Virchows Arch [Pathol Anat] (1981) 393:165–181

Virchows Archiv A

Primary Adenocarcinomas of the Human Urinary Bladder: Histochemical, Immunological and Ultrastructural Studies

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Summary. Neoplastic and non-neoplastic tissue specimens from ten patients with primary adenocarcinoma of the urinary bladder were examined. Most of these tumors were associated with either foci of transitional cell carcinoma and/or with glandular metaplasia of the bladder epithelium. The mucin produced by the neoplastic cells was PAS, alcian blue, mucicarmine, PB/KOH/PAS, and RPB/KOH/PAS-positive. ABH isoantigens of these tumors were not always deleted. Ultrastructurally, the neoplastic cells resembled goblet cells. Their plasma membrane had numerous microvilli with prominent glycocalyx. Proliferation and attenuation of tight junctions were noted. The gap junctions were few and small. Two types of desmosomes were found. The ultrastructural features of the neoplastic cells were attributed in part to the malignant transformation and in part to the direction of their differentiation. We have not observed any distinctive morphologic, histochemical, immunologic or ultrastructural features that might be diagnostic for these adenocarcinomas.

Key words: Urinary bladder adenocarcinomas – ABH isoantigens – Ultrastructure

Primary adenocarcinomas of the human urinary bladder are relatively rare. They comprise 2% of the carcinomas arising in the urinary bladder (Mostofi 1975). The clinicopathological behavior of these tumors has been reported (Mostofi et al. 1955; Deture et al. 1975; Daroca et al. 1976; Jacobs et al. 1977; Austin and Stafford 1978; Fuselier et al. 1978; Kramer et al. 1979, and Jones et al. 1980). A diagnosis of adenocarcinoma in bladder raises the question whether the lesion is a primary or a

This study was supported by the Institute of International Education, New York; the Charlton Fund, Tufts University School of Medicine; and Grants #CA-15776 and CA 23776 from the National Cancer Institute

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0340-1227/81/0393/0165/$03.40

metastatic tumor. The frequency of these tumors seems to be similar, as deduced from a study reported by Melicow (1955), in which, out of 209 adenocarcinomas in bladder, 100 were metastatic. Metastatic adenocarcinomas of intestinal, prostatic and gastric origin are the leading secondary tumors in the bladder. Furthermore, it is often difficult to distinguish primary from metastatic adenocarcinoma by histopathology alone. In an attempt to identify distinctive diagnostic features of primary adenocarcinomas of the bladder, we studied ten cases using immunological, histochemical and electron microscopic techniques. The results obtained in this analysis are the subject of this report.

Materials and Methods

Sixteen specimens of primary adenocarcinoma of the urinary bladder were obtained from ten patients. We considered as primary adenocarcinomas of the urinary bladder those malignant neoplasms which arise from the bladder epithelium (i.e., urothelium), and more than 50% of their tumor mass revealed histological features of adenocarcinoma. None of the patients had a known primary tumor in another location, and there was no history of either chemotherapy or radiotherapy of the tumors prior to their removal. In one patient, tumor specimens were obtained on three separate admissions. Fourteen specimens were obtained at surgery and two at autopsy. Eleven surgical specimens were obtained by transurethral resection and three by cystectomy. Cytological specimens were obtained from seven patients prior to surgery. For histopathological examination, the specimens were fixed in 10% buffered formalin; embedded in paraffin; sectioned and stained with hematoxylin and eosin. Since there is no grading system for primary adenocarcinomas of the urinary bladder, we graded the tumors as well-differentiated, moderately and poorly differentiated adenocarcinomas. The tumors were given a pathological stage according to the criteria of Jewett (1973). The stages of invasion include 0, none; A, submucosa; B_1, superficial muscle; B_2, deep muscle; C, fat; and D, adjacent organs or metastases. Sections from nine patients were stained with either periodic acid-Schiff (PAS), PAS-alcian blue, alcian blue pH 2.0 and mucicarmine. In addition, two histochemical techniques, periodate-borohydride/KOH/PAS (PB/KOH/PAS) and rapid periodate-borohydride/KOH/PAS (RPB/KOH/PAS) and their control periodate-borohydride/PAS (PB/PAS) were used. These techniques are thought to be specific for mucin which is produced by normal epithelium of the lower gastrointestinal tract; by adenocarcinomas which arise from this epithelium and their metastases. In these techniques, the treatment of KOH removes the O-acyl ester from the side chains of the sialic acid found in the mucin and thereby increases the PAS reactivity (Culling et al. 1975).

The presence or absence of ABH isoantigens, which are thought to serve as a predictor of tumor behavior in transitional cell carcinomas (Cummings 1980), was studied with the Specific Red Cell Adherence (SRCA) test (Alroy et al. 1978). The SRCA test was done by the following protocol: A deparaffinized section of formalin-fixed tissue was stained with hematoxylin and washed in isotonic Tris-saline buffer (TSB), pH 7.4, for 5 min and the excess buffer was drained off. The slide was placed in a Petri dish lined with moist filter paper. The section was covered with human antisera (Dade blood grouping serum for anti-A or anti-B, Miami, FL) or *Ulex europeus* agglutinin I (Vector Laboratories, Burlingame, CA), which specifically binds to H isoantigen. Each lot of antiserum was tested for potency and specificity using agglutination of a panel of red blood cells with human blood groups (A, B, AB and O). The slide was rinsed 3 times with TSB to remove unbound antiserum or *Ulex* extract. Excess TSB was drained off and the slide returned to a Petri dish. The tissue section was then covered with a suspension of erythrocytes ("indicator" erythrocytes), which correspond to the patient blood type, and was incubated for 15 min. During the incubation, erythrocytes sediment and adhere to the tissue section via the antiserum or the *Ulex* extract. The slide was inverted in a brisk movement and placed on two wooden applicators within a Petri dish. The slide only touched the TSB solution. This enabled the erythrocytes which did not adhere to the tissue section to sediment to the bottom of the Petri dish. The TSB solution was aspirated with a Pasteur pipette and replaced with cold 2% glutaraldehyde in Millonig's phosphate buffer, pH 7.4, and the section with the indicator erythrocytes was fixed for 30 min at room temperature. The section was then washed 3 times and stained with eosin. Negative result was defined as an absence of adhering indicator erythrocytes. Positive result was defined when the epithelial cells were covered by the

adhering erythrocytes. The presence of indicator erythrocytes at the lumen of the blood vessels served as a built-in positive control (Fig. 4), while the connective tissue that lacked the ABH isoantigens served as a negative control (Fig. 5).

