CONTENTS

Hepatic Monooxygenase Activity and Hepatocellular Morphology in Chickens Treated with 3-Methylcholanthrene. S. J. Buynitzky, A. E. Wade, J. F. Munnell, and W. L. Ragland ................................. 1

Absorption and Disposition of Oxarbazole in Man and Laboratory Animals. David Benziger, Sally Dorrbecker, Thomas Goehl, and Jerome Edelson ................................. 8


The Metabolism and Elimination of Cimetidine, a Histamine H2-Receptor Antagonist, in the Rat, Dog, and Man. Donald C. Taylor, Peter R. Cresswell, and David C. Bartlett ................................. 21

The Metabolism of α-Aminobenzothiophene-3-propionic Acid (the Sulfur Analog of Tryptophan) in the Rat. Talmage R. Bosin, Rex G. Bickers, and Alan Dinner ................................. 31

Identification of the Metabolites of Trichlorocarbanilide in the Rat. James T. Warren, Rebecca Allen, and Dean E. Carter ................................. 38

A Relationship between the Metabolism of Bumetanide and Its Diuretic Activity in the Rat. Steven C. Halladay, Dean E. Carter, and I. Glenn Sipes ................................. 45

Absorption, Metabolism, and Excretion of "C-Tosifen in the Dog and Rat. C. Lin, R. Foester, J. Lim, T. Hsu, J. B. Morton, and S. Symchowicz ................................. 50

Continued on page 2
Role of the Enterohepatic Circulation in the Elimination of Phenytoin in the Rat.

A. Monaem El-Hawari and Gabriel L. Plaa ........................................ 59

Excretion of Phenytoin into Semen of Rabbits and Man: Comparison with Plasma Levels. Brian N. Swanson, Regina M. Leger, William P. Gordon, Robert K. Lynn, and Nicholas Gerber .......................... 70

Disposition of Primidone, Phenylethylmalonamide, and Phenobarbital in the Rabbit. Richard J. Hunt and Kenneth W. Miller ................................ 75

The Disposition of threo-α-(2-Piperidyl)-2-trifluoromethyl-6-(4-trifluoromethylphenyl)-4-pyridinemethanol Phosphate in Mice. Ho Chung, Harold H. Gillum, and Robert S. Rozman ........................................... 82

Age-dependent Renal Accumulation of Cephaloridine in the Rabbit. J. S. Wold and S. A. Turnipseed ............................................. 87

Distribution and Excretion of Chlordecone (Kepone) in the Rat. John L. Egle, Jr., Suzanne B. Fernandez, Philip S. Guzelian, and Joseph F. Borzel-Leca ......................................................... 87

Rat Hepatic Microsomal Cytochrome(s) P-450 Induced by Polybrominated Biphenyls. John G. Dent, Clifford R. Elcombe, Karl J. Netter, and James E. Gibson ............................................................................ 96

Note. Metabolism of Meseclazone in Man. Syd H. Dromgoole, Kenneth E. Nyman, Daniel E. Furst, Wilfred A. Kolman, and Harold E. Paulus ........................................... 102

Current Literature ........................................................................... 105

Announcements ............................................................................ 108
CONTENTS


Formation of Sulfone Metabolites from Chlorpromazine and Perazine in Man. Ursula Breyer-Pfaff, Hannelore Kret, Hannelore Rassner, and Axel Prox .................................................... 114

Comparison of Biliary Excretory Function and Bile Composition in Male, Female, and Lactating Female Rats. Curtis D. Klaassen and Stephen C. Strom ........ 120

The Disposition of 3-Deazaauridine in Mice. Richard L. Cystyk, Paul E. Gormley, Mary Ellen D’Anna, and Richard H. Adamson ..................... 125

Dihydropyrimidinase: Stereochemistry of the Metabolism of Some 5-Alkylhydan-
toines. Kenneth H. Dudely and Susan B. Roberts .................. 133

Dihydropyrimidinase: Metabolism of Some Cyclic Imides of Different Ring Size. James H. Maguire and Kenneth H. Dudely ....................... 140

Metabolism and Tissue Distribution of Mono-2-ethylhexyl Phthalate in the Rat. I. H. Chu, David C. Villeneuve, Viateur Secours, Claire Franklin, Gail Rock, and Andre Viau .............................................. 146

