

DERIVATION OF NEPHROGENIC ADENOMAS FROM RENAL TUBULAR CELLS IN KIDNEY-TRANSPLANT RECIPIENTS

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ABSTRACT

Background Nephrogenic adenomas are benign, tumor-like lesions within the urothelial mucosa of the urinary tract that are not uncommon in renal-transplant recipients. We investigated the origin of nephrogenic adenomas in renal-transplant recipients.

Methods Tissue sections were analyzed by fluorescence in situ hybridization with the use of probes for the X and Y chromosomes, by immunohistochemical methods with the use of antibodies to renal tubular antigens, and by lectin histochemical methods. Forty-six nephrogenic adenomas from 29 patients were analyzed.

Results All nephrogenic adenomas in 14 female recipients of transplants from male donors and 10 male recipients of transplants from female donors showed the same sex-chromosome status as the donor kidney, but not the same sex-chromosome status as the recipient's surrounding bladder tissue. The nephrogenic adenomas from all 6 female recipients of transplants from female donors showed female chromosomes, and those from the 16 male recipients of transplants from male donors showed male chromosomes. The presence of aquaporin 1, PAX2, and lectin-binding capacity for peanut agglutinin, *Lotus tetragonolobus* agglutinin, and *Sophora japonica* agglutinin in nephrogenic adenomas indicated an origin from renal tubular cells.

Conclusions Nephrogenic adenomas in renal-transplant recipients are derived from tubular cells of the renal transplants and are not metaplastic proliferations of the recipient's bladder urothelium. (N Engl J Med 2002;347:653-9.)

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NEPHROGENIC adenomas are rare, benign, tumor-like lesions within the urothelial mucosa of the urinary tract. Most nephrogenic adenomas are found in the bladder, but other locations (pelvic urothelium, ureter, and urethra) have been reported.¹⁻⁶ They occur in patients with chronic bladder inflammation or previous genitourinary surgery, and they are particularly frequent in renal-transplant recipients.⁷⁻¹⁶ The pathogenesis of these lesions is enigmatic. The favored hypothesis is that nephrogenic adenomas are metaplastic alterations of resident urothelial tissue, and therefore

the term "nephrogenic metaplasia" is used synonymously. Another hypothesis postulates development from hamartomatous cells.¹⁷ In this study, we investigated the origin of nephrogenic adenomas in renal-transplant recipients by analysis of sex chromosomes using fluorescence in situ hybridization and by immunohistochemical detection of aquaporins and other antigens of the nephrons, collecting ducts, and urothelium.

METHODS

Patients

From March 1994 through February 2001, 29 renal-transplant recipients underwent cystoscopy because of hematuria or dysuria, followed by transurethral resection of a nephrogenic adenoma. The patients' ages ranged from 16 to 78 years (median, 49.6). Forty-six nephrogenic adenomas were resected, including 17 recurrent lesions. The interval between renal transplantation and the diagnosis of nephrogenic adenoma was 6 to 120 months (median, 44.6). Table 1 shows the sexes of the donors and recipients of the renal transplants. Post-transplantation renal-biopsy specimens were available from all patients and were obtained before any manifestation of a nephrogenic adenoma. Quantification of the grade of renal rejection in post-transplantation biopsies was performed with the Banff 97 classification.¹⁸

Histologic Examination

Specimens from transurethral resections were completely embedded in paraffin and cut into serial sections 4 to 6 μm in thickness. One section was stained with hematoxylin and eosin, and adjacent sections were used for fluorescence in situ hybridization, immunohistochemical analysis, and lectin staining. In selected cases, sections that were analyzed by fluorescence in situ hybridization were restained with hematoxylin and eosin to compare sex-chromosome analysis and histologic details in the same tissue section. Nephrogenic adenoma was diagnosed when typical histologic characteristics (tubular or cystic proliferations, or both, with or without papillary formations)⁵ were seen.

Fluorescence in Situ Hybridization

Food and Drug Administration–approved X and Y centromeric probes, directly labeled with Spectrum Orange and Spectrum Green (Vysis), were used according to the protocols of the manufacturer.

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TABLE 1. CHARACTERISTICS OF PATIENTS WITH NEPHROGENIC ADENOMAS AFTER RENAL TRANSPLANTATION.

