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REVIEW OF REVIEWS

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A preference for reviews of topics of more general interest has been expressed by the readership. I am quite willing to accede because it's the path of least resistance for me. Although it may not be too difficult to grasp the important implications of a major breakthrough, with the rapid advances being made today in so many areas, it is not so easy to pretend to be sophisticated and knowledgeable about the specific nuances of the technology. I shall henceforth give more emphasis to books and articles of broader interest, yet I shall not capitulate completely and will still on occasions call your attention to some good in-depth reviews.

DRUG DEVELOPMENT

For its twenty-fifth anniversary, the editors of *Perspectives in Biology and Medicine* invited a select number of authors to contribute their judgment on the major achievements of the quarter century. Of some interest to pharmacologists are essays on DNA (Crick), technology in creative biology research (Yalow), and animal models for human disease (Rust). Of even more relevance are the views expressed by Hubbard on the development of medicinals (1). He considers the 25 years just concluded the golden age of drug development, and gives as examples penicillin-resistant antibiotics, the benzodiazepams, potent nonsteroidal analgetics (agonist-antagonist analgetics were omitted), the battery of anticancer agents, cimetidine, and an impressive array of cardiovascular drugs for the control of edema, hypertension, and the arrhythmias. For the latter conditions, he includes the potent antidiuretic, furosemide, β-blockers, and calcium channel blockers.

Clearly, despite the claims of a drug lag, the pharmaceutical industry has been active and innovative. While it is difficult to downplay these very significant achievements, to me, the breakthroughs are hardly commensurate or as spectacular as those made 25 years earlier between 1932–1957. Most significant were the sulfonamides, penicillin, streptomycin, the broad spectrum antibiotics, antimalarials, ACTH, corticosteroids, antihistamines, opiate antagonists, carbonic anhydrase inhibitors, chlorothiazides, and phenothiazines. However, since all the developments spanned my career, let us not quibble, and call the last half century the golden age of drug development.

Hubbard ends on an editorial note denouncing current regulatory practices and sets up some straw men to demolish. Although I do not totally subscribe to Hubbard's view, neither do I wholly disagree. There is a difference between regulation and overregulation. The former practice is essential, as tragedies with sulfonamide, thalidomide, diethylstilbestrol and so forth have proven. We are better off without the latter practice. Overregulation reflects politically generated unionism and is espoused by bureaucrats, zealous consumer advocates, and self-seeking lawyers. There can be no question that overregulation results in serious loss of benefit, but unfortunately this loss is less apparent and difficult to measure. Clearly, greater emphasis is needed on evaluating not only the medical costs but also the social and economic losses when a useful drug is hindered from reaching the market. However, as long as we keep spawning more and more legalists to define and dictate what the individual and complexes can do, the medical and lay public can only become more deeply enmeshed in a morass of advocacy.

Volume I of a new series, *Chronicles of Drug Discovery,* contains essays by the discoverers of novel drugs describing the thinking and the events in the laboratory that led to each creation (2). The editors, Bindra & Ledniger, tried to have the authors write informal, candid narratives, but the stories fall short of the claims of the publisher on the book cover, "lively, absorbing accounts provide a fascinating look at the creative processes of chemists and pharmacologists." A notable exception is the article by Stähle relating how a clinical investigator allowed his secretary to self-administer intranasally for a cold a 0.3% solution of clonidine and found to his surprise and embarrassment that she developed hypotension, bradycardia, dry mouth, and slept for 24 hours! In contrast, most of the other presentations are dry structure-activity accounts of huge screening projects, tinged occasionally with bits of interesting insight, usually about the dispositional properties of the compounds that sometimes helped to reduce the odds. Even when serendipity played a role in ferreting an innovative prototype, however, the discovery originated from a systematic screening program.

I always marvel that two drugs developed in the laboratory of my chief, Chauncey Leake, were one-shot events. Divinylether and nalorphine were conceptualized and predicted to be active drugs without certain adverse effects. Each was the only substance synthesized to do the job and both found the market place.

