

Proliferative Lesions of the Ovary, Uterus, Vagina, Cervix and Oviduct in Rats

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INTRODUCTION

Primary ovarian tumors are generally uncommon in rat strains used in toxicologic studies; however, these tumors have been reported to occur with some frequency in certain strains (4, 9). Ovarian tumors have been experimentally induced in rats (12, 23, 32). Primary spontaneous tumors of the uterus (except for uterine stromal polyps in some strains), vagina, cervix, or oviduct are uncommon in rats typically used in toxicologic studies, although certain experimental strains such as the Eker and Donryu rats have been reported to develop spontaneous uterine tumors (8, 13, 19). There are few chemically related effects observed in these organs in chronic carcinogenicity studies. Although various tumors throughout the reproductive tract have been induced experimentally, most spontaneous tumors of the female rat reproductive tract are incidental findings at necropsy or routine histologic screening, (6, 11, 15, 17, 18).

Non-neoplastic proliferative lesions of the ovary, uterus, vagina, cervix and oviduct are infrequent in most strains of rats commonly used in toxicologic studies (1, 3,

9, 11, 15). Although the incidence of spontaneous non-neoplastic proliferative lesions increases with age, the incidence of these lesions overall is low (3, 15).

The following classification scheme is based upon morphologic characteristics in hematoxylin and eosin (H&E) stained preparations. The tumors of the ovary are divided into three major categories according to their presumed histogenesis and direction of differentiation: epithelial tumors, sex cord-stromal tumors, and germ cell tumors. The tumors of the uterus, vagina, cervix and oviduct are divided into epithelial and nonepithelial based on presumed histogenesis. The classification scheme is based upon that proposed by the National Toxicology Program and the WHO Histologic Classification of Ovarian Tumors (2, 15, 18).

MORPHOLOGY OVARY

NEOPLASMS OF EPITHELIAL ORIGIN

Cystadenoma/Cystadenocarcinoma (Figures 1-4)

Grossly, cystadenomas may present as single or multiple ovarian cysts, whereas cystadenocarcinomas appear as large cystic masses. Microscopically, cystadenomas

have papillary infoldings lined by cuboidal or columnar epithelium. The lesions are usually unilateral and range from microscopic to over a centimeter in diameter. Single or multiple fronds protrude from the cyst wall into the lumen. Diagnosis of cystadenocarcinoma is based upon atypia, multilayering, local invasion, or peritoneal metastases.

Cystadenoma must be differentiated from papillary hyperplasia of a cyst lining by the presence of distinct fronds in the case of the former, and simple infoldings of hyperplastic epithelium in the latter. Also, hyperplasia is usually diffuse and characterized by infoldings of epithelium that have short unbranched papillary extensions; whereas, neoplastic papillae are focal in origin and more structurally complex.

Tubulostromal Adenoma/Tubulostromal Carcinoma (Figures 5 & 6)

Tubulostromal adenomas consist of tubules lined by cuboidal epithelium that resembles ovarian surface epithelium. These lesions vary from microscopic to several centimeters in diameter and are frequently bilateral. Tubules may be identified that are continuous with downgrowths of the surface epithelium. The tubules may be interspersed between packets of variably vacuolated or luteinized cells of probable sex cord origin. The sex cord component is variable and may form a major component of the tumor, which may lead to the primary diagnosis being of the sex cord component.

Differentiating tubulostromal adenoma from epithelial hyperplasia is difficult. Criteria for adenoma include: a distinct mass of well-differentiated tubulostromal elements and compression of the adjacent tissue. A diagnosis of tubulostromal carcinoma is based upon metastasis, local invasion, and/or high mitotic index. Few or numerous cysts with blood or thrombi have been reported in tubulostromal carcinomas.

Mesothelioma (Figures 7 & 8)

These tumors resemble mesotheliomas in other sites and are composed of cuboidal to columnar epithelium in a papillary or frond-like pattern on the surface of the ovary or within the ovarian bursa. Malignant mesotheliomas in the Sprague-Dawley rat resemble adenocarcinomas, but upon close examination have fronds on the surface of the ovary which extend into cyst-like spaces of the primary mass.

NEOPLASMS AND NON-NEOPLASTIC PROLIFERATIVE LESIONS OF OVARIAN SEX CORD-STROMAL ORIGIN

Hyperplasia

Hyperplasia of the sex cord-stroma is characterized by one or more foci or a diffuse increase in granulosa, luteal,

or thecal cells as pure or mixed populations. The ovaries may be marginally enlarged with a diffuse, bilateral, hyperplastic change, or foci may arise in atrophied ovaries with little evidence of compression.

Differentiation between hyperplasia and adenoma of the sex cord-stromal cells is difficult. Focal small lesions up to a few (approximately 2-3) mm in diameter are considered hyperplastic and larger lesions are considered neoplasms. When the change is diffuse and bilateral, a more dramatic change such as a 2- to 3-fold increase in ovarian size is used as the criterion to shift a diagnosis of hyperplasia to neoplasia. Cellular pleomorphism is not a good criterion for separating hyperplasia from neoplasia because the cells of sex cord-stromal tumors are often monomorphic.

Granulosa Cell Tumor (Figures 9-12)

These tumors are usually unilateral but can be bilateral. They vary greatly in size and tend to be solid with a smooth or slightly lobulated surface. They grow in a variety of histological patterns including solid sheets, cystic, pseudofollicular, trabecular, and sertoliform. The tumor cells resemble normal granulosa cells with round to oval nuclei, coarsely stippled chromatin, and scant cytoplasm. There may be a variable picture with thecal cell and/or luteal cell areas in the tumor, but granulosa cells predominate. Fibroblasts, collagen, and blood vessels support the tumor. The granulosa cell neoplasm must be distinguished from focal granulosa cell hyperplasia and from focal granulosa cell nodules arising in a tubular adenoma. Malignant granulosa cell tumors are quite large and present as palpable abdominal masses with increased cellular pleomorphism (polyhedral or spindle form), a high mitotic index, necrosis, and hemorrhage. Invasion and metastases are rare.

Thecoma (Figures 13-16)

Thecomas can be large and are circumscribed but non-encapsulated. Densely packed fusiform cells in whorled patterns are characteristic, giving the tumor a nodular appearance. The cytoplasm may contain lipid-laden vacuoles but this is not a dominant feature. Collagen is mainly between bundles of cells rather than around individual cells so that a silver stain for reticulin would differentiate the thecoma from a fibroma. Malignant thecomas are characterized by cellular pleomorphism, multiple areas of necrosis, mitotic figures, and invasion of the periovarian tissue.

Luteoma (Figures 17-19)

(Synonyms: *Leydig cell tumor, lipid cell tumor*)

Luteomas consist of large, round to polyhedral cells that resemble luteinized cells. They contain abundant eosinophilic or vacuolated cytoplasm with round to oval nuclei without much stippling.

Sertoli's Cell Tumor (Figures 20-22)

Sertoli's cell tumor occurs unilaterally as a solid, encapsulated, white/yellow, lobulated mass with occasional cysts. Over half of these tumors arise near the hilus and compress adjacent structures. It has a thin, fibrous capsule and resembles its testicular counterpart's seminiferous tubules separated by fibrovascular stroma. It has a characteristic tubular pattern of elongated tumor cells arranged perpendicular to the tubular basement membrane. The cells have basal nuclei and abundant, lightly eosinophilic, vacuolated cytoplasm. Malignancy is diagnosed when the capsule is disrupted and/or there is implantation on the peritoneal surfaces.

Sertoliform tubular adenoma

Sertoliform tubular adenomas are well-circumscribed, pale tan/white nodules or masses that range from 2–10 mm in diameter. They replace ovarian tissue and may or may not cause compression. Irregular tubules of pale, vacuolated cells with indistinct cell boundaries may give a syncytial appearance. Tumor cells often have round, intracytoplasmic, hyalin-like inclusions. Sertoliform tubular adenoma differs from the Sertoli's cell tumor in that the tubular cells lack basal nuclei and vertically oriented cytoplasm. This tumor is seen more commonly in Sprague-Dawley rats than in other strains. This tumor was previously classified with the epithelial tumors described as tubular adenomas.

OVARIAN NEOPLASMS OF GERM CELL ORIGIN

Teratoma

(*Synonyms: benign teratoma, benign cystic teratoma, dermoid cyst, mature teratoma, adult teratoma, malignant teratoma, immature teratoma*)

Teratomas are tumors containing any combination of well-differentiated ectodermal, mesodermal, and endodermal elements. Benign or mature tumors are predominantly cystic but may be solid. Foci of white bone or cartilage on the cut surface may be present. Microscopically, the cysts are lined by epithelium that may be cuboidal, enteric, respiratory, or keratinized squamous in nature. Mucin, keratin, or hair may be seen within the cyst. Mature nervous tissue and gastrointestinal elements are common, but a number of other tissues can often be discerned, such as muscle, hair follicles, cartilage, and bone. Usually, teratomas of the ovary are benign. The occasional malignant version has poor differentiation and most commonly is composed of neural tissue. Neural rosettes may be seen.

Yolk Sac Carcinoma (Figures 23-25)

(*Synonyms: endodermal sinus tumor, yolk sac tumor*)

Grossly, yolk sac carcinomas are unilateral, dark, gelatinous or cystic masses that have been observed to be

up to 2.5 cm in diameter. Cystic spaces within the tumor contain serosanguineous fluid. Microscopically, there are nests, ribbons, or individual cells embedded in an abundant, eosinophilic, PAS-positive matrix. The cells are round to oval with single, central or polar, sharply defined, basophilic nuclei. The cells have distinct boundaries and are mostly of uniform size, although a few binucleated cells, giant cells, or trophoblasts have been noted. Areas of necrosis can be encountered and metastasis by local invasion or vascular channels can occur.

Choriocarcinoma (Figures 26-29)

(*Synonym: chorionepithelioma*)

Choriocarcinomas are described at necropsy as dark or hemorrhagic, cystic ovarian masses. Microscopically, the tumors are composed of hematocysts, hemorrhage, cytotrophoblasts, syncytiotrophoblasts, and/or trophoblastic giant cells. Cytotrophoblasts are rounded with centrally located, hyperchromatic or vesicular nuclei that are 5-10 microns in diameter.

Syncytiotrophoblasts are distinctly outlined, multinucleated cells with granular, basophilic cytoplasm. Giant cells are large, irregular cells with abundant cytoplasm and single, large nuclei up to 50 microns in diameter. Most choriocarcinomas are found in young animals and are associated with early fatality (1, 2).

MISCELLANEOUS NEOPLASMS OF THE OVARY

Fibroma/Fibrosarcoma (Figures 30 & 31)

Some difficulty may arise in morphologically distinguishing between fibromas/fibrosarcomas and thecomas. However, collagen fiber deposition can be used as a feature for differentiating fibromas/fibrosarcomas from thecomas (See description of thecoma).

Fibromas of the ovary are well-differentiated tumors consisting of fibroblasts and collagen. Collagen fibers are usually around individual fibroblasts unlike in thecomas where collagen is interspersed between bundles of tumor cells.

Hemangioma/Hemangiosarcoma

Hemangiomas/hemangiosarcomas consist of both capillaries and cavernous vascular channels which contain erythrocytes and are lined by large, plump endothelial cells.

Metastatic/Systemic Tumors (Figure 32)

Systemic tumors of the rat ovary are rare. One study reported involvement of rat ovaries in generalized abdominal mesothelioma and one case of a pancreatic adenocarcinoma that had spread throughout the abdominal cavity (16). Lymphoblastic lymphomas and large granular

lymphocyte lymphoma (LGL, Mononuclear cell leukemia or Fischer rat leukemia) may secondarily involve ovaries, as well as numerous other organs. Histiocytic sarcoma may involve the ovaries in the rat (30). The neoplastic histiocytes typically contain a dark, basophilic nucleus and abundant, distinctly eosinophilic cytoplasm.

DISCUSSION

Ovarian tumors are divided into three major categories, which are named according to their presumed histogenesis and directions of differentiation: epithelial tumors, sex cord-stromal tumors, and germ cell tumors. The morphology of the majority of rodent and human ovarian tumors is similar; however, morphologic counterparts do not always exist (2).

Granulosa cell tumors are the most common sex cord-stromal tumors in F344 rats. They are uncommon, although they do occur, in Sprague-Dawley rats (2, 16). In the Fischer 344 rat, these tumors are mostly benign although malignant tumors do occur.

Cystadenomas/cystadenocarcinomas are generally uncommon spontaneous tumors in the rat, accounting for 1-4% of the primary ovarian tumors in F344 rats (1, 2) and 2% or less in Sprague-Dawley rats (11, 16). Cystadenocarcinomas are more common than cystadenomas.

Tubulostromal tumors are rare in F344 rats (1, 2).

Hyperplasia of the sex cord-stromal cells is quite common in old Wistar rats and probably other strains of rats but tends not to be diagnosed by some pathologists because it is viewed as a normal aging change. It is seen most commonly in 2-year carcinogenicity studies.

Teratomas of the rat ovary have only recently been reported in the literature as a result of the development of the genetically susceptible Tera strain (21). This hereditary feature appears to be due to an autosomal recessive trait that results in ovarian or testicular teratomas in about 25% of either sex. The teratomas have been described as containing tridermic tissues such as bone, epithelium, and neural tissues. Spontaneous (non-hereditary) benign and malignant teratomas of the rat ovary have been reported in an old untreated Wistar rat and a Donryu rat, respectively (18).

Spontaneous ovarian yolk sac carcinoma has been reported in the rat, but not as frequently reported as that in the mouse ovary (1). The yolk sac carcinoma of the rat differs from the yolk sac tumor of humans because the rodent yolk sac is composed of visceral and parietal layers. The parietal yolk sac lies on a thick basement membrane (Reichert's membrane) which it secretes.

Spontaneous ovarian choriocarcinoma has been reported only once in the rat (1).

Fibromas and fibrosarcomas are rare in the rat ovary. Only two fibromas and no fibrosarcomas were reported

out of a total of 204 ovarian tumors from 39,851 female F344 rats from the National Toxicology Program (1, 2). A study on a wide variety of ovarian neoplasms in 5,903 aged Sprague-Dawley rats reported no fibromas or fibrosarcomas (11). In a follow-up study, neither of the tumors were reported among the 210 spontaneous ovarian tumors from 7,748 Sprague-Dawley rats (16).

Vascular tumors of the ovaries are even more rare in rats than fibromas/fibrosarcomas.

