active treatment rather than a negative lack of treatment or, as Professor Stjernsward puts it, 'a waste-paper basket alternative' runs throughout the text and unifies the whole. The holistic and interdisciplinary nature of palliative care is emphasised by comprehensive and well-written chapters on ethical, cultural and spiritual issues and bereavement. The section on rehabilitation is noteworthy in that it covers topics as diverse as stoma management and music therapy as well as incontrovertibly demonstrating that rehabilitation is an intrinsic part of palliative medicine.

The importance of research in palliative care is a recurring theme throughout the book, and a specific section is devoted to this topic. Studies in this field are, however, relatively sparse, and the reasons for this are acknowledged and duly addressed. In particular, Calman and Hanks refer to the widespread view that 'scientifically rigorous clinical research is incompatible with the basic tenets of palliative care', and they put forward cogent arguments to refute this. This section of the book is extremely wide-ranging, and discussion is not limited to research into pharmacological and non-pharmacological symptom management as nursing, psychological and social issues are also well covered. The fact that palliative care crosses the traditional barriers of discipline and specialty is highlighted in the section on education and training. The authors stress that all the members of any hospital-based or domiciliary team caring for patients with cancer, be they doctors, nurses, social workers, physiotherapists or clergy, need at least a working knowledge of the philosophy of palliative care and suggest that this subject should become an integral part of the curriculum of all student health care professionals.

Although multiauthorship can bring problems through inevitable variability of both style and approach, these are not very apparent and there is a uniformly high standard of presentation throughout the book. Despite a degree of overlap between chapters there is surprisingly little repetition. The textbook is well indexed and all of the chapters are more than adequately referenced. In parts, the text is rather dry and it is tempting to speculate that it could be lightened by more case histories and illustrations.

The book concludes with a thought-provoking dissertation on the global perspective of palliative medicine. Each year fifty million people die worldwide. At least 10% die of malignant disease, and it is likely that this proportion, in addition to the numbers dying from AIDS-related diseases, will continue to increase. Given that even in resource-rich, developed nations there is inadequate application of the available knowledge on palliative care, it is perhaps not surprising that globally this field of medicine is badly neglected. To rectify this situation changes are necessary not only in medical practice but also in political, socioeconomic, social and ethical arenas. The World Health Organization has designated palliative care a priority in its Global Cancer Control Programme, and encouraging progress is already being achieved.

The *Oxford Textbook of Palliative Medicine* is a book both to dip in to, at leisure and when faced with an urgent clinical problem to solve, and to read systematically to gain a full insight into this field. Whilst its publication undoubtedly represents a coming of age of palliative medicine as a specialty in its own right, it is equally obvious that this new specialty must continue to evolve.

Carol L. Davis

Chemoradiation. An Integrated Approach to Cancer Treatment
Edited by M.J. John, M.S. Flam, S.S. Legha & T.L. Phillips,
Philadelphia: Lea & Febiger, 1993. 688 pp. £75.00.

This book sets out to put forward the rationale for and history to date of integrating chemotherapy and radiation in the management of cancer. The book is divided into five sections, with a brief introduction, the biological principles underlining combined modality therapy, a clinical section covering 17 disease sites, a section on toxicity and an appen-

dix summarising current clinical trials addressing the issue. The second section includes some basic information about the mechanisms and action of both radiation and cytotoxic drugs, but most attention is focused on their use as sole modalities with little information about possible interactions. The clinical chapters are comprehensive and give an excellent overview of combined modality therapy in the individual disease sites. The section on toxicity tends to reproduce some of the information included in the clinical chapters. Overall, this book may be useful as a reference source in a departmental library but it is unlikely to be of everyday relevance to the majority of oncology clinicians.

G.M. Duchesne

New Approaches in Cancer Pharmacology: Drug Design and Development

Edited by P. Workman, Berlin: Springer-Verlag, 1992, 103 pp.

This European School of Oncology Monograph recounts the deliberations of a Task Force set up to examine current progress and to anticipate future trends in cancer drug discovery and pharmacology. The underlying theme is the need for more effective drugs and the exciting opportunities offered by the present understanding of the discrete molecular aberrations of malignant cells which provide targets for selective attack. The contributors are all acknowledged experts in their fields and this short monograph is well written, authoritative and readable.

