Table I. Estrogenic Potentiation in Mice by Spiro(cyclohexane-1,2'-indan)-1',4-dione

Group	Treatment	Wt of mouse (g), mean ± SE	Wt of uterus (mg), mean ± SE	Uterine ratio
1	Arachis oil, 0.1 ml	12.1 ± 0.7	28.0 ± 2.0	232.2 ± 10.4
2	Stilbestrol, 0.1 μg	16.8 ± 0.5	148.1 ± 7.9	881.5 ± 70.2
3	**1b**, 0.1 μg	14.1 ± 0.4	35.5 ± 2.8	251.6 ± 19.5[a]
4	**1b**, 100 μg	13.3 ± 0.7	28.3 ± 2.1	212.7 ± 10.4[a]
5	**1b**, 0.1 μg, + stilbestrol, 0.1 μg	15.2 ± 0.7	145.0 ± 12.8	957.1 ± 72.6[b]
6	**1b**, 100 μg, + stilbestrol, 0.1 μg	14.1 ± 0.5	192.3 ± 12.6	1366.9 ± 79.5[c]

[a] Not significant ($p > 0.05$) when compared with arachis oil control. [b] Not significant ($p > 0.05$) when compared with stilbestrol (0.1 μg) control. [c] $p < 0.05$ when compared with stilbestrol (0.1 μg) control.

such effects.

In the light of these preliminary findings, the investigation of related compounds in this chemical series appears justified, since the use of an intrinsically inactive compound which will, nevertheless, potentiate estrogenic activity may be of value in reducing the undesirable side effects associated with the clinical use of a wide range of estrogenic drugs.

Experimental Section

Melting points were determined using a capillary apparatus and were uncorrected. Ir spectra were recorded on a Perkin-Elmer 357 spectrophotometer and uv spectra with a Pye Unicam SP800 spectrophotometer. NMR spectra were determined on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Where analyses are indicated only by symbols of the elements, the results obtained for those elements are within ±0.4% of theoretical values. Elemental analyses were performed by Mr. G. Crouch, School of Pharmacy, University of London.

2-(β-Ethoxycarbonylethyl)indanone. Ethyl acrylate (12 g, 0.12 mol) was added to a well-stirred mixture of α-indanone (14.4 g, 0.10 mol), triton B (2 ml), and hydroquinone (2 mg) in dioxane (50 ml) at such a rate that the temperature was maintained at about 50°. After addition was complete the reaction mixture was stirred at room temperature for a further 18 h before pouring into H_2O (100 ml) and extracting with $CHCl_3$ (three times). The combined $CHCl_3$ extract was dried (Na_2SO_4) and evaporated in vacuo and the residue distilled to afford the title compound (13.1 g, 51.7%): bp 170–180° (0.4 mm) [lit.[3] bp 208–209° (13 mm)].

2,2-Bis(β-ethoxycarbonylethyl)indanone. The title compound was prepared according to the procedure described for 2-(β-ethoxycarbonylethyl)indanone. The crude product was distilled, bp 190–195° (1.0 mm), to yield a colorless oil (7.0 g, 48.9%): ir (film) 1750 (five-membered cyclic C=O), 1730 cm^{-1} (ester C=O). Anal. ($C_{19}H_{24}O_5$) C, H.

Spiro(3-ethoxycarbonylcyclohexane-1,2'-indan)-1',4-dione (1a). The above indanone (23.2 g, 0.1 mol) was gradually added to a well-stirred suspension of metallic sodium (2.0 g) in dry toluene (150 ml) under an atmosphere of N_2 at 100 °C. After the vigorous reaction had subsided the mixture was refluxed for 4 h, cooled, and acidified with 10% AcOH. The mixture was extracted with $CHCl_3$ (three times); the combined $CHCl_3$ extracts were washed with H_2O and aqueous Na_2CO_3 and dried (Na_2SO_4). The $CHCl_3$ was evaporated and the residue distilled in vacuo to afford 1a (12.1 g, 42.2%): bp 182–190° (0.7 mm); ir (film) 1740 (β-keto ester C=O), 1720 (β-ester keto C=O), 1710 cm^{-1} (aromatic C=O); uv (EtOH) 247 nm (ε 50). Anal. ($C_{17}H_{18}O_4$) C, H.

Spiro(cyclohexane-1,2'-indan)-1',4-dione (1b). A mixture of the dione 1a (6.4 g, 0.03 mol) in 50% aqueous EtOH (100 ml) and HCl (33%, 40 ml) was boiled under reflux for 6 h and then poured into H_2O (250 ml). The mixture was extracted with Et_2O (three times). The combined Et_2O extracts were washed with H_2O and aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation gave a residue which distilled in vacuo to afford an oil, bp 156–158 °C (0.7 mm), which slowly crystallized from Et_2O (4.0 g, 83.6%): mp 75 °C; ir (KBr) 1715 (six-membered cyclic C=O), 1705 cm^{-1} (aromatic C=O); NMR ($CDCl_3$) δ 7.45 (4 H, aromatic ring), 3.25 (2 H, $-ArCH_2C-$), and 2.5 (8 H, $-CH_2CH_2C=O$); uv (EtOH) 269 nm (ε 583). Anal. ($C_{14}H_{14}O_2$) C, H.

