Clinical Decision Making

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Introduction and Conceptual Framework

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

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

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

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

1. **Pattern recognition** — the recognition of characteristic combination of clues or signs (e.g., cutaneous reaction patterns, radiologic patterns, histopathologic patterns, hematological patterns).

2. **Problem-based medicine**

3. **Diagnosis based on clinical probability** — i.e., that certain diseases occur much more commonly than others.

The best diagnosticians can use all of these approaches interchangeably, combining great analytic skill, a systematic approach, but utilizing, also, good clinical intuition, which can make the diagnostic process faster and less expensive.
In this new century, veterinarians more than ever should try to consider a scientific approach to clinical decision making. The scientific approach or method is founded on several key values or standards, which are linked:

1. **Objectivity** — evaluating the evidence free from bias as much as is humanly possible; bias develops from our past experiences.

2. **Open-mindedness** — a commitment to changing one's views in the face of evidence that these views are inaccurate.

3. **Skepticism** — non-acceptance of findings until verified. In our case, don't accept evidence unless it has been well proven through testing.

4. **Accuracy** — gathering and evaluating information for accuracy. In our case, it is evidence-based medicine. Rather than continue to write abstractly about these disparate concepts, I will attempt to illustrate them by working through what would seem to be a “very straight forward” case. I will then challenge readers in relation to HOW and WHY they make clinical decisions.

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**Case Presentation**

**Signalment**

Magic is a two-year-old desexed female Australian mist cat. This is an Australian breed, based on initial crosses between Burmese (50 percent), Abyssinian (25 percent) and Australian domestic crossbred cats.

**Presenting Complaint**

The cat may have ingested a sewing needle.

**History**

The owner observed the cat playing with a sewing needle. The needle allegedly had no thread attached. The owner tried to intervene and stop the cat from playing with the needle; however, when the owner caught the cat, there was no needle to be found. To complicate matters further, the cat then ate 100 grams (6.25 oz.) of commercial tinned cat food.

**Physical Findings**

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

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**Questions for Consideration:**

**What is your Clinical Assessment?** *(This is easy.)*

1. The cat may or may not have swallowed a sewing needle.

2. The needle may or may not have had attached thread.

3. If so, there may be as a consequence a variety of clinical problems.

**What are the potential problems?**

1. Penetration of the pharynx.

2. Penetration of the esophagus.

3. Migration of the needle from the stomach to other sites.
   a. Which sites?
   b. Why these sites?

4. Complications related to these — i.e., intestinal plication.
   a. When does plication occur?

**What would you do next?** *(This is a bit harder.)*

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

**Radiology**

1. Chest?
2. Abdomen?
3. Whole cat, in one go?
4. How many views?
Questions:
(1) Where is the needle?
(2) Do we need a 2nd radiograph?

CRITICAL QUESTIONS
• How should we manage this case?
• On what basis should we make decisions regarding clinical management?

Lateral radiograph of Magic

How do we manage this patient?  
(This may be controversial.)
2. Conservative - use drugs, other techniques.
3. Endoscopic removal.
4. Surgical removal.

On what basis should we make decisions regarding clinical management?
1. Look up in textbooks.
   Ask colleagues.
3. Ask local experts/specialists.
5. Post a question on VIN.

But before we do that, what are the unique considerations of the present case?
1. The cat has been presented early.
2. We cannot be sure whether or not there is thread attached to the needle.
3. The cat has just eaten a large meal.
4. It is a young, healthy patient that should cope okay with anesthesia and surgery, if they are done in an appropriate manner.
5. Money is not an issue with these owners.

Is endoscopic removal a viable possibility?
1. In general, yes - although needles are hard to catch and hard to safely retrieve.
2. You need good equipment and great expertise.
3. In this case, the ingestion of food immediately prior to presentation would have made endoscopic removal very problematic. Furthermore, anesthesia would be contraindicated in this setting.

