OVARIAN TUMOR OF THE BRENNER TYPE

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In 1907 Brenner (1) described a new type of ovarian tumor which he designated oophoroma folliculare. He believed that this type was the most mature form of the folliculoid granulosa-cell tumor. R. Meyer (2) reinvestigated the available material and showed that the Brenner tumor is macroscopically, as well as microscopically, a well defined tumor of the ovary, and has no relation to the granulosa-cell tumor. According to his statistics there were 21 cases reported in the literature, 5 being of his own observation. Since Meyer's publication, Bettinger (3) has reported two cases and Weinzierl (4) one new case, the latter being the only instance of bilateral Brenner tumor known at present.

REPORT OF A CASE 1

K. G., aged fifty-nine years, white, a housewife, was admitted July 18, 1933. She had been well until two years before, when she began to suffer increasing discomfort in the lower abdomen and dizzy spells. The menopause had occurred twelve years ago, and there had been no bleeding or discharge since. Two years ago a diagnosis of pelvic tumor had been made by a physician.

Physical examination on admission revealed the following irregularities: an atrophic vaginal mucosa, left rectocele, and a large, round, dense mass about the size of a full-term fetal head, filling the pelvis. A diagnosis of multiple fibroids of the uterus with possible calcification was made. Laparotomy, July 19, 1933, revealed a solid tumor of the left ovary and a normal right ovary. Left salpingectomy and oophorectomy and suspension of the uterus were performed. Convalescence was uneventful. The patient was discharged nine days later.

1 Case presented at the Pathological Conference sponsored by the Cancer Commission of the California Medical Association Dec. 16, 1933.
The tumor measured $14 \times 8 \times 8.5$ cm. It was very firm, partially lobulated, and covered with a thin transparent capsule. On section, it was gray-white, lobulated, and showed a few scattered cysts ranging in size from a pin-head to a pepper grain. The texture was coarse and fibrous, and the color gray-white to pale gray-yellow.

**Microscopic Findings:** Sections of different parts of the tumor showed a fibrous connective tissue predominating, resembling ovarian stroma. Hyaline degeneration was present. Scattered throughout the connective-tissue stroma were numerous large and small, irregularly outlined nests and cords of epithelial cells, some closely and others loosely packed. The nests and cords were made up of fairly large polygonal cells, with a lightly stained cytoplasm, containing fair-sized, deeply stained nuclei. Surrounding the nests was a well demarcated wall of dense connective tissue, the latter being mostly cellular in its closest proximity to the nests. Often the cell cords were arranged in deep layers, surrounding cyst-like formations of various sizes, with sharply defined membranes. The cells were either symmetrically distributed, several layers deep, or eccentrically arranged with a rim only two layers thick on one side and several layers thick on the other. In the small, as well as in the larger cysts, van Gieson stain brought out small, homogeneous, pale yellow-staining colloids, as well as a reticular structure resembling the fibrin mesh-work of a serum coagulum. Small cell groups were found, each consisting of a few cells, totalling the size of a primordial follicle. The largest of these cell groups usually showed a small but sharply limited vacuole, centrally or eccentrically located. The capsule of the tumor did not show epithelial elements, although the epithelial nests were often close to it. The tumor was moderately vascular, but there was no evidence that the epithelial elements were derived from the blood or the lymphatic system.

This tumor is the solid type of Brenner tumor described by R. Meyer, in contrast to the small intracystic type in which the tumor nodules are attached to the cyst wall. Clinically the case is comparable with previously reported cases in its occurrence at an advanced age, absence of post-climacteric hemorrhages, size, and non-malignancy.
FIG. 4. **EPITHELIAL CORD, SHOWING POLYGONAL CLOSELY PACKED CELLS WITH IRREGULAR SPINDLE-SHAPED OR ANGULATED NUCLEI**

FIG. 5. **EPITHELIAL CORD OF IRREGULAR OUTLINE, SHOWING SWELLING OF THE CELLS WITH PERIPHERAL CAVITY FORMATION CONTAINING COLLOID**
In recent years a new orientation of our knowledge of the histogenesis of ovarian tumors has taken place, as a result of the critical investigations of R. Meyer and others, among whom may be mentioned Sternberg (5), H. O. Neumann (6), Frankl (7), Habbe (8), Löffler and Priesel (9). They have recognized certain tumor entities and described their histological characteristics.