Ovarian dysgerminomas in the rat have not been reported (4). Occasional cases have been reported in other species (5, 20, 33). The marked resemblance of this tumor to the classical testicular seminoma is reflected in the synonym—ovarian seminoma.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA FOR NEOPLASMS AND NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE OVARY IN RATS

OVARIAN NEOPLASMS OF EPITHELIAL ORIGIN

Cystadenoma/Cystadenocarcinoma

1. Cystadenomas are single or multiple cysts lined by cuboidal or columnar epithelium with infoldings that form papillary structures
2. Usually unilateral and range from microscopic to over a centimeter in diameter
3. Single or multiple fronds protruding from the cyst wall into the lumen
4. Differential diagnoses: cystic papillary hyperplasia and mesothelioma
5. Cystadenocarcinomas are large cystic masses. Criteria of malignancy are focal atypia and/or local invasion

Tubulostromal Adenoma/Tubulostromal Carcinoma

1. Vary from microscopic to several centimeters in diameter and are frequently bilateral
2. Criteria for differentiating adenoma from epithelial hyperplasia include: a distinct mass of tubulostromal elements, compression of the adjacent tissue, and a diameter of at least 2-3 mm.
3. Consist of tubules lined by cuboidal epithelium resembling ovarian surface epithelium. Tubules are continuous with downgrowths of the surface epithelium in some areas
4. Variable ratio of tubular to non-tubular components and degree of tubular dilation
5. Tubules may be interspersed between packets of variably vacuolated or luteinized cells of probable sex cord origin. Sex cord component is variable and may form a major component of the tumor

which may lead to primary diagnosis being the sex cord component

6. Diagnosis of malignancy based upon metastasis, local invasion, and/or high mitotic index. Few or numerous cysts with blood or thrombi may be present

Mesothelioma

1. Composed of cuboidal to columnar epithelium in a papillary or frond-like pattern on the surface of the ovary or within the bursa
2. Resemble mesotheliomas in other sites of the body
3. Malignant tumors resemble adenocarcinomas, but have a frond-like pattern on the surface of the ovary and within cysts in the primary mass

NEOPLASMS AND NON-NEOPLASTIC PROLIFERATIVE LESIONS OF OVARIAN SEX CORD-STROMAL ORIGIN

Hyperplasia

1. Characterized by focal or diffuse increase in granulosa, luteal, or thecal cells as pure or mixed populations
2. May occur in atrophic ovaries and have little evidence of compression
3. Sometimes ovaries can be marginally enlarged with a diffuse, bilateral, hyperplastic change
4. Differentiated from tumors of the sex cord-stromal cells by size. Focal lesions up to 2-3 mm are considered hyperplastic, and larger lesions are considered tumors. When change is diffuse and bilateral, a 2- to 3-fold increase in ovary size is used to shift a diagnosis of hyperplasia to neoplasia

Granulosa Cell Tumor

1. Variety of histologic patterns - solid, cystic, microfollicular, sertoliform, and tubular
2. Tumor cells characteristically resemble normal granulosa cells with round to oval nuclei and coarsely stippled chromatin. Cytoplasm is variable depending upon the degree of luteinization
3. Stroma may be composed of varying amounts of theca cells, fibroblasts, collagen, and blood vessels
4. Distinguished from focal granulosa cell hyperplasia and from focal granulosa cell nodules arising in tubular adenoma by compression and size
5. Malignant granulosa cell tumor characterized by cellular pleomorphism, high mitotic index, necrosis, invasion, and metastasis

Thecoma

1. Microscopic to grossly evident masses
2. Densely packed fusiform cells usually in whorled patterns giving a nodular appearance

3. Areas of vacuolated cells may be present
4. Circumscribed but non-encapsulated

Luteoma

1. Circumscribed masses consisting mainly of large polygonal cells resembling luteinized cells
2. Tumor cells have abundant eosinophilic or vacuolated cytoplasm

Sertoli's Cell Tumor

1. Characteristic tubular pattern of elongated tumor cells arranged perpendicular to the tubular basement membrane
2. Tumor cells have basal nuclei and abundant, lightly eosinophilic, vacuolated cytoplasm
3. Thin fibrous capsule
4. Arise near hilus and compress adjacent structures
5. Malignant tumors disrupt the ovarian capsule and/or implant on peritoneal surfaces

Sertoliform Tubular Adenoma

1. Grossly, pale/white nodules or masses, 2-10 mm in diameter
2. Usually well-circumscribed and demarcated from remaining ovarian tissue; may or may not have compression
3. Irregular tubules replacing ovarian tissue
4. Tubules composed of pale, vacuolated cells with indistinct cell boundaries giving a somewhat syncytial appearance
5. Tumor cells often contain round, intracytoplasmic, hyalin-like inclusions

OVARIAN NEOPLASMS OF GERM CELL ORIGIN

Teratoma

(Synonyms: *benign teratoma, benign cystic teratoma, dermoid cyst, mature teratoma, adult teratoma, malignant teratoma, immature teratoma*)

1. Benign (mature) tumors are predominantly cystic but may be solid. Well-differentiated ectodermal, mesodermal, and endodermal elements may be present
2. Mature nervous tissue and gastrointestinal structures most common within cysts; other tissues may be present
3. Malignant (immature) teratomas contain some immature elements, most often neuroectodermal. Usually solid masses with a small, cystic component; but occasionally, predominantly cystic
4. Malignancy based on extension through the ovarian bursa, hemorrhage and necrosis, and poor differentiation

Yolk Sac Carcinoma

(Synonym: *endodermal sinus tumor, yolk sac tumor*)

1. Unilateral, dark, gelatinous or cystic masses up to

- 2.5 cm in diameter. Cystic spaces contain serosanguineous fluid
2. Tumor cells embedded in an eosinophilic, PAS-positive matrix
 3. Pleomorphic, round to oval tumor cells arranged singly, in nests, rows, or ribbons, or in large clusters
Binucleated and/or giant tumor cells
 4. Areas of necrosis or necrosis of individual tumor cells may be present
 5. Spread by local invasion or vascular spread

Choriocarcinoma

(Synonym: *chorionepithelioma*)

1. Dark or hemorrhagic, grossly
2. Composed of hematocysts, sheets of cytotrophoblasts, syncytiotrophoblasts, and/or trophoblastic giant cells, with areas of hemorrhage
3. Trophoblastic giant cells resemble those in deciduomas

MISCELLANEOUS NEOPLASMS OF THE OVARY

Fibroma/Fibrosarcoma

1. Fibromas are well-differentiated consisting of fibroblasts and collagen

Hemangioma/Hemangiosarcoma

1. Consist of both capillaries and cavernous channels which contain erythrocytes; lined by large, plump endothelial cells

Metastatic/Systemic Tumors

1. Mesotheliomas, pancreatic adenocarcinoma, lymphoblastic lymphoma, large granular lymphocyte (LGL) lymphoma (Mononuclear Cell or Leukemia), and diffuse histiocytic sarcoma have been reported

MORPHOLOGY

NEOPLASMS OF THE UTERUS, VAGINA, CERVIX AND OVIDUCT

UTERINE NEOPLASMS OF EPITHELIAL ORIGIN

Endometrial Adenoma (Figures 33 & 34)

Endometrial adenomas arise from the epithelium lining the uterine mucosa or comprising the endometrial glands. Spontaneous occurrence of these tumors is rare. Grossly, these tumors form well delineated solitary masses that may compress, but not invade the surrounding endometrium or adjacent myometrium. The tumor cells within

endometrial adenomas are usually well-differentiated, and usually form acinar structures within a delicate fibrous stroma, or may form papillary fronds that extend into the uterine lumen. Proliferation of decidual tissue is occasionally observed in or associated with endometrial neoplasms in F344 rats.

Endometrial Adenocarcinoma (Figures 35-37)

Endometrial adenocarcinomas are poorly circumscribed growths that usually invade the surrounding myometrium, extend into and occlude the uterine lumen or metastasize to distant sites. The neoplastic epithelial cells form solid nests, cords, papillary or acinar structures that are within or supported by a stroma. The neoplastic epithelium may be well-differentiated or may have typical characteristics of anaplasia characterized by cellular and nuclear atypia, and pleomorphism. The tumor cells may be cuboidal to columnar and are usually one, two or more cell layers thick. In some instances, the multiple cell layers may give a piling or crowding effect. The lumens of the acinar structures formed by the tumor cells may be cystic or distended and may contain accumulations of cellular debris, mixed populations of inflammatory cells, and eosinophilic secretory material. Occasionally, hyalinized areas of fibrosis are within the stroma separating tumor cells. Focal areas of necrosis and hemorrhage may also be present. Endometrial adenocarcinomas with squamous differentiation may be seen and have been termed adenoacanthomas.

Squamous Cell Carcinoma (Figures 38 & 39)

Primary squamous cell carcinoma of the uterine horns and body is rare, although squamous differentiation of neoplastic epithelia in endometrial adenocarcinomas may be observed. Primary squamous cell carcinoma of endometrial epithelial origin should be distinguished from squamous cell carcinomas arising from the vaginal or cervical epithelium.

UTERINE NEOPLASMS OF NONEPITHELIAL OR UNDETERMINED ORIGIN

Yolk Sac Carcinoma (Figures 40 & 41)

(Synonyms: *endodermal sinus tumor, yolk sac tumor*)

Yolk sac carcinomas involve primarily the horns of the uterus. Many of these tumors have regions showing features characteristic of the fetal membranes, the parietal and visceral yolk sacs. Yolk sac carcinomas are characterized by rosettes, nests, rows, ribbons or large clusters of neoplastic endodermal cells that appear fairly uniform in size, but in some instances may show size variation and formation of multinucleated giant cells. These cells are in a characteristic abundant amorphous hyalinized basement membrane-like material that stains pale pink with mucicarmine stain and purplish with PAS stains and is positive

for laminin. In rats, yolk sac carcinomas have been reported to metastasize to distant sites such as the peritoneum, ovaries, and lymph node, and occasionally to the lung, liver, spleen, kidneys and thymus.

Teratoma

(*Synonyms: benign teratoma, mature teratoma*)

Teratomas of the uterus have been reported to occur rarely in rats (24). They are usually well encapsulated. The tumor cells and matrix are derived from endodermal, ectodermal and mesodermal germ layers. The structures within the tumors may consist of endodermal cysts lined by columnar epithelium and goblet cells usually arranged in folds resembling intestinal villi, or transverse and longitudinal bands of smooth muscle surrounding endodermal cysts. Pancreatic tissue with islets of Langerhans have been observed in these tumors. Endodermal cysts lined by bronchial-like epithelium associated with cartilage, thymus-like, thyroid or salivary gland tissue may be observed. Keratin-filled ectodermal cysts lined by multiple layer's of flattened epithelium and often surrounded by adipose tissue, sebaceous glands or hair follicles can be observed. Nervous tissue including neurons, meninges, neuroglial cells and neurons have been reported in these tumors. Other tissue types that may be present are cartilage, bone tissue, bone marrow, striated muscle and renal tissue containing embryonal glomerular structures and tubules.

Mixed Müllerian Tumor, Malignant (Figures 42-44)

(*Synonyms: carcinosarcoma, mixed mesodermal tumor, malignant*)

Grossly, these tumors are characterized as being polypoid, but show evidence of local invasion. They are spontaneous and usually malignant tumors that are thought to originate from the pluripotent mesodermal cells of the müllerian ducts. Microscopically, the tumors show highly infiltrative growth and are comprised of epithelial and mesenchymal elements. Mitotic figures are observed frequently in both components. The epithelial structures consist of glands of squamous anaplastic epithelium. The mesenchymal part of the tumor is subdivided into homologous and heterologous types. In the homologous type, the mesenchymal component of the tumor is differentiated towards fibrous, smooth muscle and/or endometrial stroma-like tissue. In the heterologous type, the mesenchymal part of the tumor has areas of striated muscle, cartilage, bone and/or adipose tissue. This tumor must be differentiated from teratomas, which contain tissue derived from three germ layers (versus two for the mixed müllerian tumors), and adenocarcinomas, which do not have the sarcomatous elements. There is a benign variant of the müllerian mixed tumor in which both epithelial and mesenchymal components are well differentiated.

Embryonal Carcinoma

(*Synonym: undifferentiated malignant teratoma*)

Embryonal carcinomas are composed of poorly differentiated round or fusiform tumor cells. The round tumor cells contain abundant eosinophilic cytoplasm; whereas, the cytoplasm of the fusiform cell is moderately scant. The tumor cells have large nuclei with prominent nucleoli, and mitotic figures are usually abundant. The tumor cells will infiltrate into the myometrium. Yolk sac carcinoma has been reported to occur within these tumors. Areas of well-differentiated bone, cartilage or skin have been reported to occur within these tumors.

Choriocarcinoma (Figure 45)

(*Synonyms: chorioncarcinoma, chorionepithelioma*)

Choriocarcinomas are composed of small round cells resembling cytotrophoblasts and giant cells with multiple or single large nuclei. The tumor cells are found between areas of hemorrhage and necrosis. Tumor cells will usually infiltrate the myometrium and produce large regions of necrosis and hemorrhage.

Endometrial Stromal Polyp (Figures 46-48)

Endometrial stromal polyps occur most often in older rodents. Most polyps are composed of abundant amounts of loosely or compactly arranged spindle-shaped or stellate endometrial stromal cells that contain numerous small blood vessels and often large and distended endometrial glands.

Endometrial Stromal Sarcoma (Figures 49 & 50)

Endometrial stromal sarcomas may arise within polyps or may be found in the wall of the uterus, or present as malignant tumors partly bulging into the uterine lumen. The neoplastic cells are usually spindle-shaped with indistinct borders and usually loosely arranged in sheets or in fascicles that run perpendicular to one another or form whorling patterns. The tumor cells may be within a fibrillar matrix. Giant cells may be present and focal areas of necrosis and associated inflammatory cells or hemorrhage can be seen, although this is very uncommon. Stromal sarcomas may spread by infiltration into the myometrium, cervix and adjacent abdominal structures. Differential diagnoses include fibrosarcoma, leiomyosarcoma, malignant histiocytic sarcoma and schwannoma.

Leiomyoma (Figure 51)

Smooth muscle neoplasms of the uterus arise from the myometrium. Leiomyomas are solitary well-circumscribed masses that may compress the surrounding myometrium and adjacent endometrial tissues. The cells are arranged in interlacing bundles and are within a delicate collagenous stroma that stains blue while the muscle bundles stain red using a Masson's trichrome stain. The tumor cells stain positively for desmin and smooth muscle actin.

Leiomyosarcoma (Figure 52)

Leiomyosarcomas are poorly delineated masses that have unorganized and invasive growth patterns. Leiomyosarcomas appear more cellular due to decreased amount of fibrillar eosinophilic cytoplasm. The cells are usually spindle-shaped, but may be pleomorphic. Focal areas of necrosis or hemorrhage may be present in the neoplasm. The tumor cells stain positively for desmin and smooth muscle actin, and stain red with Masson's trichrome stain.

Schwannoma, Malignant (see description under cervix)***Fibroma, Fibrosarcoma, Hemangioma, Hemangiosarcoma***

Other mesenchymal neoplasms of the uterus include hemangioma, hemangiosarcoma, fibroma and fibrosarcoma all which are histomorphologically similar to those observed in other organs.

METASTATIC/SYSTEMIC NEOPLASMS OF THE UTERUS***Mononuclear Cell Leukemia***

(Synonyms: Large granular lymphocyte lymphoma, Fischer rat leukemia)

Mononuclear cell leukemia is the most commonly observed systemic neoplasm in the uterus of the F344 rat.

NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE UTERUS***Endometrial Hyperplasia (Figure 53)***

Histologically, endometrial hyperplasia can range from focal areas of hyperplastic glands lined by mitotically active simple low columnar epithelium to secretory, fluid-filled, cystically dilated endometrial glands, lined by flattened simple cuboidal epithelium. Overall, the change is characterized by increased numbers and size of endometrial glands. Whether this lesion is associated with persistent hormonal stimulation is unknown. Spontaneously occurring cystic endometrial hyperplasia does not appear to be preneoplastic.

Focal Glandular Hyperplasia

Glandular hyperplasia is characterized by focal proliferation of endometrial glands lined by enlarged columnar epithelial cells. The glandular epithelium has abundant eosinophilic cytoplasm, and large round vesicular nuclei with prominent nucleoli. Cellular pleomorphism and atypia may be present with concomitant loss of the normal glandular architecture and uniformity, and lumens may not be obvious. This type of hyperplasia is often observed following administration of uterine carcinogens.

Hyperplasia of the Endometrial Stroma (Figure 54)

Stromal hyperplasia, with or without involvement of the endometrial glands, has been observed in F344 rats, and the cause is unknown. This change is characterized by increased number of stromal cells with few or no endometrial glandular elements.

Deciduoma (Figures 55 & 56)

Deciduomas are usually observed in young adult rats, and are composed of cells with variable appearances: "mesometrial cells," "glycogenic cells," "decidual cells," and "capsule cells." The "mesometrial" cells are closest to the mesenteric attachment side of the uterus and are fibroblast-like, and the "glycogenic" cells have clear vacuoles or spaces. The "decidual" cells are relatively large, eosinophilic, and epithelial-like; whereas, the "capsular cells" are fibrocyte-like and separate the decidual cells from the smooth muscle cells of the uterine wall.

Decidual Reaction (Figure 57)

This lesion occurs in older rats usually as part of another lesion such as endometrial stromal polyp. The cells are composed of large, eosinophilic cells resembling the decidual cells of a deciduoma.

Adenomyosis (Figure 58)

Adenomyosis occurs most frequently in aged rats. This lesion is characterized by the presence of non-neoplastic endometrial glands and stroma within the myometrium. There is no degree of cellular atypia present in the endometrial glands within the myometrium. This lesion should not be confused with endometriosis which is a disorder that occurs in species that menstruate and is characterized by the presence of ectopic endometrial tissue located throughout the peritoneal cavity. Nor should this lesion be misdiagnosed for endometrial adenocarcinoma which may be associated with a fibroproliferative reaction and cells appear much less differentiated.

VAGINAL AND CERVICAL NEOPLASMS OF EPITHELIAL ORIGIN***Squamous Cell Papilloma, vagina (Figure 59)***

Squamous cell papilloma of the vagina is composed of extensions of neoplastic squamous epithelial cells supported by a moderately dense fibrovascular core. The tumors usually arise from the surface epithelium of the cervix or vagina and show an exophytic growth pattern. Tumor cells are not infiltrative and do not invade into the underlying vaginal stroma.

