cells/mL for the L1210 leukemia. A portion (0.1 mL) of the resulting cell suspension was injected intraperitoneally into each recipient animal. Dosage levels of all compounds except 8 were administered over a range of 50–150 mg/kg by intraperitoneal injection, beginning 24 h after tumor implantation, once daily for 6 consecutive days. The test compounds were injected as fine suspensions following homogenization in 2–3 drops of 20% aqueous Tween 80 and then made up to volume with isotonic saline. All drugs were administered intraperitoneally in a volume of 0.5 mL. For any one experiment, animals were distributed into groups of five mice of comparable weight and maintained throughout the course of the experiment on Purina Laboratory Chow pellets and water ad libitum. Control tumor-bearing animals given injections of comparable volumes of vehicle were included in each experiment. Mice were weighed during the course of the experiments, and the percent change in body weight from onset to termination of therapy was used as an indication of drug toxicity. Determination of the sensitivity of ascitic neoplasms to these agents was based on the prolongation of survival time afforded by the drug treatments.

General Procedure for the Preparation of *N,N'*-Bis(arylsulfonyl)hydrazines. The appropriate arenesulfonyl chloride (0.02 mol) was added in portions to an ice-cold, stirred solution of hydrazine or methylhydrazine (0.01 mol) in pyridine (4 mL) over a period of 20 min. After an additional 30 min, the reaction mixture was poured into a mixture of 25 mL of ice and concentrated hydrochloric acid (1:1, v/v). The solid that separated was filtered immediately, washed with cold water, and dried. Recrystallization from glacial acetic acid afforded the analytically pure product.

N-Methyl-*N,N'*-dibenzoylhydrazine (**12**) was prepared with use of benzoyl chloride in a procedure analogous to the one described for the *N,N'*-bis(arylsulfonyl)hydrazines.

Acknowledgment. This research was supported in part by U.S. Public Health Service Grant CA-02817 from the National Cancer Institute.

Registry No. **6**, 6272-36-2; **7**, 94905-07-4; **8**, 94905-08-5; **9**, 94905-09-6; **10**, 94905-10-9; **11**, 94905-11-0; **12**, 21150-15-2; hydrazine, 302-01-2; methylhydrazine, 60-34-4; benzenesulfonyl chloride, 98-09-9; 4-methylbenzenesulfonyl chloride, 98-59-9; 4-methoxybenzenesulfonyl chloride, 98-68-0; 4-chlorobenzenesulfonyl chloride, 98-60-2; 2-naphthalenesulfonyl chloride, 93-11-8; benzyl chloride, 98-88-4.

Book Reviews

Development of Target-Oriented Anticancer Drugs (Progress in Cancer Research and Therapy. Volume 28). Edited by Yung-Chi Cheng, Barry Goz, and Mimi Minkoff. Raven Press, New York. 1983. xv + 246 pp. 18 × 26 cm. ISBN 0-89004-161-X. $39.00.

This book is a collection of papers presented in a symposium sponsored by the Cancer Research Center and other departments of North Carolina School of Medicine at Chapel Hill in 1983. It is divided into three parts: membrane transport, enzyme activity, and gene function.

An introductory chapter entitled "Cancer Chemotherapy and the Medicinal Chemist" was provided by J. A. Montgomery, who emphasized that drug development is a closely integrated team effort which should consist of medicinal chemists, chemotherapists, and biochemical pharmacologists. Montgomery believed, with examples of work done in his laboratory, that the most approachable area of research is the design of enzyme inhibitors. This is certainly true, provided we recognize the fact that interference with enzyme functions does not necessarily produce anticancer or even cytotoxic agents and sometimes may even produce toxicity.

Four papers were presented under the membrane transport approach. I. D. Goldman et al. used computer simulations and computer analyses to study the cellular pharmacology of 4-aminoantifolates and found that many previously reported concepts with regard to the antifolate pharmacology were incorrect. They concluded that, among factors which contribute to the antifolate action, a study of the structural sites of antifolate molecules for binding to DHFR may not be as important as to exploit the sites that govern the transport and polyglutamylation. Of course, as the authors pointed out, that structural modifications that favorably alter one parameter could deleteriously alter another parameter, and therefore structural modifications that enhance the transport or polyglutamylation in tumors may not necessarily provide similar advantages in host tissues. A. R. P. Paterson et al. found that nitrobenzylthioinosine (NBMPR) is a potent inhibitor of nucleoside transport, and since neoplastic cells differ from host tissues in the NBMPR sensitivity, the difference may be used to preferentially destroy the neoplastic cells with combinations of NBMPR-P and high doses of cytotoxic adenosine analogues, such as tubercidin or nebularine. W. H. Prusoff reported the historical development of nitrosourea nucleosides as anticancer agents and offered a number of approaches to the development and delivery of nitrosourea drugs. Concepts in new folate analogues design were presented by F. M. Sirotnak, who suggested that positions 5, 10, and the γ-carboxyl group (the site for polyglutamylation) of antifolates could be the logical points for structural modification. The author also pointed out that much information gathered are still controversial and further study is needed.

Under the area of enzyme activity approach, seven groups of investigators presented their views. J. Jolivet and B. A. Chabner discussed their studies on methotrexate polyglutamates (MTXPG) in cultured human breast cancer cells and confirmed that the MTXPGs, which retained much longer intracellularly than MTX, are stronger inhibitors of human thymidylate synthetase in vitro than the parent antifolate. The prolonged tissue retention of the MTXPGs may also be responsible for some chronic drug toxicities. Since leucovorin (5-CHO-FH_4) prevents the formation of higher MTXPG derivatives from MTX by interfering with the action of folylpolyglutamate synthetase, the enzyme responsible for polyglutamation, this preventive action may be related to the mechanism of leucovorin rescue. J. J. McGuire et al. gave a detailed report on their study of folylpolyglutamate synthetase (FPGS) and various agents tested for substrate and/or inhibitory activity of rat liver FPGS. They believed that searching for certain prodrugs, which are substrates for FPGS and are converted to potent enzyme inhibitors in vivo, could be an approach for new drug development. An example of such a prodrug was illustrated by the authors as 5,8-dideazaisopteroylglutamate (IAHQ). Y.-C. Cheng and R. W. Brockman suggested the use of the principle of collateral sensitivity—the phenomenon of increased sensitivity of tumor cells resistant to one drug to a second drug with a different mode of action—could be a fruitful approach for new drug development, provided that the biochemical mechanisms of resistance (such as transport defects for a drug, increased enzymic catebolism of a drug, deficiency of drug-activating enzyme, increase in the level of target enzyme, etc.) be understood and more information on mechanisms of clinical resistance be gathered. This valuable and practical approach, therefore, is useful only in designing compounds with known mechanism of action. Y. M. Rustum, using the example of a FU-prodrug 5'-deoxy-5-fluorouridine (dFUR, not to be confused with the well-known 5-FUDR, which is 2'-deoxy-5-fluorouridine), emphasized the development of prodrugs that should be activated in target tissues rather than in biological systemic compartments for selective anticancer activity. T. M. Saverese et al. discussed various bio-

chemical considerations in the design of analogs of 5′-deoxy-5′-methylthioadenosine (MTA), the latter was involved in the polyamine biosynthesis and a methionine-salvaging pathway. P. L. Carl gave a report of his not-yet-successful work to develop the site-directed antitumor prodrugs designed to be locally activated by the tumor-associated enzyme plasmin. Finally, S. Rockwell discussed the various aspects of the use of chemical agents in combination with radiation to destroy hypoxic solid tumor cells. They believed that bioreductive alkylating agents may be more useful in this regard than the more conventional electron-affinic agents such as misonidazole and metronidazole. In addition, they pointed that the routine screening methods may not be adequate for uncovering useful radiosensitizing agents.

