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Book Review

Drug Stereochemistry. Analytical Methods and Pharmacology
Second edition, revised and expanded
(Clinical Pharmacology Series/18)
Edited by Irving W. Wainer
Published 1993 Marcel Dekker Inc., New York
432 pages
ISBN 0 8247 8819 2 $165.00

The fact that Drug Stereochemistry, edited by Irving Wainer, is here appearing in a second edition only four years after the appearance of the first edition is illustrative of the rapid advances being made in this field. Both the title of the book and the subtitle may be misleading. First, the volume is concerned almost entirely with the problems of chiral drug molecules, rather than discussions on the stereochemistry of the individual drug, and secondly, there is in fact little, if any, pharmacology included. The methodological chapters relate mainly to separation science—which includes methods of preparing pure enantiomers as well as analytical methods—while the experimental science describes the differences in behaviour of enantiomers in biological systems. Nevertheless, this edition represents a well-integrated, readable and compact collection of chapters on the synthetic, analytical and pharmacokinetic implications of chirality.

The opening chapter on the early history of stereochemistry (again strictly speaking, the early history of optical isomerism) reminds us that the concept of drugs existing as mirror image molecules is not new, and it is only the more recent availability of synthetic and separation methods that has given a new impetus to the consideration of the implications of dosing drugs as racemates. Indeed, it is faintly shocking to realise that dosing with a mixture of two drugs of different (but unattributed) activities was so readily accepted, simply because the tools to solve the problem were not available. Not everyone was guilty of this complacency—at least one major pharmaceutical company claims never to have marketed a racemate, taking the view that the preparation of the pure, active, characterized entity was the target molecule for the development chemist, and that obtaining the correct isomer was part of the synthetic problem. Sometimes, of course, the lack of awareness of optical isometry can pose considerable puzzles and I can give two examples in my own experience. One concerned a radioimmunoassay that consistently gave results twice that of an HPLC assay despite both methods being validated by all the usual methods; the natural reaction was to assume the radioimmunoassay method lacked specificity (despite all indications to the contrary). With hindsight, it looks as if this could be put down to drugs in the biological fluid being richer in the immunoreactive species than the standard that was used in the radioimmunoassay. Paradoxically it was the immunoassay that had the high specificity; it was the use of an inappropriate standard that was giving the wrong answer, whereas the non-chiral HPLC method had no such complication.

The second example concerned the isolation of two drug metabolites in urine as glucuronide conjugates by HPLC. The two compounds were undoubtedly different, having distinctly different retention times on HPLC (non-chiral columns). Hydrolysis of each produced an identical aglycone as measured by all the usual methods of GC, mass spectrometry and NMR. Optical isometry was considered, but did not seem able to explain the initial HPLC separation of the conjugates. The truth was only revealed on the realization that β-glucuronic acid itself is asymmetric and the two conjugates were therefore different—the classical method of separating optical isomers by reaction with an optically pure acid to obtain separable esters.

Similar examples can be found in the literature. For example, the pharmacokinetic literature contains many analyses demonstrating long terminal half-lives attributed to "deep" compartments; it can now be seen that the differing half-lives can often be attributed to enantiomeric forms of drugs administered as racemates, for example warfarin.

The value of this book is that it re-emphasizes the existence of enantiomers. Much work in the field over the last decade has concentrated on analysis and synthesis, but it now appears that the problems in both those areas are now clearly recognized and future trends will be in improving the solutions, rather than new insights.

It was the chapters on the implications of stereochemistry in biological systems that I found the most interesting. These chapters also concentrated to a large part on differences in enantiomers, but for the future, when drug products contain only pure compounds and not the 50% impurity, as famously described by Ariens, it will be the true stereochemistry in the study of drug transport and activity that will be the focus of attention, rather than the incidental matter of optical isomerism.

There were two aspects of editorial control that could be improved. There is an excellent early chapter on nomenclature. This would seem to be an opportunity to standardize on a consistent style for the rest of the book; however, each author then seems to use the style that suits him, even mixing styles in the same paragraph. I appreciate that in many cases where the chapters are reviewing the literature, the authors may feel it necessary to use the style of the referred work, but unless this sort of book tries to conform to agreed standards, the literature will continue to confuse. The second editorial lapse is to allow some chapters to get away with quoting references without giving full titles of the papers—including two chapters from the editor himself!

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Book Review

Drug Resistance in Oncology
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672 pages
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Drug resistance in cancer chemotherapy is a big problem and new approaches are desperately needed. Although the majority of children can now be cured by multi-modality treatment, which includes chemotherapy, the outlook for adult cancer patients is poor. Best estimates are that some 20% of patients are potentially curable with currently available chemotherapy and achieved cure rates are lower than this. So why doesn't conventional cancer chemotherapy work? The answer is inherent and acquired drug resistance and the collection of articles edited by Dr Teicher looks at the problem from a number of perspectives.

