School of Veterinary Medicine

Sheri Ross
Nephrology/Urology/Hemodialysis
BSc, DVM, PhD,
Diplomate ACVIM

Dr. Ross is originally from Saint John, New Brunswick, Canada and attended The Atlantic Veterinary College at the University of Prince Edward Island. Following completion of her DVM program in 1996, she completed an internship in Small Animal Medicine and Surgery at the University of Minnesota where she remained to complete a Small Animal Internal Medicine Residency and PhD in Nephrology and Urology. Dr. Ross served as an Assistant Clinical Professor in the Veterinary Clinical Sciences Department at the University of Minnesota for two years. She then completed a Fellowship in Renal Medicine and Hemodialysis at the University of California Veterinary Medical Center-San Diego, after which she accepted a permanent position on the UCVMC-SD clinical faculty.

A Diplomate of the American College of Veterinary Internal Medicine, Dr. Ross enjoys all aspects of internal medicine with a particular emphasis on the urinary tract. She is skilled at hemodialysis, uroendoscopy, voiding urohydropulsion and other methods of non-surgical urolith removal. Dr. Ross's specific research interests include the influence of diet on the progression of chronic kidney disease, renal transplantation, hemodialysis, feline acute ureteral obstruction, and urolith management. She enjoys clinical research and has collaborated with other veterinary colleges and industry.

Dr. Ross has authored several scientific articles and textbook chapters and has been the recipient of many regional and national awards for both teaching and research. In addition to teaching veterinary students, she has frequently lectured to veterinarians throughout the US, Australia, and Asia. Dr. Ross currently resides in San Diego with her husband and three cats.

UCDAVIS

School of Veterinary Medicine

Julie R. Fischer
Nephrology/Urology/Hemodialysis
DVM, Diplomate ACVIM

Julie Fischer received her Doctor of Veterinary Medicine degree from the University of Tennessee College of Veterinary Medicine (1996). She completed a small animal internship in medicine and surgery at the Atlantic Veterinary College, University of Prince Edward Island, Canada, and then a residency in small animal internal medicine at Kansas State University. Dr. Fischer served as a clinical instructor at Kansas State, and then entered private specialty practice in San Jose, California. She is a Diplomate of the American College of Veterinary Internal Medicine.

Dr. Fischer joined the Nephrology Service at UC Davis in 2001, pursuing a long-held interest in kidney disease. Following intensive training in nephrology and hemodialysis, she opened the UCVMC-San Diego's Companion Animal Hemodialysis Service, one of only five active veterinary hemodialysis centers in the country. The UC Davis and UCVMC-SD programs jointly administer the only post-residency training programs in veterinary nephrology and hemodialysis.

Over the ensuing years, the service has expanded to meet the needs and expectations of regional veterinarians and pet owners. The UCVMC-SD now offers consultation and management for all upper and lower urinary tract problems, including urinary stone diseases, complicated infections, prostatic diseases and acute and chronic kidney diseases, as well as provision of routine and emergency hemodialysis services. Dr. Fischer is helping to develop a kidney transplant program in San Diego, a cooperative venture between UC Davis, the UCVMC-SD, and the Veterinary Specialty Hospital. She currently directs the Nephrology/Hemodialysis and Urology programs at the UCVMC-SD

Some of Dr. Fischer's specific interests include novel applications of blood purification techniques, kidney transplantation, clinical pathology, and the clinical training of veterinary students and house officers. She also enjoys writing and has published scientific journal articles and textbook chapters on urinary diseases as well as on other internal medicine topics. Dr. Fischer has spoken locally, nationally and internationally, and lectures in UC Davis' veterinary medical core curriculum.

UCDAVIS

UC Veterinary Medical Center
San Diego

N

Mira Mesa Blvd.

Sorrento Valley Rd.

805

56

5

FROM DOWNTOWN SAN DIEGO I-805
Exit Sorrento Valley Rd. Take the first right onto Vista Sorrento Pkwy. Take the first right onto Sorrento Valley Rd. The building is located (0.6 miles) on the right.

FROM DOWNTOWN SAN DIEGO I-5
Exit Sorrento Valley Rd. Take the first left onto Roselle St. Take the first right onto Sorrento Valley Blvd. Take the first right onto Sorrento Valley Rd. The building is located (0.6 miles) on the left.

FROM NORTH COUNTY
Take I-5, stay on the left lanes and transition onto I-805 South. Exit Sorrento Valley Rd. and make a right. The building is located (0.6 miles) on the left.
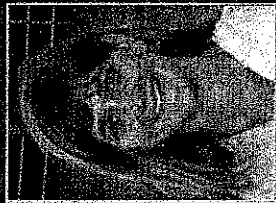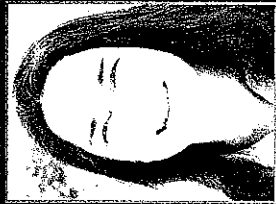
FROM I-15
Take 56 West to I-5 South. Stay in the left lanes and transition onto I-805 South. Exit Sorrento Valley Rd. and make a right. The building is located (0.6 miles) on the left.

10435 Sorrento Valley Rd.
San Diego, CA 92121
Phone: 858-875-7505
Fax: 858-875-7583
Emergency: 858-875-7505
www.ucvmc-sd.vetmed.ucdavis.edu

Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats

Sheri J. Ross, DVM, PhD, DACVIM; Carl A. Osborne, DVM, PhD, DACVIM; Claudia A. Kirk, DVM, PhD, DACVN, DACVIM; Stephen R. Lowry, PhD; Lori A. Koehler; David J. Polzin, DVM, PhD, DACVIM

Objective—To determine whether a renal diet modified in protein, phosphorus, sodium, and lipid content was superior to an adult maintenance diet in minimizing uremic episodes and mortality rate in cats with stage 2 or 3 chronic kidney disease (CKD).

Design—Double-masked, randomized, controlled clinical trial.

Animals—45 client-owned cats with spontaneous stage 2 or 3 CKD.

Procedures—Cats were randomly assigned to an adult maintenance diet (n = 23 cats) or a renal diet (22) and evaluated trimonthly for up to 24 months. Efficacy of the renal diet, compared with the maintenance diet, in minimizing uremia, renal-related deaths, and all causes of death was evaluated.

Results—Serum urea nitrogen concentrations were significantly lower and blood bicarbonate concentrations were significantly higher in the renal diet group at baseline and during the 12- and 24-month intervals. Significant differences were not detected in body weight; Hct; urine protein-to-creatinine ratio; and serum creatinine, potassium, calcium, and parathyroid hormone concentrations. A significantly greater percentage of cats fed the maintenance diet had uremic episodes (26%), compared with cats fed the renal diet (0%). A significant reduction in renal-related deaths but not all causes of death was detected in cats fed the renal diet.

