Congenital Renal Diseases

By George E. Lees. DMV, MS

Veterinary Clinics of North America: Small Animal Practice, Volume 26 Number 6,November 1996

Although much less common than acquired renal disorders, congenital kidney diseases are a frequent cause of renal failure in dogs. Congenital renal diseases also occur in cats, but they are not as common as in dogs. By definition, congenital kidney disease means that renal lesions either were present at birth or developed because of some defect that existed when the animal was born. Discovery of renal disease in a young animal typically raises the question of whether the disease is congenital; however, juvenile animals can be afflicted by acquired renal disorders. Additionally, congenital renal diseases sometimes do not produce clinical signs until affected animals are middle aged or older. Thus, the patient's age by itself is not a reliable indicator of where an animal with renal disease has a congenital lesion.

Several congenital renal disorders are known to be inherited, at least in certain kindreds or breeds (Table 1). In some other breeds, observation of similar renal lesions in a number of related animals suggests that the condition is inherited. However, the causative defect, pathogenesis, and mode of inheritance for most hereditary nephropathies are unknown. Additionally, congenital kidney lesions (e.g./ renal dysplasia) that have a familial occurrence in certain breeds also occur sporadically in many other breeds. Thurs, mere discovery of a congenital renal lesion does not mean that the condition was inherited by the affected individual.

Table 1. DOG AND CAT BREEDS IN WHICH A RENAL DISEASE IS KNOWN OR SUSPECTED TO BE INHERITED

Breed	Pathologic Type	Mode of Inheritance
Dogs		
Certainly Inherited*		
Samoyed	Primary glumerulopathy	X chromosome linked
Bull Terrier	Primary glomerulopathy	Autosomal dominant
English Cocker Spaniel	Primary glomerulopathy	Autosomal recessive
Lhasa Apso/Shih Tzu	Renal dysplasia	Not determined
Norwegian Elkhound	Tubulointerstitial disease	Not determined
Basenji	Renal tubular dysfunction	Not determined
Probably Inherited†		
Miniature Schnauzer	Undetermined	—
Standard Poodle	Renal dysplasia	—
Soft-coated Wheaten Terrier	Renal dysplasia	—
Soft-coated Wheaten Terrier	Glomerulonephritis	—
Doberman Pinscher	Primary glomerulopathy	—
Chow Chow	Renal dysplasia	—
Chinese Shar Pei	Amyloidosis	—
Beagle	Amyloidosis	—
Beagle	Unilateral renal agenesis	—
Bernese Mountain Dog	Glomerulonephritis	—
Possibly Inherited‡		
Keeshond	Undetermined	—
Bedlington Terrier	Undetermined	—
Golden Retriever	Renal dysplasia	—
Alaskan Malamute	Renal dysplasia	—
Newfoundland	Primary glomerulopathy	—
Rottweiler	Primary glomerulopathy	—
Cairn Terrier	Infantile polycystic kidneys	—
Pembroke Welsh Corgi	Telangiectasia	—
Cats		
Certainly Inherited*		
Persian (longhaired)	Polycystic kidney disease	Autosomal dominant
Abyssinian	Amyloidosis	Not determined
Probably Inherited†		
Persian-cross	Infantile polycystic kidneys	—

*Mode of inheritance known or genetic basis indicated by studies of many (>25) related animals
†Genetic basis suggested by studies of 5 to 25 animals, some being closely related
‡Genetic basis suggested by studies of a few (<5) closely related animals or of unrelated animals

Many inherited nephropathies cause chronic renal failure with progressive deterioration of the kidneys both functionally and morphologically until advanced end-stage changes predominate at death. With the opportunity to gradually adapt to declining kidney function throughout most of their lives, affected animals often do remarkably well until their disease is near terminal. This has at least two noteworthy consequences. First, owners of these animals usually are not emotionally prepared for the devastating news that their pet has such an irreversible, life-threatening disease. Second, pathologic examination of kidney tissue obtained at this late stage of disease often fails to elucidate the primary renal lesions(s) because secondary changes (e.g., inflammation, fibrosis, and mineralization) dominate the scene. To discern the pathogenesis of inherited nephropathies, onset and progression of primary renal lesions must be characterized early in the course of disease.

PATHOLOGIC TYPES OF FAMILIAL KIDNEY DISEASES

Congenital kidney diseases that are known to be inherited, as well as those that are at least suspected to be familial, are characterized by primary renal lesions of several different pathologic types (Table 2). Additionally, secondary lesions arising from various compensatory, degenerative, and inflammatory processes are commonly seen and often obscure the primary lesions.

Table 2. PATHOLOGIC TYPES OF FAMILIAL KIDNEY DISEASE RECOGNIZED IN DOGS AND CATS

Pathologic Type	Breed	References
Type undetermined	Keeshond	43
	Bedlington Terrier	60
	Miniature Schnauzer	55
Renal dysplasia	Lhasa Apso and Shih Tzu	7,59,61,64
	Standard Poodle	21
	Soft-coated Wheaten Terrier	26,55
	Golden Retriever	18,42
	Alaskan Malamute	13,41,60
	Chow Chow	12
Primary glomerulopathies		
Hereditary nephritis	Samoyed	1,2,36–38,74–79,84
	Bull Terrier	31–33,39,42,57,72
	English Cocker Spaniel	25,30,45–48,50,62,67,71,73
Idiopathic glomerulopathy	Doberman Pinscher	15,66,82
Glomerulosclerosis	Newfoundland	44
Atrophic glomerulopathy	Rottweiler	18
Polycystic kidney disease	Persian (longhaired) cats	3–5,17,19,20
	Cairn Terrier	51
Tubulointerstitial disease	Norwegian Elkhound	27–29
Unilateral renal agenesis	Beagle	70,81
Telangiectasia	Pembroke Welsh Corgi	54
Amyloidosis	Abyssinian cats	10,14,22
	Chinese Shar Pei	23
	Beagle	9
Glomerulonephritis	Bernese Mountain Dog	52,68
	Soft-coated Wheaten Terrier	49
Fanconi's syndrome	Basenji	7,8,11,24,58,83

Type Undetermined

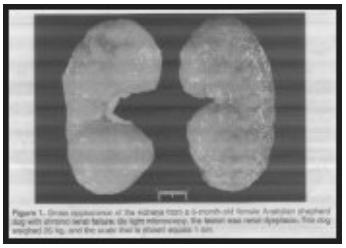
All five puppies in an inbred Keeshond litter had congenital kidney disease.43 The condition was called renal cortical hypoplasia, which was an accepted diagnostic term when the dogs were evaluated. Subsequent studies of most conditions that were once called renal cortical hypoplasia, however have let to their reclassification as renal dysplasia or hereditary nephritis. Descriptions of lesions seen in the Keeshonds are not sufficient for accurate categorization of their disease.65 Similarly, the type of nephropathy in three young Bedlington Terrier littermates was not deetermined.60 In a more recent report, features of a juvenile renal disease in Miniature Schnauzers resembled renal dysplasia, but the investigators felt that examination of more dogs affected at various stages of the disease was needed before the condition could be correctly classified.55

Renal Dysplasia

Renal dysplasia is defined as disorganized development of renal parenchyma that is due to abnormal differentiation. Generally, lesions that are associated with dysplasia include presence of structures that are inappropriate to the stage of development of the organism or the development of structures that are anomalous. Familial renal dysplasia has not been described in cats, but renal dysplasia is a common cause of renal failure in juvenile dogs. (Fig. 1).

The light microscopic features of canine renal dysplasia have been described.64 The most consistent feature is evidence of asynchronous differentiation, which is manifested by the presence of fetal or immature glomeruli and/or tubules within an otherwise mature kidney. Fetal glomeruli and tubules are found mostly in radial segments extending from the subcapsular surface to the corticomedullary junction and are associated with various degrees of interstitial fibrosis. Adjacent cortical tissue is more normally developed, but immature glomeruli are often scattered in these areas as well. Occasionally, isolated primitive tubules are found in the inner cortex surrounded by loose mesenchyme. Less consistently observed microscopic features of canine renal dysplasia include persistent mesenchyme in the medulla, persistent metanephric ducts, atypical tubular epithelium, and dysontogenic metaplasa. Common secondary changes include compensatory hypertrophy and hyperplasia of glomerular tufts and tubules, interstitial fibrosis, tubulointerstitial nephritis/pyelonephritis,, dystrophic mineralization, cystic glomerular atrophy, microcystic tubules, retention cysts, and glomerular lipidosis.