Species, Sex, and Developmental Differences in the O- and N-Dealkylation of Ethylmorphine by Hepatic Microsomes. Donald E. Nerland and Gilbert J. Mannering .............................................. 150

Metabolism and Disposition of Δ1-Tetrahydrocannabinol by the Isolated Perfused Rabbit Lung. Francis C. P. Law .................................................. 154

Continued on page 2
Levodopa Pharmacokinetics: Alterations after Benserazide, a Decarboxylase Inhibitor. H. J. DOLLER, J. D. CONNOR, D. R. LOCK, R. S. SLOVITER, B. H. Dvorchik, and E. S. Vesell .................................................. 164


The Absorption, Excretion, and Biotransformation of 3,4,4'-Trichlorocarbanilide in Humans. Richard A. Hiles and C. Grant Birch .................................................. 177


Pharmacokinetic Model of Presystemic Metabolism. Wayne A. Colburn and Milo Gibaldi ................................................................. 193


Current Literature .................................................... 201

Announcements ...................................................... 204

---

DRUG METABOLISM AND DISPOSITION:
the biological fate of chemicals

Information for Subscribers

Published bimonthly, one volume per year.

Annual Subscription Rates — U. S. A. AND POSSESSIONS: personal, $40.00; institutional, $50.00. FOREIGN: personal, $43.00; institutional, $53.00. Institutional (multiple-reader) rate applies to libraries, schools, hospitals, group practices, and federal, commercial, and private institutions and organizations.

Single issues when available, $7.00 in U.S.A., $7.50 elsewhere. Vol. 1, No. 1, the Symposium on Microsomes and Drug Oxidations is not available as a single issue of the journal. It may be purchased as a bound book for $30.00.

Change of address: Publisher must be notified 60 days in advance.

New subscriptions and renewals are entered to begin with the January issue.

Subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Correspondence on business matters should be addressed to the publisher.

Reprints of individual articles are available only from authors.

Microfilm: For availability, inquire of The Williams & Wilkins Company.

Instructions to Authors are published in the January–February issue of each volume, or a copy may be obtained from the Editor, Dr. Kenneth C. Leibman, Box J-267, College of Medicine, University of Florida, Gainesville, Fla. 32610.

THE WILLIAMS & WILKINS COMPANY

428 East Preston Street Baltimore, Maryland 21202 U. S. A.
Studies on Metabolism of Bromazepam. VI. Reduction of 2-(2-Amino-5-bromobenzoyl)pyridine, a Metabolite of Bromazepam, in the Rabbit, Rat, and Guinea Pig. HIDEO SAWADA AND AKIRA HARA 205

Metabolism of Levorotary 4,5-Dihydrodiazepam in the Rat. L. ÓTVÖS, Zs. TEGYEY, L. VERECZKEY, M. LEDNICKZY, J. TAMÁS, É. PÁLOS, AND L. SZPORNY 213


Microsomal Mixed-function Amine Oxidase: Oxidation Products of Piperazine-substituted Phenothiazine Drugs. SAMIR S. SOFER AND DANIEL M. ZIEGLER 232

Postnatal Development of Phenytoin Metabolic Activity in Rat Liver Microsomes. DAVID A. BLAKE, FRANCES COHEN, AND BARBARA C. MIYASAKI 240

Influence of Pregnancy and Folic Acid on Phenytoin Metabolism by Rat Liver Microsomes. DAVID A. BLAKE, JERRY M. COLLINS, BARBARA C. MIYASAKI, AND FRANCES COHEN 246

Phenytoin Metabolism in the Rat: Pharmacokinetic Correlation between in Vitro Hepatic Microsomal Enzyme Activity and in Vivo Elimination Kinetics. JERRY M. COLLINS, DAVID A. BLAKE, AND PATRICIA G. EGNER 251

2,3,7,8-Tetrachlorodibenzofuran in a Commercially Available 99% Pure Polychlori-
nated Biphenyl Isomer Identified as the Inducer of Hepatic Cytochrome P-448 and Aryl Hydrocarbon Hydroxylase in the Rat. JOYCE A. GOLDSTEIN, J. RONALD HASS, PATRICIA LINKO, AND DONALD J. HARVAN .......................... 258

