Human Heredity 11e

PRINCIPLES AND ISSUES

Michael R. Cummings

Human Heredity

Principles & Issues

ELEVENTH EDITION

Michael R. Cummings

Illinois Institute of Technology

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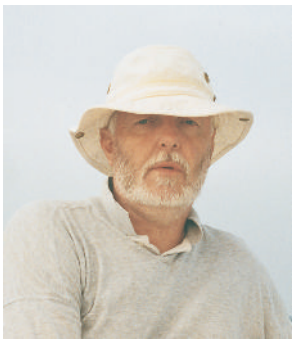
To my daughter, Kerry Eileen, whose *joie de vivre* and passion for life sustain one's faith in the human spirit.

About the Author



MICHAEL R. CUMMINGS received his Ph.D. in Biological Sciences from Northwestern University. His doctoral work, conducted in the laboratory of Dr. R. C. King, centered on ovarian development in *Drosophila melanogaster*. After a year on the faculty at Northwestern, he moved to the University of Illinois at Chicago, where for many years he held teaching and research positions. In 2003, he joined the faculty in the Department of Biology at the Illinois Institute of Technology, and currently holds the title of Research Professor.

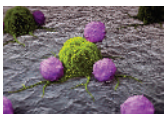
At the undergraduate level, he has focused on teaching genetics, human genetics for nonmajors, and general biology to majors and nonmajors. He has received awards given by the university faculty for outstanding teaching, has twice been voted by graduating seniors as the best teacher in their years on campus, and has received several teaching awards from student organizations.

His current research interests involve the organization of DNA sequences in the short-arm and centromere region of human chromosome 21. He is engaged in a collaborative effort to construct a physical map of this region of chromosome 21 for the purpose of exploring molecular mechanisms of chromosome interactions.

In addition to *Human Heredity*, Dr. Cummings is the author and coauthor of a number of other widely used college textbooks, including *Biology: Science and Life*; *Concepts of Genetics*; *Genetics: A Molecular Perspective*; *Essentials of Genetics*; and *Human Genetics and Society*. He has also written articles on aspects of genetics for the *McGraw-Hill Encyclopedia of Science and Technology* and has published a newsletter on advances in human genetics for instructors and students.

He and his wife, Lee Ann, are the parents of two adult children, Brendan and Kerry, and have two grandchildren, Colin and Maggie. He is an avid sailor, enjoys reading and collecting books (biography, history), appreciates music (baroque, opera, and urban electric blues), and is a long-suffering Cubs fan.

Contents



1 A Perspective on Human Genetics 2

1-1 Genetics and Translational Medicine 2

1-2 Genetics Is the Key to Biology 4

1-3 What Are Genes and How Do They Work? 4

Exploring Genetics: Genetic Disorders in Culture and Art 5

1-4 How Are Genes Transmitted from Parents to Offspring? 6

1-5 How Do Scientists Study Genes? 8

Some basic methods in genetics. 8

Genetics is used in basic and applied research. 9

1-6 Has Genetics Affected Social Policy and Law? 10

The misuse of genetics has affected social policy. 10

Eugenics was used to pass restrictive immigration laws in the United States. 10

Eugenics was used to restrict reproductive rights. 11

The decline of eugenics in the United States began with the rise of the Nazi movement. 12

1-7 What Impact Is Genomics Having? 13

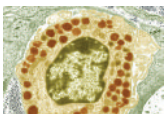
Identifying and using genetic variation in genomics. 13

Health care uses genetic testing and genome scanning. 13

Stem-cell research offers hope for treating many diseases. 14

Biotechnology is impacting everyday life. 14

1-8 What Choices Do We Make in the Era of Genomics and Biotechnology? 15



2 Cells and Cell Division 18

2-1 Cellular Links to Genetic Disease 18

2-2 The Chemistry of Cells 19

2-3 Cell Structure Reflects Function 20

There are two cellular domains: the plasma membrane and the cytoplasm. 20

Organelles are specialized structures in the cytoplasm. 22

The endoplasmic reticulum folds, sorts, and ships proteins. 23

Molecular sorting takes place in the Golgi complex. 23

Lysosomes are cytoplasmic disposal sites. 23

Mitochondria are sites of energy conversion. 24

The nucleus contains chromosomes. 25

2-4 The Cell Cycle Describes the Life History of a Cell 26
Interphase has three stages. 26
Cell division by mitosis occurs in four stages. 27
Cytokinesis divides the cytoplasm. 30
2-5 Mitosis Is Essential for Growth and Cell Replacement 30
2-6 Cell Division by Meiosis: The Basis of Sex 31
Meiosis I reduces the chromosome number. 31
Meiosis II begins with haploid cells. 31
Meiosis produces new combinations of genes in two ways. 32
2-7 Formation of Gametes 35

3 Transmission of Genes from Generation to Generation 42
3-1 Mom, Murder, and MMA 42
3-2 Heredity: How Are Traits Inherited? 43
3-3 Mendel's Experimental Design Resolved Many Unanswered Questions 44
3-4 Crossing Pea Plants: Mendel's Study of Single Traits 45
What were the results and conclusions from Mendel's first series of crosses? 45
The principle of segregation describes how a single trait is inherited. 47
Exploring Genetics: Ockham's Razor 48
3-5 More Crosses with Pea Plants: The Principle of Independent Assortment 49
Mendel's crosses involving two traits. 49
Analyzing the results and drawing conclusions. 49
The principle of independent assortment explains the inheritance of two traits. 50
3-6 Meiosis Explains Mendel's Results: Genes Are on Chromosomes 52
Exploring Genetics: Evaluating Results: The Chi-Square Test 54
3-7 Mendelian Inheritance in Humans 54
Segregation and independent assortment occur with human traits. 55
Pedigree construction is an important tool in human genetics. 57
3-8 Variations on a Theme by Mendel 59
Incomplete dominance has a distinctive phenotype in heterozygotes. 60
Codominant alleles are fully expressed in heterozygotes. 61
Many genes have more than two alleles. 61
Genes can interact to produce unique phenotypes. 62

4 Pedigree Analysis in Human Genetics 68
4-1 Pedigrees and Dead Presidents 68
4-2 Pedigree Analysis Is a Basic Method in Human Genetics 69
There are five basic patterns of Mendelian inheritance. 70
Analyzing a pedigree. 70
4-3 Autosomal Recessive Traits 71
Cystic fibrosis is an autosomal recessive trait. 71
Exploring Genetics: Was Noah an Albino? 74

4-4 Autosomal Dominant Traits 75
Marfan syndrome is inherited as an autosomal dominant trait. 75
4-5 Sex-Linked Inheritance Involves Genes on the X and Y Chromosomes 76
X-linked dominant traits. 77
X-linked recessive traits. 77
Color blindness is an X-linked recessive trait. 78
Some forms of muscular dystrophy are X-linked recessive traits. 80
4-6 Paternal Inheritance: Genes on the Y Chromosome 81
4-7 Non-Mendelian Inheritance: Maternal Mitochondrial Genes 82
Exploring Genetics: Hemophilia and History 83
4-8 An Online Catalog of Human Genetic Traits Is Available 84
4-9 Many Factors Can Affect the Outcome of Pedigree Analysis 85
Phenotypes are often age-related. 85
Penetrance and expressivity cause variations in phenotype. 85
Common recessive alleles can produce pedigrees that resemble dominant inheritance. 86

5 The Inheritance of Complex Traits 92
5-1 All the King's Men 92
5-2 Polygenic Traits Are Controlled by Two or More Genes 93
Phenotypes can be discontinuous or continuous. 93
What are complex traits? 95
5-3 Complex Traits and Variation in Phenotype 95
Defining the genetics behind continuous phenotypic variation. 95
How many genes control a complex polygenic trait? 96
5-4 The Additive Model for Complex Traits 97
Averaging out the phenotype is called regression to the mean. 98
5-5 Multifactorial Traits: Multiple Genes and Environmental Effects 98
The Genetic Revolution: Dissecting Genes and Environment in Spina Bifida 99
Several methods are used to study complex traits. 100
5-6 Heritability Measures the Genetic Contribution to Phenotypic Variation 101
Heritability estimates are based on known levels of genetic relatedness. 101
5-7 Twin Studies and Complex Traits 102
The biology of monozygotic and dizygotic twins. 102
Concordance rates in twins. 103
We can study complex traits such as obesity using twins and family studies. 104
What are some genetic clues to obesity? 105
Animal models and single genes for obesity. 105
Scanning the genome for obesity-related genes. 106
5-8 Genetics of Height: A Closer Look 107
Haplotypes and genome-wide association studies. 107
Genes for human height: what have we learned so far? 108
5-9 Skin Color and IQ Are Complex Traits 108
Skin color is a complex trait. 108
Intelligence and intelligence quotient (IQ): are they related? 109
IQ values are heritable traits. 110
What is the controversy about IQ and race? 110
Scientists are searching for genes that control intelligence. 111

6 Cytogenetics: Karyotypes and Chromosome Aberrations 116

6-1 Facing a Life-Changing Decision 116

6-2 The Human Chromosome Set 117

6-3 Making a Karyotype 120

6-4 Analyzing Karyotypes 121

What cells are obtained for chromosome studies? 122

Amniocentesis collects cells from the fluid surrounding the fetus. 122

Chorionic villus sampling retrieves fetal tissue from the placenta. 124

Noninvasive prenatal diagnosis 125

6-5 Variations in Chromosome Number 126

Chromosome abnormalities in humans are common. 126

Polyploidy changes the number of chromosomal sets. 126

Triploidy. 127

Tetraploidy. 127

Aneuploidy changes the number of individual chromosomes. 127

Autosomal monosomy is a lethal condition. 128

Autosomal trisomy is relatively common. 128

Trisomy 13: Patau syndrome (47,+13). 128

Trisomy 18: Edwards syndrome (47,+18). 129

Trisomy 21: Down syndrome (47,+21). 129

6-6 What Are the Risks for Autosomal Trisomy? 130

Maternal age is the leading risk factor for trisomy. 130

Why is maternal age a risk factor? 131

6-7 Sex Chromosome Aneuploidy 131

Turner syndrome (45,X). 132

Klinefelter syndrome (47,XXY). 132

XYY syndrome (47,XYY). 132

What can we conclude about sex-chromosome aneuploidy? 133

6-8 Structural Changes Within and Between Chromosomes 134

Deletions involve loss of chromosomal material. 134

Translocations involve exchange of chromosomal parts. 135

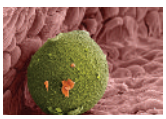
6-9 What Are Some Consequences of Aneuploidy? 136

6-10 Other Forms of Chromosome Changes 137

Uniparental disomy. 137

Copy number variation. 137

Fragile sites appear as gaps or breaks in chromosomes. 139



7 Development and Sex Determination 144

7-1 Sex: Is It Nature or Nurture? 144

7-2 The Human Reproductive System 145

The male reproductive system. 146

The female reproductive system. 148

There are differences in the timing of meiosis and gamete formation in males and females. 150

7-3 A Survey of Human Development from Fertilization to Birth 151
Development is divided into three trimesters. 153
Organ formation occurs in the first trimester. 153
The second trimester is a period of organ maturation. 153
Rapid growth takes place in the third trimester. 154
Birth is hormonally induced. 155

7-4 Teratogens Are a Risk to the Developing Fetus 156
Radiation, viruses, and chemicals can be teratogens. 156
Fetal alcohol syndrome is a preventable tragedy. 157

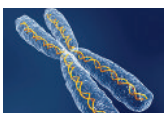
7-5 How Is Sex Determined? 158
Environmental interactions can help determine sex. 158
Chromosomes can help determine sex. 158
The human sex ratio changes with stages of life. 158

7-6 Defining Sex in Stages: Chromosomes, Gonads, and Hormones 159
Exploring Genetics: Sex Testing in the Olympics—Biology and a Bad Idea 160
Sex differentiation begins in the embryo. 161
Hormones help shape male and female phenotypes. 161

7-7 Mutations Can Uncouple Chromosomal Sex from Phenotypic Sex 163
Androgen insensitivity can affect the sex phenotype. 163
Mutations can cause sex phenotypes to change at puberty. 164

7-8 Equalizing the Expression of X Chromosome Genes in Males and Females 164
Dosage compensation makes XX equal XY. 164
Mice, Barr bodies, and X inactivation can help explain dosage compensation. 165
Mammalian females can be mosaics for X chromosome gene expression. 165
How and when are X chromosomes inactivated? 167

7-9 Sex-Related Phenotypic Effects 167
Sex-influenced traits. 167
Sex-limited traits. 168



8 The Structure, Replication, and Chromosomal Organization of DNA 172

8-1 Are DNA Vaccines the Answer? 172

8-2 DNA Is the Carrier of Genetic Information 173
DNA can transfer genetic traits between bacterial strains. 174
DNA carries genetic information in viruses. 175

8-3 The Chemistry of DNA 176
Understanding the structure of DNA requires a review of some basic chemistry. 176
Nucleotides are the building blocks of nucleic acids. 177

8-4 The Watson–Crick Model of DNA Structure 178

8-5 RNA Is a Single-Stranded Nucleic Acid 182
The Genetic Revolution: What Happens When Your Genes Are Patented? 182

8-6 DNA Replication Depends on Complementary Base Pairing 183
Stages of DNA replication. 184

8-7 The Organization of DNA in Chromosomes 185
Chromosomes have a complex structure. 185
Centromeres and telomeres are specialized chromosomal regions. 187
The nucleus has a highly organized architecture. 187

9 Gene Expression and Gene Regulation 192

9-1 Cows as a Cause of Death 192

9-2 The Link Between Genes and Proteins 193
How are genes and enzymes related? 193
Genetic information is stored in DNA. 194
The relationship between genes and proteins. 194

9-3 The Genetic Code: The Key to Life 194

9-4 Tracing the Flow of Genetic Information from Nucleus to Cytoplasm 196

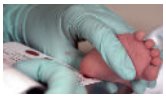
9-5 Transcription Produces Genetic Messages 196
Messenger RNA is processed and spliced. 198

9-6 Translation Requires the Interaction of Several Components 199
Amino acids are subunits of proteins. 199
Messenger RNA, ribosomal RNA, and transfer RNA interact during translation. 200
Translation produces polypeptides from information in mRNA. 201
Exploring Genetics: Antibiotics and Protein Synthesis 204

9-7 Polypeptides Are Processed and Folded to Form Proteins 204
How many proteins can human cells make? 204
Proteins are sorted and distributed to their cellular locations. 205

9-8 Protein Structure and Function Are Related 206
Improper protein folding can be a factor in disease. 207

9-9 Several Mechanisms Regulate the Expression of Genes 208
Chromatin remodeling and access to promoters. 209
DNA methylation can silence genes. 209
RNA silencing controls gene expression in several ways. 209
Translational and post-translational mechanisms regulate the production of proteins. 210



10 From Proteins to Phenotypes 214

10-1 Protein Malfunctions Cause Genetic Disorders 214

10-2 Proteins Are the Link Between Genes and the Phenotype 215

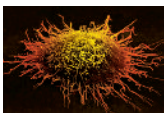
10-3 Enzymes and Metabolic Pathways 216

10-4 Phenylketonuria: A Mutation That Affects an Enzyme 217
How is the metabolism of phenylalanine related to PKU? 217
How does the buildup of phenylalanine produce intellectual disability? 219
PKU can be treated with a diet low in phenylalanine. 219
The Genetic Revolution: PKU 220
How long must a PKU diet be maintained? 220
What happens when women with PKU have children? 221

10-5 Other Metabolic Disorders in the Phenylalanine Pathway 221

10-6 Genes and Enzymes of Carbohydrate Metabolism 221
Galactosemia is caused by an enzyme deficiency. 223
Lactose intolerance is a genetic variation. 223
10-7 Defects in Transport Proteins: Hemoglobin 223
Hemoglobin disorders. 225
Sickle cell anemia is an autosomal recessive disorder. 226
Treatment for sickle cell anemia includes drugs for gene switching. 227
Exploring Genetics: The First Molecular Disease 228
10-8 Pharmacogenetics and Pharmacogenomics 228
Taste and smell differences: we live in different chemosensory worlds. 229
Drug sensitivities are genetic traits. 231
Sensitivity to anesthetics. 231
Allele variations and breast cancer therapy. 231
10-9 Ecogenetics 232
What is ecogenetics? 233
Sensitivity to pesticides varies widely in different populations. 233

11 Genome Alterations: Mutation and Epigenetics 238
11-1 Are Some Flame Retardants Dangerous? 238
11-2 Mutations Are Heritable Changes in DNA 239
11-3 Detecting Mutations and Measuring Mutation Rates 240
Mutations and pedigree analysis. 240
Measuring mutation rates. 241
Why do some genes have different mutation rates? 241
11-4 Mutations Can Be Spontaneous or Induced 242
Errors in DNA replication cause spontaneous mutations. 242
Chemical changes in bases can cause mutations. 243
Radiation is a source of mutations. 243
How much radiation are we exposed to? 243
Chemicals can cause mutations. 244
Base analogs. 244
Exploring Genetics: What About Irradiated Food? 245
Chemical modification of bases. 245
11-5 Mutations at the Molecular Level: DNA as a Target 246
Many hemoglobin mutations are caused by nucleotide substitutions. 246
Frameshift mutations are caused by nucleotide deletions and insertions. 247
Mutations can involve more than one nucleotide. 248
11-6 Mutations Can Be Repaired 249
Cells have several DNA repair systems. 249
Genetic disorders can affect DNA repair systems. 250
11-7 Mutations, Genotypes, and Phenotypes 251
11-8 Epigenetic Changes Involve Reversible Alterations to the Genome 252
DNA is modified by epigenetic changes. 253
What is imprinting? 254
Genetic imprinting is involved in genetic disorders. 254
Epigenetics and behavior. 256



12 Genes and Cancer 262

12-1 Decisions About Cancer Testing 262

12-2 Cancer Is a Genetic Disease 263

12-3 Cancer Begins in a Single Cell 264

12-4 Cancer Develops in Several Steps 265

12-5 Cancer-Causing Mutations Disrupt Cell-Cycle Regulation 266

12-6 Two Classes of Cell-Cycle Regulatory Genes Are Involved in Cancer 268
- The *RB1* tumor-suppressor gene controls the G1/S checkpoint. 268
- The *ras* genes are proto-oncogenes that regulate cell growth and division. 269

