In cats, hyperthyroidism is most commonly caused by autonomously functioning thyroid gland adenomas and is clinically and histologically similar to toxic nodular goiter in humans. In elderly humans, a mild to moderate lifetime deficiency of iodine increases the risk of thyroid gland autonomy and toxic nodular goiter. Hyperthyroidism in cats is hypothesized to be caused by the same mechanism as that proposed for the development of toxic nodular goiter in humans in that a mild to moderate iodine deficiency decreases production of T4 by the thyroid gland, which causes a reciprocal increase in the release of TSH through hypothalamic-pituitary gland feedback. This increase in the amount of circulating TSH increases the efficiency of iodine utilization by thyrocytes, allowing the serum T4 concentration to remain within reference limits.

Objective—To compare concentrations of urinary iodide (UI) in euthyroid and untreated hyperthyroid cats.

Animals—118 euthyroid and 88 hyperthyroid client-owned cats from 2 nonreferral veterinary practices.

Procedures—Iodide concentration was measured in 5 urine samples collected every 3 to 12 months from selected cats, and variability of results between euthyroid cats and hyperthyroid cats prior to the diagnosis of hyperthyroidism was evaluated via 1-way ANOVA, after logarithmic transformation of UI concentrations (logUIs). The UI concentration in hyperthyroid cats was measured at diagnosis and 2 to 6 weeks and 3 to 6 months after treatment for hyperthyroidism. The pretreatment logUI in hyperthyroid cats was compared with that in euthyroid cats, taking into account the effects of renal function on UI concentration. Iodine intake was estimated in euthyroid cats following calculation of the volume of daily urine output, with a fixed value for iodine concentration in feces.

Results—The variability of UI concentrations did not differ significantly between hyperthyroid (n = 10) and euthyroid (8) cats. The logUI increased 2 to 6 weeks after initiation of treatment in hyperthyroid cats (n = 80) and was lower in azotemic versus nonazotemic cats. Hyperthyroid cats had a lower logUI than euthyroid cats, and there was no evidence of deficient iodine intake in euthyroid cats.

Conclusions and Clinical Relevance—The logUI was lower in cats with azotemia and with untreated hyperthyroidism, compared with that in euthyroid cats from the same population. Additional studies are needed to determine whether iodine intake plays a role in the development of hyperthyroidism in cats. (Am J Vet Res 2009;70:741–749)

**Urinary iodide concentration in hyperthyroid cats**

Jennifer Wakeling, VetMB, PhD; Jonathan Elliott, VetMB, PhD; Aviva Petrie, MS; David Brodbelt, VetMB, PhD; Harriet M. Syme, BVetMed, PhD

**Objective**—To compare concentrations of urinary iodide (UI) in euthyroid and untreated hyperthyroid cats.

**Animals**—118 euthyroid and 88 hyperthyroid client-owned cats from 2 nonreferral veterinary practices.

**Procedures**—Iodide concentration was measured in 5 urine samples collected every 3 to 12 months from selected cats, and variability of results between euthyroid cats and hyperthyroid cats prior to the diagnosis of hyperthyroidism was evaluated via 1-way ANOVA, after logarithmic transformation of UI concentrations (logUIs). The UI concentration in hyperthyroid cats was measured at diagnosis and 2 to 6 weeks and 3 to 6 months after treatment for hyperthyroidism. The pretreatment logUI in hyperthyroid cats was compared with that in euthyroid cats, taking into account the effects of renal function on UI concentration. Iodine intake was estimated in euthyroid cats following calculation of the volume of daily urine output, with a fixed value for iodine concentration in feces.

**Results**—The variability of UI concentrations did not differ significantly between hyperthyroid (n = 10) and euthyroid (8) cats. The logUI increased 2 to 6 weeks after initiation of treatment in hyperthyroid cats (n = 80) and was lower in azotemic versus nonazotemic cats. Hyperthyroid cats had a lower logUI than euthyroid cats, and there was no evidence of deficient iodine intake in euthyroid cats.

**Conclusions and Clinical Relevance**—The logUI was lower in cats with azotemia and with untreated hyperthyroidism, compared with that in euthyroid cats from the same population. Additional studies are needed to determine whether iodine intake plays a role in the development of hyperthyroidism in cats. (Am J Vet Res 2009;70:741–749)
iodine intake, and the amount of fecal iodine excretion. In healthy cats, the UI concentration of a urine sample accurately reflects the amount of recent intestinal excretion. In contrast, rats with chronically high dietary intake of iodine have an increased risk of developing adenomatous thyroid gland changes, compared with rats fed lower amounts of iodine.

