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ORIGINAL INVESTIGATION

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Trisomy 7 in non-neoplastic tubular epithelial cells of the kidney

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Abstract The cellular origin of trisomy 7 in non-neoplastic kidney tissue specimens from 10 patients, seven with malignant tumors and three with non-neoplastic kidney diseases, was studied by the MAC (morphology antibody chromosomes) technique, which allows analysis of cellular morphology/histology, immunophenotype, and chromosomal aneuploidy by conventional cytogenetics, and/or fluorescent in situ hybridization in both interphase and mitotic cells. In primary cultures, trisomy 7 was detected primarily in cytokeratin-positive cells. Among freshly isolated renal cells, the trisomy was mainly observed in proximal tubular cells positive to brush-border antigen, and, to a lesser extent, in distal tubular cells positive to Tamm-Horsfall glycoprotein. The frequency of trisomy 7 in lymphocytes expressing CD3 or CD22 antigens isolated from non-neoplastic and tumor tissues was substantially lower than in the epithelial cells and was not increased compared with that in control lymphocytes from peripheral blood. The results thus demonstrate that the non-neoplastic kidney cells with trisomy 7 are mainly normal epithelial cells, preferentially those of the proximal tubule.

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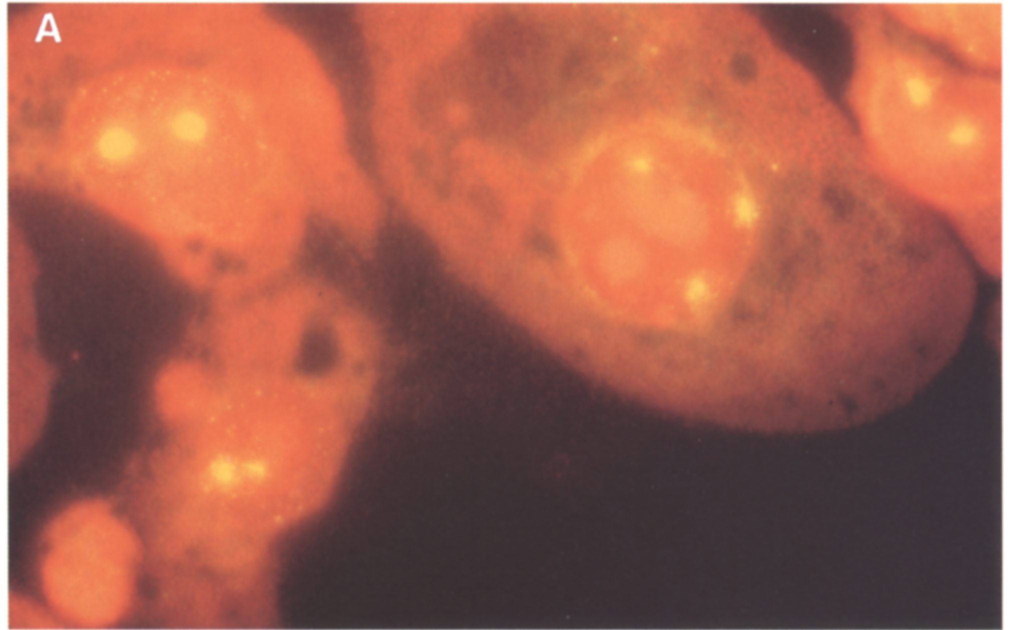
Introduction

