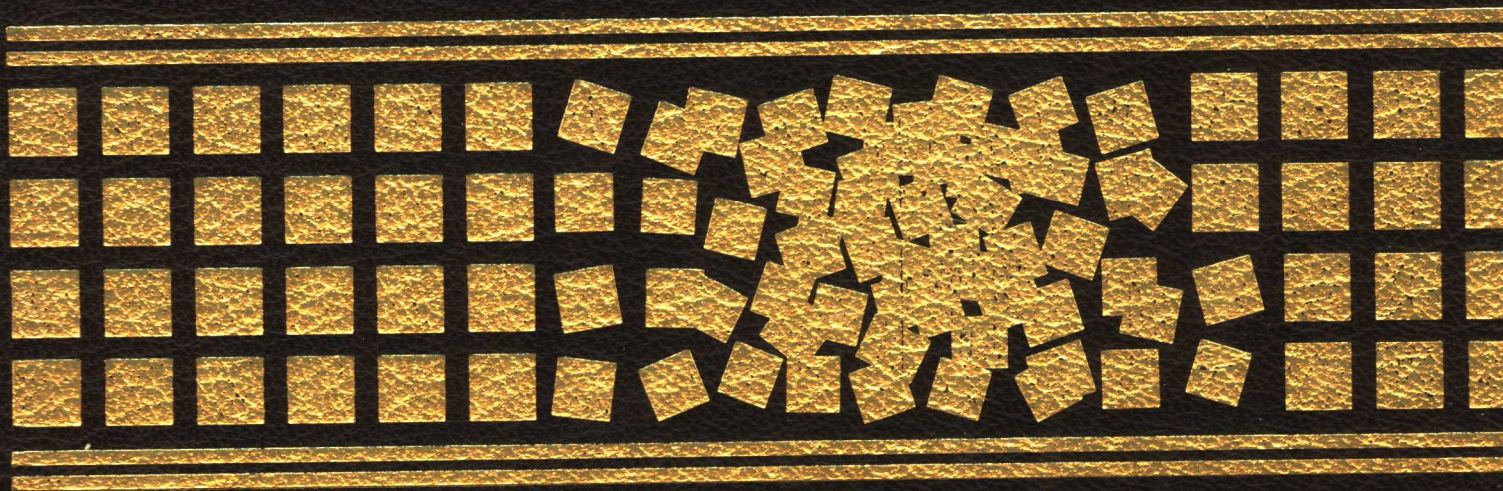


# **CANCER**

## **Principles & Practice of Oncology**

**6th Edition**



*[www.LWWoncology.com](http://www.LWWoncology.com)*

*Vincent T. DeVita, Jr.*

*Samuel Hellman*

*Steven A. Rosenberg*



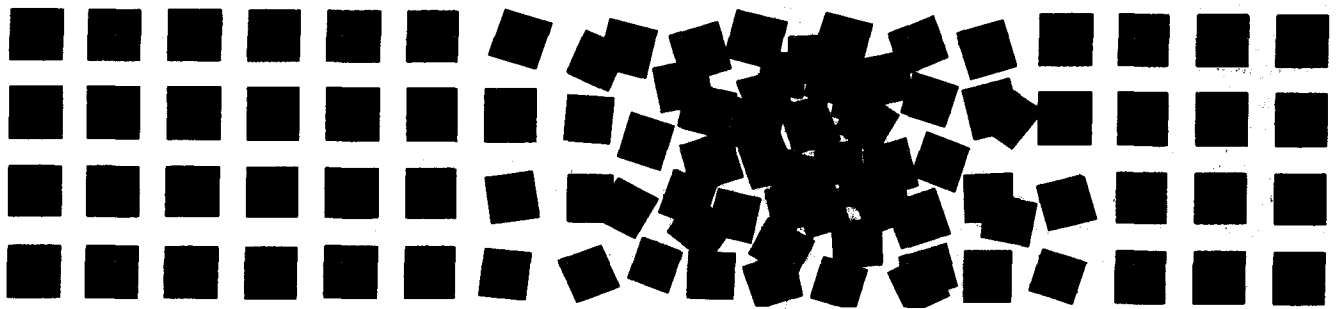
LIPPINCOTT WILLIAMS & WILKINS



# **CANCER**

*Principles & Practice  
of Oncology*

*6th Edition*



*[www.LWWoncology.com](http://www.LWWoncology.com)*



**LIPPINCOTT WILLIAMS & WILKINS**

A **Wolters Kluwer** Company

Philadelphia • Baltimore • New York • London  
Buenos Aires • Hong Kong • Sydney • Tokyo

