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REVIEW OF REVIEWS

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When my inspirational teacher, Chauncey Leake, died early in 1978, the world lost a distinguished citizen who had achieved much during a rich and varied career. Chauncey was a great teacher, an imaginative and innovative pharmacologist, medical historian, philosopher, scientific statesman, health science administrator, humanitarian, and bon vivant. He left a great legacy for his pupils to continue, among them the Review of Reviews. Shortly after his death, the galley proofs for the 1978 volume were placed in my hands by his faithful secretary, Mia Silverman, and we both commiserated upon the end of the series. While talking on the phone to our editor, Bob George, over the death of Chauncey, sentiment and a moment of weakness during my sadness motivated me to volunteer to continue Review of Reviews. I should have had my head examined. Until very recently, my career, in distinct contrast to Chauncey's, had been restricted mainly to intensive research in opiate pharmacology and drug metabolism.

Chauncey was broad in his interests, enthusiastic about the accomplishments of others and dedicated to communicating and popularizing science to the masses. He devoted a lifetime to this end. Beginning in 1940, Chauncey distributed a monthly bulletin without charge to pharmacologists, physicians, and scientists all over the world informing them of interesting original research papers, reviews, and books. The sheet had the caption, "Calling Attention To," (Post or wastebasket as you wish). Subsequently, it appeared in *Current Contents,* which he served since its inception as Chairman of the Editorial Advisory Board. As reviews in pharmacology became more technical and symposia volumes more diverse, Chauncey believed that an annual survey of them might aid in maintaining perspective and balance for the discipline as a whole. And so Review of Reviews was started in 1961.

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In attempting to fill Chauncey's shoes, I find it extremely difficult to assess with any modicum of confidence current pharmacologic advances. The scope of pharmacology is continually increasing and reviews of pharmacologic material are increasing in number and importance. The character of the reports is also changing. One trend is the reviewing of progress more often by fields in book form. As Chauncey often mentioned, although such volumes bring together current data and opinion in that area, they tend to serve the experts in the field rather than those interested in general progress. They do not offer the broad coverage of pharmacology and toxicology as does the *Annual Review of Pharmacology and Toxicology*. In assuming Chauncey's duties, let me state that it is not possible for me to provide the comprehensive coverage in the Leake style. Because my assignment was late and I am already well past the deadline, I can only present some opinions on some selected reviews and monographs.

One of the "hottest" areas being repeatedly reviewed is concerned with the enkephalins and the endorphins. Although some ascribe the discovery of these opiate peptides to the direct consequence following the isolation of the opiate receptor, in actuality, the concept of an endogenous opiate-like ligand existed long before the opiate receptor was isolated and, indeed, vain attempts were made before Hughes, Kosterlitz, and their associates (1) achieved success. Unquestionably, the characterization of the opiate receptor greatly accelerated the search to find its endogenous ligand. The finding of ligands in the brain with opiate-like activity has given an exciting new dimension to the research of brain function. The implications of this development are immense because these substances are involved with new types of neurons. A thorough knowledge of the nature of these nerve cells should facilitate the understanding of brain function and the basis of certain neurologic and behavioral disorders. Although the explosive impact of their discovery has still not subsided, the research pace has become less frenetic and more systematic. It is time now for someone to review this magnificent accomplishment with more balance and perspective, developing historically the background and the cumulative knowledge that culminated in the isolation of the enkephalins and the endorphins.

Recent reviews (2–8) including our own (9) do not meet these criteria. Although they adequately indicate the current state of the art and provide some thoughtful perspectives, they also reflect some degree of competitive bias among the investigators who are deeply involved in this area of research. A monograph on the endorphins has appeared (10), but it is not truly a review. It provides a potpourri of studies from many laboratories reported at a conference. My criticism (which is shared by others) is that such a volume is useful for the active investigator in the field but suffers from lack of critical editorial review and provides no background development and perspective for the novice and the generalist.

Similar objections can be directed at two other volumes which report the happenings of separate conferences on opiates and endorphins. The usefulness of one was enhanced by its appearance within six months after the meeting (11), whereas publication of the other (12) was far too delayed. On the other hand, broader coverage of the opiates was accorded in two other volumes. One, edited by Fishman, *The Bases of Addiction* (13), aimed to stimulate interdisciplinary communication by organizing workshops on selected topics on the bases of addiction and then by publishing the results of these presentations and discussions. Pharmacologists and semiprofessionals would profit also by reading the contributions by the psychologists, psychiatrists, clinicians, epidemiologists, and sociologists. Finally, a volume *Developments in Opiate Research,* edited by Albert Herz (14), describes and analyzes the opiates with respect to acute effects, tolerance, and physical dependence in relationship to receptors, sites of action, and interactions with neurotransmitters. The topics reviewed are selected from areas of research ongoing in this very active laboratory.

My favorite review for the year is one that is available free but not freely available, at least in many medical libraries. Joseph Larner has written an excellent authoritative informative review on cyclic nucleotide metabolism which appeared in *Current Concepts* (15). There are many reviews and monographs on cyclic AMP but none has hit the mark as his has for teachers as well as for investigators who need more than a textbook knowledge of the subject without becoming enmeshed in the intricate details of methodology, experimental design, and controversies. Larner's review provides the background, the state of the art, and concepts in proper perspective, and for an old-timer like me who needs to become oriented and updated in the field, I find it invaluable and fascinating. Likely, even the experts would profit from the review. *Current Concepts* is provided by the Upjohn Co. as a public service to physicians and scientists, but since it is not archival, I can only hope the editors circulate it widely. A more technical and comprehensive assessment of cyclic nucleotides and nervous system function has been written by Nathanson with 698 references (16).

