

Antineoplastic and Immunosuppressive Agents

Part II

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Preface

Over the past two decades a number of attempts have been made, with varying degrees of success, to collect in a single treatise available information on the basic and applied pharmacology and biochemical mechanism of action of antineoplastic and immunosuppressive agents. The logarithmic growth of knowledge in this field has made it progressively more difficult to do justice to all aspects of this topic, and it is possible that the present handbook, more than four years in preparation, may be the last attempt to survey in a single volume the entire field of drugs employed in cancer chemotherapy and immunosuppression. Even in the present instance, it has proved necessary for practical reasons to publish the material in two parts, although the plan of the work constitutes, at least in the editors' view, a single integrated treatment of this research area.

A number of factors have contributed to the continuous expansion of research in the areas of cancer chemotherapy and immunosuppression. Active compounds have been emerging at ever-increasing rates from experimental tumor screening systems maintained by a variety of private and governmental laboratories throughout the world. At the molecular level, knowledge of the modes of action of established agents has continued to expand, and has permitted rational drug design to play a significantly greater role in a process which, in its early years, depended almost completely upon empirical and fortuitous observations. In addition, the rapid expansion in our knowledge of cancer etiology has begun to afford opportunities for the development of new types of agents with the capacity to inhibit the neoplastic process. Recent advances in our knowledge of viral carcinogenesis, and the consequent expansion of the field of cancer chemotherapy to agents which affect the processes of viral replication and virus-induced transformation of mammalian cells, are factors which are already having a profound influence on drug design and development. Modification and enhancement by pharmacological means of immune defenses to neoplastic growth is another area which is only beginning to be exploited by the chemotherapist. Many major advances still remain to be made to take full advantage of potential synergistic interactions between chemotherapy and surgery and/or radiation therapy: these three major modalities have developed almost independently despite the continuing efforts of several outstanding groups of investigators to bridge the gap between them at both the experimental and applied levels.

In addition to the rapid growth of these research areas, a second feature which strikes the editor who attempts to survey cancer chemotherapy and immunotherapy is the frequency with which, as in so many other areas of science, fundamental advances have been made unexpectedly, seemingly almost fortuitously. While such random progress may be expected to be a characteristic of the early development of any new research field, it appears to have played an unusually large role in cancer research, and the recent history of cancer chemotherapy shows that major findings have continued to emerge unpredictably, despite retrospective attempts of scientific historians to detect a previously discernable rationale in such developments. The unusually prominent role of chance in the development of antineoplastic and immunosuppressive agents may

be a reflection of the slow and difficult progress in our knowledge of cancer etiology: when the location of a target is still shrouded in darkness, it is probably inevitable that direct hits will continue to be a consequence of accident rather than design. It is to be hoped that the current efforts of public and private research funding agencies to superimpose order and modern management techniques on the apparently random development of this and other biomedical sciences will not have the paradoxical effect of slowing the progress they are designed to enhance.

The volume is divided into two parts. The first, has two major sections on general considerations in the areas of antineoplastic and immunosuppressive agents, with chapters included on (a) test systems for both classes of drugs, (b) the clinical utility of both classes of drugs in suppressing the growth of cancer and the immune responses, (c) design of new agents in several major chemical and biochemical classes, (d) the role of cell cycle kinetics in the utility of these therapeutic agents, (e) pharmacologic factors of importance in their optimal utility, (f) selective toxicity, (g) tests predictive of cytotoxic potency, (h) mechanisms of resistance, (i) combination chemotherapy, and (j) among the related modalities, radiation therapy and immunotherapy.

The second part of the volume describes the agents of importance in the treatment of these disease states. It includes major sections on alkylating agents, hormones, antimetabolites and a variety of other cytotoxic compounds, including inhibitors of protein and RNA synthesis, antibiotics and alkaloids, a variety of important synthetic agents and cytotoxic metal-containing compounds.

The Editors wish to express their deepest gratitude to their collaborators who have not only contributed important chapters, but have cooperated fully in the final preparation of this volume. They are also most appreciative of the invaluable editorial assistance provided by Dr. BARBARA RENKIN and the important secretarial help they have received from Miss LENORA ANTINOZZI and Miss LYNN A. BON TEMPO. Special thanks go to Dr. WILLIAM A. CREASEY who has compiled the subject index for this volume. It is our deepest hope that research workers in cancer, immunosuppression and other scientific disciplines will find this volume of use in both their intellectual and laboratory endeavors and that it may aid in the accomplishment of further advances in science for the benefit of man.

