

# Contents

<b>Abbreviations .....</b>	<b>xvii</b>
<b>1 Cancer Biology .....</b>	<b>1</b>
Introduction .....	1
Development of Cancers from Single Cells .....	2
Diversity of Tumour Cells .....	5
Differentiation of Malignant Cells .....	5
<b>2 Derangement of the Genome as a Cause of Cancer .....</b>	<b>9</b>
Introduction .....	9
The Chromosomes .....	10
Chromosomal Abnormalities in Cancer .....	11
Susceptibility to Chromosome Damage and Cancer .....	16
Constitutional Cytogenetic Abnormalities .....	17
Fragile Sites .....	17
<b>3 Derangements of the Mechanisms Controlling Growth .....</b>	<b>19</b>
Introduction .....	19
Cell Cycle .....	19
Signal Transduction .....	20
Immortalisation and Transformation .....	20
Mechanisms Leading to Autonomous Growth .....	21
Differentiation Arrest .....	23
<b>4 Multiple Steps in the Genesis of a Cancer .....</b>	<b>25</b>
Introduction .....	25
Initiation .....	26
Promotion .....	28
Tumour-promoting Phorbol Esters .....	29
Progression .....	34
Conclusions .....	36

<b>5 Multifactorial Aetiology of Cancers</b> .....	39
Introduction .....	39
Population and Familial Factors .....	39
Carcinogens .....	41
Radiation .....	43
Viruses .....	44
Viruses in the Causation of Animal Cancers .....	50
Viruses in the Causation of Human Cancers .....	50
Immunodepression and Immunosuppression .....	56
Prolonged Antigenic Stimulation .....	57
 <b>6 Oncogenes</b> .....	 61
Introduction .....	61
Translation Products of Oncogenes .....	63
Oncogene Products with Protein Kinase Activity .....	65
GTP-binding Oncogene Products .....	66
Oncogenes Whose Products Bind to DNA .....	66
Oncogene Product with Growth Factor Activity .....	69
Oncogenes Encoding Receptors for Growth Factors .....	69
Oncogenes Whose Products have Undefined Function .....	70
Some Important Non-human Oncogenes .....	71
Aberrations of Oncogenes in Cancer .....	71
Proteins Homologous to Oncogene Products .....	72
Transgenic Mice .....	73
Oncogenes in Human Tumours .....	73
Multiple Oncogene Expression .....	74
Conclusions .....	74
 <b>7 Growth Factors</b> .....	 77
Introduction .....	77
Mechanisms of Action of Growth Factors .....	78
Growth Factors in Malignant Transformation .....	79
Growth Factors for Haematopoietic Cells .....	80
Transforming Growth Factor $\alpha$ .....	81
Transforming Growth Factor $\beta$ .....	82
Epidermal Growth Factor .....	82
Platelet-derived Growth Factor .....	83
Bombesin .....	84
Insulin .....	84
Insulin-like Growth Factor I .....	85
Insulin-like Growth Factor II .....	86
Nerve Growth Factor .....	86
Chalones and Other Antiproliferative Factors .....	87
Conclusions .....	87

<b>8 The Lymphoid Tissues</b>	<b>91</b>
Introduction	91
Origin of Lymphocytes	92
T Lymphocytes	92
B Lymphocytes	94
NK, ADCC and Lymphokine-activated Killer Cells	98
Accessory Cells	99
Activation of Macrophages	101
Lymphoid Organs and Immunological Function	101
Lymphocyte Circulation	102
Organisation of Immunological Function	102
 <b>9 The Major Histocompatibility Complex</b>	 <b>107</b>
Introduction	107
Tissue Distribution of MHC Products	109
MHC Gene Products and Their Specificities	109
Immunoregulatory Function of the MHC	111
Mixed Lymphocyte Reaction	112
Graft Versus Host Reaction	113
Association of Diseases with MHC Phenotype	113
Conclusions	114
 <b>10 T Cell Differentiation</b>	 <b>115</b>
Introduction	115
The Thymus	116
T Lymphocytes in Bone Marrow	119
T Cells in Lymph Nodes	119
T Cell Subsets	119
T Cell Subsets Defined by Monoclonal Antibodies	120
T Cell Receptor	121
Genetic Mechanisms in T Cell Differentiation	122
T Cell Activation	123
Signal Transduction in T Cell Activation	125
 <b>11 B Cell Differentiation</b>	 <b>127</b>
Introduction	127
Antigen-independent B Cell Differentiation	128
B Lymphocyte Differentiation in Postnatal Life	129
Antigen-dependent B Cell Differentiation	132
B Cell Subsets	132
Immunoglobulin	134
Genetic Mechanisms in B Cell Differentiation	135
Organisation of Immunoglobulin Genes	135
Rearrangement of B Cell Genes During Ontogeny	135
Human Heavy Chain Gene Organisation	138

