The Biological Basis of Cancer

The text is designed to be used for an undergraduate course on cancer. It covers everything from the molecular to the clinical aspects of the subject, with a lengthy bibliography designed to assist newcomers with the cancer literature.

An introduction acquaints students with the biological principles of cancer and the human dimensions of the disease by considering genuine cases of cancer in fictionalized letters. Other chapters discuss cancer pathology, metastasis, carcinogenesis, genetics, oncogenes and tumor suppressors, epidemiology, and the biological basis of cancer treatment. A glossary of cancer-related terms is included.

Upper-division undergraduates with a background in freshman biology and chemistry, as well as beginning graduate students, will find this a most useful text.

The Authors

Robert G. McKinnell is a Morse/Alumni Distinguished Professor in the Department of Genetics and Cell Biology at the University of Minnesota and is a past president of the International Society for Differentiation. He was a Royal Society of London Guest Research Fellow at Oxford, and he has authored a number of books including Cloning of Frogs, Mice and Other Animals (University of Minnesota Press).

Ralph E. Parchment is professor in the Division of Hematology and Oncology at Wayne State University and was formerly at the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration. His research interests lie in cancer treatment.

Alan O. Perantoni is a principal investigator and group leader for the Developmental Biology Working Group in the Laboratory of Comparative Carcinogenesis, National Cancer Institute. He has maintained a research interest in oncogene and suppressor gene involvement in experimental carcinogenesis. He is currently engaged in studies of genetic alterations in pediatric tumors.

G. Barry Pierce is Centennial Distinguished Research Professor of Pathology at the University of Colorado Health Sciences Center and world renowned for his recognition of the stem cell origin of and differentiation of cancer cells.
The Biological Basis of Cancer

Robert G. McKinnell
Ralph E. Parchment
Alan O. Perantoni
G. Barry Pierce
We dedicate this book to our students
Contributors

Professor Robert G. McKinnell
Department of Genetics and Cell Biology
University of Minnesota
Saint Paul, Minnesota 55108-1095

Professor Ralph E. Parchment
Division of Hematology and Oncology
Wayne State University
Detroit, Michigan 48201

Dr. Alan O. Perantoni
Laboratory of Comparative Carcinogenesis
National Cancer Institute
Frederick, Maryland 21702

Professor G. Barry Pierce
Department of Pathology
University of Colorado Health Sciences Center
Denver, Colorado 80262
# Contents

**Preface**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Introduction: Letters illustrating clinical aspects of cancer • G. BARRY PIERCE</td>
<td>xvii</td>
</tr>
<tr>
<td></td>
<td>Colon cancer</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Breast cancer</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Acute leukemia</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Kidney cancer</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Squamous cell cancer</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Testicular cancer</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Stomach cancer</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Summary</td>
<td>13</td>
</tr>
</tbody>
</table>

## 1 The pathology of cancer • G. BARRY PIERCE

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Introduction</td>
<td>14</td>
</tr>
<tr>
<td>1.2</td>
<td>Benign versus malignant tumors</td>
<td>18</td>
</tr>
<tr>
<td>1.2a</td>
<td>Benign tumors</td>
<td>18</td>
</tr>
<tr>
<td>1.2b</td>
<td>Malignant tumors</td>
<td>21</td>
</tr>
<tr>
<td>1.3</td>
<td>The diagnosis of benign and malignant tumors</td>
<td>24</td>
</tr>
<tr>
<td>1.4</td>
<td>Tumor grading and staging</td>
<td>24</td>
</tr>
<tr>
<td>1.5</td>
<td>Classification and nomenclature</td>
<td>25</td>
</tr>
<tr>
<td>1.6</td>
<td>Metastasis</td>
<td>27</td>
</tr>
<tr>
<td>1.7</td>
<td>Tumor markers</td>
<td>28</td>
</tr>
<tr>
<td>1.8</td>
<td>How cancer kills</td>
<td>29</td>
</tr>
<tr>
<td>1.8a</td>
<td>Organ failure</td>
<td>29</td>
</tr>
<tr>
<td>1.8b</td>
<td>Obstruction of the gastrointestinal tract, ducts, and hollow organs</td>
<td>30</td>
</tr>
<tr>
<td>1.8c</td>
<td>Cachexia and infection</td>
<td>32</td>
</tr>
<tr>
<td>1.9</td>
<td>Spontaneous regression</td>
<td>33</td>
</tr>
</tbody>
</table>
CONTENTS

