Cornell University
College of Veterinary Medicine
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18th Annual

Fred Scott Feline Symposium

July 28–30, 2006

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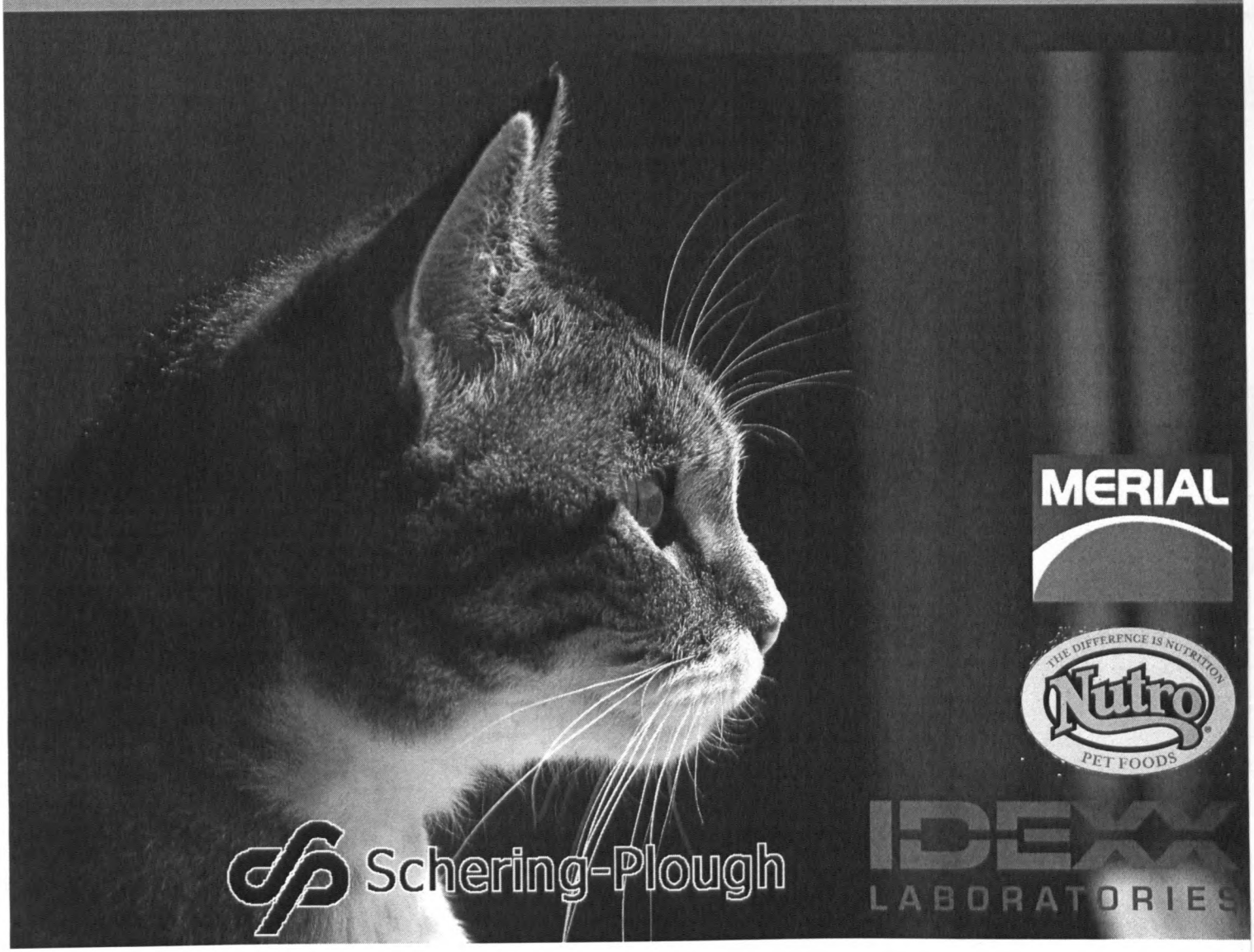

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General Information and Logistics

18th Annual Fred Scott Feline Symposium
July 28 - 30, 2006

Course Overview

This year's 18th Annual Fred Scott Feline Symposium will educate and update veterinarians in feline anesthesiology and pain control; the role indoor housing plays in health and disease; updates on feline hemotropic mycoplasmas, hematology, and clinical pathology; and selected topics in feline liver disease and the impact of body condition on disease and management strategies.

Accreditation and Continuing Education Credit

The College of Veterinary Medicine at Cornell University accredits this symposium for a maximum of 16 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.

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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 29. The certificate verifies your attendance at the 18th 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. Buffington on Friday or Dr. Robertson on Saturday: If you signed up to have lunch with a speaker on Friday or Saturday 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.

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

18th Annual Fred Scott Feline Symposium
July 28 - 30, 2006

- 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 28, 2006

7:30 - 8:00 am	Registration Continental Breakfast ***Sponsored by MERIAL***	Hagan Room
8:00 - 8:15	Welcome - *James Richards*	Lecture Hall I
8:15 - 9:15	Indoor Housing: Implications for Health and Disease I *Tony Buffington* • Indoor Housing, is there a problem? • Disease examples Idiopathic cystitis Obesity	Lecture Hall I
9:15 - 9:30	Break	Hagan Room Atrium
9:30 - 10:30	Indoor Housing: Implications for Health and Disease I (continued)	Lecture Hall I
10:30 - 10:45	Break	Hagan Room Atrium
10:45 - 11:45	Indoor Housing: Implications for Health and Disease I (continued)	Lecture Hall I
11:45 -1:15 pm	Lunch	Cafeteria
1:15 - 2:15	Indoor Housing: Implications for Health and Disease II *Tony Buffington* • What can we do about it? • Communicating with clients • Treating the environment • Follow-up	Lecture Hall I
2:15 - 2:30	Break	Hagan Room Atrium
2:30 - 3:30	Indoor Housing: Implications for Health and Disease II (continued)	Lecture Hall I
3:30 - 3:45	Break	Hagan Room Atrium
3:45 - 5:15	Indoor Housing: Implications for Health and Disease II (continued)	Lecture Hall I
6:30 - 9:00	**Annual Picnic** at the Six Mile Creek Vineyard Maps at the registration desk.	

Saturday, July 30, 2005

7:30 - 8:00 am	Continental Breakfast ***Sponsored by IDEXX Laboratories, Inc.***	Hagan Room Atrium
8:00 - 9:00	Recognition of Pain in Cats *Sheilah Robertson*	Lecture Hall I
9:00 - 9:15	Break	Hagan Room Atrium
9:15 - 10:15	Pediatric Anesthesia *Sheilah Robertson*	Lecture Hall I
10:15 - 10:30	Break	Hagan Room Atrium
10:30 - 11:30	Management of Perioperative and Acute Pain *Sheilah Robertson*	Lecture Hall I
11:30 - 1:00 pm	Lunch ***Sponsored by Schering-Plough Animal Health***	Cafeteria
1:00 - 2:00	Management of Chronic Pain *Sheilah Robertson*	Lecture Hall I
2:00 - 2:15	Break	Hagan Room Atrium
2:15 - 3:15	Pearls for the Clinician: The Infection of Cats by *Mycoplasma haemofelis* and *M. haemominutum* *Joanne Messick*	Lecture Hall I
3:15 - 3:30	Break	Hagan Room Atrium
3:30 - 5:00	Dysmyelopoiesis in the Cat: Is It a Primary or Secondary Disease and How Can I Tell the Difference? *Joanne Messick* and *Tracy Stokol*	Lecture Hall I

Sunday, July 30, 2006

8:00 - 8:30 am	Continental Breakfast	Hagan Room Atrium
8:30 - 10:00	Quantitative Measurement of Body Condition in Cats: Relationship to Disease and Management Strategies *Sharon Center*	Lecture Hall I
10:00 - 10:15	Break	Hagan Room Atrium
10:15 - 11:45	Update on Feline Liver Disorders *Sharon Center*	Lecture Hall I

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18th Annual Fred Scott Feline Symposium
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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 discount on purchases.

Exhibitors

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Faculty

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Tony Buffington, DVM, BS, MS, PhD, Diplomate ACVN

Dr. Tony Buffington is professor of veterinary clinical sciences at The Ohio State University Veterinary Hospital. Following service in the United States Coast Guard from 1968-72, he attended the University of California at Davis, where he received the DVM degree in 1981, and BS in 1976, MS in 1982, and PhD in 1988 degrees in nutrition. He is board certified in veterinary nutrition (ACVN), served as president of the ACVN in 2001, and participated in the ACVN curriculum committee, which developed a model veterinary nutrition program for veterinary colleges. At The Ohio State University he teaches a clinical nutrition elective, lectures in other medicine courses, and conducts nutrition rounds in the fourth-year general medicine and intensive care rotations. He also teaches clinical nutrition and research methods courses to resident/graduate students. Dr. Buffington's research focuses on idiopathic cystitis in cats as a naturally occurring disease analog of interstitial cystitis in human beings, and on the role of neurogenic inflammation and stress in the pathogenesis of these diseases. His other clinical interests include obesity, lower urinary tract diseases in dogs and cats, evidence-based medicine, complementary and alternative veterinary medicine, and critical care nutrition. Dr. Buffington is a member of the AVMA, four invited professional societies, and member of an NIH study section in urology. He has authored more than 75 scientific publications, 25 book chapters, and with Dr. Sarah Abood and Cheryl Holloway, the book *Manual of Veterinary Dietetics*.

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Sharon Center, BS, DVM, Diplomate ACVIM

With a background in biology and chemistry, Dr. Center completed her veterinary training at the University of California at Davis, a rotating Internship in Small Animal Medicine and Surgery, Residency in Internal Medicine at the New York State College of Veterinary Medicine, Cornell University, Ithaca, NY, and thereafter achieved board certification in the American College of Veterinary Internal Medicine. She spent 3 years in private practice and joined the veterinary faculty at Cornell in 1983 where she currently is a Professor of Internal Medicine. Her responsibilities include co-managing the Internal Medicine referral service, providing didactic lectures in the areas of hepatobiliary, renal and hematologic disorders to 3rd and 4th year veterinary students, training hospital Interns and Medicine Residents in the area of Veterinary Internal Medicine. She conducts research focused in the area of canine and feline hepatobiliary disorders, including disease characterization, diagnostic evaluations, and therapeutic interventions, nutritional management, and provides consultations in the area of hepatobiliary disease including histopathologic disease characterizations. Dr. Center's current research activities include investigation of energy utilization and body composition in clinically ill cats and dogs with the objective of refining recommendations for drug dose adjustments and nutritional support; a nationwide prospective study of chronic hepatitis in the dog, and metabolism and systemic effects of glucocorticoids in the cat. She has authored numerous research and clinical manuscripts and book chapters in the area of hepatobiliary metabolism and disease, diagnostic evaluations and treatments and has lectured widely on these topics.

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Joanne Messick, VMD, PhD, Diplomate ACVP

Joanne Messick received her Veterinariae Medicine Doctoris from the University of Pennsylvania's College of Veterinary Medicine in 1986. Following the completion of that degree, Dr. Messick completed a Residency in Veterinary Clinical Pathology and was awarded her PhD in Pathology from The Ohio State University. She soon after began working as the Associate Director for Roche Bioveterinary Laboratories until 1995 when she was hired as an Assistant Professor in the University of Illinois at Urbana-Champaign's College of Veterinary Medicine. In 2001 she was promoted to Associate Professor with Tenure where she remained until 2004 when she joined the faculty at Cornell University College of Veterinary Medicine as Associate Professor. July 1, 2006 Dr. Messick accepted a position at the Purdue University School of Veterinary Medicine as an Associate Professor of Veterinary Pathobiology.

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Sheilah Robertson, BVMS, PhD, Diplomate ACVA

Sheilah Robertson received her BVMS from the University of Glasgow, Scotland in 1980. After a short time in private mixed animal practice she spent a year as a surgical house officer at Bristol University before pursuing specialization in anesthesia. Dr. Robertson obtained her PhD from Bristol University in 1985 and is board certified by both the European and American Colleges of Veterinary Anesthesia. She has worked at University teaching hospitals in Saskatchewan, Michigan, and Florida. Her research interests are primarily focused on the pharmacokinetics and pharmacodynamics of analgesic agents in cats and horses and more recently, iguanas. She is certified by the Chi Institute in small animal acupuncture, and is currently pursuing her certificate in animal welfare through Cambridge University and the Royal College of Veterinary Surgeons.

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Tracy Stokol, BVSc, PhD

Tracy Stokol graduated in 1987 as a Bachelor of Veterinary Science from the University of Melbourne, Australia. After graduation, she worked as a veterinary associate in small animal practice in the Melbourne Metropolitan area, before returning to the University of Melbourne to begin a PhD under the supervision of Dr. Bruce Parry. After successfully defending her thesis "von Willebrand Disease in dogs in Australia" in 1993, she came to Cornell University as an instructor in Clinical Pathology. Dr. Stokol achieved board certification in Clinical Pathology in 1995 and remained at Cornell University until 2000. At that time, she moved to Boston and took a position as a post-doctoral fellow in the Department of Pathology at Brigham and Women's Hospital at Harvard University. She could not stay away from beautiful Ithaca and returned to the Department of Population Medicine and Diagnostic Sciences in May 2002. Her research interests encompass hemostatic and hematopoietic diseases in animals and basic research into mechanisms of metastasis in cancer.

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Indoor Housing

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Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis

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Date accepted: 12 February 2006

This prospective observational study evaluated client-reported recurrence of lower urinary tract signs (LUTS) and other signs of abnormalities in cats with idiopathic cystitis after institution of multimodal environmental modification (MEMO). Forty-six client-owned indoor-housed cats with idiopathic cystitis, diagnosed based on a history of recurrent LUTS and evidence of absence of urolithiasis or bacterial urinary tract infection were studied. In addition to their usual care, clients were offered recommendations for MEMO based on a detailed environmental history. Cases were followed for 10 months by client contact to determine the effect of MEMO on LUTS and other signs. Significant ($P < 0.05$) reductions in LUTS, fearfulness, nervousness, signs referable to the respiratory tract, and a trend ($P < 0.1$) toward reduced aggressive behavior and signs referable to the lower intestinal tract were identified. These results suggest that MEMO is a promising adjunctive therapy for indoor-housed cats with LUTS, and should be followed up with prospective controlled clinical trials.

Lower urinary tract signs (LUTS; hematuria, dysuria, pollakiuria, urination in inappropriate places in the client's home, with or without urethral obstruction) affect some 1.5% of cats presented to primary care veterinarians (Lund et al 1999). Moreover, abnormal elimination is a common cause of surrender of cats to animal shelters (Patronek et al 1996). Much veterinary interest has focused on inappropriate elimination behavior, urolithiasis and urethral plugs as major causes of LUTS, although a variety of reports have concluded that no specific cause could be identified in the majority of cases (reviewed in Westropp et al 2005).

LUTS may be associated with disorders affecting the bladder or urethra from within the lumen such as urolithiasis and urinary tract infection, from intrinsic abnormalities such as transitional cell carcinoma, and from disorders of other organ systems, such as behavioral elimination disorders (Neilson 2004) and idiopathic cystitis (Buffington 2004). Cats with interstitial cystitis (a subset of cats with idiopathic cystitis), for example, appear to have increased activity of their stress response system and decreased adrenocortical function in response to stressful circumstances (Westropp et al 2003, Buffington 2004).

Some cats with LUTS appear to be unusually sensitive to their surroundings, which could affect disease expression (Buffington et al 2006). The sensitivity of cats to their surroundings has long been recognized (Darwin 1872, Cannon 1929). Recent ethological studies in zoos (Carlstead et al 1992), research laboratories (Carlstead et al 1993) and boarding facilities (Kessler and Turner 1999) have documented that cats subjected to impoverished (lacking in appropriate novelty and complexity) or unpredictable environments have decreased activity levels and increased hiding behaviors.

The indoor environment of some house cats also may be monotonous and predictable, which could be stressful (Van Rooijen 1991). The success of adaptation of cats to indoor environments may thus depend on the quality of the

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environment and the adaptive capacity of the cat (Koolhaas et al 1999).

Modifications of the environment may benefit indoor-housed cats. Environmental enrichment has been documented to improve animal health and welfare in most (Widman et al 1992, Carlstead and Shepherdson 2000, Buffington 2002, Van de Weerd et al 2003), but not all circumstances (Newberry 1995). We define multimodal environmental modification (MEMO) as institution of changes in the cat's environment to attempt to reduce LUTS by decreasing the likelihood of activation of the stress response system. These changes include client education, and variable combinations of changes in the cat's inanimate physical environment and diet, as well as its interactions with other cats, other animals, and humans in the cat's environment (Westropp and Buffington 2004). We agree with van Praag et al (2000) that, given our current state of knowledge, the relative importance of single contributing factors cannot be easily isolated in any particular case. This may be because an individual's responses (both positive and negative) to its environment depend on its unique life history, expectations and the context (environment) in which it lives. The role of single variables on environmental enrichment have been studied, particularly the effects of socialization and general activity (Bernstein 1973, Rosenzweig et al 1978), but results generally have revealed that no single variable can account for all consequences of enrichment (van Praag et al 2000). Thus, MEMO attempts to include and extend the concept of environmental enrichment to include as many features of the cat's environment as possible (Buffington 2002, Rochlitz 2005).

Based on the potential role of environment on LUTS, provisional recommendations for MEMO of indoor-housed cats have been suggested (Buffington 2002). The present study was designed to begin to investigate the effects of MEMO on recurrence of LUTS in indoor-housed cats with idiopathic cystitis.

Materials and methods

Male and female cats between 1 and 10 years of age evaluated by clinicians at The Ohio State University Veterinary Hospital or primary care practices in the Columbus, OH area for recurrent LUTS were referred for inclusion (Table 1). Clients were offered entry into this study if their cat had suffered at least two bouts of LUTS in the 10 months preceding the study, although the median frequency (weekly) was much higher (Table 2, Fig 1).

Clinical signs included variable combinations of hematuria, dysuria, stranguria, urination in inappropriate places in the client's house, and pollakiuria. Although clinical evaluation varied by practice, absence of evidence of both bacterial urinary tract infection (based on presence of concentrated urine, and absence of pyuria or observable microorganisms) by urinalysis and radiodense uroliths by plain radiological imaging was required of all patients for inclusion (Buffington et al 1997). Due to the severity of disease in these cats, prior therapy had included a variety of treatments, including variable combinations of drug and individual environmental interventions (diet, litter box) before referral for inclusion into the study. Based on client report, a specific regimen of MEMO had not been prescribed for any of the cats before referral for potential inclusion into the study.

Informed consent for inclusion in the MEMO study was obtained from clients with cats meeting the inclusion criteria. An interview with the client was conducted either in person or by telephone to obtain a review of systems and environmental history (Westropp and Buffington 2004). The history included a standardized questionnaire that each client completed in its entirety. Questions were asked about LUTS and a variety of clinical signs pertaining to various other organ systems, and about the cat's current environment (questionnaire available at www.indoorcat.org). Clients also were questioned about aspects of their cat's behavior including the frequency of observed nervous, fearful or aggressive behavior. These terms were not defined for the client unless asked; if asked, terms were defined according to standard dictionary definitions: nervous generally means easily excited or irritated, jumpy, timid, or apprehensive; fearful generally means fleeing, hiding or withdrawing from stimuli that would not be thought to affect cats in this way, and aggressive generally means hostile, injurious, or destructive.

Based on the interview, a MEMO plan was developed in collaboration with the client based on environmental factors identified during the interview. The objectives of the plan were to: 1) empower clients to understand how their efforts would contribute to the cat's recovery and remission of LUTS, 2) help the client manage the cat's environment, and 3) help reduce the cat's perception of environmental threat, whatever the potential source(s).

Table 1. Description of subjects (mean ± SD), and number of recurrences (%) during MEMO therapy

Housing	Male	Female	Age	Cats/household	Follow-up	Cats suffering recurrences after initiation of MEMO therapy
			Years	Number	Days	Number (%)
All						
Single	6	6	4.5 ± 2.5	1	319 ± 135	3 (25%)
Multiple	18	16	4.7 ± 2.4	3.2 ± 1.8	304 ± 95	10 (29%)
No drug						
Single	6	5	4.5 ± 2.4	1	347 ± 147	2 (18%)
Multiple	15	12	4.9 ± 2.4	2.9 ± 1.2	298 ± 101	7 (26%)
Drug						
Single	0	1	4	1	168	1 (100%)
Multiple	3	4	3.9 ± 2.1	4.6±3.1	305 ± 95	3 (43%)

Recommendations included variable combinations of provision of information concerning the physiological abnormalities underlying the disease and explanation of the futility of 'blaming the patient' for the client's frustration associated with occurrence of LUTS. Clients also were assured that the indoor environment they provided had not caused a disease in a previously healthy cat, but rather had unmasked an underlying abnormality that may have been congenital (Buffington 2004). Suggestions for reducing the effect of environmental and/or social stressors included avoiding punishing the cat, diet change to a canned food if acceptable to the client and the cat (offering a canned food in addition to current diet was recommended; if accepted, the dry food was gradually removed), increasing water intake, change to an unscented, clumping litter if acceptable to the client and the cat, institution of improved litter box management, provision of climbing structures, viewing and resting perches, scratching posts, and audio and video sensory stimulation when the client was absent from the home as appropriate, increased client interaction with the cat, and identification and resolution of conflict in multiple cat households (Westropp and Buffington 2004). Clients were encouraged to identify changes they believed to be most relevant to their particular circumstances, and instructed to make changes to the environment sequentially and slowly (over several days) to permit the cat to adapt to the changes made.

The plan was provided to the client and reviewed with them in person, or over the phone if mailed. A copy of 'From the Cat's Point of View' by Gwen Bohnenkamp was provided to each client to be sure clients had a specific information resource to consult during the change process. Clients also were provided with the address of The Indoor Cat Initiative website (http://www.indoorcat.org), and encouraged to visit it to review recommendations provided for specific areas for MEMO identified during the interview. Printed recommendations were provided to clients without Internet access.

Eight cats, which had not previously been exposed to medication, were started on drug therapy by the attending clinician in addition to referral for MEMO. Drug therapy was not considered to be a component of MEMO, but to be a separate therapy to which MEMO was added, so both overall results and results from the cats that had 'drug+' and had not 'drug−' received drug therapy in addition to MEMO were determined.

Follow-up telephone or electronic mail contacts were made to determine the progress and success of the recommended interventions on an approximately monthly basis. Clients also were encouraged to request assistance whenever questions or concerns arose. When problems implementing the MEMO recommendations arose, the plan was modified as appropriate in collaboration with the client. Information concerning the effects of MEMO on other clinical signs that may have been present along with the LUTS was obtained at the start and end of the interaction with each client.

Statistical evaluation

Initial and final client-reported frequencies of LUTS and other signs were compared using the Wilcoxon signed rank test using statistical software (Prism, Version 4, GraphPad Software, San Diego, CA). For each sign, only cases that

Table 2. Effect of environmental enrichment on client-reported signs of abnormalities in cats with idiopathic cystitis (median, 25th, 75th percentage quartile)

Have you ever seen your cat: (0 = never, 1 = once, 2 = q year, 3 = q month, 4 = week, 5 = daily)		*N*	Pre	Post	*P**
Strain to urinate, attempt to urinate frequently, or urinate outside its litter box? Have you ever seen blood in your cat's urine?	All	46	4 (4,5)	0 (0,3)	**<0.0001**
	Drug−	38	4 (4,5)	0 (0,3)	**<0.0001**
	Drug+	8	5 (5,5)	0 (0,1)	**0.008**
Act fearful?	All	31	4 (3,5)	3 (0,4)	**0.0002**
	Drug−	24	4 (3,5)	3 (0,3)	**0.0002**
	Drug+	7	4 (3,4.5)	4 (3,4)	0.84
Act nervous?	All	33	5 (3,5)	3 (1.5,4)	**0.002**
	Drug−	25	5 (3,5)	3 (1,4)	**0.003**
	Drug+	8	5 (4,5)	4 (2.75,4.25)	0.38
Cough, gag, sneeze or wheeze?	All	15	3 (3,4)	2 (0,3)	**0.03**
	Drug−	12	3 (3,4)	2 (0,3)	**0.05**
	Drug+	3	4 (3.5,4.5)	3 (1.5,4)	1.0
Act aggressive?	All	13	4 (3,4)	3 (0.5,3.5)	**0.09**
	Drug−	10	4 (3.25,4)	3 (1,3)	**0.04**
	Drug+	3	3 (1.1,3.5)	2 (1,3)	1.0
Have diarrhea or constipation, strain to defecate?	All	8	3 (2.5,4.5)	2 (0,2.5)	0.20
	Drug−	6	3 (3,3.75)	2 (0.5,2)	**0.09**
	Drug+	2	1,5	5,0	ND*
Produce hairballs, or vomit?	All	25	3 (2,3)	3 (1.5,3)	0.44
	Drug−	19	3 (2.5,3)	3 (2,3)	0.62
	Drug+	6	3 (2,3)	3 (3,3)	0.63
Scratch at its ears	All	7	3 (2,4)	0 (0,5)	0.44
	Drug−	6	3 (3,3.75)	0 (0,3.75)	0.19
	Drug+	1	1	4	ND
Appear 'itchy' or scratch at its skin or lose hair	All	7	3.5 (2,4.5)	2 (0,4)	0.56
	Drug−	4	4 (3,5)	1 (0,2)	0.25
	Drug+	3	1 (0.5,2.5)	4 (2,4)	0.75
Have 'runny' eyes?	All	9	3 (0.5,5)	3 (2,4.5)	0.94
	Drug−	7	3 (2,5)	3 (2,4)	0.69
	Drug+	2	0,4	3,4	ND

*ND = not determined due to small sample size.

reported a frequency greater than once at the start or end of the study were included, so number of cases analyzed differed between signs (Table 2).

Results

Participation in the study was offered to 73 clients with cats having idiopathic cystitis. Of these, owners of 27 cats did not participate after initial contact for the following reasons. Four did not meet inclusionary criteria (two for age, and two for the presence of stones in the urinary tract). Two were euthanased and four withdrawn when clients decided that the cat's disease was too severe to treat. Thirteen clients were extremely hard to reach, and were dropped from the study after repeated attempts to contact them over a 3 month period failed; sporadic contact was maintained with the other four for 6–12 months, during which no signs of recurrence were reported. Data are thus reported for a total of 46 cats. Descriptive data for these cats and LUTS recurrences during the study are presented in Table 1. Effects of MEMO on client-reported signs of abnormalities are presented in Table 2

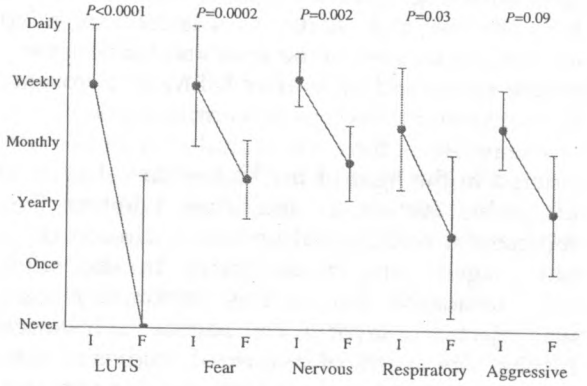

Fig 1. Effects of 10 months of environmental enrichment on abnormal signs in cats with idiopathic cystitis (median, 25th, 75th percentage quartiles). I = initial, F = final, LUTS = lower urinary tract signs.

for all cats having the sign greater than once before or after the study as a group, and with cats divided into 'drug−' and 'drug+' groups.

In addition to initial client education, the most commonly followed MEMO recommendations were to read the information provided (additional client education), increase the amount of time interacting with the cat, change to a canned diet, and add another litter box. In the multiple cat households, clients with two cats made a total of four changes, nine made three, six made two, eight made one, and details of specific changes were unavailable from nine clients. Specifically, clients reported making variable combinations of changes in the cat's physical environment (12), increases in time spent interacting with the cat (10), change to a canned food (10), increases in litter box number, location and cleaning frequency (nine), and specific efforts to reduce inter-cat conflict (three). In addition to these changes, pharmacological therapy was prescribed for seven cats; amitriptyline for five and acepromazine for two.

In the single cat households, owners of three cats made a total of three changes, one made two, five made one, and details of specific changes were unavailable from one client. Specifically, clients reported making changes in the cat's physical environment (four), change to a canned food (four), increases in litter box number, location and cleaning frequency (three), and in time spent interacting with the cat (two). Pharmacological therapy (clomipramine) was prescribed for one cat.

During the approximately 10 month average time of follow-up, no signs referable to the lower urinary tract were observed in 70–75% of the cats, resulting in a highly statistically significant decrease in frequency of LUTS (Table 2, Fig 1), regardless of inclusion of drug therapy into the treatment plan (Table 2). In cats suffering recurrent episodes, the clients reported that the LUTS resolved spontaneously without additional veterinary intervention. Significant reductions in fearfulness, nervousness and upper respiratory signs, as well as trends toward reductions in aggressiveness and lower intestinal tract signs, also were reported by clients (Table 2).

Discussion

The most important result of this study was the highly clinically and statistically significant reduction in LUTS by addition of MEMO to usual therapy. Moreover, MEMO was found to have a positive effect on some aspects of the cat's behavior, and on signs referable to some other body systems. These changes are consistent with reductions in the output of the stress response system of cats, which has been found to be abnormal in cats with feline interstitial cystitis, a cystoscopically defined subset of idiopathic cystitis (Buffington 2004).

Other studies of cats with LUTS also have proposed a role for the external environment in recurrence of signs. A 1925 description of cats with LUTS suggested that confinement to the house played a role in the development of the signs (Kirk 1925). In 1971, Caston reported an increased number of cases of cats with LUTS during a period of earthquake aftershocks in California after the Sylmar-San Fernando earthquake. He recommended, among other things, that treatment include, "An effort ... to determine the stress, and, where possible, remove it" (Caston 1973). More recently, Cameron et al (2004) found several stress factors associated with idiopathic cystitis, including inter-cat conflict.

Descriptions of a variety of other approaches to therapy for cats with LUTS have reported rates of recurrence that may be compared with the frequency of recurrence of LUTS we observed during the 10 months of the study. In one study, clinical signs recurred in 13 of 33 cats (39%) within 1 year regardless of treatment (Barsanti et al 1982). Recurrence of LUTS in cats provided only diet therapy also has been reported (Markwell et al 1999). In this study, recurrence of LUTS occurred in 11% of cats fed the canned, and 39% of cats fed the dry form of

a commercial diet designed to result in production of an acidic urine. Fourteen cats in the present study were switched from a dry to a canned food as part of MEMO. Ten of these lived in multiple cat households and four experienced a recurrence, whereas none of the four singly housed cats suffered a recurrence. Thus, the overall rate of recurrence of LUTS in cats in the present study was intermediate between that identified in our previous study, in which no specific MEMO recommendations were made (Markwell et al 1999). Because of the nature of the intervention in the diet study, however, the study was biased toward subjects in single cat households to reduce the availability of alternative food sources. The severity of disease in the subjects in the diet study, 71% had suffered two or fewer episodes of LUTS in the preceding 12 months, also was not as great as in the subjects of the present study. Moreover, modification of other features of the environment was not recorded or considered in the analysis. Although the diet of too few cats in the present study was changed to permit statistical analysis of these data, the data suggest that provision of canned food may have different effects depending on the number of cats in the household.

Diet may affect outcome for a variety of reasons. Nutrient content (including water), constancy vs. novelty of the diet presented, the form (dry vs. canned) of the diet and the method of feeding all may play variably important (and relatively unstudied) roles in MEMO. For example, the method of food delivery may contribute to MEMO by variable combinations of stimulation of exploratory behavior, provision of contingencies, incorporation of variation into the animal's schedule, and enabling invention (Overall and Dyer 2005, Overall et al 2005). More recently, Gunn-Moore and Shenoy reported a placebo-controlled study of oral glucosamine in the management of idiopathic cystitis in 40 cats (Gunn-Moore and Shenoy 2004). In this study, LUTS recurred in 26 of 40 (65%) patients within 6 months, despite the fact that the owners of 90% of the cats also started feeding more canned cat food. Thus, diet change alone may not be sufficient to effect remission in cats with more severe cases of idiopathic cystitis.

Pharmacological therapy was incorporated into the treatment of eight cats in the present study. Pharmacological approaches to the treatment of various causes of LUTS in cats have been reported previously (Marder 1991, Buffington et al 1997, Chew et al 1998, Kruger et al 2003). Administering oral medications can be stressful for some cats and clients, so it is recommended that pharmacotherapy be reserved for recurrent, severe cases, and only after MEMO approaches have proven inadequate to control signs.

The results of the current study need to be considered in the light of the biological behavior of idiopathic cystitis to determine whether they represent a real clinical benefit. Inclusion of an unmanaged comparison group in the study was considered, but for this exploratory study was rejected in favor of comparison to historical results. The dearth of published studies of environmental therapy for idiopathic cystitis suggested that a preliminary trial of the approach was indicated to determine if any beneficial effects could be identified. Although observational studies provide weaker empirical evidence than do experimental studies, they can provide useful preliminary evidence to inform decisions concerning the advisability of subjecting a therapeutic approach to prospective randomized controlled trials. Because potentially relevant and durable clinical results were identified in this study, further prospective controlled trials seem indicated.

The mechanism(s) of the clinical benefit was not determined by the study. Based on our other studies of cats with severe cystitis, one possibility is that MEMO resulted in decreased activation of the stress response system (Buffington 2004). Our observation that there were reductions in abnormalities in other systems is consistent with this possibility; beneficial behavioral changes also have been observed by others during therapeutic trials of cats with idiopathic cystitis (Gunn-Moore and Cameron 2004). Psychosocial stress (Harhaj and Antonetti 2004) has been shown to increase epithelial permeability (as we have identified in the urothelium; Lavelle et al submitted for publication) by reducing tight junction integrity (Apodaca 2004) in a variety of tissues (Bredy et al 2004, Ma et al 2004) by complex mechanisms, which may activate peripheral nociceptive and inflammatory responses. Additionally, experimental studies of rodents subjected to early adverse experience have documented psychoneuroendocrine abnormalities, which may be compensated for, if not repaired by, MEMO (Newberry 1995, van Praag et al 2000, Laviola et al 2004). These studies may be pertinent to cats with idiopathic cystitis, as the psychoneuroendocrine abnormalities identified in some of these cats may be the result of early adverse experience (Westropp and

Buffington 2004). The form that the MEMO takes in any particular case, however, must be carefully considered to assure that it results in an improvement in the biological functioning of the animal (Widman et al 1992, Newberry 1995, Hart 1996).

In conclusion, MEMO resulted in significant improvement of LUTS in cats with idiopathic cystitis, as well as improvement of signs referable to some other organ systems. Indoor housing and stress have been associated with a number of common disorders of cats, including behavioral problems (Heidenberger 1997), diabetes (Rand et al 2004), dental disease, hyperthyroidism, obesity, separation anxiety disorder, and urolithiasis (Buffington 2002). Given the increased disease in indoor-housed cats, and the ease and safety associated with MEMO, we recommend that this approach be offered to all clients with indoor-housed cats as part of preventative health care. As has been advocated by behaviorists for behavioral inappropriate urination and urine marking (Hart 1996), we recommend institution of MEMO for cats with idiopathic cystitis before institution of drug therapy, as in our clinical experience, such therapy is more likely to be effective in enriched environments. To the authors' knowledge, studies of the effects of MEMO on indoor-housed cats with disorders other than idiopathic cystitis have not been reported, but given the present results it may be worthy of investigation. This is not to say that stress causes any of these disorders, only that stress reduction may play an adjunctive role in the therapy of some chronic feline disorders, as it may in humans (Barrows and Jacobs 2002).

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Evaluation of the effects of stress in cats with idiopathic cystitis

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Objective—To determine the effects of stress in cats with feline idiopathic cystitis (FIC) by evaluating bladder permeability, sympathetic nervous system function, and urine cortisol:creatinine (C:Cr) ratios during periods of stress and after environmental enrichment.

Design—Prospective study.

Animals—13 cats with FIC and 12 healthy cats.

Procedure—Cats subjected to an acute-onset moderate stressor for 8 days received IV injections of fluorescein. Serum fluorescein concentrations were determined and compared with those of controls to evaluate bladder permeability, and urine C:Cr ratios were compared to evaluate function of the hypothalamic-pituitary-adrenal (HPA) axis. Plasma catecholamine concentrations were analyzed in a subset of cats. After 8 days of moderate stress, cats were moved to an enriched environment, and tests were repeated after 21 days.

Results—Serum fluorescein concentrations were significantly higher in cats with FIC at all time points. In the cats in which plasma catecholamine concentrations were determined, concentrations of dihydroxyphenylalanine, norepinephrine, and dihyroxyphenylglycol were significantly higher in cats with FIC at all time points, whereas no differences in urine C:Cr ratio between groups were observed.

Conclusion and Clinical Relevance—Cats with FIC appeared to have altered bladder permeability, most notably during the period of initial stress. The increase in plasma dihydroxyphenylalanine concentration suggests that there may be stress-induced increase in the activity of tyrosine hydroxylase, which catalyzes the rate-limiting step in catecholamine synthesis. In contrast, no effects of stress on C:Cr ratios were observed, which suggests there was dissociation between the sympathetic nervous system and HPA-axis responses to stress. (*Am J Vet Res* 2006;67:731–736)

Abbreviations

FIC	Feline idiopathic cystitis
TH	Tyrosine hydroxylase
NE	Norepinephrine
SNS	Sympathetic nervous system
C:Cr	Cortisol:creatinine
HPA	Hypothalamic-pituitary-adrenal

Disease of the lower portion of the urinary tract in cats is characterized by various combinations of stranguria, hematuria, periuria (inappropriate urination), and pollakiuria. Differential diagnoses for cats with these clinical signs include urolithiasis, urinary tract infection, and primary behavioral abnormalities. When results of diagnostic testing reveal no underlying cause for the signs, FIC is diagnosed. The etiology of FIC is unknown, and there are no known effective long-term treatments. Interstitial cystitis in humans is a spontaneously occurring disease that is analogous to FIC in cats.

Increased urothelial permeability is a feature of FIC and interstitial cystitis. The mucosal surface of the bladder should act effectively as a barrier to protect the urothelium from bladder contents. Defects in the mucosal lining could enhance reuptake of urine contents from the bladder[1] and contribute to clinical signs of FIC and interstitial cystitis. In a study[2] in humans, bladder wall permeability to urea instilled into the bladder lumen was observed, and results of an earlier study[3] from the authors' laboratory revealed increased permeability to sodium salicylate instilled into the bladder of cats with FIC. Orally administered fluorescein has been used as a marker for evaluating bladder permeability in humans with interstitial cystitis and has been reported to be a useful marker of altered permeability in a mouse model of cystitis when administered intravesically.[1] Fluorescein is a stable, low–molecular-weight molecule that diffuses into tissues readily. In clinically normal subjects, plasma fluorescein concentrations decrease after IV administration as fluorescein is excreted into urine. Fluorescein appears to be transported across membranes via a paracellular pathway,[4] in which intercellular tight junctions in the urothelium are the rate-limiting barriers.[5] Plasma concentrations of fluorescein after oral administration remain high for longer periods of time in women with interstitial cystitis,[6] compared with healthy subjects; impairment of tight junctions has subsequently been reported in cats[7] and humans[8] with interstitial cystitis and may be the mechanism by which fluorescein returns to the general circulation down its concentration gradient after being excreted in urine.

Clinical signs associated with FIC and interstitial cystitis may be exacerbated by stressful circumstances. Chronic stress from internal or external sources may increase activity of TH, which catalyzes the rate-limiting step in catecholamine synthesis in the locus

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coeruleus[9] and leads to accompanying increases in autonomic outflow activity. Increased TH immunoreactivity in the locus coeruleus of cats with FIC[10] and in the bladders of humans with interstitial cystitis[11] has been reported. High plasma concentrations of NE have also been detected in affected cats.[12] Norepinephrine and the locus coeruleus are important components of the physiologic response to stressful circumstances,[13] and the SNS mediates responses primarily through the rich supply of α_2-adrenoceptors in the locus coeruleus. Neurons supplying the locus coeruleus are relatively inactive during periods of low stress, but during periods of anxiety, the activity of these neurons increases, releasing more NE in the locus coeruleus.

To determine the effects of stress in cats with FIC, we conducted a series of experiments to analyze bladder permeability by use of intravenously administered sodium fluorescein. Catecholamines and their metabolites were analyzed to evaluate SNS activity, and urine C:Cr ratios were assessed as a tool for evaluating activity of the HPA axis. These studies were performed while cats were subjected to a protocol that induced a moderate degree of stress. Bladder wall permeability, plasma catecholamine concentrations, and urine C:Cr ratios were assessed again after a period of environmental enrichment to investigate the neuroendocrine effects of environmental enrichment as treatment for cats with FIC.

Materials and Methods

Thirteen cats (3 neutered males, 1 sexually intact female, and 9 spayed females) that were evaluated at The Ohio State University Veterinary Teaching Hospital were obtained as donations from clients because of the cats' history of stranguria, hematuria, pollakiuria, inappropriate urination, or a combination of these signs. Initial evaluation consisted of complete physical examination, CBC, serum biochemical analyses, urinalysis, urine bacteriologic culture, and cystoscopy. Cystoscopy was performed by use of a 9-F rigid pediatric cystoscope[a] in female cats; a 3-F flexible fiberoptic cystoscope[b] was used in male cats. FIC was diagnosed on the basis of a compatible history and findings that were in accordance with described criteria,[14] including observation of glomerulations (ie, pinpoint petechial mucosal hemorrhages) during cystoscopic imaging, after obtaining results of laboratory tests. Twelve clinically normal cats (3 sexually intact males, 1 neutered male, 7 sexually intact females, and 1 spayed female) of similar age were used as controls. Cats were housed in stainless steel cages in the animal colony and allowed to acclimate to the environment for at least 3 months. All experimental procedures were approved by The Animal Care and Use Committee of The Ohio State University.

A moderate stress protocol was designed, and each cat underwent the stress regimen on days 1, 3, and 8. Stressors included 12 hours of food deprivation, transport to the laboratory, and performance of test procedures, followed by changes in diet and housing. Diets were changed from the commercial dry food with which the cats were familiar to a new dry food, and cats were housed in a new environment (ie, metabolism cages in a different room of the vivarium). In random order, cats were brought into the laboratory in groups of 4 and placed in small holding cages while the initial tests were performed. Cats were weighed on the day of testing. The following variables were also measured: resting heart and respiratory rates and systolic blood pressure (measured by means of an ultrasonic Doppler blood flow detector[c] with a number 3 cuff on the left hind limb). Cats were restrained in right lateral recumbency for the blood pressure measurements. A venous blood sample was obtained from the jugular vein. Serum and plasma were quickly frozen at −70°C for future analysis of catecholamines and metabolites. All plasma samples collected prior to administration of fluorescein were assayed for dihydroxyphenylalanine, dopamine, dihydroxyphenylacetic acid, NE, epinephrine, and dihydroxyphenylglycol by use of reverse high-performance liquid chromatography with electrochemical detection after partial purification by absorption on alumina according to a previously described protocol.[12]

Fluorescein (250 µg/kg) was injected IV into the right cephalic vein and the time of administration recorded. Cats were returned to holding cages for 1 hour, after which blood was collected from the jugular vein for assessment of plasma fluorescein concentration. Fluorescein concentrations were determined by use of a fluorescent spectrophotometer operating at 494 nm.[d] Samples were analyzed according to a described methodology.[15]

After the venipuncture procedure, 20 µg of medetomidine/kg was administered IM into the epaxial muscles and the time was recorded. Ten minutes later, cardiovascular variables were assessed and recorded. Atipamezole (100 µg/kg) was administered IM to all cats after the degree of sedation, heart rate, and blood pressure were determined, to reverse any remaining effects of the medetomidine. Venipuncture and cardiovascular analyses were performed on days 1, 3, and 8.

After each group of 4 cats had undergone those procedures, cats were transferred to new metabolism cages and fed a new commercial diet[e] as a continuation of moderately stressful circumstances. Each cat received 100 g of food/d, and intake was recorded daily. Urine was collected daily from the metabolism cages into bottles on dry ice. After thawing at 4°C, 2 aliquots were quickly refrozen at −70°C and another sample was allowed to warm to room temperature for complete urinalysis, including urine dipstick[f] determinations. Urine pH was measured to the nearest 0.1 unit by use of a meter.[g] Frozen samples were thawed to room temperature, and urine cortisol and creatinine concentrations were assayed by means of a standard chemiluminescent protocol in the teaching hospital laboratory.

At the end of the moderate stress period (evening of day 8), cats were moved to an enriched environment. Cages were larger, and each cage contained a covered bed, 2 types of toys, and a larger litter pan. Cats were fed the same commercial dry food as before but were also offered canned food. The food was weighed daily, and intake of each type was recorded. Cats also

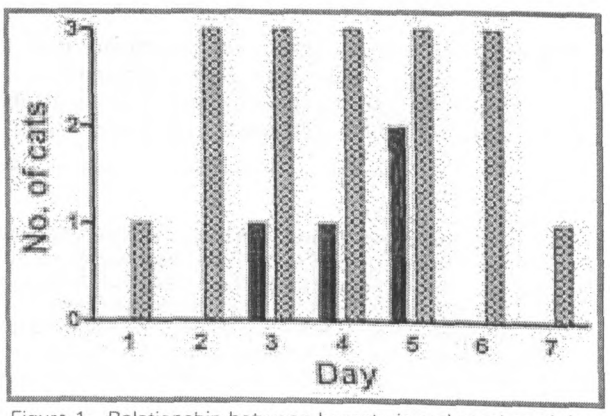

Figure 1—Relationship between hematuria and number of days of exposure to a moderate stress protocol in 13 cats with FIC (crosshatched bars) and 11 healthy cats (black bars).

had interaction with humans (in addition to the animal caretakers) for ≥ 15 min/d. The nature of the interaction with each cat was appropriate for each cat's disposition. Music was also played in the room. After 3 weeks, food was withheld on the night before testing and all previous procedures were repeated.

Statistical analysis—The effects of experimental group (ie, cats with FIC vs healthy controls), time (1, 3, 8, and 35 days), treatment (pre- vs post-treatment), and interactions among those variables were simultaneously analyzed by use of 3-way repeated-measures ANOVA. When dependent measures were ordinal scores, the Mann-Whitney test was used to compare experimental groups conditional on time. Values of $P < 0.05$ were considered significant.

Results

No differences in food intake were observed between cats in the 2 groups at any time. Abnormalities pertaining to the lower portion of the urinary tract were detected in 1 healthy cat (a sexually intact male) subsequent to commencement of the study; data from that cat were not included in statistical analyses, and the cat was released from the study. Some blood samples were not obtained from various cats during the study for several reasons (eg, impaired jugular veins or uncooperative cat).

Urinalyses and urine C:Cr ratios—During the 8 days the cats spent in metabolism cages, microscopic hematuria was detected in 30% of samples from cats with FIC, compared with 7% of samples from healthy cats ($P = 0.003$; **Figure 1**). No differences between the groups in urine C:Cr ratios were observed (**Figure 2**).

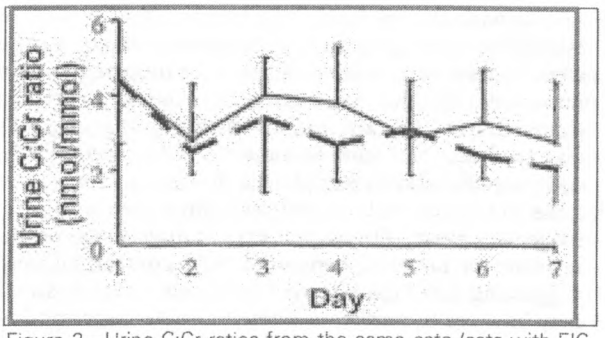

Figure 2—Urine C:Cr ratios from the same cats (cats with FIC, bold dashed line; healthy cats, solid line) as in Figure 1 during the 7 days cats were held in metabolism cages as part of a moderate stress protocol. Notice that there are no significant differences in values between groups.

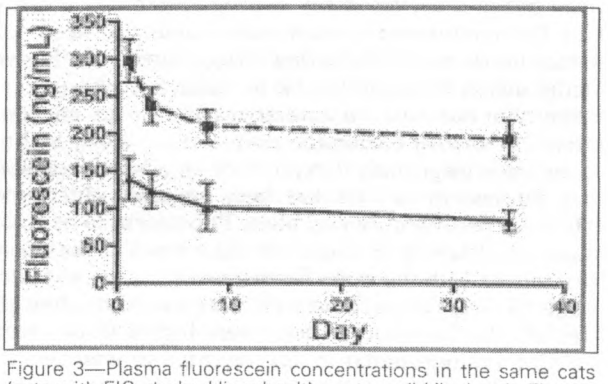

Figure 3—Plasma fluorescein concentrations in the same cats (cats with FIC, dashed line; healthy cats, solid line) as in Figures 1 and 2. Cats with FIC had significantly higher mean plasma fluorescein concentrations on all days. The moderate stress protocol ended on day 9, after which cats were moved to an enriched environment.

Plasma fluorescein concentrations—Plasma fluorescein concentrations were evaluated on all test days in all 13 cats with FIC and in the 11 healthy cats except on day 35, when only 10 healthy cats were analyzed. Cats with FIC had significantly higher mean plasma fluorescein concentrations on all days; differences were significant between groups ($P = 0.001$) and across days ($P < 0.001$; **Figure 3**). Mean ± SD plasma fluorescein con-

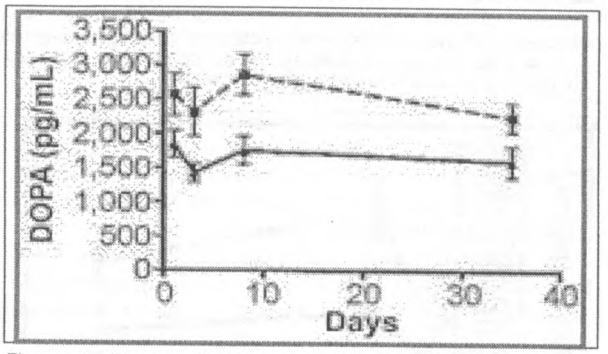

Figure 4—Plasma dihydroxyphenylalanine (DOPA) concentrations in 6 cats with FIC (dashed line) and 5 healthy cats (solid line) during the moderate stress protocol (days 1 through 8) and after a 3-week period of environmental enrichment (day 35). Notice that plasma DOPA concentrations were significantly higher in cats with FIC at all times.

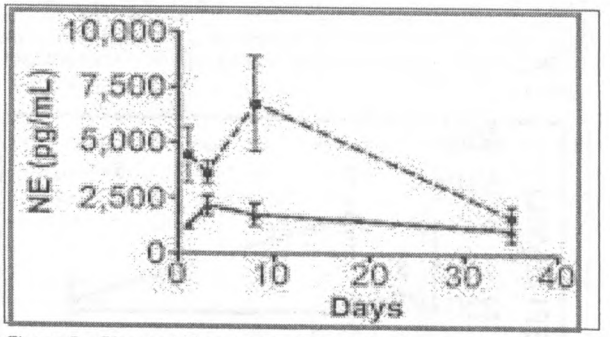

Figure 5—Plasma NE concentrations in the same cats as in Figure 4 (cats with FIC, dashed line; healthy cats, solid line) during the moderate stress protocol (days 1 through 8) and after a period of environmental enrichment (day 35). Notice that plasma NE concentrations were significantly higher in cats with FIC at all times.

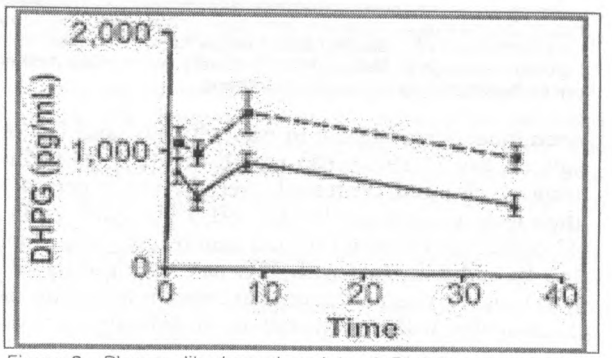

Figure 6—Plasma dihydroxyphenylglycol (DHPG) concentrations in the same cats (cats with FIC, dashed line; healthy cats, solid line) as in Figures 4 and 5. Notice that plasma DHPG concentrations were significantly higher in cats with FIC at all times.

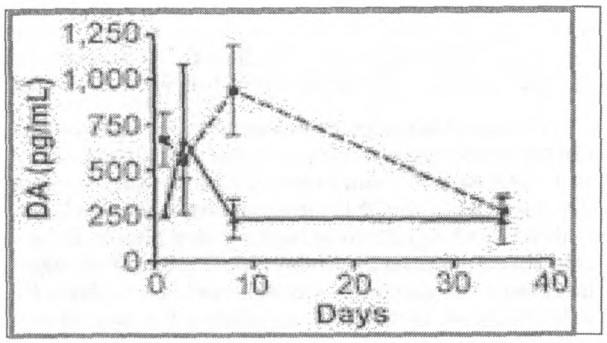

Figure 7—Plasma dopamine concentrations in the same cats (cats with FIC, dashed line; healthy cats, solid line) as in Figures 4, 5, and 6. Notice that plasma DA concentrations were frequently higher in cats with FIC than in healthy cats.

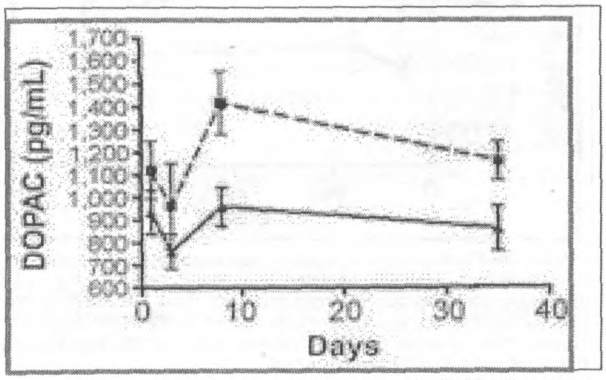

Figure 8—Plasma dihydroxyphenylacetic acid (DOPAC) concentrations in the same cats (cats with FIC, dashed line; healthy cats, solid line) as in Figures 4 through 7. Notice that plasma DOPAC concentrations were frequently higher in cats with FIC than in healthy cats.

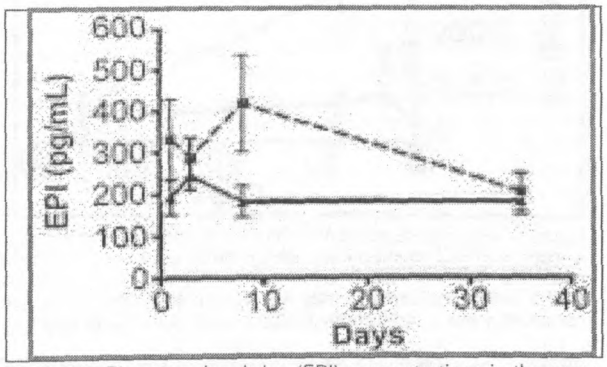

Figure 9—Plasma epinephrine (EPI) concentrations in the same cats (cats with FIC, dashed line; healthy cats, solid line) as in Figures 4 through 8. Notice that there were no significant differences between groups in concentrations.

centrations were highest in cats with FIC and healthy cats on day 1 (297 ± 103 ng/mL vs 142 ± 99 ng/mL, respectively) and decreased over the study period to their lowest values on day 35 (191 ± 90 ng/mL vs 83 ± 43 ng/mL in cats with FIC and healthy cats, respectively). In addition, cats with FIC had significantly (P = 0.01) higher plasma fluorescein concentrations on day 1, compared with concentrations on subsequent days.

Catecholamine concentrations—Because of sample processing error, plasma catecholamines and metabolites were analyzed in only 6 cats with FIC and 5 healthy cats. In those cats, plasma concentrations of dihydroxyphenylalanine (P = 0.04), NE (P = 0.03), and dihydroxyphenylglycol (P = 0.04) were significantly higher at all time points in cats with FIC than in healthy cats; **Figures 4–6**). Plasma concentrations of dopamine and dihydroxyphenylacetic acid were often higher in cats with FIC, compared with healthy cats, although the differences were not significant (P = 0.09 and P = 0.08, respectively; **Figures 7 and 8**). No significant difference between the groups in plasma epinephrine concentration was detected (P = 0.15; **Figure 9**). Data pertaining to cardiovascular variables, pupillary diameter measurements, and medetomidine analyses have been published elsewhere.[16]

Discussion

Plasma fluorescein concentrations were significantly higher at all time points in cats with FIC, compared with healthy cats, and were highest after the acute period of stress. Variables improved after the cats' stay in an enriched environment. In cats in which plasma catecholamine concentrations were determined, concentrations of dihydroxyphenylalanine, NE, and dihydroxyphenylglycol were significantly higher in cats with FIC at all times and decreased after initiation of environmental enrichment. In contrast, there were no differences between groups in the urine C:Cr ratio at any time, suggesting uncoupling of the SNS and HPA system.

Increased bladder permeability has been reported in cats with FIC[3] as well as in other animal models of cystitis[17] by assessing plasma concentrations of a drug after intravesical administration. Fluorescein is a fluorescent dye that has been used to assess membrane permeability. In an earlier study,[15] investigators observed that oral administration of fluorescein resulted in significantly higher plasma fluorescein concentrations in women with interstitial cystitis than in control subjects. Urinary fluorescein excretion was significantly lower in patients, compared with control subjects, suggesting that high plasma fluorescein concentrations may be a useful marker of altered bladder permeability. In those patients, creatinine clearance was normal, suggesting that decreased renal blood flow was not the reason underlying the decreased fluorescein excretion.