R. Meyer distinguished the granulosa-cell tumor from the Brenner tumor and called attention to the relation of the Brenner epithelium to the pseudomucinous epithelium. The granulosa-cell tumors are soft tumors with a tendency toward degeneration and hemorrhage. They are observed in every age group, from childhood to senility, and in the majority of cases cause hemorrhage with enlargement of the uterus and hyperplasia of the endometrium. In children they may lead to precocity. Habbe, who reported 33 cases from Meyer's own collection, has never seen any resemblance to Brenner's tumor. According to Meyer, even the smallest granulosa-cell tumors have all the characteristics of the large tumors, and this is equally true of Brenner tumors. He described a Brenner tumor of 1–2 mm., consisting macroscopically of a firm, connective-tissue nodule, while microscopically it showed the characteristic Brenner epithelium. In the granulosa-cell tumor the epithelial parenchyma is predominant, while the typical Brenner tumor is grossly a firm connective-tissue tumor like a fibroma, sometimes containing minute cysts.

According to Meyer, the literature contains several examples which are not of the Brenner tumor type, including one case of Brenner, one case of Schröder...
FIG. 7. Epithelial Cord Surrounded by Hyalinized and Calcified Connective Tissue

FIG. 8. Large Irregular Outlined Cyst Devoid of Epithelium Containing Mucoid Material
(10), several cases of von Werdt, and two cases of Blau-Sternberg (11). On the other hand, several cases have been reported which should be included in the Brenner group, but which, on account of the presence of pseudomucinous epithelium, were not recognized as such. As will be shown later, there is a very intimate relationship between Brenner's epithelium and pseudomucinous epithelium. Illustrative cases are described by Glockner (12), Lahm (13), Fleischmann (14), de Lemos (15), and Frankl. These tumors showed pseudomucinous epithelium such as was found by Brenner in his original tumors.

R. Meyer divides Brenner tumors into two distinct types. At one end of the series are the completely solid tumors, consisting predominantly of fibrillary connective tissue containing irregularly distributed nests of polygonal cells, while at the other extreme are pseudomucinous cystomata with small, solid, fibrous tumors, containing the typical Brenner's epithelium. Between the two main types are the mixed tumors with typical columnar and mucus-producing epithelium. In some cases the mucous epithelium is predominant; in other cases the polygonal, multi-layered epithelium. Pseudomucinous cystomata may contain small, isolated, solid Brenner tumors.

Meyer has grouped the reported cases under two heads: Group A: Solid form of Brenner tumor with small or medium-sized cysts, containing Brenner's epithelium only, rarely pseudomucinous epithelium. Group B: Ovarian cystomata with small or medium-sized solid nodules containing typical Brenner's epithelium with or without pseudomucinous epithelium. Between the two types are numerous transition types of typical, columnar, mucus-producing epithelium, typical pseudomucinous epithelium, and even goblet cells.

On this basis the cases previously reported in the literature may be grouped as follows:

**Group A: Solid Brenner Tumors With and Without Cysts**

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
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<tbody>
<tr>
<td>1-3</td>
<td>Three typical tumors of Brenner's own observation</td>
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<tr>
<td>4</td>
<td>Typical Brenner tumor (Seifried, 16)</td>
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<td>5</td>
<td>Typical Brenner tumor (Krompecher, 17)</td>
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<td>6</td>
<td>Typical Brenner tumor (Neumann, Case I)</td>
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<td>7</td>
<td>Ciliated-epithelial cystoma of the right ovary and a small, Brenner tumor in the left ovary (Neumann, Case 2)</td>
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<td>8</td>
<td>Typical solid Brenner tumor (Mandelstamm, 18)</td>
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<tr>
<td>9</td>
<td>Very small (about 2 mm.) solid Brenner nodule (R. Meyer, Case I)</td>
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<tr>
<td>10</td>
<td>Typical solid Brenner tumor (R. Meyer, Case 2, credited to Wohlwill)</td>
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<td>11</td>
<td>Small, central, typical Brenner tumor (R. Meyer, Case 3)</td>
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<td>12</td>
<td>Brenner tumor, in part with cylindrical, mucous epithelium-lined cysts, in part typical (R. Meyer, Case 4)</td>
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<td>13</td>
<td>Large, solid Brenner tumor with central cyst, partially papillary (Richter's case quoted by Sternberg, 19)</td>
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<tr>
<td>14</td>
<td>In general a typical Brenner tumor, but with typical pseudomucinous epithelium and multi-layered cell cords and cysts, with transition to cystomata containing Brenner tumors adherent to the wall (Glockner)</td>
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<td>15</td>
<td>Bilateral, solid Brenner tumor (Weinzierl, 1923)</td>
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<td>16</td>
<td>Solid Brenner tumor (Bettinger, 1932)</td>
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<tr>
<td>17</td>
<td>Atrophic ovary with minute Brenner tumors (Bettinger, 1932)</td>
</tr>
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Group B: Cystomata with Brenner Tumors Adherent to the Cyst Wall, with or without Pseudomucinous Epithelium