The book provides little support to the critics of the "me too" method but rather gives fuel to the fact, as typified in the accounts of cimetidine (Evanellia) and butadamol (Humber), that a concerted SAR study to modify known prototypic drugs is still the approach most likely to yield new and better agents. Chances for success can be improved from the information provided by computer graphics and the sophisticated tools now available for structural analysis, but in the final outcome, the wisdom, insight, and perspective provided by a good research team becomes the crucial factor.

Barbeau reviews the status of twenty years of usage of L-DOPA in the treatment of Parkinson's disease (3). He pays tribute to basic work that paved the way for the clinical trials, giving much credit to the pioneers, Carlsson and his associates. Between 1961 and 1967, L-DOPA was first tried to reverse akinesia and rigidity at relatively low doses for short periods, but the results were not convincing. Following the demonstration by Cotzias in 1967 of the relative safety and marked efficacy of much higher doses of L-DOPA given in a stepwise fashion, the drug became established for specific treatment of the disease. However, peripheral side effects, mainly vomiting and cardiac arrhythmias, were troublesome and limited its usage. The combination of a peripheral DOPA decarboxylase inhibitor with L-DOPA permitted the usage of lower doses of L-DOPA and greatly reduced these bothersome effects. Based on longitudinal studies on 80 patients for 13 years, Barbeau believes that the drug treatment has improved not only the quality of life for the patients but also life expectancy. The therapy does not prolong life directly but rather forestalls deaths due to complications of the sedentary state. Improvement in the extrapyramidal signs and symptoms is most marked the first 7–8 years, but eventually most patients develop abnormal involuntary movements and with time the dyskinesia becomes more severe. Anticholinergic agents are of some benefit, but new and better agents are still needed for the treatment of Parkinsonism.

DRUG TOXICOLOGY

Haber & Pfitzer edit the proceedings of a workshop, "Immunological Aspects of Toxicology," sponsored by the Pharmaceutical Manufacturers Association Foundation (4). The object of the workshop was to examine the

state of the art in immunology as it might be relevant to toxicology. The need for such a workshop was clearly evinced by the survey provided by Norbury on the methods currently used in industry for evaluating immunotoxic effects. The battery of tests described with little critique of their predictability and usefulness reflects a largely empirical approach. To lend assurance that a bridge might be built between immunology and toxicology, practicing toxicologists from the pharmaceutical industry were given the responsibility of capturing the essence of the presentations and discussions of the participants and providing perspective on the degree of applicability of the topics covered.

Many of the papers reflect highly scholarly and educational essays on immunology, but the practical implications of the concepts are not always in evidence. Fortunately, the rapporteurs in many instances provide instant realism. Radioimmunoassay is one area of immunology now being applied extensively for drug disposition studies by pharmacologists and toxicologists and the principles are expertly covered by Spector. The use of antibodies as drugs has become a reality; both Haber and Butler discuss the utilization of antibodies to reverse drug and endogenous hormone effects. A toxicologic application of antibody would involve the drug antibody as a scavenger in instances of overdosage. Until recently, antibodies were available only in limited quantities as complex proteins that were immunogenic when injected into a heterologous species. The problems have been largely overcome by using cell culture methods and monoclonal reagents to produce almost unlimited supplies of hybridomal antibodies. The major breakthrough occurred by fusing single antibody-secreting cells with plasma cytoma cell lines to yield a permanent hybrid cell line. The hybridomas retain the ability to produce antibodies that are identical and can be mass cultivated. The advantages and disadvantages of monoclonal antibodies are summarized by Davis.

The topology of antibody combining sites is described by Kabat and the future applicability of these concepts and techniques for the design of drugs that fit specific receptor sites is forecasted by the rapporteurs. However, they appear unduly pessimistic in stating that the information being obtained is "unquestionably far removed from toxicologic research," when even now computer graphic techniques are being applied to tailor new drugs. With the prestigious ability of the computer for storing facts, rapid calculation, and creating visual molecular models, antibodies can be utilized as models for receptors. The drug-receptor interactions can be studied on the screen by scrutinizing in detail the optimal fit of a compound to a receptor, and a potential drug can then be designed before going into the laboratory. Other forms of the interaction involving drugs as haptens can lead to information about their allergenic properties (Parker). Perhaps a little further down the pike for eventual toxicologic application are the technologic

