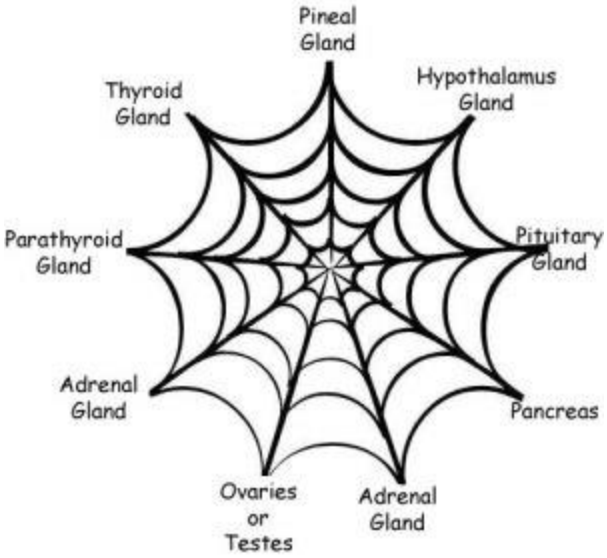
HORMONES AND THE ENDOCRINE SYSTEM



The adrenal glands produce hormones that are directly or indirectly involved in most major bodily functions. After spay/neuter, the adrenal glands must take on the additional burden of producing sex hormones to compensate for the loss of the reproductive organs. Dogs whose adrenal glands are overwhelmed by the additional requirements and cannot maintain hormonal balance may experience problems with the nervous and immune systems, body composition difficulties, blood sugar irregularities, and high or low androgen levels. The mechanism by which all of this damage occurs has not been specifically identified, however we believe an examination of the "stress response system" provides a plausible explanation for the behavioral, metabolic and orthopedic issues. This page provides specificity for the metabolic issues that spay/neuter has been shown to create. It is not a simple task to predict which of these problems will surface in any one dog, and it is not a simple task to provide hormone replacement to resolve the imbalances, as the hormone systems are a complex web of interdependent actions with feedback mechanisms to regulate these actions.

UC Davis has only recently produced peer reviewed studies which confirm:

- spay/neuter can interfere with orthopedic development [60,61]
- spay/neuter can render dogs more susceptible to behavior problems [55]
- spay/neuter can damage the immune system resulting in increased incidence of various cancers [60,61]

The 2013 UC Davis study [60] states:

"Because [spaying and] neutering can be expected to disrupt the normal physiologic developmental role of gonadal hormones on multiple organ systems, one can envision disease syndromes…to possibly be affected by [spaying and] neutering as a function of gender and the age at which [spaying and] neutering is performed."*

**Note: in this study the term "neuter" refers to both spaying of females and neutering of males*

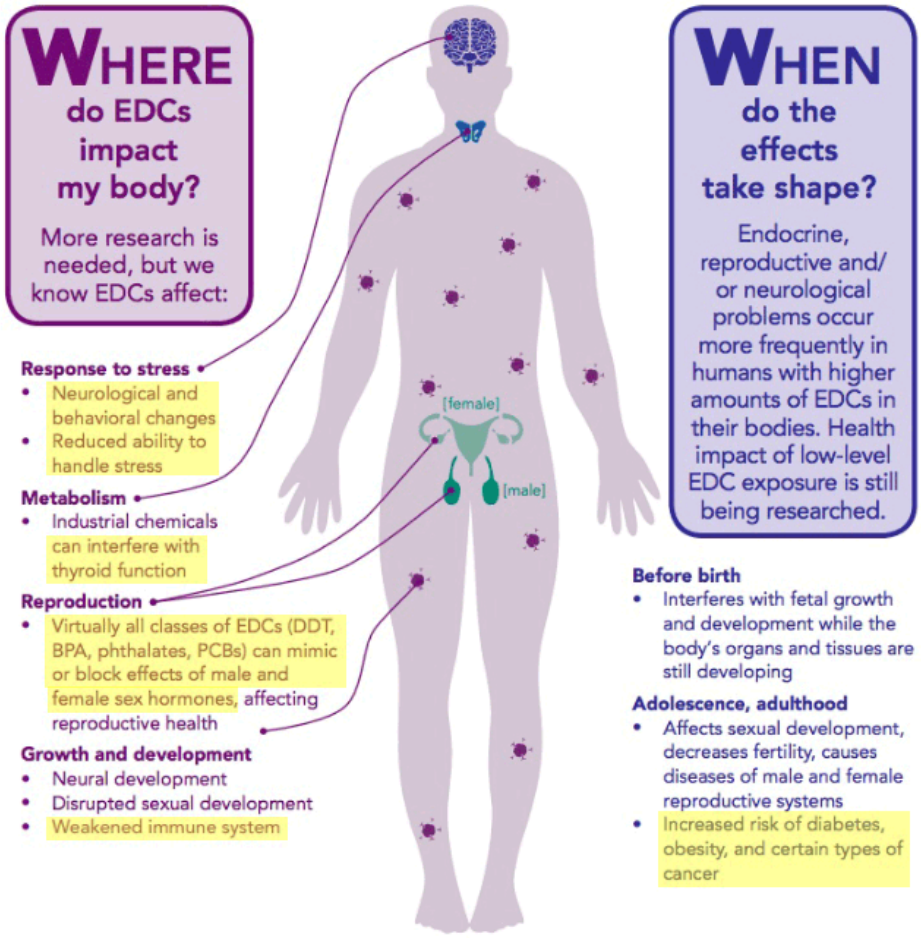
About the time UC Davis was acknowledging the possibility of disease syndromes related to spay/neuter, our dog Billy was struggling to survive the effects of an as yet unrecognized endocrine disease syndrome caused by spay/neuter. These diseases include:

