Letters

Breast carcinomas in patients on HRT

The report by Fitzgerald O'Connor *et al* about the histopathology of breast carcinomas in patients on hormone replacement therapy covers an area of great interest, as was evidenced by the coverage given to this paper in the popular media such as *The Times* newspaper.¹ However, the paper may contain some errors in statistical analysis which could invalidate some of its conclusions.

One of the main conclusions of the paper is that the tumours detected in HRT patients were statistically smaller than those detected in non-HRT patients. The authors have made this conclusion on the basis of an unpaired *t* test between the two groups. The *t* test can only be performed on values that have a normal distribution and the paper contains no evidence to show that this was so. Indeed the evidence in the paper suggests that the distribution in both HRT and non-HRT groups may not be normally distributed, since the mean and median values are different in both groups (mean 13 mm and median 17 mm in the HRT group, mean 25 mm and median 20 mm in the non-HRT group). The range of sizes in both groups was wide (4 to 50 mm in the HRT group, 7 to 55 mm in the non-HRT group). The authors should perform a suitable test for normal distribution on their size data and if the values are not normally distributed then they should use an appropriate non-parametric test.

The paper does not contain any assessment of the reliability of the measurements of the size of the tumours, and the NHS breast screening programme histopathology external quality assurance scheme has shown that there can be considerable interobserver variation in tumour size measurement. Similarly there is no assessment of the reliability of the tumour grading which is an arbitrary division of a spectrum.²

The discussion section of the paper contains statements about "a trend towards" a difference for several variables which did not show a statistically significant difference. This practice is unhelpful since random samples from a population will produce random fluctuation around a central value and another sample of tumours could show a "trend" in a different direction. This is clarified by calculating the 95% confidence intervals³ for the prevalence of these features in both groups (table). This shows the very wide confidence intervals for all these proportions, which are due to the small numbers of cases in each group, making any statements about "trends" of very dubious validity.

A final criticism of the study would be the assessment of oestrogen receptor staining where the investigators used their own semi-quantitative system, whereas most laboratories in the United Kingdom use the McCarty

H scoring system where the threshold for positivity is different.

In their discussion of the apparently smaller size of tumours in the HRT group the authors say that "the possibility of a direct slowing effect of HRT on tumour growth ought to be considered and investigated." While this is a possibility, it is one that would go against the evidence that oestrogen is an important growth factor for breast cancer and that oestrogen antagonists are often useful treatment. It was this statement that made the article headlines of the coverage in the popular media, and it is important to clarify the statistical methods of the paper in order to justify the promulgation of this view.

SIMON S CROSS

Department of Pathology, University of Sheffield,
Sheffield S10 2RX, UK

- 1 Fitzgerald O'Connor I, Shembekar MV, Shousha S. Breast carcinoma developing in patients on hormone replacement therapy: a histological and immunohistological study. *J Clin Pathol* 1998;51:935-8.
- 2 Cross SS. Grading and scoring in histopathology. *Histopathology* 1998;33:99-106.
- 3 Bland JM. Standard error of a proportion. In: Bland JM, ed. *An introduction to medical statistics*. Oxford: Oxford University Press, 1995:125-6.

Author's response

Thank you for giving me the opportunity to comment on Dr Cross's letter. His main criticisms concern his belief in the unreliability of measuring the size of breast tumours and grading them. His belief is unfounded and helps only to propagate two false conceptions, namely that pathologists cannot carry out the simple task of measurement or agree on a way of grading tumours. What the UK national external quality assessment scheme has shown is that in the majority of cases over 80% of participants' measurement of tumours were within 3 mm of the median value.¹ This is a remarkable agreement, taking into consideration that the sections examined, by more than 200 pathologists involved, were not the same but came from 50 different serial sections of the same tumour. The same article¹ has shown that consistency of grading was moderately good between the large number of observers involved. More importantly, it has been shown that complete agreement about grading can be achieved in more than 80% of cases if observers follow the much publicised simple grading criteria of Elston and Ellis.² I would like to assure Dr Cross that in our hospital, and I hope in his as well, we take our measurements and grading very seriously because we realise their essential role in planning postoperative treatment. Also, as stated in the article, almost all the studied cases were reported by the same pathologist, which excludes the problem of interobserver variation.

