

Proliferative Lesions of the Testes in Rats with Selected Examples from Mice

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ANATOMICAL REVIEW OF THE TESTES

Rat testes are similar anatomically to those of other vertebrates. They are surrounded by a three layer capsule composed of the visceral layer of the tunica vaginalis, the tunica albuginea, and the tunica vasculosa. The parietal layer of the tunica vaginalis lines the scrotum. The space between the parietal and visceral layers of the tunica vaginalis normally contains a small amount of fluid which acts as a lubricant between the testes and the scrotal wall. The visceral and parietal layers of the tunica vaginalis are lined with mesothelium and represent a double-layered sac which is a detached diverticulum of the peritoneum. Exposure of the testes at necropsy reveals a conspicuous white coat, the tunica albuginea, which is composed primarily of collagen fibers and occasional smooth muscle cells. Septae from the tunica albuginea penetrate the testicular parenchyma carrying with them blood vessels from the underlying tunica vasculosa. The rat and mouse have very little intertubular connective tissue and do not form thick connective tissue septae as do some species.

The testis can be divided into two functional units, the interstitium and the seminiferous tubules. The interstitium forms the pathway for blood and lymph circulation. Interstitial (Leydig) cells are the most frequently encountered cells along with occasional macrophages. The interstitial cells are located perivascularly and

are a major source of testosterone. They are under the direct influence of luteinizing hormone (LH) and also have binding sites for luteinizing hormone releasing hormone (LHRH).^{1,2} The cells contain abundant smooth endoplasmic reticulum and mitochondria with tubular cristae typical of cells which participate in steroid biosynthesis. Interstitial cell neoplasms in humans can also produce androstenedione.³

The seminiferous tubule is actually a convoluted loop with both ends attached to the excretory duct system, the rete testis. The tubule has numerous tight bends and long straight sections. The straight sections are orientated along the long axis of the testicle. When a mid sagittal section of the testis is taken, longitudinal and cross sections of the seminiferous tubules can be visualized along with portions of the intratesticular excretory system. The tubulus rectus is the portion of the seminiferous tubule which connects to the intratesticular rete testis. It is lined with Sertoli-like cells with no germinal epithelial component. This tubular segment may be misinterpreted as representing atrophic germinal epithelium if not recognized. The intratesticular rete testis is lined by flattened to cuboidal epithelium and forms a narrow channel beneath the tunica albuginea. It is continuous through the tunica albuginea where the ducts form the extratesticular rete testis. The extra testicular rete testis is closely attached to the head of the epididymis through a series of channels, the ductuli efferentes, which empty into the duct of the epididymis. The extratesticular rete testis is embedded in adipose tissue at the head of the epididymis and it along with the epididymis are routinely separated from the testicle when the testes

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are weighed in toxicopathological studies.

The seminiferous tubule is bathed in lymphatic fluid. The wall, outside to inside, is defined by the endothelial cell layer of the lymphatic space, a layer of collagen, basement membrane, myoid cell layer, basement membrane, collagen layer, basement membrane, and cells of the germinal epithelium. Only peritubular myoid cells can be distinguished by light microscopy.

Spermatogenesis is highly organized and complex. It occurs in wave-like fashion along the length of the tubule. The various stages (I-XIV) have been well characterized by Leblond and Clermont.⁴ Other detailed analyses of spermatogenesis staging are also available.^{5,6}

Three types of spermatogonia are recognized: The stem cell spermatogonia, proliferative spermatogonia, and differentiating spermatogonia. Stem cell spermatogonia seldom undergo mitosis and are relatively resistant to toxic injury whereas those spermatogonia undergoing more active mitosis are more susceptible to various toxic insults. Stem cell spermatogonia can repopulate the germinal epithelium where loss due to toxicity or other means has occurred. Total loss of spermatogonia obviously results in permanent sterility.

Situated along the seminiferous tubule basement membrane are Sertoli cells. They have a very complex structure and extend from the basement membrane to the tubule lumen. They are intimately associated with spermatogenesis and have been assigned several important functions.⁵ They are capable of steroid biosynthesis and also secrete inhibin and androgen binding proteins. They have cell surface receptors for follicle stimulating hormone (FSH) and testosterone and are known to play an important role in the blood/testis barrier, now more appropriately named the Sertoli cell barrier. The hormonal regulatory mechanisms involved in the Sertoli cell's influence on spermatogenesis have not been clearly defined.

PRESERVATION TECHNIQUES

The testes are often routinely preserved in 10% neutral buffered formalin. Although this fixative is convenient and adequate for most routine studies, other fixatives result in fewer fixation artifacts. Both Bouin's and Carnoy's solutions are superior to formalin for preservation of the testes.

Prior to immersion in the fixative the tunica albuginea should be opened on either side of the testis to allow more rapid penetration by the fixative. Once adequate fixation has been achieved the fixative can be replaced with buffered saline solution or 70% ethanol. This will prevent excessive protein cross linkage and will facilitate more accurate immunocytochemical analysis of the tissue if needed. Various preservation methods

comparing the resulting histomorphology of the testes have been published.^{4,5,6}

SECTIONING METHODS

The importance of a standardized sectioning method for the testes cannot be over-emphasized. The largest testicular area containing all of the inherent anatomical features of the organ is the desired standard. This can be attained by making mid-sagittal parallel cuts along the long axis of the testis. The parallel cuts will be through the prominent serpentine spermatogenic vessels in the tunica albuginea on one side and include the sites of attachment of the head and tail of the epididymis on the other. The stained and mounted section will include longitudinal and cross sections of the seminiferous tubules, the tubulus rectus, and will include the intratesticular rete testis (Fig. 1).

The epididymis is often removed from the testicle in toxicopathological studies. The fatty area at the head of the epididymis should be carefully trimmed to preserve the extratesticular rete. The epididymis should then be sectioned along its long axis to allow analysis of the head, body, and tail.

CLASSIFICATION OF TESTICULAR NEOPLASMS

Primary neoplasms of the testis are classified as those originating from gonadal stroma, germ cells, adnexae, and those of varying mesenchymal origin.⁷ Due to the complexity of the cellular components of the testes a diversity of potential neoplastic growths may occur. Fortunately, for those dealing with rats, only interstitial cell neoplasms occur with any frequency. Since many of the testicular neoplasms are extremely rare or as yet unreported in rats, some examples of rare testicular tumors of the testes in mice were included as examples in this review.

Neoplasms of Gonadal Stroma

Interstitial (Leydig) Cell Adenoma/Carcinoma
Sertoli Cell Adenoma/Carcinoma
Mixed Gonadal Stromal Cell Adenoma/Carcinoma

Neoplasms of Germ Cell Origin

Seminoma, Benign/Malignant
Choriocarcinoma
Yolk Sac Carcinoma
Embryonal Carcinoma
Teratoma, Benign/Malignant

Neoplasms of Adnexae

Rete Testis Adenoma/Carcinoma

Neoplasms of Serous Membranes

Malignant Mesothelioma

Other Potential Testicular Neoplasms

Leiomyoma/Leiomyosarcoma
Hemangioma/Hemangiosarcoma
Lymphangioma/Lymphangiosarcoma
Fibroma/Fibrosarcoma
Neurofibroma/Neurofibrosarcoma/Schwannoma
Lipoma/Liposarcoma

NEOPLASMS OF GONADAL STROMA

Interstitial (Leydig) Cell Adenoma/Carcinoma

The most frequently encountered neoplasm of the rat testis is the interstitial cell adenoma. The incidence rate varies according to strain ranging from 1-2% in Long Evans to nearly 100% in Fischer 344 rats. Interstitial cell neoplasms are commonly encountered in 1-year-old Fischer 344 rats and become increasingly more frequent with age. Their recognition and diagnosis is not difficult when the growths are large. The problem confronting most pathologists is separating focal interstitial cell hyperplasia from early neoplastic growth.

Hyperplasia vs. Neoplasia

Interstitial cell hyperplasia occurs in two forms, either focal or diffuse, and is not recognized grossly. Interstitial cells have both LH and LHRH surface receptors.^{1,2} Genetic predisposition and hormonal imbalances appear to play a major role in the development of interstitial cell hyperplasia and neoplasia.^{8,9} Disruption of the hypothalamic-pituitary-testicular axis resulting in sustained LH hypersecretion is suspected of playing a key role in the proliferative response of interstitial cells.¹⁰

Diffuse interstitial cell hyperplasia is easily recognized microscopically and appears as increased numbers of cells evenly distributed throughout the testicular interstitium. It occurs in some hypogonadal states and occasionally following atrophy of the seminiferous tubules, but is not a precursor of interstitial cell neoplasia. The proliferative cell growth is dispersed between the tubules rather than displacing or destroying them, as is the case with interstitial cell neoplasms. The example shown is from a mouse chronically treated with a synthetic LHRH agonist (Figs. 2, 3).

Focal interstitial cell hyperplasia presents a diagnostic dilemma in long term drug or chemical safety studies. Focal or multifocal interstitial cell hyperplasia increases in incidence, multiplicity, and severity with age, especially in high incidence strains and often progresses to neoplasia. The differentiation between focal interstitial cell hyperplasia and early interstitial cell neoplasia cannot be ascertained accurately on a histomorphological basis.

Due to the difficulty in separating these two entities, guidelines based on lesion size have been utilized in an attempt to standardize the diagnosis of interstitial cell adenoma. Two arbitrary criteria have been developed. The criterion used by the U.S. National Toxicology Program (NTP) is as follows: Any focus of interstitial cell proliferation having a diameter equal to or greater than the diameter of an adjacent seminiferous tubule is considered to be an interstitial cell adenoma.¹¹ European pathologists use a guideline of at least three diameters of adjacent seminiferous tubules and in addition the proliferative focus must also have morphological features consistent with interstitial cell neoplasms. We know that even the smaller lesions may already be autonomous neoplasms. It is not uncommon, however, to find twenty or more interstitial cell nodules whose size may range from 1 to 3 tubular diameters in a single testis. When the size criterion is set at 3 diameters or larger seldom more than 3 neoplasms per testis are found. The perivascular assemblage of proliferative interstitial cells would appear as focal nodules when cut in cross section, but the section does not reflect the three dimensional growth pattern which is probably one of proliferation and coalescence into increasingly larger cell masses (Fig. 6). Since fewer neoplasms are encountered when the size criterion is set at 3 tubular diameters, it appears that this guideline incorporates the concept of coalescence, enlargement, and compression; primary features of interstitial cell neoplasia.

It is recommended for standardization purposes that 3 tubular diameters be set as the arbitrary separation of focal interstitial cell hyperplasia from interstitial cell neoplasia. Classical histopathology guidelines require evidence of autonomous growth before proliferative cellular lesions are diagnosed as neoplasms. Two or more of the following criteria should be met before a lesion is diagnosed as an interstitial cell neoplasm.

- (a) The cell mass is 3 seminiferous tubular diameters or larger.
- (b) There is symmetrical peripheral compression of adjacent seminiferous tubules (lesions of one tubule diameter or less often compress portions of adjacent tubules).
- (c) There is evidence of cellular pleomorphism or reduction in the nuclear/cytoplasmic ratio (Fig. 10).
- (d) A typical endocrine sinusoidal vascular network has developed (Fig. 12).
- (e) There is increased mitotic activity (Fig. 9).
- (f) There is evidence of coalescence of adjacent cell masses (Fig. 6).

Standardized sectioning of the testes in rodents, as described earlier, plays a critical role in defining a potential treatment associated testicular response, especially important when focal interstitial cell hyperplasia and/or neoplasia is present. The number and approximate size of

lesions in each testicle must be recorded to accurately reflect a treatment associated effect and to allow others to make an accurate comparison with the data.

Interstitial (Leydig) Cell Adenoma

Grossly, interstitial cell adenoma can be recognized as a discrete yellow or yellowish-brown focus or foci at an early stage of development. Later stages may replace the entire testicle and contain cystic regions filled with blood and/or brown to reddish fluid.¹²

Microscopically, these neoplasms vary in size and when observed at an early stage of development are difficult to separate from foci of interstitial cell hyperplasia. The small adenomas and hyperplastic foci when stained with hematoxylin and eosin are composed of a fairly uniform cell population which contain abundant eosinophilic finely vacuolated cytoplasm. The nucleus is centrally located with marginally dispersed chromatin and a single nucleolus (Figs. 11, 12). Mitotic activity is usually sparse. As the cell masses progressively enlarge, they cause compression of adjacent seminiferous tubules, develop a blood sinus network characteristic of other endocrine tissues, and commonly develop blood or brownish fluid-filled cavities (Fig. 7). The neoplasms tend to be multifocal and bilateral.^{13,14} Cellular morphology is variable in larger neoplasms. Often tumors, even smaller ones, contain a population of poorly differentiated small dark cells with scanty cytoplasm. Superficially, one could mistake them as being of lymphoid origin (Fig. 10). Elongated or spindle shaped variants with varying cytoplasmic vacuolation also occur (Fig. 13). Other variants contain distended finely vacuolated clear cytoplasm (Fig. 14). The cytoplasmic vacuoles are most often lipid in character and with frozen sections stain positive with "Oil Red O". Often the nuclear/cytoplasmic ratio is reduced in neoplastic cells. Most interstitial cell neoplasms, however, will contain islands of cells with typical interstitial cell morphology which aids in diagnosis. Crystalloids of Reinke, cytoplasmic cigar-shaped crystalline structures, are often found in interstitial cell neoplasms in man. They can best be demonstrated with special stains such as Masson's or phosphotungstic acid hematoxylin. Although frequently found in interstitial cell neoplasms in man, according to our experience and that of others they are normally not found in interstitial cells of the rat.⁹

A small number of interstitial cell neoplasms may contain glandular, tubular, or papillary structures, some cystic, lined with cuboidal or columnar cells (Fig. 15). These structural variants have been shown to be of interstitial cell origin and represent a form of interstitial cell metaplasia.¹⁵

Interstitial (Leydig) Cell Carcinoma

Carcinoma is rare and this specific diagnosis is made only

when invasion into adjacent parenchyma, testicular tunics, spermatic cord, or a distant metastatic site is found. Interstitial cell carcinomas may have cellular morphology similar to the benign lesions but they generally tend to have larger regions of hemorrhage, a more pleomorphic cell population, and increased mitotic activity (Fig. 17). Metastases are rarely encountered but when found usually occur as emboli in testicular veins or in spermatic cord vessels (Fig. 16). The spermatic cord and regional lymph nodes are often the metastatic site of malignant testicular neoplasms and should be examined microscopically when testicular neoplasms are noted at necropsy. A lung transplantation metastasis from a rat interstitial cell carcinoma is shown in Figure 18.

Sertoli Cell Adenoma/Carcinoma

Synonyms. Sustentacular cell tumor, tubular adenoma, sex cord stromal tumor, androblastoma.

Sertoli cell neoplasms in rats and mice are a rare occurrence.¹⁶ Two neoplasms have been described in detail in the rat.^{17,18} Both were unilateral and considered to have been carcinomas based on mitotic activity and local invasiveness.

The typical Sertoli cell neoplasm is composed of interdigitated rows of tubules lined with elongated palisading cells situated on a thin fibrovascular stromal basement membrane (Fig. 19). The cells are arranged perpendicular to the basement membrane and most often contain cytoplasmic vacuoles (Fig. 20). The tumor can also be composed of a diffusely cellular population without a clear tubular arrangement, however, tubular structures can usually be found which aid in diagnosis.¹⁹

Mixed Gonadal Stromal Adenoma/Carcinoma

Mixed gonadal stromal neoplasms are also rare in rats. The one case presented here was from a 112-week-old Wistar rat which had been treated with CdCl₂.²⁰ The neoplasm consisted of an admixture of interstitial cells and tubules of varying size lined with spindle-shaped cells with typical Sertoli cell morphology (Figs. 21, 22, 23).

NEOPLASMS OF GERM CELL ORIGIN

Seminoma (Benign/Malignant)

Synonyms. Dysgerminoma, seminal carcinoma, spermatoblastoma, spermatocytoma, germinoma.

Seminoma rarely occurs in the rat or mouse. Five seminomas have been well described, three in Wistar rats^{21,22} and two in mice, one in a B₆C₃F₁, and another in an NMRI strain.^{16,23} All of the neoplasms resembled spermatocytic seminomas. Due to the rarity of these neoplasms in rats and mice there is insufficient informa-

tion to define morphological variants as occur in humans. In two of the rat and one of the mouse neoplasms the tumor cells filled or partially filled seminiferous tubules. In the remaining two neoplasms, the cells were extratubular and had infiltrated the interstitium. The cells were arranged in rounded tubule-like structures or were in diffuse sheets. Lymphocytic infiltrates or fibrovascular trabeculae, common in seminoma in man and the dog, were not present in these neoplasms. The cellular morphology of the five neoplasms was similar. They were composed of large round or polygonal cells with distinct cell borders and a central round to oval hyperchromatic nucleus with one or two distinct nucleoli. The tinctorial characteristics of the cytoplasm varied from tumor to tumor but was usually eosinophilic to slightly basophilic. Mitotic figures, including atypical or bizarre forms, were a common feature.

The neoplasm depicted in Figures 24 and 25 is similar to the spermatocytic seminoma described in man. Two of 669 outbred male Wistar rats were found to have seminomas in one report.²¹ An additional spermatocytic seminoma, approximately 1 cm. in diameter, was also described in a Wistar rat.²² Figure 26 shows a spermatocytic seminoma in a NMRI mouse at 105 weeks of age. All seminomas in rodents should be considered malignant based on growth patterns and clinical history in other species, including man.

Choriocarcinoma

Spontaneous choriocarcinoma in rats was unreported until recently when the neoplasm was recognized in a control male Sprague-Dawley rat from a subchronic toxicity study.²⁴ The neoplasm was found in cervical lymph nodes and lung. A single case of spontaneous choriocarcinoma has been reported in a DDD mouse.²⁵ Choriocarcinomas may arise in gonads, placenta, or from pluripotent cells deposited in the mediastinum or abdomen. These tumors are malignant and tend to metastasize at a very early stage of development.^{26,27} They are usually accompanied by extensive hemorrhage and necrosis.

The neoplasm is characterized by the presence of trophoblastic giant cells and smaller darker staining cytotrophoblasts (Figs. 27, 28). The trophoblastic giant cells secrete luteotropic and mammatropic hormones. Immunohistochemical stains of the depicted tumor were positive for human chorionic gonadotropin and prolactin. No primary site was identified for the rat tumor, however, it was postulated that the original site may have been the testicle where it had undergone necrosis and resorption after metastasizing to the cervical lymph nodes and lung.

The choriocarcinoma lacks an inherent vascular stroma and must receive nourishment by diffusion of tissue fluids. It is characteristically located at the periphery of tissues because of this inherent feature.²⁴

Both trophoblastic giant cells and cytotrophoblasts must be present to diagnose choriocarcinoma.

Yolk Sac Tumor, Embryonal Carcinoma, Teratoma

The cellular origin of the yolk sac tumor, embryonal carcinoma, and teratoma is controversial in the rat. Historically, all have been classified as being of germ cell origin, however, they have been experimentally produced in the mouse, rat, and hamster from the egg cylinder or the visceral yolk sac. Both structures, free of germ cells, can give rise to yolk sac tumor, embryonal carcinoma, or combinations, including malignant teratoma. This confusing pattern of cellular differentiation has been attributed to primitive multipotent stem cells in these extraembryonic structures. The spontaneous neoplasms, extremely rare or as of yet unreported in the rat, are still considered to be of germ cell origin in other species including man.^{7,28}

Yolk Sac Adenoma/Carcinoma

Synonyms. Endodermal sinus tumor, yolk sac tumor.

Spontaneous yolk sac neoplasms of the testis have not been reported in the rat. The neoplasm has been classified as being of germ cell origin but recent experimentation has shown that the rat yolk sac tumors can develop from the extraembryonic portion of the egg cylinder or from the visceral yolk sac which are free of germ cells.^{29,30,31} The growth is rare in all species but can arise in the ovaries, testis, or in extragonadal sites.^{32,33} Various experimental methods can be used to induce yolk sac tumors and include fetectomy of 12-day rat fetuses with exteriorization of the visceral yolk sac outside of the uterus, injection of mouse sarcoma virus into the placental tissue of fetectomized rats, puncture of the pregnant uterine wall during mid pregnancy, or implantation of an 8-day old embryo or the extraembryonic portion of a 9-day old egg cylinder under the kidney capsule of a synergistic rat.^{30,31} Similar experimental methods can be used in mice and hamsters to produce the neoplasm in 4 to 8 months. Experimentally induced yolk sac carcinoma is depicted in Figures 29 and 30.

