

EXPERIMENTAL TUMORS OF THE PENIS

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Up until now, there have been no reports in the literature of obtaining an experimental form of tumor of the penis. A model tumor of this nature could be used to study the patterns of growth and extension, and the routes of metastasis for cancer of the penis, for testing various therapeutic agents, and for histological investigation of the stages in the tumor process of this localization. We performed an experimental work on creating a model tumor of the penis from 1960-1962, in the S. P. Botkin hospital vivarium.

EXPERIMENTAL METHOD

We used 12 male rabbits of different ages, one of them albino, and the rest, of the chinchilla breed. As the cancerogenic agent, we selected 9,10-dimethyl-1, 2-benzanthracene, applied in the form of a 0.1-1% benzene solution. The solution was applied to the head of the penis and the internal leaf of the foreskin (using an average of 5-6 drops of solution for each application). The animals were smeared every other day; we performed a total of 110 applications (the first 35 smears with the 0.1% solution, the subsequent 75 smears with the 1% solution), over a course of 7 months.

In 8 of the 12 rabbits, the cancerogenic influences were combined with the creation of an experimental phimosis, i.e., with the artificial production of a constriction of the foreskin, in order to hold the cancerogenic solution inside the preputial sack. The method of forming an artificial phimosis was developed with some difficulties. The initial attempts that were undertaken to sew the edges of the prepuce and to apply metal clamps did not lead to a lasting constriction of the foreskin. The best method for forming a phimosis in the rabbits was the circular passage of a silk ligature between the outer and inner leaves of the preputial sack at its very edge. The ends of the suture were drawn up and joined, as the purse-string suture used in surgery, so that the opening remaining in the foreskin was adequate for urination, but did not allow passage of the head of the penis. The cancerogenic solution was introduced into the closed preputial sack with the aid of a pipette. This method permitted the prolonged retention of the foreskin constriction (up to 4 months without interruption), and in case the thread was cut through or the knot came untied, we could put another "purse-string" suture into place.

EXPERIMENTAL RESULTS

Four of the rabbits died before completion of the applications, from viral catarrhs of the upper respiratory passages. No macroscopic changes were noted in their genitalia. The first tumor changes visible to the naked eye were observed in the skin of the preputial sack 4 months after initiation of the applications. These were typical papillomas of the skin—flat, dry, with short projections.

An average of 5 months after beginning the applications (after approximately 75 smearings), macroscopic tumor changes began to appear in the skin of the penile body and in the outer leaf of the foreskin. In total, tumors visible to the naked eye were noted on the body of the penis and the outer leaf of the foreskin in 7 out of the 8 animals that survived to the end of the series of applications. The tumors grew rapidly, and fused into a massive conglomerate with surface ulceration and bleeding.

The first tumor of the penis in the location that is characteristic for man was noted only after 9 months following initiation of the applications, on the inner leaf of the foreskin in rabbit No. 10. This was a round formation, with a diameter of approximately 1 cm, on a pedicle, with long projections and a pale, moist surface. In the course of a

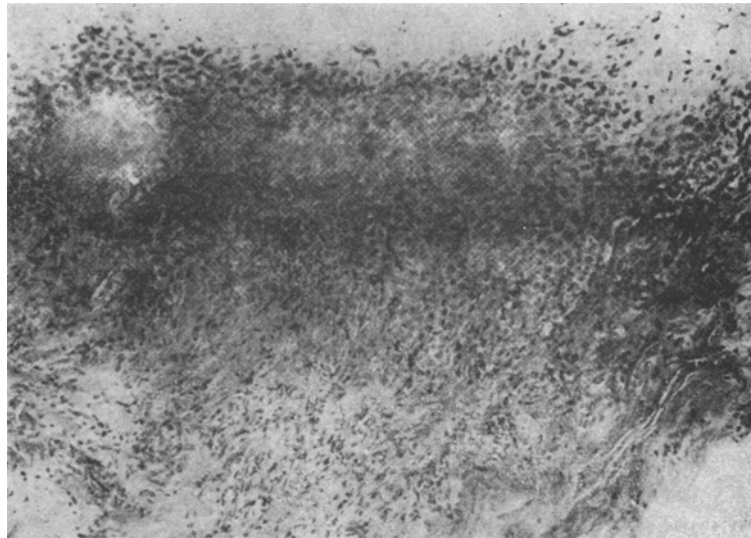


Fig. 1. Consultation on the preparations was obtained from Active Member of the AMN SSSR Professor L. M. Shabad.

month, papillary neoplasms visible to the naked eye appeared on the glans and inner leaf of the foreskin in 2 more animals (No. 3 and 9). Thus, 9-10 months after beginning the applications, tumors of the penis, corresponding to the localization characteristic for man, arose in 3 of the 6 animals surviving until that time. Two of these animals (No. 9 and 10) belonged to the group of animals with an artificial phimosis, and the latter existed in them longer than in the other animals (6 months). As we emphasized earlier [2], macroscopic tumors of the glans or inner leaf of the foreskin were not obtained in a single one of the 4 rabbits without phimosis.

