

Ovarian Neoplasms in F344 Rats and B6C3F1 Mice

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The National Toxicology Program (NTP) classification system for rat and mouse ovarian tumors is presented. The classification system is based on previous classification systems and on a review of all the primary ovarian tumors from the archives of the National Cancer Institute (NCI) and NTP Carcinogenesis Testing Programs. The relative frequency and principal diagnostic features of 204 ovarian tumors from 39,851 female F344 rats and 587 ovarian tumors from 41,102 female B6C3F1 mice are described. The most frequently observed neoplasms in F344 rats were malignant granulosa cell tumors (29% of primary rat ovarian neoplasms observed), benign undifferentiated sex cord-stromal tumors (26%), benign granulosa cell tumors (16%), and benign Sertoli cell tumors (7%). The most frequent neoplasms in B6C3F1 mice were cystadenomas (24%), tubulostromal adenomas (24%), benign granulosa cell tumors (21%), and benign teratomas (8%).

Introduction

Ovarian cancer is diagnosed in 18,000 American women each year (1). The large amount of information available on histologic patterns and clinical history of human ovarian neoplasms has resulted in complex classification schemes. Such a degree of complexity is not justified as yet in rodents, nor is a complex scheme practical in routine toxicologic assessment of study data. Classifications proposed for ovarian tumors in mice have been based on both hormonal activity (2) and ovarian histogenesis (3). In a recent description of a large number of ovarian neoplasms in Han:NMRI mice (4), the method of classification was based on the World Health Organization Scheme for domestic animals (5) and a modified version for mice (3).

The classification for ovarian tumors presented in this paper is based on those reports detailed above (3-5), modified after discussions with speakers and participants at the National Toxicology Program (NTP) Comparative Ovarian Pathology Round Table Workshop (September 24-25, 1985) and a review of primary ovarian tumors from the archives of the National Cancer Institute (NCI) and NTP Carcinogenesis Testing Programs. The NTP completes, on the average, more than 20 two-year carcinogenicity studies in both rats and mice each year and a similar number of short-term toxicity studies. The initial histopathological assessment of tissues from animals in these studies is carried out by

more than 50 pathologists in various toxicology testing facilities under contract to the NTP. Classification systems for neoplasms used in a large-scale toxicology and carcinogenicity program such as this must meet three major requirements: the system must be sufficiently practical for convenient use in the field; it should facilitate uniformity of diagnosis between pathologists at different institutions in different geographical locations; and it must allow for unambiguous interpretation by toxicologists and regulatory authorities. The purpose of this paper is to give an account of the NTP Ovarian Tumor Classification System and a description of the morphological features and relative frequency of ovarian tumors found in F344 rats and B6C3F1 mice.

Materials and Methods

The tumors reported in this paper were found during histological examination of control and treated F344 rats and B6C3F1 mice used in more than 300 chronic carcinogenicity studies conducted by the NCI and NTP. The majority of these studies consisted of control, low, and high dose groups, with 50 male and 50 female rats or mice in each group. This represents a database of 39,851 female F344 rats and 41,102 female B6C3F1 mice for which the ovaries were examined. Initial histopathological examination of these animals was carried out by staff pathologists at various testing facilities under contract to the NCI or NTP.

The animals were necropsied by or under supervision of the laboratory pathologists. The ovaries were removed from the carcass, fixed in 10% buffered formalin, embedded in paraffin, sectioned at 5 to 6 μ m, and stained with hematoxylin and eosin. Additional special

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stains were employed in some cases. All available sections of ovarian neoplasms were examined by the authors without reference to previous diagnoses.

Results

Two hundred four primary ovarian tumors from F344 rats and 587 primary ovarian tumors from B6C3F1 mice were observed. Occasionally, multiple ovarian tumors occurred in a single animal. The tumors were placed in five major categories: epithelial, sex cord-stromal, germ cell, soft tissue, and secondary (metastatic or invasive) neoplasms. An outline of the classification system devised during this study is given in Table 1, and the relative frequency of each tumor type is shown in Table 2. The category of soft tissue tumors was used for those neoplasms having the same morphologic features as soft tissue tumors originating elsewhere in the body, such as smooth muscle and endothelial cell tumors (5,6). The morphologic features and differential diagnoses of these neoplasms are discussed in the order of their appearance in the classification system.

Epithelial Tumors

Tumors in this category are considered to be derived from the surface (coelomic, germinal) epithelium (mesothelium) of the ovary (7).

Cystadenoma and Cystadenocarcinoma. In humans, both of these neoplasms usually arise as the result of neoplastic transformation of an epithelial inclusion cyst (7). Cystadenomas consisted of single or multiple ovarian cysts lined by cuboidal or columnar epithelium that infolded to form papillary structures (Plates 1-3). The connective tissue beneath the epithelium had a varied population of stromal cells which markedly influenced the appearance of the tumor. In addition to pop-

Table 2. Number and relative frequency of primary ovarian tumors in F344 rats and B6C3F1 mice.

Tumor	Number		Frequency (% of tumors)	
	Rat	Mouse	Rat	Mouse
Cystadenoma	2	143	1	24
Cystadenocarcinoma	6	5	3	1
Tubulostromal adenoma	2	138	1	24
Tubulostromal adenocarcinoma	2	0	1	0
Mesothelioma	2	0	1	0
Granulosa cell tumor, benign	33	122	16	21
Granulosa cell tumor, malignant	59	37	29	6
Luteoma, benign	2	19	1	3
Thecoma, benign	8	2	4	< 0.5
Thecoma, malignant	1	1	< 0.5	< 0.5
Fibroma	2	0	1	0
Sertoli cell tumor, benign	14	3	7	1
Sertoli cell tumor, malignant	4	0	2	0
Sertoliform tubular adenoma	2	0	1	0
Sex cord-stromal tumor, benign	53	2	26	< 0.5
Sex cord-stromal tumor, malignant	10	1	5	< 0.5
Teratoma, benign	0	48	0	8
Teratoma, malignant	0	28	0	5
Choriocarcinoma	1	7	< 0.5	1
Yolk sac carcinoma	1	14	< 0.5	2
Hemangioma	0	15	0	3
Hemangiosarcoma	0	2	0	< 0.5
Total	204	587		

Table 1. National Toxicology Program ovarian tumor classification.

Type of tumor	Specific tumor name
Epithelial	Cystadenoma/cystadenocarcinoma Tubulostromal adenoma/ tubulostromal carcinoma Mesothelioma
Sex cord-stromal	Granulosa cell tumor Luteoma (includes Leydig cell tumor, lipid cell tumor) Thecoma Fibroma/fibrosarcoma Sertoli cell tumor Sertoliform tubular adenoma Undifferentiated sex cord-stromal tumor
Germ cell	Dysgerminoma Teratoma Choriocarcinoma Yolk sac carcinoma
Soft tissue tumors	
Secondary (metastatic/invasive) tumors	

ulating the papillary interstitium, stromal cells were frequently seen in the adjacent cyst wall. Very small (< 2 mm diameter) cystadenomas were seen that consisted of a single small cyst with very few papillae. In the absence of other criteria, diagnosis of malignancy was based on focal atypia and/or local invasion (Plate 4). Cystadenomas accounted for only 1% of primary ovarian tumors in rats, but represented 24% of those observed in mice. Cystadenocarcinomas were more common than cystadenomas in rats, in contrast to mice, where the overwhelming majority of these types of neoplasms were benign (Table 2).