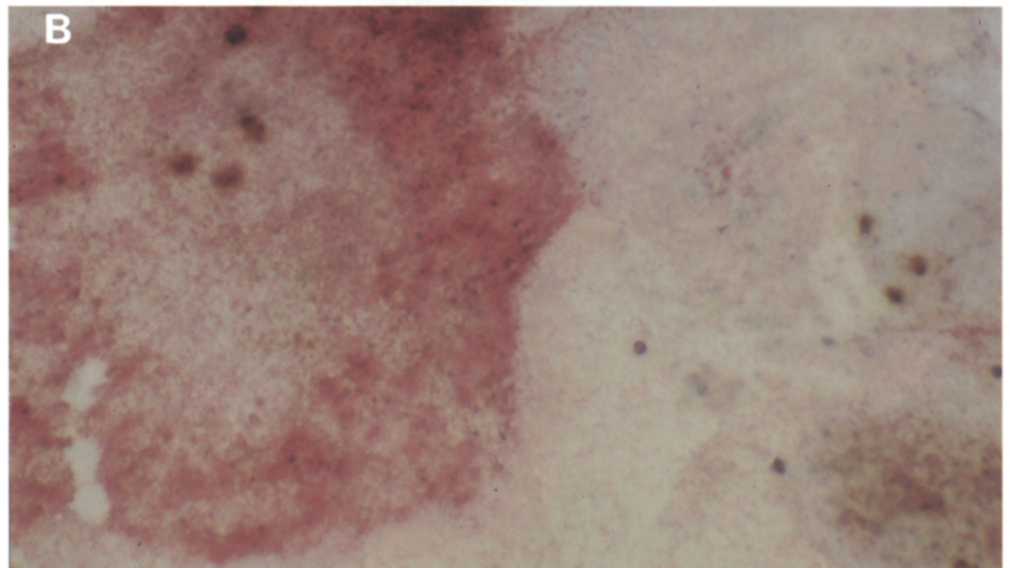
Trisomy 7 has been reported in tumors of the bladder, brain, kidney, colon, lung, ovary, prostate, and thyroid, in normal brain, kidney, liver, lung, and placenta, and in non-neoplastic lesions/disorders, such as atherosclerotic plaques, Dupuytren's contracture, Peyronie's disease, gliosis, and rheumatoid and pigmented villonodular synovitis (Becher et al. 1983; Ochi et al. 1983; Gibas et al. 1986; Lee et al. 1987; Somers et al. 1987; Bigner et al. 1988; de Jong et al. 1988; Delozier-Blanchet et al. 1988; Wurster-Hill et al. 1988; Heim et al. 1989; Kovacs and Brusa 1989; Tiainen et al. 1989; Babu et al. 1990; Elfving et al. 1990; Ikeuchi et al. 1990; Teyssier et al. 1990; Vanni et al. 1990; Tharapel et al. 1991; Bardi et al. 1992; Dal Cin et al. 1992; Emanuel et al. 1992; Fletcher et al. 1992; Ermis et al. 1993; Mertens et al. 1993; Moertel et al. 1993). Recently, Dal Cin et al. (1992) reported that the trisomic cells observed in non-neoplastic kidneys may be T lymphocytes. Elfving et al. (1995), however, could not confirm these findings. To resolve these controversial results, we adopted the MAC (morphology antibody chromosomes) methodology for normal and malignant kidney cells. The MAC technique allows the study of cellular morphology/histology, immunophenotype and chromosomal aneuploidy in both interphase and mitotic cells (Knuutila et al. 1994).

Materials and methods

Tissue

Kidney tissues were obtained at surgery from seven patients with malignant renal tumors and from three patients with non-neoplastic kidney diseases (Tables 1, 2). From all tumor patients, tissues were taken from a macroscopically normal part of the kidney at a distance of about 5 cm from the tumor. From four tumor patients (nos. 7–10), additional samples were taken from the tumor and from the area surrounding the tumor. Each sample was divided into two parts, one of which was frozen in liquid nitrogen and stored at –80°C for tissue sections, the other being used for cell suspensions. Cytospin preparations processed as described below were made from peripheral blood of six healthy persons aged 18 to 47 years.





