

## Leader

# Borderline nuclear changes in cervical smears: Guidelines on their recognition and management

National Coordinating Network (National Cervical Screening Programme), British Society for Clinical Cytology, and Royal College of Pathologists' Working Party

### Introduction

The term "borderline nuclear abnormality" was introduced in 1986 by the British Society for Clinical Cytology (BSCC)<sup>1</sup> in its recommendations on the terminology of cervical smears. It was to be used in cases in which there is genuine doubt as to whether the changes being reported are neoplastic. The term constitutes a holding category rather than a diagnosis.

Recent advice issued by the BSCC, with the aim of standardising the collection of statistical data states that, except where patients are being followed up for previous abnormal smears, negative reports should not be issued where an early repeat smear is required.<sup>2,3</sup> The result of the smear should be categorised as either inadequate for screening, or as showing borderline nuclear changes if there is genuine doubt as to whether changes present are neoplastic. Only if the patient's smear *does not* warrant an early recall should the smear be termed negative.

The proportion of smears in which borderline nuclear changes are reported varies (fig 1). The proportion reported as showing borderline nuclear changes and negative (early repeat advised) rises and falls in inverse relation to the number reported as mildly dyskaryotic (fig 2).

Women in whom borderline nuclear changes have been reported, and in whom such classification is not justified, may then have a prolonged course of follow up, or even therapeutic intervention, neither of which are warranted by the risk of progression to cancer. The problem is compounded by the fact that

few long term studies have been done which define the risk of developing cervical intra-epithelial neoplasia (CIN) or cancer in women identified as having borderline nuclear changes in their cervical smears.<sup>4-6</sup> The natural tendency in reporting smears is, therefore, to err on the side of caution and, if there is any doubt about the clinical importance of changes in a smear, to report borderline nuclear changes, thus ensuring that a follow up smear will be done within a relatively short period of time.

The fact that interregional, interlaboratory, and interobserver differences exist has implications for the management of the screening programme, and for the women it identifies.

This variation may be due to genuine differences in the number of smears in which such changes are present in different parts of the country, or to differences in reporting practice and interpretation. Clear guidelines are therefore needed for the recognition of borderline nuclear changes. They are also needed for the management of women in whom such changes have been reported in their smears, because some women may be being referred unnecessarily early for colposcopic examination. These cytological abnormalities cannot, however, be ignored because, very occasionally, women with borderline nuclear changes are found to have CIN or even cancer.<sup>4</sup>

In 1992 the National Coordinating Network (NCN) of the National Cervical Screening Programme asked representatives of the British Society for Clinical Cytology

National Coordinating Network (National Cervical Screening Programme), British Society for Clinical Cytology, and Royal College of Pathologists' Working Party

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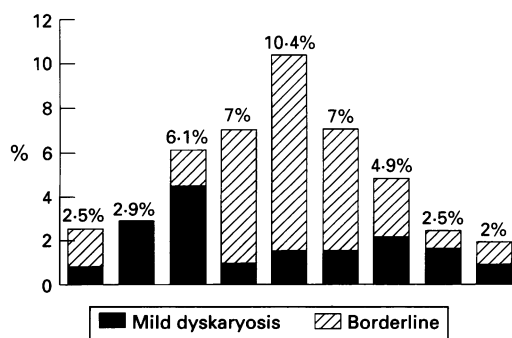


Figure 1 Graph showing variation in number of smears reported as showing borderline nuclear changes (taken from nine laboratories in one region).

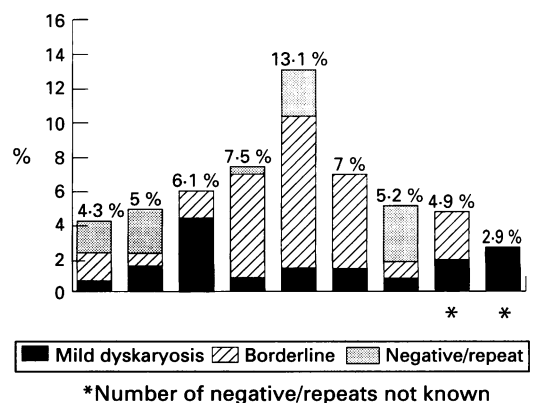
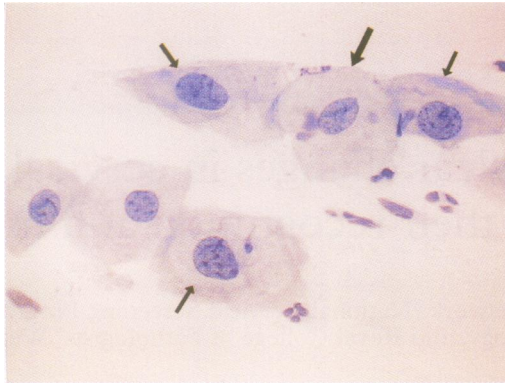
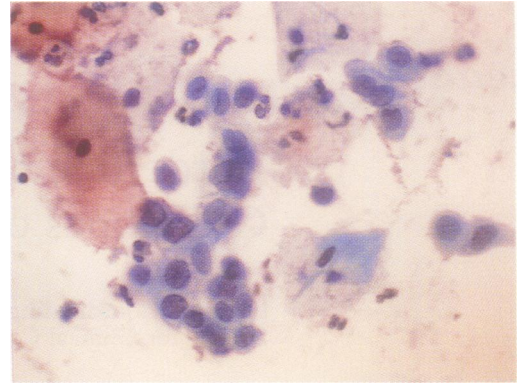


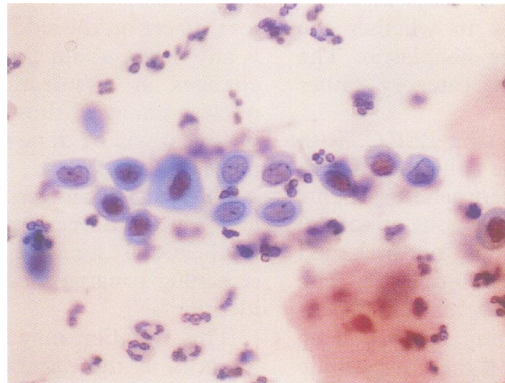
Figure 2 Graph showing proportion of smears reported as showing borderline nuclear changes or negative (early repeat advised) rises and falls in inverse relation to number of smears reported as mildly dyskaryotic.



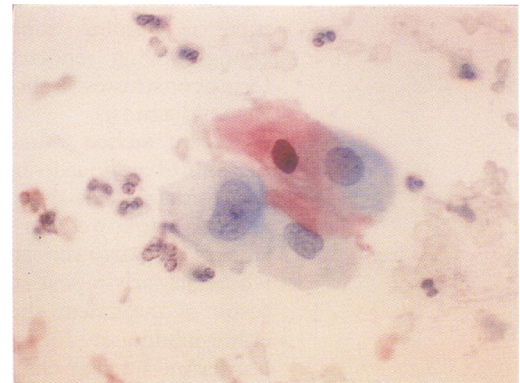
**Figure 3.** Mild dyskaryosis. The cells marked by the small arrows are mildly dyskaryotic. They have increased nuclear:cytoplasmic ratios and the nuclei are hyperchromatic and somewhat irregular in outline. There is an abnormal chromatin distribution. The cell indicated by the large arrow also has a slightly increased nuclear:cytoplasmic ratio, but the chromatin is more evenly dispersed. This cell shows borderline nuclear changes.



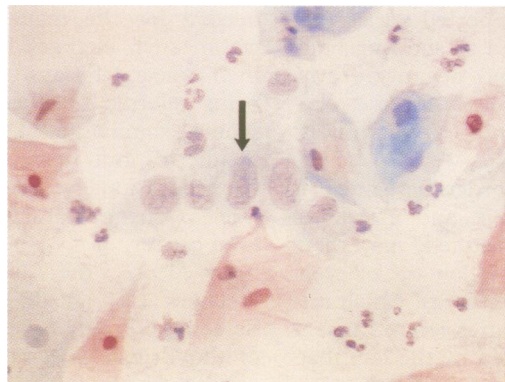
**Figure 4.** Severe dyskaryosis. The cells have high nuclear:cytoplasmic ratios and irregular nuclear outlines with rather poorly defined nuclear membranes. The nuclei vary in shape and size and have a coarse chromatin pattern. Contrast with fig 5.



