

we are exploring the possibility that the increased binding affinity of selected glucocorticoid esters may be used to develop antiglucocorticoids^{15-19,32} or compounds capable of alkylating glucocorticoid receptor site(s).

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were determined on a Beckman IR-8 or a Perkin-Elmer 297 spectrometer. NMR spectra were determined on a Varian A-60 or on a Varian T-60 spectrometer in CDCl₃ with a Me₄Si internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. All compounds synthesized or submitted to the competitive binding assay appeared to be pure as shown by TLC and showed the expected IR and NMR spectra.

Trimethyl orthobutanoate³³ was synthesized from butyronitrile. The known 11 β ,17 α ,21-trihydroxy-4-pregnene-3,20-dione 17-acetate was synthesized from cortisol essentially according to the procedure of Gardi, Vitali, and Ercoli²⁵ but substituting triethyl orthoacetate for trimethyl orthoacetate. Similarly, 11 β ,17 α ,21-trihydroxy-4-pregnene-3,20-dione 17-butanoate³⁴ was synthesized from cortisol. The 11 β ,17 α ,21-trihydroxy-4-pregnene-3,20-dione 17-pentanoate was a gift from Westwood Pharmaceuticals, Inc., Buffalo, NY.

Conditions for Esterifying the C-21 Hydroxy Group of Cortisol and of Cortisol 17-Esters. Cortisol or the appropriate cortisol 17-ester (500 mg, 1.1–1.2 mmol) was dissolved in 1 mL of pyridine and 1 mL of acetic, propionic, butyric, or valeric anhydride. The solution was allowed to stand at room temperature overnight. Water was added, and the mixture was extracted with CH₂Cl₂ twice. The organic extracts were combined, washed twice with 10% HCl, dried (MgSO₄), and concentrated to dryness under vacuum. The residue was chromatographed on 100 g of

silica gel, eluting with CHCl₃-acetone. The esters obtained are listed in Table I.

Competitive Binding Study. In a typical experiment, six male Sprague-Dawley rats weighing 80–100 g were decapitated, and the thymus glands were exercised and freed of blood and connective tissue. The pooled thymuses were weighed, and a volume (100 mL/1 g of tissue) of TED buffer (0.01 M Tris, 0.0015 M EDTA, 0.001 M dithiothreitol, pH 7.4) containing 10% glycerol was added. The tissue was minced with a pair of scissors and homogenized in a glass-Teflon homogenizer at 4 °C (ten complete strokes of the motor-driven pestle were applied). The homogenate was centrifuged (Beckman LS-10 ultracentrifuge using an SW-30 rotor) for 1 h at 100000g, 4 °C, and the supernatant fraction (cytosol) was retained. The supernatant was treated with a charcoal suspension (1 g of activated charcoal, 50 mg of Dextran T-70 in 10 mL of TED buffer) that was 20% of the total volume of the supernatant and stirred at 4 °C for 10 min to remove any endogenous steroid. The mixture was centrifuged twice at 15000 rpm in a Sorvall refrigerated centrifuge at 4 °C to ensure removal of the charcoal.

Conical tubes (2 mL, polyethylene) containing 2 × 10⁻⁸ M (1,2-³H)dexamethasone (Amersham, 25 C/mmol), 2 × 10⁻⁸ M [³H]dexamethasone and 2 × 10⁻⁶ M cold dexamethasone, and 2 × 10⁻⁸ M [³H]dexamethasone and a 1- to 100-fold excess of cold test compound were allowed to incubate with 0.5 mL of the above cytosol preparation at 4 °C for 4 h. After the incubation period, the tubes were each treated with 100 μ L of the above charcoal suspension, vortexed, and incubated for 10 min at 4 °C. The tubes were then centrifuged in a Beckman clinical centrifuge at 1800 rpm for 5 min at 4 °C. Two-hundred microliters of the supernatant from each tube was assayed for radioactivity in 7 mL of ACS scintillation fluid (Amersham) using a Packard Tricarb liquid scintillation counter. Each sample was counted for 5 min, and the raw counts per minute were used in the calculation of specific binding. Each experiment was run making triplicate determinations of competition. All experiments were repeated using a different pool of cytoplasm at least twice and in selected cases three times.