What about surgery?
Advantages
1. It likely will resolve the problem.
2. It has a high success rate.
3. There should be minimum morbidity involved.
4. It makes more money for the clinic.
5. It takes away all the possible complications associated with a penetrating object and thread.

Disadvantages
1. It is invasive.
2. It costs the owner more money.
3. There will be some pain and morbidity for the patient.

Ask learned colleagues
1. Dr. Dick Churcher (Australian internist) strongly recommended surgery based on his experience with migrating needles in the United Kingdom (U.K.). He had seen them migrate to the liver or thoracic cavity.
2. Veterinary Information Network (VIN) – A U.K. surgeon recommended surgery to be sure the cat would be okay. He said the needle might pass without surgery, but he couldn’t be sure this would happen.

Veterinary textbooks
A wide variety of textbooks were consulted, but they did not prove helpful in this case.

Evidence-Based Medicine using Electronic Databases
1. Look at veterinary databases, which are most reliable.
2. Also, look at medical databases. These are less reliable, but more information is available for certain topics, such as those pertaining to this case.
3. Case series are much more helpful than individual case reports when looking for overall recommendations.
4. Look at: (i) year of the report, (ii) the country of origin, and (iii) the institution. These are very germane to the quality and applicability of the data.
5. Textbooks are also useful, but generally they are rated low down in the list compared to original peer-reviewed papers.
Veterinary Database (CAB)
In this instance, the search was technically difficult since you needed some patience to find the correct key words (stomach, cat, needle). Only limited information was available, consisting of only two case series.

1. Gunsser (1978). Sewing needles and fish hooks as foreign bodies in dogs and cats. Diagnosis and therapy. In this report of 57 dogs and 15 cats, six of the nine cats with gastric needles passed the needles spontaneously in three to four days.

2. Felts et al. (1984). Thread and sewing needles as GI foreign bodies in the cat: a review of 64 cases. In this report from the Animal Medical Center in New York City, most cases had thread and required surgery.

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

What about individual case reports (like this one)?
1. They tend to be written to highlight unusual or dramatic sequelae, e.g., Hunt et al. (1991) reported on the suspected cranial migration of two sewing needles from the stomach of a dog into the heart.

2. They tend not to report simple, happy, unchallenging outcomes.

What about human medical databases (Medline or PubMed)?
1. An enormous number of cases have been reported as case reports, case series, or large case series.

2. Most published reports talk about foreign bodies generically rather than just sewing needles.

3. Some case series have as many as 18,200 cases!

4. Gün et al. (2003) reported on 49 cases of safety pin ingestion in which 41 percent were passed spontaneously, while the remaining cases required endoscopy or surgery.

5. In reviewing many of the case series available, it is apparent that: the majority of foreign bodies that reach the stomach continue to pass through without sequelae; prokinetic drugs are not helpful; common sites of trouble are the pylorus, duodenal flexure, and ileocecal valve; and pins are rarely a problem because of Jackson's axiom, i.e., the blunt weighted end passes first.

How did we manage our patient?
1. We hospitalized the patient.

2. We monitored rectal temperature, demeanor and appetite every eight to 12 hours. We were watching for and anticipating signs of early peritonitis, pancreatitis, ileus, partial intestinal obstruction, etc.

3. The cat was fed judiciously three times daily with small meals of a commercial tinned cat food that was finely mashed up using a fork.

4. Another radiograph was taken the following morning. The needle was not within the intestinal tract.

5. The cat had a good appetite for tasty food while she was in the hospital.

6. The cat's temperature was marginally elevated during the first 36 hours.

7. No feces were passed for three days.

8. The cat was given amoxicillin (100 mg orally twice daily) during hospitalization.

9. She was also given some Coloxyl (50 mg orally) every 12 hours from day three on.
A milestone occurred on day four when the needle was passed:
1. The needle was attached to a segment of stool.
2. The needle measured 3.8 cm in length.
3. It had a cotton thread attached, folded in two. The thread measured 74 cm.
4. Presumably, the stool pulled the needle and thread through the rectum.

