Polycystic kidney and liver disease in Springbok:
I. Morphology of the lesions

WILLIAM O. IVERSON, GEORGE H. FETTERMAN, ELLIOTT R. JACOBSON, JOHN H. OLSEN, DAVID F. SENIOR, and EARL E. SCHOBERT

College of Veterinary Medicine, University of Florida, Gainesville, Florida, Departments of Pathology, Children's Hospital of Pittsburgh and School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, and Busch Gardens, Tampa, Florida

Polycystic kidney and liver disease in Springbok: I. Morphology of the lesions. Spontaneous polycystic kidney and liver disease in an inbred herd of Springbok (*Antidorcas marsupialis*) was studied by light microscopy, transmission electron microscopy, and microdissection. Springbok are a small species of gazelle of the family *Bovidae* native to South Africa. Since 1976, 18% of all live calves born have had nephromegaly and died within 2 weeks of birth. Examination of kidney and liver from ten calves which had died or were sacrificed since 1978 revealed bilateral, symmetrical nephromegaly due to moderate to marked focal dilatation of tubules predominately in the outer zone of the medulla. Microdissection of renal tissue from three affected calves indicated polycystic kidneys had cysts in all of the bends of Henle's loops, over half of the ascending limbs, and about one fourth of the collecting ducts. All of these calves had proliferation and cystic dilatation of bile ducts in most hepatic portal areas. The bile ducts were irregularly dilated and confluent with only a slight increase in periductular connective tissue. Ultrastructural studies revealed no consistent changes in the basement membranes of either the renal or hepatic cysts. This disease has several features similar to the autosomal recessive form of polycystic kidney disease in man and may prove a useful animal model.

Maladies polykystiques rénale et hépatique chez la Springbok: I. Morphologie des lésions. La maladie polykystique rénale et hépatique spontanée survenant dans une souche pure de Springbok (*Antidorcas marsupialis*) a été étudiée en microscopie optique, en microscopie électronique, et par microdissection. Le Springbok est une petite espèce de gazelle de la famille des *Bovidae*, originaire d'Afrique du Sud. Depuis 1976, 18% de tous les petits vivants ont eu une néphromégalie, et sont morts dans les deux semaines suivant la naissance. L'examen des reins et du foie de dix petits morts ou sacrifiés depuis 1978 a mis en évidence une néphromégalie bilatérale et symétrique due à une dilatation focale modérée ou marquée des tubules prédominant sur la zone externe de la médulla. La microdissection de tissu rénal provenant de trois petits atteints a montré que les reins polykystiques avaient des kystes sur toutes les extrémités des anses de Henlé, sur plus de la moitié des anses ascendantes, et sur environ le quart des tubes collecteurs. Tous ces petits avaient une prolifération et des dilatations kystiques des canaux biliaires dans la plupart des aires portales hépatiques. Les canaux biliaires étaient irrégulièrement dilatés et confluents avec seulement une discrète augmentation du tissu conjonctif péricanaliculaire. Des études ultrastructurales n'ont pas mis en évidence de changement notable des membranes basales dans les kystes rénaux ou hépatiques. Cette maladie a plusieurs caractéristiques identiques á la forme autosomale récessive de polykystose rénale chez l'homme et pourrait constituer un modèle animal utile.

Polycystic kidney disease is a heritable disorder in which there is diffuse cystic involvement of both normally differentiated kidneys [1, 2]. The disease exists in man in two forms that are not always clearly distinguishable clinically. Patients with the autosomal dominant form of polycystic kidney disease (PCKD) usually do not become symptomatic until the third or fourth decades [3, 4]. PCKD is the third most common cause of renal failure in the United States, and autopsy studies suggest this form may occur in as many as one out of every 800 individuals, making it one of the most common genetic disorders [5]. Liver cysts have been found in 29% of patients over 10 years of age with documented autosomal dominant PCKD. These cysts are usually large and do not communicate with the biliary passages [3]. The autosomal recessive form of PCKD is much less common, includes cystic changes of the biliary system in nearly all cases and is usually fatal [4, 6].

Investigations of PCKD disease have relied upon a large variety of chemically and mechanically induced models in laboratory animals [7–11] and examinations of human polycystic kidneys obtained at nephrectomy or autopsy [4, 12, 13]. The spontaneous occurrence of polycystic kidneys has been reported in many species. Although its occurrence with cystic liver disease in animals is less frequent than in man, this association has been reported in lambs, a calf, piglets [14], related cats [15], and related Cairn Terriers [16]. None of these species has proven productive as breeding colonies to provide additional affected animals for investigations into the pathogenesis of the disease.

We report herein the occurrence of polycystic kidney and liver disease in an inbred herd of Springbok (*Antidorcas marsupialis*). The Springbok is a South African gazelle of the family *Bovidae* that breeds well in captivity. Adult males and females weigh 30 to 35 kg and 25 to 30 kg, respectively. The disease was recognized as an important contributing factor causing increased herd neonatal mortality since 1976.

Methods

Springbok were maintained in a fenced 1-acre grassy paddock at Busch Gardens in Tampa, Florida. They were fed approximately 1 kg of a commercial grain mix per 100 kg body weight, as well as alfalfa and timothy hay and water ad libitum. All births were the result of matings of the adult females with one male that had been herd sire since 1974. The male and most of

Table 1. Springbok births and deaths with nephromegaly 1976–1980

Year	Total adult females	Live births		Neonatal deaths with nephromegaly		Total affected as percent of total live births
		Males	Females	Males	Females	
1976	10	5	5	1	2	30%
1977	13	9	4	0	0	0
1978[a]	13	5	13	1	3	22
1979	15	4	10	1	3	26
1980[a]	24	14	13	3	1	14
Totals for 5 years		*37*	*45*	*6*	*9*	*18%*

