Multicentricity and recurrence of breast cancer

SIR—In response to Sacchini's Nov 9 commentary[1] on multicentricity and breast cancer recurrence, we feel that it is essential that some factual errors with respect to Vaidya and colleagues'[2] study are corrected, and, more importantly, that the biological and therapeutic implications of this study are emphasised.

Both Holland and colleagues'[3] and Vaidya's[2] studies used the same Egan's correlated pathological-radiological method, and the overall frequency (63%) as well as the distribution of multicentric foci (MCF) in terms of their distances from the primary tumour were similar in the two investigations. However, Vaidya and co-workers did further two-dimension and three-dimension analyses and took the size of each breast into account. They showed that the distributions of primary tumours and MCF in the four breast quadrants differed significantly (p=0·034). The primary tumour was more common in the upper outer quadrant whereas MCF were widely distributed in all four quadrants. MCF were present beyond the index quadrant (25% of breast volume including the tumour) in as many as 79% of breasts that harboured MCF, and in half the cases when all breasts were considered. Thus, even if a quadrant were excised, 50% of patients would still have MCF left behind, which is in variance with the suggestion in Holland's earlier study[3] that MCF are contained within the index quadrant in 90% of cases.

The biological significance of Vaidya and colleagues'[2] study is, in a way, paradoxical. In large studies of breast conservative therapy that were reviewed, greater than 90% of early breast recurrences occurred in the index quadrant; this is true whether or not radiotherapy is given.[4] In view of the new findings, if MCF were giving rise to these recurrences then half would have occurred in other quadrants, and, therefore, MCF probably do not give rise to early breast recurrence. MCF in the index breast probably behave in a fashion similar to putative MCF present in the contralateral breast, since recurrence rate in the remaining quadrants of the index breast is even less than that in the contralateral breast.[5] We also know that local recurrence occurs in the index quadrant irrespective of clear margins, which suggests that it does not arise from overlooked tumour. We therefore propose that the recurrence arises (*a*) from circulating metastatic cancer cells lodging in the highly vascular surgical bed (local relapse does harbinger a poorer prognosis), or (*b*) from local transfection of surrounding breast epithelium by nuclear material released from the original malignant clone resulting in insertional mutagenesis. Thus although the margins of excision are morphologically clear they may be genetically unstable. The logical sequel to this study is a clinical trial to test whether radiotherapy to the index quadrant alone can achieve good local control. We have begun pilot studies.

*Michael Baum, *Jayant S Vaidya, Indraneel Mittra*
*Department of Surgery, Institute of Surgical Studies, University College London, London W1P 7LD, UK; and Department of Surgery, Tata Memorial Hospital, Bombay, India

1 Sacchini V. Multicentricity and recurrence of breast cancer. *Lancet* 1996; **348:** 1256–57.
2 Vaidya JS, Vyas JJ, Chinoy RF, Merchant NH, Sharma OP, Mittra I. Multicentricity of breast cancer: whole organ analysis and clinical implications. *Br J Cancer* 1996; **74:** 820–24.
3 Holland R, Veling SHJ, Mravunac M, Hendricks JHCL. Histological multifocality of Tis, T1-1 breast carcinomas: implications for clinical trials of breast conserving surgery. *Cancer* 1985; **56:** 979–90.
4 Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Sem Surg Oncol* 1992; **8:** 161–66.
5 Kurtz JM, Amalric R, Brandone H, et al. Local recurrence after breast conserving surgery and radiotherapy. Frequency, time course and prognosis. *Cancer* 1989; **63:** 1912–17.

Author's reply

SIR—In reply to Baum and colleagues, I clearly stated in my commentary that the discrepancy in the finding of multicentricity of breast cancer in Vaidya's[1] and Holland's[2] papers may have been due to the fact that "Holland et al carried out one-dimensional analysis instead of two-dimensional analyses, and they did not take size of the breast into account". I also emphasised a possible biological difference: "moreover, multicentricity foci may differ from residual tumour in biological potential and hence clinical progression".

In stating that "MCF in the index breast probably behave in a fashion similar to putative MCF present in the contralateral breast" Baum and colleagues should consider that the risk of contralateral breast cancer was three times higher with respect to the new primary ipsilateral carcinoma when conservative surgery plus radiotherapy was given.[3] This finding reflects the role of radiotherapy on multicentric foci, and may be an argument against radiotherapy to the tumour-bed only.