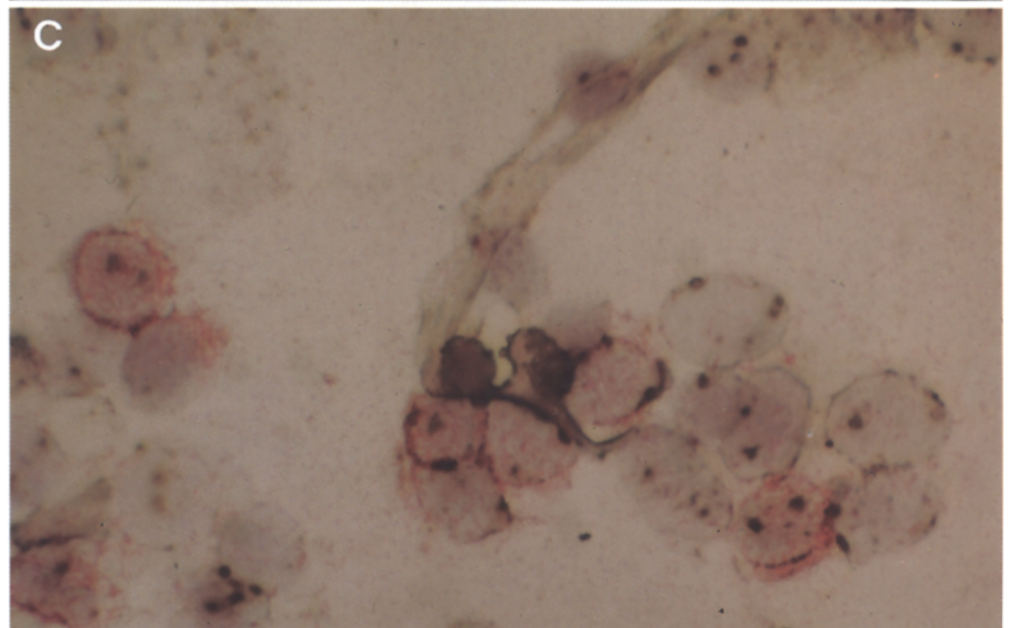


Fig. 1 **A** Epithelial cells from an in situ culture preparation from patient 2. Trisomic cell in the *center*. The preparation was hybridized using the chromosome-7-specific probe pa7tl and detected with an FITC fluorochrome. **B** Cytokeratin-positive (*left*) and cytokeratin-negative cells with trisomy 7 on an in situ culture preparation from patient 1. APAAP immunostaining. Probe detection by DAB/H_2O_2 precipitation reaction. **C** CD3-positive and CD3-negative cells with disomy and trisomy 7, respectively, on a cytospin preparation of magnetically sorted cells from patient 6. APAAP immunostaining and DAB/H_2O_2 probe detection

Cell suspensions

The samples were minced and disaggregated in collagenase II (200 IU/ml) at 37°C (Kristoffersson et al. 1988). Cells from the suspensions were processed in three different ways: 1) in cultures for standard G-banding analysis, 2) in cultures followed by MAC preparations (patients 1–6), and 3) by magnetic cell sorting (miniMACS; Miltenyi Biotec GmbH, Gladbach, Germany) for enrichment of lymphocytes (patients 5–10) and for the study of renal parenchymal cells.

Standard G-banding analysis

Some 10^6 cells were cultured on collagen-R-coated chamber slides in RPMI 1640 medium for 5–7 days, as previously described (Elfving et al. 1995). The cultures were harvested in situ after colcemid and hypotonic treatment. The cells were then fixed with methanol:acetic acid and, after air-drying, G-banded with Wright's stain (Elfving et al. 1995).

Cell cultures and simultaneous study of cellular morphology, immunophenotype, and aneuploidy by the MAC technique

The suspended cells (10^6/ml) were cultured for 2–4 days on collagen-R-coated chamber slides as described above. After colcemid treatment (0.4 µg/ml) for 12 h, the cells were washed roughly with fresh culture medium to remove all non-adherent cells, including lymphocytes. The monolayer cells were then treated in situ with mild hypotonic solution for 20 min (Knuutila et al. 1994) and left to dry overnight. The preparations were first stained for immunophenotype determination. Mouse monoclonal anti-CD3 (Leu4; Becton Dickinson, Erembodegem, Belgium) and anti-CD22 (Leu 14) antibodies were used to label T and B lymphocytes, respectively. Epithelial cells were labeled by mouse antibodies recognizing cytokeratins 8, 18, and 19 (NCL-5D3; Novocastra Laboratories, Jesmond, United Kingdom). The bound antibodies were demonstrated by the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique (Fig. 1B) (Knuutila et al. 1994). The slides were then treated with pepsin, and in situ hybridization was performed. To confirm the APAAP results, the immunoperoxidase technique was adopted to the first three specimens (Knuutila et al. 1994). As the results appeared to be concordant, the frequency data presented relates to the results obtained by the APAAP immunostaining.

