

Antitumor Drug Resistance

Editors: B. W. Fox and M. Fox



Springer-Verlag
Berlin Heidelberg New York Tokyo

Antitumor Drug Resistance

Contributors

N. K. Ahmed · B. Barlogie · W. T. Beck · A. Begleiter
A. K. Belousova · J. R. Bertino · J. M. Boyle · J. Brennand
C. T. Caskey · T. A. Connors · B. Drewinko · M. Fox · H. Fuji
G. J. Goldenberg · J. F. Henderson · B. T. Hill · J. A. Houghton
P. J. Houghton · M. M. Ip · J. G. McVie · M. Moore · P. S. Schein
D. Scott · K. D. Tew · D. M. Tidd · M. J. Tisdale · J. R. Uren
J. V. Watson · A. D. Welch · J. M. Whitehouse

Editors

B. W. Fox and M. Fox



Y074651



Springer-Verlag

Berlin Heidelberg New York Tokyo 1984

Professor BRIAN W. FOX, Ph. D.

Dr. MARGARET FOX

Paterson Laboratories, Christie Hospital and Holt Radium Institute,
Wilmslow Road, Withington, Manchester M20 9BX, Great Britain

With 99 Figures

ISBN 3-540-13069-1 Springer-Verlag Berlin Heidelberg New York Tokyo
ISBN 0-387-13069-1 Springer-Verlag New York Heidelberg Berlin Tokyo

Library of Congress Cataloging in Publication Data. Main entry under title: Antitumor drug resistance. (Handbook of experimental pharmacology; v. 72) Includes bibliographical references and index. 1. Antineoplastic agents. 2. Drug resistance. 3. Tumors - Chemotherapy. I. Ahmed, N.K. II. Fox, Brian W. III. Fox, Margaret. IV. Series. [DNLM: 1. Drug resistance. 2. Antineoplastic agents - Pharmacodynamics. 3. Neoplasms - Drug therapy. W1 HA51L v. 72/QZ 267 A633] QP905.H3 vol. 72 615'.1s [616.99/4061] 83-27139 [RC271.C5]

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machine or similar means, and storage in data banks. Under § 54 of the German Copyright Law where copies are made for other than private use, a fee is payable to "Verwertungsgesellschaft Wort", Munich.

© by Springer-Verlag Berlin Heidelberg 1984

Printed in Germany

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check its accuracy by consulting other pharmaceutical literature.

Printing and bookbinding: Brühlsche Universitätsdruckerei, Giessen
2122/3130-543210

List of Contributors

- N. K. AHMED, Division of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, 332 North Lauderdale, P.O. Box 318, Memphis, TN 38101/USA
- B. BARLOGIE, Medical Oncology, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, 6723 Bertner, Houston, TX 77030/USA
- W. T. BECK, Division of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, 332 North Lauderdale, P.O. Box 318, Memphis, TN 38101/USA
- A. BEGLEITER, The Manitoba Institute of Cell Biology and the Department of Medicine, University of Manitoba, 100 Olivia Street, Winnipeg, Manitoba R3E 0V9, Canada
- A. K. BELOUSOVA, Laboratory of Biochemical Pharmacology, All-Union Cancer Research Center, Moscow 115478, USSR
- J. R. BERTINO, Departments of Internal Medicine and Pharmacology, Yale University School of Medicine, 333 Cedar Street, P.O. Box 3333, New Haven, CT 06510/USA
- J. M. BOYLE, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Wilmslow Road, Withington, Manchester M20 9BX, Great Britain
- J. BRENNAND, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Wilmslow Road, Withington, Manchester M20 9BX, Great Britain
- C. T. CASKEY, Howard Hughes Medical Institute Laboratories, Departments of Medicine, Cell Biology and Chemistry, Baylor College of Medicine, Houston, TX 77030/USA
- T. A. CONNORS, MRC Toxicology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey SM5 4EF, Great Britain

