

# PAPILLOMAS OF THE VAGINA IN MICE CAUSED BY INTRAVAGINAL APPLICATION OF POLYURETHANE

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Polyurethane is being used increasingly in industry and everyday life [10]. Its use in medicine has also been reported. Polyurethane has begun to be used in replacement surgery [1, 2]. Sponge, including synthetic, is often used as a container for contraceptives [9]. However, the molecule of this polymer contains a urethane group, which makes the study of its potential carcinogenic action extremely important.

The object of the present investigation was to study the carcinogenic action of polyurethane when introduced intravaginally into mice.

## EXPERIMENTAL METHOD

Experiments were carried out on virgin female mice of line CC57W, mostly intact but in some cases castrated (in previous experiments, following intravaginal administration of a carcinogen, castration accelerated the carcinogenic process in the epithelium of the cervix uteri). Castration was carried out 5-8 days before the beginning of the introduction of polyurethane. The initial age of the animals was 1.5-2 months.

A small piece of polyurethane sponge weighing about 1 mg was introduced into the vagina (attempting to place it as deep as possible into the vagina) with ophthalmic forceps twice a week for a period of 60-64 days. At the end of the experiment the animals were killed with chloroform.

The material was fixed in 10% formalin solution and embedded in paraffin wax. In 20 cases total frontal sections were cut through the uterus and vagina along the long axis of the organ so that the preparation contained the various parts of the uterus, the cervix, and the vagina at the same time. In the other cases, transverse sections were cut—through the middle third of the vagina, where the greatest changes took place. The sections were stained with hematoxylin-eosin, and in 20 cases in addition with hematoxylin-mucicarmine (to detect mucus in the epithelium).

Only those cases in which histological studies were carried out were taken into account.

## EXPERIMENTAL RESULTS

The results obtained are shown in the table.\*

Pathohistological Changes in the Epithelium of the Cervix Uteri and Vagina of Mice Following Intravaginal Introduction of Polyurethane

Animals	No. of animals	Pathohistological changes		
		initial	focal epithelial	papillomas
Intact	60	29	11	17
Castrated	16	7	—	9
Total	76	36	11	26

The initial changes in the epithelium (see table, column 1) consisted mainly of disturbances of maturation, as revealed by irregularity of the thickness of the different parts of the epithelium and the formation of small endophytic epithelial processes; cases are included in column 2 of the table, in which epithelial processes, invading the underlying connective tissue particularly deeply and forming side branches were present in certain parts of the mucous membrane of the vagina and cervix; column 3 contains cases in which exophytic nodules of mixed

\*All the pathohistological changes corresponded to those observed in the precancer period in experiments which have already been completed and described in which the carcinogenic substance 9, 10-dimethyl-1,2-benzanthracene was introduced intravaginally into mice. Characteristic bifunctional changes also appeared in the epithelium [4, 5]. For this reason the same classification of the pathological changes is used as was previously adopted by the author [4]. It corresponds to the general classification of precancerous changes proposed by L. M. Shabad [7, 8].

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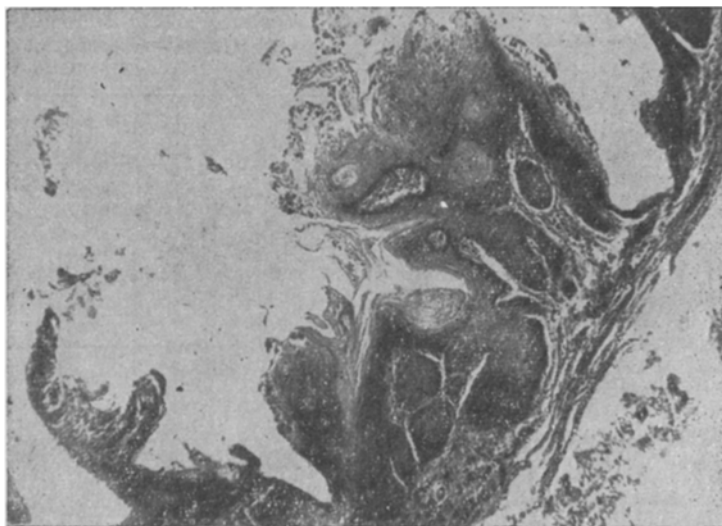


Fig. 1. Papilloma in the vagina of a mouse arising following intravaginal applications of polyurethane. The epithelium of the papilloma is stratified squamous, keratinizing. Hematoxylin-eosin. Magnification 70x.

epithelial and connective tissue hyperplasia were found, morphologically similar to papillomas, but differing from the usual papillomas in a very characteristic feature: in some cases their epithelium showed signs of being stratified squamous, and to some extent keratinizing, while in other cases it was stratified squamous and prismatic (forming mucus) simultaneously (Figs. 1 and 2). The bifunctional nature of the epithelium of the papillomas was found in 12 cases.

It is clear from the table that in the group of intact mice papillomas appeared in 17, and endophytic foci of proliferation in 11 of 60 cases; initial changes were present in 29 animals (in 3 mice the mucous membrane of the vagina appeared normal). In the group of castrated mice papillomas were found in 9 and initial changes in 7. In this group no animals without pathological changes were found. The number of castrated animals was small and it was, therefore, difficult to compare the rate of development of the pathological changes in the two groups of animals (castrated and intact). Foci of proliferation were also found in the mice with papillomas.

