

Renal Medullary Amyloidosis in Dorcas Gazelles

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Abstract. Between January 1976 and September 1987 renal medullary amyloidosis (RMA) was diagnosed in 17 Dorcas gazelles; the necropsy prevalence rate was 17/32 (53%). The most severe amyloid deposits were in the renal medulla; glomeruli were spared. Renal cortical lesions of interstitial fibrosis and tubular atrophy and dilatation significantly correlated with RMA ($P < 0.01$) and were considered to be secondary changes. There were varying degrees of lymphoplasmacytic inflammation and tubular cast formation which did not significantly correlate with RMA. Amyloid was confirmed histochemically and by electron microscopy and was identified as AA type by the permanganate method. Progressive renal failure was the cause of death or necessitated euthanasia in 7/17 (41%) gazelles. RMA in Dorcas gazelles does not appear to be familial. A high prevalence of chronic or recurring *Actinomyces (Corynebacterium) pyogenes* infections may be an important factor.

Currently, classification of the amyloidoses is based in part on the nature of the fibril protein.⁵ Reactive systemic amyloidosis, in which the fibril protein (AA) is believed to be derived by proteolytic cleavage from an acute phase protein (SAA), is the most common form in man²² and is the only form of systemic amyloid reported in nonhumans.¹ Any organ can be involved in reactive systemic amyloidosis, but renal involvement occurs with greatest frequency.^{14,15} Renal amyloid also has the most serious consequences, since deposition of amyloid in glomeruli causes disruption of the glomerular filtration barrier, with resultant proteinuria and associated sequelae.¹⁵ In addition, deposition of amyloid in the peritubular interstitium can lead to ischemia and pressure atrophy of nephrons with subsequent interstitial scarring and loss of renal function.¹⁵

Involvement of the renal medulla with amyloid is rare in man²⁶ and most animals,¹⁵ but may be the predominant form of renal amyloidosis in cats^{3,15,18} and cattle.^{9,10,15} In cattle, there is a spectrum from predominantly glomerular to predominantly medullary amyloidosis;^{9,10} the glomerular form can lead to the nephrotic syndrome^{10,13,19} as in other species, but the medullary form is usually subclinical.¹⁰

We have identified a syndrome of renal medullary amyloidosis (RMA) in a herd of Dorcas gazelles at the National Zoological Park (NZN). In contrast to medullary amyloidosis in cattle, RMA in Dorcas gazelles frequently leads to renal failure and death. This paper reports the occurrence and describes the gross and light microscopic features of renal medullary amyloidosis

in Dorcas gazelles. The clinical aspects of the disease will be published elsewhere.

Materials and Methods

Dorcas gazelles are small ruminants indigenous to desert regions of Northeast Africa. Body weights in adults range from 10 to 15 kg. The National Zoological Park (NZN) maintains a herd of Dorcas gazelles with an average year-end population of about 20 animals. Twice yearly each animal is treated prophylactically with anthelmintics, and a complete blood count and serum chemical analyses are done. Needle biopsies of the kidney were done laparoscopically on five gazelles with persistently elevated serum urea nitrogen and creatinine (>50 mg/dl and >2.0 mg/dl, respectively). When indicated, euthanasia was by the intravenous injection of a commercial preparation (T-61, American Hoechst Corp., Somerville, NJ). Complete necropsies were done on each animal that died or was euthanized. Biopsy specimens were fixed in Trump-McDowell solution, embedded in paraffin, sectioned at 4–6 μm , and stained with hematoxylin and eosin (HE). Representative sections of all tissues collected at necropsy were fixed in 10% neutral buffered formalin and processed similarly. Selected kidney sections were stained with periodic acid-Schiff (PAS) and Gomori's trichrome. Kidney and other selected tissues were stained with Congo red, and replicate sections of kidney were stained with Congo red after oxidation in potassium permanganate²⁴ in order to distinguish AA amyloid from other types. For electron microscopy, kidney sections from selected biopsy and necropsy cases were post-fixed in 1% osmium tetroxide, dehydrated in graded alcohols, and cleared with propylene oxide before epoxy resin embedding. Sections 0.5–1.0 μm thick were stained with 0.1% methylene blue for orientation. Ultrathin sections were cut

