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REVIEW OF REVIEWS ◆6784

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The pace of scientific progress continues to accelerate and as a consequence pharmacologic information is becoming increasingly fragmented. The human mind finds it difficult to digest too many facts and the natural response has been to retreat, realign, and restrict. The consequence has been the printing of an increasing number of specialty journals with a limited circulation. Although the scattered data can be retrieved by computers and some sense as to the nature of the contents of an article can be gleaned from the listing of the title, the only way the information can be assimilated is through studying reviews, monographs, and textbooks. For the professional, textbooks are generally too little and too late with the information. Comprehensive reviews and monographs serve the experts but there is increasing need today for more reviews, especially continuing annual ones in well-established areas as well as mini-reviews of "hot" areas.

REVIEWS

Pharmacologists will welcome the appearance of *Trends in Pharmacological Sciences* (TIPS) which is intended to communicate information of interest to pharmacologists and those involved in closely related disciplines (1). Published by Elsevier in association with the International Union of Pharmacology (IUPHAR), the journal consists of newsy items, announcements, book reviews, historic and philosophic commentaries, and, best of all, short reviews on topics of current interest.

The inaugural issue contains messages from the publisher, the editor, and the president of IUPHAR, Peter Waser. In an editorial, John Burns, capable and popular past president of IUPHAR who played a major role in getting TIPS launched, outlines some of the challenges to pharmacology.

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In the section entitled "Viewpoint," Cuthbert provides an essay on areas that are peculiar to pharmacology—bioassay, pharmacokinetics, structure-activity relationships, and receptors. In defining these interests of pharmacology my predecessor and teacher Chauncey Leake was one of the most articulate and effective spokesmen for pharmacology. Cuthbert appears to be an able successor in this regard. Without minimizing the importance of modern techniques that utilize NMR, IR mass spectrometry, and gas chromatography, he deftly points out that without sensitive pharmacologic bioassay procedures, the discovery of many potent important endogenous substances would not have been possible. As excellent examples he mentions two very recent discoveries and the tools required—enkephalins and the mouse vas deferens, and prostacyclin and rings of arteries incubated with platelets. His brief thoughts on the vindication of receptors as a concept is provocative but could have been given more extensive coverage. It is hoped that this is planned for the future. He views Rang and Paton's 1965 studies on ^{14}C-atropine binding to a component of intestinal muscle as being the first definitive demonstrator of the existence of a receptor. Many might argue that Waser's findings a decade earlier on *d*-tubocurarine binding to the neuromuscular junction should be first, but because saturable binding was not demonstrated Cuthbert credits Waser with a near miss. Others will contend that conclusive data was not really obtained until bungarotoxin was utilized to identify the nicotinic receptor. This controversy is not likely to be resolved because absolute proof is rarely possible to obtain so that "conclusive" becomes a relative term that reflects the eyes of the beholder. Hence, the title of the column "Viewpoint" is apt, and more such reviews would be appreciated.

Two other articles on receptors are contained in the same issue, a theoretic consideration by E. J. Ariens and an essay on adrenoreceptors by R. P. Ahlquist. I still remember how a noted author of a popular pharmacology text rejected with considerable vehemence Ahlquist's β-adreno-receptor concept when it was first proposed. He considered the notion to be utterly useless and opposed it bitterly; however, he now embraces the concept in his book. Today with the identification of dual histamine and dopamine receptors and conjectures of μ, σ, and K opiate receptors, the notion of multiple receptors is gaining increasing acceptance. Also in this issue, U. Trendelenburg attempts to provide a critical perspective on the conceptual development of extraneuronal uptake as a means of terminating drug action of the catecholamines and concludes that the mechanism serves a useful physiological function.

Ernest Chain writes an interesting account of the early years of penicillin discovery. He stresses in particular that neither Sir Alexander Fleming nor he had aimed to discover an antibiotic. Fleming reported in 1929 that the

mold, *P. notatum* induced lysis in *Staphyloccus aureus* and followed up on this phenomenon because of its scientific interest. Chain rediscovered Fleming's report in the literature because he was also interested in bacterial lysis. When Chain confirmed that his purified preparation of penicillin was highly inhibitory on staplylocci and found it also to be nontoxic in mice, he decided to exploit the discovery. He emphasized that major progress in practical clinical medicine can be achieved by following up basic discoveries rather than relying solely on mission-oriented programs.

