Cortisol Abnormality as a Cause of Elevated Estrogen and Immune Destabilization

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To be published in *Medical Hypotheses,* 2003

I have long regarded adrenal dysfunction as a wellspring of excess estrogen which may contribute to hormonal imbalances, immune destabilization, and increased vulnerability to disease. As a practicing clinician, I have consistently found elevated total estrogen as part of an endocrine-immune derangement present in many common diseases of dogs and cats. Ninety percent of these cases involve spayed females and neutered or intact males, so the elevated estrogen cannot be attributed to ovarian activity. Sick and intact females, tested outside their estrus period, frequently have an elevated estrogen level as well.

The pattern of derangement identified in thousands of cases over three decades involves insufficient cortisol, high estrogen, and abnormally low IgA, IgG, and IgM levels. This pattern 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 complications, autoimmunity, and cancer. Moreover, the same set of imbalances is often present as an underlying enabling mechanism in multiple illnesses.

The adrenal cortex produces a variety of vital hormones. Among them is cortisol, the primary glucocorticoid made in the middle cortex layer (zona fasciculata). Endogenous cortisol controls inflammation,[1] a function that inspired the development of cortisone drugs, pharmaceutical versions of cortisol. A profound loss of cortisol can lead to a critical state of deranged metabolism and an inability to deal with stress and infections. Cortisol exerts a discriminating regulatory effect on molecular mediators. These mediators trigger activity related to both immunity and inflammation. A normal level of cortisol seems to be required for healthy responses.[2] Cortisol deficiency may result in an unresponsive immune system, whereas too much cortisol—like too much cortisone medication—suppresses immune responses.

Adrenocorticotropic hormone (ACTH) from the pituitary stimulates cortisol production. ACTH is controlled in turn by the hypothalamic corticotropic-releasing factor (CRF) in a classical feedback loop. When cortisol blood concentrations rise to a certain level, CRF secretion slows, inhibiting ACTH and subsequent cortisol secretion.

The androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are the most abundant circulating hormones in the body. These substances, known as prohormones because they metabolize into other hormones, are primarily made in the zona reticularis of the adrenal cortex. Through enzymatic actions, they convert to androstenedione, androstenediol, testosterone, and further to the estrogen compounds estrone and estradiol.[3] Androstenedione is the most important precursor of estrone, the most abundant circulating estrogen in postmenopausal women. Androstenediol has inherent estrogenic activity. [4]

The exact biological function of adrenal androgens and the mechanisms underlying their control is still the object of debate. However, it is well known that both may have androgenic and estrogenic effects.[5]

Veterinary researchers have found numerous genetic defects resulting from contemporary linebreeding and inbreeding practices.[6] Since the 1970s I have reported a cortisol defect in cats and dogs.[7] I believe this stems largely from questionable breeding practices.

Other potential causes for cortisol deficiency include prolonged stress and toxicity, which may be a significant acquired cause of adrenal cortical dysfunction. Harvey states that the 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."[8]

When the zona fasciculata cannot make enough cortisol, or for some reason the cortisol is excessively bound

(inactive) and thus not recognized by the hypothalamus-pituitary system, the pituitary continues to release ACTH in order to stimulate more cortisol. The zona reticularis also responds to ACTH. This part of the adrenal gland, as noted above, produces androgens that can convert to the estrogen compound estrone, or to testosterone, which may then convert in part to the more potent estrogen compound estradiol.

Some researchers say that an interface or transition zone of tissue between the zona fasciculata and reticularis of the adrenal cortex is capable of directly producing sex hormones, including estrogen compounds.[9, 10] Excess estrogen promotes CRF release from the hypothalamus and ACTH from the pituitary, and contributes to hormonal imbalances and deleterious effects in the body.