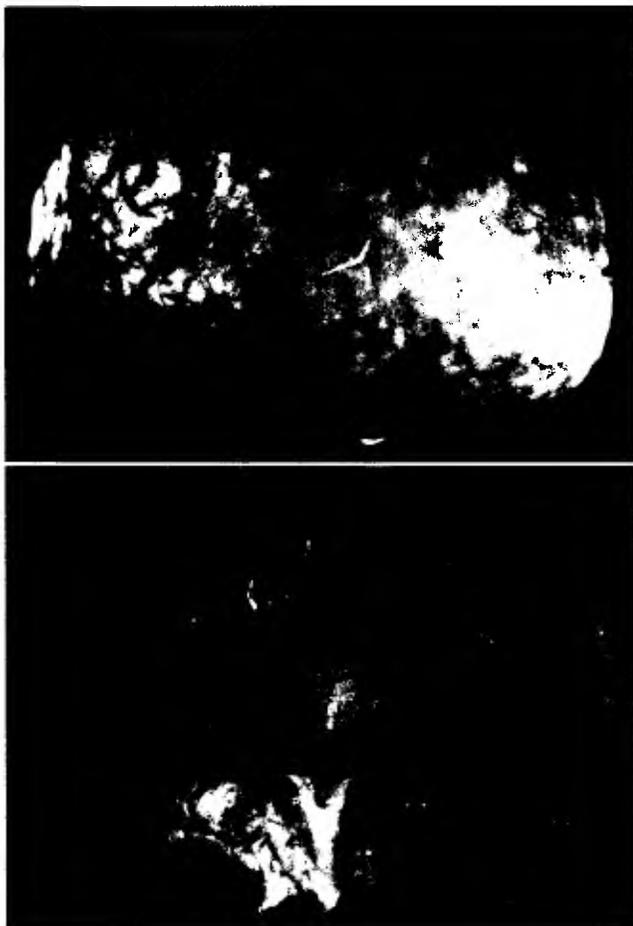


Fig. 1. Renal medullary amyloidosis. Kidney is shrunken, capsular surface is irregular.

Fig. 2. Cut surface of kidney. Medulla is pale, white streaks radiate to the capsular surface. Tip of renal papilla is missing, indicating previous necrosis.

with a diamond knife and stained with uranyl acetate and lead citrate, and electron micrographs were taken.

Pathology records and histopathology slides for all Dorcas gazelles aged 9 months or older were reviewed for the period January 1976 to September 1987. All available clinical and pathology records were reviewed to identify any underlying inflammatory diseases that might incite amyloid deposition. Available pedigrees were examined to determine if renal medullary amyloidosis (RMA) has a hereditary basis. For each case of RMA confirmed by Congo red stain, sections of kidney were examined by plain and polarized light microscopy. Severity of amyloid deposition, tubular dilatation and atrophy, tubular cast formation, interstitial fibrosis, and interstitial lymphocytic inflammation were graded separately on a subjective scale of 1–3, with 3 being most severe. Each case was also ranked in decreasing order of severity according to each of the above categories, as well as age, and the degree of correlation between RMA and each category was determined using Kendall's rank correlation method.¹⁶

Results

Between March 1984 and March 1987 renal medullary amyloidosis (RMA) was diagnosed by closed renal biopsy in five Dorcas gazelles with persistently elevated serum urea nitrogen and creatinine. All five died or were euthanized due to renal failure within 9 months of diagnosis. A review of pathology records and histopathology slides for all Dorcas gazelles greater than 9 months of age for the period January 1976 to September 1987 revealed 12 additional cases of RMA. The necropsy prevalence rate for the study period was 17/32 (53%). Renal failure was the cause of death or necessitated euthanasia in 7/17 (41%). Ages ranged from 1.7 years to 13 years, with a mean of 6.7 years. The sex ratio was four males : ten females (the sex ratio of the population is skewed in favor of females by herd management practices).