advances that have been made in molecular biology and genetics using recombinant DNA, hybridoma, lymphoid, and bone marrow chimera methodology for assessing mechanisms of immunologic responsiveness; these may have an impact on embryogenesis and neoplastic transformation. Also, some enlightenment may occur in the foreseeable future with respect to the modes by which drugs may intervene in the immune system. Fringe benefits can be expected from the knowledge gained on studies of the surface receptors and secretory products of single clones of T cells. Despite the rapid advances being made in immunology and the likelihood of rapidly changing technology in the field, the volume should enjoy a good shelf life because of the emphasis accorded to fundamental principles by the academicians and the insight provided by the practitioners to application.

Clinical Toxicology of Drugs: Principles and Practice is an edited text by Skoutakis on the toxicology of certain drugs that are more commonly seen in the emergency room (5). The information is mostly there but not always the perspective. However, the volume is far more than a clipped recital of package inserts of the toxicology of the drugs. Although the authors do not have a primary role in the management process, they are able to convey some degree of familiarity and expertise to the subject matter by virtue of their specialized interest in drugs and the fact that they are often on the scene. However, there are some inconsistencies in the discussion of the various drugs. The chapters on salicylates, acetaminophen, iron, and digoxin appear to be some of the better ones.

One of the most unbalanced and imprecise chapters is on narcotic analgesics. Much space is wasted on providing the structures of phenylpiperidine drugs that have not been major problems and are not even available now licitly or illicitly. Nalorphine is also no longer on the market, but it and levallorphan were and still are useful antidotes for treating narcotic agonist overdosage. Hypothermia is not an endocrinologic effect of the narcotics and although respiratory depression is by far the most important consideration in acute overdosage, it receives little more treatment than some secondary effects that may not even be drug-related (hepatitis, ulceration, urinary tract infection, and so on). The fact that seizure-like activity can be observed on the electroencephalogram does not necessarily mean that convulsions will be observed clinically; it may be true for meperidine and dipropoxyphene but would be rare indeed for heroin or morphine. I am not aware that narcotic overdosage is a common cause of death among adult patients; even among pediatric patients it is a relatively rare event. There is little pharmacologic rationale for using phenobarbital, chlorpromazine, chloral hydrate, or diazepam for treatment of narcotic abstinence in the infant; this is well-substantiated by the more carefully designed studies.

Despite these criticisms, on balance, I believe the authors have provided

a valuable toxicologic text. The most useful feature is the comprehensive up-to-date references provided at the end of each chapter, and although the treatment of the subject matter may not always be as authoritative as desired, it is usually informative and relatively free of major glaring errors.

A computer system for chemical and toxicological data available to researchers in academia, government, and industry is described by Milne and associates (6). The Chemical Informative System (CIS) was developed jointly by a number of government agencies and has important applications to problems of chemical pollution. With continuing reports of chemical spills, explosions, and illegal dumping of toxic wastes, ready access to reliable and relevant information from a mass of data becomes essential. CIS can be utilized to obtain physical, chemical, toxicologic, and regulatory information about chemical substances. Some interesting applications of CIS by EPA's emergency response team during environmental emergencies are described. Even greater utility of CIS is predicted for the future as more databases are added to CIS and as additional links are established between CIS and commercial bibliographic systems.

DRUG DEPENDENCE

Research monograph series 41, published by the National Institute on Drug Abuse, has finally appeared after considerable delay because of governmental cutbacks. The much-awaited volume edited by Harris contains the Proceedings of the 43rd Annual Meeting of the Committee on Problems of Drug Dependence (7). Papers of interest to pharmacologists include a touching tribute by Jaffe to Abe Wikler, one of the giants of opiate research. A method of differentiation of the opiate receptor type by producing selective tolerance with different opiate agonists is described by Herz. Several papers dealing with various aspects of buprenorphine action are included. Jasinski reports that buprenorphine 20 mg orally or 2 mg sublingually would be suitable as daily maintenance doses in treating narcotic addiction. Sublingual buprenorphine was found to be 15 times more potent than intramuscular morphine by Wallerstein. Tolerance and physical dependence potential of buprenorphine in monkeys were judged to be weak by Yanagita. Mello indicates that buprenorphine may be more effective than methadone in suppressing heroin self-administration and Bhargava reports that tolerance development to buprenorphine is reduced by hypothalamic peptides MIF and its cyclo (Leu-Gly) analog.

