Intraepithelial leukocytes in endometriosis and adenomyosis: comparison of eutopic and ectopic endometrium with normal endometrium

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Intraepithelial leukocytes (IEL) are recognized as an important component of most mucosal surfaces but have received scant attention in the human female reproductive tract. The aim of the present study was to characterize, quantify and compare IEL populations in normal endometrium (n = 30) and in eutopic and ectopic (endometriotic or adenomyotic lesions) endometrium from women with endometriosis (n = 30) or adenomyosis (n = 15) at different menstrual cycle phases in order to assess the role of IEL in these common but poorly understood disorders. IEL populations were examined in formalin-fixed, paraffin-embedded sections using a streptavidin-biotin-peroxidase complex technique and quantified in relation to epithelial cell numbers. IEL in control endometrium and eutopic endometrium in endometriosis and adenomyosis varied during the menstrual cycle, with CD45+, CD43+ and CD56+ cells increasing from the proliferative to the late secretory phase. IEL were elevated in surface compared with glandular epithelium in the proliferative and early secretory phases. Throughout the menstrual cycle there were no significant differences in IEL between eutopic and ectopic endometrium in adenomyosis. Endometriotic foci, however, contained elevated levels of CD45+, CD3+ and CD8+ cells and reduced numbers of CD56+ cells compared with the corresponding eutopic endometrium and these did not vary with menstrual cycle phase. In contrast, ectopic endometrium in adenomyosis showed some cyclical changes with CD56+ cells increasing significantly in the late secretory phase. It is possible these differences may play a role in the pathogenesis of endometriosis and the associated complications.

Key words: adenomyosis/endometriosis/endometrium/intraepithelial leukocytes/menstrual cycle

Introduction

The human endometrium contains numerous cells of lymphoid origin which are present in both stromal and intraepithelial locations (Morris et al., 1985; Bulmer et al., 1991; Pace et al., 1991; Jones et al., 1996, 1998). Endometrial stromal leukocytes have been characterized extensively and comprise T lymphocytes, macrophages and granulated lymphocytes (eGL) which vary in proportion during the menstrual cycle (Bulmer et al., 1991). In contrast, the study of intraepithelial leukocytes (IEL) in the human endometrium has been relatively neglected, although Pace et al. (1991) reported variations in IEL with menstrual cycle phase similar to those observed in stromal leukocytes (Bulmer et al., 1991; Klentzeris et al., 1992; Jones et al., 1996). The role of IEL in the human endometrium is unknown. Although they may function in mucosal immunity to antigenic challenge, IEL may play a crucial role in implantation and early placentaion, since surface IEL are the first maternal immune cells to encounter the allogeneic implanting blastocyst.

Endometriosis is a common gynaecological condition characterized by the presence of endometrial tissue outside the uterine cavity. Even in mild forms, endometriosis is often associated with infertility (Cornillie et al., 1990; Thomas, 1991; Haney, 1993). Adenomyosis has some similarities to endometriosis, being characterized by the presence of ectopic endometrium within the myometrium, although the definition and pathogenesis of adenomyosis are disputed (Garcia et al., 1987; Ryan et al., 1990; Fox and Wells, 1995). Adenomyosis, however, is not usually associated with infertility. To date, there have been no studies of IEL populations in endometriosis or adenomyosis. The aim of the present study was to quantify and compare leukocyte populations in the epithelium of eutopic (normally situated) and ectopic (endometriotic and adenomyotic foci) endometrium from patients with endometriosis and adenomyosis with those in normal endometrium at different phases of the menstrual cycle in order to investigate the possible relationship between IEL and the infertility associated with endometriosis.