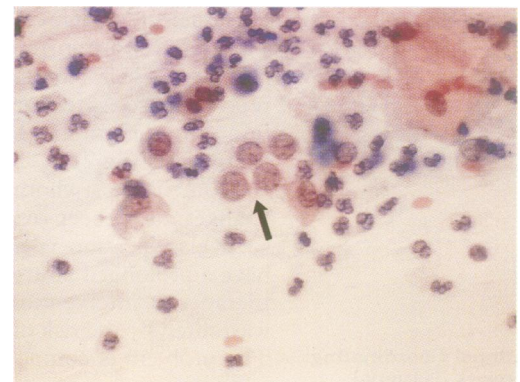
**Figure 5.** The four central cells are normal immature metaplastic squames. The nuclei are of uniform shape and size and have well defined membranes. The chromatin is evenly dispersed and small nucleoli are seen. Contrast with fig 4.



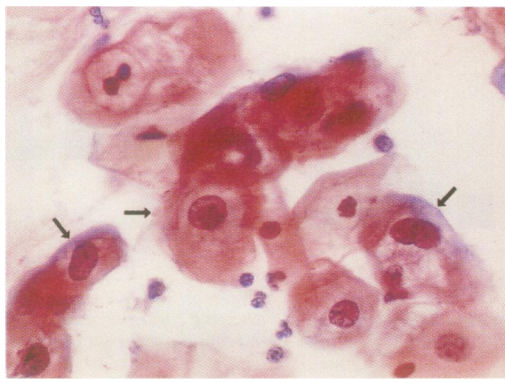
**Figure 6.** Pale dyskaryosis. These mildly dyskaryotic cells have pale-staining nuclei, but note the raised nuclear:cytoplasmic ratios and irregular nuclear outlines and chromatin distribution.



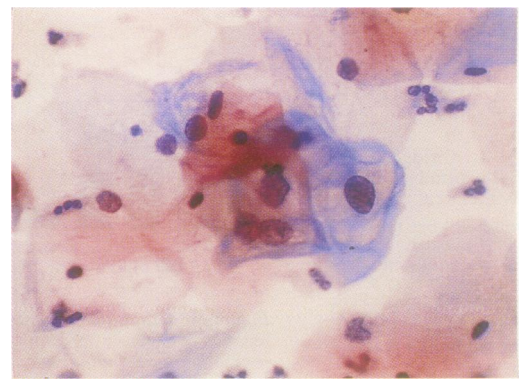
**Figure 7.** Pale dyskaryosis. The group of mild and moderately dyskaryotic cells arrowed has pale-staining nuclei in comparison with the surrounding normal squames and polymorphs, but note the anisonucleosis and abnormal chromatin distribution.



**Figure 8.** Pale dyskaryosis. The group of severely dyskaryotic cells arrowed is of small cell type and shows pale nuclear staining with multiple small nucleoli. The abnormal chromatin distinguishes them from immature metaplastic squames.



**Figure 9.** Mild dyskaryosis with koilocytosis. In the cells indicated by an arrow there is perinuclear clearing of the cytoplasm with a hard margin to the vacuole. These are typical koilocytes. The two marked cells to the left also have features of mild dyskaryosis.



**Figure 10.** Mild dyskaryosis with koilocytosis. The cell to the right of centre is another example of a cell with mild dyskaryosis and koilocytosis. Compare this cell with that indicated in fig 14 in which there are borderline nuclear changes.

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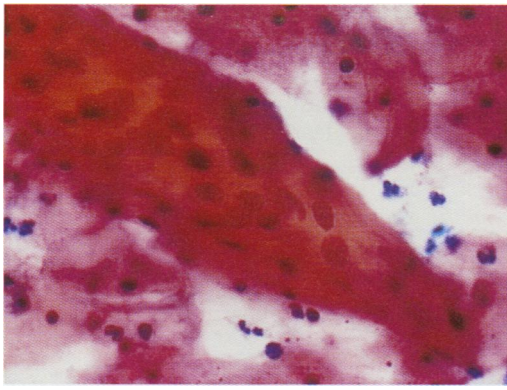


Figure 11. Borderline nuclear changes with dyskeratosis. The nuclei in this "spike" of dyskeratotic cells are enlarged and there is some irregularity of outline but the chromatin remains evenly dispersed.

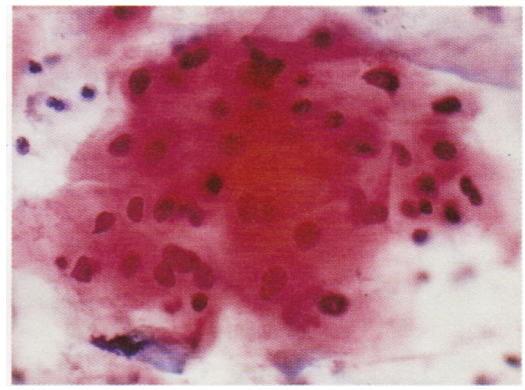


Figure 12. Borderline nuclear changes with dyskeratosis. The cells have increased nuclear: cytoplasmic ratios and variably condensed nuclear chromatin.

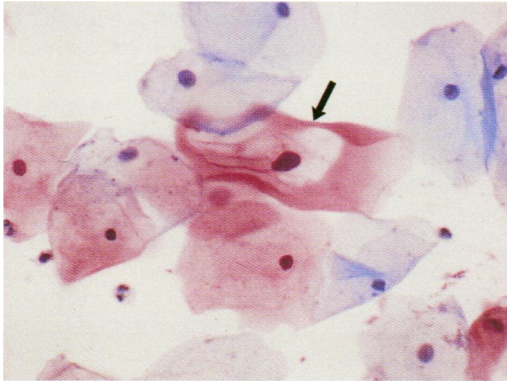


Figure 13. Borderline nuclear changes with koilocytosis. In addition to the perinuclear halo with condensed cytoplasmic rim, typical of a koilocyte, in the cell indicated by the arrow there is nuclear enlargement, slight nuclear irregularity, and pyknosis.

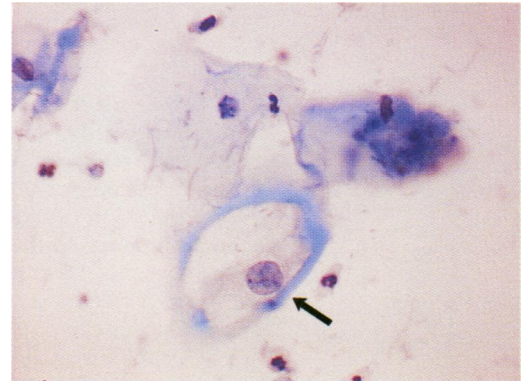


Figure 14. Borderline nuclear changes with koilocytosis. Contrast the cell indicated, in which there is an increased nuclear: cytoplasmic ratio, smooth nuclear outline, and fine, evenly dispersed chromatin with that in fig 10 in which there is mild dyskaryosis.

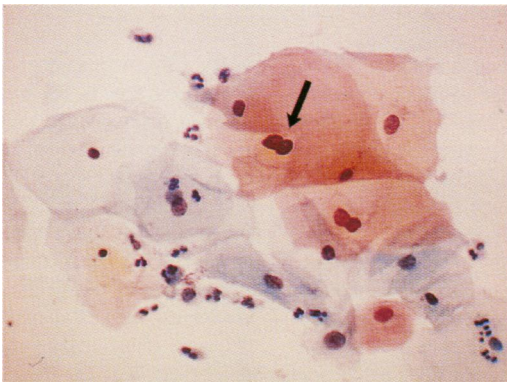


Figure 15. Borderline nuclear changes in cells with HPV infection. The binucleate cell, indicated, has enlarged, pyknotic, and somewhat irregular nuclei.