Tumor tissue for the electron microscopic study was obtained during surgery from six patients. In addition, non-neoplastic epithelium (i.e., urothelium) was obtained from tumor-free bladder walls. All of these patients' specimens were immediately minced into 1–5 mm^3 tissue blocks and were fixed for 2 h in 2% glutaraldehyde in 0.1 M sodium cacodylate, pH 7.4, at 4° C. They were rinsed and stored in 0.1 M cacodylate, pH 7.4, at 4° C. Tissue blocks, 1–2 mm^3, were post-fixed in 1% osmium tetroxide in 0.1 M cacodylate buffer, pH 7.4, for 1 h at 4° C, dehydrated in a graded ethanol series, embedded in Epon-812, and sectioned with an LKB-8801 ultramicrotome. For characterization of the cell surface coat, 1–2 mm^3 fixed tissue blocks were post-fixed in 2% Ruthenium red and 1% osmium tetroxide in cacodylate buffer for 3 h at 20° C, and then processed with the rest of the specimens. Thick sections (1 μm) were stained with toluidine blue, thin sections (50–70 nm) were stained with uranyl acetate and lead citrate.

For freeze-fracture, 3–5 mm^3 glutaraldehyde-fixed tissue blocks were immersed overnight in 20% glycerol in Millonig's phosphate buffer, pH 7.4 (v/v), and were fractured according to the method of Moor and Mühlethaler (1963) in a Balzers BAF-301 freeze-etch device. Thin sections and freeze-fracture replicas were photographed in either a Philips EM-200 or -300 electron microscope.

For the Scanning Electron Microscope (SEM), 5 mm^3 tissue blocks were postfixed in 1% osmium tetroxide in 0.1 M phosphate buffer, pH 7.4, for 30 min; dehydrated in ascending alcohol solutions, and dried in a Denton DCP-1 critical point drying apparatus. The tissues were cemented to specimen stubs, spattered with gold, and examined in a JOEL JSM 35 U SEM.

Results

Clinicopathological Findings

The pertinent clinical, pathological, cytological and immunological information for individual patients is summarized in Table 1.

Eight patients were male and two female. The ages of the patients ranged from 45 to 87 years. All but one were admitted with a suspected or known bladder tumor. In Case 6, the bladder carcinoma was an incidental finding at the time of autopsy. Urinary cytology examinations revealed the presence of neoplastic cells in four out of seven patients. In Case 5, the presence of signet ring cells suggested adenocarcinoma. All the patients had an invasive carcinoma at the time of surgery. There was no preferred anatomical site for the development of these carcinomas. The neoplasms in four patients had an exophytic growth with invasive fronts while, in the others, the neoplasms we observed were sessile. Three patients had multiple tumors at the time of surgery. Grossly, all the tumors had a similar appearance, exhibiting smooth, shiny and slimy surfaces.

Findings in Non-neoplastic Urothelium

The histological, immunological and ultrastructural observations are summarized in Table 2.

Foci of glandular metaplasia, which included alcian blue-positive goblet cells, were found in Cases 2 and 9, while chronic cystitis cystica was present in the non-neoplastic urothelium of Cases 6 and 8. Histologically, normal urothelium was present in five cases. The urothelium in four of these indicated the presence of ABH isoantigen (positive SRCA test results). The one patient with a negative test result had H (O) isoantigen.

Table 1. Adenocarcinomas of the urinary bladder

Case	Age Sex	Blood Group	SRCA Test Results	No. & Size of Tumors (cm)	Tumor Grade and Stage	Others	Urine Cytology	Tumor Location
1	77 M	AB	B-positive A-negative	$2.0 \pm 1.0 \times 0.6$[b]	MD[c] C	TCC-component	Positive	Dome
2	48 M	B	Negative	$6.0 \times 2.5 \times 0.3$[b]	MD[c] C	TCC-component	Negative	Trigone
3	87 F	O	Negative	$1.0 \times 0.5 \times 0.3$[b]	MD[c] B_2		Negative	NR
4	54 M	A	Positive	$6.5 \times 6.5 \times 2.0$[b] $6.8 \times 7.0 \times 2.0$[b]	MD[c] B_2		Negative	Entire bladder but trigone
5[a]	84 M	O	negative	1) $0.3 \times 0.3 \times 0.3$[b] 2) $1.2 \times 0.6 \times 0.3$ $0.8 \times 1.0 \times 0.2$ $0.6 \times 0.4 \times 0.2$ $1.2 \times 0.8 \times 0.4$ 3) $8.0 \times 3.0 \times 3.0$	PD[d] D		Positive as adeno-carcinoma	Dome, lateral & posterior walls
6	45 M	A	Positive	$7.0 \times 7.0 \times 7.0$	PD[d] C		ND	Trigone
7	70 M	B	Negative	$8.0 \times 7.0 \times 5.0$[b]	PD[d] C	TCC-component	ND	Posterior mid-line
8	56 F		ND	$1.0 \times 2.0 \times 1.0$	PD[d] C	TCC-component	Positive	Trigone, ori-fices, dome
9	63 M	O	Negative	microinvasive	PD[d] A	Extensive *in* situ carcinoma	Positive	Posterior wall
10	50 M	O	Negative	$0.9 \times 0.5 \times 0.3$	PD[d] A	TCC-component	ND	Posterior urethra

NR = not recorded; ND = not done

[a] This patient hat three separate admissions

[b] Specimen obtained for electron microscopy

[c] Moderately differentiated

[d] Poorly differentiated

Table 2. Histological, ultrastructural and immunological features of non-neoplastic bladder epithelium in these patients

Case	Histopathology	Thin Section EM	SEM	SRCA Test
2	Foci of glandular metaplasia	Microvilli, glycocalyx, few AUM plaques	Few microridges, microvilli	B-positive
4		Microvilli, glycocalyx, no AUM plaques	Pleomorphic microvilli	A-positive
6	Foci of cystitis cystica	ND	ND	A-positive
7		Microvilli, glycocalyx, no AUM plaques	Pleomorphic microvilli	B-positive
8	Chronic cystitis	ND	ND	ND
9	Foci of glandular metaplasia	ND	ND	O-negative

