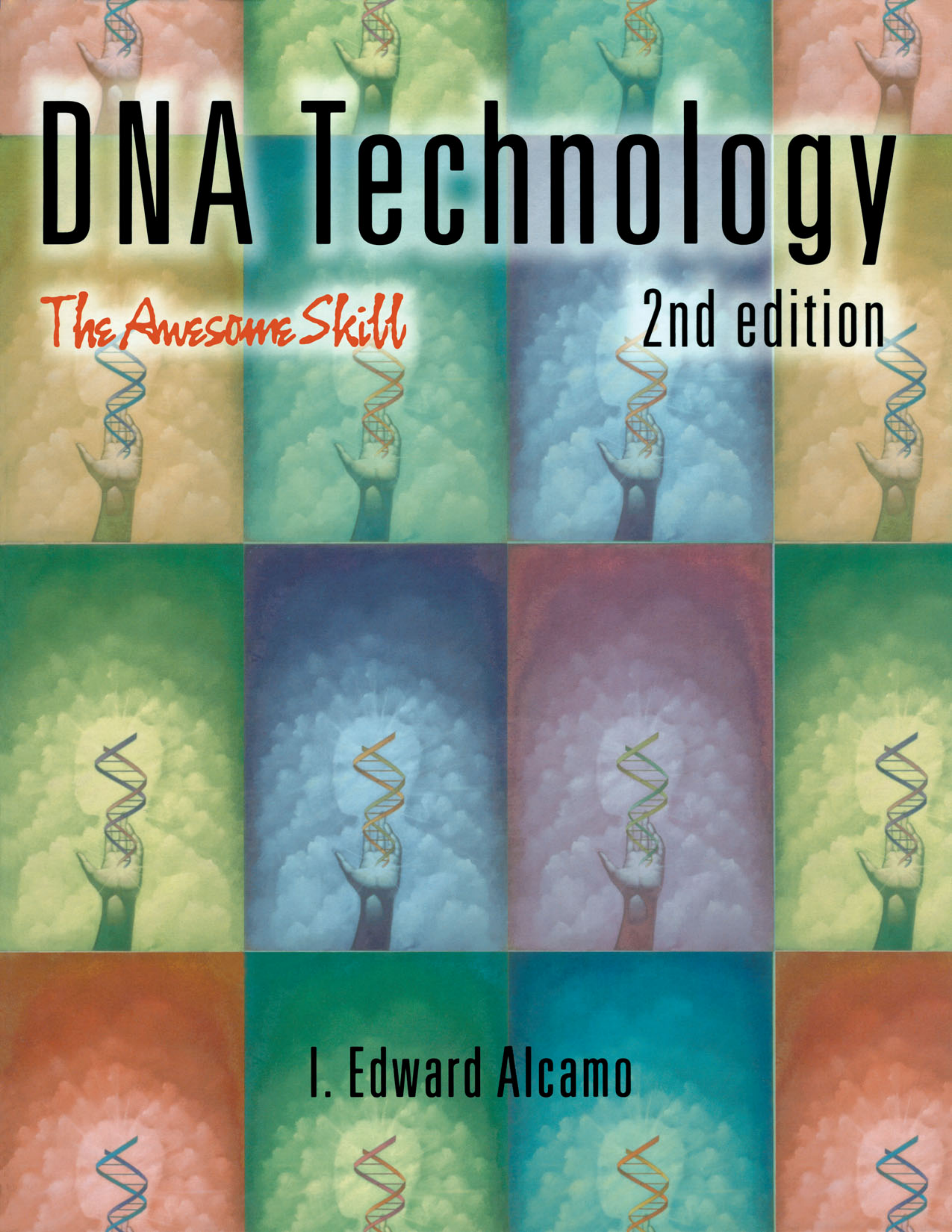

DNA Technology

The Awesome Skill

2nd edition

I. Edward Alcamo

DNA TECHNOLOGY

SECOND EDITION

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DNA TECHNOLOGY

SECOND EDITION

The Awesome Skill

I. Edward Alcamo

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Farmingdale, New York

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Dedication

I am pleased to dedicate this book to the bacterium *Escherichia coli* (*E. coli*, as it is commonly known). For over a half-century *E. coli* has been the hammer-and-nail of DNA technology. Scientists used it as a model organism in the 1950s to prove that DNA is the hereditary material; they employed it during the 1960s to learn how genes work and to decipher the genetic code; in the 1970s, *E. coli* was the first organism to have its genes altered biochemically; in the 1980s, molecular biologists put it to work as a living factory to produce an array of genetically-engineered drugs and medicines; during the 1990s, scientists used it to develop transgenic animals and plants; and now, in the twenty-first century, *E. coli* continues to illustrate how bacteria and other microorganisms play key roles in the interest of science and for the betterment of humanity.

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Preface

Most Americans would recognize the following words without too much difficulty:

"*We hold these truths to be self-evident, that all men are created equal...*"

Few, however, would identify the source of these words correctly:

"*We wish to suggest a structure for the salt of deoxyribonucleic acid (DNA)...*"

The first line is taken from the Declaration of Independence, a document that sparked a revolution in history and politics and gave birth to a country. The second is the opening line from a document that stimulated a different revolution—a revolution in science and medicine. This is from a scientific article published on April 23, 1953, in *Nature* magazine. The authors were James D. Watson, an American graduate student, and Francis H. C. Crick, a British biochemist and Watson's mentor. In the article, Watson and Crick suggested a structure for DNA, and in so doing, they spurred the age of DNA technology. Like the American revolution, the DNA revolution changed the scheme of things forever.

In the fifty years since publication of the Watson-Crick article, scientists have attained an understanding of genes and their activity that has stretched their imaginations to the limit. Where the gene was once an incomprehensible bead on a string, it has since become a segment of DNA that can be identified, removed, altered, and treated almost like a plaything. The gene research conducted since 1953 has encouraged even the most conservative scientists to speak in glowing terms of the practical applications of DNA technology. To some, the implications of gene knowledge are more important to the future of the human species than any scientific knowledge uncovered to date. Indeed, in 1983, the editors of Time magazine referred to DNA technology as "...the most awesome and powerful skill acquired by man since the splitting of the atom."

AUDIENCE AND ORGANIZATION

