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REVIEW OF REVIEWS

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NEW JOURNALS AND INFORMATION RETRIEVAL

There seems to be no end to the announcements of new journals, particularly volumes related to drugs. These additions place an increasing burden on libraries already hampered in recent years by severe budgetary restrictions. Publishers, confident of a captive audience, have not hesitated to support the spawning of new journals. This proliferation, plus current administrative economic policies, have forced libraries to be more selective in their purchases. The library of my own institution, the University of California at San Francisco, has one of the largest holdings in health sciences periodicals in the country, subscribing to nearly 4000 journals. Although numerous new journals on drugs have existed for at least two years, if not longer, many are not on our subscription list; fifteen years ago, acquisition of a new primary source journal was nearly automatic. Small wonder that the libraries at private institutions, with limited budgets, are beset with major problems in maintaining a viable collection.

Some relatively new pharmacologic journals include: *Pharmacotherapy*, *Pharmacological and Biochemical Properties of Drug Substances*, *Research Communications in Substance Abuse*, *Developmental Pharmacology and Therapeutics*, the *International Journal of Clinical and Pharmacological Research*, *Acta Pharmacologica Sinica*, the *International Journal of Crude Drug Research*, *Clinical Neuropharmacology*, the *Journal of Medical Therapeutics*, *Drug Development Research*, the *Journal of Clinical Psychopharmacology*, *Theory in Psychopharmacology*, *Pediatric Pharmacology*, *Methods and Findings in Experimental and Clinical Pharmacy*, the *Annual Drug Data Report*, *Investigational New Drugs*, the *Journal of Anticancer Agents*, *Drug Development Research*, *Reviews in Pure and Applied Pharmacological Sciences*, *Biopharmaceutics and Drug Disposition*, *Drug Nutrient Interactions*, *Drugs of*

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the Future, Clinical Pharmacy of Clinical Therapeutics, Immunopharmacology, the *International Journal of Immunopharmacology,* the *Journal of Immunopharmacology,* the *Journal of Autonomic Pharmacology,* the *Journal of Cardiovascular Pharmacology,* and the *Journal of Clinical Psychopharmacology and Therapeutic Drug Monitoring*. Some recent journals in the area of toxicology include the *Journal of Applied Toxicology, Fundamental and Applied Toxicology, Veterinary and Human Toxicology, Drug and Chemical Toxicology, Aquatic Toxicology, Human Toxicology,* the *Journal of the American College of Toxicology, Neurotoxicology, Drug Chemical Toxicology,* and *Regulatory Toxicology and Pharmacology*.

As information is generated more and more rapidly, the burden of keeping up with the literature becomes greater each year. This has led to increased efforts to develop new services that not only can publish information faster but also will provide easier access to information already published. Terrant describes the electronic technology that has had a striking impact on reducing the cost of publishing (1). This technology includes hardware (especially computers), software, storage devices, word processors, communications media, micrographics, audio and video devices, and input/output devices. He predicts that in the future data-oriented information will proliferate and that this information will be submitted by authors in computer-readable form. Increased technology will lead to improvements in data processing and wider application of the data-base approach. Dissemination of information will be enhanced by more customized packaging and by increased computer-based publishing of materials that can be delivered on-line or on computer-readable media.

ALLELOPATHIC AGENTS

Putnam has authored a fascinating account of allelopathic chemicals (2). The term alludes to agents used for chemical warfare between plants whereby one plant releases chemicals that have an adverse effect on neighboring plants. For example, sorghum is grown to produce allelopathic chemicals that control the growth of certain types of weeds. In addition, the succession of various plant species in old fields and in cut-over forests has long intrigued ecologists; the appearance and disappearance of species and the changes in dominance by species has been shown to be related in part to allelopathy. A wide variety of allelopathic compounds exist; Putnam mentions thirteen types with varying herbicidal effects. These natural products can be useful for either suppressing weeds or imparting weed resistance and can thereby affect crop growth and nitrogen fixation. Not only do allelopathogens have important argicultural applications, but I believe these highly potent substances might find utility as pharmacologic tools and therapeutics agents.

ANTIBIOTICS

Combined antibiotic therapy in the treatment of certain serious bacterial and polymicrobic infections is a well-accepted treatment modality. Establishing the proper combination to use and the condition to treat is difficult, however. Isenberg and associates (3) review the problems in correlating in vitro with clinical studies to demonstrate synergetic effects between combinations of antibiotics and present the results of a comprehensive cooperative study attempting to resolve some of these problems. They conclude that the efficacy of a single antibiotic for a specific infection cannot be used to predict its behavior in combination. A combination may be effective not only against organisms usually susceptible but also against some resistant bacterial species that are resistant to the individual components of the combination.