*Acquisitions Editor:* Stuart Freeman

*Developmental Editors:* Susan Rhyner, Managing Editor; Anne Snyder, Senior Developmental Editor; and Stephanie Harris, Associate Developmental Editor

*Supervising Editor:* Toni Ann Scaramuzzo

*Production Editors:* Kim Langford and Shannon Garza, Silverchair Science + Communications

*Manufacturing Manager:* Tim Reynolds

*Compositor:* Silverchair Science + Communications

*Printer:* Quebecor World, Taunton, MA

6th edition

© 2001 by LIPPINCOTT WILLIAMS & WILKINS

530 Walnut Street

Philadelphia, PA 19106 USA

LWW.com

Copyright © 1993, 1989, 1985, 1982 by J.B. Lippincott Company. All rights reserved. This book is protected by copyright. No part of this book may be reproduced in any form or by any means, including photocopying, or utilized by any information storage and retrieval system without written permission from the copyright owner, except for brief quotations embodied in critical articles and reviews. Materials appearing in this book prepared by individuals as part of their official duties as U.S. government employees are not covered by the above-mentioned copyright.

Printed in the USA

---

**Library of Congress Cataloging-in-Publication Data**

Library of Congress Control Number: 89-649-721

Cancer: principles and practice of oncology [edited by] Vincent T. DeVita, Jr., Samuel Hellman, Steven A. Rosenberg; 319 contributors.—6th

ISSN 0892-0567

ISBN 0-781-72229-2

---

Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner.

The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of health care providers to ascertain the FDA status of each drug or device planned for use in their clinical practice.

10 9 8 7 6 5 4 3 2 1

---

# PREFACE

---

The rapid pace of change in knowledge of the scientific basis and clinical practice of oncology presents a daunting challenge to the oncologist. The extraordinary increase in understanding of the molecular basis of cellular processes, the rise of biotechnology, and the steady refinement of each of the major treatment approaches have impacted every phase of the care of the cancer patient. In addition, an increased appreciation of the coordinated role of each of the main treatment modalities in the care of an individual cancer patient has emphasized the need for oncologists to be familiar with developments in all treatment modalities. Each edition of this text, first published in 1982, has attempted to help the oncologist keep pace with these changes.

In this sixth edition of *CANCER: Principles and Practice of Oncology*, we have again attempted to provide a comprehensive resource describing the science underlying recent clinical developments as well as complete information to aid the clinician in the panorama of clinical care ranging from cancer prevention to the care of the terminally ill patient. To accomplish this, the book has been divided into four parts.

**PART 1: Essentials of Modern Oncologic Science** presents a summary of the major areas of modern bioscience carefully distilled to provide the background necessary for an understanding of recent developments in oncology. Thus chapters on molecular biology, genomics, proteomics, signal transduction, and immunology present a primer for the oncologist in these important areas.

**Part 2: Principles of Oncology** has been reorganized to present in further detail the specific scientific areas of greatest relevance to the oncologist, including new chapters on cytogenetics, the cell cycle, apoptosis, and angiogenesis, as well as chapters on the etiology of cancer, and a clear description of modern epidemiologic methods and the incidence of and mortality from cancer.

Chapters on the principles underlying the four modalities of cancer treatment—surgery, radiotherapy, chemotherapy, and biologic therapy—present the basis for continuing changes in the development and application of these treatments. The pharmacology of cancer chemotherapeutics is presented, and a new section is introduced on the rapidly changing area of cancer biotherapeutics as these agents have entered into the practice of oncology.

