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# ORIGINALS

# The Efficacy of Urinary Cytology in the Detection of Urothelial Tumours

## Sensitivity and Specificity of Urinary Cytology

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Summary. The sensitivity and specificity of urinary cytology in the detection of urothelial tumours using voided urine and applying simple smear preparation and staining techniques have been assessed. Of the 2704 patients under investigation 207 had urothelial tumours. The first urine analysis was positive in 66% of the patients with urothelial carcinoma; an additional 23% of the patients showed positive cytology in repeat smears, resulting in a sensitivity of 89%. The efficacy of urinary cytology depends on the tumour type: for grade 2 tumours, 79% were cytologically positive, 92% of grade 3 and 98% of the grade 4 tumours. The diagnostic efficacy in cases of carcinoma-in-situ, squamous cell carcinoma and adenocarcinoma was comparable with that of grade 4 carcinomas. Grade 0-1 tumours did not result in positive cytology. In eleven cases of lithiasis and in two cases of cyclophosphamide therapy the cytological diagnosis was positive but no neoplasm could be established histologically; these represent true false positive diagnoses. Thus, the false positive rate, 13 out of 165, was 7.88% and the false negative rate, 61 out of 207, was 29.4% when grades 0-1 were included, but 8.75% (14 out of 160) when grades 0-1 were excluded.

Key words: Urinary cytology - Urothelial tumours.

Urinary cytology has attained wide acceptance as a routine laboratory investigation for the early diagnosis as well as the follow-up of bladder cancer (9, 19, 20, 25). But like every diagnostic procedure it has its limitations and pitfalls even in the hands of experts using different refined cell collection and smear preparation techniques (8, 10, 14, 30, 31). The present study was undertaken to evaluate the efficacy of urinary cytology using voided urine and applying simple smear preparations and staining techniques, since the published data concerning the reliability of urinary cytology vary greatly (Table 1). We have assessed the sensitivity (the ability to detect patients with cancer) and the specificity of urinary cytology (the capacity to distinguish between patients with cancer and those with non-malignant conditions).

## MATERIAL AND METHODS

During the period 1970-1975, 5495 urine specimens from 2704 patients with a great variety of urothelial lesions were analysed. Patients with carcinoma of the prostate or carcinoma of the kidney were excluded from this analysis. It is clear that the urine of several patients was analysed repeatedly.

### Cytological Techniques

For urinary cytology the whole sample of urine was centrifuged at 2000 rpm for 10 minutes. The centrifugate was divided into three portions, one for a non-permanent smear for Phase Contrast Microscopy, one for a Papanicolaou smear and one for a May-Gruenwald-Giemsa (M. G. G.) smear.

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Table 1. Cytological diagnoses in cases of urothelial cancer

| Author | Total number of cases | Positive histology (grade 2, 3, 4 tumours) | % correct positive cyt. diagnoses | False positive diagnoses (False suspicious in brackets) |
|---|---|---|---|---|
| Papanicolaou, 1945 | 240 | 76 | 71% | 2 |
| Harrison et al., 1951 | 614 | 67 | 100% | 15 |
| Silberblatt, 1953 | 494 | 32 | 81% | 8 |
| Orell, 1969 | 185 | 89 | 55% | 0 |
| Crabbe et al., 1956 | 1800 | 63 | 90% | 10 |
| Foot et al., 1958 | 678 | 131 | 62% | 6 |
| Johnson, 1964 | not mentioned | 165 | 64% | 3 |
| Umiker, 1964 | not mentioned | 28 | 86% | - |
| Schiffer, et al., 1968 | 107 | 43 | 95% | 8 |
| Tsai et al., 1968 | 115 | 27 | 84% | 9 |
| Park et al., 1969 | 524 | 86 | 90% | 2 |
| Puntala et al., 1969 | 157 | 25 | 68% | 5 |
| Harris et al., 1971 | 335 | 20 | 100% | (2) |
| Sarnacki et al., 1971 | 1400 | 453 | 62% | 29 |
| Schoonees et al., 1971 | 163 | 114 | 70% | 0 |
| Forni et al., 1972 | 8249 | 7 | P.S.* | 3 |
| Reichborn, Hoeg, 1972 | 245 | 88 | 85% | 34 |
| Wiggishof, McDonald, 1972 | 153 | 84 | 82% | 0 |
| Esposti, Zajicek, 1972 | 448 | 274 | 78% | (1) |

* P.S.: Population screening.

