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Adrenal Toxicity in Dogs and Cats as a Contributing Cause of Hormonal and Immune Destabilization

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Key words: dogs; cats; adrenal cortex toxicity; endocrine–immune imbalances; cortisol disruption; testing for endocrine–immune imbalances; low-dosage cortisone therapy.

The adrenal cortex is regarded as the organ most vulnerable to toxicity within the endocrine system. The production of cortisol, among the many steroidal hormones produced by the cortex, may suffer as a result. In a veterinary clinical practice, household dogs and cats with a wide variety of diseases ranging from allergies to cancer commonly have a cortisol deficiency or defect that triggers endocrine imbalances and immune system destabilization. The causes of deficient cortisol are linked primarily to genetics but also to acquired adrenal damage likely stemming from environmental toxins. An innovative blood test to determine relevant endocrine–immune imbalances in pets and a treatment method based on low-dosage steroidal medication, as a form of cortisol replacement therapy, are described. Despite a prevailing reluctance to use steroidal medications long term because of the fear of side effects, extended and even life-time usage of these medications at low, physiologic dosages has been applied successfully for decades and appears to be gaining wider acceptance. The validity of a combined testing and treatment method for humans based on the veterinary model deserves investigation as a tool with which to identify and correct toxic damage to adrenal function.

COMMON ADRENAL DEFICITS IN PETS

Household pets are intimately exposed to a multitude of toxic compounds. Among them are lawn and garden compounds, rat poison, insect and snake bites, anti-flea chemicals and other pesticides, antifungal drugs, anesthetic agents, cleaning and disinfectant solutions, lead in paint and water, building and decorating materials, fumes outgassing from synthetic carpets and a multitude of chemical additives contained in highly processed commercial diets. Sensitive animals may develop a variety of mild to severe symptoms following exposure. Immediate reactions include diarrhea, vomiting, ulcers, skin rashes or anaphylactic shock.

In veterinary medicine, toxic overloads are viewed primarily as threats to the organs of detoxification, such as the liver and kidneys. High blood urea nitrogen (BUN) or liver enzyme counts accompany actual toxicity problems. One would expect the medical effects of toxins to be short lived and clear up following treatment and no further exposure. The health of the animal should then return to normal. In the author's experience, this is not always the case.

The adrenal glands are the most toxin-vulnerable organ in the endocrine system. The majority of toxic damage has been observed in the adrenal cortex, where steroidal hormones are produced, and such disturbances can 'fundamentally affect the whole body physiology and biochemistry' (Harvey, 1996). Indeed, the entire process of steroidogenesis 'poses multiple molecular targets' for disruption (Harvey and Johnson, 2002) and this is particularly relevant to adrenal function (Harvey and Everett, 2003).

For more than 30 years the author has focused his clinical practice on endocrine–immune imbalances, and specifically on a widespread but generally unsuspected defect originating in the adrenal cortex that has a serious impact on the production of cortisol. In many thousands of feline and canine cases he has linked a cortisol deficiency to a repetitive pattern of hormonal imbalances that compromises immune competence and acts as an underlying 'enabling' mechanism for multiple disorders ranging from chronic allergies and viral diseases to autoimmunity and cancer.

In dogs and cats this disturbance appears to be largely genetic in nature, resulting from contemporary inbreeding practices. However, it can also be acquired, as for instance through adrenal exposure to toxins. Whether genetic or acquired, the cortisol defect triggers systemic consequences.

Much is written about risks of elevated cortisol as a normal reaction to stress and trauma, and about the anti-inflammatory and immunosuppressive effects of pharmacologic dosages of cortisone, the synthetic version of cortisol. However, at a basal level, the body's own cortisol exerts a discriminating regulatory effect on molecular mediators that turn on or off the activity related to immunity and inflammation. A normal level of cortisol appears necessary for a normal immune and inflammation response

