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Familial renal disease in Soft-coated Wheaten Terriers

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ABSTRACT

In two litters of Soft-coated Wheaten Terriers, having the same parents, chronic renal failure developed in five out of ten dogs. The dogs died, or were destroyed on humane grounds, at 7 to 30 months of age.

Clinical signs were inappetence, weight loss, vomiting, depression and, in two cases, polydipsia and polyuria. The laboratory data revealed isosthenuria, non-regenerative anaemia, extremely high serum urea nitrogen, and creatinine values.

Pathoanatomical findings included small kidneys with an irregular and pale external surface. Cortical lesions were mostly segmental in distribution, and consisted of loss of glomerular elements and increased interstitial connective tissue. Medullary lesions were severe, diffuse in distribution, and consisted of loss of tubules and proliferation of connective tissue.

The clinical, laboratory, and pathoanatomical findings show similarities to renal diseases seen in young dogs of other breeds.

INTRODUCTION

Familial progressive renal disease in dogs has been described in detail in Cocker Spaniels (Krook, 1957; Persson, Persson & Aasheim, 1961; Freudiger, 1965; Johnson, Denhart & Graber, 1972; English & Winter, 1979), Norwegian Elkhounds (Finco *et al.*, 1970; Finco, 1976; Finco *et al.*, 1977), Samoyeds (Bernard & Valli, 1977; Bloedow, 1981), Dobermans (Wilcock & Patterson, 1979; Chew *et al.*, 1983), Lhasa Apso and Shih Tzu dogs (Hoppe & Hageltorn, 1979; O'Brien *et al.*, 1982). Lesions with similar clinical and pathological findings have been reported as case reports in many other breeds, e.g. Basset (Watson & Canfield, 1979), Malamute (Kaufman, Soirez & Tasker, 1969), Poodle (Holshuh,

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1981), Cavalier King Charles Spaniels (Hoppe, 1982), Swedish Foxhound (McIntee & Teale, 1973), Keeshound (Klopfer, Neumann & Trainin, 1975), Miniature Schnauzer (Chandler *et al.*, 1979), Bedlington Terrier (Oksanen & Sittnikow, 1972), Yorkshire terrier (Klopfer, Nobel & Kaminski, 1978), German Shepherd (Finco & Rowland, 1978), Dachshunds (Chandler *et al.*, 1979) and Flat Coated Retrievers (Eriksen & Grøndalen, 1981).

This report presents the clinical, laboratory, and pathoanatomical findings from two litters of Soft-coated Wheaten Terriers, having the same parents and of which five out of 10 dogs, two males and three females, developed chronic renal failure.

MATERIALS AND METHODS

The dam and the sire, both imported from Sweden, were mated twice. Litter I consisted of five pups, two males (Cases 1a and 1b) and three females (Cases 1c, 1d, and 1e). Litter II consisted of two males (Cases 2a and 2b) and three females (Cases 2c, 2d and 2e). One male dog, case 1b, was hit by a car at about 3 months of age and died. Hence, no renal function data are given for this animal.

The diseased dogs: Cases 1a, 1c, 2a, 2c and 2d were admitted for clinical examination from 7 to 30 months of age because of inappetence, weight loss and vomiting. Three of the dogs, Cases 1a, 1c, and 2a, were clinically examined by one of the authors (J. G.) and laboratory investigations performed.

Urine: Multistix (Ames), Specific Gravity (SpG).
Blood: Packed cell volume (PCV), White blood cell count (WBC), differential count.
*Serum**: Protein, calcium, phosphorous, sodium, potassium, liver enzymes, alkaline phosphatase, creatinine, and urea nitrogen.

Case 1a was examined twice with an interval of 30 days. Case 2c was examined by a colleague and destroyed (laboratory data not obtained). Case 2d died before being clinically examined.

The owners of the remaining dogs (Cases 1d, 1e, 2b, and 2e) and the owner of the dam and the sire were contacted, and these dogs were clinically examined. Laboratory data were obtained at 33 and 35 months (Case 1d), 30 months (Case 1e), 7, 11, 20, and 32 months (Case 2b), and 17 and 22 months (Case 2e) respectively. The dam was examined at 86 months of age, the sire at 60 months (Table I).

Radiographical examinations of the kidneys, including intravenous urography, were performed twice in Case 2b at 20 and 32 months of age.

The five diseased dogs were necropsied and subjected to routine patho-anatomical investigation. Tissues selected for microscopic evaluation were fixed in neutral buffered 10 per cent formalin, processed by standard techniques, sectioned

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at about 5 μm, and stained with haematoxylin and eosin. The kidney sections were also stained with the elastin van Gieson method for collagen and elastic fibres, and with the Periodic acid-Schiff method.