The book is sub-divided into five sections covering physiological, biological, biochemical, hormones/growth factors/onco-

genes, and clinical aspects. Each section contains chapters on specific aspects which, in general, provide a comprehensive overview of the particular field. The first section on the "physiology" of drug resistance is a refreshingly new approach. The specific aspects covered include angiogenesis, tumour blood flow, pH, oxygenation and the extracellular matrix. In addition, the use of NMR to predict drug resistance is covered. These various areas have largely been the preserve of radiation biologists and it is encouraging to see so much space devoted to them in a volume on drug resistance. That said, more examples of systematic studies probing the potential role of tumour physiology in resistance to chemotherapy would have been appropriate. In fact, drug resistance really only gets a passing mention in this section reflecting perhaps the potential rather than the proven role of tumour physiology.

The section on biological resistance brings the reader into the mainstream of drug resistance studies. In particular, the concept of tumour heterogeneity and the evolution of drug resistant clones is dealt with well in the first two chapters in this section. The subject of therapeutic resistance in leukaemias is confined to data on murine P388 tumours, but the chapter is a useful compendium of results in this tumour model. The chapter by Teicher covers in detail her work on in-vivo drug resistance using EMT-6 tumour models, although irritatingly the page heading is in-vitro resistance. This chapter makes the important point that tumour-host interactions through, for example, growth factors can have a major impact on the outcome of in-vivo chemotherapy and that a greater awareness of the problem, and the mechanisms underlying the effect, is needed.

Biochemical resistance is the section of the book where most experimental and clinical oncologists will feel at home. The "industry standards", i.e. glutathione, glutathione-*S*-transferases, metallothioneins, *p*-glycoprotein and topoisomerases as mediators of drug resistance are reviewed in a concise and authoritative manner. The chapter on tumour cell drug metabolism by Chapman and Powis is particularly interesting, although the jury is still out on the clinical relevance of this area. In addition, the chapter by Sladek on oxazaphosphorenes is an excellent review of what is known in one specific area which nevertheless relates to agents which are amongst the most widely used and effective drugs in cancer medicine. Although any book cannot be completely comprehensive, the omission of antimetabolite resistance is a weakness of this section, particularly as drug mechanisms in this area are amongst the most thoroughly defined. Also, the failure to mention the DNA repair protein O^6-methylguanine methyl transferase as a resistance mechanism may also be seen by some as an omission, as again this is a particularly well-defined area.

The final major section of the book covers hormones, growth factors and oncogenes in relation to drug resistance. The chapter on anti-oestrogen resistance is highly readable, comprehensive and an excellent review of this interesting and clinically important area. The other chapters in this section are less clearly related to clinical drug resistance and once again, in some cases, only a passing reference is made to drug resistance. The final and only chapter in the section on clinical aspects of drug resistance is a concise overview of the incidence of inherent and acquired clinical drug resistance in various types of cancer. With the exception of the haematological malignancies, this overview makes predictably depressing reading. However, as Ayash and colleagues conclude, clinical trials specifically designed to study drug resistance are few. With the increasing use of molecular biological techniques, studies on the importance of defined molecular mechanisms of drug resistance in the clinical setting will be examined more frequently, the much cited work of Chan et al being one such example. Once molecular mechanisms are defined and understood, the development of drugs and protocols to circumvent drug resistance becomes feasible. In informing the reader and stimulating discussion this book should play an important role in achieving this goal.

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Book Review

Man & Mouse. Animals in Medical Research
Second Edition
William Paton
Published 1993 Oxford University Press, Oxford
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During the course of reading this book I received (by fax) a copy of a press release issued by an anti-vivisectionist group which documented the animal studies carried out by myself and colleagues in the same institution. The tenor of the report was that these studies were a waste of time and animals, and of no relevance to the human situation. My immediate reaction to the report was one of annoyance, that the reasons for performing the work were not properly understood, and that a false picture was being presented to the public.

This problem of communicating the scientific process in the biomedical field to the general public is a major theme in Professor Paton's excellent book, and one aim of the author is to present some insights into this for the general public. In this Professor Paton would appear to succeed very well, although it is for non-scientists to give a definitive comment on this.

Whilst discussion of the scientific process is one major thread in this book, there are many others which combine to present a comprehensive account of the current debate on animal use in biomedical work. There are well-constructed and clearly-written chapters on the definitions of "animal" and "experiment", the ethical issues involved, the benefits that have accrued from animal experiments, pain and suffering, and the alternatives, with relevant examples where appropriate.

This second edition incorporates discussion of the new 1986 Act (UK) and a new chapter on the use of animals and alternatives in toxicity testing, an area of particular interest to me. In this chapter, Professor Paton outlines clearly the many pressures (including financial) to reduce the number of animals used in toxicity testing, and the crucial role that the chemical industry has already played in changing current practice. Set against this, in the context of drug discovery, Professor Paton argues that drug discovery is now suffering from lack of animal experimentation. This latter argument was new to me, but must be an important element in the debate on future animal use in the biomedical sciences.

This book is almost unique in presenting an argument for animal use that is accessible to scientists and lay readers alike. It should be read widely by those embarking on a career in biomedical sciences to inform them of the issues involved in animal testing; I am sure that established workers would also find this book informative. I also believe that the uncommitted lay reader would be convinced of the arguments for animal experimentation presented in this book, but I fear that they will not convince the committed anti-vivisectionist—but then nothing will do that!

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