

DEVELOPMENT AND REGRESSION OF HEXESTROL-INDUCED CHANGES IN THE SPERMATIC TRACT OF THE RABBIT

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Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 50,
No. 10, pp. 122-126, October, 1960

Original article submitted October 26, 1959

In experimental studies of changes in the male sexual apparatus under the influence of estrogens, only a few authors have given particular attention to the spermatic tracts. Atrophy of the epithelium in the epididymis and in the vas deferens has been described. Edema of the mucosa [1] and hypertrophy of the fibromuscular tissue [4] have also been reported; the latter, however, is not always observed, and depends on the period of sexual activity. T. Martins and J. R. Valle [2] found that estrogen in vitro enhances the motor activity of the vas deferens. H. Burrows [1] found scattered instances of planocellular metaplasia with keratinization in the epididymis in mice. Great interest attaches to the report of Vazquez-Lopez concerning two instances of a small carcinoma of the epididymis and one case of hyperplasia of the head of the epididymis occur-

ing in hamsters as a result of prolonged treatment with estrogens. Unfortunately, the author [3] did not give data on the histological examination.

METHODS

Observations were conducted on rabbits weighing 2-2.5 kg. All the animals were injected subcutaneously with hexestrol in a 2% solution in oil at the rate of 0.45 ml per animal (0.009 g of hexestrol) three times a week. In the first series (24 animals) the duration of the experiments was from 3 to 311 days, hexestrol being injected regularly until the end of the experiments. In the second series (17 animals) hexestrol was injected for the first three months, after which the injections were stopped so that the regression of hexestrol-induced changes could be studied. The experiments lasted for from 30 to 464 days after the injections were stopped.

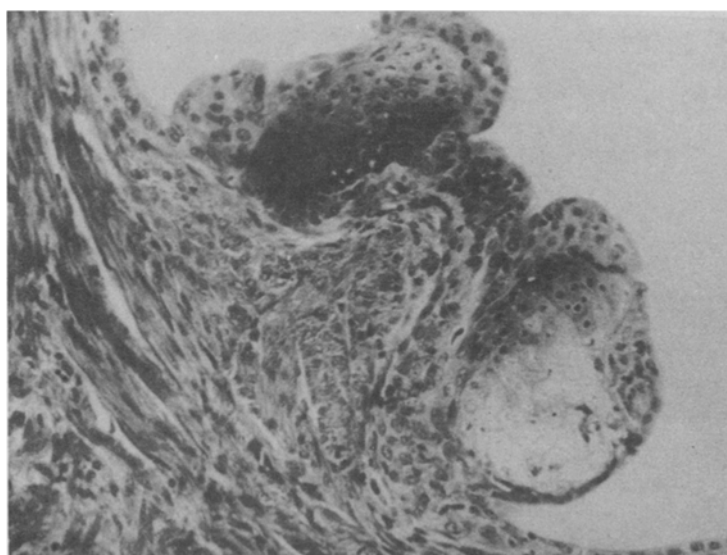


Fig. 1. Focal proliferation of epithelium with atypical keratinization in tubules of the tail of the epididymis. Experiment on 71st day of hexestrol administration (total amount injected, 0.279 g). Stained with hematoxylin and eosin. Ocular 4, objective 8. Magnification 250 ×.

For the histological examination, tissue biopsies were fixed in 10% formalin, imbedded in celloidin-paraffin, and stained with hematoxylin and eosin and with van Gieson's stain. In some instances, staining with toluidine blue by the method of Gram, Mallory, and Heidenhain was also employed. Various portions of the spermatic tracts and testes were subjected to examination.

RESULTS

Under the influence of hexestrol, atrophy develops in the testes during the first 2-3 months; spermatogenesis stops, and the cells of the spermatogenic epithelium degenerate, along with some of the Sertoli cells; the convoluted seminiferous tubules diminish markedly in size. In the stroma, the number of interstitial cells increases. Testicular atrophy continues as long as hexestrol is injected.

