The relationship between urinary infection, cystoscopic appearance, and pathology of the bladder in man

for Testing Significance in a $2 \times 2$ Contingency Table. Cambridge University Press, London.


II Squamous change in the bladder epithelium

**SYNOPSIS** The occurrence of squamous change in the bladder epithelium was studied in bladder biopsies from patients with recurrent urinary infections or symptoms of cystitis and comparisons were made with sections taken at necropsy from control subjects. Two types of squamous change, termed 'vaginal' and 'cornified', are described. Vaginal change was frequent in females, and seemed to be a normal finding in them, but was not observed in males. It did not seem to be caused by urinary infection. Cornified change was also common in females and was found in one (infected) man. Like vaginal change it was most often found in sections from the trigone. Urinary infection may predispose to its formation but we were unable to prove this. Squamous change did not seem to cause symptoms, and could not usually be recognized at cystoscopy. The varieties described are so common that they are unlikely to be markedly precarcinomatous.

The literature concerning the significance of squamous epithelial change in the bladder is inadequate. During a prospective study of women with recurrent urinary infections we took 50 bladder biopsies (usually from the trigone) from 41 patients who presented with recurrent or persistent symptoms suggesting infection. Twenty-four developed urinary infection during follow up but in 11 there was no evidence of infection throughout prolonged observation; six were regarded as of uncertain bacilluric status as they were observed for too short a time. Only one biopsy was taken at each cystoscopy. The frequency with which squamous change was found in these biopsies, and its nature, was compared with that in sections made at necropsy from the trigones, and in some cases the vaults also, of bladders from 42 control subjects. We could find no evidence of previous urinary infection in 30 of these but 12 had suggestive evidence of antemortem infection.

Details of patients and controls, and our bacteriological and statistical methods, have been given elsewhere (Marsh, Banerjee, and Panchamia, 1974).

**Histological Classification**

Two types of squamous epithelium were found:

1. **VAGINAL SQUAMOUS EPITHELIUM (FIG 1)**

This thick epithelium was composed largely of polygonal cells with clear cytoplasm; the epithelial
margin adjacent the lamina propria was scalloped, with prominent rete pegs. Although intercellular bridges are said to be absent in this variety (Cifuentes, 1947) they were nearly always found.

2 CORNIFIED SQUAMOUS EPITHELIUM (FIG 2) Abnormal cornification was found, often in a thinner, less scalloped, epithelium; scalloping was sometimes absent, and cornification was usually of minor degree.

The change from transitional to squamous epithelium occurred abruptly in both varieties (fig 3).

Sometimes cornification was found in scalloped epithelium of vaginal type. Such mixed cases were doubly indexed into both vaginal and cornified epithelium groups. The sum of these groups therefore exceeds the number indexed under 'unspecified squamous epithelium'. This term was used to indicate the occurrence of any kind of squamous epithelium, for the significance of its subdivision into vaginal and cornified types was not immediately apparent.

Despite early postmortem examination of the bladder in control subjects, the nature of the trigonal epithelium could not be assessed because of autolysis in four 'uninfected' and two 'infected' controls. Squamous epithelium appeared to resist autolysis better than transitional epithelium.

Results

SQUAMOUS CHANGE AND SEX (TABLE 1) Vaginal change was common in females but was not found in males. Cornified change was fairly common in females and was found in only one male. The differences between males and females with regard to vaginal and unspecified squamous change were highly significant, whether sections from trigone and vault, or only those from trigone, were considered, and the same trend was evident when infected and uninfected subjects were considered separately. The more frequent finding of cornified change in females than in males did not reach our significant level.

