Ovarian Neoplasia in the Sprague-Dawley Rat

by David J. Lewis*

Macroscopic and microscopic characteristics of 210 spontaneous ovarian tumors from 7748 Sprague-Dawley rats are described. The tumors were classified as tubular adenoma, anaplastic adenocarcinoma, papillary cystadenoma, papillary cystadenocarcinoma, mesothelioma, sertoliform tubular adenoma, Sertoli’s cell tumor, granulosa cell tumor, thecal cell tumor, polycystic sex cord/stromal tumor, and lipid cell tumor. The histogenesis of the tumor types is discussed.

Introduction

Spontaneous ovarian tumors are rare in most rat strains (1-5). The notable exception is the Osborne-Mendel strain, in which approximately 33% of rats over 18 months of age develop granulosa cell tumors (6). Reports describing more than just a few individual tumors are consequently rare. The sparsity of rat ovarian tumors and the lack of substantial reports are in contrast to the detailed and comprehensive knowledge of human tumors typified by several detailed reviews and classifications (7-9).

The classification of ovarian tumors is notoriously difficult in all species (2), and the low incidences of ovarian tumors in rats makes the diagnosis and classification especially difficult. These problems have prompted the opinion expressed by some workers that, except for a few well-described tumor types, it may be impossible to make precise diagnoses (10). These difficulties led to a recent detailed review of all ovarian tumors in the Huntington Research Centre (HRC) archives since 1978. This review (11) described 158 tumors from 5903 Sprague-Dawley rats, along with a suggested classification system. Since the publication of this review, ovarian tumors have continued to be monitored in our laboratory, and the present report describes the results of this continued work.

The classification system employed in this work is deliberately simple and based mainly on histological criteria with consideration of some histogenic factors. No attempt has been made to take clinical information into account, as data concerning endocrine function are not routinely available for rat ovarian tumors which are rarely suspected or diagnosed prior to death. The classification and diagnoses presented here are not, therefore, claimed to be the ultimate classification of rat ovarian neoplasia, but rather a reflection of the state of the art and a working model for future work and discussion.

Materials and Methods

All ovarian tumors from 7748 Sprague-Dawley rats (6338 CD, Charles River, Wilmington, MA, USA and 1410 CFY Anglia Laboratory Animals, Huntingdon, Cambridgeshire, UK) held in the HRC archives since 1975 were reviewed. The rats were untreated control animals from life-span carcinogenicity and toxicity studies. The majority of these studies ran for a minimum of 104 weeks. Both decedents and animals examined at termination were included.

At necropsy, a detailed macroscopic examination was performed, including macrophotography of unusual/representative lesions, and samples of a comprehensive range of organs and tissues, including ovaries fixed in 10% neutral buffered formalin. Samples were embedded in paraffin wax, sectioned at 5 μm, and routinely stained with hematoxylin and eosin (HE). Additional sections from selected tumors were stained by the periodic-acid-Schiff reaction (PAS), Alcian blue-PAS stain, Masson's trichrome, and reticulin stain. Frozen sections of selected tumors were stained with Oil-Red-O.

Results

The tumor types, incidences, and age relationship are given in Table 1. After consideration of clinical history, necropsy, and microscopic findings, pathologists in our laboratory assign factor(s) considered to be contributory to death for all animals that die or are killed in extremis during the course of a study. Examination of these factors revealed that ovarian tumors were considered contributory to death in only 16 cases out of a total of 210 ovarian tumors from 7748 rats. Most of these

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cases involved malignant tumors (Table 1). Of the remaining ovarian tumors, few caused detectable clinical signs, and most were unsuspected prior to necropsy. No significant differences were detected between rats from the two sources.

