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 professional 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.” 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 screening 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. 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. Some 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 Technology 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. PAPNET 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.

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Dr Faraker and Boxer comment: We are pleased that NSI take rapid review as a method of internal quality assurance for cervical cytology. We have clearly 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 paper 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 the use of the Rescreening lap. 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 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 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 severity 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 increase 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 cell found, 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 unlikely that it will be 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.


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”.2

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 al3 and recently has been mentioned briefly in abstract form.4 In contrast to Chetty et al, 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.5 All samples had been fixed in formalin, processed routinely, and stained in paraffin wax. Prior to incubation with the bcl-2 protein antibody (clone 124; Dako, Glostrup, Denmark), the sections were microwaved for 4 x 5 minutes at 700 W. In our study, all lymphoid aggregates in the bone marrow samples from the patients who were 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. We have found considerably higher numbers of bcl-2 positive cells in malignant aggregates (mean value 78% per node) than in reactive nodules (mean value 40%). 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.

Thus, in contrast to the conclusions suggested by Chetty et al., 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.

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Drs Chetty and Gatter comment:

We would like to thank Drs Skalová and Fakán 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 cognizance 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 immunostaining 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 Skalová and Fakán 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


This 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. Objective questions are provided for self-assessment. This book is a concise, well-organized book designed for basic surgical training and is very 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 were the case, the book would be comprehensive. Nevertheless, we have confirmed the presence of numerous bcl-2 positive cells in apparently reactive benign lymphoid aggregates as lymphomatous involvement is a considerable hazard and unnecessary over-treatment of patients cannot be reliably ruled out.


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 Macintosh, contains over 2500 photographs with more than a quarter as photomicrographs of skin histology. In addition to this 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 electronic versions of the Histopathology of the Skin and the rapid 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. For someone 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 angiomyolipomatous lymphangiomyomatosis. Many of the included disorders was in places unorthodox such as including porokeratoses and Hailey Hailey as ichthyoses. I wondered also why they included lymphoma of the mouth in a dog? Apart from the irritating pop-up-like tings that were 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 DnPRP-Path standard.

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Cytopathology for Histopathologists

February 3-7 1997

This is an intensive course in basic cytopathology suitable for all candidates preparing for the MRCPATH 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 comprise lectures, microscopy sessions and discussions. Topics will include cytopathology of the cervix, urinary, 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 Lasiu (Dr Nick Francis (Cytology of infectious disease). The course is limited to 30 participants. Royal College of Pathologists’ annual fee for CPD or CME credits is envisaged (as per 1996). The course fee is £350.00, which includes lunches, 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 (precipitated 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, monocytic disorders, low grade and high grade lymphoproliferative disorders, an update of the FAB classification of MDS, immunohistological marrow problems, detection of minimal disease in B-cell and T-cell lymphomas, immunohistological 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 Skalová, Department of Pathology, 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).