SQUAMOUS CHANGE AND SITE OF BIOPSY (TABLE 1) For all subjects studied (patients or controls, infected or uninfected, females or both sexes) vaginal, cornified, and unspecified squamous change were all found more often in sections from the trigone than in those from outside it. This difference was significant when unspecified squamous change was studied in sections from females, which suggests it was not due to a bias between males and females with regard to the site of biopsy.
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<table>
<thead>
<tr>
<th>Sex</th>
<th>Site of Biopsy</th>
<th>Type of Squamous Change</th>
<th>Unspecified</th>
<th>Vaginal</th>
<th>Cornified</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>Trigone</td>
<td>Present</td>
<td>23 (17)</td>
<td>23 (17)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>23 (17)</td>
<td>20 (20)</td>
<td>4 (4)</td>
<td>24 (18)</td>
<td>4 (4)</td>
<td>24 (18)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Female</td>
<td>Outside trigone</td>
<td>Present</td>
<td>24 (20)</td>
<td>50 (32)</td>
<td>12 (10)</td>
<td>62 (42)</td>
<td>28 (24)</td>
<td>46 (28)</td>
<td>11 (10)</td>
<td>59 (42)</td>
<td>25 (24)</td>
<td>45 (28)</td>
<td></td>
</tr>
</tbody>
</table>

Table I Squamous epithelial change in relation to sex and site of biopsy in patients and controls

1Figures in parentheses refer to sections taken from the trigone; figures not in brackets also include sections taken from outside the trigone and any in which the site of origin was uncertain.

2Figures in parentheses here refer to sections from female patients and controls only; figures not in brackets refer to both sexes.

The following are significantly related:
Vaginal squamous change and sex (all sections): x² 8-6290, 0.005 > p > 0.001
Vaginal squamous change and sex (trigonal sections): x² 7-8993, 0.005 > p > 0.001
Unspecified squamous change and sex (all sections): x² 8-3115, 0.005 > p > 0.001
Unspecified squamous change and sex (trigonal sections): x² 7-9124, 0.005 > p > 0.001
(2a = 0.05)
Unspecified squamous change and site of biopsy (sections from females): x² 4-0222, 0.05 > p > 0.025.

SQUAMOUS CHANGE AND INFECTION

(TABLE II)
The prevalence of vaginal change in biopsies from infected and uninfected subjects was virtually the same, irrespective of the site of biopsy and whether the latter was from patient or control. Although cornified change was approximately twice as common in infected as in uninfected subjects, and the only man whose biopsy showed cornified change was infected, this difference was not significant.

We have previously demonstrated a strong correlation between the degree of subepithelial lymphocytic infiltration in the bladder and the occurrence of urinary infection (Marsh et al, 1974). The apparent lack of correlation between infection and squamous change was supported by a similar lack of correlation between squamous change and the subepithelial lymphocytic grading (table III); this was so whether all subjects or only females were considered and was irrespective of the site of biopsy.

SQUAMOUS CHANGE AND SYMPTOMS

The finding of squamous change was compared with symptoms present in patients at the time of biopsy, and the frequency of symptoms during the prebiopsy observation period, in the manner previously described (Marsh et al, 1974).

Consideration of the mean scores, and the distribution of scores, provided no evidence that the occurrence of symptoms at the time of biopsy,
or the frequency of symptoms before it, was related to the presence of squamous change (of whatever type).

**Squamous Change and Cystoscopic Appearance**

A local abnormality (other than changes suggestive of lymphocyte follicle formation) was found in only three of 16 cystoscopies performed on patients with squamous change. In two patients (one with vaginal, the other with cornified epithelium) a white or yellow plaque was seen on the trigone. In one, who had cornified epithelium, yellow nodules suggestive of malakoplakia were seen. A white film was observed on the trigone of another patient, but there was no squamous change in the biopsy.

**Discussion**

There has been longstanding controversy over the significance of squamous change in the bladder. Oestrogens have been thought to predispose to its formation, for it has been found in normal women and female neonates but not in normal men (Cifuentes, 1947; Ney and Ehrlich, 1955; Tyler, 1962; Streitz, 1963); however it has also been described in prepubertal girls (Streitz, 1963) and postmenopausal women (Cifuentes, 1947; Tyler, 1962). Longstanding urinary infection has been considered an important predisposing factor (Heymann, 1905; Stirling and Ash, 1941; Connery, 1953; Abeshouse andTankin, 1956; Politan, 1956; Holley and Mellinger, 1961; Smith, Webb, and Price, 1962; Clarke and Gherardi, 1962; Streitz, 1963; O'Flynn and Mullaney, 1967), a view which has experimental support (Ball, Field, Roe, and Walters, 1964). It is also widely believed to be precarcinomatous (Politan, 1956; Holley and Mellinger, 1961; Roe, 1964; Ball et al, 1964; O'Flynn and Mullaney, 1967). Most of these studies antedate modern methods of diagnosing urinary infections, and in none of them were infected and uninfected subjects compared.