**Tubular Adenoma**

Macroscopically, tubular adenomas were usually detected as firm, pale masses and ranged in size from 5 to 20 mm (Table 2). Microscopically, the tumors were composed of simple invaginations of the surface epithelium in the form of narrow tubules lined by cuboidal cells (Plates 1 and 2). Nuclei were generally round, with few mitoses. Focal evidence of tubular branching was detected. Along the tumor surface, and occasionally in cysts, many of the epithelial cells, from all tumors, contained prominent, round, homogeneous, eosinophilic, PAS positive, cytoplasmic inclusions that also stained positively with phloxine-tartrazine. Focally, in some tumors, short, irregular papillary projections from the tumor surface were present. These were continuous with both the surface epithelium and the underlying tubular structures. Occasionally, traces of Alcian blue positive material were detected in the lumina. The interstitium contained variable numbers of densely packed cells which resembled granulosa cells, but lacked the characteristic nuclear chromatin pattern. This sometimes resulted in a complex admixture of epithelial tubules and interstitial cells, in which the former were sometimes difficult to identify. Thinner sections, cut at
3 μm, were useful in these cases, as were reticulin-stained preparations.

Anaplastic Adenocarcinoma

At necropsy, this single neoplasm was detected as a cream mass (16 × 12 × 9 mm) in the right ovary. The tumor was composed of poorly differentiated tubules and acini (Plates 3 and 4), and the cells demonstrated nuclear pleomorphism and prominent mitoses. The tubular basement membrane was often indistinct. The tubular cells were irregularly arranged, with prominent multilayering. There were abundant reactive stroma and prominent infiltration of neutrophils, with areas of necrosis. The tumor had infiltrated periovarian tissue, but distant metastases were not detected.

Papillary Cystadenoma

Macroscopically, one of these two tumors was detected as a cyst 7 mm in diameter, the other as a 5 mm diameter nodule. Both neoplasms consisted of a simple cyst filled with complex papillomatous projections. Little nuclear pleomorphism and few mitoses were detected. The cells had round nuclei and sparse cytoplasm. The cysts contained amorphous eosinophilic material, which stained negatively with mucin stains.

Papillary Cystadenocarcinoma

At necropsy, this tumor appeared as a cystic mass of the left ovary (30 × 22 × 19 mm), with a few nodules (up to 5 mm diameter) on the peritoneal surfaces and a few milliliters of serosanguineous fluid in the abdomen. Macroscopically, the tumor had definite adenomatous and papillomatous patterns with cystic spaces. The cuboidal cells were arranged in acini and papillomatous projections with areas of multilayering. Occasionally, mitoses and slight nuclear pleomorphism were detected. The peritoneal metastases were microscopically identical to the primary tumor.

Mesothelioma

The two mesotheliomas classified as benign were not detected at necropsy. These tumors were composed of superficial papillary projections from the ovarian surface. The cells were cuboidal, with round nuclei and few mitoses and continuous with cells of the ovarian surface epithelium. The lesions were multifocal.

Malignant mesotheliomas were present macroscopically as large masses (≤ 70 × 55 × 42 mm), with variable numbers of nodules throughout the peritoneal cavity and serosanguineous fluid in the abdomen (Table 3). The tumors were all characterized microscopically by a pronounced tubulopapillary pattern (Plate 5), sometimes with stromal hyalinization. The implantation metastases (Plate 6) were similar to the primary tumors but frequently were only superficial deposits, rarely demonstrating invasive growth into the underlying tissue. Metastatic deposits were found in the lungs of one case.

Sertoliform Tubular Adenoma

At necropsy, these tumors were characterized as discernible pale/white nodules or masses (Plate 7), generally within the size range of 2 to 10 mm (Table 4). The tumors were composed of variable numbers of pale tubules (Plates 8 and 9) and either formed simple round/oval profiles or complex digitating profiles. The tubules were usually solid, although occasionally, accumulations of eosinophilic, PAS-positive material were present in the center. The tubules were composed of pale, weakly eosinophilic cells with indistinct cell boundaries, giving a syncytial appearance. Variable numbers of round eosinophilic, PAS-positive inclusions which resembled hyaline droplets, and vacuoles (lipid) were present in the cytoplasm. Nuclei were round or oval and occasionally had densely stained grooves. A few mitoses were detected in some tumors. The tubules had a distinct basement membrane with a fine peritubular stroma. The density of the discernible tubular elements varied within individual tumors, with a corresponding amount of stromal cells. Reticulin staining emphasized the tubular pattern and also revealed groups of stromal cells surrounded by reticular fibers. The tumor nodules were usually well-circumscribed and demarcated from the remaining ovarian tissue, which sometimes appeared compressed. Occasionally, tumors were detected in which the entire ovary was replaced by neoplastic tubules.
Table 4. Sertoliform tubular adenomas: necropsy findings from typical cases.