For the detection of trisomy 7, we adopted an α-satellite repeat sequence probe for interphase and metaphase cells (pα7tl) (Waye et al. 1987) and a whole-chromosome painting probe (LA07NS01; American Type Culture Collection, Rockville, MD, USA) for metaphase cells. For one part of the preparation, the α-satellite probe was detected enzymatically and, for the other part of the preparation, a fluorescein isothiocyanate (FITC) fluorochrome (Fig. 1A) was used (Knuutila et al. 1994). The two detection systems gave identical results. The whole-chromosome painting probe was detected with the FITC fluorochrome. Both immunophenotype (cellular morphology) and in situ hybridization signals could be seen and studied simultaneously. For interphase cells, the in situ signals were scored only on those cells from which both the immunostaining and cellular morphology could be studied.

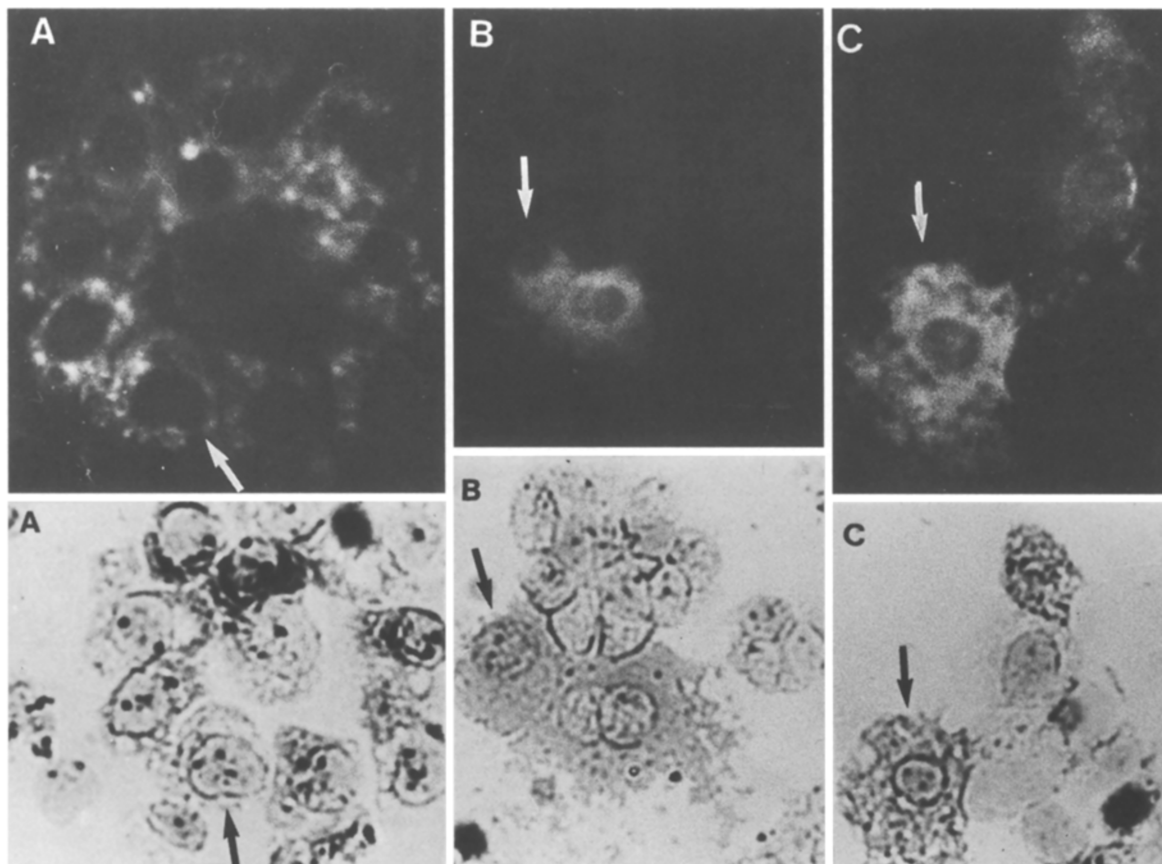


Fig. 2 Brush border (**A**, **B**) and Tamm-Horsfall (**C**) positive cells with trisomy 7 (*arrows*) on cytospin preparations of uncultured cells from patients 6, 10, and 7, respectively. Immunofluorescence staining and DAB/H_2O_2 probe detection. During microscopy, both visible light and UV light were on. Immunophenotype and in situ hybridization signals can be seen simultaneously. For the photograph of the immunophenotype, only UV light was used, whereas signal detection was photographed with only visible light

