Nuclear size and shape of epithelial cells from the endometrium: lack of value as a criterion for differentiation between normal, hyperplastic, and malignant conditions

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SUMMARY Nuclear area and shape of epithelial cells were measured in cytological specimens from 10 patients with cystic hyperplasia of the endometrium and four patients with adenomatous hyperplasia. Only specimens from patients with histologically confirmed widespread disease of the endometrium were accepted in the study. The mean nuclear area in cystic hyperplasia was significantly lower than in adenomatous hyperplasia. Results from previous measurements with the same method in normal and malignant conditions were compared with those from hyperplastic conditions. Both cystic and adenomatous hyperplasia differed from normal endometrium but not from malignant conditions. The scatter in values in the different conditions overlapped to such a degree as to make nuclear size of little importance as a diagnostic criterion. There were no differences in nuclear shape between normal, hyperplastic, and malignant conditions.

Reports on the ability of modern cytological cell samplers to replace curettage in the assessment of endometrial disorders show both high sensitivity and specificity of the cytological method in the detection of malignant endometrial lesions. Many authors have also reported the cytological detection of hyperplasia of the endometrium. Success in this field is variable as sensitivity varies between 20% and 90% in accuracy tests. This may be because of variation in the sampling ability of the different types of instruments used, but may also reflect difficulties in interpretation of sampler material.

The nuclei of hyperplastic epithelium from material aspirated from the endometrium are said to be larger than nuclei from normal endometrial epithelium but smaller than those found in malignant conditions. Irregular shape of the nuclei is said to be characteristic of adenomatous hyperplastic conditions. Thus it may be possible with this material to identify a hyperplastic condition by using nuclear size and shape as diagnostic aids. On the other hand, measurements of multiple parameters in histological specimens have shown that nuclear size and shape are of little importance in the discrimination between different conditions of the endometrium. Other investigators have found that in histological specimens nuclear size may be used to predict whether the hyperplasia will proceed to malignancy.

Measurements of nuclei in epithelial cells in cytological sampler material have shown that the use of nuclear area as a diagnostic criterion to differentiate between malignant and normal endometrium is of little value in that particular type of material because of the great scatter in the values. Furthermore, the shape of the nuclei in normal and malignant conditions shows little variation, and normal and malignant nuclei tend to vary in the same way (see accompanying paper, p 496).

The diagnostic value of nuclear size and shape in the detection of hyperplasia in cytological sampler material is still an open question. The morphometric study of normal and malignant conditions (p 496) was therefore extended to include hyperplastic endometrium.

Material and methods

The cytological material was available from a study of 400 cases in which cell sampling had been fol-
Nuclear size and shape of epithelial cells from the endometrium

![Graph](image)

**Fig. 1** Relation between the mean nuclear area and standard deviation (SD) for each case.

The mean nuclear area (MNA) in cystic hyperplasia was $45 \pm 10 \, \mu m^2$ and for adenomatous hyperplasia $62 \pm 11 \, \mu m^2$. This difference is statistically significant ($p < 0.01$). Using the $\chi^2$ test a MNA of $60 \, \mu m^2$ gave the greatest discrimination between cystic and adenomatous hyperplasia. Nine of 10 cases (90%) were placed correctly in the cystic and three of four (75%) correctly in the adenomatous group ($\chi^2 = 5.92$, $p = 0.01$).

Cases with low MNA values tended to have low standard deviations (SD) while cases with high values showed greater variation in SD, but occasional cases with high values showed low SDs (Fig. 1). The variation coefficient for the cystic hyperplasia group was $17\% \pm 4$ and for the adenomatous hyperplasia group $20\% \pm 11$.

The range of MNA values was from 25 to 90 $\mu m^2$ in cystic hyperplasia (Fig. 2). Only one of the cases showed uniformity in the recordings. This case had low MNA values compared with the others. Most of the recordings in cystic hyperplasia were between 30 and 60 $\mu m^2$, but one case showed values from 50 to 95 $\mu m^2$. In adenomatous hyperplasia the scatter had a different pattern, with most of the recordings higher than 50 $\mu m^2$, but one case showed recordings between 39 and 54 $\mu m^2$ (Fig. 2).

The nuclei were round or nearly round in both cystic and adenomatous hyperplasia. Mean form factor was 0.97 ± 0.02 and 0.94 ± 0.04 respectively; the range of values of both conditions was the same (0.84–1.0).

