

Adrenal-Immune Disturbance in Animals Offers Therapeutic Insights for Multiple Human Disorders

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In thousands of cases spanning three decades, I have identified an unrecognized endocrine-immune disturbance as a major trigger of multiple disorders in dogs and cats, including allergies, epilepsy, viral diseases, inflammatory bowel, autoimmunity, and cancer. In most cases, and for seemingly unrelated conditions, I have restored health by correcting this disturbance with the same therapeutic program.

I strongly believe this clinical approach offers important diagnostic and treatment promise for common human diseases that may also have a similar mechanism of endocrine-immune imbalance.

The problem originates with genetic or acquired disturbance to the adrenal cortex production of cortisol. A domino effect ensues, affecting the hypothalamus-pituitary-adrenal axis. Estrogen, from the apparent conversion of adrenal androgens, is overproduced. Thyroid hormones are blocked. Immune function becomes compromised. I consistently see this scenario in sick patients, and *every* cancer patient I treat has it.

CLINICAL EVOLUTION

Early in my career I realized I was just providing temporary relief for most of my patients. I was practicing what I had been taught in veterinary school, but I was merely treating medical effects, and doing no real healing. I felt frustrated. I wanted to make a difference in the health of my patients. So I embarked on a personal mission to better understand the causes of sickness.

The process started in 1969 when a medical research laboratory contracted me to inspect their animal-testing environment. Instead of a fee I asked the laboratory to run antibody levels on my patients. I did this to develop a better sense of immune function in relation to norms, disease, and effects of treatment. The laboratory monitored five immunoglobulins for me: IgA, IgD, IgE, IgG, and IgM.

After two years I was able to define normal and abnormal ranges for what I considered the most significant antibodies relating to viruses, bacteria, fungal conditions, and hypersensitivity. For me, the most relevant antibodies were IgG, IgM, and, in particular, IgA.

I first applied these standards to Sunshine, a very sick Golden Retriever puppy. The young dog had a serious autoimmune-like problem with horrible inflamed skin. Antibody levels were quite low. I prescribed a standard daily dosage of cortisone to reduce the inflammation and an antibiotic to handle the bacteria. Within a few days the dog was much better.

I retested for antibodies and was shocked. The antibodies were clearly improved from baseline levels before treatment.

How could this occur? I had expected the anti-inflammatory effect. After all, cortisone is used for that purpose. But everybody knows (or at least believes) that cortisone suppresses immune cells. So why did the antibodies increase?

I started reading physiology and endocrinology books seeking an explanation. I found basic information, but no explanation.

I learned that cortisol, the primary adrenal glucocorticoid hormone produced in the middle cortex layer (zona fasciculata), exerts an anti-inflammatory effect. This action inspired the development of cortisone (synthetic cortisol) drugs. Cortisol also serves as a “stress hormone,” causing the release of glucose to fuel a response to danger. Less understood is its role as a regulator of the immune system. Cortisol is stimulated by the pituitary’s adrenocorticotropic hormone (ACTH), which, in turn, is controlled by the hypothalamic corticotropin-releasing factor (CRF). Secretion is governed by a classical feedback loop. When blood concentrations rise to a certain level, cortisol inhibits CRF secretion. This then inhibits ACTH and cortisol secretion.

I learned that when the zona fasciculata cannot make enough cortisol, or for some reason the cortisol is excessively bound (inactive) or defective and thus not recognized by the system, the pituitary continues to release ACTH in order to stimulate more cortisol. Somehow this results in elevated estrogen in the body.

I wondered if a physiologically significant amount of estrogen could be pushed into the system by abnormal adrenal-hypothalamus-pituitary activity stemming from a cortisol defect or deficiency. Could this added estrogen contribute to inflammation? The research says that estrogen stimulates histamine release. Histamine causes inflammation. Could cortisone medication correct a cortisol deficiency, turn off the ACTH demand, and reduce the adrenal stimulation of estrogen? Could this help explain in part why cortisone so effectively brings down inflammation?

The questions piled up. Over time, and with continued clinical investigation, the practical answers came that enabled me to effectively test and treat my patients.

