Cornell University
College of Veterinary Medicine
Feline Health Center

19th Annual

# Fred Scott Feline Symposium

## Dedicated to Dr. Jim Richards

**July 27–29, 2007**

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College of Veterinary Medicine
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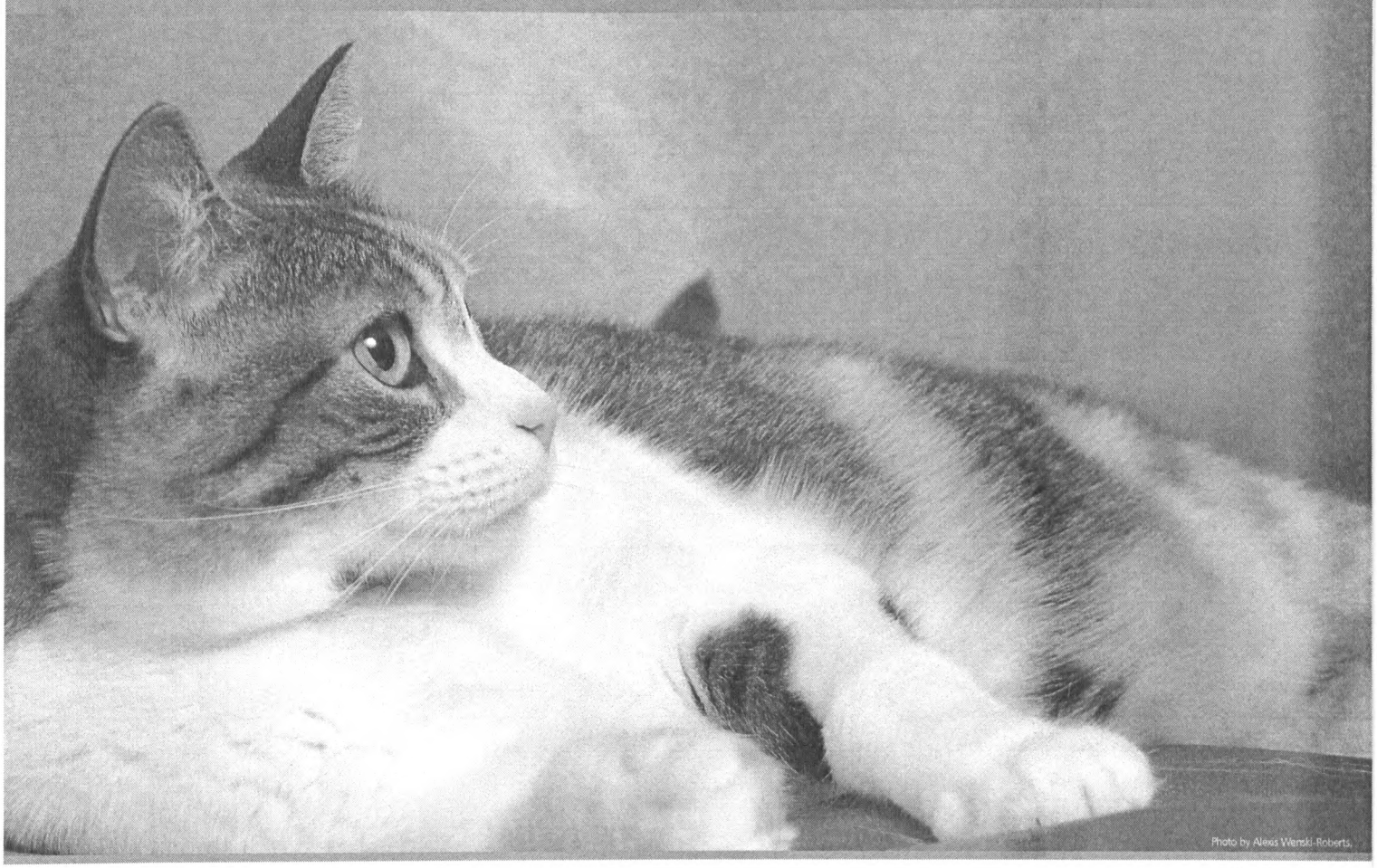
19th Annual

# Fred Scott Feline Symposium

## Dedicated to Dr. Jim Richards

**July 27–29, 2007**



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Information about the Cornell Feline Health Center at the College of Veterinary Medicine at Cornell University contact:

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# General Information and Logistics

## 19th Annual Fred Scott Feline Symposium
## July 27 - 29, 2007

### Course Overview

This year's 19th Annual Fred Scott Feline Symposium will educate and update veterinarians in feline cardiology, renal disease, inflammatory bowl disease, heartworm associated respiratory disease, hepatic amyloidosis, mycobacterial disease, and other timely topics.

### Accreditation and Continuing Education Credit

The College of Veterinary Medicine at Cornell University accredits this symposium for a maximum of 17 hours of continuing education credit. Each attendee should claim only those hours of credit that he/she actually spends in the educational lectures. You are asked to sign-in at the registration desk on the first day so that there is evidence of your attendance.

For questions about accreditation and continuing education credit please contact:

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### Evaluation

It is important for the Cornell Office of Continuing Education, faculty, corporate sponsors, and exhibitors to receive your feedback. We ask that you complete the evaluation form and return it to the registration desk before you leave the symposium. The information you provide us is essential in the development of future educational programs. We welcome and encourage your comments on all aspects of this symposium.

### Certificate of Participation

You will receive a certificate of participation, which will be available at the registration desk during lunch on Saturday, July 28. The certificate verifies your attendance at the 19th Annual Fred Scott Feline Symposium.

### Meals

Meal tickets are in the back of your nametag for:

- Lunch on Friday and Saturday. These lunch meal tickets are to be turned into the cafeteria cashier after you select your lunch on Friday and at the cafeteria entrance on Saturday.
- Lunch with Dr. DiBartola on Friday: If you signed up to have lunch with Dr. DiBartola on Friday please turn in your ticket to the staff member at the meeting room entrance.

## Tours

If you registered to participate in a tour of the college during lunch on Friday or Saturday you will find an admittance ticket in the back of your nametag. Please meet in the Atrium at the beginning of your lunch break.

## Course Materials

The course materials that are distributed during this symposium are under the auspices of the Office of Continuing Education at the College of Veterinary Medicine at Cornell University. Duplication of these materials is prohibited.

## Disclaimer

The lectures offered during this symposium will include some discussion of off-label use and commercial products and/or services. The opinion and recommendations expressed by the faculty are their own.

Agenda

# Agenda

## 19th Annual Fred Scott Feline Symposium
## July 27 - 29, 2007

- All lectures will be held in Lecture Hall I in the Veterinary Education Center.
- Continental Breakfasts and breaks will be located in the Hagan Room.

### Friday, July 27, 2007

| | | |
|---|---|---|
| 7:30 - 8:00 am | Registration<br>Continental Breakfast<br>***Sponsored by MERIAL*** | Hagan Room |
| 8:00 - 8:15 | Welcome - *Fred Scott* | Lecture Hall I |
| 8:15 - 9:15 | Good Clinical Decision Making - Concerning a controversial case!<br>*Richard Malik* | Lecture Hall I |
| 9:15 - 9:30 | Break | Hagan Room Atrium |
| 9:30 - 10:30 | Medical Management of Chronic Renal Failure in Cats<br>*Stephen DiBartola* | Lecture Hall I |
| 10:30 - 10:45 | Break | Hagan Room Atrium |
| 10:45 - 12:15 pm | An Exercise in Diagnostic Reasoning: Nasal bridge ulcers in a young cat<br>*Richard Malik* | Lecture Hall I |
| 12:15 -1:30 | Lunch | Cafeteria |
| 1:30 - 2:30 | Renal Diseases of Cats Part I (including case presentations)<br>*Stephen DiBartola* | Lecture Hall I |
| 2:30 - 2:45 | Break | Hagan Room Atrium |
| 2:45 - 4:15 | Renal Diseases of Cats Part I (including case presentations)<br>*Stephen DiBartola* | Lecture Hall I |
| 4:15 - 4:30 | Break | Hagan Room Atrium |
| 4:30 - 5:30 | Hepatic Amyloidosis - Not that easy to diagnose!<br>*Richard Malik* | Lecture Hall I |
| 6:30 - 9:00 | **Annual Picnic** at the Six Mile Creek Vineyard<br>Maps at the registration desk. | |

## Saturday, July 28, 2007

| | | |
|---|---|---|
| 7:30 - 8:00 am | Continental Breakfast<br>***Sponsored by IDEXX Laboratories, Inc.*** | Hagan Room Atrium |
| 8:00 - 9:30 | Non-tuberculous Mycobacterial Diseases<br>*Richard Malik* | Lecture Hall I |
| 9:30 - 9:45 | Break | Hagan Room Atrium |
| 9:45 - 10:45 | Do Bacteria Have a Role in Feline Inflammatory Bowel Disease?<br>*Kenneth Simpson* | Lecture Hall I |
| 10:45 - 11:00 | Break | Hagan Room Atrium |
| 11:00 - noon | A Stepwise Approach to Treating Feline Inflammatory Bowel Disease<br>*Kenneth Simpson* | Lecture Hall I |
| Noon - 1:00 pm | Lunch<br>***Sponsored by Schering-Plough Animal Health*** | Cafeteria |
| 1:00 - 2:30 | ENT Disease of Cats<br>*Richard Malik* | Lecture Hall I |
| 2:30 - 2:45 | Break | Hagan Room Atrium |
| 2:45 - 3:45 | Feline Cardiology Smorgasbord: What's new, what's real, what's on the horizon<br>*Mark Rishniw* | Lecture Hall I |
| 3:45 - 4:00 | Break | Hagan Room Atrium |
| 4:00 - 5:00 | Nocardia Infections<br>*Richard Malik* | Lecture Hall I |
| 5:00 - 7:30 | *Tribute to Dr. Jim Richards* | |

## Sunday, July 29, 2007

| | | |
|---|---|---|
| 8:00 - 8:30 am | Continental Breakfast | Hagan Room Atrium |
| 8:30 - 10:00 | HARDs in Cats: Heartworm disease is not what you thought it was! Part I<br>*Ray Dillon*<br>***Sponsored by Pfizer Animal Health*** | Lecture Hall I |
| 10:00 - 10:15 | Break | Hagan Room Atrium |
| 10:15 - 11:45 | HARDs in Cats: Heartworm disease is not what you thought it was! Part II<br>*Ray Dillon*<br>***Sponsored by Pfizer Animal Health*** | Lecture Hall I |

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## 19th Annual Fred Scott Feline Symposium
## July 27 - 29, 2007

## Corporate Sponsors

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## Annual Picnic

The annual picnic will be held at the Six Mile Creek Vinyard and includes a wine tour for those who sign-up at the registration desk. Wines served at the picnic are from Six Mile Creek Vinyard and the vineyard is offering our guests a 20% discount on purchases.

# Exhibitors

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Faculty

# Faculty

## 19th Annual Fred Scott Feline Symposium
## July 27 - 29, 2007

### Stephen DiBartola, DVM, Diplomate ACVIM

Dr. Stephen DiBartola received his DVM from the University of California, Davis. He completed a Small Animal Medicine and Surgery Internship at Cornell University and a Residency in Small Animal Medicine at the Ohio State University. He is currently a Professor of Medicine and Head of the Small Animal Medicine Section of the Veterinary Clinical Sciences Department of The Ohio State University. Dr. DiBartola is the author of the textbook *Fluid Electrolyte and Acid Base Disorders in Small Animal Practice* that was published in 2006 by Elsevier.

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### Ray Dillon, DVM, MS, MBA, Diplomate ACVIM

Dr. Ray Dillon, a Professor in Department of Clinical Sciences at Auburn University, received his DVM from Texas A&M University in 1973 Magma Cum Laude. He was an intern and clinical resident at Auburn University earning his MS in Internal Medicine in 1977. He received a MBA in 2001 with Highest Honors from Auburn University. He was board certified in the American College of Veterinary Internal Medicine in 1978. Dr. Dillon was the first recipient and continues to hold the Jack O Rash Chair in Medicine at Auburn University. He was Head of the Section of Medicine for over 20 years and was Interim Director of the Scott-Ritchey Research Center. In his role, Dr. Dillon was given the charge by Dr. Hoerlein, Head of the Small Animal Clinic in 1978, to build a medicine section at Auburn University. With Dr. Dillon's leadership, since that time, every faculty and resident trained in small animal medicine has been successful and are Diplomates of the American College of Veterinary Medicine. The small animal medicine section has grown from an original senior faculty of 2, to a faculty of 15 specialists, including internal medicine, dermatology, oncology, and emergency critical care. Dr. Dillon has over 100 scientific publications and 500 scientific presentations, many at international forums including lectures in 12 different countries.

He has been active in cardiopulmonary research, with an emphasis on inflammatory lung disease and congestive heart failure of dogs and cats. In addition to his clinical duties, he has been directly associated with over 22 million dollars of research over the past 12 years including collaborative research with Harvard University Respiratory Biology Program and University of Alabama at Birmingham Heart Failure Center.

Dr. Dillon's accomplishments as a clinical scientist has been recognized though awards such as the Phi Kappa Phi Scholar for Auburn University, Exceptional Achievement in Auburn University Outreach, and the Beecham Award for Research Excellence. He is considered one of the leading authorities on lung injury and heartworm disease of dogs and cats. In 1997, he was honored as the Comparative Medicine Scholar for Tuft's University College of Veterinary Medicine; and received the AVMA Foundation Award for Feline Research in 1999. Dr. Dillon was honored with the Outstanding Alumnus Award for 2003 by the College of Veterinary Medicine at Texas A&M University. Dr. Dillon was the founding President of the American College of Veterinary Internal Medicine Foundation.

Currently, in addition to his research into mechanism of inflammatory lung disease of cats, he is active in research involving the molecular mechanism of myocardial remodeling associated with volume overload. In 2005, Dr. Dillon was the Principle Investigator of the Auburn University CVM project in a multi-center NIH grant with UAB Medical School for an 18 million dollar award investigating the Mechanism of Heart Failure. Dr. Dillon is active in teaching internal medicine to the veterinary professional students and graduate students/residents, and receives referral cases at the Auburn University Teaching Hospital.

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## Richard Malik, DVSc, DipVetAn, MVetClinStud, PhD, FACVSc, FASM

Richard Malik graduated from the University of Sydney in January 1981. He initially trained in Veterinary Anaesthesia and Intensive Care, then moved to ANU where he completed a PhD in neuropharmacology at the John Curtin School of Medical Research. He subsequently completed a Postdoctoral fellowship at the Neurobiology Research Centre at the University of Sydney, before returning to his alma mater as a Medicine Resident in the Veterinary Teaching Hospital. He remained there for 16 years in a variety of positions, most notable as the Valentine Charlton Senior Lecturer in Feline Medicine (1995-2002). Since 2002 Richard has worked as a Senior Consultant in the Post Graduate Foundation in Veterinary Science, and he finds time also to see cases in a number of practices in the Eastern suburbs of Sydney. Richard is a Member of the College in Canine Medicine and a Fellow in Feline Medicine, and a registered specialist in Small Animal Medicine in NSW. Richard has strong and varied research interest, most notable infectious diseases (such as cryptococcosis and mycobacterial infections), genetic diseases, diseases of cats in general, and most recently diseases of koalas. Richard has a strong commitment to veterinary continuing education, and to collegiate interactions with small animal colleagues in Asia.

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## Mark Rishniw, BVSc, MS, Diplomate ACVIM

Dr. Mark Rishniw received his BVSc in Veterinary Medicine from the University of Melbourne in 1987and a MS from Washington State University in 1994. He is boarded in internal medicine and cardiology. Currently, he is finishing his PhD, has a part-time postdoctoral position at Cornells College of Veterinary Medicine and is Director of Clinical Research with the Veterinary Information Network. He has authored or co-authored over 45 articles in veterinary medicine. Dr. Rishniw's research interests include molecular methods of disease investigation, clinical research of cardiac disease and evidence-based cardiac medicine.

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## Kenneth W. Simpson, BVM&S, PhD, MRCVS, Dipl. ACVIM, Dipl. EVCIM-CA

Dr. Simpson graduated from the University of Edinburgh (BVM&S) in 1984 and is a Diplomate of the American and European Colleges of Veterinary Internal Medicine. He is a Professor of Medicine at Cornell University's College of Veterinary Medicine with clinical and research interests in internal medicine and gastroenterology.

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## July 27-29, 2007

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# Clinical Decision Making

**Professor Richard Malik DVSc PhD FACVSc FASM**

Post Graduate Foundation in Veterinary Science, Conference Centre, Building B22, University of Sydney, NSW 2006 Australia

**Introduction and conceptual framework**

**Reasoning is** a term used to refer to mental activity through which we transform available information in order to reach conclusions (*in our case the diagnosis of disease*). It requires **decision making** (choosing between alternatives) and **problem solving** (finding paths to desired goals – *in our case determining plans to prove or disprove diagnostic possibilities or therapeutic approaches*).

As veterinarians in small animal practice, not a day goes by that we do not make critical decisions about the investigation and treatment of cases under our care. Interestingly, most of us have received very little specific training in clinical decision making as part of our undergraduate curriculum, and most continuing education forums emphasize the acquisition of new knowledge, rather than philosophical approached to diagnostic and therapeutic decision making.

In small animal medicine, we are frequently confronted with disease conditions we have never encountered before. This makes life challenging and interesting, but it can also make life very stressful! We try our best to use common sense, deductive reasoning and to work things out from first principles using a pathophysiologic approach. Unfortunately, some things are counter-intuitive, for example, the disease necrotizing sialoadenitis, in which patients present with signs that appear referable to mandibular salivary gland disease, but generally respond completely to anticonvulsant drugs such as phenobarbitone. It is therefore vital that we learn through our working life how to draw on the experience of junior colleagues (fresh out of veterinary school), senior colleagues (with vast experience, and special 'local' knowledge), textbooks, local and international experts and medical and veterinary electronic data bases, and resources such as the Veterinary Information Network (VIN).

In relation to diagnosis, there are at least three important conceptual approaches:

(i) Pattern recognition, the recognition of characteristic combination of clues or signs (e.g. cutaneous reaction patterns, radiologic patterns, histological patterns, hematological patterns)

(ii) Problem-based medicine, and

(iii) Diagnosis based on clinical probability (i.e. that certain diseases occur much more commonly than others).

**The best diagnosticians can use all these approaches interchangeably, combining great analytic skill, a systematic approach, but utilizing also good clinical intuition, which can make the diagnostic process faster and less expensive.**

Google Scholar — puts from literature not just from authors

In this new century, veterinarians more than ever should try to consider a scientific approach to clinical decision making. The 'scientific approach or method' is founded on several key values or standards, which are linked:

1. ***Objectivity*** - evaluating the **evidence** free from bias as humanly possible; bias develops from our past experiences
2. ***Open-mindedness*** **-** a commitment to changing one's views in the face of **evidence** that these views are inaccurate
3. ***Skepticism*** **-** non-acceptance of findings until verified– in our case don't accept **evidence** unless it has been well proven through testing
4. ***Accuracy*** - gathering and evaluating information for accuracy – in our case **evidence-based medicine**)

Rather than continue to write abstractly about these disparate concepts, I will attempt to illustrate them by working through what would seem to be a "very straightforward" cases.

I will then challenge different members of the audience, in relation to HOW and WHY they make clinical decisions.

## Case presentation

**Signalment**
Magic is a two-year-old desexed female Australian Mist cat. This is an Australian bred, based on initial crosses between Burmese (50%), Abyssinian (25%) and Australia domestic crossbred cats.

**Presenting complaint**
The cat may have ingested a sewing needle.

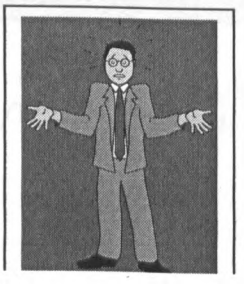
**History**
The owner observed the cat playing with a sewing needle. The needle allegedly had not thread attached. The owner tried to intervene and stop the cat playing with the needle; however when the owner caught the cat, there was no needle to be found. To complicate matters further, the cat then ate 100 rams of commercial tinned cat food, which the owner had been preparing.

**Physical findings**
No abnormalities were detected on physical examination. Coughing was not noted, nor was vomiting or regurgitation during the duration of the physical examination. No foreign bodies or lesions were detected within the oral cavity. A thread was not evident in the vicinity of the lingual frenulum when the tongue was elevated by application of pressure to the intermandibular space. The abdomen was palpated gently, however no pain, discomfort or abnormal structures were evident.

**Questions**

**(1) What is your clinical assessment?**

**(2) What would you do next?**



## Clinical Assessment (this is EASY)

1. the cat **may** or **may not** have swallowed a sewing needle
2. the needle may or may not have had attached thread
3. if so, there may be as a consequence a variety of clinical problems

## What are the potential problems?

1. Penetration of pharynx
2. Penetration of oesophagus
3. Migration of needle from stomach to other sites
   a) which sites?
   b) why THESE sites?
4. Complications related to thread i.e. intestinal plication
   a) when does plication occur?

## What would you do next? (this is a BIT harder)

1. Radiology
2. CT
3. MRI
4. Endoscopy
5. Haematology, biochemistry and urinalysis plus FIV and FeLV

## Radiology

1. Chest?
2. Abdomen?
3. Whole cat, in one go?
4. How many views?

**Questions**

- **Where is the needle?**
- **Do we need a 2nd radiograph?**

## CRITICAL QUESTIONS

- **How should we manage this case?**
- **On what basis should we make decisions regarding clinical management?**

**# HOW DO WE MANAGE THIS PATIENT? (this may be CONTROVERSIAL)**

1. Conservative - do nothing
2. Conservative - use drugs, other techniques
3. Endoscopic removal
4. Surgical removal

**#On what basis should we make decisions regarding clinical management?**

1. Look up text books
2. Ask colleagues
3. Ask local experts/specialists
4. Consult veterinary and medical databases – CAB, Medline, PubMed
5. Post a question on V.I.N.

**#But before we do that, what are the UNIQUE considerations of the present cas e?**

1. The cat has been presented EARLY
2. We cannot be sure if there is thread attached, or NOT
3. The cat has just eaten a LARGE meal
4. It is a young healthy patient that should cope OK with anaesthesia and surgery, if done in an appropriate manner
5. Money is not an issue with these owners
6. There is time to THINK and RESEARCH the best course of action

## Is endoscopic removal a viable possibility?

1. In general, yes - although needles are hard to catch and hard to safely retrieve
2. You need good equipment and GREAT expertise
3. IN THIS CASE, the ingestion of food immediately prior to presentation would have made endoscopic removal very problematic, furthermore anaesthesia would be relatively contraindicated in this setting

## What about surgery?

***Advantages***

1. likely will resolve the problem
2. high success rate
3. minimum morbidity
4. makes more money for the clinic - $$$$$$
5. takes away all the possible complications associated with penetrating object and thread

***Disadvantages***

1. invasive
2. costs the owner more money
3. some pain and morbidity for the patient

## Ask learned colleagues

1. Dr Dick Churcher (opinionated Australian internist) STRONGLY recommended surgery based on his experience with migrating needles in the UK; had seem them migrated liver, thoracic cavity etc

2. V.I.N. ~ UK surgeon RECOMMENDED surgery TO BE SURE it would be OK; but said it might pass, but couldn't be sure this would happen

## Veterinary Textbooks

Consulted a wide variety – NOT very helpful in this specific instance

## EVIDENCE BASED MEDICINE using electronic databases

1. Look at veterinary data bases (most reliable)
2. Also, look at medical data bases (less reliable, but MORE information available for certain topics, such as this one)
3. Case series MUCH MORE HELPFUL than individual case reports when looking for overall recommendations
4. (i)Year of the report and (ii) the country of origin and (iii)institution are very germane to the quality and applicability of the data
5. Textbooks useful, but generally rated low down in the list compared to original peer-reviewed papers

## Veterinary Database (CAB)

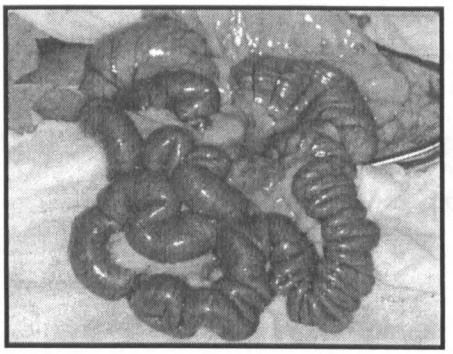
In this instance, was technically difficult. Needed some patience to find the correct key words (stomach, cat, needle). Only limited information available, both two **case series**.

1. Gunsser (1978) in German language Journal 'Sewing needles and fish hooks as foreign bodies in dogs and cats' 57 dogs and 15 cats
   - of 9 cats with gastric needles, 6/9 passed spontaneously in 3-4 days

2. Felts *et al* (1984) *JAVMA* Thread and sewing needles as GI foreign bodies in the cat: a review of 64 cases (from the Animal Medical centre in New York City)

   - most had thread and required surgery

Enough information is available to give you an impression that both good and bad outcomes were possible, but there is insufficient quality data to be definitive in recommending treatment strategies. Interestingly, young cats were overrepresented and the presence of thread must be suspected, as it is the incentive for curiosity and play.



Intestinal plication from a string foreign body in a cat

## What about individual case reports? (like THIS one)

1. tend to be written to highlight UNUSUAL or dramatic sequelae
2. tend not to report simple, happy, unchallenging outcomes
3. e.g. Hunt et al (1991) Suspected cranial migration of two sewing needles from the stomach of a dog. *Vet Rec* - migrated into the heart! Twice!!

## What about human medical databases (Medline or PubMed)

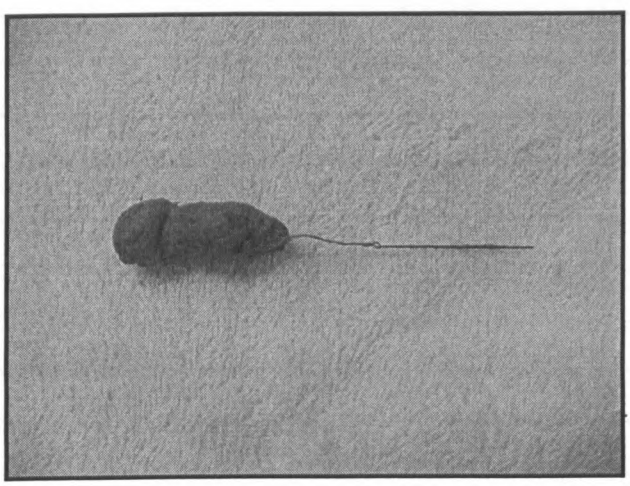
1. Enormous number of cases - case reports, case series, LARGE case series
2. Most talk about FBs generically rather than JUST sewing needles
3. some case series have 18,200 cases !!!
4. Gun *et al* (2003) *Paediatric Surgery International* which concentrates on safety pin ingestion (49 cases) **- 41% passed spontaneously**; the others required endoscopy or surgery
5. Reviewing MANY of the case series available, majority of FBs that reach the stomach continue to pass through without sequelae, prokinetic drugs NOT helpful,sites of trouble are pylorus, duodenal flexure, ileocaecocolic valve, pins are rarely a problem because of Jackson's axiom i.e. the blunt weighted end passes first

## How did we manage our patient?

1. Hospitalised the patient
2. Monitored rectal temperature, demeanour and appetite (every 8 to 12 hours) - we were watching and anticipating signs of early peritonitis, pancreatitis, ileus, partial intestinal obstruction, etc
3. The cat was fed judiciously using commercial tinned cat food ~ small meals three times daily, finely mashed up using a fork
4. Took another radiograph the following morning – the needle was no within the intestinal tract.
5. The cat had a good appetite for TASTY food while in hospital
6. Temperature was marginally elevated for the first 36 hours
7. No faeces was passed for 3-days
8. The cat was given amoxicillin (100 mg orally twice daily) during hospitalisation
9. She was also given some Coloxyl (50 mg orally) every 12 hours from day 3

## A milestone occurred on day 4 when the needle was passed

1. It was attached to a segment of stool
2. The needle measured 3.8 cm
3. It had a cotton thread attached, folded in two; the thread measured 74 cm
4. Presumably the stool pulled the needle and thread through the rectum



## Further reading

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## Medical Management of Chronic Renal Failure in Cats

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## Treatment Options for Cats in Chronic Renal Failure

- Renal transplantation
- Hemodialysis
- Conservative Medical Management

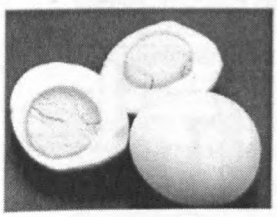
## Medical Management of CRF in Cats

- Caveats ...
  - Don't pass judgment on a lethargic dehydrated cat with markedly abnormal laboratory results
  - 2 to 3 days of conscientious intravenous fluid therapy can produce remarkable results

## Medical Management of CRF in Cats

- Nutritional considerations
- Phosphorus binders
- H2 receptor blockers
- Alkali replacement
- Potassium supplementation
- SQ fluids at home by the owner
- Anabolic steroids
- ACE inhibitors
- Management of hypertension
- Hormone replacement (erythropoietin, calcitriol)

## Medical Management of CRF in Cats
### Nutritional Considerations



- Unlimited access to fresh water at all times
- Minimum of 20% of calories from high quality protein (3.5 g/kg/day when consuming 70 kcal/kg/day)
- Additional calories from carbohydrates and fats

## Medical Management of CRF in Cats
### Nutritional Considerations

- Commercial modified-protein cat foods provide 22-29% of calories from protein
- These foods also are phosphorus and sodium restricted

## Medical Management of CRF in Cats
### Nutritional Considerations

- Try to strike a balance between dietary modification and the cat's willingness to eat
- Monitor adequacy of nutritional therapy by serial evaluation of:
  - Body condition score
  - Weight
  - Hair coat
  - Serum albumin concentration

## Medical Management of CRF in Cats
### Nutritional Considerations

- Rationale behind protein restriction
  - Relief of uremic symptoms
  - Can hyperfiltration be reduced?

rat study - to reduce protein in cats; people to point in world + hyperfil - they'd be malnourished

3 studies to support renal diets

## Medical Management of CRF in Cats
### Nutritional Considerations

- Start modified diet when moderate azotemia persists in the hydrated state before they feel bad and will be less likely to accept it.
- Change diet gradually
- Try to acclimate cat to new diet while appetite is still good

## Medical Management of CRF in Cats
### "Diet Effects"

- Median survival in CRF cats fed "renal" diets ranged from 12-23 months compared to 7 months in cats fed "normal" diets
- Diet with longest median survival was restricted in protein, phosphorus, and sodium but high in potassium and eicosapentanoic acid (EPA)

*Plantinga et al. Vet Rec 147:185, 2005*

Waltham

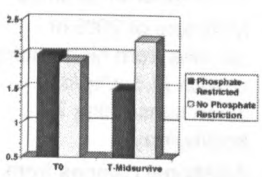
## Medical Management of CRF in Cats
### "Diet Effects"

- 50 CRF cats: 29 fed restricted protein-phosphorus (RPD) diet; 21 rejected the diet and were fed a "normal" (NPD) diet
- At mid-point serum Pi and PTH were significantly higher in NPD and lower in PRD cats than at the start of the study
- Phosphorus binders were required at some point in 34% of RPD cats to control serum PTH
- Median survival was 633 days in RPD vs 264 days in NPD cats

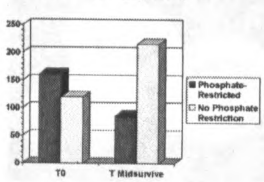
*Elliott et al. J Sm Anim Pract 41:235, 2000*

## Medical Management of CRF in Cats
### "Diet Effects"

Serum Pi (mmol/L)

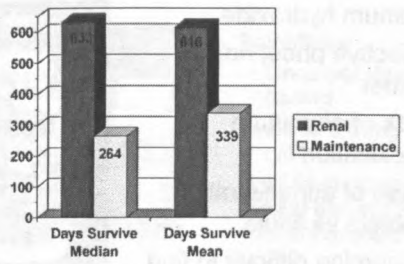



Serum PTH (pg/mL)




*Elliott et al. J Sm Anim Pract 41:235, 2000*

## Medical Management of CRF in Cats
### "Diet Effects"




*Elliott et al. J Sm Anim Pract 41:235, 2000*

Sherry Ross Hills

## Medical Management of CRF in Cats
### "Diet Effects"

- 45 CRF cats: 23 fed adult maintenance diet and 22 fed a "renal" diet low in protein, phosphorus, and sodium with supplemental PUFA over 2 years
- SCr did not differ between groups but cats fed the maintenance diet had more uremic crises and deaths attributable to CRF than did those fed the "renal" diet

*Ross et al. JAVMA 229:949, 2006*

## Medical Management of CRF in Cats
### Phosphorus Restriction

- Rationale behind phosphorus restriction
  - Reversal of renal secondary hyperparathyroidism
  - Improvement in tubulointerstitial lesions
  - Prevention of soft tissue mineralization (including kidneys)

## Medical Management of CRF in Cats
### Phosphorus Restriction

- 84% of cats with CRF have renal secondary hyperparathyroidism based on measurement of serum PTH
- Reduction in serum phosphorus and PTH concentrations can be achieved by dietary restriction of phosphorus alone in approximately 67% of CRF cats whereas phosphorus binders must be added in the remaining 33%

*Barber et al. J Sm Anim Pract 39:108, 1998*
*Barber et al. J Sm Anim Pract 40:62, 1999*

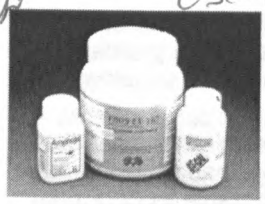
## Medical Management of CRF in Cats
### Phosphorus Restriction

- Ideally, monitor renal secondary hyperparathyroidism by serial measurement of serum PTH
  - Normal, 3-25 pg/ml (depending on lab)
- Evaluate serum phosphorus concentration after 12 hour fast
- Aim for serum phosphorus concentration of 2.5 to 5.0 mg/dL

## Medical Management of CRF in Cats
### Phosphorus Restriction

- Modified-protein diets for cats also are phosphorus-restricted (0.25-0.50% on a dry matter basis)
- Initially try dietary phosphorus restriction alone (expected to be successful in 67%)
- If inadequate, add phosphorus binders (expected to be necessary in 33%)

## Medical Management of CRF in Cats
### Phosphorus Binders



- Aluminum hydroxide
- Calcium acetate
- Calcium carbonate

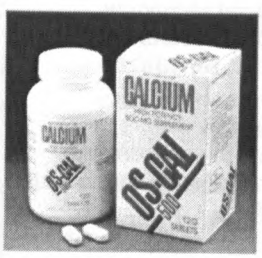
Start at 90-120 mg/kg/day divided and given with within 2 hours of feeding

Slightly lower dosage of calcium acetate may be possible due to more efficient phosphate binding

## Medical Management of CRF in Cats
### Phosphorus Binders

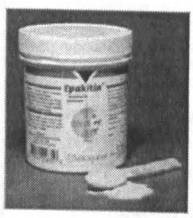
- Aluminum hydroxide
  - Effective phosphorus binder
  - Risk of aluminum intoxication?
  - Ease of administration: Tablets vs liquid
  - Becoming difficult to find


## Medical Management of CRF in Cats
### Phosphorus Binders




- Calcium carbonate
  - Effective phosphorus binder
  - Also provides calcium
  - Use with caution in patients receiving calcitriol due to risk of hypercalcemia

## Medical Management of CRF in Cats
### Epakitin: Chitosan/Calcium Carbonate




- Studied in 10 normal and 6 CRF cats for 21-35 days
- Dosage used (1 g per 5 kg body weight q12h) supplied 20 mg/kg $CaCO_3$ q12h
- Digestibility of dietary Pi and serum Pi decreased
- May have beneficial effects as an oral adsorbent for urea and ammonia

*Wagner et al Berl Münch Tierärztl Wschr 117:310, 2004*

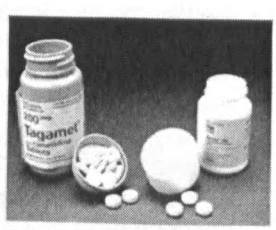
## Medical Management of CRF in Cats
### Uremic Gastroenteritis

- Plasma gastrin concentrations are high in cats with CRF
- Degree of hypergastrinemia correlates with severity of CRF
- Potential clinical manifestations
  - Anorexia
  - Vomiting
  - Gastrointestinal bleeding

*Goldstein et al. JAVMA 213:826, 1998*

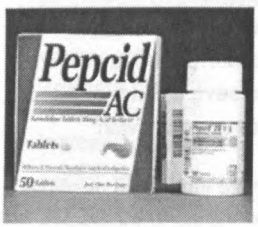
## Medical Management of CRF in Cats
### H2 Receptor Blockers

- Decrease gastric acid secretion
  - Cimetidine (5 mg/kg q12h)
  - Ranitidine (2 mg/kg q12h)
  - Famotidine (1 mg/kg q24h)



Cats don't compensate for metabolic acidosis as vigorously as dogs

## Medical Management of CRF in Cats
### H2 Receptor Blockers




- Famotidine
  - Once per day dosing
  - 2.5 to 5.0 mg per cat
- Data from prospective clinical trial in CRF cats not available

## Medical Management of CRF in Cats
### Metabolic Acidosis

- Respiratory compensation for metabolic acidosis is limited in cats compared to dogs
- Cats may not increase renal ammoniagenesis efficiently in metabolic acidosis
- Many commercial cat foods are acidifying – should be avoided

## Medical Management of CRF in Cats
### Metabolic Acidosis

- 59 cats with CRF: 20 mild (SCr 2.0-2.8 mg/dl); 20 moderate (SCr 2.9-4.5 mg/dl); 19 severe (SCr > 4.5 mg/dl)
- Acidemia found in 53% of severe group and 15% of moderate group
- $pCO_2$ averaged 33-35 mmHg in all groups (minimal respiratory compensation)

*Elliott et al. J Sm Anim Pract 44:65, 2003*

## Medical Management of CRF in Cats
### Metabolic Acidosis

- 55 cats with CRF: 34 showed no progression over an average of 388 days; 14 showed "step-wise" progression between 2 visits; 7 showed "gradual decline over ≥ 3 visits
- Only 1 stable cat had acidosis
- Acidosis was most common in 5 cats experiencing "step-wise" progression
- Acidosis was a late feature of CRF in cats

*Elliott et al. J Sm Anim Pract 44:261, 2003*

or citrate

K gluconate in acidosis too

## Medical Management of CRF in Cats
### Alkali Replacement

- Consider if serum bicarbonate concentration < 14 mEq/L (normal, 14-21 mEq/L)
- Sources: sodium bicarbonate, potassium gluconate, potassium citrate
- Use of potassium gluconate or citrate also provides potassium supplementation
- Future studies are needed to determine if early intervention with alkali salts is beneficial in cats with mild to moderate CRF

## Medical Management of CRF in Cats
### Alkali Replacement

- Sodium bicarbonate
  - 84 g $NaHCO_3$ in 1 L water (1 mEq/ml)
  - 1 mL per 5 kg body weight q12h to q8h
  - Keep capped and refrigerated
  - Desired serum bicarbonate concentration 14-21 mEq/L

## Medical Management of CRF in Cats
### Potassium Supplementation

- 20-30% of CRF cats are hypokalemic
- Factors contributing to hypokalemia
  - Anorexia
  - Loss of muscle mass
  - Polyuria
  - Vomiting

## Can feeding a potassium deficient diet cause CRF in normal cats?

- 9 normal cats fed 44% protein and 0.32% potassium diet for 100 weeks
- Intermittent hypokalemia occurred in 7/9 cats
- 3/9 developed moderate to severe renal disease
- Increased $FE_K$ occurred concurrently with development of azotemia
- Histology: lymphoplasmacytic interstitial nephritis

*DiBartola et al. JAVMA 202:744, 1993*

## Potassium supplementation of normokalemic cats with CRF

- Cats fed 0.78% potassium diet 1 month before and during 6 month study
- Standard medical management of CRF with K gluconate or Na gluconate
- Normokalemic CRF cats had lower muscle $K^+$ than normal control cats
- Serum $K^+$ and $FE_K$ were unchanged during treatment in both groups
- Changes in GFR and RBF did not differ between treatment groups

*Theisen et al. J Vet Int Med 11:212, 1997*

## Medical Management of CRF in Cats
### Potassium Supplementation

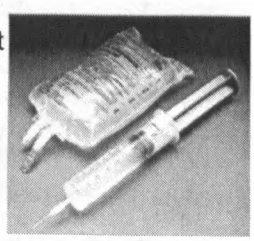
- Should normokalemic CRF cats receive potassium supplementation?
  - Pro: Oral potassium gluconate supplementation at 2 to 4 mEq/day is unlikely to be harmful
  - Con: Evidence for improvement in GFR and RBF is lacking

## Medical Management of CRF in Cats
### Potassium Supplementation

- Potassium gluconate 2 to 4 mEq per day
- Potassium citrate 2.5 to 5.0 mEq per day
- Metabolism of organic anion provides alkalinization

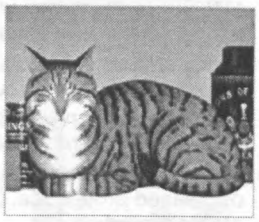

## Medical Management of CRF in Cats
### Supplemental Fluids

- Owners can administer fluids subcutaneously at home to avoid the stress of veterinary visits
  - Fixed daily volume
  - Variable depending upon cat's condition



## Medical Management of CRF in Cats
### Anabolic steroids

- Theoretical benefits
  - Promote erythropoiesis
  - Promote protein anabolism
  - Increase red cell 2,3-DPGA
  - Promote calcium deposition in bone



## Medical Management of CRF in Cats
### Anabolic steroids

- No proven effectiveness in cats with CRF
- Several products
  - Methyltestosterone
  - Stanozolol (hepatotoxic in cats) - Winstrol
  - Oxymetholone
  - Nandrolone decanoate

## Medical Management of CRF in Cats
### Anabolic steroids

- Stanozolol (25 mg IM followed by 2 mg PO q12h for 28 days) was hepatotoxic in cats
  - Anorexia, decreased grooming, decreased activity within 7-10 days
  - Markedly increased ALT and mildly increased ALP
  - Hyperbilirubinemia
  - Vitamin K-responsive coagulopathy
  - Hepatic lipidosis and cholestasis with minimal hepatocellular necrosis
  - Liver enzyme activity returned to normal within 4 weeks after discontinuing drug

*Harkin et al. JAVMA 217:681, 2000*

## Medical Management of CRF in Cats
### ACE inhibitors

- Potential detrimental effects of angiotensin II in CRF
  - Efferent vasoconstriction > afferent vasoconstriction increases intraglomerular pressure (↑ $P_{GC}$) and contributes to proteinuria
  - Mesangial cell contraction decreases surface area available for glomerular filtration (↓ $K_f$)
  - Increased protein traffic in mesangium stimulates cytokine release and promotes fibrosis (glomerular sclerosis)
  - Increased reabsorption of proteins in proximal tubules up-regulates genes for inflammatory mediators

may be responsible for increasing cytokines

Benazepril 0.5 mg/kg bem

## Medical Management of CRF in Cats
### Effects of benazepril on glomerular hemodynamics

- Benazepril (0, 0.4, 0.7, 1.6 mg/kg/day) given to cats with 11/12 Nx over 6 mos
- Minimal effects on systemic BP (average decrease of 8 mmHg) and GFR
- Ratio of efferent/afferent vasoconstriction decreased and $K_f$ increased significantly in all treated groups (no net effect on SNGFR)
- No enhanced anti-hypertensive effect above 1 mg/kg/day

*Brown et al. Am J Vet Res 62:375, 2001*

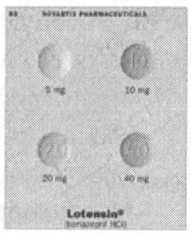
## Medical Management of CRF in Cats
### Role of proteinuria

- 136 client-owned cats: 28 normal, 14 non-azotemic hypertensive, 66 azotemic non-hypertensive, 28 azotemic hypertensive
- Hypertension if present treated with amlodipine
- Age, SCr, UPC were correlated with survival; hypertension was not
- SCr independently correlated with proteinuria; increased age was not associated with increased UPC
- 90% of cats had UPC < 1.0

*Syme et al. J Vet Int Med 20:528, 2006*

## Medical Management of CRF in Cats
### ACE inhibitors

"It remains uncertain whether in animals with naturally-occurring renal disease rapid disease progression is because of the proteinuria causing renal injury or if the proteinuria is simply a marker for a disease process that is intrinsically more rapidly progressive."