12-7 Mutant Cancer Alleles Impair DNA Repair Systems and Genome Stability 270
- Mutant DNA repair genes cause a predisposition to breast cancer. 270
- *BRCA1* and *BRCA2* are DNA repair genes. 271
- Breast cancer risks depend on genotype. 271

12-8 Colon Cancer Is a Model for the Development of Cancer 271
- FAP causes chromosome instability and colon cancer. 272
- HNPCC is caused by DNA repair defects. 273

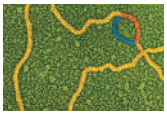
12-9 Hybrid Genes and Cancer 274
- Some chromosome rearrangements cause leukemia. 274

12-10 Genomics, Epigenetics, and Cancer 276
- Sequencing cancer genomes identifies cancer-associated genes. 276
- Epigenetics and cancer. 277
- New therapies for treating cancer. 277

Exploring Genetics: The Cancer Genome Atlas (TCGA) 279

12-11 Cancer and the Environment 280

The Genetic Revolution: Cancer Stem Cells 280
- Some viral infections lead to cancer. 281
- What other environmental factors are related to cancer? 281



13 An Introduction to Genetic Technology 286

13-1 Making Choices About Biotechnology 286

13-2 What Are Clones? 287
- Animals can be cloned by several methods. 287

13-3 Cloning Genes Is a Multistep Process 289
- DNA can be cut at specific sites using restriction enzymes. 290
- Vectors serve as carriers of DNA to be cloned. 291
- Recombinant DNA molecules are inserted into host cells for cloning. 291

13-4 Cloned Libraries 292

13-5 Finding a Specific Gene in a Library 292

Exploring Genetics: Asilomar: Scientists Get Involved 293

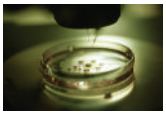
13-6 A Revolution in Cloning: The Polymerase Chain Reaction 295

13-7 Analyzing Cloned Sequences 296
- The Southern blot technique can be used to analyze cloned sequences. 296
- DNA sequencing is one form of genome analysis. 297

Exploring Genetics: DNA Sequencing 300
13-8 DNA Microarrays Are Used to Analyze Gene Expression 300

14 Biotechnology and Society 306
14-1 The Origin of DNA Profiles 306
14-2 Biopharming: Making Human Proteins in Animals 307
Human proteins can be made in animals. 308
Transgenic plants may replace animal hosts for making human proteins. 309
14-3 Using Stem Cells to Treat Disease 309
Stem cells provide insight into basic biological processes. 310
Stem-cell-based therapies may treat many diseases. 311
14-4 Genetically Modified Foods 312
Transgenic crop plants can be made resistant to herbicides and disease. 312
Enhancing the nutritional value of foods. 312
Functional foods and health. 314
What are some concerns about genetically modified organisms? 314
14-5 Transgenic Animals as Models of Human Diseases 315
Scientists use animal models to study human diseases. 316
14-6 DNA Profiles as Tools for Identification 316
Making DNA profiles. 316
DNA profiles are used in forensics. 317
DNA profiles have many other uses. 318
Exploring Genetics: Death of a Czar 319
14-7 Social and Ethical Questions About Biotechnology 320

15 Genomes and Genomics 324
15-1 Genomics and Personalized Medicine 324
15-2 Genome Sequencing Is an Extension of Genetic Mapping 325
Recombination frequencies are used to make genetic maps. 326
Linkage and recombination can be measured by lod scores. 328
Recombinant DNA technology radically changed gene-mapping efforts. 328
15-3 Genome Projects Are an Outgrowth of Recombinant DNA Technology 329
15-4 Genome Projects Have Created New Scientific Fields 331
15-5 Genomics: Sequencing, Identifying, and Mapping Genes 332
Scientists can analyze genomic information with bioinformatics. 333
Annotation is used to find where the genes are. 333
As genes are discovered, the functions of their encoded proteins are studied. 335
15-6 What Have We Learned So Far About the Human Genome? 335
New disease-related types of mutations have been discovered. 335
Nucleotide variation in genomes is common. 336
15-7 Using Genomics to Study a Human Genetic Disorder 337
15-8 The Human Microbiome Is Our Other Genome 338
15-9 Proteomics Is an Extension of Genomics 339
15-10 Ethical Concerns About Human Genomics 339
Exploring Genetics: Who Owns Your Genome? 340



16 Reproductive Technology, Genetic Testing, and Gene Therapy 344

16-1 Genetic Technology and Reproduction 344

16-2 Infertility Is a Common Problem 345
- Infertility is a complex problem. 345
- Infertility in women has many causes. 346
- Infertility in men involves sperm defects. 346
- Other causes of infertility. 347

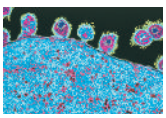
16-3 Assisted Reproductive Technologies (ART) Expand Childbearing Options 347
- Intrauterine insemination uses donor sperm. 347
- Egg retrieval or donation is an option. 349
- In vitro fertilization (IVF) is a widely used form of ART. 349
- GIFT and ZIFT are based on IVF. 350
- Surrogacy is a controversial form of ART. 350

16-4 Ethical Issues in Reproductive Technology 351
- The use of ART carries risks to parents and children. 351

16-5 Genetic Testing and Screening 352
- Exploring Genetics: The Business of Making Babies 353
- Newborn screening is universal in the United States. 353
- Both carrier and prenatal testing are done to screen for genetic disorders. 353
- The use of PGD raises ethical issues. 355
- Prenatal testing is associated with risks. 356

16-6 Therapy for Genetic Disorders 356
- What are the strategies for gene transfer? 357
- Gene therapy showed early promise. 357
- Recent successes in gene therapy. 358
- Exon skipping and gene therapy. 358
- There are ethical issues associated with gene therapy. 360
- Gene doping is a controversial form of gene therapy. 361

16-7 Genetic Counseling Assesses Reproductive Risks 361
- Why do people seek genetic counseling? 362
- How does genetic counseling work? 362



17 Genes and the Immune System 366

17-1 Components of the Immune System Are Genetically Controlled 366

17-2 The Body Has Three Levels of Defense Against Infection 367
- The skin is not part of the immune system but is the first level of defense. 367
- There are two parts to the immune system that protect against infection. 368

17-3 The Inflammatory Response Is a General Reaction 368
- Genetic disorders cause inflammatory diseases. 368

17-4 The Complement System Kills Microorganisms 370

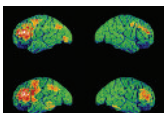
17-5 The Adaptive Immune Response Is a Specific Defense Against Infection 371
- How does the immune response function? 371
- The antibody-mediated immune response involves several stages. 372

Antibodies are molecular weapons against antigens. 374
T cells mediate the cellular immune response. 375
The immune system has a memory function. 376

17-6 Blood Types Are Determined by Cell-Surface Antigens 377
ABO blood typing allows for safe blood transfusions. 377
Rh blood types can cause immune reactions between mother and fetus. 378

17-7 Organ Transplants Must Be Immunologically Matched 378
Successful transplants depend on HLA matching. 379
Biotechnology makes xenotransplants possible. 380

17-8 Disorders of the Immune System 381
Overreaction in the immune system causes allergies. 381
Exploring Genetics: Peanut Allergies Are Increasing 382
Autoimmune reactions cause the immune system to attack the body. 383
Genetic disorders can impair the immune system. 383
HIV attacks the immune system. 384
Are some people more resistant or more susceptible to HIV infection? 384



18 Genetics of Behavior 390

18-1 Human Behavior Is a Complex Trait 390

18-2 Models, Methods, and Phenotypes in Studying Behavior 391
There are several genetic models for inheritance and behavior. 391
Defining behavior and its phenotypes. 392
Exploring Genetics: Is Going to Medical School a Genetic Trait? 393

18-3 The Nervous System Is the Focus of Behavior Genetics 394
Synapses interconnect cells in the nervous system. 395
Synapses are involved in many human behavioral disorders. 396

18-4 Single-Gene Mutations Cause Behavioral Disorders 397
A synaptic malfunction underlies these behaviors. 397

18-5 Huntington Disease Is a Model for Neurodegenerative Disorders 398
The molecular basis of Huntington disease. 398

18-6 Animal Models: The Search for Behavior Genes 399
Transgenic animals are used as models of human neurodegenerative disorders. 399
A mouse model for Huntington disease. 399
Potential therapies for HD. 400

18-7 The Genetics of Complex Behavioral Disorders 400
Schizophrenia and bipolar disorder are complex traits with genetic and environmental contributions. 400
Genetic models for schizophrenia and bipolar disorders. 401
Genomic approaches to schizophrenia and bipolar disorder. 402
At least five behavioral disorders share a genetic relationship. 402
Epigenetics and mental illness. 403

18-8 Genetics and Social Behavior 403
Alzheimer disease is a complex disorder. 404
Genomic approaches in AD. 405
Addictive behavior has genetic and environmental components. 405

18-9 Summing Up: The Current Status of Human Behavior Genetics 407

19 Population Genetics and Human Evolution 412

19-1 Natural Selection Drives Evolution 412

19-2 How Can We Measure Allele Frequencies in Populations? 413
- We can use the Hardy–Weinberg law to calculate allele and genotype frequencies. 413
- Populations can be in genetic equilibrium. 414

19-3 Using the Hardy–Weinberg Law in Human Genetics 414
- Calculating the frequency of alleles and genotypes with the Hardy–Weinberg law. 414
- Heterozygotes for many genetic disorders are common in the population. 416
- Calculating the frequency of X-linked alleles. 416

19-4 Measuring Genetic Diversity in Human Populations 417
- Mutation generates new alleles but has little impact on allele frequency. 417
- Genetic drift can change allele frequencies 418
- Natural selection acts on variation in populations. 418

19-5 Natural Selection Affects the Frequency of Genetic Disorders 419
- Selection can rapidly change allele frequencies. 420

19-6 Genetic Variation in Human Populations 421
- Are there human races? 421

19-7 The Evolutionary History and Spread of Our Species (*Homo sapiens*) 424
- Our evolutionary heritage begins with hominids. 424
- Early humans emerged almost 5 million years ago. 424
- Our species, Homo sapiens, originated in Africa. 424
- Ancient migrations dispersed humans across the globe. 425

19-8 Genomics and Human Evolution 426
- The human and chimpanzee genomes are similar in many ways. 426

The Genetic Revolution: Tracing Ancient Migrations 427
- Neanderthals are closely related to us. 428
- Do we carry Neanderthal genes? 429
- Have we identified all our human relatives? 429

Appendix 435

Glossary 447

Index 457

Preface

Genetics is a relatively young science that has made major strides since the beginning of the twentieth century. A closer examination reveals that progress in genetics, like all science, moves forward in fits and starts. At the moment, unexpected discoveries are opening new subdisciplines, re-energizing old ones, and expanding the role of genetics as one of the foundations of biology. For example, epigenetics is providing answers to old questions and is rapidly emerging as an important field linking the environment with the genome and providing insights into the evolution of our species. New approaches in gene therapy offer hope that this field can finally live up to the hopes and expectations that it can be used to treat genetic disorders. Other findings are also rapidly moving from the laboratory to medical practice. These include discoveries about the role of stem cells in the development of cancer and the mobilization of the immune system to fight cancer. The contents of this edition, like the others that have preceded it, have been extensively rewritten and updated to reflect these discoveries, but as with past editions, the underlying rationale and aims have remained constant.

This book is written for a one-term human genetics course for students in humanities, social sciences, business, engineering, and other fields. It assumes that the students who come to this course will have little or no background in biology, chemistry, or mathematics and will have personal, professional, or intellectual reasons for wanting to learn something about human genetics. The book is also intended to serve those who will become *consumers* of genetic-based health care services and those who may become *providers* of health care services.

Because genetic knowledge and technology is rapidly being transferred to many areas of our society, it is imperative that the general public, elected officials, and policy makers outside the scientific community have a working knowledge of genetics to help shape how genetics and its associated technologies will be used in our society. To communicate this knowledge, *Human Heredity* is written to transmit the principles of genetics in a straightforward and accessible way, without unnecessary jargon, detail, or the use of anecdotal stories in place of research-based content. Some descriptive chemistry is used after an appropriate introduction and definition of terms. In the same vein, no advanced math skills are required to calculate elementary probabilities or to calculate genotype and allele frequencies.

Goals of the Text

From its beginnings, this book has held to a few simple goals for teaching students about human genetics. This edition continues that tradition with the following goals:

1. Present the concepts underlying human genetics in clear, concise, jargon-free language to give students a working knowledge of genetics. Each chapter presents a limited number of clearly stated concepts and examples to assist learning a complex topic.
2. Begin each chapter with a relevant example in the form of a case study that nonmajors can understand and which provides examples that students can apply to themselves, their families, and their work environments.

3. Examine the social, cultural, and ethical implications associated with the use of genetic technology.
4. Explain the origin, nature, and amount of genetic diversity present in the human population and how that diversity has been shaped by natural selection.

To achieve these goals, emphasis has been placed on clear writing and the use of accompanying photographs and artwork that teach rather than merely illustrate the ideas under discussion.

Organization

Although it is without formal divisions, the text is organized into four sections: Chapters 1 through 7 cover cell division, transmission of traits from generation to generation, and development. Chapters 8 through 12 emphasize molecular genetics, mutation, and cancer. Chapters 13 through 16 include recombinant DNA technology, genomics, and biotechnology. These chapters cover the basic methods of genetic technology and how they are used in agriculture, medicine, and the biotechnology industry. In addition, these chapters cover genetic screening, genetic testing, and genetic counseling. Chapters 17 through 19 cover specialized topics: the immune system, the genetics of behavior, and population genetics and human evolution.

Instructors teaching genetics to nonmajors come from many different backgrounds and use a wide range of instructional formats, including active learning, peer-to-peer instruction, and adaptive learning. To facilitate this array of approaches, the book is organized to allow both students and instructors to use the material no matter what order of topics is selected. After the first section, the chapters can be used in any order. Within each chapter, outlines and end-of-chapter activities let the instructor and students easily identify and explore central ideas.

What's New in the Eleventh Edition

Each chapter has been updated to reflect the latest advances in genetics. Listed below are some of the most significant revisions in this edition.

Chapter 1: A Perspective on Human Genetics

- New chapter opening photo
- New opening case study on translational medicine
- Revised and updated text throughout

Chapter 2: Cells and Cell Division

- Text edited throughout for clarity
- Revised Figure 2.6 The Nucleus
- Revised Figure 2.7 The Cell Cycle

Chapter 3: Transmission of Genes from Generation to Generation

- Revised Section 3-3 Mendel's Experimental Design
- Revised Section 3-4 Crossing Pea Plants

Chapter 4: Pedigree Analysis in Human Genetics

- New chapter opening photo
- Edited and revised Section 4-2 Pedigree Analysis
- Revised Section 4-3 Autosomal Recessive Traits
- Revised Section 4-4 Autosomal Dominant Traits
- Replaced Figure 4.20 OMIM Home Page
- Redrawn Figure 4.23 Common Autosomal Trait

Chapter 5: The Inheritance of Complex Traits

- Revised Section 5-2 Polygenic Traits Are Controlled by Two or More Genes
- Revised Section 5-3 Complex Traits and Variation in Phenotype
- Revised Section 5-9 Skin Color and IQ Are Complex Traits

- Replaced and updated Figure 5.12 Obesity in the United States
- New Figure 5.17 Skin Color and Latitude

Chapter 6: Cytogenetics: Karyotypes and Chromosome Aberrations

- Revised Section 6-2 The Human Chromosome Set
- Section 6-4 Analyzing Karyotypes, new subsection on noninvasive prenatal diagnosis
- Revised Section 6-7 Sex Chromosome Aneuploidy
- New Figure 6.1 Human Chromosome
- New Figure 6.2 Telomeres
- New Figure 6.12 Free Fetal DNA

Chapter 7: Development and Sex Determination

- New chapter opening photo
- Revised Section 7-2 The Human Reproductive System
- Revised Section 7-3 Human Development
- Revised Figure 7.10 Sex Determination
- Revised Figure 7.11 The Segregation of Sex Chromosomes

Chapter 8: The Structure, Replication, and Chromosomal Organization of DNA

- Revised Section 8-3 The Chemistry of DNA
- Revised Section 8-6 DNA Replication

Chapter 9: Gene Expression and Gene Regulation

- Revised Section 9-4 Tracing the Flow of Genetic Information
- Revised Section 9-6 Translation Requires the Interaction of Several Components
- Revised Section 9-9 Several Mechanisms Regulate the Expression of Genes
- New Figure 9.5 mRNA Processing
- New Figure 9.8 Transfer RNA Molecule
- New Figure 9.13 Prion Protein Folding
- Revised Table 9.2 Amino Acids Commonly Found in Proteins

Chapter 10: From Proteins to Phenotypes

- Revised Section 10-4 Phenylketonuria: A Mutation That Affects an Enzyme
- Revised Section 10-8 Pharmacogenetics and Pharmacogenomics

Chapter 11: Genome Alterations: Mutation and Epigenetics

- Reorganized and revised entire chapter
- Revised and expanded Section 11-3 Detecting Mutations and Measuring Mutation Rates
- New Section 11-4 Mutations Can Be Spontaneous or Induced
- Revised Section 11-5 Mutations at the Molecular Level
- Revised Section 11-6 Mutations Can Be Repaired
- Revised Section 11-8 Epigenetic Changes
- New Figure 11.4 Errors in DNA Replication
- New Figure 11.5 Base Pairing in Tautomeric Shifts
- New Figure 11.13 Proofreading in DNA Polymerase
- Revised Figure 11.14 Base-Pair Substitutions
- New Figure 11.15 A DNA Repair System
- New Figure 11.19 Epigenetic Changes to DNA
- New Figure 11.24 The Hypothalamus