Difficulty may be associated with distinguishing papillary hyperplasia of a cyst lining from papillary cystadenoma. Distinct fronds of neoplastic epithelium can be readily differentiated from simple infolding of a hyperplastic epithelium lining. Borderline cases present a challenge for the pathologist. In many cases, neoplastic papillae have a focal site of origin, while hyperplasia is more diffuse and is characterized by epithelial infolding with short unbranched papillary structures. Care should be taken not to mistake the ciliated fimbria of the oviduct for papillary tumors, especially if these are present in a cystic ovarian bursa or are associated with complex degenerative or inflammatory processes. The majority of papillary cystadenomas are nonciliated. Primary abdominal mesothelioma may also be confused

with an ovarian cystadenoma. The presence of fronds within a cyst and the characteristic arrangement of the epithelium in a cystadenoma allows distinction between these tumors.

Tubulostromal Adenoma and Tubulostromal Adenocarcinoma. These neoplasms originate from downgrowths of the ovarian surface epithelium, which are typically seen in aging mice. They were previously subdivided at the NTP into "pure tubular adenoma" and "benign mixed tumor;" however, review of all ovarian tumors in the NCI/NTP archives revealed that they form a continuous morphological spectrum. In view of the prominence of the intertubular cells of sex cord-stromal origin in the great majority of these tumors in the B6C3F1 mouse, it was considered appropriate to designate these tumors as tubulostromal adenomas.

These tumors were rarely seen in rats, but accounted for 24% of primary ovarian neoplasms in mice. Tubulostromal adenomas were composed of delicate tubules lined by cuboidal epithelium that resembled, and in some sections was continuous with, the surface epithelium of the ovary (Plate 5). The tubules were separated by packets of cells of probable sex cord-stromal origin. The ratio of tubular to nontubular components, the degree of tubular dilatation, and the amount of vacuolation or luteinization of the cells between the tubules were highly variable, resulting in a wide range of morphological appearances (Plate 6).

The malignant counterpart of this tumor, the tubular adenocarcinoma, has recently been reported in Han:NMRI mice (4). They were only found in mice more than 24-months old and appeared histologically benign, lacking invasiveness and having few mitoses; however, 50% of these tumors metastasized to the lungs. Tubular adenocarcinomas were not seen in B6C3F1 mice in the NCI/NTP archives, possibly because the majority were sacrificed or died at 24 months or less. Two tumors in rats, one of which had a moderately high mitotic index, were classified as tubulostromal adenocarcinomas on the basis of local invasion.

Ovarian epithelial hyperplasia with epithelial downgrowths is commonly seen in aging mice and must be distinguished from tubular adenoma. This hyperplasia may also occur as a consequence of chemical toxicity. Diagnosis of tubular adenoma can be based on the presence of a distinct mass of tubulostromal elements, at least 2 to 3 mm in diameter, which compress or replace adjacent tissue. Differentiation between dense tubular adenomas and granulosa cell tumors is aided by the use of Alcian blue staining to highlight the narrow rim of acid mucopolysaccharides lining the tubules of these tumors (4). Nodules of granulosa cells are sometimes present within a tubular adenoma. These may in some instances progress to form granulosa cell tumors (8).

Mesothelioma. Two ovarian mesotheliomas were seen in rats (Plate 7). These tumors, which were contained entirely within the ovarian bursa, were composed of simple cuboidal epithelium in a papillary pattern and resembled benign mesothelioma in other sites (9).

Sex Cord-Stromal Tumors

Sex cord-stromal tumors are composed of varying combinations of sex cord and stromal derivatives which may exhibit ovarian or testicular differentiation (10).

Granulosa Cell Tumor. Granulosa cell tumors are composed of granulosa cells with or without theca cells in their stromal component (11) and must be distinguished from the other sex cord-stromal tumors. Granulosa cell tumors were the most common neoplasm in both species. The most characteristic feature of these tumors was their cellular morphology, which resembled that of the normal granulosa cell. The nuclei were round to oval and had coarsely stippled chromatin. Nuclear grooves and Call-Exner bodies were uncommon, in contrast to human granulosa cell tumors (7). Depending on the degree of luteinization, the amount of cytoplasm ranged from scanty to moderate and was faintly eosinophilic and finely granular or vacuolated. Luteinization was often accompanied by some loss of the characteristic nuclear stippling. The stroma of these tumors was composed of widely varying amounts of fusiform and sometimes lipid-laden thecal cells, fibroblasts, collagen, and blood vessels. This stroma formed trabeculae on which the granulosa cells were aligned, or surrounded nests and islands of cells, resulting in a wide variety of histological patterns paralleling those seen in women (7). Histological patterns included microfollicular and sertoliform patterns, a tubular pattern (Plates 8 and 9) which resembled tubular adenoma at low magnifications, and a cystic type (Plate 10). A smaller proportion of granulosa cell tumors had a thecomatous or sarcomatous pattern where the granulosa cells were fusiform, or were composed largely of solid sheets of cells in a diffuse arrangement. Tubules consisting of a single layer of cuboidal epithelium were a component of some tumors, as were varying numbers of ceroid-laden cells.

Malignant granulosa cell tumors frequently became very large, but were often still contained within the ovarian bursa (Plates 11 and 12). High mitotic rate, necrosis, invasion, and a high degree of cellular pleomorphism were histological criteria for malignancy. Metastases from granulosa cell tumors in mice have been reported in lungs, lymph nodes, liver, spleen, kidney, pancreas, diaphragm, and peritoneum (2,4,12,13).

Granulosa cell tumors must be distinguished from focal granulosa cell hyperplasia and from focal granulosa cell nodules arising in tubular adenoma. The latter distinction may generally be achieved on the basis of the discrete nature and uniformity of the neoplasm and the extent of compression or displacement of surrounding tissues.

Granulosa cell tumors must also be distinguished from the other sex cord-stromal tumors which exhibit a continuous morphologic spectrum (see following section). It has been suggested that stromal elements in granulosa cell tumors may represent nonneoplastic stromal proliferation (14). Diagnoses of luteoma, thecoma, and fibroma should therefore be reserved for those tumors

where luteal cells, thecal cells, and fibrocytes, respectively, form the major component of the tumor.

Luteoma. Luteomas were composed of highly luteinized cells with round to oval nuclei without significant stippling and with extensive pale granular cytoplasm. Intranuclear cytoplasmic invaginations and mast cells were present in some of these tumors (Plate 13). Malignant luteomas were not observed.

Thecoma and Fibroma. We have followed human pathology practice in including fibromas and fibrosarcomas in the sex cord-stromal group of tumors (7,10,14). Tumors arising from ovarian stromal cells form a continuous spectrum from the typical fibroma, which is predominantly composed of fibroblastic collagen-forming cells, to the typical thecoma, which mainly contains plump lipid-laden cells (10,14). While thecomas typically contain lipid, small amounts of lipid may also be seen in ovarian fibromas (7).

Thecomas consisted of whorls of spindle-shaped cells resembling fibroblasts (Plate 14), but they contained lipid. Collagen deposition was predominantly between bundles of cells. Two thecomas were considered to be malignant on the basis of pleomorphism (Plate 15) and multiple areas of necrosis suggestive of rapid growth.

Two ovarian fibromas were observed in rats (Plate 16). These were well-differentiated tumors with morphological features similar to fibromas in other sites.

Sertoli Cell Tumor. Sertoli cell tumors resembled their testicular counterpart (Plate 17). They were characterized by seminiferouslike tubules separated by fibrovascular stroma, lined by cells with basally located nuclei and abundant faintly eosinophilic cytoplasm extending into the lumen. Sertoli cell tumors accounted for 9% of ovarian tumors in rats, while they represented less than 0.5% of ovarian tumors in mice. Malignancy was diagnosed on the basis of focal necrosis, hemorrhage, and local invasion.