Enrichment of lymphocytes by magnetic activated cell sorting

For enrichment of lymphocytes present in the uncultured cell suspension, the cells were labeled with a 1:10 dilution of mouse anti-CD22 (Leu14) and anti-CD3 (Leu 4) monoclonal antibodies at 4°C for 35 min. After labeling, cells were washed twice with ice-cold phosphate-buffered saline containing 0.5% bovine fraction V albumin (BSA, Boehringer Mannheim, Mannheim, Germany). Finally, cells were resuspended in the same buffer at a final concentration of 10^7 cells/80 µl. Magnetic cell sorting microbeads coated with anti-mouse IgG (Miltenyi) were then added to the cell suspension at a final concentration of 20 µl/10^7 cells, and the cells were incubated for 15 min at 8–12°C. Lymphocytes attached to the beads were collected by the MiniMACS column separation system according to the instructions of the supplier. The collected cells were resuspended in the culture medium and cytospin slides were made. Slides were then air-dried for further treatment.

The cytospin preparations of enriched lymphocytes were immunostained by the APAAP technique using the Leu4, Leu14, and anti-cytokeratin antibodies as described above (Fig. 1C). Cytospin preparations of cells not attached to immunobeads were stained by APAAP using anti-cytokeratin or by the indirect immunofluorescence (IF) technique using rabbit antibodies against the brush border (BB) antigens of rat renal tubules, and rabbit anti-human Tamm-Horsfall (TH) glycoprotein antibodies (Fig. 2) (Ekblom et al. 1981; Holthöfer et al. 1983; Miettinen and Linder 1976). Simultaneous evaluation of the immunophenotype by IF and in situ hybridization signals was assessed using a UV light source and interference filters for FITC, and the hybridization signals obtained by the diaminobenzidine(DAB)/hydroxide peroxidase precipitation reaction by means of visible light (Knuutila et al. 1994).

Frozen sections

Cryostat sections, 5–6 µm thick, were placed on aminoalkylsilane-treated glass slides, and left to dry at 20°C for 24–72 h. Prior to in situ hybridizations, some of the slides were stained with the antibodies against cytokeratin, BB, or TH (Knuutila et al. 1994) for APAAP and/or IF. Before in situ hybridizations, both the immunostained and non-immunostained sections were treated with pepsin and NaSCN, air-dried, and the in situ hybridizations and signal detection with the DAB/hydroxide peroxidase precipitation enzymatic system were performed as described (Knuutila et al. 1994).

Results

Trisomy 7 in cell cultures (patients 1–6)

No CD3-positive or CD22-positive cells were seen on the cell culture slides. The frequency of cytokeratin-positive epithelial cells was always more than 50%.

The frequencies of interphase nuclei with trisomy 7 in cytokeratin-positive non-malignant tissue ranged from 5% to 9% (Tables 1, 2, Fig. 1C). In cytokeratin-positive metaphase cells, the corresponding frequency range was slightly, but not significantly, higher ($P > 0.05$), viz., between 5% and 13%. The frequencies of trisomy 7 among all cells from the same specimens did not vary significantly from those of cytokeratin-positive cells, and these frequencies corresponded to those seen in the G-banded analyses (Tables 1, 2).

