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Inverted Urinary Papilloma

Report of Five Cases and Review of the Literature

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Summary. Five new cases of inverted urinary papilloma are described and 13 previously reported cases are reviewed. All 18 examples were seen in adult males, with ages ranging from 26 to 79 years (average 57 years). Ten patients presented with symptoms of bladder outlet obstruction and 8 with haematuria. With one probable exception all of the tumours were solitary. Sixteen were found in the region of the bladder neck and prostatic urethra, and only 2 occurred in other sites. The papillomas were pedunculated or sessile and ranged in size from a few mms to 3 cms in greatest diameter. Most had smooth surfaces in contrast to the usual exophytic papillary urothelial neoplasms. Microscopically they showed a striking resemblance to the inverted papillomas of the nasal cavity and paranasal sinuses. In those examples where the stalk or base of the papilloma was included in the sections, there was no evidence of invasion of the underlying smooth muscle. Fourteen of the patients have been followed for periods ranging from 7 months to 11 years (average 2.5 years) and no recurrences have been documented. Simple local resection, by the transurethral route where possible, appears to be adequate treatment for these distinctive papillomas.

Key words: Urinary Tract — Bladder — Urothelium — Inverted Papilloma — Transitional Cell Carcinoma.

Introduction

Since the first description of inverted urinary papilloma (inverted urothelial papilloma, inverted papilloma of bladder) by Potts and Hirst in 1963, there have been only sporadic reports of the tumour (Trites, 1969; Assor and Taylor, 1970; Inada and Ochíai, 1971; Sullivan *et al.*, 1971; Pienkos *et al.*, 1973; Cummings, 1974; Matz *et al.*, 1974) and this unusual papilloma does not appear to have gained general recognition, particularly outside Australasia. Several recent accounts of neoplasms of the urinary bladder do not mention it (Thackray, 1966; McGovern, 1969; Mostofi and Leestma, 1971; Vidyarthi, 1971) and in some instances these papillomas have been histologically misinterpreted as infiltrating transitional cell carcinomas, as discussed by Trites (1969), Hardy and Allen (1972) and Pienkos *et al.* (1973).

This report describes 5 new cases of inverted urinary papilloma and reviews 13 previously published cases, with the object of further emphasizing the distinctive histomorphology and apparently excellent prognosis of this tumour when treated by local endoscopic resection. One of our cases occurred on the left lateral wall of the bladder and seems to be only the second published example seen outside the region of the bladder neck and prostatic urethra.

Table 1. Clinical and pathological data on 5 cases of inverted urinary papilloma

Case No.	Age (years)	Sex	Clinical features	Site of papilloma	Gross appearance	Details of follow-up
1	49	M	bladder outlet obstruction	bladder neck	polypoidal tumour, 3 cms in diameter, 1 cm in height	cystoscopy one month after diagnosis. No recurrence, then lost to follow-up
2	79	M	bladder outlet obstruction	bladder neck	fragmented. Small papilloma approx. 0.5 cm in diameter	clinical observation 9 months. No recurrence of symptoms. Carcinoma of prostate
3	72	M	bladder outlet obstruction	bladder neck	fragmented. Small papilloma approx. 1 cm in diameter	cystoscopy and repeat biopsy of site of papilloma at 2 months. Clinical observation 10 months. No recurrence
4	54	M	bladder outlet obstruction	bladder neck	smooth-surfaced fragment approx. 0.5 cm in diameter	cystoscopy after approx. 1 year & 8 months. No recurrence. Then lost to follow-up
5	52	M	intermittent haematuria	left lateral wall of bladder	fragmented. Papilloma approx. 1.5 cm in diameter	cystoscopy at 3 and 7 months. No recurrence

The Present Study

The cases were selected from the files of the Divisions of Histopathology of The Queen Elizabeth Hospital and The Institute of Medical and Veterinary Science, solely on the basis of histology. The principal histological feature used for diagnosis in either intact or fragmented specimens was the inverted configuration of the papillomas (Inada and Ochiai, 1971); any tumour which was too fragmented for the overall architecture to be assessed was rejected. There were 5 acceptable cases and these are summarized in Table 1.