Materials and methods

Tissues

All paraffin tissue blocks were retrieved from archive files in the Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK. Ethical approval for the project was granted by the Newcastle Joint Ethics Committee. Thirty cases of ovarian (n = 28) and Fallopian tube (n = 2) endometriosis were selected at different phases of the menstrual cycle (10 proliferative; 10 early secretory; 10 late secretory). Two blocks of tissue were examined from each case: one from the uterine endometrium (eutopic) and the other from the endometriotic foci (ectopic). Fifteen cases of extensive deep adenomyosis were examined with the corresponding eutopic endometrium and adenomyotic foci from patients with endometriosis and adenomyosis with those in normal endometrium at different phases of the menstrual cycle in order to investigate the possible relationship between IEL and the infertility associated with endometriosis.
for non-endometrial pathology, such as leiomyomata or benign ovarian cysts, were included as controls. The endometrium from all cases showed histological changes consistent with the menstrual dates provided. Patients currently receiving hormone therapy were excluded, as were cases in which the ectopic foci showed evidence of active inflammation, which was assessed by neutrophil polymorph and plasma cell infiltration. The separation of specimens into early (days 14–22) and late (day 23 onwards) secretory phases was based on previous studies which have shown maximal changes in the endometrial leukocyte populations in the late secretory phase (Morris et al., 1991; Jones et al., 1996). All tissues had been fixed in 10% neutral buffered formalin for 24–48 h and routinely processed into paraffin wax. Sections were cut at 3 µm and mounted on lysine or aminopropyltriethoxysilane (APES) coated slides depending on the pre-treatment required.

**Immunohistochemistry**

Details of primary monoclonal antibodies, specificities, dilutions and pre-treatment requirements are given in Table I. Sections were labelled with a streptavidin-biotin peroxidase complex technique as described previously (Jones et al., 1996). Briefly, sections were deparaffinized, rehydrated, incubated for 10 min with 0.5% hydrogen peroxide in methanol to block endogenous peroxidase activity, and washed in tap water. For trypsin pre-treatment sections were incubated in distilled water at 37°C (5 min) and transferred into a 0.1% trypsin solution with 0.1% calcium chloride in distilled water at 37°C for the appropriate time. After rinsing in tap water the sections were washed with 0.1% calcium chloride in distilled water at 37°C (5 min) and transferred into a 0.1% trypsin solution at 37°C (5 min) and finally with streptavidin-biotin peroxidase complex (Dako, High Wycombe, UK) diluted 1:500 in TBS (30 min) and finally with streptavidin-biotin peroxidase complex (Dako) (30 min). Sections were washed in TBS between each incubation. The reaction was developed for 5 min with 3,3’-diaminobenzidine (DAB) (Sigma Chemical Co., Poole, UK) containing 0.02% hydrogen peroxide. Sections were lightly counterstained with Mayer’s haematoxylin, dehydrated, cleared in xylene and mounted in DPX.

**Quantification**

Positive cells showed brown membrane or cytoplasmic reactivity and were identified as intraepithelial if clearly flanked by two epithelial cells and situated above the epithelial basement membrane (Pace et al., 1991). Cells were counted per 300 epithelial cells at ×400 magnification in both surface and glandular epithelium. Qualitative assessment was used for CD45RA and CD57, since positive cells were rarely identified. Differences between groups were analysed using the Mann–Whitney test.

**Results**

**Variation in IEL in control, eutopic and ectopic endometrium**

The number of CD45(LCA)+, CD43(MT1)+ and CD56+ IEL in glandular epithelium in control endometrium and eutopic endometrium in endometriosis increased from the proliferative to the late secretory phase (CD45: control $P = 0.0025$, eutopic $P = 0.0113$; CD56: control $P = 0.0009$, eutopic $P = 0.0002$; CD43: control $P = 0.0015$, eutopic $P = 0.0191$) but in surface epithelium only CD68(KP1)+ IEL increased significantly (control $P = 0.003$, eutopic $P = 0.0029$) (Figure 1, Table II). In contrast, the number of CD68+, CD3+, CD4+ and CD8+ IEL was low and showed few significant changes throughout the cycle (Figure 1, Table II). While the number of CD3+ IEL in control glandular epithelium increased ($P = 0.0173$) from the proliferative to the late secretory phase,