The final chapter in **PART 2** deals with the design and analysis of clinical trials as well as research data and management. As more and more patients are entering clinical trials, knowledge of these areas by the practicing oncologist is of special importance.

**PART 3: Practice of Oncology** provides the practicing clinician with the specific, practical information needed for the management of each cancer patient. Increased emphasis on cancer prevention relating to diet, tobacco, chemopreventive agents, fat, exercise, retinoids, naturally occurring dietary anticarcinogens, and many other areas are covered in detail. A new chapter on the role of surgery in cancer prevention details the emerging use of surgery in preventing cancer in high-risk individuals. Modern techniques of cancer screening, molecular pathology, imaging, and endoscopy are detailed in this section as well.

The hallmark of this book from its inception to the present and a major reason it has gained worldwide acceptance as a definitive source of cancer information has been the description of the treatment of cancer patients by stage of presentation with a tightly coordinated description of the role of each of the treatment modalities in the care of individual patients. To ensure a balanced multidisciplinary approach, each of the major treatment chapters is co-authored by a surgeon, a medical oncologist, and a radiation oncologist. Each of the major treatment sections is preceded by an updated, brief chapter describing the molecu-

lar biology of that cancer and the prospects this new information holds for the improved management of cancer patients.

Increased emphasis on supportive care, palliative care, and the quality of life of the cancer patient has led to an enlargement of sections dealing with these areas, including increased information on pain control and the nutritional, sexual, and psychosocial management of the cancer patient as well as issues related to the specialized care of the terminally ill.

PART 4: **Newer Approaches in Cancer Treatment** looks to the future of developments in oncology with special sections on gene therapy, molecular therapy, preventive and therapeutic cancer vaccines, image-guided surgery, and proton beam radiation therapy. In this section, we have attempted to identify those areas that we think will be of increasing value in the several years after the appearance of this text.

As we enter the twenty-first century, both the incidence and mortality of many of the major cancers are beginning to decline. We believe that the dissemination of carefully coordinated information of the scientific foundation and practice of oncology has played and will continue to play an important role in decreasing the devastating impact of cancer on modern society. We present the sixth edition of *CANCER: Principles and Practice of Oncology* to provide the practicing oncologist with the practical as well as cutting-edge information needed to provide the best possible care for each individual patient.

Vincent T. DeVita, Jr., MD

Samuel Hellman, MD

Steven A. Rosenberg, MD, PhD

---

# CONTENTS

---

## PART 1

### ESSENTIALS OF MODERN ONCOLOGIC SCIENCE

#### 1

#### *Essentials of Molecular Biology: Basic Principles* ..... 3

LANCE A. LIOTTA

EDISON T. LIU

Storage and Transmission of Genetic Information 3

Reading the Genetic Code and Production of Encoded Proteins 7

Protein Structure and Function 8

Subcellular Molecular Structure 9

Different Pathways to Cancer 12

Suggested Readings 15

#### 2

#### *Essentials of Molecular Biology: Genomics and Cancer* ..... 17

LANCE A. LIOTTA

EDISON T. LIU

Understanding Cancer at the Molecular Level: The New Frontier 17

Genetic Mechanisms of Cancer Progression: Cancer Is a Genetic Disease 17

Cancer Genes: Models of Action 18

Molecular Profiling: Prognosis and Treatment Tailored  
to the Individual Patient 20

Postgenome Challenge for Molecular Medicine	21
cDNA Microarrays Are a New Tool to Analyze Gene Expression Patterns in Human Cancer	22
Technology for Tissue Microdissection Brings Molecular Analysis to the Tissue Cell Level	24
Tumor Tissue Arrays	25
Beyond Functional Genomics to Cancer Proteomics	25

### 3

<i>Essentials of Signal Transduction</i> .....	31
--	----

CHRISTOPHER L. CARPENTER  
LEWIS C. CANTLEY

The Sensory Machinery: Ligands and Receptors	31
Propagation of Signals to the Cell Interior	34
Efficiency and Specificity: Formation of Multiprotein Signaling Complexes	38
Regulation of Protein Levels: Transcription, Translation, and Proteolysis	39

