1a was a particularly potent venoconstrictor, threshold responses being obtained at a concentration of 1 ng/ml. By comparison, canine intrapulmonary veins have also been reported[21] to be very sensitive to PG endoperoxide analogues. The ED_{50} (95% confidence interval) of **1a** for contraction of the canine saphenous vein was 5.8 (5–6.7) ng/ml. Additional experiments showed that venoconstriction induced by **1a** was not blocked by indomethacin and that **1a** did not possess vasodilator activity.[22]

It should be noted that the 60:40 mixture of **1a**:**1b** was tested on platelets and the isolated saphenous vein. The effects were not substantially different from that of **1a**, thus suggesting that **1a** and **1b** possess similar activities and potencies.

The results of this study indicate that endoperoxide mimicry is not restricted to heterobicyclo[2.2.1]heptane analogues of PGH_2 and that other bicyclic systems may share similar biological properties. We are presently investigating the stereochemistry of the acetal chiral center in **1** and the biological properties of homologues of **1**.

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Philip S. Portoghese,* Dennis L. Larson
Anthony G. Abatjoglou
Department of Medicinal Chemistry, College of Pharmacy

Earl W. Dunham
Department of Pharmacology, Medical School

Jonathan M. Gerrard, James G. White
Department of Pediatrics, Medical School
University of Minnesota, Minneapolis, Minnesota 55455

Received November 5, 1976

Book Reviews

Advances in Carbohydrate Chemistry and Biochemistry. Volume 31. Edited by R. Stuart Tipson and Derek Horton. Academic Press, New York, N.Y. 1975. xii + 416 pp. 15 × 23.5 cm. $18.50.

"Advances in Carbohydrate Chemistry and Biochemistry", Volume 31, consists of seven chapters and is a welcome addition to this series.

The chapter on deamination of carbohydrate amines offers a comprehensive survey of the current status of nitrosation as a means of effecting deamination of carbohydrate and cyclitol amines. The reaction is certainly the most widely used one for deaminating carbohydrate amines and its usefulness as well as its limitations are adequately presented. The section dealing with the application of the reaction to synthetic and structural problems is an important one and serves to illustrate the most fruitful use of the reaction, namely, in degradation studies during the structural elucidation of carbohydrate amines. The formation of rearrangement products, depending on the stereochemistry of the substrate amines, imposes severe limitations on the synthetic utility of the nitrosation deamination reaction. Consequently, it would have been valuable if the author had included a short section on new methods for carrying out deaminations. Even though these reactions have not been used in the carbohydrate field to date, it might have served to stimulate carbohydrate chemists to use them in the future.

The chapter on the reaction of ammonia with acyl esters of carbohydrates by Gelpi and Cadenas deals with this interesting but complex reaction in a clear and concise way. It also summarizes the application of this reaction for the preparation of nitrogenated derivatives of carbohydrates and nitrogen-containing heterocyclic compounds. A description of the influence of the solvent, and the structure and configuration of the starting material, is included. At the end of the chapter there are two very useful tables which give a list of acylated monosaccharides and disaccharides and their reaction products with ammonia. The yield, physical constants of the final products (melting points, $[\alpha]_D$, etc.), and references are included in the tables.

The chapter on chemistry and biochemistry of apiose by Watson and Orenstein is unnecessarily lengthy and contains too many historical details which may be interesting to read but are of little consequence to investigators in this area of research. Isolation, characterization, chemical synthesis, and biosynthesis of apiose have been discussed in this chapter and it also contains many useful references. In recent years many branched chain sugars have been isolated from antibiotics. The possible role of these branch-chained sugars and apiose containing polysaccharides in resisting microbiological degradations has been discussed.

The application of specific degradation techniques to the elucidation of polysaccharide structures is lucidly presented in the fourth chapter. The examples used to illustrate the various degradation reactions are well chosen and range from plant gums to blood group polysaccharides. Although the techniques described in this chapter were developed primarily for polysaccharides, the methods have been successfully applied to the degradation of a number of carbohydrate-containing antibiotics of varying complexity in a number of laboratories and this review will be invaluable to workers in these areas as well.

