SARDS CASE REPORT #2

Hormone replacement in a Beagle affected with Sudden Acquired Retinal Degeneration Syndrome (SARDS)

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ABSTRACT

Objective: To describe the laboratory findings, hormone replacement therapy, and outcome of one dog affected with Sudden Acquired Retinal Degeneration Syndrome (SARDS). Animal studied: An 11-year-old neutered male Beagle diagnosed with SARDS on November 30, 2005. The client reported persistent signs of obesity, insomnia, depression, and heavy coat growth. Procedure: An endocrinology and immunology blood panel was performed four months post-SARDS diagnosis, which indicated below normal levels of cortisol, IgA, IgG, IgM; and elevated levels of total estrogen. T3 and T4 were at the low end of the normal range. Hormone replacement therapy was initiated by the dog's general-practice veterinarian. The dog received injectable Kenalog 2.15mg IM. Additionally, methylprednisolone/ Medrol 2mg po, sid; and levothyroxine 0.2mg po, bid were dispensed to the client. The endocrinology and immunology panel was repeated at one, two, four, and seven months after hormone replacement therapy was initiated. Results: Cortisol levels demonstrated a steady rise and returned to within normal limits by the fourth month. Total estrogen levels demonstrated a steady decline, returning to within normal limits by the seventh month. T3 and T4 levels rose to the mid-normal range by the seventh month. The client reported significant improvement in clinical signs of obesity, insomnia, depression, and coat growth. Ophthalmic follow-up evaluation 11 months after onset indicated limited vision return OS and verified original SARDS diagnosis. Conclusion: Treatment with low, physiological-levels of replacement glucocorticoid and thyroid hormones improved clinical signs and caused a decline in total estrogen production in this SARDS-affected dog.

Plain English Translation

Only the more complex terms and concepts have been translated so please read the column on the left first.

This paper discusses the symptoms, treatment and results of a Beagle diagnosed with SARDS. This dog had a blood test to measured adrenal hormones and immunoglobulins (immune system function). The test indicated low levels of cortisol and immunoglobulins; and high levels of adrenal estrogen. The dog was then treated with a low-dose steroid injection, and tablets of Medrol (a cortisol replacement), and thyroid hormone. The blood test was repeated four more times over the next six months. All previously abnormal hormones and immunoglobulin levels returned to normal. The owner reported significant improvement in the dog's obesity, insomnia, depression, and heavy coat; and minor improvement in vision.

KEY WORDS: sudden acquired retinal degeneration syndrome, SARDS, canine blindness, hypercortisolism, glucocorticoids, adrenal estrogen

DESCRIPTION OF THE CASE

The owner of an 11-year-old neutered male Beagle contacted the author for assistance in helping the dog adjust to blindness. The dog was diagnosed with SARDS by a certified veterinary ophthalmologist one month earlier on November 30, 2005. Electroretinogram (ERG) produced no discernable wavelength. Other findings included slow pupillary light reflex (PLR) OU and negative menace response OU. The client reported clinical signs of obesity, insomnia, depression, and heavy coat growth to the author, which developed prior to vision loss and persisted into the spring of 2006. Body weight was 38 pounds at onset compared to historical weight of 32 pounds. The client reported the dog was restless, waking three to four times per night; that training sessions had improved the dog's attitude, but the dog "still acted depressed;" and that he had developed a much thicker coat in early 2006.

The retina did not demonstrate any electrical activity at the time of blindness. The dog did not blink when the doctor quickly brought her hand up to the dog's face.

Two months after vision loss (January 31, 2006) thyroid levels were ordered by the general practice veterinarian (Antech Diagnostics, Mississippi). T4 was 1.5 ug/dL (normal range: 1.0-4.0 ug/dL) and Free T4 (EQ) was 8.0 pmol/L (normal range 8-40 pmol/L). Levothyroxine (Butler)1.2mg po, bid was dispensed to the client.

Four months after vision loss (March 27, 2006) an endocrinology and immunology blood panel (National Veterinary Diagnostic Services, California) was ordered by the general practice veterinarian. Results indicated below normal levels of cortisol, IgA, IgG, IgM; and elevated levels of total estrogen. T3 and T4 were within normal limits at the low end of normal range. (table 1) Body weight was 35.7 pounds.

Table1. Immunology and endocrinology panel #1

Hormone		3-27-06 Results	Normal range
Cortisol	ug/dL	0.52 L	1.00-2.50
Total estrogen	pg/mL	25.40 H	20.00-25.00 (males)
T3	ng/dL	113.02	100.00-200.00
T4	ug/dL	2.36	2.00-4.50
IgA	mg/dL	43 L	70-170
IgG	mg/dL	817 L	1,000-2,000
IgM	mg/dL	84 L	100-200

Glucocorticoid replacement therapy was initiated by the dog's general-practice veterinarian. The dog received injectable Kenalog (Bristol-Meyers Squibb) 2.15mg IM. Methylprednisolone/Medrol (Pharmacia UpJohn) 2mg po, sid was dispensed to the client.

The dog was given several forms of *low-dose* cortisol replacements— one by injection, one in pill form. (Injections enter the body and go to work quickly.) The dog was also given thyroid replacement hormone pills.

On April 25, 2006 (one month after glucocorticoid replacement was initiated) the endocrinology and immunology panel was repeated. Results indicated a rise in cortisol, T3, T4, IgA, IgG, and IgM levels; and a decline in total estrogen. (table 2) Body weight was 34 pounds.

