

Volume 231
OCTOBER-DECEMBER
1984

The Journal of PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

*A Publication of The American Society
for Pharmacology and Experimental Therapeutics*

Founded by John J. Abel 1909

EDITOR

Eva King Killam

ASSISTANT EDITOR

Mannfred A. Hollinger

EDITORS FOR SPECIFIC FIELDS

Analgesia and Drug Abuse
Joseph Cochlin

Autonomic Pharmacology
Joseph J. McPhillips
Robert E. Stitzel

Behavioral Pharmacology
John A. Harvey

Cardiovascular Pharmacology
Leslie E. Bailey
Henry R. Besch, Jr.
Theodore M. Brody
Donald V. Priola

Cell Pharmacology
Toshio Narahashi
George B. Weiss

Chemotherapy
H. George Mandel

Developmental Pharmacology
Bernard L. Mirkin

Drug Metabolism and Disposition
Edward Bresnick
Jordan L. Holtzman

Endocrine Pharmacology
Paula H. Stern

Gastrointestinal Pharmacology
Thomas F. Burks

Immunopharmacology
Sydney Spector

Neuropharmacology
Edmund G. Anderson
S. J. Enna
Charles O. Rutledge

Prostaglandins and Leukotrienes
John C. McGiff

Pulmonary Pharmacology
Mannfred A. Hollinger

Renal Pharmacology
William O. Berndt

Toxicology
Curtis D. Klaassen

EDITORIAL ADVISORY BOARD

Martin W. Adler
Edson X. Albuquerque
Lewis Aronow
Michael D. Baillie
Robert L. Balster
Paul Bass
John A. Bevan
C. Paul Bianchi
Ruth E. Billings
David A. Blake
Floyd E. Bloom
Gary Brooker
Carl K. Buckner
David B. Bylund
Theodore J. Cicero
Doris H. Clouet
Leonard Cook
Charles R. Craig
E. E. Daniel
William C. de Groat
Louis Diamond
Walter R. Dixon
James S. Douglas
J. W. Downie
Sue Piper Duckles
Linda Dykstra
Hugh L. Evans
James A. Ferrendelli
Gregory D. Fink

Lawrence J. Fischer
William W. Fleming
Ray W. Fuller
Timothy S. Gaginnella
Gerard L. Gebber
James W. Gibb
Shri N. Giri
Frank R. Goodman
Charles W. Gorodetzky
Theodore E. Gram
Thomas P. Green
Garrett J. Gross
A. James Hance
T. Kendall Harden
Harold F. Hardman
Louis S. Harris
R. Adron Harris
Richard J. Head
William R. Hewitt
Stephen G. Holtzman
Jerry B. Hook
David M. Jacobowitz
Barbara A. Jakschik
Donald R. Jasinski
E. H. Jeffery
Alain F. Junod
Conan Kornetsky
Edwin A. Kroeger
Tony J.-F. Lee

Wayne Levin
Louis Levy
Roberto Levi
George E. Lindenmayer
Stephen L. Lipsius
Walter Lovenberg
Benedict R. Lucchesi
K. U. Malik
William D. Matthews
Thomas A. McCalden
Donald E. McMillan
Jerry Mitchell
Perry B. Molinoff
W. H. Morse
Kevin Mullane
Jose M. Musacchio
Mary J. Mycek
Robert A. Neal
Philip Needleman
Robert F. O'Dea
Achilles J. Pappano
William A. Pettinger
Larissa A. Pohorecky
Russell A. Prough
James W. Putney, Jr.
Arthur Raines
G. Alan Robison
C. R. Ross
Carl E. Rosow

