

Contents

Preface viii

Acknowledgments ix

Dedication x

1 The History and Impact of Genetics in Medicine 1

- Gregor Mendel and the Laws of Inheritance 1
- DNA as the Basis of Inheritance 3
- The Fruit Fly 4
- The Origins of Medical Genetics 4
- The Impact of Genetic Disease 6
- Major New Developments 6
- The Societal Impact of Advances in Genetics 8

SECTION A THE SCIENTIFIC BASIS OF HUMAN GENETICS

2 The Cellular and Molecular Basis of Inheritance 9

- The Cell 9
- DNA: The Hereditary Material 9
- Chromosome Structure 10
- Types of DNA Sequence 11
- Transcription 14
- Translation 15
- The Genetic Code 16
- Regulation of Gene Expression 16
- RNA-Directed DNA Synthesis 17
- Mutations 17
- Mutations and Mutagenesis 21

3 Chromosomes and Cell Division 24

- Human Chromosomes 24
- Methods of Chromosome Analysis 26
- Molecular Cytogenetics 27
- Chromosome Nomenclature 28
- Cell Division 29
- Gametogenesis 32
- Chromosome Abnormalities 33

4 Finding the Cause of Monogenic Disorders by Identifying Disease Genes 42

- Position-Independent Identification of Human Disease Genes 42
- Positional Cloning 43

The Human Genome Project 44

Identifying the Genetic Etiology of Monogenic Disorders by Next-Generation Sequencing 47

5 Laboratory Techniques for Diagnosis of Monogenic Disorders 50

- PCR (Polymerase Chain Reaction) 50
- Application of DNA Sequence Polymorphisms 50
- Nucleic Acid Hybridization Techniques 52
- Mutation Detection 54
- Sequencing-Based Methods 57
- Dosage Analysis 60
- Towards Genome Sequencing as a Clinical Diagnostic Test 64

6 Patterns of Inheritance 66

- Family Studies 66
- Mendelian Inheritance 66
- Multiple Alleles and Complex Traits 75
- Anticipation 75
- Mosaicism 76
- Uniparental Disomy 77
- Genomic Imprinting 77
- Mitochondrial Inheritance 80

7 Population and Mathematical Genetics 83

- Allele Frequencies in Populations 83
- Genetic Polymorphism 88
- Segregation Analysis 88
- Genetic Linkage 89
- Medical and Societal Intervention 92
- Conclusion 93

8 Risk Calculation 94

- Probability Theory 94
- Autosomal Dominant Inheritance 95
- Autosomal Recessive Inheritance 97
- Sex-Linked Recessive Inheritance 98
- The Use of Linked Markers 99
- Bayes' Theorem and Prenatal Screening 99
- Empiric Risks 100

9 Developmental Genetics 102

- Fertilization and Gastrulation 102
- Developmental Gene Families 103
- The Pharyngeal Arches 114
- The Role of Cilia in Developmental Abnormalities 115

- The Limb as a Developmental Model 115
- Developmental Genes and Cancer 119
- Positional Effects and Developmental Genes 121
- Hydatidiform Moles 121
- Epigenetics and Development 121
- Sex Determination and Disorders of Sex Development 123
- Twinning 127

SECTION B GENETICS IN MEDICINE AND GENOMIC MEDICINE

- 10 Common Disease, Polygenic and Multifactorial Genetics 130**
 - Types and Mechanisms of Genetic Susceptibility 130
 - Approaches to Demonstrating Genetic Susceptibility to Common Diseases 131
 - Polygenic Inheritance and the Normal Distribution 132
 - Multifactorial Inheritance—the Liability/Threshold Model 133
 - Identifying Genes That Cause Multifactorial Disorders 134
 - Disease Models for Multifactorial Inheritance 137
- 11 Screening for Genetic Disease 144**
 - Screening Those at High Risk 144
 - Carrier Testing for Autosomal Recessive and X-Linked Disorders 144
 - Presymptomatic Diagnosis of Autosomal Dominant Disorders 145
 - Ethical Considerations in Carrier Detection and Predictive Testing 147
 - Population Screening 147
 - Criteria for a Screening Program 148
 - Prenatal and Postnatal Screening 149
 - Population Carrier Screening 151
 - Genetic Registers 152
- 12 Hemoglobin and the Hemoglobinopathies 154**
 - Structure of Hb 154
 - Developmental Expression of Hemoglobin 154
 - Globin Chain Structure 155
 - Synthesis and Control of Hemoglobin Expression 156
 - Disorders of Hemoglobin 156
 - Clinical Variation of the Hemoglobinopathies 161
 - Antenatal and Newborn Hemoglobinopathy Screening 162
- 13 Immunogenetics 164**
 - Immunity 164
 - Innate Immunity 164
 - Specific Acquired Immunity 166
 - Inherited Immunodeficiency Disorders 171
 - Blood Groups 174