Pharmacological Results. Female albino mice of an ICI strain, 23–25 days old, were randomly distributed into groups of ten. Groups 1–4 received no treatment on the first day, followed by arachis oil (0.1 ml), stilbestrol (0.1 μg), and **1b** (0.1 or 100 μg), respectively, once daily for three consecutive days. Groups 5 and 6 received **1b** (0.1 or 100 μg) on the first day, followed by **1b** (0.1 or 100 μg) together with stilbestrol (0.1 μg), on each of the three following days. All compounds were administered by subcutaneous injection in 0.1 ml of arachis oil. The group receiving vehicle alone served as controls. Free access to food and water was allowed throughout the experiment. The mice were sacrificed by cervical dislocation 24 h after the last injection and the body and uterine weights were determined. Uterine ratios were then calculated as uterine wt (mg)/body wt (g) × 100.

References and Notes

(1) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 3447 (1951).
(2) B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endocrinology*, **49**, 429 (1951).
(3) N. P. Shusherina, R. Ya. Levina, and M. Yu. Lure, *Vestn. Mosk. Univ., Ser. Mat., Mekh., Astron., Fiz., Khim.*, **12** (6), M3 (1957).

Book Reviews

Chemistry of Winemaking. Edited by A. Dinsmoor Webb. American Chemical Society, Washington, D.C. 1974. viii + 311 pp. 16 × 23.5 cm. $16.95.

A. Dinsmoor Webb and 12 contributors have presented 13 papers discussing all aspects of wine production including specific aspects of commercial and home wine making. These original contributions published in this "Advances in Chemistry Series" were written in mid-1973 by various specialists belonging mainly to the Department of Viticulture and Enology of the University of California, in Davis, as well as to well-known Institutes from France, Germany, and the trade.

The chemistry of wine making as a biological–technological sequence, discussed by F. Drawert, describes the influence of each step in the process of wine making on the chemical composition of the chemical components in the wine. The composition of grapes, as well as other fruits such as apples, pears, cherries, blackberries, and strawberries, is discussed by J. F. Gallander. This complete review (277 references are cited in literature) deals with water, sugars, and organic acids which are essential for the quality of wine. Vitamins, enzymes, pectins, aromatic volatiles, and nitrogenous and phenolic substances such as anthocyanins are also discussed. The chemistry of red color is discussed by P. Ribereau-Gayon, a well-known wine analyst. After describing the different anthocyanins and tannins which give red wine its color and organoleptic character, a practical method of classi-

fication and identification of wines by their anthocyanins is given. "Chemistry of Winemaking from Native American Grape", by A. C. Rice, reviews the chemical differences between European (vinifera) and American (labrusca) strains. Special wine-making practices are given in order to reduce acidity and increase alcohol content of "labrusca" and direct hybrids.

G. Thoukis, working for one of the biggest American wine growers, describes how to make wine physically, chemically, and biologically stable without altering the color, clarity, bouquet, flavor, and taste. The present status of methods for wine analysis and possible future trends by M. A. Amerine discuss methods required by legal or regulatory standards in the U.S. and in winery operations. Gas–liquid chromatography is being increasingly used for such analyses. Practical and fundamental aspects of malolactic fermentation are reviewed by R. E. Kunkee. Conditions which wine makers can use for better control of the fermentation including bacterial inoculation and inhibition with fumaric acid are presented. The importance of a small amount of pyruvic acid as an end product rather than as an intermediate in the bacterial conversion of L-malic acid to L-lactic acid and CO_2 is described in detail in the paper by R. Morenzoni.

Other papers discuss the analytical fractionation of the phenolic substances of grapes and wine and some practical uses of such analyses (V. L. Singleton), wine control quality and evaluation (R. G. Peterson), chemical aspects of distilling wines into brandy (J. F. Guymon), some aspects of the wooden container as a factor in wine maturation (V. L. Singleton), and the chemistry of home wine making (A. Dinsmoor Webb). Home wine-making chemistry and technology are considered for the production of dry white, dry red, sweet table, and flor sherry wines. The basic procedures and equipment and encountered problems are described and applied to each of the four table wines listed above.

This book should be of interest to those medicinal and biochemists involved in the production of fermentation products. It is also of particular interest to those students and practitioners, irrespective of their area of specialization, who consider wine as a medicinal substance and who are involved in home wine making. The last paper in this volume will be of particular interest.

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Annual Review of Pharmacology. Volume 15. Edited by H. W. Elliott, R. George, and R. Okun. Annual Reviews, Palo Alto, Calif. 1975. 518 pp. 15 × 23 cm. $12.00.

The publishers and their Editorial Committee are to be commended for the high quality reviews presented in the 15th Annual Review of Pharmacology. This volume is consistent with previous issues in providing a series of monographs which cover a wide range of pharmacological topics at a very reasonable cost. The vast interdisciplinary nature of biomedical science in general, and drug research in particular, is reflected in the varied scientific background of the contributors. The Editorial Committee is to be complimented for the nonparochial approach by which reviews were solicited.

