Correspondence

Rapid review of cervical cytology

I read with interest the recent report by Faraker and Boxer.¹ The salient result of their endeavour is the claim to have reduced the false negative rate in their laboratory from 5.0% to 0.4%. They are to be lauded for such enviable statistics. However, the reality of a broader view of the cytology scene is not compatible with those figures. Their article commences by citing Dr Koss's paper which calls attention to the tragedy of the high incidence of false negative smear reports issued by cytology laboratories. Dr Koss states that "it is clear that the error rate of cytologic screening for precancerous lesions and invasive cancer of the uterine cervix is quite substantial."² Reports of false negative rates vary, reflecting numerous factors including the negative motivation in addressing this most humbling of revelations. What must be appreciated and accepted is the intrinsic search limitation of manually screening millions of cells each working day. The authors state that "errors must be due to a major lapse in concentration" and that "There is not usually anything difficult about false negative smears". It is time we jettisoned the myth that cytology is a 'simple test'. The fact that interpretation of abnormalities may frequently be less problematic than the monotonous search does in no way obviate the cumulative difficulty of this applied science. With that said, it is hard to posit a mechanism to account for the empirical claim of improving on the meticulous conventional microscopic search for a 'needle in the haystack' by a second rapid partial rescreen. One should anticipate further pickup by such a process does indeed represent cases missed due to major lapses.

It is also interesting that in spite of the authors' excellent results with the combination of conventional screening and rapid rescreening, they admit PAPNET's superiority. They conclude that where they should find 21 of a theoretical 25 false negatives, PAPNET will find 24 of 25. Further, they derive their false negative maximum of 25 as 5% of the total—the suggested benchmark.³ This benchmark is based on the intrinsic limitations of manual cytology. It is this limit which is extended another 25–30% by PAPNET. The added spectrum of sensitivity afforded by PAPNET pertains to cases characterised by a scant number of small abnormal cells. Therefore, PAPNET should reveal more than 30 false negatives in the authors' archives—an improvement of 50%. The value of this improvement is then formulated in solely financial terms. The source of their economic evaluation is not given and is erroneous. A more appropriate source of economic impact is to be obtained from professional studies addressing this aspect. Scientific analysis of cost effectiveness of PAPNET testing has appeared in the literature. In a comparison of various methods of health intervention using the model developed under contract from the US Congress Office of Technological Assessment, PAPNET testing is cost effective.

The Pap test is not, as popularly believed, a "cheap and easy" test. It is a serious scientific challenge requiring many resources. PAP-

NET testing is, even as inadvertently demonstrated by Faraker and Boxer, an improvement in the quality of cytology. The reason being it assists cytologists in overcoming a major intrinsic limitation of cervical cytology: the search for suspect cells. Its ultimate value is to be judged by women—and their loved ones.

STEPHEN FRIST

Medical Director
NSI Europe B.V.,
Zekeringstraat 39,
1014 BV Amsterdam,
The Netherlands

- 1 Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology. Four years experience and quality assurance implications. *J Clin Pathol* 1996;49:587–91.
- 2 Koss LG. The papanicolaou test for cervical cancer detection. A triumph and a tragedy. *JAMA* 1989;261:737–43.
- 3 Achievable standards, benchmarks for reporting, criteria for evaluating cervical cytology. Report of a working party set up by the Royal College of Pathologists, the British Society for Clinical Cytology and the NHS Cervical Screening Programme. *Cytopathology* 1995; 6(Suppl 2):1–32.

Drs Faraker and Boxer comment:

We are pleased that NSI take rapid review as a method of internal quality assurance for cervical cytology sufficiently seriously to write to this journal. There are errors and distortions in their letter that we would like to correct.

