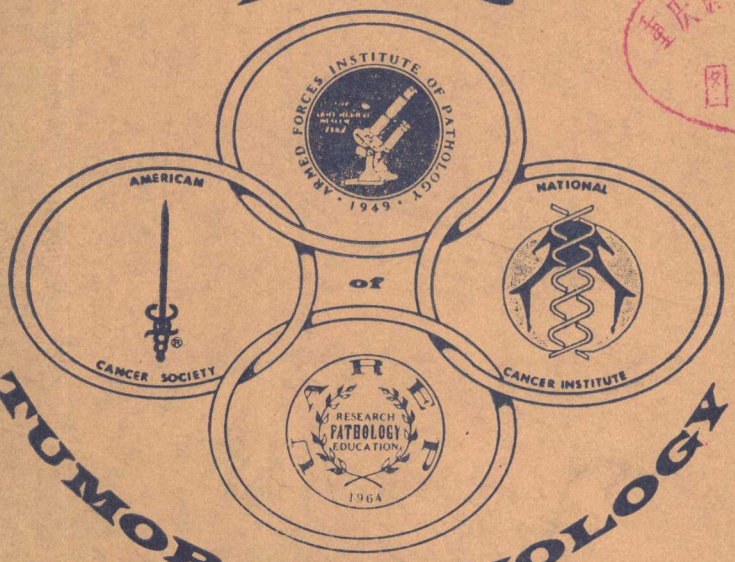
TUMORS OF THE URINARY BLADDER

11

ATLAS OF TUMOR PATHOLOGY



ATLAS OF TUMOR PATHOLOGY

Second Series
Fascicle 11

TUMORS OF THE URINARY BLADDER

by

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ATLAS OF TUMOR PATHOLOGY

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EDITOR'S NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences–National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was made by the press at the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final fascicle of the first Atlas, the National Academy of Sciences–National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this new series, the term chosen for the World Health Organization's series "International Histological Classification of Tumours" (when available) is shown by an asterisk if it corresponds to the authors' choice, or as the first synonym in bold print if it differs from the authors' heading. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information for better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index will be included in each fascicle.

It is the hope of the Editor, the Editorial Advisory Committee, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will be appreciated.

Harlan I. Firminger, M. D.

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Dr. Harlan I. Firminger, Editor, and the reviewers selected by him made many helpful suggestions regarding this fascicle.

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I am also grateful to the authors of the first series fascicle on Tumors of the Urinary Bladder, Dr. N. B. Friedman and Dr. J. E. Ash, for permission to utilize two coior plates.

Mr. Donald Yeager and his staff of Baltimore, Maryland were responsible for printing of negatives taken by the author.

Certain concepts presented in this fascicle are new and depart from the traditional views. The author is solely responsible for this.

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Leopold G. Koss, M. D.

TUMORS OF THE URINARY BLADDER

Contents

TUMORS OF THE URINARY BLADDER

EPITHELIA OF THE URINARY BLADDER

EMBRYOLOGY

The mammalian bladder is of complex embryologic derivation. In the earliest stages of embryonal development, the primordium of the bladder is a part of the cloaca, a vesicular space derived from the primitive gut. Into this space the lower intestine opens posteriorly, the wolffian ducts laterally, and the omphalo-allantoic duct anteriorly. When the embryo reaches the length of 5 mm., a membrane, the urorectal septum, begins to separate the future rectum from the ventrally located future bladder and urogenital sinus. This process of partitioning is normally completed in 16 mm. embryos. The proximal portion of the anterior chamber of the former cloaca becomes the urinary bladder and a portion of the urethra. The distal part, the urogenital sinus, participates in the formation of the genital organs. The obliterated omphalo-allantoic duct becomes the urachus. The wolffian ducts become the spermatic ducts in the male and the vestigial Gärtner's ducts in the female.