Squamous Cell Carcinoma, vagina (Figures 60 & 61)

Squamous cell carcinoma of the vagina consists of cords, islands or nests of anaplastic squamous epithelium showing downward growth into the underlying stroma.

The neoplastic squamous epithelial cells are large and polygonal and have large vesicular nuclei containing prominent nucleoli. Mitotic figures may be common. The neoplastic epithelium is usually well-differentiated and keratinized or may be very dysplastic. Many of the centers of the nests or islands of neoplastic cells may contain desquamated cells, nuclear or keratinized debris.

VAGINAL AND CERVICAL NEOPLASMS OF NON-EPITHELIAL OR UNDETERMINED ORIGIN

Vaginal Polyp (Figure 62)

Vaginal polyps are composed of normal or hyperplastic squamous epithelium overlying a dense prominent fibromuscular core. The overlying squamous epithelium may have focal areas of hyperkeratosis. Mitotic figures may be present. The cells do not show infiltrative growth into the underlying stroma.

Granular Cell Tumor, vagina & cervix (Figures 63 & 64)

Granular cell tumors consist of round large tumor cells with granular pale eosinophilic cytoplasm. The cytoplasm of the neoplastic cells contain PAS-positive (and Alcian blue-positive) granules. The nuclei of the tumor cells are usually centrally located and are small, round, uniform and hyperchromatic. The cells are within a delicate connective tissue stroma, and are not encapsulated. Tumor cells are rarely infiltrative.

Schwannoma, malignant, cervix (Figures 65 & 66)

(Synonym: neurilemoma)

Schwannomas or neurilemmas are composed of fibrillar tissue arranged in an Antoni type A pattern showing palisaded nuclei with whorls, and knot-like formations resembling Verocay bodies, or an Antoni type B pattern in which neoplastic cells are randomly arranged and are associated with loosely organized stroma that may be cystic. The neoplastic cells must be differentiated from fibrosarcoma, leiomyosarcoma or endometrial stromal sarcoma. The neoplastic cells are positive for S-100 protein.

NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE VAGINA AND CERVIX

Squamous Cell Hyperplasia, vagina (Figure 67)

This proliferative lesion is characterized by increased thickness of the vaginal epithelium that may result in downward projections within the underlying stroma. The thickened squamous epithelial surface may have areas of hyperkeratosis, and mitotic figures are occasionally seen.

Cystic dilation, vaginal fornix

Cystic dilation of the vaginal fornix is seen in older F344 rats, usually older than 20 months of age. These cysts appear grossly as green or yellow nodules, and may be misdiagnosed as a neoplasm. Microscopically, however, one can clearly discern that the nodules are cysts filled with cellular and keratinous debris.

Stromal hypertrophy, cervix (Figure 68)

This lesion is observed most often in aged rats. It is characterized by diffuse increased proliferation of the fibromuscular stroma of the portio vaginalis uteri without architectural distortion. This proliferative lesion should not be confused with leiomyoma or fibroma of the cervix.

NEOPLASTIC LESIONS OF THE OVIDUCT

Papillary Adenoma, oviduct (Figure 69)

Papillary adenomas of the oviduct consist of tumor cells arranged in fronds consisting of slender branching projections supported by a fine fibrovascular stroma. The tumor cells are columnar and the projections of tumor cells extend into the lumen of the oviduct. The epithelial tumor cells usually have basally located, round, uniform hyperchromatic nuclei and mitotic figures are rare.

Carcinoma, oviduct (Figure 70)

Carcinoma of the oviduct consists of neoplastic epithelial cells arranged in papillary fronds consisting of slender branching projections. The tumor cells are columnar, on a fibrovascular stroma, and extend into the lumen of the oviduct. Surrounding tissues such as the peritoneum and adjacent organs may be infiltrated by neoplastic cells. Carcinoma of the oviduct is very rare in rats.

DISCUSSION

Spontaneous neoplasms of the uterus, vagina, cervix and oviduct are uncommon in rats. Endometrial stromal polyps and deciduoma are the two most common proliferative lesions observed in rats at 1 year of age (3). By 2 years of age the incidence of spontaneous endometrial stromal polyp can be as high as 37% in control F344 rats from NTP studies (15).

In older rats, cystic endometrial hyperplasia is common; however, it does not occur at the same frequency as that observed in mice. Cystic endometrial hyperplasia in rats is often diffuse and does not represent a preneoplastic change in the uterine endometrium. This lesion must be differentiated from focal glandular hyperplasia in which cellular atypia is present and is usually seen in response to uterine carcinogens (15). By 24 months of age or older, the incidence of cystic endometrial hyperplasia may range from 10%-19% in the F344, Sprague-Dawley, Wistar

European and Wistar Japan rats (3). In contrast, the incidence of endometrial adenomas and carcinomas in Sprague-Dawley rats at 24 to 28 months of age is usually less than 1%, but in F344 rats up to approximately 2%. This low incidence may be related to the time (usually 24 months of age) at which rats are sacrificed at the end of 2-year carcinogenicity studies. However, when rats are not sacrificed at the end of a 2-year study, by 3 years of life, it has been reported that in the Han:Wistar rat the incidence of uterine adenocarcinoma for a lifetime study was 39%; whereas, the incidence of uterine adenocarcinomas observed in rats in this same study sacrificed at two years was 5.2% (7).

Many of the uncommon tumors such as choriocarcinoma, yolk sac carcinoma, teratoma and embryonal carcinoma observed in the uterus of rats have been experimentally induced, or occur rarely as spontaneous tumors (15,25-28). Spontaneously occurring yolk sac carcinomas have been reported in the uterus of mice (31); however, the spontaneous occurrence of this tumor is rare in rats, although they are readily inducible experimentally (26). Malignant mixed müllerian tumors of the uterus have been described to occur spontaneously in the Lewis rat (14).

Squamous cell carcinoma can be often induced in the uterus, vagina and cervix of rats in response to chemical carcinogens; however, this tumor rarely occurs spontaneously. In the case of primary squamous cell carcinoma of the uterus, metastasis from the cervix or vagina must be ruled out.

Mesenchymal tumors of vascular, smooth muscle or fibrous origin are uncommon in the uterus, vagina, cervix and oviduct of rats. The F344/N rat, a strain commonly used in long-term toxicology/carcinogenesis studies, has a low incidence of leiomyomas and leiomyosarcomas with incidences in two-year studies less than 0.1% for both tumor types, and 0.4% and 0.6%, respectively, in life span studies (10, 29).

Spontaneous proliferative lesions of the oviducts in rats are extremely rare. Chemically induced carcinomas of the fallopian tube have been described in rats (22).

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA FOR NEOPLASTIC AND NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE UTERUS, VAGINA, CERVIX AND OVIDUCT IN RATS

EPITHELIAL NEOPLASMS OF THE UTERUS

Endometrial Adenoma

1. Solitary and well-delineated, often with

- compression of adjacent tissue
2. May be exophytic and papillary, or endophytic and glandular (tubular)
3. Epithelium usually a single layer of cuboidal to columnar epithelial cells
4. Cells are well or moderately well differentiated
5. Proliferation of decidual stroma may be present focally

Endometrial Adenocarcinoma

1. Poorly circumscribed and often invasive
2. Epithelium may be arranged in glandular (tubular) structures, papillary fronds, or a combination
3. Epithelium may range from moderately well differentiated to undifferentiated
4. Squamous differentiation may be present
5. Cells are usually columnar to tall cuboidal with abundant eosinophilic cytoplasm and large vesicular nuclei
6. Neoplastic cells may form two or more layers of tubules or papillary fronds
7. Scirrhous reaction may be present
8. Decidual stroma may be present focally
9. Metastasis most often to the lung

Squamous Cell Carcinoma

1. Large masses involving the uterine horn or body of the uterus.
2. Epithelium may be arranged in nests and cords.
3. Cells are large and polygonal with abundant eosinophilic cytoplasm and prominent vesicular nuclei
4. Areas of kerationization or keratinic debris may be present
5. Stroma may be scant, or may be abundant (scirrhous reaction)
6. May be locally invasive
7. Must differentiate from squamous cell carcinoma of cervical or vaginal origin

UTERINE NEOPLASMS OF NONEPITHELIAL OR UNDETERMINED ORIGIN

Teratoma

(Synonyms: *benign teratoma, mature teratoma*)

1. Usually well-encapsulated
2. Composed of mature derivatives of endodermal, ectodermal and mesodermal germ layers
3. Endodermal cysts lined by columnar and goblet-type epithelium resembling intestinal villi
4. Pancreatic tissue with islets of Langerhans are common

5. A range of other tissue-types may be seen

Mixed Müllerian Tumor, Malignant

(Synonyms: *carcinosarcoma, mixed mesodermal tumor, malignant*)

1. Polypoid, but show evidence of local invasion
2. Composed of epithelial and mesenchymal elements
3. Highly infiltrative growth
4. The epithelial structures consist of glands of squamous anaplastic epithelium
5. The mesenchymal part of the tumor is subdivided into homologous and heterologous types
6. Benign variant is composed of well-differentiated epithelial and mesenchymal components

Embryonal Carcinoma

(Synonym: *undifferentiated malignant teratoma*)

1. Poorly differentiated round or fusiform cells
2. Yolk sac carcinoma may be present in these tumors
3. Areas of well-differentiated bone, cartilage or skin may be present

Choriocarcinoma

(Synonyms: *chorioncarcinoma, chorionepithelioma*)

1. Small round cells resembling cytotrophoblasts and giant cells with multiple or single large nuclei
2. Cells are between areas of hemorrhage and necrosis
3. Infiltrates myometrium

Yolk Sac Carcinoma

(Synonyms: *endodermal sinus tumor, yolk sac tumor*)

1. Rosettes, nests, cords, or papillary structures of neoplastic cells
2. Hyalinized eosinophilic, PAS-positive extracellular matrix
3. Cytoplasm of neoplastic cells is finely vacuolated and may contain droplets of hyaline material similar to the extracellular matrix

Endometrial Stromal Polyp

1. Solitary or multiple
2. Sessile or on a long stalk
3. Predominantly loosely arranged endometrial stromal cells with blood vessels and a few entrapped glands
4. Glands are lined by low cuboidal epithelium and may be multiple and cystic
5. Surface epithelium is usually low cuboidal, however, squamous metaplasia, hyperplasia, inflammation, or ulceration may be present
6. Stroma may become edematous or infarcted
7. Decidual alteration may be focal

Endometrial Stromal Sarcoma

1. Cells are pleomorphic with indistinct cell borders and slightly spindle-shaped

2. May arise in a stromal polyp
3. Larger tumors invade the uterine wall, often with necrosis
4. Invasion into adjacent tissues may occur

Leiomyoma

1. Myometrial nodule that may show compression of the endometrium and adjacent normal myometrium
2. Well-differentiated smooth muscle cells arranged in interlacing bundles
3. Cytoplasm is eosinophilic and fibrillar with indistinct cell boundaries
4. Collagen is present in variable amounts between the bundles of muscle fibers and individual cells
5. Nuclei are elongated with rounded ends and may have aggregated chromatin near the nuclear membrane and occasionally a prominent nucleolus
6. Mitotic figures are rare

Leiomyosarcoma

1. Large with ill-defined borders
2. Minimal pattern of interlacing muscle fiber bundles
3. May be hypercellular
4. Nuclei and cytoplasm may vary in size and shape, from elongated to round to oval
5. Numerous mitotic figures
6. Fibrosis and necrosis are common

Schwannoma, Malignant

See description of schwannoma (malignant) of the cervix.

Fibroma

1. Well-differentiated fibroblasts within an abundant collagenous stroma
2. Cells are arranged in broad, streaming interlacing bundles
3. Blood vessels are not prominent
4. Cells are spindle shaped with eosinophilic cytoplasm and single elongated nucleus with inconspicuous nucleoli
5. Rare mitotic figures

Fibrosarcoma

1. Haphazard bundles of pleomorphic cells ranging from round to oval to plump spindle cells
2. Collagen may or may not be present
3. Marked variation in nuclear size and shape
4. Giant cells occasionally present
5. Numerous mitotic figures
6. Usually infiltrate adjacent myometrium or endometrium

Hemangioma

1. Vascular channels that vary in size but are

- often the size of normal capillaries
- 2. Endothelium resembles normal endothelium
- 3. Are most common in the endometrium, although they may be present at any site within the uterus

Hemangiosarcoma

- 1. Cavernous and/or capillary-size, irregular vascular spaces
- 2. Spaces are lined by plump, elongated, anaplastic, endothelium whose nuclei and cytoplasm tend to bulge into the vascular space lumen
- 3. Nuclei are large and hyperchromatic
- 4. Mitotic figures are often present
- 5. Hemorrhage, necrosis and thrombosis may be present

NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE UTERUS

Endometrial Hyperplasia

- 1. Early, endometrial stroma is edematous and endometrial glands are enlarged and more numerous
- 2. Glandular epithelium is usually columnar to tall cuboidal, and hyperplastic
- 3. Mitotic figures are common
- 4. Glandular epithelium may become low columnar or cuboidal, and hypocellular
- 5. Endometrial stroma may become dense and contain increased collagen
- 6. Inflammatory cell infiltrates may be present, but minimal
- 7. No invasion of adjacent myometrium

Focal Glandular Hyperplasia

- 1. Focal proliferation of glands lined by enlarged columnar epithelial cells
- 2. Glandular epithelium have abundant eosinophilic cytoplasm, and large round vesicular nuclei with prominent nucleoli
- 3. Pleomorphism and atypia may be present
- 4. Glandular architecture and uniformity may be lost, and lumens may not be obvious

Hyperplasia of the Endometrial Stroma

- 1. Increased cellularity of the endometrium consisting of spindle-shaped stromal cells
- 2. Usually not associated with proliferation of glandular epithelium

Deciduoma

- 1. Occurs in young rats
- 2. Composed of cells with variable appearances: "mesometrial cells," "glycogenic cells," "decidual cells," and "capsule cells"

Decidual Reaction

- 1. Occurs in older rats usually as part of another lesion such as endometrial stromal polyp.
- 2. Consists of large, eosinophilic cells resembling the decidual cells of the true deciduoma

Adenomyosis

- 1. Well-differentiated endometrial glands are present in the myometrium and sometimes extend to the serosa
- 2. Glands may be surrounded by endometrial stroma
- 3. Epithelium may have mitotic figures; however, atypia is not present

VAGINAL AND CERVICAL NEOPLASMS OF EPITHELIAL ORIGIN

Squamous Cell Papilloma, vagina

- 1. Composed of extensions of neoplastic squamous epithelial cells supported by a moderately dense fibrovascular core
- 2. The tumors usually arise from the surface epithelium of the cervix or vagina and show an exophytic growth pattern
- 3. Tumor cells are not infiltrative and do not invade into the underlying stroma

Squamous Cell Carcinoma, vagina

- 1. Consist of cords, islands or nests of anaplastic squamous epithelium showing downward growth into the underlying stroma

VAGINAL AND CERVICAL NEOPLASMS OF NON-EPITHELIAL OR UNDETERMINED ORIGIN

Vaginal Polyp

- 1. Squamous epithelium overlying a dense, prominent, fibromuscular core
- 2. Epithelium may have focal areas of hyperkeratosis
- 3. No infiltration of stroma

Granular Cell Tumor, vagina and cervix

- 1. Consists of round, large cells with granular pale eosinophilic cytoplasm
- 2. Cells contain PAS-positive (and Alcian blue-positive) cytoplasmic granules
- 3. Cells are within a delicate connective tissue stroma, however tumor is not encapsulated
- 4. The tumors are rarely infiltrative

Schwannoma, malignant, cervix

(Synonym: neurilemoma)

- 1. Antoni type A pattern with whorls, knotty, and rope-like formations resembling Verocay bodies
- 2. Antoni type B pattern with areas of cystic, loosely organized tissue, with haphazardly

arranged neoplastic cells

3. Foam (xanthoma) cells, mitotic figures, and/or giant cells may be present

NON-NEOPLASTIC PROLIFERATIVE LESIONS OF THE VAGINA AND CERVIX

Squamous Cell Hyperplasia, vagina

1. Characterized by increased thickness of the vaginal epithelium
2. May result in downward projections within the underlying stroma
3. The thickened squamous epithelial surface may have areas of hyperkeratosis
4. Mitotic figures are occasionally seen

Stromal Hypertrophy of the cervix

1. Hypertrophy of the fibromuscular stroma of the portio vaginalis uteri with no distortion

NEOPLASMS OF THE OVIDUCT

Papillary Adenoma, oviduct

1. Epithelial cells arranged in papillary fronds consisting of slender branching projections
2. Cells are columnar, on a fibrovascular stroma, and extend into the lumen of the oviduct
3. Epithelial cells usually have basally located round, uniform hyperchromatic nuclei
4. Mitotic figures are rare

Carcinoma, oviduct

1. Epithelial cells arranged in papillary fronds consisting of slender branching projections
2. Cells are columnar, on a fibrovascular stroma, and extend into the lumen of the oviduct
3. Surrounding tissues such as the peritoneum and adjacent organs may be infiltrated
4. Very rare

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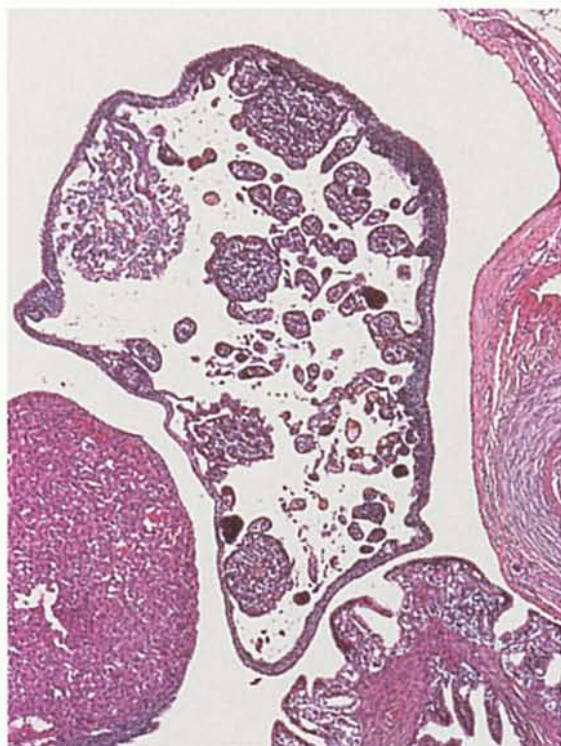


Fig. 1 - Cystadenoma, ovary.