Sertoliform Tubular Adenoma. The diagnosis of sertoliform tubular adenoma refers to a neoplasm of the rat which has previously been described as tubular adenoma (15-18). Following discussions with other speakers at the NTP Round Table Conference, these tumors have been designated as "sertoliform tubular adenoma" in order to avoid confusion with the morphologically different tubular ("tubulostromal") adenoma of the mouse, as described previously. Only two sertoliform tubular adenomas were seen in F344 rats; they are, however, considerably more frequent in Sprague-Dawley rats and have previously been described in detail in this strain (19). The rationale for their inclusion in the sex cord-stromal group of tumors will be discussed elsewhere by workers more familiar with this neoplasm (20).

Sertoliform tubular adenomas were composed of rounded cells with abundant eosinophilic, vacuolated cytoplasm which formed solid or tubular arrangements (Plate 18). Although the tubular areas resembled those in Sertoli cell tumors, they lacked the basal nuclei and vertically oriented cytoplasm of the latter neoplasms.

Undifferentiated Sex Cord-Stromal Tumor. Thirty-one percent of ovarian tumors in rats and less than 1%

of ovarian tumors in mice were considered to be of sex cord-stromal origin, but they were insufficiently differentiated to be further classified (Plates 19-21). Many of these tumors would correspond to those previously classified by other authors as theca-granulosa cell tumors (2).

The tumors were solid or lobulated and were composed of a spectrum of cell types ranging from granulosa cells to stromal cells, with the majority of cells having intermediate morphological characteristics. The lobulated tumors were covered by a cuboidal epithelium resembling the normal ovarian surface epithelium. Malignant sex cord-stromal tumors of this type were diagnosed on the basis of necrosis, high mitotic rate, and invasion.

Germ Cell Tumors

Neoplasms of germ cell origin may remain undifferentiated (dysgerminoma); may differentiate toward somatic tissue (teratoma) or embryonic membranes (choriocarcinoma, yolk sac carcinoma); or may contain a mixture of these tissue types.

Occasionally, neoplasms were seen with features of more than one germ cell tumor type. These were classified according to the major component.

Dysgerminoma. Dysgerminomas are composed of large round cells with clear cytoplasm, which resemble primordial germ cells morphologically, histochemically, and ultrastructurally (7,21). These tumors are similar in appearance to the testicular seminoma. Ovarian dysgerminoma may be confused with histiocytic sarcoma (7). No dysgerminomas were observed in the NTP collection; one has been reported in a BALB/c mouse (3). This tumor consisted of polygonal cells with amphophilic cytoplasm and centrally placed nuclei. The nuclei were 10 to 15 μ in diameter, with finely granular chromatin and prominent single nucleoli. The tumor cells were divided into small fascicles by fine connective tissue septae.

Teratoma. Teratomas were common in B6C3F1 mice, accounting for 13% of primary ovarian tumors, but were not observed in rats. Benign teratomas (Plates 22-27) contained one or more cysts, together with a wide variety of well-differentiated tissues. Mature nervous tissue and gastrointestinal structures of varying complexity were most common; however, a wide range of other tissues were seen, including hair, sebaceous glands, melanocytes, skeletal muscle, cartilage, and bone. Occasionally, small teratomas were seen that were entirely contained within the ovary. Careful examination of additional sections was often necessary before these tumors could be distinguished from nonneoplastic ovarian cysts. Malignant teratomas were diagnosed on the basis of extension through the ovarian bursa (Plate 28), areas of hemorrhage and necrosis suggestive of rapid growth, and poor differentiation. The major component of malignant teratomas was immature nervous tissue, which commonly contained

neural rosettes or structures resembling primitive neural tube (Plate 29).

Choriocarcinoma. Choriocarcinomas have recently been described in detail (22). Seven choriocarcinomas were seen in mice and one in a rat. The tumors were described at necropsy as dark or hemorrhagic cystic lesions; one had previously been diagnosed as a hemangiosarcoma and another as a hemangioma. The earliest occurrence was in a mouse dying at the age of 29 weeks. On microscopic examination, the tumors were seen to be composed of hematocysts, sheets of cytotrophoblasts, syncytiotrophoblasts, and/or trophoblastic giant cells, with areas of hemorrhage (Plate 30). The cytotrophoblasts were rounded, with centrally located hyperchromatic or vesicular nuclei ranging from 5 to 10 μ in diameter. The syncytiotrophoblasts were multinucleate cells with granular basophilic cytoplasm. The giant cells were large irregular cells with abundant cytoplasm and single large nuclei up to 50 μ in diameter (Plate 31).

Yolk Sac Carcinoma. Thirteen ovarian yolk sac carcinomas were seen in mice and one tumor was seen in a rat. The tumors were characterized by an eosinophilic, periodic acid-Schiff positive matrix in which were embedded nests and ribbons of tumor cells (Plate 32). These cells were generally small and uniform, with sharply outlined borders (Plate 33). The intercellular matrix of these tumors was found to stain positively for laminin by immunogold methods (23).

Soft Tissue Tumors

This term is used for those tumors having the same appearance as soft tissue tumors originating elsewhere in the body, such as smooth muscle and endothelial tumors (5,6).

Hemangioma and Hemangiosarcoma. Hemangiomas and hemangiosarcomas were only seen in mice. These neoplasms were differentiated from the angiomatous changes commonly seen in the ovary of aging B6C3F1 mice on the basis of displacement of adjacent tissue, necrosis, thrombosis, and atypia of endothelial cells (Plates 34 and 35).

Discussion

Terminology used by pathologists for the classification of neoplasms plays a crucial role in the interpretation and statistical analysis of data derived from rodent carcinogenesis studies (24). Much of the terminology used for classification of neoplasms is based on tissue histogenesis, even though the normal histogenesis of many tissues, including the ovary (25), remains to be clearly established. Furthermore, many classification schemes were developed for human lesions, which may or may not have a rodent counterpart.

In order to ensure uniformity for both human and animal studies, the World Health Organization (WHO) set up expert committees to devise appropriate classification systems. The history of these committees has

been briefly reviewed (26). In carcinogenesis studies, rodents are being used as models for potential human responses. It would therefore appear logical to use a common system for both medical and veterinary classification in order to provide a basis for comparative studies (27). Thus, in the present study, a classification scheme was devised on the basis of the WHO classifications for human (28) and animal (5) ovarian tumors.

Evaluation of the significance of rodent carcinogenicity test data for human risk assessment is not always straightforward. For example, malignant epithelial tumors account for almost 90% of human ovarian cancers (21), but are uncommon in rats and mice; whereas the common tubulostromal adenoma of the mouse ovary has never been shown to evolve into a form comparable to human ovarian epithelial tumors (29). It has been suggested that the difficulty in finding a suitable model for human epithelial neoplasms may reflect the protection of the surface epithelium of the ovaries of most laboratory animals from local carcinogens by the ovarian bursa, unlike the human ovary, which is freely exposed to the peritoneal cavity (29).

For more than 10 years, the NCI/NTP carcinogenesis testing programs have judiciously used a combination of neoplasms to assist in evaluating evidence of carcinogenicity (30). In the case of the ovary, the authors are in agreement with the proposal of McConnell (30) that for the purposes of quantitative risk estimation, all types of germ cell neoplasms could be combined, as could all sex cord-stromal neoplasms; however, germ cell neoplasms should not be combined with sex cord-stromal neoplasms.

The authors present this description of the morphological features, classification, and relative frequency of primary ovarian neoplasms in a large population of F344 rats and B6C3F1 mice in the hope that it may stimulate further progress toward uniformity of classification and diagnosis.