Because of individual differences in gastrointestinal transit time, variability in drug absorption rates for orally administered medications, and the need for anesthesia in administering drugs intravesically, we administered fluorescein IV to assess bladder permeability in our cats. No adverse reactions were encountered in any cat during the course of the study, and to our knowledge, only 1 report[18] of an adverse reaction to fluorescein in cats has been reported. Increased bladder permeability may allow fluorescein to be reabsorbed, delaying its excretion. As a result of technical problems with the urine fluorescein assay, we were not able to assess urine fluorescein concentrations; however, all plasma concentrations were higher in cats with FIC, a finding similar to that reported in women with interstitial cystitis.[15]

The etiology of altered bladder permeability is not fully understood. However, activation of the SNS may increase epithelial permeability, permitting substances

encountered in the environment greater contact with sensory afferent neurons; increased activation of sensory afferent neurons could subsequently lead to development of local inflammation.[19] Altered bladder permeability has been reported in cats with FIC[3] and may be mediated via the SNS. Sympathoneural-epithelial interactions appear to play an important role in permeability. For example, 1 group of investigators[20] revealed that application of NE to strips of urinary bladder tissue induced release of nitric oxide from the urinary bladder epithelium. Application of capsaicin also induced nitric oxide release from the bladder epithelium as well as from nervous tissue in the urinary bladder. In light of other reports[21,22] in which it was proposed that nitric oxide may increase urothelial permeability, those results suggest that some of the alterations in permeability associated with SNS activation may be mediated by NE via this mechanism. In addition, psychologic stress may lead to increased cytokine production and development of inflammation. In the present study, both groups of cats had higher plasma fluorescein and catecholamine concentrations during the stress portion of the study, suggesting that stress plays a role in membrane permeability. We cannot rule out the possibility that the high fluorescein concentrations detected were not a result of decreased renal blood flow because renal blood flow was not evaluated. However, the ability to concentrate urine and findings of serum renal variables in reference range were part of the inclusion criteria for cats in our study.

In the subset of cats for which plasma catecholamines were measured, plasma concentrations of dihydroxyphenylalanine and NE were significantly higher, compared with concentrations in controls. High serum concentrations of other catecholamines and metabolites were detected in cats with FIC, as well. The marked increase in dihydroxyphenylalanine concentrations suggested that there was a stress-induced increase in serum TH activity because dihydroxyphenylalanine is the first reaction product in the catecholamine synthetic pathway. Increased TH immunoreactivity in the locus coeruleus of cats with FIC[10] and high TH immunoreactivity in the bladders of humans with interstitial cystitis[11] have been reported.

Although plasma catecholamine concentrations were high in cats with FIC, no differences between affected and healthy cats were detected in the urine C:Cr ratios. We had hypothesized that the urine C:Cr ratio would be high in cats with FIC because the test is a sensitive indicator of adrenal response to stress and results reflect HPA-axis activity. However, the ratios were similar in healthy and affected cats. In an earlier study,[23] we found that cortisol release in response to ACTH stimulation was reduced during stressful periods in cats with FIC. In that study, adrenal gland size was significantly smaller in cats with FIC than in healthy cats. Microscopic examination of the adrenal glands did not reveal fibrosis, hemorrhage, inflammation, infection, or necrosis as causes of the reduced size; the primary histologic abnormality observed was that the zona fasciculata and zona reticularis (the zones responsible for production of cortisol and other steroid hormones) were markedly smaller than in healthy cats. These results, combined with observations of increased plasma concentrations of corticotrophin-releasing factor[24,25] and ACTH[26] in response to stress in the absence of a comparable increase in plasma cortisol concentrations, suggest that there is decreased adrenocortical reserve in cats with FIC.

Glucocorticoid administration reportedly decreases plasma catecholamine concentrations, inhibits synthesis of catecholamines, and may attenuate the increased plasma catecholamine concentrations induced by certain stressors.[27] These findings suggest that glucocorticoids may inhibit sympathoneural outflow activity; results suggest that lack of cortisol resulted in or perpetuated the observed heightened SNS activity. An increase in SNS outflow activity could also explain why clinical signs of FIC follow a waxing and waning course in cats and humans and are aggravated by environmental stressors.[28,29] Amitriptyline and other tricyclic antidepressant drugs with sympatholytic activity have been used to ameliorate the severity of the chronic form of the disease in both species.[30,31]

The present study had several limitations concerning plasma fluorescein concentrations and catecholamine analyses. In regard to the bladder permeability testing, although plasma concentrations of fluorescein were higher in cats with FIC at all times, we did not assess urine fluorescein concentrations simultaneously, a procedure that would have yielded information about fluorescein excretion in cats. Plasma catecholamine concentrations were determined on blood samples obtained via external jugular venipuncture, which could have been an acute stressor for the cat and resulted in artificially increased plasma concentrations at that moment. However, mean and SD values derived from the cats in this study were comparable to values from other studies in which plasma NE concentrations were evaluated after jugular catheters were placed and cats had been allowed to acclimate to the noninvasive collection process.[12] Because of study design, placement of jugular catheters was not possible in our cats, but this hindered our ability to collect blood samples from every cat at every designated sampling time over the course of the study.

It was not possible to match groups according to sex. Although the numbers of male and female cats were similar, the control population contained more sexually intact cats. Cats with FIC were obtained as donations, and most had been neutered or spayed, whereas many of the control cats were purchased and had not been sexually altered at the time of enrollment into the study. It is known that sex may influence plasma catecholamine concentration. In a study[32] evaluating the sympathoadrenal response to estradiol administration in postmenopausal women, there was no difference in plasma epinephrine concentrations after transdermal estradiol supplementation; however, plasma NE concentrations were significantly lower during estradiol treatment. In the group of cats in which plasma catecholamines were analyzed, there were more spayed female cats in the FIC group and it is possible that the effects of estrogen artificially decreased NE concentrations in the control group. However, results of previous work in our laboratory support that high concentrations of NE[12] and high TH

immunoreactivity in the locus coeruleus[10] may be observed in cats with FIC. Similar findings have been reported[33] in women with interstitial cystitis. Urinary cortisol excretion in men is similar to that in women.[34]

The experimental protocol in the present study was designed to determine what, if any, effects a period of moderate stress would have in cats with FIC. Clinical signs of exacerbated disease (eg, hematuria) and significantly higher plasma fluorescein concentrations were observed in many cats during the stress period. Increased plasma concentrations of dihydroxyphenylalanine and NE in cats with FIC were also observed, despite any differences in the urine C:Cr ratios between the 2 groups. Housing cats for 3 weeks in an enriched environment appeared to decrease plasma fluorescein and catecholamine concentrations, suggesting that further studies should be implemented in cats with FIC to evaluate this as a treatment option.

a. Karl Storz, Endoscopy America Inc, Culver City, Calif.
b. Five Star Medical Inc, Charlottesville, Va.
c. Model 811-BL, Aloha, Ore.
d. Turner Quantech Fluorometer, FM109515, Barnstead/Thermolyne, Dubuque, Iowa.
e. Iams maintenance chicken-based dry formula, Dayton, Ohio.
f. Chemstrip 9, Boehringer, Mannheim, Indianapolis, Ind.
g. PHM95 pH/ION METER radiometer analytical A/5, Copenhagen, Denmark.

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External and internal influences on disease risk in cats

C. A. Tony Buffington, DVM, PhD, DACVN

Owners surrender millions of cats to animal shelters each year for euthanasia.[1] Inappropriate elimination, most commonly associated with urologic signs, was the most common reason given for abandoning the cat. Oral disease recently was reported to be the most common health problem of cats, with a prevalence ranging from 23 to 67% of cats examined.[2] Obesity is also a common problem of cats; the prevalence ranges from 1.8 to 40% and appears to be increasing. Hyperthyroidism, first reported in 1979, also appears to be diagnosed with increasing frequency. The causes of these problems have not yet been clearly elucidated and may be influenced by both internal and external factors. Internal factors include the cat's genetic and experiential background as well as its temperament. External factors include such variables as the complexity of the environment, resource quality and availability, and presence of sources of threat and conflict. Of course, these factors are not mutually exclusive and vary over a continuum that includes elements of each.[3]

The external environment has long been recognized to influence the risk of infectious diseases in animals. Indoor housing has become increasingly common veterinary advice to owners of pet cats to avoid exposure to infectious diseases, as well as injury from vehicles or other animals. Although studies of comparative mortality between indoor housed cats and those permitted access to the outdoors are not available in the North American veterinary literature, indoor housed cats are thought by many to be at reduced risk. Recently, the AVMA stated that it "strongly encourages owners of domestic cats in urban and suburban areas to keep them indoors."[4]

As early as 1925, Kirk[5] suggested that "too close confinement to the house" (an external factor) and Persian breed (an internal factor) may increase the risk of signs of lower urinary tract disease. Results of subsequent epidemiologic studies have confirmed this suspicion.[6,7] Other studies suggest that indoor-housed cats and some breeds also may be at increased risk for odontoclastic resorptive lesions, obesity, and hyperthyroidism.

The question of the merits of indoor housing to promote the welfare of cats (and the different opinions on what constitutes animal welfare in general) is a subject of controversy among experts.[8,9] The purposes of this report are to briefly review some of the epidemiologic data concerning the role of environment on disease risk, to describe some physiologic factors that may mediate the effects on susceptible cats, and to suggest some interventions that may reduce the disease-related risk of the environment on indoor cats.

Epidemiologic Factors

External—Available epidemiologic studies of **feline urologic syndrome** (FUS) suggest an overall incidence rate of somewhat less than 1% and a prevalence rate from 1 to 6%; a recent study[10] reported a prevalence rate of approximately 1.5%. Many environmental risk factors for FUS have been investigated, using case-controlled studies.[6,11,12] Case-controlled studies often report results as **odds ratios** (OR). The OR is calculated by dividing the odds of exposure of cats in the diseased group to a factor by the odds of exposure of cats in the control group to the same factor. An OR of 1 indicates no association between the factor and the disease. The higher the OR, the greater the association between the presence of the factor and the presence of the disease; the lower the OR, the greater the association between the presence of the factor and the absence of the disease. It is important to state that such studies can identify associations, but they are powerless to determine causality. Odds ratios often are reported as a mean and its 95% **confidence interval** (CI). The larger the CI, the lower the precision of the estimate; if the CI includes 1, no inference of difference in risk can be inferred.[13]

Excessive body weight and decreased activity were associated with increased risk for FUS in some studies, and cats that only had access to indoor litter pans had an increased risk of FUS, compared with cats that were allowed to eliminate outdoors. Living with other cats also may increase the risk,[7,14] suggesting that social interactions or a horizontally transmitted infectious agent may play a role in the development of FUS. The lack of difference between cases and controls in viral disease rates[7,15] and the increase in risk associated with increasing amounts of time spent indoors (**Table 1**) seems to argue against an infectious agent as a common cause in multiple-cat households. A case-controlled study of cats with FUS in New Zealand during

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Table 1—Risk (odds ratio [OR]) of indoor housing for development of feline urologic syndrome (FUS), calcium oxalate urolithiasis, odontoclastic resorptive lesions (ORL), obesity, and hyperthyroidism. An attempt was made to extract the most pertinent results from the cited studies, but readers are encouraged to consult the original study for further details

Study	Cases	Controls	Measured variable	OR	95% CI[a]
				Indoor housing	
FUS					
Jones et al[7]	193	378	Uses litter tray (sleeps inside)	11.25	1.89–66.69
			Sleeps inside (uses litter tray)	16.03	2.28–113
Reif et al[11]					
	2	11	51–99% outdoors	0.16	0.04–0.77
	8	27	50% outdoors	0.24	0.10–0.55
	37	28	1–49% outdoors	1.51	0.83–2.73
	54	35	0% outdoors	2.17	1.23–3.82
Walker et al[14]					
	32	115	12–24 hours outdoors	0.37	0.22–0.51
	181	312	3–12 hours outdoors	0.66	0.52–0.85
	82	98	0.5–2 hours outdoors	1.19	0.86–1.65
	33	10	< 0.5 hour outdoors	4.85	2.36–9.96
	51	27	None	2.82	1.74–4.58
	51	37	Variable	2.02	1.30–3.15
	7	5	Don't know	1.95	0.61–6.19
Willeberg[8]					
Winter	0	7	12–24 hours outdoors	NR	NR
	22	52	0.5–12 hours outdoors	0.56	0.30–1.06
	45	53	< 0.5 hour outdoors	2.28	1.21–4.28
Summer	5	18	12–24 hours outdoors	0.42	0.15–1.19
	24	56	0.5–12 hours outdoors	0.56	0.30–1.04
	38	38	< 0.5 hour outdoors	2.55	1.37–4.75
Calcium oxalate urolithiasis[24]	84	258	Indoors only vs all other outdoors	3.25	NR ($P < 0.005$)
ORL[17]					
	7	12	≥ 7 hours outdoors	1.00	NA
	10	5	1–6 hours outdoors	4.3	1.1–15.9
	16	10	Not out	4.5	1.3–15.2
Obesity[b]					
Scarlett et al[18]	2,023[c]		Apartment (yes/no)	1.6	1.2–2.1
			Very active	1.00	NA
			Active	1.9	1.2–3.0
			Inactive	5.2	3.1–8.6
			Very inactive	15.8	4.6–54.1
Robertson[19]	644[c]		Predominantly inside	1.4	1.0–2.2
Allan et al[20]	202[c]		Being inactive	3.95	1.56–9.97
Hyperthyroidism					
Scarlett et al[21]					
	7	29	≥ 75% of time outdoors	0.43	0.18–1.06
	34	71	Occasionally outdoor	1.00	0.52–1.92
	15	17	Strictly indoor	2.15	1.00–4.71
			Strictly indoors/mostly outdoors[c]	4.0	1.3–12.1
			Predominantly indoors/mostly outdoors[c]	11.2	2.6–48.0
Kass et al[22]					
	16	20	75–100% outdoors	0.38	0.39–1.71
	33	30	50–74% outdoors	1.13	0.63–2.01
	47	46	25–49% outdoors	0.94	0.57–1.54
	71	65	1–24% outdoors	0.97	0.64–1.48
	207	187	0% outdoors	1.00	NA
Martin et al[23]					
	6	6	Mostly outdoors	3.3	0.9–12.5
	40	59	Sometimes outdoors	1.8	0.8–3.8
	18	17	Rarely outdoors	1.9	0.7–5.1
	14	36	Indoors only	1.00	NA

[a]Cases and controls were combined.
NR = Not reported. NA = Not applicable.
[a]For studies reporting number of cases and controls but not 95% confidence interval (CI), the CI were calculated from the data.[118] [b]Not case-control studies. [c]Logistic regression model in which all cats were used.

1991 to 1993 was recently reported. In addition to the aforementioned factors, an increased incidence also appeared to occur after moving a cat to a new house within the previous 3 months and during winter months; further analysis revealed a highly substantial association with rainy days during the previous month rather than with season. Access to outdoor prey was found to be protective against FUS.

Dental disease is reported to be the most common disease of pet cats. The 2 most common problems are periodontal disease and **odontoclastic resorptive lesions (ORL)**. In 1992, Van Wessum et al[16] reported that ORL were present in 62% of cats examined in Holland and 67% of cats examined in the United States. Two case-controlled studies[2,17] were performed to evaluate potential risk factors for ORL in feline

teeth. In the first study,[2] cats with ORL were more likely to be older, female, taking medications, and drinking city versus well water. They were less likely to play with toys, have owners who cleaned their teeth, or be fed diets with higher magnesium, calcium, phosphorus, and potassium contents. Without food intake information, the significance of the differing mineral content of the diets is unclear, although it may suggest that diets designed to influence recurrence of FUS were fed. Indoor housing was not identified as a significant risk factor in this study. In a subsequent study,[17] an OR of 4.5 was associated with a history of dental disease (gingivitis, calculus, or periodontal disease), and OR of 4.4 and 4.5 were found for city residence and indoor housing, respectively. Consumption of commercial treats appeared to be protective (OR = 0.3).

Obesity is also a common problem in cats. In a study[18] of the body condition score of more than 2,000 cats evaluated at veterinary hospitals in the northeastern United States, veterinarians reported that 25% of cats were overweight, and owners estimated that 29% of their pets were overweight. Factors associated with obesity included apartment dwelling, inactivity, sex (male), neutered, mixed breeding, and certain dietary factors. The OR for indoor housing ranged from 1.6 to 15.8, depending on the variable measured. The investigators suggested that the increased risk of obesity in apartment-dwelling cats may have been attributable to inactivity and boredom. A recent study[19] of obesity in cats living in metropolitan Perth, Western Australia, in which cats were categorized as underweight, correct-weight, or overweight by their owners, revealed an OR of 1.4 for indoor housing and 1.8 for living in houses with 1 or 2 other cats. The OR for neutered cats was 2.8. In a recently reported study[20] of obesity in an urban cat population in New Zealand, inactivity was identified as significant following univariate analysis but not in the combined logistic-regression analysis.

Prior to 1979, hyperthyroidism in cats was a rare condition. A study performed in 1988[21] identified an OR of 4 to 11.2 for indoor housing, 1 of the strongest risk factors evident in the study. In a subsequent study,[22] no increased risk for indoor housing was identified, whereas the OR for litter use was 3.10 (1.13 to 8.55). The authors commented that these findings complemented those of Scarlett et al.[21] A third study[23] did not identify a difference between cases and controls in housing status.

Internal—Just as environments can range from benign to challenging to threatening, animals also vary in their sensitivity to environmental stimuli. The identification of differences in breed susceptibilities suggests that internal as well as environmental factors can influence disease risk in cats. Internal factors include breed, temperament, and experiential variables. The most commonly assessed internal factors in the aforementioned epidemiologic studies investigating disease risk factors were purebred status and length of coat. In his 1984 review,[6] Willeberg concluded that Siamese cats had a low risk of FUS (OR, between 0.5 and 0.8), whereas Persians were at an increased risk (OR, between 1.4 and 4.3) for FUS. He also pointed out that studies that had not found a difference in risk between purebred and nonpurebred status may have grouped breeds of reduced risk with those of increased risk. More recently, Jones et al[7] reported there was an increased risk of FUS among long-haired, but not purebred, cats in his final stepwise conditional logistic regression model, on the basis of cases and matched controls. For cats with calcium oxalate urolithiasis, an increased risk among Persian and a decreased risk among Siamese cats has been reported.[24]

For dental disease and obesity, no clear breed predilection has been reported. For cats with ORL, neither study[2,17] included sufficient numbers of purebred cats to evaluate breed as a risk factor, although van Wessum et al[25] reported that Asian Shorthairs, Siamese, and Abyssinians were at increased risk. For obesity, both purebred[18] and crossbred[19] cats have been reported to be at increased risk. For hyperthyroidism, a reduced risk has been reported for Siamese[21,22] and Himalayans.[22]

As in other species, individual differences in temperament have been reported in cats.[26-28] Variations in response to the environment occur both among species and within individuals,[29,30] and the range of variation is large. Despite application of an identical stressor, Dumas et al[29] found as much as a 12-fold range in stress response among different strains of rats. Individual variation in experience also influences responses to the environment.[31-33] Some of this variation may be attributable to differences in early experience.[34] For example, it has been shown that short (3-hour) periods of maternal deprivation in rodent pups can result in permanent changes in the CNS, which can predispose the adult animals to visceral hyperalgesia.[35]

Some individual cats also may be unusually sensitive to features of indoor housing environments because of the differences between the behavioral heritage of cats and that of more social animals, including humans and many other domestic species. Cats appear to live as a relatively solitary species, often choosing population densities of < 50 cats/km^2.[36] Although free-ranging male and female cats occupy overlapping home ranges of approximately 100 m in diameter, they avoid meeting each other by keeping to a time schedule.[37]

Most of the epidemiologic studies of disease risk factors, conducted for more than a quarter century, have identified indoor housing as a consistent external risk factor for a variety of diseases in cats. Differences among the studies, particularly those that did not find increased risk, may have occurred for a variety of reasons. The first, of course, is that indoor housing really is not a risk factor. However, the fact that it has been identified in different diseases studied at different times and different places seems to argue against this interpretation. Variation in sample sizes and the questions asked undoubtedly also contributed to the differences. Additionally, the studies that did not identify increased risk for indoor housing were the most recently conducted. If the majority of cats in both case and control groups were housed indoors, it would be difficult to isolate this as a risk factor. Similar arguments may be made for breed as an internal risk factor,

Table 2—Risk (OR) of breed status for FUS, calcium oxalate urolithiasis, obesity, and hyperthyroidism. An attempt was made to extract the most pertinent results from the cited studies, but readers are encouraged to consult the original study for further details

Study	Cases	Controls	Breed	OR	95% CI
FUS					
Jones et al[7]	193	378	Domestic longhair	2.68	1.24–5.81
Walker et al[14]	437	604	Purebred	1.35	0.86–2.11
	32	115	Domestic longhair	1.01	0.76–.34
Calcium oxalate[24]	8	13	Persian	8.0	NR ($P < 0.025$)
	4	31	Siamese	0.57	NR[a]
Obesity					
Scarlett et al[18]	2,023*		Purebred (yes/no)	2.0	1.2–3.3
Robertson[19]	644		Crossbred	2.1	1.1–4.2
Hyperthyroidism					
Scarlett et al[21]	56	117	Non-Siamese	9.6	1.9–48.6
Kass et al[22]	5	13	Himalayan	0.29	0.09–0.89
	29	55	Siamese	0.44	0.26–0.74
	2	2	Burmese	0.79	0.11–5.88
	73	55	Domestic longhair	0.94	0.61–1.44
	8	7	Persian	0.94	0.33–2.69
	268	216	Domestic shorthair	1.00	NA
	4	3	Manx	1.18	0.26–5.35
Martin et al[23]	10	22	Siamese	0.4	0.2–1.1

[a]Not significant.
See Table 1 for key.

particularly small sample size (Table 2). Individual variation in experience also influences responses to the environment.[31-33] Thus, in any given environment, the response of any particular animal cannot be predicted. Moreover, both the animal and the environment are constantly changing.

Although the available epidemiologic studies permit one to formulate the hypothesis that indoor housing and breed status may increase disease risk, they cannot be used to test the hypothesis. They also do not permit identification of what features of indoor housing or breed status increase or decrease disease risk. For example, Jones et al[7] found no apparent interaction between breed and long hair, suggesting that long-haired cats may be at increased risk of FUS, because their owners may be reluctant to let them out during wet weather. Similarly, Scarlett et al[21] suggested that if some breeds were at increased risk for ORL, it may reflect owner reluctance to permitting valuable animals access to the outdoors (although it seems that all purebreds would be at increased risk if this were the case).

Physiologic Factors

The sensitivity of cats to their surroundings and their responses to threatening stimuli have been studied for decades[38,39]; indeed, Cannon's description of the fight or flight response resulted from studies of cats. Masserman[40] investigated cats' responses to environmental threats during the 1940s. He reported[41] that cats deprived of food for 24 hours that were exposed to an innocuous puff of air while they were eating (that elicited no response when administered at other times) became fearful and easily startled by minor stimuli. Later studies suggested that housing the cats in individual cages also may have increased susceptibility to the stressor.[42] Ethological studies in zoos,[43] research laboratories,[44,45] and boarding facilities[46] demonstrate that cats subjected to impoverished or unpredictable environments have decreased activity levels and increased hiding behaviors. For example, Carlstead et al[44] recently reported effects of caging and stress on the physiologic variables and behavior of healthy domestic cats. They found that unpredictable manipulations, such as unfamiliar caretakers or altered feeding schedules, resulted in increased urine cortisol concentrations, enhanced adrenal sensitivity to adrenocorticotropic hormone, and reduced pituitary sensitivity to luteinizing hormone-releasing hormone. Active exploratory and play behaviors were suppressed, and stressed cats spent more time hiding. The investigators concluded that the unpredictable environment had induced a stress response in the cats. Similar problems have been reported in carnivores housed in zoos.[47]

The indoor environment of some house cats also may be monotonous and predictable. This unchanging and nonstimulating predictability also is considered by some researchers to be stressful.[48] The success of adaptation of cats to indoor environments may thus depend on the quality of the environment and the adaptive capacity of the cat.[49]

The stress response involves immune, neurologic, and vascular alterations that underlie the behavioral response.[50,51] In response to epithelial injury or exposure to a noxious stimulus, such as an invading microorganism, a variety of local cells become activated and generate cytokine, lipid, and neuropeptide inflammatory mediators. Epithelial cells slough, taking organisms with them, and local vessels dilate and become more permeable. The vascular response permits blood flow to increase, and the increased permeability may lead to plasma extravasation and accumulation of inflammatory cells from the vascular space into the local tissues. Local sensory nerve fibers also are activated to initiate local responses and signal the CNS of tissue damage.

If the problem is severe, the hypothalamic-pitu-

itary-adrenal (HPA) axis and the pontine locus coeruleus-norepinephrine (LC-NE) systems may be activated by sensory neurons or by blood-borne inflammatory mediators. Activation of the HPA axis leads to release of cortisol from the adrenal cortex, which may act to increase endothelial permeability[52] or to modulate the local reaction to avoid tissue damage. Activation of the LC-NE system is associated in the periphery with release of epinephrine and NE from the adrenal medulla and NE from sympathetic postganglionic nerve terminals.

The environment also may result in an uncontrolled or inappropriate stress response by reducing the animal's perception of control of the environment[53] or by increasing its perception of threat. Animals have been selected by evolution for reproductive success. Essential criteria for reproductive success include the ability to find mates and to perceive and respond to environmental threats to sustain life long enough to ensure transmission of genetic material.[54] To find mates and reproduce, animals must act in the environment. Their actions result in acquisition of new information from the environment, collected by all the appropriate sensory apparatus of the animal (pheromonal, olfactory, gustatory, auditory, cutaneous, and visual). These signals are integrated by the CNS[55,56] and are perceived by the animal as not threatening or threatening in a constant reiterative cycle with a time constant of milliseconds.[57]

If the animal perceives no threat, the initial course of action may progress. If a threat is perceived, a stress response occurs, resulting in different actions.[58,59] Stress response mechanisms have been selected over millennia and are therefore complex and interactive, with multiple fail-safe backup systems. These may have developed initially as local defense responses to noxious environmental stimuli and have been built on and expanded as the vascular and nervous systems developed increasing complexity.[60]

The responses of the HPA axis recently were the subject of a comprehensive review.[58] In the classical view, secretion of glucocorticoids was thought to help mediate ongoing or pending stress responses[61]; this hypothesis was replaced by the view that they suppressed the stress response, preventing it from injuring the host. In contrast, Sapolsky et al[58] now suggest that glucocorticoids may permit, stimulate, or suppress an ongoing stress response or prepare for a subsequent stressor. Responses of the HPA axis may be activated peripherally by environmental factors or centrally by the perception of threat.

The LC-NE system contains the largest number of noradrenergic neurons in the body and is the most important source of NE in the CNS.[62] The LC plays important roles in orienting behaviors, vigilance, and autonomic activity.[63,64] The association between stress factors and FUS[7,65] suggests the possibility of dysfunction of neural circuits that coordinate elimination behaviors.[64] Barrington's nucleus, a candidate region for integration of forebrain activity with visceral function, is located in the dorsolateral pons.[64,66] Neurons from this nucleus also project to the LC. A substantial increase in tyrosine hydroxylase (the rate-limiting enzyme of catecholamine synthesis) immunoreactivity in the LC of cats with feline interstitial cystitis (FIC) has been reported.[67] In healthy cats, acute environmental (noise, restraint) stressors that increase LC activity also increase plasma NE concentrations.[68] Cats with FIC also have increased plasma NE,[69] as well as enhanced stimulus-induced local NE release from the urinary bladder[70] and down regulation of central α-2 adrenoceptors (α-2 AR).[a] In normal feline spinal column, α-2 agonists inhibit transmission of noxious afferent signals to the brain.[71,72] The receptors appear to be located on the central processes of sensory neurons.[73-75] Although spinal α-2 AR activation can inhibit nociceptive input acutely, these receptors seem to become desensitized or down regulated after chronic stimulation.[74,76]

The catecholamines also have complex pro- and anti-inflammatory actions on the immune system, including mediating a shift from cellular to humoral immunity. Although beyond the scope of this review, recent evidence suggests that many important interactions occur between the immune and neuroendocrine systems.[77] Moreover, the responses observed in clinically normal animals may not be identical with those observed in animals with naturally occurring diseases. In cats with FIC, for example, the sympathetic nervous system appears to be chronically activated, whereas the HPA axis responds normally to corticotropin releasing factor (CRF) infusion. This could mean that the HPA axis is not involved in this disorder or that CRF receptors have been desensitized by a chronic increase in corticotropin hormone release. The complexities of the interactions between the LC-NE and CRF systems have only recently begun to be understood but may play a role in various disease processes.[56]

Several physical and mental stressors can activate the HPA and LC-NE systems and their subsequent physiologic responses. In rodents, restraint,[78] water avoidance,[79] alterations in environmental temperature[80-82] or lighting,[82,83] and even changing rooms in an animal housing facility[84] can induce the same stress responses as local stimuli at all epithelial surfaces investigated. Recently, evidence has accumulated that indicates that external stressors also can activate the vascular system component of the stress response.[84-86] These studies suggest that endothelial permeability is regulated by a complex interplay between mast cells and nerves. Evolutionarily, increasing endothelial permeability during the stress response may have been conserved, because it permitted circulating defense molecules to gain access to extravascular spaces or circulating neurotransmitters to activate sensory neurons to provide more rapid information updates to the CNS. These observations suggest that acute stress responses occur commonly and are extinguished in most animals without progression to pathologic consequences.

Stress response mechanisms may underlie the increased endothelial and epithelial permeability in response to physical and mental stressors that has been reported to occur in some diseases of the urinary bladder[87] and gingival tissues,[88,89] as well as the skin,[90] lung,[91] and gastrointestinal tract.[92,93] Additionally,

inflammation has been associated with toxic nodular goiter[94] (the common human thyroid disorder most closely resembling hyperthyroidism) and obesity,[95] both of which are exacerbated by stressors.[96-98] What factors result in pathologic changes localized to 1 organ system and why some animals appear to be more susceptible than others are crucial research questions.[99,100]

Provisional Recommendations

Bracke et al[5] recently presented a list of needs formulated to be used for overall welfare assessment (OWA) of sows. The list included availability of food, water, and rest areas and the opportunity for social contact, reproduction, kinesis (locomotion, play, and stretching[101]), exploration, body care (grooming, thermoregulation, comfort-seeking, evacuation, and territorialism), and reactivity (predictability and controllability, self protection, ability to avoid danger, and aggression). To the author's knowledge, such an OWA list has not yet been assembled for indoor pet cats, but some recommendations are available.[102-105] The consensus seems to be that cats appear to benefit from appropriate access to resources, control of interactions with owners, and a tolerable intensity of conflict.

The research[40] demonstrating that behavioral abnormalities can result from blowing an innocuous puff of air into a cat's face while it eats suggests that cats should be fed individually in a quiet location where they will not be startled by other animals, sudden movement, or activity of an air duct or appliance that may begin to operate unexpectedly. Cats may prefer dry or canned foods[106]; offering choices in separate, adjacent containers rather than replacing the usual food with a new food permits cats to express their preferences. If experimental studies support the associations between nutrients and ORL or ingredients and hyperthyroidism, specific diet recommendations may be necessary. Feeding behavior also includes predatory activities. These may be simulated by hiding small amounts of food around the house or by putting dry food in a container from which the cat has to extract individual pieces[45] or move to release the food pieces, if such interventions appear to appeal to the cat.[104] Cats also seem to have preferences for water. Consideration may be given to freshness, taste, movement (water fountains, dripping faucets, or an aquarium pump-bubbled air into a bowl), and shape of container (some cats seem to resent having their vibrissae touch the sides of the container when drinking). Food and water bowls should be cleaned regularly unless individual preference suggests otherwise.

Cats interact with both the physical structures and other animals, including humans, in their environment. The physical environment should include opportunities for climbing, scratching, hiding, and resting. Cats seem to prefer to monitor their surroundings from elevated vantage points; provision of climbing frames, hammocks, platforms, raised walkways, shelves, or window seats has been recommended.[104,105] Playing a radio to habituate cats to sudden changes in sound and human voices also has been recommended,[107] and videotapes to provide visual stimulation are available.[104]

Some cats may prefer to be petted and groomed, whereas others may prefer play interactions with owners.[108] The play interactions with cats may include lures, laser pointers, or teaching behaviors.[103,104] Cats also may enjoy playing with toys, particularly those that are small and mobile and that mimic prey characteristics.[109,110] For cats that prefer novelty, a variety of toys should be provided and rotated or replaced regularly.[110]

In multiple-cat houses, cats also interact with each other. Because cats housed in groups do not appear to develop distinct dominance hierarchies or conflict resolution strategies to the extent that some other species do, they may attempt to circumvent agonistic encounters by avoiding others or decreasing their activity.[111] Unrelated cats housed together in groups appear to spend less time interacting with conspecifics than related ones do.[112] These cats may prefer to have their own separate food and water sources, litter box, and resting areas to avoid competition for resources and to permit cats to avoid unwanted interactions.[111] Published guidelines for introducing new cats into a home are available and may be recommended to clients adding cats to their household.[103]

Placing litter boxes in quiet, convenient locations could help improve conditions for eliminative behavior. If different types of litter are provided, it may be preferable to offer them in separate boxes, because individual preferences for litter type have been documented.[113] For cats with a history of lower urinary tract problems, unscented clumping litter should be considered.[114] Litter boxes should be cleaned regularly; some cats seem quite sensitive to dirty litter boxes. Litter box size and whether or not it is open or covered also may be important to some cats.[115,116]

Because of the dearth of controlled trials, it currently is not possible to prioritize the importance of any of these suggestions or to predict which would be most appropriate in any particular situation. Appropriately designed epidemiologic studies[117] may be able to identify particularly important factors, after which intervention trials could be performed to determine their efficacy in circumstances where owners successfully implemented the suggested changes.

The prognosis for diseases affected by environmental factors may depend on the animal, the housing situation, and the client. Animal factors include genetic predisposition and prior individual experience, the duration of the problem, the frequency of occurrences, and for FUS, the number of areas and different types of surfaces soiled. Housing factors include the number of cats in the household, the number of affected cats, the advisability of allowing limited outdoor access, and the feasibility of rearranging the environment. Client factors include the owner's ability to identify modifiable causes, the strength of bond to affected cats, their willingness to pay for treatment, the amount of time available to devote to solving the problem, and the willingness to accept and use adjunctive medications as indicated.

Ethological and behavioral studies demonstrate that captivity may elicit a stress response in some cats. Behaviorists report that indoor cats are disproportionately more often represented among cats with behav-

ioral problems evaluated by pet behavior counselors, most of which are related to improper housing conditions.[118] Moreover, available epidemiologic evidence suggests that indoor housing is a risk factor for some common diseases of cats. Risk factors, however, must be kept in perspective. Indoor housing is likely to interact in complex ways with other factors. These factors may include unidentified microorganisms and predispositions in some cats. What these predispositions may be remains to be determined, but the breed predispositions found in epidemiologic studies of some problems suggest they may be partially genetically determined.

Outdoor living increases the risk of cats for fighting, accidental injury, and exposure to infectious diseases. Although cats appear to have evolved as solitary hunters, evidence suggests that they are capable of living indoors in quite high population densities under appropriate circumstances.[111] The challenge is to develop, validate, and promulgate recommendations to enrich the indoor environment so the advantages of removal from exposure to outdoor risks are sustained.

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ANESTHESIA FOR EARLY KITTEN STERILIZATION

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Introduction

Prepubertal gonadectomy (usually at 6-16 weeks of age) of kittens is becoming a more acceptable technique amongst the veterinary community. However, some veterinarians are still hesitant to embrace this practice due to lack of experience with neonatal surgery and anesthesia (Kustritz et al. 2000; Spain et al. 2002). The purpose of this session is to review the anesthetic and perioperative issues unique to neonates and to review effective and safe anesthetic techniques for this population of kittens.

Overpopulation and resultant euthanasia of healthy cats is a serious welfare issue in many countries. The source of these kittens is both from pet-owned and feral cat populations. An important step towards alleviating this problem is early age gonadectomy. Early age neutering has been a controversial issue for many years but there is now data to suggest that there are several benefits associated with it and few detrimental short or long term problems and so this procedure should no longer be reserved exclusively for shelters and cat rescue organizations.

The most common age for neutering cats is between 5 and 8 months of age but does not appear to be based on scientific evidence but rather reflects the age most veterinarians feel the risks of anesthesia and surgery are minimal. Previously held concerns related to early age neutering included some of the following concerns: retarded growth, growth plate fractures, obesity, diabetes mellitus, urinary incontinence, feline urologic syndrome and obstruction, vaginitis, perivulvar dermatitis and behavioral changes. Several studies involving a considerable number of cats indicate that these fears are no longer warranted (Stubbs & Bloomberg 1995; Stubbs et al. 1996; Howe 1997; Howe et al. 2000; Kustritz 2002; Spain et al. 2004). Spain and others (Spain et al. 2004) have recently published long term data (mean of 3.9 years, but with some data from as long as 11 years after early age gonadectomy) on 1,660 cats and concluded there was no association with this practice and increased rates of relinquishment, medical or behavioral problems. In fact for male cats the procedure may be beneficial as it reduced the incidence of abscesses (likely due to decreased fighting), decreased aggression, sexual behaviors and urine spraying. In both males and females, early neutering was correlated with fewer reports of asthma, gingivitis and hyperactivity. Cats that underwent early-age gonadectomy were shyer and male cats tended to hide more; the association between these findings and the procedure are not clear and could also reflect a stressful even such as being adopted at an early age. Regardless, the behavioral benefits appear to outweigh any negative effects.

In a survey of New York veterinarians, over 90% stated there were benefits to early spaying and neutering of dogs and cats, but almost 60% believed that this would be

associated with an increased risk of anesthetic complications (Spain et al. 2002). However, contrary to these beliefs there are several reports of suitable anesthetic regimens for young kittens with good outcomes (Faggella & Aronsohn 1993; Howe 1997; Kustritz 1999; Kustritz 2002; Robertson et al. 2003).

The key issues relating to kitten anesthesia are:

- Hypothermia
- Hypoglycemia
- Altered metabolism and excretion of drugs
- Monitoring

Neonates are more prone to hypothermia due to their large surface area to body weight ration and lack of body fat. Hypothermia results in bradycardia which has a large impact on neonates since their stroke volume is fixed and cardiac output is rate dependant. A drop in body temperature will also slow metabolism of drugs and delay recovery. Shivering in recovery is unpleasant, increases wound pain, and because of the increased metabolic rate and oxygen demands, hypoxemia and acidosis may ensue. Kittens should be kept warm throughout the perioperative period. The prep room and operating rooms should be warm; in human neonatal units the preferred temperature is 78°F. Kittens should not be placed on the cold metal surfaces of cage floors or on tables. Holding cages should contain warmed blankets or circulating water blankets. An alternative is to line the cages and table tops with "bubble packing" which can easily be washed. Prep solutions can be warmed to body temperature and alcohol which evaporates and removes body heat can be substituted with sterile saline.

Neonates have limited glycogen reserves and should not be fasted for more than a few (2-3) hours. They should be offered small amounts of soft food within an hour following the procedure.

It is tempting to assume that inhalant anesthesia alone would be ideal in neonates because agents like isoflurane are minimally metabolized. However, when inhalant agents are relied upon as the sole anesthetic, high concentrations (a large "dose") are needed and of the anesthetic agents in use today this group have the most cardiovascular and respiratory depressant effects. In neonatal foals, the use of inhalant agents alone is associated with a higher mortality rate compared to injectable techniques (Confidential Enquiry into Perioperative Equine Fatality). In addition, when multiple kittens require surgery in a short period of time, inhalant anesthesia is impractical and is some situations may not be available.

It is better to practice "balanced anesthesia" where several different drugs are used in combination to achieve specific goals, for example analgesia, muscle relaxation, and loss of consciousness. Injectable agents may be combined to provide a complete anesthetic or may be used with an inhalant agent to reduce the amount of inhalant required.

Fagella and Aronsohn (Faggella & Aronsohn 1993) performed an excellent study with 6-14 week old kittens and evaluated different combinations of tiletamine/zolazepam (Telazol ®), ketamine, midazolam, butorphanol and oxymorphone. In their study tiletamine/zolazepam was most reliable for male kittens, but for females they recommended midazolam and ketamine (MK) followed by intubation and isoflurane vaporized in oxygen (for doses see table below) although they reported excitement in some females following the injectable protocol and neurological signs during recovery in one of the twelve kittens given this combination. In male kittens the time from injection to induction was approximately 5 minutes and mean time to sternal recumbency and standing were 77 and 103 minutes respectively. In the females, induction times using MK was approximately 5 minutes and time to extubation, sternal and standing were 2.8, 20 and 36 minutes respectively. The disadvantage of the findings of this study was the different protocols needed based on sex. It may be inconvenient to have more than one drug combination and in some cases (e.g. feral cats) the sex is not always known prior to injection.

In another study (Howe 1997), the investigators identified clear goals that they wanted the anesthetic technique to meet; these were:

- Adequate sedation for catheter placement
- Adequate post-operative analgesia without excessive sedation
- That it was similar to those used in older animals to minimize confusion and avoid adding to the drug inventory

They found that acepromazine, butorphanol and glycopyrrolate given by IM injection followed by inhalant agents met these criteria (Howe 1997), and was also found to be suitable for male and female kittens.

In an attempt to find an acceptable injectable only protocol Robertson and others (Robertson et al. 2003) evaluated the combination of medetomidine (40µg/kg), ketamine (20 mg/kg) and buprenorphine (20µg/kg) [MKB] combined and given subcutaneously to 7-12 week old kittens (average weight 0. 9 kg) for castration or ovariohysterectomy. At the end of surgery, 0.5 mg/kitten of atipamezole was injected IM. This technique was compared to a mask induction with isoflurane followed by an IM injection of butorphanol. There was no difference between the time to loss of toe pinch reflex after the start of isoflurane administration and injection of MKB; this took on average 4 minutes in both groups. The kittens in the isoflurane group were sternal approximately 4 minutes after the inhalant was discontinued and the MKB group was sternal approximately 9 minutes after atipamezole injection. Oxygen saturation as measured by pulse oximetery was lower in the MKB group who were breathing room air. There was no difference between groups in intra-operative heart rate or blood pressure (Doppler measurement). All kittens regardless of anesthetic technique recovered uneventfully and ate within 30 minutes, all appeared comfortable and wound palpation did not elicit an aversive response. Body weights were recorded for 2 weeks after surgery and compared to a similar group that did not undergo surgery and there were no differences in weight gains between groups. This injectable technique is easy to use and is ideal when large

numbers of kittens are to be sterilized in a short period of time as it does not require dedication of an anesthesia machine to each animal. If injection, prepping and surgery are well coordinated, this is a very time-efficient protocol.

Monitoring is recommended and should include physical assessment of level of anesthesia and color of the mucus membranes. The heart rate or pulse rate can be measured with a Doppler and if used on a limb, blood pressure can easily be monitored with a pediatric cuff and sphygmomanometer. Pulse oximetry is easy to perform and probes can be attached easily to the paw. A rectal temperature should be obtained at the completion of the procedure.

Delayed recovery is usually a result of hypothermia, residual drug effects, hypoglycemia, or a combination of these. This can be remedied by further warming, administration of a reversal agent (if indicated) or providing an easily assimilated glucose source such as 50% dextrose or "karo" syrup.

Table 1. Summary of anesthetic techniques for kittens

Protocols	**Dose mg/kg**	**Route**	**Comments**
Acepromazine Butorphanol Glycopyrrolate Ketamine Isoflurane or halothane	0.055 0.22 0.011 11 as needed	IM IM IM IM Mask or endotracheal tube	In kittens up to 24 weeks of age
Telazol (tiletamine and zolazepam)	11	IM	Effective for 6-14 weeks old male kittens.
Midazolam Ketamine Plus inhalant agent	0.22 11 as needed	IM IM Endotracheal tube	Suitable for female kittens. Can mix midazolam and ketamine together
Isoflurane Butorphanol	As needed for induction 0.4	By mask, for induction IM after induction	
Medetomidine Ketamine Buprenorphine Atipamezol	0.04 20 0.02 0.5 mg/kitten	Mixed together and given SQ IM at end of procedure	

Young kittens can be anesthetized safely for elective surgery. Several combinations of injectable and inhalant agents are suitable. In a busy shelter situation the injectable combination of medetomidine, ketamine and buprenorphine provides sufficient anesthesia and analgesia for males and females with rapid recovery following atipamezole injection.

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Assessment and management of acute pain in cats

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Abstract: Cats are popular pets, but until recently, their peri-operative and traumatic pain had been seriously underestimated and under-treated. The lack of treatment stems from difficulty in recognizing pain, lack of licensed analgesic drugs, fear of toxic side effects, and lack of information specific to cats. Fortunately, in the last decade, many advances have been made in feline analgesia. It is now obvious that because of the cat's unique metabolism, species-specific studies are essential. Opioids are the mainstay of any analgesic protocol for acute pain and can be used with few side effects. Other drugs that can be utilized include the α_2-agonists, local anesthetics, and non-steroidal anti-inflammatory drugs. Pain assessment in cats is challenging and developing, and validating pain scoring systems remains an important goal. The information in this article will help the critical care and emergency clinician formulate a safe and effective analgesic plan for feline patients.

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Introduction

Based on several market surveys (http://www.avma.org/membshp/marketstats/sourcebook.asp, http://www.appma.org/membership/survey.asp, http://www.aahanet.org/index.html) and publications by professional organizations,[1] the number of pet owning households has increased by over 10% in the past 15 years. Of note is that cats recently overtook dogs as the most popular pet with current numbers estimated at between 70 and 77.7 million in the United States alone. Concurrent with this has been a long awaited increase in the publication of studies relevant to assessment and alleviation of pain in this species which has previously lagged behind the information available for dogs. However, feline practitioners are still faced with several challenges including the cat's unique metabolism of many drugs and the lack of licensed analgesic drugs. In the field of emergency medicine, the veterinarian will deal primarily with acute pain that may be related to trauma, non-elective surgical procedures, or medical diseases. Acute pain has a wide variety of causes and sources (soft tissue, orthopedic, ocular, somatic, visceral), variable intensity (from minor lacerations to multiple fractures, acute peritonitis, or pancreatitis), and expected duration (days to weeks), which may all require a different approach to treatment.

The aim of this paper is to review current knowledge of acute pain assessment in cats, and the most useful drugs and techniques for its alleviation.

What Is Pain and How Do We Measure It?

Pain is a complex, multidimensional experience involving both sensory and affective components. All mammals possess the neuroanatomic and neuropharmacologic components necessary for transduction, transmission, and perception of noxious stimuli (nociception). A recent consensus statement indicated that animals are capable of emotions and, therefore, do experience pain, although it is unclear whether all species, including humans, feel pain with the same qualities and intensities.[2]

Cats are under-treated for pain.[3–6] When veterinarians were asked their opinion on an exploratory laparotomy in dogs and cats, they considered this procedure equally painful in both species, yet only 56% of cats received analgesics compared with 71% of dogs.[5] To overcome this bias, we must understand why cats come in second in the pain stakes. The reason for under-treating feline pain is not lack of compassion by caregivers. The most often cited reasons for withholding analgesics from cats are difficulty in recognizing and assessing pain, the limited number of analgesics with market authorization, lack of published information, and the fear of adverse side effects.[5]

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If we want to say we have treated pain, we must first recognize it and measure it in some way. In 2003, the American Animal Hospital Association introduced pain management standards that must be met for accreditation and a mandate is that pain must be assessed in all patients regardless of the presenting problem. This is one of the biggest challenges feline practitioners face. We must know first if they do indeed hurt and, if so, how much. To assess pain in animals, we must observe them carefully and know what behaviors indicate pain; by definition, this is subjective and, compared with humans and young children who can communicate, there is more room for error. Put simply, in humans, pain is what the patient says it is and in animals it is what we decide it is.

Currently, there is no gold standard for assessing pain in animals. The issue in animals is complex because we must consider differences in species-specific responses to pain, but even within a species there is considerable variation. Few veterinarians would disagree that the different temperaments of individual cats complicates the picture. Investigators looking for objective measure of pain have failed to find a good correlation between physiologic variables (respiratory rate, heart rate, blood pressure) or plasma cortisol levels and pain scores in cats because these are influenced by many factors other than pain.[7–9] Changes in wound sensitivity have correlated well with visual analog pain scores in cats[10] suggesting that palpation, which is a simple clinically applicable technique, is a valuable tool and should be incorporated into an overall assessment protocol.

In an emergency clinic, a pain scoring system must be simple and quick to perform, but be valid, reliable, and sensitive. Observation of behavior is undoubtedly the best means of assessing the degree of pain experienced by a cat[11]; however, in the emergency setting, the veterinarian may have had no prior contact with the cat and will require the owner's input on what is normal for that particular patient. More information can be gathered if you first observe the cat from a distance, then assess its response to a person's approach, and finally interact with it by stroking it and palpating the wound or area you suspect is painful.[7] Use of a dynamic interactive visual analog scale (DIVAS) by one individual unaware of treatments detected both differences between 2 analgesics and between treated and untreated cats.[12] Acute pain related to trauma may result in a depressed, immobile, and silent cat that is tense, distanced from its environment and that tries to hide and does not respond to stroking or attention. Alternatively, cats can be manic and aggressive, growling, hissing, and rolling around their cage; these are difficult patients to assess and treat and are discussed later.

Cats with abdominal pain adopt a hunched sternal posture, with their head hung lower than their body, elbows drawn back, stifles forward and abdominal muscles tensed. Cats may lick, chew, and self-mutilate an injured area and this is documented following onychectomy.[13] If part of the treatment involves bandaging or taping, the observer must differentiate between pain and the dislike of restrictive dressings. Levy et al.[14] reported that bandages alone caused a 200% increase in urine cortisol, suggesting that cats find this stressful. Cats that are comfortable can perform normal functions including stretching, back arching, climbing into a litter box, grooming and adopting normal postures such as laying curled up in lateral recumbency.

Regardless of the scoring system adopted, it should become part of the routine assessment – temperature, pulse, respiration, and pain score ('TPRP'). Analgesic intervention should restore normal behavior and lower the pain score.

Why Treat Pain?

Treating pain has obvious welfare benefits but also many other less obvious dividends pertinent to traumatized or critically ill cats. These include better cardiovascular stability, decreased metabolic and hormonal responses, and less catabolism and immunosuppression.[15] Surgical or accidental trauma results in primary (at the site of injury) and secondary (at sites distant to the injury) nociceptive sensitization that can lead to prolonged and intensified pain.[16,17] The benefits of pre-emptive analgesia in limiting central sensitization and 'wind-up' has been a controversial topic in human medicine but can be demonstrated.[18] In animals, there is good evidence that this is a worthwhile strategy[19,20] and data in cats are encouraging.[21] In emergency practice, the patient is often not seen until already in pain, but early intervention is still beneficial – the longer it takes before initiating an analgesic plan, the harder it becomes to achieve relief.

Drug Strategies for Alleviating Acute Pain

There are several factors to consider when choosing an analgesic drug for feline patients, including the unique metabolism of cats, availability of species-specific data including both the pharmacokinetic and pharmacodynamic profile of the drug, and also ease of administration (Table 1).

Hepatic metabolism

Cats have a reputation for adverse drug reactions; some of these are warranted and others are not. Cats have a low capacity for hepatic glucuronidation of exogenou-

Table 1: Drugs that can be used in cats for the treatment of acute pain. See text for further details

Drug	Dose (mg/kg)	Route	Comments
Opioids			
Butorphanol	0.1–0.4	IV, IM	Short acting (less than 90 minutes) Increasing the dose does not provide more intense or longer periods of analgesia
Buprenorphine	0.01–0.02	IV, IM, transmucosal	
Fentanyl	0.005–0.01 25 μg/hour patch	IV transdermal	May take up to 12 hours to reach effective plasma concentration. Uptake affected by body temperature
Hydromorphone	0.05–0.1	IV, IM	SQ route associated with vomiting Doses of 0.1 mg/kg and higher can produce hyperthermia
Meperidine	5–10	IM	Must not be given IV
Morphine	0.2–0.5	IV, IM	May be less effective in cats compared to other species due to lack of active metabolites
Oxymorphone	0.05–0.01	IV, IM	
NSAIDs			Do not use in hypotensive or hypovolemic patients
Carprofen	1–4	SQ	Not licensed for cats in USA Should not be repeated
Ketoprofen	1–2	SQ	Not licensed for cats in USA Can be repeated with care (1–5 days at 1 mg/kg)
*Meloxicam	0.2 or 0.1	SQ, IV, PO	One dose. Dose dependent on degree of pain (e.g., orthopedic versus soft tissue).
	0.1		Repeat once daily for 3 days
	0.025 (0.1 mg/cat) lean weight		Alternate day or twice weekly.
Local anesthetics			
Lidocaine	2–4	Local anesthetic blocks	Duration of action 1–2 hours Constant rate infusions not recommended in cats due to cardiovascular depression
Bupivacaine	2	Local anesthetic blocks	Duration of action 4–5 hours
α_2-agonists			Use with great care in cats with cardiovascular disease
Medetomidine	0.005–0.02 0.01	IV, IM, SQ epidural	Low doses combined with an opioid offer good sedation and analgesia
Other			
Ketamine	2	IV	No published data in cats on the efficacy of low dose constant rate infusions

*Only licensed NSAID for cats in the USA (injectable, one dose at 0.3 mg/kg SQ). The author and editor do not advise using this 0.3 mg/kg dose as further dosing is frequently required. Based on experience the 0.2 or 0.1 mg/kg (still effective dosages) followed daily with reduced dosages permits management of pain for an extended period of time. The oral formulation is off-label, however, this has been used in cats with careful attention to dose delivered. IM, intramuscular; IV, intravenous; PO, per oral; NSAID, non-steroidal anti-inflammatory drug; SQ, subcutaneous.

sly administered drugs which has a molecular genetic basis.[22–24] Domestic cats have fewer hepatic UDP-glucuroninosyltransferase (UGT) isoforms, and mutations of UGT and pseudogenes have been identified by cloning techniques. Exposure to plants that contain phytoalexins stimulate development of these pathways but cats have historically been obligate carnivores and this may, in part, explain the differences between species. These metabolic differences can lead to toxic side effects if doses and dosing intervals are not adjusted. In contrast, if the parent compound must be metabolized to an active component via this pathway, the drug may be less effective. Deficient glucuronidation pathways explain the cat's susceptibility to the adverse side effects of phenolic drugs such as acetaminophen (paracetamol) and long half lives of other drugs such as carprofen[25,26] and salicylates.[26,27] Cats produce very small amounts of the active metabolite morphine-6-glucuronide (M-6-G) which contributes to the overall analgesic profile of morphine; this may explain why morphine seems less effective in cats compared with other species.[28]

Drugs

The analgesic drugs that are most useful to the critical care and emergency clinician are the opioids, α_2-agonists, and local anesthetics. The NMDA receptor antagonist, ketamine, has been used extensively in cats for chemical restraint but may also have analgesic actions. With care, the non-steroidal anti-inflammatory drugs (NSAIDs) may also have a place for acute pain management.

Opioids

Opioids comprise the backbone of pain management in the critical care or emergency patient because of their efficacy, good safety margin and versatility. The lethal dose of individual opioids is not well documented in the cat, but in the rat, the median lethal dose of morphine is 64 mg/kg and for buprenorphine it is 234 mg,[29] which is 32 and over 4000 times the recommended analgesic dose, respectively. The safety of opioids is also enhanced by their reversibility with drugs such as naloxone or naltrexone. Butorphanol, buprenorphine, fentanyl, meperidine (pethidine), morphine, hydromorphone, and oxymorphone have all been used clinically in cats.[11,30] Butorphanol is classified as an agonist-antagonist (having a ceiling effect), buprenorphine as a partial agonist, and the others are opioid agonists. The opioid agonists have a linear dose–response and can be titrated to effect. Buprenorphine behaves like an opioid agonist and the so-called 'bell-shaped' curve is not seen at clinical doses. It is a misconception that cats are at a high risk of excitement or 'morphine mania' following opioid administration. Such reports were based on early literature when excessive doses (20 mg/kg of morphine) were administered.[31,32] Recent studies show that with appropriate dosing the behavioral effects usually include euphoria, with purring, rolling, and kneading with the front paws.[33–36] One exception is butorphanol which has been associated with dysphoric behavior.[37] An elevated body temperature is a concern in a sick or injured cat as the cause may be infection, administration of certain drugs or overzealous warming and the cause must be identified so that the correct treatment can be started. The practitioner should also be aware of opioid-related hyperthermia in cats. At doses of morphine >1 mg/kg, cats may become hyperthermic[38] and meperidine at 3 times clinically recommended doses resulted in temperatures as high as 41.7 °C (107 °F).[39] This phenomenon appears to be dose related, but even at commonly used clinical doses, some opioids may result in elevated body temperature. In a retrospective clinical study (Niedfeldt and Robertson, unpublished data), there was a strong association between the use of hydromorphone (at 0.05–1.0 mg/kg intramuscular [IM] or intravenous [IV]) and hyperthermia. Some of these cats had received only 1 dose, and others 2 or more. Rectal temperatures over 40 °C (104 °F) were recorded in 75% of the cats that received hydromorphone and a peak temperature of 42.5 °C (108.5 °F) occurred in 1 cat. Temperatures over 40.5 °C (105 °F) are cause for concern and may respond to external cooling such as fans and application of cool water to the fur.

However, higher temperatures are potentially life-threatening and in the study by Niedfeldt (2004, unpublished), 2 cats were open-mouth breathing and panting with body temperatures over 41.5 °C (107 °F). These cats responded quickly to naloxone but this opioid antagonist also reverses the analgesic effects of hydromorphone. The high incidence of hyperthermia at clinical doses has greatly reduced the use of hydromorphone in the author's clinical practice.

Cats treated with a transdermal fentanyl (TDF) patch had higher rectal temperatures than those given butorphanol.[40]

Opioids cause marked mydriasis in cats; this may cause them to bump into objects and they may not see a handler approaching. For these reasons, approach slowly while talking to the cat so it is not startled. Also, keep them out of bright light while their pupils are dilated.

Nausea, vomiting, and salivation can be seen after morphine and hydromorphone injection but is uncommon after buprenorphine, meperidine, or butorphanol.[33,34,41] The incidence of nausea and vomiting is also related to the route of administration; subcutaneous (SQ) hydromorphone results in a higher incidence of vomiting than the IV or IM route.[41] When administered to painful cats or in combination with acepromazine, the incidence of opioid-induced vomiting is considerably less.