The cell pellet for the Papanicolaou smear was fixed with Esposti's fixative (10% acetic acid, 48% methanol, 42% distilled water). The cell suspension can be kept overnight in the refrigerator. The cells should remain at least 30 minutes in the fixative but we preferred longer fixation times (up to 12 hours). After fixation the cell suspension was centrifuged for 3-5 minutes at 2000 rpm and the supernatant was decanted. One drop of the sediment was spread evenly over the slide and the smears air-dried in a horizontal position. When the smears were dry (8-10 minutes) they were stained beginning in the haematoxylin bath.

For the M.G.G. smear all the fluid remaining after decanting the supernatant was removed either by aspiration or by blotting the inside of the centrifuge tube with filter paper without touching the sediment. A mixture of equal quantities of Esposti's fixative or 20% albumin was added to the sediment. After 3-10 minutes the cell suspension was centrifuged at 2000 rpm. The supernatant was decanted and one drop was spread evenly over the slide. The smears were air-dried and stained in May-Gruenwald solution for 1-3 minutes, rinsed with buffer solution, stained in Giemsa solution for 12 minutes, rinsed with distilled water, air-dried and mounted. Optimal cell retrieval and nuclear morphology were reached with this method. Great care was taken not to damage the unfixed cells and all contact with formalin vapour was avoided as this destroys the morphology of the cells. It is necessary to replace the supernatant urine by a non-salt containing solution (Esposti's fluid or 20% albumin), to avoid the high hypertonicity of the urine in which the cells are immersed during the last

Table 2. Cytological criteria for atypia and malignancy of Papanicolaou and M. G. G. -stained urothelial cells

| | Atypia | | Malignancy | |
|---|---|---|---|---|
| | Papanicolaou | M. G. G. | Papanicolaou | M. G. G. |
| Nucleoli | Round to oval | Same | Irregular shapes | Same |
| | One macronucleolus | Same | Two macronucleoli | Same |
| | Or two prominent nucleoli | Same | More than two prominent nucleoli | Same |
| Chromatin | Slightly prominent nuclear envelope | - | Very prominent nuclear envelope | Open chromatin structure: "sieve-like" chromatin |
| | Slightly coarse chromatin | No open chromatin structure | Coarse chromatin Irregular distribution of chromatin | Granulated chromatin broad irregular bands |
| Nuclear size and shape | Slightly enlarged nuclei | Same | Giant nuclei | Same |
| | Regular oval (grade 1 tumours) or round | Same | Irregular shapes | Same |
| | Slight anisokaryosis | | Pronounced anisokaryosis and polymorphism | Same |
| Cell polarity and cell crowding | Regular arrangement in cell groups | Same | Irregular arrangement in cell groups | Same |
| | Nuclear overlapping may occur | No nuclear overlapping | Pronounced nuclear overlapping | Same |
| Nucleolus/ nucleus ratio | Large nucleolus in large nucleus (favourable) | Same | Large nucleolus in small nucleus (unfavourable) | Same |

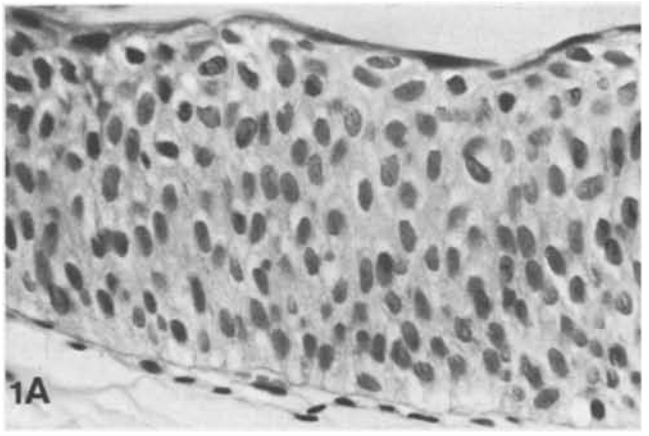
minutes of the drying process, which disrupts the cells completely. The short contact with the alcohol in which the cells are slightly fixed provided further protection for the cells during drying. From the remaining sediment a smear was made of the unfixed sediment for phase contrast microscopy. This preparation was only used to make a provisional diagnosis (34).