### Table I. Primary monoclonal antibodies used on paraffin-embedded sections

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Specificity</th>
<th>Dilution</th>
<th>Pre-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAKO-CD45</td>
<td>Dako*</td>
<td>Leukocyte common antigen, CD45</td>
<td>1:10</td>
<td>Trypsin 5 min</td>
</tr>
<tr>
<td>NCL-CD43</td>
<td>Novocastra Laboratoriesb</td>
<td>T cells and large granular lymphocytes; recognizes CD43 epitope</td>
<td>1:40</td>
<td>Trypsin 5 min</td>
</tr>
<tr>
<td>NCL-CD45RA</td>
<td>Novocastra Laboratories</td>
<td>B cells; recognizes CD45 RA epitope</td>
<td>1:60</td>
<td>No pre-treatment</td>
</tr>
<tr>
<td>DAKO-CD68</td>
<td>Dako</td>
<td>CD68; macrophages, recognizes a 110 kDa glycoprotein primarily expressed as an intracytoplasmic molecule</td>
<td>1:50</td>
<td>Trypsin 10 min</td>
</tr>
<tr>
<td>NCL-CD3-PS1</td>
<td>Novocastra Laboratories</td>
<td>22/26/30 kDa lymphocyte surface associated molecule associated with the T cell antigen complex, represents the ε chain of CD3</td>
<td>1:100</td>
<td>Microwave citrate buffer</td>
</tr>
<tr>
<td>NCL-CD4–1F6/CD8–144</td>
<td>Novocastra Laboratories</td>
<td>Specific for epitope on external domain of the CD4 molecule</td>
<td>1:30</td>
<td>Microwave EDTA buffer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This antibody was a kind gift from Dr A. Appleton, Department of Pathology, Newcastle University. It was originally a gift from Dr D.Y. Mason, Oxford, UK</td>
<td>1:200</td>
<td>Microwave EDTA buffer</td>
</tr>
<tr>
<td>CD56</td>
<td>Zymed Laboratoriesc</td>
<td>Specific to two isoforms of human neural cell adhesion molecule (N-CAM or NKH1)</td>
<td>1:750</td>
<td>Microwave EDTA buffer</td>
</tr>
<tr>
<td>NCL-CD57</td>
<td>Novocastra Laboratories</td>
<td>110 kDa cell surface antigen, present on natural killer cells, CD57</td>
<td>1:25</td>
<td>Trypsin 5 min</td>
</tr>
</tbody>
</table>

*aDako Ltd, High Wycombe, UK.
*bNovocastra Laboratories, Newcastle upon Tyne, UK.
*cZymed Laboratories, California, USA.
CD4+ and CD8+ cells did not differ significantly with menstrual cycle phase (Figure 1, Table II).

As in endometriosis, in eutopic endometrium in adenomyosis there was a significant increase in CD43+ (P = 0.037) and CD56+ cells (P = 0.012) in glandular epithelium from the proliferative to the late secretory phase (Figure 1); there were no variations with menstrual cycle phase in CD45+, CD68+, CD3+, CD4+ or CD8+ cells in adenomyosis (Figure 1).

In endometriotic foci there were no significant differences with menstrual cycle phase in any IEL populations examined.

In contrast, in ectopic endometrium in adenomyosis there were some cyclical changes, the number of CD56+ cells increasing significantly from the proliferative to the early and late secretory phases (P = 0.037) (Figure 1).

**Differences between surface and glandular IEL**

The number of CD45+, CD43+ and CD68+ IEL was elevated in surface compared with glandular epithelium in the proliferative (CD45: control P = 0.0009, eutopic P = 0.0173; CD43: control P = 0.0013, eutopic P = 0.0008; CD68: control P =
Intraepithelial leukocytes in endometriosis

**Table II. Comparison of intraepithelial leukocytes (IEL) in surface and glandular epithelium**

<table>
<thead>
<tr>
<th></th>
<th>CD45</th>
<th>CD43</th>
<th>CD56</th>
<th>CD68</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control surface</td>
<td>9.4 ± 2.6</td>
<td>8.1 ± 1.5</td>
<td>0.1 ± 0.1</td>
<td>6.3 ± 2.8</td>
<td>3.8 ± 1.3</td>
<td>4.5 ± 1.5</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Control glandular</td>
<td>0.8 ± 0.7</td>
<td>1.0 ± 0.9</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.1 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>Eutopic surface</td>
<td>10.4 ± 3.4</td>
<td>10.0 ± 2.1</td>
<td>1.4 ± 0.6</td>
<td>6.3 ± 0.8</td>
<td>5.4 ± 1.9</td>
<td>1.8 ± 0.6</td>
<td>5.9 ± 2.0</td>
</tr>
<tr>
<td>Eutopic glandular</td>
<td>4.0 ± 1.2</td>
<td>2.3 ± 0.7</td>
<td>0.5 ± 0.2</td>
<td>0.5 ± 0.3</td>
<td>1.4 ± 0.7</td>
<td>0.2 ± 0.1</td>
<td>1.5 ± 0.5</td>
</tr>
</tbody>
</table>