In some cases of exstrophy of the bladder, this complex embryonal origin is reflected in the variety of epithelial types, such as mucus-producing glandular epithelium, squamous epithelium, and the urothelium that may be seen side by side lining the bladder (figs. 1-4). Bladder epithelium retains the potential for producing these various epithelial types in the normal adult; this may be reflected in benign histologic variants of bladder epithelium and in bladder cancer.

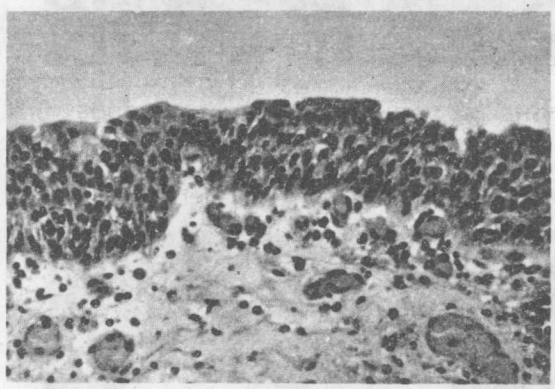

Figure 1
EPITHELIAL VARIANTS IN URINARY BLADDER
(Figures 1–4 from same case of exstrophy)
Almost mature urothelium was encountered in the urinary bladder of a 4 year old boy with exstrophy; the surface layer contains elongated, mucus-producing cells. X250.

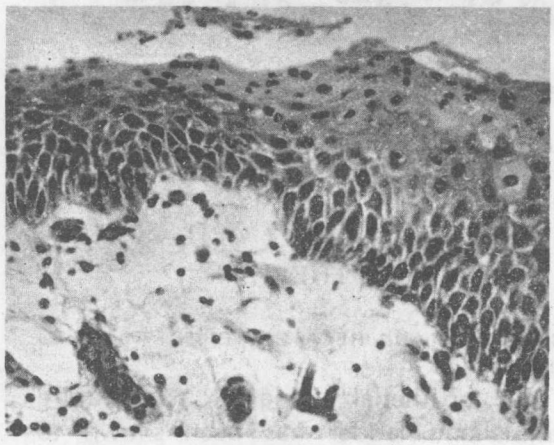

Figure 2
EPITHELIAL VARIANTS IN URINARY BLADDER
(Figures 1–4 from same case of exstrophy)
This photomicrograph shows squamous epithelium in the urinary bladder of the same patient. X250.

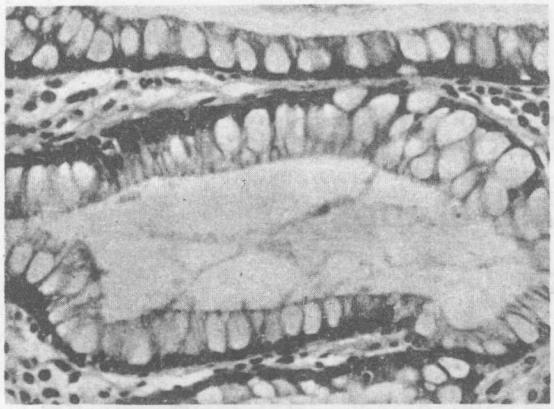

Figure 3
EPITHELIAL VARIANTS IN URINARY BLADDER
(Figures 1–4 from same case of exstrophy)
Illustrated in this photomicrograph is mucus-producing intestinal type epithelium with goblet cells. X250.

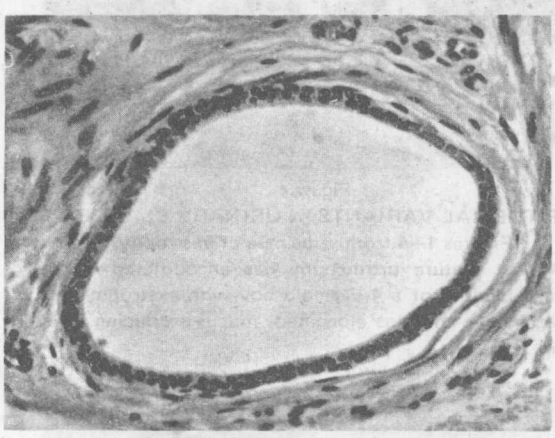

Figure 4
EPITHELIAL VARIANTS IN URINARY BLADDER
(Figures 1–4 from same case of exstrophy)
Intramural cysts are lined by a low cuboidal epithelium. X250.