Renal dysplasia is most common in the Lhasa Apso and Shih Tzu breeds, and because the condition is so widespread in these two breeds, it is presumed to e a familial disorder.7,59,61,64 However, the cause, pathogenesis, and mode of inheritance of the condition are unknown. Other dog breeds that have been the subject of reports suggesting familial occurrence of a nephropathy having light microscopic features consistent with renal dysplasia include the Soft-Coated Wheaten Terrier,26,56 Standard Poodle,21 Alaska Malamute,13,41,80 Golden Retriever,18,42 and Chow Chow.12 Additionally, sporadic cases of renal dysplasia in many other breeds have been reported. 64



Primary Glomerulopathies

Hereditary nephritis refers to a specific group of inherited glomerular diseases that are caused by defective synthesis of type IV collagen, which is a major structural component of glomerular capillary basement membranes (GCBM). Alport syndrome is the most common form of hereditary nephritis in humans.40 Affected persons develop renal failure as children or young adults. Genetic transmission of Alport syndrome is X chromosome-linked in most families, but autosomal transmission is seen in some kindreds. Studies of hereditary nephritis in humans have shown that the condition is caused by mutations of genes for type IV collagen.34 Each collagen IV monomer is a triple helix of component peptides (*a* chains), and six different *a*(IV) chains have been identified. The genes for human *a*5(IV) and *a*6(IV) chains are on the X chromosome. Analyses of the *a*5(IV) gene in X chromosome-linked Alport syndrome kindreds have now identified more tan 70 different mutations of this gene. Human genes for *a*3(IV) and *a*4(IV) chains are on chromosome 2, and mutations of each of these genes have been found in families with autosomal forms of Alport syndrome.53

The distinctive morphologic feature of hereditary nephritis is widespread multilaminar splitting of the GCBM that is only seen with transmission electron microscopy (TEM).40 Sequential examinations of affected individuals show that the lesions of GCBM ultrastructure evolve in a progressive fashion and that lesions can be seen with TEM before light microscopy demonstrates any changes. The light microscopic features of hereditary nephritis are nonspecific. Primary glomerular lesions are basement membrane duplication and thickening with progression to various degrees of glomerulosclerosis and periglomerular fibrosis. Other lesions that are often seen, particularly in dogs that have progressed to end-stage renal failure, include cystic glomerular atrophy, interstitial fibrosis, tubulointerstitial inflammation, dystrophic mineralization, and tubular dilation. As with renal dysplasia, these changes probably are due to secondary degenerative and and inflammatory processes, and they can easily obscure the primary lesions. Late in the course of disease, light microscopic diagnoses of glomerulonephritis, interstitial nephritis, or pyelonephritis frequently have been made in cases of hereditary nephritis.

An X chromosome-linked form of hereditary nephritis in a family of Samoyed dogs has been studied extensively.1,2,36-38,74-79,84 The form of canine hereditary nephritis affecting this kindred of Samoyeds is the most fully characterized example of inherited kidney disease in dogs that presently exists. The causative genetic mutation, mode of inheritance, and pathogenesis of the condition have been identified. As with X-linked Alport syndrome in humans, hereditary nephritis in Samoyeds is caused by an *a*5(IV) gene defect. The mutation is a single T for G nucleotide substitution, changing a conserved glycine residue (GGA) to a stop codon (TGA).84

Based on observation of characteristic ultrastructural GCBN lesions using TEM, several other dog breeds are suspected to have different forms of hereditary nephritis. An autosomal dominant form of hereditary nephritis has been described in Bull Terriers.32,33,39,42,57,72 Affected dogs have the distinctive abnormalities of GCBM ultrastructure that are associated with hereditary nephritis.42 Similar lesions were seen in a 4-year-old Miniature Bull Terrier with renal failure that had some Bull Terriers among his ancesotrs.31

English Cocker Spaniels are affected by an inherited kidney disease that was originally called renal cortical hypoplasia.25,30,46,62 The condition, which is inherited as an autosomal recessive trait, usually is call familial nephropathy in more recent reports.45,50,67,71,73 When kidney tissue from a Cocker Spaniel with familial nephropathy was examined with TEM in New Zealand, GCBM changes that closely resembled those of Alport syndrome in humans were recognized.67 In ongoing studies at Texas A&M University, we have also observed GCBM changes typical of hereditary nephritis in all English Cocker Spaniel dogs with familial nephropathy tat we have examined with TEM.47,48 We believe that familial nephropathy in English Cocker Spaniel dogs is a form of hereditary nephritis that should be due to an *a*3(IV) or *a*4(IV) gene defect, which we are presently trying to identify.

A familial nephropathy affecting Doberman Pinschers in the United States and Canada has been described.15,66,82 The primary renal lesion in these dogs develops in their glomeruli, but the expected spectrum of secondary compensatory, degenerative, and inflammatory glomerular and/or tubulointerstitial lesions are seen as well, especially with more advanced disease. Some affected females also have unilateral renal agenesis. By light microscopy, the dominant renal lesion is a sever multifocal to diffuse membranoproliferative glomerulonephritis that is often accompanied by sever tubulointerstitial inflammation. Cystic glomerular atrophy commonly accompanies sever interstitial nephritis. Using TEM, studies of kidneys from affected dogs have demonstrated two distinct ultrastructural lesions of the GCBM. 66 The first lesions, which was more common (seen if five of eight cases), was characterized by multifocal thickening of the GCBM with lamellation of the lamina densa and resembled the ultrastructural lesion associated with hereditary nephritis. The second lesion was less common (seen in three of eight cases), but was characterized by marked attenuation of the lamina densa with thickening of the GCBM caused by intramembranous and/or subepithelial deposits of randomly dispersed collagen fibers. This second lesion resembles an abnormality seen in human hereditary osteo-onychodysplasia (nail-patella syndrome). Further studies are needed to fully characterize the primary lesion(s) and pathogenesis of the familial kidney disease that affects Doberman Pinscher dogs.

A juvenile renal disease characterized by glomerulosclerosis and glomerulofibrosis has been described in three related Newfoundland dogs.44 Under light microscopy, glomeruli exhibited massive hyalinization caused by mesangial sclerosis and capillary collapse. The eosinophilic hyaline glomerular deposits appeared to be collagen (rather than amyloid) when examined with special stains. Using TEM, glomerular mesangial areas were shown to be greatly dilated and filled with amorphous material in which many cross-banded collagen fibrils were imbedded. Ultrastructural features of the condition resembled those of a nephropathy recently recognized in humans (i.e., collagenofibrotic glomerulopathy)35 and were somewhat similar to the less common of the two lesions seen in the Doberman Pinschers.66 Juvenile glomerulopathy in another Newfoundland dog has been described,6 but that dog's glomerular lesion had notably more mesangial cell proliferation that was seen in the Newfoundland littermates.44

Renal disease caused by severe, diffuse, global, atrophic membranous glomerulopathy has been described in four related juvenile Rottweiler dogs with kidney failure.16 The dominant abnormality seen by light microscopy was cystic glomerular atrophy, with 30% to 50% of the renal corpuscles in 3-pm sections having no glomerular tufts and 40% to 50% of the corpuscles having tufts that were les than 50% of normal size and located within relatively dilated urinary spaces. The atropic glomerular tufts also had irregularly thickened basement membranes. Ultrastructure of the GCBM in these dogs was not studied. Secondary renal lesions included mild interstitial fibrosis, tubular atrophy, hyalin cast formation, and mineralization of glomerular capsules and tubular basement membranes.

