

Why Are Comorbidities the “New” Norm for Cats?

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Introduction

The observation that comorbidities are seen frequently in cats is not, unto itself, surprising. Cats are living longer than ever, and things “wear out” over time. But is this a new problem? Perhaps we are simply recognizing comorbidities because we are screening/looking for problems before they become clinically evident. Yet, some conditions, for example hyperthyroidism (Peterson), diabetes (Prah), and CKD (Lefebvre, Lulich, Reynolds, Ross), are actually becoming more common.

What Mechanisms May Cause Comorbidities?

As with any other species, over time, oxidative stress from normal, or enhanced, wear-and-tear results in cellular injury or death through complex free radical pathways. Free radicals are by-products of normal metabolism such as mitochondrial cellular respiration, phagocytosis, digestion, and inflammation. Additionally, they are formed by exogenous agents, including drugs, xenobiotics (chemicals found in an organism not normally produced or expected to be present in it, e.g., smoke, fire retardants) and ionizing radiation (including that from the sun). If the cell's ability to neutralize free radicals is exceeded, permanent damage occurs and results in DNA damage, cell injury, inflammation, fibrosis, cell death or the inability to reverse neoplastic transformation. Free radicals are balanced by endogenous antioxidant systems and their neutralization by these mechanisms contributes to the outcome for the patient. (Mandeleker)

Anecdotally, some claim that cats are a species prone to inflammation. Lymphocytes and plasma cells are arguably the most common cellular infiltrates in cats suggesting chronic antigenic stimulation. In small doses, inflammation is protective; chronically, however, it can be detrimental with inflamed tissues possibly even undergoing malignant transformation as it is currently believed to be the case with IBD transforming to small cell alimentary lymphoma. (Morrison)

Might infectious agents play a role in comorbidities? Could recrudescence of regressive Feline Leukemia virus (FeLV) or loss of cell mediated immune control of Feline Infectious Peritonitis (FIP) (e.g., dry renal FIP) contribute to this phenomenon of developing comorbidities? At the present time, there is no evidence for this, but any significant disease could allow reactivation (FeLV) or suppression of cell mediated immunity (FIP).

We know little about the feline immune system specifically. Could a compromised immune system result in disease beyond infection? (Singer) We speculate on immunosenescence in cats, but this is mostly extrapolated from research in other species. (Scherk) Similarly, many of our beliefs regarding physiology and pathophysiology, along with therapy (including nutrition) are extrapolated.

It is reasonable, from a traditional pathophysiologic approach to look for direct underlying mechanisms, such as the role of ischemia in the development of CKD (Brown) or the interesting studies looking at the effects of Crandall Rees feline kidney (CRFK) cell antibodies associated with vaccination on the development of CKD. (Lappin, Whittemore, Finch, Conroy)

Cats are intriguing. In the more studied canine, finding hyperthyroidism coexisting with diabetes mellitus (DM) is rare. Of course, hyperthyroidism is far more common in cats, but none-the-less, these two conditions are not infrequently seen together in this species. Similarly, diabetes is seen with any chronic inflammatory disease, including (but not only) pancreatitis. Chronic kidney disease (CKD) is also commonly unmasked or already present in cats with hyperthyroidism. Cardiac changes are seen with hyperthyroidism. Degenerative joint disease (DJD) may be present in any cat with any disorder, and concurrence between CKD and DJD has been noted. (Marino) Interestingly, a relationship has been suggested between fractured patellae in cats with retained deciduous teeth (“knees and teeth syndrome”). (Langley-Hobbs) An association between periodontal disease (PD) and the risk of developing CKD has been verified: cats with Stage 3 or 4 PD have greatest risk for developing CKD. While these are also the oldest cats, a relationship between the two conditions is made more likely, however, given that the Trevejo study included 169,242 cats. Obesity has been shown to be associated with DJD, DM, cardiac disease, respiratory illness, and other diseases. Since obesity is seen in 11.5% to 63% of pet cats, this has significant impact. (Scarlett 1994, Tarkosova) Unfortunately, as reported by Campigotto, only 9,886,899 of 19,015,888 cats even had one body weight measurement in their medical record. Asthma, idiopathic inflammatory bowel disease (IBD), pancreatitis, cholangitis, cholecystitis, triaditis, idiopathic cystitis (IC), and even dermatologic conditions are seen more commonly in cats housed strictly indoors. (Buffington 2002)

A shortlist of speculated pairings is shown in Table 1. Some of these may not have direct relationships and may be coincidental. Many studies consist of only small numbers of cats, so the power is insufficient to draw solid conclusions with some of these combinations.