Clinical Presentation and Operative Findings

All 5 inverted papillomas occurred in males, with ages ranging from 49 to 79 years. Four of the patients presented with symptoms of bladder outlet obstruction, and in all of these the papilloma was situated at the bladder neck. However, in one of these subjects (Case 2) the obstructive urinary symptoms may have been primarily related to an associated adenocarcinoma of the prostate, and the inverted papilloma was possibly only an incidental cystoscopic finding, as in the second case of Trites (1969). In the remaining case, the inverted papilloma was found on the left lateral bladder wall in a patient presenting with intermittent haematuria. All of the tumours were solitary. In no case was the diagnosis of inverted urinary papilloma suspected at cystoscopy.

Pathological Findings

In 4 cases the papillomas were received in fragments and the gross morphology and size could only be inferred by their attempted reconstruction. However, the tumours had predominantly smooth surfaces with a few small papillary areas. The largest measured 3 cms, and

the smallest approximately 5 mms, in greatest diameter. The papilloma in Case 1 was pedunculated; in the remainder, pedicles could not be identified in continuity with the tumours, probably because of fragmentation.

Histologically these tumours consisted of covering urothelium from which arborizing cords of epithelial cells extended into the subjacent fibrovascular stroma (Figs. 1 and 2). The epithelial cells were relatively uniform with ovoid to elongated nuclei, some of which had a longitudinal nuclear groove (Fig. 3), similar to that seen in the cells of the Walthard rests, the epithelial cells of Brenner tumours of the ovary, and in the nests of von Brunn in the urinary tract (Bransilver *et al.*, 1974). Although the epithelial cells were hyperchromatic in one instance (Case 1, Fig. 1), mitotic activity was inconspicuous in all cases. In some areas the cords showed peripheral palisading of cells (Fig. 3), and in the more cellular papillomas, palisading of cells around small stromal blood vessels produced scattered pseudo-rosettes. In all tumours the epithelial cords contained microcysts or crypts in which eosinophilic PAS-positive colloid-like material was present (Fig. 1). In Cases 1 and 5 a few crypts also contained a minute amount of mucin-like matter and, occasionally, as in Cases 1 and 2, a crypt was lined by uniform low columnar cells with basally situated nuclei (Fig. 4); elsewhere, however, these had the typical configuration of inverted papillomas; intestinal glands and renal tubular structures were not present. In 3 of the tumours small foci of squamous metaplasia were apparent.

The proportion of epithelial elements to stroma varied considerably, and in Cases 2 and 4 the papillomas were cellular with little stroma. In contrast, the tumour seen in Case 3 had an abundant stroma with loose myxoid areas (Fig. 1); in these, there were moderate numbers of blood vessels, some of which showed mucoid intimal proliferation. Occasionally, stromal lymphocytes, plasma cells and mast cells were present, principally in the superficial zones where a few neutrophils were also seen in some cases. In Case 1 in which the pedicle was identifiable there was no evidence of invasion of the underlying smooth muscle.

Treatment and Follow-up

Four patients were treated by transurethral resection of the inverted papilloma. The remaining patient (Case 1) was thought to have prostatic hyperplasia and the papilloma was locally excised during the course of a suprapubic prostatectomy. This patient was lost to follow-up after one month, but the other subjects have been followed by clinical observation, and in most instances cystoscopy, for periods of 7 months to approximately 1 year 8 months. In no case has recurrence of the papilloma been suggested clinically or documented at cystoscopy. One patient (Case 3) died from a myocardial infarct 10 months after diagnosis, but no necropsy was performed.

Discussion

We have been able to collect 5 cases of inverted urinary papilloma from 2 major centres in a city with a population of less than one million; 4 of these were seen in a 3-year period, suggesting that the tumour is not excessively rare. However, there have been only 13 cases of inverted urinary papilloma previously published; these are summarized in Table 2. The case reported by Borski (1970) was originally diagnosed as a hamartoma of the bladder, but the clinical features, illustrations of the histology and proposed pathogenesis of the lesion, namely that it developed as a result of epithelial hyperplasia with invagination, leave little doubt that it represents an inverted papilloma. More recently, Borski (1974) has agreed that the most likely diagnosis in his case would be a urothelial papilloma of the inverted type. Both Hirst (1972) and Trites (1974) have encountered other cases of inverted papilloma since their original reports. Trites (1974) has seen 3 cases that were not reported in detail in his 1969 article. They all concerned men of middle to advanced years, but this could reflect patient selection in a veterans' hospital. No follow-up details are available on one of the patients. The second has been observed for

