

# PROLIFERATIVE LESIONS OF THE LOWER URINARY TRACT IN RATS

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## INTRODUCTION

The primary function of the lower urinary tract is the transport of urine from the renal pelvis through the ureters to the urinary bladder where it is stored until eliminated. The urethra serves as a conduit for excretion of the urine from the urinary bladder. The lower urinary tract consists of the ureters, urinary bladder, and urethra. All of these areas are lined by transitional epithelium, which is commonly referred to as urothelium. Spontaneous neoplasms of the rat urinary bladder, urethra, and ureters are rare (1), but the incidence may be high in certain strains such as the brown Norway rat (2). The urinary bladder of the rodent serves as an excellent target for urinary bladder carcinogenesis as evidenced by the induction of urinary bladder tumors in rats with a variety of carcinogens (3, 4).

The primary metabolically active cells of the urinary bladder are the transitional epithelial cells. These

cells normally have a very low mitotic index in the post-weaning animal (5). However, they readily respond to stimuli, such as crystals, calculi, and chemicals (6), within the urine and are susceptible to injury because of their location. Since the entire urinary tract is lined by transitional epithelium, theoretically the urinary bladder, urethra, and ureters could all develop similar proliferative lesions. However, spontaneous or induced urethral and ureteral proliferative lesions are rare in the rat. The reason for the lack of proliferative lesions at these sites may be that urine containing toxicants passes through them quickly as compared to the more lengthy contact in the urinary bladder. Attempts to induce neoplasms in the ureters of experimental animals have been relatively unsuccessful. The urinary bladder is the most susceptible area of the lower urinary tract, apparently because of its storage function and extended exposure time to urinary toxicants. The purpose of this guide is to present a morphological classification of proliferative lesions of the urinary bladder, urethra, and ureters in rats.

## STRUCTURE AND FUNCTION

### URETERS

The ureters originate from the renal pelvis and enter into the dorsal wall of the urinary bladder separately, lateral to the entrances of the vasa deferentia in the male. An intramural part courses through the musculature of the urinary bladder in a slightly oblique direction, serving as a barrier to reverse movements of urine. The wall of the ureter is composed of transitional epithelium, a fibrous lamina propria, an inner circular and outer longitudinal layer of smooth muscle fibers, and an adventitia. The mucosa has low longitudinal folds.

### URETHRA

The urethra of females is a short tube, slightly flattened dorsoventrally, extending from the neck of the urinary bladder to an external opening in the clitoral fossa just anterior to the vaginal orifice. The urethra of the male is a long duct extending from the urinary bladder to the pelvic girdle (membranous urethra), and continues through the penis as the penile urethra, opening on the tip of the penis. The urethra of both males and females is lined with transitional epithelium.

### URINARY BLADDER (Figures 1 & 2)

The urinary bladder is located in the posterior abdominal cavity at the midline of the body ventral to the colon. The urinary bladder can be divided into dorsal and ventral areas, as well as the blind dome which is referred to as the fundus or vertex.

The urothelium rests on a basement membrane and a small amount of connective tissue. Since there is no muscularis mucosa to separate the mucosa from the submucosa, some investigators refer to the area beneath the urothelium simply as subepithelial connective tissue rather than the submucosa. The subepithelial connective tissue rests upon a coat of smooth muscle, the outer surface of which is covered by the adventitia. The urothelium is a highly specific structure composed of a variable number of layers in different species.

Histologically, the transitional epithelium of the normal urinary bladder of the rat consists of three distinct layers. The most superficial layer is composed of large cells sometimes referred to as umbrella cells, since they cover a number of smaller underlying cells. Scanning electron microscopy indicates that the surface cells are routinely pentagonal or hexagonal and are of similar size and shape. With transmission electron microscopy, these cells are shown to have a characteristic luminal asymmetric membrane and fusiform vesicles. The fusiform vesicles are believed to allow for expan-

sion of the urinary bladder as it fills with urine. Beneath the superficial layer is the intermediate layer, and the third layer is a simple basal layer.

### PREPARATION OF THE URINARY BLADDER, URETHRA, AND URETERS

The urinary bladder should be inflated with fixative for proper microscopic evaluation. The urinary bladder of rodents can be inflated via two methods (4). The first and less effective of the two is to inject the fixative into the lumen through the muscular wall with a small gauge (24-26 GA) needle. This sometimes results in the deposition of the fixative into the bladder wall rather than the lumen, resulting in microscopic distortion or loss of the bladder epithelium and making interpretation of the urothelium difficult. The second and preferred method is inflation through the urethra with a blunt needle. In either case, the bladder should be filled but not over inflated. If the urinary bladder is already full of urine, the urine can be withdrawn by either method and the bladder refilled with fixative.

The urinary bladder will usually stay inflated in the males if the coagulating glands and seminal vesicles are removed *in toto* with the urinary bladder. It may be necessary to place a ligature around the neck of the bladder of female rats to prevent the fixative from leaking. The distended bladder should be immersed in fixative after proper inflation. For electron microscopy, the urinary bladder should be divided longitudinally into halves after one hour of inflation by glutaraldehyde. For light microscopy, the urinary bladder may be inflated with a fixative such as 10% neutral buffered formalin. Other fixatives, such as ethanol or Bouin's solution, may be preferable for specific immunohistochemical or *in situ* hybridization studies.