1.10 Dormancy 34
1.11 Initiation, latency, promotion, and progression 35
1.12 Latency 35
1.13 Progression to the autonomous state 36
1.14 Selection and cellular heterogeneity 37
1.15 A developmental concept of cancer 39
1.16 Apoptosis 47
1.17 Summary 48

2 Metastasis • ROBERT G. MCKINNELL 50

2.1 Introduction 50
2.2 The metastatic cascade 53
2.2a Disruption of the basement membrane 55
2.2b Cell detachment 57
2.2c Cell motility 60
2.2d Invasion 62
2.2e Penetration of the vascular system 65
2.2f Cancer cells in the circulation 66
2.2g Arrest of circulating cancer cells (stasis) 67
2.2h Extravasation, growth of metastases, and metastasis of metastases 67
2.3 Are there genes that control metastasis? 68
2.4 Soil and seed hypothesis of Paget 71
2.5 Is metastasis limited to malignant cells? 71
2.6 How do we know a metastasis to the liver is not a primary neoplasm of the liver? 75
2.7 Why study metastasis? 77
2.8 Summary 78

3 Carcinogenesis • ALAN O. PERANTONI 79

3.1 Introduction 79
3.2 What is a carcinogen? 80
3.3 Carcinogenesis as a multistage process 80
3.4 Chemical carcinogenesis 82
3.4a Organic compounds 86
3.4b Inorganic compounds and asbestos 89
3.4c Naturally occurring chemicals 92
3.5 Radiation 92
3.5a Ultraviolet radiation 92
3.5b Ionizing radiation 94
3.5c Endogenous ionizing radiation 96
3.6 Radon 96
3.7 Viral carcinogenesis 98
3.8 Endogenous carcinogenesis 99
3.9 Metabolism of xenobiotics 101
3.9a Host defenses 101
3.9b Inducibility of xenobiotic metabolism 102
3.9c Metabolic activation of chemical carcinogens 104
3.9d Inactivation of chemical carcinogens 105
3.9e Systemic distribution of chemical carcinogens 106
3.9f Mechanisms for carcinogen suppression 106
3.10 Modulation of carcinogenesis 107
3.11 Tumor promotion 110
3.12 Tumor progression 111
3.13 Alternative pathways for carcinogenesis? 112
3.14 Federal regulations 112
3.15 Summary 114

4 Cancer genetics • ROBERT G. MCKINNELL 115

4.1 Introduction 115
4.2 Chromosomes and cancer 116
4.2a Aneuploidy 116
4.2b Euploidy does not preclude genetic change 117
4.2c Cancers with chromosomal aberrations 121
4.3 Chromosome damage, mutation, and vulnerability to cancer 124
4.4 Hereditary cancers 125
4.4a Retinoblastoma 125
4.4b Wilms’ tumor 126
4.4c Hereditary conditions that increase cancer risk 127
4.5 Familial cancer syndromes 127
4.5a Colon cancer 127
4.5b Breast cancer 129
4.5c Prostate cancer 131
4.6 Summary 131
4.7 A postscript concerning genetic services for familial cancer patients 132

5 Cancer-associated genes • ALAN O. PERANTONI 133

5.1 Introduction 133
5.2 What is an oncogene? 133
CONTENTS

5.3 Proto-oncogenes function in signal transduction, cell cycle regulation, or differentiation 136
5.4 Genetic approaches to delineate proto-oncogene function 137
5.5 Classification of proto-oncogenes/oncogenes 139
  5.5a Growth factors and their receptors 139
  5.5b Nonreceptor tyrosine kinases 142
  5.5c GTP-binding proteins: ras activation 143
  5.5d Cytoplasmic serine/threonine kinases 143
  5.5e Negative regulation of ras signaling 145
  5.5f Nuclear signaling 145
  5.5g Transcriptional activation 145
5.6 Regulation of DNA synthesis and the cell cycle 147
5.7 Signal transduction in general 149
5.8 Mechanisms of oncogene activation 150
5.9 Carcinogens and oncogene activation 152
5.10 Oncogene cooperation 153
5.11 Normal cells suppress tumor growth 154
5.12 Suppressor genes 154
  5.12a The Rb locus 155
  5.12b p53 suppressor gene 156
  5.12c Apoptosis and its role in growth regulation 157
  5.12d Other defined suppressors 159
5.13 Where pathology meets molecular biology 160
5.14 Summary 161

