
รายงานวิจัยฉบับสมบูรณ์

# โครงการ "การศึกษาถึงผลของภาวะ Metabolic acidosis ของร่างกาย ต่อการควบคุมระดับพาราไทรอยด์ฮอร์โมน และการเปลี่ยนแปลงของระดับแคลเซียม ฟอสฟอรัส ในเลือดของแมวไทยที่อยู่ในภาวะไตวายเรื้อรังโดยธรรมชาติ

# "The Role of Metabolic Acidosis on Parathyroid Hormone Secretion, and Changes in Calcium-phosphorus Homeostasis in Siamese Cats with Naturally Occurring Feline Chronic Renal Failure."

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เดือน ธันวาคม พ.ศ. 2547

**รายงานวิจัยฉบับสมบูรณ์**

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# "The Role of Metabolic Acidosis on Parathyroid Hormone Secretion, and Changes in Calcium-phosphorus Homeostasis in Siamese Cats with Naturally Occurring Feline Chronic Renal Failure."

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**สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย**

(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

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# บทคัดย่อ

**รหัสโครงการ :** PDF - RSA4580003 รศ.สัตวแพทย์หญิง ดร. รสมา (ธุมชัย) ภู่สุนทรธรรม

**ชื่อโครงการ :** การศึกษาถึงผลของภาวะ Metabolic acidosis ของร่างกายต่อการควบคุมระดับพาราไทรอยด์ฮอร์โมน และการเปลี่ยนแปลงของระดับแคลเซียม ฟอสฟอรัส ในเลือดของแมวไทยที่อยู่ในภาวะไตวายเรื้อรังโดยธรรมชาติ

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**ระยะเวลาโครงการ** : 3 ปี

โรคไตวายเรื้อรังในแมวเป็นโรคซึ่งพบได้บ่อยในแมวไทย แมวป่วยจะแสดงอาการน้ำหนักตัวลด เบื่ออาหาร ปัสสาวะบ่อยและกินน้ำมาก จากผลของการศึกษาของผู้วิจัยในระยะ 3 ปีตั้งแต่มกราคม 2544 – ธันวาคม 2547 ที่โรงพยาบาลสัตว์เล็ก คณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย พบว่ามีแมวป่วยด้วยโรคไตวายเรื้อรังทั้งสิ้น 117 ราย เป็นแมวเพศผู้ตอน 40.2% เพศผู้ไม่ตอน 23.2% เพศเมียตอน 23.2% และเพศเมียไม่ตอน 11.1% ไม่ทราบเพศ 4.3% พบโรคไตวายเรื้อรังนี้มากที่สุดในแมวที่มีอายุมากกว่า 7 ปี (33.3%) น้อยกว่า 5 ปี (24.8 %) อายุ 5-7 ปี (20.5%) และไม่ทราบอายุที่แน่นอน (21.4%) แมวป่วยด้วยโรคไตวายเรื้อรังส่วนใหญ่เป็นแมวพันธุ์ไทยผสมและพันธุ์ไทย (92.3%) จากผลการติดตามการรักษาไปข้างหน้าเป็นเวลา 60 วันในแมวป่วยพบว่าแมวป่วยด้วยโรคไตวายเรื้อรังมักตรวจพบภาวะโลหิตจางโดยมีค่าเม็ดโลหิตแดง ค่าเม็ดโลหิตแดงอัดแน่น และค่าฮีโมโกลบินที่ลดลง มีการเพิ่มของระดับพาราไทรอยด์ฮอร์โมนร่วมกับการเพิ่มของฟอสฟอรัสในเลือด ซึ่งบ่งชี้ถึงการเกิดภาวะ Renal secondary hyperparathyroidism โดยเฉพาะในกลุ่มแมวป่วยโรคไตวายเรื้อรังในระยะสุดท้ายซึ่งส่งผลทำให้แมวป่วยเสียชีวิต
นอกจากนี้การศึกษาในครั้งนี้ ยังทำการศึกษาในแมวป่วยด้วยโรคไตวายเรื้อรังร่วมกับเกิดภาวะกรดเกินจำนวน 8 ตัวจากแมวที่ศึกษาในส่วนนี้ 21 ตัว พบว่าภาวะกรดเกินที่เกิดขึ้นทำให้มีการเพิ่มของระดับพาราไทรอยด์ฮอร์โมน ระดับฟอสฟอรัสและระดับโปตัสเซียมในเลือดของแมวป่วยด้วยโรคไตวายเรื้อรัง แมวป่วยส่วนใหญ่ที่มีภาวะกรดเกินนี้เป็นแมวป่วยที่อยู่ในระยะสุดท้ายของโรคไตวายเรื้อรังซึ่งมักจะเสียชีวิตในเวลาต่อมา

**คำหลัก** : แมว โรคไตวายเรื้อรัง ภาวะกรดเกิน

## Abstract

**Project Code:** RSA44580003 Rosama (Thumchai) Pusoonthornthum

**Project Title:** "The Role of Metabolic Acidosis on Parathyroid Hormone Secretion, and Changes in Calcium-phosphorus Homeostasis in Siamese Cats with Naturally Occurring Feline Chronic Renal Failure."

**Investigator:** Dr. Rosama (Thumchai) Pusoonthornthum

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**Project period:** 3 years

Feline chronic renal failure (CRF) was observed with increased frequency in Siamese and Siamese-mixed breed cats. CRF cats often demonstrate clinical signs of weight loss, anorexia, and polyuria/polydipsia. One hundred seventeen Siamese and Siamese-mixed breed cats with CRF presented to Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University between January 2001 to December 2004 were studied. Information on breed, gender, age, type of food given, and environmental factors were asked by standard questionnaire to identify risk and protective factors. CRF cats with blood urea nitrogen (BUN) concentrations of more than 50 mg/dl, serum creatinine level of more than 2.1 mg/dl, and urine specific gravity of between 1.008 and 1.014 were followed prospectively for 60 days. Siamese cats with CRF had significantly lower in red blood cells, hemoglobin, and pack cell volume than control cats ($p<0.01$) at day 0,14,30 and 60. Parathyroid hormone levels on day 0 were 50.51+/-19.65 pg/ml, 79.41+/-28.12 pg/ml, and 183.37+/-50.12 pg/ml in controls, uremic, and end-stage groups, respectively. Cats in end-stage group had significantly increased levels of parathyroid hormone when compared to control ($p<0.01$) and uremic group ($p<0.05$) at day 0, 14, and 30. Serum phosphorus levels were also increased significantly in end-stage group ($p<0.001$) indicated of renal secondary hyperparathyroidism. Adjusted calcium was increased significantly on day 30 in uremic and end-stage groups. However, total and ionized calcium levels in the uremic and end-stage groups remained within the normal range. All cats in end-stage group died before completed the sixty days of follow-up. This study reveals that parathyroid hormone level is significantly increased in Siamese cats with end-stage chronic renal failure and the development of renal secondary hyperparathyroidism decreased its survival rate. Metabolic acidosis was studied in 28 cases of naturally occurring feline Chronic renal failure and

followed prospectively for 60 days. A low venous blood pH (<7.270) was found in 8 of the 21 CRF cases (38.1%) on the first day of diagnosis. Acidaemia was associated with increased in PTH, phosphorus, and potassium levels. Cats with naturally occurring CRF do not show evidence of acid-base disturbances until the disease is advanced.

**Key words:** Feline, CRF, Acidosis

# สารบัญ



# สารบัญของภาคผนวก

## 1. Introduction

Feline chronic renal failure (CRF) is very commonly seen in small animal veterinary practice. It has been estimated that, in many cases, clinical and laboratory signs of this syndrome are not evident until loss of more than two-thirds of functioning nephrons has occurred (1). Nevertheless, owners will present cats at variable stages of the disease (2), ranging from subclinical (only detected on routine laboratory rests as elevated creatinine and inadequate urinary concentrating ability) to severe azotaemia, where the animal's condition is incompatible with life without supportive measures such as dialysis or transplantation.

Chronic renal failure (CRF) is the most common renal disease in dogs and cats in Thailand. CRF is defined as primary renal failure that has persisted for an extended period, usually months to years. Regardless of the causes(s) of nephron loss, irreversible renal structural lesions characterize CRF (3). In United States, DiBartola et al. (1987) found that CRF is a common disease especially in older cats. In his study, he found that 53% of affected cats were older than 7 years, but animals ranged in age from 9 months to 22 years (4). In Thailand, our study indicated that CRF was commonly observed especially in old cats

with the mean age of 6.06 years old. It was found that the age of CRF cats ranged from 5 months to 17 years old. A survey of 36 feline patients with CRF indicated that the mean age of cats with CRF was 7.4 years (5). In a study of the age distribution of renal failure in cats, 37% of cats were younger than 10 years, 31% were between 10 and 15, and 32% were older than 15 (6). Recent report also indicated that feline chronic renal failure was recognized with increased frequency in Maine coon, Abyssinian, Siamese, Russian blue, and Burmese cats (7). From the results of our study, we found that 18 CRF cats were Siamese-mixed breed and another 2 CRF cats were Siamese. Forty-nine percent of those CRF cats were older than 7 years old.

Metabolic acidosis is a well-recognized component of CRF in dogs and human. It results primarily from the limited ability of failing kidneys to excrete hydrogen ions, secondary to disordered ammoniagenesis, decreased filtration of phosphate and sulphate compounds, and decreased maximal renal tubular proton secretion (8). Bicarbonate wasting may also contribute. Bicarbonate wasting and chloride retention result in hyperchloremic (normal anion gap) acidosis. When phosphate and organic acid (uric acid, hippuric acid, lactic acid) retention is sufficient, high-anion-gap acidosis results. In retrospective case

series, 63% and 80% of cats with CRF had metabolic acidosis (6,8). From our one year study of feline chronic renal failure at Chulalongkorn University Veterinary Teaching Hospital between November 2001 and October 2002, we followed 13 CRF cats prospectively for 2 months and found that cats with CRF with end stage renal failure developed acidosis, and hypocalcemia at the end of our study(9). When we followed another group of CRF cats for 2 months, we found that CRF cats developed metabolic acidosis on day 0 and day 60 of the study which due to decreased in bicarbonate level in blood and increase lost from the kidney.

From one study in UK, eighty cats with chronic renal failure (CRF) were evaluated in a prospective study to investigate the prevalence and etiopathogenesis of renal secondary hyperparathyroidism (RHPTH), using routine plasma biochemistry and assays of parathyroid hormone (PTH), blood ionized calcium and 1,25 dihydroxycholecalciferol (1,25[OH]2D3). Hyperparathyroidism was a frequent sequela of CRF in that study, affecting 84 per cent of cats with CRF, the severity and prevalence of RHPTH increasing with the degree of renal dysfunction (10). However, significant ionized hypocalcemia was present only in cats with end-stage renal failure. A number of cats were hyperparathyroid in the absence of

abnormalities in the parameters of calcium homeostasis measured in that study(10). Feline chronic renal failure causes much concern to cats' owners in Thailand and remain one of the most common renal problems for cats with advanced age. More than 70% of cats presented to Chulalongkorn University Veterinary Teaching Hospital with chronic renal failure died within one year after first diagnosis (9). Recent report suggested that Siamese cats may have breed predisposition for feline chronic renal failure (7). Whether Siamese (or Siamese-mixed breed) cats with naturally occurring feline chronic renal failure demonstrated genetic predisposition to this disease remain to be investigated.

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## 2. Project objective (s):

1.To determine the proportional morbidity ratio of Siamese cats with naturally occurring feline chronic renal failure.

2.To identify the risk and protective factor for Siamese cats with naturally occurring feline chronic renal failure.

3. To investigate the prevalence and etiopathogenesis of renal secondary hyperparathyrodism in Siamese cats with various stages of naturally occurring feline chronic renal failure.

4. To investigate the role of metabolic acidosis on parathyroid hormone secretion and changes in serum electrolytes especially calcium, phosphorus, sodium, and potassium in Siamese cats with naturally occurring feline chronic renal failure.

# 3. Materials and Methods:

Criteria for selection of cases :

Cases with CRF will be selected on the basis of history, full clinical examination, plasma biochemistry screen, urinalysis, and/or radiography. All cats admitted to hospitals with the history of azotemia (BUN> 50 mg/dl and serum creatinine levels>2.1 mg/dl) (12), polyuria, polydipsia, anorexia, weight loss, and/or isosthenuria will be included in this study. Cases of prerenal, postrenal and primary acute renal failure are identify on the basis of history, physical findings, laboratory tests and response to therapy and will be excluded from the study.

Criteria for selection of control cats:

Control cats will consist of those without azotemia, polyuria, polydipsia, weight loss, and isosthenuria admitted to the same veterinary hospital as the CRF cats for vaccination. Health status of control cats will be determined by history, physical examination, and, if necessary, urinalysis and radiography. Cats with a history of urinary tract disease, and those with a history of receiving special treatment for urinary tract disease will be excluded.

# 4.Results of the Project:

# Results of Part I:

To Determine the Proportional Morbidity Ratio of Siamese Cats with Naturally Occurring Feline Chronic Renal Failure.

**Project Achievement According to the Project Plan:**

Total number of cats(n) with CRF were collected and received information retrospectively for three years period. = 117 cats

Total number of cats (n) with CRF were collected and follow - up prospectively for three years period. = 28 cats.

Total number of control cats collected during the three year study. = 19 cats

Total number of cats presented to CUVTH within the same peroid = 18,682 cats.

The proportional morbidity ratio of Siamese cats with naturally occurring feline chronic renal failure in cat present to CUVTH = 6 CRF cats per1000 cats

**Summary of progress to date as related to project objectives** :

For Part II of the project (Retrospective study):

Please see attached papers.

For Part III and IV of the project (prospective study) :

Please see attached papers

# Results of Part II:

## Identify the Risk and Protective Factors for Siamese Cats with Naturally Occurring Feline Chronic Renal Failure.

Table 1 Number and percentage of cats with CRF according to different gender

| Gender | Number of cats (n/N)(%) |
|---|---|
| Male castrated | 47/117 (40.2%) |
| Male intact | 26/117 (23.2%) |
| Female spayed | 26/117 (23.2%) |
| Female intact | 13/117 (11.1%) |
| Unknown | 5/117 (4.3%) |

n = number of cats according to different gender
N = total number of cats with CRF

Table 2 Number and percentage of cats with CRF according to different ages

| Age (year) | Number of cats (n/N)(%) |
|---|---|
| < 5 | 29/117 (24.8%) |
| 5-7 | 24/117 (20.5%) |
| 7-10 | 29/117 (24.8%) |
| >10 | 10/117 (8.5%) |
| Unknown | 25/117 (21.4%) |

n = number of cats according to different age
N = total number of cats with CRF

Table 3 Number and percentage of cats with CRF according to different breed

| Breed | Number of cats (n/N)(%) |
|---|---|
| Siamese-mixed | 99/117 (84.6%) |
| Siamese | 9/117 (7.7%) |
| Persian | 3/117 (2.6%) |
| Others | 1/117 (0.9%) |
| Unknown | 5/117 (4.2%) |

n = number of cats according to different breed
N = total number of cats with CRF

Table 4 Number and percentage of CRF cats according to different weights

| Weights (kg) | Number of cats (n/N) (%) |
|---|---|
| 1-3.9 | 36/117 (30.8%) |
| 4-6.9 | 38/117 (32.5%) |
| Unknown | 43/117 (36.7%) |

n = number of cats according to different weights
N = total number of CRF cats

Table 5 Number and percentage of CRF cats according to frequency of feeding

| Frequency of Feeding | Number of cats (n/N) (%) |
|---|---|
| Once a day | 2/117 (1.7%) |
| Twice a day | 16/117 (13.7%) |
| Three times a day | 2/117 (1.7%) |
| More than three times a day | 1/117 (0.9%) |
| Ad libitum | 5/117 (4.3%) |
| Unknown | 95/117(77.7%) |

n = number of cats according to frequency of feeding
N = total number of CRF cats

Table 6 Number and percentage of CRF cats according to different type of water sources

| Source of Water | Number of cats (n/N) (%) |
|---|---|
| Tap water | 20/117 (17.1%) |
| Well water | 1/117 (0.9%) |
| Filtered water | 2/117 (1.7%) |
| Boiled water | 2/117 (1.7%) |
| Others | 2/117 (1.7%) |
| Unknown | 90/117 (76.9%) |

n = number of cats according to different type of water sources
N = total number of CRF cats

Table 7 Number and percentage of CRF cats according to frequency of water given

| Frequency of Water Given | Number of cats (n/N) (%) |
|---|---|
| Once a day | - |
| Two times a day | - |
| Three times a day | - |
| More than three times a day | - |
| Ad libitum | 27/117 (23.1%) |
| Unknown | 90/117 (76.9%) |

n = number of cats according to frequency of water given
N = total number of CRF cats

Table 8 Number and percentage of CRF cats according to different type of housing

| Type of Housing | Number of cats (n/N) (%) |
|---|---|
| House | 21/117 (17.9%) |
| Townhouse | 2/117 (1.7%) |
| Commercial Building | 5/117 (4.3%) |
| Unknown | 89/117 (76.1%) |

n = number of cats according to different environment
N = total number of CRF cats

Table 9 Number and percentage of cats with CRF according to different type of building they lived near.

| Type of Building | Number of cats (n/N) (%) |
|---|---|
| Factory | 5/117 (4.3%) |
| Hospital | 1/117 (0.9%) |
| Chemical warehouse | 1/117 (0.9%) |
| Gas station | 1/117 (0.9%) |
| Unknown | 99/117 (93.0%) |

n = number of cats according to different type of building
N = total number of CRF cats

Table 10 Number and percentage of cats with CRF according to different type of raising

| Type | Number of cats (n/N) (%) |
|---|---|
| Outdoor | 18/117 (15.4%) |
| Indoor | 8/117 (6.8%) |
| Others | 1/117 (0.9%) |
| Unknown | 90/117 (76.9%) |

n = number of cats according to different type of raising
N = total number of CRF cats

Table 11 Number and percentage of cats with CRF according to different type of food

| Type of Food | Number of cats (n/N) (%) |
|---|---|
| Dry | 25/117 (21.4%) |
| Canned | 5/117 (4.3%) |
| Home-made | 21/117 (17.9%) |
| Unknown | 66/117 (56.4%) |

n = number of cats according to different type of food
N = total number of CRF cats

Table 12 Number and percentage of cats with CRF according to different type of food

| Type of Food Ingredients | Number of cats (n/N) (%) |
|---|---|
| Pork | 2/117 (1.7%) |
| Chicken | 1/117 (0.9%) |
| Fresh water fish | 4/117 (3.4%) |
| Tuna | 13/117 (11.1%) |
| Shrimp | 2/117 (1.7%) |
| Squid | 1/117 (0.9%) |
| Unknown | 94/117 (80.3%) |

n = number of cats according to different type of food ingredients
N = total number of CRF cat

# Results of Prospective Study

# Results of Part III:

Investigation of the Prevalence and Etiopathogenesis of Renal Secondary Hyperparathyrodism in Siamese Cats with Various Stages of Naturally occurring Feline Chronic Renal Failure.

**Table 13** Mean±S.E.M. for complete blood count in control cats.

| Blood Results | Normal Value # | Control cats | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Hemoglobin (g/dl) | 12-17.8 | 13.29±0.41 | 13.14±0.59 | 12.84±0.41 | 12.12±1.09 |
| Hematocrit (%) | 38-55 | 43.8±1.71 | 39.89±1.98 | 38.98±1.49 | 41.44±2.10 |
| Red Blood Cell ($x10^6$cells/µl) | 5.22-8.46 | 8.35±0.27 | 8.61±0.48 | 8.72±0.27 | 8.66±0.52 |
| White Blood Cell (cells/µl) | 6,000-17,000 | 17,097.7±2,250 .28 | 14,725±1,284.0 9 | 13,798.3±1,655 .78 | 16,200±2,50 5.37 |
| Neutrophils (cells/µl) | 3,000-11,500 | 11,033.8± 1,625.94 | 9,726.33± 999.53 | 8,082.55± 816.63 | 10,107± 1,671.64 |
| Bands (cells/µl) | 0-300 | 0± 0 | 13.67± 13.68 | 79.83± 39.28 | 35.63± 27.99 |
| Eosinophils(cells/µl) | 100-1,000 | 1,251.58± 457.62 | 907.07± 264.68 | 1,179.53± 384.35 | 1,335.13± 447 47 |
| Lymphocytes(cells/µl) | 1,500-5,000 | 4,699.32±422.2 2 | 3,970.49±497.5 6 | 4,244.03± 482.43 | 4,529.13± 636.18 |
| Monocytes(cells/µl) | < 2000 | 112.96± 32.74 | 107.44± 32.05 | 225.05± 66.79 | 193.13± 86.18 |

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases.In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis.p. 3-20.

**Table 14** Mean±S.E.M. for complete blood count in all cats with chronic renal failure.

| Blood Results | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Hemoglobin (g/dl) | 12-17.8 | 8.72± 0.64 | 8.17± 0.97** | 7.86± 1.25*** | 8.02± 0.68** |
| Hematocrit (%) | 38-55 | 31.8± 2.26*** | 28.17± 3.89** | 31.82± 5.02* | 30.38± 1.93** |
| Red Blood Cell ($x10^6$cells/µl) | 5.22-8.46 | 6.06± 0.39*** | 5.47± 0.83*** | 5.91± 0.87*** | 6.14± 0.45*** |
| White Blood Cell (cells/µl) | 6,000-17,000 | 21,760.9± 4,491.59 | 18,874.3± 5,746.44 | 23,168± 5,045.67* | 17,912± 1,705.51 |
| Neutrophils (cells/µl) | 3,000-11,500 | 14,626.2± 2,597.79 | 14,659± 5,272.62 | 19,287.4± 5,034.46 | 11,790.8± 1,369.1 |
| Bands (cells/µl) | 0-300 | 22.04± 15.60 | 0± 0 | 0± 0 | 0± 0 |
| Eosinophils(cells/µl) | 100-1,000 | 1,542.27± 849.20 | 1,356.34± 411.02 | 1,372.8± 780.0 | 1,303.24± 412.05 |
| Lymphocytes(cells/µl) | 1,500-5,000 | 5,268.95± 2126.5 | 2,543.66 ± 563.51 | 2,201.6± 217.39 | 4,502.92± 908.39 |
| Monocytes(cells/µl) | < 2000 | 301.49± 118.48 | 186.71± 123.28 | 306.2± 142.03 | 315.02± 152.04 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis.p. 3-20.

