

Chronicles of Drug Discovery

Volume 3



EDITED BY
Daniel Lednicer



ACS Professional Reference Book

NEW TITLE

This fascinating new book, **Chronicles of Drug Discovery, Volume 3**, offers a unique insight into the drug discovery process through informal histories presented by the drugs' inventors. It provides a compilation of accounts describing the events leading from the initial discovery to successful introduction on the market of fourteen important new drugs, including RU 486 (mifepristone) and taxol. Many chapters outline in detail the chemical/biological rationale which led to the discovery. The volume also includes drugs with a wide selection of therapeutic indications and presents a broad range of development strategies.

Contents:

- Mifepristone
- Loratadine
- Enalapril and Lisinopril
- Esmolol
- Aztreonam
- Camptothecin and Taxol
- Ranitidine
- Misoprostol
- Flecainide
- Diltiazem
- Ganciclovir
- Etoposide
- Amsacrine

Daniel Lednicer, National Cancer Institute, Editor
ACS Professional Reference Book
350 pages (1993)
Clothbound: ISBN 0-8412-2523-0—\$84.95
Paperbound: ISBN 0-8412-2733-0—\$34.95

Order from:

American Chemical Society
Distribution Office, Dept. 74
1155 Sixteenth Street, NW
Washington, DC 20036

Or CALL TOLL FREE

1-800-227-5558 (in Washington, DC, 202-872-4363) and use your credit card! FAX: 202-872-6067

ACS PUBLICATIONS
Essential Resources for the Chemical Sciences

Biochemistry

Biochemistry (ISSN 0006-2960) is published weekly except for the first week in January by the American Chemical Society at 1155 16th St., N.W., Washington, DC 20036. Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *Biochemistry*, Member & Subscriber Services, P.O. Box 3337, Columbus, OH 43210. Canadian GST Reg. No. R127571347. Printed in the USA.

American Chemical Society

1155 16th St., N.W.
Washington, DC 20036
(202) 872-4600
TDD (202) 872-8733; FAX (202) 872-4615

Member & Subscriber Services

American Chemical Society
P.O. Box 3337, Columbus, OH 43210
(614) 447-3776; (800) 333-9511

Journals Department

American Chemical Society
2540 Olentangy River Road
P.O. Box 3330, Columbus, OH 43210
(614) 447-3600, Ext 3171
TELEX 6842086; FAX (614) 447-3745

Publications Division

Robert H. Marks, Director

Journals Department: Charles R. Bertsch, Head

Editorial Office: Mary E. Scanlan, Manager; Kathleen E. Duffy, Anne C. O'Melia, and Joseph E. Yurvati, Journals Editing Managers; Deborah K. Miller, Senior Associate Editor; Daniel R. Kelsey, Associate Editor; Amy S. McKee, Barbara I. Taylor, and Beth A. Welch, Assistant Editors; David L. Norris, Staff Editor

Advertising Office: Centcom, Ltd., 1599 Post Road East, P.O. Box 231, Westport, CT 06881

© Copyright 1994 by the American Chemical Society. Copyright permission: An individual may make a single reprographic copy of an article in this publication for personal use. Reprographic copying beyond that permitted by Section 107 or 108 of the U.S. Copyright Law is allowed, provided that the appropriate per-copy fee is paid through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923. For reprint permission, please write to the Copyright Administrator, Publications Division, at the ACS Washington address. Bulk reprints: For quotes and information on placing an order, please call (202) 872-4539 or write to the Distribution Office at the ACS Washington address.

The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48-1984.

Editorial Information

Instructions to authors and copyright status form are printed in the first issue of each volume. Please conform to these instructions when submitting manuscripts.

Manuscripts for publication should be submitted to the Editor, Gordon G. Hammes, Duke University Medical Center, P.O. Box 3673, 081 Yellow Zone, Duke South, Durham, NC 27710. Correspondence regarding accepted papers and proofs should be directed to the Journals Department at the address above. Page charges of \$30.00 per page may be paid for papers published in this journal. Payment does not affect acceptance or scheduling of papers.