Researchers working in the field of rheumatoid arthritis and autoimmune rheumatic diseases believe that hormone balance is a crucial factor in the regulation of immune and inflammatory responses. Generally, estrogen in physiologic concentrations enhances humoral immune responses and depresses cellular-mediated responses. At higher and pharmacological concentrations the hormone has a number of inhibitory actions. Elevated estrogen, for instance, is associated with atrophy of the thymus gland. Androgens, by contrast, tend to suppress both humoral and cellular types of mechanisms.[11] An examination of the endocrinology literature reveals, however, that mechanisms through which sex hormones regulate immune and inflammatory responses are poorly understood.[12]

POSSIBLE ROLES OF ADRENAL ESTROGEN

I have developed an endocrine-immune blood test that measures cortisol, total estrogen, T3 and T4, and IgA, IgG, and IgM antibody levels. The measurement for estrogen includes all estrogen compounds in the body, that is estradiol, estrone, and estriol.

The test shows a consistent link between clinical signs of various illnesses and total estrogen outside of a normal range. Intact female animals are not tested during their estrus period. In out-of-estrus females, intact males, and neutered pets, normal levels are as follows:

- Males: 20-25 pg/ml
- Females: 30-35 pg/ml

Elevated estrogen appears to contribute to a number of negative effects:

- **Cortisol impairment.** Studies have shown that estrogen inhibits cortisol synthesis by specific interference with enzyme activity,[13] thereby exacerbating a cortisol deficiency and initiating hormonal imbalances.
- **Thyroid hormone impairment.** Estrogen causes an increase in serum thyroxine-binding globulin, which may slow the entry of thyroxine into cells and thereby reduce thyroid hormone action in tissue.[14] Elevated estrogen may also directly inhibit thyroid glandular release.[15] Cortisol appears to be involved in the normal transference of T4 to T3, and the entry of T3 into cells.[16] By interfering with cortisol synthesis, estrogen may indirectly impair thyroid function. These combined effects may slow the overall metabolism and interfere with many basic physiologic functions.
- **Inflammation.** My patients' blood tests consistently show an association between inflammatory conditions and the pattern of low cortisol, high estrogen, and low antibody levels. Studies have shown that cortisol inhibits the production and accumulation of excess histamine in tissue[17] and the synthesis of prostaglandins, mediators of the inflammatory response.[18]
- **Cancer.** In humans, estrogens are involved in the development of breast and endometrial cancer.[19] All the dogs and cats I test and treat for cancer have impaired cortisol and high estrogen, along with deregulated immune cells.
- **Autoimmunity.** The same abnormal hormonal pattern is found in pets with autoimmune conditions. Immune cells are suppressed and appear to be stripped of normal regulation and the ability to distinguish between host tissue and foreign matter. Lahita has reported that recent data indicates "increased estrogen levels might initiate autoimmune diseases in many women and men."[20]
- **Aggressive behavior.** Many unpredictable and aggressive animals have the endocrine-immune disturbance. In humans, Finkelstein provides evidence suggesting "that estrogen may play a significant role in the production of aggressive behavior in both sexes."[21]

TREATMENT

I initiate corrective therapy when testing indicates the presence of imbalances. The protocol involves the use of various cortisone medications, either standard pharmaceutical compounds or a natural bio-identical preparation made from an ultra extract of soy. All

plant material—the part of soy which increases body estrogen levels—has been removed. The compound is administered at low, physiologic dosages sufficient to compensate for deficient cortisol and re-regulate the immune system. These therapeutic dosages are significantly lower than standard pharmacologic levels used for short-term treatment and are usually needed for the duration of the patient's life.

This innovative use of a standard medication consistently restores lost immune competence. Most canine conditions require additional T4 thyroid medication. For some species-specific reason, most affected felines require only steroid replacement. This treatment approach has proven to be effective, safe, and free from side effects in thousands of cases.

After two weeks of therapy, patients are retested. There is usually a clear normalization of the key endocrine-immune markers along with parallel clinical improvements, indicating that a significant healing process is underway. In general, animals recover and maintain good health as long as the program is maintained. A supportive hypoallergenic diet eliminates the risk of food reactions which can nullify the therapy.