- hypothyroidism
- Cushings disease/syndrome
- Atypical Cushings disease
- hyperestrinism
- diabetes

Billy developed four of the five aforementioned diseases and was tested multiple times for the fifth. None of the veterinarians we consulted (and there were many) could explain why Billy was so sick. To further complicate matters, even though Billy's symptoms were completely consistent with a diagnosis of type 2 diabetes, every veterinarian we consulted advised us that dogs do not develop type 2 diabetes. There was no indication in the veterinary literature that there were any proactive studies underway to determine how or why these five diseases were emerging, and certainly the concept of treatment for these diseases (excepting hypothyroidism) left little hope for cures or even quality of life.

As Billy's health deteriorated, we concluded the odds of Billy contracting 4 of the 5 diseases independently were tiny. We looked for a common denominator for the five diseases and concluded it must be hormonal, i.e. disruption of the endocrine system. Because Billy had 6 times the normal amount of estradiol for a male dog and NO testosterone, the

idea that neutering caused all of his hormone imbalances was not a quantum leap. We found a close correlation between what Billy was experiencing and studies on both humans and wildlife on the effects of exposure to a class of chemicals termed endocrine disruptors (EDs) – also described in the literature as endocrine disrupting chemicals (EDCs). The red flag that caught our attention was the fact that EDs studied in nature often "chemically castrate" their male victims, producing the same symptoms as Billy's "physical castration" (i.e., neutering). Endocrine disruptors that are familiar to most people include:



- DDT
- BPA
- dioxin
- PCBs
- atrazine/herbicides
- cadmium
- lead
- triclosan
- phthalates
- arsenic

EDs can act in a number of ways in different parts of the body. They perform one or more of the following biologic actions:

- reduce the production of hormones in endocrine glands
- affect the release of hormones from endocrine glands
- copy or counteract the action of hormones at target tissues
- speed up the metabolism of hormones and so reduce their action

Spay/neuter, by removing the endocrine glands associated with sex hormones (testes and ovaries), eliminates the production (#1 above) and release (#2 above) of sex hormones from the testes or ovaries. Conclusion: **Spay/neuter functions as a very efficient endocrine disruptor**.

Impact of EDs/EDCs

As stated in the diagram above, *"Virtually all classes of EDs can mimic or block effects of male and female sex hormones"* (see: Hormone Health Network website). When we compare the effects of spay/neuter with the effects of EDs/EDCs in the graphic above, the high level of correlation serves to confirm our hypothesis that:

*Spay/neuter affects a dog's organ systems in a similar manner as exposure to most EDs/EDCs (e.g., DDT, phthalates, BPA, PCBs). This is critically important because despite the recent emergence of studies that are connecting spay/neuter to orthopedic problems, behavior problems and cancer, the veterinary community is **still** defending spay/neuter as a procedure that is **beneficial** for our dogs.*

The effects of EDs/EDCs (highlighted in yellow in the above diagram) and the effects of spay/neuter that show a high degree of correlation would be:

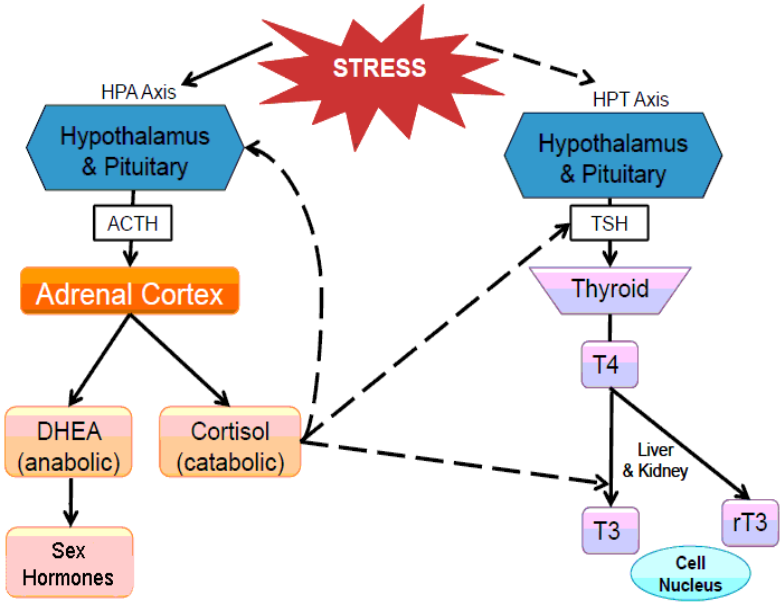
ED/EDC Disease Related Symptoms	Spay/Neuter Correlating Impairment
Neurological changes*	**Increased cognitive impairment**
Behavioral changes*	**Behavioral changes in females and males**
Reduced ability to handle stress*	**Sex hormone production is additional burden on adrenal glands. When a spayed/neutered dog experiences high stress situations, the adrenal glands can become overwhelmed.**
Compromised thyroid function	**Three fold increased risk of hypothyroidism as compared to intact dogs[26,27]**
Weakened immune system	**Increased risk of persistent or recurring urinary tract infections by a factor of 3-4.[41,42] Increased risk of recessed vulva, vaginal dermatitis, and vaginitis.[43]Increased incidence of allergic reactions.[92,34]**
Increased risk of Diabetes	**Increased risk of Diabetes with Hypothyroidism, Cushings and hyperestrinism, all emerging diseases**
Increased risk of obesity	**Increased risk of obesity by a factor of 1.6-2 in females, and triple the risk of obesity in males. It is common and associated with many health problems [30,31,32]**
Increased risk of Cancer	**Increased incidence of Cancer**