Specific opioids

Butorphanol is a μ antagonist, which produces analgesia through its κ agonist activity. It is commonly used in cats in North America, and is generally given at doses from 0.1 to 0.4 mg/kg.[3] More recently, its analgesic properties have been called into question in both dogs and cats.[42] Butorphanol exhibits a 'ceiling' effect after which increasing the dose does not produce any further analgesia.[37,43] Butorphanol appears to be an effective visceral, but poor somatic analgesic.[43] Both clinical studies and experimental investigations indicate that butorphanol is short acting (<90 minutes)[34,43] and requires frequent dosing to be effective. Butorphanol is a poor analgesic choice in the face of both somatic and visceral pain, but would be a reasonable choice for acute visceral pain such as that associated with acute cystitis or enteritis.

Meperidine is only given by the IM or SQ route because of reports of excitement after IV dosing. In clinical studies (3.3–10 mg/kg IM), it appears to have a fast onset but short duration of action[12,44] and research studies suggest that at a dose of 5 mg/kg its duration of action is less that 1 hour.[33]

Morphine has been widely used in cats and doses of 0.1–0.2 mg/kg are effective in clinical cases and do not cause excitement.[11] Both clinically[11] and in research models[34] onset of action is slow. Morphine appears less effective in cats compared with dogs and this may be

related to their limited production of the active morphine metabolites morphine-6-glucuronide[45] which may contribute significantly to morphine's overall analgesic effect in humans.[46]

Oxymorphone has been a popular analgesic for many years in the USA.[35,47,48] Using a visceral pain model, Briggs et al.[48] reported that a combination of oxymorphone and butorphanol produced a greater degree of analgesia than either drug used alone and that this could be further enhanced by adding acepromazine. Clinically, oxymorphone does not appear to be associated with hyperthermia and is effective for many different types of pain with duration of effect of 2–4 hours.

Hydromorphone has become popular in veterinary medicine and has, to a great extent, replaced oxymorphone because it is less expensive.[49] Doses of 0.05–0.2 mg/kg of hydromorphone are generally recommended.[49] The relationship between dose and thermal antinociception (a measure of analgesia) of IV hydromorphone administration has been studied in cats. At doses of 0.025 and 0.05 mg/kg there was a small increase in thermal antinociception of short duration [Robertson, unpublished observations]. An IV dose of 0.1 mg/kg produced a substantial increase in thermal antinociception for up to 7 hours.[50] Route of administration has a significant effect on quality and duration of analgesia and side effects. When the analgesic and side effects of 0.1 mg/kg given by the IV, IM, or SQ route were compared, the IV route produced the greatest intensity and duration of antinociceptive effect with the least incidence of vomiting and salivation.[41]

In contrast to the study by Briggs et al.[48] a combination of hydromorphone (0.1 mg/kg IM) and butorphanol (0.4 mg/kg IM) did not have additive effects on thermal antinociception, but rather produced a longer lasting (up to 9 hours) but less intense effect than hydromorphone alone.[51]

Buprenorphine is the most popular opioid used in small animals practice in the UK[5] and is also widely used in the rest of Europe, Australia, and South Africa.[4,6] In research cats, it has been studied after IM,[34] IV, and oral transmucosal (OTM)[52] administration. IM doses of 0.01 mg/kg resulted in a slow onset (2 hours) of analgesia with a variable duration ranging from 4 to 12 hours.[34] Systemic uptake of buprenorphine after OTM dosing is almost 100% complete[53] in cats. The pH of the cat's mouth is between 8 and 9, which would enhance absorption, and this may explain the effectiveness of this route in cats compared with other species with a neutral oral pH.[53] There was no difference in onset of analgesia (within 30 minutes), time to peak effect (90 minutes) or duration of action (6 hours) when 0.02 mg/kg was administered by the IV or OTM route in research cats.[52]

In clinical studies, buprenorphine produced better analgesia than morphine in cats undergoing a variety of soft tissue and orthopedic procedures,[54] was superior to oxymorphone for sterilization (with or without onychectomy)[35] and provided longer pain relief than meperidine (pethidine) following ovariohysterectomy.[55] Buprenorphine rarely causes vomiting or dysphoria and has not been associated with hyperthermia (Niedfeldt and Robertson, unpublished data).

There is very little information in the veterinary literature about the effect of organ dysfunction on the metabolism of opioids. In humans with severe renal impairment, the metabolism of buprenorphine following single dosing or infusions was little affected and although metabolite concentrations increased these are unlikely to have significant pharmacological actions.[56] The effect of buprenorphine on gastrointestinal activity is discussed later.

Fentanyl is a potent, short acting pure μ agonist which is commonly used as a constant rate infusion (CRI).[30] In a cat specific study, 10 μg/kg IV provided rapid onset (peak action <5 minutes) of significant analgesia that lasted 110 minutes, with no excitement, salivation or vomiting.[36] In that study, plasma fentanyl concentrations and analgesia were closely correlated and it was concluded that at a plasma value of >1.07 ng/mL fentanyl provides analgesia, which is similar to that reported for dogs[57] and humans.[58] This data should be the basis of formulating more rational CRI and target controlled infusion protocols for cats.

Transdermal delivery systems

In the critical care setting, there has been great interest in transdermal delivery of drugs because they may offer a 'hands off' approach to pain management and could provide a constant delivery of drug thereby avoiding peaks and troughs seen with intermittent bolus administration.

A transdermal (matrix patch) delivery system for buprenorphine is now available for use in humans (Transtec).[a] In cats, there is systemic uptake after application of a 35 μg/h patch but plasma concentrations were very variable and over a 4-day period, no effective analgesia was demonstrated.[59,60]

The transdermal fentanyl (TDF) patch has been used for acute perioperative pain in cats.[40,61,62] Plasma fentanyl concentrations are variable after patch placement in cats[40,61] and in one study,[63] 2 out of 6 cats never achieved plasma fentanyl concentrations above 1 ng/mL. Factors affecting plasma levels include the size of the patch compared with the weight of the cat, skin permeability, and body temperature. In critical care patients, hypothermia, hypovolemia, and decreased skin perfusion will decrease absorption. Mean serum levels in normo-

thermic (38 °C) cats were 1.83 ± 0.63 ng/mL compared with 0.59 ± 0.30 ng/mL in hypothermic (35 °C) animals.[64] In cats weighing <4 kg, placement of a 25 μg/h patch with full exposure of the adhesive layer resulted in a steady state plasma concentration of 1.78 ± 0.92 ng/mL compared with 1.14 ± 0.86 ng/mL when only one-half of the adhesive was exposed.[65] In general, cats achieve steady state plasma concentration within 6–12 hours after patch placement[66] and this persists for up to 18–20 hours[64] after removal. During the uptake phase, other opioids must be administered to provide analgesia and all, except butorphanol, could be used. TDF patches have proved useful in a clinical setting.[40,61,62]

The use of various drugs compounded in transdermal creams has become popular in veterinary medicine despite the lack of scientific studies.[67] Fentanyl compounded in pluronic lecithin organogel failed to be absorbed through the skin of the inner pinna or dorsum of the shaved neck of cats even after a dose of 30 μg/kg, therefore, these formulations cannot be recommended.[36]

Although not classified as an opioid, tramadol has weak binding affinity at μ-receptors and is thought to activate monoaminergic spinal inhibition of pain. In dogs, this drug shows promise for acute pain.[68] A dose of 1–2 mg/kg IV has been suggested for cats, but there are as yet no published reports of controlled clinical studies.

The morphology and sequencing of feline opioid receptors has not been extensively studied[69] but marked inter-cat variation in analgesic response to butorphanol has been reported[37] suggesting that cats also express genetic variability. This highlights the importance of careful assessment of pain in cats as one analgesic at a set dose is unlikely to be equally effective in all patients even with the same injury.

α_2-adrenoceptor agonists

Medetomidine is not licensed for use in cats in the USA but is in several other countries. Medetomidine provides dose-related sedation, muscle relaxation, and analgesia in cats[70] and can be excellent in an emergency setting as it provides reliable sedation and will allow the clinician to perform a clinical examination, take radiographs and perform minor procedures such as bandaging and jugular catheter placement. However, the main concern with its use in a critical care setting is its cardiovascular effects.

Although doses of between 40 and 150 μg/kg have been recommended, clinical experience shows that 20 μg/kg IM provides reliable sedation and analgesia for up to 1 hour. However, even this lower dose causes a significant decrease in cardiac output, stroke volume, and heart rate[71] Bradycardia and decreased stroke volume contribute to the decrease in cardiac output which is substantial, dropping from a mean of 1.3 to 0.49 L/min 15 minutes after treatment; this is accompanied by a 3-fold increase in systemic vascular resistance.[71] At 10 μg/kg IM, medetomidine caused a drop in ejection fraction from a mean of 55 to 43% and a 25% decrease in peak ventricular filling rate.[72] Some authors have cautioned against the use of medetomidine in cats with cardiac disease,[72] whereas others have suggested it may be beneficial in cats with left ventricular hypertrophy and outflow obstruction.[73]

In human medicine, there is great interest in the use of α_2-agonists where low doses of dexmedetomidine have provided excellent sedation, reduced opioid requirements and maintained respiratory and cardiovascular stability in intensive care settings.[74] Dexmedetomidine usage has been reported in cats, and combined with ketamine or butorphanol, minimal cardiovascular effects were reported[75] but because of expense, this drug is not widely used clinically.

The future success of medetomidine in veterinary clinical practice lies with the use of so-called 'microdoses' in the range of 1–5 μg/kg (IV or IM)[76] or as a CRI (1–2 μg/kg/hour) with or without opioids but critical evaluation of the cardiovascular effects of these protocols have not been undertaken in cats.

The actions of medetomidine can be reversed with atipamezole[76] and certainly the ability to antagonize potentially dangerous cardiovascular complications or inadvertent overdose is an advantage. However, in dogs, rapid reversal with IV atipamezole may induce hypotension,[77] therefore, unless it is a life-threatening situation, the IM route should be used or the dose can be given by slow (over 2–3 minutes) IV titration until the desired effect is achieved. This latter technique can be used to maintain mild sedation and analgesia. If medetomidine is used the patient's temperature should be monitored as hypothermia can occur.[76] Xylazine results in hypoinsulinemia and hyperglycemia and although the endocrine effects of medetomidine in the cat are not well documented it should be avoided in diabetic patients. Medetomidine induces vomiting in a high percentage of cats[78] so should not be used when an increase in intraocular or intracranial pressure must be avoided. A further side effect of the α_2-agonists is profound diuresis.

Medetomidine is best reserved for use in previously healthy cats that require sedation following acute trauma, for example a fracture where blood loss is not an issue. Medetomidine should not be given to cats with cardiovascular disease, pre-existing hypovolemia, or head trauma.

Local anesthetics

Local anesthetics can be used for regional blockade (epidural analgesia), to block specific nerves (intercos-

tal, limbs), and infiltrated into wounds or fractures (surgical or traumatic).[30,79] The value of these techniques is underestimated in trauma and surgery patients where they can provide complete analgesia with minimal side effects and whenever possible the clinician should use local anesthetics. Lamont[30] offers a good review of techniques including brachial plexus block. A particularly useful technique is to implant a 'soaker' catheter into a wound (for example, large laceration, degloving injury, post-amputation wound) to provide a method for maintaining continuous analgesia. Lidocaine (2–4 mg/kg) can be repeated every 2–3 hours or as needed based on wound palpation. Bupivacaine is longer acting and 2 mg/kg would be expected to last 4–5 hours. Both these drugs can be diluted with sterile saline to provide a suitable volume. Some authors recommend a combination of lidocaine plus bupivacaine to achieve a fast onset and longer duration of action; in this case the total dose of local anesthetic should not exceed 2 mg/kg.

Topical anesthetic creams can be applied to shaved skin to provide analgesia for venipuncture, large-bore catheter placement, bone marrow aspiration or a variety of other critical care procedures. The 2 commercially available agents are an over-the-counter liposome-encapsulated formulation of lidocaine (ELA-Max®, LMX™)[b] and a prescription only mixture of lidocaine and prilocaine (EMLA® cream).[c] Transdermal absorption did occur after application of 15 mg/kg of ELA-Max®, but plasma concentrations remained significantly below toxic values.[80] There was no systemic uptake of the components of EMLA® cream and its use subjectively eliminated the usual signs of discomfort seen with jugular catheter placement.[81]

In dogs, systemic lidocaine infusion has shown beneficial effects as an analgesic in surgery patients[82] and as an anesthetic sparing technique with no adverse cardiovascular effects.[83,84] In cats, increasing plasma concentrations of lidocaine caused a dose-dependant decrease in isoflurane requirements.[85] Despite a significant reduction in the dose of inhalant agent, lidocaine produced more cardiovascular depression than an equipotent dose of isoflurane alone and was associated with an increase in blood lactate concentration[86] and, for these reasons, cannot be recommended in cats. This study emphasizes once again the importance of species-specific studies.

Epidural drugs

Opioids, α_2-agonists, local anesthetics, or combinations of these drugs can be administered via the epidural route in cats.

Opioids exert their major analgesic effect in the dorsal horn of the spinal cord and intrathecal or epidural administration provides long lasting analgesia with fewer systemic side effects. Morphine (0.1 mg/kg), fentanyl (4 μg/kg), meperidine (pethidine), and methadone have been used successfully via the epidural route in cats[87–92] with morphine being the most clinically useful in terms of analgesia achieved, duration of action and lack of side effects. In 1 study, 2 out of 23 cats that received epidural morphine had urinary retention.[92] Lidocaine or bupivacaine are often co-administered with an opioid to enhance analgesia.[30]

Epidural administration of medetomidine (10 μg/kg) was found it to be superior to fentanyl (4 μg/kg)[90] and systemic effects were mild and short lived.[89]

Epidural techniques may be an option for cats with tail, abdominal, pelvic or hind-limb pain, or that require surgery at these sites. Opioids alone can provide good thoracic analgesia with minimal systemic effects. Epidural injection is technically more challenging in cats because of their small size and because the spinal cord ends more caudally; entering the subarachnoid space is more likely. If this occurs, half of the epidural dose may still be administered.[30]

Ketamine

Ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate receptor that has been implicated in central sensitization. In human medicine, ketamine is being re-examined for its analgesic potential.[93] In dogs, sub-anesthetic doses of ketamine (2.5 mg/kg) given preoperatively provided better postoperative analgesia than the same dose given at the end of surgery[94] and low dose ketamine infusion in dogs after major surgery is opioid sparing.[20]

Ketamine is widely used in cats as a dissociative anesthetic agent, but there is little information on its role as an analgesic. One study demonstrated a weak visceral analgesic effect[95] and anesthetic protocols that incorporate ketamine provide better postoperative analgesia than those without.[21]

Low dose ketamine (2 mg/kg IV) produced excellent sedation in cats with an initial increase in thermal antinociception but after sedation had worn off there was a delayed onset of significant hyperalgesia or allodynia when even handling and stroking the cats prompted aversive behavior.[96,97] It should be noted that in these studies cats did not undergo any painful procedures. Ketamine can only inhibit NMDA receptors if they have been opened by a noxious stimulus[98] and this may explain the difference between the use of ketamine to sedate pain-free cats compared with those in pain or undergoing surgery. The benefits of using low doses or infusions of ketamine in cats to alleviate pain warrants further study.

Cerebellar dysfunction following general anesthesia is reported to be linked to the use of ketamine in Persian cross cats[99] but anecdotally happens in other breeds and mixed breeds. The cause is unknown, but can range from mild to severe and is usually permanent.

NSAIDs

The use of this group of analgesics in cats has recently been reviewed.[100] They can provide up to 24 hours of analgesia, and are not subject to the legal regulations of opioids. Although several are licensed for use in cats in other countries, only one (injectable meloxicam) is in this class are currently labeled for feline use in the United States.

These drugs act to inhibit cyclo-oxygenase (COX) enzymes and because there is considerable species variation in COX expression, the efficacy and safety of a drug in one species cannot be assumed in another. It was believed that COX-1 was responsible for normal homeostatic functions such as maintenance of gastric mucosal integrity, platelet function, and renal autoregulation, while COX-2 was associated with inflammation. The development of COX-2 selective NSAIDs was hailed as a breakthrough in preventing toxicity from these drugs, but continued reports of problems associated with their use suggest that the simple COX-1/COX-2 concept is flawed and much more complex than previously believed. It is now known that in some species constitutive COX-2 is produced in the kidney and central nervous system and is required for normal function.

As a group, NSAIDs have a lower safety margin than opioids or α_2-agonists and are not reversible. There is potential for NSAID toxicity in cats since their limited ability to glucuronidate exogenous drugs results in prolonged duration of effect with the potential for drug accumulation. The mean half-life of carprofen in cats is approximately 20 hours, twice that of the dog, but can vary from as short as 9 hours up to 49 hours.[25,26] The use of carprofen, meloxicam and ketoprofen is well documented in cats.[12,44,55,101,102]

As in other species, the contraindications to NSAID use are gastrointestinal ulceration or bleeding, platelet dysfunction, renal dysfunction, and concurrent corticosteroid use. Renal autoregulation is prostaglandin dependant in the face of hypotension and NSAIDs must not be given in the face of volume depletion (vomiting, diarrhea, hemorrhage, or other fluid losses) or in situations such as sepsis where low blood pressure is likely or has been confirmed. Cats appear to be particularly susceptible to the adverse renal effects of NSAIDs.

In some situations, for example, the stable normovolemic trauma patient, these drugs can be valuable for alleviating acute pain. Carprofen has a long history in the United Kingdom where the injectable formulation (4 mg/kg) is licensed for a single treatment. However, clinically there seems little benefit of the 4 mg/kg dose over 2 mg/kg,[12] and the lower dose is recommended. There have been reports of gastrointestinal toxicity generally associated with concurrent disease and prolonged administration of the oral formulation.[103] Problems with repeated dosing are likely a result of individual variation in pharmacokinetics.

Meloxicam is a COX-2 selective NSAID that is available as an injectable and oral formulation. In the USA, only the injectable formulation (0.3 mg/kg) is approved for cats and for one dose only. Its use at lower doses (0.1–0.2 mg/kg) appears to be effective and may be preferred over the approved dose. The honey flavored oral liquid marketed for dogs is widely used (off label) in cats because it is palatable and has been used for longer periods.

Ketoprofen is available as an injectable formulation but oral preparations are commonly compounded. The pharmacokinetics and clinical efficacy of ketoprofen are well documented.[55,101,104] and it has been used for up to 5 days to treat cats with musculoskeletal pain[105] Because it is a potent COX-1 inhibitor, it may interfere with platelet function.

There seems to be little difference in the efficacy of the NSAIDs described above for the treatment of acute surgical pain.[101,102] Comparison of injectable NSAIDs given subcutaneously at extubation following ovariohysterectomy (carprofen 4 mg/kg, ketoprofen 2 mg/kg, and meloxicam 0.2 mg/kg), resulted in 9 out of 10 cats in each group having desirable overall clinical assessment scores for 18 hours. Despite the cats' apparent comfort, none of the NSAIDs prevented postoperative wound tenderness.[101] If used as part of an analgesic plan, the choice of agent will depend on personal preference, and intended duration of use.

Effects of analgesics on gastrointestinal function

The effects of pain itself and the analgesics and sedatives used in the critical care setting on bowel function must be considered. Pain can cause bowel stasis, abdominal distension, discomfort, and vomiting adding to the overall misery of the patient. Analgesic intervention often results in a dramatic improvement but if therapy is continued for days or weeks the effects on gastrointestinal function should be monitored.

IM acepromazine (0.1 mg/kg) combined with buprenorphine (0.01 mg/kg) or medetomidine (50 μg/kg) alone provided good restraint and did not alter orocaecal transit time in cats, whereas ketamine (5 mg/kg) and midazolam (0.1 mg/kg) did decrease gastrointestinal motility.[106] The use of TDF patches has not sparked comments about constipation and transdermal bupre-

norphine patches did not affect food intake or frequency of bowel movements.[60] However, systemic treatment with buprenorphine can cause inappetence in some cats after 2–3 days, which often resolves when the dose is reduced (author's own observations), or if there are no contraindications, NSAID therapy can begin and opioid doses decreased or stopped.

In humans, immobility contributes to constipation and this no doubt also applies to animals; although it may be difficult to encourage a cat to exercise, it should be given room to move around and the chance to interact with humans and toys while hospitalized.

Opioid antagonists that work only at peripheral sites and do not antagonize centrally mediated analgesia show great promise in humans[107] for treating ileus but have not been used widely in veterinary medicine.

Special Situations

Management of fractious patients

Fractious cats are a challenge in the emergency setting because the clinician is unable to examine the patient and may have no history or access to previous blood work. It is often unclear if the cat is painful or not. However, physical restraint is often ineffective and can lead to further stress and even worsening of wounds or fractures if the cat continues to resist and becomes explosive. Clinicians often resort to placing these cats in an anesthetic chamber and administering inhalant agent. Great care should be taken as endogenous catecholamines combined with a high concentration of inhalant agent can be a lethal combination. Isoflurane and sevoflurane do not sensitize the heart to catecholamines as much as halothane and these newer agents may reduce the incidence of complications.

Alternative techniques include oral (transmucosal) drug administration. If the cat is injured and, therefore, painful, OTM buprenorphine (0.02–0.03 mg/kg) may be sufficient to sedate the cat. Oral xylazine, detomidine, or medetomidine combined with ketamine can provide useful sedation[108,109] as can ketamine alone.[109]

Head trauma

In several situations such as high-rise syndrome or hit-by-car scenarios, cats have multiple injuries and require analgesic intervention and or anesthesia, but may also have head trauma. In these situations, opioids are the first drug of choice as respiratory depression (which would include hypercapnia and cerebral vasodilation) is unusual at clinical doses. Medetomidine causes unpredictable vomiting and increased intracranial pressure (ICP) and should be avoided.

The use of ketamine in the face of head trauma is controversial but it appears that ketamine may in fact be neuroprotective.[110] In a space-occupying model of brain edema in cats, ketamine (2 mg/kg IV) decreased ICP and improved cerebral perfusion pressure and in a cytotoxic model ketamine had no effect on ICP.[111]

In summary, there is now considerable feline-specific analgesic data available and this can be incorporated into clinical practice. Opioids should be the first choice of drug, with buprenorphine a top choice because of its efficacy and lack of side effects. Local anesthetic techniques are under-utilized and time spent learning specific blocks will be time well spent. With care, the α_2-agonists and NSAIDs can also be used. Ketamine may have a role to play in overall pain management but still requires further study in cats.

Footnotes

[a] Transtec; Napp Pharmaceuticals, Cambridge, UK.
[b] ELA-Max® or L.M.X™; Ferndale Laboratories, Ferndale, MI.
[c] EMLA® Cream; AstraZeneca LP, Wilmington, DE.

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Managing Pain in Feline Patients

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Pet-owning households in the United States increased from 56% to 62% between 1988 and 2002, and recent statistics show that the 77.7 million pet cats outnumber dogs by almost 13 million [1]. Despite this, our understanding and treatment of pain in this species have lagged behind what is available for dogs. When questioned, veterinarians considered surgical procedures in dogs and cats to be equally painful but treated cats less often [2]. The undertreatment of surgical, traumatic, and chronic pain resulted from the difficulty in recognizing and assessing pain, lack of species-specific data on analgesic agents, fear of side effects, and lack of licensed products for cats.

The need for perioperative pain management is great, because most pet cats are spayed or castrated, and in the United States, many are also declawed. The incidence of chronic pain in cats is not well documented, but osteoarthritis is more prevalent than previously thought [3], challenging us to find safe and effective ways to make these animals comfortable.

Over the past few years, a better understanding of the cat's unique metabolism, combined with research and clinical studies, has led to more rational and effective drug choices for our feline patients.

Pain assessment

The benefits of pain management are numerous; however, to treat pain, we must first recognize it. Assessment of pain in animals is not an easy task but is essential for successful pain management. Pain is a complex multidimensional experience involving sensory and affective (emotional) components. It is now accepted that animals do experience pain even if they cannot communicate it in the same way that human beings do. Pain is a subjective and individual experience. We cannot "feel" another person's

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pain, and it is well documented that after identical surgical procedures, different people do not experience the same quality and intensity of pain. In animals, pain is what the observer says it is; because all judgments are subjective, if we "get it wrong," the animals suffer.

There is no "gold standard" for assessing pain in animals. Many different scoring methods have been published, but few have been validated. It is now clear that each species exhibits pain differently and that we must take into account the different types and sources of pain, such as acute versus chronic pain and visceral compared with somatic pain. There is no question that as more studies focus on species-specific pain behaviors and the different types of pain, our ability to recognize pain in animals will improve, but we must accept that it is currently a subjective and inaccurate science. Ignoring pain simply because it is difficult to measure is not an option, however.

Most pain assessment studies have focused on acute postoperative pain, and more has been published about dogs than about cats. Investigators have failed to find a good correlation between physiologic variables (eg, heart rate, blood pressure) or plasma cortisol levels and pain scores in cats [4–6]. Conversely, changes in wound sensitivity have correlated well with visual analog pain scores in cats [7], suggesting that this simple clinically applicable technique is a valuable tool and should be incorporated into an overall assessment protocol. Recent adaptations of gait analysis platforms and pressure mats to suit cats show great promise for studying acute musculoskeletal [8] and arthritis pain [9].

Any pain-scoring system that is adopted for use must be valid, reliable, and sensitive as well as simple and quick to perform in a busy clinical setting. There are many to choose from (for a review, see the article by Robertson [10]), including simple descriptive scales, numeric rating scales, and visual analog scales, which are faulted for large interobserver variability [11]. It is now accepted that systems including behavior assessments and observation and interaction with the animal are most reliable. Knowledge of normal behavior of the individual animal evaluated is essential, and, often, the owner and technicians who spend a lot of time with the animal are the best judges. Deviations from normal behavior suggest pain, anxiety, or some combination of stressors.

Pain assessment after surgery should be an integral part of care just as temperature, pulse, and respiration are. In general, the more frequent the observations, the more likely it is that subtle signs of pain will be detected, but this must be weighed against what is practical.

Signs that suggest pain in cats include a hunched posture with the head held low, squinted eyes, sitting quietly and seeking no attention, trying to hide, or resentment at being handled. Excessive licking or biting at a surgical incision should initiate a prompt reassessment for pain. A cat sitting quietly in the back of the cage after surgery may be in pain and ignored by caretakers; interacting with the cat is essential. Once the effects of anesthesia have worn off, cats should perform normal tasks, such as grooming and

climbing into a litter box, if they are comfortable. Most cats dislike bandages, even the tape used to secure intravenous catheters, and respond by shaking their legs, biting at the bandage, or throwing themselves around. These reactions could indicate pain or dislike of the bandage, so it is important to differentiate between the two by palpation.

Cats may experience chronic pain associated with dental and gum disease, cancer, interstitial cystitis, chronic wounds, dermatitis, or osteoarthritis. Compared with dogs, little is known about degenerative joint disease in cats, but radiographic evidence in geriatric cats suggests the incidence may be as high as 90% [3]. The behavioral changes that accompany osteoarthritis may be insidious and easily missed or assumed to be inevitable with advancing age. Because of their lifestyle, lameness in cats is not a common owner complaint, but changes in behavior, including decreased grooming, reluctance to jump up on favorite places, and soiling outside the litter box, should prompt the veterinarian to look for sources of chronic pain. Other changes that owners report are altered sleeping habits (an increase or decrease), withdrawing from human interaction, hiding, and dislike of being stroked or brushed.

Drug metabolism

Cats have a low capacity to handle drugs that require hepatic glucuronidation, which has recently been explained by molecular genetic studies [12–14]. Domestic cats have fewer hepatic UDP-glucuroninosyltransferase (UGT) isoforms, which represent major phase II drug-metabolizing enzymes, as a result of mutations of UGT and the presence of pseudogenes. It is suggested that because cats are carnivores, they had no evolutionary need to develop systems that metabolized the phytoalexins, a group of compounds found in cruciferous plants. The clinical consequence of this is twofold: toxic side effects may occur if doses and dosing intervals are not adjusted, or, alternatively, if the parent compound is metabolized to an active component via this pathway, the drug may be less effective. The cat's susceptibility to toxic side effects of phenolic drugs, such as acetaminophen (paracetamol), and the long half-life of aspirin can be explained by the deficient glucuronidation pathway.

Analgesic drugs

The "classic" analgesic drug categories include the opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics. The α_2-agonists, such as xylazine and medetomidine, provide analgesia in addition to sedation and muscle relaxation. Other drugs with potential as analgesic agents in cats include ketamine and other *N*-methyl-D-aspartate (NMDA)

inhibitors, such as amantadine; the tricyclic antidepressants amitriptyline and clomipramine; gabapentin, an anticonvulsant agent; and tramadol.

Opioids

In this section, some general features of opioids unique to cats are discussed, and individual drugs and different routes of administration are also covered.

Opioids are the mainstay of analgesic protocols in most species but have historically been avoided in cats because of a fear of producing excitement. Using expressions like morphine or opioid "mania" is unjustified and stems from the early literature when excessive doses were administered [15,16]. More recent studies show that at appropriate doses, opioids can have beneficial analgesic effects and that behavioral effects usually include euphoria, with purring, rolling, and kneading with the front paws [17–19]. Meperidine, methadone, morphine, oxymorphone, hydromorphone, buprenorphine, butorphanol, and fentanyl are now commonly used in cats alone or in conjunction with acepromazine, benzodiazepines, or α_2-agonists in clinical practice [20].

It is now apparent that individuals are unique with respect to number, morphology, and distribution of opioid receptors and that these differences are genetically determined [21]. This is proposed as the reason for the marked variability in response of human beings to opioids, with some individuals experiencing excellent pain relief and others only little. The morphology and sequencing of feline opioid receptors have not been extensively studied [22] compared with other species, but in controlled research environments, marked variation in analgesic response to opioids has been reported [23], suggesting that cats also express genetic variability. This underscores the importance of careful assessment of pain in cats, because one analgesic at a set dose is unlikely to be equally effective in all patients.

Elevation in body temperature after a medical or surgical procedure may be caused by infection, administration of certain drugs, or overzealous warming, and the cause must be identified so that appropriate treatment can be initiated. In cats, opioid-related hyperthermia is something the practitioner should be aware of. At doses of morphine greater than 1 mg/kg, cats may experience hyperthermia [24], and meperidine (Demerol, pethidine) at three times clinically recommended doses resulted in temperatures as high as 41.7°C (107°F) [25].

Although this phenomenon seems to be dose related, commonly used opioids at clinical doses may result in elevated body temperature. In cats that underwent onychectomy, the use of transdermal fentanyl (TDF) patches was associated with higher rectal temperatures (1.0°C above baseline) 4 to 12 hours after patch application compared with cats that received butorphanol [26]. Newer and more potent opioids, including

alfentanil, produce elevated rectal temperatures in cats anesthetized with isoflurane [27]. In a retrospective study comparing the use of buprenorphine or hydromorphone in a clinical setting (Niedfeldt R, DVM; Robertson S, BVMS, PhD, unpublished data, 2004), there was a strong association between the use of hydromorphone and hyperthermia. There was no change in mean rectal temperature in cats treated with buprenorphine in the 20-hour postanesthetic period, and only a few cats had temperatures higher than 40°C (104°F), but none exceeded 40.8°C (105.5°F). In contrast, those cats that received hydromorphone had elevated temperatures from 1 to 5 hours after anesthesia, with temperatures higher than 40°C (104°F) being recorded in 75% of the 74 cats and a peak temperature of 42.5°C (108.5°F) occurring in 1 cat. Administration of the NSAID ketoprofen had no impact on the incidence of hyperthermia (Niedfeldt R, DVM; Robertson S, BVMS, PhD, unpublished data, 2004).

Research studies support these clinical findings: hydromorphone at doses of 0.025 and 0.05 mg/kg (intravenous) was not associated with changes in skin temperature, but 0.1 mg/kg produced an increase of 1.0°C to 2.0°C in skin temperature (K. Wegner, DVM; S.A. Robertson, BVMS, PhD, unpublished data, 2004) [28].

In contrast to many other species, opioids cause marked mydriasis in cats. Resultant effects on their vision may cause them to bump into objects, and they may not see a handler approaching. For these reasons, they should be approached slowly, while being spoken to, so that they are not startled. They should also be kept away from bright light while their pupils are dilated. In research models, opioid-induced mydriasis does not correlate with the duration of analgesia.

When used alone for premedication in pain-free cats, some opioids may cause nausea, vomiting, and salivation; this is common after morphine and hydromorphone but not after buprenorphine, meperidine, or butorphanol [17,18,29]. The incidence of nausea and vomiting also depends on the route of administration; subcutaneous hydromorphone results in a higher incidence of vomiting than the intravenous or intramuscular route [29]. When administered with acepromazine, the incidence of vomiting is considerably less.

Little is known about opioid dependence in cats, and if this group of drugs is used for chronic pain management, this could be an issue if treatment were suddenly withdrawn. In this author's experience, cats frequently become inappetent after 2 to 3 days of opioid treatment, and this may be a result of decreased gastrointestinal motility.

Specific opioids and their actions in cats

The pure μ-agonist opioids (morphine, meperidine, oxymorphone, hydromorphone, and fentanyl) are subject to stringent regulatory controls (US Drug Enforcement Administration schedule II). Opioids not subject to such tight controls, for example, butorphanol, are popular for veterinary use

because of their convenience, and this drug is licensed for use in cats. Butorphanol is a μ-antagonist and produces analgesia through its κ-agonist activity. It is the most commonly used opioid in cats in North America and is generally given at doses from 0.1 to 0.4 mg/kg [30]. More recently its analgesic properties have been questioned in dogs and cats [31]. Agonist-antagonist opioids, such as butorphanol, exhibit a "ceiling" effect, after which increasing doses do not produce any further analgesia [23]. Butorphanol seems to be an effective visceral but poor somatic analgesic [32]. Clinical studies and experimental investigations indicate that butorphanol is short acting (<90 minutes) [18,23] and requires frequent dosing to be effective. In addition to an injectable formulation, butorphanol is available as a tablet. These produced better analgesia than placebo when used for several days after declawing surgery [33]. Butorphanol is a poor analgesic choice for surgical patients in which there will be somatic and visceral pain, but it would be a reasonable choice for acute visceral pain, such as that associated with interstitial cystitis. Its ceiling effect limits its use to minor procedures, and frequent dosing is inconvenient and expensive.

Meperidine is licensed for use in cats in the United Kingdom, where it is widely used. This drug is only given by the intramuscular or subcutaneous route because of reports of excitement after intravenous dosing. In clinical studies (3.3–10 mg/kg administered intramuscularly) it seems to have a fast onset but short duration of action [34,35]. Research studies that used a thermal stimulus to assess analgesia suggest that at a dose of 5 mg/kg, its duration of action is less that 1 hour [17]. Methadone is widely used in Europe and is said to produce good sedation and short-lived analgesia in cats, although there are few published data about this drug in cats. Clinical doses are generally 0.1 to 0.5 mg/kg administered intramuscularly or subcutaneously. Neither methadone nor meperidine is commonly used in cats in the United States.

Morphine has been widely used in cats, and doses of 0.1 to 0.2 mg/kg are effective in clinical cases and do not cause excitement [36]. In thermal threshold models, morphine produces significant hypoalgesia [18,37]. Clinically [36] and in research models [18], onset of action is slow. Morphine seems to be less effective in cats compared with dogs, and this may be related to cats' limited production of morphine metabolites [38]. Cats produce little of the metabolite morphine-6-glucuronide (see section on drug metabolism), which may contribute significantly to morphine's overall analgesic effect in human beings [39].

Oxymorphone has been a popular analgesic for many years in the United States [19,40]. Oxymorphone is up to 10 times more potent than morphine, but its duration of action is not well documented. Using a visceral pain model, Briggs et al [41] reported that a combination of oxymorphone and butorphanol produced a greater degree of analgesia than either drug used alone and that this could be further enhanced by adding acepromazine.

Hydromorphone has become popular in veterinary medicine and has replaced oxymorphone to a great extent because it is less expensive [42].

Doses of 0.05 to 0.2 mg/kg are generally recommended, and hydromorphone combined with acepromazine (0.05–0.2 mg/kg) produces excellent sedation and chemical restraint [42].

In our laboratory, we examined the relation between dose, thermal antinociception (a measure of analgesia), and change in body temperature after administering hydromorphone to cats. At doses of 0.025 and 0.05 mg/kg (intravenous), there was a small increase in thermal antinociception of short duration and no change in skin temperature. An intravenous dose of 0.1 mg/kg produced a substantial increase in thermal antinociception for up to 5 hours but was accompanied by a 1.0°C to 2.0°C increase in skin temperature [28] and has been implicated in postanesthetic hyperthermia in a clinical setting (Niedfeldt R, DVM; Robertson S, BVMS, PhD, unpublished data, 2004). Route of administration has a significant effect on the quality and duration of analgesia and side effects. When doses of 0.1 mg/kg given by the intravenous, intramuscular, or subcutaneous route were compared, the intravenous route produced the greatest intensity and duration of antinociceptive effect, with the least incidence of vomiting and salivation [29]. In contrast to the study by Briggs et al [41], a combination of hydromorphone and butorphanol did not have additive effects on thermal antinociception but instead produced a longer lasting (up to 9 hours) but less intense effect than hydromorphone alone [43].

Buprenorphine is a partial μ-agonist and is a US Drug Enforcement Administration schedule III drug. Buprenorphine is the most popular opioid used in small animal practice in the United Kingdom [2] and is also widely used in the rest of Europe, Australia, and South Africa [44,45]. In research cats, it has been studied after intramuscular [18], intravenous, and buccal [46] administration. Intramuscular doses of 0.01 mg/kg resulted in a slow onset (2 hours) of analgesia, but once established, this lasted at least 6 hours [18]. Buprenorphine was almost 100% bioavailable after buccal administration [47], which is much higher than in human beings. The effectiveness of this route in cats is thought to be a result of the alkaline (pH 8–9) environment of the cat's mouth [47]. The buccal route (0.02 mg/kg) was also shown to be as effective as the intravenous route, providing analgesia for more than 6 hours in research cats [46]. In a clinical setting, buccal administration has proved to be simple, effective, and well accepted by cats and can be mastered by owners for at-home treatment. In clinical studies, buprenorphine has produced better analgesia than morphine [48], oxymorphone [19], and pethidine [49]. Buprenorphine rarely causes vomiting or dysphoria and has not been associated with hyperthermia; these features, combined with ease of administration, efficacy, and long duration of action, make it an ideal drug for perioperative use in cats.

A transdermal delivery system for buprenorphine is now available for use in human beings in several European countries (Buprenorphine TDS, Transtec; Gruenenthal GmbH, Aachen, Germany). Radbruch [50] reported that 81% of more than 3000 patients with chronic pain received good pain

relief. Murrell and colleagues [51] reported systemic uptake after application of a 35-μg/h patch in cats, which was not associated with significant increases in thermal threshold. A 52.5-μg/h patch and 70-μg/h patch are available, but they have not been tested in cats.

Fentanyl is a potent, short-acting, pure μ-agonist that is most commonly used to supplement general anesthesia, where it can be given as intermittent boluses or by infusion [20].

A more popular formulation is TDF patch that releases fentanyl over several days. These are intended for treatment of cancer-related pain in people [52] but have been used for acute perioperative pain in cats [26,53,54]. They provide a "hands-off" approach to pain management that is especially attractive in cats that are difficult to medicate. The plasma concentrations associated with analgesia are reported to be greater than 1 ng/mL in dogs [55] and people [56], and recent work would suggest that this is also true in cats [57]. Plasma fentanyl concentrations are variable after patch placement in cats [26,53], and in one study [58], two of six cats never achieved plasma fentanyl concentrations above 1 ng/mL.

Factors affecting plasma levels include the size of the patch compared with the weight of the cat, skin permeability, and body temperature. Mean serum levels in normothermic (38°C) cats were 1.83 ± 0.63 ng/mL compared with 0.59 ± 0.30 ng/mL in hypothermic (35°C) animals during isoflurane anesthesia [59]. In cats weighing less than 4 kg, placement of a 25-μg/h patch with full exposure of the adhesive layer resulted in a steady-state plasma concentration of 1.78 ± 0.92 ng/mL compared with 1.14 ± 0.86 ng/mL when only half of the adhesive was exposed [60]. In general, cats achieve steady-state plasma concentration faster than dogs (6–12 hours compared with 18–24 hours, respectively) [61], and this persists longer after patch removal in cats (up to 18–20 hours) [58] compared with the rapid decline seen in dogs [62]. TDF patches have proved useful in a clinical setting for routine ovariohysterectomy [54] and were at least as good or better than butorphanol for onychectomy [26,53]. The dangers of accidental or deliberate human ingestion must be considered, and TDF patches should not be placed on cats that are being discharged to a home with young children.

The use of various drugs, including fentanyl, compounded in transdermal creams has become popular in veterinary medicine but is only based on empiric information [63]. The American Veterinary Medical Association has stated that "no published scientific data exist to document the proper regimen of a gel product necessary to deliver a safe, yet effective, dose of any drug in any species." For instance, although widely used for treatment of hyperthyroidism, methimazole in pluronic lecithin organogel (PLO) applied to the inner pinnae of cats produces no measurable plasma drug levels [64]. In our laboratory, fentanyl compounded in PLO cream failed to be absorbed through the skin of the inner pinnae or dorsum of the shaved neck even after a dose of 30 μg/kg; measurable plasma levels were obtained in one cat after it was observed licking the application site [57].

Although not classified as an opioid, tramadol has weak binding affinity at μ-receptors and is thought to activate monoaminergic spinal inhibition of pain. In dogs, this drug shows promise for acute [65] and chronic [66] pain. A dose of 1 to 2 mg/kg administered intravenously has been suggested for cats, but there are as yet no published reports of controlled clinical studies.

Epidural administration of opioids

Opioids exert their major analgesic effect in the dorsal horn of the spinal cord, and intrathecal or epidural administration provides long-lasting analgesia with fewer systemic side effects. Morphine (0.1 mg/kg), fentanyl (4 μg/kg), pethidine, and methadone have been used successfully via the epidural route in cats [67–72]. Morphine is probably the most appropriate opioid with regard to duration of action and quality of analgesia combined with the fewest systemic effects. Epidural injection is technically more challenging in cats because of their small size, and because the spinal cord ends more caudally, entering the subarachnoid space is more likely. If this occurs, half of the epidural dose may still be administered [20].

Nonsteroidal anti-inflammatory drugs

The NSAIDs have the advantage of being long acting, providing up to 24 hours of analgesia, and they are not subject to the regulations of opioids. NSAIDs have not been widely used in cats, however, primarily because of the fear of toxicity. NSAIDs inhibit the cyclooxygenase enzymes COX-1 and COX-2 that are responsible for prostaglandin synthesis. In general, COX-1 is responsible for normal homeostatic functions, such as maintenance of gastric mucosal integrity, platelet function, and renal autoregulation, whereas COX-2 is generally associated with inflammation. The development of COX-2–selective NSAIDs was hailed as a breakthrough in preventing toxicity from these drugs, but continued reports of problems associated with their use suggest that the simple COX-1/COX-2 concept is flawed. It is now known that some constitutive COX-2 is produced in the kidney and central nervous system and is required for normal function. There is considerable species variation in COX expression, so that safety in one species cannot be assumed in another, a fact particularly relevant to the cat, where few pharmacokinetic and pharmacodynamic studies have been performed.

There is considerable potential for NSAID toxicity in cats. Their deficiency and variability of glucuronidation pathways result in slow metabolism of several NSAIDs, leading to prolonged duration of effect and drug accumulation. For example, the mean half-life of carprofen in cats is approximately 20 hours, twice that of the dog, but can vary from 9 to 49 hours [73,74]. More recently, newer NSAIDs have become available for veterinary use, and based on reports of their pharmacokinetic profiles and efficacy, carprofen, meloxicam, and ketoprofen are now being used in cats [34,35,49,75,76]. Although licensed for use in cats in some countries, this is

restricted to short-term use only, and no drugs in this class are labeled for feline use in the United States.

Carprofen was one of the first "newer" NSAIDs to be studied in cats, and this drug has a long history in the United Kingdom, where the injectable formulation (4 mg/kg) is licensed. Carprofen causes limited COX inhibition [73], which may explain its good safety record in widespread clinical use in cats. Renal autoregulation may be particularly important during anesthesia, where hypotension is common, and NSAIDs that affect renal autoregulation through COX inhibition are often avoided. Because of its limited potential for COX inhibition, carprofen is used before surgery but is only approved for a single dose.

There have been reports of gastrointestinal toxicity, which has generally been associated with concurrent disease and prolonged administration of the oral formulation [77]. Problems with repeated dosing are likely a result of individual variation in pharmacokinetics.

Meloxicam is a COX-2–selective NSAID that is available as an injectable and oral formulation. In the United Kingdom only, the injectable formulation (0.3 mg/kg) is approved for cats; preoperative administration is permitted and may be continued for a maximum of 3 days. The honey-flavored oral liquid marketed for dogs is widely used (off label) in cats because it is palatable.

Ketoprofen has been used as an analgesic in cats for some years, but because it is a potent COX-1 inhibitor, it is not licensed for preoperative use. The pharmacokinetics and clinical efficacy of ketoprofen are well documented [69,75,78].

There seems to be little difference in the efficacy of the NSAIDs described previously in the acute perioperative setting [75]. Comparison of three injectable NSAIDs given subcutaneously at extubation after ovariohysterectomy (carprofen, 4 mg/kg; ketoprofen, 2 mg/kg; and meloxicam, 0.2 mg/kg) resulted in 9 of 10 cats in each group having desirable overall clinical assessment scores for 18 hours. Despite the cats' apparent comfort, none of the NSAIDs prevented postoperative wound tenderness [75]. Choice of agent depends on personal preference, convenience of dosing, and intended duration of use.

There is only one clinical report on the use of NSAIDs for onychectomy in cats [19]. Those authors concluded that for declawing surgery, with or without sterilization, buprenorphine resulted in lower cumulative pain scores than ketoprofen.

Comparison of opioids and nonsteroidal anti-inflammatory drugs for surgical pain

Carprofen and meperidine have been compared when given subcutaneously at the end of surgery. Two hours after ovariohysterectomy, meperidine (10 mg/kg administered intramuscularly) provided better

analgesia than carprofen, but from 2 to 20 hours, carprofen was superior, and the cats that received carprofen required less "rescue analgesia" [35]. Injection of carprofen before castration or ovariohysterectomy was found to be more effective than meperidine given at the end of surgery [34] and seemed to offer good analgesia for 24 hours. A single dose of ketoprofen (2 mg/kg administered subcutaneously) given at the end of anesthesia outperformed a single dose of buprenorphine or meperidine [49].

The combined use of an opioid and an NSAID has not been critically evaluated, and a multimodal approach may produce better results than a single agent, because each drug works at a different part of the pain pathway.

Long-term use of nonsteroidal anti-inflammatory drugs in cats

In dogs and people, NSAIDs form the basis for managing chronic pain. Pharmacokinetic data are only available for single doses of NSAIDs in cats, and no studies have examined the metabolism or safety of chronic administration. As noted previously, most NSAIDs have a relatively long half-life in cats, and repeated dosing must be done carefully to avoid toxicity. Even when NSAIDs are approved for cats, none carries a label for more that 5 days of use, although long-term off-label dosing is now common. The key to successful chronic NSAID administration in cats is to use the lowest effective dose.

As in dogs, cats receiving NSAIDs for chronic pain should be monitored for side effects related to renal and hepatic function and gastrointestinal erosions. There are no accepted monitoring guidelines, but a biochemistry panel, packed cell volume, and total protein measurement before initiating treatment and repeated at 1 and 4 weeks and then every 4 to 6 weeks are recommended. Continual reassessment of the patient by the veterinarian and owner is important so that the dose can be tapered to the smallest effective amount.

Only one published study has evaluated the use of NSAIDs for musculoskeletal pain in cats. Sixty-nine cats with acute or chronic locomotor disorders were randomly assigned to receive meloxicam (liquid formulation, 0.3 mg/kg orally on day 1 and then 0.1 mg/kg for 4 more days) or ketoprofen (tablet formulation, 1 mg/kg orally for 5 days) [79]. Based on general attitude, appetite, weight bearing, lameness, and pain on manipulation, both drugs were equally effective, but meloxicam was more palatable and easier to administer. With care, meloxicam can be used long term in cats, and doses as low as 0.025 mg/kg administered three to four times a week can markedly improve the comfort of cats with cancer-related pain or osteoarthritis (author's personal experience).

Local anesthetic drugs

Local anesthetic blocks provide excellent analgesia in cats, but these techniques are underused. Local and regional blockade inhibits pain

transmission, which decreases anesthetic requirements and may limit central sensitization. A review of techniques is outside the scope of this article and is available elsewhere [20].

Newer formulations and routes of administration of local anesthetic drugs show promise. Phospholipid-encapsulated bupivacaine has a long residence time at the site of application and has provided effective analgesia after onychectomy in cats [80]. Two topical anesthetic creams are available: an over-the-counter liposome-encapsulated formulation of lidocaine (ELA-Max) and a prescription-only eutectic mixture of lidocaine and prilocaine (EMLA cream). These are applied to shaved skin to provide analgesia in advance of venipuncture, catheter placement, or skin biopsies. Transdermal absorption did occur after application ELA-Max at a dose of 15 mg/kg, but plasma concentrations remained significantly below toxic values [81]. A lidocaine patch (Lidoderm) is marketed for topical analgesia in people with postherpetic neuralgia. Horses with musculoskeletal pain showed clinical improvement after local patch application, and plasma levels were undetectable [82]. Currently, there are no reports on the safety or efficacy of this technique in cats.

α_2-Adrenoceptor agonists

This group of drugs, which includes xylazine, medetomidine, and, more recently, dexmedetomidine, provides sedation, muscle relaxation, and analgesia in cats. They are not commonly used for their analgesic effect alone because of the profound sedation and cardiovascular depression that accompanies their use. The vasoconstriction and decrease in cardiac output associated with α_2-agonists precludes their use in cats with cardiovascular disease or preexisting hypovolemia.

These drugs are excellent when used as part of the anesthetic protocol for healthy surgical patients because they make cats easier to handle, decrease anesthetic requirements, and provide analgesia. After ovariohysterectomy, medetomidine at a dose of 15 μg/kg provided similar pain relief as butorphanol at a dose of 0.1 mg/kg and was better than placebo treatment [83]. In painful and fractious cats, oral administration of medetomidine, which likely results in transmucosal uptake, is a useful technique [84].

Epidural administration of medetomidine (10 μg/kg) was found it to be superior to fentanyl (4 μg/kg) [70], and systemic effects were mild and short-lived [69]. This technique may be an option for cats undergoing caudal abdominal, pelvic, or hind limb surgery.

Ketamine

Ketamine has traditionally been viewed as a dissociative anesthetic used for chemical restraint in cats. More recently, ketamine, an NMDA antagonist, has been studied for its analgesic properties, because spinal

NMDA receptors are involved in the process of central sensitization and "wind-up" [85].

In a research model, a weak visceral analgesic effect of ketamine was reported [86]. Anesthetic protocols incorporating ketamine provide better postoperative analgesia in cats after ovariohysterectomy [87]. Ketamine (2 mg/kg administered intravenously) resulted in a brief increase in thermal antinociception, followed by a later period of significant hyperalgesia [88]. It should be noted that cats did not undergo any painful procedures in the latter study and that the effect of ketamine may be different when used for sedation alone compared with its use in surgical patients. Although popular and effective in dogs undergoing major surgery, low-dose ketamine infusions have not been critically evaluated in cats.

Other NMDA antagonists, such as amantadine at a dose of 3 to 5 mg/kg administered orally [89], have been suggested for treating chronic pain in cats, and there are anecdotal reports of its success.

Other analgesic agents and treatment modalities

Tricyclic antidepressants, including amitriptyline, clomipramine, and imipramine, can provide relief in human beings with chronic neuropathic pain. Amitriptyline (2.5–12.5 mg/kg administered orally once daily) has been used to treat feline interstitial cystitis with few side effects [90], and it may be effective for other chronic pain syndromes, including osteoarthritis.

The anticonvulsant gabapentin is clinically effective in diabetic-induced neuropathic pain in people, although the mechanism of action is not clear [91]. Based on individual case reports, this drug shows promise in cats [92], and suggested doses have been published [89].

Combinations of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate are being used with some success in cats with osteoarthritis and cancer as part of a multimodal approach to pain relief (Duncan Lascelles, BVSc, PhD, personal communication, January 2004).

Many cats tolerate acupuncture and massage surprisingly well, and these treatment modalities can provide significant pain relief. It is difficult to document the efficacy of acupuncture, because each patient is unique and is treated differently even if the underlying cause (eg, osteoarthritis) is the same. Large-scale prospective trials of complimentary therapies should be undertaken in veterinary medicine as they have been in human medicine.

Summary

In the past 10 years, great strides have been made in the field of feline analgesia. A better understanding of the cat's unique metabolism has led researchers to realize that extrapolation across species boundaries is unwise, and this has resulted in feline-specific studies. The opioids are now used

more commonly in cats, with good analgesic effect and few side effects. Excellent acute pain management is achievable in cats by using opioids, NSAIDs, α_2-agonists, and local anesthetics. Although much of the research data has compared the use of single drugs, a multimodal approach using agents that work at different parts of the pain pathway is commonly used in clinical settings, with added benefit. Compared with dogs, few pain-scoring systems have been developed for cats, and this remains an important goal.

Management of chronic pain in cats is a challenge because of the potential problems with long-term NSAID use; however, reports of low doses given at extended intervals are encouraging. As we gain experience with less traditional analgesics, such as amitriptyline, amantadine, and gabapentin, and critically evaluate complimentary therapies, our ability to provide comfort to this population of cats will improve.

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Pearls for the Clinician:
The Infection of Cats by *Mycoplasma haemofelis* and *Mycoplasma haemominutum*

Joanne B. Messick, VMD, PhD, Dip. ACVP

1. The prevalence of hemotrophic mycoplasma infections in anemic cats in the United States is about 25%.

2. Non-anemic cats can still be infected.

3. Be careful about comparing the literature regarding prevalence of these parasites because – populations being tested are different (anemic, ill, healthy, random, etc.), cut-offs to define anemia are different, and tests used to detect infection are different.

4. *M. haemofelis* may cause overt hemolytic anemia, whereas the anemia due to *M. haemominutum* infection is mild, but may be worse if there is a concurrent disease.

5. Chronic infections may promote MPD in FeLV and/or FIV infected cats.

6. PCR is exquisitely sensitive for detecting infection
   - Remember the dark side of PCR
   - Blood donor cats should be tested by PCR
   - Always submit a fresh blood smear (air dry) for microscopic evaluation

7. Treatment with doxycycline effectively controls acute infection and enrofloxacin may also be effective, but none of the antibiotics tested to date consistently clears the parasites.

8. Oh, treat the fleas – there is evidence that they can transmit *M. haemofelis*.

"Pearls" for the Clinician:

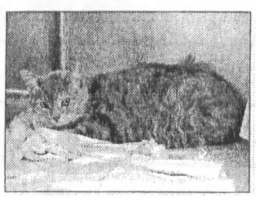
The Infection of Cats by *Mycoplasma haemofelis* and *Mycoplasm haemominutum*

Joanne B. Messick

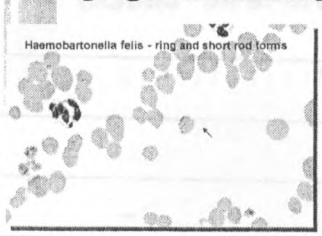
Cornell University
College of Veterinary Medicine

Pathogenicity: *Mycoplasma haemofelis* (*M. felis* / Ohio –large form)

- Clinical Signs
  - Hemolytic anemia
  - Fever
  - Anorexia,
  - Depression
  - Chronic carriers, perhaps for life



The parasites by light microscopy

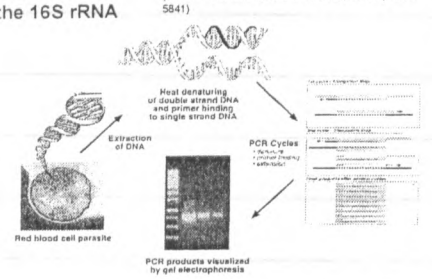


- *M. haemofelis* may have small coccoid, rod, and ring forms
- *M. haemofelis* is larger - more parasites per each RBC and more total RBCs infected than *M. haemominutum*
- Don't forget to prepare a fresh blood smear!!!

PCR of *M. haemofelis* and *M. haemominutum* based on the 16S rRNA gene

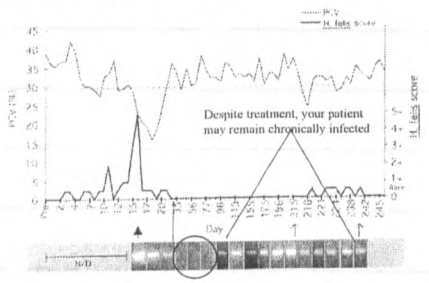
- Several different PCR assays are available
- Better than microscopy, but PCR can have a dark side!!