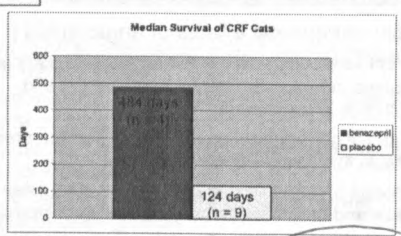

*Syme et al. J Vet Int Med 20:528, 2006*

## Medical Management of CRF in Cats
### ACE inhibitors: BENRIC Study

- 192 CRF cats treated with benazepril (0.5-1.0 mg/kg/day) vs placebo for up to 3 yrs
- Renal endpoint (78 cats): need for fluid Rx or euthanasia or death due to CRF
- Median renal survival: 637 days (benazepril) vs 520 days (placebo): Not significantly different
- Benazepril worked rapidly (< 7 days), significantly decreased proteinuria, did not affect SCr, and was well tolerated

*King et al. J Vet Int Med 20:1054, 2006*

## Medical Management of CRF in Cats
### ACE inhibitors: Benazepril




Data for CRF cats with initial UPC ≥ 1.0

*King et al. J Vet Int Med 20:1054, 2006*

Supports using proteinuria

## Medical Management of CRF in Cats
### ACE inhibitors: BENRIC Study

- *Benazepril decreased proteinuria but did not affect survival time*
  - In humans, ACE inhibitors slow progression of CRD independent of effects on BP and effect is greatest when treatment is started early
  - If proteinuria plays a role in progression of CRD in cats, early treatment with benazepril seems justified
  - If proteinuria is simply a marker of renal disease in cats, the best course of action is unclear

*King et al. J Vet Int Med 20:1054, 2006*

## Medical Management of CRF in Cats
### ACE inhibitors: Benazepril

- 61 cats with CRF treated with benazepril (0.5-1.0 mg/kg/day) vs placebo for 6 mos
- UPC was significantly lower in benazepril-treated cats at 4 and 6 mos
- 93% of benazepril-treated cats remained in IRIS stage 2 or 3 (SCr 1.6-5.0 mg/dL) compared to 73% of placebo-treated cats
- Survival and SCr did not differ between groups

*Mizutani et al. J Vet Int Med 20:1074, 2006*

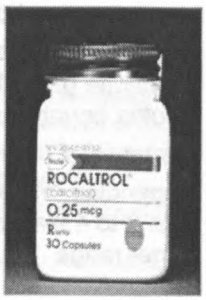
## Medical Management of CRF in Cats
### Hormonal Replacement

- Erythropoietin
- Calcitriol

Calcitriol is blunts cont output PTH - is a brake in feedback loop

## Medical Management of CRF in Cats
### Hormonal Replacement: Calcitriol

- Reduces PTH secretion by occupying calcitriol receptors on parathyroid glands
- Enhances gastrointestinal absorption of calcium and may correct ionized hypocalcemia



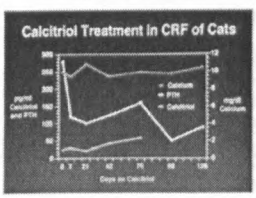

## Medical Management of CRF in Cats
### Hormonal Replacement: Calcitriol

2.5 to 3.5 ng/kg = Usual Dosage

| 0 | 5 | 10 | 15 | 20 |
|---|---|---|---|---|
| PTH Suppressed | ↑GI Absorption of Calcium | ↓ Appetite/Weight | Hypercalcemia | |

↑ Goal

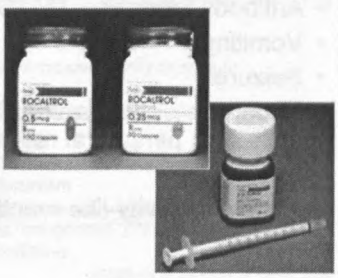
## Medical Management of CRF in Cats
### Hormonal Replacement: Calcitriol




- Used only after hyperphosphatemia controlled (i.e., Ca × Pi < 60-70)
- Watch for hypercalcemia (especially with Ca containing Pi binders)
- Rapidly lowers serum PTH concentration

## Medical Management of CRF in Cats
### Hormonal Replacement: Calcitriol

- Extremely low dosage required: 2 to 4 ng/kg/day
- Requires reformulation by compounding pharmacy

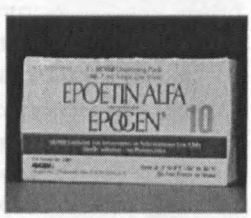



## Medical Management of CRF in Cats
### Hormonal Replacement: Calcitriol

- Monitoring patients on calcitriol
  - –Clinical appearance may be unreliable
  - –Follow serum PTH concentration
- Long-term benefit to animal unknown

## Medical Management of CRF in Cats
### Hormonal Replacement: rhEPO

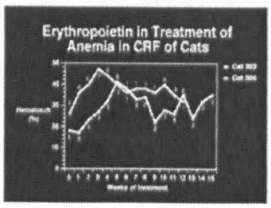
- Effects in treated cats
  - – Resolution of anemia
  - – Weight gain
  - – Improved appetite
  - – Improved haircoat
  - – Increased alertness
  - – Increased activity




*Not approved for use in cats*

use Epogen only from now

## Medical Management of CRF in Cats
### Hormonal Replacement: rhEPO




- Consider in symptomatic cats with PCV < 20%
- Starting dosage 100 U/kg SQ 3X per week
- Supplement with $FeSO_4$ 5 to 50 mg/day (oral iron may be poorly tolerated)
- When PCV > 30% decrease to 2X per week

## Medical Management of CRF in Cats
### Hormonal Replacement: rhEPO

- Monitor serum iron status
- Monitor PCV weekly using same technique (table top centrifuge or Coulter counter) every time
- Target PCV range: 30 to 40%
- Depending on severity of anemia may take 3 to 4 weeks for PCV to enter target range

## Medical Management of CRF in Cats
### rhEPO: Adverse Effects

- Antibody formation: MAJOR problem
- Vomiting
- Seizures
- Hypertension (improved $O_2$ delivery to tissues increases peripheral resistance)
- Uveitis
- Hypersensitivity-like reactions at injection site

## Medical Management of CRF in Cats
### rhEPO: Adverse Effects

- High risk of antibody formation (20-40%)
- Occurs 30 to 160 days after starting treatment
- Progressive decrease in PCV and marked increase in bone marrow M:E ratio while receiving EPO
- Discontinue EPO if antibody formation suspected
- Prolonged transfusion dependence may result

consid chemo post BSOT

## Medical Management of CRF in Cats
### Recombinant Feline Erythropoietin

- rfEPO used to treat 19 anemic CRF (100 U/kg SC 3X/wk) cats and 7 CRF cats with red cell aplasia due to prior rhEPO treatment (400 U/kg SC 3X/wk)
- Reached target PCV (30-40%) in 3 wks
- Appetite and activity increased
- MCV and serum iron decreased in first 8 wks of Rx
- Elemental iron supplementation 2 mg/kg/day (some cats experienced GI upset)

*Randolph et al. Am J Vet Res 65:1355, 2004*

Serum ferritin

## Medical Management of CRF in Cats
### Recombinant Feline Erythropoietin

- Uncommon adverse effects
  - Median systolic BP did not change, but 2 cats had recorded systolic BP > 180 mmHg
  - Seizures (unassociated with polycythemia or hypertension) in 1 cat
  - Excoriations and licking at injection site in 2 cats
  - Anaphylaxis and death in 1 cat

*Randolph et al. Am J Vet Res 65:1355, 2004*

## Medical Management of CRF in Cats
### Recombinant Feline Erythropoietin

- Unexpected serious adverse effect
  - 5/19 (26%) CRF cats not previously treated w/ rhEPO and 3/7 (43%) CRF cats previously treated w/rhEPO developed RCA after a median of 14.5 weeks of Rx
  - M:E increased (30:1 to > 100:1) and some developed marrow lymphocytosis
  - Similar to 20-40% frequency of RCA in cats treated with rhEPO

*Randolph et al. Am J Vet Res 65:1355, 2004*

## Medical Management of CRF in Cats
### Recombinant Feline Erythropoietin

- Possible reasons for red cell aplasia (RCA) in rfEPO treated cats
  - Allelic variation (no evidence found)
  - Differences in glycosylation (unlikely)
  - Other conformational changes (most humans with RCA after rhEPO Rx have been treated with 1 product – Eprex®)
  - Route of administration (more common in humans after SC vs IV administration)

*Randolph et al. Am J Vet Res 65:1355, 2004*

## Medical Management of CRF in Cats
### Hypertension

- 20/103 (19.4%) cats with CRF had systolic BP > 175 mmHg (95% CI: 13-28%)
- Cardiac abnormalities (gallops, murmurs, arrhythmias) and ocular lesions (hemorrhage, retinal detachment) were common
- Severity of azotemia was not associated with hypertension

*Syme et al. JAVMA 220:1799, 2002*

## Medical Management of CRF in Cats
### Hypertension

- 69 cats with hypertensive retinopathy and systolic BP > 170 mmHg
- Associated disorders
  - 26 cats: no identifiable cause; *mildly azotemic*
  - 22 cats: CRF
  - 12 cats: no identifiable cause; non-azotemic
  - 5 cats: hyperthyroidism
  - 2 cats: diabetes mellitus
  - 1 cat: hyperaldosteronism
- Conclusion: "primary hypertension in cats may be more common than currently recognized" (?)
- Good response to amlodipine

*Maggio et al. JAVMA 217:695, 2000*

## Medical Management of CRF in Cats
### Hypertension: "White Coat Artifact"

- Makes it difficult to decide if a cat is truly hypertensive
- Mean 24-hr systolic blood pressure by radiotelemetry:
  - Normal cats: 126 mm Hg
  - CRF cats: 148 mm Hg
- During clinical examination:
  - Normal cats: 143 mm Hg
  - CRF cats: 170 mm Hg

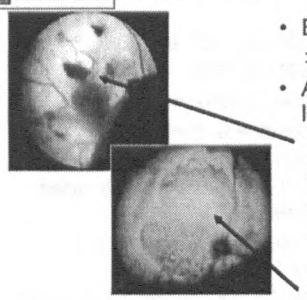
*Belew et al. J Vet Int Med 13:134, 1999*

## Medical Management of CRF in Cats
### Blood Pressure Assessment

- Patient, trained technician
- Quiet, undisturbed environment
- Sufficient time for acclimation
- Correct cuff size
- Several sequential measurements
- Average sequential readings

Retinal exam + BP

## Medical Management of CRF in Cats
### Hypertension: To treat or not?



- BP consistently > 175 mm Hg
- Any high BP and fundic lesions:
  - Retinal hemorrhage
  - Vascular tortuosity
  - Retinal edema
  - Intra-retinal transudate
  - Retinal detachment

## Medical Management of CRF in Cats
### Management of Hypertension

- Dietary salt restriction
  - Commercial cat foods designed for CRF usually also are sodium-restricted
  - Variations in sodium intake (2.2, 4.4, 8.7 mEq/kg/day) did not affect BP in normal and remnant kidney cats
  - Low sodium intake may be associated with RAAS activation resulting in increased urinary $FE_K$ and hypokalemia
  - Sodium restriction did not have beneficial effect on BP and had potentially adverse effects on potassium balance that could contribute to renal injury (hypokalemic nephropathy)

*Buranakarl et al. Am J Vet Res 65:620, 2004*

does ↓Na help ↓K along? don't know

## Medical Management of CRF in Cats
### Management of hypertension

- Furosemide
  - Risk of dehydration and pre-renal azotemia
- Limited success with beta-blockers (e.g., propranolol) and ACE inhibitors (e.g., enalapril)

## Medical Management of CRF in Cats
### Management of hypertension

- 30 hypertensive (> 175 mmHg) cats: 16 CRF, 7 idiopathic, 5 azotemic hyperthyroid, 2 non-azotemic hyperthyroid
- Cardiac or ocular abnormalities in 87%
- 20 controlled with amlodipine 0.625 to 1.25 mg q24h alone
- 10 required addition of an ACE inhibitor, beta blocker, or thiazide at some point
- No to few adverse effects (hypotension in 1 cat)

*Elliott et al. J Sm Anim Pract 42:122, 2001*

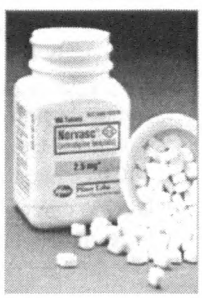
## Medical Management of CRF in Cats
### Management of hypertension

- Conclusions
  - CRF was most common underlying problem in hypertensive cats
  - Hyperthyroidism only causes mildly increased blood pressure unless accompanied by CRF
- Questions
  - Does control of BP slow progression of CRF in cats?
  - What target should be set for BP control (< 165 mmHg?)

*Elliott et al. J Sm Anim Pract 42:122, 2001*

## Medical Management of CRF in Cats
### Management of Hypertension

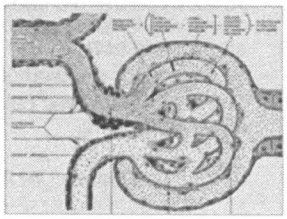
- Amlodipine
  - Start with 0.625 mg PO q24h
  - Recheck BP in 7-14 days
  - If BP > 175 mmHg, increase to 1.25 mg PO q24h
  - Goal: BP < 165 mmHg
  - Expect good control in 60%



## Medical Management of CRF in Cats
### Management of Hypertension

- Calcium channel blockers preferentially dilate afferent arteriole: lower systemic BP; preserve GFR
- ACE inhibitors preferentially dilate efferent arteriole: minimal effect on systemic BP in cats; decrease $P_{GC}$
- Ideal treatment may be a combination

$K_f(P_{GC}-P_T-\pi_{GC}) = GFR$



## Medical Management of CRF in Cats
### Urinary Tract Infection

- UTI occurs in 30% of CRF cats
- Females > males
- Usually *E. coli*
- Low USG in CRF cats may predispose to UTI
- Treat with appropriate antibiotic therapy

*Barber et al. J Vet Int Med 13:251, 1999*

## International Renal Interest Society (IRIS) Classification: Feline CRD

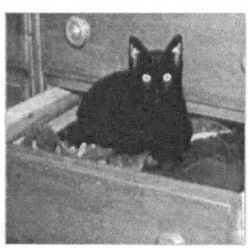
| Creatinine | Stage I Non-azotemic CKD | Stage II Mild renal azotemia | Stage III Moderate renal azotemia | Stage IV Severe renal azotemia |
|---|---|---|---|---|
| *mg/dL* | *< 1.6* | *1.6-2.8* | *2.9-5.0* | *> 5.0* |
| *Prevalence** | 33.6 % | 37.2 % | *15.4 %* | *14.1 %* |

silent — clinically apparent

*Distribution of 786 Cases of CRD in Cats (Elliott et al. ACVIM Proceedings, 2003)

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Non-thyroidal illness (CRF) lowers T4 and makes diagnosis of hyperthyroidism difficult
- Hyperthyroidism increases GFR and RBF and masks underlying renal disease



## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- 30 days after bilateral surgical thyroidectomy in hyperthyroid cats:
  - GFR decreased from 2.5 to 1.5 ml/min/kg (40% decrease)
  - SCr increased from 1.3 to 2.0 mg/dL
  - BUN increased from 27 to 35 mg/dL

*Graves et al. Am J Vet Res 55:1745, 1994*

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Regardless of treatment (methamizole, bilateral thyroidectomy, radioiodine)
  - SCr increased from 1.6 to 2.2 mg/dL at 30 days and 2.4 mg/dL at 90 days
  - BUN increased from 30 to 36 mg/dL at 30 days and 37 mg/dL at 90 days

*DiBartola et al. JAVMA 208:875, 1996*

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Iatrogenic hyperthyroidism (50 μg/kg T4 SQ daily for 30 days) in previously normal cats
  - Increased GFR from 2.9 to 3.4 ml/min/kg
  - Increased RPF from 10.1 to 12.2 ml/min/kg
  - Decreased BUN from 22 to 17 mg/dL
  - Decreased SCr from 1.1 to 0.7 mg/dL

*Adams et al. Can J Vet Res 61:53, 1997*

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- 15/22 hyperthyroid cats had GFR < 2.25 ml/min/kg before radioiodine (9 were azotemic and 5 were not)
- 30 days after radioiodine, 13/15 were azotemic
- The 2 non-azotemic cats had persistently high T4 after radioiodine

*Adams et al. Vet Radiol & Ultrasound 38:231, 1997*

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- GFR of 2.25 ml/min/kg was useful for predicting outcome after radioiodine
  - 13/15 cats with GFR < 2.25 ml/min/kg developed azotemia 30 days after treatment
  - 0/7 cats with GFR > 2.25 ml/min/kg developed azotemia 30 days after treatment

*Adams et al. Vet Radiol & Ultrasound 38:231, 1997*

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Subclinical renal disease is common in hyperthyroid cats. Why?
  - Coincidental finding in a geriatric population?
  - Hyperthyroidism contributes to development of chronic renal disease in cats?
    - 60% of renal perfusion pressure is transmitted to the glomerular capillary bed in cats *Brown et al. Am J Vet Res 54:970, 1993*
    - Intraglomerular hypertension may contribute to progression of renal disease and glomerular sclerosis

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Should hyperthyroidism be treated in cats with CRF?
  - CON: The effects of hyperthyroidism reduce azotemia and improve appetite
  - PRO: Hyperthyroidism could contribute to progression of renal disease and has many other deleterious systemic effects

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

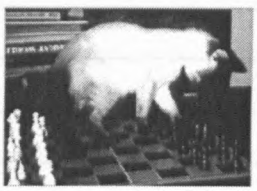
- Identification of cats at risk for adverse renal outcome after treatment of hyperthyroidism
  - GFR determination is ideal but impractical (cats with GFR < 2.25 ml/min/kg are at risk)
  - BUN, SCr and USG have limitations
    - BUN, SCr artificially decreased by increased GFR; SCr also decreased by loss of muscle mass
    - Some cats (10-15%) retain substantial concentrating ability in presence of CRD
  - Use information from palpation of kidneys and ultrasound exam

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

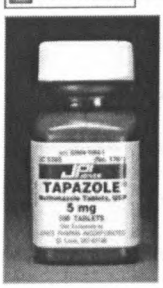
- Diagnosis of hyperthyroidism in geriatric cats with CRD is difficult
  - CRD is a non-thyroidal illness that can lower T4 to within the normal range
  - Palpation of a thyroid nodule is a practical and useful diagnostic tool
  - Pertechnetate scan is the "gold" standard

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- What is the "best" way to manage hyperthyroid cats with chronic renal disease?



## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney




- Tapazole "challenge"
  - 2.5 mg PO q24h
  - Gradually increase to maximal tolerated dose (up to 5 mg PO q12h)
  - Re-evaluate renal function every 10 days before increasing dosage
- Definitive therapy (surgery, radioiodine) if rendering cat euthyroid does not adversely affect renal status

## Medical Management of CRF in Cats
### Hyperthyroidism and the Kidney

- Definitive treatment of hyperthyroidism (surgery, radioiodine) may render some cats hypothyroid
- Hypothyroidism could adversely affect renal function
- CRF cats rendered hypothyroid should be supplemented with 0.1 mg l-thyroxine PO q24h

Cats are very tolerant of females
local - like I eidgid leg - or otherwise
not general like people / horses
Take several months to get better

Devon - muscular dystrophy
DK hard to get up - look at aldosterone producing tumour
in adrenals

Myotonia Congenita Chloride channel muscle
"squinting goat syndrom"

Urticaria pigmentosa - erythema only in patchy
Devon Rex cyclosporin 25mg BD

Doxy monohydrate - doesn't cause eos irritate
20% pododem "LP" with Doxy 5mg/kg
L-P pododem can sometimes occur nasal planum

When you google - use several variation on the
topic you want to search - like cat or cats or feline
ulcerative

mps bite dermatitis just like Eos histo they don't EG
See also T Herpes - want to find inclusions

Acyclovir bad in cats but new generation Famcyclovir
1/2 25mg 125 mg qd 14 d. eod IV
Acyclovir cream topically if you can - the topical cleared the cat
Does Herpes virus have something TO do with EG in cats

IF: Omega Verbagen antiviral

Helen Powers
Herpes in Skin

# Refractory ulcers on the nasal bridge of a young cat:

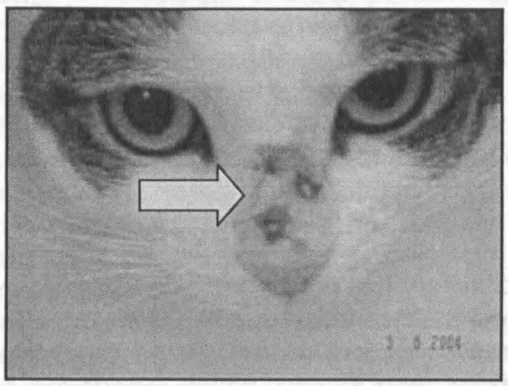
## An exercise in Diagnostic Reasoning

**Professors Richard Malik[1,2] DVSc DipVetAn PhD FACVSc FASM & Paul J. Canfield[2] DVSC PhD FACVSc Grad Cert Higher Ed FRCPath**

[1]Post Graduate Foundation in Veterinary Science and Faculty of [2]Veterinary Science, University of Sydney, NSW 2006 Australia

**CASE STUDY**

**Presenting complaint and history**: An eight-month-old castrated male domestic crossbred cat is presented for multiple non-healing ulcers on the bridge of its nose.



**Physical findings:** The lesions do not appear to be pruritic. There are no lesions like this on the nasal planum or on the digital pads. There is no suppuration from the lesions. There are no current signs of nasal cavity disease such as sneezing or nasal discharge. The cat is constitutionally well. The lesions did not respond to a four week course of cephalexin, and have persisted while the cat has been boarding in the clinic for seven days.

1. **What is your clinical assessment?**
2. **How would you investigate this case further?**

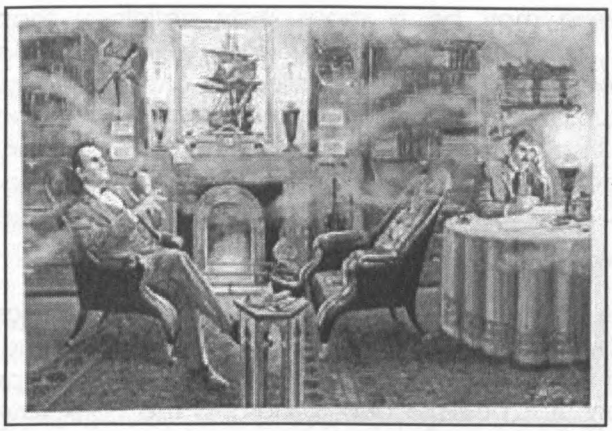
# Background concepts to be explored

Let us start with some key definitions. **Reasoning** refers to mental activity through which we transform available information in order to reach conclusions. In this specific instance (**clinical reasoning**), we refer to the integration of historical, physical, laboratory and imaging findings in order to make a diagnosis. It requires **decision making** (choosing between alternatives) and **problem solving** (finding paths to desired goals) – in this case, determining plans to prove, or disprove, the diagnostic possibilities and/or approaches to therapy.

When we trained as clinicians in Vet School, the major focus was on providing an overview of the many disease conditions that can affect the various body systems in disparate animal species. This was underpinned by **"Problem-orientated medicine"**, a conceptual approach which was has been well accepted in veterinary medicine since the 1970s, and is taught in most veterinary colleges in North America and Australia.

It should be borne in mind that one of the factors that make teaching diagnostic reasoning so tricky is that **expert clinicians do not follow a fixed pattern of patient examination and evaluation**. *From the outset, they are generating, refining and discarding diagnostic hypotheses.* The questions they ask in the history are driven by the hypotheses they are working with "in the moment". Even *the physical examination is somewhat driven by specific key potential findings*, rather than a pre-ordained checklist. For example, when evaluating a patient with sudden collapse and pale mucous membranes, the student palpates the abdomen while waiting for a finding to strike him; on the other hand, the expert clinician is on a focused search mission, e.g. is there a palpable abdominal mass (spleen?) which may be hemorrhaging into the peritoneal space. Negative findings are often just as important as positive findings.

In problem-orientated medicine, presenting complaints, clinical signs, abnormal physical findings and laboratory test results, information from imaging modalities and so forth can all be entered as **"Problems"** in a Problem List. **This Problem List forms the cornerstone of the patient's medical record.** These problems are then resolved, if possible, into a smaller number of entities which reflect the ***key underlying disease processes*** giving rise to the patient's signs. The advantage of this approach is that it can be applied to any disease, simple or complex, and it works (or should work) even for disease conditions that the clinician has never seen before, or not even heard about! The trouble with this system is that it is cumbersome, tedious for simple cases, expensive and not well suited to the majority of software systems used in veterinary practice. *It is VERY USEFUL, however, in developing a conceptual framework to explain to undergraduates the logic which underpins analytic diagnostic reasoning.* It should form the cornerstone for clinical decision making when combined with information from textbooks and electronic data bases.



Sherlock Holmes - a great believer in Problem based analysis. Dr Watson can be seen suffering from passive smoking on the right.

Experienced clinicians, if they are honest, will admit that much of the time they can recognise the cause of many patients' problems by utilizing mental "short-cuts", usually characteristic patterns of historical clues, clinical signs and physical findings. Such **"pattern recognition"** has been frowned upon by some influential veterinary educationalists. This is illogical, as in my experience the best human and veterinary internists have the most sophisticated pattern recognition skills! **The reason why this intuitive style of diagnostic reasoning is so disdained is that it may let you down if not utilized with checks and balances.** This is because some patients do not have the "classic pattern", while other patients with "a classic pattern" can have a completely different disease, or a concurrent significant other problem. *Indeed, the presence of multiple concurrent diseases is an under-rated problem when dealing with complex cases, especially when matters are further complicated by preliminary treatments that have been given by other veterinarians.* This is why veterinary medicine can be so challenging. Unfortunately this has resulted in 'throwing out the baby with the bathwater', because **an intuitive, thoughtful clinician can harness both pattern recognition AND analytic diagnostic reasoning to sort out challenging internal medicine cases.**

The novice veterinary practitioner typically uses a "shot gun" approach to diagnostic testing, hoping to hit a target without really knowing what that target is. The increasingly accepted concept of a minimum data base – consisting of a complete blood count, a biochemical panel, urinalysis, chest and abdominal radiographs and abdominal ultrasound – is the current expression of this approach, although it has merit in complex cases or in situations where there is no limit to the cost of the "work up". **The expert diagnostician, on the other hand, usually has one or two specific targets in mind, and efficiently adjusts the testing strategy with this in mind.** Uncertainty in veterinary medicine is compounded by the information overload that characterizes the modern world in which we live. It has been said that a good human internist needs at least two millions bits of information to practice medicine. In order to cope, most good clinicians use **cognitive shortcuts**, or **heuristics**, to organize complex unstructured material from the clinical evaluation into a manageable format.

Psychologists have found that people rely on three basic types of heuristics. Pattern recgnition is an example of the **representative heuristic**, where the clinician weighs the probability that the patient's *key clinical features* match those of patients with the leading diagnostic hypothesis under consideration. For example, a cat with sudden onset of oculonasal discharge, sneezing, conjunctivitis, tracheal hypersensitivity and fever but no mouth ulcers is most likely to have a viral upper respiratory infection, with feline Herpesvirus the most likely specific etiological agent. The clinician using the representative heuristic can reach erroneous conclusions if they fail to consider the underlying prevalence of two (or more) conflicting diagnoses. For example, in a cattery with a history of chlamydiosis and solid vaccination program against viral

respiratory pathogens, *Cl felis* infection may be a more likely aetiology than Herpesvirus in this particular scenario. In either case, specific testing with a "gold standard" test e.g. multiplex PCR using an appropriately collected oropharyngeal swab is required to confirm the presumptive diagnosis. Mistakes also occur when considering a pattern based on *too small* a number of observations. In veterinary medicine, BREED often plays an important role in recognizing patterns of disease e.g. muscular dystrophy in Devon Rex cats, polycystic kidney disease in Persian cats, and so forth.

A second commonly used cognitive shortcut, the **availability heuristic**, involves judgments made of the ease with which similar cases, including ones with unusual patterns or outcomes, can be brought to mind. Clearly vast clinical experience helps here, and so does a retentive memory. It is possible also to harness the corporate memory of the practice when using this heuristic, for example a type of envenomation commonly seen in that area, or a poisonous plant seen in a particular location. Errors with this heuristic can be related to recall bias, e.g. where bizarre diagnoses or catastrophic outcomes are recalled with clarity and force out of proportion to their true value. For example, we are much more likely to recall the intestinal foreign body that "got stuck" and caused an obstruction, rather than the many other cases which passed without noticeable adverse sequellae. Obviously, recent experience is easier to recall and therefore more influential with this heuristic in relation to clinical judgments.

The third commonly used cognitive shortcut, the **anchoring heuristic**, involves estimating probability by starting from a given point (the anchor) and adjusting to the new case from there. Although this can be a powerful tool, using the wrong anchor can be very misleading, whereas using the correct anchor can be of great benefit. For example, a colleague asks you to evaluate a Dachshund with posterior paralysis that is thought most likely to be referable to intervertebral disc prolapse. You conduct a detailed neurological examination and are puzzled by the presence of lower motor neuron signs in the hindquarters (hypotonia, reduced tendon jerks and withdrawal responses), and have not had the opportunity of taking a history in which the owners report that the dog's bark is altered, that it had been regurgitating and that the owners had removed an *Ixodes*tick 24 hours prior to the development of posterior paralysis! No wonder you are confused – you have started from an erroneous reference point – the dog has "classical" tick paralysis, not a disc prolapse! Anomalous laboratory results often cause anchoring heuristic headaches, e.g. the finding of an allegedly elevated thyroxin value in a cat with no goiter and normal history and physical examination! Sometimes BREED associations can provide the wrong anchor, e.g. making a diagnosis of arrhythmogenic right ventricular cardiomyopathy ("Boxer cardiomyopathy) in a Boxer dog with incessant tachycardia, when the dog instead has a re-entrant junctional tachycardia.

Cognitive scientists studying the thought processes of expert clinicians have observed that internists groups data into packets or "chunks", which are stored in their memories and manipulated to generate diagnostic hypotheses. Because short term memory typically holds seven to ten items at a time, the number of chunks of information that can be actively integrated into hypothesis generating activity is likewise limited. The cognitive shortcuts listed above play a critical role in generating diagnostic possibilities, many of which are discarded as rapidly as they are formed.

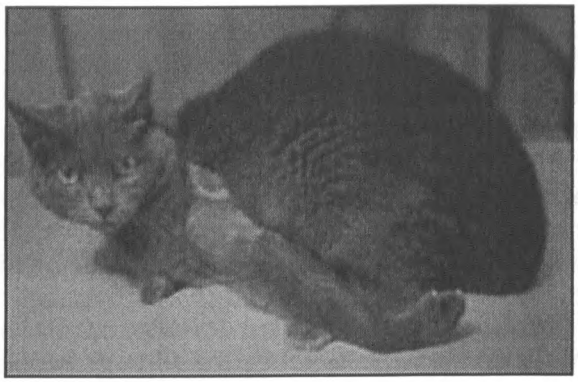
Most of the time, **linear logic** is used in conducting clinical investigations. For example, the investigation of a canine patient with nasal discharge would typically involve examining the area (observation, palpation, percussion), diagnostic imaging (radiographs, cross sectional imaging [computed tomography(CT) or magnetic resonance imaging (MRI)], anterior and posterior rhinoscopy and obtaining

appropriate tissue specimens (washings, pinch biopsies) for laboratory investigations (cytology, culture, histology, polymerase chain reaction testing). Nine times out of 10 this provides the correct diagnosis, but often at the cost of a very expensive and invasive investigation. Sometimes *non-linear logic* (i.e. **"lateral thinking"**) can produce a stunningly correct diagnosis. For example, finding that the nasal discharge developed one week after starting a peanut supplement to the diet in preparation for a dog show can suggest the diagnostic of allergic rhinitis secondary to food allergy. This presumptive diagnosis can be confirmed inexpensively by removing this food supplement form the diet, observation, and possibly subsequent provocative exposure. Another pertinent example would be the sudden development of multifocal intracranial signs in a young adult dog. The detailed neurological examination suggests multifocal central nervous system disease (differential diagnosis granulomatous meningoencephalitis, cerebral cryptococcosis, etc), which is usually investigated by cross sectional imaging of the brain, cerebrospinal fluid (CSF) analysis and serological testing. However the observation that the owners are young, university students with unusual dress sense and multiple piercings, suggests further history taking (Have you noticed any hash cookies missing form your stash?), observation in hospital and a urinary toxicology screen may be more prudent, less invasive and more cost effective than a full neurological work-up!

**Finally, it must be acknowledged that in some instances certain clinical entities are so bizarre that their diagnosis is almost counterintuitive, and instead relies on recognizing a particularly arcane pattern of clinical findings.** For example, the entity referred to as *necrotizing sialadenoadenitis* refers to a condition in which there is painful enlargement of one or more mandibular salivary glands, associated with dyspagia, drooling of saliva and even infarction of the salivary gland parenchyma. A logical diagnostic approach would involve inspection of the affected glands and their ducts, imaging of the glands, biopsy or even surgical removal of the glands – however all these measures prove to be unhelpful, and empiric discovery of the effectiveness of certain anticonvulsants has led to the proposal that this condition is actually a form of "limbic epilepsy". The recently described *oropharyngeal pain syndrome of Burmese cats* and *phenobarbitone-responsive gastroparesis and vomiting* are other pertinent examples. Another entity in this category is sudden acquired ret8inal degeneration – a disease in which dogs suddenly develop peripheral blindness (bilaterally dilated pupils that fail to respond to light) associated with Cushingoid physical findings; the diagnosis is made by exclusion by detecting a normal fundoscopic examination (initially) with an absent electroretinal electrical response (ERG) to a flash stimulus. It is only possible to immediately recognize these rare bizarre entities through expert knowledge, intuitive leaps or therapeutic trials (if you are the first person to encounter such an entity). However, the use of electronic databases, Boolean logic and *sophisticated key word searches* using search engines such as **Google™** and **Google Scholar™** can often be very helpful in finding information on such diagnostic oddities.

