

PROLIFERATIVE LESIONS OF THE KIDNEY IN RATS

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INTRODUCTION

The specific terminology adopted here for proliferative lesions of the rat kidney is based on morphology, cell population origin and conceptual distinctions between certain processes. In setting criteria, emphasis has been given to the use of easily recognizable histological features as a guide for distinguishing lesions that have been associated with a degree of diagnostic subjectivity. This attempt to introduce uniformity into kidney lesion nomenclature must be viewed as an evolving process, requiring modification of terms and/or criteria as new relevant information becomes available from experimental studies. Several recent publications (1, 12, 32) have provided additional descriptive information regarding some of the rat kidney proliferative lesions covered in this paper, sometimes with minor differences in classification.

The generic lesions which embrace the proliferative states encountered in the rat kidney are regeneration, hyperplasia and neoplasia. Hypertrophy, karyomegaly, and chronic progressive nephropathy are also dealt with briefly. The non-neoplastic proliferative states are associated mainly with the epithelium of renal tubules and renal pelvis, and the glomerulus. The neoplasms occurring in the rat kidney are classified according to the

established or putative site of cellular origin. Renal neoplasms therefore fall into one of three broad categories based on derivation from 1) epithelium 2) connective tissue or 3) embryonal primordia. Epithelial tumors comprise renal tubule neoplasms for which the standard terms renal tubule adenoma and carcinoma are recommended, and tumors of the epithelial lining of the renal pelvis, termed transitional or squamous cell carcinoma. Tumors of connective tissue origin include renal mesenchymal tumor (a complex tumor composed of diverse connective tissue types), and lipomatous tumors (lipoma, liposarcoma). Nephroblastoma is an embryonal tumor of the rat kidney.

MORPHOLOGY

GLOMERULUS-ASSOCIATED PROLIFERATIVE LESIONS

Proliferative lesions associated with the renal corpuscle involve Bowman's capsule, the mesangium and the juxtaglomerular body. None of the lesions has been associated with neoplasia in the rat.

Bowman's Capsule Hyperplasia (Figure 1)

The single cell layer of the parietal epithelium of Bowman's capsule can undergo an increase in the

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number of cells, representing hyperplasia. At the same time, the hyperplasia involves a metaplastic change from the normal squamous epithelium to cuboidal cells resembling those of proximal tubules. Hyperplasia of Bowman's capsule epithelium has been observed in rats following exposure to lead (38) and in spontaneously hypertensive rats (16). It sometimes occurs spontaneously in aging conventional rats, but is more common in males than females.

Mesangial Cell Hyperplasia

Mesangial hypercellularity in the glomerular tuft represents mesangial cell proliferation, sometimes with an increase in mesangial matrix. This condition is also termed mesangioproliferative glomerulonephritis (1). Mesangial cell hyperplasia in the rat can accompany immunologically-mediated glomerular injury, inflammatory change, or be chemically-associated e.g. as one component of a nephrotic syndrome induced by puromycin (35).

Juxtaglomerular Cell Hyperplasia (Figure 2)

An increase in the number of the renin-secreting myoepithelial cells of the juxtaglomerular apparatus, surrounding the afferent arteriole, has been induced by angiotensin-converting enzyme inhibitor drugs (42). The condition is reversible upon drug cessation.

PROLIFERATIVE LESIONS OF RENAL TUBULES

Renal Tubule Cell Hypertrophy

Although not a proliferative entity, renal tubule cell hypertrophy has been included here to underline its distinction from renal tubule hyperplasia. Tubule cell hypertrophy designates an apparent increase in size of individual tubule cells without an overall increase in cell number. One example of proximal tubule cell hypertrophy is sometimes observed in residual nephrons of very advanced stages of chronic progressive nephropathy (CPN).

Karyomegaly (Figure 3)

DNA replication without completion of the mitotic process of cytokinesis leads to conspicuous nuclear enlargement indicative of increased ploidy levels (24). Karyomegaly has been observed in tubule cells, particularly during the administration of some known renal carcinogens. Indeed, its presence in subchronic studies suggests that a test compound may have carcinogenic properties. However, karyomegaly is not regarded as a preneoplastic lesion because there is no evidence that affected cells contribute to the initial formation of proliferative foci (11,19,28).

Renal Tubule Regeneration (Figure 4)

Renal tubule cell regeneration is observed after injury to normal tubule epithelium and may be restricted to specific segments of the nephron. The term regeneration is reserved for the process resulting in replacement of lost cells to restore a damaged tubule back to its normal state with no long-term or persistent overproduction of cells. Regenerating epithelium is characterized by basophilia and, temporarily, a higher than normal mitotic rate demonstrable by increased mitotic figures and/or DNA synthesis-labeling index. During restoration of a normal tubule, regenerating cells may show a transition from flattened to low cuboidal forms. Regeneration in proximal tubules is classically exemplified by the epithelial response following coagulative necrosis induced by mercuric chloride (15) and hexachlorobutadiene (23) but also can be the consequence of single cell necrosis. It should be noted that tubule basophilia generally implies increased cell replicative rate and as such may represent regeneration, simple hyperplasia or a combination of both.

Renal Tubule Hyperplasia (Figures 5-8)

Hyperplasia of renal tubule epithelium implies an increase in the number of lining cells but without proliferation beyond the well-defined, basement-membrane-bound integrity of the individual tubule structure. Renal tubule hyperplasia can be subdivided into the morphological categories of *simple* and *atypical*. Atypical tubule hyperplasia usually has a focal distribution and the foci can be readily counted. Simple hyperplasia often is multifocal and much more frequent, in which case the severity should be graded. In both cases, the hyperplasia may involve a cluster of tubule cross-sections because of extension of the proliferative response along the convolutions of a single tubule segment.

In *simple tubule hyperplasia* (Figures 5, 6) there is an increase in the number of epithelial cells but the single cell layer of the lining is maintained. The tubule with simple hyperplasia may or may not exceed normal dimensions or may be slightly smaller due to decreased cell size (e.g. see under Chronic Progressive Nephropathy). Increased cross-sectional diameter is sometimes due to dilation of the tubule lumen. It should be noted that, due simply to overcrowding and/or tangential sectioning, the single cell layer sometimes may have a misleading pseudo-stratified appearance, as illustrated in hyperplastic tubules involved in pyelonephritis secondary to renal papillary necrosis (21).

Atypical hyperplasia of renal tubules (Figures 7,8) is characterized by a prominence of atypical cells and/or complex proliferation of the lining beyond the normal single cell layer. Atypical cells are identified by cell and

nuclear pleomorphism including obvious or bizarre variation in cell and nuclear size, and increased nucleus to cytoplasm ratio. Complex proliferation of the lining can take several forms: 1) focal projections of epithelium into the tubule lumen, 2) multilayered epithelial lining (as in Figure 7), or 3) obliteration of the lumen by epithelial cell proliferation to produce a solid tubule but without any internal neovascularization (Figure 8). Atypical tubule hyperplasia is invariably accompanied by an increase in tubule dimensions because of the increased cell number. In some cases there also may be conspicuous dilation of the tubule lumen. The staining pattern of the cells may further describe the hyperplasia depending on whether the cells are predominantly basophilic, eosinophilic, clear or oncocytic but these are not essential qualifiers. Where the lumen is markedly dilated the hyperplasia also can be designated as of cystic type. The term oncocytic refers to pale eosinophilic cells with finely granular cytoplasm which at the ultrastructural level are packed with mitochondria (6). Immunocytochemical demonstration of cytochrome c oxidase, the final enzyme of the mitochondrial respiratory chain, is a specific marker for renal oncocytes (29), but periodic acid Schiff orange G also has been used to selectively stain oncocytic tubules.

In the renal parenchyma, hyperplasia is mainly observed in the proximal tubule segments because these are the most common sites affected by disease process or xenobiotic-induced injury. However, any part of the renal tubule appears to have the potential for hyperplasia as a response to chemical perturbation. An example of simple hyperplasia affecting tubule segments other than proximal nephron is the medullary collecting tubule hyperplasia observed as an adaptive response in potassium deficiency (39).

Renal tubule hyperplasias may be reversible, for example those associated with potassium deficiency, pyelonephritis (21), and nitrotriacetate administration (2). The size of hyperplastic lesions has been demonstrated to be an important determinant in reversibility but limits have not been clearly defined. Studies with a non-genotoxic carcinogen (2) suggest that proliferative lesions including simple and atypical hyperplasias less than twice the cross-sectional diameter of a normal glomerulus may be reversible upon cessation of exposure. With administration of renal carcinogens, atypical tubule hyperplasia also can be recognized as part of a continuum preceding formation of tubule adenomas and carcinomas (11, 20, 40). Thus, an increased incidence of renal tubule neoplasia would be expected to be associated with increased incidence of atypical tubule hyperplasia.

Chronic Progressive Nephropathy (CPN)

The term chronic progressive nephropathy is

adopted here, according to Barthold (7), for the spontaneous, age-related renal disease of rats. Although frequently classified as regeneration, the basophilic tubules of early and progressive stages of CPN actually represent a simple hyperplasia (along with single cell necrosis and regeneration) mainly affecting proximal tubules (Figure 5). This is because the epithelium is highly proliferative (26, 36) and the increased cell turnover results in a sustained increase in cell number per nephron segment. The simple tubule hyperplasia of CPN is always associated with thickened basement membrane except at the very commencement of the process. It is not recommended that the simple hyperplasia constituting a major component of this spontaneous age-related renal disease be scored as a separate entity of hyperplasia, but incorporated into the overall diagnosis of CPN, which should be graded according to severity. On the other hand, diffuse or frequent foci of simple hyperplasia without basement membrane thickening (or other characteristic features of CPN) should be distinguished, and graded independently from that associated with CPN. In the very advanced stages of CPN, atypical tubule hyperplasia can be seen, again accompanied by prominent basement membrane thickening. Unlike simple hyperplasia associated with CPN, atypical hyperplasia should be scored regardless of whether it is part of the CPN process or not. Certain chemicals, including non-genotoxic carcinogens, can exacerbate CPN leading to earlier appearance and increased severity of the hyperplasia and other CPN-associated lesions.

