

# THE EICOSANOIDS

Edited by  
**Peter Curtis-Prior**

 WILEY



# **The Eicosanoids**

---



---

# The Eicosanoids

---

*Edited by*

**Peter Curtis-Prior**

*Cambridge Research Institute, Cambridge*

*and*

*Anglia Polytechnic University, UK*



John Wiley & Sons, Ltd

Copyright © 2004      John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester,  
West Sussex PO19 8SQ, England

Telephone (+44) 1243 779777

E-mail (for orders and customer service enquiries): [cs-books@wiley.co.uk](mailto:cs-books@wiley.co.uk)  
Visit our Home Page on [www.wileyeurope.com](http://www.wileyeurope.com) or [www.wiley.com](http://www.wiley.com)

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to [permreq@wiley.co.uk](mailto:permreq@wiley.co.uk), or faxed to (+44) 1243 770620.

This publication is designed to provide accurate and authoritative information with regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

#### ***Other Wiley Editorial Offices***

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 33 Park Road, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Canada Ltd, 22 Worcester Road, Etobicoke, Ontario, Canada M9W 1L1

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

#### ***British Library Cataloguing in Publication Data***

A catalogue record for this book is available from the British Library

ISBN 0 471 48984 0

Typeset in 9/10pt Times by Dobbie Typesetting Ltd, Tavistock, Devon

Printed and bound in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire

This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

# Contents

---

List of Contributors vii

Preface xi

Preface from *Prostaglandins* xiii

Acknowledgements xvii

Foreword xix

## SECTION ONE BIOSYNTHESIS AND METABOLISM 1

- 1 Perspectives on the Biosynthesis and Metabolism of Eicosanoids 3  
*Robert C. Murphy, Rebecca C. Bowers, Jennifer Dickinson and Karin Zemski Berry*
- 2 Control of Eicosanoid Production by Cellular and Secreted Phospholipase A<sub>2</sub> 17  
*Marise Andreani, Jean-Luc Olivier and Gilbert Béréziat*
- 3 Mechanisms of PGH Synthase-1 (COX-1) Activity and Role of Radical States 29  
*Carol Deby and Ginette Deby-Dupont*
- 4 Regulation and Function of Prostaglandin Synthase-2/Cyclooxygenase II 43  
*Harvey R. Herschman*
- 5 Mammalian Lipoxygenases 53  
*Shozo Yamamoto, Hiroshi Suzuki, Natsuo Ueda, Yoshitaka Takahashi and Tanihiro Yoshimoto*
- 6 Biosynthesis and Biological Effects of 5-oxo-EET and Other Oxoeicosatetraenoic Acids 61  
*William S. Powell*
- 7 Synthetic Eicosanoids 69  
*Norrie. H. Wilson*

## SECTION TWO ANALYTICAL METHODS 95

- 8 Perspectives of Analytical Methods for Eicosanoids 97  
*Jay Y. Westcott and Angelo Sala*
- 9 Enzyme Immunoassays of Metabolites and Enzymes Using Acetylcholinesterase as Label 103  
*Christophe Créminon and The Late Jacques Maclouf*
- 10 Bioassay of Eicosanoids 111  
*Robert L. Jones*
- 11 Gas Chromatography and Mass Spectrometry in Eicosanoid Analysis 117  
*Michinao Mizugaki, Takanori Hishinuma, Naoto Suzuki and Junichi Goto*

- 12 Time-resolved Fluoroimmunoassay in Eicosanoid Analysis 123

*Werner Schlegel and Harald John*

## SECTION THREE BIOCHEMICAL AND MOLECULAR PHARMACOLOGY 129

- 13 Perspectives and Clinical Significance of the Biochemical and Molecular Pharmacology of Eicosanoids 131  
*Subhash P. Khanapure and L. Gordon Letts*
- 14 Eicosanoid Antagonists 163  
*Kiyoshi Yasui and Akinori Arimura*
- 15 Biosynthesis and Degradation of Anandamide, an Endogenous Ligand of Cannabinoid Receptors 179  
*Natsuo Ueda and Dale G. Deutsch*
- 16 Inhibitors of Eicosanoids 189  
*K. D. Rainsford*
- 17 Biology and Chemistry of Products of the Isoprostane Pathway 211  
*L. Jackson Roberts II and Jason D. Morrow*
- 18 Insight into Prostanoid Functions: Lessons from Receptor-knockout Mice 219  
*Yukihiko Sugimoto, Shuh Narumiya and Atsushi Ichikawa*

## SECTION FOUR IMMUNOLOGY, ENDOCRINOLOGY AND METABOLIC REGULATION 227

- 19 Perspectives and Clinical Significance of Eicosanoids in Immunology, Endocrinology and Metabolic Regulation 229  
*Milan R. Henzl*
- 20 Prostaglandins and the Immune Response 237  
*Diana C. Fleming and Rodney W. Kelly*
- 21 Leukotrienes in Aspirin-intolerant Asthma 247  
*Anthony P. Sampson and Stephen T. Holgate*
- 22 Essential Fatty Acids 257  
*Yoeju Min and Michael A. Crawford*
- 23 Endothelial Secretory Function and Atherothrombosis 267  
*Stefan Chlopicki and Richard J. Gryglewski*

- 24 Molecular Regulation of Pancreatic Islet Prostaglandin Synthesis and its Relevance to Diabetes Mellitus 277**  
*R. Paul Robertson*
- 25 Prostaglandins, Leukotrienes and Bone 289**  
*Carol C. Pilbeam and Lawrence G. Raisz*
- 26 Ageing and Prostaglandins 299**  
*A. Hornykch*

## SECTION FIVE INFLAMMATION 319

- 27 Perspectives and Clinical Significance of Eicosanoids in Pain and Inflammation 321**  
*Burkhard Hinz and Kay Brune*
- 28 Antiinflammatory Steroids 327**  
*Françoise Russo-Marie*
- 29 Eicosanoids and Algesia in Inflammation 333**  
*Lynne Murray, Henry Sarau and Kristen E. Belmonte*
- 30 Cyclooxygenase-2 in Cancer 341**  
*Ovidiu C. Trifan and Jaime L. Masferrer*
- 31 Cytokines and Eicosanoids in Arthritis 347**  
*K. D. Rainsford*

## SECTION SIX CIRCULATORY SYSTEM 359

- 32 Perspectives and Clinical Significance of Eicosanoids in the Circulatory System 361**  
*The Late James B. Lee*
- 33 Aspirin and Activated Platelets 373**  
*Artur-Aron Weber*
- 34 Generation of Vasoactive Prostanoids by the Cyclooxygenase-2 Pathway in the Cardiovascular System of the Rat 387**  
*P. J. Kadowitz, S. R. Baber, M. M. Mazim, M. Keebler, H. C. Champion, T. J. Bivalacqua, D. B. McNamara and A. L. Hyman*
- 35 Eicosanoid Generation and Effects in Cardiac Muscle and Coronary Vessels 393**  
*Karsten Schrör*

## SECTION SEVEN DIGESTIVE SYSTEM 405

- 36 Perspectives and Clinical Significance of Eicosanoids in the Digestive System 407**  
*Chi Hin Cho, Joshua Ka Shun Ko and Marcel Wing Leung Koo*
- 37 Eicosanoids and Liver Regeneration 415**  
*David A. Rudnick and Louis J. Muglia*
- 38 Eicosanoids and the Intestine 423**  
*Klaus Bukhave and Jorgen Rask-Madsen*
- 39 Eicosanoids and Stomach Physiology 431**  
*Brigitta M. Peskar*

