Book Reviews

From Medical Chemistry to Biochemistry. The Making of a Biochemical Discipline. By Robert E. Kohler. Cambridge University Press, Cambridge. 1982. ix + 399 pp. 16 × 23.5 cm. $34.50.

With the approach of the diamond jubilee of the establishment of medicinal chemistry, it would have been appropriate if the word, medicinal chemistry, would have been indexed or otherwise mentioned in this book by a historian of science on the borderline between biology, chemistry, and medicine. No such entry has been made. Neither does one find the names of bona fide medicinal chemists in this volume; only a few eminent natural products chemists are mentioned whose studies in their later years included structure–activity relationships of variants of their earlier natural prototypes. Instead, this book traces the still unresolved power struggle of academic biologists and physiologists on the one side and chemists on the other side trying to carve out lucrative niches for the emerging composite field of biochemistry in their own respective university departments. Attempts to agree on their roles in medical chemistry also failed. Medical chemistry has been and remains analytical chemistry concerned with the analysis of body fluids and tissues for diagnostic purposes. While it uses biochemical techniques, it has not contributed to the conception or basic methodology of these tests.

The role of biochemists in industrial laboratories has also been ignored in Kohler's book. His account presents a comprehensive and well-documented history of empire building in European and American universities, where domineering personalities with strong administrative instincts—not always scientific preeminence—carved out their own areas of interest at the expense of, instead of cooperating with, their colleagues. It is significant that the same derogatory remarks made by physiologists, as well as by chemists, about biochemistry a century ago have been voiced by biochemists, when molecular biology recently began to trespass on their turf. These battles and intrigues went on in Tübingen, in Freiburg, at Illinois and NYU, and dozens of other institutions. Anyone interested in these arguments and even scandals fought out bitterly in graduate and medical schools by the classical greats of chemistry and biomedical sciences will get his or her money's worth out of these stories.

Maybe it is just as well that medicinal chemistry—as contrasted sharply with Kohler's medical chemistry (urinalysis and the like)—arrived on the scene belatedly. Even so, we had to insist on our own identity. Pharmacology had staked out several medicinal chemical areas as its own, and it was fortunate that pharmacologists were soon so overwhelmed with biomechanistic problems that they abandoned their intrusions into topics that could be solved more efficiently by chemists. Chemists, in turn, should stay away from pinching the tails of mice or dissecting renal arteries of dogs. If they want to see what happens if they do not stay on their side of methodological innovation, let them read the book under review. This history of smoldering conflict between chemists and biologists of varying ilk should teach us the need to cooperate with, rather than to impose adamant measures on, our colleagues across the aisle.

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Dopamine Receptor Agonists. Volumes 1 and 2. Edited by Arvid Carlsson and J. Lars G. Nilsson. Swedish Pharmaceutical Press, Stockholm. 1983. 220 + 256 pp. ISBN 91 86274-10-4. 300 kronor.

These two small volumes (published as a supplement to *Acta Pharmaceutica Suecica*) record the presentations at the Symposium on Dopamine Receptor Agonists held in Stockholm, April 20–23, 1982, under the auspices of the Swedish Academy of Pharmaceutical Sciences. Volume 1 contains sections entitled "Opening Sesssion" and "Functional Aspects and Classification of Dopamine Receptors". Volume 2 contains sections entitled "Structure–Activity Relationships", "Clinical Aspects", and "Posters".

The editors/organizers have succeeded in assembling an impressive roster of pharmacologist and medicinal chemist researchers in the dopamine area, who reflect the broad spectrum of biological and chemical aspects of this neurotransmitter. A brief introductory section by Arvid Carlsson and a lucid description of classification of dopamine receptors by Keith A. Wreggett and Philip Seeman set the stage for the succeeding material in the volumes. It is this reviewer's personal prejudice that the other papers in the "Opening Session" section should have been placed elsewhere in the volume, in that they record specific studies rather than contributing to a broadly based, general introduction. The section (Volume 2) on "Clinical Aspects" comprises four short papers on four different topics, which seems inadequate for the title of the section.

Overall, the two volumes are excellent. The individual papers are well written, and they report some exciting and significant work. The shorter "Poster" reports are of similar high quality. Printing is very good, and few typographical errors were noted. A defect in the two volumes is their lack of any index.