Severely affected kidneys were generally smaller and firmer than normal. The capsular surfaces were uneven, with raised, irregular, coalescing pale tan areas and intervening dark red-brown recessed areas (Fig. 1). These changes were usually bilateral, but not always symmetrical; in a few instances one kidney was much smaller, firmer, and paler than the other. The renal capsule always peeled easily from the cortical surface. On cut surface, the renal medullae were usually firm and pale yellow-white, with fine white streaks often radiating from the papilla to the corticomedullary junction (Fig. 2). Evidence of papillary necrosis was noted in two gazelles, in which the tips of the papillae were absent, leaving small, semicircular, cleft-like defects (Fig. 2). The cortices sometimes had a coarse granular appearance, with prominent white streaks radiating from the corticomedullary junction to the capsular surface (Fig. 2). Several gazelles had scattered cortical cysts 0.2–1.0 cm in diameter in one or both kidneys. Some affected animals had kidneys with mild or no gross lesions.

Histologically, there was widening of the medullary interstitium by eosinophilic homogeneous material, which encroached upon medullary tubules and collecting ducts (Fig. 3). This material stained pale orange-red with Congo red and exhibited the characteristic green birefringence of amyloid when examined with polarized light. Oxidation in potassium permanganate eliminated the affinity for Congo red, indicating that the amyloid fibrils are composed of the AA protein. Amyloid deposition was most prominent around tubular basement membranes in mildly affected kidneys (Fig. 4). In advanced cases, widespread atrophy of epithelium left only outlines of medullary tubules and collecting ducts (Fig. 3). The amyloid deposits tended to be evenly distributed throughout the medulla, gradually diminishing towards the corticomedullary junction.

