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The pck rat: A new model that resembles human autosomal dominant polycystic kidney and liver disease

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The pck rat: A new model that resembles human autosomal dominant polycystic kidney and liver disease.

Background. The pck rat is a recently identified model of polycystic kidney disease (PKD) and liver disease (PLD) that developed spontaneously in the rat strain Crj:CD/SD. Its pattern of inheritance is autosomal recessive.

Methods. To characterize this new model, we studied pck rats derived from F9 breeding pairs from Charles River Japan and control Sprague-Dawley rats. Blood and tissues (kidneys, liver, and pancreas), obtained from these rats at 1, 7, 21, 70, and 182 days of age, were used for biochemical determinations, light and electron microscopy, and immunohistochemistry.

Results. The pck rats develop progressive cystic enlargement of the kidneys after the first week of age, and liver cysts are evident by day 1. The renal cysts developed as a focal process from thick ascending loops of Henle, distal tubules, and collecting ducts in the corticomedullary region and outer medulla. Flat and polypoid epithelial hyperplasia were common in dilated tubules and cysts. Apoptosis was common and affected normal, as well as dilated tubules, but less frequently cysts lined by flat epithelium. The basement membranes of the cyst walls exhibited a variety of alterations, including thinning, lamellation, and thickening. Focal interstitial fibrosis and inflammation were evident by 70 days of age. Segmental glomerulosclerosis and segmental thickening of the basement membrane with associated effacement of the podocyte foot processes were noted in some rats at 70 days of age. The PKD was more severe in male than in female pck rats, as reflected by the higher kidney weights, while there was no gender difference in the severity of the PLD. Mild bile duct dilation was present as early as one day of age. With age, it became more severe, and the livers became markedly enlarged. Even then, however, there was only a mild increase in portal fibrosis, without formation of fibrous septae. Slight elevations of plasma blood urea nitrogen levels were detected at 70 and 182 days of age.

Conclusions. The pck rat is a new inherited model of PKD and PLD with a natural history and renal and hepatic histologic abnormalities that resemble human autosomal dominant PKD. This model may be useful for studying the pathogenesis and evaluating the potential therapies for PKD and PLD. The identification of the *pck* gene may provide further insight into the pathogenesis of autosomal dominant PKD.

Key words: cyst development, tubular epithelial hyperplasia, glomerular basement membrane, apoptosis, inherited disease.

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Autosomal dominant polycystic kidney disease (ADPKD) is genetically heterogeneous. Much of the understanding of its pathogenesis derives from studies in animal models. While chemically induced models were initially used, an increasing number of inherited models of renal cystic disease have been identified in recent years [1–4]. Unfortunately, while some of them resemble human autosomal recessive polycystic kidney disease (ARPKD), none of the spontaneously inherited models are a perfect paragon for ADPKD. The Han:SPRD rat, which has been extensively used as a model of ADPKD, significantly differs from the human disease, mainly by the predominant involvement of proximal tubules in the heterozygote state and by the lack of extrarenal manifestations, except for a few liver cysts in old females [5–8]. Recently, a number of *Pkd1* and *Pkd2* gene-targeted mice have been generated, but the phenotypic expression of the disease in the heterozygote state has been very mild [9–12]. The compound heterozygote Pkd2−/WS25 most closely resembles human ADPKD. Many studies, mainly using spontaneously occurring models of inherited disease, have shown that the course of the renal cystic disease can be markedly altered by therapeutic interventions [13, 14]. However, the results of treatment are inconsistent and vary between animal models. Therefore, it has become essential to determine to what extent observations in a particular rodent strain can be extrapolated to human ADPKD. Because of its size, a closely homologous rat model of human ADPKD would have great advantages. The pck rat is a recently identified model of PKD that developed spontaneously in the rat Crj:CD/SD or registered name of Charles River Japan "cesarean derived SD (Sprague-Dawley) strain," the original stock of which was introduced from Charles River (Wilmington, MA, US). It has many features that

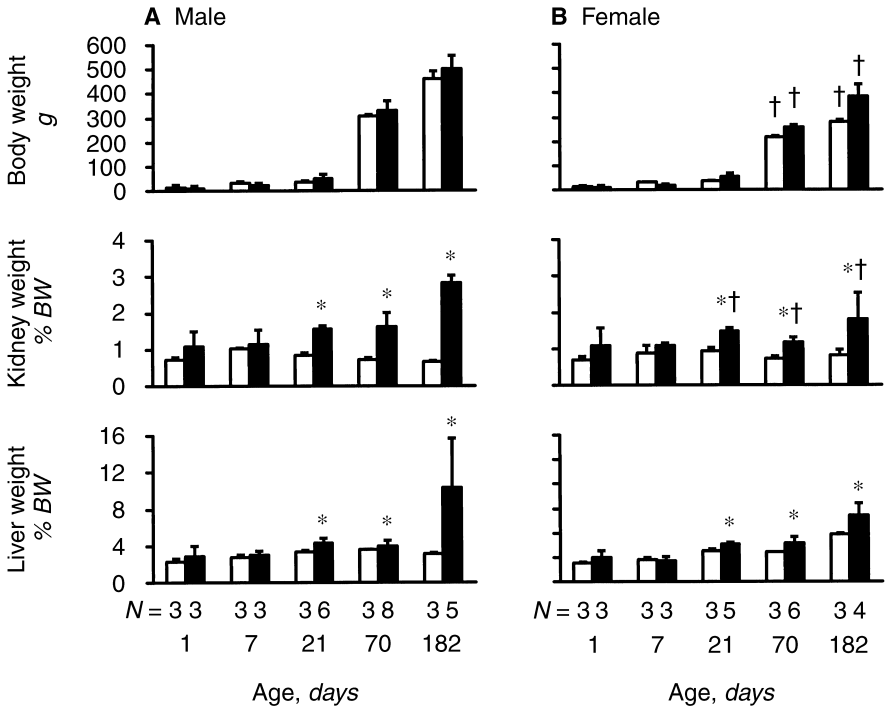

Fig. 1. Body, kidney, and liver weights in Sprague-Dawley (SD; □) and polycystic kidney (pck; ■) control rats. *$P < 0.05$ vs. SD rats; †$P < 0.05$ vs. male rats.

resemble human ADPKD, although the pattern of inheritance is autosomal recessive [15].

METHODS

The pck rat colony

The colony of pck rats was derived by breeding pairs (F9 generation) obtained from Charles River Japan (Tokyo, Japan). SD rats obtained from Charles River (USA) were used for controls.

