HUMAN GENETICS

Concepts and Applications

second edition

Ricki Lewis

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dedicated to
Benjamin Lewis, a gentle
and great
man

preface

Genetics has arrived at the dinner table. From daily updates of a celebrated murder trial bemoaning "the mind numbing intricacies of DNA evidence" to reports on presymptomatic tests for breast cancer, to the tragedy of an athlete suddenly felled by a previously undetected inherited heart anomaly and lighter media fare on whether genes cause everything from thrill-seeking behavior to infidelity, genetics has entered the public consciousness.

With the arrival of genetics in people's everyday lives have come heightened expectations—and heightened fears. We've seen impatience and disappointment expressed over limited strides in gene therapy, and suspicion concerning the validity of DNA evidence in forensics. Yet at the same time, the public has become aware that the information that new genetic tests can reveal may be misused. Against a backdrop of health care cost cutting, the ability to predict an individual's specific medical future, which the human genome project is making possible in a piecemeal manner, is terrifying.

Some of the confusion the public has with understanding genetic issues is that a sound bite, tabloid headline, talk show squabble, or 200-word newspaper article cannot convey the complexity of genetics. Consumers must settle with just the end result, and often a heavy dose of speculation. It is the goal of this book to create genetically informed citizens, so that they can decide for themselves if DNA evidence is truly "mind numbing"—or a fascinating application of basic biology.

"If It Isn't Broken—Don't Fix It"

So wrote one reviewer of *Human Genetics*, first edition. In response, this edition retains the organization, breadth, and tone of the first edition. Again, approximately three-quarters of the book in general covers basic concepts (chapters 1–16), and the final quarter presents applications primarily through new technologies (chapters 17–21). The table below presents the concepts/applications paradigm of the text.

What's New in This Edition

Changes in the second edition have one goal (besides the obvious updating)—to improve clarity and ease-of-learning.

concepts/applications paradigm

Concept Chapter	Application Chapter
2 Cells	16 The Genetics of Cancer
	18 Gene and Protein Therapy
3 Human Development	20 Reproductive Technologies
6 Matters of Sex (linkage)	21 The Human Genome Project
8 DNA Structure & Replication	19 Agricultural & Environmental Biotechnology
9 Gene Function	12 When Gene Frequencies Stay Constant
10 Gene Mutation	13 Changing Gene Frequencies
11 Cytogenetics	14 Human Origins and Evolution
15 The Genetics of Immunity	17 Genetic Engineering

Pedagogy

Each chapter has its own mini-glossary, so students can learn terms in context. The back of the book has one comprehensive glossary.

Questions are now of two types: simply, Review (straight recall) and Applied (critical thinking and cases which include considerations of bioethical issues). There are more questions altogether, with many new ones.

The new Technology Timelines trace the evolution of ideas and discoveries to technology. The timelines, in the last quarter of the book, include looks at transplantation, immunotherapy, cancer diagnosis, patenting life forms, development of taxol, and assisted reproductive technologies. Many figures are improved—to be clearer and less complex.

Back by popular demand, stories of real people bring concepts alive and help students to remember them. New tales explore:

- a little girl for whom the light of day is deadly
- colorblindness in a famous chemist
- the truth about werewolves
- a baby girl with a boy's karyotype
- a 62-year-old new mother
- a girl who donated her heart to her father.

Boxed readings continue to tackle controversial topics—some new readings so "hot" that requests for photos were denied! They include:

- embryos as research subjects
- fetal tissue for transplants
- blaming genes for violent behavior
- the inheritance of homosexuality
- the safety of transplants of pig tissue.

Pace

Throughout the text, material is presented at a slightly slower pace (compared with the first edition) to ensure full comprehension. "Familiarity" is the key to overcoming sciencephobia, and accordingly, Chapter 1 focuses on genetics in the news. The unfolding tale of the genetic roots of breast cancer is used to introduce major terms and subdivisions of the field of genetics.

Mendelian genetics is expanded to two chapters, Mendel's Laws (Chapter 4) and Extensions and Exceptions to Mendel's Laws (Chapter 5). Let students learn the basics before grappling with concepts that puzzle even geneticists! "Extensions and Exceptions" include maternal inheritance, uniparental disomy, and linkage.

