Antineoplastic and Immunosuppressive Agents
Part II

Contributors

H. T. Abelson · R. H. Adamson · K. C. Agarwal · K. C. Agrawal · L. L. Bennett
J. R. Bertino · B. K. Bhuyan · T. A. Connors · W. A. Creasey · T. L. Dao
L. S. Dietrich · A. DiMarco · G. B. Elion · B. W. Fox · S. Frederiksen
E. J. Freireich · G. R. Gale · G. F. Gause · I. H. Goldberg · B. Goz
A. P. Grollman · M. M. Hart · C. Heidelberger · R. Hilf · G. H. Hitchings
D. H. W. Ho · S. B. Horwitz · C. J. Kensler · H. Kersten · H. Klenow · I. H. Krakoff
W. B. Kremer · P. F. Kruse · J. Laszlo · G. A. LePage · T. L. Loo
D. B. Ludlum . E. Mihich · R. J. Milholland · C. A. Nichol · H. F. Oettgen
B. W. O'Malley · R. E. Parks · A. R. P. Paterson · M. K. Patterson · S. Penman
D. H. Petering · H. G. Petering · P. Pietsch · C. C. Price · W. H. Prusoff
D. J. Reed · F. Rosen · A. C. Sartorelli · J. Škoda · C. G. Smith
C. A. Strott · J. A. Straw · D. M. Tidd · D. W. Visser · G. P. Wheeler
J. L. Wittliff · D. W. Yesair

Editors

Alan C. Sartorelli and David G. Johns

With 128 Figures

Springer-Verlag Berlin · Heidelberg · New York 1975

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 devloped 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
Winter, 1974/75

Alan C. Sartorelli
David G. Johns

Part I Table of Contents

Section A: General Considerations: Antineoplastic Agents

Section B: General Considerations: Immunosuppressive Agents

Part II Contributors

HERBERT T. ABELSON, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139/USA

RICHARD H. ADAMSON, Section of Pharmacology and Experimental Therapeutics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014/USA

K. C. AGARWAL, Division of Biological and Medical Sciences, Brown University, Providence, RI 02912/USA

KRISHNA C. AGRAWAL, Department of Pharmacology, Yale University, School of Medicine, 333 Cedar Street, New Haven, CT 06510/USA

L. L. BENNETT, JR., Biochemistry Research, Southern Research Institute, 2000 Ninth Avenue South, Birmingham, AL 35205/USA

JOSEPH R. BERTINO, Department of Pharmacology, Yale University, School of Medicine, 333 Cedar Street, New Haven, CT 06510/USA

B. K. BHUYAN, The Upjohn Company, Kalamazoo, MI 49001/USA

T. A. CONNORS, Chester Beatty Research Institute, Fulham Road, London SW3/Great Britain

WILLIAM A. CREASEY, Department of Internal Medicine and Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510/USA

THOMAS L. DAO, Department of Breast Surgery and Endocrine Research Laboratory, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14203/USA

L. S. DIETRICH†, Department of Biochemistry, University of Miami, School of Medicine, Biscayne Avenue, Miami, FL 33152/USA

A. DIMARCO, Instituto Nazionale, Per Lo Studio e La Aura Dei Tumori, Via Venezia 1, 20133-Milano/Italy

GERTRUDE B. ELION, The Wellcome Research Laboratories, Burroughs Wellcome Company, 3030 Cornwallis Road, Research Triangle Park, NC 27709/USA

BRIAN W. FOX, Cristie Hospital and Holt Radium Institute, Paterson Laboratories, Manchester 20 Lancaster/Great Britain

SUNE FREDERIKSEN, Universitetes Biokemiske Inst. B, Juliane Maries vej 30, DK-2100 Copenhagen/Denmark

EMIL J FREIREICH, Department of Developmental Therapeutics, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, TX 77025/USA

GLEN R. GALE, Department of Pharmacology, Medical University of South Carolina, 80 Barre Street, Charleston, SC 29401/USA

G. F. GAUSE, Academy of Medical Sciences of USSR, Institute of New Antibiotics, Bolshaia Pirogovskaia, 11, Moscow/USSR

IRVING H. GOLDBERG, Department of Pharmacology, Harvard Medical School, Boston, MA 02115/USA

BARRY GOZ, Department of Pharmacology, University of North Carolina, School of Medicine, Chapel Hill, NC 27514/USA

ARTHUR P. GROLLMAN, Department of Pharmacology, Albert Einstein College of Medicine and Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461/USA

MICHAEL M. HART, Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014/USA

CHARLES HEIDELBERGER, McArdle Laboratory for Cancer Research, University of Wisconsin, 450 N. Randell Avenue, Madison, WI 53706/USA

RUSSELL HILF, The University of Rochester, School of Medicine and Dentistry and Strong Memorial Hospital, 260 Crittenden Boulevard, Rochester, NY 14642/USA