In sick animals I consistently found low cortisol, high estrogen (no matter whether the animal was male, female, or neutered), and low antibodies. Repeated testing showed the same hormonal imbalance coinciding with abnormal levels of IgA, IgG, and IgM antibodies. The result, in case after case: poor resistance against viral, bacterial, and fungal infections and a greater susceptibility to disease.

I found that cortisone therapy initially lowers estrogen and increases antibody levels. Continued cortisone usage, however, causes antibodies to fall again—an immunosuppressive effect that occurs even with very low cortisone dosages. Eventually, I came to the conclusion that the elevated estrogen must be binding thyroid hormones, thus slowing the metabolism and the body's ability to process the cortisone. Even if blood tests showed thyroid to be "normal," estrogen was invariably high and antibodies low. Moreover, I would often find slower than normal heart rate, lower than normal temperature, and higher than normal levels of cholesterol and triglycerides, all markers of a thyroid problem.

If I treated dogs simultaneously with cortisone and thyroid hormone, the estrogen level decreased and the antibodies increased and stayed in the normal immunocompetence range. Canine patients improved. They seemed to process the cortisone and disallow toxic buildup. For some species-specific reason, most cats needed only the cortisone, not the thyroid.

I eventually figured out effective dosages of cortisone replacement that worked both therapeutically and for long-term use without side effects. These levels of dosages turned out to be physiologic, that is, significantly lower than conventional pharmacologic levels. The low dosages lower estrogen and increase antibodies. In my therapy program, I utilize a combination of pharmaceutical and plant-based (natural) cortisone preparations, depending on the severity and stage of disease. Many once-sick animals have been on this program for their entire lifetimes and remained healthy.

For years I thought that the inner cortex layer, called the zona reticularis and which also responds to ACTH, produced estrogen. I later learned that this zone produces the androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), the most abundant circulating hormones in the body. These substances are known as prohormones in that they metabolize into other hormones. Through enzymatic actions they can convert to androstenedione, androstenediol, testosterone, and further to the estrogen compounds estrone and estradiol. Androstenedione, for instance, is the main precursor of estrone, the most abundant circulating estrogen in postmenopausal women. Androstenediol, converted from DHEA, has inherent estrogenic activity.¹ I believe these androgen-to-estrogen processes may be producing the elevated estrogen.

CAUSES OF AN EPIDEMIC

In thousands of cases I have repeatedly observed the same endocrine-immune dysfunction operating. It undermines homeostasis and sets the stage for malabsorption and digestive disorders, allergies, lung and urinary tract problems, sluggish liver function, strange or aggressive behavior, epilepsy, obesity, deadly viral and bacterial infections, periodontitis, vaccine reactions, autoimmunity, and cancer. Younger animals with the defect develop diseases typically seen in older animals. Moreover, the defect often causes not just one illness, but multiple illnesses.

I consider the problem in pets to be largely genetic. Early on, I observed similar problems among littermates and along familial lines: severe hypersensitivity, inflamed skin with ulcerations and itchiness, malabsorption, and internal systems seemingly out of control. I began to suspect that contemporary breeding practices—namely inbreeding and linebreeding for a fashionable appearance instead of for function and hardiness—were causing

narrowed gene pools, compromised health, and shortened longevity. Many genetic disorders among purebred pets, a result of contemporary breeding practices, have been reported.² However, other than my published papers: the endocrine-immune abnormality described here has not been reported.

The abnormality goes beyond purebreds. As affected purebreds have mated with mixed breeds the defect has proliferated. I believe it is extremely widespread and an unrecognized cause of the disease epidemic among household pets.

Food intolerances, poor diet, sensitivities to parasites, stress, and aging, also enter into the equation. Environmental toxicity could be another significant, yet largely unrecognized, factor. It is generally recognized adrenal gland is the most vulnerable organ in the endocrine system for toxins, and within the adrenal gland “the majority of effects” have been observed in the cortex. Such disturbances can “fundamentally affect the whole body physiology and biochemistry.”³

Whatever the original cause, correction of the disturbance with appropriate low-dosage cortisone (along with thyroid replacement in dogs) generally restores immunocompetence and health. Even severely diseased animals make comebacks, living long and healthy lives. But animals deteriorate when pet owners, for whatever reason, stop the therapy. Signs of previous illness return. The treatment funds a deficit, realigns a hormonal derangement, resets the metabolism, and restores coherence to an incoherent immune system. It controls disease and supports the health of the animal for as long as the program is maintained. Used therapeutically, it can save animals who might otherwise be destined for euthanasia. Used preventively to determine the presence of imbalance in asymptomatic animals, it can help avoid future suffering and premature death.