The American Chemical Society and its Editors assume no responsibility for the statements and opinions advanced by contributors.

Registered names and trademarks, etc., used in this publication, even without specific indication thereof, are not to be considered unprotected by law.

Subscription and Business Information

Subscriptions are available only on a calendar year basis. (For membership information, contact Office of Member Services at the ACS Washington address.)

New and renewal subscriptions should be sent with payment to American Chemical Society, Department L-0011, Columbus, OH 43268-0011. Rates do not apply to non-member subscribers in Japan, who must enter subscription orders with Maruzen Company Ltd., 3-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103, Japan. Tel: (03) 272-7211.

1994 subscription prices including postage.

		U.S.	Canada, Mexico	Europe*	All Other Countries*
Printed					
Members	1 yr	\$ 108	\$ 200	\$ 351	\$ 422
	2 yr	\$ 194	\$ 378	\$ 680	\$ 822
Nonmembers		\$1328	\$1420	\$1571	\$1642
Microfiche					
Members	1 yr	\$ 108	\$ 108	\$ 156	\$ 156
	2 yr	\$ 194	\$ 194	\$ 290	\$ 290
Nonmembers		\$1328	\$1328	\$1376	\$1376
Supplementary material on microfiche		\$ 50	\$ 80	\$ 80	\$ 80

* Air service included.

Printed edition single issue prices: current year, \$27.00; 1992-93, \$31.00; 1990-91, \$23.00; prior year, \$44.00. Foreign postage additional. Mail orders and requests for back volume prices should be sent to Microforms & Back Issues Office at the ACS Washington address.

Phone orders can be placed for printed, microfiche, and microfilm editions by calling the ACS TOLL FREE at (800) 333-9511 from anywhere in the United States and Canada. Phone orders can be charged to Visa, MasterCard, or American Express accounts.

Changes of address must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to Member & Subscriber Services. Please allow 6 weeks for change to become effective. Claims for missing numbers will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated (a) North America, more than 90 days beyond issue date; (b) all other foreign, more than 180 days beyond issue date. Claims are handled by Member & Subscriber Services.

Supplementary material is noted in the table of contents with a ■. It is available as photocopy (\$10.00 for up to 3 pages and \$1.50 per page for additional pages, plus \$2.00 for foreign postage) or as 24X microfiche (\$10.00, plus \$1.00 for foreign postage). Canadian residents should add 7% GST. See supplementary material notice at end of journal article for number of pages. Orders must state whether for photocopy or for microfiche and give complete title of article, names of authors, journal, issue date, and page numbers. Prepayment is required and prices are subject to change. Order from Microforms & Back Issues Office at the ACS Washington address. Supplementary material except structure factors also appears in the microfilm edition.

Cover: Based on λ repressor-DNA complex—courtesy of David Richardson.

Biochemistry

EDITOR: GORDON G. HAMMES

Duke University Medical Center, P.O. Box 3673, 081 Yellow Zone, Duke South, Durham, North Carolina 27710
[Phone (919) 681-3250; FAX (919) 681-8344 or (800) 334-0892]

ASSOCIATE EDITORS:

MARY D. BARKLEY, LOUISIANA STATE UNIVERSITY
MARC G. CARON, DUKE UNIVERSITY
EARL W. DAVIE, UNIVERSITY OF WASHINGTON
PERRY A. FREY, UNIVERSITY OF WISCONSIN
PAUL L. MODRICH, DUKE UNIVERSITY

WILLIAM W. PARSON, UNIVERSITY OF WASHINGTON
JAMES F. RIORDAN, HARVARD MEDICAL SCHOOL
JOSEPH J. VILLAFRANCA, BRISTOL-MYERS SQUIBB
LESLIE WILSON, UNIVERSITY OF CALIFORNIA, SANTA BARBARA