Further Reading

Veterinary references

Human references
Refractory Ulcers on the Nasal Bridge of a Young Cat: An Exercise in Diagnostic Reasoning

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Case Study
Presenting Complaint and History:
An eight-month-old castrated male domestic crossbred cat is presented for multiple non-healing ulcers on the bridge of its nose.

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

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

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

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

Questions:
(1) What is your clinical assessment?
(2) How would you investigate this case further?
and it works (or should work) even for disease conditions that the clinician has never seen before, or not even heard about! The trouble with this system is that it is cumbersome, tedious for simple cases, expensive and not well suited to the majority of software systems used in veterinary practice. It is very useful, however, in developing a conceptual framework to explain to undergraduates the logic that underpins analytic diagnostic reasoning. It should form the cornerstone for clinical decision making when combined with information from textbooks and electronic databases.

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

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

Heuristics
Psychologists have found that people rely on three basic types of heuristics. Pattern recognition is an example of the representative heuristic, where the clinician weighs the probability that the patient's key clinical features match those of patients with the leading diagnostic hypothesis under consideration. For example, a cat with sudden onset of oculonasal discharge, sneezing, conjunctivitis, tracheal hypersensitivity and fever but no mouth ulcers is most likely to have a viral upper respiratory infection, with feline herpesvirus the most likely specific etiological agent. The clinician using the representative heuristic can reach erroneous conclusions if they fail to consider the underlying prevalence of two (or more) conflicting diagnoses. For example, in a cattery with a history of chlamydiosis and a solid vaccination program against viral respiratory pathogens, Chlamydia felis infection may be a more likely etiology than herpesvirus in this particular scenario. In either case, specific testing with a "gold standard" test, e.g., multiplex PCR using an appropriately collected oropharyngeal swab is required to confirm the presumptive diagnosis. Mistakes also occur when considering a pattern based on too small a number of observations. In veterinary medicine, breed often plays an important role in recognizing patterns of disease, e.g., muscular dystrophy in Devon Rex cats, and polycystic kidney disease in Persian cats.

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

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

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

**Linear and Non-Linear Logic**

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

**Counterintuitive Diagnoses**

Finally, it must be acknowledged that in some instances certain clinical entities are so bizarre that their diagnosis is almost counterintuitive, and instead relies on recognizing a particularly arcane pattern of clinical findings. For example, the entity referred to as necrotizing sialadenoadenitis refers to a condition in which there is painful enlargement of one or more mandibular salivary glands, associated with dysphagia, drooling of saliva and even infarction of the salivary gland parenchyma. A logical diagnostic approach would involve inspection of the affected glands and their ducts, imaging of the glands, biopsies or even surgical removal of the glands. However, all these measures prove to be unhelpful, and empiric
discovery of the effectiveness of certain anticonvulsants has led to the proposal that this condition is actually a form of "limbic epilepsy". The recently described oropharyngeal pain syndrome of Burmese cats and phenobarbitone-responsive gastroparesis and vomiting are other pertinent examples. Another entity in this category is sudden acquired retinal degeneration - a disease in which dogs suddenly develop peripheral blindness (bilaterally dilated pupils that fail to respond to light) associated with Cushingoid physical findings; the diagnosis is made by exclusion by detecting a normal fundoscopic examination (initially) with an absent electroretinal electrical response (ERG) to a flash stimulus. It is only possible to immediately recognize these rare, bizarre entities through expert knowledge, intuitive leaps, or therapeutic trials (if you are the first person to encounter such an entity). However, the use of electronic databases, Boolean logic, and sophisticated key word searches using search engines such as Google™ and Google Scholar™ can often be very helpful in finding information on such diagnostic oddities. The process of clinical reasoning revolves around generating testable hypotheses. These should be confirmed with further test(s), or response to therapy, but if the test results or therapeutic response is not supportive, hypotheses need to be discarded or substantially modified.