[a] Several does had two births per calendar yer. Twins are very rare.
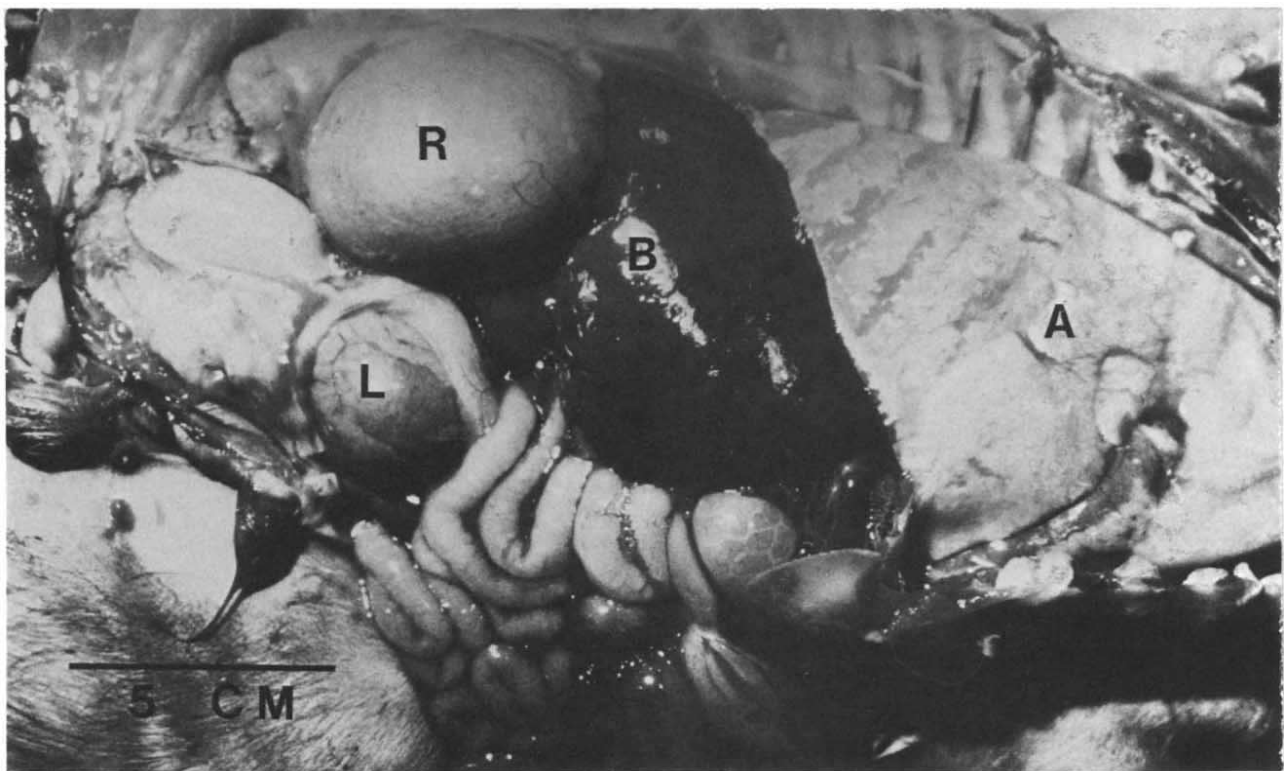
Fig. 1. *Calf N80-451 in left lateral recumbancy with viscera in situ as seen at necropsy.* Marked nephromegaly is readily apparent. Abbreviations are: **A,** right lung; **B,** liver; **R,** right kidney; **L,** portion of left kidney. Reference line equals 5.0 cm.

the females were descendants of the original foundation sire and two dams purchased in 1965 from Germany.

Materials and specimens from three sources were used in this study. Microscopic slides of tissues from four Springbok that died during 1978 and 1979 were obtained from the archives of the Animal Diagnostic Laboratory, Florida Department of Agriculture, for review. Formalin fixed wet tissue from four neonatal Springbok calves that died with nephromegaly in 1979 (C79 series) were submitted to the University of Florida Veterinary Medical Teaching Hospital (VMTH) for diagnostic evaluation. Nine calves born in 1980 (N80 series) were transported to the VMTH. Four calves had palpable nephromegaly at birth. One affected calf (N80-96) died at 11 days of age despite

supportive fluid and antibiotic therapy. A second calf (N80-442) died at 2 days of age. The seven live calves were anesthetized, catheterized, and used for renal clearance studies (to be published separately). After completion of these studies (3 to 5 hr later), each calf was euthanatized with sodium pentobarbital given intravenously, exsanguinated, and necropsied.

