

# EXPERIMENTAL REPLACEMENT OF THE EPITHELIUM OF THE UTERUS BY STRATIFIED SQUAMOUS EPITHELIUM

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In the course of investigations of the effect of intravaginal applications of estrogen and intracervical application of a powerful carcinogen (9,10-dimethyl-1,2-benzanthracene) on the epithelium of the genital tract in mice, in some cases the author observed replacement of the uterine epithelium by stratified squamous epithelium [1, 2]. After further study of such cases it was concluded that the discovery of stratified squamous epithelium in the uterus was the result of migration of epithelium from more caudal parts of the genital tracts into the uterus.

In the present investigation the reasons for the migration of stratified squamous epithelium into the uterus were investigated, with particular reference to the possible importance of inflammatory changes in the uterus and disturbances of maturation and growth of the epithelium in the vagina itself (both these phenomena have usually accompanied administration of the estrogen and carcinogen).

## EXPERIMENTAL METHOD

Inflammatory changes were produced in the uterus of mice by introducing polyurethane sponge and linen thread into the cornu and cervical canal. Access to the uterus for intracervical introduction of the sponge was obtained by a small incision in the suprapubic part of the midline of the abdomen (the uterus was extracted by gentle traction on the cellular tissue of the adnexa by forceps). The sponge was then fixed by a circular ligature applied to the cornu. The thread was also introduced by a needle in the same way or per vaginam. In the latter case, after laparotomy and mobilization of the uterus into the wound of the abdominal wall (as in the case of introduction of the polyurethane sponge) the thread was passed into the cervical canal after the needle under visual control, using a small nasal speculum. The needle was brought out of the uterine cavity through the wall of the cornu near its apex. The wound was closed by two continuous sutures — one to the muscle and the other to the skin of the abdominal wall.

Observations continued after this operation for about 1.5 months (from 42 to 47 days). Otherwise the method was identical with that described previously [1, 2]. The animals were sacrificed with chloroform; the abdomen was opened immediately after respiration ceased. Next, 2-3 drops of cold water were applied to the body of the uterus by means of an ophthalmic pipet. This caused a contraction of the longitudinal muscle of the uterus, shortening the cornua and making them relatively straight. The whole cadaver of the animal was fixed in 10% formalin solution. The uterus and vagina were then resected from the cadaver in one piece and embedded in paraffin wax. Sections were cut in the frontal plane along the long axis of the organ so that the preparation contained epithelium of the various parts of the uterus, the cervix uteri, and the vagina at the same time. The sections were stained in two ways: with hematoxylin-eosin and with Heidenhain's hematoxylin and mucicarmine.

## EXPERIMENTAL RESULTS

Examination under the microscope showed that pathological changes were present mainly in the uterus, and took the form of the development of inflammation and replacement of the uterine epithelium by stratified squamous epithelium (corresponding to the results of the previous observations). As the table shows, the appearance of stratified squamous epithelium in the uterine cavity and replacement of the uterine epithelium were observed in two-thirds of cases (in 14 of 21 experiments) after intracervical introduction of the thread and the polyurethane sponge. These changes were observed in about one-third of animals following intracervical application of the carcinogen (in 6 of 19 cases) and intravaginal administration of estrogen (in 26 of 68 cases).

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Distribution of Cases with Replacement of Uterine Epithelium by Stratified Squamous Epithelium among Groups of Experiments

Experimental conditions	Number of animals		Duration of experiments (in days)
	Total	With replacement of uterine epithelium by stratified squamous	
Intracervical introduction of:			
Polyurethane sponge	15	10	42-47
Linen thread	6	4	42-47
Carcinogen	19	6	138-386
Intravaginal administration of estrogen*	68	26	7-18
Total	108	46	

\* Previous investigations.

The periods of observation in the different groups of experiments varied as follows: \* the shortest were after administration of estrogen (7-18 days), they were about 2.5-6 times longer after intracervical application of the thread or polyurethane sponge (42-47 days), and much longer (138-386 days) after intracervical application of the carcinogen.

It was clear from the histological preparations that the stratified squamous epithelium in the uterine cavity retained a direct connection with the epithelium lining the cervical canal and the vaginal cavity (see the figure a). This was found in all groups of the experiment. The uterine epithelium was always easily distinguishable from epithelium invading the uterus. No case of well marked keratinization of the stratified squamous epithelium advancing into the uterine cavity was observed. It resembled only the proestral epithelium of the vagina. In other words, the experiments showed that stratified squamous epithelium penetrated into (invaded) the uterine cavity from areas of the genital tract situated more caudally in all groups of the experiments with their different conditions.

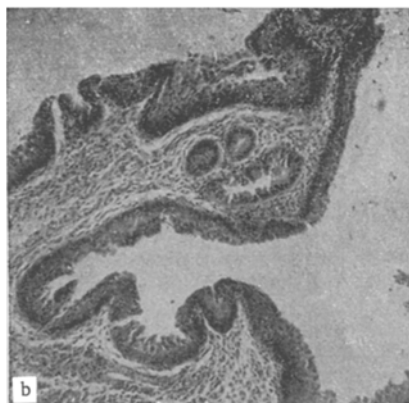
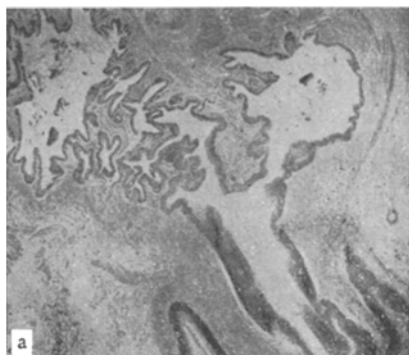
Most commonly invasion of stratified squamous epithelium was observed into the uterine cavity as far as the caudal third or quarter of the cornua, but sometimes nearly total replacement of the uterine epithelium was observed.