Other articles include a review by J. Wepiere and J.-P. Marty on percutaneous absorption of drugs. Paul Greengard gives a timely brief discussion of current thinking on the possible roles of cyclic nucleotides and phosphorylated proteins as mediators of the actions of neurotransmitters and psychoactive drugs, and he outlines similarities and differences between the cyclic AMP and GMP systems and phosphorylated protein as physiologic effectors within the nervous system. Ebashi describes muscle contraction and pharmacology and points to the need to evaluate Ca^{2+} in drug action.

MONOGRAPHS

The National Institute on Drug Abuse continues to publish timely and informative monographs on drug abuse. Each volume provides the current state of the problem and the thoughts of many experts in a specific area related to drug abuse. *NIDA Research Monograph No. 19,* entitled *The International Challenge of Drug Abuse,* includes a series of overviews of drug abuse in various countries after which some biologic and psychobiologic aspects of drug dependence are discussed (2). The most useful sections, however, are the two that summarize the current status of L-acetylmethadol (LAAM) and naltrexone for the treatment of the heroin recidivist. LAAM appears to be readily accepted by addicts, but acceptance of naltrexone is poor (5 to 10%); however, naltrexone appears useful for treating well-motivated patients.

Research Monograph 20, Self-Administration of Abuse Substances: Methods for Study, focuses mainly upon methodologic approaches for studying various behavioral categories of substance abuse by humans, namely, food, alcohol, drugs, and tobacco (3). There appears to be a consensus that some of the animal models of self-administration are valid for extrapolation to human situations.

Monograph 21, Phencyclidine Abuse: An Appraisal, appears at a time when phencyclidine (Angel Dust) abuse is becoming an increasingly serious problem (4). The drug used to be easily available because it was used in veterinary medicine as an immobilizer, but the notoriety it gained as a substance of abuse has resulted in a precipitous decline in its application.

However, it is easily synthesized and the PCP available today on the street comes from illicit sources. The drug is most commonly smoked or snorted but is also ingested orally or injected intravenously. The acute toxic effects are dose-related and result in combativeness, catatonia, convulsions, and coma. Patients may exhibit agitation, hostility, thought disorders, and paranoia. After the acute phase passes, some individuals, especially chronic abusers, develop a prolonged toxic psychosis. The editors are to be congratulated for providing a useful and timely compendium.

Monograph 23, QuaSAR Quantitive Structure Activity Relationship of Analgetics, Narcotic Antagonists and Hallucinogens, draws on Hansch analysis, molecular mechanics, and spectroscopic and pharmacolochemical methods to reveal the correlation of molecular properties with biologic activity (5). We agree with the editors that the proceedings demonstrate progress in achieving understanding but we still have a long way to travel.

NIDA also sponsored a *Handbook on Drug Abuse.* Edited by Du Pont, Goldstein, and O'Donnell, it updates and coordinates the knowledge on drug abuse (6). While the handbook is designed primarily for drug abuse professionals, pharmacologists will find many topics of interest within the volume. There is an excellent overview of drug treatment by J. H. Jaffe and a series of papers on treatment modalities. Of especial interest are Goldstein's review of advances in basic research relevant to drug abuse and articles on inhalants, amphetamines, sedative-hypnotics, and PCP.

Another monograph which is not part of its series but resulted from a conference sponsored by NIDA is entitled *Membrane Mechanism of Drug Abuse* (7). It is edited by Sharp & Abood and represents an attempt to relate mechanism of drug action to membrane function. There is accumulating information that many drugs mediate their effects ultimately by altering ionic flux, and this may result from drug interactions with glycolipids in the membrane. Opiates, for example, decrease Ca^{2+} at nerve endings in the brain and Ca^{2+} is an effective morphine antagonist. The rank order of binding of opiates to cerebroside sulfate yields an excellent correlation with analgetic potency. An important lesson to be learned from this volume is that more than just receptor proteins may be involved in drug action and the role of glycolipids in this respect is gaining increasing attention.

