Virchows Arch. A Path. Anat. and Histol. 386, 189–200 (1980)

Virchows Archiv A

Acquired Cystic Transformation of the Kidneys of Haemodialysed Patients

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Summary. In the present study, the kidneys of patients who had been on maintenance haemodialysis for variable periods of time were examined at autopsy. In 21 of the 22 patients, multiple pinhead-size to pea-size, non-loculated cysts were observed both in the cortex and the medulla.

In some of the cysts (4/20 patients), papillary adenomata were observed which were visible by light microscopy in 3 cases and macroscopically in 1 case. Clinical complications resulting from haemorrhage or neoplastic transformation were not observed in any of the patients of this series. Similar cysts, smaller in size and fewer in number, were also observed in kidneys of uraemic patients who had not been dialysed. Thus, the lesion does not appear to be a specific consequence of maintenance haemodialysis. It appears more likely that extensive cystic transformation of the kidneys of patients in terminal renal failure is made possible by prolonged survival on maintenance haemodialysis. The possibility of malignant transformation of the papillomata cannot be refuted, but epidemiological surveys fail to document more frequent occurrence of renal carcinoma in dialysed patients.

Key words: Haemodialysis – Kidney – Cystic transformation – Neoplastic transformation.

Introduction

In the past, little attention has been focused on the macroscopic and microscopic findings in the kidneys of haemodialysed patients. In 1975, Zobel et al. described obliterative fibrosis of the intima of renal arteries in patients with terminal renal failure on maintenance haemodialysis. However, these authors did not mention the occurrence of cysts in their report.

Recently Dunnill et al. (1977) described acquired cystic disease of the kidney as a hazard of maintenance haemodialysis. In the view of these authors, the

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0340-1227/80/0386/0189/$02.40

occurrence of microcysts and the associated abnormalities of tubular epithelium, resulted from some specific effect of haemodialysis.

In the literature, renal cysts have been described in a variety of renal diseases other than polycystic and multicystic disease (E. Potter, 1972). Such diseases include tuberous sclerosis, trisomy D, Zellweger's cerebrohepatorenal syndrome, medullary sponge kidney, medullary cystic disease or familial juvenile nephronopthisis etc. However, in non-uraemic patients with glomerulonephritis, cyst formation is not commonly observed.

Apart from the report of Dunnill et al. (1977), the incidence and morphological characteristics of such cysts in haemodialysed patients have not been studied systematically. Such detailed analysis is of interest for two reasons. On the one hand, the occurrence of cystic transformation, at least in advanced cases, may create problems in the differential diagnosis of the underlying renal disease and on the other, the changes may be of some clinical interest in view of the suggestion of Dunnill et al. (1977) that proliferating adenomata in such cysts may transform spontaneously into renal cell carcinoma. In the present study, the kidneys of 20 haemodialysed patients who came to autopsy were examined systematically to determine the extent of microcystic transformation and the morphological characteristics of this phenomenon.

Table 1. Clinical data and autopsy findings in 22 hemodialysed patients

	Age	Sex	Renal disease	Duration of haemo-dialysis	Hyper-tension	Urinary tract infection	Renal weight (g) (two kidneys)
B.D.	19	m	Goodpasture	0.8 y	+	−	140
M.M.	38	f	GN	2.0 y	+	−	95
S.B.	37	f	GN	1.3 y	−	+	45
B.E.	48	m	GN	1.0 y	+	−	110
B.D.	32	m	fGN	4.0 y	+	−	55
E.E.	53		GN	3.3 y	−	−	100
N.G.	33	f	GN	6.0 y	+	−	95
H.W.	36	m	GN	2.3 y	+	−	110
K.K.	21	f	fGN	1.8 y	−	−	240
F.E.	30	f	GN(?)-T	2.3 y	(+)	−	40
W.H.	56	m	GN	3.4 y	+	−	55
Z.A.	67	f	GN(?)	0.8 y	(+)	+	100
G.I.	53	f	GN	1.8 y	+	−	80
V.Ch.	60	f	U	8.2 y	(+)	+	75
S.H.	58	f	GN	1.1 y	+	−	110
T.H.	38	m	GN-T	5.0 y	+	−	45
A.Z.	43	f	GN	2.0 y	+	−	95
B.T.	40	f	GN	7.2 y	−	−	70
K.A.	57	f	GN	0.8 y	−	−	80
B.K.	35	m	GN	1.2 y	+	−	100
W.A.	51	m	U	5.2 y	+	+	160
D.K.	34	m	GN	0.8 y	+	−	90

GN = glomerulonephritis; fGN = familial GN; T = transplantation (analysis refers to patient's own kidneys); U = unknown

Patients and Methods

Some clinical data comprising age, sex, underlying renal disease, duration of haemodialysis, presence of hypertension and urinary tract infection together with the autopsy finding of renal weight are listed in Table 1.