New Haven and Bethesda
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ALAN C. SARTORELLI
DAVID G. JOHNS

Part I Table of Contents

Section A: General Considerations: Antineoplastic Agents

- Chapter 1 Agents of Choice in Neoplastic Disease. C. GORDON ZUBBOD
Chapter 2 Evaluation of Antineoplastic Activity: Requirements of Test Systems. ABRAHAM GOLDIN, STEPHEN CARTER, and NATHAN MANTEL
Chapter 3 Rational Design of Alkylating Agents. W. C. J. ROSS
Chapter 4 Rational Design of Folic Acid Antagonists. J. A. R. MEAD. With 2 Figures
Chapter 5 Rational Design of Purine Nucleoside Analogs. JOHN A. MONTGOMERY
Chapter 6 Rational Design of Pyrimidine Nucleoside Analogs. LEROY B. TOWNSEND and C. C. CHENG
Chapter 7 Basic Concepts of Cell Population Kinetics. L. F. LAMERTON. With 5 Figures
Chapter 8 Clinical Applications of Cell Cycle Kinetics. BAYARD CLARKSON. With 3 Figures
Chapter 9 Metabolic Events in the Regulation of Cell Reproduction. ELTON STUBBLEFIELD and SANDRA MURPHREE. With 1 Figure
Chapter 10 Site of Action of Cytotoxic Agents in the Cell Life Cycle. H. MADOC-JONES and F. MAURO. With 3 Figures
Chapter 11 Pharmacokinetic Models for Antineoplastic Agents. DANIEL S. ZAHARKO and ROBERT L. DEDRICK. With 4 Figures
Chapter 12 Absorption, Distribution, and Excretion of Antineoplastic and Immunosuppressive Agents. VINCENT T. OLIVERIO. With 3 Figures
Chapter 13 Transport of Antineoplastic Agents. M. T. HAKALA
Chapter 14 Metabolism of Cancer Chemotherapeutic Agents via Pathways Utilized by Endogenous Substrates. DAVID G. JOHNS. With 7 Figures
Chapter 15 Metabolism of Cancer Chemotherapeutic Agents via Pathways Utilized by Xenobiotics. A. M. GUARINO and C. L. LITTERST. With 3 Figures
Chapter 16 Theoretical Considerations in the Chemotherapy of Brain Tumors. ALAN L. COWLES and JOSEPH D. FENSTERMACHER
Chapter 17 The Constancy of the Product of Concentration and Time. L. B. MELLETT. With 5 Figures
Chapter 18 Biochemical Aspects of Selective Toxicity. J. FRANK HENDERSON
Chapter 19 Mechanisms of Resistance. R. W. BROCKMAN. With 7 Figures
Chapter 20 Combination Chemotherapy: Basic Considerations. ABRAHAM GOLDIN, JOHN M. VENDITTI, and NATHAN MANTEL. With 6 Figures
Chapter 21 Combination Chemotherapy: Clinical Considerations. EMIL FREI, III and JEFFREY A. GOTTLIEB
Chapter 22 Tests Predictive of Cytotoxic Activity. THOMAS C. HALL
Chapter 23 Metabolic Changes Induced by Ionizing Radiations. PAUL TODD. With 2 Figures
Chapter 24 Radiation Research: Survival Kinetics. L. J. TOLMACH and L. E. HOPWOOD. With 7 Figures
Chapter 25 Clinical and Laboratory Investigation of Combination Radiation and Chemical Therapy. R. L. SCOTTE DOGGETT and MALCOLM A. BAGSHAW. With 1 Figure
Chapter 26 Tumor Immunotherapy. A. FEFER

Section B: General Considerations: Immunosuppressive Agents

- Chapter 27 Evaluation of Immunosuppressive Agents. MALCOLM S. MITCHELL. With 2 Figures
Chapter 28 Immunosuppressive Agents. EVAN M. HERSH
Chapter 29 Clinical Utility of Immunosuppressive Agents. JULES E. HARRIS and RAMESH C. BAGAI

Author Index

Subject Index

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Part II Table of Contents

Section C: Alkylating Agents

Chapter 30

Chemistry of Alkylation. CHARLES C. PRICE

Introduction	1
Reaction Mechanism	1
References	5

Chapter 31

Molecular Biology of Alkylation: An Overview. DAVID B. LUDLUM. With 5 Figures

Introduction	6
Alkylation of DNA	6
Effects of Alkylating Agents on Bacteriophage	9
Cellular Modification of Damaged DNA	11
Functional Capacity of Alkylated Template	14
References	15