**Table 15** Mean±S.E.M. for complete blood count in cats with uremic stage CRF.

| Blood Results | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Hemoglobin (g/dl) | 12-17.8 | 8.43±0.89 | 8.55±0.69 | 8.45±0.57 | 8.07±0.78 |
| Hematocrit (%) | 38-55 | 31.36±3.44 | 32.68±2.45 | 32.83±1.94 | 30.35±2.64 |
| Red Blood Cell ($x10^6$cells/µl) | 5.22-8.46 | 5.37±0.56 | 5.80±0.37 | 6.09±0.37 | 5.59±0.47 |
| White Blood Cell (cells/µl) | 6,000-17,000 | 15,180±3,700.53 | 14,873.33±3,552.57 | 16,520.00±3,181.26 | 14,165.00±2,486.16 |
| Neutrophils (cells/µl) | 3,000-11,500 | 9,515.20±2,110.15 | 9,594.15±2,060.26 | 12,846.78±2,515.70 | 9,926.00±1,708.28 |
| Bands (cells/µl) | 0-300 | 47.93±35.71 | 78.33±58.07 | 12.42±11.50 | 0.00±0.00 |
| Eosinophils(cells/µl) | 100-1,000 | 2,284.87±1,219.82 | 2,376.05±1332.19 | 1,097.67±615.67 | 625.15±219.47 |
| Lymphocytes(cells/µl) | 1,500-5,000 | 3,217.26±845.45 | 2,550.65±505.21 | 2,259.68±506.97 | 3,049.20±1,000.50 |
| Monocytes(cells/µl) | < 2000 | 397.6±75.12 | 250.83±127.79 | 303.28±101.92 | 250.55±126.54 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis.p. 3-20.

**Table 16** Mean±S.E.M. for complete blood count in cats with end-stage CRF.

| Blood Results | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Hemoglobin (g/dl) | 12-17.8 | 8.23±0.88 | 6.07±0.77 | 3.60 | 7.20 |
| Hematocrit (%) | 38-55 | 29.96±3.08 | 18.40±2.30 | 13.10 | 23.30 |
| Red Blood Cell ($x10^6$cells/µl) | 5.22-8.46 | 5.77±0.50 | 3.50±0.43 | 2.92 | 6.02 |
| White Blood Cell (cells/µl) | 6,000-17,000 | 25,324.29±5,720.49 | 15,406.67±7,691.31 | 38,140.00 | 18,320.00 |
| Neutrophils (cells/µl) | 3,000-11,500 | 17,974.97±2,924.52 | 13,073.33±7,153.23 | 36,233.00 | 11,358.40 |
| Bands (cells/µl) | 0-300 | 22.34±20.90 | 0.00±0.00 | 0.00 | 0.00 |
| Eosinophils(cells/µl) | 100-1,000 | 646.29±463.53 | 367.47±144.67 | 0.00 | 2,564.80 |
| Lymphocytes(cells/µl) | 1,500-5,000 | 6,338.34±3,066.58 | 1,665.87±572.41 | 1,907.00 | 4,213.60 |
| Monocytes(cells/µl) | < 2000 | 342.34±166.28 | 0.00±0.00 | 0.00 | 183.20 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis.p. 3-20.

**Table 17** Mean±S.E.M. for blood chemistry values in control cats.

| Blood Chemistry | Normal Value# | Control cats | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| AST (units) | 23-66 | 29.38± 3.61 | 28± 1.46 | 1. 26± 22 | 50.27±21.13 |
| ALT (units) | 21-102 | 56.23± 5.14 | 57.5± 4.10 | 53.42± 4.35 | 70.27±14.11 |
| BUN (mg%) | 10-28 | 24.92± 1.15 | 25.9± 0.97 | 26.33± 0.62 | 25.45±1.63 |
| Creatinine(mg%) | 0.5-1.5 | 1.52± 0.09 | 1.58± 0.09 | 1.49± 0.09 | 1.53±0.13 |

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 18** Mean ± S.E.M. for blood chemistry values in all cats with chronic renal failure.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| AST (units) | 23-66 | 43.91± 6.52 | 36.14± 5.45 | 26.8± 11.96 | 28± 6.99 |
| ALT (units) | 21-102 | 68.64± 17.99 | 56.29± 16.03 | 33.8± 15.09* | 69.4± 25.73 |
| BUN (mg%) | 10-28 | 147.36± 30.48*** | 86± 14.89** | 110± 49.11** | 111± 29.41** |
| Creatinine(mg %) | 0.5-1.5 | 7.59± 1.96** | 4.26± 1.09** | 4.06± 1.81** | 4.42± 0.57*** |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 19** Mean ± S.E.M. for blood chemistry values in cats with uremic stage CRF.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| AST (units) | 23-66 | 33.86± 4.94 | 31.00± 3.88 | 31.00± 4.06 | 25.83± 4.42 |
| ALT (units) | 21-102 | 61.29± 14.63 | 56.17± 10.11 | 54.83± 13.77 | 48.83± 9.30 |
| BUN (mg%) | 10-28 | 57.86± 7.74 | 51.83± 7.34 | 62.83± 12.35 | 107.50± 31.22 |
| Creatinine(mg %) | 0.5-1.5 | 3.27± 0.66 | 3.07± 0.49 | 3.02± 0.37 | 5.13± 1.60 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 20** Mean ± S.E.M. for blood chemistry values in cats with.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| AST (units) | 23-66 | 53.43± 7.65 | 45.33± 3.43 | 26.00 | 55.00 |
| ALT (units) | 21-102 | 81.14± 25.54 | 79.67± 21.19 | 23.00 | 166.00 |
| BUN (mg%) | 10-23 | 202.57± 29.57 | 121.67± 9.74 | 260.00 | 123.00 |
| Creatinine(mg %) | 0.5-1.5 | 10.61± 2.24 | 6.03± 1.25 | 8.70 | 5.60 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
*** = $p<0.001$ when compared with controls

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 21** Mean ± S.E.M. for blood chemistry values in control cats.

| Blood Chemistry | Normal Value # | Control cats | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Na (mEq/L) | 151-161 | 157.5±1.89 | 155.6±0.64 | 150.36±1.86 | 154±3.53 |
| K (mEq/L) | 3.5-5.1 | 3.86±0.11 | 4.04±0.11 | 4.33±0.15 | 4.35±0.18 |
| Calcium(mg/dl) | 9.3-11.7 | 9.38±0.15 | 9.36±0.15 | 9.51±0.16 | 9.73±0.23 |
| Phosphorus (mg/dl) | 2.9-7.7 | 4.69±0.35 | 5.01±0.28 | 4.85±0.30 | 4.62±0.35 |
| Albumin(g/dl) | 2.6-4.3 | 2.38±0.06 | 2.46±0.06 | 2.48±0.08 | 2.39±0.07 |

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 22** Mean ± S.E.M. for blood chemistry values in all cats with chronic renal failure.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Na (mEq/L) | 151-161 | 147.64± 4.01 | 153.57± 1.90 | 151.8± 67.77 | 153.4± 2.44 |
| K (mEq/L) | 3.5-5.1 | 4.17± 0.16 | 4.45± 0.25 | 4.54± 2.03 | 4.18± 0.19 |
| Calcium(mg/dl) | 9.3-11.7 | 8.87±0.36 | 8.83± 0.31 | 8.90± 3.97 | 9.52± 0.43 |
| Phosphorus(mg/dl) | 2.9-7.7 | 12.86± 2.48** | 6.30± 1.04 | 7.58± 3.38** | 10.20± 3.97 |
| Albumin(g/dl) | 2.6-4.3 | 2.30± 0.11 | 2.23± 0.14 | 2.08±0.93* | 2.22± 0.07 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 23** Mean ± S.E.M. for blood chemistry values in all cats with uremic CRF.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Na (mEq/L) | 151-161 | 148.14± 2.69 | 150.67± 4.50 | 150.50± 1.11 | 151.83± 2.03 |
| K (mEq/L) | 3.5-5.1 | 4.20± 0.22 | 4.25± 0.23 | 4.60± 0.29 | 4.48± 0.20 |
| Calcium(mg/dl) | 9.3-11.7 | 8.80± 0.30 | 8.57± 0.42 | 8.77± 0.40 | 9.17± 0.19 |
| Phosphorus(mg/dl) | 2.9-7.7 | 5.23± 0.33 | 4.78± 0.22 | 5.90± 0.88 | 9.65± 3.13 |
| Albumin(g/dl) | 2.6-4.3 | 2.58± 0.27 | 2.10± 0.14 | 2.56± 0.25 | 2.78± 0.28 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 24** Mean ± S.E.M. for blood chemistry values in all cats with end-stage CRF.

| Blood Chemistry | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| Na (mEq/L) | 151-161 | 148.71± 5.65 | 151.33± 2.56 | 156.00 | 155.00 |
| K (mEq/L) | 3.5-5.1 | 4.46± 0.15 | 4.35± 0.33 | 5.30 | 4.50 |
| Calcium(mg/dl) | 9.3-11.7 | 9.00± 0.50 | 9.27± 0.21 | 9.60 | 11.10 |
| Phosphorus(mg/dl) | 2.9-7.7 | 17.04± 2.65 | 7.90± 1.34 | 11.20 | 6.50 |
| Albumin(g/dl) | 2.6-4.3 | 2.39± 0.13 | 2.40± 0.14 | 1.80 | 2.50 |

* = $p<0.05$ when compared with controls.
** = $p<0.01$ when compared with controls.
#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 25** Mean ± S.E.M. for complete blood gas in control cats.

| Parameter | Normal Value # | Control cats | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| pH | 7.32-7.44 | 7.35± 0.01 | 7.35± 0.01 | 7.34± 0.01 | 7.33± 0.02 |
| P CO2 (mmHg) | 38-46 | 33.89± 1.44 | 36.38± 1.65 | 31.34± 2.63 | 34.16± 1.80 |
| P O2 (mmHg) | 35-40 | 36.55± 8.62 | 30.29± 1.94 | 43.1± 15.40 | 35.3±2.37 |
| HCO3 a (mEq/L) | 24-34 | 18.63± 0.97 | 20.04± 0.74 | 16.8± 1.32 | 18.04± 0.89 |
| HCO3 s (mEq/L) | 24-34 | 18.94± 0.85 | 19.78± 0.63 | 17.7± 0.57 | 18.45± 0.77 |
| CO2 | | 19.69± 1.00 | 21.18± 0.76 | 17.76± 1.41 | 19.09± 0.93 |
| O2 SAT. | | 54.49± 8.64 | 53.6± 4.11 | 54.65± 7.80 | 62.81± 4.87 |

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 26** Mean ± S.E.M. for complete blood gas in all cats with chronic renal failure.

| Parameter | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| pH | 7.32-7.44 | 7.27± 0.04 | 7.37± 0.02 | 7.20± 0.16 | 7.26± 0.05 |
| P CO2 (mmHg) | 38-46 | 34.01± 3.39 | 35.88± 2.58 | 33.46± 5.82 | 31.28± 4.40 |
| P O2 (mmHg) | 35-40 | 36.36± 6.94 | 29.77± 6.49 | 46.26± 18.57 | 44.28±22.80 |
| HCO3 a (mEq/L) | 24-34 | 15.5± 1.31 | 20.7± 1.15 | 17.6 ± 4.25 | 13.64±1.76* |
| HCO3 s (mEq/L) | 24-34 | 15.81± 1.26* | 20.57± 0.97 | 17.04± 3.97 | 14.32±1.29* |
| CO2 | | 16.56± 1.34 | 21.82± 1.20 | 18.62± 4.41 | 14.60±1.86* |
| O2 SAT. | | 54.03± 9.09 | 48.27±10.66 | 55.64± 14.22 | 43.48± 15.34 |

* = $p<0.05$ when compared with controls.

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 27** Mean ± S.E.M. for complete blood gas in all cats with uremic stage CRF.

| Parameter | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| pH | 7.32-7.44 | 7.37±0.01 | 7.34± 0.03 | 7.34± 0.02 | 7.27±0.04 |
| P CO2 (mmHg) | 38-46 | 37.10±3.08 | 34.69±2.52 | 38.49±1.58 | 37.52±0.77 |
| HCO3 a (mEq/L) | 24-34 | 21.22±1.61 | 18.67±1.39 | 20.86±0.71 | 17.68±1.76 |

* = $p<0.05$ when compared with controls.

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

**Table 28** Mean ± S.E.M. for complete blood gas in all cats with end-stage CRF.

| Parameter | Normal Value # | Cats with chronic renal failure | | | |
|---|---|---|---|---|---|
| | | Day 0 ($D_0$) | Day 14 ($D_{14}$) | Day 30 ($D_{30}$) | Day 60 ($D_{60}$) |
| pH | 7.32-7.44 | 7.19±0.04 | 7.37±0.01 | 7.35 | 7.29 |
| P CO2 (mmHg) | 38-46 | 36.90±4.37 | 37.30±2.65 | 43.60 | 33.90 |
| HCO3 a (mEq/L) | 24-34 | 13.62±1.12 | 21.65±1.93 | 24.30 | 15.00 |

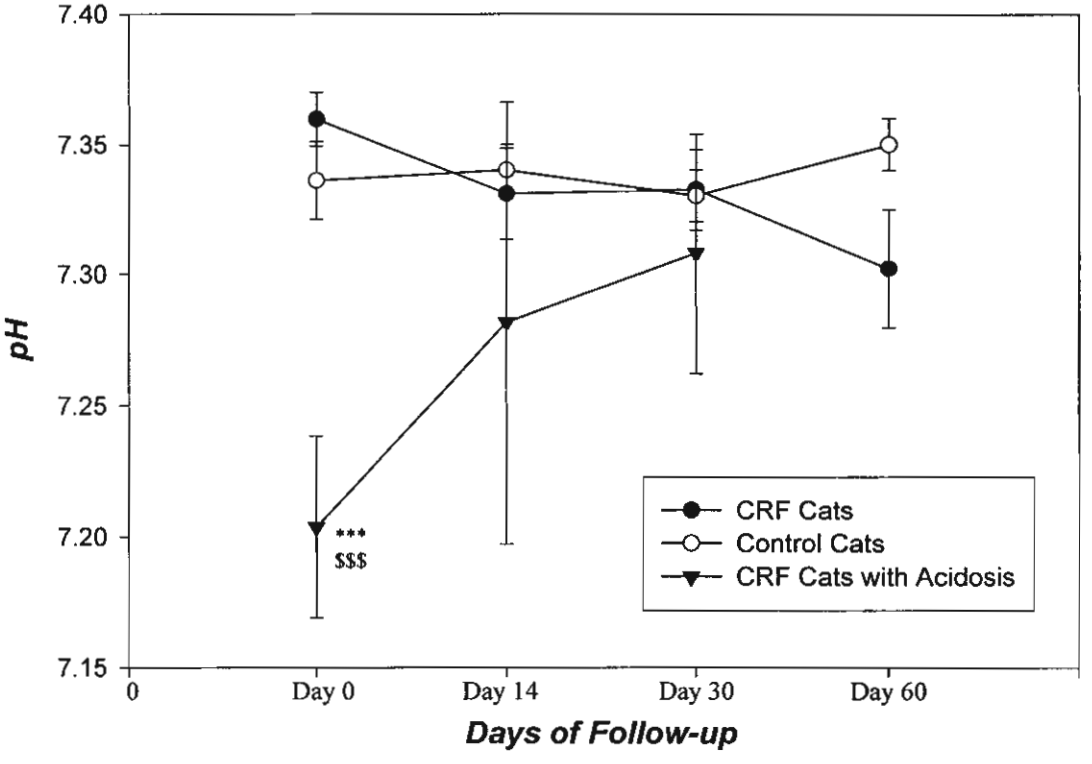
* = $p<0.05$ when compared with controls.

#Normal Reference Value from Sodikoff C.H. 1995a. Serum chemical tests. Laboratory profiles of small animal diseases. In: A guide to laboratory diagnosis. 2nd ed. Mosby-Year Book. St.Louis. p. 3-20.

# Results of Part IV:

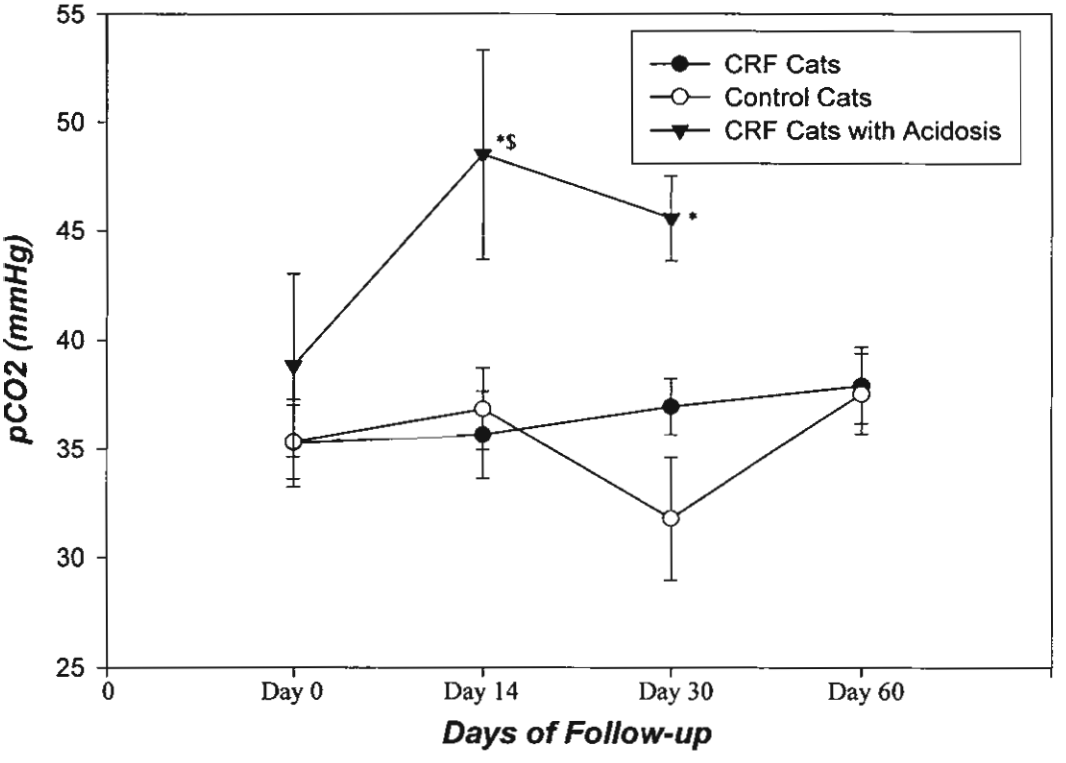
The Role of Metabolic Acidosis on Parathyroid Hormone Secretion and Changes in Serum Electrolytes especially Calcium, Phosphorus, Sodium, and Potassium in Siamese Cats with Naturally Occurring Feline Chronic Renal Failure.