GEORGE H. HITCHINGS, The Wellcome Research Laboratories, Burroughs Wellcome Company, Research Triangle Park, NC 27709/USA

DAH HSI W. HO, Department of Developmental Therapeutics, The University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, TX 77025/USA

SUSAN B. HORWITZ, Department of Pharmacology, Albert Einstein College of Medicine, New York, NY 10461/USA

CHARLES J. KENSLER, Life Sciences Division, Arthur D. Little, Inc., Cambridge, MA 02140/USA

HELGA KERSTEN, Physiologisch-Chemisches Institut der Universität Erlangen-Nürnberg, Wasserturmstraße 5, 8520 Erlangen/Federal Republic of Germany

HANS KLENOW, Universitetes Biokemiske Institute B, Juiane Maries vej 30, DK-2100, Copenhagen, Denmark

IRWIN H. KRAKOFF, Sloan-Kettering Institute for Cancer Research, 444 East 68 Street, New York, NY 10021/USA

W. B. KREMER, Veterans Administration Hospital and Duke University, Medical Center, Fulton Street and Erwin Road, Durham, NC 27706/USA

PAUL F. KRUSE, JR. †, Biomedical Division, The Samuel Roberts Noble Foundation Inc., P.O. Box 878, Ardmore, OK 73401/USA

JOHN LASZLO, Veterans Administration Hospital and Duke University Medical Center, Fulton Street and Erwin Road, Durham, NC 27706/USA

G. A. LEPAGE, University of Alberta, Cancer Research Unit, McEachern Laboratory, Edmonton 7 Alberta/Canada

TI LI LOO, Department of Developmental Therapeutics, The University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, TX 77025/USA

DAVID B. LUDLUM, Department of Cell Biology and Pharmacology, University of Maryland, School of Medicine, 660 West Redwood Street, Baltimore, MD 21201/USA

ENRICO MIHICH, Cancer Drug Center, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14203/USA

R. J. MILHOLLAND, Cancer Drug Center, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14203/USA

CHARLES A. NICHOL, Wellcome Research Laboratories, 3030 Cornwallis Road, Research Triangle Park, NC 27709/USA

HERBERT F. OETTGEN, Institut für Immunbiologie, 7800 Freiburg (Brsg.) Federal Republic of Germany

BERT W. O'MALLEY, Department of Cell Biology, Baylor College of Medicine, Houston, TX 77025/USA

ROBERT E. PARKS, JR., Division of Biological and Medical Sciences, Brown University, Providence, RI 02912/USA

A. R. P. PATERSON, University of Alberta, Cancer Research Unit., Edmonton 7, Alberta/Canada

M. K. PATTERSON, JR., Biomedical Division, The Samuel Roberts Noble Foundation Inc., Ardmore, OK 73401/USA

SHELDON PENMAN, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139/USA

DAVID H. PETERING, Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI/USA

HAROLD G. PETERING, Department of Environmental Health and Biological Chemistry, University of Cincinnati, Cincinnati, OH/USA

PAUL PIETSCH, Division of Optometry, Indiana University, 800 East Atwater, Bloomington, IN 47401/USA

CHARLES C. PRICE, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104/USA

WILLIAM H. PRUSOFF, Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510/USA

DONALD J. REED, Department of Biochemistry and Biophysics, Oregon State University, Corvallis, OR 97331/USA

FRED ROSEN, Cancer Drug Center, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14203/USA

ALAN C. SARTORELLI, Department of Pharmacology, Yale University, School of Medicine, 333 Cedar Street, New Haven, CT 06510/USA

JAN ŠKODA, Department of Molecular Biology, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Flemingovo nam. 2, Prague 6, Dejvice/Czechoslovakia

CHARLES G. SMITH, E. R. SQUIBB & SONS, Inc., Princeton, N. J. 08540/USA

JAMES A. STRAW, Department of Pharmacology, The George Washington University School of Medicine, 1331 H Street NW, Washington, DC 20005/USA

CHARLES A. STROTT, National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, MD 20014/USA

DAVID M. TIDD, Churchill Hospital Research Institute, Headington, Oxford, OX3 7LJ/Great Britain

DONALD W. VISSER, Department of Biochemistry, University of Southern California, School of Medicine, Los Angeles, CA 90033/USA

GLYNN P. WHEELER, Cancer Biochemistry Division, Southern Research Institute, 2000 Ninth Avenue South, Birmingham, AL 35205/USA

JAMES L. WITTLIFF, School of Medicine and Dentistry and Strong Memorial Hospital, The University of Rochester, 260 Crittenden Boulevard, Rochester, NY 14642/USA

DAVID W. YESAIR, Life Sciences Division, Arthur D. Little Inc., Cambridge, MA 02140/USA

Part II Table of Contents

Section C: Alkylating Agents

Chapter 37

Chapter 38

Chapter 39

Chapter 40

Section E: Antimetabolites

Chapter 41

Chapter 42

Chapter 43

Chapter 44