In cats, it is therefore possible that a lifetime deficiency or excess of iodine could cause adenomatous changes in thyroid glands as cats mature. An association between the ingestion of canned food and the development of hyperthyroidism has been repeatedly detected in cats. Some canned cat foods contain excessive or deficient iodine concentrations, with a wide range of iodine concentrations reported. In adult humans, a dietary intake of 100 to 200 µg of iodine/d is recommended, and there is evidence of an increased risk of thyroid gland disease with long-term intake of iodine higher or less than this limited range.

Some dietary iodine supplementation programs in geographic regions of iodine deficiency have triggered hyperthyroidism in elderly humans with non-toxic nodular goiter. This form of iodine-induced hyperthyroidism is limited to those humans with preexisting, autonomously functioning nodules that are highly capable of converting iodine to thyroid gland hormones and that are not susceptible to the Wolff-Chaikoff effect. In addition, a study of Moroccan children before an iodine supplementation program was introduced and 1 year after the program was stopped revealed that hypothyroidism was more prevalent after than before the supplementation program. The increase in prevalence took place despite a similar degree of iodine deficiency prior to and after the program. This finding suggests that the thyroid gland is able to sustain thyroid gland hormone production better when the dietary intake of iodine is constantly suboptimal as opposed to when intake varies between suboptimal and optimal. Therefore, it is also possible that highly variable iodine intake could contribute to the development of hyperthyroidism in cats. Cats that consume various flavors of wet cat food reportedly have an increased risk of developing hyperthyroidism, compared with those that consume only 1 flavor.

Direct interactions between changes in dietary intake of iodine and serum concentrations of thyroid gland hormones in cats have been reported. Two studies involving cats revealed decreases in serum free and total T4 concentrations after short-term (1- to 2-week) increases in iodine intake, and the decrease in serum T4 concentration was proportionate to the amount of iodine consumed. However, a third study revealed no significant difference in free T4 concentrations between cats fed a diet high in iodine versus those fed a diet low in iodine for a 3-month period. Iodine is primarily removed from the body by renal excretion. In healthy cats, the UI concentration of a urine sample accurately reflects the amount of recent iodine intake, and the amount of fecal iodine excretion is constant in relation to body weight. Therefore, the UI concentration can be used to estimate dietary iodine intake in healthy cats.

In humans, CKD results in a marked decrease in renal clearance of iodide, with a concurrent increase in serum inorganic iodide concentration in humans with end-stage renal disease. Accumulation of iodide in the body happens despite a decrease in dietary intake (attributable to decreased appetite) and is persistent even after several weeks of restricting the amount of iodide consumed. Although it is uncommon for cats to be azotemic when hyperthyroidism is diagnosed, CKD is commonly diagnosed in hyperthyroid cats after treatment for hyperthyroidism. Hyperthyroidism hides the biochemical signs of renal disease by increasing the glomerular filtration rate and decreasing muscle mass, thus lowering the plasma creatinine concentration in affected cats. In most cats that develop CKD in the months after successful treatment for hyperthyroidism, it is likely that renal disease already existed when hyperthyroidism was diagnosed.

To the authors’ knowledge, the relationship between UI concentration and dietary iodine intake has not been evaluated in hyperthyroid cats. Physiologic changes associated with hyperthyroidism, such as an increase in fecal volume, a decrease in gastrointestinal transit time, and renal disease, may alter the kinetics of iodide excretion by the body such that the UI concentration no longer accurately reflects the degree of iodine intake. In addition, hyperthyroidism causes polyphagia, which might increase the amount of iodine consumed. The purpose of the study reported here was to compare UI concentrations in euthyroid and untreated hyperthyroid cats. Specifically, we sought to compare the variability of UI concentrations in cats prior to the diagnosis of hyperthyroidism with those of euthyroid cats > 8 years old, evaluate the effect of treatment on the UI concentration in hyperthyroid cats, determine the effect of renal disease on UI concentration, and compare UI concentrations in hyperthyroid cats at diagnosis with those of an age-restricted population of euthyroid cats. Another purpose was to estimate daily dietary iodine intake among those euthyroid cats that had a plasma creatinine concentration within the reference range.

Materials and Methods

Animals—The Royal Veterinary College feline research group examines, diagnoses, and treats cats at 2 nonreferral veterinary practices in London. At each visit, historical and clinical data are recorded, and blood and urine samples are collected for routine biochemical analysis and urinalysis. Data collected in these research clinics are recorded in a central database that was used to identify suitable cats for this retrospective study. Included diseased cats had one or more of the following conditions: CKD, hypertension, or hyperthyroidism. Healthy cats > 8 years old that had been evaluated for routine (every 6 to 12 months) health screening were also included. All cats were evaluated between September 1994 and May 2007. The ethics and welfare committee of the Royal Veterinary College approved the diagnostic protocol. Owner consent was obtained prior to sample collection.
Sample collection—Jugular venous blood samples were collected into heparinized tubes. Plasma was separated from the blood cells within 6 hours after collection, for measurement of plasma concentrations of various analytes (total protein, albumin, creatinine, urea nitrogen, bilirubin, cholesterol, potassium, chloride, sodium, calcium, phosphorus, and tT4) and plasma activities of alanine transferase and alkaline phosphatase.