Renal Tubule Adenoma (Figures 9,10)

Renal tubule adenoma is a small neoplasm representing epithelial cell proliferation beyond the well-defined structure of an individual tubule. Adenomas lack areas of hemorrhage and degeneration, but single cell necrosis and cell pleomorphism may be present (18). Early vascular ingrowth (neovascularization) sometimes is discernible within the epithelial foci. Mitoses are characteristically infrequent. Clustering of cells within the lesion to form new lumens (minilumens) also can occur. Minilumen formation, if present, and early neovascularization are particularly useful criteria for distinguishing adenoma from atypical tubule hyperplasia in cases where there is difficulty in deciding whether the epithelial proliferation has exceeded the integrity of a single tubule.

Adenomas are usually larger in cross-sectional diameter than tubule hyperplasias. They are rounded or irregular in shape and of solid or cystic form. Depending on size, adenomas may cause slight compression of the surrounding parenchyma but in the rat kidney they usually are not associated with a circumscribing pseudocapsule. Compression alone cannot be used to

distinguish adenomas from tubule hyperplasia as marked luminal dilation of a single tubule can compress surrounding nephrons. As discretionary qualifiers, cell morphology can be described as basophilic, eosinophilic, clear, or oncocytic, according to staining characteristics. Oncocytomas are regarded as distinct entities in some classifications (32). The architectural organization of adenomas is similar to that of carcinomas (described below), particularly the well-differentiated variants of carcinoma. Adenomas (and the subsequent carcinomas) may arise from various segments of the nephron depending on the site of action of the carcinogen. For example, N-(4'-fluoro-4-biphenyl)acetamide (11) induces renal tubule tumors in the straight segment of proximal tubule (outer stripe of the outer medulla) while dimethylnitrosamine tumors involve the proximal convoluted tubule of the cortex (20).

Renal Tubule Carcinoma (Figures 11-13)

Large renal tubule tumors have been described in the literature primarily as adenocarcinomas and/or carcinomas. The distinction between the two terms has been based on the degree of glandular differentiation in adenocarcinoma versus solid sheets of cells in carcinoma, although often there is a mixed architecture. To avoid confusion over what is essentially a single entity, the term *carcinoma* is adopted here, in harmony with human nomenclature. As discretionary qualifiers, histologic variants of renal tubule carcinoma can be recognized based on staining characteristics and architectural pattern. Accordingly, carcinomas can be described as 1) basophilic, eosinophilic, clear or mixed, or as 2) tubular, lobular, papillary or solid. Clear cell tumors lack staining because of their high content of lipid and/or particulate glycogen (5). Well-differentiated basophilic and eosinophilic tumors tend to be tubular or papillary carcinomas whereas tumors consisting of clear cells are usually lobular or solid in form. The larger tumors frequently show a mixture of tinctorial and architectural patterns, often with some cellular pleomorphism. More rarely, carcinomas may be exclusively of anaplastic type.

In contrast to adenomas, carcinomas are typified by prominent areas of hemorrhage and/or necrosis, and an arborizing vascular pattern, features which first tend to be present in tumors exceeding 0.5 cm diameter (18). The stroma is typically a thin framework of blood vessels and supporting connective tissue cells ramifying between tumor cell lobules and within papillary fronds, but in anaplastic tumors the stroma can be scirrhous in nature. Additional features which may be present in carcinomas but not usually in adenomas include scattered to frequent mitotic figures and sometimes clear evidence of local invasion by neoplastic foci from

the tumor edge into the immediately adjacent parenchyma. Mitotic figures are particularly frequent in anaplastic tumors but are not often observed in clear cell carcinomas. Aberrant and redundant basement membrane is usually discernible in carcinomas.

Renal tubule carcinomas usually are circumscribed fleshy growths increasing in size typically by expansion, thus causing compression of the surrounding parenchyma with or without pseudocapsule formation. They occasionally reach dimensions of many centimeters, particularly when induced by potent renal carcinogens. Anaplastic tumors, however, can show a true infiltrative mode of growth between preexisting tubules.

In long-term exposure studies with renal tubule carcinogens, metastasis to distant organs is infrequent, but relatively common in experiments using single doses of dimethylnitrosamine (17). The studies with this genotoxic chemical indicate that renal tubule tumors grow progressively and have the potential for metastatic behavior, mainly to the lung, providing the rat survives long enough for the tumor to reach a critical size (exceeding 2 cm diameter in the dimethylnitrosamine study). Primary tumors which metastasize can display a variable or mixed histological pattern often with cell pleomorphism.

PROLIFERATIVE LESIONS OF RENAL PELVIS

Transitional Cell Hyperplasia (Figures 14-18)

The cells lining the renal pelvis consist predominantly of cuboidal epithelium over the papilla but transitional epithelium (urothelium), similar to bladder epithelium, comprises the remainder (41). Transitional cell hyperplasia of the renal pelvis (synonymous with urothelial hyperplasia) occurs with or without atypia, according to the variability of the cells. In *transitional cell hyperplasia without atypia*, the cells are uniform throughout and do not vary from the normal transitional cell type. *Transitional cell hyperplasia with atypia* is characterized by the presence of cellular pleomorphism, nuclear abnormalities, increased cytoplasmic basophilia, haphazard arrangement and more obvious mitotic activity.

Transitional cell hyperplasias can arise at any part of the renal pelvic surface and may be focal or multifocal. Discretionary qualifiers relate to the mode of growth from the original lining. *Simple* transitional cell hyperplasia is a sessile or uniform thickening of the renal pelvis lining without prominent outward or inward focal growth. *Papillary* transitional cell hyperplasia is an exophytic projection of the lining into the renal pelvic space, often accompanied by a conspicuous, reticular core of underlying connective tissue. *Nodular* transitional cell hyperplasia can be either exophytic or

endophytic (inverted) represented by solid, nodule-like foci of transitional cells.

Various forms of transitional cell hyperplasias occur as responses to bacterial infection (25), urinary tract toxins and carcinogens, calculi, or in association with renal papillary necrosis (4). Papillary hyperplasia, without atypia, is particularly associated with infective processes in the urinary tract, while nodular transitional cell hyperplasia is more typically a response to papillotoxic chemicals. The inverted form occurs infrequently in the rat but has been observed in nitrotriacetate exposure (3). Chemical carcinogens that target the urinary tract can induce atypical transitional cell hyperplasia, which is regarded as a preneoplastic lesion (27).

Transitional Cell Carcinoma (Figures 19, 20)

Tumors arising from the renal pelvis lining can be of two types, transitional cell and squamous cell carcinomas (18). Transitional cell carcinoma is more common, but mixtures of the two forms are occasionally encountered in which case the diagnosis used should be based upon the predominant cell type. Both tumor types are poorly demarcated growths that tend to proliferate within the renal pelvis at first, and then invade and deform the renal parenchyma.

In ***transitional cell carcinoma***, the tumor cells may be arranged in papillary or frond-like structures, or cords, where there is minimal deviation from normal transitional urothelium, or in solid areas with cellular atypia including marked cell and nuclear pleomorphism and haphazard arrangement. Proliferation within the renal pelvic space is of the papillary or nodular form whereas invasion of the kidney tissue usually occurs by cords or irregular masses of cells. Mitotic figures may be frequent. Typically these tumors are associated with a prominent inflammatory reaction with conspicuous accumulations of neutrophil leucocytes and prominent tracts of hemorrhage and necrosis.

Squamous Cell Carcinoma (Figure 21)

Squamous cell carcinoma of the renal pelvis differs from the transitional cell tumor in consisting of squamoid cells arranged in sheets, or irregular islands, usually associated with keratinization and pearl formation. In contrast to the relatively delicate stromal framework of many transitional cell carcinomas, the aggregates of squamous cells often are set within a well-developed fibrocollagenous stroma. Small deposits of mineralization also may be present.

TUMORS OF RENAL CONNECTIVE TISSUE

Renal Mesenchymal Tumor (Figures 22,23)

This connective tissue neoplasm, the subject of much confusion, has been described under a diversity of terms ranging from nephroblastoma to hemangioendothelioma (18). The confusion with nephroblastoma arises because all mesenchymal tumors also contain epithelial profiles. These, however, are not *de novo* elements but represent sequestered glomeruli, tubules or urothelial nests surviving as remnants of preexisting nephrons or renal pelvis lining (19). Sometimes these epithelial remnants become hyperplastic, and in the case of glomerular capsules and tubules, dilated to form cysts.

Because of their infiltrative mode of growth, ***renal mesenchymal tumors*** (RMT) are irregular in shape with a poorly delineated outline. They appear to originate near the corticomedullary junction and involve the outermost zones of the kidney at first, spreading toward and into the renal pelvis with time. RMT of small size tend to be fibrous in texture but larger tumors are multiloculate with prominent cystic cavities, areas of hemorrhage and degeneration, and gelatinous tissue. Mitotic activity is common and the tumors have the potential to grow and fill the abdominal cavity, causing death. The tumors can be locally invasive, into the body wall, and metastasis also occurs in a small proportion of cases. RMT, therefore, should be considered a malignant neoplasm.