Yolk Sac Carcinoma

Figures 31 through 33 show a spontaneous yolk sac carcinoma from the ovary of a CD-1 mouse and the characteristic metastatic growth pattern. Histologically, the malignant neoplasms are composed primarily of cuboidal cells with shapes ranging from oval to angular. The cell nucleus is dark with closely clumped chromatin and contains one or two inconspicuous nucleoli. The nucleus to-cytoplasm ratio approaches 1:1. The cells are usually arranged in disorganized clusters or in irregular ribbons which may form into single cell tubular structures

or rosettes, known as Schiller-Duval bodies in human yolk sac tumors. Often the neoplastic cells are lined on a conspicuous pink basement membrane. The most characteristic feature of the spontaneous tumors is the presence of abundant pink proteinaceous fluid in which cells or papillary structures of the neoplasm appear to be suspended. The malignant neoplasms spread aggressively to peritoneal surfaces and grow as nests or large colonies but seldom invade into the parenchyma of solid organs.

The matrix between individual or groups of cells has staining characteristics similar to Reichert membrane of the parietal yolk sac. Alpha-fetoprotein is produced by the visceral yolk sac cells and elevated serum levels may be found in tumor-bearing animals.^{30,31}

Embryonal Carcinoma

Synonym. Undifferentiated malignant teratoma.

Spontaneous embryonal carcinoma has not been reported in rats. It can be produced experimentally by injecting mouse sarcoma virus into the placentas of fetectomized rats. This methodology produces embryonal carcinoma in about 5% of the rats, whereas yolk sac tumors develop in about 80% of the animals.³³ Grossly the neoplasm contains yellowish regions of necrosis and numerous areas of hemorrhage.

Microscopically, the experimental tumors have a malignant epithelial or embryonic appearance with round or polyhedral cells with indistinct cell boundaries and abundant mitotic figures. The nuclei are large with coarse granular chromatin and prominent nucleoli. The cells may occur in solid sheets or have interspersed areas of acinar, papillary, or tubular structures. The neoplasm lacks organoid features but is multipotent and may on occasion contain foci of yolk sac carcinoma or well-differentiated tissues such as cartilage, bone, or skin. They have little stroma without inflammatory cell infiltrates. Hemorrhage and necrosis are often present.

Teratoma (Benign/Malignant)

Spontaneous teratoma of the rat testis has not been reported but can be produced experimentally.^{29,34} It occurs spontaneously in outbred strain 129 mice.³⁵ These tumors may be benign or highly malignant. Histologically, the benign forms can be relatively simple containing well-developed neural, epithelial, and mesenchymal components (Figs. 34, 35) The malignant forms may have one or more cell types of very primitive cell lineage and often are invasive or metastasize widely. The malignant neoplasms often contain embryoid structures resembling embryonic stages of development or they can present as embryonal carcinoma with areas of cellular differentiation into specific cell lineages. The pattern of growth usually allows the identity of one or more tissues of different germ cell lineage in conjunction with a more embryonic and less

differentiated component. The term teratocarcinoma has been applied, however, malignant teratoma is the preferred classification.

NEOPLASMS OF ADENEXAE

Rete Testis Adenoma/Carcinoma

Proliferative lesions involving the rete testis rarely occur in the rat but can include hyperplasia, adenoma, and carcinoma. The tubulus rectus is the terminal short segment of the seminiferous tubule in approximation to the intratesticular rete testis. This short segment is lined with cells resembling Sertoli cells as opposed to the intratesticular rete testis which is lined with flattened or cuboidal cells. Figure 36 depicts a region of rete testis hyperplasia with irregular tubules lined with flattened to cuboidal epithelium. Intertubular connective tissue may be increased which sets it apart from adjoining normal parenchyma. On rare occasions rete tubule hyperplasia may occur in conjunction with interstitial cell neoplasms.³⁶

Figures 37 and 38 depict a region of rete epithelial papillary hyperplasia in a tubule subjacent to vessels of the pampiniform plexus. This is the usual location for lesions of the intratesticular rete testis. The papillary structures are lined with crowded cuboidal to low columnar cells which suggest they are of tubulus rectus origin. The cells, although crowded along the basement membrane, do not have a pseudostratified appearance which assists in differentiating hyperplasia from adenoma.

Adenoma of the rete testis, as shown in Figure 39, is composed of complex branching papillary structures lined with crowded cuboidal to columnar cells which often have a pseudostratified appearance. Mitotic figures may occasionally be found. Variation in cellular and nuclear size is common and the delicate stroma supporting the papillary structures is well vascularized. Tubular lumina are distorted and not well defined. Compression of adjacent normal tissues may occur.

Rete tubule carcinoma in rats forms irregular tubular or papillary structures which are locally infiltrative.³⁷ The tubules are lined with a pleomorphic cell population ranging from flattened cuboidal to low columnar epithelium frequently with areas of squamous differentiation. Mitotic figures are rare to frequent dependent upon how rapid the neoplasm is growing. The tubule lumina commonly contain varying amounts of macrophage and neutrophil cellular debris (Figs. 40, 41). The carcinoma has an infiltrative and aggressive growth pattern³⁶ and may be accompanied by a marked scirrhous response, hemorrhage, and necrosis.^{16,20}

NEOPLASMS OF SEROUS MEMBRANE

Mesothelioma

One of the most frequent sites of mesothelioma in the rat is the testes. The incidence rate is usually less than 1% in most strains but in F344 rats has been reported to be 1.4%.¹⁶ Grossly, the neoplasms may be visible as single or multifocal roughened beige or white spots on the tunica vaginalis or may consist of extensive white to tan velvety plaques covering large areas of the testes, epididymides and peritoneal surfaces. Most mesotheliomas of the testes arise from the tunica vaginalis and are easily recognized. Difficulty arises in separating focal villous hyperplasia from actual tumor.

Mesothelial Hyperplasia

Mesothelial hyperplasia is represented by focal thickening or villous projections of mesothelial cells without stratification.¹⁶ The villous projections do not develop a supporting fibrovascular stalk (Fig. 42). Fibrosis, which may have been related to prior or on-going irritation, often accompanies mesothelial hyperplasia.

Malignant Mesothelioma

True mesotheliomas are complex branching structures lined with single or stratified layers of cuboidal shaped cells. The supporting fibrous stalk is usually prominent and well vascularized (Figs. 43, 44). Growth over the testicular tunica vaginalis extending to the epididymides and spermatic cord with seeding of the peritoneal cavity and peritoneal viscera is common. Mesotheliomas found in the peritoneal cavity frequently arise from the testicular tunics. Testicular mesotheliomas are frequently bilateral and multifocal and even early growths should be considered malignant.

POTENTIAL TESTICULAR NEOPLASMS OF MESENCHYMAL ORIGIN

Benign or malignant neoplasms of other mesenchymal cell origin may potentially occur, those of smooth muscle or vascular origin being the most likely. Neoplasms of fibrous tissue, lymph vessels, or nerve may also occur. The diagnosis of these tumors is based on standard histomorphological criteria.

RECOMMENDED NOMENCLATURE WITH DIAGNOSTIC CRITERIA FOR THE TESTES

Interstitial (Leydig) Cell Hyperplasia, Diffuse

1. Increased numbers of cells evenly distributed between seminiferous tubules, most often bilateral

2. Cell morphology similar to normal interstitial cells
3. Little or no compression of tubules
4. Associated with hypogonadal states or seminiferous tubule atrophy

Interstitial (Leydig) Cell Hyperplasia, Focal/Multifocal

1. Can occur prior to 1 year of age, especially in high incidence strains such as the Fischer 344
2. Occurs as individual or multiple nodules, usually bilateral
3. Is considered to be hyperplasia and not adenoma if the nodule diameter is less than 3 seminiferous tubule diameters
4. Asymmetrical compression of adjacent seminiferous tubules may be present
5. Mitotic figures are rare to absent
6. Usually has not developed a typical endocrine sinusoidal network
7. Well-differentiated cell morphology
8. No evidence of coalescence with adjacent nodules

Interstitial (Leydig) Cell Adenoma

1. Cell mass is 3 seminiferous tubular diameters or larger
2. There is symmetrical peripheral compression of adjacent seminiferous tubules
3. There is cellular pleomorphism or reduction in the nuclear/cytoplasmic ratio
4. There is a typical endocrine sinusoidal network
5. Mitotic activity may be increased
6. Coalescence of adjacent cell mass
7. Blood or brown fluid-filled cysts may occur
8. Glandular or tubular structures lined with cuboidal or columnar-type cells may occur

Interstitial (Leydig) Cell Carcinoma

1. All of the features of the interstitial cell adenoma may be present
2. Usually increased mitotic activity
3. Hemorrhage may be more prominent than in adenomas
4. Paramount diagnostic feature is invasion of adjacent structures including the testicular tunics, blood vessels, spermatic cord, and/or the presence of distant metastatic growth

Sertoli Cell Adenoma

Has not been reported in the rat but in other species, including man; the following criteria can be used to diagnose Sertoli cell adenoma:

1. Solitary nodule with peripheral compression
2. Well-defined cellular morphology; typical columnar cells palisaded along the basement membrane

3. Lack of or few mitotic figures

Sertoli Cell Carcinoma

1. Usually unilateral
2. Locally invasive
3. Areas of poor cellular differentiation
4. Mitotic index may be increased

Mixed Gonadal Stromal Adenoma

1. Admixture of well-differentiated Sertoli and interstitial cell components
2. Peripheral compression without evidence of local invasion
3. Absence of or rare mitotic figures

Mixed Gonadal Stromal Carcinoma

1. Poorly differentiated cell population
2. Evidence of invasion of adjacent testicular parenchyma or distant metastasis
3. Increased mitotic rate

Seminoma (Benign/Malignant)

1. Numbers in rats are inadequate to delineate potential subclassifications and to adequately define benign vs. malignant characteristics
2. Neoplasms thus far described are characteristic of spermatocytic seminomas
3. Neoplastic cells may be confined to seminiferous tubules
4. Cells resemble spermatogonia but are usually larger and often develop bizarre forms with a high mitotic index
5. There may be invasion of the testicular interstitium with the formation of broad sheets of neoplastic cells
6. Seminoma should be considered malignant based on historical evidence in other species

Choriocarcinoma

1. Characterized by the presence of trophoblastic giant cells and smaller cytotrophoblasts
2. Highly malignant and metastasizes early in development
3. May arise in the testes or other extragonadal sites
4. Lacks an inherent vasculature and is usually located at the periphery of affected tissues
5. Is usually hormonally active

Yolk Sac Carcinoma

1. Most experimentally induced carcinomas have growth patterns mimicking the parietal and visceral layers of the fetal membrane
2. Metastases are common to the abdominal viscera and tend to be superficial with little or no parenchymal invasion

3. Elevated alpha feto-protein levels may be present

Embryonal Carcinoma

1. Spontaneous neoplasm has not been reported in the rat
2. Highly undifferentiated cell population with abundant mitotic figures
3. Occurs in sheets of embryonic appearing cells with interspersed areas of acinar, papillary, or tubular structures
4. May contain features of malignant teratoma
5. Hemorrhage and necrosis often present
6. Scant stroma without inflammatory infiltrates
7. Local invasion and metastatic spread is a constant feature

Benign Teratoma

1. Not reported in the testes of the rat
2. Occurs spontaneously in outbred 129 strain mice
3. Well-differentiated neural, epithelial, and mesenchymal components with no evidence of local invasion or distant metastases

Malignant Teratoma

1. Not reported in the testes of the rat
2. May be composed of embryonal carcinoma with differentiation into one or more neural, epithelial or mesenchymal components
3. Locally invasive with a tendency to metastasize widely

Rete Testes Hyperplasia

1. Consists of disorganized tubules or cysts lined with single layered cuboidal to low columnar cells
2. Papillary structures are not formed as in adenoma
3. Capsule formation or compression of adjacent testicular parenchyma is not present
4. May be mixed with interstitial cell neoplasms

Rete Testes Adenoma

1. Irregular dilated to cystic tubules containing papillary structures lined with single to multilayered cuboidal to low columnar epithelium
2. Peripheral expansion with compression of adjacent testicular parenchyma and formation of a capsule
3. Occurs in the absence of interstitial cell neoplasms

Rete Testes Carcinoma

1. Irregular dilated or cystic tubules with papillary projections
2. Tubules lined with pleomorphic cell population ranging from cuboidal to stratified low columnar; there may be regions of squamous differentiation
3. Mitotic figures are rarely encountered

4. Interlobular connective tissue stroma may be abundant
5. Local invasion of the testicular tunics or parenchyma may be present
6. There may be an accompanying scirrhous response, hemorrhage, and/or necrosis
7. No distinct fibrous encapsulation

Mesothelial Hyperplasia

1. Not identified grossly
2. Usually unilateral and localized
3. Focal thickening or villous projections lined with cuboidal mesothelial cells without stratification or a supporting fibrovascular stalk
4. May be accompanied by fibrosis and/or localized inflammatory infiltrates indicative of a localized inflammatory response

Malignant Mesothelioma

1. Grossly appears as white to beige plaques over the tunica vaginalis or associated with the epididymides
2. Comprised of complex branching papillary structures lined with single or stratified layers of cuboidal cells
3. Prominent and well-vascularized supporting fibrous stalk
4. Seeding of the peritoneal cavity and viscera is common

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Hijura Iwata, Biosafety Research Center, Shiznoka, Japan; Drs. Nyska and Pirak, Life Sciences Research, Ness Ziona, Israel; members of the European Society of Toxicologic Pathologists; and Dr. Tuomari and the pathology staff at Bristol-Myers-Squibb Institute for Medical Research, New Brunswick, N.J., for distributing the manuscript to fellow colleagues and for returning their comments and suggestions for incorporation into this publication. We also wish to thank all of the numerous individuals who supplied photomicrographs of the many unusual or rare testicular lesions. Last, but not least, we want to acknowledge Sharron McConnell for the long hours she devoted to the organization, preparation, and typing of this manuscript.

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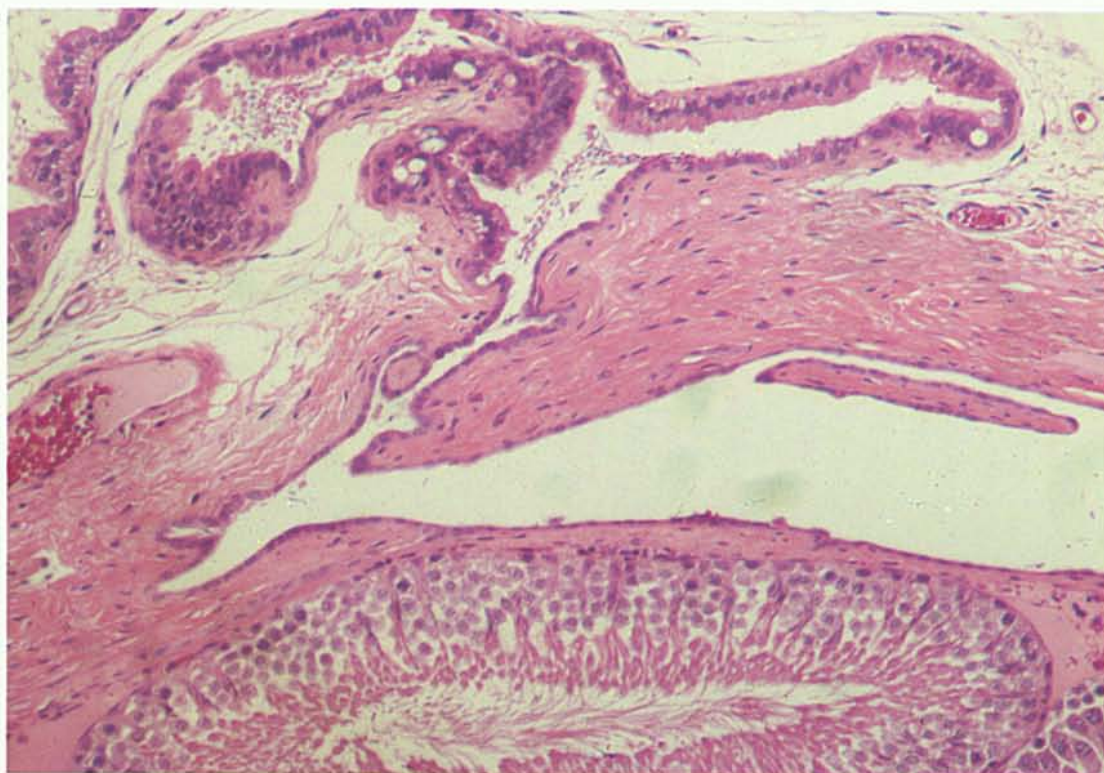


Fig. 1 – Longitudinal section of rat testis including the intra- and extratesticular rete testis and the passage through the tunica albuginea. 40x, H&E

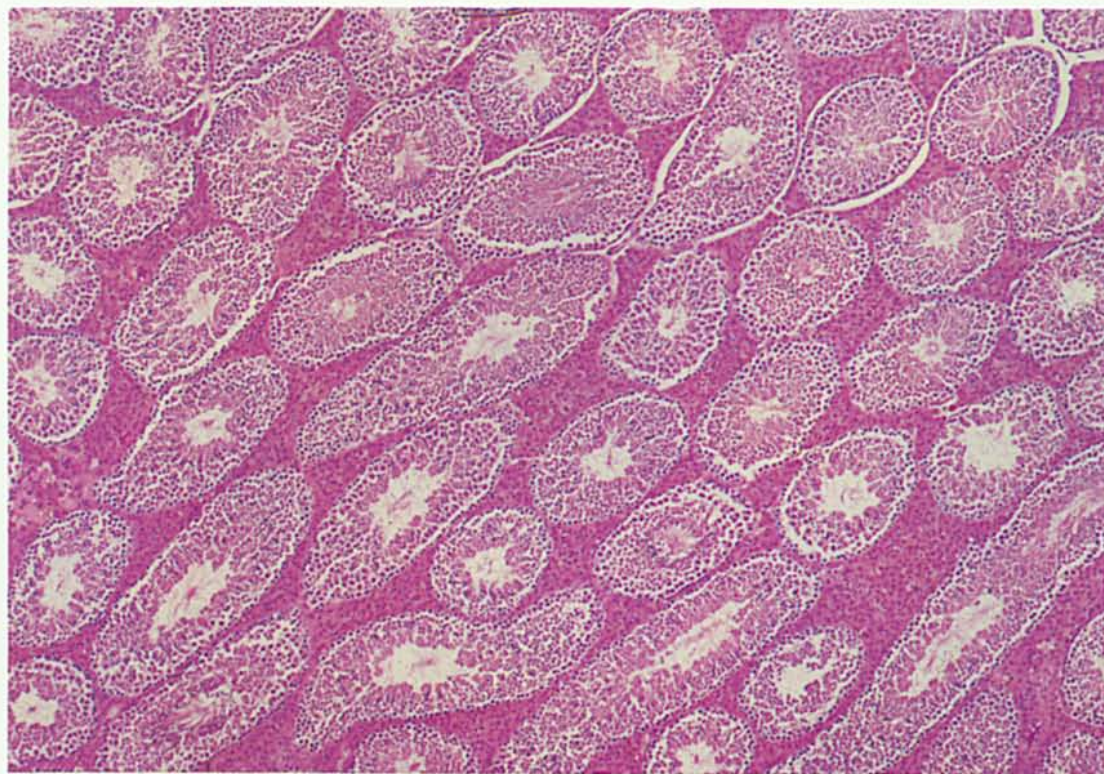


Fig. 2 – Diffuse interstitial cell hyperplasia, CD-1 mouse, treated chronically with an LHRH agonist. 40x, H&E

