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Epithelial Hyperplasia in Human Polycystic Kidney Diseases

Its Role in Pathogenesis and Risk of Neoplasia

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The importance of tubular epithelial hyperplasia in polycystic kidney diseases has become apparent during the last decade. Micropapillary hyperplasia occurs in autosomal dominant polycystic kidney disease, in localized cystic disease, and in acquired cystic disease. Neoplastic or severely dysplastic epithelial hyperplasia occurs in von Hippel–Lindau disease. A histopathologically distinctive epithelial hyperplasia occurs in tuberous sclerosis. In each of these conditions, epithelial hyperplasia may be related to cyst formation and may also impose an increased risk of malignancy—a risk that seems to be highest in patients under treatment with long-term hemodialysis for end-stage kidney disease. Although hyperplasia in some of these diseases may share a common pathway of development, it is more probable that the histopathologic differences reflect different pathogenetic pathways that converge on a common endpoint. (Am J Pathol 1987, 129:92–101)

RECENT STUDIES have led to the rediscovery of epithelial hyperplasia as an important histopathologic feature of human polycystic kidney disease (PKD).[1–3] Epithelial hyperplasia in PKD was described in Europe more than 100 years ago[4,5] and ascribed to neoplasia.[4,6] Epithelial micropapillary hyperplasia, apparently progressing to benign neoplasia, was described in America in 1920.[7]

Evan and Gardner[8] rekindled interest in the abnormality when they described the small intratubular polyps that result from epithelial hyperplasia in the experimental model of renal cystic disease induced by diphenylamine. Evan, Gardner, and Bernstein[3] were able to show similar micropapillary epithelial hyperplasia in human "adult," autosomal dominant PKD (AD-PKD).

Epithelial hyperplasia is common to several forms of human renal cystic disease, both congenital and acquired,[9,10] a fact not widely recognized. In this paper we review the morphologic characteristics of abnormal cell growth in some polycystic kidney diseases and discuss its potential significance in relation to the pathogenesis of cysts and to the risk of malignant degeneration.

Epithelial Hyperplasia and Micropolyp Formation

Autosomal Dominant Polycystic Kidney Disease

Micropapillary hyperplasia in AD-PKD is evident as uneven and irregularly distributed enlargement and overgrowth of the epithelium that lines ducts and tubules (Figures 1 and 2). It results in intraluminal projections of cells that are seemingly piled upon one another and in micropolyps that are partially vascularized (Figure 3). It occurs not only on the walls of macroscopic cysts but also along the walls of minimally dilated tubules and ducts. It is uneven in its

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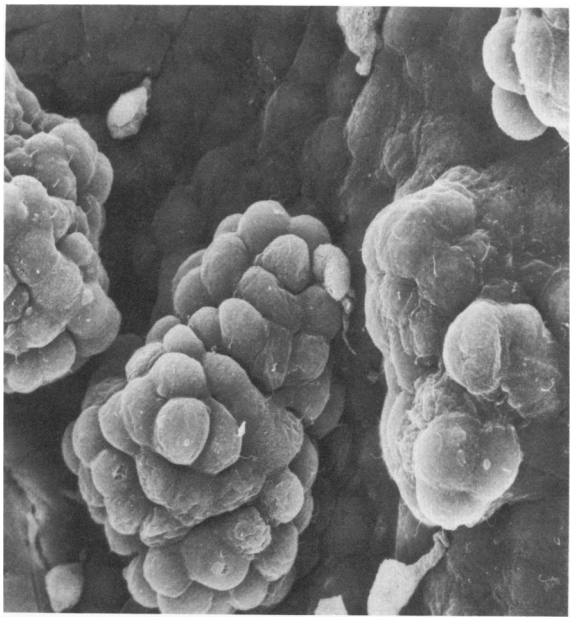

Figure 1—Autosomal dominant polycystic kidney disease. Scanning electron micrograph shows micropolyps, covered with hyperplastic epithelium, projecting into a cyst. (×600)

distribution, which suggests that only some cells participate in the hyperplastic response and that not all segments of the nephron are affected.

Identification of cell type and site of origin by morphologic criteria is often difficult. Some cells have remnants of surface specializations typical of specific segments of the nephron, eg, remnants of brush border, but many cells have lost their distinctive characteristics.

