Book Reviews

Neurotransmitters, Drugs, and Brain Function. Edited by R. A. Webster. John-Wiley & Sons, Ltd., Chichester, U.K. 2001. vi + 534 pp. 17 × 25 cm. ISBN 0-47197819-1. $145.00.

This is an unusual book. Edited by Roy Webster of the Department of Pharmacology at University College London, most of the 23 chapters are authored either by himself or by one of five colleagues in the department. Two chapters have dual authorship. Half of the book is devoted to basic aspects of the function of neurotransmitters and their role in synaptic transmission, with the latter half focusing on neurotransmitters in the context of behavior, disease states, and drug action. The contents are based on lectures given during a neuropsychopharmacology course for final year undergraduate students of pharmacology, physiology, psychology, and neuroscience. The authors deliberately set out to make a readable rather than a merely factual text, and references have been highly selected and minimized in number. There is a good sprinkling of citations to the 2000 literature, but there is no author index. The subject index is adequate.

One of the potential anxieties about such an approach to authorship is that an idiosyncratic and didactic view of the subject matter may be presented. Although the British authorship means that many of the examples used for disease prevalence, treatment modalities, patterns of drug introductions, and (ab)use, inter alia, represent the U.K. situation, such fears are unfounded here. The book is clearly written and is without bias. It is full of useful illustrations, much wisdom, and (surprisingly for this type of volume) replete with chemical structures. The book admirably fulfills its stated aim of appealing to students and postgraduates in the neurosciences, but medical students will find it hard-going and too advanced for their needs. On the other hand, specialists in the fields covered will find it lacking, particularly in the sections focusing on disease and drug action, which are of necessity limited in scope. Nevertheless, it should find a place on their bookshelves, if only to alert them to research areas other than their own. The first half of the book on basic aspects of neurotransmission is a delight and is a must for medicinal chemists who want to maintain or improve their knowledge of neuropharmacology.

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Organic-Chemical Drugs and Their Synonyms. 8th Edition. Edited by Martin Negwehr and Hans-Georg Scharnow. Wiley-VCH, Weinheim, Federal Republic of Germany. 2001. xvii + 4680 pp (in six volumes). 17 × 25 cm. ISBN 3-529-30247-6. $1435.00.

This "extensively enlarged" edition of "an international survey" lists over 16 000 chemically uniform drugs and approximately 130 000 nonproprietary names, brand names, and numeric or alphanumeric code designations. The work includes listings known to the editors up to March 2001, obsolete drugs, and the so-called "drugs of the future". Also included are drugs that are macromolecular or that have no definite molecular formula. The set comprises four volumes of drug listings plus two index volumes.

The drugs are listed in the first four volumes according to their increasing molecular formula. The somewhat limited spectrum of information for each drug includes and is arranged as follows: (1) consecutive number; (2) molecular formula; (3) Chemical Abstracts Service (CAS) registry number; (4) structural formula; (5) systematic name; (6) synonyms; (7) terse statement of pharmacological characterization of the drug and/or its therapeutic use. There are no literature citations in the entire set.

Volume 5 contains the alphabetical synonym index. Volume 6 contains the organic group index, group index (reference part), and CAS number index.

This massive six-volume compendium is a convenient source of information for names, synonyms, and chemical structures of a huge population of drugs (in the broadest definition of that term) from all parts of the world. The editors concede that the pharmacological characterization sections of the listings are not complete, and this section of each monograph should not be considered to be a criterion upon which the reader would infer the full pharmacologic spectrum and utility of a chemical entity listed. Indeed, the absence of any literature references compromises the dependability of the "biology" statements.

The price of this set of books will discourage its purchase by most individuals, but it deserves a prominent place in industrial, academic, and governmental libraries. Chemists, pharmacologists, clinicians, and individuals involved in marketing and in patent matters will find these volumes a useful source of rapidly and easily accessible information.

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Anticancer Agents, Frontiers in Cancer Chemotherapy. ACS Symposium Series 796. Edited by Iwao Ojima, Gregory D. Vite, and Karl-Heinz Altman. American Chemical Society, Washington, DC. 2001. xii + 364 pp. 15.5 × 23.5 cm. ISBN 0-8412-3745-A. $140.00.