RESULTS

Clinical findings

The duration of clinical signs of the diseased dogs varied from about 2 to 16 weeks. The dogs were admitted because of inappetence, vomiting, diarrhoea (Case 1c) and weight loss. They were moderately dehydrated, the mucous membranes were pale, and the smell from the mouth was uraemic. In one dog (Case 1c) a systolic heart murmur was observed. Two dogs (Cases 1a and 2a) had polydipsia and polyuria. The clinical examination of Cases 1d, 1e, 2b, and 2e did not reveal signs of illness. However, the owner of Case 2b, who was also the owner of Case 1a, reported multiple episodes of inappetence and diarrhoea in the former.

Laboratory findings

The laboratory data are given in Table I. Blood smears of the diseased dogs revealed non-regenerative anaemia. The results of the other investigations were normal.

Radiographical findings

When examined at 20 months of age (Case 2b), the length of the left kidney was 7·1 cm. At 32 months of age the length was 6·9 cm. The length of the second lumbar vertebra was 2·9 cm. Normal length of the left kidney is 2·5–3·5 times the length of the second lumbar vertebra (Kealy, 1979). Thus, the left kidney was smaller than normal. An irregular shape was suspected from the radiographs.

Gross pathologic findings

The carcasses were pale and emaciated. Major pathologic lesions were confined to the kidneys, which were pale and reduced in size. The external renal surface was irregular. In one case (1c), the surface was granular and pitted. The capsules were thickened and adhered to the cortex. The cortex had a firm texture and showed variable thickness. From depressed areas of the cortex, excessive connective tissue radiated to the medulla. Numerous cysts, up to 2–3 mm in diameter, were seen in the cortex. This was most pronounced in Case 1c. There were no macroscopical lesions in the renal pelvis or lower urinary tract.

Extra-renal changes due to the uraemia were of minor degree, but included in one case (1c) a uraemic gastritis and in two cases (1a and 2a), moderate necrosis and calcification of the parietal pleura. The parathyroid glands were pale and were macroscopically enlarged in three cases (1a, 1c, and 2d). There were no macroscopical signs of 'rubber jaw'.

TABLE 1. Laboratory data on two litters of Wheaten terriers

			Hematology						Serum						Urine	
					Diff. count. %											
Case no	Age when examined, months	Clinical condition*	PCV	WBC mm³	N	E	lymph.	Monoc.	Urea mMol/l (3·4–7·8)†	Creatinine μMol/l (75–100)†	Ca mMol/l (2·2–2·9)†	P mMol/l (1·3–2·9)†	Prot. g/l (60–80)†	Alb. g/l (30–37)†	Sp.G	Protein
1a	14	D	20	12·4	86	—	12	12	59	611	2·3	3·4	65	31	1006	–
1c	30		25	7·5	57	5	38	—	63	716	1·7	4·5	56	28	1010	
	33	D	28	9·4	93	—	6	1	68	1101	1·2	6·1	61	30	1008	+
1d	33	H	53	9·2	72	16	10	2	9·9	281	2·1	1·0	68	38	1013	–
	35								10·3	268	2·4	0·8	65	32	1010	–
1e	30	H	56	16·9	57	4	34	5	6·5	101	2·8	1·1	68	42		
2a	7	D	24	9·2	70	3	22	5	85	1071	1·6	5·2	75	26	1006	–
2b	7		43	11·6	69	13	9	9	10·1	233	3·1	2·1	63	32		
	11		42	16·4	60	7	34	—	13·3	231	2·9	1·3	67	33	1006	–
	20		44	12·9	63	8	22	7	16·9	261	2·9	2·0	66	31	1006	–
	32	H	39	8·3	67	3	21	9	16·9	255	2·7	1·4	76	25	1008	–
2c	7	D														
2d	7	D														
2e	17		48	14·9	64	25	7	4	5·3	123	2·8	1·3	69	38	1038	–
	22	H							4·4	139	2·4	0·5	68	31	1032	–
Dam	84	H	55	6·7	84	5	10	1	6·2	121	2·7	1·1	70	32	1055	–
Sire	60	H							12·6	144	2·9	1·2	73	33	1030	–

* D: diseased and dead. H: clinically healthy.

† Normal values, Department of Biochemistry The Norwegian College of Veterinary Medicine.

