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REVIEW OF REVIEWS

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Science is becoming increasingly popular. This is easily evident by the success of newly introduced scientific magazines for general reading. *Discover, Science 82, Omni,* and *Science Digest* seem to have growing circulations because the articles are well-written, well-illustrated, and the topics are well-selected. There could, however, be more written about drugs and I would like to call your attention to some popular books published on the subject besides the usual texts, monographs, and reviews.

BOOKS ON DRUGS FOR THE LAITY

Silverman, with Lee and Lydecker, co-authors of *Pills and the Public Purse,* consider the best solution for increasing drug costs to be national drug insurance (1). They view national health insurance as inevitable, pointing out that every major industrialized country in the world has provided a program of national health insurance and in most of the plans, the cost of prescription drugs is covered. Whether or not one agrees with their opinions, the book makes highly interesting reading, even though it is less provocative than its two predecessors; the present volume is less accusatory than *Pills, Profits and Politics* and *The Drugging of the Americas.* The authors indicate that times have changed and by inference one gains the impression they feel that the drug industry has matured and accepted more moral responsibilities while still prospering. In making their case the authors attempt to provide a reasoned analysis of the complexities affecting drug costs and their consequences.

Tribute is paid to the American drug industry for making the major innovations in the treatment of diseases since the end of World War II in 1945 and for providing the most cost-effective form of medical treatment.

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However, they indicate that the early cries by management that government overregulation is ruining the industry were exaggerated and cite some supporting data. From 1940 to 1975, 64% of the 971 newly introduced single drug entities were developed in the United States and this has resulted in an unprecedented profit for their innovators. The authors provide statistics indicating that these profits have continued to mount steadily during this period but note that much of this increase can be accounted for by inflation. They contend also that the continuing profits bely the riskiness of the business, but then the figures for the industry as a whole hardly allay the fears of any single concern which might face huge losses with one bad product. Some prime examples to remember are polio vaccine, elixir of sulfamilamide, thalidomide, DES, etc; also, the more recent debacle with ticrynafen might offset much of the gains with cimetidine. Fortunately, industrial ingenuity and responsibility combined with government regulation, have resulted in far more winners than losers; and a company needs only to have one big winner to come out well ahead in the black.

The authors take a moderate advocacy stance in support of patient package inserts (PPI). While they ardently believe that the patient has the right to know, and cite polls indicating that most patients desire more information about the reasons for taking prescribed drugs and the common risks that might be involved, they acknowledge that PPI have not solved the problem. The limited use of PPI has provided mixed results on drug compliance and its expanded use will increase the costs for drugs.

As advocates for generic drugs, the authors consider the battle essentially won. One of the factors contributing to the victory was the fact that some brand-name companies, which alleged generic drugs might be inferior in quality and untrustworthy, had in fact been buying some generics and marketing them under their own name. Another factor is that brand-name companies have moved into the generic market and are marketing formerly patented drugs of their competitors under their generic names. However, the authors believe that the enormous savings predicted for prescribing generic drugs are unrealistic and project that the maximum savings would be less than 6%.

Of all the positions the authors take to improve the quality of drug therapy and to reduce costs, the one analyzing the prescribing habits of the physician or drug utilization review (DUR) is the least controversial. It has received the endorsement of physicians, pharmacists, patients, insurance companies, and the drug industry. Indeed, the Pharmaceutical Manufacturers Association Foundation was one of the first institutions to support an intensive survey of drug utilization at a large country hospital. Unfortunately, acceptance of DUR by the outside community has been highly

disappointing but there are good reasons. Most of the DUR programs involving larger numbers of patients were carried out by means of computers, and such facilities are seldom available in smaller towns and cities. Furthermore, the methods of maintaining patient drug profiles vary considerably from pharmacy to pharmacy. The beneficial effects for patients appear to warrant the costs of such a program but who should pay for it remains an unsolved problem.

The final conclusions by the authors are dispassionate and have an optimistic overtone. Instead of battle lines, the round table is envisioned for drug manufacturers, regulatory agencies, medicine, pharmacy, and consumer groups to resolve their differences. To exemplify this new atmosphere, the conciliatory talks of the PMA president and the FDA Commissioner are quoted. Like good bourbon, Silverman has mellowed with aging but knowing both, I prefer smoothness in taste to that in talk.