Few attempts have been made to quantify the prevalence of hyperplastic epithelium and micropolyps within the polycystic kidney. Evan et al[3] had found dilated and cystic tubules to be affected in each of four kidney specimens, and a more recent study by Gregoire et al[11] confirmed the presence of epithelial micropolyps in 90% of 87 patients, even in those without renal insufficiency or severe renal enlargement. Grantham et al[12] found markedly hyperplastic epithelium in 5% of 387 cysts in kidneys obtained from 10 patients and concluded that epithelial hyperplasia, even without micropolyps, is the central element in cyst enlargement.

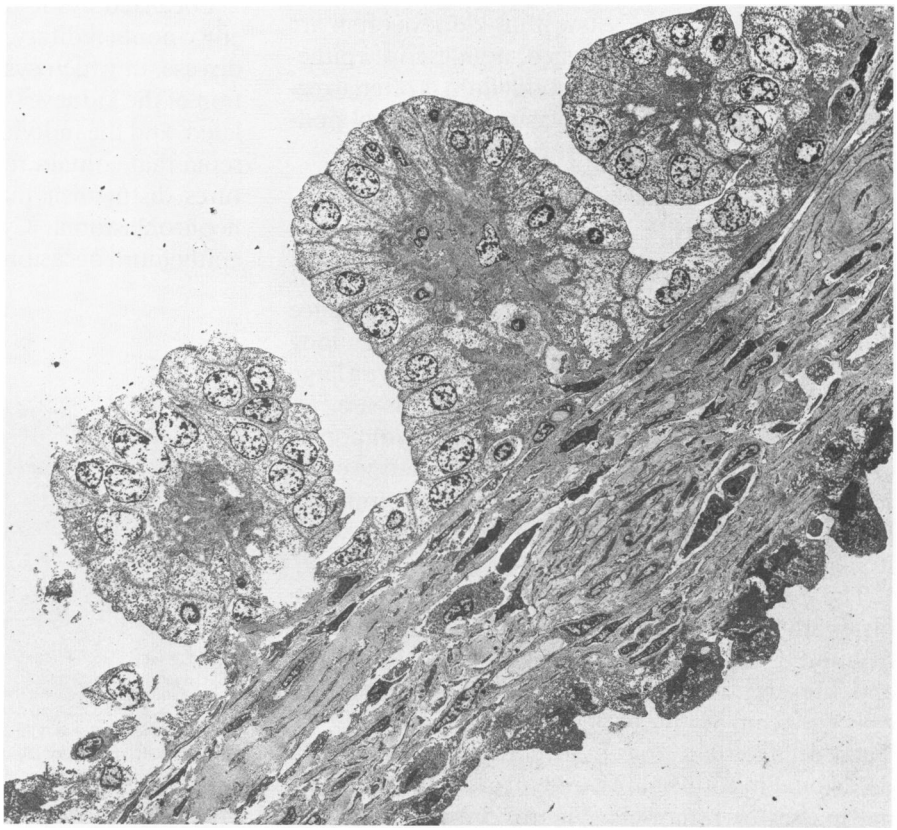

Figure 2—Autosomal dominant polycystic kidney disease. Low-magnification transmission electron micrograph shows two adjacent cysts separated by a thin septum. The epithelium lining one of them is hyperplastic and thrown into micropapillary projections, whereas the epithelium lining the other is atrophic. (×750)