Figure 16. Dyskeratosis without dyskaryosis. The cells are arranged in a conical or spike formation and have an orderly pattern. There is no nuclear abnormality.

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Figure 17. Dyskeratosis without dyskaryosis. The cells are arranged in a pearl or concentric whorl and show a tendency to elongation and flattening of the peripheral nuclei. There is no substantial nuclear abnormality.

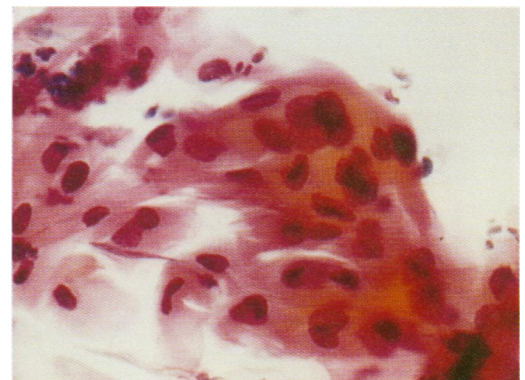


Figure 18. Dyskaryosis and dyskeratosis. The cells have dense, orangeophilic cytoplasm and there is nuclear enlargement, hyperchromasia, and irregularity of nuclear outline, typical of mild dyskaryosis.

(BSCC) and the Royal College of Pathologists (RCPath) to set up a working party.

Its remit was to: (i) examine the circumstances under which borderline nuclear changes are most commonly recorded; (ii) define the appearances which justify such a report; (iii) issue guidelines on the appropriate follow up procedures; and (iv) indicate at what stage these changes should precipitate referral for colposcopy. The working party was also asked to say when, in its opinion, a negative or unsatisfactory report would be more advisable and to clarify the distinction between borderline nuclear changes and mild dyskaryosis.

The recommendations set out here are intended to expand and clarify advice which has been offered before.<sup>1</sup>

### Borderline nuclear changes

Borderline nuclear changes are most commonly reported in

- the presence of human papilloma virus (HPV) infection (warty smears)
- inflammatory epithelial changes
- the presence of an intrauterine contraceptive device or cervical polyp
- atrophic smears.

The problems relating to each of these circumstances, with guidance on their interpretation, are set out below.

Borderline nuclear changes should be reported only when there is genuine doubt as to whether the changes are neoplastic and when the smear is of a suitable quality for evaluation. Dyskaryosis, in even a small number of cells, should be appropriately reported according to the grade of the nuclear changes. The smear should not be classified as borderline. Similarly, uncertain nuclear changes should not be ignored even if the remainder of the smear might have been thought to be unsatisfactory.

A report of borderline nuclear change should be made only when the entire smear has been evaluated. In circumstances where it will elicit a clinical recommendation it should be reported by the medical staff. The report should include a description of the cellular changes and should be coded as "borderline". As with all cervical smears any discrepancy between the opinions of the medical and screening staff should be discussed.

Dyskaryotic cells in which there are pronounced degenerative changes should be reported as ungradable dyskaryosis or as dyskaryosis of at least a certain minimum degree. Every attempt should be made, in all such cases, to find dyskaryotic cells in which the nuclei are better preserved and grading is possible.

To assist in the recognition of the minimum changes diagnostic of typical mild dyskaryosis and pale dyskaryosis, the working party offers the following guidelines.

### Recognition of mild dyskaryosis and pale dyskaryosis

(1) In mild dyskaryosis (fig 3) well preserved

cells show the following changes:

- nuclear enlargement
- an increased nuclear : cytoplasmic ratio in which the nucleus occupies no more than half of the total area of the cell
- irregularity of the nuclear outline
- an abnormal chromatin pattern
- hyperchromasia (this may be present but is not a requirement).

Small dyskaryotic cells (fig 4) should be distinguished from normal parabasal cells and metaplastic squames (fig 5).

(2) Cells with pale dyskaryosis (figs 6–8):

- may be mildly, moderately, or severely dyskaryotic and may be shed from carcinoma or CIN
- have high nuclear:cytoplasmic ratios in accordance with the grade of dyskaryosis
- have nuclei which are paler than those in the accompanying polymorphs
- have a nuclear membrane which is not delineated by a condensation of the chromatin
- have fine but irregularly distributed pale chromatin which may vary from cell to cell; the chromatin irregularity may be minimal
- may occur in the absence of more typical dyskaryosis

### (1) BORDERLINE NUCLEAR CHANGES WITH CYTOLOGICAL EVIDENCE OF HUMAN PAPILLOMAVIRUS (HPV) INFECTION

There is always a degree of subjectivity in distinguishing borderline nuclear changes from mild dyskaryosis in the presence of cytological evidence of HPV infection (figs 9–15).

The members of the working party were agreed, however, that no cell with evidence of HPV infection is normal, and that no smear in which there is evidence of HPV infection should be reported as negative whether or not there is a substantial nuclear abnormality.

Koilocytes (figs 9, 10, and 13) are regarded as pathognomonic of HPV infection.<sup>7</sup> The koilocyte is characterised by a large, sharply demarcated perinuclear halo surrounded by a condensed cytoplasmic rim. Groups of dyskeratotic cells, or single dyskeratotic cells, are also frequently present when there is HPV infection, but are not specific and may be seen in other circumstances. HPV infection in squamous epithelium often leads to bi- or multinucleation; and in immature metaplastic squamous epithelium there may be nuclear pyknosis rather than koilocytosis.

Cells in which there is dyskaryosis, in addition to cytoplasmic features of HPV infection, should be reported according to the grade of dyskaryosis, regardless of the cytoplasmic changes.<sup>8</sup>

Abnormally keratinised or dyskeratotic squamous cells with bland, elongated, or oval nuclei may form sheets of cells with characteristic shapes sometimes termed "rafts", pearls, or spikes. In spikes the cells form a conical shape (fig 16); in rafts the cells are orientated in the longitudinal axis of the raft, and in a pearl, in the plane of the margin of the whorl (fig 17).

Smears containing squames with these characteristics should be examined with particular care, but in the absence of nuclei

which are disorderly, enlarged, and irregular and which represent keratinised dyskaryotic cells (fig 18) they can be reported as negative. Although the cells may overlie a more serious abnormality, this is not always the case, and this possibility should not influence the pattern of reporting. Nor should these changes be confused with the more widespread changes seen in atrophic smears (fig 19).

In a screening smear anucleate squames demand careful evaluation, but in the absence of any other abnormality such smears are negative. In a gynaecologically indicated smear, such as from a prolapse, anucleate squames should be commented on but should not alter the classification of negative. The cells are indicative of hyperkeratosis. They may form sheets and clusters which stain very variably (figs 20 and 21).

Borderline nuclear changes should be reported in cells with HPV related changes only in the following circumstances:

- when koilocytes show milder nuclear changes than those required for a diagnosis of mild dyskaryosis (figs 13–15)
- when there are small dyskeratotic cells, often arranged in groups, which have variable nuclear enlargement with increased nuclear:cytoplasmic ratios and condensed nuclear chromatin (fig 12)

#### (2) BORDERLINE NUCLEAR CHANGES IN THE PRESENCE OF INFLAMMATION

The features described below apply to all forms of inflammation regardless of the infecting organism and whether an infecting organism can be identified.

Smears in which there is severe inflammatory epithelial change (not simply a polymorphonuclear exudate), but in which no specific organism can be identified, should be repeated only when the smear is unsatisfactory, shows borderline nuclear changes, or contains clearly dyskaryotic cells. Severe inflammatory changes do not preclude the presence of dyskaryosis.

Smears in which there is inflammatory epithelial change may be reported as normal or negative, providing that the smear is satisfactory for interpretation.

Smears should not be reported as showing borderline nuclear changes just because a specific organism, such as trichomonas, is present if there are no cytological features warranting this description. Nor should a smear be repeated simply because a specific organism has been identified. It is acceptable to report the presence of the organism without asking for a repeat smear.