Renal weights and dimensions were obtained. Small amounts of renal cortex and medulla, and liver, were minced immediately in a cold 4% phosphate-buffered formaldehyde—1% glutaraldehyde solution [17], postfixed in 1% osmium tetroxide, and processed for electron microscopy. Renal and hepatic cyst walls were identified from 1-μ sections stained with toluidine blue. Appropriate areas of blocks from two affected (N80-442
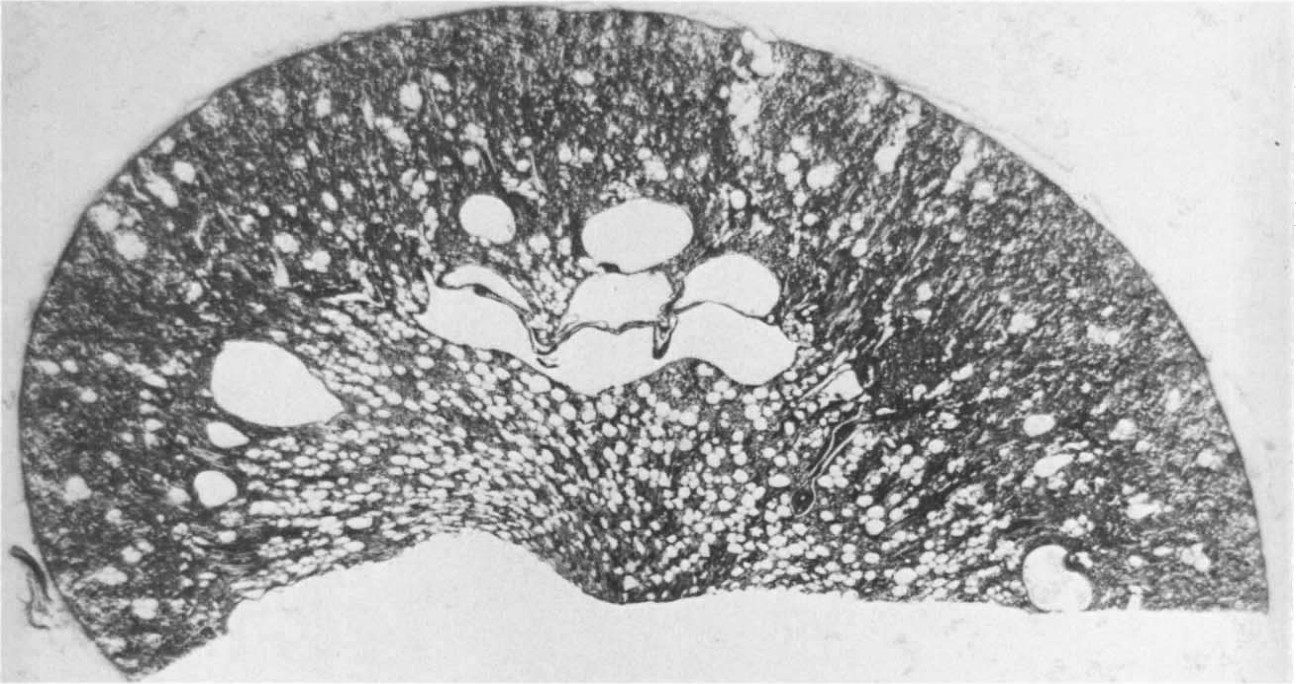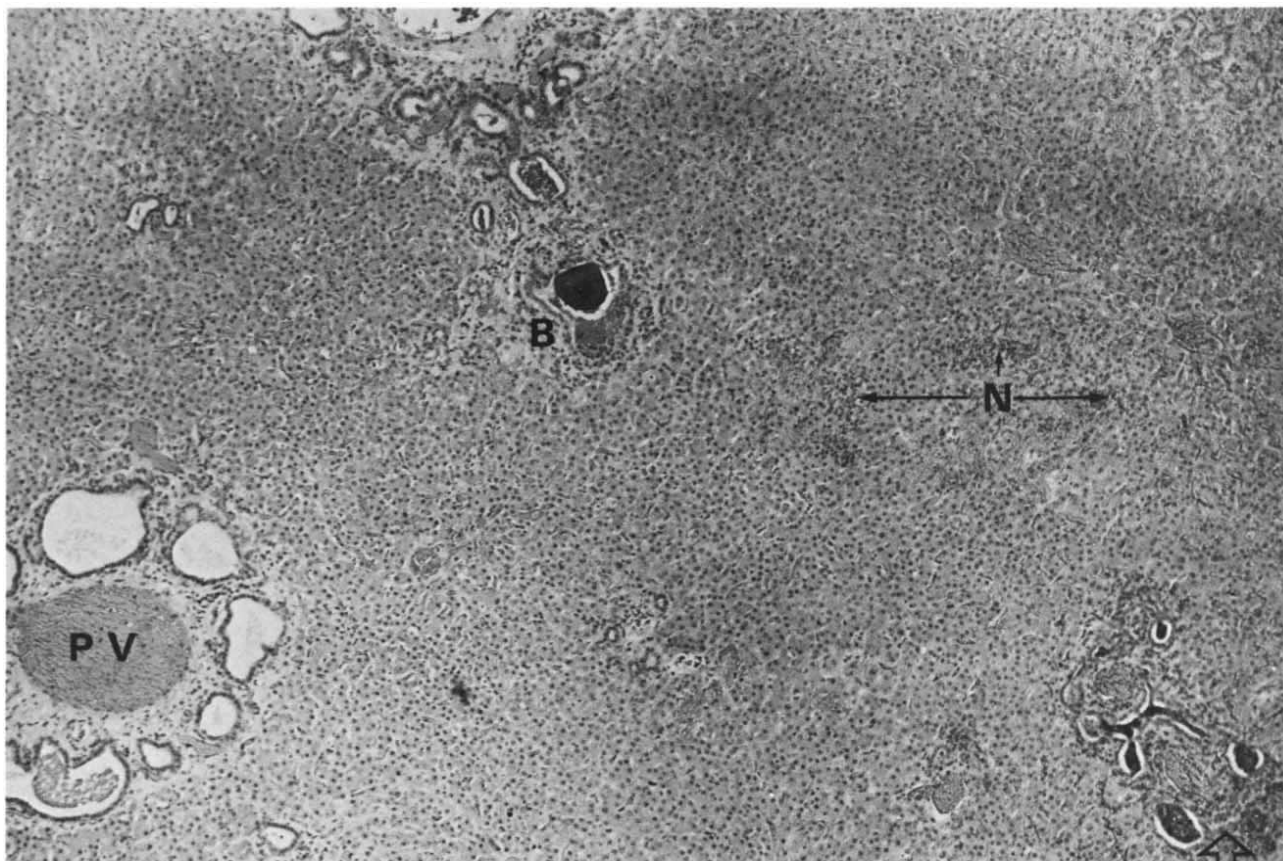
Fig. 2. *One half of a renal coronal section from affected Springbok calf C79-452.* (Hematoxylin and eosin, ×7.9).
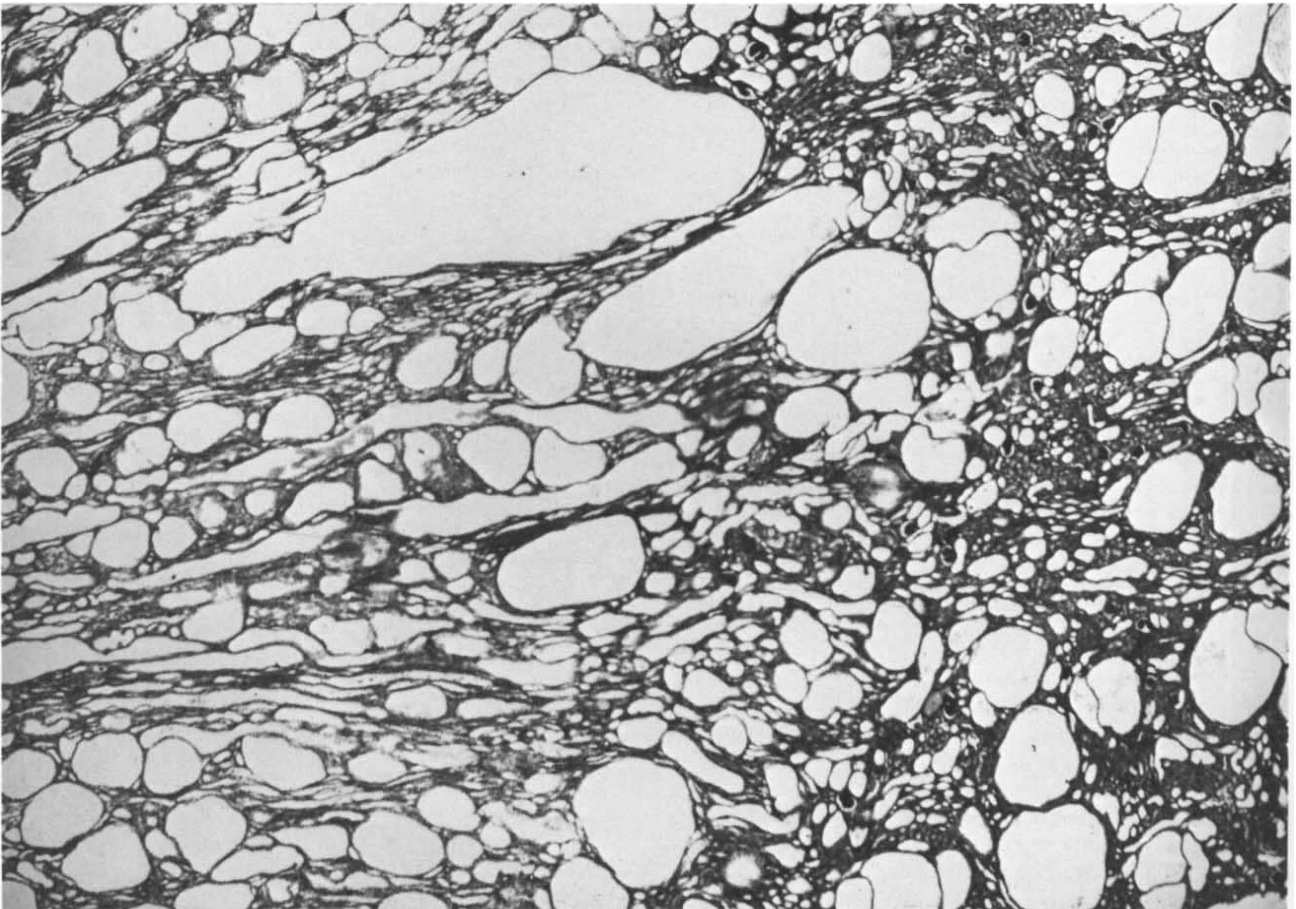
Fig. 3. *Photomicrograph of the outer zone of the renal medulla from calf N80-96.* The largest cysts present are located in the ascending limb of Henle's loops and in collecting ducts. (Hematoxylin and eosin, ×23).