### 4

<i>Essentials of Immunology</i> .....	43
---------------------------------------	----

NICHOLAS P. RESTIFO  
JOHN R. WUNDERLICH

T Cells and Cellular Immunity	43
Antigen Presentation to T Cells	44
Specialized Antigen-Presenting Cells	50
T-Cell Recognition of Antigens	51
T-Cell Maturation	53
Activation of Mature T Cells	55
States of Mature T Cells	59
Functions of Mature T Cells	60
Cytotoxic Effector Cell Mechanisms	61
B Cells and Humoral Immunity	64
Summary	67

## PART 2

## PRINCIPLES OF ONCOLOGY

### 5

<i>Molecular Biology of Cancer: Cytogenetics</i> .....	77
--	----

MAZIN B. QUMSIYEH  
PEINING LI

History of Cancer Cytogenetics	77
Chromosome Structure and Function	77

<b>Cytogenetic Methods</b>	79
<b>International System of Cytogenetic Nomenclature</b>	82
<b>Mechanisms and Implications of Chromosomal Abnormalities in Cancer</b>	82
<b>Cautions to Exercise in Interpreting Chromosomal Abnormalities Seen in Cancer Studies</b>	86
<b>Clonal Evolution and Chromosome Evolution</b>	87
<b>Constitutional Chromosomal Abnormalities Predisposing to Cancer Development</b>	88
<b>Data Mining in Cancer Cytogenetics</b>	89
<b>Glossary</b>	89

## 6

### *Molecular Biology of Cancer: The Cell Cycle* ..... **91**

MICHAEL B. KASTAN

STEPHEN X. SKAPEK

**Mechanics of the Cell Division Cycle** 91

**Control of the Cell Division Cycle** 99

**Implications for Cancer** 102

## 7

### *Molecular Biology of Cancer: Apoptosis* ..... **111**

STANLEY J. KORSMEYER

SANDRA S. ZINKEL

**Apoptosis** 111

**Genetics of Cell Death** 112

**Death Receptors** 113

**Caspases** 113

**The Bcl-2 Family** 114

**Bcl-2 Family Members Play Critical Roles in Tissue Homeostasis** 117

**Role of Mitochondria** 118

**Cell Proliferation and Apoptosis** 118

**Possibilities for Therapeutic Intervention** 118

**Conclusions** 119

## 8

### *Molecular Biology of Cancer: Invasion and Metastases* ..... **123**

WILLIAM G. STETLER-STEVENSON

DAVID E. KLEINER, JR.