- B. DREWINKO, Section of Hematology, Department of Laboratory Medicine, Box 73, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, 6723 Bertner, Houston, TX 77030/USA
- M. FOX, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Wilmslow Road, Withington, Manchester M20 9BX, Great Britain
- H. FUJI, Molecular Immunology, Roswell Park Memorial Institute, New York State Department of Health, 666 Elm Street, Buffalo, NY 14263/USA
- G. J. GOLDENBERG, The Manitoba Institute of Cell Biology and the Department of Medicine, University of Manitoba, 100 Olivia Street, Winnipeg, Manitoba R3E 0V9, Canada
- J. F. HENDERSON, Cancer Research Unit, The University of Alberta, Edmonton, Alberta T6G 2H7, Canada
- B. T. HILL, Laboratory of Cellular Chemotherapy, Imperial Cancer Research Fund Laboratories, P.O. Box 123, Lincoln's Inn Fields, London WC2 3PX, Great Britain
- J. A. HOUGHTON, Division of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, 332 North Lauderdale, P.O. Box 318, Memphis, TN 38101/USA
- P. J. HOUGHTON, Division of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, 332 North Lauderdale, P.O. Box 318, Memphis, TN 38101/USA
- M. M. IP, Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Institute, New York State Department of Health, 666 Elm Street, Buffalo, NY 14263/USA
- J. G. MCVIE, Clinical Research Unit, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
- M. MOORE, Immunology Division, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Wilmslow Road, Withington, Manchester M20 9BX, Great Britain
- P. S. SCHEIN, Division of Medical Oncology, Department of Pharmacology, Georgetown University Hospital, 3800 Reservoir Road, N.W., Washington, DC 20007/USA
- D. SCOTT, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Wilmslow Road, Withington, Manchester M20 9BX, Great Britain
- K. D. TEW, Division of Medical Oncology, Department of Medicine, Georgetown University Hospital, 3800 Reservoir Road, N.W., Washington, DC 20007/USA

D. M. TIDD, School of Biological Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, Great Britain

M. J. TISDALE, CRC Experimental Chemotherapy Group, Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, Great Britain

J. R. UREN, Genex Corporation, 16020 Industrial Drive, Gaithersburg, MD 20877/USA

J. V. WATSON, MRC Clinical Oncology and Radiotherapeutics Unit, Medical Research Council Centre, The Medical School, University of Cambridge, Hills Road, Cambridge CB2 2QH, Great Britain

A. D. WELCH, National Cancer Institute (National Institutes of Health), Drug Evaluation Branch, Division of Cancer Treatment, Blair Building, Room 428, 900 Rockville Pike, Bethesda, MD 20205/USA

J. M. WHITEHOUSE, Department of Medical Oncology, CRC and Wessex Regional Medical Oncology Unit, Centre Block CF99, Southampton General Hospital, Southampton SO9 4XY, Great Britain

Preface

The study of tumour resistance to anticancer drugs has been the subject of many publications since the initial discovery of the phenomenon by J. H. Burchenal and colleagues in 1950. Many papers have been published since then reporting development of resistance to most of the well-known anticancer agents in many different animal tumour systems, both *in vivo* and *in vitro*. Many different mechanisms of resistance have been described, and it is clear that the tumour cell has a wide diversity of options in overcoming the cell-killing activity of these agents.

Definition of the magnitude of the phenomenon in the clinic is, however, much more problematical, and it is with this in mind that the initial chapter, seeks to outline the problem as the clinicians see it. It appears that the phenomenon of true resistance to a drug, as the biochemist would recognise it, is an important cause of the failure which clinicians experience in treating the disease. The extent of the contribution of this phenomenon to the failure of treatment cannot easily be evaluated at the present time, but it is hoped that the development and application of new and more sophisticated techniques for the analysis of cellular sub-populations may help to give a more exact estimate and to shed some light on the causes of failure of many of the present therapeutic techniques.

The purpose of this book is to bring together in a single volume the results of many years' work by key people in this field. The different studies of the mechanisms of resistance are considered; in a separate section, the ways in which tumours adapt to different drug groups, taken primarily from the experimental field, but also – where recognised – from the clinical field, are described. The armoury of experimental techniques is rapidly expanding; along with improved methods of measuring drug transport and DNA repair, monoclonal and polyclonal antibodies are being employed in different ways. One of the main aims has been to identify specific changes which take place in the biochemistry of the tumour cell, especially at the cell surface, when it exhibits resistance to an anticancer drug. We are already learning about the changing levels of specific proteins, e.g. enzymes and cell-surface glycoproteins; with the newer concepts in immunology and the application of powerful techniques such as flow cytometry, a better understanding of the depth and extent of the problem of resistance is being achieved. The greatest emphasis in this book has been placed on the individual mechanisms determined to be those by which tumours have become resistant to specific drugs, and on the experimental observations and arguments that have led to the present understanding of these mechanisms.