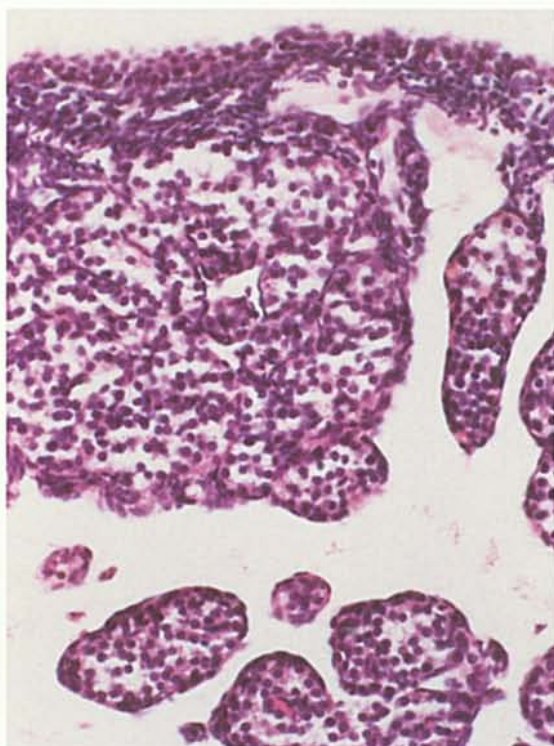


Fig. 2 - Higher magnification of Figure 1.

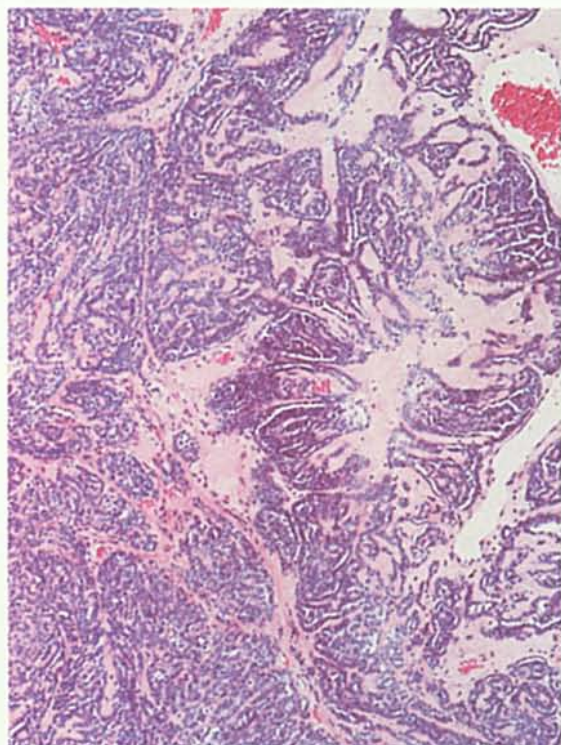


Fig. 3 - Cystadenocarcinoma, ovary.

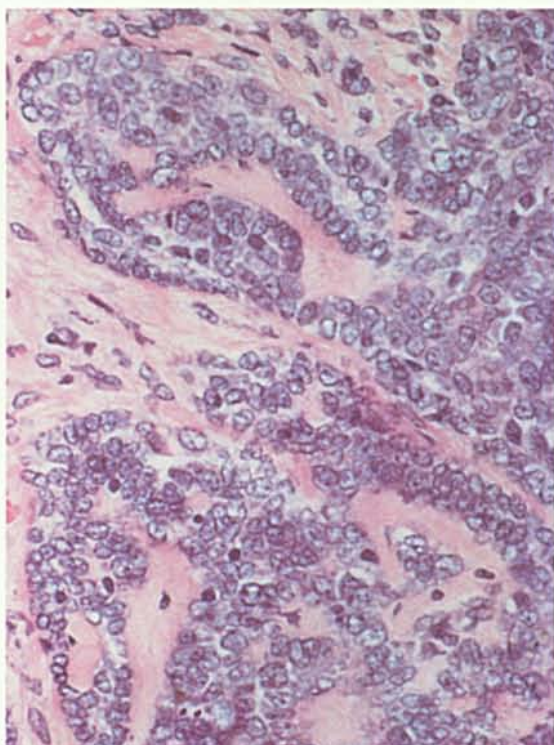


Fig. 4 - Higher magnification of Figure 3.

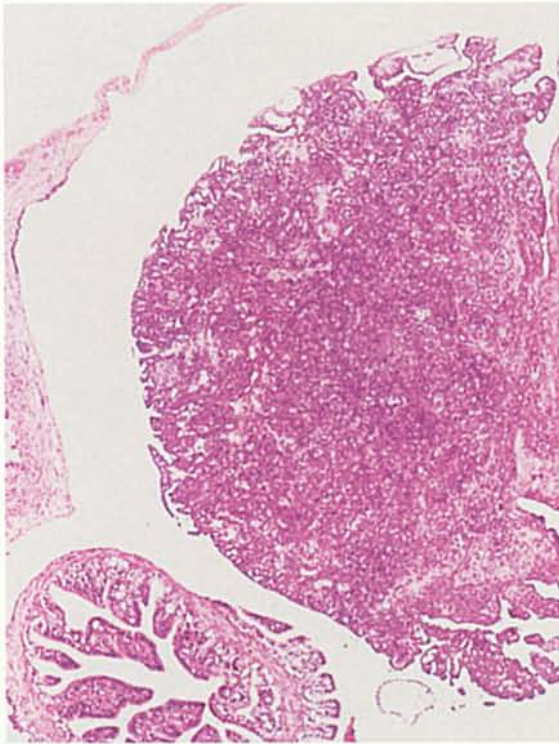


Fig. 5 - Tubulostromal adenoma, ovary.

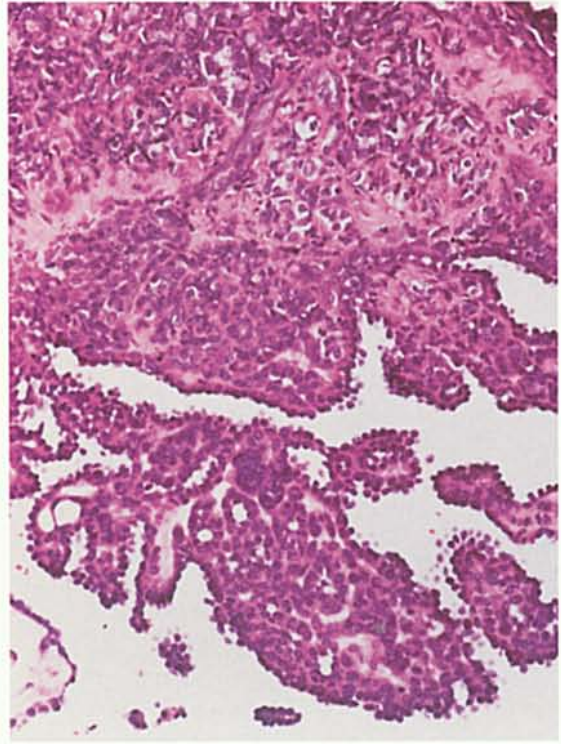


Fig. 6 - Higher magnification of Figure 5.

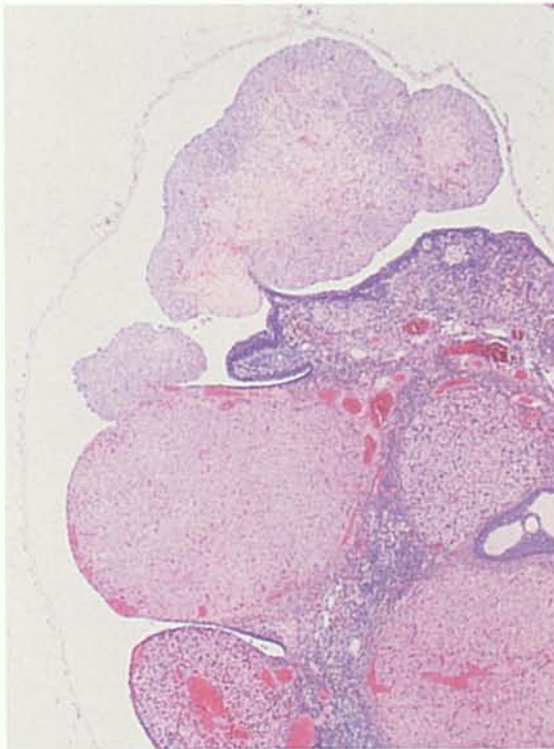


Fig. 7 - Mesothelioma, ovary.

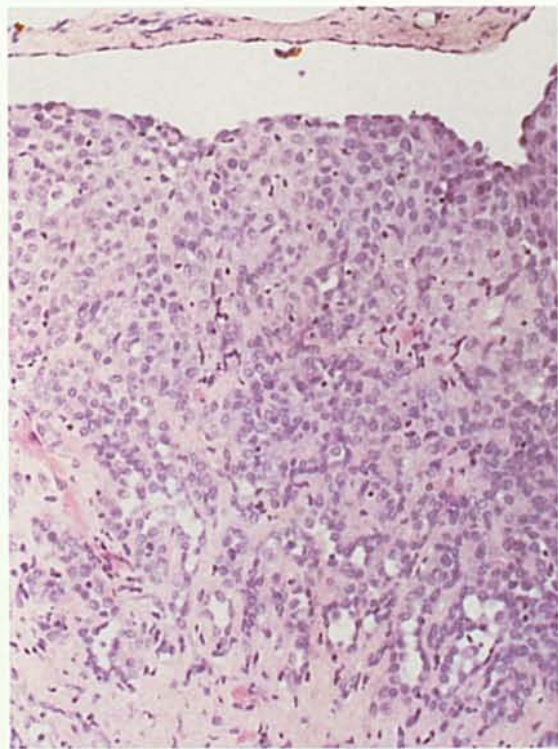


Fig. 8 - Higher magnification of Figure 7.

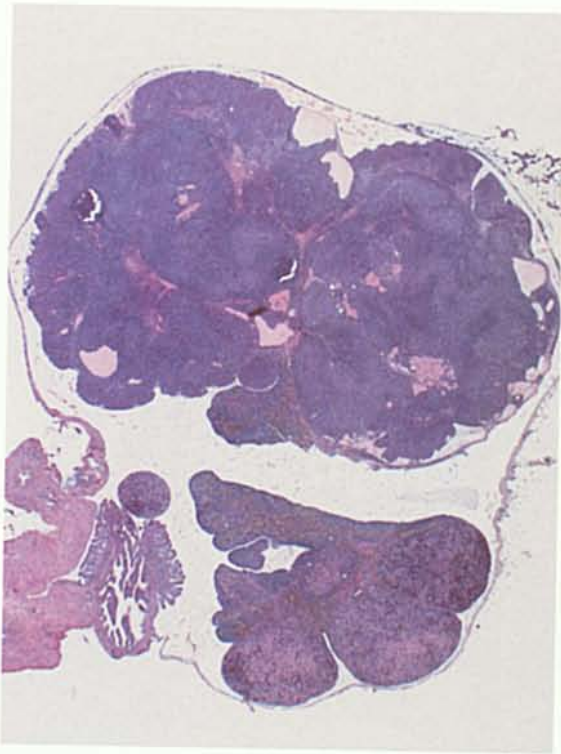


Fig. 9 - Granulosa cell tumor, ovary.

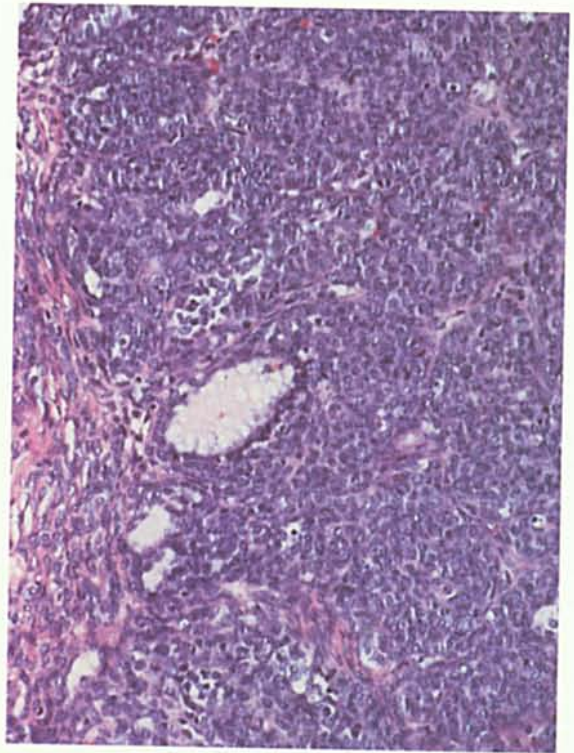


Fig. 10 - Higher magnification of Figure 9.



Fig. 11 - Malignant granulosa cell tumor, ovary.

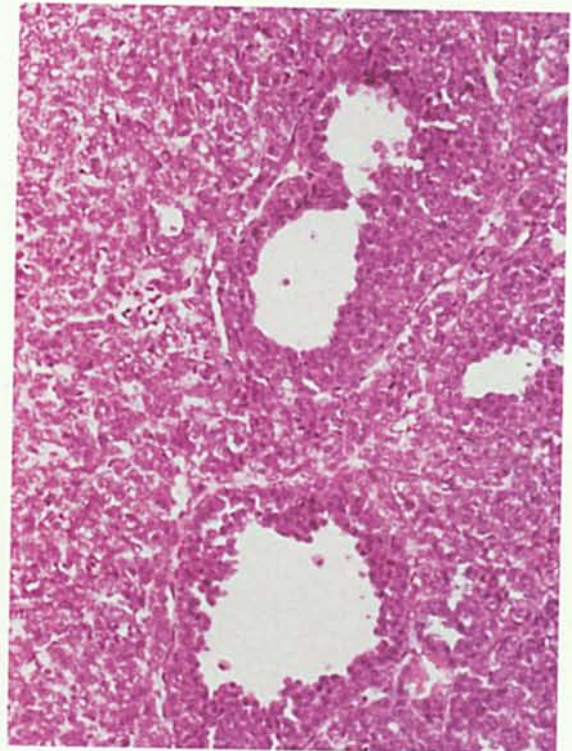


Fig. 12 - Higher magnification of Figure 11.

