

Correspondence: Pseudomyxoma peritonei and the cytologist

The recent paper by Pfitzer and Richartz describes the results of fine needle aspiration in a series of five patients with pseudomyxoma peritonei¹. The findings are significant because pseudomyxoma peritonei is not common and is unfamiliar to many medical practitioners, but it occurs with sufficient frequency that most pathologists and clinicians may expect to encounter an occasional case^{2,3}.

It is important to remember that 'pseudomyxoma peritonei' is simply a description for a macroscopic appearance, analogous to 'ascites', and the behaviour, treatment and prognosis depend on the underlying lesion². Thus, inflammatory conditions may be associated with a localized collection of mucus adjacent to a ruptured viscus. On the other hand, progressive, diffuse pseudomyxoma peritonei is generally considered to be a neoplastic process. Although Pfitzer and Richartz state that it is still a matter of conjecture as to which cells play a role in the production of the mucus, most workers in this field believe that neoplastic mucus-secreting cells within the peritoneal cavity are responsible²⁻⁴. These cells may have very low grade cytology, and some authors refer to them as being adenomatous, but their relentless (although slow) progressive growth ending in the death of the patient if untreated suggests that they are best classified as malignant (i.e. mucinous adenocarcinoma)^{2,5}.

Pfitzer and Richartz found no epithelial cells in any of their patients, although mesothelial and fibroblast-like cells were identified¹. This finding is consistent with the low cellularity of most cases of pseudomyxoma peritonei due to well differentiated adenocarcinoma; mucinous tumour cells may be difficult to find even in histological sections². Whenever acellular mucin is found in a percutaneous biopsy or aspirate, it raises the possibility of a mucinous neoplasm, and investigations to identify the source of the mucin are indicated. If the patient also has abdominal distension, the finding of mucinous material is presumptive (although not diagnostic) evidence of pseudomyxoma peritonei due to a mucinous neoplasm; the source of the mucin should be identified, since staging, therapy and prognosis depend on the primary site.

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I have just read an article in the 1995, October issue of *Cytopathology* on the subject of 'Cytology of pseudomyxoma peritonei' written by P. Pfitzer and G. Richartz¹. Although the contents of the article are interesting, the authors' review of the literature is incomplete, since they fail to cite two contributions which were made from this laboratory. These are:

- 1 Gupta RK *et al.* Cytodiagnosis of pseudomyxoma peritonei in cases suspected of ovarian tumours. *Diagnostic Cytopathol* 1993; **9**: 682-4.
- 2 Gupta RK *et al.* Aspiration cytodiagnosis of pseudomyxoma peritonei in a male arising from an appendiceal cystadenocarcinoma. (Test and Teach). *Pathology* (J. of Royal College of Pathologists, Australia) 1994; **26**: 285, 343-4.

I also question the validity of the use of vimentin and cytokeratin in their presentation, since it is not cost effective. I would like to know if they recommend the use of the above panel of immunomarkers for the diagnosis of pseudomyxoma peritonei, or are the markers used only for research purposes. An answer to the above queries in the form of a letter in the Journal will be appreciated.

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Dr Gupta's criticism of our article, 'Cytology of pseudomyxoma peritonei', is absolutely justified, and we apologize for not having noticed his two contributions of 1993 and 1994. He reports on four female and one male case, which naturally are a valuable contribution to the 'little information available on the cytodiagnosis of pseudomyxoma peritonei'. The observations agree completely.

By using vimentin and cytokeratin markers we were able to prove that the elongated spindle-shaped fibrous cells within the mucinous background were reactive mesothelial cells. The immunomarkers were only applied for the identification of the cells, and were intended to address the question as to whether endothelial cells were involved.