Six papers were presented under the gene function approach. A. Bloch introduced an interesting concept of using agents that could inhibit proliferation-associated process and simultaneously induce tumor cell differentiation at the G_1 stage of cell cycle. This interesting concept may be considered concurrently with an equally interesting concept of "promine" and "retine" reported in 1966 by A. Szent-Györgyi. It has been recognized that cancer is the result of a disorder of normal cell differentiation. Philosophically, it can even be viewed that the transformation from normal to cancer cells could well be a residual built-in cellular information in the evolutionally more advanced cells to revert back to the primitive and non-differentiation-type cells in order to avoid death and to achieve longevity. This proposed differentiation therapy, properly investigated, would circumvent problems such as drug toxicity and drug resistance. Other presentations in the gene function approach, including K. W. Kohn's DNA interstrand cross-linking (not DNA–protein cross-linking) agents and P. O. P. Tso and co-workers' nonionic oliganucleotide analogues and mismatched double-stranded RNAs as chemotherapeutic agents for specific target delivery. S. T. Crooke et al. believed that interactions with DNA are responsible for many antineoplastic, mutagenic, carcinogenic, teratogenic, cytotoxic, and antiarthritic actions and that DNA behaves as a series of allosterically interacting receptors which interact with many different ligands. A thorough understanding of the drug–DNA interactions should provide information for the rational design of drugs for inducing specific effects; I. J. Fidler suggested the use of conventional chemotherapy to reduce the large metastatic tumor burden followed by the use of activated macrophages (produced by liposomes containing specifically designed peptides which possess immunopotentiating activity) to lyse the remaining heterogeneous metastatic cells for the effective treatment of metastatic solid tumors. Finally, G. H. Hitchings, in a title of "Rational design of anticancer drugs: Here, imminent or illusive?", presented another approach to inhibit the enzyme dihydrofolate reductase (DHFR) by developing antagonists to the cofactors of DHFR, and particularly emphasized the role of the cofactor NADPH (the reduced nicotinamide adenine dinucleotide phosphate) in the DHFR action. He believes that the progress in cancer chemotherapy has been, and probably will continue to be, slow.

Although most of the presentations were actually progress reports of works conducted in the laboratories of the speakers and their collaborators, the volume as a whole collected the thoughts of investigators who are among the tops in the field of cancer research. Since the areas of these researchers are, with few exceptions, so vastly different from one another's study, it is regrettable that the usual question-and-answers or discussion sections were not provided after each presentation during the symposium. Collected thoughts and scholastic interchanges, even arguments, at the meeting are often valuable to the readers. The whole field of cancer research is so enormously diversified that the experimentation of each investigator to the entire subject is like, as said in an ancient Chinese story, many blind people touching an elephant. Since none of them has ever "seen" an elephant before, the part that was touched by each individual—the leg, the trunk, the ear, the tusk, the tail, etc.—may be real and correct, but only through exploration to other parts of the elephant can one actually get the entire "vision" of the whole animal. That day will come, as long as each of us work very hard at it.

This book stimulates the thinking of all researchers working in the field of oncology, and it is therefore recommended to anyone who is not satisfied in doing nothing but me-too research.

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Peptide and Protein Reviews. Volume 3. Edited by Milton T. W. Hearn. Marcel Dekker, New York. 1984. viii + 226 pp. 15.5 × 23.5 cm. ISBN 08247-7241-5. $63.00.

Many of the recent advances in recombinant DNA technologies have their origins in protein chemistry. In fact, the revolutionary developments currently underway in molecular biology, biotechnology, and the more specialized disciplines are due substantially to the renaissance in all areas of peptide and protein chemistry.

"Peptide and Protein Reviews", Volume 3, delivers the latest techniques, concepts, and applications in this burgeoning field and includes strategies used to prepare human proinsulin by total synthesis and semisynthesis, as well as by recombinant DNA technology, structural, conformational, and biological aspects of the melanotropins, the structure and regulation of elastin, periplasmic carbohydrate binding proteins, with a model of the protein associations leading to a chemotactic signal, and advances in X-ray studies on the lens crystallins.

Staff

Handbook of Vitamins: Nutritional, Biochemical, and Clinical Aspects (Food Science and Technology Series). Volume 13. Edited by Lawrence J. Machlin. Marcel Dekker, New York. 1984. x + 614 pp. 185 × 26 cm. ISBN 0-8247-7051-X. $95.00.

Since 1948, no new vitamins have been discovered and it is unlikely that any more will be identified. Yet vitamin research in the past few decades had continued at an exciting pace as scientists examine the effects of vitamins, their metabolism, their influence on disease resistance, and the numerous interactions of vitamins with other nutrients, drugs, alcohol, smoking, disease states, age, and environmental pollutants.

From this vast body of widely scattered information, "Handbook of Vitamins" carefully collects the most important material on vitamins in these areas and others and includes the most recent findings in the field. In concise, self-contained chapters, 19 renowned experts systematically detail the chemistry, availability and content in food, methods of bioassay and chemical analysis, metabolism, function, history, methods for evaluating overt or marginal deficiencies, nutritional requirements, and much more. A subject index is also included.

Staff

Toxins as Tools in Neurochemistry. Edited by F. Hucho and Y. A. Ovchinnikov. Walter de Gruyter, Berlin, New York. 1983. xiv + 368 pp. 17.5 × 24.5 cm. ISBN 3-11-009593-9. $81.80.

This book is the outcome of the proceedings of a symposium which took place in West Berlin in March 1983. It was organized jointly by members of the USSR Academy of Sciences and the Free University of Berlin. The aim of the meeting was to review our knowledge regarding the application of toxins in studying various aspects of neurochemistry. Participants in the symposium were primarily from Germany and from the USSR.

The book is subdivided into four main sections: (1) Sodium Channels; (2) Palytoxins; (3) Acetylcholine Receptors; and (4) Calcium Channels, Axonal Toxins, Presynaptic Toxins, Cardiotoxin and New Venoms. This is a multiauthored volume and consists of a collection of camera-ready chapters (in the interest of minimizing delay in the conference proceedings). As a result, the references are quite recent (up to 1983), and therefore essentially present the current status of the areas of investigation covered in this book.

The authors, as well as the editors, should be complimented on assuring the high scientific quality of the individual chapters, the general uniformity in style of the presentation of the data, as well as the quality of the English language in these chapters, which is not the primary language of most of the authors.

In general terms, the book assembles a variety of diverse topics, all tied together with a common thread dealing with Toxins as Tools in Neurochemistry. It is disappointing that the only toxins dealt with in this book were those obtained from natural sources in the environment. The book would have been much more complete if an additional section were dedicated to the use of *synthetic toxins* as tools in neurochemistry, particularly those utilized for the selective destruction of specific neurotransmitter systems in vivo.

A novice in the area might not find this book helpful as an introductory treatise to the subject, because of its specialized nature. The chapters are short and concise, and therefore, in general, terms provide just a small window into a large area of investigation. The book should be extremely useful to investigators who are already involved in research related to the effect of naturally derived toxins and their use as tools in neurochemistry. An adequate number of references has been presented in each chapter, which allows the reader to refer to other papers in this area, if so desired. To the investigator familiar with the area and literature in the field, therefore, this could be a very useful working text. It provides a good general overview of advances in this field of investigation.

The diversity of topics presented and the quality of the resulting chapters indicate that the symposium itself, which served as a stimulus for this book, must have provided a spirited and educational experience to all those who participated in the March 1983 meeting on Toxins as Tools in Neurochemistry.

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Neurobiology of the Trace Amines. Edited by A. A. Boulton, G. B. Baker, W. G. Dewhurst, and M. Sandler. The Human Press Inc., Clifton, NJ. 1984. xx + 597 pp. 15.5 × 23.5 cm. ISBN 0-89603-063-6. $59.50.

The recent development of very sensitive and specific techniques for measuring biogenic amines has meant that attention could now be focused on compounds of neurochemical interest which are outside the traditional group of the catecholamines, serotonin and acetylcholine. These other biogenic amines are generally referred to as the "trace amines" (TA's) due to the fact that they occur in the brain in much lower concentrations (0.01–100 ng/g) than the aforementioned group.

This book is based on the proceedings of the meeting "Trace Amines and the Neurosciences" held in Edmonton, Canada, in July 1983. The introduction consists of a brief historical survey by Dewhurst, which is then followed by a very useful overview of the TA's by Boulton who is one of the most active researchers in this field. The rest of the book is divided into four sections, i.e., analysis, physiology and pharmacology, behavior and clinical studies. Each section consists of a series of invited communications, which are then followed by short free communications. Due to the fact that their sum total is almost 50, only certain papers can be mentioned here.

The analytical section contains useful reviews of methodology by Durden, Saavedra, and Baker et al. It is unfortunate that in the paper by Saavedra the chemical structures of tyramine, octopamine, and *N*-methyloctopamine are all incorrect. In the physiology and pharmacology section the chapter by Philips on TA's in the rat is of interest as it stresses the very rapid turnover rates of some of these compounds. Juorio discusses the effects of various psychotropic drugs on the metabolism of the TA's. In the free communications section Jones reports on the interactions between the TA's substance P, and the enkephalins. The section on behavior starts with a review by Jackson and Jenkins of the effects of phenylethylamine (PE) in rats. The possibility of PE acting as an endogenous amphetamine is discussed by various authors in this section. The possible roles of the TA's in depression, schizophrenia, and other neurological diseases is the subject of the final part of the book. One of the most interesting studies in this section is a report on the effects of a first parachute jump on the urinary levels of PE. This study is unusual in the sense that the authors used human subjects directly without apparently first studying the effects in rats!