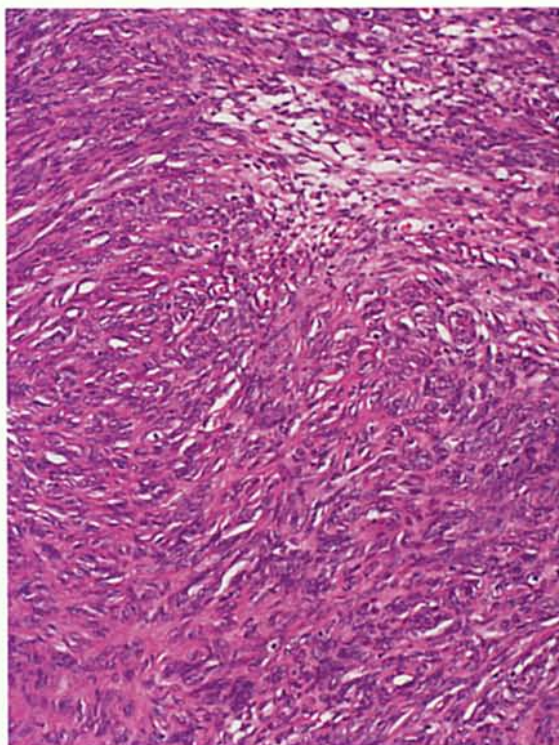


Fig. 13 - Thecoma, ovary.

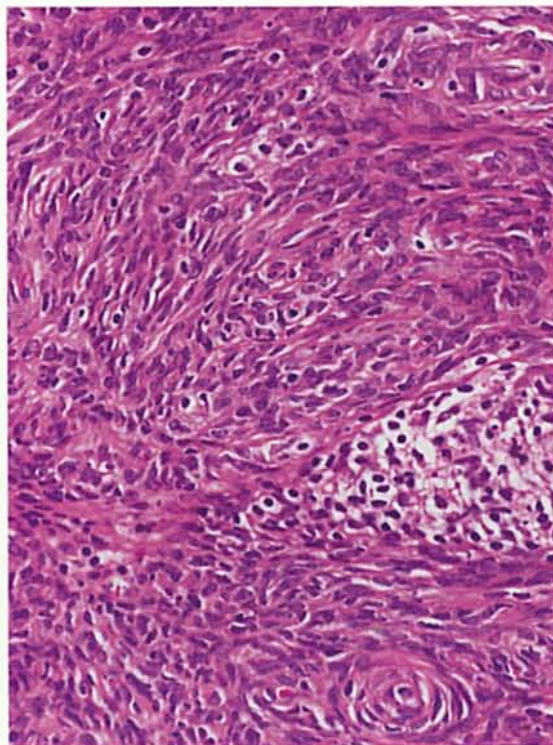


Fig. 14 - Thecoma, ovary.

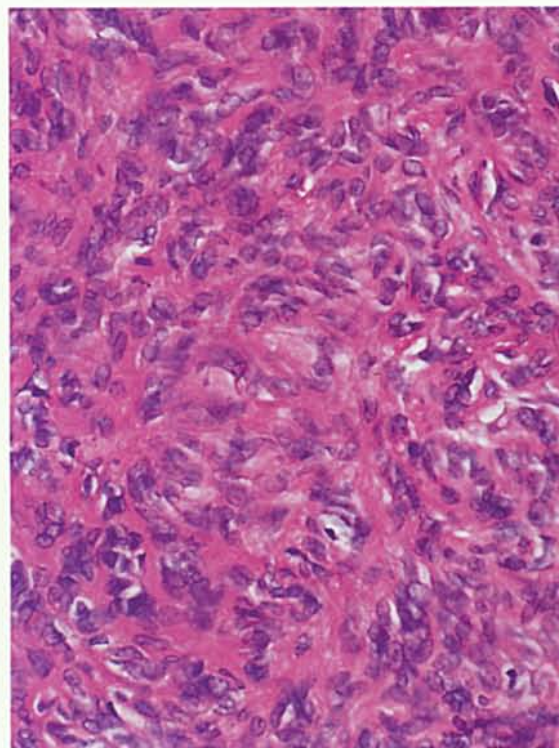


Fig. 15 - Thecoma, ovary.

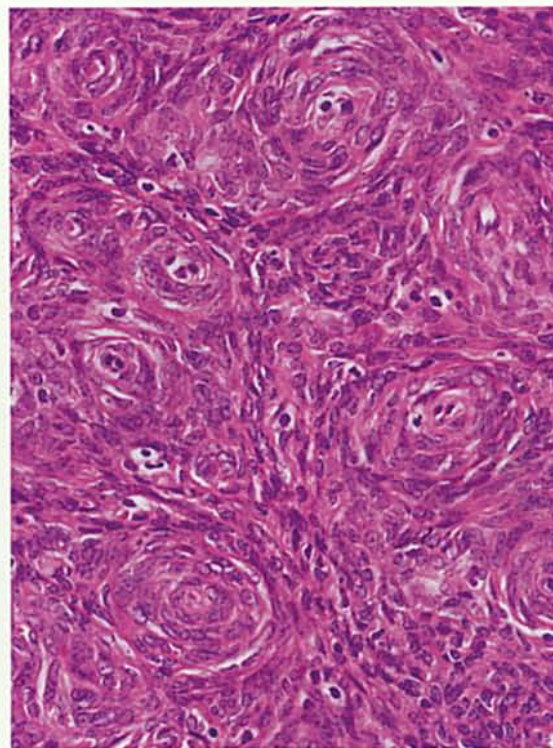


Fig. 16 - Thecoma, ovary.

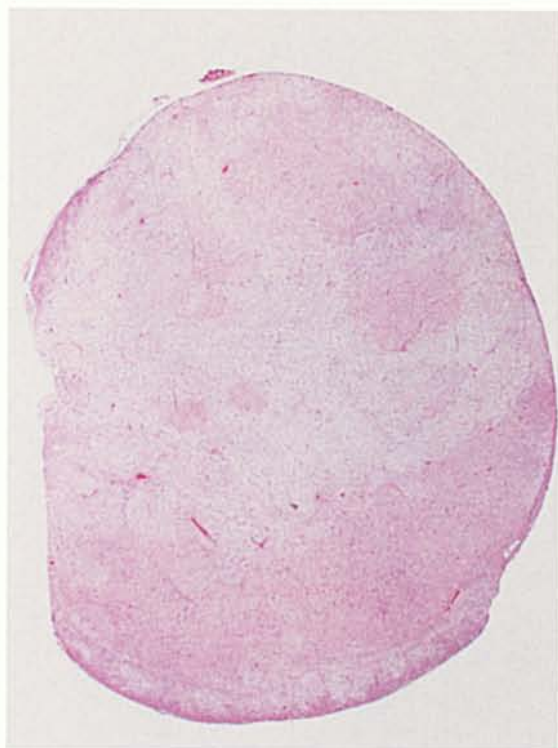


Fig. 17 - Luteoma, ovary.

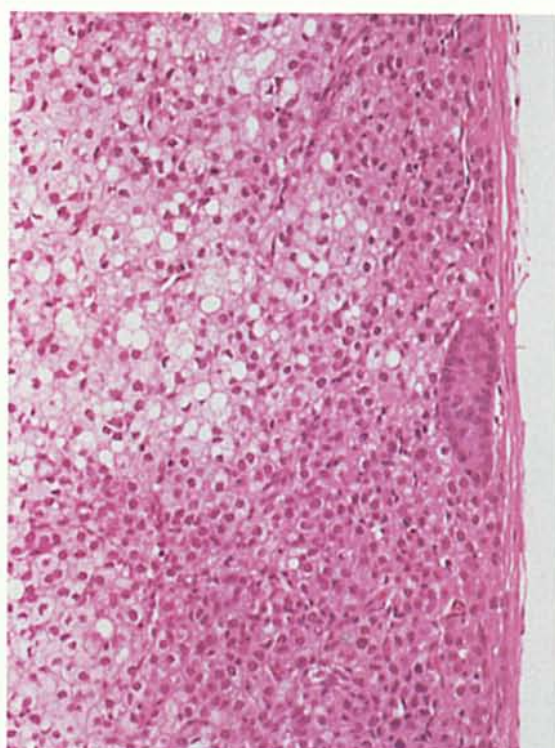


Fig. 18 - Luteoma, ovary.

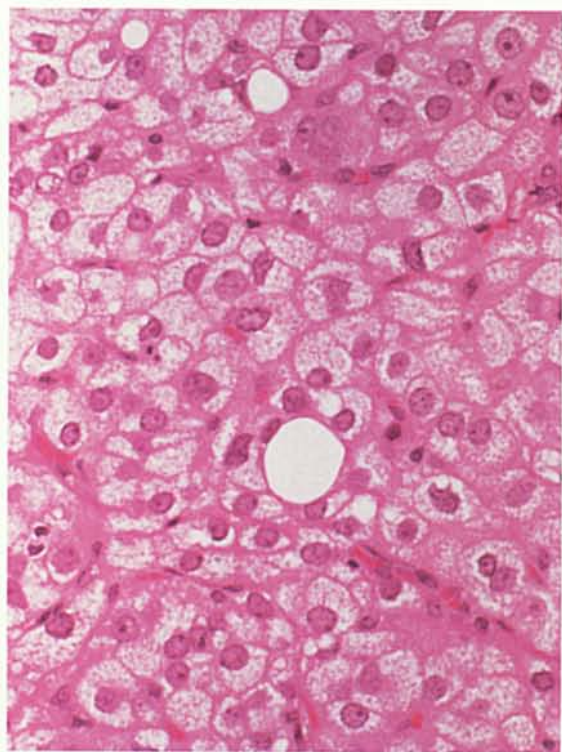


Fig. 19 - Higher magnification of Figure 18.

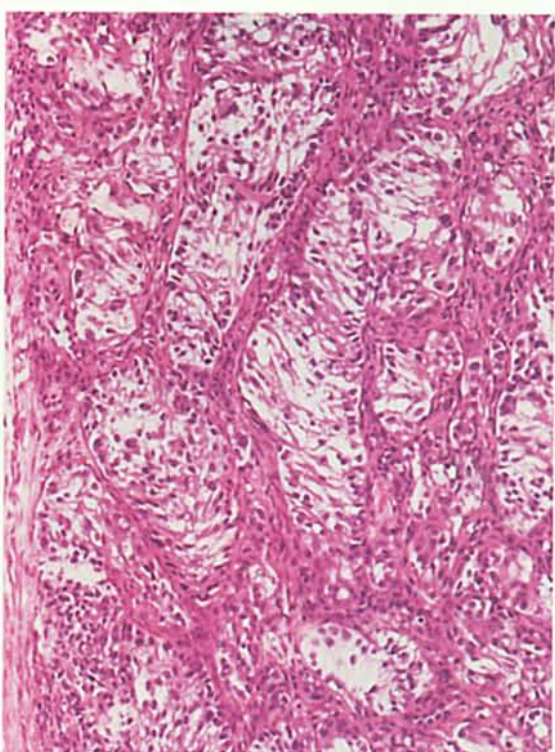


Fig. 20 - Sertoli's cell tumor, ovary.

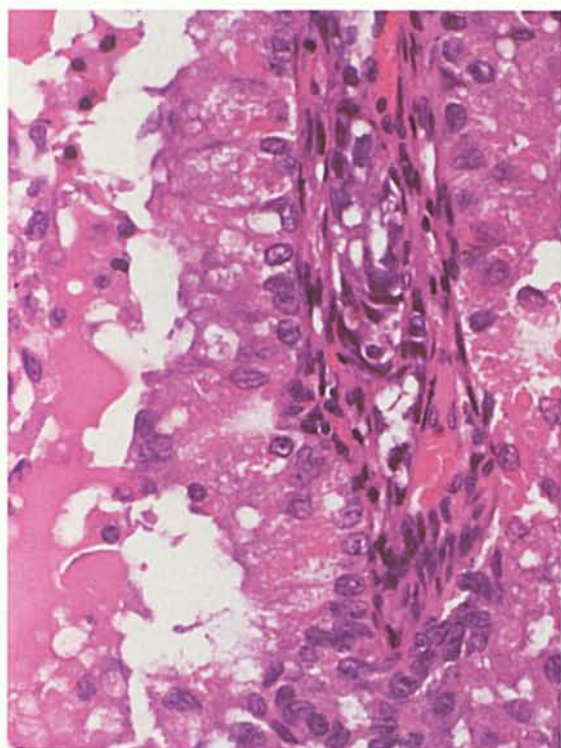


Fig. 21 - Sertoli's cell tumor, ovary.

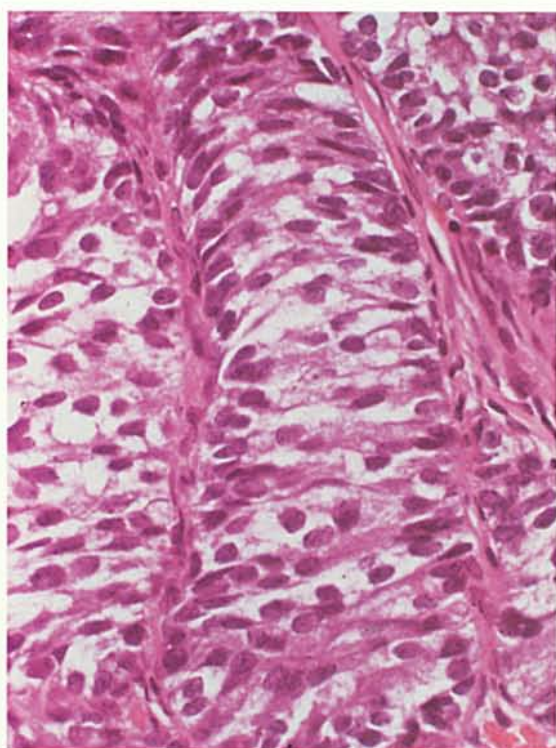


Fig. 22 - Sertoli's cell tumor, ovary.

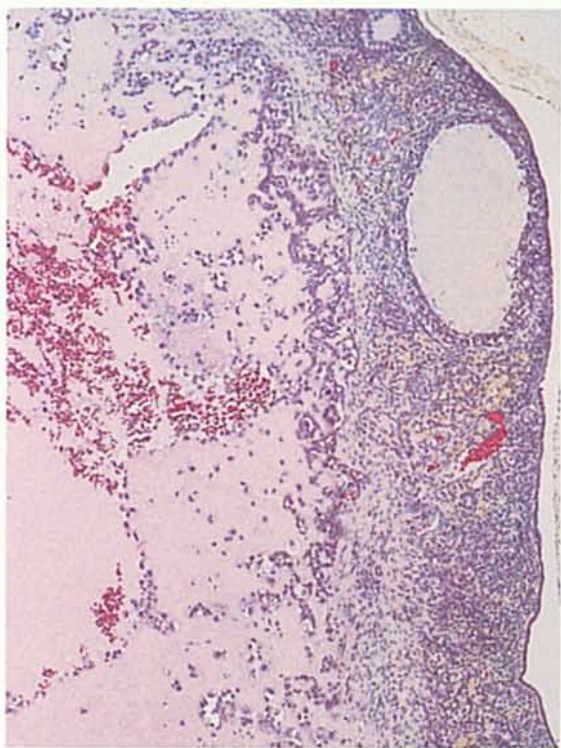


Fig. 23 - Yolk sac carcinoma, ovary.

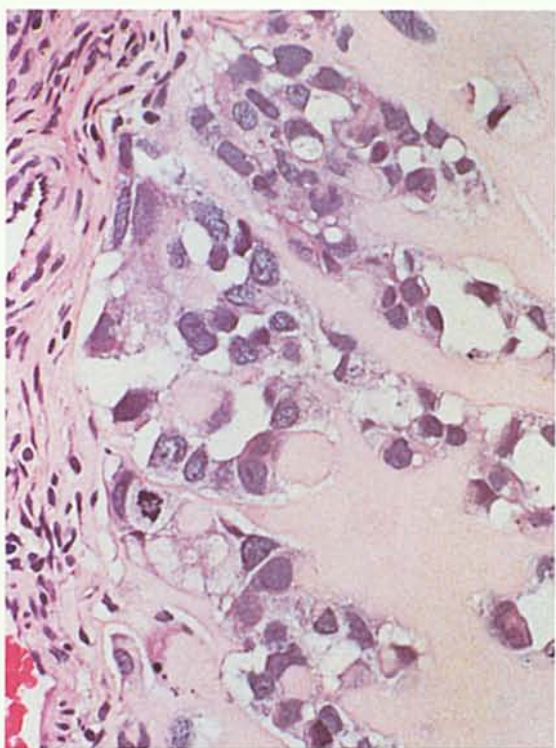


Fig. 24 - Higher magnification of Figure 23.