CHARACTERISTIC	VALUE
Age — yr	
Median	49.6
Range	16–78
Sex — no./total no. of patients (%)	
Male	13/29 (45)
Female	16/29 (55)
Interval from transplantation to diagnosis of nephrogenic adenoma — mo	
Median	44.6
Range	6–120
Reason for cystoscopy — no./total no. of patients (%)	
Microhematuria	13/29 (45)
Macrohematuria	8/29 (28)
Dysuria	8/29 (28)
Sex of donor and recipient — no./total no. (%)	
Female donor, male recipient	
Patients	4/29 (14)
Nephrogenic adenomas	10/46 (22)
Male donor, female recipient	
Patients	12/29 (41)
Nephrogenic adenomas	14/46 (30)
Male donor, male recipient	
Patients	9/29 (31)
Nephrogenic adenomas	16/46 (35)
Female donor, female recipient	
Patients	4/29 (14)
Nephrogenic adenomas	6/46 (13)
Recurrences — no./total no. of patients (%)	
0	17/29 (59)
1	7/29 (24)
2	5/29 (17)
Therapy — no./total no. of patients (%)*	
Basic therapy with antithymocyte globulin	11/29 (38)
Basic therapy without antithymocyte globulin	18/29 (62)
Banff 97 grade of rejection — no./total no. of patients (%)†	
0	9/29 (31)
Borderline	1/29 (3)
1	7/29 (24)
2	11/29 (38)
Chronic	1/29 (3)

*Basic therapy consisted of corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus, or others), and antiproliferative agents (azathioprine or mycophenolate mofetil). Antithymocyte globulin was given in cases of biopsy-proved vascular rejection (Banff 97 grade, 2).

†Banff grades are from Racusen et al.¹⁸

Because tissue sections and not cytologic preparations were analyzed, some nuclei were cut through, and single cells did not show all sex chromosomes on the sections. We therefore assigned male chromosomal status to nephrogenic-adenoma tissue in a female patient if at least 75 percent of all nuclei of the nephrogenic-adenoma tissue showed one clear-cut Y chromosome, identified as a green, dotlike intranuclear hybridization signal, and no nuclei of the adjacent bladder tissue showed Y chromosomes. Similarly, we assigned female chromosomal status to nephrogenic adenoma tissue in a male patient if the nuclei of the nephrogenic-adenoma tissue did not show Y chromosomes and at least 75 percent of the nuclei of the adjacent bladder tissue showed Y chromosomes. Evaluation of fluorescence signals was performed on transparencies. Three female and three male patients who had nephrogenic adenomas without preceding renal transplantation (five patients with bladder endometriosis and one with prostatic hyperplasia) served as controls for fluorescence in situ hybridization experiments.

Immunohistochemical Analysis and Lectin Staining

Antibodies against aquaporins (water-channel membrane proteins) of the proximal tubules (aquaporin-1, dilution 1:400, Chemicon) and of the collecting ducts (aquaporin-2, 1:50, Chemicon) were used. In addition, Leu-M1 (1:10, Becton Dickinson); epithelial membrane antigen (1:50, Dako); vimentin (1:20, Immunotech); cytokeratins Cam 5.2 (undiluted, Becton Dickinson), CK7 (1:200, Dako), CK8 (1:25, Dako), and CK20 (1:20, Neomarkers); and PAX2, a transcription factor in renal development (1:100, Zymed), were used. Signal detection was performed with the peroxidase-antiperoxidase reaction. Antigen retrieval for aquaporin-1, aquaporin-2, and PAX2 was performed by microwave pretreatment in citrate buffer (pH 6.0) for 20 minutes at 120 W and three times for 5 minutes each at 450 W. Tumor-free renal tissue from five nephrectomy specimens (removed for renal tumor) and tumor-free bladder tissue from five cystoprostatectomy specimens served as controls. Evaluation was performed with use of a semiquantitative scale, with – indicating negative, + moderate, ++ strong, and +++ very strong staining. The avidin-biotin method was used to analyze the lectin-binding properties for *Lotus tetragonolobus* agglutinin, which is specific for proximal tubules and the thin limb of Henle's loop¹⁹ (200 µg per milliliter, Sigma); *Sophora japonica* agglutinin, which is specific for the proximal tubules and collecting ducts¹⁹ (50 µg per milliliter, Vector Laboratories); and *Arachis hypogaea* agglutinin (peanut agglutinin), which is specific for the distal tubules and collecting ducts²⁰ (50 µg per milliliter, Vector Laboratories). Negative controls were achieved by blocking the lectins with their corresponding sugars (α -L-fucose for *L. tetragonolobus* agglutinin, N-acetyl- β -D-galactosamine for *S. japonica* agglutinin, and β -D-galactose for peanut agglutinin) before the staining procedure.²¹