By quoting us out of context, the impression is given that we believe all screening errors are due to major lapses in concentration and, therefore, the detection of these false negatives by rapid review should be anticipated. Our paper¹ clearly states that we have identified three categories of screening error: those due to misinterpretation; those due to the scarcity of abnormal cells on the slide; and those due to a major concentration lapse. The latter cause accounted for only 10 of the 62 false negatives in the study group. As these conclusions were drawn from reviewing false negative smears that had been detected by rapid review, it is evident that rapid review is able to detect more than just errors due to major concentration lapse. Dr Frist states that it is hard to posit a mechanism for rapid review detecting abnormalities missed by full screening. We must remind the author that in science, counterintuitive observations are frequently true and that evidence precedes and must be explained by theory. The fact that the efficacy of rapid review is unexpected does not make it untrue.

We did not, as stated, derive our false negative rate from the 5% suggested benchmark. It would be ridiculous to suggest that merely because a benchmark is suggested, we would assume that to be our false negative rate. Again, our paper clearly states how we calculated our false negative rate. It is derived from the number of false negatives detected by targeted full rescreening and by rapid review, and by using a correction factor to adjust for the sensitivity of rapid review.

We fully agree that professional studies addressing the economic impact of such methods are more appropriate than our simple calculations and were therefore interested to see the editorial by Professor Hutchinson in *Acta Cytologica*.² In her cost effectiveness analysis for evaluating alternative rescreening strategies, it was determined that for a cytologist with a 75% sensitivity, the in-

creases in the sensitivity of screening provided by rapid review and PAPNET are almost identical (9.4% and 9.9%, respectively). What is not similar is the cost for each additional abnormal case discovered, which is calculated as \$348 for rapid review and \$4486 for PAPNET rescreening.

Dr Frist states that we admit PAPNET's superiority over rapid review and that we inadvertently demonstrated this. We did neither. We compared our detection rate by rapid review to that quoted for PAPNET which was determined by an entirely different study design. What we were suggesting was that if the two studies could be directly compared, PAPNET would produce only a tiny additional yield for a huge extra cost. However, the only valid way to compare rapid review with PAPNET is to apply both techniques to the same population of slides in a laboratory which can practise both rapid review and PAPNET screening to a high standard. It is possible that PAPNET is superior to rapid review, but in the present state of evidence it is equally possible that it is no better, or worse. The answer to this question could be determined by PAPNET screening of our archived slides which have already undergone rapid review. If NSI are willing to fund such a study, we would be delighted to participate.

- 1 Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology: Four years experience and quality assurance implications. *J Clin Pathol* 1996;49:587–91.
- 2 Hutchinson ML. Assessing the costs and benefits of alternative rescreening strategies. *Acta Cytol* 1996;40:4–8.

Bcl-2 protein does not help to distinguish benign from malignant lymphoid nodules in bone marrow biopsy specimens

We read the recent article by Chetty *et al* with interest.¹ The authors concluded that strong bcl-2 immunoreactivity in lymphoid cells and their aggregates in bone marrow specimens is indicative of the malignant lymphomatous nature of these lymphoid cells and can be used to detect minimal residual lymphomatous infiltration. They also mentioned in the Abstract, but not in the Results section, that "reactive lymphoid nodules did not show the same degree of bcl-2 positivity, and negative cells could be discerned within the reactive nodules".¹

The possible role of anti-bcl-2 protein immunostaining in distinguishing benign from malignant lymphoid infiltrates in bone marrow specimens was first proposed by Ben-Ezra *et al*² and recently has been mentioned briefly in abstract form.³ In contrast to Chetty *et al*,¹ we have observed a strong bcl-2 protein immunoreactivity in various proportions of lymphoid cells in both reactive and malignant lymphoid aggregates in all bone marrow specimens in our recent study.⁴ All samples had been fixed in formalin, processed routinely and embedded in paraffin wax. Prior to incubation with the bcl-2 protein antibody (clone 124; Dako, Glostrup, Denmark), the sections were microwaved for 4 × 5 minutes at 700 W. In our study, all lymphoid aggregates in the bone marrow samples from the patients with a previously diagnosed lymphoma were consistently strongly positive for bcl-2 protein. In addition, all lymphoid aggregates with benign

morphology in patients without any history of lymphoma displayed a consistent positive reaction for bcl-2 protein.¹ We have found considerably higher numbers of bcl-2 positive cells in malignant aggregates (mean value 78% per nodule) than in reactive nodules (mean value 60%). Nevertheless, we have confirmed the presence of numerous bcl-2 positive cells in apparently reactive benign nodules in all of our specimens. There were, however, always some bcl-2 negative cells in lymphoma bone marrow infiltrates in our material.¹