Table 2. Immunology and endocrinology panel #2

Hormone		4-25-06 Results	Normal range
Cortisol	ug/dL	0.70 **L**	1.00-2.50
Total estrogen	pg/mL	25.27 **H**	20.00-25.00 (males)
T3	ng/dL	117.64	100.00-200.00
T4	ug/dL	2.61	2.00-4.50
IgA	mg/dL	50 **L**	70-170
IgG	mg/dL	967 **L**	1,000-2,000
IgM	mg/dL	98 **L**	100-200

Consecutive test results are availble in a table on page 5.

On May 30, 2006 (two months after glucocorticoid replacement was initiated) the client reported that insomnia had improved. The endocrinology and immunology panel was repeated. Results indicated a further rise in cortisol, T3, T4, IgA, IgG, and IgM levels (IgG and IgM were within normal limits); and a further decline in total estrogen. (table 3) Body weight was 34 pounds.

Over time, levels of thyroid, cortisol and immunoglobulins (IgA, IgG, IgM) rose steadily and adrenal estrogen declined, until all returned to normal.

Table 3. Immunology and endocrinology panel #3

Hormone		5-30-06 Results	Normal range
Cortisol	ug/dL	0.82 **L**	1.00-2.50
Total estrogen	pg/mL	25.13 **H**	20.00-25.00 (males)
T3	ng/dL	122.64	100.00-200.00
T4	ug/dL	2.91	2.00-4.50
IgA	mg/dL	62 **L**	70-170
IgG	mg/dL	1,077	1,000-2,000
IgM	mg/dL	103	100-200

On July 24, 2006 (four months after glucocorticoid replacement was initiated) the endocrinology and immunology panel was repeated. Results indicated a further rise in cortisol, T3, T4, IgA, IgG, and IgM levels (cortisol was within normal limits); and a further decline in total estrogen. (table 4) Body weight corresponded with pre-SARDS weight of 31.8 pounds.

Table 4. Immunology and endocrinology panel #4

Hormone		7-24-06 Results	Normal range
Cortisol	ug/dL	1.03	1.00-2.50
Total estrogen	pg/mL	25.02 **H**	20.00-25.00 (males)
T3	ng/dL	127.64	100.00-200.00
T4	ug/dL	3.18	2.00-4.50
IgA	mg/dL	69 **L**	70-170
IgG	mg/dL	1,193	1,000-2,000
IgM	mg/dL	109	100-200

On September 12, 2006 (nearly seven months after glucocorticoid replacement was initiated) the client reported a significant improvement in insomnia and depression. Episodes of waking and restlessness had declined from three to four episodes per night to once per night. The dog's "depression improved as his blood (work) improved." The client also reported an anecdotal episode in which the dog seemed to demonstrate some degree of vision: While driving with the dog, the client noted a buzzard in the road approximately 300-400 feet ahead. As the buzzard flew off, the client reported that the dog's head "lifted to follow the bird." As the bird flew over the truck, "the dog turned his head to watch it from the rear window." The endocrinology and immunology panel was repeated. Results indicated a further rise in cortisol, T3, T4, IgA, IgG, and IgM levels (IgA was within normal limits); and a further decline in total estrogen, which was also within normal limits. (table 5) Body weight was 31.1 pounds.

Table 5. Immunology and endocrinology panel #5

Hormone		9-12-06 Results	Normal range
Cortisol	ug/dL	1.16	1.00-2.50
Total estrogen	pg/mL	24.88	20.00-25.00 (males)
T3	ng/dL	129.88	100.00-200.00
T4	ug/dL	3.31	2.00-4.50
IgA	mg/dL	78	70-170
IgG	mg/dL	1,353	1,000-2,000
IgM	mg/dL	127	100-200

Consecutive results are compared in Table 6, Figure 1, and Figure 2.

On October 11, 2006 the dog was re-examined by the certified veterinary ophthalmologist. Physical examination revealed advanced retinal degeneration and attenuated blood vessels OU, a negative menace response OD, and a *positve menace response* OS. ERG findings were unchanged. The original diagnosis of SARDS was verified and amended to include "limited vision returned." The ophthalmologist reported definite, limited vision in the left eye and speculated that such limited vision may be insufficient to register on ERG.

Table 6. Comparison of blood panel results and body weight

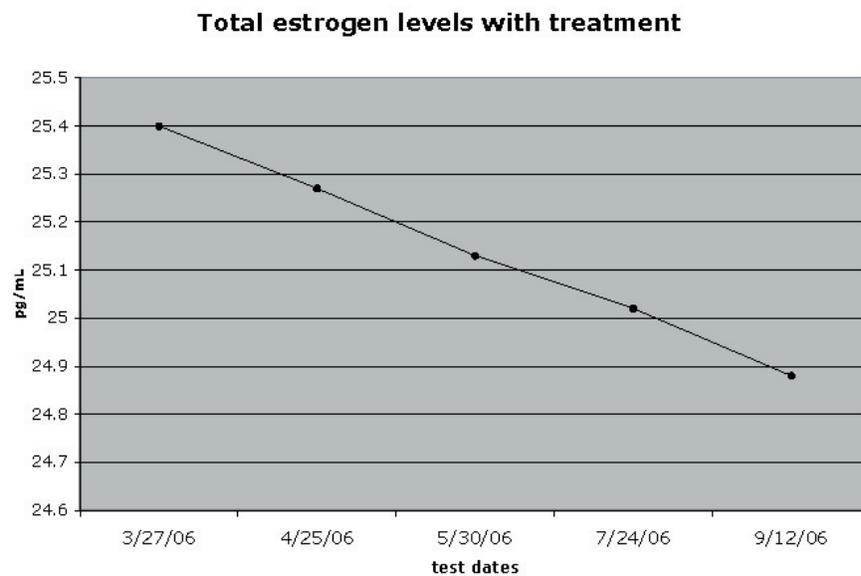|		3-27-06	4-25-06	5-30-06	7-24-06	9-12-06
Cortisol	ug/dL	0.52 L	0.70 L	0.82 L	1.03	1.16
Total estrogen	pg/mL	25.40 H	25.27 H	25.13 H	25.02 H	24.88
T3	ng/dL	113.02	117.64	122.64	127.64	129.88
T4	ug/dL	2.36	2.61	2.91	3.18	3.31
IgA	mg/dL	43 L	50 L	62 L	69 L	78
IgG	mg/dL	817 L	967 L	1,077	1,193	1,353
IgM	mg/dL	84 L	98 L	103	109	127
Weight	lbs	35.7	34	34	31.8	31.1

