

# Unrecognized Endocrine-Immune Defects in Multiple Diseases

## AN EFFECTIVE VETERINARY MODEL MAY OFFER THERAPEUTIC PROMISE FOR HUMAN ILLNESS

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**F**or nearly three decades, I have treated multiple serious diseases in cats and dogs by correcting an unrecognized endocrine-immune imbalance caused by a cortisol deficiency or defect. The cortisol abnormality creates a domino effect on feedback loops involving the hypothalamus-pituitary-adrenal axis. Estrogen becomes elevated, thyroid hormone becomes bound, and B and T cells become deregulated. Diseases with this aberration as a primary etiological component range from allergies and strange behavior to severe cases of autoimmunity and cancer. I have consistently and successfully treated and controlled the condition, even in critical cases, with a long-term physiological (not pharmacological) cortisone replacement combined with thyroid hormone (in dogs). The treatment represents a major healing modality for many seemingly unrelated chronic animal diseases. In humans, this endocrine-immune dysfunction appears to exist and, as in veterinary medicine, has been overlooked by researchers and clinicians. Testing and treatment patterned after the animal model may offer significant clinical benefits for challenging human afflictions.

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Years ago, as a new practitioner, I became frustrated by the constant battle with canine and feline allergies and diseases for which medical training provided little guidance other than treating symptoms. In an attempt to understand causality and explore the possibility of more effective treatments I began my own clinical research.

In both young and old animals, I frequently found similar problems among littermates and along familial lines: severe hypersensitivity, widespread inflamed skin, ulcerations and pruritis, malabsorption, and out

of control internal systems. The path of inquiry led to the strong suspicion that contemporary breeding practices were causing narrowed gene pools, compromised health, and decreased lifespan.

For many conditions involving inflammation and pruritis, veterinary medicine commonly relies on an effective family of cortisol-type drugs (cortisone) for short-term therapy. As with human medicine, however, there is considerable reluctance about using these drugs long-term because of well-known side effects. Even with this concern in mind, I reasoned that cortisone therapy might in some way address an endocrine abnormality due to an unexplained genetic disturbance. Since cortisone is an adrenal hormone replacement, my attention turned to the adrenal glands.

Continued investigations indicated the presence of an unrecognized genetic flaw involving two of the three layers of the adrenal cortex and differing from the classic Addison's and Cushing's syndromes. Specifically, I found a problem in cortisol production causing a significant and damaging domino effect on other hormones and the immune system. Cortisol, the primary adrenal glucocorticoid, is produced in the middle cortex layer. This critical hormone stimulates several processes that serve to increase and maintain normal concentrations of glucose in blood, exerts a potent anti-inflammatory effect, and acts as a regulating factor for normal immune function.

Cortisol is secreted in response to a single stimulator: adrenocorticotrophic hormone (ACTH) from the anterior pituitary. ACTH is itself secreted under control of the hypothalamic corticotrophic-releasing factor (CRF). Cortisol secretion is suppressed or stimulated by classical feedback loops. When blood concentrations rise above a certain threshold, cortisol inhibits CRF secretion. This, in turn, inhibits ACTH and cortisol secretion.

However, when the adrenal gland is unable to produce enough cortisol, or for some reason the cortisol is bound and therefore not recognized by the system, the pituitary continues to produce ACTH in order to extract more cortisol.

The inner cortical layer, where adrenal estrogen is produced, also responds to ACTH. Constant ACTH stimulation in a situation where cortisol is bound or deficient produces a release of adrenal estrogen into the system. The estrogen activates a direct feedback on the hypothalamus. CRF is induced to stimulate the pituitary to release ACTH, releasing yet more estrogen from the inner layer of the adrenal cortex and raising the level of total estrogen in the system.

The influence of excess estrogen is a major confounding factor, causing the following: a histamine-like effect on capillaries, leading to inflammation from blood components spilling into adjacent tissue; binding of thyroid hormone and cortisol; and further deregulation of lymphocytes and antibodies.