This book represents the current state of the art in this field. In most areas of research the role of these TA's is far from clear. Traditional biogenic aminologists should read this book if they are tired of investigating their usual amine and are looking around for new areas to study.

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Catechol Estrogens. Edited by George R. Merriam and Mortimer B. Lipsett. Raven Press, New York. 1983. xviii + 279 pp. 16 × 23.5 cm. ISBN 0-89004-892-4. $44.00.

Considerable interest in the formation and possible physiological roles of catechol estrogens has developed over the past few years among steroid biochemists and endocrinologists. This book on the 2- and 4-hydroxyestrogens is a compilation of the proceedings of the International Workshop on Catechol Estrogens, held in February 1982 at the Fogarty International Center of the National Institutes of Health. This workshop, organized by Drs. George R. Merriam and Mortimer B. Lipsett, brought together key researchers in order to present recent research developments in the area of catechol estrogens and to discuss the conflicting results of the biologic effects of these steroids.

The book is divided into four main sections—Chemistry and Formation, Assay and Metabolism, Biologic Activities, and Neuroendocrine Effects. Each section consists of several chapters and concludes with a final chapter summarizing the discussions of that particular section of the meeting. The book begins with a brief chapter entitled "Historical Perspective" by Dr. Jack Fishman. The initial isolation, identification and synthesis of the catechol estrogens by Gallagher and Fishman are recounted, as well as the contributions from the laboratories of Engel, Breuer, and Knuppen.

The section entitled Chemistry and Formation of Catechol Estrogens begins with their synthesis, properties and isolation. Included in this chapter is a description of an interesting isotope effect observed during the efficient high-pressure liquid chromatographic separation of synthesized catechol estrogens. The remaining three chapters of this section concern the three different enzymatic assays for estrogen 2/4-hydroxylase activity and the formation of the catechol estrogens. The radioenzymatic assay involving the isolation of radiolabeled methoxyestrogens was used to quantitate the production of the catechol estrogens by a coupled enzymatic assay in various tissues. Developmental and hormonal controls on the levels of enzymic activity were also described using this assay. The radiometric assay measures the release of ^3H_2O from specifically labeled estrogens. The third enzyme assay involves the isolation of radiolabeled catechol estrogens from the microsomal incubations. The presentations discuss the similarities of the assays for monitoring the enzymatic activity present in the liver and the assays for monitoring the enzymatic activity present in the liver and the contrasting results obtained by the assays from CNS tissues. The final chapter of this section is a summary of the discussions of the speakers and participants on this topic that occurred at the workshop.

The second section on the Assay and Metabolism of the Catechol Estrogens begins with chapters on chemical assays (GC/MS), radioimmunoassays, and radioenzymatic assays for measuring the levels of catechol estrogens in plasma and urine samples. The next three chapters of this section consist of a summary of research on the further metabolism of the catechol estrogens, the rapid metabolic clearance of the catechol estrogens when introduced in the body, and the possible role(s) of one particular metabolite, 2-hydroxyestrone, in physiological functions. The final chapter on catechol estrogen metabolism focuses on the possible formation of chemically reactive intermediates during catechol estrogen formation and the suggestion that these intermediates may be involved in the development of cancer. The chapter on the summary of the discussions from this section concentrated on the rapid metabolic clearance of the catechol

estrogens and the implications of this clearance on in vivo studies.

Chapters on the interactions of catechol estrogens with estrogen receptors and transport proteins begin the section on Biologic Activities of the Catechol Estrogens, and the authors describe the diminished binding affinity of the catechol estrogens for these proteins. Presentations on the interactions of the catechol estrogens in catecholamine synthesis and metabolism and with dopamine receptor binding proteins provide potential research leads but no clear answers to possible roles of catechol estrogens in the CNS. The potential role of catechol estrogens in regulating prostaglandin production in the uterus was also described in this section. The summary of the discussion emphasizes the need for more accurate determinations of catechol estrogen concentrations in the tissues of interest.

The final section on Neuroendocrine Effects of Catechol Estrogens contains papers on the in vivo effects of catechol estrogens on gonadotropin and prolactin secretion in animals and man, suggesting that the catechol estrogens behave as weak estrogens. Studies on the effects of catechol estrogens on sexual behavior, such as lordosis, did not provide sufficient evidence to indicate a possible effect of the catechol estrogens. The summary emphasized the questions of the effects of catechol estrogens that remain unanswered.

In summary, this book reviews much of the current information on the catechol estrogens—their chemistry, biochemistry, metabolism, and possible physiological roles. The book was published in 1983, over 1 year after the workshop at NIH, but still reflects the current status of the field. The well-written chapters accurately describe the research by key investigators in the area and present their analyses on the biological relevance of the catechol estrogens. The summaries of discussions from each section are excellent presentations of the questions, discussions, and debates that arose at the workshop. They also reflect the opposing views of the participants on the importance of the 2- and 4-hydroxyestrogens. This book does not provide the final answers but does indicate directions for future research in the field. The book is well-organized and well-written and contains an extensive subject index. It is highly recommended for chemists, biochemists, pharmacologists, and endocrinologists actively involved in steroid hormone research.

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Advances in Pharmacology and Chemotherapy, Volume 20. Edited by S. Garattini, A. Goldin, F. Hawking, and R. J. Schnitzer. Academic Press, New York, 1984, viii + 241 pp. 15.5 × 23.5 cm. ISBN 0-12-032920-4. $40.00.

This volume, similar to its predecessors in this series, is a collection of six independent articles that are quite different from each other in subject matter, scope, style, and form of presentation.

The first, brief (20 pp) but important article, by J. M. Venditti, R. A. Wesley, and J. Plowman, provides an outline and up-to-date analysis of the in vivo test systems and strategies currently used by the National Cancer Institute for the preclinical screening of new antitumor agents. These involve the use of a prescreen (P383 leukemia) and of a tumor panel which includes leukemia L1210, melanoma B16 as well as mouse breast, colon, and lung tumors, and human tumor xenografts of the same types. Analysis of the experimental results based on completed testing of 1085 compounds generally supports the rationale of tumor panel screening as it reveals basic differences between the selective responses of the employed tumor models to certain new or established drugs. However, a new plan is presently in the development stage which places emphasis on the sequential process of "progressive selection" of drugs for clinical efficacy. In addition, the future application of an in vitro/in vivo screening method involving human clonogenic assays is proposed.

An article by A. F. Hadfield and A. C. Sartorelli presents a very useful literature review on the pharmacology of "prodrugs" of 5-fluorouracil and *ara*-C. These two important chemotherapeutic agents have been the center of a great deal of research effort aimed at the synthesis and pharmacologic development of a variety of different types of "prodrugs" that would improve their clinical utilities; therefore, they provide good examples for an evaluation of the scope and limitation of the prodrug approach in cancer chemotherapy. Several of the prodrugs described appear to have improved drug-delivery mechanisms and/or tumor-targeting properties as compared to the parent compounds, and some improved therapeutic results in tumor-bearing animals have been reported; however, their clinical evaluation is still incomplete. By reviewing and integrating the data from over 200 reports (7 pages of references), the authors performed a useful service.

In the third, most broadly based article, M. Nasr, K. D. Paull, and V. L. Narayanan describe the method of computer-assisted structure–activity correlations currently used at the NCI for analysis of the cancer chemotherapy screening data, including "substructure" searching and biological data retrieval. Specifically, the authors present the structure–activity evaluation of more than 14 000 compounds from the NCI data file, representing different classes of Michael acceptors, including α,β-unsaturated ketones, lactones, and lactams, based on their antitumor activities against P388 and L1210 mouse leukemias. The conclusions of such an analysis may be useful in the design of more effective antitumor agents.

The remaining three articles are of narrower scope. There are two single-agent reviews: the first, by A. K. Tyagi and D. A. Cooney, describes the biochemical pharmacology, metabolism, biological activities, toxicology, and clinical studies of L-alanosine, "a novel, natural antitumor agent"; the second, by E. Groll, deals with praziquantel (a pyrazinoisoquinoline derivative) which is a clinically effective antiparasitic drug. In the third article, A. Jori describes the biochemical and pharmacologic properties of three sugar alcohols that may be used as "non-cariogenic" natural sweeteners, to replace sugars in food with the aim of obtaining dietary control of dental caries.

On the whole, the book is informative and useful to those medicinal chemists and pharmacologists who are interested in any one of the above topics.