The statistical methods used are accepted statistical methods and the results were clearly interpreted either as significant or not,

and when not, the presence of a logical clear trend in a specific direction was pointed out, as a statistically significant difference might emerge if a larger number of cases is examined. Our semiquantitative scoring method for receptor assessment is based on McCarty's H scoring system,³ and its results have been repeatedly proved to correlate closely with other quantitative and semiquantitative methods.^{4,5}

It is interesting to note that all our results were confirmed by another, entirely independent, study which was published almost simultaneously in the *Journal of Clinical Oncology*.⁶ What is needed now is to find out why breast cancer, on average, seems to be less aggressive in women with histories of HRT intake, and why breast cancer mortality is lower in this group of patients.⁷ And, if we want to find the truth, we should keep an open mind about all the theoretically possible explanations including a slowing down effect on aggressive tumours, a stimulating effect on low grade tumours, or a more frequent screening.⁸

SAMI SHOUSA

Department of Histopathology, Imperial College of
Science, Technology and Medicine, Charing Cross
Hospital, London W6, UK

- 1 UK National Coordinating Group for Breast Screening Pathology. Consistency of histopathological reporting of breast lesions detected by screening: findings of the UK National Quality Assessment (EQA) Scheme. *Eur J Cancer* 1994;30A:1414-19.
- 2 Robbins P, Pinder S, de Klerk N, *et al*. Histological grading of breast carcinomas: A study of interobserver agreement. *Hum Pathol* 1995;26:873-9.
- 3 Shousha S, Peston D. Immunohistochemical demonstration of oestrogen and progesterone receptors in paraffin sections of breast carcinoma. *Curr Diagn Pathol* 1997;4:176-80.
- 4 Goulding H, Pinder S, Cannon P, *et al*. A new immunohistochemical antibody for the assessment of estrogen receptor status on routine formalin-fixed tissue samples. *Hum Pathol* 1995;26:291-4.
- 5 Barnes DM, Harris WH, Smith P, *et al*. Immunohistochemical determination of oestrogen receptor: comparison of different methods of assessment of staining and correlation with clinical outcome of breast cancer patients. *Br J Cancer* 1996;74:1445-51.
- 6 Holli K, Isola J, Czuzik J. Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. *J Clin Oncol* 1998;16:3115-20.
- 7 Willis DB, Calle EE, Miracle-McMahill HL, *et al*. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control* 1996;7:449-57.
- 8 Colditz GA. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. *J Natl Cancer Inst* 1998;90:814-23.

CD-ROM review

Atlas of Pathology: Gynecologic Cytopathology—Cervix (CD-ROM). By C Marsan, A-M Bergemer, J L Gripari, and V Molin. (£116.04.) Springer-Verlag, 1998. ISBN 3 540 14655 5.

Getting a CD-ROM for review opens new ways of experimenting with this medium. We therefore established a plan to evaluate this CD in our institution. The outcome, however, was rather disappointing. I will try to

Status	Percentage of HRT cases positive	Percentage of non-HRT cases positive
Nodal metastasis	26 (8 to 44)	41 (22 to 59)
Oestrogen receptor	82 (68 to 96)	78 (62 to 93)
Progesterone receptor	54 (35 to 72)	52 (33 to 71)
Bcl-2	87 (75 to 99)	79 (65 to 94)
P53	29 (13 to 45)	45 (27 to 63)
E-cadherin	48 (31 to 66)	72 (56 to 89)

give a short overview of the reasons for this, but to start with a positive point, installation was simple and worked on various computers in our department.

For pathologists, the information provided was too brief and the images (around 800) were adequate but not optimal, as critical pathologists always say! There was a substantial difference in the quality of the images. However adding your own pictures was quite easy.

Our residents found it hard to learn about cervical cytology from this CD-ROM. Though they could easily access specific parts of the cervix, they were then confronted with 200 to 400 pictures with very short explanations and no consensus on the findings. Furthermore, the slide show images moved too fast and did not add extra information. Our technicians found similar difficulties.

Adding sound would probably improve this CD substantially and make it better value. The text accompanying the slides was too short and should be reviewed.

In summary, this electronic way of presenting pathology will in the near future provide a great deal more information than a book can. At present, however, CD-ROMs seem to be based too much on the format of books and classical slides.

HANS VAN DER LINDEN

Book reviews

Molecular Aspects of Cancer and its Therapy. Edited by A Mackiewicz and P B Sehgal. (DM 188.00.) Birkhauser, 1998. ISBN 3 7643 5724 X.