DNA Technology: The Awesome Skill explores the scientific revolution fostered by the myriad uses of DNA research. Written for the mature reader with a limited science background, the book presents the applications and implications of DNA technology. Laboratory techniques are deemphasized in favor of discussions with practical significance. It is hoped that the reader will come away thinking: "So that's what DNA technology is all about!"

DNA Technology: The Awesome Skill is divided into three major sections. In the first section (three chapters), the reading flows through several themes: the discovery of the laws of genetics by Gregor Mendel, the realization that DNA is the hereditary material, and the Watson-Crick work on the structure and replication of DNA. The next section (two chapters) summarizes the development of thought leading to DNA technology and recounts some of the technical problems requiring attention before DNA technology could bear fruit.

In the third section, seven chapters survey contemporary DNA technology and its uses in various fields. For example, one chapter describes the pharmaceutical products of DNA technology, and another explains genetic diagnoses and therapies; still other chapters survey medical forensics, gene detectives, and genetically engineered plants and animals; and a final chapter details the effort to decipher all 100,000 human genes. It is hoped that on completing this book you will better understand and appreciate the breathtaking developments in DNA technology going on in today's world.

SPECIAL FEATURES

To increase the effectiveness of your learning experience, several features have been incorporated into the chapters. Perhaps they will reduce the anxiety of approaching a new topic and enhance your ability to absorb the concepts.

1. Each chapter opens with a **Chapter Outline** that lets you know how the main topics interrelate with one another and with the subtopics.
2. The section entitled **Looking Ahead** presents several broad objectives that you should attain by reading the chapter.
3. **Pronunciations** of difficult terms are presented in the margins of the text so you can have more confidence in using them.
4. A **Marginal Glossary** provides review definitions of terms from the nearby text or from an earlier chapter.
5. Major terms and the names of investigators have been **boldfaced** to point up the key elements and researchers in DNA technology.
6. The **Questionline** series presents questions about DNA technology as they might be asked by your contemporaries. The answers contain brief summaries of information in the text.
7. The **Summary** brings together the key points in the chapter and relates them to one another in a few paragraphs. It is always a good idea to read the summary before beginning the chapter.
8. The **Review** gives you an opportunity to test your mastery of the chapter by presenting ten broad questions that cover its contents.
9. **For Additional Reading** presents a list of current, broad-based articles related to DNA technology. They should be available in most libraries.
10. The **Illustration Program** includes a number of electron micrographs, flow diagrams, and display features to help you put the text information in perspective.