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

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

The trouble with "pattern recognition" and "probability" is that you must either have a lot of experience (preferably including time spent working alongside senior expert clinicians), or you must do a lot of rote learning, to make these diagnostic considerations work for you. Local knowledge and the counsel of a senior colleague can be very helpful in this setting, which is unhelpful for new graduates or locums, and sometimes a good veterinary nurse/technician with a long corporate memory can be helpful!

Another important theme is that the patterns can be completely different in different species; for small animal clinicians this is of key importance because diseases in cats and dogs present in different ways, and occur with different frequencies. Hence, the commonly voiced viewpoint that "cats are not small dogs". This is more of a problem for people whose thinking style is less reliant on a problem-based approach.

Clinical Intuition
Another consideration, that almost no one mentions, is that certain individuals make intuitive clinicians. The current television series, "House," concerning a taciturn but brilliant internist (Gregory House MD played by the English actor Hugh Laurie) is based on this premise. Probably such individuals would have made good criminal investigators, as there is without doubt an art as well as a science in diagnostic reasoning. Interestingly, the character, Gregory House, was based in part on Sherlock Holmes, hence the pun on the word House/Ho(l)me(s). I have no doubt that detective Robert Goren (from Law and Order Criminal Intent) would have also made an outstanding veterinary internist, as he would have been a sophisticated exponent of pattern recognition, problem-orientated medicine, and also, clinical intuition.
Guidelines for Consideration
Whatever way you like to approach the diagnosis of disease, be aware:

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

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

1. What can you deduce from the signalment, history, clinical signs and physical findings:
   - The time course of the disease process? - construct a time/sign diagram
   - Which organ system(s) are affected?
   - What pathological process(es) are likely involved?
   - Is a pattern emerging? - does it fit all the facts?
   - The nasal bridge region. They have failed to respond to antibiotics and corticosteroids.

2. Detect and describe physical, laboratory and imaging findings. Include useful “patterns”.
3. Consider the pathophysiologic basis for the observed findings. An approach that considers the underlying physiological derangements is most useful in planning pharmacological and other interventions.
4. What conclusions can you draw, i.e., define a problem or problems. Try and move from the general to the specific, but try to move further toward the specific as you get additional information such as laboratory and imaging data.
5. How can you obtain the evidence to support your conclusions (i.e., what is your plan for further investigation)?
6. Are there implications for ongoing management, while you investigate further?
7. Consider using textbooks and electronic databases using key word searches to help in difficult cases. Do not be afraid to ask your colleagues (senior and junior) for their opinions, but do not necessarily let them take over your own clinical reasoning.

Diagnostic Reasoning
This talk will flesh out some of these issues by proving that we all use a combination of problem solving, pattern recognition, clinical intuition, and probability to work out what is wrong with our patients.

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

We will also try to demonstrate that there are many patterns; including imaging patterns (e.g., air bronchogram, alveolar pattern), dermatological patterns (“cutaneous reaction patterns”), hematological patterns (e.g., stress leukogram response), clinical chemistry patterns (e.g., high ALT with hyperthyroidism, increased ALP without jaundice in Cushing’s disease), cytological patterns (e.g., capsulated yeast with narrow necked budding with cryptococcosis) – and that there is nothing wrong with using all of them.
lower urinary tract disease; once we have made this connection, it is easy to sort out the specific diagnosis (infection, stones, neoplasia, etc). Likewise, we are comfortable about recognizing clinical syndromes. Clinical syndromes are really just patterns; e.g., Horner’s syndrome (ptosis, miosis, third eyelid prolapse) is a sophisticated pattern that tells us something is interfering with sympathetic innervation of the eyeball; we then just need to remember the corresponding neuroanatomic pathway to work out the complete differential diagnosis (T1-T3 spinal cord disease, brachial plexus disease, cervical disease and middle ear disease). The presence of Horner’s syndrome with concurrent ipsilateral facial nerve paralysis is an even more complex pattern, and strongly suggestive of middle ear disease. But you still need diagnostics to work out whether the problem is infectious, polypoid or neoplastic in origin.