6 Cancer in nonhuman organisms • ROBERT G. MCKINNELL 162

6.1 Introduction 162
6.2 Plant tumors 164
6.3 Invertebrate animals 166
  6.3a Drosophila melanogaster 166
  6.3b Other invertebrates 167
6.4 Cancer in selected poikilothermic (cold-blooded) vertebrates 168
  6.4a Fish 168
  6.4b Amphibia 170
  6.4c Reptiles 176
6.5 Cancer in selected ectothermic (warm-blooded) vertebrates 176
  6.5a Birds 176
  6.5b Mammals 177
6.6 Summary 180
7 Epidemiology • ROBERT G. MCKINNELL

7.1 Introduction 181
7.2 Cancer in fossil humans: A brief digression concerning paleopathology 186
7.3 Epidemiology of selected human cancers 187
   7.3a Lung cancer 187
   7.3b Breast cancer 189
   7.3c Skin cancer 192
   7.3d Prostate cancer 197
   7.3e Colorectal cancer 199
   7.3f Cervical cancer 201
   7.3g Hodgkin’s disease 202
7.4 Occupational cancers 203
7.5 AIDS-related cancers 203
   7.5a Kaposi’s sarcoma (KS) 203
   7.5b Other AIDS-related malignancies 204
7.6 Diet, nutrition, and cancer 204
   7.6a Dietary fiber and colorectal cancer 206
   7.6b Correlations between food substances and cancer prevalence: Significance 207
   7.6c Dietary fat 208
   7.6d Vitamin A (beta-carotene) 209
   7.6e Vitamin C (ascorbic acid) 210
   7.6f Vitamin E 210
   7.6g Selenium 210
   7.6h Non-nutrient compounds in food that may protect against cancer 211
   7.6i Alcohol 212
7.7 Exercise as it relates to cancer 213
7.8 Tobacco as a lifestyle hazard 215
7.9 Other lifestyle hazards 216
7.10 Summary 216

8 Cancer treatment • RALPH E. PARCHMENT

8.1 Introduction 218
8.2 Eradicating cancer cells with conventional modalities: Surgery, radiotherapy, and chemotherapy 219
   8.2a Surgery as a cancer treatment 219
   8.2b Radiation therapy as a cancer treatment 220
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2c</td>
<td>Cytotoxic chemotherapy as a cancer treatment</td>
<td>222</td>
</tr>
<tr>
<td>8.3</td>
<td>Cytoreduction theory and cancer “cure”</td>
<td>226</td>
</tr>
<tr>
<td>8.3a</td>
<td>Absolute versus fractional cytoreduction</td>
<td>226</td>
</tr>
<tr>
<td>8.3b</td>
<td>What is a cancer cure anyway?</td>
<td>228</td>
</tr>
<tr>
<td>8.3c</td>
<td>The success and failure of multimodality therapy</td>
<td>230</td>
</tr>
<tr>
<td>8.3d</td>
<td>Complicating factors that decrease log-cell kill</td>
<td>237</td>
</tr>
<tr>
<td>8.4</td>
<td>The evolution of treatment for intermediate-stage breast cancer</td>
<td>244</td>
</tr>
<tr>
<td>8.5</td>
<td>Summary</td>
<td>247</td>
</tr>
</tbody>
</table>

9 Biotherapy • RALPH E. PARCHMENT  

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1</td>
<td>Introduction</td>
<td>250</td>
</tr>
<tr>
<td>9.2</td>
<td>Targeting differentiation markers for delivery of cytotoxic agents</td>
<td>252</td>
</tr>
<tr>
<td>9.3</td>
<td>Trophic factors in tissue renewal and therapy</td>
<td>253</td>
</tr>
<tr>
<td>9.3a</td>
<td>Antagonism of trophic factors to decrease tumor mass</td>
<td>256</td>
</tr>
<tr>
<td>9.3b</td>
<td>Antagonism of steroid trophic factors</td>
<td>258</td>
</tr>
<tr>
<td>9.3c</td>
<td>Carcinoma of the prostate</td>
<td>258</td>
</tr>
<tr>
<td>9.3d</td>
<td>Carcinoma of the breast</td>
<td>259</td>
</tr>
<tr>
<td>9.3e</td>
<td>Carcinoma of the uterus</td>
<td>262</td>
</tr>
<tr>
<td>9.3f</td>
<td>Interferon-alpha: A protein antagonist of trophic factors in the immune system</td>
<td>262</td>
</tr>
<tr>
<td>9.3g</td>
<td>Interleukin-2 and tumor-reactive lymphocytes</td>
<td>263</td>
</tr>
<tr>
<td>9.3h</td>
<td>Corticosteroids</td>
<td>264</td>
</tr>
<tr>
<td>9.3i</td>
<td>Treating hematologic side effects of cytotoxic therapy with hematopoietic trophic factors</td>
<td>265</td>
</tr>
<tr>
<td>9.4</td>
<td>Differentiation therapy</td>
<td>265</td>
</tr>
<tr>
<td>9.4a</td>
<td>Retinoic acid for acute promyelocytic leukemia</td>
<td>267</td>
</tr>
<tr>
<td>9.5</td>
<td>Biotherapy with uncertain mechanism: BCG therapy for in situ bladder carcinoma</td>
<td>267</td>
</tr>
<tr>
<td>9.6</td>
<td>Future directions</td>
<td>268</td>
</tr>
<tr>
<td>9.7</td>
<td>Summary</td>
<td>269</td>
</tr>
</tbody>
</table>