This clinical experience demonstrates the potent regulatory influences of cortisol and estrogen in immune function. It shows, perhaps for the first time, how an adrenal combination of abnormal cortisol and high estrogen interact to substantially deregulate and weaken immunity and contribute to multiple diseases.

For decades, William Jefferies, M.D., clinical professor emeritus at the University of Virginia School of Medicine, has used low-dosage steroid replacement for human patients with "adrenocortical deficiency" and reported improvement for allergies, autoimmune disorders, and chronic fatigue.[22] The medical community has largely ignored his clinical research because of an ingrained fear of using cortisone long-term under any circumstances. A similar fear exists in veterinary medicine. At conventional pharmacologic dosages, cortisone does indeed create side effects. In the past practitioners often shuddered at any suggestion of long-term cortisone, and, as the old saying goes, "threw the baby out with the bathwater."

Recently, resistance to long-term physiologic doses of cortisone appears to be eroding. Medical researchers have reported successful applications of low-dosage cortisone in rheumatoid arthritis,[23] polymyalgia rheumatica—a systemic inflammatory disorder of the aged[24] — and sepsis.[25] However, none of these studies link specific conditions to an overall mechanism wherein an abnormality of cortisol triggers excess estrogen, HPA destabilization, interference with thyroid, and deregulation of the immune system. I believe that this pattern of hormone-immune imbalance is a widespread but largely unrecognized mechanism among pets, and may contribute to various human illnesses.

TESTING THE HYPOTHESIS IN HUMANS

The presence of such imbalances in humans could most readily be tested among symptomatic men and postmenopausal (non-ERT) women. First, a baseline blood test would be taken to measure cortisol, total estrogen, T3/T4, and IgA, IgG, and IgM antibody levels, along with a 24-hour urine test for active hormones and other relevant markers. The urine test permits the clinician to compare results against the blood test. This is an important evaluation because some blood values (such as cortisol and thyroid) may appear normal in a blood test but in fact involve excessively bound, inactive hormone fractions. Blood tests alone may not indicate whether or not the hormone is working. The urine test helps answer this question and contributes to a more accurate assessment and effective treatment.

Jefferies' clinical experience with human patients suggests that low-dosage cortisol replacement therapy could be applied to symptomatic patients who are tested and found to have the endocrine-immune imbalances described in this article. If their health status improves and retesting shows a reduction in total estrogen, one could conclude that a hypocortisol syndrome with wide systemic impact has been clinically corrected. Such a result would argue for further investigation of this testing and therapy method for various illnesses.

Even though post-menopausal women are deficient in estradiol, their estriol and estrone are often very high not only from the possible interface layer but because the tissue enzyme aromatase converts DHEA and DHEAS and other androgens into total estrogen.

Gruber states that estrogen synthesis increases in non-ovarian tissues as a function of age and body weight even though little is known about the factors that regulate estrogen production in the post-menopausal population.[26] Longcope and colleagues observed a "marked increase in the ratio of estrogens to androgens in acute illness" among postmenopausal women. Conditions included heart attack, unstable angina, respiratory illnesses, and congestive heart failure.[27] One physician with whom I have been

communicating commented that his sickest postmenopausal (non-ERT) patients have the highest total estrogen levels and the lowest immunoglobulins.[28]

Estradiol alone, and not total estrogen, is currently the standard measurement in patients, yet in postmenopausal women, estrone is the major estrogen.[29] Estriol, generally considered to be a weaker compound than estradiol and estrone, is present in significantly greater concentration in premenopausal women,[30] and may have significant though currently unidentified biological activity. I believe that total estrogen, including estrone and estriol, is a more meaningful indicator of estrogen activity than estradiol alone.