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Achievable standards, benchmarks and criteria for reporting cervical smears

The October 1995 edition of *Cytopathology* included (as a supplement) a report produced by a Joint Working Party of the Royal College of Pathologists, the British Society for Clinical Cytology (BSCC) and the NHS Cervical Screening Programme¹. This recommended that 'the BSCC guidelines for judging the adequacy of a cervical smear² should not be used by the laboratory to decide whether or not a routine cervical smear is adequate'. This statement followed the recognition that strict application of the guidelines could lead to a high percentage of inadequate smears. It is essential to examine the historical background to this statement in order to assess its likely impact.

The Papanicolaou smear has been a routine screening procedure for over three decades, yet laboratory criteria for smear adequacy have remained ill defined. Current generally accepted laboratory criteria for an unsatisfactory smear include excessive blood, inflammation, air-drying, cytolysis and inadequate squamous cells^{3,4}.

Whether or not an adequate smear sample should contain cells which have been gathered from the transformation zone of the cervix (that is metaplastic cells, endocervical cells and mucus) has been debated for over a decade^{5,6}. There is evidence from retrospective studies that smear samples without endocervical cells should (especially in women of child-bearing age) be repeated, since: (i) smears without endocervical cells present, have a lower detection rate for cervical precancerous lesions^{5,7,8}; (ii) women who develop cervical cancer have been found to have a high proportion of previous smears without endocervical cells⁶. These findings have been recognized in the Bethesda System for reporting smears now widely used in the USA⁴, and in the Netherlands which has a national policy for reporting smears without endocervical cells as inadequate.

A BSCC booklet on taking cervical smears emphasizes how most cervical cancers develop in the transformation zone, and states that 'If the test is to be reliable care must be taken to scrape all this vulnerable area of the cervix'⁹. Austoker re-emphasizes this in a practical guide for GPs, and although acknowledging that the main evidence of a smear's adequacy is a sufficient quantity of squamous epithelial cells, she goes on to say that 'An indication that the transformation zone has been properly sampled is the additional presence of endocervical columnar cells and recognizable metaplastic cells'¹⁰.

National guidance on smear quality was issued in the UK through an intercollegiate working group on cervical cytology screening in 1987¹¹. A National Audit Office (NAO) report in 1992 found that the guidance issued with respect to what constituted an adequate smear was not always followed¹². Laboratories which had been audited had adopted differing approaches to dealing with inadequate smears. The NAO considered that further guidance produced by the BSCC would lead to greater consistency.

In 1990 the BSCC issued a statement¹³ in *Cytopathology* regarding the cell content of cervical smear samples. Later that year the BSCC guidelines for judging the adequacy of a cervical smear were issued². These guidelines stated: 'The ideal smear sample should contain endocervical cells, metaplastic cells, endocervical mucus and squamous cells. Squamous cells and at least two of the three other elements should be present in an adequate smear'. A workshop and circulation of cytology slides amongst colleagues representing all cytology laboratories in the Oxford region demonstrated that when the

BSCC guidelines were used, agreement could be reached on the adequacy or inadequacy of smears in 80% of cases².

It is now 5 years since the BSCC guidelines were published, and considerable inter-laboratory variation persists in the proportion of inadequate smears reported by cytopathology laboratories nationally¹⁴. Unfortunately the BSCC have been accused, in the past, of giving contradictory advice to laboratories about the need to check smear samples for cells from the transformation zone¹⁵. The latest working party might now be criticized for using cost considerations, in the absence of any further epidemiological evidence, to judge the importance of checking for transformation zone cells in screening samples. Whether cytopathology laboratories will now develop a nationally consistent approach to reporting the adequacy of smear samples remains to be seen.

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We welcome the recently published guidelines ‘Achievable standards, benchmarks for reporting and criteria for evaluating cervical cytopathology’¹, which have helped to clarify many controversial points in the reporting of cervical smears. Nevertheless, there is one aspect of the Guidelines which concerns us.