Over a number of years Hand has written a series of essays on European and American folk medicine. The essays have been combined into a single volume entitled "Magical Medicine" (2). On glancing atE the table of contents, it was obvious that the topics were wide-ranging but I was disappointed not to find more on herbal medicine. However, on browsing through the chapters it is easy to become engrossed in the narration. The book can be recommended for light reading.

The folkloric components of medicine with respect to folk belief, customs, and ritual are engagingly and sometimes humorously chronicled. Diseases can be caused by demons, by divine retribution after sinning, or by the "evil eye." Cures can be effected by magical transference to other persons, animals, or plants by performing weird rituals (wrapping a snake around the neck or rubbing the neck thrice with the hand of a dead person to remove a goiter, kissing a dog to cure a sore throat, spitting in a frog's mouth to cure asthma, wearing a red necklace to stop a nosebleed, etc.) and of course, by using plant or animal products. Tops of plants were used to cure maladies of the head and the roots of plants for those of the legs; also urine of a faithful wife was used to cure sore eyes, blood of a black cat to cure shingles, bed bugs' or cockroaches' legs for chills, and various parts of the mole to cure or prevent a variety of diseases. Generally no explanations are provided for the cause or cure of the diseases and in most instances can not be expected. As the author points out, magical and fanciful kinds of curatic practice seem to predominate in the folk tale rather than any rudimentary kind of medical science based on the long practice and enriching experience of folk medical practitioners. A treatise on the evolution of folk medical ideas and theories and the possible interplay with scientific medicine is a task yet for someone to undertake.

TEXTBOOKS

The seventh edition of *Review of Medical Pharmacology* by Meyers, Jawetz, and Goldfien has appeared (3). The laudatory aspects of the book—readability, information relevance, and price—are still factors that will continue to make the book popular, but some annoying negative and uncritical statements still persist, such as "the advances in research on salicylates have been minor since 1900" and "Reasonable dosages of propoxyphene combined with other symptomatic medication appear to be useful in relieving the narcotic withdrawal state, just as strychnine in the past." However, some criticisms I made concerning the sixth edition have been remedied, but it would be certainly presumptuous of me to claim credit for the following changes which improve the text. The possibility that the beneficial effects of antipsychotic drugs in schizophrenia and their extrapyramidal side effects might be attributable to antidopaminergic effects are now considered; the section, however, is not one of the better written ones. The chapter on narcotic analgetics now includes a readable discussion of endorphins and the enkephalins, the brain peptides with opiate-like action. However, not all my suggestions were noted. Phencyclidine (PCP, Angel Dust) is still not discussed in drugs of abuse, despite the fact that in recent years it has been quite a problem, enough of one for the National Institute on Drug Abuse to publish a monograph about it. The next edition of the text will have new authors and I hope that they will retain the useful features of this best-seller.

Di Palma edits the second edition of *Basic Pharmacology in Medicine* (4). The updated version corrects some deficiences in the first edition. The advantages of the text are conciseness and readability. Its main deficiency is that in not providing a better link between the basic mechanisms of drug action with their descriptive pharmacologic profile, the opportunity to capitalize pedagogically is often lost. For example, in discussing antipsychotic drugs, mention is made in passing that they possess antidopaminergic effects but no mention is made that this property correlates nicely with binding and clinical potency of the various drugs in this series. The antidopaminergic action of the antipsychotic drugs provides an even more plausible explanation of their extrapyramidal side effects and this was not appreciated. Although the data are less conclusive, a case might also have been made of the possible development of supersensitivity to dopamine as a mechanism for tardive dyskinesia. With respect to narcotic analgetics, allusion to the brain peptides with opiate action was cursory and imprecise. The enkephalins are less, not more, potent than morphine as analgetics and no mention was made of β-endorphin, which is more potent. The correlation of opiate binding sites with pain pathways and endorphin density in the central

nervous system was not considered. Furthermore, the statement that morphine does not interfere with conduction of pain impulses in the brain is at odds with more recent findings that reveal descending supraspinal inhibition of afferent noxious stimuli by opiates. One can also question the categorization of nalbuphine as a semisynthetic derivative of morphine while restricting nalorphine to opiate antagonists when pharmacologically nalbuphine resembles nalorphine much more than morphine. Considering the nonnarcotic analgetics, no rationale is provided for the use of acetylcysteine for the treatment of acetaminophen overdosage, even though it is well-established that under conditions of acetaminophen overdosage there is depletion of sulfhydryl-containing compounds in the liver. With respect to the effect of colchicine and gout, there has been considerable literature for a number of years discussing the roles of microtubular function and phagocytosis on intracellular crystallization of urate crystals and the symptoms of gout; the omission of such relevant matters is inexcusable. In the chapter on drug dependence, the chief drug of abuse in the United States, alcohol, is not mentioned and the delirium tremens was not associated with physical dependence and the withdrawal response; Isbell and Fraser demonstrated this nearly 30 years ago.