Conclusions and Clinical Relevance—The renal diet evaluated in this study was superior to an adult maintenance diet in minimizing uremic episodes and renal-related deaths in cats with spontaneous stage 2 or 3 CKD. (*J Am Vet Med Assoc* 2006;229:949–957)

ABBREVIATIONS

CKD	Chronic kidney disease
PUFA	Polyunsaturated fatty acid
BCS	Body condition score
SUN	Serum urea nitrogen
Tco₂	Total carbon dioxide concentration
PTH	Parathyroid hormone
UPUC	Urine protein-to-urine creatinine ratio
UTI	Urinary tract infection

Chronic kidney disease is among the most common clinical diagnoses of middle-aged to older cats. During 1990, the prevalence of renal failure among cats of all ages reported to the Purdue Veterinary Medical Database was 16 cases/1,000 cats examined.[1] In 2000, the prevalence was 96 cases/1,000 cats examined.[a]

Chronic kidney disease is characterized by progressive structural lesions, resulting in impairment of renal excretory, biosynthetic, and regulatory functions. In dogs and humans, CKD is progressive and irreversible, leading to uremia and death within months to years after initial diagnosis.[2,3] Spontaneous CKD in cats is also progressive, although the rate of progression is highly variable and episodes of progression may be interspersed with long periods of clinically stable renal function.[4-6]

For the past several decades, dietary modification has been the mainstay of therapy to minimize extrarenal manifestations of spontaneous CKD in cats. The benefits and risks associated with various dietary modifications have been evaluated in controlled studies of cats with induced CKD.[7-9,b] However, we could find only 1 report[10] of a clinical trial designed to evaluate the effect of a renal diet in cats with naturally occurring CKD. Although the investigators concluded that dietary modification was beneficial, the study was not randomized or masked. Thus, there is a need for randomized, double-masked, controlled clinical trials to evaluate the long-term safety and effectiveness of renal diets in cats with naturally occurring kidney disease.

The purpose of the study reported here was to test the hypothesis that a renal diet (modified in protein, phosphorus, sodium, and lipid composition) is superior to an adult maintenance diet in minimizing uremic episodes and renal-related deaths in cats with stage 2 or 3 CKD. To examine the impact of diet on development of uremic crisis, mortality rate, and progression of renal failure, a combination of dietary modifications commonly recommended to manage CKD was used.[3] This type of study is likely to provide a more informative and efficient evaluation than separate clinical trials in which the therapeutic efficacies of dietary components are studied individually. In addition, studying a

combination of dietary modifications encompasses evaluations of the overall interactions of various dietary components.

Materials and Methods

Cats—For design of this controlled study, we considered the question of whether it was ethical to feed an adult maintenance diet to cats with CKD and substantial renal dysfunction. Because available evidence[7-10] suggested that modifications of several components (protein, phosphorus, sodium, and lipids) in the renal diet used in the present study minimized extrarenal manifestations of stage 4 CKD, in the authors' opinion, feeding a maintenance diet to such cats would have been unethical. Thus, cats with stage 2 or 3 CKD (serum creatinine concentrations ranging from 2.1 to 4.5 mg/dL) were evaluated. If a diet modified for kidney failure proved to be beneficial in cats with stage 2 or 3 CKD, it is plausible that the diet would be effective in cats with stage 4 CKD. This assumption is supported by results of a nonrandomized, open clinical trial in which dietary modifications were found to be beneficial to cats with all stages of CKD.[10]

Client-owned cats were recruited from the Minneapolis–Saint Paul area by mailing a description of the study to area veterinarians asking for referrals. Cats were also recruited from the University of Minnesota Veterinary Medical Center patient population by use of a medical records search and direct owner contact. Cats were considered for enrollment if they were 1 year of age and had a history consistent with stable CKD for at least 4 weeks. During the first screening visit, cats were evaluated by means of a defined medical history, physical examination, indirect blood pressure measurement, and serum creatinine concentration measurement. If serum creatinine concentration was from 2.1 to 4.5 mg/dL and there was no evidence of prerenal azotemia (dehydration, hypotension, volume depletion, or comorbid conditions), cats were reevaluated 7 to 21 days later. At that time, if serum creatinine concentration did not increase or decrease by > 20% from the initial value and remained from 2.1 to 4.5 mg/dL, renal function was judged to be stable and the cat was provisionally enrolled for study.

After provisional acceptance, cats were reevaluated on the basis of results of a medical history, physical examination, CBC,[c] serum biochemical profile,[d] urinalysis, indirect blood pressure determination, survey abdominal radiography, serum total thyroxine concentration,[e] and ELISA tests for FeLV and FIV.[f] All cats were then fed a combination diet for 6 weeks (Table 1). At the end of 6 weeks, 45 cats of 7 breeds

(domestic short hair, n = 31; domestic long hair, 7; Siamese, 4; Maine Coon Cat, 1; Birman, 1; and Himalayan, 1) and ranging in weight from 2.47 to 7.65 kg (5.4 to 16.8 lb; mean ± SD, 4.27 ± 1.08 kg [9.4 ± 2.4 lb]) met the following inclusion and exclusion criteria and were subsequently enrolled in the study. Included were cats > 1 year of age (mean ± SD, 12.9 ± 3.9 years; range, 4 to 19 years) with stable renal function (as defined). Excluded were cats expected to die of nonrenal illness before the study was complete; cats with diabetes mellitus, hyperthyroidism, FeLV, or FIV infection; cats with overt clinical signs or uremia (eg, anorexia, lethargy, and vomiting); and those being concurrently treated with corticosteroids, H_2-blocking drugs, parenterally administered fluids, vitamin supplements, phosphate binders, alkalinizing agents, potassium supplements, recombinant human erythropoietin, or vitamin D supplements. At the time of diet assignment, all cats had documented renal disease for a minimum of 11 to 13 weeks.

Diets—This study was designed to compare a typical adult feline dry and moist maintenance diet with a diet designed specifically for treatment of feline chronic kidney failure[g] (ie, the renal diet; Table 1). Both diets provided complete and balanced nutrition for the maintenance of adult cats as substantiated by the Association of American Feed Control Officials (AAFCO) feeding trials (renal diet) or by exceeding the minimum AAFCO nutrient profile for an adult cat (maintenance diet).[11] The digestibility of each diet was determined via diet digestibility testing. Apparent protein digestibility was 78.8% (dry) and 77.3% (moist) for the renal diet and 83.4% (dry) and 82.5% (moist) for the maintenance diet.

Principle characteristics of the renal diet were reduced quantities of protein, phosphorus, and sodium, compared with the maintenance diet. The renal diet was supplemented with PUFAs, whereas the maintenance diet was not.[h]

Feeding protocol—After qualifying for the study, all cats were acclimated for > 6 weeks (run-in period) to a diet formulated to represent the nutritional average of the renal diet and maintenance diet (Table 1). The goal was to gradually decrease consumption of the amount of the regular diet while increasing the amount of the combination diet, so that cats would be consuming at least 80% of the combination diet for 3 weeks, prior to random assignment to the study diets. Cats were fed this combination diet to minimize variability associated with consumption of different diets fed by owners before being enrolled in the study. This strategy was also cho-

Table 1—Composition of a combination diet, a renal diet, and a maintenance diet fed to cats with spontaneous CKD.