Loh & Ross have edited *Neurochemical Mechanism of Opiates and Endorphins* (8). The contents include a review of four decades of opiate research, articles on opiates—receptor interactions, chemistry and pharmacology of the endorphins, opiate interactions with messenger systems, neurotransmitters, macromolecules, and membranes. As is usual with books having many authors, the quality and the freshness of the papers vary considerably. Several authors have rewarmed and updated earlier presentations, but there are also some new slants provided by some of the younger

writers. The reader may find it confusing and puzzling if the arguments of each author are accepted on faith because the explanations for the mechanism of opiate action are so varied. The approaches have included attempts to implicate acetylcholine, dopamine, norepinephrine, serotonin, γ-aminobutyric acid, calcium flux, cyclic nucleotides, endogenous opiate peptides, phospholipids, cerebroside sulfate, and various brain proteins. Although some of the authors have attempted to clear the clouds by invoking unifying concepts, until the gaps are filled with more solid data, confusion will persist.

The nonexpert will find the volume informative and stimulating, and the expert will find it informative, provocative, and sometimes annoying. In this latter regard, one's point of view will be largely colored by whether one believes that speculations and new data should first stand the scrutiny of rigorous review as required by refereed journals. Most readers will enjoy the notions that the editors and their collaborators have advanced even though there may be some deficiencies in hard data. In the final wash, it is not how and where a manuscript appears but whether the science is good.

TEXTBOOKS

Several textbooks have appeared; nearly all are revisions of earlier editions. It is an onerous undertaking these days to write a general text in pharmacology, and authors compromise by either writing a book in specialized areas or becoming editors. Even with these adaptations, none of the books have been able to keep pace with the original papers, which appear at an unprecedented rate. Vane's illuminating studies in 1976 on the role of aspirin on prostacyclin synthesis and platelet aggregation have not been included in any of the texts. Perhaps, mini-reviews, which are gaining increased acceptance, will facilitate the task of those who need to pass on the knowledge in a style that is comprehensible and meaningful.

Clinical Pharmacology, edited by Melmon & Morelli, has been expanded and vastly improved (9). To achieve better balance in subject matter, 400 pages have been added and the case presentations in the first edition regretfully had to be dropped. This book is likely to become the most important one in clinical pharmacology if it is not already so. Teachers and researchers should enjoy the discussions in fundamental pharmacologic principles which generally go beyond those presented in most basic pharmacology texts. However, general practitioners, who expect to see a detailing of the minutiae with respect to the art of management, may be disappointed with the emphasis on principles.

Drug administration is discussed in the book under three headings: basic principles, pathophysiologic and pharmacologic considerations, and evalu-

ation of effects. In general, the presentations by the invited authors are relevant, authoritative, and lucid, but if one looks hard enough one can find faults. In Unit I, which deals with basic principles, the presentations are without question scholarly, but at times may be overly technical. Also, there is a fair amount of overlap in the discussions on factors affecting drug disposition by the various authors writing on related topics. A major deficiency in this section is the omission of a chapter on biostatistics and dose-response relationships.

Unit II, on pathophysiologic and pharmacologic considerations, is the "nitty gritty" and provides the basis for rational therapy. The chapter on genetic factors appears out of place. Aspirin is used loosely as the generic equivalent for salicylates—"described before the Christian era," "rediscovered by Stone," "one of the oldest compounds, senior to quinine, colchicine and digitalis." In actuality, Stone reported on a decoction of the willow bark in 1763; aspirin was not synthesized until 1852 and was only introduced into medicine in 1899. The marketing of several new nonsteroidal antiinflammatory agents and their increasing popularity dictate their consideration; they are to be preferred over acetaminophen and phenacetin for reducing joint and muscle inflammation when salicylates are not tolerated.

Unit III on recognition and evaluation of effects of drug administration is a hodgepodge of topics of interest to clinical pharmacologists and includes illuminating essays on drug reactions, drug interactions, drug abuse, and drug economics as well as on treatment of poisoning, placebo therapy, and decision making. It is of interest to add that recent findings in placebo therapy may have an organic basis, at least in the treatment of pain since endorphin levels have been reported to increase after placebo medication.