The prefatory chapter of this volume assumes the form of an autobiographical sketch of the scientific career of the distinguished Soviet pharmacologist, S. V. Anichkov. This chapter, which illuminates the dedication, perseverance, and unbridled enthusiasm with which this great scientist has pursued his studies of drug research, should serve as an inspiration to budding young pharmacologists everywhere.

Of the 22 review articles presented, the majority belongs to the areas of neuropharmacology and environmental pharmacology and toxicology. Chapters relating to neuropharmacology begin with a review of structural activity relationships of narcotic analgesics in in vitro systems (H. W. Kosterlitz and A. A. Waterfield) which should be quite appealing to medicinal chemists. A review of the phenomena of tolerance to and dependence on the narcotics (D. H. Clouet and K. Iwatsubo) and a chapter devoted to the pharmacology of marihuana (W. D. M. Paton) reflect the considerable amount of ongoing research in these areas. Other reviews pertaining to the central nervous system include a timely consideration of how drugs may effect trytophan transport and thus alter brain serotonin synthesis (R. Paoletti, C. Sirtori, and P. F. Spano) and an up-to-date review of amino acids as central neurotransmitters (F. V. DeFeudis). Peripheral nervous system pharmacology is represented by a review of the pharmacology of the esophageal motor function (J. Christensen), a review of drug effects on the end plate of skeletal muscle (D. Colquhoun), and an interesting discussion of cholinergic receptor protein and its relationship to its membrane environment (J. B. Cohen and J. P. Changeux). The intense current concerns about environmental pharmacology and toxicology are illustrated by monographs on genetic toxicology (M. Legator and S. Zimmerman), carbon monoxide effects in humans (R. D. Stewart), cadmium toxicity (D. W. Fassett), and mycotoxins (G. N. Wogan). A review by D. H. Frost and P. M. Lish demonstrates how animal nutritional biochemical studies have changed the attitude toward selenium from that of a toxic environmental hazard to consideration as an essential tissue element and beneficial therapeutic agent. Another chapter devoted to toxicology, though obviously not from environmental sources, considers the relationship of oral contraceptive therapy to breast tumors and cervical cancer (V. A. Drill).

Chapters focused on pharmacodynamic principles include a discussion of how hemodynamic changes alter the pharmacokinetics of drug disposition (G. R. Wilkinson) and a description of the binding of sulfonamides to carbonic anhydrase as a prototype of drug interactions with enzymatic proteins (J. E. Coleman). A discussion of recent advances in the electrophysiological effects of antiarrhythmic drugs and important considerations of their pharmacokinetic properties is presented (B. I. Sasyniuk and R. I. Ogilvie). The current interests in immunopharmacology are represented by reviews on pharmacological enhancement of host defense mechanisms (G. W. Jordan and T. C. Merigan) and mechanisms of immunologic release of chemical mediators of inflammation (M. Kaliner and K. F. Austen). Other topics discussed in this volume are the effects of prostaglandins on the pulmonary circulation (P. J. Kadowitz, P. D. Joiner, and A. L. Hyman), the effects of drugs on uric acid in man (W. N. Kelly), and a particularly relevant review of the status of research on antidiabetic agents in the aftermath of the University Group Diabetes Program report (J. H. Karam, S. B. Martin, and P. H. Forsham).

The final two reviews are devoted to a historic discussion of Spanish pharmacology (F. G. Valdecasas), which is interesting reading and adds further to the international flavor which this book has consistently tried to achieve, and Chauncey Leake's review on reviews which once again serves as a convenient source for locating important recent review articles in the major areas of pharmacology.

The reviews on the whole are up to date, well documented, and reflect the current thrust of some of the major research areas in pharmacology and toxicology. In addition to author and subject indexes for the current volume, the book includes valuable cumulative indexes for contributing authors and chapter titles for Volumes 11–15. As might be anticipated in a volume with such a wide range of topics and contributors, there is considerable variation in the depth of coverage. Frequently, however, this may be attributed to differences in the state of knowledge in the varied research areas and does not detract significantly from the value of the book. The more superficial reviews have the advantage of appeal to a much wider audience.

In the way of criticism, many of the reviews have general, nondescriptive titles which in some cases are not indicative of the narrow scope of the text. In addition, several of the chapters could be greatly improved by the addition of visual aids to assist in emphasizing important concepts, clarifying hypothetical schemes, and making the reviews "more readable". A further, minor criticism is that the sequence of monographs does not always follow a logical pattern of association.

An overall assessment of the 15th Annual Review of Pharmacology would be a most favorable one. This book continues to satisfy its primary objectives and is an essential addition to any biomedical library.

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Basic and Therapeutic Aspects of Perinatal Pharmacology. Edited by P. L. Morselli, S. Garattini, and F. Sereni. Raven Press, New York, N.Y. 1975. xv + 440 pp. 15.5 × 24.5 cm. $18.95.