If the smear cannot be interpreted because of a heavy inflammatory exudate, it should be reported as unsatisfactory and not as showing borderline nuclear changes.

When there is a heavy trichomonal infection in an otherwise normal follow up smear after identification of dyskaryosis, it should not be regarded as negative in terms of returning the patient to routine re-call even when the smear looks satisfactory: difficulties may be experienced in identifying persistent dyskaryosis in such circumstances.

Inflammatory and borderline nuclear changes may involve mature squamous cells (as described above) metaplastic cells, or endocervical cells. These last two will be considered below.

#### (i) Metaplastic cells

A wider range of morphological features is acceptable as normal in immature squamous metaplasia than it would be in mature squames or endocervical cells because of the underlying range of maturation present in this cell type.

Occasionally it may be difficult, particularly when inflammation is present, to determine whether cells are glandular or are metaplastic squames (fig 22). In these circumstances it is more important to evaluate the nuclei and to ensure that they are normal than to determine the type of cell (figs 23 and 24)

The following pointers may be helpful in recognising those cellular features which are often seen with inflammation and can be described as negative or normal:

- nuclear enlargement with normal nuclear:cytoplasmic ratios (fig 25)
- a minor variation in nuclear shape but with smooth nuclear membranes (figs 25 and 26)
- nuclear pyknosis or karyorrhexis (fig 27)
- the presence of nucleoli which do not have an irregular outline
- the condensation of chromatin under the nuclear membrane (fig 26)
- bi- or multinucleation (figs 28 and 29)
- intracytoplasmic polymorphs (fig 30)
- increased density of cytoplasmic staining
- metachromatic cytoplasmic staining
- pulled out strands of cytoplasm, so-called spider cells (fig 31)

Metaplastic cells should be described as showing borderline nuclear changes only when the cytologist is unable to make the distinctions listed above (fig 32). This is usually when:

- there is an increase in the nuclear:cytoplasmic ratio in the absence of signs of cellular degeneration or overt dyskaryosis
- mild hyperchromasia occurs in enlarged nuclei
- the chromatin pattern is coarsened slightly.

The presence of a smooth or only minimally irregular nuclear membrane may be helpful in distinguishing borderline nuclear changes from mild dyskaryosis, although its presence does not preclude dyskaryosis. A simple fold in the nucleus does not, in the opinion of the working party, warrant a diagnosis of borderline nuclear change.

Mature squames, which may originate from either native or metaplastic squamous epithelium, may also show borderline nuclear changes. These may be associated with inflammatory nuclear changes and are identified using the same diagnostic criteria as those given above for metaplastic squames.

Metaplastic cells in a cervical smear are usually squamous, but in a small number of women, particularly those who have had previous treatment of a cervical abnormality—for example, cone biopsy, laser therapy, loop excision, etc—columnar cell metaplasia may

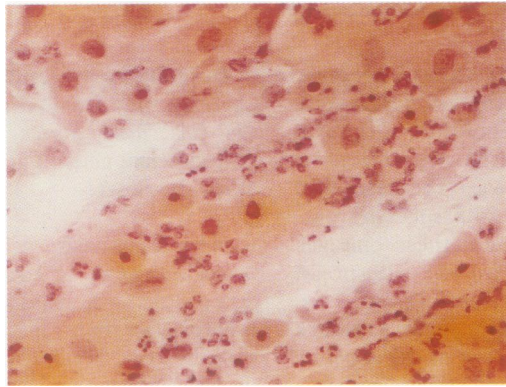


Figure 19. Normal negative atrophic postmenopausal smear. Note the characteristic orangeophilia of the cytoplasm in this atrophic smear. Note also the small, dense, pyknotic nuclei. The nucleus in the central cell shows early karyorrhexis with very coarse chromatin clumping.



Figure 20. Anucleate squames. Note the refractile quality of these cells which show a typical yellow-orange staining reaction.

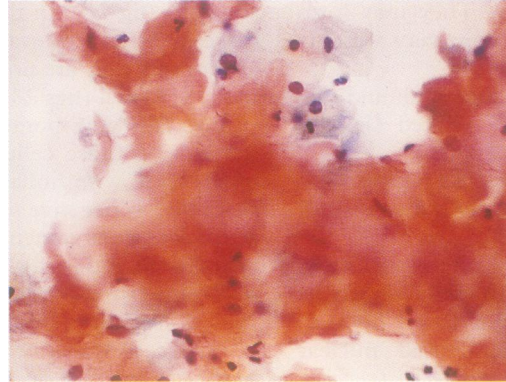


Figure 21. Anucleate squames.

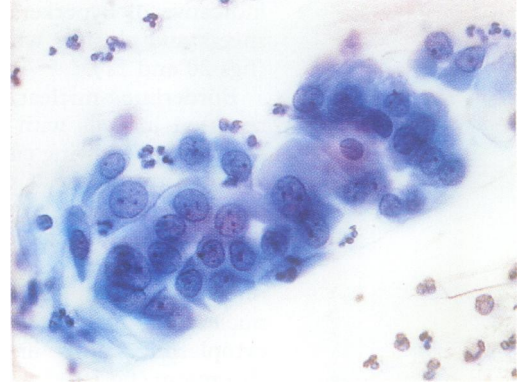


Figure 22. Negative smear showing inflammatory change. Some variation in nuclear size and shape is noted but chromatin is finely divided and the nuclear membranes remain well defined.

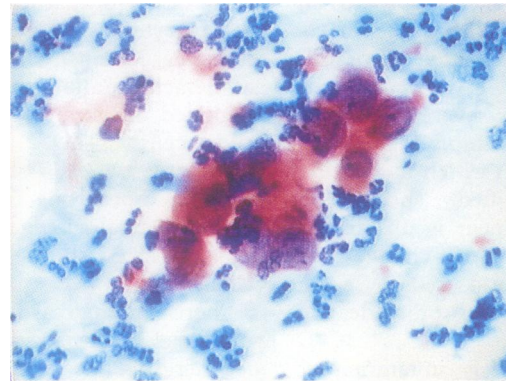


Figure 23. Borderline nuclear changes. These cells show variation in nuclear size and shape, indistinct nuclear borders, and some of the nucleoli are angular. The chromatin is, however, only finely granular. The slight opacity of their cytoplasmic staining suggests that they are immature metaplastic squamous cells rather than endocervical cells.

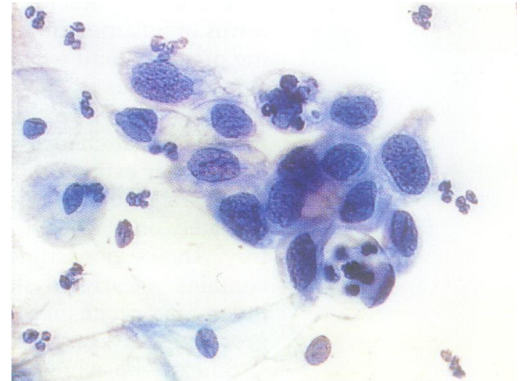


Figure 24. Dyskaryosis in metaplastic squames. Mild and moderate dyskaryosis is present. Note that two of the cells contain ingested polymorphs.

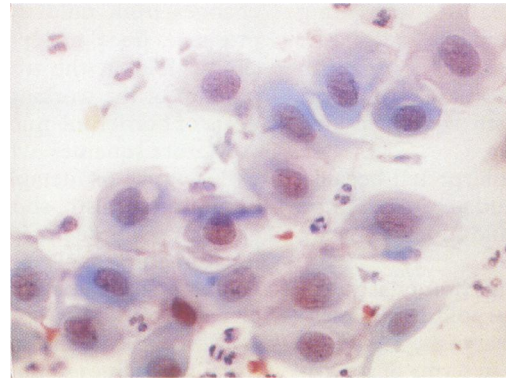


Figure 25. Negative smear showing inflammatory change. These metaplastic squamous cells have enlarged nuclei but the nuclear outlines are smooth and the chromatin, although speckled, is evenly distributed. The cytoplasm is slightly opaque and there are cytoplasmic projections. Note the hard-edged intracytoplasmic vacuoles which may cause indentation of the nuclear outline.