**Figure 1** Mean +/- SEM of pH for Control Cats, CRF Cats, and CRF Cats with Acidosis.



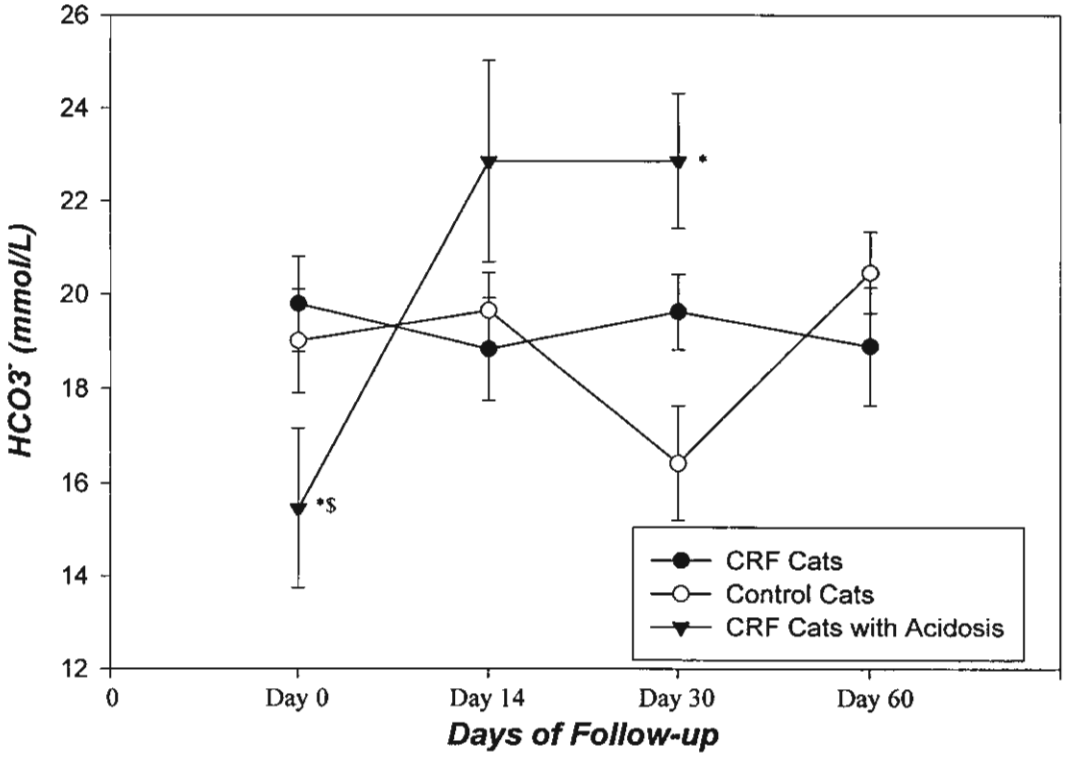

**Note:** *** = $p < 0.001$ when compared with controls
$$$ = $p < 0.001$ when compared between non-acidotic and acidosis CRF groups

**Figure 2** Mean +/- SEM of pCO2 for Control Cats, CRF Cats, and CRF Cats with Acidosis.



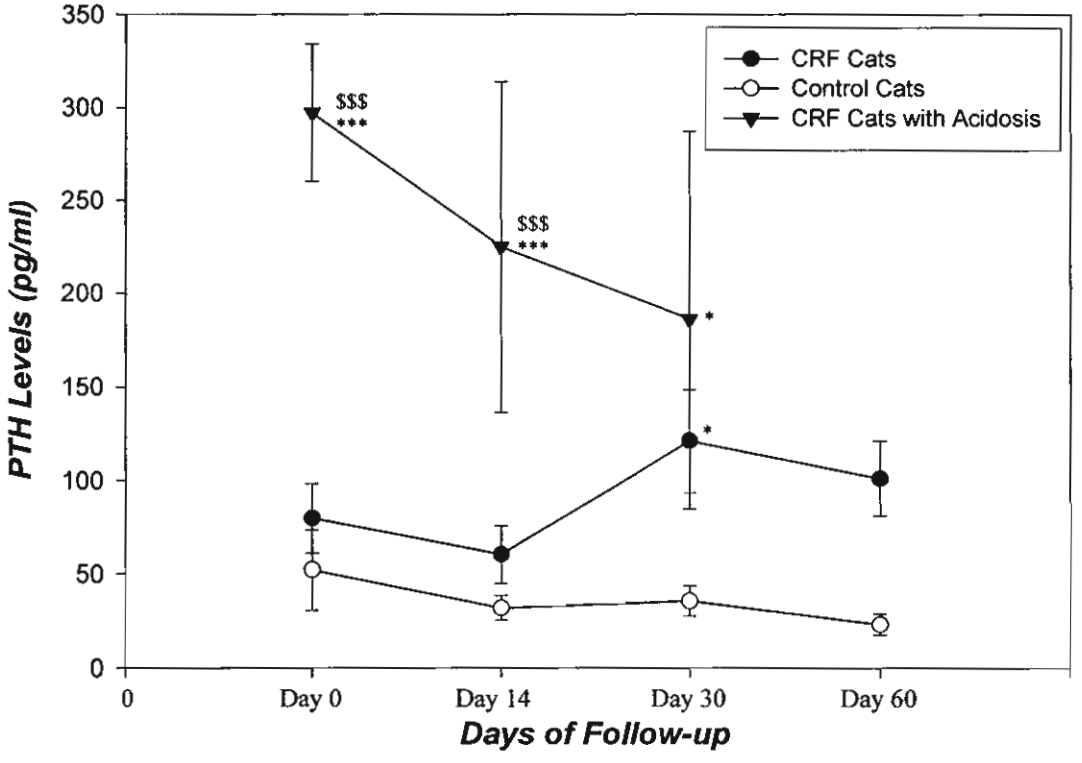

**Note:** * = $p < 0.05$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 3** Mean +/- SEM of $HCO3^-$ for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and acidosis CRF groups

**Figure 4** Mean +/- SEM of PTH Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls
*** = $p < 0.001$ when compared with controls
$$$ = $p < 0.001$ when compared between non-acidotic and acidosis CRF groups

**Figure 5** Mean +/- SEM of Total Calcium Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.

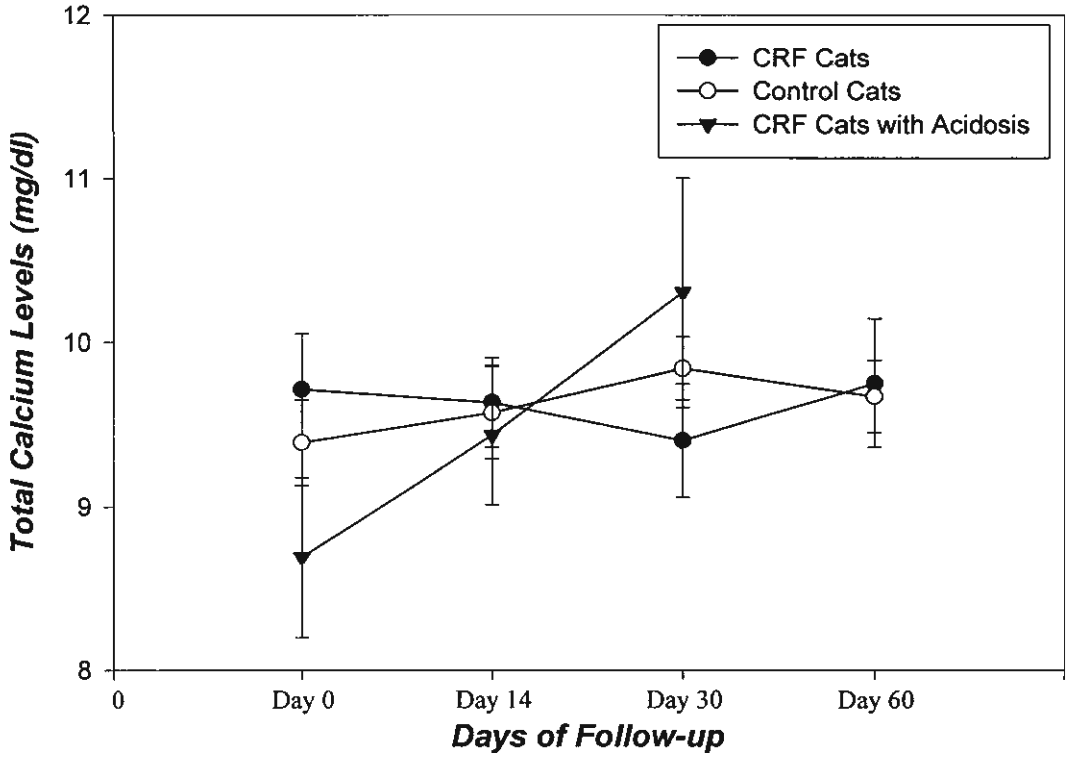
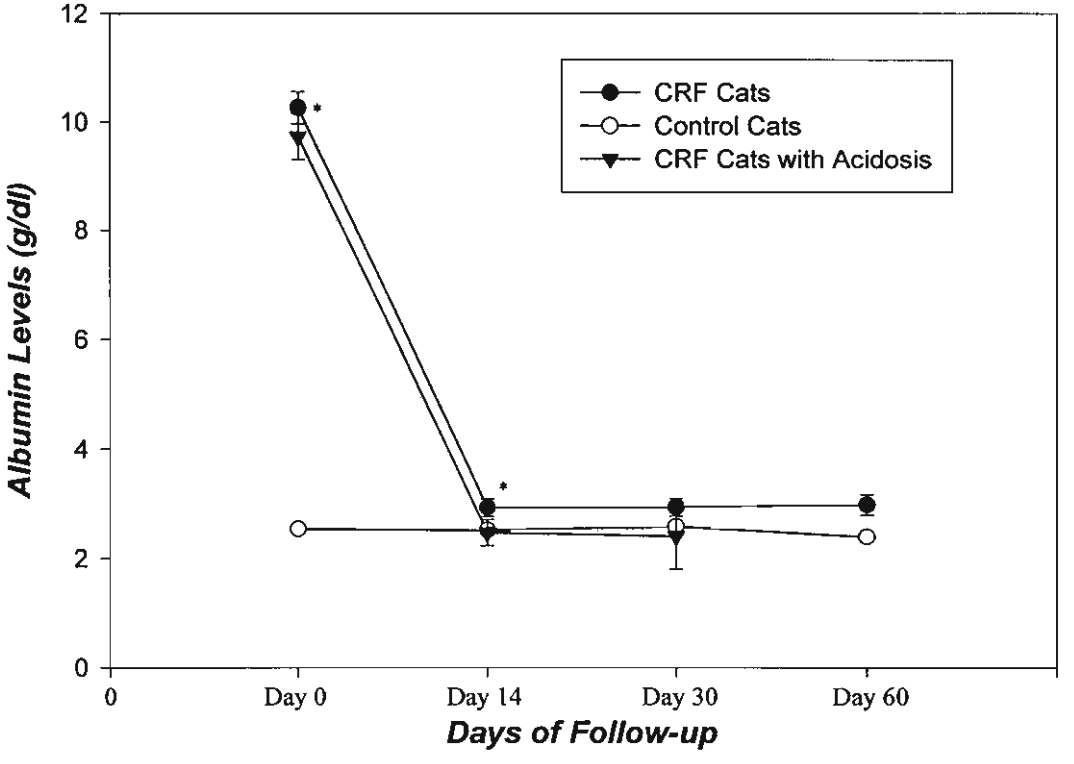
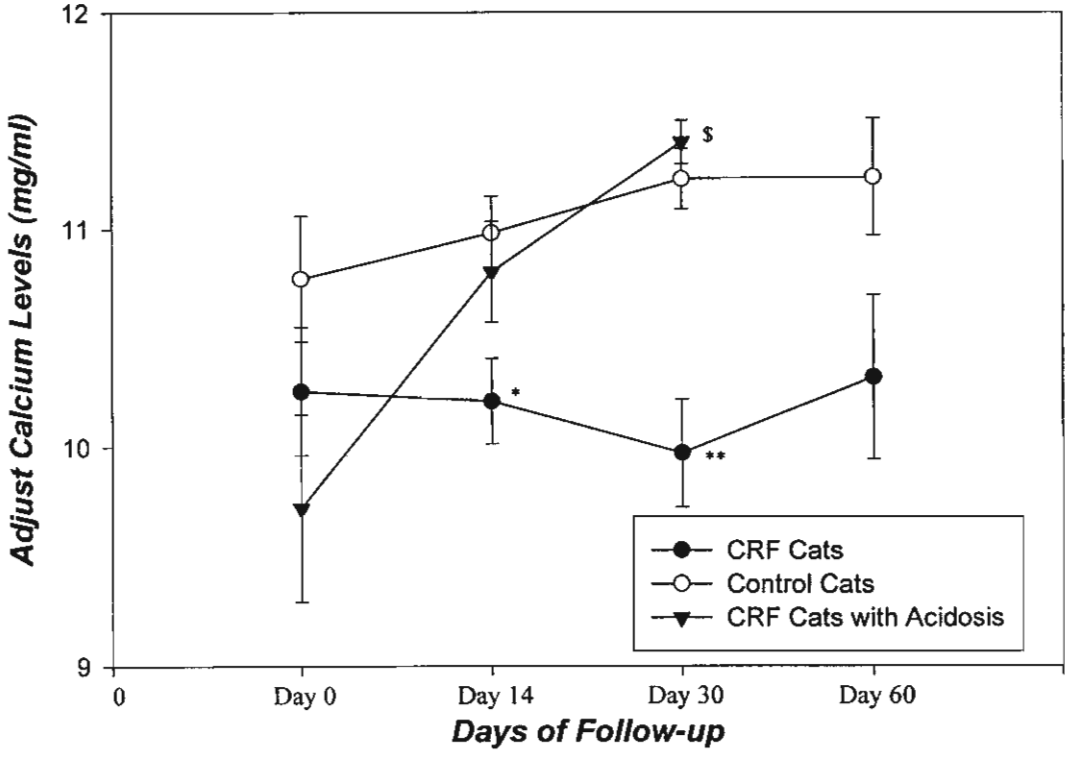


**Figure 6** Mean +/- SEM of Albumin Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.



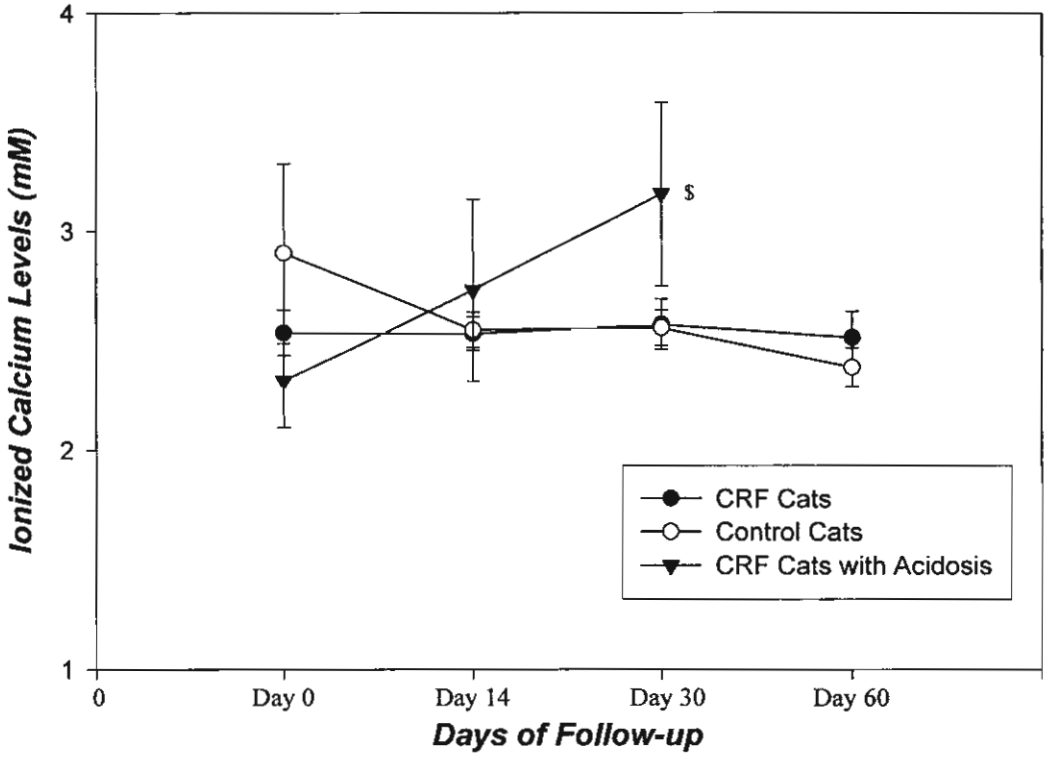

**Note:** * = $p < 0.05$ when compared with controls

**Figure 7** Mean +/- SEM of Adjust Calcium Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.



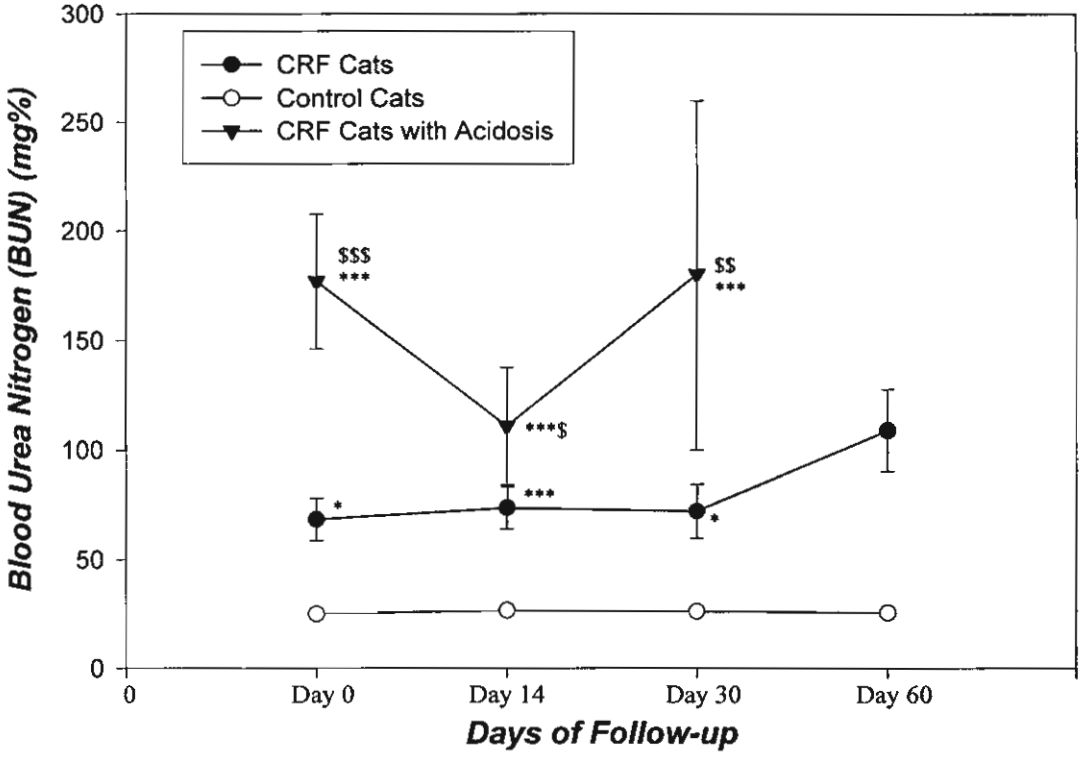

**Note:** * = $p < 0.05$ when compared with controls
** = $p < 0.01$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 8** Mean +/- SEM of Ionized Calcium Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.



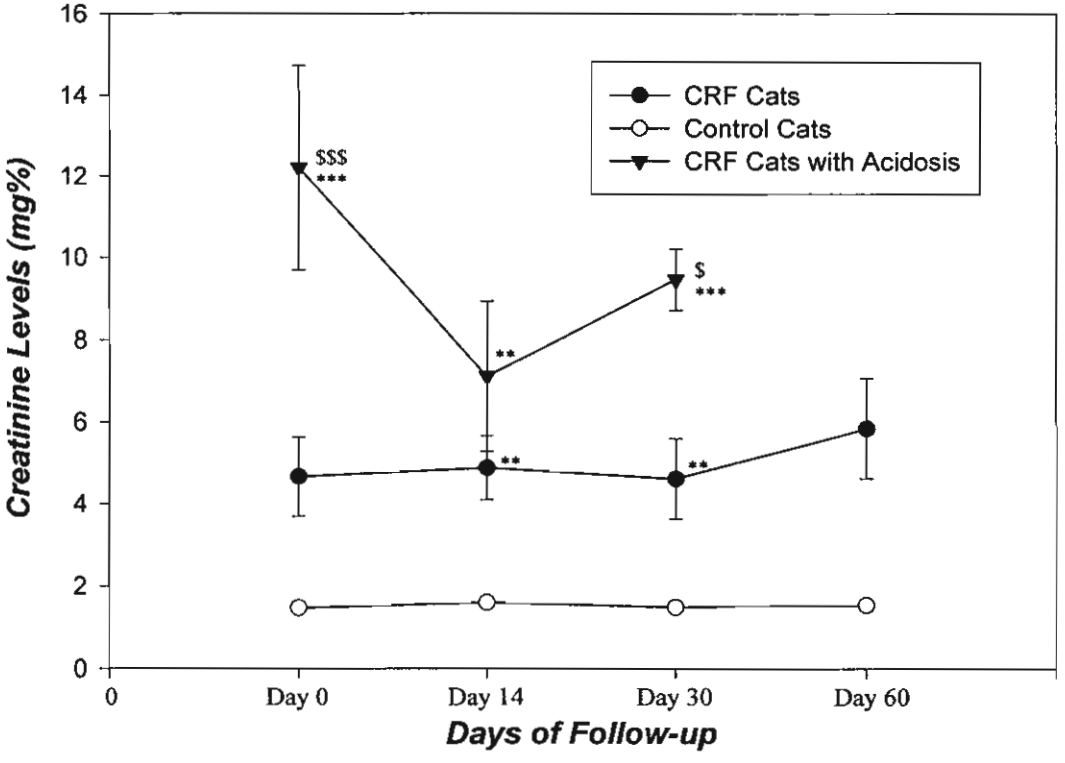

**Note:** $ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 9** Mean±SEM of Blood Urea Nitrogen (BUN) for Control Cats, CRF Cats, and CRF Cats with Acidosis.