REFERENCES

1. Benson, M. D., Lurain, J. R., and Newton, M. Ovarian tumor antigens. *J. Reprod. Med* 28: 17-109 (1983).
2. Lemon, P. G., and Gubareva, A. V. Tumors of the ovary. In: *Pathology of Tumors in Laboratory Animals*, Vol. 2 (V. S. Turosev, Ed.), IARC Science Publications, Lyon, 1979, pp. 385-409.
3. Frith, C. H., Zuna, R. E., and Morgan, K. T. A morphologic classification and incidence of spontaneous ovarian neoplasms in three strains of mice. *JNCI* 67: 693-702 (1981).
4. Rehm, S., Dierksen, D., and Deerberg, F. Spontaneous ovarian tumors in Han:NMRI mice: histologic classification, incidence, and influence of food restriction. *JNCI* 72: 1383-1395 (1984).
5. Nielsen, S. W., Misdorp, W., and McEntee, K. Tumors of the ovary. *Bull. WHO* 53: 203-215 (1976).
6. Stewart, H. L. Tumors of the soft tissues. In: *Pathology of Tumors in Laboratory Animals*, Vol. 2 (V. S. Turosev, Ed.), IARC Science Publications, Lyon, 1979, pp. 487-525.
7. Scully, R. E. Tumors of the ovary and maldeveloped gonads. Armed Forces Institute of Pathology, Washington, DC, 1979.
8. Murphy, E. D., and Russell, E. S. Ovarian tumorigenesis following genic deletion of germ cells in hybrid mice. *Acta Unio Int. Contra Cancrum* 19: 779-782 (1963).
9. Cabral, J. R. P., and Neal, G. E. Testicular mesotheliomas in

- rats exposed to N-2-fluorenylacetamide (FAA). *Tumori* 69: 195-199 (1983).
10. Young, R. H., and Scully, R. E. Ovarian sex cord-stromal tumors: recent advances and current status. *Clin. Obstet. Gynecol.* 11: 93-134 (1984).
11. Young, R. H., and Scully, R. E. Ovarian sex cord-stromal tumors: recent progress. *Int. J. Gynecol. Pathol.* 1: 101-123 (1982).
12. Bielschowsky, M., and D'Ath, E. F. Spontaneous granulosa cell tumors in mice of strains NZC/B1, NZO/B1, NZY/B1 and NZB/B1. *Pathology* 5: 303-310 (1973).
13. Beamer, W. G., Hoppe, P. C., and Whitten, W. K. Spontaneous malignant granulosa cell tumors in ovaries of young SWR mice. *Cancer Res.* 45: 5575-5581 (1981).
14. Fox, H. Sex cord-stromal tumours of the ovary. *J. Pathol.* 145: 127-148 (1985).
15. Cotchin, E. Spontaneous tumors of the uterus and ovaries in animals. In: *Animal Tumors of the Female Reproductive Tract* (E. Cotchin and J. Marchant, Eds.), Springer-Verlag, New York, 1977, pp. 26-65.
16. Engle, E. T. Tubular adenomas and testis-like tubules in the ovaries of aged rats. *Cancer Res.* 6: 578-582 (1946).
17. Fukuishi, R., Wang, H. H., Yoshida, A., Hirota, H., and Mori, H. Induction of ovarian tumours in rats with N-butyl nitrosourea. *Gann* 66: 323-325 (1975).
18. Knowles, J. F. Cancer of rat ovaries: Sertoli cell or granulosa-thecal cell tumours? *Br. J. Cancer* 48: 301-305 (1983).
19. Gregson, R. L., Lewis, D. J., and Abbott, D. P. Spontaneous ovarian neoplasms of the laboratory rat. *Vet. Pathol.* 21: 292-299 (1984).
20. Lewis, D. J. Ovarian neoplasia in the Sprague-Dawley rat. *Environ. Health Perspect.* 73: 77-90 (1987).
21. Scully, R. E. Ovarian tumors. *Am. J. Pathol.* 87: 686-720 (1977).
22. Alison, R. H., Lewis, D. J., and Montgomery, C. A. Ovarian choriocarcinoma in the mouse. *Vet. Pathol.*, in press.
23. Majeed, S. K., Alison, R. H., Boorman, G. A., and Gopinath, C. Ovarian yolk sac carcinoma in mice. *Vet. Pathol.* 23: 776-778 (1986).
24. Greaves, P., and Faccini, J. M. *Rat histopathology: a glossary for use in toxicity and carcinogenicity studies.* Elsevier, New York, 1984, Preface, pp. vii-viii.
25. Ashley, D. J. B. Evan's histological appearances of tumors. Tumors of the ovary. Churchill Livingstone, New York, 1978, pp. 663-704.
26. Institute of Laboratory Animal Resources. Historical developments in the histologic classification and typing of tumors in man and lower animals. *JNCI* 64: 180-181 (1980).
27. Morgan, K. T., Frith, C. H., Swenberg, J. A., McGrath, J. T., Zulch, K. J., and Crowder, D. M. A morphologic classification of brain tumors found in several strains of mice. *JNCI* 72: 151-160 (1984).
28. Serov, S. F., Scully, R. E., and Sobin, L. H. International histological classification of tumours, no 9. Histological typing of ovarian tumours. WHO, Geneva, 1973.
29. Fox, H. Human ovarian tumors: classification, histogenesis, pathogenesis and criteria for experimental models. In: *Biology of Ovarian Neoplasia* (E. D. Murphy and W. G. Beamer, Eds.), UICC, Geneva, 1980: 22-33.
30. McConnell, E. E., Solleveld, H. A., Swenberg, J. A., and Boorman, G. A. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* 76: 283-289 (1986).
31. Alison, R. H., Morgan, K. T., Haseman, J. K., and Boorman, G. A. Morphology and classification of ovarian neoplasms in F344 rats and B6C3F1 mice. *JNCI*, in press.

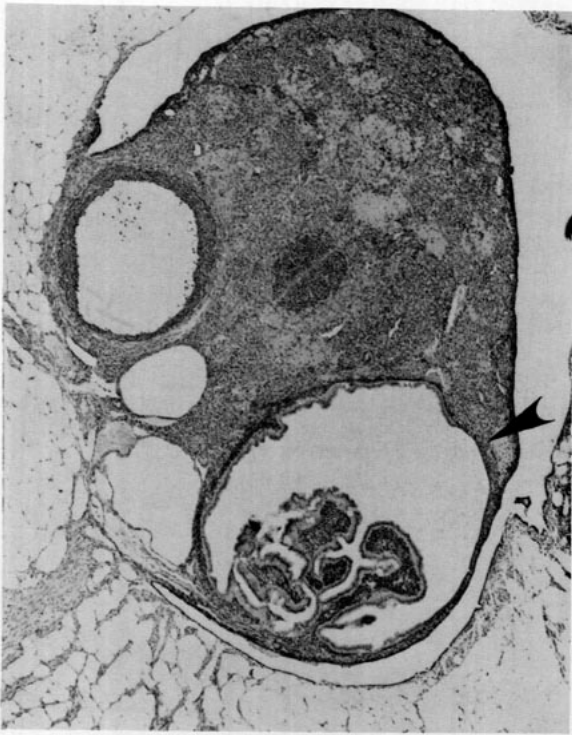


PLATE 1. Small cystadenoma (♣) within ovary.

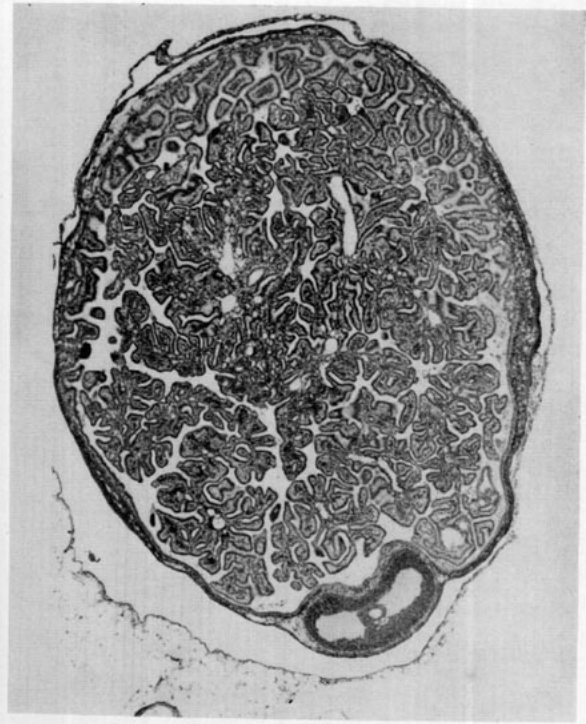


PLATE 2. Large cystadenoma displacing majority of ovarian tissue. Reprinted with permission (31).

