figure 7.7 (left) A cotton plant attacked and destroyed by insects. (right) A transgenic cotton plant engineered to be insect-resistant.

© Agricultural Research Service/USDA

Figure 7.8 **Transgenic Flavr Savr Tomatoes** These tomatoes were engineered to ripen on the vine before shipping and to withstand transport long distances without softening. Vine ripening was thought to improve taste and flavor. Consumer demand for this product was low; some thought it still tasted like the typical store-bought tomato. The product was eventually withdrawn from the market.

© Tom Myers/Photo Researchers, Inc.

As an example, let's consider herbicide-resistant crops. The bacterial protein encoded by the transplanted genes is broken down in our digestive system when the plant is eaten. In studies with mice, the protein was not poisonous even in very high doses. This protein does not contain any amino acid sequences that are similar to any known toxins or allergens. After 15 years of widespread use, no human health risks associated with these crops have been identified.

However, several environmental risks related to transgenic crops have been identified, including the transfer of the transplanted genes to wild plants by crossbreeding. This may ultimately reduce biodiversity, with a possible negative impact on the environment.

This problem and others related to transgenic crops are the same as those we face using conventional crops. Even though transgenic crops have a different genetic history from that of conventional crops, their effects on the environment are very similar.

As gene transfer technology becomes more sophisticated, novel combinations of traits may be developed, requiring specific management plans. For example, if production of pharmaceutical products in plants becomes common, it will be necessary to develop safeguards to keep such plants out of the food supply and to ensure that transgenes for those proteins are not transferred to wild plants.

Humans have been genetically modifying agricultural plants and animals for more than 10,000 years using selective breeding and crossbreeding to produce the diversity of domesticated plants and animals we depend on for our food. Biotechnology has changed only the way and the rate at

which these changes are made. It has increased the specificity and predictability of changes that can be made and also expanded the range of species that can donate genes. To continue improving plants and animals by conventional breeding and biotechnology, research, testing, and public education must address scientific questions, economic issues, health safeguards, and public perceptions.

7.4 Essentials

- **Safeguards are needed in developing and using transgenic organisms to produce food and drugs.**

7.5 Can Transgenic Animals Be Used to Study Human Diseases?

Information gained from the **Human Genome Project** (discussed in Chapter 10), which has sequenced all the human genes, combined with genome information from plants and other animals, shows that many genes found in the human genome are also present in other species, including the mouse and even the fruit fly, ***Drosophila***. Because of these similarities, a growing set of transgenic animals (Figure 7.9) is being generated and used to explore mechanisms of human disease and to test drugs developed to treat genetic disorders. These **animal models** of human disease are important in research. Without an animal model, it is often difficult to study new drug treatments and the underlying causes of a disease. Models of specific human diseases can be created by transferring human disease genes into animals. These transgenic animal models can be used to:

- produce an animal with symptoms that mirror those in humans
- study the early stages of development and progress of a disease
- develop and test drugs that hopefully will cure or treat the animal model of the human disease

Eventually, this information and the drugs developed using animal models will be used to treat human diseases.

Because of the close genetic similarity between mice and humans, mice have been used extensively as animal models of human diseases (Figure 7.10).

Human Genome Project the project that is deciphering the organization, sequence, and function of all human genes

Drosophila a fruit fly used as a model genetic organism

animal models animals used in laboratory work to mimic human diseases

Figure 7.9 The mouse on the left was genetically engineered to be obese (normal mouse is on the right). The obese mouse is used as a model organism to study the genetic control of body mass and weight.

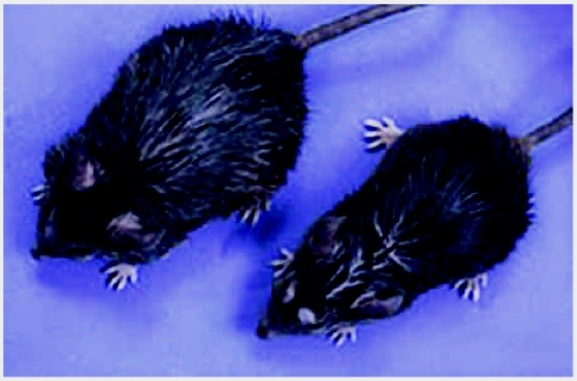


Figure 7.10 **Some Genetically Engineered Mice Used as Model Organisms to Study Human Diseases**

The *rhino mouse* is used to study immune deficiency conditions.

