The Biological Basis of Cancer

This is a revised and updated edition of a text used in courses on cancer biology and is listed by the U.S. National Cancer Institute for all those wanting to learn about cancer. It covers everything from the molecular basis of cancer to clinical aspects of the subject, and has 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. Other chapters discuss cancer pathology, metastasis, carcinogenesis, genetics, oncogenes and tumor suppressors, epidemiology, and the biological basis of cancer treatment. Also included are an appendix with descriptions of common forms of cancer, a glossary of cancer-related terms, a comprehensive reference section, and color plates to illustrate the pathology of many of the types of cancer discussed in the text.

Upper-level undergraduates with background in biology, as well as beginning graduate students, will find this text invaluable.

Robert G. McKinnell is Professor Emeritus of Genetics, Cell Biology, and Development at the University of Minnesota, where he taught a course on the biology of cancer for thirty years. His research interests are focused on a herpesvirus-induced renal adenocarcinoma that occurs in the Northern Leopard Frog, Rana pipiens.

Ralph E. Parchment is Chief Scientific Officer at SciTech Development in Detroit. His expertise is in the field of in vitro drug safety testing and its application to designing clinical trials to evaluate new anticancer agents.

Alan O. Perantoni is a principal investigator and Chief of the Differentiation and Neoplasia Section in the Laboratory of Comparative Carcinogenesis, National Cancer Institute. He has maintained a research interest in oncogene-suppressor gene involvement in experimental carcinogenesis. He is currently engaged in studies of aberrant signaling mechanisms in pediatric tumors.

Ivan Damjanov is Professor of Pathology at the University of Kansas School of Medicine. He is interested in developmental aspects of neoplasia and diagnostic pathology of urogenital tumors.

G. Barry Pierce is Centennial Distinguished Research Professor of Pathology Emeritus at the University of Colorado Health Sciences Center. He is world renowned for his recognition of the stem cell origin of and differentiation of cancer cells.
The authors dedicate this book to two deserving groups. First, we recognize students who we confidently expect will make a greater impact on cancer than anyone has been able to do thus far. We are optimistic that these young scholars, committed to their research, will be rewarded by the eventual conquest of cancer. The other group is no less deserving. Let it be known that patients, who are the motivating force behind this book, despite enduring difficult treatment modalities, inspire us with their spirit – they have captured our respect and accordingly we dedicate this effort to them.

For Beverly Kerr McKinnell who revealed extraordinary courage when learning that she had what Susan Sontag termed “the barbarian within”; that cancer claimed her life all too soon despite incredible bravery on her part and the care of many compassionate and dedicated people in the healing professions. She is missed terribly.

A note about this dedication: Beverly, wife of Robert G. McKinnell, died just months before this revised edition appeared. She and Robert are witnesses to the horrific reality that few families indeed escape the awfulness of cancer lethality.
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Preface

This version of The Biological Basis of Cancer is referred to as a “second edition” which, of course, it is. The term “second edition” does little to inform the reader to what extent material has been updated or rewritten. Major changes were mandated throughout by the rapid pace of cancer research and the translation of new findings into improved clinical care. Be that as it may, some fundamental aspects of cancer do not change. The letters in the Introduction are such. The letters are provided to introduce the student to the impact of cancer on the lives of ordinary people and the resultant need for cancer research. That impact and need are the same today as they were several years ago and are perhaps best reflected in the remarkable cathartic writings of author John Gunther (Death Be Not Proud) on the untimely loss of his seventeen-year-old son in 1947 from a brain tumor to the recent trials and triumphs over cancer of international cycling star Lance Armstrong (It’s Not About the Bike: My Journey Back to Life). Similarly, the distinction of benign versus malignant, as well as the concept of tumor grading and staging and certain other aspects of cancer discussed in the chapter on pathology remain the same. Other material has been carefully revised or rewritten – there is an entirely new Chapter 8 devoted to measures recommended by cancer organizations, and the authors of this book, to hopefully (and likely) reduce risk for cancer. Chapter 10 presents a new therapeutic modality that was not established in 1998 – molecular therapy that specifically treats the molecular cause of cancerous growth. It also includes new clinical strategies not available to the oncologist in 1998: controlling blood supply to tumors and molecular profiling of patients to identify those few individuals who are extremely susceptible to particular drug toxicities. New to this revised edition are brief essays highlighting the contributions of major cancer researchers – this has been done to remind students that insights into cancer come from the endeavors of gifted scientists and physicians. The lives of the highlighted cancer researchers may even inspire and stimulate some students to go forth and do likewise. It is worth repeating that this book was originally designed for undergraduate students and beginning graduate students. Our intended audience has remained unchanged. However, students of any age with education in the biological sciences and time to pause and reflect will be able to master this material. We continue to hope that others, even
nonbiologists with an interest in cancer, will find reading this book understandable and rewarding.

