

# CONTENTS

## SECTION

# A

## PRINCIPLES OF HUMAN GENETICS

### 1 The history and impact of genetics in medicine 3

- Early beginnings 3
- Gregor Mendel and the laws of inheritance 3
- The chromosomal basis of inheritance 5
- The fruit fly 5
- The origins of medical genetics 6
- Classification of genetic disease 6
- Definitions 7
- The impact of genetic disease 7
- Major new developments 8

### 2 The cellular and molecular basis of inheritance 11

- The cell 11
- DNA: the hereditary material 11
- Chromosome structure 13
- Types of DNA sequences 14
- Transcription 17
- Translation 18
- The genetic code 18
- Regulation of gene expression 19
- RNA-directed DNA synthesis 20
- Mutations 21
- Mutagens and mutagenesis 24

### 3 Chromosomes and cell division 29

- Human chromosomes 29
- Methods of chromosome analysis 31
- Molecular cytogenetics 34
- Chromosome nomenclature 37
- Cell division 38
- Gametogenesis 42
- Chromosome abnormalities 44

### 4 DNA technology and applications 55

- Principles of DNA technology 55
- Techniques of DNA analysis 60
- Applications of the techniques of DNA analysis 64
- Possible biological hazards of DNA technology 75

### 5 Developmental genetics 81

- Fertilization and gastrulation 81
- Developmental gene families 82
- The limb as a developmental model 87
- Developmental genes and cancer 88
- Position effects and developmental genes 89
- Hydatidiform moles 89
- Sexual differentiation and determination 90
- Twinning 93

### 6 Patterns of inheritance 97

- Family studies 97
- Mendelian inheritance 97
- Non-Mendelian inheritance 106

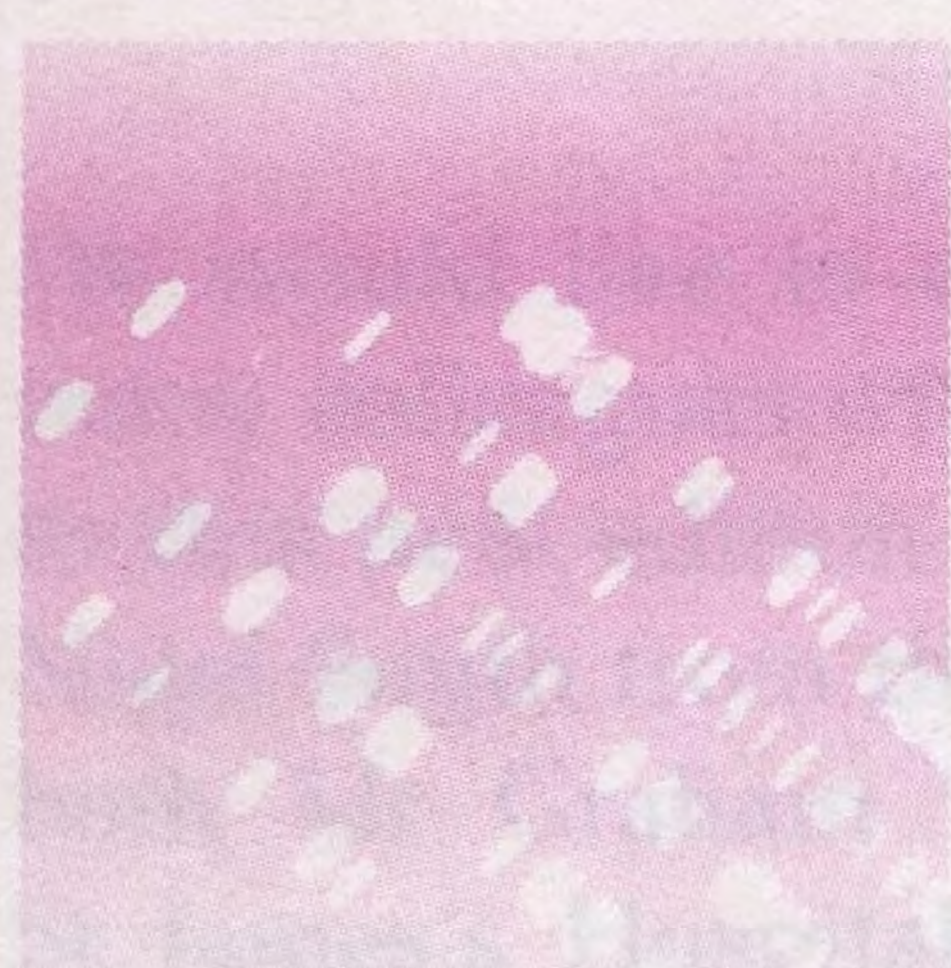


**7 Mathematical and population genetics 113**

- Allele frequencies in populations 113
- Genetic polymorphism 120
- Segregation analysis 120
- Genetic linkage 121
- Medical and societal intervention 124