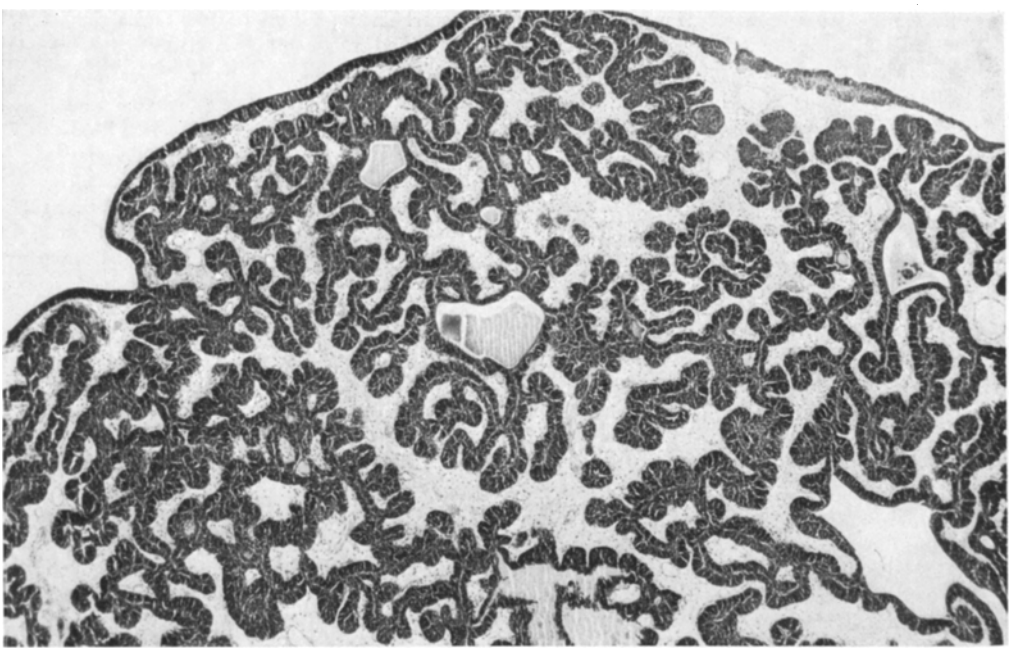

Fig. 1. Typical architecture of an inverted urinary papilloma. Crypts containing colloid-like material are apparent in the arborizing epithelial cords. Case 3, HE ×40

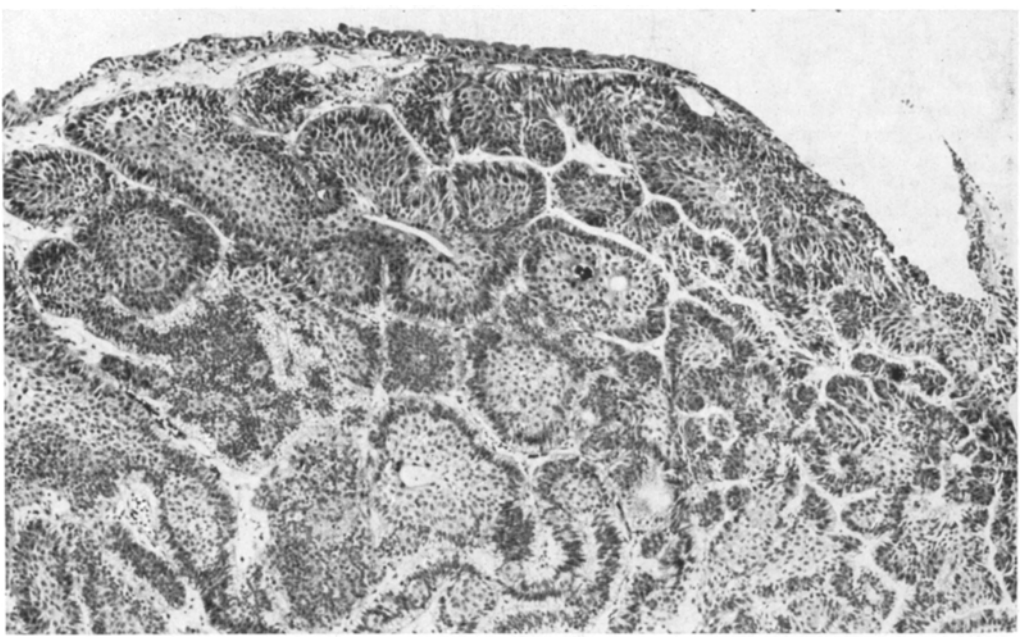

Fig. 2. Low power view of an inverted urinary papilloma. Cords and nests of epithelial cells extend into the subjacent fibrovascular stroma. The black spot near the centre represents an artifact. Case 5, HE ×80