Appendix: Description of selected tumors • G. BARRY PIERCE  

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1</td>
<td>Adenocarcinoma of the breast</td>
<td>271</td>
</tr>
<tr>
<td>A.2</td>
<td>Adenocarcinoma of the prostate</td>
<td>274</td>
</tr>
<tr>
<td>Section</td>
<td>Title and Pages</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>A.3</td>
<td>Adenocarcinoma of the colon 275</td>
<td></td>
</tr>
<tr>
<td>A.4</td>
<td>Squamous cell carcinoma 276</td>
<td></td>
</tr>
<tr>
<td>A.5</td>
<td>Teratocarcinomas 280</td>
<td></td>
</tr>
<tr>
<td>A.6</td>
<td>Liver cell carcinoma 285</td>
<td></td>
</tr>
<tr>
<td>A.7</td>
<td>Lung cancer 287</td>
<td></td>
</tr>
<tr>
<td>A.8</td>
<td>Malignant melanoma 288</td>
<td></td>
</tr>
<tr>
<td>A.9</td>
<td>Retinoblastoma and neuroblastoma 290</td>
<td></td>
</tr>
<tr>
<td>A.10</td>
<td>Wilms’ tumor (nephroblastoma) 290</td>
<td></td>
</tr>
<tr>
<td>A.11</td>
<td>Sarcomas 293</td>
<td></td>
</tr>
<tr>
<td>A.11a</td>
<td>Fibrosarcoma 294</td>
<td></td>
</tr>
<tr>
<td>A.11b</td>
<td>Liposarcoma 294</td>
<td></td>
</tr>
<tr>
<td>A.11c</td>
<td>Chondrosarcoma 294</td>
<td></td>
</tr>
<tr>
<td>A.11d</td>
<td>Leiomyosarcoma 294</td>
<td></td>
</tr>
<tr>
<td>A.11e</td>
<td>Osteosarcoma 294</td>
<td></td>
</tr>
<tr>
<td>A.12</td>
<td>Leukemia 296</td>
<td></td>
</tr>
<tr>
<td>A.13</td>
<td>Hodgkin’s disease 297</td>
<td></td>
</tr>
</tbody>
</table>

Glossary 299
References 311
Index 373
Preface

University of Minnesota undergraduate students were in the streets and at the barricades during the early 1970s. The war in Vietnam was of considerable concern to them and, of course, to many others. The streets were hazardous. Police helicopters hovered overhead, tear gas was in the air, and police truncheons came down on the young heads of demonstrators. The then president of the University of Minnesota, Malcolm Moos, entered into the midst of the fray and urged students to return to the classrooms. Moos simultaneously pleaded with professors to develop academic material that would entice demonstrating young people to return to the classroom. The Biology of Cancer was born of those skirmishes. It was reasoned that cancer was of more immediate interest to distressed undergraduates than the nephridia of earthworms or the aquatic larvae of sea urchins. That was indeed the case. A seminar room with eight seats was reserved for the first offering; 80 students showed up. The Biology of Cancer has been offered ever since at the University of Minnesota.

The course was (and still is) designed for undergraduates. The goal of this book is to provide an understandable text that relates directly to cancer. Some would say that if one understands modern cell biology (or molecular biology or genetic biology), then one understands cancer biology. That is not the belief of the authors. Cancer biology is more than simply modern cell biology. Certain areas of cancer research are not covered now, and never will be covered, in conventional biology classes. Pathology as it relates to cancer is an example. Who in a cell biology class explains why it is that the spread of cancer so often occurs prior to detection? This is discussed in Chapter 1. What biology class examines in detail contemporary therapy for cancer? The last two chapters are devoted to this subject.