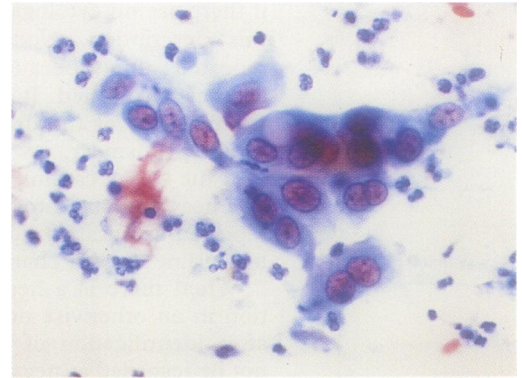
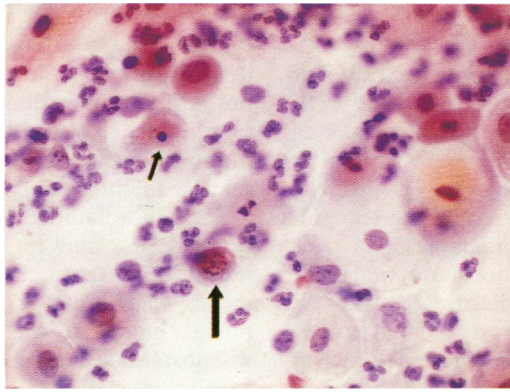
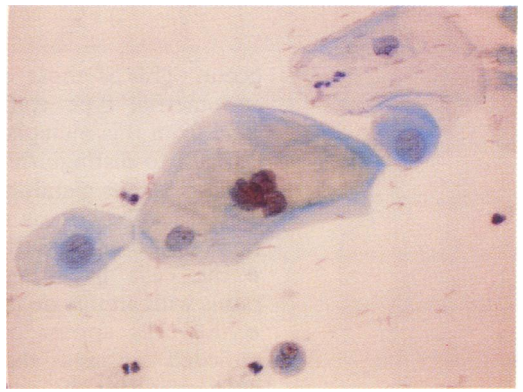


Figure 26. Negative smear showing inflammatory epithelial change. These metaplastic squames show mild variation in nuclear size and shape with binucleation. The nuclear outlines are enhanced by condensation of the chromatin beneath the nuclear membrane. Small round nucleoli (a feature of reactive metaplastic cells) and occasional intracytoplasmic vacuoles are present.

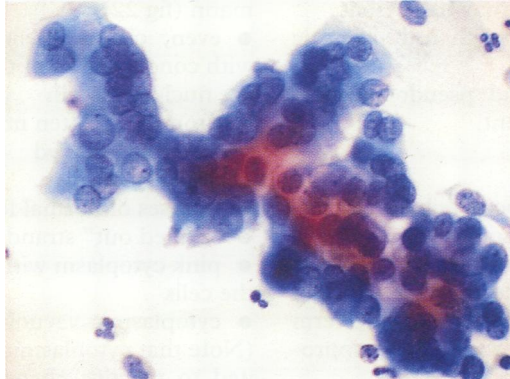
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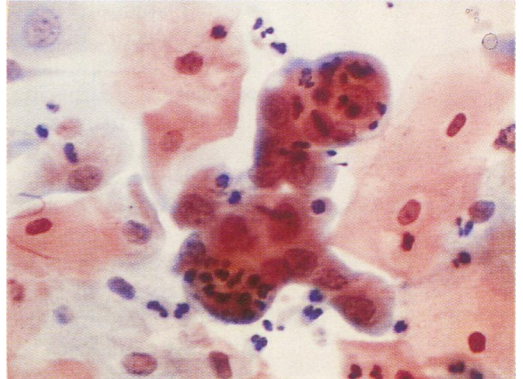
**Figure 27.** Pyknosis and karyorrhexis. The cell marked by the small arrow has the dense featureless nucleus typical of pyknosis. In the cell marked by the broad arrow the nucleus has disintegrated to form dense, coarse nuclear fragments. This is karyorrhexis.



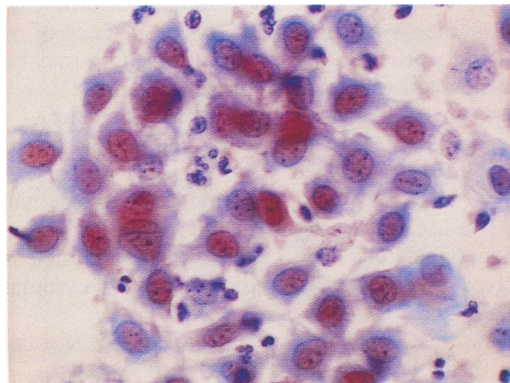
**Figure 28.** Negative smear showing multinucleation, seen in the absence of other features of HPV infection. This is not necessarily due to HPV. The presence of intracytoplasmic glycogen should not be confused with a perinuclear halo.



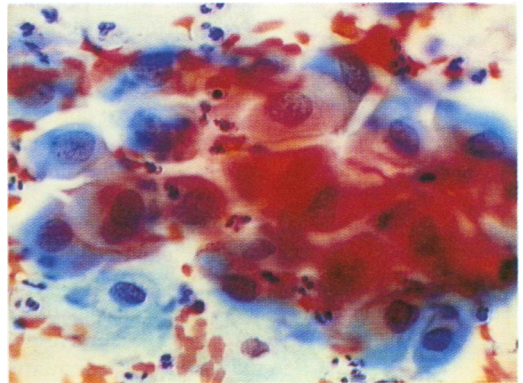
**Figure 29.** Negative smear showing multinucleation also in endocervical cells. It may occur in the presence or absence of typical HPV changes in the squamous cells.



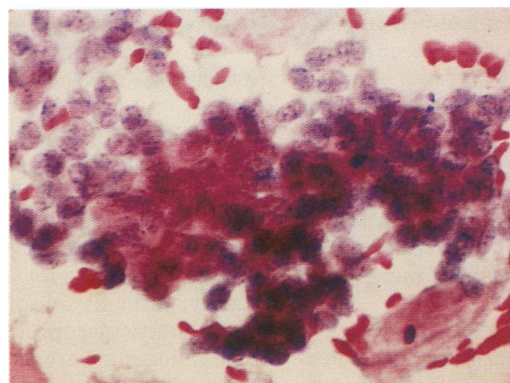
**Figure 30.** Negative smear showing inflammatory epithelial change. Polymorphs have been engulfed by this cluster of metaplastic cells. There are reactive cellular changes similar to those seen in fig 26.



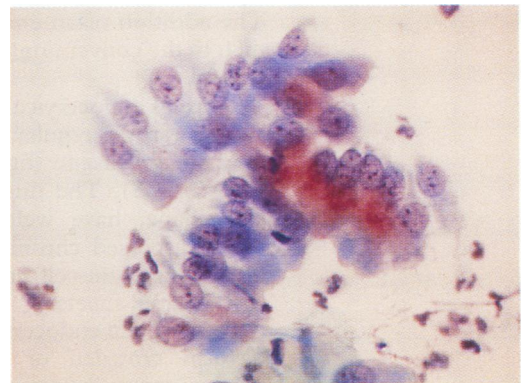
**Figure 31.** Negative smear: these are typical "spider" metaplastic cells with fine cytoplasmic projections.



**Figure 32.** Borderline nuclear changes in metaplastic cells. The cells have increased nuclear: cytoplasmic ratios and show mild anisonucleosis. Some of the nuclei look folded and the chromatin is finely granular.



**Figure 33.** Tuboendometrioid metaplasia. The cells form a crowded disorderly group and have high nuclear: cytoplasmic ratios with only scanty cytoplasm. There is, however, only slight variation in nuclear size and shape and the chromatin is finely and evenly dispersed.



