Book Review

Introduction to Radiobiology
M. Tubiana, J. Dutreix, A. Wambersie and D.K. Bewley. Basingstoke, Taylor and Francis, 1990. 361 pp. ISBN 0 85066 763 1 £19.00.

THIS PUBLICATION is a new English translation of a French textbook, originally published in 1986. From the outset it should be stated that the book is clear in layout, with a large amount of well-collated information contained within a small 372-page paperback format. As is clear from the title, the prospective purchasers are trainees in radiology, radiation medicine and nuclear medicine, plus scientists involved with cancer or radiation. Overall, they will be reasonably pleased with their purchase, as long as they are prepared to work hard in both understanding new concepts or extracting specific information. This is not a easy read, nor a bland overview of the subject.

The layout of the book progresses in a logical way from the initial deposition of energy by radiation, radiation chemistry and subcellular biology; through cellular radiology, normal tissues and tumours, hypoxia, fractionation, chemical modifiers and high linear energy transfer and finally to the whole-animal effects of radiation. This covers the syllabus of radiobiology with the possible exception of radionuclide therapy. The subheadings are also reasonably informative.

To my mind, obtaining information from specific sections was heavy going. The use of figures is extensive, but most of them are packed with information which will prove difficult to digest for the genuine beginner. I think this represents a dilemma for all "introductory" texts: to include material and hence be a good source for further inquiry; or to omit for ease of reading. This dilemma could be solved by the use of concise chapter summaries. The reader could then compare his understanding of the chapter with the authors' intentions, and return to the misunderstood sections.

The chapters on physics and chemistry present a standard view. The role of the direct versus the indirect effect of ionising radiation on DNA is discussed, but their importance *in vivo* omitted. In living cells, indirect radical action only occurs within a small domain (25 nm); radical migration is limited and water is relatively excluded from packed DNA within chromatin. Thus, the difference between these modes of action may have no relevance to the cell. The chapter about the effects of radiation on DNA has been expanded to 50 pages to reflect the increased interest of this subject in recent years. This covers a broad range of issues but could, in my opinion, be expanded further to cover even more up to date developments in the subject. This is the area of radiobiology which is going to expand the most, and if this were reflected by the book, it would stand clear of its rivals.

One comment particularly relevant to this chapter is that certain important statements are made dogmatically, as if they were not the subject of any further debate. For example, the authors state that a "double-strand break involves the breakage of the two strands of DNA at points less than three nucleotides apart". This statement is not referenced and not supported by any experimental evidence. A double-strand break can be produced by a large variety of lesions clustered within a domain of DNA. To define the nature of the broken end is extremely difficult, and will remain the subject of investigation and debate for many years to come. The authors further suggest that double-strand breaks can be produced by single events or the interaction of two independent particles. This represents the thesis of Chadwick and Leenhouts in their book *The Molecular Theory of Radiation Biology* (1981) but the debate has moved on a considerable way since then. Goodhead has long argued that the likelihood of two independent ionisations occurring in the same DNA domain is extremely low. The nature of the relationship between induced damage and dose should be discussed more in this context. These are relatively small points in the context of the whole book, but reflect a slight disappointment with the coverage of this most exciting area of radiobiology.

Cell survival curves are well covered: the authors seem much happier in this subject. The marked cell cycle effects upon cell survival seems to beg further discussion of how differences in cell cycle distribution could affect the nature of the cell survival curve of asynchronous populations. The sections on tissues and tumours are good. This partly reflects the more static nature of these subjects. The sections on fractionation, hypoxia and sensitisers provide a good balance of scientific discussion and clinical trials. Indeed, the later sections of the book seem to read more easily and still provide the necessary information.

Overall, this is a well balanced book, and good value in paperback. It rates well alongside established competitors. My criticism is that the early chapters are heavy going and the molecular radiobiology section is still too brief, with some inaccuracies.

Simon Powell
Radiotherapy Research Unit
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey SM2 5NG U.K.