Increasing signs of atrophy are also observed in various divisions of the spermatic tract during this period. It is only in the tubules of the rete testis, whose structure is very simple, that no perceptible changes occur. The cilia disappear from the ductuli efferentes testis, and the stereocilia from the tubules of the ductus epididymidis. The epithelium becomes smooth, and the cells decrease in size. The excretion of secretory granules stops. In the lumen, there is a decrease in the number of spermatozoa and desquamated cells of spermatogenic epithelium; the diameter of the tubules is reduced. In the vas deferens and the ejaculatory duct there is also a reduction in the size of the epithelial cells and a contraction of the lumen. In some cases one sees a considerable amount of karyorrhexis of epithelial cells in the ductus epididymidis and the am-

pulla of the vas deferens; in the ampulla and the ejaculatory duct edema is also found, and a moderate infiltration of the stroma and epithelium with lymphocytes and pseudoeosinophils. In the tubules of the tail of the epididymis, mild proliferation is observed here and there, and thickening of the epithelial layer without definite differentiation.

In two cases (after 71 and 180 days) we found multiple small foci of an unusual type of stratified squamous epithelium with atypical keratinization in the tubules of the ductus epididymidis, in the region where it passes over into the first part of the vas deferens (Fig. 1). In the early stages of development these foci are limited proliferations in the form of intraepithelial nests of tiny cells with a small amount of basophilic protoplasm and a dark round nucleus. These cell clusters protrude into the lumen. A layer of dedifferentiated cells of pre-existing epithelium frequently remains over them. Later, a palisade-like layer of cells with a slightly elongated form appears at the base of the cluster. Mitoses are found in these cells. In the central and upper layers of the epithelial cell proliferation, the cells become larger and the protoplasm lighter, while the nuclei become pycnotic or undergo karyorrhexis. As a result the cells change into non-nucleated lamellae forming stratified layers. Some of these are stained shades of blue-violet with Gram's stain. In the tubule membrane proper, mild lymphocytic infiltration is often noted near the epithelial proliferations. Epithelium with mitoses in individual cells. In the same experiment, focal proliferation of stratified squamous epithelium with atypical keratinization was found in the ampulla of the vas deferens, but in two other experi-

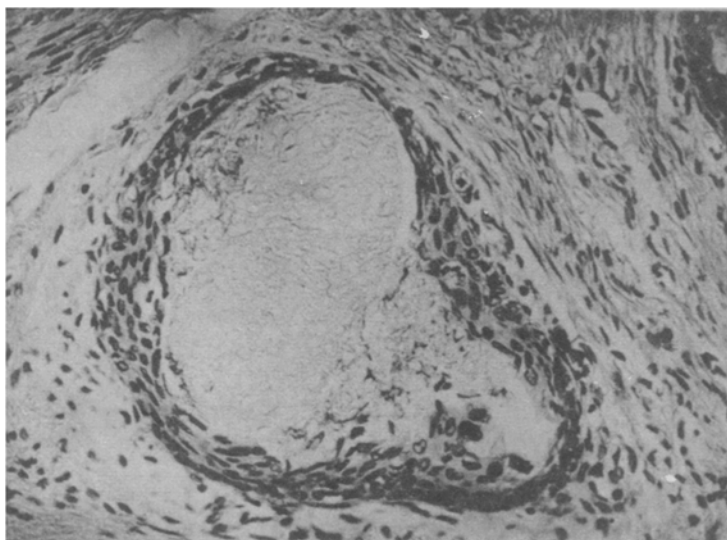


Fig. 2. Keratinization and desquamation of epithelium in tubule of the tail of the epididymis. Experiment on 50th day after termination of hexestrol administration. Stained by van Gieson's method. Ocular 4, objective 8. Magnification 250 x.