Following introduction of the thread, polyurethane sponge, and estrogen, the epithelium lining the uterine cavity was the first to be replaced. The epithelium of the glands was replaced somewhat later. Usually even with total replacement of the lining epithelium, individual uterine glands remained intact (see the figure b). However, in the experiments with intracervical application of the carcinogen, the stratified squamous epithelium spreading over the surface of the uterine mucous membrane and replacing the epithelium lining the uterus also advanced into the ducts of the glands, replacing their epithelium also. In addition, at about the level of those parts of the intermediate portion bordering on the uterus, the appearance of characteristic gland-like structures could be seen, also formed by epithelium of proestral type.

Following intracervical and intravaginal introduction of the foreign bodies, their remains were frequently visible in the uterine cavity. In every case, whatever the form of the experiment, inflammatory changes were present in the uterus. The number of leukocytes infiltrating the mucous membrane of the body and cervix of the uterus varied considerably from one part to another. Usually leukocytes were found as individual cells lying some distance from one another and not forming zones of dense infiltration. However, here and there in the subepithelial connective tissue, dense areas of infiltration with leukocytes could be seen.

The vaginal epithelium was normal in appearance. In some cases it was keratinized. This was evidently the feature distinguishing it most essentially from the epithelium invading the uterine cavity.

\* The experiments were carried out at different times and for different purposes.



Introduction of polyurethane sponge into the right uterine cornu (47 days). a) Part of uterus and adjacent portions of more caudal part of the genital tract. Stratified squamous epithelium is advancing into the uterus, covering two-thirds of the left cornu and almost completely replacing the uterine epithelium of the right cornu. Magnification  $7\times$  (loupe). Hematoxylin-eosin; b) part of the top right hand corner of figure a under higher power. The only part of the right cornu where remains of glands preserving the uterine epithelium can be found in the mucous membrane.  $180\times$ . Hematoxylin-eosin.

When comparing the results of the experiments described in this paper with those of earlier experiments in which estrogen was introduced into the vagina or a carcinogen into the cervical canal, the first point to be made is that new results have been obtained confirming the ability of the stratified squamous epithelium, in certain conditions, to invade the uterus and replace the uterine epithelium. In the histological sections which were prepared, the penetration of stratified squamous epithelium from more caudal areas of the genital tracts into the uterine cavity was proved conclusively.

It was not one of the aims of this investigation to determine in what experimental conditions this invasion of the uterus by stratified squamous epithelium took place more rapidly. With the number of animals used, the very different periods of the experiment, and the technique adopted for assessment of the histotopographical features of the epithelia, this would be impossible. Invasion of the uterus by stratified squamous epithelium, which was observed in experiments in different conditions, always took place in the presence of the same common condition — the presence of inflammatory changes in the uterus. Following intravaginal application of estrogen, or intracervical application of the powerful carcinogen 9,10-dimethyl-1,2-benzanthracene, or of polyurethane and linen thread, a direct connection was found between the stratified squamous epithelium invading the uterus and the same epithelium of the more caudal portions of the genital tracts in 46 cases. Clear differences between the morphological characteristics of the uterine epithelium and of the epithelium replacing it persisted even when, under the influence of a high estrogen level, the uterine epithelium, prismatic in normal conditions, underwent reorganization accompanied by some degree of flattening of its cells [2].

Following intracervical application of the linen thread and the polyurethane sponge, the products of inflammation and destruction, escaping from the uterine cavity into the cervical canal and vagina, caused no marked excessive proliferation of the epithelium within the periods of these experiments. In other words, in these experiments the invasion of the uterus by stratified squamous epithelium was not accompanied by changes in the vaginal epithelium.

The durations of these experiments were evidently too short for manifestation of the carcinogen action of polyurethane [11]. Application of estrogen caused changes in the vaginal epithelium relatively quickly. Prolonged application of estrogen is known to cause the development of tumors in the vagina [9, 14]. Tumors have also been found to develop in the vagina in experiments in which a carcinogen has been applied intracervically [1]. The results obtained show, first, the importance of inflammatory changes in the uterus in the pathogenesis of processes associated with the appearance of stratified squamous epithelium in that organ. In the author's earlier experiments, in which a carcinogen was introduced per vaginam into mice, in roughly 90% of the animals precancerous changes and carcinoma of the vagina developed [1]. However, these procedures were not accompanied by the development of inflammatory changes in the uterus, and there was no evidence of the replacement of the uterine epithelium by stratified squamous epithelium.

Consequently, judging by the experimental results, the inflammatory changes in the uterus are one of the causes of the invasion of the uterus by stratified squamous epithelium. Disturbances of maturation and growth of the epithelium actually in the vagina were of no importance in this respect.

These results may evidently be used to determine the possible causes of the appearance of stratified epithelium in the cavity of the human uterus. This means that when an interpretation is sought of the genesis of the different pathological squamous-cell structures arising in the uterine cavity, and, in particular, the genesis of the squamous-cell metaplasia of the epithelium of the thinner portion of the cervix uteri and the adjacent areas of the endometrium, this ability of the cervical epithelium to invade the uterus and replace the uterine epithelium must be borne in mind. At the same time, the possibility of a true squamous-cell metaplasia of the uterine epithelium is not ruled out. Such a metaplasia has frequently been reported in both clinical and experimental conditions [3-8, 10, 12, 13].

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.

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