Polycystic Kidney Disease

Polycystic kidney disease characterized by autosomal dominant inheritance and late onset renal failure has been described in Persian and Persian-cross cats.4,5,19,20 The primary renal lesion in polycystic kidney disease is formation and progressive enlargement of multiple cysts in both kidneys. In affected cats, renal cysts differ in size (<2 mm to 2.0 cm), number (11 to 196 per kidney), morphologic character, and location in the kidney (in both cortex and medulla).20 Grossly, the kidneys become enlarged (2 to 3 times normal) and irregular, and the gross renal changes often are slightly to severely asymmetrical. Microscopically, renal cysts are lined by cuboidal and flattened cuboidal epithelial cells that lack a brush border. Although it probably is a secondary change, a chronic tubulointerstitial nephritis also is seen in affected cats. A few Persian cats with polycystic kidney disease have also had cysts in other organs, usually the liver. Hepatobiliary hyperplasia and fibrosis have been seen microscopically in affected cats.20

Several related longhaired kittens that died before 7 weeks of age with severely polycystic kidneys have been described.17 Affected kittens also had cystic bile ducts.

Polycystic kidney disease has also been reported in three 6-week-old Cairn Terrier puppies from two related litters.51 Both kidneys of affected pups were enlarged and contained multiple, variable-sized cortical and medullary cysts. Hepatic lesions, characterized by diffuse bridging portal fibrosis and dilated proliferative biliary ductules, were also found. The renal and hepatic lesions in these pups

were thought to be analogous to those of infantile polycystic kidney disease in children.

Tubuloinerstitial Nephropathy

A familial renal disease in Norwegian Elkhounds has been described primarily as a noninflammatory tubulointerstitial disease.27-29 The kidneys of affected dogs are normal at birth, but advancing interstitial fibrosis leads to marked cortical thinning. Primary glomerular disease has not been detected by light microscopic, TEN, or immunofluorescent studies, but periglomerular fibrosis with hyperplasia and hypertrophy of parietal epithelium is a prominent early change. Lesions in dogs with more advanced disease consist of generalized interstitial fibrosis with glomerular sclerosis and atrophy. Tubular changes are mild except in sever cases in which tubular atrophy, microcystic tubules, and dystrophic mineralization are seen. Minimal degrees of interstitial nephritis are found only in dogs with advanced disease.

Unilateral Renal Agenesis

Unilateral renal agenesis has been described in Beagles.70,81 Affected dogs were from colonies that were maintained to produce research subjects, and the lesion was discovered at necropsy. The existing solitary kidney generally is larger than normal. Some of the female dogs also have dysgenesis of their genital tract on the affected side, and polycystic renal disease has been described in a few Beagles with a solitary kidney. Mode of inheritance is unknown.

Telangiectasia

Multiple vascular lesions involving the kidneys and various other organs have been been described in eight Pembroke Welsh Corgi dogs that were not known to be related.54 All had bilateral renal involvement and kidney size was unequal in half the cases. Many red-black nodules of various sizes were grossly visible on the capsular and cut surfaces of the kidneys. Some nodules were cystic and contained clotted blood. Lesions were found in both cortical and medullary regions, but especially in the outer medulla. Microscopically, the lesions were cavernous, blood-filled spaces lined with simple endothelial cells.

Amyloidosis

Familial occurrence of renal amyloidosis has been reported in dogs and cats. The type of amyloid deposits found in affected animals indicates that the condition is a form of reactive or secondary amyloidosis, which is an acquired disease. Pathogenesis of reactive amyloidosis is complex and incompletely understood. Familial conditions that predispose animals to the development of reactive amyloidosis presumably operate by genetically controlled mechanisms that promote the molecular events that underlie the disease. The kidneys, which probably are not intrinsically defective, become affected because they exist in an individual who is predisposed to formation of amyloid deposits.

Amyloid, which is an extracellular accumulation of fibrillar protein in a beta-pleated sheet conformation, is identified by light microscopy via its unique appearance when stained with Congo red and examined with polarized light. Permanganate oxidation makes the deposits in patients with reactive amyloidosis lose their affinity for Congo red, which helps to differentiate this condition from other types of amyloidosis. Within the kidney, amyloid may be deposited in glomerular tufts, in the interstitium (especially in the medulla), or in the walls of renal vessels. Secondary renal changes include papillary necrosis, which has been attributed to the effects of deep medullary vascular or interstitial amyloid deposits, and interstitial nephritis. Some animals with reactive amyloidosis also have amyloid deposits in other organs, namely the liver, spleen, gut, pancreas, heart, prostate gland, thyroid gland, and lymph nodes.

Familial secondary amyloidosis has been described in Abyssinian cats,10,14,22 Chinese Shar Pei dogs,23 and in a family of Beagles.9 In the Abyssinian cats the Shar Pei dogs, which have been studied most extensively, moderate to severe medullary interstitial amyloid deposits are found more consistently than glomerular deposits are found In Shar Pei dogs, extrarenal amyloid deposits are commonly seen, especially in the liver. The causative defect and mode of inheritance for familial amyloidosis have not been identified in dogs or cats. Studies of Shar Pei dogs, however, have suggested that the underlying defect may cause dysregulation of systemic inflammatory reactions involving interleukin-6, which is a pleiotropic cytokine.69 The disease that affects Shar Pei dogs may be analogous to a human disorder called familial Mediterranean fever.

Immune-Mediated Glomerulonephritis

Familial occurrence of renal disease caused by immunologically mediated mechanisms of glomerular injury has been described in Bernese Mountain Dogs52,68 and Soft-Coated Wheaten Terriers.49 The glomerulopathies in these dogs differ from other familial glomerular diseases (e.g., hereditary nephritis) in that deposits of immune reactants, as demonstrated by electron microscopy and/or immunohistochemical studies, are prominent and consistently found in the glomerular lesions. As with amyloidosis, immune-mediated glomerulonephritis essentially is an acquired disease, and familial occurrence of the disease probably is caused by some genetic predisposition to immunologic responses that produce the lesion. However, pathogenesis of all immune-mediated glomerular disorders is complex, and the fundamental defect that causes any form of familial immune-mediated glomerulonephritis in dogs has not been identified.

Primary renal lesions are those of membranoproliferative glomerulonephritis as seen by light microscopy. In affected Bernese Mountain Dogs, TEM shows subendothelial deposits of immune complexes, and immunohistochemical studies consistently demonstrate presence of IgM and C3 in the deposits; IgA and IgG are only found accasionally.52,68 High serum levels of antibody against *Borrelia burgdorferi* were found in all affected Bernese Mountain Dogs that were tested, but the relationship of borreliosis to the pathogenesis of renal lesions in the dogs was not established. Pedigree analysis suggested that glomerulonephritis in Bernese Mountain Dogs is inherited as an autosomal recessive trait and that its expression is influenced by a second gene locus with a sex-linked dominance exchange.68

Membranoproliferative glomerulonephritis has been recognized in closely related Soft-Coated Wheaten Terriers.49 Other dogs in the same families have protein-losing enteropathies, and several dogs have exhibited both intestinal disease and glomerulonephritis. Results of ultrastructural and/or immunohistochemical studies of glomerular lesions in these dogs have not been reported, but the mechanism of glomerular injury is suspected to be associated with immune complex deposition. Mode of inheritance is unknown. Familial glomerulonephritis in Soft-Coated Wheaten Terriers must be differentiated from renal dysplasia, which also occurs in this breed.

Functional Renal Tubular Disorders

Several familial disorders characterized by abnormal renal tubular cell transport of one or more substances have been described in dogs. Several of these conditions (e.g., cystinuria, uric aciduria) are clinically important only because they cause excessive amounts of sparingly soluble compounds to appear in the urine thus predisposing affected animals to development of urolithiasis. Formation of uroliths can lead to renal parenchymal disease associated with secondary infection, obstruction to urine flow, and/or direct stone-induced injury to adjacent tissues; however, clinical signs attributable to kidney disease generally occur only as complications of urolithiasis. Readers interested in these conditions should consult the veterinary literature regarding urolithiasis; they are not further described in this article.

A constellation of renal tubular transport defects that is similar to Fanconi's syndrome in humans has been described in Basenji dogs.7,8,11,24,58,83 The primary abnormalities are derangements of proximal renal tubular function causing reduced reabsorption of filtered solutes (e.g., glucose, amino acids), which therefore are abnormally abundant in the urine that is excreted. Affected dogs, however, do not all exhibit the same spectrum or severity of impaired tubular transport, and the disorder's fundamental cause and mode of inheritance have not been identified. Renal lesions are functional rather than structural, and light microscopic findings associated with the disease are both inconsistent and nonspecific.

