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Tumor of Mesonephric Origin in a Diverticulum of the Urethra

An Ultrastructural Study

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Summary. A case of a rare tumor arising in a diverticulum of the urethra was studied. Light microscopy revealed the typical structures of mesonephric tumor with obvious infiltration of the muscularis. Electron microscopic appearance indicated that the tumor cells were immature and not totally characteristic of any tissue of origin. Apart from appearances suggesting rapid growth, cellular inclusions of various appearance were found.

Key words: Bladder neoplasm – Mesonephric origin – Urethral diverticulum – Electron microscopy

It is well established that benign and malignant tumors may arise from remanents of the mesonephric duct in the lower genital tract, i.e. the uterine cervix, broad ligament, parametrium and vagina. Mesonephric tumors of the urinary bladder are very rare. In 33 cases in the world literature they have been reported as benign bladder adenomas (Friedmann and Kuhlenbeck 1950; Goldman 1972; Kalloor and Shaw 1970; Konnak 1973; Koswick et al. 1976; Molland et al. 1976; Peterson and Matsumoto 1978; Raghavaiah et al. 1980; Taneja et al. 1974).

Malignant tumors of nephrogenic or mesonephrogenic origin of the bladder and urethra have only been described as isolated cases (Altwein et al. 1975; Cea et al. 1977; Chrostoffersen and Moeller 1972; Dow and Young 1968; Konnak 1973; Murayama et al. 1978; Roberts and Melicow 1977). Two cases of mesonephric adenomas located within a diverticulum of the urethra have been described (Peterson and Matsumoto 1978; Roberts and Melicow 1977). We have reported clinical data on an additional case of mesonephric carcinoma originating within a diverticulum of the urethra of a 39 year old female (Leistenschneider et al. 1981). Transurethral electroresection was done in two steps. Cystectomy and ureterosigmoidostomy were

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performed after pretreatment with radiation. The follow up of 20 months revealed no recurrence. The paper presented here deals with the morphological, and in particular, the ultrastructural findings in this tumor. Electron microscopic findings of benign tumors of mesonephric origin in the urinary bladder have been reported by Molland et al. (1976) and Raghavaiha et al. (1980).

Material and Methods

The material used was the tissue fragments from both transurethral resections for light and electron microscopy. The tissue of the cystectomy could be examined only by light microscopy because of fication delay. In addition to routine Haematoxilin and Eosin stain, periodic-acid-Schiff (PAS), Alcian blue and the Kossa reaction were applied to histological sections. For electron microscopy tumor tissue fragments were fixed in 5% glutaraldehyde (pH 7.3 with 1/15 mol. Phosphate buffer), postfixed with osmium tetroxide and embedded in araldite. Ultrathin sections were examined with a Zeiss EM10 electron microscope after staining with uranyl acetate and lead citrate.

Results

1. Light Microscopy

The biopsy specimen (Fig. 1) showed a flat, superficial erosion, beneath which the pseudopolypoid and papillary structure of the tumor could be observed (Fig. 1a, b). The epithelium which consisted mainly of a single layer, was primarily cuboidal but sometimes cylindrical and showed enlarged nuclei with dense chromatin. In the base of the diverticulum near the lamina propria and muscularis banching tubular structures of varying width and with atypical epithelium were found (Fig. 1d). The epithelium contained irregularly formed enlarged nuclei rich in chromatin and often showed the typical hob-nail pattern with a bud-like elevation in the lumen of the tubule. Mitoses were frequently seen and in semithin sections enlarged prominent nucleoli were obvious (Fig. 1c).

In the cystectomy specimen (Fig. 2) which was systematically examined a small rest of the tumor tissue was found at the edge of the diverticulum. In addition, there were unusual ducts extending from this area to the outer layer of the bladder musculature. These ducts (Fig. 2a), which contained single-layered as well as multilayered epithelium, were surrounded by loose connective tissue containing lymphocytes and histiocytes and were partially cystic. Occasionally weakly acidophilic finely granulated material-containg a few desquamated epithelial cells was found in the lumen. Some parts of the walls of these cysts extended into the lumina. They contained narrow epithelial folds as well as thin-walled blood vessels and lymphocytes, with histiocytes in the stroma (Fig. 2b). In this area the epithelium showed abnormalities, particularly hyperchromasia of the nuclei, anisonucleosis, and large nucleoli (Fig. 2c). The random positioning of the tubules did not show the typical appearance of invasive malignant growth.