The sixth and latest edition of the text by Meyers, Jawetz & Goldfien (10) can hardly hurt its popularity with students. Readability, conciseness, information relevance, and price will continue to operate in its favor. However, although a new edition appears every two years, some major advances have been overlooked or ignored. It is especially disappointing that some basic discoveries having clinical relevance were not covered. For example, numerous studies have defined the loci of opiate action in the CNS, and the concensus is that the periaqueductal gray region is one of the sensitive sites. This finding is supported by clinical studies indicating that electrical stimulation of this area produces profound analgesia. Moreover, there is reasonably good correlation between physiologic, histologic, and biochemic binding studies with respect to the various sites of opiate action as well as with the distribution of enkephalinergic neurons. It is surprising that the enkephalins were not even mentioned, for this discovery has wide implications and was announced in 1975 by Hughes, Kosterlitz, and associates. Endogenous peptides with opiate-like activity have created an explosion of

interest and I predict that the two innovators will have a free trip to Stockholm in the near future.

In the chapter on antipyretic analgetics, the schematic illustration of the fate of phenacetin is confusing and provides little or no quantitative information of the relative importance of the metabolites on activity and toxicity and the pharmacologic basis for the toxic effects of the metabolites. The statement that the acute toxicity on phenacetin is less than that of aspirin is misleading. Although the toxic effects of the salicylate may predominate in a mixture of the two compounds, the acute lethal dose of phenacetin is about the same as that of aspirin and the toxicity of phenacetin would become increasingly apparent with each successive dose. Also, the treatment of the role of prostaglandin in the action of aspirin is cursory considering that so much meaningful work has been published in this area.

In the chapter on antipsychotic tranquilizers, it is stated that the wealth of biochemical data in physiologic data on the compounds cannot be organized into a unified concept, even though numerous papers indicate the existence of dopamine receptors in the CNS and of a good rank order correlation between binding of antipsychotic drugs with postsynaptic dopamine receptor sites and clinical potency. Under "Drug Abuse," although the discussion places the problem in perspective, it is surprising that PCP is not considered. Also, in the treatment of diabetes the potential usefulness of somatostatin might have been covered.

Some sections have been updated. Changes are more noticeable in the chapters on cardiovascular agents, diuretics, cancer chemotherapy, and mechanism of action of antimicrobial agents, although with respect to the latter chapter, it is not clear why a discussion of the sulfa drugs was deleted. In the chapter listing the possible effects of drugs on common laboratory procedures, it would have been helpful to have been provided with specific examples of how diagnosis was seriously impaired by the presence of the drugs.

Drug Interactions by Hansten continues to be a useful reference text (11). It is more than just an encyclopedic recital of infinite possibilities of interactions between drugs. An attempt to maintain clinical relevance has been made by categorizing the degree of clinical significance of the drug interaction with differing typefaces in the text and index. It would be helpful to have a brief paragraph in each chapter summarizing the major interactions that have been established to have clinical significance. It may also be time to include a separate chapter on environmental factors that may affect drug action.

McMillan (12) has revised his handy self-instruction text on central nervous system pharmacology which is useful for rapid orientation and review. The book is easy to digest and contains a surprising amount of

information. However, there are some misleading or imprecise statements. The effects of morphine taken orally are difficult to predict because the drug is rapidly conjugated during and after absorption rather than because it is "not well absorbed." Propoxyphene should be considered a narcotic analgesic because of its "pharmacology" rather than its "chemistry." To me the involvement of serotonin in the antinociceptive effects of the opiates is rather convincing and this is amply supported by anatomic and chemical evidence. Much of the "difference" in the chemical structures of meperidine and methadone from the phenanthrene alkaloids of opium disappears when the molecules are considered on a three-dimensional basis. Phenacetin is given greater emphasis than acetaminophen which is widely used and has largely supplanted phenacetin in proprietary remedies. Despite these criticisms, I believe that this inexpensive soft-cover should gain increasing popularity among students, especially the less talented and less motivated ones. However, even the more serious student should find it useful as a stepping stone for consulting more detailed textbooks.

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