(J of Clin Microbiol Dec. 2005 Vol.43, No12, p.5835-5841)



J Clin Microbiol (36)462-466, 1998
AJVR(59)1215-1220, 1998

Experimental infection



J of Microbial Methods 34:235-243, 1999

Pathogenicity: *Mycoplasma haemofelis* (*M. felis*/Ohio –large form)

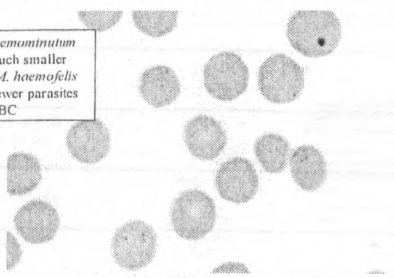
- *M. haemofelis* may act as a pathogenic agent
- *M. haemofelis* may be a cofactor in disease and/or act as an opportunist
  - FeLV
  - FIV

Pathogenicity: *M. haemominutum* (*H. felis* - CA)

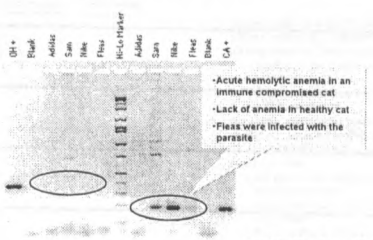
- Clinical Signs
  - Mild or no clinical signs — Foley JE, et al., AJVR, Vol 59, Dec. 1998
  - Mild or absence of anemia
    - If concurrent di sease, ie. M. haemominutum in patient with LSA, anemia is worse
  - Chronic carriers do not responsive to antibiotics
    - Disease(s) associated with chronic infection have not been investigated
- In cats that are coinfected with *M. haemominutum (or M. haemofelis)* and FeLV or FIV — George JW, et al., AJVR, Vol 63, Aug. 2002
  - Anemia is more severe
  - Hfsm may induce MPD in FeLV infected cats

M. haemominutum (*H. felis* - CA or Hfsm) in blood smear

M. haemominutum are much smaller than *M. haemofelis* and fewer parasites per RBC

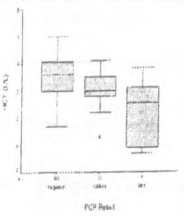


PCR and *M. haemominutum* (H.felis - CA or HFsm)



Am Anim Hos Assoc 40:423-427,2004

Hemoplasma infection and anemia



- HCT values for both *M. haemominutum* and *M. haemofelis* were lower than negative cats
- HCT values for *M. haemofelis were lower than M. haemominutum infected cats*
  - Overt hemolytic anemia with *M. haemofelis*
  - Data suggests a mild compensated hemolytic anemia (normalized or slightly low HCT) with *M. haemominutum*
    - With concurrent disease these cats may develop overt anemia
    - Treatment may be indicated for these cats(?)

PCR detection

<25% PCV

Organism	% anemic cats (no.)	% of cats without anemia (no.)
M.haemofelis	14.3 (4)	2.3 (3)
M.haemominutum	7.1 (2)	13.3 (17)
M.haemofelis *M.haemominutum*	7.1 (2)	0.8 (1)
TOTAL	28.6 (8/28) *M.haemofelis* = 21.4 *M.haemominutum* = 14.3	15.6 (20/128) *M.haemofelis* = 3.1 *M.haemominutum* = 14.1

28/156= 17.9%cats were anemic

- 21.4% of anemic cats had a *M. haemofelis* infection
- 13.3% of cats with NO anemia were infected with *M. haemominutum*

Jensen, Lappin, Kamkar & Regan, AJVR 2001

PCR detection of hemotrophic mycoplasmas in cats without signs

Numbers	*M. hf % infected*	*M. hm % infected*	*Location*
102	1.96%	15.7%	Japan
138	0.7%	14.5%	United States
128	3.1%	14.1%	United States
426	1.4%	16.9%	United Kingdom

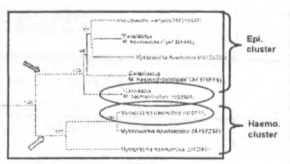
PCR detection of hemotrophic mycoplasma in cats with signs

Numbers	*M. hf* % infecte	*hm* % infected	Location
40	40%	12.5	Canada
147	23.1	4.1%	Australia
82	17.0%	15.9	United States
28	21.4%	14.3%	United States
30	20%	10%	Spain

PCV < 29%

PCV < 25%

Phylogeny: based on the 16S rRNA gene



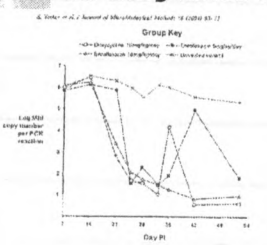
- *M. haemofelis* and *M. haemominutum are different!!*
  - Morphology
  - Disease & response to treatment
  - Phylogeny, they are different species

Similarity between *M. haemofelis* and *Candidatus* M. haemominutum is 83%

Candidatus M. haemominutum is most closely related to M. haemosuis

Foley and Pedersen, IJSEM 51:2001

Which antibiotics are best and do they clear the *M. haemofelis*?



- There was no significant effect of either antibiotic treatment on PCR assay results (Dowers et al.,2002)
  - Unable to say which treatment was better
  - Sustained clearance from blood in 3/12 treated cats
- All three antibiotic treatment regimes were effective at reducing *M. haemofelis* copy number (Tasker et al.,) 2004)
  - No significant differences between 3 treatment groups
  - Sustained clearance was not addressed
  - No significant differences between the 3 treatment groups

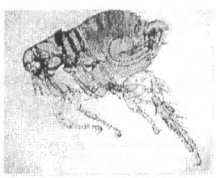
M. haemofelis (*H. felis-OH* or Hflg) in blood smear

In experimentally infected cats

- Azithromycin appears ineffective in controlling clinical disease or clearing the organisms
  Westfall DS, et al., AJVR 62:2001
- Enrofloxacin (10 mg/kg q 24 h) and doxycycline (5 mg/kg q 12 h) for 14 days have anti-*M. haemofelis* effects
  -May promote clearance

Dowers KL, et al., JAVMA 221:2002

Transmission



- Fleas infected with *M. haemofelis* can transmit the parasite
- Transmission of *M. haemominutum* by fleas was not successful
  - Low number of fleas might be responsible for these negative findings

  Lappin MR, et al, ACVIM 2003, abstract
- 40% of flea samples were PCR positve for haemoplasma species
  - *M. haemominutum* was the only species identified in this study and it was also detected in fleas collected from dogs

  Shaw SE, et al., Vet Micro, 102:183-188, 2004

M. haemominutum (*H. felis*- CA or Hfsm) in blood smear

In chronically infected cats:

- Treatment with doxycycline failed to clear parasites by PCR
  Foley JE, et al., AJVR,59:1581-1588,1998
- Imidocarb dipropionate given IM at 5 mg/kg twice with a 2 week interval failed to consistently clear *M.haemofelis* or *M. haemominutum*
  Lappin MR, et al., Vet Therap, 2:2002

ACVIM Consensus Statement

- Canine and Feline Blood Donor Screening for Infectious Disease

Table 2. Recommendations for infectious disease screening of healthy feline blood donors.

Disease	Disease Agent(s)	Screening	Test
Feline leukemia virus (FeLV) infection	FeLV	Recommended	ELISA
Feline immunodeficiency virus (FIV) infection	FIV	Recommended	ELISA
Hemotropic[1]	*Mycoplasma haemofelis*, *M. haemominutum*	Recommended	Microscopy, PCR
Babesiosis	*Babesia gibsoni*, *B. conradae*, *B. vogeli*	Conditional[2]	IFA, PCR, culture
Cytauxzoonosis	*Cytauxzoon felis*	Conditional[2]	Microscopy
Ehrlichiosis	*Ehrlichia canis*-like	Conditional	PCR
Anaplasmosis	*Anaplasma phagocytophilum*	Conditional	IFA, PCR
Neorickettsiosis	*Neorickettsia risticii*		

ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent antibody; PCR, polymerase chain reaction.
[1]See text for more specific recommendations.
[2]Geographic or breed restrictions might apply.

Wardrop KJ, et al., JVIM 19:135-142, 2005

The "Pearls"

- The prevalence of hemotrophic mycoplasma infections in anemic cats in the United States is about 25%
- Non-anemic cats can still be infected
- Chronic infections may promote MPD in FeLV and/or FIV infected cats
- PCR is exquisitely sensitive to detect infection
  - Remember the dark side
  - Blood donor cats should be tested
  - Always submit a fresh blood smear for microscopic evaluation
- Treatment with doxycycline effectively controls acute infection and enterofloxacin may also be effective, but none of the antibiotics tested to date consistently clears the parasites
- Oh, treat the fleas – there is evidence that they can transmit *M. haemofelis*

Dysmyelopoiesis in the Cat:

Is it a Primary or Secondary Disease and How Can I Tell the Difference?

Joanne Messick and Tracy Stokol

Dysmyelopoiesis is a general term that describes a heterogeneous group of blood disorders characterized by the presence of a peripheral cytopenia(s) despite a normal to hypercellular bone marrow - specifically for that lineage. Thus, hematopoiesis is ineffective. Morphologic abnormalities in one or more cell line in the blood and/or bone marrow is also characteristic of these disorders. Three general types of dysmyelopoiesis have been described in the cat, which include myelodysplastic syndrome (MDS), secondary dysmyelopoiesis, and congenital dysmyelopoiesis.

In 1976, the French-American-British cooperative group first described a system for classification of MDS in man. This system was subsequently applied and then modified to better describe the syndromes seen in cats. The subclassification of MDS into myelodysplastic syndrome with excessive blasts (MDS-EB) and myelodysplastic syndrome with refractory cytopenia (MDS-RC) appears to be useful in predicting the severity of clinical signs and prognosis. All of the cats in a recent report with a diagnosis of MDS-EB had short survival time. On the other hand, cats diagnosed with MDS-RC were less sick and tended to survive longer. FeLV infection has been associated with clonal proliferation of hematopoietic cells in some cats with MDS. This suggests a possible etiologic role for FeLV in the pathogenesis of this syndrome. It is well known that acute myeloid leukemia, pure red cell aplasia (experimentally-induced) and aplastic anemia are also associated with FeLV infection.

The most common cytopenia in cats is anemia, however dysplasia is often reported in all cell lines. Features of dyserythropoiesis may include circulating rubricytes without polychromasia (macrocytes), megaloblasts, abnormal nuclear shape, nuclear fragmentation and asynchronous maturation of the nucleus. The sequence of maturation of this lineage is often shifted, having increased numbers of immature forms. Abnormal cytoplasmic granulation, hypersegmentation, hyposegmentation (pseudo-Pelger-Huet anomaly), cell gigantism and overrepresentation of immature forms/maturational arrest are features of dysmyelopoiesis. In the megakaryocytic lineage, dsyplastic features including micromegakaryocytes, large platelets, multiple separate nuclei or a single non-lobed nucleus, abnormal cytoplasmic granularity and vacuolation have been reported. None-the-less, it was recently reported that dysplastic changes in the bone marrow are not a reliable feature for distinguishing MDS from secondary dysmyelopoiesis.

Dysplastic changes in the blood and bone marrow are also commonly seen with IMHA and pure red cell aplasia as well as with other diseases in the cat. Thus, it may be somewhat difficult to distinguish these secondary dysplasias from MDS. A high number of small lymphocytes in the marrow aspirate adds support to a diagnosis of IMHA and pure red cell aplasia. Marked macrocytosis and megaloblastic changes are reported to be more prominent in MDS, whereas erythroblasts and myeloblasts comprised <6% of all the nucleated cells in the marrow of cats with secondary dysmyelopoiesis. Detection of increased numbers of myeloblasts in the marrow of cats appears to be clinically useful for predicting a poor prognosis in cats with MDS. To distinguish immune-mediated diseases from MDS, response to an immune suppressive treatment regime may be a useful clinical tool.

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2. Hisasue M, Nishigaki K, Hiromi K, et al., Clonality analysis of various hematopoietic disorders in cats naturally infected with feline leukemia virus. *J Vet Med Sci* 2000,62:1059-1065.
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5. Weiss DJ. New insights into the physiology and treatment of acquired myelodysplastic syndromes and aplastic pancytopenia. *Vet Clin Small Anim* 2003, 33:1317-1334.
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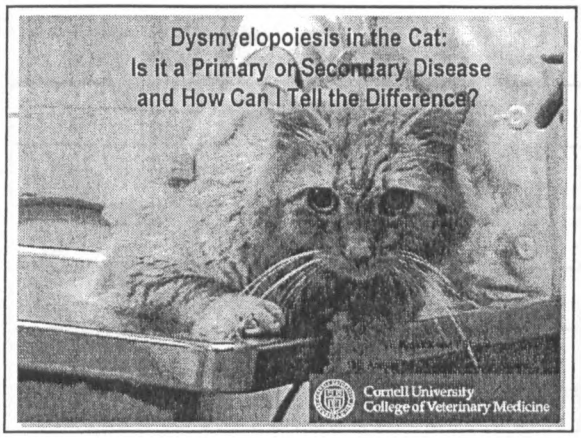
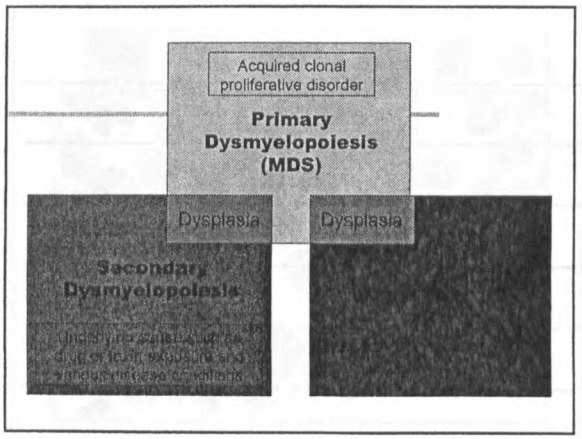


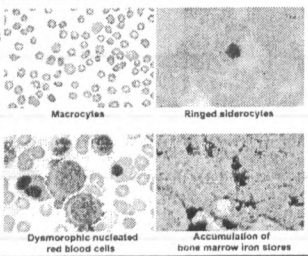
Dysmyelopoiesis

- From Greek
  - ✓ dys (bad, disordered, abnormal); muelos (marrow); poïsis (to make)
  - ✓ General term for hematologic disorders characterized by abnormal development or growth of hematopoietic cells
- Three types described in cats
  - ✓ Primary dysmyelopoiesis - MDS
  - ✓ Secondary dysmyelopoiesis
  - ✓ Congenital dysmyelopoiesis



Dysplasia - dyserythropoiesis

- Macrocytosis/megaloblasts
- Bizarre nuclear configurations
- Ringed sideroblasts
- Nuclear-cytoplasmic asynchrony
- Asynchronous maturation
- Low reticulocyte count
- Abnormal Fe metabolism



Dysplasia - dyserythropoiesis

- Macrocytosis/megaloblasts
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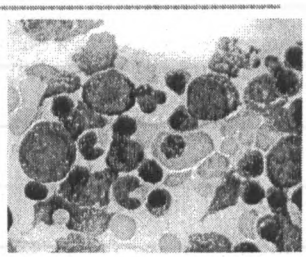
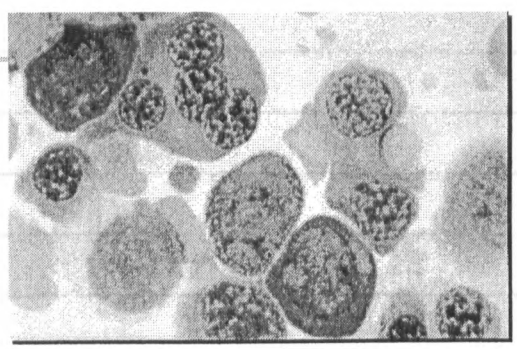
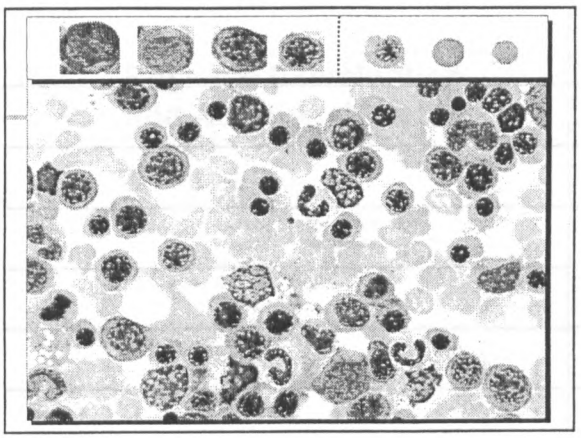
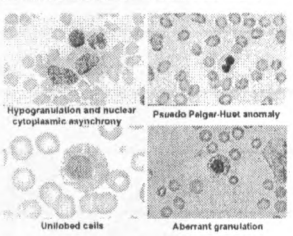


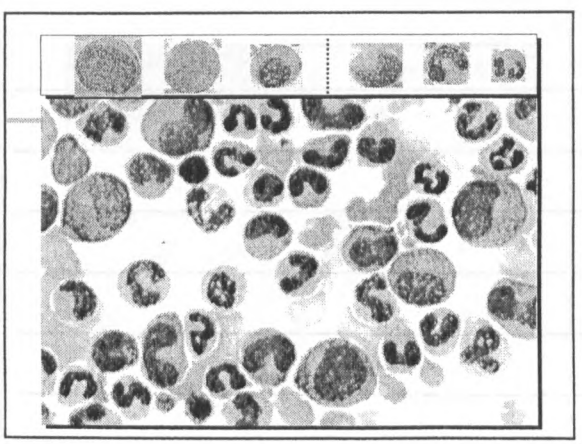




Dysplasia - dysmyelopoiesis

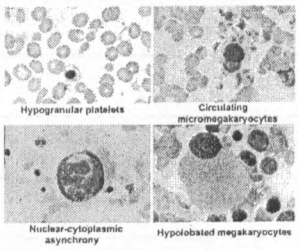
- Hypogranulation or aberrant granulation
- Nuclear-cytoplasmic asynchrony
- Asynchronous maturation
- Pseudo Pelger-Huet anomaly
- Defective adhesion, phagocytosis, and bacterial killing

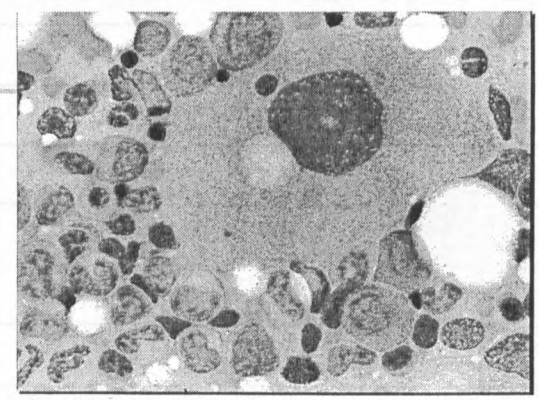


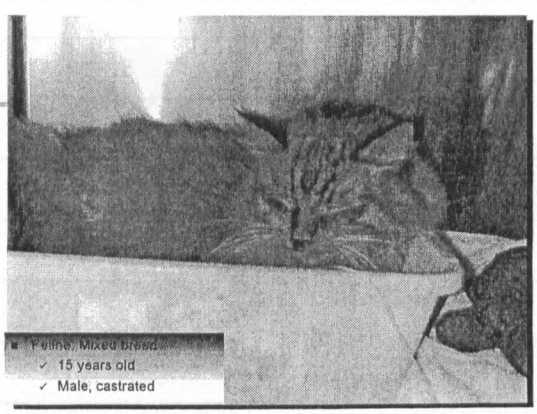


Dysplasia - dysmegakaryopoiesis

- Giant, agranular platelets
- Micromegakaryocytes
- Mononuclear or hypolobated megakaryocytes
- Abnormal platelet function







- Feline, Mixed breed
  - ✓ 15 years old
  - ✓ Male, castrated

Physical Examination and Additional Testing

- History and Physical Examination
  - ✓ rDVM referral for severe anemia
  - ✓ Pale mucous membranes
  - ✓ Lethargy
- Additional Testing
  - ✓ CBC and Chemistry panel
  - ✓ Reticulocyte count
  - ✓ Coombs testing
  - ✓ FeLV testing
  - ✓ Bone marrow evaluation

Laboratory Data

TEST	RESULTS 5-02-01	Reference Range
Red Blood Cells	1.50	6.9 0 $10.9 X 10^6/µl
Hemoglobin	2.9	10.1$16.4 g/dl
Hematocrit	8.7	32.0 $ 52.0 %
MCV	58	40 $ 52 fl
MCHC	33.7	29 $34 g/dl
WBC	13.5	5.30 - 16.6 X 10^3/µl
Platelets	adequate	

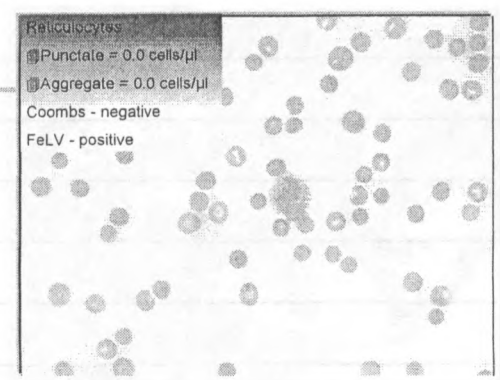
Reticulocytes

Punctate = 0.0 cells/µl

Aggregate = 0.0 cells/µl

Coombs - negative

FeLV - positive



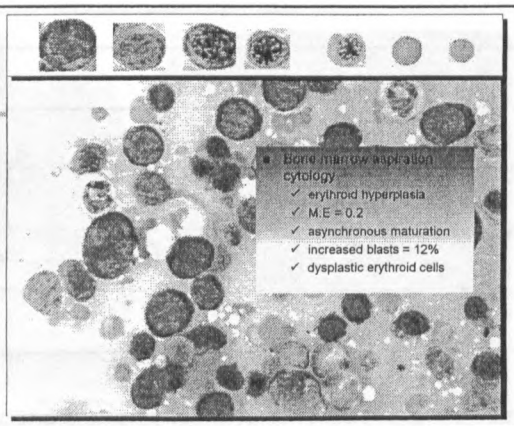
Differential Diagnosis

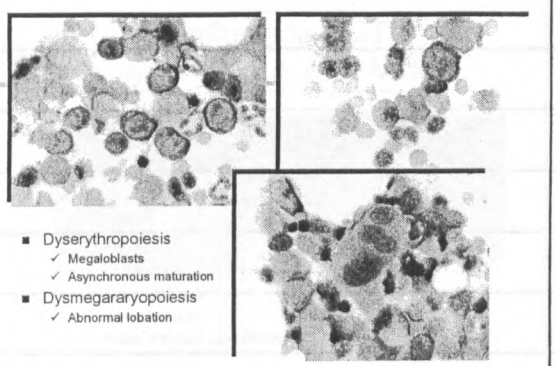
- Non-regenerative, normocytic normochromic anemia
  - ✓ Systemic disease
    - Anemia of chronic disease
      - Uremia
      - Liver disease
      - Hypothyroidism
      - Infection
      - Neoplasia
  - ✓ Too early for regenerative response
  - ✓ No systemic disease
    - Aplasia
    - Fibrosis
    - Infiltration
    - Dyserythropoiesis (primary (MDS), secondary, or congenital)

Normal findings are as important as abnormals, especially in prioritizing your list of differentials!

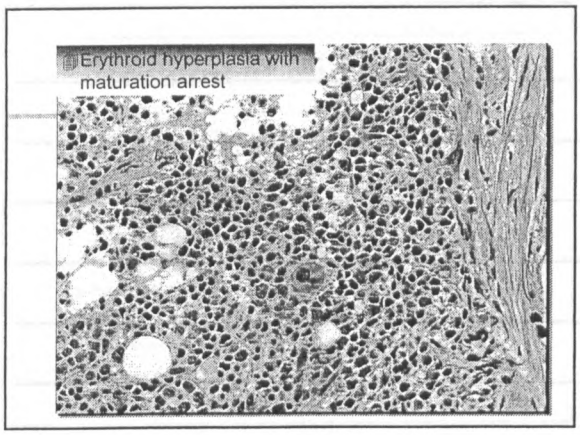
Bone Marrow Evaluation

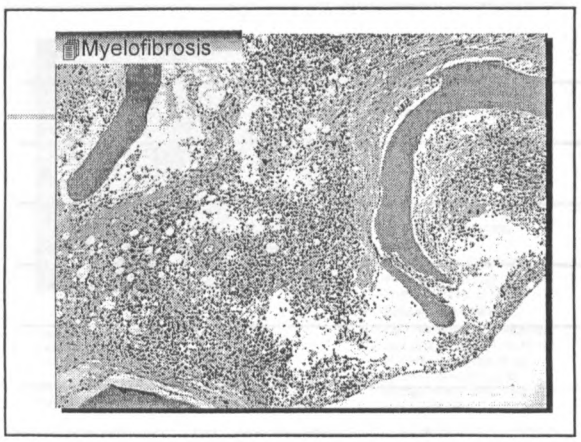
- Severe, non-regenerative anemia with macrocytosis

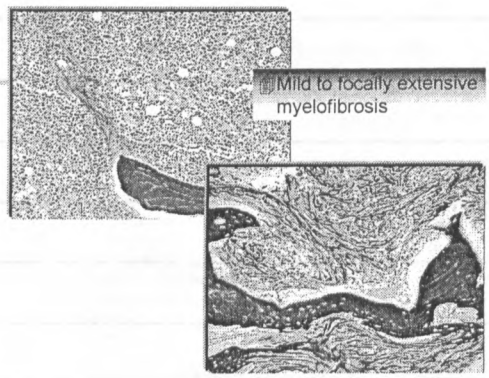


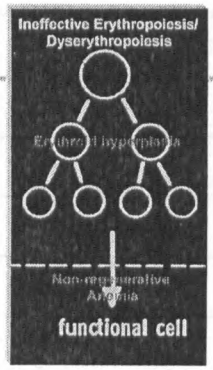


- Dyserythropoiesis
  - ✓ Megaloblasts
  - ✓ Asynchronous maturation
- Dysmegararyopoiesis
  - ✓ Abnormal lobation



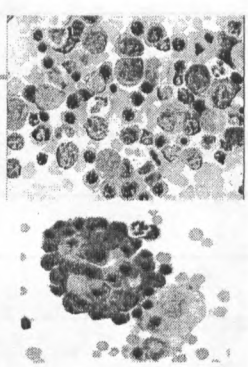






- Cytopenia in blood
  - ✓ Non-regenerative, refractory anemia
- Erythroid hyperplasia in marrow
  - ✓ Ineffective erythropoiesis
  - ✓ Fibrosis
- Dyserythropoiesis in blood and/or marrow
  - Elliptocytes, dacrocytes, and megalocytes
  - Asynchronous maturation, multinuclearity, nuclear fragmentation, megaloblastoid changes, cytoplasmic basophilia

- Ineffective erythroid production:
  - ✓ Early erythroid hyperplasia
  - ✓ Marrow destruction of precursors
  - ✓ Primary (MDS) or Secondary dyserythropoiesis



Dysplasia is NOT synonymous with MDS

- Drugs and chemotherapeutic agents
- Congenital disorders
  - ✓Poodle macrocytosis
  - ✓Congenital dyserythropoiesis
  - ✓Vitamin B12 in giant schnauzers
- Acquired
  - ✓Vitamin B12/folic acid deficiency
  - ✓Iron deficiency
  - ✓Lead toxicity
- Various disease conditions

Treatment and Outcome

- Treatment
  - ✓ Doxycycline (200 mg PO q 24 hours)
  - ✓ Ranitidine (0.5 ml IV BID)
  - ✓ Sucralfate (1 g slurry PO TID)
  - ✓ Prednisone (60mg PO BID)
  - ✓ Azothioprine
  - ✓ Transfusion and rhEPO
- Potential Outcomes
  - ✓ Response to immunosuppressive therapy
  - ✓ Failure to respond to treatment
  - ✓ Static disease or progress to blastic leukemia

Category	Blood	Bone Marrow
Dyserythropoiesis (MDS-Er)	Normocytic, normochromic anemia	M:E 1:1, 10% myeloblasts, nuclear fragmentation, binuclearity, asynchronous maturations, mild sideroblastosis
Sideroblastic dyserythropoiesis		sideroblastic
Dyserythropoiesis with excess blasts (MDS-EB)	Normocytic anemia	M:E 1:1, >10% myeloblasts, nuclear fragmentation, binuclearity, asynchronous maturations
Myelodysplasia (MDS-RC)	Pancytopenia, hypersegmentation	M:E >1, 10% myeloblasts, nuclear fragmentation, binuclearity, asynchronous maturation of all three lineages
Sideroblastic myelodysplasia	Pancytopenia, hypochromasia, erythrocytes, siderocytes, leukopenia	<10% blasts, sideroblastic, asynchronous maturation and giant granulocytic precursors

Weiss D. J. et al., Vet Clin Path, 1999; Vol 28, No 2, p 59-63

Weiss D. J., JAVMA, 2006; Vol 228, No 6, p 893-897

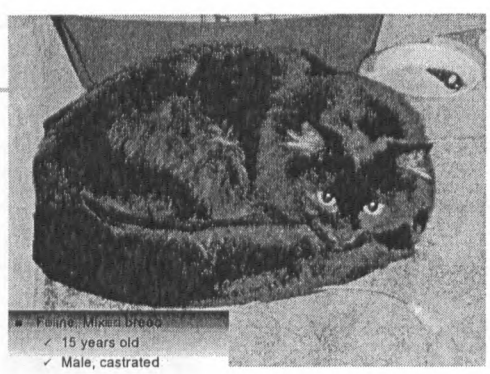
- Cytopenia (anemia) with concurrent hyperplasia (erythroid)
- Asynchronous erythroid maturation with high numbers of erythroblasts (12%)
- Bilineage dysplasia
- FeLV status (62% of MDS-EB and 25% of cats with MDS-RC in 2006 study), age of cat, absence of response to therapy and terminal blast cell crisis (AML-Er)

Literature Search

- 34 Cases of dysmyelopoiesis in cats between 1996 and 2005
  - ✓ 13/34 = 38%, MDS-EB
  - ✓ 8/34 = 23.5%, MDS-RC

  } 61.5%
  - ✓ 12/34 = 35.2%, secondary dysmyelopoiesis (IMHA, PRCA, ITP, LSA, chemotherapy, GN, FIP)

Weiss D. J., JAVMA, 2006; Vol 228, No 6, p 893-897



- Feline, Mixed breed
  - ✓ 15 years old
  - ✓ Male, castrated

Physical Examination and Additional Testing

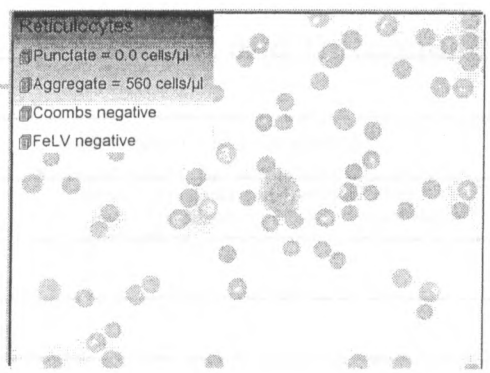
- Physical Examination
  - ✓ Pale mucous membranes
  - ✓ No organomegaly
- Additional Testing
  - ✓ CBC
  - ✓ Reticulocyte count
  - ✓ FeLV testing
  - ✓ Bone marrow evaluation

Laboratory Data

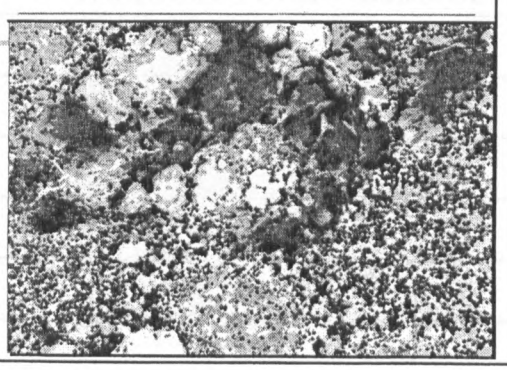
TEST	RESULTS 5-02-01	Reference Range
Red Blood Cells	3.01	6.9 $10.9 X 10^6/µl
Hemoglobin	4.64	10.1$16.4 g/dl
Hematocrit	15.0	32.0 $ 52.0 %
MCV	48.7	40 $ 52 fl
MCHC	31.7	29 $34 g/dl
WBC	13.5	5.30 - 16.6 X 10^3/µl
Platelets	adequate	

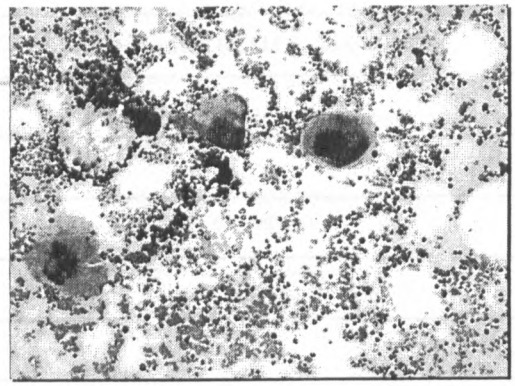
Reticulocytes

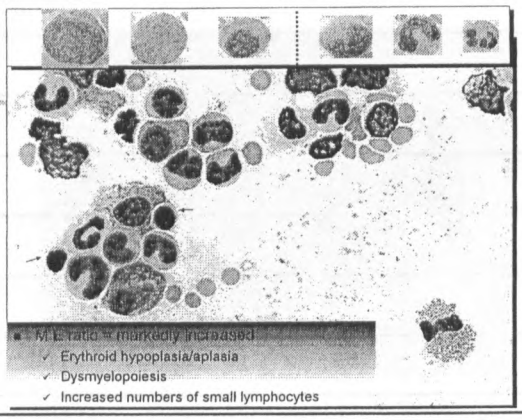
- Punctate = 0.0 cells/µl
- Aggregate = 560 cells/µl
- Coombs negative
- FeLV negative



Bone Marrow Evaluation



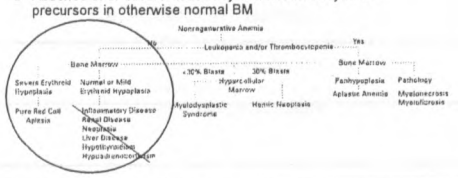




- M:E ratio = markedly increased
  - ✓ Erythroid hypoplasia/aplasia
  - ✓ Dysmyelopoiesis
  - ✓ Increased numbers of small lymphocytes

Pure Red Cell Aplasia

- Characterized by
  - Anemia, reticulocytopenia
  - Leukocyte and platelet counts WNL
  - Secondary dysmyelopoiesis (giant bands and metamyelocytes and increased cytoplasmic basophilia)
  - Absence of or severe deficiency of nucleated erythroid precursors in otherwise normal BM



Pure Red Cell Aplasia

- Cats infected with FeLV subtype C
- Young FeLV-negative cats
  - ✓ Condition requires prompt, aggressive, often long-term treatment with immunosuppressive drugs

Stokol T and Blue JT, Pure red cell aplasia in cats: 9 cases (1989-1997). J Am Vet Med Assoc (1999) 214:75-9

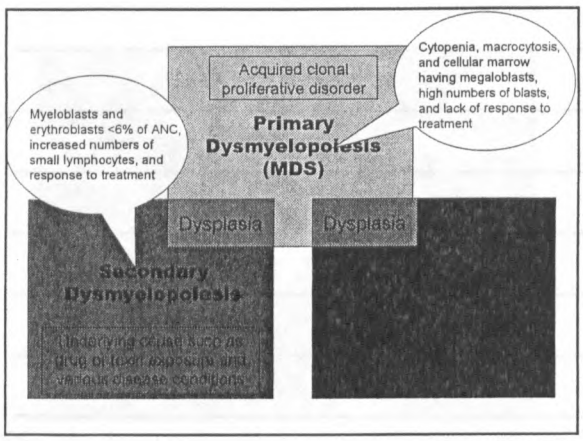
Treatment and Outcome

- Prednisolone, 5 mg/kg BW, orally, BID
- Cyclosporine A, 6.25 mg/Kg BW orally, BID
  - ✓ Plan to continue therapy until parameter normalizes
  - ✓ Dosage to be decreased very slowly and monitored at 2 week interval

Treatment and Outcome

TEST	RESULTS 5-02	RESULTS 6-06	Reference Range
Red Blood Cells	3.01	5.70	6.9 – 10.9 X 10^6/µl
Hemoglobin	4.64	8.72	10.1 – 16.4 g/dl
Hematocrit	15.0	27.1	32.0 – 52.0 %
MCV	48.7	47.6	40 – 52 fl
MCHC	31.7	32.1	29 – 34 g/dl
WBC			5.30 - 16.6 X 10^3/µl
Platelets	adequate	adequate	

DX: Secondary dysmyelopoiesis due to PRCA


Acquired clonal proliferative disorder
Primary Dysmyelopoiesis (MDS)
Cytopenia, macrocytosis, and cellular marrow having megaloblasts, high numbers of blasts, and lack of response to treatment
Myeloblasts and erythroblasts <6% of ANC, increased numbers of small lymphocytes, and response to treatment
Dysplasia
Dysplasia
Secondary Dysmyelopoiesis

Feline Hepatic Lipidosis Syndrome: Pathophysiology & Management

SA Center, DVM, Dipl ACVIM, College of Veterinary Medicine, Cornell University, Ithaca, NY, 14853.

The feline hepatic lipidosis syndrome (HL) is a potentially lethal intrahepatic cholestatic syndrome observed in over conditioned (obese) cats associated with anorexia and catabolism. This circumstance commonly complicates other liver disorders in the cat and a thorough approach to its management entertains therapeutic maneuvers thought to have benefit in many jaundiced cats. Successful recovery from feline liver disorders improves with early diagnosis and requires a committed effort to provide nutritional and metabolic support. Since cats have a unique propensity for accumulation of lipid vacuoles in their hepatocytes, there has been confusion in some cases where the HL syndrome was diagnosed in an individual having only minor to moderate cell vacuolation (histopathology or cytology). In the HL syndrome > 80% of hepatocytes are involved; in health, only 5% of hepatic weight is attributed to triglyceride. The disorder is best considered a syndrome as it has a multifactoral pathogenesis leading to malnutrition. The old term "idiopathic" associated with this condition is obsolete since in most cases (> 85% in the author's clinic) a more primary disease condition can be identified as the underlying problem.

Disorders Associated with Secondary Feline Hepatic Lipidosis Syndrome

Other liver disorders:
- Cholangiohepatitis
- Choledochitis
  - extrahepatic bile duct obstruction
- Chronic suppurative hepatitis
- Portosystemic vascular anomaly
- Bile duct adenocarcinoma
- Hepatic lymphosarcoma

Neoplasia (non-hepatic):
- Urinary bladder
  - transitional cell carcinoma
- Metastatic carcinoma
- Intestinal adenocarcinoma
- Intestinal lymphosarcoma

Pancreatitis

Diabetes mellitus

Small intestinal diseases
- Eosinophilic enteritis
- Lymphocytic/plasmacytic enteritis
- Chronic bowel obstruction
- Salmonella enteritis

Renal disorders:
- Chronic FUS
- Pyelonephritis
- Chronic interstitial nephritis

Hyperthyroidism

Severe Anemia

Pyometra

Cardiomyopathy

Central neurologic disease

Consult the Detailed Table on the Next Page for Specific Disorders in 157 Cats with Severe HL College of Veterinary Medicine, Cornell University

Clinical Features: *(data cited from 150 cats with severe HL, College of Veterinary Medicine, Cornell University)*
In N. America, the DSH is the most popular pet cat and most commonly affected with HL. There is no sex predisposition. Although middle aged cats are most commonly affected, cats with HL have ranged in age from 1 to 16 years. Cats with Secondary HL tend to be older (mean = 10; 1.5-15 yrs) vs cats with Idiopathic HL (mean = 7; 1-16 yrs). Most cats with HL were assessed as "over-conditioned or obese before their illness; Body wt: mean 4.0 (1.8-7.2 kgs) and have recently lost > 25% of their body weight (dehydration contributes to weight loss). Affected cats have usually been anorectic for > 7 days.

Recent Survey in the Author's Hospital: Disorders in Cats with Severe Hepatic Lipidosis
College of Veterinary Medicine, Cornell University, Ithaca, NY

Conditions Associated with Severe Hepatic Lipidosis Syndrome in 157 Cats
(several disorders in some cats)

	n
Other Hepatic Disorders	*31*
Cholangitis / Cholangiohepatitis Syndrome: 27	
Extrahepatic bile duct occlusion: 3	
Portosystemic vascular anomaly: 1	
Pancreatitis	*17*
GI Related	*59*
Inflammatory bowel disease: 44	
Peritonitis: 5	
GI foreign body: 2	
Esophageal necrosis/stricture: 2	
Stomatitis: 1	
Chronic diaphragmatic hernia: 1	
Jejunostomy site sepsis: 1	
Intestinal abscess: 1	
Chronic jejunal intusception: 1	
Constipation / Obstipation: 1	
Diabetes Mellitus	*4*
Respiratory Related	*6*
Asthma: 2	
Chylothorax: 2	
Pleural Effusion: 1	
Laryngeal hemiplegia: 1	
Septicemia	*4*
Urologic / Renal Related	*7*
Glomerulosclerosis / Glomerulonephritis: 3	
Nephritis, ARF: 2	
Hydronephrosis: 1	
Feline Lower Urinary Tract Syndrome: 1	

	n
Neoplasia	*22*
LSA: 10	
Lung Carcinoma: 3	
Liver Carcinoma: 1	
Adenocarcinoma: 5	
pancreatic: 2	
small intestine: 1	
Carcinomatosis: 1	
Osteocondroma: 1	
Metastatic TCCA: 1	
Cardiovascular	*4*
HCM: 3	
Restrictive CM: 1	
Hyperthyroid	*3*
Anemia	*5*
Neurologic Disease	*4*
Social interactions in home: new pet, new house	*8*
Miscellaneous	*13*
Trauma: 2	
Steatitis: 1	
Metronidazole toxicity: 1	
Hypothyroidism: 1	
Painful tooth: 1	
Declaw complications: 1	
Cat lost (1 week): 2	
Antibiotics caused vomiting / anorexia: 2	
Trichobezoar: 1	
Chronic FIP: 1	
Idiopathic (no cause for anorexia identified)	*2*

History: clinical history is usually vague: lethargy, hiding, inappetence, vomiting, diarrhea or constipation, or signs relating to the underlying disease process. There is solid no association with FeLV, FIV, or FIP.

Physical Assessments: include dehydration, weakness, non-painful hepatomegaly (> 95%), jaundice (variable severity, depends on chronicity and primary disease), signs of "primary disease", ptyalism (food aversion, hepatic encephalopathy, fairly uncommon). Carefully palpate the abdomen considering gut thickness and looking for anterior abdominal pain (IBD, pancreatitis).

Neck Ventroflexion: may be observed in severely affected cats. Consider: severe K or P depletion, thiamine deficiency (also look for poorly responsive pupils, dementia, neurologic signs), hyperthyroidism, cervical trauma, epaxial muscle weakness (myopathy, myasthenia gravis).

Factors Promoting Development of Hepatic Lipidosis: Mechanisms in All Species & Cat Specific

Nutritional Conditions:

Starvation: 2 weeks or longer:	↑ mobilization of FFA from adipose
	↓ protein, ↓ choline: ↓ synthesis of apoproteins and lipoproteins
	↓ synthesis of apoproteins & lipoproteins
Chronic Under Nutrition:	↓ synthesis of apoproteins & lipoproteins impaired export of VLDL from liver impaired adaptation to efficient β-oxidation
Protein Depletion:	↓ synthesis of apoproteins & lipoproteins
	The impaired export of VLDL from liver ↑ susceptibility to peroxidation & free radical injuries
	↓ Enzyme activity
Depletion of Myoinositol,/ Choline:	↓ synthesis of apoproteins and lipoproteins choline, methionine, impaired export of VLDL from liver
Chronic Parenteral Nutrition:	excessive calorie:protein nitrogen ration deficiency of essential fatty acids
	↑ de novo hepatic fatty acid synthesis
	↓ hepatic VLDL formation
	hepatotoxic products: tryptophan breakdown moieties
Parenteral Nutrition in Cats:	experimental evidence this leads to lipidosis,
Medium Chain TG in cats:	mechanism unknown

Miscellaneous

Intestinal Bacterial Overgrowth:	formation of toxic bile acids, endotoxins, dietary inadequacies
Diabetes Mellitus:	↑ adipose lipolysis
Carnitine Deficiency:	impaired preprocessing of FA for β-oxidation, impaired dispersal of fatty acids from liver, impaired
ratio of	mitochondrial acyl-CoA ratio impairing β-oxidation.
Peroxisome Dysfunction:	impaired preprocessing of FA for β-oxidation, ↓ oxidation of long-chain FA
Mitochondrial Dysfunction:	↓ β-oxidation of FA
Congenital ↓ LPL:	hypertriglyceridemia → hepatic fat accumulation
Pregnancy:	impaired mitochondrial β-oxidation
Hepatic Hypoxia:	↓FFA oxidation or exportation, energy used for maintenance of euglycemia
HepaticRregeneration:	metabolism deviated to reparative processes

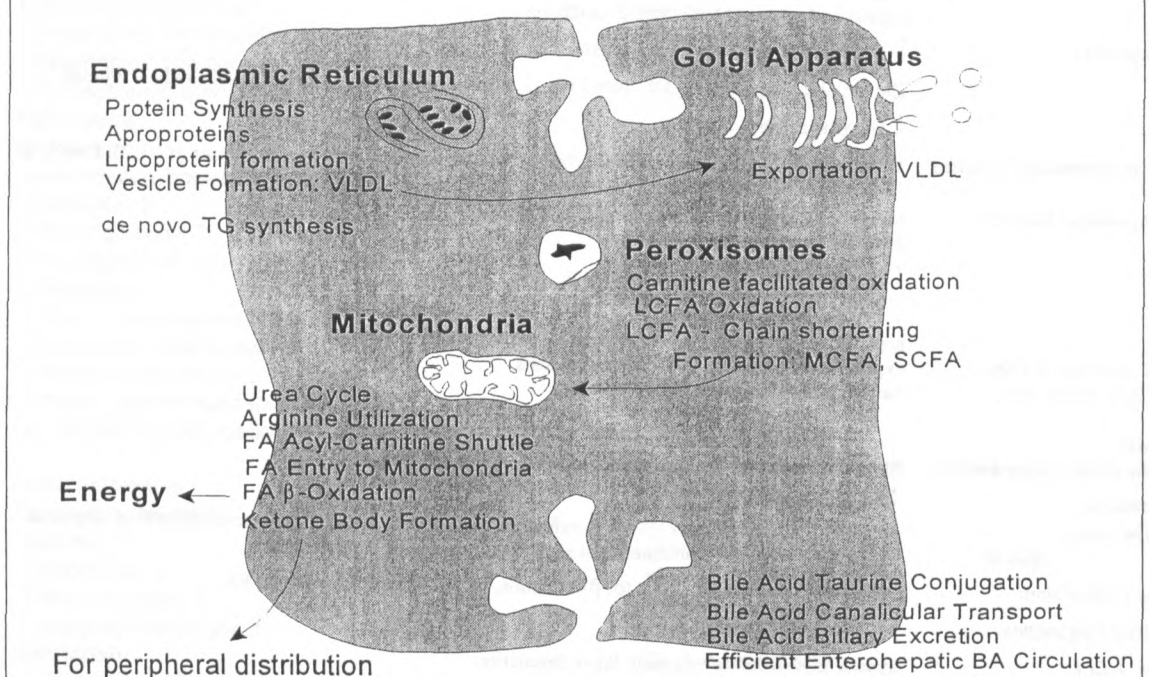
Toxins:

Inflammatory Bowel Dz:	altered intestinal flora → endotoxins, noxious bile acids
Chronic Alcohol Intake:	direct hepatic injury, metabolite mediated injury, altered nutrient metabolism, ↑ TG deposition
CCl_4:	metabolites produced by p-450 microsomes: toxin → free radicals → lipid peroxidation
	↓ cell protein synthesis, ↓ synthesis & export lipoproteins
Ethionine, Phosphorus:	↓ apolipoprotein synthesis → ↓ lipoprotein exportation
Puromycin	ethionine: ↓ ATP in hepatocyte
Hypoglycin (Akee tree:)	↓ fatty acid β-oxidation and metabolism by conversion to non- metabolizable CoA & carnitine
derivatives.	
Aflatoxins:	inhibit RNA synthesis & thus synthesis of proteins & enzymes, suppressed glucose metabolism. protein depletion increases susceptibility
Orotic Acid:	impaired assembly or exportation of VLDL from the liver
Bacterial toxins & Endotoxins:	impaired fatty acid oxidation, ↓ apoprotein synthesis

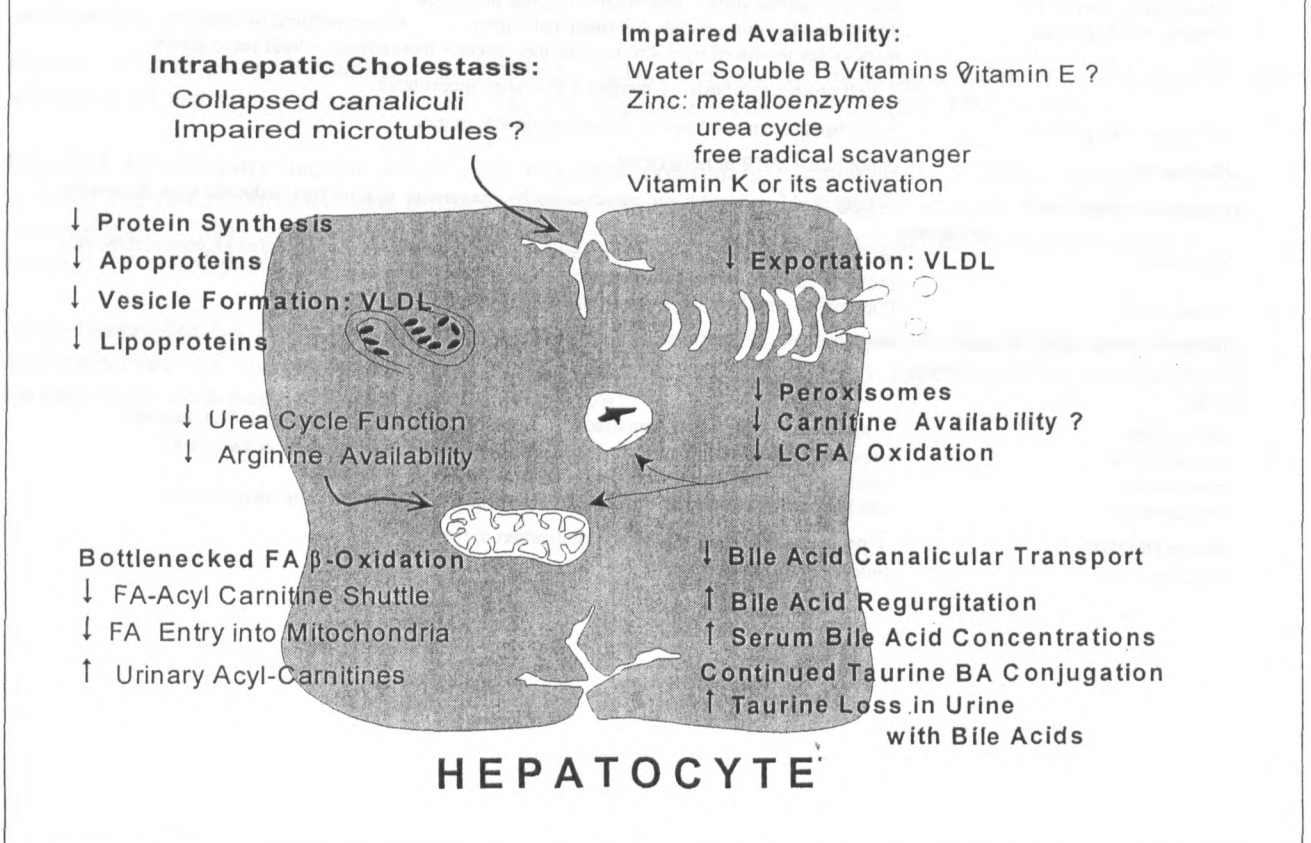
Drugs:

tetracycline:	↓ apoprotein production, impaired VLDL exportation, impaired mitochondrial function
valproic acid:	impaired fatty acid oxidation & decreased availability of coenzyme A & carnitine
amiodarone:	lysosomal phospholipidosis is due to accumulated drug metabolites
methotrexate:	mechanism undetermined, suspected ↓ lipotrope availability (↓ folate metabolism)
glucocorticoids:	↑ peripheral lipolysis → ↑ FFA mobilization to the liver
NSAIDs:	mitochondrial toxins

Normal Hepatocyte & Functions Relevant to Hepatic Lipidosis



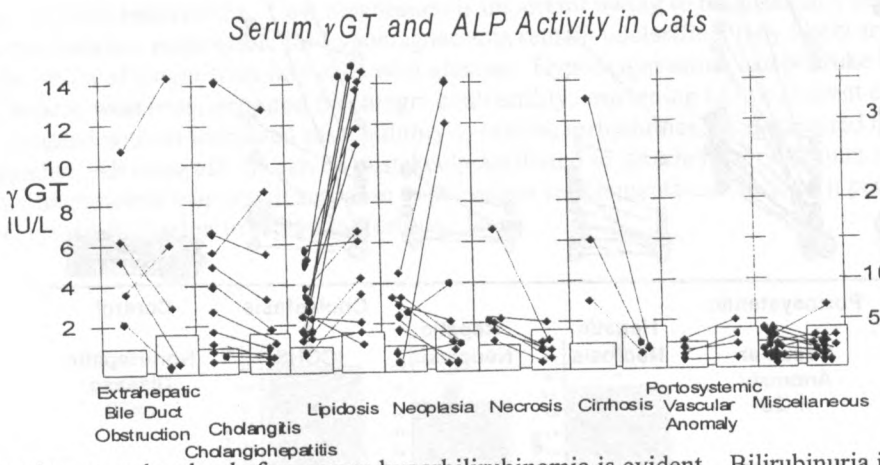
Altered Hepatocyte Function That May Exist in Hepatic Lipidosis



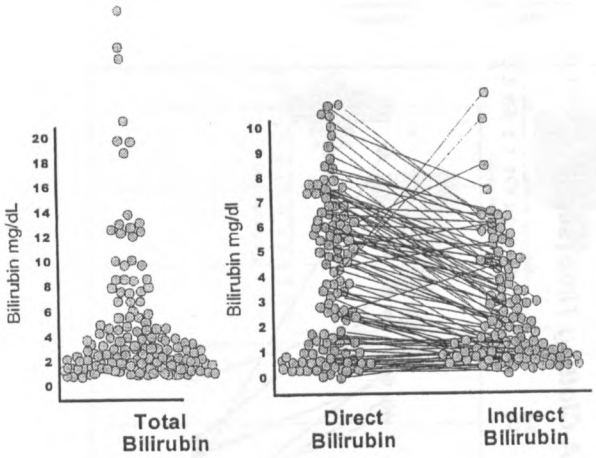
Clinicopathologic Features:

Hematology: Mild anemia, non-regenerative, *poikilocytes* very common, heinz bodies may be numerous and be associated with hemolysis (oxidant injury, low P associated with a re-feeding phenomenon). Leukocytosis is variable depending on the underlying primary disease process. A mature neutrophilia is most common. Platelet numbers are normal, serum jaundiced, total protein reflects dehydration.

Serum Biochemistry: *Liver enzymes* reflect the cholestatic nature of the lesion. Serum ALP fold increase usually > fold increase GGT activity if no underlying cholangiohepatitis, biliary tree obstruction or pancreatitis. ***The only feline cholestatic disorder in which this observation exists.*** The ALP values may approximate those seen with extrahepatic bile duct obstruction (EHBDO).



Bilirubinuria: may develop before serum hyperbilirubinemia is evident. Bilirubinuria is always abnormal in the cat. *Total bilirubin* values may increase to > 10 mg/dl, as high as that seen with EHBDO. Bilirubin fractionation (van den Bergh: into direct and indirect bilirubin) is not useful in achieving a definitive diagnosis.

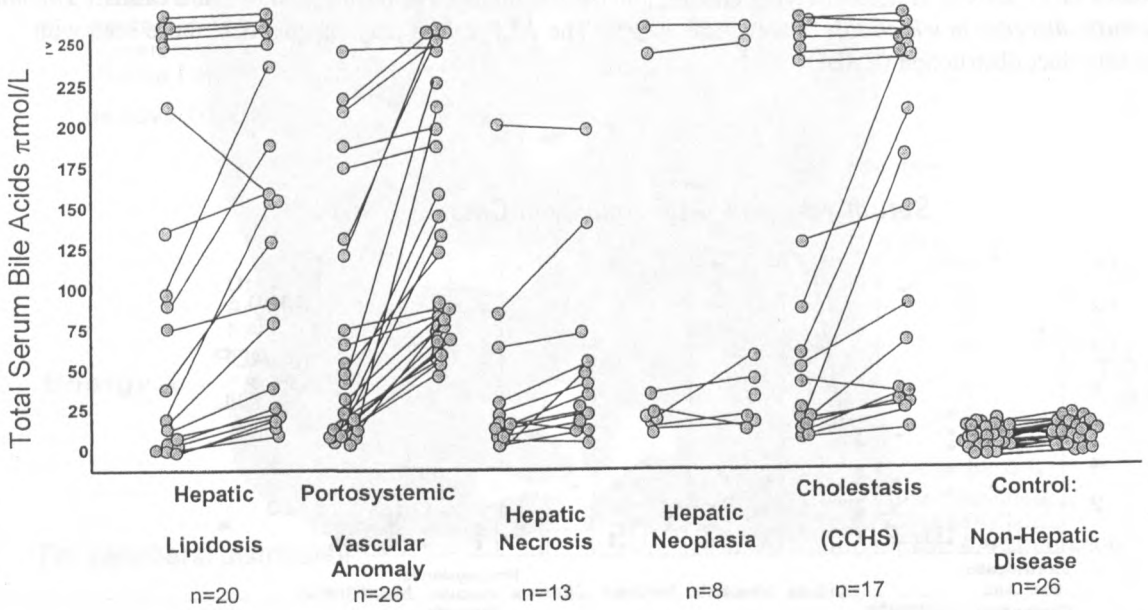


Serum proteins: albumin & globulins are usually normal in idiopathic HL. *Hypoalbuminemia* develops in some as a consequence of prolonged starvation (negative nitrogen balance), a negative acute phase response, or perhaps, liver failure. *Globulins* are usually normal unless the primary disease is a necroinflammatory / infectious disorder. *Glucose* is commonly normal, although cats with diabetes mellitus may have a higher risk for developing HL. Mild to moderate hyperglycemia is observed in 30-40% of cats likely related to stress and obesity.

