Table of contents

List of Contributors xi

Preface xiii

1 An Introduction to Pathology Techniques 1

Elizabeth McInnes

- 1.1 Animal Considerations 2
- 1.2 Necropsy 2
- 1.3 Lung Inflation with Fixative 5
- 1.4 Fixation 5
- 1.5 Making Glass Slides 6
- 1.5.1 Trimming 6
- 1.5.2 Tissue Processing 9
- 1.5.3 Embedding 9
- 1.5.4 Microtoming 9
- 1.5.5 Staining 9
- 1.5.6 Quality Control 11
- 1.6 Special Histochemical Stains 12
- 1.7 Decalcification 13
- 1.8 Immunohistochemistry 13
- 1.9 Tissue Crossreactivity Studies 15
- 1.10 Electron Microscopy 15
- 1.11 In Situ Hybridisation 16
- 1.12 Laser Capture Microscopy 16
- 1.13 Confocal Microscopy 16

- 1.14 Image Analysis 17
- 1.15 Digital Imaging 17
- 1.16 Spermatocyte Analysis 17
- 1.17 Good Laboratory Practice 17
- 1.18 Inhalation Studies 18
- 1.19 Continuous• |Infusion Studies 18
- 1.20 Carcinogenicity 19
- 1.21 Biologicals 19
- 1.22 The Pathology Report 20
- 1.23 Conclusion 20

References 20

2 Recording Pathology Data 23

Cheryl L. Scudamore

- 2.1 What is a Pathology Finding? 24
- 2.2 Standardisation of Pathology Findings 24
- 2.2.1 Semiquantitative Analysis 24
- 2.2.2 Nomenclature/Controlled Terminology 26
- 2.2.3 Ontological Approach 28
- 2.3 'Inconsistencies' in Pathology Recording 28
- 2.3.1 Diagnostic Drift 28
- 2.3.2 Thresholds 28
- 2.3.3 Lumping versus Splitting 29
- 2.4 Blind Review 30
- 2.5 Historical Control Data: Pros and Cons 30

2.6 The Use of Peer Review in Pathology 32

References 32

3 General Pathology and the Terminology of Basic Pathology 35

Elizabeth McInnes

- 3.1 Cellular Responses to Insults 35
- 3.2 Inflammation 41
- 3.3 Circulatory Disturbances 46
- 3.4 Disorders of Tissue Growth 52
- 3.5 Tissue Repair and Healing 53
- 3.6 Neoplasia 54
- 3.7 Immune System 55

References 57

4 Common Spontaneous and Background Lesions in Laboratory Animals 59

Elizabeth McInnes

- 4.1 Rats 62
- 4.2 Mice 63
- 4.3 Dogs 66
- 4.4 Minipigs 66
- 4.5 Non• | Human Primates 67
- 4.6 Rabbits 67
- 4.7 Experimental Procedures 67
- 4.8 Causes of Death in Rats and Mice 67
- 4.9 Conclusion 68

References 69

5 Target Organ Pathology 72

Elizabeth McInnes

- 5.1 Skin 72
- 5.2 Eye 76
- 5.3 Gastrointestinal Tract 78
- 5.4 Liver 83
- 5.5 Respiratory System 85
- 5.6 Urinary System 89
- 5.7 Lymphoreticular System 94
- 5.8 Musculoskeletal System 95
- 5.9 Cardiovascular System 97
- 5.10 Endocrine System 99
- 5.11 Reproductive System 102
- 5.12 Central and Peripheral Nervous System 104
- 5.13 Ear 106

References 106

6 Clinical Pathology 112

Barbara von Beust

- 6.1 Clinical Pathology in Study Phases and Good Laboratory Practice 112
- 6.1.1 Preanalytic Phase: Study Plan 113
- 6.1.2 Analytic Phase: Data Generation 114
- 6.1.3 Postanalytic Phase: Data Interpretation and Reporting 114
- 6.1.4 Good Laboratory Practice 114
- 6.2 What is Measured in Clinical Pathology? 115

- 6.2.1 Interference by Haemolysis, Lipaemia and Icterus 116
- 6.3 Haematology 117
- 6.3.1 Manual and Automated Techniques in Haematology 118
- 6.3.2 Haematocrit and Red Blood Cell Mass 119
- 6.3.3 Blood Cells 120
- 6.3.4 The Standard Haematology Profile 124
- 6.3.5 Bone Marrow 125
- 6.4 Coagulation 125
- 6.4.1 Standard Coagulation Profile 126
- 6.4.2 Prothrombin Time 127
- 6.4.3 Activated Partial Thromboplastin Time 127
- 6.4.4 Fibrinogen 127
- 6.5 Clinical Chemistry 127
- 6.5.1 Metabolites 127
- 6.5.2 Enzymes 129
- 6.5.3 Electrolytes and Minerals 129
- 6.5.4 Standard Chemistry Profiles 130
- 6.6 Urinalysis 131
- 6.7 Acute•]Phase Proteins 131
- 6.8 The Biomarker Concept 132
- 6.9 Reference Intervals 133
- 6.10 Instrumentation, Validation and Quality Control 133
- 6.11 Data Analysis and Interpretation 134