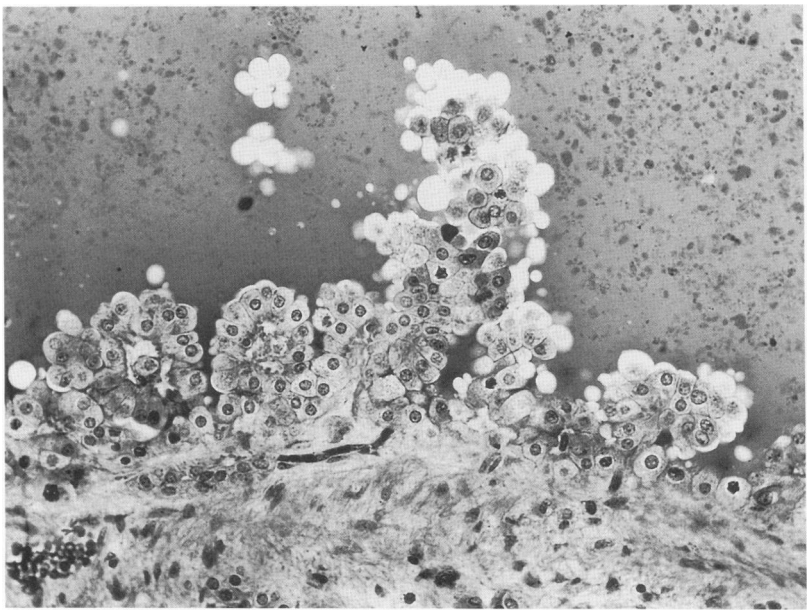

Figure 3—Autosomal dominant polycystic kidney disease. The epithelium lining a 2-mm cyst is hyperplastic, with intraluminal projections of piled-up cells and partially vascularized micropolyps. (Azure II–methylene blue stain, ×200)

Von Hippel–Lindau Disease

Von Hippel–Lindau disease (cerebroretinal angiomatosis) is a dominantly inherited syndrome of cerebellar and retinal hemangioblastomas, pancreatic cysts and tumors, and epididymal cysts and tumors. It also includes the less popularized occurrence of renal cysts and tumors.[13,14] Cysts within kidneys often are described as lined with flattened, nondescript epithelium.[15] In fact, however, the epithelium is often irregularly hyperplastic and neoplastic, with mural nodules of clear-cell hypernephroma (Figure 4).[16,17]

Tuberous Sclerosis

Tuberous sclerosis (Bourneville's disease, epiloia) is also a dominantly inherited disorder. The occurrence of small renal cysts as incidental findings has long been known.[18] An occasional patient may have a large number of cysts described as polycystic disease.[19,20] Severe cystic disease without angiomyolipomas occurs in young patients, sometimes antedating clinical recognition of the tuberous sclerosis complex.[21] Diffuse cystic disease persists into adult life,[22–24] when it may be associated with chronic renal failure.[25]

The cysts in tuberous sclerosis have a distinctive histopathologic appearance that differentiates them from other forms of renal cystic disease.[26] Bernstein and Meyer[22] described large eosinophilic epithelial cells that seem unique to the disorder (Figure 5).[24,27,28] These cells contain large, hyperchromatic nuclei, with occasional mitotic figures, and form small intraluminal masses or tumorlets (Figures 5 and 6).[19,28] The cellular abnormality appears to be common, even in noncystic kidneys, and its presence may serve as a diagnostic marker.[19]

Localized Cystic Disease

Localized cystic disease is an uncommon, apparently nonhereditary, and benign form of renal cystic disease, in which cyst formation is confined to a portion of the kidney.[29–31] The cystic area is not encapsulated, and the individual cysts are separated by coarse septa that contain renal parenchyma. These two features distinguish the condition from benign cystic nephroblastoma. Cysts are lined with hyperplastic epithelium, occasionally with myriads of micropapil-

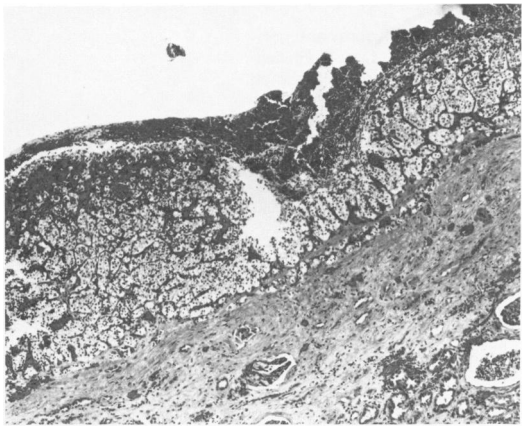

Figure 4—Von Hippel–Lindau disease. Radical nephrectomy in a 27-year-old man with a history of cerebellar hemangioblastoma showed the kidney to contain cysts and a tumor. Several cysts were lined with hyperplastic and atypical epithelium, and one of the cysts contained polypoid mural nodules of tumor cells. (H&E, ×40)