| Case number | Tumor location | Description |
|-------------|----------------|-------------|
| 1           | Left ovary     | Firm, white mass, 5 mm diameter |
| 2           | Right ovary    | Pale mass, 8 x 6 x 5 mm |
| 3           | Right ovary    | Pale mass, 10 x 10 x 6 mm |
| 4           | Right ovary    | Yellow nodule, 3 mm diameter |
| 5           | Right ovary    | Firm, pale nodule, 4 mm diameter |
| 6           | Right ovary    | Firm, pale nodule, 5 mm diameter |
| 7           | Right ovary    | Pulmonary, white mass, 15 x 12 x 3 mm |
| 8           | Right ovary    | Firm, pale mass, 7 x 5 x 3 mm |
| 9           | Right ovary    | Palenodule, 3 mm diameter |
| 10          | Left ovary     | Firm, white mass, 19 x 13 x 12 mm |
| 11          | Right ovary    | Firm, white nodule, 4 mm diameter |
| 12          | Right ovary    | Firm yellow |
| 13          | Right ovary    | Brown, 3 x 3 x 2 mm |
| 14          | Left ovary     | Palenodule, 6 x 5 x 4 mm |
| 15          | Left ovary     | Mass, 8 mm diameter |
|             | Right ovary    | Mass, 10 mm diameter |

In two cases, infiltration of tubular elements into periovarian tissues was detected, and these lesions were classified as malignant. Little nuclear pleomorphism and no detectable increase in mitotic activity were observed. These tumors were both from the left ovary and were measured as 15 mm diameter and 15 x 9 x 7 mm at necropsy.

Sertoli's Cell Tumor

Both tumors originated as masses in the right ovary and were 20 and 30 mm in diameter. Microscopically, the tumors varied. One tumor had a well-defined pattern of tubules lined by a single layer of columnar/cuboidal cells with pale cytoplasm (Plates 10 and 11). The other tumor was composed of an admixture of three distinct components (Plates 12 and 13). The tumor had prominent palisaded columnar cells and fine fibrovascular septae. At the center of the palisaded cells were polygonal cells with pale or clear cytoplasm and occasionally, accumulations of eosinophilic, PAS-positive material. Solid tubules, usually elongated, occasionally round or oval in profile, with basally located nuclei, were present. The apical cell margins were indistinct and appeared to be composed of fine intertwining fibrils. Tubules that resembled those of the sertoliform tubular adenomas were present (Plate 13).

Granulosa Cell Tumor

Macroscopically, these neoplasms were variable in size (from 1 mm diameter to 54 x 44 x 40 mm) and were contained within the distended bursa (Plate 14), (Tables 5 and 6). Evidence of hemorrhage was occasionally a feature. Histologically, the tumors were similar to those of other species. Several patterns were present. In the follicular form, intrafollicular spaces contained eosinophilic, PAS-positive material. The solid form was characterized by solid sheets of uniform cells, broken only occasionally by blood vessels. The trabecular pattern was distinguished by palisaded cells surrounded by connective tissue septae. The oval cells of the diffuse (sarcomatous) type were slightly elongated and resembled thecaI cells, but reticulin staining demonstrated reticular fibers around groups of cells rather than around individual cells. Call-Exner bodies were not a prominent feature in rats. Many, particularly larger, granulosa cell tumors contained areas of hemorrhage and necrosis with siderocytes and lipofuscin granules.

Malignant granulosa cell tumors showed local invasion and/or distant metastases to the kidneys, lungs, and lymph nodes. One tumor contained areas of large lutein cells (Plates 15 and 16) in the primary but only typical granulosa cells were present in the pulmonary metastases (Plate 17).

Luteoma

A single luteoma arising as a mass in the left ovary measured 10 mm in diameter at necropsy. The tumor cells resembled highly luteinized granulosa cells.