- 14 The Genetics of Cancer...and Cancer Genetics 177**
 - Differentiation Between Genetic and Environmental Factors in Cancer 177
 - Oncogenes 179
 - Tumor Suppressor Genes 182
 - Epigenetics and Cancer 185
 - Genetics of Common Cancers 186
 - DNA Tumor Profiling and Mutation Signatures 188
 - Genetic Counseling in Familial Cancer 193
- 15 Pharmacogenetics, Personalized Medicine and the Treatment of Genetic Disease 200**
 - Pharmacogenetics 200
 - Drug Metabolism 200
 - Genetic Variations Revealed by the Effects of Drugs 201
 - Personalized Medicine 202
 - Treatment of Genetic Disease 204
 - Therapeutic Applications of Recombinant DNA Technology 206
 - Gene Therapy 207
 - RNA Modification 210
 - Targeted Gene Correction 210
 - Stem Cell Therapy 210

SECTION C CLINICAL GENETICS, COUNSELING, AND ETHICS

- 16 Congenital Abnormalities, Dysmorphic Syndromes, and Learning Disability 215**
 - Incidence 215
 - Definition and Classification of Birth Defects 216
 - Genetic Causes of Malformations 219
 - Environmental Agents (Teratogens) 225
 - Malformations of Unknown Cause 228
 - Counseling 229
 - Learning Disability 229
- 17 Chromosome Disorders 236**
 - Incidence of Chromosome Abnormalities 236
 - Disorders of the Sex Chromosomes 239
 - 'Classic' Chromosome Deletion Syndromes 243
 - Microarray-CGH 245
 - Chromosome Disorders and Behavioral Phenotypes 250
 - Chromosomal Breakage Syndromes 250
 - Indications for Chromosomal/Microarray-CGH Analysis 253
- 18 Inborn Errors of Metabolism 255**
 - Disorders of Amino Acid and Peptide Metabolism 255
 - Disorders of Carbohydrate Metabolism 260
 - Disorders of Steroid Metabolism 261
 - Disorders of Lipid and Lipoprotein Metabolism 262

Lysosomal Storage Disorders 263
Disorders in the Metabolism of Purines, Pyrimidines,
and Nucleotides 265
Disorders of Porphyrin and Heme Metabolism 266
Disorders in the Metabolism of Trace Elements
and Metals 266
Peroxisomal Disorders 268
Disorders of Fatty Acid and Ketone Body
Metabolism 269
Disorders of Energy Metabolism 269
Prenatal Diagnosis of Inborn Errors of
Metabolism 271

19 Mainstream Monogenic Disorders 273

Neurological Disorders 273
The Hereditary Ataxias 274
Inherited Peripheral Neuropathies 275
Motor Neurone Disease (MND) 278
Neurocutaneous Disorders 278
Muscular Dystrophies 281
Respiratory Disorders 286
Inherited Cardiac Conditions (ICCs) 289
Connective Tissue Disorders 291
Renal Disorders 296
Blood Disorders 298

20 Prenatal Testing and Reproductive Genetics 303

Techniques Used in Prenatal Diagnosis 303
Prenatal Screening 306
Indications for Prenatal Testing 309
Special Problems in Prenatal Diagnosis 311
Termination of Pregnancy 312
Preimplantation Genetic Diagnosis 313

Assisted Conception and Implications for Genetic
Disease 313
Non-Invasive Prenatal Testing (NIPT) 314
Prenatal Treatment 315

21 Genetic Counseling 317

Definition 317
Establishing the Diagnosis 317
Calculating and Presenting the Risk 318
Discussing the Options 319
Communication and Support 319
Genetic Counseling—Directive or
Non-Directive? 319
Outcomes in Genetic Counseling 319
Special Issues in Genetic
Counseling 320

22 Ethical and Legal Issues in Medical Genetics 323

General Principles 323
Ethical Dilemmas in the Genetics Clinic 325
Ethical Dilemmas and the Public Interest 327
Conclusion 330

Glossary 332

Appendix: Websites and Clinical Databases 349

Multiple-Choice Questions 351

Case-Based Questions 360

Multiple-Choice Answers 365

Case-Based Answers 375

Index 382