I relate the loss of critical immune system function to poor resistance and immune cells which cannot properly defend against viral, bacterial, and fungal infections, or protect the body against cancer. The regulation loss is probably related to autoimmune damage, as well. Repeated clinical testing has shown that the endocrine imbalance described here coincides with abnormal levels of IgA, IgG, and IgM immunoglobulins.

The outer adrenal cortical layer, where the mineralcorticoid hormone is manufactured, appears to play no discernible role in this endocrine-immune derangement. A deficiency of mineralcorticoid secretion, which governs sodium and potassium levels, is associated with Addison's disease. An excess of cortisol is the biomarker for Cushing's syndrome.

Cortisone preparations have many of the chemical actions of cortisol. They are, in fact, converted to cortisol in the body. I reasoned that if the endocrine-immune imbalance originated in an inadequate supply of cortisol, and that if therapeutic treatment with cortisone preparations reduced a significant degree of clinical signs, at least in the short term, perhaps smaller, long-term physiological doses of cortisone rather than the large, conventional pharmaceutical doses might be effective in regulating the condition long-term. In human medicine, William Jefferies, M.D., emeritus clinical professor of internal medicine at the University of Virginia, has treated humans for decades using this approach and reported improvement among

patients with allergies, autoimmune disorders, and chronic fatigue.<sup>1</sup>

Over time I developed a testing and treatment strategy that proved to be safe and highly effective. The central modality is replacement of the cortisol deficiency/defect with physiological doses of various cortisone preparations. This normalizes the activity of ACTH, stops the overproduction of adrenal estrogen and the blockage of thyroid, and re-regulates the immune system. A second important modality is the simultaneous use of thyroid hormone. This is necessary in all canine cases, and in about 10 percent of feline cases. The contrasting thyroid requirement between dogs and cats is an apparent species-specific variation.

Elevated estrogen causes a binding effect on thyroid hormone resulting in retarded metabolic activity, impairing detoxification and the liver's ability to process the cortisol replacement. In this situation, even physiologic doses of cortisone may accumulate in the body and create side effects. By giving cortisol and thyroid replacement simultaneously, the body is able to effectively utilize the cortisol without side effects developing.

Once the hormone imbalance has been identified through the testing procedure described below, it is of paramount importance to initiate a hypoallergenic diet at the same time the hormone replacement program is started. The combination of daily feeding a commercial pet food, which typically has poor quality ingredients, and deregulated IgA in the digestive tract often leads to malabsorption and food allergies. The therapy program will not succeed if animals continue eating food to which they are sensitive. Within a few weeks, as animals improve on the program, pet owners can introduce different foods back into the diet one at a time, but should stay alert for signs of sensitivity to specific foods.

In the late 1970s, I wrote a series of reports in veterinary journals describing my findings and protocols.<sup>2</sup> As I uncovered these biochemical complexities in my research, I found no germane research in veterinary medicine to provide guidance. To my knowledge, the comprehensive endocrine-immune abnormality described here has not been reported elsewhere in major veterinary endocrine texts. However, many other genetic disorders among purebred pets, a result of contemporary breeding practices, have been reported.<sup>3</sup>

In the beginning, the flawed endocrine-immune mechanism appeared to be involved as an aggravating factor, that is, exacerbating allergies and sensitivities to food and parasites such as fleas. But with time, and a pro-

liferation of breed-specific animals, gene pools have become narrower and narrower. I have consistently identified this mechanism in overt life-threatening diseases like severe autoimmunity and cancer, as have other veterinarians using this approach. It appears not only to cause typical allergy problems but because of its deregulating impact on the immune system also sets the stage for killer diseases. Younger animals with the defect are developing diseases previously seen only in older animals. Moreover, it often causes not just one illness but multiple disorders.

Research and clinical outcomes clearly identify this mechanism as a major factor in the etiology of common diseases. Associated diseases and disorders include 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, vaccinosis, autoimmunity, and cancer.

The endocrine-immune derangement is not limited to purebreds. Affected purebreds have mated with mixed breeds until the mechanism is now widely established among both groups. I now find formerly breed-specific disorders appearing in other breeds as well as in mixed breeds.