Urine was collected by cystocentesis, and a full urinalysis (USG as measured by refractometry; semiquantitative biochemical urinalysis, and microscopic sediment examination) was performed on the date of collection. Residual urine was centrifuged at 1,000 X g for 10 minutes and the supernatant stored at −80°C until analyzed for UI concentration. The UI analyses were performed in batches between June 2005 and August 2007.

Identification and evaluation of euthyroid cats—Healthy euthyroid cats were identified on the basis of clinical history and results of physical examination and routine laboratory analyses (plasma biochemical analysis, PCV determination, and urinalysis). None of the cats in this category was receiving medication other than antiparasitic drugs. To be classified as euthyroid, cats were required to have values for plasma and free T4 concentrations that were within reference ranges (19 to 55 nmol/L and 19 to 40 pmol/L, respectively) when measured; however, additional criteria were applied that varied according to the plasma creatinine concentration. For the purpose of the study, nonazotemic cats (plasma creatinine concentration ≤ 177 µmol/L) were required to have a plasma T4 concentration < 40 nmol/L, and azotic cats (plasma creatinine concentration > 177 µmol/L) were required to have a plasma T4 concentration < 30 nmol/L. Different inclusion criteria for azotic and nonazotemic cats were used because plasma T4 concentration decreases with some nonthyroidal illnesses, including CKD. Cats with CKD that had T4 measurements in the range of 30 to 55 nmol/L were excluded because azotic cats with a T4 value in this range may have hyperthyroidism.

Identification and evaluation of hyperthyroid cats—Hyperthyroidism was diagnosed in cats on the basis of a plasma T4 concentration that exceeded the upper reference limit (reference range, 19 to 55 nmol/L) or results of a T3 suppression test that exceeded the reference limit (T4 > 25 nmol/L after administration of one 25-µg T3 tablet 3 times/d for 7 doses). Total T4 analyses for most cats, including all hyperthyroid cats and cats with CKD, were processed at 1 commercial laboratory; however, a subset of T4 analyses in euthyroid cats was performed at the Royal Veterinary College laboratory by use of the same methods.

Cats identified with hyperthyroidism were treated with carbimazole (5 mg, q 8 h, for 10 to 21 days), usually with a reduction to twice-daily dosing thereafter, depending on the clinical response. After initiation of treatment, cats were reexamined every 2 to 3 weeks until their condition was considered stable and every 6 to 8 weeks afterward. Some cats subsequently underwent unilateral or bilateral thyroidectomy on the basis of their age, health status, and tolerance of the medication and owner preference. Only successfully treated cats (ie, those with a plasma T4 concentration < 40 nmol/L) were included in the study. For cats that did not tolerate orally administered medication, the treatment start date was considered to be the date of thyroidectomy. Renal function was assessed by measurement of plasma creatinine concentration and USG prior to and after successful treatment of hyperthyroidism.

Identification of cats with CKD—Chronic kidney disease was diagnosed in cats on the basis of clinical signs (eg, polydipsia, polyuria, or vomiting), results of renal palpation (ie, identification of subjectively small or misshapen kidneys), results of full urinalysis and bacteriologic culture of urine (when necessary), plasma electrolyte concentrations, plasma creatinine concentration, plasma urea nitrogen concentration, and PCV. Renal function was assessed in accordance with the staging system of the IRIS. Cats were classified as having normal renal function when the plasma creatinine concentration was < 140 µmol/L. Cats with a plasma creatinine concentration ≥ 140 µmol/L were separated into 2 groups: plasma creatinine concentration from 140 to 177 µmol/L (IRIS category 2a) and plasma creatinine concentration > 177 µmol/L (IRIS category ≥ 2b). For hyperthyroid cats, the IRIS category was based on the mean plasma creatinine concentration after treatment for hyperthyroidism (within 4 months of treatment initiation). For euthyroid cats, the plasma creatinine concentration on the date of urinalysis was used. Cats were considered to have CKD when the plasma creatinine concentration exceeded the upper reference limit (ie, > 177 µmol/L) and the USG was > 1.035. With the exception of hyperthyroid cats after treatment, cats were excluded from the study when the plasma creatinine concentration was > 250 µmol/L at the time of assessment and urinalysis; hence, only cats with a mild degree of CKD were included in the study. Cats with CKD were also excluded when they had received a prescription low-protein renal diet that may have influenced the UI concentration.