IS THIS CONGENITAL ADRENAL HYPERPLASIA?

I have found nothing in the medical literature—veterinary or human—exactly describing this endocrine-immune pattern and its broad medical effects. Congenital adrenal hyperplasia (CAH) has some similarities. This human condition is characterized by a deficiency of cortisol and an increase in androgens, the result of a deficiency in the adrenal enzymes that make cortisol. Once considered a rare inherited disorder with severe manifestations, a mild form is now said to be common although frequently undiagnosed. Patients with the mild form are fre-

quently unable to mount sufficient stress responses to trauma and infection.⁴

It is possible that a similar enzyme disturbance could be operating in household pets. I have not tested for enzyme deficiencies or for androgen levels.

There are at least two clear dissimilarities between CAH and the endocrine-immune defect I have identified in animals. CAH involves hypertrophy of the adrenal glands and frequent deficiency of aldosterone, the mineralocorticoid produced by the outer layer of the cortex. I have neither in affected animals.

I am a clinician, not a researcher. I have learned what I know first-hand from testing and treating my patients over many years. Looking back, I was very fortunate to uncover a therapeutic path that has worked magnificently. While researchers now recognize that the hypothalamic-pituitary-adrenal axis, as part of the neuroendocrine system, has central importance to immune homeostasis,⁵ they still admit to a lack of clear understanding about countless details and interactions.

TESTING FOR THE MECHANISM

Years ago I developed a special blood test to monitor the key hormonal and immune levels and relationships for cortisol, total estrogen, T3, T4, IgA, IgM, and IgG. The reference ranges evolved from clinical observation in thousands of cases. Comprehensive tests such as these are not utilized routinely by veterinarians.

An initial test gives me baselines before therapy starts. High estrogen and low antibodies are the major clues I look for. Two weeks after therapy begins I retest to see how values have shifted and adjust the program accordingly. Once values normalize and clinical signs abate, I retest on a six-month or annual basis.

I compare hormone relationships to each other and to the immune system, rather than relying on individual levels. Cortisol itself, even if the value is normal, may be in a bound (inactive) state to some degree due to the nature of the cortical defect. T3/T4 could show normal, but also be bound. Moreover, a singular hormone level found in the high normal range for one animal could be an inadequate level for another, while a low level for one animal might be too high for another. For these reasons I compare the range of test values with clinical signs. Generally, I look to bring down total estrogen, raise antibodies, and free up T3/T4. This typically parallels a clinical improvement in the patient.

Earlier, I included T cell testing and found that the mechanism also suppresses T cells. However, due to the significant added cost, I dropped T cell measurement from the panel.

Standard tests measure only one estrogen compound: estradiol. I test for total estrogen, that is, all the estrogen compounds in the body. I feel this is a more accurate indicator because of the potential for the estrogens to exert a blocking effect on cortisol and thyroid. Just a slight variation out of normal is enough to disturb hormonal and immune activity. As I mentioned earlier, elevated estrogen binds thyroid hormones to a varying degree, enough to slow down overall metabolism, and trigger additional problems.

About 90 percent of my cases involve neutered animals. Thus, in the case of spayed females, and males (intact or otherwise), I attribute the high estrogen level to probable androgen-to-estrogen conversion. Testing of female dogs and cats with intact ovaries is conducted when animals are not in estrus, and therefore not producing a high level of ovarian estrogen.

APPLICATION FOR HUMANS

Does this endocrine-immune disturbance exist in humans? And if so, can a similar treatment protocol be applied?

I have suggested to interested physicians that they test their human patients for the same range of hormonal-immune relationships that I test in my animal patients. That means a blood test measuring cortisol, total estrogen, thyroid (T3/T4), and immunoglobulins. Other factors could be added, such as T cells and the androgen precursors to estrogen, in order to develop a more precise picture. Researchers have begun looking at the immune and inflammatory modulating effects of androgen/estrogen ratios and concentrations.⁶

Patients can be retested at biweekly or monthly intervals to monitor changing relationships. The bottom line is that hormonal replacement must be measured against B and T cell levels.