Both pretransplantation and post-transplantation graft-biopsy specimens were available for 13 patients. Immunohistochemical analysis for Cam 5.2 was performed in these 13 patients to demonstrate casts of detached tubular cells within the tubular lumina. The interval between transplantation and graft biopsy ranged from 5 to 721 days. The proliferation index was evaluated by the MIB1 antibody (1:50, Dako) to detect Ki-67 antigen in the nuclei of the tubular cells. In addition, the expression of PAX2 was investigated. The results of pretransplantation and post-transplantation graft biopsies were compared.

Statistical Analysis

Medians and standard deviations are reported. The Wilcoxon-Mann-Whitney U test and Fisher's exact test were used.

RESULTS

Fluorescence in Situ Hybridization

In 14 of 14 nephrogenic adenomas from female recipients of renal transplants from male donors, a male chromosomal status was demonstrated within the epithelial component (Fig. 1). In 10 of 10 nephrogenic adenomas from male recipients of renal transplants from female donors, a female chromosomal status was demonstrated (Fig. 2). By contrast, the stromal component of all nephrogenic adenomas had the sex-chromosome status of the recipient. In 6 of 6 nephrogenic adenomas from women with renal transplants from female donors, a female chromosomal status was demonstrated, and in 16 of 16 nephrogenic adenomas from men with renal transplants from male donors, a male chromosomal status was demonstrated. In each nephrogenic adenoma from the renal-transplant recipients, the epithelial component had the same sex-chro-

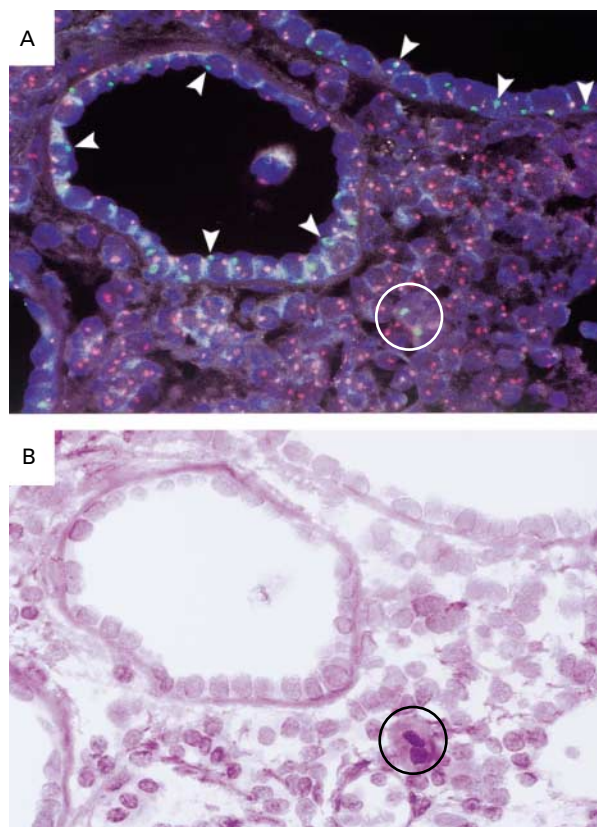


Figure 1. Nephrogenic Adenoma of a Female Patient with a Renal Transplant from a Male Donor ($\times 600$).

In Panel A, fluorescence in situ hybridization of a tissue section demonstrates the male sex-chromosome status of the epithelial component. Arrowheads indicate Y chromosomes; the circle encloses two male epithelial cells within the female bladder stroma, most likely representing cells of an adjacent adenoma tubule; red signals indicate X chromosomes, and green signals Y chromosomes. Panel B shows hematoxylin-and-eosin staining of the same tissue section after a fluorescence in situ hybridization destaining procedure to demonstrate identical morphologic details. The circle encloses the two male epithelial cells.

mosome status as the donor (Table 2). The control group of nephrogenic adenomas not associated with a kidney graft had the expected sex-chromosome status.