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Immunopharmacology of Endotoxicosis. Proceedings of the 5th International Congress of Immunology Satellite Workshop. Kyoto, Japan, August 27, 1983. Edited by M. D. Agarwal and M. Yoshida. Walter De Gruyter, Inc., New York. 1984. xiv + 376 pp. 17 cm × 24 cm. ISBN 3-11-009887-3. $DM 170.

This book groups together papers describing recent progress in various aspects of endotoxicosis. The first aspects are the immunopharmacological reactions elicited by endotoxins which include beneficial as well as toxic properties. The influence of various pharmacological agents on the course of endotoxicosis is obviously important and forms the second aspect of the book. Finally, problem-oriented themes were chosen in the hope of arriving at a consensus as to the site and nature of endotoxin action. It follows that bacterial endotoxin remains a valuable tool to understand molecular aspects of host–parasite interactions in a variety of organs and cell types.

Staff

Natural Products and Drug Development. Edited by P. Krogsgaard-Larsen, S. Brøgger Christensen, and Helmer Kofod. Munksgaard, Copenhagen. 1984. 560 pp. 16.5 × 24 cm. ISBN 87-16-09563-4. $42.35.

This volume represents the Proceedings of the Alfred Benzon Symposium 20 held at the Royal Danish Academy of Sciences and Letters, Copenhagen, in August, 1983.

Among the compelling reasons for the continuing investigation of natural products is the fact that Nature offers a wide variety of novel biodynamic structures for pharmacological evaluation and for synthesis and modification by the medicinal chemist. This theme was addressed at the symposium by a group of international experts under the general headings: Terrestial Sources for Active

Constituents and Lead Structures, Marine Sources for Active Constituents and Lead Structures, Marine Sources for Active Constituents and Lead Structures, Antimicrobial and Antitumor Compounds, Natural Products as Experimental Tools and Leads in Drug Design and, finally, CNS-Active Natural Products in Drug Development.

Thirty-two papers and their postpresentation discussions constitute neither a pean of praise for the study of natural products nor an apology for the apparent lack of marketable products arising therefrom. Rather, one notes a critical and welcome appraisal of the problems to be encountered in today's innovative approaches to an understanding of Nature's chemical factory.

The book should appeal not only to the medicinal chemist but to all others with a present and possible future interest in the development of useful drugs from naturally occurring compounds.

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The Total Synthesis of Natural Products. Volume 6. Edited by John ApSimon. Wiley-Interscience, New York. 1984. ix + 291 pp. 16 × 23.5 cm. ISBN 0.471-09900-7. $44.00.

Researchers engaged with the chemistry of natural products will find a valuable manual in this new volume in the series "The Total Synthesis of Natural Products".

The opening chapter of the book "The Total Synthesis of Aromatic Steroids 1972–1981" written by D. Taub is a continuation of the previous review which appeared in Volume 2 of this series. The author summarizes the major developments on the asymmetric synthesis of aromatic steroids involving chirality transfer by amino acid mediated asymmetric cyclization and the new synthetic route based on the intramolecular cycloaddition of orthoquinodimethanes. This well-written article is extremely informative and presents an important perspective in this area of natural products.

The second chapter in this volume is a relatively short review on "Gene Synthesis" written by S. A. Narang, W. L. Sung, and R. H. Wightman. It was a pioneering task to give an overlook of the chemical and enzymatic syntheses of oligonucleotides as well and to introduce nonspecialists into the problems of this type of chemistry. The size of chapter, however, limited the depth and details of the literature covered.

The third and at the same time the most fascinating chapter of this book "The Total Synthesis of Triterpenes 1973–1981" is written by J. W. ApSimon, K. E. Fyfe, and A. M. Greaves, who have made considerable contributions to this field. This chapter surveys the literature on the syntheses of triterpenes from 1973 in the same style as it did in the previous review which appeared in Volume 2. The chapter is divided into two major parts; one is connected with the synthesis of triterpenes with steroidal ring system and the other one with the synthesis of nonsteroidal tetra- and polycyclic triterpenes including (+)-alnusenone, friedelin, and serratenediol. The most valuable feature of the review is the clear recepitulation of the approaches for the synthesis of these complex molecules, giving considerable information about the stereochemistry of triterpenes as well.

The longest chapter of the book deals with "The Total Synthesis of Carbohydrates 1972–1980" written by A. Zamojski and G. Grynkiewicz. This review is also a continuation of a previous chapter of Volume 1 and represents a high standard in covering the literature in an area which develops rapidly. The authors describe a clear summary of the different approaches for the synthesis of mono-, di-, and trisaccharides, starting with the survey of precursors followed by exposition of the synthesis of different furan and pyran derivatives. The final section of the chapter deals with the total syntheses of cyclitols.

The last chapter of this volume entitled "The Total Synthesis of Pyrrole Pygments 1973–1980" is written by A. J. Jackson and K. M. Smith. This area of natural products has also been reviewed previously by the same authors in Volume 1. This excellent and very informative chapter reviews first the synthesis of simple pyrroles, then the synthesis of di-, tri-, and tetrapyrrolic compounds, and finally the transformations of these precursors into porphyrins. Separate sections deal with the synthesis of bile pigments and corrins. It should be mentioned that this chapter reports the total synthesis of vitamin B_{12} performed by Woodward and Eschenmoser.

Volume 6 of "The Total Synthesis of Natural Products" includes a brief subject index but no author index. In addition to the references, the majority of the chapters contains suggested reading for the topic reviewed that helps the researchers in broadening their knowledge on the field in question. The standard of production of the volume is excellent.

In summary, Volume 6 continues the high scientific level of this excellent series and it could be useful not only for the experts on the total synthesis of natural products but to all organic chemists as well.

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The Alkaloids. Chemistry and Pharmacology. Volume XXIII. Edited by Arnold Brossi. Academic Press Inc., Orlando. 1984. xix + 399 pp. 15.5 × 23.5 cm. ISBN 0-12-469523-X. $85.00.

Volume XXIII presents updated reviews of pharmacologically important classes of alkaloids. The articles on "Tropolonic *Colchicum* Alkaloids", last reviewed in Vol. XI (1968), and "*Cephalotaxus* Alkaloids", briefly discussed in a chapter on "*Erythrina* and Related Alkaloids" in Vol. XVIII (1981), with updated literature until 1983, offer pertinent information on biochemical, pharmacological, and clinical experience gained with representative compounds.

The additional four articles discuss alkaloids never reviewed in this text. "Azafluoranthene and Tropoloisoquinoline Alkaloids", on the other hand, compounds related to muscarine (obtained from the toxic mushroom *Amanita muscaria*, which interacts with acetylcholine receptors), deals with alkaloids of great importance to experimental pharmacology. "Maytansinoids" belong to a relatively new class of antitumor agents of complex chemistry and challenging structural features. The article on "Constituents of Red Pepper Species" describes the pungent principles of pepper species widely used throughout the world as spices in food. A detailed discussion of these substances seems highly justified.

Articles on alkaloidal substances of relevance to health, medicine, and drug research, written by experts in these fields, will continue to be of interest to medicinal and organic chemists.

Staff

The Leucotrienes: Chemistry and Biology. Edited by Lawrence W. Chakrin and Denis M. Bailey. Academic Press, New York. 1984. xi + 308 pp. 16 × 23.5 cm. ISBN 0-12-166750-2. $52.00.