Figure 1.
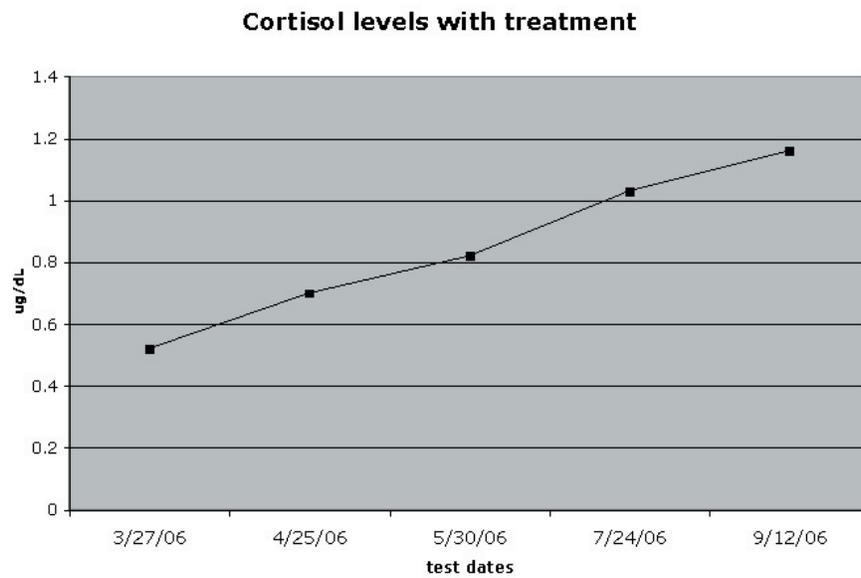
Figure 2.

DISCUSSION

Sudden Acquired Retinal Degeneration Syndrome is a rare but devastating condition characterized by acute-onset, irreversible, bilateral blindness in middle-aged dogs. Complete vision loss typically occurs between 24 hours and four weeks. Researchers describe a rapid loss of photoreceptor cell outer segments, followed by a more gradual degeneration of the remaining retina. (1,2,3) Excitotoxicity (4) and apoptosis (5) are reported as two possible causes of photoreceptor cell death in SARDS.

The vision loss of SARDS typically comes on quickly and affects both eyes.

Excitotoxicity = cells are "excited to death"

Apoptosis = a self-destruct, suicide message inside the cell

Adrenal Gland Activity Associated with SARDS

Dogs affected with SARDS routinely present with signs suggestive of Cushing's disease, or more specifically, signs of hypercortisolism close to the time of vision loss. (1,2,3,6,7) Early on, researchers speculated that hypercortisolism associated with SARDS was the physiological response to some unidentified stress. (7) Only a minority of these dogs are actually diagnosed with Cushing's disease, however. (2,8) Dogs affected with SARDS also demonstrate elevated levels of adrenal sex hormones (androstendione, estradiol, progesterone, 17-OH progesterone, and testosterone) within the first year of blindness. (9,10) One explanation for this pattern of events is Selye's model of stress adaptation, which describes the progression from adrenal gland hyperactivity (hypercortisolism) to adrenal gland exhaustion (cortisol insufficiency). In Selye's model, adrenal activity is marked by three stages: alarm, resistance, and exhaustion. (11)

Many dogs with SARDS also have symptoms of excess cortisol (hunger, thirst, elevated liver enzymes, weight gain, confusion, depression, insomnia, panting, infections, etc.) but few are actually diagnosed with Cushing's disease. In addition, dogs with SARDS develop excess levels of adrenal sex hormones sometime within the first year of blindness. One explanation for this pattern is the stress model developed by Hans Selye MD, the father of endocrinology. He describes the transition from a period of high cortisol production to a period of low cortisol called adrenal exhaustion.

The Alarm Phase of Stress Adaptation (normal stress response)

During the alarm phase the body responds to both physical and psychological stressors with increased adrenocortical activity. Hypothalamic-pituitary-adrenal (HPA) activity and the resulting cortisol secretion normally return to baseline levels when the stressor is resolved.

When the body is stressed or irritated, the brain (the **h**ypothalamus) signals the **p**ituitary gland to release ACTH. This hormone signals the **a**drenal glands to increase cortisol production. (This group of glands/organs is called the HPA axis.) When the stressor stops, so does this chain of events. The brain recognizes that there is sufficient cortisol in the bloodstream. This signals the pituitary gland to reduce ACTH production and cortisol production returns to normal.