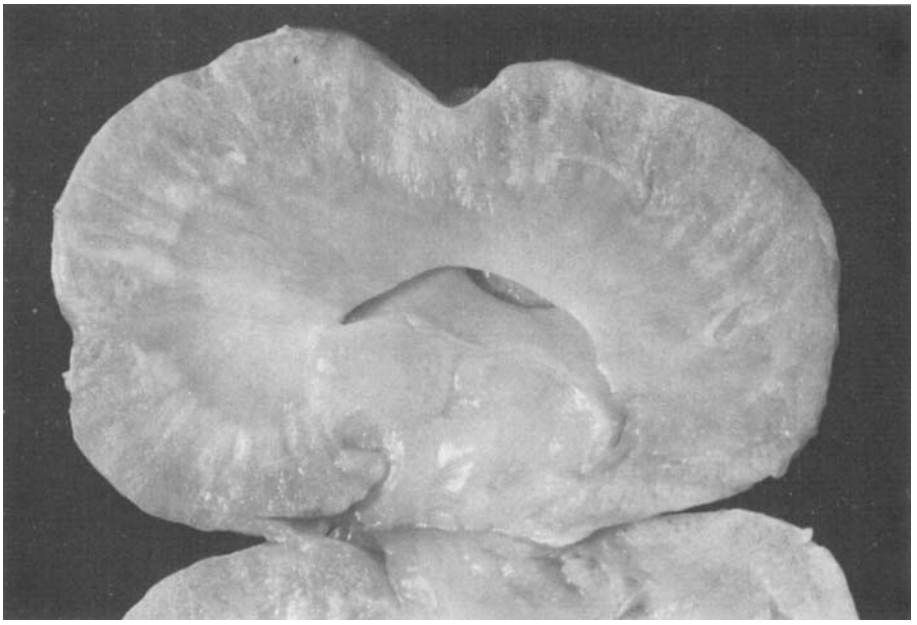

FIG. 1. Case 2a. The external surface of the kidney is irregular, the cortex showing variable thickness with strands of connective tissue radiating into the medulla. Numerous small cysts are seen on the cut surface.

Microscopic pathologic findings

Histological examination of the kidneys revealed an irregular, collagenous thickening of the capsule. The cortex showed changes which were segmental in distribution. In one case (1c) the lesions were more diffuse in distribution. Within affected areas the glomeruli were small, shrunken and hypercellular. Sometimes glomeruli with a 'foetal' appearance were observed. The capillary tuft often adhered to Bowman's capsule. Calcified remnants of glomerular capillary tufts were seen. Bowman's capsules were severely dilated, containing an eosinophilic, homogeneous or finely granular material. The epithelium of the parietal part of the capsule often showed proliferation and loosening of the cells to the capsular space. Periglomerular fibrosis was present.

The interstitium of the affected cortical areas contained increased amounts of collagenous connective tissue, stretched as cords of variable thickness from the capsule to the medulla. Within these areas scattered foci of mononuclear inflammatory cells, mostly lymphocytes, but also a few plasma cells and macrophages, were found. Tubules were reduced in number and in severely affected areas dilated tubules were lined by a flattened epithelium. The lumina often contained an eosinophilic, homogeneous or slightly granular material. Thickening and calcification of the tubular basement membranes was a striking feature in some

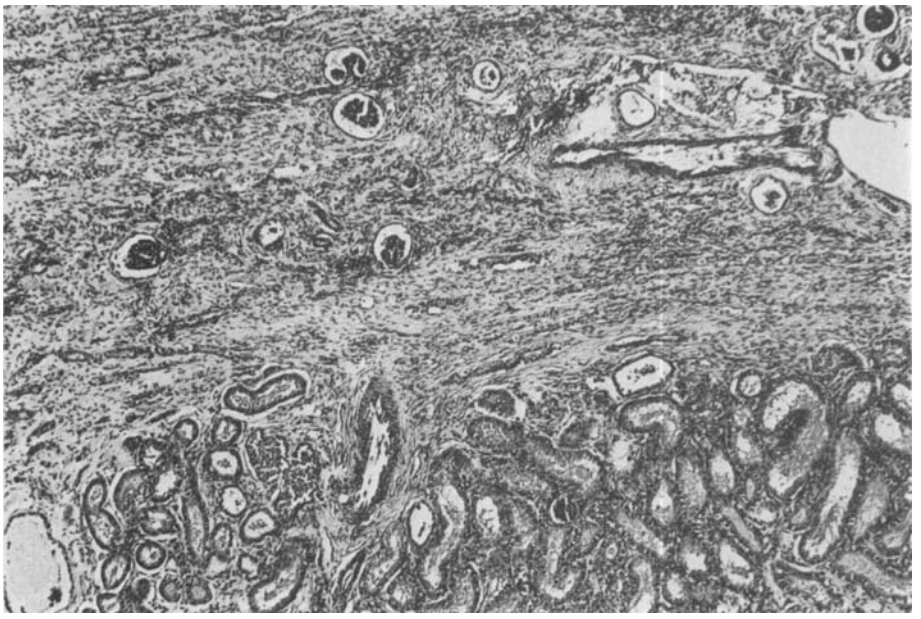

FIG. 2. Cortical lesion showing segmental distribution. Shrunken and hypercellular glomeruli surrounded by collagenous tissue and some scattered foci of inflammatory cells. Haematoxylin and eosin × 58.