This book is an excellent choice for medicinal chemists wanting a brief, personalized, and contemporary account of the present status of the biology and chemistry of the leucotrienes. The volume contains a series of essays written by various experts actively engaged in research in this area. In virtually every chapter references extend into 1983 and the book itself is relatively easy to read and free of errors of commission. In most chapters the authors give a summarizing overview and an opinion as to where future advances are likely. Chapter 1, by K. Frank Austen and Robert Lewis of Harvard Medical School, consists of a brief (12 page) historical overview highlighting key experimental observations and indicating the advances which ensued. This chapter is a concise and thoroughly enjoyable gem. Chapter 2, by E. J. Corey of Harvard's Chemistry Department and by David Clark and Anthony Marfat of Pfizer, is the longest in the book (88 pages). It is one of those more likely to have archival value and contains a detailed summary of the structure elucidation, total synthesis, and the role total synthesis played in structural elucidation of the leucotrienes. This very detailed chapter includes syntheses of analogues as well as of the natural products. Its impact is, however, lessened by the frustration of having to turn pages back and forth in almost every instance to find the formula charts which go with the text. Chapter 3, by David Aharony, J. Bryan Smith,

and Melvin Silver of Thomas Jefferson University, summarizes in 20 pages the properties of platelet arachidonate lipoxygenase (PAL), the role of platelets in hemostasis, and the effects thereon of your PAL's products and of inhibitors of the enzyme. After a terse beginning, the chapter moves on to impart much interesting and useful detail. Chapter 4, by Charles Parker of Washington University School of Medicine, St. Louis, devotes 10 pages to a discussion of lipoxygenases in leucocytes and other mammalian cells and is a highly personalized account, including significant material not in print at the time the book was prepared. Chapter 5, by Barbara Jakschik and Christine Kuo, also of Washington University, draws upon the authors' experimental experiences to treat the characterization of leucotriene formation in 23 excellent pages. The identity of the products and the time course of the leucotriene cascade is discussed. Next, in Chapter 6, Michael Bach of Upjohn discusses inhibitors of leucotriene synthesis and action. This area of medicinal chemical research holds forth great promise of a fundamental modality against asthma and medicinal chemists will read this thoughtful, balanced, and critical 30-page chapter with especial interest. The point of action and selectivity of various inhibitors is an important feature of this chapter. Chapter 7, by P. Bhattacherjee and K. E. Eakins of the Wellcome Research Laboratories in England, discusses, in 19 pages, the possible medicinal significance of lipoxygenase products in mediation of inflammation and the putative consequences of their inhibition. Chapter 8, by Priscilla Piper of the Royal College of Surgeons of England, in London, devotes 15 interesting pages to the pharmacological actions of the leucotrienes. In Chapter 9, Donald Payan, Daniel Goldman, and Edward Goetzl of the University of California at San Francisco devote 14 pages to the regulation of human leucocyte function by arachidonate-derived leucotriene products. The pulmonary pharmacology of leucotrienes is treated in the 21-page Chapter 10 by A. G. Leitch and J. M. Drazen of Harvard Medical School. The book then concludes in Chapter 11 with a 28-page discussion of the pharmacologic antagonism of the leucotrienes by Robert Krell, Frederick Brown, Alvin Willard, and Ralph Giles of ICI, Wilmington. Here is a discussion of leucotriene receptors, their putative subtypes, their substrate requirements, and the putative consequences of their occupation and blocking. Not much is known in this field as yet and the discussion focuses on existing controversies and gaps.

In sum, the editors have done an outstanding job of assembling a series of self-contained critical contemporary essays on a fast-moving area of present medicinal chemical and pharmacological interest. The overall evenness of coverage and the comparatively brief lapse between completion and publication are most impressive. The sad element in my reaction comes from considering the relatively sketchy present state of knowledge of the leucotrienes and the intensity with which the area is being pursued. Inevitably this volume will become comparatively quickly dated. My advice to the medicinal chemist is to buy this book now and enjoy it.

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Stereochemistry and Biological Activity of Drugs. Edited by E. J. Ariens, W. Soudijn, and P. B. M. W. M. Timmermans. Blackwell Scientific Publications, Inc. 1984. 204 pp. 15 × 24 cm. ISBN 0-632-01155-6. $37.00.

This book is a compilation of papers presented at an international meeting under the auspices of the Dutch Society of Pharmacology, the Medicinal Chemistry Section of the Royal Dutch Chemical Society, and the Dutch Society of Clinical Pharmacology and Biopharmacy. The book presents some very interesting papers that discuss the possible uses of stereoisomeric compounds as tools in gaining a better understanding of the structural requirements for binding to enzymes and receptors. The first two papers contain very basic information and nomenclature along with some of the general aspects that provide for a good beginning for this book. The third paper presents a number of examples of stereoselective drug metabolism. Drugs that are used therapeutically as well as toxic xenobiotics are examined in this chapter. The fourth paper describes points of possible stereoselectivity in the distribution of drugs. The fifth paper presents some discussion of conformationally flexible and rigid analogues of acetylcholine. Advantages and disadvantages for controlling the geometry of flexible drug molecules are discussed in this paper. The sixth paper points out some NMR studies in the investigation of isomeric substances binding to receptors. A very good summary on the advantages and disadvantages of the use of bioactive racemates and specific isomers is presented in the next paper. The followng paper is an excellent review of the action of isomeric adrenergic drugs and their action on the adrenergic nervous system. Several papers follow on the action of isomeric drugs in different nervous systems. One of the chapters discusses peptides and the use of D-amino acid residues and the ramifications of such changes. The chapter by Timmermans provides a set of diverse drug areas and the importance of stereoselectivity in these areas. A final paper is presented on racemates and specific isomers used in clinical practice. The book concludes with a summary by Soudijn of the important findings and concepts discussed at the meeting.

The book provides a nice blend of introductory material and information up to 1983 on the action of different isomers of drugs and substances affecting a variety of biological systems. There is a divergence of style and emphasis as one might expect since it is a multiauthored book. However, the various papers are well-written and referenced. Most of the papers have helpful illustrations and a subject index provides for quick access to material of interest. The book has some excellent discussions and is very informative and an extremely good purchase for those seeking knowledge in the area of stereochemistry and drug activity.

Division of Medicinal Chemistry and Pharmacognosy **Duane D. Miller**
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New Drugs Annual: Cardiovascular Drugs. Edited by Alexander Scriabine. Raven Press, New York. 1984. x + 273 pp. 16 × 24 cm. ISBN 0-89004-931-9. $41.50.

This is the second volume of a series describing the actions of cardiovascular drugs. Thirteen chapters in six sections describe antihypertensive drugs (enalapril, celiprolol, nitrendipine, and muzolimine), antiarrhythmic drugs (verapamil and clofilium), antianginal drugs (diltiazem, bepridil, molsidomine, and alinidine), vasodilators (buflomedil), cardiac stimulants (prenalterol), and cerebral drugs (flunarizine). The chapters are written by experts in their respective fields and the volume is under the capable direction of Alex Scriabine, who is a coauthor on the nitrendipine chapter.

My own interests in recent years have centered on cardiovascular drugs, but it is extremely difficult to keep abreast of the total pharmacologic profile in this fast-moving field. The present series of volumes does much to remedy this situation; here the cardiovascular specialist and nonspecialist will find succinct and timely reviews of the properties of important new drugs. Most of the chapters embrace both animal and clinical pharmacologic studies including disposition, interactions, etc. I found the volume, and its predecessor, to be most useful. And, finally, the price is right. These volumes will probably adorn many a library and individual workers shelves.

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Advances in Heterocyclic Chemistry. Volume 34. Edited by A. R. Katritzky. Academic Press, New York. 1983. ix + 450 pp. ISBN 0-12-020634-X. $89.00.

The five chapters of this volume are all comprehensive reviews of topics not recently reviewed in depth in English. The longest and probably the most generally interesting is "The Formation of Anionic σ-Adducts from Heteroaromatic Compounds:

Structures, Rates, and Equilibria" by G. H. Illuminati and F. Stegel (University of Rome). These Meisenheimer adducts are obtained by the reaction of heteroaromatic compounds such as nitropyridines with anions such as alkoxide.

Nitropyridines are prominent also as precursors of the subject compounds in "The Chemistry of the Triazolopyridines" by G. Jones and R. Sliskovic (University of Keele). A drug in this class is the antidepressant trazodone.

The first two chapters are reviews of "The 3*H*-Pyrazoles" and "The 4*H*-Pyrazoles" by M. P. Sammes (University of Hong Kong) and the editor of this valuable series, A. R. Katritzky (University of Florida). These nonaromatic compounds, also called pyrazolenines and isopyrazoles, are perhaps less familiar than the 1*H*-pyrazoles, and these reviews are welcome.

The remaining chapter, a review of "Pyrans, Thiopyrans, and Selenopyrans" by J. Kuthan (Prague Institute of Chemical Technology), covers many structures not frequently considered by medicinal chemists. The true pyrans, of course, are not uncommon in natural products, examples being the cannabinols and the polyether antibiotics.

The usual high standards of this series are maintained. The prices are high for individual purchase, but the series should be in the libraries of most chemistry departments, pharmacy schools, and other institutions and corporations engaged in medicinal chemistry.

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Reviews in Biochemical Toxicology. 6. Edited by Ernest Hodgson, John R. Bend, and Richard M. Philpot. Elsevier Science Publishing Co., Inc., New York. 1984. ix + 270 pp. 16.5 × 24.5 cm. $49.50.

In their brief preface, the editors of this series state the belief that "... the study of mechanism, rather than routine testing, is the key to further progress" in toxicology. The content and emphasis of Volume 6 reflect this belief and, indeed, several of the chapters concentrate heavily on the biochemical and bioorganic mechanisms of the metabolism of foreign compounds and on the molecular aspects of the interaction of these compounds and their metabolites with cellular constituents.