ABOUT THE SECOND EDITION

I vividly recall the summer of 1995. All the ducks seemed to be in line as I completed the first edition of this book. Then I got word that, for the first time, the base sequence of a chromosome had been worked out. Because this was such an important breakthrough in DNA technology, I had to call and hold the presses while I warmed up my trusty Mac.

But that's the way it is with DNA technology. Rarely does a day go by when I'm not clipping an article from a magazine and stuffing it into the file. Keeping up with DNA technology is an exhilarating but unending battle. As soon as I finish marveling at one momentous discovery, it's time to marvel at something new. The "oohs and ahs" never seem to stop. Indeed, it has been said that the developments in DNA technology will outrace the ability of writers to report them.

And so it's been with this book. When the first edition appeared on bookshelves, gene therapy was in its infancy, Neanderthals were still on the succession line to modern humans, and a complex organism had never been cloned from a single cell. Today, all that has changed: thousands of patients are receiving gene therapy; DNA analyses show that Neanderthals evolved separately from modern humans; and Dolly, the first mammal cloned, is a historical landmark (and the mother of her own offspring).

For those reasons and so many more, the second edition of *DNA Technology: The Awesome Skill* is more a necessity than a luxury. I've tried to keep you abreast of what's going on in the field so you can be a more educated citizen, and I've enhanced the features of the first edition with more of what readers found useful. Broad strokes are used to identify the principles of DNA technology, and they are combined with some salient terminology and insights; the research leaders have been noted prominently so you can watch for their names in the media; and enough fields have been surveyed so you can be confident in discussing all of them.

Scientists are dreamers, and DNA technology has given them much to dream about. We hope that, as you tune into the world of DNA technology, your mind will also begin to stir. Perhaps you will be at the forefront of the next generation of discovery.

ACKNOWLEDGMENTS

Though authors generally receive credit (and sometimes vilification) for books as this, the truth of the matter is that many gifted and talented individuals lend their expertise to the final product. I am pleased to acknowledge the contributions of Fran Agliata, Tom Gagliano, Connie Mueller, Judi Wolken, and Barbara Elliot. Fran designed the book and supervised its production, while lending her creativity to each page. Tom is the artistic guru who translated my ideas to much of the finished artwork in this edition. Connie hunted down the beautiful photographs reproduced in this book. Judi edited the work, and Barbara typed the manuscript with care and precision.

I was particularly fortunate to work with Jeremy Hayhurst, senior editor at Harcourt/Academic Press. Jeremy brought a wealth of experience to the project and provided a boost when it was needed most. He is a knowledgeable, attentive, and well-versed editor; I respect him greatly, and I hold him in high esteem.

I also benefited from the substantial talents of numerous colleagues who shared their insights and served as reviewers of the manuscript. They include Professors John Lammert of Gustavus Adolphus College, Victor Fet of Marshall University, Dennis Bogyo of Valdosta State University, Pattle Pun of Wheaton College, and Robert J. Sullivan of Marist College.

My wife and children continue to be my inspiration. Michael Christopher is a corporate attorney in New York; Patricia Joy is a business consultant, also in New York; Tracey Lynn is a computer whiz; and Elizabeth Ann has just completed her doctorate at MIT in molecular biology (they say the apple doesn't fall far from the tree).

Charlene Alice, my wife of six months, is my future. Her warm heart, gentle smile, and firm resolve encourage me to keep writing when I'd prefer to vege out. She's there to help me tolerate the bad times and celebrate the successes. My life has taken on new meaning since she became my copilot.

To each of the above, I extend a warm and gracious word of thanks.

And I am pleased that you, the reader, have picked up this book. I hope it gives you a glimpse of the world of DNA technology and spurs you to become part of the biological revolution that is now taking place.