Trisomy 7 in renal lymphocytes (patients 5–10)

The magnetic bead enrichment improved the lymphocyte yield in non-neoplastic tissues: about 10% of the cells in

Table 1 Trisomy 7 in renal cells from patients 1–6. Studies on tissue sections and cell cultures

Patient no.	Diagnosis	Kidney area[a]	Type of ISH[b]	Number of cells with trisomy 7[c]				Frequency (%) of cells with trisomy 7[c]			Frequency (%) of cells with trisomy 7 by karyotype analysis of cultured cells[d]
				Tissue section				Cell cultures			
				Tubular	Glomerular	Interstitial	Total	CD3+/ CD22+	CD3-/ CD22–	CK+	
1	Renal cell carcinoma	C	I	35	5	8	48	–	9	9	6
			M:C					–	9	16	
			M:P					–	11	NS	
2	Pyelitis	–	I	29	4	3	36	–	10	8	11
			M:C					–	11	13	
			M:P					–	14	14	
3	Renal cell carcinoma	C	I	20	1	–	21	–	10	9	11
			M:C					–	8	9	
			M:P					–	9	NS	
4	Wilms' tumor	C	I	NS	NS	NS	NS	–	8	5	0
			M:C					–	6	8	
			M:P					–	6	NS	
5	Pyelitis	–	I	NS	NS	NS	NS	–	3	5	4
			M:C					–	4	5	
6	Benign cysts		I	34	2	3	39	–		6	7

See the footnotes to Table 2

Table 2 Trisomy 7 in renal cells from patients 5–10 and controls 1–6. Studies on tissue sections, cell cultures, and uncultured cell suspensions

Patient no.	Diagnosis	Kidney area[a]	Type of ISH[b]	Number of cells with trisomy7[c]				Frequency (%) of cells with trisomy 7[c]					Frequency (%) of cells with trisomy 7 by karyotype analysis of cultured cells[d]
				Tissue section				Cell suspensions					
				Tubular	Glomerular	Interstitial	Total	CD3+/CD22+	CD3-/CD22–	CK+	BB+	TH+	
5	Pyelitis	–	I	NS	NS	NS	NS	0	4	3	4	2	4
6	Benign cysts		I	34	2	3	39	0.1	2	3	6	4	7
7	Renal cell carcinoma	A	I	–	–	5	5	0	11	NS	NS	NS	48–52,X,–Y,add(3)(p13),+5,+7,+12,+19,+20 +22[cp5]/46,X,–Y,–3,+5,+7,–8,+12[6]/46,XY[30]
		B	I	2	2	32	36	0	5	2	3	2	2
		C	I	27	3	51	81	0	5	2	4	2	2
8	Renal cell carcinoma	A	I	–	–	39	39	–	24	28	18	7	50,X,–X,+3,+7,+16,+17,+20[22]
		B	I	5	0	12	17	0.2	4	2	3	2	6
		C	I	42	9	9	60	NS	NS	NS	NS	NS	NS
9	Renal cell carcinoma	A	I	–	–	15	15	0.4	25	30	NS	NS	49,X,–Y,+7,+7,+12,+der(17)t(3;17)(q11;q25)[10]/46,XY[2]
		B	I	5	1	20	26	0	6	5	4	3	3
		C	I	34	2	10	46	0	4	2	4	2	4
10	Renal cell carcinoma	A	I	NS	NS	NS	NS	0.6	11	NS	NS	NS	41–44,X,–X,–3,der(8)t(3;8)(q11;p11),–14, –18[cp11]/46,XX[39]
		B	I	NS	NS	NS	NS	0.5	9	2	4	2	6
		C	I	2		1	3	0.3	3	4	2	1	5
Controls 1–6			I					0–0.4		–			
			M:C					0–0.5		–			

[a] *A* Tumor (all except patient 8 were BB-antigen positive), *B* close to the tumor, *C* far (> 5 cm) from the tumor
[b] *I* Interphase cytogenetics with α-satellite centromeric probe, *M:C* metaphase in situ hybridization (ISH) with centromeric probe, *M:P* metaphase with whole-chromosome painting probe
[c] *CK* Cytokeratins 8, 18 and 19, *BB* brush border antigens; TH Tamm-Horsfall glycoprotein, *NS* not studied, – no positive cells were observed. Number of cells studied: *in situ cultures*, for interphase cells at least 1000, for metaphase cells at least 200; *uncultured suspended cells*, for CD3+/CD22+, CD3–/CD22–, CK+ at least 1000, for BB and TH from 150 to 1000 (mean 400 cells)
[d] Based on 100 cells analyzed in each sample

the preparations were small lymphocyte-like CD3-positive or CD22-positive T or B lymphocytes, respectively, whereas in negatively selected cells, the lymphocyte frequency was less than 1‰. The yield of the selection varied in neoplastic tissues from less than 0.1% (patient 8) to 30% (patient 10).