Fig. 25 - Yolk sac carcinoma, ovary.

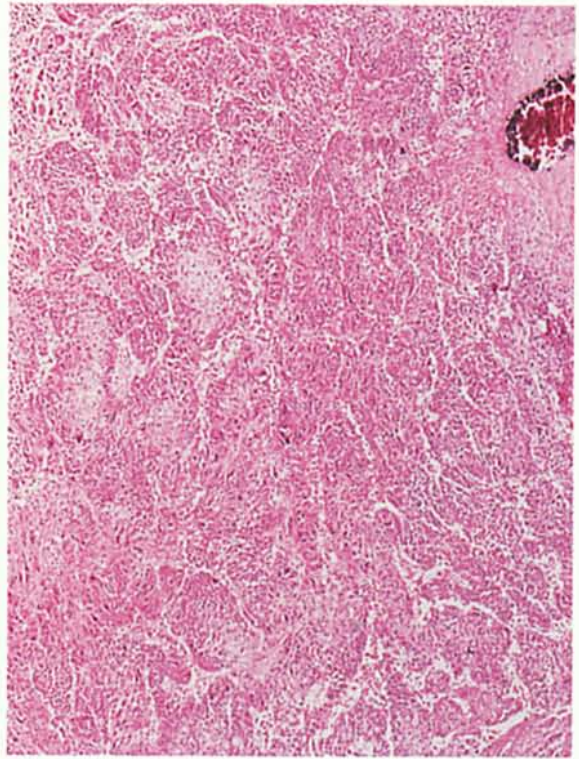


Fig. 26 - Choriocarcinoma, ovary.

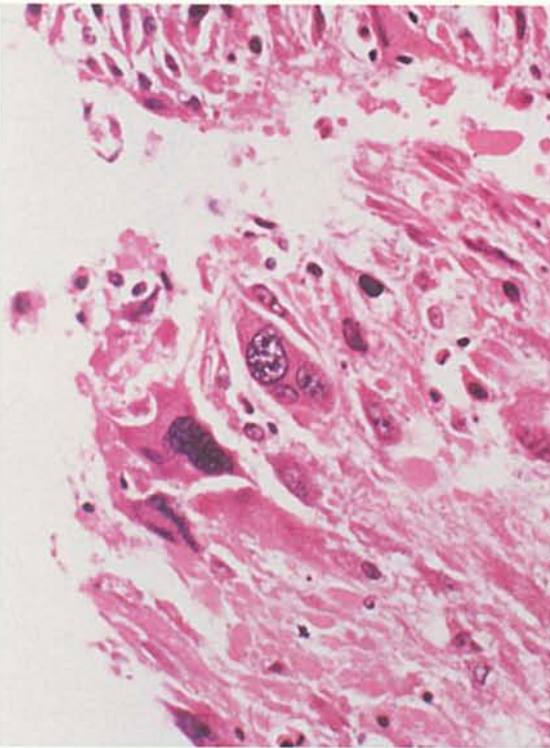


Fig. 27 - Higher magnification of Figure 26.

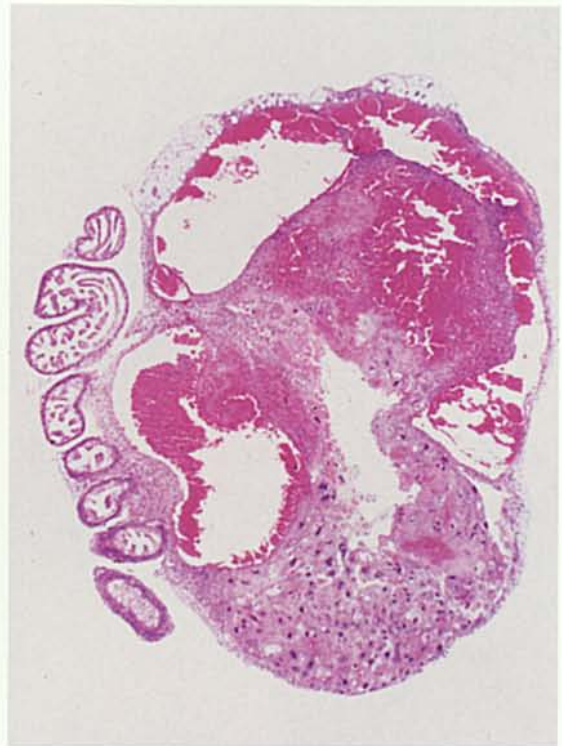


Fig. 28 - Choriocarcinoma, ovary.

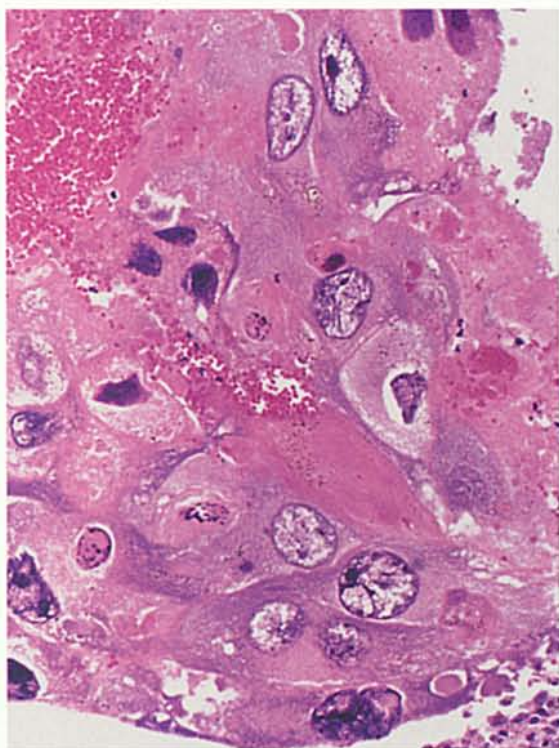


Fig. 29 - Higher magnification of Figure 28.

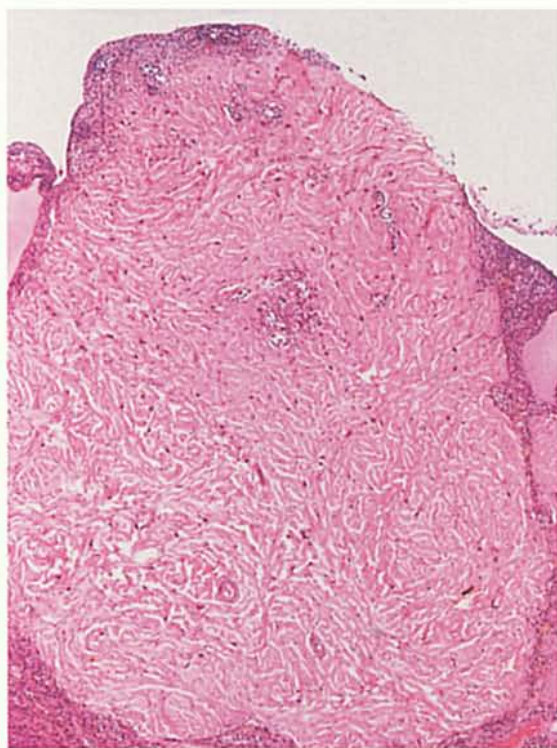


Fig. 30 - Fibroma, ovary.

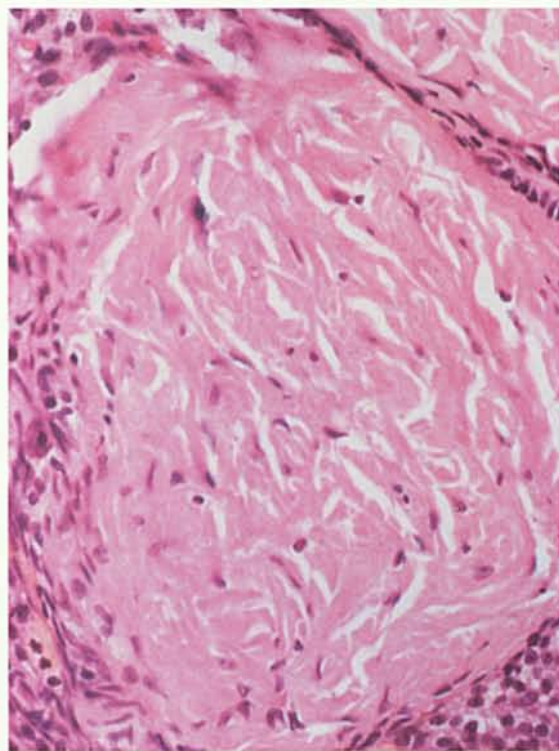


Fig. 31 - Higher magnification of Figure 30.

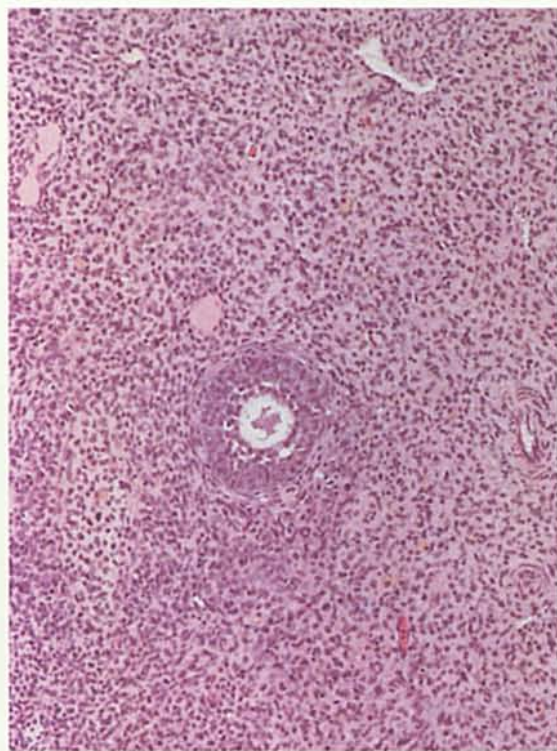


Fig. 32 - Histiocytic sarcoma, ovary.

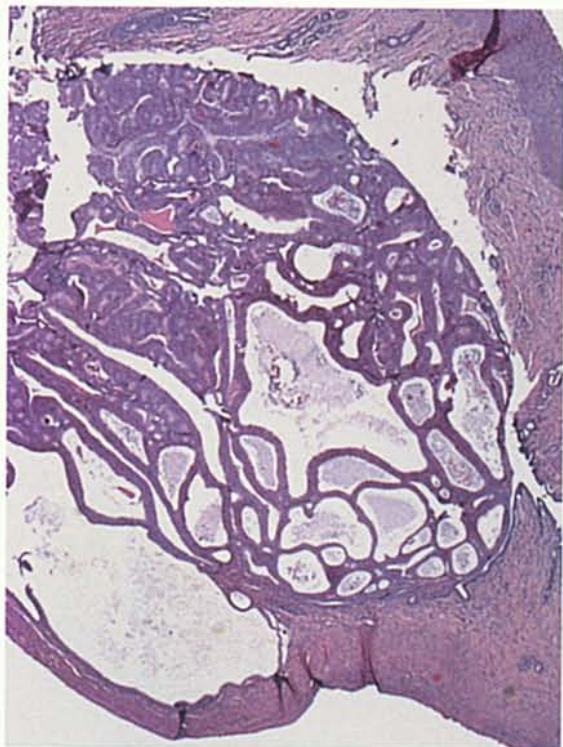


Fig. 33 - Endometrial adenoma, uterus.

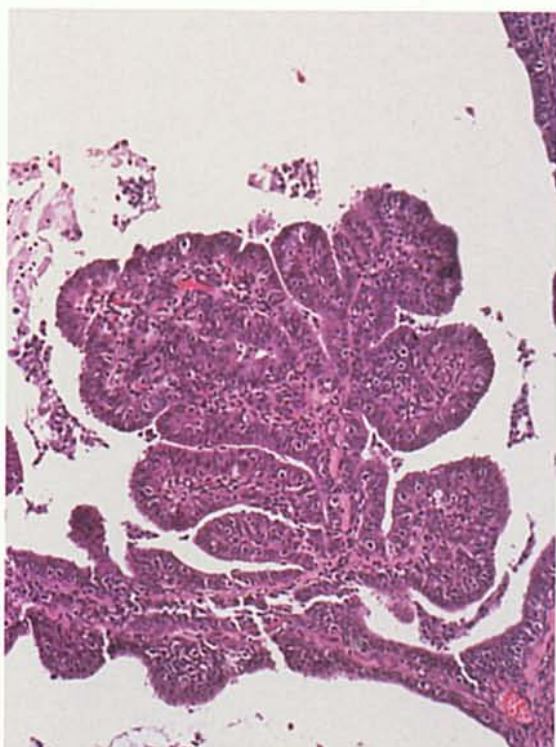


Fig. 34 - Higher magnification of endometrial epithelial cells forming papillary structures.

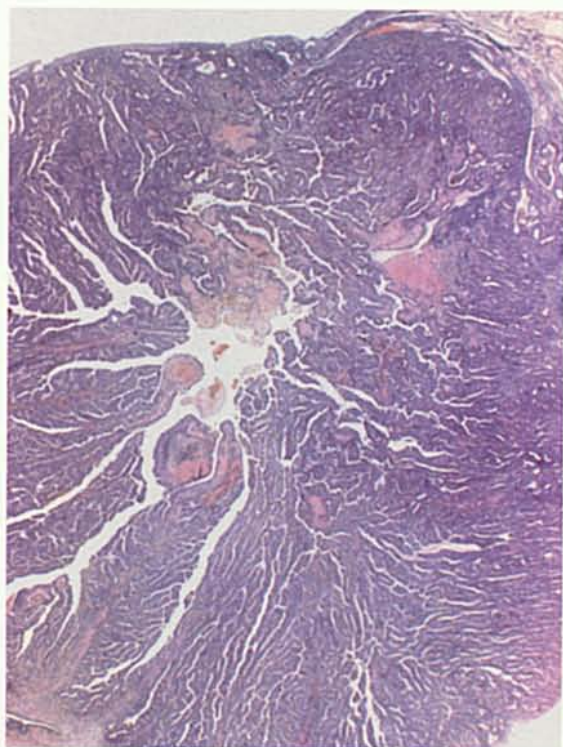


Fig. 35 - Endometrial adenocarcinoma, uterus.

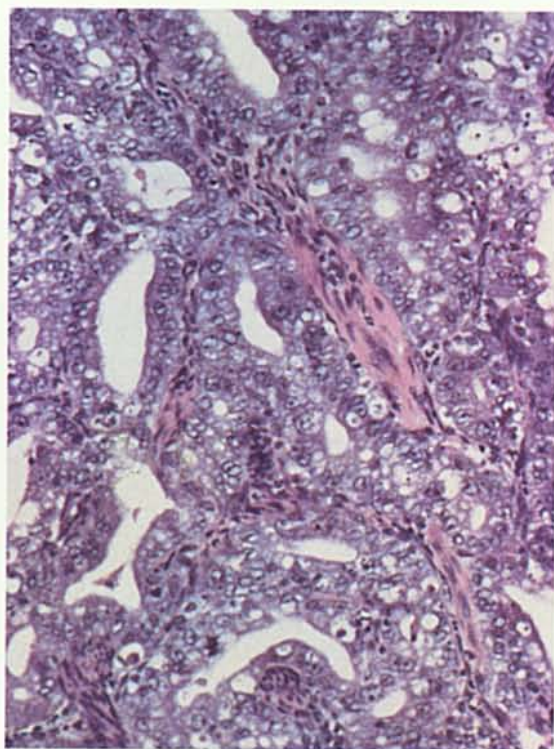


Fig. 36 - Higher magnification of Figure 35.



Fig. 37 - Endometrial adenocarcinoma with invasion into the adjacent myometrium and serosa.