The Resistance Phase of Stress Adaptation

The resistance phase occurs following a prolonged period of stress. Elevated cortisol production continues but falls to a level *only slightly above* normal. Prolonged exposure to elevated cortisol results in loss of hypothalamic sensitivity. Cortisol production continues unabated. (12) Researchers involved in the neuroendocrine theory of aging have also described it as adrenal maladaptation or hyperadaptosis and consider it to be a precursor of Cushing's disease. (13,14) This may explain why some SARDS-affected dogs eventually test positive for Cushing's disease.

During the resistance phase, adrenal activity adapts to chronic stressors by initiating a preferential pathway of steroidgenesis. Levels of precursors (pregnenolone, progesterone, and 17-OH progesterone) decline as they are consumed by continuous cortisol production. Sex hormone production is also sacrificed in preference for cortisol production. This scenario is referred to as the "pregnenolone steal." (15,16) (figure 3)

However, if the stressor is non-stop, cortisol is constantly secreted. The brain becomes numb to it and never signals the adrenal gland to relax. The adrenal gland becomes stuck in overdrive.

The adrenal gland adapts to chronic stress by rerouting normal hormone production to meet the high demand for cortisol. So, during the resistance phase, cortisol production is high and progesterone and estrogen are low. This is an important point: *the production and flow of adrenal hormones is flexible and adaptable*.

Figure 3.

Steroid Biosynthesis During Resistance Phase

Understanding these charts:

Large, bold text indicates hormones that are being produced in excess.

Bold arrows indicate the pathway where the most activity is occurring.

Small or broken arrows indicate a reduction in hormone production.
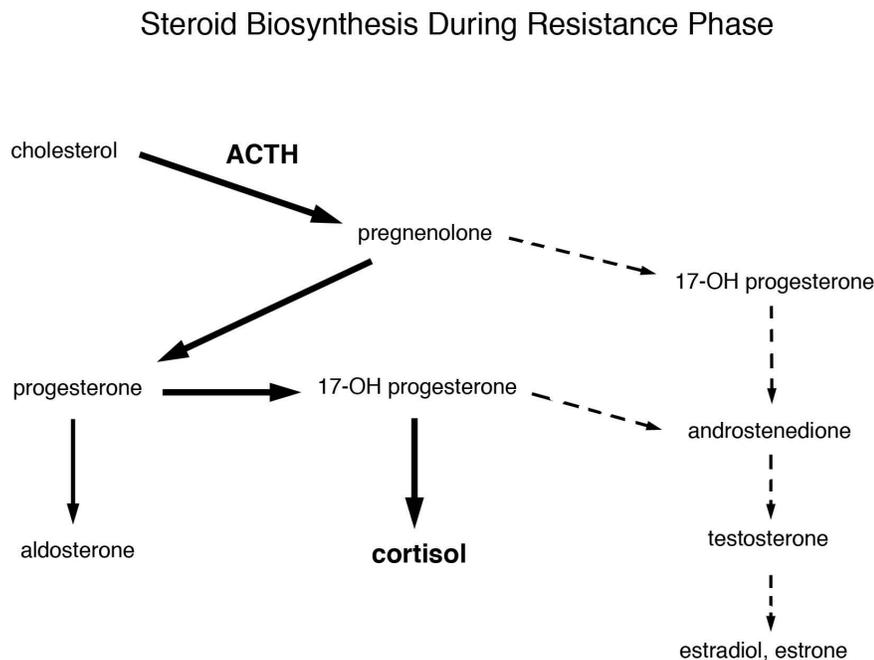
The Exhaustion Phase of Stress Adaptation

In the final phase of the general adaptation syndrome—exhaustion—the adrenal glands can no longer sustain elevated cortisol production. Both humans and dogs passing into this stage typically present with declining levels of serum cortisol and thyroid hormones (T3 and T4) and rising levels of total estrogen. (17,18) Hyperestrogenism produces effects similar to hypercortisolism including: fatigue, depression, irritability, seizures, hyperpigmentation, in humans (19,20,21,22); aggression, renal disease, and bone marrow depression in dogs (23,24,25); and hepatic dysfunction, histamine release, thyroid binding and immunoglobulin suppression in both species. (18,21,23,25,26)

Adrenal estrogen production is dependent on hormone precursors such as progestagens (progesterone, 17-OH progesterone) and androgens (androstendione, testosterone), which may also be elevated. (figure 4) Elevated progestagen levels impair glucose tolerance, increase core body temperature, and stimulate appetite and weight gain in humans (27,28) Elevated androgen levels result in acne, central obesity, and alterations in hair growth patterns. (20)

Figure 4.

Steroid Biosynthesis During Adreno-cortical Exhaustion Phase
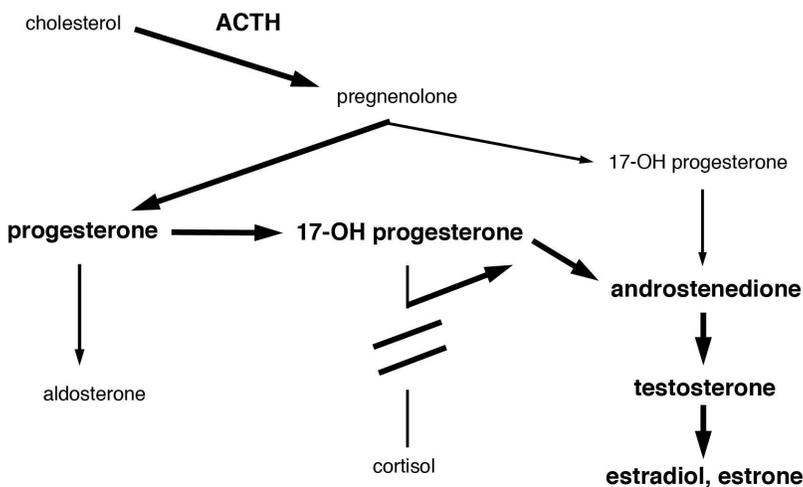
Glucocorticoid replacement is reported to normalize excess adrenal estrogen production in both dogs and humans. (17,18)