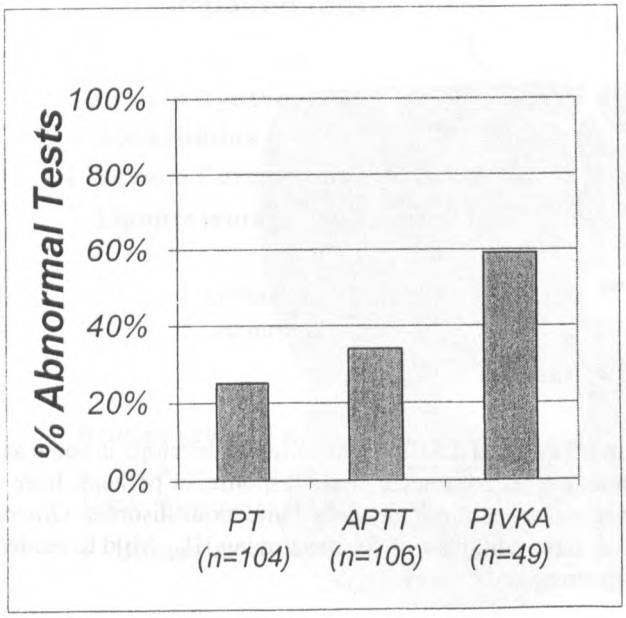
Hypoglycemia: is rare in the cat with liver disease.

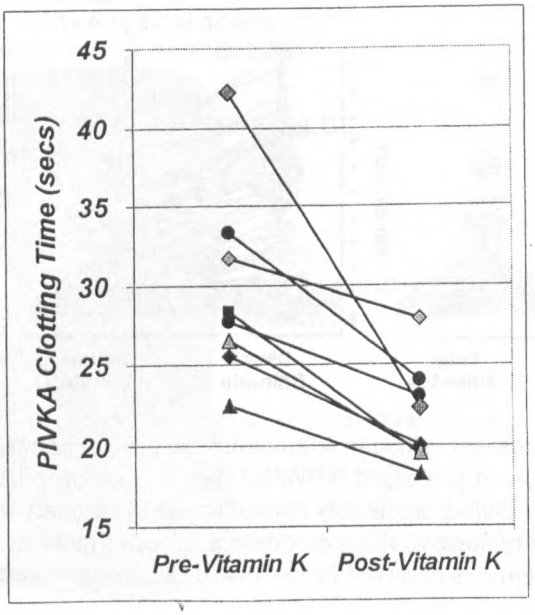
Cholesterol: is variable, but usually is normal. High or low values reflect underlying disorders (high: diabetes mellitus, renal insufficiency, pancreatitis, EHBDO; low: malabsorption (severe inflammatory bowel disease), pancreatic exocrine insufficiency, liver failure or portosystemic shunt, pathology proteinuria).

Serum Bile Acid Values: may be normal after a 12 hour fast in mild lipidosis but usually are abnormal at all testing intervals. ***Testing bile acids in a jaundiced patient does not assist the diagnostic process*** (redundant if jaundice due to liver disease). Bile acid profiles in HL cats show a pattern consistent with reduced enterohepatic bile acid circulation: this likely is associated with their apparent vitamin K deficiency. Loss of taurine conjugated bile acids in urine depletes taurine stores in the inappetent cat. See Figure next page for bile acids measured in cats with HL.



CoagulationTests: e abnormal in > 50% of HL cats. ↑ Prothrombin Time, ↑ Partial Thromboplastin Time, ↓↓ Fibrinogen (< 50 mg/dl, normal > 150 mg/dl), and sometimes ↑ FDPs., ↑↑↑ d dimers. However, an ↑ PIVKA clotting time is most common (reflects vitamin K deficiency). *Bleeding tendencies* are rare. Only 2/73 cats with severe HL surveyed for hemorrhage developed major bleeding problems leading to death. Most coagulopathies are vitamin K_1 responsive.



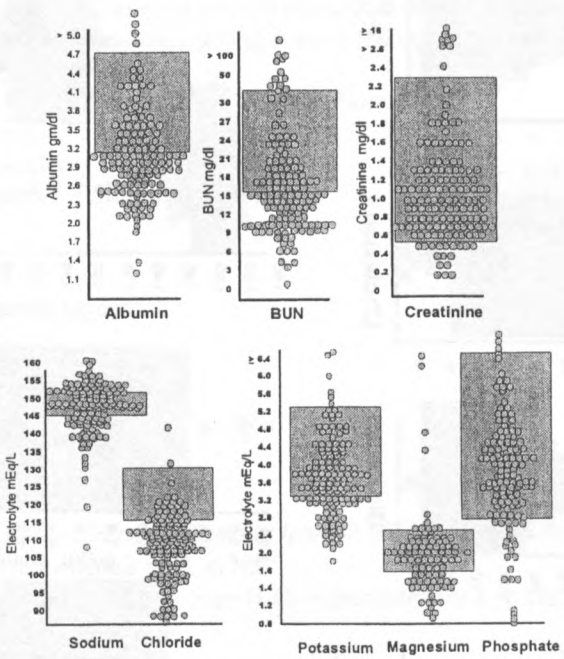


BUN &Creatinine: BUN is subnormal or low despite initial dehydration (60%) thought to be due to c0mpromised liver function, ↓ Urea cycle function, and inappetance. The creatinine is usually normal (cats mobilize muscle tissue when catabolic.)

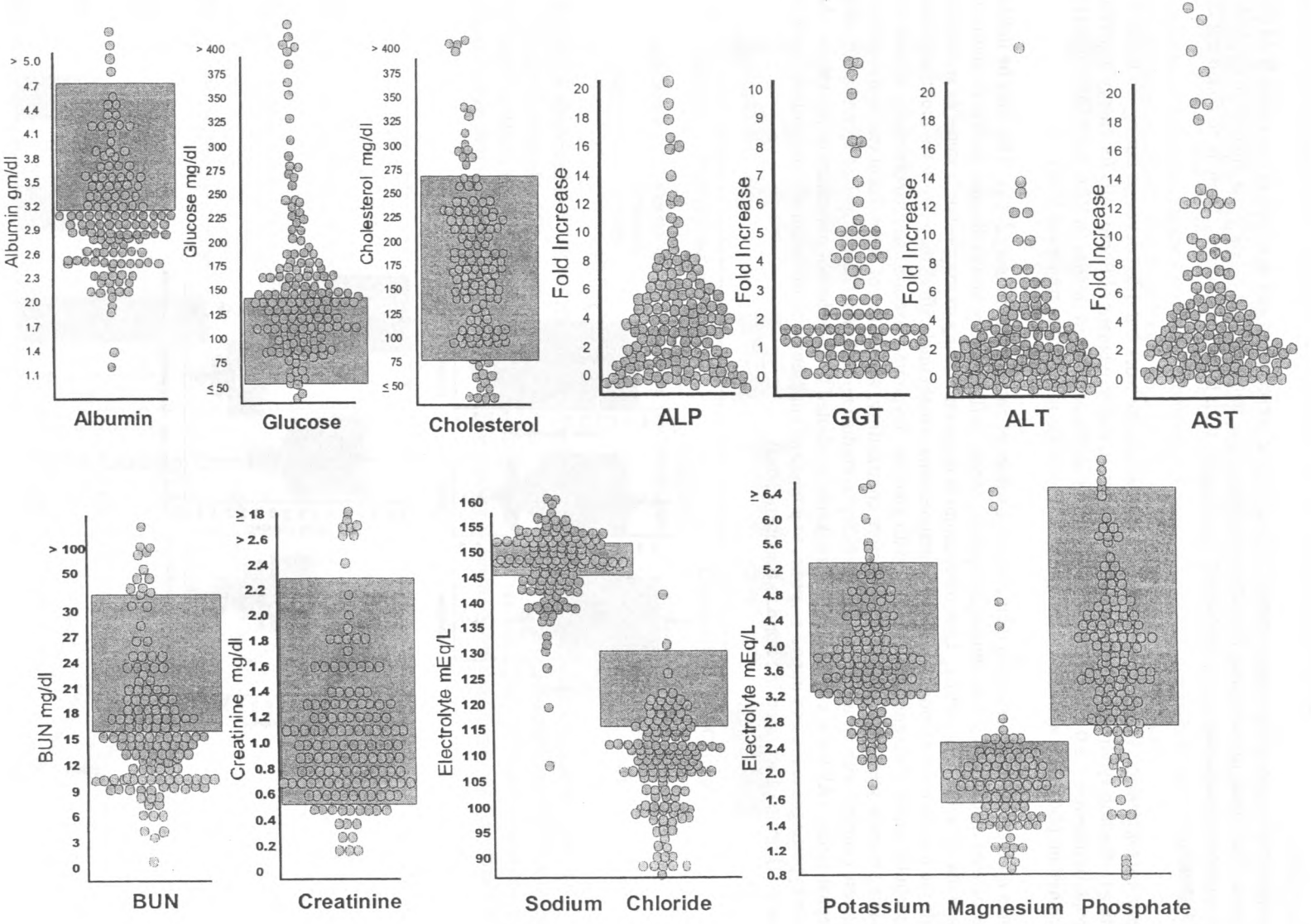
Electrolytes:
Hypokalemia is present in approximately 30% of cats at presentation and develops in most once fluid therapy is initiated. This leads to weakness, formation of dilute urine, anorexia, gut hypokinesis, metabolic alkalosis, increased renal ammonia production and is associated significantly with failure to survive. There is no consistent change in Na^+ or Cl^- trends.

Hypophosphatemia: is uncommon on admission laboratory work but often develops during the initial 2 days of feeding (refeeding syndrome invokes insulin stimulation and movement of P into cells for energy generation). Hypophosphatemia < 2.0 mg/dl is associated with an insidious or overt decline in RBC mass (hemolysis) and requires IV potassium phosphate administration. (Further discussion in regard to treatment later).

Hypomagnesemia: is observed on admission in a subset of cats (approximately 30%). This may be linked to a number of associated disorders such as cholangiohepatitis, sepsis, inflammatory bowel disease, enteric or multicentric lymphoma, or acute pancreatitis. Low magnesium is important owing to magnesium's status as an enzyme cofactor. While the mechanisms responsible for hypomagnesemia remain unclarified, they likely are multifactorial and involve transcellular shifts of magnesium into cells with glucose. Hypomagnesemia can provoke many clinical manifestations including muscle weakness, impaired diaphragm contractility, worsening of pre-existent cardiomyopathy (muscle weakness coupled with an increased susceptibility to cardiac arrhythmias), and impaired mental acuity feigning hepatic encephalopathy. All these effects can be mistakenly attributed to disorders of potassium or phosphate. Additionally, severe hypomagnesemia can impair response to potassium supplementation because it perpetuates renal potassium wasting. (Further discussion in regard to treatment later).



Summary of Clinicopathologic Features of FHL (157 Cats)



Abdominal Ultrasonography Ultrasonographic detection of hepatomegaly, and evaluation of liver echogenicity is quite helpful in prioritizing differentials in cats with cholestatic liver disease. The HL liver is large and diffusely hyperechoic relative to normal liver echogenicity (compared to falciform fat). Comparison to renal echogenicity is unreliable, presumably due to renal tubular fatty vacuolation . US examination may disclose a primary underlying disease process. Aspirate for cytology sample ONLY after vitamin K_1 has had an opportunity to work (12- 24 hours).

Acid-Base Status

Traditional Acid-base Determinations:

Reflect relationship between pH, HCO_3^-, and pCO_2, as described by the Henderson Hasselbalch equation. With this concept the pH is a function of HCO_3^-, and pCO_2 giving the impression that each are independent. ***THIS IS WRONG*** as only the pCO_2 is Independent

Stewart's Theory of Acid-base Chemistry in Biologic Systems:

Governed by 3 Physical Laws:

1. electroneutrality is maintained
2. dissociation equilibria for incompletely dissociated solutes are satisfied
3. conservation of mass occurs

Involves 3 Independent Variables:

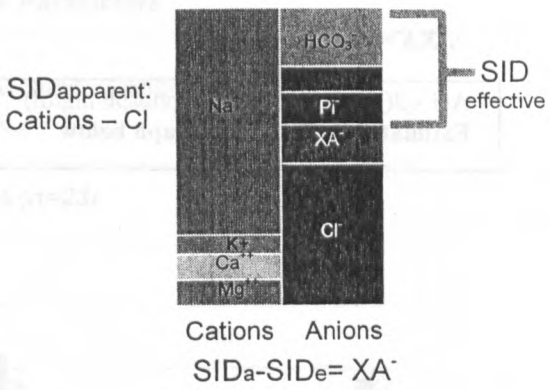
1. SID = Strong Ion Difference
2. Total Concentration of Weak Acids = Stewart's A_{tot}^-
3. pCO_2

Strong Ions = Completely Dissociated at pH of Body Fluids:

1. Strong Cations: Na^+, K^+, Ca^{+2}, Mg^{+2}
2. Na is the only one present in high enough concentrations to have a strong influence on SID
3. Strong Anions: Cl^-, Unmeasured Strong Anions (lactate, acetate, β-hydroxybutyrate, sulfates)

Weak Anions = Incompletely Dissociated at pH of Body Fluids

1. HCO_3^- = dependent
2. Albumin = independent
3. Phosphate (inorganic) = independent



For BE Calculations That Reflect Impact of Strong Ions on BE You Must Consider the Following Factors:

1. Δ BE Free H_2O: represented by Δ in Na^+
2. Δ BE Cl^- : determined from Δ in Free H_2O: represented by Δ in Na^+
3. Δ BE Albumin
4. Δ BE Phosphate (added later by Stewart, Fencl)

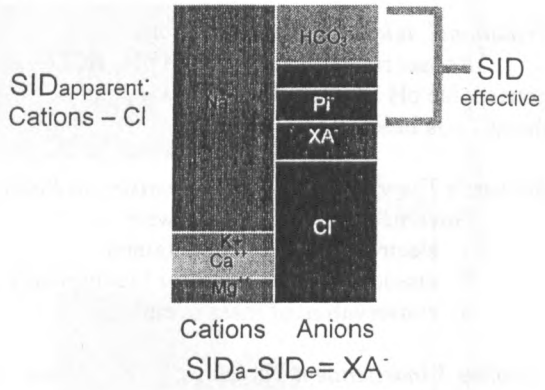
How to Calculate These Factors:

1. Δ Free H_2O: = z(Na^+ measured – Na^+ normal) (z for dogs = 0.25, z for cats = 0.22)
2. Δ BE (Cl^-)= normal Cl^- for species – corrected Cl^-
   Corrected Cl^- = Cl^- measured x $\frac{\text{Normal } Na^+}{\text{Measured } Na^+}$
3. Δ BE Albumin = 3.7*(Albumin normal –Albumin measured)
4. Δ BE (Unmeasured Anions) = Δ BE total – [Δ BE Free H_2O - Δ BE (Cl^-) + Δ BE Albumin]
   Δ BE total = derived from acid-base measurements

Revised Method Based on Figge, Stewart, Fencl

1. ***Apparent SID*** = all strong ions **measured routinely**
   $Na^+ + K^+ + Ca^{+2} + Mg^{+2} - [Cl^-]$ all in mEq/L
2. ***Effective SID*** = weak anions measured routinely that contribute "-" charge to the acid-base electroneutrality
   (HCO_3^-) + (proteins$^-$) & (phosphate$^-$) all in mEq/L (mmol/L is more correct)
   This calculation reflects how the concentrations of HCO_3^-, Albumin (protein), and Phosphate influence SID due to change of charge with pH

3. ∴ ***Apparent SID – Effective SID*** = 0 normally
ELSE have a Strong Ion Gap = SIG = XA^-
XA^- = Unmeasured Anions



Formulas from DiBartolas Fluid Therapy Book: pg 550

Anion Gap (AG) : $(Na^+ + K^+) - (Cl^- + HCO_3^-)$
AG Adjusted:
AG observ * 0.25(normal alb – observ alb)

XA^- = Unmeasured Anions
XA^-: $(Na^+ + K^+ + Ca^{+2} + Mg^{+2}) - (Cl^-) - SID_e$

SIG = Strong Ion Gap
A_{tot}^- = protein & phosphate adjusted to mEq/L
A_{tot}^- = (2(alb mg/dl) + 0.323phosph mg/dl)
AG = SIG + A_{tot}^-

∴ **XA^-**= Anion Gap - A_{tot}^-

AG -(2(alb mg/dl) + 0.323phosph mg/dl)
Estimates the SIG: see graph below

Inorganic Strong-Ion Difference $[SID]_i$ $[SID]_i = [Na^+] - [Cl^-]$

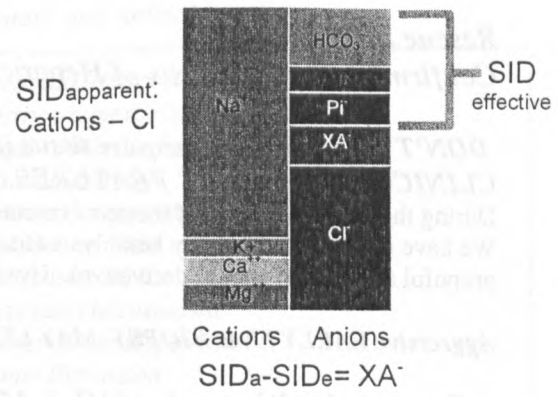
Δ Unmeasured anions =
Base Excess – (Δ Free Water + Δ Cl^- + Δ Albumin + Δ Phosphate)
(Phosph included if high): *Classic Early Stewart*

For Dogs:
$[Cl^-]_{corrected} = [Cl^-] * (146/[Na^+])$
Δ Free Water = $0.25([Na^+] - 146)$
Δ Chloride = $110 - [Cl^-]_{corrected}$
Δ Albumin = 3.7(3.1 – [Albumin]) or Δ Protein = 3.0(7.2 – [Protein])

For Cats:
$[Cl^-]_{corrected} = [Cl^-] * (156/[Na^+])$
Δ Free Water = $0.22([Na^+] - 156)$
Δ Chloride = $120 - [Cl^-]_{corrected}$
Δ Albumin = 3.7*(3.1 – [Albumin]) or
Δ Protein = 3.0(7.2 – [Protein])

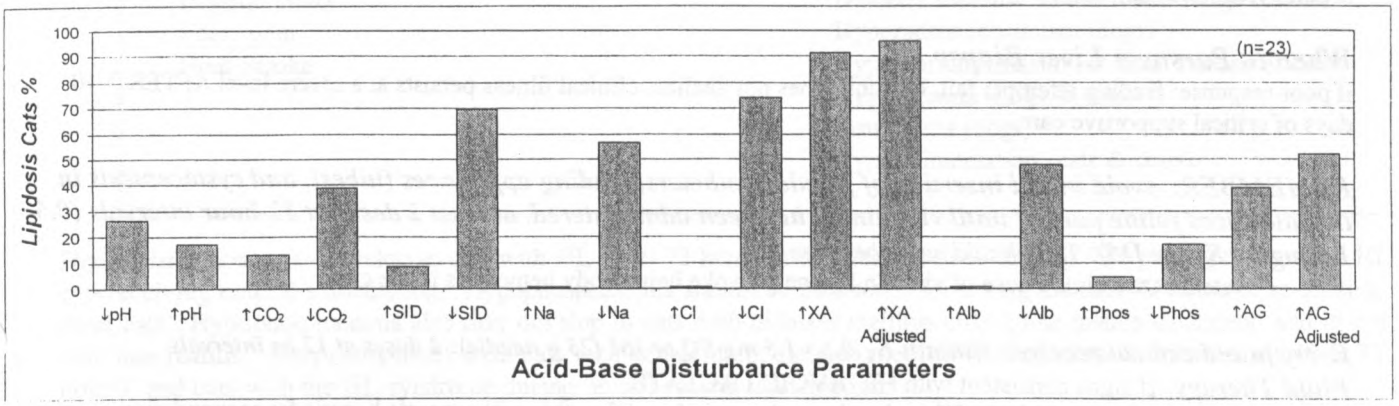
Classification of Primary Acid-base Disturbances

	Acidosis	*Alkalosis*
Respiratory	↑ pCO_2	↓ pCO_2
Nonrespiratory		
Abnormal SID		
Water excess / deficit	↓ SID, ↓ Na^+	↑ SID, ↑ Na^+
Imbalance of Strong Anions		
i. Cl- excess / deficit	↓ SID, ↑ Cl^-	↑ SID, ↓ Cl^-
ii. Unidentified anion excess	↓ SID, ↑ XA^-	---
Nonvolatile Weak Acids		
Serum Albumin	↑ Albumin	↓ Albumin
Inorganic Phosphate	↑ P(inorganic)	↓ P (inorganic)



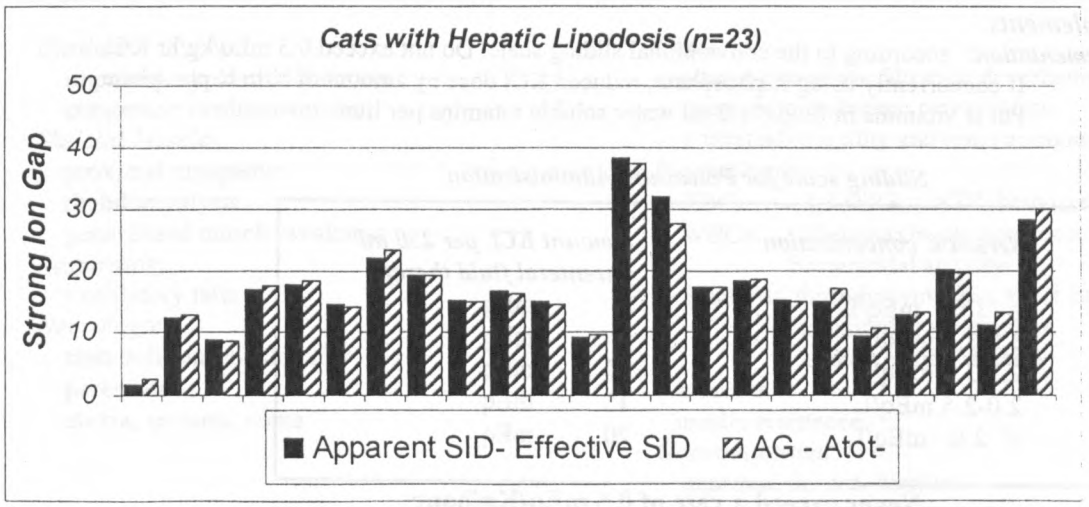
As SID ↑ positively, H+, a weak cation ↓ & pH ↑ maintaining electroneutrality

Normal SIG = 0 mmol/L, Normal AG: 8-15 mmol/L



Calculation of the Unmeasured Anions: Using Two Methods Applicable in Practice

XA^- = Apparent SID – Effective SID or XA^- AG – A_{tot}-



What is apparent is that cats with hepatic lipidosis have a large Unmeasured Anion Gap

This likely reflects Lactic Acid based on prior measurements in a small number of severely affected cats.

Rescue Strategy
Confirming the Diagnosis of Hepatic Lipidosis:

DON'T be in a hurry to acquire tissue if hepatic lipidosis is a primary consideration: USE CYTOLOGY & CLINICOPATHOLOGIC FEATURES to make a Presumptive Diagnosis:.
During the initial few days of therapy / rescue, these animals have high risk for anesthetic / surgical complications. We have observed heinz body hemolysis after: etomidate and diazepam sedation (propylene glycol carrier), and after propofol anesthesia (phenol derivative). Usually, the heinz body crisis hits about 12-hours after drug administration.

Aggressive EARLY Liver BIOPSY MAY LEAD TO DEATH:

A Presumptive Diagnosis of HL is Made on the Basis of:
Signalment, physical examination, clinicopathologic data, and abdominal ultrasound. This justifies hepatic needle aspiration for cytology. However, this procedure is only done after vitamin K_1 response. Liver biopsy is really not necessary to diagnose HL, however it *IS NECESSARY* to diagnose cholangitis / cholangiohepatitis (suppurative or non-suppurative) and other liver disorders. Make sure that > 80% of hepatocytes are vacuolated on aspiration cytology and that hepatocytes were sampled, not just omental / falciform fat.

When to Pursue a Liver Biopsy ?
if poor response: feeding attempts fail, bilirubin does not decline, clinical illness persists at a severe level AFTER 7-10 days of critical supportive care.

REMEMBER: Avoid initial insertion of jugular catheters, feeding appliances (tubes), and cystocentesis in the jaundiced feline patient until vitamin K_1 has been administered, at least 2 doses at 12-hour intervals (0.5-1.5 mg/kg SQ or IM). *This should never be given IV.*
Note that too high a dose of vitamin K_1 can provoke heinz body hemolysis in the cat.

Every jaundiced cat receives vitamin K_1: 0.5 - 1.5 mg SQ or IM (25 g needle): 2 doses at 12 hr intervals.
Fluid Therapy: If signs consistent with HE, AVOID LACTATE.
AVOID GLUCOSE [unless hypoglycemia (rare!)] as this will promote hepatic fat accumulation, worsen K depletion by renal loss, and aggravate early hypokalemia.
IV Catheter: Initially avoid jugular catheter placement owing to coagulopathy (wait for vitamin K response).

Fluid Supplements:
KCl Supplementation: according to the conventional sliding scale. Do not exceed 0.5 mEq/kg/hr KCl.
If concurrently using K phosphate, reduced KCl dose by amount of K in K phosphate.
Put B vitamins in fluids: 1-2 ml water soluble vitamins per liter.

Sliding scale for Potassium Administration

Serum K concentration	*Amount KCl per 250 ml parenteral fluid therapy*
> 3.5 mEq/L	5 mEq
3.0-3.5 mEq/L	7 mEq
2.5-3.0 mEq/L	10 mEq
2.0-2.5 mEq/L	15 mEq
< 2.0 mEq/L	20 mEq

Never exceed a rate of 0.5 mEq/Kg/hour

Phosphate Supplementation: Initial dose of 0.01 to 0.03 mmol/kg/hr Usually use the high dose rate. Even if the initial phosphate is not low, upon refeeding hypophosphatemia may be encountered.
Monitor serum phosphate concentrations every 3 to 6 hours (during and immediately after discontinued supplementation).
Discontinue phosphate infusion when serum phosphorus > 2 mg/dl. *Complications: Too much phosphate* can result in hypocalcemia and soft tissue calcium-phosphate deposition. Calcium-phosphorus product > 58 mg/dl = mineralization.
Iatrogenic hyperkalemia: failure to appropriately reduce KCl infusion rate. *Parenteral requirements resolve* once alimentation established.

Causes of Hypophosphatemia: ↓ Intestinal Absorption, Transcellular Shift into Cells, and ↑ Renal Elimination.

Conditions Associated with Hypophosphatemia in Humans and Animals

Hypophosphatemia in Humans

↓ Intestinal absorption

↓ Dietary intake

↓ Food Digestion / assimilation

malabsorption syndromes
steatorrhea
vomiting / diarrhea

Vitamin D deficiency: steatorrhea/other

Phosphate-binding antacids

Transcellular shifts

Respiratory alkalosis	Insulin Rx
Sepsis	Parenteral Glucose
CNS disorders	Hyperalimentation
Salicylate toxicity	Re-feeding Syndrome
Hepatic coma	
Fear, pain	
Heat Stroke	

Increased Urinary Excretion

Primary hyperparathyroidism
Renal tubular defects
Diuretic therapy
Sodium bicarbonate administration
Diabetes mellitus
Corticosteroid Rx
Hyperadrenocorticism

Recovery from Hypothermia

Volume Expansion

Parenteral fluids
Hyperaldosteronism

Hypophosphatemia in Animals

Hepatic lipidosis (cats)
Diabetes mellitus: ketoacidosis (dogs & cats)
Hyperadrenocorticism (dogs)
Hyperparathyroidism (1° & 2°) (dogs & cats)
Hypothermia (dogs & cats)
Insulinoma (dogs)
Hyperalimentation (cats & dogs)

Hypophosphatemia can develop in cats with HL 12 to 72 hours after initiation of re-feeding. We preemptively treat HL cats receiving enteral alimentation. Hypophosphatemia should be monitored for during the first 72 hours of re-feeding these cats. Hypophosphatemia also may develop in cats with diabetes mellitus undergoing insulin treatment, and in cats with pancreatitis. We preemptively treat cats with ketoacidotic diabetes mellitus (during initial insulin therapy (first 72 hours), and cats with the HL syndrome during initial enteral alimentation.

Clinical Signs of Hypophosphatemia

Clinical signs of hypophosphatemia are largely related to depletion of cellular ATP and RBC 2,3-DPG.

Cardiac

impaired myocardial function
congestive cardiomyopathy

Skeletal Muscle

proximal myopathy
rhabdomyolysis
generalized muscle weakness

Respiratory

ventilatory failure

Neurologic

metabolic encephalopathy
paresthesias
ataxia, seizures, coma

Renal

altered phosphate filtration & reabsorption
impaired bicarbonate regeneration
↓ titrateable acidity and renal ammonium

Hematologic

RBCs: ↓ 2,3 DPG, ↓ ATP, hemolysis
WBCs: ↓ chemotaxis, phagocytosis, bactericidal activity
Platelets: thrombocytopenia, short survival
impaired clot retraction
hemorrhagic diatheses

Endocrine

insulin resistance

Gastrointestinal

anorexia, nausea, diarrhea

Hypomagnesemia

Hypomagnesemia has been observed in approximately 30% of critically ill veterinary patients and is suggested to portend a poor prognosis. (Martin, 1994, Toll, 2002) Because serum magnesium represents less than 1% of total body magnesium it does not accurately reflect true body magnesium status. Since approximately 20% of magnesium is bound to albumin; measured total serum magnesium may be spuriously low in hypoalbuminemic animals. A suggested correction algorithm used for humans is: Corrected serum Mg (mmol/L)=measured total Mg (mm/L) + 0.005 (40-Albumin G/L). There are many clinical manifestations of hypomagnesemia which may directly reflect low magnesium or concurrent electrolyte aberrations (e.g. hypokalemia or hypocalcemia). Commonly involved systems include cardiovascular, central and peripheral nervous, and skeletal muscle. Clinical signs are variable and vague. *Low magnesium thwarts normal potassium conservation and promotes inappropriate kalliuresis resulting in loss of intracellular potassium and a reduced resting membrane potential.* The influence of magnesium on potassium involves diminished intracellular potassium stores secondary to enhanced cell potassium efflux due to reduced membrane pump function. This results in failed maintenance of the intracellular potassium gradient. Hypokalemia secondary to hypomagnesemia may be refractory to parenteral potassium provision, but will correct once magnesium depletion is corrected. Heightened cardiac excitability and arrhythmias may derive from hypomagnesemia. Diuretic administration (e.g. furosemide) may hasten onset of potassium and magnesium urinary losses. Neurologic signs associated with hypomagnesemia with or without hypokalemia or hypocalcemia is associated with enhanced excitability of muscles and nerves owing to increased acetylcholine release and increased cell calcium in skeletal muscles. In the presence of hypokalemia, hypomagnesemia may induce generalized muscle weakness, dysphagia, or dyspnea (esophageal, respiratory muscle affects). In the presence or hypocalcemia, hypomagnesemia may promote muscle fasciculations, ataxia, or seizures. Deficiency of magnesium also may lead to refractory hypocalcemia associated with impaired release of PTH, diminished PTH synthesis, and skeletal resistance to PTH, all relating to impaired magnesium dependent adenylate cyclase function. Treatment of refractory hypocalcemia in this circumstance requires parenteral magnesium along with calcium.

Clinical Manifestations of Magnesium Deficiency

Gastrointestinal
- Anorexia
- Nausea
- Adynamic ileus

Metabolic
- Refractory hypokalemia: (requires Mg correction)
- Refractory hypocalcemia: (requires Mg correction)

Hematologic
- Hemolysis / anemia
- Platelet aggregation

Cardiovascular
- Arrhythmias: atrial, ventricular
- Hypertension
- Digoxin sensitivity enhanced

Neuromuscular
- Weakness: skeletal muscle, diaphragm
- Hyperreflexia
- Ataxia
- Muscle fasciculations
- Confusion
- Seizures
- Coma

Causes of Hypomagnesemia and Magnesium Deficiency

Gastrointestinal Losses
- Anorexia
- Maldigestion / malassimilation

Renal Losses
- Primary tubular:
  - Renal tubular acidosis
  - Postobstructive diuresis
  - Diuretic phase ARF
- Diuresis:
  - Mannitol, furosemide, glucose, fluid
- Drugs: diuretics, aminoglycosides, cyclosporin, certain chemotherapeutic drugs

Renal Losses: Continued
- Hormone Induced Loss
  - Hyperthyroidism
  - Hypoparathyroidism
- Other Renal Losses
  - Hypercalcemia
  - Hyperphosphatemia

Redistribution
- Insulin: Diabetes Rx
- Acute pancreatitis
- Catecholamine excess

Acute management of hypomagnesemia requires intravenously magnesium using magnesium sulfate (8.13 mEq/g) and magnesium chloride (9.25 mEq/g) salts, both available as 50% solutions; these are administered as 20% solutions (or lower) in 5% Dextrose and water. A recommended dose is 0.75 to 1.0 mEq/kg/day administered by CRI. Slow restitution of body magnesium stores takes several days in a patient that is truly deficient. A lower dose of 0.3 to 0.5 mEq/kg/day is recommended for an additional 2-5 days. While a much higher dose is advocated for life-threatening ventricular arrhythmias (0.15-0.3

mEq/kg (100 mg/kg) given over 5-15 minutes) this has not been necessary in cats managed by the author .(Dhupa, 1998) Daily monitoring of serum magnesium is essential during supplementation as overdose may precipitate hypocalcemia, hypotension, AV and bundle branch blocks, and respiratory muscle weakness. Overdoses are treated with calcium gluconate given IV as 50 mg/kg slow bolus followed by 10 mg/kg/hour constant rate infusion (CRI).

Re-Feeding Phenomenon

The re-feeding syndrome describes a potentially lethal condition defined by severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing initial re-feeding (oral, enteral, or parenteral). Cats with FHL, like humans with kwashiorkor, appear to have heightened risk. Pathomechanisms underlying the re-feeding syndrome involves a rapid shift from a purely catabolic state (prolonged anorexia) to one converting to rapid onset carbohydrate utilization. Shifted metabolism evokes insulin release, cell uptake of glucose, phosphate, potassium, magnesium and water, and enhances protein synthesis. With nutritional support, tissue anabolism increases furthering cell requirements for phosphate, potassium, glucose and water with increased demand for adenosine triphosphate (ATP), 2,3 diphosphoglycerate (2,3 DPG), and creatine kinase (CK).

Hypokalemia, by far the most common electrolyte abnormality in FHL, can promote enteric atony causing ileus, vomiting, and constipation, reduced urine concentration, neuromuscular dysfunction causing skeletal muscle and diaphragmatic weakness, paralysis, paresthesias, rhabdomyolysis, confusion, and metabolic alkalosis that can worsen hepatic encephalopathy.

While less common on initial presentation than hypokalemia, severe hypophosphatemia also can produce a plethora of clinical signs. Because phosphorus is integral to cellular metabolism as a component of cell membranes, nucleic acids, and nucleoproteins, is involved in glycolysis, and is a key component of a vital enzyme systems involving ATP, 2,3 DPG, and CK, its deficiency can provoke widespread organ dysfunction (reflecting impaired cell energy pathways and diminished oxygen availability). Reduced RBC ATP may lead to cell membrane fragility, dysfunction, and hemolysis. Impaired skeletal muscle function manifesting as weakness, myopathy and rhabdomyolysis have each been observed in FHL. Hypophosphatemia manifesting as a re-feeding phenomenon typically appears within the first 48 hours of initial feeding; effects are clinically overt when phosphate is $\leq$ 1.5 mg/dl.

Least common is symptomatic hypomagnesmia that also may develop in FHL associated with pancreatitis and re-feeding. Low magnesium is important owing to magnesium's status as an enzyme cofactor. While causal mechanisms remain unclarified, they likely are multifactorial and involve transcellular shifts of Mg into cells with glucose. Hypomagnesemia also can provoke many clinical manifestations (described below). Most important are muscle weakness, impaired diaphragm contractility aggravating pre-existent asthma, worsening of pre-existent cardiomyopathy (muscle weakness coupled with an increased susceptibility to cardiac arrhythmias), and impaired mental acuity once again feigning hepatic encephalopathy.

Hyperglycemia induced by carbohydrate intake, gluconeogenesis, diabetes mellitus, or fluids supplemented with glucose aggravates electrolyte depletion through osmotic diuresis and may provoke symptomatic hypothiaminosis. Because thiamine functions as a co-factor for a number of enzymatic reactions (e.g. transketolases) increased glucose metabolism may provoke clinical signs associated with thiamin insufficiency (Wernecke's encephalopathy; see above under vitamin supplementation). Glucose supplementation is strongly contraindicated in FHL as it not only can heighten the chance of a re-feeding syndrome but also metabolically compromises adaptation to efficient fatty acid oxidation, and potentiates hepatic TG accretion through enhanced lipogenesis.

Nutritional Support:

Cats with liver disease *rarely require protein restricted diets*. Consider the following when selecting a diet for your patient. The underlying systemic disease problems often will guide diet selection. * **Summarized from** http://nss.vet.ohio-state.edu/Vdm/Nutrient: Dr. T. Buffington's tables from Ohio State.

Nutritional "Extremes" for Cats		% Energy
Low Calorie	< 3.0 kcal / gm DM	
High Calorie	> 4.5 kcal / gm DM	
Low Protein	< 7 gm / 100 kcal	< 28%
High Protein	> 10 gm / 100 kcal	> 40%
Low Fat	< 2 gm/ 100 kcal	< 18%
High Fat	> 5 gm / 100 kcal	> 40%
Low Fiber	< 0.25 gm / 100 kcal	
High Fiber	> 1.5 gm / 100 kcal	
Low Sodium	< 100 mg / 100 kcal	
DM = dry matter		

HOWEVER, PLEASE NOTE: MOST CATS WITH LIVER DISEASE DO NOT REQUIRE PROTEIN RESTRICTION

This table summarizes feline diet characteristics important for consideration in the patients with hepatic encephalopathy. If portal hypertension is a problem, the sodium content should also be consulted.

Commonly Available Diets:Approximate Protein & Energy Compared To Typical Feline Carnivore Prey Characteristics.

			Energy Distribution%		
Feline	***Source***	***kcal / can or cup or unit***	***Protein***	***Fat***	***Sodium mg / 100 kcal***
Maintenance: canned average		Variable	44	48	200
Maintenance: dry average		Variable	34	34.2	180
Canine / Feline a/d	Hills	185	36.4	54	156
Feline g/d: canned	Hills	165	32.4	40.5	66
Feline g/d: dry	Hills	297	31.6	40.5	79
Maximum Calorie: canned	Iams	340	32.8	66.0	101
Feline L/d: canned	Hills	164	28.8	47.7	48
Feline L/d: dry	Hills	505	28.4	46.8	62
Multi-Stage Renal: canned	Iams	205	26.4	48.6	116
Multi-Stage Renal: dry	Iams	535	25.6	47.7	102
Clinicare	Abbott	(237) 1 kcal/ml	34.4	45	53
Clinicare RF	Abbott	1 kcal/ml	22.4	57	52
Feline K/d: canned	Hills	219	24.0	48.6	64
NF Formula: canned	Purina	234	24.0	51.3	30
NF Formula: dry	Purina	398	28.8	27.0	50
Low Phosphorus / Protein: canned	Waltham	287	22.8	77.4	120
Low Phosphorus / Protein: dry	Waltham	381	23.1	46.8	40
Feline S/d: canned	Hills	215	35.2	63.9	181
Feline W/d: canned	HIlls	148	44.0	39.6	116.0
Feline W/d: dry	Hills	281	44.0	25.2	74.0
Feline R/d: canned	Hills	116	45.6	25.2	94.0
Feline R/d: dry	Hills	263	45.6	26.1	86
Feline DM: canned	Purina	194	47.6	45.0	80.0
Feline DM: dry	Purina	592	52.8	35.1	20.0
Mouse	Prey	193 / 4 oz	41	50	na
Cricket	Prey	137 / 4 oz	42	41	na
Squab (pigeon) meat and skin	Prey	333 / 4 oz	26	74	na
Squirrel, raw	Prey	136 / 4 oz	75	25	na
Human Baby Food: meats	Various	117-169	43-58	42-60	Variable

Nutritional Support: ESSENTIAL CORNERSTONE OF THERAPY for JAUNDICED CATS

Initial Feeding: Use oral feeding or nasogastric (NG) tube. Avoid food aversion response.
STOP oral route if marked salivation, nausea or struggling to get away from the food.
After a few days of rehydration, corrected electrolytes, improved vitality, consider placing an E-tube or G-tube.

Feeding Tubes: Nasogastric / Nasoesophageal at first, then either E-tube (preferred) or G-tube.

General Tips for Feeding Tube Care: Maintenance of tube hygiene is essential. Flush with warm water after each feeding (10 ml). Investigate tube volume so you know how much fluid is needed to flush the entire tube and yet not fill the gastric space with calorie free water. Avoid putting pill form of medications that can cause concretions (some ground up medications congeal in liquid form) in narrow feeding tubes; this may lead to tube occlusion.

If G-Tube: *Aspirate tube* before feeding to evaluate gastric emptying: > 10 ml = gastric hypokinesia that may reflect either electrolyte derangements or pain derived from gastrostomy tube (site infection, leakage, insertion causing mechanical restriction of gastric motility.

Check Ostomy Site: 1-2x daily for the first 10 days. Perform cytology on ANY discharge. Avoid infection as this complicates recovery. Visually inspect the anchoring sutures.

If Persistent Vomiting: *CHECK ELECTROLYTES*
rule out severe hypokalemia,
ensure that feeding tube is not causing gastric outflow obstruction
radiographic contrast injection (Renografin®) or by use of ultrasound (US).
Provide some exercise: may stimulate enteric motility

Antiemetics:

Metoclopramide: 0.01-0.02 mg/kg/hr IV constant rate infusion / 24 hours
0.2 - 0.4 mg/kg SQ 20 min. before meal

Ondansetron: 5 HT_3 receptor antagonist (expensive, oral only)
0.1-1.0 mg/kg q 12-24 hrs

IF Still Persistent Vomiting: Double check for tube problems (contrast radiography, US)

Trickle feed: Slow rate / 24 hours continuous
Infusion pump & liquified diet
Re-new food q 4-6 hours to avoid bacterial contamination.

If Tube occlusion: Problem typically restricted to G-tubes.
Use solutions that can digest food: Coca Cola, papaya juice, or pancreatic enzymes;
Let dwell 20 to 40 minutes; then flush with lukewarm water
Do Not Attempt to Clear Tube with a Solid Stilette: may penetrate tube or patient.
May need to re-evaluate tube patency/position with contrast injection.

Diet to Feed: ***DO NOT* restrict protein UNLESS signs of hepatic encephalopathy.**
Feed maximum calorie balanced feline foods.

How Much to Feed: 60-90 kcal/kg body wt per day. Start with a liquid diet through NG tube.
Initially administer 5 ml of lukewarm water at 2-hr intervals 2-to 3-times to determine the likelihood of emesis & gastric atony. Food is progressively introduced over a 2 to 4 day interval to achieve intake of between 250 to 400 kcal per day for the average sized cat.
Initial feeding is delayed for 24-hours after G-tube insertion to allow return of gastric motility and to permit formation of an initial wound seal around the insertion site.
Feeding through an E-tube may be initiated after full recovery from the anesthetic restraint.

AVOID RELIANCE ON APPETITE MODIFIERS
diazepam, Oxazepam, Cyproheptadine: *DO NOT ENSURE ADEQUATE NUTRITIONAL INTAKE*
Diazepam and Oxazepam are benzodiazepines which are considered hepatoencephalogenic toxins
These require hepatic biotransformation and conjugation for elimination (the HL cat is deficient in these processes).

If Neck Ventroflexion:

Check electrolytes: K and P, provide supplements as appropriate.

Administer thiamine: 100 mg in fluids (B-soluble vitamins, and in food)
Parenteral administration by IM route may result in collapse, although this is rare.

Provide B-soluble vitamins in fluids.

Consider the possibility of other Underlying Disorders & Submit Appropriate Tests EARLY in Illness: cervical weakness (neurologic disease, vertebral injury), muscle weakness (myopathy, myasthenia gravis (very rare)), hyperthyroidism, organophosphate toxicosis, even hepatic encephalopathy.

Supplements Routinely Used in Rescuing Cats with Hepatic Lipidosis

Vitamin K: 0.5 to 1.5 mg/kg PO at 12 hour intervals parenterally, ***NOT*** IV and ***NOT*** PO, 2-3 doses only.

Vitamin E: 10 IU/ kg PO per day until convinced of recovery

Water Soluble Vitamins: 1 - 2 ml B Soluble vitamins per liter, keep covered from light.

Thiamine: 100 mg orally, use B-soluble vitamins in fluids NOT SQ or IM injection → collapse (rare).

B_{12}-Cobalamin: B-soluble vitamin supplementation in fluids and commercially available critical care diets (commercial pet foods are supplemented with stable, pharmaceutical grade vitamin B_{12}) can provide therapeutic B_{12} for many patients. However, those with severe inflammatory bowel disease or malabsorption due to infiltrative bowel disease (such as lymphoma) may require parental "loading" and protracted therapy with parenterally administered B_{12} (1 mg IM). Frequency of dose administration is determined based on sequential plasma B_{12} concentrations (5 -7 day intervals to once monthly have been determined in individual cats).

Contents of a Fortified B-Vitamin Complex Used in Crystalloid Fluids in Cats with FHL

Thiamine hydrochloride (Vitamin B1):	50 mg
Riboflavin 5' Phosphate sodium (Vitamin B2):	2.0-2.5 mg
Niacinamide (Vitamin B3):	50-100 mg
d-panthenol (Vitamin B5):	5-10 mg
Pyridoxine HCl (Vitamin B6):	2-5 mg
Cyanocobalamin (Vitamin B12):	*variable* 0.4 to 50 mcg
(Low B12 values necessitate additional supplementation in deficient cats, IM)	
Benzyl alcohol (preservative):	1.5% (no adverse consequences noted in FHL cats)

l-Carnitine: 250 mg PO / day has been used as a routine supplement in the author's hospital for the theoretical reason of promoting fatty acid oxidation, increasing loss of CN-ester fatty acids in urine, and retention of lean body mass. Metabolic response to l-CN has recently been proven in obese healthy cats undergoing weight loss.

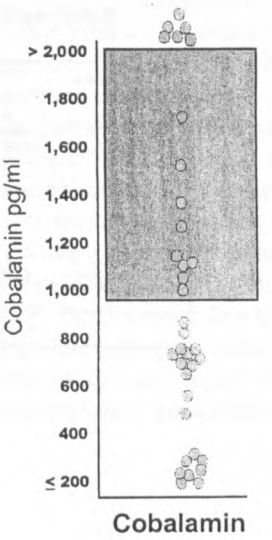
GSH donor: Markedly low GSH has been demonstrated in liver tissue from cats with HL. May see hemolysis not attributable to electrolyte aberrations (severe hypophosphatemia), Especially prudent if heinz bodies are present on RBCs.

N-acetylcysteine: 140 mg/kg IV, then 70 mg/kg IV at 12 hour intervals.
Dilute 10% NAC (Mucomyst®) to a 5% or less solution, filter before infusion.

s- Adenosylmethionine (SAMe; Denosyl-SD4):
20 mg/kg PO BID. Follow NAC as PO thiol (GSH) donor. Since SAMe is given with food in the HL cat which is on continuous nutritional support and since the presence of food reduces SAMe bioavailability, we have empirically increased the total dose by BID administration.

Serum B_{12} Concentrations in HL. *(Consult graphic)*

Normal > 950 pg/ml in the population summarized. A theoretical association between B_{12} insufficiency and HL exists since B_{12} has pivotal importance in transmethylation reactions involving DNA, protein, lipoprotein, and carnitine synthesis, plays a role in transsulfuration (maintaining reduced GSH and sulfate availability), and cell repair/regeneration. Vitamin B_{12} also is known to stimulate appetite in deficient patients. Prospective evaluation of plasma B_{12} concentrations in cats with HL revealed that 40% (before treatment with B-soluble vitamins) have subnormal values. Primary diseases provoking HL were recognized in > 90% and included: IBD, cholangiohepatitis and cholecystitis, pancreatitis, septic peritonitis, and toxicosis. All cats presenting with HL having IBD tested to date have had subnormal plasma B_{12} concentrations. Nearly 30% of cats with other primary conditions also had subnormal B_{12} values. B_{12} deficiency may limit methylation reactions and thus the ability to export VLDLP from the liver. This may reflect underlying disease and possibly is important as an etiopathogenic factor in some cats. Severe bowel disease or an abnormal diet produces acquired B_{12} deficiency.

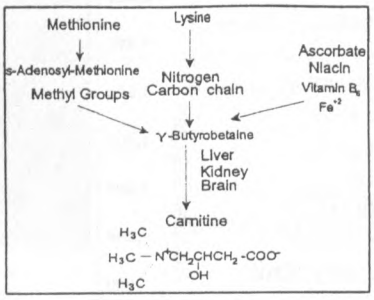


Carnitine (CN): is a conditionally essential nutrient primarily involved with regulating substrate flux across cell membranes. It can be synthesized *de novo* or acquired from supplements. The primary function of L-CN is to facilitate transposition of long-chain fatty acids into mitochondria and to modulate the intracellular (mitochondrial) ratio of acetyl-coenzyme A (acetyl-CoA) to CoA. The later influence frees CoA for other metabolic reactions, maintaining a ratio of acetyl-CoA:CoA conducive for continued β-oxidation of fatty acids. Experimental evidence suggests that L-CN also influences activity of the *pyruvate dehydrogenase enzyme complex* by decreasing the intramitochondrial acetyl-CoA/CoA ratio (forming Acetyl-CN). These effects favor oxidative utilization of glucose and pyruvate and have a diminishing influence on lactate production; *Figure below.*

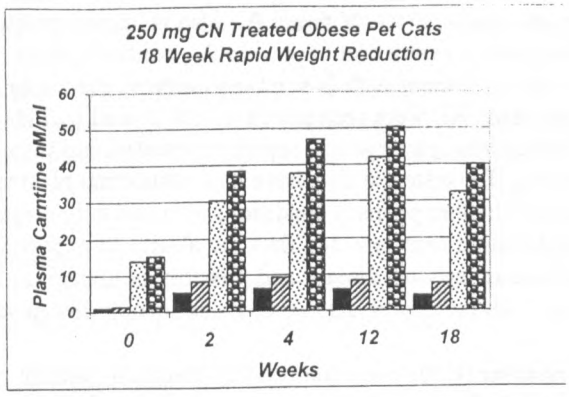
Available clinical data is insufficient to assess the role of L-CN in liver disease with certainty. However, a proposed value in HE relates to the influence of NH_3 on brain energy metabolism. Prolonged severe hyperammonemia disrupts the malate-aspartate shuttle that indirectly transfers reducing equivalents from the cell cytosol to mitochondria (electrons from cytosolic NADH are transported to the electron transport chain) and also inhibits the TCA enzyme *α-ketoglutarate dehydrogenase*. Sustained inhibition of *α-ketoglutarate dehydrogenase* and by effect the TCA cycle, disrupts cell energy metabolism, favoring lactate and alanine formation from pyruvate. The well documented accumulation of lactate and alanine in CSF and brain tissue in cerebral edema and HE reflects the suppressive influence of NH_3 on brain energy availability. In the portocaval-shunted rat model of HE, L-CN attenuates NH_3-precipitated encephalopathy, possibly by improving mitochondrial respiration and integrity of the BBB; Rudman et al, 1977; Hearn et al, 1989; O'Connor et al, 1990; Therrien et al, 1997. With this model, L-CN attenuates CSF (and brain) alanine and lactate concentrations and increases CSF taurine and brain glutamate concentrations without changing NH_3 or glutamine concentrations; Thierrien et al, 1997. These changes correspond with *in vitro* effects of L-CN in a hyperammonemic test system where it normalizes oxidation of α-ketoglutarate and improves mitochondrial function; Bellei et al, 1989. Collectively, L-CN is thought to increase pyruvate oxidation and TCA cycle flux, as well as flux through glutamate dehydrogenase. *These affects are IN ADDITION to the primary value of CN in HL.*

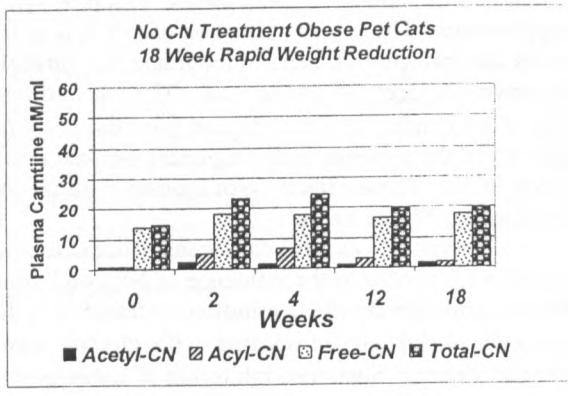
L-CN is recommended for cats with FHL for several reasons. Hepatic CN synthesis may be limited in these catabolic cats because of hepatic dysfunction and impaired availability of one or more of its synthetic substrates: lysine, SAMe, Fe^{2+}, Vitamin C, succinate, and pyridoxal phosphate (see Figure). The ability of cats with FHL to appropriately provide CN for FA oxidation and FA dispersal in order to strategically facilitate a net negative fatty acid flux remains undetermined. Study of CN supplementation in obese cats undergoing weight loss demonstrated increased concentrations of acetyl-CN, the end product of fatty acid oxidation, and led to a higher acyl-CN:total CN ratio consistent with an enhanced rate of fatty acid oxidation (see Figure). Further work substantiates that supplemental CN facilitates fatty acid oxidation, fat mobilization, conserves lean body mass in obese cats undergoing weight reduction, and can attenuate the degree of hepatic lipid accumulation in modeled FHL. Improved survival in cats with severe FHL has been achieved in the author's hospital by administering CN at a dose of 250-500 mg CN /cat per day. Medical grade CN should be used where possible as there is a wide diversity in bioavailability of different commercial products. Further benefits may be achieved with L-CN owing to its influence on the metabolic derangements associated with hyperammonemia and HE.