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Book Reviews

Amino Acids, Peptides and Proteins. Volume 11. Specialist Periodical Reports. By R. C. Sheppard, Senior Reporter. The Chemical Society, Burlington House, London. 1981. xxi + 552 pp. 13.5 × 22.5 cm. \$131.50.

The latest volume in this continuing series covers the literature published during 1978 and continues to follow the time-honored style and format of its predecessors. The usual major topics are reviewed by the dedicated staff of "Reporters": amino acids (G. C. Barrett); structural investigations of peptides and proteins (R. Harrison, M. Rangarajan, and A. Dell); X-ray structure (W. D. Mercer); conformational interactions in solutions (R. H. Pain and eight other contributors); peptide synthesis (I. J. Galpin and M. F. J. Galpin); chemical structure and biological activity of hypothalamic releasing hormones (D. H. Coy), posterior pituitary peptides (M. Manning, M. Kruszinski, and W. H. Sawyer), pancreatic hormones (D. Brandenburg, D. Saunders, and B. E. Rudolph), gastrointestinal hormones (D. Gillesen and R. O. Studer), vasoactive peptides (P. D. Roy), and the enkephalins and endorphins (P. W. Schiller); and, lastly, complexes of amino acids, peptides, and proteins (R. W. Hay and D. R. Williams). As in

other volumes, reaction schemes and structural formulas are strategically placed in the text, tables are used generously, and an author index is provided. Sad to note is that purchasers of Volume 11 will have to pay almost exactly twice as much as they did for Volume 10, and *eight times* more than for Volume 6.

Staff

Biochemistry of Disease. Volume 8. Polyamines in Biology and Medicine. Edited by David R. Morris and Laurence J. Marton. Marcel Dekker, New York. 1981. xiv + 459 pp. 15 × 23 cm. \$55.00.

Polyamines are multivalent ligands whose ubiquitous presence in plants, animals, and microorganisms signals their strategic participation in a variety of processes essential for cell growth and function. Putrescine, spermidine, and spermine are the most biologically significant members of the class of polyamines, and alterations in their metabolism are associated with a large number of both neoplastic and nonneoplastic clinical conditions. Research on the biology of polyamines has been remarkably active during

recent decades, and the need to assess past, present, and future directions in the field was met by a workshop held in July 1979 at Colby-Sawyer College, New London, NH. Contributions by the participants in this conference form the basis of this book.

The volume is divided into three major sections that deal with the following aspects of polyamines: biosynthesis and metabolism; biological functions; and relationships to clinical medicine.

The first section on Biosynthesis of Polyamines contains nine chapters which are concerned with catalytic mechanisms of polyamine biosynthesis in prokaryotic and eukaryotic organisms and plants, the cellular and pharmacological regulation of the enzymes involved in polyamine biosynthesis, the formation and role of polyamine conjugates, and the functional significance of polyamine oxidation by amine and diamine oxidases. Of particular interest to the medicinal chemist are the chapters "The Biosynthesis of Putrescine" (Chapter 1), "Aminopropyl Group Transfers in Polyamine Biosynthesis" (Chapter 2), "Amide-Bond-Forming Reactions of Polyamines" (Chapter 7), and "Oxidation of Polyamines and Diamines" (Chapter 8).

The second section on Biological Functions of Polyamines consist of seven chapters whose primary concerns are the theoretical basis for polyamine-poly-nucleotide interactions, the role of polyamines in protein synthesis and in stimulation of animal cell proliferation, studies of the physiological effects of putrescine and spermidine in *E. coli*, and the biochemistry and biological effects of polyamine antimetabolites. Noteworthy are the following two chapters: "Interactions of Polyamines with Polynucleotides" (Chapter 10) rigorously reviews the basic ideas of modern polyelectrolyte theory and indicates how these concepts can be used to explain the types of molecular interactions observed between polyamines and nucleic acids; "Polyamines and Protein Synthesis" (Chapter 11) elucidates the molecular basis for polyamine participation in protein synthesis and clearly indicates how the charge density and inherent conformational flexibility within the linear structure of spermine allow it to stabilize a tRNA structure different from that stabilized by polyvalent inorganic cations. These two chapters are particularly significant because they allow one to understand and appreciate why polyamines, as ligands, do not merely interact in a manner similar to that of inorganic polyvalent cations but have additional biochemical functions which are uniquely defined by their more complex molecular structures. A lengthy chapter on "Polyamine Antimetabolites: Biochemistry, Specificity and Biological Effects of Inhibitors of Polyamine Synthesis" provides an excellent summary of the chemical and biochemical properties of these polyamine antimetabolites. The recent and significant development of α -(difluoromethyl)ornithine, a potent irreversible inhibitor of ornithine decarboxylase, as a pharmacological agent is discussed in this chapter (as well as in Chapters 14, 22, and 23). Well-focused toward the interests of medicinal chemists, this chapter on antimetabolites is highly recommended for reading.