The definitive diagnosis was always based on the permanant Papanicolaou and M. G. G. smears.

## Interpretation of the Smears

The smears were reported as follows: (1) negative for malignancy (2) atypical (non malignant) cells are present (3) highly suspicious or positive for malignancy. For the classification of the Papanicolaou smears we used the cytological criteria of atypia and malignancy as described by Koss, 1968 (18); (Table 2, Figs. 1B, 2B, 3B, and 4B).

During the alcohol fixation necessary for the



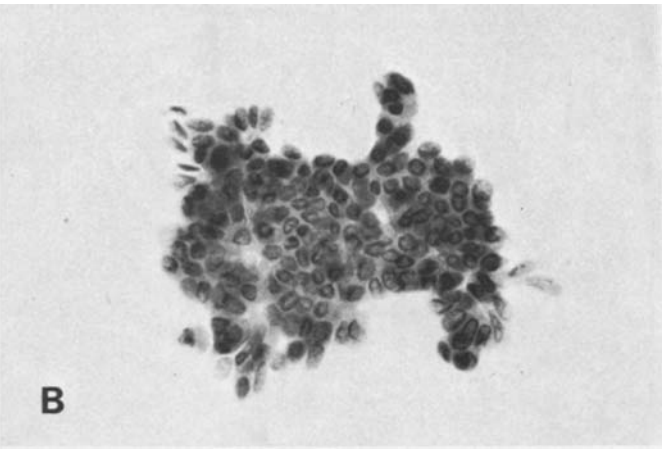
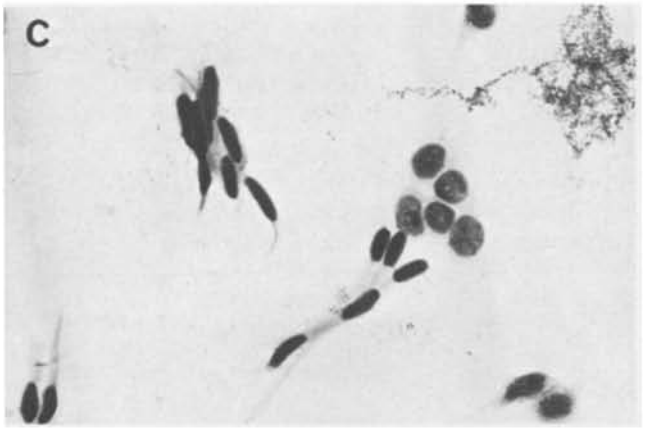



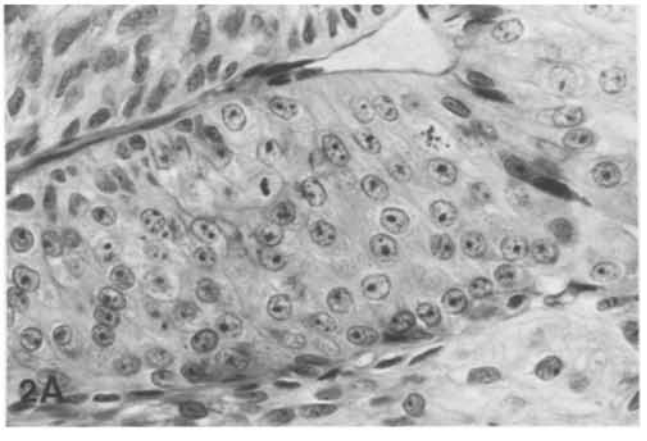

Fig. 1 A-C. Same patient with a grade 1 papillary tumour.

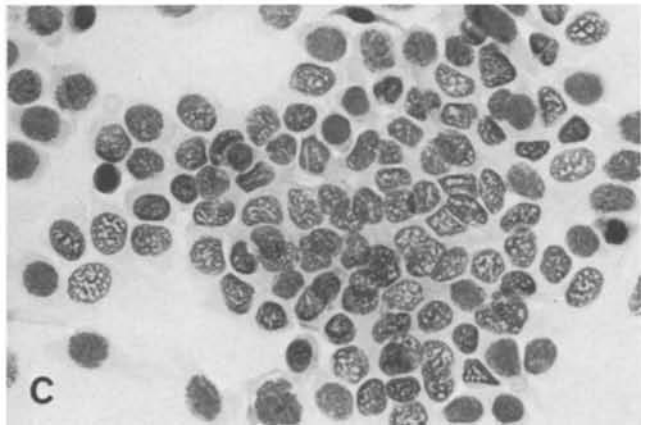
A: Tumour section. The covering epithelium is slightly and irregularly thickened but shows no appreciable deviation. x 350