RATIONAL BASIS FOR ANTIHYPERTENSIVES

Beyer & Peuler (4) provide a perspective on the current understanding of the factors that relate to hypertension in people and laboratory animals. The interactions of several physiologic systems relating to the modulation of blood pressure and to the prevention and treatment of essential hypertension are emphasized. Dietary control of weight and salt intake are vitally important with or without drugs. When arterial pressure cannot be controlled by weight and salt regulation, combined therapy modulating vasoconstriction and volume reduction should be instituted.

In a concise review, Freis (5) gives a critical, balanced analysis of the pros and cons for treating mild hypertension. There is a growing body of opinion that all patients with hypertension—no matter how mild or uncomplicated—should be treated. Freis provides some staggering statistics on the results of putting this policy into practice. He estimates that at least 40 million people have a diastolic pressure between 90–99 mm Hg and most are asymptomatic. He anticipates poor drug compliance from such persons; those who do comply are subject to the risks of drug toxicity. The addition of 40 million patients to lifelong treatment programs would cost about $20 billion a year based on a conservative estimate of $500 per patient per year for drugs, professional services, and laboratory tests. Consequently, Freis proposes a compromise approach. Since myocardial infarction is the most frequent complication in mild hypertension, only subjects having additional multiple risk factors (cigarette smoking, left ventricular hypertrophy, hypercholesteremia, and glucose intolerance) should have drug therapy. He recommends beginning the treatment with a diuretic alone but, should complications develop, the regimen can be intensified with additional drugs and adjunct measures.

OPIOPEPTINS

Endorphin is the generic term originally proposed for endogenous peptides having opioid-like activity, but the appellation has not gained universal acceptance and has often been associated with the peptide series related to β-endorphin. In view of the fact that three distinct families of opioid peptides with separate biochemical and neuronal pathways are now recognized, we propose using *opiopeptins* as a generic term to cover the three types classified as enkephalinergic, dynorphinergic, and endorphinergic.

A concise and informative review of the three opiopeptin types is provided by Höllt, who describes the current state of knowledge on their processing, distribution, and receptor selectivity (6). All native opioids isolated from mammals thus far belong to one of three families with distinct precursors. Pro-opiomelanocortin (POMC) is the common precursor for β-endorphin and ACTH; pro-enkephalin A is the common precursor for met-enkephalin and leu-enkephalin as well as for several larger residues having potent opioid-like activity and containing either leu-enkephalin or met-enkephalin as fragments; prodynorphin (or pro-enkephalin B) is the precursor of leu-enkephalin and a number of larger fragments containing leu-enkephalin, such as dynorphin A, dynorphin B, α-neo-endorphin, and β-neo-endorphin.

The peptides belonging to POMC are localized mainly in the pituitary gland, from where they are released into the circulation in response to hypothalamic activation. POMC-derived peptides are also localized in the arcuate nucleus of the hypothalamus. Axons of these cells project to the amygdala nuclei and the midbrain periaqueductal gray area. In contrast, peptides derived from pro-enkephalin A and B have a much more ubiquitous distribution in the central nervous system, and their sites correspond fairly well to opioid recognition or binding sites in the thalamus, hypothalamus, striatum, brainstem, and spinal cord. Although enkephalin A and enkephalin B appear to have pathways in close proximity and might even co-exist in some neurons, the hypothalamic-posterior pituitary pathways contain essentially pro-enkephalin B. A single precursor peptide can generate peptides with different receptor selectivities; furthermore, the selectivity changes as the processing continues. This suggests that the processing enzymes play a key role in determining the relative receptor specificity of the processed peptide.

Shah & Donald have edited a volume entitled *Endorphins and Opiate Antagonists in Psychiatric Research* (7). They attempt to gain wider appeal by adding *Clinical Implications* to the title. Progress in the latter area has been agonizingly slow, however, and in order to give substance to the book, the authors have had to cover basic considerations in detail. In contrast, the rate of progress in this facet of the subject has been so phenomenal that much of the information is dated. In a major oversight, no mention is made of the highly

significant and potent peptide dynorphin, identified in 1979. However, my criticism about obsolescence is attenuated in part by the editors' attempt to place emphasis on the clinical aspects of the peptides. The shelf life of this volume will be short but it can be recommended. Its main value rests in its summary of the field to 1980, its comprehensive biobibliography, and its provocative, if not always solidly based, concepts.