Fig. 4. *Typical hepatic lesions in affected calves.* Most portal areas have hyperplastic, cystic bile ducts. This calf (C79-452) also had suppurative cholangitis *(open arrow)* and foci of necrosis (**N**) which contained gram negative bacilli. Other abbreviations are: **PV**, interlobular portal vein; **B**, intraductular bile plug. (Hematoxylin and eosin, ×240).

and N80-500) and two normal (N80-446 and N80-475) calves were thin-sectioned, stained, and examined with a Zeiss EM-9 electron microscope.

A complete necropsy was performed and representative portions of all tissues were fixed in 10% neutral-buffered formalin. Bone marrow was fixed in Bouin's solution. Selected tissues were processed by standard procedures, embedded in paraffin, sectioned at 5 to 7 μ, and stained with hematoxylin and eosin. In several cases sections were also stained with Masson's trichrome stain, by the periodic-acid Schiff reaction, Perls' method for ferric iron, Grocott's methenamine silver, or with the Brown-Hopps gram stain [18].

Blocks of formalin-fixed wet kidney tissue from three affected (N80-96, N80-442, and N80-451) and three normal (C80-9, N80-473, and N80-475) calves were studied by microdissection. The Oliver technique for microdissection and staining of the nephron was used [19, 20]. Care was taken that the blocks from each kidney included both cortex and medulla. In the dissection, several hundred complete nephrons were identified and noted from each kidney. Camera lucida tracings were made of many nephrons.

As part of the study, we measured 15 representative proximal tubules and attached glomeruli from five of the six kidneys. These nephrons were taken at random except that in each kidney care was taken to obtain five arising in the outer third of the cortex, five from the middle third, and five from the inner third.

Results

Gross observations. Nephromegaly was seen at necropsy of six male and nine female Springbok calves that died or were sacrificed from 1976 through 1980 (Table 1). The enlarged kidneys were symmetrical, smooth, reniform, and always occurred bilaterally (Fig. 1). Affected kidneys were one and one-half to three times the size of the kidneys in normal healthy calves of comparable ages. The mean total renal weight expressed as percentage of body weight was 2.1% in affected animals compared to 0.65% in normal calves. Scattered 1- to 2-mm cysts were present throughout the cortex and corticomedullary junction. Kidneys of both normal and affected calves were unipapillary with a crest. The N-80 series of animals all had small amounts of urine in the urinary bladder or had produced urine while catheterized. The ureters were patent. No gross abnormalities of the liver, brain, or circle of Willis were found.