***The process of clinical reasoning revolves around generating TESTABLE HYPOTHESES. These should be confirmed with further test(s), or response to therapy, but if the tests results or therapeutic response is not supportive, hypotheses need to be discarded or substantially modified.***

Unfortunately, the generation and evaluation of appropriate diagnostic possibilities is a skill not all clinicians posses to the same degree, and this is likely a consequence of the fact that people intrinsically think in different ways!

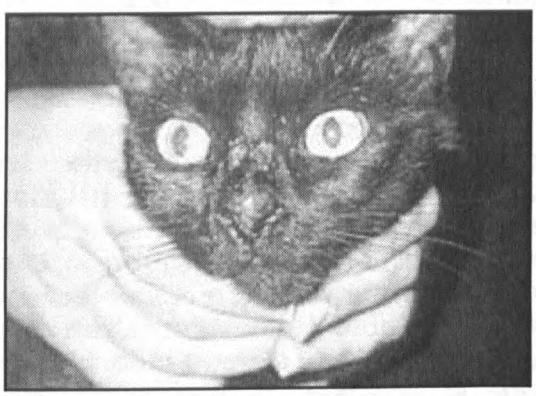


This cat has stiffness and unyielding rigidity of ONE thoracic limb. The cat is otherwise well. There may be clues in the history that HELP establish the diagnosis.

**WHAT ARE THE CLUES?**

**WHAT IS YOUR DIAGNOSIS?**

A further critical component of diagnostic reasoning relates to probability theory, or if you will, a "racing form guide approach" to diagnosis. This can be summed up by the expression "common things occur commonly". Thus, when confronted by a characteristic combination of clinical findings, or an anatomic diagnosis, then, **based on chance, certain diseases are much likely to be encountered than others,** at least in given geographical regions. For example, it is possible to say that of the many potential causes of polydipsia/polyuria in dogs, most patients in a general practice setting will have diabetesmellitus, h yperadrenocorticism or renal insufficiency (The exact order may vary from country to country, or region to region because of differences in the gene pool and environmental factors such as feeding and day length in different geographical regions). Other diseases, such as diabetes insipidus, are much less likely to be encountered.



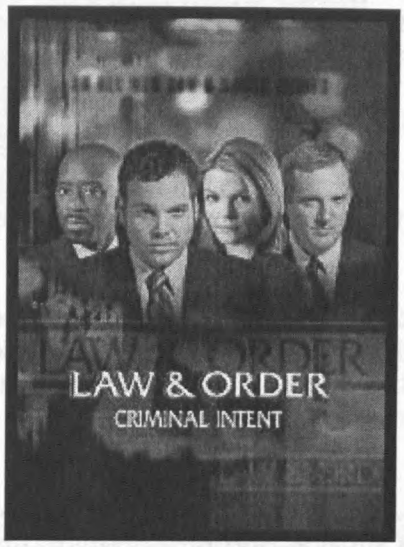
This cat has multifocal lesions on the nasal bridge region. They have failed to response to antibiotics and corticosteroids.

**WHAT IS YOUR DIAGNOSIS?**

The trouble with "pattern recognition" and "probability" is that you must either have a lot of experience (preferably including time spent working along side senior expert clinicians), or do a lot of rote learning, to make these diagnostic considerations work for you. **Local knowledge and the counsel of a senior colleague can be very helpful in this setting**, which is unhelpful for new graduates or locums, and **sometimes a good veterinary nurse/technician with a long corporate memory can be helpful!** Another important theme is that the patterns can be COMPLETELY DIFFERENT in different species; for small animal clinicians this is of key importance because diseases in cats and dogs present in different ways, and occur with different frequencies. Hence, the commonly voiced viewpoint that "cats are not small dogs". This is more of a problem for people whose thinking style is less reliant on a problem-based approach.

Another consideration, that almost no-one mentions, is that certain individuals make intuitive clinicians. The current TV series "House", concerning a taciturn but brilliant internist (Gregory House MD played by the English actor Hugh Laurie) is based on this premise. Probably such individuals would have made good criminal investigators, as there is without doubt *an art* as well as a science in diagnostic reasoning.

Interestingly, the character Gregory House was based in part on Sherlock Holmes, hence the pun on the word House/Ho(l)me(s). I have no doubt detective Robert Goren (from Law and Order Criminal Intent) would have also made at outstanding veterinary internist, as he would be have been a sophisticated exponent of pattern recognition, problem-orientated medicine and also clinical intuition.




**Bobby Goren – a GREAT exponent of Problem-based medicine and pattern recognition**

**Can YOU be a vetective??**

Whatever way you like to approach the diagnosis of disease, **be aware**:

- Of the strengths and limitations of each type of diagnostic approach
- That jumping to a conclusion is natural, but may be harmful - always ask yourself "What evidence I am basing this on?", and question the veracity of the evidence. If in doubt, do another more definitive test to confirm your first impression.
- That your previous experiences can mislead you in some cases (i.e. **keep an open mind**).
- Of accepting evidence too readily, just because it fits in with your bias or others' views – **always ask yourself 'how' and 'why' about evidence, i.e. maintain objectivity and 'healthy skepticism'**.
- That your emotions and the way you like to think and operate can sometimes adversely affect your capacity to reach decisions and solve problems – know yourself!
- Remember that **a single key finding can confirm or refute a presumptive diagnosis**.

We believe it is healthy to try to cultivate a stereotyped approach to the diagnostic process by answering the following questions:

1. What can you **deduce** from the signalment, history, clinical signs and physical findings:
    - The time course of the disease process? - construct a time/sign diagram
    - Which organ system(s) are affected?
    - What pathological process(es) are likely involved?
    - Is a pattern emerging? – does it fit all the cats?

2. **Detect and describe** physical, laboratory and imaging findings. Include useful "patterns".

3. Consider the **pathophysiologic basis** for the observed findings. An approach that considers the underlying physiological derangements is most useful in planning pharmacological and other interventions.

4. What conclusions can you draw i.e. define a problem or problems. **Try and move from the general to the specific.** But try to move further to the specific as you get additional information such as laboratory and imaging data.

5. How can you obtain the evidence to support your conclusions (i.e. what is your plan for further investigation)?

6. Are their implications for on going management, while you investigate further?

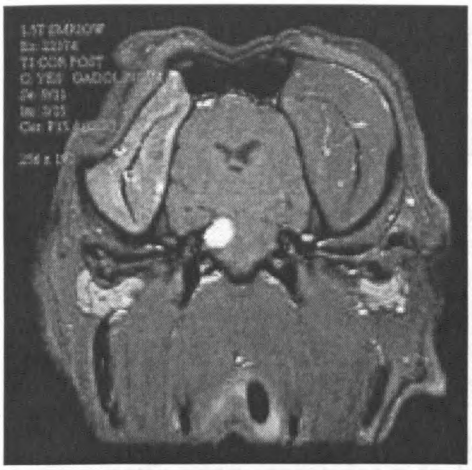
7. Consider using textbooks and electronic databases using *key word searches* to help in difficult cases. Do not be afraid to ask your colleagues (senior and junior) for their opinions, but do not necessarily let them take over your own clinical reasoning.

This talk will flesh out some of these issues by proving that WE ALL USE A COMBINATION of problem solving, pattern recognition, clinical intuition and probability to work out *what is wrong with our patients.*

**Importantly, we will try to convince you there is nothing wrong with developing YOUR OWN clinical style, which takes into account (i) the way you learn, (ii) the way you "think" and (iii) whether or not you have a certain type of retentive memory, or not, and (iv) whether you have *reliable* clinical intuition.**

We will also try to demonstrate that there are many patterns; including imaging patterns (e.g. air bronchogram, alveolar pattern), dermatological patterns ('cutaneous reaction patterns'), hematological patterns (e.g. stress leukogram response), clinical chemistry patterns (eg high ALT with hyperthyroidism, increased ALP without jaundice in Cushing's disease), cytological patterns (e.g. capsulated yeast with narrow necked budding with cryptococcosis) – and that there is nothing *wrong with using all of them.*

For example, we are all comfortable that the combination of dysuria, haematuria, pollakiuria and stranguria are together suggestive of lower urinary tract disease; once we have make this connection, it is easy to sort out the specific diagnosis (infection, stones, neoplasia, etc). Likewise, we are comfortable about recognizing clinical syndromes. **Clinical syndromes are really just patterns**, e.g. Horner's syndrome (ptosis, meiosis, third eyelid prolapse) is a *sophisticated* pattern that tells us something is interfering with sympathetic innervation of the eyeball; we then just need to remember the corresponding neuroanatomic pathway to work out the complete differential diagnosis (T1-T3 spinal cord disease, brachial plexus disease, cervical disease and middle ear disease). The presence of Horner's syndrome with concurrent ipsilateral facial nerve paralysis is an even more complex pattern, and strongly suggestive of middle era disease. But you still need diagnostics to work out whether the problem is an infectious, polypoid or neoplastic in origin.



This dog presented for masticatory muscle atrophy, absence of blink reflex (ipsilateral) but normal menace reflex and dazzle response.

**What is your pattern recognition diagnosis?**

**What is your problem-based diagnosis?**

The importance of using ALL TECHNIQUES will be emphasized in the accompanying presentation. Many clinical examples will be used. This will include some common and well recognised patterns, some more arcane patterns, and also cases where pattern recognition must be tempered by a problem orientated approach.

# Differential diagnosis of diseases affecting the nasal bridge of cats

Infections affecting the skin and subcutis of the naso-ocular region are seen from time to time in feline practice. We have investigated in excess of 20 of these cases since 1987 and the likely pathogenesis of these infections has become apparent over the years. The key finding is that infections affecting this anatomic region develop through two different mechanisms.

**Cases with infection of the naso-ocular region but *without* concurrent nasal signs**
These cases likely result from contaminated cat-scratch injuries. Presumably the claw(s) of the feline perpetrator are contaminated by viable, potentially-pathogenic, saprophytic organisms. These are inoculated in such large numbers that non-specific defense mechanisms (bleeding, inflammation, neutrophilic phagocytosis, lysozyme) of the victim are overwhelmed. This results in a localised, variably invasive infection of an otherwise immunocompetent host. A wide range of microorganisms can be cultured from such cases including a variety of bacteria and fungi normally residing in soil, rotting vegetation, humus or dirt. Lesions are typically on the bridge of the nose, but they may also occur more laterally or involve the nasal planum.

In our referral centre in eastern Australia, opportunistic pathogens isolated from such cases (a total of 7 cats between 1987 and 2003) have comprised the bacteria *Corynebacterium pseudotuberculosis* (1 case), *Mycobacterium avium* (1 case) and *Nocardia nova* (1 case), and the fungi *Cryptococcus neoformans* (1 case), *Exophiala jeanselmei* (2 cases) and *Paecilomyces lilacinus* (1 case). *Mycobacterium avium*, *Exophiala jeanselmei*,*Alternaria* species and *Sporothrix schenckii* have been reported to produce similar lesions by others. Conceptually similar mycobacterial infections or mycotic lesions can develop on the cornea following cat scratch abrasions. The biologic behaviour of these infections depends on the virulence of the pathogen, the initial dose of organisms inoculated, the subsequent host response, the effect of subsequent medical and surgical interventions and the chronicity of the lesion.

Although the precise location and appearance of lesions is quite variable from case to case, the relatively consistent anatomic distribution of lesions which will be apparent from this presentation is strongly suggestive of a cat-scratch-aetiology. One differential diagnosis for florid disease at this anatomic site is insect-bite hypersensitivity. However, the punctate nature of the primary lesions, frequent concurrent involvement of the ears and toes and characteristic eosinophilic histology distinguishes the underlying allergic basis. A further important diagnostic possibility is ulcerative dermatitis due to feline herpesvirus type 1, which is associated with eosinophilic inflammation, mild concurrent upper respiratory signs and in some cases characteristic viral inclusion bodies in biopsy specimens; definitive diagnosis depends on amplification of Herpesvirus amplicons using PCR, ideally on fresh tissue specimens. This infection may respond to topical agents used to treat cold sores in people, or the systemic anti-herpes agent famciclovir. A recent paper has shown the usefulness of intralesional interferon-omega in the management of a refractory case. Presumably the location of ulcerative lesions in these cases is related to the habit of cats to clean their noses of exudates by grooming via their antebrachium, with subsequent inoculation of virus into the dermis of the nasal bridge.

The main focus of this short note is to alert clinicians to the likely pathogenesis for infections of this anatomic region. Importantly, even though saprophytic organisms generally considered to be of low virulence are isolated from these patients, in most cases there is no predisposing immunodeficiency state. Thus, the infection merely reflects a breach in the integrity of normal cutaneous barriers and an especially heavy inoculum of infectious agent. Unfortunately these infections may be difficult to cure, as some causal strains are locally invasive and the region does not have an especially rich blood supply or mobile skin nearby to facilitate reconstructive surgical procedures. Furthermore, many of these saprophytic organisms demonstrate resistance to commonly used antimicrobials both *in vitro* and *in vivo*, and this can be especially problematic for the fungal pathogens.

One may speculate as to why cat scratch-related infections occur at this site rather than elsewhere. Firstly, it is a very commonly involved site. Secondly, it is a location that cats cannot reach with their tongue, whereas scratch wounds elsewhere may be cleansed of potentially pathogenic microbes before an infection is established. Thirdly, the predilection area is sparsely covered by hair, so injuries from claws may penetrate more deeply into the subcutis compared to areas afforded the protection of a longer hair coat. Finally, growth of many saprophytic species may be favored at the lower temperatures encountered at this anatomic prominence. It must be emphasized, however, that lesions attributable to a similar range of pathogenic saprophytes can develop on the body wall or distal extremities following contamination by soil or dirt of cat fight lacerations or abrasive injuries to the pads or interdigital spaces. Likewise, contaminated penetrating wounds of the caudoventral abdominal region often result in mycobacterial panniculitis of the inguinal fat pad.

*Diagnostic work-up*

Investigation of these cases typically involves obtaining representative material for cytology, histology and appropriate culture. Cytology and histology generally show pyogenic or pyogranulomatous inflammation and usually causal organisms can be visualised using special stains (DiffQuik, Gram, Ziehl-Neelsen, periodic acid Schiff, silver stains). A variety of staining techniques may be required, and in some cases an exhaustive search of smears or histologic sections is required to detect the infectious agents. Mycobacteria, fungi and *Nocardia* species may sometimes be detected in DiffQuik-stained smears because of a negative, rather than positive, staining reaction. The laboratory should be warned of the possibility of a fastidious saprophytic pathogen, as these organisms often have specific growth requirements (e.g. special

culture media, reduced temperature of incubation, requirement for high carbon dioxide concentration etc) and/or require several days or even weeks to become detectable as visible colonies *in vitro*. Ideally, a small portion of the biopsy specimen should also be frozen in case polymerase chain reaction techniques or additional culture studies are required at a later date.

Many authorities would also recommend obtaining a minimum data base consisting of a complete blood count, serum biochemistry profile, urinalysis and possibly tests for feline immunodeficiency virus (FIV) and feline leukaemia virus before embarking on therapy. Concurrent metabolic problems such as renal insufficiency or diabetes mellitus may render the cat somewhat immunodeficient, while the presence or liver or kidney dysfunction may affect the selection of the most appropriate antimicrobial agent(s) or limit doses that can be safely given (e.g. amphotericin B in cats with pre-existing renal insufficiency). A positive FIV-status does not preclude a satisfactory response to appropriate therapy, as it is generally impossible to discern the stage and impact of the FIV infection until *after* the cat has received appropriate therapy. Indeed, in the authors' experience, concurrent FIV infection is most often an epiphenomenon in this cohort of patients reflecting the cats' outdoor lifestyle and propensity to fight.

*Therapy*

The treatment of these cases involves long courses of carefully selected antimicrobials based on accurate species identification, *in vitro* susceptibility data (ideally from a specialist reference laboratory) and information from the human and veterinary literature available through electronic databases. Additionally, many of these patients require complete surgical excision of grossly infected tissues to assist the host's non-specific immune response. Given the severity of the pathology in long-standing cases and the diffusion barriers resulting from tissue necrosis and fibroplasia, it is understandable that adequate levels of antimicrobials may not be achieved throughout all affected tissues. Thus, the best chance for a successful outcome for certain cats is to use an approach reminiscent of oncologic surgery, by removing as much infected tissue as possible using *en bloc* resection following preliminary antimicrobial therapy which is extended into the intra-operative period and continued post-operatively. Residual microscopic foci of infection can then be targeted by the high concentrations of antibiotics achieved during and after surgery.

This may be done at the outset (for convenience and to minimise the number of procedures to which the patient must be subjected), or after a microbiological diagnosis has been made e.g. by aspiration biopsy or resection of a small representative tissue specimen. In the latter scenario, it is possible to ensure that effective levels of appropriate antimicrobial agents are obtained in the peri-operative period. This may be advantageous if a major reconstructive procedure is required to remove an extensive lesion with clear margins. In some cases, surgery alone may be effective in resolving the infection (e.g. Bostock et al 1982), although routine use of follow-up antimicrobials is strongly recommended to guard against the possibility of the surgical margin being seeded with infectious material. Generally speaking, in the absence of complete surgical excision, these infections require treatment with long courses of antimicrobials, at least for several weeks, and typically for many months, depending on exactly which organism is involved and how much infected tissue can be safely resected at the outset. In some cases, combination therapy with two or more antimicrobial is superior to monotherapy with a single agent. Infections caused by organisms capable of intracellular survival (e.g. *Mycobacteria* spp, *Nocardia* spp) and fungi require the longest courses of therapy, and should ideally be treated not only until the lesion appears grossly normal, but for an additional period exceedingly the lifespan of macrophages in the tissues i.e. a further two months. Additional information on diagnosis and treatment of

representative infections of this type can be found in the bibliography.

*Prevention*
Although the vast majority of cat scratch injuries to the face heal without any untoward sequelae, the possibility of opportunistic infections developing should be borne in mind when recommending treatment for feline patients with cat scratch injuries seeking veterinary advice by telephone or by consultation. Thorough cleansing of contaminated scratch wounds using saline or a dilute antiseptic (e.g. 0.05% chorhexidine) would seem prudent, followed by instillation of an ointment containing both antibacterial and antifungal agents (and *without* corticosteroids) and possibly a short course of an antibiotic such as doxycycline monohydrate (5mg/kg twice daily for 3 to 5 days). Although it is impossible to choose an agent with a spectrum sufficiently broad to cover all potentially-pathologic saprophytes, doxycycline has useful activity against many saprophytic mycobacteria, some *Nocardia* species, oropharyngeal organisms such as *Pasteurella* spp and obligate anaerobes that may have been inoculated simultaneously via bite wounds. Additionally, it is generally well tolerated, devoid of significant toxicity (e.g. retinotoxicity, nephrotoxicity) and available in conveniently sized tablet and paste formulations in Australia, New Zealand and South Africa (VibraVet®; Pfizer Animal Health), which facilitates dosing and owner compliance. The use of a formulation containing the monohydrate salt is strongly recommended, as it is less irritant to the stomach and oesophagus than conventional human formulations utilising the hydrochloride salt.

*Cases with naso-ocular infection and concurrent signs of nasal cavity disease*
These cases are not the main focus of this communication, but are included for completeness. In these patients, the primary problem starts with infection of the nasal cavity by infectious propagules (typically spores) of saprophytic fungi filtered by the nasal passages. This may be facilitated by a pre-existing cause of nasal injury. Involvement of the naso-ocular region develops subsequent to the infection spreading to the nasal planum or penetrating the overlying bones to reach the subcutis over the nasal bridge. Most of these cases are attributable to cryptococcosis and in many of these patients the nasal planum is affected prominently. We have also seen this type of disease progression with invasive aspergillosis and rhinitis caused by the termite mycoparasite *Metarhizium anisopliae*. Similar findings have also been reported in a cat with invasive bacterial rhinitis caused by an *Actinomyces* species.

These cases can be investigated either by directing attention to the primary site of infection i.e. the nasal cavity, by cytological examination of nasal swabs or washings (e.g. for budding, capsulate yeasts), serum cryptococcal antigen titre determinations, anterior/posterior rhinoscopy, cross-sectional imaging and biopsy of affected turbinates. Alternatively, needle aspirates or incisional biopsies can be obtained from the subcutaneous lesions and submitted for cytologic and histologic investigations and culture. Invasive mycotic rhinosinusitis is generally treated with one or a combination of antifungal agents administered systemically. Although monotherapy with azoles such as itraconazole or fluconazole is convenient for owners and effective in many patients, some cases do not respond and require amphotericin B e.g. as twice weekly subcutaneous infusions, to effect a cure. Unusual fungal infections may sometimes be more susceptible to other classes of antifungal agent such as terbinafine, or newer azoles such as voriconazole or posaconazole. Although topical therapy using clotrimazole 'soaks' has been used by others to treat cases such as this, the authors believe systemic therapy is preferable due to the invasive, granulomatous nature of the infection and the propensity in cats for bony erosion (including the cribriform plate) to occur in association with these infections.

The major differential diagnosis in these cases is invasive nasal neoplasia which can also breach the integrity of overlying nasal bones to invade the subcutaneous tissues of the nasal bridge and/or forehead. In our practice, lymphoma is the commonest sinonasal malignancy in the cat, followed by adenocarcinoma and osteosarcoma, whereas solar-induced squamous cell carcinoma is the most common cancer of the nasal planum.

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19th Annual
Fred Scott Feline Symposium
July 27-29, 2007

Dedicated to the memory of Dr. Jim Richards

Jim, circa 1979, at OSU CVM Fun Night

# Renal Diseases of Cats

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# Renal Diseases of the Cat

**But**

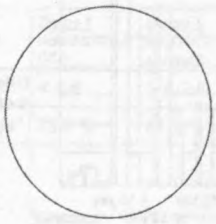
***How would you ad-dress a Cat?***

**So first, your memory I'll jog,**

**And say: A CAT IS NOT A DOG.**

**T.S. Eliot, 1939**

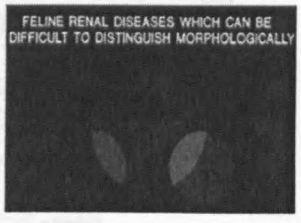
# Renal Diseases of Cats



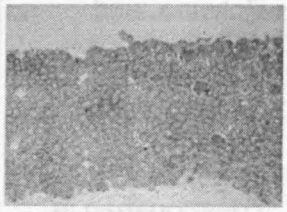
- Chronic Interstitial Nephritis
- Lymphosarcoma
- Glomerulonephritis
- Polycystic Kidney Disease
- Pyelonephritis
- Amyloidosis
- Neoplasia, unspecified

# Renal Diseases of Cats

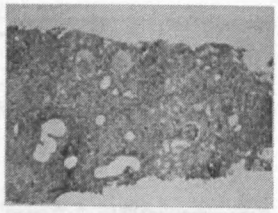
- Diseases that can be distinguished morphologically
  - Amyloidosis
  - Lymphosarcoma
  - PKD
  - FIP




# Renal Diseases of Cats

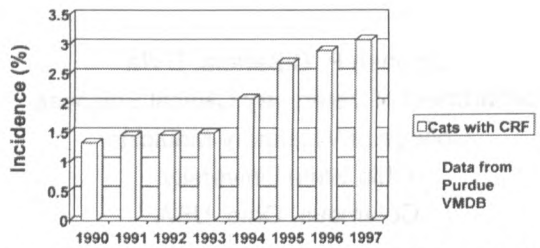


Normal feline renal biopsy



Chronic interstitial nephritis

## CRF in Cats: Incidence

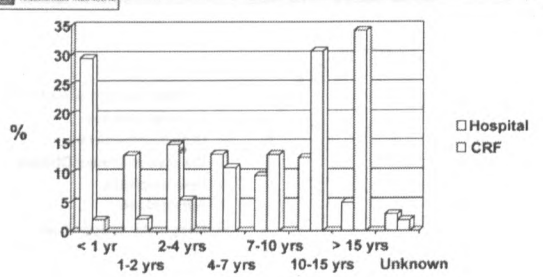



**Overall prevalence of CRF in cats: 3,139/161,201 = 1.95%**

## CRF in Cats: Signalment

- Older cats
- No sex predilection
- No breed predilection
  - Amyloidosis in Abyssinian, Oriental Shorthair, Siamese
  - Polycystic kidney disease in Persian

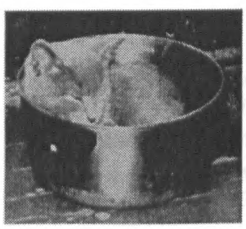
## CRF in cats: Age



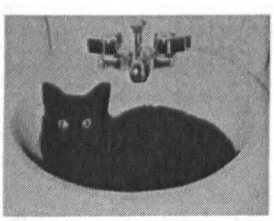

Data from Purdue VMDB

## CRF in Cats
### Common Clinical Signs

- Anorexia
- Lethargy
- Weight loss

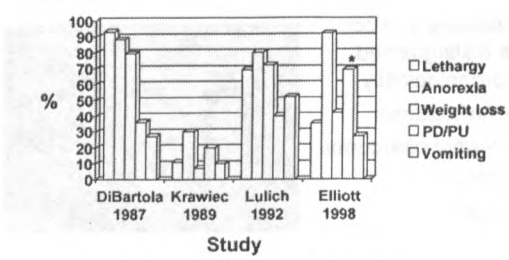


## CRF in Cats
## Less Common Clinical Signs



- Polyuria and polydipsia less commonly recognized by owners
- Vomiting less common than in dogs with CRF

## Clinical Signs in Cats with CRF

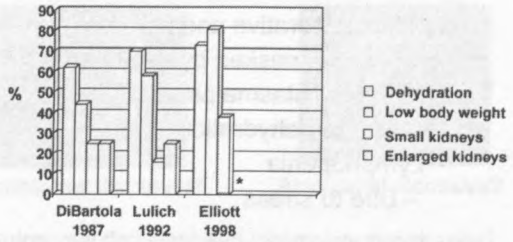



** Cats with advanced disease that had polydipsia*

## CRF in Cats
### Physical findings

- Dehydration
- Poor body condition
- Variable kidney size
  - Normal cat kidneys are approximately 4 cm in length

## Cats with CRF
### Physical Findings




** % of affected cats with renomegaly not reported*

## CRF in Cats
### Serum Chemistry

- Azotemia
- Hyperphosphatemia
- Decreased total $CO_2$ (advanced disease)
- Hypercholesterolemia (nonspecific)
- Hypokalemia (20 to 30%)

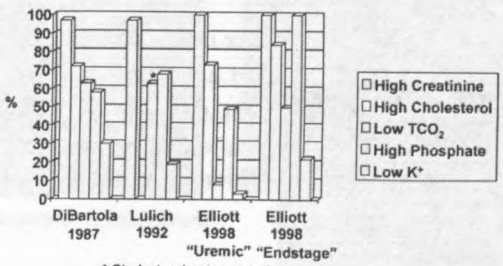
## International Renal Interest Society (IRIS) Classification: Feline CRD

| Creatinine | Stage I Non-azotemic CKD | Stage II Mild renal azotemia | Stage III Moderate renal azotemia | Stage IV Severe renal azotemia |
|---|---|---|---|---|
| *mg/dL* | *< 1.6* | *1.6-2.8* | *2.9-5.0* | *> 5.0* |
| *Prevalence** | 33.6 % | 37.2 % | *15.4 %* | *14.1 %* |

silent — clinically apparent

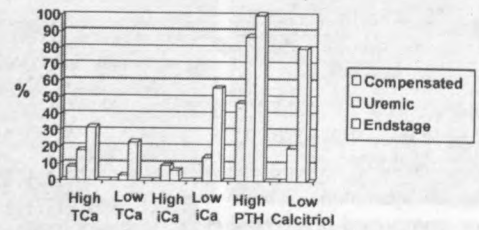
*Distribution of 786 Cases of CRD in Cats (Elliott et al. ACVIM Proceedings, 2003)

## Cats with CRF
### Serum Chemistry Findings




** Cholesterol not reported*

## Cats with CRF
### Renal Secondary Hyperparathyroidism




*Barber & Elliott, J Sm Anim Pract 39:108, 1998.*

## CRF in Cats
### Hematology

- Nonregenerative anemia
  - May be masked by dehydration
- High total plasma proteins
  - Due to dehydration
- Lymphopenia
  - Due to stress

## CRF in Cats
### Urinalysis

- Isosthenuria
  - Some cats (10-15%) with CRF maintain considerable concentrating ability; 85-90% are isosthenuric
- Proteinuria
  - Consider glomerular disease if marked and sediment inactive
- Glucosuria
  - May be present in up to 20% of cats with CRF (tubular dysfunction?)
- White blood cells
  - Consider UTI (lower vs upper)

## Amyloidosis

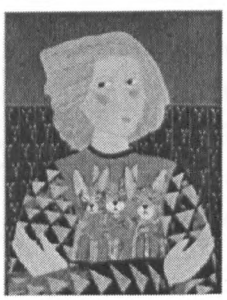
- Tissue deposition of proteins with specific biophysical conformation (beta-pleated sheet)
- Extracellular eosinophilic deposits on H&E
- Congo red positive deposits demonstrate green birefringence when viewed under polarized light
- Reactive systemic amyloidosis (AA protein) most common in domestic animals
- Clinical signs reflect the organs involved and their reaction to the amyloid deposits
- Tissue tropism of AA protein: kidney, liver, spleen

## Renal Amyloidosis in Abyssinian Cats

Amyloidosis:

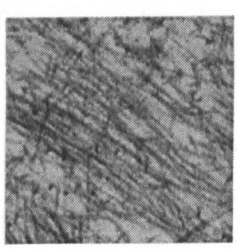
Rare in domestic cats

Common in Abyssinian cats

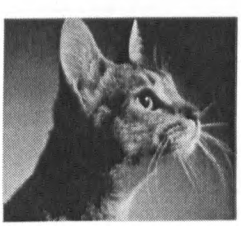


## Amyloidosis in Oriental Shorthair and Siamese Cats

- Oriental shorthair and Siamese cats also develop amyloidosis
- Severe liver involvement may lead to rupture and hemoabdomen
- As in Abyssinians, fibrils are composed of amyloid A (AA) protein



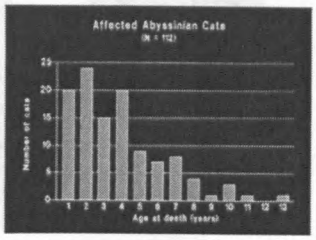
## Renal Amyloidosis in Abyssinian Cats



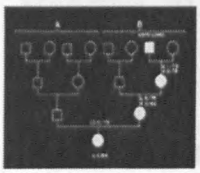
- Sex ratio of affected cats
  - 1.4:1.0 M:F
  - Not significant (likely affected by cattery demographics)

## Renal Amyloidosis in Abyssinian Cats

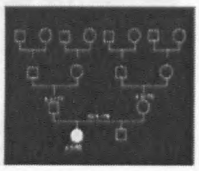
Age of onset and rate of progression variable




## Renal Amyloidosis in Abyssinian Cats: Inheritance



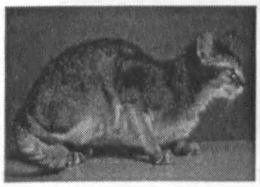
Autosomal dominant?



Autosomal recessive?

Autosomal dominant with incomplete penetrance?

## Renal Amyloidosis in Abyssinian Cats



- Clinical findings
  - Poor haircoat
  - Weight loss
  - Lethargy
  - Polyuria/polydipsia
  - Dehydration
  - Small irregular kidneys

## Renal Amyloidosis in Abyssinian Cats

- Laboratory Findings
  - Nonregenerative anemia
  - Azotemia
  - Hyperphosphatemia
  - Metabolic acidosis
  - Isosthenuria
  - Variable proteinuria

## Renal Amyloidosis in Abyssinian Cats

| | | |
|---|---|---|
| Age (mos) | 8 | 9 |
| USG | 1016 | 1015 |
| Urine Protein (mg/dl) | 300 | 500 |
| BUN (mg/dl) | 93 | 80 |
| Creatinine (mg/dl) | 2.3 | 1.7 |
| Pi (mg/dl) | 8.0 | 10.0 |
| Albumin (g/dl) | 2.8 | 2.8 |
| Cholesterol (mg/dl) | 382 | 486 |
| Biopsy | POS | POS |

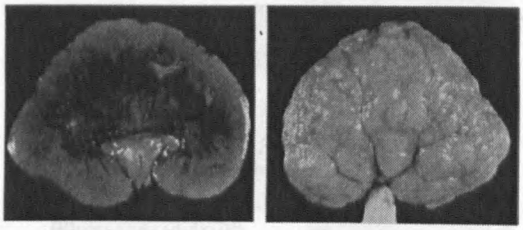
Glomerular amyloidosis

| | | | | | | |
|---|---|---|---|---|---|---|
| Age (mos) | 9 | 13 | 21 | 25 | 28 | 35 |
| USG | 1060 | 1069 | 1022 | 1018 | 1013 | 1012 |
| Urine Protein (mg/dl) | 10 | 50 | 100 | 10 | 10 | 10 |
| BUN (mg/dl) | 26 | 28 | 27 | 41 | 49 | 55 |
| Creatinine (mg/dl) | 1.0 | 1.4 | 1.7 | 2.4 | 2.0 | 3.8 |
| Pi (mg/dl) | 7.7 | 5.6 | 5.9 | 5.3 | 5.2 | 6.1 |
| Albumin (g/dl) | 2.9 | 3.2 | 2.8 | 2.7 | 3.0 | 2.6 |
| Cholesterol (mg/dl) | 123 | 144 | 106 | 117 | 144 | 191 |
| Biopsy | NEG | NEG | NEG | NEG | ND | ND |

ND = not done

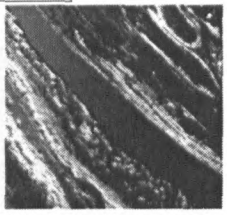
Medullary amyloidosis

## Renal Amyloidosis in Abyssinian Cats

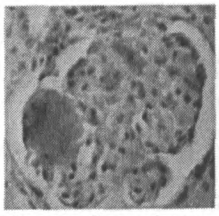


Lugol's iodine can be used to presumptively identify medullary amyloid deposits at necropsy

## Renal Amyloidosis in Abyssinian Cats

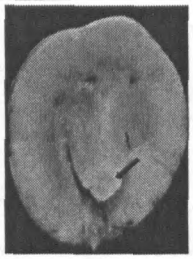


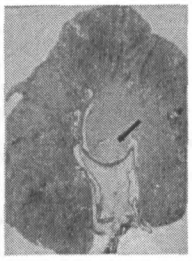
100% of affected cats *have medullary* involvement



75% of affected cats *have glomerular* involvement

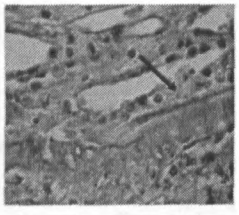
## Renal Amyloidosis in Abyssinian Cats

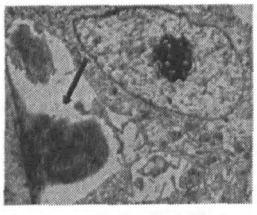




Papillary necrosis results from ischemia due to medullary amyloid deposits

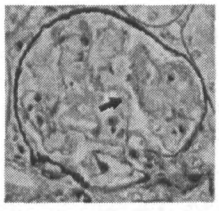
## Renal Amyloidosis in Abyssinian Cats





Medullary interstitial amyloid deposits separate tubular cells from basement membrane

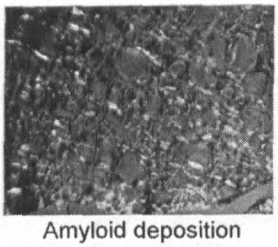
## Renal Amyloidosis in Abyssinian Cats



Subepithelial deposits of amyloid fibrils can be mistaken for immune complex deposits on light microscopy

## Renal Amyloidosis in Abyssinian Cats

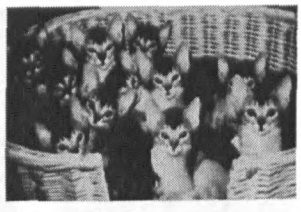
- Other tissues affected
  - Thyroid gland
  - GI tract
  - Spleen
  - Heart
  - Liver
  - Adrenal gland
  - Pancreas



Amyloid deposition in thyroid gland

## Renal Amyloidosis in Abyssinian Cats

- Despite other organ involvement clinical signs are related primarily to chronic renal failure



## Pyelonephritis in Cats

- Clinically: poorly documented
- Experimentally:
  - Anorexia
  - Lethargy
  - Fever
  - Dehydration
  - Weight loss

## Acute Pyelonephritis in Cats
### Clinical Findings

- Fever
- Painful kidneys
- Leukocytosis with left shift
- Pyuria and bacteriuria on UA
- Positive urine culture (*E. coli*)
- Dilute urine
- Variable azotemia

## Chronic Pyelonephritis in Cats
### Clinical Findings

- Anorexia, lethargy, weight loss
- Small, irregular kidneys
- Hemogram may be normal
- Urine sediment may be normal
- Urine culture may be negative
- Dilute urine
- Variable azotemia

## Chronic pyelonephritis or lower urinary tract infection?

- Cats with chronic pyelonephritis may have few clinical findings localizing infection to the kidneys
- Bacterial UTI is common in cats with CRF

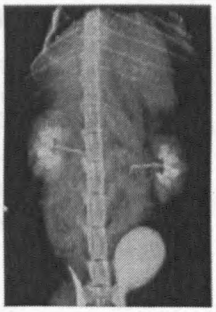
## Urinary Tract Infection in Cats with CRF

- *E. coli* urinary tract infection occurred in 30% of cats with CRF
- Females more commonly affected
- Low USG may predispose to UTI

*Barber, Rawlings, Markwell et al. ACVIM Proceedings, 1999*

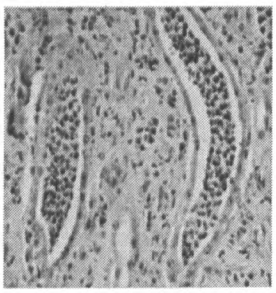
## Acute pyelonephritis in Cats

- Excretory urography
  - Dilated renal pelvis
  - Blunted diverticuli
- Renal ultrasound
  - Dilated renal pelvis
  - Dilated proximal ureter

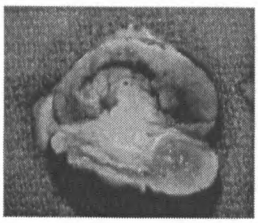


## Pyelonephritis in Cats

- Marked interstitial inflammation
  - Severe in medulla
  - Prominent neutrophilic component
- Interstitial fibrosis