The final section on Relationship of Polyamines to Clinical Problems has seven chapters. Several focus on the clinical implications of monitoring levels of polyamines and their metabolites in neoplastic disease states and nonneoplastic conditions that include pregnancy, fertility, cystic fibrosis, uremia, aging, and allergic states, as well as some conditions of specific endocrinologic interest. Three chapters focus on the pharmacological aspects of the use of inhibitors of polyamine biosynthetic pathways. One of these chapters deals with *S*-adenosylmethionine decarboxylase inhibitors, another deals with ornithine decarboxylase inhibitors, and a third deals with the implications of the interrelationship of pyridoxal phosphate and polyamine levels in clinical as well as laboratory situations.

This volume, which is an attempt to provide an updated, broad, and critical view of polyamine research, has succeeded admirably in its intent. Most chapters are well organized and provide a convenient outline to their specific content. Where included, discussions on "Unresolved Issues and Future Directions of Research" are most helpful. Some chapters have notes added in proof and references as recent as 1981, which attest to the up-to-date nature of the book. The editors recognize that there is considerable overlap in the material presented in various chapters. However, this does not detract from the volume but actually makes it even more useful to investigators in a wide variety of disciplines who might want to focus on only a small number of chapters.

This book is dedicated to the memory of Chandrakant Dave, whose untimely death in 1978 deprived those working in the field of polyamines of a gifted researcher and fine friend. It is indeed a fitting tribute to him. This volume should become an indispensable source book for a broad spectrum of investigators, whether they consider their interests in polyamines as primary or peripheral.

*Department of Physiology and
Biophysics
Washington University School of
Medicine
St. Louis, Missouri 63110*

Janice R. Sufrin

Metal Ions in Biological Systems. Volume 12. Properties of Copper. Edited by Helmut Sigel. Marcel Dekker, New York and Basel. 1981. xx + 353 pp. 15 × 23 cm. \$57.50.

The development of our knowledge of the biological roles of copper is among the more recent advances that have taken place in our understanding of the elements essential for the growth and development of living organisms. In the past 15 years, this subject has advanced from one which could be adequately covered by a single text (by Peisach, Aisen, and Blumberg, 1966) to one where several volumes might now be inadequate. Despite the tremendous increase in research activity regarding the biochemistry and biology of copper, its biological functions in the animal are still not well understood. It is the intent of this volume, therefore, to consider those chemical properties of copper which may be of value in understanding its roles in biological organisms. Volume 13 of this series will deal with the copper proteins.

The individual chapters are concerned primarily with recent developments in copper biochemistry and are well referenced. Introductory chapters are on the topics of "Coordination Chemistry of Copper with regard to Biological Systems", by R. F. Jameson, and "Copper(II) as Probe in Substituted Metalloproteins", by I. Bertini and A. Scozzafava. More specific chapters follow on "Copper(III) Complexes and their Reactions", by D. W. Margerum and G. D. Owens, "Copper-Catalyzed Oxidation and Oxygenation", by H. Gampp and A. D. Zuberbuhler, and "Copper and the Oxidation of Hemoglobins", by J. M. Rifkind. This is followed by a discussion of "Transport of Copper" by B. Sarkar, which includes transport phenomena in both healthy and diseased states. The final chapter covers the "Role of Low Molecular Weight Copper Complexes in the Control of Rheumatoid Arthritis", by P. M. May and D. R. Williams. This includes therapeutic effects of clinically used complexes, as well as a section on the design of complexes for control of inflammation.

