Tubular Adenomas and Testis-Like Tubules of the Ovaries of Aged Rats

Earl T. Engle, Ph.D.

(From the Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York 32, N.Y.)

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An examination of the ovaries of aged Wistar rats has revealed the presence of tubules that are lined by cells that bear a striking resemblance to the Sertoli cell of the seminiferous tubules. The occurrence of occasional tubules in otherwise normal ovaries of senile rats may have some relation to the three cases in which the entire ovary is replaced by a tubular adenomatous growth.

MATERIALS

The material presented here is a result of histological examination of the ovaries of 34 rats from the Wistar series, which were 900 days of age or older. Of this group, 20 were 900 days or slightly older, 10 were 1,000 days or slightly older, and 4 were 1,100 days or more old. For comparison, tissues of 15 female rats of this series ranging between 600 and 900 days, were examined. The animals were killed and autopsied by the staff of the Wistar Institute. In most instances the ovaries were removed with the ovarian capsules and adjacent tubes, fixed in Bouin's fluid, and shipped in 70 per cent alcohol. Both ovaries were imbedded together and cut at 8 μ in this laboratory. Usually 2 slides, each with 10 to 16 sections, were saved from the middle of the ovary. One slide was stained with Harris hematoxylin and eosin, the other with Masson's trichrome stain. Subsequently other staining methods were used for special purposes.

AGE CHANGES

Secondary follicles and corpora lutea were present in the ovaries of 17 of the 34 rats, while in the remaining 17 the ovary showed generalized atrophy and consisted of a mass of epithelioid cells, the so-called interstitial cells of the ovary. In several of the most atrophic ovaries the general pattern was that of an ovary in a post-irradiation state. Varying amounts of a brownish lipochrome pigment were present in these completely atrophied ovaries.

The atrophic ovaries were evenly distributed between the 900 day old rats and the older ones. In this series all of the pronounced changes referable to the atrophy of aging occurred in the group of female rats which were 900 or more days old. The ovaries of the 15 rats of this series which were 600 or more, but less than 900 days old, were all quite normal, with abundant primordial ova, follicles and corpora lutea.

In this sample of 15 younger rats there were no ovaries that consisted only of an interstitial cell mass. Small follicles without ova were present in the ovaries of both groups of rats.

In the ovaries of some of the old rats there were series of tubules that have not been described previously in the normal rat. They were characterized by epithelial cells with vague cytoplasmic borders and nuclei characteristic of those of Sertoli cells of the seminiferous tubule. The nuclear structure of the Sertoli cell in the rat testis is neither so constant nor so definite as it is in man, but even in the rat it affords a definite character for histological diagnosis. The nuclei are oval, slightly tapering at one end, or are "football" shaped. A fold or groove of the nuclear membrane results in a deeper stained line apparent over the surface of the nucleus (Fig. 1). This nuclear groove is characteristic of the nucleus of the Sertoli cell in man and many lower animals. This detail of nuclear structure has been described in other organs for the Brenner tumor of the human ovary and for the Walthard cell rests by Danforth (2).

These tubules were located most frequently near the hilum of the rat's ovary, although in two instances they were seen in the cortex opposite the hilum. In several rats in which these tubules were found in the ovary near the hilum similar tubules were found in the ovarian capsule near its attachment to the ovarian hilus. Tubules of the paraoophoron are sometimes present in association with the tubules that bear the cells with the Sertoli cell nucleus. In one case the tubules of the paraoophoron showed cellular structure...
and configuration, which were identical with the ductuli efferentia of the testis. Communication or continuity between the two sets of tubules was not demonstrated.

The tubules contain no epithelial elements other than the cells described. There are no cells similar to spermatogenic elements. A distinct basement membrane is present. Arey (1) has devoted considerable space to the factors related to this peculiar type of nuclear groove, which he describes as having a "puffed wheat" appearance. He refers to this type of nucleus as "common and characteristic of the Brenner tumor and Walthard island," and also of the Sertoli cell nucleus, although he says "it can be found also occasionally in the nuclei of connective tissue, smooth muscle and ordinary epithelium." Nuclear grooves, bars, folds and other modifications of symmetry may occur in any tissue, but not with the degree of frequency requisite for its acceptance as a diagnostic character. The grooved nucleus is characteristic of the nucleus of the Sertoli cell.

**Tubular Adenomas**

Three rats showed such complete involvement of the ovaries with the tubular structures described above

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**Fig. 1.**—Drawing of tubule in ovarian cortex of a 900 day old Wistar rat, No. 978. The cytoplasm and nuclear structure of this tubule are characteristic of 9 isolated tubules in the ovaries of aged rats, and of the tubular adenomas described.
that they were designated as tumors of the tubular adenoma group.

In one rat, number 1005 g, which was 1,000 days old, both ovaries were affected. The ovaries were not larger than usual for an adult rat. No cortical ova, no follicles, nor any corpora lutea were seen.

A single ovary was available for another rat, number 978, which was autopsied at 900 days of age. In this ovary the tubular adenoma did involve the entire organ. Several small, old corpora lutea were present, and solid masses of interstitial cells of atretic follicles could be identified. The ovary was only slightly larger than that of an adult rat.