CLINICAL FEATURES

Consideration of the signalment of an affected animal, its age at the onset of clinical signs, the predominant clinical syndrome produced, and the distinctive clinical features of the conditions aids recognitions and differentiation of familial nephropathies in dogs and cats (Table 3).

Table 3. SOME CLINICAL FEATURES OF FAMILIAL KIDNEY DISEASES RECOGNIZED IN DOGS AND CATS

Breed	Lesion Type	Gender Predilection	Age at Clinical Onset			Clinical Syndrome	Distinctive Features	
			Low	High	Avg.		Proteinuria	Renomegaly
Keeshound	Unkn	None	2 mo	6 mo	—	CRF	No	No
Bedlington Terrier	Unkn	None	—	—	6 mo	CRF	No	No
Miniature Schnauzer	Unkn	None	4 mo	36 mo	—	CRF	No	No
Lhasa Apso/Shih Tzu	Dyspl	None	1 mo	36 mo	10 mo	CRF	No	No
Standard Poodle	Dyspl	None	3 mo	24 mo	—	CRF	No	No
Wheaten Terrier	Dyspl	None	1 mo	30 mo	—	CRF	No	No
Golden Retriever	Dyspl	None	3 mo	24 mo	—	CRF	No	No
Alaskan Malamute	Dyspl	None	4 mo	11 mo	7 mo	CRF	No	No
Chow Chow	Dyspl	None	5 mo	18 mo	8 mo	CRF	No	No
Samoyed	HN	M>F	—	—	1 y	CRF	All	No
Soft Terrier	HN	None	11 mo	8 y	3.5 y	CRF	All	No
English Cocker Spaniel	HN	None	6 mo	24 mo	—	CRF	All	No
Doberman Pinscher	Glom	None	4 mo	72 mo	27 mo	CRF	All	No
Newfoundland	Glom	None	2 mo	12 mo	—	CRF	All	Some
Rottweiler	Glom	None	6 mo	12 mo	—	CRF	All	No
Persian cats	PKD	None	3 y	10 y	—	CRF	No	Much
Cairn Terrier	PKD	None	—	—	6 wk	CRF	No	Much
Norwegian Elkhound	Tl dis	None	6 mo	5 y	—	CRF	No	No
Beagle	I-Kid	None	—	—	Birth	None	No	Some
Welsh Corgi	Telang	None	2 y	8 y	—	Hematuria	No	No
Abyssinian cats	Amyl	F>M	1 y	5 y	3.2 y	CRF	Some	No
Chinese Shar Pei	Amyl	F>M	1 y	8 y	4.1 y	CRF	Most	No
Beagle	Amyl	None	5 y	11 y	7 y	CRF	All	No
Bernese Mountain Dog	GNins	F>M	2 y	7 y	4 y	CRF	All	No
Wheaten Terrier	GNins	F>M	2 y	11 y	6 y	CRF/NS	All	No
Basenji	RTD	None	1 y	6 y	2–4 y	Fanconi's	No	No

Unkn = unknown; Dyspl = renal dysplasia; Hn = hereditary nephritis; Telang = telangiectasis; Glom = primary glomerulopathy; PKD = polycystic kidney disease; Amyl = amyloidosis, Tl dis = tubulointerstinal disease; GNins = immune-mediated glomerulonephritis; I-Kid = unilateral renal agenesis; RTD = functional renal tubular disease; M = males; F = females, CRF = chronic renal failure; NS = nephrotic syndrome

Gender Predilection

Most congenital renal diseases affect both males and females with similar frequency, but some conditions show a predilection for one gender. In X-linked hereditary nephritis, affected males develop proteinuria when they are 3 to 5 months of age, and they rapidly progress to renal failure, usually before 1 year of age.38,79 Carrier females develop proteinuria at about the same age as affected males, but because they have a normal as well as a mutated copy of the *a*5(IV) gene, carrier females do not lose kidney function as rapidly. These carriers, however, develop renal failure during middle age more often than do their unaffected sisters.1

Familial renal diseases that affect females notably more often than males are amyloidosis in Abyssinian cat14,22 and Chinese Shar Pei dogs23 and immune mediated glomerulonephritis in Bernese Mountain Dogs.68 The glomerulonephritis in Soft-Coated Wheaten Terriers also occurs in females slightly more often than in males.49 All these conditions are examples of genetic predispositions to the development of acquired renal disorders, but the significance of this observation is unknown.

Age at Onset of Clinical Signs

Most dogs with renal dysplasia or a primary glomerulopathy come to veterinary attention for signs related to their nephropathy before they are 2 years old, and these conditions often cause renal failure in dogs as young as 3 to 6 months of age. The form of hereditary nephritis that occurs in Bull Terriers, however, is unlike the other primary glomerulopathies in the affected dogs often are more than 2 years old when renal failure develops. Although some affected Bull Terriers have renal failure by 1 year of age, others are up to 8 years old before renal failure develops, and the average age when renal failure is diagnosed is 3.5 years.72

Animals with the other pathologic types of congenital renal disease also usually are more than 2 years old when their nephropathy first becomes clinically apparent. Norwegian Elkhounds with tubulointerstitial disease sometimes develop renal failure when less than 1 year old; however, progression of the disease is highly variable, and many affected dogs do not have renal failure until they are several years old.27,29 The familial forms of amyloidosis and glomerulonephritis also typically cause clinical signs to emerge when affected animals are 3 to 6 years old, but some animals with these conditions show signs at younger or older ages. Onset of clinical signs due to Fanconi's syndrome is quite variable in affected Basenji dogs; but for many of these dogs, illness begins when they are 2 to 4 years old.7

Persian and Persian-cross cats with autosomal dominant polycystic kidney disease usually are young to middle-aged adults (3 to 10 years old) when manifestations of their disease become clinically apparent.4,5 However, a kindred of Persian-cross cats with an infantile form of polycystic kidney disease that was diagnosed before the kittens were 7 weeks old has been described,17 and the Cairn terrier puppies were 6 weeks old when their kidneys were found to by polycystic.51

Clinical Syndrome

Most congenital kidney diseases cause affected animals to develop chronic renal failure, with the usual spectrum of clinicopathologic abnormalities associated with this syndrome. Onset of illness frequently is insidious and typically occurs late in the pathologic course of disease. The most common clinical signs are polyuria, polydipsia, lethargy, reduced appetite, weight loss, and vomiting. Physical exam findings often include poor hair coat, thinness, dehydration, pallor, oral ulceration, and halitosis. Laboratory testing usually reveals impaired urine concentrating ability, azotemia, hyperphosphatemia, and nonregenerative anemia Metabolic acidosis may also be found, especially late in the course of disease.

The conditions that often cause affected dogs to have substantially impaired renal function during adolescence (i.e., renal dysplasia and primary glomerulopathy) are associated with stunted growth. Additionally, because renal secondary hyperparathyroidism often occurs while the bones of these dogs are still developing, these conditions also sometimes produce skeletal abnormalities (e.g., fibrous osteodystrophy), which often affect the maxilla and/or mandible most prominently (Fig.2). Occasionally, facial deformity is the first abnormality noticed by owners of such dogs.

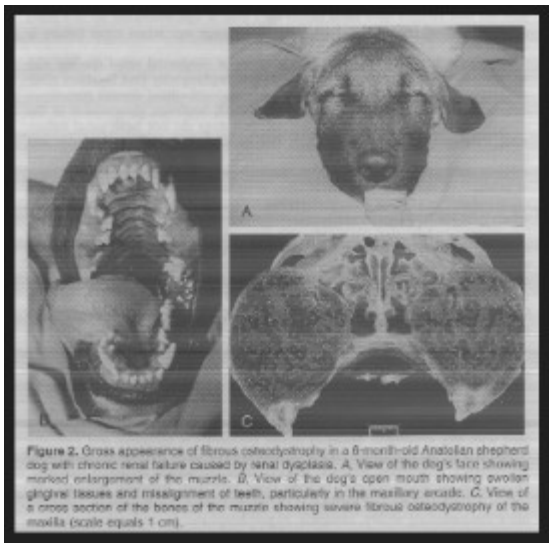


Figure 2. Gross appearance of fibrous osteodystrophy in a 6-month-old Anatolian shepherd dog with chronic renal failure caused by renal dysplasia. A, View of the dog's face showing marked enlargement of the muzzle. B, View of the dog's open mouth showing swollen gingival tissues and misalignment of teeth, particularly in the maxillary arcade. C, View of a cross section of the bones of the muzzle showing severe fibrous osteodystrophy of the maxilla (scale equals 1 cm).