The current state of the art with regard to interactions of certain immunoglobulins with polysaccharide antigens is reviewed in the fifth chapter. Recent advances in this important area of biochemistry are concisely presented. Emphasis is given to the importance of binding between polysaccharides and immunoglobulins in the analysis of structures in both of these important classes of compounds.

The chemistry and interactions of seed galactomannans have been summarized by Dea and Morrison. The chapter is well written and will be fairly easy to read even by those who are beginning to work in this area of research. The current knowledge of the basis of the interaction of galactomannans with other polysaccharides has been dealt with in detail. The article also discusses the botanical significance of galactomannan in *Leguminoseae*, their occurrence, isolation, and purification. The commercial exploitations of galactomannans have also been described. The reviewers particularly enjoyed the discussion on the "fine structure" determination of galactomannans and the use of physicochemical methods for the determination of molecular weight, conformation, and molecular shape of these complex natural products.

The last chapter on the bibliography of crystal structure of carbohydrates, nucleosides, and nucleotides by Jeffrey and Sundaralingam follows the same format as in Volume 30. The contents of this chapter, like their previous one, are very useful and easy for an organic chemist to use.

Chemical Research Department **A. K. Ganguly**
Schering Corporation **A. K. Mallams**
Bloomfield, New Jersey 07003

Antineoplastic and Immunosuppressive Agents. Part I. Edited by Alan C. Sartorelli and David G. Johns. Springer-Verlag, New York, Heidelberg, Berlin. 1974. 762 pp. $105.80.

The enormity of the task which Drs. Sartorelli and Johns have undertaken, namely to encompass in a single treatise the chemistry and rational drug design, biochemistry, and metabolic features, pharmacokinetics, preclinical and clinical pharmacology and toxicology of antineoplastic agents, singly, in combination and with various modalities as well as immunosuppressives is truly exceptional. The scope and successful achievement of the goals are mind-boggling to say the least and make it understandable why the cost of Part I can be in excess of $100.

This treatise is composed of six sections. The first two are incorporated into Part I which is composed of 29 chapters. Twenty-six of these deal with general considerations relating to antineoplastic drugs and associated therapeutic regimens and the latter three, in a similar vein, are concerned with immunosuppressive agents. These chapters contain more than 640 pages and additionally have nearly 100 pages for the author index alone. Such an undertaking would be unthinkable without the involvement of more than 40 established cancer researchers, many associated with our National Cancer Institute either directly or by grant support. The contributing authors read as a lexicon of individuals who have contributed in a major way to the development and progress achieved to date in cancer research and immunosuppressives. The breadth of knowledge presented is such that probably multiple reviewers would be highly appropriate in order to do full justice to this book.

As with all multiple-author books, one may be concerned with uniformity of presentation and cohesiveness of the chapters. The editors, however, have established a style and an orientation that is remarkably effective in presenting a lucid and well-organized flow of material. In addition, it would have been impossible for such a breadth of material to be written by several authors alone.