With the exception of patients with clinically diagnosed polycystic disease, reflux nephropathy or urinary tract malformation, all haemodialysed patients who came to autopsy during the past 9 years were analyzed. The patients came from three different dialysis centers. Kidneys were removed at autopsy, sectioned in a sagittal plane and inspected macroscopically. In addition, macrophotographs were taken. Furthermore, tissue specimens fixed in formalin and (in a majority of cases) one half kidney (holoptic section) were sectioned after embedding in paraffin. The sections were stained by Masson Goldner, van Gieson and with PAS.

Findings

In none of the patients had the presence of cysts been suspected by the physicians in charge on the basis of clinical findings. No patient had macroscopic haematuria and no patient died for reasons directly or indirectly related to the presence of cysts.

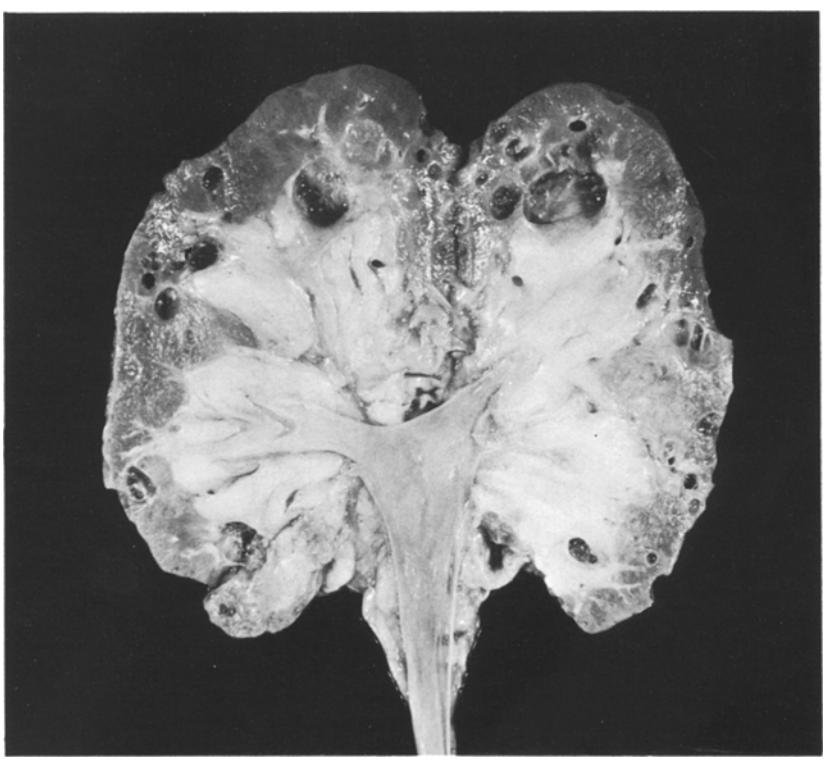

Fig. 1. Macroscopic view of the kidney of 48-year-old male patient (B.E.) with chronic glomerulonephritis. Note reduced size of the kidney and narrow rim of parenchyma; numerous cysts of variable size in cortex and medulla