The frequency of lymphocytes with trisomy 7 was never higher than 0.6%, corresponding to the finding in the lymphocyte samples of the peripheral blood of six healthy controls (Table 2). Thus, we could not demonstrate an increased frequency of trisomy 7 in lymphocytes present in the renal tissue. In lymphocyte-depleted preparations, the frequency of cytokeratin-positive cells with the trisomy varied from 2% to 4% in non-malignant specimens from patients 5–7, 9 and 10, and from 28% to 30% in specimens of malignant tissues from patients 8 and 9. Both of these tumors had trisomy 7 as a clonal change (Table 2). The frequency of trisomy 7 in the BB antigen-positive cells was usually higher than or equal to that in the cytokeratin-positive cells, whereas in the TH-positive cells, it was considerably lower (Fig. 2).

Trisomy 7 in tissue sections (patients 1–10) .

In agreement with the results obtained with freshly isolated cells using the antisera against BB and TH (Tables 1, 2), the findings indicated that most of the trisomic cells were of proximal tubular cell origin. Calculation of the frequencies of trisomic cells among different types of cells was considered to be unreliable, because the hybridization capacity of the probe varied greatly, not only between different preparations, but also between different types of cells. Scoring of frequencies was also hindered by the high rate of false negative signals, a well-known problem in the evaluation of tissue sections. Furthermore, although overlapping cells did not pose a problem in tubular cells, this was the case for glomerular cells, which frequently overlapped. The numbers of trisomic cells observed in the different cell types are shown in Tables 1,2.

The trisomic cells found in the tissue sections were restricted mainly to the tubules, lined by the basement membrane (Tables 1, 2, Fig. 3). Based on the histology and cellular morphology, the trisomic cells in non-malignant areas were mainly of proximal tubular origin. Furthermore, for some cases, we demonstrated them to be BB-positive. In the non-malignant tissue sections, more than 90% of the trisomic cells were of proximal tubular origin. The origin of the remaining trisomic cells was distal tubular, glomerular, or interstitial. Trisomy 7 therefore appears to be present also in these renal structures.