The only minor criticism that this reviewer has is in the organization of the first 26 chapters which relate to general considerations of antineoplastic drugs. The first two chapters deal in general terms with single drug selection (C. G. Zubrod) and evaluation methods of antineoplastic activity (A. Goldin, S. Carter, and N. Mantel). It may have been more appropriate to have placed chapter 22 which considers predictive tests for cytotoxic action together with the second chapter 2. Chapters 3–6 present clearly rational design and synthesis of new alkylating agents (W. C. J. Ross) and antimetabolites. The latter includes chapters on folic acid antagonists (J. A. R. Mead), purine nucleosides (J. A. Montgomery), and pyrimidine nucleosides (L. B. Townsend and C. C. Cheng). Next, there is a very useful section of four chapters, chapters 7–10, which are concerned with presenting the importance of cell cycle kinetics in chemotherapy considerations. They include basic concepts (L. F. Lamberton), clinical applications (B. Clarkson), metabolic sequences in cell replication (E. Stubblefield and S. Murphree), and the mechanism of action of cytotoxins in the cell cycle (H. Madoc-Jones and F. Mauro). Closely related to these are the mathematical considerations of pharmokinetics modeling in chapter 11 (D. S. Zaharko and R. L. Dedrick) and the approaches in determining optimal dosage schedules in man (chapter 17 by L. B. Mellett). In this regard it may have been preferable to have these two chapters presented contiguously. Other pharmacological and biochemical factors which influence drug action are considered and reviewed in subsequent chapters. Included are chapter 12 in which absorption, distribution, and excretion parameters are presented not only for anticancer agents but for immunosuppressives (V. T. Oliverio); transport phenomena presentation in chapter 13 (M. T. Hakala) is focused on mammalian cells and tissues; and there are two specific chapters on metabolism of cancer chemotherapeutics, chapters 14 and 15, which consider the pathways associated with endogenous (D. G. Johns) and exogenous (A. M. Guarino and C. L. Litterst) substrates, respectively. Another biochemical area that is covered relates to selective toxicological differentiation between normal and neoplastic cells. This material is presented in chapter 18 (J. F. Henderson). One final chapter in the biochemical and pharmacological section is a most effective presentation of the mechanism of drug resistance (chapter 19 by R. W. Brockman).

There was one chapter, 16, which was of special interest to this reviewer. This section relates to the chemotherapy of brain tumors (A. L. Cowles and J. D. Fenstermacher). It was the only chapter singling out for chemotherapeutic consideration a specific organ or tissue. Certainly there are physiological and biochemical differences between tumor and related normal tissues in other discrete sites and organs. Perhaps a more encompassing approach would be warranted rather than one which is so narrowly drawn. However, malignant brain tumors and lesions metastatic to the CNS do show profound permeability differences when these are compared with the normal parenchyma. Undoubtedly these differences account for the special consideration by the editors of the brain. The lucid presentation by the authors is not complete especially from a physicochemical standpoint. Data, such as that generated from the research studies of C. Hansch, should certainly have been considered.

Two chapters, 20 and 21, consider combination chemotherapy. The former by A. Goldin, J. M. Venditti, and N. Mantel presents basic considerations and the latter by E. Frei III and J. A. Gottlieb discusses the clinical basis and the application in a most effective manner.

As a prelude to the application both in the laboratory and clinically of various types of radiation in concert with chemotherapy (chapter 25 by R. L. Scotte-Doggett and M. A. Bagshaw), there are two chapters on ionizing radiation. Chapter 23 (P. Todd) presents the metabolic changes on biochemical molecules and subcellular and cellular structures; chapter 24 (L. J. Tolmach and L. E. Hopwood) considers the effect of such radiation on cell kinetics.

The last chapter relating to the therapy of neoplastic disease is entitled Tumor Immunotherapy (chapter 26 by A. Fefer). This burgeoning area which is in the early stages of development both from a basic standpoint and clinically as well is most clearly presented. Certainly this area will undergo extensive proliferation in the future.

The last three chapters comprising a separate section deal with immunosuppressives. Chapter 27 (M. S. Mitchell) is an introductory one on antibody elaboration, cellular immunity, and evaluative methodology of these agents. This is followed by a survey of the various compounds (chapter 28 by E. M. Hersh) and finally in chapter 29 (J. E. Harris and R. C. Bagai) we have presented the clinical application of these drugs in organ transplantation and autoimmune diseases. The sequence is both rationale and very clearly presented.

In conclusion, this monumental work is an excellent and important contribution both to those engaged in cancer chemotherapy and researchers involved with the use of immunosuppressive agents. It has become a most significant reference and will remain so for many years since it is grandiose in concept and first-class in execution. Clearly, many of the chapters in Part I will serve as a suitable starting point for students, teachers, and researchers interested in the current state of development and future directions in these highly complex fields. The paucity of criticism is a testimonial to the excellence that the editors and authors have achieved.

