

Book Reviews

New Drugs for Asthma. Edited by Peter J. Barnes. IBC Technical Services Ltd., London (US distribution, VCH Publishers, Inc. New York). 1989. vii + 199 pp. 21.5 × 30.5 cm. ISBN 1-56081-030-0. \$95.00.

This book, based on a meeting at which the contributors spoke, discusses current trends in pharmacological approaches to the therapy of asthma. In the Introduction and in his Overview of Current Therapy, Peter Barnes notes that the prevalence, severity, and mortality of asthma are on the increase; this in spite of an increase in prescribed antiasthma therapy. While one may argue that these facts may dictate a need for new drugs to treat asthma, the increase in disease incidence, coupled to the enormous effort expended by the pharmaceutical industry in providing novel drugs, probably accounts for a parallel increase in the quantity of books on the subject in recent years.

Notwithstanding, this volume gathers together several useful and readable chapters on newer ideas on how to treat patients with older drugs, as well as chapters on new and relatively untried drugs. Included among the latter are leukotriene and platelet-activating factor receptor antagonists, some of which are in clinical trials; little information as to their usefulness in asthma, however, is currently available. More potent and selective antagonists of histamine H¹ receptors and muscarinic cholinergic subtypes are also discussed. There is a chapter on β -adrenoceptor agonists (old and new), and on attempts aimed at prolonging their durations of action. In Chapter 3, Carl Persson discusses new developments in the clinical pharmacology of xanthines, particularly enprofylline, which have a more encouraging therapeutic index and side-effect profile than those of theophylline, a relatively toxic substance. As well as having overt bronchodilator effects, xanthines may also have several "immunomodulator" actions such as inhibition of inflammatory leukocyte function, reducing edema, and interfering with T-cell activity.

Novel enzyme inhibitors for treating asthma are discussed in several chapters. Thus, drugs which are inhibitors of arachidonic acid metabolism by cyclooxygenase and/or 5-lipoxygenase may provide a means to block the synthesis of several eicosanoids, such as thromboxane, prostaglandin D₂, and the peptidoleukotrienes, which have been implicated in airway disease. In chapter 7, Ted Torphy addresses the potential utility of inhibitors of phosphodiesterase isozymes as bronchodilators and as possible anti-inflammatory agents. There are chapters on inhaled glucocorticosteroids, currently the most rapid growing approach to treating asthma, nedocromil, which is a relative of disodium cromoglycate, and on the theoretical effectiveness of drugs which interfere with cellular handling of Ca²⁺ and K⁺ ions in the airways. Barnes also has a chapter discussing neural and inflammatory peptides, such as tachykinins and bradykinin, and on the therapeutic prospects for their respective receptor antagonists in asthma. The need to develop stable nonpeptide antagonists of inflammatory peptides is, appropriately, stressed.

While the above chapters are informative to those perhaps less well-acquainted with the area, chapters on fish oil and on T-lymphocytes were particularly interesting to me. As mentioned above, inhibition of leukotriene synthesis or pharmacological effects is one aim of those developing antiasthmatic drugs. Recently, it has become apparent that leukotriene biosynthesis may also be altered by changing dietary intake of fatty acids substrates. To that end, there is a growing body of evidence that a fish oil-enriched diet, by reducing the body's ability to generate inflammatory eicosanoids, may have beneficial effects in asthma and other inflammatory diseases. In chapter 15, the role of the immune system, and activated T-lymphocytes in particular, in asthma is discussed. The authors cover potential use of low doses of immunomodulator drugs such as cyclosporin A and methotrexate, which have inhibitory effects on T-lymphocytes, in the prophylaxis of asthma.

Another article discussed the means by which inhaled drugs may be delivered to the lungs. This chapter, on various types of nebulizers and metered dose inhalers and the principles underlying their utility, was most informative to an uninformed individual such as me. Lastly, Geddes addressed the question as to whether, in fact, new antiasthmatic drugs are necessary. He contends that current drugs are, in the majority of cases, adequate and that most asthma patients' disease is controlled well. Improved patient/doctor communication, compliance with dosing regimes, and better delivery systems are suggested to be generally more desirable than new drugs. This is an interesting opinion in these days of frantic quests to discover new, expensive, antiasthmatic drugs.