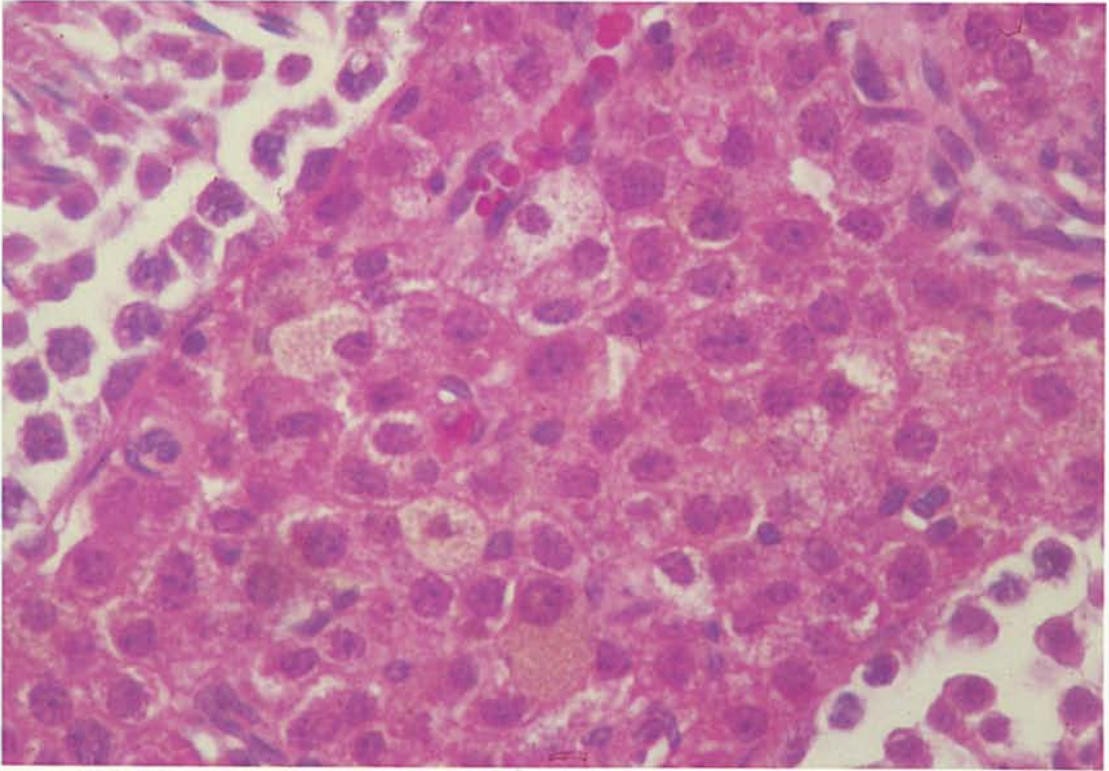


Fig. 3 – Cellular detail of diffuse interstitial cell hyperplasia from lesion in Figure 2. 400x, H&E

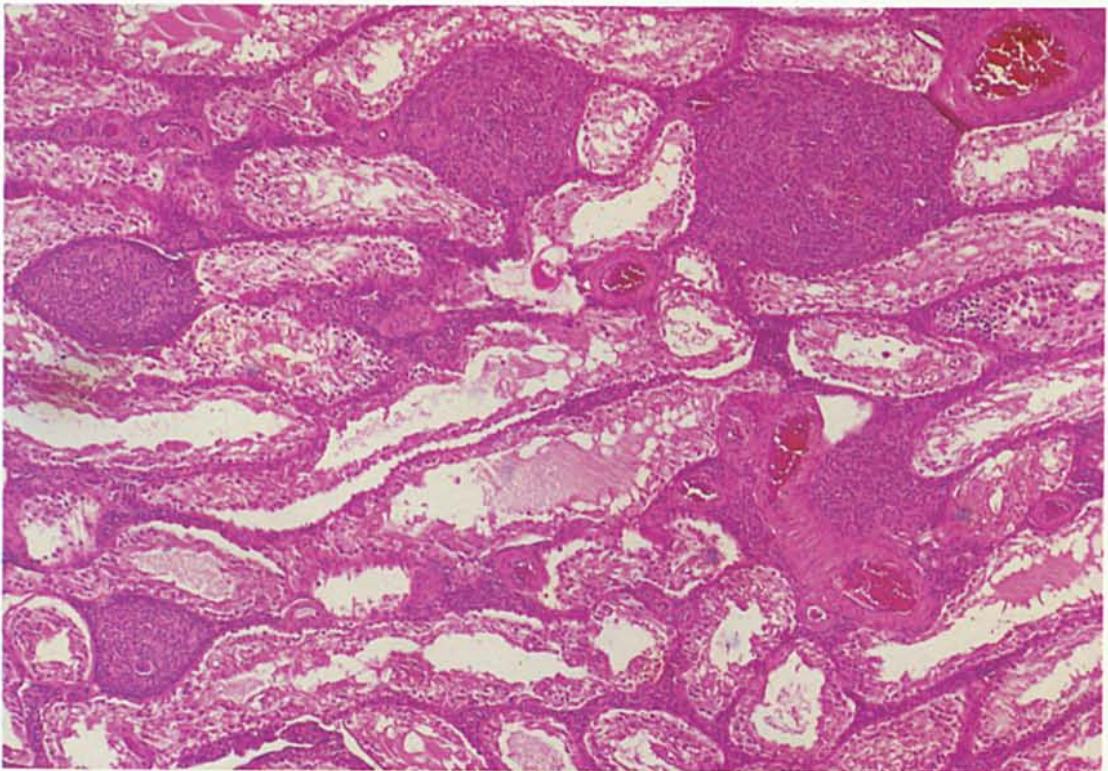


Fig. 4 – Multifocal interstitial cell hyperplasia, Long Evans rat, treated chronically with an LHRH agonist. 40x, H&E

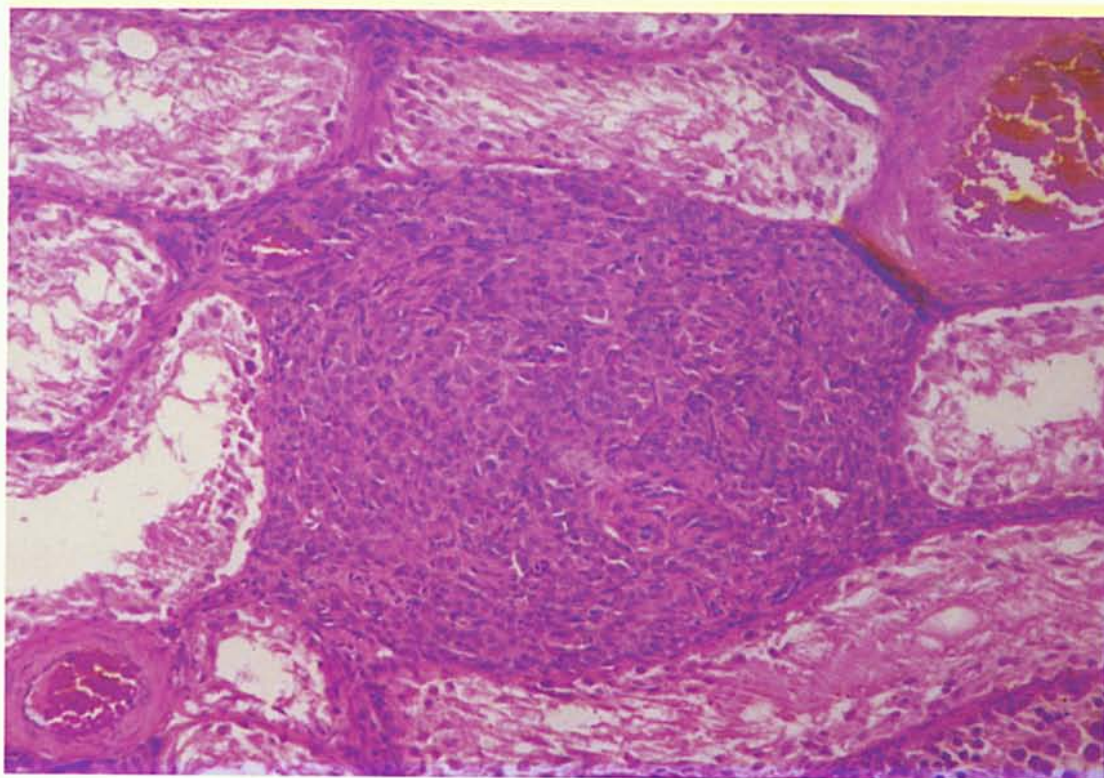


Fig. 5 – Focus of interstitial cell hyperplasia. The diameter of the cell mass is approaching three diameters of adjacent seminiferous tubules. 100x, H&E

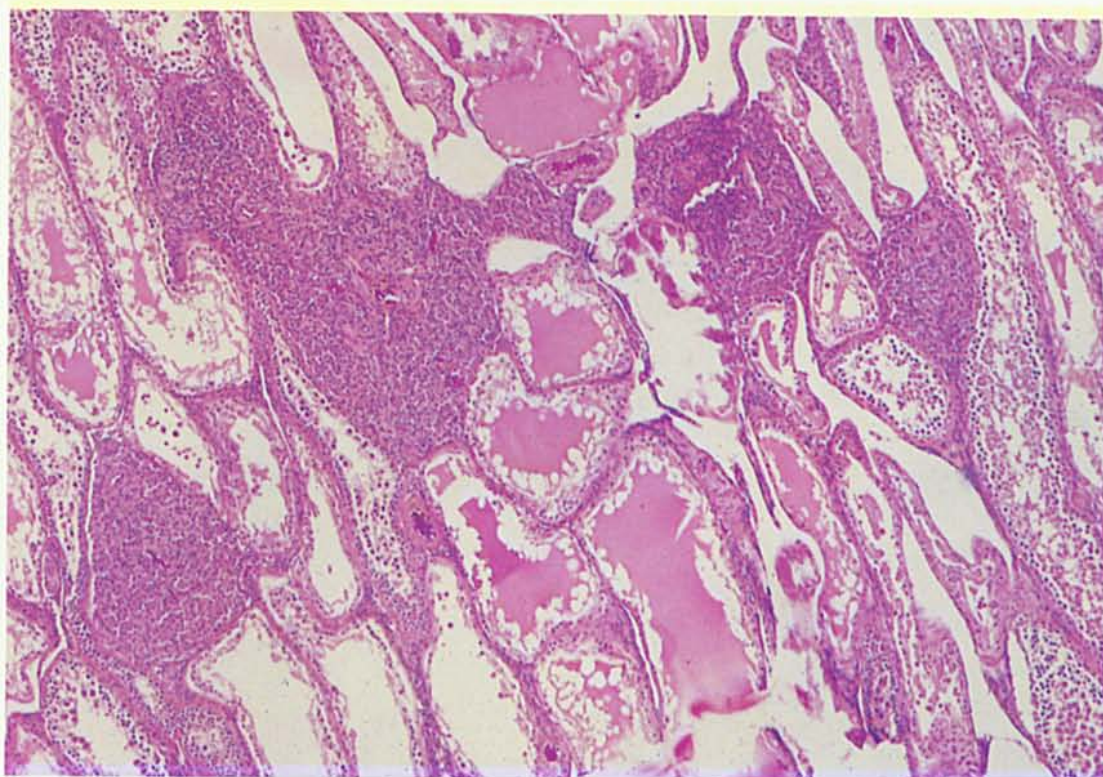


Fig. 6 – Coalescence of adjacent interstitial cell foci. According to the criteria for the diagnosis of interstitial cell adenoma, as set forth in this paper, the coalescence and size of the mass qualifies it as interstitial cell adenoma. 40x, H&E

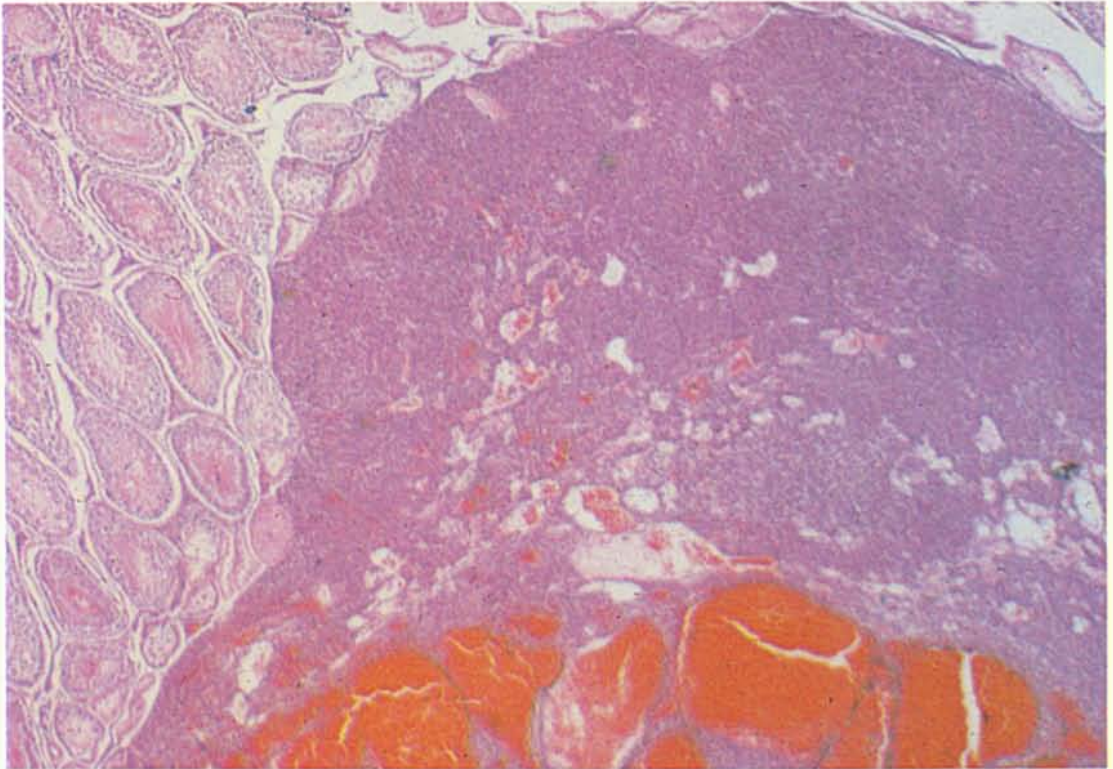


Fig. 7 – Interstitial cell adenoma. Note the development of a conspicuous vascular network and large blood-filled cysts. 40x, H&E

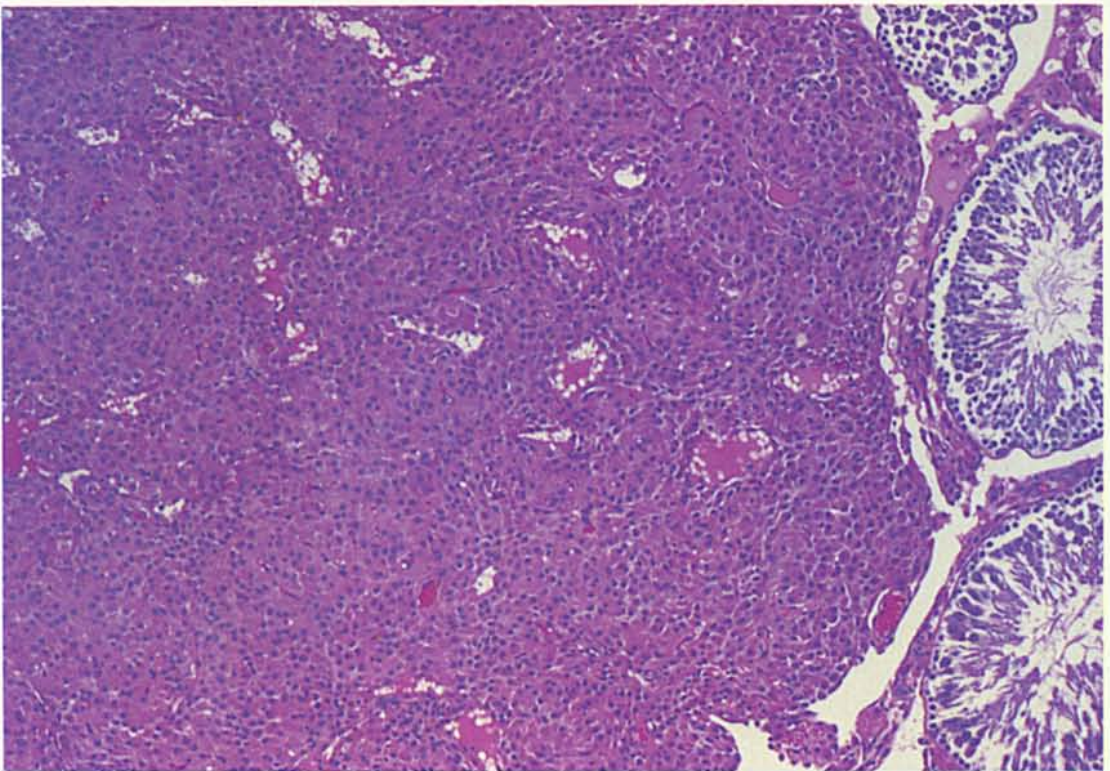


Fig. 8 – Typical interstitial cell adenoma. 63x, H&E (Photo courtesy of Dr. D. Sinha)

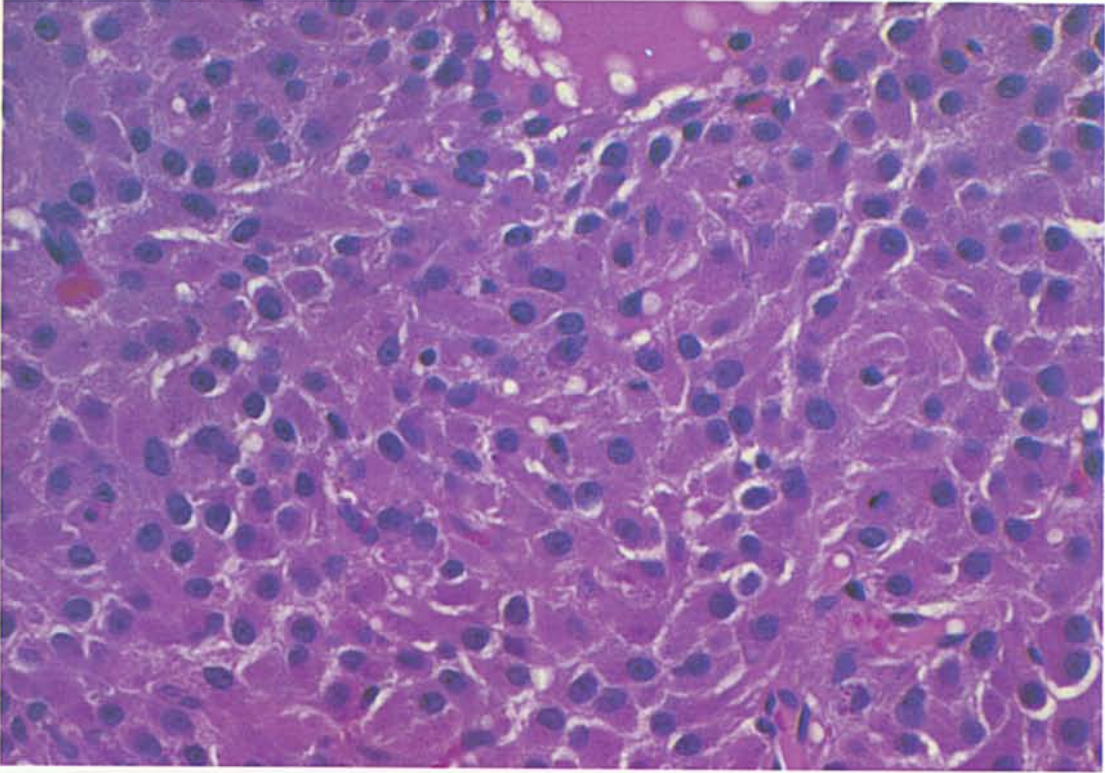


Fig. 9 – Cellular morphology of neoplasm in Figure 8. Note mitotic figures. 250x, H&E (Photo courtesy of Dr. D. Sinha)

