Advances in Inflammation Research
Volume 12

New Perspectives in Anti-Inflammatory Therapies

Volume Editors

Alan Lewis, Ph.D. Neil Ackerman, Ph.D.

Ivan Otterness, Ph.D.

Advances in Inflammation Research
Volume 12

New Perspectives in Anti-Inflammatory Therapies

Volume Editors

Alan Lewis, Ph.D.
Division of Experimental Therapeutics
Wyeth-Ayerst Research
Princeton, New Jersey

Neil Ackerman, Ph.D.
E.I. DuPont de Nemours & Co.
Biomedical Products Department
Wilmington, Delaware

Ivan Otterness, Ph.D.
Department of Immunology
and Infectious Diseases
Pfizer Central Research
Groton, Connecticut

aven Press New York

Raven Press, 1185 Avenue of the Americas, New York, New York 10036

Made in the United States of America

International Standard Book Number 0-88167-362-5
International Standard Serial Number 0197-8322

The material contained in this volume was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived.

Great care has been taken to maintain the accuracy of the information contained in the volume. However, neither Raven Press nor the editors can be held responsible for errors or for any consequences arising from the use of the information contained herein.

Materials appearing in this book prepared by individuals as part of their official duties as U.S. Government employees are not covered by the above-mentioned copyright.

9 8 7 6 5 4 3 2 1

Advances in Inflammation Research

Volume 12

New Perspectives in Anti-Inflammatory Therapies

Advances in Inflammation Research

Preface

The Inflammation Research Association comprises academic and industrial scientists largely from the United States of America whose primary goal is the design and discovery of new and improved therapies for inflammatory diseases. The Third International Meeting of the Association focused attention on immunological and biochemical targets currently under intense investigation and whose modulation may produce anti-arthritic drugs with more than just palliative actions.

It is clear that immunological mechanisms play a pivotal role in the initiation and progression of chronic inflammatory processes. The role of interleukin-1, cachectin, colony-stimulating factors, and interleukin-2 and interleukin-3 in these processes has recently attracted attention. It seems certain that the biotechnological advances made in identifying and characterizing these cytokines will be followed by the development of antagonists to further explore their pathophysiological role. Drug discovery to control the degradative processes occurring in osteoarthritis has proved slow and difficult. One such approach to identifying inhibitors of collagenase is reviewed.

Inflammatory lipid mediators now include the leukotrienes and platelet activating factor in addition to the prostaglandins. The involvement of leukotriene B_4 and related products in inflammation is contentious but progress has been made to identify its receptor and its metabolism. The purification of the human 5-lipoxygenase enzyme responsible for leukotriene synthesis will greatly assist in the development of specific inhibitors with potential anti-inflammatory properties. PAF also may play a significant role in inflammatory processes and the recent identification of PAF antagonists will clarify its pathological significance in disease. There is growing evidence for a prominent role for arachidonic acid metabolites (including prostaglandins and leukotrienes) in nonrheumatic diseases such as psoriasis, asthma, myocardial ischemia, and inflammatory bowel disease. Therapeutic modulation of these mediators consequently may result in new treatments for these diseases.

Several drugs are undergoing extensive preclinical and clinical investigation for the treatment of rheumatoid arthritis. They include cyclosporine, sulphasalazine, gamma interferon, and organoselenium compounds. The clinical evaluation of these and other new agents remains problematic, and recent insights into new approaches to demonstrate efficacy are discussed.

This volume, intended for rheumatologists, pharmacologists, and immunologists, presents a review of many of the recent approaches to the development of new therapies for the arthritides and related inflammatory diseases.

Alan Lewis
Neil Ackerman
Ivan Otterness

Acknowledgments

The chapters collected in this book were presented at the Third International Conference of the Inflammation Research Association in White Haven, Pennsylvania, on October 19 to 23, 1986.

Much of the success of this conference was made possible by the efforts of the following people: D. Argentieri, M. Bliven, R.P. Carlson, G. Ehrlich, K. Gans-Brangs, W. Hageman, L. Liauw, T. Stim, and D. Wolff, as well as the session chairmen and speakers.