Substantial proteinuria is a distinctive feature of the glomerular disorders. In dogs with hereditary nephritis (Samoyeds, Bull Terriers, English Cocker Spaniels), proteinuria is the first readily detectable abnormality that develops in affected animals, and discovery of proteinuria can be used to identify affected animals before they develop azotemia.32,38,48 Clinicopathologic findings associated with primary glomerulopathies in other breeds (Doberman Pinschers, Rottweilers, Newfoundlands) also include proteinuria, but screening for proteinuria as as aid to early diagnosis of these conditions has not been described. Proteinuria also is a consistent feature of the familial forms of immune-mediated glomerulonephritis that occur in Soft-Coated Wheaten Terriers and in Bernese Mountain Dogs; however, proteinuria is not a consistent finding in familial forms of renal amyloidosis, particularly in cats. Glomerular deposition of amyloid is associated with proteinuria, but many Abyssinian cats10 and some Chinese Shar Pei dogs23 with amyloidosis have deposits mainly in their medullary interstitium, where the lesion does not induce much urine protein loss.

Glomerular disorders that produce substantial proteinuria usually cause affected animals to have hypoalbuminemia, but the reduction of plasma albumin concentration usually is only mild to moderate in its severity. Abnormal fluid accumulation (e.g., subcutaneous edema, ascites) caused by severe hypoalbuminemia (the nephrotic syndrome) is sometimes seen in Soft-Coated Wheaten Terriers with familial glomerulonephritis; however, the hypoalbuminemia in some of these dogs is partly due to a concomitant protein-losing enteropathy.49 Ascites and/or edema due to nephrotic syndrome also is occasionally seen in Chinese Shar Pei dogs with amyloidosis.23 In most instances, however, chronic renal failure is the only clinical illness produced by a familial glomerulopathy, regardless of its pathologic type.

Persian and Persian-cross cats with polycystic kidney disease develop chronic renal failure associated with marked renomegaly.4,5 Enlarged, irregular kidneys generally can be identified by abdominal palpation. Kittens and puppies with infantile forms of polycystic kidney disease exhibit prominent abdominal distention, which is due to renal enlargement.17,51

Clinical signs exhibited by Basenjis with Fanconi's syndrome include polyuria, polydipsia, weight loss, dehydration, and weakness.7,8,24 Routine laboratory testing revels urine that is not well concentrated and contains glucose when the dog's blood glucose concentration is not excessive *i.e., renal glucosuria). Evidence of metabolic acidosis that is not associated with an increased anion gap, such as is seen with proximal renal tubular acidosis, may also be found. Specialized testing reveals excessive urinary loss (i.e., decreased fractional reabsorption) of amino acids, phosphate, sodium potassium, urate, and bicarbonate; however, affected dogs do not all show the same pattern and degree of impaired tubular function. Disease progression also is variable, but some dogs develop chronic renal failure. Affected dogs also may die suddenly of acute renal failure that is associated with papillary necrosis.7

Besides being a consistent feature of Fanconi's syndrome in Basenji dogs, renal glucosuria is sometimes observed in Lhasa Apsos and Shih Tzus with renal dysplasia,59,61 Norwegian Elkhounds with tubulointerstitial disease,27 Samoyeds and English Cocker Spaniels with hereditary nephritis,38,73 and Doberman Pinschers with primary glomerulopathy.15

Pembroke Welsh Corgis with telangiectasia have episodes of gross hematuria beginning when the dogs are 2 to 8 years old. 54 Affected dogs often go several months between episodes, but urinary bleeding can be severe enough to cause anemia and to permit formation of blood clots in the urinary space. Blood clots occasionally are seen in voided urine, and they sometimes obstruct urine flow sufficiently to cause hydronephrosis. Affected dogs may show signs of abdominal distress (abdominal splinting, whining, vomiting) or dysuria as well.

DIAGNOSIS

Diagnostic challenges associated with congenital renal disease generally occur in one of two settings. The first is when an animal, especially a young animal, is discovered to have renal failure of some other indication of kidney disease. In this setting, the first question that arises is whether the animals renal disease is due to a congenital lesion. If the condition is congenital the next question is whether the condition is inherited. Diagnosis of an inherited problem often has important implications for related animals. The second setting occurs when an animal is known to be at risk of an inherited renal disease (because of its breed or family history). In this setting, the question is whether the animal is affected. Early recognition that an animal is affected has several important benefits.

Because proper diagnosis of disease that might be inherited is crucial, the first diagnostic principle to apply when evaluating a young animal with kidney disease is to avoid making a hasty judgment based on limited data, Ignoring the admonition may lead to errors with consequences that can be quite harmful. Our experience while studying kidney disease in young English Cocker Spaniels at Texas A&M University illustrates some of the pitfalls. Many owners and breeders of English Cocker Spaniels know that the breed has an inherited nephropathy that typically causes "kidney failures" in dogs that are not yet 2 years old. With this knowledge, owners and breeders frequently assume that any dog that has kidney disease and is less than 24 months of age has the inherited condition. Since 1993,however, we have identified several English Cocker Spaniels of this age with renal failure not caused by the familial condition. These dogs made up about 25% to 33% of the suspected cases of familial nephropathy brought to our attention during that period. Using TEM, we also diagnosed the familial disease in a dog that was more than 2 years old when renal failure fist developed. Without thorough evaluation, these dogs easily could have been examples of false-positive and false-negative diagnosis of the familial nephropathy that afflicts this breed.

When a specific nephropathy is known or suspected to be inherited in a particular breed, diagnosis of the condition generally rests on recognition of the expected clinical features (which were reviewed in the previous section), exclusion of other conditions that might produce similar signs, and, finally, identification of characteristic renal lesions. The exclusion of other disorders is an important step because many acquired kidney diseases can affect young animals, including individuals at risk of having an inherited nephropathy. Examples include acute nephritis (e.g., leptospirosis), toxic nephropathy (e.g., ethylene glycol, cholecalciferol rodenticide drugs), chronic nephritis (e.g., bacterial pyelonephritis), and effects of chronic partial urinary obstruction (e.g., hydronephrosis). Exclusion of other conditions becomes even more problematic when the suspected familial condition is one that has its clinical onset in older animals because these dogs and cats have had more opportunities to develop acquired renal disease than have younger animals.

Careful interpretation of the results obtained from a thorough clinical investigation often is sufficient for the presumptive diagnosis of a congenital renal disease. To be adequately complete, the evaluation should include a detailed history, thorough physical examination, urinalysis with a microscopic examination of urine sediment, urine culture, comprehensive serum chemistry profile including electrolyte concentrations, and diagnostic imaging of the kidneys. The kidney imaging method that is most helpful generally is diagnostic ultrasound, which provides information about the size, shape, and internal architecture of the kidneys. Conditions that an experienced examiner usually can identify with sonography include causes of renomegaly such as agenesis of the other kidney, hydronephrosis, solitary renal cysts, polycystic kidney, perirenal pseudocysts, or presence of infiltrative renal parenchymal disease (e.g., inflammation, neoplasia). Additionally, ultrasound examinations can detect the aforementioned conditions before they cause renal enlargement and can revel uroliths. For kidneys that are near normal in size, sonography also can show the degree of change in cortical and medullary regions. With primary glomerular diseases, for example, the sonographic distinction between cortex and medulla often is well preserved until late in the course of disease; but with primary tubulointerstitial diseases, loss of a clear distinction between cortical and medullary areas often develops early in the course of disease. Sonography also can reliably find and characterize small, end-stage kidneys, which frequently are difficult or impossible to see with radiography. Information from renal imaging studies should be integrated with results of laboratory testing, physical exam findings, and historic details to exclude evidence of other diseases and to verify the expected clinicopathologic features of the suspected congenital disorder. However, even if diagnosis of congenital renal disease remains uncertain, the suggested evaluation should have excluded any potential treatable condition having a favorable prognosis.