Nutrient	Dry			Moist		
	Combination diet	Renal diet	Maintenance diet	Combination diet	Renal diet	Maintenance diet
Protein (% [% ME])	36	29 (23)	46 (35)	41	28 (20)	48 (38)
NFE (% [% ME])	ND	45 (36)	22 (17)	ND	38 (28)	20 (16)
Fat (% [% ME])	26	21 (41)	26 (48)	26	29 (52)	24 (46)
ME (kcal/g)	4.3	4.3	5.0	4.4	4.8	4.4
Calcium (%)	0.9	0.7	1.1	0.8	0.6	0.9
Phosphorus (%)	0.7	0.5	0.9	0.7	0.5	1.0
Sodium (%)	0.5	0.2	0.4	0.4	0.3	0.4
Potassium (%)	1.0	0.7	0.9	0.9	1.1	0.9
Crude fiber (%)	0.8	0.8	0.7	2.4	1.7	3.4
Omega-6 FA (%)	3.7	3.1	3.9	3.2	4.6	3.0
Omega-3 FA (%)	0.2	0.2	0.2	0.2	0.6	0.2
Omega-6:Omega-3*	18:1	16:1	21:1	19:1	7:1	13:1
Moisture* (%)	5.4	6.4	5.5	70.8	70.7	73.1

*Indicates percentage as fed or ratio; all other units are on a dry-matter basis as determined by chemical analysis.[g]
ME = Metabolizable energy. NFE = Nitrogen-free extract. Represents carbohydrate fraction of the food. ND = Not determined. Omega-6 FA = Omega-6 series fatty acids. Omega-3 FA = Omega-3 series fatty acids.

sen to minimize abrupt changes in dietary ingredients at the time of randomization to the renal diet or maintenance diet group. Throughout the study, owners were asked to continue the method of feeding (free-choice feeding or meal feeding consisting of any combination of canned or dry food) used prior to entry into the study. Owners were instructed to give a quantity of diet sufficient to maintain adequate nutrition on the basis of serial assessments of body weight and physical examination. Feeding was limited to a predetermined amount of food on the basis of daily caloric requirements as determined by the following formula: $1.4 \times (70 \times$ body weight [kilograms])$^{0.75}$ = kilocalories per day.[11] Owners were asked to monitor the quantity of study diet consumed and to note the amount and type of any other foods consumed by use of a printed record. When body weight decreased, owners were asked to increase the amount of food given to the cat. In instances in which the predetermined quantity of food was not consumed, owners were instructed to enhance food intake by warming the food or by adding sodium- and protein-restricted flavoring agents (eg, diluted low-sodium chicken broth or tuna water)

Study design—A randomized, double-masked, controlled clinical trial was conducted. Owners of cats that met all inclusion and exclusion criteria were asked to review and sign an informed consent form approved by the Institutional Animal Care and Use Committee of the University of Minnesota. After the 6-week run-in period and immediately prior to random assignment to the maintenance diet or renal diet, each cat was evaluated by use of a defined medical history, physical examination, BCS,[11] expanded serum biochemical panel (ie, SUN, creatinine, glucose, inorganic phosphorus, calcium, sodium, potassium, chloride, albumin, TCO_2, total bilirubin, and total protein concentrations and serum amylase, alanine transaminase, and alkaline phosphatase activities), CBC,[e] venous blood gas analysis,[i] urinalysis, quantitative aerobic bacteriologic culture of urine, indirect blood pressure measurements, serum ionized calcium analysis,[j] and serum PTH concentration analysis[j] (Table 2). Although all of these analytes were evaluated throughout the clinical trial, only analytes related to kidney disease (Hct, UPUC, blood HCO_3 concentrations, serum creatinine, urea nitrogen, phosphorus, total calcium, potassium, chloride, and PTH) were compared.

Cats were assigned to either the renal diet or maintenance diet via block randomization (blocks of 8) in a ratio of 1:1. Assignment was made via sealed, sequentially numbered envelopes. Double masking of the study was maintained by use of coded diets provided in identical packaging material.

One month after assignment to either the renal diet or maintenance diet, the status of each cat was evaluated via history, physical examination, indirect blood pressure, limited serum biochemical profile (consisting of SUN, creatinine, potassium, and TCO_2 concentrations), PCV, and total plasma solids concentration determinations.

Cats were evaluated at 3-month intervals or when signs indicative of a uremic crisis developed. Nonscheduled evaluations were performed at the owner's request. During scheduled visits at months 0, 6, 12, 18, and 24, each cat was evaluated by means of a defined medical history, physical examination, ocular funduscopic examination, BCS, expanded serum biochemical panel, serum ionized calcium, PTH concentration, CBC, venous blood gas, urinalysis, quantitative urine culture for aerobic bacteria, and indirect blood pressure measurement. On months 3, 9, 15, and 21, the same protocol was followed; however, venous blood gas analysis, serum ionized calcium, and serum PTH concentrations were not evaluated.

To encourage compliance and determine any medical problems when on-site examinations were not scheduled, telephone interviews of clients were performed monthly. The same veterinary technician performed all telephone interviews. Clients were asked to record the amount of diet eaten each day, including any food in addition to the assigned diet.

Blood samples and assays—Owners were instructed to withhold food for 8 to 12 hours prior to scheduled evaluations. Blood samples were collected via jugular venipuncture during each visit. Serum was harvested within 30 minutes by use of standard procedures. If serum for biochemical profiles could not be processed on the same day, serum obtained from centrifuged blood was stored at 4°C and evaluated the following day. During scheduled visits on months 0, 6, 12, 18, and 24, an aliquot of serum from each collection was frozen (−70°C) and saved for determinations of PTH and ionized calcium concentrations. Additionally, an aliquot of venous blood was collected in a heparinized blood gas syringe and analyzed within 20 minutes for pH and HCO_3 concentrations.

Table 2—Schedule of clinical and laboratory procedures performed during a study of a combination diet, renal diet, and maintenance diet fed to cats with spontaneous CKD.

Variable	Month of study											
	−2	−1.5	0	1	3	6	9	12	15	18	21	24
Medical history	X	X	X	X	X	X	X	X	X	X	X	X
BCS	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X	X
Serum biochemistry panel		X	X		X	X	X	X	X	X	X	X
CBC		X	X		X	X	X	X	X	X	X	X
Urinalysis		X	X		X	X	X	X	X	X	X	X
Quantitative bacteriologic urine culture		X	X		X	X	X	X	X	X	X	X
Indirect blood pressure	X	X	X	X	X	X	X	X	X	X	X	X
UPUC		X				X		X		X		X
PTH and ionized calcium			X			X		X		X		X
TT_4		X										
FELV and FIV ELISA		X										
PCV and TPP				X								
TCO_2, SCr, K$^+$, and SUN				X								
TCO_2, SCr, K$^+$, and ALT	X											
Abdominal radiography		X										X

TT_4 = Total thyroxine concentration. TPP = Total plasma protein concentration. SCr = Serum creatinine concentration. ALT = Alanine aminotransferase activity.

Urine samples and analyses—Urine was collected via cystocentesis. Urinalyses were performed with a refractometer for urine specific gravity determinations, commercial reagent strips[k] for chemical determinations, and a standard technique for sediment evaluation. Quantitative aerobic bacteriologic cultures of urine were performed on all urine samples. Urine protein concentration was determined via Coomassie brilliant blue dye precipitation and spectrophotometry.[12] Urine creatinine concentrations were determined by use of an autoanalyzer-based kinetic Jaffe reaction.[13] Urine samples for protein and creatinine determination were stored at 4°C and analyzed within 24 hours of collection.

