BIOANALYSIS OF
DRUGS AND METABOLITES,
Especially Anti-Inflammatory
and Cardiovascular

METHODOLOGICAL SURVEYS IN BIOCHEMISTRY AND ANALYSIS

Series Editor: Eric Reid

Guildford Academic Associates
72 The Chase
Guildford GU2 5UL, United Kingdom

The series is divided into Subseries A: Analysis, and B: Biochemistry
Enquiries concerning Volumes 1–11 should be sent to the above address.

Volumes 1–10 edited by Eric Reid

Volume 1 (B): Separations with Zonal Rotors

Volume 2 (B): Preparative Techniques

Volume 3 (B): Advances with Zonal Rotors

Volume 4 (B): Subcellular Studies

Volume 5 (A): Assay of Drugs and Other Trace Compounds in Biological Fluids

Volume 6 (B): Membranous Elements and Movement of Molecules

Volume 7 (A): Blood Drugs and Other Analytical Challenges

Volume 8 (B): Cell Populations

Volume 9 (B): Plant Organelles

Volume 10 (A): Trace-Organic Sample Handling

Volume 11 (B): Cancer-Cell Organelles

Edited by Eric Reid, G. M. W. Cook, and D. J. Morré

Volume 12 (A): Drug Metabolite Isolation and Determination

Edited by Eric Reid and J. P. Leppard

(includes a cumulative compound-type index)

Volume 13 (B): Investigation of Membrane-Located Receptors

Edited by Eric Reid, G. M. W. Cook, and D. J. Morré

Volume 14 (A): Drug Determination in Therapeutic and Forensic Contexts

Edited by Eric Reid and Ian D. Wilson

Volume 15 (B): Investigation and Exploitation of Antibody Combining Sites

Edited by Eric Reid, G. M. W. Cook, and D. J. Morré

Volume 16 (A): Bioactive Analytes, Including CNS Drugs, Peptides, and Enantiomers

Edited by Eric Reid, Bryan Scales, and Ian D. Wilson

Volume 17 (B): Cells, Membranes, and Disease, Including Renal

Edited by Eric Reid, G. M. W. Cook, and J. P. Luzio

Volume 18 (A): Bioanalysis of Drugs and Metabolites, Especially Anti-Inflammatory
and Cardiovascular

Edited by Eric Reid, J. D. Robinson, and Ian D. Wilson

A Continuation Order Plan is available for this series. A continuation order will bring delivery of each new volume immediately upon publication. Volumes are billed only upon actual shipment. For further information please contact the publisher.

BIOANALYSIS OF DRUGS AND METABOLITES, Especially Anti-Inflammatory and Cardiovascular

Edited by

Eric Reid

Guildford Academic Associates
Guildford, United Kingdom

J. D. Robinson

Hoechst UK
Milton Keynes, United Kingdom

and

Ian D. Wilson

ICI Pharmaceuticals Division
Macclesfield, United Kingdom

Springer Science+Business Media, LLC

Library of Congress Cataloging in Publication Data

International Bioanalytical Forum (7th: 1987: Guildford, Surrey)

Bioanalysis of drugs and metabolites, especially anti-inflammatory and cardiovascular.

(Methodological surveys in biochemistry and analysis; v. 18 (A))

"Proceedings of the Seventh International Bioanalytical Forum . . . held September 8–11, 1987, in Guildford, United Kingdom"—T.p. verso.

Includes bibliographies and indexes.

1. Anti-inflammatory agents—Analysis—Congresses. 2. Cardiovascular agents—Analysis—Congresses. 3. Arachidic acid—Derivatives—Analysis—Congresses. 4. High performance liquid chromatography—Congresses. 5. Blood—Analysis—Congresses. 6. Chemistry, Clinical—Technique—Congresses. I. Reid, Eric, date. II. Robinson, J. D. III. Wilson, Ian D. IV. Title. V. Series: Methodological surveys in biochemistry and analysis; v. 18. [DNLM: 1. Anti-Inflammatory Agents—analysis—congresses. 2. Cardiovascular Agents—analysis—congresses. 3. Chromatography, Gas—methods—congresses. 4. Chromatography, High Pressure Liquid—methods—congresses. 5. Drugs—analysis—congresses. 6. Eicosanoic Acids—metabolism—congresses. W1 ME9612NT v.18 / QV 25 I61 1987b]