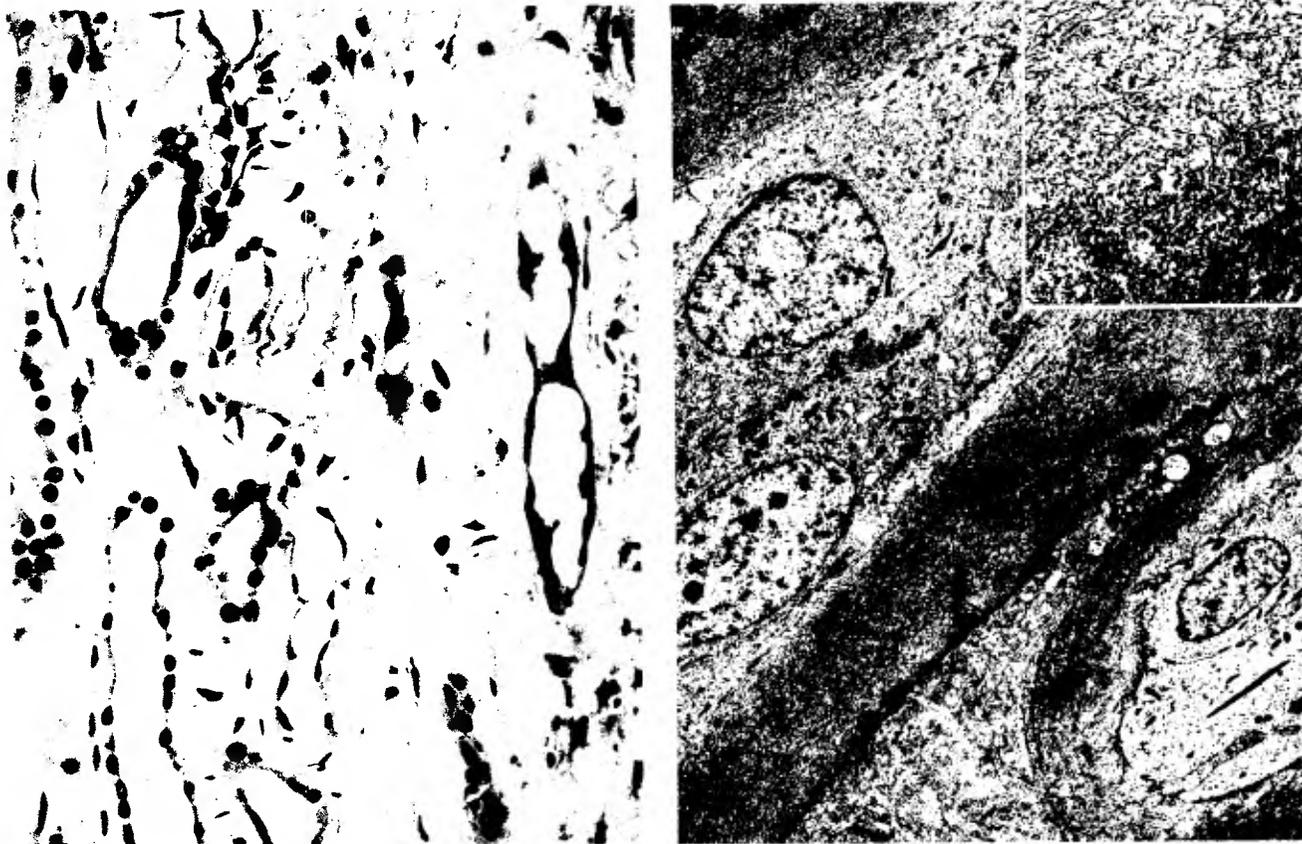


Fig. 3. Renal medulla. Amyloid encroaches on medullary tubules and collecting ducts. Atrophy and loss of many tubules. One tubule (right center) has regenerating epithelium. HE.

Fig. 4. Renal medulla, medullary amyloidosis. Tubular basement membranes (arrows) are thickened and infiltrated by amyloid fibrils. Inset: amyloid fibrils.

tion. One gazelle (84-386) also had prominent amyloid deposition in the walls of medium- and large-sized arteries throughout the kidney. Another animal (81-623) had moderate peritubular deposits in the cortex, but all others had minimal or no cortical interstitial amyloid. The glomeruli were spared in all cases.

Although the tip of the renal papilla was present in only seven of the kidney sections, coagulative necrosis of the papilla was identified in three gazelles. In one, the necrosis was extensive but limited to the tip of the papilla. The other two had patchy necrosis throughout the medulla, with extensive mineralization of the necrotic areas in one. Mineralization of medullary tubules and interstitium was noted in one case which lacked evidence of papillary necrosis.

Cortical changes included variable degrees of tubular atrophy and dilatation, interstitial and periglomerular fibrosis, and interstitial foci of lymphocytes and plasma cells (Figs. 5, 6). Trichrome stain highlighted both the medullary amyloid and the cortical fibrosis, but the two were easily distinguished in Congo red-stained

sections. Dilated and atrophied tubules frequently contained eosinophilic hyaline casts (Figs. 5, 6). The glomeruli were usually normal by light microscopy (Fig. 6), including periodic acid-Schiff (PAS)-stained sections, but some gazelles had a few sclerotic glomeruli.

Kidneys from seven gazelles with representative lesions (Table 2) were examined by electron microscopy. Amyloid was limited to the medulla in all seven. In one gazelle (87-36) focal fusion of epithelial foot processes was seen, but most foot processes were slender. Electron-dense mesangial deposits compatible with immune complexes were seen occasionally in five kidneys. In two related animals (87-36 and her female offspring, 84-386) there was splitting and splintering of the lamina densa of the glomerular capillary basement membranes, which resembled the basement membrane changes of Alport's syndrome in man.¹⁴

In all cases the most severe amyloid deposition occurred in the renal medullae (Table 1). The presence of interstitial fibrosis, and tubular dilatation and atrophy correlated significantly with RMA (Table 2). No