UROTHELIUM

SYNONYMS AND RELATED TERMS: Transitional epithelium.

The epithelial lining of the mature mammalian bladder has been shown to have certain unique structural and physiologic features. While documentation in man remains deficient, there is no indication that human urothelium differs in its essential aspects from that of other mammals.

LIGHT MICROSCOPY. The urothelium is a multilayered epithelium of variable thickness, the number of cell layers changing with the degree of bladder distension. In the rat, under controlled experimental conditions, the number of layers varies from 3 in a maximally distended bladder to 5 or 6 layers in a collapsed bladder. In the dog, a much thicker urothelium, averaging 6 to 10 layers of cells, lines the partially collapsed bladder. The average normal biopsy from man reveals 5 to 7 layers, but the cystoscopic procedure which precedes and accompanies the biopsy involves a moderate degree of bladder distension. For practical purposes, urothelium composed of more than 7 cell layers must be considered abnormal, although this matter deserves further study under controlled conditions.

Regardless of the degree of distension, normal urothelium in man and in other mammals studied to date is characterized by the presence of large superficial cells, each of which, in umbrella-like fashion, covers several smaller cells of the immediately underlying layer (fig. 5). The superficial umbrella cells, often binucleated or multinucleated, may vary in size and configuration according to the degree of bladder distension and the angle of tissue section. In distended bladders, the superficial cells are flat and thin; in contracted bladders or in situations of unimpaired growth (such as papillomas, fig. 17), a more cuboidal configuration may be observed. The presence of superficial cells may be regarded as important evidence of relative normalcy of the urothelium. Unfortunately, superficial cells appear to be loosely attached to the deeper epithelial layers; hence, they may be lost in routine biopsy material.

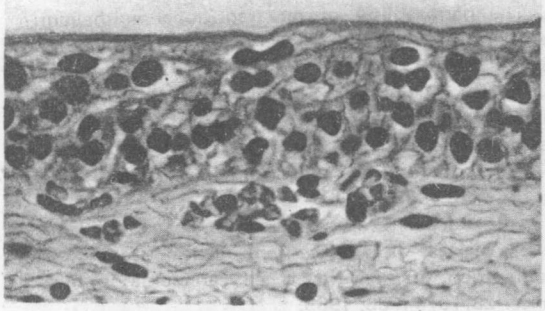

Figure 5
NORMAL HUMAN UROTHELIUM
Note the large superficial mononucleated or binucleated umbrella cells stretching over many cells of the adjacent lower epithelial layer (distended bladder). X650.

Histochemical studies (Munis and Dorfman) demonstrated the presence of glycogen in all layers of human urothelium, and the presence of a surface mucous coat. Histochemical methods also demonstrated the presence of a basement membrane, separating the epithelium from the lamina propria. The histochemical findings were subsequently confirmed by ultrastructural studies.

ULTRASTRUCTURE. **The Asymmetric Membrane System.** Electron microscopic studies have shown that the superficial urothelial cells in all mammals examined to date contain a unique membrane system; its structure, origin, and function have been elucidated in recent studies. The luminal surface of the superficial cells is lined by an asymmetric membrane, measuring about 120 angstroms in thickness and composed of three layers: a central electron-lucent layer and two outer electron dense layers of unequal thickness. The thicker of the two outer layers forms the surface of the bladder. The superficial membrane has a peculiar angular appearance, giving the impression of rigidity when compared with other biologic membranes. The membrane also forms invaginations or canals which, in the rat, vary in depth according to the degree of distension of the bladder. It has, therefore, been suggested by Koss that the invaginations contain reserve membrane insuring the integrity of the bladder surface epithelium for periods of distension. Also, numerous oblong vesicles formed by the asymmetric membrane may be found within the cytoplasm of the superficial cells in the experimental animal.

