

Contents

1	Origins of the Laboratory Mouse	1
1.1	Introduction	1
1.1.1	Phylogenetic Relationships of Laboratory Mice with Other Mammals	1
1.1.2	How the House Mouse Became a Domestic Species...	5
1.1.3	How the House Mouse Became a Model for Geneticists	8
1.1.4	The Community of Mouse Geneticists	12
1.1.5	The Main Institutions Involved in Mouse Genetics...	12
1.1.6	Books and Other Sources of Information Concerning the Mouse	13
1.1.7	The Future of Mouse Genetics.	14
	References.	15
2	Basic Concepts of Reproductive Biology and Genetics	19
2.1	Introduction	19
2.2	Reproduction in the Laboratory Mouse	19
2.2.1	The Estrous Cycle and Pregnancy	19
2.2.2	Inducing Ovulation in the Mouse (Superovulation).	24
2.2.3	Artificial Insemination	25
2.2.4	In Vitro Fertilization in the Mouse.	26
2.2.5	Ovary Transplantation	27
2.2.6	Intra Cytoplasmic Sperm Injection	28
2.2.7	Cryopreservation of Mouse Embryos and Spermatozoa	28
2.2.8	Twinning in the Mouse.	29
2.2.9	Cloning Laboratory Mice.	30
2.2.10	Mosaics and Chimeras	31
2.3	Basic Notions of Genetics	34
2.3.1	Genes and Alleles.	34
2.3.2	Allelic Interactions.	37

2.3.3	Epistasis and Pleiotropy	41
2.3.4	Penetrance and Expressivity.	43
2.4	Phenotyping Laboratory Mice: The Mouse Clinics	45
	References	46
3	Cytogenetics	51
3.1	Introduction	51
3.2	The Chromosomes of the Mouse	52
3.3	Identifying the Chromosome Pairs: The Normal Karyotype	54
3.4	Meiosis and Gametogenesis	59
3.5	Variations in Chromosome Number.	62
3.5.1	The Euploid Heteroploidies	62
3.5.2	The Aneuploid Heteroploidies	63
3.6	Variations in Chromosome Structure	68
3.6.1	The Structural Rearrangements Resulting from a Single Break	69
3.6.2	The Structural Rearrangements Resulting from Two Breaks.	69
3.6.3	Complex Structural Rearrangements	80
3.6.4	Structural Rearrangements Created in Vitro	81
3.7	Modeling Human Down Syndrome	82
3.7.1	Mouse Trisomy 16: A Model of Down Syndrome.	82
3.7.2	Ts(17 ¹⁶)65Dn: A Tertiary Trisomy Modeling Down Syndrome.	83
3.7.3	Transgenic and Transchromosomal Models of Down Syndrome	83
3.8	Conclusions	85
	References	86
4	Gene Mapping	89
4.1	Introduction	89
4.1.1	The Discovery of Linkage Groups: A Historical Perspective	89
4.2	From Linkage Groups to Genetic Maps.	91
4.2.1	Detecting Linkage and Measuring the Distances Between Loci	91
4.2.2	Ordering the Genes	96
4.2.3	Establishing a Correspondence Between LGs and Chromosomes	99
4.2.4	Positioning the Centromere	101
4.3	Genetic Markers	102
4.3.1	Markers Scored by Examination of the External Phenotype.	103
4.3.2	Electrophoretic Variant of Enzymatic Proteins	104
4.3.3	Plasmatic Proteins and Cell Surface Antigens	104
4.3.4	Polymorphisms Detected at the DNA Level	104