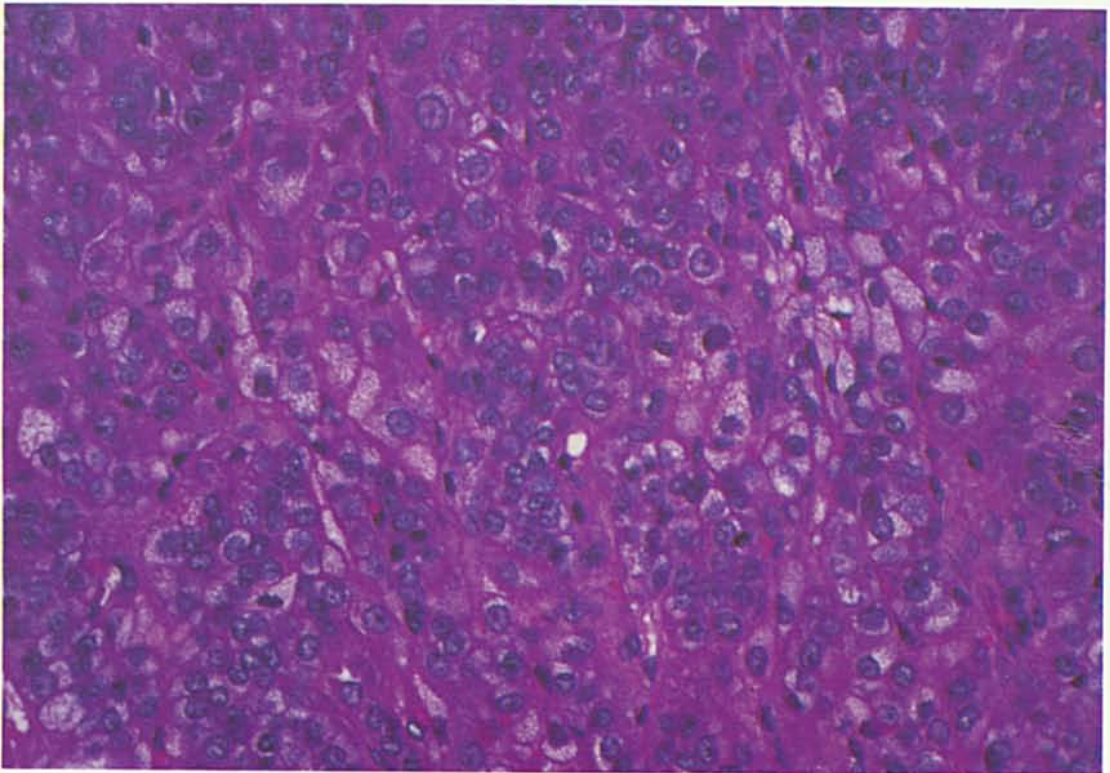


Fig. 10 – Variation of cell morphology in interstitial cell adenoma. Note small dark cell variants. 250x, H&E (Photo courtesy of Dr. D. Sinha)

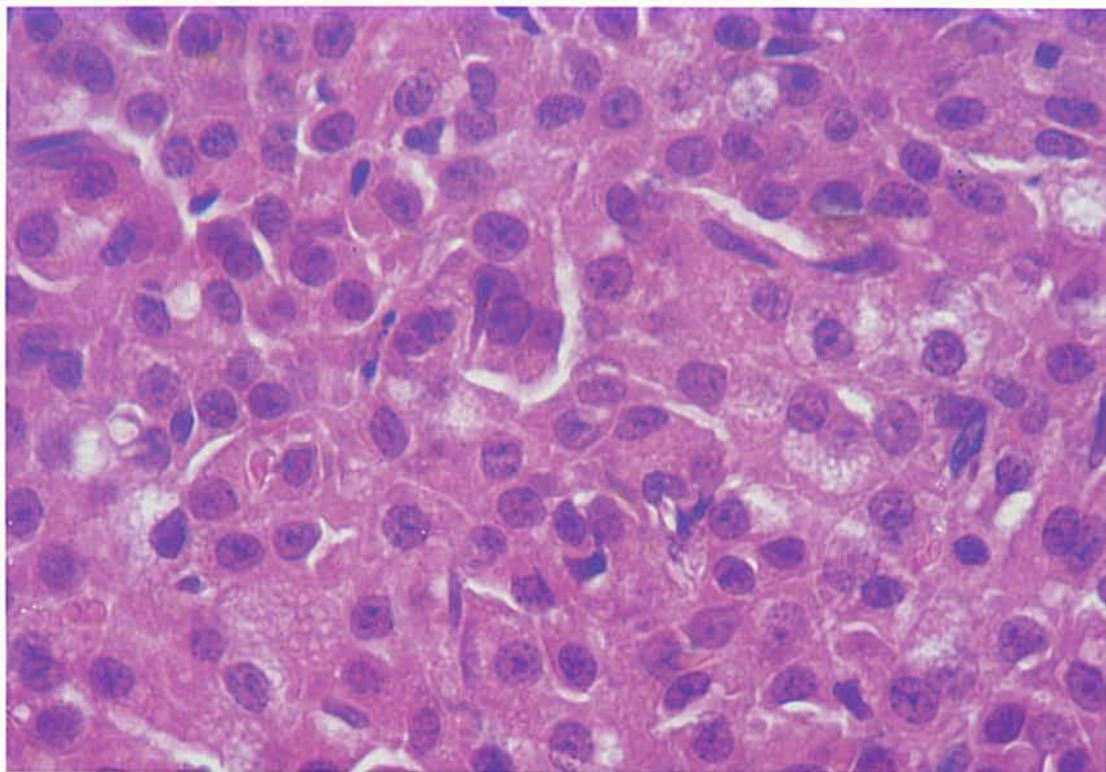


Fig. 11 – Focal interstitial cell hyperplasia. Well-defined cell morphology, lack of mitotic activity or sinusoidal network. Compare with Figure 3, diffuse interstitial cell hyperplasia. 400x, H&E

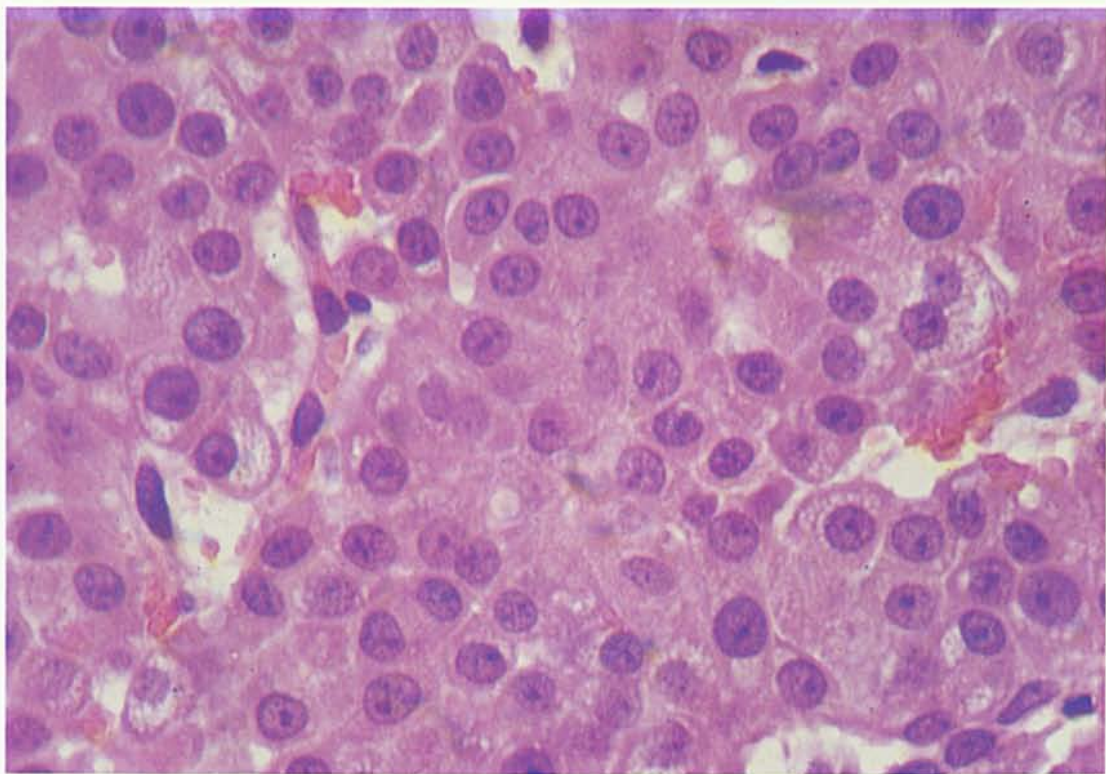


Fig. 12 – Interstitial cell adenoma. Cellular morphology similar to both diffuse and focal interstitial cell hyperplasia in Figures 3 and 11. Note, however, the development of a delicate sinusoidal network. 400x, H&E

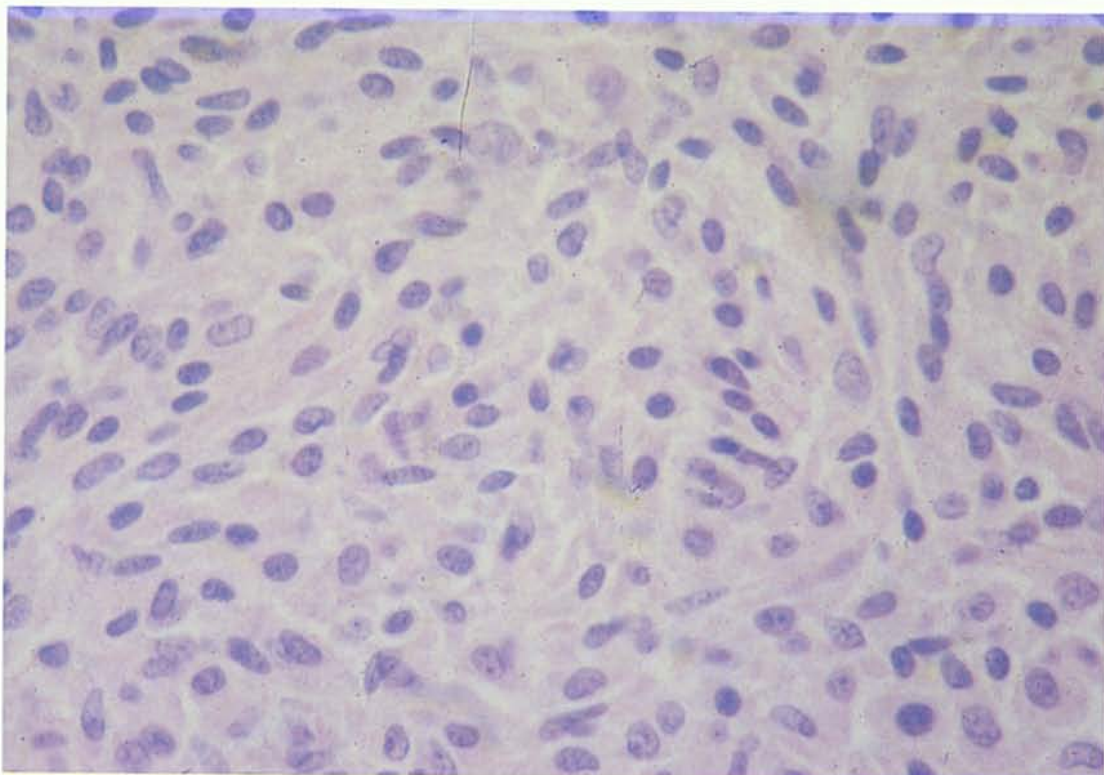


Fig. 13 – Interstitial cell adenoma from a CD-1 mouse. Note the elongated spindle shaped cells in contrast to cells in Figure 12. 400x, H&E

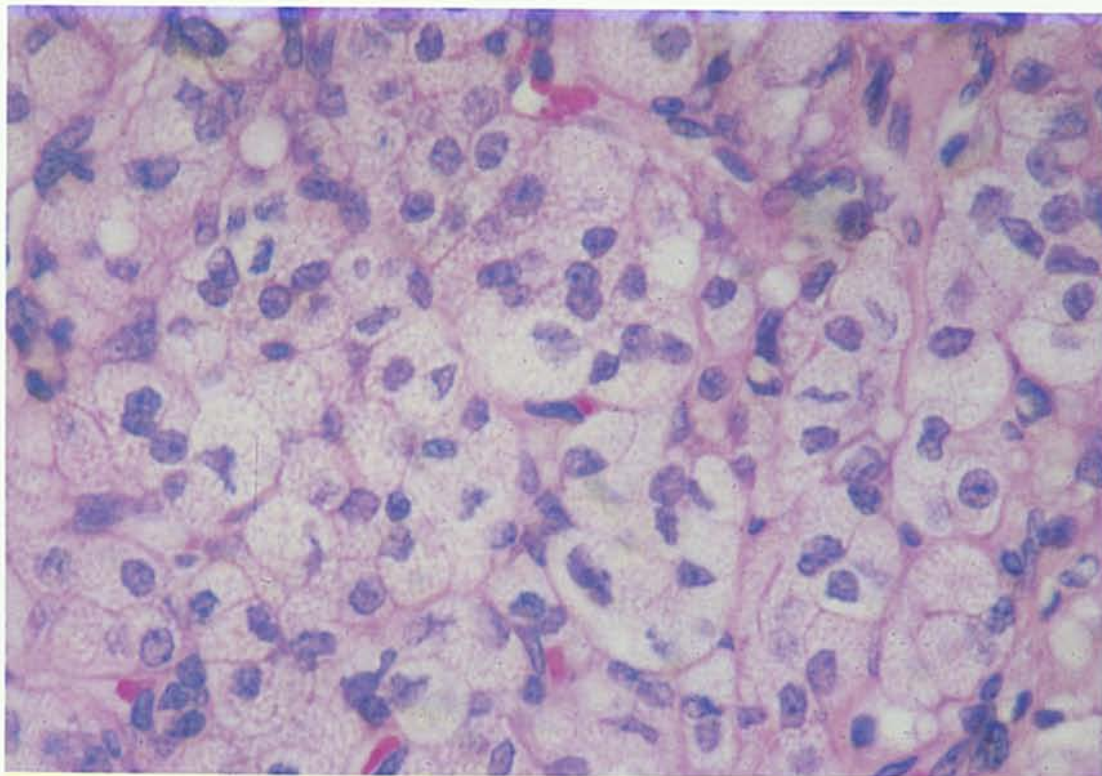


Fig. 14 – Interstitial cell adenoma from a CD-1 mouse. A morphological variant having clear, distended, finely vacuolated cytoplasm. 400x, H&E

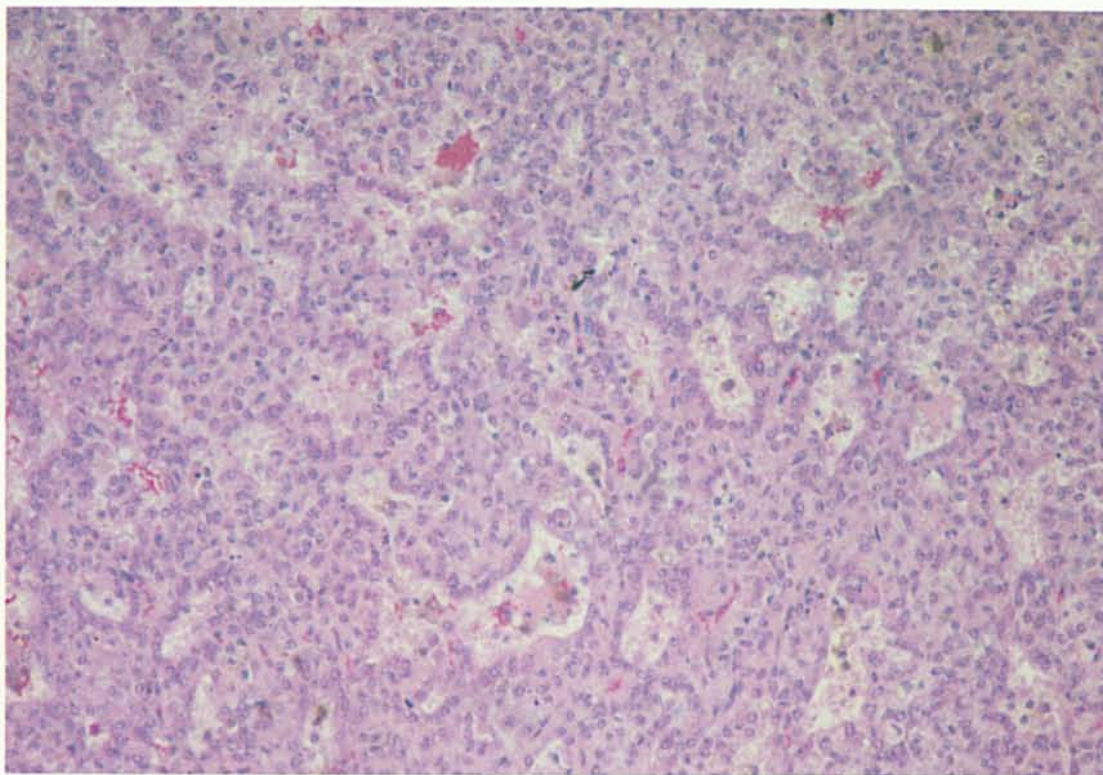


Fig. 15 – Interstitial cell adenoma from a CD-1 mouse showing the ductal-glandular pattern that also occurs in the rat. 100x, H&E

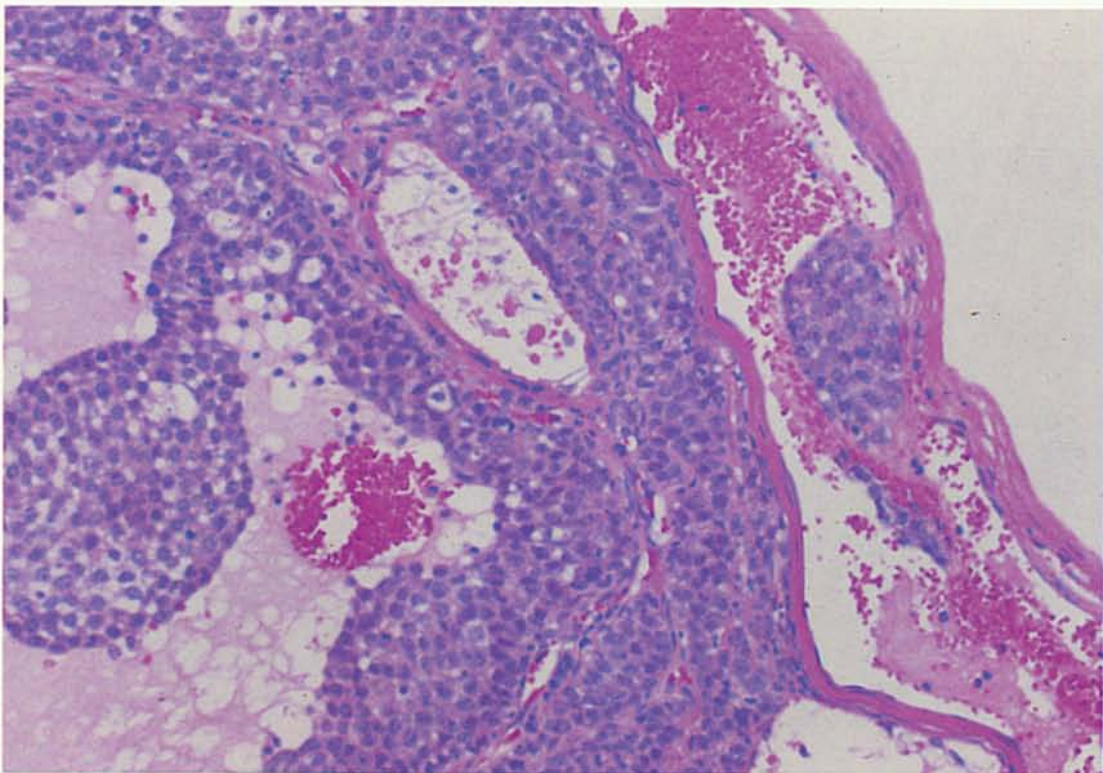


Fig. 16 – Interstitial cell carcinoma, rat. Note the tumor embolus in the adjacent vessel. 50x, H&E (Photos courtesy of Drs. L.E. Hart-Elcock and T.F. Hastings)