Immunohistochemical Analysis and Lectin Staining

The results of analysis of the nephrogenic adenomas are summarized in Table 2. Epithelial components of the nephrogenic adenomas showed immunophenotypic characteristics of renal tubular cells: prominent staining for aquaporin-1 (Fig. 3D), epithelial membrane antigen, and cytokeratins Cam 5.2 and CK7 and moderate reactivity for CK8, Leu-M1, and vimentin.

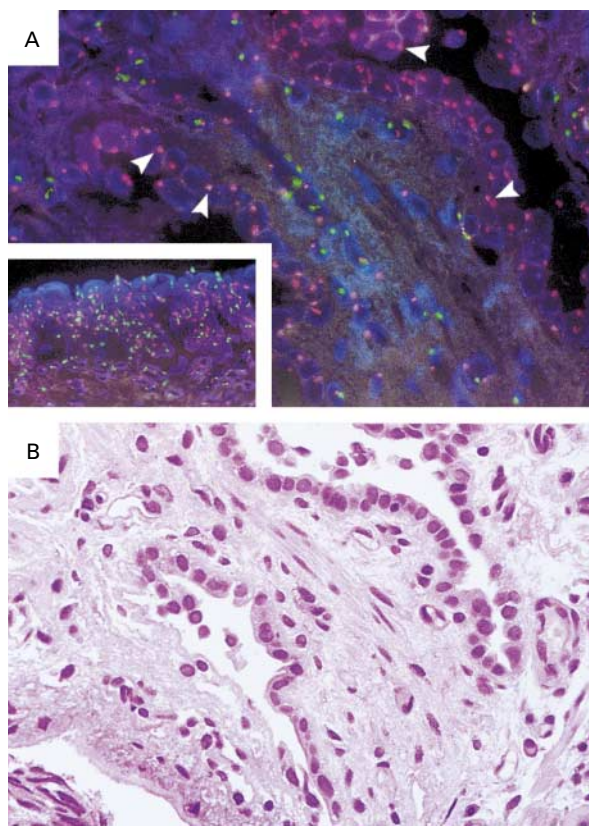


Figure 2. Nephrogenic Adenoma of a Male Patient with a Renal Transplant from a Female Donor ($\times 500$).

In Panel A, fluorescence in situ hybridization of a tissue section demonstrates the female sex-chromosome status of the epithelial component. Arrowheads indicate X chromosomes; there are no Y chromosomes in female tubules. Red signals indicate X chromosomes, and green signals Y chromosomes. The insert shows urothelial surface with normal male chromosomal status. Panel B shows hematoxylin-and-eosin staining of the adjacent tissue section.

CK20, which is expressed in urothelial cells, and aquaporin-2, which is confined to collecting ducts, were not detected. In addition, PAX2, which is usually found only during nephrogenesis, was found in epithelial components of nephrogenic adenomas, but not in the bladder urothelium (Fig. 3E). Peanut agglutinin staining was found in all 46 nephrogenic adenomas, but not in the adjacent urothelium (Fig. 3F). *L. tetragonolobus* agglutinin was found focally in 17 of the 46 nephrogenic adenomas (37 percent), but not in the adjacent urothelium. Focal staining was also found with *S. japonica* agglutinin in 26 of 46 (57 percent); however, the adjacent urothelium was positive.

TABLE 2. RESULTS OF FLUORESCENCE IN SITU HYBRIDIZATION AND IMMUNOHISTOCHEMICAL STUDIES.