## Pyelonephritis: Treatment

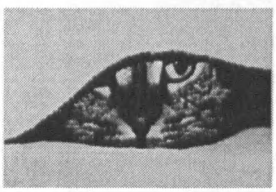


- 4 to 8 week course of bactericidal antibiotics
- Document eradication of infection
- Longterm follow-up

## Glomerulonephritis in Cats

- Young cats (mean age, 4 yrs)
- 75% are males
- No breed predilection

## Glomerulonephritis in Cats



- Proteinuria
- Hypoalbuminemia
- Hypercholesterolemia (non-specific)
- Ascites/edema (variable)
- Membranous nephropathy on biopsy

## Glomerulonephritis in Cats

- Classical nephrotic syndrome
  - Ascites/edema
  - Often non-azotemic
- Chronic renal failure
  - Weight loss, anorexia, lethargy, PU/PD
  - Azotemic

## Glomerulonephritis in Cats

- Urinary protein excretion
  - Normally < 30 mg/kg/day
  - Greater in males (17 mg/kg/day) than females (9 mg/kg/day)
  - Upr/Ucr normally < 0.7 *

*Munroe et al. Am J Vet Res 50:1906, 1989*

* Based on additional clinical experience, most normal cats are expected to have Upr/Ucr ratios < 0.3-0.4

## Glomerulonephritis in Cats

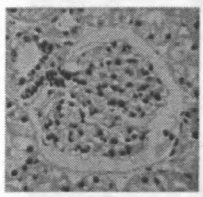
- Urinary protein excretion
  - 50-1000 mg/kg/day (normal, < 30 mg/kg/day)
- Urine protein/creatinine ratio
  - 1.2-8.2 (normal, < 0.34) *

* *Hoerauf et al: J Vet Int Med 4:132, 1990*

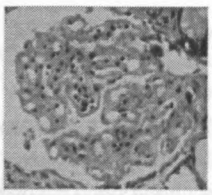
## Glomerulonephritis in Cats

- Associated diseases
  - Infectious (FeLV, FIP, FIV, Mycoplasma gateae)
  - Inlammatory (SLE, pancreatitis)
  - Neoplastic (lymphosarcoma)
  - Familial
  - Idiopathic (most cases)

## Glomerulonephritis in Cats



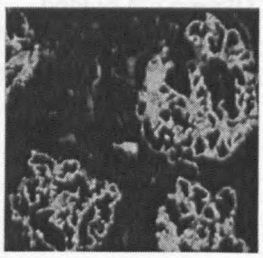
Normal Cat Glomerulus



Membranous glomerulonephritis

## Glomerulonephritis in Cats Pathology

- Membranous nephropathy on light microscopy
- IgG & C3 > IgM > IgA on immunofluorescence
- Subepithelial and intramembranous deposits on electron microscopy



## Glomerulonephritis in Cats

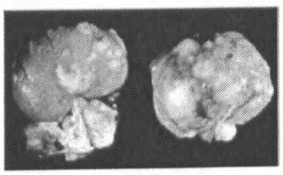
- Non-azotemic, ascites/edema
  - Blood pressure management (benazepril + amlodipine)
  - Diuretics (furosemide)
  - Sodium restriction not likely beneficial; potentially harmful
  - Corticosteroids?
- Azotemic
  - Blood pressure management (benazepril + amlodipine)
  - Conservative medical management of CRF

## Glomerulonephritis in Cats

- Prognosis
  - Non-azotemic: variable (months to years)
    - Recovery (with or in spite of treatment)
    - Stable proteinuria without progression to CRF
    - Progression to CRF
  - Azotemic: poor (months)

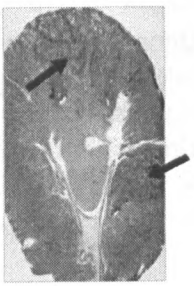
## Renal FIP

- Signs referable to non-effusive FIP
  - Fever
  - Ocular disease
  - Neurologic disease
  - Liver disease



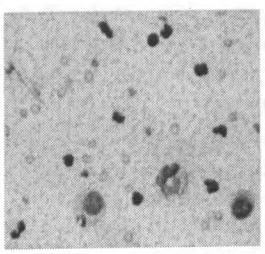
## Renal FIP

- Signs referable to renal disease
  - Renomegaly
  - PU/PD
  - Weight loss



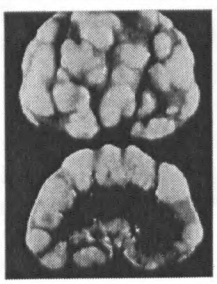
## Renal FIP

- Ultrasound-guided fine needle aspirate
  - Neutrophils
  - Macrophages
  - Lymphocytes
  - Proteinaceous background



## Renal Lymphosarcoma in Cats

- Mean age 7 yrs (2-14 yrs)
- Males & Females
- 50% are FeLV positive
- Bilateral renomegaly
- May have bone marrow involvement



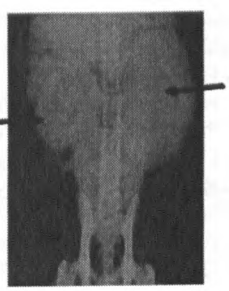
*Mooney et al. JAVMA 191:1473, 1987*

## Renal Lymphosarcoma in Cats
### Clinical Findings

- Anorexia, lethargy, weight loss
- Polyuria, polydipsia
- Nonregenerative anemia
- Azotemia and hyperphosphatemia
- Isosthenuria

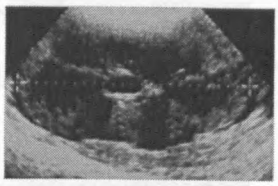
## Renal lymphosarcoma in Cats

- Much more common than primary renal neoplasia
- Often associated with alimentary form of lymphosarcoma

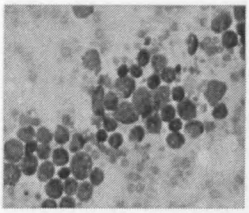


## Renal Lymphosarcoma in Cats

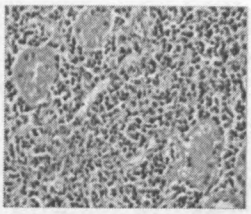
- Ultrasound exam
  - Multifocal to diffuse involvement
  - Non-cavitating hypoechoic nodules



## Renal Lymphosarcoma in Cats



Fine needle aspirate



Renal histopathology

## Renal Lymphosarcoma in Cats

- 61% responded to chemotherapy
- Survival better if FeLV-negative
- Survival better if less azotemic

*Mooney et al. JAVMA 191:1473, 1987*

## Renal Lymphosarcoma: Outcome

- 64% died of lymphosarcoma
- 40% had spread of lymphosarcoma to CNS
- 28% died of renal failure

*Mooney et al. JAVMA 191:1473, 1987*

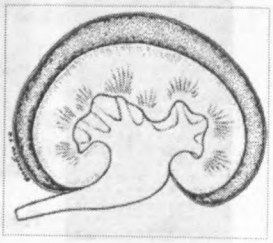
## Renomegaly in Cats

- Polycystic kidney disease
- Renal lymphosarcoma
- Hydronephrosis
- Granulomatous nephritis due to FIP
- Perinephric pseudocysts *

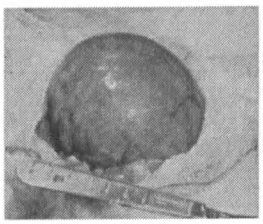
* Not a renal disease !

## Perinephric pseudocysts in cats

- Fluid-filled fibrous sac surrounding the kidney
- Not lined by epithelium
- Fluid is a transudate
- Unilateral or bilateral



## Perinephric pseudocysts in cats



- Older cats (median, 16 yrs; range, 5-19 yrs)
- Males and females
- No breed predilection

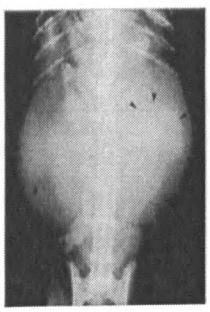
*Ochoa et al. J Vet Int Med 13:47, 1999*

## Perinephric pseudocysts in cats
### Presenting complaints

- Progressive abdominal distension over weeks to months
- Systemic signs of illness if CRF present
  - Weight loss
  - Anorexia
  - Vomiting

## Perinephric pseudocysts in cats
### Laboratory findings

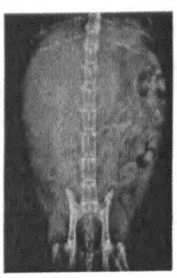
- Consistent with mild to moderate CRF
  - Azotemia
  - Isosthenuria
- Pyuria uncommon but bacterial UTI common (often *E. coli*)

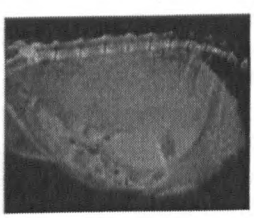


## Perinephric pseudocysts in cats

- Most (90%) have at least mild CRF at the time of diagnosis
- In some, CRF has been diagnosed 1 to 3 years before perinephric pseudocysts are recognized

## Perinephric pseudocysts in cats

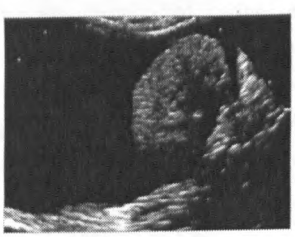




Radiographic appearance

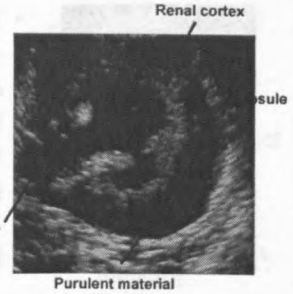
## Perinephric pseudocysts in cats

- Cannot reliably be differentiated from renomegaly on physical exam
- Ultrasonography provides definitive diagnosis

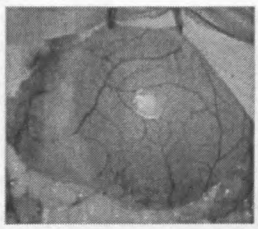


## Perinephric pseudocysts in cats

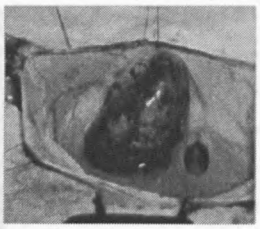
- Hypoechoic lesions of mixed echogenicity suggest perinephric abscess or hematoma




## Perinephric pseudocysts in cats



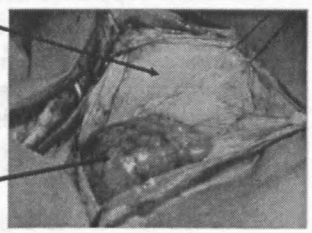
Surgical appearance before opening cyst wall



Surgical appearance after opening cyst wall

## Perinephric pseudocysts in cats
### Pathology

- Cyst wall: mature fibrous connective tissue without epithelial lining
- Kidney: interstitial fibrosis, lymphoplasmacytic interstitial inflammation

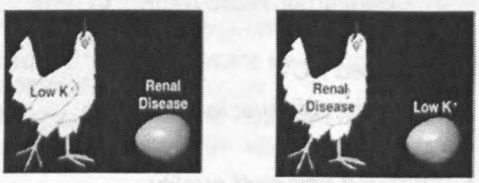


## Perinephric pseudocysts in cats
### Treatment

- Ultrasound-guided drainage (cyst will refill)
- Surgical drainage of cyst and resection of cyst wall
- Avoid nephrectomy if underlying renal disease is present (rapid progression may occur in the remaining kidney)

## Potassium depletion nephropathy in cats

**Which came first ...?**



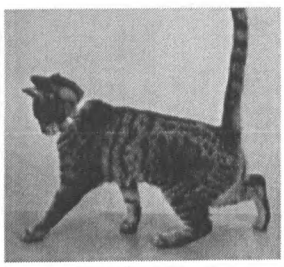

**... the potassium depletion or the renal disease?**

## Potassium depletion nephropathy in cats
### Role of diet

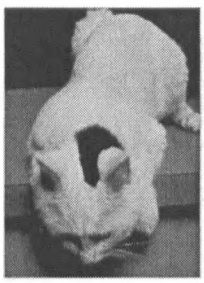
- Marginally replete in potassium
  - < 0.4% on a dry matter basis
  - 0.6 to 0.7% recommended
- Added acidifiers may promote metabolic acidosis, potassium depletion, and decreased GFR

## Potassium depletion nephropathy in cats
### Clinical findings

- Muscle weakness
- Muscle pain
- Awkward stiff gait
- Weight loss
- Poor haircoat
- Renal dysfunction
- Anemia

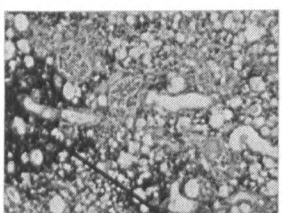


## Potassium depletion nephropathy in cats
### Laboratory findings



- Hypokalemia (often < 3.1 mEq/L)
- Azotemia
- Metabolic acidosis
- Increased CK
- Hyperphosphatemia
- Isosthenuria
- Increased $FE_K$

## Potassium depletion nephropathy in cats
### Histopathologic findings



- Multifocal chronic lymphoplasmacytic interstitial nephritis of variable severity

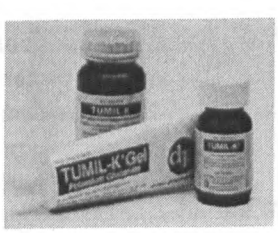
Marked infiltration of lymphocytes and plasma cells

## Potassium depletion nephropathy in cats
### Acute treatment

- Potassium-supplemented fluids
  - 0.5 to 1.0 mEq/kg/hr KCl if severe
  - Dilutional effect and increased urinary flow initially may decrease serum potassium concentration
- Start oral potassium gluconate
  - 2 to 6 mEq per day
- See response in 1 to 3 days

## Potassium depletion nephropathy in cats
### Chronic treatment

- Oral potassium gluconate (superior to KCl or $KHCO_3$)
- 2 to 4 mEq/day




## Potassium depletion nephropathy in cats
### Response to treatment

- Stabilization or improvement in renal function
- Increased PCV
- Resolution of muscle weakness
- Weight gain
- Improved hair coat quality

## Hypokalemia and renal disease

- Factors contributing to hypokalemia in cats with CRF
  - Anorexia
  - Weight loss with loss of muscle mass
  - Polyuria
  - Vomiting
- Effects of potassium depletion on renal function
  - PU/PD and concentrating defect
  - Increased $NH_4^+$ production
    - C3 activation
    - Tubulointersitital nephritis

## Can feeding a potassium deficient diet cause CRF in normal cats?

- 9 normal cats studied 100 weeks
- Diet: 44% protein and 0.32% potassium on dry matter basis
- Serum and urine chemistry monitored for 100 weeks
- Renal biopsies at 48 weeks

*DiBartola et al. JAVMA 202:744, 1993*

## Can feeding a potassium deficient diet cause CRF in normal cats?

- Intermittent hypokalemia occurred in 7/9 cats
- 3/9 cats developed moderate to severe renal disease
- Increased $FE_K$ occurred concurrently with development of azotemia
- Clinical course did not parallel severity of renal histopathology

*DiBartola et al. JAVMA 202:744, 1993*

## Potassium supplementation of normokalemic cats with CRF

- Cats fed 0.78% potassium diet one month before and during 6 month study
- Medical management of CRF and K gluconate or Na gluconate
- GFR, RBF, muscle $K^+$ evaluated

*Theisen et al. J Vet Int Med 11:212, 1997*

## Potassium supplementation of normokalemic cats with CRF

- Normokalemic CRF cats had lower muscle $K^+$ than normal control cats
- Serum $K^+$ and $FE_K$ were unchanged during treatment in both groups
- Changes in GFR and RBF did not differ between treatment groups

*Theisen et al. J Vet Int Med 11:212, 1997*

## Autosomal Dominant Polycystic Kidney Disease Humans

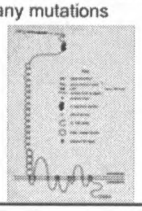
- Most common genetic disease of humans (1:500 to 1:1000 live births)
- Affects all races worldwide
- Results in endstage kidney disease in 50% of affected people by age 60
- Responsible for 8 to 10% of all endstage kidney disease in humans

## Autosomal Dominant Polycystic Kidney Disease Humans

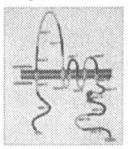
- Systemic disease: renal and extrarenal manifestations
- Renal cysts arise from all nephron segments
- Cysts in liver in pancreas
- Mitral valve defects, cerebral aneurysms, intestinal diverticuli
- Hypertension common (30-70% cases) and occurs before ESKD

## PKD1 and PKD2 Phenotypes in humans

- PKD1 (polycystin 1)
  - 85% of cases
  - Faster progression (ESKD by 54-59 yrs)
  - More often hypertensive
  - Many mutations



- PKD2 (polycystin 2)
  - 10-15% of cases
  - Slower progression (ESKD by 66-72 yrs)
  - Less often hypertensive
  - Many mutations



## Pathogenesis of Cyst Formation

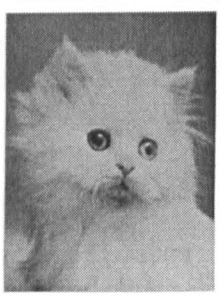
- Cyst begins as focal outpouching of tubule in any nephron segment
- As cyst enlarges and fills with fluid it eventually loses its connection with the nephron

## Loss of Heterozygosity "Second Hit" Hypothesis

- Loss of one PKD allele by germline mutation is necessary but not sufficient for expression of disease phenotype
- Loss of second PKD allele by somatic mutation ("second hit") results in disease phenotype
- "Second hit" hypothesis explains focal nature of disease and variable severity among individuals in one family sharing the same germline mutation

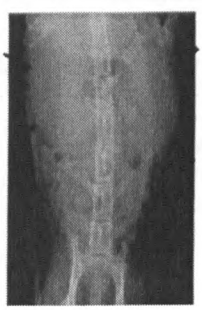
## Polycystic Kidney Disease in Cats

- 3 to 10 years of age (mean, 6 years)
- Longhaired
- Males & females
- Bilateral renomegaly
- Chronic renal failure

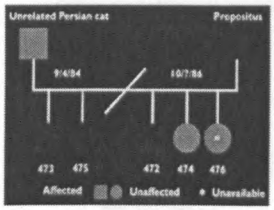


## Polycystic Kidney Disease in Cats

- History: Compatible with CRF
  - –Anorexia
  - –Lethargy
  - –Weight loss
- Physical exam: bilateral renomegaly

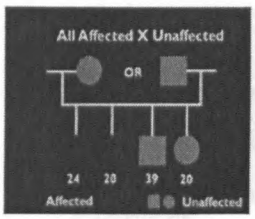


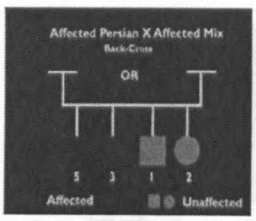
## Polycystic Kidney Disease in Cats




- 6 yr old female Persian cat presented in 1987 for evaluation of renal failure
- 2 litters used to establish breeding colony by outcrossing to DSH cats

## Polycystic Kidney Disease in Cats

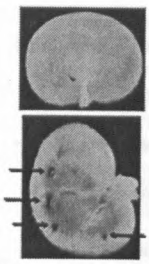



Conclusion: Autosomal dominant inheritance

## Polycystic Kidney Disease in Cats

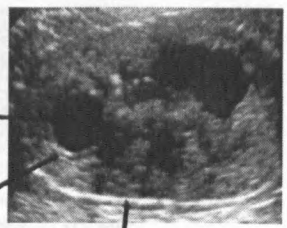
- Cysts can be detected as early as 6 to 7 wks of age by ultrasound
- Cysts increase in size and number over time



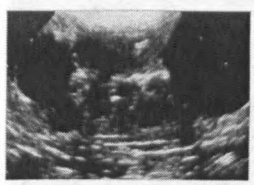

Neonatal feline kidneys

## Polycystic Kidney Disease in Cats
### Ultrasonography

- Used for diagnosis in 102 cats from breeding colony
- Cysts are:
  - Anechoic
  - Spherical
  - Sharply marginated
- Distal acoustic enhancement



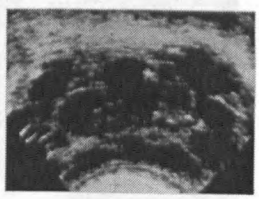

## Polycystic Kidney Disease in Cats
### Ultrasonography



- Sensitivity Number of affected cats positive on ultrasound divided by number of cats positive on renal histology
- Specificity Number of unaffected cats negative on ultrasound divided by total number of cats negative on renal histology

## Polycystic Kidney Disease in Cats
### Ultrasonography

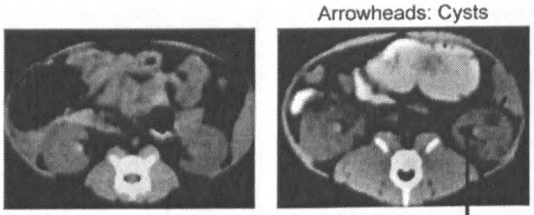
- At 16 wks (4 mos)
  - Sensitivity 75% (15/20)
  - Specificity 100% (21/21)
- At 36 wks (9 mos)
  - Sensitivity 91% (29/32)
  - Specificity 100% (32/32)



*Biller et al. J Heredity 87:1, 1996*

## Polycystic Kidney Disease in Cats
### Computed Tomography

Arrowheads: Cysts



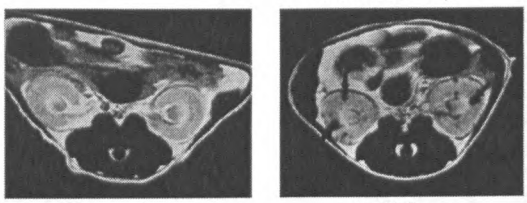
Normal cat | ADPKD cat

Renal pelvis

*Courtesy Dr. David Biller*

## Polycystic Kidney Disease in Cats
### Magnetic Resonance Imaging

Arrowheads: Cysts

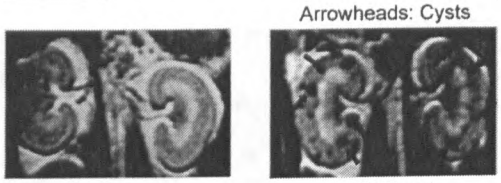


Normal cat, w/gadolinium | ADPKD cat

*Courtesy Dr. David Biller*

## Polycystic Kidney Disease in Cats
### Magnetic Resonance Imaging

Arrowheads: Cysts



Normal cat | ADPKD cat

*Courtesy Dr. David Biller*

## Blood Pressure in ADPKD Cats

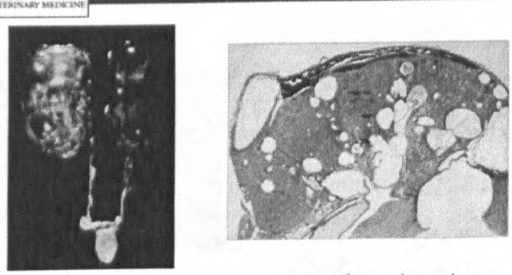
- Hypertension not detected in non-azotemic ADPKD cats or controls by radiotelemetry
- No differences in renin, aldosterone, or angiotensin II between ADPKD and control cats

*Miller et al. Am J Vet Res 60:1516, 1999*

- Mildly increased mean arterial pressure in ADPKD cats compared to controls
- Mildly increased aldosterone-to-renin ratio in ADPKD cats

*Pedersen et al. J Vet Int Med 17:21, 2003*

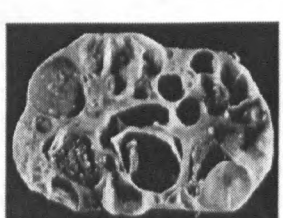
## Polycystic Kidney Disease in Cats
### Pathology



Cortical and medullary cysts of varying sizes

## Polycystic Kidney Disease in Cats
### Pathology

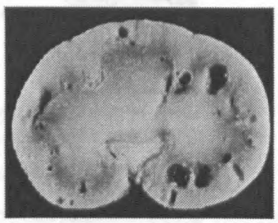
- Cysts vary in
  - Nephron segment of origin
  - Size (< 2 mm to > 2 cm)
  - Number
  - Location (cortex vs medulla)
  - Contents
  - Effect on surrounding parenchyma



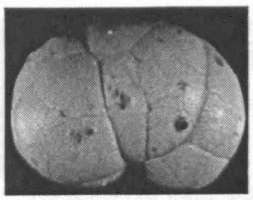
Old hemorrhage

## Polycystic Kidney Disease in Cats
### Pathology

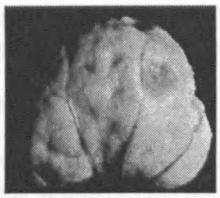
- Chronic tubulointerstitial nephritis develops but not necessarily adjacent to cysts
- Some cats develop hepatobiliary hyperplasia and fibrosis but liver cysts are uncommon



## Polycystic Kidney Disease in Cats
### Pathology



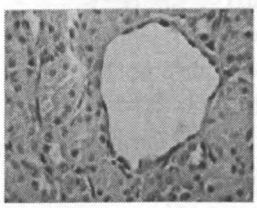
3 months old



3 years old

Progressive chronic tubulointerstitial nephritis in cats with ADPKD

## Polycystic Kidney Disease in Cats
### Histopathology



- Squamous to cuboidal epithelium
- Derived from proximal and distal tubules

## ADPKD in Persian cats is homologous to PKD1 in humans

- PKD phenotype has been linked to microsatellite markers in the feline homologue of human PKD1
- A mutation (C→A) has been identified by RFLP analysis in exon 29 of the feline polycystin 1 gene producing a stop codon at position 3284 that predicts loss of approximately 25% of the C-terminus of the protein
- No cats homozygous for the mutation have been identified suggesting the mutation is lethal for the developing fetus
- A test has been developed to test for the presence of the mutation

*Lyons et al. J Am Soc Nephrol 15:2548, 2004*
*Young et al. Mamm Genome 16:59, 2005*

## Prevalence of PKD in Persian cats presented for ultrasound screening (from the veterinary literature)

| | |
|---|---|
| Sydney Australia | 45% |
| Brisbane Australia | 42% |
| Melbourne Australia | 45% |
| United Kingdom | 49% |

*Aust Vet J 79:257, 2001; Aust Vet J 79:181. 2001; Vet Rec 149:409, 2001*

can use saliva

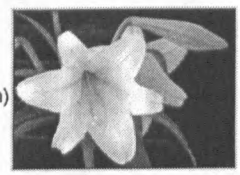
## Real time PCR assay for SNP causing ADPKD in Persian cats

- Assay amplifies a 130 bp fragment from exon 29 of the feline PKD1 gene with the SNP (C→A) in the center of the fragment
- Real time PCR (90 min) and RFLP (5 hrs) tests gave identical results and correlated with renal ultrasound results
- 165/600 (27.5%) of UK Persian cat samples submitted for screening were positive for ADPKD
- All cats evaluated were heterozygous for the mutation

*Helps et al. Mol Cell Probes 21:31, 2007*

## Renal Diseases of Cats
### Lily toxicosis

- Lilies toxic to cats:
  - Easter lily (Lilium longiflorum)
  - Tiger lily (L. tigrinum)
  - Japanese show lily (L. hybridum)
  - Rubrum lily (L. rubrum)
  - Day lily (Hemerocallis spp.)
  - Some Lilium hybrids



Easter lily

## Renal Diseases of Cats
### Other lilies toxic to cats

Japanese show lily

Rubrum lily

Tiger lily

Day lily

## Renal Diseases of Cats
### Lily toxicosis

- Toxic principle unknown; found in aqueous extracts of both leaves and flowers
- No effect on rats or rabbits
- Causes only mild GI upset in dogs
- As few as 2 leaves can be fatal to a cat

## Renal Diseases of Cats
### Lily toxicosis: Clinical course

- Vomiting and salivation 0-3 hrs post-ingestion; lasts 4-6 hrs
- Anorexia and lethargy 0-3 hrs post-ingestion; lasts throughout course
- Polyuria may occur in first 12-24 hrs
- Anuric renal failure develops in 24-48 hrs
- Death occurs in 3-7 days

## Renal Diseases of Cats
### Lily toxicosis: Physical findings

- May have abdominal or renal pain on palpation (renal edema and swelling restricted by renal capsule?)
- Dehydration can be severe; may contribute to progression to anuric ARF
- Bilateral mydriasis with responsive pupils (pain?)

## Renal Diseases of Cats
### Lily toxicosis: Laboratory features

- Severe azotemia and hyperphosphatemia (SCr disproportionately increased compared to BUN?)
- May see increased CK (reason unknown)
- Isosthenuria, glucosuria, proteinuria, cellular (early) or granular (later) casts

## Renal Diseases of Cats
### Lily toxicosis: Clinical Course

- Renal failure may be anuric, oliguric or polyuric depending upon severity of toxic insult
- Polyuria with anorexia and vomiting promote severe dehydration that may progress to anuric ARF
- Initiation of fluid diuresis within 18-24 hours of exposure may prevent anuric ARF

## Renal Diseases of Cats
### Lily toxicosis: Treatment

- Decontamination should be carried out within 6 hours of ingestion
  - Induction of emesis
  - Activated charcoal
  - Saline cathartic
- Induction of fluid diuresis within 18 hours of ingestion

for 7-10d ?

## Renal Diseases of Cats
### Lily toxicosis: Pathologic Findings

- Gross necropsy findings
  - Systemic congestion
  - Renal swelling due to edema
- Histopathology of kidneys
  - Acute tubular necrosis (proximal tubules > distal tubules)
  - Basement membranes intact
  - Evidence of tubular cell regeneration (flattening of epithelium, mitotic figures)

## Renal Diseases of Cats
### Lily toxicosis: Pathologic findings

- Additional findings
  - Pancreatic acinar cell degeneration

    *Rumbeiha et al J Vet Diag Invest 16:527, 2004*
  - Development of fibrosing pancreatitis after 2-4 weeks

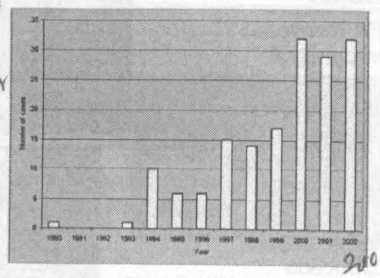
    *Langston JAVMA 220:49, 2002*

## Feline urolithiasis
### Trends over 20 years

- University of Minnesota Urolith Center
  - 1981: 78% of all stones submitted from cats were struvite; 1% were calcium oxalate
  - 2000: 35% of all stones submitted from cats were struvite; 54% were calcium oxalate
- Purdue Veterinary Medical Database
  - 1980: 3 cases of UUT urolithiasis per 10,000 cats
  - 1999: 35 cases of UUT urolithiasis per 10,000 cats

*Lekcharoensuk et al. J Am Anim Hosp Assoc 41:39, 2005*

## Ureterolithiasis in cats
### Trends over 10 years



**Cats with ureterolithiasis at UCD and NCSU between 1990 and 2002**

*Kyles et al. JAVMA 226:932, 2005*

## Ureterolithiasis in cats
### Clinical findings

- Nonspecific clinical signs: inappetence, vomiting, lethargy, weight loss
- 76% of cats with unilateral ureteroliths had azotemia (i.e. contralateral renal parenchymal disease or pre-renal azotemia)
- Ureteroliths were identified by radiology and ultrasound in 90%
- Dilatation of renal pelvis, ureter or both (i.e. evidence of obstruction) on ultrasound in 92%
- Contralateral kidney small in 56%

*Kyles et al. JAVMA 226:932, 2005*

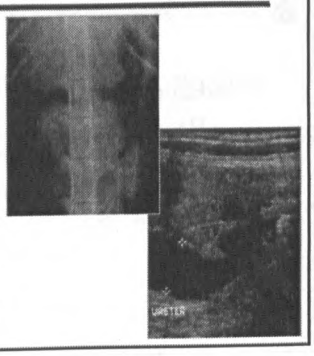
## Ureterolithiasis in cats
### Clinical findings

- 62% had nephroliths as well as ureteroliths
- 75% unilateral and 25% bilateral based on surgery
- 98% were calcium oxalate
- 8% had UTI

*Kyles et al. JAVMA 226:932, 2005*

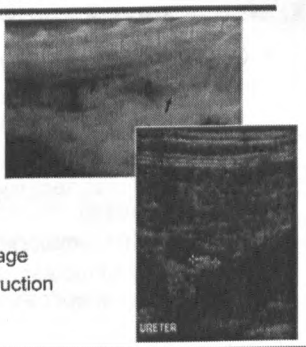
## Ureterolithiasis in cats
### *Radiology and ultrasound complement each other*

- Radiology
  - High specificity; low sensitivity
  - Good at detecting small radiopaque stones
- Ultrasound
  - High sensitivity; low specificity
  - Good at detecting evidence of obstruction




## Ureterolithiasis in cats
### Management

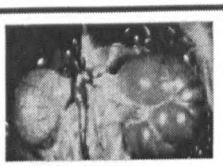
- Factors to consider
  - Urolith size
  - Urolith location
  - Duration of signs
  - Evidence of renal colic
  - Serum biochemistry
  - Evidence of renal damage
  - Evidence of renal obstruction

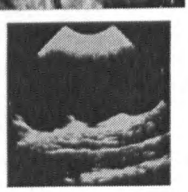



## Complete ureteral obstruction
### Experimental dogs

- GFR recovered completely if obstruction relieved within 4 days
- GFR recovered 46% if obstruction relieved after 14 days
- No recovery of GFR after 40 days of obstruction

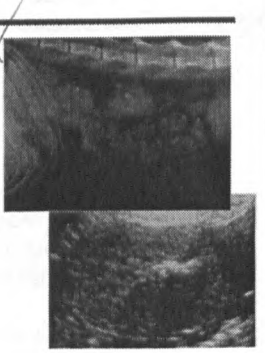
*Vaughan et al. J Urol 106:27, 1971*





## Ureterolithiasis in cats
### Management

- Conservative medical management
  - Fluids
  - Diuretics
  - Tamulosin (α-A1 adrenoceptor antagonist)
- Lithotripsy
- Surgery
  - Ureterotomy
  - Ureteroneocysostomy



## Ureterolithiasis in cats
### Management

- Evidence justifying medical management
  - Minimal compromise of renal function
  - Absence of infection
  - No apparent renal colic
  - Lack of progressive renal pelvic and ureteral dilatation
- Evidence justifying surgical intervention or lithotripsy
  - Worsening azotemia
  - Infection (may require nephropyelocentesis to identify)
  - Suspicion of complete obstruction
  - Stone not moving on serial imaging
  - Documented retrograde movement of stone

## Ureterolithiasis in cats
### Management

- When and how to intervene?
  - Typically don't know how long kidney has been obstructed in cats
  - Often don't know if obstruction is complete or partial
- How long to wait?
  - Up to 2 weeks in human medicine where patient typically knows when stone entered ureter (renal colic) and up to 98% of stones < 5 mm will pass
  - Trend in cats is toward early intervention (median of 3 days in *Kyles et al. JAVMA 226:937, 2005*)

## Ureterolithiasis in cats
### Medical management

- Promote urine flow and stone movement into bladder using fluid therapy and diuretics
- Stones moved into bladder in 4 of 7 cats that responded to medical therapy (decreased SCr)
- Stones moved into the bladder in 5 of 16 cats that did not respond to medical therapy (unchanged SCr)
- 12-month survival: 66% (vs 91% for surgery)

*Kyles et al. JAVMA 226:937, 2005*

## Ureterolithiasis in cats
### Surgical management

- Ureterotomy for stones in proximal ureter
- Ureteroneocystostomy for stones in distal ureter
  - Tension on ureter can be decreased by renal descensus and psoas cystopexy
- Postoperative complications in (31%)
  - Uroabdomen
  - Recurrence of obstruction (especially with ureteroneocystostomy)
- Complications higher with nephrostomy tubes (46%)
  - Tube dislodgement
  - Uroabdomen

*Kyles et al. JAVMA 226:937, 2005*

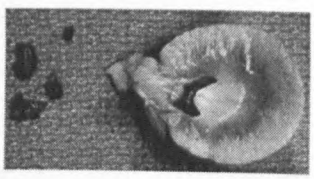
## Ureterolithiasis in cats
### Surgical management (continued)

- CRF common with cats with unilateral disease (76%) at time of diagnosis and persisted after surgery in 50%
- 12-month survival: 91% (vs 66% for medical management)
- Cause of death or euthanasia: recurrence of ureterolithiasis (40%) or CRF

*Kyles et al. JAVMA 226:937, 2005*

## Dried solidified blood calculi in cats

- 19/48 occurred in the upper urinary tract
- Not visible on plain radiographs
- Unexplained renal pelvic and proximal ureteral dilatation on ultrasound exam
- No mineral content



*Westropp et al. J Vet Int Med 20:828, 2006*

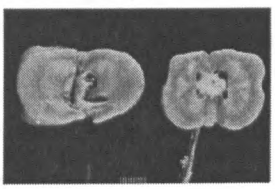
## Ureterolithiasis in cats
### Management: Retrograde movement

- Progressive renal damage may result from intermittent obstruction and relief of obstruction ("ball valve effect")
  - Antegrade movement causes stone to lodge in ureter with obstruction and proximal ureteral dilatation
  - Retrograde movement of stone into dilated proximal ureter and relief of obstruction may occur with gravity when cat jumps down

*Dalby et al. JAVMA 229:1119, 2006*

## Ureterolithiasis in cats
### Big kidney-little kidney syndrome

- "Big kidney-little kidney" syndrome
  - One kidney acutely obstructed
  - One kidney chronically diseased from previous episodes of intermittent obstruction and relief of obstruction by retrograde stone movement



## Case 239969 First presentation

- 14 year old female domestic shorthair cat
- History: Vomiting after eating for past 2 months
- Physical: No abnormalities, weight 8.0 lbs

## Case 239969 Hemogram

| Analyte | Units | Day 1 |
|---|---|---|
| Total protein | g/dL | 7.5 |
| PCV | % | 42 |
| WBC | /µL | 6,400 |
| Bands | /µL | 0 |
| Segs | /µL | 3,100 |
| Lymphs | /µL | 2,900 |
| Monos | /µL | 100 |
| Eos | /µL | 300 |

## Case 239969 Serum Chemistry

| Analyte | Units | Day 1 |
|---|---|---|
| $CO_2$ | mEq/L | 16 |
| Calcium | mg/dL | 9.1 |
| Phosphorus | mg/dL | 4.4 |
| Sodium | mEq/L | 156 |
| Potassium | mEq/L | 4.7 |
| Chloride | mEq/L | 124 |
| Total protein | g/dL | 7.6 |
| Albumin | g/dL | 3.5 |
| BUN | mg/dL | 27 |
| Creatinine | mg/dL | 2.2 |
| Thyroxine | µg/dL | 3.0 |