We assume our students have an introduction to modern biology. Accordingly, we jump immediately into fundamental concepts of pathology as they relate to cancer. After all, this is why the students elect to take a course in cancer biology. Metastasis (Chapter 2), the most feared aspect of cancer, is why much of cancer treatment is palliative. Because it is so fundamental to an understanding of cancer, it is presented immediately after pathology. Metastasis occurs as a result of a number of steps, each of which has a counterpart in normal biology. We explain how
these otherwise normal activities result in this profoundly malignant attribute of cancer. After the first two chapters define cancer, we next examine the causes of cancer (Chapter 3). Some cancers are hereditary. We discuss those known to be so and consider the nature of genetic change found in some tumors (Chapter 4). What we know about specific genes that regulate cancer cell expression is considered in Chapter 5. DNA-containing viruses may contribute to the cause of some cancers in humans — the oncogenic effect of DNA-containing viruses was discovered first in a frog cancer. The frog cancer and other animal cancers are described in Chapter 6. Cancer probably takes more years of life in the United States than any other disease (the death of a child with leukemia is not equivalent to a 90-year-old man dying of a stroke — in the former, perhaps seven or more decades of life are lost due to cancer; the old man in the latter instance, although dying of a common condition, has already outlived his life expectancy, and thus the number of life-years lost are nil. Nuns are more vulnerable to the ravages of breast cancer than random other women. Our knowledge of who is vulnerable to which cancer and how many people are involved is considered in epidemiology (Chapter 7). The design of drugs and treatment is not an arcane endeavor. The various modalities for cancer therapy are rational and based on biology. The biological basis of drug action is considered in Chapters 8 and 9. The appendix briefly describes some common cancers, and a glossary follows.

It is altogether too easy for a student working in a laboratory and taking courses to forget the reason for cancer research, the people afflicted with this most feared disease. Authentic cancer cases are described in the Introduction in the form of letters with comments concerning those cases. Although the study of cancer biology does not require a consideration of cancer victims, we have found that many students show compassion for these individuals and come to appreciate how cancer biology can enhance their understanding of what occurs in cancer patients. In some cases, this understanding augments their desire to learn more cancer biology.

Skeptics may argue that undergraduates do not have an adequate background to understand cancer properly. Of course they do not. Neither do they have an adequate background to understand ecology, plant physiology, parasitology, and evolution. That is why we have developed an undergraduate biology curriculum and a text to study the biology of cancer. Just as a student begins to comprehend other aspects of biology while taking introductory courses, so too does an understanding of cancer begin with taking a cancer biology course. Even in the late 1990s, courses in cancer biology are relatively rare. This book may encourage offerings of cancer biology in other colleges and universities.

The subject matter of cancer is fascinating to most people including nontraditional students. Attorneys, nurses, doctors, and other professional people occasionally attend our classes. We anticipate that libraries will make this book available to their patrons. Our book about cancer goes far beyond popular accounts, but it is not the turgid reading material found in a medical text. We intend that it be understandable to most educated adults. The text is not designed as a self-help
manual to assist in diagnosis or treatment. Questions about one's medical care should be discussed with one's physician. Rather it is designed to provide understanding of the biological and medical basis of contemporary studies in cancer.

Compiling the pages of a text is labor. Our labors have been eased by Debra L. Carlson, Augustana College, Sioux Falls, South Dakota; Julie A. Thompson, Division of Epidemiology, School of Public Health, University of Minnesota; and Kristine S. Klos, Department of Genetics and Cell Biology, University of Minnesota. They read the text with a critical eye, surgically ablated sentences that were difficult to understand, rearranged prose to make better sense, caught errors in English, and applied their healing skills to phrases in need of treatment. We are in their debt. The authors are exceptionally appreciative of the cooperation and continued efforts of Françoise Bartlett and Christina Viera to enhance this book during its production.

Finally, we thank students who have and will take a course in the biology of cancer. In a conversation with a distinguished Scottish scientist, one of us commented that he wished he had more time for the laboratory. Perhaps, he thought, it would be better not to teach at all but rather devote full time to laboratory pursuits. The Scot, a fellow of the Royal Society of London, responded, “Appreciate your students and give thanks that you must teach – there will be days upon days when research does not go well – that is the way of research. But if you teach, you will leave the lab for a lecture, and your flagging spirits will be rejuvenated by the enthusiasm and youthful concerns of your students. Then, with vigor renewed, return to the lab.” The authors of this book say, “Thank you, students.”