Table 5. Granulosa cell tumors: necropsy findings.

| Case number | Tumor location | Description |
|-------------|----------------|-------------|
| 1           | Right ovary    | Red nodule, 1 mm diameter |
| 2           | Left ovary     | Dark, edematous mass, 40 x 40 x 16 mm |
| 3           | Right ovary    | Pale mass, 5 x 5 x 4 mm |
| 4           | Right ovary    | Firm, hemorrhagic mass, 54 x 44 x 40 mm |
| 5           | Left ovary     | Firm mass, 24 x 24 x 22 mm |
| 6           | Left ovary     | Pale mass, 7 x 6 x 5 mm |
| 7           | Left ovary     | Dark mass, 12 mm diameter |
| 8           | Left ovary     | Firm, pale, hemorrhagic mass, 28 x 22 x 19 mm |
| 9           | Right ovary    | Hemorrhagic mass, 10 x 9 x 7 mm |
| 10          | Left ovary     | Dark mass, 7 mm diameter |
| 11          | Right ovary    | Firm, hemorrhagic mass, 15 x 12 x 9 mm |
| 12          | Right ovary    | Hemorrhagic mass, 12 mm diameter |
Table 6. Malignant granulosa cell tumors: necropsy findings.

| Case number | Tumor location | Description |
|-------------|----------------|-------------|
| 1           | Left ovary     | Grossly enlarged, cystic, 30 x 22 x 20 mm |
| 2           | Lumbar lymph nodes | Enlarged and hemorrhagic, 30 x 30 x 22 mm |
| 3           | Lungs          | Left lobe, subpleural mass, 14 x 14 x 11 mm |
| 4           | Right ovary    | Firm, hemorrhagic mass, 54 x 45 x 40 mm |
| 5           | Right ovary    | Hemorrhagic, cystic mass, 21 x 15 x 7 mm |
| 6           | Right kidney   | Dark, subcapsular mass, 7 mm diameter |
| 7           | Left ovary     | Hemorrhagic mass, 21 mm diameter |
| 8           | Lungs          | Mass, 10 mm diameter |

Thecal Cell Tumor

These tumors showed considerable variation in size (Table 7). Some thecal cell tumors were detected only at microscopy, whereas others formed large masses (up to 44 x 35 x 30 mm). Microscopically, thecomas were composed of densely packed fusiform cells, usually arranged in pronounced whorled patterns, giving a nodular appearance (Plates 18-20). The fusiform cells exhibited distinct pericellular reticular fibers and contained variable lipid. Mature collagen fibers were sparse in small tumors. In larger neoplasms, extensive necrosis was often present, with only perivascular persistence of viable tissue. Focal areas of mineralization were also a common feature of the larger tumors. Areas of hyalinization were occasionally present in some tumors, but in one small tumor were extensive, with areas of apparent osteoid and chondroidlike differentiation.

Table 7. Thecal cell tumors: necropsy findings.

| Case number | Tumor location | Description |
|-------------|----------------|-------------|
| 1           | Right ovary    | Pale, firm mass, 10 mm diameter |
| 2           | Left ovary     | Mass, 44 x 35 x 30 mm |
| 3           | Right ovary    | Firm mass, 31 x 26 x 17 mm |
| 4           | Right ovary    | Pale mass, 10 x 10 x 6 mm |
| 5           | Left ovary     | Mass, 10 mm diameter |
| 6           | Right ovary    | Pale, firm mass, 9 mm diameter |
| 7           | Left ovary     | Firm mass, 15 x 14 x 10 mm |

Table 8. Polycystic sex cord-stromal tumors: necropsy findings.

| Case number | Tumor location | Description |
|-------------|----------------|-------------|
| 1           | Right ovary    | Polycystic mass, 90 x 65 x 50 mm |
| 2           | Left ovary     | Cystic, hemorrhagic mass, 29 x 25 x 20 mm |
|             | Abdominal adipose tissue | Multiple cystic, nodular masses, up to 7 x 6 x 5 mm |
| 3           | Right ovary    | Polycystic mass, 55 x 65 x 45 mm |
|             | Omentum        | Soft, pale nodules, up to 1 mm diameter |
|             | Diaphragm      | Soft, pale nodules up to 1 mm diameter |
| 4           | Right ovary    | Polycystic mass, 20 x 31 x 15 mm |

Polycystic Sex Cord-Stromal Tumor

Macroscopically, four tumors were identified as large polycystic masses (Table 8, Plate 21). These tumors were virtually identical in structure, with large cystic spaces lined by flattened cells and narrow interstitial stroma composed of loosely packed cells showing focal luteinization (Plates 22 and 23). The cells could not be identified as thecal nor granulosa cells. Reticulin staining demonstrated reticular fibers around both groups of cells and individual cells. In two tumors, peritoneal metastases identical in structure to the primary were present.