The generous financial support of the following companies contributed immeasurably to the overall success of the meeting:

Abbott Laboratories
Boehringer Ingelheim Ltd.
Burroughs Wellcome Company
CIBA-GEIGY Corporation
Collagen Corporation
E.I. DuPont de Nemours & Company
Hoffmann La Roche, Inc.
Eli Lilly & Company
McNeil Pharmaceutical
Merck & Company, Inc.
Merrell Dow Pharmaceuticals, Inc.
Ortho Pharmaceutical Corporation
Panlabs, Inc.
Pfizer Central Research
Schering Corporation
Smith Kline & French Laboratories
Stuart Pharmaceuticals, ICI Americas
Syntex Research
The Upjohn Company
Warner Lambert
Wyeth Laboratories

Contributors

Neil R. Ackerman
E. I. DuPont de Nemours & Co., Inc.
Biomedical Products Department
Experimental Station E–400/2273
Wilmington, Delaware 19898

Christopher W. Benjamin
Cell Biology
The Upjohn Company
Kalamazoo, Michigan 49001

Bruce Beutler
The Howard Hughes Medical Institute
The University of Texas
Health Science Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75235

Robert J. Bonney
Merck Sharp and Dohme Laboratories
P.O. Box 2000
Rahway, New Jersey 07065

Pierre Braquet
Institut Henri Beaufour
17, Avenue Descartes
F-92350 Le Plessis Robinson
France

Kay Brune
Institute of Pharmacology and Toxicology
University of Erlangen-Nürnberg
D-8520 Erlangen
Federal Republic of Germany

Richard D. R. Camp
Institute of Dermatology
St. Thomas's Hospital
Lambeth Palace Road
London SE1, England

Hilary A. Capell
Centre for Rheumatic Diseases
University Department of Medicine
Glasgow Royal Infirmary and Rheumatology Unit
Gartnavel General Hospital
Glasgow, Scotland

Dennis A. Carson
Scripps Clinic and Research Foundation
10666 North Torrey Pines Road
La Jolla, California 92037

George W. Carter
Immunosciences Research
Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

Anthony Cerami
The Laboratory of Medical Biochemistry
1230 York Avenue
New York, New York 10021

P. E. Chabrier
Institut Henri Beaufour
17, Avenue Descartes
F-92350 Le Plessis Robinson
France

Joseph Chang
Wyeth Laboratories, Inc.
P.O. Box 8299
Philadelphia, Pennsylvania 19312

Pojen P. Chen
Scripps Clinic and Research Foundation
10666 North Torrey Pines Road
La Jolla, California 92037

Richard A. Chizzonite
Department of Molecular Genetics
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

John L. Cleveland
Laboratory of Viral Carcinogenesis
Division of Cancer Etiology
National Cancer Institute
Frederick Cancer Research Facility
Frederick, Maryland 21701

Philip Davies
Merck Sharp and Dohme Research Laboratories
P.O. Box 2000
Rahway, New Jersey 07065

K. Dietzel
Institute of Pharmacology and Toxicology
University of Erlangen-Nürnberg
D-8520 Erlangen
Federal Republic of Germany

Gene DiPasquale
Clinical Pharmacology and Experimental Therapeutic
Stuart Pharmaceuticals
Division of ICI Americas, Inc.
Wilmington, Delaware 19897

Niall S. Doherty
Merrell Dow Research Institute
2110 East Galbraith Road
Cincinnati, Ohio 45215

George E. Ehrlich
Ciba-Geigy Pharmaceuticals
556 Morris Avenue
Summit, New Jersey 07901

Stuart W. Evans
Laboratory of Molecular Immunoregulation
Division of Cancer Treatment
National Cancer Institute
Frederick Cancer Research Facility
Frederick, Maryland 21701

William L. Farrar
Laboratory of Molecular Immunoregulation
Division of Cancer Treatment
National Cancer Institute
Frederick Cancer Research Facility
Frederick, Maryland 21701

Christa Fiedler-Nagy
Department of Pharmacology
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Jerome H. Fleisch
Pulmonary Research Group
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Sherman Fong
Scripps Clinic and Research Foundation
10666 North Torrey Pines Road
La Jolla, California 92037

Daniel E. Furst
Department of Medicine/ Rheumatology
University of Iowa Hospitals and Clinics
E400
Iowa City, Iowa 52242