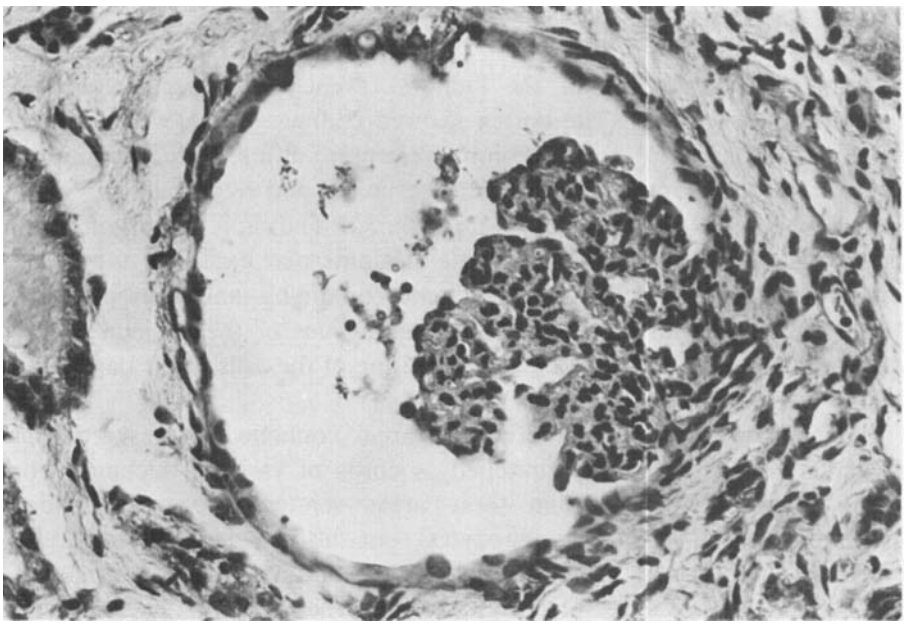

FIG. 3. Shrunken and hypercellular glomerular tuft with proliferation of parietal epithelial cells and periglomerular fibrosis. Periodic acid—Schiff × 360.

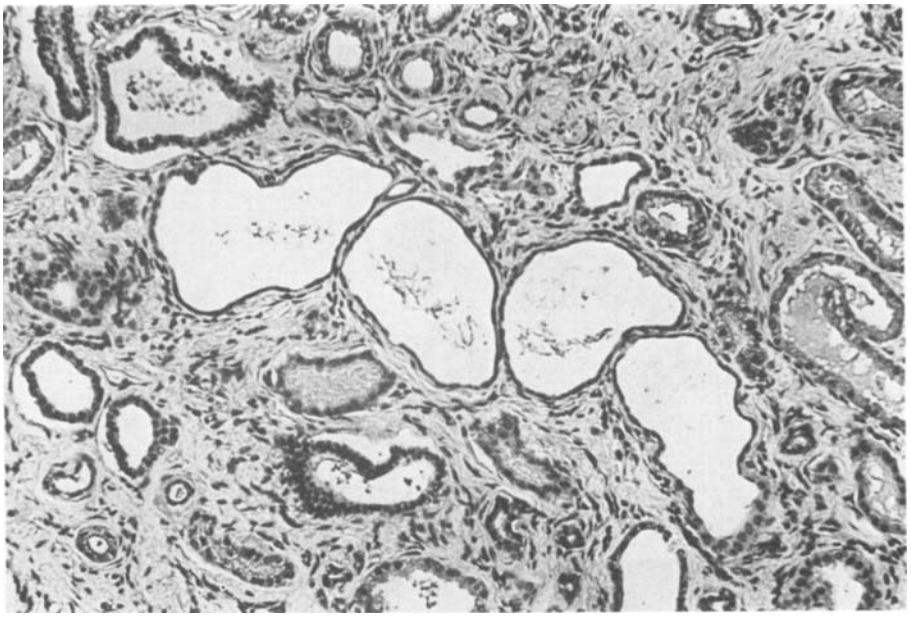

FIG. 4. Cortical interstitium with excessive connective tissue. Tubules are dilated and contain eosinophilic material. Haematoxylin and eosin x 145.

cases. Sometimes calcified remnants of tubuli were seen. Vascular lesions were not present.