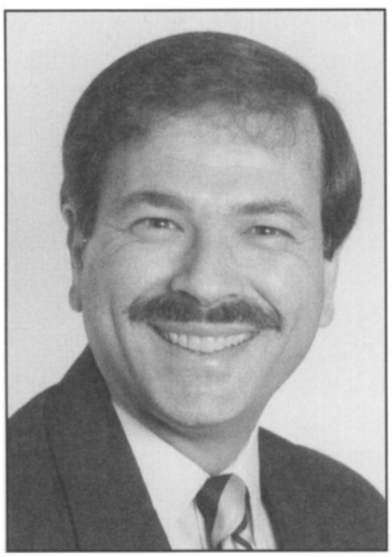
AN INVITATION TO READERS

I would love to say I'm taking a vacation after this edition, but the truth of the matter is that I'm already thinking about the third edition. I have no idea what it will contain, but that goes with the territory. Science is an ever-changing buffet table with something for everyone. And keeping up with the directions and applications of DNA is a never-ending job.

And so I would like to enlist your help. You could help me immensely if you would send along copies of any articles you spot in your community newspapers or magazines and help me keep this book as up-to-date as possible. I'd also like to know how well the book fills your needs and how I can improve the next edition. I can be reached at the Department of Biology, State University of New York, Farmingdale, New York 11735. If you care to give me a buzz, I'm at 631-420-2423. And if you have an e-mail connection, you can try me at alcamoie@farmingdale.edu.

Best wishes for a successful learning experience in today's most exciting field of science, and welcome to the wild and wonderful world of DNA technology.

E. Alcamo
Fall, 1999



The Roots of DNA Research 1

CHAPTER OUTLINE

Looking Ahead

Introduction

Inheritance Factors
- Chromosomes and Factors
- Genes and DNA

Relating DNA to Heredity
- Bacterial Transformations
- The Hershey-Chase Experiment

Summary

Review

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:

- 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 all 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 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.

gene
a segment of a DNA molecule that, among other functions, provides chemical information for the synthesis of protein in a cell.

DNA
an ancronym for deoxyribonucleic acid, the organic substance of heredity and the material of which genes are composed.

The gene basis for heredity has been strengthened in the past fifty years, and it 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, "did DNA serve in a living cell?"

INHERITANCE FACTORS

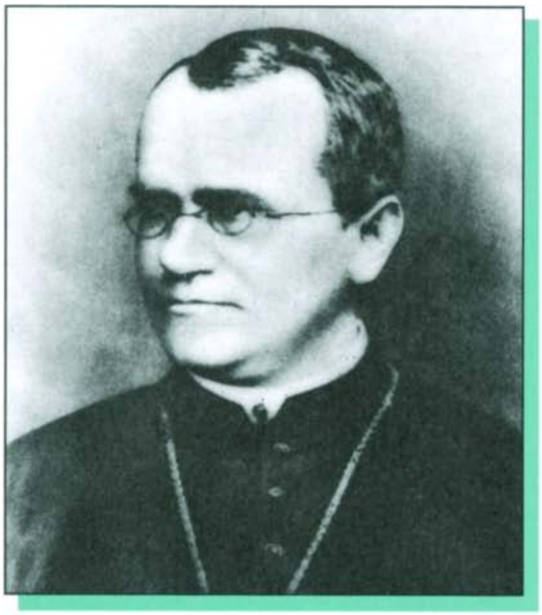
By the 1850s, scientists were questioning the blood theory of inheritance: They could see quite clearly that semen contained no blood, and it was apparent that blood was not being transferred to the offspring. But if blood was not the hereditary substance, then what was?

At that time, a relatively obscure Austrian monk named **Gregor Mendel** (pictured in Figure 1.1) 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.

The region in which Mendel lived 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 in his garden were pea plants with wrinkled seeds and other plants with smooth seeds; some had green pods, and others had yellow pods; some had white flowers, and others had red flowers. Figure 1.2 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.