Chapter 32

Mechanism of Action of 2-Chloroethylamine Derivatives, Sulfur Mustards, Epoxides, and Aziridines. T. A. CONNORS. With 2 Figures

Introduction	18
The Mechanism of Alkylation	19
Mechanism of Action at the Cellular Level	20
A. Long Term Effects of the Alkylating Agents	22
B. Antineoplastic Effects	22
C. Effects on Hemopoietic Tissue	23
D. Effects on Spermatogenesis	23
E. Effects on the Immune Response	24
Mechanism of Action at the Macromolecular Level	24
A. Reactions with Enzymes and Coenzymes	25
B. Reaction with Nucleic Acids	25
Distribution and Metabolism of Alkylating Agents	28
Conclusions	29
References	30

Chapter 33

Mechanism of Action of Methanesulfonates. BRIAN W. FOX. With 1 Figure

Introduction	35
Whole Tissue Studies	35
A. Antitumor Activity	35
B. Spermatogenesis	37

VIII

Table of Contents

C. Hemopoietic Effects	37
D. Immunosuppressive Properties	38
E. Miscellaneous Effects	38
Metabolism and Distribution Studies	39
Cellular Studies	40
Studies at the Molecular Level	41
Mutagenic Action	41
Conclusions	42
References	42

Chapter 34

Mechanism of Action of Mitomycins. HELGA KERSTEN. With 7 Figures

Introduction	47
Molecular Mechanism of Action	48
A. Interaction with DNA <i>in Vitro</i>	48
B. Interaction with DNA in Intact Cells (DNA Damage and Repair)	52
C. DNA Synthesis and Degradation	53
D. RNA Metabolism	54
E. Synthesis of Enzymes	56
Biological Effects of Mitomycins Related to Molecular Mechanism of Action	56
A. Mutagenicity	56
B. Chromosome Breakage	56
C. Viruses, Phage, and Episomal DNA	57
D. Mitosis	59
E. Immunological Aspects	59
References	60

Chapter 35

Mechanism of Action of Nitrosoureas. GLYNN P. WHEELER

Introduction	65
Chemistry	65
Pharmacological Considerations	69
Reactions with Biological Materials	69
A. Alkylation	69
B. Carbamoylation	72
Biochemical Effects	73
A. Synthesis of Macromolecules	73
B. Enzyme Levels and Inactivation of Enzymes	75
Biological Effects	76
A. Effects upon Cell Cycle and Cytotoxicity during the Cycle	76
B. Genetic Effects	78
Conclusions	79
References	79

Section D: Hormones

Chapter 36

Mechanism of Action of Glucocorticoids. FRED ROSEN and RICHARD J. MILHOLLAND

Introduction	85
------------------------	----

Table of Contents

IX

Biochemical Effects of Glucocorticoids on Lymphoid Tissues	86
A. DNA Metabolism	86
B. RNA and Protein Metabolism	88
C. Carbohydrate Metabolism	91
D. Changes in Enzyme Activity	94
Glucocorticoid Receptors	94
A. Studies in Animals	96
B. Whole Cell Studies <i>in Vitro</i>	96
C. Broken-Cell System	98
Possible Mechanism of Action and Basis for Resistance to Glucocorticoids	98
References	100

Chapter 37

Mechanisms of Action of Estrogens. RUSSELL HILF and JAMES L. WITTLIFF. With 5 Figures

Introduction	104
Chemical Structure and Steroidogenesis	104
Actions on Target Organs	108
A. Accessory Sex Organs	108
B. Pituitary and Hypothalamus	108
C. Lipogenesis and Cholesterol	109
D. Antiestrogens	109
E. Breast and Breast Cancer	111
F. Additional Effects of Estrogens	113
Biochemical Basis of Action	113
A. Specific Estrogen Binding Proteins	113
B. Macromolecular Synthesis	118
C. Carbohydrate Metabolism	122
References	125

Chapter 38

Mechanism of Action of Androgens. RUSSELL HILF. With 1 Figure

Introduction	139
Biosynthesis of Androgens	139
Relative Potency of Androgens	142
Actions on Target Organs	142
A. Testis and Male Accessory Sex Organs	142
B. Ovaries and Female Accessory Sex Organs	143
C. Pituitary	143
D. Breast and Breast Cancer	144
E. Metabolic Actions	145
F. Antiandrogens	145
Mechanisms of Action	146
A. Effects of Androgens on Synthesis of Macromolecules	147
B. Androgen Receptor Macromolecules	149
C. Energy Metabolism and Enzyme Changes	151
References	153