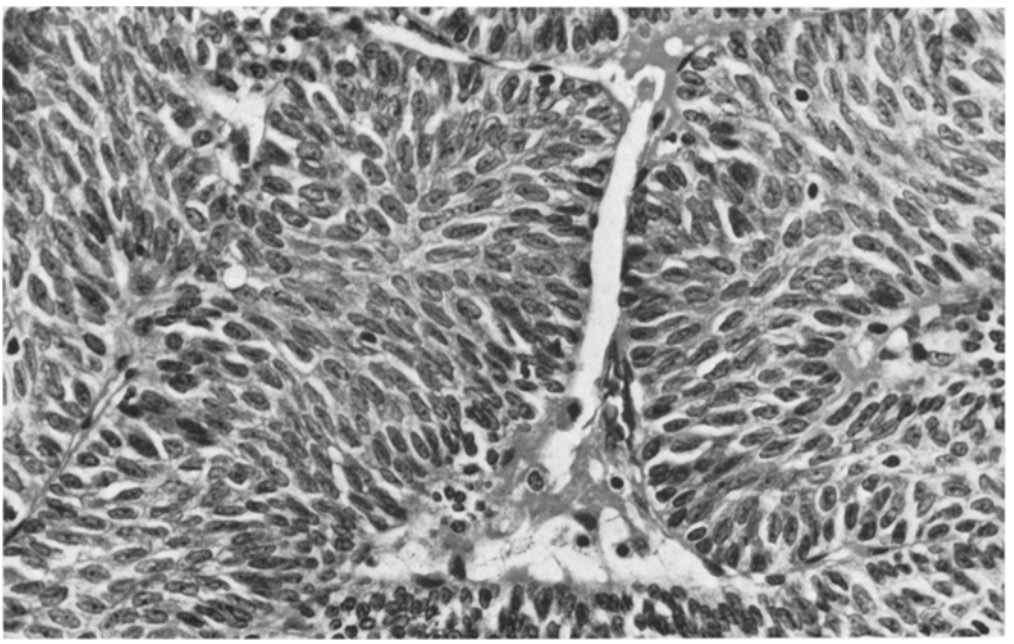

Fig. 3. Detail of cellular morphology of an inverted urinary papilloma. Occasional pyknotic nuclei are present but there are no mitoses. Some nuclei have a longitudinal groove, and at the periphery of the cords there is a suggestion of palisading of cells. Case 4, HE ×400

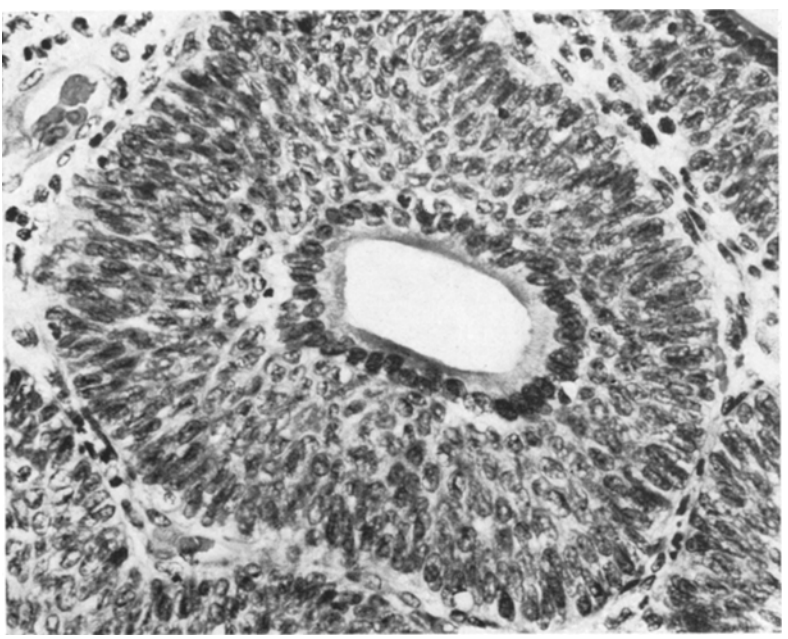

Fig. 4. Columnar cells lining a crypt of an otherwise typical inverted papilloma. Case 1, HE ×400

Table 2. Clinical and pathological data on 13 previously reported cases of inverted urinary papilloma