**Figure 34.** Normal endocervical cells forming a palisade.

occur. This is most commonly to tubal or endometrial type epithelium<sup>9</sup> and the cells shed from this metaplastic epithelium may be difficult to distinguish from severe squamous dyskaryosis or glandular dyskaryosis (fig 33). The following criteria may aid in the recognition of tubo-endometrioid metaplasia

- the cells have high nuclear:cytoplasmic ratios with almost no cytoplasm
- the cells appear in crowded or "super-crowded" groups—that is, there is nuclear overlapping to the extent that the details of the individual nuclei cannot be distinguished
- the nuclear membranes are well defined
- the nuclear chromatin is evenly dispersed and finely granular
- inconspicuous nucleoli may be present
- the cells are often smaller than dyskaryotic squames or glandular cells
- rosettes, feathering, and pseudostratification are not usually apparent.

#### (ii) Endocervical cells

In most smears it should be possible to distinguish reactive changes in columnar cells from dyskaryosis, but in a small number of cases the observer will be unable to make this distinction. Only in these cases should the term borderline nuclear change be used and appropriate follow up recommended.

Atypical columnar cells, which may be difficult to distinguish from true dyskaryosis, are found in a variety of circumstances—for example, when polyps are present, when there is inflammation, and when the woman is wearing an intrauterine contraceptive device (coil) (IUCD). In the presence of a polyp or IUCD atypical columnar cells are often associated with the presence of reactive changes in immature and mature metaplastic cells (see below).

Every attempt should be made to classify the nuclear changes in endocervical cells even when the material is autolysed or poorly preserved. A smear that is satisfactory for the screening of normal populations, however, may not be adequate for the follow up of endocervical abnormalities. Such smears must contain endocervical and squamous cells as these women may be at risk of having both squamous and glandular cell abnormalities. The addition of an endocervical brush specimen to the conventional spatula smear may be helpful.

Normal endocervical cells, when present in sheets, form a regular "honeycomb" pattern or regular palisade (fig 34) and may be ciliated (fig 35). The nuclei are regular in size and shape, have well defined membranes, finely dispersed chromatin, and small nucleoli. Dyskaryotic cell groups may merge with such normal sheets.

Dyskaryotic endocervical cells typically:

- form crowded or super-crowded three-dimensional clusters with feathered edges (figs 36 and 37) or rosettes (fig 38)
- form disorganised cell groups
- may appear pseudostratified in appropriately orientated epithelial cell strips
- show nuclear changes that are less obvious

than disturbances in the cellular architecture but which may include the following: variation in nuclear size and shape, abnormal chromatin dispersion with loss of definition of the nuclear membrane (fig 39).

Certain inflammatory changes in the endocervical cells may be reported as negative or normal, and these can be distinguished from those warranting a report of borderline nuclear change by the following criteria:

- substantial variation in nuclear size but with maintenance of normal nuclear:cytoplasmic ratio (fig 22)
  - rounded or "ballooned" nuclei with minimal or no irregularity of contour
  - evenly dispersed or finely granular chromatin (fig 22)
  - even, clearly defined nuclear membrane with condensation of the nuclear chromatin at the nuclear margin
  - prominent, often multiple, nucleoli but not irregularly shaped or disproportionately enlarged nucleoli
  - mitoses of normal form
  - "pulled out" strands of cytoplasm
  - pink cytoplasm with a hazy pink overlay on the cells
  - cytoplasmic vacuolation (figs 22 and 40). (Note that cytoplasmic vacuolation is not limited to reactive changes and, particularly in postmenopausal women, should be interpreted with caution as similar vacuolated groups may be shed from endometrial and ovarian carcinoma (figs 41 and 42).
- In the absence of overt dyskaryosis the following changes may be classified as borderline nuclear changes:
- three-dimensional cell groups with disorderly cell arrangements (fig 43)
  - irregular of coarse "grainy" chromatin
  - hyperchromasia with intercellular variation in the depth of nuclear staining.
  - an irregular nuclear membrane not due to distortion by a cytoplasmic vacuole.

#### (3) BORDERLINE NUCLEAR CHANGES IN ATROPHIC SMEARS

The term atrophic smear is used in this context to mean smears obtained in peri- or postmenopausal women, women who are breast feeding, or postnatal, and in women using low oestrogen or progestagen only contraceptives.

Cytological expression of HPV changes and dyskaryosis tend to be diminished in atrophic smears.

The working party felt that when a postmenopausal smear is satisfactory and adequate for screening, there should be very few occasions when it would be impossible to describe the smear as either negative or clearly dyskaryotic.

The tendency for atrophic smears to be scanty, difficult to spread, and air-dried can cause particular problems in interpretation. The following features (figs 11 and 44) can be regarded as normal:

- a tendency for cells to form a "crazy-paving" or pavement-like pattern due to air-drying (fig 45)
- cells with a high nuclear:cytoplasmic ratio
- cells with dense orangeophilic cytoplasm

with smaller cells looking as though they have denser cytoplasm and nuclei than larger ones

- a variation in cytoplasmic staining, often of an orange-yellow hue
- nuclear pyknosis and karyorrhexis.

Small orangeophilic cells mixed with cells with pyknotic nuclei are typical of a particular pattern of atrophic smear and should be reported as negative (fig 19). They should be distinguished from the dyskeratotic cells described above (fig 12) which often form small clusters or aggregates, and should be reported as negative, borderline nuclear changes, or dyskaryotic according to their nuclear characteristics.

Occasionally such smears with an "orangeophilic" pattern may contain cells with increased nuclear:cytoplasmic ratios and degenerate, but irregular nuclei. If dyskaryosis cannot confidently be excluded the use of the borderline category may be justified with a recommendation to follow up in a few months (postnatally) or after local oestrogen therapy (postmenopausally).

Individual cells in atrophic smears may have the nuclear features of dyskaryosis (fig 46) and screeners should not be deterred from identifying these cells as dyskaryotic, if this is appropriate, or as borderline nuclear changes if they are uncertain.

Sheets of small dyskaryotic cells, sometimes with mitoses (fig 46), should be distinguished from non-neoplastic sheets of atrophic parabasal cells (fig 47).

Dyskaryosis in an inflamed, atrophic smear may present the following picture:

- crowded cell groups with moulded, overlapping nuclei (figure 46)
- nuclear membranes which are indistinct; the chromatin appears to blend with the nuclear membrane
- mitoses that may be atypical

Generalised nuclear enlargement, as opposed to individual nuclear enlargement, raises the possibility that these are not cells shed from CIN. Other explanations, including folate deficiency, candida, or other infections should be considered.

Variation in nuclear size with a full spectrum of sizes from the small but normal, to the large, is also less likely to be important clinically, particularly when the nuclear:cytoplasmic ratio is similar in all cells when the nuclear chromatin is evenly dispersed; the nucleoli, if present, are small; and when there is a smooth nuclear membrane.

There may, in pregnancy, be sampling difficulties associated with the presence of a large ectopy and the more peripheral position of the transformation zone. The usual postnatal smear from the woman who is breast feeding is atrophic (fig 48).

There is a tendency for the expression of cytological atypia, even in the presence of persistent CIN, to diminish in pregnancy (Stanbridge CM, personal communication), and smears taken in pregnancy should not, therefore, be regarded as necessarily indicating an improvement in the condition of the cervix if previously reported dyskaryosis diminishes or is absent.

Except for this proviso, the working party did not think that there was any necessity for the reporting of abnormal smears and the general follow up arrangements to be changed by the fact of pregnancy. Special arrangements, however, may need to be made for the management of abnormal smears in pregnancy.

## Management of patients with borderline nuclear changes in their cervical smears

### GENERAL RECOMMENDATIONS

(1) A single screening smear in which there are borderline nuclear changes is not an indication for colposcopy.

(2) Colposcopic examination should not be recommended until at least two mildly dyskaryotic smears or two smears with borderline nuclear changes have been reported. Two mildly abnormal smears should not be regarded as necessarily indicating the need for colposcopy if the cytopathologist indicates that the cytological changes are diminishing in severity or are of a very mild degree.