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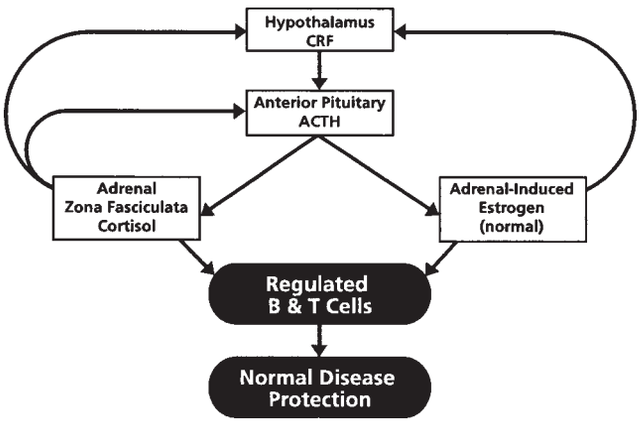

Figure 1. Normal relationships and feedback activity between the adrenal cortex and the hypothalamus and pituitary, and in turn a healthy regulatory influence on the immune system.

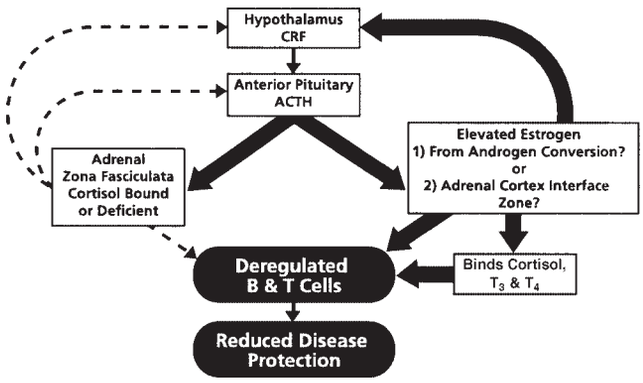

Figure 2. Genetic and toxicity factors can interfere with cortisol production, triggering excess ACTH and estrogen release. A vicious cycle results. A cortisol deficiency is aggravated, thyroid function is affected and the immune system is destabilized.

(see Fig. 1). A deficiency of cortisol may result in an unresponsive immune system, whereas too much cortisol or too much cortisone medication suppresses immune responses.

In animals it has been found that a deficiency of active cortisol disturbs the hypothalamus–pituitary–adrenal feedback loop. As a result, pituitary adrenocorticotropic hormone (ACTH) attempts to elicit more cortisol from the cortical zona fasciculata layer. The author has found that this activity consistently promotes a measurable and physiologically significant increase in serum estrogen. The added estrogen may come from ACTH-stimulated zona reticularis androgens, some of which convert to estrogens in peripheral tissue (Parker, 1995), or from 'interface' cortical tissue that may produce estrogen compounds directly (Symington, 1969; Roberts, 1999). In any case, elevated estrogen is consistently measured in all animals with the endocrine–immune disturbance (male and female, intact or neutered) and thus cannot be attributed to ovarian activity (see Fig. 2).

Elevated estrogen also appears to disturb the immune system (Cutolo *et al*., 2002). In addition, the hormone also impairs the synthesis of cortisol (Gell *et al.*, 1998).

Both cortisol insufficiency and elevated estrogen interfere with thyroid hormones (Gross *et al.*, 1971; Jefferies, 1996; Arafah, 2001). As observed by the author, the combination disturbs thyroid function and slows down metabolic processes, including the ability to eliminate waste products. Waste remains in the body longer, undermining health. Toxins and medications that enter the body are also processed less efficiently, potentially leading to further harm and side-effects.

An existing endocrine–immune disturbance of the nature just described renders an animal less able to cope with stress, pathogens and chemical and toxic challenges, whatever the source.

As noted earlier, toxins may also *cause* a cortisol defect. Such defects may be of a short-term or permanent nature. The author's clinical observations over many years suggest that the cortical zona fasciculata tissue, where cortisol is produced, is by far the most vulnerable adrenal target of toxicity rather than a more widespread cortical impact. A harmful effect on the production of aldosterone, synthesized in the zona glomerulosa, has been encountered only rarely.

TESTING METHODOLOGY FOR ENDOCRINE–IMMUNE IMBALANCES

A blood test developed by the author measures cortisol, total estrogen, T_3/T_4 levels and IgA, IgG and IgM, and serves as an accurate diagnostic tool for endocrine–immune imbalances (see Table 1). The typical imbalances seen in sick animals involve low or defective cortisol, elevated total estrogen, deficient or excessively bound thyroid hormones and low IgA, IgG and IgM levels. Years ago, a separate testing method to determine T cell function was conducted and showed that T cells were similarly weakened by hormonal imbalances. However, due to the expense of T cell testing this measurement was discontinued.

