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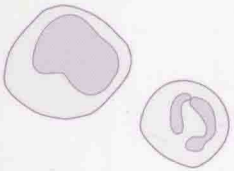
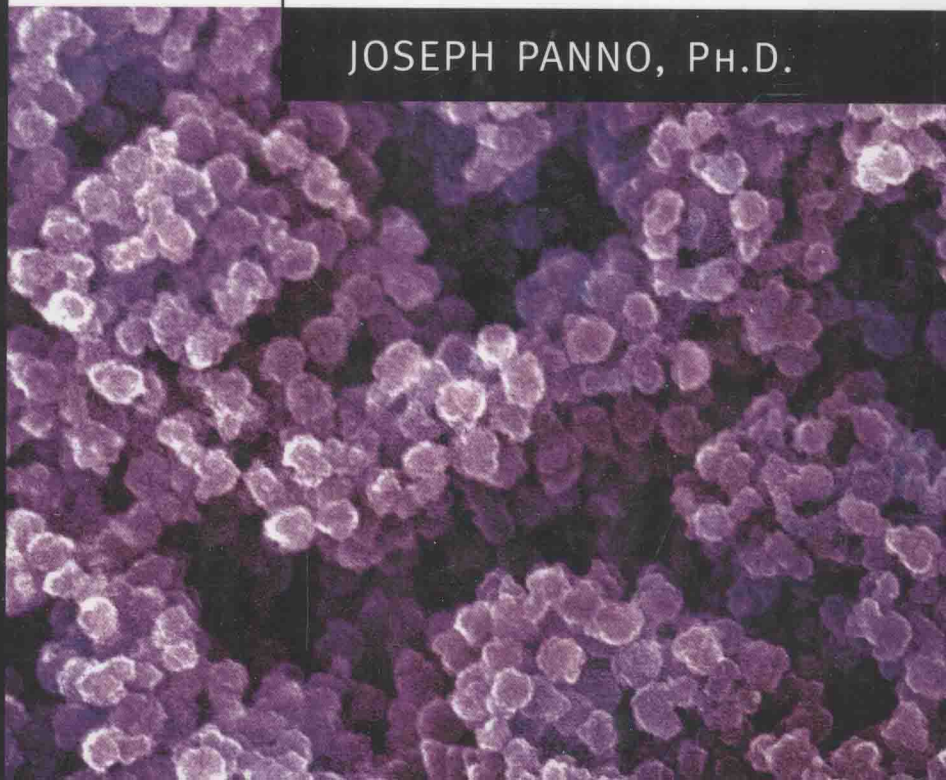
THE new biology

GENE THERAPY

Treating Disease by Repairing Genes



JOSEPH PANNO, PH.D.



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Treating Disease by Repairing Genes

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GENE THERAPY: Treating Disease by Repairing Genes

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This book is printed on acid-free paper.

For my wife, Diana,
who worked with me in the lab for many years,
and for my daughter Eleanor,
who knew about cells before she could read or write.

PREFACE

The New Biology set consists of the following six volumes: *The Cell, Animal Cloning, Stem Cell Research, Gene Therapy, Cancer,* and *Aging.* The set is intended primarily for middle and high school students, but it is also appropriate for first-year university students and the general public. In writing this set, I have tried to balance the need for a comprehensive presentation of the material, covering many complex fields, against the danger of burying—and thereby losing—young students under a mountain of detail. Thus the use of lengthy discussions and professional jargon has been kept to a minimum, and every attempt has been made to ensure that this be done without sacrificing the important elements of each topic. A large number of drawings are provided throughout the series to illustrate the subject matter.

The term *new biology* was coined in the 1970s with the introduction of recombinant DNA technology (or biotechnology). At that time, biology was largely a descriptive science in danger of going adrift. Microbiologists at the turn of the century had found cures for a few diseases, and biologists in the 1960s had cracked the genetic code, but there was still no way to study the function of a gene or the cell as a whole. Biotechnology changed all that, and scientists of the period referred to it as the new technique or the new biology. However, since that time it has become clear that the advent of biotechnology was only the first step toward a new biology, a biology that now includes nuclear transfer technology (animal cloning), gene therapy, and stem cell therapy. All these technologies are covered in the six volumes of this set.