After the death of the animals, the penis was removed and subjected to histological investigation (imbedded in celloidin, stained with hematoxylin-eosin). An average of 3 total sections of the Kristellerovskii type were prepared from each macropreparation of the rabbit penes.



Fig. 2. Total section of the penis from rabbit No. 10. There is a branched papilloma on the inner leaf of the foreskin. On the outer leaf of the foreskin, there is a massive cancer, with tissue breakdown. Magnification 4x.

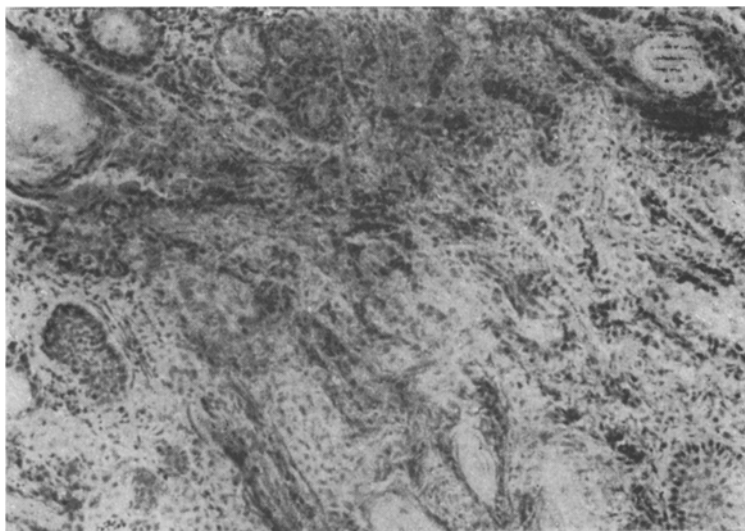


Fig. 3. Typical picture of cornifying, squamous cell cancer. Individual pearl formations can be seen. Magnification 130 x.

For convenience in studying the histological preparations*, we divided the material into three groups. The first consisted of the 4 animals that died before the end of the series of applications; the second was made up of 4 rabbits that survived the end of the applications and then quickly died; the third group represented the 4 rabbits that died last (11½ -18½ months after initiation of the applications).

In 3 rabbits of the first group, we noted diffuse hyperplasia of the epithelium on the glans and inner leaf of the foreskin, and in one of these animals (No. 1)—individual foci of epithelial thickening in the glans (up to 25-30 layers), with projection of individual epithelial extensions down into the underlying tissue. Diffuse hyperplasia of the epithelium was observed in the skin on the body of the penis and the outer leaf of the foreskin. In one of the rabbits of the first group (No. 4), that died 3 months and 24 days after initiation of the applications (50 smearings), a coniform epithelial growth was observed on the very tip of the glans penis, subsurface extensions of which projected down into the underlying tissue (papilloma with the beginning of infiltrative growth), and on the dorsal surface of the glans there was

The Connection between Histologically Demonstrated Changes and the Number of Applications and the Duration of Life of Rabbits Following Initiation of the Applications, as well as the Presence of Experimental Phimoses

Group of animals	No. of applications	Duration of life of the rabbits after initiation of applications	Glans and inner leaf of the foreskin		Outer leaf of foreskin and skin on body of penis	
			focal proliferates	papillomata	papillomata	cancer
			exp. nos. of rabbits with tumor changes			
First	21-91	52 days—6 months	1, 4	4	4	4
Second	110	7 months—10 mo., 22 days	2, 5, 11	5	5, 11	—
Third	110	11½ months—18½ months	3, 9, 10	3, 9, 10	3, 7, 9, 10	3, 7, 9
With phimosis			1, 2, 5, 9, 10, 11	5, 9, 10	5, 9, 10, 11	9, 10
Without phimosis			3, 4	3, 4	3, 4, 7	3, 4, 7

* Consultation on the preparations was obtained from Active Member of the AMN SSSR Professor L. M. Shabad.

a focus of epithelial cell proliferation. The deep epithelial extensions in this focus consisted of clear cells which were scattered in the connective tissue, losing their connection with one another—the beginning of infiltrative growth (Fig. 1). On the outer leaf of the foreskin, there was a large focus of cornifying, squamous cell cancer, and close by—3 papillomata with massive cornification.

