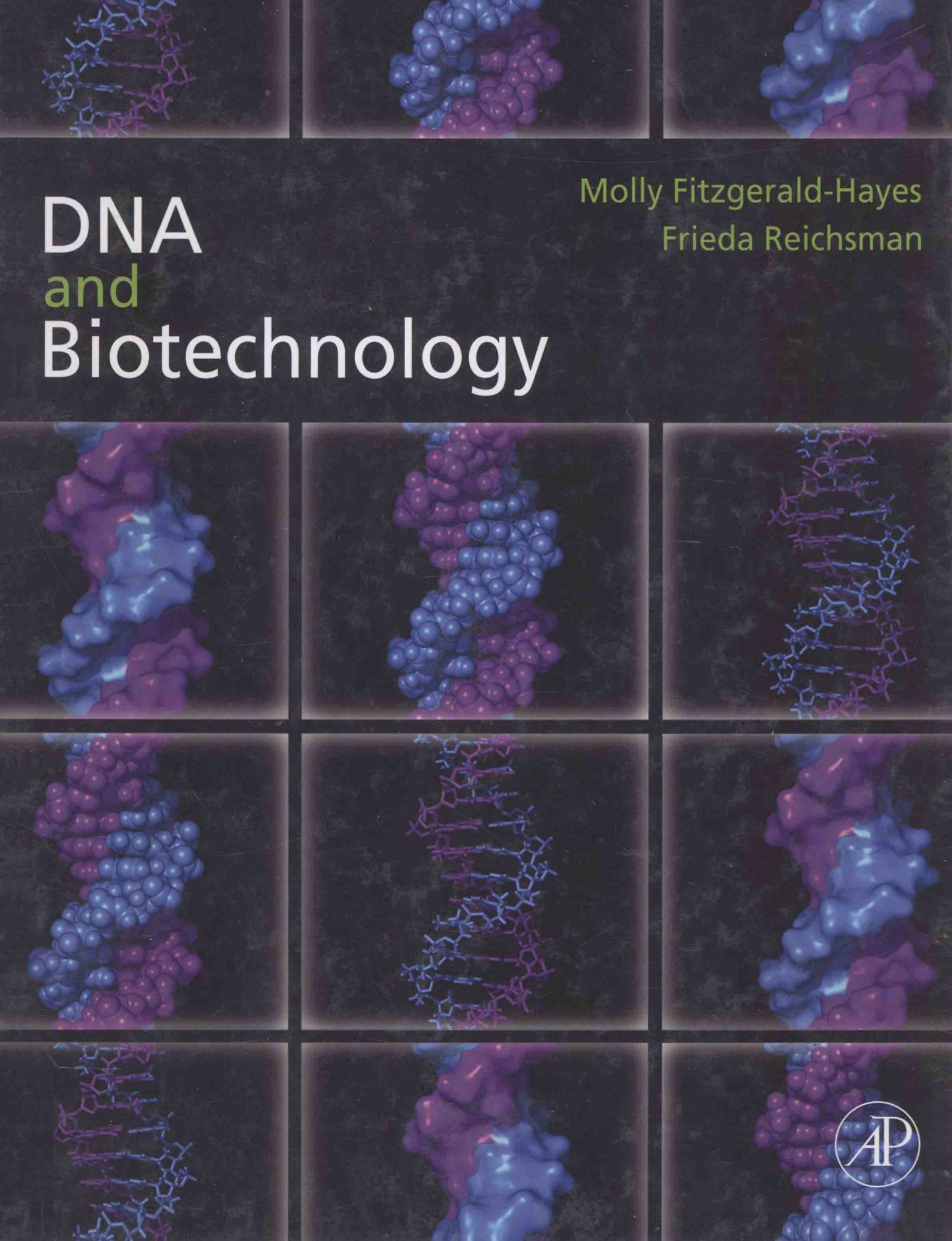

# DNA and Biotechnology

Molly Fitzgerald-Hayes
Frieda Reichsman

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Third Edition

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Frieda Reichsman



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## The Buck Stops Here

The authors are responsible for the contents of this book, including any mistakes. Others who contributed to drafts of the book are not responsible for the final product after the text was revised—this was our task. In the end, the authors take full responsibility for getting it right, and if not, our most sincere apologies are extended—as well as the hope that you will contact us with corrections at dnabiotechnology3@gmail.com

We hope you enjoy reading *DNA and Biotechnology*!

Molly Fitzgerald-Hayes and Frieda Reichsman

# Introduction

## ABOUT THE AUTHORS

As friends and colleagues for many years, we've taught university non-science majors, retirees, clubs, Elderhostel classes, and various community groups about DNA, genes, and the human genome. We've enjoyed giving hands-on DNA workshops for K-12 teachers and middle and high school students, and we have even taught people how to isolate their own DNA from the cheek cells inside their mouths (safe, painless, cheap, and easy!).

The invitation to write the new edition of Alcamo's book brought a surge of anticipation and excitement, and years of work! We hope that the book reflects Ed Alcamo's clear and fluent writing style about science. To bring the 3rd edition as up to date as is possible (for a printed book), we added several new chapters covering advances in gene therapy, stem cells, drug design and development, bioinformatics, and animal and plant biotechnology.

## ABOUT OUR TARGET AUDIENCE

We wrote *DNA and Biotechnology* for a wide audience that includes college and high school students as well as laypeople with varying backgrounds in science. Our goal for the book is to help people to better understand how genes control cell function, how persistent and ingenious scientists tracked down the means of control, and how we as a society now use this knowledge to explore further, to heal, and to attempt to improve life. We tried to make this book very readable without oversimplifying the picture of a living cell, full of the thousands of molecular machines made from protein and RNA parts, reading the DNA genome, and performing the functions that make life possible.