ND = not done

Microridges seen by SEM are a common surface feature of luminal membrane of normal bladder urothelium in many species (Hicks 1976; Jacobs et al. 1976), but are rare in man (Kjaergaard et al. 1977; Merk et al. 1977). Microridges were infrequently observed in the non-neoplastic urothelium of one patient (Case 2; Fig. 1). In spite of the overall absence of microridges, every sample of non-neoplastic urothelium had positive SRCA test results. On the other hand, pleomorphic microvilli, which are thought by some investigators to serve as a marker for malignant urothelial cells (Hicks 1976; Hicks and Wakefield 1976), were numerous in two of our patients (Cases 4 and 7, Fig. 2). Corresponding thin sections from all three cases revealed that the luminal membranes contain glycocalyx. Rare plaques of Asymmetric-Unit-Membrane (AUM) were observed (1) at the luminal membrane, and (2) in fusiform vesicles (Fig. 1, inset). The plaques were present in the same patient (Case 2) whose bladder had revealed sparse microridges. A thin layer of "mucous film" was noted to cover most of the control urothelium in all three patients (Fig. 3).

Findings in the Adenocarcinomas

Various amounts of neoplastic transitional cells were observed in the adenocarcinomas of five of the ten patients. In eight patients, the neoplastic cells formed papillary projections and glands (Fig. 5). In the remaining two patients (Cases 1 and 5), signet ring cells were the most prominent feature (Fig. 4). Signet ring cells were occasionally present in tumors with papillary projections. Extensive mucin was observed in all bladder carcinomas except in Case 3, where it was sparse. The mucin in all tumors was positive for PAS, PAS-alcian blue, alcian blue pH 2, mucicarmine, PB/KOH/PAS and RPB/KOH/PAS, but all were PB/PAS-negative. The car-

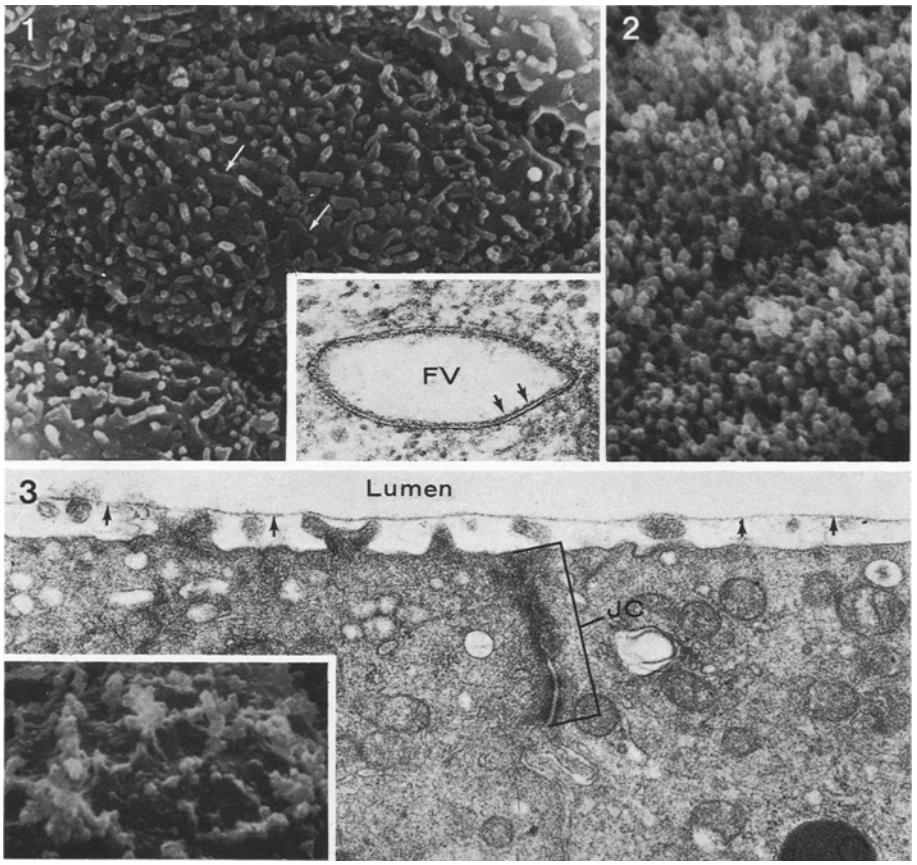

Fig. 1. Scanning electron micrograph of non-neoplastic transitional cell epithelium obtained from Case 2. It illustrates a polygonal cell covered by uniform microvilli, and a few microridges (*arrows*). ×7,500. *Inset:* AUM (*arrows*) forms the limiting boundary of a fusiform vesicle (Case 2). ×103,000

Fig. 2. Laminal surface of non-neoplastic transitional cell covered by pleomorphic microvilli. ×9,600

Fig. 3. Two non-neoplastic transitional cells joined by junctional complex (*JC*). Their surfaces have a few microvilli which are covered by a thin "mucous film" (*arrows*). ×2,300. *Inset:* En face view of microvilli on the bladder surface which is covered with a "mucous film". ×15,000

cinomas in six patients had negative SRCA test results (Fig. 4), while in two patients it was positive (Fig. 5). In the carcinoma of the patient who had AB isoantigens, the SRCA test was positive with isoantigen B, but not with A.

Ultrastructurally, the neoplastic transitional cells seen in these tumors resembled those previously described (Fulker et al. 1971; Alroy et al. 1979; Alroy 1980; Alroy and Gould 1980; Alroy et al. 1981). The nuclei were large, with prominent nucleoli. Cytoplasmic organelles in the transitional cells were sparse (Fig. 6). Intracytoplasmic luminae (Alroy et al. 1979) and cilia were noted, and numerous desmosomes were present.