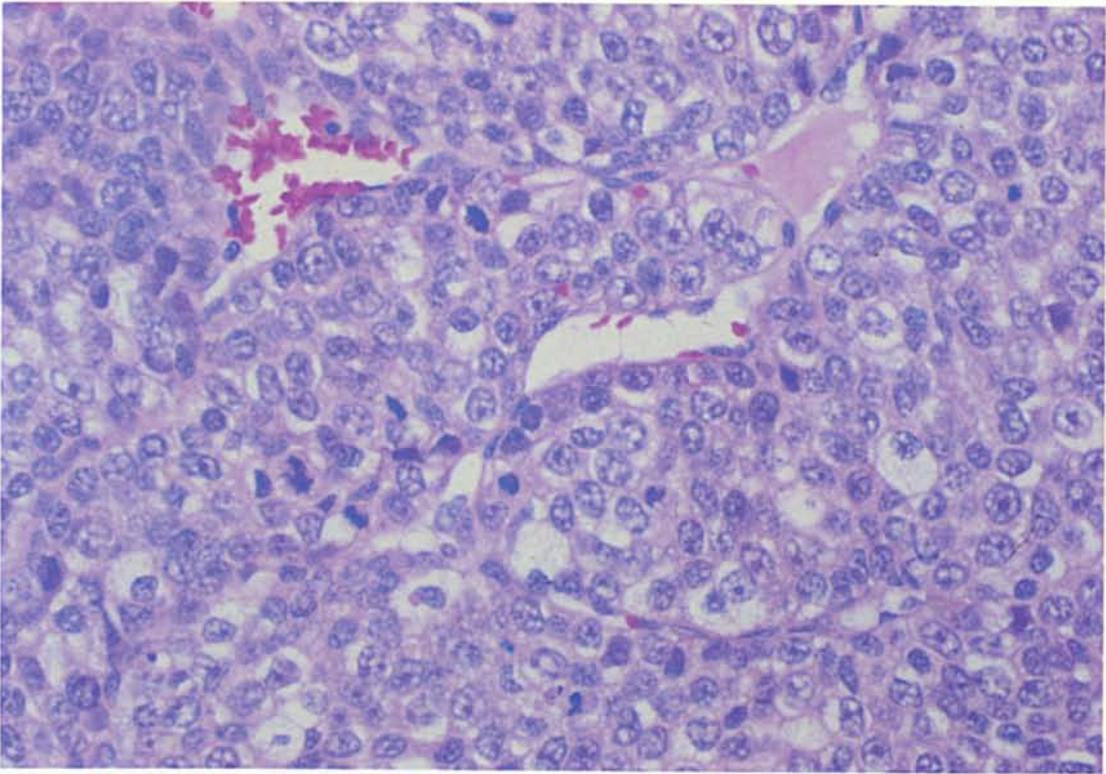


Fig. 17 – Cellular morphology of carcinoma in Figure 16. Pleomorphic cell population and numerous mitotic figures. 250x, H&E

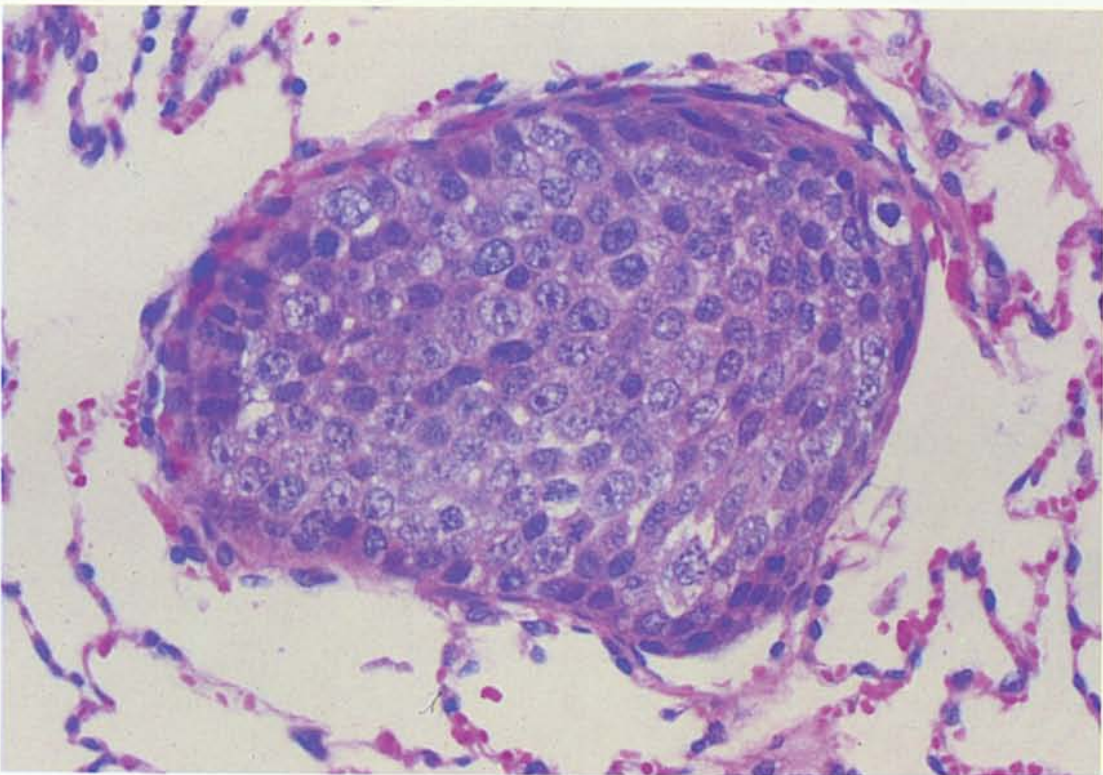


Fig. 18 – Metastatic interstitial cell carcinoma in a rat's lung from the neoplasm depicted in Figs. 16 and 17. 250x, H&E

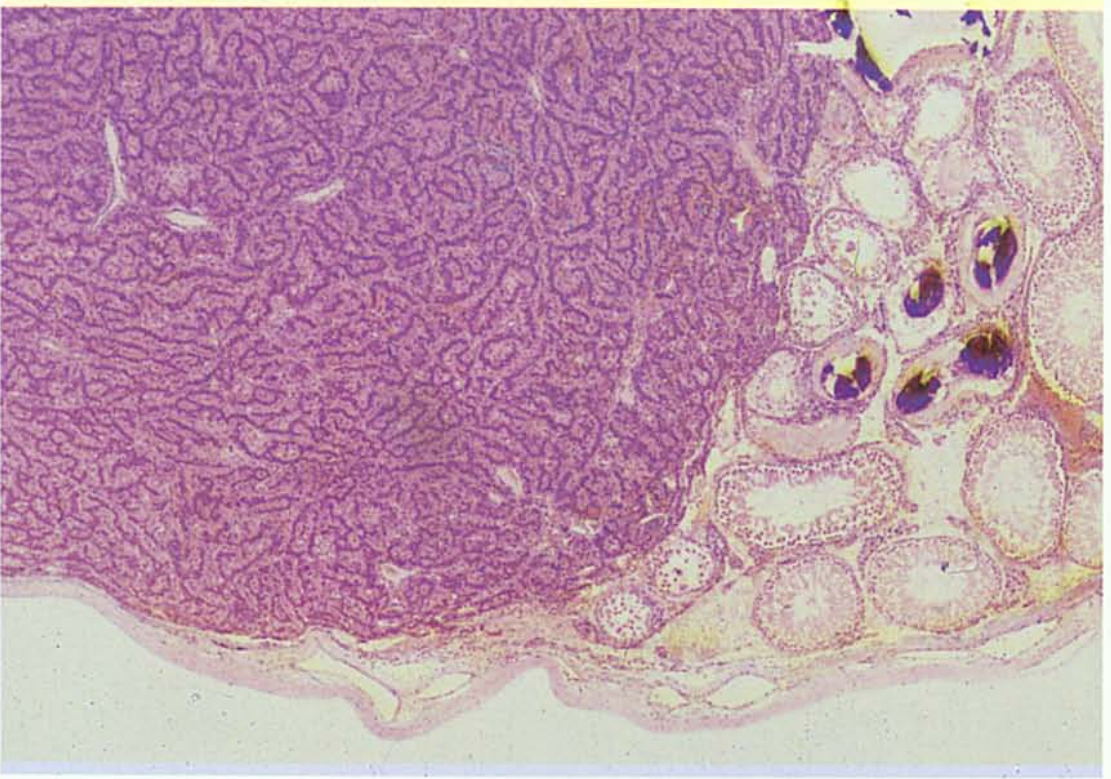


Fig. 19 – Sertoli cell carcinoma, testis, rat. 10x, H&E (Photos. courtesy of Dr. M. Elwell)

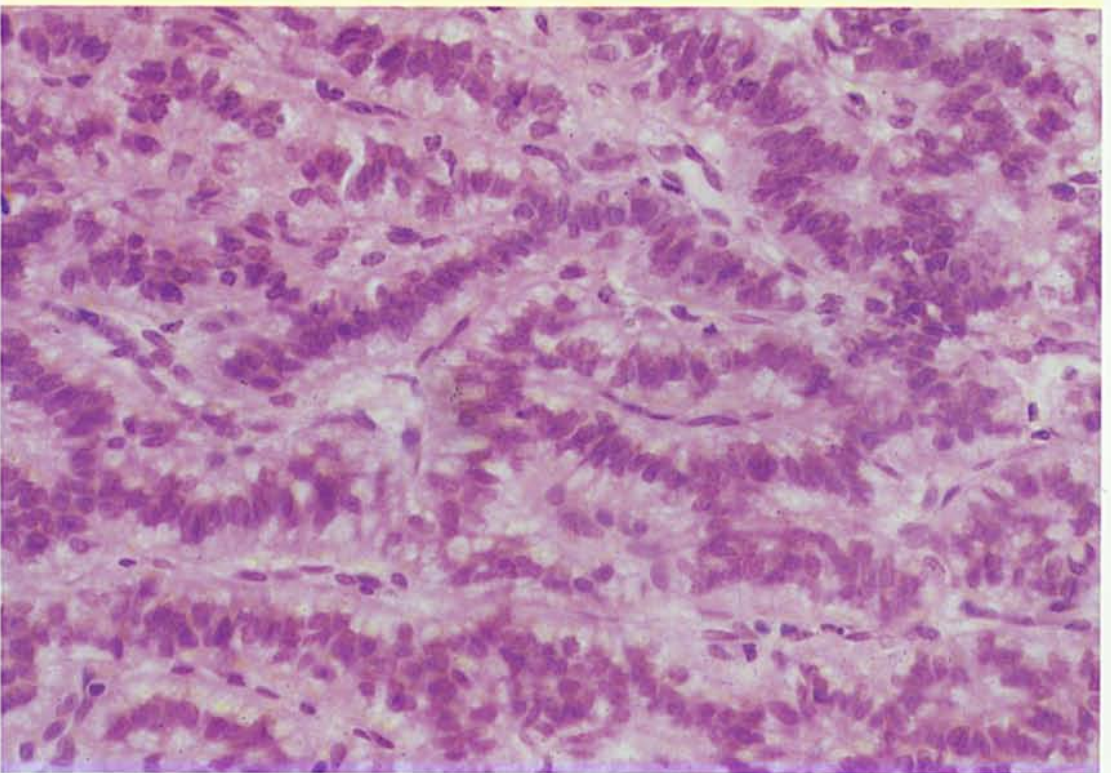


Fig. 20 – Cellular morphology of neoplasm in Figure 19. Note the typical palisaded cell growth with vacuolated cells lined upon a thin fibrous basement membrane. 100x, H&E

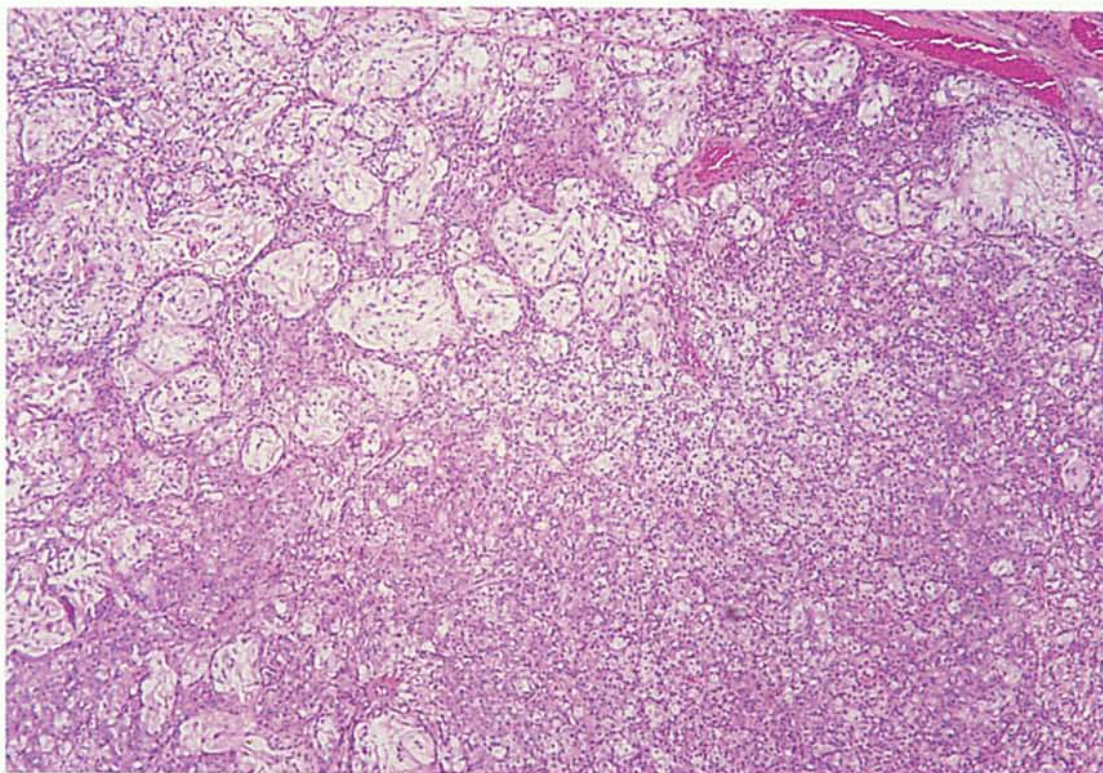


Fig. 21 – Sertoli/interstitial cell neoplasm (mixed gonadal-stromal tumor). Tubules lined with Sertoli-like cells upper left and interstitial cell component lower right. CdCl₂ treated Wistar rat. (Photos courtesy of Drs. S. Rehm and M.P. Waalkes)

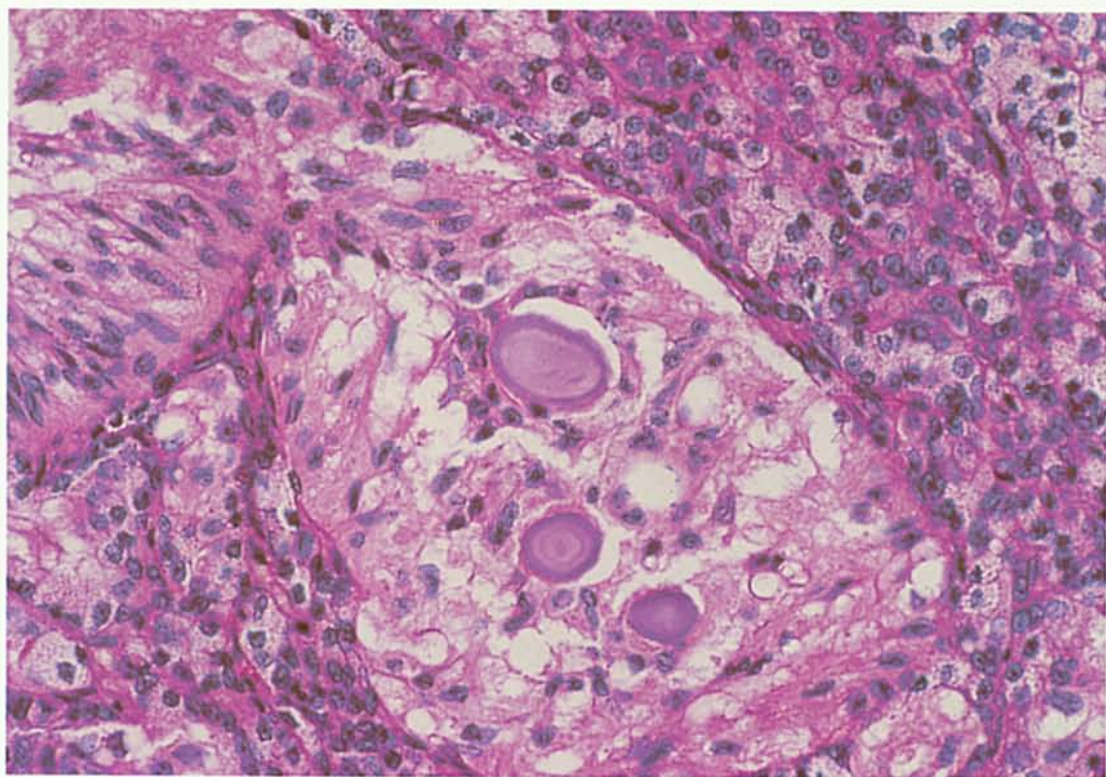


Fig. 22 – Higher power view of neoplasm in Figure 21 showing typical Sertoli cells lining pseudotubules which contain concentrically laminated mineralized concretions resembling psammoma bodies. 250x, H&E

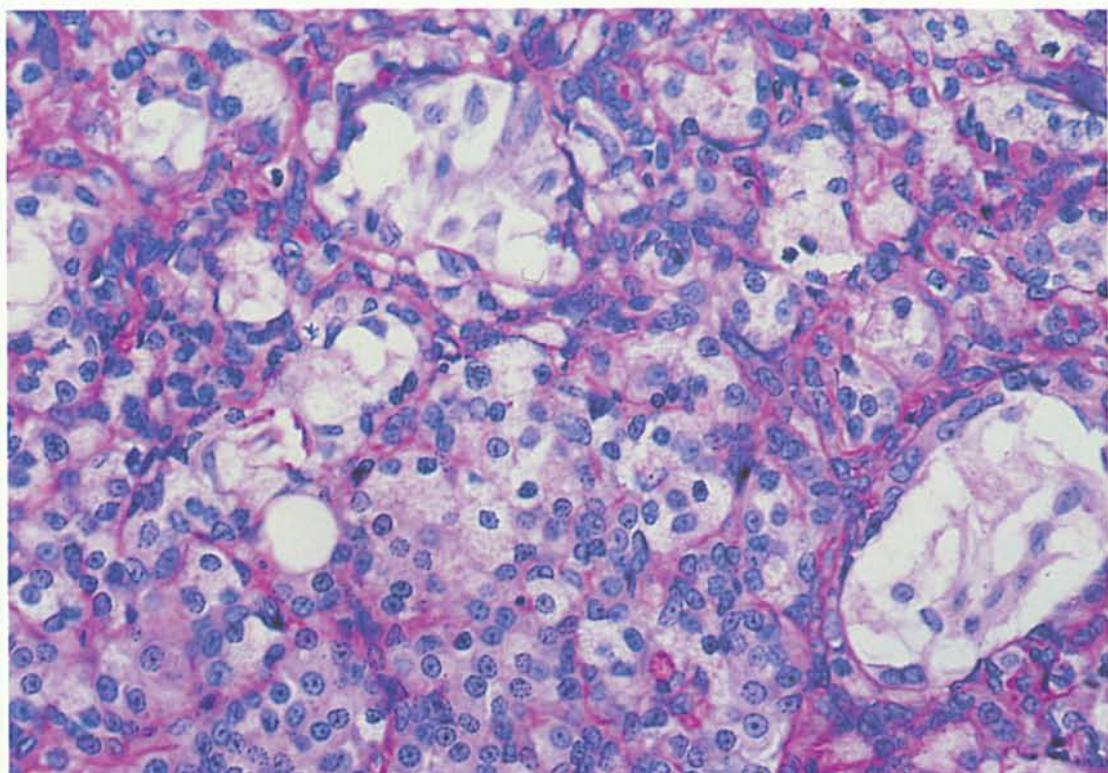


Fig. 23 – Same neoplasm as Figures 21 and 22 showing the interstitial cell component, 250x, H&E