Measurement of UI concentration—A modified Sandell-Koltoff method was used to measure UI concentration. Before processing, urine samples were routinely diluted with distilled water (50:50); however, many concentrated samples (ie, USG > 1.050) required greater dilution than this, with the maximum dilution required being 1:19. For the assay, 200 µL of diluted urine was incubated with 0.8 mL of ammonium persulphate at 100°C for 1 hour to remove substances that might interfere with the assay results. Aliquots of the resulting digest (50 µL) were transferred to a 96-well plate and incubated for 30 minutes with 150 µL of arsenious acid and 25 µL of ceric ammonium sulfate. The resulting color change in the sample was determined spectrophotometrically by measuring the change in absorbance at 405 nm.

The assay was validated by measurement of intra-assay and interassay coefficients of variation (n = 10 urine samples/test), determination of the limit of detection, analytic recovery of potassium iodate from feline urine to which it had been added, and dilutional parallelism of urine samples with a high measured iodide concentration. The limit of detection of the assay was
calculated as mean + 1.96 SD of repeated measurements of a blank (distilled water) sample. The UI concentration was normalized to urine concentration, as defined by a USG of 1.010, with a correction factor of (1 – USG) X 100, to yield an index of UI concentration. In a subset of cats, urine creatinine concentrations were available, and the correlation between UI normalized to urine creatinine concentration and UI normalized to solute concentration (USG) was evaluated.

Variability of UI concentration with time
Urinary iodide concentrations were determined in 5 urine samples collected at various time points from euthyroid cats > 8 years of age and from hyperthyroid cats prior to diagnosis and treatment. Urine samples were collected for a minimum period of 12 months (maximum, 6 years). These data were also used in power calculations to determine the number of samples required to detect a difference between hyperthyroid and euthyroid groups in subsequent analyses.

Effect of treatment on UI concentration in hyperthyroid cats
When samples were available, UI concentration was measured in hyperthyroid cats at the time of, or prior to, diagnosis and at 2 to 6 weeks and 3 to 6 months after treatment for hyperthyroidism began. To assess the effect of treatment type on UI concentration, a subgroup of 28 cats that underwent thyroidectomy was identified (9 were treated by surgery alone, 11 were successfully treated with carbimazole prior to surgery, and 8 were unsuccessfully treated with carbimazole prior to surgery). In that subgroup, UI concentration was measured prior to diagnosis and 2 to 8 weeks after surgery.

Comparison of UI concentrations in hyperthyroid and euthyroid cats
Urinary iodide concentration was measured in untreated hyperthyroid cats and was compared with UI concentration in euthyroid cats. Potentially confounding factors such as age, body weight, plasma tT4 concentration, reported appetite, and whether food was withheld from the cat prior to urine collection were also recorded. Cats were considered to have had food withheld prior to sample collection when the owner reported that the cat had not been fed for at least 12 hours. Cats for which withholding of food had not been recorded or cats that were reported to have eaten in the 12 hours before sample collection were classified as not having had food withheld. Appetite was categorized as good or increased or as normal or decreased on the basis of clinical record entries made on the date of cystocentesis. Renal function was assessed as previously described, and euthyroid and hyperthyroid cats were classified in accordance with the IRIS system.

Estimation of iodine intake—Iodine intake was only estimated for nonazotemic euthyroid cats. It was estimated from the UI concentration with the assumption that a typical cat produces 15 mL of urine/kg/d, with a USG of 1.050 and a fixed rate of fecal iodine excretion of 14 mg/kg/d.

Statistical analysis—Statistical analysis was performed by use of a standard statistical package. Data were assessed for normality of distribution graphically and with the Kolmogorov-Smirnov test. Age and body weight were compared between euthyroid and hyperthyroid groups by means of an independent samples t test. Breed and sex were compared with a χ2 test with continuity correction. Data for UI concentration had a right-skewed distribution; therefore, values were logarithmically transformed (logUI). The correlation between the logarithm of UI values normalized to a USG of 1.010 and the logarithm of the ratio of UI concentration to urine creatinine concentration was examined by calculation of the Pearson correlation coefficient. The geometric mean (central 95% range) was used as a summary measure of the distribution of the data. The range containing the central 95% of the data was estimated as the inverse logarithm of (mean logUI ± 1.96 X SD logUI).

For the evaluation of variability in UI concentrations with time for the same cat, a measure of agreement was calculated by use of a separate 1-way ANOVA for data from hyperthyroid and euthyroid cats. In each ANOVA, the 5 logUI measurements from each cat represented a group. The SE of the measurement was multiplied by 2.83 to provide a measure of agreement that estimated the maximum likely difference between 2 UI concentration measurements for the same cat. The data were also examined graphically by means of a Bland-Altman approach in which the mean logUI for each cat was plotted against the associated SD for each cat.

Values of logUI for hyperthyroid cats before treatment were compared with those after treatment by use of a paired t test after confirmation that the differences were normally distributed. Results for that analysis are reported as mean difference (95% CI).