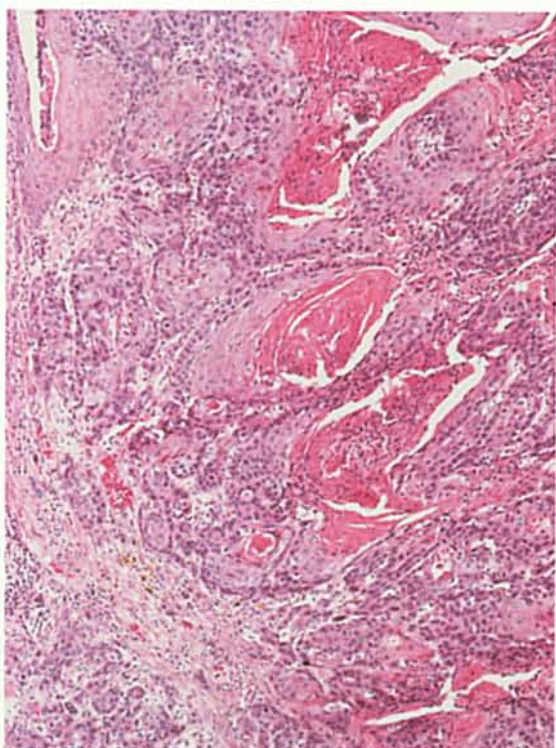


Fig. 38 - Squamous cell carcinoma, uterus.

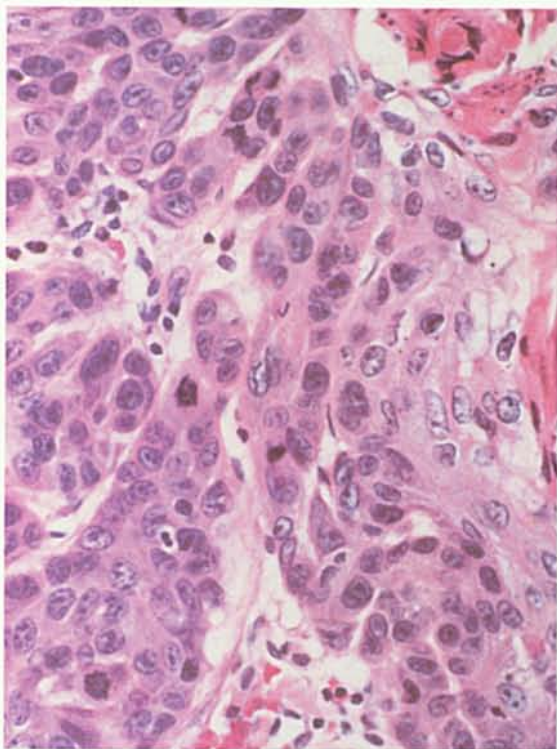


Fig. 39 - Higher magnification of Figure 38.



Fig. 40 - Yolk sac carcinoma, uterus.

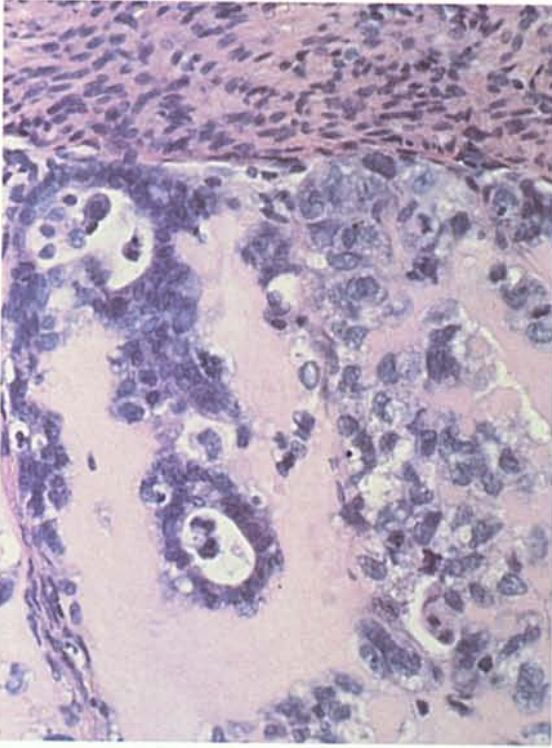


Fig. 41 - Higher magnification of Figure 40.

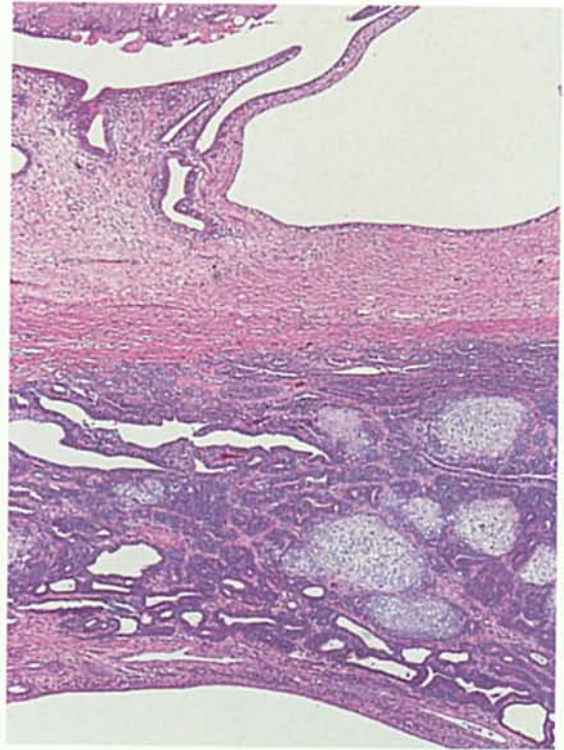


Fig. 42 - Mixed müllerian tumor, malignant, uterus.

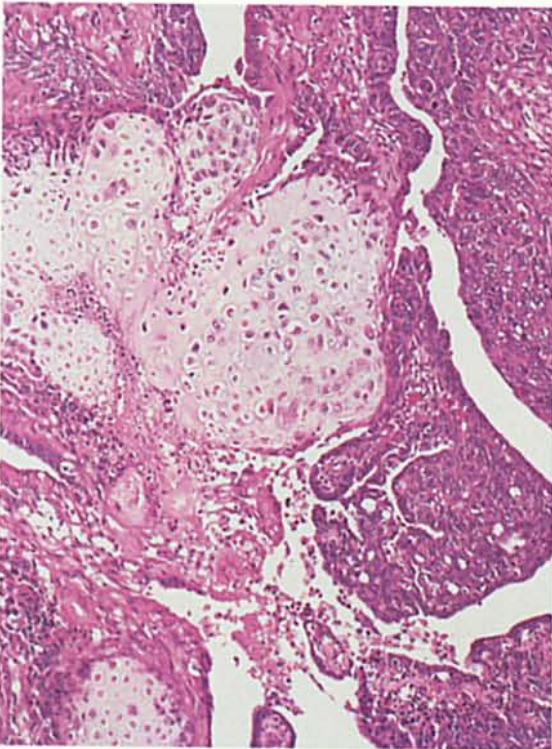


Fig. 43 - Mixed müllerian tumor, malignant, uterus.

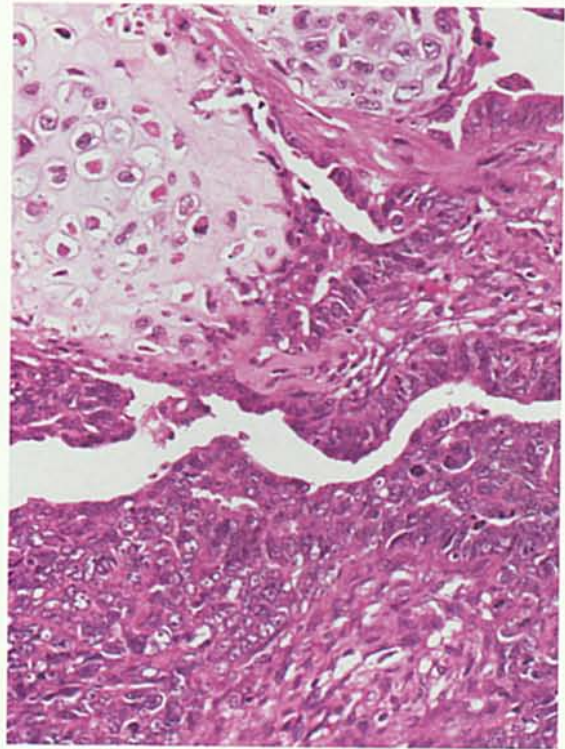


Fig. 44 - Mixed müllerian tumor, malignant, uterus.

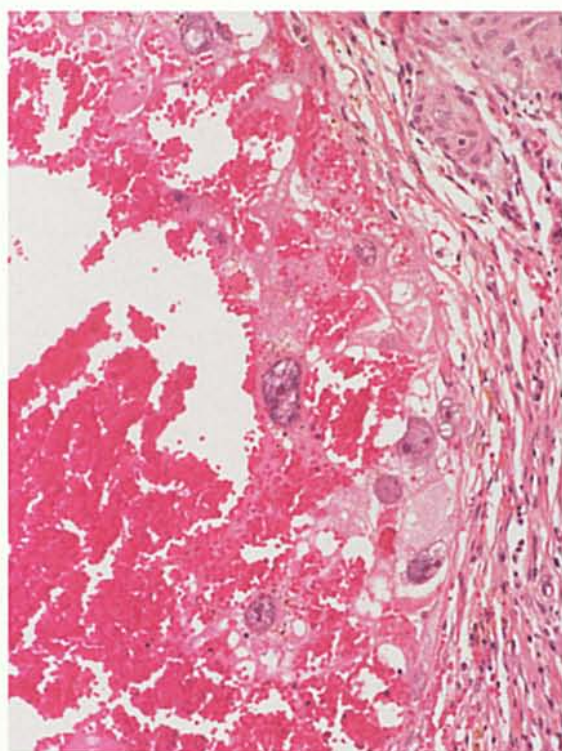


Fig. 45 - Choriocarcinoma, uterus.



Fig. 46 - Stromal polyp, uterus.



Fig. 47 - Stromal polyp, uterus.

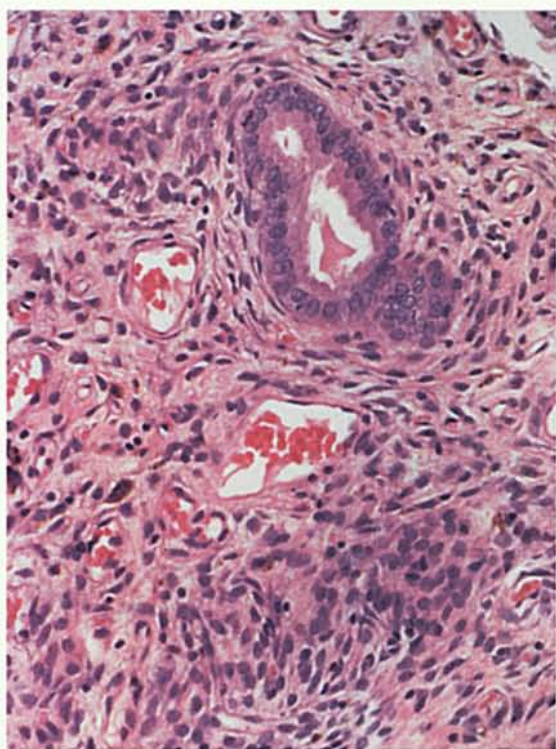


Fig. 48 - Higher magnification of Figure 47.

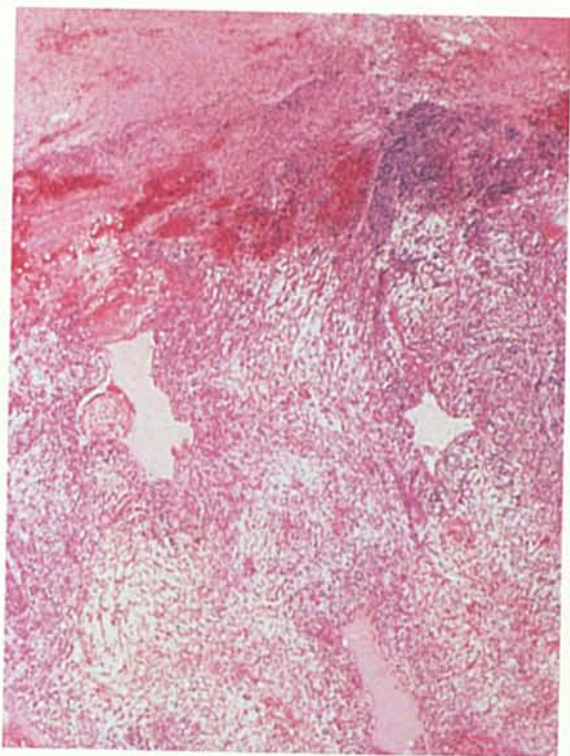


Fig. 49 - Endometrial stromal sarcoma, uterus.

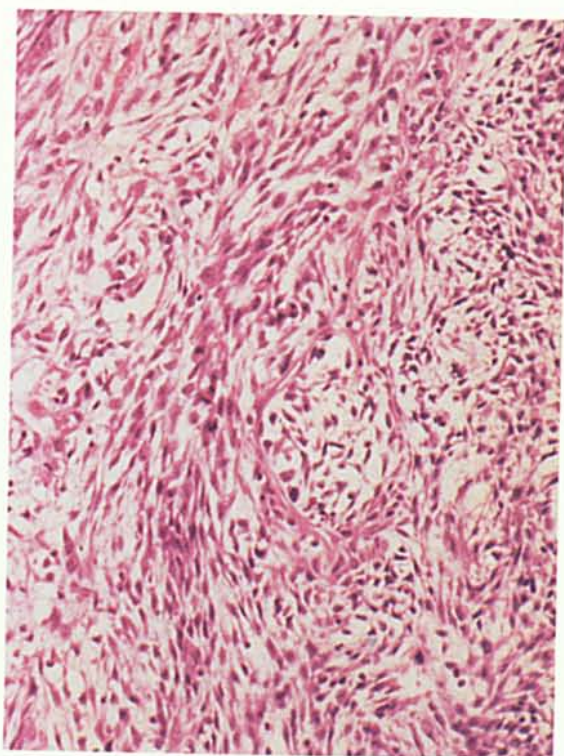


Fig. 50 - Endometrial stromal sarcoma, uterus.

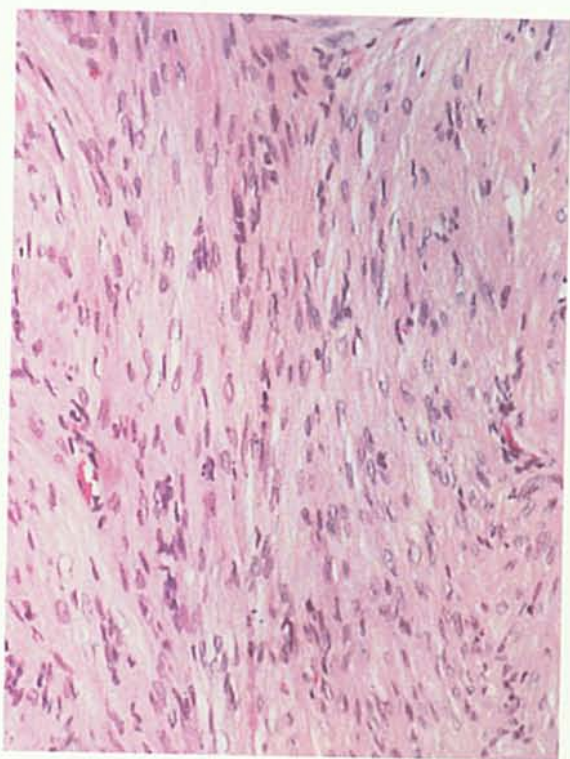


Fig. 51 - Leiomyoma, uterus.

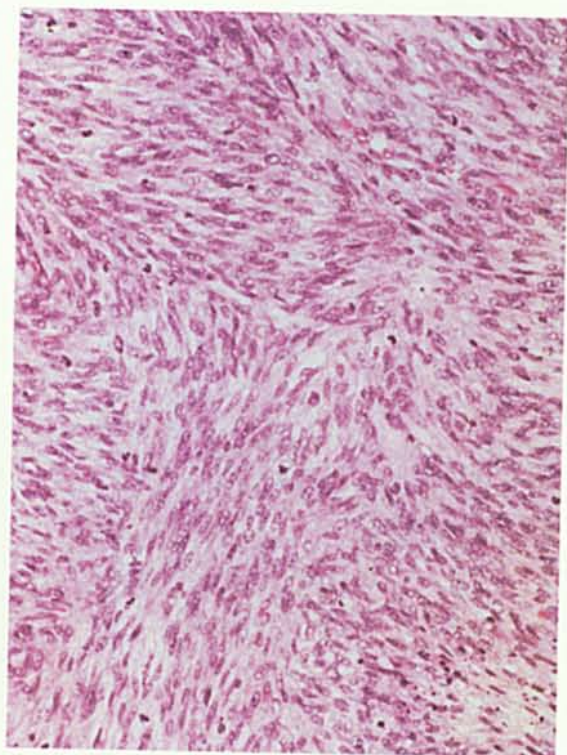


Fig. 52 - Leiomyosarcoma, uterus.