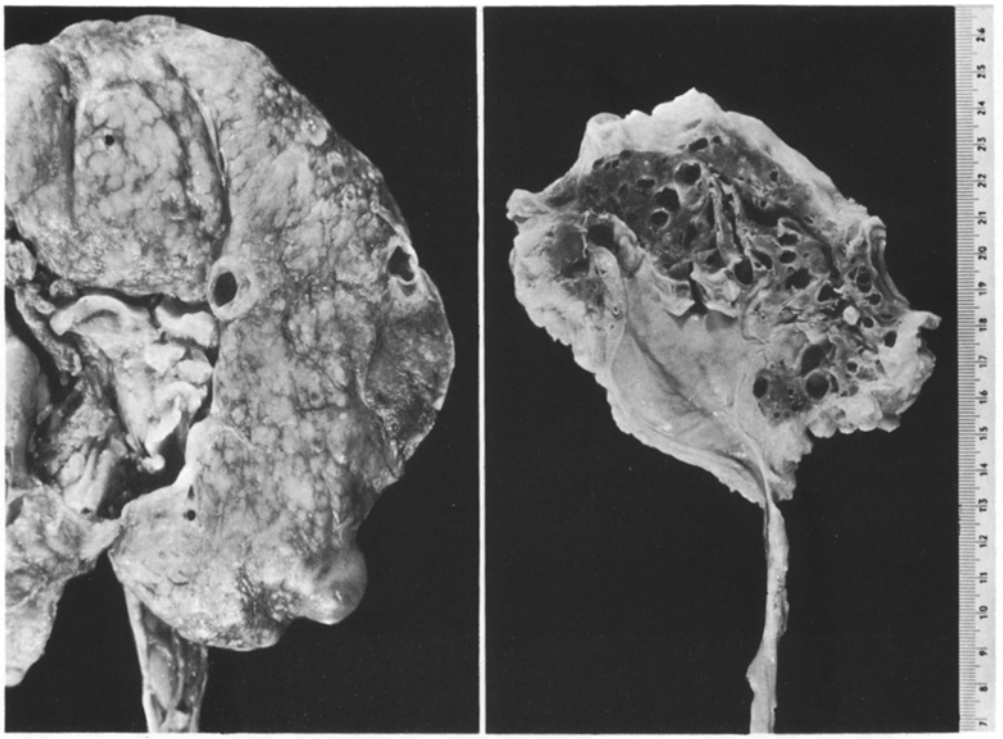

Fig. 2. Left kidney of 34-year-old male patient (D.K.) with chronic glomerulonephritis. Note outer surface of the kidney with several cysts of variable size protruding over the surface

Fig. 3. Kidney of 51-year-old male patient (B.A.) with unknown renal disease. Longitudinal section with opened renal pelvis. Kidney reduced in size. Note cystic transformation of the entire remaining renal parenchyma. Diameter of cysts ranging from microscopic size up to 1 cm

Macroscopical Findings (Figs. 1–4)

Renal size and renal weight were reduced without exception in all the patients under study. All except one patient had single or multiple randomly distributed, non-loculated cysts both in the renal cortex and in the renal medulla with a diameter varying in general from 1–10 mm (Figs. 1–4). The majority of cysts was found in the outer cortex. The distribution of the cysts was uniform affecting both poles and both kidneys. The cysts were thinwalled and usually contained clear fluid. None was infected or contained macroscopically visible concretions or blood. The renal surface usually exhibited the characteristic "granular atrophy" of kidneys in endstage renal failure. Occasionally, cysts projected above the renal surface (Fig. 2), but the cysts which occurred in the medulla, did not usually protrude into the calyces and never caused urinary tract obstruction. Pronounced cystic transformation with the appearance of more than 20 cysts was observed in 4 of the 20 cases. As shown in Fig. 3, complete cystic

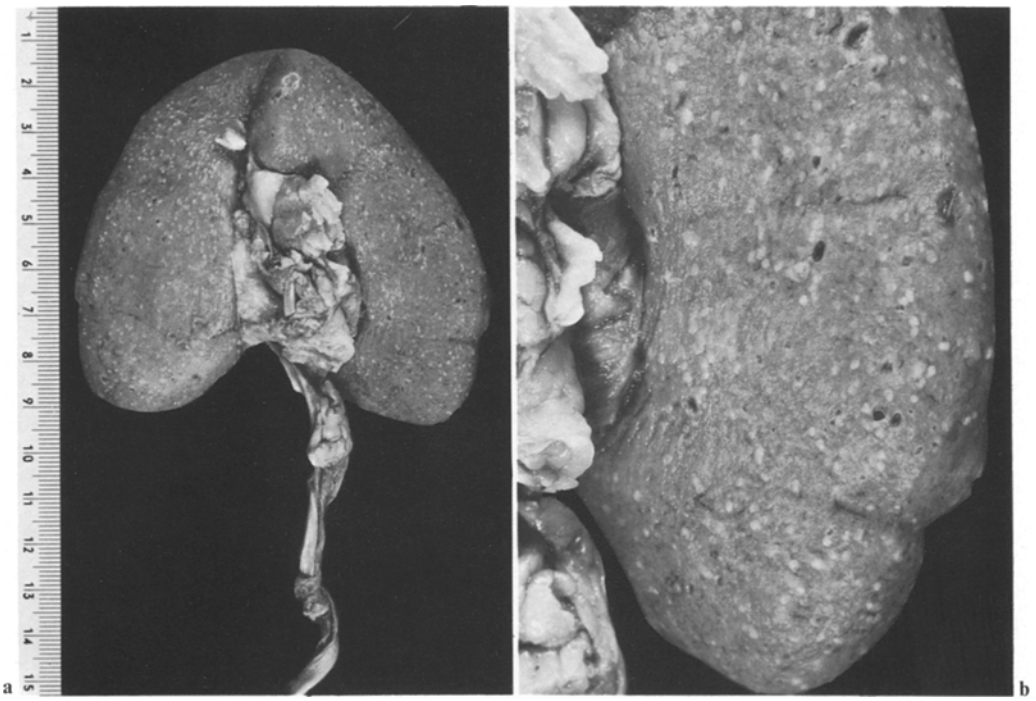

Fig. 4a and b. Macroscopic view and close up view of left kidney of 35-year-old male patient (B.K.) with chronic glomerulonephritis. Note numerous small pinhead or lentil size cysts on renal surface. In addition, multiple pinhead-size white-coloured adenomata visible on surface

transformation of the entire residual renal parenchyma was observed in one of these cases.