This volume in a series of Monographs of the Mario Negri Institute for Pharmacological Research, Milan, concerns itself with numerous aspects of perinatal pharmacology, ranging from basic metabolic differences in the newborn to the ethics involved in perinatal research. The first four chapters present the basic problem, i.e., the basic dilemmas encountered in drug therapy of the newborn. The emphasis is based on the premise that a baby is not merely a miniature adult. The following section covers basic metabolic systems of the placenta and fetus, as compared to the mother, as well as placental transfer of many agents including local anesthetics, pesticides, morphine, hexachlorophene, digitalis, and salicylates. An entire section is devoted to the effects of narcotics on the fetus and newborn and covers physiological as well as psychological considerations. This is followed by the development of metabolic systems in the fetus including the microsomal mixed function oxidase system and phenobarbital induction. Further studies are discussed dealing with antiepileptics, drug–protein binding in the neonate, cardiovascular drugs, and renal drugs. The authors point out that many drugs are contraindicated for children, pregnant women, and especially breast feeders and it is of utmost importance to heed these warnings. The last section of the book concludes with the ethics involved in clinical trials of research in perinatal pharmacology.

The area of pharmacology appears to be an open field and it is quite apparent that we need to know much more concerning perinatal pharmacology. The book may be a valuable tool to those involved in this area of research. It is easily understood and may find use in graduate level courses.

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Drug Metabolism Reviews. Volume 3. Edited by F. J. DiCarlo. Marcel Dekker, New York, N.Y. 1975. xiv + pp. 16 × 23.5 cm. $29.50.

This latest volume in the series contains eight chapters consisting mainly of timely and significant discussions of topics in the area of drug metabolism. A section entitled Current Topics in Drug Metabolism and Pharmacology is included and contains the last four chapters. While these latter chapters are of interest, they are somewhat tangential to the purpose of the series which presumably is to review major topics in drug metabolism.

The first chapter is a rather thorough presentation of the available material on sex-related differences in drug metabolism. Included is an interesting section on possible mechanisms for the differences reported in the rat. The next chapter covers a somewhat neglected area in drug metabolism, namely, the lung. The author has presented the full range of the subject including relevant physiology, enzymology, distribution, etc. Much of the data is summarized in the extensive tables which the reader will find useful reference material. The third chapter is on the metabolism of brain acetylcholine and includes a section on analytical methods as well as one on drug effects. Next follows a well-written chapter on the metabolism of cyclophosphamide. The text is well illustrated with formulas and figures which make the discussion easy to follow.

The first chapter in the current topics section of the book deals with the relationship between human experimentation and drug discovery in the United States. Many of the readers will no doubt be interested in this essay; however, it would seem to be more appropriately published in a journal dealing in science news items. To some extent the next three chapters could also be contained in other review volumes. There is a chapter on the effects of route of administration on drug disposition, one on environmental effects on drug action, and one on interaction methylenedioxyphenyl compounds. The last one in particular seems to be a very thorough coverage of the subject and should serve as a useful update on the literature in this area.

In general, the book is nicely bound and printed; the subject index is a little sparse which decreases the utility of the volume somewhat as a reference work. This book is recommended to persons wishing detailed accounts of several specific areas of current interest in the field of drug metabolism.

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The Fate of Drugs in the Organism. A Bibliographic Survey. Volume I. Edited by V. Hirtz. Marcel Dekker, New York, N.Y. 1974. xiv + 579 pp. $59.50.

This is the initial volume in a series being issued under the auspices of the French Society for Pharmaceutical Science and Technology (Societe Francaise des Sciences et Techniques Pharmaceutiques), written in English. It is a result of a project started in 1967 to provide better access to pertinent data on the fate of drugs in the organism which are generally scattered throughout the scientific literature making their access very difficult. The bibliography is intended as an enabling tool to the literature and is not a collection of data.

The current volume covers the period from 1948 to 1967 and provides an analysis of articles from 27 journals selected for articles which are generally rich on information regarding drug fate. It surveys 3000 references from these journals and includes a table covering some 4000 medicinal agents discussed in these references. Each of the future volumes will also cover 3000 references and the project is to be expanded to include 70 or more journals.

The book is divided into three basic parts: part I lists the 3000 references numbered sequentially; part II is an analytical table of references listed alphabetically according to drug; part III is a list of the empirical formulas of all agents listed in part II given in order of increasing number of carbon atoms in the molecule.

In the analytical tables in part II, each reference to a drug is monitored using a series of 17 key words. The year of publication of the reference and the number of references cited in the publication are also given.

The first four key words, *Absorption*, *Distribution*, *Excretion*, and *Metabolism* refer directly to the fate of drugs. The next three, *Isolation*, *Identification*, and *Assay*, deal with chemical analytical techniques used in studying the fate of drugs. The eighth key, *Labeled Molecules*, is noted whenever the technique involves drugs containing radioactive atoms. The next three keys, *Man*, *Animal*, and *In Vitro*, note the test subject or tissue on which the drugs were studied. The twelfth key, *Dosage Form*, applies to the effect of the product forms of the drug and their biopharmaceutic characteristics. The keys, *Pharmacology*, *Synthesis*, and *Kinetics*, are used to code only studies related to the fate of a drug in an organism. The last two keys, *General Review* and *Association*, note studies on drug doses, prior reviews, and drugs not considered individually but studied in association with one or more other drugs.