Ronald P. Rubin
Robert R. Ruffolo, Jr.
Betty I. Sasyniuk
Arnold Schwartz
Lewis S. Seiden
Eric J. Simon
Roger P. Smith
Roger D. Speakman
John L. Sutko
Boris Tabakoff
Robert I. Taber
A. E. Takemori
Robert E. Ten Eick
Thomas R. Tephly
Richard E. Tessel
C. D. Thron
U. Trendelenburg
Betty M. Twarog
Norman J. Uretsky
Ladislav Volicer
Martin A. Wasserman
I. M. Weiner
Benjamin Weiss
Richard M. Welch
David P. Westfall
Grant R. Wilkinson
Martin M. Winbury
Barry B. Wolfe
Ben G. Zimmerman

BOARD OF PUBLICATIONS TRUSTEES

William W. Fleming, *Chairman*: James A. Bain, Joseph R. Bianchine, Joel G. Hardman, Eva King Killam, Bettie Sue Masters, Jerry R. Mitchell, Clement A. Stone, Palmer W. Taylor, Vincent G. Zannoni

EXECUTIVE OFFICER OF THE SOCIETY

Kay A. Croker

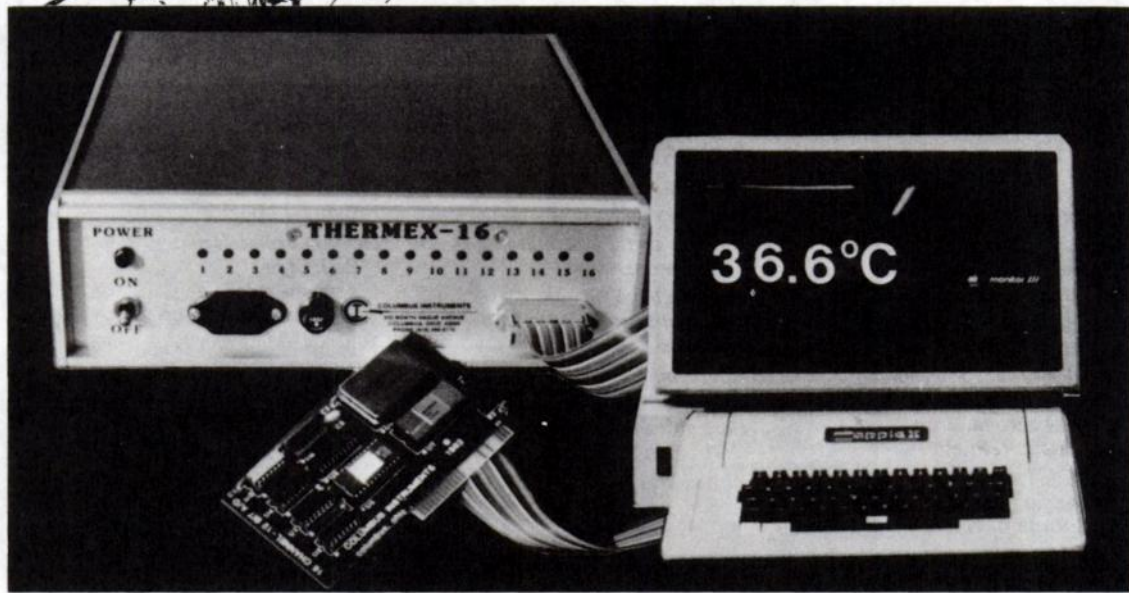
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (ISSN 0022-3565) is published monthly by The American Society for Pharmacology and Experimental Therapeutics, 428 E. Preston Street, Baltimore, MD 21202. Annual dues includes \$60.00 for journal subscription. Second class postage paid at Baltimore, MD and at additional mailing offices. POSTMASTER: Send address changes (Form 3579) to Williams & Wilkins, 428 E. Preston St., Baltimore, MD 21202. Indexed by *Current Contents* and *Index Medicus*. Subscription rates \$140.00 (\$165.00 foreign); institutions \$220.00 (\$250 foreign) single copy \$16.00 (\$19.00 foreign). Copyright © 1984 by The American Society for Pharmacology and Experimental Therapeutics

COPYRIGHT © 1984 BY THE WILLIAMS & WILKINS COMPANY

Apple — THERMOMETER

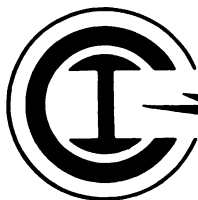


"THERMEX-16" — 16 channels thermometer interface to Apple II* computers.