Macroscopically visible haemorrhage was never observed. In extrarenal organs, particularly liver, pancreas or testis, no cysts were found.

Microscopical Findings (Fig. 5–7)

No tissue reaction to the presence of cysts was observed in the surrounding parenchyma, in particular there was no cellular infiltration or fibrosis. The wall of the cysts was covered by flat or single layer epithelium (Fig. 5). In close proximity to the cysts, crystalline deposits were commonly observed, consisting of tuft- or sheaf-like birefringent crystals. Such crystals did not stain with the van Kossa reaction and presumably represented oxalate. In 4 cases, papillary adenomata, approximately 100 μ across, were observed, which were covered by single line high cuboidal epithelium (Fig. 6a–c). The epithelial cells of the adenomata did not show any cellular atypia. In 3 patients, such adenomata were found only in 1 cyst and in 1 patient they were found in several cysts. In the latter case, in addition, multiple, large, solid tumors, 0.5–2 cm across,

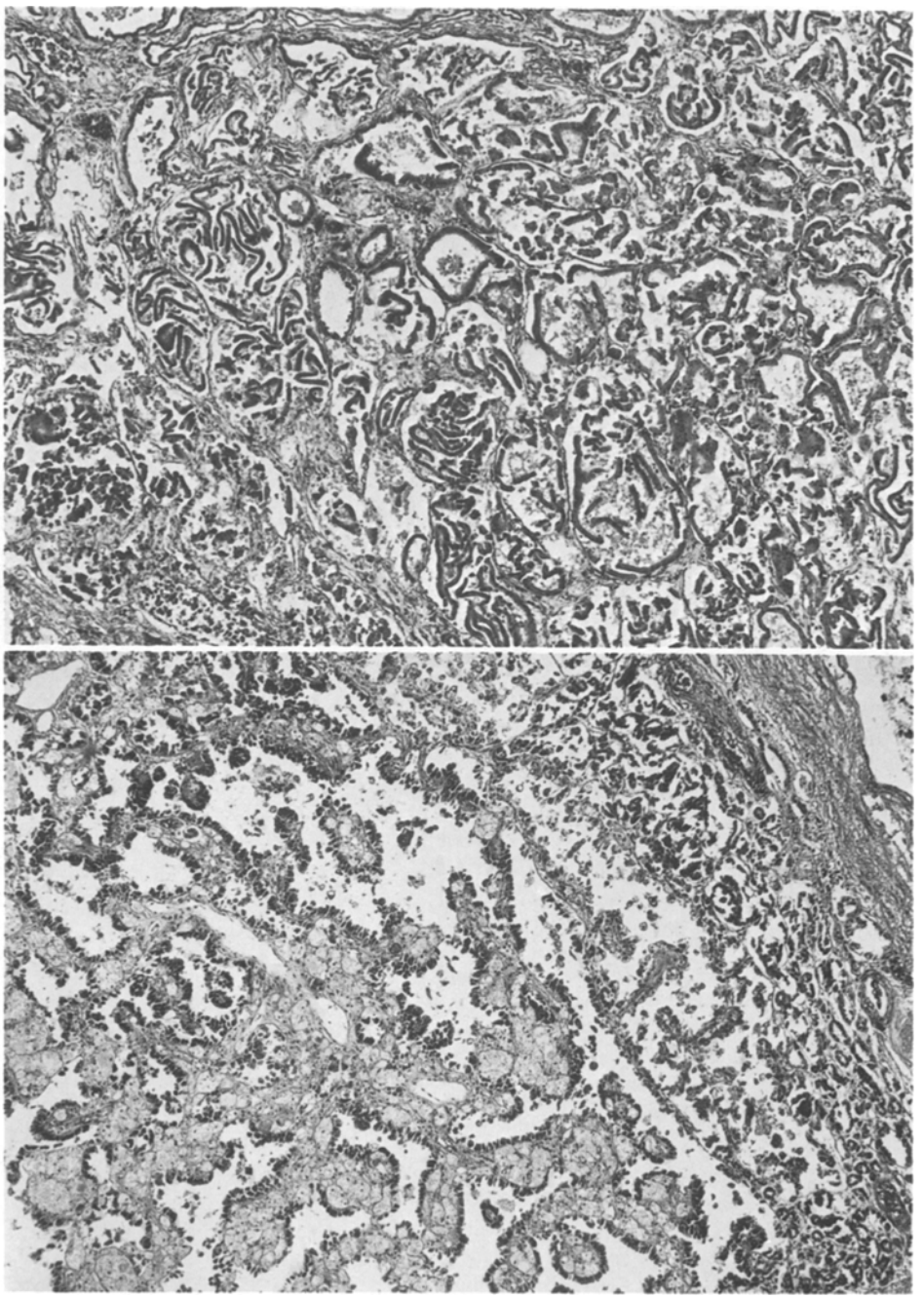

Fig. 5. Kidney of 38-year-old female patient with glomerulonephritis (M.M.). Histological section, Masson Goldner stain, magnification × 35. Note numerous cysts with single layer epithelium of cuboidal cells damaged by autolysis. In several cysts papillary arrangement of epithelium

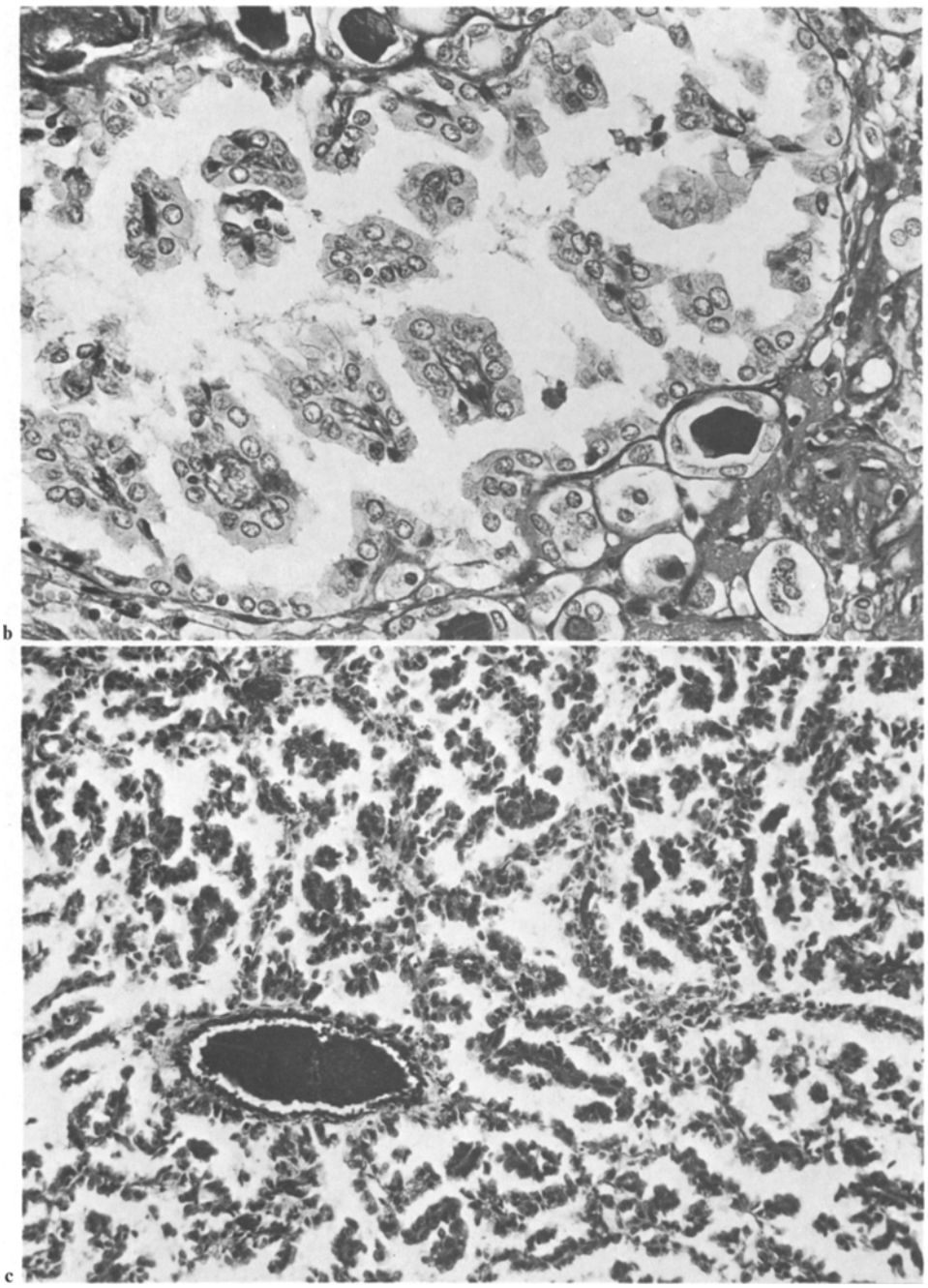

Fig. 6a–c. Three different types of papillary adenoma, encountered in renal cysts of dialysed patients. (Masson Goldner stain; magnification **a** ×100; **b** ×250; **c** ×100). **a** Note corse villi covered by darkly stained and slightly pleomorphic epithelial cells. The stroma consists of foam cells. **b** Small cysts filled with small papillary adenoma. Note uniform, bright cuboidal epithelial cells and scanty stroma. **c** Detail of the large tubulo-papillary adenoma. Note small, uniform, dark stained epithelial cells. Little stroma visible