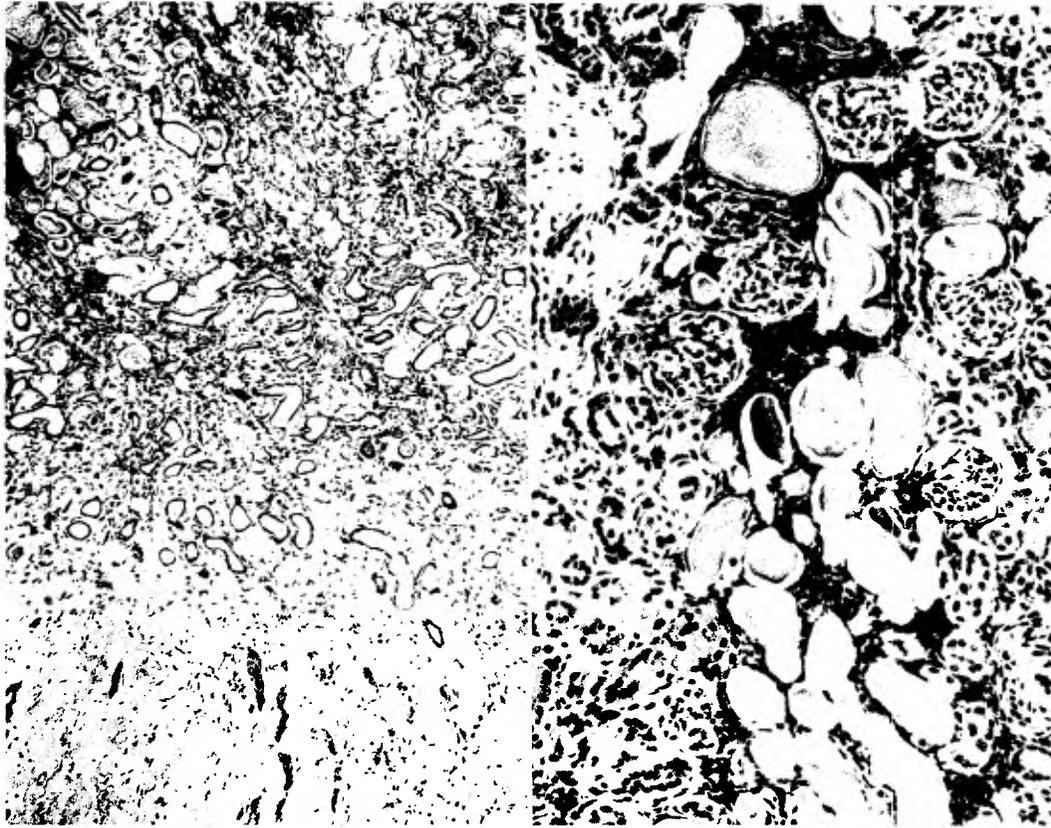


Fig. 5. Renal corticomedullary area, advanced medullary amyloidosis. Widespread tubular atrophy; remaining tubules are dilated and contain hyaline casts. HE.

Fig. 6. Renal cortex, gazelle with advanced medullary amyloidosis. Glomeruli are juxtaped due to loss of intervening tubules. Surrounding tubules are dilated and contain hyaline casts. HE.

significant correlation was found between RMA and age, inflammation, or tubular casts.

Examination of available pedigree information revealed no evidence of a hereditary basis for RMA in Dorcas gazelles. The only underlying disease which occurred with any regularity in the Dorcas gazelle population as a whole was infection by *Actinomyces* (formerly *Corynebacterium*) *pyogenes*, which tended to be chronic or recurring. During the study period an antemortem or post-mortem diagnosis of *A. pyogenes* infection was made in 11 gazelles; nine of which were found to have RMA at biopsy or necropsy (Table 1).

Discussion

The pattern of renal amyloid in these gazelles is unusual in that deposition was most prominent in the medullae, with sparing of glomeruli and little or no involvement of cortical interstitium. Renal medullary amyloidosis (RMA) also frequently led to renal failure and death and had a high prevalence rate at necropsy, making RMA the current leading cause of death among Dorcas gazelles at the National Zoological Park (NZP).

In contrast, RMA in cattle frequently occurs in conjunction with glomerular amyloidosis, and if the glomerular component is mild, it is usually a subclinical disease.¹⁰ Although there are no published necropsy prevalence rates for cattle, in one large abattoir survey RMA was diagnosed in only 2.7% of 1,326 beef cattle and 2.6% of 378 dairy cattle.⁹ In addition, RMA occurs independently of age in Dorcas gazelles, but is considered an age-related change in cattle.⁹

The kidney appeared to be the primary site of amyloid deposition in this study, since the most severe amyloid deposition always occurred in the kidney, and in 7/14 cases amyloid was limited to the kidney. Moreover, no cases of amyloidosis without renal involvement were identified in Dorcas gazelles. Gross changes similar to those seen in these gazelles have been reported in other species with RMA,^{2,3,18} but these findings are obviously not specific.

The mechanism by which RMA impairs renal function in the gazelle probably involves obstruction at the level of the medullary tubules and collecting ducts, leading to atrophy and eventual loss of nephrons, with

Table 1. Summary of pathology data.