Medullary lesions were diffuse and generalized, more severe than cortical lesions, and consisted of loss of tubules and a marked and diffuse increase in interstitial collagen. The cellular reaction was, however, much less pronounced than in the cortex. Some calcified remnants of tubules were seen. A striking feature in all cases was a marked dilation of tubules and collecting ducts and an adenomatoid proliferation of the epithelium. In one case (1c), infiltrations of mononuclear inflammatory cells were seen in the papilla.

Microscopic examination of the parathyroid gland showed a diffuse proliferation of light chief cells (Cases 1a, 1c, and 2d). The mandible had early changes of fibrous osteodystrophy (Cases 1a, 1c, and 2d).

DISCUSSION

Five out of ten dogs having the same parents suffered from chronic renal failure. The age of the dogs, when admitted for examination, varied from 7 to 30 months. In litter I the average age was 22 months, the average age in litter II was only 7 months. Males and females seemed to be affected to an equal degree. Sex predilection is not reported among breeds in which familial renal disease has been described, except for Samoyed dogs, in which males seemed to be more severely

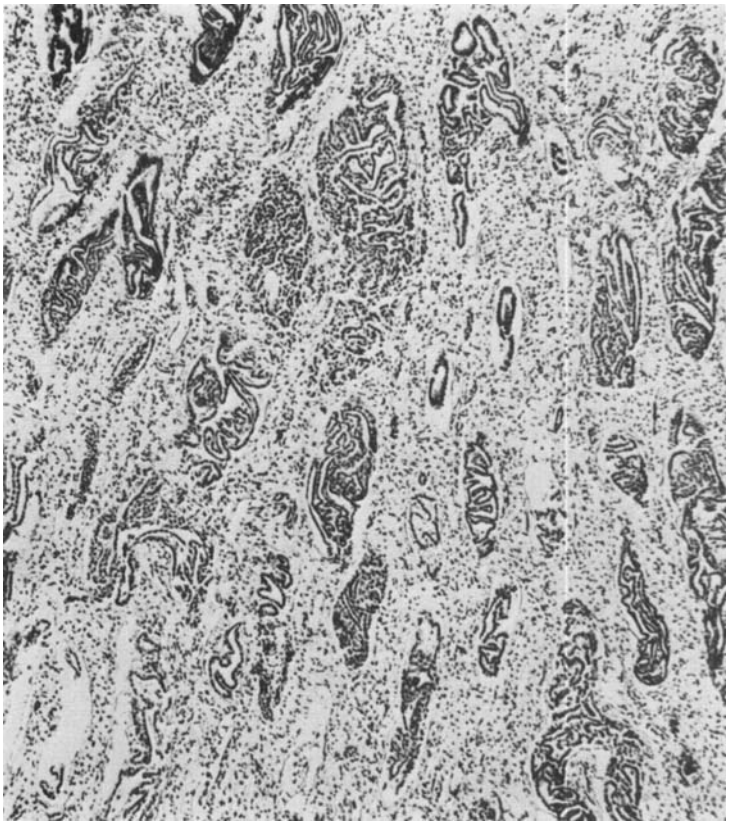

FIG. 5. Generalized distribution of medullary lesions. Increased amount of connective tissue with incipient cellular reaction. A marked adenomatoid proliferation of the tubular epithelium. Haematoxylin and eosin × 68.

affected than females (Bloedow, 1981). The clinical signs, which included weight loss, inappetence, vomiting, diarrhoea, polydipsia, polyuria and anaemia, are the same for any chronic renal disease.

The laboratory data, obtained at different times from three of the dogs, indicated severe non-regenerative anaemia and WBC counts within the lower range of normal values. The differential counts revealed great variations, even within the same dog, probably depending on the general condition on the day the data were obtained.

Specific gravity of the urine varied from 1006 to 1010, which is evidence of impaired concentrating ability. The biochemical analyses of the serum in two of the dogs revealed extremely high urea and creatinine values, hypoalbuminaemia, hyperphosphataemia and hypocalcaemia.