Baum and colleagues' assertion that "local recurrence occurs in the index quadrant irrespective of clear margins" is not wholly true. Many workers have shown an increased risk of local recurrences in both invasive and in-situ breast cancer when the resection margin is involved, emphasising the origin or recurrences from the residual primary disease. The implant of circulating metastatic cells in the higher vascular bed of the excised tumour may be another, less frequent, mechanism of local recurrences. This mechanism may be common in local relapses after demolitive surgery, in which local relapses themselves represent a poor prognostic factor. In conservative surgery of the breast, local recurrences and distant metastases are partly independent events that occur at different times, and several predicting factors also differ.[2] The biological hypothesis stated by Vaidya[1] is undoubtedly of interest, and could be the basis of further studies.

Virgilio Sacchini
Breast Department, European Institute of Oncology, 20141 Milan, Italy

1 Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer, whole-organ analysis and clinical implications. *Br J Cancer* 1996; **73:** 820–24.
2 Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas: implications for clinical trials of breast conserving surgery. *Cancer* 1985; **56:** 979–90.
3 Veronesi U, Marubini E, Del Vecchio M, et al. Local recurrence and distant metastases: partly independent events. *J Natl Cancer Inst* 1995; **87:** 19–27.

SIR—Sacchini[1] suggests that the emerging technique of magnetic resonance imaging (MRI) might be able to detect multiple foci of breast cancer in vivo. There is already evidence to this effect with the various forms of MRI mammography proving consistently better than traditional radiographic mammography in this respect.[2,3]

In our initial series of 45 patients with invasive breast cancer, dynamic MRI mammography detected multicentric disease that had not been previously identified by clinical examination or radiographic mammography in 14 (31%) women.[3] We have also used dynamic MRI mammography to screen a separate group of 105 women for residual tumour or local recurrence 1–2 years after breast-conserving surgery and radiotherapy and found clinically significant lesions in only nine (8·5%). Clinical and mammographic follow-up is continuing for these patients, and at a median of 341 (IQR 168–451) days after MR mammography no further lesions have been identified. The discrepancy between the number of multicentric lesions identified in the evaluation of the primary cancers and

those discovered at follow-up implies that the radiotherapy and hormonal treatment given after breast conserving surgery might be controlling the multicentric disease not excised with the primary tumour. These findings may help to explain why local recurrence after breast conserving surgery without radiotherapy is generally accepted to be greater than 30%.[4] The true rate of multicentric disease is probably even higher than that detected by MRI mammography because, at the resolution achieved with this technique, lesions less than a few millimetres in diameter can be missed. Even accepting this potential inaccuracy, we have found that only about 29% of those multicentric lesions identified by MRI are visible on X-ray mammography.

The use of MRI mammography to evaluate women with primary breast cancers would undoubtedly increase the number of mastectomies done for multicentric disease that would previously have remained undetected. It is therefore important that, before MRI mammography becomes a clinically established technique, a prospective trial is done to compare the outcome of women assessed with traditional imaging techniques and those evaluated with MRI mammography. Such an investigation would establish whether any clinical benefit is accrued from the increased detection of multicentric disease.

*P J Drew, L W Turnbull, M J Kerin, P J Carleton, J N Fox

*University of Hull Academic Surgical Unit, Castle Hill Hospital, Hull HU16 5JQ, UK; and Centre for MR Investigations, Hull Royal Infirmary, Hull

1 Sacchini V. Multicentricity and recurrence of breast cancer. *Lancet* 1996; **348:** 1256–57.
2 Cross MJ, Harms SE, Cheek H, et al. New horizons in the diagnosis and treatment of breast cancer using magnetic resonance imaging. *Am J Surg* 1993; **166:** 749–55.
3 Kerslake RW, Carleton PJ, Fox JN, et al. Dynamic gradient-echo and fat-suppressed spin-echo contrast-enhanced MRI of the breast. *Clinical Radiology* 1995; **50:** 440–54.
4 Fisher B, Redmond C, Poisson R, et al. Eight year results of a randomised clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989; **320:** 822–28.