## SECTION EIGHT NERVOUS SYSTEM 445

- 40 Perspectives and Clinical Significance of Arachidonic Acid Release, Action and Metabolism in the Nervous System 447**  
*Christopher D. Breder*

- 41 Eicosanoid Pathways in the Ageing of the Central Nervous System 457**  
*Hari Manev and Tolga Uz*
- 42 Arachidonate Metabolites in the Neurophysiological System: the Fever Pathway 463**  
*Ji Zhang and Serge Rivest*
- 43 Prostanoids in Pain 473**  
*Tony L. Yaksh, Patrick W. Mantyh and Camilla I. Svensson*
- 44 Eicosanoids: Roles in the Pathophysiology of Cerebral Ischaemia 481**  
*Robert W. Hickey and Steven H. Graham*
- 45 NSAIDs in the Treatment of Alzheimer's Disease 487**  
*Paul S. Aisen*
- 46 Prostaglandins and Eicosanoids in Mental Illness 493**  
*A.I.M. Glen and B.M. Ross*
- 47 Essential Fatty Acids: Eicosanoid Precursors in the Treatment of Huntington's Disease 499**  
*Krishna Vaddadi*

## SECTION NINE REPRODUCTIVE SYSTEM 507

- 48 Perspectives and Clinical Significance of Eicosanoids in Obstetric and Gynaecological Practice 509**  
*I. Z. MacKenzie*
- 49 Prostaglandins and Male Reproductive Physiology 517**  
*Rodney W. Kelly*
- 50 Prostaglandin F<sub>2α</sub>: the Luteolytic Hormone 525**  
*John A. McCracken*
- 51 Prostaglandins in Implantation 547**  
*Norman L. Poyser*
- 52 Parturition and the Clinical Interruption of Pregnancy 559**  
*S. Cowan and A.A. Calder*
- 53 Foetal and Neonatal Ductus Arteriosus 569**  
*Kazuo Momma*

## SECTION TEN CONCLUSIONS AND CORRELATIONS 583

- 54 Biochemical Interactions of Platelet-activating Factor with Eicosanoids 585**  
*Joseph T. O'Flaherty and Robert L. Wykle*
- 55 Eicosanoid Precursors as Pharmaceuticals 593**  
*The Late David F. Horrobin*
- 56 Pharmaceutical Exploitation: Cyclooxygenase and Lipoxygenase Inhibitors 599**  
*Paola Patrignani and Maria G. Sciulli*
- 57 Pharmaceutical Exploitation: Eicosanoids and their Analogues 613**  
*David F. Woodward and June Chen*

Epilogue 617

Index 619

# List of Contributors

---

**Paul S. Aisen** Department of Neurology, Georgetown University Medical Center, 1 Bles Building, 3800 Reservoir Road NW, Washington, DC 20007, USA

**Marise Andreani** Laboratoire de Physiologie et de Physiopathologie, University Pierre and Marie Curie, 9 Quai Saint Bernard, 75252 Paris Cedex 05, France

**Akinori Arimura** Discovery Research Laboratories, Shionogi & Co. Ltd, 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan

**S. R. Baber** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**Kristen E. Belmonte** Respiratory and Inflammation, Centre for Excellence in Drug Discovery, GlaxoSmith-Kline, UW2532, 709 Swedeland Road, King of Prussia, PA 19406, USA

**Gilbert Béréziat** University Pierre and Marie Curie, Case 256 Batiment à 5 Etage, 7 Quai Saint Bernard, 75252 Paris Cedex 05, France

**T. J. Bivalacqua** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**Rebecca C. Bowers** Division of Cell Biology, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA

**Christopher D. Breder** Division of Neuroscience, Clinical Design and Evaluation, Bristol-Myers Squibb Co., Wallingford, CT, USA

**Kay Brune** Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nürnberg, Fahrstrasse 17, 91054 Erlangen, Germany

**Klaus Bukhave** The Royal Veterinary and Agricultural University, Copenhagen, Denmark

**A. A. Calder** Department of Obstetrics and Gynaecology, University of Edinburgh, UK

**H. C. Champion** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**June Chen** Department of Biological Sciences, Allergan Inc., 2525 Dupont Drive, Irvine, CA 92612, USA

**Stefan Chlopicki** Department of Pharmacology, Jagiellonian University Medical College, Grzegórska 16, 31-531 Kraków, Poland

**Chi Hin Cho** Department of Pharmacology, Faculty of Medicine, The University of Hong Kong, Hong Kong, China

**S. Cowan** Department of Obstetrics and Gynaecology, University of Edinburgh, UK

**Michael A. Crawford** Institute of Brain Chemistry and Human Nutrition, London Metropolitan University, 166-220 Holloway Road, London N7 8DB, UK

**Christophe Créminon** CEA, Service de Pharmacologie et d'Immunologie, Département de Recherche Médicale, CEA-Saclay, 91191 Gif-sur-Yvette Cedex, France

**Carol Deby** Centre for Oxygen Research and Development, Institut de Chimie, B6a, Université de Liège, 4000 Liège, Belgium

**Ginette Deby-Dupont** Centre for Oxygen Research and Development, Institut de Chimie, B6a, Université de Liège, 4000 Liège, Belgium

**Dale G. Deutsch** Department of Biochemistry and Cell Biology, State University of New York at Stony Brook, Stony Brook, NY 11794-5215, USA

**Jennifer Dickinson** Division of Cell Biology, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA

**Diana C. Fleming** Medical Research Council Human Reproductive Science Unit, University of Edinburgh Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9ET, UK

**Junichi Goto** Department of Pharmaceutical Sciences, Tohoku University Hospital, 1-1 Seiryō-machi Aoba-ku, Sendai 980-8574, Japan

**A. I. M. Glen** Ness Foundation, UHI Millennium Institute, Ness House, Dochfour Business Centre, Inverness IV3 8GY, UK



**Steven H. Graham** Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Richard J. Gryglewski** Department of Pharmacology, Jagiellonian University Medical College, Grzegorzeczka 16, 31-531 Kraków, Poland

**Milan R. Henzl** Stanford University Medical School, 4210 Ynigo Way, Palo Alto, CA 94306, USA

**Harvey R. Herschman** Department of Biological Chemistry, David Geffen School of Medicine at UCLA, 341 Boyer Hall, 611 Charles E. Young Drive East, Los Angeles, CA 90095-1570, USA

**Robert W. Hickey** Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Burkhard Hinz** Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nürnberg, Fahrstrasse 17, 91054 Erlangen, Germany

**Takanori Hishinuma** Department of Pharmaceutical Sciences, Tohoku University Hospital, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

**Stephen T. Holgate** Respiratory Cell and Molecular Biology, Division of Infection, Inflammation and Repair, Southampton University School of Medicine, Southampton, UK

**A. Hornyh** Department of Nephrology, European Hospital George Pompidou, 20 Rue Leblanc, 75908 Paris Cedex 15, France

**The Late David F. Horrobin<sup>†</sup>** Chairman, Laxdale Ltd, Kings Park House, Laurehill Business Park, Stirling FK7 9JQ, UK

**A. L. Hyman** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**Atsushi Ichikawa** Department of Physiological Chemistry, Graduate School of Pharmaceutical Sciences and Department of Pharmacology, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

**Harald John** IPF Pharmaceuticals GmbH, 30625 Hannover, Germany

**Robert L. Jones** Department of Pharmacology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, NT, Hong Kong

**Philip J. Kadowitz** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**M. Keebler** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**Rodney W. Kelly** Medical Research Council Human Reproductive Science Unit, University of Edinburgh Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9ET, UK