If orientation of the urinary bladder is important, the ventral or other surface of the urinary bladder can be identified with a dot of India ink or other indelible ink at the time of necropsy. The ink will remain on the bladder wall during processing and can be visualized with the microscope.

For most routine studies, the inflated urinary bladder can be removed from the fixative and divided sagittally into two halves. These halves may be embedded into a single paraffin block with the luminal side down, and a single section may be taken for two complete sagittal sections of the urinary bladder and urethra. If the urinary bladder is a target organ or bladder lesions are expected, the urinary bladder should be divided sagittally following fixation and the mucosa should be carefully examined with a dissecting microscope. Suspect lesions can be identified and the urinary bladder can be trimmed to include the suspect lesions for

sectioning.

A method of trimming which provides more mucosal surface for microscopic examination involves dividing each bladder half into three to five strips and embedding the strips on end in paraffin block(s) for sectioning (1). Since the lesions in the urinary bladder mucosa may be extremely small and multifocal, serial sectioning (completely through the bladder) may be necessary and has been shown to significantly increase the identification of microscopic lesions in the mouse (7). Sixty-two (12%) of 517 bladder carcinomas in a mouse study would not have been diagnosed if only one section per bladder half, rather than serial sections, had been examined.

Ureters can be embedded on end and sectioned for microscopic examination. This provides only a limited area for review. A better method is to remove the ureters in their entirety, remove the serosal fat, coil each ureter on a small square piece of gelfoam and place in formalin for fixation. After fixation, the square of gelfoam can be bisected and each half can be embedded on end. The gelfoam is sectioned in conjunction with the coiled ureter. This method provides multiple cross sections of each ureter for examination.

## MORPHOLOGY

### NONNEOPLASTIC LESIONS

#### **HYPERPLASIA**

Hyperplasia usually precedes the development of neoplasia and may occur in the urinary bladder, urethra, or ureters. Its distribution may be focal, multifocal, or diffuse and its form simple, papillary, or nodular (8-10).

#### ***Simple Hyperplasia (Figures 3 & 4)***

Simple hyperplasia is defined as an increase (either focal or diffuse) above the normally defined three layers of urothelium. Simple hyperplasia may be quantitated as minimal, mild, moderate, or marked. Confirming minimal hyperplasia, particularly if focal, may require extensive serial sectioning of the bladder, scanning electron microscopy, or even labelling index analyses with tritiated thymidine or bromodeoxyuridine. (11).

#### ***Papillary Hyperplasia (Figures 5-9)***

Papillary hyperplasia differs from simple hyperplasia in that the urothelial surface is irregular due to papillary projections into layers of urothelial cells with a fibrovascular supporting stroma. Papillary hyperplasia induced by chemicals is generally focal.

Diffuse papillary hyperplasia, referred to as papillomatosis, occurs with urolithiasis (12).

#### ***Pleomorphic Microvilli (Figure 10)***

Demonstrated by scanning electron microscopy, pleomorphic microvilli have been identified on the surface of hyperplastic transitional epithelial cells. They are induced by urinary toxicants.

#### ***Nodular Hyperplasia (Figure 11)***

Nodular hyperplasia (epithelial downgrowths) may occur in conjunction with either simple or papillary hyperplasia. These nodular downgrowths exist as solid islands or cords of hyperplastic transitional epithelial cells that extend into the subepithelial connective tissue. Although focal areas of nodular hyperplasia may appear to have no connection to the mucosa, serial sections show areas of nodular hyperplasia continuous with the mucosa. Acute and/or chronic inflammation may accompany the hyperplasia, which may be focal, multifocal, or diffuse.

#### ***SQUAMOUS METAPLASIA (Figure 12)***

Squamous metaplasia may occur in the transitional epithelium in response to prolonged or continued injury. Squamous metaplasia is characterized by the replacement of the transitional epithelium with squamous epithelium. The more advanced lesions demonstrate intercellular bridges and keratinization. These areas may give rise to squamous cell carcinomas.

#### ***DIVERTICULA (Figure 13)***

Diverticula consist of downgrowths of the transitional epithelium into the muscular tissue. They have been described in both the ureter and the urinary bladder of the mouse and rat and have been mistaken as transitional cell carcinomas because of their location within the muscularis (12, 13). The lesion exists as a down-growth into the wall of either the urinary bladder or the ureter, and the surface epithelium may extend through the muscularis into the adventitia. Distinguishing diverticuli from carcinoma may be difficult, but the epithelium in diverticuli is normal or hyperplastic but without dysplasia. The lesion appears to be associated with chronic irritation as a result of crystalluria or calculi (14).

### NEOPLASTIC LESIONS

#### ***EPITHELIAL NEOPLASMS***

Urinary bladder tumors induced in rats develop most commonly in the vertex or fundus of the urinary bladder (1). This area is likely to be in longer contact

with urine containing toxicants or their metabolites due to the anatomical position of the urinary bladder.

### ***Papillomas (Figures 14-17)***

Papillomas occur as papillary formations projecting into the lumen. The epithelium shows little or no pleomorphism, atypia, or anaplasia and is well-differentiated. Papillomas may have a slender narrow stalk (pedunculated) or a broad base (sessile). A characteristic distinguishing pedunculated papilloma from papillary hyperplasia is the presence of a fibrovascular core having a complex branching of secondary or tertiary stalks (15).