Study design

Blood and tissue (kidneys, liver, and pancreas) samples were obtained from pck and control SD rats at 1, 7, 21, 70, and 182 days of age under pentobarbital (50 mg/kg body weight, IP) anesthesia. Blood samples were obtained by cardiac puncture. The kidneys, liver, and pancreas were placed into preweighed vials containing 10% buffered formaldehyde. In some animals, specimens from the renal cortex and medulla were fixed in 2.5% glutaraldehyde in 0.1 mol/L cacodylate buffer for electron microscopy. Urine samples were obtained by bladder puncture in 182-day-old pck and control SD rats.

Histology and immunohistochemistry

Four micrometer tissue sections stained with hematoxylin and eosin and Masson's trichrome were used for the histologic analysis of the kidney, liver, and pancreas. To determine the origin of the cysts, kidney sections were stained for the tubular markers lysozyme for the proximal tubule (BioGenex, San Ramón, CA, USA) [16], Tamm-Horsfall protein for the thick ascending loop (Cortex Biochem, San Leandro, CA, USA) [17], and epithelial membrane antigen for the distal tubule and collecting duct (BioGenex) [18]. To assess the presence and rate of apoptosis, renal and hepatic sections were stained using the ApopTag Peroxidase Kit (Intergen, Purchase, NY, USA).

Electron microscopy

Glutaraldehyde-fixed renal cortex and medulla from pck and control SD rats were processed in bloc with uranyl acetate and were embedded in epon. Semithin sections were examined, and areas of interest were selected. Ultrathin sections were stained with lead citrate and examined using a Phillips CM-10 electron microscope.

Biochemical determinations

Plasma concentrations of creatinine, blood urea nitrogen, bilirubin, alkaline phosphatase, and aspartate aminotransferase (AST) were measured using a Hitachi 977 analyzer. Urine protein was measured using a BCA Protein Assay Reagent Kit (Pierce, Rockford, IL, USA). Urine creatinine was measured using a Beckman Analyzer.

Data analysis

Results are presented as means ± standard deviation (SD). Conventional parametric and nonparametric meth-

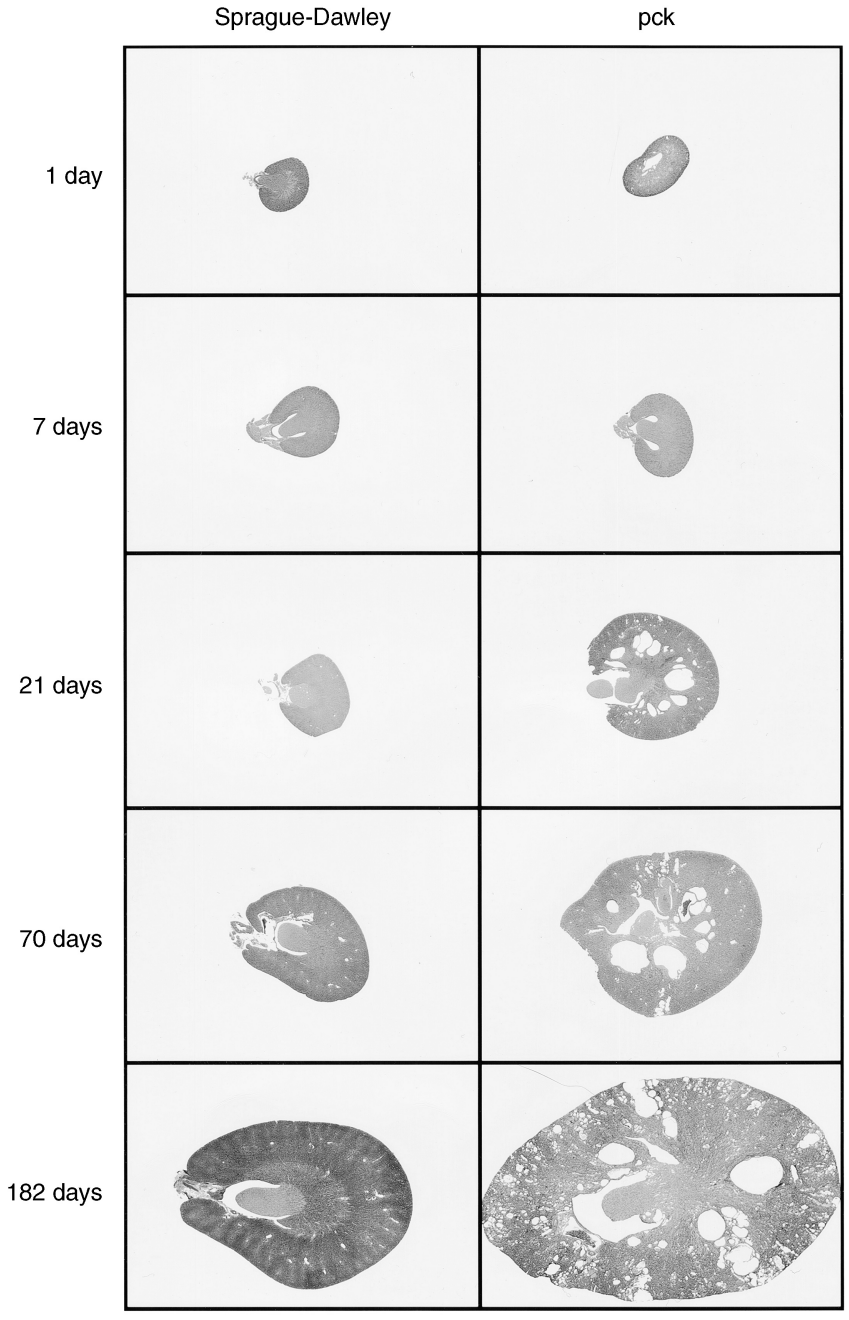

Fig. 2. Representative cross sections of kidneys from control SD and pck rats at 1, 7, 21, 70, and 182 days of age (hematoxylin and eosin, ×50).

ods were used for statistical analysis. All tests were two sided with *P* values of 0.05 or less to indicate statistical significance.

RESULTS

Macroscopic appearance of the kidney, liver, and pancreas

The growth of the pck rats was comparable to that of control SD rats. On the other hand, the absolute and relative kidney and liver weights, after the first week of age, were consistently higher in the pck than in the control SD rats (Fig. 1). The PKD was more severe in male than in female pck rats, as reflected by the higher kidney weights, while there was no gender difference in the severity of the polycystic liver disease (Fig. 1). The enlargement of the kidneys and the liver was progressive and most marked in the older animals (Fig. 2). Close examination of the liver in the older animals revealed an irregular surface with numerous macroscopic cysts resembling human polycystic liver disease (Fig. 3). No lesions were detected in the pancreas (data not shown).