Copper-containing enzymes and proteins are widely distributed in both animals and plants. For anyone wishing to follow the enlargement of our understanding of the biological roles of an essential trace element, which is occurring at a rapid pace, this volume makes an admirable introduction. It should appeal to biochemists and medicinal chemists as well as to biologists and clinicians involved with trace element research. The editor and authors are to be commended for providing a volume with the necessary underlying chemistry and factual biological data to promote the advance of this intriguing area of research.

*Massachusetts College of Pharmacy
and Allied Health Sciences
Boston, Massachusetts 02115*

William O. Foye

Biological Roles of Copper. Ciba Foundation Symposium. Number 79 (New Series). Excerpta Medica, Amsterdam. 1980. viii + 343 pp. 9.5 × 6.5 cm. \$56.50.

Ciba Foundation Symposia are well known for their presentation of topics at the forefront of knowledge in biological and medicinal areas, and this volume, reporting a conference on March 11-13, 1980, continues a tradition of timeliness and reporting of subjects in a state of rapid development. In addition to the formal presentations on specific topics, the discussions of the participants are presented in full. In this volume, the present state of our knowledge of the various roles of copper in mammalian metabolism is considered. Many of the aspects of copper biochemistry

included are of relatively recent concern, and a complete picture of the biochemical and pathological affects of copper has not yet been drawn. Those questions still unanswered regarding copper deficiency, excess, or the role of various copper proteins are brought out, and in common with previous symposia, the discussions succeed in pointing the way to future research.

The topics covered in the various chapters include the dietary sources of copper; absorption, transport, and distribution of copper; metabolic interactions with other trace elements; copper proteins and copper enzymes, with a separate chapter on caeruloplasmin; the superoxide dismutases; the role of copper with biogenic amines and amine oxidases; and the role of copper in the synthesis of elastin and collagen. A discussion of the pathology and diagnosis of copper deficiency is followed by chapters on copper deficiency in ruminants and in humans. Other clinical concerns are taken up in the chapters on the role of copper in fetal and neonatal development and its role in neurological and hepatic functions.

The concluding chapters, probably of more interest to medicinal chemists, are concerned with therapeutic uses of copper-chelating agents and the anaerobic potentiation of copper toxicity and some environmental considerations. The chapter on therapeutic uses is confined mainly to an equilibrium analysis of a model system for reactions between penicillamine and copper(I). Penicillamine is used for a number of disorders, including Wilson's disease, in which there is an accumulation of copper in the brain and kidney. The use of copper complexes in the treatment of rheumatoid arthritis is mentioned in the discussion following this chapter. The treatment of the effects of copper on anaerobic bacteria brings into question the environmental effects of copper used as an animal-feed supplement. The use of sewage sludge as an agricultural fertilizer is also questioned because of the often high content of copper.

The book is recommended reading for those whose research or clinical interests involve either copper or the effects of trace metals on mammalian biochemistry in general. The inclusion of the discussions makes an entertaining presentation of a topic still in an active state of development.

Massachusetts College of Pharmacy
and Allied Health Sciences
Boston, Massachusetts 02115

William O. Foye

Introduction to Alkaloids: A Biogenetic Approach. By Geoffrey A. Cordell. Wiley-Interscience, New York. 1981. xvi + 1055 pp. 17 × 24 cm. \$50.00.

Alkaloids for a long time have been of interest to organic, natural products and medicinal chemists, pharmacologists, and other investigators since they often possess interesting structures and useful biological activities. There is, however, available no current comprehensive book covering such aspects as history, chemistry, biosynthesis, and utility of the alkaloids. The unique approach used in writing this book was to draw together the hundreds of diverse alkaloid skeleta on the basis of their biogenesis or biosynthesis. Unfortunately, these concepts have not always been realized.