**FOR: PYROGENIC ACTIVITY, INFLAMMATION
HYPOTHERMAL ONCOLOGY
AND BLOOD CIRCULATION MAPPING**

- Accuracy $\pm 1/10^{\circ}\text{C}$ at 22°C ambient
- Resolution $1/10^{\circ}\text{C}$
- Range 0°C to 50°C for biological applications
(other ranges available on request)
- Displays, prints and stores results on the disc from all 16 channels
- Variety of rectal, intravenous, hypodermic and implantable probes available
- Optional program for plotting temp. curves versus time available



COLUMBUS INSTRUMENTS INTERNATIONAL CORPORATION

950 N. HAGUE AVE., COLUMBUS, OHIO 43204 U.S.A.
PHONE: (614) 488-6176

TELEX: 246514

AUTHOR INDEX

- Asano, T., 141
Assens, F., 173
Baghdoyan, H. A., 173
Bailey, J. C., 206
Baumann, P. A., 166
Bayorh, M. A., 85
Bennett, W. F., 146
Bhatnagar, R., 56
Bianchi, C. P., 197
Bolger, G. T., 8
Borison, H. L., 189
Breese, G. R., 61
Brown, D. R., 114
Builder, S., 146
Cannon, J. G., 56
Carter, W. H., Jr., 97
Cline, W. H., Jr., 23
Clouet, D. H., 38
Collen, D., 146
De Cock, F., 146
De Herdt, P., 166
DeLander, G. E., 91
Dewey, W. L., 97
Ellington, K. R., 61
Fadul, S., 109
Fehr, B., 166
Feuerstein, G., 85
Fleming, W. W., 181
Flynn, J., 56
Fowler, B. A., 66
Fung, H.-L., 124
Garzón, J., 33
Gerber, J. G., 109
Goering, P. L., 66
Haggstrom, G. D., 120
Halpert, J., 16
Hicks, P. E., 159
Hidaka, H., 141
Hirschowitz, B. I., 120
Hobson, J. A., 173
Hoyng, C. F., 146
Ilhan, M., 56
Jaim-Etcheverry, G., 131
Janis, R. A., 8
Johnson, C. L., 1
Kachur, J. F., 97
Kalinyak, K., 1
Kamen, B. A., 43
Kaplita, P. V., 189
Kawasaki, H., 23
Kopin, I. J., 85
Kovacs, R. J., 206
Krakower, G. R., 43
Kreisberg, J. I., 48
Kwok, Y. C., 137
Lai, C.-M., 72, 80
Landa, M. E., 131
Langer, S. Z., 159
Lee, N. M., 33
Lee, T., 56
Levy, G., 72, 80
Long, J. P., 56
Maitre, L., 166
Marafino, B. J., Jr., 146
Maurer, S. C., 8
McCarley, R. W., 173
McCarthy, L. E., 189
McKay, D. B., 102
Medgett, I. C., 159
Millecchia, R., 181
Miller, R. J., 114
Monaco, A. P., 173
Moore, G. J., 137
Morrison, R. A., 124
Nagase, H., 153
Narayan, S. R., 197
Näslund, B. M. A., 16
Nies, A. S., 109
Ogez, J., 146
Ozaki, H., 153
Patrick, K. S., 61
Payne, N. A., 109
Pennica, D., 146
Portoghese, P. S., 91
Rardon, D. P., 206
Rodrigo-Angulo, M. L., 173
Rubio, M. C., 131
Salwa, J., 146
Sánchez-Blázquez, P., 33
Sarmiento, J. G., 8
Sawutz, D. G., 1
Schneider, A. S., 102
Schulz, J. C., 181
Schwartz, D. W., 48
Smith, R. P., 189
Stassen, J. M., 146
Su, C., 23
Tagashira, E., 97
Tajiri, D., 146
Takemori, A. E., 91
Triggle, D. J., 8
Urakawa, N., 153
Venkatachalam, M. A., 48
Waldmeier, P. C., 166
Westfall, D. P., 181
Whitsett, J. A., 1
Yacobi, A., 72, 80
Yonehara, N., 38
Zukowska-Grojec, Z., 85