PATIENT No.	Sex*			IMMUNOHISTOCHEMICAL RESULTS†								
	RECIPIENT	DONOR	NEPHROGENIC ADENOMA	AQP1	LEU-M1	AQP2	EMA	CK7	CK8	CK20	CAM 5.2	PAX2
1	F	M	M	++	-	-	+	+++	++	-	++	No
2	F	M	M	+	+	-	++	++	++	-	++	No
3	F	M	M	+++	+	-	+	++	+	-	+++	Yes
4	F	M	M	+++	-	-	+	++	-	-	++	Yes
5												
Initial adenoma	F	M	M	+	-	-	++	+	++	-	++	No
First recurrence	F	M	M	+	-	-	++	+	+	-	++	No
6												
Initial adenoma	F	M	M	++	-	-	++	++	-	ND	++	Yes
First recurrence	F	M	M	+++	+	-	++	++	+	-	++	Yes
7	F	M	M	+++	-	-	+	++	+	-	++	Yes
8	F	M	M	++	+	-	+	+	-	-	++	Yes
9	F	M	M	++	-	-	+	+++	++	-	+++	No
10	F	M	M	++	-	-	+	++	++	-	++	Yes
11	F	M	M	+	-	-	+	++	+	-	++	Yes
12	F	M	M	+	-	-	+	++	-	-	++	No
13												
Initial adenoma	M	F	F	+	-	-	-	+	-	-	++	Yes
First recurrence	M	F	F	ND	ND	ND	ND	ND	ND	ND	ND	Yes
Second recurrence	M	F	F	+++	-	-	++	+++	+	-	+++	Yes
14												
Initial adenoma	M	F	F	++	+	-	+	++	-	-	++	Yes
First recurrence	M	F	F	++	+	-	++	+++	++	-	+++	No
15												
Initial adenoma	M	F	F	++	+	-	+	+	+	-	+	Yes
First recurrence	M	F	F	++	+	-	+	+	++	-	++	Yes
16												
Initial adenoma	M	F	F	++	+	-	++	++	+	-	++	Yes
First recurrence	M	F	F	++	-	-	+	++	+	-	++	Yes
Second recurrence	M	F	F	+	-	-	+	++	+	-	++	Yes
17	F	F	F	+	-	-	++	+++	++	-	+++	Yes
18												
Initial adenoma	F	F	F	++	+	-	+	+	+	-	++	Yes
First recurrence	F	F	F	+	-	-	+	++	+	ND	++	ND
19												
Initial adenoma	F	F	F	++	ND	ND	ND	ND	ND	ND	ND	ND
First recurrence	F	F	F	++	-	-	+	++	+	-	++	Yes
20	F	F	F	++	-	-	++	++	++	-	++	ND
21	M	M	M	+	+	ND	ND	ND	ND	ND	ND	Yes
22	M	M	M	++	-	-	+	++	++	-	++	No
23	M	M	M	++	+	-	++	++	+	-	++	Yes
24	M	M	M	++	+	-	+	+	-	-	+	No
25	M	M	M	+	+	-	+	+	+	-	++	Yes
26												
Initial adenoma	M	M	M	++	+	-	++	+	+	-	++	Yes
First recurrence	M	M	M	++	-	-	++	++	+	-	+++	Yes
Second recurrence	M	M	M	++	-	-	++	+	++	-	++	Yes
27												
Initial adenoma	M	M	M	+	-	-	+	+++	+	-	+++	Yes
First recurrence	M	M	M	+	+	-	++	+	+	-	++	Yes
Second recurrence	M	M	M	+	+	-	++	+	+	-	++	Yes
28												
Initial adenoma	M	M	M	+++	-	-	++	++	+	-	++	Yes
First recurrence	M	M	M	++	-	-	++	+	+	-	++	ND
Second recurrence	M	M	M	++	-	-	+	++	+	-	ND	Yes
29												
Initial adenoma	M	M	M	+	+	-	+	-	+	-	++	Yes
First recurrence	M	M	M	++	-	-	+	++	-	-	++	Yes

*The sex of the recipient and donor of the graft, and the sex-chromosome status of the nephrogenic adenoma, as determined by fluorescence in situ hybridization, are given.

†The results are scored as - negative, + moderate, ++ strong, and +++ very strong. AQP1 denotes aquaporin-1, AQP2 aquaporin-2, EMA epithelial membrane antigen, and ND not done.