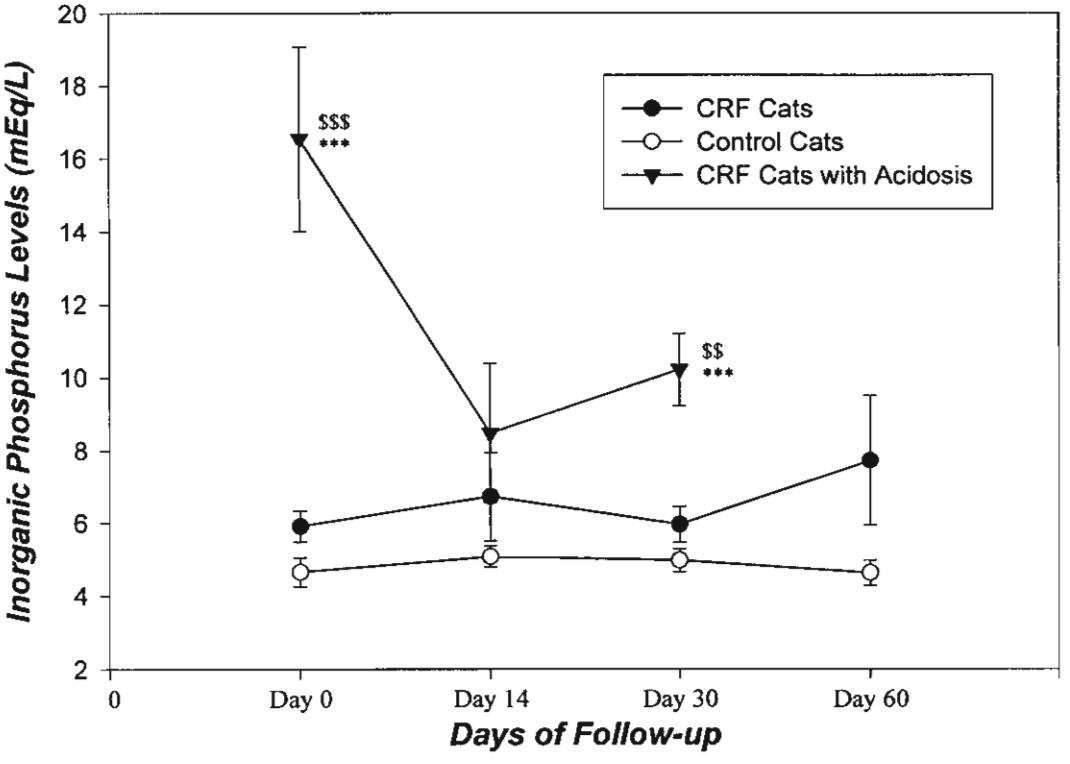

**Note:** * = $p < 0.05$ when compared with controls
*** = $p < 0.001$ when compared with controls
$ = $p < 0.001$ when compared between non-acidotic and CRF cats with acidosis
$$$ = $p < 0.001$ when compared between non-acidotic and CRF cats with acidosis

**Figure 10** Mean +/- SEM of Creatinine Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** ** = $p < 0.01$ when compared with controls
*** = $p < 0.001$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF with acidosis
$$$ = $p < 0.001$ when compared between non-acidotic and CRF with acidosis

**Figure 11** Mean +/- SEM of Inorganic Phosphorus Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** *** = $p < 0.001$ when compared with controls

$$ = $p < 0.01$ when compared between non-acidotic and CRF cats with acidosis

$$$ = $p < 0.001$ when com pared between non-acidotic and CRF cats with acidosis

**Figure 12** Mean +/- SEM of Sodium Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.

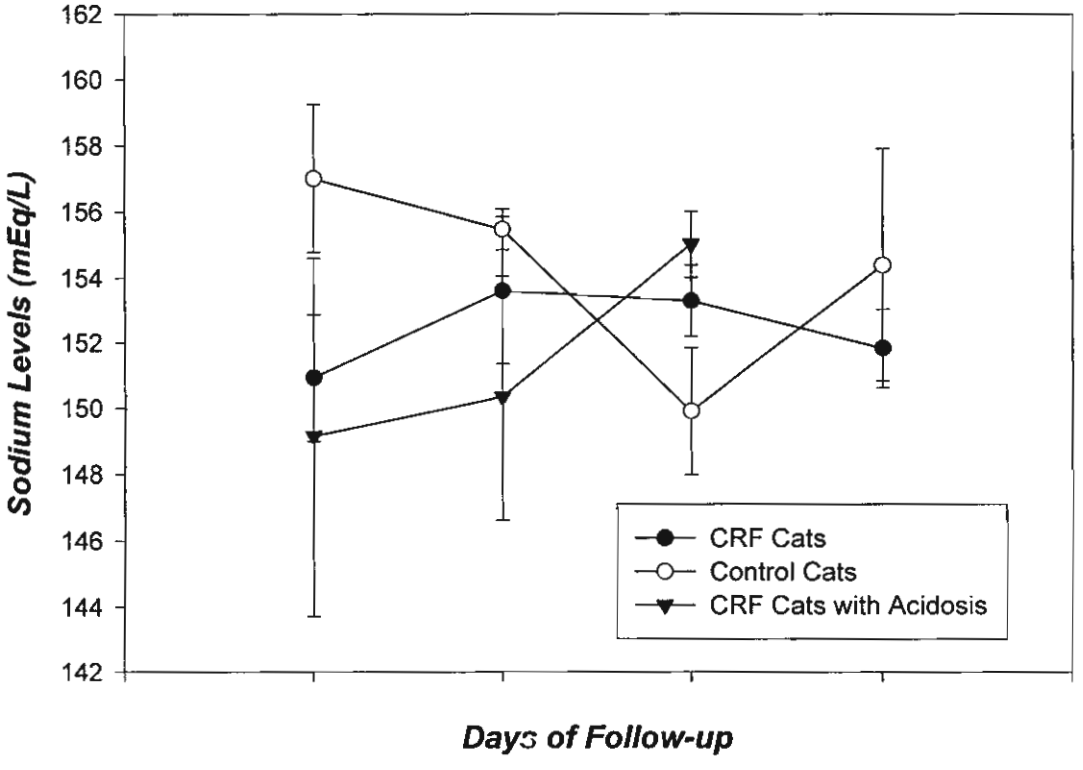
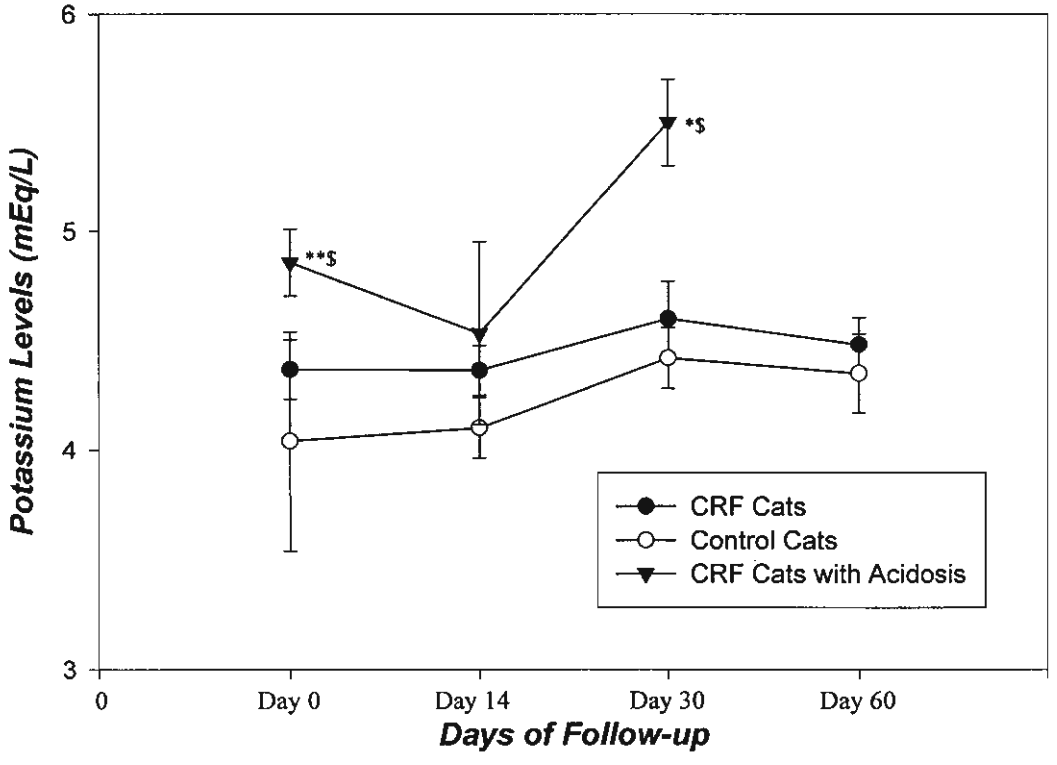


**Figure 13** Mean +/- SEM of Potassium Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls
** = $p < 0.01$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 14** Mean +/- SEM of AST Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.

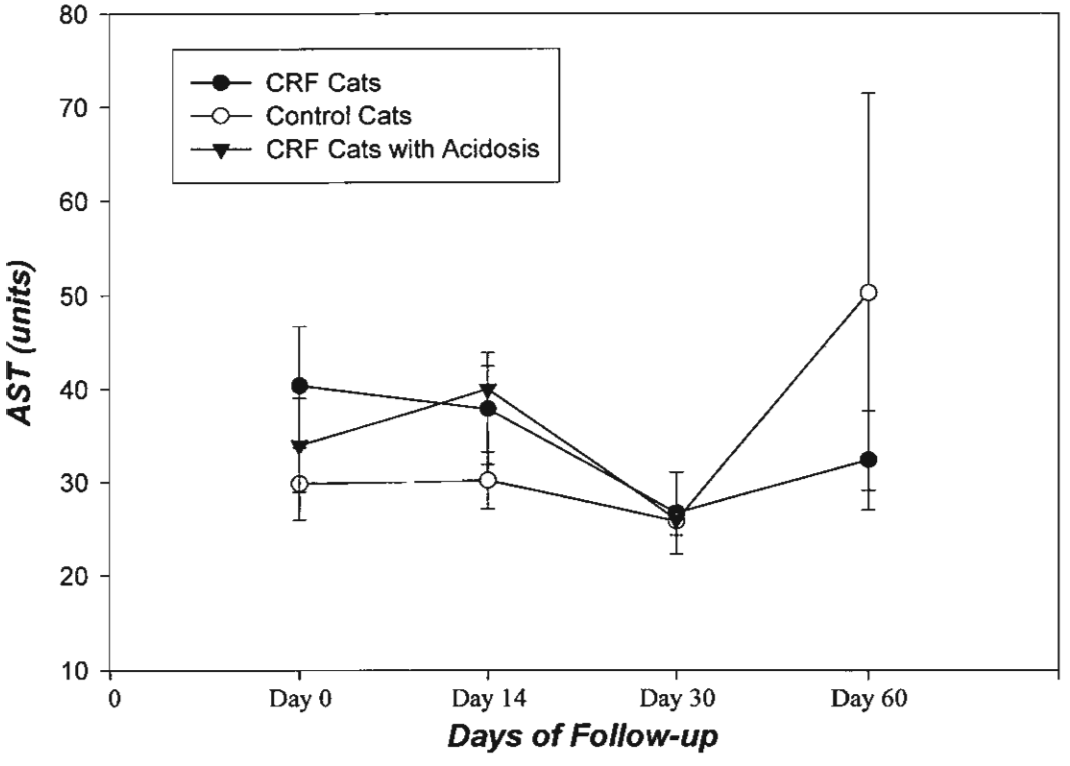
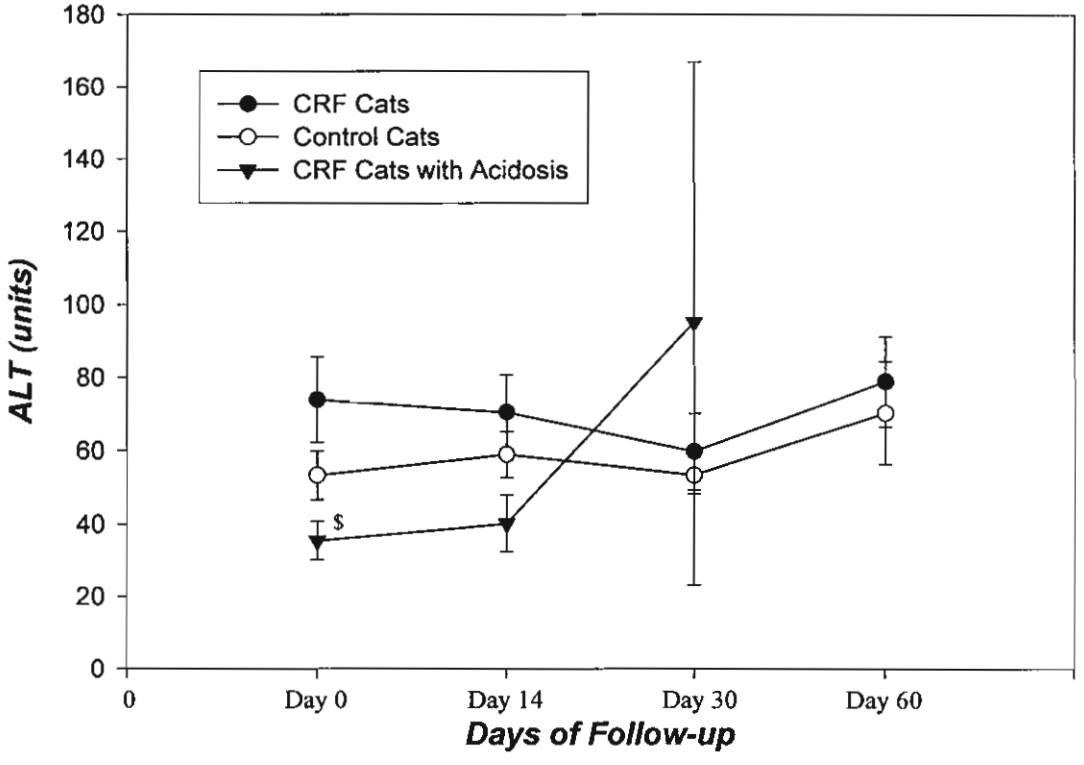
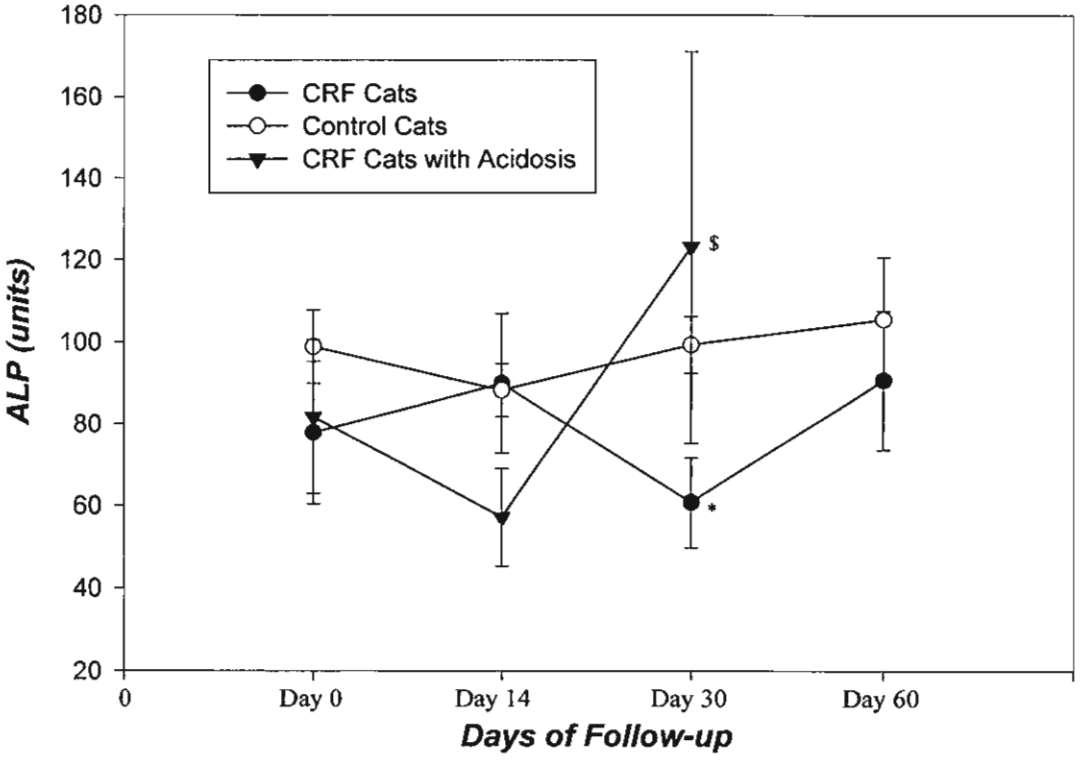


**Figure 15** Mean +/- SEM of ALT Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.



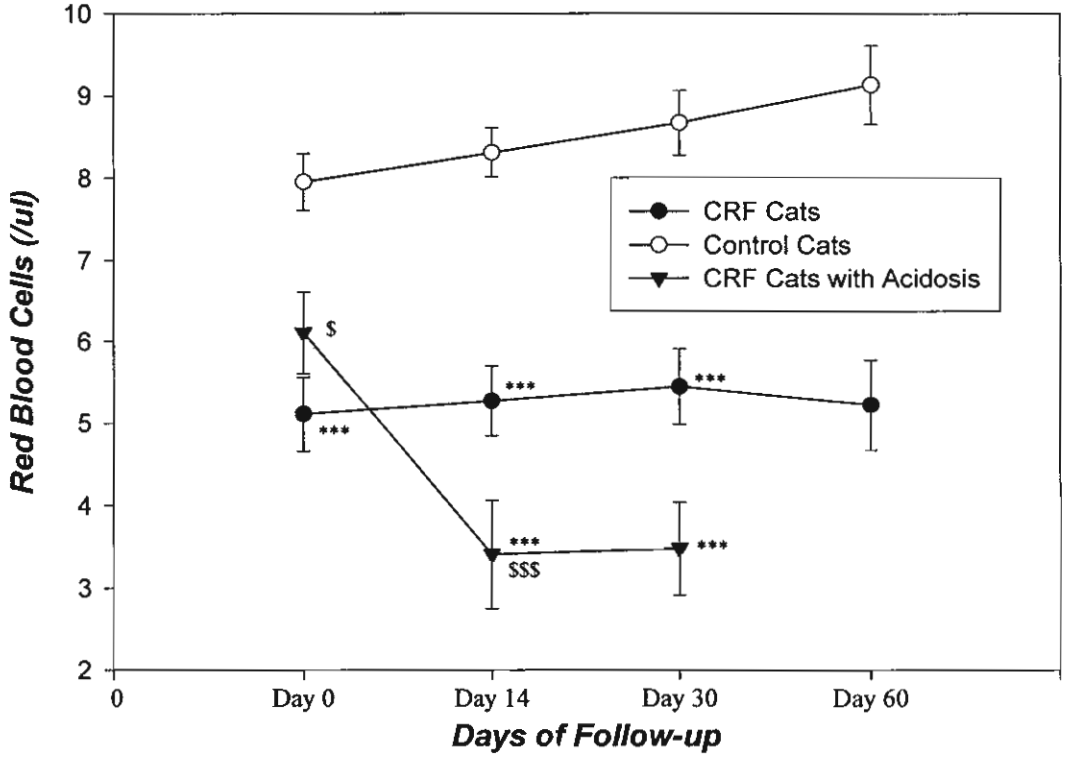

**Note:** $ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 16** Mean +/- SEM of ALP Levels for Control Cats, CRF Cats, and CRF Cats with Acidosis.



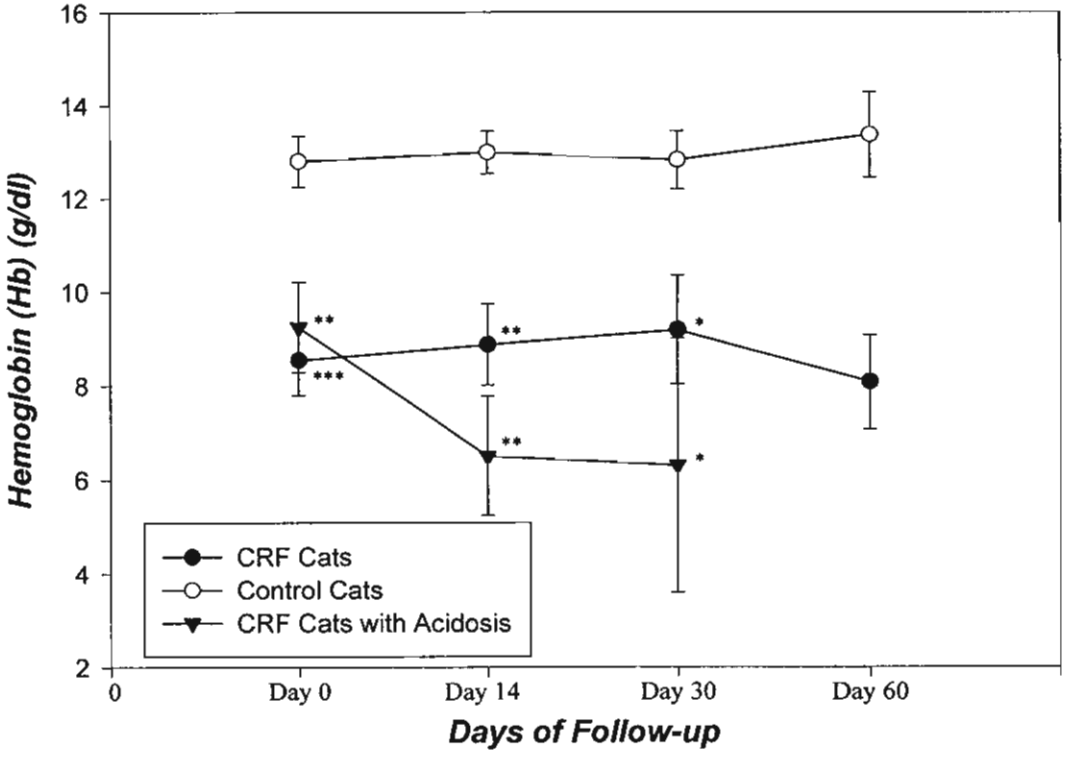

**Note:** * = $p < 0.05$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis

**Figure 17** Mean +/- SEM of Red Blood Cells for Control Cats, CRF Cats, and CRF Cats with Acidosis.



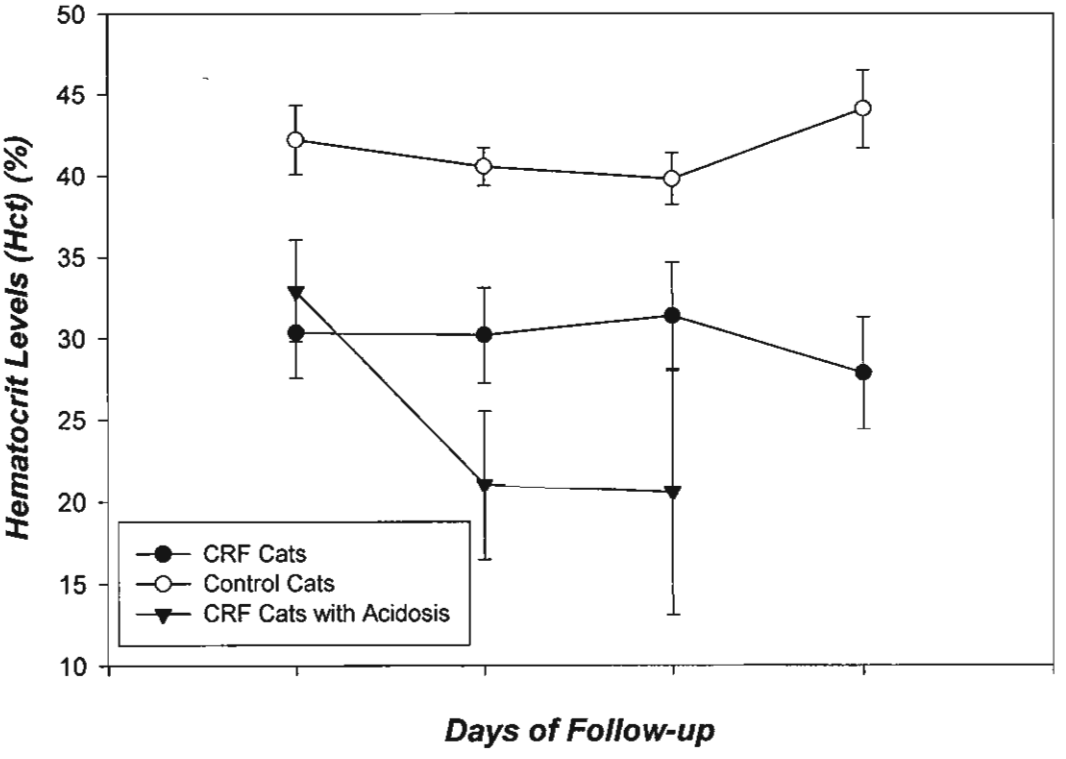

**Note:** *** = $p < 0.001$ when compared with controls
$ = $p < 0.05$ when compared between non-acidotic and CRF cats with acidosis
$$$ = $p < 0.001$ when compared between non-acidotic and CRF cats with acidosis