## ABOUT LEARNING FEATURES IN THE BOOK

The 3rd edition includes features designed to make learning about DNA much easier:

**Chapter Outline:** Each chapter starts with a convenient outline that gives you a succinct overview of how the topics and subtopics interrelate.

**Hot Topic Box:** Every chapter draws in readers with a recent, attention-grabbing news headline, brief story, and explanation of its relevance to the scientific information in the chapter.

**Looking Ahead:** This section presents broad learning objectives that orient readers to fundamental goals for understanding and communicating about the chapter topics.

**Special Topic Boxes:** These sections emphasize people and scientific discoveries that have a special connection or relevance to chapter topics.

**Boldface Terms:** New terms are introduced using boldface type. All boldface terms are defined in the Glossary at the end of the book.

**Summary Statements:** Short summary statements punctuate each chapter, helping readers to identify important points and orient themselves when reviewing the information.

**Summary:** The summary at the end of each chapter brings together the key points and relates them to each other more immediately than the full chapter treatment allows.

**Review Questions:** Ten broad-based review questions provide an opportunity for readers to test their recall and comprehension of the information in the chapter.

**Additional Reading:** Recommendations include both current and historically relevant sources (books, newspapers, magazine and research articles, and web sites) that help readers delve further into topics of particular interest.

**Glossary:** A glossary at the end of the book defines the boldface terms introduced in each chapter.

## ABOUT USING THE BOOK

### Organization of Chapters (3rd edition)

Chapter 1: The Roots of DNA Research
Chapter 2: The DNA Double Helix
Chapter 3: DNA in Action
Chapter 4: Tools of the DNA Trade
Chapter 5: Working with DNA

Chapter 6: Human Genomics
Chapter 7: Bioinformatics
Chapter 8: DNA Forensics
Chapter 9: Exploring Cell Fate
Chapter 10: Human Genetic Diseases
Chapter 11: Gene Therapy
Chapter 12: Stem Cell Research
Chapter 13: Pharmaceutical Biotechnology
Chapter 14: Animal Biotechnology
Chapter 15: Agricultural Biotechnology
Chapter 16: Genes and Race

The 16 chapters in *DNA and Biotechnology* are arranged in three groups that give teachers the flexibility to select chapters based on the scientific background of the students in the class. The first five chapters (Chapters 1–5), form a core of content that is essential for understanding the rest of the book. This core includes the basic structure and functions of DNA, RNA, and proteins in cells (Chapters 1 and 2), explains how gene expression controls cell function (Chapter 3), and describes the recombinant DNA cloning technologies that fundamentally changed DNA research (Chapters 4 and 5).

Building on the foundation of the first five chapters, Chapters 6–10 provide an opportunity for readers who are curious about the role of DNA and genes in modern research. Automated DNA sequence analysis has become routine, and hundreds of genome sequences have been analyzed, in addition to the entire human genome (Chapter 6). The deluge of primary sequences has fed the emerging bioinformatics field, which uses information technology to store, explore, and annotate DNA, RNA, and protein sequences (Chapter 7). DNA technology has enabled us to seek out and identify specific DNA sequences in many contexts, with applications in fields such as criminal forensics (fingerprinting) and medical diagnostics (Chapter 8). Molecular genetics research explains how multiple genome mutations can cause a cell to lose growth control and turn into a cancer cell (Chapter 9). The chromosome locations of genes and mutations that cause many genetic diseases such as cystic fibrosis, sickle cell anemia, muscular dystrophy, Huntington's disease, and many more, have been identified (Chapter 10). These chapters tie together the basic functions of genes and proteins in cells (Chapters 1–5) with the advances in DNA based technologies in the research lab, many of which harness the same molecules. The biological mechanisms employed by the cell to replicate DNA and make RNA have led to the development of the most important techniques used in molecular biology and genetics.

Chapters 11–16 focus on several specialized applications of DNA biotechnology. For example, finding a mutant gene that causes a genetic disease opens the door to the possibility of a gene therapy treatment (Chapter 11). The science of human embryonic stem cells is described, as are the very exciting iPS (induced pluripotent stem) cells, which are derived from adult human skin cells but look and act like embryonic stem cells (Chapter 12). New genetic strategies for designing drugs and the development of nanocarriers that deliver drugs directly into cells are just two examples of new areas of pharmaceutical research (Chapter 13). Advances include transgenic animals and plants genetically engineered to produce antibiotics, drugs, and hormones (Chapters 14 and 15). DNA research shows that individual human genomes are almost identical in DNA sequence and that all people have exactly the same genes. What does this mean about our understanding of "race"? (Chapter 16).

# Contents

Chapter 1

# The Roots of DNA Research



**My Genome, Myself: Seeking Clues in DNA**

The New York Times, November 17, 2007
By Amy Harmon

The exploration of the human genome has long been relegated to elite scientists in research laboratories. But that is about to change. An infant industry is capitalizing on the plunging cost of genetic testing technology to offer any individual unprecedented—and unmediated—entree to their own DNA.

For as little as $1,000 and a saliva sample, customers will be able to learn what is known so far about how the billions of bits in their biological code shape who they are. Three companies have already announced plans to market such services, one yesterday.

Offered the chance to be among the early testers, I agreed, but not without reservations. What if I learned I was likely to die young? Or that I might have passed on a rogue gene to my daughter? And more pragmatically, what if an insurance company or an employer used such information against me in the future?

But three weeks later, I was already somewhat addicted to the daily communion with my genes. (Recurring note to self: was this addiction genetic?)

[To read on, go to http://tinyurl.com/2zuqsh.]

From the preceding article, we can see that we are at the start of an era of personalized genomes. How long will it be before, alongside tongue depressors, cotton balls, and blood pressure cuffs, a plastic card with your DNA chip becomes a routine part of a visit to the doctor's office? The article represents the type of advances that 150 years of research has brought us, research that started with the studies discussed in this chapter.