It has been shown that, in the rat, the membrane is assembled in the Golgi apparatus within the superficial urothelial cells (Hicks; Koss). It has also been suggested that the membrane is packaged in the form of the oblong vesicles, and thus travels from the Golgi area to the surface to be incorporated there into the superficial membrane (Koss).

In man, the ultrastructural appearance of the superficial cells of the urothelium shows the characteristic angulated surface and the asymmetric membrane (fig. 6). Oblong vesicles have not been demonstrated to date. Sparse round vesicles have

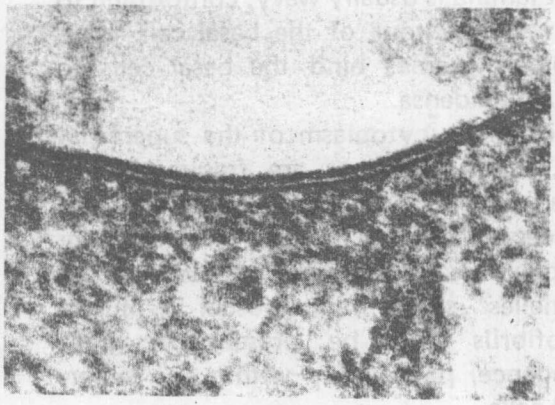

Figure 6
NORMAL HUMAN UROTHELIUM
This electron micrograph reveals that the luminal plasma membrane is composed of three layers. The two electron-opaque layers are of uneven thickness; the upper luminal layer is the thicker of the two, thus justifying the term "asymmetric membrane." X165,000.

been noted. It is not clear, at the time of this writing, whether the asymmetric membrane in the human bladder has the same substructure and functions as in the rodent.

PHYSIOLOGIC SIGNIFICANCE OF THE ASYMMETRIC MEMBRANE. The role of the asymmetric membrane in the rat as an important element in the urine-blood barrier has been demonstrated by Hicks. A variety of chemicals damaging the membrane, including events occurring during experimental carcinogenesis, increase markedly the permeability of the bladder to lithium. There are, to date, no comparable studies in man.

OTHER ULTRASTRUCTURAL ASPECTS OF THE BLADDER EPITHELIUM. The superficial cells of the urothelium are bound to each other by tight junctions and to the cells of the deeper layer by desmosomes. Desmosomes also bind together cells of the deeper layers. The epithelium rests on a basement lamina which, in normal epithelium, is fairly straight. In abnormal epithelium, the basement lamina is usually wavy, conforming to the wavy contour of the basal cell layer. Hemidesmosomes bind the basal cells to the lamina densa.

Within the cytoplasm of the superficial cells, large lysosomes are frequently observed. Smaller lysosomes may be observed in deeper cells. A function of the Golgi complex was discussed above. Other organelles show no unusual features. Tonofibrils may be present in great abundance, particularly within the superficial cells.

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PROLIFERATIVE VARIANTS OF BLADDER EPITHELIUM

The presence of epithelial buds, cell nests (Brunn's nests), and cysts (cystitis cystica and glandularis) in the lamina propria of the bladder has been traditionally considered abnormal, and attributable either to inflammation or to unknown proliferative stimuli. The only reasonably systematic study of these proliferative events in autopsy material by Morse in 1928 may lend itself to a different interpretation. Morse observed the proliferative lesions in the lower urinary tract in 108 of 125 autopsied cases. Fifteen of these patients were below the age of 20; in five, proliferative lesions were present. Inflammation, although generously interpreted, was found in only 58 percent of the bladders.