(3) Referral for colposcopic assessment, on the basis of persistent mild cytological abnormalities, should be regarded as a continuation of the screening process. It should not imply a mandatory need for treatment. Nor, in the absence of an abnormal finding at colposcopy, is the presence of a mildly abnormal smear an indication for cone biopsy or loop excision. Cytological surveillance by smear should continue at the discretion of the colposcopist or cytopathologist.

(4) When borderline nuclear changes have been reported and are then followed by two satisfactory and normal or negative smears, routine screening should recommence, provided that neither of the follow up smears has been taken (i) in pregnancy (Stanbridge CM, personal communication), (ii) in the period immediately after having given birth when smears may underestimate the degree of abnormality, or (iii) when there is a heavy trichomonal infection even when the smear is satisfactory. It may be difficult to identify dyskaryosis in such circumstances.

(5) It is generally not advisable to allow more than three mildly abnormal smears before recommending colposcopy, whatever the age of the patient. The management of borderline nuclear changes may be modified by the age of the patient only in as much as it may be wiser to refer for colposcopic assessment any woman over the age of 40 years who has had two abnormal smears.

(6) Pregnancy is not a reason for postponing colposcopic assessment, but the colposcopist may feel it wise to delay biopsies until after delivery unless an invasive lesion is suspected.

(7) Previous smears should be routinely reviewed when reporting a smear taken at follow up of any abnormality.

### RECOMMENDATIONS FOR THE MANAGEMENT OF BORDERLINE NUCLEAR CHANGES IN SQUAMOUS CELLS

(1) Smears with HPV or borderline nuclear changes should be repeated at six to 12

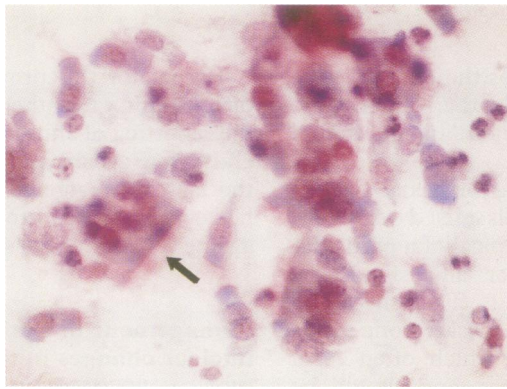


Figure 35. Normal ciliated endocervical cells forming a palisade.

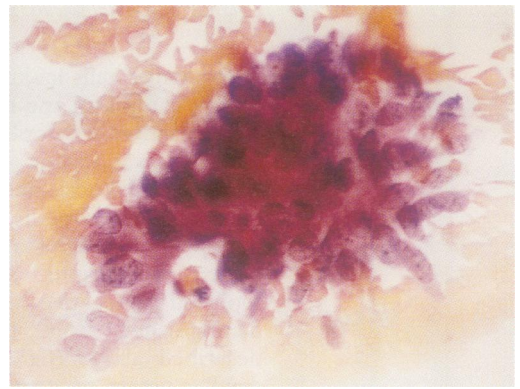


Figure 36. Dyskaryosis in endocervical cells. A cluster of endocervical cells with a three-dimensional configuration and feathering of its edge, a feature commonly seen in endocervical dyskaryosis.

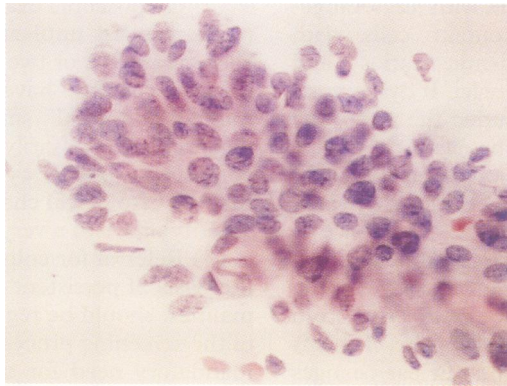


Figure 37. Dyskaryosis in endocervical cells. This irregular cluster of endocervical cells shows loss of normal architecture and polarity with indistinct feathering of its edge.

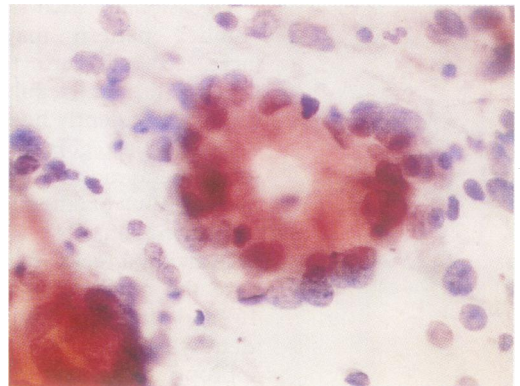


Figure 38. Dyskaryosis in endocervical cells. The endocervical cells have formed a rosette. There is considerable variation in nuclear size and shape.

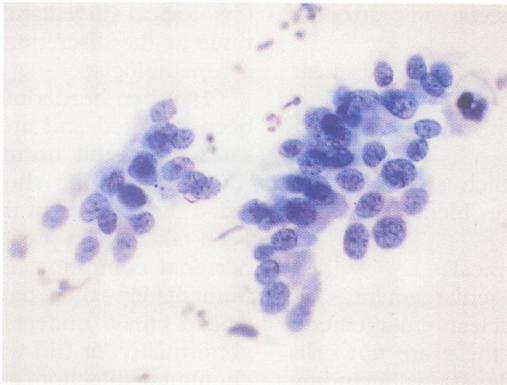


Figure 39. Dyskaryosis in endocervical cells. These endocervical cells are multilayered. The nuclei vary only a little in size and shape. There are no mitoses but the chromatin is coarsely granular and the nuclear outlines are poorly defined.

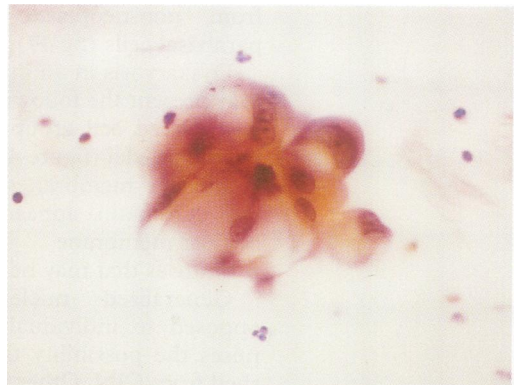


Figure 40. Negative smear with IUCD-related changes. This cluster of endocervical cells has prominent, well defined vacuoles which indent some of the nuclei (see also figs 22,25 and 26).

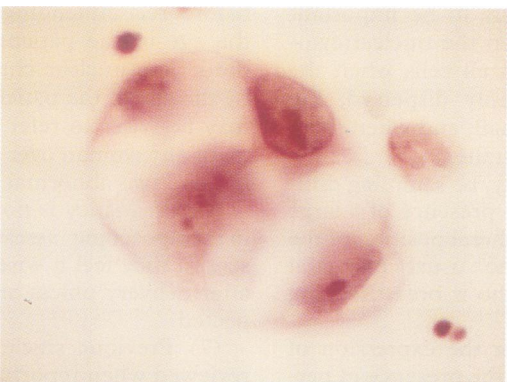


Figure 41. Vacuolated cells from an ovarian carcinoma to contrast with the normal vacuolated cells in fig 40. The edges of the vacuoles are less well defined, appear to have a scalloped edge, and overlap rather than indent the nuclei, although some nuclear indentation is present. The nuclei vary in size and shape and contain very large angular nucleoli.

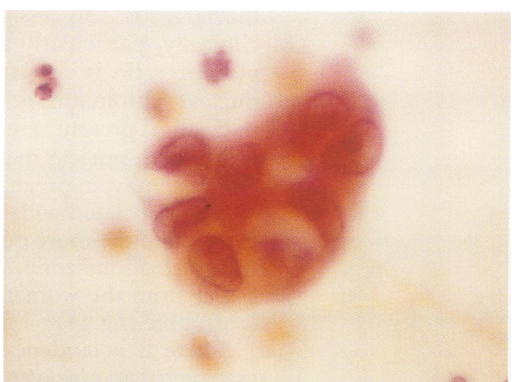


Figure 42. Cells from an ovarian carcinoma containing poorly defined vacuoles. Note the macronucleoli.