Case 18. Cystoma ovarii (pseudomucinosum) with Brenner tumor adherent to the wall (von Werdt, Case 3)
Case 19. Large, pseudomucinous cystoma with small Brenner tumor and small pseudomucinous cysts (Lahm)
Case 20. Small, solid Brenner tumor in pseudomucinous cystoma (R. Meyer, Case 5)
Case 21. Cystoma with "oophoroma" (Krompecher, Case 1, doubtful)
Case 23. Very large pseudomucinous cystoma with a Brenner tumor about as large as a goose egg, containing a small pseudomucinous cyst (de Lemos, 1919)
Case 24. Large cystoma serosum and large solid tumor with epithelial cords of Brenner type, with pseudomucinous epithelium. (O. Frankl "Fibroma ovarii adenocysticum carcinoides serosum, partim pseudomucinosum," 1927)

The tumors are clinically benign, without recurrences, metastases, or fatalities. Permanent cures are known ranging from several to eighteen years. The tumors are most frequently observed in patients of advanced age; two patients were in the third decennium, one in the fourth, four in the fifth, five in the sixth, and one in the eighth. In other words, women over forty years are three times more frequently affected than women below that age. Fifty per cent of the cases occur in women over fifty years of age. Fourteen solid tumors, partially cystic, and 7 with marked cystic degeneration showed no differences in age distribution or clinical symptoms.

The tumors are almost invariably unilateral, the only exceptions being Weinzierl's case and the doubtful one of Krompecher. In one instance the other ovary was transformed into a large, epithelial, multilocular cystoma.

The uterus is in most cases without abnormalities. Three patients had fibromyomas, and one a very small fibroma. Hemorrhages from the uterus have not been observed. The menses were in general without irregularities, even in nulliparae of twenty-six, twenty-nine, and fifty-four years. The influence of birth and abortion is unknown due to the incompleteness of the available data. No clinical symptoms are produced and removal of the tumors is without difficulty.

In general the tumors are small, but examples up to 25 cm. in diameter have been seen.

The histologic structure of the solid tumors corresponds, generally speaking, to the description of Brenner. They are made up of a firm, fibrillar connective tissue, with a tendency to hyaline degeneration; occasionally small calcified areas are found. Embedded in the connective tissue are solid nests and rows of epithelial cells which are sometimes intercommunicating. The cell nests are more or less widely separated, according to the size of the tumors. The cell cords show arborization with knob-like formations at the ends. The epithelium in its original form is considered indifferent by some authors; it is not squamous-cell, since it neither forms fibrils nor intercellular bridges. It consists of polygonal, closely packed cells with irregular, spindle-shaped or angulated nuclei, oval nuclei being rarely seen. The cells have a tendency to swell and form larger polygonal structures with a definite membrane which roughly corresponds to squamous-cell epithelium. Here and
there a coagulated secretion is seen, caused by a degeneration of one or more cells, forming round or irregularly shaped vacuoles either eccentrically or centrally located, which sometimes coalesce and form larger cysts. A colloidal substance mixed with degenerated cells is usually found in the smaller cysts, while the larger ones contain a mucin-like secretion, sometimes containing minute colloidal droplets. The cysts are lined with flat, cuboid, low-columnar or typical columnar epithelium; the different cell forms may be indiscriminately mixed. Rarely are the cysts lined throughout with columnar epithelium. In larger cavities the cells are pushed in all directions, or are partially compressed; the lining seldom consists of more than one layer.