Eur J Cancer, Vol. 27, No. 4, pp. 516–518, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00
© 1991 Pergamon Press plc

Letters

Yolk Sac Tumour of the Vagina with Hepatoid Differentiation

Amedeo Boscaino, Luigi Maria Terracciano, Patrizia Sapere and Gaetano De Rosa

THE YOLK sac tumour (YST) is the rarest among the malignant childhood tumours of the vagina [1–3]; this, probably, has been reported in the literature as neoplasm of various terminology and often underdiagnosed [2]. We document a peculiar case of

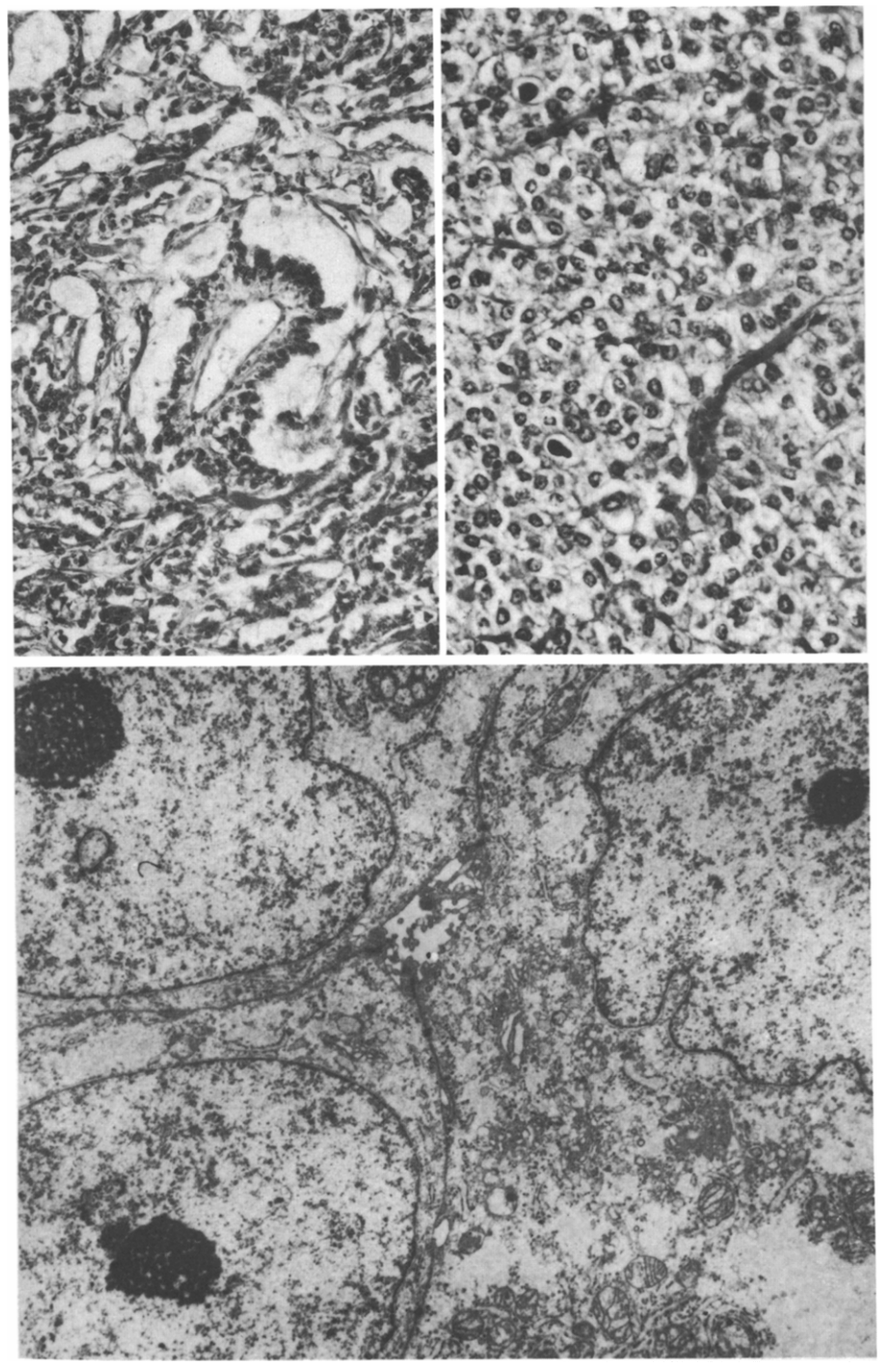

Fig. 1. Upper left: reticular pattern with typical Schiller–Duval bodies (× 106). Upper right: large polygonal cells with prominent borders, central nuclei and sometimes evident nucleoli; gland-like spaces can be seen. (EE × 270). Lower: polyedral cells with intercellular acinar spaces, with delicate microvilli resembling biliary canaliculi (× 3000).

YST of the vagina with areas of hepatoid differentiation. Indeed we observed a polypoid lesion, 4 cm in maximum diameter, growing from the right posterior vaginal wall into vaginal lumen from a 6-months-old female child with a history of vaginal bleeding.

At light microscopic examination, a part of the tumour was found to be composed of a loose network of cystic spaces lined by flattened epithelial cells with clear cytoplasm PAS positive, diastase resistant and hypercromic, with large nuclei containing prominent nucleoli. Typical Schiller–Duval bodies were seen (Fig. 1 upper right); droplets hyaline eosinophilic PAS positive, diastase resistent was present. In the other fields the tumour showed masses of large, poligonal epithelial cells with prominent cell borders, abundant clear to eosinophilic cytoplasm and round central nuclei with prominent single nucleoli; sometimes the cellular masses are perforated by gland-like spaces containing mucin (Fig. 1).

Immunoperoxidase studies demonstrated that staining for alpha-fetoprotein (AFP) was positive; the tumour showed no

Correspondence to G. De Rosa.
The authors are at the Institute of Pathology, Second Medical School, University of Naples, Via S. Pansini 80131, Italy.
Revised 2 Jan. 1991; accepted 3 Jan. 1991.

immunoreaction for A1AT and human chorionic gonadotropin. The ultrastructural examination showed the presence of closely apposed polygonal cells containing intercellular canaliculi characterised by a lot of delicate microvilli and intercellular junctions consistent with hepatoid differentiation (Fig. 1).