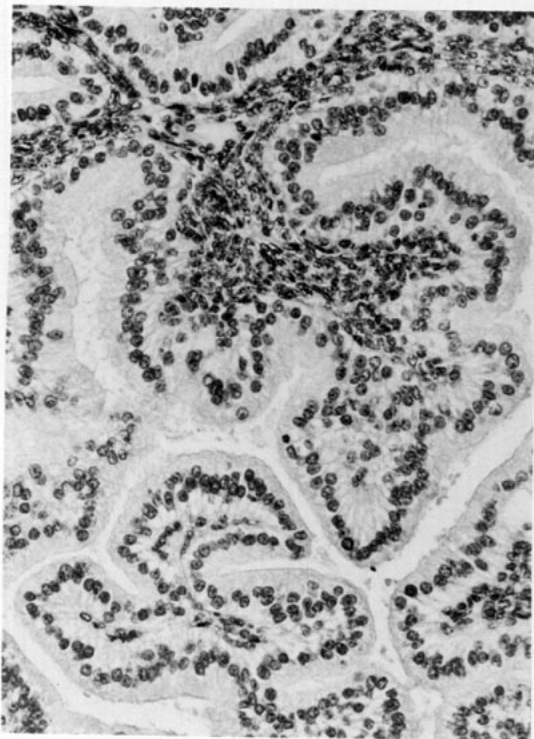


PLATE 3. Cystadenoma; columnar epithelium, varying amounts of subepithelial stromal cells. Reprinted with permission (31).



PLATE 4. Borderline cystadenocarcinoma; nuclear crowding, free tumor cells between papillae (♣).

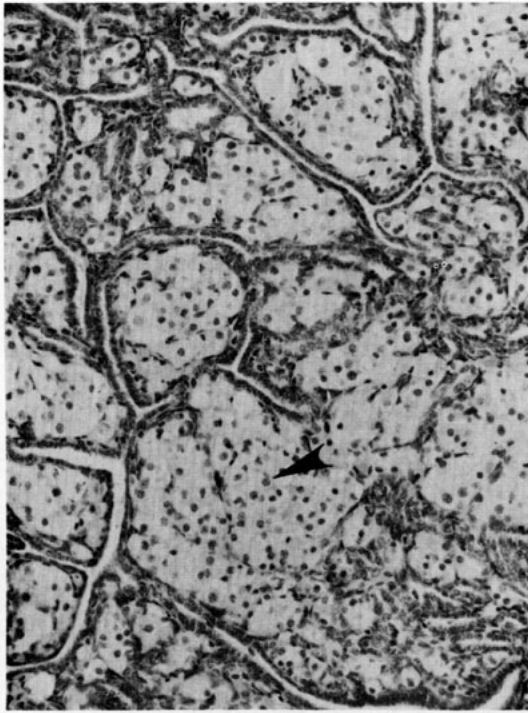


PLATE 5. Tubulostromal adenoma; tubules lined by cuboidal epithelium, luteinized granulosa cells between tubules (♦).

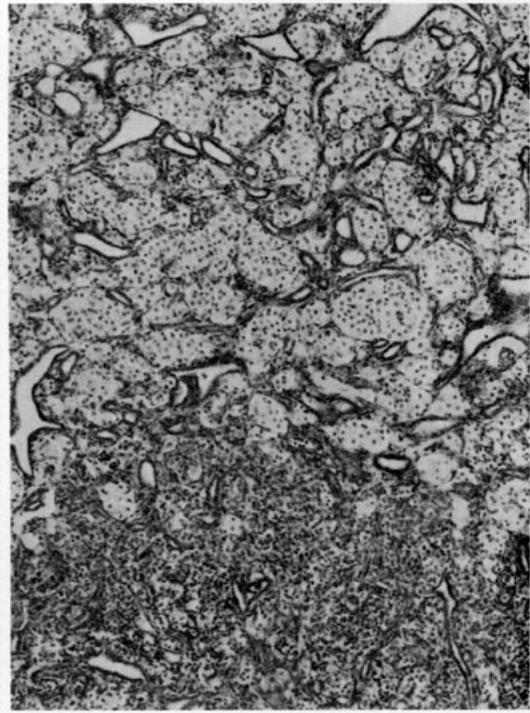


PLATE 6. Tubulostromal adenoma; note variation in intertubular cells. Reprinted with permission (31).



PLATE 7. Mesothelioma; single layer "epithelium" with hob-nail appearance (♦). Reprinted with permission (31).



PLATE 8. Granulosa cell tumor; tubular pattern. Reprinted with permission (31).

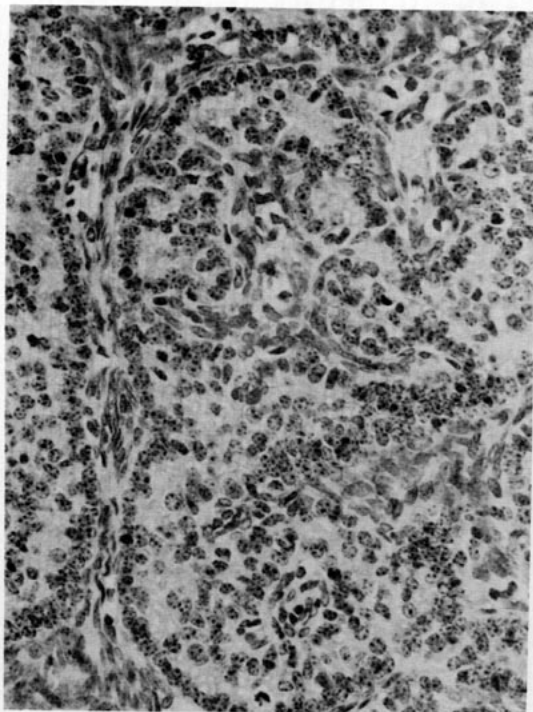


PLATE 9. Granulosa cell tumor; high power of Plate 8 showing palisading of granulosa cells against stromal elements. Note characteristic stippled nuclei of granulosa cells. Reprinted with permission (31).



PLATE 10. Malignant granulosa cell tumor; large blood-filled cysts.

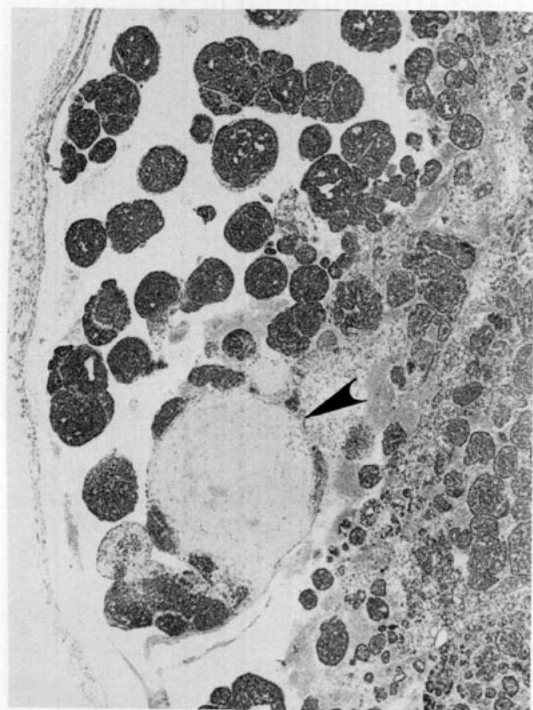


PLATE 11. Malignant granulosa cell tumor; islands of cells contained by ovarian bursa, focal necrosis and thrombosis (●). Reprinted with permission (31).