Light Chain Organisation .....	138
Isotype Switch .....	140
<b>12 B Cell Activation .....</b>	<b>143</b>
Introduction .....	143
T Cells in B Cell Activation .....	144
Accessory Cells in B Cell Activation .....	147
B Cell Activation by Cross-linking Immunoglobulin .....	148
Soluble Factors in B Cell Activation .....	149
Type A Factors .....	150
Type B Factors (BCGFs) .....	151
Type C Factors (BCDFs) .....	152
Transferrin .....	152
Interferon .....	152
Other Factors .....	153
Cellular Events in B Lymphocyte Activation .....	154
Conclusions .....	157
<b>13 Immunoregulatory Mechanisms .....</b>	<b>161</b>
Introduction .....	161
Systems Controlling Immunological Function .....	161
Suppressor Mechanisms .....	163
Idiotypes .....	164
Idiotypes on T Cells .....	165
Idiotypic Regulatory Network .....	165
Immunological Tolerance .....	166
Regulatory Mechanisms in B Cell Malignancies .....	168
<b>14 Technology of Investigation and Diagnosis .....</b>	<b>171</b>
Introduction .....	171
Hybridoma Technology and Monoclonal Antibodies .....	171
Principles of Hybridoma Technology .....	172
Gene Cloning .....	173
Gene Probing .....	174
Immunodiagnostic Methods .....	176
Collection of Specimens .....	177
Immunological Methods .....	177
Rosette Formation .....	179
Immunofluorescence on Cryostat Sections .....	180
Immunohistochemical Methods .....	180
Paraffin Sections .....	180
Cryostat Sections .....	182
Imprints and Cyto centrifuge Preparations .....	185
Histochemical Stains .....	188
Periodic-acid Schiff .....	188

Non-specific Esterase .....	188
Acid Phosphatase .....	190
Tartrate-resistant Acid Phosphatase .....	190
Alkaline Phosphatase .....	190
Other Enzyme Reactions .....	191
Flow Cytometry .....	191
Ultrastructural Analysis .....	193
Conclusions .....	194
 <b>15 B Cell Neoplasia</b> .....	 199
Introduction .....	199
Immunological Abnormalities in Lymphoid Malignancies .....	200
Chromosomal Abnormalities in B Cell Malignancies .....	201
Oncogene Activation in B Cell Neoplasia .....	204
Immunoglobulin Gene Rearrangements .....	205
 <b>16 B Cell Leukaemias</b> .....	 209
Introduction .....	209
Acute Lymphoblastic Leukaemia .....	211
Phenotype of ALL Cells .....	212
Prognosis in ALL .....	213
B-Chronic Lymphocytic Leukaemia .....	214
Lymphocyte Kinetics .....	218
Morphology .....	219
Phenotype .....	220
Cellular Abnormalities in CLL .....	221
Malignant Stem Cell .....	223
B Cell Prolymphocytic Leukaemia .....	223
Morphology and Phenotype .....	223
Hairy Cell Leukaemia .....	224
Morphology and Phenotype .....	225
Bone Marrow in HCL .....	228
Spleen and Liver in HCL .....	229
Chronic Cold Agglutinin Disease .....	231
Lymphoplasmacytoid Lymphoma .....	231
Plasma Cell Dyscrasias .....	232
Multiple Myeloma .....	232
Malignant Stem Cell .....	233
Plasma Cell Leukaemia .....	234
Localised Plasmacytoma .....	234
Solitary Plasmacytoma of Bone .....	234
Extramedullary Plasmacytoma .....	235
Monoclonal Gammopathy of Undetermined Significance .....	235
Heavy Chain Diseases .....	236
Lymphosarcoma Cell Leukaemia .....	237

