

# The Effect of Calculi on Transitional Epithelium

## A Clinical and Cytological Study

F. de Ruiter\*, M. E. Beyer-Boon, and H. J. de Voogt

The Departments of Urology and Pathology, University Hospital, Leiden, The Netherlands

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**Summary.** An analysis has been made of the 9 false-positive cytologic diagnoses in 4 000 samples of urine from 1 500 patients. They could be traced to 23 patients who had stones in their urinary tract. After removal of the stones the urinary cytology became negative. Thorough clinical examination excluded malignancy. The histological findings in one of these patients offers a possible explanation for the exfoliation of malignant cells and gives support to the hypothesis that stones can cause reversible changes of the urothelium with the appearance of a malignancy. A causal relationship between stones in the urinary tract and the development of urothelial cancer could not be established.

**Key words:** Urinary cytology, stones, urothelium.

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### Introduction

Though irritation and even damage of the urothelium by stones can be assumed by the appearance of erythrocytes in the urine, little is known about the effect of stones on the epithelial cells.

Since the introduction of urinary cytology as a routine diagnostic procedure this method has proved to be valuable for detection and follow-up of urothelial cancer. At the same time however, it became clear that other, non malignant lesions of the urothelium can exfoliate atypical cells which can confuse the inexperienced observer. When malignant cells are found in the urine it is our policy to examine the patient very thoroughly for urothelial malignancy and to follow up carefully.

However despite such intensive analysis, in a few cases malignancy could not be detected and we decided to analyse these "false-positive" cases further. To our surprise all patients appeared to have stones in the urinary tract at the moment of exfoliation of atypical cells.

### Material and Methods

During the period 1970-1974 some 4 000 samples of urine from 1 500 patients attending the department of urology were examined cytologically. Among these samples were those from 23 patients who had microscopic or gross hematuria and who appeared to be suffering only from stones in the urinary tract.

In the urinary sediment from 13 of these 23 patients atypical cells were found on one or more occasions, some of which were very suspicious of malignancy. Despite intensive clinical examination, in none of the 23 patients could a malignancy be found.

All samples of urine were examined in the way we described earlier (de Voogt 1973). Most of the samples were fresh-voided urine, but some of them were taken by catheterization. Every sediment was immediately examined by phase-contrast-microscopy and thereafter smears were made for staining as described by Papanicolaou and Giemsa. All cytological diagnoses were made according to the classification of Papanicolaou. Cytological criteria for malignancy were derived from the work of Kalnins et al. (1970).

Atypia classification III (Papanicolaou) is recorded when the smears show: 1) predomin-

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\* present address: St. Lucas Hospital, Apeldoorn