Lipoid Cell Tumor

A single lipoid cell tumor was detected macroscopically as a nodule (13 mm diameter) adjacent to the hilus. Microscopically, the tumor was composed of large, round eosinophilic cells, often with large vacuoles.

Secondary Tumors

The ovaries were involved in cases of lymphoma, but true metastatic deposits were extremely rare. Ovarian involvement was detected in five cases of generalized abdominal mesothelioma in which ovarian deposits were identical to those elsewhere in the abdomen.

In this series, the ovaries were the site of only one metastatic tumor: a pancreatic adenocarcinoma that had spread throughout the abdominal cavity. Coincidentally, the ovary involved was the site of a granulosa cell tumor.

Discussion

Some workers have considered true tubular adenomas unique to the mouse ovary (12). In mice, tubular adenomas have been shown to originate from downgrowths of the surface epithelium (4,13-15).

Murine tubular adenomas with prominent granulosa-like interstitial cells have been termed "complex tu-
bular adenomas” (13–15). Granulosa cell tumors are reported to possibly develop from complex tubular adenomas (14,16). Complicated adenomatous and tubular patterns have been described in granulosa cell tumors (2,3). These tumors presented considerable diagnostic problems and the researchers suggested that when such components formed a large part of a tumor, alternative diagnoses should be considered.

The recent identification of two clear examples of tubular adenomas in rats and the association with granulosa cell tumors in mice led to a detailed review of all granulosa cell tumors. During this review, five tumors were identified in which tubular elements were admixed with prominent granulosalike cells. Alcian blue staining, shown to be useful in the differentiation of murine complex tubular adenomas and granulosa cell tumors (15), confirmed the tubular presence. The continuity of some tubular elements with the surface epithelium suggests that surface epithelium is a likely origin. A constant feature of these tumors was cytoplasmic inclusions. Similar inclusions were not detected in granulosa cell tumors, nor in malignant mesotheliomas. The origin of these inclusions is uncertain. There are two obvious suggestions: inclusions represent a storage of products of intracellular synthesis and the accumulation of an absorbed extracellular material. Ovarian mesothelial cells are known to be capable of phagocytosis (17). Whatever their origin, these inclusions would at present appear of diagnostic value for tubular adenomas in rats.

The single tumor classified as an anaplastic adenocarcinoma was histologically similar to those induced in rats by the clipping method with 7,12-dimethylbenz(a)anthracene (18,19). The tumor strongly resembled neoplasms of the uterine endometrium occasionally encountered in our rats and may represent the equivalent of the endometrioid adenocarcinoma reported in women (7–9,20).

Papillary cystadenomas are rare in rats at HRC (11), only two cases were detected. The single malignant counterpart metastasized by transcoelomic spread. Similar tumors have been reported previously (21,22), but are rare. In women, such tumors account for approximately 90% of all ovarian cancers (8); they are relatively common in old hens (4,12,23,24), and they are also relatively common in dogs (23,25).

The nomenclature of the epithelial ovarian tumors is controversial (26), particularly the terminology of serious adenocarcinomas and mesotheliomas. It is generally accepted that most if not all of the epithelial ovarian tumors arise from the surface epithelium (8,25). There is also general agreement that this epithelium is in fact a modified mesothelium (25,26). It has been suggested that many of the human epithelial ovarian tumors are in fact mesotheliomas (26) that demonstrate various forms of differentiation of the pluripotent Mullerian epithelium (27,28). However, in view of the long-established and entrenched epithelial/adeno/adenocarcinoma terminology, these terms have been used in the present work.

The diagnosis of mesothelioma was reserved for cases which were histologically indistinguishable from other mesotheliomas, such as those arising from the tunica vaginalis, the abdominal coelomic mesothelium (generalized abdominal mesothelioma), and the pleura. Although in human classification mesotheliomas are rarely included, a few isolated cases have been described (29).