Author(s)	No. of cases	Age (years)	Sex	Clinical features	Site of papilloma	Gross appearance	Treatment and follow-up
Potts and Hirst (1963)	1	63	M	urinary obstruction	bladder base near internal urethral orifice	smooth, pedunculated tumour $3 \times 2 \times 2$ cm, pedicle 1 cm long and 0.5 cm thick	local excision, prostatectomy. Cystoscopy at 18 months. Clinical observation 11 years (Hirst, 1972). No recurrence
Trites (1969)	3[a]	56	M	haematuria	prostatic urethra	sessile polyp, with a 2.5 cm base	transurethral resection. Cystoscopy at 3 years. No recurrence
		79	M	obstructive urinary symptoms; later haematuria after removal of inverted papilloma	bladder neck region	one fragment in 20 gm of tissue	transurethral resection. Cystoscopy at 1 year 7 months. No recurrence. Carcinoma of prostate
		59	M	haematuria	prostatic urethra	2 cm polypoidal mass with slender stalk	no details
Assor and Taylor (1970)	1	26	M	haematuria, suprapubic pain	apex of trigone	tan-coloured polypoidal lesion with a smooth surface	transurethral resection. Cystoscopy at 5 and 10 months. No recurrence
Borski (1970)	1[b]	45	M	obstructive urinary symptoms	bladder neck	papillary and smooth 2 cm tumour	transurethral resection. Cystoscopy at 6 months. No recurrence
Inada and Ochiai (1971)	1	27	M	intermittent painless haematuria	trigone	pedunculated papillomatous tumour, the size of a small finger	transurethral resection. Observation for 4 years. No recurrence

Sullivan *et al.* (1971)	2	71	M	bladder neck obstruction	bladder neck	piece of tissue covered on one surface by mucosa	local excision, retropubic prostatectomy. Cystoscopy at 3 years. No recurrence
		45	M	haematuria	bladder base	pedunculated solid tumour, $2 \times 1 \times 1$ cm	transurethral resection. Cystoscopy at 3 years. No recurrence
Pienkos *et al.* (1973)	1	46	M	haematuria	trigone distal to left ureteric orifice	pedunculated, avascular, with smooth external surface $1.5 \times 1.5 \times 1.0$ cm	transurethral resection. No details given of follow-up
Cummings (1974)	1	68	M	obstructive urinary symptoms	bladder neck	pedunculated tumour received as 2 smooth-surfaced fragments up to $2.5 \times 1.2 \times 0.5$ cm	transurethral resection. Papilloma predominantly composed of squamous epithelium. Associated prostatomegaly. No follow-up given
Matz *et al.* (1974)	2	68	M	haematuria, loin pain	renal pelvis	pale nodular excrescence 1.5 x 1.2 x 0.4 cm	nephro-ureterectomy. No details of follow-up in original article. Observation for 2 years with no evidence of recurrent tumour or metastases (Matz, 1974)
		75	M	bladder outlet obstruction	bladder neck	2 small papillomas. Pale nodule 0.6 cm in diameter received	transurethral resection. Cystoscopy at 2 years 6 months. No recurrence

[a] The third case was only mentioned in an addendum.
[b] Originally reported as a hamartoma of the bladder.

5 years without evidence of recurrence, and the third has been followed for 3 years with no evidence of recurrence on repeated cystoscopy. Furthermore, Pienkos *et al.* (1973) cited a verbal review of cases seen at the Armed Forces Institute of Pathology in which Price stated that he had seen 13 additional cases of inverted papilloma of the bladder.

The addition of the cases in the present report brings the number of published cases of inverted urinary papilloma to 18 and although this number is still small, certain trends are apparent. The tumours have all occurred in adult males with ages ranging from 26 to 79 years, and with an average of 57 years. Although eight patients presented with haematuria, symptoms of bladder outlet obstruction were the commonest presenting features in our cases, and were seen in a total of 10 patients. The obstructive urinary symptoms were undoubtedly related to the predominant localization of these papillomas to the region of the bladder neck and prostatic urethra; it has been suggested that the pedunculated papillomas in the former site may prolapse into the bladder outlet to produce a ball-valve type of obstruction (Potts and Hirst, 1963). These obstructive symptoms led to a pre-operative diagnosis of prostatism in several patients and at least 3 had a prostatectomy as well as removal of the papilloma (Potts and Hirst, 1963; Sullivan *et al.*, 1971). In fact, some of the patients have had associated prostatomegaly (Cummings, 1974) in keeping with the maximal incidence of inverted urinary papilloma in the middle-aged and elderly. With the probable exception of Case 2 of Matz *et al.* (1974), all of the papillomas have been solitary; these authors described two papillomas in their case, but only one was biopsied, the other being fulgurated. In addition to Case 5 of the present series, in which the inverted papilloma was seen on the left lateral bladder wall, Matz *et al.* (1974), have described a case situated in the left renal pelvis. Similarly, Pienkos *et al.* (1973) mentioned a personal communication from Price recording an inverted papilloma in a renal pelvis, but this case does not seem to have been published. We believe that with increasing recognition of this tumour, inverted papillomas will eventually be described in all areas of the urothelial passages.