EDITORIAL ADVISORY BOARD

ROBERT H. ABELES
Brandeis University
DAVID S. AULD
Harvard Medical School
JOSEPH AVRUCH
Massachusetts General Hospital
GERALD T. BABCOCK
Michigan State University
ROBERT L. BALDWIN
Stanford University
ROBERT M. BELL
Duke University
STEPHEN J. BENKOVIC
The Pennsylvania State University
E. MORTON BRADBURY
University of California, Davis
BILL R. BRINKLEY
Baylor College of Medicine
MICHAEL J. CHAMBERLIN
University of California, Berkeley
JOSEPH E. COLEMAN
Yale University
MINOR J. COON
The University of Michigan
DAVID DAVIES
NIDDK, National Institutes of Health
WILLIAM F. DEGRADO
Dupont-Merck Pharmaceuticals
JACK E. DIXON
The University of Michigan
RUSSELL F. DOOLITTLE
University of California, San Diego
RAYMOND A. DWEK
University of Oxford
MAURICE EFTINK
University of Mississippi
JULI FEIGON
University of California, Los Angeles
ALAN R. FERSHT
University of Cambridge
IRWIN FRIDOVICH
Duke University
ERROL C. FRIEDBERG
University of Texas
CARL FRIEDEN
Washington University
MARTIN GELLERT
National Institutes of Health
LILA M. GIERASCH
University of Texas Southwestern
Medical Center
IRVING H. GOLDBERG
Harvard Medical School

JACK GORSKI
University of Wisconsin
ROBERT HASELKORN
University of Chicago
CLAUDE HÉLÈNE
Museum National d'Histoire Naturelle,
Paris
JOHN W. B. HERSHEY
University of California, Davis
GEORGE P. HESS
Cornell University, Ithaca
STEFAN HIGHSMITH
University of the Pacific
PETER C. HINKLE
Cornell University, Ithaca
DICK HOEKSTRA
University of Groningen
BARRY HONIG
Columbia University
TONY E. HUGLI
Scripps Clinic & Research Foundation
LINDA JEN-JACOBSEN
University of Pittsburgh
HANS JÖRNVALL
Karolinska Institute, Stockholm
H. RONALD KABACK
Howard Hughes Medical Institute, UCLA
NEVILLE R. KALLENBACH
New York University
CLAUDE B. KLEE
National Cancer Institute
JUDITH P. KLINMAN
University of California, Berkeley
ROBERT J. LEFKOWITZ
Duke University
TOMAS LINDAHL
Imperial Cancer Research Fund, London
PHILIP W. MAJERUS
Washington University
ROWENA G. MATTHEWS
University of Michigan
HENRY METZGER
NIAMS, National Institutes of Health
CHRISTOPHER MILLER
Brandeis University
LUCIANO MUELLER
Bristol-Myers Squibb
GARY L. NELSESTUEN
University of Minnesota
BERT O'MALLEY
Baylor College of Medicine

DEMETRIOS PAPAHAJIOPOULOS
University of California, San Francisco
ARTHUR PARDI
University of Colorado
DAVID C. PHILLIPS
University of Oxford
M. THOMAS RECORD
University of Wisconsin
DAVID W. RUSSELL
University of Texas Southwestern
Medical Center
J. EVAN SADLER
Washington University
HAROLD A. SCHERAGA
Cornell University, Ithaca
PAUL R. SCHIMMEL
Massachusetts Institute of Technology
JOACHIM SEELIG
University of Basel
G. GRAHAM SHIPLEY
Boston University
ANTERO G. SO
University of Miami
LINDA L. SPREMULLI
University of North Carolina
JOANNE STUBBE
Massachusetts Institute of Technology
IGNACIO TINOCO, JR.
University of California, Berkeley
OLKE C. UHLENBECK
University of Colorado
BERT L. VALLEE
Harvard Medical School
DENNIS E. VANCE
University of Alberta
JANE M. VANDERKOOI
University of Pennsylvania
MARTHA VAUGHAN
National Institutes of Health
DENNIS R. VOELKER
National Jewish Center for Immunology
and Respiratory Medicine
TERESA S. WANG
Stanford University
SAVIO. WOO
Baylor College of Medicine
PETER E. WRIGHT
Scripps Clinic & Research Foundation
CHENG-WEN WU
Institute of Biomedical Science, Taiwan