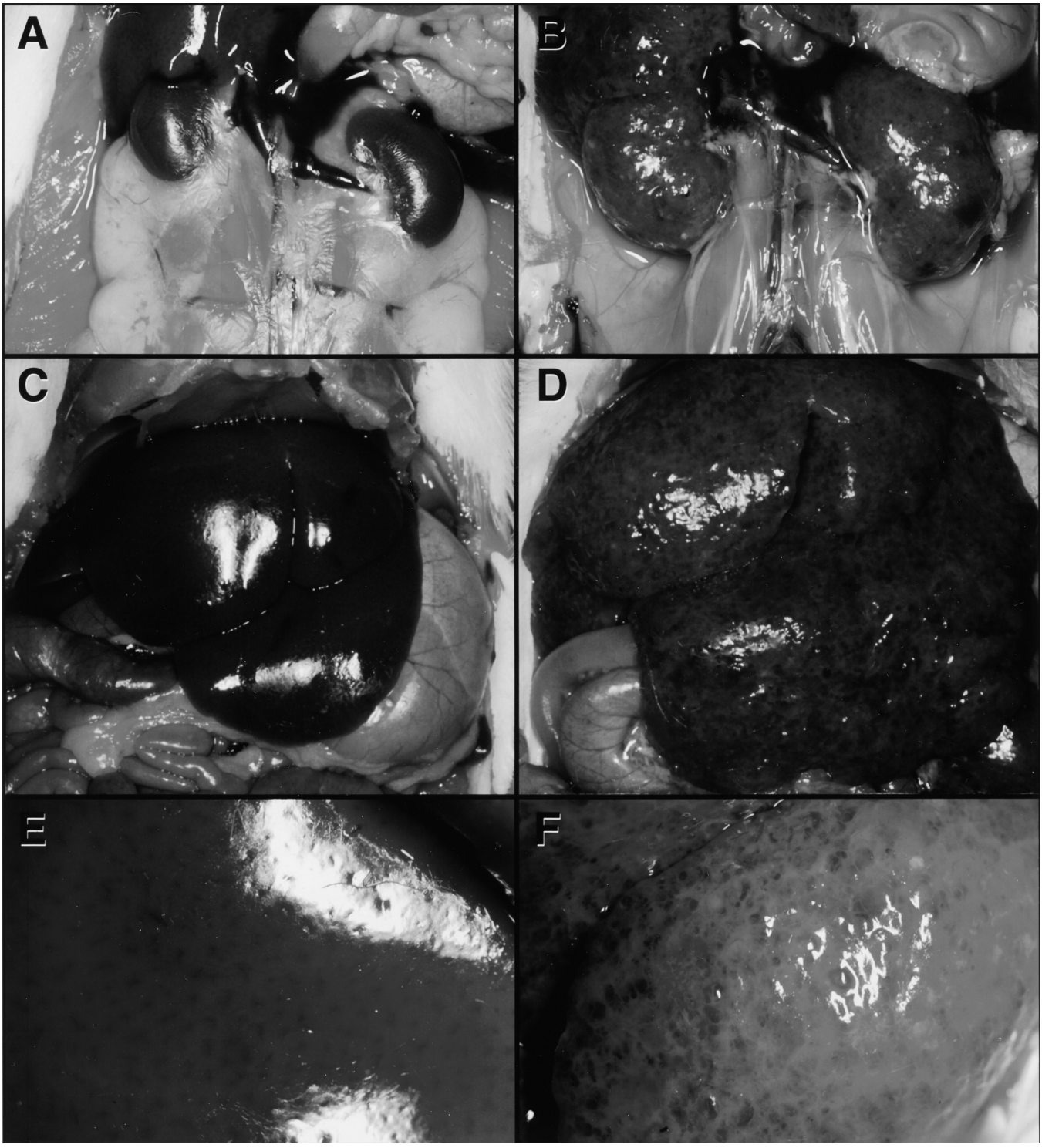

Fig. 3. Gross anatomy of the kidneys (*A* and *B*) and livers (*C–F*) from control SD (A, C, and E) and pck (B, D, and F) rats.

Microscopic examination of the kidney

Examination of the kidneys at one and seven days of age revealed no abnormalities in the pck as compared with the control SD rats, except for mild focal tubular dilation in the corticomedullary region at seven days of age (data not shown). Renal cysts were evident at 21 days of age as greatly dilated tubules, predominantly at the corticomedullary region and outer medulla (Fig. 4). The development of the cysts occurred as a focal process, with well-developed cysts surrounded by normal-