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

Differential Diagnosis of Diseases Affecting the Nasal Bridge of Cats

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

Cases with Infection of the Naso-Ocular Region but without Concurrent Nasal Signs

These cases likely result from contaminated cat-scratch injuries. Presumably the claw(s) of the feline perpetrator are contaminated by viable, potentially-pathogenic, saprophytic organisms. These are inoculated in such large numbers that non-specific defense mechanisms (bleeding, inflammation, neutrophilic phagocytosis, lysozyme) of the victim are overwhelmed. This results in a localized, variably invasive infection of an otherwise immunocompetent host. A wide range of microorganisms can be cultured from such cases including a variety of bacteria and fungi normally residing in soil, rotting vegetation, humus or dirt. Lesions are typically on the bridge of the nose, but they may also occur more laterally or involve the nasal planum.

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

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

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

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

**Diagnostic Evaluation**

Investigation of these cases typically involves obtaining representative material for cytology, histology and appropriate culture. Cytology and histology generally show pyogranulomatous inflammation and usually causal organisms can be visualized using special stains (Diff-Quik, Gram, Ziehl-Neelsen, periodic acid Schiff, silver stains). A variety of staining techniques may be required, and in some cases an exhaustive search of smears or histologic sections is required to detect the infectious agents. Mycobacteria, fungi, and Nocardia species may sometimes be detected in Diff-Quik-stained smears because of a negative, rather than positive, staining reaction. The laboratory should be warned of the possibility of a fastidious saprophytic pathogen, as these organisms often have specific growth requirements (e.g., special culture media, reduced temperature of incubation, requirement for high carbon dioxide concentration, etc.) and/or require several days or even weeks to become detectable as visible colonies in vitro. Ideally, a small portion of the biopsy specimen should also be frozen in case polymerase chain reaction techniques or additional culture studies are required at a later date.

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

**Therapy**

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

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

**Prevention**

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

**Cases with Naso-Ocular Infection and Concurrent Signs of Nasal Cavity Disease**

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

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

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

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Mycobacterial Panniculitis

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

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

Clinical Signs: Infections tend to start in the inguinal region, usually following contamination of cat-fight injuries (e.g., raking wounds inflicted with the hind claws). The infection may spread to contiguous subcutaneous tissues of the ventral and lateral abdominal wall and perineum. Penetrating injury by sticks, metallic objects, and vehicular trauma may also give rise to these infections, as can cat- and dog-bite injuries contaminated with soil or dirt. Sometimes infections start in the axilla, flanks, or dorsum. Early in their course, infections resemble cat-fight abscesses, but without the characteristic fetid odor and turbid pus. Instead, a circumscibed plaque or nodule is apparent. Later, there is progressive thickening of the nearby subcutis to which overlying skin becomes adherent. Affected areas become denuded of hair and numerous punctate fistula appear, discharging watery exudate. Fistula are intermingled with focal purple depressions (thinning of the epidermis over accumulations of pus). The “lesion” gradually increases in area and depth, and may eventually involve the entire ventral abdomen, adjacent flanks or limbs. If cats are presented promptly for veterinary attention and the lesion confused with an anaerobic cat-bite abscess, surgical drainage and administration of a β-lactam is typically followed by wound breakdown and development of a non-healing suppurating tract surrounded by indurated granulation tissue. Some affected cats with infections develop systemic signs, becoming depressed, pyretic, inappetent, losing weight and being reluctant to move. Occasionally, cats develop the hypercalcemia of granulomatous disease, although this is rarely symptomatic. Surprisingly, other cats remain comparatively well despite extensive disease. Usually the problem remains localized to the skin and subcutis. Although adjacent structures such as the abdominal wall can be affected eventually, spread to internal organs or lymph nodes is very unusual.