B: Papanicolaou-stained specimen. Large cluster of cells (tissue fragment). No nuclear overlapping, little anisokaryosis, slightly prominent nuclear envelopes and some what coarse chromatin. x 350

C: M. G. G. -stained specimen. Some cells have oblong nuclei and long cytoplasmic tails. The nuclei of these cells are dark and opaque. x 350



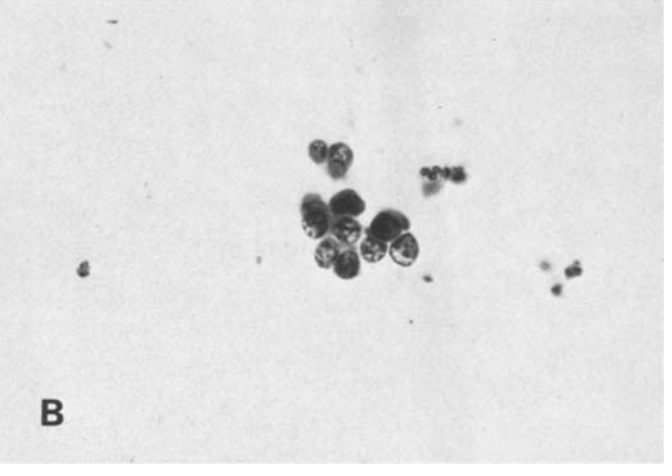
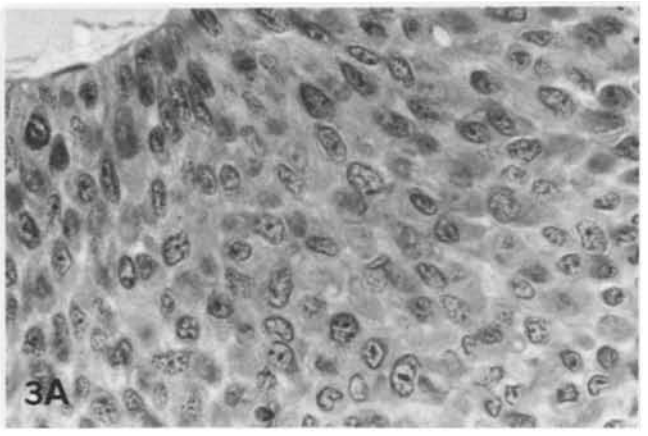



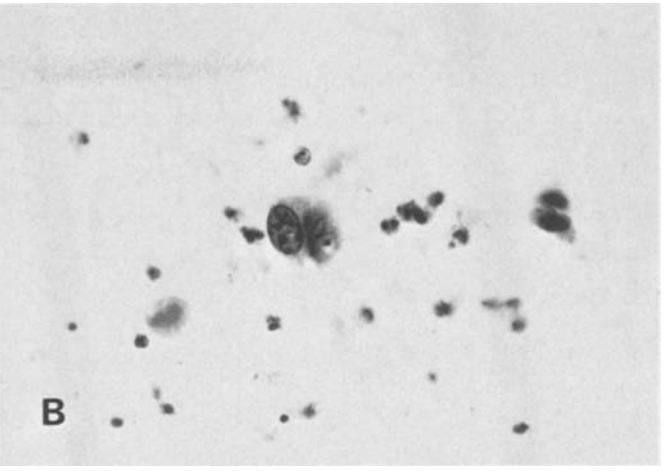

Fig. 2 A-C. Same patient with a grade 2 papillary tumour.