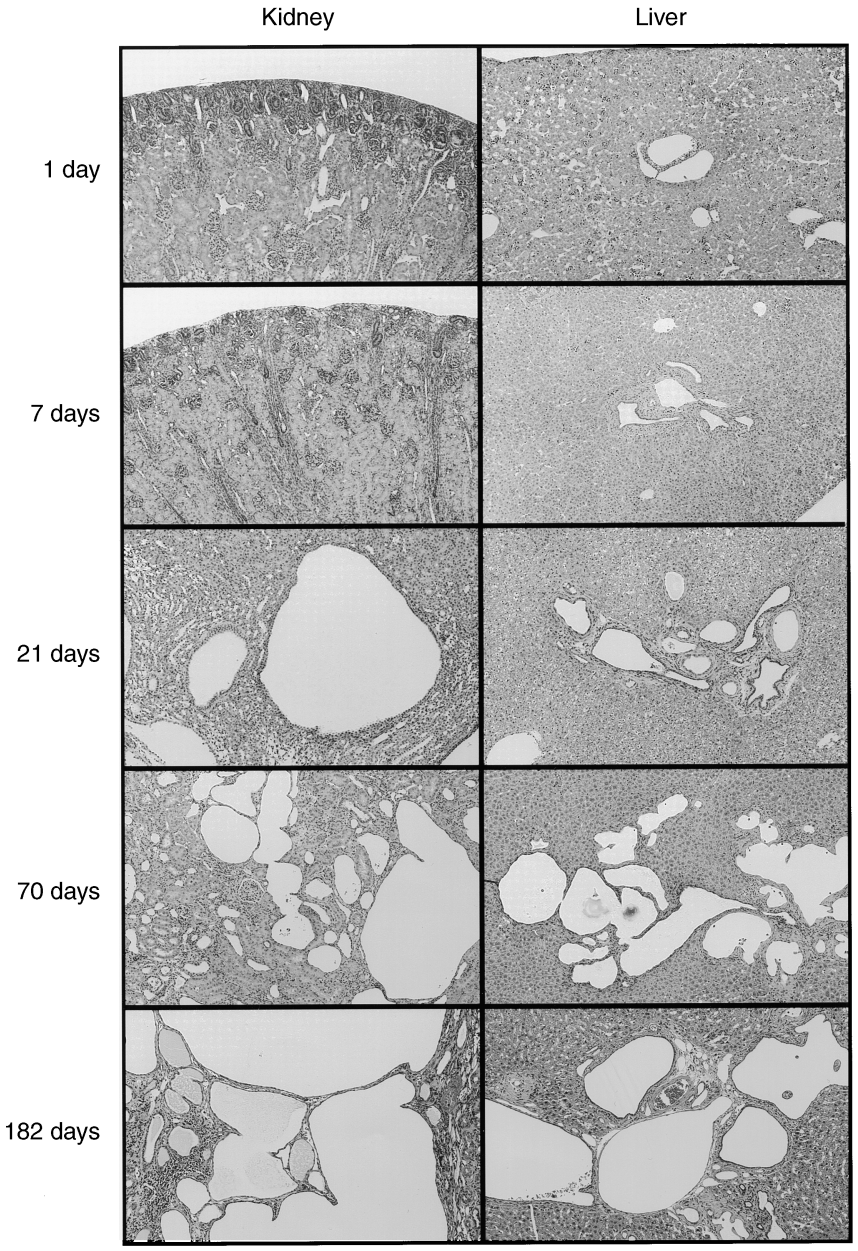

Fig. 4. Representative kidney and liver tissue sections from pck rats at 1, 7, 21, 70, and 182 days of age (hematoxylin and eosin, ×100).

appearing tubules. The cysts increased in number and size with advancing age and were evident in the renal cortex by 70 days of age (Fig. 4). The cells lining the cysts ranged from tall cuboidal to flat and derived predominantly from the thick ascending limb, distal tubule, and collecting duct, as demonstrated by lack of staining for lysozyme (Fig. 5A) and positive staining for Tamm-Horsfall protein and/or epithelial membrane antigen (Fig. 5 B, C). In some cysts, flat or polypoid epithelial cell hyperplasia was noted (Fig. 6). Apoptotic nuclei were very rare in the older control SD rats, while they were markedly increased in number in the pck rats. At one and seven days of age, many apoptotic nuclei were present in the inner medulla and nephrogenic zone in both the control SD and pck rats. In the older pck rats, apoptotic nuclei were present in normal tubules, in focally dilated tubules, and in cellular casts and were less frequent within cells lining larger cysts (Fig. 7). Apoptotic nuclei were observed more frequently in cysts lined by hyperplastic or cuboidal epithelium than in those lined by flat epithelium. Focal interstitial fibrosis and inflammation and proximal tubule dilation were evident by 70 days (Fig. 8A). The renal arteries and arterioles were normal, however, segmental glomerulosclerosis was noted in a few rats at 70 days (Fig. 8B). Ultrastructurally, the basement membranes of the cysts in the pck rats exhibited a variety

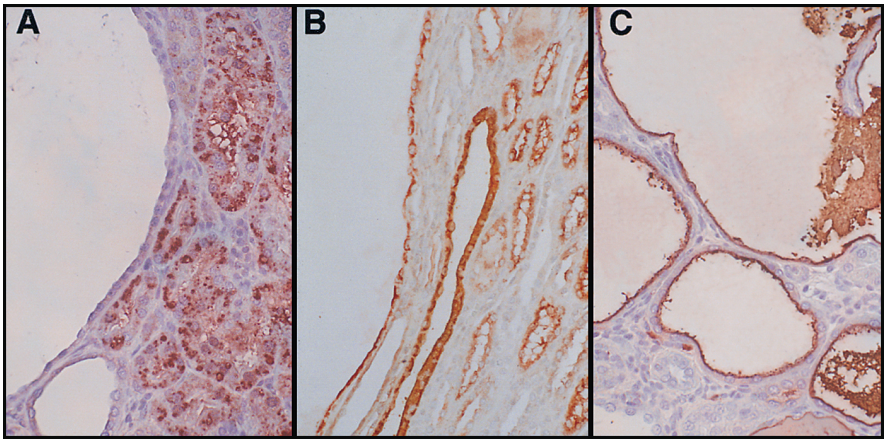

Fig. 5. Immunohistochemical staining for lysozyme (*A*), Tamm-Horsfall protein (*B*), and epithelial membrane antigen (*C*) of kidney tissue sections from pck rats at 70 days of age. Original magnification ×100. Reproduction of this illustration in color was partially funded by Merck & Co., Inc.

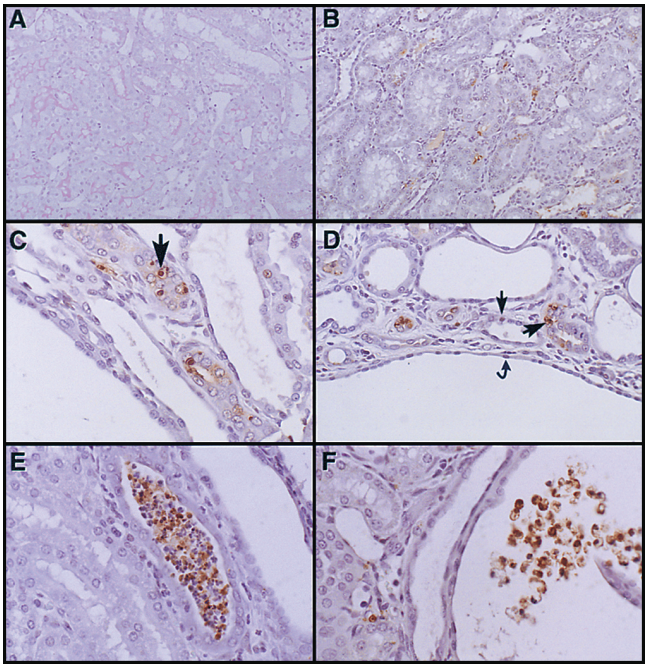

Fig. 7. Immunohistochemical staining for apoptosis in renal sections from control SD (*A*) and pck rats (*B* to *F*) at 21 (A and B) and 70 (C to F) days of age. Apoptotic nuclei were observed in normal and focally dilated tubules (arrows) and cellular casts (E and F) and less frequently within cells lining larger cysts (curved arrow; ×200). Reproduction of this illustration in color was partially funded by Merck & Co., Inc.