**Joshua Ka Shun Ko** Department of Pharmacology, Faculty of Medicine, The University of Hong Kong, Hong Kong, China

**Subhash P. Khanapure** Nitro Med Inc, 12 Oak Park Drive, Bedford, MA 01730, USA

**The Late James B. Lee\*** School of Medicine and Biomedical Sciences, University at Buffalo, USA

**Gordon Letts** NitroMed Inc., 12 Oak Park Drive, Bedford, Massachusetts 01730, USA

**Marcel Wing Leung Koo** Department of Pharmacology, Faculty of Medicine, Hong Kong Baptist University, Hong Kong, China

**I. Z. MacKenzie** Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

**The Late Jacques Maclouf** U348 INSERM I.F.R. Vaisseaux-Lariboisière, Hôpital Lariboisière, 8 Rue Guy Patin, 75475 Paris Cedex 10, France

**Hari Manev** The Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor Street, Chicago, IL 60612, USA

**Patrick W. Mantyh** Department of Preventive Sciences, University of Minnesota, Minneapolis, MN 55455, USA

**Jaime L. Masferrer** Oncology Department, AA5C, Pharmacia Corporation, 700 Chesterfield Parkway North, Chesterfield, MO 63198, USA

**M. M. Mazim** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

**John A. McCracken** Department of Animal Science, University of Connecticut, Storrs, CT 06269-4040, USA

**D. B. McNamara** Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

<sup>†</sup>Correspondence to Dr Crispin Bennett, Research Information Manager (cbennett@laxdale.co.uk)

\*Correspondence to Professor Peter Curtis-Prior, Editor (pc-p@cambridgehealth.org.uk)

- Yoeju Min** Institute of Brain Chemistry and Human Nutrition, London Metropolitan University, 166–220 Holloway Road, London N7 8DB, UK
- Michinao Mizugaki** Department of Pharmaceutical Sciences, Tohoku University Hospital, 4-4-1 Komatsushima, Aoba-ku, Sendai, 981-8558 wcl, Japan
- Kazuo Momma** Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
- Jason D. Morrow** Departments of Pharmacology and Medicine, Vanderbilt University, Nashville, TN 37232, USA
- Louis J. Muglia** Department of Pediatrics, Washington University School of Medicine, St Louis, MO 63110, USA
- Robert C. Murphy** Division of Cell Biology, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA
- Lynne Murray** Imperial College School of Medicine, SAF Building, Exhibition Road, Leukocyte Biology, BMS Division, South Kensington, London SW7 2AZ, UK
- Shuh Narumiya** Department of Physiological Chemistry, Graduate School of Pharmaceutical Sciences and Department of Pharmacology, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan
- Joseph T. O'Flaherty** Department of Internal Medicine, Section on Infectious Disease, Wake Forest University School of Medicine, Winston Salem, NC, USA
- Jean-Luc Olivier** Laboratory of Medical Biology, Faculty of Medicine of Nancy, France
- Paola Patrignani** Department of Medicine and Aging, Division of Pharmacology, "G. D'Annunzio" University of Chieti School of Medicine, 66013 Chieti, Italy
- Brigitta M. Peskar** Department of Experimental Clinical Medicine, Ruhr-University of Bochum, Bochum, Germany
- Carol C. Pilbeam** University of Connecticut Health Center, 63 Farmington Avenue, Farmington, CT 06030-2806, USA
- William S. Powell** Meakins-Christie Laboratories, Department of Medicine, McGill University, 3626 St Urbain Street, Montreal, Quebec, Canada H2X 2P2
- Norman L. Poyser** Division of Biomedical and Clinical Laboratory Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD, UK
- K. D. Rainsford** Biomedical Research Centre, School of Science and Mathematics, Sheffield Hallam University, Howard Street, Sheffield S1 1WB, UK
- Lawrence G. Raisz** University of Connecticut Health Center, 63 Farmington Avenue, Farmington, CT 06030-2806, USA
- Jørgen Rask-Madsen** Department of Medical Gastroenterology, Herlev Hospital, University of Copenhagen, Denmark
- Serge Rivest** Laboratory of Molecular Endocrinology, CHUL Research Center and Department of Anatomy and Physiology, Laval University, 2705, Boul. Laurier, Québec, Canada G1V 4G2
- L. Jackson Roberts II** Departments of Pharmacology and Medicine, Vanderbilt University, Nashville, TN 37232, USA
- R. Paul Robertson** Pacific Northwest Research Institute, Seattle, WA 98122, USA
- B. M. Ross** Ness Foundation, UHI Millennium Institute, Ness House, Dochfour Business Centre, Inverness IV3 8GY, UK
- David A. Rudnick** Department of Pediatrics, Washington University School of Medicine, St Louis, MO 63110, USA
- Françoise Russo-Marie** BIONEXIS, CEA Saclay Bâtiment 520, 91191 Gif-sur-Yvette Cedex, France
- Angelo Sala** Department of Pharmacological Sciences, Via Balzaretti, 20133 Milan, Italy
- Anthony P. Sampson** Respiratory Cell and Molecular Biology, Division of Infection, Inflammation and Repair, Southampton University School of Medicine, Southampton, UK
- Henry Sarau** Respiratory and Inflammation, Centre for Excellence in Drug Discovery, GlaxoSmithKline, UW2532, 709 Swedeland Road, King of Prussia, PA 19406, USA
- Werner Schlegel** Universitätsklinikum Münster, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Albert-Schweitzer-Strasse 33, D-48149 Münster, Germany
- Karsten Schrör** Institut für Pharmakologie und Klinische Pharmakologie, Universitätsklinikum Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany
- Maria G. Sciuili** Department of Medicine and Aging, Division of Pharmacology, "G. D'Annunzio" University of Chieti School of Medicine, 66013 Chieti, Italy
- Yukihiko Sugimoto** Department of Physiological Chemistry, Graduate School of Pharmaceutical Sciences and

Department of Pharmacology, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

**Hiroshi Suzuki** Department of Biochemistry, Tokushima University, School of Medicine, Kuramoto-cho, Tokushima 770-8503, Japan

**Naoto Suzuki** Department of Pharmaceutical Sciences, Tohoku University Hospital, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

**Camilla I. Svensson** Department of Anesthesiology, University of California, San Diego, La Jolla, CA 92093, USA

**Yoshitaka Takahashi** Department of Molecular Pharmacology, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan

**Ovidiu C. Trifan** Oncology Department, AA5C, Pharmacia Corporation, 700 Chesterfield Parkway North, Chesterfield, MO 63198, USA

**Natsuo Ueda** Department of Biochemistry, Kagawa University School of Medicine, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

**Tolga Uz** The Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor Street, Chicago, IL 60612, USA

**Krishna Vaddadi** Department of Psychological Medicine Monash Medical Centre, (Monash University), 246 Clayton Road, Clayton 3186, Victoria, Australia

**Artur-Aron Weber** Institut für Pharmakologie und Klinische Pharmakologie, Universitätsklinikum Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany

**Jay Y. Westcott** National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA

**Norrie H. Wilson** Division of Biomedical Sciences, University of Edinburgh, 1-3 George Square, Edinburgh EH8 9XD, UK

**David F. Woodward** Department of Biological Sciences, Allergan Inc., 2525 Dupont Drive, Irvine, CA 92612, USA

**Robert L. Wykle** Department of Biochemistry, Wake Forest University School of Medicine, Winston Salem, NC, USA

**Tony Yaksh** Department of Anesthesiology, University of California, San Diego, La Jolla, CA 92093, USA

**Shozo Yamamoto** Department of Food and Nutrition, Faculty of Home Economics, Kyoto Women's University, Imakumano, Higashiyama-ku, Kyoto 605-8501, Japan

**Kiyoshi Yasui** Discovery Research Laboratories, Shionogi & Co. Ltd, 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan

**Tanihiro Yoshimoto** Department of Molecular Pharmacology, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan

**Karin Zemski Berry** Division of Cell Biology, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA

**Ji Zhang** Laboratory of Molecular Endocrinology, CHUL Research Center and Department of Anatomy and Physiology, Laval University, 2705 Boul. Laurier, Québec, Canada G1V 4G2

# Preface

As the year 2000 approached, there developed in people around the world a sense of anticipation, positive for some but negative for others. However, in both groups of people there was a deep desire to mark such a rare moment in history. It was at this time that it was first suggested to me as *the* ideal moment for a new, comprehensive volume on the biomedical significance of polyunsaturated acids and their derivatives, bringing together the important discoveries and developments which had taken place in this area since the publication of a previous book with which I had been involved (Curtis-Prior 1988). It was that prompting which has led to this latest book, *The Eicosanoids* (see also Acknowledgements).