When the adrenal glands can no longer produce cortisol, they produce another, somewhat similar hormone instead—adrenal estrogen. *The symptoms of adrenal estrogen closely resemble the symptoms of excess cortisol.*

Hyperpigmentation = darkening skin
Thromboembolism = blood clots
Hypertension = high blood pressure resulting in kidney damage
Renal disease = kidney disease
Bone marrow depression = failure of the immune system, low levels of immunoglobulin (IgA, IgM, IgG)
Hepatic dysfunction = liver disease, elevated liver enzymes
Histamine release = stuffy nose, itchy eyes, increased allergies
Thyroid binding = thyroid hormone is "bound up" and cannot function

Elevated progesterones and androgens—the precursors of estrogen—cause weight gain, heat intolerance (panting) appetite increase, thick coats, acne (small flesh-colored bumps), bilateral bald patches, and obesity.

When the adrenal glands could no longer produce cortisol (they were exhausted) the adrenal gland activity "spilled over" into the adjacent hormone pathway. This resulted in elevated levels of adrenal estrogen. *When one path is blocked, hormone activity was rerouted down another pathway.* A good analogy would be boating down a river. If a dam was built across the river, the water would back up and you would have to steer your boat down a different branch of the river to continue on your trip.

The dog discussed here demonstrated several of these patterns. Similar to other SARDS-affected dogs, this dog experienced elevated adrenal sex hormone levels within the first year of blindness. Prior to treatment this dog demonstrated below normal levels of cortisol and in conjunction with elevated estrogen as described in Selye's model of adrenal exhaustion. This dog experienced suppressed immunoglobulin levels, which are also indicative of hyperestrogenism and adrenal exhaustion.

As cortisol production waned, adrenal activity "spilled over" into the adjacent pathway causing a rise in sex hormone production. (figure 4) While only estrogen levels (estradiol and estrone) were assayed, this dog also exhibited clinical signs of elevations in other adrenal sex hormones, specifically, the androgens (alterations in coat growth and obesity). These results suggest that adrenal exhaustion (cortisol depletion) had developed within four months of vision loss.

Additionally, as reported in other dogs and humans, this dog's elevated estrogen levels returned to normal following oral replacement of glucocorticoid and thyroid hormones. Reestablishment of normal glucocorticoid levels is suspected to interrupt chronic ACTH stimulation (17,18) and curtail the "spill-over" effect.

When cortisol levels were returned to normal with medication (Medrol and injections) the brain realized this and stopped sending the chronic message (*"Make cortisol!"*) to the adrenal glands. The adrenal glands relaxed. They stopped their over-activity, which was only producing excess estrogen. This reduced the "spill over" and adrenal estrogen levels returned to normal.

Apoptosis / Programmed Cell Death

Cellular mitochondria play a key role in apoptosis. Factors such as viral infections, pro-oxidants, neurotoxins, ishchemia, and hormone levels trigger apoptosis and damage mitochondrial membranes. This is known as the premitochondrial phase of apoptosis. Membrane damage induces cellular changes such as increased calcium levels and antioxidant depletion, resulting in loss of mitochondrial membrane function. This is referred to as the mitochondrial phase. During the final phase of apoptosis (the postmitochondrial phase) caspases and other apoptosis-inducing factors are released, degrading cellular components. (30)

The process of apoptosis includes many steps, but very simply put, tiny organs inside each cell (the mitochondria) are destroyed. Once these are destroyed, enzymes break down the the rest of the cell.

The plasma membrane of photoreceptor cells contains gated ion channels, which control the influx of calcium ions ($Ca2+$) into the cells. In photoreceptor outer segments $Ca2+$ controls light adaptation. In photoreceptor inner segments $Ca2+$ regulates cell metabolism, glutamate release, gene expression, and cell death. (31) In pathological conditions of cellular overload, especially in conjunction with oxidative stress, mitochondrial $Ca2+$ uptake triggers collapse of mitochondrial membrane potential and delayed cell death. (32)

Calcium passes through retinal cells and helps produce vision. When too much calcium enters the retinal cells it can destroy the mitochondria and initiate apoptosis or cell death.

Apoptosis is a common final pathway in multiple retinal disorders including glaucoma. It is also prevalent in other systems such as the central nervous system (CNS) and immune system. Apoptosis is modulated in these systems by glucocorticoids and sex hormones. Glucocorticoid excess is reported to cause apoptosis in thymus and T-cells of mice, cells of the brain and CNS. (33,34) Glucocorticoid excess induces intracellular calcium overload and excitotoxicity. (35) The retina has many steroid receptors resulting in steroid accumulation in the retina. (36)

Both excess cortisol and excess estrogen (both steroids) allow more calcium than normal to pass into cells. These steroids can accumulate in the retina over time and can trigger cell death.