This molecular and cell biology update grew out of the inauguration of the International Institute for Cell and Molecular Biology (UNESCO) in Warsaw, Poland. Cancer biology is a rapidly advancing field and update volumes may be out of date by the time they are published. Although the preface was written at the end of 1997, the 10 contri-

butions are supported by 1997 and even a few 1998 references. This is an unusual book. The authors were invited to present personal perspectives and have responded with a series of scholarly and thoughtful essays. The most successful contributions are those providing overviews of broad topics: Genetic control of metastasis (J M Backer and C V Hamby); Tumour immunology (A Maraveyas, D Hrouda and A G Dalglish); Cytokines in the host-tumour interaction (P B Sehgal); Gene therapy of cancer (M Wiznerowicz, S Rose-John and A Mackiewicz); and Genetic instability and tumour cell variation (G P Hemstreet). These are not only instructive and richly referenced but should (as stated by the editors) be accessible to both beginners and advanced biomedical scientists. The remaining five chapters are more specific: Cytokines in breast cancer dyshesion (I Tamm, T Kikuchi, I Cardinale, J S Murphy and J G Krueger); Breast cancer susceptibility genes (A Jasinka, K Sobczak, P Kozlowski, M Napierala, W J Krzyzosiak); Genetic alterations in lung cancer (E Jassem and J Jassem); Antisense strategy for cancer therapy (T Skorski, C Szczylik and B Calabretta); and Oligonucleotide therapeutics for human leukaemia (M Ratajczak and A M Gewirtz). This book will be of particular interest to molecular oncologists and cancer biologists and should be available in medical libraries.

JEREMY R JASS

Vascular Morphogenesis: In Vivo, In Vitro, In Mente. Edited by C D Little, V Mironov, and E H Sage. (DM 188.00.) Birkhauser, 1998. ISBN 3 7643 3920 9.

I always knew the day would come when the lack of a classical education would cause embarrassment. That day came when this book arrived and I glanced at the title. (In vitro, in vivo—no problem, but in mente?). Had I missed something after 21 years of postgraduate education in the sciences? I excused my own ignorance when I discovered that what the editors were introducing here was an entirely new field of study that encompassed the mathematics and computer simulation of vascular morphogenesis (in mente = "in mind"). This concept made up the third and last part of what is clearly an excellent book. Mind you, after marvelling at

the anatomical figures in the first two parts of the book I did wince at the inevitable complex formulae in the third. However, the mathematicians do well to guide us through the fractals and simulations using simple language in the figure legends.

The foreword by Judah Folkman reassures all of us working in the field of vascular biology (and, of course, antiangiogenic tumour therapy) that this book should be taken seriously. There is a wealth of information on both in vivo and in vitro methodologies and their limitations. At the same time I was left with an appreciation of the vasculature and its place in the great scheme of living tissue without having to read it from cover to cover.

As the vasculature is now considered to play a pivotal role in many disease processes (both inflammatory and neoplastic), this book could not have appeared at a better time. I will cherish my free copy.

A ANTHONY

Corrections

In the paper by Lwaleed *et al* in the March issue (Development and validation of an assay for urinary tissue factor activity, p 219), the Aim in the abstract should read: "To optimise an assay for urinary tissue factor (uTF) activity."

In the paper by Nagler *et al* in the May issue (Histopathological study of the human submandibular gland in graft versus host disease, pp 395–397), some additional corrections arrived too late to be incorporated in the published paper. These are:

On p 395, column 2, para 2, line 10, the rat antihuman monoclonal antibody is CDw52.

On p 396, column 2, para 3, line 4: the sentence should read "...we feel that the dose of irradiation received—a total dose of 19.2 Gy—would not have..."

On p 397, reference 36 is now a full paper: *Bone Marrow Transplantation* 1997;20:575–80.

IMPORTANT CORRECTION

Best Practice: *Helicobacter pylori*, May 1999

A serious error was introduced into this article during the editing process. On page 343, column 2, line 13, the sentence should read: "The British Society of Gastroenterologists and the Maastricht Working Party suggest screening patients **under** 45 years of age for *H pylori* before endoscopy, to reduce endoscopy workload."

We greatly regret this mistake, which was in no way the responsibility of the authors.