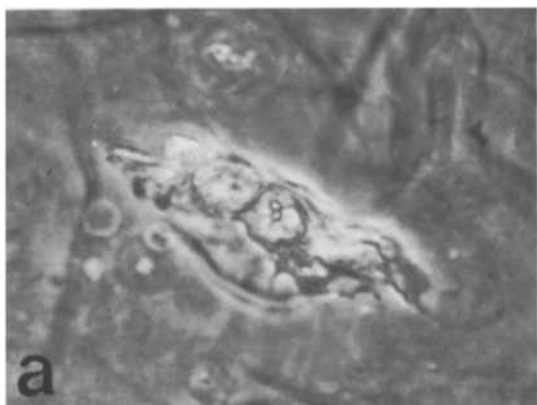


Fig. 1

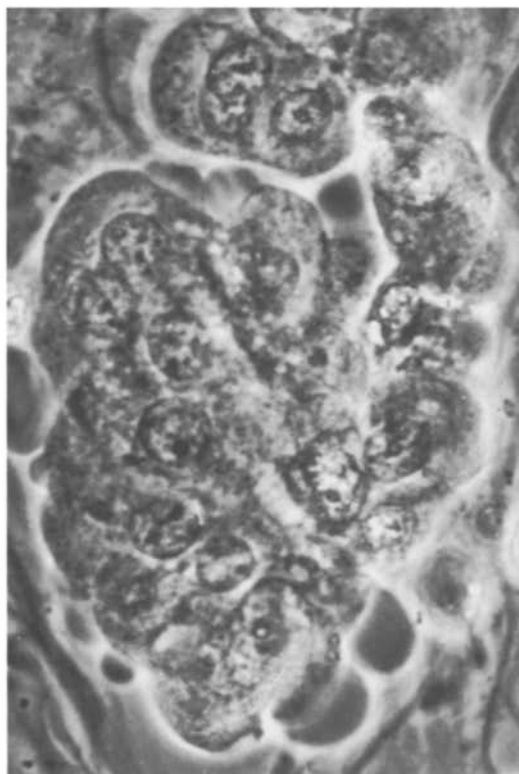


Fig. 2

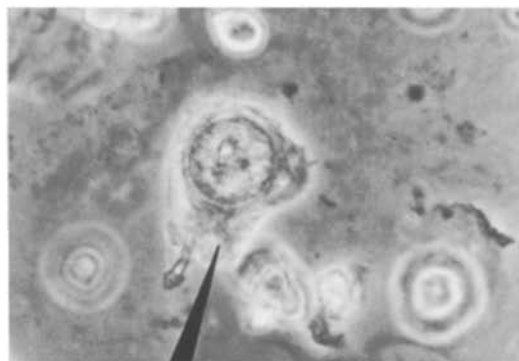
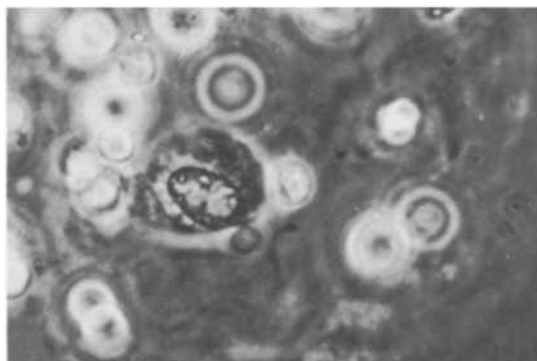


Fig. 3

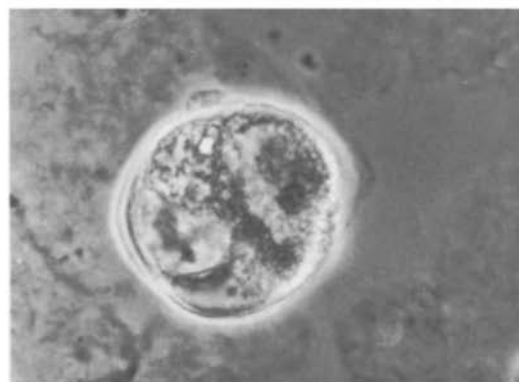


Fig. 4

Fig. 1. Multinucleated cells. a. with only slight atypia; b. with severe atypia

Fig. 2. Cluster of transitional cells with atypia

Fig. 3. Two cells, which are suspicious of malignancy (Cl. IV. Pap.)

Fig. 4. Two cells with definite malignant appearance

All cells from Fig. 1-4 are from patients suffering only from stones in the urinary tract. Phase contrast 400 x

antly single epithelial cells with an increased nuclear-cytoplasmic ratio; 2) some variations of nuclear size; 3) single small nucleoli; and 4) some abnormality of chromatin structure, (Figs. 1 and 2). The diagnosis "suspect or positive for malignancy" (cl. IV-V Pap.) is made when single cells or cell clusters show: 1) large nuclei with variations in size and shape; 2) abnormalities of structure, staining intensity and distribution of chromatin; and 3) large and multiple nucleoli, (Figs. 3 and 4).

In many normal as well as abnormal smears, cells with two or more nuclei were seen.

During the same period 18 patients were treated for carcinoma of the renal pelvis and ureter. The case-histories of these patients were re-examined.

## Results

Of the 23 patients, 18 were men and 5 were women. Their ages varied from 47 to 87 years. The localization of the stones in their urinary tract is given in Table 1.

In 10 patients stones were passed spontaneously or removed surgically. On chemical analysis

all stones proved to be predominantly calcium oxalate.

Of these 10 patients 4 remained free of stones and on regular cytological follow-up (for 6 to 18 months) no more atypical cells were found in their urine (Table 2). The other 6 patients, after a stone-free interval redeveloped stones but in only one of them was there a recurrence of a classification IV cytologic diagnosis. This was a patient with medullary sponge-kidneys and multiple stones in the cysts which were passed at irregular intervals (Table 3).

Of the remaining 13 patients, where stones were not removed or passed, 3 showed atypical or positive cytology on one or two occasions but on repeated examinations this could not be confirmed. Nine patients had negative cytology, even though bi- or multinucleation was noted in nearly all of them.

In one of the patients with positive cytology, a filling defect in the contrast in the left distal ureter was seen on I. V. P. Because of the repeated positive cytology (Fig. 5) a ureteric tumor was suspected and it was decided to operate. The distal ureter was excised and reimplantation of the ureter in the bladder performed.