Pending another systematic study of the proliferative epithelial lesions, they must be interpreted as reflecting the spectrum of normal variants of bladder epithelium. The

inflammatory theory often cannot be sustained in biopsied cases when these changes are incidentally observed. The association of these lesions with carcinoma of the bladder will be discussed.

BRUNN'S NESTS

SYNONYMS AND RELATED TERMS: **von Brunn's nests;** von Brunn's follicles.

These are best defined as nodular thickening of the urothelium, resulting in nests of cells lying in the lamina propria adjacent to, or in direct continuity with the epithelium. There are no characteristic gross or cystoscopic findings. The nests are made up of small urothelial cells and are either solid or contain a central lumen, wherein an accumulation of colloid material may be observed (fig. 7). Brunn's nests are most commonly observed within the trigone, but occasionally are seen elsewhere in the bladder. Transition of Brunn's nests to cystitis glandularis is a frequent event (fig. 8). In such cases, the central lumen of Brunn's nests becomes enlarged and is lined by columnar, mucus-secreting cells.

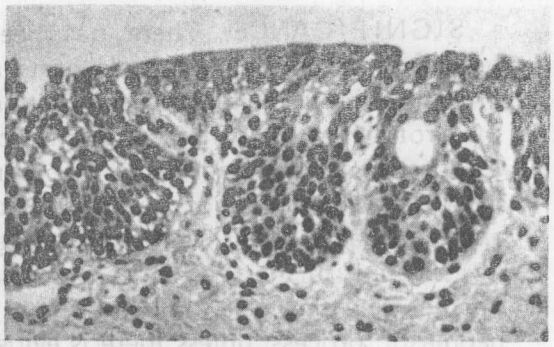

Figure 7
BRUNN'S NESTS, TRIGONE
(Figures 7 and 8 from same case)

Brunn's nests were an incidental finding in the trigone of the bladder. There was no evidence of bladder cancer. There are finger-like dips of urothelium, occasionally with a central lumen. By serial sections, the lumen could be traced to an invagination of the surface. X250.

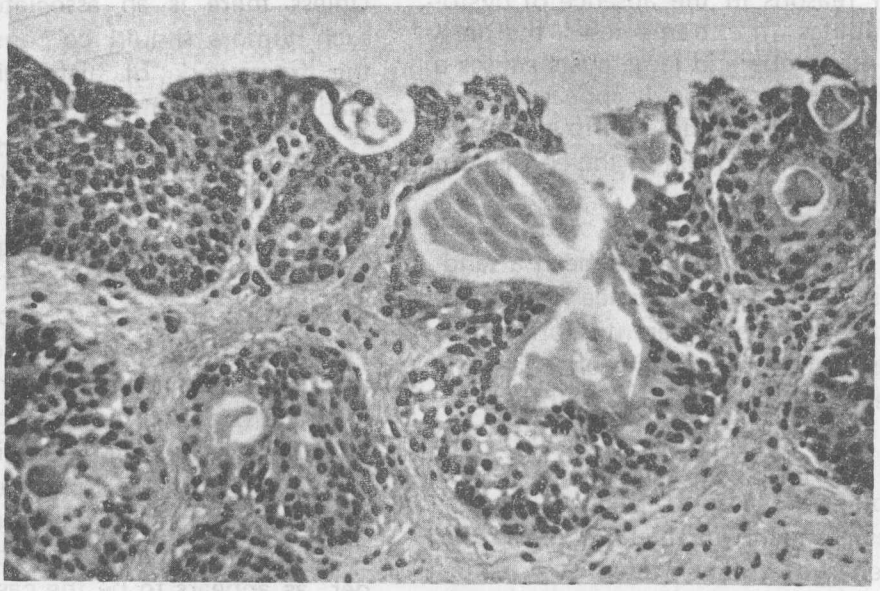

Figure 8
BRUNN'S NESTS
(Figures 7 and 8 from same case)

This illustrates a transition of Brunn's nests to cystitis glandularis. Formation of glandlike spaces filled with secretions can be readily observed as a function of surface epithelium. X250.