Fig. 53 - Endometrial hyperplasia, cystic, uterus.

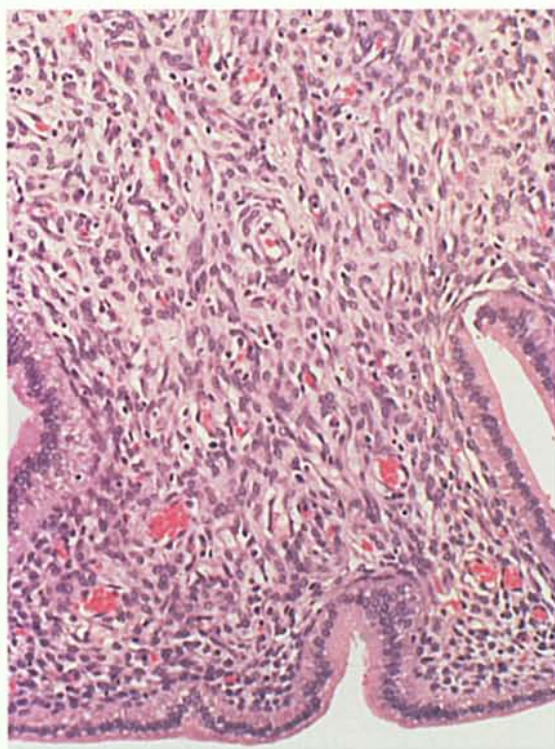


Fig. 54 - Hyperplasia of the endometrial stroma, uterus.



Fig. 55 - Deciduoma, uterus.

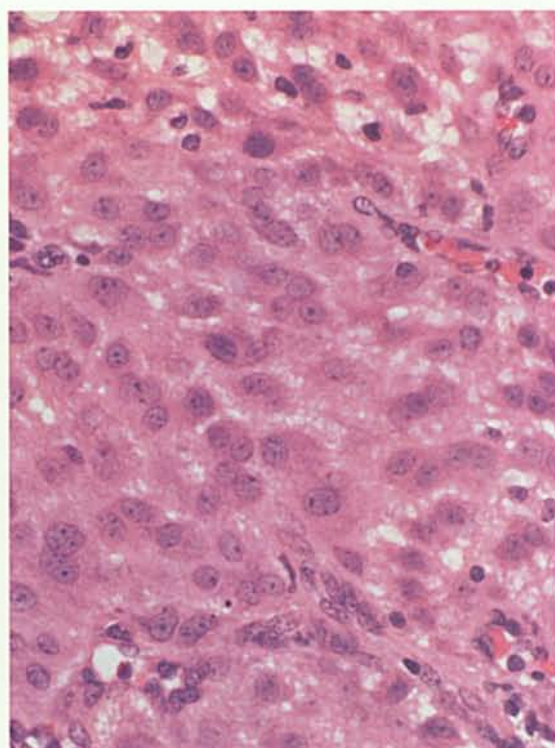


Fig. 56 - Higher magnification of Figure 55.

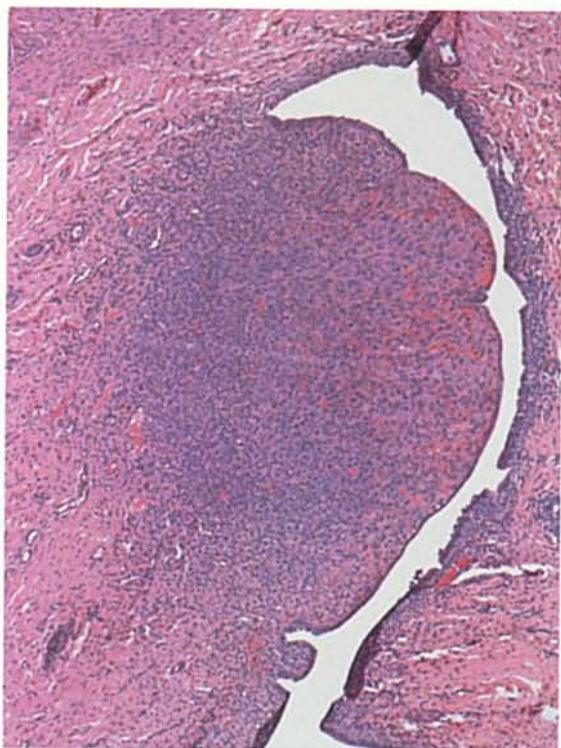


Fig. 57 - Decidual reaction, uterus.

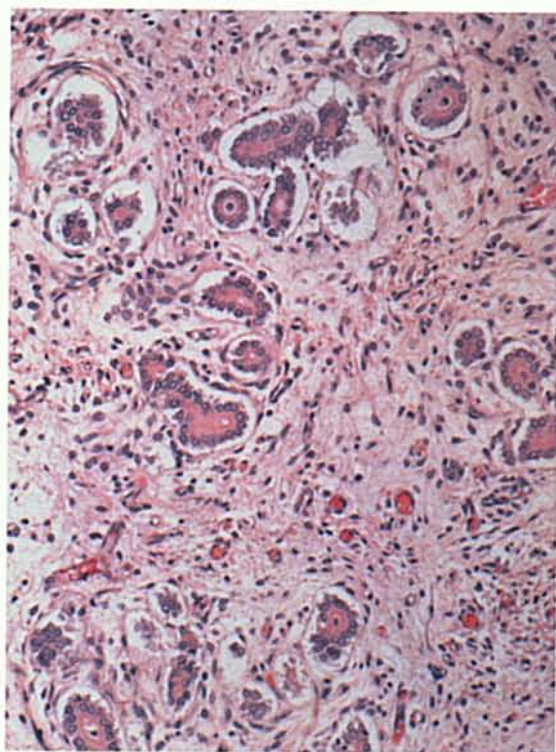


Fig. 58 - Adenomyosis, uterus.



Fig. 59 - Squamous cell papilloma, vagina.

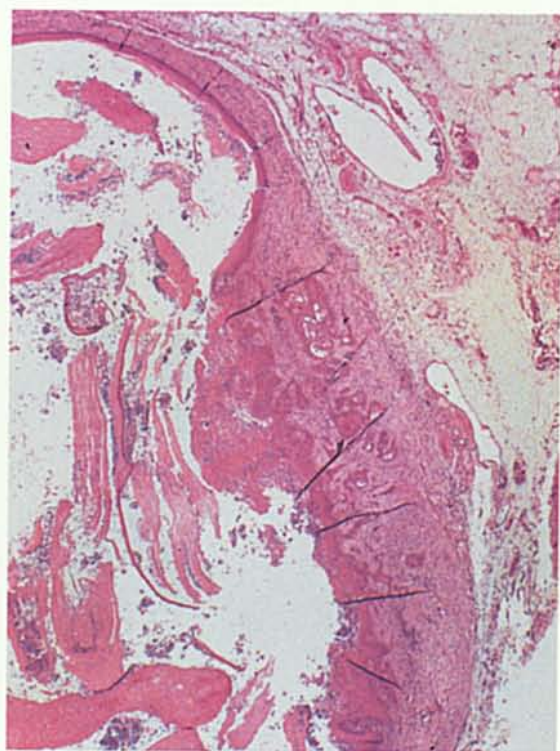


Fig. 60 - Squamous cell carcinoma, vagina.

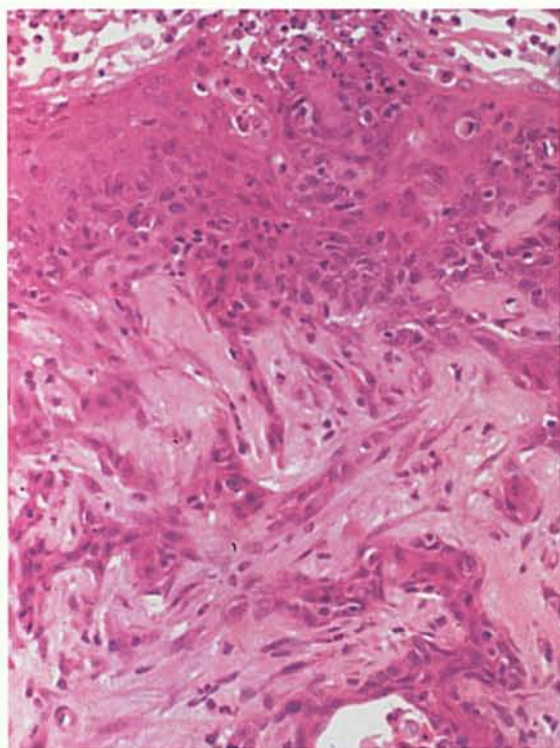


Fig. 61 - Squamous cell carcinoma, vagina.



Fig. 62 - Polyp, vagina.

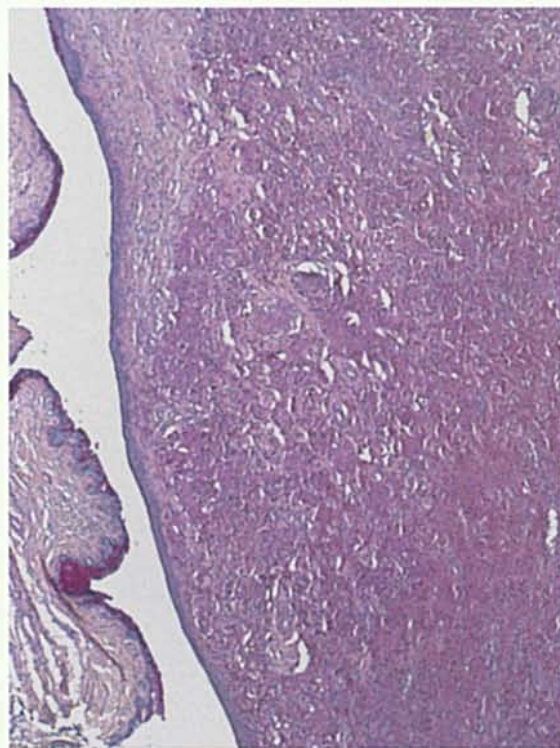


Fig. 63 - Granular cell tumor, vagina.

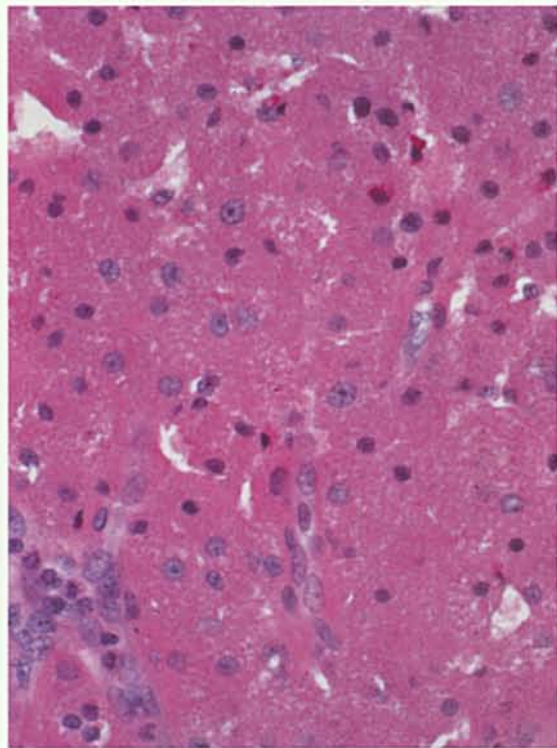


Fig. 64 - Granular cell tumor, vagina.



Fig. 65 - Schwannoma, malignant, cervix.

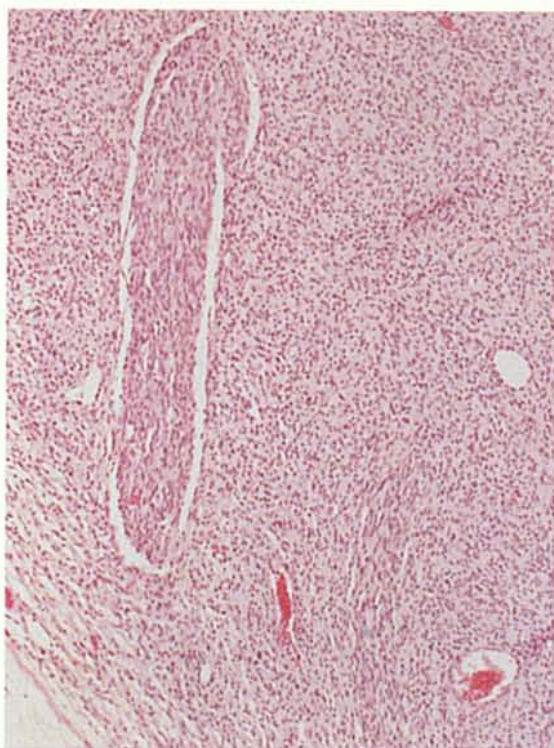


Fig. 66 - Schwannoma, malignant, cervix.



Fig. 67 - Squamous cell hyperplasia, vagina.

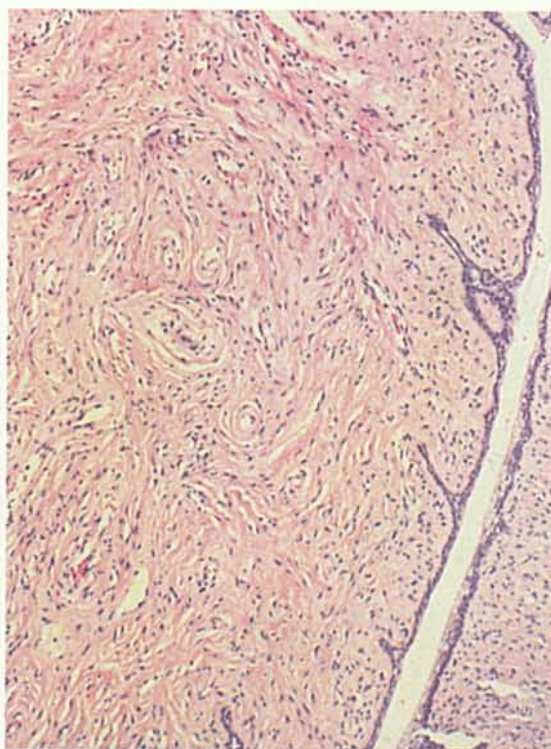


Fig. 68 - Stromal hypertrophy, cervix.

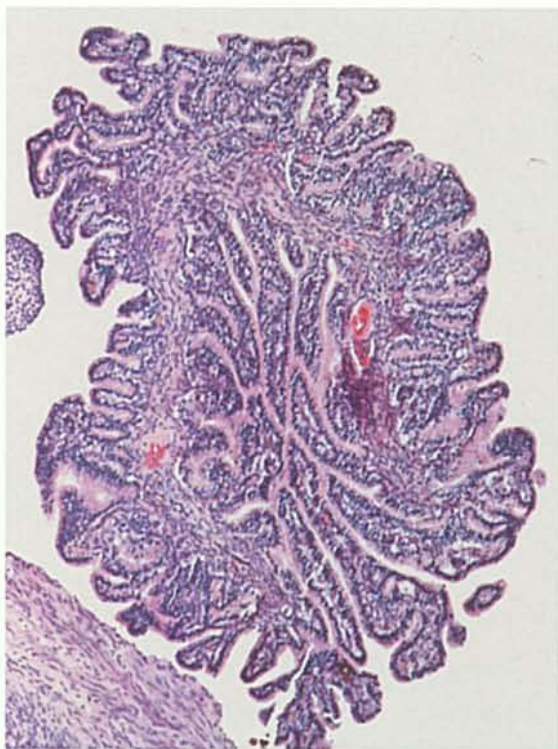


Fig. 69 - Papillary adenoma, oviduct.



Fig. 70 - Carcinoma, oviduct.