Chapter 9, Gene Function, proceeds much more slowly, with frequent new tables to reinforce basic concepts. This is probably the most difficult chapter, and its clarity is much improved.

Chapter 15, Genetics of Immunity, is presented in a simpler format, proceeding from normal immunity, to abnormal immunity, to transplants, to immunotherapy.

Chapter 19, Agricultural Biotechnology, expands beyond the Plant Biotechnology chapter of the first edition to include animal applications and environmental biotechnology.

Chapter 21 is a complete look at the human genome and other genome projects.

Expanded coverage of key topics throughout:

- DNA fingerprinting (12)
- Pedigree analysis (4, 5, 6)
- Behavior genetics (5, 7)
- Race (1, 13)
- DNA repair (8)
- Gender identity (6)
- Alzheimer's disease genes (10)
- Fetal cell sorting (11)
- Transgenic technology (17, 19)
- Apoptosis (2)
- Telomeres (2, 16)
- Breast cancer (1)
- Triplet repeat disorders (10)
- Genomic imprinting (5, 6)
- Emerging viral diseases (13)
- Ancient DNA analysis (14)
- Xenotransplantation (15)
- Knockout genes (17)

Aids to the Student

Full Color Illustrations and Photographs. The dazzling visuals of *Human Genetics* present the concepts of genetics in detail and in color—contributing to the text's lively, student-friendly feel. Figure 9.2 from page 161 has been reproduced here as an example of the clarity and visual presentation of the illustrations.

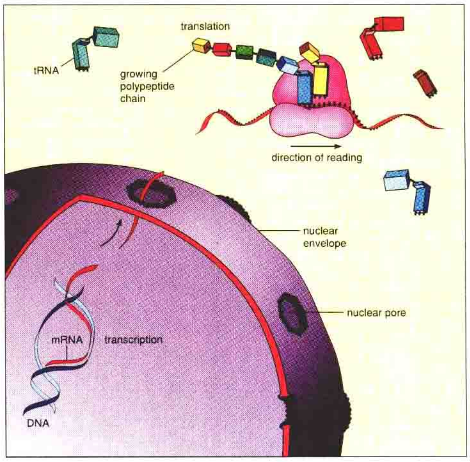

figure 9.2
An mRNA molecule transcribed from a section of DNA exits the nucleus and enters the cytoplasm, where it associates with a ribosome to begin translation.

Chapter Outlines. An outline at the beginning of every chapter provides the student with a brief overview of the topics to be discussed in the chapter.

Real-Life Scenarios. Real-life vignettes, usually found in the chapter introductions, put the study of genetics into a *human perspective*. Included are numerous examples from the news and from the author's experience as a genetic counselor that amplify concepts and spark interest in the science.

Technology Timelines. New to this edition, the "Technology Timelines" trace the intellectual evolution of scientific discovery to useful technology. The timelines can be found in Chapters 15–21 and offer the nonscience student a historical perspective without disrupting the flow of the narrative. A timeline from Chapter 15 is reproduced here.

Technology Timeline

Transplantation

1899 First allograft—a kidney from dog to dog.

1902 Pig kidney is attached to blood vessels of woman dying of kidney failure.

1905 First successful corneal transplant, from a boy who lost an eye in an accident to a man whose cornea is chemically damaged. Works because cornea cells lack antigens.

1940s First kidney transplants on young people with end-stage kidney failure.

1950s Blood typing predicts success of potential donor-recipient matches for organ transplants.

1960s First effective immunosuppressant drugs revive interest in human allografts. Kidney xenografts between baboons and chimpanzees.

1967 First human heart transplant. Patient lives eighteen days.

1968 Uniform Anatomical Gift Act passes. Requires informed consent from next of kin before organs or tissues can be used for organ donation.

1970s Transplants fall out of favor because they extend life only briefly and do not correct underlying disease, and because surgical complications and rejection reactions are common.

1980s Improved immunosuppressant drugs, surgical techniques, and tissue matching, plus ability to strip antigens from donor tissue, reawaken interest in transplants.