The cell is at the very heart of the new biology and thus figures prominently in this book series. Biotechnology was specifically designed for studying cells, and using those techniques, scientists gained insights into cell structure and function that came with unprecedented detail. As

knowledge of the cell grew, the second wave of technologies—animal cloning, stem cell therapy, and gene therapy—began to appear throughout the 1980s and 1990s. The technologies and therapies of the new biology are now being used to treat a wide variety of medical disorders, and someday they may be used to repair a damaged heart, a severed spinal cord, and perhaps even reverse the aging process. These procedures are also being used to enhance food crops and the physical characteristics of dairy cows and to create genetically modified sheep that produce important pharmaceuticals. The last application alone could save millions of lives every year.

While the technologies of the new biology have produced some wonderful results, some of the procedures are very controversial. The ability to clone an animal or genetically engineer a plant raises a host of ethical questions and environmental concerns. Is a cloned animal a freak that we are creating for our entertainment, or is there a valid medical reason for producing such animals? Should we clone ourselves, or use the technology to re-create a loved one? Is the use of human embryonic stem cells to save a patient dying from leukemia a form of high-tech cannibalism? These and many other questions are discussed throughout the series.

The New Biology set is laid out in a specific order, indicated previously, that reflects the natural progression of the discipline. That is, knowledge of the cell came first, followed by animal cloning, stem cell therapy, and gene therapy. These technologies were then used to expand our knowledge of, and develop therapies for, cancer and aging. Although it is recommended that *The Cell* be read first, this is not essential. Volumes 2 through 6 contain extensive background material, located in the final chapter, on the cell and other new biology topics. Consequently, the reader may read the set in the order he or she prefers.

ACKNOWLEDGMENTS

I would first like to thank my friend and mentor, the late Dr. Karun Nair, for helping me understand some of the intricacies of the biological world and for encouraging me to seek that knowledge by looking beyond the narrow confines of any one discipline. The clarity and accuracy of the initial manuscript for this book was greatly improved by reviews and comments from Diana Dowsley and Michael Panno, and later by Frank Darmstadt, Executive Editor; Dorothy Cummings, Project Editor; and Anthony Sacramone, Copy Editor. I am also indebted to Ray Spangenburg, Kit Moser, Sharon O'Brien, and Diana Dowsley for their help in locating photographs for the New Biology set. Finally, I would like to thank my wife and daughter, to whom this book is dedicated, for the support and encouragement that all writers need and are eternally grateful for.

INTRODUCTION

When we get sick it often is due to invading microbes that destroy or damage cells and organs in our body. Cholera, smallpox, measles, diphtheria, AIDS, and the common cold are all examples of what we call an infectious disease. If we catch any of these diseases, our physician may prescribe a drug that will, in some cases, remove the microbe from our bodies, thus curing the disease.

Unfortunately, most of the diseases that we fall prey to are not of the infectious kind. In such cases, there are no microbes to fight, no drugs to apply. Instead, we are faced with a far more difficult problem, for this type of disease is an ailment of our genes. Since the 1990s, scientists have identified several thousand genetic disorders that are known to be responsible for diseases and conditions such as cancer, senility, diabetes, and asthma. Gene therapy attempts to cure these diseases by replacing the damaged gene that is causing the problem.

Although there are thousands of genetic defects that could, in principle, be treated with gene therapy, only a small percentage are considered practical candidates for this type of treatment. Diseases that qualify for gene therapy are debilitating disorders that affect more than 1 percent of the population, the conventional treatments for which are ineffective, costly, or difficult to administer. Many people opt for gene therapy simply because it is their best chance for a normal life, even if they are not completely cured. Gene therapy is a new, potentially dangerous procedure and thus requires careful attention to the selection process. Consequently, all clinical trials are carefully screened and monitored by government granting agencies. For example, trials conducted in the United States are regulated by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), while trials in the United Kingdom are controlled by the Gene Therapy Advisory Committee, established by the Department of Health.