Definitive diagnosis of most congenital renal diseases ultimately rests upon demonstration of characteristic lesions in kidney specimens obtained at necropsy or by biopsy. The pathologic studies that are necessary for definitive diagnosis depend on the lesion being evaluated. For some lesions (renal dysplasia, amyloidosis, telangiectasia), light microscopic evaluations alone are sufficient for diagnosis. For this reason, and because light microscopic findings contribute to the diagnosis of all renal lesions, a portion of any available kidney specimen(s) should be preserved in 10% buffered formalin and processed for routine light microscopy. Especially for evaluation of glomerular diseases, however, TEM and/or immunopathologic studies often are needed as well. Specimens that will be satisfactory for such evaluations can be preserved properly only when they are first collected. Therefore, we also routinely preserver portions of the specimen for TEM in Karnovsky's fixative *4% paraformaldehyde and 6.25% glutaraldehyde in 0.1 mol/L sodium cacodylate buffer with0.05% CaCl2; pH, 7.4) and for immunofluorescence studies in Michael's transport medium or snap-frozen with dry ice or liquid nitrogen. Preservation of such specimens is not particularly difficult or expensive. If light microscopy shows that further studies are not needed, the specimens can be discarded. However, if TEM or immunopathologic studies are required, they can be performed only if suitable specimens were saved appropriately when the tissue was fresh.

When a congenital renal disease is identified, questions about inheritance of the condition are frequently asked. For breeds in which the diagnosed congenital lesion is known to be familial based on previous studies of other affected individuals, genetic counseling can be provided. For all other instances of particular congenital lesions is specific breeds, inheritance of the condition remains unknown unless and until studies of other related animals show familial occurrence of the disease. Evaluation of many (almost all) animals in several (at least 2 to 3) generations of an affected kindred generally is needed to determine that a disease is inherited. Such studies are difficult to perform for many reasons, which explains why so little is known bout the inheritance of many congenital renal diseases in dogs and cats.

For some breeds in which familial kidney diseases are known to occur, strategies can be used to promote early diagnosis of affected animals, especially in kindreds that are suspected to carry the defect. One benefit of early diagnosis is that affected and/or carrier animals are sooner identified and removed from he breeding population, thus minimizing promulgation of the defect. Early diagnosis also can increase opportunities to use therapeutic interventions that might slow disease progression or ameliorate signs. Even for the conditions that progress to fatal outcomes regardless of treatment, early diagnosis can be beneficial to owners by permitting them to adjust to and plan for their pet's premature demise. Another benefit of early diagnosis is that progress in characterizing the disease can be made more rapidly. Pathologists have more opportunities to examine primary lesions at early stages of disease and a greater number of thorough postmortem evaluations are performed when participants have time to make the necessary preparations.

The process of early diagnosis generally involves two steps: screening, then confirmation. Selection of the screening test depends on the lesion that is expected. For polycystic kidney disease, renal sonography is the most sensitive screening test and confirmation is obtained by finding that cysts progressively increase in number and/or size as time passes. Screening for other inherited nephropathies generally involves analysis of urine. For glomerular diseases, monitoring for development of proteinuria is an effective strategy. Proteinuria, of course, has many possible sources, but proteinuria that is persistent, substantial, and not otherwise explained by associated urinalysis findings (such as hematuria, pyuria, or bacteriuria) usually is of glomerular origin. Detection of such proteinuria in an animal that is at risk of familial glomerular disease often is sufficient for presumptive diagnosis of the condition. In all forms of canine hereditary nephritis studied to date (that of Samoyeds, Bull Terriers, and English Cocker Spaniels), for example, affected dogs have been identified by finding proteinuria well before the onset of renal failure.32,38,48 For all types of familial glomerular disease, however, confirmation of the diagnosis requires appropriate pathologic studies often including TEM and/or immunopathologic examinations. Other familial kidney diseases in which specific urinalysis findings are indicators of potentially affect subjects include Fanconi's syndrome in Basenjis (glucosuria) and telangiectasia in Pembroke Welsh Corgis (hematuria). Diagnosis of Fanconi's syndrome is confirmed by finding persistent glucosuria that is not associated with hyperglycemia and by finding evidence (e.g., amino aciduria) of other defects in renal tubular function. Pathologic studies are needed to confirm telangiectasia, but compatible sonographic findings should suffice for antemortem diagnosis.

Early diagnosis of renal dysplasia is problematic because an effective screening technique has not been described. Renal sonography might be useful; however, it is a relatively expensive albeit noninvasive test, and studies demonstrating that sonography is sensitive for early detection of renal dysplasia have not been reported. Monitoring urine specific gravity for evidence of poor urine concentrating ability might also be helpful; however, low values could be observed for many reason. Excepts for groups of subjects with very high risk of renal dysplasia, such lack of specificity (i.e., high frequency of false-positives) makes this strategy impractical for common use.

Performing a kidney biopsy for antemortem diagnosis of a congenital renal disease might be necessary. For animals in which the disease has induced chronic renal failure, however, biopsy is rarely indicated because clinical evaluation usually is sufficient for a presumptive diagnosis and the patient needs all the functioning renal parenchyma that remains. Renal biopsies have a more appropriate role in early diagnosis of congenital kidney dieses, the type of lesion suspected determines the biopsy procedure that should be used. Wedge biopsy is recommended for reliable diagnosis of renal dysplasia because characteristic lesions (e.g., fetal glomeruli) are distributed in a segmental pattern.64 In the renal cortex, regions of nearly normal tissue are found adjacent to areas of dysplastic tissue, and a needle biopsy might contain a sample only of a comparatively normal portion and thus be misleading. In contrast, lesions that characterize hereditary nephritis have a diffuse pattern of glomerular involvement and a reliable diagnosis can be made using the random sample of glomeruli obtained with a needle biopsy of renal cortex. While studying canine hereditary nephritis at Texas A&M University, we have been uniformly successful diagnosing the condition using tissue from an ultrasound-guided percutaneous needle biopsy procedure.47,48 This biopsy method usually is suitable for diagnosis of glomerular diseases, but investigators studying atrophic glomerulopathy in Rottweilers found that the technique did not yield adequate cortical tissue for diagnosis when they performed it in tow dogs.16

TREATMENT

For congenital kidney disease, effective treatment generally is not available. In addition, most of these conditions are intrinsically progressive. The few disorders that are not progressive (e.g., unilateral renal agenesis) ordinarily are clinically inapparent unless they become complicated by an acquired disease. Many affected animals have or will develop renal failure and may benefit from the various therapeutic strategies used for management of chronic renal failure, as detailed elsewhere in this volume. Such therapy may reduce clinical signs of uremia and it may also slow the rate of deterioration of renal function that might otherwise occur. For

example, Samoyed dogs with X-linked hereditary nephritis that were fed a modified diet (restricted in protein, lipid, calcium, and phosphorus) survived 53% longer than did affected dogs fed a regular diet.79 However, the dietary modification began at weaning and the dogs only survived until thy were abut 12 months old instead of dying when they were about 8 months old.