Thus, in contrast to the conclusions suggested by Chetty *et al.*,¹ we believe that bcl-2 expression should not be used as a discriminating criterion for the malignant nature of lymphoid aggregates. Overdiagnosis of bcl-2 positive reactive benign lymphoid aggregates as lymphomatous involvement is a considerable hazard and unnecessary over-treatment of patients cannot be reliably ruled out.

A SKÁLOVÁ
F FAKAN

Department of Pathology,
Faculty Hospital, Ed. Beneš 13,
305 99 Olzeň,
Czech Republic

- 1 Chetty R, Echezarreta G, Comley M, Gatter K. Immunohistochemistry in apparently normal bone marrow trephine specimens from patients with nodal follicular lymphoma. *J Clin Pathol* 1995;48:1035-8.
- 2 Ben-Ezra JM, King BE, Harris AC, Todd WM, Kornstein MJ. Staining for bcl-2 protein helps to distinguish benign from malignant aggregates in bone marrow biopsies. *Mod Pathol* 1994;7:560-4.
- 3 Neilson JR, Oates JL, Lumley M, Leyland MJ, Crocker J. Patterns of bcl-2 staining in bone marrow biopsies from patients with follicular lymphoma [abstract]. *J Pathol* 1995;175:154A.
- 4 Fakan F, Skálová A, Kuntscherová J. Expression of bcl-2 protein in distinguishing benign from malignant lymphoid aggregates in bone marrow biopsies. *Gen Diagn Pathol* 1996; in press.

Drs Chetty and Gatter comment:

We would like to thank Drs Skálová and Fakan for their comments on our paper. Our intention was not that bcl-2 immunostaining be used as a sole discriminant in separating benign from malignant lymphoid nodules in the bone marrow. The findings in our study are consonant with the staining profile/pattern of nodal follicular lymphoma and reactive follicular hyperplasia.

Reliance on immunohistochemistry alone, without cognisance of morphological and clinical features, is hazardous at the best of times. We are certainly not advocating the use of bcl-2 immunohistochemistry to diagnose follicular lymphoma in the bone marrow without a good index of suspicion. The index of suspicion is heightened by the strong immunorepression of bcl-2 in follicular lymphoma. It must also be remembered that quantitation of immunohistochemical staining is far from an exact science, but we are heartened to see that Drs Skálová and Fakan found "considerably higher numbers of bcl-2 positive cells in malignant aggregates than in reactive nodules".

In conclusion, bcl-2 immunohistochemistry, taken in conjunction with other relevant markers and the morphological and clinical features, is of use in separating follicular lymphomas from reactive aggregates.

Book reviews

Pathology for Surgeons in Training: an A to Z. Gardner D, Tweedle D. (Pp 408; £27.50.) Arnold. 1996. ISBN 0340 603747.

This book is the second edition of a short text which was originally called *Pathology for the Primary FRCS*. The text remains very similar to the original book although it has been slightly lengthened. Many of the medical dictionary type conditions are well described although special pathology is not a requirement for surgeons in training. Obviously, conditions such as abscess, AIDS, actinomycosis, amoebiasis, ageing, and amyloid are good general pathological conditions that might well be expected for the exam. There are, however, a number of unusual conditions found within the book—for example, antineoplastic drugs, the spine, space and air travel, "sludging of the blood" (a rather slang term), scrotum and retina. The book is well laid out and many important conditions, which will be expected knowledge for the new basic surgical trainee, are well covered.

I think the authors could look through their text again and perhaps extract some of the more specialised pathology, such as lymphoedema and ulcerative colitis (why ulcerative colitis and not Crohn's disease?). If this culling and, perhaps, some appropriate additions were made, this would be a very excellent book for surgeons in training.