Tubular structures which resemble seminiferous tubules with Sertoli-like cells but are devoid of spermatogenic tissue are commonly encountered in the ovaries of aged rats and mice (10,30–34). Tubular adenomas composed of these Sertoli-like cells have been described in rats by several workers both as spontaneous (28,32) and induced (35,36) neoplasms. In order to distinguish between tubular adenomas of this sertoliform differentiation and the tubular adenomas composed of cuboidal downgrowths of the surface epithelium, the term “sertoliform tubular adenoma” has been adopted. The sertoliform tubules have been induced by hypophysectomy and were considered to be related to gonadotropin deficiency (30,32,37). A decrease in the relative number of gonadotropin-producing cells has been demonstrated in the pituitary of aging anestrus rats (38).

Similarly decreased levels of LH and FSH have been measured in aging rats (39,40). These tubules may therefore be regarded as an indication of secondary ovarian senescence (30). Furthermore, if their apparent Sertoli differentiation is correct, these tubules may represent a manifestation of latent androgenic ovarian potential following loss of gynecoid influences (32). Similar tumors have been classified as Sertoli’s cell neoplasms by some authors (10). Following administration of human chorionic gonadotropin, the tubules undergo luteinization, with an ultrastructural appearance suggestive of steroidogenesis (37). However, no histological evidence of hormonal activity has been found in any tissues.

The differential diagnosis of hyperplasia and adenomas of these sertoliform tubules is difficult because of the diffuse nature of the lesion. However, when the tubular proliferation becomes extensive, with macroscopically detectable enlargement and nodule or mass formation, other ovarian structures become replaced or compressed; the tubules form a macroscopically distinct nodule or mass, and a neoplastic diagnosis is considered not inappropriate. The histogenesis of sertoliform tubules is uncertain (36); possible origins include granulosa cells (34,37), tubular surface epithelial downgrowths (13,15), rete-ovarian (19), residual hilar medullary tissue (36), persisting embryonic influences (35), or deficiency cells (37). It is possible to find apparent evidence suggestive of origins from rete ovarii, tubular epithelial downgrowths, follicles, and deficiency cells, thus, the histogenesis remains obscure. The vivid multipotency typical of the embryonic period demonstrated in mature ovarian tissues of mice (13) may offer at least a partial explanation for the problem.

Some reports have failed to find evidence of mitoses in sertoliform tubules (37), and few others have commented on their presence. However, the present study
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the hilus suggests an adrenal rest origin (8). Unlike humans,
adrenal rests are rarely observed in rats, but may
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endothelial hyperplasia has been reported in rats (8)
and mice (33) with granulosa cells tumors, but hyper-
plasia is a relatively common finding in aged rats in our
laboratory, and therefore, factors other than ovarian
tumors appear more influential in its development.
Granulosa cell tumors with several different patterns
were all composed of well-differentiated cells that re-
ssembled normal granulosa cells, and even the malignant
forms were well differentiated. These tumors were
classified as sex cord-stromal tumors.

In rats, tumors of the granulosa-thecoma cell types ap-
pear less mixed than in some other species, and no cases
were considered to warrant the diagnosis of mixed gran-
ulosa-thecoma cell tumor. Thecal cell tumors were the
third most common tumor type and similar histologically
to those of other species. The differential diagnosis of
thecoma and fibroma is often difficult (7,8), but the pres-
ence of hyalinization, whorled pattern, tendency to
nodular growth, pericellular reticulin fibers, and lipid-rich
cytoplasm favors a diagnosis of thecoma (2,3). These
criteria were used in the present study, and no cases
of fibroma were seen. The single thecoma with pro-
nounced areas of hyalinized ground substance with areas of osteoid and chondroid-like differentiation would
appear to be analogous to some forms reported in
women (41).

The four tumors designated cystic sex cord-stromal
tumors were all characterized by a grossly polycystic
appearance with a slightly loose stroma, focally abun-
dant lipid, and both pericellular and nonpericellular
reticulin patterns. Although only a low mitotic rate and
little nuclear pleomorphism were demonstrated, the
malignant nature was confirmed by peritoneal meta-
stases in two cases. In the literature, the only similar
tumor traced in rats was characterized by clefts rather
than cysts and was tentatively classified as a thecal cell
tumor (3). The presence of four cases in this series sug-
gests a definite entity and warrants separate classifi-
cation, under a descriptive term, until the histogenesis
can be elucidated.