Management of chronic renal failure in young animals presents some special difficulties. Meeting nutritional requirements of patients with renal failure without exceeding their capacity to excrete excess quantities of the nutrients or their metabolites is more difficult in young, growing animals than it is in adults. In metabolic terms, the gap between the intakes they need and those that they can tolerate without suffering serious disturbances of homeostasis is wider for patients with renal failure that have nutrient requirements for growth as well as maintenance. Stunted growth is often observed in animals that develop renal failure before they are 2 years old. Skeletal abnormalities associated with renal secondary hyperparathyroidism, are both more common and more difficult to manage when kidney failure occurs before skeletal development is complete. When evaluating hyperphosphatemia and monitoring success of therapeutic efforts to control this problem in young animals with renal failure, use of age-matched reference ranges for interpretation of laboratory test results is important. In healthy Beagles, for example, mean values for serum inorganic phosphorus concentration were 7.8 mg/dL in 2- to 3-month-old dogs, 4.4 mg/dL in 11- to 14-month-old dogs, and 4.0 mg/dL in 14- to 18-month-old dogs.63

Animals with progressive congenital renal diseases that predictably lead to fatal outcomes may be candidates for renal transplantation. As progress is made in ongoing efforts to develop successful renal transplant programs for cats and dogs, this treatment modality may become more widely available. Most congenital renal diseases would not attack the grafted kidney (the familial forms of amyloidosis and glomerulonephritis are likely exceptions to the generality). Moreover, early diagnosis of the condition would increase the opportunity to plan for the procedure and thus perform it before the animal becomes critically ill, while kidney transplantation is more likely to be successful. Application of advancing biomedical technologies to solve the problems of congenital renal diseases in dogs and cats, however, should be focused mainly on reducing the production of affected animals. Investigating the pathogenesis of these conditions will lead to discovery of their underlying genetic causes, as well as to reliable methods for identification of genetic carriers before they are used for breeding.

References

1. Baumal R, Thorner P, Valli VEO, et al: Renal disease in carrier female dogs with X-linked hereditary nephritis. Am J Pathol 139:751-764, 1991
2. Bernard MA, Valli VE: Familial renal disease in Samoyed dogs. Can Vet J 18:181-189, 1977
3. Biller D, Pflueger S, Miller L, et al: Autosomal dominant polycystic kidney disease (PDK) in cats [abstract]. J Am Soc Nephrol 2:250, 991
4. Biller DS: Polycystic kidney disease. *In* August JR (ed): Consultations in Feline Internal Medicine, ed 2. Philadelphia, WB Saunders, 1994 pp325-330
5. Biller DS. Chew DJ, DiBartola SO: Polycystic kidney disease in a family of Persian cats. J Am Vet Med Assoc 196:1288-1290, 1990
6. Booth K: A case of juvenile nephropathy in a Newfoundland dog. Vet Rec 127:596-597, 1990
7. Bovee KC: Renal dysplasia and renal Fanconi syndrome in the dog. *In* Proceedings of the Fourth American College of Veterinary Internal Medicine Forum, Washington, DC, 1986, pp 13, 41-43
8. Bovee KC, Joyce T. Blazer-Yost B, et al: Characterization of renal defects in dogs with a syndrome similar to Fanconi syndrome in man. J Am Vet Med Assoc 174:1094-1099 1979
9. Bowles MH, Mosier DA: Renal amyloidosis in a family of beagles. J Am Vet Med Assoc 201:569-574, 1992
10. Boyce JT, DiBartola SP, Chew DJ, et al: Familial renal amyloidosis in Abyssinian cats. Vet Pathol 21:33-38, 1984
11. Breitschwerdt EB, Ochoa R. Waltman C: Multiple endocrine abnormalities in Basenji dogs with renal tubular dysfunction. J Am Vet Med Assoc 182:1348-1353, 1983
12. Brown CA, Crowell WA, Brown SA, et al: Suspected familial renal disease in Chow Chows. J Am Vet Med Assoc 196:1279-1284, 1990
13. Burk RL, Barton CL: Renal failure and hyperparathyroidism in an Alaskan Malamute pup. J Am Vet Med Assoc 172:69-72, 1978
14. Chew DJ, DiBartola SP, Boyce JT, et al: Renal amyloidosis in related Abyssinian cats. J Am Vet Med Assoc 181:139142, 1982
15. Chew DJ, DiBartola SP, Boyce JT, et al: Juvenile renal disease in Doberman Pinscher dogs. J Am Vet Med Assoc 182:481-485, 1983
16. Cook SM, Dean DF, Golden DL, et al: Renal failure attributable to atrophic

glomerulopathy in four related Rottweilers. J Am Vet Med Assoc 202:107-109, 1993
17. Crowell WA, Hubbell JJ, Riley JC: polycystic renal disease in related cats, J Am Vet Med Assoc 175:286-288, 1979
18. deMorais HSA, DiBartola SP, Chew DJ: Juvenile renal disease in golden retrievers [abstract]. J Vet Intern Med 9:210, 1995
19. DiBartola SP, Biller DS, Eaton KA, et al: Polycystic kidney disease in Persian cats is an autosomal dominant trait [abstract]. J Vet Intern Med 9:210, 1995
20. DiBartola SP, Biller DS, Radin MJ, et al: Autosomal dominant polycystic kidney disease (ASPKD) in Persian cats: Morphologic featrues [abstract]. J Am Soc Nephrol 5:620, 1994
21. DiBartola SP, Chew DJ. Boyce JT: Juvenile renal disease in related Stadard Poodles. J Am Vet Med Assoc 183:693-696, 1983
22. DiBartola SP, Hill RL, Fechheimer NS, et al: Pedigree analysis of Abyssinian cats with familial amyloidosis. Am J Vet Res 47:2666-2668, 1986
23. DiBartola Sp, Tarr MJ, Webb DM, et al: Familial renal amyloidosis in Chinese shar pei dogs. J Am Vet Med Assoc 197:483-487, 1990
24. Easley JR, Breitschwerdt EB: Glucosuria associated with renal tubular dysfunctions in three Basenji dogs. J Am Vet Med Assoc 168:938-943, 1976
25. English PB, Winter H: Renal cortical hypoplasia in a dog. Aust Vet J 55:181-183, 1979
26. Eriksen K. Grondalen J: Familial renal disease in soft-coated wheaten terriers. J Small Anim Pract 25:489-500, 1984
27. Finco DR: Familial renal disease in Norwegian elkhound dogs: Physiologic and biocheimcal examinations. Am J Vet Res 37:87-91, 1976
28. Finco DR: Familial renal disease in Norwegian elkhound dogs: Morphologic examinations. Am J Vet Res 38:941-947, 1977
29. Finco DR, Kurtz HJ, Low DG, et al: Familial renal disease in Norwegian elkhound dog. J Am Vet Med Assoc 156:747-760, 1970
30. Freudiger U: Die kongenitale nierenrindenhypoplasie beim bunten cocker-spaniel. Schweiz Arch Tierheilkd 107:547-566, 1965
31. Hood JC, Craig AJ: Hereditary nephritis in a miniature bull terrier. Vet Rec 135:138-140, 1994
32. Hood JC, Robinson WF, Clark WT, et al: Proteinuria as an indicator of early renal disease in bull terriers with hereditary nephritis. J Small Anim Pract 32:241-248, 1991
33. Hood JC, Robinson WF, Huxtable CR, et al: Hereditary nephritis in the bull terrier: Evidence for inheritance by an autosomal dominant gene. Vet Rec 126:456-459, 1990
34. Hudson BD, Reeders ST, Tryggvason K: Type IV collagen: Structure, gene organization, and role in human diseases. J Biol Chem 268:26,033-26,036, 1993
35. Ikeda K, Yokoyama H, Tomosugi N, et al: Primary glomerular fibrosis: A new nephropathy caused by diffuse intra=-glomerular increase in atypical type III collagen fibers. Clin Nephrol 33:155-159, 1990
36. Jansen B, Thorner P, Baumal R, et al: Samoyed hereditary glomerulopathy (SHBG): Evolution of splitting of glomerular capillary basement membranes, Am J Pathol 125:536-545, 1986
37. Jansen B, Tryphonas L, Wong J, et al: Mode of inheritance of Samoyed hereditary glomerulopathy: An animal model for hereditary nephritis in humans. J Lab Clin Med 104:551-555, 1986
38. Jansen B, Valli VEO, Thorner P, et al: Samoyed hereditary glomerulopathy: Serial clinical and laboratory (urine, serum biochemistry, and hematology) studies. Can J Vet Res 51:387-393, 1987
39. Jones BR, Gething MA, Badcoe LM, et al: Familial progressive nephropathy in young bull terriers. N A Vet J 37:79-82, 1989
40. Kashtan CE, Michael AF: Alport syndrome: From bedside to genome to bedside. Am J Kidney Dis 22:627-640, 1993
41. Kaufman CF, Soirez RD, Tasker JP: Renal cortical hypoplasia with secondary hyperparathyroidism in the dogs. J Am Vet Med Assoc 155:1679-1685, 1969
42. Kerlin RD. VanWinkle TJ: Renal dysplasia in golden retrievers. Vet Pathol 32:327-329, 1995
43. Klopfer U, Neumann F, Trainin R: Renal cortical hypoplasia in a Keeshond litter. Vet Med Small Anim Clin 70:1081-1083, 1975
44. Koeman JP, Biewenga WJ, Gruys E: Proteinuria associated with glomerulosclerosis