With the current clinical awareness of the importance of drug fate and the role that biopharmaceutics and pharmacokinetics play in the safety, effectiveness, and factors influencing the action of drugs, a rapid access to such data would be valuable to both the clinician and to the basic researcher in the field. It is rather unfortunate that this bibliographic survey covers rather a limited number of publications and the volume covers these only to 1967. Except for quick or initial surveys, it would be necessary for most researchers to refer back to the basic indexes and abstracts for more complete coverage. Researchers with access to extensive library resources would find only limited use for this volume. Others with limited resources may find this volume useful but may hesitate to acquire the book due to its relatively high cost. Researchers looking for references to drug interference on normal metabolism or drug effects on enzyme systems affecting drug metabolism will be disappointed because these are not included.

Since the analytical tables of part II are the heart of the volume, one wonders why this was not considered for the first part of the book. The listing of the references in part I is useless without the analytical tables. Part III which covers pages 547–579 is

somewhat redundant since the empirical formula of each compound is already given in the analytical tables. Eliminating these pages should have some effect on the cost of this volume. It is hoped that this excellent attempt to bring widely dispersed information into a more accessible form will be rapidly updated, expanded, and made less expensive, so that it may be useful and available to all clinicians and researchers seeking this information.

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Advances In Drug Research. Volume 8. Edited by A. B. Simmonds. Academic Press, London. 1974. 338 pp. 16 × 23.5 cm. $26.00 (£9.80).

The volume of the series is divided into five chapters beginning with a short chapter by B. M. Bloom entitled, "The Rate of Contemporary Drug Discovery", followed by topical reviews on "*Amantadine*" *by David Parkes*, "*Prostaglandin Antagonists*" *by* Alan Bennett, "Hypothalamic Amines and the Release of Gonadotropins and Other Anterior Pituitary Hormones" by Catherine A. Wilson, and "Gastric Antisecretory and Antiulcer Agents" by Paul Bass.

In Bloom's chapter, adapted from a presentation made at the 5th Industrial Affiliates Symposium on the Effect of Regulatory Agencies on Scientific and Industrial Productivity in 1972, he carefully scrutinizes the present decrease and availability of new prescription drugs in the United States. This decrease is analyzed in terms of the 1962 amendments to the U.S. Food and Drug Act, as well as rationalized in terms of therapeutic targets becoming smaller after initial successes are found (e.g., CNS drugs, diuretics). He also points out that many areas exist where progress is presently being made (e.g., chemotherapeutic agents), but little progress is made in significantly complex disease states such as hypertension, angina, and atherosclerosis, where basic knowledge of biology and pathology is not clear and research protocols must be long and labored in these areas suffering from somewhat underdeveloped clinical methodology. Bloom concludes that the unfulfilled therapeutic needs remain very great, in an atmosphere where many decry the inherent risks of drug development.

The chapter by Parkes on amantadine is more or less a monograph dealing with the fundamental pharmacological properties of this compound, which is of proven value in A_2 influenza, and shows unrelated effectiveness in Parkinson's disease. A short presentation of structure–activity relationships of analogs, a discussion on pharmacokinetics and metabolism, and short discussions on toxicology and pharmacodynamics of the agent are presented. The major portion of the chapter is devoted to the clinical pharmacology of amantadine in Parkinson's disease and its mechanism of action, side effects, etc. Its antiviral spectrum is also surveyed.

The review on prostaglandin antagonists by Bennett is organized on the pharmacological basis, dealing primarily with three groups of antagonists: 7-oxaprostaglandins, dibenzoxazepine hydrazides, and polyphloretin phosphate. Although a short analysis of structure–activity relationship factors is presented, the major portion of the chapter is devoted to the spectrum of effects of these antagonists on various tissues; e.g., smooth muscle, eye, and tissues with cAMP can be measured and others. Some efforts are devoted to classification of receptors and mode of action as well as presenting a prospective view for the future. This chapter definitely points up the complex nature of the action of prostaglandins in different tissues and the relatively unplowed fields in the search for antagonists to specific actions in various tissues.

The chapter on hypothalamic amines and the release of gonadotrophins by Wilson is one which provides much useful information even to those who are only slightly familiar with the functions of neurotransmitters in the brain. The chapter covers the anatomical distribution of brain amines and metabolism of these amines including biosynthesis, storage, release, catabolism, and uptake as well as the ontogeny and circadian rhythms of brain amine levels and metabolism. The neuroendrocrinology of gonadotropin release, including ovulation and feedback mechanisms relating to FSH-LH, is presented in considerable detail. The complex relationships between gonadotropin levels and various amines, an area of considerable importance and present conflict, especially the effect of gonadotropins on brain amine levels, are discussed. A portion is devoted to the importance of brain amines to the release of gonadotrophins, including a review of the effects of many inhibitors of catecholamines and 5-HT synthesis, and amine depletors. Effects of other autonomic agents including acetylcholine, atropine, and dibenamine are mentioned. The effects of brain amines on the release of other anterior pituitary hormones are also included.

After reading the chapter on gastric antisecretory and antiulcer agents, one cannot fail to recognize the complexity of this disease state and the multivariant pharmacological approaches which have been taken in an attempt to control its acute and chronic effects. This chapter is broad in scope, surveying experimental methods for evaluating these drugs followed by discussion of various classes of agents, including nonanticholinergic agents, gastric antihistamines, catecholamines and sympatholytics, gastrin inhibitors, pepsin inactivation, agents which produce healing effects on mucosal lesions, prostaglandins, enterogastrones and other endogenous substances, and some miscellaneous compounds. This chapter presents a number of exciting questions from medicinal chemists, pointing out possible avenues of approach to the development of compounds useful for the treatment of this disease.