Essays by some 93 authors are included. So many contributors usually require a heavy editorial hand to insure a standard of quality in the presentations. However, a perusal of this work makes it obvious that the editors have given the writers free rein because there is much redundancy and some inconsistency among the chapters.

Most of the clinical topics in the volume deal with either the use of narcotic antagonists for reducing a postulated hyperactive state in the endogenous opioid peptides or the application of β-endorphin for a putative hypofunctional state. The bulk of the clinical investigations concern the role of opioid peptides in the treatment of schizophrenia and depression. The results are paradoxical in the sense that both narcotic antagonists and β-endorphin have been reported to alleviate certain, albeit different, signs and symptoms of schizophrenia. It appears that either agent might be palliative in some aspects of the disorder, but the benefits are minimal and the effects probably do not influence the primary pathologic processes. A better case can be made for the use of β-endorphin in the panic states, since the locus ceruleus is concerned mainly with central noradrenergic activity and opiates have been established to have inhibitory effects at the site. A plausible case can be argued for hypoendorphinergism in chronic pain states, although the supporting data are rather thin. In sum, the data are suggestive but not definitive and more controlled studies are in order.

The basic contributions to the volume in general have more substance than the clinical studies and are informative. There is substantial data indicating that some opioid peptides can modulate the analgetic effect of opiates even though they may not be active per se. The evidence now points overwhelmingly to the fact that a family of opioid receptors exists with varying sensitivities to different agonists. Despite being peptides, a good body of evidence supports the fact that central sites can be affected and responses to most opiopeptins can be obtained after peripheral administration.

A hypothesis that might decrease the number of subsets of opioid receptors is contained in the model proposed by Lee and her associates for the β-endorphin receptor (8). Based on both pharmacologic and binding data, β-endorphin is suggested to combine at a locus having both a μ and an δ recognition site. The authors argue that since β-endorphin is as potent as morphine in the guinea-pig ileum and as potent as the enkephalins in the mouse vas deferens, and since β-endorphin displaces either type of ligand equally well and is in turn displaced to about the same degree by opiate alkaloids and the enkephalins, β-endorphin

must combine simultaneously with at least two sites. Structure-activity relationship studies are cited to indicate that an intact β-endorphin molecule is required for expressing full biological as well as binding activity. Thus, shortening the β-endorphin chain by removing the middle peptide sequences reduces biologic activity and binding. Also, modifications of the five N-terminal amino acids with the methionine-enkephalin sequence reduces both binding to brain tissue and biological potency and, although less critical, sequential removal of C-terminal amino acids also results in a gradual decrease in binding and pharmacologic activity. As a consequence, Lee and her colleagues suggest that the site of β-endorphin resides at its N-terminus and at another site 14–24 carbons removed, the first site being the δ-site where the enkephalins bind and the second being the μ-site where alkaloidal agonists can interact. Although each of these two types of ligands can exhibit activity by binding to its respective receptor, β-endorphin must bind simultaneously at both sites. Thus, the β-endorphin receptor is viewed as a complex containing both μ- and δ-binding loci. Based on other evidence, the authors further propose that the enkephalin site may be associated with a protein and the morphine site with a lipid. This concept has the advantage of unifying a great deal of information hitherto explained in terms of multiple opiate receptors, but like all other operational postulates, good and bad, it needs to be verified by the isolation of the receptor.

ANALGETICS

Lednicer has edited a monograph, entitled *Central Analgetics;* it is the inaugural volume in the series *Chemistry and Pharmacology of Drugs* (9). Topics for subsequent volumes include diuretics, cardiovascular agents, and antineoplastic agents. The series is aimed toward research chemists, pharmacologists, and graduate students. In the Lednicer volume the coverage of the field is incomplete. Four areas related to opiate-like analgetics and opioid peptides are discussed; the treatment of these subject matters falls somewhere between that of a chapter in a comprehensive textbook and an in-depth review. In general, the chapters are readable and informative and the errors noted are generally remarks made in passing on details not related to the main thrust of the chapter.

The first chapter, authored by Mohrland and concerned with neuronal sites and pathways involved in analgetic action, is readable and fairly comprehensive. It emphasizes primarily the aspects of pain concerned with its perception. Such an approach can hardly be faulted, because the knowledge on this facet of the topic is the most extensive. However, the uninitiated might gain a distorted perspective of the field, since it is well recognized that opiates also act by altering reactivity to pain and, even though the information is sparse in this

area, this component might well be more important for pain relief than altering the perception of noxious stimuli.

