

THE DEVELOPMENT OF SYNESTROL-INDUCED CHANGES IN THE REPRODUCTIVE SYSTEM OF THE MALE RABBIT

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Considerable changes are brought about in the male reproductive system by the action of estrogens. Several investigations have been devoted to their experimental study. In particular, changes in the accessory sex glands of the rabbit were described in our previous paper [1], in which the relevant literature is cited.

The question of the permanence of the estrogen-induced changes, however, has received little study. There are observations [3] of the restoration of the normal relationships in the genitourinary system of mice after cessation of the administration of polyanol.

During the study of the changes in the testes in mice under the influence of synestrol and testosterone propionate, the partial or total regression of these changes was observed [5] after discontinuation of the hormones.

In the present research we investigated the development of changes due to synestrol in the reproductive system of male rabbits.

EXPERIMENTAL METHOD

Experiments were carried out on 28 male rabbits, weighing on the average 2.0-2.5 kg, which received regular subcutaneous injections thrice weekly of 0.45 ml of a 2% oily solution of synestrol (0.009 g synestrol). Eleven rabbits died from intercurrent diseases (pasteurellosis, pneumonia) during the first three months (i.e., during the administration of synestrol), and these serve as controls. The remaining 17 rabbits received synestrol injections for three months (a total of 0.351 g of the pure substance). The experiment lasted for 30 to 464 days after cessation of the administration of synestrol. The material was fixed in 10% formalin and embedded in celloidin-paraffin wax. Histological sections were stained with hematoxylin-eosin and by Van Gieson's method. Individual sections were stained with mucicarmine and toluidine blue, and by Gram's, Mallory's and Heidenhain's methods.

EXPERIMENTAL RESULTS

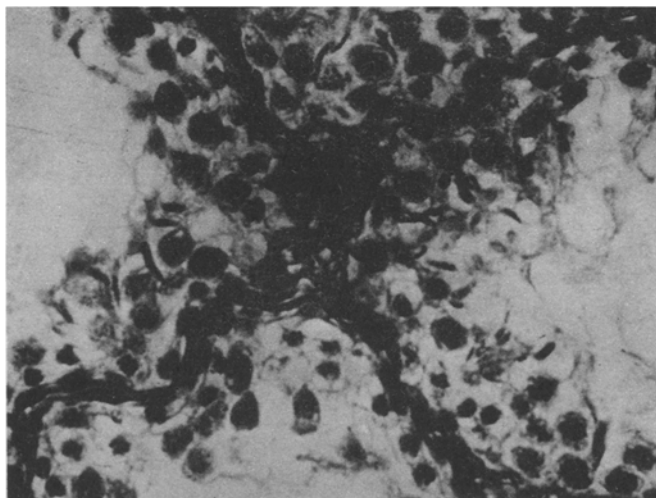
The administration of synestrol was accompanied by the development of a complex group of changes in the

accessory sex glands. At an early stage, hyperemia and edema developed and the stroma and epithelium were infiltrated with pseudoeosinophilic leukocytes and lymphocytes. Signs of degeneration were observed in the epithelium: karyorrhexis, desquamation, and more rarely, vacuolation of the cells. Secretion was diminished and ceased altogether, and the epithelium gradually lost its organ-specific differentiation and underwent atrophy. At the same time these changes were accompanied by focal proliferation of the epithelium and its metaplasia into transitional and stratified squamous epithelia, with keratinization in certain cases.

In the urethra, at the level of the prostatic vesicle and distally to it, infiltration of the stroma and epithelium with pseudoeosinophilic leukocytes and lymphocytes developed under the influence of synestrol. The accumulation of leukocytes and cellular detritus caused a cystic dilatation of the glandular crypts. In the epithelium, proliferation was observed along with the loosening and destruction of the individual cells. In some cases the transitional and prismatic epithelium in the distal part of the urethra was replaced by stratified squamous epithelium.

In the testes, spermatogenesis was arrested under the influence of the synestrol. The cells of the spermatogenic epithelium and also a proportion of the Sertoli cells degenerated. In the majority of the convoluted tubules, therefore, only one row of epithelial cells was preserved, lying on the basal membrane. Under these circumstances the convoluted tubules decreased sharply in size as they descended. Occasional tubules were hypertrophied. An increase in the number of interstitial cells was observed in the stroma.

After the administration of synestrol had been discontinued, a rapid disappearance of the infiltration with lymphocytes and leukocytes in the accessory sex glands was observed. On the 30th day no infiltration could be seen in the majority of the glands, and only in the seminal vesicle did small collections of lymphoid cells remain until 2½ months.



Renewal of spermatogenesis in the convoluted tubules of the testes. Mitoses. Experiment showing the action of synestrol. Duration of observations 120 days. Stained with hematoxylin-eosin. Zeiss 8× ocular, Zeiss 8 × objective magnification 600 ×.

Proliferation of the epithelium ceased at the same time. The epithelium, where previously it had undergone proliferation, now regressed. One basal layer of cells remained, and the overlying layers were desquamated. In the prostatic vesicle small groups of cells sometimes disintegrated in situ, to form intraepithelial cysts. Their nuclei were dissolved and their protoplasm was converted into an amorphous mass, giving a mucin reaction. Small areas of epithelial proliferation, without metaplastic differentiation into stratified squamous epithelium, underwent regression during the period of 1-2½ months after the administration of synestrol had been discontinued. The layers of stratified squamous epithelium degenerated more slowly. In the prostatic vesicle they were present until the sixth month.