Robert R. Gorman
Cell Biology
The Upjohn Company
Kalamazoo, Michigan 49001

Erich Graf
A. Natterman and Cie. GmbH, Research Laboratories
P.O. Box 350120
D-5000 Cologne 30
Federal Republic of Germany

Ueli Gubler
Department of Molecular Genetics
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Robert E. Handschumacher
Department of Pharmacology
Yale University School of Medicine
333 Cedar Street
Box 3333
New Haven, Connecticut 06510

Nabil Hanna
Smith Kline & French Laboratories
709 Swedeland Road
Philadelphia, Pennsylvania 19479

Matthew W. Harding
Department of Pharmacology
Yale University School of Medicine
333 Cedar Street
Box 3333
New Haven, Connecticut 06510

John L. Humes
Merck Sharp and Dohme Laboratories
P.O. Box 2000
Rahway, New Jersey 07065

J. A. Hunter
Centre for Rheumatic Diseases
University Department of Medicine
Glasgow Royal Infirmary and Rheumatology Unit
Gartnavel General Hospital
Glasgow, Scotland

Sally M. Kennedy
Biogen Research Corp.
14 Cambridge Center
Cambridge, Massachusetts 02142

Patricia L. Kilian
Department of Immunopharmacology
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Robert D. Krell
Stuart Pharmaceuticals
Division of ICI Americas, Inc.
Wilmington, Delaware 19897

Peter Kuhl
A. Natterman and Cie. GmbH. Research Laboratories
P.O. Box 350120
D-5000 Cologne 30
Federal Republic of Germany

Alan J. Lewis
Division of Experimental Therapeutics
Wyeth-Ayerst Research
CN–8000
Princeton, New Jersey 08540

Sigurd Leyck
A. Natterman and Cie. GmbH. Research Laboratories
P.O. Box 350120
D-5000 Cologne 30
Federal Republic of Germany

Alice H. Lin
Cell Biology
The Upjohn Company
Kalamazoo, Michigan 49001

Peter T. Lomedico
Department of Molecular Genetics
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Winston S. Marshall
Pulmonary Research Group
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

J. Martel-Pelletier
Department of Medicine
University of Montreal
Notre-Dame Hospital Research Center
Montreal, Canada

J. M. Mencia-Huerta
Institut Henri Beaufour
17, Avenue Descartes
F-92350 Le Plessis Robinson
France

Robert N. Moore
Department of Microbiology
University of Tennessee
Knoxville, Tennessee 37996

Kevin M. Mullane
Research Department
Pharmaceuticals Division
Ciba-Geigy Corporation
Summit, NJ 07901
(Formerly at Department of Pharmacology
New York Medical College
Valhalla, New York 10595)

J. Nolan
Departmentof Pharmacology
A. H. Robins Company
1211 Sherwood Avenue
P.O. Box 26609
Richmond, Virginia 23261

B. Nürnberg
Institute of Pharmacology and Toxicology
University of Erlangen-Nürnberg
D-8520 Erlangen
Federal Republic of Germany

Ivan Otterness
Department of Immunology and Infectious Diseases
Pfizer Central Research
Groton, Connecticut

Kathryn A. Paganelli-Parker
Department of Immunopharmacology
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Michael J. Parnham
A. Natterman and Cie. GmbH Research Laboratories
P.O. Box 350120
D-5000 Cologne 30
Federal Republic of Germany.

J. P. Pelletier
Department of Medicine
University of Montreal
Notre Dame Hospital Research Center
Montreal, Canada

K. Phadke
Immunology and Connective Tissue Research
Eli Lilly and Company
P.O. Box 618
Indianapolis, Indiana 46206

Walter C. Pickett
Lederle Laboratories
Middletown Road
Pearl River, New York 10965

T. Pullar
Centre for Rheumatic Diseases
University Department of Medicine
Glasgow Royal Infirmary and Rheumatology Unit
Gartnavel General Hospital
Glasgow, Scotland

Victor Radoux
Scripps Clinic and Research Foundation
10666 North Torrey Pines Road
La Jolla, California 92037

Lynn E. Rinkema
Pulmonary Research Group
The Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Richard A. Roberts
Medicinal Chemistry Department
Stuart Pharmaceuticals
Division of ICI Americas, Inc.
Wilmington, Delaware 19897

Marek Rola-Pleszczynski
Immunology Division
Department of Pediatrics
Faculty of Medicine
University Sherbrooke
Sherbrooke, Quebec
Canada J1H 5N4

