

THE EPITHELIAL LINING OF THE FEMALE TRIGONE AND URETHRA

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RECENTLY, much work has been published concerning the musculature of the trigone and urethra (Hutch, 1968). However, little has been written about the epithelial lining of the trigone and urethra and this paper presents facts in disagreement with the views expressed in the standard anatomical and urological textbooks. The importance of this epithelium in the ætiology of recurrent cystitis in women is briefly discussed, and this aspect will be dealt with more fully in a further publication on this subject.

Embryology of the Female Trigone and Urethra.—The urinary bladder, trigone, and urethra are developed partly from a segment of the Wolffian duct system, partly from the cloacal tissues, and partly from the remnants of the cloacal membrane. The urogenital sinus, or ventral part of the cloaca, becomes separated from the rectum by the appearance of the urorectal septum between them. This separation is complete by the sixth week of intra-uterine life, and at this stage the urogenital sinus is closed caudally by the cloacal membrane. The Wolffian duct arises from the posterior part of the bladder so formed and the ureter is formed from this as a bud growing cranially. The caudal part of the Wolffian system incorporated in the posterior wall of the bladder expands both cranially and caudally to form the trigone, the posterior bladder wall and the entire female urethra. While this is happening the cloacal membrane breaks down forming the ectodermal covering of the vulva including the skin of the external urethral meatus and the hymen.

Zuckerman (1940) has shown that some of the tissues derived from the Mullerian and Wolffian systems, the tissues in the urogenital sinus, and the tissues of the cloacal membrane are sensitive to œstrogens. Under physiological and experimental conditions œstrogens produce a squamous response with proliferation, cornification, and desquamation of the epithelium. He states that although there are developmental distinctions between the various urogenital tissues that respond to œstrogen stimulation, the embryological components of the urogenital system intermix at their points of contact. Thus the caudal end of the Mullerian and Wolffian ducts are invaded by the epithelium from the primarily endodermal urogenital sinus and the caudal region of the sinus is in turn invaded by the ectodermal cells from the cloacal membrane area.

It will be appreciated, therefore, that in the region of the female trigone and urethra there exist tissues of various origins sensitive to and responding to varying tissue levels of œstrogens.

There is some experimental evidence that by giving animals œstrogens the normal tissues of the urethra and trigone can be replaced by stratified squamous epithelium. Thus Burns (1939) gave œstrogens to 12 young opossums and produced extreme cornification of the urethra and urogenital sinus so that complete urinary obstruction occurred. Hundley *et al.* (1935) gave œstrogens to spayed female dogs and found that the urethral epithelium changed from transitional to squamous.

Historical Descriptions.—In the standard anatomical and urological textbooks, *Gray's Anatomy* (1967), Smith (1963), Thomson-Walker (1948), Hinman (1935), the distal part of the female urethra is said to be covered with stratified squamous epithelium and this merges proximally with the transitional epithelium of the bladder neck and trigone. Tyler (1962) described his findings in 102 post-mortem studies and 22 biopsies of the trigonal epithelium. He found squamous epithelium extending along the entire urethra up to but not encircling the ureteric orifices in 43 per cent. of the pre-menopausal women and 35 per cent. of the post-menopausal

women. He found none in 16 stillbirths and scattered patches on the trigone in 2 out of 25 full-term foetuses. In 23 males only one had squamous epithelium on the trigone but this patient had been given oestrogens for treatment of his prostatic carcinoma. Heymann (1906) found trigonal squamous epithelium in 10 out of 20 adult females, none in 5 males, and none in 5 female children. Moench (1942) noticed in post-mortem studies that in some females the epithelium was squamous and keratinised and postulated that this change might be related to the female hormones.

The squamous epithelium has been described by other writers but they have thought this change pathological due to inflammation of the trigone. Thus, in 1929, Canny Ryall described pseudomembranous trigonitis in which there was a veil or cloud of greyish pink which covered the trigone either patchily or completely. In 1924 Pelouze discussed trigonitis areata alba where the trigone was covered with a faint opalescence. In 1935 he also described an obscure pseudomembranous trigonitis in which the changes were similar to true pseudomembranous trigonitis but were less obvious.