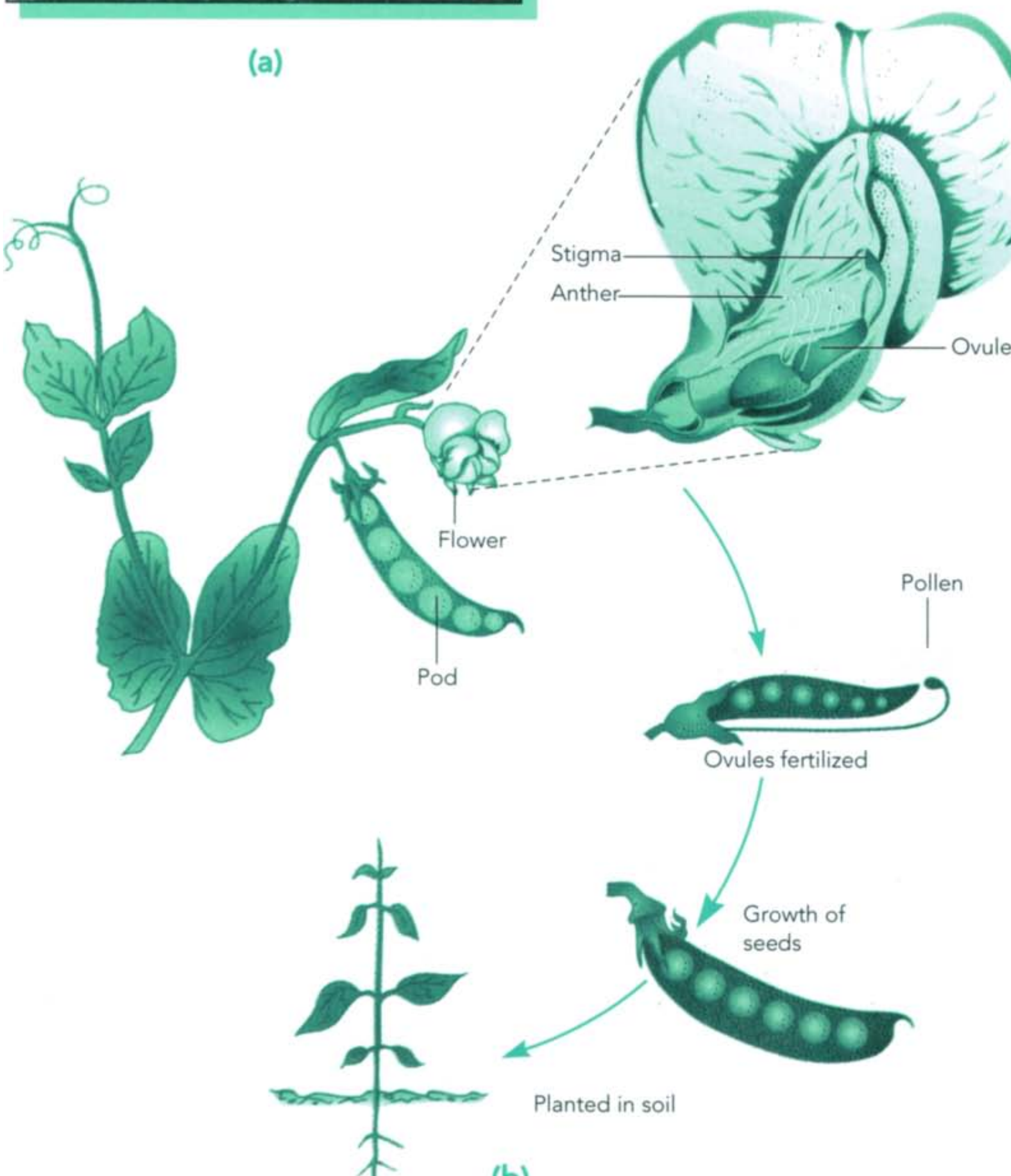
Mendel studied pea plants by crossing plants having a certain characteristic with others having a contrasting characteristic. He then studied how traits were expressed in the offspring plants. Mendel found, for example, that by breeding selected tall plants to



(a)

FIGURE 1.1

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.