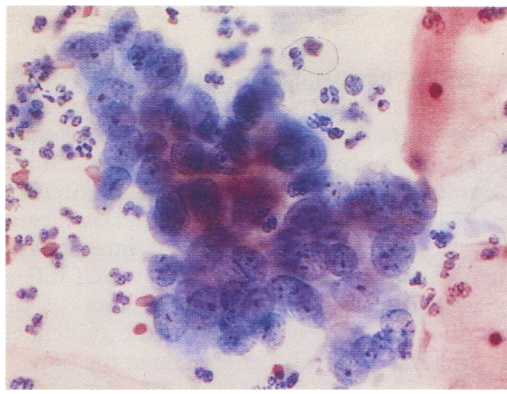


Figure 43. Borderline nuclear changes in a crowded three-dimensional group of endocervical cells. There is some granularity of the nuclear chromatin pattern but the nuclear membranes are distinct.

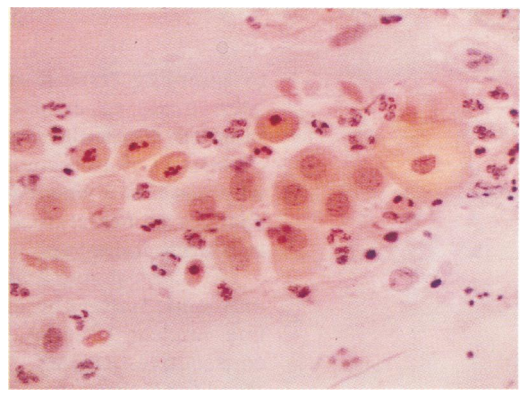


Figure 44. Negative atrophic smear from postmenopausal women. Although some of the cells show nuclear pyknosis and karyorrhexis, most have pale, evenly stained nuclei with finely dispersed chromatin.

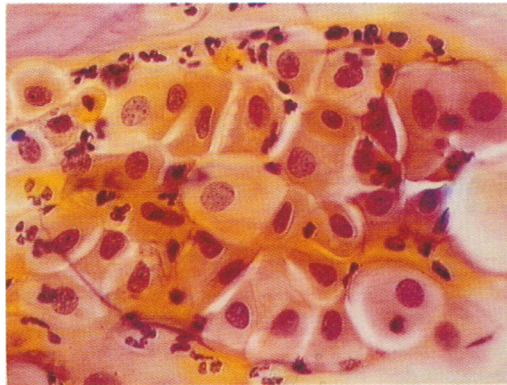


Figure 45. Negative atrophic smear taken from a postnatal woman. The cells form a flat mosaic pattern and have yellow-orange cytoplasm which increases in density with decreasing size of cells.

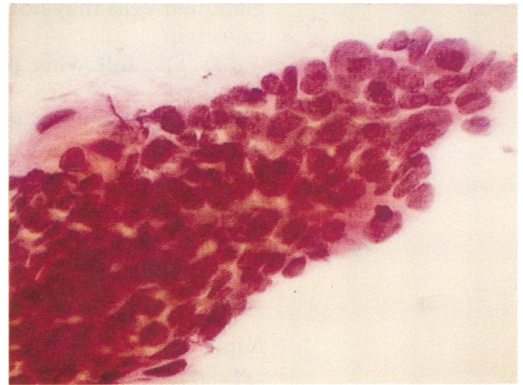


Figure 46. Dyskaryosis in an atrophic smear. The nuclei are crowded and there are high nuclear:cytoplasmic ratios. In focusing through this cluster, considerable variation in size and shape of nuclei could be seen with nuclear moulding. Occasional mitotic figures were noted. Compare with fig 47.

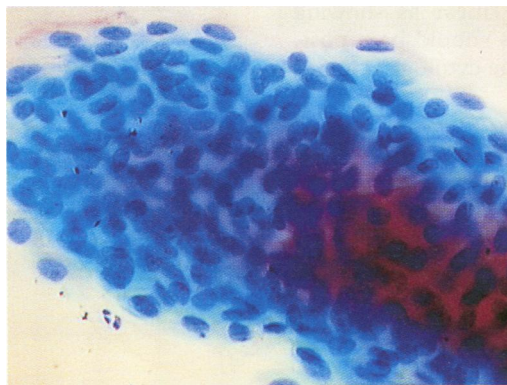


Figure 47. Negative atrophic smear. These are parabasal cells. There is little variation in the size and shape of the nuclei and all the nuclei have a distinct nuclear border. The nuclear:cytoplasmic ratio is normal for parabasal cells and mitotic figures are not seen. Compare with fig 46.

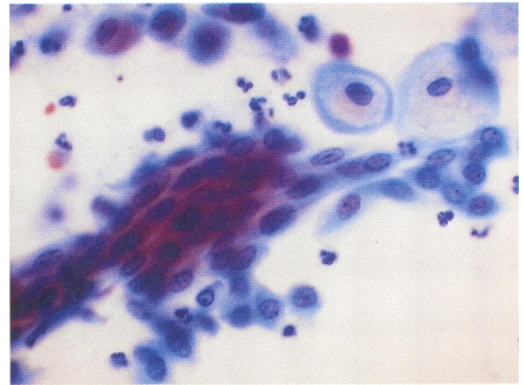


Figure 48. Negative atrophic smear from a postnatal woman. This field consists of parabasal cells arranged either singly or in sheets. The appearance of the cell in the top right hand corner of the field suggests that there may be HPV infection.

monthly intervals at least once before referring the patient for colposcopy. Bearing in mind that these lesions often regress,<sup>6</sup> and that there is a spectrum of change between HPV with borderline nuclear change and HPV with mild dyskaryosis, the cytopathologist should exercise discretion in deciding whether colposcopy should be recommended after two abnormal smears, or whether a third repeat should be requested.

(2) In the context of follow up after treatment of CIN 2 or 3, detection of mild dyskaryosis in only one smear warrants a referral for colposcopic assessment. In patients with only borderline nuclear changes

in their smear, however, cytological follow up may continue.

(3) In women who have borderline nuclear changes in an atrophic smear interpretation of the smear may be easier after the patient has applied a topical oestrogen. The cytopathologist should recommend this if it is felt to be appropriate.

#### RECOMMENDATIONS FOR THE MANAGEMENT OF BORDERLINE NUCLEAR CHANGES IN ENDOCERVICAL CELLS

(1) Endocervical cells may be more difficult to interpret than squamous cells in a cervical smear. They are also more likely to be subject

to sampling error if special efforts have not been made to ensure that they have been sampled. Particular care should, therefore, be exercised before recommending that a woman who has had a smear with borderline nuclear changes in her endocervical cells is returned to routine follow up.

(2) Colposcopic assessment should be recommended after the identification of borderline nuclear changes in no more than *two* consecutive smears. The repeat interval should be three to six months. The report should indicate that further interpretation from the cytological material may not be possible and that in some instances the abnormal glandular cells may not necessarily be of cervical origin.

(3) The following precautions are recommended:

(i) If, in a woman wearing an IUCD, borderline nuclear changes persist it may be necessary to consider removing the device and repeating the smear in six months when the irritation has settled. If after that the borderline nuclear changes are still evident colposcopic assessment should be recommended.

(ii) Referral for colposcopy should not imply a need for cone biopsy because the cytological changes may be explained by, for example, cervicitis, tubo-endometrioid metaplasia, polyp or microglandular hyperplasia.

### Conclusion

A decision to describe a smear as showing borderline nuclear changes should be a positive one and not because the cytologist cannot decide.

There will inevitably be areas in which differences of opinion will remain in the interpretation of cytological preparations. This is true of any subjective assessment. Despite the use of similar criteria for diagnosis and protocols for the classification of cytological abnormalities, interpretation depends on the emphasis which different observers place on the importance of different cytological features. These guidelines and recommendations are made in the hope that they will reduce the degree of interobserver differences in the interpretation of cervical smears.

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