The endocrine–immune test described here measures total serum cortisol. But the test by itself does not really indicate whether the circulating cortisol is active, bound or defective, and how much of it actually works. *The important question is whether cortisol works or not*. The answer comes from analyzing the other hormonal and antibody

Table 1—Normal endocrine–immune serum values[a] developed for dogs and cats

Cortisol ($\mu g\ dl^{-1}$)	Total estrogen ($pg\ ml^{-1}$)	T_3 ($mg\ dl^{-1}$)	T_4 ($\mu g\ dl^{-1}$)	IgA ($mg\ dl^{-1}$)	IgG ($mg\ dl^{-1}$)	IgM ($mg\ dl^{-1}$)
1–2.5	30–35 female[b] 20–25 male	100–200	2–4.5	70–170	1000–2000	100–200

[a] Hormone values apply to dogs and cats of all ages. Antibody values apply to animals above the age of 6 months or 1 month after their last round of puppy and kitten vaccinations. Antibody levels in younger animals may be suppressed and thus not represent true values because of the impact of vaccines on immature immune systems.
[b] The range is for spayed or out-of-estrus animals.

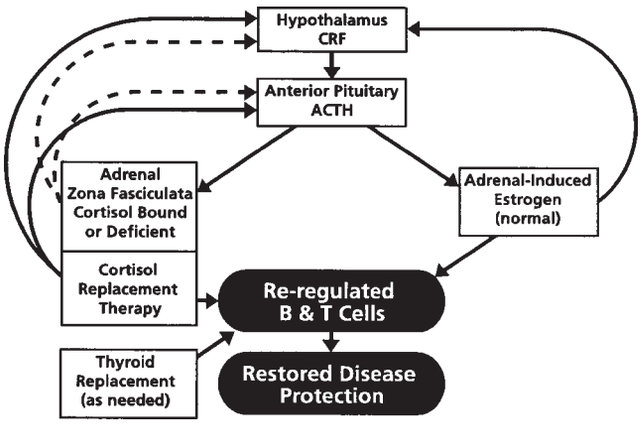

Figure 3. Correction of cortisol deficit with cortisol replacement therapy restores normal hypothalamus–pituitary–adrenal relationships and immune system integrity. Thyroid replacement is typically required for canines, but not for felines.

measurements. For instance, a low or even normal cortisol value along with elevated estrogen and low antibodies clearly indicates the presence of endocrine–immune imbalances. The cortisol may be excessively bound or defective. Either situation appears to promote elevated estrogen and contribute to deregulation of the immune system, expressed as low antibody levels.

Standard tests measure only one estrogen compound: estradiol. Tests reported here are for total estrogen, namely estradiol, estrone and estriol. This provides a more accurate indicator because of the potential for estrogen compounds to impair cortisol and thyroid hormones. In animals, a slight upward variation of total estrogen out of a normal range (20–25 pg ml^{-1} for males and 30–35 pg ml^{-1} for spayed or non-estrus females) is associated with disturbed hormonal and immune activity.

The described test is based on a simple blood draw. After the draw at the veterinary clinic, the blood is spun down in a serum separator tube and refrigerated. It is shipped cold and refrigerated at the laboratory until testing. If the blood is not kept cold the results will be invalid, with excessively high hormone and antibody results. Animals are retested 2 or 3 weeks after the start of therapy.

Imbalances are corrected with the long-term use of very-low-dosage cortisone that serves as a cortisol replacement. Depending on the individual case, either synthetic medications (Vetalog, Medrol, Prednisolone, Prednisone) or bio-identical 'natural' hydrocortisone derived from soy is used. Most dogs, but very few cats, also require a thyroid prescription (such as Soloxine, a T_4 replacement) as part of the therapy program. This approach restores healthy antibody levels and effectively eliminates a major underlying cause of multiple diseases (see Fig. 3).