While genetics appears to be the overwhelming cause of the imbalance, environmental factors such as food intolerance, poor diet, sensitivities to parasites, pollution, stress, and aging also enter into the equation.

Whatever the original cause, correction of the defect with appropriate levels of cortisone, thyroid and other hormones as needed in a long-term hormone replacement and therapy program consistently helps even severely diseased animals to live long and healthy lives.

The therapy does not cure. It funds a deficit, realigns a hormonal derangement, resets the metabolism, and restores normalcy to a dysfunctional immune system. It controls disease and supports the health of the animal for as long as the program is maintained. When pet owners stop the therapy, animals deteriorate and signs of previous illness return.

I have personally treated thousands of dogs and cats with this approach. As I write this, about two hundred other veterinarians are successfully using the program in the U.S. and elsewhere.

I have also worked with interested equine veterinarians and breeders and found a widespread endocrine-immune defect present in horses. Many common equine ailments have been corrected using the criteria

described here. In the case of horses, most respond to thyroid replacement alone, while a few require both thyroid and cortisol.

The volume of global clinical experience clearly indicates that animals who might otherwise be destined for euthanasia or a life of suffering can be effectively tested and treated. It is also clear that the endocrine-immune test described below can be used preventively to determine the presence of imbalance even in asymptomatic animals.

Though it is beyond my capacity as a clinician to explore the molecular details of this widespread yet overlooked problem, a thorough investigation into its genetic and biochemical nature is clearly warranted.

### TESTING FOR THE ENDOCRINE-IMMUNE IMBALANCE

I have developed a test that measures a critical range of hormonal and immune relationships: cortisol, total estrogen, T3, T4, IgA, IgM, and IgG, and therefore the impact of the HPA axis on the immune system. Cortisol itself, even if the value is normal, may be partially or completely bound (inactive) due to the nature of the genetic defect. Therefore, looking at the cortisol-estrogen-immunoglobulin relationship is essential. A cortisol problem likely exists if the estrogen level is high and the immunoglobulins are low.

The test is available to veterinarians through National Veterinary Diagnostic Services in Lake Forest, California. Veterinarians do not routinely utilize comprehensive tests such as these. They tend not to measure these levels and often prescribe steroids that may be too strong or not appropriate, a practice that frequently results in side effects.

Standard tests measure only one component of estrogen—estradiol. Total estrogen is a more accurate measurement because various estrogen compounds may be present in varying quantities. Estrogen can exert a dramatic blocking effect on cortisol and thyroid hormones; just a slight variation out of the normal range is enough to cause hormonal and immune complications. Elevated estrogen can bind thyroid hormone, rendering it partially or totally inactive, slowing overall metabolism, and triggering additional problems in the body. Much of the thyroid hormone in the body may in fact be inactive even if thyroid values in the test are normal.

The critical value of this test to the clinician is that it offers a comparative view of endocrine-immune relationships. A singular hormone level

found in the high normal range for one animal may be an inadequate level for another, while a low level for one animal might be too high for another. Each animal, like each human, is biochemically individual. Reading empirical levels alone without considering the relationship of one hormone to another or of one hormone to a body system is like “missing the forest for the trees,” as the old expression has it. In this case, the relationships are usually low cortisol, high estrogen, and deregulated immune cells. If the hormonal values in this test fall into the normal range, but if the animal is chronically ill and the immune cells are low, the therapy approach is the same, only the practitioner would use even less cortisone and thyroid than usual. Retesting after two weeks provides a gauge for determining the efficacy of the therapy. If the immunoglobulin values increase, and symptoms decrease, the course is correct. This is usually what happens.

Earlier, I included T cell values in the panel and found that the defect described here also suppresses T cells. However, due to the significant added cost for this measurement, I dropped T cells from the blood test panel.

More than 90 percent of the cases I treat involve neutered animals. Thus, in the case of female animals, there is no influence of ovarian estrogen, only adrenal estrogen. Among the female dogs and cats with intact ovaries, testing and therapy are conducted when animals are not in estrus and not producing a high level of ovarian estrogen.