1984 Doctors at Loma Linda University Medical Center transplant a baboon's heart into "Baby Fae," who was born with half a heart. She lives twenty days before rejecting the xenograft.

1992 Surgeons at the University of Pittsburgh Medical Center transplant a baboon's liver into a thirty-five-year-old man with hepatitis. The man lives for seventy-one days, dying of an unrelated cause.

1995 An AIDS patient receives bone marrow from an HIV-resistant baboon.

Boxed Readings. Topical boxed readings add interest to the ideas discussed, and have been updated or replaced throughout to reflect growing knowledge in the field. Boxed Reading 6.2, "A Werewolf—or A Genetic Variant?," reproduced here, is one of the new boxed readings in this edition.

Key Concepts. To be certain the students understand the concepts discussed in the book, every chapter contains internal summaries of key concepts. An example of a "Key Concepts" section is reproduced here from page 239.

Key Concepts

Immunotherapy uses immune system components to fight disease. Hybridomas, artificial cells consisting of a B cell fused with a cancer cell, produce monoclonal antibodies (MAbs) that can target specific antigens. Cytokines boost immune function and destroy cancer cells.

Chapter Glossary. Also new to this edition, each chapter concludes with a glossary of all the key terms (boldfaced terms) found in the chapter. A complete single glossary still appears at the end of the text.

End-of-Chapter Questions. The questions at the end of each chapter are now of two types, "Review" and "Applied," with many new questions added. "Review Questions" are straight recall and "Applied Questions" challenge critical-thinking skills and case analysis. Many applied questions involve bioethical issues.

Suggested Readings. References are provided at the end of every chapter to allow for further study above and beyond what is presented in the text. The information in the text is often drawn from these sources.

Supplementary Material

Instructor's Manual and Test Item File. An Instructor's Manual/Test Item File, prepared by Holly Ahern, Adirondack Community College, is available to instructors and features the transparency list, chapter learning objectives, key concepts, related readings. The Test Item File contains 20 to 30 objective questions per chapter that can be used to generate exams.

A Werewolf—or a Genetic Variant?

reading 6.2

Since the Middle Ages, about fifty "ape men," "dog men" or "human werewolves" have been reported in the medical literature. Because of the phenotype of extreme hairiness, these individuals often wound up in circus side shows. We know today that they have congenital generalized hypertrichosis (CGH), which is inherited as a sex-linked dominant condition.

Geneticists know relatively little about hair. We do know that three types of hair grow throughout human development. The early fetus has short, fine hair called vellus, and the older fetus has long, fine hair called lanugo. The long, thick hair that cascades from our scalps and coats our bodies after birth is called terminal hair.

In CGH, a person has more hair follicles, and hence denser and more abundant terminal hair. Unlike hirsutism, caused by a hormonal abnormality that makes a woman grow hair in places where it is usually more pronounced in males (for example, a mustache), CGH causes excess facial and upper body hair that covers extensive areas of skin (figure 1). The hair growth is milder and patchier in females because of hormonal differences and the mitigating presence of a second X chromosome.

Researchers studied a large Mexican family that had nineteen relatives with CGH. The pattern of inheritance was distinctive for sex-linked dominant inheritance, which is quite rare. In one portion of the pedigree, depicted in figure 2, an affected man passed the trait to all four of his daughters, but to none of his nine sons. Because sons inherit the X chromosome from their mother, and only the Y from their father, they could not have inherited CGH from their affected father.

The mutant gene that causes CGH is atavistic, which means that it controls a trait also present in ancestral species. A version of the gene is probably present in chimpanzees and other hairy primates. Sometime in our distant past, the wild type form of the gene must have mutated in a way that enables humans to grow dense hair only on their heads and in areas dictated by sex hormones.

figure 1

This six-year-old boy has congenital generalized hypertrichosis (CGH).

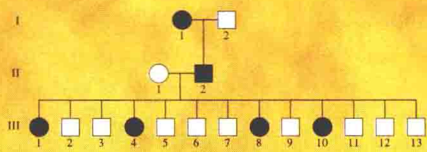

figure 2

Part of the pedigree of the large Mexican family with CGH. Note that the affected male in the second generation has passed the condition to all of his daughters and none of his sons. This is because he transmits his X chromosome only to females.