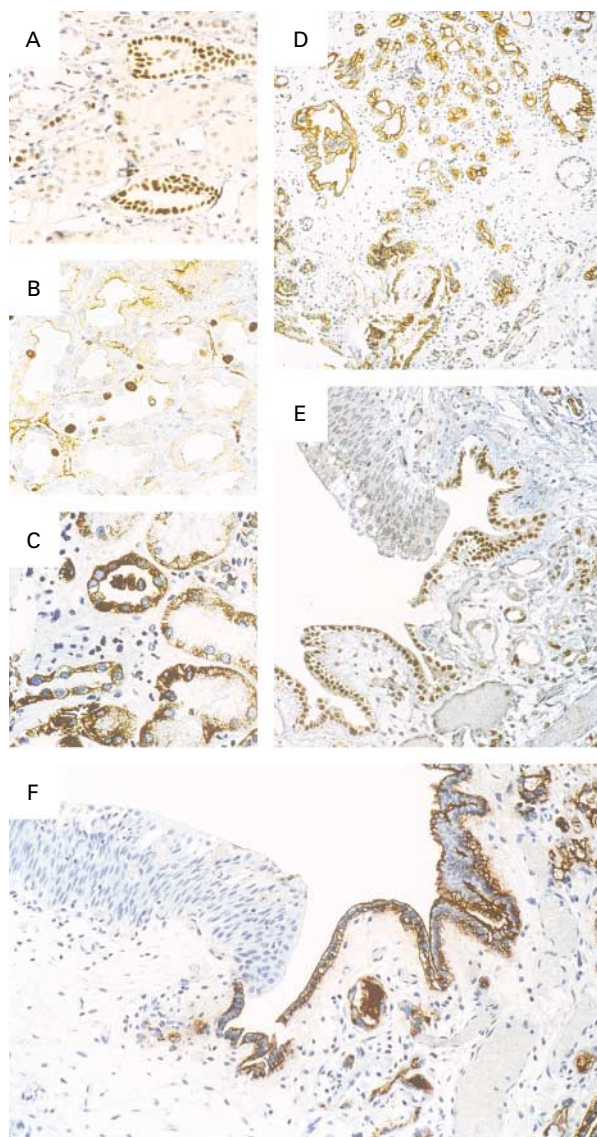


Figure 3. Immunohistochemical Findings.

Panels A, B, and C show post-transplantation renal-biopsy specimens. Panel A shows expression of the transcription factor PAX2 in the nuclei of renal tubular cells ($\times 400$). Panel B shows renal tubular cells expressing Ki-67 antigen as a marker of cell proliferation (MIB1, $\times 400$). Panel C shows an intratubular cast (Cam 5.2, $\times 400$). Panels D, E, and F show tissue sections from nephrogenic adenomas. Panel D shows the expression of aquaporin-1 ($\times 200$). Panel E shows the expression of PAX2; the urothelium shows no expression ($\times 200$). Panel F shows peanut agglutinin staining; the urothelium shows no staining ($\times 200$).

In renal-graft biopsies, we demonstrated casts of detached cells within tubular lumina (Fig. 3C) in 7 of 13 patients (54 percent). However, the number of casts was highly variable. The proliferation index was low, at 0.11 to 1.43 percent of all nuclei of tubular cells in post-transplantation biopsy specimens (Fig. 3B). It was slightly higher than in pretransplantation biopsy specimens from these patients, at 0.08 to 1.17 percent, but this difference was not statistically significant. In 3 of the 13 patients (23 percent), we demonstrated PAX2 expression in tubular epithelial cells in post-transplantation biopsy specimens (Fig. 3A). Expression of this antigen was associated with interstitial renal-transplant rejection.

Comparison between Patient Groups

No significant differences were found between female and male recipients in age, frequency of graft rejection, interval from transplantation to the diagnosis of nephrogenic adenoma, or frequency of recurrence. We also found no significant difference in these variables between patients who had received basic anti-rejection therapy and those also treated with anti-thymocyte globulin.

DISCUSSION

Nephrogenic adenoma was initially described as a benign hamartomatous bladder lesion by Davis in 1949.¹⁷ The term “nephrogenic adenoma” was introduced in 1950 by Friedman and Kuhlenbeck²² because of the lesion’s histologic similarities to renal tubules. Although nephrogenic adenomas are rare, a high incidence has been noted in recipients of renal transplants.⁷⁻¹⁶ Other possible predisposing factors are genitourinary trauma,^{23,24} mechanical irritation or genitourinary surgery,^{4,10,14,25-31} local chemical irritation,^{14,26,32-34} irradiation, and chronic inflammation. The idea that nephrogenic adenomas are metaplastic proliferations of resident urothelial mucosa is widely accepted^{3,11,25,35,36} but has never been proved. Redondo Martinez and Rey Lopez³⁷ and Strand and Alfert³⁸ reported nephrogenic adenomas after cystectomy that were located in a sigmoid neobladder and an ileal conduit, findings that argue against metaplasia of resident urothelial mucosa.

In our fluorescence in situ hybridization experiments, we found that nephrogenic adenomas from women who received renal transplants from male donors had a male sex-chromosome status (XY), whereas the surrounding bladder tissue had a female sex-chromosome status (XX). The reverse was found in nephrogenic adenomas from men with transplants from female donors. These results demonstrate that nephrogenic adenomas in patients with renal transplants originate from the graft.