A detailed study of the origin of resistance is basic to further progress in the treatment of cancer. It could not only modify the course of treatment, but may also, as our knowledge of "intrinsic resistance" increases, modify the type of initial treatment used, based as it is on a rapid analysis of the spectrum of sensitivity of the tumour. Although, to some extent, clonogenic assays, xenografts and renal capsule implant systems are being used for the initial analysis, the need for speed is paramount in making the early decision required for effective therapy. It is clear that some indicator of drug sensitivity at the time of the pathological investigation would be ideal, and in order to arrive at this level of diagnostic efficiency, flow cytometry will be a necessary intermediate stage in the study of properties of tumour subpopulations. Identifying a spectrum of sensitive and resistant cells in a tumour will provide a more rational basis for the choice of a drug or drug combination. More detailed pharmacokinetic data in humans are also needed if we are to take advantage of the sensitivity pattern obtained by subpopulation studies at the pathological level.

A knowledge of the genetics of the tumour, as well as that of the host, is important to understanding the sensitivity spectrum of a new tumour, and a knowledge of these factors could ultimately provide a basis for optimising the therapeutic index of the drug. The flow cytometry analytical technique will, again, be a useful tool for the effective manipulation of these factors.

During the preparation of this book it has become clear that the word "resistance" requires further description. It seems to us that "resistance" is a word that can justifiably be related only to the property of a single cell. It could be defined as the ability of a single tumour cell to survive a local concentration of a damaging drug that would otherwise have been expected to kill it. This could be an innate property of the cell (intrinsic resistance) or could have been acquired by a rapid adaptive response (adaptive resistance). If a cell were to survive a low concentration of a damaging agent and divide, probably in the face of the loss of many similar cells within the population of which it is a part, it could form the basis of a new population of resistant cells through a series of divisions. These may be further selected for reduced sensitivity (selected resistance) or actively become adapted by expressing alternative biochemical pathways, enhanced protective group synthesis, etc. (acquired resistance). In all such cases the type of resistance would merely describe the property of a single cell within the system being studied.

The tumour mass, which includes the population of tumour cells within its matrix, exhibits an overall sensitivity – usually measured according to changes in volume, number or weight – part of which may be a reflection of the tumour cell population it contains. The overall response of the tumour-cell population depends on the average sensitivity of the cells within it. The acquisition of resistance by a whole tumour could thus be the result of a shift in the proportion of intrinsically sensitive and resistant cells, influencing the overall average sensitivity of the population. The term "resistant tumour" is so widely used, however, that to speak of the "population resistance" of a tumour or tumour-cell population in this context would seem to be more accurate. It must be recognised that this is an average property of the tissue, and may not involve anything other than a change in the proportion of existing cells.

This collection of chapters, we believe, achieves the interim aim of bringing together the many parameters that are presently considered to constitute the nature of resistance in tumour populations; we hope that they will provide a basis for further discussions to substantially improve the efficacy of drug treatment of cancer in humans.

We would like to thank the many authors who adhered very closely to the timetable for submission of their chapters; we regret the omission of two of the originally planned chapters from the latter half of the book at such a late date that alternatives could not be found. However, much of the material that was to be presented in these is well covered in other contributions.

In particular we thank the Chief Editor, Professor A.D. Welch, for his continued vigilance, Mr. Ric Swindell for the indexing and Ms. Gillian A. Simpson for the typing of the necessary correspondence. Finally, the courtesy and efficiency of Mrs. Doris Walker of Springer-Verlag is much appreciated.

Manchester

BRIAN W. FOX
MARGARET FOX

Contents

Section I: Concepts of Drug Resistance

CHAPTER 1

Clinical Setting. J. M. WHITEHOUSE

A. Introduction	3
B. Resistance – A Clinical Phenomenon?	4
C. Disease Assessment	6
D. Drug Selection	9
E. Measurement of Response	11
F. Can Resistance be Quantified Clinically?	13
G. Factors Influencing Changes in Tumour Volume	13
I. Heterogeneous Target Populations of Tumour Cells	13
II. Changes in Histology	14
III. Second Malignancy	15
IV. Miscellaneous Factors Contributing to Tumour Volume	15
H. Influence of Clinically Determined Drug Resistance on Management	16
I. Resistance and Toxicity	16
II. Resistance and Survival	18
References	19