College of Pharmacy and Allied Health Professions
Northeastern University
Boston, Massachusetts 02115

Albert H. Soloway

Antineoplastic and Immunosuppressive Agents. Part II. Edited by Alan C. Sartorelli and David G. Johns. Springer-Verlag, New York, Heidelberg, Berlin. 1975. 1067 pp. $149.70.

This part of the monumental, awe-inspiring work undertaken by Sartorelli and Johns maintains the same very high quality standards which they have set in Part I. This volume of the sequence is concerned with those drugs which are of importance in disease treatment. There are specific sections on alkylating agents, hormones, antimetabolites, and other cytotoxic substances. One chapter in the latter section deals specifically with new antineoplastic agents, several of which are under clinical investigation.

Typical of the type of excellent presentation is the chapter of fluorinated pyrimidines by Heidelberger in which is presented in logical sequence, the rationale for drug development, chemical syntheses, various biological effects, biochemical mechanisms of action, metabolism, resistance, preclinical and clinical pharmacology, and usage in man. In some cases as with arabinosylcytosine, there are two separate chapters—one presenting synthesis, biological activity, and a description of biochemical actions, and the second one being totally devoted to clinical pharmacology and its use in man. This variation may be attributable in part to the various expertises of the authors and the objectives of the editors and on this basis, it is acceptable. The end result, however, is that different drugs and drug classifications are given varied emphasis in the text. In some cases, this treatment does present some limitation. For example, the alkylating agent, cyclophosphamide, certainly an extremely important clinical drug, is not discussed in a separate chapter whereas the antimetabolite 8-azaguanine, of markedly lesser clinical importance, is. In general, the antimetabolites are presented in greater detail than are some other drug categories. Perhaps this treatment is understandable because of the greater information which we have on their mode of action. This criticism, however, is of a minor nature when one considers what the editors have been able to assemble and accomplish. The litany of authors is impressive, for many such as Heidelberger, Freireich, Elion, Hitchings, Price, Sartorelli, and others have made significant and major contributions.

Clearly, this volume and its companion will remain for many years as the definitive reference books for those engaged in cancer and immunosuppressive research and treatment. The editors are to be commended highly for their accomplishments.

College of Pharmacy and Allied Health Professions
Northeastern University
Boston, Massachusetts 02115

Albert H. Soloway

Antihypertensive Agents. ACS Symposium Series 27. Edited by E. L. Engelhardt. The American Chemical Society, Washington, D.C. 1976. vii + 96 pp. 15 × 23 cm. $13.50.

The four papers contained in this volume comprise the symposium on antihypertensive agents sponsored by the Division of Medicinal Chemistry presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 8, 1975. The compilation of these papers provides a concise and useful overview of the present status of antihypertensive agents currently in use or in clinical stages of development as of 1975. Of particular interest to the synthetic medicinal chemist are the first three chapters which comprehensively survey the three basic classifications of antihypertensive agents: β-adrenergic blocking agents, such as propranolol and practolol; centrally acting agents, such as clonidine and methyl-Dopa; and peripherally active agents, such as the vasodilator, hydralazine.

In his review of the β-blockers, Clarkson considers the influence of structural modification on the pharmacological properties most relevant to antihypertensive activity and summarizes the available evidence concerning the structural properties required for β-adrenergic blocking activity. A wide variety of experimental and clinical agents are included in this comprehensive discussion. Hoefke's review of centrally acting antihypertensive agents discusses the current theories concerning the site and mechanism of action of clonidine and methyl-Dopa. Structure–activity relationships within the clonidine and methyl-Dopa series are also discussed. The discussion, by Francis, of the peripherally acting antihypertensive agents is concerned largely with the relationships between vasodilation activity and structural modification within the hydralazine and diazoxide series. Agents affecting noradrenergic mechanisms, while not gaining favorable acceptance on the U.S. market, are also discussed from a clinical point of view. Finally, angiotensin II inhibitors and their efficacy in treating hypertension are discussed in brief. The final chapter, by Onesti, discusses the clinician's use of various antihypertensive drugs in providing optimal therapy. The saluretic diuretics, while not discussed in the previous chapters, are included in this discussion as an integral part of the antihypertensive therapeutic armamentarium.