The final diagnosis was YST with areas of hepatoid differentiation.

In the female genital tract YST is most frequently encountered in the ovary [4, 5]. It is exceedingly rare in the vulva [2, 3 ,6]. The cases of YST of the vagina or uterine cervix bring the total number of reports in the world literature to approximately 50.

Microscopically the YST has more than one histopathological pattern: festoon, reticular, solid and polyvescicular. A peculiar variant of YST with hepatoid differentiation has been described in the ovary [7]. The clinical presentation of the vaginal YST must prompt us to differentiate it from botryoid sarcoma; the diagnosis is evident on histological examination.

Differential diagnosis must be also made with clear cell carcinoma. In YST diagnosis must be based upon the absence of hobnail pattern, the presence of Schiller–Duval bodies and the various histological patterns characteristic of YST and the immunohistochemical demonstration of AFP.

In the adult YST with an predominantly hepatoid pattern differential diagnosis must be made with a metastasis of hepatocellular carcinoma [7]. However, the clinical examination showing the presence of areas with typical YST patterns aid in the diagnosis.

The prognosis for these tumours with modern chemotherapy without radiation therapy or ablative surgery is very good.

1. Dewhurst J, Ferreira HP. An endodermal sinus tumour of the vagina in an infant with seven year survival. *Br J Obstet Gynecol* 1981, **88**, 859–862.
2. Copeland LJ, Sneige N, Ordonez NG, *et al.* Endodermal sinus tumor of the vagina and cervix. *Cancer* 1985, **55**, 2558–2565.
3. Wilkinson EJ. *Pathology of the Vulva and Vagina.* Edinburgh, Churchill Livingston, 1987.
4. Clement PB, Young RH, Scull RE. Extraovarian pelvic yolk sac tumors. *Cancer* 1988, **62**, 620–626.
5. Harms D, Janig U. Germ cell tumours of childhood. *Virchows Arch (Pathol Anat)* 1986, **409**, 223–239.
6. Dudley AG, Young RH, Lawrence WD, Scully RE. Endodermal sinus tumor of the vulva in an infant. *Obstet Gynecol* 1983, **61**, 76S–79S.
7. Prat J, Bhan AK, Dickersin GR, Robboy SJ, Scully RE. Hepatoid yolk sac tumor of the ovary (endodermal sinus tumor with hepatoid differentiation). *Cancer* 1982, **50**, 2355–2368.