Immunohistochemical and lectin staining was per-

formed to characterize the cell type in the nephrogenic adenomas. Aquaporin-1, a membrane protein of water channels, is expressed in the proximal renal tubule and the descending thin limb of Henle's loop, but not in the other nephron segments, the collecting ducts, and the urothelial cells.^{39,40} Extrarenal aquaporin-1 has been reported in capillary endothelium and red cells.^{39,40} Aquaporin-2 is selectively expressed in renal collecting ducts.^{39,40} We found prominent staining for aquaporin-1 but not for aquaporin-2 in nephrogenic adenomas. We also investigated the epithelial cells of nephrogenic adenomas for antigens that are not specific to the kidney. Leu-M1 is expressed in the proximal tubular cells but not in the distal tubules, collecting ducts, and urothelial cells; cytokeratins CK7 and CK8 and epithelial membrane antigen occur in the renal tubules, collecting ducts, and urothelial cells.⁴⁰⁻⁴² A moderate-to-strong immunoreactivity with antibodies against these antigens was shown. CK20, which is found in urothelial cells⁴³ but not in nephrons and collecting ducts, was not detected in the nephrogenic adenomas of our patients.

Binding of *L. tetragonolobus* agglutinin and *S. japonica* agglutinin, which are typically found in mature proximal tubular cells, was demonstrated in many of the nephrogenic adenomas we studied. Binding of peanut agglutinin, which is usually found in mature distal tubules, has been reported in nephrogenic adenomas,⁴⁴ and was found in all the adenomas we studied. This finding suggests that the adenomas arise from an early developmental stage of the renal tubules, since free peanut-agglutinin receptors occur in embryonal renal mesonephric and metanephric tubules.⁴⁴ All our immunohistochemical and lectin-binding analyses suggest that the adenomas originate from renal tubular cells.

The PAX genes encode a family of transcription factors that act as key regulators during organogenesis.⁴⁵ PAX2 and PAX8 seem to be required for the development and proliferation of the renal tubules. After renal differentiation, PAX2 expression is down-regulated in mature tissue, and usually no expression is seen in the adult kidney.⁴⁵ Expression of PAX2 in some biopsy specimens from the transplanted kidneys of our patients with nephrogenic adenoma might indicate an activation of tubular precursor-cell antigens. The presence of aquaporin-1 in nephrogenic adenomas, together with PAX2, peanut agglutinin, and *L. tetragonolobus* agglutinin, argues against an origin in urothelial cells. Aquaporin-1 is strictly confined to renal tubules and has never been reported to be expressed in urothelium; furthermore, urothelium does not bind peanut agglutinin and *L. tetragonolobus* agglutinin.

Detachment of viable renal tubular cells probably occurs throughout life. A high incidence of detach-

ment is possible in renal diseases and hypoxic conditions.⁴⁶⁻⁴⁹ Seeding and implantation of neoplastic or non-neoplastic cells in distant tissues are known in the literature, as in the case of endometriosis.⁵⁰

It seems that in certain circumstances, urothelial mucosa is able to incorporate renal cells, but how implantation of tubular cells after seeding is mediated remains to be clarified in further investigations. Allogeneic renal tubular cells, already implanted, have to survive in the environment of the recipient's connective tissue. We looked at some nephrogenic adenomas for evidence of rejection but found none (data not shown).

Our results show that nephrogenic adenomas in renal-transplant recipients originate not from the recipient's bladder urothelial mucosa, but from renal tubular cells of the transplanted kidney. In our opinion, the terms "nephrogenic adenoma" and "nephrogenic metaplasia" are imprecise; we think these lesions are a kind of renal tubular satellite. Seeding, implantation, and growth of renal cells in urothelial mucosa may be enhanced by increased loss of tubular cells, trauma, infection, and immunosuppression.

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CORRECTION

Derivation of Nephrogenic Adenomas from Renal Tubular Cells in Kidney-Transplant Recipients

Derivation of Nephrogenic Adenomas from Renal Tubular Cells in Kidney-Transplant Recipients . The last sentence in the left-hand column of page 654 should have read, "Three female and three male patients who had nephrogenic adenomas without preceding renal transplantation, five patients with bladder endometriosis, and one with prostatic hyperplasia served as controls," rather than "Three female and three male patients who had nephrogenic adenomas without preceding renal transplantation (five patients with bladder endometriosis and one with prostatic hyperplasia) served as controls." We regret the error.