Blood pressure measurement—All blood pressure determinations were performed in a dedicated room that was not used for any other procedure during the study. Systolic blood pressure measurements were obtained by use of an ultrasonic Doppler monitor[l] and standard techniques.[14]

Management of cats—With the exception of diet, the protocol used to manage CKD was the same for all cats. Likewise, the same protocols were used to manage nonuremic events.

Hypokalemia—In the present study, 9 (20%) of the cats were hypokalemic (serum potassium concentration, < 3.7 mmol/L) on at least 1 visit. Five of these cats (renal diet, n = 3; maintenance diet, 2) were mildly hypokalemic at the time of diet assignment. Treatment was withheld, and serum potassium concentration was reevaluated 1 month after diet assignment to determine whether the new diet had affected the serum potassium concentrations of these cats. The hypokalemia was resolved in all 5 cats at that time. Of the remaining 4 cats, 2 were treated with potassium citrate[m] at a dose of 40 to 75 mg/kg given orally every 12 hours and continued as needed to maintain their potassium concentration ≥ 3.7 mmol/L. The other 2 cats developed hypokalemia coincident with malnutrition secondary to advanced neoplasia.

Hypertension—Seven cats (renal diet, n = 5; maintenance diet, 2) developed hypertension during the 2-year study period. For the purpose of therapeutic intervention in this study, cats were considered to have hypertension if systolic blood pressure was > 175 mm Hg on 3 successive visits during a 2-week time period, if evidence of hypertensive retinopathy was associated with a systolic blood pressure > 175 mm Hg, or if systolic blood pressures exceeded 200 mm Hg. All cats requiring treatment were administered amlodipine besylate[n] PO at 0.625 mg/cat once daily. Response to treatment was determined after 7 to 14 days of administration. Dosage adjustment was not required in any cat.

UTIs—During the study, UTIs were detected in 2 of the 22 cats fed the renal diet. One cat subsequently had 2 reinfections, and the other cat had 2 relapses after the initial diagnosis of UTI. Initial episodes of UTI were treated for 21 days with an appropriate antimicrobial as determined by antimicrobial susceptibility testing. Response to treatment was evaluated via urinalysis and quantitative bacterial culture of urine. Recurrent UTIs were detected via follow-up cultures and were treated with an appropriate antimicrobial.

Metabolic acidosis—Cats with serum TCO_2 concentrations < 11.0 mmol/L were further evaluated by use of venous blood gas analysis. The decision to treat cats with metabolic acidosis was based on blood HCO_3 concentrations. Twelve cats (renal diet, n = 2; maintenance diet, 10) with venous blood HCO_3 concentration < 15.0 mmol/L were treated with potassium citrate (40 to 75 mg/kg [18.2 to 34.1 mg/lb], PO, q 12 h) with the goal of maintaining blood HCO_3 concentration from 15 to 24 mmol/L. Response to treatment was deter-

mined by measurement of venous blood HCO_3 concentrations 10 to 14 days after initiating treatment.

Hyperphosphatemia—Hyperphosphatemia (serum phosphorus concentration > 6.0 mg/dL) was detected in 5 cats (renal diet, n = 2; maintenance diet, 3) during the study. Of these, 1 cat (maintenance diet) had high phosphorus concentration at the time of diet assignment. Treatment of this cat with orally administered phosphorus-binding agents was withheld to determine whether the assigned diet would affect the serum phosphorus concentration. One month after diet assignment, the serum phosphorus concentration had returned to reference range. To maintain serum phosphorus concentration < 6 mg/dL in the other 4 cats, aluminum hydroxide[o] was given orally (50 to 90 mg/kg [22.7 to 40.1 mg/lb], q 12 h).

Diagnosis of uremic crisis—A diagnosis of uremia, a primary end point of the study, was made by 2 clinicians (RH and JL) unaware of the diet history and not involved in patient management. A diagnosis of uremic crisis was established when all 3 of the following criteria were evident: owner's observation of at least 2 clinical signs consistent with uremia, including signs of depression, lethargy, anorexia, vomiting, uriniferous breath odor, or uremic stomatitis; serum creatinine concentration at least 20% > the previously determined value when the patient was without clinical signs; and no plausible alternative explanation for these clinical signs as determined by medical history and physical examination, serum biochemical profile, CBC, urinalysis, abdominal radiography, and indirect blood pressure determinations.

In 1 cat, an extrarenal cause was unequivocally determined to have resulted in an episode of uremia. The cat was trapped outdoors with restricted access to food and water for several days in the winter. After correcting the dehydration with lactated Ringer's solution given parenterally, the serum creatinine concentration was similar to that observed prior to the uremic episode. Therefore, the cat remained in the study.

Management after uremic crisis—Cats that reached the primary end point of the study (eg, uremic crisis) were provided with appropriate medical care but were not reintroduced into the study. However, the commercially available renal diet was fed to all cats after development of a uremic crisis, including all cats that had been previously fed the maintenance diet. In our judgment, continuing to feed an adult maintenance diet after onset of a uremic crisis would be unethical. To minimize bias, an intention-to-treat analysis was used in which uremic cats were evaluated until death or until completion of the study as if they belonged to their initially randomly assigned diet groups.[15]

Causes of illness or death—Based on medical history, physical examination, laboratory results, objective criteria defining uremic crisis, and necropsy results when available, the cause of death or uremic crisis was classified as definitely not renal, possibly renal, probably renal, or definitely renal. Cats classified in the first or second category were considered to have died from a nonrenal event. Cats classified in the third or fourth category were considered to have died from a renal event.

Owner consent for necropsy was requested for all cats that died during the study. After completion of the gross postmortem examination, tissue samples were obtained and stored in neutral-buffered 10% formalin. Paraffin-embedded tissue was sectioned at 4 μm, stained with H&E, and examined via light microscopy.

Statistical analysis—At the time of diet assignment, clinical characteristics (blood and urine analytes, body weight,

and BCS) were compared between the 2 dietary groups by use of an ANOVA parametric test (body weight, Hct, calcium, phosphorus, potassium, and chloride) or a Mann-Whitney nonparametric test (BCS, SUN, creatinine, HCO_3, PTH, and UPUC), depending on whether the variable passed normality and equal variance testing.[15,16]

Means of BCS, body weights, Hcts, UPUCs, blood HCO_3, SUN, creatinine, calcium, phosphorus, potassium, and chloride were compared between the 2 diet groups during 12- and 24-month intervals. Because of differences related to dates of enrollment and deaths, it was not possible to collect data from all cats at the intervals specified by the study design. To permit comparison between groups with incomplete data at the 12- and 24-month intervals, the mixed-model procedure for analysis of repeated measures was used.[17] The repeated-measures analysis appropriately accounts for the correlation between repeated observations. Intention-to-treat analysis was used for all comparisons.[15]

Kaplan-Meier estimates of the distribution of times from baseline to uremic crisis or death were computed, and log-rank analysis (Mantel-Cox) was performed to compare the survival curves between the groups.[18] In addition, the Cox proportional hazard regression model was used to evaluate the association between diet and relative risk of development of uremic crises.[19] Relative risk reduction was calculated by computing $(1 - \text{relative risk}) \times 100\%$. For all comparisons, $P < 0.05$ was considered significant.