Chapter 39

Mechanism of Action of Progesterone. BERT W. O'MALLEY and CHARLES A. STROTT.
With 1 Figure

Biologic Responses to Progesterone	158
The Uptake and Metabolism of Progesterone	159
Binding of Progesterone to Target Cells	162
Sequence of Events in the Action of Progesterone	163
References	167

Chapter 40

Pharmacology and Clinical Utility of Hormones in Hormone Related Neoplasms.
THOMAS L. DAO

Introduction	170
Hormone-Induced Tissue Growth and Neoplasia.	171
Antineoplastic Property of Steroid Hormones as Related to Their Biological Activities.	172
A. Estrogens and Antiandrogenic Effect.	172
B. Androgen and its Antiestrogenic Effect.	173
C. Antineoplastic Effect of Estrogen and Hypothalamic-Pituitary Regulation of Prolactin.	174
D. Effect of Progestogens on Endometrium, Mammary Gland, and Kidney, and Their Antitumor Activity	174
E. Corticosteroids and Their Antitumor Activity	175
F. Direct Effect of Steroid Hormones on Tumor Growth	176
Metabolism of Steroids in Cancer	177
A. Metabolism of Estrogens	177
B. Metabolism of Androgens	179
Clinical Use of Hormonal Steroids in the Treatment of Cancer.	179
A. Cancer of the Prostate	179
I. Diethylstilbestrol (α, α' -diethyl-4,4'-stilbenediol)	179
II. Chlorotrianisene (tri- <i>p</i> -anisylchloroethylene, TACE)	180
III. Corticosteroid Therapy.	180
B. Cancer of the Breast.	180
I. Androgen Therapy	181
1. Testosterone	181
2. Dihydrotestosterone (Stanolone, Androstanolone, Androstan-17 β -ol-3-one)	181
3. 17 α -Methyltestosterone	182
4. Fluoxymestrone (9 α -fluoro-11 β -hydroxy-17 α -methyltestosterone, Halotestin).	182
5. 19-Nor-Testosterone	182
6. Δ^1 -Testololactone (Teslac)	182
7. Other Synthetic Androgens	183
II. Estrogen Therapy	183
III. Adrenocorticoid Therapy	184
IV. Progesterone	185
C. Endometrial Carcinoma	186
D. Carcinoma of the Kidney	186
E. Lymphomas and Leukemia	187
Conclusions	187
References	188

Section E: Antimetabolites

Chapter 41

Fluorinated Pyrimidines and Their Nucleosides. CHARLES HEIDELBERGER. With 10 Figures

Introduction	193
Rationale	193
Syntheses	195
Physical, Chemical, and Conformational Properties	197
Tumor-Inhibitory Properties	198
Other Biological Effects	199
A. Inhibition of the Growth of Cultured Cells	199
B. Antiviral Activity	199
C. Mutagenic Activity	200
D. Teratogenic Activity	200
E. Effects on Chromosomes	200
F. Effects on Bacterial Cell Walls	201
G. Antifungal Effects	201
H. Immunosuppression	201
Biochemical Summary	201
A. Metabolic Degradation of the Pyrimidine Ring	202
B. Anabolic Reactions along the Ribonucleotide Pathway	202
C. Anabolic Reactions along the Deoxyribonucleotide Pathway	203
D. Nucleoside Catabolic Reactions	203
Inhibition of DNA Synthesis	203
A. Cellular	203
B. Enzymatic Mechanism	204
Incorporation into DNA	204
Effects on RNA Synthesis	205
A. Mammalian	205
B. Microorganisms	206
C. Effects on Ribosome Biosynthesis	206
Incorporation into RNA	207
A. Total Cellular	207
B. Viral RNA	208
C. Transfer RNA	209
D. Ribosomal RNA	210
E. Messenger RNA	210
Consequences of Incorporation into RNA	211
A. Mutagenesis to RNA Viruses	211
B. Effects on Protein Synthesis	211
C. Effects on Enzyme Induction	212
D. Coding Properties	213
E. Translational Errors	214
Pathways of Activation and Resistance	215
A. Role of Catabolism	215
B. Activation	216
C. Resistance	217
Effects on the Cell Cycle	217

Preclinical Pharmacology	219
Clinical Use.	219
Clinical Pharmacology	221
References	223