Helicobacter pylori infection in children

SIR—In her Nov 9 news item, Fricker (p 1301)[1] reviews Staat and colleagues'[2] report of the prevalence of *Helicobacter pylori* infection among American children and adolescents. It is now accepted that *H pylori* is an infection that almost always arises in childhood.[3] It is not, however, known which age group are at particularly high risk of becoming infected. In Staat's study the prevalence of infection increased with age from 16·7% in 6–9-year-olds to 26% in 10–14-year-olds and 29% in 15–19-year-olds. This finding could potentially be very important since it suggests that infection is acquired throughout the first two decades of life and therefore could influence treatment or vaccination strategies. This is contrary to evidence from developing countries that infection mainly occurs in very young children.[3] Staat and colleagues suggest that their findings are unlikely to be due to a cohort effect and we agree with them. Nevertheless, we believe that there is a much more likely explanation for their findings.

Staat and co-workers used an ELISA system to document the presence or absence of *H pylori* infection. Serological assays have often proven to be inaccurate in identifying *H pylori* infection in children. The serological response to *H pylori* depends on the antigen used, and commercial ELISA kits may be much less sensitive than western-blot techniques, especially in young children. It is well established that adult cutoff values will fail to diagnose up to 50% of children who are infected with *H pylori*. Raymond and colleagues have shown that a second-generation EIA test is 100% sensitive and specific in children over 10 years but failed to diagnose 20% of infected children under 10 years.[4] The ELISA system used by Staat et al was validated in an earlier study,[5] but this validation was based on a population that included very few young children. This ELISA test might not be sensitive in identifying very young children who are infected with *H pylori*. This lack of sensitivity could have resulted in an apparent rather than a real increase in the prevalence of infection during the first two decades of life. This drawback in the study should be recognised, otherwise potentially misleading conclusions may be drawn in relation to the epidemiology of *H pylori* infection in children.

Prospective studies with large cohorts of uninfected children in high-risk populations are required to answer many of the questions raised in this interesting study. If, however, serology is to be used to screen children, the cutoff points must be validated using serum from a very young population. Urea breath testing presents a more ideal but also a more expensive approach to studying this important issue.

*Marion Rowland, David Vaughan, Brendan Drumm

Department of Paediatrics, University College, Dublin; and *Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland

1 Fricker J. *Helicobacter* infection is common in US children. *Lancet* 1996; **348:** 1301.
2 Staat MA, Kruszon-Moran D. A population-based serological survey of *Helicobacter pylori* infection in children and adolescents in the United States. *J Infect Dis* 1996; **174:** 1120–23.
3 Mitchell HM, Li YY, Hu PJ, et al. Epidemiology of *Helicobacter pylori* in Southern China: identification of early childhood as the critical period for acquisition. *J Infect Dis* 1992; **166:** 149–53.
4 Raymond J, Kalach N, Bergeret M, et al. Evaluation of a serological test for diagnosis of *Helicobacter pylori* infection in children. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 415–17.
5 Best LM, Veldhuyzen van Zanten SJO, Sherman PM, et al. Serological detection of *Helicobacter pylori* antibodies in children and their parents. *J Clin Microbiol* 1994; **32:** 1193–96.

Abdominal aortic screening programme

SIR—We started a screening programme for aortic aneurysms in general practice, similar to that described by Jones and colleagues (Nov 9, p 1320),[1] in 1991 in the Éast Glamorgan area, coordinated by a hospital consultant. Patients were first requested to attend hospital for ultrasound screening by a consultant radiologist. We achieved an attendance rate of only 25%. By 1994 we realised the benefit of screening patients at the general practices; from May, 1994, to save money, the screening was done by a specially trained nurse, rather than radiologist, and only hypertensive patients were screened because of the finding[2,3] that the incidence of aortic aneurysms in those with hypertension is about double that of the normal population. 25 of the local general practices have been requested to submit lists of their male (aged 60–80) and female (aged 65–80) hypertensive patients (Jones et al looked at men only). So far all practices have cooperated. Aortas are thought to be aneurysmal when their diameters exceed 3 cm. Small aneurysms (3–4 cm) are re-scanned after 12 months and moderate aneurysms (4–5 cm) after 6 months. Surgery is advised for aneurysms greater than 5 cm. This protocol is identical to that of Jones and colleagues.

1659 men and 1474 women have so far been screened (73% attendance rate). Normal aortas have been found in 99% of women and 95% of men. 21 men and four women have had aneurysms greater than 5 cm requiring surgery; one died, and no other major complications have been reported. The inexpensive screening programme has been highly effective.

M G Guest, I M Williams, A J Cronin, M H Lewis, R K Winter

East Glamorgan General Hospital, Church Village, Pontypridd, Mid Glamorgan CF38 1AB, UK