Book Reviews

Lung Cancer Differentiation. Implications for Diagnosis and Treatment

Edited by S.D. Bernal & P.J. Hesketh, New York: Marcel Dekker, 1993, 302 pp. \$175.00.

The term 'differentiation' is used in biology and pathology to describe the qualitative changes involved in the process of cell specialisation. The term is not defined in this book, which purports to be a monograph on the biology and clinical implications of differentiation in lung cancer. What the volume is, in fact, is a diverse collection of essays on a whole range of biological and clinical aspects of pulmonary neoplasia ranging from the role of the extracellular matrix in cell differentiation to an evaluation of population-based screening for the early detection of lung cancer. Some chapters (for example those on the epidermal growth factor receptor and on small-cell lung cancer antigens) are useful, well written and up to date, but the book suffers badly from a lack of direction and there are some glaring omissions. A most striking example is a complete lack of discussion of lung tumour histological classification, which is based entirely on morphological assessment of cell differentiation. The WHO classification of lung cancer is not even reproduced in tabular form. Other areas poorly covered include non-small-cell lung cancer differentiation markers (involucrin is referred to only once for example) and, in the clinical section, the role of surgical resection in the various histological subtypes of lung cancer.

An introductory chapter providing an overview of the biology of differentiation and the particular problems of lung cancer might have addressed some of these deficiencies.

Overall, therefore, the book is poorly edited and does not adequately cover the remit suggested in its title. It would be difficult to justify recommending its purchase.

F.A. Carey

Progress and Perspectives in Chemoprevention of Cancer Seroeni Symposia Publications, Vol. 79

Edited by G. de Palo, M. Sporn & U. Veronesi, New York: Raven Press, 1993, 316 pp. \$139.00.

This book is volume 79 in the series of *Serono Symposia*. I am ashamed to say that I have missed the first 78 so it is difficult for me to place the book in context! It would appear however to be a book of a 'meeting' that was held in Milan in March 1991, so it is 2½ years out of date. The Gulf War coincided with the conference and therefore a number of potential participants did not actually make it to Milan.

The basic material is fairly comprehensive and has not suffered from the passage of time. De Flora and his colleagues from Genoa have written an excellent introductory chapter describing various mechanisms of action and interaction of agents used in cancer chemoprevention, and Moon, who could be seen as the Virchow of this area of pathology, contributes his usual lucid description of the activity of retinoids on experimental mammary cancer. There are a number of other short papers on mechanisms of various agents, the best being by Jordan, who was one of the first experimental pathologists to realise that tamoxifen had potential as a chemosuppressive agent. The clinical studies, which include the pharmacology of some of the drugs in use, are dominated by the Milan group, and rightly so as it reflects their dominant position in this area of clinical oncological research.

Another substantial contribution, historically, has been made by Hong of the M.D. Anderson hospital. He has

organised and reported on a series of well-thought-out logical trials in the area of head and neck cancers, including cancers of the mouth. At least three of his trials have reached the giddy heights of publication in the *New England Journal of Medicine*, and he was the first to use the extremely cost-effective model of successfully treated lung and head and neck cancer patients for testing potential chemopreventive agents. He argued persuasively that the biggest risk factor for lung cancer is previous lung cancer, just as is the case for contralateral breast cancer following breast cancer. He was also the first to report that mortality and second smoking-related cancers in the aerodigestive tract are legitimate endpoints for this kind of study. The recent clinical trial from the Royal Marsden by Powles *et al.* is presented in embryo form. The full report has now been published elsewhere.

The main drawback with this book is that it is based on a conference 2½ years ago and there is still no real evidence that scientists and clinicians outside the authorship of this book have taken up the standard and followed in the crusade.

There have been a number of meetings on chemoprevention in the last 3 or 4 years, and sadly it tends to be the same faces and the same presentations given at each of them. It is not surprising, therefore, to find some of these articles in different forms in other symposia proceedings. Overall, however, it is a nicely produced book, and for a newcomer to the area of chemoprevention a comprehensive introduction to the key issues and the key players.