The hallmark of RMT is the heterogeneity of connective tissue cell types typically occurring within a single tumor (19). The basic cell form is a fibroblastic spindle cell, found at the invading edge of the growth infiltrating between normal renal tubules and forming fibrosarcomatous sheets, sometimes with a herringbone or swirling pattern. A characteristic feature is that the spindle cells may encircle sequestered renal tubules in multilayered fashion. Less cellular areas contain stellate cells which form a reticular network resembling primitive mesenchyme or myxomatous tissue. Smooth muscle fibers are invariably present in all but the smallest of RMT, but may require special staining techniques, such as haem-phloxine-saffron, for visualization. Such fibers are sparsely distributed throughout areas of low cell density, particularly encircling cystic spaces. Occasionally smooth muscle is more profuse and areas of frank leiomyosarcoma merge with areas of fibrosarcoma. In about one third of RMT there is a conspicuous development of abnormal vascular structures compatible with hemangioma, hemangioendothelioma or hemangiosarcoma (Figure 23). These areas merge with fibrosarcomatous sheets indicating that the potential for neoplastic vascular differentiation is an integral component of RMT. Other cellular elements

which may occur less frequently include rhabdomyoblasts, mature striated muscle, cartilage and on rare occasion, osteoid tissue. Extensive and sometimes abnormal deposition of collagen as a product of the tumor cells is also a prominent feature, as well as a well-developed reticulin network. Any one of the above cellular elements can dominate, so that the tumor, or major parts of it, can be qualified as a fibromatous (predominantly collagenous), fibrosarcomatous, leiomyosarcomatous, rhabdomyosarcomatous, or hemangiosarcomatous variant. Notwithstanding the characteristic cellular heterogeneity of RMT, tumors in an early stage of development may contain only fibroblastic spindle cells.

RMT has been associated mainly with chemical induction, particularly nitrosocompounds, but also occurs spontaneously in the rat, although rather infrequently (18).

Lipomatous Tumors (Figures 24, 25)

Although they most probably represent a continuum, these renal tumors can be discriminated into two distinct entities, lipoma and liposarcoma, based on size and cell composition (13,14,18). Lipomatous tumors have, on occasion, been referred to as renal or lipomatous hamartoma (9,37) which is a misnomer, as well as mixed (malignant) tumor of kidney (13).

Lipomas are small lesions, usually less than 0.5 cm in diameter, located deep in the outer stripe of outer medulla. They are histologically monomorphic consisting of an interstitial aggregate of mature fat cells (lipocytes) often incorporating a few normal tubule profiles. Neovascularization of lipomas is not prominent and they lack evidence of mitotic activity, hemorrhage or necrosis.

Liposarcomas are larger neoplasms which because of their infiltrative mode of growth, have an irregular, poorly demarcated outline, similar to RMT. They consist of an admixture of mature lipocytes, lipoblasts (foam and "signet-ring" cells), and relatively undifferentiated mesenchymal cells. In contrast to RMT, differentiation is exclusively along the fat cell lineage, and other connective tissue elements as neoplastic vascular tissue, smooth muscle, striated muscle, cartilage and osteoid are absent. Collagen and reticulin also are not formed in significant amounts. Large areas of liposarcoma may consist of well differentiated fat cells but other parts of the same tumor can show an intermingling of these mature cell forms with more primitive lipoblasts. Poorly differentiated mesenchymal stem cells are found particularly at the invading edge, and in larger tumors, they form conspicuous, densely cellular islands contrasting with the surrounding sheets of mature lipocytes (Figure 25). Preexisting epithelial elements in the form of tubule remnants, glomeruli, epithelium-lined cysts

and urothelial islands become sequestered within the tumor tissue as in RMT. However, these remnants tend to develop thickened basement membrane and become atrophic or cystic. Blood vessels of non-neoplastic type, sometimes with thickened muscular walls, are quite prominent, along with noticeable red cell extravasation. Areas of frank hemorrhage or necrosis are not uncommon. Mitotic activity is infrequent and usually restricted to the areas containing undifferentiated mesenchymal cells.

Renal Fibrosarcoma

Fibrosarcomas resembling those from other sites are very occasionally encountered in the rat kidney in chronic bioassays (32). These tumors consist exclusively of a densely cellular monomorphic population of basophilic fibroblast-like spindle cells. The heterogeneous spectrum of secondary mesenchymal cell types that characterizes RMT is not present. In addition, fibrosarcomas lack sequestered preexisting tubules and glomeruli except perhaps at the tumor periphery which tends to be well delineated. Prominent collagen deposition also is absent. Little published information is available on these tumors and whether they are a distinct entity from RMT or represent a variant of this connective tissue neoplasm is not known.

TUMORS OF EMBRYONAL TISSUE

Nephroblastoma (Figures 26, 27)

In the rat, nephroblastoma is essentially an epithelial tumor derived from metanephrogenic blastema (8,22). Small tumors are located in the outer cortex as a monomorphic focus of highly basophilic blastemal cells. Typically, with increase in size to macroscopic dimensions, nephroblastomas become circumscribed growths well demarcated from the surrounding parenchyma. They have the potential to grow to large multilobulate masses with time.

The pathognomonic features of rat nephroblastoma are highly basophilic blastema and attempted organoid differentiation along the epithelial pathway into nephric elements. The tumor cells comprising the blastema are of undifferentiated epithelioid form with scant cytoplasm, poorly defined cell borders and large hyperchromatic or vesicular nuclei. These blastema-like cells are densely packed into clusters, balls or columns which may appear roughly circular in cross-section. The blastema cells also can be arranged in anastomosing cords, alveolar or papillary patterns, and rarely, as a cylindromatous variant. On occasion, the blastemal cells can be spindle-shaped with a fascicular pattern mimicking sarcoma. Although very early lesions can be exclusively blastemal, organoid differentiation almost

always is present in macroscopic tumors, either in the form of primitive tubules, well-differentiated epithelial ducts, or as glomerulus-like structures. Newly formed tubules range from simple rosette formations to well-formed basophilic tubules. Epithelial ducts lined by mature cuboidal or columnar epithelium sometimes appear to form a branching system ramifying through the clumps of blastemal cells. Primitive glomeruloid formations may occur in over 50% of rat nephroblastomas (22) as discrete sacs of very small hyperchromatic cells supported by a stalk of eosinophilic matrix, without vascularization.

The supporting stroma in rat nephroblastoma can vary from well-developed bands of mature fibrocytes, collagen and blood vessels, to relatively structureless tracts with the appearance of areolar tissue. On rare occasion, adult type striated muscle also has been observed (30). Tumor growth often is associated with some chronic inflammatory reaction in the surrounding compressed parenchyma, forming an encircling pseudocapsule in larger tumors. Small nests of blastemal cells may be seen within and just beyond the pseudocapsular band of fibrous tissue indicative of local invasion. Mitotic figures usually are frequent in nephroblastoma, involving the blastema and tubule formations. Consequently, nephroblastoma should be regarded as a malignant neoplasm even though metastases are rare. Nephroblastoma is encountered spontaneously at a very low frequency in chronic bioassays.

DISCUSSION

Renal tubule neoplasms are the most common spontaneously occurring primary neoplasm of the kidney in most strains of rat (18) although liposarcoma appears to be the predominant renal tumor of the Osborne-Mendel strain (13). In special inbred strains, other renal tumor types may predominate. Thus, nephroblastoma is the most frequent spontaneous renal neoplasm in the Nb hooded (22) and WAB/Not rat (31), while transitional cell carcinomas of the renal pelvis are dominant in the DA/Han (10). However, in the commonly-used strains of laboratory rat, spontaneous RMT and nephroblastoma are very infrequent, and carcinoma of the renal pelvis is rare. Many chemicals have been found to induce increased incidences of renal tubule tumors. In contrast, the number of chemicals associated with the induction of RMT and carcinoma of the renal pelvis is more limited. Very few chemicals have induced nephroblastomas and then usually by transplacental administration (8,18). There have been no unequivocal instances of lipomatous tumor induction by

chemical agents as yet (18).

A number of different terms have been used by various authors to designate atypical tubule hyperplasia, the most common being variations on atypical cell foci and dysplastic foci. To avoid ambiguity, atypical hyperplasia has been preferred in this classification scheme over dysplasia because the latter represents a specific diagnostic entity of anomalous kidney development in some species. In this context, dysplasia is a field change of disorganized development due to abnormal and asynchronous differentiation of renal parenchyma, usually accompanied by secondary compensatory, degenerative and inflammatory changes (34).

With respect to the distinction between renal tubule hyperplasia and adenoma, it should be remembered that hyperplastic change can affect a substantial length of a single nephron structure. In the cortex, this means that adjacent convolutions of the same hyperplastic tubule may give the erroneous impression of an adenoma.

Discrimination between renal tubule adenomas and carcinomas cannot be based solely on tumor cytology or organization. Likewise, size cannot be used rigidly for their distinction, particularly as lesion diameter in a single section will not necessarily represent the true dimensions of the tumor. Used in conjunction with cellular features such as pleomorphism, frequent mitoses and aberrant basement membrane, the presence of areas of hemorrhage and/or necrosis are useful guides for assisting the diagnosis of carcinoma. These criteria, representing a step in the progression of renal tubule tumors and characterizing the larger rat neoplasms, including those which metastasize to distant organs, are easily recognizable and not prone to subjectivity between pathologists. Moreover, hemorrhage and degeneration have been used in human oncology for distinguishing small renal carcinomas from adenomas (33). However, it is generally recognized that there is an evolutionary continuum from adenomas to carcinomas (18, 28) and therefore it is recommended that the two entities be combined for the purpose of carcinogenicity assessment. At the same time, the ability to discriminate adenomas from carcinomas might become an important dimension in some two-year bioassays where evidence of limited progression, along with data on tumor incidence and latency, could be indicative of a weak rather than strong carcinogenic potency.