Adrenal sex hormones (estrogen and progesterone) oppose glucocorticoid-induced apoptosis by providing neuroprotection in some systems. Systemic administration of estradiol has been shown to protect rat retinas from photoreceptor degeneration. (37) Estrogen rapidly modulates intracellular signaling pathways by activating protein kinase C in certain cell types. This enzyme plays a key role in regulating apoptosis. (38) Sudden withdrawal of estrogen levels (estrogen deficiency) leads to increased apoptosis in brain tissue of chicks. (39) On the other hand, accumulation of *excessive* estrogen may also contribute to apoptosis. (36)

When these hormones are lower than normal, *or* much higher than normal, it may set the stage for apoptosis.

The role of progesterone as an anti-apoptotic agent is also unclear. This may be influenced by which specific genes are responsible for apoptosis in specific systems. (40) Sudden withdrawal of progesterone increases excitoxicity and apoptosis in brain tissue of mice (41) but has no anti-apoptotic effect in rat neural retinal tissue. (42)

An Endocrine Model of SARDS

To date, SARDS has generally been addressed as a retinal pathology, however increasing evidence suggests that sudden retinal degeneration is one clinical sign of broader adrenal gland dysfunction. The author proposes the following model to describe the clinical course of SARDS-affected dogs and potential, therapeutic interventions.

Stage I of SARDS: Hormone-induced photoreceptor apoptosis

At the onset of blindness, SARDS-affected dogs clinically demonstrate the resistance phase of the stress adaptation response. Cortisol levels are only *slightly* elevated during the resistance phase, (11) which is sufficient to cause signs of hypercortisolism but typically insufficient for a positive Cushing's diagnoses.

Elevated steroids (cortisol and estrogen) increase intracellular Ca2+, which upregulate cell death in photoreceptor cells. (31) The author submits that this period of elevated cortisol and estrogen levels may trigger excitotoxicity and initiate apoptosis in SARDS.

Stage II of SARDS: Advanced adrenal disease

SARDS-affected dogs can develop at least two distinct adrenal-related pathologies: Cushing's disease and adrenal exhaustion. These conditions arise from the prolonged demand for cortisol production during the resistance phase of stress adaptation.

Approximately 20% of SARDS-affected dogs will ultimately develop Cushing's disease. Researchers implicate chronic activation of the HPA axis in hyperadaptosis, the precursor phase of Cushing's disease. (13)

Another portion of SARDS-affected dogs will develop adrenal exhaustion as demonstrated by rising adrenal sex hormone activity and declining cortisol production. (9,45) Elevations in sex hormones result in the persistent complaints from clients. Hyperestrogenism produces fatigue, depression, and seizures in humans (19,20,21,22); aggression, renal disease, and bone marrow depression in dogs (23,24,25); and hepatic dysfunction, histamine release, thyroid binding and immunoglobulin suppression in both species. (18,21,23,25,26) Elevated progestagen levels impair glucose tolerance, increase core body temperature, and stimulate appetite and weight gain in humans. (27,28) Elevated androgen levels result in acne, central obesity, and alterations in hair growth patterns. (29)

When clinical signs of hyperestrogenism are present in conjunction with normal cortisol values, a diagnosis of atypical Cushing's disease is sometimes made. (46) The author suggests that the terms atypical Cushing's, hyperestrogenism, and adrenal exhaustion may all describe a similar state.

SARDS-affected dogs are frequently dismissed as "otherwise healthy." The author submits that this may not be an accurate assessment of these dogs if they routinely develop adrenal exhaustion (cortisol insufficiency) and hyperestrogenism. Elevated adrenal sex hormone activity can cause poor quality of life issues, which in turn, may cause the client to needlessly euthanize the dog.

When dogs first go blind from SARDS they appear to be moving from the resistance phase of the stress response into the exhaustion phase: cortisol production may remain elevated for a period, but will begin to decline. This will be accompanied by rising estrogen. This scenario of hormone imbalance may trigger retinal cell death.

In time, some SARD dogs will develop Cushing's disease and another portion will develop adrenal exhaustion.

The longer an individual produces excess cortisol, the greater the chances of developing Cushing's disease. Dogs diagnosed with "borderline" Cushing's may be at a greater risk of developing SARDS.

In the months that follow blindness hormone levels may reverse. Cortisol drops too low and estrogen and the other sex hormones rise too high. The sex hormones can mimic many of the same symptoms caused by excess cortisol.

Atypical = *non*-typical. In this case, having the symptoms of Cushing's disease but having a negative Cushing's test (no Cushing's tumor).

In the author's opinion dogs with SARDS are *not* otherwise healthy and their adrenal hormones should be periodically tested to prevent and protect these dogs from the damaging effects of excess estrogen, which include liver degeneration, kidney failure, and cancer growth.

RECOMMENDATIONS

The dogs described in this and the author's previous case-report showed improvement from low-level glucocorticoid and thyroid hormone replacement during adrenal exhaustion. (45) Benefits were evident in both clinical signs and laboratory values. This case also suggests that visual acuity may improve when adrenal hormone levels are promptly returned to normal. Clients with SARDS-affected dogs should be encouraged to pursue estrogen/ adrenal sex hormone testing and glucocorticoid/thyroid hormone replacement therapy for adrenal exhaustion, if indicated.

Future research should include consecutive measurements of adrenal sex hormone activity, including testing *at the onset* of blindness and continuing for a period of up to a year or more. Such data would provide a more comprehensive picture of adrenal activity in SARDS-affected dogs. Slightly elevated cortisol production at the time of vision loss (as compared to subsequent readings) would suggest the resistance phase of the stress adaptation response. (28,29) Such a scenario would further implicate chronic stress for its involvement in SARDS.