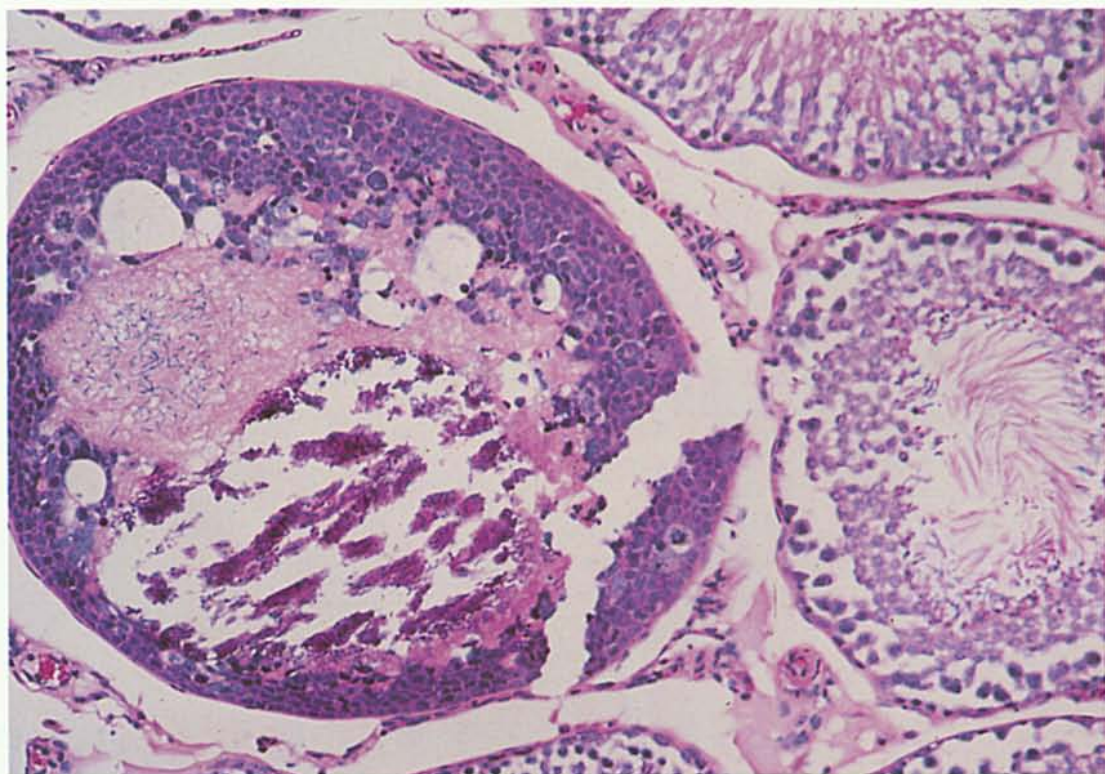


Fig. 24 – Spermatocytic seminoma, in a Wistar rat, which had been treated with $CdCl_2$, 100x, H&E (Photos courtesy of Dr. M. Elwell)

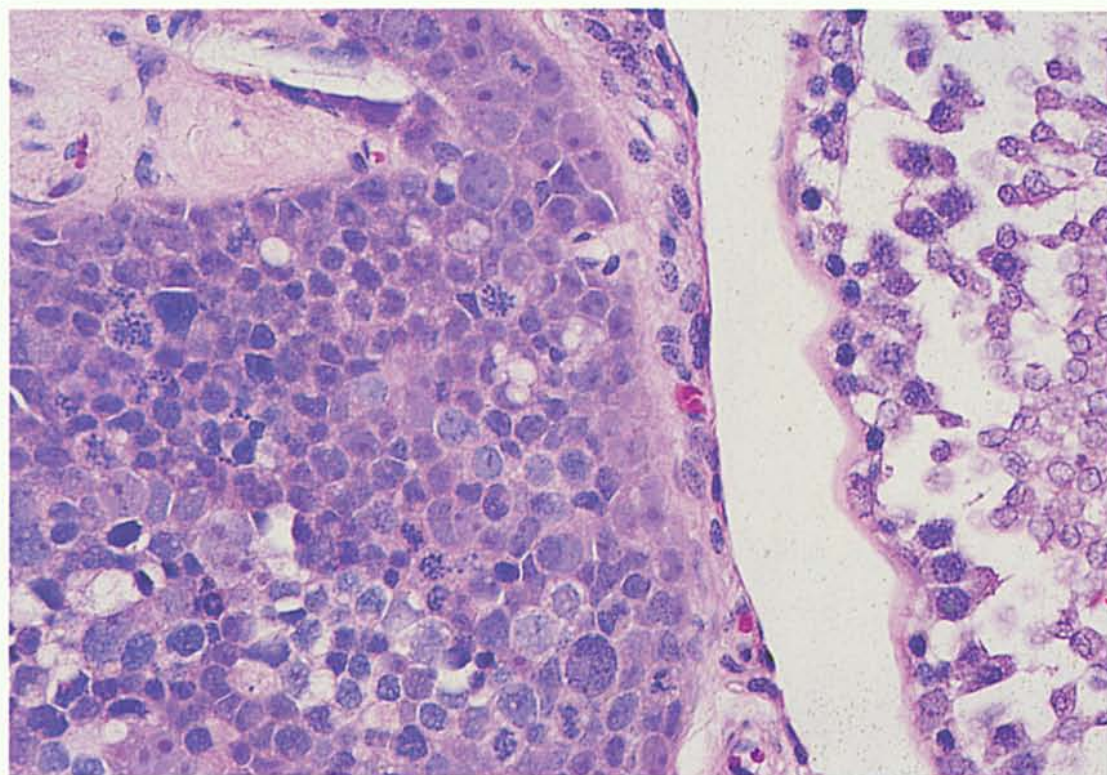


Fig. 25 – Cellular morphology of neoplasm in Figure 24 showing the pleomorphic cell population and bizarre mitotic figures typical of seminomas in other species. 250x, H&E

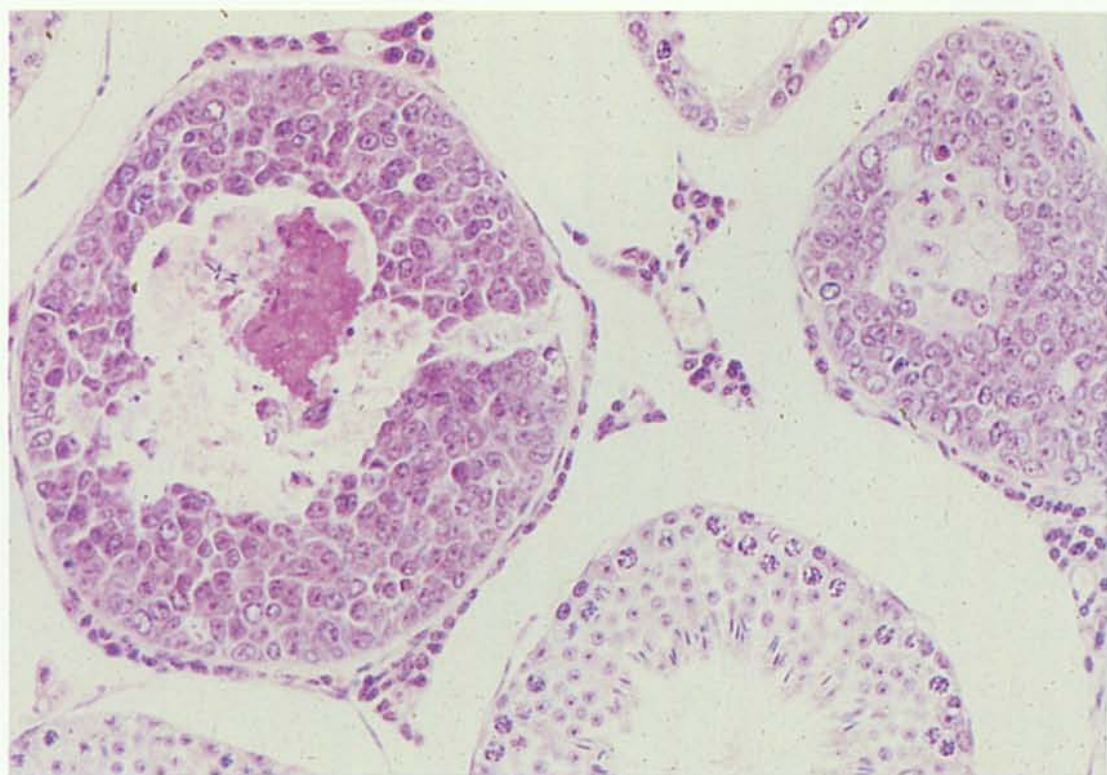


Fig. 26 – Spermatocytic seminoma, testis, NMRI mouse, 105 weeks of age. 72x, H&E (Photo courtesy of Dr. H. Westen)

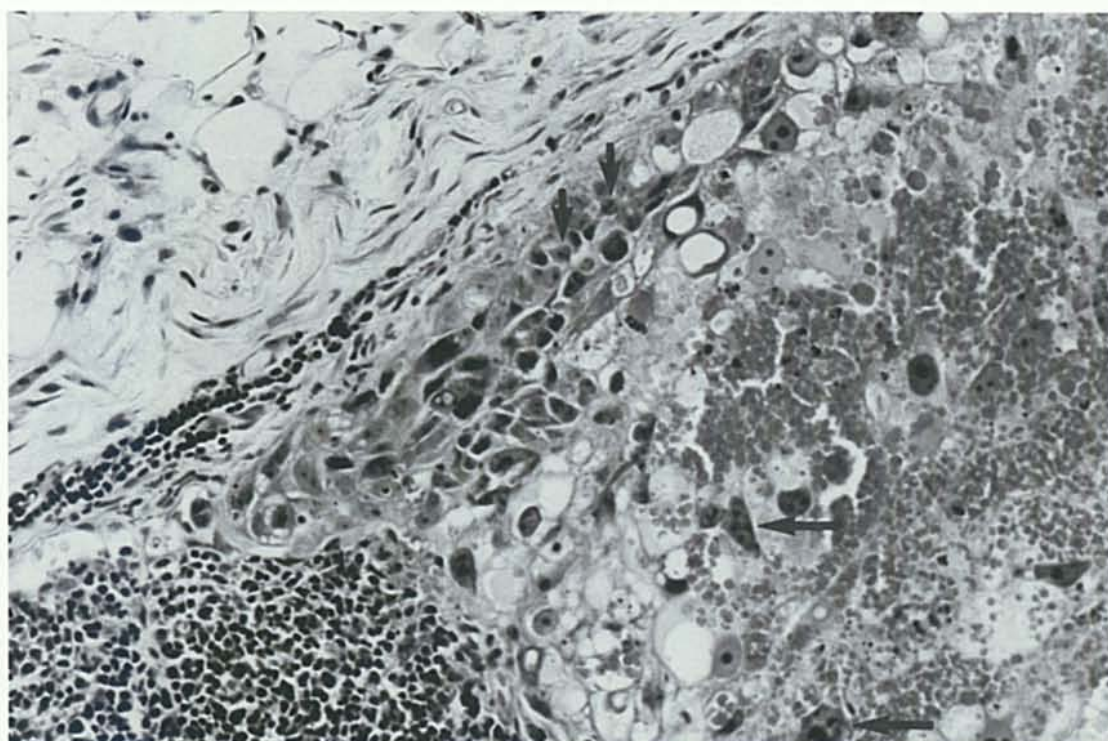


Fig. 27 – Choriocarcinoma, cervical lymph node, Sprague Dawley rat. Nodule surrounded by fibrous tissue. Note the presence of small cytotrophoblasts (short arrows), trophoblastic giant cells (long arrows) and hemorrhage toward the inner area of the nodule. (Photos courtesy of Pirek, et. al. (1991) with permission of Veterinary Pathology)

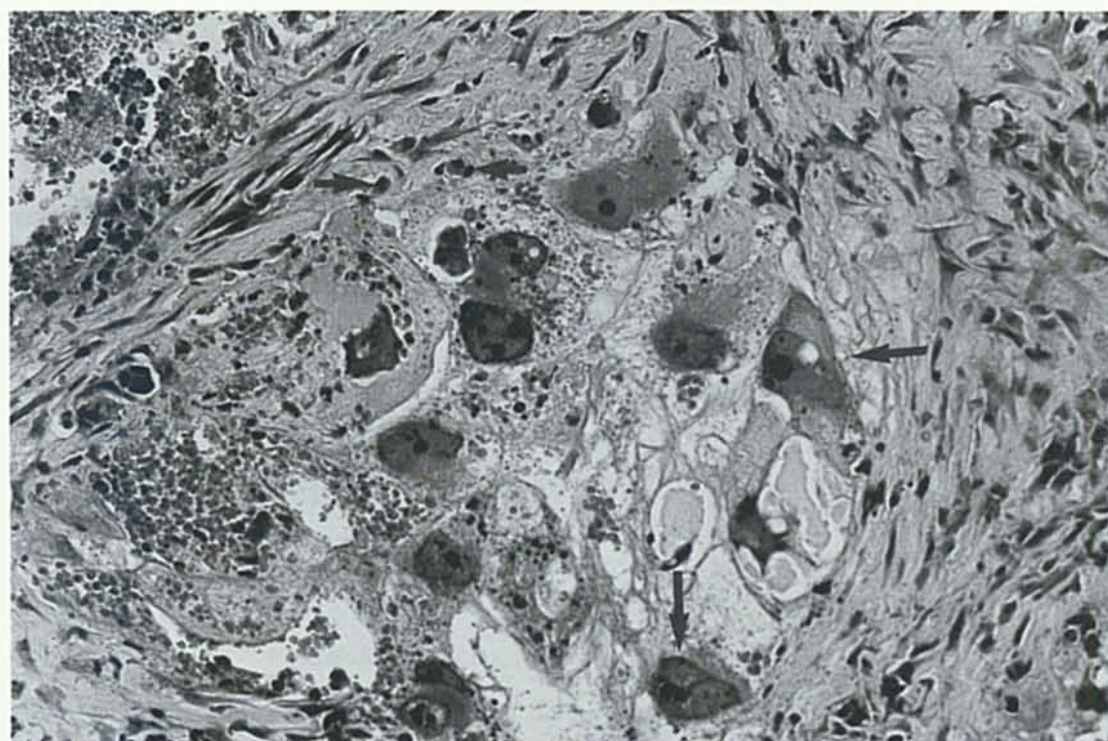


Fig. 28 – Choriocarcinoma, cervical lymph node. Trophoblastic giant cells (long arrows) with giant nuclei containing one or multiple nucleoli. Small cytotrophoblasts are identified with short arrows. Note phagocytized erythrocytes in the cytoplasm of trophoblastic giant cells.

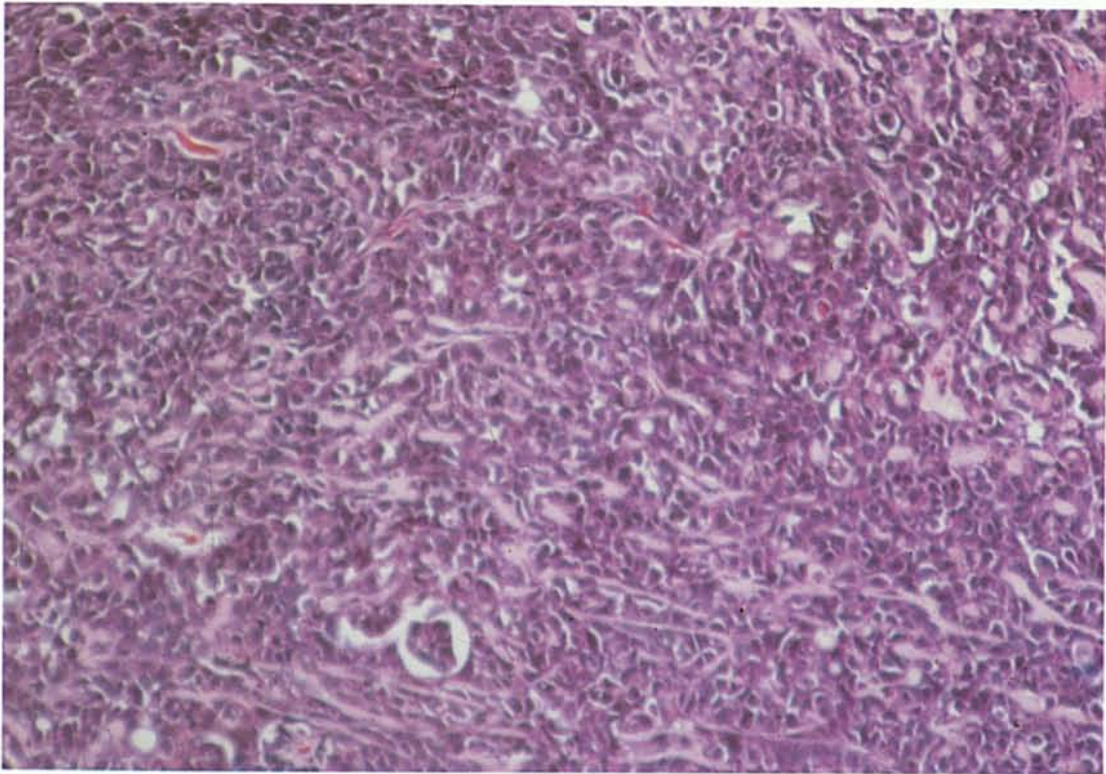


Fig. 29 – Experimental yolk sac carcinoma in a rat. 100x, H&E (Photo courtesy of AFIP and Dr. G. Migaki)

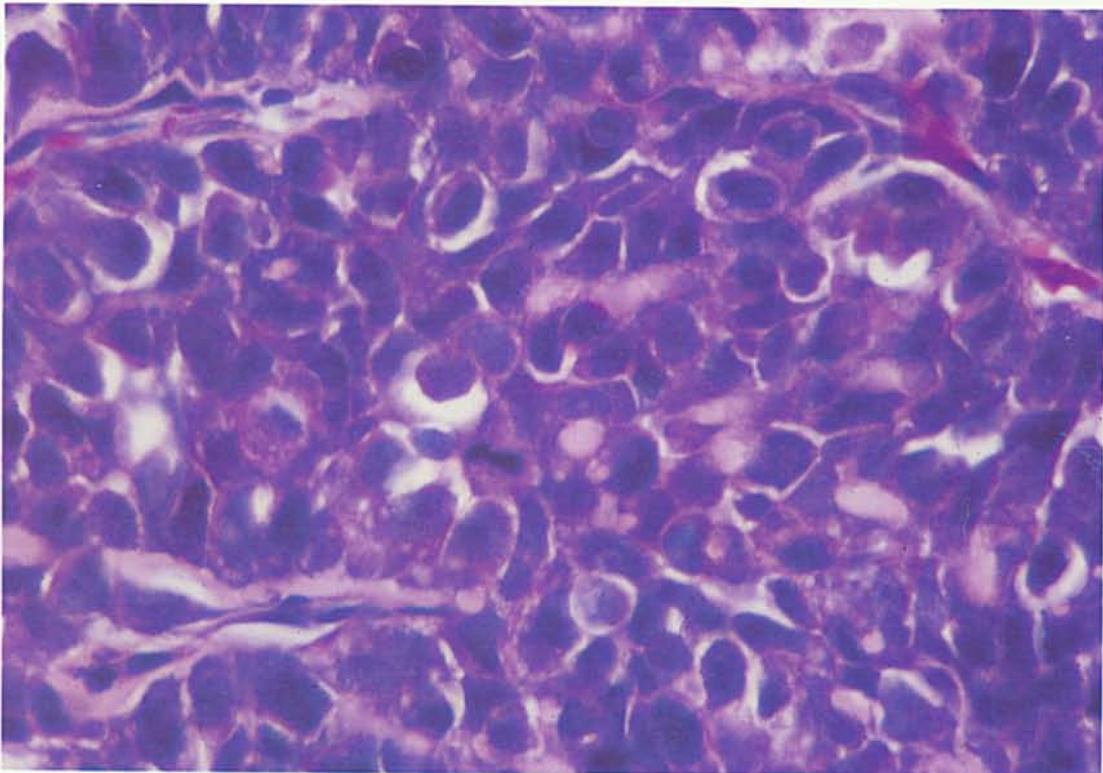


Fig. 30 – Cellular morphology of previous neoplasm. (Compare with Figure 32, spontaneous yolk sac carcinoma in the mouse.) 400x, H&E