For female patients, clinicians will have to consider ovarian estrogen. The level of total estrogen will obviously vary according to the stage of the monthly cycle at which testing is done, age, and use of birth control pills or estrogen replacement. Reproductive age females might be tested in mid-cycle when the ovarian estrogen level is highest and again just prior to menses when it is

at the lowest level. Reproductive-age women should be tested on the seventh day of the cycle, when estrogen is lowest, and again on the twenty first day, when estrogen is highest. The difference between the two scores should reflect non-ovarian estrogen in the system. One physician who uses hormones routinely in his practice was surprised to find, after I discussed this mechanism with him, that his sickest postmenopausal (non-ERT) patients had high estrogen levels and low antibody counts. The possible reason for this, I suggested, is the impact of low/bound cortisol and added estrogen from adrenal androgen conversion. Estrogen synthesis is known to increase in non-ovarian tissues as a function of age and body weight.⁷ Even though postmenopausal, these women may actually be in a state of relative estrogen dominance.

The clinician might also want to obtain a 24-hour urine sample from the patient in order to test for active T3, T4, cortisol, total estrogen, and any other relevant markers. This would allow a comparison to blood values, which may test out as normal but in fact involve significantly bound hormones. Often it is not known if the hormone is working or not. The urine test can help answer this question and contribute to a more effective treatment.

Can a comprehensive endocrine-immune strategy help human cancer patients? The imbalance exists in each and every animal cancer case referred to me. Therapy outcomes are usually positive, even in advanced cases when hormone replacement therapy is combined with excision, chemotherapy, or radiation.

What about AIDS? In cats, the feline immunodeficiency virus (FIV) involves a retrovirus similar to HIV. Veterinarians put down symptomatic cats, yet I have a 70 percent recovery rate among such patients. They remain disease-free as long as they are maintained on low-dosage cortisone. Cats testing positive for the virus do not develop clinical signs once they go on—and stay on—the program. I suggest that when a human is exposed to the HIV virus, whether or not he or she develops symptoms of AIDS may depend on the strength of his or her endocrine-immune connections. If an imbalance is found through testing, correction with appropriate hormone replacement could be a significant strategy for both prevention and therapy.

Can this mechanism contribute to human inflammatory bowel conditions such as colitis and Crohn's disease? There is currently an epidemic of inflammatory gut conditions among dogs and cats. I consis-

tently find the imbalance in affected animals. The therapy works well. The typical low cortisol/high estrogen combination destabilizes and depletes IgA, a global antibody most active in the mucous membranes of the body, including the gut lining. Low IgA suggests an absorption problem. The animal (or human) may not absorb oral medication, so I begin therapy with intramuscular injections of cortisone, or, in the case of life-threatening conditions, intravenous drips, along with thyroid replacement and a hypoallergenic diet, which minimizes the risk of food-related reactions. This total approach quickly lowers the estrogen level and raises IgA. Once IgA rises to a certain point and the inflammation has subsided, I switch to oral medication. The same approach works for IgA-related conditions elsewhere. Animals with chronic bowel disorders (including food allergies), respiratory and urinary tract disorders, and anaphylactic and vaccine reactions invariably have abnormal IgA levels.

William Jefferies, M.D., of the University of Virginia, has described the safe and effective use of physiologic dosages of cortisone for decades in human patients with “adrenocortical deficiency.”⁸ He has reported improvement among patients with allergies, autoimmune disorders, and chronic fatigue⁹ yet the medical community has largely ignored his research. The reason, he states, relates to the “unique situation in which a normal hormone, one that is essential for life, has developed such a bad reputation that many physicians and patients are afraid to use it under any circumstances.”¹⁰ This comment accurately describes my experience in veterinary medicine. At pharmacologic dosages, cortisone does indeed create side effects. Practitioners shudder at any suggestion of long-term cortisone, even small physiologic dosages acting as a hormone replacement for deficient cortisol.