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Frontiers of NMR in Molecular Biology. Edited by David Live, Ian M. Armitage, and Dinshaw Patel. Wiley-Liss Publishers, New York. 1990. xi + 283 pp. 15.5 × 24 cm. ISBN 0-471-56731-0. \$78.00.

Frontiers of NMR in Molecular Biology presents the proceedings of an Abbott Laboratories-UCLA Symposia Colloquium, held at Park City, Utah, January 12-19, 1989. The text is divided into five sections; Peptides and Peptide-Protein Interactions, Proteins, Carbohydrates, Nucleic Acids, and Discussion/Summaries with a total of 25 separate research papers. Investigators from a variety of disciplines present research on the use of heteronuclear and homonuclear 2D and 3D NMR techniques for the determination of the structure and dynamics of a variety of biomolecules, as well as complexes of biomolecules. Contributors describe a broad-range of NMR techniques for the conformational analysis of biomolecules in solution, some of which are summarized below.

Summer, Hare, and co-workers presented work on the determination of the three-dimensional structure of the first zinc finger domain from the GAG protein of HIV-1 using a novel NMR/distance geometry/NOE back-calculation approach. In this approach the three-dimensional structures generated using intramolecular distances obtained from NOE data in a distance geometry calculation is then used to back-calculate the NOESY spectrum. The structure of the zinc finger is continually refined until the experimental spectrum and the calculated NOESY spectrum are identical. The refined structure is now representative of the true solution structure which gave the observed experimental spectrum.

Zuiderweg and Fesik presented two papers describing the application of heteronuclear 3D NMR experiments to solving structural problems in molecular biology. Specifically the experimental details of the HMQC-COSY and HMQC-NOESY 3D NMR experiments, and their use to extract information from regions of the spectra with severe overlap were presented. By application of the HMQC-NOESY experiment, NOE data could be extracted from a region of the spectrum that was unresolved in the normal 2D NOESY experiment. Papers by Bothner-By et al., Hawrot et al., Fesik et al., Shon et al., and Pelton et al. involved the study of different biological complexes, varying from peptide membrane interactions to DNA duplexes using 2D NMR experiments. Papers by Redfield, Jones et al., and Scheraga presented research involving computer simulation of 2D NMR data or use of 2D NMR data to generate protein structures. The remaining papers deal with a wide range of topics using various NMR techniques for the determination of structural and dynamic properties of biomolecules in solution.

The reader is presented, in short research papers, an overview of the state of the art in the use of 2D and 3D NMR experiments to solve structural problems involving biomolecules. Most of the papers are well referenced, with references through early 1989.

By presenting a wide overview of the use of NMR in molecular biology, the text is a valuable reference tool for the practicing medicinal chemist interested in structural studies of biomolecules. This text will be a valuable tool for beginning graduate students in the field to use as a template in their own research and for the multidisciplinary use of NMR in biology and chemistry.

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Nitro Compounds. Recent Advances in Synthesis and Chemistry. Edited by Henry Feuer and Arnold T. Nielsen. VCH Publishers, Inc., New York. 1990. xvi + 636 pp. 16 × 24 cm. ISBN 0-89573-270-x. \$125.00.

This is the third book in the *Organic Nitro Chemistry Series* which is directed toward organic nitro chemistry in its broadest sense by including related classes of compounds such as nitramines, nitrates, nitrones, and nitrile oxides. The present volume consists of four chapters. In the first chapter the nitro function as a leaving group is reviewed. In particular, the growing utility of nitro compounds in carbon-carbon bond formation, the versatility of Michael and nitroaldol condensations in producing valuable intermediates with predictable stereochemistry, the facile transformation of the nitro group into other functionalities, and the specificity of Diels-Alder reactions of unsaturated nitro compounds are thoroughly treated. The second chapter reviews the topic of nitro sugars. New syntheses of carbohydrates use improved methodologies for introducing a nitro group by amine oxidation and for assembling the carbon skeleton by the nitroaldol reaction. The third chapter thoroughly describes the chemistry of nitrogen pentoxide, its synthesis, and its utility in the preparation of nitroaromatic, alicyclic, and heterocyclic compounds and nitramines. In the final chapter the chemistry of aliphatic fluoronitro compounds is comprehensively reviewed.