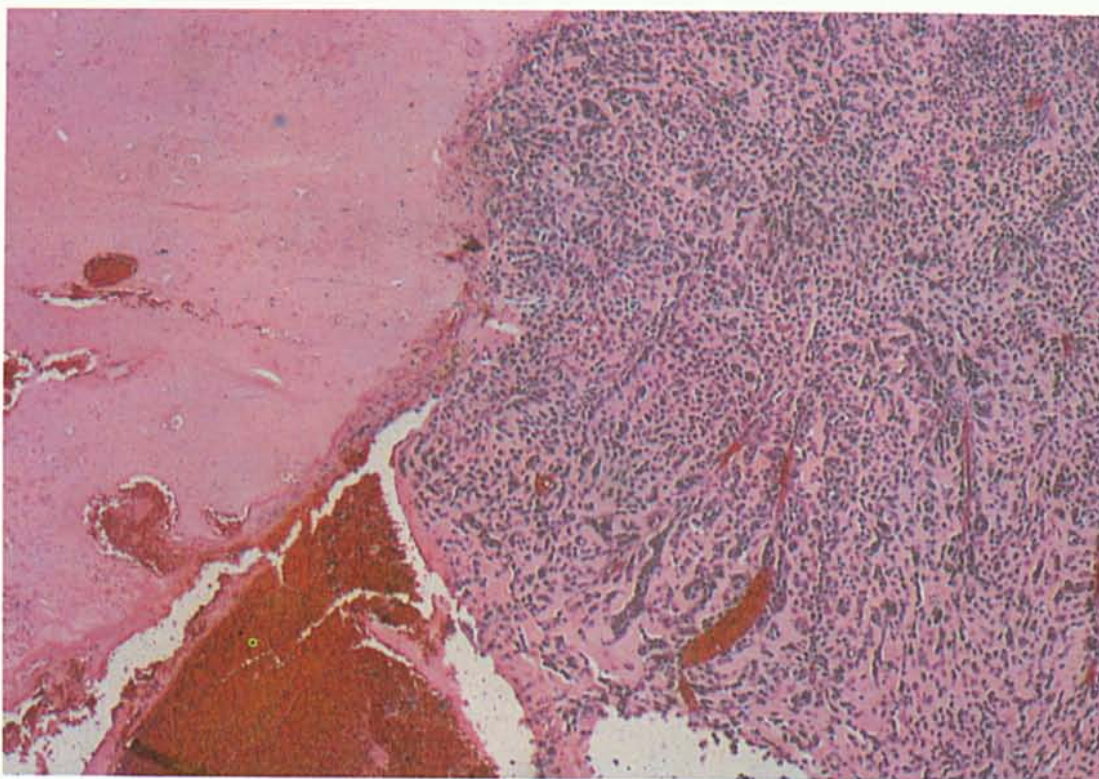


Fig. 31 – Spontaneous yolk sac carcinoma, ovary, CD-1 mouse. 40x, H&E

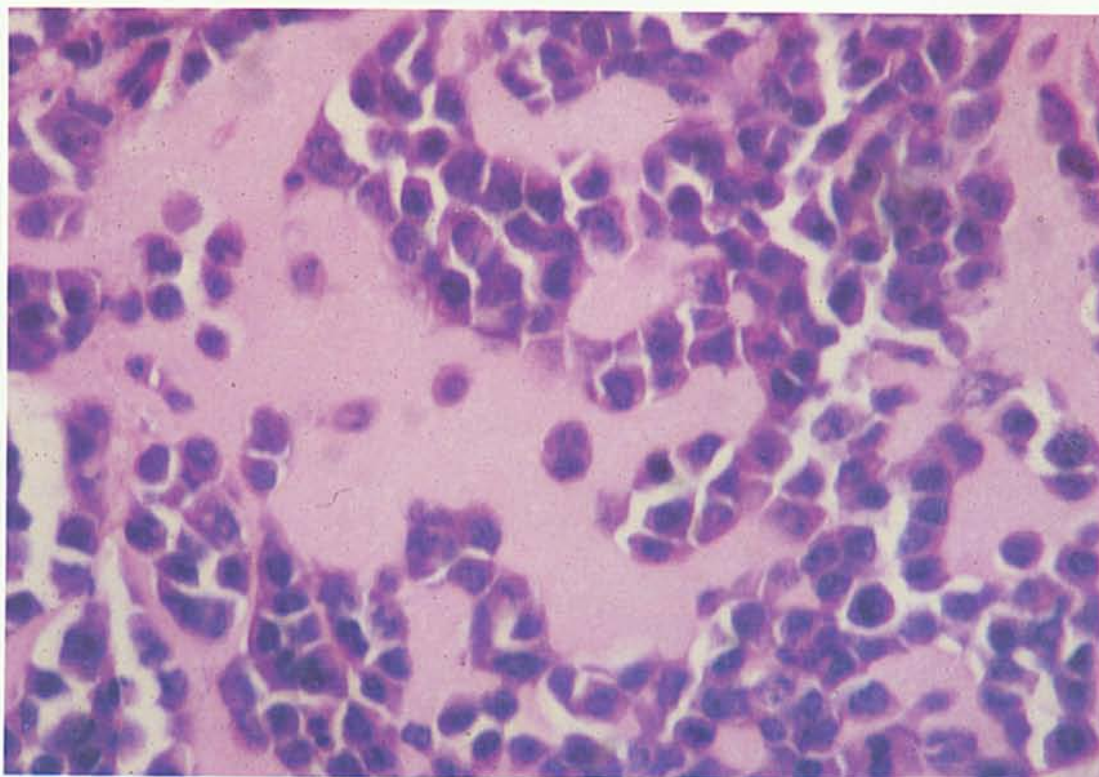


Fig. 32 – Cellular morphology of neoplasm in Figure 31. Small cuboidal to angular cells with dark compact nuclei suspended in pink proteinaceous fluid. 400x, H&E

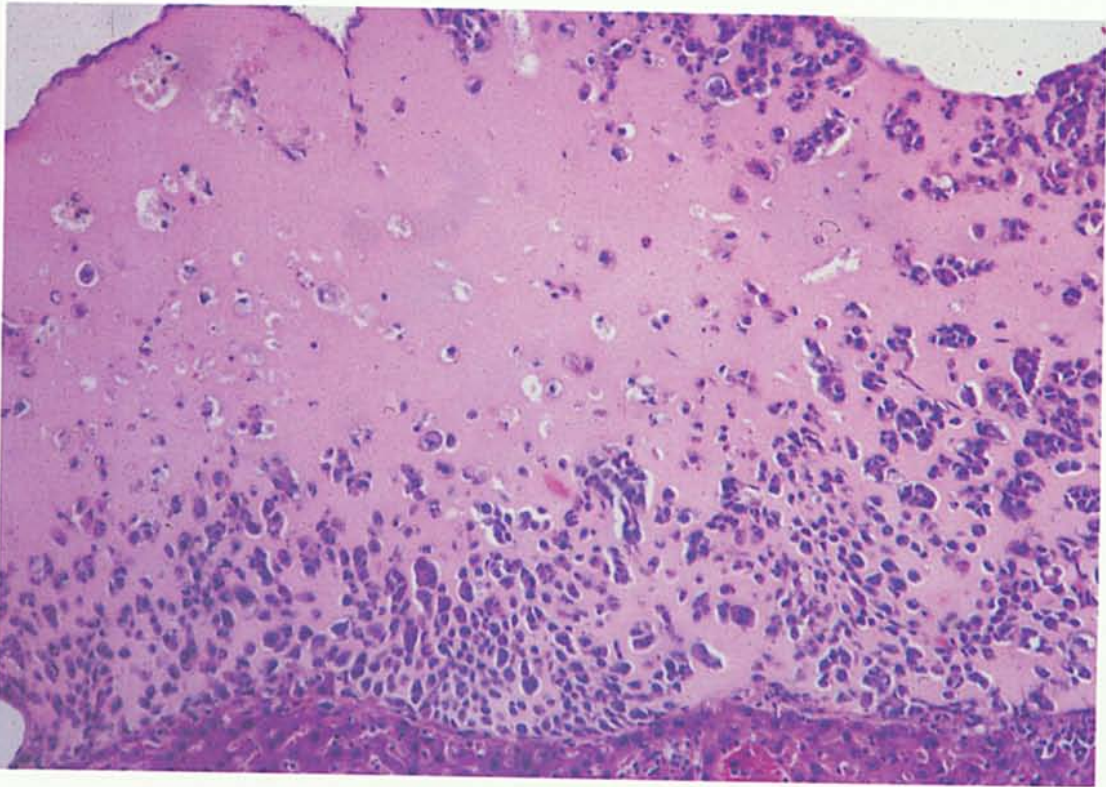


Fig. 33 – Typical metastatic growth on the liver of a yolk sac carcinoma. Note the lack of invasion of the liver parenchyma. 100x, H&E

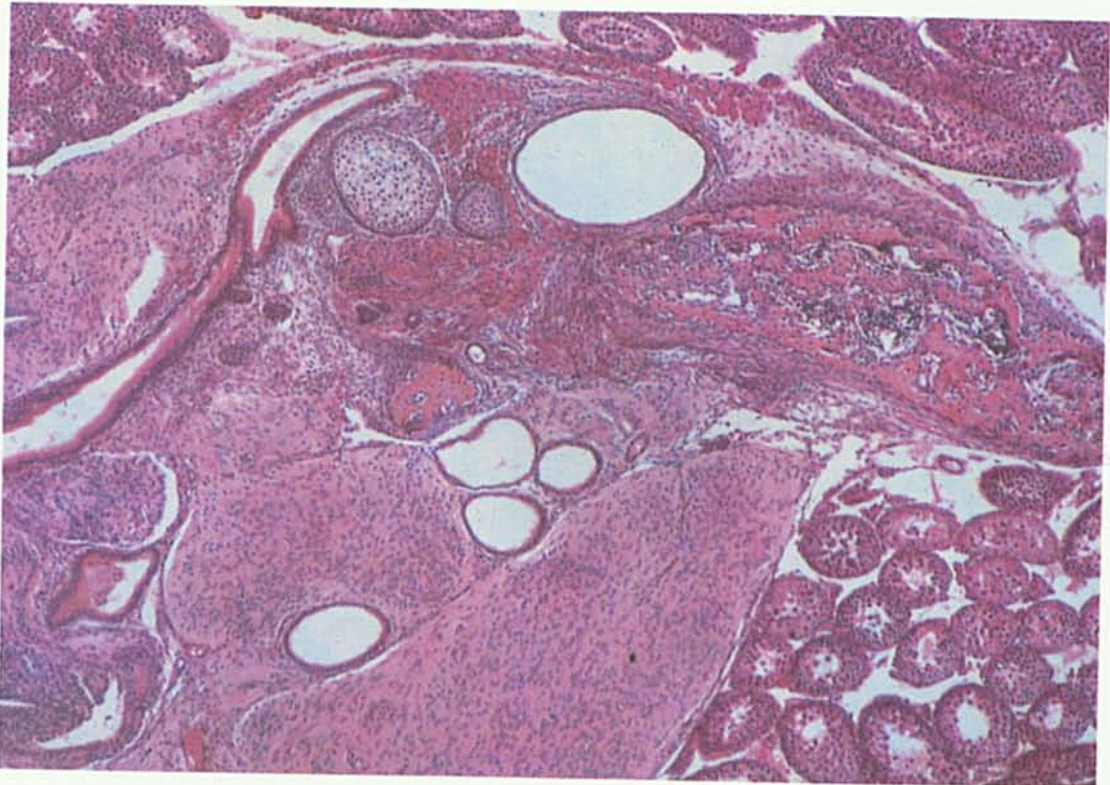


Fig. 34 – Benign teratoma, testis, strain 129 mouse. Note the different, well differentiated types of tissue including bone, hyaline cartilage, myoid cells, and ciliated epithelium lining ducts and cystic structures. 40x, H&E (Photo courtesy of AFIP and Dr. G. Migaki)

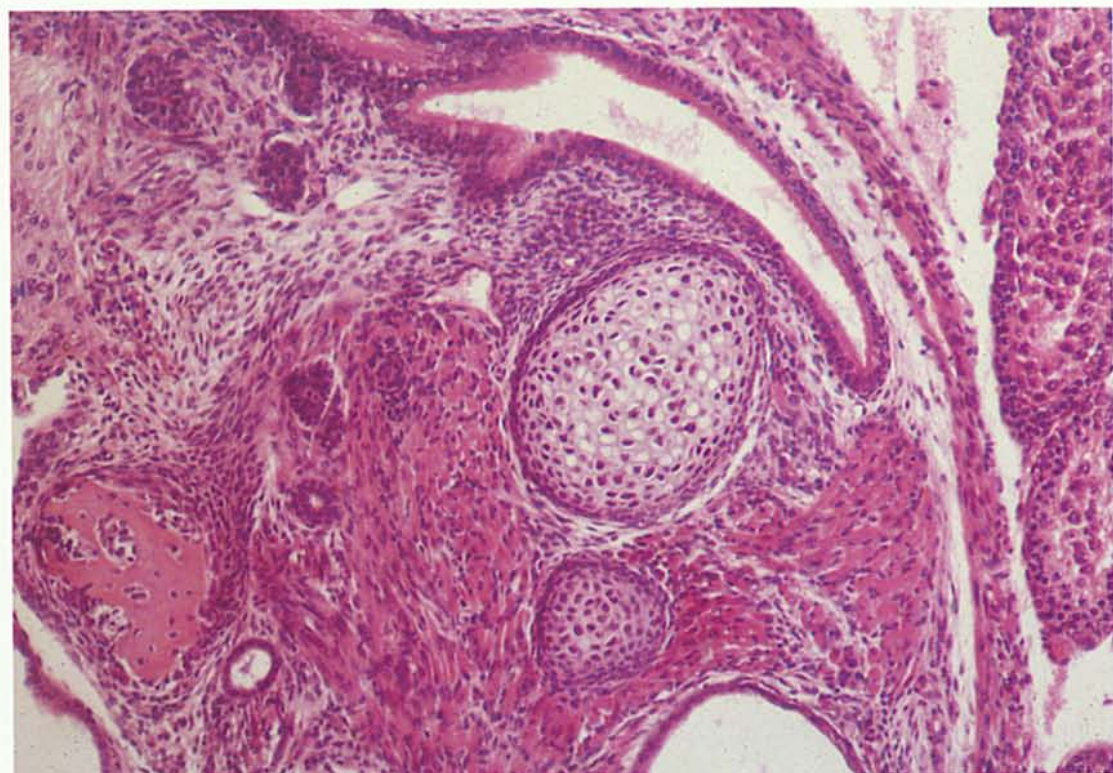


Fig. 35 – Higher power view of neoplasm in Figure 34. 100x, H&E

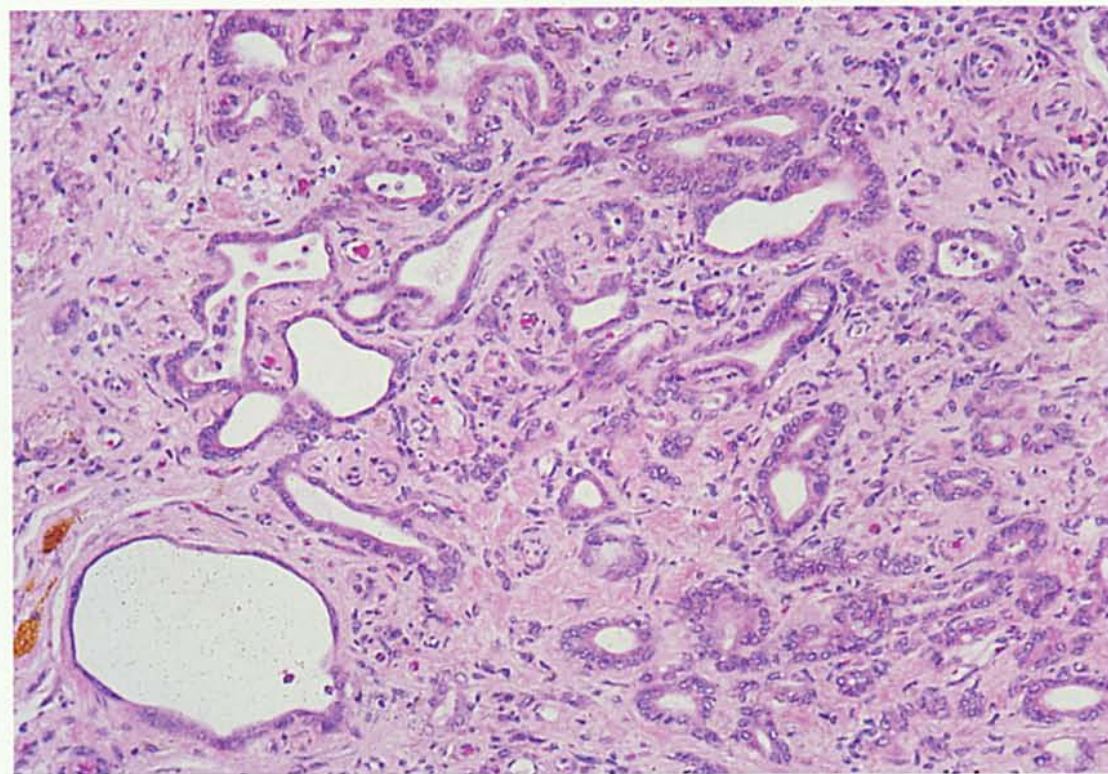


Fig. 36 – Rete testis hyperplasia. Wistar rat treated with CdCl₂. Unencapsulated nodular area composed of irregularly-shaped ducts set in a fibrous stroma. 10x, H&E (Photos courtesy of Drs. S. Rehm and M.P. Waalkes)

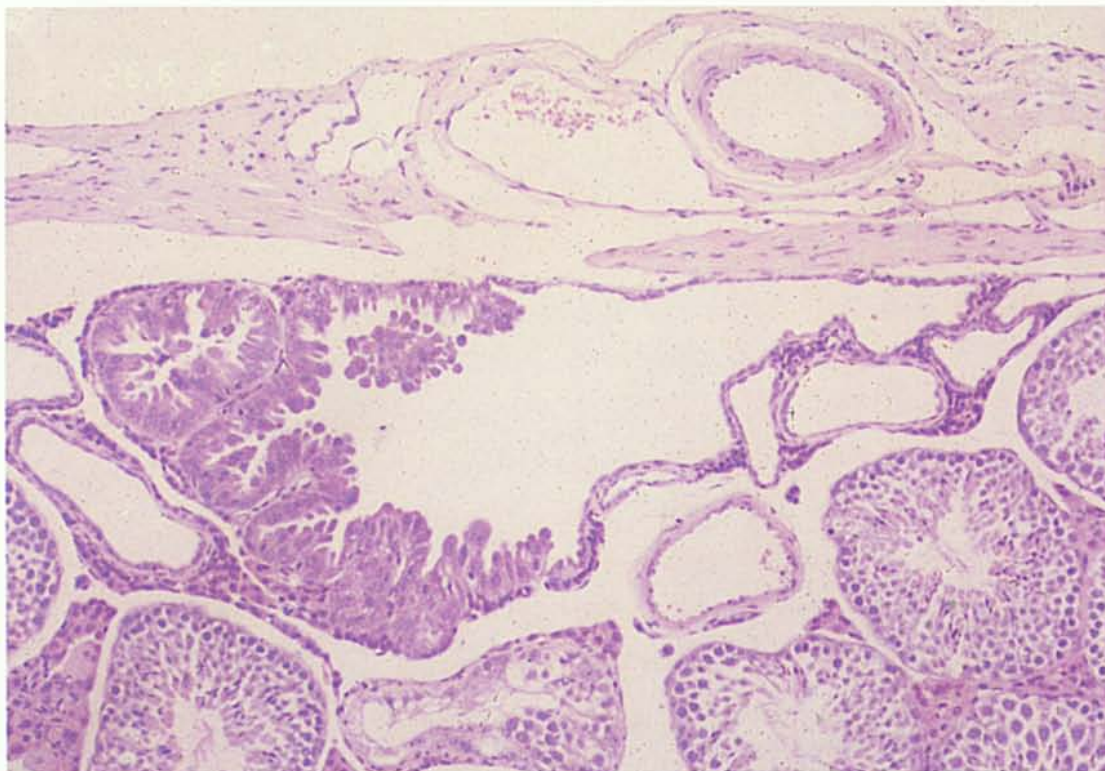


Fig. 37 – Papillary hyperplasia of the intratesticular rete testis, possibly in close approximation to the tubulus rectus. Note the adjacent vessels of the pampiniform plexus. CD-1 mouse. 33x, H&E (Photo courtesy of Dr. H. Westen)

