Guide to Clinical Trials

B. Spilker, New York: Raven Press, 1991, 1156 pp. \$162.50.

This enormous single author book is written to explain the practical details of clinical trials. The 133 chapters cover the details of trial design, writing a protocol, aspects of statistics, the interpretation of response and efficacy data, how to publish results and the regulatory and managerial aspects of trials.

Within the chapters Dr Spilker tries to explain the basic principles of what is to be discussed or investigated and to give a flow diagram or table of how to go about getting the data, or analysing it. He writes clearly but the text is often rather tediously generalised so that, for example, in the discussion of trial size there is a brief resume of α and β errors, but little insight into how the trial size relates to the clinical importance of the question (whether, for example, the size of any difference needs to be quantified precisely). There is little insight into the importance of statistical methodology generally. Some of the chapters appear strangely out of place. There are for example 33 pages on preparing an article for publication and assessing the quality of a paper you have read. Much of this consists of pages of tables. There is a long series of chapters on the goals and strategies of marketing and drug development which may be of interest to pharmaceutical companies but seem somewhat beside the point for clinicians.

Almost everything and anything to do with trials is touched on in this book. That is both a strength and a weakness. I suppose that the professional group who would find it most valuable are the clinical co-ordinators of research in pharmaceutical companies, especially in the USA (there are concessions to regulatory authorities elsewhere in the world). I don't really recommend it for oncologists involved in trials since it is not detailed enough in certain key areas and contains much information and advice which is redundant for cancer trials.

R.L. Souhami

Introducing New Treatment for Cancer. Practical, Ethical and Legal Problems

Edited by C.J. Williams, Chichester: John Wiley & Sons, 1992, 492 pp. £24.95.

This book is long overdue. There can be few investigators involved in testing new cancer treatments who have not been concerned by at least some of the many difficult problems discussed. The international list of contributors include lawyers, ethicists, social scientists, statisticians, pharmacologists, editors of medical journals, physicians working for pharmaceutical companies, radiotherapists, medical oncologists and specialists in community care. The book is divided into five sections. Section 1 deals with legal (UK and international) and ethical aspects of clinical trials and with patients' attitudes to such therapy. In addition there are chapters on informed consent, research ethics committees and a summary of the Royal College of Physicians report on Research Involving Patients. Informed consent comes up again in Section 2 which discusses specific issues in trials of new cancer treatments including the question of whether patients in trials do better than those treated routinely. There are chapters on phase I studies, 'the uncertainty principle' design for randomised trials, randomisation before consent (Zelen) designs, interim analysis and experiments on the dying. Section 3 considers the pharmaceutical industry's role and economic issues. Section 4 discusses trials for pre-malignant lesions and chemoprevention trials and the final section concerns itself with reporting policies, overviews and the adoption of new treatments into clinical practice. Prior to each section the editor, Chris Williams, gives a very helpful outline of the areas to be discussed. Here he does not merely summarise the views expressed, but focuses the more impor-

tant elements as well as voicing personal views which may not always coincide with those of the chapter authors. This serves as a most refreshing highlight to the controversial aspects, particularly those surrounding informed consent. The story of the reaction of the late Dr Franz Ingelfinger (editor of the *New England Journal of Medicine*) on learning that he had oesophageal cancer illustrates beautifully the important difference between what the cancer patient may want in terms of information and what others believe he should have. For this experienced physician his illness was much easier to cope with when he found a more traditionally paternalistic doctor who was prepared to make the treatment decisions for him. In section 2, various specific problem areas are covered. For example, in his introduction the editor touches on the difficulty of testing new drugs in chemosensitive tumours. If one uses the new drug first and it turns out to be ineffective then there will be a delay in introducing standard effective treatment and drug resistance may be induced. On the other hand if one waits till the patient no longer responds to standard treatment, then multiple drug resistance may have developed and the true efficacy of the new drug will not emerge. Williams suggests that trials should randomise patients to the new drug followed by the phase II drug on progression. This is a very unwieldy solution which would not provide any *general* truths about the safety or not of using new drugs in previously untreated patients and could not possibly be repeated for each drug because of the large number of patients that would be required. Unfortunately this problem is not developed further in the book and is the principal omission in what is otherwise a comprehensive examination of the dilemmas facing new cancer drug investigators. Section 3 deals with the pharmaceutical industry and economic considerations. It is the weakest section. The chapter on economic evaluation of cancer treatments is, in places, banal (e.g. Figure 2), in others confusing ('The efficacy and effectiveness of chemotherapy in solid tumours are ambiguous'), and in others still poorly described (Figure 4). A discussion of the implications for governments struggling to finance ever more costly health care is lacking. At the end of each chapter there is a useful brief biography of the authors and a reference list. The text is well laid out and a reasonably comprehensive index has been compiled. Dr Williams is to be congratulated on assembling an intriguing list of authors who have put together a fascinating book which, although not offering any particularly novel solutions to the many problems involved in the introduction of new cancer treatments, certainly has them discussed clearly and, for the first time, grouped in a single text.