RB56.5.A56I68 1987

615'.77

88-22412

ISBN 978-1-4757-9426-7

ISBN 978-1-4757-9424-3 (eBook)

DOI 10.1007/978-1-4757-9424-3

Based on proceedings of the Seventh International Bioanalytical Forum
entitled Bioanalysis of Drugs and Metabolites, Especially
Anti-Inflammatory and Cardiovascular, held September 8–11, 1987,
in Guildford, United Kingdom

© Springer Science+Business Media New York 1988
Originally published by Plenum Press, New York in 1988
Softcover reprint of the hardcover 1st edition 1988

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted
in any form or by any means, electronic, mechanical, photocopying, microfilming,
recording, or otherwise, without written permission from the Publisher

Senior Editor's Preface

Whereas the 'bioactive analytes' coverage of Vol. 16 included endogenous peptides, the present book features eicosanoids, besides drugs. Awareness of the therapeutic potential of such agents was evidenced by the keen participation of company staff in the Bioanalytical Forum (September 1987) which gave rise to this book.

The Forum series, whilst still focused on blood-level determinations, has shown trends which mostly match changes in the analytical scene. Reflecting the tendency of newer drugs to be even more potent than the CNS-active drugs that featured in Vol. 16, analytical concern is increasingly with ng/ml or even pg/ml levels. Yet reliable measurement is still needed at the $\mu\text{g/ml}$ level too, notably in re-investigating old-established drugs for pharmacokinetic properties indicated in the text. Both Vol. 16 and the present book manifest the increasing attention to drug chirality.

Metabolite investigation is increasingly aided by NMR (see 'Notes' in Sect. #F). For bioanalysis in general, chromatographic separations have played a cardinal role since the 1970's. Capillary GC has at last burgeoned in the drug-assay area, somewhat reducing the dominance gained by HPLC (for which fluorescence detection is gaining ground). Analysts increasingly seek instrumentation that may be of daunting cost even if the aim is subtlety rather automation. For sample preparation, solvent extraction still serves skilled practitioners as a powerful tool, although largely superseded by 'cartridge' extraction notwithstanding evident pitfalls. In respect of publishing assay methodology, our policy that method-descriptions must include the 'rationale' no longer needs strong advocacy; moreover, it is no longer rare for analysts in pharmaceutical companies to publish their methods. Now an analyst faced with setting up a method may be daunted by the swollen literature. For the analyte in question, the customary **Analyte Index** in this book (or earlier volumes) may list the actual compound, or chemically kindred compounds with analytical pertinence. The Table on p. 218 augments the coverage for two therapeutic classes that feature in this book, viz. cardiovascular and anti-inflammatory drugs. (Eicosanoids may likewise be anti-inflammatory, although some may be pro-inflammatory.)

There has been a trend, noted with relief by the Editors, towards better compilation of publication texts. Yet some texts have undergone extensive editing, acceptable to the authors. Erratic alternation of the terms 'serum' and 'plasma', and of the synonymous terms 'precision' and 'reproducibility', caused some trouble in the editing,

as did non-appreciation that % values for bought-in solutions (notably ammonia) may be on a weight basis, not made evident by the manufacturer. Notwithstanding the shortcomings or lateness of some texts, authors are thanked for compiling them amidst other pressures. Elsevier and the American Chemical Society are also thanked, for Figures now reproduced with source acknowledgement.

This Editor has generally respected authors' phrasing, whilst shuddering when the term 'incubate' is encountered in a 0° context. He remains a 'diehard' in certain respects, notably in favouring 'M' rather than 'mol/l', and a wt./ml basis for drug concentrations in test samples; he regards 'mmol/l' as a fatuous fashion. Concerning infelicitous **abbreviations**, a distinction is made between electron-capture (detector context; 'ECD') and electrochemical ('EC', never 'ECD'); the hallowed GC term 'FID' means free induction decay to NMR practitioners, who may pardon the term 'Fid' as introduced editorially. The convention for '°C' throughout the book is '°'.