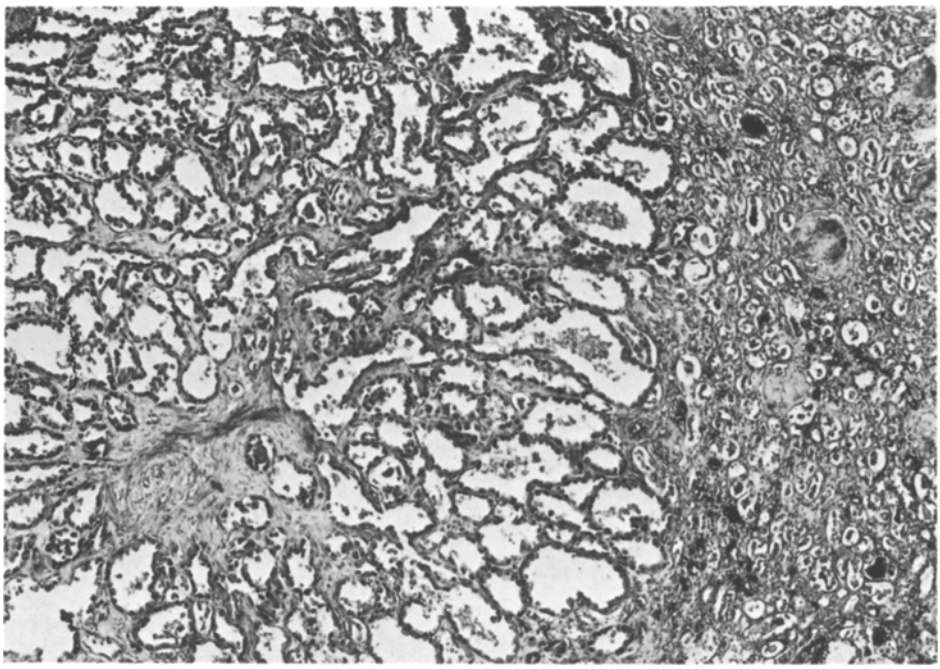

Fig. 7. Tubular adenoma (Masson Goldner stain, magnification × 35). To the right remnant kidney tissue, to the left adenomatous tissue. Note closely packed tubular cavities lined by hypertrophic cuboidal cells with darkly stained nuclei

with tubular differentiation were observed (see Fig. 7a). Such tumors contained darkly staining epithelial cells of smaller size but without cellular atypia. Neither in the papillary adenomata nor in the solid tumors were mitoses, clear cells ("Pflanzenzellen"), peritumoral fibrosis, peritumoral lymphocytic infiltration or infiltrating growth of the tumor observed. Regional lymph nodes were examined and did not show evidence of metastases.

In the microscopic sections, the content of the cysts was usually not visible. In one case, minor haemorrhage into one cyst was observed by microscopy.

Discussion

The present study is in agreement with the report of Dunhill et al. (1977) and shows that apparently acquired multiple cysts, unrelated to the underlying renal disease, can be demonstrated in a majority of patients with terminal renal insufficiency who are kept alive on haemodialysis. In 2 patients, cysts in the patient's own kidneys were demonstrable even after prolonged renal homotransplantation. This finding suggests that cyst formation is an irreversible process. By chance, apart from 2 patients all had suffered from glomerulonephritis (do-

cumented by the occurrence of a nephritic syndrome and/or by renal biopsy). Since the glomerulonephritic process in itself does not lead to cyst formation, the conclusion of Dunnill et al. (1977) that such cysts are acquired during terminal renal failure seems reasonable. Several findings in the present investigation differ from those of Dunnill et al. (1977) and deserve comment. Multilocular cysts, enlargement of kidneys through cyst formation, haemorrhage into the urinary tract or retroperitoneum or transformation into malignant tumors were not observed in any of the patients of the present series. Minor haemorrhage into a cyst was observed in 1 case only, by light microscopy. In no case were the renal cysts directly or indirectly related to the cause of death.