Synthesis of L-Carnitine



Data from a Study of Obese Pet Cats Undergoing Rapid Wt. Loss
1 Grp received medical Grade L-CN, 1 Grp a Placebo





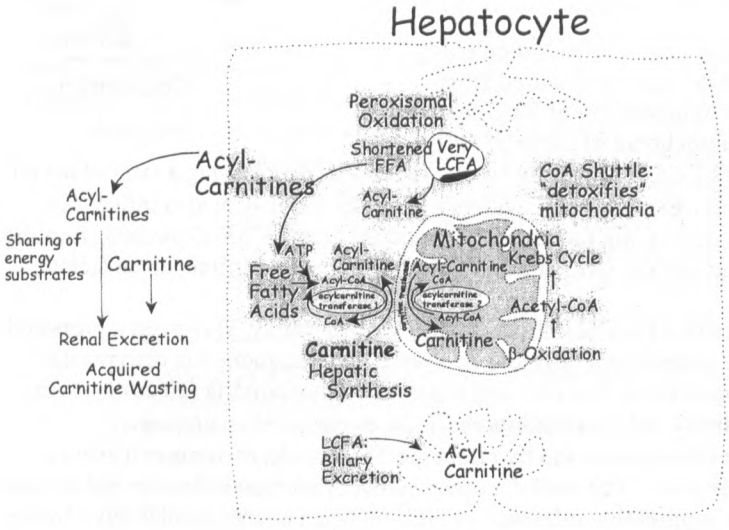
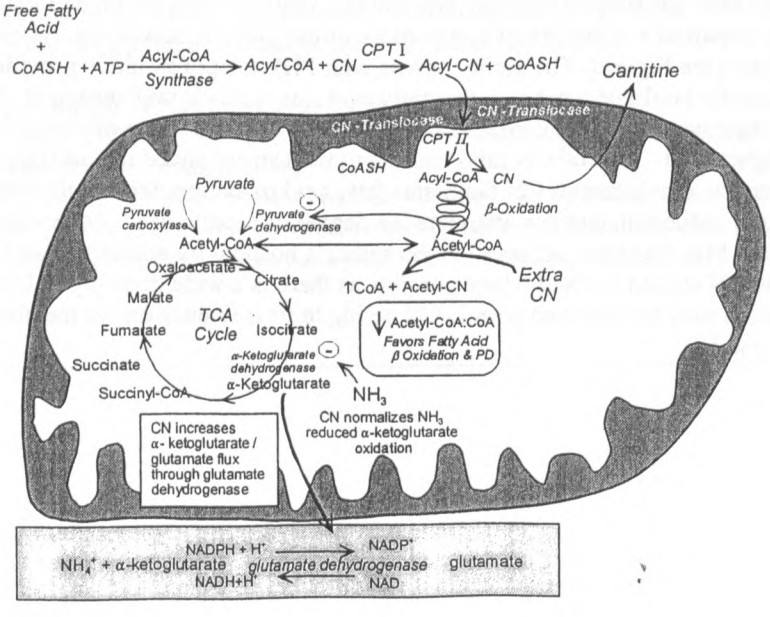
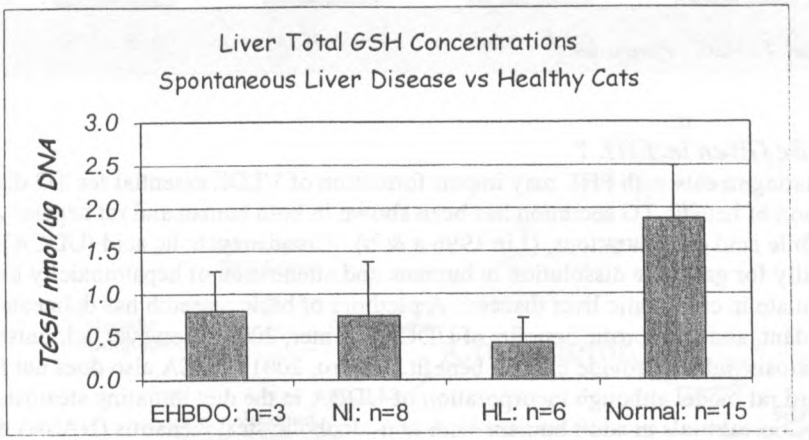


Diagram Showing the Benefits That L-CN MAY Provide
Thwarting Metabolic Disturbances with Hyperammonemia and HE

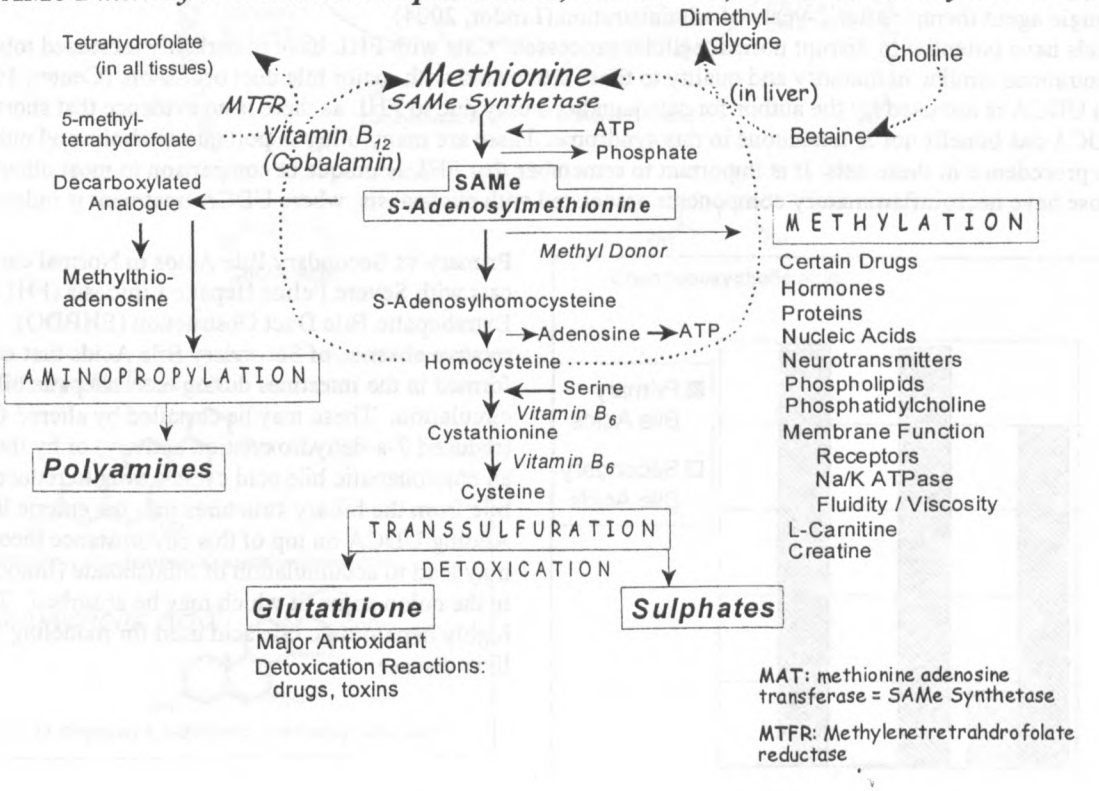


Glutathione / Thiol Donor Supplementation:

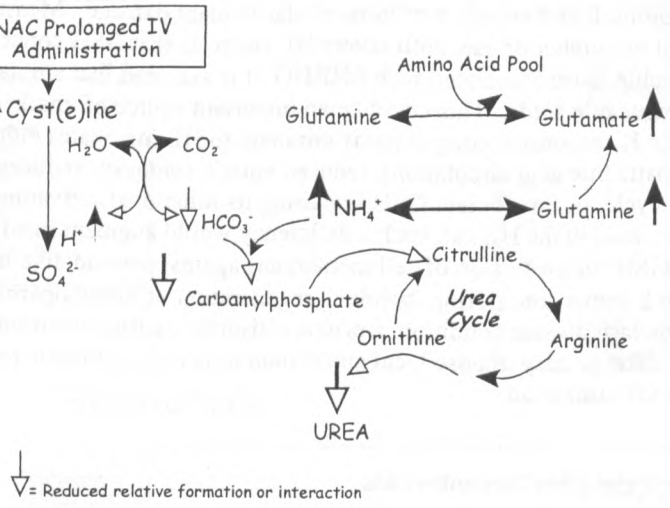
Similarities between the feline HL syndrome and kwashiokor in children (protein malnulnutrition and death due to HL) exist in histology, clinicopathologic features, and ultrastructural hepatic morphology. Children dying from kwashiorkor have reduced tissue concentrations of vitamin E and evidence of intracellular oxidant damage. Measurement of hepatic tissue and RBC GSH concentrations in a small of number of cats with severe HL suggests that GSH concentrations are subnormal. Since serum bile acid profiles in HL resemble those associated with EHBDO, it is assumed that similar membranocytolytic hepatic damage derives from retained injurious bile acids. This could be an important source of marked transaminase, ALP and GGT activities in the HL cat. The vitamin K responsive coagulopathy common to HL implicates either impaired enteric uptake (derived from a deranged enterohepatic bile acid circulation), reduced enteric synthesis, reduced activation / rejuvenation of vitamin K in the hepatic epoxidase cycle, or insufficient GSH impairing its functional activation. While a similar reduction in vitamin E status remains unsubstantiated in the HL cat, such a deficiency would augment insufficient GSH concentrations by virtue of increased requirement of GSH for protection of cell membranes against peroxidative injury. Furthermore, low GSH would promote insufficient vitamin E status considering its role in regeneration of α-tochoperol from the topheroxy radical. Since HL is most commonly a secondary disease condition, a primary disorder causing necroinflammatory tissue injury which is inexorably linked to oxidant tissue damage may impose local and distant injury via cytotoxic metabolites each potentiated by GSH deficiency and augmenting GSH utilization.



SAMe Pathway and Relationship to Thiols, Cobalamin, and Transmethylation Reactions



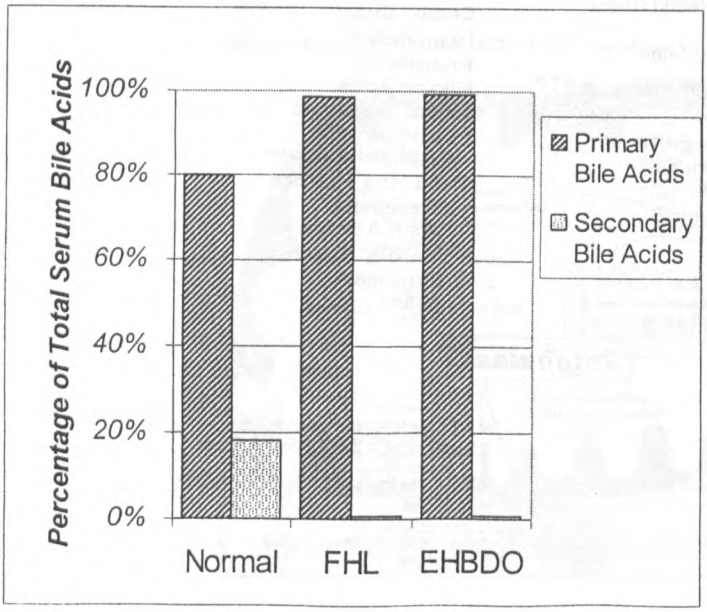
Problem Affiliated with Slow Infusion of N-Acetylcysteine: Impaired Ammonia Detoxification



Ursodeoxycholic Acid: Should This Be Given in FHL ?

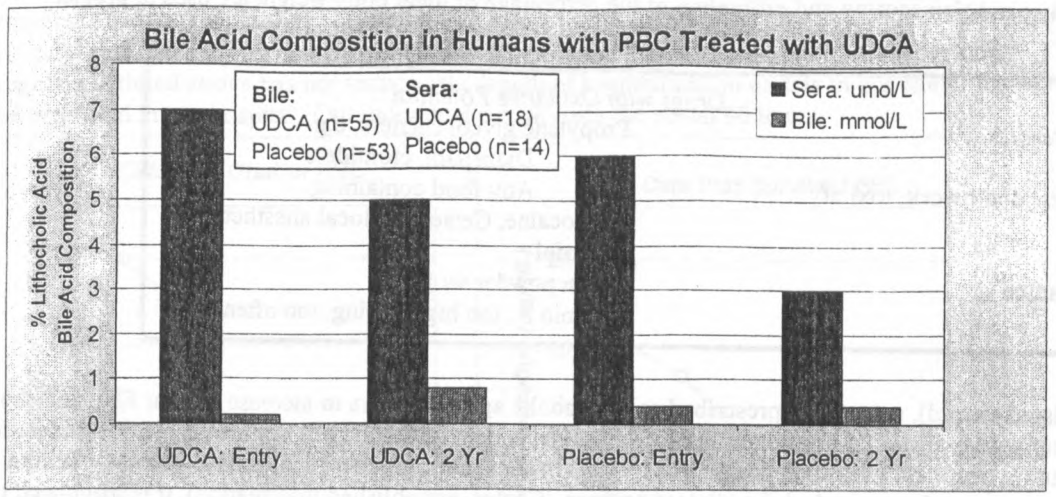
Hydrophobic bile acids accumulating in cats with FHL may impair formation of VLDL essential for TG discharge from the liver. Dose dependent suppression of hepatic TG secretion has been shown in both human and rat hepatocytes exposed to increased but physiologically relevant bile acid concentrations. (Lin 1996 a & b). Ursodeoxycholic acid (UDCA), a synthetic hydrophilic bile acid, is used therapeutically for gallstone dissolution in humans and attenuation of hepatotoxicity imposed by membranocytolytic bile acids that accumulate in cholestatic liver disease. A plethora of basic research has delineated cytoprotective, antiinflammatory, antioxidant, and antifibrotic benefits of UDCA.(Center, 2004) However, administration of UDCA to obese children with hepatic steatosis did not provide clinical benefit.(Vaigro, 2001) UDCA also does not facilitate regression of hepatic steatosis in a standard rat model although incorporation of UDCA in the diet initiating steatosis ameliorated the syndrome.(Okan, 2002) Clinical trials in adult humans with non-alcoholic steatohepatitis (NASH) describe variable results with UDCA including clinicopathologic and histologic benefits but no change in hepatic fat content after months of therapy. (Laurin, 1996, Kiyici, 2003). The most recent multi-institutional prospective study showed that UDCA had no benefit as single agent therapy after 2-years of administration.(Lindor, 2004)

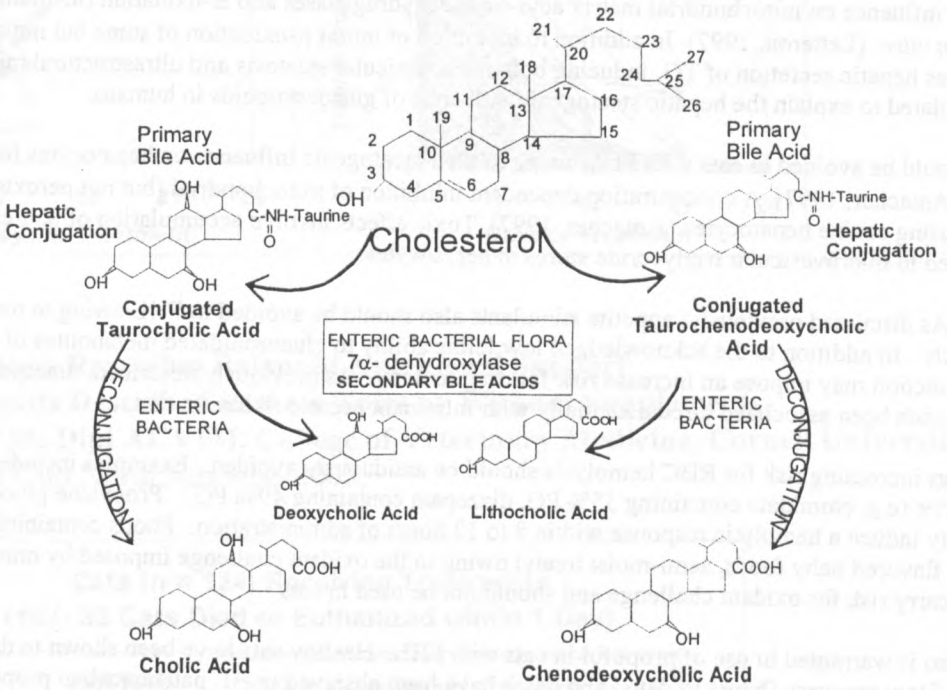
All bile acids have potential to disrupt normal cellular processes. Cats with FHL have remarkably increased total serum bile acid concentrations similar in quantity and quality to those associated with major bile duct occlusion. (Center, 1993) Treatment with UDCA is not used by the author for cats jaundiced only due to FHL as there is no evidence that short term exposure to UDCA has benefit nor is innocuous in this syndrome. There are many other important metabolic and nutritional issues that take precedence in these cats. It is important to remember that FHL is unique in comparison to most other feline liver disorders as those have necroinflammatory components associated with cholestasis, where UDCA treatment is indeed indicated.

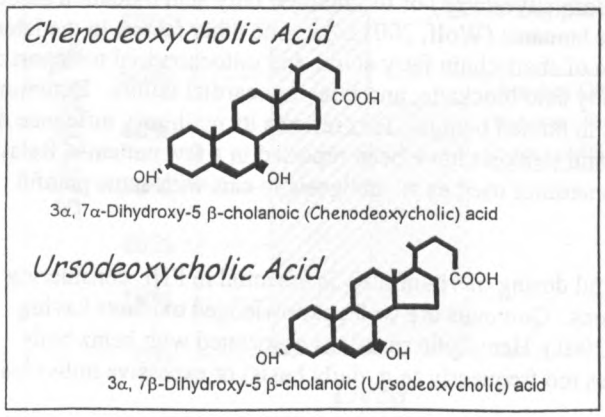


Primary vs Secondary Bile Acids in Normal cats and in cats with Severe Feline Hepatic Lipidosis (FHL) and Extrahepatic Bile Duct Obstruction (EHBDO). Note the relative absence of Secondary Bile Acids that normally are formed in the intestines during enterohepatic bile acid circulation. These may be curtailed by altered flora (reduced 7-a-dehydroxylation activity) or by the absence of an enterohepatic bile acid cycle owing to reduced egress of bile from the biliary structures into the enteric lumen. Adding UDCA on top of this circumstance theoretically may lead to accumulation of lithocholate (lithocholic acid) in the colon some of which may be absorbed. This is a highly hepatotoxic bile acid used for modeling cholestatic liver disease.

The following graph shows the increase in lithocholate in sera and bile in humans with Primary Biliary Cirrhosis treated with UDCA: data from before and after 2 years of treatment. UDCA treatment was associated with an increase in the percent of lithocholate in bile and had a smaller decline in serum lithocholate compared to baseline. There are a few other studies that show similar phenomena.







Drugs to Avoid

Any drug dose calculated for over-conditioned cats with FHL should be based on estimated lean body mass to avoid inadvertent over-dosing. Body condition scoring and estimation of the percentage of ideal body weight are used to predict appropriate dosing.

Stanazolol	*Drugs with Oxidative Potential:*
Other Anabolic Steroids (?)	Propylene glycol carriers: e.g.
Tetracyclines	Diazepam, etomidate
Appetite stimulants: don't work, toxicity	Any food containing
Diazepam	Benzocaine, Cetacaine: local anesthetics
Oxazepam	Propofol
Cyproheptadine	Onion powder w/ foods
	Vitamin K: too high dosing, too often

Stanozolol (a 17-alpha alkylated steroid), sometimes prescribed as an anabolic agent, appears to increase risk for FHL and should be avoided. (Harkin, 2000) Because several steroid hormones impose a dose-dependent inhibition of bile flow, careful consideration should be given before instituting treatment with such drugs.(Vore, 1997) In some cats, glucocorticoids have clinically facilitated onset of FHL when treatment was targeting an underlying disease process. (Center, unpublished information) It is speculated that this reflects the inhibitory influence on mitochondrial matrix acyl-CoA dehydrogenases and B-oxidation (medium and short chain fatty acids) demonstrated *in vitro*. (Letteron, 1997) In addition to inhibition of initial β-oxidation of some but not all fatty acids, dexamethasone reduces hepatic secretion of TG, inducing both microvesicular steatosis and ultrastructural mitochondrial lesions. Such effects are speculated to explain the hepatic steatogenic influence of glucocorticoids in humans.

Tetracyclines also should be avoided in cats with FHL owing to their steatogenic influence on hepatocytes from many different mammalian species.(Amacher, 1997) A concentration dependent inhibition of mitochondrial (but not peroxisomal) β-oxidation has been proven *in vitro* using canine hepatocytes.(Amacher, 1997) Toxic effects involve accumulation of non-esterified fatty acids subsequently converted to microvesicular triglyceride stores in hepatocytes.

Appetite Stimulants: As discussed previously, appetite stimulants also should be avoided in FHL owing to the unreliable respons potential hepatotoxicity. In addition to the acknowledged low feline ability to glucuronidated metabolites of some drugs, FHL induced hepatic dysfunction may impose an increase risk for drug toxicity. As previously described, diazepam, oxazepam, and cyproheptadine have each been associated circumstantially with fulminant hepatic failure in cats.

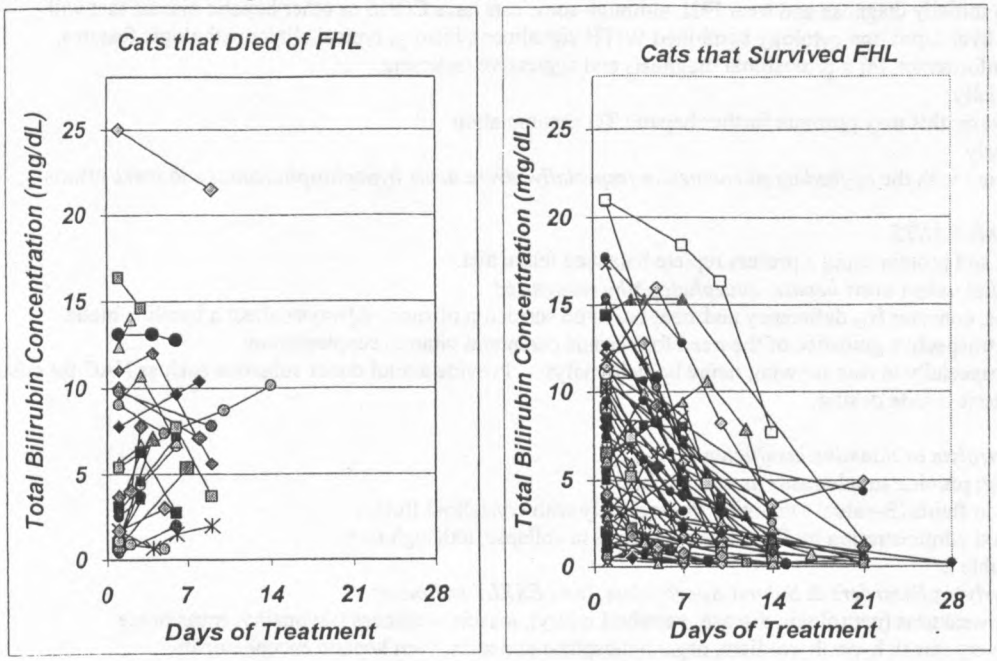
Oxidant Drugs: Drugs increasing risk for RBC hemolysis should be assiduously avoided. Examples include products containing a propylene glycol carrier (e.g. etomidate containing 35% PG, diazepam containing 40% PG). Propylene glycol carriers injected intravenously typically induce a hemolytic response within 8 to 12 hours of administration. Foods containing onion powder also should be avoid (e.g. flavored baby foods, semi-moist treats) owing to the oxidant challenge imposed by onion derivatives. Cetacaine and benzocaine also carry risk for oxidant challenge and should not be used in cats.

Propofol: Caution also is warranted in use of propofol in cats with FHL. Healthy cats have been shown to develop heinz bodies after propofol anesthesia. Slow recovery (hours to days) and death have been observed in HL patients when propofol was used to for short term restraint (feeding tube placement) or for exploratory laparotomy. It remains undetermined whether toxicity relates to the phenol derivative status of propofol (cats generally do not metabolize phenol derivatives well) or to impaired fatty acid oxidation associated with a "propofol infusion syndrome" described in critically ill pediatric humans; (Wolf, 2001), or some other factor. In the later syndrome, propofol impairs mitochondrial electron transport, oxidation of short-chain fatty acids, and mitochondrial transport of long-chain fatty acids. Affected humans demonstrate metabolic acidosis, fatty acid blockade, and fatal myocardial failure. Buprenorphine (at high concentrations) also has been associated with hepatic steatosis in human beings. This reflects its inhibitory influence on mitochondrial B-oxidation and respiration. In man, cytolytic hepatitis and steatosis have been reported in a few patients. Relationship to aggravating FHL has not yet been determined. Buprenorphine is sometimes used as an analgesic in cats with acute painful pancreatitis.

Vitamin K: Too High Dosing or Too Frequent Administration: Careful dosing of vitamin K_1 is essential in FHL considering that some of these cats present with low circulating RBC GSH concentrations. Quinones are well acknowledged oxidants having heightened toxicity in GSH depleted cell systems.(Cho,1997; Chung, 2001) Hemolytic reactions associated with heinz body formation have developed in cats with FHL receiving appropriate doses too frequently (e.g. daily basis) or excessive individual (e.g. > 1.5 mg/kg per treatment beyond 3 doses at 12 hour intervals).

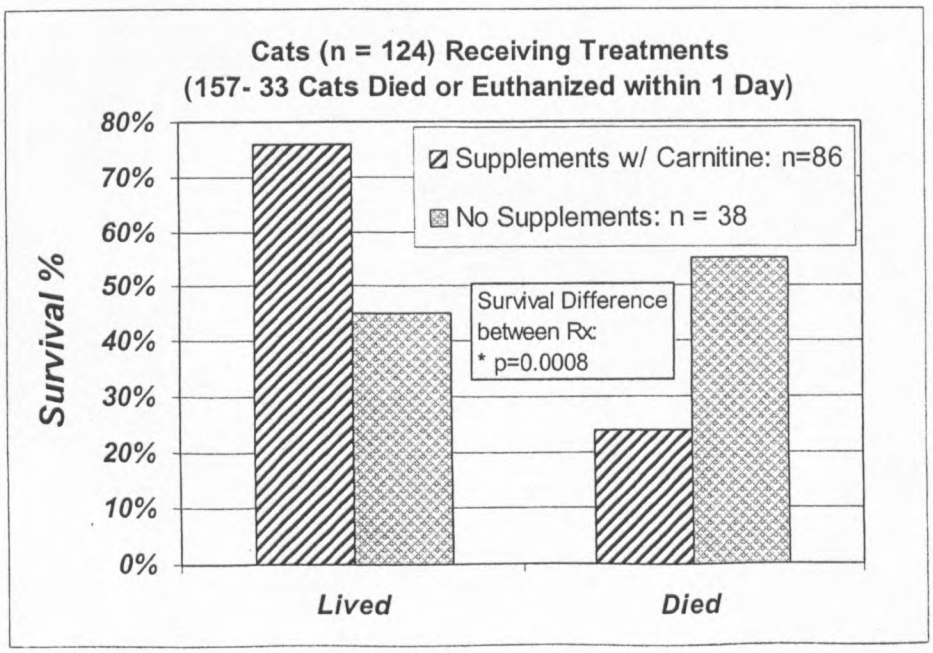
Predicting Recovery

Cats making a successful clinical recovery from HL demonstrate a gradual reduction in serum enzyme activities and total bilirubin concentrations over time. Generally, within 10 days the total bilirubin concentration declines by ≥ 50% while serum enzyme activity may remain near values documented at the time of case admission. Cats with severe HL making a successful recovery required 10 days (median) of hospitalization; those that died did so by day 7 (median). Surviving cats my require up to 21 days of hospital care, depending on the owner's nursing skill and desire to participate in the cat's care. Treatment with l-carnitine and the regimen outlined above has not reduced the length of hospitalization of cats in our clinic. However, a chance of recovery > 85% can be estimated in our hospital if an individual cat survives the initial 96 hours.



Survival in Cats with Severe

Hepatic Lipidosis Receiving Balanced Nutritional Support
And Supplements Described in these Notes or Without Supplements
S. Center, DVM, Dipl ACVIM, College of Veterinary Medicine, Cornell University, Ithaca, NY
Published: Vet Clin North America, 2005,



Treatment Guideline Does & Don'ts

1. *Don't rush to sedate / anesthetize,* place a central jugular line, apply an E- or G- tube for feeding, do cystocentesis, or aspirate liver *UNTIL* vitamin K has been given and a reasonable response interval permitted (12-24 hrs).
2. Avoid using general anesthetics until electrolyte and hydration deficits are addressed and abnormalities attenuated.
   Avoid propofol and any sedative / analgesic containing propylene glycol as a carrier. Masking down is the least noxious method.
3. Consider that FHL is most often a Secondary Disorder: THEREFORE→ *Look for an underlying cause.*
4. A liver biopsy is *NOT* necessary to initially diagnose and treat FHL although some cats have CCHS or other hepatic disease that will EVENTUALLY require biopsy. A liver aspiration cytology combined WITH signalment, history, typical clinicopathologic features, and US imaging provides enough information for a provisional diagnosis and aggressive treatment.
5. *Avoid lactate* containing fluids, initially.
6. *Do not supplement fluids with dextrose:* this may promote further hepatic TG accumulation.
7. Correct electrolyte abnormalities early.
8. Anticipate electrolyte shifts associated with the *re-feeding phenomenon (especially severe acute hypophosphatemia)* and make efforts to thwart their occurrence.
9. *Do NOT RELY ON APPETITE STIMULANTS*
   Ensure intake of a adequate energy and protein using a protein replete balanced feline diet.
   Avoid feeding a protein restricted diet unless overt hepatic encephalopathy recognized.
10. Ensure adequate B soluble vitamins, consider B_{12} deficiency and treat based on suspicion of such. Always collect a baseline blood sample for B_{12} determination for retrospective guidance of the need for chronic parenteral vitamin supplentation.
11. Anticipate antioxidant depletion, especially in cats showing heinz body hemolysis. Provide a thiol donor substrate such as NAC for crisis, followed more chronically with enteric SAMe dosing.

If Neck Ventroflexion: *consider electrolyte or thiamine insufficiency*

Check electrolytes: K, P, Mg; provide supplements as appropriate.

Administer thiamine: 100 mg in fluids (B-soluble vitamins given slowly with crystalloid fluids)
Parenteral administration by IM route may result in collapse, although rare

B-soluble vitamins in fluid: consult Table 2.

Consider the possibility of other Underlying Disorders & Submit Appropriate Tests EARLY in Illness:
cervical weakness (neurologic disease, vertebral injury), muscle weakness (myopathy, myasthenia gravis (very rare)), hyperthyroidism, organophosphate toxicosis, even hepatic encephalopathy.

Body Condition Assessments: Considerations Important for Feline Health Care

SA Center, DVM, Dipl ACVIM, Professor, Internal Medicine

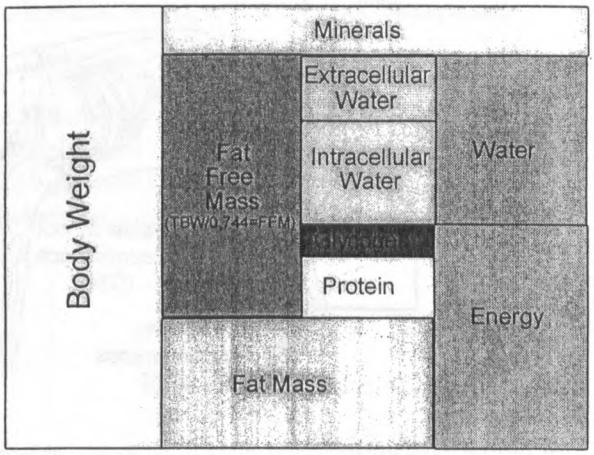
Introduction

Body Composition and Its Determination

Objective information quantifying body composition has research as well as clinical value in veterinary medicine.

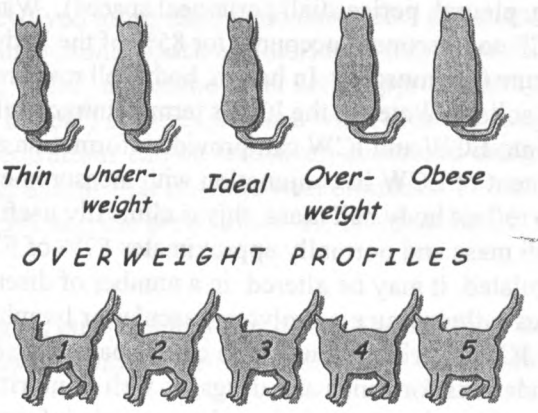
Accurate estimation of the total body water (**TBW**) compartment can be used to quantify body composition in terms of fat mass (**FM**) and fat free mass (**FFM**). The relationship of FFM and FM to body components and energy storage are illustrated in ***Figure 1*** (adapted from Elliot D, 2002). Since a large component of body FFM is comprised of skeletal muscle, this body partition is often used synonymously with Lean Body Mass (**LBM**). Investigations in a spectrum of species (but limited investigation specifically of the cat), suggest that a mean value of 0.744 describes the hydration status of FFM. (Spray, 1950; Wang, 1999) Using this relationship one can derive LBM if FFM is known: FFM/0.744 = LBM.

Figure 1

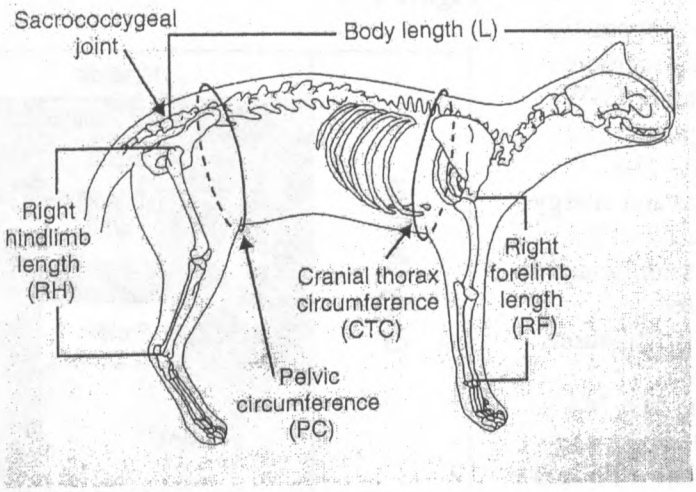


Body composition (% fat, % lean body mass) can reflect variables influencing the physical, nutritional, and metabolic status of an individual. The FFM represents the body partition where most energy utilization occurs and contributes an important volume to the water-soluble distributional space. Body composition is quantitatively defined by measuring either TBW using isotope dilution techniques (e.g. doubly labeled water, deuterium, others), FM is estimated with dual x-ray absorptiometry (DEXA), or body potassium is quantified with a whole body scintillation counter to quantify body cell mass. Each methodology is complicated by a number of factors. Isotope dilution studies require injection of a criterion reference, equilibrium time, collection of multiple venipuncture samples to confirm steady state isotope equilibration in the body water pool, and isotope quantification requiring difficult analytic procedures and expensive equipment. Absorptiometry requires general anesthetic patient restraint and expensive equipment. Whole body potassium isotope detection (natural abundance isotope) requires a prolonged counting interval with expensive equipment; since the subject must remain still during the counting procedure, animals require chemical restraint during that procedure. Because of the many complicating factors, these methodologies cannot be applied "real time" in clinical veterinary practice for objective estimation of body condition. Consequently, in both general practice and clinical nutrition studies, "operator dependent" body condition estimation is commonly achieved by assignment of body condition scores [BCS].

Estimation of BCS requires practice and involves physical and visual assessment of the patient's physique using palpation, and visual and descriptive criteria. While BCS can be consistently appraised by the same operator, the score is subjective and cannot quantify either FFM or FM.



Another method for determining body condition that is applicable in the clinical arena is determination of morphometric measurements. This approach is somewhat cumbersome requiring carefully measured lengths of body segments and application of a regression formula, as illustrated here.



Cats**

$$\%BF = -0.02(L^2_{[cm]}/BW_{[kg]}) - 4.12(RF_{[cm]}) + 1.48(PC_{[cm]}) - 1.16(CTC_{[cm]}) + 92.93$$

$$\%BF = \frac{0.04(PC_{[cm]}) - 0.0004(L^2_{[cm]}/BW_{[kg]}) - 0.08(RF_{[cm]}) + 1.11}{BW_{(kg)}}$$

Key: %BF = percent body fat, HS = length of right rear limb from the calcanean tuber to the mid-patellar ligament (hock to stifle), PC = pelvic circumference, L = body length from nose to sacrococcygeal junction, RF = length of right forelimb from shoulder to carpus, CTC = cranial thoracic circumference, BW = body weight.

An alternative objective method for quantification of FFM and FM is based on bioelectrical impedance analysis (BIA). This technique provides more information than just body condition as it determines TBW as well as its distribution within the intracellular and extracellular compartments (ICW or ICF, ECW or ECF). Understanding the theoretical concepts that provide the framework for BIA assessment requires appreciation of these water compartments.

Total body water (TBW) is traditionally described as distributed into two distinct compartments separated by cell membranes: the extracellular (ECF: 38%-46%) and intracellular (ICF: 50-58%) partitions. The ECF compartment reflects all water bearing fluids outside cell membranes including: the aqueous components of plasma, lymph, interstitial fluids, and fluids within organs (e.g. CSF in the central nervous system, aqueous humor and vitreous in the eye, and glandular secretions, fluids within the urinary and gastrointestinal tract), as well as fluids in potential third spaces (e.g. pleural, pericardial, peritoneal spaces). Water in the ECF is termed extracellular water (ECW). The ICF compartment accounts for 85% of the body cell mass where the majority of the resting energy expenditure occurs (i.e. muscle). In health, body cell mass reflects muscle, viscera, blood, and brain but not ECF or extracellular solids. Water in the ICF is termed intracellular water (ICW). Quantitative determination of TBW partitions into ECW and ICW can provide information about a subjects hydration status as well as body condition. Measurement of ECW in conjunction with measurement of TBW can be used to deduce ICW. Since ICW is considered to reflect body cell mass, this is clinically useful information.

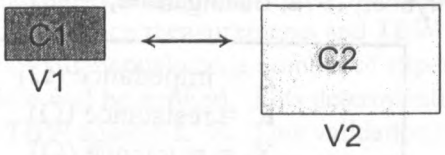
The ICW reflects body cell mass and normally approximates 57% of FFM. While the ratio of the ECW:ICW is normally tightly regulated, it may be altered in a number of disease conditions owing to physiologic and pathologic changes influencing electrolytes, vascular or lymphatic integrity, or cell viability. Real time knowledge of the ECW:ICW distribution can help clarify pathophysiologic disease mechanisms, facilitates optimal dose recommendations for fluids and drugs, as well as nutritional recommendations (energy requirements for LBM). It may provide other diagnostic and prognostic information considering that a number of complicated interactions between change in body condition and water retention have been characterized in illnesses, during cancer chemotherapy, after surgical procedures, or subsequent to sepsis where body mass may deplete by up to 40% and ECW expand by up to 25%. In fact, the ratio of the ECW:ICW, considering ECW to

represent metabolically active body cell mass, has been used as a predictor of mortality in critically ill malnourished humans. When measured sequentially, this ratio can also serve as an index of nutritional support or the response to nutritional provisions.

In review, the relationship between FFM, FM, and TBW is based on assumptions that FFM has a fairly constant and known water content (mean 73% to 74 %). Consequently, the FFM partition can be deduced from TBW data by dividing TBW by an established hydration factor (0.74 for many species and humans). (Wang, 1999) However, it also is important to recognized body water estimates predicting FFM and FM can generate errors reflecting altered hydration status of FFM related to age, sex, species, breed, and disease or therapeutic changes associated with fluid administration.

Isotope Dilution Assessment of TBW Using a Criterion Reference: Deuterium

Isotope dilution methods for quantifying TBW rely on the principle of $C_1V_1 \leftrightarrows C_2V_2$ [where C_1 = concentration in volume 1 (V_1) and C_2 = concentration in volume 2 (V_2)] such that the volume of a biological fluid in V_2 can be calculated after administration and equilibration when the concentration of the tracer C_2 is determined;



A tracer must be non-toxic, not metabolized, easy to administer, must be evenly and rapidly distributed in the fluid volume under investigation, and should not be excreted or secreted from the fluid compartment under investigation. Precision in dilution studies is limited by the dynamic state of the body where, there is a continual exchange of constituents with the environment.

Deuterium, a non-toxic stable isotope is the "tracer of choice" for TBW quantification. It can be measured using infrared spectroscopy that exploits the spectra differences between deuterium and water. Fourier transform infrared spectroscopy (FTIR) uses the O-D stretch resonating at 2,720-2,735 cm^{-1} to measure deuterium; the O-H in the "regular" water bond does not stretch or bend at this wavelength. This technique can measure TBW with a precision of 1-2%, allowing use of low tracer deuterium doses and small blood samples and has been used successfully to estimate TBW in cats.(Jennings, 1999; Backus, 2000)

However, deuterium dilution overestimates TBW owing to hydrogen exchange with non-aqueous hydrogens on amino, imino, sulfhydryl, carboxy, and alcohol groups. (Culebras, 1977, Culebras, 1977) Overestimation of TBW also can occur when isotope is lost through urinary or respiratory moisture during equilibration. The rapid equilibration of deuterium oxide within TBW (20 minutes to 8 hours) permits experiments in which TBW is measured to be conducted during a single day.

Dilution Assessment of ECW Using a Criterion Reference:

An ideal tracer for ECW quantification would diffuse freely through capillary membranes but not penetrate cell membranes, distribute equally and equilibrate rapidly within the extracellular subcompartments, should not be metabolized during equilibration, must not be osmotically active, and must be only slowly eliminated. Bromide has evolved as an ideal candidate tracer for quantifying the ECW compartment. However, because it has the same distributional space as chloride, it may overestimate ECW due to penetration into the intracellular water of RBC, WBC, and some other cells (approximately 10% of the dose). A mathematical correction ("distributional factor") is therefore used when bromide is applied as a criterion reference for ECW estimation Bromide concentrations can be sensitively measured using a simple HPLC method because there are no interfering physiological anions that co-elute with bromide. The accuracy of bromide for estimation of the ECW space approximates 5% and the precision of the bromide HPLC assay is within 1%.(Miller, 1989; Wong, 1989; vanKreel, 1994)

Bioelectrical Impedance Analysis *(much of this discussion has been adapted from cited references, the Xitron BIA Instrumentation Handbook, and D. Elliot's PhD thesis, University of California at Davis, College of Veterinary Medicine).*

Bioelectrical Impedance analysis has emerged as a popular, rapid, and non-invasive method for estimation of body composition in human beings. It also provides an ideal method for the objective estimation of body fluid compartment volumes because it is accurate, safe, inexpensive, rapid, reliable, highly reproducible, and

easy to perform. Widely applied in humans in the physical fitness industry as well as for research and clinical medical investigations, BIA employs the physics of conductance of an electrical current to estimate body composition by quantifying TBW and ECW and inferring ICW. These values are then used to predict FFM, FM and body cell mass.

The BIA method is based on the principle of Ohm's law where: electric current flowing through a conductor is equal to the voltage / resistance: $I = E/R$

I = current (amperes) E= potential difference between two points (volts) R= resistance (ohms)

Impedance (Z) is the frequency dependent opposition of a conductor to the flow of an alternating electric current. This opposition has two components or vectors: Resistance (R, in ohms) and Reactance (X_c in ohms), linked mathematically as: $Z^2 = R^2 + X_c^2$: (Nyboer, 1972; Baumgartner, 1988)

Where:

Z = impedance (Ω) R = resistance (Ω) X_c = reactance (Ω)

Phase sensitive electronics can be used to quantify resistance and reactance. *Resistance* is the pure opposition of the conductor to current flow (representing the sum of all the phase vectors) and is the reciprocal of conductance. *Reactance* is the opposition to current flow produced by the capacitance of the cell membrane and tissue interfaces (representing the sum of all the out of phase vectors) and is the reciprocal of capacitance or the storage of an electrical charge by a condenser for a brief interval; (Nyboer, 1972; Baumgartner, 1988; Lukaski, 1988) *Capacitance* causes the administered current to lag behind the voltage and causes a phase shift that is represented geometrically as the phase angle (Φ) or the arc tangent of the ratio of Xc/R.(Lukaski, 1996) The phase angle reflects the bodies ability to function as a resistor. In humans, the phase angle (*characteristic frequency)* is generally between 8 and 15 degrees.(Baumgartner, 1988) At low frequencies, *reactance* is small relative to *resistance* and consequently, *reactance* is often erroneously disregarded and *resistance* used interchangeably with *impedance*.(Lukaski, 1985). *Impedance* is directly related to conductor length and inversely related to the cross sectional area of the conductor.(Nyboer) Thus, impedance can be expressed as $Z = \rho (L/A)$

Where

L= length (cm) A = cross sectional area (cm^2) ρ = specific impedivity (ohm-centimeter)

The relationship of impedance to conductor volume is derived by multiplying the equation by L/L:

$Z = \rho (L^2/AL)$ Since volume is equal to area times length, AL can be substituted for volume:

$Z = \rho (L^2/V)$ If the conductor is assumed to be of homogenous composition with a fixed cross sectional area and uniform distribution of current density, then the last equation can be rearranged to

$V = \rho L^2/Z$

Where

V = volume of the cylinder (cm^2) ρ = specific resistivity of the cylinder (ohm/cm) L= length of the cylinder (cm) Z = impedance of the cylinder (ohm)

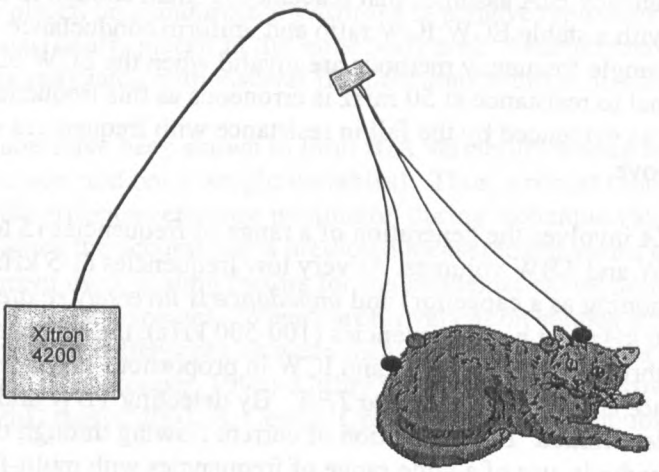
In the end it is evident that volume of the conductor is proportional to its length squared, divided by the impedance. Extrapolation of this equation to measure electrical impedance and thus volume in a human or in animals depends on the assumption that the body is essentially a cylinder or series of cylinders of known length

with uniform cross-sectional area and resistivity.(Hoffer, 1969) Since the body is not a conductor of uniform composition and thickness, the geometrical shape of the body is best characterized as a series of cylinders (5 = two arms, two legs, and the trunk). Since resistance is inversely proportional to the cross sectional area, the legs and arms constitute the areas with greatest resistance, having the smallest cross sectional areas. While the arm of humans contributes only about 4% of the weight, it accounts for 45% of the whole body resistance. In humans, the trunk region contributes about 45% to body weight but accounts for only 10% of the whole body resistance. (Baumgartner, 1988) The contribution of body regions to BIA measurements in the cat are somewhat different owing to the location of sending and sampling electrodes on the trunk.

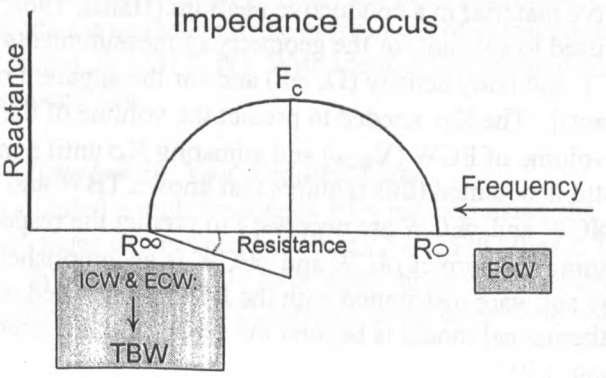
A *proportionality constant*, "*specific resistivity*" (the reciprocal of *conductivity)* must be determined to perform valid BIA body compartment estimations. Since electrical conduction in biological tissues is mainly ionic, *specific resistivity* is directly proportional to fluid volume and the number of free electrolyte ions in a fluid.(Kushner, 1992) The value of ρ (describing the amount of resistance to current flow per unit length of the conductor) is unknown but assumed to be constant within a group of experimental subjects within a single species. Resistivity varies depending on tissue microstructure, hydration status, and electrolyte concentrations. It is these factors that can be confounded by change in hydration status such as dehydration, polydipsia, or fluid therapy. To determine resistivity, impedance measurements and TBW determined by a criterion reference (such as deuterium), must be performed simultaneously on a number of experimental subjects that represent the population to which a BIA procedure will be applied. This determinations "specific resistivity" proportionality constant by regression analysis of TBW against L^2/Z. This validation has been done for anesthetized cats (D. Elliot PhD thesis, 2004) and at Cornell for non-sedated cats. (Center, et al, 2005).

Technique for BIA Recording

A BIA measurement is performed by placing four electrodes on the body. While in man this is applied in a wrist–ankle configuration, in cats our validation work confirms that a neck-tailhead configuration provides the best determinations.



A very small (imperceptible) electrical current is imposed at an induction electrode (about 800 μA); this current exceeds interfering noise caused by muscle contractions and external equipment. As the current travels through conducting materials in the body it undergoes a slight delay at cell interfaces. The current is subsequently detected by a voltage sensing electrode. The relationship between *impedance, resistance, reactance* and *phase angle* depend on the current *frequency* and are described as an *impedance plot*, shown here;



At very low frequencies (e.g. 5 kHz) the impedance of cell membranes and tissue interfaces is too large for conduction of the current within cells. The current is conducted ***ONLY*** through the ECW space . Volume calculated from resistance or impedance measured at low frequency is therefore assumed to be ECW. This measurement of impedance is considered resistive with no reactive component.(Luskaski, 1996) When the frequency of the current is increased, reactance increases because the capacitive properties begin to retard current flow, the resistance decreases, and the phase angle increases. Ultimately, the effect of cell membrane capacitance is diminished and the current penetrates all cell membranes. The *characteristic frequency* (f_c) is the frequency at which reactance is maximal; this differs between species. Once the frequency exceeds the f_c , reactance decreases as cell membranes and tissue interfaces loose their capacitive ability and the applied current penetrates both ICW & ECW: reflecting TBW. The proportion of current flowing through the ICW at any given frequency depends on where the f_c occurs. In young healthy humans, the f_c is near 40 kHz, but the f_c is not constant among individuals and can vary over a wide range of values.(Lofgren, 1951). The f_c in cats ranges between 50 to 65 kHz confirmed by two independent studies in healthy cats.(D. Elliot, 2004, thesis, SA Center, Cornell University, 2005)

Single Frequency vs Multiple Frequency BIA: Which is Better ?

Single Frequency BIA has been used in a variety of species where it has been calibrated against an isotope dilution criterion reference. Typically, 40 to 50 kHz is used and the length of the "cylinder" generally taken as the height of the subject or (less commonly) the distance between detection electrodes. Correlation coefficients ranging from 0.6 to 0.98, standard error of the estimate of 0.3 to 1.0 kg, and coefficient of variations of 2.0 to 3.4% have been shown for humans. Typical errors in a 70 kg person with 60% TBW relative to body weight and 18% body fat, in predicting TBW and FFM are 3-8% and 3.5-9%, respectively.(Kushner, 1992) Equipment set to function on humans at an appropriate *fc* is not set appropriately for cats.

Single frequency BIA assumes that reactance is small enough to be ignored and that body tissue hydration remains constant with a stable ECW:ICW ratio and uniform conductance. Unfortunately, equations used to estimate TBW by single frequency methods are invalid when the ECW:ICW is abnormal. The assumption that TBW is proportional to resistance at 50 mHz is erroneous as this frequency is too low for the current to fully penetrate all cells, as evidenced by the fall in resistance with frequencies exceeding 50 kHz, as shown in the impedance plot above.

Multifrequency BIA involves the generation of a range of frequencies (5 to 1,000 kHz) which permits specific delineation of ECW and TBW volumes. At very low frequencies (1-5 kHz), the current does not pass through cell membranes (functioning as a capacitor) and *impedance is inversely related to ECW.* The ECW is best predicted at frequencies < 10 kHz. At high frequencies (100-500 kHz), the capacitance of cell membranes dissipates and the current flows through both the ECW and ICW in proportions dependent on their relative conductivity and volumes: *impedance is inversely related to TBW.* By detecting TBW and ECW, the ICW can be derived and the ECW:ICW ratio determined The proportion of current flowing through the ICW depends on the f_c. Since the f_c varies among individuals, use of a wide range of frequencies with multi-frequency BIA allows for individual variation in f_c. Referring to the impedance plot above, the ECW is optimally measured at zero frequency (R_o) and TBW optimally measured at infinite frequency ($R\infty$). Since neither R_o or $R\infty$ can be practically measured, these values are interrogated by interpolation and extrapolation respectively from response to a range of frequencies. Several mathematical methods have been proposed for analysis of complex BIA data sets. The *Cole-Cole model* that describes the variation or resistance and reactance of biological tissues with difference frequencies, is the most commonly used analytic model along with equations derived from *Hanai's mixture theory* that describes the effects of a suspension on non-conductive material in a conductive medium.(Hanai, 1968; Cole, 1972; DeLorenzo, 1997) *Scaling factors* are used to account for the geometry of measurements between a defined electrode array, the resistivity of the ECF and body density (Ω, cm) and for the apparent resistivity of the ECW and ICW [(ρICW/ρECW) = Kρ (constant)]. The Kρ needed to predict the volume of the ICW (V_{ICW}) is derived by the iterative prediction of V_{ICW} and volume of ECW (V_{ECW}) and adjusting Kρ until a minimum mean error between the predicted and measured ratio is obtained (this requires that known TBW and ECW volumes have been determined). Thus, independent ρICW and ρECW are necessary to predict the respective volumes with the BIA electrical recording data. Determining the correct ρICW and ρECW is accomplished by iterative mathematical calculations performed by software distributed with the BIA system used in our work. (Xitron 4200 BIA analyzer). A discussion of the mathematical model is beyond the scope of this presentation, but is comprehensively reviewed in DeLorenzo, 1997.

Thus, with mathematical models, multifrequency BIA predicts TBW:

$$TBW = V_{ICW} + V_{ECW}$$

And, multifrequency BIA predicts FFM:

$$FFM = (d_{ECW}V_{ECW}) + (d_{ICW}V_{ICW})$$

d_{ICW} = mean density of ECW and associated materials (1.106)
d_{ICW} = mean density of ICW and its associated materials (1.521)

Factors Affecting Impedance Measurements: BIA may be influenced by hydration status, recent consumption of food and water, skin and air temperature, recent physical activity, patient age, size, shape and posture, and accidental electrical conductance of an examination table. Each of these can be controlled for. Since electrode positioning and instrumentation can have a substantial influence on measured values, a standard technique / methodology must be strictly applied to achieve reliable TBW and ECW predictions. If careful technique is applied, coefficients of variation ranging between 0.3 and 2.9% can be achieved over short and long term studies.

Considerations for Replicable Measurements

BIA should be performed with the patient *recumbent* on a *non-conductive surface*. The time of recumbency should be standardized; we have done our studies with cats restrained in lateral or sternal recumbency for 5 minutes. In man, impedance increases within the first 10 minutes of reclining due to redistribution of body fluids, change in skin temperature, or blood flow; the influence of these variables on cats has not been determined. In humans, appendages must not contact other body parts as this disturbs the applied electric current causing artefactually low resistance and impedance values. Since we do not use appendage electrode placement, this has minimal influence on feline measurements. Alteration in the "standard" orientation of an arm or leg with respect to trunk also may influence resistance and impedance measurements. Measurements in cats are less affected by these variables owing to the limited number of limb orientations that a non-sedated cat will permit. Electrodes must be placed on *standardized positions* to achieve reproducible measurements with the source and detector electrodes consistently placed in the same body area. Measurements are best *recorded after an 8 hour fast* to avoid variations associated with visceral fluid accumulations or ion fluxes associated with food assimilation.

Population specific features have been shown to limit BIA variability among individual humans (i.e. age, gender, race, height, body mass score, and body weight variables). Thus, a robust representative population of subjects must be represented in the criterion reference population during technique validation at which time scaling factors are determined. Since the accuracy of a predicted measurement varies according to the reference population and individual equipment used, scaling factors for the mathematical modeling of TBW and ECW must be set for each type of instrument for each species. When careful validation studies and subject measurements are followed, most studies have shown that differences between measured criterion values and predicted values are small and statistically insignificant.(Houtkooper, 1996) Utility in the cat has been proven by two independent studies, one at UCD (D. Elliot, PhD thesis, 2001; S. Center, Cornell University, unpublished data).

The Future for Multifrequency BIA ?

Multifrequency BIA is safe, provides real time measurements, is portable, and provides reproducible measurements objectifying body composition. It is not associated with adverse effects as the applied current is below the limit of sensory detection. A detailed study of multifrequency BIA has been completed in anesthetized healthy cats in which the criterion reference standards deuterium (TBW) and bromide (ECW) were used (Elliot, PhD thesis, University of California, Davis, 2001) using the Hydra ECF/ICF Bio-Impedance Analyzer (Model 4200 Xitron Technologies, San Diego, CA) has been published. (Elliott D, et al: Evaluation of multifrequency bioelectrical impedance analysis for the assessment of extracellular and total body water in healthy cats. J Nutr. 2002 Jun;132(6 Suppl 2):1757S-9S) With identical equipment we have proven that this methodology can be applied to non-sedated cats.

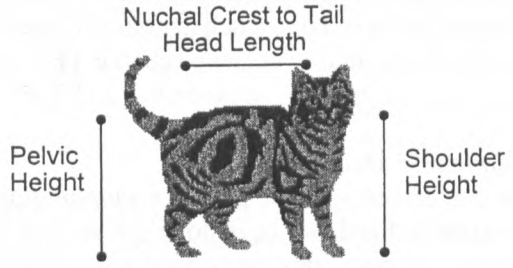
Cornell BIA Validation in Non-Sedated Cats

We have cross validated a multifrequency BIA method using the ***Xitron 4200 Hydra ECF/ICF Bio-Impedance Analyzer*** against values determined by Elliot (2001, PhD thesis, UC Davis), and criterion reference standards for TBW and ECW. We independently have determined scaling factors for non-sedated cats and have applied the method to clinically ill animals. Validation studies were done with clinically healthy cats and deuterium and

bromide criterion reference determinations of TBW and ECW. Our findings were statistically compared to findings in clinically healthy anesthetized cats and demonstrate that this procedure can be done in the clinical arena for routine case assessments.

Method: Physical and Morphometric Measurements

Body weight (BW) to the nearest 0.01 kg, body condition scores (BCS, 5-point system) and morphometric measurements (scapula height, pelvic height, body length: nuchal crest to tail head, tip of nose to tail head) were recorded for these validation studies. All measurements were made on the right side of the cat with body extended in a natural standing posture with maximal lengths recorded. Measurements indicated here are most useful for BIA body composition predictions.



Criterion Reference Studies

Sodium Bromide: ECW Space

After bromide concentrations were proven to achieve stability (3 to 6 hours) in venous blood, samples were collected before (0 hr), and 3 and 6 hours after administration of a tracer dose of NaBr (30 mg/kg body wt. elemental bromide). Concentrations of were determined by HPLC.

Deuterium as a Criterion Reference for TBW Volume

The ability to achieve stable deuterium concentrations by 6 to 8 hours after subcutaneous administration of a tracer dose (0.15 gm/kg of 99.9% atom percent excess [APE]) has previously been determined in our laboratory in healthy cats. Venous blood collected at 0, 6, and 8 hours relative to dose administration, were used to determine deuterium dispersal in total body water. Deuterium was measured using Fourier transform infrared spectroscopy (FTIR).

Calculation of ICW_D :

Differences between TBW_D and ECW_{Br}:

$$ICW_D = TBW_D - ECW_{BR}$$

Dilution Predicted Fat Free Mass (FFM_D):

Calculated from TBW_D according to:

$$FFM_D = \frac{TBW_D}{0.744}$$

0.744 is the fractional moisture content for lean body mass used in this study. (Wang, 1999)

Dilution Predicted Fat Mass (FM_D):

Calculated as the difference between body weight and fat free mass:

$$FM_D = BW - FFM_D$$

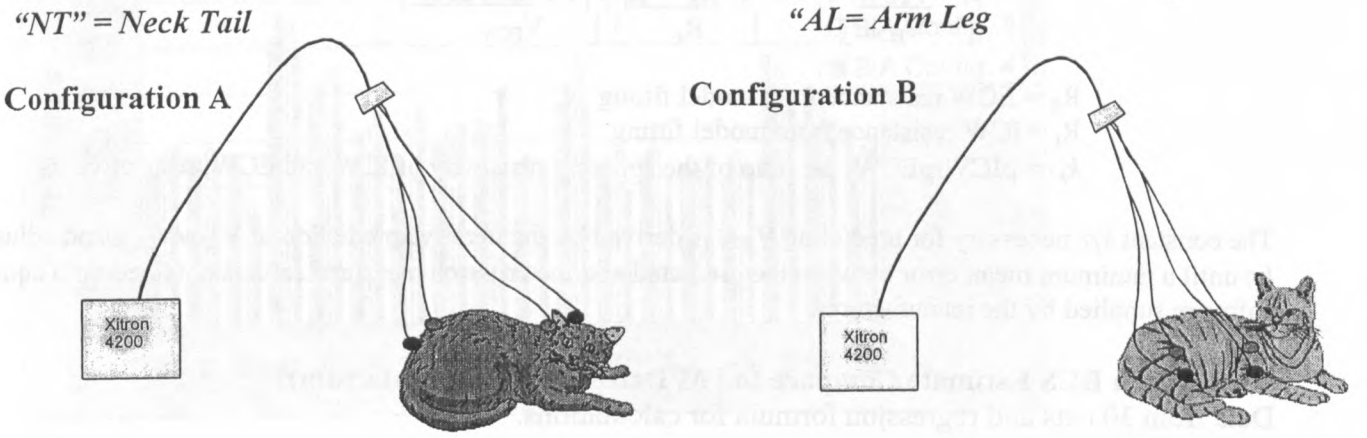
BIA Methodology:

Before deuterium and bromide studies were initiated, a minimum of 10 simultaneous multifrequency BIA impedance measurements were recorded at 50 frequencies (spanning 5kHz to 1000 kHz) from two electrode configurations (A, B). Sterilized re-usable intradermal tetrapolar platinum electrodes were used for these studies. A number of configurations were recorded to determine the best method for clinical measurements.