An entity of transitional cell papilloma of the renal pelvis, implying a solitary papillary outgrowth of uniform transitional cells without atypia, confined within the renal pelvic space and without local invasion, has not been included in nomenclature for the rat. This is because the proliferative lesions encountered in the rodent renal pelvis appear to represent either epithelial hyperplasia or possess the hallmarks of early transitional

cell carcinoma.

Discrimination of RMT from nephroblastoma requires particular caution. In RMT, the heterogeneous range of neoplastic connective tissue types is distinguishable from the predominant, highly basophilic blastema of nephroblastoma. Tubular and glomerular structures in nephroblastoma are neoplastic elements representing differentiation along the epithelial pathway, while those in RMT are sequestered remnants of once-normal parenchyma. In addition, the irregular growth of RMT contrasts with the usually rounded and circumscribed form of nephroblastoma.

Because RMT has the frequent potential for differentiating into neoplastic vascular tissue, including areas consistent with hemangiomas and hemangiosarcomas, it is doubtful whether vascular neoplasms constitute a separate group from RMT in the rat kidney. Therefore, it is recommended that renal tumors comprising predominantly neoplastic vascular tissue be designated as hemangiomatous or hemangiosarcomatous variants of RMT.

Finally, it should be noted that composition tumors can occur in the rat kidney. Thus, neoplasms consisting of true mixtures of two distinct tumor types of separate origin have been observed in experimental studies using versatile carcinogens that can induce more than one renal tumor type. Composition tumors mainly have involved the collision and subsequent intimate admixture of RMT with renal tubule carcinoma (18). When encountered in bioassays, composition tumors should not be scored as such but rather as the individual tumor entities contributing to the mixture.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA FOR THE RAT KIDNEY

GLOMERULUS - ASSOCIATED PROLIFERATIVE LESIONS

Bowman's Capsule Hyperplasia

1. Diffuse, bilateral.
2. Increased number of cells in parietal lining.
3. Change from normal squamous to cuboidal cells.
4. Cells may resemble proximal tubule epithelium with brush border or may show basophilia without brush border.

Mesangial Cell Hyperplasia

1. Diffuse, bilateral.

2. Increase in mesangial cell number.
3. May be an increase in mesangial matrix.

Juxtaglomerular Cell Hyperplasia

1. Diffuse, bilateral.
2. Increase in granular myoepithelial cells.
3. Increase in size of juxtaglomerular body.

PROLIFERATIVE LESIONS OF RENAL TUBULES

Renal Tubule Cell Hypertrophy

1. Focal or diffuse, unilateral or bilateral.
2. Increase in tubule cell size.
3. No increase in tubule cell number per unit area.

Karyomegaly

1. Diffuse, scattered, bilateral.
2. Marked enlargement of tubule cell nucleus.
3. Individual cells only.
4. May be accompanied by cell enlargement.

Renal Tubule Regeneration

1. Focal or diffuse, bilateral.
2. Basophilic tubule cell cytoplasm with increased mitotic activity.
3. Cell number and tubule size usually not increased.
4. Occurs following renal tubule injury e.g. coagulative necrosis, single cell necrosis.
5. Restores tubule to normal morphology.

Simple Tubule Hyperplasia

1. Focal, multifocal or diffuse, unilateral or bilateral.
2. Increase in number of tubule lining cells but essentially retaining the single cell layer.
3. Proliferation restricted to within the individual tubule structure.
4. Tubule dimensions may be normal, decreased, or increased through lumen dilation or increased cell number.
5. Cells usually basophilic, or eosinophilic.

Atypical Tubule Hyperplasia

1. Focal or multifocal, unilateral or bilateral.
2. Increase in number of tubule lining cells with cellular atypia and/or complex proliferation within the tubule.
3. Atypia characterized by marked cell and nuclear pleomorphism including increased nucleus to cytoplasm ratio and marked variability in cell and nuclear size.
4. Proliferation restricted to within the individual tubule structure.

5. Tubule dimensions consistently increased through lumen dilation and/or increased cell number.
6. No vascular ingrowth.
7. Cells usually basophilic, but may be eosinophilic, clear or oncocytic.

Renal Tubule Adenoma

1. Usually single and unilateral but can be multiple and bilateral.
2. Usually located in the cortex or outer stripe of outer medulla.
3. Round or irregular shape, usually without encapsulation.
4. Extension beyond the confines of the original tubule structure.
5. Early vascular ingrowth within epithelial foci sometimes evident.
6. Lacks areas of hemorrhage or necrosis but there may be single cell necrosis.
7. Cells usually well-differentiated but sometimes pleomorphic.
8. Cells can be eosinophilic, basophilic, clear or oncocytic.
9. Sometimes cell organization to create minilumens.

Renal Tubule Carcinoma

1. Usually single and unilateral but can be multiple and bilateral.
2. Circumscribed, fleshy growths usually of rounded form.
3. Increase in size typically by expansion, with compression of surrounding parenchyma; may also be focal invasion into adjacent parenchyma.
4. Prominent vascular arborization in a delicate stromal framework; stroma occasionally scirrhous.
5. Prominent areas of hemorrhage and/or necrosis.
6. Composed of basophilic, eosinophilic or clear cells, but can be mixed, or occasionally anaplastic.
7. Tubular, lobular, papillary or solid pattern, or mixed.
8. Range from well-differentiated through pleomorphic to occasionally anaplastic cells.
9. Typically, aberrant or redundant basement membrane.
10. Mitotic activity scattered to relatively frequent in basophilic and eosinophilic cell tumors, less frequent in clear cell tumors, prominent in anaplastic tumors.

PROLIFERATIVE LESIONS OF RENAL PELVIS

Transitional Cell Hyperplasia

1. Focal or multifocal, unilateral or bilateral.

2. Multicellular thickening of transitional cell lining without atypia.
3. Simple, papillary or nodular.
4. Occurs as a response to infection, urinary tract toxins, calculi or renal papillary necrosis.

Transitional Cell Hyperplasia With Atypia

1. As above except,
2. Atypia present involving cell and nuclear pleomorphism, cytoplasmic basophilia and haphazard arrangement.
3. Can occur as a response to urinary tract carcinogens.

Transitional Cell Carcinoma

1. Typically single and unilateral.
2. Irregular growth originating in the renal pelvis but later invading the kidney substance.
3. Transitional epithelium, well-differentiated or pleomorphic, arranged in cords, papillary fronds or solid sheets.
4. Stroma usually a delicate connective tissue framework.
5. Often associated with accumulations of neutrophils and tracts of hemorrhage and necrosis.
6. Mitotic activity may be common.

Squamous Cell Carcinoma

1. Single and unilateral.
2. Irregular growth originating in the renal pelvis but invading the kidney substance.
3. Squamous epithelial cells arranged in sheets, tongues or irregular islands.
4. Keratinization and pearl formation usually present.
5. Fibrocollagenous stroma can be well developed.
6. Deposits of mineralization may be present.
7. Mitotic activity may be common.

TUMORS OF RENAL CONNECTIVE TISSUE

Renal Mesenchymal Tumor

1. Single or multiple, unilateral or bilateral.
2. Poorly demarcated irregular outline due to infiltrative mode of growth.
3. Small tumors fibrous in texture, larger tumors multiloculate, cystic, gelatinous, hemorrhagic.
4. Heterogeneous cell composition with spindle cell the basic type but also stellate cells and smooth muscle fibres; less commonly, rhabdomyoblasts, striated muscle, cartilage, osteoid. (The earliest tumors may consist only of fibroblastic spindle cells.)
5. Areas of fibrosarcoma intermixed with primitive

mesenchyme, myxomatous tissue and often neoplastic vascular tissue; also may be areas of leiomyosarcoma or less commonly rhabdomyosarcoma.

6. Preexisting glomeruli, renal tubules and pelvic urothelium survive within the tumor tissue as tubule profiles, cystic spaces, nests of transitional epithelium; the epithelium may become hyperplastic.
7. Collagen deposition marked and sometimes in abnormal clumps; reticulin prominent.
8. Mitotic activity frequent.

Lipoma

1. Usually single and unilateral.
2. Usually less than 0.5cm diameter.
3. Usually located at the corticomedullary junction.
4. Consists of a monomorphic aggregate of mature fat cells.
5. Lacks mitotic activity, hemorrhage or necrosis.

Liposarcoma

1. Usually single and unilateral.
2. Poorly demarcated, irregular outline due to infiltrative mode of growth.
3. Mixture of mature fat cells, lipoblasts and poorly differentiated mesenchymal cells.
4. Preexisting glomeruli, renal tubules and pelvic urothelium sequestered within the tumor tissue; these elements may become atrophic or cystic, with thickened basement membrane.
5. Focal red cell extravasation common, and in larger tumors, hemorrhage and necrosis.
6. Mitotic activity sparse and mainly involves poorly differentiated mesenchyme.

Renal Fibrosarcoma

1. Single and unilateral.
2. Tend to be well delineated from renal parenchyma.
3. Densely cellular, monomorphic population of basophilic spindle cells.
4. Preexisting glomeruli and tubules do not become sequestered into tumor interior.
5. Collagen deposition not prominent.