This volume is based on a symposium cosponsored by the Divisions of Medicinal Chemistry and Organic

Chemistry at the 219th American Chemical Society National Meeting, March 26−30, 2000, San Francisco, CA. Although this publication accurately reflects the general theme of the symposium, several of the papers presented at the meeting are not included. In some cases, their general content is covered by chapters provided by other individuals in the same organization or in collaborating research groups. In addition, a few chapters have been added that were not included in the original symposium.

The book is divided into 19 chapters. The first two are basically reviews describing approaches to anticancer agents as carried out by the National Cancer Institute and George Pettit's plant natural products group at Arizona State University. Chapter 1, from the NCI, is seriously flawed because it contains *no* chemical structures. This is particularly troublesome because most of the lead compounds, such as flavopiridol and the paullones, are quite new and do not appear elsewhere in the volume. Fortunately, except for this chapter, all the others contain adequate structural representations. Chapters 3−10 are devoted to classes of compounds that are believed to exert their anticancer activity through interaction with tubulin and microtubules: taxoids (paclitaxel), epothilones, sarcodictyins, cryptophycins, and related structures. Chapters 11−13 describe farnesyl transferase inhibitors (BMS-214662 and Sch-66336), which are currently in clinical trial. The title of Chapter 13 has an amusing, faintly erotic error because it claims to describe *fornesyl* transferase inhibitors. Chapters 14 and 15 are focused on tyrosine kinase inhibitors (PKI166 and STI571, the latter recently marketed as Gleevec by Novartis). The remaining chapters (16−19) deal with approaches that are not as far along in providing clinical candidates: metalloproteinase inhibitors, VEGF inhibitors (antiangiogeneisis), antitumor vaccines, and antibody targeting of cytotoxic agents. The volume contains a useful subject index (22 pages), and the references that appear at the end of each chapter are current (several citations from year 2000).

Efforts aimed at the discovery of new anticancer agents have shifted in recent years from an essentially empirical approach based on the selective toxicity of agents against tumor cells in culture or in whole animals to a more rational approach in which a molecular target, such as an enzyme, is first identified. An agent selected by screening against the molecular target is then assumed to exert its anticancer activity by this mechanism. However, when the compound is found to be cytotoxic against tumor cells in culture at concentrations much lower (orders of magnitude) than those effective against the isolated molecular target, one needs to question the assumed mechanism of action. Many of the agents identified as acting on tubulin seem to fall into this class. For example, in Chapter 10 the authors state the following:

"Although the molecular target and mechanism of cryptophycin is believed to be cellular tublin and the inhibition of microtubule polymerization, the limited sensitivity of several existing in vitro tubulin or microtubule polymerization assays was, in general, not sufficient for structure−activity purposes (with 50% inhibition concentrations occurring at low- to mid-*micromolar* range for most cryptophycin analogs). In contrast, cryptophycins exhibited very potent cytotoxicity toward most of the human malignant carcinoma cell lines tested in culture. In the 72 h MTT cell-based assays the IC_{50}s for crytophycin 1 and 52, for example, were in the range of 20−100 *picomolar* against several human tumor cell lines."

Some authors have explained the potent cytotoxic activity (nanomolar) of paclitaxel and epothilone analogues compared with their relatively low activity (micromolar) in tubulin assays by suggesting accumulation of high concentrations of the drugs at the active site within cells. However, studies with mutated cells that overexpress tubulin or P-glycoprotein show unexplained variations in tubulin binding and cytotoxicity within these classes of compounds.

In any drug discovery effort, it is intellectually satisfying to take an approach based on an isolated molecular target where we think we understand the mechanisms involved. However, we should not assume that what is discovered by this methodology in vitro will necessarily apply in much more complicated in vivo systems. In some cases, the mechanism-based approach may lead to useful agents, even when the original hypothesis is not correct. This was the case with etoposide, which was assumed to act on tubulin but was later found to exert its anticancer effect through inhibition of topoisomerase. More recently, studies with flavopiridol, which inhibits cyclin-dependent kinases in vitro and whose X-ray crystal structure indicates that it is bound in the active site of CDK2, suggest that other mechanisms may be involved in its promising anticancer activity.

This book gives a current picture of the anticancer drug discovery process in selected areas and should thus be of value to those working in the field. However, some important approaches are not covered, and the very rapid pace of anticancer research makes any publication of this sort somewhat dated

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