We will begin with the work of a monk in the 1850s whose different ideas and meticulous methods of investigation yielded a foundation from which the next two generations of scientists could grow, toward an understanding of heredity at the molecular level. And grow they did, developing the roots of what we now know to be DNA science. As you will see, researchers often had to struggle against preconceived notions of what could (and could not) be the biological material that transferred characteristics from one generation to the next. It took persistence to establish DNA, a material with only four components, as a carrier of information, when proteins, which have 20 components, were much more familiar and well understood. (In fact we can wonder about what preconceived notions the scientists and students of the future will discover concerning our generation). Here we will retrace the steps of these persistent, open-minded scientists who paved our way to DNA.

## LOOKING AHEAD

DNA technology has its foundations in genetics, the science of heredity. It is appropriate, therefore, to open this book by exploring the insights and experiments that led scientists to recognize DNA as the hereditary substance. When you have completed the chapter, you should be able to do the following:

- Understand the differences between prokaryotic and eukaryotic cells.
- Recognize how the experiments of Gregor Mendel focused attention on cellular factors as the basis for inheritance.

- Understand the circumstances under which Mendel's experiments were verified and how Sutton related Mendel's "factors" to cellular units called chromosomes.
- Show how Morgan related eye color in fruit flies to chromosomes.
- Appreciate the origin of the term "gene" and describe how the gene concept emerged.
- Recount Miescher's work on nuclei, and conceptualize how Feulgen and Mirsky contributed to the insight that genes are composed of DNA.
- Understand the significance of Griffith's experiments in bacterial transformation, and conceptualize how the transforming principle was identified as DNA.
- Explain the seminal experiments of Hershey and Chase, and describe why their results pointed to DNA as the substance controlling protein and nucleic acid synthesis.
- Increase your vocabulary of terms relating to DNA technology.

## INTRODUCTION

In past centuries, it was customary to explain **inheritance** by saying, "it's in the blood." People believed that children received blood from their parents and that a union of bloods led to the blending they saw in one's characteristics. Such expressions as "blood relations," "blood will tell," and "bloodlines" reflect this belief.

However, by the 1850s, scientists were questioning the blood theory of inheritance. They could see quite clearly that semen contained no blood, and it was apparent that blood was not being transferred to the offspring. But if blood was not the hereditary substance, then what was?

It was a long road to understanding that DNA mediates inheritance. By the end of the 1800s, the blood basis of heredity was challenged and eventually discarded. In its place, scientists developed an interest in nucleic acid molecules organized into functional units called **genes**. Scientists guessed that genes control heredity by specifying the production of proteins. But even the gene basis of heredity was hard to believe because the amount of nucleic acid in the cell seemed insignificant.

The gene basis for heredity has become one of the foundation principles of biology. In the pages ahead, we will explore the development of the gene theory and note how interest grew in DNA as the substance of the gene. Long before scientists could apply the fruits of DNA research to modern technology, they had to learn what DNA was all about. "What purpose," they asked, "does DNA serve in a living cell?"

### Box 1.1 Cell Geography Sets the Stage

The term "cell," in general, refers to a small room or compartment. The smallest compartment of an organism that is considered to be alive is a cell, and so it is regarded as the fundamental unit of life. Cells are the natural environment for all the processes discussed in this book. Getting the lay of the land, then, is important in understanding DNA and how it works.

There are two kinds of biological cells: **prokaryotic** and **eukaryotic**.

Prokaryotic cells (Figure 1.1A) contain one continuous space in which cellular materials are organized, but not separated by membranes. A cell wall surrounds all prokaryotic cells. Prokaryotes are usually single-celled organisms and include both bacteria and archaea. The archaea live in extreme environments (for example, boiling hot thermal vents, freezing cold arctic waters, and oil wells).

In contrast, eukaryotic cells (Figure 1.1B) contain subcellular compartments. A membrane surrounds each compartment, and there are several different types of compartments, called **organelles**. Eukaryotic cells are usually 10- to 100-fold larger than prokaryotic cells (though there are a few exceptionally large bacteria that defy this rule). Eukaryotes include both single-celled organisms (the majority) and multicellular organisms. Of the eukaryotes, only plant cells are surrounded by a cell wall, and its composition is very different than a prokaryotic cell wall.

In eukaryotes, each type of cellular compartment is specialized. The **nucleus** is home to the vast majority of the DNA, where is it complexed with proteins. The endoplasmic reticulum and the Golgi complex compartments are involved in protein synthesis and trafficking (that is, sending proteins to their correct destinations). Mitochondria possess a membrane specialized for energy production. Chloroplasts are centers for photosynthesis.

A prokaryote's DNA is tightly coiled with proteins in a region called the **nucleoid**. The nucleoid is not a compartment; it is just the DNA and proteins compacted together. In prokaryotes, some membrane-associated functions, such as energy production, are accomplished by the plasma membrane.

The presence or absence of subcellular compartments leads to differences in how cellular events take place. Compartments allow for increased complexity and regulation. For example, in prokaryotes, RNA synthesis and protein synthesis take place in the same compartment, so while RNA is being made from a DNA template, it can also be read nearly simultaneously to synthesize a protein. In eukaryotes, RNA synthesis occurs in the nucleus, and protein synthesis occurs in the cytoplasm. The separation or uncoupling of these processes into compartments allows