Case #	Age	Sex	Amyloid Organ Distribution	Cause of Death	<i>A. pyogenes</i> Infection Site
87-595	9 yr 5 mo	M	Kidney, liver	Renal failure	Flank
87-36	2 yr 11 mo	F	Kidney only	Euthanasia, renal failure	Submandibular
86-571	8 yr 11 mo	F	Kidney only	Pneumonia	Lung
86-161	8 yr 5 mo	M	Kidney, liver, spleen, adrenal, rumen, esophagus	Renal failure	Urine, foot,* tendon*
86-50	3 yr 9 mo	F	Kidney, liver, abomasum	Euthanasia, renal failure	None
85-567	10 yr	F	Kidney, spleen	Renal failure	None
85-94	5 yr 10 mo	M	Kidney, liver, spleen	Euthanasia, renal failure	None
85-41	2 yr 6 mo	F	Kidney, spleen	Bacteremia	Mandible
84-386	9 yr 4 mo	F	Kidney, heart, abomasum	Renal failure	Mandible
84-148	6 yr 10 mo	F	Kidney only	Renal failure	None
83-611	1 yr 7 mo	F	Kidney, spleen, adrenal	Tetanus	None
82-102	3 yr 8 mo	M	Kidney only	Inanition due to mandibular abscess	Mandible
81-740	6 yr	F	Kidney only	Spiral colon impaction	None
81-674	4 yr 9 mo	F	Kidney only	Spiral colon impaction	None
81-623	11 yr	F	Kidney, liver, spleen	Lung abscess	Mandible
78-356	13 yr	F	Kidney only	Euthanasia, perineal hernias	Mandible
76-01	5 yr 6 mo	M	Kidney only	Maladaptation	None

* = not confirmed by culture.

progressive interstitial fibrosis in the medulla and cortex. The strong correlation between medullary amyloid, tubular atrophy and dilatation, and interstitial fibrosis support this view and make it unlikely that the cortical changes represent superimposed tubulo-interstitial nephritis. Similar cortical lesions are seen with RMA in other species, and similar mechanisms are thought to be responsible for the changes.^{4,6,7,15}

In advanced cases of RMA, tubular dilatation with cast formation resembled the renal "thyroidization" frequently seen with chronic pyelonephritis in humans.^{8,11} The correlation between RMA and tubular casts was not significant. Urinalysis data (primarily on samples collected from holding cage floors) was available for six animals, including two (87-595 and 87-36) that had marked tubular cast formation (data not shown). Only one animal (87-595) was proteinuric (30–100 mg/dl range by the reagent strip method; Multistix, Ames Division, Miles Laboratories, Inc., Elkhart, IN),

but this finding is of questionable significance, since all samples from this animal were heavily contaminated by fecal material. The lack of pronounced proteinuria would suggest that most tubules containing casts are obstructed distal to the casts. Similarly, in chronic pyelonephritis, the cast-containing tubules have been shown to represent sequestered segments of tubules that have been pinched off by the inflammatory process.¹¹

In five of seven kidneys examined by electron microscopy, occasional mesangial immune complex deposits were seen. These may have been related to *A. pyogenes* abscesses, since three of the five had recent histories of infection. Splitting and splintering of the glomerular basement membrane was seen ultrastructurally in two related gazelles, which resembled the basement changes of Alport's syndrome in man.¹⁴

Renal papillary necrosis is a common finding with RMA in other species^{2,3,6,12} and was seen in three of

Table 2. Ratings and rank correlation of medullary amyloid, cortical changes, and age.