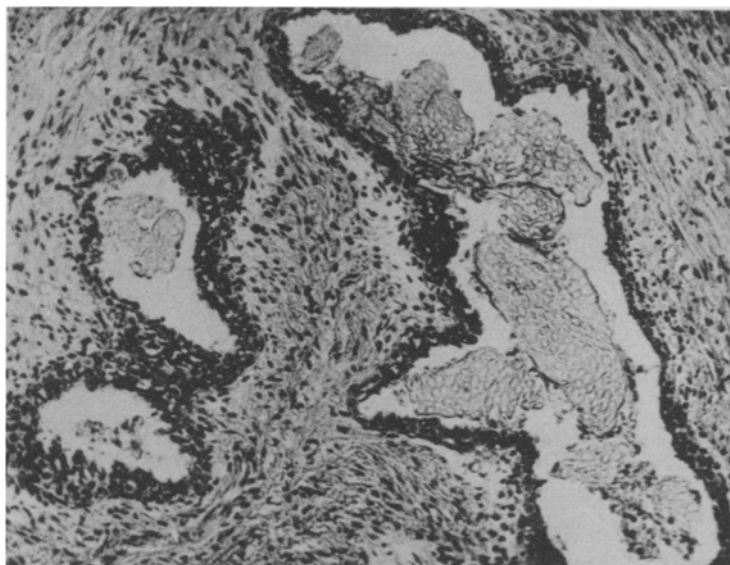


Fig. 3. Desquamated keratinized sheets in tubules of the tail of the epididymis. Normal differentiation of epithelium. Experiment on 270th day after termination of hexestrol administration. Stained by van Gieson's method. Ocular 4, objective 8. Magnification 250 \times .

After the injections of hexestrol are stopped, the atrophy and collapse of the convoluted tubules in the testes remain for several months. But by the end of the second month infrequent mitoses appear in the epithelial cells. In some animals mitoses appear in large numbers after four months, while in others proliferation occurs later. After eight months spermiogenesis is restored, the convoluted tubules grow to their normal size, and the number of interstitial cells decreases. In the spermatic tracts, pronounced atrophy and collapse of the tubules remains for a long time. But after 5-6 months the epithelium gradually becomes thicker, and mitoses are encountered infrequently in the epithelial cells; after seven months cilia appear in the ductuli efferentes; after nine months stereocilia are seen in the ductus epididymidis, and the lumen of the ducts is filled with spermatozoa and desquamated epithelial cells. The ampullae of the vasa deferentia are markedly dilated, and the epithelium becomes flat as it undergoes histological accommodation. In the ductuli efferentes one often encounters multiple small intraepithelial cavities as late as 5½ months; these are the result of cell degeneration. In one experiment 50 days after hexestrol injections were stopped, stratified squamous epithelium with keratinization and desquamation of cells was found (Fig. 2). In other parts of the duct we encountered regions of thickened epithelium with indications of vertical anisomorphism, but with pycnotic nuclei and desquamation of individual cells, and at the base of the layer there was differentiation of the elements (at 30 and 270 days; Fig. 3) desquamated cornified sheets and scales were found in the lumen of tubules in the tail of the epididymis; the wall of these

tubules was covered with epithelium consisting of one or two rows of cells. These changes in the condition of the structures of the multilayered flattened epithelium enable us to say that the epithelial metaplasia is of temporary and transient character.

SUMMARY

The author studied the changes that occur in the spermatic tract of rabbits during and after the administration of hexestrol. Under the influence of hexestrol administration lasting for from 3 to 311 days, atrophy of the epithelium occurs along with partial collapse of various portions of the duct system, as well as edema and moderate cellular infiltration of the distal portion of the duct system. Metaplasia of the epithelium into the stratified squamous type, with atypical keratinization, was observed in the distal portion of the ductus epididymidis in 5 out of 41 animals; in one rabbit the ampulla of the vas deferens was also involved. From two to seven months after the cessation of hexestrol administration (which was continued for three months in this group) a slow restoration of specific differentiation occurred. The dependence of atrophic and regenerative changes in the vas deferens on similar changes in the testes is emphasized.

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