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REVIEW OF REVIEWS

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HERBAL MEDICINE

Within the past decade there has been a resurgence of interest in plant products with biologic activity. In large part, the stimulus has been provided by the People's Republic of China opening its doors. Successes there in preventive medicine, eradication of certain parasitic and venereal diseases, acupuncture, and burn therapy as well as extensive research projects in materia medica were a revelation to the West.

The massive program mentioned above was the consequence of political as well as practical considerations. During the early years after the Communist Party assumed control of China, there was dire need of physicians throughout the country, and particularly in rural areas. To Mao Zedong and the party planners the solution was simple: Mao deemed that "Chinese traditional medicine is a vast valuable national treasure which should be intensively exploited and improved." A ukase was issued, therefore, that Western-trained physicians and traditional Chinese practitioners should merge their knowledge and skills to serve the people. As a consequence, relative to other biologic sciences, pharmacology assumed an exalted position as an intensive program to justify established herbal remedies and to discover new ones was launched. Numerous projects were initiated at research institutes and universities throughout the country to isolate and identify active constituents of known herbal remedies and to screen other natural products for possible therapeutic application.

Concerted efforts were also made to provide a rational basis for Chinese traditional medicine. However, the basic conceptualizations of such a system cannot be buttressed or refuted by experimentation. Whatever the merits of these past theories, it is my personal view that these concepts have long outlived their usefulness. I am not alone in such views, but surprisingly few investigators have made such a flat assertion. Likely, most of the current in-

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vestigators in this field do not believe it worth the bother to criticize openly the outmoded traditional theories. Perhaps many refrain either out of fear of offending or just fear. In any event, the scientifically trained pharmacologists in China obviously ignore the traditional theories by performing research on herbal remedies using the experimental approach. The new knowledge emanating from these projects has been truly impressive, and many reviews and monographs have dealt with these matters. Although the programs in more Westernized countries are not nearly so extensive, there is no state of dormancy as evidenced by several recent monographs describing ongoing research on plant products with biologic activity.

Balandrin et al provide a concise overview of extractable plant chemicals and their economic importance and cite some more recent examples of pesticides, alleochemicals, and potential medicinals (1). They point out, however, that most species of higher plants have never been described, much less surveyed, for chemical or biologically active constituents, and that new sources of commercially valuable materials remain to be discovered. Only about 5–15% of 250,000–750,000 species of higher plants have been surveyed for biologically active compounds. Balandrin et al anticipate that biologically active plant materials will play an increasingly significant role in the development of new products for regulating plant growth as well as for insect and weed control. Advances in the biotechnology of chromatographic and spectroscopic techniques as well as in methods of culturing plant cells and tissues should provide new means for the commercial processing of plants and the chemicals they produce. They gloom their predictions by warning that if the current trend of destruction of tropical forests continues at its present rate, plant scientists may have only a few decades remaining to investigate the plant kingdom for useful chemicals. On a more optimistic beat, I should point out that marine plants and animals, although by no means immune, are less likely to be affected by human machinations, and the surface has scarcely been scratched concerning the active constituents of these natural products.

Takemi and associates edit *Herbal Medicine: Kampo, Past and Present* (2). "Kampo" refers to Japanese herbal medicine in the Chinese tradition. This volume contains articles by invited speakers that were presented at a conference convened by the foremost commercial concern dealing with herbal remedies in Japan on the occasion of its ninetieth anniversary. The topics include a potpourri of history, philosophic concepts, political science, and pharmacology both basic and clinical. Of particular interest is the presentation by Hosoya on the pharmacology of Kampo prescriptions, in which he describes attempts to identify the optimal combination of the various ingredients that yields the desired pharmacologic activity. Qian traces traditional medicine in China from its early days to the current research programs to identify and isolate the active

constituents in natural products. Nishioka's paper on the discovery of active components in rhubarb with novel biologic activities, and Shibata's on quality control of extract preparations are also worth reading.