The first gene therapy trial, conducted in 1991, was designed to treat an immune system disorder known as adenosine deaminase (ADA) deficiency. ADA weakens the immune response so that the individuals suffering from this disorder are unable to fight off even mild infections. There were only two patients in that trial, one of whom showed a modest recovery, while the second patient, a young girl named Ashi DeSilva, showed a dramatic improvement. This trial proved to the research community that gene therapy could work. Many other gene therapy trials were launched throughout the 1990s, but none of them lived up to their expectations. Indeed, a trial conducted at the University of Pennsylvania in 1998 ended in disaster when one of the patients, a young man named Jesse Gelsinger, died as a direct result of the treatment. The consequences of this trial were profound as they affected not only gene therapy but also all experimental therapies that involve human subjects. Critics at the time pointed out that gene therapy should not be called a therapy at all, but an experimental procedure, a status that it retains to this day.

Since the birth of recombinant DNA technology, in the early 1970s, scientists have dreamed of using their new "tool kit" to cure genetic diseases, and now it appears that dream may come true. But the fulfillment of that dream is producing a therapy that is extremely hazardous and surprisingly difficult to apply. The complicating element of the therapy is reliance on a virus to carry the therapeutic gene into the patient's cells. Generally, the virus, known as a vector, is injected into the bloodstream, where it comes into contact with cells of the immune system. The immune system destroys most of the vector particles before they can enter the appropriate cells, thus abolishing much of the therapeutic effect. When the vector gains access to some of the cells the immune system treats this like any other infection and tries to kill the cells harboring the vector. The immune system attack on the infected cells has two consequences: The immune system kills the cells containing the vector, thus further minimizing any therapeutic effect or, if the number of cells harboring the vector is very high, the immune system will damage or destroy whole organs in an attempt to rid the body of the vector, with potentially fatal consequences for the patient. Despite these very substantial problems, the number of disorders being treated with gene therapy has increased from a few in 1990 to more than 600 in 2004, and

of all the technologies provided by the new biology, gene therapy holds the promise of unlimited potential for curing disease and reversing the effects of age.

This book, another volume in the New Biology set, discusses the science behind gene therapy, as well as the ethical and legal issues associated with this therapy. Earlier chapters describe genetic diseases that may be treated with this therapy and the viruses that are used to deliver therapeutic genes to the cell. These discussions are followed by two case studies: the first involves Ashi DeSilva, the first patient ever treated with this therapy, and the second profiles the case of Jesse Gelsinger. The future prospects of gene therapy are examined from the perspective of its one great success (DeSilva) and its greatest failure (Gelsinger). Two chapters are devoted to the ethical and legal debate surrounding this powerful, but often dangerous therapy. The final chapter provides background material on cell biology, recombinant DNA technology, and other topics that are relevant to gene therapy.

CONTENTS

.1.