We support the proposal in the Guidelines of recording whether or not indicators of transformation zone sampling are present in the smear, whilst reporting the smear overall as negative. This leaves the final decision as to whether this is an adequate smear up to the smear-taker, who can combine this information with relevant clinical findings. However,

we do not agree with the Guideline suggesting that smears without transformation zone indicators taken from women during 'follow up' of significant abnormalities (i.e. CINII or worse) should be reported as inadequate. First, this introduces double standards—why should a similar smear from one category of patient be reported differently to another? It implies that a smear without indicators of transformation zone sampling is suboptimal, but the report recommends reporting these as negative within the screening population. These follow-up smears will presumably be taken at colposcopy, and in this situation the smear is usually taken by an experienced operator working in an ideal clinical environment. Second, on a more practical point following cone biopsy, it may be very difficult to obtain endocervical cells due to scarring, etc. Third, what is meant by 'follow up'? Does this mean the first 5 years following treatment, or longer?

Lastly, at a time when we are increasingly encouraged to practise evidence-based medicine, we were disappointed that no references were cited to support this change in practice which will have resource implications for both cytology laboratories and colposcopy clinics.

Following discussion with our colposcopists, we have decided not to implement this part of the document, but will report the presence or absence of indicators of transformation zone sampling to allow the smear-taker to make a judgement on adequacy based on a combination of cytological and clinical data.

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Lupus erythematosus (LE) cells in pleural fluid: initial diagnosis of systemic lupus erythematosus by cytologic examination

The cytologic evaluation of body fluids may yield valuable information in the diagnostic work-up of patients with generalized, non-specific signs and symptoms. We report a case of systemic lupus erythematosus (SLE) wherein the initial diagnosis was strongly suggested by the presence of lupus erythematosus (LE) cells in the pleural fluid at the time of routine cytologic examination.

A 43-year-old female presented with new onset grand mal seizures, followed by headache, neck stiffness and photophobia. Her past medical history was remarkable only for rheumatoid arthritis for 13 years.

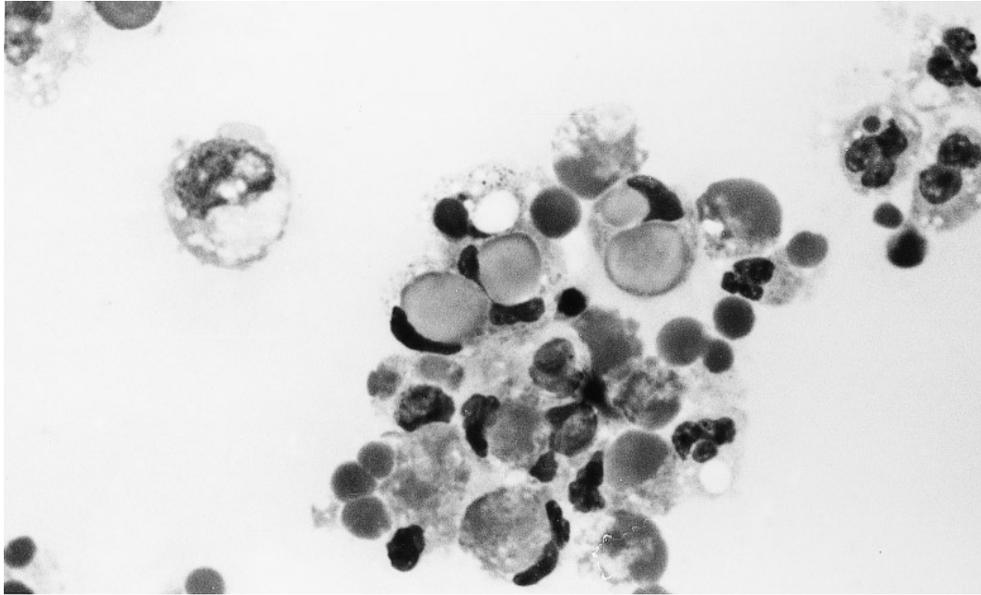


Figure 1. Typical 'LE' cell in pleural fluid cytopsin preparation demonstrates single large homogeneous inclusion within neutrophil (Diff-Quik stain, $\times 400$).