Configuration A: Electrodes were situated 1 cm distal to the nuchal crest (occipital protuberance) and 1 cm proximal to the tail head (lumbosacral junction) area, hereafter referred to as Neck-Tail (NT) configuration.

Detection electrodes were placed 2.5 cm from induction electrodes. These configurations were used with cats in both sternal and left lateral recumbency.

Configuration B: Electrodes were situated at the right elbow and right knee (lateral condyle of the right humerus and lateral aspect of the proximal tibia at the level of the femorotibial joint). Detection electrodes were placed 2.5 cm from induction electrodes.



Electrodes are positioned subcutaneously parallel to the skin surface and at right angles to the long axes of limbs or trunk. Electrode "wires" are suspended from plastic hangers positioned above the recording surface. Feliway® (Abbott Laboratories) is used to promote a relaxed environment (pheromone promotes a calm response in cats). Cats are restrained manually only with heavily insulated latex industrial gloves. Repeated measurements of resistance (R) and reactance (X_c) were obtained, and the corresponding impedance (Z), and phase angle (θ) computed from R and X_c at 50 frequencies ranging from 5 kHz to 1,000 kHz. Path-length between each of the tetrapolar electrode configurations were recorded to determine whether path length or body "height" measurements were best for volume predictions..

BIA Calculations:

The Z and θ spectral data for each electrode array and body position was fitted to an enhanced version of the Cole-Cole model of current conduction through heterogenous biological tissues using iterative nonlinear curve fitting algorithms specifically developed for use with the Hydra bioimpedance analyzer and built into the software.(DeLornzo, 1997) This enhanced modeling program extends the original Cole-Cole model allowing frequency invariant time delays caused by the speed at which electrical information is transferred through a conductor to yield the resistance of extracellular fluid (R_E) and intracellular fluid (R_I), respectively.(DeLorenzo, 1997; Elliott, 2001) The volume of ECW and ICW was predicted from the modeled R_E and R_I using equations formulated from Hanai's mixture theory describing effects of non-conductive material on the apparent resistivity of the surrounding conductive fluid.(Delorenzo, 1997, Elliott, 2001) The predicted ECW volume for each combination of electrode arrays, body length (paths) and body positions (sternal and left lateral recumbencies) was determined from R_E according to the following equation (included in the Hydra software, and as specifically detailed in the software Hydra manual):

$$V_{ECW} = k_{ECW} \left\lceil \frac{L^2 \sqrt{Wt}}{R_E} \right\rceil^{2/3}$$

V_{ECW} = the predicted total extracellular water (liters)
k_{ECW} = scaling factor accounting for the geometry for measurements between a defined electrode array, the resistivity of the ECF, and body density (Ω.cm)
L = measured body length or current path length (cm).
R_E= ECW resistance from model fitting (Ω)
Wt = body weight (kg)

The constant: k_{ECW} is established as the mean value of

$$k_{ECW} = V_{ECW} / \left\lceil \frac{L^2 \sqrt{Wt}}{R_E} \right\rceil^{2/3}$$

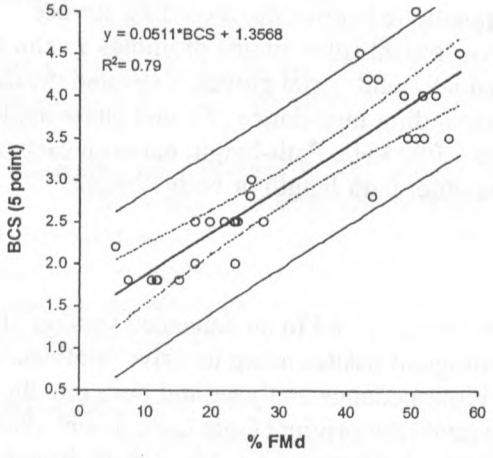
The volume of the intracellular water (V_{ICW}) was predicted from further extrapolation of Hanai's theory according to the relationship:

$$\left\lceil 1 + \frac{VICW}{V_{ECW}} \right\rceil^{5/2} = \left\lceil \frac{R_E + R_I}{R_I} \right\rceil \left\lceil 1 + \frac{k\rho\, VICW}{V_{ECW}} \right\rceil$$

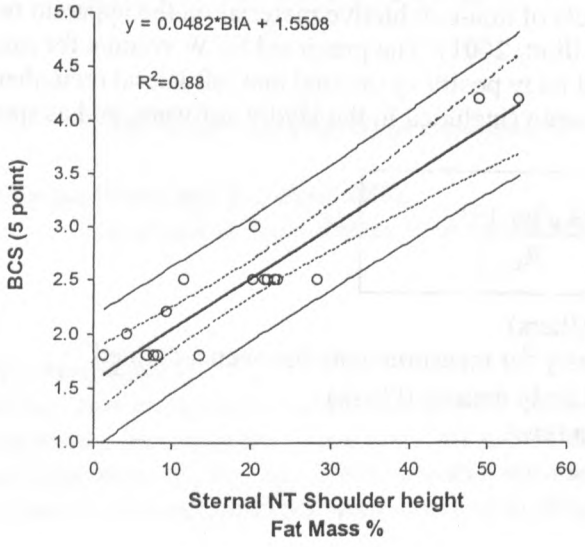
R_E = ECW resistance from model fitting
R_I = ICW resistance from model fitting
$k\rho$ = ρICW/ρECW, the ratio of the apparent resistivity of ICW and ECW, respectively.

The constant $k\rho$, necessary for predicting V_{ICW} is derived by the iterative prediction of V_{ICW}/V_{ECW} and adjusting $k\rho$ until a minimum mean error between the predicted and the criterion measured ratio is obtained with equipment software supplied by the manufacturer.

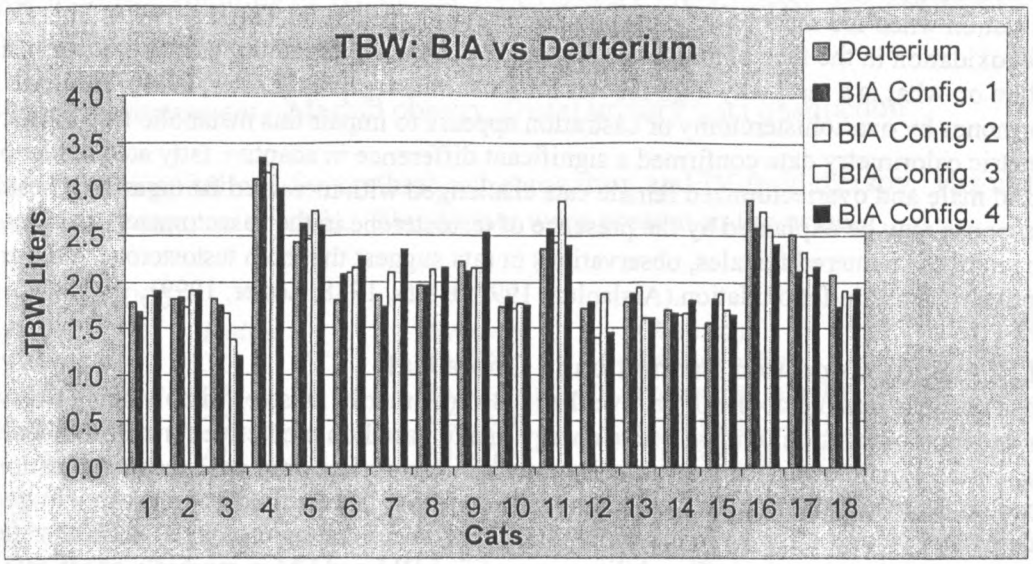
How Does a BCS Estimate Compare to FM Determination (Deuterium)?
Data from 30 cats and regression formula for calculations.



How Does BCS Estimate Compare to FM Determination (BIA) ?



How Does TBW_d Compare with TBW_{BIA}



Feline Energy Utilization & Body Composition

Obese Cats-FM > 30%: Energy Utilization and Body Composition

Obesity:

Obesity is the most common nutritional disorder in adult humans and children living in industrialized countries. Similarly, over-conditioning is an increasingly common health issue for pet cats. (Scarlett, 1994; Lund, 1999) While there are a number of factors favoring obesity, the common thread is consistent or intermittent consumption of food (fuel) exceeding daily energy requirements; excess energy being stored as adipose. Over consumption of food and lack of exercise are strongly implicated causal factors for over-conditioning in pet cats, particularly in neutered females. It is well established in humans that as little as the consistent ingestion of 5% excess energy beyond daily requirements results in insidious weight gain and obesity over a single year. (Jequier, 2002) The contribution of a subnormal RER to feline obesity has not been previously investigated. Rather, there have been measurements of MER in free living cats deduced from metabolizable energy requirements to maintain stable body weight or estimates made using doubly labeled water. These methods quantify daily energy utilization rather than "inherent" short term energy consumption at rest, as can be achieved with indirect calorimetry. We have investigated whether a subset of obese cats have a subnormal RER (total or per body weight unit: kg, $kg^{0.75}$, LBM kg) by comparing their RER and body composition measurements to similar measurements in adult mature neutered cats with a BCS ≥ 2.5 but < 4.0. We have found that $< 30\%$ of obese cats (BCS of ≥ 4, % fat mass $\geq 30\%$) have a low RER/kg or $kg^{0.75}$ body weight with only 5% having a subnormal RER per kg LBM. Unexpectedly, normalization of RER to LBM kg and $kg^{0.75}$ demonstrated a significantly higher RER in obese cats compared to healthy mature adult neutered cats. Thus, an inherently low RER is uncommonly affiliated with obesity in cats suggesting that gluttonly and lack of exercise are more important contributing factors.

Obesity imposes complex effects on energy utilization. While FM is traditionally considered to be "relatively" inactive as a site of metabolic energy utilization, recent evidence suggests that metabolic contributions of fat mass to RER may be considerable in morbidly obese humans. Unique metabolic activity of adipose tissue involves a number of neuroendocrine functions that influence fat uptake and storage in adipocytes, fatty acid mobilization and oxidation, as well as appetite and cytokine flux.(Bray, 2004) The influence of obesity on metabolism is complicated by the concurrent increase in LBM associated with body fat accretion; studies in obese humans indicate an expanded TBW compartment consistent with an increased LBM accounting for approximately 20% of the excess weight.(Saunders, 1993)

Many studies in obese humans have shown a large variability in RER among individuals, as we have found in obese cats. A large proportion of this variability in humans relates to differences in body composition. While the FFM alone accounts for 60 to 85% of the RER variation, the FM also can have an important influence on energy requirements. In lean humans, the influence of FM on RER is negligible. However, the FM becomes important in obese humans in which a higher RER occurs compared to non-obese subjects.(Weinsier, 1998) Our data suggests a similar phenomenon in obese cats considering that overall these cats have a significantly higher total RER and RER per LBM kg.

Compared to other species, most cats maintain body condition by consuming a relatively high fat diet, typical of a meat-based carnivore diet (relatively devoid of carbohydrates). It is known that cats can increase their rate of fatty acid oxidation when fed meat based diets containing supplemental fat. (Lester, 1999). This flexible feline response to fat oxidation in the face of a high-fat diet may account for the ability of most cats to maintain a normal body condition on what is a markedly high fat diet for most other species.(Lester, 1999) However, reducing the sex hormones by ovariohisterctomy or castration appears to impair this metabolic flexibility in the cat where stoichiometric calorimetry data confirmed a significant difference in adaptive fatty acid oxidation between vasectomized male and ovariectomized female cats challenged with increased fat ingestion.(Lester, 1999) While this response may be explained by the presence of testosterone in the vasectomized male cats or by the absence of estrogen in the neutered females, observations in rats suggest that both testosterone and estrogen can provide an adaptive increase in fat oxidation.(Arslanlan, 1997; Hatta, 1988, Lester, 1999).

Clinical Value of BIA Body Condition Estimation in Obese Cats

Since adipose tissue is less metabolically active than LBM (primarily muscle), simply being overweight can confound accurate recommendation of appropriate energy intake based on predictive formulas. Increased FM also can impose risk for iatrogenic complications associated with inappropriate drug dose recommendations, anesthetic administration, and fluid therapy. In fact, administration of too large a fluid volume can iatrogenically cause pulmonary edema and pleural effusion in morbidly obese cats, necessitating prolonged hospitalization, oxygen therapy, and diuretic administration. The ability to quantify LBM and FM in morbidly obese cats may assist in avoiding these therapeutic misadventures and in estimating more appropriate feeding guidelines. However, the latter recommendations require further investigation.

Case Example:

2 Yr DSH Cat: Jerry BWt.: 9.52 kg (20.9 lbs) BCS: 5.0 +

Abrupt onset vomiting (9 X), no history of dietary indiscretion. No diarrhea or constipation but Jerry has been anorectic.

Physical Assessment: Morbid obesity, Distal urinary tract obstruction

Jerry was hospitalized for urethral catheterization and IV fluid therapy. His urinalysis disclosed RBC tntc, WBC tntc, no crystals. Blood clots were present in the urine.

June 20, 2006

CBC:	*Patient*	*Reference*
PCV (%)	31	(32-52)
Hb (g/dl)	9.8	(10.1-16.4)
RBC (mill/µl)	7.7	(6.9-10.9)
MCV (fl)	42	(40-52)
MCH (pg)	14	(13-16)
MCHC (g/dl)	32	(29-34)
RDW (%)	15.5	(13.6-20.3)
Retic (%)	Nd	(0-1.5)
WBC (thou/µl)	15.9	(5.3-16.6)
Segment N (thou/µl)	15.3	(2.3-11.0)
Band N (thou/µl)	0.0	(0-0.3)
Lymph (thou/µl)	0.2	(1.2-6.9)
Mono (thou/µl)	0.5	(0.1-1.1)
Eosin (thou/µl)	0	(0.1-2.3)
Baso (thou/µl)	0	(0-0.2)
Plat (thou/µl)	321	(201-523)
MPV (fl)	13.6	(10.8-19.8)
TP - Refract (g/dl)	7.3	(5.9-7.5)
RBC Morphology:	No abnormalities	
WBC Morphology:	No abnormalities	
Plasma Appearance:	Clear	

Chemistry		*Reference*
Sodium (mEq/L)	156	(146-156)
Potassium (mEq/L)	5.2	(3.8-5.6)
Chloride (mEq/L)	120	(112-123)
Tot CO_2 (mEq/L)	17	(12-21)
Calcium (mg/dl)	8.0	(8.2-11.5)
Phosphorus (mg/dl)	7.3	(3.0-6.6)
Mg (mEq/L)	2.3	(1.5-2.5)
T. Protein (g/dl)	6.1	(6.7-8.5)
Albumin (g/dl)	3.4	(2.9-4.3)
Globulin (g/dl)	2.5	(3.1-5.1)
Urea (mg/dl)	50	(17-35)
Creatinine (mg/dl)	2.1	(0.7-2.1)
Glucose (mg/dl)	132	(63-140)
Cholesterol (mg/dl)	219	(73-265)
Lipase (U/L)	101	(102-224)
Amylase (U/L)	501	(489-2100)
ALT (U/L)	27	(29-186)
AST (U/L)	52	(13-46)
ALP (U/L)	9	(15-96)
GGT (U/L)	2	(0-2)
CK (U/L)	2,604	(56-529)
T. Bili (mg/dl)	0.2	(0 - 0.2)
Anion Gap (mEq/L)	19	(17-29)
Venous pH	7.41	(7.38-7.42)

FeLV: neg
FIV: neg
FCV (IFA): 1:400 +
1:1600

Urinary Catheterization maintained and working well throughout the day. Intravenous fluids administered at a rate of 30 mls/hr (720 ml/day; body weight: 9.52 kg or 20.9 lbs). Buprenorphine 0.2 cc(0.3mg/ml = 0.06 mg, 0.06/9.52=0.006 mg/kg) BID, Cosequin 2 caps SID, Orbax 22 mg, 1 Tab PO SID (22 mg/9.52 kg =2.3 mg/kg), Prazosin 0.5 mg BID (0.5 mg/9.52 kg = 0.05 mg/kg per dose).

Standard or Conventional Dosing:

Buprenophine: 0.005-0.01 mg/kg concentration Buprenex = 0.3 mg/ml
sublingually at a dose of 0.066 mL per kg

Orbifloxacin: 2.5-7.5 mg/kg/day

Prazosin: 0.03 mg/kg IV

The urethral urinary catheter was removed, Jerry was able to urinate, and he was sent home. The next day Jerry was unable to urinate (4 x straining, no urine produced). He vomited clear fluid, remained anorectic, and drank a small amount of water. Buprenorphine was dispensed in an attempt to provide analgesia. That afternoon, Jerry was represented unable to urinate. A large volume of bloody urine was easily expressed from the urinary bladder. Buprenorphine was continued, owner was instructed on bladder evacuation and a discussion about bethanecol was held.

Repeat Chemistry June 25, 2006
June 20, 2006

CBC:	*6/20*	*6/25*	*Reference*
PCV (%	31	28	(32-52)
Hb (g/dl)	9.8		(10.1-16.4)
RBC (mill/µl)	7.7		(6.9-10.9)
MCV (fl)	42		(40-52)
MCH (pg)	14		(13-16)
MCHC (g/dl)	32	30.6	(29-34)
RDW (%)	15.5		(13.6-20.3)
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Eosin (thou/µl)	0		(0.1-2.3)
Baso (thou/µl)	0		(0-0.2)
Plat (thou/µl)	321	156	(201-523)
MPV (fl)	13.6		(10.8-19.8)
TP - Refract (g/dl)	7.3		(5.9-7.5)
RBC Morphology:	No abnormalities		
WBC Morphology:	No abnormalities		
Plasma Appearance:	Clear		

Chemistry	*6/20*	*6/25*	*Reference*
Sodium (mEq/L)	156	159	(146-156)
Potassium (mEq/L)	5.2	7.3	(3.8-5.6)
Chloride (mEq/L)	120	117	(112-123)
Tot CO_2 (mEq/L)	ND	ND	(12-21)
Calcium (mg/dl)	8.0	9.2	(8.2-11.5)
Phosphorus (mg/dl)	7.3	16.1	(3.0-6.6)
Mg (mEq/L)	2.3		(1.5-2.5)
T. Protein (g/dl)	6.1	6.1	(6.7-8.5)
Albumin (g/dl)	3.4	2.6	(2.9-4.3)
Globulin (g/dl)	2.5		(3.1-5.1)
Urea (mg/dl)	50	> 130	(17-35)
Creatinine (mg/dl)	2.1	8.8	(0.7-2.1)
Glucose (mg/dl)	132	195	(63-140)
Cholesterol (mg/dl)	219	137	(73-265)
Lipase (U/L)	101		(102-224)
Amylase (U/L)	501		(489-2100)
ALT (U/L)	27	153	(29-186)
AST (U/L)	52		(13-46)
ALP (U/L)	9 26		(15-96)
GGT (U/L)	2		(0-2)
CK (U/L)	2,604		(56-529)
T. Bili (mg/dl)	0.2	0.5	(0 - 0.2)
Anion Gap (mEq/L)	19		(17-29)
Venous pH	7.41		

Urinary catheter passed, flushed, no urine flowing. Repeated catheterization and urine flowing well. Thoracic radiograph suggests perihilar edema. Abdominal radiographs does not disclose overt urocystoliths. Owner unable to administer oral medications. Terazocin (1/2 capsule, 1 mg PO) administered as an alpha blocker. Orbax 2.[illegible] mg 1 PO SID, cyproheptadine 1 (4mg tab) PO BID (antihistamine; 1-4 mg/cat PO once daily usually used for appetite stimulation). A gallop rhythm recognized. Cat discharged for at home care.

June 26, 2006: Jerry returns to the local clinic, passed another urinary catheter, urine very bloody. Not eating or drinking. Last PM noted dyspneic. Lateral thoracic radiograph discloses caudodorsal patchy pulmonary infiltrates. Normosol administered 30 ml /hour. Buprenorphine continued. With repeated obstructions and pulmonary complications cat was referred for ICU care and second opinion at Cornell.

On presentation Jerry had an unkempt coat, dandruff, and labored ventilation. A gallop rhythm was ausculted, mucous membranes were extremely pail, and CRT was difficult to appraise. The urinary bladder was markedly distended but it was impossible to palpate other visceral structures. A large quantity of very bloody urine passed along with small "stones" while Jerry was being stabilized in an oxygen cage.

Laboratory work attached.

6/26/06 Jerry had a severe non-regenerative anemia, a neutrophilic leukocytosis with a left shift (6,000 bands/ul) and toxic neutrophils and thrombocytopenia (98,000 / ul). A urinalysis discloses severe hematuria, bacteriuria (coccoid organisms), and 5-20 WBC / HPF. A chemistry profile confirms a high anion gap (37 mEq/L), azotemia (BUN = 238, creatinine = 11.8, phosphate = 20.0 mg/dL, Mg = 4.7 mEq/L). Panhypoproteinemia (albumin = 2.1, globulins = 3.1) are consistent with severe bleeding or volume overload. Mild hyperglycemia persisted, the ALT and AST were 2- and 5- fold increased, respectively, and the cat was hyperbilirubinemia (0.8 mg/dL). A coagulation profile disclosed: aPTT > 60 secs (14-18 secs), PT = 21 secs (14-22 secs), TCT= 9.5 secs (5-8 secs), Fibrinogen = 500 mg/dL (76-270 mg/dL), and Factor XII:C = 8% (60-150%). Hereditary Factor XII deficiency (Hageman trait), an Autosomal recessive feline trait is likely. Homozygotes usually have Factor XII:C < 10%; Jerry is likely homogygous for the trait. While Factor XII is a contact group factor and can cause marked prolongation of *in vitro* clotting times (aPPT, ACT) it DOES NOT cause an *in vivo* bleeding diathesis.

Jerry was given 36 ml of Packed RBCs and then provided fluid therapy with 0.9% NaCl at 30 ml/hour. NaCl was selected owing to stat electrolyte assessments (Thoracic radiographs, abdominal ultrasound and cardiology consultation were completed.

Abdominal ultrasound discloses a "mass-like" lesion in the urinary bladder, and bilateral mild hydronephrosis. The right ureter was proximally dilated.

MF-BIA is completed: ECF = 0.67 L, ICF = 0.60 L, FFM or LBM = 1.58, % Body Fat or Fat Mass = 82%.

Cardiology Consultation: severe left atrial enlargement, moderate right atrial enlargement, normal myocardial thickness, normal valve morphology, and hyperdynamic systolic function. A probable diagnosis of restrictive cardiomyopathy was made but the influence of volume overload complicated the interpretation. A repeat echocardiogram will be necessary to clarify issues.

Several transfusion of packed RBC were necessary to maintain the Jerry's PCV. He became markedly jaundiced presumably due to RBC hemolysis despite blood typing and cross matching of his blood to donor blood (he was given only A+ blood). Alternatively, he may have begun to develop HL. After a judicious reduction in IV fluid administration, treatment with furosemide, and IV Unasyn, Jerry improved. Removal of the cystic blood clot was deemed essential along with a perineal urethrostomy and insertion of an esophageal feeding tube. The feeding tube was essential because the owner was unable to administer oral medications and because this morbidly obese cat was anorectic and jaundiced with high risk for developing hepatic lipidosis.

Post-operatively, Jerry made a smooth recovery. A urine culture and sensitivity revealed an Enterococcus spp susceptible to Clavamox. On July 4th he was discharged for at home care. There have been no continued outstanding problems, no dyspnea, fatigue, or coughing.

Re-evaluation 7/10/06: body weight 8.6 kg (from 9.52 kg).

This morbidly obese cat (82% body fat) had a LBM of 1.58 kg (total body weight was 9.52 kg !). Since a cat with normal BCS (2.5) has approximately 15% body fat and can tolerate 30 ml/lb fluids per day (66 ml/kg per day), this cat received 30 ml/hour per day for several days before referral and for the first day of referral that was clearly more than he could handle. He has a LBM similar to a normal sized cat that would have received 270 to 320 ml per day total to achieve hydration. The obstructive urinary problem aggravated his overhydration. His total body water was 1.267 when over-hydrated, the day BIA was determined. Drug dosing in this cat may have increased his susceptibility to circulatory insufficiency (low blood pressure due to vasodilation with prazosin, terazocin, and cyproheptadine. Truly, a complicated feline case.

BIA in Hyperthyroid Cats: What Happens to Lean Body Mass and Fat Mass ?

Hyperthyroid Cats

The sympathetic nervous system plays an important role in the regulation of energy intake and energy expenditure.(Astrup, 1995) It has long been recognized that hyperthyroidism produces a condition of excess sympathetic discharge / effect. This endocrinopathy is a well described illness affecting older adult cats and leads to profound weight loss despite polyphagia. On physical assessment, severely affected cats demonstrate marked weight loss consistent with reduced body fat and muscle atrophy. There have been no assessments of energy utilization in hyperthyroid cats or in approximation of their LBM to our knowledge.

We determined BIA body composition and measured RER by indirect calorimetry in a number of hyperthyroid cats. Most hyperthyroid cats referred to our hospital have been treated with methimazole before referral for radioactive Iodine therapy (I^{131}) (drug discontinued at least 10 days before indirect calorimetry and body condition assessments). Thus, extreme body condition changes due to hyperthyroidism are often somewhat attenuated. Nevertheless, these cats are significantly different from mature adult neutered cats in body composition and RER values having a significantly lower body weight (kg, $kg^{0.75}$), LBM and FM weights. However, weight loss affects both LBM and FM partitions in most of these cats such that % FM and % LBM are proportional to what is found in healthy adult neutered cats. Our observations are similar to those in human beings, as body FM (absolute and % FM) are not significantly different from clinically healthy cats. (Lonn, 1998; Acotto, 2002) However, our BIA determinations confirm that some of these hyperthyroid cats catabolized body fat excessively.

Our findings document a significantly increased RER and weight loss similar to that described in hyperthyroid humans. While the overall total RER is not significantly different from mature adult neutered cats, when investigated on the basis of LBM it is significantly greater (1.8 fold). The long recognized increase in energy expenditure in hyperthyroidism (confirmed in man and rodents) reflects increased thermogenesis and enhanced protein turnover.(Magnus-Levy, 1895) In addition to the high adrenergic tone and enhanced thermogenesis (metabolism) the ingestion of a high protein feline diet by the polyphagic hyperthyroid cat may contribute to their increased RER via meal induced thermogenesis.(Westerterp, 1999) In man, protein degradation is a predominant metabolic feature of hyperthyroidism, promoting a negative nitrogen balance and skeletal muscle wasting (atrophy).(Loeb, 1996). The difference we have observed between hyperthyroid cats and humans in body composition may reflect the feline propensity for conserving fat in the face of undernutrition or catabolism. A significantly higher RQ in hyperthyroid cats compared to healthy adult neutered cats is consistent with a lower rate of fatty acid oxidation and increased utilization of either protein or carbohydrate fuels. However, since RQ is influenced by the ingested diet and the cats we have studied receive a variety of different foods (of varying fat and protein content), we are unable to substantiate this hypothesis. While cats are known to be unable to reduce their rate of protein metabolism (as pure carnivores), they have been shown to increase their rate of fatty acid oxidation when fed high fat meat based diets or when supplemented with carnitine. (Lester, 1999, Center, 2000). One recent study in hyperthyroid humans has verified a stable total body fat partition (approximating 27% of total body weight) despite a nearly 1.4 fold increase in RER (compared to commonly used prediction formulas).(Lonn, 1998), consistent with our findings.

So, how does this information help you ? Body condition assessments in hyperthyroid cats by BCS usually describe an undernourished animal and the expectation for a relatively larger ECF compartment / gross body weight. This is not the case. Fluid therapy and drug dosing in these animals, aside from the hypermetabolism, should follow guidelines normally used in euthyroid cats with normal BCS.

Restitution of euthyroidism in human beings results in accretion of FFM that is demonstrable within 3 months. Re-evaluation of some of our feline patients after restitution of euthyroidism demonstrates normalization of RER and increased body weight and LBM within 1 month of I^{131} therapy. Within just 1 month, a reduction in RER by approximately 30% (into the normal range) has been documented. Accompanying this reduction in RER is an increase in body weight associated with a greater LBM partition and reduced FM partition. While lipid stores are protected from lipolysis during recovery from hyperthyroidism in man, this does not seem to be the case in the cat.(Lonn, 2005) The cat may more closely resemble the rat where adipose tissue lipoprotein lipase activity increases during restitution of euythroidism causing a reduction in body fat stores. While lipid stores are protected in humans recovering from hyperthryoidism, the major body composition change involves muscle tissue as also may occur in cats. Thus far our BIA findings and clinical observations of cats recovering from hyperthyroidism suggest that body weight restoration involves recovering lean tissue in limbs and trunk with only modest change in total body fat mass, as described in man. (Acotto, 2002)

Feline Resting Energy Requirements:
Do ill cats demonstrate a consistent increase in RER to justify provision of the commonly prescribed MER illness coefficient or factor?

Critically ill or injured humans are often characterized as having increased energy expenditure and negative nitrogen balance which correlate with illness severity or extent of injury.(Hwang, 1993; Frankenfield, 1994; Brown, 1993). However, not all evidence supports these contentions. (Kinney, 1995, Cerra, 1987, Weissman, 1984, Surgery, 1982; Flancbaum, 1999; Reid, 2004; Hulst, 2005) In human medicine, indirect calorimetry is considered an integral part of nutritional support regimens in large hospitals, and remains the gold standard by which all other methods for estimating energy requirements are tested. Indirect calorimetry provides accurate, reliable measurements of RER over relatively short periods of time.(Flancbaum, 1999) However, the RER of clinically ill cats has not been widely investigated. In veterinary medicine, arbitrarily selected activity or "stress" factor / coefficient, commonly termed "illness" energy quotients or factors have been recommended to supplement the MER energy costs of illness.(Gross, 2001) These factors are assumed to account for stress, catabolism, or hypermetabolism that elevate daily energy requirements above healthy MER. However, the practice of estimating total daily energy requirements using predictive formulas with added stress "factors" are applied remains controversial both in human and veterinary medicine.(Swinamer, 1990; Brandi, 1988; Weissman, 1986, Reid, 2004) Studies in humans confirm that approximately 30-50% of critically ill patients are normometaoblic, 15-20% hypometabolic, and 35-65% hypermetabolic.(Swinamer, 1990; Brandi, 1988; Weissman, 1986, Mann, 1985; Cortes, 1989; Makk, 1990). If RER is not measured but rather estimated, patients may receive an energy intake either above or below their respective needs by 50% or more.(Weissman, 1986; Reid, 2004) The extent of which under or overfeeding can influence outcome in critically ill patients remains unclear. However, some work suggests that overfeeding is associated with high morbidity and mortality in some conditions; e.g. leading to pulmonary, hepatic, and infectious consequences.(Vo, 1987) On the other hand, multiple-organ dysfunction is higher in patients with large caloric deficits. (Bartlett, 1982). Variability in day-to-day energy measurements in critically ill humans have been reported in patients hospitalized in intensive care units; values range between 15% to 30% with variability reflecting treatment and nutritional modifications as well as the severity and type of illness and their co-morbidities.(Weissman, 1986; Vermeij, 1989). Critically-ill patients undergo marked LBM depletion, especially skeletal muscle, irrespective of the adequacy of nutritional support or protein supplementation. (Read, 2004).

To determine whether a patient can be classified as hypermetabolic or hypometabolic, the measured RER is compared with a range of values determined in healthy unstressed individuals. In the absence of a "normal range", comparison to predictive expenditure calculations using the Kleiber equation or some derivative of that equation, is commonly used. However, there is an inherent problem in using body weight for these calculations because of the wide differences in body condition (FFM or LBM) among individuals as well as variations in hydration status. Measured body weight may not reflect true body weight because of hydration variability associated with illness (altered oncotic pressure, pure water or electrolyte loss), as well as intravenous fluid therapy.(Weissman, 1992). A further complication is that the type of nutritional support can influence energy expenditure through diet-induced thermogenesisis. In critically ill humans, feeding carbohydrate and fat versus providing only pure carbohydrate, imposes a lower "fuel associated" energy expenditure. Providing critically ill humans with energy approximating their measured RER causes smaller meal induced variations in energy expenditure as compared to overfeeding (over feeding causes an increased RQ and increased thermogenesis).(Talpers, 1992; Takala, 1993). Variation in body temperature also can substantially influence energy expenditure; each degree Fahrenheit above normal temperature in humans increases energy expenditure by 7% (or 13% /°C). (DuBois, 1921; Field, 1982) Placing patients on controlled mechanical ventilation also influences their energy expenditure, reducing it by 15-20%. Thus, technical, therapeutic, hydration, and nutritional variables can generate a hypometabolic response in critically ill patients. A number of studies in human patients have correlated a hypometabolic condition with poor case outcome in patients with multiple organ dysfunction associated with renal failure, sepsis, sepsis syndrome, septic shock.(Kreymann, 1993; Showmaker, 1988; Tuchschmidt, 1992; Forsberg, 1991; Carlsson, 1984; Soop, Clin Nephrol, 1989) Unfortunately, there appears to be no consistent relationship between injury severity score (ISS) and measured RER in human trauma patients. This opinion is supported by an expert panel setting NIH human health nutritional guidelines. Using FFM as the basis for expressing RER, however, normalizes measured or calculated values.

Estimated RER using indirect calorimetry in ill cats and values recommended by a number of predictive formulas will be demonstrated for ill cats during this presentation (replicating data here will prohibit publication). We have been unable to demonstrate a significant consistent relationship that can be confidently recommended as

a predictive equation using any measure of body weight, including LBM (kg) in ill cats. While the mean and median RER in ill cats per LBM (kg) resembles values derived from the Kleiber formula for energy utilization, linear regression of predicted and measured RER does not support this impression.

Based on collective data derived from our feline metabolic projects, Prediction Formulas for RER Are Inconsistent in Their Accuracy and Can Lead to either Overnutrition or Undernutrition in individual feline patients.

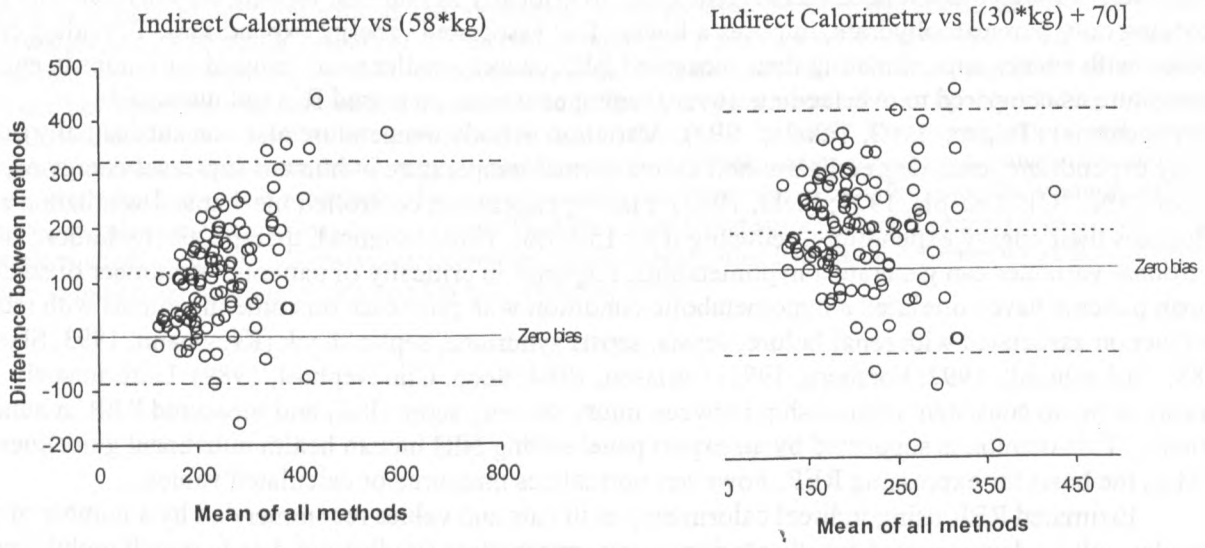
High variability of RER among healthy and ill cats reflects a number of variables such as energy ingestion, dietary formulation, body composition, thyroid function, and inherent differences in metabolism as well as variables associated with disease (e.g. fever, inflammation, infection, and altered hydration status).

The concept of body cell mass (BCM) may explain RER association with illness. It has been well documented in man that altered body composition (increase or decrease in LBM [fat free mass]) does not change linearly with BCM. The BCM, defined as "that component of body composition containing the oxygen-exhanging... work performing tissue", is proposed as a better expression basis for RER comparisons.(Schwenk, 1996; Moore, 1963) Unfortunately, it is not easily or promptly measured and has not been used in veterinary clinical patients. However understanding this BCM concept provides a reasonable explanation for the variability in RER measurements per LBM kg in clinical patients.

Energy utilization is inhomogeneous in the BCM where visceral organs consume approximately 24-fold more energy per kg mass per day than skeletal muscle. (Wade, 1962; Nelson, 1992) While estimates suggest that muscle mass accounts for more than 80% of the BCM, this tissue accounts for only 1/3 of energy consumption with the exception of the individual that is physically active. (Carpenter, 1995) The BCM does not change linearly with declining LBM as peripheral tissue loss in severe illness is not accompanied by a similar decline in visceral structures. In some cases, the liver and spleen enlarge owing to chronic inflammation, hematopoietic or erythrophagic activity, or other enhanced mononuclear / phagocyte activities that can increase energy utilization. Thus, altered visceral organ prominence, as a component of LBM and BCM, may attenuate the absolute decline in RER caused by diminishing muscle mass and remains unaccounted for with measurements of LBM. This visceral function may contribute to the high metabolic rate in hyperthyroid cats and to the sustained metabolic rate demonstrated in obese cats (RER/ per kg LBM).

To investigate the limits of agreement of two traditionally used prediction formulas, we demonstrate Altman Bland bias plots for intact healthy adults, neutered mature healthy adult cats, cats with hyperthyroidism, obese cats, and cats with different health problems. The wide differences shown in these plots and the bias values indicated on each graph suggest that these prediction formulas are not reliable in either healthy or ill cats for closely guiding feeding allowances. The dictum appears to persist: feeding to response is the safest nutritional recommendation one can make.

Altman Bland Plots for Measured & Predicted RER in All Healthy & Ill Cats



Clinical Pathology Report for Alice Hadden

Case #: **178543**	Species: **Feline**	Admission Date:	Discharge Date:
Owner: **Calabrese,Susan**		Clinician(s):	
Patient: **Jerry**		Service:	Location:
Breed: **American Domestic Shorthair**		Referring Vet:	
Color: **Blk/wht**		Reason for Visit:	
DOB: **4/1/02**	Sex:	Discharge Status:	

HEMATOLOGY

aHCT (32-52 %)

06/26/06 21:00c VB-E	12 %
06/29/06 07:30c VB-E	21 %
06/30/06 07:30c VB-E	20 %
07/03/06 14:00c VB-E	23 %

aHB (10.1-16.4 g/dL)

06/26/06 21:00c VB-E	3.6 g/dL
06/29/06 07:30c VB-E	6.9 g/dL
06/30/06 07:30c VB-E	6.3 g/dL
07/03/06 14:00c VB-E	7.1 g/dL

aRBC (6.9-10.9 mill/uL)

06/26/06 21:00c VB-E	2.7 mill/uL
06/29/06 07:30c VB-E	4.8 mill/uL
06/30/06 07:30c VB-E	4.4 mill/uL
07/03/06 14:00c VB-E	5.1 mill/uL

aMCV (40-52 fL)

06/26/06 21:00c VB-E	45 fL
06/29/06 07:30c VB-E	44 fL
06/30/06 07:30c VB-E	45 fL
[illegible]/03/06 14:00c VB-E	46 fL

[illegible]H (13-16 pg)

06/26/06 21:00c VB-E	14 pg
06/29/06 07:30c VB-E	14 pg
06/30/06 07:30c VB-E	14 pg
07/03/06 14:00c VB-E	14 pg

aMCHC (29-34 g/dL)

06/26/06 21:00c VB-E	30 g/dL
06/29/06 07:30c VB-E	33 g/dL
06/30/06 07:30c VB-E	32 g/dL
07/03/06 14:00c VB-E	31 g/dL

aRDW (13.6-20.3 %)

06/26/06 21:00c VB-E	17.2 %
06/29/06 07:30c VB-E	17.6 %
06/30/06 07:30c VB-E	19.1 %
07/03/06 14:00c VB-E	21.6 %

aRETIC (0.1-0.6 %)

06/26/06 21:00c VB-E	0.3 %
06/29/06 07:30c VB-E	1.2 %
06/30/06 07:30c VB-E	2.1 %
07/03/06 14:00c VB-E	2 %

RETIC-abs (8.6-55.8 thou/uL)

06/26/06 21:00c VB-E	8.1 thou/uL
[illegible]6/29/06 07:30c VB-E	57.6 thou/uL
[illegible]/30/06 07:30c VB-E	92.4 thou/uL
07/03/06 14:00c VB-E	102 thou/uL

HEMATOLOGY

NUCL RBC (0-0 /100WBC)

06/26/06 21:00c VB-E	1 /100WBC
06/29/06 07:30c VB-E	3 /100WBC
07/03/06 14:00c VB-E	1 /100WBC

aWBC (5.3-16.6 thou/uL)

06/26/06 21:00c VB-E	42.8 thou/uL
06/29/06 07:30c VB-E	34.9 thou/uL
06/30/06 07:30c VB-E	44.6 thou/uL
07/03/06 14:00c VB-E	25.2 thou/uL

SEGMENT N (2.3-11 thou/uL)

06/26/06 21:00c VB-E	34.2 thou/uL
06/29/06 07:30c VB-E	28.3 thou/uL
06/30/06 07:30c VB-E	38.8 thou/uL
07/03/06 14:00c VB-E	23.2 thou/uL

BAND N (0-0.1 thou/uL)

06/26/06 21:00c VB-E	6 thou/uL
	Extends to the rare metamyelocyte.
06/29/06 07:30c VB-E	4.9 thou/uL
06/30/06 07:30c VB-E	3.6 thou/uL
07/03/06 14:00c VB-E	0 thou/uL

LYMPH (1.2-6.9 thou/uL)

06/26/06 21:00c VB-E	1.7 thou/uL
06/29/06 07:30c VB-E	1 thou/uL
06/30/06 07:30c VB-E	1.3 thou/uL
07/03/06 14:00c VB-E	1.5 thou/uL

MONO (0-1.1 thou/uL)

06/26/06 21:00c VB-E	0.9 thou/uL
06/29/06 07:30c VB-E	0.3 thou/uL
06/30/06 07:30c VB-E	0.9 thou/uL
07/03/06 14:00c VB-E	0.3 thou/uL

EOSIN (0.1-2.3 thou/uL)

06/26/06 21:00c VB-E	0 thou/uL
06/29/06 07:30c VB-E	0.3 thou/uL
06/30/06 07:30c VB-E	0 thou/uL
07/03/06 14:00c VB-E	0.3 thou/uL

BASO (0-0.2 thou/uL)

06/26/06 21:00c VB-E	0 thou/uL
06/29/06 07:30c VB-E	0 thou/uL
06/30/06 07:30c VB-E	0 thou/uL
07/03/06 14:00c VB-E	0 thou/uL

PLAT SMEAR

06/26/06 21:00c VB-E	Low

Platelet clumps noted on smear. Platelet clumping falsely decreases the platelet cour and prevents accurate enumeration. Theref any provided count is a minimum count. Clumps are small.

HEMATOLOGY

PLAT SMEAR

06/29/06 07:30c	VB-E	**Low**
06/30/06 07:30c	VB-E	**Low**
07/03/06 14:00c	VB-E	**Adeq**

Platelet clumps noted on smear. Platelet clumping falsely decreases the platelet count and prevents accurate enumeration. Therefore, any provided count is a minimum count.

aPLAT (201-523 thou/uL)

06/26/06 21:00c	VB-E	98 thou/uL
06/29/06 07:30c	VB-E	44 thou/uL
06/30/06 07:30c	VB-E	65 thou/uL

aMPV (10.8-19.8 fL)

06/26/06 21:00c	VB-E	**19.1** fL
06/29/06 07:30c	VB-E	20.1 fL
06/30/06 07:30c	VB-E	21.7 fL

TP-REF (5.9-7.5 g/dL)

06/26/06 21:00c	VB-E	**6** g/dL
06/29/06 07:30c	VB-E	**6.7** g/dL
06/30/06 07:30c	VB-E	**6.6** g/dL
07/03/06 14:00c	VB-E	**6.9** g/dL

RBC MORPHOLOGY

06/26/06 21:00c	VB-E	**no significant abnormalities**
06/29/06 07:30c	VB-E	**no significant abnormalities**
06/30/06 07:30c	VB-E	**polychromasia (mild)**
07/03/06 14:00c	VB-E	**polychromasia (mild)**
		anisocytosis (mild)

PARASITES

06/26/06 21:00c	VB-E	**None Seen**
06/29/06 07:30c	VB-E	**None Seen**
06/30/06 07:30c	VB-E	**None Seen**
07/03/06 14:00c	VB-E	**None Seen**

WBC EXAM

06/26/06 21:00c	VB-E	**toxic changes in neutrophils (mild)**
06/29/06 07:30c	VB-E	**toxic changes in neutrophils (mild)**
06/30/06 07:30c	VB-E	**toxic changes in neutrophils (mild)**
07/03/06 14:00c	VB-E	**no significant abnormalities**

PLASMA APPEARANCE

06/26/06 21:00c	VB-E	**Normal**
06/29/06 07:30c	VB-E	**icterus (Moderate)**
06/30/06 07:30c	VB-E	**icterus (Moderate)**
07/03/06 14:00c	VB-E	**Normal**

REVIEWED BY

06/26/06 21:00c	VB-E	**Tracy Stokol, BVSc PhD DACVP**

IMMUNOLOGY

XMATCH

06/28/06 13:49r	VB-PC	AS3-01
		Major (compatible)
		AR-15
		Major (compatible)
06/28/06 13:30c	VB-E	PATIENT
		Auto (compatible)

URINALYSIS

VOLUME

06/26/06 21:00c	UV-NA	**2** mL
07/14/06 12:21r	UY-NA	**1** mL

COLOR

06/26/06 21:00c	UV-NA	**Red (Md)**
07/14/06 12:21r	UY-NA	**Yellow (Lt)**

TURBIDITY

06/26/06 21:00c	UV-NA	**Clear**
07/14/06 12:21r	UY-NA	**Slt Cldy**

SP GRAV

06/26/06 21:00c	UV-NA	**1.021**
07/14/06 12:21r	UY-NA	**1.024**

cpH

06/26/06 21:00c	UV-NA	**6.5**
07/14/06 12:21r	UY-NA	**6**

cProtein

06/26/06 21:00c	UV-NA	**500** mg/dL
07/14/06 12:21r	UY-NA	**30** mg/dL

cGlucose

06/26/06 21:00c	UV-NA	**Negative** mg/dL
07/14/06 12:21r	UY-NA	**Negative** mg/dL

cKetone

06/26/06 21:00c	UV-NA	**Negative** mg/dL
07/14/06 12:21r	UY-NA	**Negative** mg/dL

cBilirubin

06/26/06 21:00c	UV-NA	**Negative** mg/dL
07/14/06 12:21r	UY-NA	**Negative** mg/dL

cHemoprot

06/26/06 21:00c	UV-NA	**4+**
07/14/06 12:21r	UY-NA	**2+**

PROT-SSA

06/26/06 21:00c	UV-NA	**3+**
07/14/06 12:21r	UY-NA	**1+**

WBC

06/26/06 21:00c	UV-NA	**5-20** /HPF
07/14/06 12:21r	UY-NA	**None Seen** /HPF

RBC

06/26/06 21:00c	UV-NA	**>100** /HPF
07/14/06 12:21r	UY-NA	**<5** /HPF

BACTERIA

06/26/06 21:00c	UV-NA	**Mod**
		Cocci.
07/14/06 12:21r	UY-NA	**None Seen**

EPITH CELL

06/26/06 21:00c	UV-NA	**Very few**
07/14/06 12:21r	UY-NA	**None Seen**

SPERM

06/26/06 21:00c	UV-NA	**None Seen**
07/14/06 12:21r	UY-NA	**None Seen**

FAT DROP

06/26/06 21:00c	UV-NA	**None Seen**

URINALYSIS

FAT DROP

07/14/06 12:21r	UY-NA	**Mod**

[illegible]RIS

[illegible]/26/06 21:00c	UV-NA	**None Seen**
07/14/06 12:21r	UY-NA	**None Seen**

CASTS

06/26/06 21:00c	UV-NA	**None Seen** /LPF
07/14/06 12:21r	UY-NA	**None Seen** /LPF

CRYSTALS

06/26/06 21:00c	UV-NA	**None Seen**
07/14/06 12:21r	UY-NA	**None Seen**

ROUTINE BLOOD CHEMISTRY

hSODIUM (146-156 mEq/L)

06/26/06 21:00c	SS-NA	158 mEq/L
06/28/06 08:30c	VB-NA	175 mEq/L
06/29/06 07:30c	VB-H	169 mEq/L

hPOTASSIUM (3.8-5.6 mEq/L)

06/26/06 21:00c	SS-NA	6.6 mEq/L
06/28/06 08:30c	VB-NA	3.2 mEq/L
06/29/06 07:30c	VB-H	3.7 mEq/L

hCHLORIDE (112-123 mEq/L)

06/26/06 21:00c	SS-NA	**115** mEq/L
06/28/06 08:30c	VB-NA	134 mEq/L
06/29/06 07:30c	VB-H	130 mEq/L

[illegible]ICARB (12-21 mEq/L)

[illegible]/26/06 21:00c	SS-NA	**13** mEq/L
[illegible]6/28/06 08:30c	VB-NA	22 mEq/L
06/29/06 07:30c	VB-H	23 mEq/L

ANION GAP (17-29 mEq/L)

06/26/06 21:00c	SS-NA	37 mEq/L
06/28/06 08:30c	VB-NA	**22** mEq/L
06/29/06 07:30c	VB-H	**20** mEq/L

NA:K

06/26/06 21:00c	SS-NA	**24**
06/28/06 08:30c	VB-NA	**55**
06/29/06 07:30c	VB-H	**46**

hUREA N (17-35 mg/dL)

06/26/06 21:00c	SS-NA	238 mg/dL
06/28/06 08:30c	VB-NA	141 mg/dL
06/29/06 07:30c	VB-H	**23** mg/dL

hCREAT-rb (0.7-2.1 mg/dL)

06/26/06 21:00c	SS-NA	11.8 mg/dL
06/28/06 08:30c	VB-NA	4.4 mg/dL
06/29/06 07:30c	VB-H	**0.8** mg/dL

hCALCIUM (8.2-11.5 mg/dL)

06/26/06 21:00c	SS-NA	**8.3** mg/dL
06/28/06 08:30c	VB-NA	**8.6** mg/dL
06/29/06 07:30c	VB-H	**8.6** mg/dL

[illegible]OSPHATE (3-6.6 mg/dL)

[illegible]6/26/06 21:00c	SS-NA	20 mg/dL
06/28/06 08:30c	VB-NA	12.1 mg/dL

ROUTINE BLOOD CHEMISTRY

hPHOSPHATE (3-6.6 mg/dL)

06/29/06 07:30c	VB-H	**5.8** mg/dL

hMAGNES-xb (1.6-2.1 mEq/L)

06/26/06 21:00c	SS-NA	4.7 mEq/L
06/28/06 08:30c	VB-NA	3.7 mEq/L
06/29/06 07:30c	VB-H	**2.1** mEq/L

hTOT PROT (6.7-8.5 g/dL)

06/26/06 21:00c	SS-NA	4.7 g/dL
06/28/06 08:30c	VB-NA	5.3 g/dL
06/29/06 07:30c	VB-H	5.6 g/dL

hALB-blk (2.9-4.3 g/dL)

06/26/06 21:00c	SS-NA	2.1 g/dL
06/28/06 08:30c	VB-NA	2.1 g/dL
06/29/06 07:30c	VB-H	2.1 g/dL

GLOBULIN (3.1-5.1 g/dL)

06/26/06 21:00c	SS-NA	2.6 g/dL
06/28/06 08:30c	VB-NA	**3.2** g/dL
06/29/06 07:30c	VB-H	**3.5** g/dL

A/G

06/26/06 21:00c	SS-NA	**0.81**
06/28/06 08:30c	VB-NA	**0.66**
06/29/06 07:30c	VB-H	**0.6**

hGLUCOSE (63-140 mg/dL)

06/26/06 21:00c	SS-NA	177 mg/dL
06/28/06 08:30c	VB-NA	**104** mg/dL
06/29/06 07:30c	VB-H	**113** mg/dL

hALT/P5P (29-186 U/L)

06/26/06 21:00c	SS-NA	216 U/L
06/28/06 08:30c	VB-NA	**182** U/L
06/29/06 07:30c	VB-H	350 U/L

hAST/P5P (13-46 U/L)

06/26/06 21:00c	SS-NA	357 U/L
06/28/06 08:30c	VB-NA	263 U/L
06/29/06 07:30c	VB-H	529 U/L

hALK PHOS (15-96 U/L)

06/26/06 21:00c	SS-NA	**22** U/L
06/28/06 08:30c	VB-NA	**19** U/L
06/29/06 07:30c	VB-H	**53** U/L

hGGT (0-3 U/L)

06/26/06 21:00c	SS-NA	**<3** U/L
06/28/06 08:30c	VB-NA	**<3** U/L
06/29/06 07:30c	VB-H	**<3** U/L

hTOT BILI (0-0.2 mg/dL)

06/26/06 21:00c	SS-NA	0.8 mg/dL
06/28/06 08:30c	VB-NA	7.4 mg/dL
06/29/06 07:30c	VB-H	8.2 mg/dL

hDIR BILI (0-0.1 mg/dL)

06/26/06 21:00c	SS-NA	0.3 mg/dL
06/28/06 08:30c	VB-NA	4.2 mg/dL
06/29/06 07:30c	VB-H	4 mg/dL

ROUTINE BLOOD CHEMISTRY

IND BILI (0-0.2 mg/dL)

06/26/06 21:00c	SS-NA	0.5 mg/dL
06/28/06 08:30c	VB-NA	3.2 mg/dL
06/29/06 07:30c	VB-H	4.2 mg/dL

hAMYLASE (489-2100 U/L)

06/26/06 21:00c	SS-NA	807 U/L
06/28/06 08:30c	VB-NA	745 U/L
06/29/06 07:30c	VB-H	580 U/L

hCHOLESTER (73-265 mg/dL)

06/26/06 21:00c	SS-NA	127 mg/dL
06/28/06 08:30c	VB-NA	164 mg/dL
06/29/06 07:30c	VB-H	177 mg/dL

hCK (71-502 U/L)

06/26/06 21:00c	SS-NA	178 U/L
06/28/06 08:30c	VB-NA	482 U/L
06/29/06 07:30c	VB-H	517 U/L

hIRON (57-156 ug/dL)

06/26/06 21:00c	SS-NA	36 ug/dL
06/28/06 08:30c	VB-NA	97 ug/dL
06/29/06 07:30c	VB-H	292 ug/dL

hTIBC (208-378 ug/dL)

06/26/06 21:00c	SS-NA	209 ug/dL
06/28/06 08:30c	VB-NA	263 ug/dL
06/29/06 07:30c	VB-H	292 ug/dL

%SAT (20-61 %)

06/26/06 21:00c	SS-NA	17 %
06/28/06 08:30c	VB-NA	37 %
06/29/06 07:30c	VB-H	100 %

SPECIAL BLOOD CHEMISTRY

LIPEMIA

06/26/06 21:00c	SS-NA	13
06/28/06 08:30c	VB-NA	25
06/29/06 07:30c	VB-H	32

HEMOLYSIS

06/26/06 21:00c	SS-NA	7
06/28/06 08:30c	VB-NA	5
06/29/06 07:30c	VB-H	0

ICTERUS

06/26/06 21:00c	SS-NA	1
06/28/06 08:30c	VB-NA	7
06/29/06 07:30c	VB-H	8

SPECIMEN SUMMARY

HEMATOLOGY

06/26/06 21:00c	Venous Blood, EDTA
06/29/06 07:30c	Venous Blood, EDTA-microtainer
06/30/06 07:30c	Venous Blood, EDTA-microtainer
07/03/06 14:00c	Venous Blood, EDTA

IMMUNOLOGY

06/28/06 13:49r	Venous Blood, packed cells-AS3-01
06/28/06 13:49r	Venous Blood, packed cells-AR-15

SPECIMEN SUMMARY

IMMUNOLOGY

06/28/06 13:30c Venous Blood, EDTA-PATIENT

[illegible]ALYSIS

[illegible]/26/06 21:00c Urine, voided, no anticoagulant

07/14/06 12:21r Urine, cystocentesis, no anticoagulant

ROUTINE BLOOD CHEMISTRY

06/26/06 21:00c Separated serum, no anticoagulant

06/28/06 08:30c Venous Blood, no anticoagulant

06/29/06 07:30c Venous Blood, heparin-2 microtainers

SPECIAL BLOOD CHEMISTRY

06/26/06 21:00c Separated serum, no anticoagulant

06/28/06 08:30c Venous Blood, no anticoagulant

06/29/06 07:30c Venous Blood, heparin-2 microtainers

Diagnostic Laboratory Report for Alice Hadden

Case #: **178543** Species: **Feline**	Admission Date:	Discharge Date:	
Owner: **Calabrese,Susan**	Clinician(s):		
Patient: **Jerry**	Service:	Location:	
Breed: **American Domestic Shorthair**	Referring Vet:		
Color: **Blk/wht**	Reason for Visit:		
DOB: **4/1/02** Sex:	Discharge Status:		

*** This report does not reflect results for today. ***

Bacteriology

ANAER - Anaerobic Bacterial Culture

06/30/06 82316-06 Bladder swab

Sample: Bladder swab

Culture Result: No Anaerobic organisms isolated

URCUL - Urine Culture

06/28/06 80578-06 Urine swab

Sample: Urine swab

Qty: Few

Culture Result: Staphylococcus epidermidis

Qty: Moderate

Culture Result: Enterococcus faecalis

06/30/06 82316-06 Bladder swab

Sample: Bladder swab

Qty: Moderate

Culture Result: heavily encapsulated E coli

Qty: Many

Culture Result: Enterococcus faecalis

07/14/06 87444-06 Urine

Sample: Urine

Culture Result: No Growth (NG)

Comparative Coagulation

APTT - Activated Partial T'plast Time

06/28/06 80578-06 Citrated Plasma

APTT Control: 16.50

Interp (APTT): >60

CF7 - Coagulation Factor VII

06/28/06 80578-06 Citrated Plasma

FVII Control: 100

FVII Test: 8 (50 - 150 %)

FIBRIN - Fibrinogen (clottable)

06/28/06 80578-06 Citrated Plasma

Fibrinogen Ctl: 191 mg/dl

Fibrinogen: 500 mg/dl (75 - 270 mg/dl)

PT - Prothrombin Time (PT)

06/28/06 80578-06 Citrated Plasma

PT Control: 18.00

*** This report does not reflect results for today. ***

Comparative Coagulation

PT - Prothrombin Time (PT)

06/28/06 80578-06 Citrated Plasma

PT Test: 21.00 (14 - 22 seconds)

TCTME - Thrombin Clotting Time (TCT)

06/28/06 80578-06 Citrated Plasma

TCT Control: 6.50

TCT Test: 9.50 (5 - 8 seconds)

CORNELL UNIVERSITY - COLLEGE OF VETERINARY MEDICINE
VETERINARY MEDICAL TEACHING HOSPITAL
HISTOPATHOLOGY REPORT

Case #: **178543**	Species: **Feline**	Admission Date: **6/26/06**	Discharge Date: **7/4/06**
Owner: **Calabrese,Susan**		Clinician(s): **Ramstedt,K / Goldstein,R**	
Patient: **Jerry**		Service: **Medicine I SAC**	Location: **icu-16a**
Breed: **American Domestic Shorthair**		Referring Vet: **Delaney,Mari**	
Color: **Blk/wht**		Reason for Visit:	
DOB: **4/1/02**	Sex: **Male, castrate**	Discharge Status: **Alive**	

Histo Number: **S06-623**
Receipt Date: **6/30/06**
Approval Date: **7/7/06**

Previous Numbers:
Slides Prepared: **1**
Examining Pathologist: **Miller,A.**
Pathologist-in-charge: **McDonough**

Tissue	Diagnosis	
Urinary bladder	**(7301-0360.0)**	**Congenital diverticulum urachus**
Urinary bladder	**(7300-1000.0)**	**Cystitis, inflammation urinary bladder**
Urinary bladder	**(7300-8023.A)**	**Polyp bladder A**

Malignancy Codes

A - Benign - no premalignant significance
B - Benign - having premalignant significance
D - Neoplasm - malignancy not determined
E - Malignant neoplasm - non-infiltrating
F - Malignant neoplasm - differentiated
G - Malignant neoplasm - undifferentiated (anaplastic)
H - Malignant neoplasm - differentiation not determined
I - Malignant neoplasm - metastatic site

Histological Description:
Slide 1:
Urinary bladder (apex): Four sections of an irregular thickening of the mucosa at the apex of the bladder are examined. Diving deep into the connective tissue of the bladder is a furrow that is lined by numerous mildly hyperplastic transitional epithelium and is supported by a dense fibrovascular tissue. The underlying submucosa is loosely separated by clear fluid (edema) and infiltrated by small numbers of lymphocytes, plasma cells, neutrophils and macrophages, some of which contain intracytoplasmic golden brown pigment (hemosiderin). Small caliber blood vessels are numerous and prominent in the submucosa.