Microscopic observations. All renal and hepatic lesions found by light microscopy were recorded and graded according to severity. Renal changes consisted of moderate to marked
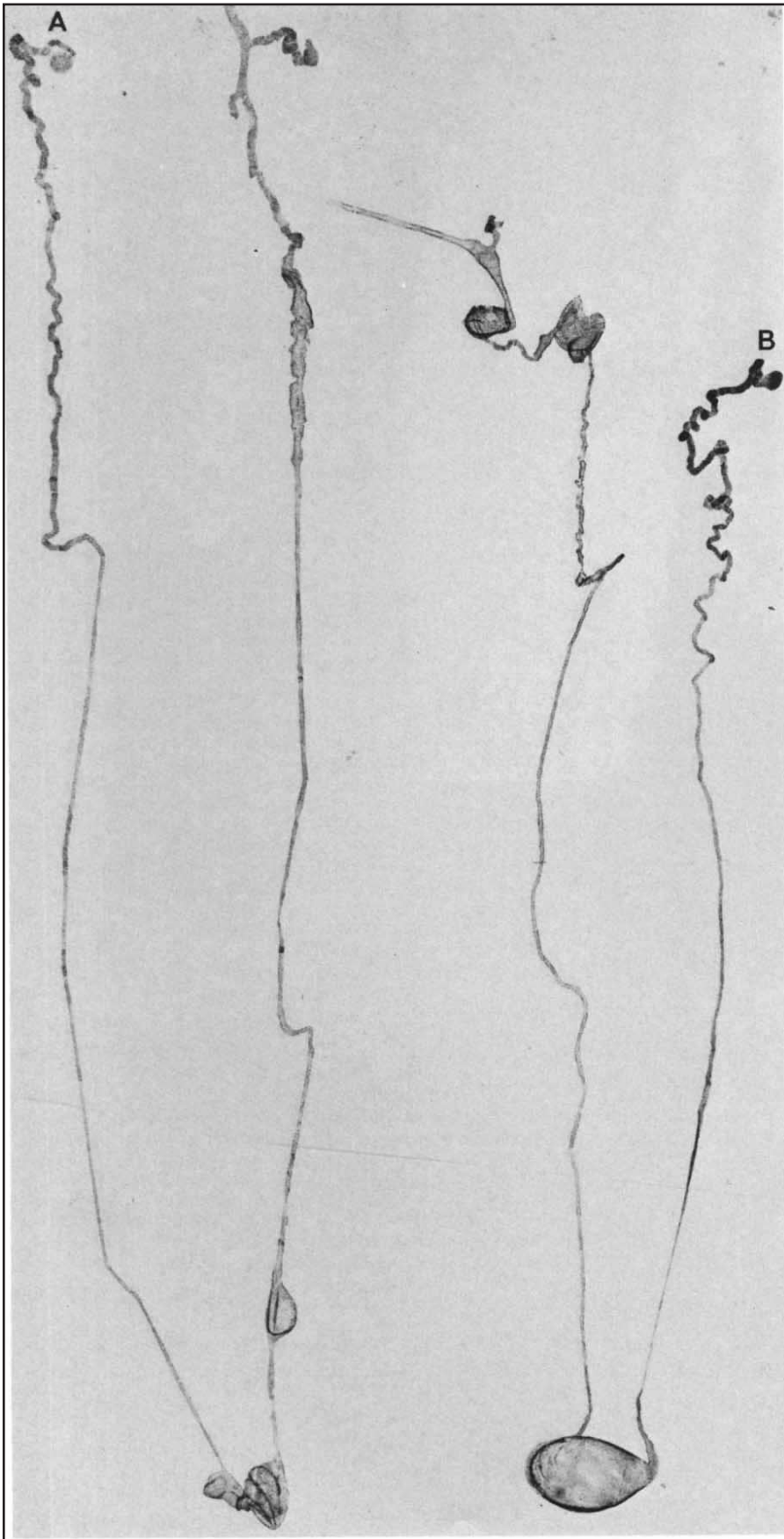
Fig. 5. *Mosaic photomicrographs of two complete nephrons.* Nephron **A,** from polycystic kidney N80-442, displays a cyst in the bend of the loop of Henle and another in the ascending limb. Irregular dilatation and a few small diverticula are present in the distal convoluted tubule. Nephron **B,** from polycystic kidney N80-451, shows a cyst at the bend of the loop of Henle and two cysts and several tiny diverticula in the distal convoluted tubule. The collecting duct is irregularly dilated. (Reduced to ×34 from ×200).
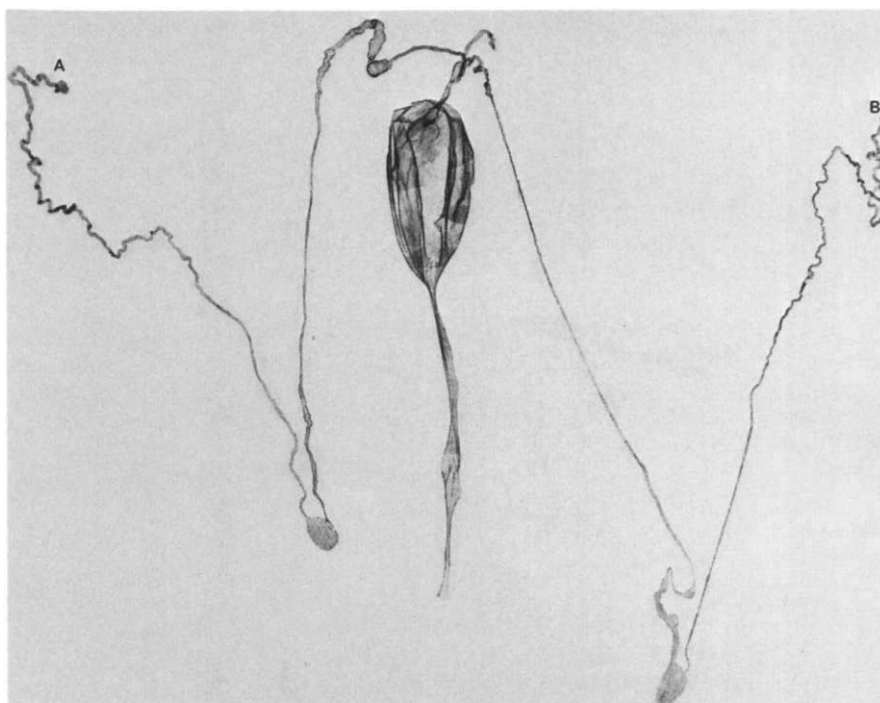
Fig. 6. *Mosaic photomicrograph of a large cyst of a collecting duct from polycystic kidney N80-96.* Two complete nephrons are attached to the collecting duct just above point at which it becomes cystic. The letters **A** and **B** mark the glomeruli of the two nephrons. The proximal tubules appear normal. Each nephron presents a cyst at the bend of Henle's loop as well as irregular dilatation of the ascending limb and of distal convoluted tubule. (Reduced to ×13 from ×100).

focal dilatation of tubules predominately in the outer zone of the medulla but also involved portions of the inner zone. Dilated tubules were also scattered throughout the cortex and extended occasionally to the capsule (Figs. 2 and 3). The largest cysts in the sections were present in the cortex. The distribution of the cysts was similar in all affected calves though the largest cysts tended to be in calves that survived the longest, for example, C79-452 and N80-96. The cystic, dilated tubules were lined by a single layer of attenuated or flattened epithelium. Focal polypoid hyperplasia of lining epithelial cells could usually be seen in one or two cysts per section. Glomeruli were adequate in number. The urinary space of some glomeruli was slightly to moderately dilated in a few affected animals. Subcapsular glomeruli were small and juvenile. A few additional renal lesions present in calves that died naturally included foci of necrosis, papillary necrosis (in one calf), and pyelonephritis; in three of these animals gram negative bacilli were demonstrated with special stains.

All calves that had polycystic kidneys from which liver was available for examination had proliferation and cystic dilatation of bile ducts in most portal areas. Liver tissue from one affected calf (C79-818) was not available for examination. The bile ducts were dilated irregularly and confluent, with only a slight increase in periductular connective tissue. Hyperplasia of bile ductular epithelium frequently formed folds which projected into the lumena producing a tortuous appearance. Greenish yellow bile pigment was present in the bile ducts of most affected animals, however, there was no cholestasis in the parenchyma. Four calves that died naturally had suppurative cholangitis; three of these animals also had foci of necrotizing

hepatitis and one had demonstrable gram negative bacilli in the liver (Fig. 4).

Other tissues that were examined from normal and affected calves were lung, heart, thymus, lymph nodes, forestomachs, abomasum, duodenum, jejunum, ileum, colon, pancreas, adrenals, thyroids, pituitary, cerebrum, cerebellum, eyes, bone and bone marrow, testicles, and urinary bladder. Acute splenic necrosis, interstitial pneumonia, lymphadenitis, and hypopyon were found in calves 13286, C79-452, C79-711, and C79-818, respectively. All of these calves died spontaneously with additional lesions compatible with septicemia. The mean age at death of affected calves that died naturally was 6 days.

Microdissection studies. A small number of glomeruli, varying from 1 to 4% of the total examined in the three kidneys, were found to have tiny cysts. Proximal tubules were normal in all three of the affected kidneys. There was no significant difference in mean glomerular diameter or mean diameter and length of proximal tubules between the normal and affected animals.