Chang et al (3) have edited a volume containing the proceedings of an international symposium held recently in Hong Kong on Chinese medicinal products. In the symposium, there were 89 presentations with special emphasis given to 8 areas. Two of these were concerned with hepato-pharmacology and anticancer agents. Separate sessions were devoted to three drug topics, namely ginseng, gossypol, and abortifacient proteins. With respect to the latter agents, particularly impressive are the detailed studies by Pan and his associates establishing the chemistry and structure of trichosanthin. In the presentation of two general sessions, Hosoya reports studies on the construction of prescriptions in ancient Chinese medicine, Hsu on the processing of medicinal herbs, and Zimmerman on the possible mechanism of action of traditional oriental drugs for bronchitis. In a subject that is seldom discussed, Wang & Hu describe the toxicity and side effects of some Chinese medicinal herbs. With a more modern approach to systematizing the knowledge on Chinese medicines, Lee & Chang discuss the establishment of a computerized data base that provides on-line information with respect to botanical, chemical, pharmacological, and clinical reports on common Chinese medicinal materials.

Lien & Li describe Chinese plants with anticancer properties and provide an analysis of the structure-activity relationships of the active principles (4). In recent years over a thousand species of plants have been screened in China for either antitumor or cytotoxic activity, and many have been reported to be active experimentally. The authors list in their compilation 120 species of plants belonging to some 60 different families that have been shown to exhibit anticancer activity in established cell lines in vitro and animal models in vivo. Whenever available, clinical data are also included. Among the active chemical groups present in plants discussed are the sesquiterpenes, diterpenes, triterpenes, steroids, alkaloids, and others. This treatment of the subject includes an examination of the structure of the active components and their possible mechanism of action.

DRUG DEPENDENCE

The Committee on Problems of Drug Dependence provides an updated authoritative monograph on the testing of drugs for physical dependence potential and abuse liability, terms that have been defined operationally for laboratory evaluation (5). Physical dependence refers to pharmacologic events that occur consequent to repeated drug administration, whereas abuse potential is used with reference to events that precede or accompany strong drug-seeking be-

havior. Even though both physical dependence and abuse potential frequently occur together, they are distinguishable and can be evaluated separately.

Some compounds can be observed to produce physical dependence (that is, withdrawal signs after repeated drug administration) and not be abused, while other agents can produce abuse with behavioral consequences at doses that do not necessarily produce tolerance and physical dependence (e.g. cocaine). Physical dependence potential of a substance can be quantified by measuring the intensity of certain physiologic and biochemical events that appear upon immediate discontinuance of an agent following chronic administration. The abuse potential of a drug can be assessed by observing and analyzing the drug seeking, drug discrimination, and drug-taking behavior associated with self-administration of the pharmacologic agent.

The usefulness of the tests resides in their predictive value in human situations. Although the validity of animal testing procedures is subject to controversy, the debates do not negate the need for such methodology. There are instances in which drugs passing animal screens show abuse liability in humans, and street users have been able to discover abusable drugs or drug combinations that were never tested in animals or suspected of abuse liability even after extensive clinical use. Despite such deficiencies, laboratory procedures for assessment of liability potential are widely used in academic, governmental, and industrial research.

In general, the predictive value of testing procedures can be best demonstrated on drug classes that have a distinct pharmacologic profile and a long history of physical dependence and abuse liability. In such instances, an uncharacterized agent can be easily classified by comparison tests with prototypic drugs and further identified by substitution tests for cross-tolerance and cross-dependence. The best example of this is the opiate group, but even in this drug class problems surfaced when the mixed agonist-antagonists and partial agonists appeared on the scene. For rational explanations it then became necessary to utilize additional tests and to invoke the concept of multiple opioid receptors.