Undefined but well-known abbreviations include GC, HPLC and TLC. MS (mass spectrometry), NPD (nitrogen-phosphorus detector), t_r (retention time) and RIA (radioimmunoassay) are usually defined in the article concerned, as are the HPLC modes NP (normal-/straight-phase) and RP (reversed-phase; C-18 and ODS are synonymous), and i.s. denoting internal standard, about which E. Reid made a plea in Vol. 7 (1978; #A-6).- "To ascertain what a particular author means by the term 'internal standard', one often has to scrutinize the small print in the paper. When taken through the full procedure, it allows for any idiosyncrasy (wobble) in the particular sample." Happily the latter usage now prevails.

Support for the Forum, much appreciated, came from U.K. pharmaceutical companies: Beechams, Glaxo, ICI and Smith Kline & French.

*Guildford Academic Associates
72 The Chase, Guildford
Surrey, GU2 5UL, U.K.*

ERIC REID
12 April 1988

Contents

The 'NOTES & COMMENTS' ('NC' items) at the end of each Section include comments (listed on each 'NC' title page) made at the Forum on which the book is based, along with some supplementary material.

	Senior Editor's Preface , with an abbreviations list	v
	List of Authors	xii
#A	EICOSANOIDS AND RELATED ANALYTES (<i>pathways: p. 63</i>)	1
#A-1	The use of HPLC in studies of the stereoselective metabolism of prostaglandin D ₂ - CLIVE ROBINSON	3
#A-2	Analysis of eicosanoids by GC-MS/MS - J.C. FRÖLICH, K-H. MARX, H. BIPPI, J. FAULER, B. ROSENKRANZ & U. FÖRSTERMANN	15
#A-3	Quantitative determination of several prostaglandins and thromboxane B ₂ in the isolated perfused rat brain CLAUDIA WEBER, KLAUS BELSNER, BARBARA OSIKOWSKA-EVERS, INGE LUHMANN & MICHAEL HÖLLER	23
#A-4	Analytical methods for [³ H]-enisoprost, an anti-secretory PGE ₁ analogue, and its metabolites - L.A. ALLAN, A.J. HAWKINS, J. FIRTH, R.D. BROWNSILL, J.A. STEINER & C.W. VOSE	29
#A-5	Identification of a new metabolite of leukotriene B ₄ by RP-HPLC and GC-MS analysis - JOACHIM FAULER, KARL-HEINZ MARX & VOLKHARD KAEVER	37
#A-6	Radioimmunoassay of eicosanoids: its application in the development of anti-inflammatory and analgesic drugs - FRANK CAREY, DUNCAN HAWORTH & ROBERT A. FORDER	43
#NC(A)	NOTES and COMMENTS relating to the foregoing topics	51
	<i>including Notes on:</i>	
#NC(A)-1	Developing methods for a thromboxane synthetase inhibitor and a prostacyclin analogue in biological fluids: problems and some solutions - M.V. DOIG & R.A. CLARE	53
#NC(A)-2	The stereochemical analysis of monohydroxyfatty acids, particularly 12-hydroxy-5,8,10,14-eicosatetraenoic acid - P.M. WOOLLARD	57

#B	ANTI-INFLAMMATORY DRUGS	65
#B-1	Analysis of the actions of anti-inflammatory drugs, with particular reference to effects on interleukins and leucocytes - K.D. RAINSFORD	67
#B-2	Immunoassay of beclomethasone 17,21-dipropionate and metabolites - W.N. JENNER & D.J. KIRKHAM	77
#B-3	HPLC analysis of anti-inflammatory agents (non-steroidal and steroidal) - J.C. McELNAY	87
#B-4	Analytical approaches adopted during the development of flurbiprofen - A. BYE, W. ADAMS & D. KAISER	97
#B-5	The assay of diclofenac and metabolites: a review - P.H. DEGEN	107
#B-6	Enantiomeric analysis of 2-phenylpropionic acid NSAID's in biological fluids by HPLC - A.J. HUTT & J. CALDWELL ..	115
#NC(B)	NOTES AND COMMENTS relating to the foregoing topics including a Note on:	127
#NC(B)-1	The determination of suprofen in biological fluids - C.J. DYDE, M.F. BARKWORTH & K.D. REHM	129
#C	ACE INHIBITORS AND CALCIUM ANTAGONISTS	133
#C-1	Analysis of angiotensin-converting enzyme inhibitors in biological fluids - A. RAKHIT	135
#C-2	The analysis of ACE inhibitors by immunoassay - J.D. ROBINSON & S. LEWIS	143
#C-3	The use of stable-isotope methodology in pharmacokinetic studies involving flunarizine - ROBERT WOESTENBORGH, PHILIP TIMMERMAN, ACHIEL VAN PEER & JOS HEYKANTS	149
#NC(C)	NOTES and COMMENTS relating to the foregoing topics including Notes on:	157
#NC(C)-1	Assay problems with nifedipine - P.S.B. MINTY & F.A. TUCKER	159
#NC(C)-2	Detection of the metabolites of some dihydropyridine-type calcium antagonists in urine and plasma - K-D. RÄMSCH & D. SCHERLING	163
#D	VARIOUS CARDIOVASCULAR DRUGS	167
#D-1	The study of chiral cardiovascular drugs: analytical approaches and some pharmacological consequences - RICHARD L. LALONDE, MICHAEL B. BOTTORFF & IRVING W. WAINER ..	169
#D-2	Development of a chiral capillary GC method for the quantitation of the enantiomers of cromakalim in biological fluids - B.E. DAVIES	179