A: Tissue section. Note the large nucleoli and the disorderly arrangement of the nuclei. Two mitotic figures are present. x 350

B: Papanicolaou-stained specimen. Prominent nuclear envelope and irregular distribution of the chromatin. x 350

C: M. G. G. -stained specimen. "Open" nuclei with "sieve like" chromatin. x 350



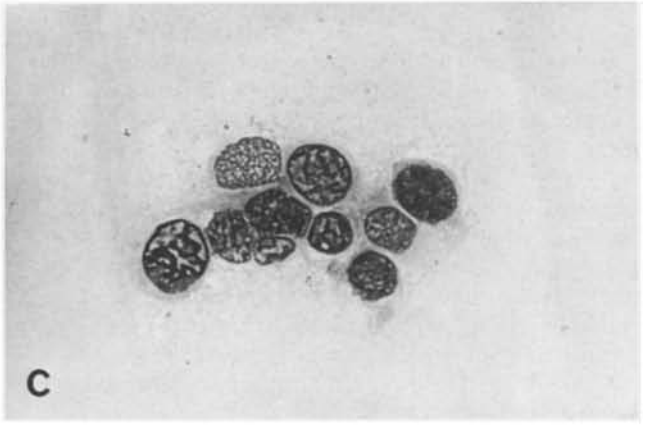
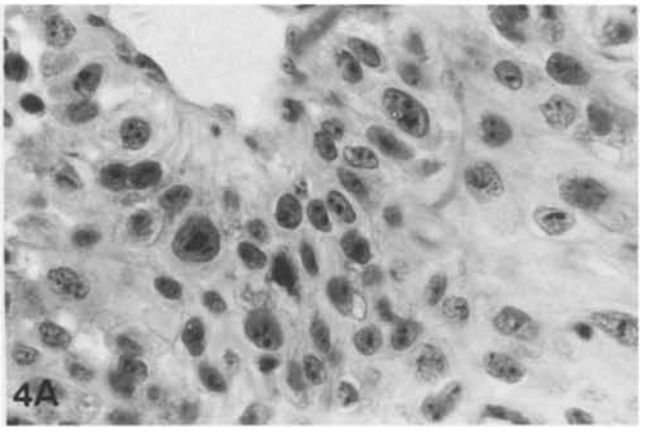



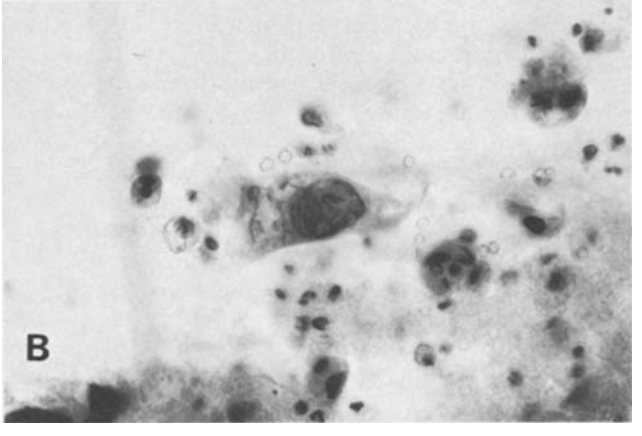

Fig. 3 A-C. Same patient with a grade 3 papillary tumour.

A: Tissue section. The cellular abnormality is considerable. Abnormal nuclear shapes are observed. x 350

B: Papanicolaou-stained specimen. Coarse chromatin and two macronucleoli. x 350

C: M. G. G. -stained specimen. Note the irregular broad bands in the nuclei. x 350



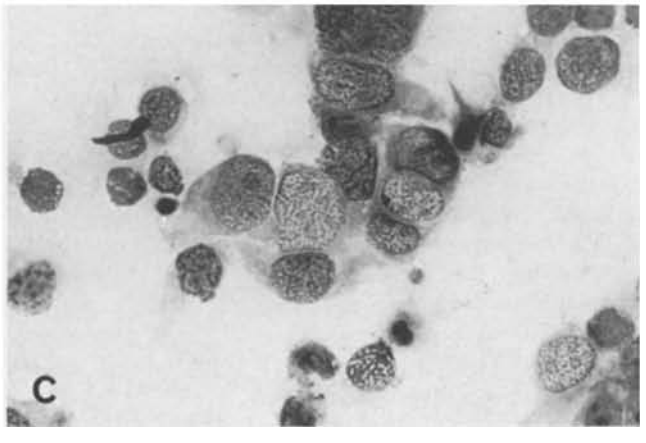




Fig. 4 A-C. Same patient with a grade 4 tumour.