SIGNIFICANCE. There has been a tendency to consider Brunn's nests as a manifestation of abnormal proliferation of the urothelium. This interpretation is open to question. Brunn's nests may be observed in incidental biopsies of a normal bladder and the male urethra. Until the matter is investigated further, it appears advisable not to view the nests of Brunn as a true neoplastic process, unless there is evidence of cytologic abnormalities. It must be pointed out that neoplastic epithelial changes, for example carcinoma in situ, may involve the nests of Brunn.

CYSTITIS CYSTICA* AND GLANDULARIS

DEFINITION. These are cysts present in the lamina propria of the bladder, often in intimate relationship to the epithelium and nests of Brunn. In many instances, this is an incidental finding in biopsies obtained for other reasons in the absence of cystoscopic findings. In extreme cases, the presence of numerous and large cysts causes a characteristic cystoscopic appearance of "cobblestone" epithelium due to elevations caused by cysts. Redness of the epithelium is sometimes recorded.

HISTOLOGIC FEATURES. Although in some of the writing there has been a tendency to separate cystitis cystica from cystitis glandularis, the differentiation is not based on sound histologic criteria. The cysts are lined by simple or stratified epithelium. The simple epithelium may be cuboidal or resemble colonic epithelium with goblet cells. The stratified epithelium resembles islands of urothelium, except for the presence of a lumen lined by cuboidal to columnar cells; within the latter, mucus-secreting cells may be observed. The resemblance of epithelium in cysts to that observed in exstrophy of the bladder is striking (compare figs. 1, 3, and 4). The lumina of the cysts often contain products of cell secretion, predominantly mucus (fig. 9). It is not unusual to observe cyst formation within Brunn's nests (fig. 8). The stroma separating the various cystic and solid epithelial structures is usually free of leukocytes or other signs of acute or chronic inflammation. Occasionally, an inflammatory process sets in after biopsies or treatment. The cysts are confined to the lamina propria of the bladder. If glandular structures occur within the muscularis, the possibility of an adenocarcinoma must be urgently considered.

Variants of cystitis cystica and glandularis have been described as adenomatoid tumors of the bladder and as other dysontogenic tumors (Friedman and Ash). Occasionally, such islands of glandular epithelium may form solitary tumor masses. Unless there is an associated carcinoma, such tumors should be considered within the framework of histologic variants of bladder epithelium.

SIGNIFICANCE. The documentation that lesions of cystitis cystica and glandularis are reversible is very poor. On the other hand, there is histologic evidence of occasional association of cystitis glandularis and cystica and related abnormalities with bladder cancer, usually adenocarcinoma, and less commonly with urothelial carcinoma. There is no statistical evidence whether or not this association is incidental. It may be that the presence of numerous cysts or Brunn's nests is a predisposing factor to carcinoma of the bladder, as appears to be the case with exstrophy. However, this point requires elucidation by further prospective study.

*Preferred terminology of the World Health Organization's series "International Histological Classification of Tumours". Geneva, 1973.