#D-3	The determination of amiodarone and desethylamiodarone by HPLC - B.J. STARKEY, A.J.E. GREEN & G.P. MOULD	185
#D-4	The assay of hydralazine: a review - P.H. DEGEN	193
#D-5	Approaches to the analysis of two cardiovascular drugs in plasma - R.D. McDOWALL, J.C. PEARCE, G.S. MURKITT, J.A. JELLY, W.J. LEAVENS, K.A. FERNANDES & R.M. LEE ...	201
#NC(D)	NOTES and COMMENTS relating to the foregoing topics ...	207
	<i>including Notes on:</i>	
#NC(D)-1	Quantitative analysis of flesinoxan in plasma and urine at the pg/ml level using GC-ECD - M.P. VAN BERKEL, H. DE BREE & K. SIERAT	209
#NC(D)-2	Assay of nitroglycerin and metabolites by capillary GC - STEPHEN H. CURRY & HAE-RYUN KWON	213
#NC(D)-3	HPLC-fluorescence method for the determination of the new β_1 -adrenoreceptor blocking agent nebivolol in human plasma - ROBERT WOESTENBORGH, LUC EMBRECHTS & JOS HEYKANTS	215
	<i>Table of additional assay procedures (#B & #C besides #D)</i>	218
#E	VARIOUS DRUGS AND SEPARATORY APPROACHES	223
#E-1	The routine use, and column-stability implications, of several column-switching HPLC methods for determining drugs in plasma and urine - J.B. LECAILLON, C. SOUPPART, J.P. DUBOIS & A. DELACROIX	225
#E-2	Micellar liquid chromatography - JOHN G. DORSEY	235
#E-3	Determination of nefopam and its desmethyl metabolite in biological fluids by paired-ion RP-HPLC - A.J. WOODWARD, P.A. LEWIS, J. MADDOCK & D. DONNELL	245
#E-4	An assay for idaverine in plasma and urine at picogram level - D.J.K. VAN DER STEL, O.A.M. BROCKHOFF & H. DE BREE	251
#E-5	Pitfalls in the enantioselective analysis of chiral drugs - JOHN CALDWELL, JOHN F. DARBYSHIRE, STEPHEN M. WINTER & ANDREW J. HUTT	257
#NC(E)	NOTES and COMMENTS relating to the foregoing topics ...	263
	<i>including Notes on:</i>	
#NC(E)-1	Chiral differences in the disposition of the quaternary anticholinergic drug oxyphenonium bromide - KARLA G. FEITSMA, BEN F.H. DRENT, ROKUS A. DE ZEEUW & DIRK K.F. MEIJER	265
#NC(E)-2	Quantitation of danazol in serum using HPLC column switching with UV detection - H.M. HILL & K. SELINGER ..	269