Values of logUI for hyperthyroid cats were compared with those of euthyroid cats by means of 2-way ANOVA, with IRIS category and hyperthyroid status as the 2 factors. The assumptions were verified via examination of the residuals. A value of P < 0.05 was considered significant for all analyses.

Results

Urinary iodide measurement—Interassay and intra-assay coefficients of variation were < 12% over the range of measured concentrations (70 to 591 µg/L), and the recovery of iodide from control samples of known iodide concentrations ranged from 100% to 113%. Mean ± SD apparent iodide concentration of a blank (distilled water) sample evaluated in triplicate was 6.9 ± 4.2 µg/L, with a calculated limit of detection of 15 µg/L. The assay had excellent dilutional parallelism (R2 = 0.999). There was a significant (P < 0.001) correlation between UI concentration normalized to USG and the ratio of UI concentration to urine creatinine concentration (n = 208 samples; R2 = 0.81).

Variability of UI concentration with time—The UI concentration was measured in samples from 18 cats > 8 years old (5 samples/cat; 3- to 12-month intervals between samples). In 10 hyperthyroid cats, UI concen-
Urinary iodide concentration in all cats was highly variable, with variability in UI concentration that exceeded 10-fold in some cats. The geometric mean UI concentration was 280 µg/L (central 95% range, 73 to 1000 µg/L).

Figure 1—Bland-Altman plot of mean and SD logUI in hyperthyroid (circles; n = 10) and euthyroid (asterisks; 8) cats. Each point represents 1 cat, and for each cat, the mean and SD logUI were calculated from measurement of UI concentration in 5 urine samples.

Figure 2—Box-and-whisker plots of the effect of treatment on UI concentration in hyperthyroid cats before treatment for hyperthyroidism (white boxes; 55 azotemic and 32 nonazotemic cats), 2 to 6 weeks after treatment was initiated (light gray boxes; 52 azotemic and 28 nonazotemic cats), and 3 to 6 months after treatment was initiated (dark gray boxes; 21 azotemic and 23 nonazotemic cats). Azotemia was defined as a plasma creatinine concentration > 177 µmol/L after treatment. In hyperthyroid cats with and without azotemia, UI concentrations were significantly (P < 0.001) higher 2 to 6 weeks after treatment but not 3 to 6 months after treatment (P = 0.48), compared with values before treatment. The central box in the plot represents the interquartile range, and the middle line in that box represents the median. Whiskers represent values outside the interquartile range up to a maximum of 1.5 box lengths from the upper and lower edges of the box. If the data were to have a perfect normal distribution, these upper and lower whisker limits would approximately represent the 2.5th and 97.5th percentiles (= 2.04 X SD from the mean). Asterisks represent outlier datum points.

Figure 3—Box-and-whisker plot of the effect of surgery on UI concentration in hyperthyroid cats. The UI concentration prior to treatment (white boxes) and 2 to 8 weeks after surgery (light gray boxes) is represented in each pair of plots. All cats were treated surgically, and groups consisted of those treated with surgery alone (surgery only; n = 9), cats whose hyperthyroidism was controlled with carbimazole prior to surgery (controlled carbimazole; 8), and cats treated unsuccessfully with carbimazole prior to surgery (not controlled carbimazole; 11). In all groups, the UI concentration increased after surgery. See Figure 2 for remainder of key.

Figure 4—Histogram of mean logUI in hyperthyroid and euthyroid cats as classified in accordance with the staging system of the IRIS. Cats were classified as having normal renal function (plasma creatinine concentration < 140 µmol/L; dark gray boxes; 52 euthyroid and 30 hyperthyroid cats), with IRIS category 2a (plasma creatinine concentration from 140 to 177 µmol/L; light gray boxes; 25 euthyroid and 25 hyperthyroid cats) or IRIS category ≥ 2b (plasma creatinine concentration > 177 µmol/L; white boxes; 41 euthyroid and 33 hyperthyroid cats). There was a significant effect of thyroid status (P = 0.002) and renal function (P = 0.001) on UI concentration. Whiskers represent 95% CIs.
1,079 µg/L) for the hyperthyroid cats and 254 µg/L (69 to 929 µg/L) for the euthyroid cats. The Bland–Altman plot of mean versus SD log UI for each cat revealed a lack of a so-called funnel effect, indicating that the SD was independent of the magnitude of the measurement (Figure 1). There was no significant (P = 0.85) difference in mean SD of the log UI values between the 2 groups. There was little difference in the variability of UI concentrations in the prehyperthyroid group. (maximum likely difference in log UI, 0.886) and euthyroid groups (maximum likely difference in log UI, 0.908). Results of power calculations derived from these data suggested that a total sample size of 200 cats would yield, on the basis of a 2-tailed t test, a power of 0.8 to detect a difference in mean log UI between 2 groups (effect size, 0.4; α = 0.05).