Results

Clinical findings—Forty-five cats met all eligibility criteria and were accepted for study. The treatment group consisted of 22 cats fed the renal diet, and the control group consisted of 23 cats fed the maintenance diet. Fourteen neutered males were in the maintenance diet group, and 8 were in the renal diet group. Nine spayed females were in the maintenance diet group, and 14 were in the renal diet group. The renal diet group consisted of 16 cats with stage 2 CKD and 6 cats with stage 3 CKD, whereas the maintenance diet group consisted of 17 cats with stage 2 CKD and 6 cats with stage 3 CKD.

At the time of diet assignment, all cats had stage 2 or 3 CKD for a minimum of 11 weeks. At that time, there were no significant differences in clinical characteristics (age, weight, BCS, and systolic blood pressure) between the 2 groups (Table 3). Mean values for CBC and serum biochemical analytes were within the

University of Minnesota Veterinary Medical Center reference range for each group, with the exception of SUN, creatinine, and serum PTH concentrations. With 2 exceptions, there were no significant differences between groups in serum, urine, and blood biochemical measurements. Significantly higher blood HCO_3 concentrations were observed in the renal diet group, compared with the maintenance diet group. However, mean blood HCO_3 concentrations in both groups were within the laboratory's reference range. Significantly higher SUN concentrations were observed in the maintenance diet group, compared with the renal diet group. However, there was no difference in magnitude of high mean serum creatinine concentration in both groups. Because of differences in SUN and HCO_3 at baseline, covariance analysis was used to evaluate adjusted means for equal values at baseline at each interval (6, 12, 18, and 24 months). The results of this covariance analysis did not change the conclusions; therefore, only the baseline data and repeated-measures analysis for the 12- and 24-month intervals are reported.

At the time of diet assignment, nephroliths were detected in 13 (renal diet, n = 8; maintenance diet, 5) of the 45 cats via survey abdominal radiographs. Results of ELISA tests for FIV and FeLV were negative. Serum thyroid hormone concentrations were within reference range (2 to 4 μg/dL) for all 45 cats.

Feeding protocol—Throughout the study, the method of feeding did not differ between groups; 26 cats (renal diet, n = 15; maintenance diet, 11) were fed meals, 12 cats (renal diet, 4; maintenance diet, 8) were fed free choice, and 7 cats (renal diet, 3; maintenance diet, 4) were fed meals of canned food in combination with free-choice dry food. Likewise, the type of food consumed did not differ between groups; 5 cats (renal diet, n = 3; maintenance diet, 2) consumed canned food, 22 cats (renal diet, 10; maintenance diet, 21) consumed dry food, and 18 cats (renal diet, 9; maintenance diet, 9) consumed a combination of dry and canned food. Three cats (renal diet, n = 2; maintenance diet, 1) were frequently (> 50% of the time) given a small amount (< 5 mL/meal) of low-sodium chicken broth or tuna juice mixed with their meal to encourage intake. One cat (renal diet) was given small amounts

Table 3—Mean ± SE values for hematologic, serum, and urinary analytes obtained at diet assignment and during 12- and 24-month intervals in cats with spontaneous CKD that were fed a renal diet (n = 22) or a maintenance diet (23).

Variable	Reference range	Diet assignment			12-month interval			24-month interval		
		Renal	Maintenance	P value	Renal	Maintenance	P value	Renal	Maintenance	P value
BCS	NA	3.2 ± 0.1	3.1 ± 0.1	0.67	3.2 ± 0.1	3.2 ± 0.1	0.82	3.1 ± 0.1	3.3 ± 0.1	0.37
Body weight (kg)	NA	4.2 ± 0.2	4.2 ± 0.2	0.92	4.1 ± 0.2	4.3 ± 0.2	0.49	4.0 ± 0.2	4.3 ± 0.2	0.39
Hct (%)	26–42	34.2 ± 0.8	32.3 ± 0.9	0.13	34.3 ± 0.9	32.7 ± 0.9	0.20	34.3 ± 0.8	32.9 ± 0.9	0.22
SUN (mg/dL)	14–33	40.9 ± 2.3	49.1 ± 2.2	0.009	38.9 ± 2.2	50.8 ± 2.1	< 0.001	40.1 ± 2.3	52.2 ± 2.3	< 0.001
Creatinine (mg/dL)	0.6–1.4	2.5 ± 0.1	2.9 ± 0.2	0.09	2.6 ± 0.1	2.9 ± 0.1	0.08	2.7 ± 0.1	3.1 ± 0.2	0.08
HCO_3 (mmol/L)	17–26	19.7 ± 0.4	17.5 ± 0.6	0.009	19.8 ± 0.5	16.9 ± 0.5	< 0.001	19.7 ± 0.4	16.8 ± 0.4	< 0.001
Calcium (mg/dL)	8.9–11.3	10.0 ± 0.1	9.9 ± 0.1	0.40	10.2 ± 0.1	10.0 ± 0.1	0.26	10.3 ± 0.1	10.1 ± 0.1	0.17
Phosphorus (mg/dL)	3.8–8.2	3.8 ± 0.2	4.0 ± 0.2	0.40	3.8 ± 0.1	4.2 ± 0.1	0.04	3.8 ± 0.2	4.4 ± 0.2	0.02
PTH (pmol/L)	0–4	7.0 ± 1.7	5.2 ± 0.9	0.98	6.0 ± 1.0	4.9 ± 1.0	0.45	5.1 ± 0.8	5.5 ± 0.8	0.74
Potassium (mmol/L)	3.9–5.3	4.2 ± 0.1	4.3 ± 0.1	0.51	4.3 ± 0.1	4.2 ± 0.1	0.35	4.3 ± 0.1	4.2 ± 0.1	0.68
Chloride (mmol/L)	117–128	123.3 ± 0.6	124.6 ± 0.6	0.12	122.7 ± 0.4	124.2 ± 0.4	0.009	121.9 ± 0.4	123.3 ± 0.4	0.01
UPUC	< 0.5	0.13 ± 0.17	0.17 ± 0.14	0.17	0.16 ± 0.04	0.22 ± 0.04	0.27	0.21 ± 0.04	0.26 ± 0.04	0.38

NA = Not applicable. To convert kilograms to pounds, multiply by 2.2.

(< 1 tsp/meal) of a commercially available canned adult maintenance diet to enhance intake.

Cats were considered to be compliant if > 85% of their daily caloric requirement was supplied by the assigned diet. Dietary compliance was excellent throughout the study; only 4 cats were noncompliant. In the renal diet group, 2 cats stopped eating their assigned diet, 1 at 6 months with a presumptive diagnosis of feline infectious peritonitis and 1 at 21 months after diagnosis of renal carcinosarcoma. Both cats were subsequently offered a variety of commercially available adult maintenance foods in combination with various human foods to encourage intake. Neither cat had a uremic crisis or died from renal-related causes. In the maintenance diet group, 2 cats stopped eating their assigned diet, 1 at 6 months, after a diagnosis of systemic mast cell tumor, and 1 at 18 months, after 2 months of progressive inappetance and weight loss that stabilized when diet was changed to a commercially available canned adult maintenance diet. Neither cat had a uremic crisis or died from renal-related causes. Because of the analysis used in this clinical trial (ie, intention-to-treat), for the duration of the study, these cats were evaluated as if they belonged to their initial randomly assigned diet group.