### ***Carcinomas (Figures 18-23)***

The diagnosis of carcinoma can be made on morphology alone and invasion need not be present if pleomorphism and atypia are demonstrated. Experimentally-induced malignant neoplasms of the urothelium may be classified according to histologic pattern, cell type, and depth of invasion (4, 8, 16-19). Malignant epithelial lesions classified by histologic pattern may be further classified as papillary or non-papillary carcinomas. Transitional cell carcinomas may project into the lumen as exophytic growths, or they may grow into the subepithelial tissue as endophytic growths. Urinary bladder carcinomas commonly invade locally through the muscle wall but only occasionally metastasize to the regional lymph nodes and the lungs. Carcinoma *in situ* is a flat and non-invasive neoplastic lesion of the bladder epithelium. Full-thickness cellular atypia and dysplasia are present, often with mitoses. Transitional epithelial cells may undergo squamous cell differentiation and develop into transitional cell carcinomas with squamous differentiation or squamous cell carcinomas (8, 20).

### ***MESENCHYMAL NEOPLASMS (Figure 24)***

Experimentally-induced primary mesenchymal tumors of the rat urinary bladder occur much less frequently than epithelial tumors. The most common are vascular tumors, such as hemangioma and hemangiosarcoma. Mesenchymal tumors of muscle origin are extremely rare in the rat urinary bladder. Undifferentiated carcinomas may be distinguished from poorly differentiated sarcomas by electron microscopic identification of characteristic cell membranes or immunocytochemical identification of cytofilaments (21).

### ***HEMATOPOIETIC NEOPLASMS***

Hematopoietic neoplasms usually only involve the urinary bladder in extensively metastasizing or infiltrating cases. Lymphoblastic lymphoma and large granular lymphocyte (LGL) lymphoma may involve the urinary

bladder in advanced cases. Histiocytic sarcoma, a nonlymphoid neoplasm, may also involve the serosal surface of the urinary bladder or ureters if the neoplasm is present in the abdominal cavity.

### ***METASTATIC NEOPLASMS***

Metastatic neoplasms other than hematopoietic neoplasms to the urinary bladder are rare in the rat.

## **DISCUSSION**

Since light microscopic and ultrastructural characteristics of the urothelium of the urinary bladder of the rat have been extensively studied and characterized and since many urinary bladder lesions in humans are similar in both morphology and behavior to those induced in rats, this species makes an excellent model for studying urinary bladder carcinogenesis. Furthermore, urinary bladder toxicity and neoplasia can be induced with a variety of chemicals in the rat. Because of extensive studies of the morphology and character of preneoplastic and neoplastic progression and a wealth of dose-response information already available, this target organ provides one of the best models for the study of the mechanism of carcinogenesis.

Hyperplasia is an uncommon spontaneous lesion, but is a common finding in the urinary bladder of animals treated with bladder carcinogens and certain other compounds. Urothelial hyperplasia is a primary response to many urothelial carcinogens, but may also be secondarily associated with acute or chronic cystitis or calculus formation (6, 12, 22-24).

An incidence of 23.8% (75/324) was reported for simple hyperplasia in male control Sprague-Dawley rats (1). However, in many cases the hyperplasia appeared to be secondary to prostatitis.

Papillary hyperplasia occurs much more frequently in rats than in mice both as a spontaneous and induced lesion. The incidence of papillary hyperplasia in male control Sprague-Dawley rats has been reported to be 4.3% (14/324) (1). Papillomatosis or diffuse papillary hyperplasia are frequently observed in association with urinary calculi, but are reversible if the calculi are removed (12).

Pleomorphic microvilli have been identified in rats given various urinary bladder carcinogens as early as eight weeks after initiation of exposure. They also have been observed in other experimental cancer models, as well as in humans. Thus, a strong correlation had been suggested between the presence of pleomorphic microvilli and bladder cancer. However, in more recent studies in rats and mice (13), pleomorphic villi were induced within four days but disappeared three

days later. This suggests that they are indicative of increased proliferation which occurs as part of an acute or chronic toxic response and may not necessarily indicate a preneoplastic change (24).

Nodular hyperplasia is comparable morphologically to von Brunn's nests or cystitis cystica in humans. In contrast to carcinomas, nodular hyperplasia does not have cellular atypia or dysplasia. An incidence of 0.30% (1/324) has been reported in male control Sprague-Dawley rats (1).

Neoplasms of the urethra and ureters are rare in the rat, although neoplasms of the urinary bladder sometimes infiltrate into the urethra. The reason for this may be due to the quick passage of urine through the ureters and urethra as compared to the urinary bladder. Spontaneous urinary bladder neoplasms are also rare but are noted occasionally in rats (1, 25-27). A high incidence of spontaneous urinary bladder and ureter tumors have been reported in the brown Norway rat (2). In a large study performed at the International Research and Development Corporation (IRDC) in Mattawan, Michigan, involving the evaluation of the dose response and *in utero* exposure to saccharin in the Sprague-Dawley rat, 2,500 second generation male rats were administered a control diet or a diet with one of six dose levels of saccharin (1). No bladder tumors were found in the control group, but five bladder neoplasms (4 papillomas and 1 carcinoma) were found in the 1% sodium saccharin group. Some of these were believed to have been spontaneous tumors since the background historical incidence of spontaneous bladder tumors at IRDC in male Sprague-Dawley rats was 0.8%.

## RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

### A. NONNEOPLASTIC LESIONS

#### Hyperplasia

##### *Simple Hyperplasia*

1. An increase above the normally defined three layers of urothelium
2. May be either focal or diffuse
3. May be quantitated as minimal, mild, moderate, or marked
4. Does not have cellular atypia or dysplasia

##### *Papillary Hyperplasia*

1. The urothelial surface is irregular due to papillary projections of epithelium with a fibrovascular supporting stroma

2. Diffuse papillary hyperplasia is termed papillomatosis

##### *Nodular Hyperplasia*

1. Solid islands or cords of transitional epithelial cells that extend into the lamina propria
2. May be focal, multifocal, or diffuse
3. Acute and/or chronic inflammation may accompany the hyperplasia
4. May occur in conjunction with either simple or papillary hyperplasia

##### *Squamous Metaplasia*

1. May occur in response to prolonged or continued injury
2. Characterized by the replacement of the transitional epithelium with squamous epithelium
3. More advanced lesions demonstrate intercellular bridges and keratinization

##### *Diverticula*

1. Consist of downgrowths of the transitional epithelium into the muscular tissue, may extend into the adventitia
2. May occur in either the urinary bladder or the ureteral wall
3. Epithelium in diverticulum is normal or hyperplastic but without dysplasia

### B. NEOPLASTIC LESIONS

#### Primary Epithelial Neoplasms

##### *Papilloma*

1. Occur as papillary formations projecting into the lumen
2. Presence of a fibrovascular core that has a complex branching of secondary or tertiary stalks
3. Epithelium shows little or no pleomorphism, atypia, or anaplasia and is well-differentiated
4. May have a slender narrow stalk (pedunculated) or a broad base (sessile)

##### *Carcinoma*

1. Histologic cell type can be classified as transitional cell, transitional cell with squamous differentiation, squamous cell, adenocarcinoma, or undifferentiated
2. May project into the lumen as exophytic growths, or they may grow into the subepithelial tissue and muscle wall as endophytic growths
3. Classified according to histologic pattern: either papillary or non-papillary
4. Diagnosis of carcinoma can be made on

morphology alone and invasion need not be present if pleomorphism and atypia are demonstrated

5. Carcinoma *in situ* is a flat and non-invasive neoplastic lesion with full-thickness cellular atypia and dysplasia, often with mitoses
6. May under go squamous cell differentiation and develop into transitional cell carcinomas with squamous differentiation or squamous cell carcinomas

### Primary Mesenchymal Neoplasms

1. Hemangioma and hemangiosarcoma are most common
2. Leiomyoma and leiomyosarcoma are very rare

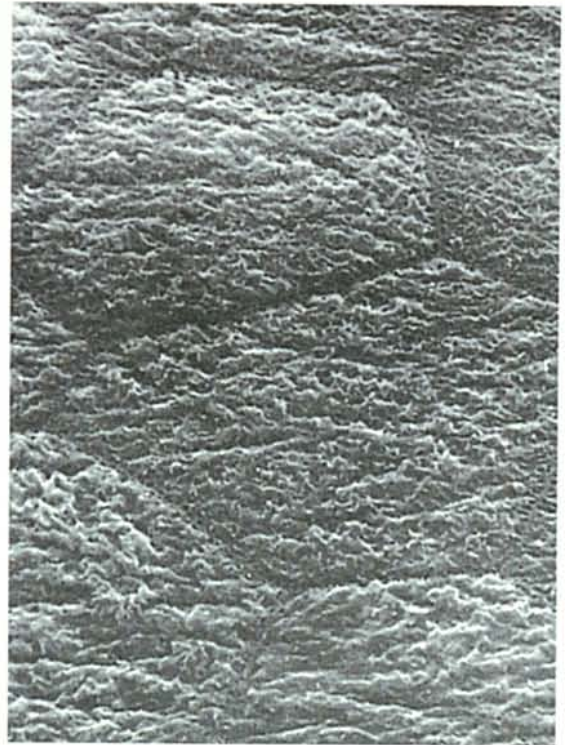
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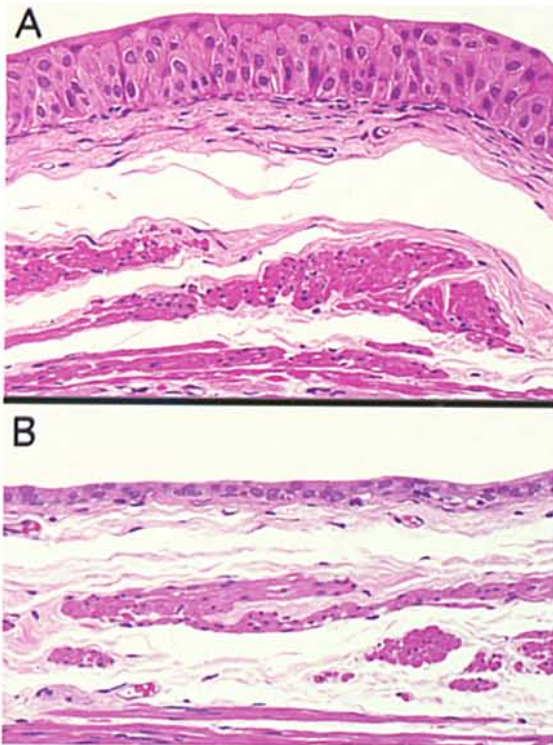
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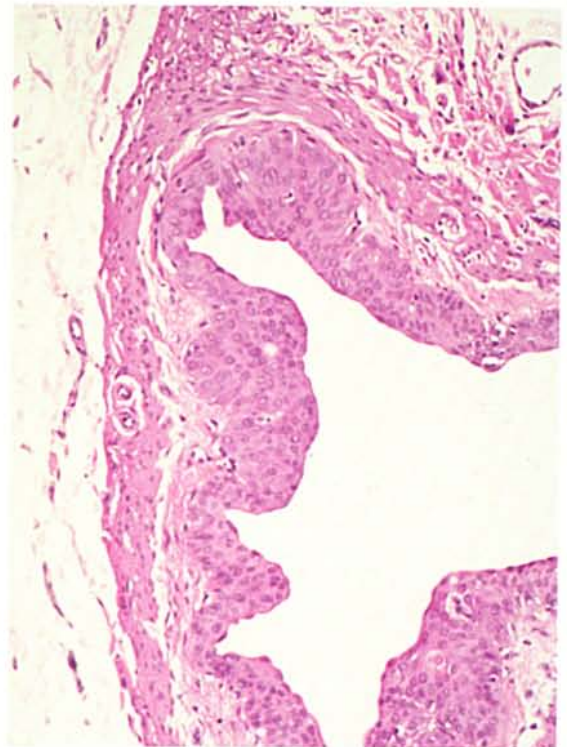
**Fig. 1**— Normal urothelium of a rat with three cell layers and numerous fusiform vesicles in the surface layer. (Transmission electron microscopy; Uranyl acetate-lead citrate)