Chapter 42

Arabinosyleytosine. WILLIAM A. CREASEY. With 1 Figure

Introduction	232
Synthesis and Structure-Activity Relationships of the Arabinosides	232
Assay Methods for Arabinosyleytosine	234
Biological Actions	235
A. Antitumor Effects in Experimental Systems	235
B. Other Biological Effects	236
Metabolic Fate of Arabinosyleytosine	237
Biochemical Studies with Arabinosyleytosine	239
A. Uptake and Phosphorylation of Ara-C	239
B. Inhibition of DNA Biosynthesis	241
C. Ribonucleoside Diphosphate Reductase	242
D. DNA Polymerase	243
E. Incorporation of Ara-C into Nucleic Acids	244
F. Miscellaneous Biochemical Effects	245
G. Resistance to Arabinosyleytosine	246
Conclusions	248
References	249

Chapter 43

Clinical Pharmacology of Arabinosyleytosine. D. H. W. HO and EMIL J. FREIREICH. With 1 Figure

Introduction	257
Effect of Route of Administration	257
A. Intravenous Administration — Single Dose	257
I. Volume of Distribution	257
II. Half-Life	258
III. Metabolism	259
1. Plasma	259
2. Leukemic Cells	259
IV. Excretion	259
B. Oral Administration	259
I. Absorption	259
II. Effect of 1-(β -D-ribofuranosyl)-4-hydroxy-3,4,5,6-tetrahydropyrimidine-2-(1H)one (Tetrahydrouridine, THU)	259
C. Intrathecal Administration	260
D. Intramuscular and Subcutaneous Administration	260
Toxicity	260
A. Myelosuppression	260
B. Megaloblastosis and Unbalanced Growth	261
C. Chromosomal Aberrations and Teratogenesis	261
D. Other Toxic Effects	261
Effect of Schedule, Dose, and Strategy of Treatment	261
A. Effect of Duration of Continuous Infusion on Clinical Toxicity	261

B. Effect of Dose and Schedule on Pharmacological Findings	262
I. Dose	262
II. Schedule	262
C. Clinical Results for Acute Leukemia and the Relationship of Schedule to Effectiveness	263
Combination Chemotherapy	263
A. Ara-C and Cyclophosphamide	263
B. Ara-C and 1,3-bis(2-Chloroethyl)-1-Nitrosourea (BCNU)	264
C. Ara-C and 6-Thioguanine (TG)	264
D. Ara-C and Methyl M. tomeycin (Porfiromycin)	264
Resistance to Ara-C as Related to Kinase: Deaminase Ratios and to Intracellular Ribonucleotide Concentrations	264
Perspectives	266
A. Tetrahydrouridine (THU)	266
B. 1- β -D-Arabinofuranosylcytosine 5'-Adamantoate (AdO-Ara-C)	266
C. Other Ara-C Analogs	266
I. 2,2'-O-Cyclocytidine (Cyclocytidine)	266
II. Arabinosylcytosine 3-N-Oxide (Ara-C-3-N-Oxide)	267
D. Sparing Action by Uridine	267
References	267

Chapter 44

Halogenated Pyrimidine Deoxyribonucleosides. WILLIAM H. PRUSOFF and BARRY GOZ.
With 4 Figures

Introduction	272
Chemistry	272
A. Synthesis	272
I. Synthesis of Nucleosides Halogenated in the Pyrimidine Moiety	272
II. Synthesis of Radioactive Halogenated Nucleosides and Nucleotides	273
III. Synthesis of Nucleosides Halogenated in the Sugar Moiety	273
IV. Synthesis of Nucleotides Halogenated in the Pyrimidine Moiety	274
V. Synthesis of Halogenated Nucleic Acid	274
B. Stability of Nucleosides	275
C. Steric Effects	277
D. Ionization Effects	277
E. Molecular Conformation	278
Metabolism	279
A. Anabolism	279
B. Catabolism	282
C. Enzyme Inhibition	285
D. Augmentation of Utilization of Halogenated Deoxyribonucleosides	288
I. Inhibition of Thymidylate Synthetase	288
II. Inhibition of Nucleoside Phosphorylase	289
III. Inhibition of Pyrimidine Degradation	290
IV. Complex Formation	291
V. Alteration of Structure	291
VI. Improved Regimens	291
Physical Effects of Incorporation of Halogenated Uracil Derivatives into DNA	292
A. Increased Lability to Stress	292
B. Increased Density	292
C. Increased Temperature (T_m) for DNA Denaturation	292
D. Decreased pH for DNA Denaturation	294
E. Increased Sensitivity to Heat Degradation	294