- 6.12 Reporting 135
- 6.13 Food Consumption and Body Weight (Gain) 136
- 6.14 Organ Weights 136
- 6.15 Examples of Typical Clinical Pathology Profile Changes in Toxicologic Clinical Pathology 136
- 6.15.1 Reduced Red Blood Cell Mass due to Chronic Disease 138
- 6.15.2 Stress Response 139
- 6.15.3 Reduced Red Blood Cell Mass due to Excessive Blood Sampling 139
- 6.15.4 Common Artefacts 139
- 6.16 Microsampling 140
- 6.17 Conclusion 141

Acknowledgments 141

References 141

7 Adversity: A Pathologist's Perspective 145

Bhanu Singh

- 7.1 LOAEL, NOEL and NOAEL: Definition 146
- 7.2 Adversity 147
- 7.3 Determining Adversity using Pathology Findings: Factors to Consider 149
- 7.3.1 Severity 149
- 7.3.2 Functional Effect 150
- 7.3.3 Primary versus Secondary Effects 151
- 7.3.4 Physiological Adaptability 152
- 7.3.5 Reversibility of the Lesion 152
- 7.3.6 Pharmacological Effect 153

- 7.4 Communicating NOAEL in Toxicity Studies 153
- 7.5 Conclusion 154

References 154

8 Limitations of Pathology and Animal Models 157 *Natasha Neef*

- 8.1 Limitations of In Vivo Animal Models 157
- 8.1.1 Traditional Laboratory Species Used as General Toxicology Models 157
- 8.1.2 The Test Article May Not have Sufficient Pharmacological Activity in Routine Toxicology Species 158
- 8.1.3 The Model May Not Identify Hazards Related to Causation or Exacerbation of Pathology that is Unique to Humans or Undetectable in Animals 159
- 8.1.4 The Model May Not Identify Hazards with Low Incidence/Low Severity 159
- 8.1.5 Potential for Misinterpretation of Reversibility/Recovery for Low•]Incidence Findings 160
- 8.1.6 Potential for Over•] or Underestimation of the Relationship to Test Article of Findings that have High Spontaneous Incidence in Laboratory Species, but are Relatively Rare in Humans 160
- 8.1.7 Exclusive Use of Young, Healthy Animals Kept in Ideal Conditions Gives Limited Predictivity for Aged/Diseased Human Populations 161
- 8.2 Efficacy/Disease Models as Toxicology Models 162
- 8.3 Limitations of Efficacy/Disease Models as Toxicology Models 164
- 8.3.1 Lack of Validation as Safety/Toxicology Models 164
- 8.3.2 Disease Models Rarely Have All the Elements of the Equivalent Human Disease 165
- 8.3.3 Limited Sensitivity Produced by Increased Interanimal Variability amongst Diseased Animals and/or Low Animal Numbers 165

- 8.3.4 Lack of Historical Data 166
- 8.3.5 Risk Associated with Nonregulated Laboratory Conditions 166
- 8.4 Limitations of Pathology within In Vivo Toxicology Models 167
- 8.4.1 Anatomic Pathology Evaluation Will Not Identify Hazards with No Morphological Correlates 167
- 8.4.2 Limitations of Pathology when Evaluating Moribund Animals or Animals Found Dead on Study 168
- 8.4.3 Limitations of Anatomic and/or Clinical Pathology End Points within other Types of In Vivo Preclinical Safety Study 168
- 8.4.4 Limitations of Histopathology Related to Sampling Error 169
- 8.4.5 Limitations of Quantitative Anatomic Pathology 170
- 8.4.6 Limitations of Pathology Related to Subjectivity and Pathologist Error 173
- 8.4.7 Anatomic Pathology Error/Missed Findings 173
- 8.4.8 Subjectivity and Pathologist Variability 175
- 8.5 Managing Risk Associated with Subjectivity and the Potential for Pathologist Error 176
- 8.5.1 Choice of Study Pathologist 176
- 8.5.2 Peer Review 176
- 8.5.3 Review of the Anatomic Pathology Data 177
- 8.5.4 Review of Anatomic Pathology Data Interpretation 177

References 179

Glossary 184

Index 187