Small papillary adenomata were seen in 4 out of 22 patients and in 1 of these patients tubular adenomata were also found. The incidence and extent of tumor formation were considerably less than in the study of Dunnill et al. (1977); at comparable duration of haemodialysis he found multiple adenomata in 5 out of 13 patients. The occurrence of adenomata in renal cysts has been described repeatedly in literature (Gardner et al., 1978); according to Ashley (1978) the appearance of adenomata in contracted kidneys is a common and non-specific phenomenon. Dunnill et al. (1977) speculated that accumulation of carcinogenic substances during haemodialysis may predispose to the appearance of malignant renal tumors. The assumption that renal carcinoma is more frequent in dialysed patients is not supported by epidemiological evidence. The question of whether or not malignant tumors are generally more frequent in haemodialysed patients is still unsettled. The information in the literature is conflicting: some authors have found an increased incidence (Matas et al., 1975; Sutherland et al., 1977), while other investigators failed to observe an increased incidence, after allowing for the well known association of analgesic abuse and uroepithelial carcinoma (Jacob et al., 1979). Specifically, an increased incidence of renal cell carcinoma has not been observed (Jacob et al., 1979).

It is of note, however, that one patient of the present authors had haemorrhage into a right sided renal cyst. The cyst was removed surgically and contained a papilloma with the cellular characteristics of malignancy (Fig. 8). This patient is still on dialysis. Consequently, the possibility of malignant transformation of microadenomata can not be definitely excluded. The issue is difficult to settle in view of the known difficulty in distinguishing between renal adenoma and renal carcinoma (Ashley, 1978).

The pathogenetic mechanisms leading to cyst formation in uraemic patients remain unclear. Experimentally, cysts arise only if both ischaemia and urinary tract obstruction are present; isolated ischaemia and isolated elevation of pressure in the urinary tract cause atrophy rather than cyst formation (Hebler, 1930; Heptinstall, 1966). It is tempting to speculate that the simultaneous occurrence of ischaemia resulting from intimal fibrosis of arteries (Zobel et al., 1975) and tubular obstruction by oxalate crystals, intratubular organic matter or scar formation, may lead to renal cysts in the kidneys of patients with end stage renal failure. Several substances have been shown to cause cyst formation in experimental animals (Carone et al., 1974; Safough et al., 1970; Krocker et al., 1972). The non-obstructive origin of such cysts has been clearly demon-