Effect of treatment on UI concentration in hyperthyroid cats—Eighty hyperthyroid cats were identified that had been successfully treated with carbimazole, thyroidectomy, or both, and for which there were 2 stored urine samples (1 obtained prior to treatment and 1 obtained 2 to 6 weeks after treatment). The UI concentration was significantly (P < 0.001) higher 2 to 6 weeks after treatment, compared with the value before treatment (mean [95% CI] difference, 109 µg/L [56 to 162 µg/L]), and this difference was apparent in cats with and without evidence of CKD (Figure 2). Urinary iodide concentration in cats with well-controlled hyperthyroidism appeared to return to the pretreatment concentrations by 3 to 6 months after treatment. There was no significant difference (P = 0.46; n = 44) between UI concentrations measured before and 3 to 6 months after treatment (mean [95% CI] difference, 37 µg/L [−59 to 133 µg/L]).

To assess whether the increase in UI concentration after treatment was confined to cats treated with carbimazole, the effect of surgery on UI concentration was examined. Urinary iodide concentration was measured for each cat before treatment and 2 to 8 weeks after surgery (median, 28 days; range, 11 to 52 days; n = 28). The UI concentration increased significantly (P < 0.001) after surgery, compared with the value before treatment (mean difference, 233 µg/L [147 to 319 µg/L]). This change was evident in cats treated with surgery alone (P = 0.02; 9) and even in cats in which hyperthyroidism had been controlled with carbimazole prior to surgery (P = 0.04; 11; Figure 3).

Comparison of UI concentrations in hyperthyroid and euthyroid cats—Urinary iodide concentration was measured in 118 euthyroid cats and in 88 hyperthyroid cats before treatment for hyperthyroidism (Figure 4). Hyperthyroid cats had lower body weights (P < 0.001), were older (P = 0.01), and were less likely to be purebred animals (P = 0.001) than the euthyroid cats (Table 1). The 2-way ANOVA in which the mean log UI of these 2 groups of cats was compared revealed a significant (P < 0.001) effect of renal disease and hyperthyroidism on log UI (Table 2). These results were the same irrespective of whether IRIS category in the hyperthyroid cats was classified according to mean plasma creatinine concentration after treatment.

Table 1—Characteristics of euthyroid cats and hyperthyroid cats before treatment for hyperthyroidism,* stratified according to whether cats were azotemic (plasma creatinine concentrations, > 177 µmol/L) or nonazotemic (plasma creatinine concentration, ≤ 177 µmol/L).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Euthyroid</th>
<th>Hyperthyroid</th>
<th>Euthyroid</th>
<th>Hyperthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonazotemic</td>
<td>Azotemic</td>
<td>Nonazotemic</td>
<td>Azotemic</td>
</tr>
<tr>
<td><strong>No. of cats</strong></td>
<td><strong>Value</strong></td>
<td><strong>Value</strong></td>
<td><strong>Value</strong></td>
<td><strong>Value</strong></td>
</tr>
<tr>
<td>Age (y)</td>
<td>76</td>
<td>12.7 ± 2.6</td>
<td>39</td>
<td>14.2 ± 3.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77</td>
<td>4.6 ± 1.1</td>
<td>41</td>
<td>3.7 ± 1.0</td>
</tr>
<tr>
<td>Purebred breed</td>
<td>77</td>
<td>16 (21)</td>
<td>41</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Female sex</td>
<td>76</td>
<td>46 (61)</td>
<td>41</td>
<td>26 (63)</td>
</tr>
<tr>
<td>Creatinine concentration (µmol/L)</td>
<td>77</td>
<td>131 (118–148)</td>
<td>41</td>
<td>209 (197–227)</td>
</tr>
<tr>
<td>UI concentration (µg/L)</td>
<td>77</td>
<td>350 (239–516)</td>
<td>41</td>
<td>249 (118–397)</td>
</tr>
</tbody>
</table>

Values for age and body weight are reported as mean ± SD. Values for breed and sex are reported as number (percentage). Values for analyses are reported as median (interquartile range).

Table 2—Results of a 2-way ANOVA to assess the difference in UI concentration (µg/L) between euthyroid cats and untreated hyperthyroid cats, taking into account the effect of renal function.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of cats</th>
<th>Geometric mean</th>
<th>Central 95% range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid gland function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>118</td>
<td>304*</td>
<td>82–1,132</td>
</tr>
<tr>
<td>H</td>
<td>88</td>
<td>222</td>
<td>56–879</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>82</td>
<td>315†</td>
<td>97–1,020</td>
</tr>
<tr>
<td>IRIS category 2a</td>
<td>50</td>
<td>290</td>
<td>83–1,014</td>
</tr>
<tr>
<td>IRIS category ≥ 2b</td>
<td>74</td>
<td>206</td>
<td>46–989</td>
</tr>
</tbody>
</table>

*Values are significantly different (P < 0.002) between groups. †Values are significantly different (P = 0.001) among groups. The linear trend for log UI to decrease with increasing IRIS severity category was significant (P < 0.001).