**Early secretory**

<table>
<thead>
<tr>
<th></th>
<th>CD45</th>
<th>CD43</th>
<th>CD56</th>
<th>CD68</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control surface</td>
<td>6.8 ± 0.9</td>
<td>4.8 ± 0.8</td>
<td>0.8 ± 0.4</td>
<td>2.2 ± 4.1</td>
<td>2.0 ± 0.9</td>
<td>0.3 ± 0.2</td>
<td>2.1 ± 0.8</td>
</tr>
<tr>
<td>Control glandular</td>
<td>4.1 ± 1.5</td>
<td>2.2 ± 0.5</td>
<td>0.8 ± 0.6</td>
<td>0.0 ± 0.0</td>
<td>1.2 ± 0.4</td>
<td>0.3 ± 0.2</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>Eutopic surface</td>
<td>6.6 ± 1.4</td>
<td>6.3 ± 1.6</td>
<td>1.3 ± 0.4</td>
<td>0.9 ± 1.2</td>
<td>1.1 ± 0.4</td>
<td>0.6 ± 0.3</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>Eutopic glandular</td>
<td>2.1 ± 0.9</td>
<td>0.8 ± 0.3</td>
<td>0.4 ± 0.3</td>
<td>0.0 ± 0.0</td>
<td>0.4 ± 0.3</td>
<td>0.0 ± 0.0</td>
<td>0.8 ± 0.3</td>
</tr>
</tbody>
</table>

**Late secretory**

<table>
<thead>
<tr>
<th></th>
<th>CD45</th>
<th>CD43</th>
<th>CD56</th>
<th>CD68</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control surface</td>
<td>13.9 ± 2.8</td>
<td>9.2 ± 1.1</td>
<td>5.1 ± 1.2</td>
<td>3.1 ± 1.8</td>
<td>4.0 ± 1.7</td>
<td>1.1 ± 0.4</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>Control glandular</td>
<td>9.2 ± 1.9</td>
<td>7.1 ± 1.5</td>
<td>4.3 ± 1.1</td>
<td>0.9 ± 0.4</td>
<td>1.8 ± 0.7</td>
<td>0.6 ± 0.3</td>
<td>1.7 ± 0.7</td>
</tr>
<tr>
<td>Eutopic surface</td>
<td>13.4 ± 2.5</td>
<td>10.6 ± 2.6</td>
<td>11.8 ± 3.4</td>
<td>0.7 ± 0.5</td>
<td>1.4 ± 0.4</td>
<td>0.4 ± 0.2</td>
<td>2.8 ± 1.2</td>
</tr>
<tr>
<td>Eutopic glandular</td>
<td>11.5 ± 2.5</td>
<td>7.5 ± 1.7</td>
<td>11.6 ± 4.3</td>
<td>1.1 ± 0.8</td>
<td>0.8 ± 0.3</td>
<td>0.3 ± 0.2</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

Data are numbers of IEL per 300 epithelial cells (±SEM).

0.006, eutopic $P = 0.0004$) and early secretory (CD45: control $P = 0.02$, eutopic $P = 0.0113$; CD43: control $P = 0.046$, eutopic $P = 0.002$; CD68: control $P = 0.022$, eutopic $P = 0.0113$) phases in control and eutopic endometrium. Although elevated IEL numbers were also seen in the late secretory phase only CD68+ surface IEL were significantly more numerous in control endometrium only ($P = 0.022$) (Table II).

Similarly, CD3+ and CD4+ surface IEL were significantly elevated in the proliferative phase compared with glandular IEL (CD3: control $P = 0.005$, eutopic $P = 0.023$; CD4: control $P = 0.0015$, eutopic $P = 0.0312$), but these differences were not significant in later phases of the cycle. Surface CD8+ IEL were more abundant in the proliferative ($P = 0.0312$) and early secretory ($P = 0.021$) phases in eutopic endometrium only.