M.H. Cullen

Breast Cytology in Clinical Practice

S. Catania & S. Ciatto, London: Martin Dunitz, 1991, 136 pp. £39.95.

Fine needle aspiration cytology is used increasingly in the investigation and management of breast disease, and to be successful, requires the combined skills of clinician, radiologist and cytopathologist.

First published in Italy, in 1989, this book is particularly directed to the practical problems of obtaining material from breast lesions and providing adequate preparations for cytopathological evaluation. There is useful discussion of the role of the cytopathologist, with guidance on the interpretation and practical application of results. Although mainly concerned with FNA, the indications for examination of cyst fluids and nipple discharge are also presented in the light of considerable clinical experience.

In addition the 14 sections (120 pages) with references and illustrations cover a number of other aspects, including historical background, physical examination of the breast, use of ultrasound and stereotaxis, and the measurement of oestrogen-receptor content. Possible hazards of needle aspira-

tion, and the occasional complications of breast aspiration in particular, are discussed in detail.

As might be expected in a multi-author book there is some variation in the quality, and some overlap in content of the contributions. It is a pity that the layout of text and photographs in a major section, on instruments and techniques, is disjointed, making reading uncomfortable. Many of the detailed photographs, although not difficult to understand, have no legends, and are separated from the relevant text.

I agree with Professor David L. Page in his foreword that 'the value of this slim, multi-author volume lies in the wealth of clinical experience presented.'

Anyone faced with having to start using fine needle aspiration of the breast in clinical practice, and more especially with being the aspirator, should find this book helpful.

J. Lamb

Xenobiotics and Cancer. Implications for Chemical Carcinogenesis and Cancer Chemotherapy

Edited by L. Ernster, H. Esumi, Y. Fujii, H.V. Gelboin, R. Kato & T. Sugimura, Tokyo/London: Japan Scientific Press/Taylor & Francis Ltd, 1991, 368 pp. £85.00.

This volume describes the Proceedings of the 21st International Symposium of the Princess Takamatsu Cancer Research Fund, which was held in Tokyo, 1990. This Symposium was largely concerned with the metabolic activation of chemical carcinogens and anti-cancer drugs, with the defense mechanisms against their action, and with the biomonitoring methods available for detecting exposure to those compounds. Publications of conference proceedings are often rather dreary volumes, consisting of highly specialised chapters, bearing little relation to each other. This book in contrast provides an excellent survey of current biochemical thinking on chemical, molecular biological and pharmacological aspects of carcinogenesis. The authors are world experts in their respective fields and the topics for the chapters have in general been logically thought out. The result is an impressive, almost text-book like, discussion of chemical carcinogenesis, which will be of value to all post-graduates and research workers in this field.

The book is divided into six sections and carries 30 chapters, each by different authors. The first section comprises reports of two keynote lectures, the first covering cytochrome P450 distribution and function (Gelboin *et al.*) and the second covering the importance of the balance between active oxygen species and antioxidants in the carcinogenesis process (Ernster). The cytochrome P450 multi-enzyme family is the primary factor responsible for the activation and detoxification of xenobiotics and the utility of monoclonal antibodies and cDNA expression for the mapping of P450 distribution and function was concisely summarised by Gelboin. The concept was presented by Ernster that chemical carcinogenesis and its prevention may have as a common denominator the metabolic activation of a xenobiotic, which may result in the production of active oxygen (which is involved in the initiation, promotion and progression stages of carcinogenesis) or of antioxidant mechanisms which can scavenge these radicals and prevent their harmful effects.