**The Metastatic Cascade** 123

**Oncogenesis: Metastasis and Tumorigenesis Are under Separate Genetic Control** 125

**Angiogenesis: Balance of Positive and Negative Effectors** 126

**Tumor Heterogeneity and Clonal Dominance** 126

**Defining the Invasive Phenotype** 126

**Cell-Cell Adhesion Suppresses or Facilitates Metastasis Formation** 127

**Cell-Extracellular Matrix Interactions in Tumor Progression** 129

**Intravasation, Extravasation, and Orthotopic Effect** 134



# 9

## **Biology of Cancer: Angiogenesis. . . . . 137**

ISAIAH J. FIDLER  
ROBERT S. KERBEL  
LEE M. ELLIS

**Neoplastic Angiogenesis: The Balance of Proangiogenic and  
Antiangiogenic Molecules 137**

**Lymphoid Cell-Mediated Angiogenesis 140**

**Regulation of Angiogenic Factor Expression in Tumors 140**

**Endogenous Inhibitors of Angiogenesis 140**

**Clinical Utility of Angiogenesis 141**

**Antiangiogenic Therapy: Issues and Expectations 143**

**Antiangiogenic Therapy as a Component of Other Antineoplastic  
Regimens 144**

**Conclusions 144**

# 10

## **Etiology of Cancer: Viruses. . . . . 149**

### **SECTION 1 RNA Viruses 149**

ERIC M. POESCHLA  
GARY L. BUCHSCHACHER, JR.  
FLOSSIE WONG-STAAAL

**Retroviral Genetics: Selective Access to the Growth Control Genes of the Cell 149**

**Mechanisms of Retroviral Oncogenesis 150**

**Human T-Cell Leukemia Virus Type I 152**

**Human T-Cell Leukemia Virus Type II 154**

**Human Immunodeficiency Virus 154**

**Hepatitis C Virus 155**

### **SECTION 2 DNA Viruses 158**

PETER M. HOWLEY  
DON GANEM  
ELLIOTT KIEFF

**Hepadnaviruses and Hepatocellular Carcinoma 158**

**Papillomaviruses and Human Cancer 161**

**Epstein-Barr Virus 168**

**Kaposi's Sarcoma-Associated Herpesvirus (Human Herpesvirus-8) 171**

# 11

## **Etiology of Cancer: Chemical Factors. . . . . 179**

STUART H. YUSPA  
PETER G. SHIELDS

**The Nature of Chemical Carcinogens: Chemistry and Metabolism 180**

**Animal Model Systems and Multistage Carcinogenesis 181**

**Protection against Chemical Carcinogens: DNA Repair, Tumor Suppressor Genes,  
and Transforming Growth Factor- $\beta$  184**

**Genetic Susceptibility to Chemical Carcinogenesis in Experimental Models 184**

<b>Determination of Chemical Carcinogens for Humans and Population-Based Risk Assessment</b>	<b>185</b>
<b>Molecular Epidemiology of Cancer Risk from Chemicals</b>	<b>186</b>
<b>Mutational Spectrum of Human Cancers</b>	<b>190</b>
<b>Tobacco Smoking and Cancer Risk</b>	<b>190</b>

## 12

<b><i>Etiology of Cancer: Physical Factors</i></b>	<b>195</b>
--	------------

ROBERT L. ULLRICH

<b>Interactions of Radiation with Cells and Tissues</b>	<b>195</b>
---	------------

<b>Ionizing Radiation and Cancer</b>	<b>197</b>
--------------------------------------	------------

<b>Ultraviolet Light</b>	<b>202</b>
--------------------------	------------

<b>Asbestos</b>	<b>204</b>
-----------------	------------

## 13

<b><i>Etiology of Cancer: Cancer Genetics</i></b>	<b>207</b>
---	------------

ALLEN E. BALE

SUZANNE J. BROWN

<b>Cancer as a Genetic Disease</b>	<b>207</b>
------------------------------------	------------

<b>Mechanisms of Cancer Predisposition</b>	<b>207</b>
--	------------

<b>Gatekeepers, Caretakers, and Landscapers</b>	<b>211</b>
---	------------

<b>Clinical Characteristics of Cancer Families</b>	<b>211</b>
--	------------

<b>Multisystem Genetic Syndromes with a High Risk of Cancer</b>	<b>212</b>
---	------------

<b>Nonsyndromic Hereditary Cancer</b>	<b>215</b>
---------------------------------------	------------

## 14

<b><i>Epidemiology of Cancer</i></b>	<b>219</b>
--------------------------------------	------------

<b>SECTION 1 <i>Epidemiologic Methods</i></b>	<b>219</b>
---	------------

MARGARET A. TUCKER

<b>Observational Studies</b>	<b>219</b>
------------------------------	------------

<b>Descriptive Studies</b>	<b>221</b>
----------------------------	------------

<b>Analytic Studies</b>	<b>221</b>
-------------------------	------------

<b>Intervention Studies</b>	<b>226</b>
-----------------------------	------------

<b>Future Directions</b>	<b>227</b>
--------------------------	------------

<b>SECTION 2 <i>Descriptive Epidemiology: Cancer Statistics</i></b>	<b>228</b>
---	------------

PHILIP COLE

BRAD RODU

<b>Descriptive Epidemiology</b>	<b>228</b>
---------------------------------	------------

<b>Perspectives</b>	<b>238</b>
---------------------	------------

<b>SECTION 3 <i>Analytic Epidemiology: Cancer Causes</i></b>	<b>241</b>
--	------------