Student Study Guide. The study guide, written by David Fromson and Ina Katz, California State University, Fullerton, is available to students as an additional resource for answering questions and solving problems (ISBN 24032).

Microtest III. Microtest is a computerized classroom management service that comprises a database of objective questions suitable for preparing exams and a grade-recording program. The software requires no programming experience and is available in DOS, Windows, and Mac formats.

Transparencies. A set of 50 transparencies is available free to adopters and consists of 50 illustrations from the text.

Case Study Workbook. This workbook was written by Ricki Lewis and is available to students and instructors for additional reading and problem-solving (ISBN 22287).

Answer Key to the Case Study Workbook. This answer key contains the answers and solutions to the case studies covered in the Case Study Workbook.

Gene Game Software. This software program, written by William Sofer of the State University of New Jersey-Rutgers, is an easy to use, interactive Macintosh software game. It requires students to use critical thinking skills and apply the scientific method in cloning a fictitious fountain of youth gene. The *Gene Game* can be packaged with this text (ISBN 24893).

Explorations in Cell Biology and Genetics CD-ROM. This CD-ROM is an interactive multimedia program developed by George Johnson, of Washington University, and WCB. It calls on students to manipulate variables and examine how they impact the results as they explore genetics-related topics such as: Constructing a Genetic Map, Reading DNA, Exploring Meiosis: Down Syndrome, and more. The CD-ROM is compatible with both Windows and Macintosh systems (ISBN 29214).

Genetic Inheritance: Peas and *Drosophila* Software. This software program, developed by Mark Browning, Purdue University, allows the student to simulate hundreds of genetic crosses right at his/her computer to gain valuable practice in the quantitative aspects of genetics. Both the pea and *Drosophila* experiments investigate Mendel's laws of dominance, segregation, independent assortment and how numbers of offspring affect test results. Once the student has mastered these concepts, he/she can be further challenged with the *Drosophila* experiments exploring the concepts of monohybrid, dihybrid, and trihybrid crosses, as well as the determination of linkage, map distances, and gene order on chromosomes. The software can also be packaged with the text (Mac ISBN 28861, Windows ISBN 35225).

Acknowledgments

A chapter in the first edition was dedicated to a two-year-old who died of a failed treatment for her inherited disease. This edition is dedicated to another young person living with an illness discussed in the text, but one well enough to contribute to the book. The unforgettable Blaine was born with spina bifida. His view of genetic screening, in Chapter 14, brings a perspective to the topic that I never could. I "met" Blaine on the Internet, where, for a school project, he had posed the question, "If we had the technology to eliminate disabilities from the population, would that be good public policy to do so?" He opened a worldwide debate.

Many thanks to my family and cats, to the wonderful team at William C. Brown Publishers (Michael Lange, Elizabeth Sievers, Terry Stanton, Carla Kipper, Margaret Horn, Jeff Storm, Brenda Ernzen, Janice Hancock, Gail Wheatley, Anne Cody, Shirley Lanners, Mary Davidson Stanton, Patrick Reidy), to all of the reviewers, and especially to my friend in cyberspace and reviewer extraordinaire, George Hudock.

Blaine Deatherage-Newsom is a young man born with spina bifida who contributed an essay on prenatal screening to chapter 14.

Reviewers

I thank the reviewers of the first and second editions for their valuable observations and suggestions.

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chapter one

Overview of Human Genetics

A Look Ahead

The year is 2001. A nurse draws blood from a young pregnant woman for a routine prenatal exam. In the patient's blood are a few immature red blood cells from the fetus. The nurse sends the blood sample to a laboratory, where a technologist, using an instrument that recognizes and separates out unusual cells, collects a few fetal cells. So begins the scrutiny for clues to the health of this developing person.

An initial peek within the cells, at the chromosomes that carry genes, reveals the first piece of information—the child will be a boy, shown when a fluorescent dye homes in on and highlights a Y chromosome in each cell. A closer look at specific genes reveals much more.