Table 1. Comorbidity combinations recognized

Chronic kidney disease (CKD) + hyperthyroidism
CKD + degenerative joint disease (DJD) (Marino)
CKD + heart failure (Belanger)
CKD + periodontal disease (PD) (Trevejo, Finch)
Hyperthyroidism + diabetes mellitus (DM) (Hoenig p 1101)
DM + obesity (Hoenig p 1103)
DM + CKD (Perez-Lopez)
DM + lower urinary tract disorders (Greco)
DM + urinary tract infections + hyperthyroidism + CKD (Mayer-Roenne)
Obesity + DJD/DM/cardiac disease/respiratory illness (Scarlett 1994, Tarkosova)
Triaditis (Simpson)
Hypertension + hyperthyroidism
Hypertension + CKD
Hypertension + hyperaldosteronism
Knees and teeth syndrome (Langley-Hobbs)
CKD + thin body condition/ PD/cystitis (Greene)
Underweight + DJD/DM/CKD/hyperthyroidism/neoplasia (Saito, Campigotto)

It's Become Complicated: More Than Physical

Apart from the mechanics of cells and pathology, recent focus in some arenas of human medicine has been towards complex diseases rather than simply organ-specific disease. Since the 1800s, medicine has been based in the understanding of physiology with cause and effect and Koch's postulates to explain the development of disease. It has enabled us to create tools for the diagnosis and treatment of illness. Science is a way of thinking and approaching a problem, however, so new concepts arise. Incorporating an understanding of cellular communication through immunologic defense mechanisms improved the field of biomedicine. (Kirkengen) The body can be viewed as being more integrated rather than system-restricted.

Cats appear to be similar to human patients with chronic complex disease states. Fleshner states that: "The disparity between physical and psychological stressors is an illusion. Host defence mechanisms respond in adaptive and meaningful ways to both." In humans, the term "complex diseases" is used to describe the coexistence of conditions, such as Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) with other syndromes, such as those of chronic pain, Chronic Fatigue Syndrome (CFS) or Irritable Bowel Syndrome (IBS). (Kirkengen) This is analagous to the complex Buffington has called "Pandora Syndrome" in cats. (Buffington 2014) The fact that unrelated organ systems are affected negatively within the same individual is thought to be due to psychoneuroimmunology, the complex interrelationship between the mind, the immune and neurologic systems, all ultimately manifesting as disease in disparate body systems. In Pandora Syndrome, Buffington describes a similar interrelatedness of genetics, the fetal environment (i.e., the effects of stress on the queen), and creating a susceptible individual who, when placed in a provocative situation or environment, may become sick. This is not an easy disease model to test as we don't know what to measure. (Buffington 2014)

Any organism that feels threatened, whether the threat is real or speculative, has hormonal, neurological and immunological responses. If these responses remain activated or are reactivated repeatedly, it becomes that being's new norm. Some individuals respond more benignly than others in whom the emotional, psychological and physiological state will result in a negative or diseased state. Lifestyle, environment, and experiences all play important roles as well as those of the mother (or queen) while the fetus was *in utero*. Does this say something about how cats experience life? With us?

Re-evaluating what we believe we know

While we recognize more combinations of diseases, we must also continue to challenge what we believe we understand. New findings are showing us that even within the traditional bioscience perspective, we may need to re-evaluate our beliefs. McLeland has shown that the histologic changes we associate with CKD, occur in cats without clinical or laboratory evidence of CKD. In fact, renal aging in cats *without* CKD is characterized by increasing glomerulosclerosis, tubular atrophy, interstitial inflammation, fibrosis and fibrointimal hyperplasia.