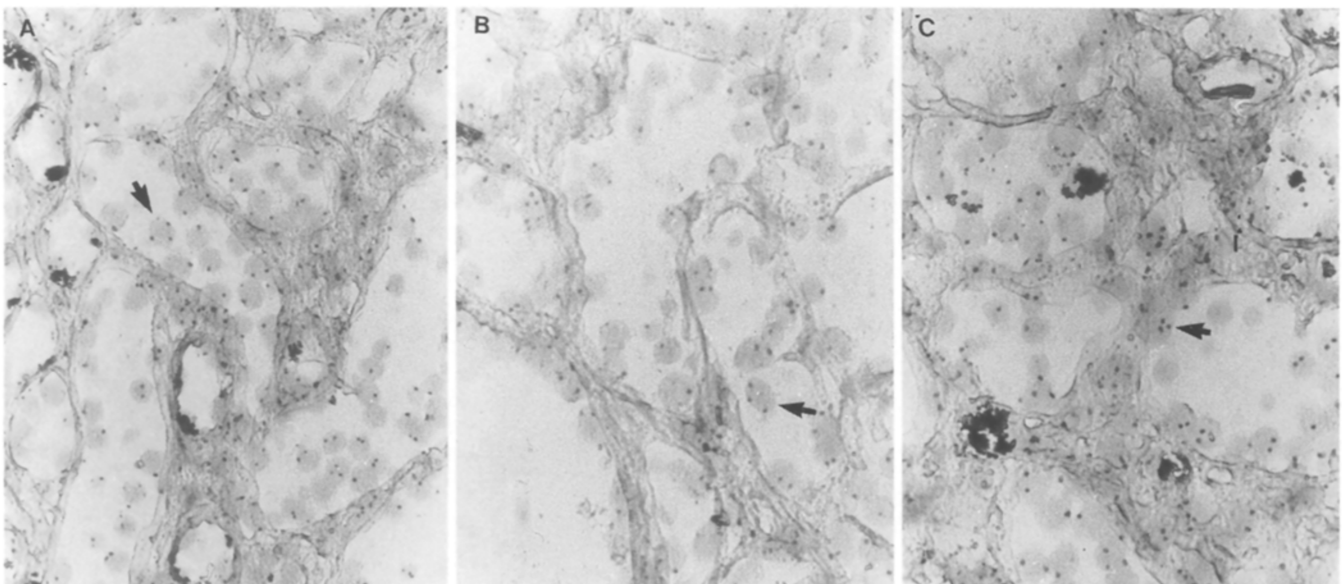
Discussion

In this study of non-neoplastic kidney tissue, we found trisomy 7 in epithelial cells, but not in infiltrating T or B lymphocytes. Similar results were recently reported by Elfving et al. (1994). We further demonstrate that the trisomic cells are predominantly proximal tubular cells.

Three major methodological factors in our study may potentially cause misleading results: 1) incorrect interpretation of the immunophenotype of immunostained cells or tissues, 2) false positive hybridization signals caused by cross-hybridization of the probe or the incorrect interpretation of the number of signals, and 3) too few cells may have been studied.

To avoid antibody cross-reactivity and misinterpretation, we adopted, for each antibody, the immunostaining technique (APAAP, immunoperoxidase or immunofluorescence) that, in our hands, has worked successfully for these antibodies. Furthermore, the results of APAAP staining of suspended cells were confirmed by the im-

Fig. 3 Trisomic cells (*arrows*) in proximal tubules on tissue sections from a non-tumor area in patient 1



munoperoxidase technique. It is important to note that, in addition to immunostaining, the classification of cells was based on tissue and cellular morphology. Generally, no discrepancies were found between immunostaining and the morphologic evaluation. The CD3-positive or CD22-positive cells morphologically resembled lymphocytes and the cytokeratin-positive cells grew in the same way as epithelial cells. However, occasionally, some cells with a clearly epithelial morphology were CD3-positive in the tumor specimens. A special risk, in our view, appears to be the possibility that some malignant epithelial cells may cross-express lymphoid antigens. In tissue sections of the human kidney, antibodies against BB and TH specifically label the epithelial cells of the renal proximal or distal tubules, respectively. The antibodies against BB recognize several cell surface antigens enriched at the apical BB membranes of the proximal tubular cells (Miettinen et al. 1980), and are a good marker of these cells in tissue sections (Holthöfer et al. 1983). Other cells also express some of the antigens, and the antibodies are not specific for proximal tubular cells in cell cultures. However, in freshly isolated renal cell suspensions, the antibodies reliably identify proximal tubular cells. The TH glycoprotein or uromodulin is made by the epithelial cells of the distal straight tubules, but the antigen is also found in the distal convoluted tubules (Sikri et al. 1981). In tissue sections, the antibodies to TH bind only to the distal tubular cells, but we do not know how the in vitro culture conditions affect the expression of this antigen, and thus the antibodies were not used to identify cultured cells.

To minimize false positive signals, the study was also performed on metaphase cells, in which chromosomal morphology can be evaluated. Furthermore, we used two different probes for mitotic cells and two different systems for probe detection on interphase cells.

Finally, in contrast to our previous study (Elfving et al. 1994), the number of cells analyzed was large. For most antibody-cell morphological features, at least 1000 interphase cells and 200 metaphase cells were scored.

Our study thus demonstrates that the kidney cells harboring trisomy 7 consist mainly of non-neoplastic epithelial cells of the proximal tubule and, albeit to a lesser extent, cells of the distal tubule, glomerulus, and interstitial cells. The biological significance of these findings and their relationship, if any, to tumor development remains to be clarified. Further studies are also required to investigate the cellular origin of the other trisomies repeatedly seen in normal kidney tissue (Elfving et al. 1990, 1995; Dal Cin et al. 1992).

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