Physical examination was unremarkable with the exception of nuchal stiffness. Computed tomography (CT) scan of the head revealed a subarachnoid haemorrhage and cerebral angiogram demonstrated two aneurysms. The patient underwent craniotomy and clipping of the aneurysm without complications. Post-operatively she experienced difficulty in swallowing and was diagnosed with true vocal cord paralysis on the left side requiring placement of a PEG tube for feedings. She then developed low-grade fevers with occasional temperature spikes to 39.1°C. Physical examination revealed decreased breath sounds bilaterally with egophany, and a chest x-ray showed bilateral pleural effusions. Thoracentesis was performed and the pleural fluid cytology showed neutrophils with large homogeneous smooth inclusions classic for LE cells in a background of acute and chronic inflammatory cell (Fig. 1). On the basis of these findings, the possibility of SLE was raised, and the patient was reevaluated by the Rheumatology service for possible rheumatoid arthritis with pleural involvement *versus* a new diagnosis of SLE. Serum studies were performed and revealed a markedly elevated anti-nuclear antibody (ANA) titre of 1:1280 as well as a significantly elevated titre of antibody to double-stranded DNA (60 U/ml, normal <5 U/ml). Antibody against the Sm antigen was also detected. With these findings the patient was diagnosed as having SLE. Her fevers and pleural effusions improved with the administration of intravenous steroids. She was subsequently started on oral prednisone therapy and discharged for follow up.

A number of different autoantibodies may be detected in SLE patients, the most notable of which are those directed against nuclear components. The action of such antibodies leads eventually to denaturation and homogenization of dead or injured cells, which form haematoxylin bodies. These structures are then engulfed by phagocytic cells (most commonly neutrophils, occasionally eosinophils and macrophages), resulting in the formation of 'LE cells'.

Though LE cells were initially described in the bone marrow¹ and peripheral blood², they have been described in body fluid effusions³. However, the presence of LE cells in a pleural fluid as the initial finding in a new case of SLE, such as seen in the present case, has only rarely been reported⁴⁻⁶.

In order for the clinical significance of LE cells to be appreciated, they must be distinguished from 'pseudo-LE cells' or 'tart cells'^{1,3}. In contrast to true LE cells, 'tart' cells can be found in most serous effusions regardless of their etiology and result from the phagocytosis of nuclear debris by macrophages. Reliable distinction from LE cells can be made on the basis of the non-homogeneous character of the phagocytized material in the pseudo-LE cells in contrast to the smooth homogeneity seen in true LE cells.

The formation of LE cells was originally thought to represent an *in vitro* phenomenon, as serous fluids (as well as peripheral blood) typically contain greater numbers of such cells when allowed to stand at room temperature. However, serous effusions processed soon after removal from the patient may also contain significant numbers of such cells, indicating that their formation clearly occurs *in vivo* as well.

The use of the classic LE cell preparation/test on peripheral blood for the diagnosis of SLE has become obsolete, replaced by serologic studies for the presence of various autoantibodies. However, as illustrated by the present case, the cytopathologist still has the opportunity to observe LE cells in serous effusions from these patients, and should conduct a deliberate search for such cells in unexplained effusions occurring in the typical young female patient population.

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Rapid review

A recent issue of *Cytopathology* (1995, Vol. 6, issue 6) contained several articles on rapid rescreening of cervical smears. We would like to comment on some of the points made in the articles.

The editorial by Dr Wolfendale¹ made the point that good training, good working conditions, etc., may be more important factors for quality performance in the laboratory than rapid rescreening. Whilst we agree with this statement, the fact remains that some form of quality control checking measure should be in place, and we believe rapid rescreening is the most effective of the checking methods which are currently available. Rapid rescreening has been repeatedly demonstrated to be a more effective alternative to random 10% rescreening as a method of quality control²⁻⁴. It has the added advantage of rapidly identifying poor performance, although we concede that rapid rescreening may not reduce the death rate.