Chapter 12: Genes and Cancer

- Revised Section 12-5 Cancer-Causing Mutations
- Revised Section 12-7 Mutant Cancer Alleles
- Revised Section 12-10 Genomics, Epigenetics, and Cancer
- Revised Figure 12.5 The Eukaryotic Cell Cycle
- New Figure 12.6 Normal and Mutant Tumor-Suppressor Genes
- Revised Figure 12.16 Gene Fusion in 9;22 Translocation
- New Figure 12.19 Cigarette Consumption and Lung Cancer
- Updated Table 12.1 Estimated New Cancer Cases
- Updated Table 12.3 Colorectal Cancer in the United States
- New Table 12.7 Cancer-Related Genes Inactivated by Hypermethylation

Chapter 13: An Introduction to Genetic Technology

- Revised Section 13-5 Finding a Specific Gene in a Library
- New Figure 13.12 Extinct Ground Sloth

Chapter 14: Biotechnology and Society

- Revised Section 14-6 DNA Profiles as Tools for Identification
- Revised Table 14.1 Some Products Made by Recombinant DNA Technology

Chapter 15: Genomes and Genomics

- Revised Section 15-6 What Have We Learned So Far About the Human Genome?
- New Section 15-8 The Human Microbiome Is Our Other Genome
- Revised Section 15-9 Proteomics Is an Extension of Genomics
- Revised Figure 15.5 History and Timeline for Genome Projects
- New Figure 15.11 Single Nucleotide Polymorphisms
- New Figure 15.14 Body Sites Sampled for Human Microbiome Project

Chapter 16: Reproductive Technology, Genetic Testing, and Gene Therapy

- Revised Section 16-3 Assisted Reproductive Technologies
- Revised Section 16-5 Genetic Testing and Screening
- Section 16-6 Therapy for Genetic Disorders, new subsection on exon skipping therapy
- New Figure 16.7 Stages in the IVF Procedure
- New Figure 16.8 Injection of Single Sperm into Egg
- Revised Figure 16.16 Gene Therapy
- New Figure 16.17 Exon Skipping
- Revised and updated Figure 16.18 Gene Therapy Clinical Trials 2014
- New Table 16.3 History of Gene Therapy

Chapter 17: Genes and the Immune System

- Revised Section 17-7 Organ Transplants Must Be Immunologically Matched
- Revised Section 17-8 Disorders of the Immune System
- New Figure 17.16 Herrick Twins
- New Figure 17.18 Jim Finn
- New Figure 17.19 Allergic Response
- Revised Table 17.5 Some Autoimmune Diseases

Chapter 18: Genetics of Behavior

- Reorganized and revised
- Revised Section 18-2 Models, Methods, and Phenotypes in Studying Behavior
- New Section 18-3 The Nervous System Is the Focus of Behavior Genetics
- Revised Section 18-4 Single-Gene Mutations Cause Behavioral Disorders
- Revised Section 18-5 Huntington Disease Is a Model for Neurogenerative Disorders
- Revised Section 18-6 Animal Models: The Search for Behavior Genes
- Revised Section 18-7 The Genetics of Complex Behavioral Disorders
- Section 18-8 Genetics and Social Behavior, new subsection on addictive behavior
- New Figure 18.2 The Human Nervous System
- New Figure 18.3a Synapses and Synaptic Transmission
- New Figure 18.11 Genetic Relationship Between Psychiatric Disorders
- New Figure 18.14 Heritability of Addictive Behaviors
- Revised Figure 18.15 Metabolism of Alcohol
- Revised Table 18.2 Selected Neurotransmitters and Some Processes They Affect
- New Table 18.3 Selected Recreational Drugs and the Neurotransmitters They Mimic
- New Table 18.4 Some Behavioral Disorders Associated with Synaptic Defects
- New Table 18.5 Important Risk Factor Genes for Alzheimer Disease
- New Table 18.6 Genes Involved in Nicotine Addiction

Chapter 19: Population Genetics and Human Evolution

- Revised Section 19-7 The Evolutionary History and Spread of Our Species
- Revised Section 19-8 Genomics and Human Evolution
- New Figure 19.11 Hominin Evolution
- New Figure 19.14 Cave in Denisova, Siberia

Features of the Book

Numbered Chapter Outlines

The beginning of each chapter contains an outline of the primary headings, providing an overview of the main concepts, secondary ideas, and examples. To help students grasp the central points, many of the headings are written as narratives or summaries of the ideas that follow. These outlines also serve as convenient starting points for students to review the material in each chapter. To make the outlines more useful, they have been numbered sequentially and used to organize the summary, the questions, and the problems at the end of each chapter. In this way, students can relate examples and questions to specific topics in the chapter more easily and clearly.

First Section Case Studies

The first section of each chapter contains a case study that is directly related to the main ideas of the chapter, often drawn from real life. Topics include the use of DNA fingerprinting in court cases, the cloning of milk cows, the use of exome sequencing to diagnose a genetic disorder, and the development of *in vitro* fertilization (IVF) and the birth of Louise Brown—the first IVF baby. These case studies are designed to promote student interest in the topics covered in the chapter and to demonstrate that laboratory research often has a direct impact on everyday life. These case studies are linked to another case presented in the ***Genetics in Practice*** section at the end of the chapter.

The Genetic Revolution

The Genetic Revolution is a feature that emphasizes the past, present, and future impact of genetic technology on our daily lives, from genetic testing at birth to the future of cancer therapy. Accompanying questions are designed to be used for classroom discussion, research topics, and student presentations.

Exploring Genetics

Exploring Genetics feature boxes present ideas and applications that are related to and extend the central concepts in a chapter. Some of these examine controversies that arise as genetic knowledge is transferred into technology and services. Accompanying questions are designed to be used for classroom discussion, research topics, and student presentations.

Marginal Glossary

A glossary in the page margins gives students immediate access to definitions of terms as they are introduced in the text. This format also allows definitions to be identified when students are studying or preparing for examinations. The definitions have been gathered into an alphabetical glossary at the back of the book. Because an understanding of the concepts of genetics depends on understanding the relevant terms, more than 350 terms are included in the glossary.

End-of-Chapter Features

Genetics in Practice: Relevant Case Studies

A case study is included at the end of each chapter, illustrating the impact of genetics in our society. These contain scenarios and examples of genetic issues related to health, reproduction, personal decision making, public health, and ethics. Many of the case studies and the accompanying questions can be used for classroom and other activities.

Summary

Each chapter ends with a summary that restates the major ideas covered in the chapter. The beginning outline and ending summary for each chapter use the same content and

order to emphasize major concepts and their applications. Each point of the summary outline is followed by a brief restatement of the chapter material covered under the same heading. This helps students recall the concepts, topics, and examples presented in the chapter. It is hoped that this organization will minimize the chance that they will attempt to learn by rote memorization.

Questions and Problems

The summary's focus on the chapter's main points is continued in the ***Questions and Problems*** at the end of each chapter. The questions and problems are presented under the headings from the chapter outline. This allows students to relate the problems and questions to specific topics presented in the chapter, focus on concepts they find difficult, and work the problems that illustrate those topics. The questions and problems are designed to test students' knowledge of the facts and their ability to reason from the facts to conclusions. To this end, they use an objective question format and a problem-solving format. Because some quantitative skills are necessary in human genetics, almost all chapters include some problems that require students to organize the concepts in the chapter and use those concepts in reasoning to a conclusion. Answers to selected problems are provided in an appendix. Answers to all questions and problems are available in the Instructor's Manual on the password-protected Instructor Companion Site.

Pedagogical Features

Genomic Databases as Resources

To make students aware of the array of genomic resources available to them, genetic disorders mentioned in the book are referenced by their indexing numbers from the comprehensive catalog available online as *Online Mendelian Inheritance in Man* (*OMIM*). OMIM (updated daily) contains text, pictures, and videos, along with literature references. Through Entrez, OMIM is cross-linked to databases containing DNA sequences, protein sequences, chromosome maps, and other resources. Students and an informed public need to be aware of the existence and relevance of such databases, and to be up to date, textbooks must incorporate these resources.

Students can use OMIM to obtain detailed information about a genetic disorder, its mode of inheritance, its phenotype and clinical symptoms, mapping information, biochemical properties, the molecular nature of the disorder, and a bibliography of relevant papers. In the classroom, OMIM and its links are valuable resources for student projects and presentations.

Online Learning and Teaching Solutions

The online learning and teaching solutions that accompany this edition are designed to aid student learning as well as to assist the instructor in preparing lectures and examinations and in keeping abreast of the latest developments in the field. Instructor materials are available to qualified adopters. Please consult your local Cengage learning consultant for details. You may also visit the Brooks/Cole biology site at ***www.cengage.com/biology*** to see samples of these materials, request a desk copy, locate your learning consultant, or purchase a copy online.

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MindTap is a fully online, highly customizable learning experience built upon Cengage Learning content. MindTap combines student learning tools—readings, multimedia, activities, and assessments—into a singular Learning Path that guides students through their course. Instructors personalize the experience by customizing authoritative Cengage Learning content and learning tools, including the ability to add their own content in the Learning Path via apps that integrate into the MindTap framework seamlessly with Learning Management Systems. New to this edition! Chapter opening videos, assignable homework, and a digital Study Guide.

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- Cross-compatible capability. Import and export content into other systems.

Instructor Companion Site

Everything you need for your course in one place! This collection of book-specific lecture and class tools is available online via ***www.cengage.com/login***. Access and download PowerPoint presentations, images, instructor's manual, videos, and more.

Cooperative Learning: Making Connections in General Biology, Second Edition

A collection of separate, ready-to-use, short cooperative activities that have broad application for first-year biology courses. They fit perfectly with any style of instruction, whether in large lecture halls or flipped classrooms. The activities are designed to address a range of learning objectives, such as reinforcing basic concepts, making connections between various chapters and topics, data analysis and graphing, developing problem solving skills, and mastering terminology. Since each activity is designed to stand alone, this collection can be used in a variety of courses and with any text. Authored by Mimi Bres and Arnold Weisshaar.

A Problem-Based Guide to Basic Genetics

Provides students with a thorough and systematic approach to solving transmission genetics problems, along with numerous solved problems and practice problems. Written and illustrated by Donald Cronkite of Hope College.

Virtual Biology Laboratories: Genetics and Genetics 2 (Pedigree Analysis) Modules

These "virtual" online experiments expose students to the tools used in modern biology, support and illustrate lecture material, and allow students to "do" science by performing experiments, acquiring data, and using the data to explain biological phenomena.

Gene Discovery Lab

This is a CD-ROM lab manual that provides a virtual laboratory experience for the student in doing experiments in molecular biology. It includes experiments that use nine of the most common molecular techniques in biology, an overview of scientific method and experimental techniques, and Web links to provide access to data and other resources.

Acknowledgments

Over the course of eleven editions, many reviewers have given their time to improve the pedagogy, presentation of concepts, and ways of inspiring students. From edition to edition, a number of reviewers went to extraordinary lengths to keep my ideas and writing on the straight and narrow path and to make suggestions that have greatly improved the book. George Hudock of Indiana University, H. Eldon Sutton of the University of Texas, and Werner Heim of Colorado College generously gave me access to their collective wisdom, and helped me learn and relearn many of the nuances involved in writing about genetics. I am most grateful for their efforts.

In the last edition, Daniel Friderici of Michigan State University examined the text, figures, and problems from a student's point of view, and helped me present each chapter's important concepts in a straightforward and engaging way. In addition, I greatly appreciate his many suggestions on how to improve the end-of-chapter questions, problems, and how to frame the answers so that the questions become effective teaching tools. I am also very grateful to Patricia Matthews of Grand Valley State University who spent many hours scrutinizing the text, helping me clarify and streamline my writing, pointing out inconsistencies in word use, and improving the flow of ideas throughout the text.

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Elizabeth T. Wood, *University of Arizona*
Denise Woodward, *Pennsylvania State University*

At Cengage Learning, it was once again a pleasure to work with Peggy Williams, Senior Product Manager. Her vision about how to increase the pedagogical value of texts and her extensive knowledge of the market have strengthened and enhanced the book. Hal Humphrey was the content project manager who pulled together all the resources and people needed to put this edition together. The content developer, Suzannah Alexander, oversaw the preparation of this edition. Her attention to detail and gentle nudging kept the project on schedule.

Lauren Oliveira , Casey Lozier, and Kellie Petruzzelli coordinated the digital package for the book. Photo research was handled by Priya Subbrayal at PreMedia Global, whose hard work provided many excellent choices for photos.

Lynn Lustberg at MPS Limited eased the book through all the twists and turns involved in production.

Contacting the Author

I welcome questions and comments from faculty and students about the book or about questions and issues related to human genetics. Please contact me at: cummings.chicago@gmail.com.

Michael R. Cummings

Human Heredity

1 A Perspective on Human Genetics

CHAPTER OUTLINE

1-1 Genetics and Translational Medicine

1-2 Genetics Is the Key to Biology

1-3 What Are Genes and How Do They Work?

Exploring Genetics Genetic Disorders in Culture and Art

1-4 How Are Genes Transmitted from Parents to Offspring?

1-5 How Do Scientists Study Genes?

1-6 Has Genetics Affected Social Policy and Law?

1-7 What Impact Is Genomics Having?

1-8 What Choices Do We Make in the Era of Genomics and Biotechnology?

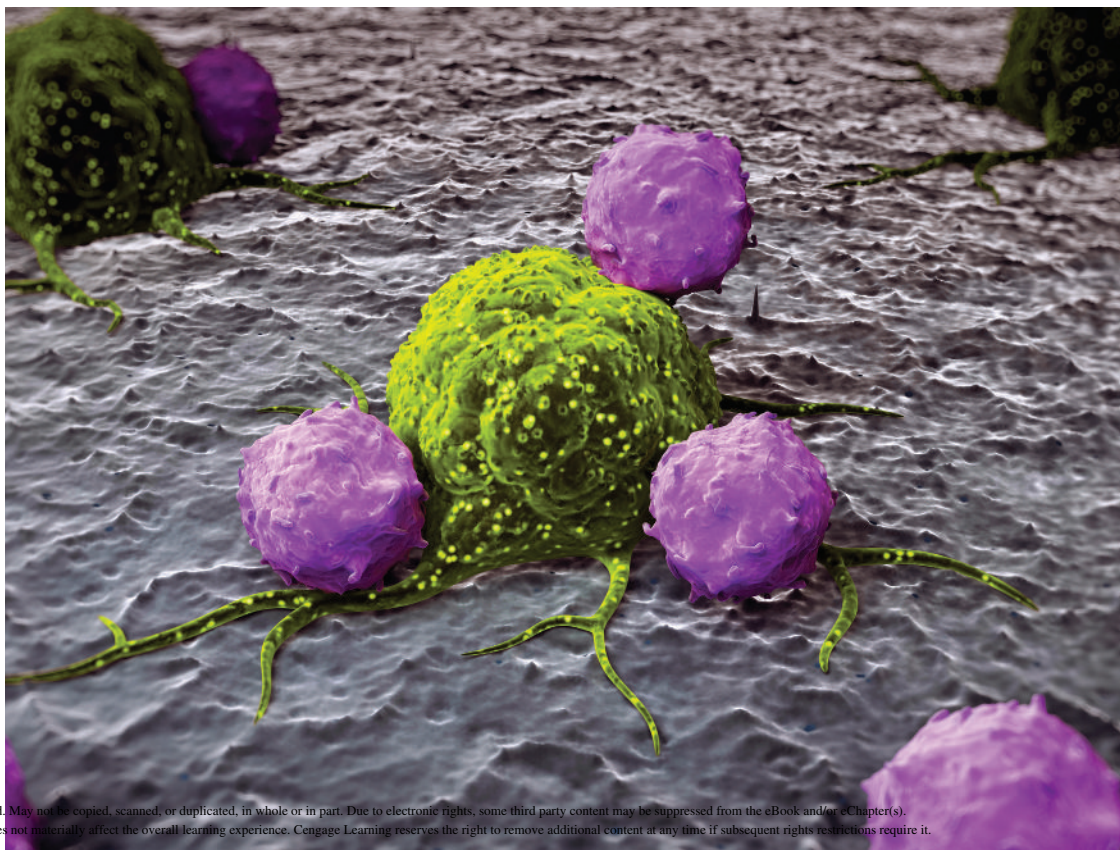
1-1 Genetics and Translational Medicine

CASE STUDY

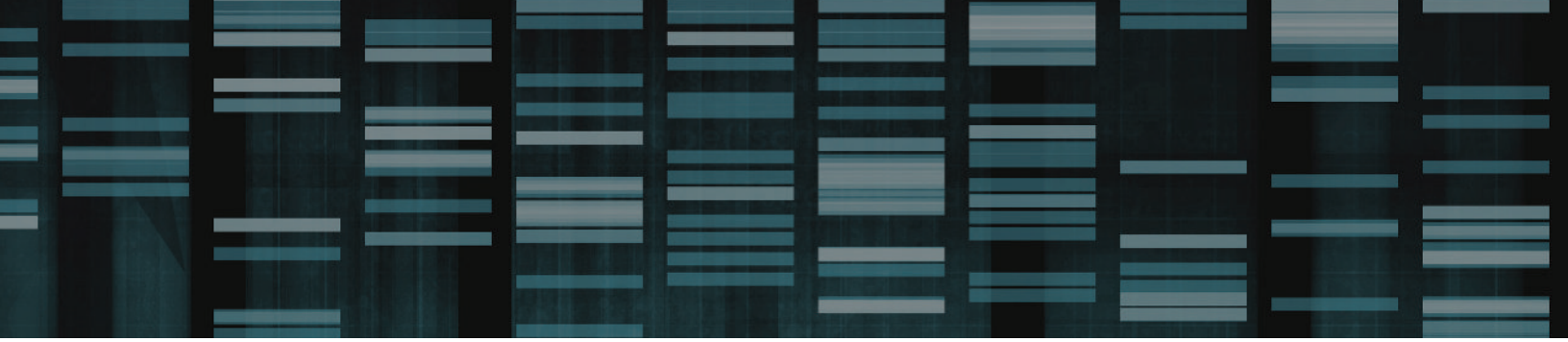
Cancer is a feared and devastating disease that will affect one in three Americans in their lifetime. Although the number of cancer deaths has declined in recent decades, one in four deaths in the United States is still caused by cancer. Because age is the greatest risk factor for cancer, more than 75% of new cancer cases occur in those who are 55 and older. This segment of the population is increasing in size, and, as a result, cancer may soon become the leading cause of death in the United States.