Notice to Contributors (Revised July 1, 1983)

Scope of Submitted Manuscripts

The Journal invites for review original papers dealing with the interactions of chemicals with biological systems. Any aspect of pharmacology and therapeutics is included, but descriptive case reports without dose response or mechanism studies are usually not accepted. Manuscripts dealing primarily with new methods will be reviewed only if data are presented showing new or more reliable pharmacological information has been obtained by use of the methods or the methods are shown to lead to new or more reliable data than were previously attained.

Submission of Manuscripts

Manuscripts should be submitted in *four* copies to Dr. Eva King Killam, Editor in Chief, Journal of Pharmacology and Experimental Therapeutics, Department of Pharmacology, School of Medicine, University of California, Davis, California 95616, and accompanied by a check or purchase order for \$30.00 *manuscript handling fee* (in U.S. funds payable to ASPET). If submission of the manuscript handling fee entails personal financial hardship to the author, the fee will be waived. In that event the authors should submit a request for waiver of the fee at the time the manuscript is submitted.

Manuscripts should be typewritten double spaced in the English language using one side only of approximately 21.6 by 28 cm paper. One original drawing or photograph of each line figure and three (3) clear copies will be sufficient, 4 original drawings or photographs are required of each halftone figure. Pages should not be stapled together.

It is understood that neither the manuscript nor the data it contains have been previously published nor are being submitted elsewhere for publication. Manuscripts are accepted for review with the understanding that all authors listed have approved submission of the paper and that persons cited for unpublished work have approved such citation.

Authors submitting a manuscript do so with the understanding that if it is accepted for publication, copyright in the article, including the right to reproduce the article in all forms and media, shall be assigned exclusively to the Society for Pharmacology and Experimental Therapeutics. No reasonable request by the author for permission to reproduce any of his or her contributions to the journal will be refused. It will be necessary for *all* authors to sign an assignment of copyright form which will be mailed from the Editorial Office on acceptance of the manuscript. The only exceptions will be manuscripts on work done by employees of the U.S. Federal Government.

Organization of the Manuscript

In most cases manuscripts should contain the following sections in the order listed: 1) title page; 2) running title page; 3) abstract; 4) introduction; 5) methods; 6) results; 7) discussion; 8) acknowledgments; 9) references; 10) footnotes; 11) tables; 12) legends for figures; 13) figures; and 14) index terms. Each section should begin on a new page and all pages should be numbered consecutively.

1. Title page. This should contain the complete title of the manuscript, the names of all authors and the laboratory of origin.

2. Running title page. 1) Each published paper needs a running title to appear at the top of each page in the Journal. The running title should contain no more than 35 spaces, including punctuation. It should convey the sense of the full title. Commonly used abbreviations (such as "ATP," "ACh," etc.) may be used in the running title. 2) This page should also contain the name, address and telephone number of the person to whom page proof should be sent. 3) A list of abbreviations used in the paper should appear on this page. Additionally, each abbreviation should be defined the first time it is used in the text.

3. Abstract. The abstract should present in a concise form the purpose, the general methods, the findings and the conclusions of the manuscript. Abstracts should be limited to 200 words; abstracts of more than 250 words will not be accepted.

4. Introduction. This section should not be labeled, but should begin on a new page. It should contain a clear statement

of the aims of the reported work or of the hypotheses which the work was designed to test. A brief account of the background of the reported work may also be given in this section.