Biliary Excretion of N,N-Dimethyl-4-aminoazobenzene in the Rat: Effects of Pretreatment with Inducers and Inhibitors of the Mixed-function Oxidase System and with Agents that Deplete Liver Glutathione. WALTER G. LEVINE AND THEODORE T. FINKELSTEIN ........................................ 265


Alterations in the Pharmacokinetics of [3H-Δ4-Tetrahydrocannabinol in Mice by Bacterial Endotoxin. B. R. MARTIN, J. MONTGOMERY, W. L. DEWEY, AND L. S. HARRIS .......................... 282

Quantitation of N-Demethylantipyrine in Biological Samples and Isolation and Characterization of Its Glucuronic Acid Conjugate. C. E. HIGNITE, C. TSCHANZ, D. H. HUFFMAN, AND D. L. AZARNOFF ........................................ 288


The Metabolism of (2-Cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy)acetic Acid in Chimpanzee and Man. A. G. ZACCHEI, T. I. WISHOWSKY, B. H. ARISON, AND G. HITZENBERGER ........................................... 303

The Physiological Disposition of (2-Cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy)acetic Acid in the Rat, Dog, Rhesus Monkey, and Baboon. A. G. ZACCHEI, T. I. WISHOWSKY, AND L. S. WATSON ............................................... 313

Elimination of Radioactivity following Administration of [15,16-3H]Naltrexone to Rats and Guinea Pigs. THOMAS M. LUDDEN, MOHINDER S. BATHALA, LOUIS MALSPIES, MARY A. DRUM, AND RICHARD H. REUNING .......... 321


Note. Placental and Milk Transfer of Disopyramide and Metabolites. A. KARIM, C. KOOK, AND J. CAMPION ........................................ 346

Current Literature ............................................................. 349

Announcements .................................................................. 351
DRUG METABOLISM AND DISPOSITION:
the biological fate of chemicals

Kenneth C. Leibman, Editor

Editorial Advisory Board

M. W. Anders
John E. Baer
John R. Bend
Frank J. Bullock
Arthur K. Cho
Dominick Cinti
Edward Cone
C. E. Cook
Jerome Edelson

Henry M. Fales
Alberto Frigerio
James M. Fujimoto
Theodore E. Gram
Ernest Hodgson
Howard B. Hucker
David Kuperfer
Walter G. Levine
Franz Oesch

Donald Perrier
Russell A. Prough
Robert J. Roberts
Morton A. Schwartz
Don W. Shoeman
Bitten Stripp
Samson Symchowicz
Elliot S. Vesell
William J. Waddell

Board of Publications Trustees

James A. Bain, Chairman
Daniel L. Azarnoff
Eva King Killam

Norman Kirschner
Kenneth C. Leibman
Gilbert J. Mannering
Walter Modell

Executive Officer
Houston Baker

July/August 1978

Vol. 6, No. 4

CONTENTS

Chromatographic and Electrophoretic Heterogeneity of the Cytochromes P-450
Solubilized from Untreated Rat Liver. MARGARET WARNER, MARIO VELLA
LAMARCA, AND ALLEN H. NEIMS .................................................. 353

Deuterium Isotope Effects on the Metabolism and Toxicity of Phenacetin in Ham-
sters. S. D. NELSON, W. A. GARLAND, J. R. MITCHELL, Y. VAISHNAV, C. N.
STATHAM, AND A. R. BUCKPITT .................................................. 363

The Biotransformation of p-Xylene to a Toxic Aldehyde. J. M. PATEL, C. HARPER,
AND R. T. DREW ................................................................. 368

Microsomal Metabolism of Cyclohexene: Hydroxylation in the Allylic Position.
KENNETH C. LEIBMAN AND ELSA ORTIZ ........................................ 375

Metabolism of Thioacetamide and Thioacetamide-S-oxide by Rat Liver Microsomes.
WILLIAM R. PORTER AND ROBERT A. NEAL .................................... 379

Synthesis and Characterization of Glucuronides of 5'-Hydroxy-Δ9-tetrahydrocanna-
binol and 11-Hydroxy-Δ9-tetrahydrocannabinol. SHARON PALLANTE, MICHAEL
A. LYLE, AND CATHERINE FENSELAU ........................................ 389

