Book Reviews

Tamoxifen: Molecular Basis of use in Cancer Treatment and Prevention

H Wiseman, John Wiley: Chichester, 1994, 209 pp. £29.95.
ISBN 0 471 94316 9.

This book provides a timely overview of this important anti-cancer drug. An introductory chapter includes useful synopses of each of the following chapters. The next four chapters deal with aspects of the chemistry, pharmacology, metabolism and clinical use of tamoxifen and its actions on the oestrogen receptor. Many of these individual topics have been extensively reviewed elsewhere, but it is useful to have them all brought together in one volume. Where appropriate, the author has often prefaced discussion of each topic with a brief general introduction to the biological background. For example the chapter on Metabolism and Toxicology (Chapter 3) begins with a useful summary of the CYP nomenclature used for classifying cytochrome P450 enzymes. The author covers most of the major areas of interest and current controversy. The references at the end of each chapter though not comprehensive, are sufficient to allow the reader to gain entry into the literature of a particular field. These are commendably up to date, some predating publication of the book by only a month or two. An example (p. 27) is a reference to a recent hypothesis that proposes how tamoxifen produces liver DNA adducts.

More than half the book is concerned with apparently oestrogen-independent actions of tamoxifen, the later chapters reflecting the author's personal research interests. This is nevertheless welcome, as it provides a different emphasis from most reviews on this drug. The first of these later chapters describes how tamoxifen modulates certain oncogenes and growth factors. Again there is a simple introduction to oncogenes and the relevant growth factor accompanied by clear diagrams illustrating their functions. This chapter also includes a discussion of mechanisms of resistance. Inhibition of enzymes is the main subject of the following chapter. These include enzymes in cell signalling pathways, such as protein kinase C (PKC), and calmodulin-dependent enzymes. There follows a discussion of the role of the anti-oestrogen binding site (AEBS). A minor criticism here is that the discussion of the structural requirements for ligand binding refers to the work of Van den Koedijk *et al.* on the rat AEBS. Their later, potentially more relevant, study on the human AEBS shows a different structure-activity relationship.

A discussion of the effect of tamoxifen and 4-hydroxy-tamoxifen on cholesterol synthesis forms a useful prelude to a following chapter on the antioxidant action of tamoxifen. The first 17 pages of this chapter are a general description of cell membrane structure and function. However, this lengthy introduction is a necessary background to the discussion that follows. In this, the basis thesis is that tamoxifen protects the cell membrane against lipid peroxidation by decreasing membrane fluidity. A variety of beneficial consequences proposed to result from this action include inhibition of metastasis, reversal of the multidrug resistance phenotype and cardio-protection.

The penultimate chapter describes the actions of tamoxifen on the yeast *Saccharomyces cerevisiae*. Analogies with mammalian control mechanisms justify the use of the yeast model. These include similarities in Ras- and PKC-mediated pathways, and in functions of calmodulin. Moreover, the model may help to validate tamoxifen as a candidate drug for use in fungal infections caused by *Candida*.

The brief concluding chapter compares tamoxifen with some of its major competitors, to which the book also refers

earlier. This last chapter also mentions an approach to the design of a compound, structurally similar to tamoxifen, which could treat prostatic cancer.

In attempting to cover all aspects of tamoxifen's actions, the treatment of some topics has been at times uncritical of interpretations found in the literature. Occasionally this has led to factual errors and contradictory statements. For example, it is probably not true that ovarian cancer cells can metabolise tamoxifen to 4-hydroxytamoxifen (p. 22). Induction of TGF β (p. 63) is a more likely basis for the anti-carcinogenic effect of tamoxifen than suppression of hydrogen peroxide production by neutrophils (p. 147). 4-Hydroxytamoxifen is a potent inhibitor of the growth of MCF-7 cells (p. 22). This is incompatible with the later statement (p. 165) that it does not inhibit yeast cell growth 'probably because it is a polar compound and is unable to enter the yeast cell'. Of the tamoxifen analogues toremifene and droloxifen (p. 27), only the latter has a shorter half-life than the parent drug. Moreover, this is not necessarily advantageous as the literature claims (p. 197). Compared with tamoxifen, it will lead to a lower exposure of the drug for a given dose. However, these are minor criticisms. Generally, the broad coverage is beneficial, serving to stimulate though this suggests fruitful avenues for further research.