5. Methods. This section should contain explicit, concise descriptions of all new methods or procedures employed. Modifications of previously published methods should be described. Commonly used methods require only a citation of the original source. When methods are described, the description should be such as to enable the reader to judge their accuracy, reproducibility and reliability and to repeat the experiment. Very extended descriptions of methods may be submitted for deposit with the American Society for Information Science National Auxiliary Publications Service (NAPS) c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10017. A text reference or footnote stating that the full description is available from NAPS permits interested readers to obtain the information, and does not occupy an inordinate amount of Journal space. There is a nominal charge to authors for this procedure; those who request the complete information from NAPS pay a small fee.

6. Results. This section ordinarily contains the experimental data to be presented but not extended discussions of their significance. Results should usually be presented in graphic or tabular form, rather than discursively. Graphic presentation of data is often preferred but there should not be duplication in text, tables and figures. Sufficient data must be given to allow readers to judge the variability and reliability of the results. Statistical tests used and the data analyzed should be explained so that the findings can be interpreted and evaluated.

7. Discussion. This section should present conclusions to be drawn from the results. Speculative discussion is not discouraged, but the speculation should be based on the data presented and identified as such. The discussion should be as concise as possible, within the limits of the ideas which the authors wish to propose and adequate discussion of related work by others.

8. Acknowledgments. These may be included at the end of the text of the manuscript, but should have a separate heading. Gifts and assistance can be acknowledged here but financial support should appear in a footnote to the title.

9. References. In text citations, give the author's name and the year of publication (e.g., McCarthy, 1952; Ruth and Gehrig, 1929). With more than two authors, the text citation should contain the name of the first author, followed by "*et al.*," and the date (e.g., Kennedy *et al.*, 1960). In the list of references, entries should be arranged alphabetically by author, and not numbered. All authors' names should be given. If reference is made to more than one publication by the same authors in the same year, suffixes (a, b, c, etc.) should be added to the year in the text citation and in the list of references.

The list of references should contain, in sequence, the following information; authors' names and initials, title of the cited article, title of the journal in which the article appeared (abbreviated; see below), volume number of the journal, inclusive pagination and year of publication. Abbreviations for journals should conform to the Biosis List of Serials (BioSciences Information Services of Biological Abstracts, Philadelphia, PA 19103). Citations of personal communications or of unpublished observations should be given in parentheses at the appropriate place in the text not in the list of references. A paper may not be cited as "in press" unless it has been accepted for publication. In such cases the name of the journal must be given.

Except in extraordinary circumstances, no more than four references should be cited in support of any given point. The authors are responsible for the accuracy of such citations and are urged to take the utmost care in proofreading citations and reference list.

10. Footnotes. All footnotes to the title, authors' names or text should be indicated by arabic numeral superscripts, not by letters or other symbols. The footnotes should be typed in sequence on a separate page not a text page. Footnotes to tables are discussed under Tables, below.

11. Tables. Each table should be on a separate page. Tables should be numbered consecutively with arabic numerals, and should be designed to fit the column or page size of the Journal. A brief descriptive title should be given at the top of each table. The table number should be given in capital letters, the title in boldface upper and lower case letters (e.g., TABLE 3. **Uptake of labeled drug by rat liver slices**). The footnotes to the tables should be referenced by italicized lower case superscript letters (*a*, *b*, *c*, etc.) and should appear beneath the table involved, not on a separate page of the manuscript. Extensive tabular material not absolutely essential to the manuscript will be accepted for deposit with the ASIS/NAPS (see "Methods," above). In such instances a footnote in the published paper will refer the interested readers to NAPS from which copies may be obtained. Note *Statistics* below for expressions of probability.

12. Legends for figures. These should be numbered consecutively in arabic numerals and should appear on a separate page of the manuscript. Legends should explain the figures in sufficient detail so that frequent referral to the text is unnecessary, but efforts should be made to avoid unnecessary length. Abbreviations in the legends should conform to those in the text (see "Abbreviations," below).