Happily, the child will not have any of the more common inherited disorders. Had he had a family history of inherited illness—such as cystic fibrosis or muscular dystrophy—he might have been conceived in the laboratory and tested when he was just 8 cells in size, not even large or complex enough to be considered an embryo. If one cell sampled from the 8 proved normal, the remaining seven cells would then have been implanted in his mother.

Despite the fetus' apparently healthy genetic background, some blood cells from the umbilical cord will be set aside at birth and deep-frozen for long-term storage. Should he need a bone marrow transplant later in life to treat anemia or cancer, his own cord blood cells will be grown in the laboratory into new bone marrow, tailor-made for his body.

Other results from the prenatal test indicate that the boy will be able to design his lifestyle to minimize the effects of certain potentially unhealthy inherited characteristics. A panel of tests to type the genes that predispose him to develop heart disease make it clear that a lifelong low-fat diet and regular exercise can extend his life. The same measures may help prevent or delay colon cancer, since he has inherited a pair of susceptibility genes. Many, many other inherited traits are not checked because they will not affect health. Hair and eye color, childhood freckles and future baldness, will remain surprises.

The child that this fetus will become could be your son. The scenario surrounding his gestation and birth takes place in the near future, but every one of the tests he undergoes is performed today; each is described later in the book. Other genetic screening tests, for fetuses as well as newborns, have been available for many years.

Until recently, we didn't know the nature of most genes that cause disease. However, an ongoing global scientific effort called the **human genome project** is rapidly adding more genes to the collection of those we can test for. The project's goal is awesome—deciphering the complete genetic makeup, or **genome,** of humans.

Once a basic life science, human genetics is rapidly becoming a medical discipline. The human genome project will alter the way we view illness, as the potential to identify our inherited strengths and weaknesses becomes reality. The project will also reveal the many ways that people differ from each other.

Genetics in the News

Genetics is the study of inherited variation and traits. **Genes** are biochemical instructions that determine those inherited traits; they consist of sequences of building blocks of **deoxyribonucleic acid** (DNA). Genes strung together make up the larger **chromosomes.** Humans have 23 pairs of chromosomes, which include two copies of each of about 70,000 genes.

A gene's sequence of DNA building blocks is like a language that instructs a cell to manufacture a particular protein. An intermediate language, encoded in the building block sequence of **ribonucleic acid** (RNA), literally translates a gene's message into a protein's amino acid sequence. It is the protein that determines the trait, although we do not in most cases understand precisely how this happens. Because a gene is a long sequence of DNA, it can vary in many ways, just as the letters in this sentence can be rearranged to communicate a different message. Variants of a particular gene, different because they include changes in the DNA sequence, are called **alleles.**

A generation ago, studying genetics meant examining patterns of trait transmission in fruit flies, bacteria, bread mold, corn, and other species whose physical characteristics or chromosomes are easy to study. A generation before that, biologists did not even know what type of chemical comprised the genetic material. While today's genetic researchers still use experimental organisms to unravel the details of how genes control traits, and even to serve as "models" of human disorders, the study of human genetics has grown explosively, touching our lives in a variety of ways. Genetics is no longer a topic reserved for textbooks—it is increasingly finding its way into the public consciousness (figure 1.1). Following are some familiar applications of human genetics.

Forensics

In a recent infamous criminal case, a woman and a man were found brutally murdered, a "trail of blood" seemingly leading to the woman's ex-husband. A technique called DNA fingerprinting (chapters 8 and 12) compared several DNA sequences in white blood cells on a bloody glove at the crime scene, on socks in the accused man's bedroom, and in his car. These particular DNA regions vary greatly from person to person, and can therefore be used to identify individuals.

The DNA sequences on the three pieces of evidence matched those from blood samples taken from the two victims and the accused man. However, as defense attorneys effectively argued, DNA fingerprinting, no matter how accurate, cannot reveal *how* blood arrives at a crime scene. In the end, a demonstration that the glove did not fit the accused man's hand, and allegations that another person could have planted the evidence, swayed the jury more than the expert testimony on DNA evidence (figure 1.2). The accused was O. J. Simpson, and the jury acquitted him.