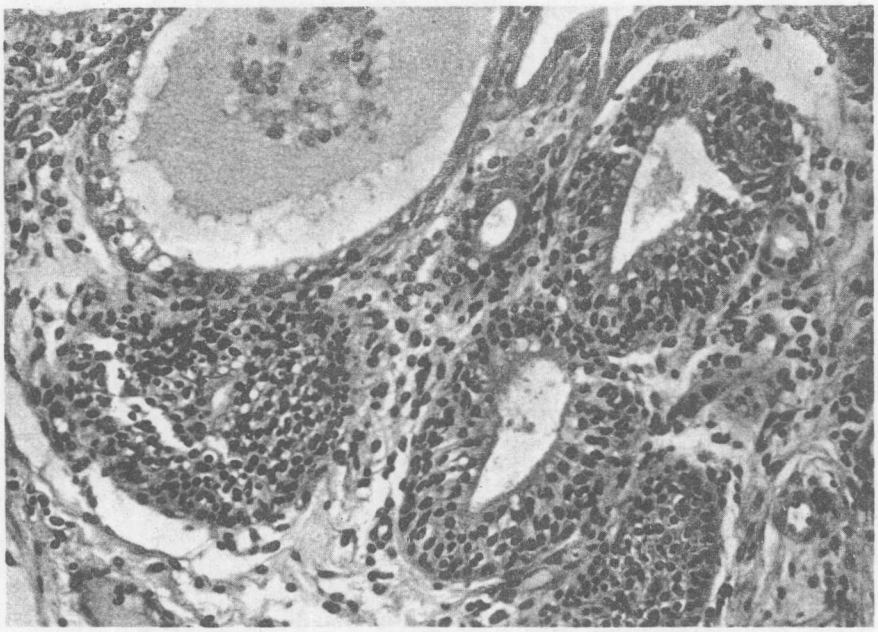

Figure 9
CYSTITIS CYSTICA AND GLANDULARIS

Biopsy from a 43 year old man with "cobblestone" appearance of the trigone and adjacent bladder. Note the cystic spaces of various sizes. The cyst lining varies from a single layered to multilayered epithelium. There is mucus in the lumina of some cysts. The intervening stroma is infiltrated with lymphocytes. X250.

SQUAMOUS METAPLASIA

It is possible that in some instances squamous metaplasia also represents a histologic variant of bladder epithelium. However, this change is most commonly observed in the presence of chronic irritation and inflammation and, therefore, it is described on page 103.

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EPITHELIAL TUMORS OF THE BLADDER

Carcinoma of the bladder must be conceived as a focal expression of epithelial abnormalities that may be quite diffuse. This general statement is applicable to all histologic types of carcinoma of the bladder.

The clinical events in a fatal carcinoma of the bladder are but the tip of the iceberg, and may reflect clinically silent epithelial abnormalities of long duration. Therefore, the assessment of bladder cancer in terms of 5-year survival is inadequate from the biologic point of view, although it reflects to some extent clinical salvage. This is particularly important in assessing the well differentiated (low grade) papillary lesions, where only a follow-up of 10 or more years may give information on the true significance of the disease.

The histologic classification of carcinoma of the bladder is, therefore, to some extent unsatisfactory in terms of prognosis, except for high grade (poorly differentiated) cancers in which an unfavorable outcome within a short span of time can be anticipated.

CLASSIFICATION

The classification of tumors of the urinary bladder is based on three essential criteria:

Pattern of histologic differentiation (i.e., urothelial, squamous, or glandular)

Pattern of growth (i.e., papillary, nonpapillary, confined to the epithelium, or infiltrating the bladder wall).

Degree of cytologic abnormality or grading, based mainly on the assessment of nuclear and mitotic abnormalities.

For purposes of this fascicle, the epithelial tumors of the bladder will be discussed in the following order:

Inverted papilloma of the urinary bladder

Papillary urothelial tumors
- Papillary tumors without significant cytologic abnormalities (papillomas and papillary carcinomas, grade I)
- Papillary carcinomas, grades II and III

Nonpapillary carcinomas
- Invasive urothelial carcinoma (transitional cell carcinoma)
- Squamous cell (keratinizing) carcinoma
- Spindle and giant cell carcinoma
- Adenocarcinoma
- Carcinoma, mixed types

Carcinoma of bladder associated with other diseases: lithiasis, diverticula

Metastatic spread of carcinoma

Precancerous lesions of the urothelium
- Nonpapillary carcinoma in situ

Involvement of ureters, urethra, and renal pelvis in urothelial bladder cancer.