Cysts were found in from 5 to 15% of the descending limbs of Henle's loops, in 100% of the bends of the loops, and in 51 to 61% of the ascending limbs in the three affected kidneys (Figs. 5, 6, and 7). A few of the cysts of ascending limbs were massive (Fig. 8). The presence or absence of cysts in the descending limb of a nephron was unrelated to the presence or absence of cysts in the ascending limb of the same nephron.

Cysts of distal convoluted tubules were present in from 35% to 40% of nephrons studied in the three kidneys. Cysts of connecting tubules were rarely seen.

Cysts were present in from 18 to 23% of collecting ducts in
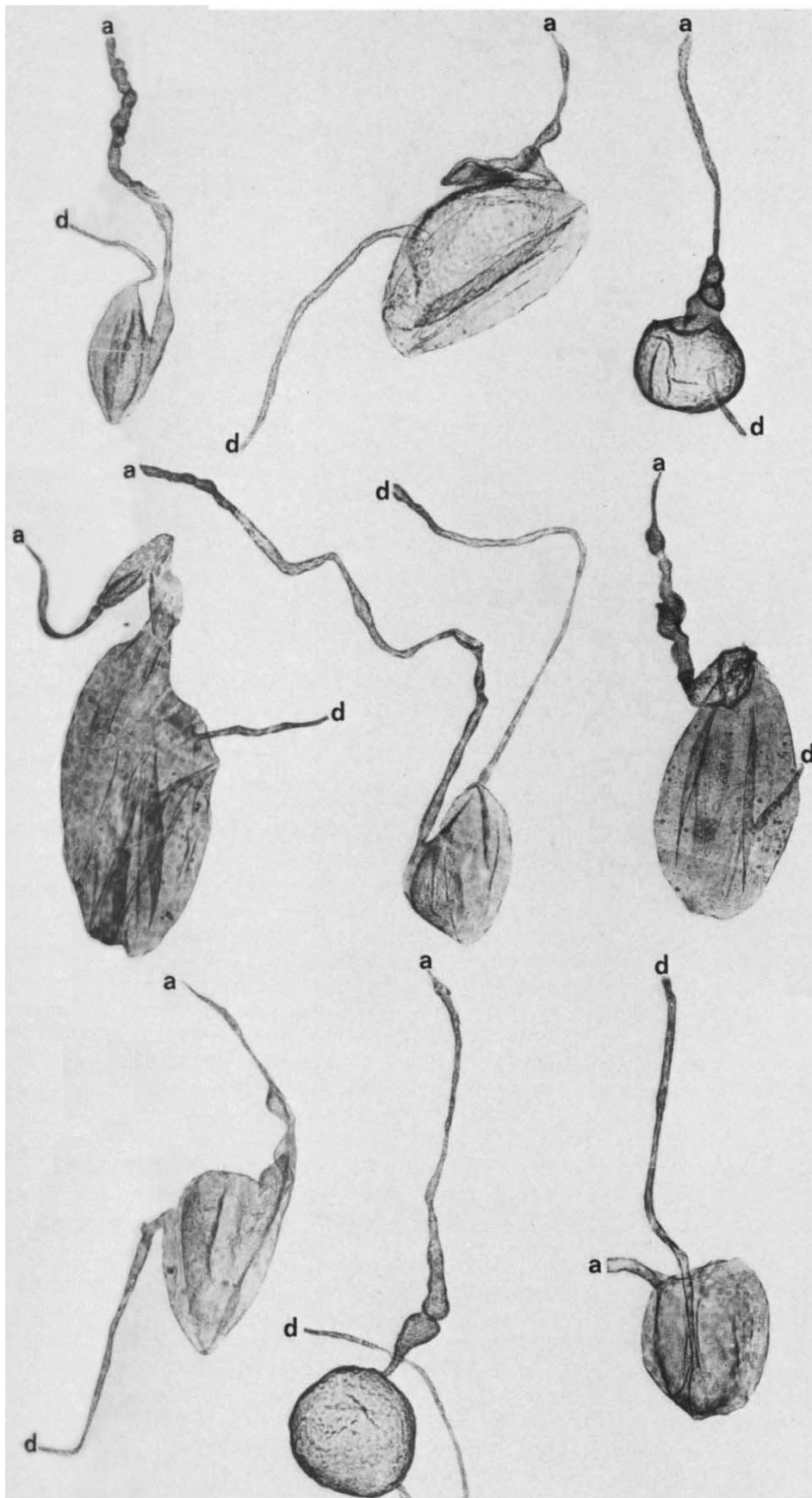
Fig. 7. *Mosaic photomicrograph of nine fragments of nephrons from polycystic kidney N80-96 to illustrate the cysts at the bend of the loop of Henle.* The severed ends of descending limbs (d) and ascending limbs (a) are also displayed. (Reduced to ×68 from ×200).
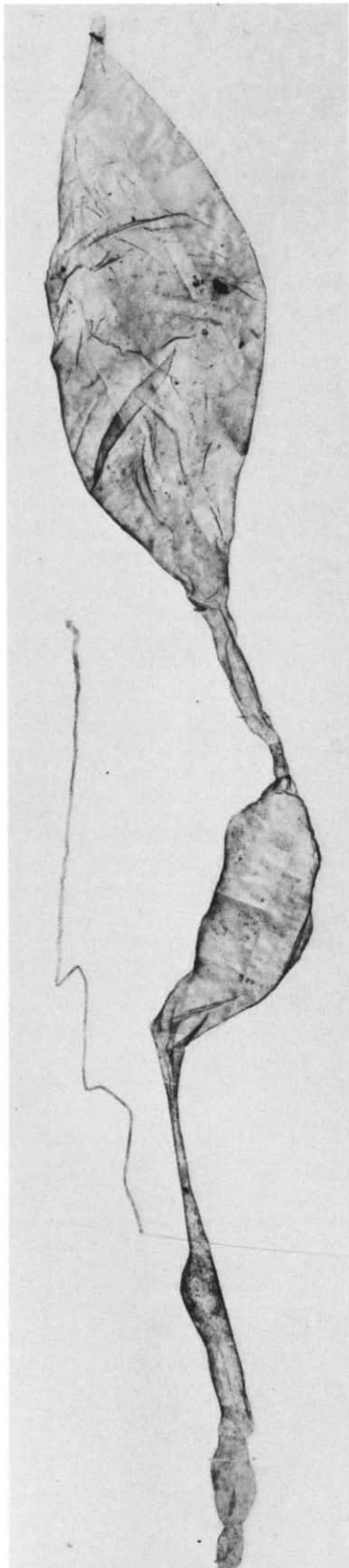
Fig. 8. *Mosaic photomicrograph of cystic ascending limb from polycystic kidney N80-451.* Ascending limb at left included for comparison is from normal kidney N80-475. (Reduced to ×27 from ×200).

the three kidneys (Figs. 6 and 9). The largest cysts encountered during microdissection of the affected kidneys were among those in ascending limbs of Henle's loops and in collecting ducts. These might measure up to 1.2 mm in diameter but rarely more.