Case #	Medullary Amyloid		Tubular Atrophy and Dilatation		Interstitial Fibrosis		Interstitial Inflammation		Tubular Casts		Age Rank
	Rating*	Rank†	Rating	Rank	Rating	Rank	Rating	Rank	Rating	Rank	
87-595‡	3+	1	3+	1	2+	2	2+	3	3+	1	4
84-386‡	3+	2	3+	2	2+	4	3+	1	3+	2	5
86-50‡	3+	3	3+	3	2+	6	1+	9	1+	11	13
84-148	3+	4	1+	11	2+	5	0	—	2+	6	8
87-36‡	3+	5	2+	5	2+	3	2+	2	2+	4	15
86-161	3+	6	3+	4	2+	1	0	—	3+	3	7
85-94	3+	7	2+	7	1+	9	0	—	1+	10	10
85-567	2+	8	1+	14	1+	10	0	—	1+	14	3
81-740‡	2+	9	2+	6	1+	15	1+	5	1+	8	9
76-01	2+	10	1+	9	1+	12	0	—	1+	12	11
81-623‡	2+	11	1+	10	1+	11	1+	8	2+	5	2
85-41	2+	12	0	—	2+	7	0	—	0	—	16
86-571	2+	13	2+	8	2+	8	1+	6	2+	7	6
82-102	1+	14	0	—	1+	13	1+	7	0	—	14
81-674	1+	15	1+	12	1+	14	1+	11	1+	13	12
78-356‡	1+	16	1+	13	1+	16	2+	4	1+	9	1
83-611	1+	17	0	—	0	—	1+	10	1+	15	17
Correlation coefficient			0.63§		0.60§		0.42		0.37		0.38

* Ratings reflect lesion severity based on a subjective scale of 0 to 3+: 0 = none (excluded from ranking); 1+ = minimal to mild; 2+ = moderate; 3+ = marked.

† Rankings are in decreasing order of severity or age.

‡ = examined electron microscopically.

§ = statistically significant correlation ($P < 0.01$).

the seven gazelles for which sections of renal papilla were available. Loss of the tip of the renal papilla was noted grossly in two other cases. Papillary necrosis in these cases is thought to result from obstruction of the medullary vasculature by amyloid, leading to ischemic necrosis of the papilla.^{6,11} Inability to autoregulate medullary blood flow as a result of amyloid-induced damage to the prostaglandin-secreting medullary interstitial cells may also be an important factor.²⁰

In all cases, the affinity for the Congo red stain was eliminated by oxidation of tissue sections in potassium permanganate, indicating that the amyloid is of the AA type.²⁴ Although immunohistochemical confirmation was not attempted in these cases, it has recently been shown that permanganate-sensitive systemic amyloid in the closely related mountain gazelle (*Gazella gazella*) cross-reacts strongly with murine monoclonal and bovine polyclonal anti-AA antibodies,¹⁷ suggesting that permanganate sensitivity is specific for amyloid A in gazelles, as in other species. It is interesting to note that the mountain gazelle of that report had heavy amyloid deposits in the glomeruli and tubular interstitium, but no mention is made of medullary involvement.

The reason for the species differences in the distribution of renal amyloid is not known, but in man it

has been shown that purified medullary amyloid-A protein has a different elution pattern on gel-filtration than glomerular amyloid-A protein.²⁶ Moreover, it is now known that the human AA protein is a heterogeneous mixture of protein fragments, and there is an association between the length of the fragment and the pattern of renal amyloid deposition.^{21,23,25} One suggested explanation for these findings is that individual variations in SAA-splitting enzymes result in formation of AA fragments of different length, leading to different AA syndromes in different individuals.^{25,26} If this is the case, interspecific variations in SAA-splitting enzymes may also exist, which might help explain the different patterns of renal amyloid deposition seen in different species.

Although pedigrees for many animals were difficult to trace and young animals were frequently shipped to other facilities and were lost to follow-up, available pedigree information suggests that RMA in Dorcas gazelles is not familial (data not shown).

Since chronic inflammatory or neoplastic diseases are thought to be the most important inciting causes of reactive systemic amyloidosis, an attempt was made to identify underlying diseases occurring in affected animals that may not be occurring in the unaffected population. The only condition that occurred with any

regularity was a chronic or recurring infection by *Actinomyces (Corynebacterium) pyogenes*, which was identified in 11 animals during the study period.²⁷ Ten of these 11 were eventually necropsied, and nine (82%) were found to have RMA. One of the 11 is still living and has normal serum chemistries but has not been biopsied. Mandibular and submandibular infections were the most common, affecting 5/11 animals. The striking contrast in the *A. pyogenes* infection rates for the amyloid affected vs. amyloid unaffected animals suggests that this organism may be an important factor in the pathogenesis of RMA in Dorcas gazelles at the NZP.

Acknowledgements

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