At cystoscopy, the diagnosis of inverted urinary papilloma was suggested only by those who had previously seen the tumours (Hirst, 1972). Nevertheless, the gross morphology of this papilloma differs from the exophytic papillary architecture of the usual urothelial neoplasms; the inverted papilloma is typically pedunculated and smooth. As discussed by Hardy and Allen (1972) and Pienkos *et al.* (1973), some cases have been histologically misinterpreted as invasive transitional cell carcinomas, but the architecture is characteristic (Inada and Ochiai, 1971), and can usually be easily recognized in the intact specimen. In our experience, the most important histological features of inverted urinary papilloma are:

1. The inverted configuration, producing a marked similarity to the inverted papillomas of the upper respiratory passages as illustrated by Ash *et al.* (1964) and Snyder and Perzin (1972).
2. A covering layer of urothelium.
3. Uniformity of the epithelial cells.
4. Very infrequent to absent mitoses.

5. Microcyst (crypt) formation.

6. Squamous metaplasia, usually seen as scattered small foci in some papillomas, but which has been described as a dominant feature in one recently published case (Cummings, 1974).

We believe that these criteria for the diagnosis of inverted urinary papilloma should be rigidly applied, otherwise invasive transitional cell carcinomas may equally be misdiagnosed as inverted papillomas, particularly in fragmented specimens where the overall architecture may be difficult to assess.

Potts and Hirst (1963) originally proposed that inverted urinary papilloma was derived from the subtrigonal glands of Home and that it represented a neoplasm rather than the type of hyperplasia described by Emmett and McDonald (1942) affecting the so-called subcervical glands of Albarran. Subsequently some authors have also accepted the entity as a neoplasm, but have proposed a urothelial origin since the occurrence of these papillomas outside the vicinity of the bladder neck is incompatible with an origin from the glands of Home (Trites, 1969). However, 3 separate recent reports have questioned the neoplastic status of inverted urinary papilloma. Pienkos *et al.* (1973) seemed to suggest that the lesion may develop as a result of stimulation of downward proliferation of transitional epithelium by chronic inflammation. Similarly, Matz *et al.* (1974), on the basis of a study of serial sections of their cases of inverted papillomas, have shown that the microcysts are in reality crypts analogous to the nests of von Brunn, and they concluded that the lesion is, in effect, a giant hyperplastic von Brunn's nest.

Even more recently, Cummings (1974) has also suggested that inverted urinary papilloma is an abnormal proliferation of hyperplastic and metaplastic epithelium resulting from inflammation. Although we agree with Matz *et al.* (1974) that inverted urinary papilloma shows features of von Brunn's nests, we consider that the available data do not permit a definite distinction between a neoplastic or hyperplastic status for the lesion and that, for the present, it is best regarded as a benign neoplasm with differentiation towards structures seen in proliferative cystitis.

On histological grounds alone Potts and Hirst (1963) suggested that inverted urinary papilloma is a benign lesion, and they supported this interpretation with a 3-year follow-up of their patient without recurrence. Their case has now been followed for over 11 years and remains free of recurrent tumour (Hirst, 1972). Exophytic transitional cell tumours, even when highly differentiated, have a recurrence rate of approximately 60 to 70 percent (Pyrah *et al.*, 1964; Blackard, 1971). In contrast to these and the inverted papillomas of the nasal cavity and paranasal sinuses, we are aware of no case of inverted urinary papilloma which has recurred after treatment.

Potts and Hirst (1963) recommended that inverted urinary papilloma should be managed by endoscopic resection and fulguration of the base. They further suggested that sessile examples should be treated, after biopsy, by transurethral resection down to muscle. All of the subsequently reported cases, including the 5 which form the basis of this report, support the efficacy of simple local excision, by the transurethral route where possible, and stress the avoidance of unnecessarily radical treatment.

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