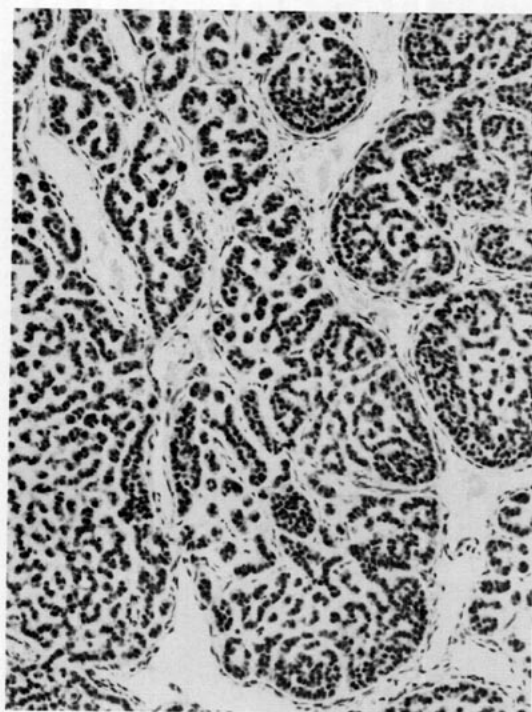


PLATE 12. Malignant granulosa cell tumor; trabecular pattern.

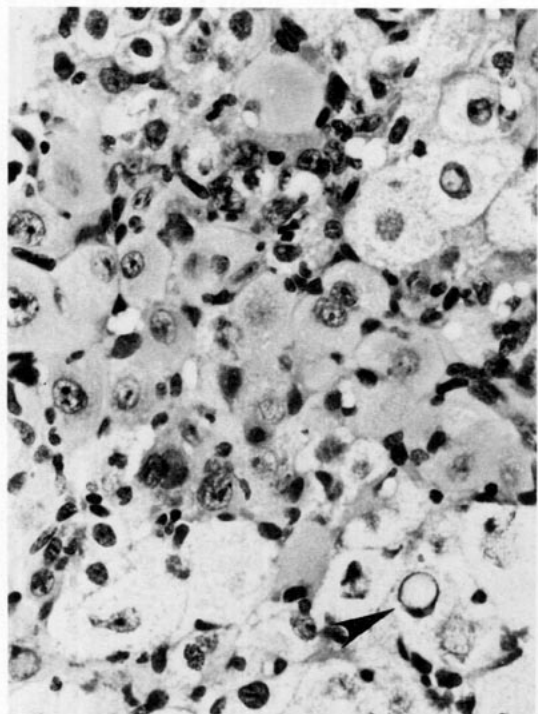


PLATE 13. Luteoma; intranuclear cytoplasmic invagination (●). Reprinted with permission (31).

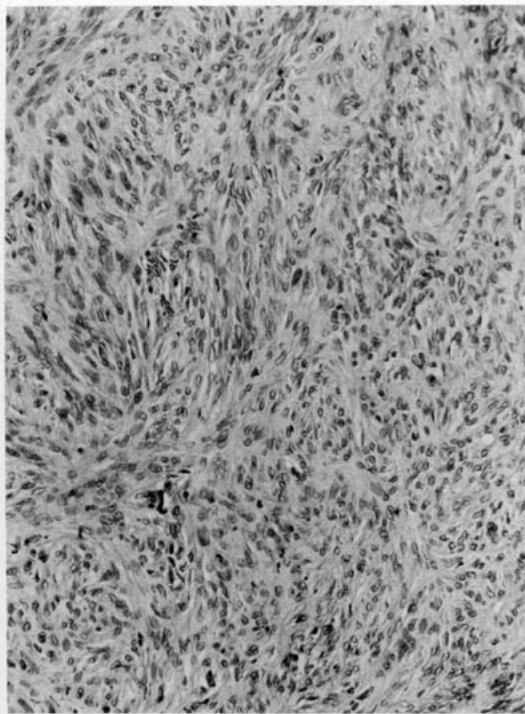


PLATE 14. Thecoma; whorls of spindle-shaped cells with lipid clefts. Reprinted with permission (31).



PLATE 15. Malignant thecoma; area of cellular pleomorphism.

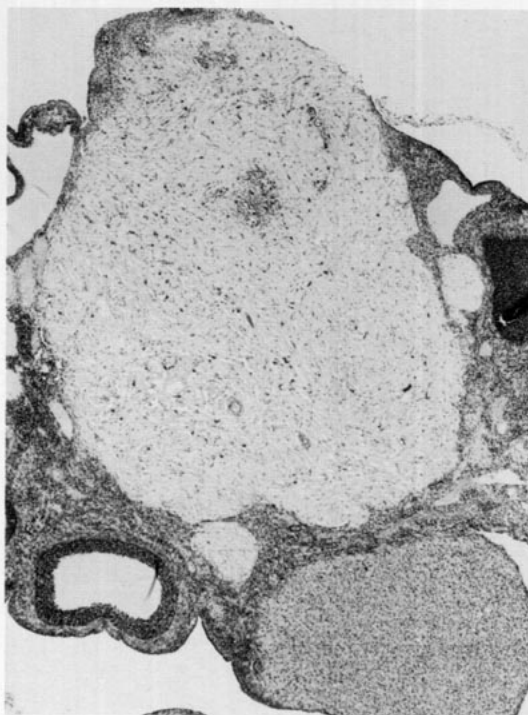


PLATE 16. Small, well-differentiated fibroma; remainder of ovary contains follicles and corpora lutea.

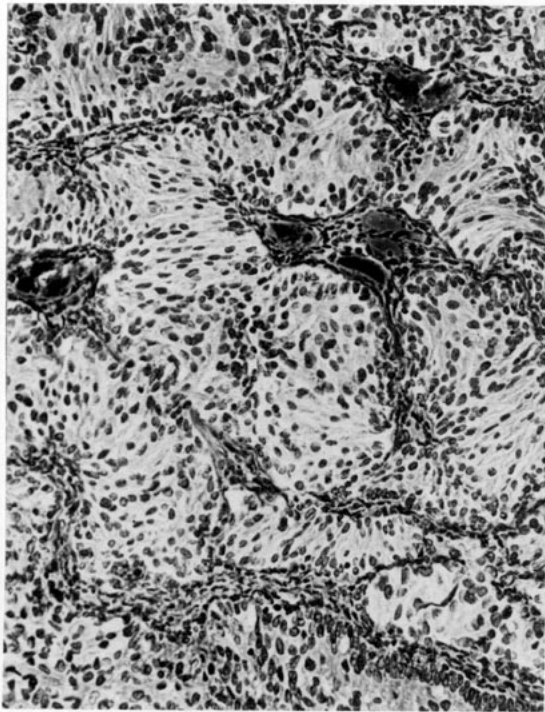


PLATE 17. Sertoli cell tumor; tubules lined by cells with basal nuclei and faintly eosinophilic cytoplasm reaching into lumen. Silver stain. Reprinted with permission (31).



PLATE 18. Sertoliform tubular adenoma; solid and tubular areas. Reprinted with permission (31).