The remarkable utility of nitro compounds as reactive intermediates in organic synthesis is clearly demonstrated in this thoroughly referenced volume. All synthetic chemists will surely find subjects of potential utility in the book. It is highly recommended for all chemistry libraries.

Staff

Oncogenes and the Molecular Origins of Cancer. Monograph 18. Edited by R. A. Weinberg. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. 1990. x + 367 pp. 15.5 × 23 cm. ISBN 0-87969-340-1. \$55.00.

This book represents a comprehensive yet succinct overview of the role of oncogenes, tumor suppressor genes, and growth factors in the etiology and progression of cancer. It is primarily intended to present basic concepts in simplified terms to an audience not familiar or expert in the oncogene/growth factor field. As such, this book has succeeded quite admirably since the research area that is covered is enormous and in some instances quite complex. The chapters are a collection of contributions from leading researchers in the field. The range of subject matter covered includes the structural and functional characteristics of retroviral oncogenes, growth factors and growth factor receptors, signal transduction mechanisms by oncogenes and growth factors, DNA tumor viruses, tumor suppressor genes, and oncogenes involved in experimental carcinogenesis and in human cancers.

Overall this is an excellent primer that provides a series of stimulating presentations that challenge the reader. Since there are multiple authors, there is a tendency at times for some unavoidable overlap and redundancy in certain topics that are covered. Nevertheless, this is a minor problem and does not distract from the continuity of this book. There are some chapters that are truly outstanding. For example Harold Varmus has presented

a cohesive and chronological survey of the oncogene/growth factor field that helps to orient the reader. Other excellent and informative chapters are those contributed by Tony Hunter on protein kinases, Frank McCormick on the *ras* oncogenes, Robert Eisenman on nuclear oncogenes, and Eric Stanbridge and Webster Cavenee on tumor suppressor genes. However, there are other chapters such as those related to signal transduction and adenovirus oncogenes that are somewhat disappointing in that they are cumbersome and difficult to negotiate. This is particularly true for the chapter on signal transduction and intracellular messengers. The information that is presented is extremely intricate and varied, which may contribute to this problem. Although the chapter is good in parts, the authors are somewhat stochastic in their presentation and fail to integrate the multiple intracellular second messenger pathways that have so far been described into some sort of concept relating to growth factor and hormonal signalling. A flow diagram(s) would have been instructive for this purpose. The closing two chapters by Robert Weinberg and Michael Bishop refocus the reader's attention to the progressive interactions that occur between different activated cellular protooncogenes and tumor suppressor genes which are necessary for cellular transformation *in vitro* and presumably for *in vivo* tumor development. Since this volume represents an effort to synthesize information on oncogenes and cancer, it would have been informative and useful to include a chapter on the general structure and biology of transforming retroviruses. Nevertheless, this book is a worthwhile addition for those researchers interested in understanding the basic mechanisms of cellular transformation as these may relate to clinical cancer.

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Principles of Drug Action. The Basis of Pharmacology. Third Edition. Edited by William B. Pratt and Palmer Taylor. Churchill Livingstone, Inc. New York. 1990. xiii + 836 pp. 18 × 25 cm. ISBN 0443-08676-1 (paperback). \$49.95.

There have been tremendous advances in the understanding of drug action since the second edition of this textbook was published in 1974. In order to present current concepts of pharmacology without substantially increasing the length of the text, the present editors have deleted chapters on drug toxicity, drug development, and drug evaluation. These sections have been replaced with ones placing greater emphasis on fundamental principles. The first two chapters deal with the molecular basis of pharmacologic selectivity and drug action. These are followed by a chapter on drug absorption, distribution, and elimination and one on the time course of drug action. Next, the principles and pathways of drug metabolism are presented. This is followed by a new chapter in which recent advances in defining the structures of drug-metabolizing enzymes and their regulation are reviewed. New techniques of molecular biology are prominent in this chapter as well as the ones on pharmacogenetics, drug resistance, carcinogenesis, and drug tolerance and physical dependence.

This edition of *Principles in Drug Action* keeps abreast of the great strides that have been made in understanding drug action. Principles are lucidly presented by contributing authors selected because of their specific expertise. The editors have integrated these contributions to achieve the consistency of style and content that characterized earlier editions. All scientists, both practitioners and students, concerned with pharmacology, medicinal chemistry, and related fields will find this edition a must for their personal libraries.

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