**Box 1.1 Continued**

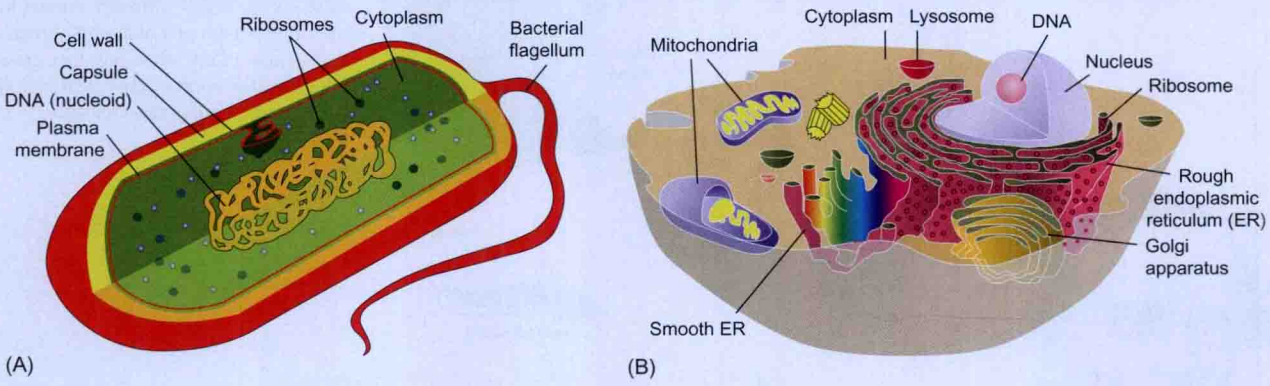



**FIGURE 1.1** (A) A generalized prokaryotic cell. (B) A generalized eukaryotic cell.

for intermediate steps to occur between them. For example, splicing of RNA in different patterns allows several different proteins to be produced from a single gene. This is one of the contributions to the complexity of eukaryotes as compared to prokaryotes.

Features common to prokaryotic and eukaryotic cells include **ribosomes**, the molecular machines that synthesize proteins (although the exact makeup of the prokaryotic and eukaryotic ribosomes is different), the plasma membrane, and the watery interior environment, the **cytoplasm**.

## DEVELOPING A THEORY OF INHERITANCE

### When Counting Counts: Mendel's Approach Yields the Basis of Modern Gene Theory

In the mid-1800s (around the same time that scientists started questioning the blood theory of inheritance), a relatively obscure Austrian monk named Gregor Mendel (pictured in Figure 1.2) was conducting experiments to reveal the statistical pattern of inheritance. Mendel's great contribution to science was the discovery of a predictable mechanism by which inherited characteristics move from parents to offspring. His work with plants laid the groundwork for intensive studies in genetics, a science that would blossom in the early part of the twentieth century.

Mendel lived in a region that relied heavily on agriculture, so it was not uncommon for educated individuals to have an interest in animal and plant breeding. Mendel had studied plant science at the University of Vienna, and he continued his interest in plants at the monastery at Brno (now a part of the Czech Republic). He began a series of experiments to learn more about the breeding patterns of pea plants. Peas were well suited for his work because they were easy to cultivate. Moreover, they had a short growing season, they could be fertilized artificially, and they resisted interference by foreign pollen.

Other important features of pea plants were their easily distinguished **traits**. Mendel observed, for example, that his garden had some pea plants with wrinkled seeds and others with smooth seeds; some had green pods, and others had yellow pods; some had white flowers, and others had red flowers. Figure 1.3 shows this diversity. The more Mendel pondered the source of variations, the more his curiosity was aroused. He set out to determine how the variations originated and how the traits were passed to the next generation.

A key ingredient in Mendel's success was the plant he used to track inherited traits. The short generation time, obvious characteristics, and ease of breeding of pea plants provided a fertile ground (so to speak) for his observations and experiments to flourish.

Mendel studied pea plants by crossing plants having a certain characteristic with others having a contrasting characteristic. He then studied how traits were expressed in the offspring plants. Mendel found, for example, that by breeding selected tall plants to selected short plants, he could obtain plants that were exclusively tall. The trait for shortness had apparently disappeared. But when he bred the tall plants from this first generation among themselves, some short plants reappeared in the next generation among the tall plants. These results were unexpected and perplexing.

Mendel's forté was mathematics. He carefully counted the plants displaying a particular characteristic and the plants having the contrasting characteristic (for example, tall plants and short plants); he discovered

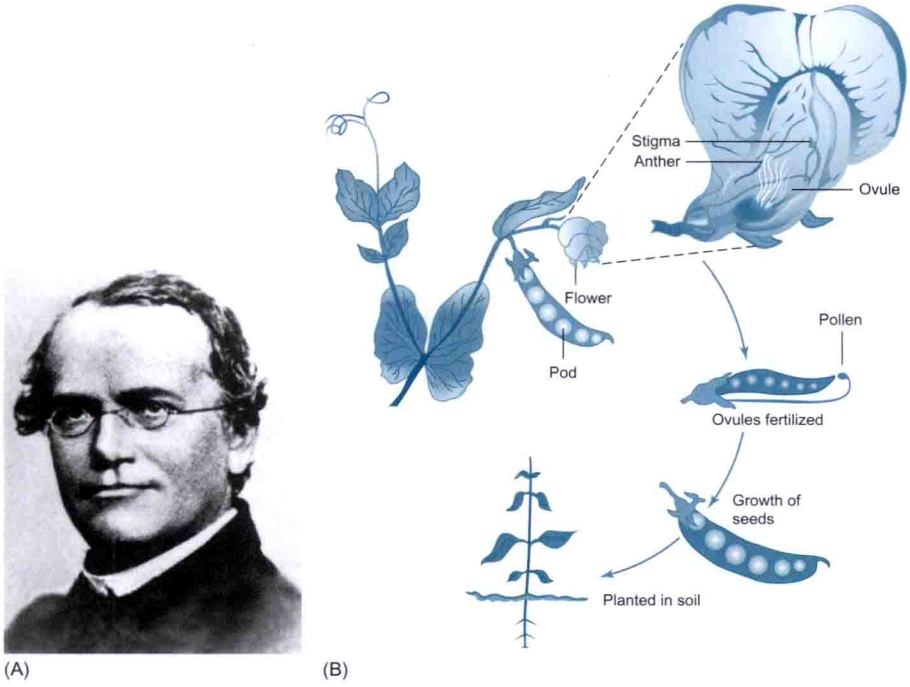



**FIGURE 1.2** Mendel and his pea plants. (A) Gregor Mendel (1822–1884), the Austrian monk who established the principles of genetics through meticulous experiments with pea plants. (B) Anatomy of the pea plant, showing the growth cycle and the reproductive features that make artificial pollination feasible.

similar ratios of traits among the offspring. He noted, for example, that crossing the first generation's tall plants among themselves always seemed to yield three tall plants for every short plant, as Figure 1.4 shows. (By that time, the monks in the monastery were noticing that peas had become a fairly regular item on the dinner table.)