Adenocarcinoma cell surfaces seen with the SEM revealed numerous microvilli, but some had smooth surfaces (Fig. 7). Mucous-secreting goblet cells projected

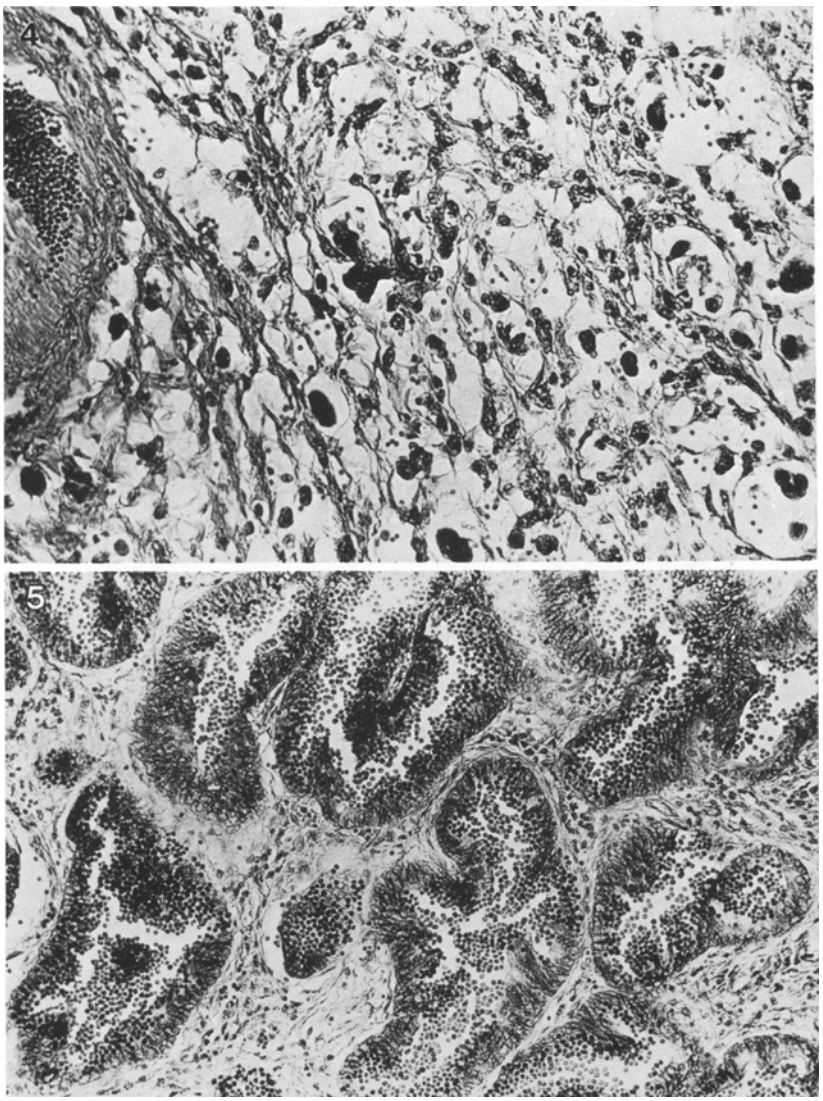

Fig. 4. Negative SRCA test result in adenocarcinoma of a patient who had B isoantigen. The luminal surface of the blood vessel is covered by indicator erythrocytes (8.9) and thus serves as a built-in control. ×110

Fig. 5. Positive SRCA test result in adenocarcinoma of a patient whose blood group is A. Indicator erythrocytes adhere to the neoplastic cells, but not to the adjacent stroma. ×108

above the surrounding epithelium (Fig. 8). Corresponding thin sections of these mucous granule-containing cells revealed that they had numerous microvilli with prominent microfilamentous cores and rootlets (Hickey and Seiler 1981) (Figs. 9 and 10). The microvilli were coated with a rich Ruthenium red-positive glycocalyx (Fig. 10). In addition, the lateral membranes were also Ruthenium red-positive (Fig. 12). Superficial granular cells were joined together at their apical poles by

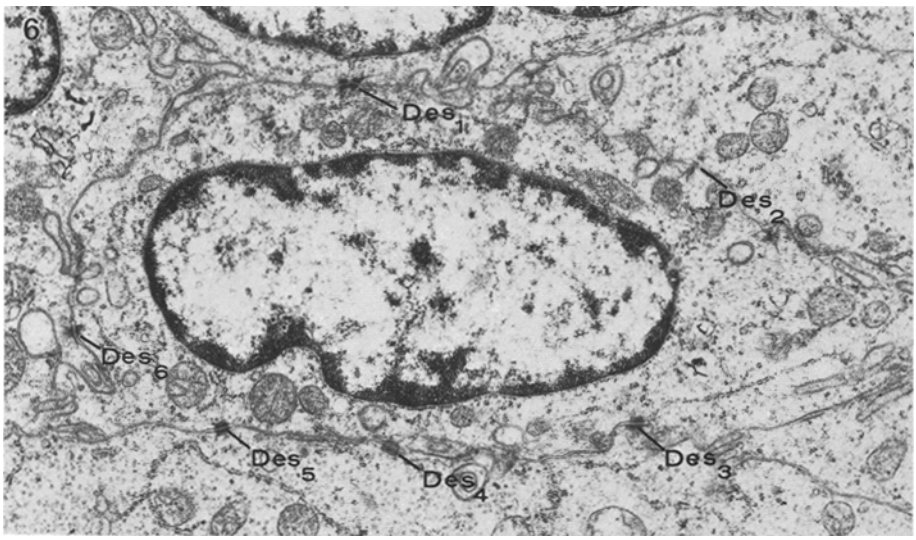

Fig. 6. Neoplastic transitional cells adjacent to the adenocarcinoma cells, containing few cytoplasmic organelles, but having numerous desmosomes (*Des*). × 57,000