However, results from the Human Genome Project and the development of new technologies have revolutionized the detection, diagnosis, and treatment of cancer, offering optimism that the impact of cancer as a public health problem can be reduced. Researchers and clinicians are now working together to rapidly move new genetic discoveries from the laboratory to the hospital bedside, a process called **translational medicine**. The diagnosis and treatment of cancer is a high priority for many of those working in translational medicine.

Translational medicine The union of research and medicine that seeks to quickly translate research findings into methods for the diagnosis and treatment of diseases.



Cells of the immune system (purple) attacking a cancer cell (green).



One of the most promising new methods involves stimulating the immune system to identify, attack, and kill cancer cells. This method, called **immunotherapy**, is one example of how basic research on the immune system developed into one of the newest and most promising tools in cancer treatment.

Immunotherapy A method for treating disease by stimulating or enhancing an immune response.

The immune system is a collection of organs, cells, and molecules produced by these cells that help protect the body against infection by viruses, bacteria, and other disease-causing agents. The immune system works by attacking anything recognized as foreign, usually by first detecting molecules on the surface of invading viruses and cells and then mobilizing to attack and inactivate or kill the invader. Cancer cells often carry surface molecules that are not recognized by the immune system. Sometimes the immune system recognizes the cancer cells as foreign but does not respond strongly enough to kill all the malignant cells. Some cancers evade the immune system by producing molecules that repress the immune response.

Scientists at the University of Pennsylvania worked to reprogram immune cells so they would recognize, attack, and kill cancerous cells. Their target was abnormal immune system cells that cause leukemia. Basic research had discovered that normal white blood cells (called B cells) and cancerous B cells that cause leukemia carry a unique surface protein called CD-19. If immune cells could be reprogrammed to attack and kill all cells carrying this protein, the treatment might bring about remission. To do this, the scientists removed immune cells from a 64-year-old man with an advanced form of leukemia called CLL. In the laboratory, the immune cells were genetically reprogrammed by inserting a gene that encodes a surface protein that binds to the CD-19 protein and triggers the death of CLL cells. The immune cells also received instructions to produce chemical signals that would trigger multiplication of other immune cells to focus on total destruction of the leukemia cells.

After modification, the immune cells were returned to the affected man's body in the hope that they would identify and kill all the cancerous cells. For the first 2 weeks after treatment, there were no changes in the number of cancer cells, although blood tests showed a large increase in the number of genetically modified immune cells. However, on day 14, the patient developed chills, nausea, and fever and tumor cells began to die in large numbers. By 28 days after treatment, there were no signs of leukemia. This therapy was extended to two other patients with advanced forms of CLL. One patient experienced complete remission; the other had temporary remission, followed by a relapse and death. In spite of the small number of patients treated and one death, the results were considered a success. The only other available treatment was a bone marrow transplant, a procedure that has a 20% risk of death and only a 50% chance of success for the survivors.

This work spurred efforts by other research teams to develop similar methods to kill leukemia cells, and the field of immunotherapy was born. In 2013, the University of Pennsylvania team reported that 15 of 32 individuals with CLL responded to immunotherapy, with 7 showing complete remission. Treatment of individuals with a form of leukemia called ALL showed 86% remission in children and 100% remission at 6 months after treatment in adults. These encouraging results led a leading scientific journal to select cancer immunotherapy as the scientific breakthrough of the year for

2013. The University of Pennsylvania has entered into an agreement with a large pharmaceutical company to further develop and market immunotherapy.

Immunotherapy doesn't help everyone with cancer, and more research is needed to understand why. But the survival of so many individuals with advanced disease gives new hope that linking genetic research with clinical medicine will dramatically change the way cancer is treated.

1-2 Genetics Is the Key to Biology

Genetics The scientific study of heredity.

Trait Any observable property of an organism.

As the first step in studying human genetics, we should ask, what *is* genetics? As a working definition, we can say that **genetics** is the scientific study of heredity. Like all definitions, this leaves a lot unsaid. To be more specific, what geneticists do is study how **traits** (such as eye color and hair color) and diseases (such as cystic fibrosis and sickle cell anemia) are passed from generation to generation. They also study the molecules that make up genes and gene products as well as the way in which genes are turned on and off. Some geneticists study why variants of some genes occur more frequently in one population than in others. Other geneticists work in industry to develop products for agricultural and pharmaceutical firms. This work is part of the biotechnology industry, which is now a multi-billion-dollar component of the U.S. economy.

In a sense, genetics is the key to all of biology; genes control what cells look like and what they do as well as how babies develop and how we reproduce. An understanding of what genes are, how they are passed from generation to generation, and how they work is essential to our understanding of all life on Earth, including our species, *Homo sapiens*.

In the chapters that follow, we will ask and answer many questions about genetics: How are genes passed from parents to their children? What are genes made of? Where are they located? How do they encode products called proteins, and how do proteins create the differences among individuals that we can see and study? Because this book is about human genetics, we will use human genetic disorders as examples of inherited traits (see Exploring Genetics: Genetic Disorders in Culture and Art). We will also examine how genetic knowledge and genetic technology interact with and shape many of our social, political, legal, and ethical institutions and policies.

Items about some aspect of human genetics appear in the media on a daily basis. These stories may report the discovery of a gene responsible for a genetic disorder, a controversy about genetic testing, or a debate on the wisdom of genetically modifying our children. In many cases, as we will see, technology is far ahead of public policy and laws. To make informed decisions about genetics and biotechnology in your personal and professional life, you will need to have a foundation based on a knowledge of genetics. In the rest of this chapter, we will preview some of the concepts of human genetics that are covered in more detail later in the book and introduce some of the social issues and controversies generated by genetic research. Many of these concepts and issues are explored in more detail in the chapters that follow.

1-3 What Are Genes and How Do They Work?

Gene The fundamental unit of heredity and the basic structural and functional unit of genetics.

DNA A helical molecule consisting of two strands of nucleotides that is the primary carrier of genetic information.

Simply put, a **gene** is the basic structural and functional unit of genetics. In molecular terms, a gene is a string of chemical subunits (nucleotides) in a **DNA** molecule (**Figure 1.1**). (DNA is shorthand for deoxyribonucleic acid.) There are four different nucleotides in DNA, each composed of a sugar, a base, and a phosphate group. The nucleotides are abbreviated as single letters:

- A for adenine
- T for thymine
- G for guanine
- C for cytosine

EXPLORING GENETICS

Genetic Disorders in Culture and Art

It is difficult to pinpoint the time in history when the inheritance of specific traits in humans was first recognized. Descriptions of people with heritable disorders appear in myths and legends of many cultures. In some of these cultures, assigned social roles—from prophets and priests to kings and queens—were hereditary. The belief that certain traits were heritable helped shape the development of many social customs.

Steve Cole/Getty Images

In some societies, the birth of a deformed child was regarded as a sign of impending war or famine. Clay tablets excavated from Babylonian ruins record more than 60 types of birth defects, along with the dire consequences thought to accompany such births. Later societies, from Roman to those of eighteenth-century Europe, regarded malformed individuals (such as dwarfs) as curiosities rather than figures of impending doom; they were highly prized by royalty as courtiers and entertainers.

Over the millennia, artists have portrayed both famous and anonymous individuals with genetic disorders in paintings, sculptures, and other forms of the visual arts. These portrayals are detailed, highly accurate, and easily recognizable today. In fact, across time, culture, and artistic medium, affected individuals in these portraits often resemble each other more closely than they do their siblings, peers, or relatives. In some cases, the representations allow a disorder to be diagnosed at a distance of several thousand years.

Throughout the book, you will find fine-art representations of individuals with genetic disorders. These portraits represent a long-standing link between science and the arts in many cultures. They are not intended as a gallery of freaks or monsters but as a reminder that being human encompasses a wide range of conditions. A more thorough discussion of genetic disorders in art is in *Genetics and Malformations in Art* by J. Kunze and I. Nippert, published by Grosse Verläg, Berlin, 1986.

Questions

1. Ancient societies used knowledge that traits are heritable in domesticating animals and developing agricultural crops. What might account for the failure to recognize that the same processes operate in humans?
2. Why do unrelated children with a disorder such as Down syndrome resemble each other more closely than they do their siblings?

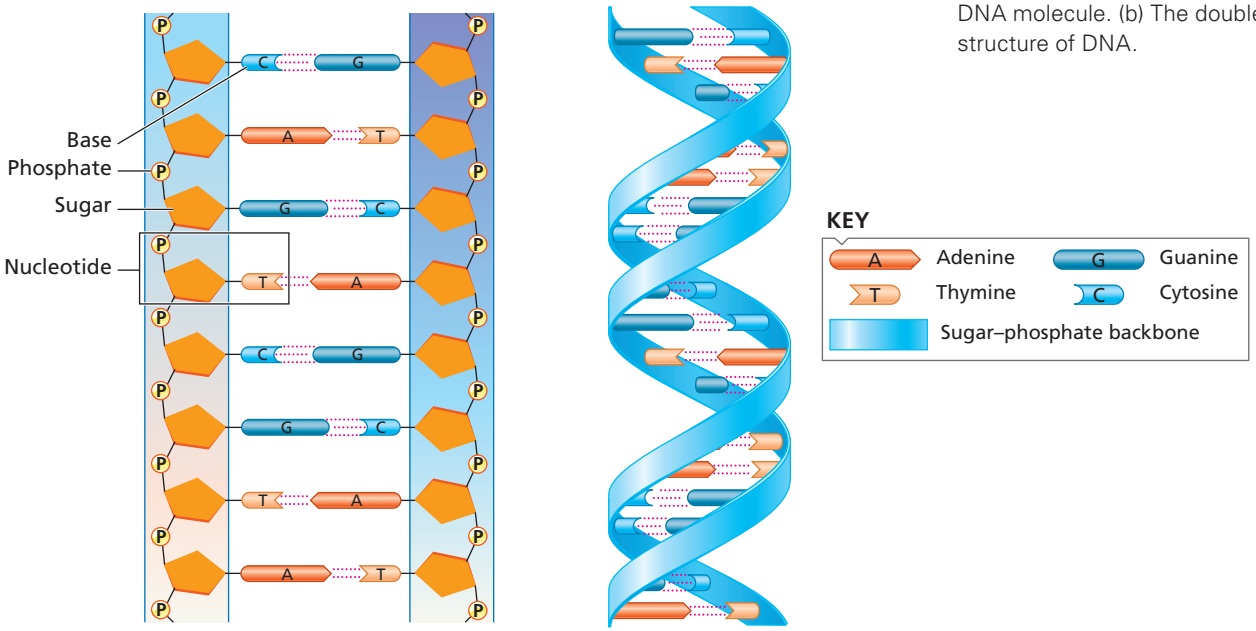
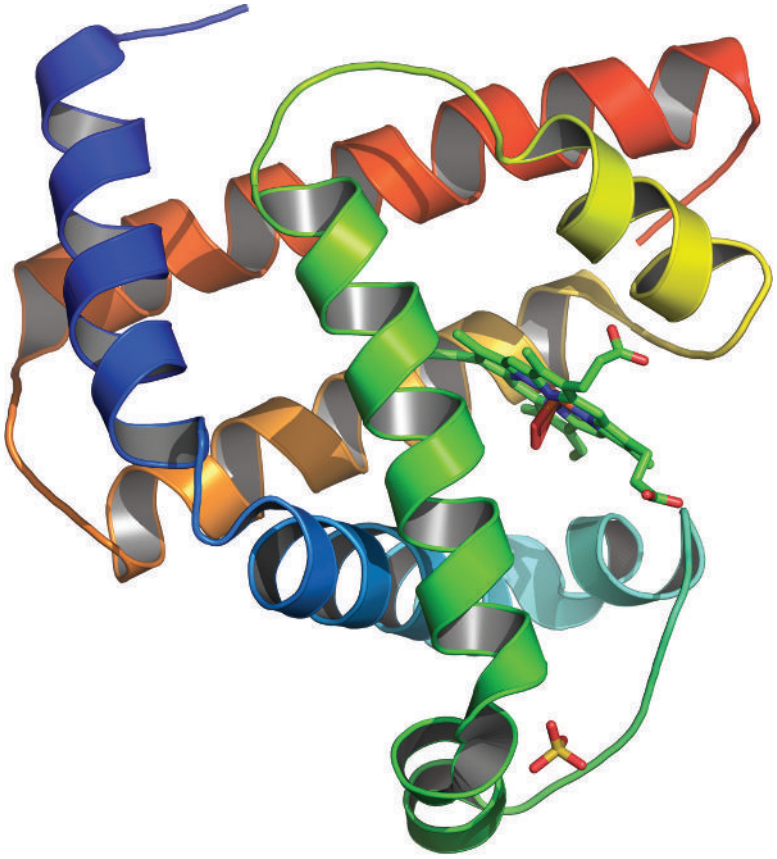


FIGURE 1.1 (a) Genes are composed of a sequence of nucleotides in a DNA molecule. (b) The double helix structure of DNA.

(a) Genes are sequences of nucleotides in DNA

(b) DNA molecule showing arrangement of polynucleotide strands



Carl Fürstenberg

FIGURE 1.2 The three-dimensional structure of a protein.

Combinations of these four nucleotides in the form of genes store all the genetic information carried by an individual. The nucleotide sequence encoded in a gene defines the chemical subunits (amino acids) that make up gene products (proteins). When a gene is activated, its stored information is decoded and used to make a polypeptide, which folds into a three-dimensional shape and becomes a functional protein (**Figure 1.2**). The action of proteins produces characteristics we can see (such as eye color or hair color) or measure (blood proteins or height). Understanding how different proteins are produced and how they work in the cell are important parts of genetics. We will cover these topics in Chapters 9 and 10.

We can also define genes by their properties. Genes are copied (replicated), they undergo change (mutate), they are expressed (they can be switched on or off), and they can move from one chromosome to another (recombine). In later chapters, we will explore these properties and see how alterations in these processes result in genetic disease.

National Library of Medicine

FIGURE 1.3 Gregor Mendel, the Augustinian monk whose work on pea plants provided the foundation for genetics as a scientific discipline.

1-4 How Are Genes Transmitted from Parents to Offspring?

Thanks to the work of Gregor Mendel (**Figure 1.3**), a European monk who lived in the nineteenth century, we know how genes are passed from parents to offspring in plants and animals, including humans. When Mendel began his experiments, many people thought that traits carried by parents were blended together in their offspring. According to this idea, crossing a plant with red flowers and one with white flowers should produce plants with pink flowers (the pink color is a blend of red and white). Mendel's experiments on pea plants showed that genes are passed intact from generation to generation and that traits are not blended. As we will see, however, things are

not always simple. There are cases in which crossing plants with red flowers and plants with white flowers *does* produce plants with pink flowers. We will discuss these cases in Chapter 3 and show that crosses between plants with red flowers and plants with white flowers that produce plants with pink flowers do not contradict the principles of inheritance discovered by Mendel.

Working at a monastery in what is now the Czech Republic, Mendel conducted research on the inheritance of traits in pea plants for more than a decade. He chose parental plants that each had a different distinguishing characteristic, called a trait. For example, Mendel bred tall pea plants with short pea plants. Plant height is the trait in this case and has two variations: tall and short. He also bred plants carrying green seeds with plants having yellow seeds. In this work, seed color is the trait; green and yellow are the variations of the trait he studied. In these breeding experiments, he wanted to see how traits such as height and seed color were passed from generation to generation.

Mendel kept careful records of the number and type of traits present in each generation. He also recorded the number of individual plants that carried each trait. He discovered patterns in the way traits were passed from parent to offspring through several generations. Based on those patterns, Mendel concluded that traits such as plant height and seed color are passed from generation to generation by "factors" that are transmitted from parent to offspring. What he called "factors" we now call genes.

Mendel reasoned that each parent carries two genes (a gene pair) for a specific trait (flower color, plant height, etc.) but that each parent contributes only one of those genes to its offspring; otherwise, the number of genes for a trait would double in each generation and soon reach astronomical numbers.

Mendel proposed that the two copies of a gene separate from each other during the formation of egg and sperm. As a result, only one copy of each gene is present in a sperm or an egg. When an egg and a sperm fuse at fertilization, the genes from the mother and father become members of a new gene pair in the offspring. In the mid-twentieth century, researchers discovered that genes are made of DNA and that this molecule is part of cellular structures known as chromosomes. Chromosomes (**Figure 1.4**) are found in the nucleus

Andrew Syred/Science Source

FIGURE 1.4 Replicated human chromosomes as seen by scanning electron microscopy.

Transmission genetics The branch of genetics concerned with the mechanisms by which genes are transferred from parent to offspring.

Pedigree analysis The construction of family trees and their use to follow the transmission of genetic traits in families. It is the basic method of studying the inheritance of traits in humans.

Cytogenetics The branch of genetics that studies the organization and arrangement of genes and chromosomes by using the techniques of microscopy.

Karyotype A complete set of chromosomes from a cell that has been photographed during cell division and arranged in a standard sequence.

Molecular genetics The study of genetic events at the biochemical level.

Recombinant DNA technology A series of techniques in which DNA fragments from an organism are linked to self-replicating vectors to create recombinant DNA molecules, which are replicated or cloned in a host cell.

Clones Genetically identical molecules, cells, or organisms, all derived from a single ancestor.

of human cells and other higher organisms. As we will see in Chapter 2, the separation of genes during the formation of the sperm and egg and the reunion of genes at fertilization is explained by the behavior of chromosomes in a form of cell division called meiosis.

When Mendel published his work on the inheritance of traits in pea plants (discussed in Chapter 3), there was no well-accepted idea of how traits were transmitted from parents to offspring; his evidence changed that situation. To many, Mendel was the first geneticist and the founder of genetics, a field that has expanded in numerous directions in the last 125 years. If you want to read more about the beginnings of genetics, the story of Mendel's work is told in an engaging book entitled *The Monk in the Garden: The Lost and Found Genius of Gregor Mendel, the Father of Genetics* by Robin M. Henig.