**Figure 18** Mean +/- SEM of Hemoglobin (Hb) for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls
** = $p < 0.01$ when compared with controls
*** = $p < 0.001$ when compared with controls

**Figure 19** Mean +/- SEM of Hematocrit Levels (Hct) for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls
** = $p < 0.01$ when compared with controls

**Figure 20** Mean +/- SEM of White Blood Cells (WBC) for Control Cats, CRF Cats, and CRF Cats with Acidosis.

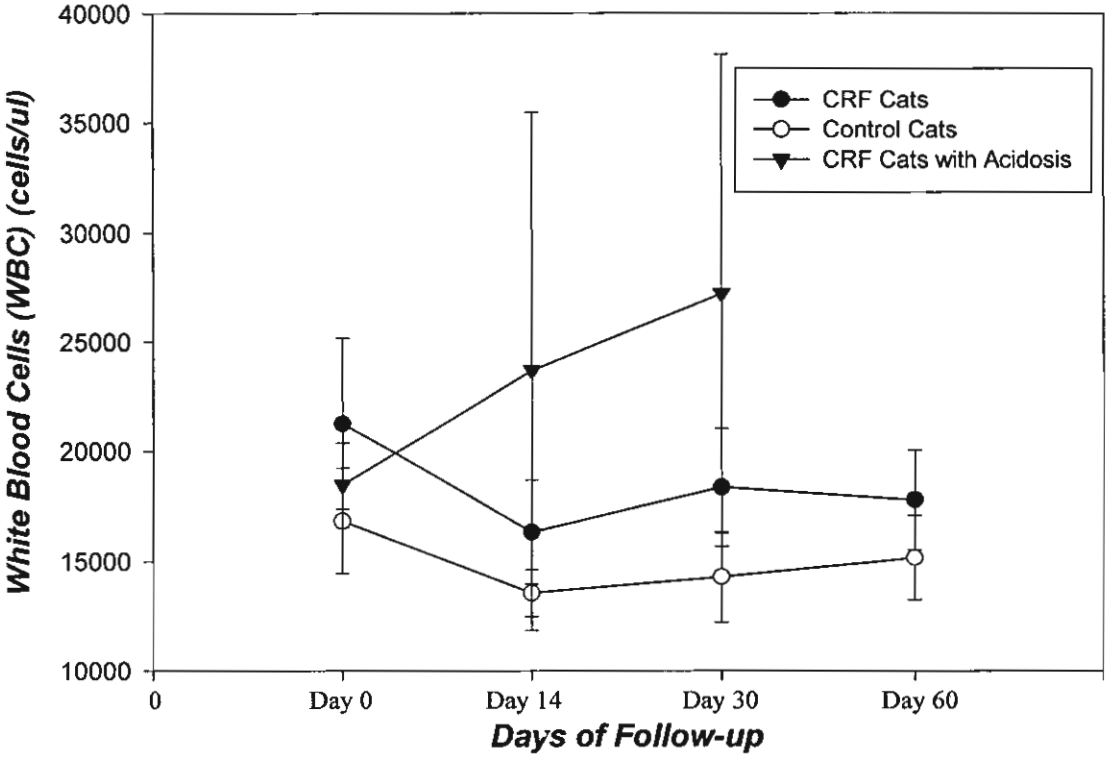
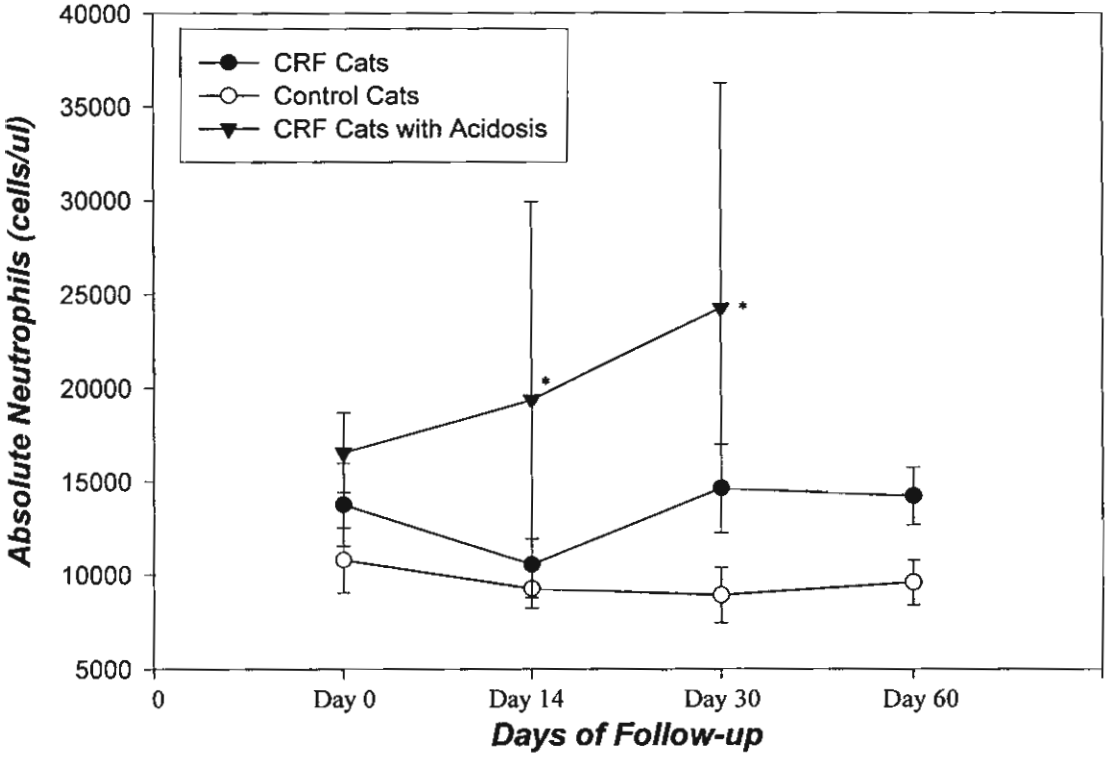


**Figure 21** Mean +/- SEM of Absolute Neutrophils for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** * = $p < 0.05$ when compared with controls

**Figure 22** Mean +/- SEM of Absolute Band Cells for Control Cats, CRF Cats, and CRF Cats with Acidosis.

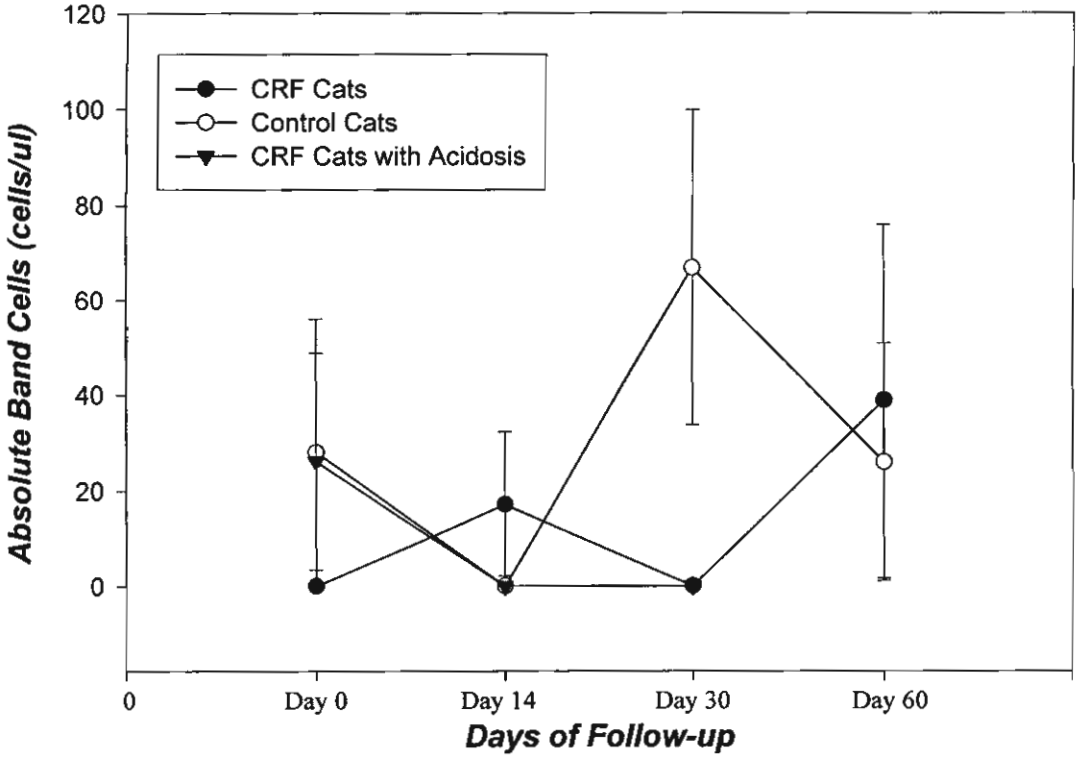


**Figure 23** Mean +/- SEM of Absolute Eosinophils for Control Cats, CRF Cats, and CRF Cats with Acidosis.

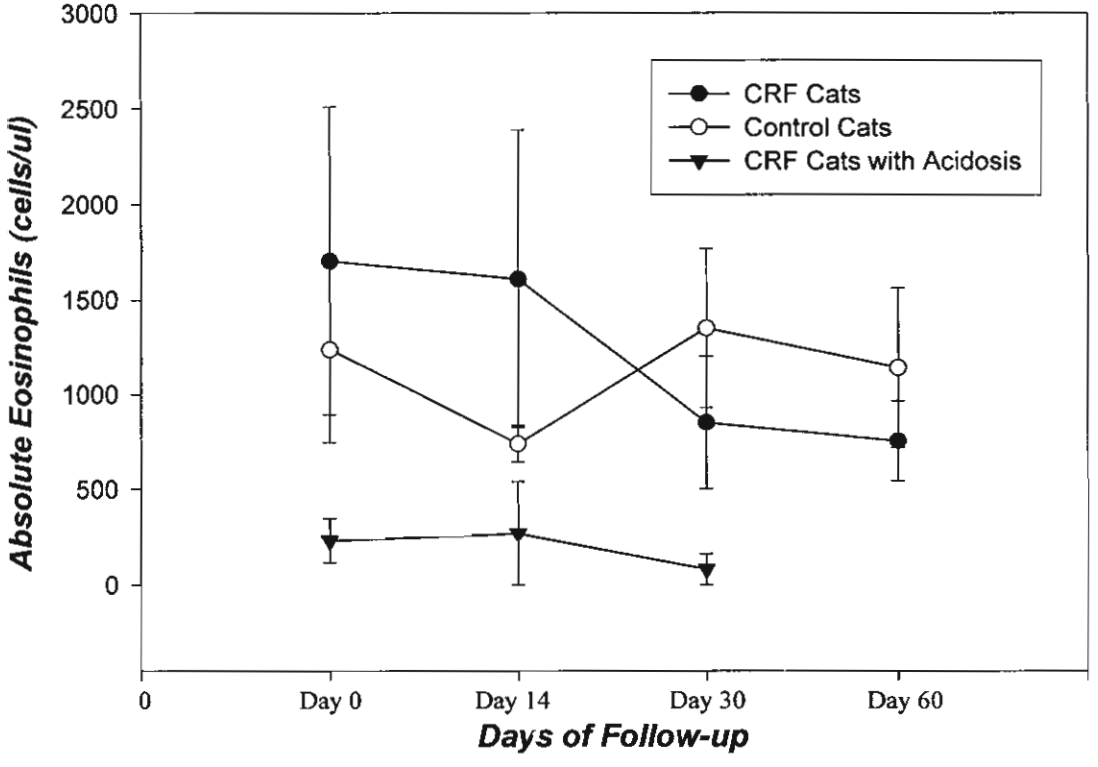


**Figure 24** Mean +/- SEM of Absolute Lymphocytes for Control Cats, CRF Cats, and CRF Cats with Acidosis.

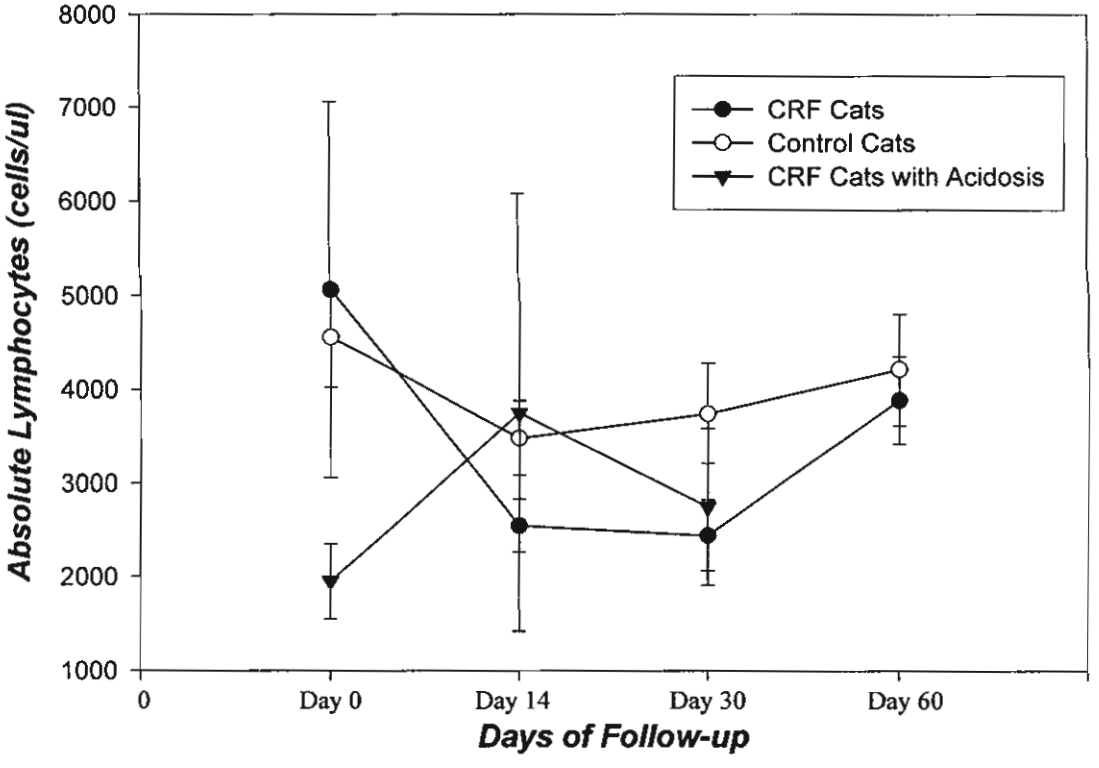
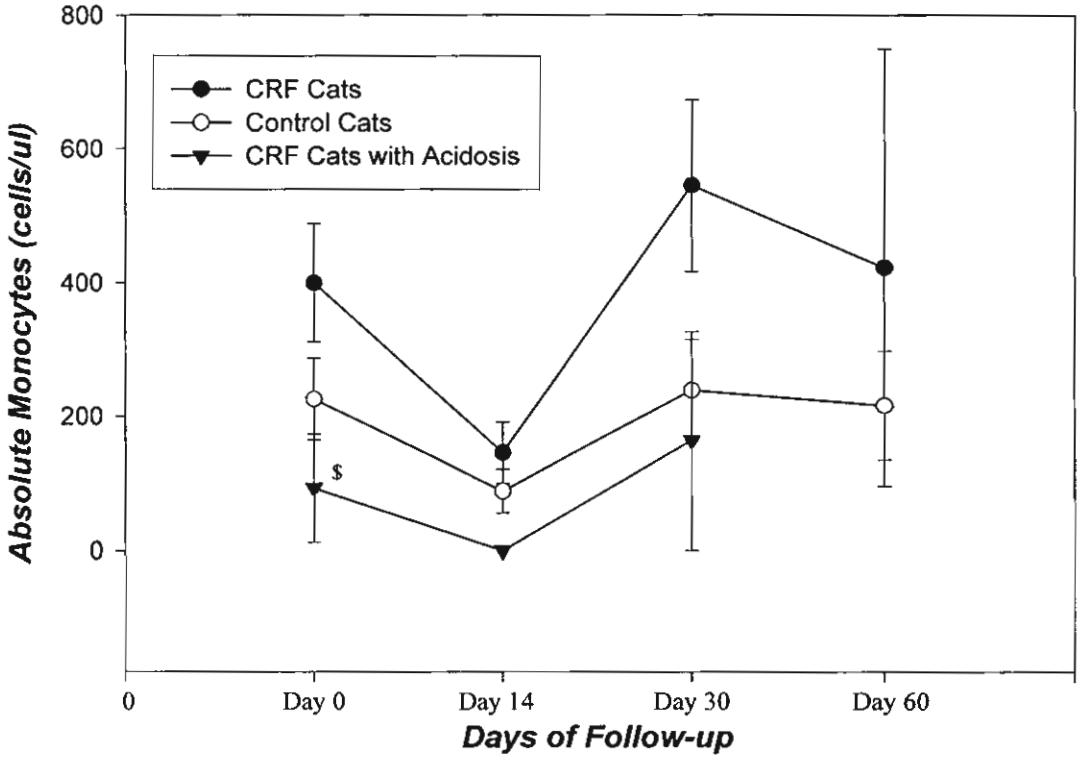


**Figure 25** Mean +/- SEM of Absolute Monocytes for Control Cats, CRF Cats, and CRF Cats with Acidosis.




**Note:** $ = $p < 0.05$ when compared between non-acidosis and CRF cats with acidosis

# 5. Discussion

The results of this study demonstrated that Siamese cat has high incidence of chronic renal failure. This spontaneous renal failure is a common cause of mortality in older and occasionally, younger cats. Twenty-five percents of affected cats in this study were younger than 5 years old. In United States, DiBartola et al. (1987) found that 53% of affected cats were older than 7 years, but animals ranged in age from 9 months to 22 years(DiBartola et al, 1987). It was also found that CRF is a common disease especially in older cats. The results of this study indicated that the incidence of renal failure in Siamese CRF cats also increased with age.

Siamese cats with CRF also had lower red blood cell, hemoglobin, and packed cell volume than control cats, most of them were within the normal reference range on the first day of diagnosis. Anemia is often found in CRF patients due to nutritional abnormalities, blood loss with iron deficiency, short survival time of RBCs, hemolysis, and depression of bone marrow function by uremia associated with toxins. Inadequate production of erythropoietin has emerged as the principle cause of anemia in human and animals with CRF (Eschbach and Adamson, 1991). However, anemia was not detected in any CRF groups on first day of diagnosis in this study especially in cats with end-stage CRF.

The prevalence of renal secondary hyperparathyroidism in Siamese cats with CRF in this study was 42 percent. All cats in the end-stage group (100%) had elevated parathyroid hormone concentrations since the first day of diagnosis. Hyperparathyroidism was a frequent sequela of CRF, affecting 84 per cent of cats with CRF in one study (Barber and Elliot, 1998). The severity and prevalence of RHPTH increasing with the

degree of renal dysfunction. Renal secondary hyperparathyroidism occurs in association with hyperphosphatemia, low circulating 1,25-dihydroxycholecalciferol(calcitriol) levels, reduced blood ionized calcium concentration, and skeletal resistance to the calcemic action of PTH. However, in early to moderate renal failure, it is difficult to dissect out the specific factors responsible for hyperparathyroidism because the increase in PTH serve to prevent hypocalcemia, hyperphosphatemia, and the decrease in calcitriol (Felsenfield, 1997). Relative or absolute deficiency of calcitriol has been hypothesized to play a pivotal role in the development of renal secondary hyperparathyroidism (Chew and Nagode, 1992). Calcitriol, the most active form of vitamin D, is formed by 1-α-hydroxylation of 25-hydroxycholecalciferol in renal tubular cells. PTH promotes renal 1-α-hydroxylase activity and formation of calcitriol. In turn, calcitriol limits PTH synthesis by feedback inhibition. Early in the course of CRF, the inhibitory effects of phosphate retention on renal tubular 1-α-hydroxylase activity limit calcitriol production. In more advanced renal failure, only serum calcium was found to correlate with serum PTH activity (Kates et al, 1997). Impaired intestinal absorption of calcium related to low serum calcitriol levels probably plays an important role in hyperparathyroidism in these patients with advanced renal failure. Excess PTH levels may also promote nephrocalcinosis and consequent progressive loss of renal function (Nagode and Chew,1993). PTH has thus been hypothesized to function as a uremic toxin, althought he precise contribution of hyperparathyroidism to the uremic syndrome remains unresolved.

All Siamese cats with renal secondary hyperparathyroidism had total calcium levels within the normal reference range and no palpable parathyroid adenoma on physical examination. There was no significant differences in mean total calcium

concentration between the three groups of cats. Hyperparathyroidism was even detected in some cats with normal serum calcium and phosphate concentrations (Polzin et al,2000). In human patients, hyperparathyroidism develops early in CRF while serum calcium and phosphorus concentrations remain within normal limits (Martinez et al, 1997).