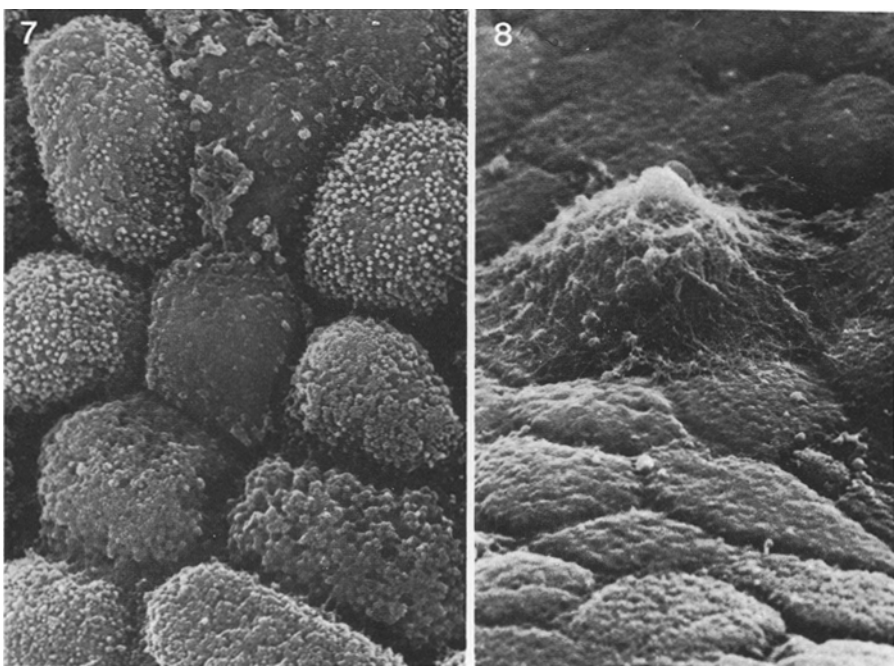

Fig. 7. Luminal surface of adenocarcinoma cells viewed by SEM. Some of the cells have pleomorphic microvilli, while others (*at center*) have a relatively smooth surface. × 4,100

Fig. 8. SEM view of mucin secretion by a neoplastic goblet cell. × 3,900

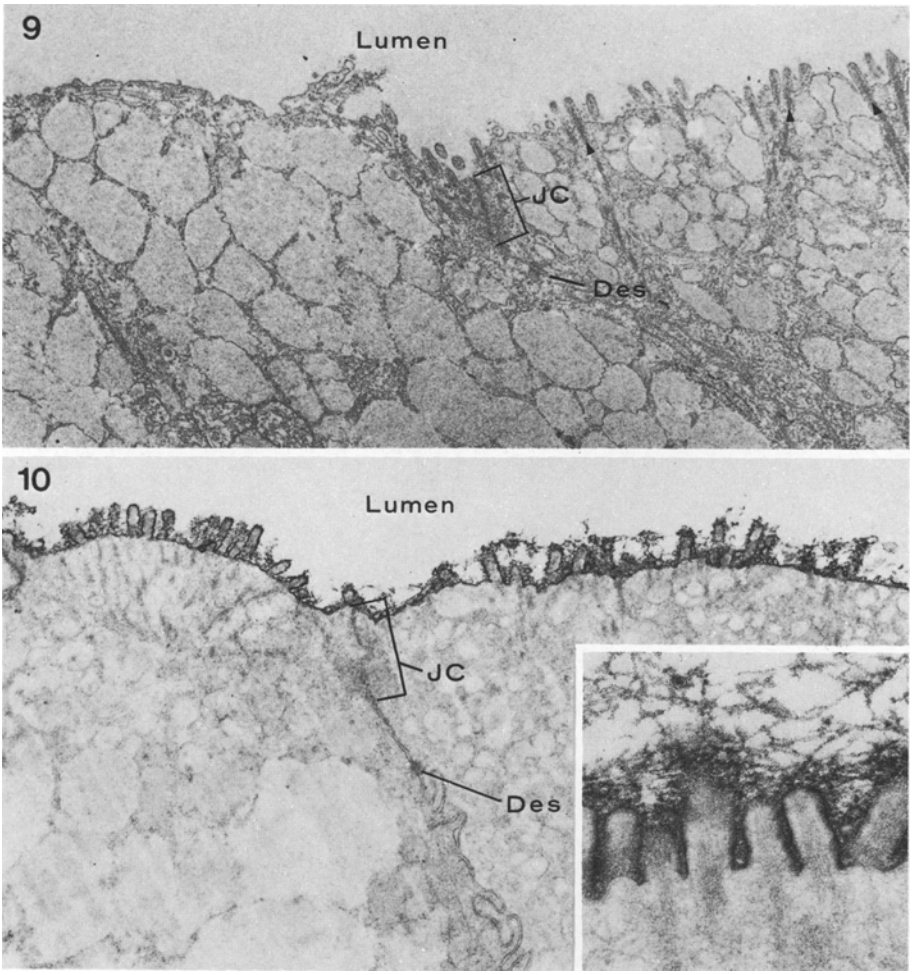

Fig. 9. Two neoplastic cells joined at their apical-lateral margins by a junctional complex (*JC*), and at their lateral plasmalemmas by a desmosome (*Des*). The cells contain numerous mucin granules. The cell on the right has numerous microvilli with prominent microfilamentous cores and rootlets (*arrows*). ×18,000

Fig. 10. Electron micrograph of neoplastic cells which were post-fixed with Ruthenium red and osmium tetroxide. The cells are joined by a junctional complex (*JC*) and desmosomes (*Des*). Their luminal surface contains numerous microvilli with prominent glycocalyx. ×21,000. *Inset:* Higher magnification of Ruthenium red-positive microvilli. The glycocalyx has a filamentous substructure. The microvillar cytoplasm has dense microfilamentous cores. ×46,000

junctional complexes (Figs. 9 and 10), which consisted of tight junctions, zonula adherentes and desmosomes. Tight junctions included regions in which the outer leaflets of the plasma membranes appeared "fused" (Fig. 11). Freeze-fracture replicas of these junctions revealed a network of branching and interlacing 6–8 nm ridges on the protoplasmic fracture (PF) face and corresponding grooves on the