1-5 How Do Scientists Study Genes?

Ideas that form the foundation of genetics were discovered by studying many different organisms, including bacteria, yeast, and insects, as well as plants and animals, including humans. Because genetic mechanisms (and often genes) are the same across species, discoveries made in one organism (such as yeast) can be applied to other species, including humans. This close genetic relationship allows researchers to study human genetic disorders using experimental organisms, including insects, yeast, and mice. Although geneticists study many different species, they use a relatively small set of investigative methods, some of which are outlined in the following section.

Some basic methods in genetics.

The most basic approach studies the pattern of inheritance as traits are passed from generation to generation; this is called **transmission genetics** (see Chapters 3 and 4). Using experimental organisms, geneticists study how traits such as height, eye color, flower color, and so on, are passed from parents to offspring. These experimental results are analyzed to establish how a trait is inherited. As we discussed in an earlier section, Gregor Mendel did the first significant work in transmission genetics using pea plants as his experimental organism. His methods form the foundation of transmission genetics—methods that are still used today.

To study the inheritance of traits in humans, a more indirect method called **pedigree analysis** is used. Pedigree analysis begins by reconstructing the pattern of inheritance associated with a trait as it passes through several generations. These results are used to determine how a trait is inherited and to establish the risk of having affected children (**Figure 1.5**). Pedigrees are constructed from information obtained from interviews, medical files, letters, diaries, photographs, and family records.

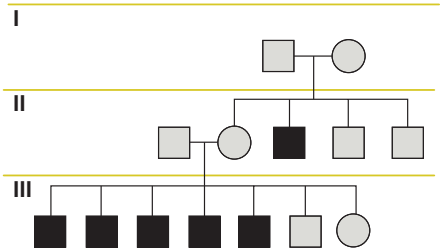


FIGURE 1.5 A pedigree represents the inheritance of a trait through several generations of a family. In this pedigree, males are symbolized by squares, females by circles. Darker symbols indicate those expressing the trait being studied; lighter symbols indicate unaffected individuals.

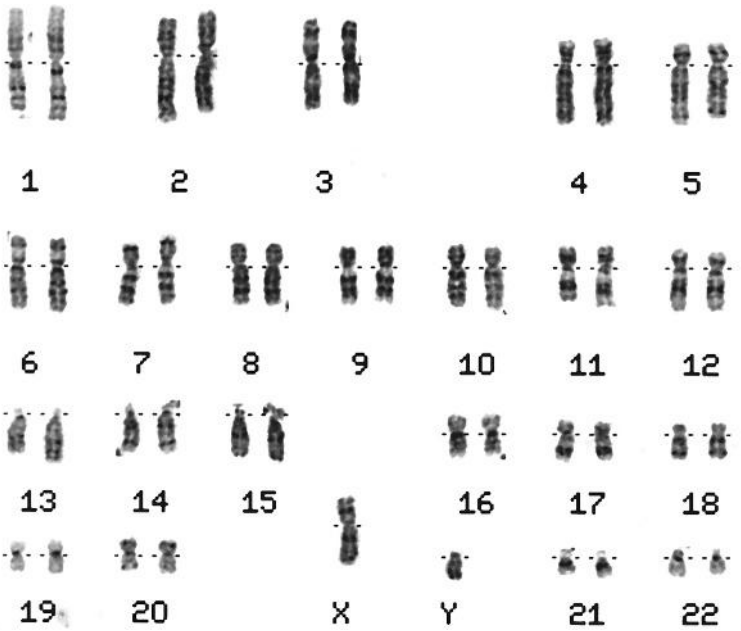
Cytogenetics is a branch of genetics that studies chromosome number and structure (discussed in Chapter 6). At the beginning of the twentieth century, observations on chromosome behavior were used to propose (correctly) that genes are located on chromosomes. Cytogenetics is one of the most important investigative approaches in human genetics and is used, among other things, to map genes and study chromosome structure and abnormalities in chromosome number and organization. In clinical settings, cytogeneticists prepare **karyotypes** (**Figure 1.6**), standardized arrangements of chromosomes that are used to diagnose or rule out certain genetic disorders. In a karyotype, chromosomes are arranged by size, shape, and other characteristics that we will describe in Chapter 6.

A third approach, **molecular genetics**, has had the greatest impact on human genetics over the last several decades. Molecular genetics uses **recombinant DNA technology** to identify, isolate, and produce millions of copies of genes (**clones**) that can be studied in the laboratory. These methods have greatly advanced our knowledge of how genes are organized and how they work at the molecular level. This technology is

used for prenatal diagnosis of genetic disorders and in **gene therapy** to transfer human genes as a treatment for genetic disorders. Cloned genes also can be transferred between individuals and between species to produce transgenic organisms. Transgenic organisms (also called genetically modified organisms—GMOs) are used in laboratory research, agriculture, and the pharmaceutical industry.

Recombinant DNA technology was used in the Human Genome Project to sequence the human **genome**, the complete set of genetic information we all carry, and has generated a new field of genetics called **genomics**. Scientists working in genomics use information from genome projects to study the origin, function, and evolution of genes and their interactions. New genomics technology is now being used to identify the genetic components of complex diseases such as diabetes, obesity, cardiovascular disease, and neurological disorders (including Alzheimer and Parkinson's) and is revolutionizing the study of human genetics.

The development and use of recombinant DNA technology has generated debate about the social, legal, and ethical aspects of genetics, including the genetic modification of plants and animals, the use of genetic testing for diagnosis and employment, and the modification of humans by gene therapy.



Courtesy of Iffi Ahmed

FIGURE 1.6 A karyotype arranges the chromosomes in a standard format so that they can be analyzed for abnormalities. This karyotype is that of a normal male.

A fourth approach studies the distribution of genes in populations. Population geneticists are interested in the forces that change the frequency of genes in a population over many generations and the way those changes are involved in evolution. **Population genetics** defines how much genetic variation exists in populations and how forces such as migration, population size, and natural selection change this variation. The coupling of population genetics with genomic technology has helped us understand the evolutionary history of our species and the migrations that distributed humans across Earth. This technology has been used to develop methods of DNA fingerprinting and DNA identification, techniques widely used in paternity testing and forensics.

Gene therapy Procedure in which normal genes are transplanted into humans carrying defective copies as a means of treating genetic diseases.

Genome The set of DNA sequences carried by an individual.

Genomics The study of the organization, function, and evolution of genomes.

Population genetics The branch of genetics that studies inherited variation in populations of individuals and the forces that alter gene frequency.

Genetics is used in basic and applied research.

Genetics is a discipline that crosses and recrosses the line between basic research and applied research, often blurring distinctions between the two. In general, scientists do basic research in laboratory and field settings to understand how something works or why it works the way it does. In basic research, there is no immediate goal of solving a practical problem or making a commercial product; knowledge itself is the goal. In turn, the results of basic research generate new ideas and more basic research. In this way, we gain detailed information about the structure and function of cells, why animals behave in certain ways, and how plants turn carbon dioxide into sugar. Among other things, basic research in genetics has provided us with details about genes, how they work, and, more importantly, what happens when they don't work properly.

Applied research is usually done to solve a practical problem or turn a discovery into a commercial service or product. Applied research uses basic methods such as transmission genetics to study the way in which a trait is inherited, and it also uses biotechnology to make products such as transgenic organisms, medicines, and nutritionally enhanced foods. In agriculture, applied genetic research has increased crop yields, lowered the fat content of pork, and created new forms of corn and soybeans that are resistant to herbicides and pests. In medicine, new diagnostic tests, the synthesis of customized proteins for treating disease, and the production of vaccines are just a few examples of applied genetic research.

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FIGURE 1.7 Transgenic corn has been genetically modified to be resistant to herbicides used to kill weeds.

Some uses of applied research are controversial and have generated debate about the merits and risks of biotechnology. Current controversies include the environmental impact of genetically modified crop plants (**Figure 1.7**), the sale and consumption of food that has been modified by recombinant DNA technology, the use of recombinant DNA–derived growth hormone in milk production, and the irradiation of food. An understanding of the basic concepts of genetics will help all of us make informed decisions about the use of biotechnology in our lives, including the food we eat, the diagnostic tests we elect to have performed, and even the breeding of our pets. This course will provide you with the basic concepts of genetics and human genetics that can be used to make these informed decisions.

1-6 Has Genetics Affected Social Policy and Law?

Genetics and biotechnology impact not only our personal lives, but they also raise larger questions about ethics, social policy, and law. We will consider current controversies surrounding genetics and biotechnology in several chapters, but you may be surprised to learn that controversies involving genetics are nothing new. In fact, genetics had a significant impact on law and social policy for a great part of the last century. As we face decisions about how to use new forms of genetic technology, it is important to know and understand the history and outcomes of past controversies so that we can avoid repeating mistakes and pitfalls.

The misuse of genetics has affected social policy.

Eugenics The attempt to improve the human species by selective breeding.

Hereditarianism The mistaken idea that human traits are determined solely by genetic inheritance, ignoring the contribution of the environment.

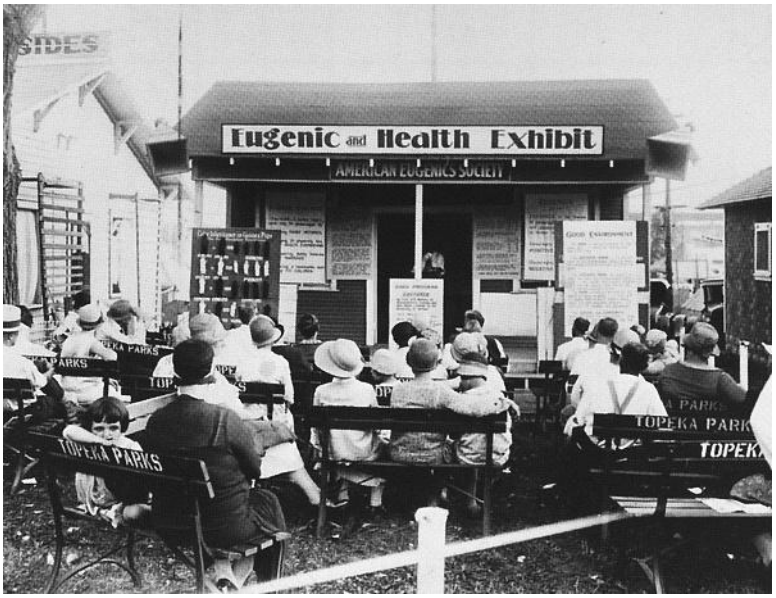
After the publication of Charles Darwin's book *The Origin of Species*, which described the role of natural selection in evolution, his cousin Francis Galton proposed that selection should be used to improve the human species. Galton started a new field, which he called **eugenics**. He claimed that by applying the principle of natural selection, we could improve the intellectual, economic, and social level of humankind through selective breeding. Bypassing legal and ethical considerations, Galton's proposals were simple: People with desirable traits such as leadership and musical ability should be encouraged to have large families, whereas those with undesirable traits such as intellectual disability and physical deformities should be discouraged from reproducing. Galton's reasoning was flawed for several reasons, including his belief that human traits are handed down without any environmental influence. The idea that all human traits are determined only by genes is known as **hereditarianism**. His proposals failed to address another important consideration: Who defines what is a desirable or an undesirable trait?

In spite of those fundamental flaws, eugenics took hold in the United States, and eugenicists worked to promote selective breeding in the human population (**Figure 1.8**) and to prevent reproduction by those defined as genetically defective. Although almost unknown today, eugenics was a powerful and influential force in many aspects of American life from about 1905 through 1933.

Eugenics was used to pass restrictive immigration laws in the United States.

In the early decades of the twentieth century, millions of Europeans flooded into the United States after the devastation caused by World War I. Faced with this wave of

immigration, eugenicists argued that high levels of unemployment, poverty, and crime among immigrants from southern and Eastern Europe proved that people from those regions were genetically inferior and would pollute the genes of Americans. After hearing testimony by eugenics experts, Congress passed the Immigration Restriction Act of 1924. As he signed the new law, President Coolidge commented that "America must remain American." This law, based on faulty and unproven eugenic assumptions, effectively closed the door to America for millions of people from southern and Eastern Europe. The law reduced entry quotas for countries such as Italy and Russia by two-thirds, while allowing large numbers of immigrants from western European countries such as France, Germany, and Great Britain, which eugenicists proclaimed as having genetically superior peoples. Europeans were not alone in facing restrictions. For other reasons, the Chinese Exclusion Acts of 1882 and 1902 had restricted immigration from Asia. In addition, a 1907 agreement between the U.S. and Japanese governments restricted the immigration of Japanese citizens. In the early decades of the twentieth century, there was little immigration from Africa, and lawmakers thus saw no need to regulate entry from that continent.



American Philosophical Society

FIGURE 1.8 In the early part of the twentieth century, eugenics exhibits were a common feature at fairs and similar events. Such exhibits served to educate the public about genetics and the benefits of eugenics as public policy. These exhibits often included contests to find the eugenically perfect family.

Immigration laws based on faulty eugenic ideas were on the books for just over 40 years. These laws were finally changed by the Immigration and Nationality Act of 1965, which was sponsored by Representative Emanuel Cellar of New York, himself a grandson of immigrants. Under this law, national quotas were abolished, and immigrants from all parts of the world were welcomed.

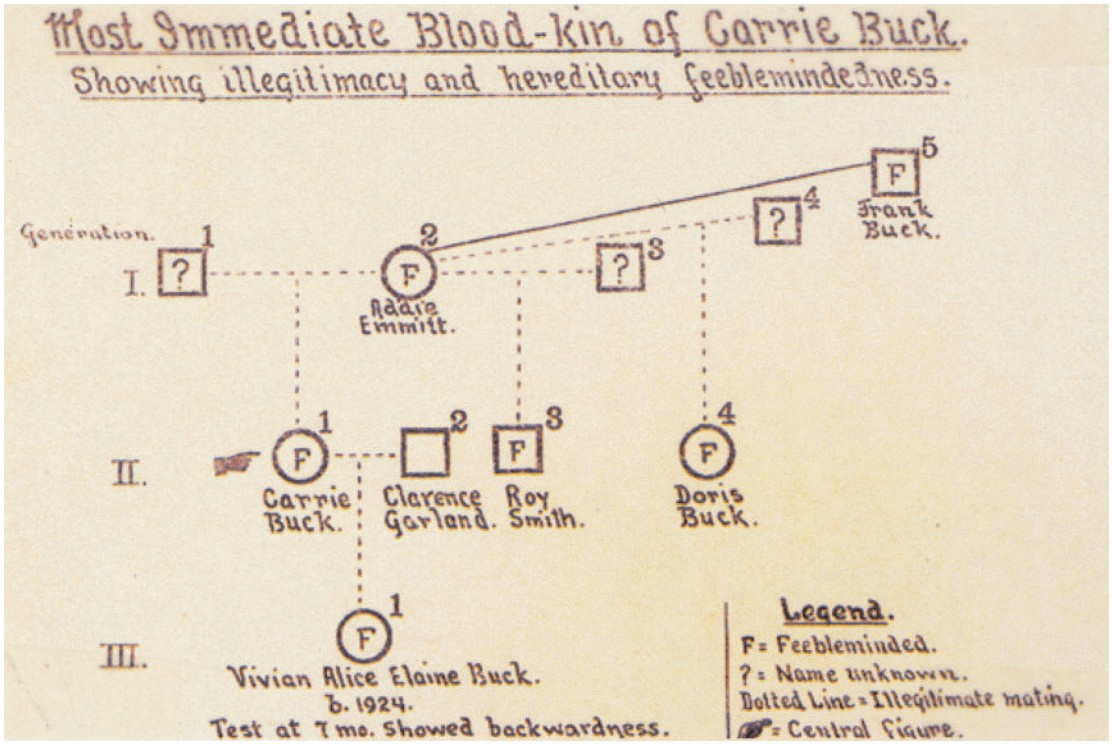
Eugenics was used to restrict reproductive rights.

In addition to setting immigration policy, the eugenics movement in the United States worked to pass laws requiring sterilization of people regarded as genetically, intellectually, and morally inferior. A committee of eugenicists concluded that up to 10% of the U.S. population should be prevented from reproducing by being institutionalized or sterilized. Eugenicists testified before committees of state legislatures, urging states to regulate reproductive rights. As a result, state laws requiring people with certain genetic disorders and those convicted of certain crimes to be sterilized were passed in many states, beginning in 1907.

In 1927, the U.S. Supreme Court (*Buck v. Bell*) upheld the right of states to use eugenic sterilization in an 8–1 decision. Oliver Wendell Holmes, one of the most respected justices of the Supreme Court, wrote the opinion. This ruling, which has never been modified or overturned, includes the following statement:

> It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the fallopian tubes. . . . Three generations of imbeciles are enough.

The three generations referred to by Holmes included a Virginia woman, Carrie Buck; her mother, Addie; and Carrie's daughter, Vivian (**Figure 1.9**). The case came to the U.S. Supreme Court to appeal the decision by a Virginia court that Carrie should be sterilized because she was feebleminded and promiscuous. In the eyes of some eugenicists, these were genetic traits. Evidence presented at trial showed that Carrie, her mother, and Carrie's daughter were all mentally unfit. Soon after the Supreme Court ruling, Carrie Buck was sterilized. At that time, she was an unmarried teenager living



Courtesy of the Harry H. Laughlin Papers, Pickler Memorial Library, Truman State University

FIGURE 1.9 A pedigree of the family of Carrie Buck, made at the Virginia Colony for the Epileptic and Feebleminded.

in a foster home with her daughter. Later investigation showed that her child, Vivian, was not "feebleminded" as claimed and that Carrie was not promiscuous but had been raped by a relative of her foster parents.