Agriculture

Agriculture reflects a rich history of controlled breeding to create new combinations of traits in livestock, fruits, and

figure 1.1

Genetics in the news.

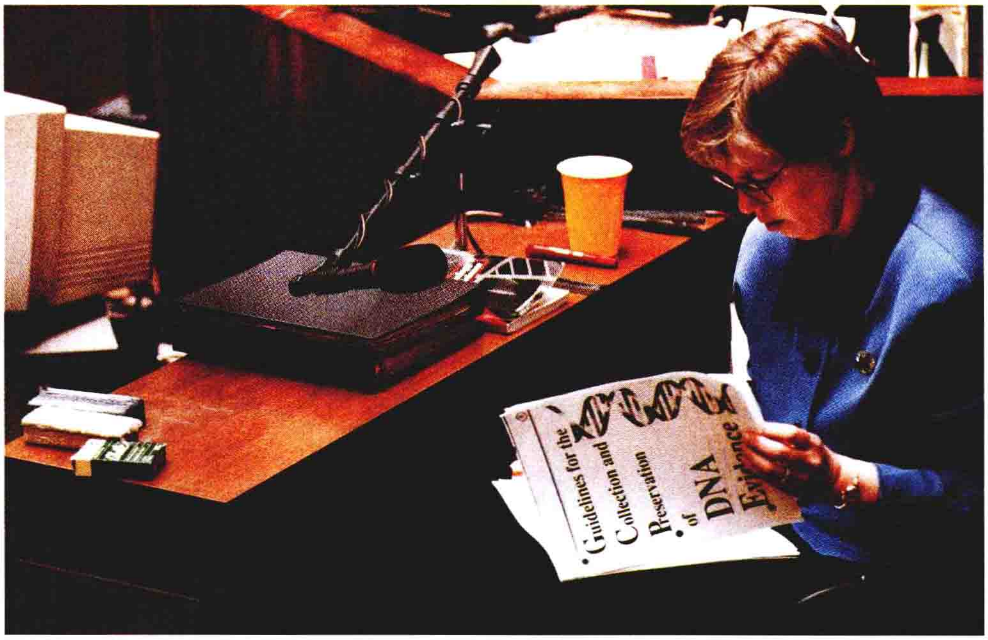

figure 1.2

At the O. J. Simpson trial, geneticist Dr. Robin Cotton presented the DNA fingerprint patterns for the defendant and the two victims. Although the DNA evidence linked the accused with the victims, it could not show how the DNA ended up on the items in evidence. The defense raised the possibility that the blood evidence was planted, and Simpson was acquitted.

vegetables. Manipulations of individual genes have added a precision not possible with traditional breeding plans, in which trait combinations passed to offspring can be unpredictable.

In 1994, a biotechnology company introduced a tomato altered so that it lacks a gene that contributes to ripening. The tomato retains its fresh flavor longer than unaltered tomatoes. However, some consumers fearfully rejected the "genetically engineered" tomato as a vegetable version of the Frankenstein monster (figure 1.3). Reading 19.1 further explores genetically altered crops.

Defining Race

The little girl in the upper right corner of figure 1.4 looks different from the little girl in the upper center—one has dark skin, and the other pale skin. Based mostly on this obvious distinction, we classify the children as members of different races, suggesting that they are in some fundamental way quite different from one another. However, the girls may be much more alike than they are different. They may have the same blood type, fingerprint pattern, height, and handedness, and they may share personality traits.

The *American Heritage and Dictionary of the English Language* defines *race* as a "local geographic or global human population distinguished as a distinct group by genetically transmitted physical characteristics." Shared inherited characteristics, rather than acquired traits like dyed hair color, are used to define race because they indicate that a group of people descended from common ancestors and are therefore closely related by blood. When people tend to mate within their population, whether due to geographical constraints, social customs or events of history, certain traits remain in that population. The combination of traits comes to define a particular race.