Many scientists of the 1850s believed that a single factor controlled a trait, but Mendel, reasoning that one of the factors was obtained from the male and one from the female, began with the assumption that each trait was controlled by two factors (although the nature of the factor was unknown). He guessed that the factors express themselves in the offspring, but that one is **dominant** over the other. For example, the factor for tall plants dominates over the factor for short plants (it suppresses the short-plant factor, which is said to be **recessive**). The factors are then passed on to the next generation. Today we know Mendel's factors as **genes**.

From his work, Mendel developed a theory of inheritance completely at odds with the blood basis of heredity. Mendel's results implied that sperm and egg cells, not blood cells, carry the factors of inheritance. Moreover, Mendel surmised that the factors are discrete units, not some vague, mysterious elements of the blood. Aware of the unconventional nature of his suppositions, Mendel avoided controversy by keeping his suppositions largely to himself.

Mendel's theory came to be known as the theory of transmissible factors. Although it was revolutionary for the times, Mendel did not stop there. For many years he investigated how one factor in the pair dominates the other factor and how a pair of factors separates during transmission to the next generation. He experimented up to the early 1860s and published his results in 1866 in the *Proceedings of the Society of Natural Sciences in Brno*. Mendel included a detailed analysis of his theories in the publication, and he communicated his findings to other scientists of the times through a series of letters. In retrospect, Mendel's observations are regarded as one of the great insights in science and the beginning of the discipline of **genetics**.

> Mendel's assumptions were different from those of other scientists studying the same topic, so he was led to interpret his observations differently, developing the concept of transmissible factors we now know to be genes.

Unfortunately, scientists of his time paid little attention to Mendel's work or its implications. One probable reason is that they had little understanding of biological chemistry. Another is that they failed to appreciate the significance of the cellular nucleus, the chromosomes, or the process of fertilization. Also, during the late 1800s, biologists were largely immersed in studying the theory of evolution, first promulgated in 1859 in Charles Darwin's epic work *On the Origin of Species*. Research on inheritance and breeding was placed on the proverbial back burner as the biological, social, and economic implications of the theory of evolution continued to capture the attention and imagination of scientists and laypeople. Not until the year 1900 would interest in genetics once again come to the forefront of science.