Biological Consequences of Incorporation of Halogenated Uracil Derivatives into DNA	295
A. Mutagenic Effects	295
B. Inhibition of Cellular Division	297
I. Cell Culture	297
II. Animals	300
C. Inhibition of Viral Replication	302
D. Effect on Oncogenic Viruses	307
E. Effects on Transformation, Conjugation, and Transduction	308
F. Inhibition of Antibody Production	309
G. Effects on Embryonic Development and Differentiation	310
H. Toxicity	313
Marker Function	314
Radiosensitization	318
Clinical Use	322
Mode of Inhibition	325
Conclusions	326
References	327

Chapter 45

Azapyrimidine Nucleosides. J. ŠKODA. With 3 Figures

Introduction	348
Review of Existing Azapyrimidine Nucleosides	348
A. 6-Azapyrimidine Nucleosides	348
B. 5-Azapyrimidine Nucleosides	350
C. 6-Azaauridine	351
I. Molecular Mechanism of Inhibitory Effects	351
II. Biological Effects	354
1. Virostatic Activity	354
2. Antineoplastic Effects	355
3. Immunosuppressive Activity	356
4. Cholesterol and Lipid Changes Induced by 6-Azaauridine	356
5. Embryotoxic Effects	356
III. Pharmacological Studies	358
IV. Clinical Application	360
1. Virostatic Effects	360
2. Antineoplastic and Antihyperplastic Effects	360
3. Effect on Psoriasis	361
D. 5-Azacytidine	361
I. Molecular Mechanism of Inhibitory Action	361
II. Biological Effects in Animal Systems	362
III. Clinical Studies	363
References	364

Chapter 46

Showdomycin, 5-Hydroxyuridine, and 5-Aminouridine. D. W. VISSER. With 1 Figure

Introduction	373
Chemistry of Showdomycin	373
Metabolism of Showdomycin	373
Inhibitory Effects of Showdomycin	374
Chemistry and Metabolism of 5-Hydroxyuridine	376
Inhibitory Effects of 5-Hydroxyuridine	377

Chemistry, Metabolism, and Inhibitory Effects of 5-Aminouridine	379
References	381

Chapter 47

6-Thiopurines. A. R. P. PATERSON and DAVID M. TIDD. With 1 Figure

Introduction	384
Metabolism of 6-Mercaptopurine and 6-Methylthioinosine	385
A. Anabolism	385
I. 6-Thioinosinate	385
II. 6-Methylthioinosinate	385
III. 6-Thioxanthylate	386
IV. Other Anabolites of 6-Mercaptopurine	386
V. 6-Thioinosine	387
B. Catabolism	387
Metabolism of 6-Thioguanine	387
A. Anabolism	387
I. 6-Thioguanosine Phosphates	387
II. Deoxythioguanosine Phosphates	388
III. Other Anabolites of 6-Thioguanine	388
IV. 6-Thioguanosine and β -2'-Deoxythioguanosine	388
B. Catabolism	389
Metabolic Effects of 6-Mercaptopurine and 6-Methylthioinosine	389
A. The Free Base, 6-Mercaptopurine	389
B. Nucleotide Anabolites	390
I. Inhibition of Purine Ribonucleotide Synthesis <i>de novo</i>	390
II. Inhibition of Purine Ribonucleotide Interconversions	392
III. Incorporation into DNA	392
IV. Resistance to 6-Mercaptopurine	393
V. Conclusions	393
Metabolic Effects of 6-Thioguanine	393
A. The Free Base, 6-Thioguanine	394
B. Nucleotide Anabolites	394
I. Inhibition of Purine Ribonucleotide Synthesis <i>de novo</i>	394
II. Inhibition of Purine Ribonucleotide Interconversions	395
III. Incorporation into DNA	395
IV. Delayed Cytotoxicity	396
V. Conclusions	396
Combination Chemotherapy	397
References	397

Chapter 48

Azathioprine. GERTRUDE B. ELION and GEORGE H. HITCHINGS

Introduction (Basic Aspects)	404
Biochemical Effects	404
Biological Effects	405
A. Classes of Lymphocytes and Their Interactions	405
B. Effects on Cells <i>in Vitro</i>	405
C. Effects on the Immune Response	407
I. Antibody Formation	407
II. Cell-Borne Immunity	407
D. Antitumor Effects	408
I. In Rodents	408
II. In Man	408
E. Comparison of 6-Mercaptopurine and Azathioprine	409