The *curly tail mouse* is used to study neural tube defects such as spina bifida.

The *obese mouse* is used to study products that can help with weight loss.

In one approach, a transgenic mouse model of Huntington disease (HD) has been developed and is being used to study this fatal genetic disorder. (Recall from Chapter 4 that members of Alan's family had this neurodegenerative disorder, which is inherited as an autosomal dominant trait.) HD transgenic mice (which have the mutant human allele for HD

inserted in their DNA) are being used to study what happens to the brain in the earliest stages of the disease, something that is impossible to do in humans. In addition, HD mice are used to link changes in brain structure with changes in behavior.

Research on these mice has identified several molecular mechanisms that play important roles in the early stages of the disease. These model organisms are also being used to screen drugs to identify those that improve symptoms or reverse brain damage. Several candidate drugs have been identified, some of which are now being tested in human clinical trials as experimental treatments for HD. Similar methods have been used to construct animal models of other human genetic disorders using mice and other organisms, including the fruit fly, *Drosophila melanogaster*.

How is biotechnology used to treat genetic diseases? It seems as though the use of recombinant DNA technology might be applied to cure genetic diseases. After all, if we can isolate a specific gene, why not just place it in a person who carries one or two mutant alleles of that gene and have the normal allele make the correct protein?

This simple idea is the basis for gene therapy trials being conducted around the world. However, in going from idea to application, two major problems exist. First, after a gene is isolated, it must be delivered to target cells and inserted into a chromosome. Then the gene must be switched on to direct the synthesis of enough of the normal protein to correct the genetic disorder. For example, someone with cystic fibrosis (CF) has problems with mucus secretion caused by ineffective chloride transport across the cell membrane. As you learned in Chapter 5, this can have life-threatening symptoms. After the gene for cystic fibrosis was identified, it was thought that transferring the normal allele into a child with CF might result in the uptake of the gene into cells and the production of a functional version of the chloride transport protein. However, in reality, this has proven to be far from the case. Some gene therapy clinical trials have been partially successful, while others have been tragic. In Chapter 10 gene therapy is explained in detail.

7.5 Essentials

- **Transgenic animals have been used to create animal models for human diseases.**
- **The same techniques are being tested to create cures for human genetic diseases.**

CASE B: Strawberries on Trial

© Index Stock Imagery/ Jupiter Images

In 1987, vandals slipped past guards, climbed over a high fence surrounding a field in California, spread rock salt, and sprayed an herbicide (a chemical that kills plants) on a large strawberry patch. Over 2000 strawberry plants were destroyed, and millions of dollars' worth of work was lost. This story may seem strange except for the fact that these strawberry plants had been sprayed with genetically engineered bacteria.

These bacteria, a strain of *Pseudomonas syringae* called "ice-minus," had been sprayed on the leaves of strawberry plants to prevent ice from forming on the leaves when the temperature dropped below freezing. Use of this transgenic bacterial strain extended the harvesting time of the strawberries and reduced plant loss caused by freezing. The strawberry plants and the strawberries themselves were not genetically modified.

After their arrest, the vandals said they would do it again if they had a chance.

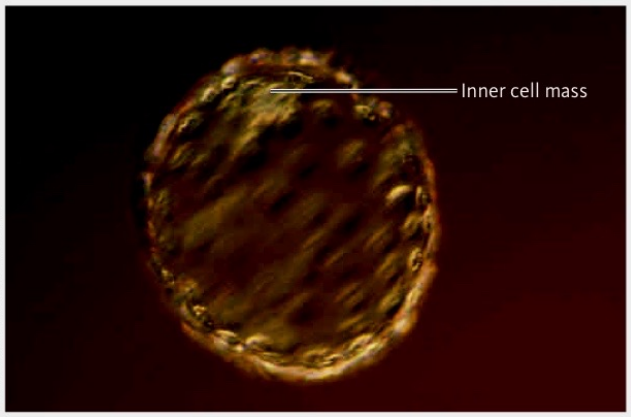
1. **Why would these people want to destroy the strawberry fields?**
2. **This type of bacteria seems to be helpful to farmers; shouldn't we do all we can to help them improve crops and keep food prices under control? Why or why not?**
3. **Scientists have also produced transgenic corn plants by implanting a gene from fireflies that makes the plants glow when the firefly gene is expressed. What advantages do you see for the corn farmer from this change?**
4. **Erwin Chargaff wrote in *Science* on June 4, 1976, "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years, in order to satisfy the ambition and the curiosity of a few scientists?" What are your thoughts on his statement? Are transgenic organisms changing the course of evolution?**