We are gratified that certain universities have chosen to use this text in their courses in the biology of cancer. We thank the instructors and seek from them and from their students suggestions on how the book can be improved in future editions. We acknowledge with appreciation the inclusion of this book in a list of references by the National Cancer Institute:


While errors are solely those of the authors, a number of readers have graciously scrutinized various stages of this text and by their efforts have minimized egregious mistakes. We are profoundly grateful for their efforts. We appreciate those who have served us in other ways to enhance this book. The list of readers and helpers includes the following: Helen Miller Alexander, University of Kansas, Lawrence, KS; Debra L. Carlson, Augustana College, Sioux Falls, SD; Elaine M. Challacombe, Owen H. Wangensteen Historical Library of Biology and Medicine, University of Minnesota, Minneapolis, MN; William L. Dahut, Medical Oncology Clinical Research Unit, National Cancer Institute, Bethesda, MD; Marie A. DiBerardino, Drexel University College of Medicine, Philadelphia, PA; John Harshbarger, George Washington University Medical Center, Washington, DC; Sherri A. Long, Health Partners and Department of Dermatology, University of Minnesota, Minneapolis, MN; Susan Kerr McKinnell, ADCS, University of Minnesota, Minneapolis, MN; Danica Ramljak, Medora Global Consulting, Inc., McLean, VA; Mark A. Sanders, Imaging Center, College of Biological Sciences, University of Minnesota, Saint Paul, MN; Michael Waalkes, NIEHS, Research Triangle Park, NC; William R. Waud, Cancer Therapeutics, Southern Research Institute, Birmingham, AL; and Michael J. Wilson, Veterans Administration Medical Center and Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN.

This tome could not have attained fruition had it not been for the extraordinary aid of James V. Curley and Chacko T. Kuruvilla, University of Minnesota Biomedical Library. The authors thank both for their superb help.

Ken Karpinski was of inestimable support during the production phase of this book. RGM is particularly in his debt and owes Ken much appreciation indeed.

Special thanks go to our editor Katrina Halliday at Cambridge University Press, Cambridge, England. She was always prepared to provide help and advice, always pleasant in doing so, and had inexhaustible patience for the authors during the production of this book.

We would be remiss indeed if we did not recognize the support of our families and their forbearance in tolerating our annoying habits relating to time management in the preparation of this book. There are no words that adequately express our appreciation.

The following paragraph appeared in the first edition of this book. It is repeated here word for word because we believe it to be pertinent as a brief statement of the
debt we owe our students. It reads: Finally, we thank students who have and will take
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 lecture, and your flagging spirits will be rejuve-
nated 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.”