The etiology of hyperthyroidism is multifactorial. (Peterson) Not only is there evidence for environmental and nutritional factors contributing to hyperthyroidism, we now have evidence that cats exposed to higher levels of the flame retardant tris(1,3-dichloro-isopropyl) phosphate have significantly higher prevalence of hyperthyroidism. Previously suggested to contribute to this condition, PBDE flame retardants have been phased out due to concerns of persistence, bioaccumulation, and the potential to cause adverse health effects. (Poutasse) Exposure to these substances, as well as other agents may partly explain why cats housed only indoors have a higher prevalence of hyperthyroidism than cats with outdoor access. (Buffington 2002)

We have become aware of the importance of meeting not just the environmental, but also behavioural needs of cats for health. This applies to all cats regardless of their living arrangement, but clearly the cat that has less control over choosing when and what they are exposed to, is in a more provocative situation - one that may result in engaging the complex psychoneuroimmunologic mechanisms that result in dis-ease. (Stella)

However, it might be worth considering whether other aspects of the safe indoor lifestyle may play a role in not just increasing the prevalence of hyperthyroidism, but also the other conditions already mentioned.

- A monotonous and overly predictable environment is stressful. (Buffington 2006) Cats may not be able to perform species typical behaviours that express their cat-like nature. In addition to increased prevalence of diseases, this psychological and physiological stress that may result in problem behaviours – unwelcome but natural behaviours, e.g., spraying or scratching -, behavior problems (e.g., obsessive grooming) or physical illness.
- Signs of stress and anxiety may be overt (e.g., changes in appetite, grooming, increased vocalization, hiding, vigilance, aggression, spraying or compulsive behaviours), or subtle (e.g., decreased activity, play, exploratory behavior/inquisitiveness, facial marking, affiliative interactions with people and other animals). (Amat)
- Buffington (2006) collated evidence from multiple studies showing that lower urinary tract diseases (idiopathic and calcium oxalate urolithiasis), (unsurprisingly) obesity and, interestingly, even dental resorptive lesions were found to be associated with indoor living. In fact, indoor and city living, had odds ratios of 4.5 and 4.4, respectively for dental lesions. (Scarlett 1999)
- Indoor confinement and physical inactivity are risk factors for developing DM. (Slingerland)

What, if anything, can we do about this new norm of comorbidities?

1. Screen healthy cats for insipient disease. (Paepe) Often sequential assessments will provide earlier identification of a problem (e.g., weight loss, changes in body condition score [BCS], muscle condition score [MCS], blood pressure, creatinine, etc.) before the values fall outside the normal reference interval.
2. Be selective. Consider the prevalence not only within the region but also age of the patient. Similar to vaccination, where the goal is to perform risk assessment of the individual, not every patient needs a comprehensive "minimum" database.
3. Be cognisant of the limitations of every test.
4. Weigh, BCS, MCS cats at every visit. Serial changes (e.g., percentage weight change) are much more meaningful than absolute numbers or scores. Blood pressure should be measured in all cats over 3 years of age as elevations suggest conditions that should be further assessed. (Taylor)
5. Nutritional intervention should be considered and implemented early. It may help modulate the impact of free radical damage. (Cupp 2008) It definitely can benefit an older cat by preventing or slowing muscle loss. Numerous studies have shown the risks of sarcopenia in the older cat, contributing to the development and progression of comorbidities. Sarcopenia results in poorer response to treatment, poorer quality of life as well as decreasing response to therapy and reduced survival in CKD, heart disease, lymphoma and other cancers. (Cupp 2010, Doria-Rose, Boyd, Freeman 2012, 2016, Finn, Krick)
6. Promote overall good health, including dental health regardless of age.
7. Become informed about the physical and social home environment. (Buffington Captivity) Teach the client about meeting environmental and behavioural needs and what signs may indicate stress in their cat. Rather than merely coping and surviving, an enjoyable, interesting and stimulating environment will improve the chance of good health outcomes.
8. Optimize hydration through attention to desirable water resources (wide, clean bowls, fresh water in easily accessible locations). Ensure that litter boxes are pleasant: clean, easy to access and enter/exit, filled with the right depth of the litter the individual cat likes.
9. Last, but certainly not in importance, provide analgesia. Be suspicious of hidden pain or discomfort. Look for, and counsel the client on, the subtle changes that may indicate that pain is present.

Summary

With such a plethora of combinations of diseases existing, it appears that comorbidities are the new norm for cats. Why conditions present concurrently and what the mechanisms for this is not known. Perhaps serious consideration needs to be given to an integrated view of health rather than a purely biomechanical one. Future thinking and research will be interesting, and results will hopefully benefit cats as well as other species.

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