

CONTENTS

Dedication ii

Preface ix

Acknowledgements x



SECTION

A

PRINCIPLES OF HUMAN GENETICS

- 1 The history and impact of genetics in medicine** 3
 - Gregor Mendel and the laws of inheritance 3
 - DNA as the basis of inheritance 5
 - The fruit fly 6
 - The origins of medical genetics 7
 - The impact of genetic disease 9
 - Major new developments 9
- 2 The cellular and molecular basis of inheritance** 12
 - The cell 12
 - DNA: the hereditary material 12
 - Chromosome structure 14
 - Types of DNA sequence 14
 - Transcription 18
 - Translation 18
 - The genetic code 20
 - Regulation of gene expression 20
 - RNA-directed DNA synthesis 22
 - Mutations 22
 - Mutations and mutagenesis 26
- 3 Chromosomes and cell division** 30
 - Human chromosomes 30
 - Methods of chromosome analysis 32
 - Molecular cytogenetics 34
 - Chromosome nomenclature 38

Cell division 40
Gametogenesis 43
Chromosome abnormalities 45

4 DNA technology and applications 55

DNA cloning 55
Techniques of DNA analysis 59
Biological hazards of DNA technology 70

5 Mapping and identifying genes for monogenic disorders 73

Position-independent identification of human disease genes 73
Positional cloning 74
The Human Genome Project 75

6 Developmental genetics 82

Fertilization and gastrulation 82
Developmental gene families 83
The limb as a developmental model 93
Developmental genes and cancer 94
Positional effects and developmental genes 95
Hydatidiform moles 96
Sexual differentiation and determination 96
Epigenetics and development 98
Twinning 101

7 Patterns of inheritance 103

Family studies 103
Mendelian inheritance 103
Multiple alleles and complex traits 113
Anticipation 114
Mosaicism 114
Uniparental disomy 115
Genomic imprinting 115
Mitochondrial inheritance 120

8 Mathematical and population genetics 122

Allele frequencies in populations 122
Genetic polymorphism 128
Segregation analysis 129
Genetic linkage 130

Medical and societal intervention 133
Conclusion 134

- 9 Polygenic and multifactorial inheritance 136**
Polygenic inheritance and the normal distribution 136
Multifactorial inheritance – the liability/threshold model 138
Heritability 139
Identifying genes that cause multifactorial disorders 140
Conclusion 143



SECTION

B

GENETICS IN MEDICINE

- 10 Hemoglobin and the hemoglobinopathies 147**
Structure of hemoglobin 147
Developmental expression of hemoglobin 147
Globin chain structure 148
Synthesis and control of hemoglobin expression 149
Disorders of hemoglobin 150
Clinical variation of the hemoglobinopathies 156
- 11 Biochemical genetics 158**
Inborn errors of metabolism 158
Disorders of amino-acid metabolism 158
Disorders of branched-chain amino-acid metabolism 163
Urea cycle disorders 163
Disorders of carbohydrate metabolism 164
Disorders of steroid metabolism 165
Disorders of lipid metabolism 167
Lysosomal storage disorders 168
Disorders of purine/pyrimidine metabolism 171
Disorders of porphyrin metabolism 171
Organic-acid disorders 172
Disorders of copper metabolism 172
Peroxisomal disorders 173
Disorders affecting mitochondrial function 174
Prenatal diagnosis of inborn errors of metabolism 176
- 12 Pharmacogenetics 177**
Definition 177
Drug metabolism 177
Genetic variations revealed solely by the effect of drugs 178

Pharmacogenetics 181

Ecogenetics 182

13 Immunogenetics 184

Immunity 184

Innate immunity 184

Specific acquired immunity 185

Inherited immunodeficiency disorders 190

Blood groups 192

14 Cancer genetics 196

Differentiation between genetic and environmental factors in cancer 196

Oncogenes 198

Tumor suppressor genes 201

Epigenetics and cancer 205

Genetics of common cancers 207

Genetic counseling in familial cancer 212

15 Genetic factors in common diseases 219

Genetic susceptibility to common disease 219

Diabetes mellitus 221

Crohn disease 224

Hypertension 225

Coronary artery disease 225

Epilepsies 227

Autism 228

Schizophrenia 228

Alzheimer disease 229

Hemochromatosis 230

Venous thrombosis 231

Atopic disease 232

Age-related macular degeneration 232



SECTION

C

CLINICAL GENETICS

16 Congenital abnormalities and dysmorphic syndromes 237

Incidence 237

Definition and classification of birth defects 238

Genetic causes of malformations 243

Environmental agents (teratogens) 248

Malformations of unknown cause 251

Counseling 252

17 Genetic counseling	253
Definition	253
Establishing the diagnosis	253
Calculating and presenting the risk	254
Discussing the options	255
Communication and support	255
Genetic counseling – directive or non-directive?	256
Outcomes in genetic counseling	256
Special problems in genetic counseling	257
18 Chromosome disorders	261
Incidence of chromosome abnormalities	261
Disorders of the sex chromosomes	271
Chromosome disorders and behavioral phenotypes	275
Disorders of sexual differentiation	275
Chromosomal breakage syndromes	277
Indications for chromosomal analysis	279
19 Single-gene disorders	282
Huntington disease	282
Myotonic dystrophy	284
Hereditary motor and sensory neuropathy	286
Neurofibromatosis	287
Marfan syndrome	289
Cystic fibrosis	291
Inherited cardiac arrhythmias and cardiomyopathies	294
Spinal muscular atrophy	296
Duchenne muscular dystrophy	297
Hemophilia	299
20 Screening for genetic disease	303
Screening those at high risk	303
Carrier testing for autosomal recessive and X-linked disorders	303
Presymptomatic diagnosis of autosomal dominant disorders	306
Ethical considerations in carrier detection and predictive testing	308
Population screening	308
Criteria for a screening program	309
Neonatal screening	310
Population carrier screening	311
Genetic registers	313

21 Prenatal testing and reproductive genetics	315
Techniques used in prenatal diagnosis	315
Prenatal screening	318
Indications for prenatal diagnosis	321
Special problems in prenatal diagnosis	323
Termination of pregnancy	325
Preimplantation genetic diagnosis	325
Assisted conception and implications for genetic disease	326
Detection of fetal cells in the maternal circulation	328
Prenatal treatment	328
22 Risk calculation	330
Probability theory	330
Autosomal dominant inheritance	331
Autosomal recessive inheritance	333
Sex-linked recessive inheritance	334
The use of linked markers	336
Bayes' theorem and prenatal screening	337
Empiric risks	337
23 Treatment of genetic disease	340
Conventional approaches to treatment of genetic disease	340
Therapeutic applications of recombinant DNA technology	342
Gene therapy	342
24 Ethical and legal issues in medical genetics	354
General principles	354
Ethical dilemmas	356
Ethical dilemmas in a wider context	359
Conclusion	362
Appendix – Websites and clinical databases	364
Glossary	366
Multiple-choice questions	378
Case-based questions	390
Multiple-choice answers	395
Case-based answers	407
Index	413