In the first chapter, Ortiz de Montellano concisely summarizes the mechanistic aspects of cytochrome P-450 catalyzed oxidations and the relationships of these mechanisms to prosthetic heme alkylation and cytochrome P-450 destruction by olefins, acetylenes, haloethylenes, 4-alkyldihydropyridines, and hydrazines. This lucid discussion is followed by a thorough and informative analysis by Wilkinson and co-workers of the interactions of methylenedioxyphenyl compounds with cytochrome P-450. The methylenedioxyphenyls and related agents which are used as insecticide synergists have proven to be valuable tools for the investigation of the mechanisms of interaction of xenobiotics with cytochrome P-450.

In the third chapter, Marx develops a chemical and structurally oriented model for the interaction of albumin and bilirubin. This is a subject that does not appear to have been given extensive attention in other review series and should be of value to workers who are interested in mechanisms of ligand binding to albumin or in bilirubin toxicity.

The importance of mercapturate formation in the disposition of foreign compounds by mammalian tissues has long been recognized, but the enzyme cysteine S-conjugate *N*-acetyltransferase, which catalyzes the final step in mercapturic acid formation, has only recently received close scrutiny. The properties of this *N*-acetyltransferase, as well as those of cysteine conjugate β-lyase and thiol *S*-methyltransferase, are summarized by Jakoby and coauthors. The latter two enzymes are of particular current interest to scientists working in the areas of bioactivation and detoxication. Another group of enzymes, the plasma cholinesterases, is the topic of a chapter by Main in which attention is focused upon purification methods and upon the physical, chemical, and kinetic properties of this important class of hydrolases.

The final three chapters are devoted to the "Biochemical Toxicology of Formaldehyde" (H. d'A. Heck and M. Casanova-Schmitz), the "Biochemical Toxicology of Diethylstilbestrol" (M. Metzler), and the "Metabolism of the Cannabinoids" (D. J. Harvey and W. D. M. Paton). These chapters are written by experienced scientists who have first-hand knowledge of their topics. A number of the papers cited were published as recently as 1983 and 1984.

As mentioned above, the editors of the *Reviews in Biochemical Toxicology* series are advocates of the mechanistic approach to toxicological research, and it is highly probable that Volume 6, as well as previous volumes in the series, will convince others of the validity of the editors' belief.

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Organometallic Compounds and Living Organisms. By John S. Thayer. Academic Press, New York. 1984. xii + 273 pp. 16 × 23.5 cm. ISBN 0-12-686080-7. $49.50.

The biological effects of organometallic compounds, i.e., those compounds having a carbon–metal bond, date back to the observation of Cadet in 1760 of the toxic effects of methylarsenicals. There has been much research in this field, particularly in the early days of what is now considered medicinal chemistry, and which took place prior to much of the development of organometallic chemistry itself. Much of the research described in this volume is of recent origin, although historical aspects are included. It is concerned chiefly with the biological effects of the organo derivatives of boron, silicon, phosphorus, arsenic, mercury, tin, and lead, with some mention of related metals.

The chapters are organized mainly on the basis of the effect of organometallics on various organisms. Following an introductory chapter on historical aspects is a chapter on medicinal applications. This takes up the organometallics which have been used as antiseptics, disinfectants, bactericides, antiparasitic agents, antiviral and antitumor agents, and in treatment of other disorders, such as arthritis, hypertension, and muscular and nervous disorders. The toxicology of organometallics is described, both lethal and sublethal, and applications to biochemical investigations are discussed.

The remainder of the chapters are concerned with effects on living organisms. These include microorganisms, fungi and algae, plants, and animals, including aquatic invertebrates. Biological alterations of metal–carbon bonds are considered, a topic which has assumed considerable importance since the discovery that methylmercury compounds can be generated by the actionof microorganisms on inorganic mercurials. The final chapter is concerned with organometallic compounds in the environment, which is a topic of concern to all in view of the huge quantities of these compounds used in agriculture as fungicides.

This book is a timely addition of recent developments to an already extensive literature on organometallics. It is not an exhaustive treatment, but the majority of references date from 1980 and later. The text is clearly written, and the broad viewpoint of the author makes it highly readable. While most of the discussions are brief, there are extensive tables and an adequate number of chemical structures. It is also well indexed with an index to chemical substances, index to organisms, and a subject index. The author is to be commended for a concise and useful volume on a topic of major importance.

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Fieser and Fieser's Reagents for Organic Synthesis. Volume 11. By Mary Fieser. Wiley, Somerset, NJ. 1984. 669 pp. 16 × 23 cm. ISBN 0-471-88628-8. $45.00.

This latest volume in this series covers reagent literature published between July 1981 and December 1982. This book, as in previous volumes, provides references to new reagents in-

troduced during this period, as well as recent references to reagents included in previous volumes, focusing on reagents that open new vistas in organic synthesis.

Staff

Modern Methods in Protein Chemistry. Review Articles. Edited by Harold Tschesche. Walter de Gruyter, Berlin, New York. 1983. ix + 464 pp. 17 × 24 cm. ISBN 3-11-009514-9. $86.40.

This is a series of reviews on selected, relatively new analytic methods in protein chemistry. Classic methods are not covered. Although the reviews stem from a meeting (The Joint Meeting of Nordic Biochemical Societies, Danp/Kiel, Germany, September 1982), the papers are general review articles on selected techniques rather than specific research papers. Most interested investigators are likely to use specific chapters rather than the entire text. The subjects covered emphasize modern analytic approaches that have generally not been adequately reviewed elsewhere. Subjects covered include HPLC, affinity electrophoresis, immunochemical methods to monitor protein synthesis, immunoelectrophoresis (several aspects), isoelectric focusing, two-dimensional electrophoresis, microsequencing methods (several aspects), and spin-labeling methods. In general, any investigator who was planning on using any of these methods for the first time would find benefit from reading the specific review involved. The basic principles involved, specific experimental protocols to use (at the level comparable to a review in *Methods of Enzymology*), and cross references are adequately provided. However, the reviews vary with respect to detail of experimental methods and the emphasis given to the author's own procedures. Most of the reviews contain references up to and including 1982 and 1983. The subject indexing is far from exhaustive.

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Mechanism of Drug Action. Edited by Thomas P. Singer, Tag E. Mansour, and Raul N. Ondarza. Academic Press, New York. 1983. xvii + 405 pp. 16 × 23.5 cm. ISBN 0-12-646680-7. $39.00.

This publication contains the proceedings of a conference entitled "Symposium on the Biochemical Basis of Drug Action" held at Stanford University on June 20–23, 1983. The first meeting organized by two of the editors (T.P.S., R.N.O.) was held in Oueretaro, Mexico, in 1980. The stated purpose for these assemblies was to bring together scientists from a diversity of disciplines who have as common goals the elucidation of rational approaches to the development of therapeutic agents. It is interesting that 11 of the 31 presentations were from research groups at Stanford and other California academic institutions.

Six areas of research bearing on drug action are the basis for the symposium. Presentations highlighting the nicotinic acetylcholine receptor, muscarinic drugs, the β-adrenergic receptor, the κ opioid receptor, and receptor stereochemistry are brief accountings of the progress in five research groups interested in receptor action. Three papers under the general heading of "Molecular and Genetic Analysis of Drug Action" address thyroid and glucocorticoid hormone action and gene amplification in methotrexate resistance.

Seven papers over a wide range of topics dealing with parasitic diseases examine glycolysis in trypanosomes, purine and pyrimidine inhibitors, schistosomiasis drug mechanisms, and the serotonin receptors in trematodes. A short section entitled "Prostaglandins and Leukotrienes" reviews the properties of prostacyclin and contains discussions on the action of prostacyclin on the vascular endothelium, cytoprotection with prostacyclin with dual enzyme inhibitors, and the leukotrienes in hypersensitivity and inflammation.

A paper on the diversity of cytochromes P-450 and their characteristics leads off the next section entitled "The Biochemical Basis of the Action of Toxic Substances". Five additional papers on this topic include metal toxicity in aquatic organisms, toxin action on adenylate cyclase, ellipticine cytotoxicity, mercuric ion reductase, and the induction of a P-450 with aryl hydroxylase activity by TCDD.

The final section of the book emphasizes CNS-directed agents. Papers on receptor control, opiate action, and mechanisms of desensitization of nucleotide cyclase action comprise one-half of the discussion. Additional topics presented are discussions of cholecystokinin, autoradiographic studies on rat brain, and an update on soluble receptors for benzodiazepine.