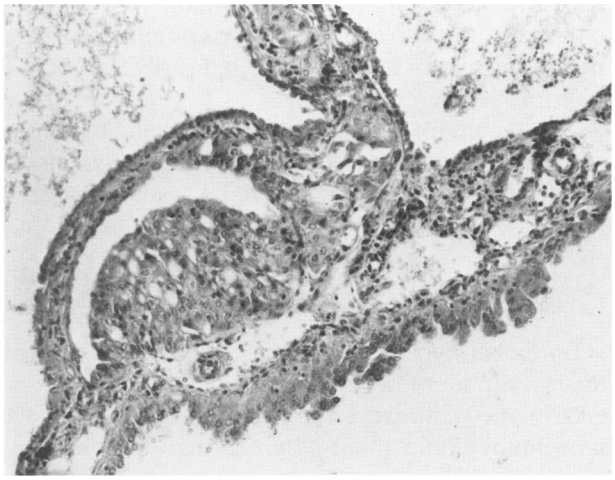

Figure 5—Tuberous sclerosis. Cysts are lined with extremely hyperplastic, eosinophilic epithelium that forms intraluminal tumorlets. (H&E, ×125)

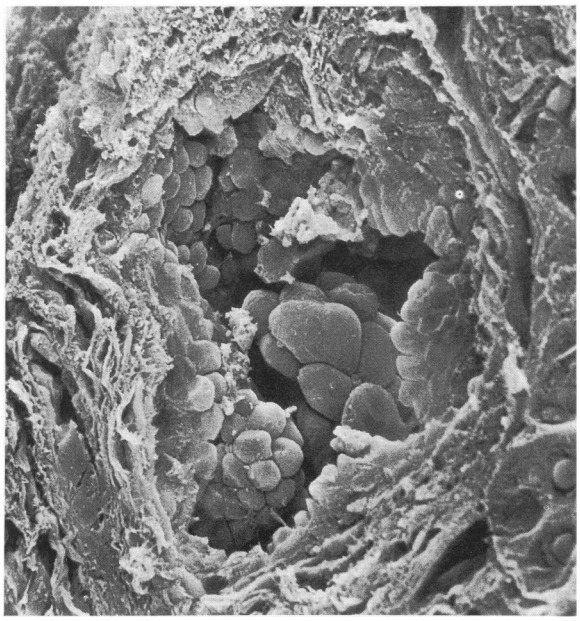

Figure 6—Tuberous sclerosis. Scanning electron micrograph of a dilated collecting duct shows it to be lined with hyperplastic epithelium forming intraluminal micropolyps. (×800)

lae (Figure 7). Their histologic appearance is indistinguishable from that of cysts in AD-PKD.[30] Despite this structural similarity, the abnormality has not been familial or associated with progressive renal failure in the small number of cases reported.

Acquired Renal Cystic Disease

The occurrence of cysts in end-stage kidneys, especially those of patients on long-term hemodialysis, has received increasing attention since its initial description by Dunnill et al in 1977.[32] The phenomenon has been described in more than 400 patients. Several recent reviews,[10,33,34] based on overlapping surveys of the literature, are in accord that acquired renal cystic disease (ARCD) develops in some 40% of patients undergoing treatment with hemodialysis. Its development correlates directly with the duration of therapy and may vary with geographic locale.[10]

Histopathologic studies[35–42] show the cysts often to be lined with hyperplastic and atypical or dysplastic epithelium that forms micropapillae and small intraluminal tumors (Figure 8). ARCD has developed in a few patients treated with peritoneal dialysis.[43] ARCD may be prevented, retarded, or reversed by functioning renal allotransplants.[44,45]

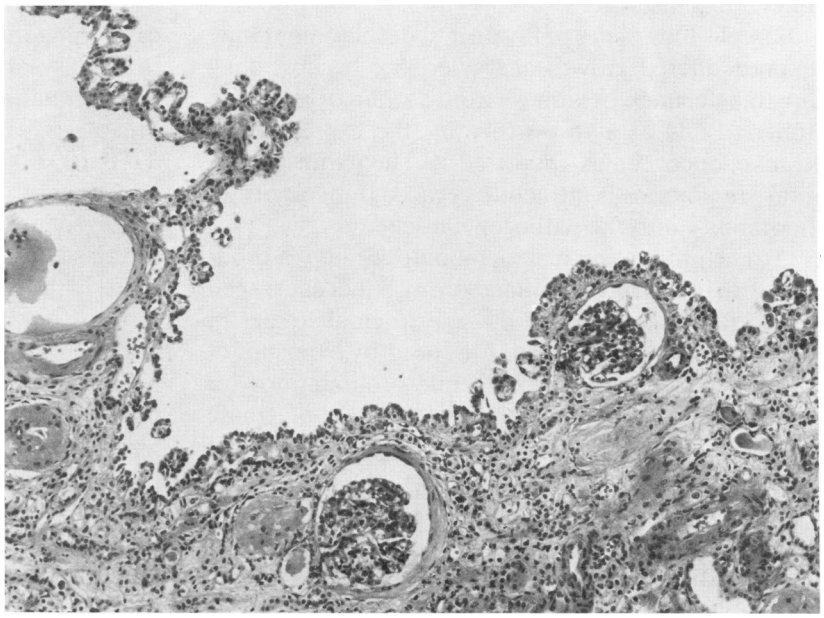

Figure 7—Localized cystic disease. A cyst is lined with hyperplastic epithelium forming innumerable micropolyps. (H&E, ×100)