## Case 239969 Urinalysis (cystocentesis)

| Analyte | Units | Day 1 |
|---|---|---|
| Color | | Straw |
| USG | | 1.025 |
| pH | | 6.0 |
| Glucose | mg/dL | Negative |
| Protein | mg/dL | 10 |
| WBC | /hpf | 7-10 |
| RBC | /hpf | 0-5 |

## Case 239969 First admission

- Urine culture not performed
- No treatment

## Case 239969: Second admission 3 months later

- Vomiting has resolved
- Presented for dentistry
- Physical: 3/6 systolic murmur left base, weight 7.6 lbs

## Case 239969
## Hemogram

| Analyte | Units | Day 90 |
|---|---|---|
| Total protein | g/dL | 8.0 |
| PCV | % | 43 |
| WBC | /µL | 6,200 |
| Bands | /µL | 0 |
| Segs | /µL | 2,600 |
| Lymphs | /µL | 2,600 |
| Monos | /µL | 300 |
| Eos | /µL | 700 |

## Case 239969 Serum Chemistry

| Analyte | Units | Day 90 |
|---|---|---|
| $CO_2$ | mEq/L | 17 |
| Calcium | mg/dL | 10.0 |
| Phosphorus | mg/dL | 4.0 |
| Sodium | mEq/L | 155 |
| Potassium | mEq/L | 4.2 |
| Chloride | mEq/L | 124 |
| Total protein | g/dL | 7.5 |
| Albumin | g/dL | 3.3 |
| BUN | mg/dL | 29 |
| Creatinine | mg/dL | 2.0 |
| Thyroxine | µg/dL | 2.6 |

## Case 239969
## Urinalysis (cystocentesis)

| Analyte | Units | Day 90 |
|---|---|---|
| Color | | Yellow |
| USG | | 1.028 |
| pH | | 6.5 |
| Glucose | mg/dL | Negative |
| Protein | mg/dL | 10 |
| WBC | /hpf | 0 |
| RBC | /hpf | 15-20 |

## Case 239969 Second admission
## Day 90

- Thoracic radiographs and EKG normal
- IV fluids administered evening before dentistry
- Discharged after dentistry on antibiotics for 3 wks

## Case 239969 Third admission
## One year later (day 455)

- History: PU/PD for one month, vomiting after eating, lethargic, decreased appetite, sneezing, nasal/ocular discharge
- Physical: 102.2°F, dehydrated, gallop rhythm, large bladder, weight 6.6 lbs

## Case 239969 Third admission
## One year later (day 455)

- Diagnosis: upper respiratory infection
- But what about … ?
  - PU/PD
  - Vomiting
  - Gallop
  - Previously heard murmur

## Case 239969
## Hemogram

| Analyte | Units | Day 455 |
|---|---|---|
| Total protein | g/dL | 8.3 |
| PCV | % | 38 |
| WBC | /µL | 34,800 |
| Bands | /µL | 800 |
| Segs | /µL | 30,200 |
| Lymphs | /µL | 2,400 |
| Monos | /µL | 1,000 |
| Eos | /µL | 400 |

## Case 239969 Serum Chemistry

| Analyte | Units | Day 455 |
|---|---|---|
| $CO_2$ | mEq/L | 21 |
| Calcium | mg/dL | 10.0 |
| Phosphorus | mg/dL | 4.5 |
| Sodium | mEq/L | 159 |
| Potassium | mEq/L | 4.1 |
| Chloride | mEq/L | 125 |
| Total protein | g/dL | 7.8 |
| Albumin | g/dL | 2.7 |
| BUN | mg/dL | 36 |
| Creatinine | mg/dL | 2.4 |
| Glucose | mg/dL | 173 |

## Case 239969
## Urinalysis (cystocentesis)

| Analyte | Units | Day 455 |
|---|---|---|
| Color | | Straw |
| USG | | 1.015 |
| pH | | 5.0 |
| Glucose | mg/dL | Negative |
| Protein | mg/dL | 30 |
| WBC | /hpf | Many |
| RBC | /hpf | Many |

## Case 239969 Third admission
## Day 455

- Urine culture: E. coli > 30,000 cfu/ml
- Treatment: SQ fluids, cefadroxil

## Case 239969 Fourth admission
## 6 months later (day 635)

- History: Anorexia for 1 week, still vomiting twice per week, decreased water intake
- Physical: T 103.1°F, dehydrated, left thyroid nodule, weight 6.0 lbs

## Case 239969
## Hemogram

| Analyte | Units | Day 635 |
|---|---|---|
| Total protein | g/dL | 7.7 |
| PCV | % | 32 |
| WBC | /µL | 16,800 |
| Bands | /µL | 0 |
| Segs | /µL | 13,100 |
| Lymphs | /µL | 2,700 |
| Monos | /µL | 200 |
| Eos | /µL | 800 |

## Case 239969 Serum Chemistry

| Analyte | Units | Day 635 |
|---|---|---|
| $CO_2$ | mEq/L | 17 |
| Calcium | mg/dL | 8.9 |
| Phosphorus | mg/dL | 3.6 |
| Sodium | mEq/L | 165 |
| Potassium | mEq/L | 4.4 |
| Chloride | mEq/L | 125 |
| Total protein | g/dL | 6.9 |
| Albumin | g/dL | 2.2 |
| BUN | mg/dL | 39 |
| Creatinine | mg/dL | 3.3 |
| Thyroxine | µg/dL | 5.5 |

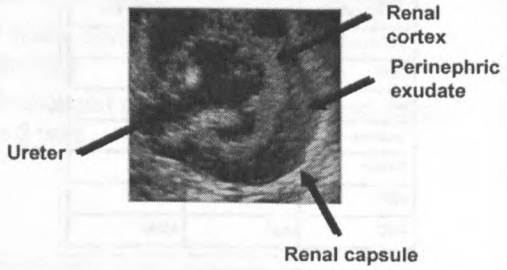
## Case 239969 Urinalysis (cystocentesis)

| Analyte | Units | Day 635 |
|---|---|---|
| Color | | Straw |
| USG | | 1.014 |
| pH | | 5.5 |
| Glucose | mg/dL | Negative |
| Protein | mg/dL | 100 |
| WBC | /hpf | 30-40 |
| RBC | /hpf | 0-2 |

## Case 239969 Fourth admission Day 635

- Urine culture: E. coli > 30,000 cfu/ml

## Case 239969 Fourth admission Day 635: Ultrasound exam




## Case 239969 Fourth admission Day 635)

- Owners elected euthanasia
  - Left perinephric abscess
  - Left pyonephrosis and pyelonephritis
  - Small irregular right kidney with chronic infarcts
  - Left thyroid adenomatous hyperplasia

## 314778 "Sneezy" Otterman

9-year-old MC Domestic Shorthair cat
Date of presentation May 12, 1996
PC Lethargy and vomiting past 4 days

## 314778 "Sneezy" Otterman History

- Diagnosed as hyperthyroid 6 mos PTA and receiving 2.5 mg methimazole daily
- Lethargy and vomiting began May 8
- Still urinating
- Was normal and active before May 8

## PE: 314778 "Sneezy" Otterman

- Weight 5.7 kg
- T 97.8°F, HR 192/min, RR 48/min
- Mucous membranes dark red; CRT < 2 sec
- Quiet
- Thyroid nodule
- III/VI right apical systolic murmur
- Left kidney feels slightly big; right kidney slightly small
- Bilateral mydriasis (direct & consensual PLR present)

## 314778 "Sneezy" Otterman

| Complete blood count (5/12/96) | | | |
|---|---|---|---|
| Protein | 7.5 | WBC × $10^9$/l | 7.1 |
| PCV (%) | 35 | Bands | 0 |
| Hb (g/dl) | 12.0 | Segs | 5.75 |
| RBC × $10^{12}$/l | 7.14 | Lymphs | 1.28 |
| MCV (fl) | 48 | Monos | 0.07 |
| MCHC (g/dl) | 34.9 | Eosinophils | 0 |
| | | Platelets | Adequate |

## 314778 "Sneezy" Otterman

| Serum chemistry profile (5/12/96) | | | |
|---|---|---|---|
| BUN | 277 mg/dl | ALT | 69 IU/L |
| SCr | 23.9 mg/dl | AST | 44 IU/L |
| Pi | 15.6 mg/dl | ALP | 18 IU/L |
| Ca | 10.1 mg/dl | CK | 1065 IU/L |
| Na | 153 mEq/L | Cholesterol | 119 mg/dl |
| K | 6.5 mEq/L | Total bili | 0.6 mg/dl |
| Cl | 113 mEq/L | T protein | 7.0 g/dl |
| Bicarbonate | 12.1 mEq/L | Albumin | 4.0 g/dl |
| Glucose | 91 mg/dl | Globulins | 3.0 g/dl |

## 314778 "Sneezy" Otterman

| Urinalysis (cystocentesis) (5/12/96) | | | |
|---|---|---|---|
| Color | Straw | Casts/lpf | None |
| Appearance | Clear | WBC/hpf | 1-2 |
| USG | 1.013 | RBC/hpf | 1-3 |
| pH | 5.0 | Epi cells/hpf | Few squamous |
| Protein | 10 mg/dl | Crystals | None |
| Glucose | Negative | Bacteria | None |
| Ketones | Negative | | |
| Bilirubin | Negative | | |
| Blood | 1+ | | |

## 314778 "Sneezy" Otterman

- Abdominal radiographs (5/12/96)
  - Left kidney enlarged, focal mineral opacities in renal pelvis
  - Right kidney not identified
  - Urinary bladder distended
- Abdominal ultrasound (5/14/96)
  - Both kidneys hyperechoic; good corticomedullary distinction
  - Left kidney 5 cm; right kidney 3 cm
  - Bladder normal

## 314778 "Sneezy" Otterman

- Doppler systolic blood pressure (5/13/96): 158 mmHg
- Urine culture (5/14/96): No growth

## 314778 "Sneezy" Otterman

- 5/12/96
  - IV 0.9% NaCl 560 ml/day (24 ml/hr)
  - 28 mg cimetidine IV BID
  - Produced approximately 65 ml urine from midnight to 8 AM 5/13 (0.6 ml/lb/hr)
- 5/13/96
  - IV LRS 900 ml/day (37 ml/hr)
  - 28 mg cimetidine IV BID
  - $Al(OH)_3$ 240 mg PO BID
  - Produced 100-150 ml urine during 24 hrs (0.3 to 0.5 ml/lb/hr)

## 314778 "Sneezy" Otterman

- 5/14/96
  - IV LRS + 16 mEq KCl/L 720 ml/day (30 ml/hr)
  - 28 mg cimetidine IV BID
  - Discontinued $Al(OH)_3$ due to difficulty administering it
  - Urinated 7 times in 24 hrs (10 to 50 ml each time)
- 5/15/96
  - IV LRS + 16 mEq KCl/L 480 ml/day (20 ml/hr)
  - 28 mg cimetidine IV BID
  - Urinated 6 times in 24 hours
  - Eating
- 5/16/96
  - IV LRS + 16 mEq KCl/L 360 ml/day (15 ml/hr)

## 314778 "Sneezy" Otterman

- 5/16/96: Owner reports many plants inside and outside of house:
  - Inside: Easter lily, Peace lily*
  - Outside: Day lily, Lily of the valley§

*** Not toxic**

**§ Contains cardiac glycosides**

## 314778 "Sneezy" Otterman

| Date | | 5/13/96 | 5/14/96 | 5/15/96 |
|---|---|---|---|---|
| BUN | mg/dl | 231 | 105 | 43 |
| SCr | mg/dl | 18.4 | 6.0 | 2.9 |
| Pi | mg/dl | 11.0 | 4.9 | 3.9 |
| Ca | mg/dl | 8.8 | 9.5 | 9.5 |
| Na | mEq/L | 159 | 162 | 154 |
| K | mEq/L | 5.2 | 3.9 | 4.0 |
| Cl | mEq/L | 128 | 123 | 118 |
| Bicarb | mEq/L | 12.1 | 22.1 | 23.4 |

## 314778 "Sneezy" Otterman

| Date | 5/23/96 | 9/5/96 | 12/8/97 |
|---|---|---|---|
| BUN (mg/dl) | 33 | 32 | 27 |
| SCr (mg/dl) | 2.5 | 2.3 | 1.4 |
| Pi (mg/dl) | 4.0 | 3.9 | 4.7 |
| Ca (mg/dl) | 9.8 | 9.4 | 9.6 |
| K (mEq/L) | 3.8 | 3.9 | 3.8 |
| HCO3 (mEq/L) | 17.1 | 18.6 | 18.3 |
| T4 (µg/dl) | 3.97 | 1.32 | 19.86 |
| Tapazole | 2.5 mg q24h | 2.5 mg q24h | 2.5 mg q24h |

## 314778 "Sneezy" Otterman

| Date | 4/1/98 | 11/2/98 | 12/4/98 | 6/7/00 |
|---|---|---|---|---|
| BUN (mg/dl) | 40 | 32 | 39 | 39 |
| SCr (mg/dl) | 1.3 | 1.8 | 1.7 | 1.7 |
| Pi (mg/dl) | 5.4 | 6.4 | 3.5 | 4.6 |
| Ca (mg/dl) | 9.3 | 9.9 | 9.4 | 10.2 |
| K (mEq/L) | 3.9 | 4.4 | 3.9 | 3.7 |
| HCO3 (mEq/L) | 16.7 | 18.1 | 17.2 | 14.0 |
| T4 (µg/dl) | 9.83 | 7.81 | 2.5 | 21.0 |
| Tapazole | 2.5 mg q12h | 5 mg AM<br>2.5 mg PM | 5 mg AM<br>2.5 mg PM | 5 mg BID |

## 314778 "Sneezy" Otterman

- Presented "dead on arrival" at OSU VTH on June 19, 2000
- Owner declined necropsy

## 370980 "Mr Butters" Pozza-Adams

- 10 year old neutered male domestic shorthaired cat
- History: Weight loss over the past few months; lethargy and inappetence over the past few days
- PE: 6 kg, T 99.9°F, P: 200/min, RR: 32/min. Pale pink mucous membranes; kidneys seem enlarged (6 cm)

## Case 370980 Hemogram

| Tot protein | 7.5 g/dL | WBC | $18.7 \times 10^9$/L |
|---|---|---|---|
| PCV | 18 % | Bands | $0.4 \times 10^9$/L (2%) |
| Hb | 6.4 g/dL | Segs | $15.9 \times 10^9$/L (85%) |
| RBC | $4.0 \times 10^{12}$/L | Lymphs | $0.2 \times 10^9$/L (1%) |
| MCV | 44 fl | Monos | $2.2 \times 10^9$/L (12%) |
| MCHC | 36.4 g/dL | nRBC | $0.4 \times 10^9$/L (2%) |
| Platelets | $191 \times 10^9$/L | Morphology | Cytoplasmic basophilia; Dohle bodies |

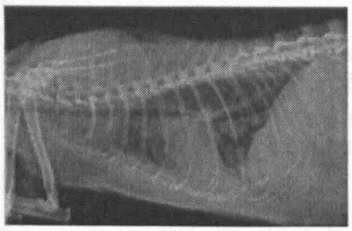
## Case 370980 Biochemical Profile

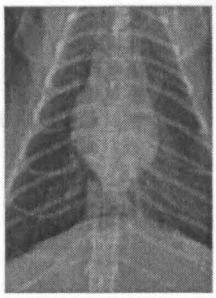
| BUN | 99 mg/dL | ALT | 87 IU/L |
|---|---|---|---|
| Creatinine | 3.0 mg/dL | AST | 197 IU/L |
| Phosphorus | 10.2 mg/dL | ALP | 36 IU/L |
| Calcium | 10.0 mg/dL | CK | 774 IU/L |
| Sodium | 159 mEq/L | Bilirubin | 0.23 mg/dL |
| Potassium | 5.0 mEq/L | Tot protein | 6.7 g/dL |
| Chloride | 125 mEq/L | Albumin | 2.9 g/dL |
| Bicarbonate | 13 mEq/L | Globulin | 3.8 g/dL |
| Cholesterol | 138 mg/dL | Glucose | 108 mg/dL |

## Case 370980 Urinalysis

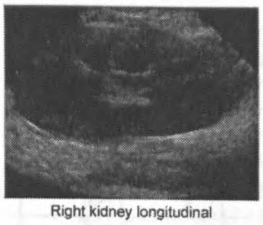
| Source | Cysto | Bilirubin | Negative |
|---|---|---|---|
| Color | Yellow | Blood | 2+ |
| Appearance | Clear | Casts | None seen |
| S.G. | 1.017 | WBC | 1-2/hpf |
| pH | 6.0 | RBC | 4-6/hpf |
| Protein | 3+ (300 mg/dl) | Epi cells | 1-2 squamous/hpf; 0-1 transitional/hpf |
| Glucose | Negative | Crystals | None seen |
| Ketones | Negative | Bacteria | None seen |

## 370980 "Mr Butters" Pozza-Adams
## Thoracic radiography



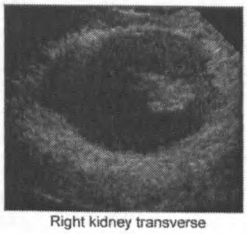


## 370980 "Mr Butters" Pozza-Adams
## Abdominal ultrasound



Right kidney longitudinal

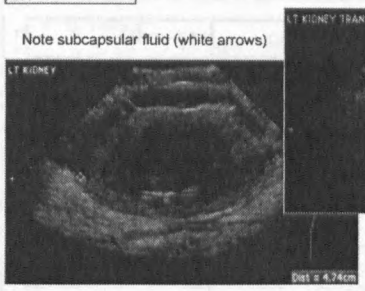
Note hyperechoic material surrounding kidney

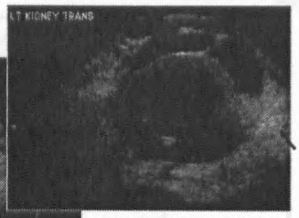


Right kidney transverse

## 370980 "Mr Butters" Pozza-Adams
## Abdominal ultrasound

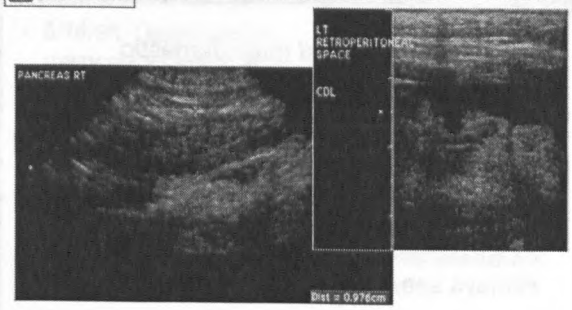
Note subcapsular fluid (white arrows)




Note hyperechoic material surrounding kidney (yellow arrows)

## 370980 "Mr Butters" Pozza-Adams
## Abdominal ultrasound



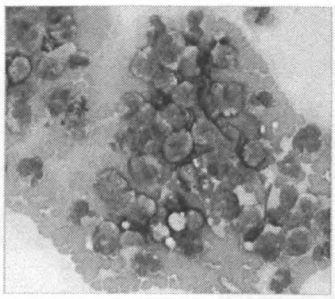

## 370980 "Mr Butters" Pozza-Adams

- Abdominal fluid cytology
  - Orange, hazy
  - SG > 1.035
  - TP 7.4 g/dL
  - WBC count 3,010/µL (80% neutrophils, 15% monocytes, 4% lymphocytes)
  - Lymphocytes appear small and well-differentiated; compatible with blood contamination

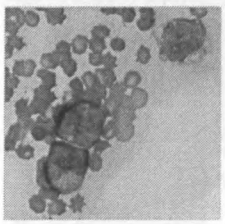
## 370980 "Mr Butters" Pozza-Adams

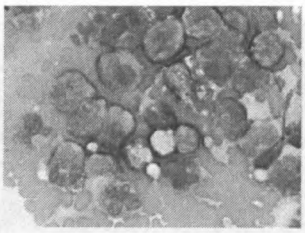
- Thoracic fluid cytology
  - Red, cloudy
  - SG 1.032
  - TP 5.2 g/dL
  - WBC count 4,380/µL (3% neutrophils, 5% monocytes, 3% lymphocytes, 89% neoplastic cells)
  - Uniform population of round cells with basophilic cytoplasm and highly convoluted nuclei (lymphoma?)

## 370980 "Mr Butters" Pozza-Adams



## 370980 "Mr Butters" Pozza-Adams





## 370980 "Mr Butters" Pozza-Adams

- "Mr Butters" deteriorated during the evening and became hypotensive
- Poor response to crystalloids, colloids, and dobutamine infusion. Suspect internal hemorrhage.
- Owner elected euthanasia

## 370980 "Mr Butters" Pozza-Adams

- Gross necropsy
  - Marked retroperitoneal hemorrhage; perinephric hemorrhage (LK > RK)
  - Extensive amount of whitish-yellow lobulated retroperitoneal tissue surrounding kidneys
- Histopathology
  - Lymphoblastic lymphoma (majority CD3+, minority CD79a+; CD20-) involving retroperitoneal space, pancreas, kidney

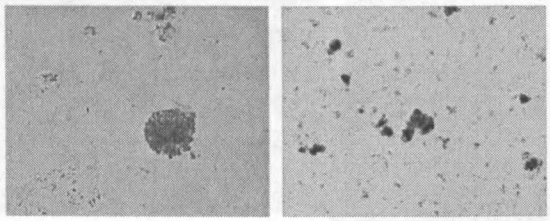
## 385887 "Boo" Cooper

- 6 month-old neutered male Persian cat
- History
  - Recently (April 21, 2007) fed a cat food on the recall list
  - Vomiting, lethargy, anorexia, and decreased water consumption 48 hrs before presentation to RDVM
  - No known exposure to lilies or ethylene glycol
  - Otherwise healthy young cat

## 385887 "Boo" Cooper

- History
  - Seen by RDVM on 4/23/07
  - BUN 130 mg/dl, SCr 13.6 mg/dl, serum phosphorus > 16.1 mg/dl, serum $K^+$ 7.5 mEq/L. USG 1.015 and many "round" crystals seen in sediment (later reported as > 10 urates/hpf by commercial laboratory)
  - Treated by RDVM with IV fluids, cimetidine, metoclopramide, sucralfate, and cefazolin

## FARF: Crystals in urine sediment



*Courtesy SVNU Panel*

## 385887 "Boo" Cooper

- Admitted to OSU VTH 4/24/07 evening
- Physical exam
  - Wt 3.2 kg; T 101.0°F, P 130/min, R 100/min
  - Systolic blood pressure (Doppler) 160 mmHg
  - Slightly depressed; well hydrated
  - Mucous membranres pink; thoracic auscultation normal
  - Kidneys normal-sized to large

## Case 385887 Hemogram (4/24/07)

| | | | |
|---|---|---|---|
| Tot protein | 7.1 g/dL | WBC | 6.6 × $10^9$/L |
| PCV | 35 % | Bands | 0 × $10^9$/L (0%) |
| Hb | 12.4 g/dL | Segs | 3.8 × $10^9$/L (57%) |
| RBC | 9.4 × $10^{12}$/L | Lymphs | 2.6 × $10^9$/L (40%) |
| MCV | 37 fl | Monos | 0.1 × $10^9$/L (1%) |
| MCHC | 35.9 g/dL | Eos | 0 × $10^9$/L (0%) |
| Platelets | 277 × $10^9$/L | Basos | 0.1 × $10^9$/L (1%) |

## Case 385887 Biochemical Profile (4/24/07)

| | | | |
|---|---|---|---|
| BUN | 250 mg/dL | ALT | 13 IU/L |
| Creatinine | 17.2 mg/dL | AST | 43 IU/L |
| Phosphorus | 17.9 mg/dL | ALP | 53 IU/L |
| Calcium | 10.1 mg/dL | CK | 1422 IU/L |
| Sodium | 152 mEq/L | Bilirubin | < 0.1 mg/dL |
| Potassium | 6.5 mEq/L | Tot protein | 6.4 g/dL |
| Chloride | 105 mEq/L | Albumin | 3.5 g/dL |
| Bicarbonate | 17 mEq/L | Globulin | 2.9 g/dL |
| Cholesterol | 128 mg/dL | Glucose | 86 mg/dL |

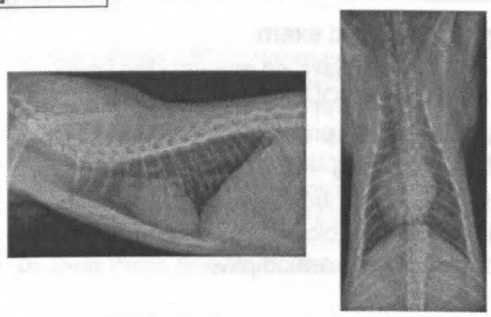
## Case 385887 Urinalysis (4/24/07)

| | | | |
|---|---|---|---|
| Source | Cysto | Bilirubin | Negative |
| Color | Light yellow | Blood | 3+ |
| Appearance | Clear | Casts | None seen |
| S.G. | 1.007 | WBC | Occasional/hpf |
| pH | 7.0 | RBC | 1-3/hpf |
| Protein | 10 mg/dl | Epi cells | Occ squam; 0-1 trans |
| Glucose | Negative | Crystals | None seen |
| Ketones | Negative | Bacteria | None seen |

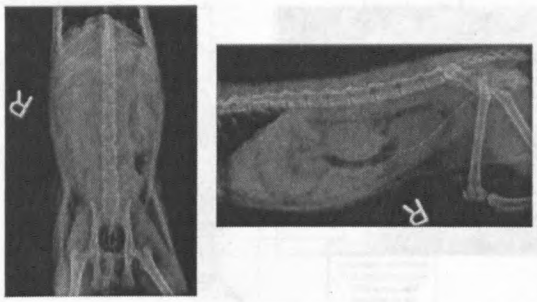
## 385887 "Boo" Cooper

- Urine culture and sensitivity: No growth

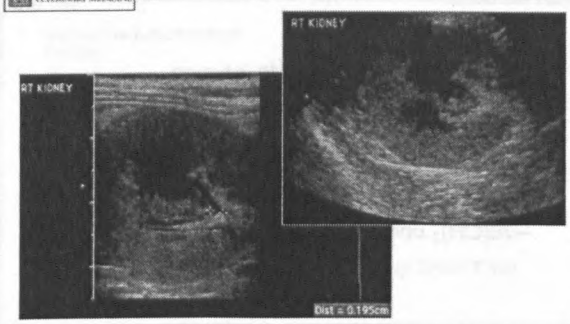
## 385887 "Boo" Cooper
## Thoracic radiography



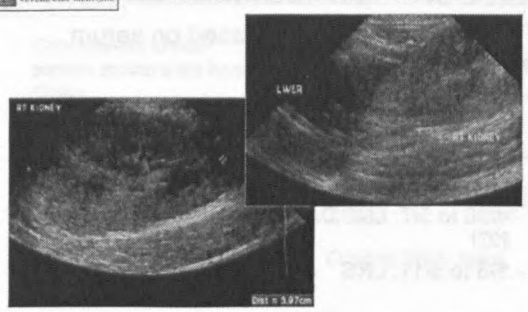
## 385887 "Boo" Cooper
## Abdominal radiography




## 385887 "Boo" Cooper
## Abdominal ultrasound



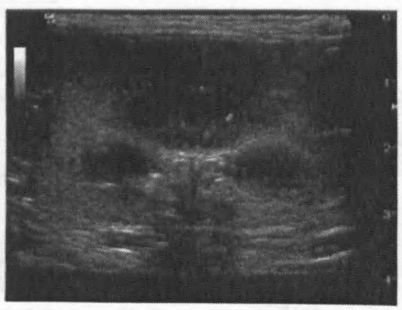

## 385887 "Boo" Cooper
## Abdominal ultrasound



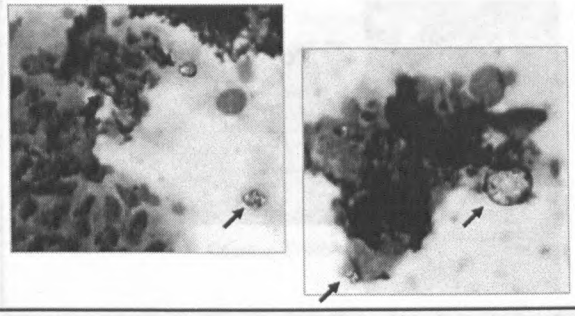

## 385887 "Boo" Cooper

- Thoracic radiographs
  - Generalized cardiomegaly
  - Hypovolemia or pulmonary under-circulation
- Abdominal radiographs
  - Kidneys symmetrical and upper limit of normal in size (3 times L2)
- Abdominal ultrasound exam
  - Hyperechoic renal cortices
  - RK = 4.0 cm; LK = 4.2 cm
  - Resistive index 0.81 (normal, < 0.6-0.7)
  - Mild bilateral pyelectasia (2.0-2.2 mm)

## Food-associated ARF: Movie
## (This is NOT Boo's kidney!)



## 385887 "Boo" Cooper
## ULS-guided renal aspirate



## 385887 "Boo" Cooper

- Ophthalmologic exam
  - Focal retinal elevation and wrinkling (early detachments) OU
- Systolic blood pressure varied between 110-170 mmHg during hospitalization
- Initially treated with amlodipine; later in clinical course blood pressure remained normal without amlodipine

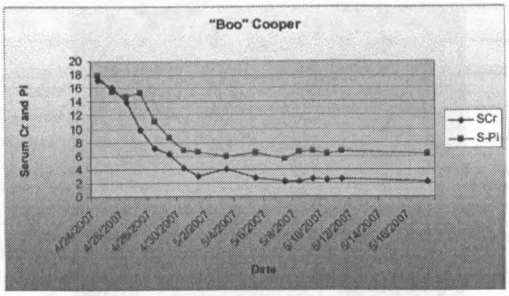
## 385887 "Boo" Cooper

- Fluid therapy (adjusted based on serum electrolytes)
  - 4/24 to 4/25: 0.9% NaCl
  - 4/26: LRS + 20 mEq/L KCl
  - 4/27 to 4/28: LRS
  - 4/29: LRS:0.9% NaCl (50:50)
  - 4/30 to 5/7: LRS:0.45% NaCl (50:50) + 10 mEq/L KCl
  - 5/8 to 5/11: LRS

## 385887 "Boo" Cooper

- Other treatments
  - First 2 days: Furosemide infusion
  - Ampicillin-sulbactam
  - Famotidine, sucralfate
  - Amlodipine initially for hypertension (later discontinued)
  - $Al(OH)_3$ once eating well

## 385887 "Boo" Cooper



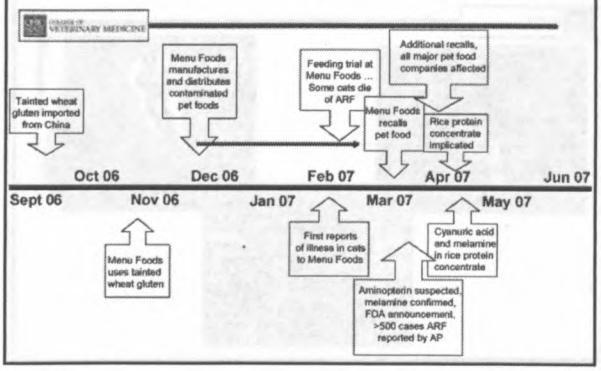

## 385887 "Boo" Cooper

- Fluid therapy: Differentiating diuretic phase of ARF from fluid therapy-induced diuresis
  - Attempts were made to decrease fluids during hospitalization
  - First time: body weight decreased, polyuria persisted, azotemia increased
  - Last time: body weight maintained, urine output decreased and level of azotemia was stable. Fluids switched to SC and discontinued over next few days

## SVNU Panel on Pet Food Recall
(ACVIM Forum, Seattle, June 6-9, 2007)

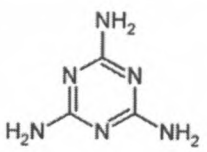
- Dr. Cathy Brown, DACVP, University of Georgia
- Dr. Denise Elliott, DACVIM and DACVN, Royal Canin
- Dr. Dru Forrester, DACVIM, Hill's Pet Nutrition
- Dr. Richard Goldstein, DACVIM, Cornell University
- Dr. Claudia Kirk, DACVIM and DACVN, Univ of Tennessee
- Dr. Kimberly May, DACVS, Communications, AVMA
- Dr. Paul Pion, DACVIM, Veterinary Information Network
- Dr. Linda Ross, DACVIM, Tufts University
- Dr. Shelly Vaden, DACVIM, North Carolina State University

## Pet Food Recall Timeline




## Melamine: FDA Report

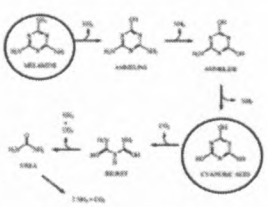
- Melamine has minimal toxicity
- Association between animal deaths and consumption of food contaminated with melamine is 'undeniable'
- Melamine may be 'associated with causative agent' or serve as marker of contamination
- A second contaminant may be responsible
- http://www.fda.gov



*Courtesy SVNU Panel*

## Cyanuric acid

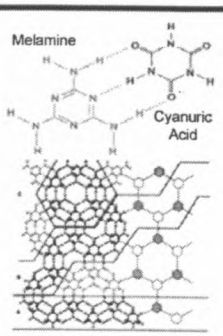
- Contaminant of rice-protein concentrate from China
- Possible widespread adulterant used to increase nitrogen content of food
- Metabolite of bacterial degradation of melamine
- Low toxicity



*Courtesy SVNU Panel*

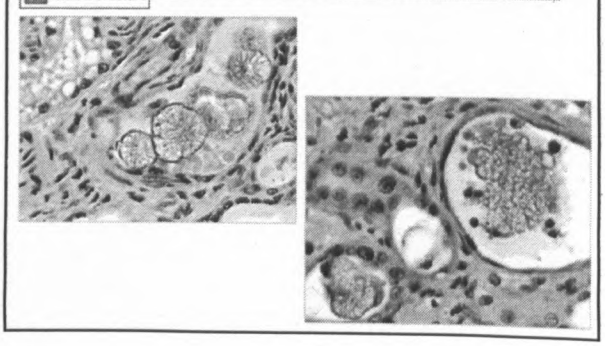
## Melamine cyanurate

- More toxic than melamine or cyanuric acid alone

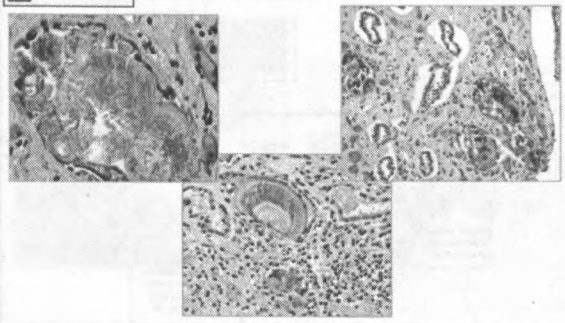



*Courtesy SVNU Panel*

*Histopathology courtesy Dr. Cathy Brown, University of Georgia*



*Histopathology courtesy Dr. Cathy Brown, University of Georgia*



## Food-associated ARF Treatment

- Confirm ingestion of recalled good
- Discontinue feeding product
- Differentiate ARF from CRF
- Correct dehydration
- Correct acid base and electrolyte abnormalities
- Establish fluid diuresis
- Monitor urine output and support as needed (e.g. furosemide)
- Maintain neutral urine pH

# Hepatic amyloidosis in cats

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The systemic amyloidoses are a group of syndromes that result from extracellular deposition of amyloid in multiple organs. Amyloid is a fibrillar protein whose accumulation in tissues causes fragility and depletion of function. Clinical signs vary according to the pattern and extent of amyloid deposition. A variety of proteins can act as amyloid precursors. These precipitate as a β-pleated sheet forming the core of the amyloid fibril. This fibril binds a circulating glycoprotein [serum amyloid P component (SAP)] and basement membrane proteins that promote secondary and tertiary folding. This ultrastructure imparts characteristic properties to amyloid, including insolubility, chemical inertness and characteristic green birefringence of Congo-red-stained sections viewed using polarized light.

In humans, potentially amyloidogenic proteins include immunoglobulin light chain fragments (which cause AL amyloidosis in some multiple myeloma patients), $\beta_2$-microglobulin (in renal dialysis patients), prion protein and atrial naturietic peptide, reflecting a diversity of associated disease processes. In systemic amyloidoses of companion animals, the precursor is almost invariably AA, an amino terminal fragment of the acute-phase protein, serum amyloid A (SAA). In humans, AA amyloidosis occurs either secondary to chronic inflammatory, infectious or neoplastic diseases (e.g. tuberculosis), or as a familial trait (e.g. familial Mediterranean fever). Familial AA amyloidosis is recognized in Chinese Shar-Pei dogs and Abyssinian cats, and DiBartola and colleagues at Ohio have done an outstanding job characterizing these respective conditions. The most common presentation of systemic AA amyloidosis in animals and man is as a nephropathy and signs of liver involvement are rare. In dogs, amyloid tends to be deposited in the glomeruli, whereas in cats there is preferential deposition in the interstitium. Abyssinian cats with amyloidosis typically present with classic signs of renal disease when less than 6-years-of-age.

A hepatic amyloidosis of cats has been described which results in spontaneous rupture of the liver. Cases present for sudden death or with acute intermittent signs associated with episodes of intra-abdominal haemorrhage. Involvement of other organs is usually subclinical, although affected cats may develop chronic renal failure if they survive sufficiently long. Risk factors associated with feline hepatic amyloidosis have not been well defined. Previous reports document clusters of cases from breeding catteries, usually involving cats under 5-years. Since affected cats are often related, the relative contribution of genetic and environmental factors has been blurred. The predominance of Siamese and their colour variants coupled with pedigree analyses, have led to the suggestion that the disease is familial in Siamese and related breeds.

Between 1997 and 1999, six cases of hepatic amyloidosis were seen at our hospital, comprising 4 Siamese-type, one domestic-shorthair and one Devon Rex. The pathophysiological event precipitating signs was acute intra-abdominal bleeding. Hepatic amyloidosis was the major disease process identified in 5 cases, but one also had concurrent chronic renal failure and FIP. The cases were sporadic, with relatives and housemates not clinically affected. Clinical signs in three of these cases had, prior to referral, been misdiagnosed as blunt trauma, immune-mediated haemolysis or coagulopathy. The diagnosis was challenging because clinical signs

were often subtle and/or transient. Affected cats cope with hypovolaemia and anaemia by becoming sedentary, and autotransfusion assists return to normality within 3 to 5 days, which may be erroneously interpreted as a favorable response to therapy. Where repeated episodes occur, astute owners recognize the signs of acute haemorrhage and may present cats when they are hypovolaemic - this is a good time to look for free blood in the abdomen using ultrasonography.

Pale mucous membranes, hypothermia and hepatomegaly were the physical findings most consistently observed. Most cases were in good body condition. Increased ALT was an important indicator of liver disease, with 5/6 cases having 5-fold or greater elevations. Biochemical evidence of a hepatopathy, however, was not invariably present. Total protein was commonly below, or near the bottom of, the normal range, consistent with haemorrhage. Polychromasia and reticulocytosis were variably present, as these features are absent for the first few days after an acute bleed. A variable, likely consumptive, thrombocytopenia was detected in half of the cases and may have contributed to ongoing intra-abdominal haemorrhage. Disorders of secondary haemostasis are possible in affected cats. Recent studies suggest that 60 to 82% of cats with liver disease show prolonged coagulation times and these abnormalities may normalize with vitamin $K_1$ therapy. This phenomenon provides justification for the anecdotal impression by ourselves and Zuber that vitamin $K_1$ may prolong survival in some feline amyloidosis patients.