For many reasons the most common audiences for symposium publication are the contributers themselves and those scientists specifically interested in a particular topic. While the former is understandable, this reviewer is doubtful that this book will be useful to scientists already working in the specific research areas addressed in the individual papers. The papers are either reviews or progress reports that are probably already in print in primary journals at the time of this review. However, for those scientists with a broad view of drug development this book allows for a quick overview of the state of the art in the many diverse areas. The individual papers are concise, well-detailed accounts of progress in many research areas.

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Presynaptic Modulation of Postsynaptic Receptors in Mental Diseases. Edited by Andre I. Salama. Annals of the New York Academy of Sciences, Volume 430. 1984. x + 139 pp. 15.5 × 23.5 cm. ISBN 0-89766-255-5.

This volume consists of eight papers presented in connection with a Symposium honoring the memory and work of the late Dr. S. Hess. The Introductory remarks of Drs. Spector and Salama testify to the esteem which Dr. Hess enjoyed among his colleagues. Two types of catecholamine receptor (the α-adrenoceptor and dopamine receptors) are the subject of five of the eight papers. The articles are by established investigators in each area: they present detailed overviews of the topics, giving a good introduction of the approaches used by each research group. There are an additional three chapters on receptor desensitization, serotonergic function in affective disorders, and autacoids acting upon imipramine recognition sites.

In summary, this small volume is a fitting tribute to Dr. Hess. This volume may be more appropriate for an Institute library rather than an individual researcher's bookshelf.

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Drug Design: Fact or Fantasy? Edited by G. Jolles and K. R. H. Wooldridge. Academic Press, London. 1984. xviii + 268 pp. 15.5 × 23.5 cm. ISBN 0-12-388180-3. $30.00.

This book is based on the Proceedings of the Third Rhone-Poulenc Round Table Conference entitled "Drug Design: Fact or Fantasy?" held in November 1982. The book's title is certain to attract the attention of medicinal chemists who are struggling with the problem of producing active compounds more efficiently than ever before. This has created great interest in the subject of rational methods for designing structures. The conference consisted of nearly 60 leading individuals, largely from European pharmaceutical industry and academia, who are directly involved in drug discovery or are working on methods for drug design.

Eleven presentations were given on topics covering prodrugs, drug carriers, transition-state analogues, traditional methods, and computer methods such as pattern recognition, QSAR analysis, molecular modeling, and graphics. Each seminar is presented in the book as a chapter, with most having reasonable bibliographies and a transcript of the ensuing discussion. The technical chapters provide background to the central theme of the book, which is the subject of the remaining five chapters. It is in these chapters where all of the participants attempt to put into perspective the

methods just described. The most interesting chapter is at the end and presents the results of splitting the participants into four "syndicates", each to answer the two questions:

Which methods, present and future, are most useful for generating new leads?

Which methods, present and future, are most useful for optimizing the activity of a chemical series?

Each syndicate selected a variety of methods for each question; however, the overall conclusions are quite similar. A better understanding of the biochemical pathways is a primary need for more efficient discovery of new leads, and QSAR and graphics can play an important role in the optimization of the activity.

The question raised by this book will remain an important one for the pharmaceutical industry for the foreseeable future. The discussions and conclusions presented in the book represent an important introduction to this question and should be of use to those in the field of drug discovery. It can be hoped that meetings of this type will continue to be held to track and influence the development of methods for drug design.

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Etoposide [VP-16]: Current Status and New Developments. Edited by Brian F. Issell, Franco M. Muggia, and Stephen K. Carter. Academic Press, Inc., Orlando, FL. 1984. xix + 355 pp. 16 × 23.5 cm. ISBN 0-12-375350-3. $30.00.

This book contains the papers presented at a symposium which was sponsored by the New York Medical Center Postgraduate Medical School on September 15–16, 1983, in New York City.

The 29 chapters (with pertinent references after each chapter) are devoted to various aspects of etoposide [VP-16], a new semisynthetic anticancer drug derived from podophyllotoxin, including an overview; the chemistry; in vivo experimental antitumor activity; mechanism and relationship of cytotoxicity to DNA breakage; effects on membrane transport processes; the clinical pharmacology in adults and in children with cancer; the absolute oral bioavailability and pharmacokinetics; the role of single-agent, combination and alternating, non-cross-resistant chemotherapies in small-cell and non-small-cell lung cancers; the role in chemotherapy of testicular cancer; the combination chemotherapy in malignant teratoma; in the treatment of refractory germinal neoplasms, breast cancer, Hodgkin's and non-hodgkin's lymphomas, diffuse large-cell lymphomas, refractory or recurrent lymphomas, Kaposi's sarcoma and other tumors; as well as a summary of the current status and future directions of research.

Each chapter is written with clarity and conciseness and has a brief introduction and discussion which point to the current status or new developments. The medicinal chemists will perhaps enjoy reading Chapter 2, entitled "The Chemistry of Etoposide" by T. W. Doyle, as it contains useful information concerning the future direction of research for the development of second-generation drug of etoposide.

Some minor printing errors to be noted include the correct use of "American mandrake or May apple" instead of "mandrake or American May apple" as shown in the Preface; "The alcoholic extract termed podophyllin" instead of "The extract termed podophyllin" on page 1; "OH-C_1 and C_4-C_1 both α instead of both β" as shown for the structure of podophyllotoxin on page 3; "the phenol group on the pendant E ring instead of C ring" as shown on line 7 from the bottom of page 59; and the structural formula shown on page 70, in which R_1 should be a solid line instead of a dotted line.

Although the literature reviewed in this book covers through the middle of 1983, books in such a dynamic field tend to become outdated when published. Nevertheless, this book does adequately summarize the state of knowledge on etoposide. This book will be of particular value to those who are interested in this area of research.

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Conformationally Directed Drug Design: Peptides and Nucleic Acids as Templates or Targets (ACS Symposium Series No. 251). Edited by Julius A. Vida and Maxwell Gordon. American Chemical Society, Washington, DC. 1984. x + 271 pp. 16 × 23.5 cm. ISBN 0-8412-0836-0. $45.00.

This volume is based on a symposium of similar title sponsored by the Division of Medicinal Chemistry at the 186th National Meeting of the American Chemical Society in Washington, DC on August 30, 1983. The subject reflects on the new era of medicinal chemistry wherein drug design is based on the *structure* of effector molecules or receptor sites. In the preface the editors cite both cimetidine and captopril as being recent successes with this approach, which differs significantly from traditional methods based on whole-animal studies or congener development.

This compilation of 11 chapters is structured to emphasize the common theme of the role of conformational structure in both peptides and nucleic acids in the design of bioactive molecules that either act on peptides or nucleic acids or are peptides or nucleic acids in their own right. Each chapter represents a recent development, or at least a recent survey, of the particular area.

Chapter 1, "Virus-Receptor Interactions", by B. N. Fields and M. I. Greene, is a short chapter on the protein–protein interactions as determined by the binding of reovirus hemagglutinin with cell receptors, especially as these studies could possibly relate to vaccine development and the like. Chapter 2, "Design of Peptide Superagonists and Antagonists", by V. J. Hruby, treats the subject of design of conformationally restricted peptides (oxytocin, enkephalin, and α-melanotrophin analogues) as a rational approach to peptide hormone and neutrotransmitter analogues. Use is made of conformational models which aid in the development of the analogues. Chapter 3, "Localization and Synthesis of Protein Antigenic Sites", by M. Z. Atassi, is a lengthy chapter which describes the author's own research into the determination of protein antigenic sites, among them those for myoglobin, lysozyme, serum albumin, and human hemoglobin. Noteworthy is the demonstration that small free peptides of synthetic origin can function as immunogens. Chapter 4, "Studies on New Microbial Secondary Metabolites with Potential Usefulness", by H. Umezawa, written, for the most part, in the first person singular, is an historical account of the impressive list of enzyme inhibitors, immunomodulators, antibiotics, antitumor agents, and the like to flow from the laboratories of Umezawa and associates. While not contributing to the theme per se, the chapter is an article well worth reading. Chapter 5, "Conformation of Nucleic Acids and Their Interactions with Drugs", by A. H.-J. Wang, reports on the use of new synthetic oligonucleotides of defined sequence and structure, both left- and right-handed, as they contribute to our understanding of drug–nucleic acid interactions. Chapter 6, "Substrate Analog Inhibitors of Highly Specific Proteases", covers the development of inhibitors for renin, kallikrein, and IgA_1 protease based on peptides modeled on the amino acid sequences around the cleavage sites of the substrate. Chapter 7, "Structural-Behavioral Activity Relationships of Peptides Derived from ACTH", by J. W. van Nispen and H. M. Greven, discusses ACTH-derived peptides, their conformation, and modifications which have resulted in Org-2766, an orally active peptide of increased potency and selectivity. Chapter 8, "Design of Novel Cyclic Hexapeptide Somatostatin Analogs from a Model of the Bioactive Conformation", by R. M. Freidinger and D. F. Veber, reviews their work on the use of a bioactive conformational model to rationalize cyclo retro isomers of somatostatins which are designed to eliminate undesired properties yet retain necessary side-chain topography. Chapter 9, "Design of Kinase Inhibitors", by G. L. Kenyon and R. E. Reddick, presents a wealth of information on inhibitors, substrates, and affinity labels for kinases and describes how these pieces of information can be utilized in drug design, including an example for an affinity label designed for creatine kinase. Chapter 10, "Design and Discovery of Aspartyl Protease Inhibitors", by D. H. Rich, F. G. Salituro, M. W. Holladay, and P. G. Schmidt, reports on the synthesis and mechanism of action of new inhibitors of aspartyl protease. Chapter 11, "Design of Peptide Analogs", by R. S. Struthers, A. T. Hagler, and J. Rivier, discusses the application of modern theoretical techniques for conformationally based design of biologically active peptides. The example developed is a simulation of GnRH, with