Dr Wolfendale suggests that rapid rescreening is only effective at detecting low grade dyskaryosis and could add to the laboratory workload. The identification of low grade dyskaryosis is not to be dismissed, as it is recognized that many of these patients are in a high risk group. The undertaking of a rapid rescreening protocol should not add to laboratory workload if it is replacing 10% random rescreening. We believe the work equates to that involved in random 10% rescreening.

The article by Mitchell *et al.*⁵ in the same issue of *Cytopathology* suggests rapid rescreening has a minimal effect on false-negative rates, as many false-negative smears have less than 200 abnormal cells per slide and escape detection regardless of the checking method used. Most cytologists would agree that smears containing less than 200 abnormal cells may be misdiagnosed as negative, but this is not true of all false-negative cases. Mitchell *et al.* state that 39% of false-negative smears are high grade, and we suggest that rapid rescreening would be successful in identifying a high proportion of these cases. Mitchell's high grade pick-up rate of 5 per 10 633 smears (0.047%) is higher than most other published figures. Faraker reports 0 high grade smears in 9633², Dudding three in 24 012 (0.012%)³, and Baker 14 in 117 890 (0.012%)⁴. Only Johnson has a higher rate of six high grade smears in 8640 (0.093%)⁶. These findings appear to endorse the use of rapid rescreening.

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Report of Working Party on Internal Quality Control for Cervical Cytology Laboratories

The editorial in the February 1996 issue of *Cytopathology* makes comments about the Scottish Office *Report of the Working Party on Internal Quality Control (IQC) for Cervical Cytology Laboratories*¹, and the combined Royal College of Pathologists (RCPath), National Health Service Cervical Screening Programme (NHSCSP) and British Society for Clinical Cytology (BSCC) working party report *Achievable Standards, Benchmarks for Reporting, Criteria for Evaluating Cervical Cytopathology*² which could lead to misunderstanding about the intentions and recommendations of the two working party documents.

The IQC document¹ was produced by the Scottish Office, and, although broadly consistent with Department of Health guidelines, has not been adopted as official NHSCSP policy. The Scottish Office did not set out to produce targets or achievable standards, and specifically recommended 'professional bodies to set and review such standards'. The RCPath/NHSCSP/BSCC working party was convened for that very purpose, with cross representation and different aims and terms of reference².

There is little overlap between the IQC and *Achievable Standards* documents, except that both recommend rapid rescreening of all negative and inadequate smears. Neither specify the precise technique to be used, which should not be too quick for the cells to be seen—and in practice is not too quick if carried out according to published methods^{3,4}. Both working parties recognize the value of this technique in allowing potential false negatives to be identified before the smear is reported, as well as providing a method of calculating sensitivity. Random rescreening of 10% of smears achieves only the latter because 90% of potential false negatives are not reviewed.

Although the Scottish Office recommends a 'target' of 95% sensitivity for primary screening, they also recommend calculating 95% confidence intervals. Thus their target is not inconsistent with the achievable range of 85–95% recommended by the RCPath/NHSCSP/BSCC. The latter range was deliberately broad, to be non-threatening and to allow 'learning curve' for introducing this new technique: comparison of results between laboratories and peer review will enable the NHSCSP to monitor different methods of rapid rescreening—and if necessary review the achievable range in the light of experience.

The IQC document should not be compared with *Borderline Nuclear Changes in Cervical Smears: Guidelines on their Recognition and Management*⁵ since the two documents had completely different objectives and have virtually no points in common. The working party which produced *Borderline Nuclear Changes* (and the later one producing *Achievable Standards*) specifically set out to 'involve themselves in the current controversy surrounding borderline smears', whereas the Scottish Office working party did not.

The Scottish Office aimed to recommend processes and methodology for internal quality control, while the RCPath/BSCC/NHSCSP dealt with professional practice and recommended targets and achievable ranges for reporting: careful reading of these documents shows that they are complementary and have no significant disagreement. We agree that all these documents aim to improve standards in cervical screening throughout the UK.

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