The book summarizes in 12 chapters the occurrence, synthesis, biosynthesis, spectroscopic properties, chemistry, and pharmacology of all the important alkaloid groups. In the first two chapters the discussion includes history, detection, isolation, and biosynthetic techniques and the formation of the alkaloid precursors. In the subsequent nine chapters, alkaloid groups derived from the nine precursors, namely, ornithine, lysine, nicotinic acid, polyacetate precursor, anthranilic acid, phenylalanine and tyrosine, tryptophan, histidine, and the isoprenoid pathway, are sequentially covered. The chapter on alkaloids derived from phenylalanine and tyrosine comprises 298 pages and is by far the longest section in the book. The final chapter deals with a discussion of miscellaneous alkaloids. At the end of each chapter or a major section references are cited under different headings such as reviews, synthesis and biosynthesis. However, no attempt has been made to cite all the references pertaining to a given group of compounds or all the alkaloids discussed. Rather, key references are provided to important research papers, reviews, book chapters, and monographs. The reader is thus required to search, if need be, for

the primary citations from the furnished references. Unfortunately, the literature cited is in most cases more than 6 years old. The appendix lists chemical compositions of alkaloid-detecting reagents. Subject index and organism index are included, but since not all references are cited, the author index is not presented and would not have been that meaningful if it were.

Each of the chapters is well written and quite readable. However, coverage of such a large number of alkaloids from the many aspects as are discussed in the book presents a formidable task. Too many errors, both typographical and substantive, have resulted. For example, page 426 (Scheme 64) alleges to show the rearrangement of morphine to apomorphine, but the structures for thebaine and morphothebaine are shown. On page 591 (Scheme 5), the structure of oxindole and that of the dimer presented in the Hendrickson synthesis of chimonanthine should have a urethane moiety in the side chain rather than the carboethoxy group shown. Incidentally, the structures of these two compounds involved in this synthesis have also been erroneously presented in the Manske's review published in 1965. This review has been cited as a reference by Cordell in the chapter discussing the chemistry of chimonanthine and the related oligomers of tryptamine. The pharmacological activity of strychnine as a "CNS depressant" alluded to on page 656 further exemplifies the errors introduced. Such errors seriously detract from the value of this treatise. Nevertheless, barring such shortcomings, the breadth and comprehensive treatment in the book are unique. Furthermore, new proposals presented in several cases for the biosynthetic formation of various alkaloids will inevitably interest researchers in this area. The concept of biomimetic chemistry which has created a revolution in synthesis during the past decade will fascinate synthetic chemists and stimulate and facilitate synthesis of other known and novel organic natural products, including alkaloids.

Advanced graduate students in chemistry, biochemistry, or pharmaceutical sciences will find this book a useful source of information. Chemists who are not familiar with alkaloids will learn the basis of the diverse alkaloidal types.

College of Pharmacy and Pharmacal Sciences
Howard University
Washington, D.C. 20059

Govind J. Kapadia

Apomorphine and Other Dopaminomimetics. Volume I. Basic Pharmacology. Edited by Gian Luigi Gessa and Giovanni Umberto Corsini. Raven Press, New York. 1981. xix + 323 pp. 18 × 25 cm. \$37.00.

Until recently the main interest in dopamine receptors of the central nervous system has focused on the mechanism of action of neuroleptic drugs. This volume reflects a growing interest in distinctions between different types of dopamine receptors and in the modulation of their functions. In such analyses, apomorphine and related dopamine agonists have provided probes that have become even more important than the neuroleptic antagonists.

The first chapter presents an historical overview of the chemistry, pharmacology, and early clinical uses of apomorphine, a compound that was prepared by cooking up morphine with hydrochloric acid in 1869 and was originally remarkable chiefly as a potent emetic. A series of papers then set the stage for more recent findings by examining the role of dopamine receptors and the manner in which several drugs interact with them and influence dopamine metabolism. A little controversy is added by one contribution that questions the existence of presynaptic dopamine receptors. An alternate explanation for feedback regulation of dopamine synthesis and release from nerve endings invokes feedback inhibition of tyrosine hydroxylase by dopamine taken up from the synaptic cleft. The final chapters deal with the actions of apomorphine and other agonists on receptors in the central nervous system and on peripheral receptors in the kidney and gastrointestinal tract.

An emerging theme is the role of calmodulin and GTP as couplers and modulators of dopamine-activated adenylyl cyclase. The topography of dopamine receptors may become clear from studies of the binding and activity of various aporphines, including

one that can alkylate receptors.