7.6 How Can Stem Cells Be Used in Biotechnology?

In Chapter 1, stem cells were identified as part of the developing embryo. These **embryonic stem cells** (ESCs) will form all the cells, tissues, and organs of the body. Because they are able to form so many different cell types, they are called

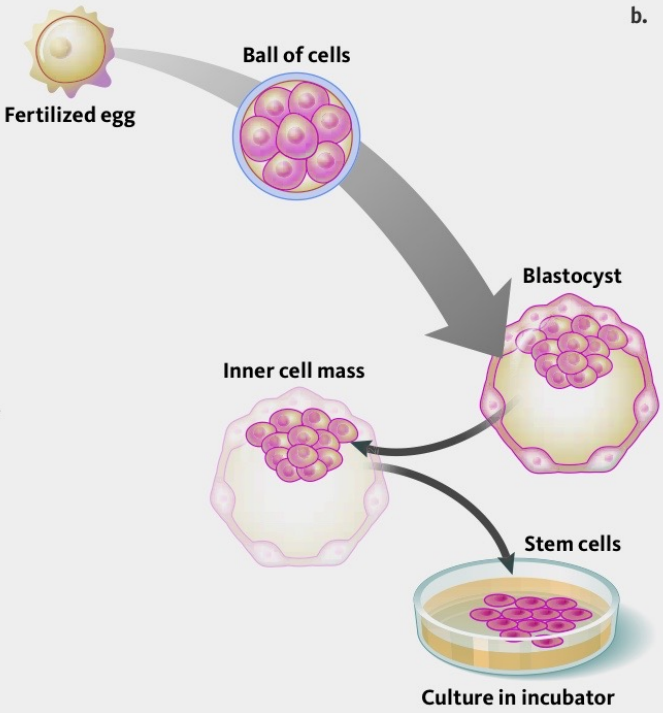
embryonic stem cells cells found in the inner cell mass of a developing embryo

Figure 7.11 **Embryonic Stem Cells (ESCs)** (a) Photograph of a human blastocyst embryo showing the location of embryonic stem cells. (b) Embryonic stem cells can be recovered and grown in the laboratory to form ESC lines that are used in research to develop treatments for human diseases.



Richard G. Rawlins, Ph.D/CMSP

a.



pluripotent cells. ESCs can be removed from the embryo and grown into a cell line in a laboratory dish (Figure 7.11).

In the laboratory, embryonic stem cells can be reprogrammed to become many different cell types, including muscle, bone, skin, and nerve tissue. Embryonic stem cells are being studied to understand the early stages of the disease process and to develop therapies to treat diseases. A second type of stem cell, the **adult stem cell**, is found in many tissues of the adult body. These stem cells can also generate different cell types to replace those that are worn out or damaged. These cells are called **multipotent** cells because they can form only a limited number of cell types. Adult stem cells have been used for several decades to treat diseases. One type of adult stem found in bone marrow divides to form new blood cells to replace those that die. In Chapter 12, we will see how bone marrow cells are used to treat blood conditions such as leukemia.

Many biotech companies are developing therapies based on the use of embryonic and adult stem cells. Many of these therapies may lead to treatment for conditions including spinal cord injury, regrowth of burned tissue, and damaged heart tissue. Several clinical trials are now under way to determine whether embryonic stem cells can be used to treat diseases.

7.6 Essentials

- **Research on embryonic stem cells may result in new treatments for disease.**
- **Adult stem cells have several uses in treating diseases.**

pluripotent stem cells from the embryo that can grow into any type of cell

adult stem cells cells found in the adult human body that give rise to new but specific cell types

multipotent cells that can grow into only a limited number of cell types

7.7 What Are the Legal and Ethical Issues Associated with Biotechnology?

In addition to the scientific and societal problems with transgenic animals and plants discussed earlier in this chapter, there are legal and ethical issues. One involves patenting these organisms and the genes that are identified.