In summary, the reviews in this volume cover several important contemporary medicinal chemistry questions. The volume should be a value to those wishing to remain abreast of developments in these areas. The book should be available in the libraries of institutions having interests in the health sciences and in the personal libraries of medicinal chemists, pharmacologists, and others working in these and related areas.

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Advances in Cyclic Nucleotide Research. Volume 5. Edited by G. I. Drummond, G. A. Robison, and P. Greengard. Raven Press, New York, N.Y. 1975. xiii + 872 pp. 16 × 23.5 cm. $46.00.

Advances in Cyclic Nucleotide Research, Volume 5, is composed of the 44 invited lectures and the abstracts of the 240 contributed papers delivered at the Second International Conference on cyclic AMP held in Vancouver, Canada, on July 8–11, 1974. The volume is most fittingly dedicated to the late Earl W. Sutherland whose pioneering discovery of cyclic AMP some 17 years ago has given useful employment to the upward of 1500 "cyclic nucleotidologists" whose work is cited in the volume.

The volume is organized in an orderly fashion, the focus moving from nucleotide cyclase to phosphodiesterase to protein kinase and then to syntheses of these topics as they apply to the mediation of the "hormone messages" in diverse tissues. Some of the more fascinating reports follow.

1. Another naturally occurring cyclic nucleotide, cytidine 3′,5′-monophosphate, newly discovered by A. Block, is found in, and stimulates the proliferation of, leukemia L1210 cells.

2. The mechanism of GTP activation of adenylate cyclase in liver, pancreas, kidney, adipose and thyroid tissues (Rodbell et al.; Schramm; Aurbach); mark also the related issues of (a) the feedback inhibition of adenylate cyclase by an intracellular "feedback regulator" (Ho and Sutherland) and (b) the restoration of hormone sensitivity to solubilized adenylate cyclase by the addition of acidic phospholipids (Levey et al.).

3. A particularly fascinating account by Bitensky and co-workers of a light-sensitive cGMP phosphodiesterase in rod outer segment which appears to modulate the sensitivity of these photoreceptors to light; also reports on the biochemical differentiation and regulation of other phosphodiesterases (Appleman and Terasaki; Wang et al.).

4. (Cyclic AMP)–(Protein Kinase) complexes, which are formed in the cytoplasm and translocated to the nucleus and which stimulate protein synthesis in the adrenal medulla (Guidotti,

Hanbauer, and Costa) and ovary (Jungmann et al.).

5. Suggestions that cyclic AMP mediates the ino- and chronotropic effects of epinephrine on heart muscle by increasing the sensitivity of myofibril calcium-sensitive ATPase and the efficiency of reabsorption of cyoplasmic calcium, respectively (Brooker; Katz et al.); also evidence that interaction between cAMP and calcium metabolism in heart muscle occurs on a beat to beat basis (Brooker).

6. Studies showing that cell proliferation, maturation, and aggregation in bacteria, fibroblasts, epithelia, thyroid, and lymphoid cells are related to intracellular levels of cyclic nucleotide; the absence of adenylate cyclase or low levels of intracellular cAMP giving rise to aberrant cell morphology and function (Torres et al.; Anderson and Pastan; Voorhees and Duell, Lissitzky et al.; Singh and Dhalla.).

Many of the chapters (lectures) are reviews of progress in various aspects of the field. One remarkably thorough, but nevertheless lucid presentation by Cuatrecasas critically reviews the results of hormone binding studies as they relate to the activation of hormone-sensitive adenylate cyclase. These studies have led to the proposal that adenylate cyclase and the hormone receptor(s) are separate molecular entities which are swimming around in a "fluid membrane" in the absence of hormone stimulation but which are brought together by hormone stimulation to form an activated, membrane-bound enzyme unit.

The interrelationship between calcium and the cyclic nucleotides in the mediation of hormone stimulation, the subject of several reports and one major review by Rasmussen et al., remains a subject which generates more heat than light. The issue seems to be impossibly complicated by the fact that cyclic nucleotides appear to regulate the flow of calcium across the cell membrane and from compartment to compartment within the cell while, at the same time, calcium regulates the activities of both adenylate and guanylate cyclases and, thus, the productions of cAMP and cGMP, respectively.

The hypothesis that the actions of cyclic nucleotides are mediated by protein kinases is still clouded by the facts (a) that for some tissues, the number of physiological functions regulated in the cell by cAMP is greater than the number of cAMP-dependent protein kinases isolated from the cell, (b) that protein kinases seem to have little substrate specificity, (c) that some protein kinases appear not to be subject to control by cAMP, etc. There is an excellent discussion of this topic by Jungmann and his co-workers.

Still other reviews document the substantial progress that has been made in elucidating the roles of the cyclic nucleotides in the physiology and metabolism of the nervous system (Greengard; Bloom et al.; Makman et al.; Perkins et al).