In two rabbits of the second group, we encountered diffuse thickening of the epithelium on the glans penis, with individual focal proliferates, in which we observed atypia of the cells and mitosis. More manifest tumor changes were observed in rabbits Nos. 5 and 11. In the first of these, the epithelium of the head of the penis was markedly thickened, with subsurface portions and "stringing out" of the epithelial extensions. On the tip of the glans, there was a coniform thickening of the epithelium—a micropapilloma. On the inner and outer leaves of the foreskin, we observed focal epithelial proliferates, with downward extension and cord formation. In rabbit No. 11, we observed a diffuse, non-uniform thickening of the epithelium on the glans, with parakeratosis. On the tip of the glans, there were 2 focal epithelial growths, extending below the surface. On the body of the penis, there was a large, branched papilloma.

The most manifest tumor changes were encountered in the histological investigation of the rabbits comprising the third group. In rabbit No. 10, the described papilloma on the inner leaf of the foreskin appeared, on microscopic investigation, as a branching formation with a developed connective tissue base and thickened epithelium (Fig. 2). Large blood vessels were present in its stroma. With large magnification, we basically saw the beginning of infiltrative growth. On the remaining surface of the inner leaf of the foreskin, and on the glans, we observed focal epithelial proliferates with subsurface extension. In rabbit No. 3, on the inner leaf of the foreskin, we noted a focal thickening of the epithelium, with papillary, exophytic growth—a papilloma. On the dorsal surface of the glans, we encountered 2 plaque-like, focal thickenings of the epithelium. In rabbit No. 9, on the tip of the glans, there was papillary growth of the epithelium—a papilloma, and on the dorsal surface of the glans and on the inner leaf of the foreskin, we observed plaque-like foci of epithelial thickening, with downward extension and cord formation. Only in Rabbit No. 7 (without phimosis) did we fail to find any significant changes in the glans or inner leaf of the foreskin, other than diffuse epithelial hyperplasia, although this rabbit survived the others by a long time. In all the animals of the third group, on the outer leaf of the foreskin and the body of the penis, we observed massive foci of cornifying, squamous cell cancer (Fig. 3), with inflammatory infiltration.

As can be seen from the table, cancer of the outer leaf of the foreskin and the skin on the body of the penis was established histologically in 5 rabbits, papillomas of these areas in 7, focal proliferation of the epithelium on the glans or inner leaf of the foreskin, with downward extension and cell atypia—in 8, and papillomata in these areas—in 5, including 2 in which there was initiation of infiltrative growth (Nos. 4 and 10). The tumor changes on the glans were more intense than on the inner leaf of the foreskin, although these surfaces were subjected to the same cancerogenic activity.

The data in the table show that tumor changes in the glans and inner leaf of the foreskin developed with great frequency in the rabbits with artificial phimosis.

In works on experimental cancer of the skin [1,4], carried out on 10 and 5 rabbits respectively, 20-40 applications to the skin of the ear or back, using a 0.5-1% solution of 9,10-dimethyl-1,2-benzanthracene in benzene, over a course of 13-21 weeks, was sufficient to obtain skin cancers in practically all the animals. Papillomata arose after only 5-7 weeks. It is thus clear that the skin of the glans penis and the inner leaf of the foreskin, devoid of hair covering and glands, is very resistant to chemical cancerogenic influences.

The most important information obtained in this work concerns the premalignant changes in the glans penis and inner leaf of the foreskin. In the majority of animals, we observed focal proliferates of the epithelium and papillomata (II and III stages of blastomogenesis, according to L. M. Shabad [3]); the I stage—diffuse non-uniform hyperplasia of the epithelium—was noted in all the rabbits. Papillomata arose from the plaque-like epithelial thickenings, but sometimes (Fig. 1) a focal epithelial proliferate became a source of cancer, without acquiring exophytic growth. In the papillomata of the glans, and especially, of the inner leaf of the foreskin, attention was drawn to the copious development of connective tissue stroma, and the lesser degree of epithelial thickening than that seen in the papillomata on the skin of other areas.

This work is prospective in nature, and has far from exhausted all the questions connected with experimental tumors of the penis. It shows a principal possibility for obtaining tumors of the penis in rabbits, including neoplasms located in the areas typical for man. In addition, it demonstrates that producing this model tumor presents major difficulties, and requires special methods. One such special method, used in our work, was the application of an artificial phimosis.

SUMMARY

An attempt to obtain experimental tumors of the penis was carried out on 12 rabbits; an artificial phimosis was created in 8 of them. The cancerogen (0.1-1% benzene solution of 9,10-dimethyl-1,2-benzanthracene) was applied to the glans penis and inner leaf of the prepuce (110 applications over a period of 7 months). Tumor changes of these surfaces were obtained in 8 rabbits (subsurface focal proliferates of the epithelium and papilloma, with the onset of infiltrative growth in 2 cases), as well as papillomata and cancers of the outer leaf of the foreskin and of the skin on the body of the penis. The tumor changes on the glans and inner leaf of the foreskin occurred predominantly in the animals with the artificial phimoses, and were clearly manifested on the glans. Creation of a model tumor of the penis presents considerable difficulties, as compared with the tumors of common skin.

LITERATURE CITED

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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 this issue.