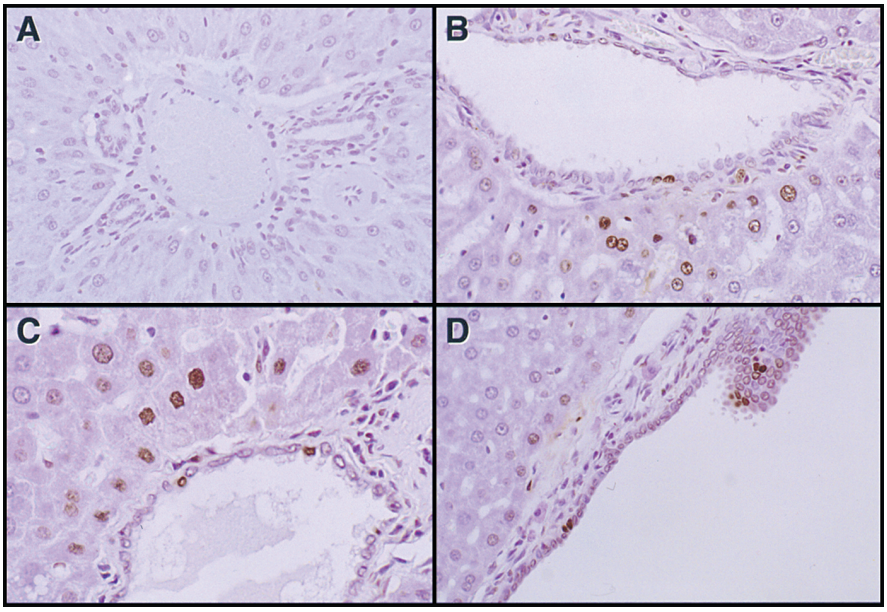

Fig. 11. Immunohistochemical staining for apoptosis in liver sections from control SD (*A*) and pck (*B–D*) rats at 21 (A and B) and 70 (C and D) days of age. Apoptotic nuclei were observed in cells lining dilated bile ducts and in adjacent hepatocytes. (A, ×150; B–D, ×200). Reproduction of this illustration in color was partially funded by Merck & Co., Inc.

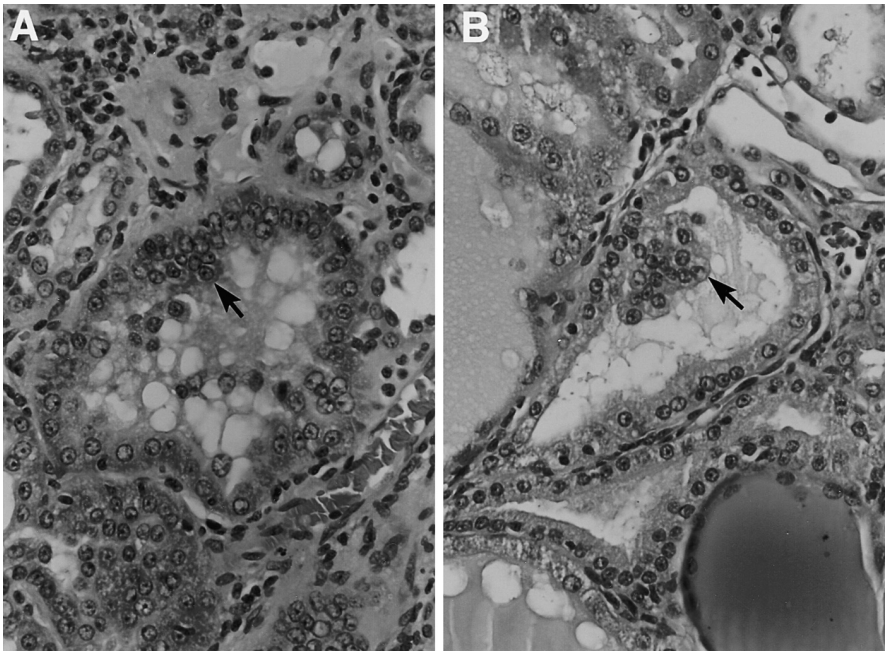

Fig. 6. Examples of flat (*A*) and polypoid (*B*) epithelial cell hyperplasia (arrows) in dilated renal tubules from pck rats (hematoxylin and eosin, ×200).

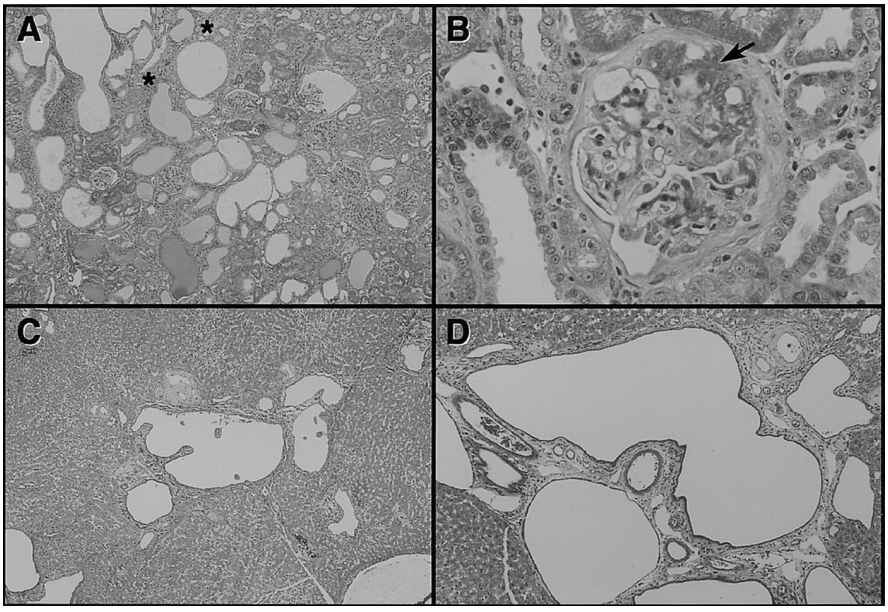

Fig. 8. Representative kidney and liver tissue sections from pck rats at 10 weeks of age. Note the presence of focal inflammation and fibrosis in the renal interstitium (*; *A*) and segmental glomerulosclerosis (arrow; *B*). There was only mild portal fibrosis in the liver without formation of septa (*C* and *D*). (Masson's trichrome; A, C ×100; B, D ×200).

of changes, including thinning, lamellation, and thickening (Fig. 9). The glomeruli also showed segmental alterations of the basement membranes with associated effacement of the podocyte foot processes (Fig. 10).