Radiography and abdominal ultrasonography were useful for detecting free peritoneal fluid, hepatomegaly and irregular hepatic borders. Furthermore, ultrasonography demonstrated consistent abnormalities in the hepatic parenchyma: a diffuse, heterogeneous echodensity with highly echogenic areas and hypoechoic foci. These features were useful in supporting a tentative clinical diagnosis and for screening at risk cats. Scintigraphy, using $I^{123}$- labeled SAP provides another non-invasive, though less accessible, method for detecting hepatic amyloid. Definitive diagnosis relies on histopathological detection of amyloid in hepatic biopsies. A cytological diagnosis can be made following fine-needle aspiration, circumventing risks associated with anaesthesia, core biopsy or celiotomy. Extracellular amyloid deposits may be overlooked unless there is a high index of suspicion for amyloidosis - the changes in DiffQuik stained smears are subtle (a fringe of extracellular pink fibrillar material) and can be confirmed by Congo Red staining of smears and polarized light microscopy.

Hepatic amyloidosis is generally a disease of young cats. Haemorrhage has been documented in cats between 8-months and 7.5- years. 5/6 cases in this series were neutered males, whereas 10/16 previous cases where data are available were entire females, the remainder neutered males. Siamese and related cats appear to be at increased risk, representing 4/6 cases in this series and approx. 95% of total reported cases. The young age of affected cats and over-representation of purebreds (especially Siamese) suggests the possibility of an underlying infectious aetiology, and pathogens including Calicivirus, *Bartonella henselae*, *Clamydophila felis* and the agents of feline infectious anaemia remain tantalizing possibilities, as all these give rise to a chronic carrier state. In one case, a chronic acute-phase response associated with FIP virus may have promoted amyloid formation.

Specific treatments for feline AA amyloidosis are not currently available. Once formed, amyloid fibrils are relatively insoluble and resistant proteolysis. Scintigraphy has demonstrated that AA amyloid deposits in humans may regress over months to years if the primary disease subsides. This has encouraged the development of therapeutic interventions targeting fibril formation. Colchicine, which reduces SAA release from hepatocytes, is used to treat familial Mediterranean fever and was used (unfortunately without success) in one of our cases. Use of glucocorticoids is

controversial since they can accelerate disease in experimental settings but may be of benefit by reducing the supply of precursors by suppressing the acute phase response. Interventions targeting the supply and processing of precursors or events in chain formation have been shown to reduce amyloid progression in mice models. These include tenidap, which blocks inflammatory cytokines thereby reducing hepatic production of SAA; small molecule anionic sulphonates and sulphates, which block the interaction between fibril core and basement membrane proteins preventing secondary and tertiary structure formation, and immunization with amyloid-beta, the precursor of amyloid associated with Alzheimer's disease.

Currently the only treatments which can be recommended for cats diagnosed with hepatic amyloidosis are cage rest, vitamin $K_1$ supplementation and antibiotics effective against putative occult pathogens such as *B henselae and M haemofelis* (e.g. doxycycline). Colchicine may have a benefit if started sufficiently early. Interestingly, a report exists of one cat that was apparently cured by treatment with a naturopathic remedy with potent anti-oxidant activity.

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Rapid growing Myco take 4-7 days to show up on a plate

If setting sample FNA - clip clean & alcohol several times - If use Iodine - let it dry 1st will inactivate organism otherwise

& feline leprosy - need to do wide excision - early - can get over & no Ab even if so that

need PCR to ID - allergy duty to culture

Janet Foley @ Davis - lots of work & this

TACMAN: $80

Canine leproid granuloma boxers nodular on ears ulcerate

when ulcerate - TNF-I ⇒ tissue necrosis - symptoms - get better? - Tx & Tb drugs if not resolving

Panniculitis syndrome in cats & dogs

myco subcutis & rapidly growing - clarithromycin

m smegmatis, fortuitum, M chelonae (LEHPC?) responds to AFB

Quin & Dox

You need to know which it is only one

other 2 Questions - needs fat, obese animal

FNA - walk needle to a nodule or pocket - if get good sample will grow easily - But you can't find it on cytology -

So tell Lab you're looking for this - Feline Leprosy

in opposite - see lots on cyto, but can't grow

You can ask for MIC - may not have it - need hi end dose

need to Tx (Doxy or Cipro - not Baytril - need hi end dose

to get into fat - Baytril will be to risky from retinopathy - if not

Origi- Marbo Tx for months after more better appearance of

Consider mod prac clofazimine or linezolid if refractory

# Nontuberculous mycobacterial syndromes in cats

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## Feline panniculitis due to rapidly growing mycobacteria

Rapidly growing mycobacteria (RGM) are a heterogeneous group of organisms that produce colonies on synthetic media within seven-days when cultured at 24°C to 45°C. They are distributed ubiquitously in nature. RGM include the *M fortuitum* group (including *M fortuitum*, *M peregrinum* and the 3rd biovariant complex), the *M chelonae/abscessus* group (including *M chelonae* and *M abscessus*), the *M smegmatis* group (including *M smegmatis* sensu stricto, *M goodii* and *M wolinkskyi*) and a variety of other species. The taxonomy of this group has been revised recently and because of this, the word 'group' is used when referring to isolates recorded in early publications. RGM are strongly linked with localized infections of immunocompetent hosts. This is because they are well adapted to a saprophytic existence and inherently have low virulence. Thus, they do not produce disease unless a breakdown in normal defense barriers provides them with a portal of entry to a favorable tissue environment. Once introduced, RGM are generally constrained by a vigorous immune response that may or may not eradicate them, but is effective enough to prevent haematogenous or lymphatic spread. RGM can produce widely disseminated disease, but only in severely immunocompromised individuals.

Mycobacterial panniculitis refers to a syndrome characterized by chronic infection of the subcutis and skin with RGM. This condition is quite common in cats, especially in Australia. RGM replicate in mammalian tissues when introduced through some break in the skin. This typically follows penetrating injury, especially when the wound is contaminated by dirt or soil. Preference of RGM for fat is a key factor in the pathogenesis and results in a tendency for disease to occur in obese individuals and in tissues rich in lipid, such as the subcutaneous panniculus and especially the inguinal fat pad. Experimental infections cannot be induced in cats that do not have appreciable subcutaneous fat. Adipose tissue offers a favorable environment for survival and proliferation of RGM by providing triglycerides for growth or protecting organisms from the phagocytic and immune responses of the host. Initial reports suggested mycobacterial panniculitis was more common in warm humid climates; however cats from temperate regions, including parts of Australia, Canada, Finland and Germany, have subsequently been reported. In Australia, the *M smegmatis* group accounts for the majority of feline cases, whereas it is a much less common cause of equivalent infections in human patients.

### Clinical signs

Infections tend to start in the inguinal region, usually following contamination of cat fight injuries, e.g. raking wounds inflicted with the hind claws. The infection may spread to contiguous subcutaneous tissues of the ventral and lateral abdominal wall and perineum. Penetrating injury by sticks, metallic objects and vehicular trauma may also give rise to these infections, as can cat and dog bite injuries contaminated with soil or dirt. Sometimes infections start in the axillae, flanks or dorsum.

Early in their course, infections resemble catfight abscesses, but without the characteristic fetid odor and turbid pus. Instead, a circumscribed plaque or nodule is apparent. Later, there is progressive thickening of the nearby subcutis to which overlying skin becomes adherent. Affected areas become denuded of hair and numerous punctate fistulae appear, discharging watery exudate. Fistulae are intermingled with focal purple depressions (thinning of the epidermis

over accumulations of pus). The 'lesion' gradually increases in area and depth, and may eventually involve the entire ventral abdomen, adjacent flanks or limbs. If cats are presented promptly for veterinary attention and the lesion confused with an anaerobic cat-bite abscess, surgical drainage and administration of a β-lactam is typically followed by wound breakdown and development of a non-healing suppurating tract surrounded by indurated granulation tissue. Some affected cats with infections develop systemic signs, becoming depressed, pyretic, inappetent, losing weight and being reluctant to move. Occasional cats develop the hypercalcaemia of granulomatous disease, although this is rarely symptomatic. Surprisingly, other cats remain comparatively well despite extensive disease. Usually the problem remains localized to the skin and subcutis. Although adjacent structures such as the abdominal wall can be affected eventually, spread to internal organs or lymph nodes is very unusual.

**Diagnosis**

*Sample collection, Cytology and Histology*

A tentative diagnosis of mycobacteriosis can be confirmed by collection of pus or deep tissue specimens. This material is used to confirm the diagnosis using appropriately stained smears, histological sections and culture. A histological diagnosis is unnecessary if appropriate samples for cytology and culture have been procured. It is vital to give the laboratory warning that mycobacterial aetiology is suspected so special procedures for processing can be adopted.

In our experience, samples of pus obtained from needle aspirates of affected tissues through intact skin provide the best laboratory specimens. This material can be obtained from a palpably abnormal portion of the subcutis. The overlying skin should be carefully disinfected with 70% ethanol prior to obtaining the specimen to preclude the isolation of saprophytic mycobacteria from the skin surface. It may be necessary to carefully move the needle in the subcutaneous space, while applying constant negative pressure, until a pocket of purulent material is encountered. Aspirated fluid should be submitted for cytology and mycobacterial culture, or inoculated immediately into a commercially prepared mycobacteria culture bottle that is subsequently submitted to the laboratory. It is only necessary to suck a small amount of liquid material into the hub of the syringe. It is easiest to submit the entire syringe to the laboratory after replacing the needle with a sterile cover. Exudate from draining sinus tracts is heavily contaminated secondary invaders and represents an inferior sample. If deep biopsies are obtained, they should be triturated in brain heart infusion broth using a sterile mortar and pestle to produce a tissue homogenate suitable for cytology and culture.

Smears prepared from aspirates or tissue homogenates should be stained using Diff Quik®, Gram stain and a modified acid-fast procedure (decolorizing with 5% sulphuric acid for only three to five minutes; RGM are *not* as acid-fast as other mycobacteria). Cytology invariably demonstrates pyogranulomatous inflammation and it is generally possible to visualize Gram positive and/or acid-fast bacilli (AFB) in smears, although an exhaustive search may be required. Histologically, there is pyogranulomatous inflammation. AFB may be hard or impossible to find in Ziehl-Nielsen (ZN) stained tissue sections and are often located in lipid vacuoles. Some US dermatologists favour Fite's stain for detecting AFB in tissues.

*Bacteriology and antimicrobial susceptibility testing*

Tissue homogenates and pus should be streaked onto blood agar plates and a mycobacterial medium such as Lowenstein-Jensen medium or 1% Ogawa egg yolk medium and incubated aerobically at 37°C and 25°C. If available, the BACTEC system can also be utilized. Moderate to heavy growth of pinpoint, non-hemolytic colonies is usually detected after 2-3 days (occasionally longer) on sheep blood agar at 37°C. A useful method which can be used to differentiate RGM from contaminant flora is by primary isolation around antibiotic sensitivity discs (first generation cephalosporins or isoxazolyl penicillins) applied to the plate after inoculation.

There is great value in determining species identification and susceptibility data in every case, as this has a big impact on antimicrobial strategies. Species identification can be carried out in a well equipped veterinary bacteriology laboratory although it if often more convenient to send the strain to a Mycobacteria Reference Laboratory following primary isolation. Identification takes into account a number of phenotypic and biochemical features. Minimum inhibitory concentrations (MICs) for ciprofloxacin, moxifloxacin, gentamicin, trimethoprim, clarithromycin and doxycycline can be determined easily using the Etest (AB Biodisk, Solna, Sweden) method. This methodology is less demanding than the 'gold standard' of broth microdilution. Antimicrobial susceptibility of clinical isolates can also be determined using disc diffusion methodology.

*Therapy*

The management of feline mycobacterial panniculitis continues to evolve in the light of clinical experience, availability of new anti-infective agents and the development of new surgical techniques. There is great variation in the severity and extent of lesions from patient to patient. Difficulty in making a prompt diagnosis is partly responsible for the chronicity, severity and refractoriness of these infections. Briefly, treatment should commence with oral antimicrobial(s) (doxycycline, a flouroquinolone and/or clarithromycin), initially chosen empirically, but subsequently based on *in vitro* susceptibility data. Sometimes long-term administration of such an agent or agents is sufficient to effect a cure, but in many severe cases it is eventually necessary to surgically resect recalcitrant tissues so that oral antimicrobial therapy will be able to cure the infection permanently. Given the extent and severity of the pathology in many of these cases, it is understandable that adequate levels of antimicrobials may not be achieved throughout all affected tissues and that in these cases the best chance for a successful outcome is to remove as much infected tissue as possible following preliminary drug therapy. Residual foci of infection can then be targeted by high concentrations of antibiotics achieved during and after surgery. Peri- and post-operative antimicrobial therapy is vital to ensure primary intention healing of the surgical incision. In the future, drugs such as moxifloxacin and pradofloxacin may prove even more effective that agents currently available.

## Disseminated*Mycobacterium avium -intracellulare* complex (MAC) infection in young cats with a putative cell mediated immunodeficiency syndrome

We have recently reported a new syndrome of disseminated MAC infection in ten young cats (1 to 5 years-of-age) from Australia or North America. A further two cats with disseminated mycobacteriosis (precise agent not identified) were recognised also. Of the twelve, ten were Abyssinian cats, one was a Somali cat and one was a domestic shorthair cat. None of the cats tested positive for either FeLV antigen or FIV antibody.

The clinical course of these infections was indolent, with cats typically presenting for weight loss, initially in the face of polyphagia, with a chronicity of up to several months. Additional clinical features included lower respiratory tract signs and peripheral lymphadenomegaly. A marked diffuse interstitial pattern was evident in thoracic radiographs, even in cats without overt respiratory involvement. Hair clipped to perform diagnostic procedures tended to regrow slowly, if at all. Diagnosis was generally made by obtaining representative tissue specimens from mesenteric lymph nodes, liver or kidney at laparotomy, or from a popliteal lymph node. The primary antecedent event was most likely colonisation of either the alimentary or respiratory tract, followed by local invasion and eventual lymphatic and haematogenous dissemination.

Nine cases were treated using combination therapy with agents effective for MAC infection in human patients. The results were generally favourable, although the disease had a tendency to recur if insufficient treatment courses were utilised. Cats were generally treated with long courses (5 to 14 months) of clarithromycin combined with either clofazimine or rifampicin, and a

fluoroquinolone or doxycycline was sometimes given also, although in the future moxifloxacin may prove to be a superior adjunctive agent in this setting.

Certain lines of Abyssinian and Somali cats likely suffer from a familial immunodeficiency that predisposes them to infection with slow-growing mycobacteria such as MAC. Studies of this problem are on-going.

## Feline leprosy syndromes

*Historical perspective*

The term feline leprosy is used to refer to a disease in which single or multiple granulomas form in the skin or subcutis in association with large numbers of acid-fast bacilli (AFB) which are nonculturable using standard methods. The condition was first recorded in the literature by Australian and New Zealand researchers in the early 1960s. Since then, the disease has been reported in Western Canada, the Netherlands, France, the UK and USA.

Historically, the causative agent of feline leprosy was purported to be *Mycobacterium lepraemurium*. This bacterium causes murine leprosy, a systemic tuberculosis-like infection of rats. Cats are thought to contract *M lepraemurium* following bite injuries from infected rodents. *M lepraemurium* is a fastidious, slow-growing organism which, with difficulty, can be cultured from large inoculae on Ogawa's egg yolk medium under special conditions. Although a few investigators have successfully grown *M lepraemurium* from infected cats, the basis of ascribing this bacterium as the etiological agent of feline leprosy was dependent on transmission studies. Interestingly, some cats appeared much more susceptible to experimental infection than others.

According to the literature, cats with feline leprosy are typically young adults (< 5 years-of-age), perhaps with a preponderance of males. Presumably these patient characteristics reflect the need for the cat to interact with a rat to become infected. The initial lesion is a focal granuloma of the subcutis. Owners become aware of solitary, or more commonly multiple, painless, raised, fleshy, tumor-like lesions, from a few millimeters up to 4 cm in diameter. These granulomas are freely movable over underlying tissues. Lesions can develop rapidly and when large, may ulcerate. Infection spreads to adjacent areas and may invade underlying tissues and drain to regional lymph nodes. Lesions can occur anywhere, but tend to be concentrated on the head and limbs. Small lesions are occasionally found on the tongue, lips and nasal plane. Lesions, even if multiple, tend to be initially concentrated in one region and have the propensity to recur following excision.

Pathologically, feline leprosy was subdivided into lepromatous or tuberculoid forms based on the no. of AFB present (multibacillary *v* paucibacillary) and the host immunological response (lepromatous *v* tuberculoid). Because the causal mycobacteria are slow-growing organisms capable of intracellular survival, the histologic picture actually depends on the host's immune response. When this response is poor, lepromatous (multibacillary) disease develops with infiltration of the dermis with large sheets of 'incompetent' foamy macrophages containing enormous numbers of organisms. AFB are usually arranged in the cytoplasm of macrophages as dense parallel accumulations which displace the nucleus to an eccentric position. Lymphoid cells and plasma cells are virtually absent from the lesions. If the host's immune response is more effective, histiocytic cells are accompanied by moderate numbers of lymphoid cells and plasma cells and multiplication of the organism is limited - the so-called tuberculoid response.

AFB in smears and tissue sections appear as long slender rods. In smears stained with Romanowsky stains such as DiffQuik or Geimsa, organisms appear as negative-staining bacilli. In smears or sections stained with modified acid-fast stains such as ZN or Fite's stain, organisms take up the carbol fuschin and are acid/alcohol fast.

*Molecular insights*

Molecular methodologies have been used to investigate presumptive feline leprosy. Of eight cases of invasive or disseminated cutaneous mycobacterial disease investigated by Siobhan Hughes and colleagues using material collected largely from New Zealand cats, four were shown to have *M lepraemurium* infections. Of the remaining cases, one cat had a disseminated *M avium* infection, the aetiology in one cat was undetermined and in two cases infection was attributable to a novel mycobacterial species. This information encouraged a reappraisal of Australian feline leprosy cases, and subsequently this work has been extended to North America by groups lead by Greg Appleyard and Janet Foley.

In Australia, cats were initially be divided into two groups based on the patients' age, lesion histology, clinical course and sequence of 16S rRNA PCR amplicons obtained from lesions. More recently, we have identified a new cohort of Australian cats from the Gippsland region of Victoria which were infected by a third novel mycobacterial species.

1. The first group consisted of young cats (typically < 4-years) which initially developed localised nodular disease affecting the limbs. Lesions progressed rapidly and sometimes ulcerated. Sparse to moderate numbers of AFB were identified using cytology or histology, typically in areas of caseous necrosis and surrounded by tuberculoid inflammation. Organisms did not stain with haematoxylin and ranged from 2-6 µm (usually 2-4 µm). *M lepraemurium* was diagnosed based on the sequence of a 446 bp fragment encompassing the V2 and V3 hypervariable regions amplified from lesions using PCR and mycobacterial primers.

2. The second group consisted of old cats (>9-years) with generalised nodular skin lesions associated with multibacillary lepromatous histology. Some cats initially had localised disease that subsequently became widespread, while others had generalised disease from the outset. Disease progression was protracted, typically taking months to years, and skin nodules did not ulcerate. Microscopically, lesions consisted of sheets of epithelioid macrophages containing large to enormous numbers of AFB 2-8 µm (mostly 4-6µm) which stained also with haematoxylin. A single unique sequence spanning a 557 bp fragment of the 16S rRNA gene was identified in lesions from these patients. The sequence was characterized by a long helix 18 in the V3 region, suggesting the new species was likely to be a fastidious, slow-grower. The 16S rRNA sequence had greatest nucleotide identity with *M leprae*, *M haemophilum* and *M malmoense*, and contained an additional 'A' nucleotide at position 105 (the only other mycobacterial database sequence with the same extra nucleotide being *M leprae*). A very slow, pure growth of a mycobacterium species was observed on Lowenstein-Jensen medium (supplemented with iron) and semisolid agar in one case. The environmental niche of this new mycobacterium species has yet to be determined, although the preponderance of cases from rural or semi-rural areas of coastal NSW suggests it is a saprophyte found more commonly in these locations than in metropolitan environments.

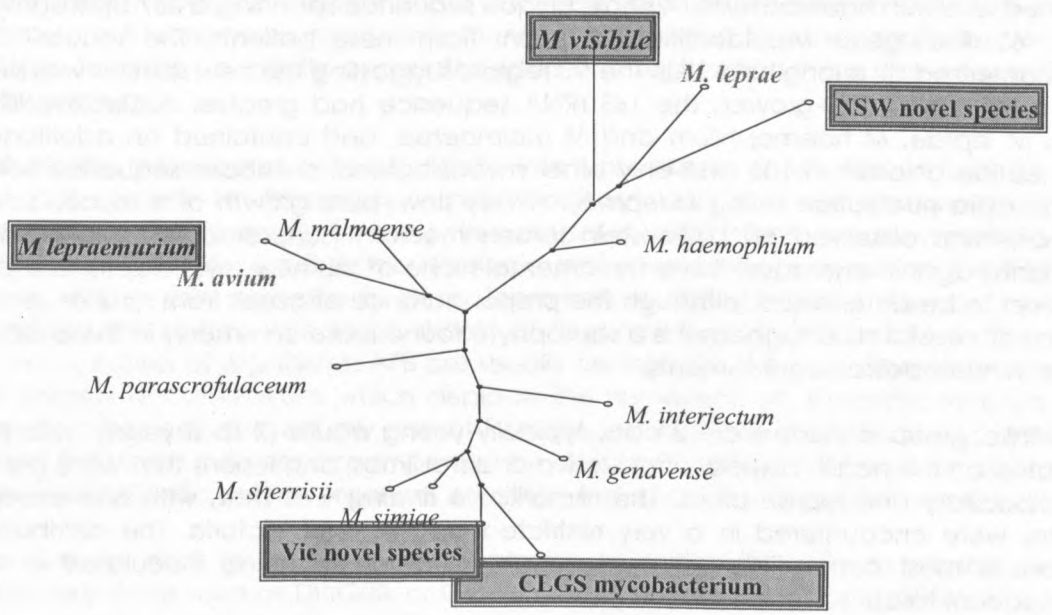
3. The third group consisted of 12 cats, typically young adults (2 to 8 years), with lesions located on the head, cornea, conjunctiva or distal limbs, and lesions that were generally multibacillary and lepromatous. The remarkable finding was that, with one exception, cases were encountered in a very restricted part of rural Victoria. The distribution of lesions is most compatible with a saprophytic organism being inoculated in tissues subsequent to cat scratch injuries.

The presence of tuberculoid pathology is generally marker of disease in an immune-competent host and such infections are often initially localised. In contradistinction, the presence of a foamy histiocytic infiltrate of the dermis and subcutis in patients with mycobacteriosis is observed almost exclusively in association with profound immunodeficiency, such as that seen with terminal HIV infection in human patients. Widespread dissemination of infection (rather than local invasion) suggests decreased immunological surveillance permits the development of disease with an organism usually considered to have limited virulence. Feline leprosy caused by the novel NSW mycobacterial species, the Victorian novel species or more rarely *M lepraemurium*, may likewise represent a manifestation of deteriorating immune competence.

For epidemiologic reasons, feline leprosy in young cats is almost invariably caused by *M lepraemurium*, the novel NSW species is almost invariably seen in old (likely immunosuppressed cats) while the novel Victorian species can occur in either immune competent or immune defective cats.

To make matters even more complex, recent work by Appleyard and colleagues has demonstrated a third mycobacterial syndrome in cats from western Canada and the USA (Idaho and Oregon) called 'feline multisystemic granulomatous mycobacteriosis'. This disease is caused by a slow-growing taxa provisionally called *M visibilis* or *M visible*. This species is capable of producing widespread dissemination to multiple internal organs, presumably in immune deficient cats. Sequence analyses demonstrate a number of nucleotide differences between *M visibilis* and both *M lepraemurium* and the novel species reported by Hughes et al.

**Figure 1. Unrooted phylogenetic tree of selected *Mycobacterium* species computed from concatenation of 16S rRNA gene, ITS and *hsp*65 sequences by maximum likelihood.**



Diagnosis of the 'feline leprosy' syndromes is usually straightforward, provided that the clinician has a high index of suspicion for the condition. Needle aspirates, crush preparations of biopsy material and histological sections stained with ZN or similar methods contain easily demonstrable AFB surrounded by variable granulomatous to pyogranulomatous inflammation. In DiffQuik stained smears, mycobacteria can be recognized by their characteristic 'negative-staining' appearance and location within macrophages and giant cells.

Material should be submitted also for culture, because occasionally slowly-growing species such as MAC and *M genavense* and the tubercle bacillus (*M bovis* or *M microti*) can produce an identical clinical presentation; in such cases optimal antimycobacterial therapy can be selected more readily on the basis of *in vitro* susceptibility results and information available in the literature. In the majority of cases, however, conventional mycobacterial culture is negative due to the fastidious nature of the causal organisms and the exact aetiology can only be proven using PCR amplification and sequence determination of gene fragments. PCR has the additional advantage of providing a rapid diagnosis. Fresh (frozen) tissue delivered to a mycobacterium laboratory with PCR facilities provides the optimal sample, although freeze-dried specimens may be more conveniently sent where tissues need to travel long distances. Sometimes PCR can be performed successfully on formalin-fixed paraffin-embedded material, although fixation conditions invariably cause some DNA degradation which may limit the success of the procedure. Recently, Hughes and colleagues have developed specific PCR assays to diagnose infections due to *M lepraemurium* and the novel species; furthermore, use of a simple restriction enzyme digest allows these assays to distinguish *M visibilis* strains also.

*Therapy*

Too few cases with a documented aetiology have been reported to provide definitive treatment guidelines. Although *M lepraemurium* and the novel species can be cultured *in vitro with difficulty*, it is currently not routine or reliable to isolate these organisms due to their slow growth and fastidious requirements. Determination of *in vitro* susceptibility data for individual isolates is therefore not possible.

Only limited experimental studies have been undertaken to determine effective drug therapy for *M lepraemurium in vitro* or *in vivo* and as yet we have limited data only for the novel mycobacterial species. Portaels and colleagues found the minimum inhibitory concentration for rifampicin of two strains of *M lepraemurium* to be 4 and 8 µg/mL, levels that should be just obtainable *in vivo*. Other drugs shown to have activity against *M lepraemurium in vitro* include ansamycin compounds (rifabutin) and sulpha drugs. There is a good deal of clinical evidence that clofazimine has efficacy *in vivo*, while it is likely that clarithromycin would be also be effective based on its wide spectrum of activity against slow-growing mycobacterial species.

The literature suggests that when *M lepraemurium* infection is diagnosed early, while disease is localized, wide surgical excision of infected tissues provides the best chance to simply and rapidly effect a cure. Aggressive resection techniques should be adopted, with *en bloc* resection of all lesions, and reconstruction of resulting tissue deficits using appropriate surgical techniques. Such an approach should be combined with adjunct antimicrobial therapy beginning a few days prior to surgery, so that effective levels of drugs are present in blood and tissues intra- and postoperatively to ensure primary intention healing. Clofazimine (at a dose of up to 10 mg/kg once daily orally; typically 25 to 50 mg every 24 to 48 hours) has the best reported success rate, although it is likely that combination therapy using two or more drugs will eventually prove superior. Drugs that could be combined with clofazimine include rifampicin and clarithromycin, although sulpha drugs, doxycycline, new fluoroquinolones such as moxifloxacin or pradofloxacin, or amikacin may in time also prove to be useful. Unfortunately, clofazimine is becoming very difficult to obtain, although some compounding pharmacies can source the dye.

In feline leprosy cases caused by novel mycobacterium species, we believe combination therapy using two or three of clofazimine (25 to 50 mg per cat orally every day or every other day), clarithromycin (62.5 mg twice daily) or rifampicin (10 to 15 mg/kg per day) represents optimal therapy. However we are currently unsure of which will prove to be the best combination, and side effects in individual cats may affect which two drugs are used in a given patient. Currently, we recommend a combination of rifampicin and clarithromycin as initial therapy. The new quinolone moxifloxacin may prove useful in future cases, as it has good antimycobacterial activity and is affordable. Other new agents such as linezolid may also have a place, although currently they are prohibitively expensive for most owners.

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# Do Bacteria Have a Role in Feline Inflammatory Bowel Disease?

**Kenneth W. Simpson, Cornell University**

Feline inflammatory bowel disease (IBD) is the term applied to a group of poorly understood intestinal disorders that are associated with vomiting, diarrhea and weight loss in cats. Diagnosis is usually based upon subjective analysis of intestinal mucosal biopsies and qualified according to the dominant mucosal infiltrate, typically lymphocytes and plasma cells (Jergens, 2002; Jergens et al., 1992; Waly et al., 2004). However, more objective studies have demonstrated increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes, and upregulation of pro-inflammatory and immunoregulatory cytokines (Nguyen Van et al., 2006; Waly et al., 2004), rather than an increase in mucosal cellularity. Abnormalities in mucosal architecture, such as crypt distortion, villous blunting and fusion, and fibrosis have also been described, and have been associated with the severity of clinical signs (Baez et al., 1999; Hart JR, 1994), and the subjective histological grade of IBD (Baez et al., 1999; Dennis et al., 1992; Hart JR, 1994; Jergens, 2002). The cause of feline IBD has not been determined, but it is suspected that IBD in cats, like IBD in people, is a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals (Hanauer, 2006; Sartor, 2006). Genetic susceptibility in people is linked increasingly to defects in innate immunity, exemplified by mutations in the innate immune receptor NOD2/CARD15, that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation.(Ahmad et al., 2002; Hanauer, 2006; Sartor, 2006; Wehkamp and Stange, 2006) This possibility is supported by studies showing the pivotal importance of the enteric microflora in the development of IBD in rodents with engineered susceptibility,(Elson et al., 2005; Kim et al., 2005), and those demonstrating an abnormal mucosa-associated flora, considered to interact most closely with the innate immune system, in people with IBD.(Kleessen et al., 2002; Mylonaki et al., 2005; Swidsinski et al., 2002; Swidsinski et al., 2005) Knowledge of genetic susceptibility and the enteric microflora in cats with IBD is limited, with some studies reporting a predisposition for purebred cats (Dennis et al., 1992), and culture based studies that show fewer lumenal microaerophilic bacteria in the duodenal juice of cats with clinical signs of gastrointestinal disease than healthy cats (Johnston et al., 2001).

It is against this background that we sought to examine the relationship of the mucosal flora to intestinal inflammation and clinical disease activity in cats with and without inflammatory bowel disease. Intestinal biopsies were collected from 27 cats: 17 undergoing diagnostic investigation of signs of gastrointestinal disease, and 10 healthy controls. Subjective duodenal histopathology ranged from normal (10), through mild (6), moderate (8), and severe (3) IBD. The number and spatial distribution of mucosal bacteria was determined by

fluorescence in situ hybridization with probes to 16S rDNA. Mucosal inflammation was evaluated by objective histopathology and cytokine profiles of duodenal biopsies.

The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of gastrointestinal disease than healthy cats ($P<0.001$). Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture ($P<0.001$) and the density of cellular infiltrates, particularly macrophages ($P<0.002$) and $CD3^+$lymphocytes ($P<0.05$). The number of Enterobacteriaceae, *E. Coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats.

These data establish that the density and composition of the mucosal flora is related to the presence and severity of intestinal inflammation in cats, and suggest that mucosal bacteria are involved in the etiopathogenesis of feline IBD.


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# A Stepwise Approach to Treating Feline Inflammatory Bowel Disease

Kenneth W. Simpson, Cornell University

How confident am I the cat has IBD?

- Clinical findings
- Clinicopathological tests
- Diagnostic imaging
- Intestinal biopsy

Have I ruled out
Systemic/ metabolic disease

Dietary intolerance/ food allergy

Infectious agents
- Protozoa
  - *Giardia*
  - *Tritrichomonas*
- Pathogenic bacteria
  - Campylobacter / Salmonella

Viral?

Structural/anatomic abnormalities

Does the cat have multiple problems or organ systems involved?

Is the cat deficient in cobalamin or folate?

Do I need a biopsy?

What and how should I biopsy?

How do I interpret the biopsy results and integrate gastric and intestinal histopathology?

Is it IBD or small cell lymphoma?

What diet should I use?

When should I use antimicrobials? corticosteriods? chlorambucil?

How do I manage concurrent disease in the liver and pancreas?

How do I assess response?

**A very brief overview!**

***Clinical findings***:

Vomiting is the most common clinical sign in cats with IBD. Vomitus often contains bile. Other findings include diarrhea, changes in appetite, weight loss and less commonly excessive borborygmi and abdominal discomfort.

The severity of disease ranges from intermittent vomiting in mild cases to intractable small bowel diarrhea, inappettance and weight loss in severe ones. The severity of the disease correlates with the degree of intestinal damage, particularly villus atrophy and fusion

Physical findings range from normal to thickened intestines, mesenteric lymphadenopathy and loss of muscle mass. Ascites or edema are extremely are in cats with IBD.

Routine laboratory testing may reveal mild to moderately elevated liver enzymes as a result of GI barrier dysfunction. However, IBD can be associated with concurrent hepatoibiliary disease and pancreatitis- "triaditis"- so the clinician must consider these disorders (Ultrasonography and fPLI aid detection of intercurrent disease). The presence of hypocalcemia would ring alarm bells for pancreatitis. Hypoalbuminemia is rare. CBC is usually normal. Eosinophilia is encountered in some cats with LP enteritis, and should prompt consideration of parasites or food intolerance/allergy, as well as mastocytosis or hypereosinophilic syndrome. Measurement of serum cobalamin and folate can aid the detection of intestinal disease- low cobalamin concentrations are common in cats with IBD (EPI should be excluded by TLI assay). Cobalamin deficiency can produce identical signs to those associated with IBD. A combination of low folate and conbalamin tends to support a diagnosis of severe IBD or GI lymphoma.

***Diagnosis***:

A diagnosis of idiopathic IBD is made by excluding systemic, parasitic, infectious, pancreatic and structural causes of chronic vomiting, weight loss or diarrhea and demonstrating histopathological abnormalities in intestinal biopsies. Keep in mind that IBD may co-exist with hepatobiliary disease and/or pancreatitis

***Treatment:*** There are no clinical trials for foods

Treatment of IBD is usually a "best guess least harm" approach employing dietary modification, vitamin supplementation, antimicrobial agents and immunosuppression. Treatment is to some extent based on the severity of the disease.

Mild to moderate disease may be associated with dietary sensitivity / intolerance, cobalamin deficiency or antibiotic responsive enteropathy.
A therapeutic dietary trial can be performed with either:1) a highly digestible diet which is gluten-free ,2) a diet limited to a single novel protein source or3) a diet containing protein hydrolysate, to determine if dietary sensitivity or intolerance are present. A response is usually observed within one to two wks. Re-challenge with the original diet is essential to demonstrate intolerance.

Cobalamin deficiency is treated with parenteral cobalamin (1ml SC q 2-3wks). Folate should be given orally if serum concentrations are low.

A therapeutic trial (21days) with Tylosin (10mg/kg PO TID), metronidazole (15mg/kg PO BID) or oxytetracycline (10-20mg/kg PO TID) can be undertaken to determine if an antibiotic responsive enteropathy is present.

In patients who fail these trials and in those with moderate to severe disease, or hypoproteinaemia, immunosuppressive agents are usually added to achieve a response. Oral prednisolone (1-2mg/kg PO BID) is the initial drug of choice. It is usually administered at an immunosuppressive dose for 2-3 wks and then decreased by 50% every 2-3wks, and continued on an alternate day basis for 2-3 months. If clinical response is poor, chlorambucil (6mg/m2 PO PO EOD (@2mg/5.3kg cat) and prednisone (5mg PO /cat/day) are initiated. Metronidazole (15mg/kg PO BID 10-14d then SID 10-14d) is frequently used in conjunction with corticosteroids to modify the microflora. However metronidazole is a potential mutagen and the author avoids long-term therapy.

Successful treatment is accompanied by a decrease in clinical signs and an increase in plasma proteins. Once a patient has had 2-3 months remission from signs it may be

possible to gradually withdraw immunosuppressive therapy. If signs recur daily medication is continued until signs resolve then gradually reduced. In patients who respond poorly to therapy or relapse after an initial response lymphoma should be ruled out.

### *Prognosis*

The prognosis for lymphoplasmacytic enteritis is variable and depends on its severity. Many patients require prolonged treatment with glucocorticoids and diet. As no accurate criteria exist for predicting response it is wise to give a guarded prognosis.

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Guilford? There are very few articles about IBD
2001 most info is handed down anecdotal

# Notes

## 19th Annual Fred Scott Feline Symposium

July 27 - 29, 2007

Gulland Paper 55 cats 28 (46) food sensitive
11 resolved on elim diet
46 had skin dz Histo in most mild-mod - in 2-3 days
28 food sen had peripheral eosinophilia Response
Notes from Home
Beef, corn, casein, wheat were found to be 1° trigger set dx
? no diff in cells from normal set 1:P, But Plasma cells won't be in villus unless plasma cells in villus - but need to know location, pathogenesis IBD but even that isn't concrete

Mucosal Health pathway - Ag go in, get sampled & processed - common Ag need to be recog and have response - Suppress, Tolerance or Active Immunity
these are the 3 actions
Its Happening just system to start with cells Igt from
TGF B, IL10 keep cells tighter
probiotics T secreting these cytokines

Tips of cells/villi - lots of receptors Tdl "Toll" like receptors
Cytokines TLR, PODS, NF-κB
move molecules thru cells to mesenteric lymph nodes
cell types etc.
If down regulation doesn't happen - you get sustained inflammation, nasty dz
Should measure cytokine levels relative to histo
Study shows architecture correlation to disease
So you need input on architect - not just whether lymph, plasma there - is there fibrosis or fusion
look for architech sign in histo atrophy

Th1 - CMI IL12 pro inflammatory - M Φ IL2 IFN
Th2 Allergic IL4 - Eos mast cells IL-6 IL10
very little IL4 in cats - they were surprised to see that
IL10 - anti inf IFN - ?
They made a model of cytokine factors - IL8 correlates to clinical sign - draw nets, M Φ, other cells
+ subjective grade
Stomatitis cats human & similar mix of cytokines

ICS can be used to monitor response
What drives inflam response - abnorm immune response to something -
In people: aggressive over response to subset of commensal bact in genet predisposed people
Rats of Oriental breeds along w/ DSH
Fail to down regulate response to normal gut activity
In boxers - histiocytic ulcerative colitis
some respond to CAPCs Budesonide - Enterolobium
Do Immunoflor studies - find bact invade enterocytes in mucosa in cats w/ signs
Enterobacteraceae, Clostridia - E coli
Correlates w/ architectural & cytokines T as well
Is it a cause or a consequence?
Probiotics, Ab - can they be of greater value?
So - evaluate based on architectural, cytokines, bact load - corr to clin signs/lab
Consequences -
B12 - IBD - these cats can't hang on to it
There is decreased circulation of B12 - they can't take it back in - ADR, wt loss, no GI signs - But always get
Folate - goes w/ B12, Alb - severe IBD or PLE
Other soluble Vit may be affected Vit K, E, D (other known Ca, Mg, Fe)

Systemic Inflammatory Response -
↑ IL12 TNFα IL23 -
germ amplified,
CRP doesn't work well in cats
LSA w/ IBD - Cort of Dogs, CSH - TCRC (T cell receptor gamma) to detect T cell process - you can do it from formalin samples?