In summary, the test reveals this cascade of pathology-causing effects:

1. **The production of insufficient or inactive cortisol in the middle layer (zona fasciculata) of the adrenal cortex.** If the cortisol is in the normal range, it may be largely bound and therefore not available for the body’s use. The presence of high estrogen and low immunoglobulins indicate that the cortisol is inactive.
2. **The presence of elevated estrogen, a result of stimulation of the inner cortical layer (zona reticularis) where adrenal estrogen is produced.** There is no relationship to cyclic ovarian production of estrogen. In about 5 percent to 7 percent of cases, the zona reticularis appears to be also defective, that is, unable to produce adequate estrogen. In this situation, the animal, in essence, has a two-layer adrenal defect. This can, and does, contribute to the sequence of reduced immune regulation.
3. **Binding of thyroid hormone.** This estrogenic effect can be ascertained by the following signs when both T3 and T4 test normal: excess sleeping; sluggishness; hyperkeratosis of the nose and pads of feet; excess pigmentation in skin of ventral abdomen; high cholesterol (not diet related); high triglycerides (not diet related); no increase in body weight; many patients are actually underweight.
4. **A major deregulation and suppression of IgA, IgM, and IgG.**

Animals are retested after two weeks and again at subsequent intervals, depending on the seriousness of the condition. Although improvements occur rapidly after a hormone replacement program is initiated, retesting serves as a yardstick to gauge progress, evaluate normalizing endocrine-immune relationships, and consider possible adjustments in medication. I use a combination of pharmaceutical and plant-based cortisone preparations for patients, depending on the severity of disease.

True genetic imbalances require life-long management. Acquired imbalances can occur as a result of stress or exposure to toxic chemicals, anesthesia, heavy metals, or pollutants. They may require only temporary management but in some cases a lifetime of replacement therapy may be needed if symptoms return after therapy is discontinued.

#### APPLICATION FOR HUMANS

Does this clinical research and therapy offer similar promise for humans? Can cancer in humans be treated this way? I find the imbalance present in *every* animal cancer case I have treat. Treatment outcomes are usually positive, even in advanced cases.

Can AIDS be treated effectively with long-term cortisone replacement? Feline immunodeficiency virus (FIV) and human immunodeficiency virus (HIV) involve similar retroviral agents. I have achieved a 70 percent success rate in treating felines with symptomatic FIV. These animals remain disease-free as long as they remain on the hormone replacement program. When a human is exposed to the HIV virus, whether or not he or she develops AIDS may depend on whether the endocrine-immune system is in balance. If the system is normal, or has been normalized through replacement therapy, the virus may be fully neutralized and rendered incapable of “causing” disease. The virus, in fact, may not cause the disease but rather overwhelms a deregulated immune system. Therefore, the immune system’s deregulation allows the disease.



Jefferies has reported in great detail on the safe and effective use of physiologic dosages of cortisone medication for a variety of human illnesses involving adrenocortical deficiency. This clinical perspective has been overlooked or dismissed by the vast majority of the medical community. In Jefferies' words, the reason 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."<sup>4</sup> This reason probably applies as well to a similar situation in veterinary medicine.

Jefferies believes that indefinite replacement with physiologic dosages of cortisone will benefit many, if not all, patients with chronic allergies and autoimmune disorders, and that replacement should not be stopped upon initial remission.<sup>5</sup> My extensive experience treating sick animals clearly indicates that this is the right course of action. In the veterinary setting, if medication is stopped, the imbalance and symptoms return.

In the human setting, I would further suggest that clinicians should test patients for the same range of hormonal-immune relationships as I do for animals. That means a blood test to measure cortisol, total estrogen, thyroid (T3/T4), and immunoglobulins. Other measurements could be added, such as T cells and perhaps other hormones, in order to develop a more precise picture of the defect's total range of impact. Patients can be retested at biweekly or monthly intervals to monitor the changing hormone and immune relationships.