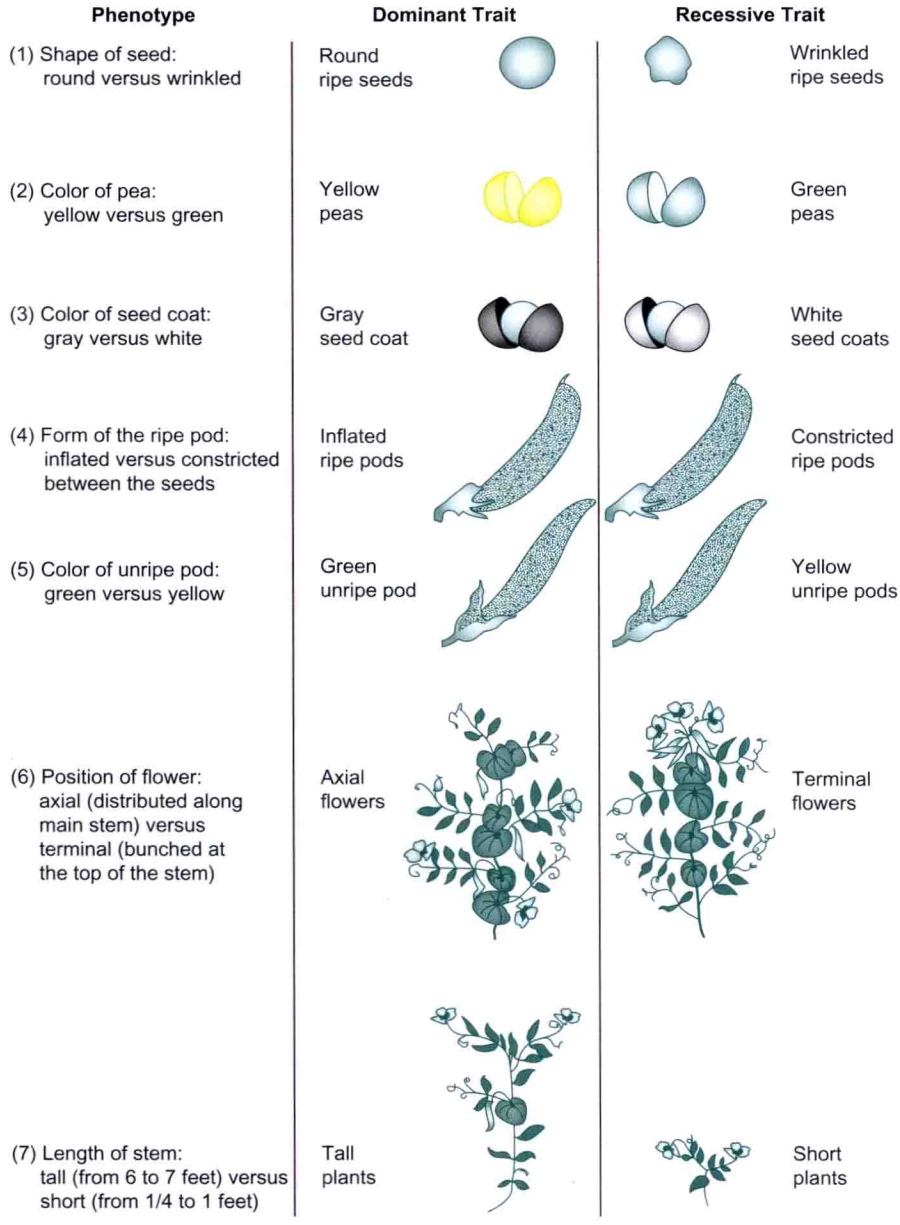



**FIGURE 1.3** The traits of pea plants studied by Mendel. The dominant allele is on the left and the recessive allele is on the right. A description of the phenotypes associated with specific alleles (traits) is provided.

In the spring of 1900, three European botanists, working independently of each other, repeated and verified Mendel's work. Each botanist cited Mendel's article in his research, and each awakened the scientific community to the work of the pioneering monk. It was not so unusual that all three should be aware of Mendel's work, but it was remarkable that the rediscovery of his theories was made almost simultaneously by three investigators; indeed, the happenstance remains one of the unusual coincidences of scientific history. Within weeks, a wave of enthusiasm for inheritance research sprang up. The discoveries made by Mendel had been forgotten for almost 40 years. Now they would change scientific thinking forever.

## Morgan's Fruit Fly Experiments Reveal That Mendel's Factors Are on Chromosomes

During the first years of the twentieth century, Mendel's experiments were carefully studied, and the belief emerged that Mendel's factors were related to parts of the cell called **chromosomes**. Chromosomes (literally "colored bodies") are threadlike strands of chemical material located in the cell nucleus. The threads

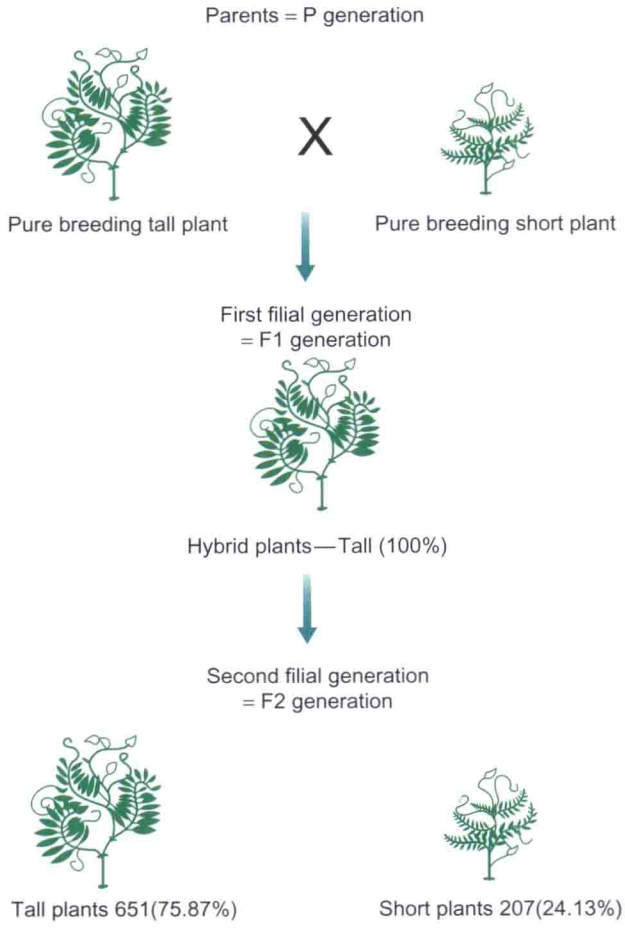
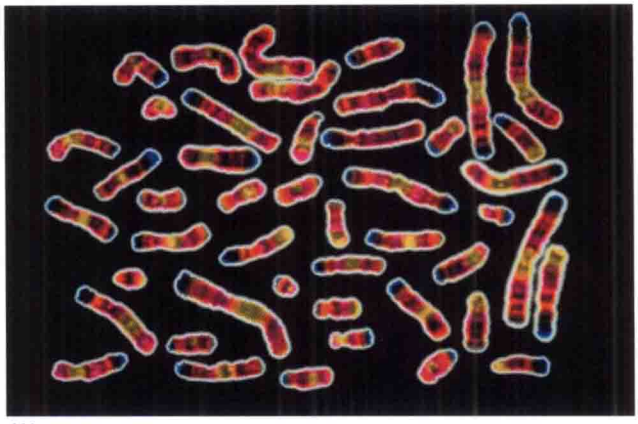



**FIGURE 1.4** Mendel's experiments with tall and short pea plants. Mendel bred purebred tall plants to purebred short plants (these constitute the P generation). He discovered that all the offspring plants were tall in the first filial (F1) generation. He then bred the tall plants of the F1 generation among themselves and found that short plants appeared as well as tall plants in the F2 generation. His meticulous calculations revealed that about 75% of the plants in the F2 generation were tall, and 25% were short. This 75% to 25% ratio was equivalent to 3:1. This led to his assumption that two "factors" for height exist in pea plants and suggested that one factor dominates over the other.