The battery of test procedures available now for identifying opioid drugs and quantifying their dependence liability is impressive. Such tests range from simple in vitro pharmacologic methods in excised organs, to chemical affinity binding measurements on homogenized tissues, to more complicated behavioral tests on intact animals and humans.

The ease of predicting physical dependence potential and abuse liability of other drug classes varies considerably. Tests for assessing general central nervous depressants are reasonably precise, especially when one considers the wide range of substances included in this category. Sleep induction, locomotor activity, electroencephalographic activity, and behavioral performance after

acute drug administration are useful parameters for categorizing sedative/hypnotics, anesthetics, anxiolytics, and antihistamines. These acute tests are greatly enhanced and complemented by tolerance, cross-tolerance, physical dependence, and cross-dependence data obtained after chronic administration that are coupled with drug self-administration tests.

Procedures for appraising stimulants also include behavioral self-administration tests after acute and chronic drug administration. Tolerance, but not physical dependence development, appears useful for characterizing this drug group. The self-administration tests, however, provide more precise information. Indeed, reinforcing efficacy analysis utilizing progressive ratio performance, rates of response, and discrete trial choice permits the detection of differences between CNS stimulants and reveals cocaine to be one of the most potent agents with respect to reinforcing efficacy.

The characterization of other types of agents for abuse liability is more difficult. Various reasons can be offered to excuse this deficiency. The newness and poor availability of compounds limit the amount of acquired information that can be retrieved. However, there may be even more complicating factors. For example, drugs of abuse that produce hallucinations can hardly be identified by this phenomenon in experimental animals. Rather, the investigator must rely on making behavioral profile comparisons of an unknown compound with a prototypic one; unfortunately there is relatively little information on such agents. Certainly, better test procedures are needed for assessing hallucinogens, anticholinergics, and dissociative anesthetics. This may not be wholly true for characterizing cannabinoid-like activity. With the isolation and identification of delta-9-tetrahydrocannabinol as the prime active principle in marihuana *(cannabis sativa),* a standard for making comparisons became available, and since then considerable information has been amassed on its acute and chronic behavioral profile.

In the final analysis, abuse liability of chemical agents needs to be evaluated in humans. In general, the principles applied in animal methodology after acute and chronic drug administration can be extended to human situations. There are limitations imposed by pharmacologic, clinical, and ethical considerations, but these are offset in part by the information that can be furnished by the subject to the investigator in a well-designed experiment. Testing in humans is complicated by the fact that there is great interindividual variability in reactivity to and tolerance for various substances—the latter phenomenon can be drastically modified by prior drug experience. Simple random assignment to drug or control group is usually not sufficient to assure equivalent groups because most drug trials are based on small samples, and the attrition rate for the needed testing over an extended period is high. In addition to matching experimental and control groups, therefore, attention should be paid both to obtaining

subjects who will represent the population likely to be administered the drug clinically and to finding methods for endpoint analysis to avoid loss of data for those who do not complete the test period.

GENERAL PHARMACOLOGY

The seventh edition of Goodman & Gilman's classic pharmacology textbook now appears with the names of four authors (6). The son of one of the original authors assumed the chief responsibility for editing the sixth edition although Goodman and Gilman remained as coauthors. With the death in 1984 of Alfred Gilman, who leaves behind the legacy of a great teacher and author, the succession of responsibility appears to be well planned.

The major revision of the text occurred in the sixth edition, in which new topics and different sequential presentations of the subject matter were made. The present revision retains this format, and the chapters in the main appear to be updated versions of the earlier presentation, even though some authors have been replaced.

The introductory material relevant to basic principles has been expanded and improved. Even though the intraspinal and intrathecal routes of drugs are discussed in the chapters on local anesthetics, these routes should also be mentioned in the general material. The discovery of opiate receptors in the spinal cord and the successful use of intrathecal or intraspinal morphine reinforces this notion.