MONOGRAPHS

The series published by the National Institute on Drug Abuse contain at least two recent volumes that are of interest to pharmacologists. Volume 32, *GC/Mass Assays for Abuse Drugs in Body Fluids,* includes detailed instructions for the quantitative measurement of the more commonly abused drugs and some of their biotransformation productions by gas chromatography and mass spectrometry (5). Before specific compounds are discussed, principles and some common operations for chemical agents in general are expertly covered in the introductory chapter. Although the methods were mostly developed by one laboratory, their reliability and applicability were subject to independent testing in the field. GC/MS instruments are becoming increasingly necessary equipment in toxicologic laboratories because of their sensitivity and specificity, and although the initial outlay may be expensive, in the long run it should prove to be economic when sensitivity and a big work load are considerations. Almost certainly there will be modification and improvement in the procedures for specific substances, but this monograph should enjoy a long shelf-life.

Monograph No. 34, edited by Harris, contains the Proceedings of 42nd Annual Meeting of the Committee on Problems of Drug Dependence (6). As usual, the papers are interdisciplinary and describe progress in the chemical, pharmacological, clinical, and psychosocial areas. Of particular

interest is the address by the Nathan B. Eddy Memorial Award Lecturer, Avram Goldstein, who describes the properties of a novel and highly potent brain opiate peptide, dynorphin. Kalant provides a very thoughtful, philosophic, and practical analysis of governmental control of individual behavior with respect to use and misuse of drugs. Chau and Harris describe work indicating that the antitussive effects of codeine are not mediated via the classic opiate receptors. Czontos, Rust, and Höllt find highly elevated levels of β-endorphin and ACTH in plasma of mothers in the first, and particularly during the second, stages of labor and suggest the levels may be sufficient to affect mother and infant. Jaffe, Kanzier, and Green report the abuse potential of loperamide is low enough to make controls unnecessary and the FDA subsequently concurred.

CLINICAL PHARMACOLOGY

The proceedings of the First World Conference on Clinical Pharmacology and Therapeutics include four plenary lectures and fifteen symposia and therapeutic sessions (7). There is a rich wealth of relevant pharmacologic information contained within these pages. Moncada and Vane provide a comprehensive authoritative review of the pharmacology and therapeutic potential of prostacyclin. Based on the studies from their laboratory and others, the authors originally proposed that aspirin-like drugs mediate their analgetic, antipyretic, and anti-inflammatory effects via inhibition of prostaglandin synthesis. Subsequently, they and their associates played a major role in the discovery of prostacyclin (PGI_2), the most potent endogenous inhibitors of platelet aggregation. They point out that a number of diseases have now been related to an imbalance in the prostacyclin/thromboxane A_2 system. Conditions which favor the development of thrombosis are associated with an increase in thromboxane A_2 and a decrease in prostacyclin formation, whereas an increased bleeding tendency can often be associated with increased prostacyclin formation plus decreased thromboxane A_2.

Kosterlitz, one of the pioneers responsible for the discovery of the enkephalins, reviews their current state. He summarizes much information with respect to the chemical properties of the opioid peptides, their distribution in the central and peripheral nervous system, their receptors, and their metabolism and pharmacological properties. Less is known about their physiology because their functions and receptors have not been clearly defined. He notes that at least two types of opiate receptors appear to exist; the mu-receptor appears to be preponderant at sites associated with analgesia, whereas the delta-receptors are prevalent in the limbic system. He points to the need to have an antagonist that interacts specifically with one type of receptor.

B. B. Brodie's pupils dedicate the Drug Metabolism Symposium in his honor on his birthday. Organized by Conney and Kato, the papers discuss environmental and genetic factors in drug metabolism. Some other symposia at the Conference include Drug Dependence, Developmental Pharmacology, Pain, Pharmacology of the Skin, Fertility Regulation, Hypertension, Chemotherapy of Cancer, and Tropical Diseases.