A: Tissue section. The cells show marked anaplasia and many mitoses. x 350

B: Papanicolaou-stained specimen. Giant nucleus with abnormal chromatin pattern. x 350

C: M. G. G. -stained specimen. Granular appearance of nuclei and marked anisokaryosis. x 350

Table 3. Localization of urothelial carcinomas

| | |
|---|---|
| Bladder | 130 |
| Bladder + renal pelvis + ureter | 6 |
| Bladder + renal pelvis | 4 |
| Bladder + urethra + ureter | 1 |
| Bladder + ureter | 4 |
| Bladder + urethra | 4 |
| Renal pelvis | 3 |
| Renal pelvis + ureter | 5 |
| Urethra | 3 |
| Total | 160 |

Papanicolaou stain the nuclei shrink, which makes it difficult to study the chromatin structure of small nuclei. "Cannon ball" cell groups do not flatten out in the smear, thus optimal staining of each nucleus in the group is impossible. Nuclear overlapping cannot be used as a diagnostic criterion, because this is also seen in alcohol-fixed cell clusters from grade 1 tumours.

The nuclear texture of M. G. G. -stained cells differs greatly from Papanicolaou-stained cells. The chromatin pattern of malignant M. G. G. -stained nuclei can be "open", with sharp contrast between the evenly distributed meshwork of threads and the background staining of the nuclear material resulting in a sieve-like appearance (Fig. 2C). The distinction between the light and dark areas in atypical cells is more subtle and the distribution of these areas is not as regular as in malignant nuclei (Fig. 1C). Other nuclear patterns observed in M. G. G. -stained malignant urothelial cells include broad irregular darkly stained bands (Fig. 3C) and a granular distribution of chromatin (Fig. 4C). With the M. G. G. method the cells do not shrink during alcohol fixation but are spread out over the entire glass surface. The nuclei are so much larger that a cytologist used to the Papanicolaou method is tempted to speak of "blown-up nuclei". Thus even in relatively small nuclei the chromatin structure is exquisitely revealed. The thick "cannon ball" cell groups flatten out at the outer border: the peripheral nuclei can therefore be analysed. Nuclear overlapping in M. G. G. -stained specimens has been seen in our laboratory exclusively in cases of urothelial carcinomas and not in grade 1 tumours or inflammatory reactions.

The Papanicolaou and the M. G. G. method often supplement each other. In some cases it is easier to reach the diagnosis in the Papanicolaou smear, in other cases the M. G. G. specimen offers more diagnostic information.

## Histological Evaluation

If atypical or malignant cells were seen, the clinical and histological diagnosis was ascertained. The urothelial tumours were histologically classified as papillary tumours grade 0, 1, 2, 3 and 4 (Bergkvist's classification, 3) (Fig. 1A, 2A, 3A, and 4A), carcinoma-in-situ, squamous carcinoma and adenocarcinoma. As papillary tumours grade 0 are rare, we have grouped them with the grade 1 tumours. In the Bergkvist classification grade 0 and 1 papillary tumours are considered as benign; grade 2, 3 and 4 tumours as malignant. The grade 1 tumours correspond with transitional cell carcinoma grade 1 of the WHO classification (36); the grade 2 tumours with transitional cell carcinoma grade 2 and the grade 3 tumours with transitional cell carcinoma grade 3. For those patients with a recurrent tumour only the latest histological report was taken into account, because we have found that in general recurrent tumour is graded higher than the preceeding one. The histological diagnosis was always within one year of the first cytological examination.

## RESULTS

Of the 2704 patients under investigation, 207 appeared to have a urothelial tumour; 47 of these patients had papillary tumours grade 0 or 1 according to Bergkvist's classification (3). The localization of the remaining 160 urothelial tumours is given in Table 3. Table 4 indicates the histological classification of the 207 detected tumours and the results of the repeated cytological urine analyses. It shows that the first urine analysis was positive in 106 of the 160 patients with an urothelial carcinoma (66%) and that in an additional 23% cancer cells were found in repeat smears.