Microscopic examination of the liver and pancreas

Mild bile duct dilation was present as early as one day of age. The number of portal triads affected and the size of the cysts increased with advancing age (Fig. 4). Apoptotic nuclei were increased in number compared with the normal control and were present in cells lining dilated bile ducts and in adjacent hepatocytes (Fig. 11). Mild portal inflammation and acute cholangitis occurred in a few animals. There was a mild increase in portal fibrosis with age, but without formation of fibrous septae (Fig. 8 C, D). No microscopic cysts or other lesions were detected in the pancreas (data not shown).

Laboratory parameters Despite marked renal and hepatic enlargement and histologic abnormalities, only a slight elevation of the plasma blood urea nitrogen levels was detected at 70 and 182 days of age (Fig. 12). The urine protein excretion was significantly higher in male

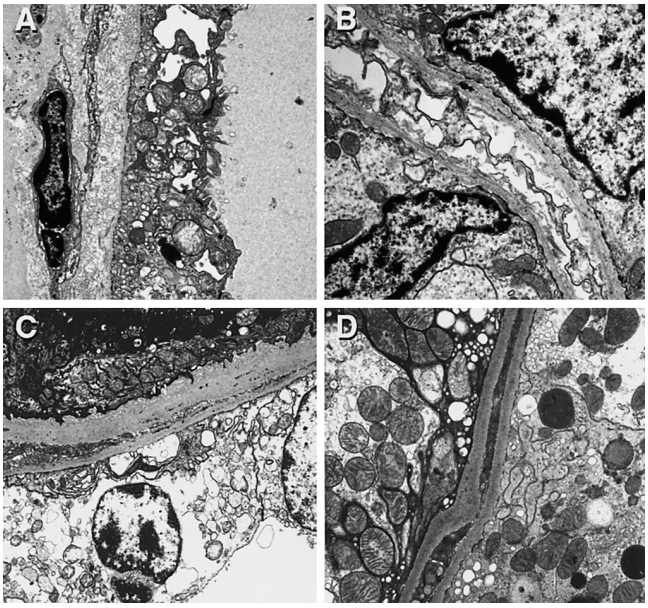

Fig. 9. Transmission electron micrographs of tubular basement membranes in 10-week-old pck (*A–C*) and control SD (*D*) rats. Ultrastructurally, the cysts in the pck rats showed a variety of basement membrane alterations. The basement membranes were thinned (A), lamellated (B), and thickened (C). Tubular basement membranes from normal rats lacked these changes (D). Magnifications: A, ×5800; B, ×9700; C, ×7400; D, ×9700.

and female pck rats than in the SD controls (5.5 ± 2.5 and 3.0 ± 1.5 vs. 0.8 ± 0.2 and 1.2 ± 0.3 mg protein/mg creatinine, $P < 0.001$). The plasma concentrations of bilirubin and alkaline phosphatase were similar in male and female pck rats and within the range reported for normal SD rats [19]. While the serum levels of bilirubin increased (0.22 ± 0.04 and 0.20 ± 0.0 mg/dL at 70 days vs. 0.50 ± 0.24 and 0.38 ± 0.09 mg/dL at 182 days for male and pck rats, respectively), those of alkaline phosphatase decreased significantly with age (687 ± 72 and 643 ± 66 U/L at 70 days vs. 340 ± 157 and 337 ± 127 U/L at 182 days for male and female pck rats, respectively).

DISCUSSION

Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive PKD (ARPKD) are the most important inherited renal cystic diseases in humans. PKD also occurs in the rat and the mouse and in many other animal species from the goldfish to the monkey [1–4]. The inherited models of PKD in rats and mice are summarized in Tables 1 and 2 [reviewed in 4]. The disease in some of these models, such as the cpk, bpk, and orpk mice, resembles human ARPKD because of the rapid progression, involvement of the collecting ducts, and association of biliary dysgenesis. The disease in pcy and kat2J mice and in ARPK and Han:SPRD rats is slowly progressive and resembles human ADPKD. None of these experimental models is genetically homologous to human ADPKD. In addition, human ADPKD is genetically heterogeneous with at least three loci: *PKD1*, *PKD2*, and *PKD3. PKD1* and *PKD2* and the genes responsible for PKD in the orpk and Kat2J mice have been identified [20–25]. The fact that their functions and the mechanisms by which their mutations cause cystic disease remain unknown indicates that the mechanisms responsible for maintenance of the differentiated renal tubular epithelial cell phenotype and the development of PKD are likely to be very complex. Therefore, the identification of new animal models and the responsible genes are likely to be very helpful for the elucidation and understanding of these complex mechanisms.

The model of PKD described in this article has been recently identified [15]. This model is different from previously reported models of PKD in rats. The pck rat is clearly different from the ARPK model described by Ohno and Kondo and Inage et al, which is characterized by the association of skeletal abnormalities and facial dysmorphism, the origin of the cysts in the collecting ducts, and the mild hepatic involvement [26, 27]. It is also strikingly different from the Han:SPRD rat, which exhibits severe cystic dilation of all nephron segments with massive renal enlargement and death from uremia at three weeks of age in the homozygous state and progressive cystic disease, which starts in the pars recta of the proximal tubules and is mostly confined to this nephron segment in the heterozygous state [5–8]. In the pck rat, the cysts involve mainly the thick ascending loops of Henle, distal tubules, and cortical collecting ducts. As in human ADPKD and acquired renal cystic disease, but to a lesser extent than in the Han:SPRD rat, the PKD in the pck rats is more severe in male than in female animals. Unique to the pck rat is the severe involvement of the liver, which resembles human autosomal dominant polycystic liver disease. The polycystic liver disease in this animal model is more severe than that described in the Pkd1 and Pkd2 knockouts and may be of particular value in studying possible therapies for polycystic liver disease [9–12].