A statement in Chapter 3, "Principles of Therapeutics," to which I take issue because it appears overly dogmatic is the assertion that "placebo is an indispensable element of the controlled clinical trial." The necessity for a placebo in clinical assessments of drug efficacy has become axiomatic, but I would argue on pharmacologic principles that its use is usually, if not always, unnecessary. If the dose-response relationship of the agent is evaluated double-blind, the low point of the dose-response curve would be in essence the placebo response. Not only is such an assessment scientifically sound but it is also justified ethically because the investigator needs to establish the safest effective dose of the agent tested, while not depriving the patient of needed medication. I would concede that in subjective evaluations, in which response sensitivity in subjects is low and the variation great, placebos may be necessary to establish drug efficacy; but in such instances the resulting data are usually not convincing.

In checking my previous review of the sixth edition (7), I note that one of my nitpickings had been dealt with. The term "tranquilizer" has now been dropped in the chapter on the history of the anesthetics. However, in the handling of the subject matter in this area I still note a lack of historical perspective. Although

the discoveries of ether, nitrous oxide, and chloroform are discussed, the advancements made after World War II are ignored. I searched in vain for the names of the inventors of halothane, enflurane, and isoflurane, nor could I find information about when these gases were introduced or what concepts had led to their development.

In general, the section on the mechanism of action of the various drug classes appears to be informative, educational, and current. An exception is the chapter on the antipsychotic agents. There are many good basic data indicating that both the beneficial and undesirable effects of the agents used to treat schizophrenia can be attributed in large part to an antidopaminergic action. Even though dopamine may not have a causal relationship to the disease process, it appears to be involved in its manifestations. The rank order of binding affinities of the antischizophrenic compounds in the brain exhibits a surprisingly good correlation with the rank order therapeutic-efficacies and the production of extrapyramidal effects. The discussion on the mechanism of action of diazepam does not include references beyond 1982. Although the role of GABA is included, the recent exciting discovery of the receptor with distinct recognition sites for diazepam, GABA, and chloride is not cited. On the other hand, the chapter on opiates includes references as late as 1984, and the reader is clued to the most recent advancements made in identifying the precursor proteins of three opioid peptide families and the multiple opioid receptors.

However, the above noted shortcomings are not major. I accorded the sixth edition high praise, and this seventh one is an improvement.

OPIOPEPTINS

Undenfriend & Meienhofer's edited monograh brings us authoritative current information on the status of the opioid peptides (8). They were able to achieve their mission because they were highly successful in enticing leading busy contributors in the field to summarize and review their areas. Although the treatment of certain topics is not ideally balanced, the volume is well worth having. Particularly impressive is the opening chapter by Numa, who describes the Herculean efforts in his laboratory leading to the elucidation of two opiopeptin precursors, preproenkephalin A and preproenkephalin B. The structure of a third opiopeptin precursor, pro-opiomelanocortin, is discussed by Cibelli, Douglass & Herbert. Thus the application of recombinant DNA technology has enabled the elucidation of the primary structure of three opiopeptin precursors, and all endogenous opioid peptides identified to date are derived from these three precursors. The striking structural similarity of these three precursor proteins to their genes suggests their close evolutionary relationship. In other chapters, Undenfriend & Kilpatrick discuss the processing of

proenkephalin B; Goldstein, the biology and chemistry of dynorphin; Paterson, Robson & Kosterlitz, the characterization of opioid receptors; Yamashiro & Li, the structure-activity relationships of β-endorphin including some native analogs with opioid antagonistic properties; Schiller, an extensive conformational analysis of enkephalins; and Hansen & Morgan, the structure-activity relationships of enkephalin peptides. The final chapter by Clement-Jones & Besser provides a fairly comprehensive review of the clinical pharmacology of the opiopeptins and covers investigations of their clinical application in pain, narcotic dependence, psychoses, and endocrine regulation. As yet, the clinical applications of the opiopeptins have been limited because their use is undoubtedly predicated upon a more thorough understanding of their physiologic roles. As one of the authors (S. Undenfriend) states:

> It is of interest that we know now far more about the chemistry and genetics of the enkephalin-containing peptides than we do about their physiological roles. It is likely that the same technologies will soon permit the full characterization of the various opiate receptors at the molecular level. At the moment, however, it appears that the application of good "old fashioned" physiology and pharmacology are still required to elucidate the role(s) of the opiate peptides in health and disease.