Present Material.—Trigonal biopsies were taken of 50 women presenting with symptoms of abacterial "recurrent cystitis" or the urethral syndrome. The biopsies were taken from as

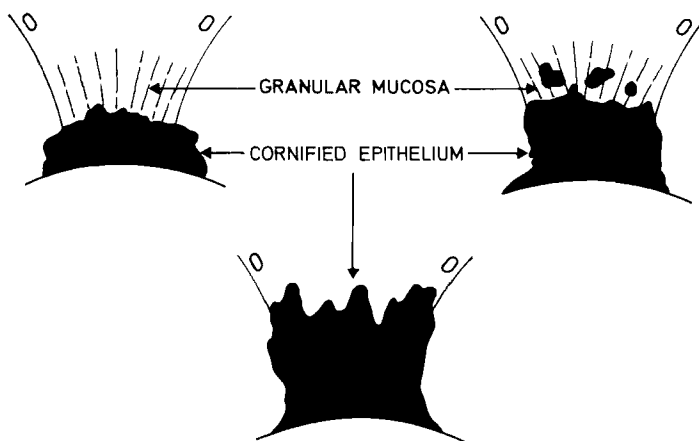


FIG. 1

Diagram of trigone showing typical examples of extent of squamous epithelium.



FIG. 2

This photomicrograph of a trigonal biopsy demonstrates that the entire surface of the biopsy is covered by squamous epithelium. $\times 37.8$, enlarged $\times 3$.

near as possible to the centre of the trigone and in all cases well away from the bladder neck. The cystoscopic appearance of the trigone varied. In some cases the trigone appeared red and rather granular. The mucosal vessels were not seen individually as on the male trigone but the trigonal tissues appeared generally hyperæmic. In others the trigone as well as being granular

Fig. 3.—This photomicrograph of a trigonal biopsy demonstrates that the entire surface of the biopsy is covered by transitional epithelium. $\times 96$, enlarged $\times 3$.

Fig. 4.—This photomicrograph (A) of a trigonal biopsy demonstrates that the surface is lined almost entirely by squamous epithelium. In the centre of the core of tissue can be seen several stages in the formation of von Brunn's nests. $\times 31.5$, enlarged $\times 2.5$. The second photograph (B) shows the two types of epithelium at a higher magnification. $\times 8$, enlarged $\times 2.5$.