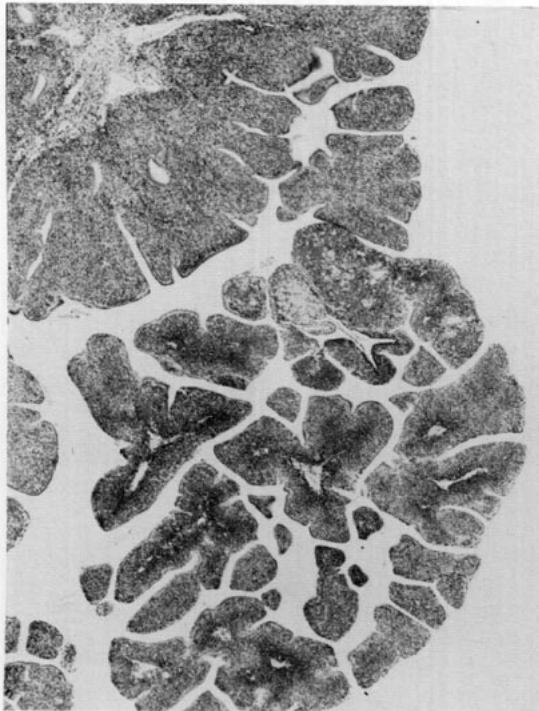


PLATE 19. Undifferentiated sex cord-stromal tumor; lobulated type. Reprinted with permission (31).



PLATE 20. Undifferentiated sex cord-stromal tumor; lobulated type, high power of Plate 19 showing cuboidal epithelium covering lobules.

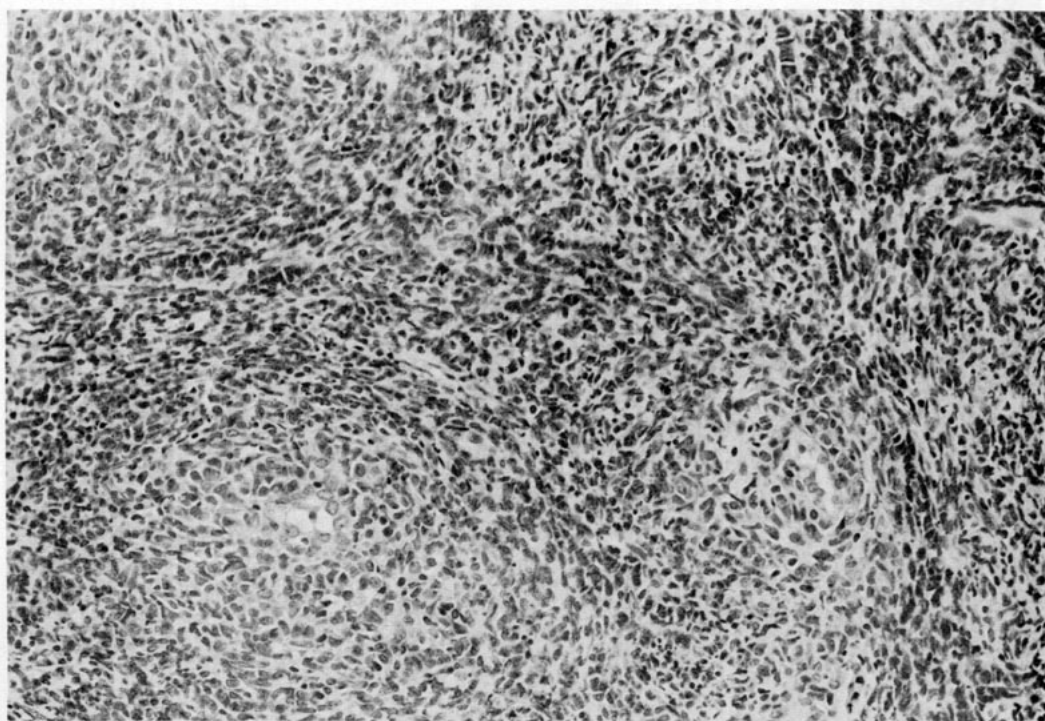


PLATE 21. Undifferentiated sex cord-stromal tumor; solid type, high power showing variation in cell morphology. Reprinted with permission (31).



PLATE 22. Small teratoma in wall of ovarian cyst (♦).



PLATE 23. Teratoma; high power of Plate 22. Tumor contains respiratory (♦) and intestinal epithelium, cartilage and bone (♦).



PLATE 24. Teratoma; section of cyst wall containing gastro-intestinal tract.

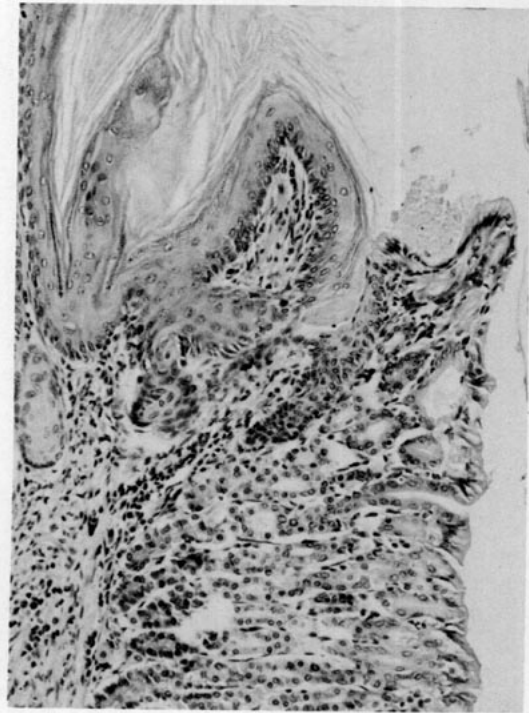


PLATE 25. Teratoma; high power of Plate 24. Stomach.

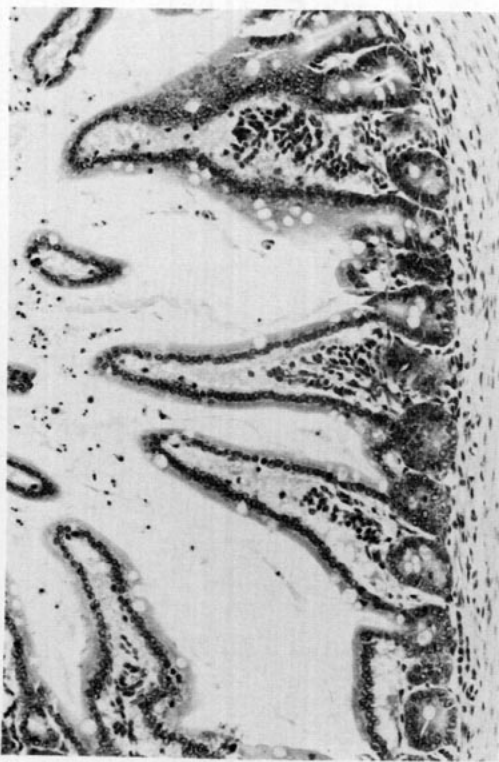


PLATE 26. Teratoma; high power of Plate 24. Small intestine.

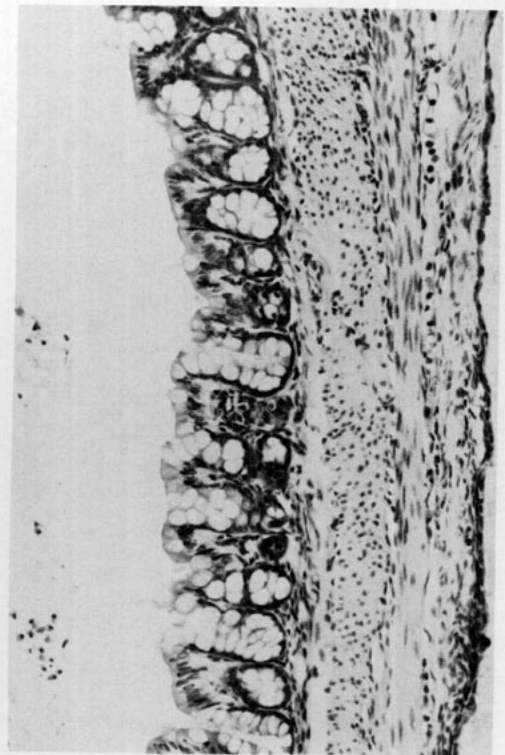


PLATE 27. Teratoma; high power of Plate 24. Large intestine with well-differentiated layers of smooth muscle.