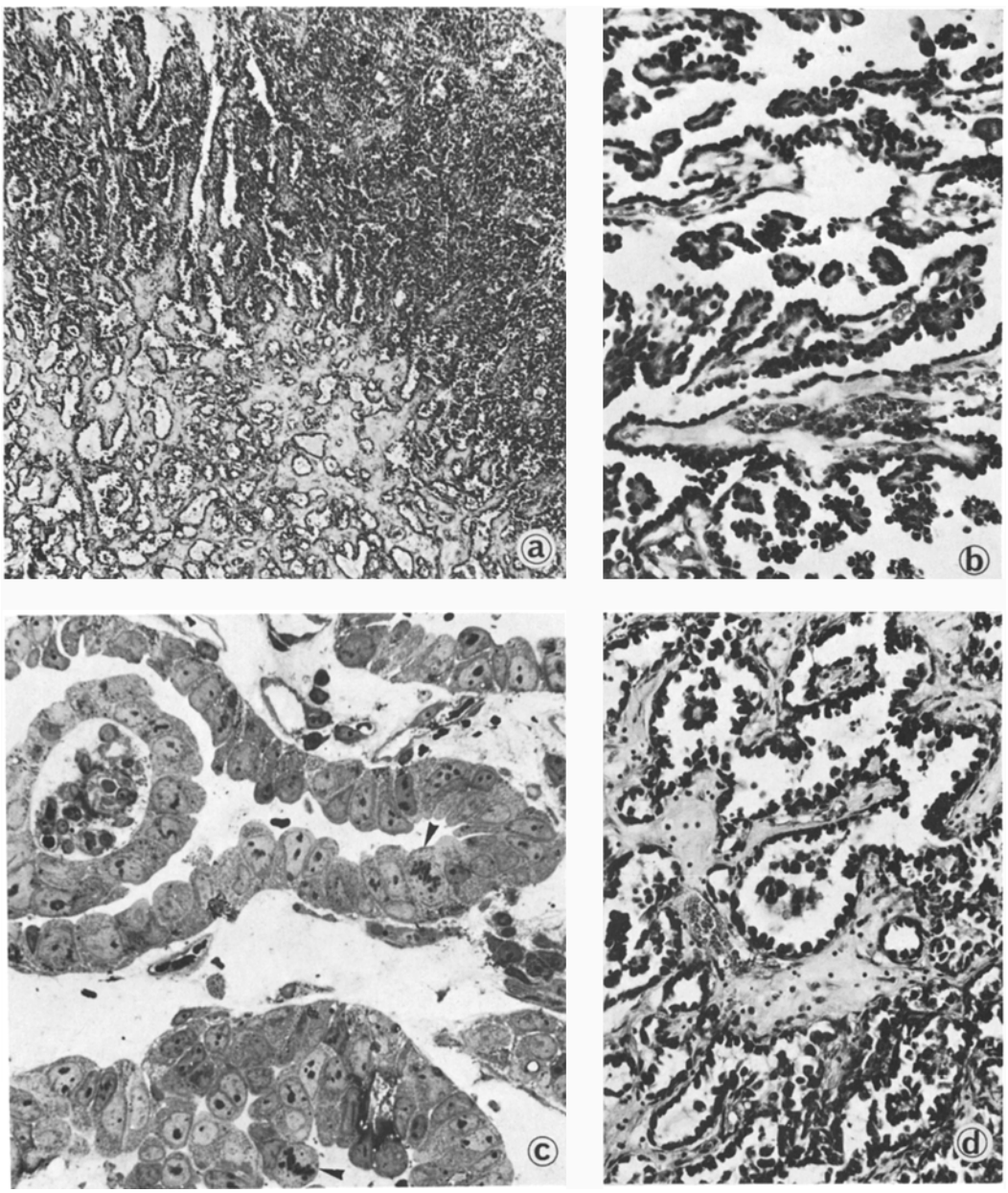

Fig. 1a–d. Characteristic light microscopic appearance of mesonephric carcinoma in the biopsy material with tubulopapillary structure and surface erosion (**a**). Typical hob-nail pattern of epithelium (**b** and **d**). Cuboidal or columnar tumor cells with mitoses *(arrowheads)* in (**c**). (**a, b**) and (**d**) paraffin sections; (**c**) semithin cut. Magnifications: (**a**) ×40, (**b**) and (**d**) ×150, (**c**) ×370