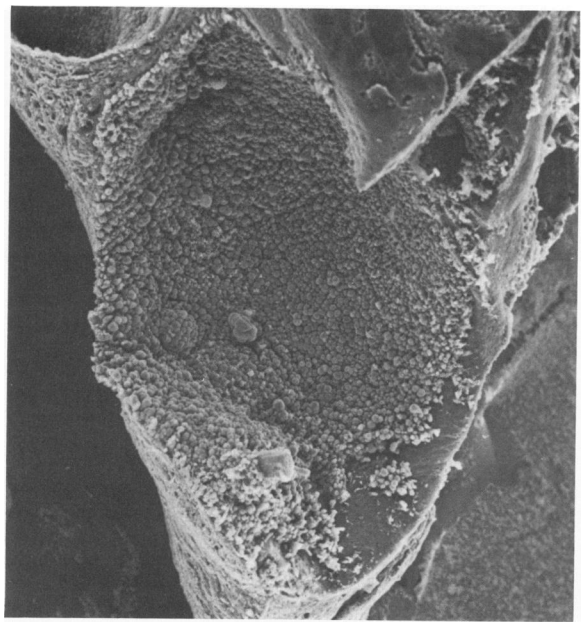

Figure 8—Acquired cystic disease. Scanning electron micrograph of a cyst from the same specimen shown in Figure 11 reveals micropapillary hyperplasia of the epithelial lining. (×90)

Pathogenesis of Epithelial Hyperplasia

In each of these disorders, the cause of alterations in epithelial growth patterns is unknown. Four suggestions, based on experimental and clinical observations, have been advanced:

1) Cell growth can be stimulated *in vitro* simply by "stretching" the support on which cells are grown.[46] Applied to renal cystic disease, the observation suggests that cyst-wall cells proliferate as a consequence of cyst expansion.

2) Cells lining sites of future cyst development may express altered growth characteristics because they are transformed. In kidneys from a strain of mice that inherit PKD as a recessive trait, the expression of C-myc oncogene is increased.[47] The "transformation" hypothesis is attractive because it incorporates heritability into the pathogenetic scheme.

3) The production of a metabolite, perhaps a product of an inborn error of metabolism,[48] that causes cell proliferation is suggested by experimental studies in which renal cystic disease is induced by exposure of rats to specific chemicals.[3] While proliferation is a morphologic characteristic of several of these models,[3] neither has a cystogenic metabolite been identified in humans nor has cystic disease developed in kidneys transplanted into humans with renal failure secondary to AD-PKD.

4) In ARCD among long-term dialysis patients, the acquisition and retention of renotropic growth factors, the retention and accumulation of cystogenic chemicals, and the alteration of basement membrane metabolism may lead to epithelial proliferation and cyst formation.[33]

The search for explanations of epithelial hyperplasia constitutes one of the more fascinating targets for future research in the field of renal cystic disease.

Malignancy in the Cystic Kidney

Epithelial hyperplasia in the cystic kidney may be the forerunner of neoplasia, as suggested by the presence of oncogene expression, variability in cell surface morphology, and micropolyp formation. The concurrent development of cysts and malignancies in the kidneys of carcinogen-fed rats[49] supports the concept. However, the rates at which benign and malignant renal tumors actually occur vary considerably among the human diseases under discussion.