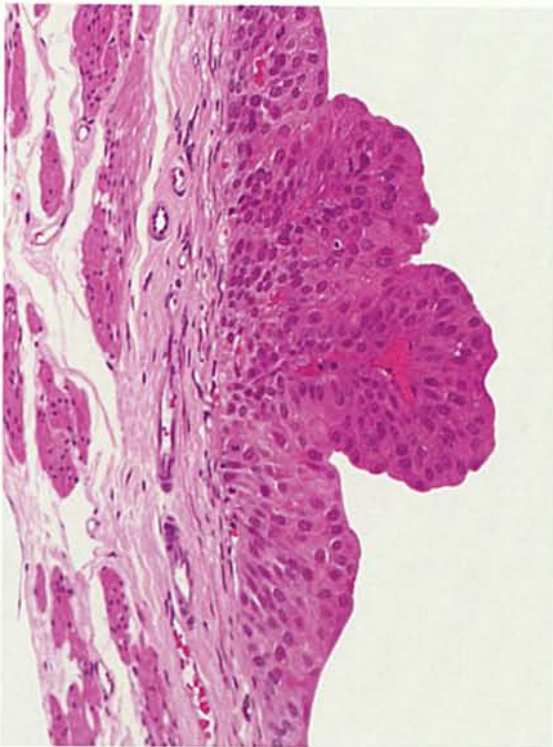
**Fig. 2**— Normal urothelium of a rat with flat polygonal superficial cells. (Scanning electron microscopy; Reprinted with permission<sup>28</sup>)



**Fig. 3**— Top: simple hyperplasia of the urinary bladder. Note uniformity of hyperplasia. Bottom: normal urothelium. (Light microscopy; H&E)



**Fig. 4**— Simple hyperplasia. Ureter is slightly distended. (H&E)



*Fig. 5 – Early focal papillary hyperplasia of the urinary bladder. (H&E)*



*Fig. 6 – Gross photograph of a urinary bladder from a rat with calculi and papillary hyperplasia.*



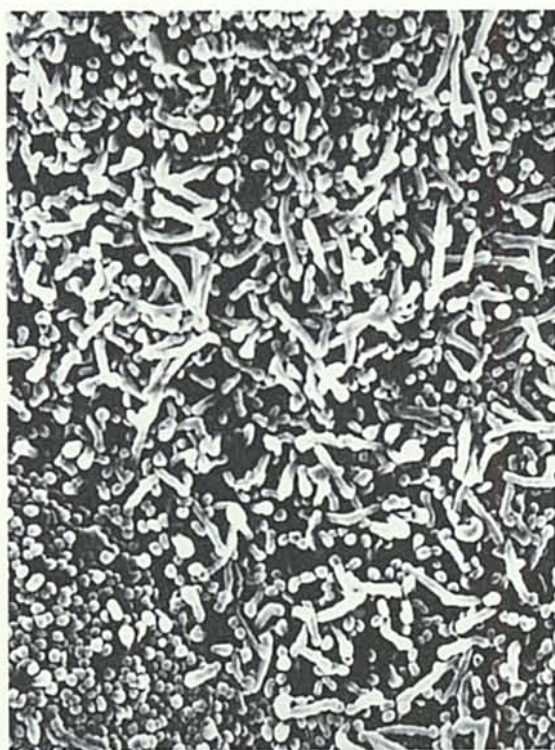
*Fig. 7 – Diffuse papillary hyperplasia (papillomatosis) of urinary bladder illustrated in Figure 6. (H&E)*