# A Stepwise Approach to Treating Feline Inflammatory Bowel Disease

Managing Emerging Enteropathies

W/D/nut loss/PDR - chronic Database - often dx'ed IBS early
↓ Abs/Gis not common - if you see it IBD, pancreas
+ hypocholesteralemia
Chronic vomiting - do rads - chronic diarrhea - they don't do it PT

Q6

Diet Modifications
Global Modification - so not what it's been early meal/etc
Optimize assimilation
highly digestable bal/restriction
Lessen digestab eg MCT
fiber
Ag modification
Novel, vs hydrolysate
Immunomodulation
altered fat comp
Probiotics - Inulin, FOS

- no studies that show changed clinical sign
see change in markers -

3, 6, 6 short, Probiotic → Streptococcus etc
Lacto
Agents no studies

Other micronutrient deficiency - K, S, D
Tx - Diet doesn't work -
little evidence that metronidazole, tem,
He says rely on antibiotics Ab
Tylosin, Prednisolone, Chlorambucil, Cyclosporin

In people going to immunosuppression (azathioprine)
make apatosis resistant Tackle by giving Bud
Budesonide is absorbed

metronidazole - may break DNA in vitro
not aptotoxic but is temporarily genotoxic
what does it do to stem cells -

He doesn't use indefinitely - only short term

He hasn't seen many problems w Chlorambucil

Canal test ?? to help distemper (thru CSF, IP)
commercially available

# Diseases of the ears, nose, throat and oral cavity of cats

**Professor Richard Malik DVSc PhD FACVSc FASM**

Post Graduate Foundation in Veterinary Science, Conference Centre, Building B22, University of Sydney, NSW 2006 Australia

In human medicine, specialist clinicians deal exclusively with the diagnosis and treatment of diseases of the ears, nose and throat (E.N.T.). In veterinary medicine, such specialisation is rare, although individuals such as Dr Anjop Venker-van Haagen have started to develop E.N.T. medicine and surgery to such an extent that it is beginning to become a veterinary discipline in its own right. This talk is given from my perspective, a veterinarian mainly interested in cats, who has been forced to better understand diseases affecting the ear, nose, throat and oral cavity to best treat the patients under my care.

Diseases affecting these anatomical areas are commonplace in feline practice. The investigation of most cases requires equipment available in the majority of small animal clinics, although in some cases the availability of rigid and flexible endoscopes for examination of the external ear canal and nasopharynx facilitates investigations considerably. In the future, use of cross-sectional imaging modalities such as computer-assisted tomography (CT) and magnetic resonance imaging (MRI) is likely to contribute extra information concerning diseases affecting these anatomical areas.

**Diseases affecting the pinna, external ear canal and middle ear**

The pinna can be affected by diseases processes which affect the skin generally. Thus, lacerations are common in cats that fight, and ultraviolet-induced solar dermatitis typically results in the development of squamous cell carcinoma (SCC) in cats with non-pigmented (white or ginger) ears that spend a lot of time outdoors. This is a big problem in places like Australia and California that receive a lot of sunlight. Cats occasionally develop aural haematomas, usually as a result of irritation affecting the ear canal that results in scratching. Harvest mite infestations can cause severe irritation of the head and ears of cats; the diagnosis is easily made by identification of orange or yellow lesions on the ears of affected cats. Smears of these coloured lesions demonstrate the large, orange/yellow mites. We have also seen a small number of cats with sarcoptic mange affecting the skin of the pinna or the external ear canal; in these cases mites were extremely abundant, as in Norwegian scabies of human patients.

As a rule, otitis externa is less common in cats that dogs. However, young cats, outdoor cats and cats that live in colonies are commonly afflicted with *Otodectes cyanotis*, which results in an irritant/allergic otitis externa. A crusty black discharge is said to be characteristic, but a similar discharge can occur with other diseases of the external canal. All cats with otitis externa should be suspected of having ear mites until proven otherwise and the availability of modern, safe and effective products like selamectin and fipronil makes it worthwhile to treat tentatively for this disease even when mites are not detected. Direct visualisation of mites is facilitated by the use of a video otoscope, which provides both excellent illumination, magnification and a good depth of field. Material should also be obtained from the ear canal for cytological examination, as some mites or eggs can be seen in smears when adult mites have been missed using otoscopy. Mites are large, pearly white, very active and are said to 'run away' from the light source, although this is not my experience. A variety of modern treatments are now available for treating *Otodectes* infections e.g. fipronil, ivermectin, milbemycin and selamectin. It is important to

Harvest mites – Orange-yellow
Saprophytic mites – Very irritating –

treat the whole cat, not just the ear canal, to repeat the treatment after three weeks, and to treat in-contact cats and dogs.

Occasionally, *Demodex catii* can cause parasitic otitis externa in cats. The diagnosis is made by microscopic examination of smears from the lining of the ear canal. Usually these cats have some underlying cause for immunosupression, for example corticosteroid therapy or FIV infection. Treatment using topical or systemic therapy is generally successful. Bacterial otitis is rare in cats, but does occur, and should be treated using a combination of systemic and topical therapy. Systemic therapy is often easier and more effective in cats with irritated ears that otic therapy and this is not cost-prohibitive as in larger canine patients. Occasional cats with allergic dermatitis get otitis externa as a component of their atopy or food allergy/intolerance, and treatment should be directed at the underlying allergic condition as well as the irritated ear canal.

Proliferative lesions can sometimes be observed in the ear canal of cats. Polyps, arising from the middle ear cavity or external ear canal, can occur in cats of all ages. When removed together with their stalk, these polyps may be cured using simple traction. If a pedicle is left behind, however, the problem usually recurs, necessitating more invasive surgical interventions in order to effect a permanent resolution. In older cats, ceruminous gland carcinomas can develop in the external ear canal. This malignancy can be cured by timely ablation of the entire horizontal and vertical ear canal. Invasive squamous cell carcinoma can occur in the ear canal of elderly cats. In my limited experience, this cancer already has invaded tissues outside the ear canal by the time diagnosis is made using cytology and cross sectional imaging.

Otitis media is not-uncommon in cats, and typically results from an ascending infection up the auditory tube from the nasopharynx. Less frequently it occurs secondary to parasitic or bacterial otitis externa. Cats with middle ear infections develop signs of peripheral vestibular disease, either unilateral or bilateral. Sometimes Horner's syndrome is present also. The diagnosis is often tentative, based on characteristic clinical signs and response to therapy. In some cases, radiographs of the tympanic bullae or CT of the head are used to confirm the anatomical diagnosis. Material for culture is sometimes obtained via myringotomy or via operative bulla osteotomy. Typically, otitis media is the result of bacterial infection with organisms that normally reside in the nasopharynx, such as *Pasteurella* species and obligate anaerobes. Acute cases often respond to a two to four week course of clindamycin, doxycycline or amoxicillin/clavulanate. Some cases, however, require surgical drainage, through a bulla osteotomy or the external ear canal (via a myringotomy), to effect a cure. Recently, LeCouteur's group have shown that these infections can sometimes extend to involve the adjacent brainstem. We have seen a very small number of cats where otitis media, and sometimes concurrent otitis externa, is referable to cryptococcosis.

**Disease of the nasal cavity, choane and nasopharynx**

In young cats, viral upper respiratory tract infections are the most common cause of nasal cavity disease. Although these infections are generally self-limiting, the author recommends prophylactic therapy using doxycycline or clindamycin to prevent adverse sequellae such as pyothorax, ascending infections of the auditory tube and chronic rhinosinusitis. Recent work suggests that interferon-omega may be useful in these cases, however it is virtually cost-prohibitive at present to recommend its routine use for this purpose. The anti-herpes agent famciclovir (1/2 125 mg tablet once a day for 7 to 14 days) deserves evaluation for the treatment of cats with acute Herpesvirus rhinosinusitis.

By far and away the most common disease of the nasal cavity of adult cats is post-viral rhinosinusitis (synonyms: snuffler cat, snuffles, etc). This a chronic disease condition thought to occur as a sequellae of Herpesvirus or Calicivirus infection of the nasal passages, which

Orofacial pain – 10 m yg Barms < 5 yr
UK – phenobarb seems to help

result in extensive destruction of turbinates, leading to residual foci of infection with secondary bacterial pathogens. These cats are presented for chronic nasal discharge, sneezing and epiphora. Severe cases may also show lassitude and inappetence. Such cases are diagnosed on the basis of a history of presumptive viral respiratory tract disease and results of endoscopic, cytologic and three dimensional imaging studies. There are no definitive diagnostic features, and usually the diagnosis is reached by excluding other differentials such as cryptococcosis, foreign bodies (e.g. grass awns, projectiles) and neoplasia. Some cases can be cured by long courses of antimicrobial therapy. Because anaerobic bacteria are likely secondary invaders in many cases, clindamycin, at an anti-anaerobic dose given for at least eight-weeks, can be curative. Such long courses are only indicated if there is *an initial and sustained* response to therapy. The rationale of continuing therapy for such a long time is based on the notion that the infection is a deep-seated osteomyelitis/chondritis. Many cases respond to antibiotics, but relapse during or after a long course of therapy. Some of these cases may respond to major surgical interventions eg radical turbinectomy via a ventral rhinotomy, or implantation of antibiotic-impregnated bone cement into the frontal sinuses. Large series of surgically managed cases have not been published, however, suggesting that surgery may help in some cases, but not others. Many cats are not severely affected, and owners often elect to ignore the problem or dose affected cats with antimicrobials intermittently, as required. Again, evaluation of new treatment protocols that use antiviral agents (interferon-omega, famciclovir) in concert with antibiotics are indicated to develop more effective treatment options for this common and frustrating condition.

Mycotic rhinitis occurs in the cat, but unlike the equivalent group of infections in dogs, aspergillosis is rare while cryptococcosis is reasonably common. Cats with cryptococcosis present for signs of rhinitis such as sneezing, nasal discharge and epistaxis. Sometimes the mucosa within the naris is swollen, or there is a polypoid mass protruding from the nostril(s). Some strains of *Cryptococcus* are invasive, and give rise to deforming disease of nearby structures, such as the nasal planum, bridge of the nose, hard palate, tooth roots, while in other cases there is involvement of the regional lymph node(s). Diagnosis is readily made by cytology of nasal discharges or aspirates from swellings, and confirmed by culture on bird seed agar or using the cryptococcal antigen agglutination test. Most cases of localised nasal cryptococcosis can be cured using monotherapy with itraconazole or fluconazole. Severe or refractory cases benefit from combination therapy using amphotericin B and flucytosine, with follow-up azole therapy. In contrast to canine aspergillosis, nasal aspergillosis in the cat is often an invasive disease, with the propensity to penetrate the overlying bones and give rise to disease of nearby structures eg the retrobulbar space, nasal bridge, palate, nasopharynx. Topical therapy (such as used in the dog) is inappropriate for such infections, which instead require treatment with itraconazole and sometimes amphotericin B. The new antifungal agent posaconazole (5 mg/kg orally with food once daily) has recently been shown to be an effective agent for this condition, offering several advantages over itraconazole and even amphotericin B.

Nasal neoplasia gives rise to progressive signs of nasal cavity disease, often with extension of the malignancy to adjacent structures, such as the bridge of the nose, the retrobulbar tissues, the nasopharynx or the olfactory lobes of the brain. In our practice, lymphosarcoma is the most common nasal malignancy, followed by squamous cell carcinoma, adenocarcinoma and tumours arising from bone or cartilage. Of these diseases, lymphoma has the best prognosis as perhaps 50% of cases (or more) attain durable remissions with multi-agent chemotherapy, and indeed some can be cured. Squamous cell carcinoma is amenable to radiotherapy and some cases partially respond to carboplatinum. Bone and cartilage tumours may be treated using sumarium and/or carboplatinum.

In some cats with nasal cavity disease, there is preferential involvement of the caudal portion of the nasal cavity, the choane or the nasopharynx. These animals usually do not have nasal discharge, epistaxis or sneezing. Instead, they have signs of stertor, snoring or halitosis and in extreme circumstances they learn to breathe through their mouth. A variety of disease processes can cause these signs. Lymphosarcoma and cryptococcosis sometimes present in this fashion. On physical examination, a mass in the nasopharyngeal region can sometimes be palpated through the soft palate (typically under sedation or anaesthesia), and a needle aspirate through the palate can be diagnostic. Such masses are readily visualised using a flexible endoscope retroflexed behind the soft palate. Alternately, a vigorous nasal flushing technique often dislodges a large portion of the offending mass, which can then be submitted for laboratory investigations and histopathology. Other disease processes which can involve the nasopharynx include blades of grass (which get caught behind the soft palate after being vomited), fish bones, grass awns, polyps arising from the opening of the auditory tube, webs of scar tissue resulting from previous viral infection (giving rise to nasopharyngeal stenosis). Foreign material can often be dislodged by flushing using a 10 mL syringe tightly wedged in one nostril or removed using a retroflexed endoscope. Counter intuitively, flushing through the least obstructed nostril is often most effective in dislodging mass lesion(s) or foreign material. It is our experience that nasopharyngeal polyps do not recur if they are removed with a substantial amount of 'stalk', and if antibiotics are given for two-weeks following the procedure. Recurrent nasopharyngeal polyps generally require bulla osteotomy as well as polyp removal to effect a cure. Be warned, some cats have bilateral polyps, and other have bifid polyps with a components in both the nasopharynx and the ipsilateral external ear canal.

**Disease of the oral cavity and pharynx**

Disease of the oral cavity is common, however many lesions are missed merely because clinicians sometimes do not take the time to properly inspect every cat's mouth during routine physical examination. This is a sin we have been guilty of. Feline dentistry is beyond the scope of the present talk, however it is important to emphasise that periodontal disease is one of the most important preventable causes of disease in domestic cats and that feeding fresh raw chicken wings, lamb shanks and other 'raw meaty bones' on a regular basis is critical to the overall health of cats.

Chronic Calicivirus infection gives rise to refractory disease of the gums and fauces. In these patients, there is sufficient antibody-mediated response to virus to produce all the classic signs of inflammation, however there is insufficient cell-mediated immunity to throw off the virus and thereby eliminate the chronic carrier state. Up until recently, treatment had involved radical extraction of molar and premolars, antibiotics such as doxycycline, metronidazole or clindamycin and (when necessary) the minimal anti-inflammatory dose of corticosteroids required to dampen down the inflammation. Recent work, however, suggests that some of these cats can be cured using feline interferon-omega, or thalidomide, and these treatments can be supplemented by local administration of topical agents such as Bonjela. The natural product slippery elm has also been used with benefit in some of these cases.

Feline resorptive lesions are an important cause of tooth and gum disease in cats, and the associated pain can cause teeth chattering, reduced appetite and weight loss in some patients. The cause of these lesions is controversial, however the requirement for extraction of affected teeth is not in doubt. It should be emphasised that recent information suggests that there is no need to completely remove the tips of tooth roots that snap-off during attempted removal of affected teeth, as these are resorbed spontaneously.

Intraoral collagenolytic granulomas are a bizarre feline manifestation of allergic disease. They may be either proliferative, or ulcerative, and are typically situated on the tongue or

palate, although they can appear in any lesion within the oral cavity. I have seen one cat with a large lesion arising from the pharynx, which also had involvement of the larynx. A very characteristic feature is the presence of yellow or white foci within the larger lesion, these areas corresponding to microscopic areas of lytic collagen, and the presence of such foci is virtually diagnostic of this aetiology. Often 'rodent ulcers' or miliary dermatitis are present concurrently. Ideally, these cases should be treated by finding and eliminating the underlying cause of the hypersensitivity reaction, e.g. fleas in cases where flea antigens are the underlying immunologic trigger. When this is not possible, monotherapy using a six to eight week course of cyclosporine is successful in many cases, and has fewer side effects than older treatments regimens such as prednisolone/chlorambucil/ gold salts. In patients with proliferative lesions, preliminary debulking using a scalpel can be very helpful also.

'Menrath's ulcer' (synonym: bleeding palatine ulcer) refers to a unusual syndrome in which, for some reason, cats with allergic skin disease develop life-threatening bleeding from an ulcer on the palate immediately adjacent to the upper canine tooth. It is thought that over grooming associated with pruritic skin disease somehow results in the papillae on the tongue abrading the hard palate until a branch of the palatine artery is eroded. When this occurs, significant haemorrhage results, however because the cat continues to lick the ulcer and therefore potentiate the haemorrhage. Because the blood emanating from the bleeding ulcer is swallowed, the owner (and veterinarian!) may not appreciate the cause of the bleeding until the cat is almost dead. By this stage, a typed blood transfusion may be required to save the patient. On-going haemorrhage is best controlled by placing a horizontal mattress or cruciate stich (using deep bites) across the ulcer so that ensuing pressure stops the haemorrhage. The ulcer can be hard to appreciate when the gums are very pale as a result of hypovolaemic shock and anaemia; for this reason, a thorough oral cavity examination is mandatory in all cats presented for severe (and typically acute) anaemia. To prevent this problem recurring in the future, efforts of the clinician should be directed towards treatment of the underlying skin disease e.g. using flea control, hypoallergenic diets, antihistamines, corticosteroids or cyclosporine, as appropriate.

The tongue can be affected by a variety of disease processes, and experienced feline clinicians routinely elevate the tongue using digital pressure in the intermandibular space to facilitate examination of the frenulum. Doing this routinely will ensure that linear foreign bodies caught around the lingual frenulum will never be missed! Squamous cell carcinoma (SCC) is the worse disease process which can affect the tongue, and typically affects its base. However, inflammatory diseases resembling lingual SCC have been encountered by the author. These lesions, which may result from secondary infection following penetration by foreign bodies, have responded promptly to debulking (biopsy) and antimicrobial therapy. We have been surprised recently to have diagnosed lingual lymphoma (rather than SCC) in a cat with a grossly abnormal tongue; this patient responded favourably to multi-agent chemotherapy.

Finally, tonsils should be examined during routine oral cavity examination. Tonsillar SCC occurs in the cat, although most cases the author has diagnosed have been presented for unilateral mandibular lymphadenomegaly. The cause of metastatic disease was not apparent until the oral cavity was examined.

Bleeding palatine ulcers — assoc ME's
Overgrooming
TE deep horizontal or conchoidal stretch
across lesions - Transfusion, Tx underlying allergy
Stomatitis?
Viral - antiviral Tx  Interferon Sub mucosal

Review of what cardiologist do — 2006? EVim

80% of SAM – get Beta Blockers

50% in CHF

23/43 said they did it based on personal experience

17/43 " no one believes but

23/43 " in consensus – no one objects –

based on responses to people

21/43 Cats spironolactone – facial excoriation

Thinks physiologic measurable change

eg gradient reduction – but paper

people showed actually made worse

CCS's Heart failure Smith et al 2004 from MN

Retrospective N = 12

7 surviving cats had transient Δ in chamber size that looked like

HCM, then resolved – was it Viral ~~induc~~ myocarditis after flu

stress

Subsequent study 2006 ?

He did study ~~@~~ Rochester Medical – Didn't see any Δ in thickness

Rishniw

**Feline Cardiology – what's new, what's real, what's not**

**Feline Hypertrophic Cardiomyopathy**

Feline HCM is the most common acquired feline cardiac disease. A familial cause exists, although DSH cats without a family history are often affected, making genetic associations difficult to prove.

***Genetic Diagnosis of HCM – blood tests for cardiac disease.*** A genetic cause of HCM was identified in a colony of Maine coon cats in 2005 (Meurs et al, 2005). A mutation in Myosin Binding Protein C was identified as the cause, and a diagnostic PCR test was developed (http://www.vetmed.wsu.edu/deptsVCGL/) to help identify affected Maine coon cats. More recently, Ragdoll HCM was also associated with a mutation in Myosin Binding Protein C (Meurs et al 2007). The mutation was different from that found in Maine coons, suggesting that it was not inherited from a common ancestor. A PCR test for the Ragdoll mutation is also available through the WSU site.

Initial screening of affected Maine coon cats was promising, however, several clinically affected cats from the original colony do not have the MyBPC mutation. Thus, it is likely that at least one other mutation is responsible for some of the HCM in Maine coons. Whether all Ragdolls with HCM have one mutation or more is unknown at this time. HCM in other breeds remains genetically undetermined. Given the huge number of mutations (>250) spanning 13 different myocardial proteins that have been identified in humans with HCM, it is likely that other cat breeds will have different mutations that account for their disease.

***NT-proBNP – don't throw away your stethoscope and X-ray machine just yet.*** A recent advance in cardiac diagnosis has been the introduction of a blood test for the diagnosis of CHF. NT-proBNP (marketed by VDxI as CardioCare) is being sold as a biomarker of cardiac disease and CHF. However, virtually no data exist for cats with HCM – most of the information the company is using is a small unpublished study performed in the UK. Most studies have examined canine heart disease and heart failure. From evidence presented at ACVIM 2007 forum, the current decision limits for dogs are too low to discriminate between heart failure and respiratory causes of dyspnea. It is probable that similar issues will exist for cats with HCM. Whether NT-proBNP will aid in the diagnosis of subclinical HCM is to be determined.

***Advances in Therapy of HCM.*** There is little evidence for therapy of HCM in cats. Most studies dealing with clinical outcomes have been conducted in cats with CHF (Bright et al 1991, Fox et al 2003), while one study examined cats with more modest disease (Amberger et al 1999). Recent studies in Maine coons with subclinical HCM failed to show any change in cardiac mass as a result of ACE-I therapy (MacDonald et al, 2006). No studies exist demonstrating any benefit of therapy prior to onset of HCM. Nonetheless, beta blockers, calcium channel blockers, anti-thrombotics and ACE-I are commonly used in subclinical HCM by veterinary cardiologists and non-cardiologist veterinarians. Most admit to having no strong basis other than belief for the use of these agents. Studies examining clinical outcomes of therapy of subclinical HCM are sorely needed.

It's not science it's gossip

***Advances in Diagnosis and Therapy of Feline aortic thromboembolism (FATE).***
FATE is a devastating sequel of HCM. Approximately 7-15% of cats with severe HCM will develop FATE. However, no studies exist that reliably predict or identify cats at high risk for FATE, and no studies currently exist demonstrating a treatment benefit. Recent echocardiographic studies have shown that left auricular flow velocities are predictive of development of spontaneous echocardiographic contrast (SEC) in cats (Schober et al 2006). SEC is considered to be a risk factor for thrombosis and FATE. Separate studies have shown that cats with HCM and SEC have similar coagulation abnormalities to cats with acute FATE (Stokol et al, unpublished data). Taken together, these studies may help identify "at risk" cats that might benefit from early intervention with antithrombotic agents.

Which antithrombotic agents to use is also debated. Aspirin appears to have no effect, although there are no controlled trials showing benefit of aspirin. Low molecular weight heparins (enoxaparin, dalteparin) may or may not be effective. Recent studies have demonstrated that therapeutic concentrations of dalteparin are sustained for only a short time, if at all, using current dosing protocols (Alwood et al 2007). Data from 2 separate studies at the same institution suggests that there is no LMWH and aspirin are equally (in)effective (Smith et al, 2004, Rush et al 2002). FAT CAT is an ongoing placebo-controlled clinical trial examining the effect of clopidogrel (Plavix) in prevention of FATE recurrence in cats that have already survived an initial event. Cats can be enrolled into FAT CAT from anywhere in the world (http://www.vin.com/FATCAT). Interim analysis of the outcomes of cats in each arm of the trial failed to demonstrate any survival benefit of Plavix administration, however only a few cats have reached the endpoint at this time.

***Steroids and HCM – fact or fiction ?***

Two retrospective studies have suggested a temporal association between the development of CHF in apparently normal cats and the administration of glucocorticoids (Rush et al 2002, Smith et al 2004). One of these suggested a reversible hypertrophy was present in some of these cats. Anecdotal evidence from practitioners suggests an association may exist between administration of glucocorticoids and development of CHF. One of the authors of the initial studies examined the effects of glucocorticoids in cats presenting to the dermatology service to receive glucocorticoid injections (Smith et al 2006). They identified an increase in plasma volume in these cats. They claimed that the cause of the plasma volume increase was associated with a transient hyperglycemia, rather than any mineralocorticoid effect (since methylprednisolone acetate [MPA] does not have mineralocorticoid effects). However, the study is flawed methodologically and statistically.

We recently performed a study of the effects of MPA in healthy research cats. Cats were injected with 30mg MPA intramuscularly, and observed for 8 weeks. Serial echocardiograms before and after MPA administration showed no difference in chamber dimensions indicative of volume overload. Total body water and extracellular fluid volume were measured (data currently unavailable). Our data suggest that there is no significant increase in cardiac volume following MPA administration.

Whether glucocorticoids can induce the onset of CHF in cats with subclinical HCM remains to be determined.

**Feline Heartworm Disease – looks awfully like asthma!**

Feline Heartworm Disease (FHWD) is a difficult diagnosis at the best of times. Cats harbor few worms, are usually amicrofilaremic, and antigen negative. Antibody positivity is not indicative of infection, but merely exposure, as antibodies will develop in response to L3 and L4 larvae. Clinical signs are variable, ranging from completely subclinical, to sudden death. Coughing (+/- vomiting) have been reported. Respiratory distress is reported. Radiographically, there may be pulmonary artery enlargement and pulmonary infiltrates.

Recent data show that cats inoculated with L3 larvae will often develop pulmonary infiltrative disease within 90 days of exposure, even if the larvae (L5 stage) are not allowed to mature to adult forms. Cats in which larval development was arrested prior to maturation developed radiographically and pathologically evident pulmonary vascular and interstitial lesions (Dillon 2007). This study suggests that pulmonary inflammatory disease can occur as early as 70-90 days post infection in cats, often mimicking feline asthma, even in the absence of maturation of larvae to adult forms. However, whether clearance of the immature forms ultimately results in clinical resolution is unknown – in this study, cats still had lesions 240 days after infection (and 150 days after larvicidal therapy). In endemic areas, HWD should be considered a cause of pulmonary disease even if adult worms are not identified.

**Feline Murmurs – now you hear it, now you don't**

Dynamic murmurs are commonly ausculted in cats. There are 2 known causes of dynamic murmurs – Dynamic RV obstruction (DRVO), and Systolic Anterior Motion of the mitral valve (SAM). These cannot be distinguished by auscultation and may or may not be associated with primary cardiac pathology. The prevalence of murmurs (dynamic and static) in cats in the general population is currently unknown – one small study found murmurs in 22% of cats (22/103), and 6 of 7 cats in this study that underwent echocardiographic evaluation had cardiac disease (Cote et al 2004) . Whether this translates into a wider population of cats is unknown.

ACVIM consensus statement JVIM 2007
mBP – validating machines is lacking~

Nemoprin – BP machine in Europe – holds promise

# *Nocardia* infections in cats

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**Introduction**

*Nocardia* spp are a genus of aerobic actinomycetes responsible for localised or disseminated infections in animals and humans.[1-10] The genus is named after Edmond Nocard, a French veterinarian working in the Canary islands, who in 1888 described the isolation of such an organism from bovine farcy, a lymphangitis of the distal limbs of cattle. Cases of human disease have increased substantially in the last two decades in association with an increasing population of immunocompromised hosts,[11] and the same is likely to occur in companion animal practice with the increased treatment of immune-mediated disease and cancer with corticosteroids, cyclosporine and cytotoxic drugs.

Information concerning companion animals with *Nocardia* infections is very limited compared to data available for human patients.[7-10] Although there are numerous well documented examples of infections in individual patients,[12-25,27-34,37,38] very few studies record a substantial number of well documented consecutive cases.[9,12,21,26,35,36] Thus, meaningful generalisations can not be drawn concerning pathogenesis, predispositions or therapy, especially in relation to disease in the cat. Furthermore, a meta-analysis of individual case reports may create a misleading overall picture, especially when cases are drawn from widely disparate geographic locations.

The aerobic actinomycetes are a large and diverse group of Gram positive bacteria which appear on microscopy as branching, filamentous cells. Members of the group are, however, often only distantly related phylogenetically. A subgroup, the "aerobic nocardiform actinomycetes", is the most important cause of mammalian infections, and includes *Mycobacteria, Corynebacteria, Nocardia, Rhodococcus, Gordona* and *Tsukamurella*.[1,2] All members of this group have cell walls containing meso-diaminopimelic acid, arabinose, galactose and mycolic acids of various chain lengths. The latter are responsible for varying acid fastness evident with appropriate staining. *Nocardia* spp are characterised additionally by an ability to grow in media containing lysozyme, production of urease, inability to grow at 50°C and formation of aerial hyphae that accounts for their characteristic colonial morphology on primary isolation.[3-5] In contrast, *Actinomyces* spp, which appear morphologically similar to *Nocardia* spp in Gram stained smears, grow either as obligate or facultative anaerobes.[1]

There has been a revolution in the taxonomy of *Nocardia* in recent years. Traditional laboratory methods for identification of *Nocardia* spp based on simple biochemical reactions and hydrolysis tests are limited in their ability to differentiate these organisms or to identify newly described species.[40] In particular, isolates belonging to the *Nocardia asteroides* complex cannot be differentiated in the routine laboratory.[41-46] In the last few years, an expanded range of biochemical and susceptibility tests, chromatographic analysis of cell wall components[47] and especially the application of new molecular techniques (particularly 16 rRNA gene sequencing) has expanded the spectrum of *Nocardia* spp with in excess of 30 species described. [48-52] Of these, the *N asteroides* complex (*N cryiacigeorgica* [*formerly N asteroides* sensu stricto], *N farcinica, N nova,*),[41-45] *N abscessus, , N transvalensis* (these three formerly included in the *N asteroides* complex), *N brasiliensis, N pseudobrasieliensis, N veterana, N africana* and *N otitidiscaviarum* (formerly *N caviae*) are the most important causes of infections in people and animals. Importantly, these different taxonomic groups are correlated with disease features and therapeutic outcomes.[1-6]

*Nocardia* are ubiquitous environmental saprophytes, occurring in soil, straw, grasses, decaying vegetable matter and water, where they comprise an important part of the microflora by breaking down organic matter and recycling nutrients. Members of this genus are metabolically versatile, with enzymatic machinery enabling them to digest herbicides, pesticides and synthetic polymers. Importantly, and unlike *Actinomyces* species, they are never a part of the normal flora of mammals, although they may be carried mechanically on the skin or claws of animals. Infection usually arises from direct inoculation of the skin or soft tissues following penetrating injuries, or by inhalation of aerosols containing organisms, possibly in dust. Fragmentation of branching nocardial filaments late in their growth cycle results in the formation of small, unicellular, spore-like cells that are easily aerosolised. [1-6]

*Nocardia* spp are facultative intracellular pathogens. A major virulence factor for these organisms is the resistance to phagocytosis of filamentous log phase cells, such as those found in environmental niches such as soil. Indeed, log phase cells are two orders of magnitude more virulent that stationary phase cultures. Complex lipids found in their cell wall contribute to virulence in a manner akin to the mycolic acids characteristic of the mycobacteriace. The nocardial envelope is structurally similar to that of other actinomycetes, with 15 to 25% of the cell wall mass comprised of peptidoglycan. Mycolic acid polymers, such as trehalose-6,6'-dimycolate ('cord factor'), are members of a group of virulence-associated, biologically active, cell wall constituents found in many actinomycetes including *Nocardia* spp and the mycobacteria. They are toxic *in vitro* and in animal models and contribute to inhibition of phagosome-lysosome fusion, acidification and oxidation in macrophages. Another important feature of *Nocardia* that impacts on the lesions they produce is their propensity to invade blood vessels and thereby produce vascular necrosis and ischemia.[4,6,8]

The life cycle of *Nocardia* results in late fragmentation of the filamentous bacterial forms; long, beaded rods are therefore often seen in purulent exudates. Sections of tissues infected with *Nocardia* spp usually demonstrate acute pyogenic inflammation. Branching, beaded, filamentous bacteria may be demonstrated within abscesses or from draining sinus tracts in smears stained with DiffQuik® or Burke's modification of the Gram stain. "Sulphur granules" (bacterial macrocolonies) may be found in exudates from *Nocardia* lesions, although less commonly in animal than in human patients. *Nocardia* spp will usually stain at least somewhat acid-fast in tissue sections; in contrast, *Actinomyces* spp and other anaerobic actinomycetes do not.[53]

The protective immune responses of mammalian patients to Nocardia are primarily T-cell mediated, as these organisms elicit little in the way of an effective humoral response. Hence, nocardiosis is especially problematic in patients with impaired cell-mediated immunity. The outcome of infection is largely determined by the ability of a given strain to resist the initial neutrophil response of the host and subsequent attack by activated macrophages. Early neutrophil mobilisation, while often insufficient to abort infection in itself, limits the extent of infection until lymphocyte-mediated cytotoxicity and activated macrophages effect a definitive response.[4,6,8]

In human patients, members of the *N asteroides* complex are responsible for about 80% of non-cutaneous invasive disease, and for most systemic and central nervous system infections. There are systematic differences in the antimicrobial susceptibility patterns and virulence for the species within the complex.[41-46] In particular, *N farcinica* has a more resistant antibiogram (resistant to tobramycin and 3rd generation cephalosporins, but susceptible to ciprofloxacin and imipenem), growth at 45°C in 3 days, striking virulence in animal models and human patients, a strong tendency to disseminate and different epidemiology.[41,43,44] *N nova*, on the other hand, is susceptible to erythromycin (with a zone of inhibition greater than 40 mm using a 15µg disc) and often to the tetracyclines and penicillins.[46,48] *N brasiliensis* is the most often-reported cause of cutaneous and lymphocutaneous disease in people, and is more common in tropical regions, including Australia.[3,5,6] Importantly, superficial nocardiosis following

implantation is not necessarily associated with compromised cell-mediated immunity, but may progress to disseminated disease in that setting.

Ubiquitous in soil and dirt, nocardiae can establish superficial infection following relatively trivial inoculation injuries, which may vary from insect bites, animal scratch or bite wounds,[73-76] puncture wounds and contaminated abrasions. Since the initial response to *Nocardia* is pyogenic, self-limiting skin lesions may initially be disregarded or treated as staphylococcal in origin. In small animal patients, *Nocardia* species have been associated with the following syndromes[7,8]: i) infections of the skin and subcutis following penetrating trauma; ii) pneumonia and purulent pleurisy (pyothorax),[39] possibly related to inhalation of grass awns or dust, and possibly in association with a co-factor such as concurrent viral disease;[9,12] iii) peritonitis;[29] and iv) disseminated disease (involving two or more body systems, sometimes including the skin, and likely starting in the lung). Purulent pleurisy/pneumonia and cutaneous/subcutaneous nocardiosis are by far the most common forms of disease reported in companion animals. The latter may initially start as an abscess; however it frequently develops into a discharging, non-healing wound, sometimes following preliminary veterinary intervention. The initial lesion tends to spread circumferentially, or by the development of contiguous satellite lesions or via the lymphatics. Draining sinus tracts often develop subsequently. There is a strong resemble in terms of clinical behaviour with what is described in human patients as "Madura foot", or actinomycotic mycetoma, although the lesions are not necessarily on an extremity. In human patients, such lesions, once established, become relentlessly progressive over a period of years and frequently do not respond to antimicrobial therapy. The differential diagnosis of subcutaneous nocardial disease in small animals includes infections with agents that incite pyogranulomatous inflammation such as Mycobacteria,[77,78] *Rhodococcus* spp, *Corynebacterium* spp and saprophytic fungi.[79] Disseminated disease is typically associated with a primary pulmonary focus with haematogenous spread to a range of tissues, typically the skin/subcutis, kidney, liver, spleen, lymph nodes and brain.[2,5]

Data from veterinary textbooks purport that *Nocardia* infections are caused by *N asteroides* or *N brasiliensis* (mainly the former), associated with 'sulphur granules' and are more common in dogs than cats.[7,8] However, this data is based on many reports prior to 1990, which predate the taxonomic reclassification of this genus. A variety of features in these publications are not in accord with our clinical experience. For this reason, cases encountered by the authors over the last 14 years were reviewed and from 2000 the senior author actively sought out additional data on similar cases encountered by colleagues in practice. This paper presents an analysis of the data from this survey. The data was scrutinised with the aim of developing a clearer understanding of the host:parasite:environment relationship for *Nocardia* spp encountered in Australia in relation to different mammalian hosts.

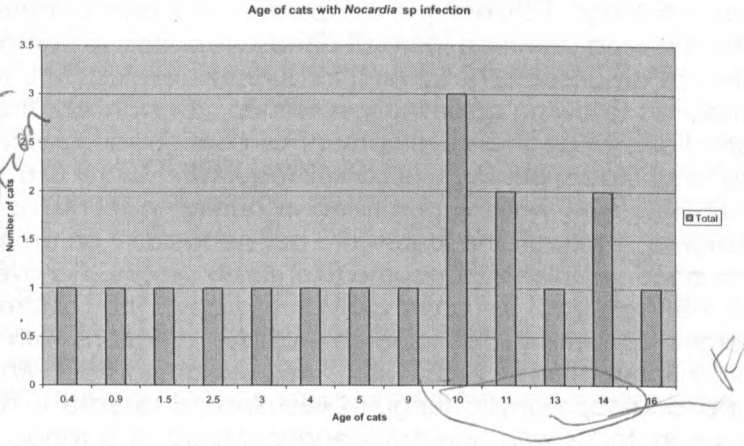
**Retrospective study of 17 new cases from Australia**

Our retrospective analysis identified 17 feline cases between 1990 and 2004. Interestingly, there were no isolates from dogs submitted to our laboratory during the study period. There were, however, one isolate from a koala (with pneumonia and purulent pleurisy) and two from dairy cows (both with mastitis). We recovered freeze dried isolates from five dogs with *Nocardia* infections from the 1950s (1953-septicaemia; 1953-no clinical history; 1953-sinus on hind limb; 1955-prescapular lymph node and lung; 1957-pyothorax and lung abscess), and a further case of bovine mastitis from 1978, but case notes for these cases were irretrievable. Interestingly, of these eight non-feline cases, six (75%) were *N nova* infections.

Most cats presented with slowly spreading lesions of the subcutis and skin associated with draining sinus tract(s). Early lesions consisted of circumscribed abscesses. The infection spread at a variable rate, generally by extension to adjacent tissues, possibly via the lymphatics. Skin overlying infected tissues sometimes sloughed. Cytological examination of exudate from draining tracts showed pyogranulomatous inflammation and evidence of tissue necrosis. The clinical course of cases was highly variable, from chronic, indolent, localised disease to

fulminating disseminated infections. Most cases would have at first have been classifiable as limited, local infections secondary to penetrating injury.