CASE HISTORIES

Case no. 1: permanent suppression of cortisol production

A three-year-old spayed female Old English Sheepdog was presented with severe localized inflammation and swelling on the backside, the result of a black widow spider bite. A therapy program of antibiotics and anti-inflammatory medication proved successful.

However, a month after the conclusion of therapy, the dog started losing hair, breaking out in welts and developed diarrhea and vomiting after eating its normal food. An endocrine–immune test revealed low cortisol, high estrogen and low IgA, IgG and IgM antibodies, a sign of deregulated B cell function (see Table 2). Previously, at the age of 1 year, the dog had been tested and its endocrine–immune status was normal. Now apparently, the spider toxin had in some way damaged the cortisol synthesis pathway sufficiently enough to cause a deficiency.

The 65 lb dog was started on 40 mg of hydrocortisone once daily and 0.6 mg of Soloxine twice daily. Clinical signs quickly resolved. A subsequent endocrine–immune test yielded improved values. Note that the level of cortisol was still below the normal range. However, the dosage was deemed therapeutically effective. The combination of active exogenous and endogenous glucocorticoids brought the immune markers back to a level that re-established immunocompetence. At the present time, the dog has been maintained on the same corrective program for 4 years and has experienced no health problems. Periodic endocrine–immune testing has revealed normal immune values.

Case no. 2: suppression of cortisol following surgery

The author has treated many animals who failed to heal properly or developed various clinical signs of illness after surgery. Testing for endocrine–immune function has routinely yielded a typical pattern of imbalances, suggesting toxic damage to cortisol synthesis from anesthetic compounds. When imbalances have been corrected with cortisol replacement (along with thyroid medication in dogs) the animals healed properly and their clinical signs abated.

One such case involved a neutered 80 lb German Shepherd male. An endocrine–immune health check at 3 months of age showed that no imbalances were present. At age 3 years the dog suffered a severe laceration on the backside. Taken to an emergency clinic, the dog received a standard pre-anesthesia (Keteset, acepromazine and Valium) and was then intubated for an inhalant anesthetic (Fluothane). The laceration was routinely cleaned and sutured.

Table 2—Endocrine–immune values at baseline and after commencement of long-term treatment

Case 1	Cortisol (μg dl^{-1})	Total estrogen (pg ml^{-1})	T_3 (ng dl^{-1})	T_4 (μg dl^{-1})	IgA (mg dl^{-1})	IgG (mg dl^{-1})	IgM (mg dl^{-1})
Baseline	0.41	37.4	121	2.7	58	850	92
Treatment[a]	0.61	34.95	150	3.2	71	1200	130

[a] Treatment values are based on blood draws usually conducted 2 or 3 weeks after initiation of therapy. Improved treatment values consistently parallel improvement in the health of animals.

A month later the incision had not yet healed. The dog was brought to the author's clinic for evaluation. An endocrine–immune test was performed that now showed substantive imbalances (see Table 3) apparently affecting the healing process. The thyroid values, although in the normal range, were interpreted as excessively bound due to the combination of low cortisol and elevated estrogen.

Cortisol replacement therapy (60 mg of natural hydrocortisone daily), along with thyroid medication (0.8 mg of Soloxine twice daily) was instituted. The dog healed satisfactorily within 2 weeks, at which time he was retested and found to have significantly improved endocrine–immune test results. Even though the cortisol level was below normal it was apparently sufficient in this individual case to promote normalization and healing. The dog has been maintained on the same program for 6 years.

Case no. 3: fatal dermal necrosis and suppression of cortisol

A 2-year-old spayed female cat was being considered for adoption. The prospective pet owner wanted to be sure the cat was healthy and asked that the author first test the animal's endocrine–immune status. The test revealed no adnormalities (see Table 4). The cat was adopted and joined another feline already in residence.

The new owner, concerned about the potential for fleas, purchased a popular anti-flea gel for her pets. The instructions advised direct application once a month to the skin between the shoulder blades. Shortly after the first application, the adopted cat developed dermal necrosis around the area of application. The second cat did not react.

The owner brought the affected cat to the clinic. Topical treatment with antibiotic and anti-inflammatory medication was initiated but failed to stop the spread of necrosis. The cat was then retested for endocrine–immune status. The values were now significantly abnormal. The pesticide had apparently harmed the cortisol synthesis.