PHILIP COLE

BRAD RODU

<b>Evaluating Carcinogenicity</b>	<b>241</b>
-----------------------------------	------------

<b>Causes of Cancer</b>	<b>242</b>
-------------------------	------------

<b>Perspectives</b>	<b>249</b>
---------------------	------------

# 15

## *Principles of Cancer Management: Surgical Oncology* ..... 253

STEVEN A. ROSENBERG

- Historical Perspective 253
- Anesthesia for Oncologic Surgery 254
- Determination of Operative Risk 256
- Roles for Surgery 259
- The Surgical Oncologist 262

# 16

## *Principles of Cancer Management: Radiation Therapy* ..... 265

SAMUEL HELLMAN

- Physical Considerations 265
- Biologic Considerations 270
- Clinical Considerations 282

# 17

## *Principles of Cancer Management: Chemotherapy* ..... 289

EDWARD CHU

VINCENT T. DEVITA, JR.

- History 289
- Chemotherapy as Part of the Initial Treatment of Cancer 290
- Clinical End Points in Evaluating Response to Chemotherapy 291
- Principles Governing the Use of Combination Chemotherapy 292
- Effect of the Biology of Tumor Growth on Response to Chemotherapy 294
- Apoptosis, Cell-Cycle Control, and Resistance to Chemotherapy 295
- Concept of Dose Intensity 300
- In Vitro* Drug-Response Assays 302

# 18

## *Principles of Cancer Management: Biologic Therapy* ..... 307

STEVEN A. ROSENBERG

- Basic Principles of Tumor Immunology 307
- Cells of the Immune System 308
- Immune Effector Mechanisms Resulting in Cell Destruction 308
- Cytokines 308
- Tumor Antigens 320
- Immunotherapy 324
- Interferons 326

## 19

**Pharmacology of Cancer Chemotherapy . . . . . 335****SECTION 1 Pharmacokinetics and Pharmacodynamics 335**

MARK J. RATAIN

Pharmacokinetics: Fundamental Principles 335

Pharmacokinetics: What's Important to the Clinician? 338

Basic Methodology of Pharmacokinetic Studies 339

Pharmacodynamics 340

Rational Use of Pharmacokinetic and Pharmacodynamic Data  
in Clinical Oncology 340**SECTION 2 Cancer Drug Development 345****Section 2.1 Identification and Screening of New Agents 345**

EDWARD CHU

MICHAEL R. GREVER

BRUCE A. CHABNER

Drug Discovery 345

Drug Development 352

Conclusion 354

**Section 2.2 Combinatorial Chemistry 356**

DAVID J. AUSTIN

Principles of Combinatorial Chemistry 356

The History of Combinatorial Chemistry 357

The Practice of Combinatorial Chemistry 359

Combinatorial Chemistry in Pharmaceutical Drug Development 360

The Future of Chemical Diversity in Drug Development 362

**SECTION 3 Antitumor Alkylating Agents 363**

OLIVER MICHAEL COLVIN

History of the Alkylating Agents 363

Chemistry and Cytotoxicity of Alkylating Agents 363

Classes of Alkylating Agents and Their Properties 363

Mechanisms of Toxicity and Drug Resistance 369

Common Toxicities 371

**SECTION 4 Cisplatin and Its Analogues 376**

STEVEN W. JOHNSON

JAMES P. STEVENSON

PETER J. O'DWYER

Platinum Chemistry 376

Evolution of Novel Platinum Complexes 377

Mechanism of Action 378

Mechanisms of Resistance 380

Clinical Pharmacology 383

**SECTION 5** *Antimetabolites* 388

EDWARD CHU

AUGUSTO C. MOTA

MIKLOS C. FOGARASI

**Methotrexate** 388**New Antifolates** 393**Other Antifolates** 393**Strategies to Permit Oral Administration of  
Fluoropyrimidines** 398**SECTION 6** *Topoisomerase Interactive Agents* 415