Metabolic activation of xenobiotics was further considered in Section 2. Much evidence was (rightly) placed on the role of cytochrome P450s, the topics discussed being the influence of the anticarcinogen dehydroepiandrosterone on P450, the pharmacogenetics and polymorphism of P450's, and the aromatase cytochrome P450 complex. The possible contribution of (non-cytochrome P450 dependent) oxygen radicals to bioactivation of carcinogens is a further important parameter, which was discussed using benzo(a)pyrene as an example. Other bioactivation processes that were reviewed were those involving glutathione conjugate formation (e.g. 1,2-dihaloalkanes), acetyltransferase and sulphontransferase

(aromatic amines). Surprisingly, epoxide hydrolase, which is involved in epoxide detoxification and which is polymorphically expressed, was not given much coverage, although the importance of the N-acetylation phenotype to the carcinogenic effect of arylamines was included.

Section 3, which partially overlaps with Section 2, is about gene regulation of xenobiotic metabolising enzymes. In a field moving as fast as this there are naturally some areas which have progressed since the reviews were written and one can find omissions such as γ -glutamyl transpeptidase. However other areas which are well reported are the regulation of cytochrome P-450, the elegant studies on the nuclear glucocorticoid receptor, regulation of DT-diaphorase, and expression of glutathione transferases. The important effects of xenobiotics on signal transduction and Ca^{2+} concentrations, (although not particularly appropriate to the section title), are also discussed.

Resistance processes to cancer drugs from the basis of Section 4. Resistance to many drugs is associated with the expression of a 170 kD glycoprotein (P-glycoprotein), whose function is clearly reviewed. Exciting prospects exist for anti-cancer agents which could block the transport activity of P-glycoprotein. Other enzymes involved in resistance which are discussed are glutathione transferases (GST), glyoxalase I and UDP-glucuronosyl transferases. The first of these enzymes appears under different roles in each of Sections 2, 3 and 4. Although it might have been a challenging task for a contributor, an overall summary with a unifying hypothesis on function, polymorphism etc. of GST might have been interesting to include.

The next shorter section covers xenobiotics as a cause of human cancer. Three papers cannot even scratch the surface of this subject, and indeed only one class of compounds (the heterocyclic amines) are considered in detail. (It however maybe appropriate to choose these as the sole example in this volume, in view of the pioneering work carried out by the Japanese on heterocyclic amines in cooked food.) To make up for the deficiency in covering other compounds there is a penetrating and thought-provoking review by Ames *et al.* pointing out the importance of concentrating our attention on natural chemicals, in addition to the synthetic chemicals which have previously occupied many regulators' minds.

One real possibility for determining which xenobiotics are involved in human cancer initiation rests in the novel disciplines of 'biomonitoring', reviewed in Section 6. These techniques allow the detection of carcinogen adducts with DNA at levels down to ca. 1 modified DNA base per cell. Screening systems to monitor qualitatively and quantitatively exposures to mixtures of carcinogens are being developed using measurements of both DNA and protein (especially haemoglobin) adducts. Four papers review the major techniques employed (^{32}P -postlabelling, immunoassays, gas chromatography/mass spectrometry) for DNA and protein adduct measurements, and the relation of these data with mutations and chromosomal changes is discussed. This is a most interesting section of the book, and an appropriate one for its conclusion. Again because of the pace of progress in this area we know now of interesting novel findings, for example relating to mutation of the p53 gene, which could not have been included at the time of writing. This sadly is unavoidable in a publication now of a meeting held 18 months ago.

The book is notable for its high quality of editing and would certainly be a valuable addition to the bookshelves of chemical or biological carcinogenicists. The range of topics reviewed, although not comprehensive, is wide and the book is a useful source of up to date knowledge on molecular findings in chemical carcinogenesis.

P. Farmer