Ironically, at a time when a charged political climate is further dividing people along race-based-on-skin-color lines, many biologists are reevaluating this definition of race. Their point—traditional race definitions emphasize skin color, which is only one of thousands of inherited

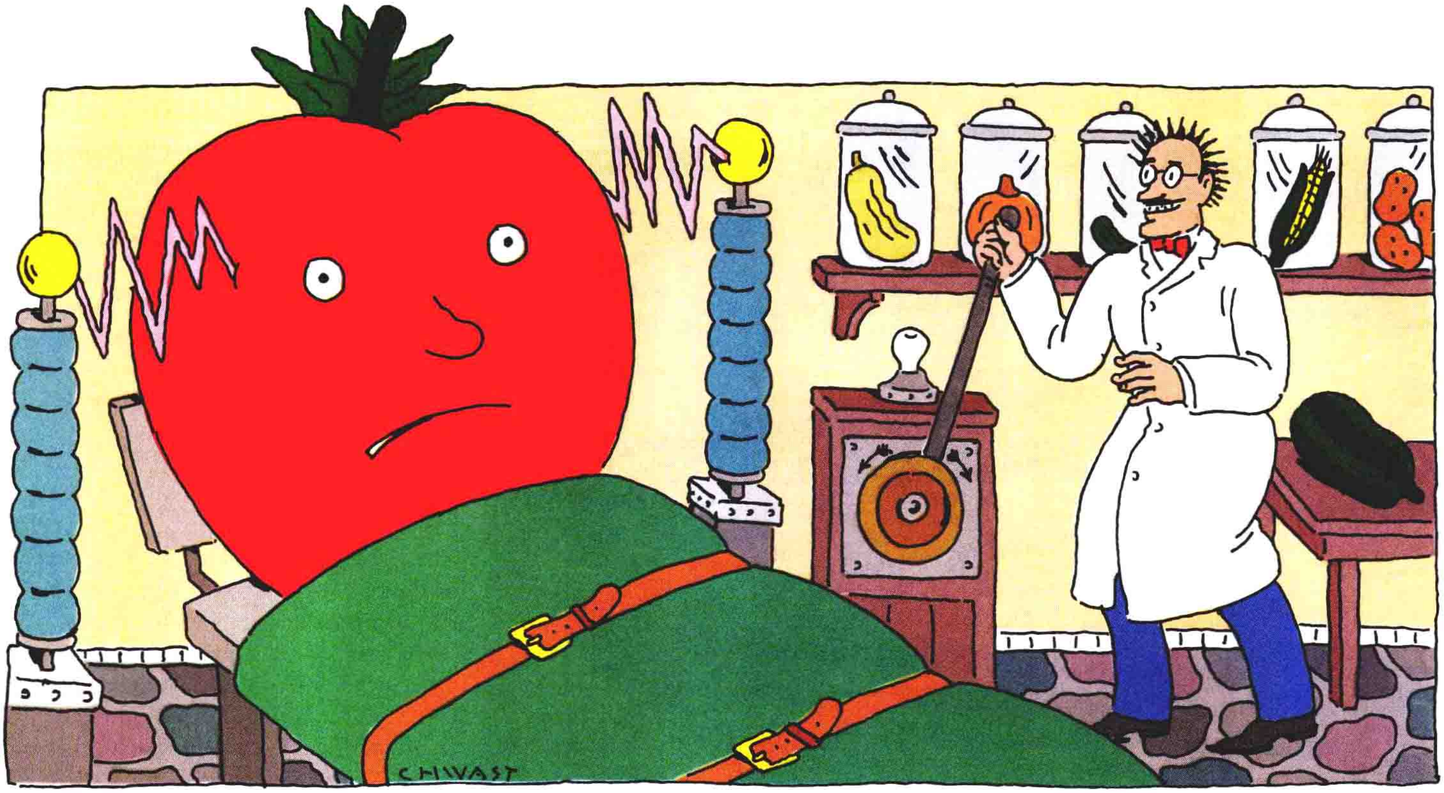

figure 1.3

This cartoon, from *Time* magazine, illustrates the public's fear of genetic manipulation.

figure 1.4

Skin color is only one way humans differ from each other. Race based on color is literally only skin deep. Two people of different skin colors may be more alike in many ways than two people of the same skin color.