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

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

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

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

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

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

Disseminated Mycobacterium Avium-intracellularare Complex (MAC) Infection in Young Cats

We have recently reported a new syndrome of disseminated MAC infection in ten young cats (one to five years old) from Australia and North America. A further two cats with disseminated mycobacteriosis (precise agent not identified) were recognized also. Of the 12, ten were Abyssinian cats, one was a Somali cat and one was a domestic shorthair cat. None of the cats tested positive for either FeLV antigen or FIV antibody.

The clinical course of these infections was indolent, with cats typically presenting for weight loss, initially in the face of polyphagia, with a chronicity of up to several months. Additional clinical features included lower respiratory tract signs and peripheral lymphadenomegaly. A marked diffuse interstitial pattern was evident in thoracic radiographs, even in cats without overt respiratory involvement. Hair tipped to perform diagnostic procedures tended to regrow slowly, if at all. Diagnosis was generally made by obtaining representative tissue speci-

mens from mesenteric lymph nodes, liver or kidney at laparotomy, or from a popliteal lymph node. The primary antecedent event was most likely colonization of either the alimentary or respiratory tract, followed by local invasion and eventual lymphatic and hematogenous dissemination.

Nine cases were treated using combination therapy with agents effective for MAC infection in human patients. The results were generally favorable, although the disease had a tendency to recur if insufficient treatment courses were utilized. Cats were generally treated with long courses (five to 14 months) of clarithromycin combined with either doxycycline or rifampicin, and a fluoroquinolone or doxycycline was sometimes given also, although in the future moxifloxacin may prove to be a superior adjunctive agent in this setting.

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

Feline Leprosy Syndromes

Historical perspective: The term feline leprosy is used to refer to a disease which, with difficulty, can be cultured from large inocula on Ogawa's egg yolk medium under special conditions. Although a few investigators have successfully grown Mycobacterium lepraemurium from infected cats, the basis of ascribing this bacterium as the etiological agent of feline leprosy was dependent on transmission studies. Interestingly, some cats appeared much more susceptible to experimental infection than others.

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

Pathologically, feline leprosy was subdivided into lepromatous or tuberculoid forms based on the number of AFB present (multibacillary vs. paucibacillary) and the host immunological response (lepromatous vs. tuberculoid). Because the causal mycobacteria are slow-growing organisms capable of intracellular survival, the histologic picture actually depends on the host's immune response. When this response is poor, lepromatous (multibacillary) disease develops with infiltration of the dermis with large sheets of "incompetent" foamy macrophages containing enormous numbers of organisms. AFB are usually arranged in the cytoplasm of macrophages as dense parallel accumulations which displace the nucleus to an eccentric position. Lymphoid cells and plasma cells are virtually absent from the lesions. If the host's immune response is more effective, histiocytic cells are accompanied by moderate numbers of lymphoid cells and plasma cells and multiplication of the organism is limited—the so-called tuberculoid response.

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

**Molecular insights:** Molecular methodologies have been used to investigate presumptive feline leprosy. Of eight cases of invasive or disseminated cutaneous mycobacterial disease investigated by Siobhan Hughes and colleagues using material collected largely from New Zealand cats, four were shown to have *M. leprae* infections.

Of the remaining cases, one cat had a disseminated *M. avium* infection, the etiology in one cat was undetermined and in two cases infection was attributable to a novel mycobacterial species. This information encouraged a reappraisal of Australian feline leprosy cases, and subsequently this work has been extended to North America by groups lead by Greg Appleyard and Janet Foley.

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

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

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

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

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

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

To make matters even more complex, work by Appleyard and Clark (2002) demonstrated a third mycobacterial syndrome in cats from western Canada and the U.S. (Idaho and Oregon) called "feline multisystemic granulomatous mycobacteriosis." This disease is caused by a slow-growing taxa provisionally called M. visibilis or M. visible. This species is capable of producing widespread dissemination to multiple internal organs, presumably in immune deficient cats. Sequence analyses demonstrate a number of nucleotide differences between M. visibilis and both M. lepraemurium and the novel species reported by Hughes et al.

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

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

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

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

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

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

Further Reading