Of the 17 cats, there were 13 domestic shorthairs, three pedigree cats (1 Siamese, 1 Persian cross, 1 British shorthair), while the status of one cat was unrecorded. The was a marked preponderance of male cats (12 castrated, 1 entire young adult, 1 entire kitten); the remaining three cats were spayed females. The age of affected cats ranged from 5 months to 16 years (median 10 years). Thus, 9 of 17 cats were 10 years-of-age or older. The key epidemiologic points were that male cats were over-represented within the cohort but that pedigree cats were not, compared to our reference hospital population. Without doubt, *Nocardia* infections were more common in cats than dogs.




**Age distribution of 17 cats with *Nocardia* infections**

The breakdown of *Nocardia* isolates by species was as follows: 9 *N nova*, 3 *N farcinica*, 2 *N cryiacigeorgica*, 1 undetermined (antibiogram suggestive of *N nova*) and 2 insufficient data retrievable. Overall, at least 9/17 (53%) and probably more than 10/17 (>59%) were *N nova* infections. The acute case with rapid progression and likely dissemination was a *N farcinica* infection. The susceptibility data for our strains were in general agreement with what has been published for strains of *Nocardia* isolated from human patients, as expected for a saprophytic pathogen.

In terms of possible predispositions, of 16 cats where sufficient information was retrievable, immediate and/or predisposing causes could be identified in all cases (as follows): renal transplant (cyclosporine, azathioprine, methylprednisolone) [1 cat]; chronic corticosteroids [3 cats] – inflammatory bowel disease progressing to lymphoma [1 cat], allergic dermatitis [1 cat]; plasmacytic stomatitis (with chlorambucil) [1 cat]; weight loss/low fat diet following chylothorax surgery [1 cat]; fight injuries [7 cats]; FIV infections [3/7 cats tested]. Thus, corticosteroids, cytotoxic drugs, likely long-standing FIV infection (all FIV-positive cats were older than 10 years), and possibly age *per se*,were identified as potential predisposing factors. Penetrating trauma, typically from cat bites or scratches, has been witnessed or suspected in the majority of skin/subcutis infections. Predisposing causes for the two cases with respiratory involvement could not be determined with certainty, although viral respiratory disease was a possibility in the kitten. The abdominal case may have resulted from penetrating injury as there was a 2 cm nodular lesion within the tissues surrounding the umbilicus.

In terms of the anatomical distribution of the lesions, 14/17 infections involved the skin and subcutis, while the remaining three cases consisted of an abdominal mass [1 cat], a sinonasal infection [1 cat] and pneumonia with purulent pleurisy [1 cat]. In two cases, skin lesions may have been the primary site of infection or a manifestation of a disseminated disease process. The lesions of the skin/subcutis were as follows: right hind limb – toe, right tarsus, nasal planum

and bridge of nose, right side of chest and medial thigh, distal limbs, angle of jaw/ventral high cervical, peri-auricular, metacarpal/tarsal pads of all feet, inguinal fat pad and lateral flanks, forelimb and inguinal panniculus. Clearly, infections of the skin and/or subcutis comprised the vast majority of cases, although the upper and lower respiratory tract and abdominal cavity could be affected also. Furthermore, the sites of infection were those expected from cat fight injuries, sites of penetrating trauma from walking on sharp objects (distal limbs) or possibly from mechanical inoculation via insect bites (nasal planum).[80]

It was of great interest that three cases with nocardial panniculitis were very reminiscent of rapidly growing mycobacterial infections in term of anatomy, lesion appearance and cytopathology; in people such lesions would be described as actinomycotic mycetomas. Two were caused by *N farcinica*, while the third was caused by *N nova*.

Several of the cats with *Nocardia* infections had secondary disease manifestations. Two cats had uveitis/keratitis; both had *N nova* infections. One cat had increased ALP and ALT activity, fever, jaundice and microangiopathic haemolytic anaemia; this patient had acute, severe disease due to *N farcinica* with sepsis, vascular injury and possibly dissemination to the liver.

Of the 17 cats: three were cured or probably cured (including one that subsequently drowned in a swimming pool and had no residual disease at necropsy); four were thought to be cured but recurred after several months (one of these responded partially to second course of therapy but was euthanased because of renal failure; three are currently receiving a second course of therapy); two cats partially responded to therapy but was euthanased, while another was improving when it died of diabetic complications secondary to treatment of renal allograft rejection; two died despite therapy (the cat with disseminated *N farcinica* infection and the kitten with pyothorax); two were euthanased (one without therapy which was found to have concurrent lymphoma at necropsy); for three cats there were either insufficient records or the patients were lost to follow up.

Certain qualitative observations can be made following a detailed analysis of the case notes. Many patients started with localised infections of limited virulence. Most of these were caused by *N nova or N cryiacigeorgica*. If treated appropriately, there was often a prompt response to therapy, even in the setting of immuncompromise. However, if definitive treatment was delayed or inappropriate because of misdiagnosis, infections became chronic, extensive and often refractory to medical and surgical interventions. Indeed, recurrence following appropriate and apparently successful therapy was common and problematic. The cat suspected of having a disseminated infection due to *N farcinica* died despite timely therapy with appropriate antimicrobials, although in hindsight this cat may have benefited from intravenous therapy using amikacin and imipenem. It is worth emphasising that amoxicillin clavulanate and the flouroquinolones were found to be ineffective in treating all *Nocardia* infections in which they were utilised.

**Metanalysis of 21 feline cases reported previously from Australia and overseas**

In general, there were many similarities between the series of cases reported here, and those cases reported previously, apart from a broader range of *Nocardia* sp represented in the literature. The latter observation may be attributable to the tendency to report a *Nocardia* case because the species isolated had never previously been described as producing disease in the cat. In the metanalysis cohort, there was a striking preponderance of male cats. Interestingly, although there was a wide spread of ages, many of the cats were older than 10, which is counterintuitive if fighting *per se* is thought to be the principal predisposing event. Insufficient cases were tested for retroviruses to make any comment concerning this potential predisposition. Of the 21 reported cases, ten cats had lesions of the skin or subcutis (abscesses or actinomycotic mycetomas), four had pulmonary disease (nodular lung lesions or empyema), one had peritonitis while two had disseminated disease. The clinical course of cases was highly variable, from chronic, indolent, initially localised disease of the subcutis to

acute and fulminating infections. There was clear evidence of spread to contiguous tissues, especially when definitive diagnosis was delayed and inappropriate therapy implemented, e.g. surgery without effective antimicrobials or corticosteroid administration. Spread was by local extension, and possibly via the lymphatics based on the anatomic distribution of lesions. Although some cases had sulphur granules in wound exudates, many did not. The prognosis appeared to be guarded overall, and of the limited number of cases that responded, all but one were treated using trimethoprim-sulphonamide combinations (dosage range: 15 to 40 mg/kg twice daily) as the chief component of therapy; the remaining cat was treated using clarithromycin. Several reports utilised ampicillin or erythromycin, either in concert with TMP-sulphonamide, or in sequential therapy. A weakness of many reports was the unrecorded period of follow-up, which made commenting on the propensity to recur impossible.

**Discussion**

A number of new, important findings were evident from this study of *Nocardia* cases. Penetrating injury or fight wounds, presumably contaminated by dirt, were responsible for most infections of the skin and subcutis, and possibly the abdominal cavity. One cat had lesions on the nasal bridge,[79] a region recently shown to be associated strongly with cat scratch injuries, while lesions that started in the inguinal panniculus region may have arisen due to contamination of raking injuries inflicted by the hind limbs. There have been a number of recent papers that have emphasised that the claws of cats may act as mechanical vectors and inoculate *Nocardia* spp into the skin and subcutis of human patients,[73-76] and the same is likely also for affected felines. The cat with abdominal involvement may have been bitten through the full thickness of the abdominal wall. In contrast, infection of the sinonasal region and lungs presumably resulted from nasal or alveolar deposition of infectious propagules from dusty environments harbouring fragmented nocardial elements.

A pertinent new observation was that *Nocardia* spp were capable of producing gross lesions indistinguishable from the panniculitis syndrome traditionally associated with rapidly growing saprophytic mycobacteria such as *M smegmatis*, *M fortuitum* and *M chelonae*. Lesions were present in either the inguinal region or the body wall, multiple draining sinus tracts were prominent, infections appeared centred on the fatty subcutaneous panniculus and organisms were present microscopically in lipid vacuoles in association with pyogranulomatous inflammation (including Langerhans type giant cells). This suggests that, like rapidly growing mycobacteria, *Nocardia* spp may favour anatomic regions high in fat. The resulting lesions in affected cats bear many similarities to the actinomycotic mycetomas described in people, where the condition tends to occur barefoot rural workers. However, unlike the situation in people, *N brasiliensis* is not the culprit. The importance of cytology and culture in such cases can therefore not be overemphasised, as choice of antimicrobials is very different for the respective classes of microorganisms. A similar case has been described in the early literature, but with a focus on microbiology rather than clinical aspects,[16] while the presence of *Nocardia* filaments in a lipid vacuole is mentioned incidentally of a human case report.[68]

Cats were much more likely to become infected than dogs in our case recruitment area. This reason for this is currently unclear, and stands in contrast to textbook accounts of disease being more common in dogs than cats. Most texts refer to the large series of 53 cases reported by Beaman and Sugar, in which distemper was said to be an important predisposition. The extremely low prevalence of distemper (and other viral respiratory pathogens) in eastern Australia may have therefore explained, in part, the lower frequency of canine nocardiosis. The discrepancy may also be referable to a high frequency, in certain regions, of *Nocardia* infections of the lungs and pleura subsequent to inhalation of grass awns contaminated by soil or dirt. The situation may have been different in the 1950s, as all five small animal isolates from our archival collection of organisms had been collected from dogs. It is worth stating also that pyothorax much more common in cats than in dogs in our case recruitment area, and most cases are polymicrobial anaerobic infections.

Male cats were markedly over-represented in comparison to female cats. A similar preponderance of males is seen in canine nocardiosis[9] and in our metanalysis of published cases. The striking preponderance of male cats may reflect their greater likelihood to roam, fight and sustain penetrating injuries, especially when young adults, although alternately it couldreflect the tendency for FIV-related immunosupression to be a predisposing cause in certain patients. There appears to be a tendency for older cats to be at increased risk for developing *Nocardia* infections. As younger cats are more likely to roam and fight, and hence to sustain predisposing wounds contaminated by soil, another mechanism must account for just over half the cases being in excess of 10 years-of-age at diagnosis. Perusal of the patient characteristics suggest that the presence of concurrent disease, either long-standing FIV infection or chronic inflammatory disorders requiring immunosuppressive therapy is likely to account, at least in part, for this predisposition. Many of the cats were receiving long-term corticosteroid therapy for conditions such as inflammatory bowel disease, plasmacytic stomatitis, allergic dermatitis and as a component of anti-rejection therapy in the setting of renal transplantation. The high proportion of cats with an identifiable cause of immunosupressioncomprising at least 7/15 cats for which sufficient information was av ailable, is in contrast to the majority of the saprophytic infectious diseases studied previously by our group such as cryptococcosis and mycobacterial syndromes.[77,78] It is worth mentioning also that rapidly growing mycobacterial infections are more common in female cats, presumably because they are more likely to be obese, and that on the whole younger cats tend to be affected (need data from old paper). Pedigree cats were not over-represented within this cohort, suggesting that unlike infectious diseases such as cryptococcosis[81] and feline infectious peritonitis, subtle immune defects in purebred cats are generally not involved in predisposing to infection with saprophytic opportunistic pathogens.

A fascinating observation was the large proportion of *N nova* infections, echoing the recent paper based on a much smaller number of cases[21] by Hirsh and Jang from a part of North America climatically similar to eastern Australia. At least 59% of our feline cases were caused by this species, and 75% of non-feline *Nocardia* infections in animals were likewise caused by *N nova*. Interestingly, the antibiograms of two isolates from Australian cats reported previously with *Nocardia* infections were typical of *N nova*.[30,73] This observation should be seen in contrast to data from human patients. Of specimens submitted to Queensland Mycobacterium Reference Laboratory from 1998 to 2002, there were a total of 518 *Nocardia* isolates: 274 respiratory and 214 from wounds (mostly of the hands and feet). From wounds, the breakdown of species was: *N asteroides* 8%, *N brasiliensis* 74%, *N farcinica* 5%, *N nova* 7%. From respiratory infections, the breakdown was: *N asteroides* 41%, *N brasiliensis* 3%, *N farcinica* 20% and *N nova* 27%. Not only is *N nova* the most common Nocardiae affecting cats in Australia, it is markedly overrepresented in feline subcutis infections compared with human wound infections. (9/17 v 15/217; P = .... using Fishers Exact test). The reason for this is not currently understood, but probably reflects the frequently with which this species in encountered in dirt or soil frequented commonly by cats. Similar considerations likely account for the over representation of *Mycobacterium smegmatis* versus other rapidly growing mycobacteria such as *M fortuitum* in cats compared to people.[77,78]

The antibiogram obtained in our laboratory provided an early indication of *N nova* infections, as isolates tended to have a 'favourable' antibiogram, with susceptibility to sulphonamides, tetracyclines (minocycline, doxycycline), macrolides (erythromycin, clarithromycin) and paradoxically ampicillin and amoxicillin but not amoxicillin clavulanate. *N nova* strains were generally resistant to fluoroquinolones. Clearly, this specific antibiogram is of great moment with respect to therapy. The *N nova* susceptibility pattern permits use of lower and therefore more tolerable doses of TMP-SMX because the sulphonamide can be given in concert with another agent such as clarithromycin or amoxicillin. A variety of drug combinations, given simultaneously or sequentially, can therefore be utilised in *N nova* infections, creating many options for long term treatment of affected cats. The failure of amoxicillin clavulanate to work *in vitro* or *in vivo* is apparently related to the potent induction of chromosomal membrane-bound β-lactamase by clavulanic acid, and certainly it has been our experience that

amoxicillin clavulanate is ineffective in treating infections caused by this species, as are the fluoroquinolones.

The majority of cats with *Nocardia* infections had a witnessed or suspected penetrating wound, usually as a result of a cat bite or scratch. As cats that tend to fight are also at increased risk of acquiring FIV infection, the interpretation of any potential direct association between FIV infection and nocardiosisis problematic , especially in the absence of data such as the CD4 count or viral load. The importance of pre-existing immunosuppressive drug therapy or concurrent disease (lymphoma, renal disease) in the study cohort is also difficult to interpret with certainty. Immunocompromise is a well-established risk factor for nocardiosis in human patients, and the same is likely true within our feline cohort. In human medicine, *Nocardia* spp are considered to be opportunistic pathogens, which tend to cause localised disease in normal hosts and more serious and/or disseminated disease in settings such as corticosteroid therapy, organ transplantation and lymphoid neoplasia. A compilation of over a thousand randomly selected cases from the human literature showed that more than 60% of nocardiosis cases are associated with pre-existing immune compromise, ranging from alcoholism and diabetes to organ transplantation and AIDS.

A number of key points concerning case management, response to therapy and prognosis can be made from a review of the patient records. Positive confirmation of the diagnosis by culture and appropriate susceptibility testing was very helpful, especially in cases where antibiogram provided several alternate drugs suitable for long-term oral therapy. Delays in making a definitive diagnosis significantly compromised the response to therapy. Monotherapy with oral antimicrobials shown to be effective *in vitro* did not invariably work *in vivo*. For example, one cat with a localised *N nova* infection susceptible to tetracyclines did not respond to appropriate doses of doxycycline (5mg/kg orally twice daily) following adequate surgical drainage (case 5), a cat with *N nova* skin lesions failed to respond to two weeks of amoxicillin (case 9), while a cat with *N farcinica* did not respond to recommended doses of TMP-SD (case 11). Such discrepancies occur also in human patients.[68] Treatment with amoxicillin clavulanate or enrofloxacin was ineffective in all cases in which these drugs were utilised. TMP-SD at a dose of 15-30 mg/kg twice daily was often effective, but not always well tolerated, resulting in excessive salivation (due to the bitter taste and according to the drug formulation), vomiting and partial to complete anorexia. For *N nova* infections, amoxicillin (20 mg/kg twice daily) combined with clarithromycin (62.5 mg to 125mg twice daily) and/or doxycycline (5 mg/kg or higher twice daily) provided an effective, affordable synergistic[63] combination in a few instances, following preliminary therapy with TMP-SD. Such combinations may prove superior to sulphonamides for long-term consolidation therapy following preliminary treatment with TMP-SMX and/or amikacin. The total duration of therapy should be in the order of at least 3 to 6 months, as shorter periods not uncommonly resulted in recurrence. Such long treatment courses of sulphonamides, especially at high doses, may result in bone marrow suppression, with anaemia and neutropenia. Based on two cats in our series and a great number of reports from the human literature, *Nocardia farcinica* infections are predictably drug resistant, highly pathogenic, and therefore require more aggressive therapy to effect a successful outcome. In such infections, initial parenteral therapy with amikacin or imipenem is recommended in addition to TMP-SMX, and linezolid and minocycline may be useful for follow-up oral theapy.[64] The availability of an injectable TMP-sulphonamide combination is of great benefit, as it ensures effective therapeutic levels can be obtained even when the patient is not eating or vomiting. Sulphamethoxazole is said to be superior to sulphadiazine as it has less propensity to cause nephrotoxicity. Linezolid demonstrates activity in vitro against all clinically important *Nocardia* species and holds promise as it is effective orally and the few patients in which it has been evaluated. It is however, extremely expensive and currently beyond the budget for most feline patients. New quinolones (e.g. moxifloxacin) and macrolides which are effective orally also offer promise for therapy in the future.

The prognosis for *Nocardia* infections should be considered guarded based on the present series of cases. With earlier diagnosis, however, and the use of synergistic or additive drug

combinations, a better prognosis can likely be offered in the future. Cases in which appropriate specimens were collected in a timely fashion, permitting effective therapy to be implemented sooner, rather than later, generally had a favourable outcome. The high rate of recurrence, even with this best case scenario, emphasises the need for long term follow-up therapy for a protracted period, probably in the order of 6 months, in order to permanently eliminate the infection. Presumably this reflects the time necessary for eradication of all organisms from the tissues by phagocytosis in the setting of an effective cell-mediated immune response.

must treat 3-6+ months like mycoplasma

**Management recommendations extrapolated from human patients**

Although is should go without saying, culture, species identification and susceptibility is mandatory when dealing with *Nocardia* cases and ideally results should be confirmed at a reference laboratory. Especially in a veterinary setting, the isolation of *N cryiacigeorgica* or *N farcinica* (which are often resistant to macrolides, tetracyclines and the penicillins) is much more problematic than dealing with *N nova* for which there is a much wider choice of well tolerated antimicrobials.

Clinical experience in human patients has shown that successful therapy requires the use of antimicrobials combined with appropriate surgical drainage or debridement. Because *Nocardia* lesions are highly exudative and the purulent fluid contains para-aminobenzoic acid (formation of which is the rate-limiting step in substrate inhibition by sulphonamides) removal of purulent material is an essential component of successful therapy. Optimal antimicrobial regimens have not been established by controlled clinical trials in humans, let alone in veterinary patients. Initial selection of a therapeutic regimen should take into account the site and severity of infection, the host immune status, potential drug toxicity and the species of *Nocardia*. Antimicrobial susceptibility testing is a useful guide to therapy in some settings, but results should be interpreted with caution, given the paucity of studies correlating laboratory data with clinical outcomes. Indeed, discrepancies between *in vitro* data and clinical outcome are well documented, and our more limited veterinary data supports this notion. The National Committee for Clinical Laboratory Standards (NCCLS) has recently approved a method for antimicrobial testing of the aerobic actinomycetes using broth microdilution, although E-test and BACTEC methods may be more useful in the routine clinical laboratory.

TMP-Sul 15-30mg/kg

Sulphonamides have been the mainstay of therapy for *Nocardia* infections since their introduction in the 1940's.[70] In human patients, they are considered the treatment of choice for nocardiosis due to *N asteroides* complex (including *N nova*). In severely ill patients, however, two or more drugs, which may include a sulphonamide, are generally prescribed. Indeed, combination therapy with amikacin and a carbapenem or third generation cephalosporin should be considered for primary therapy in the setting of severe progressive infection. Although sulphonamides are less effective *in vitro* against *N otitidiscaviarum*, they have been curative in cases of cutaneous infection. TMP-SMX is the formulation currently preferred by most clinicians, despite the absence of conclusive clinical data supporting increased efficacy compared with the traditional sulphadiazine and sulfisoxazole. In adult human patients with normal renal function and localised disease, the recommended dose of TMP-SMX is 5-10 mg/kg (TMP) and 25-50mg/kg daily (SMX) in 2 to 4 divided doses, depending on the extent of disease. In patients with primary cutaneous infection, including sporotrichoid nocardiosis, the lower end of this dosage range is sufficient when combined with appropriate surgical debridement. In severely ill or immunosupressed patients, two or more drugs, which may include sulphonamides, are frequently prescribed.Sulpha diazine may cause oliguria, azotemia and crystalluria in patients who fail to maintain a high fluid intake, although this can be prevented by alkalinising the urine. Other drugs combined with sulphonamides can have an additive or even a synergistic effect, and in particular the combination of amoxicillin and TMP-SMX is synergistic against susceptible strains such as *N nova*.

When extrapolating these guidelines to feline patients it must be borne in mind that cats not uncommonly show adverse effects when given TMP-sulphonamide combinations at high

doses or for long periods. Hence, sequential therapy, starting with a sulphonamide based combination (perhaps in combination with ampicillin/amoxicillin or amikacin), and later alternating with less toxic agents such as clarithromycin or doxycycline/minocycline may prove especially useful. Indeed,further dosing with the sulphonamide may become possible at a later point in time, a strategy pioneered by Davenport and Johnson.[18]

In summary, the choice and dose of antimicrobial drugs, and the duration of therapy, depend on the site(s) and extent of infection, underlying host factors, the species of *Nocardia* and the clinical response to initial management. Sulphonamide therapy remains the treatment of choice in human patients with nocardiosis, and it is likely to be true also for feline patients, at least for preliminary therapy. As there are sometimes issues to do with formulation, coating of tablets and the bitter taste of sulphonamides leading to excessive salivation, it has been suggested that off label use of the Tribrissen Piglet suspension (Jurox, Australia) is advantageous because it is palatable and easy to administer, with an appropriate ratio of TMP to SD of 1:5.[29] The use of additional parenteral drugs in severely ill feline patients, for example, amikacin, imipenem or ceftriaxone, may improve prognosis, especially in the immunocompromised and patients with *N farcinica* infections. In a veterinary setting, patients with disseminated disease, pulmonary involvement, advanced disease or concurrent predisposing conditions (immunosuppressive drug therapy, diabetes, FIV) may warrant initial combination drug therapy using one or more bactericidal intravenous agents. Alternative regimens are required in patients unable to tolerate, or who fail therapy with, sulphonamides. There are a number of suitable combinations that may be applicable for susceptible species, including *N nova*.

The place of surgery in the management of nocardiosis depends on the site and extent of infection. Indications for aspiration, drainage or excision of abscesses are similar to those for other chronic bacterial infections. Therapeutic aspiration is generally inadequate in patients with thick-walled multiloculated abscesses, which contain little free-flowing pus, including patients with mycetomas. Such cases require aggressive surgical debridement and drainage to effect a cure. Certain mycetoma-like lesions may benefit from *en bloc* resection and wound reconstruction, an approach that has proved especially effective in cats for lesions caused by rapidly growing mycobacteria in cats and dogs.[77,78] Such surgery should generally follow preliminary antimicrobial therapy, to ensure blood levels of antimicrobials known to be effective *in vitro* are present in the tissues during and after surgery.

**Key reference**

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MØ – unique to cat – Pulmonary Intravascular MØ in capillary bed of alveolus – Stuck there doesn't move around on systemic side

major phagocytic organ of cat is lung

They are like the Kupffer cells of the liver

Dz only you can't give cisplat to goats – endemic

↑ inflammatory lung dz – whatever goes into lung these PIM grab it and do something with it

Live Adult HW actually Suppress MØ activity

eventually worm dies and the lungs wake back up at react like crazy

2 Dz – adult dz acute big signs

larval dz – chronic cough dyspnea vomiting lethargy Anorexia ↓ wt loss

# D. immitis-A 3-Month Disease Cycle: Prevention And Testing

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## INTRODUCTION

By common definition, Dirofilaria immitis is discussed as having a 6-month life cycle (infection of host through development and sexual maturity). The assumption that clinical disease does not develop until the parasite is a 6-month-old adult is incorrect.

The initial arrival of immature L5 in the small pulmonary vessels of the lungs is associated with an intense eosinophilic pulmonary reaction and clinical and radiographic signs may be present in this 3-6 month post-infection period. This 3-month disease cycle precedes the production of microfilaria and circulating antigen by 2-3 months. Because of the difference in the host immune reaction, and mortality of the immature L5 worms, the clinical signs, diagnosis, and effects of prophylaxis are different in the dog vs the cat with heartworm infection.

## LIFE CYCLE

Adult females (27 cm long) and males (17 cm long) normally reside in the pulmonary arteries and right ventricles without causing major occlusion of blood supply. Microfilariae (315 µm long and 6-7 µm wide) are discharged into the blood stream and survive 1-3 years. The number of circulating microfilaria in dogs is increased in warm ambient temperature, after eating, and late at night. The microfilariae are ingested by a mosquito during feeding. The infective larvae (L1) migrate to the stomach and then the mouthparts (L3) during development. The rate of development can be as short as 8 days at 30°C or as long as 28 days at 18°C. After a mosquito acquires the microfilaria (L1), adequate exposure to warm temperatures must occur during the relatively short life span (1 month) of many of the mosquito vectors. The infective larvae are deposited on the skin of an animal when the mosquito feeds again and the L3 enters through the bite wound. A maximum of 10-12 L3 can be transmitted by a single mosquito.

The L3 stages molt to L4 and L5 (adults) and migrate to the pulmonary arteries arriving as L5 (1-2 cm in length) approximately 90-100 days after infection. These small L5 are distributed mainly to the caudal distal pulmonary arteries, and over the next 2-3 months, develop to sexually mature adults and migrate back toward the right ventricle. If both sexes are present, microfilaria are produced 6-7 months after L3 exposure and can be detected in the blood in the dog, rarely in the cat. The common detection methods for adult antigen are positive typically about 6-7 months after infection. High enough quantities of the glycoprotein to be detected are only associated with fully mature adult female heartworms.

**D. immitis - Heartworm or Lungworm**

Adult heartworms can live 3-5 years in the dog and 1 ½-2 years in the cat. Although an endarteritis is produced, embolization and total vascular occlusion are rare when the worms are alive. The severity of the pathology is influenced by the number of parasites but pulmonary vascular disease is also exacerbated by the shear stress of high blood flow associated with exercise. Severe pathology can be induced by low worm burdens in athletic dogs. The classically described cor pulmonale syndrome is only induced in dogs with an exercise pattern forcing right ventricular hypertrophy from increased cardiac outputs and increased pulmonary vascular resistance. In endemic areas, the average worm burden in the dog is about 15 worms and in the cat 1-3 worms. High worm burdens can be found in dogs with minimal cardiac changes if the dog is sedentary. Thus the majority of dogs and almost all cats with heartworms have no significant clinical disease associated with pulmonary hypertension or heart failure. The death of worms, either spontaneous or induced, is associated with severe pulmonary parenchymal disease. The majority of the clinical signs and most of the life-threatening aspects of heartworm disease are pulmonary function related.

**INITIATION OF DISEASE-3 MONTHS AFTER INITIAL INFECTION**

With the arrival of L5 as 1.5 cm worms in the right and left caudal arteries, small vessel disease and lung parenchymal pathology are initial insults. As would be expected of any foreign body of this size, the parasite is ejected out the pulmonary outflow tract and most are deposited in the right and left caudal pulmonary arteries. Consequently, initial damage associated with the 3-6 month post infection period is most noted in these arteries and caudal lung lobes. The host response to the infection during this initial insult is inflammatory and eosinophils can be detected in the alveolar space and interstitium.

In dogs, the majority of L5 which arrive in the lungs will survive and develop into adult heartworms. In cats, there is a high mortality rate of the initial L5 worms. Some cats will have all of the L5 will die during the next months and have no adults at 6-7 months post infection.

As the worms increase in size and grow back up the pulmonary arteries towards the heart, the surface arterial lesions become more evident. The periarteritis allows additional leakage and inflammation will extend into the lung parenchyma. At the distal capillary bed level, even the alveolar septa will develop edema and injury of the capillary beds. These lesions are significantly worse associated with dead and dying worms. High flow at critical times of early lesions will promote fibrosis rather than normal repair. Demonstration of heartworm antigen in interstitial areas distal to the physical presence of heartworms emphasize that the inflammatory response is throughout the pulmonary parenchyma. The microvascular lesions are severe when worms are alive, but become exaggerated associated with worm death. Type 1 pneumocytes are disrupted from the endothelial cells, leaving many of the alveolar sacs as denuded airways. Although more severe in lobes where heartworms are dying, similar lesions can be demonstrated in other lobes. The author has produced similar histologic lesions with cell free extracts of adult

retest like FeLV/FIV - new test when comes in household then again 4-6mo- tell o. neg dog may be explain DOS cause exposed before test can tell - NOT 1yr why to o.

microfilaria cross placenta - will be Ag neg
cause sat from mom -

heartworms. The resultant lung injury is typical of Adult Respiratory Distress Syndrome (ARDS). During these critical times of natural or induced worm death, the lung develops severe periarteritis, interstitial edema, and acute inflammatory interstitial disease. The ciliated bronchial columnar epithelium can also be damaged and undergoes necrosis.

**LUNG RESPONSE IN THE DOG** ~~used~~ called Heartworm Hyg 40 yrs ago
see subtle inflam in lungs 4-6 pi - no

After initial endothelial damage and alveolar injury, the body will either attempt to repair the lesion with normal cellular structures or repair by scarring and fibrosis. The shear forces on endothelial cells during high flow and increased permeability contribute to increased capillary bed damage, alveolar flooding, and resulting fibrosis. All of which contribute to decreased areas of gas exchange and promote the fibrosis which further increase pulmonary vascular resistance. Unfortunately, the microvascular disease cannot be radiographically evaluated and only in dogs where the disease is extreme or the exercise pattern of the dog has exacerbated the right-sided heart strain, will the typical pattern of cor pulmonale be demonstrated. The microvascular lesion of fibrosis of pulmonary capillary bed would appear to be irreversible. Chronic disease is influenced by the blood flow through the lungs and number of heartworms dying over time.

**LUNG RESPONSE TO EARLY INJURY-CAT VS DOG**

Response of the Cat Lung to Adult Heartworm

If the course of a D immitis infection is evaluated chronologically, the changing nature of the disease is evident. As the parasite first arrives in the lungs as early as 90 days after being infected by a mosquito, the lung responses with intense inflammation and "asthma-like" symptoms may develop. The cat has specialized macrophages (Pulmonary Intravascular Macrophages- PIMs) in the capillary beds of the lung that are not present in the dog. After the mature parasite develops, the clinical signs may be intermittent or absent. The parasite seems to be able to suppress the macrophage function in the lung. The cat will have classic radiographic and histologic findings of feline heartworms, but may not show clinical signs. After the adult parasite develops, the pulmonary parenchymal changes and even enlarged caudal pulmonary arteries on VD radiographs may decrease. However, at the time of worm death, the suppression of macrophage function is decreased and the lungs become extremely inflamed and the specialized macrophages may become important in the intense reaction. The result is a non-functioning lung and an acute respiratory distress syndrome. Although this reaction can occur as the result of even a single worm burden, spontaneous death of cats from heartworm infection is uncommon compared to clinical disease associated with the early 3-6 month disease. Usually severe dyspnea associated with heartworm disease and especially that which results in death is the consequence of an adult heartworm dying. After the removal of dead heartworms, there may be continued inflammatory lung disease in some cats.

L5 arrival @ 75-90 days PI – airway & parenchymal dz develops

Response of the Cat to the Early Infection

The disease associated with feline heartworm infection is a moving target, with the pathology, and resulting clinical signs, dependent on the stage of the life cycle involved. Early arrival of L5 results in classic asthma-like radiographic and clinical signs. In cats during this early part of the infection, coughing and dyspnea can be intermittent. A peripheral eosinophilia may or may not be present. Typically, the cytology of BAL reveals an eosinophilic reaction. The radiographic pattern can be dynamic and right-sided cardiac changes are not present. The inflammatory pattern in the lung parenchyma is peribronchial but may be severe enough to be a diffuse alveolar pattern. Pulmonary arterial patterns may be normal although if the periarterial inflammation is severe, the right and/or caudal pulmonary arteries may appear enlarged. Often, the inflammatory lung pattern is severe enough that the pulmonary arteries cannot be visualized.

Three Month Disease Cycle-Diagnostic And Preventative Considerations

With the initiation of pulmonary disease at 3 months after the infection, pathology and clinical signs may be present 3 months before antigen or microfilaria would be present in the blood and 3 months before heartworms could be visualized echocardiographically. Thus, dogs and cats with lesions during this early phase are "heartworm negative" by the typically applied screening tests used in practice. Although the radiographic and histopathologic lesions are present during the early phases (months 3-6 post L3 infection) in the dog, rarely are dogs presented for clinical signs during this time frame. However, because of the intense reaction of the cat lung to the arrival of these 1-2cm L5 at 3 months and/or the reaction of the lung to the higher mortality of these early young adults, clinical signs are frequently noted during this stage of the infection.

Some cats will develop these early lesions and become antibody positive, but over time (3-6 months) the young adult parasites in the distal pulmonary arteries all die. Although this form of heartworm infection could be considered as "self-curing," lesions were induced, clinical signs may have develop, and long term consequences of this infection are unknown. The alveolar and bronchial changes associated with this early form of the disease will clinically and radiographically mimic "feline asthma." Cats will develop an eosinophilic BAL cytology, radiographic bronchial lesions without pulmonary arterial changes, and clinical signs of coughing and/or dyspnea will respond to typical corticosteroid therapies. Cats that are heartworm antibody positive have been successfully infected with the L3 which have molted to the L4 and L5, typically (depending on the test methods) lived 2 ½ to 3 months, and may or may not have gone on to arrive in the distal pulmonary arteries as L5.

In a study of cats presented to practicing veterinarians with a history of coughing and/or dyspnea, 42% were heartworm antibody positive. When cats with radiographic lesions and/or positive serology were examined over a 3-month time frame, the changes demonstrated that this infection is dynamic and a diagnostic challenge. Discordant serologic results between test methods can occur because each identifies a different antibody during the initial phases of the infection.

Consideration in Dogs

With the understanding that dogs also have heartworm lesions associated with this 3-6 month post infection period, the concept of a "reach back effect" should be revisited. Monthly preventatives administered to dogs 3-4 months after infection will be heartworm negative when these medications are administered for a 1-year period. However, based on histopathologic and serology studies, this should not be considered as a successful "preventative" in the typical manner used with owners. Veterinarians assure owners that if a monthly preventative is administered, any exposure initiated in the previous month will not be successful in developing in the heart and lungs. However, to suggest that a preventative has a reach back effect 3 or 4 months would be inaccurate and incorrect; because at this point, these small young adults (L5) are typically already in the distal pulmonary arteries inducing damage at that time. As noted in the experimental studies, initiation of preventative medications 3-4 months post L3 even allow some of these worms to develop long enough to produce antigen before they die.

Dogs that are antigen and microfilaria negative can have 3-6 month old young adults at the time of initiation of monthly preventative medication. As noted in the cat, death of the immature heartworms is associated with increased pulmonary damage. Preventative medications which accelerate the death of immature heartworms is also associated with an increased inflammatory arterial and pulmonary damage during the time of worm death. However, elimination of these immature worms is preferred to allowing the worms to continue to develop, increasing their size and mass, inducing damage over the next several years, and then as a significantly larger worm burden dying and creating significantly more damage.

Natural Immunity against Adult Heartworm Cells.

We get L3 injected - L3→L4 migrate thru tissue
5 who get zapped - very interest in whether people get resp HARD

Every ferret should be on HWprevent - very suscept to adult worms - 1o exposure will get very sick

ferret ⊕ effusion - has HW postcaval syndrome
→ hematuria uveitis ⊕ cystitis

Culex - the most common NAm mosquito feeds on both Dog & Cat - some mosquitos don't like cats - so indoor, outdoor cats at risk -

mosquito -
Eggs hatch out to larvae in water 3-7 days

"Heartpoke" email -

The HARDS folk talk about in cats happens in dogs we just don't assoc it with it - if happens 3-6 no pi

Don't see lifethreating broncho constriction in dogs - Do see it in cats because they can -
Acute lung dz - type II cells get laid down - proliferate see sheets of cells that compromise $O_2$ ex at alveoli
Dog - get fibrosis - Cats get Type II proliferation Surfactant Syndrome / cat

They measured leukotrienes in BALS - they found lots in asthma & control - less in remission
- Study says NOT in cat urine - That's why people say not in cat - Ms Vance was right

IDEXX is going to put HW Ag detection FECV/FCV
Antech - free Ab testing wellness screen -

PI = post infection

Notes



c L3 from mosquito.

Serology —

Ag test - detects mostly Worm Ag only from mature female adult worm (>3 adult females) do not say - your dog doesn't have HW need to retest 4-6 mo your dog may have L3, 4 or 5 cat always low worm burden - don't waste time c inhouse snap test for Ag

most Ab test against L4

Ab testing - measures host response to developmental and adult Ag - each Ab assay will vary c target Ag He does 3-4 Ab tests in research setting - he expects change and variation - It means:
the cat has been successfully infected and the larvae have molted 2-3 mo and may or may not have an adult infection concurrently - All Ab against developmental larvae - so cats c adult worms can be neg.

7-10 cats / 1000 exposed get fully mature adult worm
10/10 dogs get adult HW
But - lots of cats get L5 - hi mortality of L5
- when L5 hit lungs they die, induce lots of inflammation

HW Ab is short lived - doesn't stay around for long after worms die - But after worms die & inflammation manifests

HW maturation probably not delayed like previously thought

# Notes



His big current study
85 cats all infected w HW Lg 8mo, 16mo cks
Grp 1 Waits 30 - Start Tx for Resolution of Lungs
2 Control
3 Wait to day 84 - L5 should be in lungs by now
Tx w 150 mcg Ivermectin SQ 2wks
25x dog dose
not allow immatures to grow up and become adults
Heidi didn't know if worked w/ or not - it did.

When L5 hits lung => eosinophilia, HARD

Cats get proliferation of smooth muscle in airway
do/don't do that & the doesn't have explanation

When you see those eos or there are basophils
no clinical signs - think HW Ly

why does Ab level persist in control - Isn't it to Cq?
Don't all Lfs go away at same time? What does Ab level persist?

If all control cats had adult worms - How many cats kill off L5 before get to be adult

Tobacia - Dirty