13. Figures. Illustrations should be submitted as unmounted glossy photographic prints, no larger than 8 by 10 inches. The authors' name and address and the number of the figure should be placed on the back of each print. A typed label is usually most satisfactory. Ball type pen should *not* be used. Note *Statistics* below for expression of probability. Illustrations must be clear enough to permit reproduction without retouching and legibility after reduction to single-column size (approximately 3½ inches in width). Uniform symbolism should be used for all illustrations in a manuscript. Symbols, numbers and letters in the illustrations must be at least 1.5 mm in height after reduction to single column size. The title of each figure should appear in the legend rather than on the figure itself. Photomicrographs and electron micrographs should be labeled with a magnification calibration in micro or Angstrom units. A statement of the magnification should appear in the figure legend.

14. Index Terms. A list of index terms useful in constructing the annual index should be included as the last page of the manuscript.

Statistics.

Wherever possible statistical probability (*P*) in tables, figures, and figure legends should be expressed as * *P* < .05, ** *P* < .01 and *** *P* < .001. For second comparisons the symbols † may be used similarly. Authors are urged to avoid unnecessary complexity and to be consistent within the manuscript. In the event of multiple comparisons within a table, footnotes, *a*, *b*, *c*, etc. should be used.

Abbreviations

Magnitudes of variables reported should be expressed in numerals. Most abbreviations are used without punctuation, with no distinction between singular and plural forms (e.g., 1 mg, 25 mg; 1 sec, 25 sec). The usual prefixes are to be used for multiples or submultiples of the basic units (e.g., kg, g, mg, µg, ng, pg). The following abbreviations, or their properly prefixed multiples or submultiples, may be used without definition in the text, tables and figures:

Units of mass

gram	g
mole	mol
equivalent	Eq
microatom	µat

Units of concentration

molar (moles/liter)	M
normal (Eq/liter)	N
percent	%

Units of electricity

volt	V
ampere	A
cycles/sec	Hz

Units of radioactivity

curie	Ci
counts per min	cpm
disintegrations per min	dpm
roentgen	r

Units of length or volume

meter	m
micron	µ
Angstrom	Å
liter (spell out in text)	l

Units of time

hour	hr or h
minute	min or m
second	sec or s

Kinetics

dissociation constant	K _d
-----------------------	----------------

Dissociation constant of

enzyme substrate complex	K _s
enzyme inhibitor complex	K _i
Michaelis constant	K _m
maximum initial velocity	V _{max}

Miscellaneous

degrees of temperature	°C
gravity	g
median doses	LD ₅₀ , ED ₅₀ , etc.
optically isometric forms	<i>d</i> -, <i>l</i> -, <i>dl</i> -
routes of drug administration	<i>i.v.</i> , <i>i.p.</i> , <i>s.c.</i> , <i>i.m.</i>
standard deviation	S.D.
standard error	S.E.

Whenever an abbreviation other than those above is to be used in a manuscript, it is to be defined in the text or in a footnote thereto, the first time it is used. Abbreviations for commonly used substances should be those recommended by the Journal of Biological Chemistry. Abbreviations for drugs may be used if properly defined on first use and if the chemical or generic name of the drug is given when the abbreviation is first used. Abbreviations may be used in the running title but not in the full title of the manuscript.

Drugs

Generic names should be used in text, tables and figures. Trade names may be mentioned in parentheses in the first text reference to the drug but should not appear in titles, figures or tables. When a trade name is used, it should be capitalized; generic or chemical names are not capitalized. The chemical nature of new drugs must be given when it is known. The form of drug used in calculations of doses (e.g., base or salt) should be indicated. When several drugs are used, it may save space to include a separate paragraph in "Methods," or a separate table or footnote, listing the relevant information about all drugs employed.