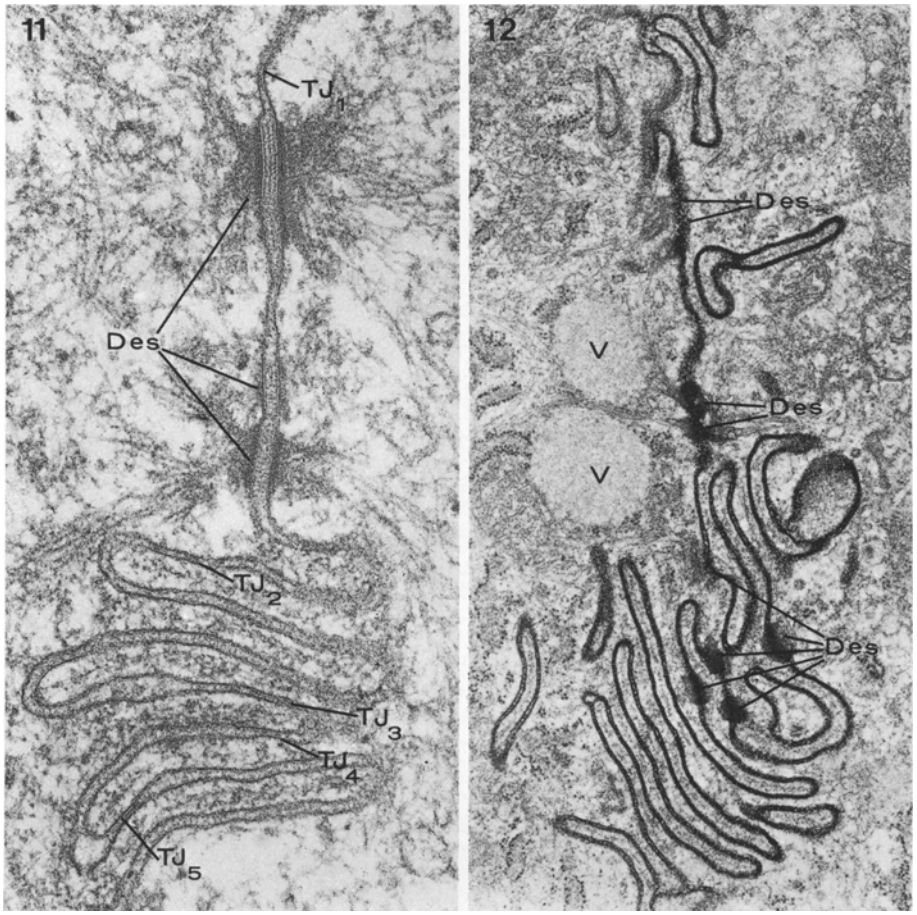

Fig. 11. Numerous tight junctions (*TJ*) and 100-F desmosomes (*Des*) between the lateral plasmalemmas of two adenocarcinoma cells. × 79,000

Fig. 12. Two adenocarcinoma cells with mucin granules (*V*). The cell surface coats of the lateral membranes are intensely stained by Ruthenium red. The cells are joined by numerous desmosomes (*Des*). × 48,000

extracellular fracture (EF) face (Fig. 13). Basally-oriented tight junctions were occasionally found away from the junctional complex (Fig. 11), as well as adjacent to the tumor stromal interface (Alroy 1980; Alroy and Gould 1980). Corresponding replicas (Fig. 13) revealed that, unlike normal urothelium (Merk et al. 1980), the network of ridges and grooves was fragmented. Isolated strands were observed within the lateral cell membrane. The few gap junctions that we observed were small (Fig. 13, inset). Desmosomes were numerous, and two varieties were noted (Figs. 11 and 12). The 70-F desmosomes (McNutt and Weinstein 1973) associated with 5–7 nm thick filaments were generally found between transitional cells and cells with glandular differentiation. The 100-F variety (McNutt and Weinstein 1973), with