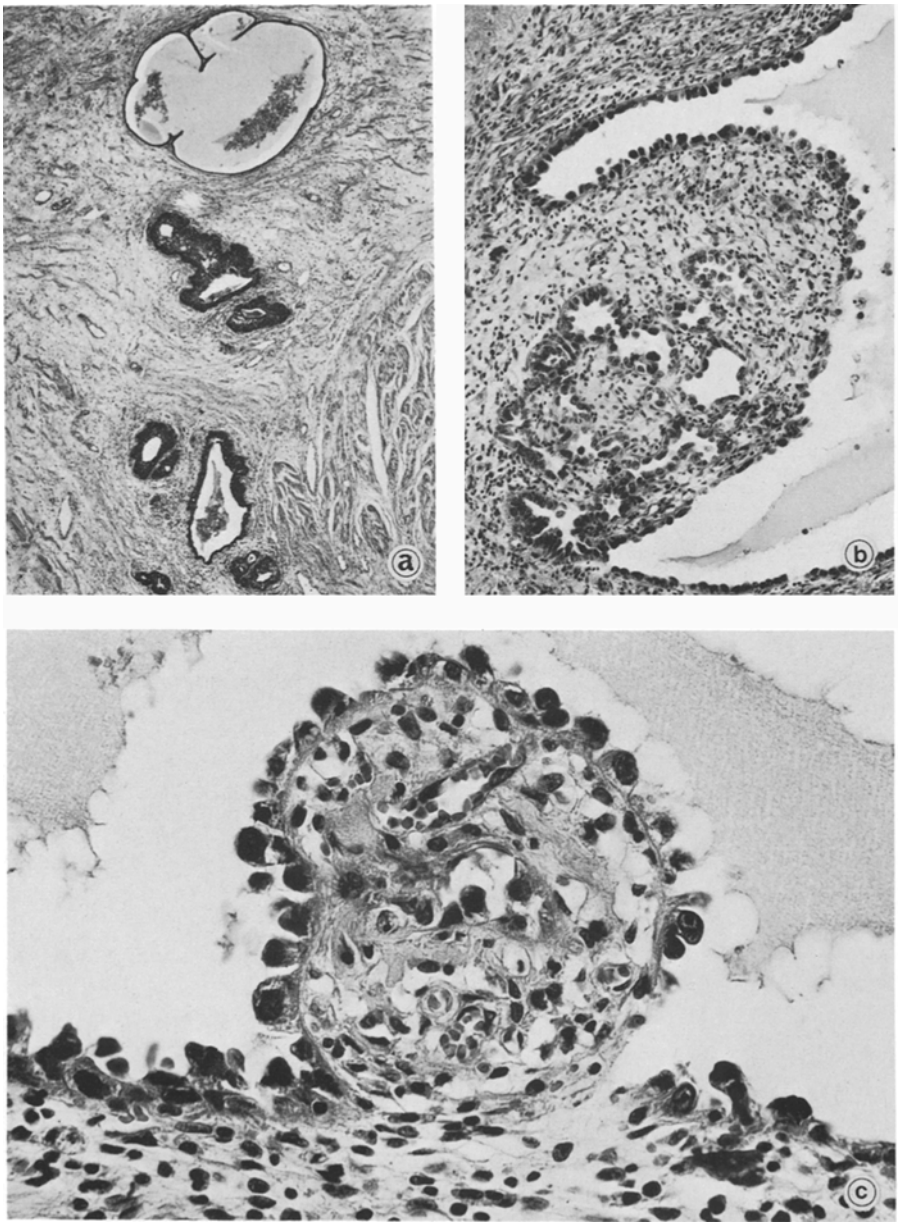

Fig. 2a–c. External portion of muscularis and lamina propria of the cystectomy specimen with ducts of varying shape (**a**) and protrusions lined by cuboidal epithelium with nuclear polymorphism (**b** and **c**), accompanied by some histiocytic infiltration of the stroma. Paraffin sections. Haemalaun-Eosin. Magnifications: (**a**) ×40, (**b**) ×150, (**c**) ×370