So, although what might be considered as "...important discoveries and developments..." is to some extent a subjective exercise and certainly every chapter in this book reveals developments of fascinating new knowledge in its field of specialism, there has been one landmark advance during these fifteen years which, among much else, has reconciled the seeming paradox that prostaglandins may be both harmful and beneficial. This was, of course, the identification and characterization of an alternative cyclooxygenase enzyme (Fu *et al* 1990; Masferrer *et al* 1990; Herschman *et al* 1993), i.e. the proposal of the coexistence of the known enzyme responsible for basal, constitutive prostaglandin synthesis (COX-1) together with a new enzyme (designated COX-2) implicated in various inflammatory and "induced" settings (Funk 2001; see also Chapter 4, this volume, Regulation and Function of Prostaglandin Synthase-2/Cyclooxygenase II). This revelation provoked a whole new wave of discovery research activity in academia and in the pharmaceutical industry. There followed a race to develop a new class of COX-2 selective inhibitors which inhibited prostaglandin production in inflammatory cells without the, hitherto, inevitable undesirable interference on the production of COX-1-generated prostaglandins fulfilling their physiological regulatory roles in the gastrointestinal tract (Warner *et al* 1999) in renal function and in the reproductive and haemostatic systems as is presented in superb detail elsewhere in this book (see for example Chapters 13, this volume, Perspectives and Clinical Significance of the Biochemical and Molecular Pharmacology of Eicosanoids and Chapter 16 Inhibitors of Eicosanoids). Some of the early fruits of this burst of scientific creativity were presented at specialized conferences in Bangkok and Boston and recorded in a state of the art "book-of-the-meetings" edited by Vane and Botting (1998), and this was later succeeded by their comprehensive monograph on the subject, entitled *Therapeutic Roles of Selective COX-2 Inhibitors* (Vane and Botting 2001). The Pharmacia drug Celebrex (celecoxib) was the first of this new generation of COX-2 selective inhibitors to receive marketing authorization (by the US FDA) for the treatment of inflammatory conditions (Penning *et al* 1997) and the second was Merck Sharp & Dohme's Vioxx (rofecoxib) (Chan *et al* 1999; Prasit *et al* 1999).

In a pivotal trial, when celecoxib was compared with ibuprofen and diclofenac in a 6 months-long arthritis safety study (CLASS), it was reported (Silverstein *et al* 1999) that the COX-2 inhibitor was associated with a lower incidence of symptomatic ulcers and

ulcer complications than the traditional COX-1 non-steroidal antiinflammatory drugs, as had been the result anticipated. However, it appears that there was some incongruity (Okie 2001; Berg *et al* 2001; Wright *et al* 2001) between this account from Silverstein and his co-workers and "...the complete information available to the United States Food and Drug Administration..." (Juni *et al* 2002) in what has been described as a "...failure in the therapeutic chain as a cause of drug ineffectiveness..." (Figueras and Laporte 2003). However, it should be noted that a subsequent major study (designated VIGOR) to compare the incidence of upper gastrointestinal events provoked by MSD's selective COX-2 inhibitor rofecoxib and the non-selective NSAID naproxen, in patients with rheumatoid arthritis, demonstrated significant clinical advantages for rofecoxib (Bombardier *et al* 2000). Whatever might be the eventual outcome of this particular and complex situation, where we well know that the worldwide clinic is the ultimate challenge of any therapeutic product, the drug target remains fascinatingly attractive, especially for industry, in the light of a global market for analgesics estimated at US \$10 billion.\*

Interestingly, there have also been reports of a herbal preparation called Nexrutine™ (Lavelle 2003). This is a new patent-pending dietary supplement containing an extract of the plant *Phellodendron amurense* and has been reported to be useful in the treatment of inflammatory diseases. It possesses COX-2-inhibitory qualities, but also protects the gastrointestinal tract against ulceration. In clinical studies, it was shown that Nexrutine inhibits COX-2 without interfering with the activity of COX-1. In animal studies, Nexrutine has proved to be as effective as naproxen in reducing pain and inflammation. However, its mechanism of action has been reported to be different from that of what might be termed *true* COX-2 inhibitors, since it does not act directly on the cyclooxygenase, but inhibits the gene responsible for the production of COX-2, as well as other inflammatory mediators.

Other novel developments treated in this book include: endogenous ligands of cannabinoid receptors, referred to as endocannabinoids (Mechoulam *et al* 1998; see also Chapter 15, this volume, Biosynthesis and Degradation of Anandamide, an Endogenous Ligand of Cannabinoid Receptors); identification of the noxious roles of cysteinyl leukotrienes in aspirin-intolerant asthma (Samson and Holgate 1999; see also Chapter 21, this volume, Leukotrienes in Aspirin-intolerant Asthma); prostaglandin receptor knock-out mice (Negishi and Katoh 2003; see also Chapter 18, this volume, Insight into Prostanoid Functions: Lessons from Receptor-knockout Mice); the biosynthesis and roles of isoprostanes (Morrow *et al*, 1990; see also Chapter 17, this volume, Biology and Chemistry of Products of the Isoprostane Pathway) and their utility in the assessment of oxidative stress status *in vivo*, in the clinic.

Finally there is in this volume (see also below) a wealth of new knowledge shared over a broad range of the actions and

\*Current nomenclature has been adopted, taking 1 billion (bn) as 10<sup>9</sup> rather than the traditional value of 10<sup>12</sup>.

interactions of eicosanoids in biomedicine and physiology, from immunology to central nervous system disorders.

The book is divided into thematic sections (see Contents) each of which begins with a chapter designated “Perspectives and clinical significance...” The intention is for these “Perspectives” chapters to provide an integrated synopsis of the subject area covered in the respective Section, indicating how the different specialist chapters (strands of the theme) relate to one another in the overall context of the theme. In this way, it is hoped that *THE EICOSANOIDS* may interest, encourage and inspire all who are fascinated by the biosciences in seeking further to understand more about the myriad roles of essential fatty acids to the benefit of human wellbeing.

Notwithstanding the unpredictability of the peaks and troughs in the evolution and development of any discipline, it appears valid, still, to look forward to even more fascinating discoveries ahead through the immortal words from Robert Browning, cited on a previous occasion (Curtis-Prior 1983):

Grow old along with me  
The best is yet to be...