TUMORS OF EMBRYONAL TISSUE

Nephroblastoma

1. Usually single and unilateral.
2. Circumscribed growths with rounded outline.
3. Highly basophilic blastema arranged typically in discrete clusters but also as anastomosing cords, alveolar, papillary or occasionally, fascicular or cylindromatous patterns.
4. Organoid differentiation present in almost all tumors as rosette formations, primitive basophilic tubules, and/or mature epithelial ducts.
5. Organoid differentiation into primitive glomeruli occurs commonly.
6. Pseudocapsule often present in larger tumors.
7. Stroma varies from delicate areolar tissue to well-developed fibrous tracts.
8. Mitotic activity relatively frequent in blastema and tubule profiles.

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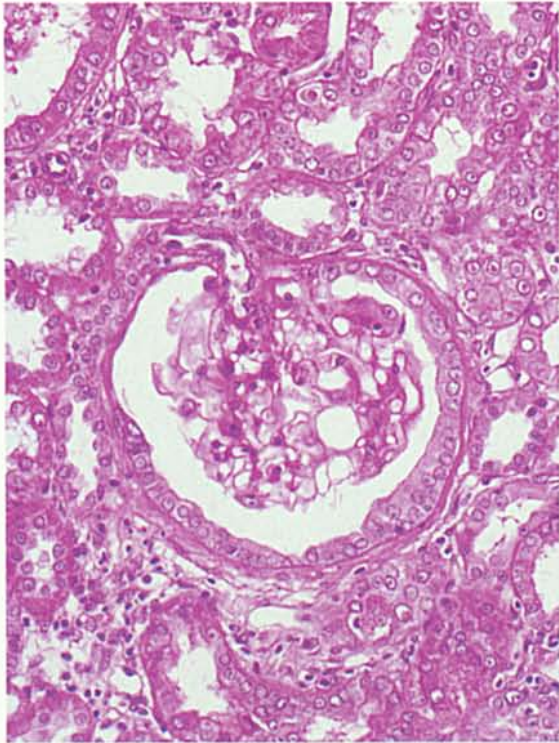


Fig. 1 – Bowman's capsule hyperplasia.

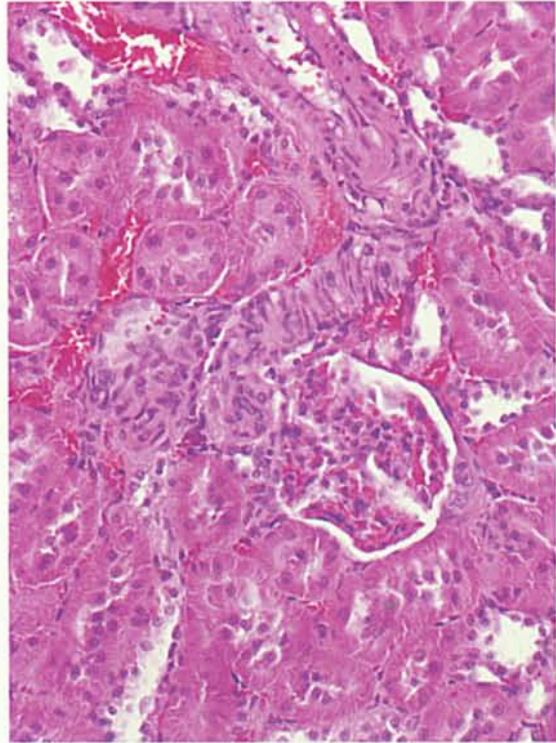


Fig. 2 – Juxtaglomerular cell hyperplasia.

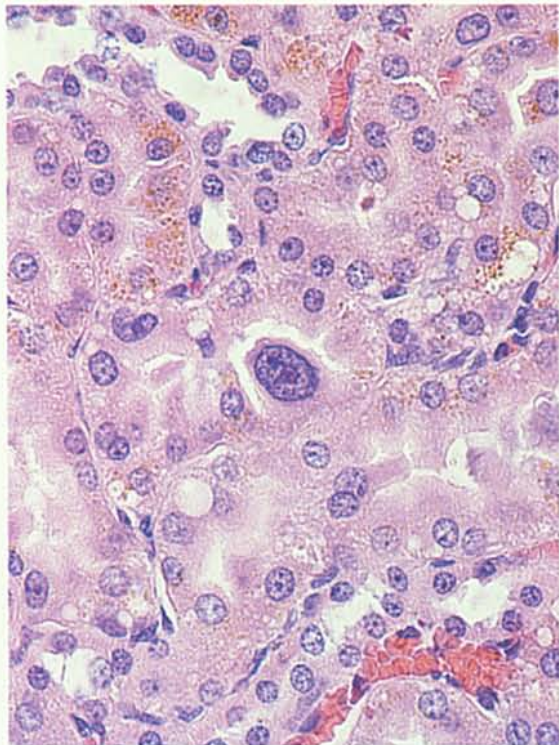


Fig. 3 – Karyomegaly.

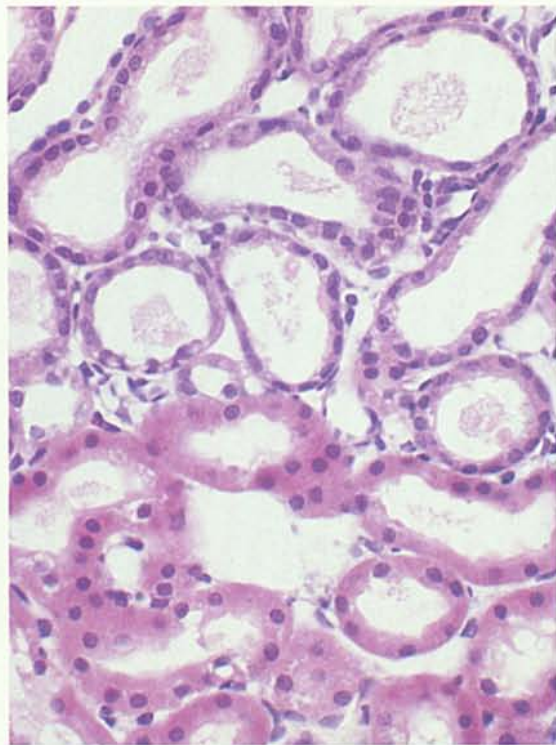


Fig. 4 – Renal tubule regeneration (perfusion fixed).

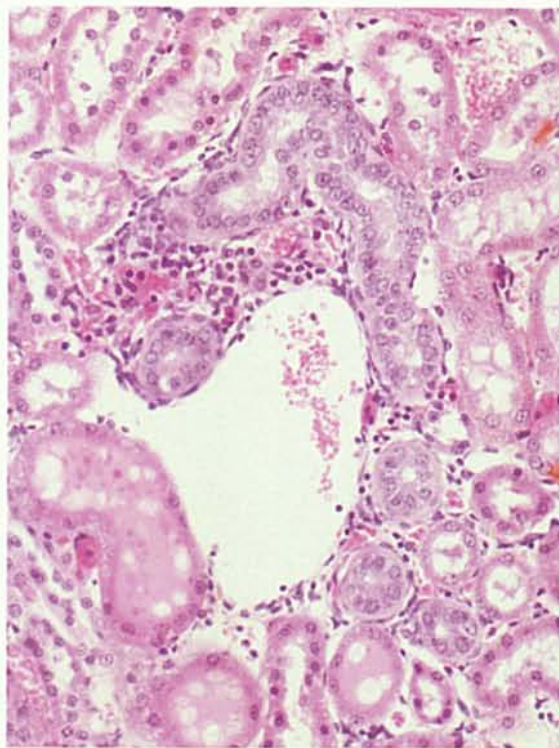


Fig. 5 – Simple renal tubule hyperplasia - proximal tubule (early CPN lesion with basement membrane thickening).

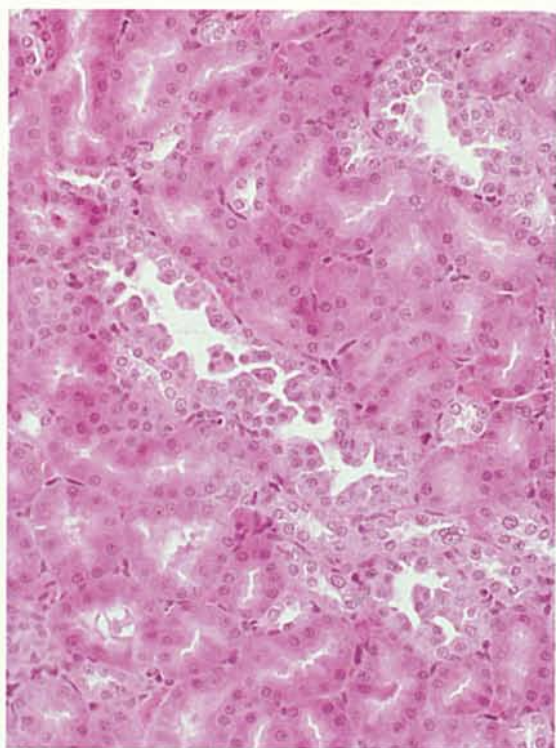


Fig. 6 – Simple renal tubule hyperplasia - collecting tube (potassium deficiency).