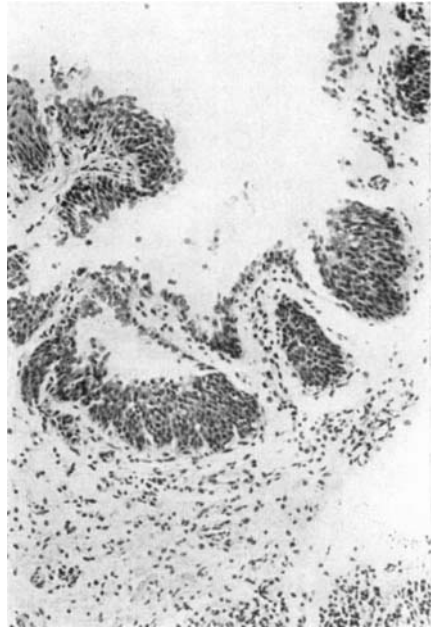


FIG. 3

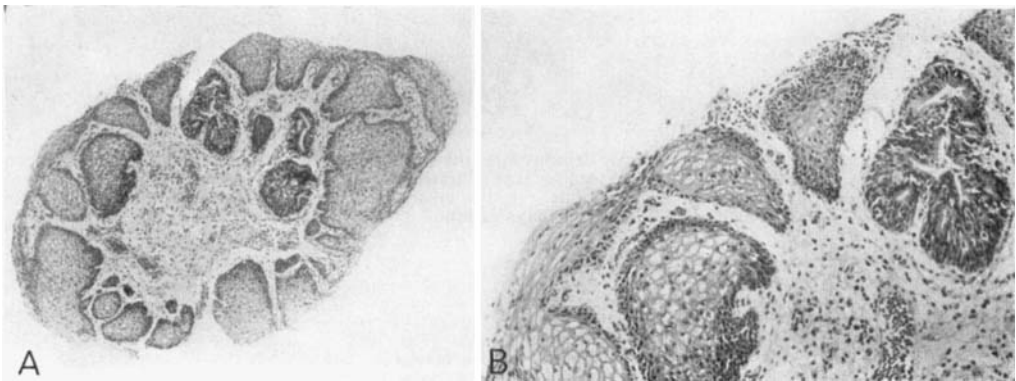


FIG. 4

was covered with a definite white membrane with clear-cut edges. The membrane varied in thickness and sometimes could be seen peeling off the underlying tissues. The membrane covered varying proportions of the trigone, being always more complete at the bladder neck but could be patchy towards the ureteric orifices. In no case did the membrane or the granularity extend above the ureteric orifices.

Biopsies from these 50 women showed that 42 of them had stratified squamous epithelium in the centre of the trigone. Most showed the changes of cornification and in some of those

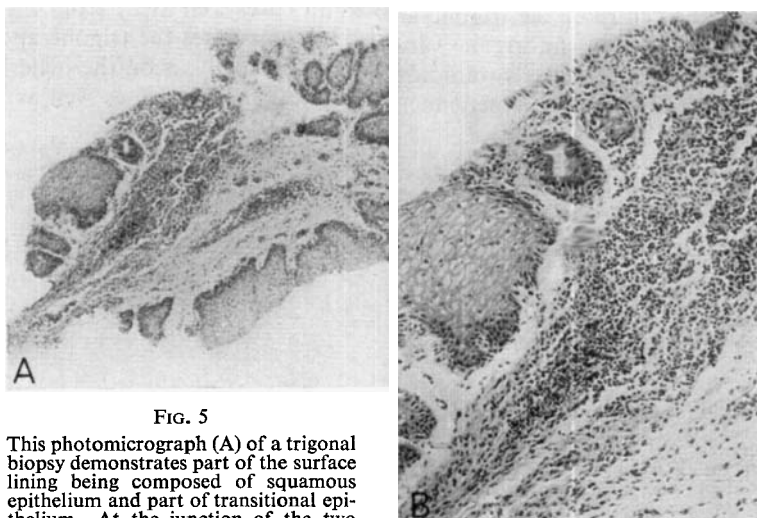


FIG. 5

This photomicrograph (A) of a trigonal biopsy demonstrates part of the surface lining being composed of squamous epithelium and part of transitional epithelium. At the junction of the two types of epithelium two stages in the formation of a von Brunn's nest can be seen. $\times 31.5$, enlarged $\times 2.5$. The second photograph (B) shows the same area at a higher magnification. $\times 80$, enlarged $\times 2.5$.