Blood ionized calcium concentration was within the normal reference range in all groups of cats. Blood ionized calcium concentrations are often reduced in cats with spontaneous CRF; in one study, over 50 per cent of cats with advanced end-stage CRF were hypocalcemic (Barber and Elliot, 1998). On the contrary, cats in the uremic group in this study had higher blood ionized calcium on day 60 of the follow-up which could indicated the increase in the severity of renal dysfunction in the uremic group.

On the basis of adjusted plasma calcium concentrations, hypercalcemia was found in 42 percent of CRF cats and 100 percents of cats in the end-stage group on day 30 of the followed-up. Hypocalcemia was not detected in any CRF cats in this study. In previous studies, hypercalcemia has been found in 10 percent of CRF cats and 15 percent of CRF cats were hypocalcemia (DiBartola and Rutgers, 1987; Lulich et al, 1992). These differences may reflect the use of different cats' population between different studies. In contrast to total calcium, elevated ionized calcium concentrations were found in 58 percent of CRF cats whereas low ionized calcium was present in 42 percent. Only approximately half of plasma total calcium is composed of ionized calcium; the remainder, both complexed and protein-bound calcium, is not only affected by changes in calcium status but also by alterations in binding affinity and concentrations of binding factors.

Sick dogs may also have disturbances in calcium homeostasis (Rosol et al, 2000), but a total calcium concentration within reference range does not ensure that calcium is distributed among the fractions as would normally be expected (Toffaletti, 1983). Although the technology for measurement of ionized calcium concentration has vastly improved (Bowers et al, 1986), evaluation of calcium status has largely relied on determination of total calcium concentration. Ionized calcium concentration is a more sensitive indicator of pathologic states than is total calcium (Gosling, 1986), especially in humans with hyperparathyroidism (Boyd et al, 1981), hypercalcemic conditions, renal disease, and critical illnesses. A number of cats were hyperparathyroid in the absence of abnormalities in the parameters of calcium homeostasis (Barber and Elliot, 1998).

Siamese cats in end-stage group were hyperphosphatemia in this study. The kidneys play a pivotal role in regulating phosphorus balance. The kidneys are the primary route of phosphorus excretion. Renal phosphorus excretion is the net of glomerular filtration less tubular reabsorption of phosphorus. If dietary phosphorus intake remains constant, a decline in GFR leads to phosphorus retention and ultimately hyperphosphatemia (Polzin et al, 2000). Our results also demonstrated a significant correlation ($r^2 = 0.69$) between serum creatinine and phosphorus concentration in CRF cats. Study in 80 cats with CRF in one study also indicated a significant correlation between plasma phosphate and PTH concentrations (Barber and Elliot, 1998). The primary consequence of hyperphosphatemia is development and progression of secondary hyperparathyroidism. Increases in serum PTH activities in dogs and humans with CRF are closely associated with the degree of hyperphosphatemia and hyperphosphatemia was

found to be 72 per cent efficient in predicting hyperparathyroidism in cats with CRF (Barber and Elliot, 1998).

All Siamese cats in end-stage CRF group died before completed 60 days of the study. Hyperphosphatemia has been directly linked to increased mortality in humans and dogs with CRF.[28-30] In humans with CRF receiving hemodialysis therapy, the adjusted relative risk of mortality was stable in patients with serum phosphate concentrations below 6.5 mg/dL but increased significantly above this level. The overall mortality risk associated with hyperphosphatemia was 1.06 per 1 mg/dL increase in serum phosphorus. An additional consequence of hyperphosphatemia is a predisposition to metastatic calcification when the Ca X $PO_4$ product is elevated. A Ca X $PO_4$ product of 42 to 52 is considered desirable for humans with renal failure.[31] The likelihood of soft tissue calcification increases greatly when the Ca X $PO_4$ product exceeds 60. Calcification is especially prominent in proton-secreting organs, such as the stomach and kidneys, in which basolateral bicarbonate secretion results in an increase in pH that promotes calcium hydrogen phosphate (brushite) precipitation.[32] However, myocardium, lung, and liver are also commonly mineralized in patients with CRF.

There was a strong inverse correlation between parathyroid hormone concentration and survival of cats with CRF especially in cats with end-stage. The higher the concentration of parathyroid hormone detected on the first day of diagnosis, the shorter of the survival time for the CRF cats. The level of parathyroid hormone concentration measured on the first day of the diagnosis of CRF may possibly be a predictor of survival for Siamese cats with CRF.

Metabolic acidosis is reported to be a common complication of feline chronic renal failure (CRF) but acid-base status of feline patients with this disease is rarely assessed by general practitioners. The results of our study demonstrated that metabolic acidosis is a well-recognized component of CRF. We found that 8 out of 21 CRF cats (38.10%) had metabolic acidosis on the first day of presentation at CUVTH. All CRF cats that develop metabolic acidosis were all in the end-stage CRF. In retrospective case series, 63 per cent and 80 per cent of cats with CRF had metabolic acidosis (DiBartola et al.,1987; Lulich et al.,1992). However, the prevalence of metabolic acidosis in one prospective study was zero among nonuremic CRF cats, 8 per cent among "uremic" cats, and 50 per cent among cats with end-stage CRF (Elliot and Barber, 1998).

In this study, we found that CRF cats with acidosis had decreased level of bicarbonate on day 0 of the study. Metabolic acidosis results primarily from the limited ability of failing kidneys to excrete hydrogen ions, secondary to disordered ammoniagenesis, decreased maximal renal tubular proton secretion (Kimmel, 1998). Bicarbonate wasting may also contribute. Bicarbonate wasting and chloride retention result in hyperchloremic (normal anion gap) acidosis. When phosphate and organic acid (uric acid, hippuric acid, lactic acid) retention is sufficient, high-anion-gap acidosis results. However, we did not measure chloride level in all CRF cats in this study so the anion gap could not be calculated from the results of this study.

A combination of tubular reabsorption of filtered bicarbonate and excretion of hydrogen ions with ammonia and urinary buffers, primarily phosphate, maintains normal acid-base balance. As renal mass declines, hydrogen ion excretion is maintained largely by increasing the quantity of ammonium excreted by surviving nephrons. However, at

some level of renal dysfunction, the capacity to increase renal ammoniagenesis further is lost and metabolic acidosis ensues. Decreased medullary recycling of ammonia caused by structural renal damage may also contribute to impaired ammonium excretion.

Chronic metabolic acidosis promotes a variety of adverse clinical effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, weight loss, and malnutrition. Alkalization therapy appears to be of value in reversing these signs as demonstrated in CRF cats with acidosis on day 14 and 30 of the study. In addition, chronic mineral acid feeding to dogs has been shown to increase urinary calcium excretion and progressive bone demineralization, the magnitude of which depends on age and dietary calcium levels. Studies of the effects of dietary acidification in cats have revealed that chronic metabolic acidosis can cause negative calcium balance and bone demineralization or negative potassium balance, which may in turn promote hypokalemia, renal dysfunction, and taurine depletion (Fettman et al.,1992). Potassium depletion is common in patients with metabolic acidosis due to gastrointestinal losses (as with diarrhea) and/or renal losses of Potassium. However, the results of this study showed that CRF cats with acidosis had significantly increased in the level of potassium on day 0 and day 30 of the follow-up. The initial plasma K+ concentration may be elevated since metabolic acidemia (except for the organic acidosis) causes K+ to move out of the cells into the extracellular fluid (Adrogue and Madias,1981). In these settings, the true state of K+ balance will become apparent as the pH is normalized.

Severe acidemia may result in decreased cardiac output, arterial pressure, and hepatic and renal blood flows and centralization of blood volume (Androgue and Madias,1998). Centralization of blood volume results from peripheral arterial

vasodilatation and central venoconstriction. Decreases in central and pulmonary vascular compliance may predispose patients to pulmonary edema during fluid administration, an effect that may be particularly important in patients with acute uremic crises requiring intensive fluid therapy. Acidemia also promotes reentrant arrhythmias and reduction in the threshold for ventricular fibrillation. Severe acidosis may also influence carbohydrate and protein metabolism, serum potassium concentrations, and brain metabolism (Androgue and Madias,1998).

Metabolic acidosis has been theorized to enhance progression of renal failure by promoting renal ammoniagenesis and activation of the alternative complement pathway (Nath et al.,1985; Nath et al.,1989). Reducing renal ammoniagenesis and renal tubular peptide catabolism was accompanied either by reduced renal tubular injury or by tubular hyperfunction in human patients with CRF. It has been concluded that metabolic acidosis neither causes nor exacerbates chronic renal injury. Furthermore, treatment of uremic acidosis was deemed unlikely to influence disease progression in patients with CRF. Studies performed in one laboratory in cats with induced CRF have likewise failed to identify an adverse effect of chronic acidosis on renal structure or function. (James K, Polzin DJ, Osborne CA: Unpublished observations).

Of great clinical importance is the observation that chronic acidosis may promote protein malnutrition in patients with CRF. Protein catabolism is increased in patients with acidosis to provide a source of nitrogen for hepatic glutamine synthesis, glutamine being the substrate for renal ammoniagenesis (Mitch and Jurkovitz, 1989; Mitch,1997). Evidence from studies of rat muscle suggests that uremia directly impairs insulin-stimulated protein synthesis independent of metabolic acidosis. On the other hand,

protein degradation is stimulated by metabolic acidosis, even in nonuremic states. The combine effects of reduced protein synthesis related to uremia and accelerated proteolysis related to acidosis promote elevations in blood urea nitrogen (BUN), increased nitrogen excretion, and negative nitrogen balance typical of uremic acidosis. Altered branched-chain amino acid metabolism appears to be involved. Chronic metabolic acidosis increases the activity of muscle branched-chain keto acid dehydrogenase, the rate-limiting enzyme in branched-chain amino acids are rate limiting in protein synthesis and play a role in regulation of protein turnover. Alkalization therapy effectively reverses acidosis-associated protein breakdown. Although glucocorticoids appear to be essential for acidosis-induced protein catabolism, this response can be blocked in uremic animals by correcting acidosis despite persistent increases in glucocorticoid levels. Excessive protein catabolism may lead to protein malnutrition despite adequate dietary intake. This process may then accelerate breakdown of endogenous cationic and sulfurcontaining amino acids, promoting further acidosis.

Acidosis poses a particularly vexing problem for patients with CRF consuming protein-restricted diets. Dietary protein requirements appear to be similar for normal humans and humans with CRF unless uremic acidosis is present. When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protect patients consuming low-protein diets from losses in lean body mass. Metabolic acidosis blocks the metabolic responses to dietary protein restriction in two ways: it stimulates irreversible degradation of the essential, branched-chain amino acids and stimulates degradation of protein in muscle (Mitch,1997). Thus, acidosis may limit the ability of humans to adapt to dietary protein restriction. Metabolic acidosis also suppresses

albumin synthesis in humans and may reduce the concentration of serum albumin. This study demonstrated an increased in albumin levels in CRF cats without metabolic acidosis on day 0 of the study then a decrease level of albumin on day 14 of the study suggested the present of hypoalbuminemia which may be due to anorexia and weight loss of CRF cats. We did not find hypoalbuminemia in CRF cats with acidosis.

There is some evidence that feline kidneys may respond differently to metabolic acidosis compared with kidneys of other mammalian species. Apparently, acidosis fails to increase the rate of production of ammonia in cultured feline proximal tubular cells (Lemieux et al.,1990). Whether this characteristic causes cats to be at increased risk for developing metabolic acidosis is unknown, but the unexpectedly high incidence of acidosis in cats with CRF would be consistent with this suggestion. Species-related differences in renal acid excretion aside, it is likely that the high incidence of uremic acidosis in cats is related, at least in part, to the acidifying nature of many cat foods.

The results of our study demonstrated that CRF cats with metabolic acidosis had increased level of PTH. The kidneys play a pivotal role in regulating phosphorus balance because kidneys are the primary route of phosphorus excretion. Renal phosphorus excretion is the net of glomerular filtration less tubular reabsorption of phosphorus. If dietary phosphorus intake remains constant, a decline in GFR leads to phosphorus retention and ultimately hyperphosphatemia. However, during the early stages of renal failure, serum phosphorus concentrations typically remain within the normal range because of a compensatory decrease in phosphate reabsorption in the surviving nephrons. This renal tubular adaptation is largely an effect of renal secondary hyperparathyroidism. Increased PTH levels promote renal excretion of phosphate by reducing the tubular

transport maximum for phosphate reabsorption in the proximal tubule via the adenylate cyclase system. When GFR declines below about 20 per cent of normal, this adaptive effect is maximized an hyperphosphatemia ensues.

In dogs and cats with CRF, serum phosphorus concentrations typically parallel serum urea nitrogen concentrations. Thus, hyperphosphatemia is common in azotemic patients but unexpected in patients with nonazotemic renal disease. The primary consequence of hyperphosphatemia is development and progression of secondary hyperparathyroidism. Increases in serum PTH activities in dogs and humans with hyperphosphatemia (Nagode and Chew, 1992; Kates et. al,1997) and hyperphosphatemia was found to be 72 per cent efficient in predicting hyperparathyroidism in cats with CRF (Barber and Elliot,1998). Hyperphosphatemia does not appear to induce clinical signs directly. However, hyperparathyroidism and soft tissue calcification may contribute to morbidity and mortality in CRF (Block et. al,1998). Secondary hyperparathyroidism causes renal osteodystrophy and PTH is a purported uremic toxin that may contribute to may signs of uremia (Massry and Smogorzewski, 1994; Nagode et. al,1996).

Hyperphosphatemia has been directly linked to increased mortality in humans and dogs with CRF (Block et. al,1998; Massry and Smogorzewski, 1994;Nagode et. al, 1996). All CRF cats with acidosis in this study died after day 30 of the study and did not survive to complete the study. In humans with CRF receiving hemodialysis therapy, the adjusted relative risk of mortality was stable in patients with serum phosphate concentrations below 6.5 mg/dL but increased significantly above this level. The overall mortality risk associated with hyperphosphatemia was 1.06 per 1 mg/dL increase in serum phosphorus. The calcium X phosphate product showed a mortality risk trend similar to that seen for

phosphate, with patients with Ca X $PO_4$ products greater than 72 having a relative mortality risk of 1.34 compared with that associated with products between 42 and 52 $mg^2/dL^2$ (Block et al,1998). Analysis of calcium revealed no correlation with relative risk of death.

In more advanced renal failure, only serum calcium was found to correlate with serum PTH activity (Kates et al,1997). Impaired intestinal absorption of calcium related to low serum calcitriol levels probably plays an important role in hyperparathyroidism in these patients with advanced renal failure.

Although renal secondary hyperparathyroidism and renal osteodystrophy are well-documented effects of CRF, clinically important renal osteodystrophy is rare in dogs and cats (Barber and Elliot, 1998). In dogs, it most often occurs in immature patients, presumably because metabolically active growing bone is more susceptible to the adverse effects of hyperparathyroidism. For unexplained reasons, bones of the skull and mandible may be the most severely affected and may become so demineralized that the teeth become movable and the jaw can be bent or twisted without fracturing ("rubber jaw" syndrome). Marked proliferation of connective tissue associated with the maxilla may cause distortion of the face. The skull and mandible do not appear to be predisposed to renal osteodystrophy in cats (Barber and Elliot,1998). Pathologic fractures are seemingly uncommon in dogs and cats with CRF. Other possible but uncommon clinical manifestations of severe renal osteodystrophy include skeletal decalcification, cystic bone lesions, bone pain, and growth retardation.

Although bone and kidneys are the classical target organs for PTH, studies have shown that in renal failure PTH may also affect function of nonclassical organs and

tissues, including brain, heart, smooth muscles, lungs, erythrocytes, lymphocytes, pancreas, adrenal glands, and testes (Bro and Olgaard,1997). Toxicity of PTH appears to be mediate through enhanced entry of calcium into cells with PTH or PTH2 membrance receptors (Nagode et al,1993). Sustained PTH-mediated calcium entry leads to inhibition of mitochondrial oxidation and production of ATP. Extrusion of calcium from cells is reduced because of the impairment of ATP production and disruption of the sodium-calcium exchanger. Persistently increased basal cytosolic calcium levels promote cellular dysfunction and death (Nagode and Chew,1992).

Hyperparathyroid-induced cellular dysfunction may lead to carbohydrate intolerance, platelet dysfunction, impaired mitochondria energy metabolism and myofiber mineralization), inhibition of erythropoiesis, altered red cell osmotic resistance, altered B-cell proliferation, sysnaptosome and T-cell dysfunction, and defects in fatty acid metabolism (Vanholder, 1998; Nagode and Chew,1993). Potential nonskeletal clinical consequences of hyperparathyroidism include mental dullness and lethargy, weakness, inappetence, and an increased incidence of infections because of immunodeficiency (Nagode and Chew, 1993). PTH has thus been hypothesized to function as a uremic toxin, although the precise contribution of hyperparathyroidism to the uremic syndrome remains unresolved.

Renal secondary hyperparathyroidism may be associated with substantial enlargement of the parathyroid glands. This finding may be of clinical importance in cats because of frequent coincident hyperthyroidism, which may be suggested by the presence of a thyroid nodule palpable in the cervical region. Hyperplastic parathyroid glands were palpable as paratracheal masses in 11 of 80 cats with spontaneous CRF (Barber and

Elliot,1998). We found one CRF cats without metabolic acidosis with enlargement of parathyroid glands but with normal plasma calcium levels. Care should be taken to differentiate parathyroid hyperplasia from hyperthyroidism in cats with paratracheal masses.

All 21 Cats with CRF in this study developed anemia both in non-acidotic group and CRF cats with acidosis. The results showed decreased in red blood cells, hemoglobin, and hematocrit levels in all CRF cats. A progressive hypoproliferative anemia is characteristic of dogs and cats with moderate to advanced CRF. Although affected by the patient's age, species, specific renal diagnosis, and concurrent diseases, the severity and progression of the anemia and clinical signs correlate with the degree of renal failure and worsen with progressive renal failure in both dogs and cats (Cowgill, 1992).

Anemia in patients with CRF is multifactorial and may be exacerbated by concurrent illness. Although experimental and clinical evidence exists for the supporting roles of shortened red cell life span, nutritional abnormalities, erythropoietic inhibitor substances in uremic plasma, blood loss, and myelofibrosis, erythropoietin deficiency has clearly emerged as the principal cause of anemia in humans and animals with CRF (Cowgill, 1992). The renal peritubular capillary endothelial cells are the major source of erythropoietin synthesis. It may also be produced by renal interstitial fibroblasts. The kidneys synthesize erythropoietin on demand in response to intrarenal tissue hypoxia cuased by either decreased oxygen carrying capacity (anemia) or decreased oxygen content (hypoxia)(Nissenson et al,1991). Many CRF patients have a relative, rather than absolute, erythropoietin deficiency in that plasma levels exceed the normal range (King et al,1992; Hocking, 1987). However, erythropoietin levels are lower than those in

equivalently anemic but nonuremic patients, Anemic cats with CRF have been reported to have erythropoietin levels similar to those of normal cats (Cook and Lothrop, 1994). Several hypotheses have been proposed to account for the erythropoietin deficient of CRF: (1) decreased renal mass resulting in an insufficient cellular capacity for new hormone synthesis, (2) lowered set point for response to the hypoxic stimulus, and (3) increased plasma proteolytic activity resulting in accelerated erythropoietin degradation (Hocking, 1987).

Other clinically important causes of anemia in dogs and cats with CRF are iron deficiency and chronic gastrointestinal blood loss. In most patients, iron deficiency can be detected only by measuring serum iron, staining bone marrow biopsy samples for iron content, or observing the response to iron supplementation. Chronic gastrointestinal hemorrhage may or may not be evident on the basis of stool color. It can be suspected on the basis of (1) a hematocrit level that is unexpectedly low relative to the magnitude of renal dysfunction and (2) an elevation in the serum urea nitrogen to serum creatinine ration.

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**Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.**

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ

1.1 Pusoonthornthum R, Pusoonthornthum P, Yibchok-anun S, Ekthamasut L, Danpitakkul M, Sudsuang S. " Serum parathyroid hormone abnormalities in cats with chronic renal failure." Proceedings of the 28 th World Congress of the World Small Animal Veterinary Association, Bangkok , Thailand. 2003.

Anticipated international journals to be published:

1.2 Pusoonthornthum R, Pusoonthornthum P, Yibchok-anun S. Renal secondary hyperparathyroidism in Siamese and Siamese-mixed breed cats with naturally occuring Chronic Renal Failure: a predictor of survival. American Journal of Veterinary Research. (submitted).

1.3 Pusoonthornthum R, Pusoonthornthum P, Yibchok-anun S. Parathyroid hormone levels in Siamese and Siamese-mixed breed cats with various stages of naturally occuring chronic renal failure. Journal of American Veterinary Internal Medicine (in preparation).

2. การนำผลงานวิจัยไปใช้ประโยชน์

2.1 เชิงสาธารณะ (มีเครือข่ายความร่วมมือ/สร้างกระแสความสนใจในวงกว้าง)

1. การเผยแพร่ทางวิชาการในการบรรยายพิเศษทางวิทยุ
จัดโดยสัตวแพทยสมาคมแห่งประเทศไทย(ในพระบรมราชูปถัมภ์)
ร่วมกับสถานีวิทยุ จ.ส. 100
เรื่อง "โรคไตวายเรื้อรังในแมว"

2. การเผยแพร่ทางวิชาการในการบรรยายพิเศษทางวิทยุ
จัดโดยคณะสัตวแพทยศาสตร์ ในรายการสัตวแพทย์สนทนา
เรื่อง "โรคไตวายเรื้อรังในแมว"

2.2 เชิงวิชาการ (มีการพัฒนาการเรียน การสอน/สร้างนักวิจัยใหม่)

3. อื่นๆ

3.1 ผลงานตีพิมพ์ในวารสารวิชาการในประเทศ

3.2 การเสนอผลงานในที่ประชุมวิชาการ

1. การเสนอผลงานทางวิชาการในการประชุม
สมาคมสัตวแพทย์สัตว์เล็กโลก (World Small Animal Veterinary Association; WSAVA) ณ ศูนย์ประชุมแห่งชาติสิริกิติ์
วันที่ 23 - 25 ตุลาคม 2544

2. การเผยแพร่ทางวิชาการในการประชุมของสัตวแพทย์จัดโดย
สมาคมสัตวแพทย์ผู้ประกอบการบำบัดโรคสัตว์แห่งประเทศไทย
ร่วมกับบริษัท ดีทแฮม (ประเทศไทย) จำกัด

**Other activities that involved with this research project:**

1. Project director was invited to present a seminar on "Feline Chronic Renal Failure "to Singapore 's Veterinarians Association on March 23, 2002 at the Sheraton Grand Hotel in Singapore.