The cysts invariably present in the bends of the loops of Henle were small. The range in diameter of the population measured was from 167 to 530 μ with a mean value of 327 μ. Other cysts appearing in the various portions of nephrons, with the exception of certain ones in ascending limbs, also tended to be small. None of the cysts, large or small, presented fibrous thickening, all being thin-walled.

No cysts were found in any nephron or collecting duct encountered in microdissection of the three normal kidneys.

Ultrastructural studies. Cyst walls from both renal tubular cysts and bile duct cysts from calves N80-446 and N80-475 (normals) and N80-442 and N80-500 (affected) were examined. Smaller cysts lined by relatively normal epithelial cells were selected and attention was directed to the basement membranes and supporting ground substance. No consistent changes of the basement membranes were seen in the sections of cyst walls examined in either the liver or kidney from the affected calves.

Discussion

The condition described in this report was recognized as a consequence of increased neonatal mortality in an inbred herd of Springbok. Nephromegaly was detected at necropsy in several of these neonates and was found to be present at birth in subsequent live calves. Affected calves never survived more than 12 days.

Several features of this disease in Springbok are similar to the autosomal recessive form of PCKD in man. When it occurs, the condition is congenital, bilateral, and lethal. All calves from which liver was examined also had cystic disease of the biliary system much like that described in Potter's type I cystic disease [2, 21, 22]. Four calves also had suppurative cholangitis, not an uncommon sequela to cystic biliary disease in man [23–25]. Bridging fibrosis with minimal bile stasis typical of congenital hepatic fibrosis [22–25] was not present in the animals examined. However, all animals examined died or were sacrificed at less than 2 weeks of age. Whether or not bridging fibrosis might have developed if the calves had survived longer is not known. The overall 5-year incidence of 18%, affecting both males and females, which resulted from mating to one herd sire, is suggestive of an autosomal recessive trait that is not sex-linked. Continuous mating of the presumably heterozygous male to his daughters and granddaughters over a period of years could have increased the number of heterozygous dams until the current level of homozygous, affected, offspring had been reached.

Although the location of cysts in the Springbok disease is somewhat different than in autosomal recessive PCKD of man (Potter type 1 or "tubular gigantism") [21], the similarities outweigh the differences. Structural features common to both Potter type 1 and the Springbok disease include bilateral involvement, symmetrical enlargement with retention of reniform outline, the presence of cysts in nephrons and collecting ducts, the lack of proximal tubular cysts, and the absence of increased interstitial connective tissue. Among the differences are the characteristic pattern of radially oriented giant fusiform
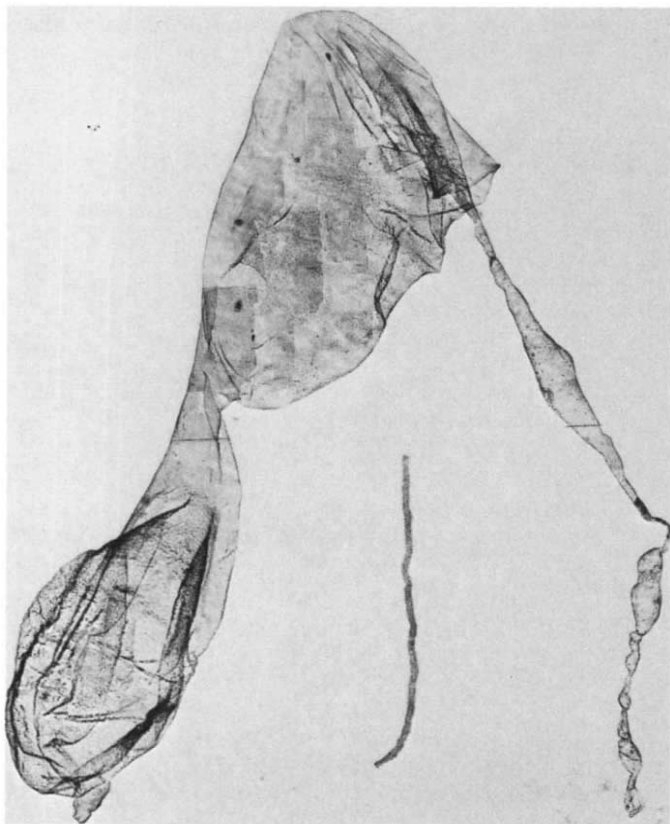
Fig. 9. *Mosaic photomicrograph of cystic collecting duct from polycystic kidney N80-541 with normal collecting duct from normal kidney N80-475 in center for comparison.* The nuclear pattern visible in areas of the cyst uppermost in picture suggests hyperplasia. (Reduced to ×29 from ×200).

cysts in the autosomal recessive PCKD of man and the universal presence of cysts at the bend of Henle's loop in the Springbok disease.

The presence of small cysts at the bend of the loop of Henle in every one of the hundreds of nephrons studied from the kidneys of the affected Springbok is of considerable interest. Many cysts at this location in the nephron may be seen in the published microdissections of human polycystic kidneys by Osathanondh and Potter [21] and also by Baxter [26]. Many such cysts are present in preparations from each of the four types of cystic renal disease in the Osathanondh and Potter classification. They are common in examples of their type 1, the infantile form of polycystic kidney disease, as well as in their type 4, a noninherited variety associated with urethral obstruction.

In an experimental model of renal cystic disease produced by intrauterine ureteral ligations in fetal rabbits, Fetterman, Ravitch, and Sherman [8] noted that the most common cysts of the nephrons resulting from the ligations were at the bends of Henle's loops. These authors suggested that the predilection of the bend of Henle's loop for formation of cysts may depend upon "a propensity for growth activity somewhat greater than that elsewhere in the nephron," and that the bend of the loop may be a "weak spot."

No serious conceptual problems are presented by the pathogenesis of such cysts in nephrons of human or rabbit kidneys under conditions of urinary obstruction in the fetal period. However, ureteral or urethral obstruction cannot be blamed for the production of cysts in infantile polycystic disease or in polycystic renal disease in newborn Springbok. Perhaps the large somewhat hyperplastic cysts of interstitial collecting ducts occurring in either condition are responsible for local obstruction of adjacent nephrons and contribute to intranephronic cyst formation [8].