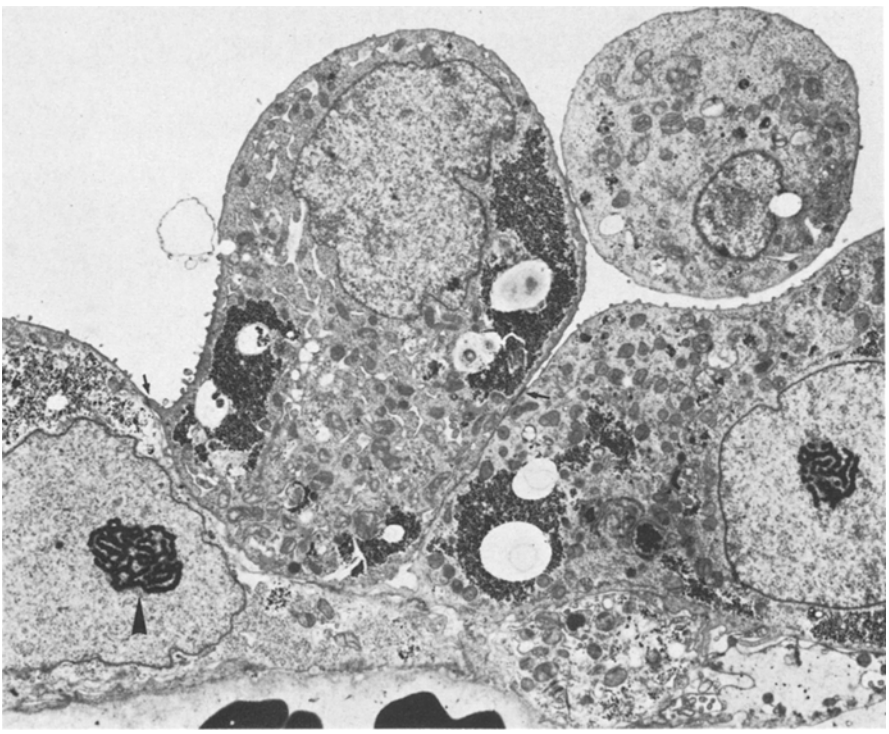

Fig. 3. Tumor cells with sparse short microvilli on the luminal surface and zonulae occludentes (*arrows*). Glycogen deposits, many mitochondria and dilatated endoplasmatic reticulum in the cytoplasm. Nuclei with folded membrane and coarse reticular nucleolonema (*arrowhead*). ×4,000

2. Electron Microscopy

Ultrastructurally (Figs. 3–5) the epithelial cells were cuboidal and low columnal with a prominent, cap-like cell apex. The luminal surface was covered with short microvilli. It was not possible to identify a trilaminar surface membrane which is characteristic of urothelial surface (Koss 1977).

Zonulae occludentes were present at the apical junctions of adjoining cells but no desmosomes were seen. The intercellular spaces were focally widened and lateral cell processes protuded into these spaces (Fig. 4e). The basal portions of the cells formed intertwining processes set upon a thin basement membrane.

The nuclei were enlarged, filling one half to two thirds of the cells. They were irregularly shaped and the nuclear membrane was folded or wavy. The meandering invaginations of nuclear membrane often presented cytoplasmatic pseudoinclusions when transsected. The nucleoli were frequently enlarged and showed coarse reticular nucleolonema (Fig. 3).

Within the cytoplasm accumulations of glycogen and many polyribosomes were present. Mitochondria were found in great numbers (Fig. 3), but were pleomorphic. They varied in size and shape, contained an irregular