The review on sequence- and gene-specific drugs by D'Incalci, Broggin and Hartley concentrates on alkylating agents and their reactions with DNA as the major biochemical events underpinning their cytotoxicities. It has been known for some time that DNA damage is attributable to single- and double-strand breaks, inter- and intra-strand cross-links and possibly to DNA-protein cross-links. The site most frequently alkylated is guanine N₇, with lesser reaction occurring at guanine O₆ and adenine N₃. The authors review methodology which now enables an understanding of how DNA base sequences influence the sites of alkylation of various clinically used alkylating agents. It is now clear that many common bifunctional alkylating agents react preferentially with guanine N₇ in contiguous runs of guanines in the major groove of DNA. The authors emphasise that these studies are carried out with parent drug and purified DNA and take no account of cellular metabolism. Minor groove binders include mitomycin C and CC-1065.

Claude Helene discussed antisense and antigene oligonucleotides and synthetic ribozymes. The major requirements of antisense oligos are emphasised: nuclease stability; preservation of RNase H activity; good cell penetration. The advantages and shortcomings of the various linker chemistries and the properties of chimaeric molecules comprising conventional phosphodiester linkers in association with methyl phosphonate, phosphorothioate or phosphoramidate units is reviewed. Other chemical manoeuvres, including coupling of oligos to hydrophobic moieties to enhance transport and attachment of alkylating residues, both to achieve nuclease stability and to increase potency, are mentioned also. A consistent theme is the high selectivity that can be achieved with antisense oligonucleotides in their effects, for example on parasitically or virally infected cells, as well as on tumour cells carrying a single point mutation in the Ha-ras oncogene, amplified c-myc or in CML cells, where the bcr-abl translocation can be targeted. Oligonucleotide-directed triple helix formation, where Hoogsteen hydrogen bonding permits the association of a third oligo strand with the nuclear DNA, is described as an 'anti-gene' strategy. The triple helix can be effectively stabilised by the attachment of a 'docking' intercalator molecule. It is envisaged that this approach will interfere with the function of transcription factors and restriction enzymes, thus disturbing differentiation and cell division. The author concludes that the

antisense approach offers the promise of high selectivity in the therapeutic setting, though there remain substantial pharmacological difficulties which must be overcome before antisense molecules can be used successfully *in vivo*.

In 'Prospects for Biological and Gene Therapies', Sikora and Guitierrez justifiably point to the failure of chemotherapy to make a major impact on the treatment of common malignancies. The authors discuss genetic immunomodulation, normal tissue protection, drug targeting and gene replacement therapy as possible future strategies. It has become clear that cytokines can significantly affect tumour growth, despite host toxicity. It is suggested that vectoring of cytokine-coding genes, enhancing the expression of MHC I and II molecules and transfecting tumour-infiltrating lymphocytes with TNF may be viable means to enhance tumour immunogenicity. In the context of normal tissue protection the authors point to the successful use of the haematopoietic colony-stimulating factors in restoring bone marrow function after ablative therapy. They propose that enhancement of these moieties in bone marrow cells by recombinant methods prior to treatment may well result in increased tolerance to conventional cytotoxic drugs. Virally directed enzyme pro-drug therapy (VDEPT) envisages the selective genetic expression in tumours of an enzyme which will convert an inactive prodrug to an active cytotoxic species within tumour cells. Examples of the use of thymidine kinase to convert Ara-A into cytotoxic Ara nucleotides and of cytosine deaminase to activate 5-fluorocytosine to the antimetabolite 5-fluorouracil are quoted. Against a background of substantial *in vitro* evidence that restoration of normal morphology and phenotype can be achieved by appropriate recombinant manoeuvres, the authors suggest that tumour-suppressor genes, notably Rb and p53, are viable candidates for 'gene replacement therapy'. As with their VDEPT proposals they stress the critical requirement for selective and efficient vector delivery.