Histological Diagnosis:
Urinary bladder (apex): Urachal diverticulum with moderate lymphoplasmacytic polypoid cystitis

Comment: The bladder mucosa is greatly thickened beyond that which is normal for the bladder. There is no evidence of a carcinoma in situ; however, the areas of irregular hyperplasia may predispose this animal to the formation of transitional cell carcinoma in the future. Areas of polypoid cystitis can variably rupture and lead to the formation of blood clots in the bladder and this may have been the source of the clot noted grossly.
SMcD:lcc 07/07/06

Chronic Inflammatory Liver Disease in the Cat: Feline Cholangitis / Cholangiohepatitis (CCHS)

SA Center, DVM, Dipl ACVIM, College of Veterinary Medicine, Cornell University, Ithaca, NY, 14853.

OVERVIEW OF CCHS

a. *Age*: Any age cat (3 mths - 19 yrs), usually middle aged or older.
b. *No breed predilection;* suppurative CCHS more common in males
c. *Insidious history*
d. *Vague signs*
e. *Acute to chronic illness*
f. *Clinical & Clinicopathologic Features:*

Weight Loss	Polydipsia
Anorexia or Polyphagia	Ptyalism
Lethargy	Pallor
Vomiting	Anemia: non regenerative
Fever	Poikilocytosis
Jaundice	Neutrophilic leukocytosis: depends on form of dz
Hepatomegaly	↑ Liver Enzymes (ALP, GGT, ALT, AST)

Remember cats develop smaller increases in ALP than dogs with similar histologic lesions.

Disorders Associated with Cholangitis /Cholangiohepatitis in the Cat (Cornell University, 2002)

Suppurative	***Non-suppurative***
Primary bacterial infection	Inflammatory bowel disease
Septicemia	Primary cholangitis
Chronic bacterial infections:	Pancreatitis
sinusitis	Extrahepatic bile duct obstruction
splenic abscess	Cholelithiasis
pyelonephritis	Cholecystitis
Cholecystitis	Neoplasia:
Cholelithiasis	Gallbladder adenocarcinoma
Pancreatitis	Bile duct cystadenoma
Inflammatory bowel disease	Malformation:
Extrahepatic bile duct obstruction	Choledochol cyst, biliary dysplasia
Acute trematode infestation	Chronic trematode infestation
Toxoplasmosis	Chronic bacterial infection
	(anywhere in the body: esp spleen

g. *Diagnosed on the Basis of Liver Biopsy.*
Suppurative
Non-Suppurative: lymphoplasmacytic
lymphocytic
bile duct destruction: sclerosing lesion
lymphoproliferative disease: "not quite neoplastic"
low grade lymphoid: neoplasia

When chronic, fibrous septa may link portal tracts forming complete or incomplete circumscribed nodules. Inflammatory cells in portal tracts extend within fibrous septa. Nonsuppurative disease often involves a mixed lymphoplasmacytic infiltrate but sometimes is primarily lymphocytic. Inflammatory lymphoid nodules may form in the hepatic parenchyma. In some cats, small and medium sized bile ducts may be destroyed by apparent targeting of cell components by lymphocytes (lymphocytes observed histologically within duct walls and seemingly results in a **vanishing bile duct syndrome** also termed sclerosing cholangitis). Eventually progresses to **Biliary Cirrhosis**.

CELLULAR INFILTRATES: Reflect Etiology & Perpetuated Inflammatory Reactions,
These Direct Appropriate Rx
This CANNOT Be Determined On The Basis Of Aspirate Cytology

Neutrophilic Infiltrates: Suppurative Cholangitis / Cholangiohepatitis

Clinical Features: A predisposition for *male cats*, a *younger* median age as compared to cats with nonsuppurative CCHS, and *acute presentation* for systemic signs, *abdominal pain*, and *fever,* have been established. Less then 50% have hepatomegaly, most are jaundiced, febrile, lethargic, and dehydrated on initial presentation. Many have an acute history of *vomiting* and *diarrhea.*

Many cats with suppurative CCHS have an underlying disorder of the biliary system that would augment development of an infection. Acute or short term inflammatory bowel disease (IBD), duodenitis, pancreatitis, or acute extrahepatic bile duct obstruction (EHBDO) are most common. Some develop necrotizing cholecystitis and some have choleliths. A subset of these cats develop hepatic lipidosis (FHL) secondary to the severity of their anorexia, vomiting and diarrhea. A few cats have developed suppurative CCHS secondary to complications from immunosuppression treatments for nonsuppurative CCHS and infection associated with feeding appliances (tubes).

Clinicopathologic Features

Hematology: Initial CBC is influenced by dehydration and systemic inflammatory response. Some cats develop a lefts shifted neutrophilic leukocytosis with toxic neutrophils.

Serum Biochemistry: Most cats develop moderate increases in activities of serum *ALT, AST*, and *γGT* and only mild increases in serum ALP activity. The exception are cats with EHBDO and/ or pancreatitis in which serum ALP activity may be markedly increased; in these an increased cholesterol is usually found. Initial biochemistry profile is affected by dehydration causing increased BUN, creatinine, and protein concentrations. Serum electrolytes are commonly normal on admission.

Radiographic & Ultrasonographic Features

Survey Abdominal Rradiographs: ***Rarely*** reveal distinguishing diagnostic features not apparent on abdominal palpation. In cats with pancreatitis, a "ground glass" appearance to the right cranial quadrant and sometimes overt abdominal effusion may be observed. An enlarged gallbladder, regional ileus, rarely mineralized cholelith(s) or emphysematous cholecystitis (exremely uncommon) may be suspected as an underlying cause of suppurative CCHS..

Abdominal Ultrasonography: Often discloses important information that assists in determining the need for exploratory surgery or liver biopsy. Coexistent EHBDO (enlarged gallbladder, distended and tortuous common bile duct and cystic duct, and obvious intrahepatic bile ducts: the too many tubes sign), cholelithiasis, cholecystitis (thickened, laminar appearance to gallbladder wall, adjacent fluid accumulation, mucocele), and pancreatitis (prominent easily visualized enlarged hypoechoic pancreas, prominent pancreatic duct, adjacent hyperechoic mesenteric fat, focal duodenal ileus or a thick "spastic" duodenal segment , focal lymphadenopathy or effusion), may be recognized by an experienced operator. The most difficult condition to image and identify is choledochitis when ducts in the porta hepatis are focally involved. Ultrasound rarely can definitively identify the site of bile duct occlusion owing to interference from bowel gas and complexity of images created by superimposition of visceral and vascular structures. ***HOWEVER:*** *There May Be No Identifiable Abnormality in cats with CCHS.*

Ultrasonographically Assisted Sampling: Hepatic Fine Needle Aspiration And *Cholecystocentesis* is useful for obtaining diagnostic samples for *anaerobic* and *aerobic* bacterial culture, demonstration of septic suppurative inflammation, and for determining the need for exploratory surgery.

Organisms associated with Suppurative Feline Cholangitis / Cholangiohepatitis

E. coli	*Staphylococcus*
α-hemolytic Streptococcus	*Bacillus*
Actinomyces	*Bacteriodes*
Enterobacter	*Clostridia*
Enterococcus	*Toxoplasmosis*

(Listed in order of prevalence, descending left column first).

We have not found mycoplasma associated with this syndrome. However, it is possible that Bartonella is an associated infectious agent based on work done by Dr. E. Breitschwerdt at NC State. Recently, using PCR, Helicobacter DNA "tracks" were found in the liver of 2 cats with CCHS. The importance of this is unclear; organisms and antigens in the gut are commonly sent to the liver via the portal circulatory bed.

Cytologic & Histologic Features

Cytologic Evaluation: Liver aspirates or imprints reveals suppurative inflammation. Often, vacuolated hepatocytes are also observed. Since HL is a non-inflammatory lesion, the presence of inflammation indicates the primary hepatic disorder is the CCHS.

Note: Infectious organisms are seen on cytology BUT ONLY RARELY ON histopathology (EXCEPT toxoplasmosis). *Therefore:* Always examine imprints of liver tissue / bile & submit a culture for *anaerobe & aerobe bacteria* if you see neutrophils.

False NEGATIVE Cultures

a. Prior Antibiotic Therapy
b. Adverse Effects of Transport or
c. Failure to Request Anaerobic Culture May

Histologic Evaluation: Severe ascending cholangitis is associated with thickening of the extra-hepatic biliary system. Histologic lesions include dilation of the intrahepatic bile ducts, periportal edema, and an accumulation of suppurative exudate within the biliary tree. Depending on the duration of inflammation / infection, varying degrees of periductal fibrosis are associated with bile duct proliferation and biliary hyperplasia. With EHBDO, lesions also are observed within large bile ducts (common, hepatic ducts)

Cholecystitis: develops in some.

Pancreatic lesions may include interstitial fibrosis, periductal fibrosis, and intraductal suppurative inflammation. In some cats, a nonsuppurative inflammatory infiltrate is found in the pancreas suggesting the presence of chronic immune mediated inflammation reflecting chronic pancreatitis.

Transformation of Suppurative CCHS to Non-Suppurative CCHS

a. In chronic disease: transformation to non-suppurative CCHS is speculated
b. Needle aspiration ***CANNOT*** make this appraisal.
c. Biopsy, vim tru cut, wedge (surgical), or laparoscopic sampling is necessary for definitive diagnosis

If Chronic Suppurative CCHS:

Look for Chronic Infectious Source: Visceral Abscess (splenic ?) Pyelonephritis ? Infected cysts ?
Polymicrobial Infection Inappropriately Treated(wrong antimicrobials, too short therapeutic interval)

Treatment: discussed in general and specific sections following Nonsuppurative CCHS description.

Nonsuppurative Cholangitis / Cholangiohepatitis

Clinical Features: Most common form of CCHS. Most cats are *middle aged or older* and have had a *long duration of illne* ranging from a few weeks to more than 5 years. Most have been *ill for ≥ 2 months* by the time a definitive diagnosis is attaine. As would be expected, *clinical signs are subtle* and may include only *episodic vomiting, diarrhea, and rare anorexia.* On physical examination, most cats with chronic disease have *hepatomegaly* and are *jaundiced.* Most cats have only rare episodes of lethargy and often display a *surprisingly good appetite. Some have signs that perfectly mimic hyperthyroidism !* Few cats have abdominal effusion.

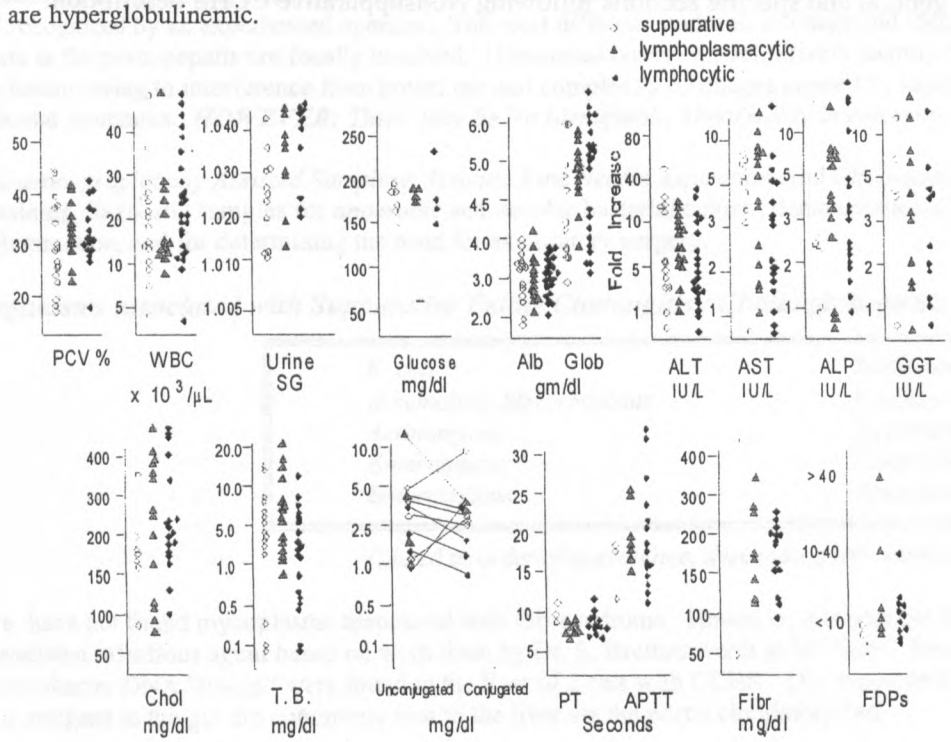
Associated Disorders: 75% of cats with Non-Suppurative CCHS Have A Predisposing / Concurrent Condition

Inflammatory bowel disease	History of EHBDO (Inflammation - Neoplasia)
Pancreatitis	Lymphoproliferative Disease
Cholelithiasis	Chronic Interstitial Nephritis
Cholecystitis	

Pancreatic Association

a. Humans with relapsing pancreatitis may have recurrent biliary/pancreatic "liths" obstructing the common duct (common duct in man fuses the biliary and pancreatic ductal systems as in cats). Liths in man are found by "screening" feces or duct contrast studies (retrograde contrast injection)
b. Lymphoid "portal triaditis" common in dogs with spontaneous & experimental pancreatitis
c. Common duct obstruction & inflammation associated with pancreatitis in cats where it may involve retrograde passage of bile and activated pancreatic zymogens (enzymes).
d. Ductal obstruction / inflammation may be associated with IBD (duodenitis)
e. Shared microcirculation: pancreas / liver dispersing infectious agents & cytokines / mediators.
f. Toxoplasmosis & Trematodes may affect both organs via circulatory and ductule systems.

Clinicopathologic Features: *Hematologic Features:* may include a regenerative or non-regenerative anemia. Some cats develop heinz body hemolysis. Rarely RBCs are macrocytic (may reflect low B_{12} concentrations owing to severe IBD, enteric lymphoma, small bowel intestinal overgrowth, or pancreatic insufficiency limiting intrinsic factor), and often demonstrate poikilocytosis (common in cats with liver disease). Cats with lymphocytic inflammation may develop a notable lymphocytosis (>14,000 / µl) without other evidence of malignant lymphoproliferative disease. These cats may have a "cross-over" lymphoproliferate disorder. Cats with lymphoplasmacytic inflammation tend to have greater magnitudes of increased ALT, AST, ALP and γGT compared to cats with lymphocytic inflammation. Most cats clinically ill from CCHS are hyperbilirubinemic and > 50% are hyperglobulinemic.



Despite certain trends in clinicopathologic features, *none can clinically distinguish cats with suppurative CCHS from those with nonsuppurative CCHS.* Cats with chronic *sclerosing cholangitis* (destruction of small to medium sized bile ducts) can develop complete occlusion of mid-sized bile ducts and seemingly, hepatic ducts. These cats mimic clinical signs seen with (EHBDO), developing episodic acholic stools and malabsorption of both fatty foods and vitamin K. These develop prolonged PIVKA clotting times. Terminally, sclerosing cholangitis cats clinically appear to have EHBDO without ultrasound evidence of large duct / gallbladder obstruction.

Radiographic and Ultrasonographic Features

Radiography: Like cats with suppurative CCHS, survey abdominal radiographs rarely reveal unanticipated diagnostic information. Rarely, discrete miliary densities are observed throughout the hepatic parenchyma, likely reflecting dystrophic mineralization of intrahepatic biliary structures or microliths. Cholecystoliths are identified in a few cats.

Ultrasonography: ***In some cats, abdominal US fails to disclose abnormalities.*** However, in many, a multifocal, hyperechoic pattern is recognized representing peribiliary inflammation and fibrosis. In some cats with chronic CCHS, the diagnosis is obfuscated by concurrent FHL which produces diffuse hyperechoic parenchyma. In some cats with chronic CCHS, portal hypertension is suspected based on Doppler assisted interrogation of mesenteric and intrahepatic blood flow. Thickened walls of large biliary structures (ducts and gallbladder) are observed in some cats. representing extension of nonsuppurative inflammation (this is most common in cats with the *sclerosing* form of CCHS). Erroneous diagnosis of EHBDO may occur in cats having a history of prior EHBDO as these animals may develop a permanently "floppy" or distended common bile duct and prominent hepatic biliary ducts.

Cytologic & Histologic Features

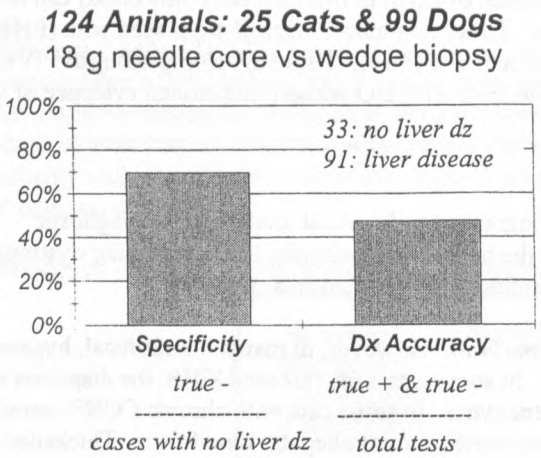
Cytology: Unlike suppurative CCHS, nonsuppurative forms of CCHS ***CANNOT BE*** *distinguished with confidence on the basis of liver aspirates or imprints.* Cytologic preps may lack evidence of inflammation or may disclose only a few inflammatory cells or evidence of FHL. Lipid vacuolation,common in ill anorectic cats may erroneously lead to a *mistaken diagnosis of FHL as the primary or sole cause of jaundice.* ***Impossible to definitively diagnose NON-suppurative CCHS with a needle aspirate.***

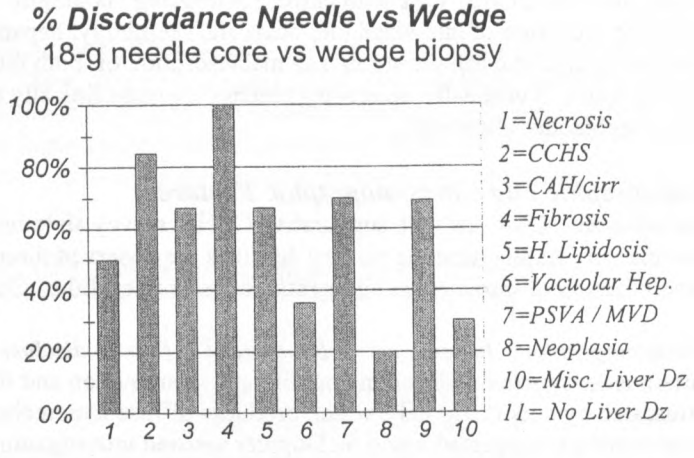
Histology: Histologically, lymphocytic or lymphoplasmacytic infiltrates surround and invade portal triads. Bile duct epithelium is focally invaded by inflammatory cells and in some cats bile duct epithelial cells become vacuolated, appear dysplastic, and drop out or disappear. Portal inflammation is associated with bile duct hypertrophy and hyperplasia. Cats with chronic severe disease deposit connective tissue around and bridging between portal triads. In some cats, particularly those with lymphoplasmacytic inflammation, small bile ducts are diminished in number (ductopenia) and residual lipogranulomatous foci remain. Application of a *cytokeratin stain* specific for biliary epithelium in the midst of periportal inflammatory infiltrates has been used to confirm bile duct dropout and suggests inflammatory "targeting" of the biliary epithelium. An "onion-skin" layering of connective tissue develops around small bile ducts in cats with the "disappearing bile duct" lesion (sclerosing cholangitis).

Although needle biopsies can disclose a diagnosis of CCHS, a *Wedge or Laparoscopic sample is preferable.* At the time of biopsy collection, ***full thickness biopsy of intestines and a small pancreatic biopsy should be collected*** because of the common association between diseases in these organ systems with CCHS. . It is important to determine whether the sclerosing cholangitis lesion is present as these patients are resistant to conventional immunosuppressive therapy. In addition, likely because of coexistent pancreatic injury, these cats (sclerosing CCHS) are more likely to become diabetic when glucocorticoid treatment is initiated. Demonstration of IBD is important in refining dietary management. It is important to recognize Sclerosing Cholangitis as these cats are resistant to conventional immunosuppressive therapy and are seeming predisposed to diabetes when treated with high dose glucocorticoid therapy. The "veracity" of 18-gauge paired needle biopsies vs a wedge hepatic biopsy from the same liver lobe is shown in the following figures. We found a discordance of >.50% using wedge sampling as the gold standard. Needle core biopsies must contain at least 15 portal triads to clearly demonstrate zonal distribution of lesions and targeted inflammation against bile duct epithelium. *Furthermore, several liver lobes should be sampled because not all liver lobes are equivalently affected.*

Nonsuppurative CCHS cannot be diagnosed with a needle aspirate (consider the discordance of the needle and wedge biopsy sampling); how could an aspiration sample be any better ?

The following graphs show diagnostic accuracy of needle biopsies using wedge biopsy as the gold standard





Pathophysiologic Mechanisms

Nonsuppurative inflammation involves immune mediated mechanisms which *perpetuate a necroinflammatory lesion involving membrane lipid peroxidation*. Measurement of glutathione (GSH) in liver tissue of cats with CCHS has demonstrated a significant reduction in concentration of this important natural intracellular antioxidant (> 60% of cats with necroinflammatory liver disease). Because of the common coexistence of inflammatory bowel disease (IBD), low grade pancreatitis, and chronic interstitial nephritis in cats with CCHS it is suspected that similar immunogenic or antigenic foci or infectious organisms inducing an immunogenic response against a similar antigenic target may be involved. In man, a well-established relationship exists between IBD and liver disease (pericholangitis) where hepatic lesions can *precede or follow* recognition of IBD. The most severe form of CCHS in affected people is termed *sclerosing cholangitis* which shares morphologic and progressive features with severe sclerosing CCHS in cats (form of CCHS where progressive loss of small and medium sized bile ducts occurs). While the pathogenesis has not been defined, hypotheses relating liver lesions to IBD in man include: 1) low grade portal bacteremia or biliary tree infections as initial, intermittent, or continuing injuries, 2) lesions induced by medical treatments for IBD, or 3) inherent host genetic or immunologic factors. There is no evidence that IBD treatment in cats generates CCHS lesions. We have observed an increased number of Himalayan cats with chronic CCHS and sclerosing CCHS. No infectious agents have as yet been confirmed as an underlying cause. Isolation of Helicobacter species (H. cholecystus) from hamsters with cholangiofibrosis and pancreatitis, the association between liver disease (involving bile ducts, gallbladder) in certain humans with Helicobacter (sp.) infections, demonstration of liver disease associated with Helicobacter in a dog (published, Fox, et al), and demonstration of Helicobacter genome by PCR in a few cats with CCHS, presents an intriguing consideration of an association between this organism and CCHS in some cats. This however, is far from proven. Helicobacter enteric infection is exceedingly common in cats (healthy and ill cats) and could be distributed to the liver in the portal blood as is the case with other enteric organisms. An association with Bartonella is possible in some cases in light of recent work showing low grade portal triad inflammation with experimental Bartonella infection in cats. FeLV, FIV, FIP and toxoplasmosis infections are not commonly associated with feline CCHS.

Lymphoproliferative Disease - Low Grade Lymphoma

Lymphoproliferative disease is suspected in some cases where CCHS involves dense infiltrates of lymphocytes lacking convincing histologic features of malignancy. In such cases, lymphocytes histologically "wander" into hepatic cords adjacent to the portal triad. A thick mantle of nonsuppurative inflammatory cells surrounding portal triads confuse differentiation between inflammation and neoplasia. A major clue for me is when the pathologist comments that "CCHS can "transform" to a malignant state" implicating a problem with clear classification. This should initiate a phone call to the pathologist to determine whether a confusing transition lesion is suspected. While this lesion may be initially controlled with immunosuppressive dosages of prednisolone (2-4 mg/kg/day) titrated to effect (ALT, AST, T Bilirubin values), remaining non-progressive for years (up to 5 years), it may subsequently resurface transformed as overt lymphoma. For recalcitrant disease (***AFTER*** *histologic characterization of a suspected lymphoproliferative CCHS lesion*), a lymphoma chemotherapy protocol may be appropriate. Some cats are suspected to have a T-cell rich B-cell lymphoma, difficult to definitively characterize without lymphocyte immunophenotyping. (see end notes regarding immunohistochemistry and CCHS study by M. Day). Cats with the lymphoproliferative lesion make a poor response to the polypharmacy approach described later in these notes without prednisolone or a lymphoma protocol (a few have responded to the Methotrexate protocol described for sclerosing CCHS). Bile ductule destruction is sometimes associated with a lymphoproliferative form of CCHS.

Definitive Diagnosis

a. ***Cannot** reliably diagnose Non-suppurative CCHS on the basis of cytology*
b. Surgical wedge or laparoscopic cup biopsies are the best method of tissue acquisition.
c. Biopsy more than one liver lobe *as involvement is variable among liver lobes in CCHS*
d. Consider collecting biopsy samples from the gut (full thickness or endoscopic) & pancreas
e. It is rare to grow bacterial organisms from the Non-suppurative CCHS cat: *BUT It Has Happened !* Without a culture you may overlook a complicating infection.
f. Metal analysis should be done (copper, iron, zinc) as a few cats with pathologic copper and / or iron have been identified with Non-suppurative CCHS. This finding emphasizes the need for antioxidants. Rarely a cat may require chelation therapy for copper.

CCHS GENERAL TREATMENT CONSIDERATIONS

1. *Look For Underlying Disease & Manage It !*
   a. Provide biliary diversion if EHBDO exists
   b. Remove any choleliths & inspissated bile & gallbladder if necrotizing cholecystitis.
   c. Look for Trematode eggs in bile if in an endemic area ! (fecal analysis before invasive sampling !!!)
   d. Treat inflammatory bowel disease: change dietary antigen exposure, metronidazole, glucocorticoids, correct subnormal B_{12}, water soluble vitamins, in some cases parenteral vitamin K.
   e. Treat active symptomatic pancreatitis: hospitalization, jejunal feeding or TPN, feed a true carnivore high protein diet of lean meat. Make sure adequate water soluble vitamin supplementation.

2. *Antimicrobials*: select non-toxic drugs with good biliary & liver tissue penetration.
   a. Provide coverage for gram "-" enteric organisms & anaerobes until histopathology & culture results available.
   b. Rare to grow organisms from cats with non-suppurative CCHS: but infection can complicate these.
   c. Treat suppurative CCHS: 3-6 months
   d. Treat non-suppurative CCHS with antimicrobials: until biopsy results are available and based on clinical response of the patient.
   e. Repeat cultures if: ↑ temperature or persistent fever,↑ WBC count. Sampling may be achieved via ultrasound guided aspiration of liver / bile.

3. *Ursodeoxycholic Acid:*
   a. Immunomodulation
   b. Cytoprotective
   c. Antifibrotic
   d. Choleretic effect
   e. Antioxidant effect
   f. Dose: 15 mg/kg PO per day, divided dose or SID (capsule or liquid suspension) given with food. ***MAKE SURE BILIARY DIVERSION HAS BEEN DONE IF EHBDO***

4. *Maintain Adequate Nutritional Intake. These cats have a tendency to develop hepatic lipidosis.*
   a. *Balanced feline ration with adequate energy*: **Avoid high carbohydrate / fiber diets.** Place a feeding tube if necessary. If symptomatic pancreatitis, use enteric jejunal feeding *l-carnitine* supplementation if hepatic triglyceride accumulation despite apparent adequate dietary intake (consult HL notes supplementation).
   Lactulose: if nitrogen intolerant to optimize nitrogen intake, assists in avoiding constipation which can augment endotoxic challenge and promote retention of encephalopathic toxins.
   b. *Supplemental Water Soluble Vitamins:* 2 x normal maintenance. Collect sample for B_{12} determination, provide initial treatment with 1 mg (= 1000 ug) B_{12} (SQ, IM) anticipating enteric malabsorption / low stores associated with severe intestinal disease as B_{12}, pancreatic insufficiency limiting intrinsic factor, or chronic disturbed bowel flora (overgrowth). Cobalamin deficiency will complicate response to critical care support. Plasma B_{12} will guide further chronic loading -supplementation.
   c. *Vitamin K_1 If Jaundiced:* initially 0.5 to 1.5 mg/kg at 12 hr intervals for 2 to 3 doses; chronic parenteral supplementation (SC, IM) in cats with severe sclerosing CCHS, chronic acholic stools or steatorrhea, or malabsorption due to chronic severe IBD (connective tissue deposition in lamina propria) based on PT (optimized) or PIVKA clotting tests or bleeding tendencies. Treatment tailored based on serial coagulation assessments. Dosing may be required anywhere from 7 to 28 day intervals.
   Toxicity in cats: heinz body hemolytic anemia if Vit K_1 dose too high or given too often. Some cats with sclerosing cholangitis require lifelong parenteral vitamin K_1 treatment.

5. *Fluid Therapy*
   a. *Polyionic fluids, NOT dextrose* supplemented unless hypoglycemia (exceedingly RARE)
   b. *Rate:* maintenance, contemporary losses, rehydration.

6. *Maintain Serum Potassium Concentrations*
   a. *Use conventional sliding scale*: See Therapeutic notes
   b. *Always Calculate* the rate of KCl administration: *avoid > 0.5 mEq/kg/hr = CARDIOTOXIC*

7. *Antioxidant therapy*
   a. *Vitamin E:* 10 IU/kg per day UNLESS chronic EHBDO or severe sclerosing CCHS (fat soluble vitamin malabsorption). Use high dose up to 100 IU/kg or injectable Vitamin E.
   b. *s-adenosylmethionine* (SAMe, Denosyl-SD4® Nutramax Laboratories)
      Dose : 20 mg/kg PO per day x 3 weeks, then 3 X weekly (not sure that intermittent Rx effective)
      Glutathione (GSH) donor increases hepatic & RBC GSH in healthy cats & in a variety of animal models of liver disease as well as humans with spontaneous hepatobiliary disorders.
      Provides a variety of beneficial effects in addition to thiol or GSH mediation.
   c. If critically ill, n-acetylcysteine (NAC) may be appropriate as an emergency thiol donor (e.g. severe acute anemia (associated with heinz body hemolysis), very high liver enzymes, critical condition). Beware of 10 to 12-hr lag between effects of drugs /drug carriers on RBC of cats with substantial liver dysfunction. e.g. propylene glycol carriers in diazepam, etomidate, or the oxidant effect of Propofol

SPECIFIC RX FOR HISTOLOGIC CLASSIFICATION

Suppurative CCHS Treatment

1. *Antimicrobials:* The cornerstone of treatment is recognition of involved infectious organisms such that optimal antimicrobial therapy may be initiated. *You need at least a gram stain of these organisms.*
   a. Select antimicrobials preferably concentrated in liver and bile and that are non-toxic to cats.
   b. Based on culture and sensitivity *whenever possible* or in some cases gram stain of organisms on cytologic preparations (if organisms fail to grow in culture this may be your only evidence of the infectious agent).
   c. *Avoid tetracyclines* as these can augment progression to hepatic lipidosis.
   d. Treat for *minimum of 3 months*, maybe longer up to 6 months.
   e. *Metronidazole* 7.5 mg/kg BID is often used with another antimicrobial. This kills anaerobes, penetrates bile and liver tissue well, has anti-inflammatory effects (cell mediated) and anti-endotoxic effects.
   f. *Enterococcus* organisms can be very difficult to eradicate, may require us of Vancomycin (see table).
   g. *Bacteroides* favors a polymicrobial infection, altering the environment favorably for survival of other bacteria. *You will not know whether you have a polymicrobial infection without gram staining & anaerobic cultures.*

The following antimicrobials are considered first line for patients with liver disease.

Gram "+" & Many Anaerobes			
Ampicillin	22 mg/kg	PO, SQ, IV	TID
Amoxicillin	10-20 mg/kg	PO	BID
Cephalexin	15 mg/kg	PO, SQ, IV	BID / TID
Expanded Spectrum Penicillins: effective against Enterobacteriaceae e.g. Pseudomonas aeruginosa. Are susceptible to B-lactamases.			
Ticarcillin	50 mg/kg	IV	TID
Piperacillin	25-50 mg/kg	IV	TID/QID
Second or third generation cephalosporins may be used for expanded coverage: Gm "+" & Many Gram "-" & anaerobes, & Bacteroides fragilis.			
Gram "+" & Many Gram "-"			
Enrofloxacin	2.5 mg/kg	PO, SQ	BID
Most Obligate Anaerobes			
Metronidazole	7.5 mg/kg	PO or rectal	BID / TID
Bactericidal to gram "+" aerobes & anaerobes. Resistant Enterococcus (cats with CCHS cholangitis esp.)			
Vancomycin	10-20 mg/kg	IV slow infusion	BID

7 - 10 days(Vancomycin is a tricyclic glycopeptide with poor oral uptake and painful when given IM. It is reserved for resistant Enterococcus, as in some cats with suppurative cholangitis / cholangiohepatitis. 90% of IV dose excreted unchanged in urine. Small amounts penetrate bile.

2. *Failure to Improve When Organisms are Known to be Present (cytology):*
   a. Was the underlying condition adequately treated ?
   b. Is there a chronic infection somewhere I overlooked ? Spleen ? Urinary tract ? Abscess elsewhere ?
   c. Transformation of suppurative to non-suppurative CCHS: need rebiopsy
   d. Development of hepatic lipidosis: aspiration cytology
   e. If response to therapy poor, *may need to re-biopsy, aspirate, collect bile: cholecystocentesis under US guidance. Rule out FHL, reinitiate cultures.*
   Cholecystocentesis: done with US & a 22 gauge spinal needle, extension tubing attached to a needle and large syringe to completely empty the gallbladder bile, using a transhepatic approach (penetrate liver parenchyma, this ↓ bile leakage into abdomen providing tampanode against the aspiration puncture. Using an US guide for bile aspiration permits better targeting during the cholecystocentesis. ***EMPTY the gall bladder or it will leak bile into the site.*** Be prepared for a *Vasovagal Response* (pathologic hypotension / bradycardia): relieve pressure on biliary structures if this occurs, give atropine. *STOP what you are doing !*
   f. Some cats develop nonsuppurative inflammation secondary to chronic suppurative inflammation. Verify using liver biopsy. ***Will not show on aspirates or cytology of a biopsy.***
   g. Add anti-inflammatory, immunosuppressive drugs to Rx regimen if transformation to non-suppurative CCHS.

3. *Choleresis:* Aids mechanical removal of organisms / toxins / bile acids / thins biliary concretions.
   a. Ursodeoxycholic Acid: (15 mg/kg PO per day with food) excellent choleretic, many other benefits.
   b. S-adenosylmethionine: SAMe may provide choleretic influence (provoking bile acid independent bile flow)

4. *Antioxidants:* Vitamin E (10 IU/kg per day) & SAMe (200 mg / day PO empty stomach) to protect against necroinflammatory / cholestatic / endotoxic oxidant injury. For critically ill cats, n-acetylcysteine may be appropriate (heinz body anemia, high liver enzymes with infection). NAC: 140 mg/kg IV over 20 minutes (10% to 20% solution diluted 1:2 to 1:4), given through a non-pyrogenic filter, then 70 mg/kg IV over 20 minutes BID to TID.

5. *Nutritional & Vitamin support:* water soluble vitamins always appropriate
   Specific B_{12} supplementation if significant IBD, bacterial overgrowth, suspect malassimilation see above for dose.

6. *Lactulose:* if constipation or suspect HE. Achieve soft stool, avoid overdosing → diarrhea, acidosis, vomiting.

7. *What to Expect in Response to Rx: Normalization of Biochemical Abnormalities:*
   a. Within 4 wks if no residual disease, underlying problem identified & eliminated, bacterial infection eradicated.

Surgical Intervention: Cats with EHBDO *Must Undergo Biliary Decompression.* The propriety of completing a cholecystectomy is determined at the time of surgery (during gross inspection of the extrahepatic biliary structures). Patency of the biliary system is determined, occlusions identified, lesions resected, choleliths removed, and mass lesions excised. If biliary tree decompression cannot be accomplished, the biliary pathway should be "rerouted" via a *cholecystoenterostomy.* Biliary diversion is a vital early therapeutic intervention in the prevention or control of septicemia in acute obstructive suppurative cholangitis. Survival in this circumstance reflects the speed of definitive treatment and biliary decompression. Cholecystoduodenostomies are more physiologic than cholecystojejunostomies. Unfortunately, the former may be difficult in the patient with severe pancreatic inflammation or fibrosis. ***Surgical intervention requires that attention be given to IV antimicrobial delivery before the infected structures are handled.*** Take care to note and avoid *Vasovagal Reflex* (**can slow and STOP the heart**) when the biliary tree is manipulated. If noted, discontinue biliary pressure and administer low dose atropine, reduce anesthetic agent, provide IV fluids and pressors as needed, and ventilate.

Summary: Treatment of Cats with Suppurative Cholangitis / Cholangiohepatitis

Nutritional Management:	Do not restrict protein. Use maintenance or maximum calorie diets: 60 kcal/kg/day
Underlying Disorders:	Identify and appropriately treat underlying conditions, especially inflammatory bowel disease, hepatic lipidosis, bile duct occlusion, and pancreatitis. Decompress biliary tree as appropriate
Antimicrobials:	*Consult Table above*
Metronidazole:	7.5 mg/kg PO BID to TID *if IBD suspected,* along with tailored antimicrobial Rx Used for its immunomodulatory influence and great anaerobic spectrum
Ursodeoxycholic Acid:	10 - 15 mg/kg daily PO, divided daily with food gives best bioavailability
Water Soluble Vitamins:	2-fold normal maintenance dose daily
Vitamin B_{12}:	1 mg IM every 7 days initially to load, individually titrated against plasma B_{12} concentration. Acquire initial plasma sample so you can discern whether this cat needs chronic supplementation.
Vitamin K_1:	*Initial Rx:* 0.5-1.5 mg IM 3 doses @ 12 hr intervals; if chronic treatment necessary, every 7 to 28 days based on sensitive PT or PIVKA clotting tests.
α-tocopherol (Vitamin E):	10 IU/kg α-tocopherol acetate
SAMe:	thiol donor & other important metabolic effects, 200 mg/day PO *(antioxidant, choleresis, other)*
n-acetylcysteine:	IV thiol / GSH donor, 140 mg/kg loading, then 70 mg/kg IV BID until enteral route established, (use non-pyrogenic filter), then use SAMe supplementation PO. Crisis GSH donor Rx appropriate if heinz body anemia, hemolysis, necrotizing hepatopathy.
Lactulose:	0.25 - 0.5 ml / kg initial dose, titrate to achieve several soft stools / day ONLY IF suspect Suspect nitrogen tolerance, to avoid constipation. Avoid overdosing → diarrhea, dehydration, acidosis, cramping.

Treatment of Cats with Non-suppurative CCHS:

1. *Prednisolone:* 2 -4 mg/kg per day.
   a. ***This may not provide full remission, in fact, full remission is rare.***
   b. Prednisolone provides immunosuppression, anti-inflammatory effects, and choleresis.
   c. Biochemistry profile q 14 days: enzymes, T. Bilirubin, glucose (minimal data base)
   d. Side Effects:

Diabetes mellitus	GI ulceration / enteritis
Hepatic lipidosis	Somnolence / Altered behavior

   e. We have seen some cats get better (on the basis of laboratory reassessment), and then develop an increase in the liver enzymes due to hepatic lipid vacuolation. Slow taper of glucocorticoids is done to deduce this change OR hepatic aspiration cytology under ultrasound guidance (best). If lipid vacuolation observed, l-carnitine, taurine, and supplemental B-vitamins along with feeding a maximum calorie carnivore diet (not protein restricted, limited carbohydrates) to avoid full-blown hepatic lipidosis syndrome. *See FHL notes.*

   f. If animal seems to be improving, sequentially evaluate serum liver enzymes and total bilirubin and slowly titrate drug therapy to alternate day (EOD) if possible.

2. *Metronidazole:* 7.5 mg/kg PO BID
   a. 50% empiric dose reduction
   b. Effective against anaerobes
   c. Treat undisclosed infectious agent ?
   d. Excellent diffuse tissue & bile penetration
   e. Modulates cell mediated immunity
   f. May benefit coexistent inflammatory bowel disease & pancreatic inflammation
   g. Reduces production of gut endotoxins

3. *Azathioprine:* NOT RECOMMENDED DESPITE WHAT YOU READ–> Myelotoxicity
   0.3 mg/kg PO EOD or every 3rd day. *Ill Advised !*
   CATS HAVE TROUBLE METABOLIZING THIS DRUG
   BE CONSERVATIVE. WATCH PATIENT RESPONSE & HEMOGRAM !!
   a. Antimetabolite. Become informed about this drug prior to use.
      I Rarely Use This in Cats: They do not metabolize it well
   b. Monitor hemogram closely as this is myelotoxic
   c. Biochemical profile initially q 14 days
   d. May induce anorexia, vomiting, diarrhea→Sick Cat

4. *Chlorambucil:* used by some clinicians as 1-2 mg per cat EOD or twice weekly.
   a. Cytotoxic, alkalating agents, influences DNA replication, lymphocytes sensitive to chlorambucil.
   b. Hematopoietic toxicity, monitor hemogram
   c. Efficacy: not sure I have observed a good response with chlorambucil in CCHS cats.

5. *Methotrexate:* 0.4mg **TOTAL DOSE** per cat ***LOW DOSE PULSE THERAPY***
   Pulse dosing (as described here) is better than chronic dosing in humans in terms of toxicity
   a. *Given over a 24 hour interval:* at 0, 12, and 24 hours, once per week.
   b. May be given IV, IM, or PO. I usually use it PO.
      If use parenterally (IV, IM) ***REDUCE Total Dose by 50%.***
   c. Antimetabolite: blocks folate metabolism in cells trapping methotrexate:
      -accumulates in hepatocytes, bile, lymphocytes
      -modulates cell mediated immune reactions
      -mechanism not completely understood but this is a powerful and underused immunomodulator
      -in man, liver dz can be caused by MTX given daily, pulse dosing avoids this IF MTX is given with FOLATE
   d. *Toxicity:* BM (rare), GI signs (rare), facial swelling (1 cat with IV administration)
   e. ***Folate Supplement:*** folic acid (folinic acid or folate) 0.25 mg/kg per day (does not block drug effect), assures vitamin adequacy. In humans, protects against methorexate systemic toxicity.
   f. *Watch for signs of immunosuppression.* I have seen treated cats develop demodex, herpes related corneal ulcers, infections around feeding tubes, pyelonephritis, stump pyometra! This dose is immunosuppressive.

I use methotrexate in cats with sclerosing cholangitis: CONFIRMED HISTOLOGIC DX.
Rx is based on studies in humans with vanishing bile duct disorders: sclerosing cholangitis & primary biliary cirrhosis.
It should not be used without histologic disease confirmation.

Summary: Treatment of Cats with Non-Suppurative Cholangitis / Cholangiohepatitis

S. Center DVM, Dipl ACVIM, Cornell University

Underlying Disorders:	Identify and appropriately treat underlying conditions, especially inflammatory bowel disease, hepatic lipidosis, bile duct occlusion, pancreatitis, acquired pancreatic insufficiency.
Nutritional Management:	Do not restrict dietary protein unless overt hepatic encephalopathy. Ensure balanced feline nutritional provision.
Prednisolone:	2-4 mg/kg daily PO Titrate to lowest effective dose; reduce dose q 10 days by 25% based on response Maintenance regimen with every other day (EOD) 1-2 mg/kg if possible. Monitor for glucose intolerance / diabetes mellitus esp. if sclerosing CCHS, may require discontinuation of glucocorticoids as an arm of therapy.
Metronidazole:	7.5 mg/kg PO BID (indefinite)
Ursodeoxycholic Acid:	10-15 mg/kg daily PO given with food, divided dose given BID if possible.
Water Soluble Vitamins:	2-fold normal maintenance dose daily
B_{12}:	1 mg IM every 7 to 28 days as shown necessary if gut malabsorption A weekly loading interval may be necessary in depleted cats: follow plasma B_{12}, then monthly vitamin supplementation by parenteral route. Severe chronic IBD, pancreatic insufficiency, enteric lymphoma, disturbed bowel flora suspected causes.
Vitamin K_1:	5 mg IM (0.5-1.5 mg/kg) every 7 to 28 days based on optimized PT or PIVKA clotting test or observed bleeding tendencies. *α-tocopherol (Vitamin E):* 10 IU/kg: α-tocopherol acetate
SAMe:	thiol / GSH donor & essential intermediary metabolite, 200 mg/day PO empty stomach
n-Acetylcysteine:	IV thiol / GSH donor, 140 mg/kg loading, then 70 mg/kg IV BID until enteral route established & initiate SAMe administration.
Lactulose:	0.25 - 0.5 ml / kg initial dose, titrate to achieve several soft stools / day Only if suspect HE (rare) or to avoid constipation
For cats with biopsy confirmed sclerosing cholangitis:	
Methotrexate:	Pulse oral therapy q 7 - 10 days based on WBC nadir and tolerance Total daily dose 0.4 mg divided into 3 treatments 0.13 mg/dose at hr 0, 12, and 24 If fail to respond after 6-8 wks, increase 0 time dose to 0.26. Can use IM in intractable cat: total dose reduced by 50%
Folate:	0.25 mg/kg PO daily ***All cats treated with MTX***

Prognosis:

1. ***Warn Clients That This Disorder Spontaneously Cycles***
   a. Intermittent bouts of hepatic inflammation and associated clinical signs
   b. Expect continued low level ↑ liver enzymes BUT usually bilirubin normalizes and remains within the normal range.
2. No long term prospective studies on Rx efficacy
3. Some cats have apparent long term remission to cure. HOWEVER, Rx withdrawal unlikely→ recrudescence
5. Deaths:
   a. Biliary cirrhosis
   b. Underlying or associated conditions: gut, pancreas, progression to lymphoma ?
   c. Many cats with CCHS, gut inflammation and pancreatic inflammation *ALSO* have chronic interstitial nephritis characterized by a lymphoplasmacytic inflammation in the kidney interstitium. Terminal illness may relate to renal insufficiency.

A diagnosis confused with CCHS: Polycystic liver disease in the Himalayan and Persian cat, others. Progresses to hepatic fibrosis and is commonly misdiagnosed as biliary cirrhosis due to CCHS on liver biopsy. No therapy is effective. These may or may not have small renal and pancreatic cysts.

Lymphoproliferative Disease / Lymphoma / Severe Destructive CCHS
Immunohistochemistry Helps Categorize these Disorders
Done on ProbeOn slides (positively charged slides), requires at least 10 tissue sections of the same biopsy (10 slides)

Feline Leukocyte Panel Immunohistochemistry Currently Available Cornell University (2005)
Ongoing Investigation: Dr. Amy Warren, Dr. Sean McDonough, Dr. Sharon Center

Antibody	Specificity
BLA-36	B Cells
CD3	T Cells
CD 18 (β2 Integrin)	Neutrophils, macrophages, T cells: usually negative, B cells: usually negative
CD45RA	B cells (non-specific nuclear stain, smooth muscle)
CD45B220	Leukocyte common antigen, lymphocytes, monocytes, granulocytes, thymocytes and malignant T and B cells.
MAC 387	Macrophages
Cytokeratin	Bile Duct epithelium, stains intermediate fibrils

We are currently using these stains to distinguish neoplastic from inflammatory infiltrates in cats with aggressive CCHS.

One author has tried to distinguish a form of CCHS termed "progressive lymphocytic cholangitis / cholangiohepatitis. (Day, M: Immunohistochemical characterization of the lesions of feline progressive lymphocytic cholangitis / cholangiohepatitis, J Comp Path 1998;119:135-147)

In this manuscript, normal feline liver (n=5), demonstrated small to moderate numbers of CD3+ T lymphocytes in portal areas and throughout sinusoids. Portal T cells were often closely associated with bile ducts, either immediately beneath the basement membrane or between bile duct epithelial cells (inter-epithelial lymphocytes). These T cells expressed surface membrane MHC Class II. A strong constitutive expression of MHC class II (cytoplasmic) by sinusoidal Kupffer cells was observed. In two normal liver samples, some large ile duct had granular, intracytoplasmic expression of M Class II. B lymphocytes (CD79+) were not found in normal liver, but there were very low numbers of CD79+ IgA plasma cells in some portal areas. Sections stained for immunoglobulin demonstrated an outlining of the space of Disse and positive staining of secretion within the lumina of larger bile ducts.

20 cats with lymphoplasmacytic CCHS were studied: clinical data from records and histopathology with immunohistochemistry (Tables published are summarized on the next page). Segregation into active and chronic forms of disease was done but criteria for such classification was not clearly defined (seemingly, the extent of portal LP infiltration with bile duct infiltration was a criteria; less inflammation and more fibrosis = chronic). An inference was therefore made that bile duct infiltration indicates active disease. This may not be true, based on clinical experience correlated with histologic changes in cats with CCHS in our patient population. Rather, these differences may reflect another form of CCHS.

While chronicity in the cited paper was identified with bridging fibrosis, not all cats with chronic CCHS had fibrosis. Immunohistochemistry detailed T and B cell involvement, expression of MHC Class II molecules, and immunoglobulin expression on plasma cells. T cells were observed to infiltrate bile ducts and to actively migrate through the limiting plate into adjacent hepatic parenchyma where they were observed to cluster around individual hepatocytes. B lymphocytes did not infiltrate bile ducts or the hepatic parenchyma, and were within portal areas as aggregates surrounded by T cells. Occasionally, these had a follicular appearance with a distinct lymphobastic center. In some, blastic B cells expressed surface membrane IgM or IgG in addition to CD79. These follicular areas contained scattered T cells. Both T and B lymphocytes expressed surface membrane MHC Class II molecules. Occasionally, T and B lymphocytes were observed within the lumen of sinusoids or dilated portal lymphatic vessels. The CD79+ plasma cells with positive IgG, IgM or IgA stains were also found within lesions of active inflammation; generally scattered in low numbers throughout the inflammatory aggregate. These were especially notable at margins of B-cell follicular aggregates. IgA bearing plasma cells were more often observed than either IgG or IgM bearing cells. No Ig expression was found associated with bile duct epithelium but Ig staining did outline sinusoids. Strong cytoplasmic MHC Class II expression was observed in sinusoidal Kupffer cells and macrophages within inflammatory lesions. Vascular endothelium and fibroblasts in areas of portal fibrosis also expressed MHC Class II. Only epithelium of larger bile occasionally expressed membrane or cytoplasmic MHC Class II, or both. Of cats included in this study, age ranged from 6 months to 12 years, included 14 DSH, 1 DLH, 2 Persian, 1 Siamese; 6 F, 12 male. Data derived from records appears incomplete, not all cats had biochemical or hematologic appraisals. Reported data: clinical signs ranged from 2

weeks to 5 months (noted for 8/20 cats) icterus (9), ascites (4), hepatomegaly (6), high liver enzymes (6), weight loss (5), sudden death (3), neurologic signs (2).

Routine Histologic Features: MJ Day, Immunohistochemical characterization of the lesions of feline progressive lymphocytic cholangitis/cholangiohepatitis. J Comp Path 1998;119:135-147.

Cases	Sample: N=necropsy, B=biopsy	Portal LP inflammation, bile duct infiltration	Neutrophil, macrophage infiltration with bile duct proliferation	Bile duct proliferation	Portal fibrosis	Bridging portal fibrosis	Classification: A=active, C=chronic
1	N	+	++	++	++	++	A
2	B	+	-	-	+	+	A
3	B	+++	-	+	+	+	A
4	B	+++	++	++	++	+	A
5	B	++	-	+	+	+	A
6	N	+	-	++	+	++	A
7	N	+	+	++	+	+	A
8	B	+	-	+	-	+	A
9	B	+	-	-	-	-	A
10	B	+++	-	+++	++	++	A
11	B	+++	+	+++	++	++	A
12	B	+	-	+++	+++	+++	C
13	N	+	+	+++	+++	+++	C
14	B	+	++	++	++	++	C
15	B	+	-	+	+	+	C
16	B	+	++	+++	+++	+++	C
17	B	+	-	++	+	+++	C
18	N	+	-	+	+	+	C
19	N	+	++	+++	+++	+++	C
20	B	+	+	+++	+++	+++	C

Cases	Sample: N=necropsy, B=biopsy	CD3+ T Cells	CD79+ B Cells	IgG+ Plasma Cells	IgM+ Plasma cells	IgA+ Plasma Cells	Bile duct membrane MHC II	Bile duct cytoplasmic MHC II
1	N	+++	Yes	+	+	++	Yes	Yes
2	B	++	No	+	+	+	No	Yes
3	B	+++	Yes	+	+	+	No	Yes
4	B	+++	No	+	+	++	No	Yes
5	B	++	Yes	+	+	+	Yes	No
6	N	++	Yes	-	+	+	Yes	Yes
7	N	++	No	-	-	+	No	Yes
8	B	++	Yes	-	-	+	No	No
9	B	++	Yes	+	-	+	Yes	Yes
10	B	+++	Yes	-	-	-	No	No
11	B	+++	Yes	-	+	++	No	No
12	B	++	No	+	+	+	No	Yes
13	N	++	No	+	-	-	No	No
14	B	+	Yes	+	+	+	Yes	Yes
15	B	++	Yes	-	+	+	No	Yes
16	B	++	Yes	-	+++	+	No	No
17	B	++	Yes	-	+	+	No	No
18	N	++	Yes	-	+	+	No	No
19	N	++	Yes	++	+++	+++	Yes	Yes
20	B	+	Yes	+	++	++	No	No

What About the Role of Helicobacter in Feline CCHS ?

In recent years, detection of Helicobacter species in bile, gallbladder tissue, or liver tissue has been demonstrated using PCR amplification with Helicobacter genus-specific primers in animals as well as humans. Many of the human studies have lacked adequate controls. Studies in veterinary patients, particularly cats, have detected Helicobacter by PCR in both diseased and normal cats. A unique species of Helicobacter (H. bilis) has been associated with biliary tree infection and biliary neoplasia in some humans (Chilean patients with cholecystitis / cholelithiasis / biliary tract neoplasia). This species and several others, are relatively more resistant to the deleterious effects of bile in vivo, adapting better to the hepatobiliary milieu. This may permit their detection and involvement with biliary tree pathology but evidence is far from conclusive. Enterohepatic cycling of the organism may also explain its detection by PCR. Studies are ongoing regarding this issue.