Eur J Cancer, Vol. 27, No. 4, pp. 518–519, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00
© 1991 Pergamon Press plc

Study Design in Evaluation of Combined Modality Treatment

Denise Howel and Margaret Jones

THE RECENT paper by Yarnold *et al.* [1] highlighted the problems of evaluating treatments with many criteria of interest (e.g. toxicity, local control and survival). Whilst agreeing that there are real problems, we would disagree with the solution proposed by these authors.

It is useful to classify a proposed trial by the system described by Schwartz *et al.* [2] i.e. as "explanatory" or "pragmatic". An explanatory trial is aimed at increasing our understanding of the mechanism of combined therapy by addressing a question such as "Does the addition of chemotherapy to radiotherapy change the biological effect, compared to radiotherapy alone?" whereas a pragmatic trial would aim to answer a question like "What combination of radiotherapy and chemotherapy gives the best therapeutic effect?" The choices of dose levels, assessment criteria and suitable subjects cannot be simultaneously appropriate for both research questions, so a decision must be made early between the two approaches.

If a two-arm explanatory trial were planned with n subjects per arm, then subjects would receive radiotherapy or the combined therapy with the same radiation dose so that any difference could be attributed to chemotherapy itself. A suitable primary assessment criterion would be biologically meaningful (e.g. local control rather than survival, since survival is affected by factors other than treatment) with toxicity as a secondary criterion. It would be possible to carry out a four-arm trial (a 2×2 factorial experiment) to investigate the possible interactive effects (positive and negative) of radiotherapy and chemotherapy with similar subject numbers to a two-arm trial. If the four combinations of two levels of radiotherapy (low/high) and two levels of chemotherapy (present/absent) were used on $n/2$ subjects each, the single and joint effects of the two modes of treatment could be obtained in one trial.

However, a factorial design is only suitable for an explanatory trial and not for a pragmatic trial [2]. To facilitate the attribution of any extra effects to chemotherapy alone, the protocols should be strictly adhered to and all other factors should be equalised. This strategy and the choice of dose levels may lead to ethical problems with human subjects in explanatory trials once the side-effects are established.

In a pragmatic trial, interest centres more on therapeutic benefit than on biological effect, so assessment criteria are likely to include long-term survival and toxicity measures as opposed to local control. Treatment combinations would be chosen to provide an acceptable level of toxicity, which might mean chemotherapy in combination with a lower radiotherapy dose than usual. The choice of the lower dose is difficult and Yarnold *et al.* discount this option, since the wrong adjustment might be made. However their suggestion of a third arm to the trial with an increased radiotherapy dose has the same problem.

Using the distinction between explanatory and pragmatic trials it can be seen that the three-arm solution proposed by Yarnold *et al.* has some of the disadvantages of explanatory trials, since the extra treatment is not one which would be given in practice, but is not sufficiently tightly controlled to claim the advantage of being able to attribute any differences to chemotherapy itself. There are very real difficulties in deciding between treatments if more than one criterion is necessary. It is possible that assessments of the various forms of toxicity could be combined into an overall index, either taking the correlations between assessments into account [3] or using their relative

Correspondence to D. Howel.
D. Howel is at the Department of Public Health Medicine, University of Leeds, 32 Hyde Terrace, Leeds LS2 9LN; and M. Jones is at the Clinical Trials and Research Unit, Yorkshire Regional Cancer Organization, Cookridge Hospital, Leeds, U.K.
Received 15 Jan. 1991; accepted 22 Jan. 1991.