Autosomal Dominant Polycystic Kidney Disease

In AD-PKD, polyps are so numerous within some cysts[11] that they might be regarded as neoplastic, an interpretation that goes back to the earliest studies of epithelial hyperplasia in PKD.[4–6] The relative frequency of recent reports (reviewed by Dees et al[49] and Ng and Suki[50]), especially of those reports describing bilateral involvement,[52,53] suggests that the rate of neoplasia is higher in AD-PKD than in the general population. We have encountered one renal cell carcinoma in 15 AD-PKD nephrectomies from 11 patients (Figure 9) and 1 in 13 autopsy specimens during a 16-year period. Gregoire et al[11] found one renal cell carcinoma in 87 surgical and postmortem cases during a 38-year period that partially overlapped ours. The frequency of renal cell carcinoma in the combined 41-year series was 3/111, or approximately 2700/100,000, compared with an expected 41-year incidence of approximately 220/100,000, based on an observed annual incidence of 5.4/100,000.[54] Despite the bias in selection of AD-PKD cases, the pooling of material from two institutions, and the degree of scrutiny employed in studying these cases, we find a significantly higher, 10-fold incidence of malignant neoplasia in AD-PKD patients than in the general population ($P < 0.001$).

Bilaterality is present in 20% of carcinomas associated with AD-PKD, in less than 5% of carcinomas that are not associated.[50] Bilaterality can be taken as a point in favor of genetic determinants, although it can also relate to the retention of mitogens and carcinogens within obstructed and cystic nephrons. Even

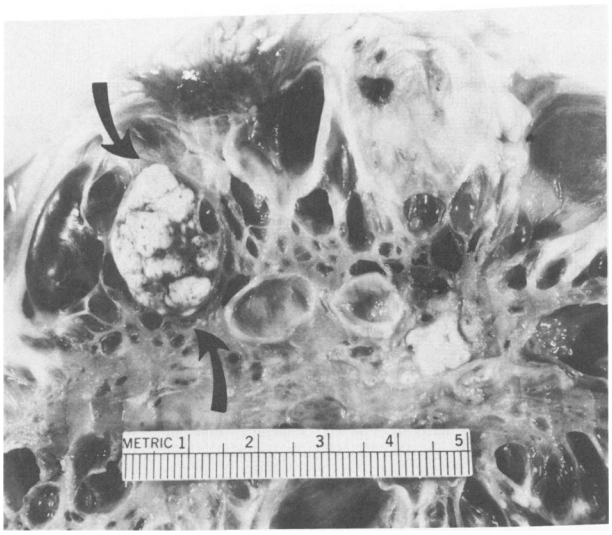

Figure 9—Autosomal dominant polycystic kidney disease. A radical nephrectomy was performed when a 2-cm renal cell carcinoma (*arrows*) developed in a cystic kidney in a 55-year-old man. The patient subsequently received a renal allograft but died a few years later of cerebral hemorrhage from a ruptured berry aneurysm.

though some tumors reported in AD-PKD have been incidental findings, the number discovered clinically and radiographically seems to be increasing. About one-third of approximately 50 grossly apparent neoplasms have been described as malignant.[50–52] Most reports of renal carcinoma in AD-PKD have been of patients not under treatment for chronic renal failure. However, the risk may be increased in patients who retain their native kidneys during long-term treatment with hemodialysis,[50] even though the first report[55] antedated the availability of hemodialysis.

Von Hippel–Lindau Disease

Renal tumors also occur in von Hippel–Lindau disease. They were recognized in the earliest description of the disease and originally were thought to be benign.[56] They clearly have malignant potential, because they are both locally invasive and distantly metastasizing.

The occurrence in a young patient of multiple hypernephromas or of hypernephromas arising in cysts (Figure 10) should prompt a search for other manifestations of von Hippel–Lindau disease. Although cysts are usually multiple and limited in number, occasional kidneys may be severely cystic, resembling AD-PKD.[13,14] Similarly, most affected kidneys contain one or a few tumors, but as many as 15 tumors in one patient have been reported.[16]

Even though the cysts are often described as lined

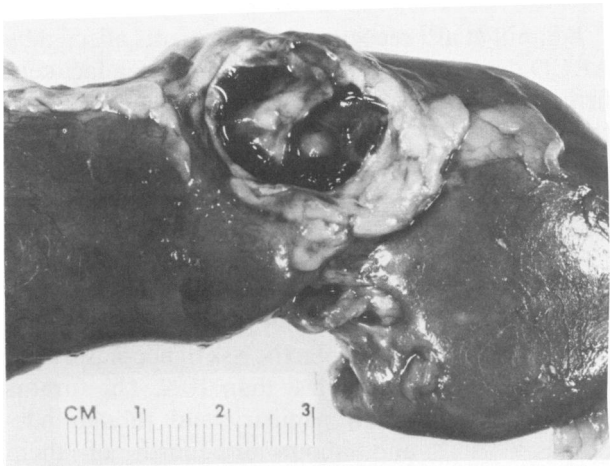

Figure 10—Von Hippel–Lindau disease. Mural nodules of pale tumor tissue were present within cysts of a kidney containing multiple tumors and multiple cysts. Postmortem examination of 31-year-old woman with cerebellar hemangioblastomas and pancreatic cysts.