Homage to a colleague

Stem cells are much in the news for a variety of very good reasons. Those reasons
need not be described in detail here because it is difficult not to be aware of their
potential merit in the treatment of cancer and other chronic, debilitating, and
lethal diseases. Stem cells merit the attention of scholars for another very important
reason. Fully differentiated cells are post-mitotic and, as such, are unlikely to be
an effective target of chemical, physical, or viral carcinogens. After all, if a cell is
truly post-mitotic, how could it ever give rise to cell progeny, either normal or
malignant? If not fully differentiated cells, what then is the target of carcinogenesis?
Stem cells either proliferate into more stem cells that retain their pluripotential
differentiative competence, or differentiate into lineage-specific mature cells. There
has emerged in the last half century the concept that cancer is a disease of stem cells.
Abnormal stem cells give rise to malignant cells which differentiate, as might be
expected, along similar but aberrant pathways; i.e., they give rise to more abnormal
stem cells and to cells that differentiate incompletely as cancer cells. The abnormal
differentiation of cancer cells has been referred to as a “caricature” of the process of
tissue renewal. The concept of cancer that originates in a caricature of the process
of differentiation is not only of theoretical value but has certain very practical
consequences – not the least of which is the notion that because there is a problem
in differentiation of these progeny of stem cells, then treatment of some cancers
by differentiation agents might give rise to cells that mature, become terminally
differentiated, and ultimately are disposed of by apoptosis. An example of such a
cancer is acute promyelocytic leukemia, which responds to all-trans-retinoic acid
with maturation, terminal differentiation, and finally apoptosis.

The concept of the stem cell origin of cancer was a lifetime passion of one of the
authors of this book. That author is Gordon Barry Pierce (see photos next page)
known to many as “Barry.” Barry’s work is described briefly in Chapter 1. Barry, for
health reasons, has finished his responsibilities with this book. We, the remaining
authors, wish herewith to express our admiration for his lifetime of cancer research
and to personally thank him for the many times he has aided us in our research and
developed our intellectual drive to understand cancer. Barry, all of us wish for you and Donna many years of happiness, and please remember we are grateful for all that you have done for us individually and collectively.

Robert G. McKinnell
Ralph E. Parchment
Alan O. Perantoni
Ivan Damjanov

Color Plate 1. Lipoma of the intestine. The tumor is well circumscribed and it is yellow like normal fat tissue.

Color Plate 2. Meningioma. The tumor was removed from the intracranial cavity of a fifty-year-old man. The tumor is benign, but due to its intracranial location, it can be lethal. This typically occurs when the tumor compresses vital centers or causes increased intracranial pressure.
Color Plate 3. Leiomyomas of the uterus. These tumors present as well-delineated nodules in the muscular wall of the uterus (myometrium). Tumor nodules may cause enlargement of the uterus, which can compress the urinary bladder and other adjacent organs. Uterine leiomyomas are informally known as “fibroids”.

Color Plate 4. Invasive squamous cell carcinoma of the uterine cervix. The tumor is composed of irregular strands of neoplastic squamous cells.
Color Plate 5. Squamous cell carcinoma of the bronchus. Compare the normal bronchial lining on the right side with the thick tumor tissue lining the bronchial cavity on the left.

Color Plate 6. Peripheral lung carcinoma. This subpleural tumor was found in a sixty-year-old woman who was not a smoker. Histologically it was an adenocarcinoma (see Color Plate 7).
Color Plate 7. Peripheral lung adenocarcinoma. The tumor is composed of hyperchromatic cells forming irregular glandlike structures.

Color Plate 8. Lung carcinoma. This centrally located bronchial carcinoma was histologically diagnosed as a small cell carcinoma (see Color Plate 9).
Color Plate 9. Small cell bronchial carcinoma. The tumor is composed of small blue-stained cells and shows areas of necrosis (top).

Color Plate 10. Carcinoma of the lung metastatic to the mediastinal lymph nodes. The lymph nodes appear enlarged and attached one to another. Histological examination confirmed that this “lymphadenopathy” was caused by metastatic carcinoma.
Color Plate 11. Metastases in the lung. These multiple nodules represent metastases from a primary colonic adenocarcinoma.

Color Plate 12. Chondrosarcoma of the femoral bone in process of destroying normal bone (for histology, see Color Plate 13).
Color Plate 13. Chondrosarcoma. The tumor is composed of malignant cartilage cells. (Color Plates 1 through 13 were provided by Ivan Damjanov and Dennis Friesen)