In Vitro Metabolism of Phenylacetone, Phenyl-2-butanol, and 3-Methyl-1-phenyl-
2-butanol by Rabbit Liver Preparations. R. CRAIG KAMMERER, ARTHUR K.
CHO, AND JOHN JONSSON ........................................................ 396

Reductive Metabolism of Nitrofurantoin in the Rat. MICHEL B. AUFRÈRE, BETTY-
ANN HOENER, AND MARY VORE ............................................... 403

Differential Effects of Walker 256 Carcinosarcoma Cells Growing Subcutaneously,
Intramuscularly, or Intraperitoneally on Hepatic Microsomal Mixed-function
Oxygenase Activity. N. E. SLADEK, B. E. DOMEYER, R. L. MERRIMAN, AND G.
T. BROPHY .................................................................................. 412

Continued on page 2

Published bi-monthly by Williams & Wilkins Co., 428 E. Preston St., Baltimore, Md. 21202,
U.S.A. Subscription price $40.00 per year individuals, $50.00 institutions, single issue $7.00.

Copyright © 1978 by the American Society for Pharmacology and Experimental Therapeutics
Second class postage paid at Baltimore, Maryland, and at additional mailing offices

Made in the United States of America
### CONTENTS

3,4,5-Trimethoxybenzoic Acid, a New Mescaline Metabolite in Humans. **LOTHAR DEMISCH, PETER KACZMARCZYK, AND NIKOLAUS SEILER** .............................. 507
Species Differences in the Disposition and Metabolism of 6,11-Dihydro-11-oxodibenzo[b]oxepin-2-acetic acid (Isoxepac) in Rat, Rabbit, Dog, Rhesus Monkey, and Man. **H. P. A. ILLING AND J. M. FROMSON** ................................. 510
Biotransformation of Methyl 5-Cyclopropylcarbonyl-2-benzimidazolecarbamate (Ciclobendazole) in Rats and Dogs. **B. C. MAYO, R. R. BRODIE, L. F. CHASSEAUD, AND D. R. HAWKINS** .............................. 518
Comparative Physiological Disposition of Ellipticine in Several Animal Species After Intravenous Administration. **MARJORY CHADWICK, DENISE M. SILVEIRA, BARBARA B. PLATZ, AND DENISE HAYES** .............................. 528
Characterization of the Metabolites of Ellipticine in Rat Bile. **ALAN R. BRANFMAN, ROBERT J. BRUNI, VERNON N. REINHOLD, DENISE M. SILVEIRA, MARJORY CHADWICK, AND DAVID W. YESAIR** .............................. 542
Metabolism of Aniline in Rats, Pigs, and Sheep. **J. KAO, J. FAULKNER, AND J. W. BRIDGES** .............................. 549
Factors Affecting the Metabolism of [14C]Acetylhydrazine in Rats. **JAMES M. WRIGHT AND JOHN A. TIMBRELL** .............................. 561
Complications in the Estimation of Hepatic Blood Flow *In Vivo* by Pharmacokinetic Parameters: The Area Under the Curve after the Concomitant Intravenous and Intraperitoneal (or Intraportal) Administration of Acetaminophen in the Rat. **K. SANDY PANG AND JAMES R. GILLETTE** .............................. 567

*Continued on page 2*
The Postnatal Development of Microsomal Epoxide Hydrase, Cytosolic Glutathione S-Transferase, and Mitochondrial and Microsomal Cytochrome P-450 in Adrenals and Ovaries of Female Rats. HASAN MUKHTAR, RICHARD M. PHILPOT, AND JOHN R. BEND ........................................... 577
Structural Requirements for the Accumulation of Chlorinated Biphenyl Metabolites in the Fetal Rat Intestine. G. W. LUCIER, O. S. McDaniel, C. M. SCHILLER, AND H. B. MATTHEWS ........................................... 584
Metabolism of Methimazole by Rat Liver Cytochrome P-450-containing Monoxygenases. PHILIP W. LEE AND ROBERT A. NEAL ........................................... 591
Partial Purification and Characterization of Dihydropyrimidinases from Calf and Rat Liver. JAMES H. MAGUIRE AND KENNETH H. DUDLEY ........................................... 601
Current Literature ......................................................... 606
Announcements ......................................................... 609, 610
Correspondence. Assay of Hepatic Microsomal Hexobarbital Hydroxylase. DAVID KUPFER ......................................................... 610

DRUG METABOLISM AND DISPOSITION:
the biological fate of chemicals

Information for Subscribers

Published bimonthly, one volume per year.