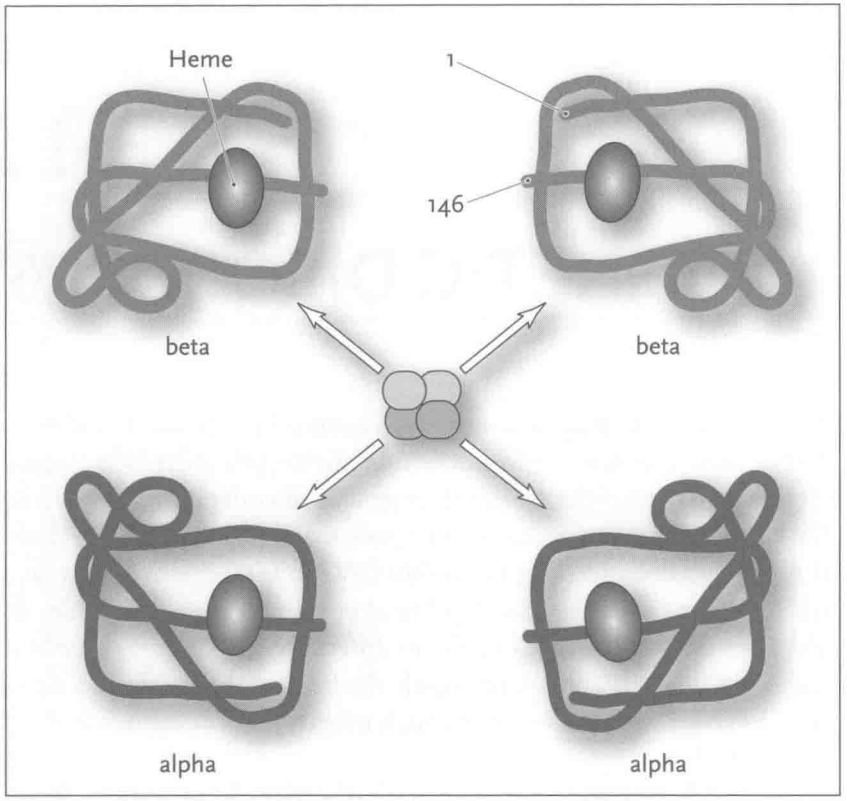
GENETIC DISORDERS

When a gene is damaged, it usually is caused by a point mutation, a change that affects a single nucleotide. Sickle-cell anemia, a disease affecting red blood cells, was the first genetic disorder of this kind to be described. The mutation occurs in a gene that codes for the beta chain of hemoglobin, converting the codon GAG to GTG and resulting in a protein that has the amino acid valine at position 6, instead of glutamic acid. It may seem like an insignificant difference, but this single amino-acid substitution is enough to cripple the hemoglobin molecule, making it impossible for it to carry enough oxygen to meet the demands of a normal adult.

Sickle-cell anemia, like many genetic disorders, is monogenic, being caused by a single defective gene. But many forms of cancer and some neurological disorders are polygenic, involving several mutated genes. The genetic disorders described in this chapter are of both kinds and are being treated in clinical trials, or will be in the near future. Taken together, these diseases account for more than 200,000 deaths in North America each year. Although the range of ailments treatable with gene therapy is extremely broad, more than 65 percent of the clinical trials are aimed at curing various forms of cancer.

Immune Deficiencies

All animals have an immune system that is designed to combat invading microbes, and without it, we face certain death from a multitude of diseases. Our immune system consists of an enormous population of white blood cells that appear in many different forms, the most impor-



Hemoglobin. The molecule consists of two alpha and two beta protein chains, each bound to an iron-containing heme group that carries oxygen. The position of the first (1) and last amino acid (146) is indicated. Ancestral hemoglobin probably consisted of a single alpha or beta chain.

tant of which are the B cells, T cells, and macrophages. B and T cells are lymphocytes that develop in bone marrow and the thymus, respectively. Macrophages are phagocytic blood cells—they confront invaders head-on by eating them—whereas B cells attack foreign material indirectly by producing antibodies. T cells control and coordinate the immune response by releasing signaling molecules called cytokines that recruit macrophages and B cells. T cells also have the remarkable ability to detect invaders that are hiding inside a cell. Even more remarkable, they can force the infected cell to commit suicide in order to control the spread of the infection.

A common form of immune deficiency is severe combined immunodeficiency-X1 (SCID-X1). This disease represents a group of rare, sometimes fatal, disorders that destroy the immune response. Without special precautions, the patients die during their first year of life. Those who survive are susceptible to repeated bouts of pneumonia, meningitis, and chicken pox.

All forms of SCID are inherited, with as many as half of the cases being linked to the X chromosome. The mother passes on this disease, since males born with this disorder usually die before reaching their reproductive years. SCID-X1 results from a mutation that cripples a receptor for a cytokine called interleukin 2 (the IL2R gene). The IL2R protein activates an important signaling molecule called Janus kinase 3 (JAK3). A mutation in the JAK3 gene, located on chromosome 19, can result in a second form of SCID. Defective cytokine receptors, and the signaling pathways they activate, prevent the normal development of T lymphocytes that play a key role in identifying invading agents, as well as activating other members of the immune system.