**Comparison of IEL between control, eutopic and ectopic endometrium**

Unlike in adenomyosis the number of CD45+ and CD43+ IEL in glandular epithelium was significantly increased in eutopic endometrium in endometriosis compared with control endometrium in the proliferative phase (CD45: $P = 0.0058$; CD43: $P = 0.014$), CD56+, CD68+, CD4+ and CD8+ cells did not differ significantly but CD3+ IEL were higher in proliferative phase eutopic endometrium compared with control endometrium in both endometriosis ($P = 0.05$) and in adenomyosis ($P = 0.032$) (Figure 1).

There were no differences in the numbers of IEL in surface epithelium between control endometrium and eutopic endometrium in endometriosis. Because of low sample numbers and the lack of significant differences in surface IEL between endometriotic eutopic and control endometrium, surface IEL were not examined in adenomyosis.

Endometriotic foci contained significantly more CD45+ and CD43+ IEL in the proliferative (CD45: $P = 0.007$; CD43: $P = 0.054$) and early secretory phases (CD45: $P = 0.0008$; CD43: $P = 0.0003$) than the corresponding eutopic endometrium (Figure 1). Similarly, CD68+, CD3+, CD4+ and CD8+ cells were increased in ectopic endometrium in the early secretory (CD8: $P = 0.0002$; CD3: $P = 0.0073$; CD68: $P = 0.042$; CD4: $P = 0.0062$) and proliferative phases (CD68: $P = 0.0084$) (Figure 1). In contrast, there were dramatically fewer CD56+ cells in ectopic than eutopic endometrium in the late secretory phase ($P = 0.0019$) (Figure 1).

In adenomyosis only the number of CD43+ cells was elevated in ectopic endometrium in the proliferative ($P = 0.047$) and early secretory ($P = 0.037$) phases (Figure 1) compared with the corresponding eutopic endometrium.

**Comparison of IEL in ectopic endometrium in endometriosis or adenomyosis**

In the early and late secretory phases the number of CD56+ cells was significantly lower in ectopic endometrium from endometriosis than adenomyosis (early secretory: $P = 0.003$; late secretory: $P = 0.028$). In contrast, foci of endometriosis contained more CD8+ cells than adenomyosis in the proliferative ($P = 0.05$) and early secretory ($P = 0.023$) phases (Figure 1). No other differences in IEL populations were detected.

**CD57(NK1)-positive natural killer cells and CD45RA(MB1)-positive cells**

CD57+ and CD45RA+ cells were rarely seen in all the intraepithelial locations studied.

**Discussion**

The results of the present study indicate that changes in glandular IEL in normal endometrium during the menstrual cycle are similar to those reported for stromal leukocytes with CD45+, CD43+ and CD56+ IEL increasing from the proliferative to the late secretory phase (Morris et al., 1985; Bulmer et al., 1991; Klentzeris et al., 1992; Jones et al., 1996); these findings are in accord with Pace et al. (1991) and suggest that IEL are influenced by the same factors as stromal leukocytes. Although CD4+ and CD8+ cells did not alter significantly during the cycle, there was a significant increase in CD3+ cells in the late secretory phase; this is most likely to be due to detection by the anti-CD3 monoclonal antibody
of cytoplasmic expression of CD3e by CD56+ endometrial granulated lymphocytes (Hayakawa et al., 1994). B cells and CD57+ NK cells were rarely detected in an intraepithelial position and this is in agreement with Pace et al. (1991).

Pace et al. (1991) reported a reduction in the CD4:CD8 ratio from the proliferative to the secretory phase. The present results also show a higher proportion of CD8+ lymphocytes in epithelium compared with stroma, suggesting preferential selection of these cells to become IEL. Together with macrophages and CD56+ endometrial granulated lymphocytes, CD8+ cells in surface epithelium probably form a first line of defence against infection. This is supported by a recent study which demonstrated that CD8+ T cells from proliferative endometrium can mediate significant cytolytic activity (White et al., 1997). However, the comparatively low proportion of the total endometrial leukocyte population accounted for by IEL implies that the epithelial leukocytes may not be crucial for maintaining mucosal immunity at this site. CD8+ T cells within both the epithelium and stroma may have a role in the secretion of cytokines into the endometrial lumen and glands, controlling the growth and function of the endometrial epithelium, stroma, and other leukocytes. The activation status and cytokine production of intraepithelial T cells is unknown as is their role in normal endometrium.