A therapeutic program of low-dosage natural hydrocortisone (7.5 mg daily) was started for this 10 lb cat in order to correct the imbalances. Two weeks later, the cat was retested. The endocrine–immune values were now normal. However, necrosis continued to spread. Additional medical treatments were unsuccessful. The cat died 10 weeks after having received a single, but fatal, application of anti-flea medicine. The cortisone therapy compensated for the cortisol damage but could not save the cat.

Case no. 4: temporary suppression of cortisol production

A 1-year-old, 70 lb non-neutered male Doberman Pinscher developed severe skin disease with multiple pustules. Testing for endocrine–immune imbalances revealed low cortisol, high estrogen and low levels of thyroid, IgA, IgG and IgM (see Table 5).

Imbalances were corrected with cortisol replacement medication (natural hydrocortisone, 50 mg daily) and a T_4 supplement (Soloxine, 0.7 mg twice daily). The skin condition cleared up. However, faced with the prospect of maintaining the dog on a lifetime of medication, the owner opted to return the animal to the breeder, who lived 150 miles away.

Three weeks after relocation, the breeder reported that signs of cortisone side-effects had developed: increased thirst, urination and appetite, and panting at night. The animal was retested. The results showed low estrogen and decreasing levels of antibodies, an indication of excess glucocorticoid presence in the body. The dog was weaned off the medication and the side-effects vanished. A new blood test showed normalization of the key endocrine–immune values.

Table 3—Endocrine–immune values at baseline and after commencement of therapy

Case 2	Cortisol ($\mu g\ dl^{-1}$)	Total estrogen ($pg\ ml^{-1}$)	T_3 ($ng\ dl^{-1}$)	T_4 ($\mu g\ dl^{-1}$)	IgA ($mg\ dl^{-1}$)	IgG ($mg\ dl^{-1}$)	IgM ($mg\ dl^{-1}$)
Baseline	0.62	27.2	154	3.2	48	650	52
Treatment	0.81	24.9	174	3.9	74	1100	121

Table 4—Endocrine–immune values at baseline, after exposure to pesticide, and after commencement of therapy

Case 3	Cortisol ($\mu g\ dl^{-1}$)	Total estrogen ($pg\ ml^{-1}$)	T_3 ($ng\ dl^{-1}$)	T_4 ($\mu g\ dl^{-1}$)	IgA ($mg\ dl^{-1}$)	IgG ($mg\ dl^{-1}$)	IgM ($mg\ dl^{-1}$)
Baseline	2.1	33.8	141	4.0	80	1500	160
After pesticide	0.32	39.2	139	3.8	52	740	56
Treatment	0.41	34.9	152	4.2	71	1300	107

Table 5—Endocrine–immune values at baseline, after relocation on continuing therapy and after discontinuation of therapy

Case 4	Cortisol ($\mu g\ dl^{-1}$)	Total estrogen ($pg\ ml^{-1}$)	T_3 ($ng\ dl^{-1}$)	T_4 ($\mu g\ dl^{-1}$)	IgA ($mg\ dl^{-1}$)	IgG ($mg\ dl^{-1}$)	IgM ($mg\ dl^{-1}$)
Baseline	0.65	26.2	87	1.9	52	750	76
Testing, on therapy after relocation	0.31	19.5	79	1.7	48	720	68
After treatment stopped	1.27	23.8	145	3.2	80	1200	140

The dog's previous home had been situated adjacent to a landfill and the confluence of busy freeways where unknown sources of environmental toxicity apparently suppressed the adrenal function, resulting in imbalances and skin disease. The medication corrected the imbalances. Once relocated, and no longer exposed to the environmental agents, the dog's adrenal function returned. In this changed situation, cortisol replacement medication had contributed to excess glucocorticoid concentrations in the body and was no longer needed.

IMPLICATIONS FOR HUMANS?

The clinical cases cited above illustrate the extent to which various exogenous toxicants may have an impact on the zona fasciculata, suppress cortisol production, and create systemic disturbances. An innovative endocrine–immune surveillance blood test developed by the author identifies an unsuspected yet consistent pattern of hormonal and immune imbalances consequent to cortisol interference. A hormone replacement program based on low-dosage cortisone (and, in dogs, thyroid medication) has the potential to correct the disturbances and symptoms.