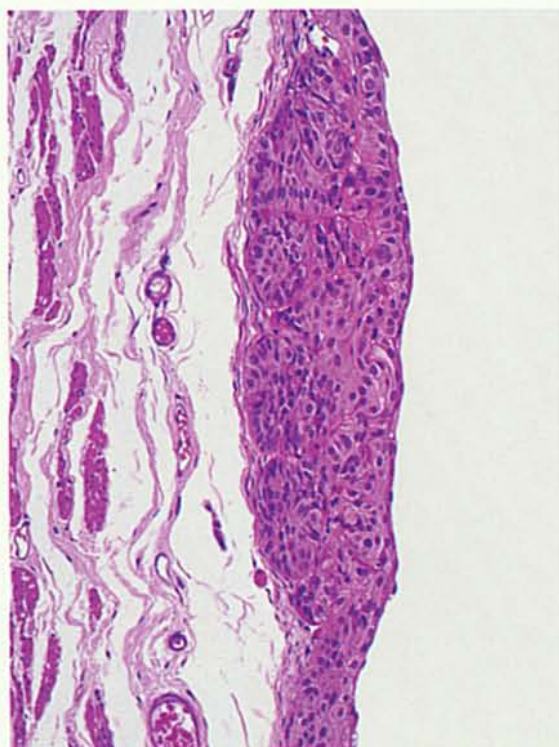
*Fig. 8 – A second illustration of diffuse papillary hyperplasia (papillomatosis) of the urinary bladder. (H&E)*



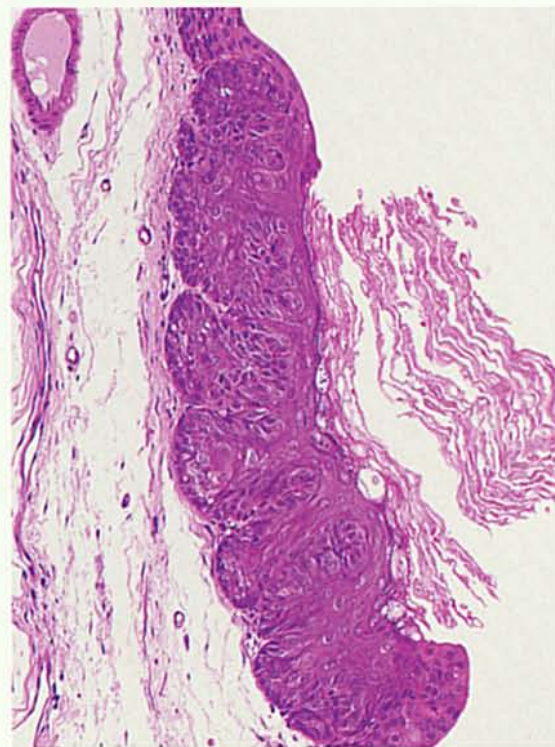
*Fig. 9 – Hyperplastic epithelium. Note cobblestone appearance. (Scanning electron microscopy).*



*Fig. 10 – Higher magnification of Figure 9 showing presence of pleomorphic microvilli.*



*Fig. 11 – Nodular hyperplasia of the urinary bladder. (H&E)*



*Fig. 12 – Focal squamous metaplasia of the urothelium of the urinary bladder. Note keratin on luminal surface. (H&E)*



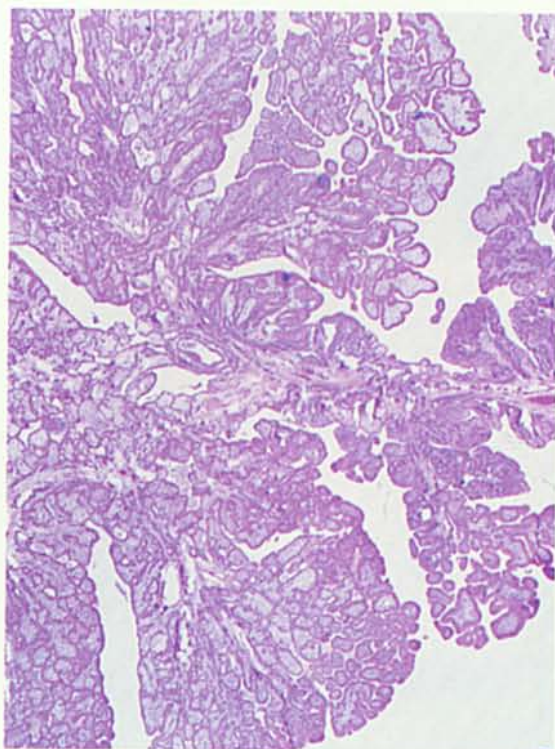
**Fig. 13** – Diffuse papillary hyperplasia both in the urinary bladder and the diverticulum. (H&E) (Photo courtesy of Dr. T. Shirai, Nagoya City University Medical School, Nagoya, Japan.)