J.G. McVie

The Carcinogenicity Debate

Edited by J.A.N. McAuslane, C.E. Lunley & S.R. Walker, Lancaster: Quay Publishing, 1992, 302 pp. £49.95.

Carcinogenicity testing is a vexed topic for many reasons. This book, however, concentrates on the test itself, its validity and prospects for improvement. There remains a general consensus that carcinogens fall into two main categories – agents that are either genotoxic or non-genotoxic – and currently both are tested in laboratory animals. This is unavoidable, partly because of the lack of adequate substitutes and especially because of pressures from regulatory bodies. Ironically, these same pressures have led to a situation in which the quality of the result can be compromised. Essentially, the problem has arisen through expectations that have been placed upon animal tests, giving them the status of a bioassay, and over a period this had led to unjustified assumptions concerning the meaning of the results. It has always been evident to the critical observer that the animal can contribute much towards an understanding of mechanisms of carcinogenesis, a point made clearly by one of the contributors, but that it can never be a truly adequate bioassay because of the variable natures of both the initiating stimuli and the ultimate biological end points. This book takes a hard look at the realities of the use of animals in carcinogenicity testing. In doing so it questions the validity of the conclusions, defines the problems and seeks ways towards improvements for the future.

Essentially, the book can be divided into four sections, dealing with the issues involved, how study design can be improved, decision-making and indications of the way forward. They are variable in quality, but all contribute valuable and interesting insights into an area where science is primarily driven by economic and regulatory pressures. The first section opens with a general review of mechanisms in carcinogenesis, which presents the background for the conclusion that there are a variety of relatively reliable tests for

genotoxic agents in which *in vitro* and *in vivo* studies complement each other, whereas for non-genotoxic agents no well-validated methods are available, a reflection of the relatively less well-understood mechanisms of action. Moreover, the relevance of such tests is questioned when animal tests are used for non-genotoxic agents, since in the majority of cases the doses required to elicit cancer are far higher than those encountered in human exposure. In subsequent chapters the validity of the rodent model for carcinogenicity testing is questioned in almost all of its aspects. The use of the maximum tolerated dose, lifetime *vs* fixed-duration studies, the importance or otherwise of using more than one animal species and the differing spectrum of tumour induction in man and rodents are all matters given serious consideration. There is a call for the development of protocols in which more use is made of current knowledge of mechanisms, for tests to take account of plasma concentrations and doses at the site of delivery to the target and for protocols to be tailored more specifically to the compounds under test. Other issues raised are, for example, whether prediction based on current knowledge could even substitute for carcinogenicity testing in certain cases and whether it makes sense to attempt to cure cancer with cancer-causing agents.

Over several decades the rodent test has been compromised by a gradual increase in rat body weight, a shortening of lifespan and an increased incidence of spontaneous tumours. This had led to a move towards fixed-duration studies as opposed to lifetime studies. Examples of these problems are clearly documented and ways of dealing with them, including dietary optimisation, are discussed. Other areas considered are the use of multistrains and the value of pooled control

data and three chapters are devoted to the importance of pharmacokinetics.

In the chapters on decision-making, difficulties in the prediction of non-genotoxic carcinogenesis are considered. Recommendations for the use of other biological data including genotoxicity tests, species differences in metabolism and exposure data for animals as well as man are made with a view to gaining a more realistic assessment of the hazards involved in the use of a particular compound and to avoid sole reliance upon carcinogenicity tests. Case studies included in this section illustrate some of these issues.

In the way forward, the plea is for a more rational approach in study design that will take account of all biological information that is relevant to the compounds under test, the classification of agents to give a tiered approach towards assessment that would be internationally acceptable, dietary improvements, a move away from the standardised sub-lifetime studies and, above all, the recognition that the rodent test is a model system rather than a bioassay that provides unequivocal answers.

Overall, the discourse in this volume illustrates the strenuous efforts than have been made to fit a square peg (the rodent test) into a neat round hole (the demands of the regulatory bodies). While those involved are conscientiously picking ways around this 'Catch 22' situation in the interest of public protection, they find themselves increasingly in difficulties with a minority of those whom they seek to protect.

P.J. O'Connor