with flattened, nondescript epithelium,[15] the epithelium is often irregularly hyperplastic, with mural nodules of clear-cell hypernephroma[16,17] (Figure 3). The two abnormalities, cysts and tumors, seem to be more than casually related, for the hyperplastic and nodular epithelial lining appears to be both the cause of tubular obstruction and the direct precursor of malignancy.

Tuberous Sclerosis

The cystic disease of tuberous sclerosis carries a risk of both chronic renal insufficiency and malignant degeneration. Patients in chronic renal failure have had cystic disease and multiple tumors together, the tumors including both angiomyolipoma[22,24,56–62] and renal carcinoma.[61,62] Severe, diffuse cystic disease is, except for the association with angiomyolipomas, grossly indistinguishable from AD-PKD.[22,24,57,60]

Epithelial hyperplasia in tuberous sclerosis appears to be linked to the development of renal cell carcinoma. While fewer than a dozen well-documented cases have been published,[61–70] the association appears not to be due to chance alone. The patients have been young, 7–39 years, and at least 4 have had bilateral tumors. One 28-year-old man had a clear-cell carcinoma and five oncocytomas in one kidney and a clear-cell carcinoma, a papillary carcinoma, and an oncocytoma in the other.[61] An 18-year-old woman had a mixed papillary and clear-cell carcinoma in one kidney and three separate papillary carcinomas in the other.[63] Most published cases have not had adequate follow-up, but one patient, a 24-year-old woman, died of metastatic disease.[67]

Acquired Renal Cystic Disease

Dunnill et al[32] recognized that patients affected by ARCD developed multiple renal tumors, a fact confirmed by more recent studies[10,71,72] (Figure 11). Although the risk of neoplasia in general may increase in patients on long-term dialysis,[73] with or without immunosuppression after renal transplantation,[74] and although renal tumors develop in noncystic kidneys,[75] renal tumors of all types, both benign and malignant, occur in about 20% of patients with ARCD.[10,33,34] If in 40% of long-term dialysis patients ARCD develops,[10,33,34] then the risk of neoplasia in all such patients is slightly less than 10%. The tumors have included benign papillary and tubular adenomas,[32,37,41,76] and about one-fourth of them have been malignant on histopathologic grounds.[38,39,41,76–79] A small proportion of the malignant tumors[32,34,36,80,81] have been clinically malignant, with metastases and deaths. Gardner and Evan[10] used published data to calculate the risk of renal adenocarcinoma among dialysis patients. The incidence was 6/1000 among all dialysis patients, and it increased to 45.5/1000 when only those with acquired cystic disease were considered.

Although epithelial proliferation in cystic kidneys does not invariably lead to the development of macroscopic tumors and malignancy, the relative infrequency with which adenocarcinomas are found in noncystic, compared with cystic, kidneys,[10] however, strongly suggests a causal relationship between epithelial hyperplasia and both cysts and tumors.

Epithelial Hyperplasia and Renal Cyst Formation

The "Obstruction" Hypothesis

We have reviewed in this paper five renal cystic diseases of patently diverse etiologies, in which epithelial cell proliferation and renal cyst formation coexist. The association, when coupled with observations of elevated intracystic pressures in AD-PKD[82] and experimental models,[8,83,84] provides the basis for the "obstruction" hypothesis of renal cyst formation. The presence of partial rather than complete obstruction is indicated by observations in both AD-PKD (cystic nephrons contribute to the final urine)[85,86] and experimental models (inulin injected into cysts can be recovered in urine from the injected kidney).[84,87] Conceptually, partial obstruction could result from epithelial hyperplasia and micropolyp formation. Cell proliferation in experimental models, demonstrated by increased thymidine uptake and cell counts, clearly precedes nephron dilatation,[84,87] Evan et al,[3] by scanning electron microscopy, found 20–30% of all micropolyps to be located at cyst outlets and 15% of cystic tubular segments to contain obstructing polyps.