4.4	High-Resolution, High-Density Genetic Maps	110
4.5	Somatic Cell Hybrids and Radiation Hybrids as Tools for Gene Mapping	111
4.6	Recombinant Inbred and Recombinant Congenic Strains	112
4.7	Establishing Consensus Maps	116
4.8	Positional Cloning of Mutations and QTLs	119
4.9	Physical Maps	121
4.10	Conclusion	122
	References	123
5	The Mouse Genome.	127
5.1	Introduction	127
5.2	The Sequence of the Mouse Genome.	128
5.2.1	The Mouse Genome is Enormous in Size, and its Structure is Complex	128
5.2.2	How Was the Mouse Genome Sequenced?	130
5.3	The Structure of the Mouse Genome.	134
5.3.1	Finding the Coding and Related Sequences.	134
5.3.2	The Canonical Architecture of a Protein-Coding Gene.	140
5.3.3	Finding the Regulatory Sequences.	144
5.3.4	Organization of Syntenic Regions at the Chromosome Level	148
5.3.5	Gene Families and Pseudogenes	150
5.3.6	Copy Number Variations	155
5.3.7	Single Nucleotide Polymorphisms.	158
5.3.8	Tandem Repeated Sequences	158
5.3.9	Interspersed Repeated Sequences: Transposable Elements.	161
5.4	The Transcriptome: Coding and Non-coding RNAs	166
5.4.1	ncRNAs Involved in Protein Synthesis	168
5.4.2	The ncRNAs Functioning as Post-transcriptional Regulators	170
5.5	Ultraconserved Elements (UCE) and Long Conserved Non-coding Sequences.	176
5.6	Mitochondrial DNA	177
5.7	Conclusions	179
	References	180
6	Epigenetic Control of Genome Expression	187
6.1	Introduction	187
6.2	X-Chromosome Inactivation in Mammals.	188
6.2.1	In Female Mammals Only One X is Transcriptionally Active.	188
6.2.2	The Mechanisms Controlling X-Chromosome Inactivation	193

6.3	Parental Imprinting of Autosomal Genes	196
6.3.1	Evidence of Genomic Imprinting in the Mouse	196
6.3.2	Characterization of the Imprinted Regions in the Mouse	203
6.3.3	What are the Molecular Mechanisms that Control Genomic Imprinting?	206
6.3.4	Genomic Imprinting Across Mammalian Species	211
6.3.5	The Origin and Evolution of the Imprinting Mechanisms in Mammals	212
6.3.6	The Pathological Aspects Associated with Genomic Imprinting	213
6.4	Conclusions	217
	References	217
7	Mutations and Experimental Mutagenesis	221
7.1	The Importance of Mutations	221
7.2	The Different Types of Mutations	222
7.2.1	Mutations Resulting from Base-Pair Substitutions in the Coding Sequences	223
7.2.2	Base-Pair Substitutions in the Non-coding Regions	228
7.2.3	Insertions, Deletions, and Duplications	231
7.2.4	Triplet Expansions	232
7.2.5	Mutations Resulting from the Insertion of Mobile Elements	233
7.2.6	Mutations Due to Non-homologous Recombination or Non-homologous End Joining	234
7.2.7	Copy Number Variations	234
7.3	Spontaneous Mutation Rates	235
7.4	Mutagenesis in the Mouse	237
7.4.1	Gametogenesis and Experimental Mutagenesis	238
7.4.2	The Induction of Mutations by Radiation	240
7.4.3	The Induction of Mutations by Chemicals	242
7.5	Protocols of Experimental Mutagenesis	246
7.5.1	Phenotype-Driven, Genome-Wide Mutagenesis	247
7.5.2	The Induction of New Mutant Alleles at Specific Loci	250
7.5.3	The Induction of Mutations in Specific Regions of the Genome	252
7.5.4	A Gene-Driven Strategy for the Production of Mutations at Specific Loci	255
7.6	Other Techniques for the Production of Mutations in the Mouse	258
7.7	Conclusions	259
	References	260