After the U.S. Supreme Court decision, sterilization laws were passed in many states. At one time or another, a total of 33 states passed laws providing for sterilization of certain individuals—most designated as feebleminded, a catchall term that covered both real and imagined disabilities. Behaviors (including alcoholism, criminal convictions, and sexual promiscuity) were used as a way to diagnose someone as feebleminded. More than 60,000 people were sterilized before the practice was ended in 1979. Of the states, five—California (20,108), Virginia (7,450), North Carolina (6,297), Michigan (3,786), and Georgia (3,284)—accounted for almost 70% of this total. In recent years, some states—including Virginia, North and South Carolina, and Oregon—have apologized officially and publicly for their involvement in eugenic sterilization. In 2013, North Carolina became the first state to offer compensation to those who were sterilized without consent and often without their knowledge. It is estimated that over 2,500 sterilized individuals are still alive, and as they are verified, they will receive shares in a $10 million compensation fund.

The decline of eugenics in the United States began with the rise of the Nazi movement.

Sterilization laws in the United States served as models for the 1933 "Law for the Protection Against Genetically Defective Offspring" passed in Germany by the Nazi government. As the use of this law was expanded, it allowed the systematic killing of people defined as socially defective, physically deformed, mentally retarded, and/or mentally ill. Later, eugenics was used as a justification for the eradication of entire ethnic groups such as Gypsies and Jews. The close association between eugenics and the government of Nazi Germany quickly led to the decline of the eugenics movement in the United States by the late 1930s.

1-7 What Impact Is Genomics Having?

The development and use of recombinant DNA technology ushered in the era of genomics when geneticists began planning ways to sequence the 3.2 billion nucleotides in the human genome in order to identify, map, and assign functions to all genes carried by humans. The Human Genome Project (HGP) began as a federal program in 1990. In 2001, the HGP and a project undertaken by private industry reported the first draft of the human genome sequence, and, in 2003, the rest of the gene-coding portion of the genome was finished. We now have a catalog of the 3 billion nucleotides and the approximately 20,000 different genes carried in our cells. Turning the results from the HGP into new methods of diagnosis and treatment has given rise to the new field of translational medicine.

Identifying and using genetic variation in genomics.

In the years after the completion of the HGP, genome sequencing revealed a surprising amount of variation in the sequence and arrangement of nucleotides in humans. Once this variation was identified, scientists began to study the type, amount, location, and effects of these variations. The simplest type of variation in a genome sequence is a single nucleotide change, called a **single nucleotide polymorphism**, or SNP (pronounced "snip") (**Figure 1.10**). Over 11 million SNPs have been identified, and scientists are using clusters of neighboring SNPs called **haplotypes** as markers to screen large numbers of individuals, looking for links between these SNPs and common complex traits and disorders. These **genome-wide association studies (GWASs)** have provided insight into genes associated with type 2 diabetes, cancers, neurodegenerative diseases (Alzheimer, Parkinson's disease), mental illness, and cardiovascular diseases. These technological advances are helping to unravel the number and identity of genes associated with complex diseases and are rapidly changing the study of human genetics.

Information from the HGP and other genomic studies are used to diagnose many genetic disorders before birth, to test children and adults to reveal carriers of genetic disease, and to scan whole genomes to detect genetic diseases and predispositions to complex disorders, including cardiovascular disease, diabetes, and cancer.

Single nucleotide polymorphism (SNP) Single nucleotide differences between and among individuals in a population or species.

Haplotype A set of genetic markers located close together on a single chromosome or chromosome region.

Genome-wide association study (GWAS) Analysis of genetic variation across an entire genome, searching for associations (linkages) between variations in DNA sequence and a genome region encoding a specific phenotype.

Health care uses genetic testing and genome scanning.

Genetic technology is now an important part of medicine, and its impact will continue to grow as information from genomics is analyzed and applied to the diagnosis and treatment of human diseases. More than 10 million children and adults in the United States have a genetic disorder, and every newborn has a 3% chance of having a genetic disorder, underscoring the need for tests that accurately diagnose heritable diseases at all stages of life.

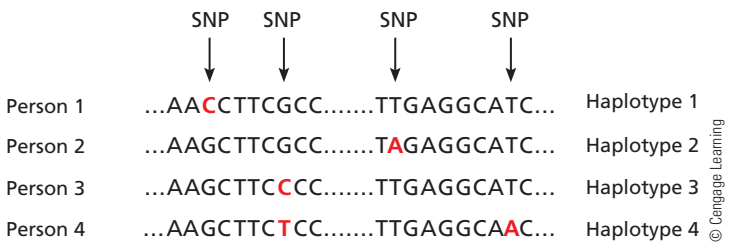
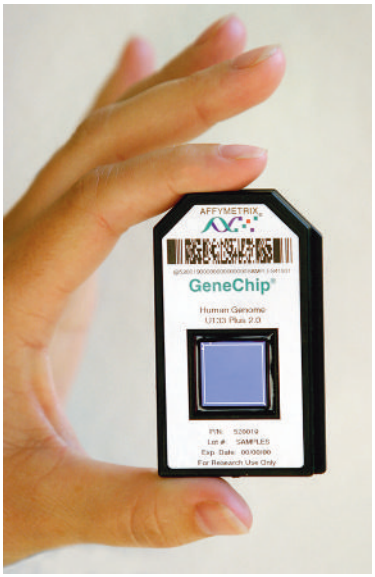


FIGURE 1.10 Single nucleotide polymorphisms (SNPs) are shown in red.



Affymetrix.com

FIGURE 1.11 A gene chip carrying the human gene set. This chip can be used to diagnose genetic disorders.

Biotechnology The use of recombinant DNA technology to produce commercial goods and services.

The genes associated with hundreds of genetic diseases, including cystic fibrosis, sickle cell anemia, and muscular dystrophy, have been isolated and used to develop genetic tests. All 50 states and the District of Columbia test newborns for a range of genetic disorders. In addition, adults can be tested to determine whether they are at risk of having a child with a genetic disorder. Couples can now obtain information to make informed decisions about family planning when genetic testing is combined with genetic counseling.

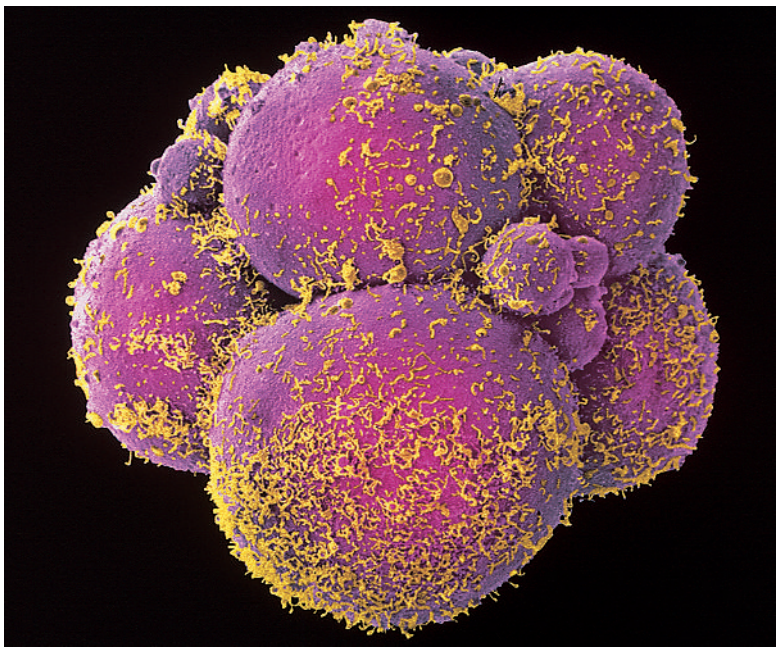
New technology has made it possible to screen an individual's entire genome, instead of testing for one genetic disorder at a time. This technology uses DNA microarrays (also called DNA chips) that carry DNA from the entire human genome (**Figure 1.11**) to determine which genetic disorders someone has, will develop, or is predisposed to. DNA microarrays are also used in diagnosing infectious diseases and cancer.

In addition to the diagnosis of inherited diseases, technology has made it possible to produce human embryos (**Figure 1.12**) through the fusion of sperm and eggs in a laboratory dish—a process called *in vitro* fertilization (IVF)—and to transfer the developing embryo to the womb of a surrogate mother. Embryos can also be frozen for transfer to a womb at a later time. We are now treating genetic diseases by transplanting normal genes that act in place of defective copies, using gene therapy. We can even insert human genes into animals, creating new types of organisms that produce human proteins used in treating diseases such as emphysema.

Stem-cell research offers hope for treating many diseases.

In the embryo, stem cells divide to form about 200 different cell types that become parts of the tissues and organs of the body. In adults, stem cells are a reservoir that provides replacements for cells lost through injury, disease, or wear and tear.

The ability to isolate stem cells from embryos and to produce stem cells from normal body cells in the laboratory (induced pluripotent stem cells [iPS]) offers the possibility of using stem cells to treat disorders such as heart disease, diabetes, and other degenerative conditions. This new field, called regenerative medicine, depends on cell-based therapies. Ethical, legal, and political controversy surrounds the creation and use of embryonic stem cells, once again emphasizing that genetic technology has advanced faster than a consensus on how to use the technology. The use of adult stem cells is less controversial, and several products used in cell-based therapies are now on the market.



Dr. Yorgos Nikas/Science Source

FIGURE 1.12 Human embryo shortly after fertilization in the laboratory. Embryos at this stage of development can be analyzed for genetic disorders before implantation into the uterus of the egg donor or that of another, surrogate mother.

Biotechnology is impacting everyday life.

Recombinant DNA technology moved quickly from research laboratories into the business world; products and services using this technology are now commonplace. The commercial use of genetically modified organisms or their products is called **biotechnology**. Those products are found in hospitals, clinics, doctors' offices, drugstores, supermarkets, and department stores; in law enforcement and the courts; and even in the production of industrial chemicals and the cleanup of toxic waste sites.

The genetic modification of food is one of the most rapidly expanding and controversial uses of biotechnology. More than 85% of the corn and 95%

of the soybeans grown in the United States is genetically modified. It is estimated that more than 80% of the processed foods in supermarkets contain ingredients from transgenic plants.

Critics have raised concerns that the use of herbicide-resistant corn and soybeans will speed the development of herbicide-resistant weeds and increase our use of and dependence on chemical herbicides. Others point to the possibility that genetically engineered traits may be transferred to other organisms, leading to irreversible and deleterious changes in ecosystems.

Animals are also being cloned and genetically modified. The cloning of Dolly the sheep (**Figure 1.13**) represented a breakthrough in cloning methods that, along with related technology, makes it possible to produce dozens or hundreds of offspring with desirable traits such as high levels of milk production, meat with low fat content, and even speed in racehorses.

Recombinant DNA technology has been used for over 30 years to produce human insulin in bacteria and other host cells for the treatment of diabetes. Now, genetically modified sheep, rabbits, and cows are being used to produce medically important human proteins in their milk. These proteins are, or soon will be, used in clinical trials to treat human diseases such as emphysema and Pompe disease.

REUTERS/HO/Landov

FIGURE 1.13 Dolly the sheep was the first mammal cloned by nuclear transfer from a somatic cell.

1-8 What Choices Do We Make in the Era of Genomics and Biotechnology?

In the span of about 35 years, we have learned how to predict the sex of unborn children, diagnose many genetic disorders prenatally, and manufacture human gene products to treat genetic diseases. We are now at a transition point where we are not only learning more about human genetics, but we are starting to *apply* genetic knowledge in ways that were unforeseen just a few years ago. These applications are colliding with social standards, public policy, and laws, forcing us to rethink what is acceptable and unacceptable in our personal and public lives.

Should we buy and eat food that comes from genetically modified plants and animals? Is milk from cloned cows safe to drink? Should we test ourselves or our children for genetic diseases even if no treatment is available? Is medicine produced from genetically modified animals safe? Should we vaccinate our children with edible vaccines produced from genetically altered plants? We are faced with an increasing number of seemingly bewildering choices. Sorting through the rhetoric and hype to find the facts that allow us to make intelligent and informed choices is a problem in modern life. Beyond these immediate personal choices is the fact that the development of biotechnology is raising new ethical questions that we must face and answer in the near future.

We can make informed personal decisions and formulate relevant laws and public policy only if we have a working knowledge of the principles of genetics as they apply to humans and understand how genetics is used in biotechnology. As a student of human genetics, you have elected to become involved in the search for answers to these important questions.

Genetics in Practice

Genetics in Practice case studies are critical-thinking exercises that allow you to apply your new knowledge of human genetics to real-life problems.

CASE STUDY

Mary and Marcie, identical twins, go to the same internist who is also a faculty member at a major medical center. At their last visit, they each received a brochure describing a genetics research program recently launched by the hospital and its affiliated university. Researchers were asking for volunteers to fill out a questionnaire and a consent form, donate a blood sample, and have their medical records encoded and transferred to a database. The goal was to enroll 100,000 participants, and the brochure noted that over 10,000 people had already agreed to participate.

The blood sample would be used to extract DNA, which would be encoded with the same number as the medical records. This DNA would be used to search for genes associated with conditions such as arthritis, diabetes, and Alzheimer disease. The idea is that researchers interested in studying arthritis would use the medical records to identify which participants have the condition and then use DNA from those individuals to find genetic similarities that are not present in participants who do not have arthritis. The genetic similarities help identify regions of the genome that contain genes associated with arthritis. These regions can then be studied in detail to identify and isolate genes that may be associated with arthritis and other inflammatory disorders.

In exchange for enrolling, participants would be informed about any genetic conditions or predispositions to genetic disease they carry and would receive free access to testing. After discussing the brochure, Mary decided to enroll, but Marcie decided she did not want to do so. She said she did not want to know what diseases she may develop or which disease genes she may carry.

At their next annual visit, Mary's internist told her that because her questionnaire indicated that some relatives had Alzheimer disease, her DNA was used in a study to identify risk genes. He said she had been identified as a carrier of a gene that greatly increased the likelihood that she would develop Alzheimer disease. The physician told her that age was the greatest risk factor, and while it was not 100% certain she would become a victim of Alzheimer disease, the gene she carries is a factor in 20–25% of all cases. Mary asked if there was anything she could do about these findings. The internist told her that exercise, controlling blood pressure and cholesterol levels, as well as participating in mentally challenging activities such as reading or playing a musical instrument may all help reduce her chances of developing this disease. Mary then asked if Marcie was going to be told about Mary's genetic risk, and the internist said that he would not tell her.

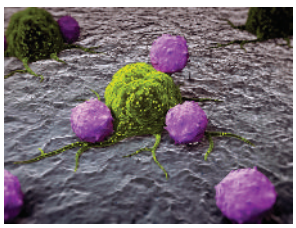
For the next few days, Mary was conflicted about the situation. Marcie was an identical twin, and if Mary carried a gene predisposing her to Alzheimer disease, Marcie must carry the same gene. Marcie did not exercise with Mary, had high blood pressure, and little interest in reading or social activities. Mary did not know whether she should tell Marcie.

1. If you were advising Mary, what would you say? Should she tell Marcie about the risk? Should she not tell her, but instead try to get Marcie to exercise and be more social? Should Mary ask their internist to talk with Marcie about this?

Summary

1-1 Genetics and Translational Medicine

- Research laboratories and pharmaceutical firms are working to move the results of genetic research from the laboratory to the bedside of patients, a process called translational medicine.



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1-2 Genetics Is the Key to Biology

- Genetics is the scientific study of heredity. In a sense, genetics is the key to all of biology because genes control what cells look like and what they do. Understanding how genes work is essential to our understanding of how life works.

1-3 What Are Genes and How Do They Work?

- The gene is the basic structural and functional unit of genetics. It is a string of chemical building blocks (nucleotides) in a DNA molecule. When a gene is turned on, the information stored in the gene is decoded and used to make a molecule that folds into a three-dimensional shape. This molecule is known as a protein (see Figure 1.2). The actions of proteins produce the traits we see (such as eye color and hair color).

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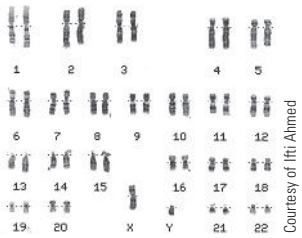
1-4 How Are Genes Transmitted from Parents to Offspring?

- From his experiments on pea plants, Mendel concluded that pairs of genes separate from each other during the formation of egg and sperm. When the egg and sperm fuse during fertilization to form a zygote, the genes from the mother and the father become members of a new gene pair in the offspring. The separation of genes during formation of the sperm and egg and the reunion of genes at fertilization are explained by the behavior of chromosomes in a form of cell division called meiosis.

1-5 How Do Scientists Study Genes?

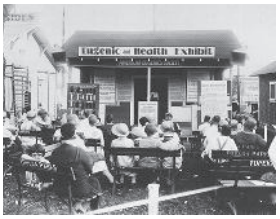
- Genes are studied using several methods. Transmission genetics studies how traits are passed from generation to generation. Cytogenetics studies chromosome structure and the location of genes on chromosomes. Molecular geneticists study the molecular makeup of genes, gene products, and the function of genes. Population genetics focuses on the dynamics of populations and their interaction with the environment that results in changing gene frequencies over several generations.



Courtesy of Ifti Ahmed

1-6 Has Genetics Affected Social Policy and Law?

- Eugenics was an attempt to improve the human race by using the principles of genetics. In the early years of the twentieth century, eugenics was a powerful force in shaping laws and public policy in the United States. This use of genetics was based on the mistaken assumption that genes alone determined human behavior and disorders, and it neglected the role of the environment. Eugenics fell into disfavor when it became part of the social programs of the Nazis in Germany.



American Philosophical Society

1-7 What Impact Is Genomics Having?

- The development of recombinant DNA technology is the foundation for DNA cloning, genome projects, and biotechnology. These developments are causing large-scale changes in many aspects of life and are affecting medicine, agriculture, and the legal system.

1-8 What Choices Do We Make in the Era of Genomics and Biotechnology?

- With the completion of the Human Genome Project, the ability to manipulate human reproduction, and the ability to transfer genes, we are faced with many personal and social decisions. The ethical use of genetic information and biotechnology will require participation by a broad cross section of society.