This paper supports previous studies, which have implicated excitotoxicity, (4) apoptosis, (5) the stress response (7,44,45) and adrenal dysfunction (9) for their involvement in SARDS.

If dogs with SARDS were to have their adrenal hormones tested at the time of blindness, and the pattern was indicative of the resistance phase, it would further support the thesis that SARDS occurs during a prolonged period of stress. The author's previous research on this topic suggests that this stress is physical in nature (physical irritation) stemming from the modern-day diet, pesticide exposure, and over vaccination.

REFERENCES

1. Acland GM, Irby NL, Aguirre GD, Gross S, Nitray SF, Notarfrancesco K. Sudden acquired retinal degeneration in the dog: clinical and morphologic characterizations of the "silent retina" syndrome. *15th Annual Meeting of the College of Veterinary Ophthalmologists* 1984; **15**: 86-104.

2. van der Woerdt A, Nasisse MP, Davidson MG. Sudden Acquired Retinal Degeneration in the dog: clinical findings in 36 cases. *Progress in Comparative Ophthalmology* 1991; **1**: 11-18.

3. Vainisi SJ, Schmidt, GM, West CS, Anderson R, Herrmann H, Ketring K, Font RL. Metabolic toxic retinopathy preliminary report. *14th Annual Meeting of the College of Veterinary Ophthalmologists* 1983; **14:** 76-81.

4. Abrams KL, Dreyer EB, Riis R. Sudden Acquired Retinal Degeneration Syndrome. *Proceedings of the Twenty-Sixth Annual Meeting of the College of Veterinary Ophthalmologists, September 15-21, 1995: General Session.* 39.

5. Miller PE, Galbreath EJ, Kehren JC, Steinberg H, Dubielzig RR. Photoreceptor cell death by apoptosis in dogs with sudden acquired retinal degeneration syndrome (abstract). *American Journal of Veterinary Research* 1998; **59:** 149-152.

6. Abrams KL, Gareen LF, Marchand KN. Factors associated with canine Sudden Acquired Retinal Degeneration Syndrome (SARDS): 350 cases (abstract). *32nd Annual Meeting of the College of Veterinary Ophthalmologists* 2001; **32**: 11.

7. Acland GM, Aguirre GD. Sudden Acquired Retinal Degeneration: clinical signs and diagnosis. *17th Annual Meeting of the College of Veterinary Ophthalmologists* 1986; **17**: 58-63.

8. Holt E, Feldman EC, Buyukmihci NC. The prevalence of hyperadrenocorticism (Cushing's syndrome) in dogs with sudden acquired retinal degeneration (SARD) (abstract). *30th Annual Meeting of the College of Veterinary Ophthalmologists* 1999; **30**: 35.

9. Carter RT, Bentley E, Oliver JW, Miller PE, Herring IP. Elevations in Adrenal Sex Hormones in Canine Sudden Acquired Retinal Degeneration Syndrome (SARDS) (abstract). *34th Annual Meeting of the College of Veterinary Ophthalmologists* 2003; **34**: 40.

10. Personal correspondence with E. Bentley DVM, June 3, 2005.

11. Selye H. *The Stress of Life* revised edition. McGraw-Hill, Incorporated: New York, 1976.

12. Young EA, Vasquez D. Hypercortisolemia, hippocampal glucocorticoid receptors, and fast feedback (abstract). *Molecular Psychiatry* 1996; **1**: 149-159.

13. Dilman VM, Dean W. *The Neuroendocrine Theory of Aging and Degenerative Disease*. The Center for Bio-Gerontology: Pensacola, 1992.

14. Personal correspondence with W. Dean MD, November 8, 2004.

15. Parker LN, Levin ER, Lifrak ET. Evidence for adrenocortical adaptation to severe illness (abstract). *Journal of Clinical Endocrinology and Metabolism* 1985; **60**: 947-952.

16. Goncharova ND, Goncharov NP. Adrenal cortical function in chronic disease (abstract). *Problemy Endokrinologii* 1988; **34**: 27-31.

17. Jeffries MK. *Safe Uses of Cortisol* third edition. Charles C. Thomas Publisher, Ltd, Springfield, 2004.

18. Plechner AJ. Cortisol abnormality as a cause of elevated estrogen and immune destabilization: Insights for human medicine from a veterinary perspective. *Medical Hypothesis* 2004; **62**: 575-581.

19. Bush TL. The adverse effects of hormonal therapy (abstract). *Cardiology Clinics* 1986; **4**: 145-152.

20. Bagshaw S. The combined oral contraceptive. Risks and adverse effects in perspective (abstract). *Drug Safety* 1995; **12**: 91-96.

21. Rossi GV. Side-effects and possible complications of oral contraceptive drugs (abstract). *American Journal of Pharmacology* 1966, **138**: 127-136.

22. Foldvary-Schaefer N, Harden C, Herzog A, Falcone T. Hormones and seizures (abstract). *Cleveland Clinical Journal of Medicine* 2004; **71**: 11S-18S.

23. Hart JE. Endocrine pathology of estrogens: species differences (abstract). *Pharmacology Therapeutics* 1990; **47**: 203-218.

24. Zayed I, van Esch E, McConnell RF. Systemic and histopathologic changes in beagle dogs after chronic daily oral administration of synthetic (ethinyl estradiol) or natural (estradiol) estrogens, with special reference to the kidney and thyroid (abstract). *Toxicologic Pathology* 1998; **26**: 730-741.