This useful and highly readable volume should be on the bookshelves for everyone engaging in research on tamoxifen. It also contains much to interest the general reader. Many research areas covered as fast moving and facts and interpretations quickly date. I hope, therefore, that the author may in due course find time to produce a revised version.

M Jarman

Drug and Hormonal Resistance in Breast Cancer: Cellular and Molecular Mechanisms

Edited by RB Dickson and ME Lippman, Ellis Horwood: Hemel Hempstead, 1995, 440 pp. £112.50. ISBN 0-13-224858-1

This is generally an excellent book giving a thorough treatment to an area of major clinical importance. The editors themselves are well known as excellent researchers in this field but they did not in fact contribute substantially to the writing. They have, however, been able to attract a first class array of writers to cover the subject comprehensively.

The book is divided into four parts with parts 2 and 3 making up about two-thirds of the book:

1. Clinical Resistance
2. Antihormonal Drugs: mechanism of action and resistance
3. Chemotherapeutic Drugs: mechanisms of resistance
4. Chemohormonal Interactions.

In Part 1 Tripathy and Henderson contribute an excellent chapter discussing the general approach for deriving mechanistic data from clinical trials while emphasising the danger of simple extrapolation and extrapolation. A chapter by Gusterson on the changing role of the pathologist in predicting tumour behaviour and response to treatment might not be expected in this book but nonetheless contains worthwhile data.

Throughout the clinical resistance section and Part 2 there is substantial repetition. For example, the data on the importance of c-erb-2 as an indicative marker of response/resistance to adjuvant chemotherapy must be mentioned in two-thirds of the chapters. It is likely, however, that the

majority of readers will be looking at individual chapters or using this as a reference text, thus repetition is inevitable to ensure comprehensiveness in the individual chapters. The chapter by Petros and Peters on dose intensity to overcome drug resistance deals with resistance more by implication than by direct reference to resistance data, and avoids dealing with the controversies. The chapters on molecular mechanisms of anti-oestrogen resistance and tamoxifen metabolism from the groups Jordon and Osborne unfortunately lack the more recent data on non-isomerisable tamoxifen derivatives, which is an important component of the current interpretation of data from this field. This illustrates a more general point: throughout there are almost no references beyond 1992. The two chapters on progestins and anti-progestins have few data on resistance to these compounds, but they provide a useful summary of data from *in vitro* models.

Part 3, dealing with chemotherapeutic drugs, has substantial overlap throughout some of the chapters on multi-drug resistance and the importance of MDR1. The chapter by Goldstein is in itself quite exhaustive, taking this area from the molecular through to importance in clinical trials. It goes outside of the breast cancer area dealing substantially with areas where MDR1 involvement is apparently more important. Further chapters on non-MDR1-associated resistance include the importance of extra chromosomal DNA, which is somewhat speculative in contrast to the chapter on fluoropyrimidine chemotherapy which deals with quite well-known data. The chapter by Harris and Carmichael gives a comprehensive discussion specifically on topoisomerase inhibitors, as well as reflecting on the relevance of multidrug resistance mechanisms to them.

Weisenthal provides a valuable discussion for those interested in *in vitro* tests to predict breast cancer sensitivity to these agents. This particular chapter is unusual in this book in that the tables are poorly annotated and reduced in value as a result of that.

The last two chapters on approaches to reversing multi-drug resistance could have been excluded since they are highly repetitive of other chapters in this section.

The three chapters on chemohormonal interactions deal with separate issues: (i) the relationship between cell kinetics and hormonal receptors and their utility for treatment selection; (ii) hormonal synchronisation before chemotherapy, reflecting that this has proven to be uniformly without benefit; (iii) an extensive laboratory-orientated discussion of the interactions of chemo- and hormonal therapy in cell culture. It would have been valuable either within the context of this last chapter or possibly by the inclusion of an extra chapter to have given a further discussion of the interaction of these drugs *in vivo*, particularly since the 'overview' analysis of 1992 of adjuvant treatments in breast cancer provided compelling indirect evidence on the additive effects of these two approaches in the adjuvant setting.