and glomerular collagen formation in three Newfoundland dog littermates. Vet Pathol 31:188-193, 1944
45. Koeman JP, Ezilius JW, Biewenga WJ, et al: Zur familiaren nephropathie der cockerspaniel, DTW Dtsch Tierarztl Wochenschr 96:174-179, 1989
46. Krook L: The pathology of renal cortical hypoplasia in the dog. Nordisk Vet-Med 9:161-176, 1957
47. Lees GE, Helman RG, Momco LD, et al: Autosomal recessive hereditary nephritis in English cocker spaneil (ECS) dogs [abstract]. J Am Soc Nephrol 6:700, 1995
48. Lees Ge, Helman RG, Homco LD, et al: Early diagnosis of familial nephropathy (FN) in English cocker spaniel (ECS) dogs [abstract]. J Vet Intern Med 9:210, 1995
49. Littman MP, Giger U: Familial protein-losing enteropathy (PLE) and/or protein-losing nephropathy (PLN) in soct-coated Wheaten terriers (SCWT) [abstract]. J Vet Intern Med 4:133, 1990
50. Macdougall DR, Nash AS, Cattanach BM: Control scheme for familial nephropathy in cocker spaniels (letter). Vet Rec 121:134, 1987
51. McKenna SC, Carpenter JL: Polycystic disease of the kidney and liver in the Cairn Terrier. Vet Pathol 17:436-442, 1980
52. Minkus G, Breuer W, Wanke R, et al: Familial nephropathy in Bernese mountain dogs. Vet Pathol 31:421-428, 1994
53. Mochizuki T, Lemmink HH, Mariyama M, et al: Identification of mutations in the alpha3 (IV) and alpha-4 (IV) collagen genes in autosomal recessive Alport syndrome. Nature Genetics 8:77-82, 1994
54. Moore FM, Thornton GW: Telangiectasia of Pembroke Welsh Corgi dogs. Vet Pathol 20:203-208, 1983
55. Morton LD, Sanecki RK, Gordon DE, et al: Juvenile renal disease in miniature Schnauzer dogs. Vet Pathol 27:455-458, 1990
56. Nash AS, Kelly DF, Gaskell CJ: Progressive renal disease in soft-coated wheaten terriers: Possible familial nephrpathy. J Small Anim Pract 25:479-487, 1984
57. Nash AS, McCandlish IAP: Chronic renal failure in young bull terriers [letter]. Vet Rec 118:735, 1986
58. Noonan CHB, Kay JM: prevalence and geographic distribution of Fanconi syndrome in Basenjis in the United States, J Am Vet Med Assoc 197:345-349, 1990
59. O'Brien TD, Osborne CA. Yano BL, et al: clinicopathologic manifestations of progressive renal disease in Lhasa Apso and Shih Tzue dogs. J Am Vet Med Assoc 180:658-664, 1982
60. Oksanen A, Sittnikow K: Familial nephropathy with secondary hyperparathyroidism in three young dogs. Nordisk Vet-Med 24:278-280, 1972
61. Osborne CA, O'Brien TD: Renal dysplasia in Lhasa apso and Shih-tzu dogs. *In* Kirk RW (ed): Current Veterinary Therapy, ed 8. Philadelphia, WB Saunders, 1983, pp 971-974
62. Persson F, Persson S. Asheim A: Renal cortical hypoplasia in dogs: A clinical study on uraemia and secondary hyperparathyroidism. Acta Vet Scand 2:68-84, 1961
63. Pickrell JA, Schluter SJ, Belasich JJ, et al: Relationship of age of normal dogs to blood serum constituents and reliability of measured single values. Am J Vet Res 35:897-903, 1974
64. Picut CA. Lewis RM: Microscopic features of canine renal dysplasia. Vet Pathol 24:156-163, 1987
65. Picut CA, Lewis RM: Comparative pathology of canine hereditary nephropathies: An interpretive review. Vet Res Commun 11:5610581, 1987
66. Picut CA, Lewis RM: Juvenile renal disease in the Doberman pinscher: Ultrastructural changes of the glomerular basement membrane. J Comp Pathol 97:587-596, 1987
67. Potter JS. McSporran KD, James MP: A suspected case of familial nephropathy in the cocker spaniel [letter]. N Z Vet J 33:65066, 1985
68. Reusch C, Hoerauf A. Lechner J. et al: A new familial glomerulonephropathy in Bernese mountain dogs. Vet Rec 134:411-415, 1994
69. Rivas AL, Tintle L, Kimball ES, et al: A canine febrile disorder associated with elevated interleukin-6. Clin Immunol Immunopathol 64:36-45, 1992
70. Robbins GR: Unilateral renal agenesis in the Beagle. Vet Rec 77:1345-1347, 1965
71. Robinson WF, Huxtable CR, Gooding JP: Familial nephropathy in cocker spaniels. Aust Vet J 62:109-112, 1985
72. Robinson WF, Shaw SE, Stanley B, et al: Chronic renal disease in bull terriers. Aust

Vet J 66:193-195, 1989
73. Steward AP, Macdougall DF. Familial nephropathy in the cocker spaniel. J Small Anim Pract 25:15-24, 1984
74. Thorner P, Baumal R, Binnington A, et al: The NCI domain of collagen type IV in neonatal glomerular basement membranes, Significance in Samoyed hereditary glomerulopathy. Am J Pthol 134:1047-1054, 1989
75. Thorner P, Jansen B, Baumal R, Valli VEO, et al: Abnormalities in the NCI domain of collagen type IV in GBM in canine hereditary nephritis. Kidney Int 35:845-850, 1989
76. Thorner P, Jansen B, Baumal R, et al: An immunohistochemical and electron microscopic study of extra-renal basement membranes in dogs with Samoyed hereditary glomerulopathy. Virchows Arch A Pathol Anat Histopathol 412:281-290, 1988
77. Thorner P, Jansen B, Baumal R, et al: Samoyed hereditary glomerulopathy: immunohistochemical staining of basement membranes of kidney for laminin, collagen type IV, fibronectin, and Goodpature antigen, and correlation with electron microscopy of glomerular capillary basement membranes. Lab Invest 56:435-443, 1987
78. Thorner PS, Baumal R, Valli VEO, et al: Production of anti-NCO antibody by affected male dogs with X-linked hereditary nephritis: A probe for assessing the NCI domain of collagen type IV in dogs and humans with hereditary nephritis. Virchows Arch A Pathol Anat Histopathol 421:467-475, 1992
79. Valli VEO, Baumal R, Thorner P, et al: Dietary modification reduces splitting of glomerular basement membranes and delays death due to renal failure in canine X-linked hereditary nephritis. Lab Invest 65:67-73, 1991
80. Vilafranca M, Ferrer L: Juvenile nephropathy in Alaskan malamute littermates. Vet Pathol 31:375-377, 1994
81. Vymetal F: Case reports: Renal aplasia in Beagles. Vet Rec 77:1344-1345, 1965
82. Wilcock BP, Petterson JM: familial glomerulonephritis in Doberman pinscher dogs. Can Vet J 20:244-249, 1979
83. Wright RP, Wright HJ: Paradoxic glucosuria (canine Fanconi syndrome) in two Basenji dogs. Vet Me 79:199-202, 1984
84. Zheng K. Thorner PS, Marrano P, et al: Canine X chromosome-linked hereditary nephritis: A genetic model for human X-linked hereditary nephritis resulting from a single base mutation in the gene encoding the *a*5 chain of collagen type IV. Proc Natl Acad Sci USA 91:3989-3993, 1994