Association between diets and clinical and biochemical characteristics—Clinical (systolic blood pressure, body weight, and BCS) and biochemical characteristics of the 2 groups were compared during the 12- and the 24-months intervals (**Table 3**). Serum urea nitrogen concentrations were significantly lower and blood HCO_3 concentrations were significantly higher in the renal diet group during the 12- and 24-month intervals. Serum chloride and phosphorus concentrations were
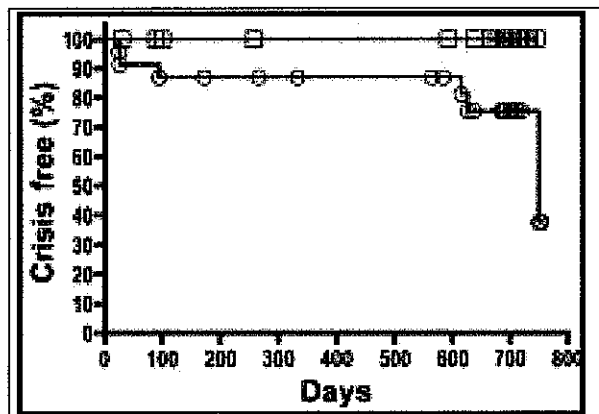

Figure 1—Kaplan-Meier analysis of development of a uremic crisis in cats with spontaneous CKD fed a renal diet (squares; n = 22) or a maintenance diet (circles; 23).

significantly lower in the renal diet group during the 12- and 24-month intervals, but remained within the laboratory reference range for each group. Significant differences were not detected in serum creatinine, albumin, cholesterol, sodium, potassium, calcium, ionized calcium, or PTH concentrations. Likewise, there were no differences between groups for systolic blood pressure, body weight, BCS, or UPUCs.

Association between diets and uremic crisis—At the conclusion of the study, none of the cats in the renal diet group had developed uremic episodes, whereas uremic episodes developed in 6 (26%) cats in the maintenance diet group (**Figure 1**). Feeding the renal diet was associated with a relative risk reduction of 99.99%, compared with feeding the maintenance diet (**Table 4**).

Of the 6 cats that developed uremic crises, 3 responded poorly to treatment and were euthanized at the owners' request 2, 10, and 40 days, respectively, after the onset of crisis. The remaining 3 cats were euthanized 97, 310, and 612 days, respectively, after the initial uremic crisis because of progressive uremia.

Association between diets and death—Kaplan-Meier analysis revealed a significant difference between groups in renal-related deaths (**Figure 2**) but not for all causes of death (**Figure 3**). When the influence of diets on mortality rate related to kidney disease was evaluated, a relative risk reduction of 99.99% was detected in the renal diet group, compared with the maintenance diet group (Table 4). At the conclusion of the study, 5 (21.7%) cats in the maintenance diet group had died from renal causes; there were no renal-related deaths in the renal diet group. Nonrenal causes of death or euthanasia in the renal diet group included feline infectious peritonitis (n = 1), hit by car (1), and renal carcinosarcoma (1). In the maintenance diet group, causes of nonrenal death included splenic round-cell neoplasia (n = 1), systemic mast cell tumor (1), and lymphosarcoma (2). The cause of death in 1 cat was not determined. Nonrenal causes of death did not differ significantly between the renal diet (13.6%) and the maintenance diet group (21.7%; Table 4).

When the influence of diet on all causes of death was evaluated by use of the Cox proportional hazards model, a relative risk reduction of 44.0% was detected in the renal diet group, compared with the maintenance diet group. At the conclusion of the study, 13.6% of cats (n = 3) in the renal diet group had died. During the same interval, 43.5% of the cats (n = 10) assigned to the maintenance diet group had died.

In summary, of the 45 cats, 30 cats (renal diet, n = 18; maintenance diet, 12) completed the 24-month

Table 4—Proportions (number of affected cats/number of cats per group [%]) and relative risk (RR) of uremic crisis or death in cats with spontaneous CKD that were fed a renal diet or a maintenance diet.

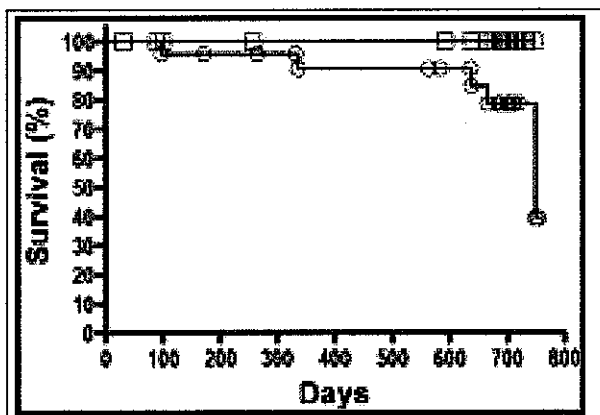| Event	Renal diet	Maintenance diet	P value	RR	95% CI
Uremic crisis	0/22 (0)	6/23 (26.1)	0.02	< 0.001	0–0.63
Renal-related death	0/22 (0)	5/23 (21.7)	0.03	< 0.001	0–0.72
All causes of death	3/22 (13.6)	10/23 (43.5)	0.07	0.56	0.27–1.02
Nonrenal-related death	3/22 (13.6)	5/23 (21.7)	0.51	0.79	0.36–1.59

CI = Confidence interval.

Figure 2—Kaplan-Meier analysis of death from renal causes in cats with spontaneous CKD fed a renal diet (squares; n = 22) or a maintenance diet (circles; 23).
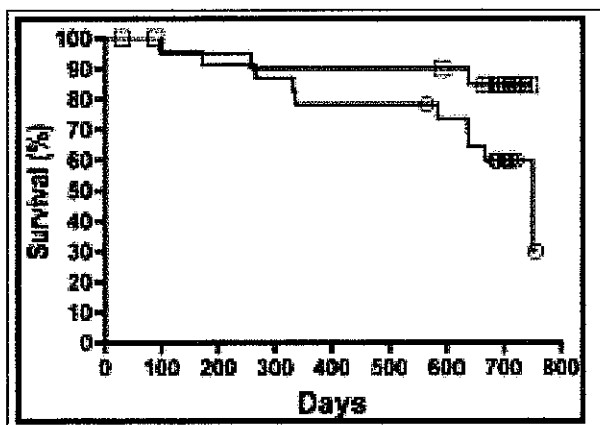

Figure 3—Kaplan-Meier analysis of death from all causes in cats with spontaneous CKD fed a renal diet (squares; n = 22) or a maintenance diet (circles; 23).

study, 13 cats (renal diet, 3; maintenance diet, 10) died during the study, and 2 cats (renal diet, 1; maintenance diet, 1) were lost to follow-up.

Necropsy results were available for 9 (renal diet, n = 1; maintenance diet, 8) of the 13 (renal diet, 3; maintenance diet, 10) cats that died during the 2-year study period. In 1 cat fed the renal diet, a renal neoplasm was detected 18 months after diet assignment. Necropsy performed 21 months after diet assignment revealed a carcinosarcoma. Of the 8 necropsies available for cats fed maintenance diet, 4 were performed in cats that had developed a uremic crisis. In all 4 cats, microscopic evaluation of the kidneys revealed marked, lymphoplasmacytic nephritis and marked interstitial fibrosis. There was no evidence of an inciting cause (eg, ureteral obstruction, pyelonephritis, or acute tubular necrosis) for the acute decompensation of renal function observed in these cats. Four cats fed the maintenance diet were euthanized because of advanced neoplasia. Similar lesions were observed in their kidneys.