The histological and clinical diagnoses for the 165 patients with a positive cytological report are given in Table 5. The great majority of these patients had an urothelial tumour, 11 had calculi and four were under treatment with cyclophosphamide. In four cases no follow-up or histology was available. Of the four patients treated with cyclophosphamide two died from lymphosarcoma and Hodgkin's disease; the other two patients (one with Kahler's disease and one

Table 4. Relationship between positive cytological report and histological grading and differentiation, Leyden University Hospital, 1970-1975

| | Total cases | 1st spec. pos. | 2nd spec. pos. | 3rd spec. pos. | >3rd spec. pos. | Total pos. |
|---|---|---|---|---|---|---|
| Grade 0-1 tumour | 47 | 0 | 0 | 0 | 0 | 0 |
| Grade 2 tumour without infiltration | 3 | 3 | - | - | - | 3 |
| Grade 2 tumour with infiltration | 35 | 10 | 14 | 1 | 2 | 27 |
| Grade 3 tumour | 53 | 36 | 11 | 2 | - | 49 |
| Grade 4 tumour | 41 | 35 | 3 | 2 | - | 40 |
| Carcinoma-in-situ | 16 | 11 | 4 | 1 | - | 16 |
| Squamous carcinoma | 8 | 8 | - | - | - | 8 |
| Adenocarcinoma | 4 | 3 | - | - | - | 3 |
| | 207 | 106 | 32 | 6 | 2 | 146 |

The data of the first two columns were subjected to a $\chi^2$ test for the contingency table: $\chi^2 = 34.8$ DF = 6. The adenocarcinomas and squamous carcinomas were grouped together. The result is highly significant ($p<0.0001$). The rate of detection of tumours of grade 2, grade 3 and grade 4 differ. The difference between grade 4 carcinomas and the combined cases of carcinoma-in-situ, squamous cell carcinoma and adenocarcinoma (all with a known high exfoliation rate) was not significant.

with Brill-Symmers disease) developed infiltrative bladder cancer during the course of their disease. The "malignant cells" in the patients with lithiasis disappeared following removal of the stones.

The analysis of 155 patients with atypical cells in the first urine specimen examined is given in Table 6. It is clear that atypical urothelial cells may be present in a great variety of conditions. In 69 patients (45%) tumour was detected within one year after the first urine analysis: 19 papillary tumours grade 1 and 50 urothelial carcinomas (Table 3). In 14 of these 50 patients repeat smears showed only atypical cells; 36 became cytologically positive. In the 19 patients with grade 1 papillary tumours cytology reflects the histology. In 86 patients (55%) no tumour growth was found during follow-up; in the majority of these cases the cytology returned to normal after the underlying condition had been treated successfully.

## DISCUSSION

From the results of this investigation (Table 4, Fig. 5) it is obvious that the efficacy of urinary cytology in detecting urothelial tumours varies with the histological grade of the tumour and the number of specimens examined. Malignant cells were never found in the urine of patients with papillary tumours of grades 0-1 (Fig. 5). The diagnostic efficacy in cases of carcinoma-in-situ, squamous carcinoma and adenocarcinoma is comparable with that of grade 4 papillary tumours. The malignant cells in these more anaplastic tumours are larger and more abnormal than in the better differentiated tumours so that they are easier to identify as cancer cells. From Table 4 it is evident that it is helpful to repeat the test, especially in cases of grade 2 tumours.

The diagnostic efficacy can be quantified by calculating the sensitivity of the test, expressed as the number of true positives divided by the sum of true positives and false negatives. The sensitivity of the test to detect any urothelial tumour in the first urine specimen is 51%. If the grade 0-1 tumours are excluded the sensitivity is 66%; this increases to 89% if three samples are investigated. The effect of repeated tests on the yield of detected tumours has also been found by Chute and Williams and other authors (4, 23, 27). It is, however, possible that this latter increase is partly due to the development of a tumour or growth of

Table 5. Histological and clinical diagnosis of 165 cases with positive cytological findings

| | |
|---|---|
| Carcinoma of the urinary tract | 146 |
| Urinary calculi | 11 |
| No follow-up | 2 |
| No histology | 2 |
| Cyclophosphamide therapy | 4 |
| Total | 165 |

Two of the four patients treated with cyclophosphamide developed urothelial cancer: the relative proportion of true positives and false positives is 146/13 (11 lithiasis patients and two patients treated with cyclophosphamide).