This book should prove to be a useful reference for those involved in the study of hypertension and antihypertensive drug design.

Pharmaceuticals Department
T. R. Evans Research Center
Diamond Shamrock Corporation
Painesville, Ohio 44077

W. P. Heilman

Chemistry, Biology, and Clinical Uses of Nucleoside Analogs. Edited by Alexander Bloch. Annals of the New York Academy of Sciences. Volume 255. 1975. 610 pp. 15 × 23 cm. $46.00.

This volume constitutes the Proceedings of a conference held in September 1974 in New York City under the auspices of the New York Academy of Sciences. As eloquently stated by the Editor and Co-Chairman, Alexander Bloch, in his introduction, the purpose of this meeting was to pause and evaluate retrospectively the progress made during the last 25 years in the area of nucleoside analogues, with a view to overcoming the "redundancy and stagnation...that interfere with creative progress." There is vivid testimony in these Proceedings that the field of nucleoside analogue research, far from being moribund, is in fact in its prime and in flourishing good health.

A total of 53 papers are included in this generous volume, and they are arranged into three major groups: (1) chemistry; (2) clinical uses; and (3) biology, biochemistry, and pharmacology. The first 12 papers are devoted to chemistry, including one by Sundaralingam which is probably the definitive statement on the use of x-ray diffraction to study nucleoside conformation. Chemical syntheses of nucleosides from several novel heterocyclic ring systems, and of nucleosides containing unusual sugars (including acyclic sugars), are also reported by a number of investigators well known to readers of this Journal. Another 12 papers deal with the clinical use of nucleoside analogues. Here

the emphasis is mainly in two areas—neoplastic disease and viral infections (especially those involving herpes and other DNA viruses). However, it should not be overlooked that certain nucleoside analogues have also shown experimental activity as immunosuppressants, antipsoriatic agents, inhibitors of platelet aggregation, coronary vasodilators, antiparasitic agents (especially against schistosomiasis and trypanosomal infections), fungicides, and antibacterials. Though it remains to be determined to what extent some of these effects can be translated into clinically useful results, there is little doubt that this will remain fertile territory for pharmacologists and clinicians in the years ahead.

The largest group of papers, 29 in all, comprise the third category, which apparently is intended to encompass all preclinical work other than chemical synthesis, and for a more "mixed bag" one could not ask. Here are a number of very interesting papers on the molecular and biochemical mode of action of nucleoside analogues, their transport across cell membranes, the design of specific in vitro and in vivo test systems for the assay of various kinds of activity (antiviral, antineoplastic, antiparasitic, and so on), the development of resistance, and the evaluation of pharmacokinetic properties in intact animals.

The entire field is magnificently summarized in two concluding papers, one by Alexander Bloch and the other by Roland Robins. If any "message" can be distilled from these papers (and from the book as a whole), it is that, in the absence of definitive knowledge about the multifaceted drug–receptor interactions associated with nucleoside analogues, the most unorthodox—even the most "outrageous"—structural modifications still deserve to be taken seriously as targets for chemical synthesis and biological evaluation.

Although the date of issue of the volume is only about one year after the conference took place, it should be noted in all fairness that some of the work reported has already been published elsewhere in full experimental detail. The principal advantages of buying the book are therefore accessibility and compactness. Technically, the overall quality is quite good. However, one cannot help remarking that, for $46, hard covers should have been provided.

Sidney Farber Cancer Institute **Andre Rosowsky**
Boston, Massachusetts 02115

Trace Element Analysis. By Vlado Valković. Taylor and Francis Ltd., London, and Halsted Press, New York, N.Y. 1975. x + 229 pp. 16 × 24.5 cm. $22.50.