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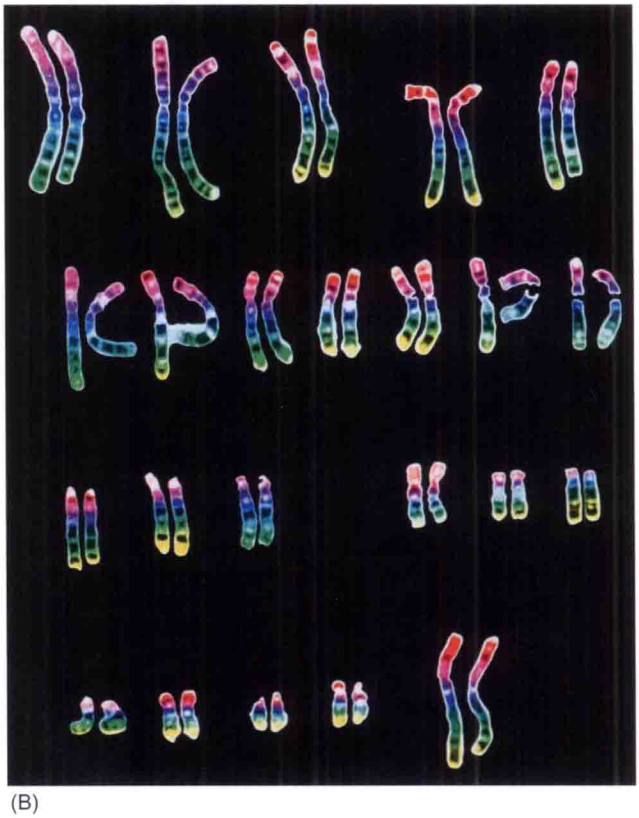

(B)

**FIGURE 1.5** Color-enhanced human chromosomes seen under a microscope after separation from the nucleus. Chromosomes assume these compact shapes during cell division. With the notable exceptions of reproductive cells and red blood cells, 46 chromosomes (23 pairs) are present in each human cell. (A) Each individual chromosome is outlined in white. (B) In a karyotype, chromosomes photographed under the microscope are cut and pasted into an orderly display from largest to smallest, except for the sex chromosomes, which are placed at the end. Images and text: Copyright © 2009 by Photo Researchers, Inc. All rights reserved.

of each chromosome consolidate and become clearly visible under the microscope (Figure 1.5) when a cell is dividing. With few exceptions, all human body cells have 46 chromosomes, and the 46 chromosomes are organized in 23 pairs. (Red blood cells have no chromosomes, and sperm and egg cells have only 23 chromosomes.) It is now known that chromosomes contain the DNA that carries the cell's genetic message.

Among the leaders in chromosome research at the turn of the century was the American biologist W. H. Sutton. In 1902, Sutton wrote that certain of Mendel's rules of inheritance could be explained if Mendel's factors were located on or in the chromosomes. Mendel had written, for instance, that inheritance factors occur in pairs, one member of the pair received from each parent. By 1900, cell biologists had established that chromosomes also occur in pairs, one chromosome derived from each parent. Moreover, Mendel theorized that during the production of sperm and egg cells,

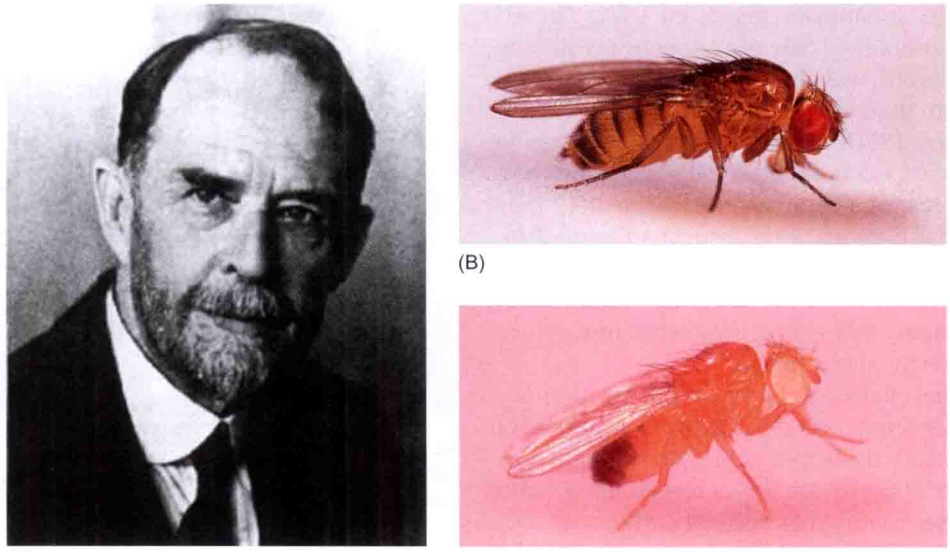


**FIGURE 1.6** Morgan and his fruit flies. (A) Thomas Hunt Morgan, whose experiments revealed that colorless white eyes in fruit flies are based on the presence of a single chromosome. His experiments related an inherited characteristic to a chromosome. (B) A fruit fly with red eyes. (C) A fruit fly with white eyes.

the paired factors separate and move as units to each cell. Studies in cell biology showed that chromosomes behave similarly during cell reproduction. Sutton pointed out that chromosomes could be the hypothetical inheritance factors Mendel thought responsible for heredity. Perhaps, he suggested, chromosomes and inheritance factors were identical.

To demonstrate the validity of the chromosomal theory of inheritance, scientists had to relate at least one trait to a cell's chromosome. But in the early 1900s, the members of a chromosome pair could not be distinguished from each other visually. Thus, it was impossible to relate a single trait to a single chromosome by sight alone.

The problem was resolved in 1910 by Thomas Hunt Morgan of Columbia University (pictured in Figure 1.6). Morgan used the fruit fly *Drosophila melanogaster* in his work. By careful observations, he determined that one of the four pairs of chromosomes in the fruit fly determines its sex. This chromosome pair, he discovered, also determines colorless white eyes. Through an exhaustive series of genetic crosses and statistical analyses, Morgan determined that the male fruit fly inherits only one chromosome for sex determination. Thus, it must also inherit only one chromosome for white eye color. Therefore, white eye color must depend on a single chromosome. By providing statistical evidence for the relationship between sex and eye color in *Drosophila*, Morgan placed the chromosomal theory of inheritance on a firm footing and enhanced the role of the chromosome as the possible vehicle of inheritance.