John Hickman reviews cell membranes and signal transduction pathways as targets for medicinal chemistry. The development of tyrosine kinase inhibitors is outlined, listing the natural products quercetin and genestein and a series of thiazolidine-diones. These compounds all compete with ATP for binding and thus offer the promise of less selectivity than erbstatin and the tyrphostins, which are non-competitive with ATP but competitive with enzyme in EGF receptor protein tyrosine kinase assays. Several tyrphostins possessing both potency and selectivity for individual tyrosine kinases are now available, and detailed *in vivo* data are keenly awaited. Attention is drawn also to the SH2 regions involved in coupling other signal transduction molecules to tyrosine kinase autophosphorylation sites: it is suggested that these *src* homology domains provide good targets for molecular intervention. Also discussed is inhibition of second messengers, notably phosphatidylinositol 3' kinase is inhibited by D-3-deoxy-3-azido-myoinositol and phospholipase C by ether lipids, two of which, ET-18-OME and SRI 62-834, are undergoing clinical evaluation. The author observes that since the biochemical pathways involved in signal transduction are linked to cell proliferation, medicinal chemists will be producing a new generation of antimetabolites complementary to those in present use.

The design of novel antiendocrine drugs is presented by Michael Jarman. New anti-oestrogens are discussed in the context of the facile metabolism of tamoxifen and its retention of partial agonist activity, which may contribute to the emergence of tumour resistance. Several congeners are currently undergoing clinical study, including droloxifene, teramefin, TAT-59 and idoxifene (CB7432). The last compound has a substantially improved affinity for the oestrogen receptor compared with the other compounds. Also in clinical study is the 7-substituted oestradiol derivative, ICI 182,780 which is devoid of agonist activity. Blockade of oestrogen biosynthesis can be achieved with aminoglutethimide, though the side-effects of this drug (sedation and corticosteroid depletion) have prompted the search for an alternative. Several compounds of varying potency are under-

going clinical study, including rogletimide, CGS 16949A and CGS 20267. Amongst the steroidal inhibitors are 4-hydroxy-androstenedione and MDL 18962. Since ovarian and testicular steroid biosynthesis is under LHRH control following its release from the hypothalamus, LHRH agonists have been used, frequently in combination with an inhibitor of oestrogen or androgen biosynthesis, to ablate hormone levels. The synthesis of new anti-androgens, specifically inhibitors of 17 α -hydroxylase/C_{17,20} lyase, based upon the model compound ketoconazole, is described. Cyclohexyl-4-pyridyl acetate is a lead compound from a group of 4-pyridylacetic acid esters which exhibit good binding affinities. Another important target for anti-androgen drug design is testosterone 5 α -reductase, and modelling and structure-activity studies are described. In his concluding discussion the author observes that, in view of the plethora of highly potent and selective aromatase inhibitors, the value of this target in breast cancer chemotherapy will surely be established in the near future.

Paul Workman writes on the design of novel bioreductive drugs, outlining the biology of hypoxia and its association with both radio- and chemoresistance. The nitroimidazole radiosensitisers are elaborated as a major strategy to circumvent radioresistance. The clinical limitations of metronidazole (potency) and misonidazole (neurotoxicity) led to the development of etanidazole and pimanidazole and subsequently of the more promising 'mixed function' compounds containing both the sensitising nitro group and an aziridine function, e.g. RSU 1069 and RB 6145. The heightened cytotoxicity of nitroimidazoles in hypoxic, as compared with oxic, cells has led to the development of a class of cytotoxic chemicals which is activated by reduction in hypoxic environments. In addition to nitroimidazoles, other classical examples are mitomycin C and the indoloquinone E09. More recently the benzotriazine di-*N*-oxides, notably SR4233, have been discovered. The latter is unique in forming strand breaks rather than DNA adducts post reduction. The one- and two-electron reducing requirements for the various activations and the associated enzymology is discussed, as is the possibility of profiling these drugs to the bioreductive phenotype of tumours. The overall approach is presented as exploiting a common established defect of solid tumours.