In the preface Valković states that the purpose of his book is to "...help research workers in physics and chemistry laboratories (and their students) in their efforts to improve analytical techniques." The author also notes that the book serves the purposes of revealing "...some of the many interesting problems that arise in astrophysics, the environmental sciences, biology, medicine and technology..." and describing "...advances in analytical methods..." for detection and quantitation of trace levels of elements. The reviewers feel that the author meets the latter two objectives quite well; the book, however, is not likely to be of great practical benefit as proposed.

The book is set out in the following chapters: (1) Elements in Nature; (2) Trace Elements in the Environment; (3) Environmental Pollution; (4) Trace Elements in Biology and Medicine; (5) General Aspects of Trace Element Analysis; (6) Activation Analysis; (7) X-Ray Emission Spectroscopy; (8) Optical Methods; (9) Mass Spectrometry. The first two chapters contain considerable discussion on the theories of cosmological synthesis of elements and the dynamic relationships that effect these levels. Contributions by radionuclides are briefly covered. In general, these early chapters are heavy, slow going, and of limited value to the understanding of subsequently covered material.

Chapters 3 and 4 constitute two of the more important contributions of the text. They mainly concern the relative abundances of elements and their distribution throughout the biosphere. Air and water pollution are discussed as they relate to trace elements. The sources of these elemental pollutants and the natural forces that redistribute them are very clearly and concisely presented. A brief but excellent discussion of elements essential for life (excluding C, H, N, O, and P) and those elements which may yet be found to be essential follows. The distribution of the elements in various tissues within the body and disease states is also presented. Many of the inorganic aspects of biochemistry, such as the importance of metallic homeostasis, which are ignored in most introductory biochemistry textbooks, are nicely presented by Valković. Furthermore, because of the extensive footnotes and tables in Chapters 3 and 4, they are probably the most potentially useful sections to biochemists and health scientists.

The last half of the book (Chapters 5–9) describes analytical methods used for trace elemental analysis. The handling of air and water samples and descriptions of types of techniques are outlined as are the methods applicable for the treatment of data. The various types of activation analysis and x-ray emission analysis are presented at a theoretical level in considerable depth. Optical methods, such as emission spectroscopy and atomic absorption, and mass spectrometry are presented less thoroughly.

The overall level of this book probably limits its use to introductory graduate-level courses in trace elemental analysis or to environmental and health scientists who desire a compact reference with some pertinent references in their specialties.

Drug Dynamics Institute **D. Michael Baaske**
College of Pharmacy **Robert V. Smith**
University of Texas at Austin
Austin, Texas 78712

High-Speed Liquid Chromatography. Volume 6. Edited by P. M. Rajcsanyi and E. Rajcsanyi. Marcel Dekker, New York, N.Y. 1975. vii + 203 pp. $15.50.

This book represents an extensive review of the current high-speed liquid chromatographic (HSLC) field. Topics reviewed include theoretical aspects of HSLC, instrumentation, and applications. The scope of the contents is admirable, and the extent of referencing is almost total (over 1000 ref). This makes for a very useful book for a number of practical applications; however, the lack of recent references is disappointing. This is perhaps understandable in a field so prone to rapid change with regard to new techniques, applications, and instrumentation. The review is current through 1973 with only a handful of 1974 references. This means, for example, that very little attention is given to the use of microparticulate columns or to the advantages of variable wavelength UV detection. The use of reverse-phase chromatography for a number of compound types also seems to have been slighted. The authors likewise fail to adequately describe column packing material or column types, giving instead only manufacturers' designations. Another rather minor point is the awkward sentence structuring encountered at times.

In short, the book accomplishes its goals, but only for a time period extending through 1973. For a basic review of HSLC, for practical, starting point information on specific separations, and for a quick and handy guide to basic theoretical aspects of the technique, the book is useful and as such could well find a place on the chromatographer's bookshelf.

Research Triangle Institute **Monroe E. Wall**
Research Triangle Park
North Carolina 27709