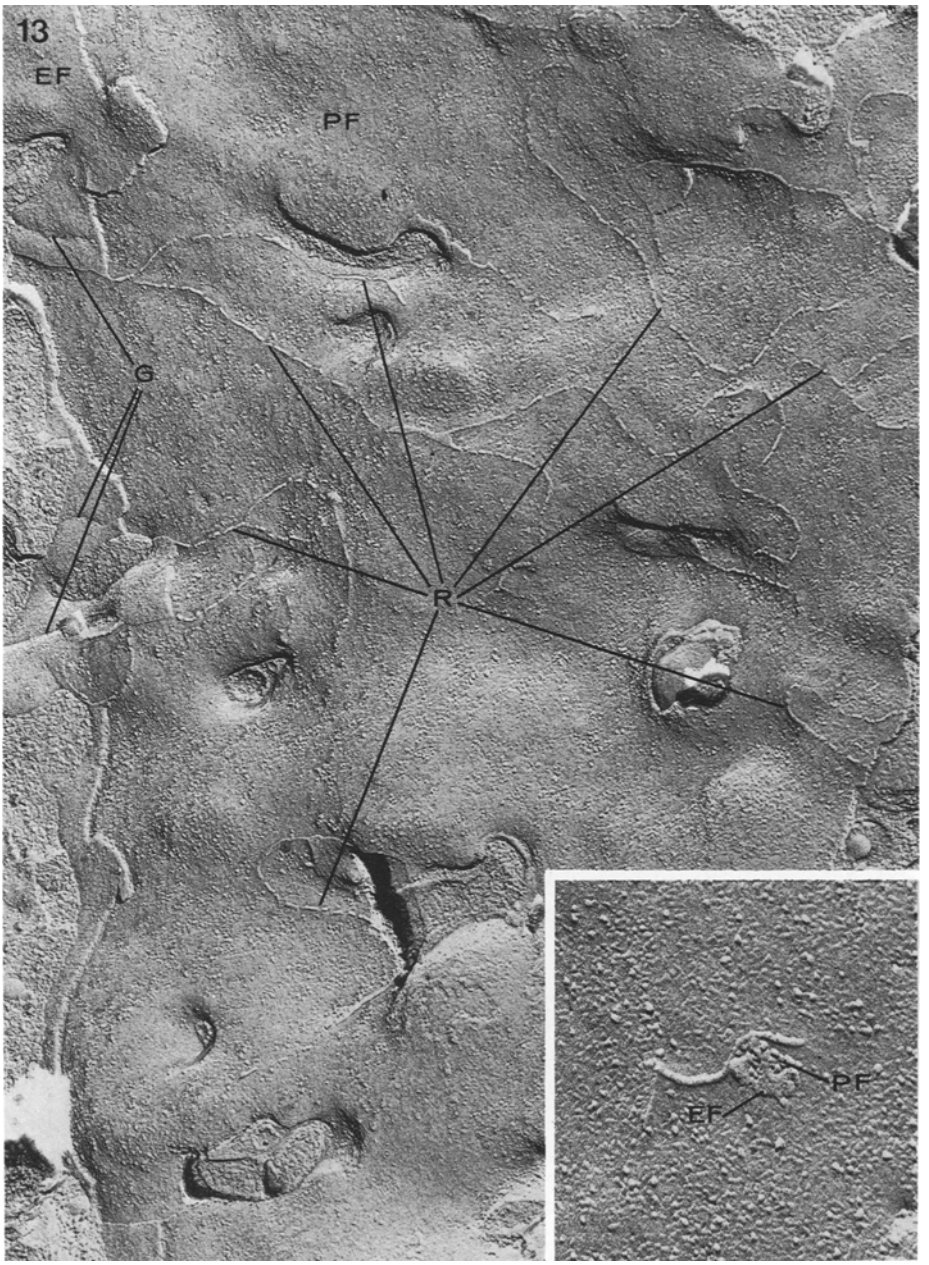

Fig. 13. Freeze-fracture replica of dispersed tight junctional strands seen within the plasma membrane of an adenocarcinoma cell. On PF-face, the tight junction appears as ridges (*R*) while, on EF-face, as grooves (*G*). ×47,000. *Inset:* Small gap junction adjacent to a tight junctional strand. >86,000

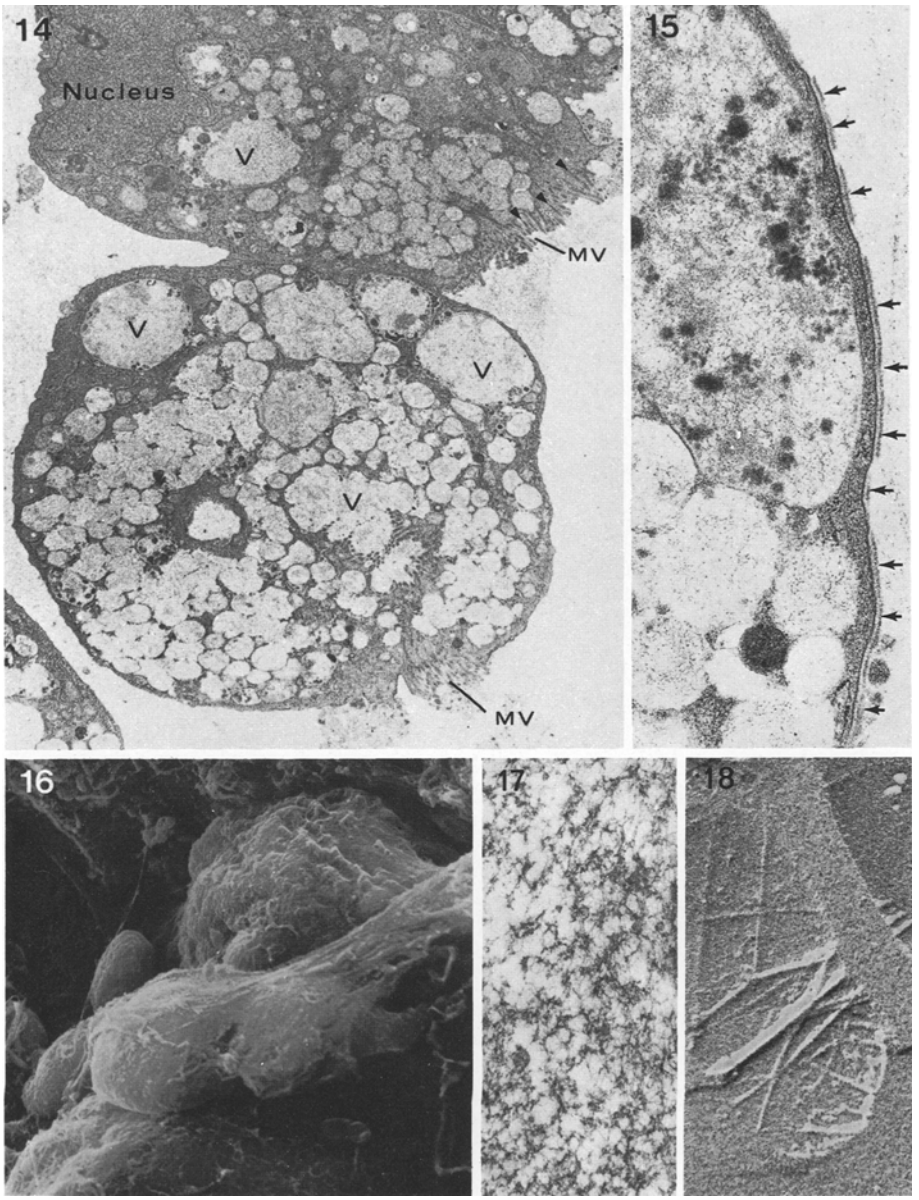

Fig. 14. Low magnification of two neoplastic signet ring cells. They contain numerous interconnected mucin granules (*V*). The cell surfaces are generally smooth, but occasional foci of microvilli (*MV*) are noted. These microvilli have prominent microfilamentous cores and rootlets (*arrows*). The cells lack a basal lamina. ×3,500

Fig. 15. Basal lamina (*arrows*) is occasionally found at the interface bebtween signet ring cells and the surrounding mucin. ×25,000

Fig. 16. SEM view of signet ring cell which is covered with mucin. ×2,000

Fig. 17. The extracellular mucin in which the signet ring cells are embedded has a fibrillar fine structure. ×29,000

Fig. 18. Freeze-fracture of mucin reveals a fibrillar component. ×65,000

10 nm thick filaments, were found between cells that feature either glandular or squamous differentiation (Alroy and Weinstein 1976; Merk et al. 1980).

Signet ring cells appeared individually or as small clusters of neoplastic cells embedded within lakes of mucin. These cells had numerous mucin granules of varying sizes. The granules were often interconnected, and appeared to be empty vacuoles, or they contained small amounts of fine fibrillar material (Figs. 14 and 15). The surfaces of the signet ring cells were generally smooth, but they occasionally had small microvilli (Fig. 14). Tight junctions, 70-F and 100-F desmosomes, which had prominent microfilamentous cores and rootlets, were observed between these cells, but gap junctions were not. In general, the signet ring cells were devoid of basal lamina. However, single (Fig. 15) or duplicated basal laminae were occasionally noted. Thick layers of mucin always engulfed the signet ring cells (Fig. 16). The mucin had a branched, fibrillar structure (Figs. 17 and 18), similar to the structure of glycocalyx seen at the luminal surface of cells in capillary adenocarcinomas (Fig. 10, inset). Tumor tissue rich in mucin apparently had very poor penetrability properties. In spite of prolonged exposure to either glycerol or Ruthenium red, these compounds infiltrated only the periphery of the tissue blocks. This phenomenon may be due to the physiochemical properties of the mucin.