In the second chapter, Vonvoigtland extends the discussion of the possible sites where analgetics might act and implicates substance P as the excitatory substance in sensory neurons. He suggests that potentially useful analgetics might be developed by looking for agents that selectively inhibit substance P release or block its receptor. He also describes animal techniques for testing analgetic activity and recommends that binding assays be utilized for screening compounds. However, insofar as in vitro procedures for purposes of screening are concerned, none approaches the usefulness of the isolated guinea-pig ileum assay. Indeed, the latter preparation can be applied to prediction of the tolerance and physical dependence properties of opioid agonists as well as to differentiate the type of opioid receptor that may be involved in the effect.

The final two chapters by Lednicer include a discussion of the potential of centrally acting regulatory peptides as analgetics. He describes the structure-activity relationships of the enkephalins as analgetics, enkephalinase inhibitors, releasers, and precursors. He speculates on the design of antagonists based on hypothetical conformations of agonist receptors and on the manners in which the compounds may interact with the models. He gives undue credit to the usefulness of receptor binding assays for establishing multiple opioid receptors, whereas in fact the evidence in quantity and quality is derived from the intact animal and isolated organ preparations. The final chapter provides a historic and chemical perspective on the structure, synthesis, and development of analgetic agents.

DRUG DEPENDENCE

The February issue of *Drug and Alcohol Dependence* commemorates its tenth birthday (10). Instead of publishing original papers, the editor, Hans Halbach, invited leading researchers in the field from five continents to write about the major problems in chemical dependencies that have been solved or need resolving. Some twenty-five essays from investigators in both basic and clinical disciplines were the result; their topics range from receptors to behavior to epidemiology.

Craig & Baker have edited a volume dealing with the treatment of and research on drug-dependent patients (11). With the present administration's desire to emphasize medical and social problem-solving at the local level and the imposition of severe budgetary cutbacks on prevention and treatment programs for the drug-dependent patient, the appearance of the book is timely and should be especially welcomed by workers in the field. The contents range from fairly comprehensive critical reviews of certain facets of drug dependence

to highly speculative essays. Treatment of heroin addicts is the main topic of interest; the alcoholic and other drug misusers are dealt with only cursorily.

Most of the pharmacologic information in this volume appears to be relevant and accurate and the psychosocial discussions are provocative and challenging. Dorus reviews opiate withdrawal techniques and their outcomes. His minimization of the abstinent state reflects unfamiliarity with handling the severely abstinent subject. While opiate abstinence is usually not life-threatening, the heavily dependent subject is a picture of abject misery after discontinuing the drug. Hyperthermia, hyperpnea, diarrhea, and vomiting are hardly innocuous and contribute to marked fluid loss that must be corrected. Fortunately, such cases are rarely seen in this country.

Lahmeyer's brief encapsulation of methadone maintenance is interesting and informative. Since its introduction by Dole & Nyswander in 1964, the importance of methadone for maintenance of the heroin recidivist has become widely recognized. Methadone gets the largest number of addicts off the street and into rehabilitative therapy more quickly, more successfully, and more cheaply than any other approach except perhaps the punitive methods used in totalitarian regimes. Non-drug intervention modalities, however successful they may be, are costly in man hours and in monies. Methadone alone, of course, cannot do the job of long-term treatment and adjunct measures can be crucial for achieving success. Such approaches, which may or may not include drugs, are covered in the chapters on residential treatment (Zarcone), behavioral treatment (Ross & Callner), group therapy (Craig), family therapy (Stanton), therapeutic communities (Bale), and defining goals (Lorei). These accounts overlap to a considerable degree and most include a description of trade techniques. Other treatment topics include a chapter on the management of addictions to psychoactive medication (Heilman, Hermos, & Bachrach) and urine analysis (Wang). The aim of most of these approaches is to promote total abstinence from drugs, but prolonging intervals between relapses is a more realistic goal.

The misuse of drugs is a characteristic peculiar to the human species and occurs in certain persons who find themselves unable to cope with stresses imposed by societal and economic pressures. Several contributors attempt to identify and define the personality variable of these individuals. Such assessments are likely to evoke controversies because they cannot be completely objective. Attitudes about drug taking vary with place and time and as a result the prevailing mores of a societal generation become a paramount factor in why and how many individuals take drugs. Much of the interpretation of these studies cannot be applied to global generalizations. Examples include the neuropsychologic assessments of drug use (Mider & Lewis) and the conclusions resulting from a comparison of the personalities of heroin and polydrug users (Penk & Robinowitz). The most tenuous presentation is the attempt to link the personality of the gambler with that of the drug taker (Custer).

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