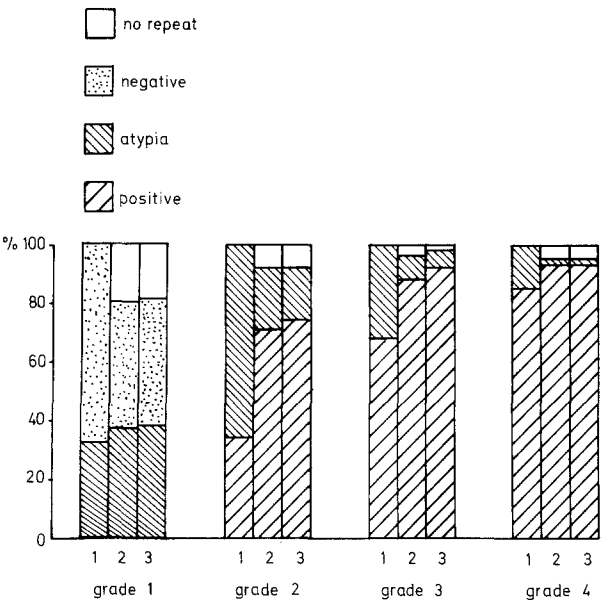



Fig. 5. A-C. Rise of diagnostic efficacy with repeat specimens. 47 patients with grade 0-1 tumours, 38 patients with grade 2 tumours (3 without infiltration), 53 patients with grade 3 tumours, 41 patients with grade 4 tumours

Table 6. Clinical and histological diagnosis of 155 patients when the cytological diagnosis of the first urinary sediment is "atypia"

| | |
|---|---|
| Papillary tumors grade 1 | 19 |
| Carcinomas, including grade 2, 3 and 4 tumors | 50 |
| Irradiation effect | 15 |
| Cyclophosphamide therapy | 10 |
| After TUR, no atypical cells in next specimen | 6 |
| Chronic cystitis | 20 |
| Urinary calculi | 7 |
| Hypertrophy of the prostate | 8 |
| Phenacetin abuse with kidney damage | 1 |
| Atypical hyperplasia of transitional epithelium | 2 |
| Cystic kidney | 1 |
| Urine from ileal segment | 2 |
| Unknown reason | 14 |
| Total | 155 |

an already existing tumour in the period between the first and the third urine samples which was a maximum of one year. The specificity of the tests is also high. This can be calculated by dividing the number of true negatives by the sum of true negatives and false positives. If we consider the test as a method to identify exclusively malignant tumours then the specificity is over 99%.

Urinary cytology proved to be ineffective in the detection of grade 0-1 papillary tumours. We found that the specimens of these patients may show abnormally high cellularity, cell clumps and numerous cells with elongated nuclei and nuclear atypia (6, 14, 17). However, we also encountered these changes in a variety of non-malignant conditions.

The presence of atypical cells in the urine of patients previously treated for an urothelial tumour is a separate problem. We agree with Reichborn-Kjennerud and Hoeg (25) that this is likely to indicate the development of a recurrent tumour and on occasion it is diagnosed cytologically long before it is seen at cystoscopy.

In 19 of the 47 patients with grade 0-1 tumours atypical cells were found. If we consider the presence of atypical cells as an indication of the presence of a papillary tumour grade 0-1, the diagnostic sensitivity for our material is 40%. These results concur with those of

Johnson (16) who investigated 65 patients with grade 0-1 tumours; in ten patients he found "suspicious cells" and in 36 patients "atypical cells", while 29 were reported as negative. There is complete agreement with the findings of Esposti et al. (9, 10), who could not detect malignant cells in any of their patients with a grade 0-1 tumour. Crabbe et al., however, (7) in their study concerning dyers, described 15 patients with histologically benign papillomas who had positive cells in their urine.

Our findings suggest that the presence of cells with the classical features of a malignant cell in non-malignant conditions is rare, which means that the test has a high specificity if the criteria enumerated in Table 2 are used. We only found cells indistinguishable from cancer cells in patients with urinary calculi and those treated with cyclophosphamide. Radiation and inflammation never induced changes resembling those in malignant cells, contrary to Cowen's report (5).

To a certain extent sensitivity and specificity are contradictory. If one aims for a high sensitivity the specificity decreases. This is one of the reasons why evaluation of published data concerning the reliability of the test is so difficult (Table 1). Absolute discrimination between atypical and malignant cells may be impossible but to strive for this separation may result in the detection of true malignancies on the one hand and on the other hand of a multitude of pre-malignant lesions, some of which may progress to cancer, such as phenacetin or calculi induced atypia, chronic cystitis and hyperplasia of the urothelium (2, 7, 19).

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