As all "Advances In ..." volumes, *Advances in Cyclic Nucleotide Research*, Volume 5, presents the ragged edge of progress in the field. Accordingly, it is not a particularly appropriate introduction to any aspect of cyclic nucleotide research. On the other hand, it is not encyclopedic in scope. It seems to be well balanced, the space devoted to each separate topic varying as the product, (excitement generated by the topic) × (the total amount of effort being expanded on research on the topic). In toto, *Advances in Cyclic Nucleotide Research*, Volume 5, promises at least to fulfill the editors' hope that it "will stimulate further productive research and provide deeper insights into the role of these compounds in cellular regulatory processes".

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Clinical Biochemistry. Principles and Methods. Volumes 1 and 2. Edited by H. Ch. Curtius and Marc Roth. Walter de Gruyter, Berlin and New York. 1974. xix + 1677 pp. 17 × 24 cm. $192.00.

This two-volume set emphasizes principles and methodology in regard to the measurement of substances of routine as well as nonroutine clinical biochemical interest. Minor discussion of actual clinical or biochemical aspects is provided. The chapters cover both more traditional areas (for instance, collection and preparation of samples, electrophoresis, quality control and normal values, hormones, lipids, enzymes, toxicology, kidney function tests) and areas of more recent clinical chemical interest (for instance, ultracentrifugation, mass spectrometry, colorimetric methods, radioimmunoassay, ion-specific electrodes, vitamins, erythrocyte enzymes). Liver function tests, gastric analysis, pancreatic function tests, and calculi are omitted, and no general discussion of immunochemical techniques is provided. The editors state in the preface that they have emphasized newer techniques and areas on which little has been written up until now. For instance, 9 pages are given to discussion of α-ketocarboxylic acids, 30 pages to glycosaminoglycans, and 16 pages to intestinal mucosa. All topics are not given this much coverage of course. For example, isoelectric focusing, isoenzymes of alkaline phosphatase, and ultracentrifugation of lipoproteins each received only a short paragraph of coverage.

This reader would like more coverage to have been given to the general, current role of "newer" techniques in clinical biochemistry. The chapter on ion-specific electrodes is an example of this, where only a paragraph and table of references is concerned with applications of ion-specific electrodes to clinical biochemical substances. The chapter primarily is concerned with introducing the principles and types of these electrodes.

There is much useful information in this book, but the book is not an encyclopedia and there is a great deal of material that is covered more comprehensively elsewhere at a lower cost.

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Protein–Metal Interactions. Edited by Mendel Friedman. Plenum Press, New York, N.Y. 1974. 692 pp. 17 × 25 cm. $39.50.

As Volume 48 in the series entitled "Advances in Experimental Medicine and Biology", this book contains the 22 papers presented at the Proceedings of the American Chemical Society Symposium on Protein–Metal Interactions held in Chicago, Ill., August 27–29, 1973, in addition to five supplemental invited papers.

At first glance, the papers of this symposium may appear to deal with subjects too diverse and incompatible to be included in the same volume. However, as one reads the volume one should gain a deeper appreciation for the unique and important functions of metals in their interactions with proteins. The metal ions serve as a common focal point and as such unify the studies presented in this book.

The 27 papers can be divided into four sections. The first two papers give a general overview of the important roles played by metal ions in life processes. Frieden convincingly relates the evolution of metal ions as essential elements to their occurrence and relative distribution in the early oceans from whence life emerged. In their paper Riordan and Vallee present an excellent review of the role and function of metal ions in metalloenzymes and indicate how the presence of metal ions facilitates the study of these macromolecules.

The next two sections constitute the bulk of the volume. Papers 3–15 cover a variety of metal–protein systems detailing the importance of metal ions in such diverse areas as enzyme catalysis, metal transport and storage, textiles, antigen antibody systems, and metabolism. These studies clearly indicate that the metal ions often play vital structural roles in the maintenance of specific protein conformations required for proper functioning. On the other hand, papers 16–24 present studies of the detrimental effects that can occur in animals and man as a result of deficiencies of essential metals such as zinc and nickel or exposure to toxic metals such as lead and mercury. These studies emphasize the essential nature of metal ions in biological processes, as well as their specificity requirements which generally do not allow for substitution by different metal ions without harmful effects.

The final three papers presented in this volume deal with three emerging spectroscopic methods used to obtain analytical and

structural information from metal-containing macromolecular systems. These are x-ray photoelectron spectroscopy, energy dispersive x-ray fluorescence spectroscopy, and perturbed gamma–gamma directional correlation. The theory, experimental technique, and application for each method are presented in concise and understandable form by the authors.

In general, the papers contained in this volume are well written, each with an extensive bibliography. This book provides an excellent collection of recent studies by leading investigators covering a variety of topics dealing with metals and proteins, and is well worth owning. This reviewer recommends this volume for those who wish to keep up to date with recent developments in this multifaceted field and for those who wish to learn more about the many functional roles played by metal ions.

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Cholinergic Mechanisms. Edited by P. G. Wasser. Raven Press, New York, N.Y. 1975. xvii + 555 pp. $29.50.

Interest in the neurotransmitters of the central nervous systems has overshadowed continuing investigations of the cholinergic nervous system. Consolidation of information from modern research of this latter system is therefore a welcome addition to the literature.