Since my research interests have shifted somewhat from drug metabolism, I am delighted to make time at least to read "Current Literature" by K. C. Leibman, editor of *Drug Metabolism and Disposition.* In each volume of the journal, founded by E. J. Cafruny, Leibman provides a brief review of topics, research papers, and books related to drug metabolism. Some topics during the past year include activation of parathion, theobromine disposition, neonatal imprinting of microsomes, disulfuram-dimethylhydrazine interaction, pharmacokinetics in disease, dietary induction, ethylene glycol acidosis, detoxification by sequestration, migraine and aspirin absorption, and biochemical events in induction. He also reviewed quite a few books including the current issue of *Progress in Drug Metabolism* (17).

A comprehensive survey of the progress in the entire field of neuropsychopharmacology from 1967 to 1977, edited by Lipton, DiMascio & Killam, covers a range of subjects from basic biochemical processes to clinical application of psychotropic drugs (18). Over 250 experts combined to contribute 149 essays and a total of 1731 pages. The subject index alone consists of 38 pages each with double columns listing about 75 entries. I did not read all the articles; in fact, other than noting the titles, I omitted most and skimmed through many but I did digest a few rather thoroughly.

The volume begins with three essays on the ethics, regulatory issues, and strategies in basic and clinical research, and then presents thirteen reviews on various aspects of the neuroanatomical and neurophysiologic mechanism of drug action. Some of the best essays are in this latter section. Particularly impressive is the summary by the Swedish investigators who opened the field of neuromapping. Their development of elegant immunofluorescence techniques enabled direct visualization of the bioamine neurons, and similar approaches are being utilized for mapping and peptide-containing neurons.

The section immediately following relates to the biochemical pharmacology of neurotransmitters and receptors with sixteen contributions, three of which emanate from the laboratories of Erminio Costa and Sol Snyder, two of the most active investigators in this area.

Peptides and neuroendocrinology are considered next in eleven papers. Although the notion that peptides might be involved in neuronal function has been around for a number of years, evidence has come to light only recently that they have a role as neurotransmitters or neuromodulators. The studies at the single neuronal level have further been extended to indicate that peptides have profound effects on animal and human behavior. Undoubtedly, during the next decade research in neuropharmacology will concentrate heavily on peptides and likely we are in the beginning of an era where substantial modification of our concepts on synaptic and brain function will result from these works.

The next topic, animal models in behavioral pharmacology, appears out of order and is incompletely covered. There are six essays that are rather tenuously linked. However, the section following with six contributions on the pharmacology of memory and learning contain an authoritative treatment of the approaches to learning and memory by Agranoff and associates. They and others have amply demonstrated that blockers of macromolecular synthesis have no effect on short-term memory which requires a fixation process. This may require RNA synthesis in addition to normally ongoing protein synthesis. The hope is offered that recent developments in noninvasive techniques in humans for studying memory and learning will enable a correlative approach to understanding the biologic basis of human memory and facilitate the testing of drugs to improve learning and memory.

The section following on the electrophysiology of drug action is highly technical and appears to be more for the experts in the field. In the next section on neurologic disorders, progress in the clinical pharmacology of extrapyramidal signs and pain is succinctly summarized. Clinical psychotropic drug assessment is then discussed in thirteen essays with respect to human models, behavioral pharmacology, regulatory issues, and biometrics. Procedures for studying the metabolism and kinetics of drugs in the clinic, as well as their biochemical mechanisms of action, are then presented (eleven papers) as well as their toxicology and side effects of drugs (six papers), the most detailed being on tardive dyskinesia by Baldessarini & Tarsy.

As might be expected, the volume includes an extensive treatment of the biochemical basis of affective disorders from etiology to therapeutic approaches. Although there is considerable overlap in the presentations, two papers on the mechanism of action of antischizophrenic agents are critical, informative, and complement each other. Broader coverage is given by the Barchas group as compared to the more technical one by Avrid Carlsson, one of the pioneers in dopamine research.

Drugs in anxiety are accorded nine topics ranging from synaptic mechanisms to clinical applications. Developmental psychopharmacology is discussed both from the pediatric and the geriatric viewpoints. The biochemical and neurotransmitter changes in the aging brain are reviewed by Domino and associates who urge, "We must learn more about the changes that occur in the aging organism so that suitable new drug therapies can be rationally devised for the mental and physical problems of the aged. Because of the special problems of the elderly, selection of drugs to be used necessitates careful consideration of the mechanism of the drug's action and the state of the nervous system on which it acts."

The volume concludes with eleven reviews under the heading, Drug Abuse. We (Way & Glasgow) review biochemical mechanisms in opiate tolerance and physical dependence while Goldstein provides a thoughtful and entertaining overview of opiate receptors and peptides. Various aspects of alcohol pharmacology are discussed separately by Okamoto, Cicero, Nello, Mendelson & Ellingboe while cannabis is looked at by both Harris & Meyer, and tobacco by Jaffee & Jarvik. Martin and associates analyze the psychopathology of the drug addict and suggest that there are causal relationships among needs, feeling state, personality, and drug abuse. They conclude and we concur with the view suggested by Dole & Nyswander that some drug abusers may have a metabolic defect involving feeling and need states. The hypothesis is considered not only viable but one that can be tested.

Finally, concluding with a textbook, the general reader in pharmacology will welcome Levine's second edition of *Pharmacology: Drug Actions and*

Reactions (19). Designed for the college undergraduate, the book has been updated and vastly improved. The main emphasis is on pharmacologic principles and the breadth and depth of the presentations are often at a level not ordinarily found in pharmacologic texts for the medical student. The text is readable, contains a useful glossary, and should stimulate the student's interest.

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