Questions and Problems

1. Summarize Mendel's conclusions about traits and how they are passed from generation to generation.
2. What is population genetics?
3. What is hereditarianism, and what is the invalid assumption it makes?
4. What impact has recombinant DNA technology had on genetics and society?
5. What are genomes?
6. What is genomics?
7. In what way has biotechnology had an impact on agriculture in the United States?
8. We each carry 20,000 genes in our genome. Genes can be patented, and over 6,000 human genes have been patented. Do you think that companies or individuals should be able to patent human genes? Why or why not?
9. If your father were diagnosed with an inherited disease that develops around the age of 50, would you want to be tested to find out whether you would develop this disease? If so, when would you want to be tested? As a teenager or sometime in your 40s? If not, would you have children?

2 Cells and Cell Division

CHAPTER OUTLINE

2-1 Cellular Links to Genetic Disease

2-2 The Chemistry of Cells

2-3 Cell Structure Reflects Function

2-4 The Cell Cycle Describes the Life History of a Cell

2-5 Mitosis Is Essential for Growth and Cell Replacement

2-6 Cell Division by Meiosis: The Basis of Sex

2-7 Formation of Gametes

2-1 Cellular Links to Genetic Disease

CASE STUDY

Leah G., 22, went to the hospital emergency room with severe leg pain after a fall while rollerblading. Despite the fact she had only a minor fall, X-rays showed a broken bone in her lower leg. There was no family history of brittle bones, but when asked about her general health, she reported that over the past few months she had tired easily and her abdomen was tender and sometimes painful. The emergency room physician ordered an abdominal MRI, which showed Leah's spleen and liver were abnormally enlarged. She left the hospital with a cast on her leg and an appointment with a genetic counselor.

The genetic counselor told Leah that because of her age, her Eastern European Jewish heritage, and her symptoms, she might have a genetic disorder called Gaucher (pronounced go-SHAY) disease. The counselor explained that affected individuals cannot break down a particular type of fat, which then accumulates in white blood cells found in the liver, spleen, and bone marrow. These enlarged white blood cells are called Gaucher cells. Her symptoms of fatigue, enlargement of the liver and spleen, as well as her easily fractured leg and age of onset in early adulthood, are all symptoms of this disease. The counselor also explained that a liver biopsy and a blood test could confirm whether or not she had this disorder. While the disorder is rare in the general

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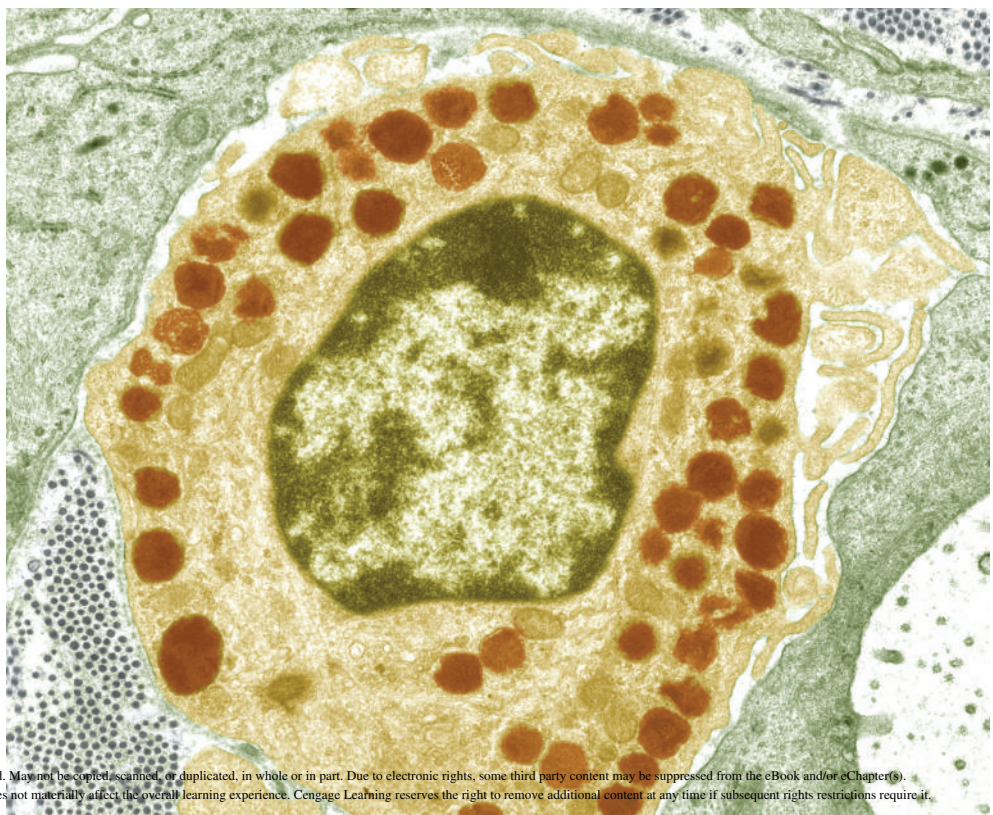
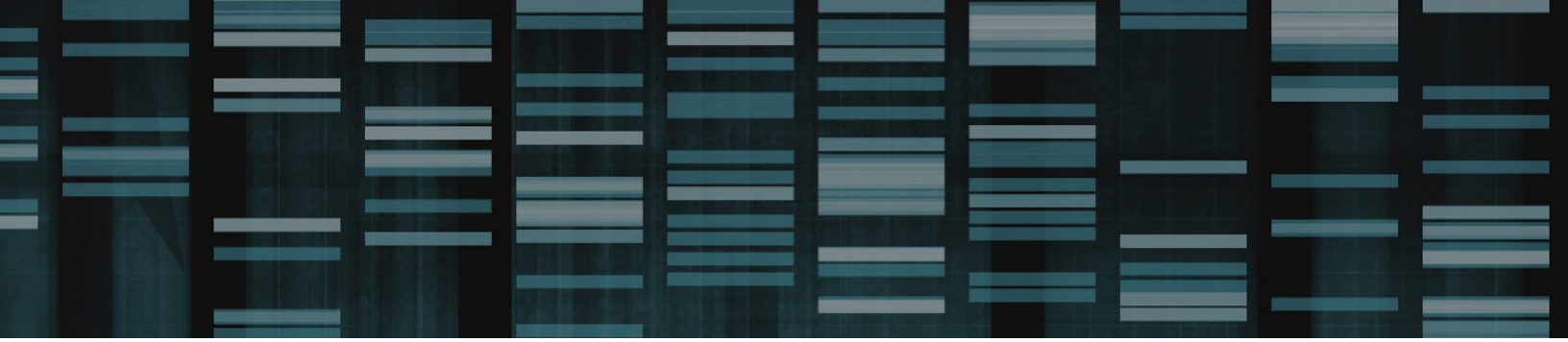


A white blood cell containing enlarged lysosomes (stained brown) associated with a lysosomal storage disease.



population, as many as 1 in 450 individuals of Eastern European Jewish descent have Gaucher disease. Leah arranged for the biopsy and blood test and for a follow-up visit with the counselor.

During her second visit, the counselor informed Leah that the biopsy and blood test confirmed that she had Gaucher disease. Leah was told that treatment for the disease, called enzyme replacement therapy (ERT), was available that used a recombinant DNA-produced form of the missing enzyme. Each intravenous treatment was done on an outpatient basis, took about 1–2 hours, and was usually done every 2 weeks at a cost of $150,000–$200,000 a year. After discussing the situation with her parents, Leah began treatments; after 6 months, most of her symptoms had disappeared.

Bone marrow transplantation is an alternative treatment for Gaucher disease and offers a less costly and permanent cure instead of relying on expensive enzyme infusions. However, because bone marrow donors are in short supply and Gaucher disease is not life-threatening and can be treated by enzyme infusion, many think bone marrow transplantation should be reserved for life-threatening diseases such as leukemia.

If you worked for an insurance company, how would you decide which treatment for Gaucher disease would be covered by insurance? As a general principle, do you agree with the idea of reserving certain treatments for specific conditions, when several options are available?

As in Leah's case, genetic testing is often a part of diagnosing a genetic disorder. In the Genetics in Practice section at the end of this chapter, discover how other methods, including genetic counseling, are used along with genetic testing to diagnose and treat genetic disorders.

2-2 The Chemistry of Cells

Cells are the basic structural and functional unit of living systems. But cells themselves are largely constructed from four classes of large molecules, often called **macromolecules** (**Table 2.1**). These components are carbohydrates, lipids, proteins, and nucleic acids. To understand how cell structure and function are related, we will briefly examine some of the structural and functional properties of cellular macromolecules. In later chapters, we will discuss how mutations disrupt the synthesis or function of these molecules, resulting in genetic disorders.

Carbohydrates include small, water-soluble sugars and large polymers made of sugars. In the cell, carbohydrates have three important functions: They are structural components of cells; they act as energy sources for the cell; and, in combination with proteins on the surface, they give cells a molecular identity.

Lipids are a structurally and functionally diverse class of biological molecules partially defined by their insolubility in water. Lipids have many functions: They are structural components of membranes, some serve as energy reserves, while others act as hormones and vitamins. Lipids are classified into three major groups: fats and oils, phospholipids, and steroids. The phospholipids play important roles in the structure and function of the cell membrane.

Macromolecules Large cellular polymers assembled by chemically linking monomers together.

Carbohydrates Macromolecules including sugars, glycogen, and starches composed of sugar monomers linked and cross-linked together.

Lipids A class of cellular macromolecules including fats and oils that are insoluble in water.

TABLE 2.1 The Main Macromolecules in Cells

Class	Subclasses	Examples	Functions
CARBOHYDRATES	**Monosaccharides** (simple sugars)	Glucose	Energy source
	Oligosaccharides (short-chain carbohydrates)	Sucrose	A common sugar
	Polysaccharides (complex carbohydrates)	Starch, glycogen	Energy storage
LIPIDS	**Glycerides** Glycerol plus fatty acids	Fats	Energy storage
	Phospholipids Glycerol, fatty acids, phosphate group	Lecithin	Structure of cell membranes
	Sterols Carbon-ring structures	Cholesterol	Membrane structure, precursor to steroid hormones
PROTEINS	**Mostly fibrous** (sheets of polypeptide chains; mostly water insoluble)	Keratin Collagen	Structure of hair Structure of bones
	Mostly globular (protein chains folded into globular shapes; mostly water soluble)	Enzymes Hemoglobin Insulin Antibodies	Catalysts Oxygen transport Hormone Immune system
NUCLEIC ACIDS	**Adenosine phosphates**	ATP	Energy carrier
	Nucleic acids (polymers of nucleotides)	DNA, RNA	Storage, transmission of genetic information

Proteins A class of cellular macromolecules composed of amino acid monomers linked together and folded into a three-dimensional shape.

Nucleic acids A class of cellular macromolecules composed of nucleotide monomers linked together. There are two types of nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which differ in the structure of the monomers.

Proteins are the most functionally diverse class of macromolecules. Proteins are polymers, made up of one or more chains of subunits, called amino acids. The varied structures of proteins are reflected in their diversity of functions. Some of these are listed in Table 2.1.

Nucleic acids are polymers made from nucleotide subunits. Nucleotides themselves have important functions in energy transfer, but nucleic acids are the storehouses of genetic information in the cell. The information is encoded in the nucleotide sequence.

The combinations of various types of these four macromolecules are the foundation for the structural and functional diversity seen in the more than 200 cell types in the human body. In the next section, we will describe some of the fundamental structural and functional aspects of cells and their contents.

2-3 Cell Structure Reflects Function

We will review some of the basic aspects of human cell structure and discuss the functions of cell components and how these functions are disrupted in genetic disorders. Although cells differ widely in their size, shape, function, and life cycle, at a structural level they are fundamentally similar—they all have a plasma membrane, cytoplasm, membranous organelles, and a membrane-bound nucleus. An idealized human cell is shown in **Figure 2.1**. A cell's shape, internal organization, and function are under genetic control, and many genetic disorders cause changes in cellular structure and/or function.

There are two cellular domains: the plasma membrane and the cytoplasm.

A double-layered plasma membrane separates the cell from the external environment. Lipids in the membrane provide structure, and a patchwork of different proteins gives the membrane many of its functional characteristics. The plasma membrane controls the exchange of materials with the environment outside the cell (**Figure 2.2**).

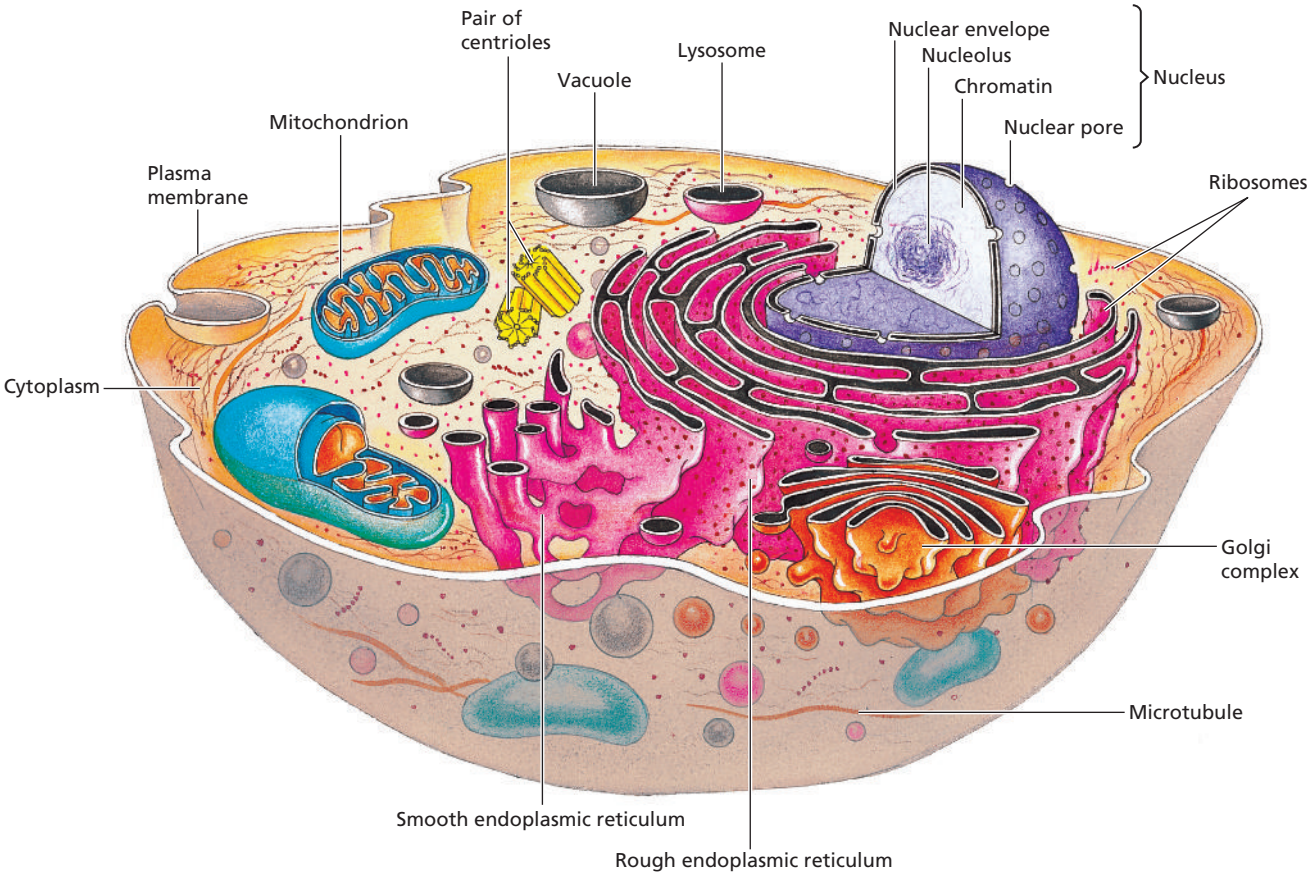


FIGURE 2.1 A diagram of a generalized human cell showing the organization and distribution of organelles as they would appear in the transmission electron microscope. The type, number, and location of organelles are related to cell function.

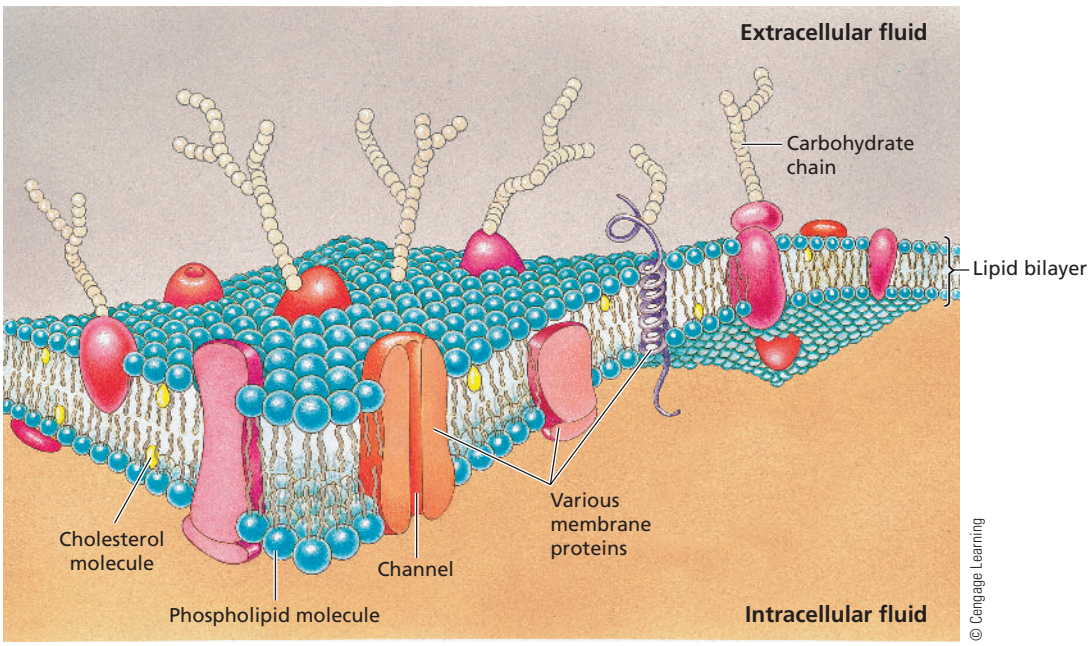


FIGURE 2.2 The plasma membrane. Proteins are embedded in a double layer of lipids. Short carbohydrate polymers are attached to some proteins on the outer surface of the membrane.