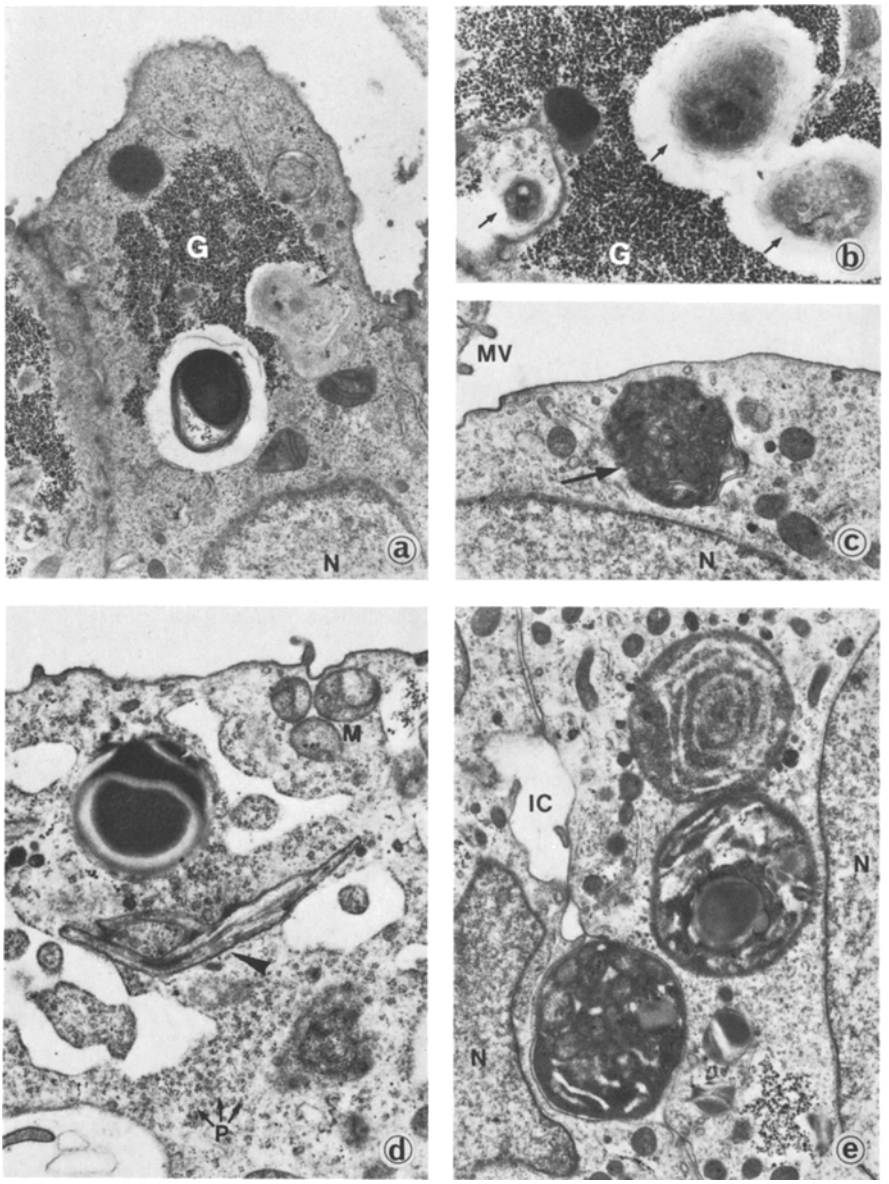

Fig. 4a–e. Cytoplasmatic inclusions, some of them (**c** and **e**) resembling to bacteriae. **a** Homogeneous and concentric lamellated inclusions (*G*, Glycogen; *N* nucleus). ×7,200. **b** Granular and amorphous material within glycogen deposits. ×1,400. **c** Multicentric lamellated inclusions (arrow) near cell surface. *MV*, Microvilli; *N*, nucleus. ×1,400. **d** Electron dense homogeneous inclusion with light halo and filamentous structures *(arrowhead)*. *P*, polyribosomes; *M*, pleomorphic mitochondria. ×13,800 **e** Inclusions of varying density with concentric substructure – one of them within the intercellular cleft (*IC*). ×10,000