The presence of xenoestrogens and phytoestrogens, chemicals which mimic estrogen and which can potentially trigger androgen-estrogen imbalance, complicate the process of assessing serum estrogen status. Such compounds appear in the environment and in food. Ubiquitous estrogenic compounds, including industrial chemicals, pesticides, and surfactants, affect wildlife and laboratory animals' immune systems. Further studies are needed to determine the immune response in humans. These compounds may affect humans in similar ways.[31] Hence, the need to measure total estrogen.

Mesiano, demonstrated in 1999 that dietary phytoestrogen compounds found in soy decrease cortisol production and, as a result, increase androgens. Such consumption, he suggests, may indirectly increase total estrogen by raising DHEA and DHEAS levels. In his opinion it is "possible that some of the estrogenic actions of dietary phytoestrogens may be mediated via their stimulation of adrenal androgen synthesis."[32]

One way to determine the influence of dietary phytoestrogens, at least in men and postmenopausal women, would be to eliminate soy from the diet of patients who test high in total estrogen, then retest the patient again after several weeks. A clear drop in estrogen level could indicate a dietary effect. An unchanged or insignificantly changed level would indicate a source for estrogen unrelated to diet.

Xenoestrogens include birth control pills and chemicalized estrogen drugs. Can these contribute to a disturbance of cortisol and thyroid, and contribute to the disease process? It seems plausible that exogenous estrogen, or even androgen supplements (such as DHEA, which can convert to estrogen in the body) could indeed contribute to imbalances and disease.

My male patients' test results make a strong argument for hypocortisolism as a primary cause of elevated estrogen. In symptomatic males with endocrine-immune imbalances, high estrogen occurs almost exclusively as a consequence of a cortisol abnormality. The rare exception is the animal whose endocrine-immune status normalizes spontaneously without any treatment after moving to another area. I assume in such cases that a significant toxic or xenoestrogenic compound, perhaps ingested or inhaled, was present in one area and not in the other.

IMPLICATIONS FOR HUMANS

Elevated estrogen participates in a broad syndrome of hormonal-immune imbalances contributing to multiple diseases in animals. Is estrogen similarly involved in human conditions?

Is an unsuspected excess of estrogen involved in AIDS? Veterinarians regard diseased cats infected with feline immunodeficiency virus (FIV), a retrovirus similar to HIV, as untreatable. Yet I have a 70 percent recovery rate among symptomatic FIV patients. These animals have a typical pattern of low cortisol, high estrogen, and disturbed immune function. Low-dosage steroid therapy corrects the underlying imbalances and restores natural immunity. Cats remain disease-free as long as they are kept on the therapy. The results raise a number of questions.

Does the virus cause the disease or do the imbalances weaken the immune system and give the virus free rein? Do the imbalances also accelerate the disease process by deregulating the immune system so that immune cells attack both viruses and host tissue? Is it not possible that in humans cortisol-estrogen-immune status may dictate whether a person develops AIDS symptoms after being exposed to the HIV virus? My clinical experience with animals suggests that HIV-positive humans be tested for endocrine-immune imbalances. If present, appropriate hormone replacement might offer a significant prevention and therapy strategy.

All of my cancer patients have the same general pattern of endocrine-immune disturbance. Based on this experience I would suggest that human cancer patients be tested for similar imbalances. If they exist, appropriate hormone replacement therapy might offer an effective treatment strategy for humans just as it does for animals, even in advanced cases.