#NC(E)-3	Simultaneous determination of etretinate, acitretin and 13- <i>cis</i> -acitretin in plasma by gradient-HPLC using automated column switching - R. WYSS & F. BUCHELI	271
#NC(E)-4	Analytical consequences of potent drugs - H. DE BREE	273
#NC(E)-5	Optimization of capillary GC conditions for the analysis of psychotropic drugs at subnanogram concentrations in plasma - H.M. HILL, D. LESSARD & L. LETARTE	277
#NC(E)-6	Comparison of an enzyme method with a capillary GC method for red blood cell sorbitol assay - R.P.B. PASSAS & D. STEVENSON	279
#NC(E)-7	The stability of antineoplastic vinca alkaloids in plasma and urine - D.E.M.M. VENDRIG, A. MEKKING, J. TEEUWSEN & J.J.M. HOLTHUIS	283
#NC(E)-8	Solid-phase extraction: personal experiences - ROBIN WHELPTON & PETER R. HURST	289
#NC(E)-9	The use of secondary ionic interactions for the solid-phase extraction of some ' β -blocking' drugs on C-18 bonded silica - R.J. RUANE, I.D. WILSON & G. P. TOMKINSON	295
#NC(E)-10	Application of solid-phase extraction techniques to the analysis of basic and acidic drugs in biological fluids - H.M. HILL, L. DEHELEAN & B.A. BAILEY	299
#NC(E)-11	The determination of drug protein binding by HPLC using a chemically bonded bovine-albumin stationary phase - N. LAMMERS, H. DE BREE, C.P. GROEN, H.M. RUIJTEN & B.J. DE JONG	301
#NC(E)-12	Retention mechanisms in reversed-phase HPLC - JOHN G. DORSEY	305
#F	DETECTION, IDENTIFICATION AND INSTRUMENTATION	311
#F-1	Advances in instrumentalized TLC - I.D. WILSON	313
#F-2	The use of fluorescence and chemiluminescence techniques for sensitive and selective detection in HPLC - U.A.TH. BRINKMAN, G.J. DE JONG & C. GOOIJER	321
#F-3	LC-MS and LC-MS-MS for biomedical analyses - A.P. BRUINS	339
#F-4	The structure elucidation of drug metabolites using thermospray LC-MS and LC-MS-MS - T.J.A. BLAKE & I.G. BEATTIE	353
#NC(F)	NOTES and COMMENTS relating to the foregoing topics including Notes on:	361
#NC(F)-1	An approach to metabolite sample preparation for mass spectrometry to aid the spectroscopist - R.D. BROWNSILL, A. GRAY & C.W. VOSE	363

#NC(F)-2	Application of NMR and mass spectrometry to the study of drug hydroxylation - C.M. WALLS, A. GRAY, R.D. BROWNSILL & C.W. VOSE	367
#NC(F)-3	Urinanalysis by ¹ H NMR: application to cephaloridine-treated rats - R. PICKFORD, I.K. SMITH & I.D. WILSON	371
#NC(F)-4	Proton NMR studies on the metabolism and biochemical effects of hydrazine <i>in vivo</i> - S.M. SANINS, J.A. TIMBRELL, C. ELCOMBE & J.K. NICHOLSON	375
#NC(F)-5	¹⁹ F NMR studies of the metabolism of trifluoromethyl-aniline - K.E. WADE, J. TROKE, C.M. MACDONALD, I.D. WILSON & J.K. NICHOLSON	383
#NC(F)-6	NMR as an aid in studying <i>N</i> -alkylformamides and metabolites - MICHAEL D. THREADGILL & ANDREAS GESCHER	389
#NC(F)-7	Flexible <i>versus</i> dedicated automation - J.C. PEARCE & R.D. McDOWALL	393
#NC(F)-8	Design of and first experiments with a bioluminescence detector for HPLC - H.M. RUIJTEN, B.E. TIMMERMAN & H. DE BREE	397
#NC(F)-9	A system approach to immunoassay using enhanced luminescence - M.R. SUMMERS, K. MASHITER, J.C. EDWARDS, J.K. MARTIN, G.P. DAVIDSON & J. HOLIAN	401
ANALYTE INDEX		405
GENERAL INDEX		410

Groupings of 'Notes' on particular themes:

Column switching (cf. #E-1): #NC(E)-2 & -3; also p. 308

Solid-phase sample processing: #NC(E)-8 to -11; also p. 308

NMR approaches: #NC(F)-2 to -6

List of Authors

Primary author

M.F. Barkworth - p. 129
 iphar Inst, Höhenkirchen-
 Siegertsbrunn, W. Germany

T.J.A. Blake - pp. 353-359
 Smith Kline & French Research,
 Welwyn, Herts.