DRUGS IN THE FUTURE

Malick & Bell edit a timely monograph on the endorphins (8). The use of "endorphin" as the generic name for peptides with opiate-like activity has

become confusing as there is now evidence that there may be endogenous substances with opiate-like activity that are not peptides, and with respect to the peptides, three classes have now been identified that have their own distinct neuronal and biosynthetic pathways. For clarity, it appears more convenient to use "opiopeptin" as the generic term for the enkephalinergic, endorphinergic, and dynorphinergic peptides.

The introductory chapter by Simon provides the background for the discovery of the opioid ligands. He incorrectly gives credit to Goldstein instead of Loh for identifying cerebroside sulfate in brain as the stereospecific binding substance for alkaloidal opiates. I would also quibble that the discovery of opiate binding sites in the brain did not trigger but rather accelerated the search for their native ligand. Smyth provides an interesting account on the biosynthesis of the opiopeptins and Dewey, a comprehensive survey of the structure-activity relationships of several hundred enkephalin derivatives. Lord, Rance, & Smith contribute a useful chapter on assay procedures, and Rossier & Bloom authoritatively describe the distribution of the enkephalins and the endorphins. Regrettably, not much was known about the dynorphins when the book went to press. By now, the precursor of dynorphin is known and it also contains α-neoendorphin and leu-enkephalin fragments. The most interesting chapter is by Cox & Baizman, who discuss the possible physiological functions of the opiopeptins. The presentation is stimulating, thorough, and critical and over 500 citations are included. Two other chapters on behavioral pharmacology (Malick & Bell) and clinical aspects (Terenius) complete the volume. Even though the book is already dated, it is a good starting point and can be recommended for both specialists and generalists.

DRUG MARKETING

Prescriptions for Death: The Drugging of the Third World by Silvermann, Lee, & Lydecker is neither as gory as its title suggests nor as ominous as portended by the publisher's descriptive summary on the book cover (9). The finger is pointed for the fourth time at the favorite target of the authors, the pharmaceutical industry. In exposing their feelings, the authors make some attempts to be fair although industry might believe otherwise. No sweeping denunciations and general condemnations are made against industry, but specific examples are documented of misrepresentation of drugs by certain irresponsible firms that make exaggerated claims or omit possible serious hazards. Documented instances are cited also to reveal that the standards for the marketing of certain drugs by companies in some deprived countries are considerably lower than those in western countries. In some examples given, the standards were inexcusably loose, but in many instances the issues are clouded. The local government and physicians were equally

culpable. If the government does not care and if physicians are willing to prescribe medication for a fee, it is difficult to fault a company for lack of altruism and a reluctance to take the lead and show how things should be done. Also, stability of a government becomes a serious consideration for rapid recouping of an investment. Morals and ethics are important but when the issues are weighing benefits and risks in a gray zone, judgments are bound to be colored towards the self-serving side. Even among the countries of the industrialized world, standards vary. The use of aminopyrine has long been banned in the United States and Great Britain, but in Switzerland it was banned only very recently, in the face of considerable resistance.

It can also be argued that overly restrictive requirements can be counterproductive. The life-saving drugs cimetidine and albuterol were available in Great Britain long before they were in the United States. When subjects suffering from bleeding ulcers and severe asthma are denied medication because of bureaucratic overconservatism, some measures must be taken to give more consideration to loss of medical benefit over potential risk factors. The loss of medical benefit generally means also loss of social benefit and economic benefit. I believe the pharmaceutical companies have not done an effective selling job and would do well to support more cost analysis studies on these facets.

The authors end on a positive note. They provide an appendix giving the code of pharmaceutical marketing practices by the International Federation of Pharmaceutical Manufacturers Association. They also point out that a new generation of industry leaders are moving more in the direction of social responsibility, and end with the quote of one company leader, "You can tell the truth and still make a decent, reasonable profit."

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