The topic of 'therapeutic drug monitoring and dose optimisation in oncology' is presented by Merrill Egorin. His theme is the need to achieve optimal dosing of anti-cancer drugs, which invariably possess low therapeutic indices, in individual patients. A sound background to pharmacokinetic and pharmacodynamic monitoring is provided, together with a critique of three dosing strategies that could be adopted. These are 'empiric dosing' (e.g. mg m⁻² as recommended for phase II studies); 'adaptive dosing' (in which patient, disease and drug characteristics are assessed in a regression model to provide an individual dose recommendation against a population database); and 'adaptive control with feedback dosing' (which allows more closely for inter-patient pharmacokinetic variability through refinements of the pharmacokinetic model on an individual basis). Approaches to the analysis of population pharmacokinetics and limited sampling strategies are clearly presented and analysed. The need for appropriate resources is stressed, as is the requirement for sensible cost-value benefit of such investigations. The author also points to the need to initiate population pharmacokinetic/pharmacodynamic modelling at the earliest stages of the clinical evaluation of a new drug, since the basic information required to undertake individual dose optimisation will be difficult, if not impossible, to obtain once the drug is established.

Gilberto Schwartzmann reviews current strategies in anti-cancer drug discovery within the EORTC. The rate of discovery of clinically useful drugs is addressed briefly and the point made that the major impact has been in the treatment of relatively rare cancers (leukaemias, lymphomas, paediatric tumours). This is attributed to the predominance of transplantable mouse leukaemias, either as prescreens or as major screening vehicles, in the tumour panels adopted for assessment and quantification of preclinical anti-tumour properties.

It is also no doubt a consequence of the drug discovery philosophy which has relied on large-throughput random screening, rather than rational drug design. The inception and evolution of the NCI compound-oriented screening programme and its benefits and shortcomings are reviewed. Also outlined is the current NCI screening programme, which is disease oriented and embraces calibrated panels of human tumour cell lines of given tissue types. The organisation of the EORTC drug discovery initiative is discussed, indicating the role played by the New Drug Development Office in coordinating and integrating the efforts of the University of Freiburg and the several collaborative EORTC preclinical groups. The chapter concludes with a brief commentary on the EORTC contributions to the development of several promising new agents including taxol, taxotere, topotecan, CPT-11, the anthrapyrazoles and suramin.

K.R. Harrap

Excited States and Free Radicals in Biology and Medicine. Contributions from Flash Photolysis and Pulse Radiolysis

R.V. Bensasson, E.J. Land & T.G. Truscott, Oxford: Oxford University Press, 1993, 431 pp. £50.00 Hardback. £23.50 Paperback.

This volume is essentially an expanded and extensively revised second edition of the earlier work on this theme by these authors, published by Pergamon in 1983 under a similar title. Like the second edition of B. Halliwell and J.M.C. Gutteridge's *Free Radicals in Biology and Medicine* (Oxford University Press, 1989), it has many elements in common with the earlier work, but there is plenty of new material to justify its purchase. The authors' aim 'is to introduce the reader to the expanding field of excited states and free radicals in biology and medicine, a discipline at the borderline of physics, chemistry, biology, pharmacology, and medicine'. While Halliwell and Gutteridge aimed their book mainly at biologists and clinicians and assumed little knowledge of chemistry, Bensasson *et al.* 'concentrate on the viewpoints of physical chemists'. As such the two volumes are complementary not only from the viewpoint taken but also in content.

The roles of free radicals and excited states in biological processes are increasingly recognised to be extensive and diverse. Any book attempting to cover this subject with reasonable breadth while retaining depth must therefore be selective. The 12 chapters of the new work still reflect the research interests of the authors, but as these are quite broad the book does provide a useful cross-section of the subject matter. Particularly appreciated was the much expanded introductory coverage, involving three chapters. These summarized energy absorption processes for light and ionising radiation, the nature and reactivity of radicals, and experimental techniques used with pulsed radiation (and light) sources. These three chapters, 100 pages in all compared with 19 pages of introduction in the 'first edition', included nine pages discussing the theoretical treatment of electron-transfer reactions. (The importance of this topic has recently been recognised by the award of the Nobel Prize to R.A. Marcus for his work in this area.) With the emphasis on the underlying framework rather than on numerous experimental examples, such 'mini-reviews' will prove more valuable for a longer time than exhaustive lists of the latest research papers.