The two volumes provide a sense of the state of dopamine research as of April, 1982. They are recommended for chemists and pharmacologists, and this reviewer believes that they are mandatory reading material for basic science researchers in the area of the dopaminergic nervous system.

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Adrenoceptors and Catecholamine Action. Part B. Edited by George Kunos. Wiley, New York. 1983. vii + 327 pp. 17 × 24 cm. ISBN 0-471-05726-6. $75.00.

As denoted by the title this is the second part of a series on catecholamines and the receptors they are capable of activating. The nine chapters are entitled (1) "Structure-Activity Relationships of Alpha-Adrenoceptor Agonists", (2) "Phosphatidylinositiol Metabolism and α-adrenoceptor Mechanisms", (3) "Release-Modulating Adrenoceptors", (4) "Adrenergic–Cholinergic Interactions", (5) "Adrenoceptors in Skeletal Muscle", (6) "Adrenergic Influence on Peripheral Hormone Secretion", (7) "Adrenoceptors and Central Cardiovascular Regulation", (8) "Adrenoceptors and the Regulation of Salivary Gland Physiology", and (9) "Microscopic Localization of Adrenoceptors".

In reading most of the chapters in this volume, a knowledge of the autonomic nervous system and understanding of drug–receptor interactions is required. The expertise of the contributors provides good insight into the respective areas covered in each of the chapters. The first chapter by Ruffolo provides an exceptional coverage of structure–activity relationships in the adrenergic area. A number of "holes" in the literature are pointed out. This chapter also has some very nice illustrations and pertinent tables for helping to convey important points. This chapter, in contrast to the latter chapters, provides relevant structures for material discussed within the chapter. A lot of very good technical knowledge is provided in the various chapters. In a number of instances, the chapters provide insights into the mechanisms of action of adrenergic drugs and the influence of catecholamines on various hormone secretions. The importance of pre- and postsynaptic interactions are discussed. The overlap with cholinergic involvement into the action of catecholamines is presented. Various methods are discussed for identifying receptors, and a discussion is presented on the importance of the techniques available today and why adrenergic receptors should be localized.

The volume is well indexed and provides, like its predecessor, a diverse set of topics on adrenergic receptors and their importance and new research possibilities. This volume is expensive for its size. It should be of prime importance to pharmacologists and those interested in the structural requirements and action of adrenergic drugs.

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LERS Monograph Series. Volume 1. Betaxolol and Other β_1-Adrenoceptor Antagonists. Edited by P. L. Morselli, J. R. Kilborn, I. Cavero, D. C. Harrison, and S. Z. Langer. Raven Press, New York. 1983. xxii + 385 pp. 16 × 24 cm. ISBN 0-89004-976-9. $38.00.

This monograph presents the proceedings of the International Symposium on Betaxolol held in Paris in March 1982 and organized by the Laboratories d'Etudes et de Recherches Synthelabo (LERS). Betaxolol (available in France under the name of Kerlone) is a β_1-adrenoceptor antagonist synthesized and developed by LERS. This volume reviews the pharmacological profile of betaxolol and assesses the clinical experience with this drug. Attention is devoted to comparison of betaxolol with other available β-blocking agents. A major portion of the book presents clinical studies with betaxolol in treatment of hypertension and angina pectris.

This volume will be of interest primarily to cardiologists and clinical pharmacologists. A subject index, but no author index, is included.

Staff

Targeted Drugs. Edited by E. P. Goldberg. Wiley, New York. 1983. xi + 296 pp. 17 × 24 cm. ISBN 0471-04884-4. $55.00.

The need to selectively target any drug is not only desirable but of utmost necessity, especially in cancer chemotherapy. All antineoplastic drugs known so far are limited to their selectivity and therefore tend to destroy all actively proliferating cells, including the normal cells. Biomedical scientists, as well as the physicians, are eager to develop drug-delivery systems that would lower or eliminate the side effects of drugs, and, thus, increase their therapeutic index. It is anticipated that substantial resources and efforts will be spent in the next decade for research to develop novel drug-delivery systems.