The present study demonstrated higher levels of IEL in surface compared with glandular epithelium; these differences were most pronounced in the proliferative and early secretory phases and are in agreement with Pace et al. (1991). Elevated numbers of IEL in surface epithelium may reflect increased antigenic challenge from the endometrial lumen. The elevated IEL in surface epithelium persisted in the period around ovulation when the vaginal and cervical environment is altered to allow sperm entry into the uterine cavity, consequently making uterine infection more likely. It would be interesting to determine whether IEL are up-regulated in epithelium after immunological challenge, or in women with genital tract infections.

The predominantly ovarian endometriotic lesions contained similar intraepithelial leukocyte populations to eutopic and control endometrium but it is noteworthy that there were no changes with menstrual cycle phase; in particular, CD56+ cells did not increase during the secretory phase of the cycle. The present results demonstrate that IEL in eutopic endometrium respond differently to changes in menstrual cycle phase compared with those in eutopic epithelium. In contrast, in foci of adenomyosis, with the exception of CD43+ cells the IEL populations were similar to those in eutopic epithelium and varied with menstrual cycle phase. When IEL in eutopic endometrium were compared in endometriosis and adenomyosis the findings were similar to those already reported for the stromal leukocytes (Jones et al., 1998); in the proliferative and early secretory phases CD3+ and CD8+ IEL were increased in endometriosis and in the late secretory phase CD56+ IEL were reduced. The reasons for the altered levels of IEL in eutopic endometrium in endometriosis remain unclear. In eutopic endometrium it appears likely that changes in leukocytes are regulated either directly or indirectly by steroid hormones. Thus, altered IEL in eutopic endometrium may be a result of an abnormal response to steroid hormones; this is supported by previous studies which demonstrated up-regulated oestrogen receptor expression in eutopic endometrium (Jones et al., 1995). Another possible explanation is that altered IEL levels are a response to other factors such as cytokines or growth factors present in the endometriotic lesions or peritoneal fluid. Previous studies which have demonstrated significant changes in stromal leukocyte populations in ectopic compared with eutopic endometrium from women with endometriosis (Jones et al., 1996) support this theory. In contrast, eutopic endometrium in adenomyosis did show some cyclical changes with increased CD56+ cell numbers in the late secretory phase. These differences in IEL populations between foci of endometriosis and adenomyosis may reflect the differing pathogenesis of these disorders (Garcia et al., 1987; Schenken, 1989; Ryan et al., 1990; Haney, 1991; Rock and Markham, 1992; Fox and Wells, 1995).

In endometriosis there were increased numbers of CD45+, CD43+ and CD3+ IEL in proliferative phase eutopic endometrium compared with control endometrium. Although these numerical changes did not persist during the secretory phase, it remains possible that T lymphocytes in eutopic endometrium in endometriosis may differ in their activation status. Activated lymphocytes may show different cytokine secretion and there is considerable evidence that successful pregnancy requires a balance of beneficial and detrimental cytokines (Hill, 1992; Wegmann et al., 1993; Loke and King, 1995). Additional studies using precisely dated tissue from the peri-implantation period would be required to investigate this further. Altered endometrial IEL populations between women with endometriosis and adenomyosis could relate to their disease pathogenesis and/or the associated infertility in the case of endometriosis.

It can be argued that investigation of IEL, although neglected, is as important as studies of stromal leukocytes. In eutopic endometrium the epithelium forms the first line of defence against immunological challenge and the first barrier to the implanting conceptus. Moreover, epithelial cells secrete a large range of cytokines and growth factors possibly involved in the control of endometrial function (Tabibzadeh and Sun, 1992; Smith, 1994). Similarly, in early endometriotic lesions the epithelium overlying the surface of the lesion is the first barrier to immune responses against the ectopic tissue. Thus, abnormalities which allow the underlying endometriotic tissue to grow and thereby establish the disease could be at the level of the epithelium and IEL. Future studies should address IEL function by determining the expression of cytokines, growth factors, activation markers and adhesion molecules.

Acknowledgements

We gratefully acknowledge the financial support provided by the Sir Jules Thorn Charitable Trust (grant 9312A). We would also like to thank the pathologists of the Department of Pathology, Royal Victoria Infirmary, for their help in obtaining specimens.

Ethical approval for the study was granted by Newcastle Joint Ethics Committee; all samples were obtained with informed consent.
References


Received on March 23, 1998; accepted on July 21, 1998