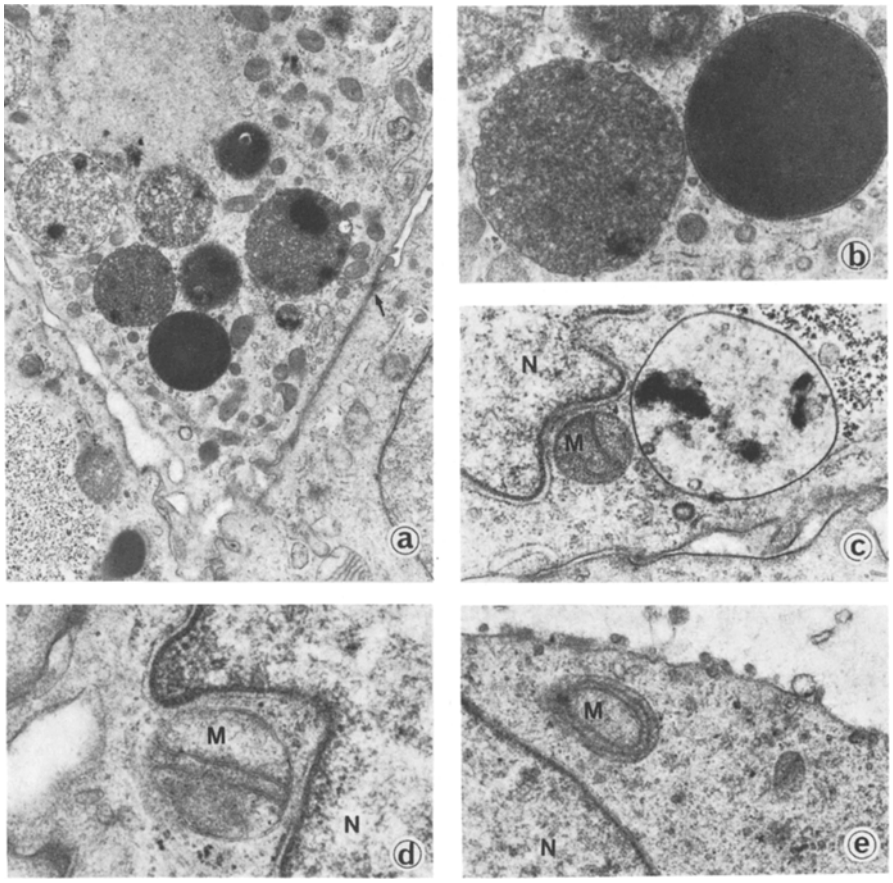

Fig. 5a–e. Membrane bound cellular inclusion with homogeneous, granular or mixed structure (**a** and **b**). Multivesicular substructure of membrane bound inclusion (**c**). Irregular dense matrix and sparse cristae of mitochondria (**c** and **d**). Ring shaped mitochondrium (**e**). Magnifications: (**a**) ×8,000, (**b**) ×15,800, (**c**) ×22,000, (**d**) ×28,400, (**e**) ×13,500

dense matrix and were sometimes ringshaped (Fig. 5). The number of irregular mitochondria in some cells suggested a compensatory hyperplasia at the organelle level. Granular endoplasmatic reticulum was prominent and in some areas dilatated.

Cellular inclusions of varying appearance were found within areas of glycogen accumulation. There were amorphous masses with a light halo, sometimes with filamentous, granular or scanty vesicular substructure and often with an electron-dense material in the center (Fig. 4). In addition homogeneous membrane-bound round inclusions with, granular and irregular multivesicular substructure (Fig. 5a, b and c) or with concentric clefts (Fig. 4e) were seen. Similar material was found as a rare occurence within widened intercellular clefts (Fig. 4e).

Comment

Remnants of the mesonephric duct can be found in the male as appendix epididymis and in the female (Gartner duct) in the mesosalpinx, the uterus, cervix uteri and the vaginal wall. Mesonephric tumors of these sites have been reported (Teilum 1954; Truskett and Lattes 1965; Wade-Evans and Langley 1961).

The occurence of mesonephric tumors in the urinary bladder is explained by the proximity of the mesonephric duct to the mesoderm which forms parts of the bladder, in particular the trigone and primitive urethra (Dow and Young 1968). This idea is supported by the fact that the trigone is often the site of mesonephrogenic bladder tumors. In addition to the possibility that the matrix of these tumors consists of dispersed mesonephric cells (Friedman and Kuhlenbeck 1950), the hypothesis of direct origination from the mesoderm has been discussed. According to Teilum (1954) the mesoderm has the power to form tubuloductular structures because of its relationship to the mesonephric ducts.

In addition to this embryological view of the histogenesis of mesonephric tumors of urinary bladder an inflammatory theory has been suggested. This postulates that these tumors represent an unusual metaplastic reaction of urothelium to chronic inflammation (Allan 1975; Koswick et al. 1976; Molland et al. 1976; Taneja et al. 1974). A combination of both theories was attempted by Goldman (1972). In his opinion the tumor represents a metaplastic change in the urothelium derived from mesoderm, as would be found in the trigone or as local mesothelial islands in endodermally derived areas of the bladder.