Cambridge 2004

Peter Curtis-Prior

pc-p@cambridgehealth.org.uk

## REFERENCES

- Berg Hrach J and Mora M (2001) Reporting of 6-month vs. 12-month data in a clinical trial of celecoxib. *J Am Med Assoc*, **286**, 2398.
- Bombardier C, Laine L, Reicin A *et al* (2000) Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Eng J Med*, **343**, 1520–1528.
- Chan CC, Bouce S, Brideau C *et al* (1999) Rofecoxib [Vioxx, MK-0966; 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. *J Pharmacol Exp Therapeut*, **290**, 551–560.
- Curtis-Prior PB (ed.) (1988) *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids*. Edinburgh: Churchill Livingstone.
- Curtis-Prior PB (1983) Trends in prostaglandin studies [Orientations des études actuelles sur les prostaglandines]. *Curr Clin Concepts*, **1**, 9–19.
- Di Marzo V (1998) Endocannabinoids and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiological relevance. *Biochim Biophys Acta*, **1392**, 153–175.
- Figueras A and Laporte J-R (2003) Failures of the therapeutic chain as a cause of drug ineffectiveness. *Br Med J*, **326**, 895–896.
- Fu JY, Masferrer JL, Seibert K *et al* (1990) The induction and suppression of prostaglandin H<sub>2</sub> synthase (cyclooxygenase) in human monocytes. *J Biol Chem*, **265**, 16737–16740.
- Funk CD (2001) Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science*, **294**, 1871–1875.
- Herschman HR, Fletcher BS and Kujubu DA (1993) TIS10, a mitogen-inducible glucocorticoid-inhibited gene that encodes a second prostaglandin synthase/cyclooxygenase enzyme. *J Lipid Mediat*, **6**, 89–99.
- Juni P, Rutjes AWS and Dieppe PA (2002) Are selective COX-2 inhibitors superior to traditional non-steroidal antiinflammatory drugs? Adequate analysis of the CLASS trial indicates that this may not be the case. *Br Med J*, **324**, 1287–1288.
- Lavelle JB (ed.) (2003) *The COX-2 Connection: Natural Breakthrough Treatments for Arthritis, Alzheimer's and Cancer*. Rochester VT: Healing Arts Press.
- Masferrer JL, Zweifel BS, Seibert K *et al* (1990) Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice. *J Clin Invest*, **86**, 1375–1379.
- Mechoulam R, Fride E and Di Marzo V (1998) Endocannabinoids. *Eur J Pharmacol*, **359**, 1–18.
- Morrow JD, Hill KE, Burk RF *et al* (1990) A series of prostaglandin F<sub>2</sub>-like compounds are produced *in vivo* in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci USA*, **87**, 9383–9387.
- Negishi M and Katoh H (2002) Cyclopentanone prostaglandin receptors. *Prostaglandin Lipid Mediat*, Special Issue: Molecular Biology of the Arachidonate Cascade, Guest Eds S Yamamoto and WL Smith, **68–69**, 611–617.
- Okie S (2001) Missing data on Celebrex. Full study altered picture of drug. *Washington Post*, **5** (Aug), A11.
- Penning TD, Talley JJ, Bertenshaw SR *et al* (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methyl phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib). *J Med Chem*, **40**, 1347–1365.
- Prasit P, Wang Z, Brideau C *et al* (1999) The discovery of rofecoxib [MK966, Vioxx, 4-(methylsulfonyl phenyl)3-phenyl-2-(5H)-furanone], an orally active cyclooxygenase-2 inhibitor. *Bioorg Med Chem Lett*, **9**, 563–567.
- Sampson AP and Holgate ST (1999) *Leukotriene Modifiers in Asthma Treatment*. London: Martin Dunitz.
- Silverstein FE, Faich G, Goldstein JL *et al* (2000) Gastrointestinal toxicity with celecoxib vs. non-steroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *J Am Med Assoc*, **284**, 1247–1255.
- Vane JR and Botting RM (1998) *Clinical Significance and Potential of COX-2 Inhibitors*. London: William Harvey Press.
- Vane JR and Botting RM (2000) *Therapeutic Roles of Selective COX-2 Inhibitors*. London: William Harvey Press.
- Warner TD, Giuliano F, Vojnovic I *et al* (1999) Non-steroid drug selectivities for cyclooxygenase-1 rather than cyclooxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci USA*, **96**, 7563–7568.
- Wright JM, Perry TL, Bassett KL and Chambers KG (2001) Reporting of 6-month vs. 12-month data in a clinical trial of celecoxib. *J Am Med Assoc*, **286**, 2398.

# Preface from *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids*, edited by P. B. Curtis-Prior (1988)

---

My purpose in preparing this volume was to provide, in a single source, a comprehensive collection of information on prostaglandins and related eicosanoids.\* The 57 chapters presented here are divided into ten sections, according to subject, and are the work of a total of almost 80 authors from over a dozen countries, distributed among four of the world's continents. Although the chapters have been edited I have tried, as far as possible, to retain the original style of each author, or group of authors, in order to present a richer, international, intercultural final product. The book has been over 5 years in the making and, in spite of the more recent possibility for authors to carry out updating procedures on their contributions, must remain less than comprehensive owing, in part, to the constant influences of man's innate curiosity and creativity providing new knowledge more quickly even than the old can be recorded. However, it is perhaps germane at this time to recall the maxim below, suggested by Dr John A. McCracken (The Worcester Foundation, Shrewsbury, Massachusetts), with which many of the "initiated" in this field will, no doubt, readily identify:

The one who places the last stone and steps across to the terra firma of accomplished discovery gets all the credit. Only the initiated know and honor those whose patient integrity and devotion to exact observation have made the last step possible.

Hans Zinsser

The demonstration of the essentiality of dietary linoleic acid, and the coining of the term "essential fatty acid (EFA)" by Burr and Burr (1930), the subsequent dawning of the real significance of this observation, plus the preliminary clinical studies of Kurzrok and Lieb (1930) showing the uterine muscle-stimulating properties of human semen, followed shortly afterwards by the observations of hypotensive actions of semen and acidic lipid extracts thereof by Goldblatt (1935) and von Euler (1935), really set the scene for the story recounted in this volume, a story which is certainly not yet completed.

Since the 1930s there has been an enormous growth and development of interest and investigation which, however, has not been a continuum. Indeed, following the initial spate of papers of the 'past historic' phase of attention to prostaglandins (Curtis-Prior 1985), there was a clear arrest of devotion during the years of the Second World War, prior to a resurgence—including the first isolation of prostaglandins (Bergstrom and Sorjvall 1957) in the postwar years, since when there has developed a rate of issue of  $4.5\text{--}5.0 \times 10^3$  publications each year, i.e. approaching 100 per

week.<sup>†</sup> The origin of this present and continuing interest in prostanoids is not entirely clear, but probably stems to a large degree from the independent and virtually simultaneous findings relating to the actions of non-steroidal anti-inflammatory drugs on prostaglandin biosynthesis in France and in Britain, especially of the effects of the most widely-used drug substance the world has yet known: aspirin, as was surmised previously by Collier (1971). At L'Institut Pasteur in Paris, Vargaftig and co-workers had spent several years examining phospholipases A and C, and showed subsequently that aspirin could block the actions of vasoactive substances normally formed by phospholipases from guinea-pig lung (Vargaftig and Dao 1971). Meanwhile, Willis and Smith at the Royal College of Surgeons of England in London had observed that the production of prostaglandins by blood platelets was presented in the presence of aspirin. The significance of these observations was quickly recognized, with legendary vision, by Vane (also at the Royal College), who corroborated them using guinea-pig lung homogenate; this led to the famous trilogy of papers published in *Nature* that year (Ferreira *et al* 1971; Smith and Willis 1971; Vane 1971). Subsequently, the work of Morley and Williams (1973) demonstrated an enhancement of paw oedema by prostaglandins which entirely corroborated the association of prostaglandins and inflammation. Although the greatest interest and the major proportion of published data relate to arachidonic acid and its metabolites, there is increasing attention being paid also to eicosanoids of the 1-series and of the 3-series.