According to Gunin estrogen generates pro-inflammatory responses as well as proliferative

changes associated with a pre-cancerous process in the uterus. Treatment with cortisone (dexamethasone) in ovariectomized rats given estradiol reverses these abnormalities.[33]

I routinely find the combination of abnormal cortisol and elevated estrogen in animals with histories of infertility and miscarriage, suggesting that reproductive failures may be caused by inflamed and immune-deregulated reproductive tract tissue. Such failures are routinely corrected by proper hormone therapy, enabling animals to conceive and produce healthy offspring. Over decades of clinical experience, William Jefferies, an emeritus clinical professor at the University of Virginia, has reported that patients with cortisol insufficiency and histories of ovarian dysfunction, infertility, and failed pregnancies achieve significantly improved conception and birth rates on low-dosage cortisone therapy.[34]

Common variable immunodeficiency (CVID) appears to be a grossly underdiagnosed enabling mechanism for a multiplicity of disorders in humans just as it is in animals, giving rise to chronic infections, autoimmune conditions, an increased risk of cancer, and poor response to immunization. In both humans and animals, CVID is characterized by low IgA, IgG, and IgM levels and abnormal T cell counts. In humans, the precise trigger for such immune dysfunction is unknown. Researchers have not linked CVID or other so-called immunodeficiency mechanisms to hormones. I suggest that exploring this connection, and looking specifically at cortisol activity, may generate major clues for diagnosis and treatment.

My clinical success and the growing clinical applications of low-dosage cortisone therapy for humans strongly argue for sustained research into the nature, magnitude, and impact of cortisol defects, including an associated estrogen-immune problem, in the etiology of disease. While it is now recognized that the hypothalamic-pituitary-adrenal axis, as part of the neuroendocrine system, has central importance to immune homeostasis,[35] we still don't understand the countless details and interactions.

Estrogen measurements are generally assumed to be expressions of ovarian function. This seems an invalid assumption, since a deficit of active cortisol—from genetics, stress, toxicity, or phytoestrogens—can initiate a significant estrogen buildup—estrogen dominance—independent of the ovaries. Estrogen dominance not only causes inflammation of many of the arteries, but it also binds active cortisol and active thyroid, and deregulates the immune system. It can also contribute to such ailments as cancer, autoimmunity, and hypersensitivity diseases. It will contribute to loss of homeostasis, deregulated immune function, and increased risk of disease among females with or without ovaries as well as neutered or intact males. In other words, none are exempt.

In humans, routine testing for a cortisol deficit and consequential hormonal-immune abnormalities, followed by an appropriate low-dosage, remedial steroid therapy program, may provide breakthrough strategies in the perpetual battle against disease.

REFERENCES

1. Munck A., Naray-Fejes-Toth. A. Glucocorticoid action. In: *Endocrinology,* Third edition, (Ed: DeGroot L). Philadelphia: W. B. Saunders Co, 1995: 1642-1654.

2. Ibid.

3. Parker, L. N. Adrenal androgens. In: *Endocrinology,* Third edition, (Ed: DeGroot L). Philadelphia: W. B. Saunders Co, 1995: 1836-47.

4. Adams, J. B. Control of secretion and the function of C19-delta 5-steroids of the human adrenal gland. *Molecular and Cellular Endocrinology,* 1985; 41: 1-17.

5. Alesci S., Koch C. A., Bornstein S. R., Pacak K. Adrenal androgens regulation and adrenopause. *Endocrine Regulations,* 2001; 35: 95-100.

6. 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.

7. Plechner A. J., Shannon M. Canine immune complex diseases. *Modern Veterinary Practice,* 1976: 917.

8. Harvey P.W. *The Adrenal in Toxicology: Target Organ and Modulator of Toxicity,* Bristol, PA: Taylor & Francis, 1996: 7.

9. Symington T. *Functional Pathology of the Human Adrenal Gland,* Edinburgh: E & S. Livingstone, 1969: 63-68.

10. Roberts E. The importance of being dehydroepiandosterone sulfate (in the blood of primates): A longer and healthier life? *Biochemical Pharmacology,* 1999; 57: 329-346.

11. Cutolo M., Seriolo B., Villaggio B., Pizzorni C., Craviotto C., Sulli A. 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.

12. Cid, M., Schnaper H. W., Kleinman H. Estrogens and the vascular endothelium. *Annals of the New York Academy of Sciences,* June 2002; 966: 143-157.