<b>17 B Cell Lymphomas</b> .....	243
Introduction .....	243
<b>B Cell Lymphomas of the Deep Cortex</b> .....	248
Well-differentiated Lymphocytic Lymphoma .....	248
Plasmacytoid Lymphocytic Lymphoma .....	252
B Immunoblastic Sarcoma .....	254
<b>B Cell Lymphomas of the Superficial Cortex</b> .....	255
Follicular Centre Cell Lymphoma .....	257
Small Follicular Centre Cell Proliferations .....	258
Mixed Follicular Centre Cell Proliferations .....	260
Large Follicular Centre Cell Proliferations .....	261
Signet-ring Cell Lymphoma .....	263
Phenotype of Follicular Centre Cell Lymphomas .....	264
Intermediate and Mantle Zone Lymphomas .....	268
<b>B Cell Lymphomas of the Medulla: Plasmacytoma</b> .....	270
<b>Undifferentiated B Cell Lymphomas</b> .....	271
<b>Extranodal B Cell Lymphomas</b> .....	275
<b>Hodgkin's Disease</b> .....	279
 <b>18 T Cell Neoplasia</b> .....	289
Introduction .....	289
Chromosomal Abnormalities in T Cell Malignancies .....	290
Gene Rearrangements in T Cell Malignancies .....	292
Immunoglobulin Genes in T Cell Malignancies .....	293
 <b>19 T Cell Leukaemias and Lymphomas</b> .....	295
Introduction .....	295
<b>T Cell Neoplasms of the Bone Marrow Compartment</b> .....	296
T Acute Lymphoblastic Leukaemia .....	297
T Prolymphocytic Leukaemia .....	298
T Hairy Cell Leukaemia .....	299
T Cell Chronic Lymphocytic Leukaemia .....	300
T <sub>h</sub> Lymphoproliferative Disease .....	302
Adult T Cell Leukaemia/Lymphoma .....	303
<b>T Cell Neoplasms of the Thymic Compartment</b> .....	306
Lymphoblastic Lymphoma .....	306
<b>T Cell Neoplasms of the Peripheral Compartment</b> .....	309
Cutaneous T Cell Lymphomas .....	309
Node-based T Cell Lymphoma .....	319
Polymorphous Type .....	322
Monomorphous Type .....	327
Immunological Phenotypes .....	334
Conclusions .....	336
 <b>20 Treatment, Treatment Failure and Future Possibilities</b> .....	345
Introduction .....	345
Treatment Failure Exemplified by Lymphocytic Leukaemia .....	346

<b>Immunotherapy</b> .....	348
<b>Monoclonal Antibodies</b> .....	348
<b>Immunotoxins</b> .....	350
<b>Antibodies Against Growth Factor Receptors</b> .....	351
<b>Adoptive Immunity with Cytotoxic T Cells</b> .....	351
<b>Activated Macrophages</b> .....	352
<b>Cytokines and Other Biological Agents</b> .....	352
<b>Interferon</b> .....	352
<b>Tumour Necrosis Factor</b> .....	353
<b>Thymic Cytokines</b> .....	354
<b>New Drugs and Other Treatments</b> .....	354
<b>Cyclosporin</b> .....	354
<b>Purine and Pyrimidine Analogues</b> .....	355
<b>Hyperthermia</b> .....	355
<b>Vaccines Against HTLV</b> .....	356
<b>Conclusions</b> .....	356
<b>Glossary</b> .....	361
<b>Subject Index</b> .....	367