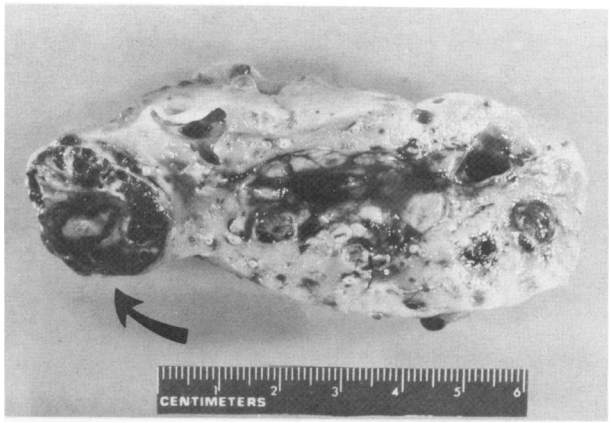

Figure 11—Acquired cystic disease. The kidneys were removed because of the development of bilateral tumors in a 47-year-old man with end-stage kidneys and acquired cystic disease. This kidney contained a 2.5-cm hemorrhagic renal cell carcinoma (*arrow*). (Photograph courtesy of Department of Pathology, Presbyterian Medical Center, Albuquerque, NM.)

Kidneys in AD-PKD contain considerable residual parenchyma. Only a small proportion of nephrons is dilated to the point of cyst formation.[9,33] The involvement of a minority of nephrons within each kidney perhaps reflects a diversity of nephrons resulting from both genetic and local influences. Studies of infants in affected families have shown focal nephronic dilatation in what was thought to be incipient AD-PKD.[88] It appears probable that progression to renal insufficiency depends on nephronic loss following compression and atrophy of adjacent parenchyma, rather than on recruitment of additional nephrons into cysts.[9]

The cysts of AD-PKD are localized to segments of nephrons, as shown in reconstructions[85] and microdissections,[89,90] and the cyst epithelia retain some of the morphologic[12,91,92] and functional[93] characteristics of nephron segments. Although cysts may develop in any portion of the nephron, they have a predilection for Henle's loops and collecting tubules.[85,89,90] Segmental localization of the abnormality, like the involvement of relatively few nephrons, does not contradict the genetic basis of the disease, as it is clear from abundant evidence of morphologic and functional heterogeneity that different segments of the nephron must operate under different genetic controls.

The "Increased Compliance" Hypothesis

Genetic abnormalities are subject to epigenetic modification. Cysts might localize, for example, at points of weakness, ie, certain segments might ordi-

narily have more compliant walls that dilate preferentially in response to distal obstruction. Dilatation could theoretically result from a primary, genetically determined weakness or increased compliance of basement membranes and surrounding interstitium, but tubular basement membranes in AD-PKD are typically thicker than normal and cannot be demonstrated to have increased compliance.[94]

While increased basement membrane compliance has not to date been supported by experimental results or direct observations, certain findings continue to suggest its presence in patients with AD-PKD. Patients reportedly exhibit increased frequencies of intracranial aneurysms,[95] colonic diverticula,[96] cysts in other organs,[97] and mitral valve prolapse.[98] All of these abnormalities might be consequent to a systemic defect in basement membrane elasticity. All occur at locations at which transmural pressure gradients are or could be increased. Altered basement membrane composition has been demonstrated in one experimental model[99] and altered basement membrane morphology in AD-PKD epithelial cultures.[100] The compliance theory remains, therefore, under consideration.

The "Transformation" and "Inflammation" Hypotheses

Two additional but as yet unsubstantiated hypotheses of cyst formation that relate disordered epithelial cell growth to renal cyst formation have emerged in recent years. One, the "transformation" hypothesis, proposes that cells lining some nephrons change in response to genetic or environmental determinants. Once transformed, these cells proliferate abnormally and, to account for apparently increased intracystic fluid volumes and accelerated rates of cyst expansion, alter their transport characteristics. The expansion of cysts could explain the findings of nephron compression[9] and elevated intracystic hydrostatic pressures in AD-PKD and in several experimental models. Cell proliferation alone, without fluid retention or accumulation, does not seem to be an adequate explanation of cyst formation, because proliferating cells would simply fill the lumens of tubules and ducts. The second hypothesis invokes the inflammatory response and altered prostaglandin metabolism within cystic kidneys to account for proliferation and nephron dilation. Either of the two might account for altered basement membranes, the former through abnormal production and the latter through increased destruction and subsequent replacement. Either could explain the heterogeneity in structure and function that characterizes cystic kidneys in animal and man.

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