Most of those who believe it is normal appear to have studied what we have called 'vaginal squamous change'. Those who believe it to be precarcinomatous and a sequel to urinary infection usually refer to leukoplakia, which they often define as 'cornification of a non-cornifying membrane' although purely cystoscopic criteria have been used. Therefore we have analysed our data according to whether vaginal or cornified change was present and, bearing in mind that the appearance may vary cyclically with menstruation, have also grouped them together as 'unspecified squamous change'. We have avoided the term 'squamous metaplasia' as this presupposes a pathological change (Willis, 1961).

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Our data suggest that squamous change of the vaginal type often occurs in females, but we could not relate it to urinary infection. We believe it to be a normal finding in women (it occurred in seven out of 16 uninfected female controls) but have no information concerning its relationship to the menstrual cycle. However Tyler (1962), in a study of 107 necropsy cases (not documented with regard to urinary infection), showed not only that squamous change was common in the bladder trigone of adult women but that it underwent cyclical menstrual changes similar to those of vaginal epithelium. Like Tyler we found that vaginal squamous change of the trigone was not limited to women of childbearing age: four of our 21 women with vaginal change were over 55 years and two were in their 80th decade. We did not find it in any men, although it has been described in men undergoing oestrogen therapy or with transitional cell carcinoma of the bladder (Henry and Fox, 1971). In all patients we studied it was more commonly found in sections from the trigone than from outside it.

Our results suggest that urinary infection may predispose to cornified squamous change, which also occurred more often in females than males. The differences were not statistically significant, but the number of biopsies studied was not large. We only found cornified change in one man (who was infected), although it often occurred in females. Like vaginal change, it was more frequently found in sections from the trigone than from outside it, although once again the difference was not significant. Because the change from transitional to squamous epithelium was characteristically abrupt, and sections from controls tended to be larger than biopsies from patients, squamous change should be identified more frequently in the control sections. However, our results were similar when patients and controls were analysed separately, and any error introduced would tend to decrease, rather than increase, the significance of any differences present.

Analysis of symptoms at the time of biopsy and over the prebiopsy observation period, suffered by women with a history of recurrent cystitis, showed no difference between those with squamous change of any type and those without it. We think it unlikely that squamous change causes symptoms. Although Henry and Fox (1971) admitted that vaginal squamous change could be found in the trigones of normal females, they considered that its association with oedema and venous dilatation in the lamina propria constituted an entity, 'pseudomembranous trigonitis', which was productive of symptoms of the urethral syndrome. Neither they nor Packham (1971), who also believed that squamous change could produce such symptoms, studied asymptomatic
Subjects or those with bacterial urinary infection, and their clinical and bacteriological criteria were not fully defined. Although we have shown elsewhere that women with the ‘urethral syndrome’ tend to have chronic inflammatory changes in the lamina propria, we see no reason to link these specifically with vaginal squamous change.

Few of our patients with squamous change (of whatever type) had the cystoscopically visible lesions emphasized by Henry and Fox (1971) and Packham (1971).

We have no direct evidence concerning the alleged predisposition of patients with leukoplakia to develop carcinoma of the bladder. The lesions we have analysed did not show changes as dyskeratosis, parakeratosis, loss of cell polarization, nuclear pleomorphism, and abnormal mitoses which are typical of true leukoplakia. The very frequency of simple squamous change would suggest that it is not itself markedly precarcinomatous. However, it is possible that larger lesions, more easily discernible on cystoscopy than were ours, may be more likely to show true leukoplakia and have a more sinister prognosis.

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References


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