Discussion

We have examined several morphological and immunological features of primary adenocarcinomas of human urinary bladder, and have compared them to non-neoplastic urothelium obtained from the same patients. The purpose of this study has been to characterize the tumor cells and to determine whether distinctive features develop in bladder neoplasms that are unique for primary adenocarcinomas and might serve as an aid in diagnosis.

Our findings are similar to previous reports (Mostofi et al. 1955; Deture et al. 1975) indicating that glandular metaplasia and cystitis cystica were observed together with adenocarcinoma of the bladder. In three of our patients, the non-neoplastic urothelium had foci of glandular metaplasia and cystitis cystica. These non-cancerous changes are generally thought to be associated with bladder adenocarcinomas (Mostofi et al. 1955; Deture et al. 1975), although the significance of the association is controversial (Koss 1979). We also confirm the reports that normal bladder urothelium of human adults had sparse AUM (Alroy et al. 1977; Merk et al. 1977; Jacob et al. 1978), and that microvilli coated with glycocalyx are present (Merk et al. 1977; Jacob et al. 1978). Both of these features have been related to malignant transformation (Hicks 1976; Hicks and Wakefield 1976). The absence of ABH isoantigens studied with the SRCA test is thought to serve as a predictor of malignancy in urothelium (Cummings 1980). All of our specimens except one had positive SRCA test results. The negative result was from a patient with H antigen, which is sometimes not expressed in urinary bladder urothelium of normal patients (Coon and Weinstein 1981).

Adenocarcinoma of the urinary bladder is rare in man (Mostofi 1975), but is more common in dogs and cattle (Panukcu 1974). As previously reported in man and animals (Panukcu 1974; Kunze 1979), we found that many of the bladder

adenocarcinomas have foci of neoplastic transitional cells. Furthermore, we confirm that papillary adenocarcinoma and signet ring cells reside within the same tumor (Mostofi et al. 1955; Deture et al. 1975). In the present study, two out of nine adenocarcinomas had positive SRCA test results but, unlike a previous report (Alroy et al. 1978), our patients were not subjected to radio- or chemotherapy. It thus appears that at least some invasive primary adenocarcinomas of the urinary bladder retain their ABH isoantigens. The presence of ABH isoantigens in adenocarcinomatous cells of the gastrointestinal tract has been related to the ability of these cells to produce mucin (Davidsohn et al. 1966). It is noteworthy that approximately 50% of the adenocarcinomas of the distal colon express these isoantigens (Abdelfattah-Gad and Denk 1980), whereas in normal mucosa they are absent (Szulman 1960).

The ultrastructure of neoplastic transitional cells, seen within adenocarcinomas of the human bladder, corresponds to earlier reports (Fulker et al. 1971; Merk et al. 1977; Alroy et al. 1979; Alroy and Gould 1980; Alroy et al. 1981). Although the neoplastic cells with glandular differentiation resemble mucinous carcinomas of other systems (Spjut and Smith 1967; Fenoglio et al. 1975; Steinbrecker and Silverberg 1976; Headington 1977; Nevalainen and Jarvi 1977), many of the ultrastructural features of our neoplasms reflect both neoplastic transformation and bidirectional differentiation. The coexistence of these phenomena have been reported in other neoplasms (Alroy and Weinstein 1976). Attentuation and proliferation of tight junctions may be associated with malignant transformation of cells (Weinstein et al. 1976), and perhaps with the cellular environment (Alroy et al. 1978; Alroy 1979). The infrequent occurrence of diminutive gap junctions in bladder tumors, including areas undergoing mucous metaplasia, is probably the result of malignant transformation (Weinstein et al. 1976). This observation differs from that in embryonic (Elias and Friend 1976) and neoplastic (Prutkin 1975) skin, where mucous metaplasia is associated with an increase in size and numbers of gap junctions. The coexistence of numerous 70-F and 100-F desmosomes (McNutt and Weinstein 1973) found in these forms of bladder adenocarcinomas may be associated with bidirectional differentiation of the tumor (Alroy and Weinstein 1976; Alroy et al. 1981).

The etiology of primary adenocarcinomas of the urinary bladder is unknown and the origin of the mucous-secreting cells is subject to speculation (Pund et al. 1952). It is well-known that luminal cells in normal urothelium have the ability to produce a mucoprotein coat (Shrom et al. 1977) that has been shown to be alcian blue-positive (Monis and Dorfman 1967). This material, identified as a glycosaminoglycan, apparently serves as an efficient defense mechanism (Parsons et al. 1980). The goblet cells present in the glandular metaplasias and adenocarcinomas observed in our study also produce an alcian blue-positive material, suggesting these abnormal cells may differentiate from the same cell population from which normal urothelium is derived. One possible explanation for the coexistence of adenocarcinomatous foci with neoplastic transitional cells and/or an epithelium exhibiting mucous metaplasia is that local environments may vary, resulting in expression of the different phenotypes (Hicks 1976; Cunha et al. 1980).

Metastatic intestinal adenocarcinomas are the most frequent secondary tumor in the bladder (Melicow 1955). Culling and his associates (1975) have suggested that the quality of mucin produced by normal and neoplastic elements of the lower gastrointestinal tract is unique. We have found that the mucin produced by primary bladder adenocarcinomas has the same PB/KOH/PAS-, RPB/KOH/PAS-positive qualities described by these authors (Culling et al. 1975). Colorectal adenocarcinomas are also reported to have a distinctive microvillar ultrastructure, which makes it possible to identify these carcinomas from other adenocarcinomas on ultrastructural grounds alone (Hickey and Seiler 1981). However, our studies have demonstrated these so-called distinctive microvilli, which contain extensive microfilamentous cores and rootlets, are present in primary adenocarcinomas of the urinary bladder.

When evaluated according to the cytological, histopathological, histochemical, immunological and ultrastructural techniques available to us, we conclude that primary adenocarcinomas have no distinctive features by which they may be distinguished from secondary adenocarcinomas in the urinary bladder.

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Accepted June 15, 1981