In the case of female patients, the clinician will have to take ovarian estrogen status into consideration. The level of total estrogen will change depending on the stage of the woman's menstrual cycle; whether or not she is pregnant; whether she is of reproductive age, perimenopausal or menopausal, or taking an estrogen replacement. A testing method will have to be structured that accommodates these individual situations. One approach for menstruating females might be to test in mid-cycle when the ovarian estrogen level is highest and again just prior to menses when it is at the lowest level, subtract to find the difference, and use that as a basis for determining non-ovarian estrogen values. The calculated non-ovarian estrogen values could then be used for comparison with immune cell values.

In addition, the clinician might want to obtain a 24-hour urine sample from the patient in order to test for active T3, T4, and cortisol. This would be an important diagnostic tool allowing a comparison to blood values,

which may test out as normal but in fact may involve a significant percentage of bound (inactive) hormones.

The other limitation of testing blood levels alone relates to the possible presence of a sluggish metabolism. In such a situation blood levels may be higher or normal because of the retarded speed of processing within the system. Growing numbers of physicians are becoming aware that hypothyroidism may exist even though thyroid blood levels appear normal. Again, the urine test can help clarify this issue.

As in veterinary medicine, little is known regarding cortisol deficiency states in humans. Jefferies suggests that mild degrees of deficiency may be due either to primary adrenal malfunction or secondary to inadequate stimulation by the pituitary or hypothalamus. One should mention the pioneering work of Hans Selye, who demonstrated that cortisol deficiency is a clear consequence of prolonged stress and contributes to some of the "diseases of civilization."<sup>6</sup>

The role genetics plays in humans is unknown. One can only speculate that an adrenal or cortisol defect could be passed on to offspring if, both parents are affected.

If the imbalance becomes expressed in children, could perhaps the impact of deregulated IgA create widespread loss of critical immunity in mucous tissue throughout the body? The effect could possibly create one or more of the following conditions: allergies, hay fever, asthma, food sensitivities, malabsorption, or digestive tract, bladder, kidney and lung problems. Testing for the imbalance and correcting the cortisol defect, if it exists, could perhaps circumvent the development of chronic health disorders in children. Among young girls, it might be easier to determine a damaging influence from adrenal estrogen at an age before ovarian estrogen is present.

I have seen an escalating severity of conditions related to this defect in generations of animals. Is there a parallel development among humans? Can we expect to see allergies and malabsorption in one generation, and an increased potential for more serious conditions like autoimmune diseases and cancer?

These are all issues to be explored once the mechanism in humans has been identified.

## CONCLUSION

The role of cortisol as an immune regulatory agent has been grossly neglected. An unknown but probably very large percentage of sick cats and dogs produce

inadequate or bound cortisol as a result of contemporary breeding practices and, to a lesser degree, stress, aging, poor diet, and other environmental factors. The cortisol defect triggers a chain of biochemical events that results in elevated estrogen, bound thyroid hormone, and deregulation of major immune system cells. I have treated thousands of pets with a wide variety of otherwise intractable health problems by correcting this endocrine-immune abnormality with a hormone replacement program.

The program consists of physiologic doses of cortisone plus thyroid replacement in dogs, and cortisone alone in most cases for cats. Continued for the long-term over the course of an animal's life, this approach effectively controls even severe diseases and contributes to health and longevity.

A test to determine the presence of the imbalance has been described, and can serve veterinarians as an

important diagnostic tool for a potentially deadly yet overlooked cause of disease. The test also serves conscientious breeders to determine the health status of breeding stock and whether certain animals should be bred or not. The rationale here is that use of this test by breeders can help to reverse an alarming rise in genetically based pathology that threatens the survival of domesticated canines and felines.

It is my belief that a similar hormonal-immune sequence is a common, yet largely overlooked factor in human pathology and should be investigated. Jefferies has reported that physiologic dosages of cortisone can improve a number of human disorders involving an adrenocortical deficiency. His work has been largely overlooked. The experience with animals and the work of Jefferies and his followers strongly argues for exploring this area that may produce major diagnostic and treatment breakthroughs.

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