(b)

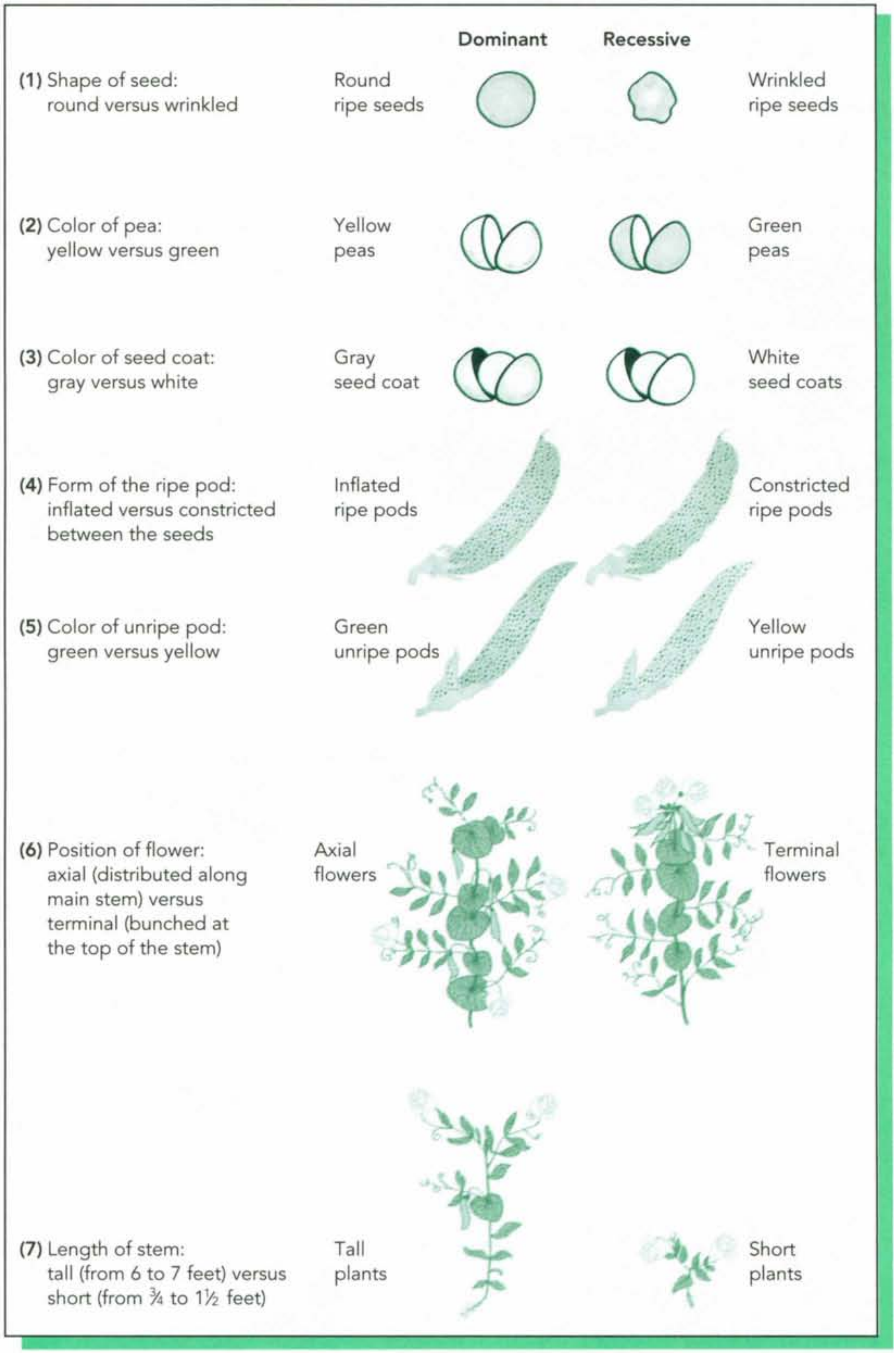


FIGURE 1.2

The traits of pea plants studied by Mendel. The dominating trait is to the left, the recessive trait to the right. An explanation of the trait is given at the far left.

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 forte 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); using his mathematical skills, he discovered **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 1.3 shows. (By that time, the monks in the monastery noted that peas had become a fairly regular item in the dinner menu.)