As might be expected from a multiauthored compilation of symposium proceedings, the contributions are of uneven quality. Many read like brief progress reports that will soon be obsolete. We are still far from the biochemical characterization of receptors that is feverishly taking place in the field of cholinergic pharmacology. On the other hand, there is no dopaminergic equivalent of the electric eel or the myoneural junction. Aporphine probes can expedite the tortuous journey into the heart of the dopamine jungle, and this volume offers a good, up-to-date introduction to their properties and application.

*Department of Biochemistry and
Pharmacology
School of Medicine
Tufts University
Boston, Massachusetts 02111*

L. Shuster

Liposomes, Drugs, and Immunocompetent Cell Functions.

Edited by C. Nicolau and A. Paraf. Academic Press, London and New York. 1981. xiv + 194 pp. 15.5 × 23.5 cm. ISBN 0-12-518 660-6. \$34.00.

This little book represents a prompt compilation of proceedings of a conference held September 2-3, 1980, in France. It was intended that there be a multidisciplinary approach in the discussion of current liposome research by 106 participants. The contributions were made in 10 addresses and 25 poster presentations.

The individual main units relate to general features of liposome studies covered in the lectures. The topics range from liposome structure and properties to application as carriers and their uses. The great range of implications of interactions in liposome-drug-cell systems seems to have been markedly compartmentalized in the individual chapters. The lectures were accorded attention in the Contents and Index, whereas poster presentations disappeared except through listing of participants. Much material of timely interest and significance has been hidden by this means.

This attractive, hard-bound book was produced expensively and promptly as a reflection of conferences on noteworthy aspects of liposome research. The lack of inclusion of discussions on the lectures implies sterile meetings, and the neglect of proper coverage of poster presentations further lessens the adequacy of this book.

*1913 Edgewater Parkway
Silver Spring, Maryland 20903*

Edgar A. Steck

Seizure Disorders: A Pharmacological Approach to Treatment. By B. J. Wilder and J. Bruni. Raven Press, New York. 1981. xii + 244 pp. 16 × 24 cm. \$24.50.

This is an excellent little book (183 pages without the references and index) written by neurologists and epileptologists for the physician treating seizure disorders. B. J. Wilder coauthored with R. P. Schmidt a similar book entitled "Epilepsy" in 1968, which was at that time very informative. Progress in the treatment of seizure disorders can be measured by comparing these books. In the treatment of no other disease is the importance of drug blood levels so critical today than in the treatment of epilepsy. Throughout the book the authors make effective use of anti-convulsant drug blood concentrations to rationally explain the efficacy and toxic side effects of the drugs.

Chapter 1 presents the current international classification of epileptic seizures. Chapter 2 deals with the pharmacological principles of medical therapy detailing physicochemical properties, e.g., drug absorption, distribution, elimination, and pharmacokinetics. Chapter 3 outlines the medical management of seizure disorders. Chapters 4-12 consist of monographs of the various classes of anticonvulsant drugs, in the order barbiturates, hydantoins, carbamazepine, valproic acid, primidone, succinimides, benzodiazepines, oxazolindiones, and other drugs and therapies. Chapter 13 discusses drug monitoring and seizure control, Chapter 14 discusses drug interactions, and Chapter 15 discusses drug toxicity. Chapter 16 is written by R. J. Perchalski on "Quantitative Laboratory Analysis of Antiepileptic Drugs". An extensive list of publications (51 pages) is included in the book as a convenience.

Unfortunately, the chemical portions of the book are filled with mistakes, and I wondered if anybody had proofread them. A review by a medicinal chemist could have eliminated the countless number of chemical errors. For example on page 106, four benzodiazepine structures are given, two of them are wrong. Mistakenly, according to the book, the first benzodiazepine was synthesized by Sternbach in 1973 (page 105). It is wrongly stated that all the commercially available hypnotic barbiturates exhibit anticonvulsant activity at anesthetic doses (page 48). Errors of this type are consistently seen throughout the book. In addition, many chemical names are wrong. The book is, however, written by physicians for physicians. Let us not tell them of the mistakes—they will never know the difference.

The book is full of good information, is up-to-date, and is recommended.

*Bristol-Myers Co.
International Division
New York, New York 10032*

Julius A. Vida