There are significant similarities between the cyst phenotypes of the pck rats and human ADPKD. In both, the kidneys can appear normal at birth, and the cystic disease is slowly progressive. In both, the renal disease is more severe in males than in females. Although the tubular segment of origin of most cysts in ADPKD remains uncertain, one study has suggested that most derive from the distal nephron and collecting ducts [28]. In both cases, the development of renal cysts appears to be a focal phenomenon. In human ADPKD, the focal development of the cysts has been explained by the two-hit hypothesis [29]. This explanation is less likely to account for the focal development of the cyst in the pck rat, which is an autosomal recessive disorder. This obser-

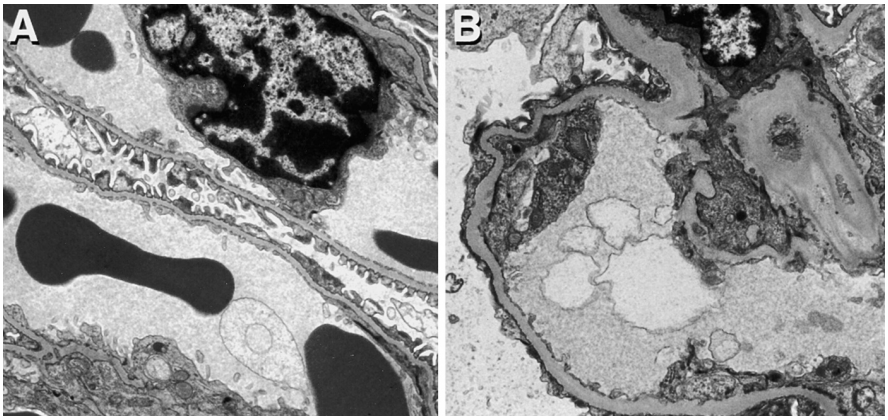

Fig. 10. Transmission electron micrographs of glomerular loops from control SD (*A*) and ten-week-old pck (*B*) rats. The glomeruli from the pck rats showed segmental thickening of the basement membrane with associated podocyte foot process effacement (B) when compared with normal rats (A). Magnification ×7400.

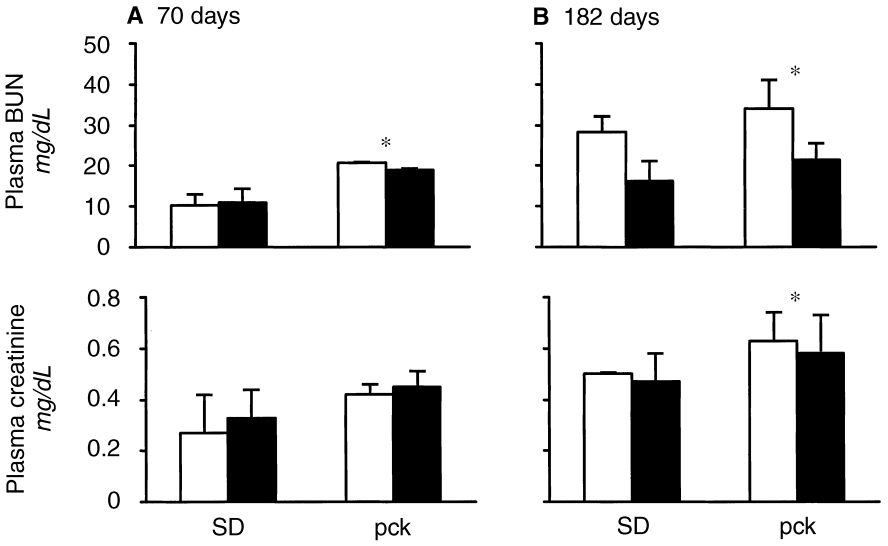

Fig. 12. Plasma blood urea nitrogen (BUN) and creatinine levels in control SD and pck rats. Symbols are: (□) male; (■) female animals. *$P < 0.05$ vs. SD rats.

vation suggests that other factors, in addition to the somatic inactivation of the *PKD* gene not affected by the germline mutation, may contribute to the focal character of ADPKD.

As in other models of PKD, we found evidence of tubular epithelial cell hyperplasia, increased rates of apoptosis, thickening and lamellation of the basement membranes in the cysts, and interstitial inflammatory infiltrates [6, 7, 30, 31]. We found that most apoptotic cells in the kidneys were not in the cysts, but in nondilated tubules. The apoptotic cells were more commonly seen in cysts with cuboidal or hyperplastic epithelium than in those with flat epithelium. These observations are consistent with the interpretation that apoptosis is prevalent at early stages of cystogenesis and down-regulated as the cysts develop. Because of down-regulation of apoptosis in well-developed cysts, the flat epithelium in these cysts may have a survival advantage despite lower rates of cell proliferation. On the other hand, we found that the thickening of basement membranes and development of interstitial inflammation and fibrosis occur at more advanced stages of the disease and, therefore, are less likely to be important in early cystogenesis.

In summary, the pck rat is a new spontaneously occurring inherited model of polycystic kidney and liver disease with a natural history and renal and hepatic histologic abnormalities that resemble human ADPKD. As such, this model may be useful in studying the pathogenesis and evaluating potential therapies for polycystic kidney and liver disease. In addition, the identification of the *pck* gene, which may be a homologue of a known human or mouse *PKD* gene or a new *PKD*-associated gene, is likely to provide further insight into the pathogenesis of ADPKD.

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Table 1. Inherited murine models of polycystic kidney disease

Mouse	Inheritance	Chromosome assignment	Progression	Renal pathology	Associated features
cpk	AR	12	rapid	PT → CD	Pancreatic and mild portal fibrosis in DBA/2J or CD1 background; biliary cysts in old heterozygotes
bpk	AR	10	rapid	PT → CD	Biliary dysgenesis
orpk	AR	14	rapid	PT → CD	Scruffy fur, growth retardation, preaxial polydactyly, biliary dysgenesis
jcpk	AR	10	rapid	G, PT, LH, DT, CD	Enlarged bile ducts, pancreatic ducts and gallbladder; glomerulocystic disease in 25% of old heterozygotes
jck	AR	11	slow	cortex, outer medulla	—
pcy	AR	9	slow	PT, LH, DT, CD	Accelerated incisor eruption, intracranial aneurysms
CFWwd	AD	—	slow	G, PT, LH, DT, CD	Hepatic cyst, thoracic aortic aneurysms, markedly attenuated in germ-free environment
CBA/N	XR	X	slow	G, PT, LH, DT	B-lymphocyte deficiency
CBA/Ca-KD	AR	—	slow	cortex and medulla	T-cell-mediated autoimmune disease
Kat and kat2J	AR	8	variable	G, PT	Sparse fur, growth retardation, facial dysmorphism, hydrocephalus, choroid plexus cysts, anemia, male sterility
Krd	AD	19	variable	medulla	Renal agenesis, hypoplasia; hydronephrosis; retinal defects; embryonic lethal in homozygotes

Abbreviations are: AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive; Definitions are: G, glomeruli; PT, proximal tubule; LH, loop of Henle; DT, disease tubule; CD, collecting duct; __, predominant involvement

Table 2. Inherited rat models of polycystic kidney disease

Mouse	Inheritance	Chromosome assignment	Progression	Renal Pathology	Associated Features
wpk	AR	—	rapid	PT → CD	—
ARPK	AR	—	slow	CD	Skeletal abnormalities, facial dysmorphism
Han:SPRD	AD	5	slow	PT, LH, DT, CD	Hepatic and pancreatic cysts (old females only); renal disease more severe in males; early lethality in homozygotes
pck	AR	—	slow	LH, DT, CD, PT	—

Abbreviations are: G, glomeruli; PT, proximal tubule; LH, loop of Henle; DT, disease tubule; CD, collecting duct; __, predominant involvement.