This book is a timely collection of ten essays covering a wide area of drug targeting, including antibody-directed drug targeting, hormone–receptor targeting, polymers as tumor-specific drug carriers, magnetic targeting of drugs, and the use of viable cells as drug carriers. In an edited volume such as this one, it is the ability of the editor to select and attract the right contributiors with the right topic that makes or breaks the success of the book. The contributors are, indeed, some of the recognized leaders in the field of drug targeting. The essays are well written and are bound to attract biologists, medicinal chemists, and physicians to further research in targeted drug-delivery systems for the drugs of their interest.

The part of this book that is of the greatest current interest is to be found in the three chapters devoted to the use of tumor-specific antibodies as vehicles for drug targeting. The technology described in these chapters will be more widely explored as more specific monoclonal antibodies to tumor-specific antigens become available and as the technology of in vitro hybridization to produce human monoclonal antibodies becomes perfected.

Overall, the editor sets out to provide a comprehensive and balanced state-of-the-art status on targeted drugs. Although this "balanced character" of the book appears to be slightly lost due to exclusion of a review on liposomal techniques for targeting drugs, it must be emphasized that many important topics are covered. Altogether, the book is well written and a must for those who are interested in novel drug-delivery systems, in general, and more specifically, in targeted drug delivery.

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Natural Product Chemistry. A Mechanistic and Biosynthetic Approach to Secondary Metabolism. By Kurt B. G. Torssell. Wiley, New York. 1983. xii + 401 pp. 16 × 23.5 cm. ISBN 0471-10378-0. $54.95.

At first glance this monograph appears to be yet another book on secondary product biosynthesis. However, the author's mechanistic approach, based on actual enzyme-catalyzed reactions and not solely representing paper chemistry, makes this book a needed addition to the literature on the biosynthesis of secondary natural products.

Though a mild criticism, it is difficult to distinguish generally accepted or proven mechanisms from purely speculative ones, even though it is stated in the preface that "The critical reader will certainly be able to differentiate the speculative from the accepted". This requires looking up the original literature and verifying a specific mechanism.

Although, from the title, the reader expects secondary product metabolism, there is a considerable amount of primary metabolism included. Perhaps as much as one-third of the material is devoted to the formation and degradation of fatty acids, carbohydrates (glycolysis, interconversion of monosaccharides, and the citric acid cycle), amino acids (all amino acid in proteins are listed and their synthesis, degradation, and interconversion discussed), and nucleotides. Besides using up space that should be dedicated to the main theme of the text, the mechanism of the biosynthetic reactions leading to secondary natural products, the treatment of the primary metabolic pathways is generally simple and contains a number of errors (for example, coenzymes do not catalyze reactions, enzymes do; or one cannot inhibit DNA, but rather DNA polymerase or the template activity of DNA; or "the physiological mechanism of action of ascorbate is not known", yet a number of years ago it has been shown that ascorbate is required for the enzyme-catalyzed hydroxylation of lysine and proline in protocollagen). A reader would gain more if he would read these sections in an up-to-date biochemistry textbook.

The book is divided into 8 chapters covering the traditional secondary metabolites. Chapter 1 is an introduction that covers an overview section on "biochemical reactions and organic reaction mechanisms", as well as a short overview of pathways and a shorter treatment of the elucidation of metabolic sequences. Perhaps a reader, especially a graduate student, would have gained more from a more thorough treatment of the methodology for the study of secondary metabolism (which is somewhat distributed in sections throughout the remaining chapters) than a considerable section on chemical ecology, which is also included in Chapter 1. Chapter 2 discusses mono-, di-, and polysaccharides, especially the primary metabolic pathways, but also the formation and metabolism of secondary carbohydrates. The shikimic acid pathway is covered in Chapter 3. Also in this chapter are a valuable section on biological hydroxylation and a short section telling the reader that total chemical synthesis is no longer required "for the purpose of proving or confirming structures", which is debatable. Chapter 4 discusses the polyketide pathway leading to a variety of compounds, including halogen compounds. This chapter also contains an excellent section on the use of NMR techniques in biosynthetic studies and a good section on oxidative coupling of phenols. The isoprenoid pathway is discussed in Chapter 5. Again, a methodology section is included, namely, an introductory treatment of "optical rotatory dispersion and circular dichroism—the octant rule".