Considerable public interest has been provoked latterly in health food preparations of seed oil of the evening primrose, an oleaginous (willow herb) plant of the genus *Oenothera* misnamed because of the resemblance of its bright yellow flowers to those of real primroses. This plant's seed is rich in linoleic acid (72%) and contains also  $\gamma$ -linolenic acid (c.9%). It is the latter component which is proposed as the active principle through conversion to prostaglandins of the 1-series (mainly  $E_1$ ) in remarkably wide-ranging therapeutic claims (Graham 1984). This is compatible with the wide-held belief that our main source of arachidonic acid is probably the meat of our diet (i.e. other animals' bodies) and, since on the one hand the 5-desaturase enzyme catalysing the further transformation of dihomo- $\gamma$ -linolenic acid to arachidonic acid is of minor importance in man, and on the other hand that activity of the 6-desaturase responsible for the formation of  $\gamma$ -linolenic acid from linoleic acid is much reduced by our modern lifestyle, as well as the pathologies of severe hepatic insufficiency, undernutrition, insulin-dependent diabetes and senescence (Pacalín *et al* 1984), it is tacitly assumed that additional dietary  $\gamma$ -linolenic acid is converted mainly to prostaglandins of the 1-series.

---

\*"Eicosanoids" is a useful term coined by Corey EJ, Nuiira H, Falek JR, Mioskowski C, Arai Y, Marfat A (1980) Recent studies on the chemical synthesis of eicosanoids. *Advances in Prostaglandin and Thromboxane Research*, 6: 19–25... "to describe the broad group of compounds derived from  $C_{20}$  fatty acids..."

<sup>†</sup>These data were kindly supplied by the Information Services (Corporate Technical Library), Upjohn Company, Kalamazoo, USA and calculated under the revised system, 1983.

However, the identification of other angiosperm plant seeds containing increased amounts of  $\gamma$ -linolenic acid, like the black-currant (*Ribes nigrum*) and borage (*Borago officinalis*), and the recent discovery, in several parts of the world, of the very important nutritional potential of the blue-green alga of the genus *Spirulina* (Chan *et al* 1981; Ciferri 1983; Devi and Venkataraman 1983) containing much higher concentrations of  $\gamma$ -linolenic acid synthesized by direct desaturation of linoleic acid, suggest they may shortly eclipse the present fashionable interest in "primrose oil". Indeed, recent advances in biotechnology could replace agricultural seed oil production altogether as a source of  $\gamma$ -linolenic and other polyunsaturated fatty acids of therapeutic potential (Ratledge 1987).

The origins of man's cognisance of the potential therapeutic importance of prostaglandins of the 3-series and their precursor polyunsaturated fatty acids has been indicated recently by Sinclair (1985).\*

About 3500 years ago, the Israelites were bored by making bricks without straw, and Moses (or perhaps Aaron) hit the sea with a rod—a poor tool for that purpose but the Lord was on his side. All the fish died. Shortly thereafter Pharaoh had an infarct followed by an epidemic of hardening of the heart amongst the Egyptians. This is the earliest indication of the importance of fish in preventing myocardial infarction.

More recently, the extremely low incidence of myocardial infarction and a tendency to bleed attributed to an Eskimo diet has emphasized the apparent protective aspects of fish oils (Dyerberg *et al* 1975), although in rats fed cod liver oil PGI<sub>3</sub> was not detectable (Hornstra and Nugteren 1981). While this observation has thrown doubt on a thromboregulatory role for 3-series prostaglandins, it cannot dispute the observed non-genetic low cardiovascular morbidity and mortality of Eskimo populations and may indicate the identity of the protective principle as the polyunsaturated fatty acid (potential prostaglandin precursor) eicosapentanoic acid (Dyerberg *et al* 1978). However, it may be significant that furanoid or urofurano acid compounds which have been shown to be minor components of fish oils (Glass *et al* 1975) may also be credited with a possible cardiovascular protective role in view of their potent hypolipidaemic properties in animal models in reducing both blood cholesterol and triglycerides (Hall 1985).

The recently-discovered arachidonic acid metabolites lipoxins, formed by human leukocytes stimulated with calcium ionophore (Serhan *et al* 1984), appear to be involved in inflammation and their possible interactions and/or associations with other eicosanoids are discussed in several contexts in this volume.

Apart from the arachidonic acid metabolites, phospholipase A<sub>2</sub> may give rise also to another lipid mediator, platelet activating factor (PAF, PAF-acether or acetyl-glycerol-ether-phosphorylcholine) (Benveniste *et al* 1972), which was first recognized by its degranulating activity of rabbit platelets (Siragnani and Osler 1971), implicated as a mediator of anaphylaxis (Henson and Pinckard 1977) and subsequently implicated in most aspects of cellular inflammation (Benveniste and Arnoux 1983). Because of the unceasing evidence of the intimate associations of eicosanoids with PAF in pathophysiological processes, a sign-post chapter (Ch. 55) has been incorporated in the final part of this volume.

The recognition of the cytokine peptide interleukin-1 (IL-1) as an inflammatory mediator inducing fever, the release of acute phase proteins and cartilage degradation led naturally to the

supposition of prostaglandin involvement in these pathophysiological processes. However, it is only recently that IL-1 has been clearly shown to activate cellular phospholipase A<sub>2</sub> and thus suggests the whole gamut of arachidonic acid metabolites and PAF as its potential secondary mediators (Chang *et al* 1986). Superimposed on this are the complicating preliminary observations that PAF itself may IL-1 production from human macrophages (Barrett *et al* 1987).

The early implication of eicosanoids in inflammation, referred to above, is evidently the visible tip of a complex metaphorical iceberg wherein the indicated interrelationship of prostanoids/eicosanoids with PAF, lipoxins and cytokines and kinins are only now beginning to be unravelled. These exciting developments in inflammation and the body homeostatic defence mechanisms, those related to cardiovascular disease and diet, recent implications of PAF in nidation and a potential further means of regulating fertility (O'Neil 1986), and the most recent suggestion of a role for eicosanoids as second messengers in the nervous system (Piorrelli *et al* 1987) are but a few of the potentially exciting avenues awaiting further elucidation in the future of "prostaglandins", and may explain why often "the true innovative researcher cannot define the eventual length or cost of a research programme" (Celsus 1985).