K BURNAND

Saunders Electronic Atlas of Dermatology—CD Rom. (£202.00.) Harcourt Brace. 1996. ISBN 0721662242.

As someone who has a computer phobia, unlike my 10 year old son, I felt rather apprehensive on being asked to review this electronic atlas. Remarkably this CD Rom, which works on Windows and Mackintosh, contains over 2500 photographs with more than a quarter as photomicrographs of skin histology. In addition, the accompanying text is concise with definitions and differential diagnoses easily found by clicking simple icons. The information provided is based on the increasingly popular, recently published volumes of *Cutaneous Medicine and Surgery*, rapidly becoming the "bible" for US dermatology residents. Even for me, the disk was very user friendly and access to information was relatively easy. Photographs can be magnified, but tend to lose their definition. Also, for some reason, many illustrations were duplicated which was rather frustrating. Overall, the histology was remarkably good, but better at high power. I was surprised that no histology was available for relatively important disorders such as sarcoidosis, leprosy and leishmaniasis. Nevertheless, the content was extensive and included rare clinical examples, such as angioimmunoblastic lymphadenopathy. Classification of skin disorders was in places unorthodox such as including porokeratosis and Hailey Hailey as ichthyoses. I wondered also why they included lymphoma of the mouth in a dog! Apart from the irritating Texan-like tune that played repeatedly whenever I clicked the mouse too often, I was glued to the screen for quite some time by this well designed atlas. It highlighted the complexity of skin disorders,

but I am not sure there is enough histology for the pathologist. It will, however, be beneficial for the connoisseur who wants to specialise in dermatopathology up to DipRC-Path standard.

R CERIO

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel: 0171 383 6244; fax: 0171 383 6662. Books are supplied post-free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in Sterling drawn on a UK bank or by credit card (MasterCard, Visa or American Express) stating card number, expiry date, and full name. (The price and availability are occasionally subject to revision by the Publishers.)

Notices

Cytopathology for Histopathologists

February 3-7 1997

This is an intensive course in basic cytopathology suitable for all candidates preparing for the MRCP and Diploma in Cytopathology examinations, as well as established histopathologists requiring revision. It is organised by the Department of Cellular Pathology, Northwick Park Hospital (Dr Eamon Leen). The programme will consist of lectures, microscopy sessions and discussions. Topics will include cytopathology of the cervix, urine, respiratory tract, serous effusions, and fine needle aspiration of breast, lymph nodes, salivary glands, and other sites. In addition, keynote lectures will be given by Dr Amanda Herbert (Overview of cervical cytology screening) and Professor Sebastian Lucas/Dr Nick Francis (Cytology of infectious disease). The course is limited to 30 participants. Royal College of Pathologists' approval for 29 CME credits is envisaged (as per 1996). The course fee is £350.00, which includes lunch, refreshments and a course dinner.

For further information, please contact: Dr Eamon Leen, Department of Cellular Pathology, Northwick Park Hospital, Harrow HA1 3UJ. (Tel: 0181 869 3312; fax: 0181 864 1933.)

Third International Course on Bone Marrow Biopsy Pathology

May 21-24 1997

Venue: Charing Cross and Westminster Medical School, London

This course, organised by the European Bone Marrow Working Group, is an update on bone marrow disorders in the format of lectures, discussions and slide seminars (precirculated slides). The meeting starts with a short course on taking and reporting bone marrow trephine biopsy specimens and the application of immunocytochemistry. Topics include cellular constituents and kinetics of bone marrow, paediatric disorders, low grade and high grade lymphoproliferative disorders, an update of the FAB classification of MDS, iatrogenic bone marrow problems, detection of minimal disease in BMTB, diseases leading to stromal fibrosis, and disorders of bone modelling.

The course is limited to 100 participants and will attract CME credits. Course fee £350.00.

For further information, please contact: Professor K Henry, Department of Histopathology, Charing Cross and Westminster Medical School, Fulham Palace Road, London W6 8RF (tel: 0181 846 7139; fax 0181 846 1364; email: k.henry@cxwms.ac.uk).