Cholinergic Mechanisms contains papers presented at a symposium held at Bolden, Switzerland, in 1974. The single volume brings together recent investigations which lead to a further understanding of the morphology of cholinergic synapses, the biosynthesis, metabolism, and transport of acetylcholine, as well as the structure of the receptor and its interactions with the neurotransmitter. Latter chapters deal with the pharmacological affects of compounds which act on the cholinergic system. Considerable attention is paid to the behavioral and central actions of cholinergic compounds. Included in this section are chapters on tremorogenic agents, cholinergic–dopaminic interregulation, and the role of the cholinergic mechanisms on narcotic agonists, sleep, memory learning, and other aspects of behavior. Clinical problems on anticholinesterase intoxication and anticholinesterase antidotes are also discussed.

The first four chapters provide an introduction for the new investigator in the field. Medicinal chemists will enjoy reading Holmstedt's report of von Baeger's thwarted attempts to enter the field of neurochemistry.

The papers reported are biologically oriented and fail to consider evidence provided by drug or chemical structure on activity. Only one paper, "The Shape of Cholinergic Molecules", deals with structure–activity relationships. The omission of this approach to the elucidation of cholinergic mechanisms will be disturbing to medicinal chemists and undoubtedly will limit their interest in the book. However, investigators initiating work in this field will find the information reported of great importance.

Cholinergic Mechanisms is well written and edited. Each chapter contains pertinent references. Although this work's usefulness is limited by its omission of the chemical approach, it provides a needed updating of the literature.

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Synaptic Receptors. Isolation and Molecular Biology. By Eduardo De Robertis. Marcel Dekker, New York, N.Y. 1975. 387 pp. $29.50.

The monograph documents important contributions of various investigators including the previous studies of the author on physiologic receptors. Introductory material in the first three chapters includes topics such as the forces involved in drug–receptor interactions, cooperative interactions, and structure of cell membrane. The information is vital for the proper orientation of the subject material. The next several chapters cover a detailed account of isolation of cholinergic nicotinic receptors from the central nervous system, the electroplax, and the skeletal muscle. Throughout the book many excellent illustrations are presented. For example, the electromicrograph of subcellular fraction from cat brain shows the beautiful functional complexes between the nerve terminal and the effector cell. The procedures for the fractionation and purification of receptor proteins are well outlined. Kinetic constants for binding of ligands to receptors are graphically illustrated. The process of origin and formation of receptors which is becoming a very important topic in a developmental biology is covered through pages 191–195. Chapter 8 includes the recent developments in the isolation and characterization of adrenergic receptors. All previous studies on the subject are critically analyzed. The author emphasizes the value of stereoisomers of adrenergic ligands in studying drug–receptor binding. The isolation of glutamate and GABA receptors is summarized in chapter 9. Over 100 pages are devoted to the inophoric properties of the receptors. Most of the illustrations come from the author's laboratory where these elegant techniques were developed. In the last chapter a model for macromolecular organization of the cholinergic receptor is presented.

The book is very easy to read and maintains excellent integrity of the subject material. This may be due to the wise choice of the author who has spent many productive years in the field. The book should be of great assistance to the students and researchers in various fields in biology.

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Immobilized Enzymes, Antigens, Antibodies, and Peptides: Preparation and Characterization. Edited by Howard H. Weetall. Marcel Dekker, New York, N.Y. 1975. vii + 661 pp. $38.50.

This book was designed primarily as a single source for the methodology of preparation and utilization of immobilized biologically active compounds. Except for the chapters on "Immobilized Enzymes and their Biomedical Applications" and "Engineering Aspects and Reactor Design of Immobilized Enzyme Systems", the other eight chapters contain enough experimental detail to achieve this goal. Three chapters describe the experimental conditions for the attachment of ligands to inorganic supports, nylon, polyacrylimide, and agarose. Another three chapters deal with enzyme entrapment either by polyacrylimide gels, cellulose fibers, or microencapsulation. Enzyme immobilization through adsorption is covered to a more limited extent. The applications of immobilized enzymes include the topics of enzyme reactors for synthesis, degradation, and analysis of substrates, in vivo biomedical applications, enzyme electrodes, affinity chromatography, radioimmunoassays, and the sequencing of peptides and proteins.

Some generalizations one finds in this treatise include (1) no single immobilization technique or support is ideal for all applications; (2) entrapment and adsorbtion offer the advantage of no direct modification of the enzyme which may effect catalytic activity; (3) entrapment restricts the accessibility of the protein to only small molecular weight ligands which in some cases is an advantage in protecting the proteins from proteolytic attack; (4) diffusion limitations are more severe with entrapped enzymes than adsorbed or covalently attached enzymes; (5) the polarity on the entrapping matrix or support may affect the pH optimum of the enzyme and the partitioning of the substrate from the bulk solution; (6) enzyme leakage is most severe for adsorbed enzymes and occurs to a lesser extent with entrapped or covalently attached enzymes; (7) enzyme stability is in most, but not all, cases improved by immobilization.

The book has numerous typographical errors in spelling, chemical formulas, and figures which detract from the otherwise knowledgeable discussion of the material. I would recommend this book to anyone who wishes to apply any immobilization technology.

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