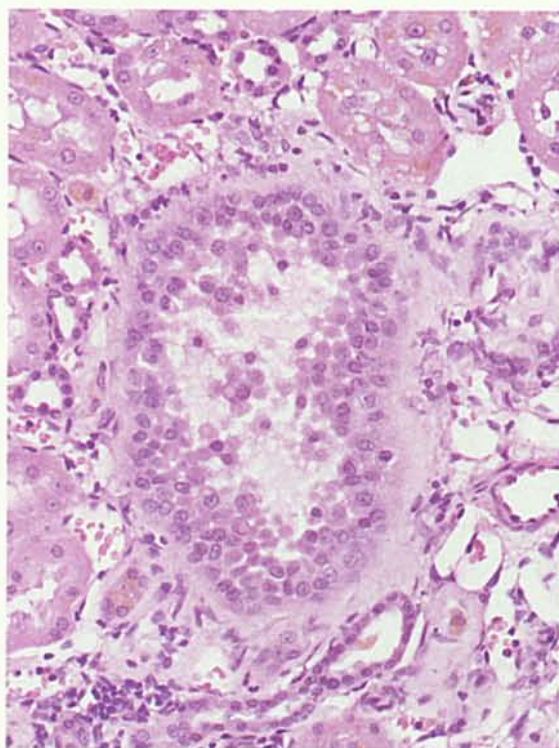


Fig. 7 – Atypical renal tubule hyperplasia (within CPN focus).

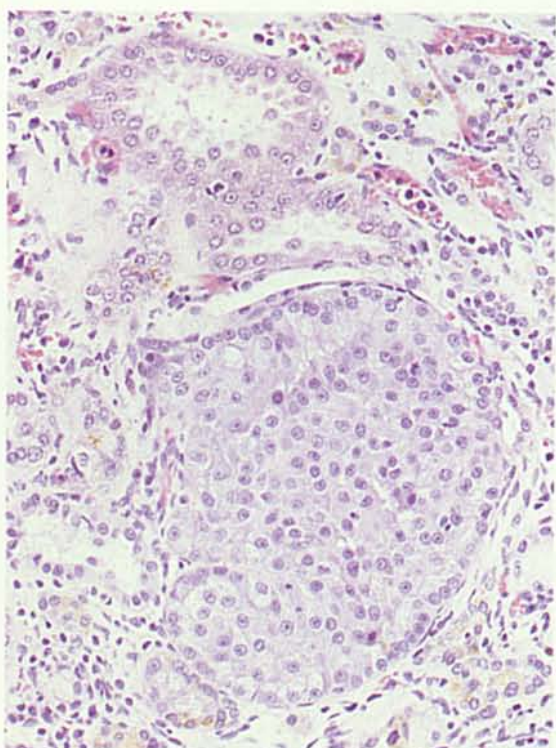


Fig. 8 – Atypical renal tubule hyperplasia - proximal tubule (chemically-induced).

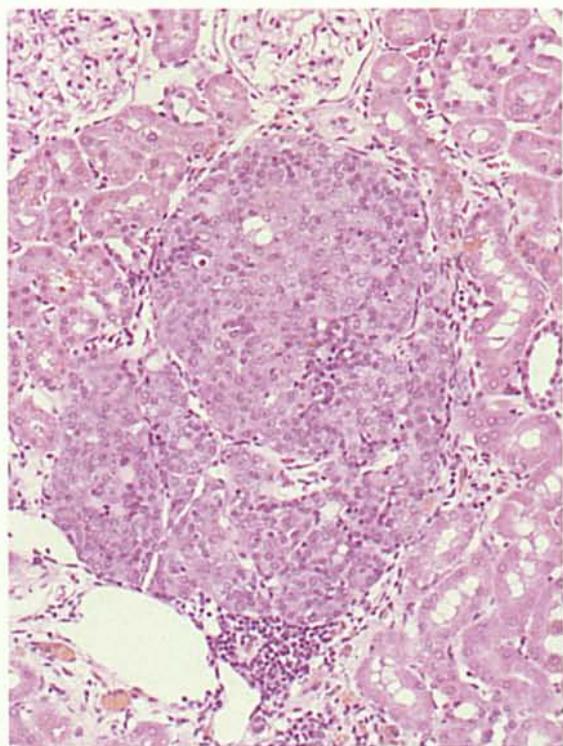


Fig. 9 – Renal tubule adenoma - basophilic.

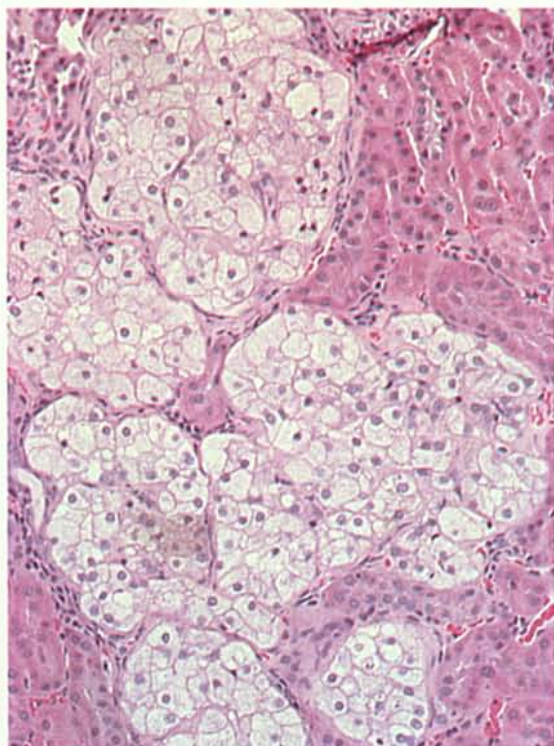


Fig. 10 – Renal tubule adenoma - clear cell.



Fig. 11 – Renal tubule carcinoma - basophilic (note areas of degeneration).

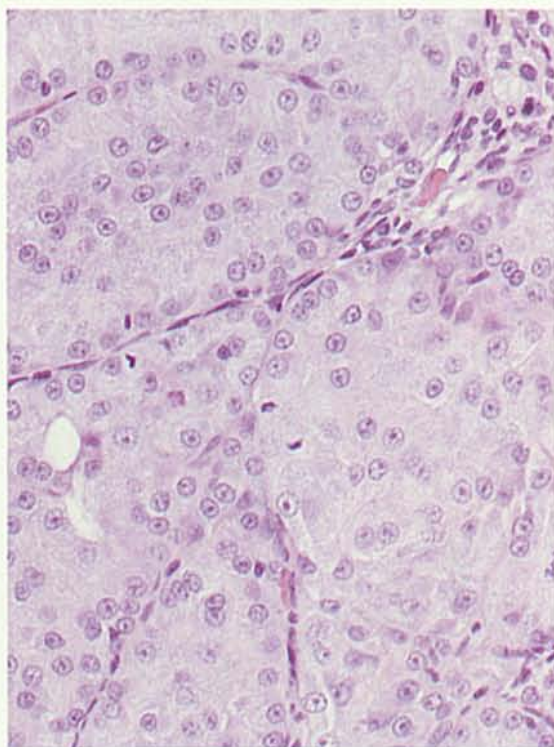


Fig. 12 – Renal tubule carcinoma - basophilic (note mitoses).

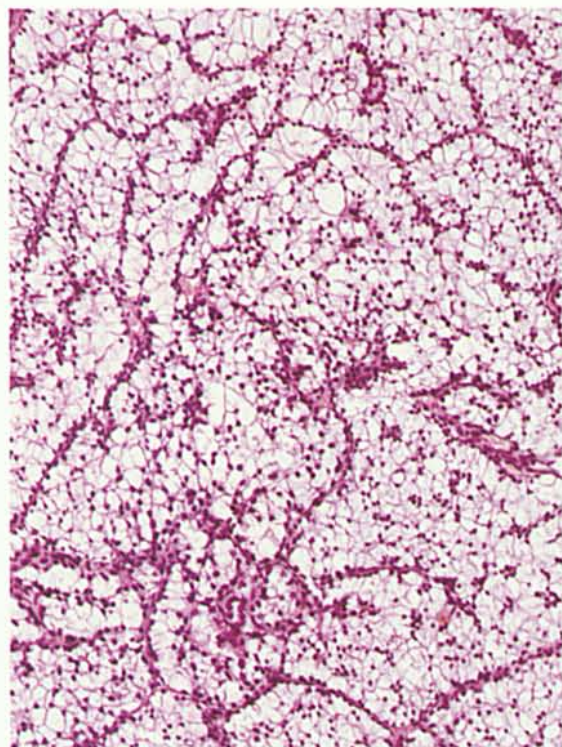


Fig. 13 – Renal tubule carcinoma - clear cell (note extensive vascularization).

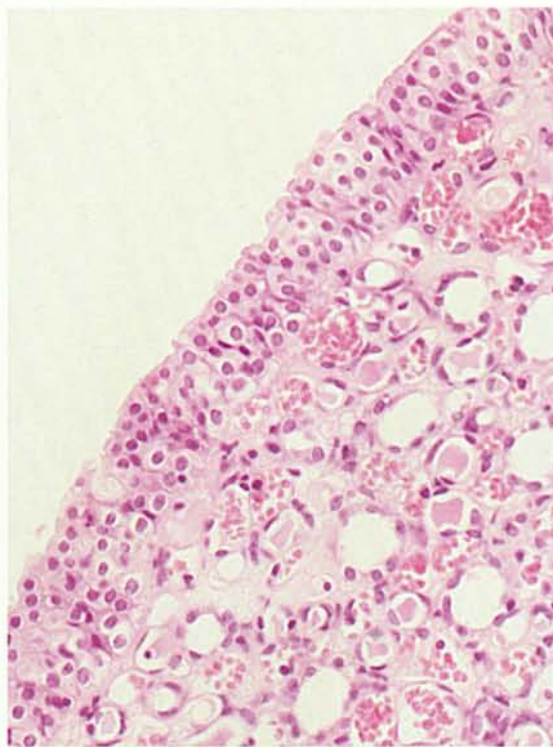


Fig. 14 – Transitional cell hyperplasia - simple, without atypia.