In the excised portion of ureter the pathologist found a very small calcium oxalate stone, which had escaped X-ray detection. The histological report first described the ureteral wall as showing ureteritis with fibrosis but, on serial sections and re-examination, the pathologist could not exclude carcinoma-in-situ (Fig. 6).

During 5 years of follow-up, the patient never again had positive cytology, nor did a carcinoma in his urinary tract develop. However, he did get two more stones.

## Discussion

A total of 9 "false-positive" cytological diagnoses of malignancy and 4 of atypia was made in 13 of 23 patients who appeared to be suffering only from stones in the urinary tract. The

Table 1. Localisation of stones in urinary tract

Number patients	Renal calyces	Renal pelvis	Ureter	Bladder
4	+	-	-	-
1	+	+	-	-
2	+	-	+	-
1	+	-	-	+
6	-	+	-	-
7	-	-	+	-
2	-	-	-	+

Table 2. Cytologic follow up of patients after removal or passage of stones

Number patients	Cytology before	Passed spontaneously	Removed surgically	Cytological control	Follow up
1	Positive	Ureteric stone	-	Negative	13 months
1	Positive	-	Ureteric stone	Negative	9 months
1	Positive	-	Renal pelvis stone	Negative	18 months
1	Positive	-	Bladder stone	Negative	6 months

Table 3. Cytologic control of patients in which stones were removed but where stones redeveloped

Number patients	Cytology before	Passed spontaneously or removed surgically	Cytological control	Still present	Follow up
1	Atypical	Renal pelvis stone	Negative	Calyceal stone	
1	Atypical	Ureteric stone	Negative	Calyceal stone	16 months
1	Atypical	Calyceal stone	Negative	Calyceal stone	18 months
1	Atypical	Calyceal stone and ureteric stone	Negative	Calyceal stone	14 months
1	Positive	Bladder stone	Atypical	Calyceal stone	6 months
1	Positive	Calyceal stone	2x neg. , 1x pos.	Calyceal stone + Renal pelvis stone	4 years

Table 4. Patients where stones were not removed

Number patients	Localisation stone	Cytology	Follow up
9	Calyceal stone Renal pelvis stone Ureteric stone	Negative	
2	Renal pelvis stone Ureteric stone	Atypical- later neg. Atypical- later neg.	10-17 months
2	Calyceal stone	4 x positive 7 x negative	5-11 months

histological changes in the ureteral wall of one of these offer a possible explanation for the exfoliation of suspicious cells into the urine. Only by repeated cytology and intensive clinical examination could malignancies be excluded.

It is well-known that non-malignant diseases of the urinary pathways can exfoliate atypical cells into the urine. Umiker (1962) calls attention to the difficulty of differentiating between atypical cells from a malignancy and those exfoliated in a patient with inflammation of or a stone in the urinary tract. In 1964 he mentions stones, benign prostatic hypertrophy, irradiation and hormone treatment as causes for cellular atypia. Forni (1964) indicates that cell atypia may occur in patients treated with chemotherapy. Taylor (1963) and Tyrrkö (1972) write about atypia caused by stones and the same is done by Wiggishof, Mac Donald (1969) and Esposti (1970).

Usually the urothelial cells in patients with inflammation, irradiation or hormone treatment can be characterized by the cytologist as

atypical, but distinctly different from malignant cells. Only the inexperienced observer might be confused. The same can be said of bi- or multinucleation of cells which can be caused by all forms of irritation but which in our experience is seen most often after catheterization. In our material only the use of cytostatic drugs and the presence of stones in the urinary tract caused the exfoliation of cells which even an experienced cytologist could not distinguish from cells exfoliated by a malignant tumour. The question arises whether a stone in the urinary tract predisposes to the development of a malignancy of the urothelium. Dunham (1968) has pointed out for example that it is seldom possible to tell whether a bladder stone causes a bladder tumour or vice-versa.