**8 Polygenic and multifactorial inheritance 127**

- Polygenic inheritance and the normal distribution 127
- Multifactorial inheritance – the liability/threshold model 129
- Heritability 130
- Identifying genes which cause multifactorial disorders 130
- Disease models for multifactorial inheritance 133
- Conclusion 134



## SECTION

**B****GENETICS  
IN MEDICINE****9 Haemoglobin and the haemoglobinopathies 139**

- Structure of haemoglobin 139
- Developmental expression of haemoglobin 139
- Globin chain structure 140
- Synthesis and control of haemoglobin expression 142
- Disorders of haemoglobin 142
- Clinical variation of the haemoglobinopathies 149

**10 Biochemical genetics 151**

- The inborn errors of metabolism 151
- Disorders of amino acid metabolism 151
- Disorders of branched chain amino acid metabolism 156
- Urea cycle disorders 156
- Disorders of carbohydrate metabolism 157
- Disorders of steroid metabolism 158
- Disorders of lipid metabolism 160
- Lysosomal storage disorders 161
- Disorders of purine/pyrimidine metabolism 164
- Disorders of porphyrin metabolism 165
- Organic acid disorders 166
- Disorders of copper metabolism 166
- Peroxisomal disorders 167
- Prenatal diagnosis of the inborn errors of metabolism 168

**11 Pharmacogenetics 169**

- Definition 169
- Drug metabolism 169
- Genetic variations revealed solely by the effects of drugs 170
- Hereditary disorders with altered drug response 173
- Evolutionary origin of variation in drug responses 174

Pharmacogenomics 174

Ecogenetics 174

**12 Immunogenetics 177**

- Immunity 177
- Innate immunity 177
- Specific acquired immunity 178
- Inherited immunodeficiency disorders 183
- Blood groups 186

**13 The genetics of cancer 189**

- Differentiating between genetic and environmental factors in cancer 189
- Oncogenes 191
- Tumour suppressor genes 195
- Genetics of common cancers 199
- Genetic counselling in familial cancer 202

**14 Genetic factors in common diseases 209**

- Genetic susceptibility to common disease 209
- Diabetes mellitus 212
- Hypertension 214
- Coronary artery disease 217
- Schizophrenia 219
- Affective disorders 221
- Alzheimer's disease 222

**15 Genetics and congenital abnormalities 225**

- Incidence 225
- Definitions and classification of birth defects 226
- Genetic causes of malformations 230
- Environmental agents (teratogens) 233
- Malformations of unknown cause 236



## SECTION

## C

CLINICAL  
GENETICS

- 16 Genetic counselling** 241  
 Definition 241  
 Establishing the diagnosis 241  
 Calculating and presenting the risk 242  
 Discussing the options 243  
 Communication and support 243  
 Genetic counselling – directive or non-directive? 244  
 Outcomes in genetic counselling 244  
*Special problems in genetic counselling* 245
- 17 Chromosome disorders** 249  
 Incidence of chromosome abnormalities 249  
 Disorders of the autosomes 250  
 Disorders of the sex chromosomes 256  
 Disorders of sexual differentiation 260  
 Chromosome breakage syndromes 262  
 Indications for chromosome analysis 263
- 18 Single gene disorders** 267  
 Huntington's disease 267  
 Myotonic dystrophy 269  
 Hereditary motor and sensory neuropathy 271  
 Neurofibromatosis 272  
 Human prion diseases 274  
 Cystic fibrosis 276  
 Spinal muscular atrophy 279  
 Duchenne muscular dystrophy 280  
 Haemophilia 282
- 19 Carrier detection and presymptomatic diagnosis** 287  
 Carrier testing for autosomal recessive and X-linked disorders 287  
 Presymptomatic diagnosis of autosomal dominant disorders 290  
 Ethical considerations in carrier detection and predictive testing 292
- 20 Risk calculation** 293  
 Probability theory 293  
 Autosomal dominant inheritance 294  
 Autosomal recessive inheritance 296  
 Sex-linked recessive inheritance 298  
 The use of linked markers 299  
 Bayes' theorem and prenatal screening 299  
 Empiric risks 300
- 21 Prenatal diagnosis of genetic disease** 303  
 Techniques used in prenatal diagnosis 303  
 New prenatal diagnostic techniques under development 306  
 Indications for prenatal diagnosis 307  
 Special problems in prenatal diagnosis 308  
 Termination of pregnancy 310  
 Prenatal treatment 310
- 22 Population screening and community genetics** 313  
 Criteria for a screening programme 313  
 Prenatal screening 314  
 Neonatal screening 316  
 Population carrier screening 317  
 Genetic registers 319
- 23 The human genome project, treatment of genetic disease and gene therapy** 321  
 The human genome project 321  
 Treatment of genetic disease 325  
 Gene therapy 327
- 24 Ethical issues in medical genetics** 337  
 General principles 337  
*Ethical dilemmas in clinical genetics* 338  
 Ethical dilemmas in a wider context 340
- Appendix** 345
- Glossary** 347
- Index** 361