Morgan, like Mendel, made careful counts and analyzed them to arrive at firm conclusions about inheritance. By doing so, he was able to provide ample evidence supporting Sutton's explanation that inheritance factors resided on chromosomes.

The next question was whether the whole chromosome or a part of a chromosome is responsible for an inherited trait. Writing in 1903, Sutton proposed that merely a part of a chromosome is the basis for a trait because not enough chromosomes are possible to account for all an individual's traits. Sutton suggested that "the chromosome may be divisible into smaller entities." Most other scientists agreed, and before long, the concept of the gene as the "smaller entity" gained prominence.

## Factors Become Genes, and DNA Is Discovered

In the early 1900s, geneticists began using the terms "inheritance unit" and "genetic particle" to describe the factors occurring on the chromosomes of Mendel's pea plants. By the 1920s, however, these terms had been discarded, and at the suggestion of the Scandinavian scientist Willard Johannsen, geneticists agreed to use the word "gene" instead. ("Gene" is derived from the Greek *gennan*, meaning "to produce.") The term was originally used as part of Darwin's word "pangenesis" to describe the theory that the whole body (including every atom and unit) "produces" itself over and over.

In a 1910 article, Johannsen suggested using "gene" because it was completely free of connection with any hypothesis. The word was and continues to be a less cumbersome term than "inheritance unit."

Scientists of the 1920s viewed the gene as a specific and separate entity sitting on the cell's chromosomes, but not strictly a part of a chromosome. Fortunately, they also reasoned that if genes were associated with chromosomes, a first step in learning the chemical nature of the gene would be to learn the chemical composition of the chromosomes; this is precisely what researchers attempted to do in the early 1900s.

One possible chemical component of chromosomes was a seemingly unique organic compound of the cell nucleus called nucleic acid. Nucleic acid was first described in 1869 by the Swiss researcher Johann Friedrich Miescher. With great difficulty, Miescher separated nuclei from human white blood cells, and he searched for evidence of protein within these nuclei. Instead of protein, however, he found a substance unlike any class of chemicals then known. Miescher named the new substance "nuclein" (relating to its source). When he identified phosphorus in nuclein, he postulated that the substance was a storehouse for phosphorus in the cell.

As Miescher continued his study of nuclein, he located it in yeast cells and kidney, liver, and testicular cells. He also made the notable observation that nuclein was abundant in sperm cells obtained from a salmon. Some years later, chemists led by Phoebus Levene (Chapter 2) used this information in their studies and determined the components of nuclein. They gave it the more descriptive and technical name **deoxyribonucleic acid (DNA)**. Coincidentally, Levene was born in 1869, the year of Miescher's first report of nuclein.

Looking for the material that makes up chromosomes, Miescher discovered in the nucleus an abundant, initially mysterious substance he dubbed nuclein. After further chemical characterization by others, it was named deoxyribonucleic acid (DNA).

By the 1920s, it was clear that chromosomes had a role in heredity, and the isolation of DNA from cell nuclei made this organic substance a good candidate for the hereditary substance. Interest in DNA was further strengthened by a 1924 discovery attributed to the German biochemist Robert Feulgen, who observed that a dye (now called Feulgen stain) turns bright purple when it reacts with DNA. (Figure 1.7 shows an example of this staining characteristic.) The dye could be used to locate cellular DNA and to determine the concentration of DNA at various times in the cell's life cycle. Isolating DNA was a difficult chore at that time, but Feulgen's dye technique allowed DNA research to leap ahead without the burden of complex chemical isolations.

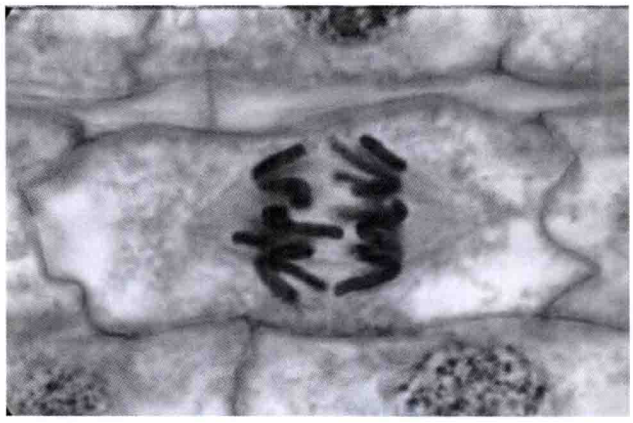

**FIGURE 1.7** Stained chromosomes. A photomicrograph of a plant cell stained with Feulgen stain to highlight the chromosomes of the cell nucleus. In this view, the chromosomes have replicated and are in the process of separating into two newly forming cells.

**TABLE 1.1 A comparison of the DNA content in the tissue cells and sperm cells of various animals**

| Organism | Tissue cells | Sperm cells |
|---|---|---|
| Cow | 6.6 | 3.3 |
| Human | 6.4 | 3.2 |
| Chicken | 2.6 | 1.3 |
| Frog | 15.0 | 7.5 |

Another observation in that period helped forge the link between DNA and heredity. In the late 1920s, Alfred Mirsky and his coworkers at New York's Rockefeller Institute reported that, with only two exceptions, all cells of an organism have virtually the same amount of DNA in their nuclei. The two exceptions are reproductive sperm and egg cells. These cells contain precisely half the amount of DNA found in nonreproductive cells such as muscle cells. Table 1.1 presents these data. Mirsky's observation correlated with the theory that sex cells are the vehicle for bringing half the genetic information from each parent to the offspring.

The Rockefeller group led by Mirsky also experimented with the **zygote**, the cell resulting from the union of sperm and egg cells. The researchers found that the zygote contains the same amount of DNA as other cells of the body. This observation reinforced the