On a light microscopic level our findings do represent the typical appearance of mesonephric tumor with tubulopapillary structures and characteristic hob-nail-pattern of epithelium. Tubular structures lined by epithelium of a hobnail or peglike character are however encountered in other carcinomas arising from glandular or ductal epithelium as for instance in the clear cell tumors of the female genital tract (Scully 1979). Herbst and Scully (1970 and 1979) believe that there is abundant evidence that the great majority of clear cell carcinoma are of müllerian duct nature. They accept that rare clear cell carcinomas in the cervix may arise from mesonephric remanents (Hart and Norris 1972; Scully 1979). In his reinvestigative studies of ovarian tumors Teilum (1976) accepted only two of those cases which had originally been suggested to be of mesonephric origin as real mesonephric tumors.

In our case we have found no tubules lined by clear cells or solid clear cell areas. This fact, the absence of significant mucin production and the isolated ductal rests found in the musculature of the outer muscular bladder wall support our diagnosis of a real mesonephric tumor. A comparable histological appearance was reported by Dow and Young (1968) and Christoffersen and Möller (1972) in cases of mesonephric carcinoma of the bladder. Konnak (1973) and Altwein et al. (1975) on the other side have found a clear cell component in mesonephric carcinomas of the urethra.

The interpretation of the results in the cystectomy specimen is somewhat problematic. The intramural tubular structures, partly demonstrating cystic dilatation, were accompanied by bud-like prominent proliferations. These structures were lined by flat or cuboidal and focal hyperplastic epithelium with and without striking nuclear abnormalities. We interpret these findings as tubular duct remnants of mesonephric origin with focal epithelial proliferation and transitions to carcinoma. This view of the light microscopic findings does not support the thesis of a tumor arising from metaplastic reaction of urothelium but favours the embryological theory of histogenesis.

Raghavaiah et al. (1980) have reported a case of nephrogenic adenoma of urinary bladder associated with malakoplakia. Malakoplakia is characterized by a distinct phagolysosomal activity of macrophages (Lou and Teplitz 1974) and it has been suggested that the material stored in the von Hansemann cells of malakoplakia is of bacterial origin (Terner and Lattes 1965). Although in our case there were some inclusions in the epithelial tumor cells which suggested a bacterial origin (Fig. 4) quite similar to those in malakoplakia, the light microscopic aspect was not characteristic for malakoplakia. Focal histiocytic proliferation and lymphocytic infiltration were present, but no Michaelis Gutmann bodies were seen. Considering the frequency of cystitis in this case the changes were considered to be secondary.

The criteria for differentiating benign from malignant mesonephric tumors of the urinary bladder have not been defined because of the rarity of malignant lesions. The obvious infiltration of the bladder musculature, the numerous mitoses and cytological abnormalities support our view of a malignant growth in this case. The ultrastructural appearance of the nuclei (enlargement, irregular margination, meandering invaginations of envelope and reticular nucleolonema) are considered to be indicative of active protein synthesis; in a tumor this implies a fast growing lesion which is usually malignant (Ghadially 1980). On the cytoplasmatic organelle level there are no specific morphological characteristics of malignancy, but an increased amount of polyribosomes indicates fast growth and, as in our case, pleomorphic mitochondria are often found in malignant tumors. The granular inclusions (Fig. 5) – sometimes with a reticular substructure – and their excretion into the lumen suggests a secretory property and may correspond to the very weak PAS-positive reaction in paraffin sections.

In agreement with the only two comparable reports of the ultrastructure of mesonephric adenoma of urinary bladder (Molland et al. 1976; Raghavaiah et al. 1980) in our case of mesonephrogenic carcinoma the electron microscopic appearance indicated that the cells were immature and not totally characteristic of any commonly cited tissue of origin.

The tubular cells lacked any of the features characteristic of normal urothelium – such as trilaminar surface membrane and the typical tripartite junctions, or the features associated with bladder tumors (Koss 1977; Smith 1981).

On the other hand epithelium of tubules have none of the specialized features of any part of the differentiated nephron. We could find no brush border – characteristic of the proximal tubule – and none of the deep infold-

ings of basement membrane and elongated mitochondria which typify the proximal and ascending thick tubules. Microvilli were present and are found in the epithelium of the Henle loop, but are not particular to these cells.

The abscence of characteristic electron microscopic findings for urothelium, or of the epithelium of the mature nephron, does not allow us to decide which of the theories of histogenesis of this tumor can be supported.

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