We re-examined the case-histories of 18 patients who were treated for tumours of the renal pelvis or ureter in the same period. In 16 patients neither their history nor their pre-operative examinations revealed the presence of stones in their urinary tract. One patient passed

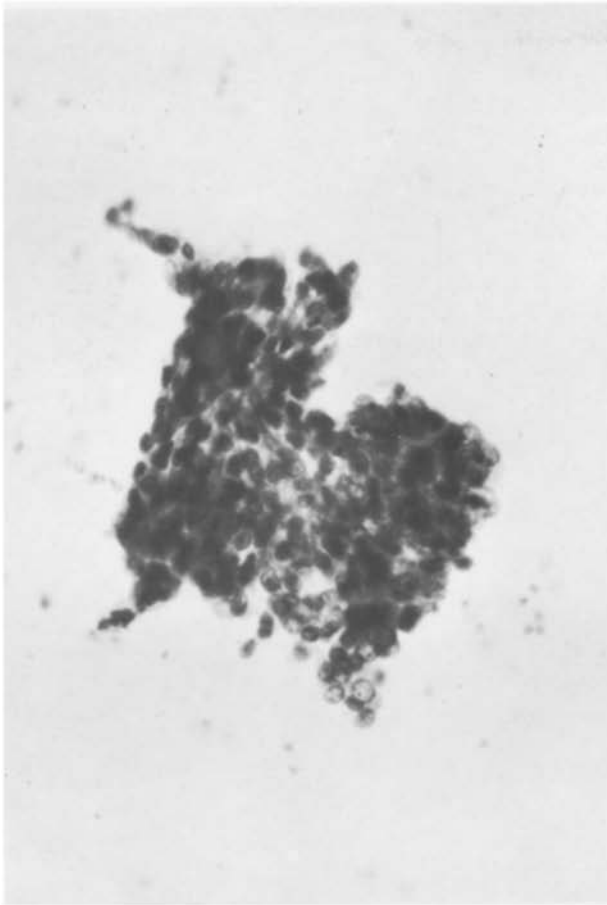


Fig. 5. Cluster of cells with irregular arrangement, polymorphic nuclei and hyperchromatism. Pap. stain 400 x

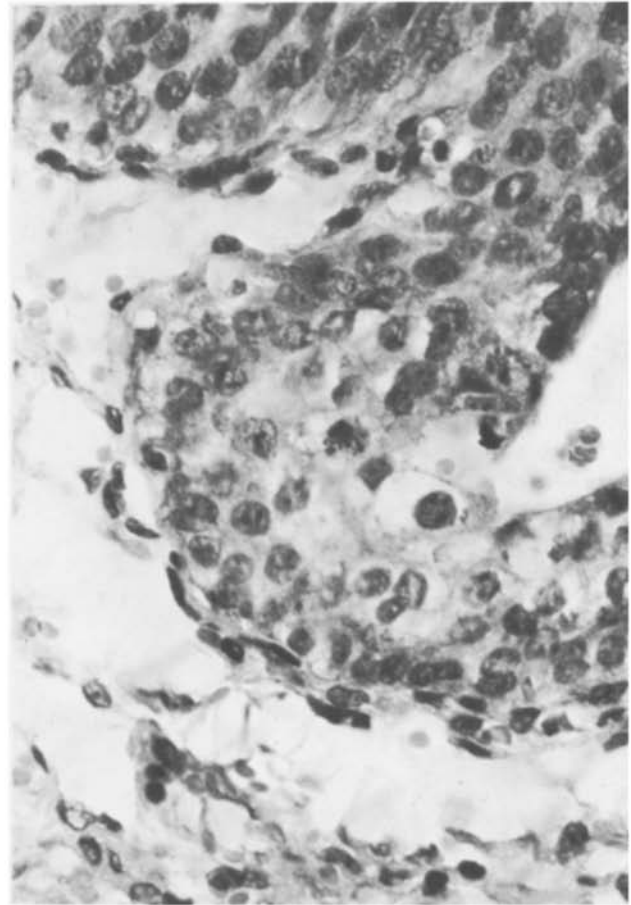


Fig. 6. Histology of ureter from same patient as Fig. 5. Note intraepithelial atypia with several mitoses. The picture of ca-in-situ. H.E. stain 400 x

a calcified necrotic papilla before a tumour was diagnosed. Another patient had a calcified tumour of the renal pelvis which probably shed a fragment of it spontaneously some years earlier. It was regrettably discarded as a small ureteric stone.

Since none of the stone-patients which we followed for up to 5 years developed a urothelial tumour, we were not able to establish any causal relationship between stones in the urinary tract and the development of urothelial cancer. It is, however, quite possible that stones can cause reversible changes of the transitional epithelium, as seen in the patient described above.

Usually the diagnosis of stones in the urinary tract is not difficult to make. The results of cytology in these cases should however be regarded with extreme caution.

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- F. de Ruiter, M.D.  
St. Lucas Hospital  
Apeldoorn, The Netherlands