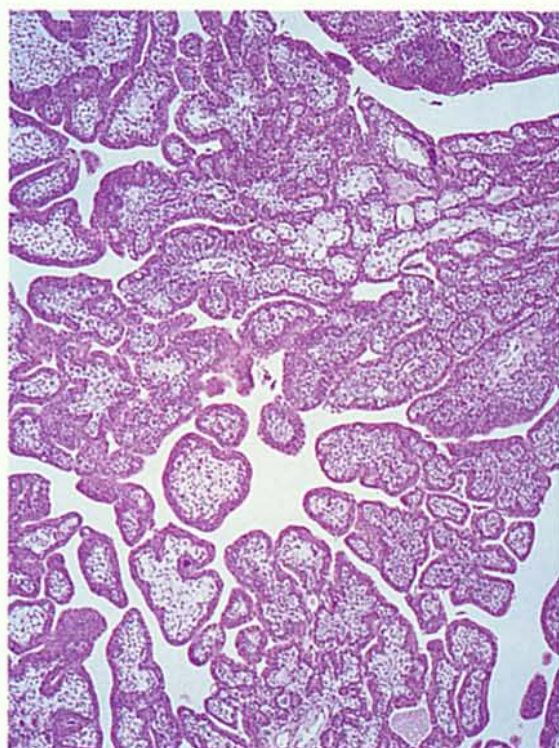
**Fig. 14** – Small sessile papilloma of the urinary bladder. (H&E)



**Fig. 15** – Small pedunculated papilloma of the urinary bladder. (H&E)



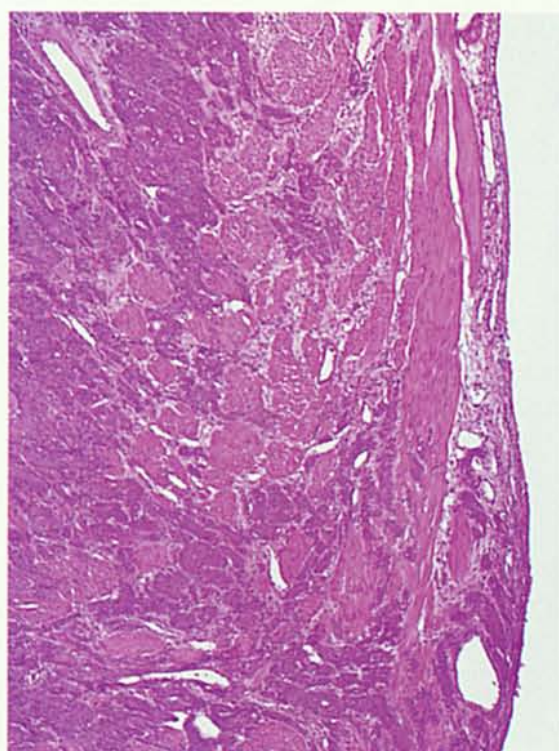
**Fig. 16** – Large pedunculated papilloma which filled the urinary bladder. (H&E)



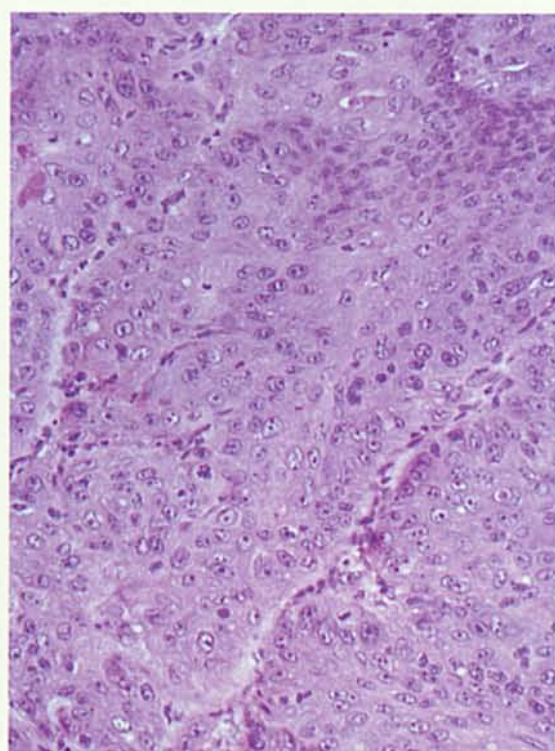
**Fig. 17** – Higher magnification of Figure 16 illustrating uniformity of transitional epithelial cells. (H&E)



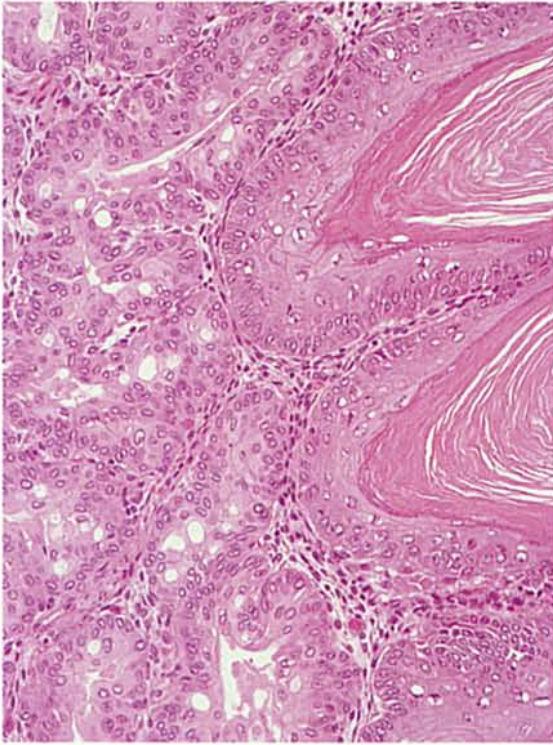
**Fig. 18** – Gross photograph of a transitional cell carcinoma of the urinary bladder of a rat. Carcinoma fills entire urinary bladder lumen.