PLATE 28. Malignant teratoma composed largely of immature nervous tissue; tumor has extended through ovarian bursa (♦).

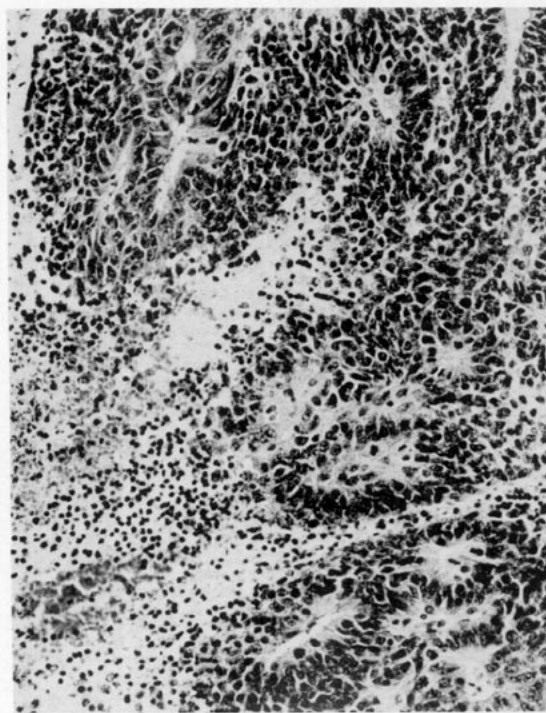


PLATE 29. Malignant teratoma; immature nervous tissue forming primitive neural tubes, high mitotic rate, area of necrosis. Reprinted with permission (31).



PLATE 30. Choriocarcinoma; ovary is replaced by multiloculated hematocyst and mass of tumor cells. Fallopian tube (♦) is uninvolved. Reprinted with permission (31).

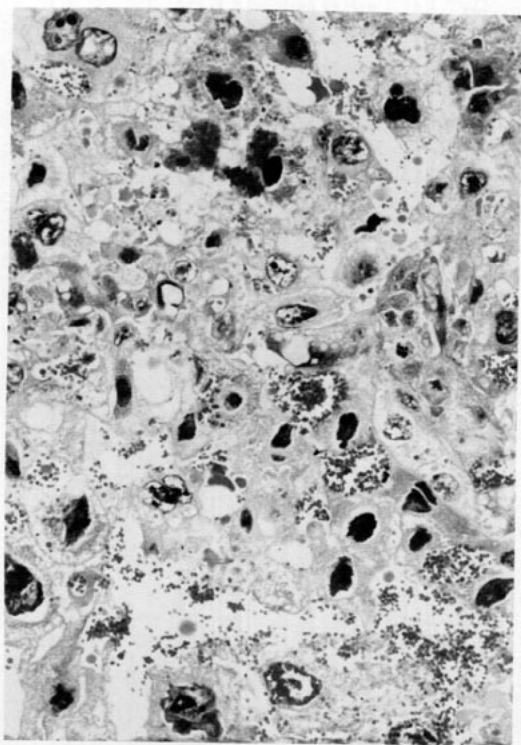


PLATE 31. Choriocarcinoma; high power of Plate 30. Pleomorphic trophoblastic giant cells with bizarre nuclei, extensive intercellular hemorrhage. Reprinted with permission (31).

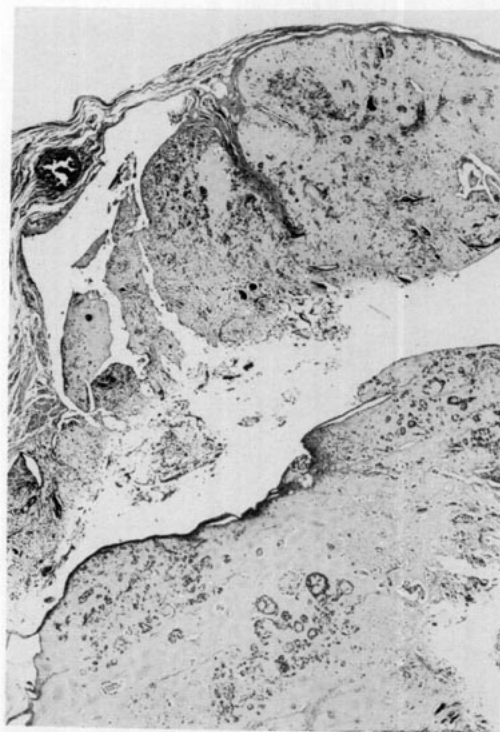


PLATE 32. Yolk sac carcinoma; nests and ribbons of tumor cells in characteristic amorphous eosinophilic matrix. Reprinted with permission (31).

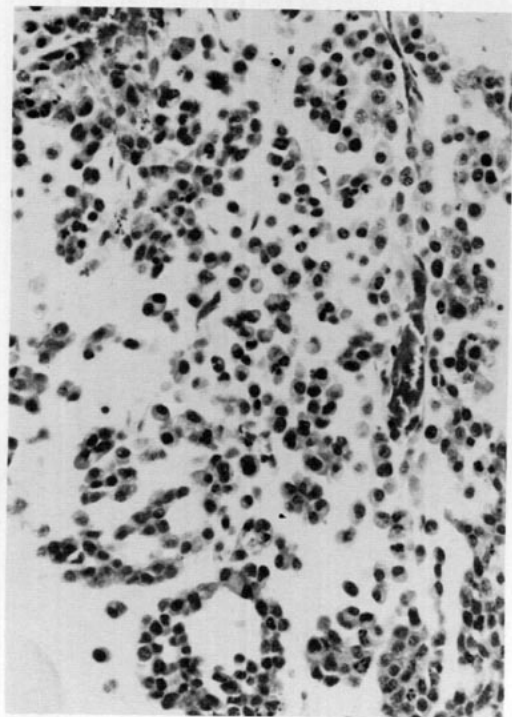


PLATE 33. Yolk sac carcinoma; uniform cells with large, often eccentrically placed nuclei. Reprinted with permission (31).



PLATE 34. Hemangioma; lakes of hemorrhage, multiple thrombi (◐), vascular channels lined by endothelium (◑).

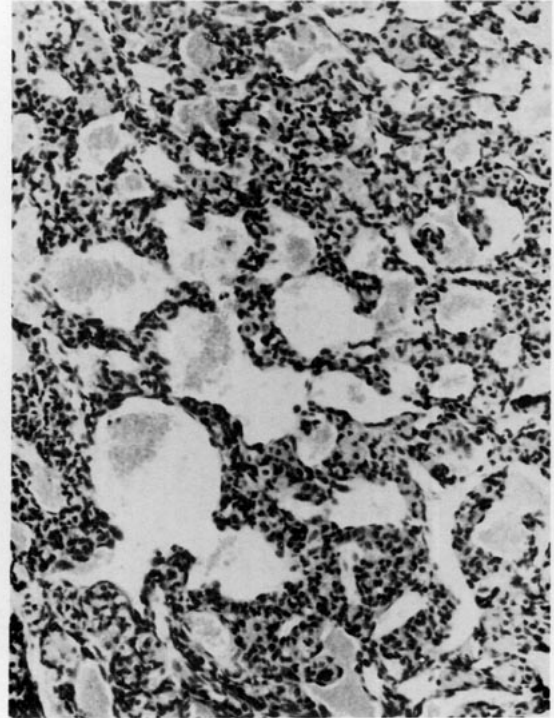


PLATE 35. Hemangioma; high power of Plate 34. Vascular channels lined by endothelial cells.