25. Terral C, Godard P, Michel FB, Macabies J. Influences of estrogens on histamines liberation by whole blood induced by allergens in vitro (abstract). *Comptes Rendus des Seances de la Societe de Biologie et de ses Filiales* 1981; **175**: 247-252.

26. Blum M, Zacharovich D, Pery J, Kitai E. Lowering effect of estrogen replacement treatment on immunoglobulins in menopausal women (abstract). *Revue française degynecologie et d'obstetrique* 1990; **4**: 207-209.

27. Rogers SM, Baker MA. Thermoregulation during exercise in women who are taking oral contraceptives (abstract). *European Journal of Applied Physiology and Occupational Physiology* 2004; **75:** 34-38.

28. Landau RL, Poulos JT. The metabolic influence of progestins (abstract). *Advances in Metabolic Disorders* 1971; **5:** 119-147.

29. Derman RJ. Effects of sex steroids on women's health: implications for practitioners (abstract). *American Journal of Medicine* 1995; **1A:** 137S-143S.

30. Reme CE, Grimm C, Hafezi F, Wenzel A, Williams TP. Apoptosis in the Retina: The Silent Death of Vision. *News in Physiological Sciences* 2000; **15:** 120-124.

31. Krizaj D, Copenhagen DR. Calcium regulation in photoreceptors (abstract). *Frontiers in Bioscience* 2002; **7:** 2023-2044.

32. Duchen MR. Mitochondria and calcium: from signaling to cell death (abstract). *The Journal of Physiology* 2000; **529**: 57-68.

33. McMurray RW, Wilson JG, Bigler L, Lianbin X, Lagoo A. Progesterone inhibits glucocorticoid-induced murine thymocyte apoptosis (abstract). *International Journal of Immunopharmacology* 2000; **22:** 955-965.

34. Kiess W, Gallaher B. Hormonal control of programmed cell death/apoptosis. *European Journal of Endocrinology* 1998; **138:** 482-491.

35. McConkey DJ, Nicotera P, Hartzell P, Bellomo G, Wylie AH, Orrnius S. Glucocorticoids activate a suicide process in thymocytes through an elevation of cytostolic Ca2+ concentration (abstract). *Archives of Biochemistry and Biophysics* 1989; **269:** 365-370.

36. Guarneri P, Cascio C, Russo D, D'Agostino S, Drago G, Galizzi G, De Leo G, Piccoli P, Guarneri M, Guarneri R. Neurosteroids in the Retina (abstract). *Annals of the New York Academy of Science* 2003; **1007:** 117-128.

37. Xiaorui YU, Rjala RV, McGinnis JF, Feng LI, Anderson RE, Xiarong Y, Sheng LI, Elias RV, Knapp RR, Xiaohong Z, Wei C. Involvement of insulin/phosphoinositide 3-kinase/akt signal pathway in 17-estradiaol-mediated neuroprotection (abstract). *The Journal of Biological Chemistry* 2004; **13:** 13086-13094.

38. Cordey M, Gundimeda U, Gopalakrishna R, Pike CJ. Estrogen activates protein kinase C in neurons: role in neuroprotection (abstract). *Journal of Neurochemistry* 2003; **84:** 1340-1350.

39. Monroe DG, Berger RR, Sanders MM. Tissue-Protective Effects of Estrogen Involve Regulation of Caspase Gene Expression (abstract). *Molecular Endocrinology* 2002; **6:** 1322-1331.

40. Yao XL, Liu J, Lee E, Ling GS, McCabe JT. Progesterone differentially regulates pro- and anti-apoptotic gene expression in cerebral cortex following traumatic brain injury in rats (abstract). *Journal of Neurotrauma* 2005; **6:** 656-668.

41. Cutler SM, Pettus EH, Hoffman SW, Stein DG. Tapered progesterone withdrawal enhances behavioral and molecular recovery after traumatic brain injury (abstract). *Experimental Neurology* 2005; **194:** 423-429.

42. Kaldi I, Berta A. Progesterone administration fails to protect albino male rats against photostress-induced retinal degeneration (abstract). European Journal of Ophthalmology 2004; **4:** 306-314.

43. Kaja S, Shao-Hua Y, Jiao W, Fujitani K, Ran L, Brun-Zinkernagel AM, Simpkins JW, Inokuchi K, Koulen P. Estrogen protects the inner retina from apoptosis and ischemia-induced loss of Vesl-1L/Hoer 1c immunoreactive synaptic connections (abstract). *Investigative Ophthalmology and Visual Science* 2003; 7: 3155-3162.

44. Levin C. Environmental factors and signs of hypercortisolism associated with Sudden Acquired Retinal Degeneration in dogs. *Journal of the American Holistic Veterinary Medical Association* 2006; **4**: 11-19.

45. Levin C. Hormone replacement therapy in a dog affected with Sudden Acquired Retinal Degeneration (SARD) in *Dogs, Diet, and Disease: An Owner's Guide to Diabetes Mellitus, Pancreatitis, Cushing's Disease, and More* (2005 printing). Lantern Publications: Oregon City, OR, 2001.

46. Ristic JM, Ramsey IK, Heath EM, Evans HJ, Herrtage ME. The use of 17-hydroxyprogesterone in the diagnosis of canine hyperadrenocorticism (abstract). *Journal of Veterinary Internal Medicine* 2002; **16**: 433-439.