DOMESTICATION OF CHEMISTRY

In his review concerning the "domestication" of chemicals by design of safer substances for human use (9), Ariens coins some new terms that sometimes interfere with readability. Despite these linguistic forays, which are sometimes distracting and annoying, he has penned a thoughtful scholarly essay. "Domestication of chemistry" he defines as "the adoption of chemistry and chemical to intimate association with and to the advantage of man." Ariens points out that in today's chemistry-dependent society with more than 60,000 man-made chemicals and with about 1000 new products being introduced on the market annually, nobody can avoid exposure to chemicals at some level or escape the inherent health risks. To domesticate chemicals requires a good comprehension of the toxicodynamics and the toxicokinetics of compounds foreign to the body (xenobiotics). Risky leads can be minimized by recognizing unsafe types of chemical structure and by applying routine in vitro screening tests early. For example, mutagenic agents are likely to have carcinogenic potential, and the correlation between alkylating ability and mutagenicity of chemical agents is extremely high. Hence, the introduction of highly electrophilic or nucleophilic groups and unsaturated bonds should, if possible, be avoided in agents that are to be used commercially, especially those that might pollute the environment.

ANALGETICS

Kuhar & Pasternak have edited a monograph on analgetics with the object of integrating the latest concepts, methodology, and findings in the experimental laboratory and clinic for the development of new and better pain relievers (10). Apparently there were delays in getting the material to press, since the volume does not cover certain exciting developments that occurred before its publication in 1984.

Apart from a few 1981 and 1982 references, the citations in most chapters seldom extend beyond 1980, suggesting that the editors experienced trouble making some of the authors meet their deadlines. As a result, when the book was published, the journey on some of the pathways the authors suggested exploring had already been completed. None of the book's authors, including myself, mentions dynorphin, which was isolated and completely sequenced in 1981. Despite this criticism, the editors have provided a useful reference and abbreviated bible for workers in the field. Frederickson's coverage of the state of the endogenous opioids up to 1981 is informative and comprehensive. Goodman & Pasternak expose their expertise and their personal bias on the various opiate receptors. Basbaum discusses the anatomic aspects of pain related to drug action and makes a strong case for modulation of pain mechanisms by descending pathways from the periaqueductal gray and medulla, as well as for a spinal site. Michine covers structure-activity relationships of opiate agonists and antagonists. Brune & Lang provide some unfamiliar names and a textbook essay on nonopioid analgesics. Wood's listing of analgesic models in analgesic testing might have been flavored by a critique similar to that in Wallenstein's evaluation of analgesics in man. Haubrich and three others discuss nonendogenous opioid peptides in nociception with particular emphasis on substance P and neurotensin. The discussion of the management of pain with opiates (Inturrisi & Foley) is prefaced by a treatment of the pharmacologic basis for their application as were the nonsteroidal anti-inflammatory agents (Kantor). Finally, in projecting future vistas, I pontificate:

> To remedy current deficiencies in the management of pain, proper communication is essential at all levels. This involves adequate orientation in the medical problems associated with pain in the curriculum for medical, dental, nursing, and pharmacy students and maintaining the education intensively for the practitioner on a continuing basis. In the treatment of the patient with severe pain, a holistic approach is, of course, essential but the advances from the experimental laboratory and the clinical must be appreciated. The major breakthroughs can only occur from the fundamental contribution emanating first from the experimental laboratory and this work can only flourish in an atmosphere that has economic, political, and philosophic support from an educated public at large.

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