P.B.C-P.  
Cambridge, 1988

## REFERENCES

- Barrett ML, Lewis GP, Ward S and Westwick J (1987) Platelet activating factor induces interleukin-1 production from human adherent macrophages. *Br J Pharmacol*, **90**, 113P.
- Benveniste J and Arnoux B (1983) *Platelet-activating Factor and Structurally-related Ether Lipids*. Amsterdam: Elsevier.
- Benveniste J, Henson PM, Cochrane CG 1972 Leukocyte-dependent histamine release from rabbit platelets. The role of IgE, basophils and a platelet-activating factor. *J Exp Med*, **136**, 1356–1376.
- Bergstrom S and Sjovall J (1957) The isolation of prostaglandin. *Acta Chem Scand*, **11**, 1086.
- Burr GO, Burr MM (1930) On the nature and the role of fatty acids essential in nutrition. *J Biol Chem*, **86**, 587–621.
- Chang J, Gilman SC and Lewis AJ (1986) Interleukin 1 activates phospholipase A<sub>2</sub> in rabbit chondrocytes: a possible signal for IL 1 action. *J Immunol*, **136**, 1283–1287.
- Celsus (1985) Primroses and prostaglandin. *Pharm J*, **235**, 607–608.
- Chen L-C, Chen J-S and Tung T-C (1981) Effects of *Spirulina* on serum lipoproteins and its hypocholesterolemic effect. *J Formosan Med Assoc*, **80**, 934–942.
- Ciferri O (1983) *Spirulina*, the edible microorganism. *Microbiol Rev*, **47**, 551–578.
- Collier HOJ (1971) Prostaglandins and aspirin. *Nature New Biol*, **231**, 17–19.
- Curtis-Prior PB (1985) Trends in prostaglandin studies. *Curr Clin Concepts*, **1**, 9–19.
- Dyerberg J, Bang HO and Hjerne N (1975) Fatty acid composition of the plasma lipids in Greenland eskimos. *Am J Clin Nutr*, **28**, 958–966.
- Dyerberg J, Bang HO, Stofferson E *et al* (1978) Eicosapentanoic acid and prevention of thrombosis and atherosclerosis. *Lancet*, **ii**, 117–119.
- Devi MA and Venkataraman LV (1983) Hypocholesterolemic effect of blue green algae *Spirulina platensis* in albino rats. *Nutrit Rep Int*, **28**, 519–530.
- von Euler US (1935) A depressor substance in the vesicular gland. *J Physiol*, **84**, 21P.
- Ferreira SM, Moncada S and Vane JR (1971) Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nature*, **231**, 237–239.
- Glass, RL, Krick TP, Sand DM *et al* (1975) Furanoid fatty acids from fish lipids. *Lipids*, **10**, 695–702.
- Goldblatt MW (1935) A depressor substance in seminal plasma. *J Physiol*, **84**, 201–218.
- Graham J (1984) *Evening Primrose Oil*. Wellingborough, UK: Thorsons.

\*This is quoted with permission from a pre-publication script kindly supplied by Professor Hugh Sinclair of his pre-dinner presentation entitled: "History of EFA and their prostanoids: some personal reminiscences", on the occasion of the Second International Congress on Essential Fatty Acids and their Eicosanoids.

- Hall H (1985) The hypolipidaemic activity of furanoic acid and furyl acrylic acid derivatives in rodents. *Pharm Res*, **5**, 233–238.
- Henson PM and Pinckard RN (1977) Basophil derived platelet activating factor (PAF) as an *in vivo* mediator of acute allergic reactions. Demonstration of specific desensitization of platelets to PAF during IgE-induced anaphylaxis in the rabbit. *J Immunol*, **119**, 1279–1286.
- Hornstra G and Nugteren D (1981) Fish oil feeding does not result in the endogenous formation of PGI<sub>3</sub> in rats. *Progr Lipid Res*, **20**, 911.
- Kurzrok R and Lieb CC (1930) Biochemical studies of human semen. The action of semen on the human uterus. *Proc Soc Exp Biol Med*, **28**, 268–272.
- O'Neill C (1986) PAF in early pregnancy. Conference papers: an International Seminar on the Therapeutic and Commercial Potential of Drugs Affecting Platelet Activating Factor (London).
- Paccalin J, Dabadie H, Bernard M *et al* (1984) Interet d'une nouvelle plante oleagineuse: l'onagre (*Oenothera biennis* ou *larmarkiana*) apport en acide  $\gamma$ -linolenique et troubles de la desaturation en pathologie. *Med Nutr*, **xxi**, 132–136.
- Piorrelli D, Volterra A, Dale N *et al* (1987) Lipoxygenase metabolites of arachidonic acid as second messengers for presynaptic inhibition of *Aplysia* sensory cells. *Nature*, **328**, 38–43.
- Ratlidge C (1987) Oleaginous yeasts and moulds. Conference papers: International Conference on Biotransformations (Cambridge).
- Serhan CN, Hamberg M and Samuelsson B (1984) Trihydroxytetraenes: novel series of oxygenated derivatives formed from arachidonic acid in human leukocytes. *Biochem Biophys Res Commun*, **118**, 943–949.
- Siraganian RP and Osler AG (1971) Destruction of rabbit platelets in the allergic response of sensitized leukocytes. 1. Demonstration of a fluid phase intermediate. *J Immunol*, **106**, 1244–1251.
- Smith JB and Willis AL (1971) Aspirin selectively inhibits prostaglandin production in human platelets. *Nature*, **231**, 235–237.
- Vane JR (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature*, **231**, 232–235.
- Vargaftig BB and Dao NN (1971) Release of vaso-active substances from guinea-pig lungs by "slow-reacting substance C" and arachidonic acid. Its blockade by non-steroidal antiinflammatory agents. *Pharmacology*, **6**, 99–108.
- Williams TJ and Morley J (1973) Prostaglandins as potentiators of increased vascular permeability in inflammation. *Nature*, **246**, 215–217.





# Acknowledgements

---

Editing this substantial volume has required, above all, a great commitment of that most valuable commodity...time. Time taken out of a life is not easily replaced, so I thank my wife for her enabling me to devote so much time to this exciting editorial adventure.

The stimulus for this book, *The Eicosanoids*, grew out of suggestions from several colleagues and especially Professor Kim Rainsford (Biomedical Research Centre, Sheffield Hallam University, UK). It was suggested that a new book in this area would be a fitting and appropriate marking of the new millennium and enable recent scientific discoveries and developments to be drawn together into a work of reference, which a number of other colleagues believed would be timely. It was, thus, through these encouragements that the idea finally took on form and became a reality.

The Editor wishes to express his appreciation to the publishers, John Wiley & Sons, for their patience and to the indefatigable and complementary Charlotte Brabants and Layla Paggetti from the London office, who have been such absolute stalwarts during these several years and to Monica Twine and her team at the Chichester Office for wisdom and support during the production phase.

It is also my great pleasure to acknowledge the consistently reliable support from staff of the Medical Library in Cambridge University, Addenbrooke's Hospital in Cambridge.

I am most grateful to Nobel Laureate Professor Bengt Samuelsson (Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden) for agreeing to contribute a Foreword to this new volume. His pioneering work, together with that of his co-workers, in their pivotal role in elucidating eicosanoid structures, truly laid the foundations for the subsequent development in our understanding of the biochemical pathways involving polyunsaturated fatty acids.

A number of the eminent scientists who were involved in a previous multi-author book on prostaglandins (see above) kindly agreed to contribute also to this new volume. To them and to the newer, distinguished contributors (particularly those who so helpfully stepped in at the proverbial "eleventh hour" as replacements to fill a totally unanticipated vacancy) I wish to express my thanks and warm appreciation for the vital part they have played in the production of this exciting book. Also, I should like to make a special point of thanking Professor Elisabeth Granstrom for her help, wisdom and in sharing her extensive knowledge in the eicosanoid field. I am indebted to many colleagues who kindly gave assistance, advice or made recommendations of potential contributors and in this regard wish to thank, particularly: Prof Shozo Yamamoto, Dr Christopher D. Breder, Dr Ignatius Tavares, Prof Alan R. Brash, Dr David Horrobin, Prof Brigitta Peskar, Dr Keith Crowshaw, Dr Bob

Coleman, Dr Howard R. Knapp, Dr Stephen Cunnane, Prof Michael Crawford, Dr A. Kirchenbaum, Dr Andrew J. Dannenberg, Prof Alastair Watson, Dr Joel K. Elmquist, Dr Denis McCarthy, Dr Martin L. Ogletree, Dr Frank Fitzpatrick, Prof Simonetta Nicosia, Prof Colin C. Funk, Dr R. Michael Garavito, Dr Krister Green, Prof Constantino Iadecola, Prof Richard J. Kulmacz, Prof William E. M. Lands, Prof W. L. Smith, Dr John A. McCracken, Prof Stephen Smith, Prof John C. McGiff, Prof Daniele Piomelli, Prof Rodolpho Paoletti, Prof Carlo Patrono, Dr Malcolm Peet, Prof Brendan J. Whittle, Dr Norman L. Poyser, Prof Ingvar Bjarnason, Prof Clifford B. Saper, Prof Flavio Cocceani, Prof K. Schroer, Prof Jorge Capdevila, Prof A. Barry Kay, Prof Tak H. Lee, Dr Jonathan P. Arm, Dr Crispin Bennett, Dr Patrick Loll, Dr Marie Therese Droy-Lefaix, Dr John Wallace and Professor K. C. Nicolaou.