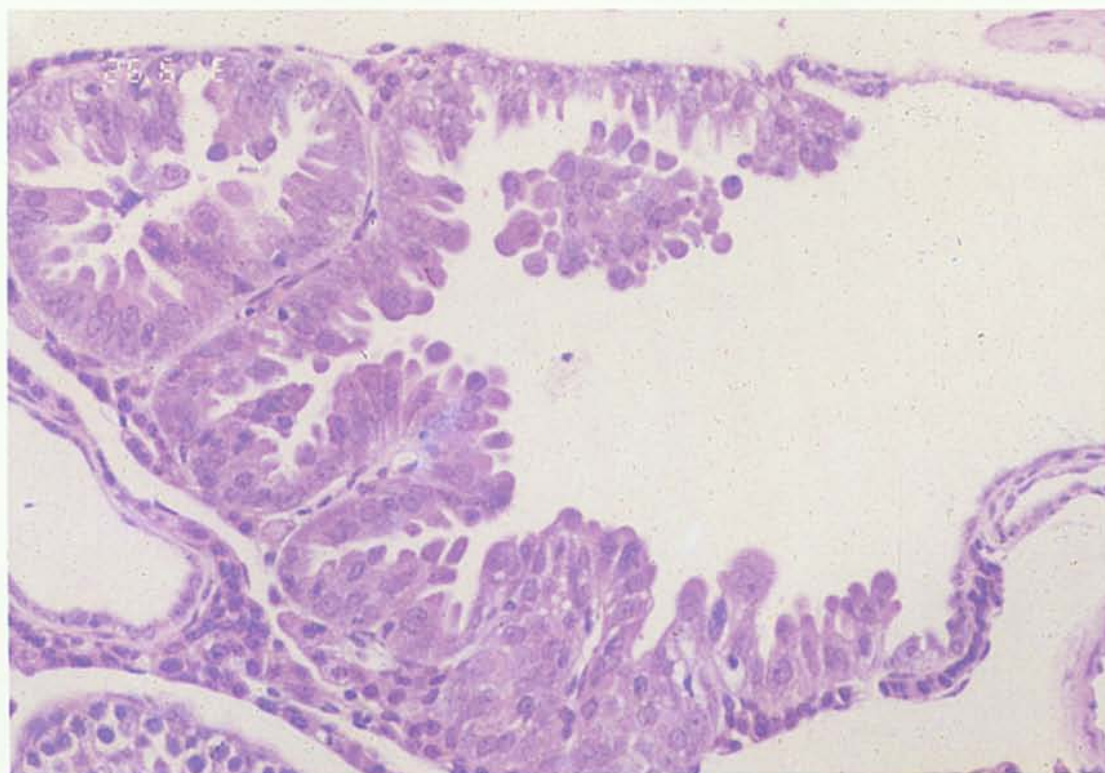


Fig. 38 – Higher power view of the previous photo showing the papillary structures lined with cuboidal to columnar epithelium with a well defined basement membrane. 66x, H&E

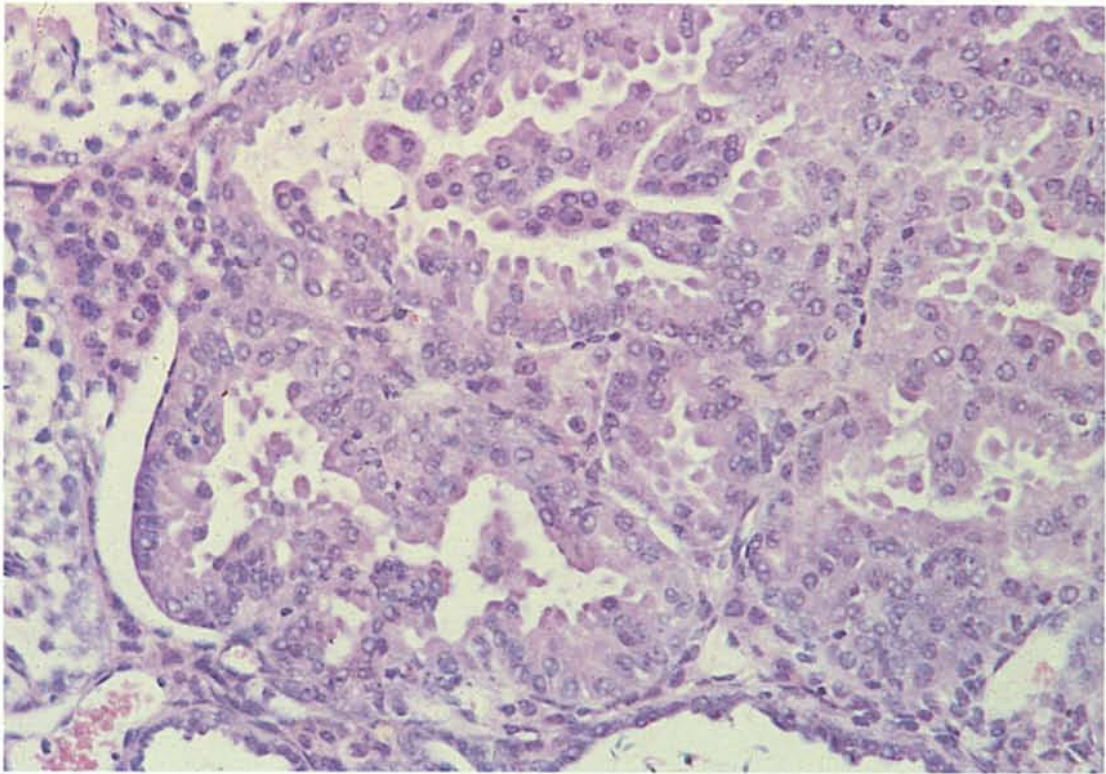


Fig. 39 – Rete testis adenoma CD-1 mouse. Note the papillary structures and the pseudostratified appearance of the epithelium. These changes assist in separating rete testis hyperplasia from adenoma. 66x, H&E (Photo courtesy of Dr. H. Westen)

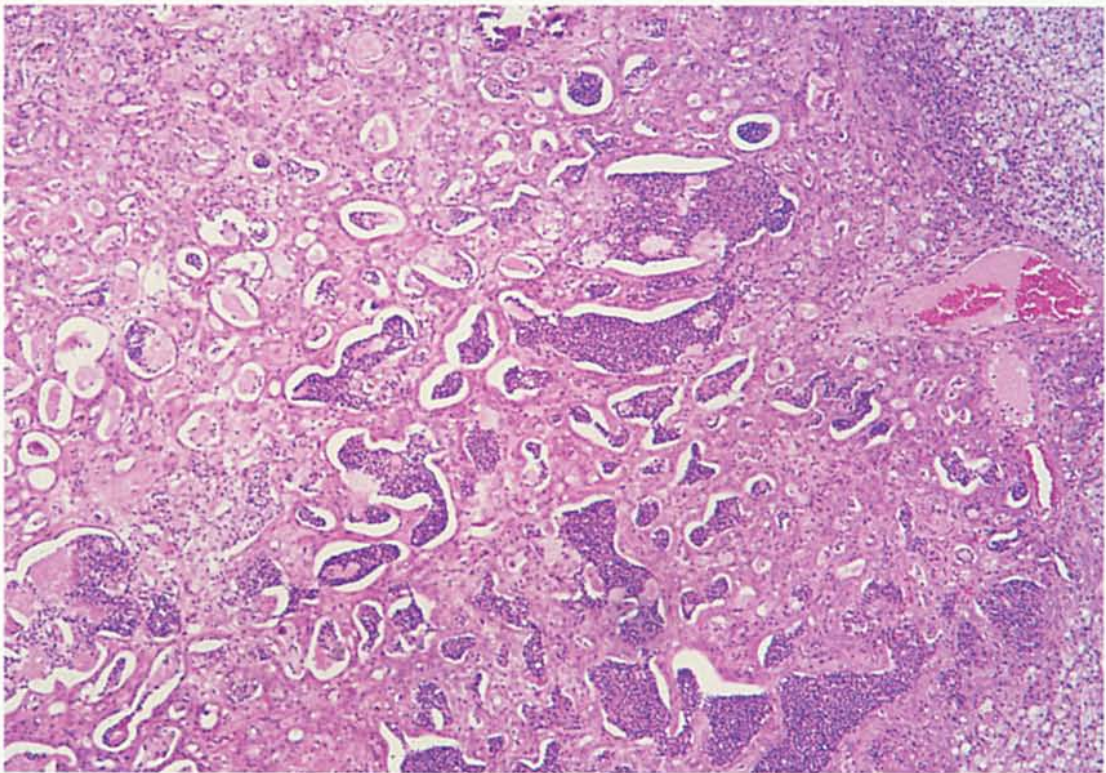


Fig. 40 – Rete testis carcinoma, Wistar rat treated with CdCl₂, 10x, H&E (Photos courtesy of S. Rehm and M.P. Waalkes)

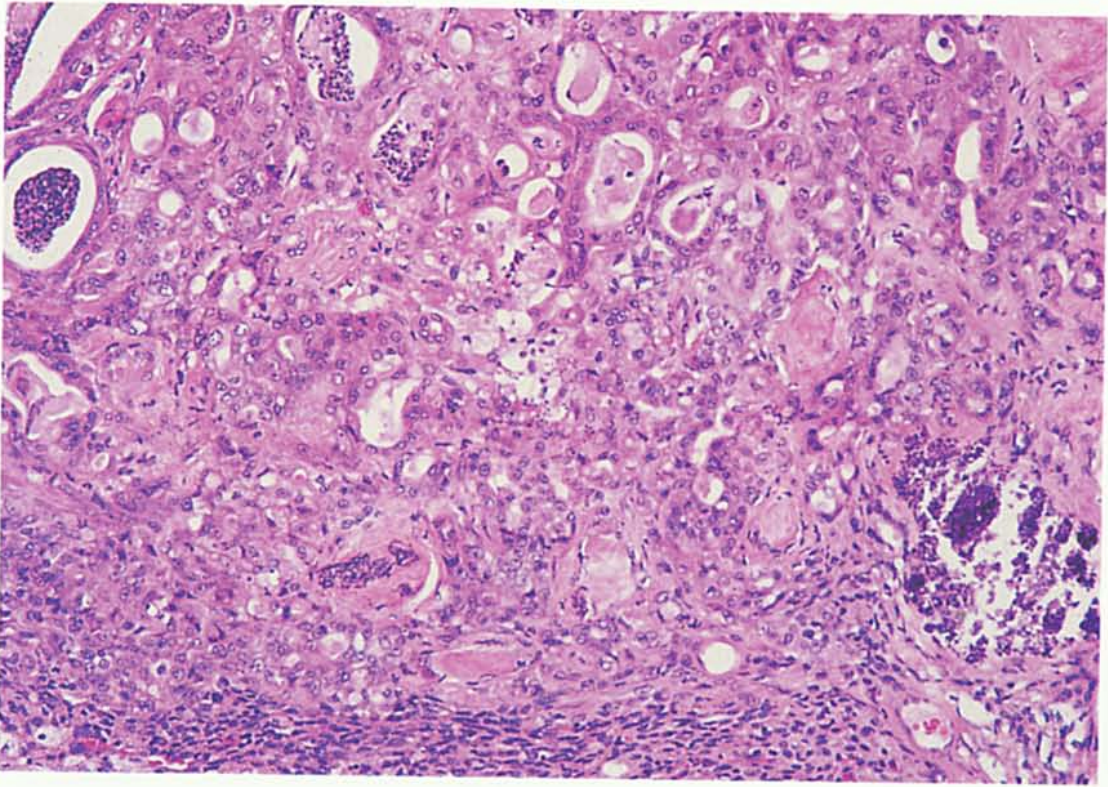


Fig. 41 – Cellular morphology of neoplasm in Figure 40. Note invasiveness of ductal epithelium and the surrounding mononuclear infiltrate. Several tubule lumina contain cellular debris. 100x, H&E

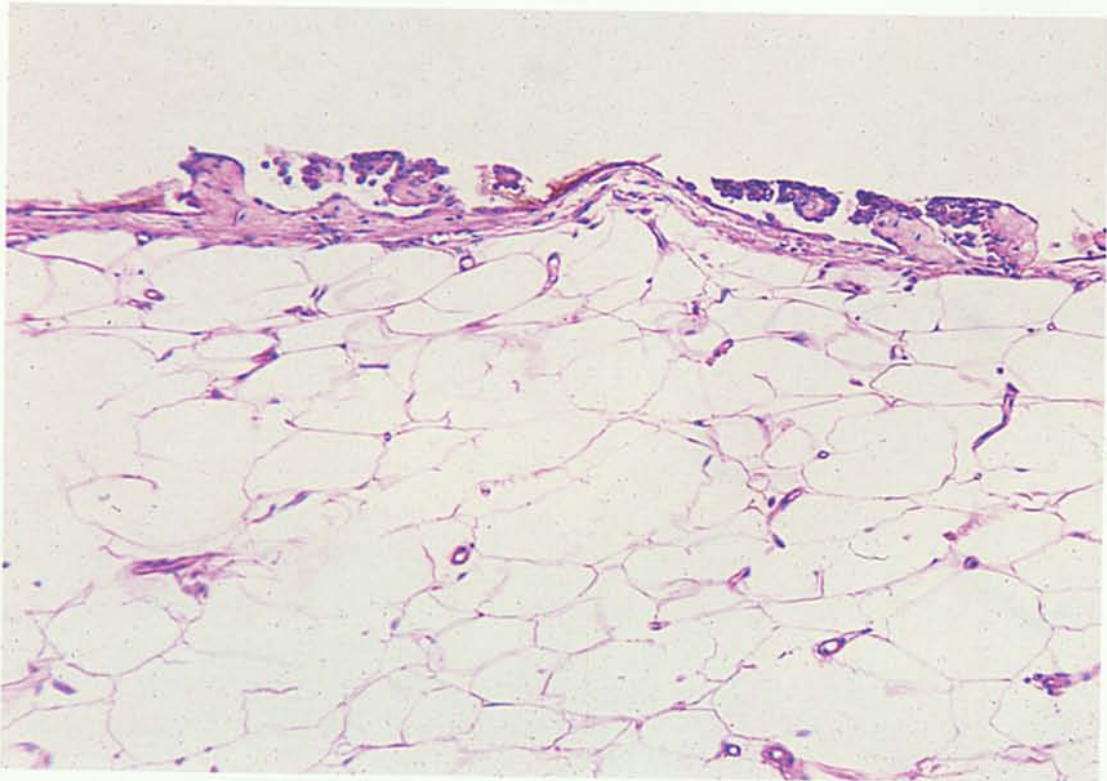


Fig. 42 – Mesothelial hyperplasia.

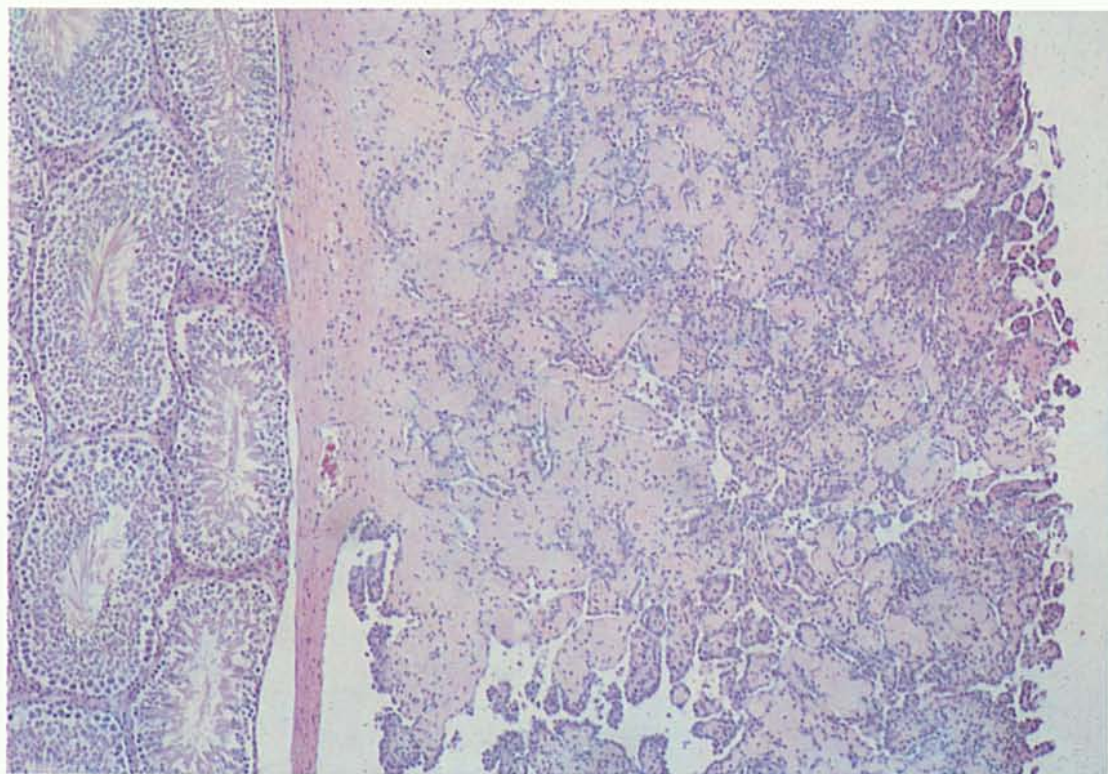


Fig. 43 – Malignant mesothelioma, tunica vaginalis, rat. Typical cauliflower-like growth pattern. 100x, H&E

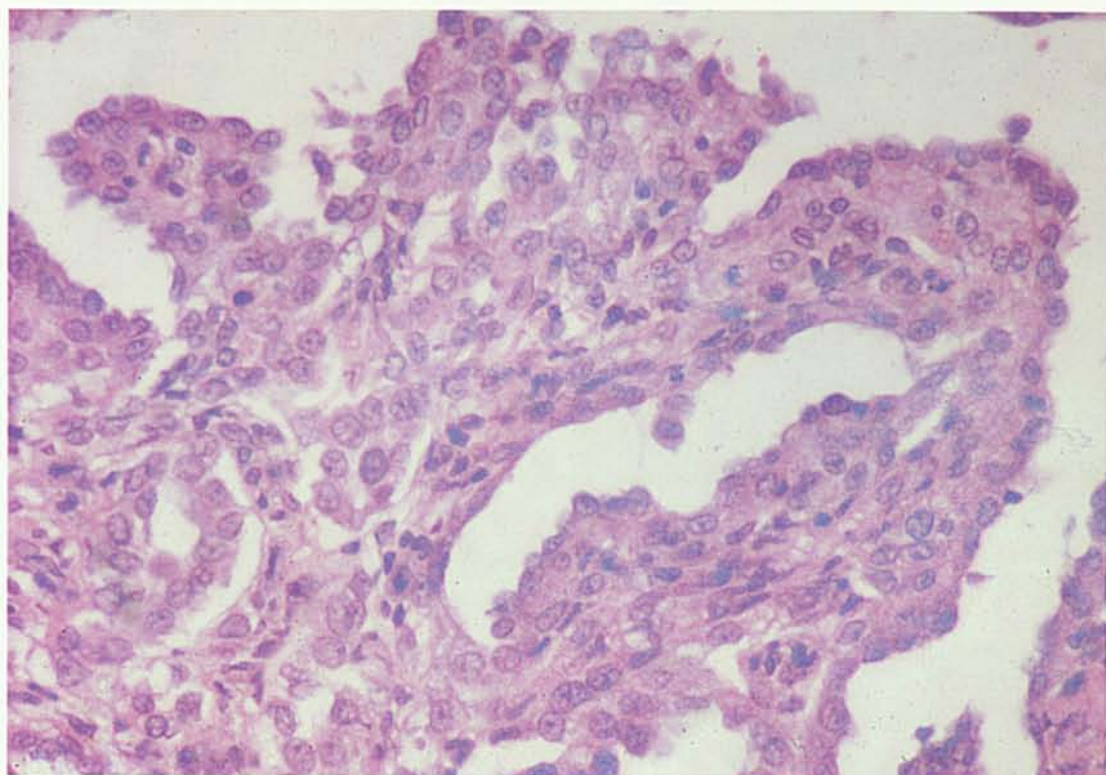


Fig. 44 – Typical papillary growth pattern of malignant mesothelioma. Note the well-developed supportive fibrous tissue stalk. 400x, H&E