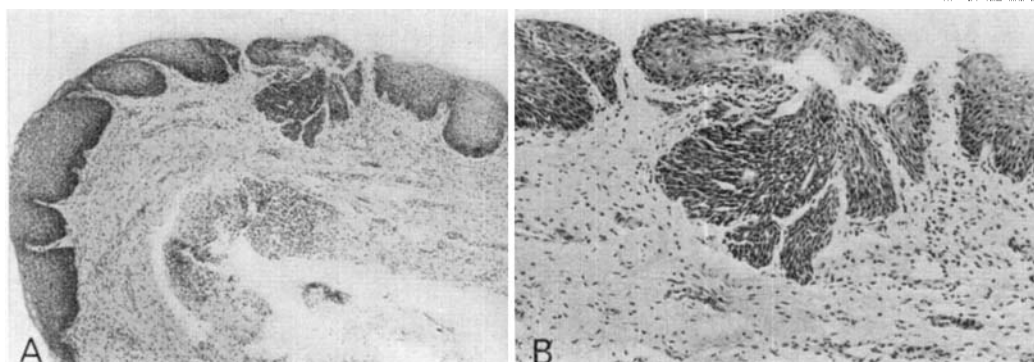


FIG. 6

This photomicrograph (A) of a trigonal biopsy demonstrates the surface covered with squamous epithelium of considerable thickness. Beneath this layer can be seen an area of transitional epithelium undergoing central cavitation, an early stage in the formation of von Brunn's nests. $\times 31.5$, enlarged $\times 2.5$. The second photograph (B) shows the same area at a higher magnification. $\times 80$, enlarged $\times 2.5$.

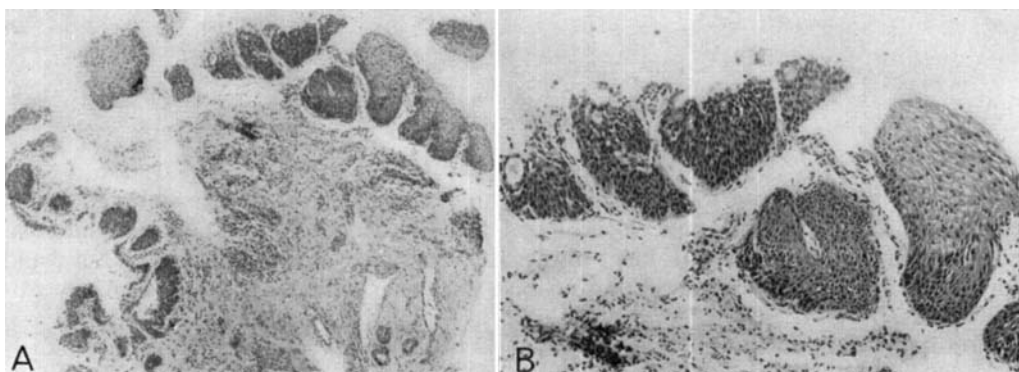


FIG. 7

This photomicrograph (A) demonstrates the patchy nature of the lining epithelium that is sometimes seen on biopsy. Areas of squamous epithelium and transitional epithelium merge into one another and often von Brunn's nests arise at the junction of the two types. $\times 31.5$, enlarged $\times 2.5$. The second photograph (B) shows the same area at a higher magnification. $\times 80$, enlarged $\times 2.5$.

with a thick white membrane keratinisation was also present. Examples of the changes are shown in diagram form in Figure 1 and in the form of photomicrographs in Figures 2 to 7. Figure 6 is a good example where the squamous epithelium can be seen overlying the normal transitional epithelium.

DISCUSSION

In many women the trigone is covered by squamous epithelium. This probably arises by extension and overgrowth of the epithelium from the oestrogen-sensitive tissues of the cloacal membrane and extends cranially to cover various proportions of the endodermal Wolffian duct derivatives, the urethra and trigone. This change seems only to occur from oestrogen stimulation and explains why it is a rare finding in children.

Although the biopsies in this series were from women with the urethral syndrome the findings of Tyler and others lead one to postulate that the squamous lining is the primary event and that perhaps the symptoms of the urethral syndrome are due to this abnormal mucosa being oestrogen-sensitive and responding to physiological changes in oestrogen levels during the menstrual cycle. During the time of high oestrogen levels the stratified epithelium becomes keratinised and appears as a thick white membrane, whereas around the menstrual period when oestrogen levels are low the mucosa appears just red and granular.

Some of this work was carried out at St Peter's Hospital, Henrietta Street, London, W.C.1, while I was Senior Registrar there in 1967. I would like to thank Mr H. K. Vernon and Mr David Wallace for allowing me to investigate their patients at that time. I would also like to thank Dr R. C. B. Pugh of the Institute of Urology for the pathological reports and the photomicrographs.

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