The U.S. Patent and Trademark Office (USPTO) decides whether new inventions can be patented and develops rules about what can be patented. Anything patentable must be novel, not obvious, and useful. These rules also state that anything that is naturally occurring cannot be patented. However, in 1972, after a landmark legal decision in a case called *Diamond v. Chakrabarty* (447 U.S. 303 [1980]), all that changed. Dr. Chakrabarty developed a bacterial strain that could break down oil. To do this, he crossed bacterial strains carrying different plasmids (gene-carrying DNA molecules found naturally in bacteria), eventually placing four different plasmids into a single strain of *Pseudomonas* bacteria. Each plasmid carried a gene that could degrade a different component of oil. Placed together in one strain, these bacteria could be used to clean up large oil spills.

At first, the USPTO refused to patent this bacterial strain on the grounds that the bacteria were naturally occurring, but the argument of Chakrabarty's attorneys won the case. Their

argument, still used today, was that the strain containing all four of these plasmids in a single type of bacteria was unique and completely different from naturally occurring *Pseudomonas*. The patent was issued in 1972.

In a later case, Harvard University applied for and received a patent on a transgenic strain of mice called the **OncoMouse** (Figure 7.12). These mice carry a human cancer gene (**oncogene**) in their DNA. (In medical terminology, *onco-* means "cancer.") As a result of carrying this gene, the mice are more susceptible to cancer and are used to test chemicals for their ability to cause cancer. This case was the first in which a transgenic mammal was patented.

In the United States, the patent for the OncoMouse was issued in 1988. But in Canada, the case *Harvard College v. Canada (Commissioner of Patents)* was not decided until 2002. The Canadian courts ruled that a patent for a mammal could not be issued. Although recombinant bacterial strains have been patented in Canada, no patents for transgenic vertebrates have been issued.

Table 7.4 addresses some of the ethical and legal questions in the patenting of transgenic organisms and genes.

More recently, the USPTO has been trying to restrict some of the patents on genes and fragments of genes. It is now necessary for patent applications to identify the usefulness of the gene the applicant is seeking to patent.

Lawsuits sometimes arise when one company claims to have patented a specific allele and has created a test for that mutation. If another mutation in that same gene were discovered, could a new patent be issued for this mutant allele? If the companies were in different countries this might be possible, but until recently, if a U.S. company tried to patent the new mutant allele, it was unlikely that the patent would be issued.

In a recent case, *Re Kubin*, the USPTO turned down a patent on a gene discovered by Immunex, a private company. The gene encodes a protein found on white blood cells that plays a part in the immune response. The patent was turned down because another company had already discovered the protein, and finding the gene for that protein was a simple laboratory technique that could be done by any scientist with a lab manual. In other words, they said, the gene did not fulfill one of the main rules for patents—the substance must not be obvious.

Figure 7.12 **The OncoMouse was the first transgenic mammal to be patented.** This mouse strain has been genetically engineered to be susceptible to cancer. It is used to identify chemicals that cause cancer and to study the early events in the transformation of normal cells to cancerous cells.

SSPL/Getty Images

BY THE NUMBERS

1 in 3500
Number of children who have an hGH deficiency

60–70%

© Kim Karpeles/Alamy

Percentage of food in stores that contains some transgenic plant material

90%
Percentage of human disease genes also present in mice

400 and rising
Number of medical products being developed as of 2011 using biotechnology

OncoMouse the first genetically modified mammal patented

oncogene a gene, when mutated, that can cause cancer within a cell

Table 7.4 **Legal and Ethical Questions about Patenting Organisms**

Question	How Are These Questions Decided?	Related Case or Legal Issue
Can we patent genes that are discovered in human DNA?	When researchers apply for patents with the USPTO, judges who specialize in patent law decide each case.	Biotech companies are discovering genes every day and patenting them, even though the genes are naturally occurring. Their argument, similar to the one used in *Chakrabarty*, is that when a gene is isolated and removed from an organism, the situation is different than that of a gene that occurs naturally in the DNA of a species.
Can we patent sections of genes that are found in human DNA?	Such patents are also allowed, even when the gene is not identified or its use is unknown.	Using the argument that when removed from the cell and its DNA, a section is different from that found in nature, biotech companies have gained ownership of DNA sequences and collect fees from other companies that want to use them. Some of these are only parts of genes that have not been identified.
Can the methods used in recombinant DNA techniques be patented?	Methods or processes can be patented if they are useful and unique.	When such methods are patented, no other company or lab can use the process without paying a fee or getting permission from the owner of the patent.
Should we be manipulating the genome of animals, plants, and people?	This ethical question is being debated every day. It is often said that this will create organisms that are very different from those that came about by evolution. Scientists usually have autonomy to work on their own, especially in privately owned biotech companies.	Laws that control what can be done in biotech labs may be written, and some already exist in countries other than the United States. One serious question here might be, who can control science?