Progression of renal dysfunction—Serum creatinine concentrations were not significantly different between groups at the beginning of the study, and the magnitude of decline in reciprocal of serum creatinine

concentration in the maintenance diet group did not differ significantly from that of the renal diet group.

Discussion

Results of the present study supported the hypothesis that feeding a diet specifically designed for treatment of cats with kidney disease was superior to an adult maintenance diet in minimizing uremic episodes and mortality rate in cats with stage 2 or 3, nonproteinuric, nonhypertensive, spontaneous CKD. In 23 cats fed the maintenance diet, there were 6 uremic episodes (26.1%) and 5 renal-related deaths (21.7%), whereas no uremic episodes or renal-related deaths occurred in 22 cats fed the renal diet. Beneficial effects of the renal diet were similar to those reported in another dietary clinical trial of cats with spontaneous CKD.[10] In that study, renal-related mortality rate in 29 cats fed a diet restricted in protein and phosphorus was approximately 33%, compared with 52% in 21 cats fed an unrestricted diet.

Criteria for timing of dietary intervention in cats with spontaneous CKD have previously been based on empirical observations. Presently, there is little debate that when clinical signs of uremia accompany azotemia, dietary modifications such as protein and phosphorus restriction are beneficial.[19-21] However, a general consensus of opinion does not exist as to when dietary intervention is warranted in cats with clinically stable CKD. A cited guideline has been to initiate protein restriction when SUN concentration exceeds 75 mg/dL.[20] One investigator recommended a staged approach in which dietary phosphorus restriction is implemented in cats with azotemia (serum creatinine concentration, 2.4 to 4.0 mg/dL or SUN concentration, 25 to 80 mg/dL) without clinical signs of uremia.[20] When clinical signs attributable to uremic toxins accompany the azotemia (ie, serum creatinine concentration > 4.0 mg/dL or SUN concentration > 80 mg/dL), phosphorus restriction is combined with protein restriction. Results of our study indicated that a renal diet (characterized by reduced quantities of phosphorus, protein, and sodium and supplemental omega-3 PUFAs) was beneficial in management of stage 2 and 3 CKD in cats. The data supported the recommendation for dietary intervention when the serum creatinine concentration exceeds 2.0 mg/dL.

A slowly progressive decrease in glomerular filtration rate indicated by a gradual increase in serum creatinine concentration was not a characteristic finding in the cats of our study. In the 6 cats that developed uremic crises, abrupt increases (43% to 371%) in serum creatinine concentrations were preceded by 3- to 21-month periods of stable serum creatinine concentrations. Of the 6 cats that developed uremic crises, radiographic evidence of nephroliths was documented in 2 of 6 cats prior to the onset of uremic crisis. Ureteroliths were not detected at necropsy of either cat. The nephroliths in 1 cat were composed of calcium oxalate; nephroliths in the other cat were composed of calcium phosphate. Nephrolioths or ureteroliths were not detected by necropsy (2 cats) or ultrasonography and survey radiography (2) in the remaining 4 cats.

In all 6 cats that developed uremic crises, abrupt increases in serum creatinine concentrations coincided

with the appearance of clinical signs typical of uremia (ie, vomiting, anorexia, dehydration, and signs of depression). Comparison of results obtained during scheduled trimonthly evaluations of the history, physical examination, CBC, urinalysis, and serum biochemical profile of the 6 cats that developed uremic crises with comparable data from the 39 cats that did not develop uremic crises revealed no trends that would allow us to reliably predict which cats were at the greatest risk of developing uremic crises and, therefore, would have been most likely to benefit from dietary modification. Because the results indicated that the renal diet delayed uremic crises and death, we recommend that renal diets be initiated for all cats with stage 2 or 3 CKD.

With the exception of the 6 cats in the maintenance diet group that developed uremic crises, significant differences in the serum creatinine concentrations of cats fed the renal diet or maintenance diet were not observed during the 24 months they were included in the study. Because 17 cats fed the maintenance diet did not develop uremic crises during the 24-month study, an alternative recommendation would be to initiate administration of the renal diet after the onset of uremic crises. However, only 3 of 6 cats in the maintenance diet group that developed uremic crises survived. In addition, increased serum creatinine concentrations were sustained following the onset of uremic crises. Furthermore, after these 3 cats were withdrawn from the study, long-term supportive treatment with orally administered phosphorus binders, potassium citrate, parenteral fluids, and a commercial renal diet was required to minimize fluid, electrolyte and acid-base deficits, and excesses. These observations support the recommendation of initiating treatment of cats with CKD with a renal diet prior to the onset of uremic crisis.

There are several possible explanations why significant differences in serum creatinine concentration were not observed in cats fed the renal diet and cats fed the maintenance diet prior to the onset of uremic crisis. It has been well established that renal structural lesions may progress without apparent functional correlates.[22] It has also been suggested that development of renal lesions may be a more sensitive indicator of kidney disease than measurement of glomerular filtration rate.[23] This apparent discrepancy between structure and function has been observed in experimental models of CKD in cats.[7,8] It is possible that differences in progressive renal lesions developed between the diet groups reported here and were responsible for the differences in outcomes between the diet groups; however, the design of the study precluded confirmation of this effect. Furthermore, the pattern of progression of CKD in cats has not been well described. Although dogs typically have a pattern of progressive increases in serum creatinine concentration,[23] it has been our experience in cats that abrupt changes in renal function may or may not result in clinical decompensation. In the study reported here, the interval between the previous determination of serum creatinine concentrations and onset of uremic crisis varied from 3 weeks to 3 months. As a consequence, rapid changes in renal function during these intervals may have been missed because, at least initially, they may not have been accompanied by alterations

in clinically detectable manifestations of CKD. An additional possibility is that biochemical effects of the diet altered the risk profile for uremia in cats in the 2 diet groups in a fashion favoring the renal diet. For example, the lower protein and phosphorus content of the renal diet may have helped reduce the risk for development of uremia. Such a benefit has been reported in a study[24] in humans and rodents.

A criticism of the present study is that at the time of diet assignment, significantly higher blood HCO_3 concentrations were observed in the renal diet group, compared with the maintenance diet group. Acidosis has been incriminated as a contributing factor in the pathophysiology of uremia in cats, dogs, and humans.[21,25,b] However, in the present study, mean blood HCO_3 concentrations in both groups were within reference range. The difference between mean blood HCO_3 concentrations of the 2 groups remained significant at baseline even when the 6 cats that subsequently developed uremic crises were removed from the analysis. In addition, in a controlled diet study[b] of 15 cats with induced renal dysfunction (mean serum creatinine concentration, 2.14 mg/dL) comparable to that of the cats in our study (mean serum creatinine concentration, 2.72 mg/dL), blood HCO_3 concentrations of 18.6 ± 1.0 mmol/L associated with consumption of an acidifying diet for 10 months were not associated with significant changes in renal function or histologic features.