No lesions of the basement membranes were found in the material examined by transmission electron microscopy in contrast to the abnormal basement membranes described by Cuppage et al [12] in human patients with the autosomal dominant form of PCKD. Occasional foci of polypoid tubular epithelial hyperplasia were found in the histologic sections examined, but their incidence and role, if any, in this disease in this species is unknown at this time.

Evan, Gardner, and Bernstein have reviewed the morphologic and physiologic evidence from human kidneys and experimental models gathered from study of polycystic kidney disease [13]. Increased intratubular pressure as measured by micropuncture has led to identification of polypoid and papillary epithelial hyperplasia along medullary collecting tubules. In other studies where intratubular pressures were normal, increased compliance of the tubular basement membrane has been proposed as a mechanism of cyst formation [27]. Micropuncture and scanning electron microscope studies will have to be performed in Springbok to evaluate these parameters in this species.

Whatever biochemical aberrations occur in this condition are present in utero because the morphologic consequence is fully developed and present at birth. The evidence for recessive inheritance implicates an enzymatic abnormality, perhaps an epithelial protein in the kidney and liver [1].

The Springbok disease, herein described, constitutes an excellent animal model for the investigation of polycystic kidney disease of recessive inheritance. This herd of Springbok may provide an important source of material to determine what enzymatic defect may be responsible for development of renal and biliary cysts.

References

1. BERNSTEIN J: Polycystic disease, in *Pediatric Kidney Disease,* edited by EDELMAN CM JR, Boston, Little, Brown and Co., 1978, vol. 2, pp. 557–565
2. KISSANE JM: The morphology of renal cystic disease, in *Cystic Diseases of the Kidney,* edited by GARDNER KD JR, New York, John Wiley and Sons, 1976, pp. 37–45
3. MILUTINOVIC J, FIALKOV PJ, RUDD TG, AGODOA LY, PHILLIPS LA, BRYANT JI: Liver cysts in patients with autosomal dominant polycystic kidney disease. *Am J Med* 68:741–744, 1980
4. HUSEMAN R, GRADY A, WELLING D, GRANTHAM JJ: Macropuncture study of polycystic disease in adult human kidneys. *Kidney Int* 18:375–385, 1980
5. HOGEWIND BL, VELTKAMP JJ, KOCH CW, DEGRAEFF J: Genetic counseling for adult polycystic kidney disease: Ultrasound a useful tool in pre-symptomatic diagnosis? *Clin Genet* 18:168–172, 1980
6. SHOKIER MHK: Expression of "adult" polycystic renal disease in the fetus and newborn. *Clin Genet* 14:61–72, 1978
7. RESNICK JS, BROWN DM, VERNIER RL: Normal development and experimental models of cystic renal disease, in *Cystic Diseases of the Kidney,* edited by GARDNER KD, New York, John Wiley and Sons, 1976, pp. 221–240
8. FETTERMAN GH, RAVITCH MM, SHERMAN FE: Cystic changes in fetal kidneys following ureteral ligation: Studies by microdissection. *Kidney Int* 5:111–121, 1974
9. EVAN AP, GARDNER KD JR: Comparison of human polycystic and medullary cystic kidney disease with diphenylamine-induced cystic disease. *Lab Invest* 35:93–101, 1976
10. EVAN AP, HONG SK, GARDNER KD JR, PARK YS, ITAGAKI R: Evolution of the collecting tubular lesion in diphenylamine-induced renal disease. *Lab Invest* 38:244–252, 1978
11. EVAN AP, GARDNER KD JR: Nephron obstruction in nordihydroguaiaretic acid-induced renal cystic disease. *Kidney Int* 15:7–19, 1979
12. CUPPAGE FE, HUSEMAN RA, CHAPMAN A, GRANTHAM JJ: Ultrastructure and function of cysts from human adult polycystic kidneys. *Kidney Int* 17:372–381, 1980
13. EVAN AP, GARDNER KD JR, BERNSTEIN J: Polypoid and papillary epithelial hyperplasia: A potential cause of ductal obstruction in adult polycystic disease. *Kidney Int* 16:743–750, 1979
14. WEBSTER WR, SUMMERS PM: Congenital polycystic kidney and liver syndrome in piglets. *Aust Vet J* 54:451, 1978
15. CROWELL WA, HUBBELL JJ, RILEY JC: Polycystic renal disease in related cats. *J Am Vet Med Assoc* 175:286–288, 1979
16. MCKENNA SC, CARPENTER JL: Polycystic disease of the kidney in the cairn terrier. *Vet Pathol* 17:436–442, 1980
17. MCDOWELL EM, TRUMP BF: Histological fixatives suitable for diagnostic light and electron microscopy. *Arch Pathol Lab Med* 100:405–414, 1976
18. LUNA LG: *Manual of histologic staining methods of the Armed Forces Institute of Pathology* (3rd ed). New York, Blakiston, 1968, pp. 72, 94–95, 184, 224–225
19. OLIVER J, MACDOWELL M, TRACY A: The pathogenesis of acute renal failure associated with traumatic and toxic injury: Renal ischemia, nephrotoxic damage and the ischemuric episode. *J Clin Invest* 30:1307–1439, 1951
20. FETTERMAN GH, FABRIZIO NS, STUDNICKI FM: Microdissection of the nephron: The method and its applications, in *Laboratory Diagnosis of Kidney Disease,* edited by SUNDERMAN FW, SUNDERMAN FW JR, St. Louis, WH Green, 1969, p. 32
21. OSATHANONDH V, POTTER EL: Pathogenesis of polycystic kidneys. (6 articles) *Arch Path* 77:459–512, 1964
22. KISSANE JM: Congenital malformations in *Pathology of the Kidney* (2nd ed), edited by HEPTINSTALL RH, Boston, Little, Brown and Co., 1974, vol. 1, pp. 89–97.
23. MURRAY IM, OCKENDEN BG, WILLIAMS R̄: Congenital hepatic fibrosis—is it a single clinical entity? *Gastroenterology* 64:653–656, 1973
24. ALAGILLE D, ODIEVRE M: Congenital hepatic fibrosis, in *Liver and Biliary Tract Disease in Children,* New York, John Wiley and Sons, 1979, pp. 253–260
25. KOCOSHIS SA, RIELY CA, BURRELL M, GRYBOSKI JD: Cholangitis in a child due to biliary tract anomalies. *Dig Dis Sci* 25:59–65, 1980
26. BAXTER TJ: Polycystic kidney of infants and children: Morphology, distribution and relation of the cysts. *Nephron* 2:15–31, 1965
27. CARONE FA, ROWLAND RG, PERLMAN SG, GANOTE CE: The pathogenesis of drug-induced renal cystic disease. *Kidney Int* 5:411–421, 1974