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REFERENCES

1. Avner E, McAteer J, Evan A: Models of cysts and cystic kidneys, in *The Cystic Kidney*, edited by Gardner K Jr, Bernstein J, Lancaster, Kluwer Academic Publishers, 1990, pp 55–98
2. McDonald R, Avner E: Mouse models of polycystic kidney disease, in *Polycystic Kidney Disease*, edited by Watson M, Torres V, Oxford, Oxford University Press, 1996, pp 63–87
3. Cowley B Jr, Gattone V II: In vivo models of PKD in non-murine species, in *Polycystic Kidney Disease*, edited by Watson M, Torres V, Oxford, Oxford Medical Publications, 1996, pp 88–110
4. Grantham J, Cowley B Jr, Torres V: Progression of autosomal dominant polycystic kidney disease (ADPKD) to renal failure, in *the Kidney: Physiology and Pathophysiology, Philadelphia*, Lippincot Williams and Wilkins, 2000
5. Kaspareit-Rittinghausen J, Rapp K, Deerberg F, *et al:* Hereditary polycystic kidney disease associated with osteorenal syndrome in rats. *Vet Pathol* 26:195–201, 1989
6. Cowley B Jr, Gudapaty S, Kraybill A, *et al:* autosomal dominant polycystic kidney disease in the rat. *Kidney Int* 43:522–534, 1993
7. Schafer K, Gretz N, Bader M, *et al:* Characterization of the Han:SPRD rat model for hereditary polycystic kidney disease. *Kidney Int* 46:134–152, 1994
8. Kranzlin B, Schieren G, Gretz N: Azotemia and extrarenal manifestations in old female Han:SPRD (cy/+) rats. *Kidney Int* 51:1160–1169, 1997
9. Lu W, Peissel B, Babakhanlou H, *et al:* Perinatal lethality with kidney and pancreas defects in mice with a targeted PKD1 mutation. *Nat Genet* 17:179–181, 1997
10. Lu W, Fan X, Basora N, *et al:* Late onset of renal and hepatic cysts in mice heterozygous for a targeted PKD1 mutation. *Nat Genet* 21:160–161, 1999
11. Kim K, Drummond I, Ibraghimov-Beskrovnaya O, *et al:* Polycystin 1 is required for the structural integrity of blood vessels. *Proc Natl Acad Sci USA* 97:1731–1736, 2000
12. Wu G, D'Agati V, Cai Y, *et al:* Somatic inactivation of PKD2 results in polycystic kidney disease. *Cell* 93:177–188, 1998
13. Torres V: New insights into polycystic kidney disease and its treatment. *Curr Opin Nephrol Hypertens* 7:159–169, 1998
14. Sweeney W Jr, Chen Y, Nakanishi K, *et al:* Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor. *Kidney Int* 57:33–40, 2000

15. Katsuyama M, Masuyama T, Komura I, *et al:* Characterization of a novel polycystic kidney rat model with accompanying polycystic liver. *Exp Anim* 49:51–55, 2000
16. Mason D, Taylor C: The distribution of muramidase (lysozyme) in human tissues. *J Clin Pathol* 28:124–132, 1975
17. Bachmann S, Metzger R, Bunnemann B: Tamm-Horsfall protein-mRNA synthesis is localized to the thick ascending limb of Henle's loop in rat kidney. *Histochemistry* 94:517–523, 1990
18. Fleming S, Lindop G, Gibson A: The distribution of epithelial membrane antigen in the kidney and its tumours. *Histopathology* 9:729–739, 1985
19. Charles River Technical Bulletin 3, 1984
20. American PKD1 Consortium: Analysis of the genomic sequence for the autosomal dominant polycystic kidney disease (PKD1) gene predicts the presence of a leucine-rich repeat. *Hum Mol Genet* 4:575–582, 1995
21. Hughes J, Ward C, Peral B, *et al:* The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. *Nat Genet* 10:151–160, 1995
22. International Polycystic Kidney Disease Consortium: The complete structure of the PKD1 gene and its protein. *Cell* 81:289–298, 1995
23. Mochizuki T, Wu G, Hayashi T, *et al:* PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science* 272:1339–1342, 1996
24. Yoder B, Richards W, Sweeney W, *et al:* Insertional mutagenesis and molecular analysis of a new gene associated with polycystic kidney disease. *Proc Assoc Am Physicians* 107:314–323, 1995
25. Upadhya P, Birkenmeier E, Birkenmeier C, *et al:* Mutations in a NIMA-related kinase gene, Nek1, cause pleiotropic effects including a progressive polycystic kidney disease in mice. *Proc Natl Acad Sci USA* 97:217–221, 2000
26. Ohno K, Kondo K: A mutant rat with congenital skeletal abnormalities and polycystic kidneys. *Exp Anim* 38:139–146, 1989
27. Inage Z, Kikkawa Y, Minato M, *et al:* Autosomal recessive polycystic kidney in rats. *Nephron* 59:637–640, 1991
28. Verani R, Silva F: Histogenesis of the renal cysts in adult (autosomal dominant) polycystic kidney disease: A histochemical study. *Modern Pathol* 1:457–463, 1988
29. Qian F, Watnick T, Qnuchic L, *et al:* The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type 1. *Cell* 87:979–987, 1996
30. Woo D: Apoptosis and loss of renal tissue in polycystic kidney diseases. *N Engl J Med* 333:18–25, 1995
31. Lanoix J, D'Agati V, Szabolcs M, *et al:* Dysregulation of cellular proliferation and apoptosis mediates human autosomal dominant polycystic kidney disease (ADPKD). *Oncogene* 13:1153–1160, 1996