CHAPTER 2

Experimental Setting. J. F. HENDERSON

A. Introduction	23
B. Origins of Resistance	23
I. Changes in the Tumor	23
1. Nongenetic Origins	24
2. Genetic Origins	25
II. Changes in the Host	26
III. Changes in Pharmacological Parameters	27
IV. Experimental Systems	27
C. Mechanisms of Resistance	27
I. Differences in Drug Concentration	28
1. Drug Uptake	28
2. Nucleotide Formation	28
3. Drug Catabolism	29

- II. Differences in Drug-Target Interaction 30
 - 1. Drug-Enzyme Binding 30
 - 2. Drug-Cell Interaction 30
 - 3. Metabolite Concentrations 31
- III. Differences in Importance of Biochemical Target 31
 - 1. Recovery from Drug Effects 31
 - 2. Alternative Pathways 31
 - 3. Concentration of Target 32
- IV. Experimental Systems 32
- D. Chemotherapy of Resistant Tumors 34
 - I. Cross-Resistance 34
 - II. Collateral Sensitivity 35
 - III. Circumvention of Resistance 35

Section II: Modification of Host-Tumor Interaction

CHAPTER 3

Drug Disposition and Pharmacology. J. G. McVIE

- A. Introduction 39
- B. Drug Absorption 41
- C. Distribution 47
- D. Metabolism 50
- E. Renal Excretion 53
- F. Dose 54
- G. Schedule Dependence 56
- H. Drug Interactions 59
- J. Conclusion 61
- References 61

CHAPTER 4

Immunological Changes. H. FUJI. With 3 Figures

- A. Introduction 67
- B. Tumor-Associated Antigens 67
- C. Altered Transplantability of Drug-Resistant Tumor Sublines 69
 - I. Tumor Transplantation in Unimmunized Animals 69
 - II. Tumor Transplantation in Preimmunized Animals 71
 - III. Adoptive Transfer of Transplantation Immunity 73
- D. Immunological Changes in Drug-Resistant Tumor Sublines Defined by Antibodies 73
 - I. Changes in Tumor Antigenicity Defined by Antisera 73
 - II. Changes in Tumor Antigenicity Defined by Monoclonal Antibody 76
- E. Cellular Immune Responses Against Drug-Resistant Tumor Sublines 78
 - I. Antibody-Forming Cell Responses 78
 - II. Cell-Mediated Cytotoxic Responses 78

F. Other Immunobiological Characteristics and Possible Mechanisms of Immunological Changes	79
G. Conclusions	82
References	83

CHAPTER 5

The Molecular Basis of Genetically Acquired Resistance to Purine Analogues in Cultured Mammalian Cells. J. BRENNAND and C. T. CASKEY

A. Introduction	89
B. The HPRT Enzyme	89
C. Biochemical Basis of Drug Resistance	90
D. Drug Resistance as a Consequence of Mutation Within the HPRT Gene	91
I. Phenotypic Variation Resulting from Non-mutational Events	91
II. Evidence that Drug Resistance Results from Mutation Within the HPRT Gene	93
III. Molecular Analysis of the HPRT Gene	94
E. Perspectives	95
References	96

Section III: Cellular Aspects

CHAPTER 6

Cell Cycle Perturbation Effects. B. DREWINKO and B. BARLOGIE. With 14 Figures

A. Introduction	101
I. General	101
II. Proliferating and Quiescent Cells	101
III. Age-Dependent Response	102
IV. Cell Synchronization	102
V. Cell Cycle Perturbation	103
VI. In Vitro Systems	104
VII. Cell Death	105
VIII. Cell Cycle Traverse Rate-Dependent Lethality	105
B. Materials and Methods	106
C. Results	107
I. Proliferating Versus Nonproliferating Cells	107
II. Age-Dependent Survival Response	109
III. Cell Cycle Perturbation	111
1. Asynchronous Cell Populations	111
2. Synchronized Cells	127
IV. Protection of Cell Kill by Inhibition of Cell Cycle Traverse	128
D. Discussion	129
References	136