CLINTON F. STEWART

MARK J. RATAIN

**Mechanism of Action of Topoisomerase Interactive  
Agents** 416**Epipodophyllotoxins** 418**Camptothecin Analogues** 422**Anthracyclines and Related Compounds** 425**Mitoxantrone and Losoxantrone** 427**Dactinomycin (Actinomycin D)** 428**SECTION 7** *Antimicrotubule Agents* 431

ERIC K. ROWINSKY

ANTHONY W. TOLCHER

**Microtubules** 431**Microtubule-Associated Proteins and Microtubule Motors** 432**Vinca Alkaloids** 432**The Taxanes** 437**Estramustine Phosphate** 445**Novel Compounds Targeting Microtubules** 447**SECTION 8** *Miscellaneous Chemotherapeutic Agents* 452

BRUCE D. CHESON

**Homoharringtonine** 452**Suramin** 453**Bleomycin** 453**L-Asparaginase** 454**Amifostine** 455**20***Pharmacology of Cancer Biotherapeutics* ..... **461****SECTION 1** *Interferons* 461

JOHN M. KIRKWOOD

**Rationale for Investigation of Interferons: Direct Regulation  
of Cell Growth, Differentiation, Antigen Expression; Indirect  
Effects Mediated through Modulation of the Host Immune  
Response** 461**Clinical Evaluation** 464



**SECTION 2 Interleukin-2 471**

JAMES W. MIER  
MICHAEL B. ATKINS

Isolation, Characterization, and Cloning of Interleukin-2 471

Interleukin-2 Receptor 472

Interleukin-2-Activated Signaling Pathways 472

*In Vitro* Effects of Interleukin-2 473

Preclinical Studies with Interleukin-2 in Tumor-Bearing Mice 473

Clinical Applications of Interleukin-2 473

Biology and Pharmacokinetics of Interleukin-2 475

Attempts to Improve Activity of Interleukin-2-Based  
Therapy 476

**SECTION 3 Hormonal Therapies 478**

CHARLES ERLICHMAN  
CHARLES L. LOPRINZI

Selective Estrogen Receptor Modulators 478

Medroxyprogesterone and Megestrol 481

Aromatase Inhibitors 482

Gonadotropin-Releasing Hormone Analogues 483

Antiandrogens 484

Fluoxymesterone 485

Diethylstilbestrol and Estradiol (Estrace) 485

Octreotide 486

**SECTION 4 Differentiation Agents 489**

RAYMOND P. WARRELL, JR.