U.A.Th. Brinkman - pp. 321-338
 Free Univ., Amsterdam

A.P. Bruins - pp. 339-351
 Rijksuniversiteit, Groningen

A. Bye - pp. 97-105
 Upjohn Research Labs., Crawley

J. Caldwell - pp. 257-261 (& see Hutt)
 St. Mary's Hosp. Med. Sch., London W2

F. Carey - pp. 43-50
 ICI Pharms., Alderley Park

S.H. Curry - pp. 213-214
 Coll. of Pharmacy, Univ. of Florida,
 Gainesville, FL

B.E. Davies - pp. 179-183
 Beecham Pharms. Medicinal Res. Cent.,
 Harlow, Essex

H. de Bree (& see Ruijten) - pp.
 (i) 209-212; (ii) 251-255;
 (iii) 273-276; (iv) 301-303
 Duphar BV, Weesp, The Netherlands

P.H. Degen - pp. (i) 107-114
 (ii) 193-200
 Ciba-Geigy, Basle

M.V. Doig - pp. 53-55
 Wellcome Res. Labs., Beckenham

J.G. Dorsey - pp. (i) 235-244;
 (ii) 305-306
 Univ. of Florida, Gainesville, FL

Co-authors, with relevant name to be consulted in left column

W. Adams - Bye

L.A. Allan - Vose (i)

B.A. Bailey - Hill (iii)

I.G. Beattie - Blake

K. Belsner - Höller

H. Bippi - Frölich

M.B. Bottorff - Wainer

O.A.M. Brockhoff - de Bree (ii)

R.D. Brownsill - Vose (i), (ii)
 & (iii)

F. Bucheli - Wyss

R.A. Clare - Doig

J.F. Darbyshire - Caldwell

G.P. Davidson - Caldwell

L. Dehelean - Hill (iii)

B.J. de Jong - de Bree (iv)

G.J. de Jong - Brinkman

A. DeLacroix - Lecaillon

R.A. de Zeeuw - Feitsma

D. Donnell - Woodward

B.F.H. Drenth - Feitsma

J.P. Dubois - Lecaillon

C.J. Dyde - Barkworth

J.C. Edwards - Summers

C. Elcombe - Nicholson (1)

L. Embrechts - Woestenborghs
 (ii)

Primary author

J. Fauler (& see Frölich) -
pp. 35-39
Medical Sch., Hannover, W. Germany

K.G. Feitsma - pp. 265-268
Rijksuniversiteit, Groningen

J.C. Frölich - pp. 15-21
Medical Sch., Hannover, W. Germany

H.M. Hill - pp. (i) 269; (ii) 277-278;
(iii) 299-300
Bio-Research Labs., Senneville, Quebec

M. Höller - pp. 23-27
Janssen Res. Foundation,
Neuss, W. Germany

A.J. Hutt (& see Caldwell) -
pp. 115-125
Brighton Polytechnic, Brighton

W.N. Jenner - pp. 77-86
Glaxo Group Res., Ware, Herts.

J.B. Lecaillon - pp. 225-233
Ciba-Geigy Pharm. Res. Centre,
Rueil-Malmaison, France

R.D. McDowall - pp. (i) 201-206;
(ii) 393-396
Smith Kline & French Research,
Welwyn, Herts.

J.C. McElnay - pp. 87-95
Queen's Univ., Belfast

P.S.B. Minty - pp. 159-161
Charing Cross & Westminster Med.
Sch., London W6

G.P. Mould - pp. 185-191
St. Luke's Hosp., Guildford

J.K. Nicholson - pp. (i) 375-381;
(ii) 383-388
Birkbeck Coll., London WC1

K.D. Rainsford - pp. 67-74
Strangeways Res. Lab., Cambridge

A. Rakhit - pp. 135-142
Ciba-Geigy Pharms. Divn., Summit, NJ

*Co-authors, with relevant name
to be consulted in left column*

K.A. Fernandes - McDowall (i)