NARCOTIC DRUGS

A succinct history of narcotic drugs is provided by Wasacz, who traces their beginning from the opium poppy, *Papaver somniferum,* to the more recent peptides found in the brain (8). The foundation of modern pharmacology began with the isolation of morphine from the opium poppy by the pharmacist, Sertürner, for it was the first demonstration that a single active constituent could account for the pharmacologic properties of a natural product. This also meant that the variations in potency of different sources of the plant could be circumvented. There is some confusion as to the precise date the task was accomplished. Usually Setürner's 1817 paper is cited because this publication aroused general interest. However, in actuality, he described the isolation of pure morphine base in 1805, but the report was largely ignored. He repeatedly called attention to his discovery in several subsequent publications, but it was not until Robiquet verified his findings in 1817 did Sertürner receive the credit he deserved. Sertürner also describes testing the isolated morphine on himself and three associates and observed flushing, vomiting, and near coma after administering 90 mg orally within an hour. Physicians and scientists had less sociologic brethren to contend with in the old days!

The chemical structure of morphine proposed by Gulland and Robinson in 1925 was widely accepted, but they had to await more than 25 years for its confirmation by synthesis, which Gates and Tschudi reported in 1952.

The discovery of narcotic antagonists was a major pharmacologic landmark. Wasacz unfairly gave almost sole credit to Weijlard and Erickson for the development of nalorphine, the first compound in this series that found practical application. In actuality the compound was conceptualized by McCawley and Hart who did the original spade work and reported on its antidotal properties. We recently tried to set the record straight (9). There were two other notable achievements that followed: (*a*) the differentiation of narcotic drugs into analgetics of the agonist and the antagonist type by Beecher and Lasagna in 1954; this discovery ultimately led to the development of potent antagonist analgetics with low addiction liability. (*b*) The development of naloxone, a pure antagonist, which became a powerful laboratory tool; Fishman and Blumberg deserve most of the credit for this innovation.

In developing the groundwork that led to the isolation of the opiate peptides, methionine and leucine-enkephalin, by Hughes, Kosterlitz, and their associates in 1975, Wasacz did not follow the usual line by stating that the characterization of the opiate receptors led to their discovery. True, the latter achievement spurred the enkephalin work, but a native ligand with opiate-like properties was believed to exist by many investigators long before the opiate receptors were characterized. In describing the various opiate peptides that have been subsequently isolated, Wasacz fails to note that their varying potencies are likely due to their selective actions on multiple types of opiate receptors rather than to differences in rates of degradation.

SUBSTANCE P

Leeman and Gamse review some of the work that led to the suggestion that Substance P may have a transmitter role, giving emphasis to more recent findings concerned with Substance P in primary sensory neurons (10). They argue that a function for Substance P in pain transmission is supported by several findings. In favor of such a role are its presence in small sensory neurons, its evoked release from the spinal cord, and its excitatory action on dorsal horn neurons, which have been reported to be activated by noxious stimuli. Moreover, the potent analgetics, morphine and its peptide agonist surrogates, which have been shown to have a spinal component in their action, also inhibit Substance P release. Finally, capsaicin, which releases then depletes Substance P by causing degeneration of Substance P neurons, has been established to produce pain locally, but produces insensitivity when administered systemically in high doses.

INFORMATION RETRIEVAL

The pace of progress in science and technology is such that there is little time to assimilate the sheer mass of data generated. The changing times dictate the need to find more effective means of communicating the cumulative information more efficiently and effectively. In the past two decades, automated information retrieval systems have been developed at a rapid rate and more than 1000 bases are available currently for computer searching. Most scientists are either unaware of these data bases or use them only in a superficial manner because they are unwilling to make the effort to learn the system. Doskocs, Rapp, and Schoolman outline the advantages of full use of existing automated data bases and provide an excellent review of the current state of the art (11). Major search services today offer on-line access

to millions of bibliographic citations. However, a multiplicity of bibliographic search system poses a major hindrance to easy on-line access to the literature and standardization is needed. In addition to the uneven quality of retrieval, there is inadequate linkage among data bases and reliance on specially trained intermediaries. Much research on information science has been directed towards overcoming the barrier to effective use of large computerized retrieval systems.

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