Carol A. Rouzer
Department of Pharmacology
Merck Frosst Canada, Inc.
P.O. Box 1005
Pointe Claire-Dorval, Québec,
Canada H9R 4P8

Bengt Samuelsson
Department of Physiological Chemistry
The Karolinska Institute
Box 60400
S-104 01 Stockholm
Sweden

John Schindler
Biogen Research Corp.
14 Cambridge Center
Cambridge, Massachusetts 02142

Th. Schneider
Institute of Pharmacology and Toxicology
University of Erlangen-Nürnberg
D-8520 Erlangen
Federal Republic of Germany

Steven Shak
Department of Molecular Biology
Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco, California 94080
(Formerly at New York University Medical Center
550 First Avenue
New York, New York 10016

Andrew Shaw
Medicinal Chemistry Department
Stuart Pharmaceuticals
Division of ICI Americas, Inc.
Wilmington, Delaware 19897

Robert J. Smith
Departmentof Hypersensitivity Diseases Research
The Upjohn Company
301 Henrietta Street
Kalamazoo, Michigan 49001

William F. Stenson
Department of Medicine
Jewish Hospital of St. Louis
St. Louis, Missouri 63110

Alvin S. Stern
Department of Protein Biochemistry
Hoffmann La Roche Inc.
Nutley, New Jersey 07110

Michael E. Weinblatt
Department of Rheumatology and Immunology
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02215

Celia A. Whitesitt
Degenerative Diseases Research Group
The Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Donald J. Wolanin
Medicinal Chemistry Department
Stuart Pharmaceuticals
Division of ICI Americas, Inc.
Wilmington, Delaware 19897

Frederick Wolfe
The Arthritis Center, Suite 230
1035 North Emporia
Wichita, Kansas 67214

David D. Wood
Ayerst Research Laboratories
P.O. Box CN 8000
Princeton, New Jersey 08540

John M. Young
Syntex Research Laboratories
3401 Hillview Avenue
Palo Alto, California 94304

Morris Ziff
Harold C. Simmons Arthritis Research Center and the Department of Internal Medicine
(Inflammation Research Unit)
University of Texas Health Science Center at Dallas
Southwestern Medical School
Dallas, Texas 75235-9030

Contents

Advances in Inflammation Research, Vol. 12.
Edited by A. Lewis et al.
Raven Press, Ltd., New York ©1988.

Emigration of Lymphocytes in Rheumatoid Synovitis

Morris Ziff

The Harold C. Simmons Arthritis Research Center and the Department of Internal Medicine (Inflammation Research Unit), The University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas 75235-9030

The rheumatoid (RA) synovial membrane is infiltrated with lymphocytes, plasma cells, macrophages, and dendritic cells. These cells synthesize large amounts of immunoglobulin (Ig) and rheumatoid factor (RF) (23). RF appears to be synthesized selectively in the RA synovial membrane. Whereas up to 12% of the immunoglobulin M (IgM) spontaneously synthesized by mononuclear cell suspensions obtained from RA synovial membranes was IgM rheumatoid factor (IgM-RF), this autoantibody constituted less than 1% of the IgM synthesized by the peripheral blood mononuclear cells of the same patients (26). This selective synthesis of RF suggests that an agent present in RA synovium stimulates the B cells of the synovium to synthesize RF, and that this agent does not stimulate the B cells of the central lymphoid tissue from which the circulating B cells presumably are derived. In the sense that the RA synovial membrane carries on a selective type of Ig synthesis, it resembles the lymph node, which also selectively synthesizes specific antibodies. Since RA synovium and normal lymph node tissue both synthesize substantial amounts of Ig and produce antibody in a selective manner, it becomes important to compare the mechanisms whereby mononuclear cell infiltrates are mobilized in the two types of tissue.

PATTERNS OF MONONUCLEAR CELL INFILTRATION IN RHEUMATOID SYNOVIAL MEMBRANE

The mononuclear cell infiltrates in the RA synovial membrane are distributed in (1) lymphocyte-rich areas, (2) transitional areas, and (3) interstitial areas (8,10,14) (Fig. 1). The lymphocyte-rich areas are composed mainly of densely aggregated, small lymphocytes of the T cell variety which, although