Jefferies believes that replacement with physiologic dosages of cortisone should not be stopped upon initial remission.¹¹ I agree. In my experience with animals, stopping the medication virtually guarantees that the imbalance and its secondary clinical signs will return.

SUMMING IT UP

I have found nothing in the literature to fully documenting the devastating effects of deficient or bound cortisol and elevated estrogen on the immune systems of household pets.

Animals born with defective adrenal glands eventually get sick. One can speculate that a cortisol defect could be passed on to offspring if both parents are affected. This appears to be a widespread problem among cats and dogs. I have seen an escalating severity of conditions related to this defect in generations of animals.

Is there a parallel development among humans with allergies and malabsorption in one generation and autoimmune diseases and cancer in the next?

Stress, poor diet and environmental toxins are other possible explanations for adrenal malfunction. Hans Selye’s seminal work in 1937 demonstrated that cortisol deficiency is a clear consequence of prolonged stress and contributes to some of the “diseases of civilization.”¹²

Jefferies’ excellent work examines the effects of mild cortisol deficiency due to either primary adrenal malfunction or secondary to inadequate stimulation by the pituitary or hypothalamus. He has reported that physiologic dosages of cortisone can improve a number of human disorders.

Recently, other medical researchers have reported successful applications of low dosage cortisone in rheumatoid arthritis and polymyalgia rheumatica, a systemic inflammatory disorder of the aged.^{13, 14} CAH is treated, in part, with cortisone replacement.¹⁵ The resemblance between adrenal defects in animals and CAH in humans strongly suggests that comparative research is warranted.

My independent clinical experience shows that low-dose cortisone, along with thyroid replacement, helps restore lost immune competence in many dogs. In most affected cats, cortisol alone works. I have learned that hormones regulate the immune system and when I normalize the key hormones I can usually restore immune competence and health to my patients.

Open-minded veterinarians who have inquired about this approach and applied it in their practices have obtained similar results. It has not been tested, however, in controlled studies. Nor has it been studied in humans. As a clinician I cannot carry out the elaborate research necessary to fully explore this largely unrecognized condition, but I believe such research could produce major diagnostic and treatment breakthroughs for humans.

REFERENCES

1. Parker, L. N. Adrenal androgens. In *Endocrinology* (Ed: DeGroot), Third Edition, Philadelphia: W. B. Saunders Co., 1995: 1836-47.
2. Lemonick M. D. A Terrible Beauty: An obsessive focus on show-ring looks is crippling, sometimes fatally, America's purebred dogs. *Time*, December 12, 1994: ; 65.
3. Harvey P. W. *The Adrenal in Toxicology: Target Organ and Modulator of Toxicity*, Bristol, PA (Taylor & Francis), 1996: 7.
4. Deaton, M., et al. Congenital adrenal hyperplasia: Not really a zebra. *American Family Physician*, March 1, 1999: 1190.
5. Cutolo M, et al. Altered neuroendocrine immune (NEI) networks in rheumatology. *Annals of the New York Academy of Sciences*, June 2002, 966: xvii.
6. Cutolo M., et al. Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis. *Annals of the New York Academy of Sciences*, June 2002, 966: 131-142.
7. Gruber, C. J., et al. Production and actions of estrogens. *New England Journal of Medicine*, 2002, 346 (5): 340-52).
8. Jefferies W. McK. *Safe Uses of Cortisol*. Springfield, IL (Charles C. Thomas Publisher), 1996.
9. Jefferies W. McK. Mild adrenocortical deficiency, chronic allergies, autoimmune disorders and the chronic fatigue syndrome: A continuation of the cortisone story. *Medical Hypotheses*, 1994; 42; 183-189.
10. Jefferies, op. cit., 185.
11. Jefferies, op. cit., 188.
12. Selye, H. Studies on adaptation. *Endocrinology*, 1937, 21;: 169.
13. Hickling P, et al. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *British Journal of Rheumatology*, 1998; 37: 930-936.
14. Cutolo M., et al. Cortisol, dehydroepiandrosterone sulfate, and androstenedione levels in patients with polymyalgia rheumatica during twelve months of glucocorticoid therapy. *Annals of the New York Academy of Sciences*, June 2002, 966: 91-96.
15. Deaton, M., et al, op. cit., 1190.