2. Preliminary results of the project was presented at the Faculty of Veterinary Science Annual Case Conference on February 2002 at Chulalongkorn University, Bangkok..

3. Project director was invited to present a seminar on " Common Renal and Urological Diseases" to Veterinarian and Veterinary Students in September, 2003 at College of Veterinary Science, Mahanakorn Institute of Technology.

4. Project director presented an oral presentation entitled" Serum Parathyroid Hormone Abnormalities in Cats with Natural Chronic Renal Failure" in World Small Animal Veterinary Association Congress on 25 October, 2003 at Queen Sirikit Convention Center, Bangkok, Thailand.

5. Project director presented a semimar entitled" Epidemiological Study of Canine Renal Failure in the year 2003 in Small Animal Veterinary Seminar on 23 March, 2004 at Plaza Athenee Hotel, Bangkok, Thailand.

6. Project director presented two semimar entitled" Epidemiology and Treatment for Canine Renal Failure in Small Animal Veterinary Seminar on 17 and 23 May, 2004 at Juladis Hotel and Resort, Kao Yai, Nakorn Ratchasrima Province, Thailand.

# ภาคผนวก

# ภาคผนวกที่ 1

การเสนอผลงานทางวิชาการในการประชุม
สมาคมสัตวแพทย์สัตว์เล็กโลก
(World Small Animals Veterinary Association, WSAVA)
ณ ศูนย์ประชุมแห่งชาติสิริกิตติ์
วันที่ 23 - 25 ตุลาคม 2545


WSAVA 2003
28th World Congress of the World Small Animal Veterinary Association
Bangkok, Thailand
24-27 October 2003

ABSTRACT SUBMISSION

Title: SERUM PARATHYROID HORMONE ABNORMALITIES IN CATS WITH CHRONIC RENAL FAILURE

AUTHORS: Pusoonthornthum R, Pusoonthornthum P, Yibchok-anun S, Ekthamasut L, Danpitakkul M, Sudsuang S.

Please check preferred presentation: / Oral

The objective of this study was to investigate the relationship between serum parathyroid hormone (PTH) level and the development of chronic renal failure (CRF) in cats. Twenty-four cats presented to Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University between January 2002 to January 2003 was studied. Cats divided into two groups. The first group (11 cats) was primarily diagnosed by the veterinarians to have chronic renal failure whose blood urea nitrogen (BUN) concentrations were more than 40 mg/dl, serum creatinine level of more than 2.1 mg/dl, and urine specific gravity of less than 1.035. The second group was the control group (13 cats) who came for vaccination at the same hospital within the same period. Cats were followed for 60 days after first diagnosis. The complete blood count, blood chemistry, electrolytes, and parathyroid hormone level were measured on the day 0, 14, 30 and 60. The results showed that CRF cats revealed significantly lower in red blood cells, hemoglobin, and pack cell volume than control cats ($p<0.05$). Blood level of BUN, creatinine, and phosphorus were significantly higher ($p<0.05$) in CRF group, which showed azotemia and hyperphosphatemia. However, ionized calcium level in CRF group was significantly lower ($p<0.05$) than control group on day 0 and 14 which may trigger the release of parathyroid hormone. The plasma PTH levels in CRF group were significantly increased ($p<0.05$) compared with the control group indicated hyperparathyroidism. Bicarbonate level in CRF cats was significant lower ($p<0.05$) on day 60. This study reveals that cats with chronic renal failure often developed anemia, azotemia, hyperphosphatemia and renal secondary hyperparathyroidism especially at late stage of CRF.

PLEASE DO NOT FOLD OR BEND
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# ภาคผนวกที่ 2

**Manuscript ที่ได้ส่งเพื่อลงตีพิมพ์ใน วารสารของ**
**สมาคมอายุรศาสตร์สัตวแพทย์แห่งประเทศสหรัฐอเมริกา**
**ใน " American Journal of Veterinary Research"**

## Calcium - Phosphorus Homeostasis and Changes in Parathyroid Hormone Secretion in Siamese Cats with Various Stages of Naturally Occurring Chronic Renal Failure

Rosama Pusoonthornthum, Pinit Pusoonthornthum, and Sirintorn Yibchok-anun

Feline chronic renal failure was recognized with increased frequency in Maine coon, Abyssinian, Siamese, Russian blue, and Burmese cats. The objective of this study was to investigate the relationship between parathyroid hormone (PTH) level, calcium and phosphorus homeostasis and the development of various stages of the naturally occurring chronic renal failure (CRF) in Siamese cats. Thirty-seven Siamese cats presented to Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University between January 2001 to December 2003 were studied. Cats were divided into three groups; uremic group (11 cats), end-stage group (8 cats), and control group (13 cats) who came for vaccination at the same hospital within the same period. CRF cats with blood urea nitrogen (BUN) concentrations of more than 50 mg/dl, serum creatinine level of more than 2.1 mg/dl, and urine specific gravity of between 1.008 and 1.014 were included into the study. All groups of cats were followed prospectively for 60 days after first diagnosis. Completed blood count, blood chemistry, electrolytes including sodium, potassium, total calcium, phosphorus, ionized calcium, and parathyroid hormone levels were measured on the day 0, 14, 30 and 60 after the first diagnosis. The results showed that Siamese cats with CRF had significantly lower in red blood cells, hemoglobin, and pack cell volume than control cats ($p<0.01$) at day 0,14,30 and 60. Parathyroid hormone levels on day 0 were 50.51+/-19.65 pg/ml, 79.41+/-28.12 pg/ml, and 183.37+/-50.12 pg/ml in controls, uremic, and end-stage groups, respectively. Cats in end-stage group had significantly increased levels of parathyroid hormone when compared to control ($p<0.01$) and uremic group ($p<0.05$) at day 0, 14, and 30. Serum phosphorus levels were also increased significantly in end-stage group ($p<0.001$) indicated of renal secondary hyperparathyroidism. Adjusted calcium was increased significantly on day 30 in uremic and end-stage groups. However, total and ionized calcium levels in the uremic and end-stage groups remained within the normal range. All cats in end-stage group died before completed the sixty days of follow-up. This study reveals that parathyroid hormone level is significantly increased in Siamese cats with end-stage chronic renal failure and the development of renal secondary hyperparathyroidism decreased its survival rate.

**Key words**: Chronic renal failure; Parathyroid hormone; Siamese cats

Chronic renal failure (CRF) is the most common renal disease in dogs and cats. In Thailand, CRF was commonly observed especially in old cats with the mean age of 7.2 years old.[1] CRF is defined as primary renal failure that has persisted for an extended period, usually months to years. Regardless of the causes(s) of nephron loss, irreversible renal structural lesions characterize CRF.[2] In United States, DiBartola et al. (1987) found that CRF is a common disease especially in older cats. In his study, he found that 53% of affected cats were older than 7 years, but animals ranged in age from 9 months to 22 years.[3] A survey of 36 feline patients with CRF indicated that the mean age of cats with CRF was 7.4 years.[4] In a study of the age distribution of renal failure in cats, 37% of cats were younger than 10 years, 31% were between 10 and 15, and 32% were older than 15.[5] Recent report also indicated that feline chronic renal failure was recognized with increased frequency in Maine coon, Abyssinian, Siamese, Russian blue, and Burmese cats.[6]

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From one study in UK, eighty cats with chronic renal failure (CRF) were evaluated in a prospective study to investigate the prevalence and etiopathogenesis of renal secondary hyperparathyroidism (RHPTH), using routine plasma biochemistry and assays of parathyroid hormone (PTH), blood ionized calcium and 1,25 dihydroxycholecalciferol (1,25[OH]2D3). Hyperparathyroidism was a frequent sequela of CRF in that study, affecting 84 per cent of cats with CRF, the severity and prevalence of RHPTH increasing with the degree of renal dysfunction.[8] However, significant ionized hypocalcemia was present only in cats with end-stage renal failure. A number of cats were hyperparathyroid in the absence of abnormalities in the parameters of calcium homeostasis measured in that study.[8] Feline chronic renal failure causes much concern to cats' owners in Thailand and remain one of the most common renal problems for cats with advanced age. More than 70% of cats presented to Chulalongkorn University Veterinary Teaching Hospital with chronic renal failure died within one year after first diagnosis.[1] Recent report suggested that Siamese cats may have breed predisposition for feline chronic renal failure.[6] Whether Siamese (or Siamese-mixed breed) cats with naturally occurring feline chronic renal failure demonstrated genetic predisposition to this disease remain to be investigated. The objective of this study was to investigate the etiopathogenesis of renal secondary hyperparathyrodism in Siamese cats with various stages of naturally occurring feline chronic renal failure.

## Materials and Methods

Cats included in this study will consist of Siamese cats and Siamese-mixed breed cats from Chulalongkorn University Veterinary Teaching Hospital and two other private veterinary hospitals in Bangkok between January 2001 and December 2003. Chulalongkorn University Veterinary Teaching Hospital was chosen as the principle-investigating center of the study, whereas the other two private veterinary hospitals were chosen as representative of regional veterinary hospitals.

**Criteria for selection of cases:**

Cases with CRF will be selected on the basis of history, full clinical examination, plasma biochemistry screen, urinalysis, and/or radiography. All cats admitted to hospitals with the history of azotemia (BUN> 50.0 mg/dl and serum creatinine levels>2.1 mg/dl),[12] polyuria, polydipsia, anorexia, weight loss, and/or isosthenuria will be included in this study. Cases of prerenal, postrenal and primary acute renal failure are identify on the basis of history, physical findings, laboratory tests and response to therapy and will be excluded from the study. CRF cats will be categorized subjectively into two groups according to the severity of the clinical signs as stated previously.[1]

**Group 1:** Control cats consist of cats without clinical signs of chronic renal failure but coming to the same veterinary hospital as the CRF cats for vaccination within the same period.

**Group 2:** CRF Cats that are presented with history, clinical signs, and/or physical findings which indicate uremic syndrome will be classified as " Uremic" CRF. Most of these animals are not judged to be in need of fluid therapy and have adequate appetites at the time of diagnosis. They may be dehydrated but response well to fluid therapy and survived for more than one month.

**Group 3:** CRF cats that are clinically dehydrated, anorexic and fail to respond to treatment, surviving less than 60 days following diagnosis will be classified as " End-stage" CRF.

**Criteria for selection of control cats:**

Control cats will consist of those without azotemia, polyuria, polydipsia, weight loss, and isosthenuria admitted to the same veterinary hospital as the CRF cats for vaccination. Health status of control cats will be determined by history, physical examination, and, if necessary, urinalysis and radiography. Cats with a history of urinary tract disease, and those with a history of receiving special treatment for urinary tract disease will be excluded.

**Methods of Evaluation of Cats:**

Control cats and cats with CRF will be examined by collection of blood sample, urinalysis, survey radiography, pneumocystography, and/or double contrast urocystography. Urine and blood samples will be collected for analysis on day 0,14,30,60 after the first diagnosis. Blood samples will be taken in the morning which owners will be requested to withhold food for eight to twelve hours prior to sampling blood. Bood sampling will be undertaking by venepuncture into heparinized tubes for plasma biochemistry, and anaerobically into heparinized blood-gas syringes for ionized calcium, blood pH, serum bicarbonate level, and/or total carbon dioxide measurement. The blood is centrifuged and the plasma harvested. A portion of the plasma will be used for biochemical testing and the remainder will be stored at -80 degree Celcius for batch analysis of hormones involved in calcium homeostasis.[9] Ionized calcium will be measured by using Atomic Absorption Spectrophotometer[a]. To estimate the loss of renal function, blood urea nitrogen (BUN) concentrations will be determined by means of a urease indophenol method using a diagnostic kit[b]. Blood samples will be evaluated for complete blood count (CBC), and blood chemistry profile including AST, ALT, total plasma calcium, total plasma protein, and serum albumin levels to assess health status and the severity of feline chronic renal failure using diagnostic kits. Other blood biochemical measurements will be made at Chulalongkorn University Veterinary Teaching Hospital using standard autoanalyzer techniques. Urine will also be collected by cystocentesis or voiding prior to fluid therapy. Quantitative bacterial urine culture and antimicrobic susceptibility tests will be performed if cats are suspected of having bacterial urinary tract infection (UTI). To obtain further information about renal disorders, urinalysis will also be performed including color, odor of urine, specific gravity, urine pH, concentration of glucose, ketones, bilirubin, protein, occult blood, and examination of urine sediment with standard techniques. Urine specific gravity will be measured by refractometer, and chemical variables will be determined with a commercial strip test reagent[c]. Appropriate urine concentrating ability (UCA) will be defined as an increased in urine specific gravity (>1.035). When urine specific gravity is less than or equal to 1.035, UCA is considered to be impaired in those cats that is azotemia or dehydrated. Survey radiograph will be performed at 6 months intervals, or sooner if cats develop signs of end-stage CRF.

**For the analysis of parathyroid hormone:**

Plasma parathyroid hormone concentration will be determined by immunoradiometric assay. When possible, samples from cats with CRF will be assay undiluted and as a dilution to avoid carboxyl terminal interference.[10] This assay has been previously validated for the measurement of parathyroid hormone in feline plasma.[11]

**Statistical analysis:**

Descriptive statistics including frequency distributions, means, standard deviations, and standard error of means (SEM) will be determined for continuous variables. Differences in the means between groups will be tested using One Way Analysis of Variances (ANOVA). With all statistical analyses, $p < 0.05$ was taken to indicate significance.

## Results

Thirty-Seven Siamese and Siamese-mixed breed cats were identified with a diagnosis of CRF during the study period. Mean age of affected cats was 6.0 years (range, 5 months to 17.3 years). Twenty-six percent of affected cats were younger than 5 years old and 55.8 percent of CRF cats were older than 7 years of age. The most common breeds of cats in this study included Siamese and Siamese-mixed

breed cats. There were 9 female cats (3 were sexually intact and 6 were neutered) and 28 male cats (12 were sexually intact and 16 were neutered) in CRF cats.

From thirty-seven cats with CRF, 19 CRF cats were followed prospectively for 60 days. Cats were divided into three groups; control group (13 cats), uremic group (11 cats), and end-stage group (8 cats). Mean plasma creatinine level was 1.49+/-0.09 mg/dl in the control cats compared to 5.12+/-1.22 mg/dl in uremic cats and 10.33+/-2.09 mg/dl in end-stage cats on first day of diagnosis. Primary renal azotemia was confirmed in all CRF cats by the combination of azotemia and submaximally concentrated urine (urine specific gravity <1.035 at the time that azotemia was discovered). Urine was all in the urinary specific gravity range of 1.008 to 1.014. Urinary sediment was usually normal, although a few cats had hyaline or granular casts. Certain cats had mild proteinuria (trace to 1 +) as determined by use of dipstrip analysis. Findings typical of CRF were observed in ultrasonographic and/or radiographic images, including decreased renal size, irregular contour, increased echogenicity of renal tissue, and loss of distinction of the corticomedullary junction on ultrasound. Cats were identified and serum was collected before the initiation of any major treatment for CRF.

Siamese cats with CRF had significantly lower red blood cells, hemoglobin, and pack cell volume than control cats ($p<0.01$) on day 0, 14, 30 and 60 of the study. Eventhough means red blood cells were $5.27 \times 10^6$ cells/ul in uremic cats and $5.42+/-0.58 \times 10^6$ cells/ul in end-stage cats, the red blood cells of CRF groups were within the normal reference range. Uremic and end-stage cats had significantly lower hemoglobin concentrations ($p<0.001$) than control cats on day 0 of the study.

Parathyroid hormone levels on day 0 of the study were 50.51+/-19.65 pg/ml in control cats, 79.41+/-28.12 pg/ml in uremic cats, and 183.37+/-50.12 pg/ml in end-stage cats (Figure 1). Cats in end-stage group had significantly increased levels of parathyroid hormone when compared to control ($p<0.01$) and uremic group ($p<0.05$) on day 0, 14, and 30. Means plasma phosphorus concentration in the uremic group was 5.81+/-0.42 mg/dl and end-stage group was 17.04+/-2.84 mg/dl. Mean plasma concentration of phosphorus were significantly elevated ($p< 0.001$) in uremic and end-stage group compared to 4.63+/-0.37 mg/dl in the control group on first day of diagnosis indicated of renal secondary hyperparathyroidism in uremic and end-stage CRF cats. All end-stage CRF cats were hyperphosphatemia on day 0, 14 and 30 of the followed-up (Figure 2). Adjusted calcium increased significantly on day 30 in end-stage group. Adjusted calcium of uremic cats on day 30 was significantly lower than control cats, however, it was within the normal reference range (Figure 3). Total and ionized calcium levels in the uremic and end-stage groups remained within the normal range (Figure 3,4). There was no significant alteration in plasma albumin concentration in the CRF cats in the present study. Plasma alkaline phosphatase increased significantly ($p<0.01$) in end-stage cats on day 30 of the follow-up when compared with controls (Figure 5). Cats in the uremic group had statistically lower alkaline phosphatase concentration than control group on day 0, 14, 30 and 60 of the study (Figure 5). Renal secondary hyperparathyroidism was diagnosed in 8 of 19 CRF cats (42%) especially in all cats with end-stage CRF. Cats with renal secondary hyperparathyroidism had significantly elevated parathyroid hormone despite normal concentration of blood ionized calcium. Parathyroid hormone level increased significantly whenever hyperphosphatemia occurred. The variation of parathyroid hormone concentration found in CRF cats depend on the magnitude of the changes in plasma phosphate concentration. There was also a significant ($p<0.05$) correlation ($r^2 = 0.69$) between serum creatinine and phosphorus concentration in CRF cats.

Information on survival time was available for all cats; CRF cats lived for 7 days to 730 days after the first diagnosis. Eleven CRF cats (11/19;58%) were alive until the 60 days of the study. Six of 8 end-stage CRF cats (66.67%) died on day 14 of the followed-up. All cats in end-stage group died before completed the 60 days of followed-up. Kaplan-Meier survival analysis was performed and indicated that cats with end-stage CRF had lowest percentage of survival time (Figure 6).

## Discussion

The results of this study demonstrated that Siamese cat has high incidence of chronic renal failure. This spontaneous renal failure is a common cause of mortality in older and occasionally, younger cats. Twenty-six percents of affected cats in this study were younger than 5 years old. In United States, DiBartola

et al. (1987) found that 53% of affected cats were older than 7 years, but animals ranged in age from 9 months to 22 years.' It was also found that CRF is a common disease especially in older cats. The results of this study indicated that the incidence of renal failure in Siamese CRF cats also increased with age.

Siamese cats with CRF also had lower red blood cell, hemoglobin, and packed cell volume than control cats, most of them were within the normal reference range on the first day of diagnosis. Anemia is often found in CRF patients due to nutritional abnormalities, blood loss with iron deficiency, short survival time of RBCs, hemolysis, and depression of bone marrow function by uremia associated with toxins. Inadequate production of erythropoietin has emerged as the principle cause of anemia in human and animals with CRF.[14] However, anemia was not detected in any CRF groups on first day of diagnosis in this study especially in cats with end-stage CRF.

The prevalence of renal secondary hyperparathyroidism in Siamese cats with CRF in this study was 42 percent. All cats in the end-stage group (100%) had elevated parathyroid hormone concentrations since the first day of diagnosis. Hyperparathyroidism was a frequent sequela of CRF, affecting 84 per cent of cats with CRF in one study.[3] The severity and prevalence of RHPTH increasing with the degree of renal dysfunction. Renal secondary hyperparathyroidism occurs in association with hyperphosphatemia, low circulating 1,25-dihydroxycholecalciferol (calcitriol) levels, reduced blood ionized calcium concentration, and skeletal resistance to the calcemic action of PTH. However, in early to moderate renal failure, it is difficult to dissect out the specific factors responsible for hyperparathyroidism because the increase in PTH serve to prevent hypocalcemia, hyperphosphatemia, and the decrease in calcitriol.[15] Relative or absolute deficiency of calcitriol has been hypothesized to play a pivotal role in the development of renal secondary hyperparathyroidism.[16] Calcitriol, the most active form of vitamin D, is formed by 1-α-hydroxylation of 25-hydroxycholecalciferol in renal tubular cells. PTH promotes renal 1-α-hydroxylase activity and formation of calcitriol. In turn, calcitriol limits PTH synthesis by feedback inhibition. Early in the course of CRF, the inhibitory effects of phosphate retention on renal tubular 1-α-hydroxylase activity limit calcitriol production. In more advanced renal failure, only serum calcium was found to correlate with serum PTH activity.[17] Impaired intestinal absorption of calcium related to low serum calcitriol levels probably plays an important role in hyperparathyroidism in these patients with advanced renal failure. Excess PTH levels may also promote nephrocalcinosis and consequent progressive loss of renal function.[18] PTH has thus been hypothesized to function as a uremic toxin, althought he precise contribution of hyperparathyroidism to the uremic syndrome remains unresolved.

All Siamese cats with renal secondary hyperparathyroidism had total calcium levels within the normal reference range and no palpable parathyroid adenoma on physical examination. There was no significant differences in mean total calcium concentration between the three groups of cats. Hyperparathyroidism was even detected in some cats with normal serum calcium and phosphate concentrations.[4] In human patients, hyperparathyroidism develops early in CRF while serum calcium and phosphorus concentrations remain within normal limits.[19]

Blood ionized calcium concentration was within the normal reference range in all groups of cats. Blood ionized calcium concentrations are often reduced in cats with spontaneous CRF; in one study, over 50 per cent of cats with advanced end-stage CRF were hypocalcemic.[3] On the contrary, cats in the uremic group in this study had higher blood ionized calcium on day 60 of the follow-up which could indicated the increase in the severity of renal dysfunction in the uremic group.