Proteinuria was only observed in one dog (Case 1c); none of the examined dogs had glycosuria. Proteinuria is usually more severe in those renal diseases where the primary lesion is glomerular. The magnitude of the proteinuria correlates more with the nature of glomerular lesion than with the stage of renal disease (DiBartola *et al.*,

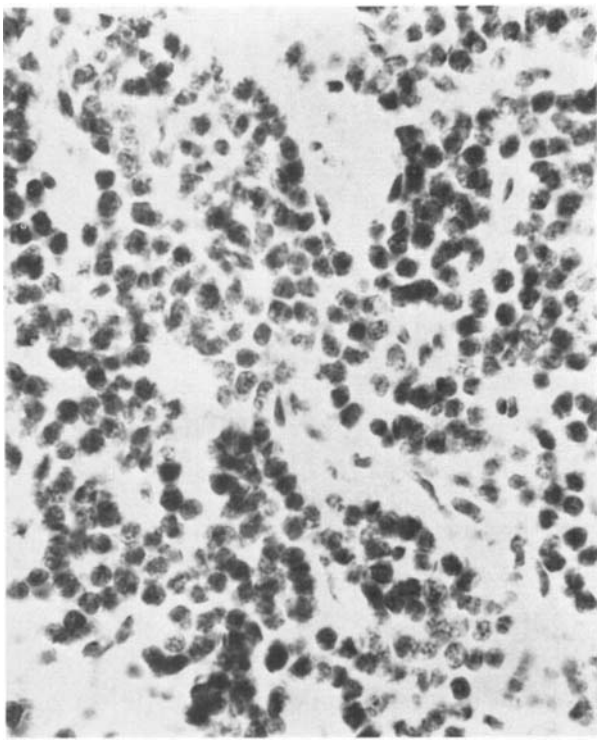

FIG. 6. Parathyroid gland. A diffuse proliferation of light chief cells. Haematoxylin and eosin × 425.

1980; Lucke *et al.*, 1980). In Samoyed and Doberman dogs, where the renal disease is thought to be primarily glomerular, proteinuria was a striking feature (Bernard & Valli, 1977; Wilcock & Patterson, 1979). A mild to moderate proteinuria was, however, also reported in Norwegian Elkhound (Finco *et al.*, 1970), Lhasa Apso and Shih Tzu (O'Brien *et al.*, 1982), where the primary lesion is not thought to be glomerular. The necropsies were performed at an advanced stage of the disease, and the morphological picture is similar to an end-stage kidney of any cause. The histological picture, however, showed similarities with renal diseases described in young animals of other breeds. The disease in Cocker Spaniels was first named renal cortical hypoplasia (Krook, 1957), but the histological picture is probably not different from an end-stage kidney (Finco *et al.*, 1977; Wilcock & Patterson, 1979).

Norwegian Elkhounds were studied at early stages of the disease, and the earliest renal lesions were characterized by periglomerular and interstitial fibrosis (Finco *et al.*, 1970; Finco *et al.*, 1977).

In Lhasa Apso and Shih Tzu dogs the cortical lesions were often segmental in distribution, medullary lesions were consistently diffuse and generally more severe than those in the cortex. Lesions in both sites commonly resulted in loss of nephrons, with replacement by collagen (O'Brien *et al.*, 1982).

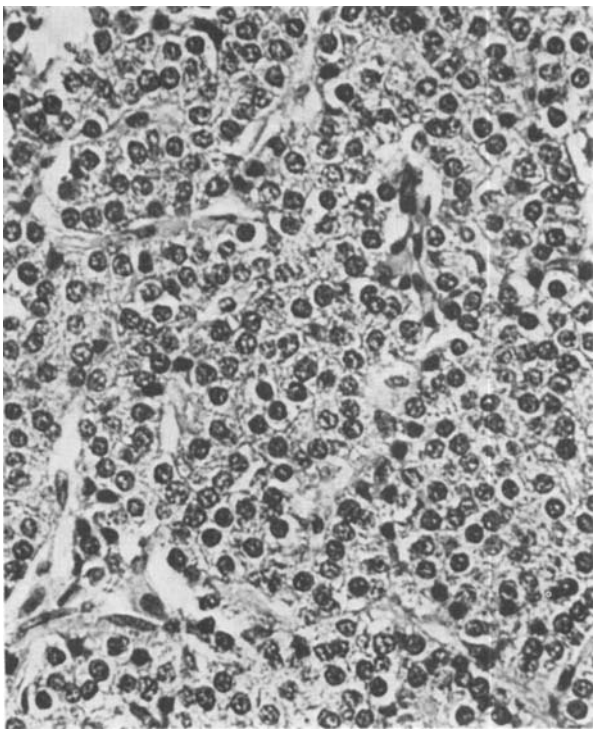

FIG. 7. Parathyroid gland from a clinically healthy 10 months old control male dog, showing mainly dark chief cells. Haematoxylin and eosin × 425.

In Samoyed dogs the lesions included a variable glomerular degeneration without acute inflammation and prominent fibrosis. The picture was consistent with a glomerulonephropathy (Bernard & Valli, 1977; Bloedow, 1981).