In March, 2010, Judge Robert W. Sweet of the U.S. District Court for the Southern District of New York, in the case *Association of Molecular Pathology v. USPTO*, decided a case that may be the tipping point for patenting of genes. The judge reviewed the patent Myriad Genetics received on the *BRCA-1* and *BRCA-2* ovarian and breast cancer susceptibility genes (see Chapter 12). In his ruling, the judge stated that the argument that the gene is somehow changed and is, therefore, not a product of nature when it is removed from the genome is not adequate. Myriad Genetics is planning to appeal the ruling, and it will no doubt go to the U.S. Supreme Court. Such decisions might completely change biotech gene patenting in the near future.

7.7 Essentials

- **Many ethical questions about the use of recombinant DNA technology are being debated.**

Spotlight on Ethics

The Asilomar Conference, February 1975

Asilomar Conference Center, Monterey Peninsula, California

In the 1970s, recombinant DNA was in its infancy. After the discovery of the structure of DNA, the idea of recombinant DNA seemed to make sense. However, some experiments made scientists think that using these techniques might cause some problems.

The Asilomar Conference was called by Dr. Paul Berg from Stanford University and other prominent scientists of the day. Berg was one of the first individuals to develop recombinant DNA technology. In 1972 he used a restriction enzyme to cut the DNA of the monkey virus SV40 and used methods similar to those discussed in this chapter to link fragments of SV40 DNA to DNA from another virus, known as bacteriophage lambda. The final step would have involved placing the recombined genetic material into a laboratory strain of *E. coli* as a host cell to allow the recombinant DNA molecule to be copied. Berg, however, did not take this last step.

Berg halted his experiment because of pleas from several fellow investigators who feared that biohazards might be associated with a host cell carrying this recombinant molecule. SV40 causes cancerous tumors in mice, and *E. coli* is found in the human intestinal tract; investigators feared inserting SV40 DNA into host cells that might escape into the environment and infect laboratory workers, who could then develop cancer.

A group of leading researchers concerned about Berg's experiment sent a letter to the president of the National Academy of Sciences requesting that he appoint a committee to study the biosafety ramifications of this new technology. This committee met in 1974 and concluded that an international conference was necessary to resolve the issue, and that, until then, scientists should voluntarily stop all experiments involving recombinant DNA technology.

The full conference was called in 1975. Its main goal was to address the potential hazards presented by recombinant DNA technology. It was one of the first scientific conferences to invite testimony of the public. A group of about 140 professionals (primarily scientists, but also lawyers and physicians) participated in the conference to draw up voluntary guidelines to ensure the safety of recombinant DNA technology. Some of these guidelines were as follows:

1. Organisms containing recombinant DNA must be contained.
2. The level of containment should match the risk of the organism to humans, animals, and plants. These risks were ranked from low to high according to their potential for causing human disease.
3. Physical barriers should be used to minimize the escape of transgenic organisms.
4. The following types of experiments were prohibited:
   a. the use of any organisms that could live in the human body
   b. the transfer of any gene that produces poisons
   c. the synthesis of any products harmful to humans, animals, and plants

QUESTIONS

1. Many scientists who participated in the conference felt that by writing their own guidelines, they avoided legislation that would control what was done. How could legislation work for the benefit and detriment of science?
2. The conference was held around the time of the Watergate break-in and the ultimate resignation of President Nixon. Do you think the ethical concerns surrounding this scandal might have influenced the outcome of the conference?
3. Should scientists control their own work?
4. With the controversies about the use of stem cells being an issue with significant political overtones, do you think that guidelines written by scientists would eliminate or reduce the controversy?
5. Who should control science? Give three reasons for your answer.
6. The book *The Andromeda Strain* by Michael Crichton was published in 1969. Research its plot and then answer this question: Could the publishing of this *fiction* book have affected this conference? Why or why not?