E = Euthyroid, H = Hyperthyroid. Normal = Normal renal function (plasma creatinine concentration < 140 µmol/L). IRIS category 2a = Plasma creatinine concentration from 140 to 177 µmol/L. IRIS category ≥ 2b = Plasma creatinine concentration ≥ 177 µmol/L.
hyperthyroid cats was estimated by use of plasma creatinine concentrations measured before or after treatment. A polynomial contrast indicated that the linear trend for logUI to decrease with IRIS category was significant (P < 0.001). There was no significant interaction between IRIS category and hyperthyroid status.

Withholding food from cats for at least 12 hours before collection of urine (vs not withholding food) had no significant effect on logUI in the apparently healthy euthyroid cats (P = 0.15; n = 76) or in both groups of cats considered together (P = 0.89; 205). In the hyperthyroid group, there was no significant (P = 1.0) difference in mean logUI in cats reported to have a good to increased appetite (n = 43), compared with mean logUI in cats reported to have a reduced to normal appetite (45).

Estimated iodine intake in euthyroid cats > 8 years of age—The median (range) estimated iodine intake was 41 µg/kg of body weight/d (22 to 116 µg/kg of body weight/d) for the apparently healthy euthyroid cats. Therefore, none of the cats had an estimated iodine intake lower than the recommended minimum of 20 µg/kg of body weight/d.

Discussion

In the study reported here, UI concentration was measured in client-owned hyperthyroid cats before and after treatment for hyperthyroidism. Results indicated that UI concentration was lower in untreated hyperthyroid cats, compared with UI concentration in euthyroid cats > 8 years of age, even when the effects of renal disease were taken into account.

The UI concentration of single urine samples was used in this study rather than 24-hour urine excretion profiles, and an indirect measure of solute concentration (USG) of the urine was used to normalize acquired UI concentration values with respect to urine concentration. This approach was validated by comparing the UI concentration normalized to USG with the UI concentration normalized to urine creatinine concentration; values for the 2 approaches were well correlated.

Overall, there was large within-cat variability with respect to UI concentrations measured at various times. This variability in UI concentration has also been detected in humans, in which it is suggested that at least 100 samples be collected from each group of humans used to compare UI concentrations in single urine samples. In our study, a power calculation based on the within-cat variability data also suggested an optimal group size was 100 cats to detect a difference in logUI between 2 groups.

Several potential confounding variables were difficult to assess and make adjustments for in the present study. It was initially hypothesized that the effect of polyphagia in hyperthyroid cats would increase the UI concentration, and therefore UI concentration was measured 2 to 6 weeks and 3 to 6 months after successful treatment in subsets of cats. Results indicated that UI concentration after treatment significantly increased (2 to 6 weeks after treatment) or was the same (3 to 6 months after treatment) as the pretreatment UI concentration. In addition, we did not detect any difference between cats reported to have a good or increased appetite and cats reported to be anorexic or have a normal appetite, although it should be considered that such measurements are highly subjective. Therefore, there was no evidence of a significant confounding effect of polyphagia on the results. Even if a confounding effect had existed, it would have tended to reduce the detected differences between the hyperthyroid and euthyroid groups.

Another finding of the present study was that UI concentration was significantly lower in cats with CKD than in cats without evidence of renal dysfunction. This finding is in agreement with findings of studies in humans that indicate that decreases in UI concentration and renal clearance of iodide are associated with a concurrent increase in plasma or serum iodide concentration. It would have been interesting to determine whether the decreased UI concentration in cats with mild CKD in the present study was associated with concurrent increases in plasma iodide concentration. Although high plasma iodide concentrations can inhibit production of thyroid gland hormones in the short term, this inhibition is eventually overcome with a concurrent increase in plasma TSH concentration in most clinically normal humans. However, in humans with preexisting thyroid gland disease and with certain other diseases such as renal disease, the Woff-Chaikoff escape mechanism may fail, and the excess plasma iodide concentration may lead to hypothyroidism.

Iodide is excreted through the kidneys primarily via glomerular filtration, with partial tubular reabsorption, and therefore excretion of iodide is dependent on both the GFR and tubular function. In the present study, we estimated the GFR and renal function by measurement of plasma creatinine concentrations because direct measurement of the GFR was not possible. Results indicated that the UI concentration was lower in hyperthyroid cats than in euthyroid cats, even when decreased renal function was accounted for in the analysis. However, renal function of cats with untreated hyperthyroidism is difficult to measure accurately because of changes in the GFR and tubular function that develop secondary to the hyperthyroid state. Values for plasma creatinine or urea nitrogen concentration, or USG obtained before treatment for hyperthyroidism are not useful for predicting renal function after treatment. The increase in GFR associated with hyperthyroidism in cats might be expected to transiently increase UI concentration. The effects of hyperthyroidism on the tubular resorption of iodide are unknown; however, once a steady state is reached, the plasma UI concentration should once again reflect the amount of iodine ingested.