On the basis of adjusted plasma calcium concentrations, hypercalcemia was found in 42 percent of CRF cats and 100 percents of cats in the end-stage group on day 30 of the followed-up. Hypocalcemia was not detected in any CRF cats in this study. In previous studies, hypercalcemia has been found in 10 percent of CRF cats and 15 percent of CRF cats were hypocalcemia.[15] These differences may reflect the use of different cats' population between different studies. In contrast to total calcium, elevated ionized calcium concentrations were found in 58 percent of CRF cats whereas low ionized calcium was present in 42 percent. Only approximately half of plasma total calcium is composed of ionized calcium; the remainder, both complexed and protein-bound calcium, is not only affected by changes in calcium status but also by alterations in binding affinity and concentrations of binding factors.

Sick dogs may also have disturbances in calcium homeostasis,[20] but a total calcium concentration within reference range does not ensure that calcium is distributed among the fractions as would normally be expected.[21] Although the technology for measurement of ionized calcium concentration has vastly

improved,[22] evaluation of calcium status has largely relied on determination of total calcium concentration. Ionized calcium concentration is a more sensitive indicator of pathologic states than is total calcium,[23] especially in humans with hyperparathyroidism,[24] hypercalcemic conditions,[25] renal disease,[26] and critical illnesses.[27] A number of cats were hyperparathyroid in the absence of abnormalities in the parameters of calcium homeostasis.[4]

Siamese cats in end-stage group were hyperphosphatemia in this study. The kidneys play a pivotal role in regulating phosphorus balance. The kidneys are the primary route of phosphorus excretion. Renal phosphorus excretion is the net of glomerular filtration less tubular reabsorption of phosphorus. If dietary phosphorus intake remains constant, a decline in GFR leads to phosphorus retention and ultimately hyperphosphatemia.[6] Our results also demonstrated a significant correlation ($r^2$ = 0.69) between serum creatinine and phosphorus concentration in CRF cats. Study in 80 cats with CRF in one study also indicated a significant correlation between plasma phosphate and PTH concentrations.[4] The primary consequence of hyperphosphatemia is development and progression of secondary hyperparathyroidism. Increases in serum PTH activities in dogs and humans with CRF are closely associated with the degree of hyperphosphatemia and hyperphosphatemia was found to be 72 per cent efficient in predicting hyperparathyroidism in cats with CRF.[4]

All Siamese cats in end-stage CRF group died before completed 60 days of the study. Hyperphosphatemia has been directly linked to increased mortality in humans and dogs with CRF.[28-30] In humans with CRF receiving hemodialysis therapy, the adjusted relative risk of mortality was stable in patients with serum phosphate concentrations below 6.5 mg/dL but increased significantly above this level. The overall mortality risk associated with hyperphosphatemia was 1.06 per 1 mg/dL increase in serum phosphorus. An additional consequence of hyperphosphatemia is a predisposition to metastatic calcification when the Ca X $PO_4$ product is elevated. A Ca X $PO_4$ product of 42 to 52 is considered desirable for humans with renal failure.[31] The likelihood of soft tissue calcification increases greatly when the Ca X $PO_4$ product exceeds 60. Calcification is especially prominent in proton-secreting organs, such as the stomach and kidneys, in which basolateral bicarbonate secretion results in an increase in pH that promotes calcium hydrogen phosphate (brushite) precipitation.[32] However, myocardium, lung, and liver are also commonly mineralized in patients with CRF.

There was a strong inverse correlation between parathyroid hormone concentration and survival of cats with CRF especially in cats with end-stage. The higher the concentration of parathyroid hormone detected on the first day of diagnosis, the shorter of the survival time for the CRF cats. The level of parathyroid hormone concentration measured on the first day of the diagnosis of CRF may possibly be a predictor of survival for Siamese cats with CRF.

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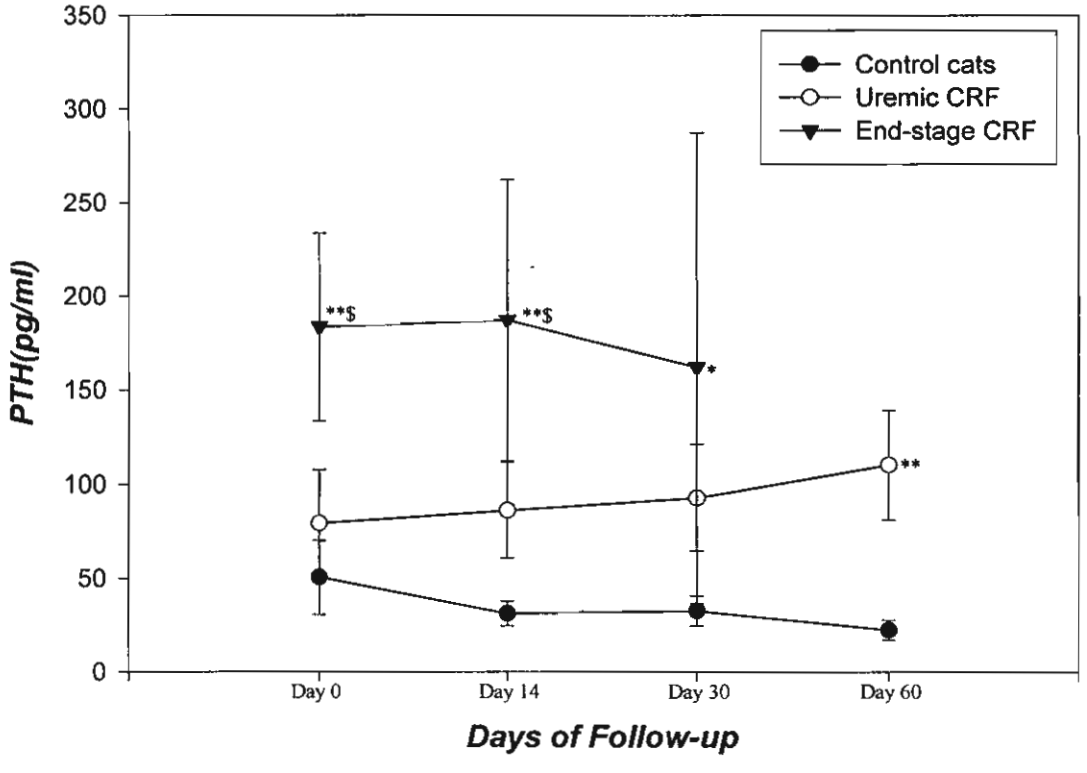
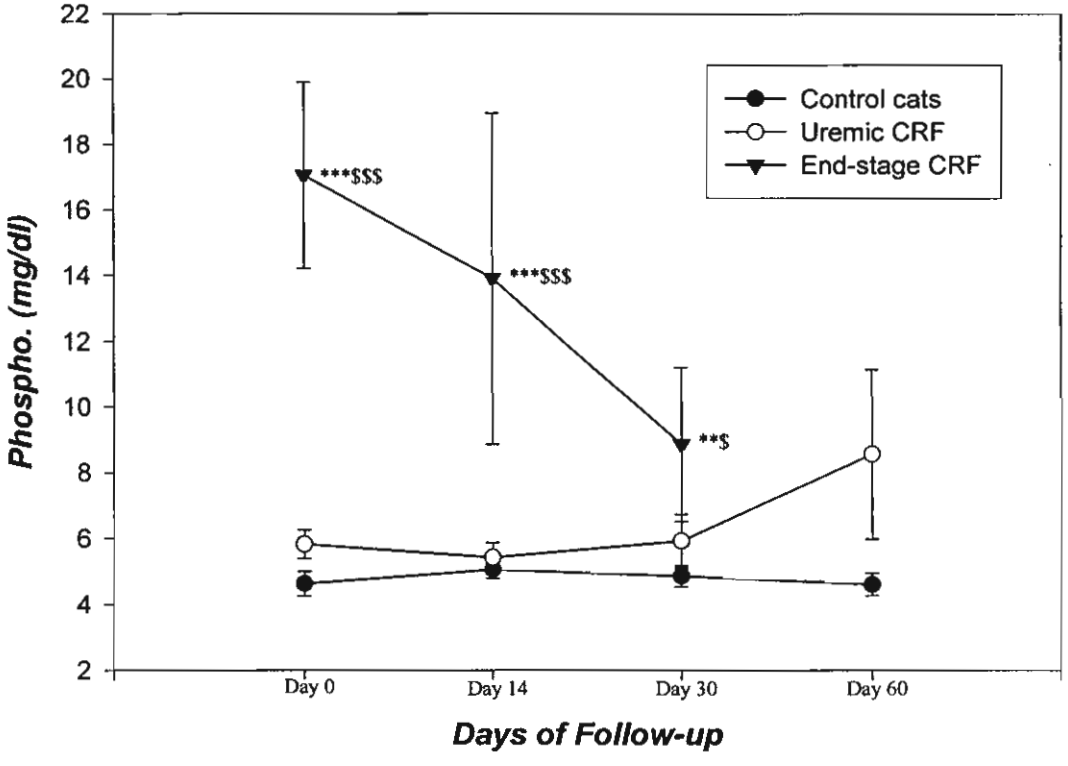
**Figure 1** Mean +/- SEM parathyroid hormone for controls and CRF cats of various stages



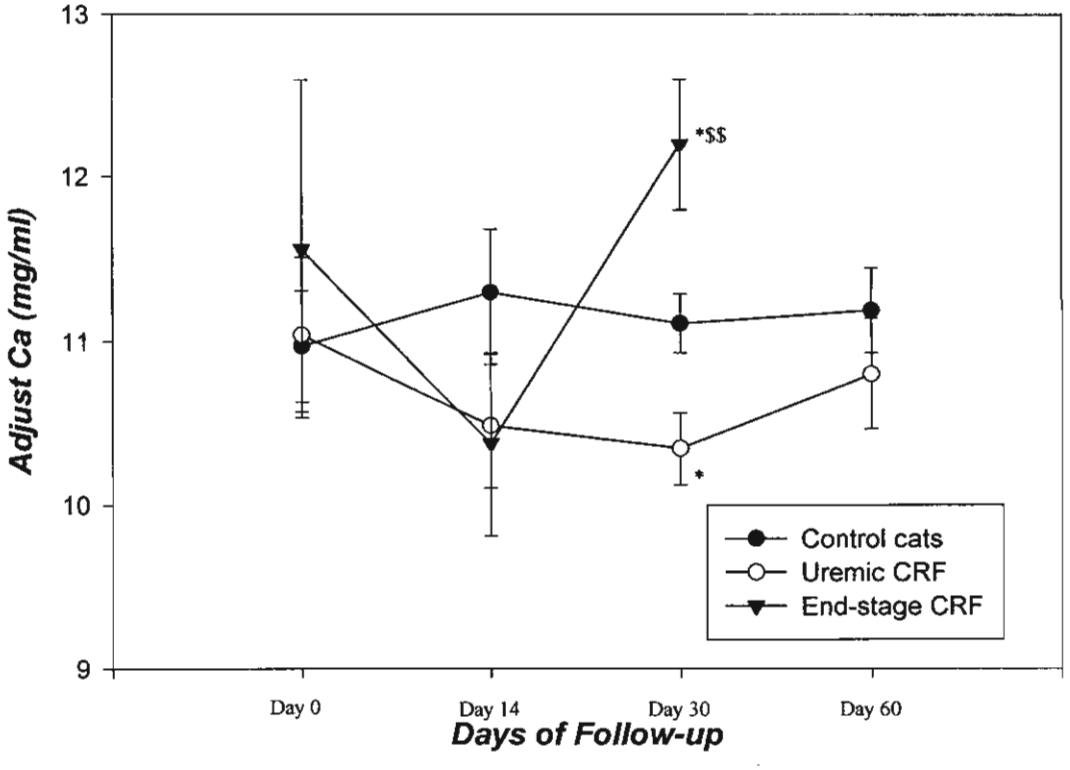

**Note:** ** = $p < 0.01$ when compared with controls
$ = $p < 0.05$ when compared between uremia and end-stage groups

**Figure 2** Mean +/- SEM phosphorus levels for controls and CRF cats of various stages



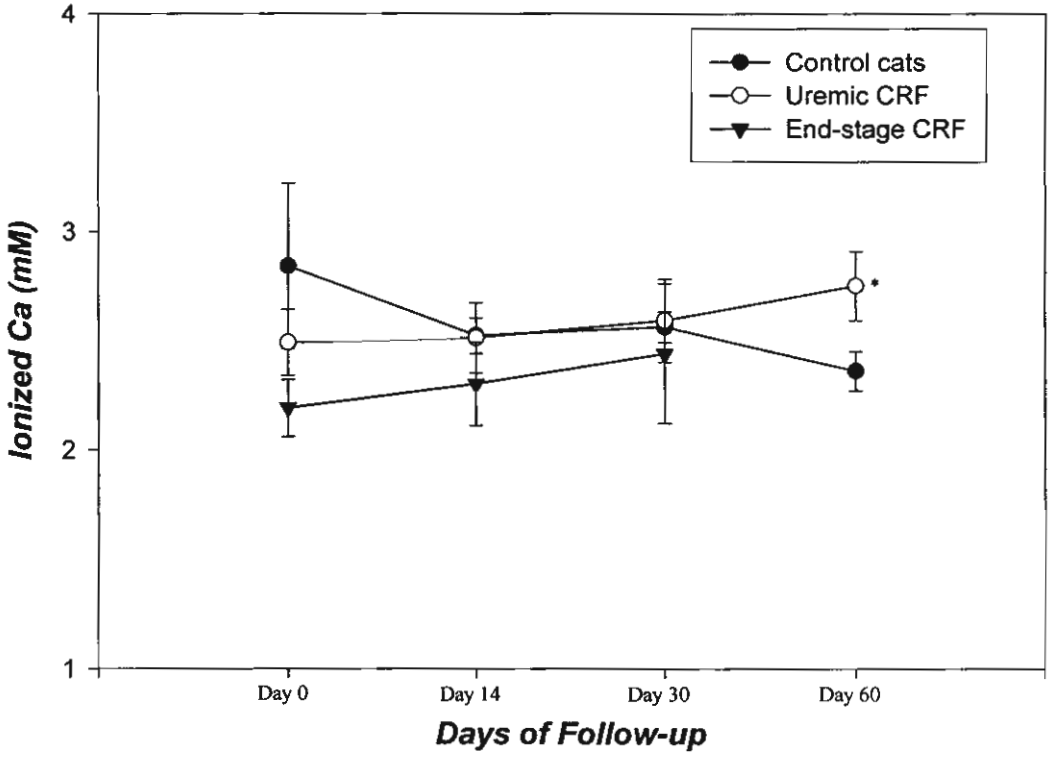

**Note:** ** = $p < 0.01$ when compared with controls
*** = $p < 0.001$ when compared with controls
$$ = $p < 0.01$ when compared between uremia and end-stage groups
$$$ = $p < 0.001$ when compared between uremia and end-stage groups

**Figure 3** Mean +/- SEM adjusted calcium for controls and CRF cats of various stages



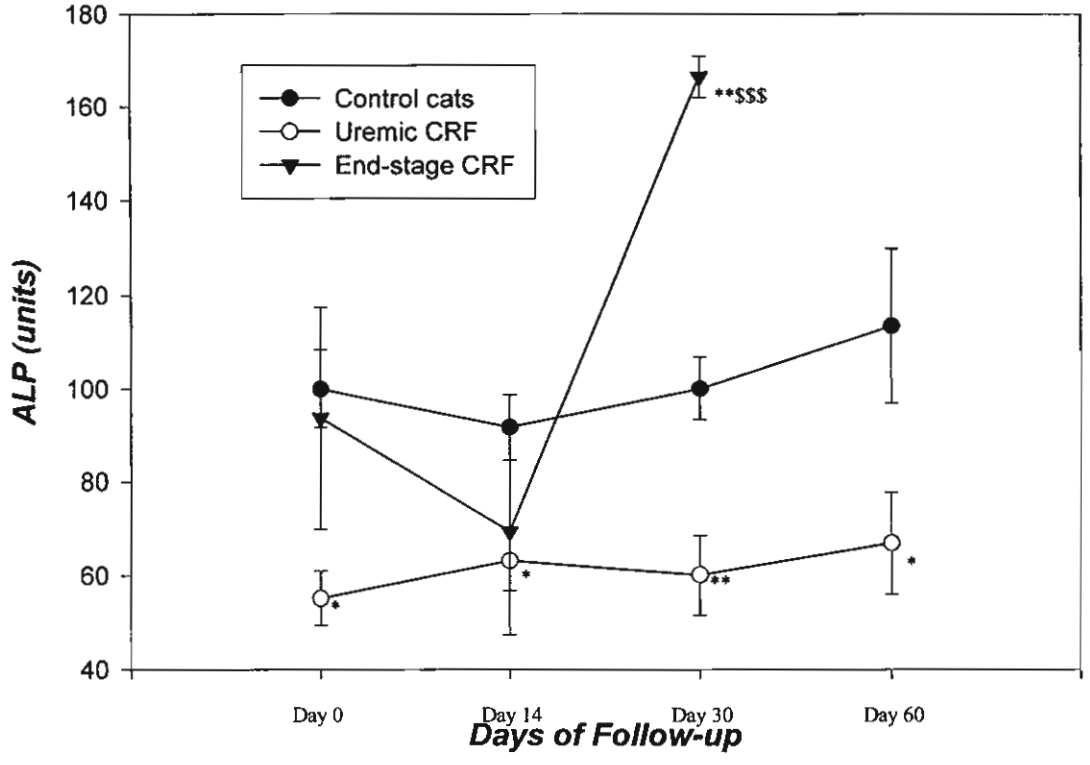

**Note:** * = $p < 0.05$ when compared with controls
$$ = $p < 0.01$ when compared between uremia and end-stage groups

**Figure 4** Mean +/- SEM total calcium for controls and CRF cats of various stages



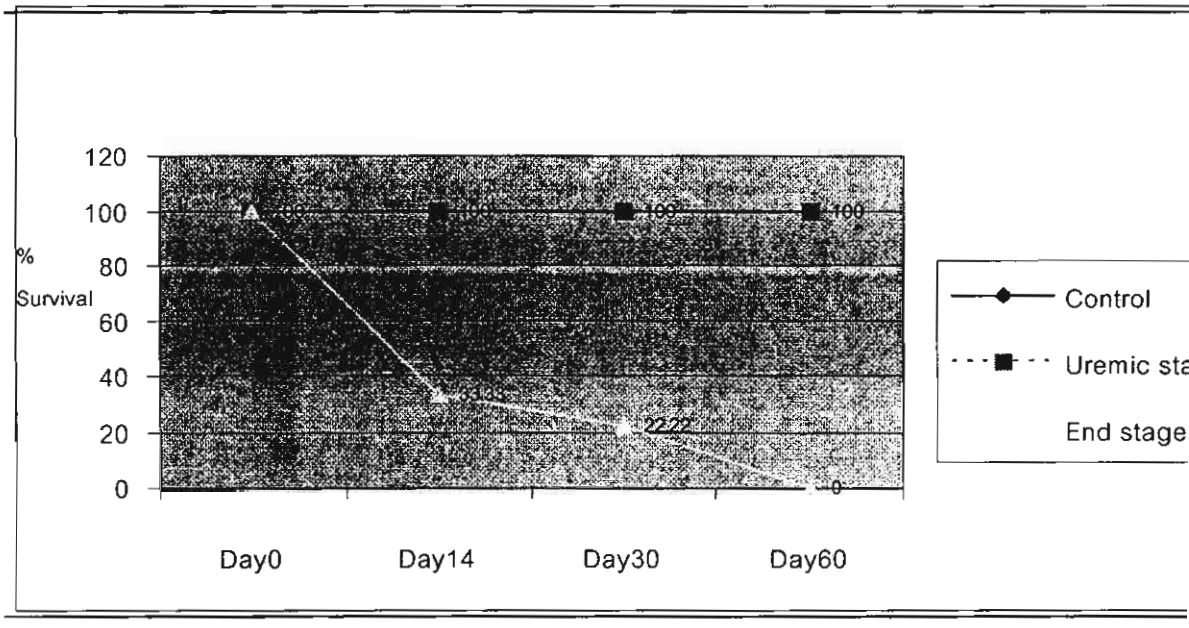

**Note:** * = $p < 0.05$ when compared with controls

**Figure 5** Mean +/- SEM alkaline phosphates levels for controls and CRF cats of various stages




**Note:** * = $p < 0.05$ when compared with controls
** = $p < 0.01$ when compared with controls
$$$ = $p < 0.001$ when compared between uremia and end-stage groups

Figure 6 Survival curve for controls and CRF cats of various stages



# ภาคผนวกที่ 3

## การเผยแพร่ทางวิชาการในการประชุมของ สัตวแพทย์จัดโดยสมาคมสัตวแพทย์ผู้ประกอบการ บำบัดโรคสัตว์แห่งประเทศไทย ร่วมกับบริษัท ดีทแฮม (ประเทศไทย) จำกัด

# ภาคผนวกที่ 4

## การเผยแพร่ทางวิชาการในการบรรยายพิเศษทางวิทยุ จัดโดยสัตวแพทยสมาคมแห่งประเทศไทย ร่วมกับสถานีวิทยุ จ.ส. 100 เรื่อง "โรคไตวายเรื้อรังในแมว"

# ภาคผนวกที่ 5

## การเผยแพร่ทางวิชาการในการบรรยายพิเศษ เรื่อง "การวินิจฉัยและการรักษาโรคไตและระบบขับถ่ายปัสสาวะส่วนล่างในสุนัขและแมว" ในการสัมนาทางวิชาการ คณะสัตวแพทยศาสตร์ มหาวิทยาลัยมหานคร