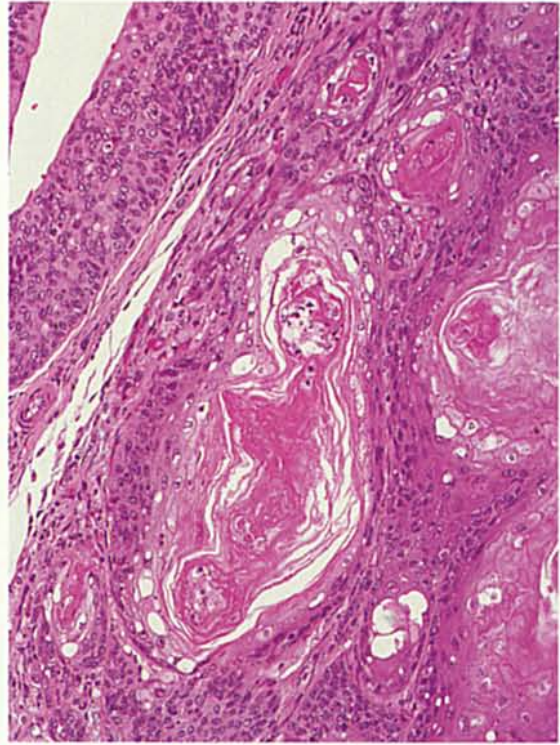
**Fig. 19** – Transitional cell carcinoma of the urinary bladder extending to the adventitia. (H&E)



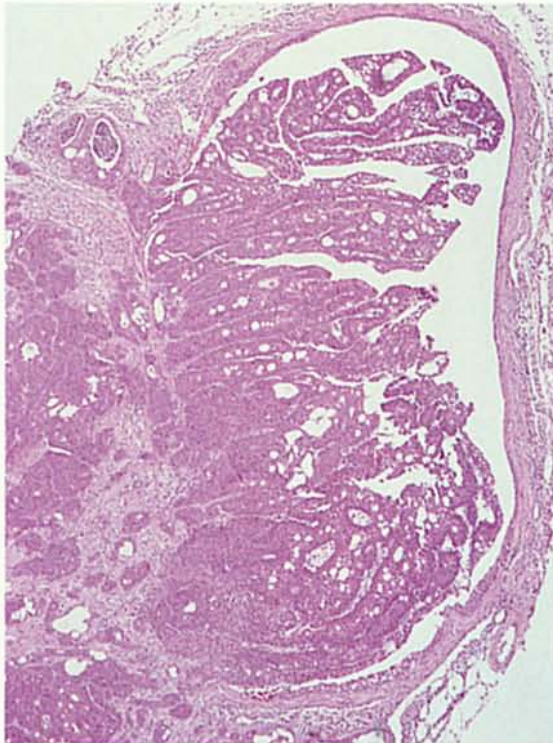
**Fig. 20** – High magnification of transitional cell carcinoma illustrating pleomorphism and high mitotic index. (H&E)



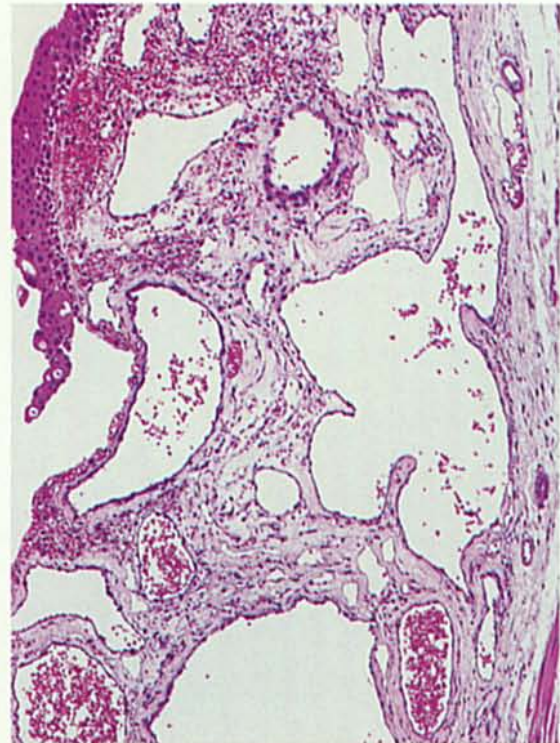
*Fig. 21 – Transitional cell carcinoma with squamous differentiation of the urinary bladder. (H&E)*



*Fig. 22 – Squamous cell carcinoma of the urinary bladder. Note production of keratin. (H&E)*



*Fig. 23– Transitional cell carcinoma of the ureter. (H&E)*



*Fig. 24 – Hemangioma of the urinary bladder. Note vascular channels. (H&E)*