The keratinized masses in the lumen of the glandular alveoli were absorbed with the aid of leukocytes the number of which decreased with time. The leukocytes were destroyed and their debris was absorbed by macrophages, which were converted into foam cells. The residues of the keratinized masses swelled, turning into a homogeneous, colloidal mass, which was gradually evacuated through the ducts. Small remnants of stratified, keratinized masses, which had lost their property of staining by Gram's method, were encountered in the lumen of the alveoli of the glands, however, at much later periods of the experiment (212, 326 and 464 days).

In the immediately following months, as regression of the synestrol-induced changes in the accessory sex glands proceeded, signs of atrophy became predominant. The changes in the accessory sex glands at this period were identical with those observed after castration.

One month after discontinuation of the administration of synestrol, no infiltration with lymphocytes and leukocytes was observed in the urethra. Detritus from the dilated glandular diverticula had been evacuated and the diverticula were smaller in size. After 2½ months, at the level of the prostate gland and distally to it, the transitional epithelium was thinned out and, in places was replaced by a two-layered prismatic epithelium, which was constantly found in this region at later periods. Until 5½ months, a stratified epithelium resembling stratified squamous epithelium was sometimes found in the distal portion of the urethra.

In the testes, the collapse and atrophy of the convoluted tubules, caused by synestrol, could be maintained until six months. Individual epithelial cells continued to degenerate. In other cells, however, occasional mitoses appeared at the end of the second month. In some animals, after four months, proliferation of the spermatogonia could be observed in the majority of the convoluted tubules. In other animals, proliferation was observed later, although eight months after administration of the hormone had been discontinued, a well-marked spermatogenesis was observed in all the animals (see Figure). The diameter of the convoluted tubules had increased to normal and the number of interstitial cells had diminished.

Restoration of the normal structure and function of the testes took place parallel with the restoration of the structure and function of the accessory sex glands. The first signs of restoration of the lost organ-specific differentiation appeared at the end of the fourth month. The glandular crypts in the seminal vesicle then became

deeper, and the epithelial cells increased in height. Proliferation of the epithelium was observed and, in connection with the accumulation of secretion, the vesicle became dilated. In the prostatic vesicle, at the fourth month, the majority of the alveoli were still in a collapsed state, but in places the epithelium had become higher, and the protoplasm, which had increased in amount, had become oxyphilic, and the oval nucleus was situated in the middle part or the lower half of the cell. At later periods the dimensions of the alveoli of the glands increased. Mitoses were encountered in the epithelial cells. Differentiation of the epithelium from a focal type became universal. Secretory granules appeared in the protoplasm of the cells and the lumen of the alveoli. The plication of the glandular alveoli increased sharply. At the end of one year the gland had acquired its normal appearance. The collapse and atrophy lasted slightly longer in the prostate gland than in the prostatic vesicle. An obvious increase in the height of the epithelial cells and a characteristic basal arrangement of the nuclei could be observed after seven months. Concurrently, dilatation of the glandular alveoli, mitoses in the epithelial cells and the formation of granules of secretion were noted. At the end of one year the gland had returned to its normal state, and many corpora amylacea were formed in the lumen of the alveoli.

The paraprostatic and bulbo-urethral glands underwent relatively slight changes during atrophy. On their return to the normal state, they showed a slight increase in the dimensions of their epithelial cells and restoration of the lumen of their terminal divisions.

The changes induced by synestrol in the accessory glands of the male reproductive system in the rabbit were thus temporary and gave way to regression. Two periods could be distinguished in the course of this regression: a period of disappearance of the infiltrative and proliferative manifestations, lasting less than one month, and a period of atrophy, lasting up to one year, and replaced by the gradual restoration of the normal, typical structure of these organs.

The morphological changes are evidence of the great metabolic disturbances produced by the action of synestrol on the male reproductive system. The hyperemia, leukocytic infiltration and epithelial proliferation taking place in these conditions suggest that synestrol increases the intensity of metabolism in the accessory sex glands, at least during the first months. The depression of the function of the testes, however, indicates the opposite action.

The complex and divergent character of the action of synestrol may account for the temporary nature of the proliferative manifestations which it induces in the accessory male sex glands. It must be considered that the "chemical castration" caused by the estrogen in the male depresses proliferation and metaplasia of the epithelium when the administration of the hormone is discontinued.

This view is in agreement with reports in the literature [2, 6] that carcinoma of the reproductive system cannot be produced in males by the action of synestrol, whereas it does occur in females. An exception to this is the communication of V. P. Konoplev [4].

SUMMARY

Synestrol was administered to 28 rabbits for a period of 3 months (a total of 0.351 gm).

After discontinuance of its administration—the experiments lasting from 30 to 464 days—a regression of the changes in the accessory sex glands was noted, the course of which could be subdivided into two periods, viz, the period of liquidation of the infiltrative proliferative phenomena (lasting less than a month), and the period of atrophy (lasting up to one year and depending on the atrophy of the testes). The typical normal structures of the organs are restored at the end of the year.

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* Original Russian pagination. See C.B. Translation.