Page Charges

Authors are assessed page charges at the rate of \$30 per printed page. With the page proof, authors will receive a request for information concerning such charges. These charges will be assessed only if they involve no personal expense to the authors. Request for waiver should be addressed to the ASPET Executive Officer at the time billing is received.

The cost of a limited number of illustrations will be borne by the Journal: the cost of excessive numbers of illustrations and of colored illustrations will have to be defrayed by the authors.

"A well-referenced basic science textbook of pharmacology, with a strong orientation to clinically important subjects."*

CARDIOVASCULAR PHARMACOLOGY SECOND EDITION

Michael J. Antonaccio, Ph.D., Editor

"The book is impressive in the extent of information presented and it is highly readable. The format is of high quality. The references are extensive and up to date. . . . The book is to be highly recommended for those working in the field of cardiac pharmacology and for the serious clinician wishing to understand the pathophysiologic mechanisms for disease and the latest pharmacologic concepts for its rational treatment."

—Clinical Cardiology

*From a review of the first edition in Modern Medicine of Canada

Maintaining the scope and standards of its acclaimed predecessor, this new, revised edition of Cardiovascular Pharmacology reviews our current understanding of the biochemical and biophysical basis of cardiac function. The book discusses the most recent pharmacologic advances and currently available therapeutic agents, along with suggestions for the most appropriate drug therapy in a specific clinical situation. Material new to the second edition covers • calcium channel blockers • renin release • presynaptic regulation • angina and congestive heart failure • the roles of prostacyclin and thromboxane in cardiovascular function.

Cardiovascular Pharmacology—a necessary reference for all physicians involved in the treatment of cardiovascular disease.

1984, 608 pages, 131 illustrations, \$43.50, #1244

CONTENTS: Fundamental Principles Governing Regulation of Circulatory Function, T. Baum / Renal Physiology and Pharmacology, J. B. Hook and R. Z. Gussin / Control of Renin Release and Its Alteration by Drugs, T. K. Keeton and W. B. Campbell / Angiotensin-Converting Enzyme and Renin Inhibitors, C. S. Sweet and E. H. Blaine / Central Transmitters: Physiology, Pharmacology, and Effects on the Circulation, M. J. Antonaccio / Prejunctional Receptors and the Cardiovascular System: Pharmacological and Therapeutic Relevance, S. Z. Langer and J. M. Armstrong / Vascular Changes in Hypertension, R. C. Webb / Antihypertensive Drugs, A. Scriabine and D. G. Taylor / Angina Pectoris and Chronic Congestive Heart Failure: Pathophysiology and Therapy, G. S. Francis and J. N. Cohn / Antiarrhythmic Drugs, B. R. Lucchesi and E. S. Patterson / Calcium Antagonists, R. K. Saini / Cardiovascular Actions of the Prostaglandins, P. J. Kadowitz et al. / Platelets and Platelet Aggregation Inhibitors, F. Seuter and A. Scriabine / Prostacyclin-Thromboxane Interactions in Hemostasis, B. J. R. Whittle and S. Moncada / Pharmacologic Basis of the Treatment of Circulatory Shock, A. M. Lefer and J. A. Spath, Jr.

Edited by Michael J. Antonaccio, Ph.D., Vice-President, Cardiovascular Research, Bristol Myers Company, Evansville, Indiana

CLIP AND MAIL THIS NO-RISK COUPON TODAY!

Order Form

Yes! Please send the book checked below. If not completely satisfied, I may return the book (with invoice) within 30 days for a full refund or credit.

- Antonaccio, ed. #1244
Bill me (plus postage/handling).
Check enclosed (NY residents, add sales tax).
Charge my credit card American Express Diners Club
VISA MasterCard 4-digit interbank #

Credit card #

Exp. date

Signature

Name (please print)

Address

Country Postal Code

Prices subject to change without notice. Prices slightly higher outside the U.S. and Canada.

Raven Press 1140 Avenue of the Americas New York, N.Y. 10036 U.S.A. qc