Molecules Structures composed of two or more atoms held together by chemical bonds.

Gases, water, and some small **molecules** pass through the membrane easily, but others are transported by energy-requiring systems. Proteins with attached carbohydrates in and on the plasma membrane provide cells with a form of molecular identity. The type and number of these molecules are genetically controlled and are responsible for many important properties of cells, including blood type and compatibility for organ transplants. Several genetic disorders, including cystic fibrosis (MIM 219700; see Chapter 4 for an explanation of MIM numbers and the catalog of human genetic disorders), are caused by defects in the plasma membrane. Cystic fibrosis (CF) is caused by a functional defect in a membrane protein that controls the movement of chloride ions across the plasma membrane. This leads to the accumulation of thick mucus in the lungs and ducts of several organs. Despite intensive therapy and drug treatments, the average survival of people with this disorder is only about 25 years. The symptoms and premature death associated with CF emphasize the important role of membranes in controlling cell function.

Organelles Cytoplasmic structures that have a specialized function.

The plasma membrane encloses the cytoplasm, which is a complex mixture of molecules and membrane-enclosed structures known collectively as **organelles**.

Organelles are specialized structures in the cytoplasm.

The cytoplasm in a human cell has an organization that is related to its function, which is reflected in the number and type of organelles it contains. In eukaryotes, cytoplasmic organelles divide the cell into a number of functional compartments. **Table 2.2** summarizes the major organelles and their functions. We will review some of them here.

TABLE 2.2 Overview of Cell Organelles

Organelle	Structure	Function
Nucleus	Round or oval body; surrounded by nuclear envelope.	Contains the genetic information necessary to control cell structure and function.
Nucleolus	Round or oval body in the nucleus containing DNA and RNA.	Produces ribosomes.
Endoplasmic reticulum	Network of membranous tubules in the cytoplasm of the cell. Smooth endoplasmic reticulum contains no ribosomes. Rough endoplasmic reticulum is studded with ribosomes.	Smooth endoplasmic reticulum (SER) is involved in producing phospholipids and has many different functions in different cells. Rough endoplasmic reticulum (RER) is the site of the synthesis of proteins for intracellular and extracellular use.
Ribosomes	Small particles found in the cytoplasm; made of RNA and protein.	Aids in the production of proteins on the RER and in ribosome complexes (polysomes).
Golgi complex	Series of flattened sacs and associated vesicles.	Sorts, chemically modifies, and packages proteins produced on the RER.
Secretory vesicles	Membrane-bound vesicles containing proteins produced by the RER and repackaged by the Golgi complex; contain protein hormones or enzymes.	Stores protein hormones or enzymes in the cytoplasm, awaiting a signal for release.
Lysosome	Membrane-bound structure containing digestive enzymes.	Combines with food vacuoles and digests materials engulfed by cells.
Mitochondria	Round, oval, or elongated structures with a double membrane. The inner membrane is extensively folded.	Completes the breakdown of glucose, producing ATP.

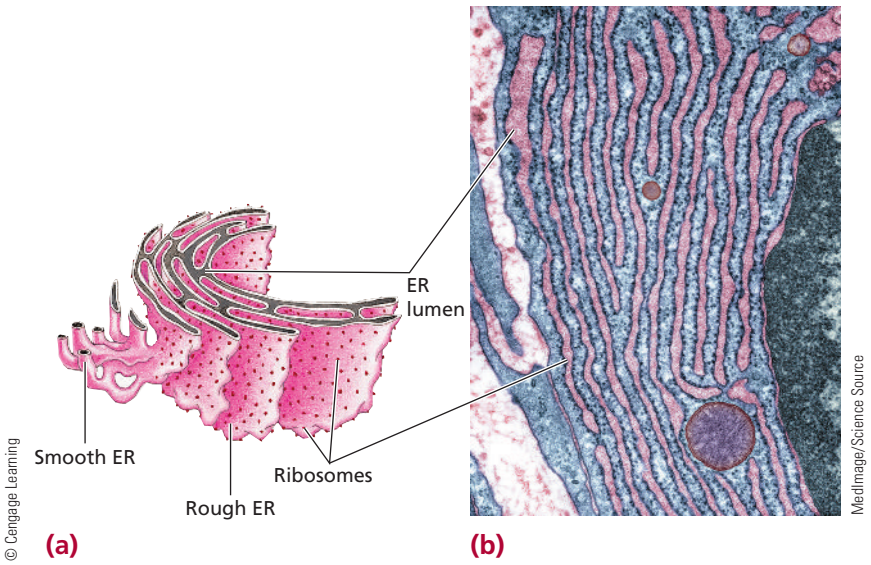


FIGURE 2.3 (a) Three-dimensional representation of the endoplasmic reticulum (ER) showing the relationship between the smooth and rough ER. (b) An electron micrograph of ribosome-studded rough ER.

The endoplasmic reticulum folds, sorts, and ships proteins.

The **endoplasmic reticulum (ER)** is a network of membrane channels and pockets (vesicles) within the cytoplasm (**Figure 2.3a**). The outer surface of the rough ER (RER) is covered with **ribosomes**, another cytoplasmic component (**Figure 2.3b**). The smooth ER (SER) has no ribosomes on its surface; the RER and SER, although interconnected, have different functions. Ribosomes are the most numerous cellular structures and can be found in the cytoplasm or attached to the outer surface of the RER. Ribosomes are involved in protein synthesis (discussed in Chapter 9). The space inside the ER is called the lumen. Ribosomes on the RER surface synthesize amino acid chains known as polypeptides that are inserted into the lumen where they are folded and modified to form proteins and prepared for transport to other locations in the cell, or tagged for export from the cell. In some genetic disorders, including cystic fibrosis (MIM 219700), defective proteins do not fold properly within the RER, and are destroyed, resulting in the clinical symptoms of the disorder. The SER functions in lipid and steroid synthesis and also plays a role in the metabolism of carbohydrates.

Endoplasmic reticulum (ER) A system of cytoplasmic membranes arranged into sheets and channels whose function it is to synthesize and transport gene products.

Ribosomes Cytoplasmic particles that aid in the production of proteins.

Molecular sorting takes place in the Golgi complex.

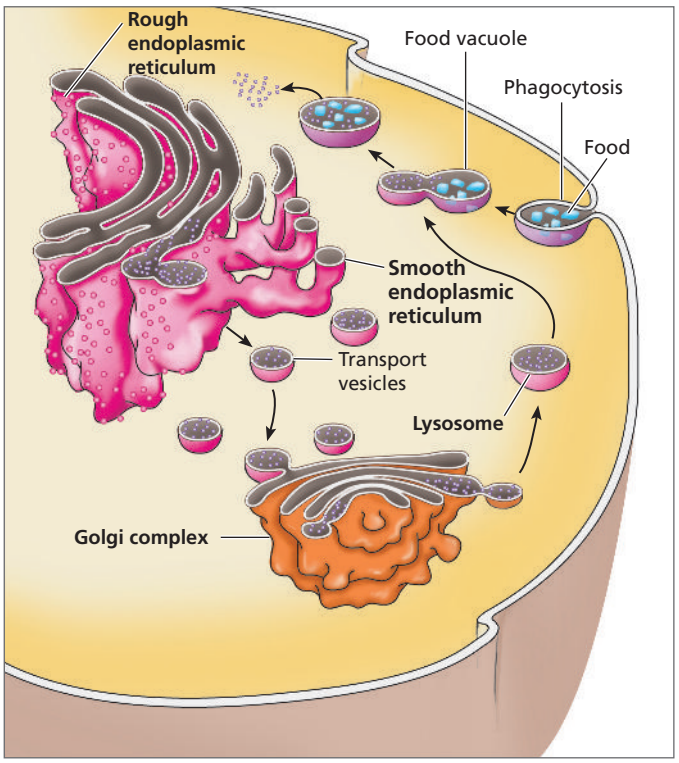
Animal cells contain clusters of flattened membrane sacs called the **Golgi complex**. The Golgi receives vesicles pinched off from the RER containing proteins. In the Golgi, these proteins are modified and sorted into other vesicles (**Figure 2.4**), which then deliver their contents to destinations inside and outside the cell. Functional abnormalities of the Golgi are responsible for a number of genetic disorders, including Menkes disease (MIM 309400, a condition associated with abnormal copper metabolism that is fatal in infancy). The Golgi complex is also a source of membranes for other organelles, including lysosomes.

Golgi complex Membranous cellular organelles composed of a series of flattened sacs. They sort, modify, and package proteins synthesized in the ER.

Lysosomes are cytoplasmic disposal sites.

The **lysosomes** are membrane-enclosed vesicles containing digestive enzymes made in the RER. In the RER, these enzymes are packaged into vesicles and transported to

Lysosomes Membrane-enclosed organelles in eukaryotic cells that contain digestive enzymes.



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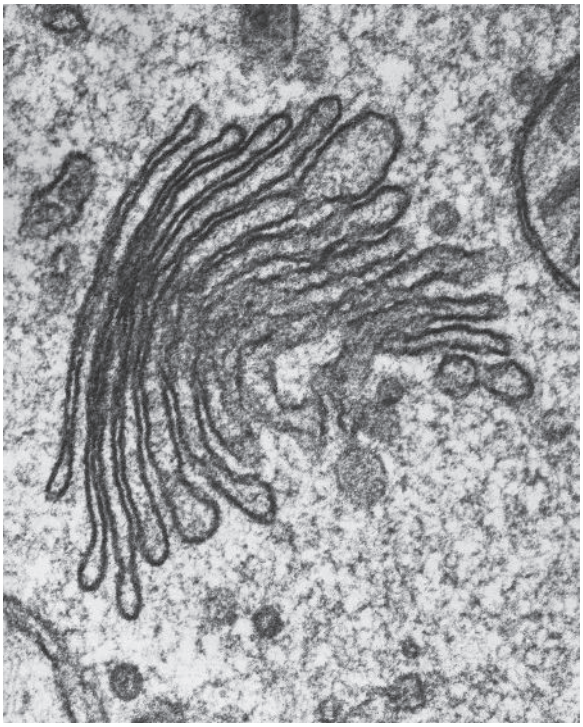

Biophoto Associates/Science Source

(a) **(b)**

FIGURE 2.4 (a) The relationship between the Golgi complex and lysosomes. Digestive enzymes are synthesized on ribosomes attached to the ER, internalized, and moved to the Golgi in transport vesicles. In the Golgi, the enzymes are modified and packaged. Lysosomes pinch off the ends of the Golgi membrane. In the cytoplasm, lysosomes fuse with and digest the contents of vesicles that are internalized at the plasma membrane. (b) A transmission electron micrograph of the Golgi complex.

the Golgi, where they are modified and repackaged into vesicles that bud off the Golgi to form lysosomes (see Figure 2.4). Lysosomes are the processing and recycling centers of the cell. Proteins, fats, carbohydrates, and worn-out organelles in the cell that are marked for destruction end up in lysosomes, where they are broken down and recycled or exported for disposal. Lysosomes are important in cellular maintenance, and about 40 genetic disorders, including Gaucher disease (MIM 230800)—described at the beginning of this chapter—disrupt lysosome function. In most of these disorders, the mutation disrupts production or function of an enzyme. When this happens, specific molecules are not digested and accumulate in the lysosomes. As the lysosomes enlarge, they become distorted, eventually altering normal cell structure and function. Disorders that affect the structure or function of lysosomes and other cellular organelles reinforce the point made earlier that the functioning of the organism can be explained by events that occur within its cells.

Mitochondria are sites of energy conversion.

Mitochondria (singular: mitochondrion) Membrane-bound organelles, present in the cytoplasm of all eukaryotic cells, that are the sites of energy production.

Mitochondria (singular: mitochondrion) are centers of energy transformation in the cell and are composed of an outer and an inner membrane (**Figure 2.5**). Mitochondria carry genetic information in the form of circular DNA molecules; they are self-replicating organelles. Mutations in mitochondrial DNA affect mitochondrial function and cause a number of genetic disorders, including Kearns-Sayre syndrome (MIM 530000) and MELAS syndrome (MIM 535000). These and other genetic disorders affecting mitochondria are discussed in Chapter 4.

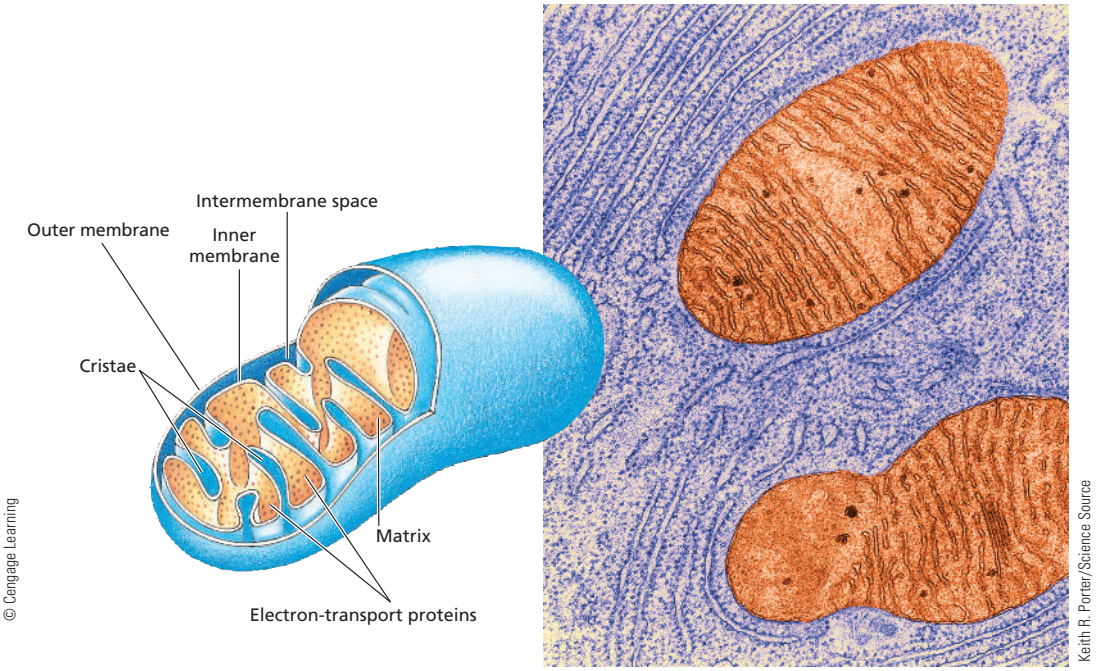

FIGURE 2.5 The mitochondrion is the center of energy transformation in the cell. (a) The infolded inner membrane forms two compartments where chemical reactions transfer energy from one form to another, allowing the cell to power many of its biochemical reactions. (b) A colorized transmission electron micrograph of a mitochondrion.

The nucleus contains chromosomes.

The largest organelle is the **nucleus** (**Figure 2.6a**). It is enclosed by a double membrane called the nuclear envelope, which is studded with pores that allow communication between the nucleus and cytoplasm (**Figure 2.6b**). Within the nucleus, dense regions known as **nucleoli** (**singular: nucleolus**; Figure 2.6a) synthesize ribosomes. Dark strands of **chromatin** are seen throughout the nucleus (Figure 2.6a). As a cell prepares to divide, the chromatin condenses to form the **chromosomes** (**Figure 2.6c**).

In humans, chromosomes exist in pairs. Most human cells, called somatic cells, carry 23 pairs, or 46 chromosomes, but certain cells, such as sperm and eggs, carry only one copy of each chromosome and have 23 unpaired chromosomes. Human males have one

Nucleus The membrane-bound organelle in eukaryotic cells that contains the chromosomes.

Nucleolus (plural: nucleoli) A nuclear region that functions in the synthesis of ribosomes.

Chromatin The DNA and protein components of chromosomes, visible as clumps or threads in nuclei.

Chromosomes The threadlike structures in the nucleus that carry genetic information.

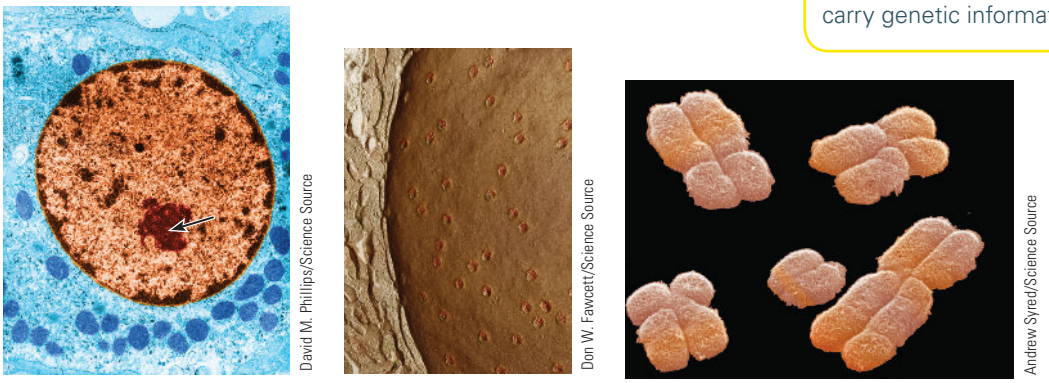

FIGURE 2.6 (a) The nucleus is bounded by a double membrane called the nuclear envelope. The nucleolus (*arrow*) is a prominent structure in the nucleus and is the site of ribosome synthesis. When the cell is not dividing, the chromosomes are dispersed throughout the nucleus as clumps of dark-staining chromatin. (b) The nuclear envelope is studded with pores, which allow exchange of materials between the nucleus and the cytoplasm. (c) Chromosomes are DNA/protein complexes. Pictured here are replicated chromosomes isolated from a dividing cell.