13. Gell J.S., Oh J., Rainey W.E., Carr B.R. Effect of estradiol on DHEAS production in the human adrenocortical cell line, H295R. *Journal of the Society for the Gynecologic Investigation,* 1998; 5:144-148.

14. Arafah B.M. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *New England Journal of Medicine,* 2001; 344 (23): 1743-1749.

15. Gross H.A., Appleman M.D., Nicoloff J.T. Effect of biologically active steroids on thyroid function in man. *The Journal of Clinical Endocrinology and Metabolism,* 1971; 33: 242-248.

16. Jefferies W.McK. *Safe Uses of Cortisol,* Springfield: Charles C. Thomas Publisher, 1996: 160, 181.

17. Ibid, 106.

18. Orth D.N., Kovacs W.J. The adrenal cortex. In: *Williams Textbook of Endocrinology,* Ninth edition, (Eds: Wilson J.D., Foster D.W., Kronenberg H.M., Larsen P.R). Philadelphia: W. B. Saunders Co, 1998: 545.

19. Gruber C. J., Tschugguel W., Schneeberger C., Huber J.C. Production and actions of estrogens. *New England Journal of Medicine,* 2002; 346 (5): 340-352.

20. Lahita R.G. The connective tissue diseases and the overall influence of gender. *International Journal of Fertility and Menopausal Studies (now International Journal of Fertility and Women's Medicine),* 1996; 41 (2): 156-165.

21. Finkelstein J., Susman E.J., Chinchilli V.M., et al. Estrogen or testosterone increases self-reported aggressive behaviors in hypogonadal adolescents. *The Journal of Clinical Endocrinology and Metabolism,* 1997; 82 (8): 2433-2438.

22. Jefferies, op. cit., 91-113, 163-166.

23. Hickling P, Jacoby R.K, Kirwan J.R. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *British Journal of Rheumatology,* 1998; 37: 930-936.

24. Cutolo M., Sulli A., Pizzorni C., 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.

25. Klaitman V., Almog Y. Corticosteroids in sepsis: A new concept for an old drug. *The Israel Medical Association Journal,* 2003; 5 (1): 51-54.

26. Gruber, op. cit., 340-352.

27. Spratt D. I., Longcope C., Cox P.M., Bigos S.T., Wilbur-Welling C. Differential changes in serum concentrations of androgens and estrogens (in relation with cortisol) in postmenopausal women with acute illness. *The Journal of Clinical Endocrinology and Metabolism,* 1993; 76 (6): 1542-1547.

28. Personal communication with David Brownstein, M.D., West Bloomfield, Michigan.

29. Gruber, op cit., 340-352.

30. Wright J.V., Schliesman B., Robinson L. Comparative measurements of serum estriol, estradiol, and estrone in non-pregnant, premenopausal women: A preliminary investigation. *Alternative Medicine Review,* 1999; 4 (4): 266-270.

31. Ahmed S.A. The immune system as a potential target for environmental estrogens: a new emerging field. *Toxicology,* 2000; 7 (150): 191-206.

32. Mesiano S., Katz S. L., Lee J. Y., Jaffe R. B. Phytoestrogens alter adrenocortical function: genistein and daidzein suppress glucocorticoid and stimulate androgen production by cultured adrenal cortical cells. *The Journal of Clinical Endocrinology and Metabolism,* 1999; 84 (7): 2443-2448.

33. Gunin A.G., Sharov A.A. Proliferation, mitosis orientation, and morphogenetic changes in the uterus of mice following chronic treatment with both estrogen and glucocorticoid hormones. *The Journal of Endocrinology,* 2001; 169: 23-31.

34. Jefferies, op. cit., 67-90.

35. Cutolo M., Bulsma W. J., Lahita R.G., Masi A.T., Straub R. H., Bradlow H.L. Altered neuroendocrine immune (NEI) networks in rheumatology. *Annals of the New York Academy of Sciences,* June 2002; 966: xvii.