J. Firth - Vose (i)

R.A. Forder - Carey

U. Förstermann - Frölich

A. Gescher - Threadgill

C. Gooijer - Brinkman

A. Gray - Vose (ii) & (iii)

A.J.E. Green - Mould

C.P. Groen - de Bree (iv)

A.J. Hawkins - Vose (i)

D. Haworth - Carey

J. Heykants - Woestenborghs
(i) & (ii)

J. Holian - Summers

J.J.M. Holthuis - Vendrig

P.R. Hurst - Whelpton

J.A. Jelly - McDowall (i)

V. Kaever - Fauler

D. Kaiser - Bye

D.J. Kirkham - Jenner

H-R. Kwon - Curry

R.L. Lalonde - Wainer

N. Lammers - de Bree (iv)

W.J. Leavens - McDowall (i)

R.M. Lee - McDowall (i)

D. Lessard - Hill (ii)

L. Letarte - Hill (ii)

P.A. Lewis - Woodward

S. Lewis - J.D. Robinson

I. Luhmann - Höller

C.M. Macdonald - Nicholson
(ii)

J. Maddock - Woodward

J.K. Martin - Summers

K-H. Marx - Frölich & Fauler

K. Mashiter - Summers

D.K.F. Meijer - Feitsma

A. Mekking - Vendrig

G.S. Murkitt - McDowall (i)

B. Osikowska-Evers - Höller

R.P.B. Passas - Stevenson

J.C. Pearce - McDowall (i) & (ii)

R. Pickford - Wilson (iii)

Primary author

K-D. Rämisch - pp. 163-164
Bayer Inst. f. Klin. Pharmacologie,
Wuppertal, W. Germany

C. Robinson - pp. 3-13
Univ. of Southampton

J.D. Robinson - pp. 143-148
Hoechst UK, Walton Milton Keynes

H.M. Ruijten [& see de Bree (iv)]
- pp. 397-399
Duphar, Weesp, The Netherlands

D. Stevenson - pp. 279-281
Univ. of Surrey, Guildford

M.R. Summers - pp. 401-402
Amersham Internatl., Amersham, Bucks.

M.D. Threadgill - pp. 389-392
Univ. of Aston, Birmingham

D.E.M.M. Vendrig - pp. 283-288
Rijksuniversiteit, Utrecht

C.W. Vose - pp. (i) 29-35;
(ii) 363-365; (iii) 367-369
Hoechst UK, Walton Milton Keynes*

I.W. Wainer - pp. 169-177
St. Jude Children's Res. Hosp.,
Memphis, TN

R. Whelpton - pp. 289-294
London Hosp. Med. Coll., London E1

I.D. Wilson - pp. (i) 295-298;
(ii) 313-320 (iii) 371-374; (iv) 383-388.
ICI Pharmls., Alderley Park

R. Woestenborghs - pp. (i) 149-155;
(ii) 215-216
Janssen Res. Foundn., Beerse, Belgium

A.J. Woodward - pp. 245-250
Simbec Res., Merthyr Tydfil, Wales

P.M. Woollard - pp. 57-58
Wellcome Res. Labs., Beckenham†

R. Wyss - pp. 271-272
Hoffmann-La Roche, Basle

*Co-authors, with relevant name
to be consulted in left column*

K.D. Rehm - Barkworth
B. Rosenkranz - Frölich
R.J. Ruane - Wilson (i)
S.M. Sanins - Nicholson (i)
D. Scherling - Rämisch
K. Selinger - Hill (i)
K. Sierat - de Bree (i)
I.K. Smith - Wilson (iii)
C. Souppart - Lecaillon

J.A. Steiner - Vose (i)

T. Teeuwssen - Vendrig
J.A. Timbrell - Nicholson (i)
B.E. Timmerman - Ruijten
P. Timmerman - Woestenborghs
(i)
G.P. Tomkinson - Wilson (i)
J. Troke - Nicholson (ii)
F.A. Tucker - Minty
M.P. van Berkel - de Bree
(i)
D.J.K. van der Stel - de
Bree (ii)
A. van Peer - Woestenborghs
(i)

K.E. Wade - Nicholson (ii)
C.M. Walls - Vose (iii)
C. Weber - Höller
S.M. Winter - Caldwell

Former 'affiliations': *G.D. Searle, High Wycombe; †Inst. of Dermatology