Reports of lipoid cell tumors in rats have not been
traced. This tumor type is believed to arise from Leydig
cells, lutein cells, or adrenal restes (7–9). The histoge-
nesis of the single lipoid cell tumor detected in this series
could not be determined conclusively. However, the
tumor's apparent extraovarian location adjacent to
the hilus suggests an adrenal rest origin (8). Unlike humans,
adrenal rests are rarely observed in rats, but may
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The author thanks W. A. Gibson, R. L. Gregson, and C. Gopinath
for assistance and helpful comments; M. W. Cannon for photographic
help; and A. Galloway for secretarial assistance.

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**PLATE 1.** Low power photomicrograph of tubular adenoma. Note short papillomatous projections along surface of tumor. H&E. Bar = 1 mm.

**PLATE 2.** Tubular adenoma. Tumor composed of narrow tubules lined by cuboidal cells. H&E. Bar = 100 μm.

**PLATE 3.** Anaplastic adenocarcinoma. Irregular tubules and abundant stroma. H&E. Bar = 1 mm.

**PLATE 4.** Anaplastic adenocarcinoma. Irregular tubules of anaplastic cells with inflammatory cell infiltration and abundant stroma. H&E. Bar = 100 μm.

**PLATE 5.** Mesothelioma. Primary tumor illustrating tubulopapillary pattern. H&E. Bar = 100 μm.

**PLATE 6.** Mesothelioma. Secondary deposits from abdominal adipose tissue. H&E. Bar = 100 μm.
PLATE 7. Sertoliform tubular adenoma. Macrophotograph. Pale mass occupying whole ovary. Bar = 2 mm.

PLATE 8. Sertoliform tubular adenoma. Low power photomicrograph showing complete replacement of ovarian structure by pale tubules. H&E. Bar = 1 mm.

PLATE 9. Sertoliform tubular adenoma. Irregular tubules composed of pale vacuolated cells with round inclusions. PAS, hematoxylin. Bar = 100 µm.
PLATE 10. Sertoli's cell tumor. Low power photomicrograph to show pronounced tubular pattern. H&E. Bar = 1 mm.

PLATE 11. Sertoli's cell tumor. Solid tubules with fine peritubular stroma. H&E. Bar = 100 μm.

PLATE 12. Sertoli's cell tumor. Junction between tubular structures and area with palisaded appearance. H&E. Bar = 200 μm.

PLATE 13. Sertoli's cell tumor. Areas of palisaded cells and sertoliiformlike tubules. H&E. Bar = 200 μm.
PLATE 14. Granulosa cell tumor. Macrophotograph. Large pale mass. Bar = 10 mm.

PLATE 15. Malignant granulosa cell tumor. Areas of hemorrhage, cysts, and prominent pale areas of lutein cells. H&E. Bar = 1 mm.

PLATE 16. Malignant granulosa cell tumor. Large, pale lutein cells. H&E. Bar = 100 μm.

PLATE 17. Malignant granulosa cell tumor. Large metastatic pulmonary deposit. H&E. Bar = 1 mm.
Plate 18. Thecal cell tumor. Small, well-differentiated tumor with nodular appearance. Adjacent sertoliform tubules. H&E. Bar = 200 μm.

Plate 19. Thecal cell tumor. Low power photomicrograph to show pronounced whorled, nodular appearance. Reticulin stain. Bar = 1 mm.

Plate 20. Thecal cell tumor. Nodular pattern with focal mineralization. H&E. Bar = 1 mm.
PLATE 21. Polycystic sex cord-stromal tumor. Macrophotograph. Tumor composed numerous pale, thin-walled cysts. Bar = 25 mm.

PLATE 22. Polycystic sex cord-stromal tumor. Variable sized cysts and pale interstitial cells. H&E. Bar = 200 μm.

PLATE 23. Polycystic sex cord-stromal tumor. Cysts lined by thin cells. Interstitial cells have slightly vacuolated appearance in this field. H&E. Bar = 100 μm.