Brenner speaks of follicles surrounded by a theca externa but according to Meyer this is erroneous. The colloidal secretion, even when spherical and simulating an ovum, is neither morphologically nor biologically a follicle, while the so-called theca externa represents a concentrically arranged connective tissue—often with hyaline degeneration—due to compression of the expanding epithelial cell nests. Brenner’s interpretation has caused a great deal of confusion and should be abandoned. A theca interna is uniformly absent, though it is sometimes found in cases of granulosa-cell tumors. Characteristic of the granulosa-cell tumor is a separation of the cell aggregations in small alveoli or cords which are separated by thin connective-tissue septa. Sometimes single epithelial cells are surrounded by delicate connective-tissue fibrils. The connective tissue of the granulosa-cell tumors does not represent the main part of the tumor, while in Brenner’s tumor the fibrous tissue is a predominant feature.

The granulosa-cell tumors often contain lipoids in large quantities, either in the form of tiny granules or large droplets. The pathologically proliferated granulosa cells have the same physiological effect as the normal granulosa cells in some cases. Clinical experience supports this theory, since hyperplasia of the endometrium was observed in a large number of patients of all ages.

Brenner’s tumor does not show storing of lipoids, nor has it a hormonal effect upon the endometrium. Meyer has demonstrated mucus in the inner layer of columnar cells around the vacuoles. Mucus-containing epithelial cells are never found in granulosa-cell tumors.

The typical Brenner tumor belongs in Group A. Tumors which contain columnar and mucus-producing epithelium in varying amount inside of solid Brenner epithelium should be placed in Group B.

Meyer calls attention to the fact that some cases were included in Group A which contained a few cysts, varying in size, and which should be placed in Group B. This latter group should also include cases with nodules of the Brenner type, of various size, attached to the walls of cystomata. Some of these cases were reported as serous, ciliated epithelial, or pseudomucinous cystomata. In the case described by Fleischmann, mixed epithelium was found. Von Werdt’s (20) case and case 12 of Meyer (his own case 4) presented a still different picture, showing a solid Brenner nodule attached to the wall of a pseudomucinous cystoma. Lahm’s solid Brenner tumor contained small pseudomucinous cysts. Finally there were other cases of solid tumors which contained Brenner epithelium mixed with pseudomucinous epithelium, as in the case of O. Frankl.
From these findings we may conclude that there not only exists a topographical but a genetic relationship between these apparently different epithelial cells. The question remains as to whether we deal here with a metaplasia or with a differentiation of mucous epithelium from undifferentiated cell material.

**Conclusion**

Macroscopically and microscopically the Brenner tumor is a well defined entity and has no relation to the granulosa-cell tumor. It exerts no hormonal effect upon the uterus. The Brenner tumor exists in a solid form, sometimes containing small cysts which are lined with a more or less pronounced mucous-producing epithelium. The cysts may be so prominent that the solid Brenner tumor appears as a nodule attached to the wall of the cyst.

The epithelial structures lie in small, irregularly distributed areas, closely packed together in a firm dense fibrous tissue which forms a predominant part of the solid tumor. The epithelial part of the tumor does not develop from the ovarian parenchyma nor from the granulosa-cell islands, but from special cell elements which are not derived from the normal cells forming the ovary, but are abnormal cell inclusions which are found in Walthard's (21) cell islands. According to R. Meyer, they originate from the celomic epithelium near the wolffian body, from which the epithelium of the müllerian duct is derived. The latter may form solid epithelial nodules, or larger formations of indifferent epithelium in abnormal locations, as in the tubes and ligaments. It may differentiate into mucous or columnar epithelium, like the surface epithelium of the ovary.

Walthard's cell islands are capable of forming tumors which not only contain mixtures of Brenner epithelium and pseudomucinous and serous cysts, but pure areas of these types of cells may occur side by side. Also pseudomucinous cysts may form without Brenner epithelium. The Brenner tumors are linked genetically with the majority of the serous, partially fibrous, and adenomatous and papillomatous cystomata, including the adenofibromas and the mixed seromucinous tumors. Only a small percentage of the pseudomucinous cysts and cystomata originate from Walthard's cell islands. The majority constitute the endodermal part of a teratomatous anlage, which dates back to the early segmentation of the ovum.

The Brenner tumors have no clinical peculiarities save their frequency of occurrence at an advanced age, 50 per cent occurring after fifty years of age. They are benign and no metastases or recurrences have been observed. Malignant tumors arising from Brenner's epithelium are, so far, not known.

**References**