Retinoids 489

Arsenic Trioxide 491

Histone Deacetylase Inhibitors 491

Vitamin D 493

Cytokines and Other Proteins 493

**SECTION 5 Therapeutic Monoclonal Antibodies: General Principles 495**

LOUIS M. WEINER  
GREGORY P. ADAMS  
MARGARET VON MEHREN

Immunoglobulin Structure: Structural and Functional  
Domains 495

Factors Regulating Antibody-Based Tumor Targeting 495

Unconjugated Antibodies 497

Immunoconjugates 500

Therapeutic Applications 501

Future Directions 505

**SECTION 6 Antiangiogenesis Agents 509**

JUDAH FOLKMAN

Guidelines to the Biologic Basis of Antiangiogenic Therapy 509

Clinical Trials of Angiogenesis Inhibitors 517

## 21

**Clinical Trials in Cancer . . . . . 521****SECTION 1 Design and Analysis of Clinical Trials 521**

RICHARD SIMON

Phase I Clinical Trials 521

Phase II Clinical Trials 523

Design of Phase III Clinical Trials 526

Analysis of Phase III Clinical Trials 531

Epidemiology of Clinical Trials 537

Metaanalysis 537

**SECTION 2 Research Data Management 539**

DOUGLAS HAGEMAN

DIANNE M. REEVES

Protocol Development 539

Protocol Implementation 540

Information Technology 543

Data Classification 544

U.S. Food and Drug Administration Recommendations 544

Data Validation 544

Direct Data Capture 545

Security 545

Summary 545

**PART 3****PRACTICE OF ONCOLOGY**

## 22

**Cancer Prevention: Preventing Tobacco-Related Cancers . . . . . 549**

HOWARD K. KOH

CHRISTINE KANNLER

ALAN C. GELLER

Tobacco and Nicotine Addiction 549

Health Effects 550

Smoking Rates and Trends 550

Cigarette Product Modification 552

Spit Tobacco 552

Cigars 552

Environmental Tobacco Smoke 552

Tobacco Industry Advertising Strategies 553

Strategies for Tobacco Control 553

Community Level and State Interventions 555

Tobacco Taxes That Fund Dedicated, Comprehensive Statewide

Tobacco Control Programs 556

Mass Media and Counter-Advertising	557
Tobacco Litigation and Tobacco Settlement	557
Proposed U.S. Food and Drug Administration Regulation	558
Conclusion	558

## 23

### ***Cancer Prevention: Diet and Chemopreventive Agents. . . . . 561***

#### ***SECTION 1 Fat 561***

WALTER C. WILLETT

Fat and Breast Cancer 562

Fat and Colon Cancer 564

Fat and Prostate Cancer 565

Other Cancers 565

Summary 565

#### ***SECTION 2 Dietary Fibers 568***

PETER GREENWALD

Sources and Types of Dietary Fiber 568

Dietary Fiber and Colorectal Cancer 568

Dietary Fiber and Breast Cancer 572

Dietary Fiber and Other Cancers 573

Public Health Implications 573

#### ***SECTION 3 Retinoids, Carotenoids, and Micronutrients 575***

SUSAN TAYLOR MAYNE

SCOTT M. LIPPMAN

Historical Perspective 575

Retinoid Biology and Pharmacology 576

Carotenoid Biology and Actions 577

Clinical Trials 577

Translational and Intermediate End Point Studies  
in Retinoid Chemoprevention 586

New Retinoids and Carotenoids 587

Conclusions 588

#### ***SECTION 4 Naturally Occurring Dietary Anticarcinogens 590***

PETER GREENWALD

Carotenoids 590

Phytoestrogens 591

Organosulfur and Organoselenium Compounds 591

Phenolic Compounds 592

Monoterpenes 593

Isothiocyanates and Indoles 593

Protease Inhibitors 594

Implications for Cancer Prevention 594

**SECTION 5** *Dietary Carcinogens* 595

PETER GREENWALD

Naturally Occurring Dietary Carcinogens 596

Products of Food Preparation and Processing 597

Synthetic Carcinogens in the Diet 599

Future Research Needs 599

**SECTION 6** *Aspirin and Other Nonsteroidal Antiinflammatory Drugs and the Risk of Cancer Development* 601

MICHAEL J. THUN

CHARLES H. HENNEKENS

Pharmacology and Toxicity of Nonsteroidal Antiinflammatory Drugs 601

Historical Evolution of the Hypothesis That Nonsteroidal Antiinflammatory Drugs Inhibit Cancer 602

Cellular Mediators of Tumor Inhibition 606

Nonsteroidal Antiinflammatory Drugs and Cancers Other Than Colorectal Cancer 607

Dose and Duration Issues in Chemoprevention 607

**SECTION 7** *Physical Activity and Body Weight* 610

GRAHAM A. COLDITZ

Colon Cancer 610

Breast Cancer 612

Obesity 613

Relationship between Obesity and Carcinoma 614

Conclusions 614

## 24

*Cancer Prevention: Role of Surgery in Cancer Prevention.* ..... **617**

RICHARD M. SHERRY

Multiple Endocrine Neoplasia 2 and Familial Medullary

Thyroid Carcinoma 617

Barrett's Esophagus and Esophageal Cancer 618

Breast Cancer 620

Ovarian Cancer 621

Colorectal Cancer 622

Testicular Cancer and Cryptorchidism 624

## 25

*Cancer Screening.* ..... **627**

BARBARA K. RIMER

JOELLEN SCHILDKRAUT

ROBERT A. HIATT

What Is Cancer Screening? 627

Evaluation of a Screening Test 628

Breast Cancer Screening 629