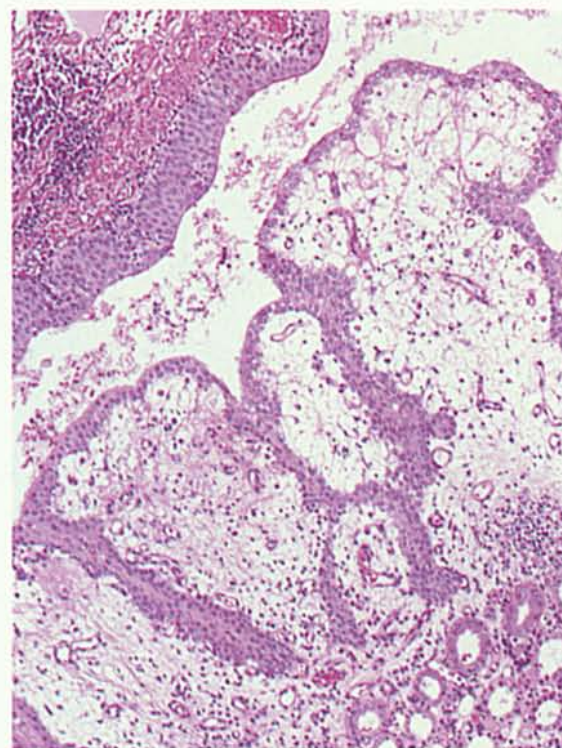


Fig. 15 – Transitional cell hyperplasia - papillary, without atypia.

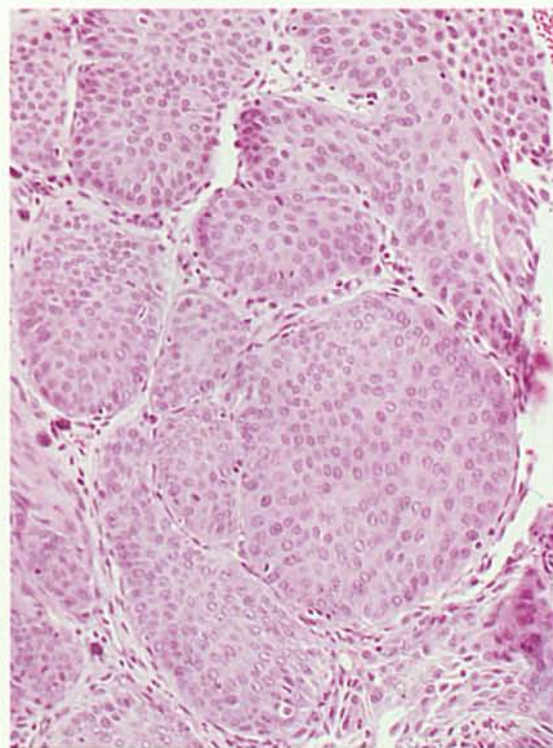


Fig. 16 – Transitional cell hyperplasia - nodular (exophytic), without atypia.

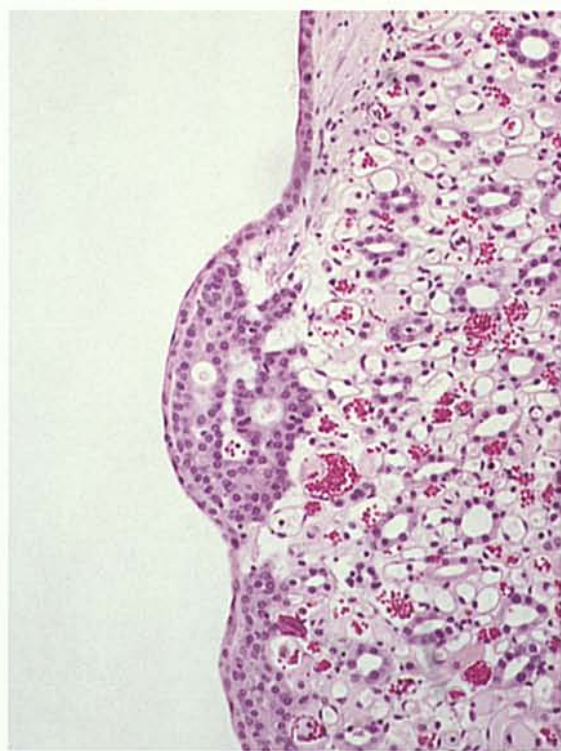


Fig. 17 – Transitional cell hyperplasia - nodular (endophytic), without atypia.

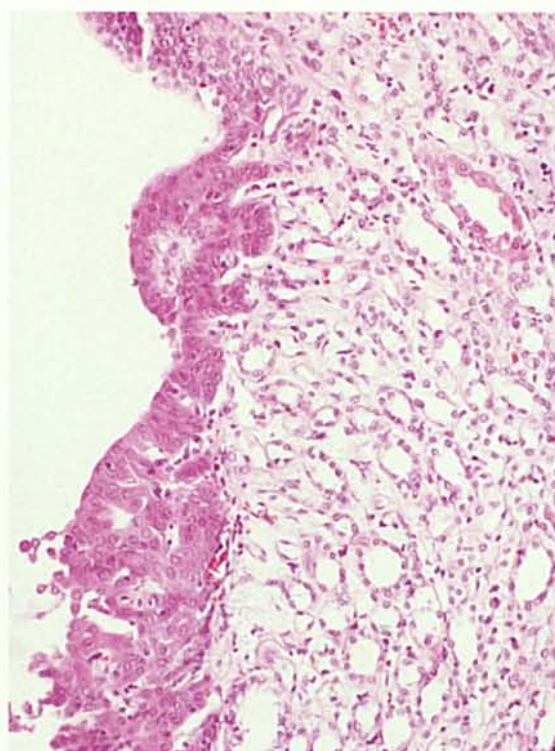


Fig. 18 – Atypical transitional cell hyperplasia.

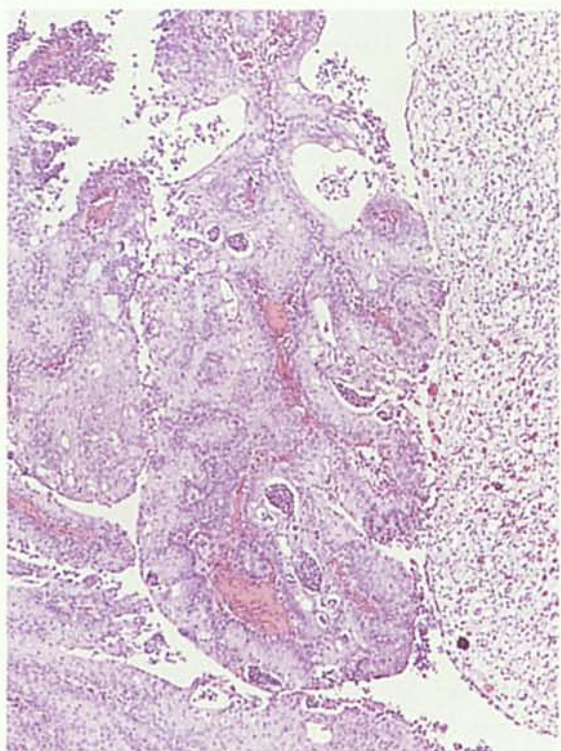


Fig. 19 – Transitional cell carcinoma - renal pelvis (note inflammation and hemorrhage).

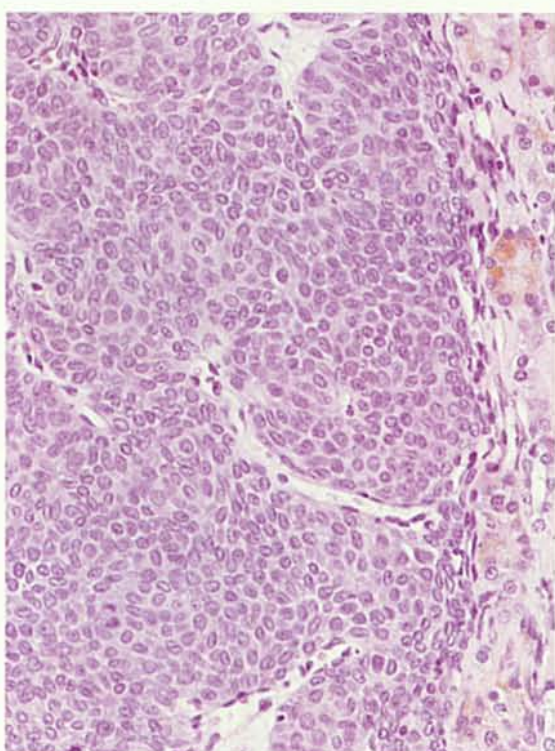


Fig. 20 – Transitional cell carcinoma - renal pelvis. Higher magnification of previous figure.