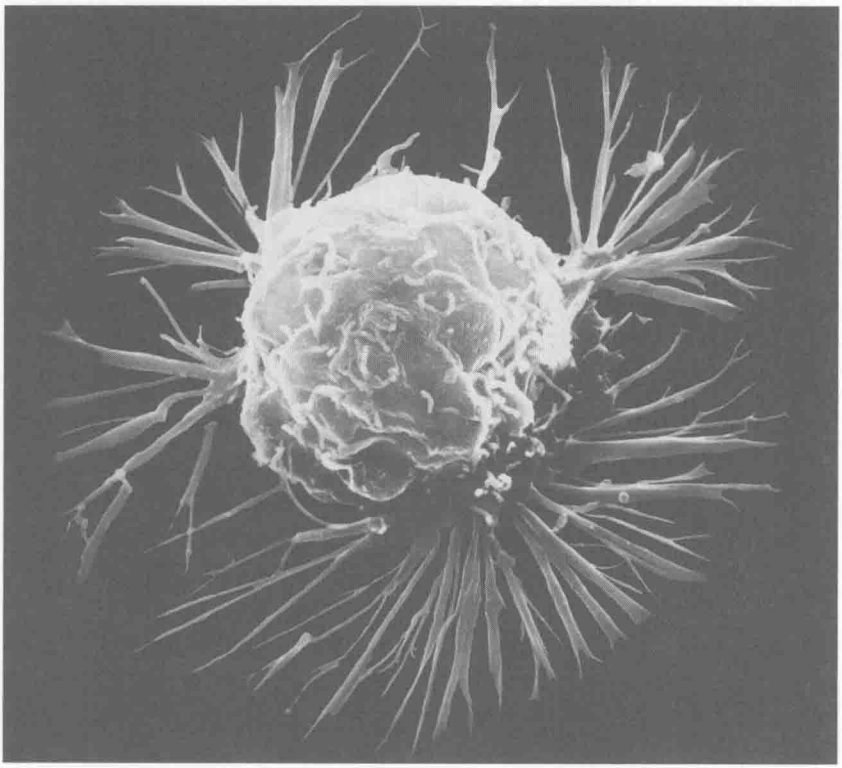
A third form of SCID is due to a mutation in the adenosine deaminase (ADA) gene, located on chromosome 20. This gene is active in T lymphocytes and the mutation leads to a toxic buildup of adenosine inside the cell, thus blocking the normal maturation and activity of this crucial member of the immune system. Some patients suffering from ADA deficiency can mount a weak immune response, but in most cases the response is abolished. The conventional treatment, involving a bone marrow transplant, has been successful in saving many lives, but acquiring a compatible tissue match for every patient is extremely difficult and sometimes impossible.

In many ways, SCID is an ideal candidate for gene therapy since the T cells can be collected from the patient and grown in culture, where the healthy gene is inserted and tested. If the T cells take up the gene and express it properly, they can then be injected into the bloodstream of the patient. It is for this reason that the very first gene therapy trial (profiled in chapter 3) involved a young patient suffering from ADA deficiency. That trial was a success, and a recent trial, involving SCID-X1, has reported complete success in curing this form of immune deficiency.

Breast Cancer

Breast cancer, like all cancers, is a genetic disorder caused by a mutation in one or more genes. Viruses cause some cancers, but the mechanism still involves a corruption of genetic information equivalent to a naturally occurring mutation.

Breast cancer is the second most common cause of cancer death in women around the world, with an estimated 50,000 deaths per year in the United States alone. Two genes, BRCA1 (breast cancer 1), located on chromosome 17, and BRCA2, on chromosome 13, were isolated in 1994. Mutations in either of these genes are associated with the occurrence of



A scanning electron micrograph (SEM) of a single breast cancer cell, showing its uneven surface and cytoplasmic projections. Breast cancer is the most common cause of cancer in women. Magnification unknown. *(SPL/Photo Researchers, Inc.)*