The endocrine–immune imbalances and medical effects routinely seen bear some resemblance to human immune deficiency syndromes, such as common variable immunodeficiency (CVID). Patients with CVID, for instance, have altered levels of IgA, IgG, IgM and T cells, just as in animals. Such patients also have an increased risk of cancer, particularly cancer of the lymph system, skin and gastrointestinal tract. All of the author's cancer patients, with all types of cancer, have similar underlying endocrine–immune imbalances. Toxins are often referred to as 'carcinogens'. Does the route of carcinogenicity pass through the adrenal cortex and disrupt cortisol synthesis, which in turn causes additional hormonal dysfunction and destabilization of the immune system?

Researchers suggest that CVID most likely develops from an interaction of genetic and environmental factors (Sicherer and Winkelstein, 1998; Lederman, 2000). The author suggests that investigating the cortisol activity may generate important clues for the diagnosis and treatment of challenging immunodeficiency conditions, as well as for cancer.

The chemical revolution has given us countless benefits but at the same time has exposed us to an unprecedented volume of previously non-existent compounds with the potential to harm both humans and animals alike. We read continually of major toxic broadsides against wildlife that cause us to pause and wonder to what degree immunocompetence in humans is being affected. Recently, changes in immune cells, antibodies and hormones among Arctic polar bears has caused concern among scientists (Cone, 2003). The changes are a result of industrial chemicals, called polychlorinated biphenyl compounds (PCBs), contaminating the marine food chain. Such chemicals can weaken the immune system with devastating results, such as when a distemper virus killed some 20 000 PCB-laden seals in Europe in 1988. Is it possible that toxic damage to cortisol synthesis contributes to such end results? There have been a number of reports in recent years describing damage to adrenal cortex function in fish, including impairment of cortisol, as a result of chronic exposure to heavy metals, pulp and paper effluents and agricultural pesticides (Leblond and Hontela, 1999; Norris *et al.*, 1999).

Defective or deficient cortisol is grossly underdiagnosed in veterinary medicine and appears to be so as well in human medicine (Jefferies, 1994). A potentially major primer for disease may thus be off the radar screen of most medical practitioners. Moreover, many doctors fear long-term cortisone usage at any dosage because of the drug's well-known side-effects and its immunosuppressant properties. It should be noted, however, that such effects relate to pharmacologic and not small, physiologic dosages of cortisone. Jefferies has reported on the safe and effective therapeutic use of long-term physiologic dosages of cortisone for decades in human patients with 'adrenocortical deficiency'. He describes significant improvement of allergies, autoimmune disorders and chronic fatigue. In animals, the author has also determined that long-term, low-dosage cortisone therapy is safe and effective for these and many other conditions as long as the practitioner is correcting an underlying cortisol-based imbalance.

Jefferies believes that replacement with physiologic dosages of cortisone should not be stopped upon initial remission, similar to what the author finds with animals. When medication is stopped, clinical signs return.

In recent years, successful application of low-dosage cortisone has been reported in rheumatoid arthritis (Hickling *et al.*, 1998), polymyalgia rheumatica, a systematic inflammatory disorder of the aged (Cutolo *et al.*, 2002) and sepsis (Klaitman and Almog, 2003). The benefits of long-term, low-dosage cortisone therapy thus appear to be gaining wider acceptance.

For humans, a similar test to that designed for animals could be developed to identify a cortisol problem and to assess the health risks resulting from a genetic defect or environmental toxicity. Given the impact of hormones on the immune system, the author strongly believes that such a test should become a standardized measurement of immune competency and be offered along with standard CBC blood chemistry and other accepted diagnostics. If imbalances exist in humans as they do in animals, corrective treatment with appropriate low-dosage cortisone preparations should be considered as a remedial option. This therapy program represents a major healing modality for many seemingly unrelated chronic diseases of animals, including catastrophic diseases. In a time where the medical risks of environmental toxicants are becoming increasingly worrisome, studies are warranted to investigate the validity of this type of comprehensive approach for humans.

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