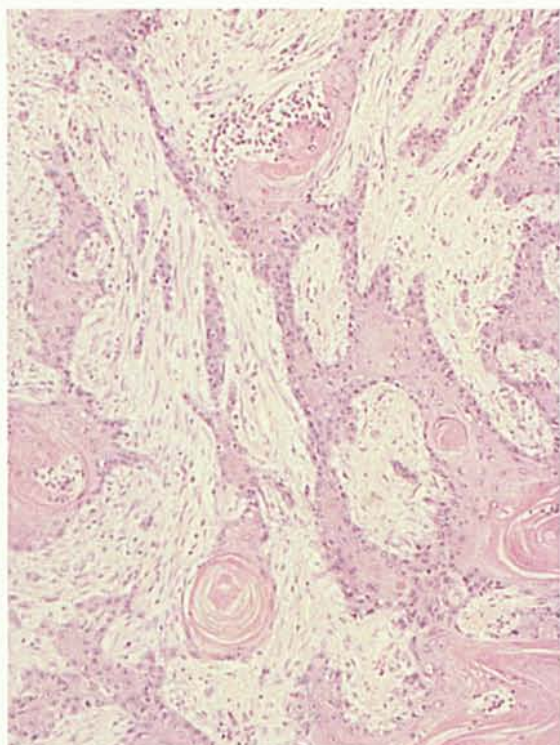


Fig. 21 – Squamous cell carcinoma - renal pelvis (note keratin pearls).

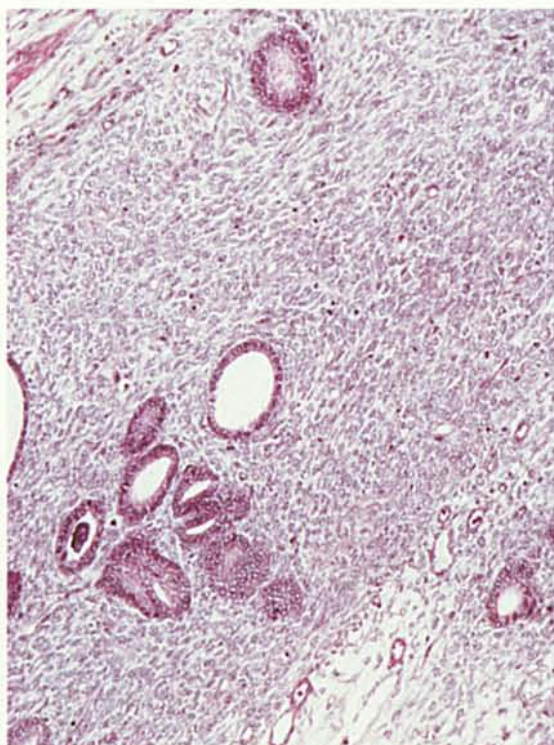


Fig. 22 – Renal mesenchymal tumor.

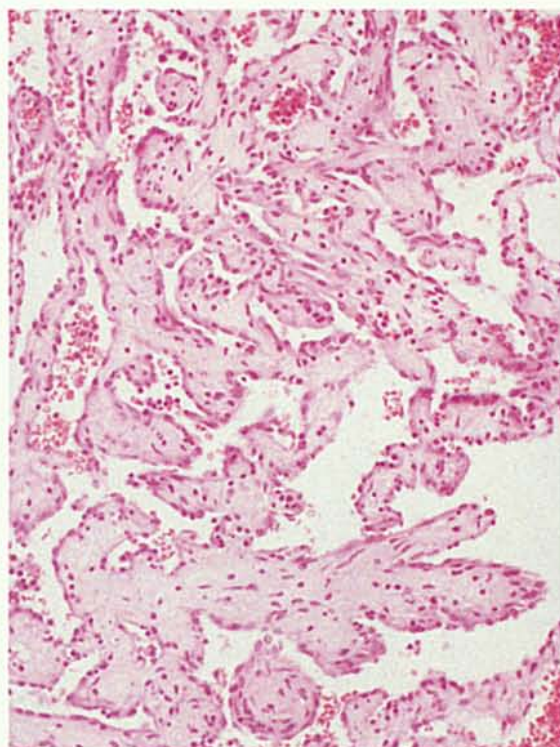


Fig. 23 – Renal mesenchymal tumor - area with hemangiosarcomatous differentiation.

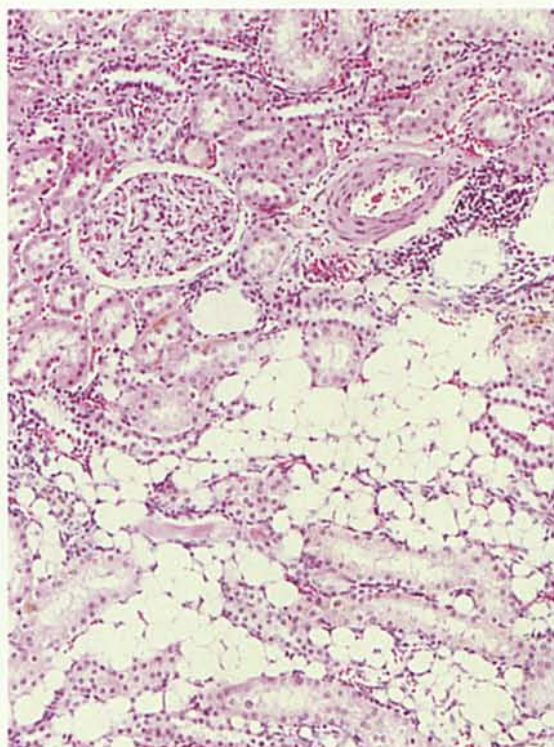


Fig. 24 – Lipoma.

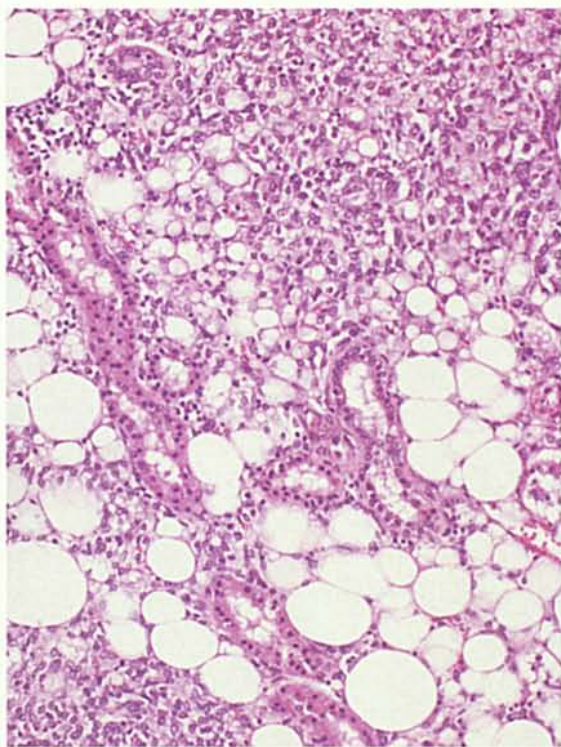


Fig. 25 – Liposarcoma.

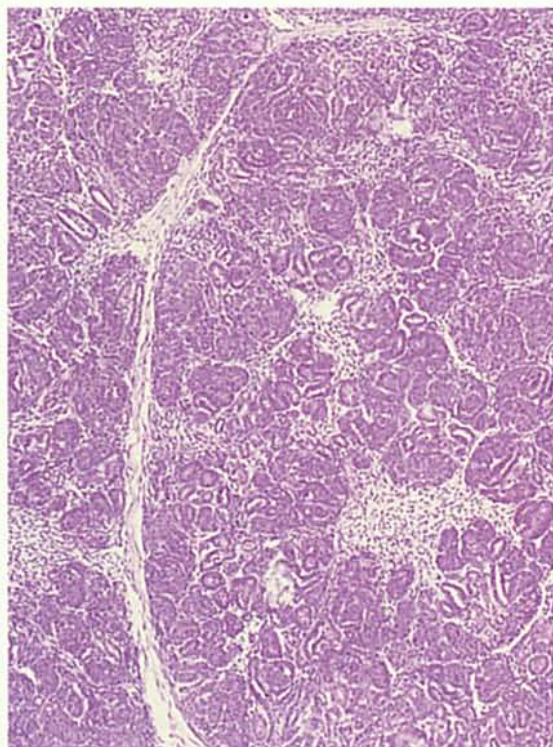


Fig. 26 – Nephroblastoma.

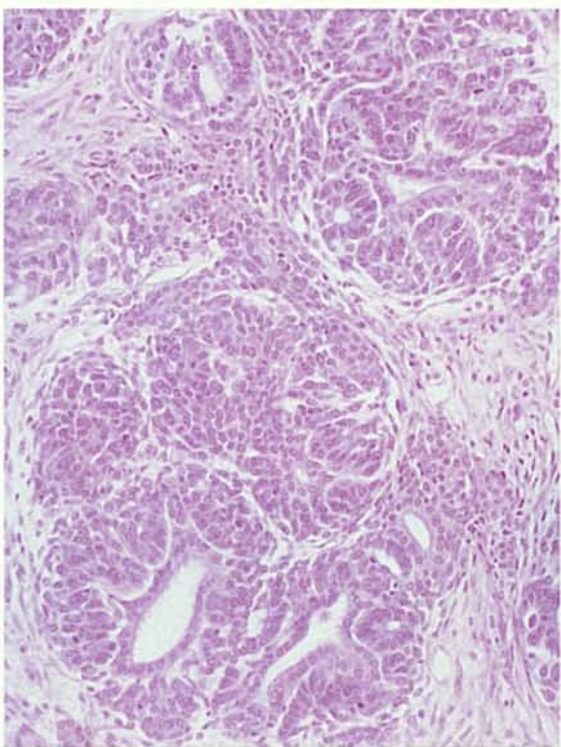


Fig. 27 – Nephroblastoma.