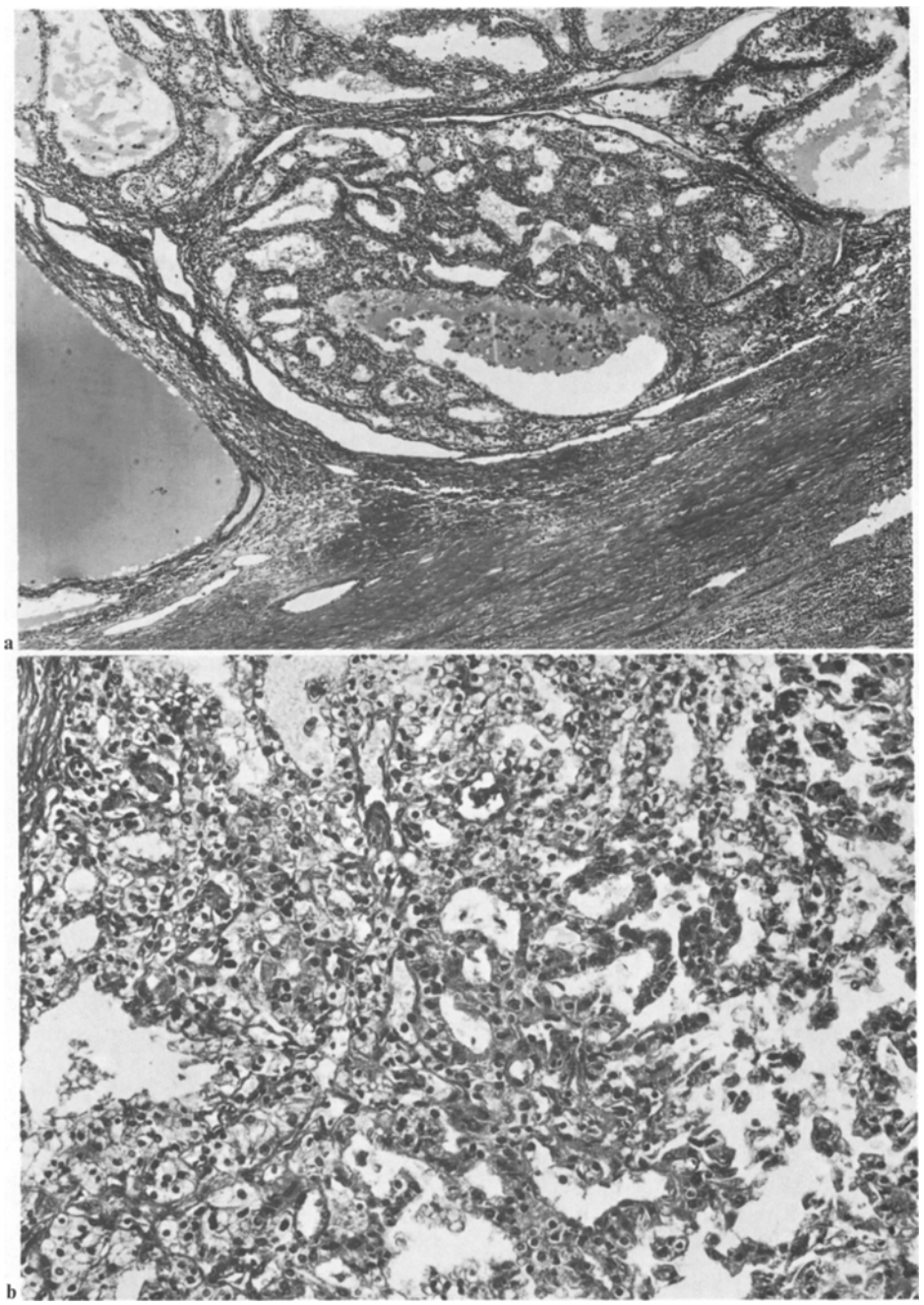

Fig. 8a and b. Malignant renal cell carcinoma in haemodialysed patient. Specimen removed at surgery (Hematoxylin Eosin stain; magnification **a** ×36; **b** ×150). **a** Malignant tumor juxtaposed to several simple renal cysts. Malignant tumor to the right simple renal cysts with single layer epithelium to the left. **b** Detail of malignant tumor. Papillary and tubular architecture, pleomorphic cells, with characteristic clear cells in some areas

strated in micropuncture studies by Carone et al. (1974). There is no positive evidence for the accumulation of analogous substances in uraemia, but the possibility cannot be positively refuted.

The cysts observed by Dunnill et al. (1977) and in the present study are clearly distinguished from the foci of "thyroid-like degeneration" as commonly observed in patients with "chronic atrophic nephritis" (Heptinstall, 1966). In such foci, clusters of tubules with flattened epithelium are observed which contain hyaline yasts in the lumen which are homogeneous or laminated; upon microdissection these structures appear to consist of closed spheres or tubes (Heptinstall, 1966). In contrast, the cysts in uraemic patients contain clear fluid and do not occur in clusters.

Single or multiple cysts occurs quite frequently in healthy individuals without renal disease (Hepler, 1930; Braasch and Hendrick, 1944; Glaser, 1952). Careful examination of adult kidneys at autopsy reveals that over 50% contain one or more small macroscopic cysts in the renal cortex.

Several lines of evidence argue against the assumption that acquired cysts represent a specific complication of maintenance haemodialysis. Previous investigators (Peipers, 1894) observed the occurrence of cysts which contained non-specific organic material in the kidneys of patients with endstage renal failure in the absence of haemodialysis. Our own experience (unpublished observations) shows that such cysts, although few in number and smaller in size, may occur prior to the onset of haemodialysis in patients with terminal renal failure. Consequently, renal cysts do not represent a phenomenon which is specific for maintenance haemodialysis. It appears likely that haemodialysis promotes cyst formation by permitting longer survival of uraemic patients with scarred kidneys.

The clinical importance of cyst formation remains to be established. The incidence of macroscopic haematuria, perirenal haemorrhage or possibly malignant transformation remain to be defined. At autopsy, acquired cysts may cause problems for the anatomist since distinction from polycystic disease may become difficult if extensive cyst formation results in enlargement of the kidneys.

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Accepted December 31, 1979

Addendum

After submission of this paper, two papers appeared which put the epithelial proliferative changes, as observed in the present studys, into a somewhat different perspective. Both in animal experiments (Evan, A.P., Gardner, K.D. Jr.: Nephron-obstruction in nordihydroguaiaretic acid-induced renal cystic disease; Kidney Int. **15**, 7–19, 1979) and in patients with adult polycystic disease (Evan, A.P., Gardner, K.D., Bernstein, J.: Polypoid and papillary epithelial hyperplasia: potential cause of ductal obstruction in adult polycystic disease, Kidney Int. **6**, 743–750, 1979), proliferative epithelial changes were found in association with cysts. This study suggests, but does not prove, an obstructive origin for such cysts. Consequently, the epithelial proliferation, as observed in the present study, may be cause rather then the consequence, of renal cystic transformation.