Sadly, I have to report that during the gestation period of this book from inception to receipt of the manuscripts several would-be contributors, who were research scientists of international repute...teachers...industrialists...colleagues and friends to many who will read this book, have died. Some of them had completed their contribution to this book, but all their names appear below, as a mark of respect for their different, but very significant contributions to the current pool of knowledge in the field of eicosanoids:

## IN MEMORIAM

Docteur Jacques Maclouf  
INSERM, Hôpital Lariboisière, Paris, France

Doctor Robin Hoult  
Division of Pharmacology and Therapeutics, GKT School of  
Biomedical Sciences, London, UK

Professor Emeritus Alan Bennett, DSc  
Academic Department of Surgery, GKT School of Medicine,  
London, UK

Professor Simonetta Nicosia  
Department of Pharmacological Sciences, University of Milan,  
Milan, Italy

Professor of Medicine Emeritus James B. Lee, MD  
University at Buffalo, New York, USA

Doctor David Horrobin  
Chairman, Laxdale Ltd, Kings Park House, Stirling, UK



# Foreword

Professor Bengt Samuelsson, Nobel Laureate

*Department of Medical Biochemistry and Biophysics, Karolinska Institute, S-171 77 Stockholm, Sweden*

This book edited by Dr Curtis-Prior is entitled *The Eicosanoids*, which term, introduced by one of the major contributors to the field, Dr E. J. Corey, includes all derivatives of 20-carbon-atom fatty acids. The emphasis in this book is of course on arachidonic acid and products formed by oxidation and further transformation.

Structure and function have always played important roles in the eicosanoid field, as well as in many other areas. It was the knowledge of the structures of prostaglandins  $E_1$ ,  $E_2$  and  $E_3$  (Bergström *et al* 1963a; Samuelsson *et al* 1963a) that paved the way for the discovery of the precursor product relationship between essential fatty acids like arachidonic acid and prostaglandins (Bergström *et al* 1964b; van Dorp *et al* 1964). And this finding made it possible to discover the inhibition of the transformation of arachidonic acid into prostaglandins by aspirin and other NSAIDs in 1971 (Vane 1971). At that time cyclooxygenase had not been discovered. This term was introduced in 1974 (Hamberg *et al* 1974a) after the endoperoxide structures  $PGH_2$  and  $PGG_2$  had been discovered. Since cyclooxygenase and COX-1/2 have become household words, I am citing from the 1974 paper (Hamberg *et al* 1974a):

“... It seems likely that  $PGG_2$  is the first stable compound formed from arachidonic acid by the ‘prostaglandin synthetase’. By the isolation of  $PGG_2$  it was demonstrated for the first time that introduction of the oxygen function at C-15 of the prostaglandin occurs by a dioxygenase reaction. We propose the name fatty acid cyclooxygenase for the enzyme that catalyzes the conversion of arachidonic acid into  $PGG_2$  by oxygenation at C-11 and C-15...”

The availability of the endoperoxides  $PGG_2$  and  $PGH_2$  was a prerequisite in the discovery of the transformation product thromboxane  $A_2$  with pro-aggregatory and vasoconstrictor effects (Hamberg *et al* 1975b) and subsequently prostacyclin with opposite effects (Moncada *et al* 1976). These findings extended the cyclooxygenase pathway products from three ( $PGE_2$ ,  $PGF_{2\alpha}$  and  $PGD_2$ ) to five. The molecular basis of the multiple biological effects of single prostaglandins has been elucidated by the discovery of subclasses of prostaglandin receptors (Narumiya 2001). The prostaglandins and their analogues are being used as therapeutic agents for induction of labour and termination of pregnancy and also more recently in the treatment of glaucoma. The identification of the receptors will probably stimulate the development of specific prostaglandin agonists and antagonists as therapeutic agents.

The isolation and cloning of cyclooxygenase constitutes another important milestone in the eicosanoid field (DeWitt *et al* 1988; Merlie *et al* 1988). Although it had been found that the cyclooxygenase can be induced (Masferrer *et al* 1990), it was through the advent of molecular biology that it was discovered that the induced cyclooxygenase activity is due to a different chemical entity, the isozyme COX-2 (Kujubu *et al* 1991; Xie *et al*

1991; O’Banion *et al* 1991). This finding momentarily gave the signal to the pharmaceutical industry to develop new and specific inhibitors of COX-2. Celebra from Searle and Pharmacia and Vioxx from Merck were the first drugs of this category and achieved multibillion dollar sales in their first year.

Structure and function also played an important role in the identification of the elusive “slow-reacting substance of anaphylaxis” (SRS-A). In 1976 Borgeat, Hamberg and Samuelsson discovered the 5-lipoxygenase pathway for transformation of arachidonic acid (Borgeat *et al* 1976). Work on the mechanism of formation of a dihydroxy acid ( $LTB_4$ ) led to the identification of an unstable intermediate ( $LTA_4$ ). This finding played a crucial role in determining the structures of the cysteinyl leukotrienes,  $LTC_4$ ,  $LTD_4$  and  $LTE_4$  (Murphy *et al* 1979; Samuelsson *et al* 1987b). The potent actions of the leukotrienes in inflammation and allergy stimulated the pharmaceutical industry to develop new drugs. Singulair and Accolate from Merck and Zeneca (now Astra-Zeneca), respectively, are now in use in the treatment of bronchial asthma.

I have touched on some of the key findings in the eicosanoid field and especially those related to structure and function. The area is still developing rapidly. This development occurs in many disciplines, such as molecular biology, physiology, pathophysiology, pharmacology and clinical applications. New compounds formed by the transformation of arachidonic acid by other lipoxygenases or a combination of lipoxygenases known as the lipoxins (Samuelsson *et al* 1987b; Serhan *et al* 1999) are still being discovered.

This book edited by Curtis-Prior provides an important update in many different fields of eicosanoid research. It is indeed a very useful summary of the state of the art in a rapidly developing area of research.

## REFERENCES

- Bergström S, Ryhage R, Samuelsson B and Sjövall J (1963a) The structures of prostaglandin  $E_1$ ,  $F_{1\alpha}$  and  $F_{1\beta}$ . *J Biol Chem*, **238**, 3555–3564.
- Bergström S, Danielsson H and Samuelsson B (1964b) The enzymatic formation of prostaglandin  $E_2$  from arachidonic acid. *Biochim Biophys Acta*, **90**, 207–210.
- Borgeat P, Hamberg M and Samuelsson B (1976) Transformation of arachidonic acid and homo- $\gamma$ -linolenic acid by rabbit polymorphonuclear leukocytes. *J Biol Chem*, **251**, 7816–7820.
- DeWitt DL and Smith WL (1988) Primary structure of prostaglandin G/H synthase from sheep vesicular gland determined from the complementary DNA sequence. *Proc Natl Acad Sci USA*, **85**, 1412–1416.
- Hamberg M, Svensson J, Wakabayashi T and Samuelsson B (1974a) Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc Natl Acad Sci USA* **71**, 345–349.