The next chapter discusses the production, detection and reactions of 'activated forms of oxygen': singlet molecular oxygen, superoxide, hydroxyl and peroxy radicals, hydrogen peroxide and (somewhat out of place, but very topical) nitric oxide and nitrogen dioxide. Of the 40 pages, disappointingly, only three are devoted to the 'biomedical properties of the activated forms of oxygen', and for fuller coverage the reader will need to turn to Halliwell and Gutteridge, to H. Sies' two volumes on *Oxidative Stress* (Academic Press, 1985, 1991), or other of the numerous multi-author works which have proliferated in this area.

The chapter on 'pyrimidines, purines and nucleic acids' is divided approximately equally into the chemistry of excited states and radical species. The latter coverage provides a useful update to the much more detailed discussion of this topic in C. von Sonntag's *The Chemical Basis of Radiation Biology* (Taylor & Francis, 1987). The chapter following, on 'amino acids, peptides and proteins', covers radical generation by light and other radicals, as well as a survey of electron migration in proteins.

Three chapters particularly reflecting the research interests of the authors follow. The (mainly excited state) chemistry of carotenoids, including β -carotene and vitamin A, and their pivotal roles in vision and photosynthesis are described. The worrying increase in malignant melanoma more than justifies a chapter devoted to the radical chemistry of melanogenesis and melanoma, and the chemical basis for the clinical interest in 4-hydroxyanisole as a route to exploit elevated tyrosinase levels in melanoma. Pulse radiolysis and flash photolysis have been ingeniously applied to unravel some of the complex reaction pathways in melanogenesis. The following chapter is devoted to photodermatology. Subjects covered include the molecular mechanisms of skin damage by UV radiation, the photochemistry and radical chemistry of drugs which have photosensitising side-effects (such as phenothiazines and non-steroidal anti-inflammatory drugs), photochemotherapy of psoriasis, the basis for phototherapy as a treatment for neonatal hyperbilirubinaemia and skin photosensitivity associated with excess porphyrins.

The final three chapters are devoted to cancer: to radiotherapy, chemotherapy and photodynamic therapy; of the three, I found the last of most value. The chapter on radiotherapy concentrates on radiosensitisation by oxygen and electron-affinic chemicals, and is too brief to add much new to von Sonntag's coverage or reviews by other authors. A reference or two to the 'meta-analysis' of radiosensitiser clinical trials, and oxygen measurements in tumours, as leads to the clinical experience would have been useful. Radiosensitiser research led directly (the same compounds) to the recent expansion in research into the selective chemotherapy of hypoxic tumour cells. The mechanisms underlying the selectivity arise from fast, free radical reactions observable directly by pulse radiolysis. It is therefore surprising that the following chapter, on cancer chemotherapy, rather neglects coverage of this important topic. The chapter concentrates instead on the reduction chemistry of anthracyclins and mitomycin C, reflecting the detailed work by one of the authors and his colleagues. The final chapter, on photodynamic therapy (PDT), describes the primary photochemical processes in PDT, brief coverage of biological aspects and current work towards new photosensitisers.

Specialists may well be disappointed with the coverage extended to any individual theme, but it is unrealistic to find in a single volume comprehensive coverage of all the contributions of flash photolysis and pulse radiolysis to free radical and excited state chemistry in biology and medicine. The title itself implies a restriction in coverage: a dozen volumes would be needed to cover in depth even the chemical aspects of free radicals and excited states in biology as a whole. The value of this book lies as much in the extensive introductory chapters as in the coverage of the selected examples. Every chapter is well constructed, with a detailed contents list, interesting historical introductions and concluding remarks. Each is well supported by extensive referencing to the single bibliography comprising over 1,500 references, thankfully including full titles of articles. A short appendix lists SI units and conversion factors, although I was disappointed that radiation chemical yields were quoted using obsolescent and non-SI *G*-values.

The book is good value for money, especially in paperback. It is an excellent complement to Halliwell and Gutteridge's coverage of free radicals in biology, and joins the latter volume as an essential purchase for all workers in the field.

P. Wardman