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

factor
Mendel's term for transmissible hereditary units now know 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

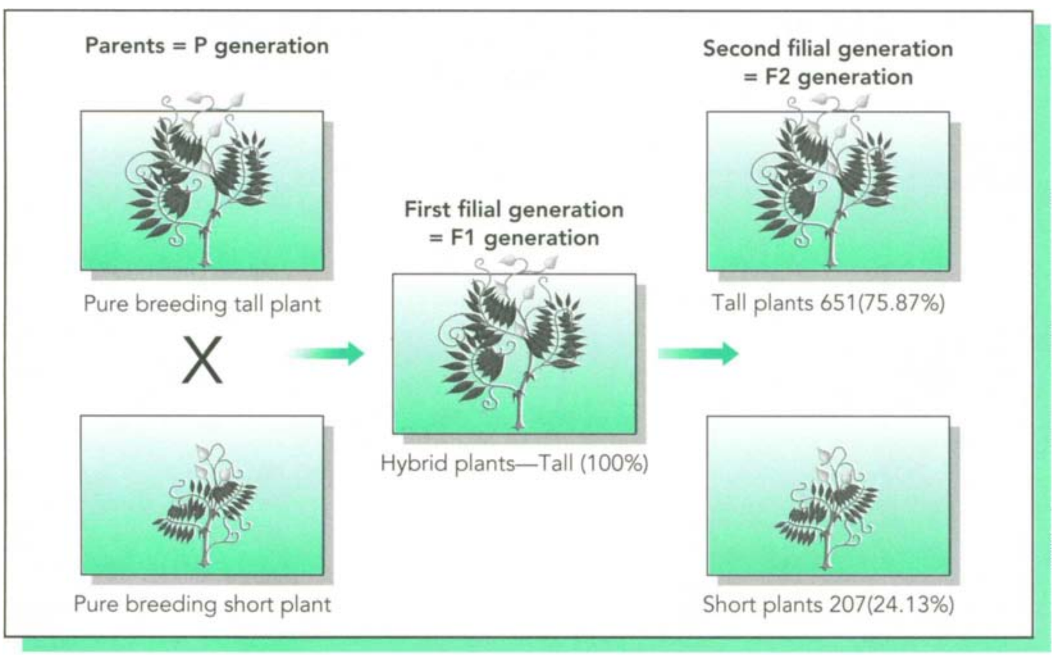


FIGURE 1.3

Mendel's experiments with tall and short pea plants. Mendel bred pure-bred tall plants (of the P generation) to pure-bred short plants. 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 grew among the 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. Partly on this basis, Mendel guessed that two "factors" for height exist in pea plants, and one factor dominates over the other.

unconventional nature of his suppositions, Mendel avoided controversy by keeping his suppositions largely to himself.

theory of transmissible factors
Mendel's theory that inheritance is controlled by cellular factors passed from parents to offspring.

Mendel's theory came to be known as the **theory of transmissible factors**. Although it was revolutionary for the times, Mendel did not stop here. For many years he studied 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 (Questionline 1.1).

evolution
the biological principle that all living things have descended from a common ancestor over the eons of time and are continuing to evolve.

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 lay people. Not until the year 1900 would interest in genetics once again come to the forefront of science.

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

QUESTIONLINE 1.1

1. **Q. When did interest in DNA as the material of heredity begin to surface?**

   A. The study of heredity was rather primitive before Gregor Mendel's work in the 1860s. Mendel proposed that heredity is based on the transfer of several "factors" from parents to their offspring. His theories, however, were not studied further until the early 1890s, and real interest in DNA did not develop until the 1940s.

2. **Q. Why was Mendel's theory novel?**

   A. Until Mendel's time, scientists were unsure how heredity worked; some believed that blood transfers inherited characteristics. Mendel's work focused attention on identifiable factors in the cells and provided a viable alternative to the blood theory.

3. **Q. When did scientists relate chromosomes to Mendel's factors?**

   A. In the early 1900s, T. H. Morgan and his colleagues proved that white eye color, an inheritable trait in fruit flies, depends on the transfer of a single chromosome from the insect parent to its offspring. Morgan's work indicated that Mendel's "factors" and chromosomes are one and the same.