Overall I found it to be highly readable and valuable, and the wide interest of such a text was emphasised to me by the large number of people that picked up the book while I was carrying it with me over a period of some weeks. Many of them requested details in order that they could purchase it. I for one, will be guarding this book in my cabinet carefully since I am sure that it is one of those which will walk very easily.

M Dowsett

Non-Reproductive Actions of Sex Steroids

Edited by GR Bock and JA Goode, John Wiley & Sons: Chichester, 1995, 307 pp. £49.95, ISBN 0 471 95513 2.

CIBA FOUNDATION SYMPOSIUM 191:
NON-REPRODUCTIVE ACTIONS OF SEX STEROIDS

The reports of the Ciba Foundation Symposia always make interesting reading, dealing as they do with topics at the

leading edge of science or medicine, and bringing together leading investigators in the area. This meeting, held in August 1994, is no exception. It turns the spotlight away from the reproductive aspects of the sex steroids, which have justifiably attracted extensive exploration, and focuses it on the wider role that these hormones play in a variety of other physiological processes.

In the first paper, Miguel Beato reviews our knowledge of how steroid hormones modulate the expression of a variety of genes by binding to hormone-responsive elements of DNA or interacting with various transcription factors to influence signal transduction pathways. The interactions of hormone, receptor and the several other factors involved are complex, and an important mechanism may involve the hormone itself changing the chromatin structure. Similarly, the concept of antihormones occupying the receptor site, thereby preventing hormone action, may be only one of several possible mechanisms, and specific binding sites for antihormones may also exist.

Etienne-Emile Baulieu points out that non-genomic mechanisms of hormone action are also important. Effects of membrane interaction and changes in membrane structure have been noted, and the role of binding proteins influencing intracellular machinery is still unclear. There are several examples of progestagens influencing biochemical activity at the membrane and also modulating calcium entry into cells.

Bruce McEwen discusses neural effects of steroids. Apart from their well-known role in reproduction, they also affect pain perception, cognitive function and mood. Oestradiol induces choline acetyltransferase activity in the forebrain and reduces synapse density. The mechanism is unclear; only a few classical oestrogen receptors exist in pyramidal cells, although the oestrogen receptor may perhaps be atypical. Interestingly, hormone replacement therapy (HRT) has been reported to ameliorate the symptoms of Alzheimer's disease.

Michael Schumacher discusses the role of sex steroids in nerve repair. Progesterone is actively synthesised and metabolised in brain tissue, and the hormone or its metabolites may accelerate the repair of myelin sheaths after injury.

There is a lesser incidence of coronary heart disease in women than in men. It is likely that oestradiol is a major factor, the mechanism, in part, involving lipoprotein changes. Francis Bayard's paper points out that direct effects on the blood vessel wall should not be ruled out. The enzymes that synthesise and metabolise oestrogens are present on the vascular wall, and their effects on cytokines, growth factors and vasoregulatory molecules are probably involved in the pathogenesis of arteriosclerosis. Following this theme, Marie Foege presents data on transplant arteriosclerosis, which is a major clinical problem. Oestradiol profoundly influences the immune system and it is notable that women are more susceptible to autoimmune diseases than men are. Oestrogens enhance the differentiation and maturation of lymphocytes and diminish suppressor T-cell function. In transplant patients, HRT is an unfavourable factor. However, in an animal model, oestradiol inhibited myointimal hyperplasia and prevented entry of macrophages, which is probably the initiating factor. Thus, oestradiol has complex effects on the vascular system, still not well defined or understood.

Madge Vickers reports that coronary heart disease is the most common cause of death in post-menopausal women and that some protection is given by HRT. She describes a proposed epidemiological study of users of HRT in the UK and elsewhere in Europe, which would address many of the unanswered questions, including the effect of HRT on vascular disease. The problems with such a trial are considerable (e.g. changing fashions in dose, type of steroid, route of administration) but if the trial were postponed, no answer would ever be forthcoming.

Torbjorn Backstrom considers the effects of oestrogen on mood. Progestogens may increase depression, and progesterone and some of its metabolites can cause anaesthesia. Indeed, this observation has been used in clinical practice. Oestrogens can alter sensory perception, locomotory activity