CHAPTER 7

Tumour Resistance and the Phenomenon of Inflammatory-Cell Infiltration

M. MOORE. With 2 Figures

A. Introduction	143
I. Heterogeneity of Tumour Cells	143
II. Intratumour Lymphoreticular Cells: Biological Implications	144
III. Methodological Approaches	145
B. Characterization of Intratumour Host-Cells	147
I. Total Host-Cell Component	147
II. Criteria for the Identification of Leucocyte Populations and Subpopulations	148
C. Intratumour Leucocytes of Experimental and Human Neoplasms: Descriptive Studies	151
I. Preliminary Considerations	151
II. Nature of Cells Infiltrating Experimental Neoplasms: Biological Correlates	151
III. Nature of Cells Infiltrating Human Neoplasms: Clinicopathological Correlates	156
IV. Factors Which Determine Leucocyte Infiltration of Tumours	161
D. Effector Functions of Intratumour Leucocytes: Experimental Neoplasms	162
I. Systemic Effector Mechanisms	162
II. Macrophage Function	166
III. T-Cell Function	168
IV. Natural Killer Function	169
V. Antibody-Dependent Cellular Cytotoxicity	170
E. Effector Functions of Intratumour Leucocytes: Human Neoplasms	171
I. Macrophage Function	171
II. T-Cell Function	171
III. Natural Killer Function	174
F. Limitations of In Vitro Functional Data	175
G. Implications for Therapy	176
References	178

CHAPTER 8

Flow Cytometric Methods for Studying Enzyme Activity in Populations of Individual Cells. J. V. WATSON. With 12 Figures

A. Introduction	187
B. Principles of Flow Cytometry	187
C. Enzyme Measurements Using Light Absorption	189
D. Enzyme Measurements Using Fluorogenic Substrates	191
I. Assays with Single Substrates	191
II. Assays Using Two Substrates Simultaneously	200
E. Conclusions	201
References	202

CHAPTER 9

Chromosome Studies. D. SCOTT. With 17 Figures

A. Introduction	205
B. Chromosome Constitution and Resistance	205
I. Derivation of Drug-Resistant Cells	205
II. Resistance to Various Classes of Antitumour Drugs	213
1. Purine Analogues	213
2. Pyrimidine Analogues	216
3. Antifolates	217
4. Alkylating Agents	228
5. Platinum Compounds	229
6. Antibiotics	230
7. <i>Vinca</i> Alkaloids	232
C. Resistance to Induced Chromosome Damage	233
D. Summary	234
References	235

CHAPTER 10

Alterations of Drug Transport. G. J. GOLDENBERG and A. BEGLEITER

A. Introduction	241
B. Mechanism of Drug Transport	241
I. Characteristics of Passive Diffusion and Mediated Transport	241
II. Kinetics of Membrane Transport	242
III. Drug Uptake by Multiple Mechanisms	244
IV. Evaluation of Drug Efflux	245
C. Antitumor Drug Resistance Due to Defects in Membrane Transport	245
I. Alkylating Agents	245
1. Nitrogen Mustard	245
2. Melphalan	250
3. Cyclophosphamide	255
4. Nitrosoureas	256
5. Chlorambucil	257
6. Busulfan	258
7. Procarbazine	258
8. Hexamethylmelamine and Pentamethylmelamine	258
II. Antimetabolites	259
1. Methotrexate	259
2. 6-Mercaptopurine and 6-Thioguanine	263
3. Fluorouracil	265
4. Arabinosylcytosine and Arabinosyladenine	266
III. Antibiotics	267
1. Actinomycin D	267
2. Daunorubicin and Doxorubicin	270
3. Bleomycin	276
4. Mitomycin C	276

IV. Alkaloids	277
1. <i>Vinca</i> Alkaloids	277
2. Colchicine	280
V. Hormones	282
1. Glucocorticoids	282
2. Estrogens	283
3. Androgens and Progestins	283
D. Future Considerations	284
References	286

CHAPTER 11

Cell Hybridisation. J. M. BOYLE. With 5 Figures

A. Introduction	299
B. Cell Fusion In Vivo	301
I. Occurrence of Multinucleate Cells	301
II. Experimental Production of Hybrids In Vivo	304
III. Modified Phenotypes of Hybrids Induced In Vivo	306
C. Use of Drug Resistance for the Selection of Hybrid Clones In Vitro	306
D. Expression of Drug Resistance in Hybrid Cells	310
I. Dominance and Complementation	310
II. Gene Dosage and Functional Hemizygoty	311
III. Multifunctional Enzymes	312
IV. Steroid Resistance and Enzymic Induction by Hormones	314
V. Segregation of Resistance	315
VI. Gene Activation	318
E. Radiation Responses of Hybrid Cells	319
I. Sensitivity to Ionising Radiation and Ultraviolet Light	319
II. Rescue of Genes from Lethally Irradiated Cells	319
F. Conclusions: Possible Therapeutic Implications of Cell Hybridisation	321
References	322