Annual Subscription Rates — U. S. A. AND POSSESSIONS: personal, $40.00; institutional, $50.00. FOREIGN: personal, $43.00; institutional, $53.00. Institutional (multiple-reader) rate applies to libraries, schools, hospitals, group practices, and federal, commercial, and private institutions and organizations.

Single issues when available, $7.00 in U.S.A., $7.50 elsewhere. Vol. 1, No. 1, the Symposium on Microsomes and Drug Oxidations is not available as a single issue of the journal. It may be purchased as a bound book for $30.00.

Change of address: Publisher must be notified 60 days in advance.

New subscriptions and renewals are entered to begin with the January issue.

Subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Correspondence on business matters should be addressed to the publisher.

Reprints of individual articles are available only from authors.

Microfilm: For availability, inquire of The Williams & Wilkins Company.

Instructions to Authors are published in the January-February issue of each volume, or a copy may be obtained from the Editor, Dr. Kenneth C. Leibman, Box J-267, College of Medicine, University of Florida, Gainesville, Fla. 32610.

THE WILLIAMS & WILKINS COMPANY
428 East Preston Street Baltimore, Maryland 21202 U. S. A.
DRUG METABOLISM AND DISPOSITION:

the biological fate of chemicals

Kenneth C. Leibman, Editor

Editorial Advisory Board

M. W. Anders
John E. Baer
John R. Bend
Frank J. Bullock
Arthur K. Cho
Dominick Cinti
Edward Cone
C. E. Cook
Jerome Edelson

Henry M. Fales
Alberto Frigerio
James M. Fujimoto
Theodore E. Gram
Ernest Hodgson
Howard B. Hucker
David Kupfer
Walter G. Levine
Franz Oesch

Donald Perrier
Russell A. Prough
Robert J. Roberts
Morton A. Schwartz
Don W. Shoeman
Bitten Stripp
Samson Symbrowicz
Elliot S. Vesell
William J. Waddell

Board of Publications Trustees

Norman Weiner, Chairman
Daniel L. Azarnoff
Eva King Killam

Norman Kirschner
Kenneth C. Leibman
Gilbert J. Mannering

Walter Modell
Paul L. Munson
Irwin M. Weiner

Executive Officer
Houston Baker

CONTENTS

Conjugation of Various Drugs in Isolated Hepatocytes. Bo Andersson, Margareta Berggren, and Peter Moldeus 611

Stereoselectivity in the Metabolism of the Enantiomers of Cyclophosphamide in Mice, Rats, and Rabbits. Peter J. Cox, Peter B. Farmer, Michael Jarmann, Ryszard W. Kinas, and Wojciech J. Stec 617

α-Methyldopamine, a Key Intermediate in the Metabolic Disposition of 3,4-Methylenedioxyamphetamine in Vivo in Dog and Monkey. K. K. Midha, J. W. Hubbard, K. Bailey, and J. K. Cooper 623

Rabbit Hepatic Microsomal O-Demethylation of Chlorotrianisene. Peter C. Ruenitz 631

Pharmacokinetics of Sulfadimidine in Normal and Diarrheic Calves. Roman Lapka, Zdena Urbanová, Božidar Kobylka, Helena Rašková, Jiří Vaněček, and Ladislav Polák 637


Biotransformation of Prochiral 2-Phenyl-1,3-di(4-pyridyl)-2-propanol to a Chiral N-Oxide Metabolite. Morton A. Schwartz, Thomas H. Williams, Stanley J. Kolis, Edward Postma, and Gino J. Sasso 647

The Absorption, Distribution, and Excretion in Mice of the Antimalarial Mefloquine, erythro-2,8-Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanol Hydrochloride. Robert S. Rozman, Nicholas A. Molek, and Robert Koby 654


Continued on page 2