the design of a target GnRH cyclic antagonist resulting.

While the content and quality vary somewhat from chapter to chapter, as one would expect in a compilation of this sort, the volume does as a whole bridge the field adequately, with emphasis being slanted toward the peptide and protein areas (three, possibly four, chapters on nucleic acids, seven chapters on peptides and proteins). The publishers are thanked for an index. The volume is recommended as a reference in the field.

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Metal Ions in Biological Systems. Volume 18. Circulation of Metals in the Environment. Edited by H. Sigel. Marcel Dekker, Inc., New York. 1984. xxiii + 397 pp. 16 × 23.5 cm. ISBN 0-8247-7226-1. $79.95.

This is the latest addition to the excellent series of monographs edited by H. Sigel dealing with various aspects of metals in biological systems, and the current text is a collection of contributed chapters discussing and evaluating various aspects of the overall question. There are a total of 11 chapters, with some authors responsible for more than a single chapter and the first and last chapters are really introductory and conclusion types rather than covering entirely new material. Chapter 2 is a crucial one, in that it details, according to its authors, the current analytical methods for inorganic speciation that can and/or have already been applied to metal ions in the environment. This reviewer found that the treatment was reasonable, except for the significant omission, almost entirely, of gas chromatographic and high-performance liquid chromatographic (HPLC) approaches for inorganic speciation. Thus, many of the described methods are not really element specific or selective, in that they use general color forming reagents that might be selective for one or more metal species. There is also a discussion of flame emission and atomic absorption spectrophotometry but relatively little on inductively coupled or direct current plasma emission spectroscopy (ICP/DCP). There is also virtually nothing described or referenced having to do with the interfacing of HPLC with element selective detection (HPLC-ICP, HPLC-GFAA, HPLC-FAA, etc.), and that too could be considered a serious deficiency for those interested in learning about these newer speciation approaches for metal ions.

The next few chapters deal with the processes of metal ions in the environment and surface complexation, and consider complex formation, hydrolysis, adsorption, chemisorption, ion exchange, stability constants of surface complexes, and related areas of importance. Several of the chapters deal with biological availability and biological transport of metal ions in animal systems, formation of chelates and derivatives in vivo, and what happens to the metal ions once they are introduced into mammalian environs. There are another three chapters that deal with metal ions in aquatic systems, the interactions of metals with organics, and regulation of metal concentrations in freshwater or saltwater. Perhaps one of the more interesting chapters in the entire text is that by Wood, which now considers microbiological strategies in resistance to metal ion toxicity. He introduces areas such as biomethylation of metals and metalloids and transport through cell membranes by various processes, binding of metal ions to cell surfaces, removal of metal ions by precipitation at the cell surface of microorganisms, and finally, genetic engineering and the management of metal-polluted industrial wastewaters.

In general, virtually all of these chapters are well written, well referenced, very up-to-date in most cases, and clearly written by experts in each field. This reviewer, perhaps of my own bent toward analytical chemistry and newer methods of inorganic analysis and speciation, found these chemistry areas to be somewhat behind the times. In view of the recent publications emphasizing GC and HPLC-detector approaches for a large number and variety of inorganic speciations, as well as some recent books in these areas, it was somewhat surprising to find them so undertreated in the entire book. This could be considered a serious omission on the part of various contributors. For those interested in The Importance of Chemical Speciation in Environmental Processes, the September, 1984 Dahlem Conference in West Berlin, FRG, was an excellent survey of just about all important analytical approaches now possible for metal/nonmetal speciation. The Proceedings of this important meeting might be of interest to readers of the current book. The other areas of environmental transport, deposition of metals in various environmental compartments, adsorption processes, biological transport, microbiology, removal from polluted wastewaters, and related environmental/biological areas are most adequately discussed and reviewed. The book is recommended to those potential readers involved or about to become involved with the area/question of metals in the environment and the various kinetic and thermodynamic processes involved in the movement and distribution of such metals.

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Books of Interest

Aminoglutethimid: Ein Antiostrogen Mit Aromatasehemmung—Ein Neues Prinzip in Der Krebstherapie—Aktuelle Onkologie 9. Edited by G. A. Nagel, R. Sauer, and H. W. Schreiber. W. Zuckschwerdt GmbH. 1984. vii + 172 pp. 15 × 21 cm. ISBN 3-88603-067-9.

Bacterial Protein Toxins. FEMS Symposium No. 24. Edited by J. E. Alouf, F. J. Fehrenbach, J. H. Freer, and J. Jeljaszewicz. Academic Press, Orlando. 1984. xx + 455 pp. 16 × 23.5 cm. ISBN 0-12-053080-5. $26.00.

A Pictorial Approach to Molecular Structure and Reactivity. Edited by Robert F. Hout, Jr., William J. Pietro, and Warren J. Hehre. Wiley-Interscience, New York. 1984. xi + 403 pp. 17 × 24 cm. ISBN 0-471-89703-5. $39.95.

The Role of Drugs and Electrolytes in Hormonogenesis. Edited by K. Fotherby and S. B. Pal. Walter de Gruyter, Berlin and New York. 1984. xii + 360 pp. 17 × 24 cm. ISBN 3-11-008463-5. 180DM.

Analytical Uses of Immobilized Enzymes. Modern Monographs in Analytical Chemistry Series. Volume 2. By George G. Guibault. Marcel Dekker, New York, 1984. ix + 453 pp. 16 × 23.5 cm. ISBN 0-8247-7125-7. $75.00.

American Drug Index 1984. Edited by Norman Billups and Shirley Billups. J. B. Lippincott, Philadelphia. 1984. ix + 702 pp. 14.5 × 21 cm. ISBN 0-397-50649-X. $24.50.

Kirk-Othmer Enclopedia of Chemical Technology. Third Edition. Index to Volumes 1-24 and Supplement. Edited by Martin Grayson, David Eckroth, Herman F. Mark, Donald F. Othmer, Charles G. Overberger, and Glenn Seaborg. Wiley, New York. 1984. 1vi + 1274 pp. 18.5 × 26 cm. ISBN 0471-04154-8. $184.00.

Kirk-Othmer Enclopedia of Chemical Technology. Third Edition. Supplement Volume. Alcohol Fuels to Toxicology. Edited by Martin Grayson, David Eckroth, Herman F. Mark, Donald F. Othmer, Charles G. Overberger, and Glenn T. Seaborg. Wiley, New York. 1984. xxviii + 924 pp. 18.5 × 26 cm. 0471-89214-9. $150.00.

Compendium of Pharmaceuticals and Specialties, 1984: Nineteenth Edition. Marcel Dekker, New York. 1984. 920 pp. 21 × 23 cm. ISBN 0-8247-7306-3. $79.75.

National Institute on Drug Abuse Research Monograph Series 49. Problem of Drug Dependence 1983. Proceedings of the 45th Annual Scientific Meeting. The Committee on Problems of Drug Dependence, Inc., National Institute of Drug Abuse. 1984. xii + 455 pp. 14.5 × 23 cm.

Friedel-Crafts Alkylation Chemistry. A Century of Discovery. By Royston M. Roberts and Ali Ali Khalaf. Marcel Dekker, New York. 1984. x + 790 pp. 18.5 × 26 cm. ISBN 0-8247-6433-1. $165.00.