Section IV: Modification of Tumor Biochemistry

CHAPTER 12

Drug Resistance and DNA Repair. M. Fox. With 4 Figures

A. Introduction	335
B. Mechanisms of DNA Repair	336
I. Excision Repair	336
1. Base Modification	337
2. Enzymatic Excision of Base Damage	337
3. Repair of Base Damage	337

4. Nucleotide Excision and Repair	338
5. Influence of Chromatin Structure on DNA Excision Repair	340
II. DNA Synthesis on a Template Containing Unexcised DNA Lesions	342
C. The Relationship Between DNA Repair and Cellular Sensitivity	345
I. Alkylating Agents	345
II. Platinum Compounds	352
III. Mitomycin C	355
IV. Bleomycin	356
D. Cell-Cycle Perturbations and Their Possible Relationships to DNA Repair	358
E. Attempts to Develop Resistance to DNA-Damaging Drugs in Cultured Cell Lines In Vitro	359
F. Conclusions	361
References	362

CHAPTER 13

Cyclic AMP and Prostaglandins. M. J. TISDALE. With 5 Figures

A. Cyclic AMP	371
I. Cyclic AMP and Neoplasia	371
II. Tumour Growth Inhibition by Cyclic AMP and Derivatives	371
III. Role of Cyclic AMP in Regression of Hormone-Dependent Mammary Tumours	373
IV. Role of Cyclic AMP in Growth Inhibition by the Antitumour Alkylating Agents	374
1. Effect on Cyclic AMP Phosphodiesterase	376
2. Effect on Specific Cyclic-AMP-Binding Proteins.	379
3. Alterations in Protein Kinase Activity	381
4. Possible Role of Cyclic AMP in the Cytotoxic Action of Alkylating Agents	382
V. Effect of Other Antitumour Agents on the Cyclic Nucleotide System	382
B. Prostaglandins	383
C. Conclusion	385
References	385

CHAPTER 14

Properties of Mitochondria. A. K. BELOUSOVA. With 4 Figures

A. Introduction	391
B. Damage of Mitochondrial Membranes by Alkylating Agents	391
C. The Structure and Functions of Energy-Coupling Complexes in Mitochondria	392
D. Search for Correlations Between Cell Sensitivity or Resistance to Alkylating Agents and Functional State of Mitochondrial Membranes	394
References	400

CHAPTER 15

Mechanism of "Resistance" Towards Specific Drug Groups. T. A. CONNORS.

With 10 Figures

A. Mechanisms of Alkylation	404
B. Mechanisms of Cytotoxicity and Antitumour Action	406
C. Selectivity of Antitumour Action of the Alkylating Agents	406
D. Patterns of Resistance	407
E. Mechanisms of Resistance	408
I. Resistance Through Decreased Cellular Uptake	409
II. Resistance by Inhibition of the Activation of Prodrugs	413
III. Resistance by Deactivation of Reactive Alkylating Agents	417
IV. Resistance by Interaction with Non-essential Nucleophiles	418
F. Conclusions	420
References	421

CHAPTER 16

Nitrosoureas. K. D. TEW and P. S. SCHEIN

A. Pharmacology	425
B. Mechanisms of Drug Resistance	426
C. Significance of Molecular Considerations	427
D. Monoadducts and Cross-Linking	428
E. Interference with the DNA Repair Process	429
F. Subnucleosomal Nitrosourea Binding	430
G. Effects on Pyridine Nucleotides	431
H. Modulation of Drug Effect with Steroids and Other Transcriptional Modifiers	432
J. Overcoming Resistance to Alkylating Agents with Nitrosoureas	433
K. Clinical Therapeutic Activity	434
L. Conclusions	438
References	439

Section V: Antimetabolites

CHAPTER 17

Antipurines. D. M. TIDD. With 6 Figures

A. Introduction	445
B. 8-Azaguanine	449
I. Metabolism and Mechanism of Action	450
II. Resistance	451
C. 6-Mercaptopurine and 6-Thioguanine	457
I. Metabolism and Mechanism of Action	457
II. Resistance	459