In the first report of renal diseases in Dobermans, the histological changes had the features of a membrano-proliferative glomerulonephritis (Wilcock & Patterson, 1979). In another report concerning Dobermans, the pathological changes were glomerular sclerosis, cystic glomerular atrophy, tubular dilatation and atrophy and a mononuclear interstitial inflammation and fibrosis. It was difficult to determine whether the glomerular lesions were primary or secondary (Chew *et al.*, 1983).

In Soft-coated Wheaten Terriers it is difficult to determine in the light microscope whether the primary renal lesions are glomerular or interstitial. Certain criteria for differentiation between these groups (Wright *et al.*, 1976) indicate, however, that the primary lesion might be interstitial. It is well known that immunologic phenomena play an important role in the development of glomerulonephritis, but immune mechanisms may also contribute to the progression of interstitial nephritis (Wright, 1979).

It is also possible that other pathogenetic mechanisms can lead to lesions in the tubular wall. Similar morphological renal lesions to those described in the breeds above have also been described in the cat in chronic stages after experimental

infections with *Escherichia coli* (Kelly, Lucke & McCullagh, 1979). The lesions were considered to represent a non-specific response to injury. In a later report from the same experiment a total increase of the amount of collagen and a change in the types of collagens, showing a decrease in basement membrane collagens, were found (McCullagh *et al.*, 1983). It might perhaps be of interest to study these changes also in these familial renal diseases in dogs.

Of the remaining four clinically healthy Wheaten Terriers, two must be regarded as 'suspicious', since they had isothenuria, increased serum creatinine and urea. The albumin values were within the lower range of normal.

The owner of dog 2b reported multiple periods of inappetence and depression. This dog was examined four times. Intravenous-urography was performed, and the kidneys were observed to be smaller than normal.

The owner of the other 'suspicious' dog, case 1d, had never observed any episodes of illness. However, the laboratory data indicate the risk of renal disease in these two dogs. The laboratory data obtained from the two remaining dogs, not mentioned above, may be regarded as being within normal limits.

In Norway, 23 individuals of Soft-coated Wheaten Terriers have been registered during the last 3 years. In Sweden 75 dogs have been registered during the same period, and among these renal disease has been reported in five dogs (Hoppe, 1982—personal communication). This indicates that chronic renal failure must be regarded as a serious problem in this breed. At this stage no conclusion can be drawn from clinical, laboratory or pathoanatomical findings about the aetiology and pathogenesis of the renal disease. Study of early stages by routine histology, electron microscopy, and immunofluorescent microscopy will be needed to characterize this, and for this purpose renal biopsies would be of great value. It is suggested that the disease is inherited, but breeding trials will be necessary to characterize the mode of inheritance. Until the aetiology is known, the breeders should avoid mating affected animals, their litter mates, their parents, and other closely related animals.

REFERENCES

BERNARD, M.A. & VALLI, V.E. (1977) Familial renal disease in Samoyed dogs. *Can. Vet. Jour.* **18,** 181.

BLOEDOW, A.G. (1981) Familial renal disease in Samoyed dogs. *Vet. Rec.* **108,** 167.

CHANDLER, E.A., EVANS, J.M., SINGLETON, W.B., STARTUP, F.G., SUTTON, J.B. & TAVERNOR, W.D. (1979) *Canine medicine and therapeutics.* p. 327. Blackwell Scientific Publications, Oxford.

CHEW, D.J., DIBARTOLA, S.P., BOYCE, J.T., HAYES, H.M. & BRACE, J.J. (1983) Juvenile renal disease in Doberman Pinscher dogs. *J. Am. vet. med. Assoc.* **182,** 481.

DIBARTOLA, S.P., SPAULDING, G.L., CHEW, D.J. & LEWIS, R.M. (1980) Urinary protein excretion and immunopathologic findings in dogs with glomerular disease. *J. Am. vet. med. Assoc.* **177,** 73.

ENGLISH, P.B. & WINTER, H. (1979) Renal cortical hypoplasia in a dog. *Austr. Vet. J.* **55,** 181.

ERIKSEN, K. & GRØNDALEN, J. (1981) Unpublished data.

FINCO, D.R. (1976) Familial renal disease in Norwegian Elkhound dogs: Physiologic and biochemical examinations. *Am. J. Vet. Res.* **37,** 87.

FINCO, D.R., DUNCAN, J.R., CROWELL, W.A. & HULSEY, M.L. (1977) Familial renal disease in Norwegian Elkhound dogs: Morphologic examinations. *Am. J. Vet. Res.* **38,** 941.