Altogether, pathological changes were found in 73 of 76 cases, including changes so severe that they corresponded, in their morphological signs, to precancerous changes following administration of a carcinogen (foci of proliferation and papillomas) in 37 of 76 cases, i.e., in about half the animals.

In all the investigated mice inflammatory changes were present in the wall of the vagina in the form of moderate infiltration of leukocytes.

Because of the experimental conditions, only the morphological character of the pathological changes in the epithelium caused by intravaginal application of the polyurethane sponge was studied. These changes were similar to the precancerous changes observed during the first three stages of the process of carcinogenesis following administration of 9,10-dimethyl-1,2-benzanthracene [4, 5]. However, the rate of development of the pathological changes was different in this case. For instance, application of the polyurethane sponge, continuing for two months, led only to the appearance of papillomas (in both intact and castrated animals), whereas at the end of this period in the experiments with the carcinogen, malignant tumors were frequently present. The problems of the subsequent fate and the nature of the pathological changes caused by polyurethane have not yet been solved and more prolonged experiments are necessary for this purpose.

The introduction of the polyurethane sponges was accompanied by the development of inflammatory foci of infiltration in the underlying connective tissue, whereas, no inflammatory changes were present during the intravaginal application of the carcinogen [4, 5]. The carcinogen evidently suppressed them [3, 6].

Prior to the clinical application of polyurethane, during experiments on animals lasting 1 year (implantation of polyurethane sponge beneath the mammary glands of mice [11], replacement of a defect in the musculoaponeurotic layer of the anterior abdominal wall of rabbits with a porous polyurethane plate [2]), no tumors developed. The use of polyurethane sponge for speeding the union of the fragment in experimental fractures of the mandible also did not lead to the appearance of tumors [14].

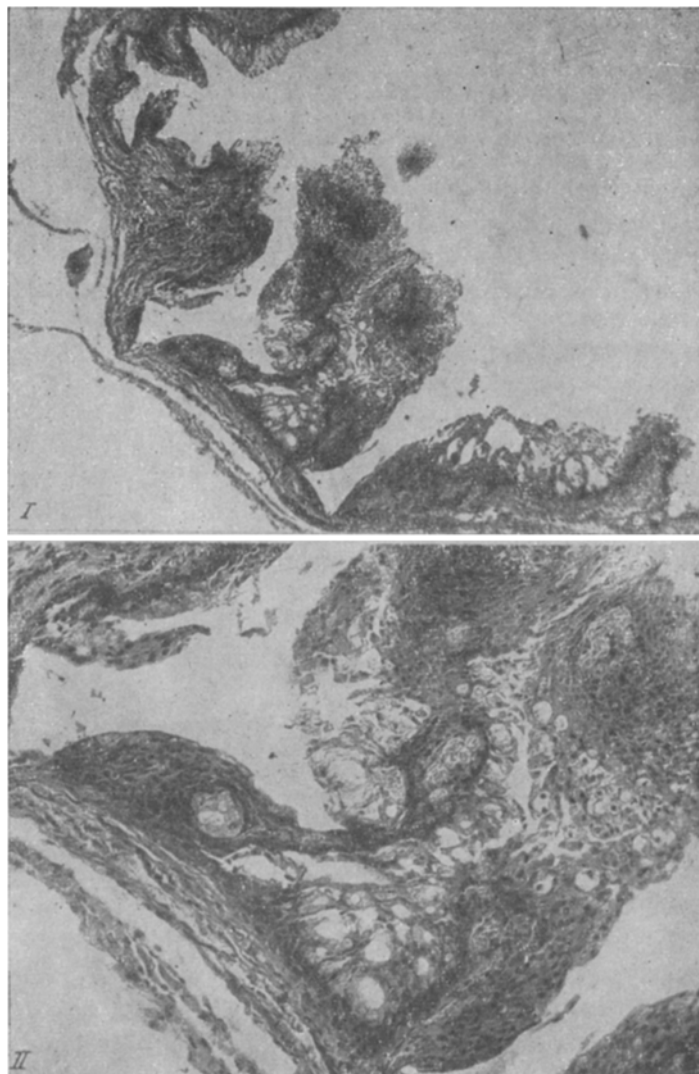


Fig. 2. Papilloma of the vagina of another mouse, also arising following intravaginal applications of polyurethane. Hematoxylin-eosin. I—Magnification 60x; II—magnification 120x. The epithelium of the papilloma showed evidence of being stratified squamous and prismatic at the same time (on staining with mucicarmine mucus is seen in the pale cells).

More recently, however, in more prolonged experiments lasting about 2 years [12, 13], implantation of polyurethane beneath the skin and in the abdominal cavity of rats has given rise to tumors. The formation of tumors was observed following implantation of polyurethane in various physical states—as plates, powder, or foam. The view has been expressed [12, 13] that parenteral administration of polyurethane is dangerous; it is also considered that workers inhaling polyurethane dust at work should remain under medical supervision. The present results correspond to some extent with this information. Both show the need for definite awareness of the risk of cancer when polyurethane is used in medical practice. Its use in contraceptives, or in replacement, plastic or reparative surgery must be considered premature.

Systematic intravaginal applications of polyurethane in mice (in the form of a synthetic sponge) thus led in the course of two months to the appearance of pathological changes morphologically similar to precancerous changes observed following application of a powerful carcinogenic substance (9, 10-dimethyl-1,2-benzanthracene) intravaginally. These results are in agreement with reports in the literature suggesting the carcinogenic action of polyurethane when administered parenterally.

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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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