8	Transgenesis and Genome Manipulations	267
8.1	Introduction	267
8.2	Transgenesis Resulting from Pronuclear Injection of Cloned DNAs	268
8.2.1	The Basic Experimental Protocol	268
8.2.2	Factors Influencing Transgenic Expression	271
8.2.3	Using Transgenic Mice for Studying Gene Function and Regulation	273
8.2.4	The Use of Transgenic Technology to Generate Tissue- or Cell-Specific Ablations	276
8.2.5	Transgenic Complementation of a Mutant Allele Identified by Positional Cloning	276
8.2.6	Using Transgenic Mice for Modeling Human Diseases	277
8.2.7	Transgenic Animals with Large DNA Inserts	279
8.2.8	Transgenic Knockdowns	280
8.2.9	Assessing the Mutagenic Activity of Chemicals with Transgenic Mice	281
8.2.10	Mutations Induced by Pronuclear Transgenesis	281
8.3	Generating Alterations in the Mouse Genome Using Embryonic Stem Cells	282
8.3.1	Embryonic Stem Cells and their Advantages	282
8.3.2	Targeted Mutagenesis in ES Cells	285
8.3.3	Induction of Mutations in ES Cells with Chemical Mutagens	301
8.4	Inducible Transgenesis: The <i>Tet-off</i> and <i>Tet-on</i> Expression Systems	302
8.5	Other Techniques for the Production of Transgenic Mice	304
8.5.1	Transgenesis by Retroviral Infection of Early Embryos	305
8.5.2	In Vivo Genome Editing: The Production of Targeted Alterations Using Engineered Nucleases	306
8.6	Conclusion	310
	References	310
9	The Different Categories of Genetically Standardized Populations of Laboratory Mice	319
9.1	Introduction	319
9.2	Inbred Strains	321
9.2.1	Inbred Mice are Isogenic and Homozygous at All Loci	321
9.2.2	Inbred Mice are Genetically Stable in the Long Term	324

9.2.3	The Genetic Purity of Inbred Strains Must be Regularly Monitored	325
9.2.4	Most Inbred Strains are Derived from a Small Number of Ancestors	333
9.2.5	Laboratory Inbred Strains have a Polyphyletic Origin	334
9.2.6	Inbred Strains Recently Derived from Wild Specimens	334
9.2.7	Phylogenetic Relationships Between Inbred Strains	336
9.3	Interstrain F1 Hybrids	337
9.4	Co-isogenic and Congenic Strains	338
9.4.1	Co-isogenic Strains	338
9.4.2	Transgenic Strains are Equivalent but not Identical to Co-isogenic Strains	339
9.4.3	Congenic Strains	340
9.5	Consomic Strains	347
9.6	Recombinant Inbred Strains and Recombinant Congenic Strains	348
9.7	The Collaborative Cross	350
9.8	Outbred and Random-Bred Stocks	353
	References	354
10	Quantitative Traits and Quantitative Genetics	361
10.1	Introduction	361
10.2	Mean and Variance: Two Essential Parameters for the Characterization of a Population	362
10.3	Why Study the Genetics of Complex Traits in Laboratory Mice?	364
10.4	The Genetic Determinism of Quantitative Traits	364
10.5	The Concept of Quantitative Trait Locus (QTL)	365
10.6	Positioning QTLs on the Genetic Map	366
10.6.1	Using Two-Generation Crosses for the Detection and Positioning of QTLs	367
10.6.2	Point-by-Point Analysis of the Progeny	369
10.6.3	The Concept of LOD Score	369
10.6.4	Threshold of Significance	371
10.7	Assessing the Strength of a QTL on the Trait Studied	371
10.8	Interval Mapping	372
10.9	Searching for Multiple QTLs Simultaneously	374
10.10	Using Recombinant Inbred and Recombinant Congenic Strains	374
10.10.1	Recombinant Inbred Strains	374
10.10.2	Advantages and Disadvantages of RIS	375
10.10.3	Recombinant Congenic Strains	376

10.11	Using Congenic Strains	377
10.12	Using Other Strains or Stocks for the Mapping of QTLs.	380
10.12.1	Consomic Strains (CS).....	380
10.12.2	The Collaborative Cross (CC): A Novel, Powerful Tool for Studying the Genetics of Complex Traits.	381
10.12.3	Interspecific Recombinant Congenic Strains (IRCS)... ..	381
10.12.4	Diversity Outbred (DO) Stock	382
10.13	Cloning QTLs.....	382
10.13.1	Analyzing the DNA Polymorphisms in the QTL Region	383
10.13.2	Quantitative Complementation.	384
10.14	The Analysis of Expression QTLs (eQTLs).	384
10.15	The Case of Modifier Genes.	385
10.16	Conclusions	386
	References.....	386
	Glossary	389