FINCO, D.R., KURTZ, H.J., LOW, D.G. & PERMAN, V. (1970) Familial renal disease in Norwegian Elkhound dogs. *J. Am. vet. med. Assoc.* **156,** 747.

FINCO, D.R. & ROWLAND, G.N. (1978) Hypercalcemia secondary to chronic renal failure in the dog: A report of four cases. *J. Am. vet. med. Assoc.* **173,** 990.

FREUDIGER, U. (1965) Die kongenitale Nierenrindenhypoplasie beim bunten Cocker-Spaniel *Schweizer Arch. Tierheilk.* **107,** 547.

HOLSHUH, H.J. (1981) Hypernatremia and hyperchloremia associated with congenital renal hypoplasia. *Canine Practice,* **8,** 27.

HOPPE, A. & HAGELTORN, M. (1979) Njurbarkshypoplasi hos Shih-tzu. *Rapport, Vaargaarda, Sweden,* **3,** 7.

JOHNSON, M.E., DENHART, J.D. & GRABER, E.R. (1972) Renal cortical hypoplasia in a litter of Cocker Spaniels. *J. Am. Anim. Hosp. Assoc.* **8,** 268.

KAUFMAN, C.F., SOIREZ, R.F. & TASKER, J.P. (1969) Renal cortical hypoplasia with secondary hyperparathyroidism in the dog. *J. Am. vet. med. Assoc.* **155,** 1679.

KEALY, J.K. (1979) *Diagnostic radiology of the dog and cat.* p. 98. W. B. Saunders & Co, Philadelphia, London.

KELLY, D.F., LUCKE, V.M. & MCCULLAGH, K.G. (1979) Experimental pyelonephritis in the cat 1. Gross and histological changes. *J. Comp. Path.* **89,** 125.

KELLY, D.F., LUCKE, V.M. & MCCULLAGH, K.G. (1979) Experimental pyelonephritis in the cat 2. Ultrastructural observations. *J. Comp. Path.* **89,** 563.

KLOPFER, U., NEUMANN, F. & TRAININ, R. (1975) Renal cortical hypoplasia in a Keeshond litter. *Vet. Med./Small anim. Clin.* 1081.

KLOPFER, U., NOBEL, T.A. & KAMINISKI, R. (1978) A nephropathy similar to renal cortical hypoplasia in a Yorkshire terrier. *Vet. Med./Small anim. Clin.* 327.

KROOK, L. (1957) The pathology of renal cortical hypoplasia in the dog. *Nord. Vet. Med.* **9,** 161.

LUCKE, V.M., KELLY, D.F., DARKE, P.G.G. & GASKELL, C.J. (1980) Chronic renal failure in young dogs—possible renal dysplasia. *J. small Anim. Pract.* **21,** 169.

MCCULLAGH, K.G., BISHOP, K.A., LUCKE, V.M. & KELLY, D.F. (1983) Experimental pyelonephritis in the cat 3. Collagen alterations in renal fibrosis. *J. Comp. Path.* **93,** 9.

MCINTEE, D.P. & TEALE, A.J. (1973) Renal cortical hypoplasia in a Swedish Foxhound. *Vet. Rec.* **93,** 260.

O'BRIEN, T.D., OSBORNE, C.A., YANO, B.L. & BARNES, D.M. (1982) Clinicopathologic manifestations of progressive renal disease in Lhasa Apso and Shih Tzu dogs. *J. Am. vet. med. Assoc.* **180,** 658.

OKSANEN, A. & SITTNIKOW, K. (1972) Familjär nefropati med sekundär hyperparathyroidism hos tre unghundar. *Nord. Vet. Med.* **24,** 278.

PERSSON, F., PERSSON, S. & AASHEIM, AA. (1961) Renal cortical hypoplasia in dogs. A clinical study on uraemia and secondary hyperparathyroidism. *Acta. Vetr. Scand.* **2,** 68.

WATSON, A.D.J. & CANFIELD, P.J. (1979) Renal failure, hyperparathyroidism and hypercalcaemia in a dog. *Austr. Vet. J.* **55,** 177.

WILCOCK, B.P. & PATTERSON, J.M. (1979) Familial glomerulonephritis in Doberman Pinscher dogs. *Can. vet. J.* **20,** 244.

WRIGHT, N.G. (1979) Pathogenetic mechanisms in canine renal disease. *The Vet. Ann.* **19,** 133.

WRIGHT, N.G., FISHER, E.W., MORRISON, W.I., THOMSON, W.B. & NASH, A.S. (1976) Chronic renal failure in dogs: A comparative clinical and morphological study of chronic glomerulonephritis and chronic interstitial nephritis. *Vet. Rec.* **98,** 288.