Chapter 6 treats the metabolism of amino acids, peptides, and proteins. Included are mostly primary metabolic interconversions of amino acids, but also cyanogenic glycosides, β-lactam antibiotics, and an excellent mechanistic discussion of the enzymatic reactions using pyridoxal phosphate as a coenzyme. A short section on the prebiotic formation of amino acids is included in Chapter 6 but seems somewhat out of place in a book dealing with biosynthetic mechanisms of secondary metabolites. The alkaloids are treated

in Chapter 7, and N-heteroaromatics are treated in Chapter 8. The latter contains sections on purines, pyrimidines, pteridines, pyrroles, and porphyrins.

The chapters are adequately referenced; however, most references are from 1960–1970, and only very few from 1980–1981. The book would have been considerably strengthened if more recent biosynthetic studies on the enzymatic formation of alkaloids could have been included, as, for example, lupine alkaloids and monoterpene indole alkaloids.

The index is adequate and lists, besides virtually all the compounds listed in the text, plant names (Latin) and general groups of compounds.

The book is well written, and major structural errors are few. The book's greatest strength is its many eloquent mechanisms, both compiled from the literature as well as proposed by the author.

Although recommended, by the publisher, as a reference book for research workers in the area of biosynthesis, this book can be rather strongly recommended for graduate students as a start in understanding secondary natural product formation. As a matter of fact, this monograph would make an excellent textbook for a course in secondary natural product chemistry and biosynthesis, if it would not be for the somewhat exuberant price.

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Calcium Antagonism in Heart and Smooth Muscle. By Albrecht Fleckenstein. Wiley, New York, Chichester, Brisbane, Toronto, and Singapore. 1983. xvi + 399 pp. 16.5 × 24 cm. ISBN 0-471-054356. $60.00.

Professor Fleckenstein, a leader in Ca antagonism research, provides an excellent summary of the fundamental role of Ca in myocardial tissue, of the mechanism of action of Ca antagonists, of the principles of cardioprotection, of Ca antagonist influence on pacemaker activity, of the effects on ectopic cardiac autorhythmicity, and of drug-induced smooth muscle relaxation and cardiovascular therapy and concludes with prospective topics in Ca antagonism research. This treatis is well referenced with literature titles and has an excellent index. Print, paper, and figures are of good quality. Only potent, clinically useful group A drugs, such as nifedipine, verapamil, D600, and diltiazen, and less specific group B substances, such as prenylamine, fendiline, terodeline, perhexiline, and carovine, are considered. This work will be most attractive to pharmacologists, biochemists, electrophysiologists, and clinicians. Medicinal chemists would experience an in-depth biological summary of considerable interest, but little is provided in the way of chemically oriented prospective topics. Biochemical discussions could provide a basis for drug design.

This book is based on the pioneering work of its author and reflects his definitions and classification of group A, B, and C compounds. For these reasons, the many studies of experimentally interesting intracellular Ca antagonists having considerable specificity of action are not discussed. β-Blockers, barbituates, hydantoins, local anesthetics, antiarrhythmics (having a Na-based mechanism), and antifibrillatory drugs are characterized as group C compounds comprising substances with "unspecific Ca antagonistic side effects" and are not considered in this work. Since structures and physical–chemical properties of compounds found in groups A and B are diverse, this reviewer anticipates that subclassifications of these materials will evolve as the details of their pharmacological–biochemical properties are refined.

Chapters are well written and interesting, providing the reader with biochemical interpretations and the significance of cellular substructures. Interrelationships of Ca and other significant cations is considered. Studies summarized wherein verapamil prevents arterial calcium overload and concomitant lenticular calcification causing cataracts in alloxan-diabetic rats are impressive. In the prospective research topics chapter, biochemical or biophysical identification of presumptive Ca receptors as related to discrimination between individual Ca antagonists is proposed; this would seem to be a most worthy endeavor. Additionally, Ca overload is a risk factor predisposing arteries to atherosclerotic degeneration. Thus, the many disease states and normal functions involving Ca-based mechanisms will provide researchers with numerous possibilities for study for many decades.

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