A single ovary from a 1,112 day old rat, number 5, was studied. It was noted at autopsy that the left ovary appeared as an ivory-hued mass, not much larger than a normal ovary. On section this ovary was lacking in all ovarian elements in that there were no follicles or any luteal tissue.

The structural characteristics of the ovarian adenomas of each of these animals were quite similar. In preparations stained with hematoxylin and eosin, obscure tubular structures could be seen throughout the organ (Fig. 2). Near the hilum were large, well-organized tubules of the types described above (Fig. 4). Adjacent sections stained so as to demonstrate the reticular (argyrophile) connective tissue fibers show that the entire parenchyma was organized into tubules of irregular shape and size (Fig. 3). The epithelium of these tubules was composed of cells with indefinite outline. The apices of the cells consisted of wavy cytoplasmic masses with no cell membranes nor any means for delimiting the cell outline. These cells were negative to mucous stains. The nuclei were variable in shape, being round or oval. The oval nucleus with the folded nuclear membrane was present but was not dominant in these small tubules.

The common feature characterizing the component cells of all tubules, including those with the Sertoli cells nuclei, was the indistinct cytoplasmic border, very similar to the condition in the testis where all spermatogenic cells are absent (Fig. 5).

These atypical growths were composed of tubules bearing cells and nuclei most characteristic of the Sertoli cell of the seminiferous tubule. These tubules may be located near the hilum or radiating from the hilum of the ovary of an old rat. There are no structural differences between the tubules that occur in small groups in the otherwise normal ovary of the aged rat and the tubules which have replaced all ovarian structure, as in the three cases described above as adenomata tubuli ovarii.

In addition to the ovarian adenomas, 2 of these rats had other tumors.

The rat with the bilateral tubular adenomas, number 1005 g, also had a fulminating squamous cell carcinoma of the uterine cornua. Other organs were not available for study.

The other number 978, had three adenomas of the mammary gland. One large tumor was in the left inguinal region, one was in the right inguinal region and a small mammary adenoma was in the right axilla. Other tissues were not available for study.

No information as to the hormonal status of the genital system of these 3 rats can be gained from the material at hand. There were no tissues from the vagina in two cases, and in one the only uterine material was the carcinomatous mass. The vagina of the third animal, number 5, was not atrophic, but there was slight keratinization of the epithelium. The endometrial stroma was completely fibrosed and endometrial glands were sparse. The luminal epithelium was columnar in type with no mitotic proliferation or secretion.

There was no direct morphological indication of any endocrine action in any of these animals.

DISCUSSION

The ovary of rats and of other animals show, with increasing age, a progressive decrease in both the number of cortical ova, and the number of developing follicles.

In the ovaries of other older rats described above there are also tubules, most frequently located near the hilum but also in the cortex, that have structural similarity to tubules of the testis, and are similar to the adenomas described except that they are not numerous. In one rat with a tubular adenoma of the ovary, an old corpus luteum was present. In the other, no follicles or corpora lutea remain, although nests of luteal or granulosa cells were seen. These tubules

DESCRIPTION OF FIGURES 2 TO 5

Fig. 2.—Photomicrograph of tubular adenoma of a 1,000 day old Wistar rat, No. 1005 g. Hematoxylin and eosin stained.

Fig. 3.—Photomicrograph from same adenoma as shown in Fig. 2. Tissue prepared by Wilder's silver method to demonstrate reticular fibers delimiting the irregular tubules.

Fig. 4.—Photomicrograph, Wilder’s silver stain, of tubules in ovarian hilum of Wistar rat, No. 1005 g.

Fig. 5.—Photomicrograph of tubules in cortex of ovary of Wistar rat No. 978. The nuclear structure and diffuse cytoplasm of the epithelium are quite similar to that seen in the Sertoli cell of the seminiferous tubule.
have many structural characteristics of the tubular form of the Brenner tumor of the human ovary.

Embryologically the testis cords develop from the gonadal medulla, while the ovary develops from the cortex of the gonadal primordia. Some significance may therefore be attached to the presence in the adult ovarian hilum of tubules characteristic of those of the testis, especially since these structures appear only after the growth and proliferation of oocytes and follicles has ceased.

Wilcox and Mossman (4) have described testis-like tubules in the ovaries of a shrew during certain stages of the reproductive cycle, where the ageing factor would not be dominant.

Other studies on induced ovarian tumors, including adenomas in mice as in the report of Furth and Butterworth (3) do not describe nor illustrate tubules or cells such as were found in these ageing rats. However, in tubular varieties of the arrhenoblastomas of the human ovary may be found the characteristic cell and nucleus referred to above as similar to the Sertoli cell of the testis.

The thoughtful suggestion of Robert Meyer that the arrhenoblastomas and other dysgerminomas probably arise from persisting embryonic influences may also apply in these cases of testis-like tubules in the ovaries of aged rats. In these cases, however, the restriction of the tubules to rats in the oldest age groups possibly indicates a type of android proliferation which was permitted only after removal of gynecoid influences.

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