Assuming that pretreatment plasma creatinine concentrations were not representative of the true renal status of cats, we attempted to define the hyperthyroid cats as having renal disease or not on the basis of their post-
treatment plasma creatinine concentration. Because the plasma creatinine concentration in hyperthyroid cats is almost invariably higher after rather than before treatment for hyperthyroidism, the approach used in the present study was likely to overestimate the effect of renal disease on UI concentration. This possible overestimation of the effect of renal function results from assigning hyperthyroid cats to a higher IRIS category for the ANOVA analysis because of the higher post-treatment plasma creatinine concentration. Indeed, as might be expected, the use of pretreatment plasma creatinine concentration in the analysis did not change the results. Our attempt to account for the effects of renal disease on UI concentration in the hyperthyroid cats prior to treatment may have been inaccurate. However, the effects of altered renal function on UI concentration would be expected to be only transient because, once the plasma iodine concentration stabilized, the amount of iodide filtered in the glomerulus would change proportionately, and a new steady state would be achieved in which iodine intake again matches iodide excretion. Thus, the only valid explanations for changes in iodine excretion (for an animal in a steady state) are changes in iodine intake or changes in the amount of iodine or iodide that is lost through routes other than the kidneys.

The proportion of ingested iodine excreted in feces may increase in hyperthyroid cats, compared with the proportion excreted in urine. A study of intestinal absorption of radiothyroxine and radiotriiodothyronine in clinically normal cats revealed that when thyroid gland hormones are secreted into the bowel through the bile and duodenal wall, they are poorly absorbed, leading to a net excretion of iodine in the feces. Most of this fecal iodine is organic iodine in T4, with approximately 10% excreted as free iodide. In the hypermetabolic state associated with hyperthyroidism, it is possible that the proportion of iodine excreted in the feces may increase, resulting in a decrease in the proportion of iodide excreted in the urine. A study of iodide, T4, and T3 metabolism revealed that fecal excretion of T4 was higher in hyperthyroid cats, compared with fecal excretion in euthyroid cats. It is therefore possible that the increase in UI concentration after treatment for hyperthyroidism and the difference between untreated hyperthyroid cats and euthyroid cats was at least in part a reflection of a change in the proportions of iodine or iodide excreted in feces versus urine.

In the present study, the marked but transient increase in UI concentration in the hyperthyroid cats in the weeks after treatment suggested that untreated hyperthyroid cats have a significant pool of stored iodine in the body. Treatment of cats with hyperthyroidism appeared to cause a significant increase in the loss of iodine from the body via the urine, presumably because of the deiodination of excess thyroid gland hormones. This increase in UI concentration was also detected in cats treated with surgery alone and is therefore not solely related to the release of iodine stored within the thyroid gland itself. Cats have a poor ability to deiodinate the inactive thyroid gland hormone rT3 and recycle their thyroid gland hormones. In cats, type I iodothyronine deiodinase is unable to use unconjugated rT3 as a substrate but can deiodinate sulphated rT3. This decreased ability to deiodinate inactive thyroid gland hormones in cats versus humans is reflected in a greater serum rT3/T4 fraction in euthyroid cats. Given that cats have a much higher metabolic clearance rate of T4 than humans, it is possible that in addition to increased plasma T4 and T3 concentrations, hyperthyroid cats will have a large circulating pool of inactive thyroid gland hormones. This pool may contribute to increased iodide excretion after treatment for hyperthyroidism.

If the UI concentrations in hyperthyroid cats in the present study were indeed reflective of iodine intake during the development of hyperthyroidism, then reduced iodine intake may be a risk factor for the development of the disease. In humans, results of large population-based studies suggest that even small decreases from optimal iodine intake, as assessed by UI concentration, can increase the risk of development of toxic nodular goiter, a disease with many similarities to hyperthyroidism in cats. Results of the present study indicate that hyperthyroid cats had a lower UI concentration at the time of diagnosis than did euthyroid cats. However, as in humans, the influences on iodine metabolism in cats are complex; a simple cause-and-effect relationship of iodine intake on the development of hyperthyroidism has not been established. Establishment of such an effect would require prospective dietary trials; however, the duration and expense of these would be a considerable obstacle to study completion. Alternatively, a study of the relationship between dietary intake of iodine and plasma TSH concentration might shed light on this relationship. However, the only commercially available TSH assay validated for use in cats is a canine TSH assay, and this assay may not be sufficiently sensitive for this purpose.

References
7. Watson SG, Radford AD, Kipar A, et al. Somatic mutations of the thyroid-stimulating hormone receptor gene in feline hyper-