Another criticism of the present study is that at the time of diet assignment, significantly higher SUN concentrations were observed in the maintenance diet group, compared with the renal diet group. This observation prompts the question as to whether the difference in occurrence of uremic crises in the 2 groups was related to a greater magnitude of renal dysfunction in the maintenance group at the time of diet assignment. Although this was possible, several lines of evidence did not support this conclusion. First, there were no significant differences in the magnitude of serum creatinine concentrations between the maintenance diet and renal diet group. There is a consensus that serum creatinine concentration is a more reliable index of glomerular filtration rate than is urea nitrogen concentration.[26] Second, if one accepts the premise that the magnitude of renal dysfunction was greater in the maintenance diet group than in the renal diet group prior to diet assignment, then one would predict that, irrespective of diet assignment, the frequency of uremic crises would be directly proportional to the magnitude of SUN concentration. After completion of this study, we tested this hypothesis by allocating cats into 2 groups on the basis of their SUN concentration values at the time of diet assignment. One group contained 21 cats with SUN concentrations greater than the overall mean concentration of 45 mg/dL, and 1 group contained 24 cats with SUN concentrations less than the mean concentration. Kaplan-Meier analysis of the effect of baseline SUN (regardless of diet) on time to uremic crisis ($P = 0.37$) and renal-related death ($P = 0.10$) did not reveal any significant differences between the 2 groups. A third line of evidence that did not support important differences in the magnitude of renal dysfunction between the 2 groups prior to diet assign-

ment was the observation that there was not a significant group difference between the number of cats with stage 2 versus stage 3 CKD.

The present study was designed to evaluate the composite effects of modifications of several dietary components in cats with spontaneous CKD. The design did not permit attribution of differences to individual nutrients. Unfortunately, testing differences in each nutrient by means of randomized clinical trials is expensive and time-consuming. In our opinion, it was reasonable and more efficient to evaluate the composite diet effect initially, and if significant effects were detected, individual dietary components could be evaluated in subsequent studies.

Results of this study were consistent with results of other studies designed to evaluate the influence of specific dietary components on the progression of induced kidney disease in cats. For example, reduction of dietary phosphorus in cats with induced kidney disease reduced the severity of renal lesions that developed during a 1-year study interval.[7] A nonrandomized, open clinical trial of cats with naturally occurring kidney disease revealed beneficial effects of dietary protein and phosphorus restriction on quality and quantity of life.[10] The findings of Finco et al[8] indicated that cats with induced renal disease fed restricted calories, regardless of protein concentration, had less severe renal lesions at the end of 1 year, compared with cats fed diets that were not restricted. These findings emphasize the value of considering individual dietary components in the overall assessment of the benefits of dietary therapy. Individually or in combination, similar dietary modifications in the present study may have minimized the number of uremic crises and mortality rate.

References

1. Lulich JP, Osborne CA, O'Brien TD, et al. Feline renal failure: questions, answers, questions. *Compend Contin Educ Pract Vet* 1992;14:127–152.
2. Churchill J, Polzin D, Osborne C, et al. The influence of dietary protein intake on progression of chronic renal failure. *Semin Vet Med Surg (Small Anim)* 1992;7:244–250.
3. Polzin DJ, Osborne CA, Ross SJ. Chronic renal failure. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 6th ed. Philadelphia: WB Saunders Co, 2005;1756–1785.
4. Elliott J, Syme HM, Reubens E, et al. Assessment of acid-base status of cats with naturally occurring chronic renal failure. *J Small Anim Pract* 2003;44:65–70.
5. Elliott J, Syme HM, Markwell PJ. Acid-base balance of cats with chronic renal failure: effect of deterioration in renal function. *J Small Anim Pract* 2003;44:261–268.
6. Syme H, Barber P, Markwell P, et al. Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation. *J Am Vet Med Assoc* 2002;220:1799–1804.
7. Ross LA, Finco DR, Crowell WA. Effect of dietary phosphate restriction on the kidneys of cats with reduced renal mass. *Am J Vet Res* 1982;43:1023–1026.
8. Adams LG, Polzin DJ, Osborne CA, et al. Effects of dietary protein and calorie restriction in clinically normal cats and in cats with surgically induced chronic renal failure. *Am J Vet Res* 1993;54: 1653–1662.
9. Finco DR, Brown SA, Brown CA, et al. Protein and calorie effects on progression of induced chronic renal failure in cats. *Am J Vet Res* 1998;59:575–582.
10. Elliott J, Rawlings JM, Markwell PJ, et al. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. *J Small Anim Pract* 2000;41:235–242.
11. Debrackeleer J. Appendix D. In: Hand MS, Thatcher CD, Remillard RL, et al, eds. *Small animal clinical nutrition*. 4th ed. Marceline, Mo: Walsworth Publishing Co, 2000;1010.
12. Lott JA, Stephan VA, Pritchard KA. Evaluation of the Coomassie Brilliant Blue G-250 method for urinary protein. *Clin Chem* 1983;29:1946–1950.
13. Cannon DC. Kidney function test. In: Henry RJ, Cannon DC, Winkelman JW, eds. *Clinical chemistry*. 2nd ed. Hargerstown, Md: Harper & Row, 1974;1535–1554.
14. Grady JL, Dunlop CI, Hodgson DS, et al. Evaluation of the Doppler ultrasonic method of measuring systolic arterial blood pressure in cats. *Am J Vet Res* 1992;53:1166–1169.
15. Motulsky H. Comparing two means: the randomization and Mann-Whitney test. In: *Intuitive biostatistics*. New York: Oxford University Press, 1995;217–224.
16. Pallant J. *SPSS survival manual*. Berkshire, UK: McGraw-Hill Education, 2001;209–216.
17. *SAS/STAT user's guide: version 8*. Cary, NC: SAS Institute Inc, 1999;3884.
18. Kleinbaum DG. *Survival analysis: a self-learning text*. New York: Springer-Verlag Inc, 1996;46–211.
19. Finco DR. Nutrition and treatment of renal disease, in *Proceedings*. 21st Annu Meet Am Coll Vet Intern Med Forum 2003;9–10.
20. Brown SA. Evaluation of chronic renal disease: a staged approach. *Compend Contin Educ Pract Vet* 1999;21:752–763.
21. Burkholder WJ. Dietary considerations for dogs and cats with renal disease. *J Am Vet Med Assoc* 2000;216:1730–1734.
22. Bourgoignie JJ, Gavellas G, Martinez E, et al. Glomerular function and morphology after renal mass reduction in dogs. *J Lab Clin Med* 1987;109:380–388.
23. Finco DR, Brown SA, Brown CA, et al. Progression of chronic renal disease in the dog. *J Vet Intern Med* 1999;13: 516–528.
24. Mitch WE. Beneficial responses to modified diets in treating patients with chronic kidney disease. *Kidney Int Suppl* 2005;94: S133–S135.
25. Uribarri J. Acidosis in chronic renal insufficiency. *Semin Dial* 2000;13:232–234.
26. Finco DR. Evaluation of renal functions. In: Osborne CA, Finco DR, eds. *Canine and feline nephrology and urology*. Media, State: The Williams & Wilkins Co, 1995;216–229.