The MNA for normal epithelium was $38 \pm 9 \, \mu m^2$ and for malignant conditions $57 \pm 16 \, \mu m^2$ (p 496). In cystic hyperplasia MNA was different from that of normal endometrium ($p < 0.05$), but not from that of malignant cases. The scatter in Fig. 2 indicates that if the range in each case is taken into consideration, recordings from cystic hyperplasia could be similar to recordings from normal as well as malignant cases. In adenomatous hyperplasia recordings were located among the upper half of the malignant recordings. Again the scatter shows that almost identical recordings could be made from a case showing adenomatous hyperplasia and a case showing a malignant condition.

At least a quarter of the recordings of MNA fall between 40 and 60 $\mu m^2$ in each condition of the endometrium, and in malignant conditions as much as half (Table). An MNA of $40 \, \mu m^2$ gives a nuclear diameter of 5.2 $\mu m$, 60 $\mu m^2$ a diameter of 6.2 $\mu m$.

**Discussion**

The cytological samples from patients with cystic...
Fig. 2  Mean nuclear area (in $\mu m^2$) from each cell group from each of 69 samples related to the condition of the endometrium. Each sample is presented as a column of marks. Each mark represents one or more cell groups.
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Range of mean nuclear areas (MNA) in the different endometrial conditions expressed as a percentage of the total number in each group

<table>
<thead>
<tr>
<th>Endometrial condition</th>
<th>MNA &lt; 40 μm²</th>
<th>40 μm² &lt; MNA &lt; 60 μm²</th>
<th>MNA &gt; 60 μm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal endometrium</td>
<td>71</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Cystic hyperplasia</td>
<td>30</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Adenomatous hyperplasia</td>
<td>0</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Malignant condition</td>
<td>15</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>

and adenomatous hyperplasia of the endometrium used in this study were highly selected. Only patients showing hyperplasia in large areas of the endometrium on histology were accepted for study. This was to ensure that hyperplasia could be expected in most of the structures in the sampler material. Since morphological criteria which differentiate clearly between normal and hyperplastic conditions in sampler material are not available, the recordings had to be made under random conditions. Hence, it was important to make sure that the smears were as representative as possible.

As in previous studies the MNA values in hyperplastic epithelium fell between those of normal and malignant conditions. The present study also confirms that the MNA is lower in cystic than in adenomatous hyperplasia. The scatter in the MNA values related to SD indicates that the size of the nuclei in normal endometrium and cystic hyperplasia varies in the same way. Contrary to previous reports no differences were found in nuclear shape in the various conditions of the endometrium.

The values in adenomatous hyperplasia differed from both normal endometrium and cystic hyperplasia, showing a constantly large MNA value from recording to recording in a given sample and the same tendency in all four cases. Judged on the basis of nuclear size and shape, the condition is similar to malignancy. The group is small, however, and firm conclusions cannot be drawn from the present data. Previous data from measurements on endometrial cells in endocervical aspirates have shown a significant difference in the MNA of cells from cases of adenomatous hyperplasia and well differentiated adenocarcinoma of the endometrium. This may reflect a difference in size between structures in exfoliated cells versus mechanically removed, rapidly fixed cells. No morphometric data from sampler material suitable for comparison with the present study have been found in the published work.

Measurements of nuclear area in normal, hyperplastic, and malignant conditions show that between 40 and 60 μm² one will find 25% of the normal, 60% of the cystic hyperplasia, 25% of the adenomatous hyperplasia, and 50% of the malignant cases. This area corresponds to a range in nuclear diameter of 5-2 to 6-2 μm. It is questionable whether even an experienced cytopathologist would be able to recognise a colony of cells with nuclei of 5 μm diameter with a variation coefficient of 17% from a colony of cells with nuclear diameter 6 μm and variation coefficient of 21%, especially if the two colonies cannot be examined in the same microscopic field.

Thus it seems that the observed differences in nuclear size between normal, hyperplastic, and malignant conditions, even if they are significant, are not large enough to be of practical use in differentiation between the various conditions. This is because of the degree of overlap in nuclear size and the range of values in the different conditions.

The cytological sampler technique is intended for the investigation of a group of patients with an incidence of carcinoma of 1 to 10% (depending on the clinical criteria for the use of the sampler). It is thus important not only to be able to detect the malignant cases but also to use diagnostic criteria which give an acceptable degree of alarm. The use of nuclear size will, on the basis of the present work, create a constantly stressed situation as so many of the normal cases will have nuclei within the limits found in malignancy. Thus its use as an important diagnostic criterion may reduce both the sensitivity and the specificity of the cytological method.

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References

5. Anastasiadis P, Ludinghausen von M, Ruhl F, Bowry AM. Die bedeutung der Aspirationszytologie für die Früherkennung


10 Ng ABP. The cellular detection of endometrial carcinoma and its precursors. Gynecol Oncol 1974;2:162–79.


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