***** Please see the section "The Stress Response System" for a more detailed explanation.

The more we learned about EDs and spay/neuter the more we became convinced that spay/neuter was responsible for many dogs developing the aforementioned five endocrine disorders (i.e., hypothyroidism, Cushings disease/syndrome, Atypical Cushings disease, hyperestrinism and diabetes). For example, in recent studies, mice exposed to the chemical DDT became insulin resistant, which is the underlying cause for type 2 diabetes. In nations where DDT is still in use, such as South Africa and India, we have seen dramatic increases in humans of all ages diagnosed with type 2 diabetes. Veterinary research does not acknowledge or explore this potential connection, so it seemed beneficial to review the studies on the human endocrine system to explain this phenomenon.

As we discussed in the Diseases Overview section, the adrenal glands in people and dogs are always responsible for producing cortisol in response to stress. After spay/neuter, the dog's adrenal glands must take on the additional responsibility of manufacturing sex hormones. However, because stress response is a primary responsibility for the adrenal glands, high levels of chronic stress will force the adrenals to devote their energy to cortisol production, and production of sex hormones will become secondary. If the stress is ongoing and significant, the production of sex hormones can be interrupted. In a spayed or neutered dog this will deprive the body of adequate sex hormones.

This diagram illustrates the relationship between stress and the HPA axis. The hypothalamus and pituitary glands direct both adrenal and thyroid gland hormone production. Due to the feedback mechanisms, chronic adrenal stress depresses hypothalamic and pituitary function. And since the hypothalamus and pituitary glands control thyroid production, anything that disrupts the HPA axis will also suppress thyroid function. We can now understand how a spayed or neutered dog's *"stress response system"* fails them. Stress will predictably cause inadequate production of DHEA and sex hormones, thyroid dysregulation, and a failure of the hypothalamus and pituitary to secrete numerous other hormones required for a stable metabolism. You can envision the hormonal disruption spreading outward to other body systems like a pebble's wake when thrown into a pond.



Proper thyroid function depends on healthy adrenal glands. In case studies where adrenal hormones are abnormal, adrenal hormone replacement therapy returned the thyroid levels to normal without the need for thyroid hormone replacement.[105] This is why we advise guardians of spayed or neutered dogs to keep a close eye on your dog's thyroid function, as it can be an "early warning system" as to when a dog's adrenal glands can no longer compensate for the hormonal imbalance created by spay/neuter. Another "early warning" sign for female dogs is incontinence – so often the product of a spay induced estrogen deficiency it is generally termed *"spay incontinence"*.

Now that we have established spay/neuter is an endocrine disruptor, and the likely basis for an endocrine disease syndrome, we want to examine the five diseases and the glands they impact as part of this endocrine disease syndrome:

1. The Thyroid Gland – Hypothyroidism

Hypothyroidism (a failure of the dog's thyroid gland to produce enough thyroid hormone) has been tied directly to spay/neuter in at least one canine study. Spay/neuter in dogs was found to be correlated with a threefold increased risk of hypothyroidism compared to intact dogs.[26,27]

2. The Adrenal Gland – Cortisol and Cushings Syndrome

According to the Hormone Health Network, Cushings consists of the physical and mental changes that result from having too much cortisol in the blood for a long period of time. Cortisol is a steroid hormone produced by the adrenal glands. Hyperadrenocorticism (overproduction of cortisol in the adrenal gland) is due 15% of the time to a **tumor in the adrenal gland** (Cushings Syndrome), or 85% of the time to a **tumor in the pituitary gland** (Cushings disease – discussed below). It is our belief the higher incidence of Cushings of both causes in the canine population is due specifically to spay/neuter and the additional stress put on the dog's hormonal complex (especially the adrenal glands) which can result in overproduction of cortisol, a deficiency of sex hormones, hormonal imbalance, and the compromise of the immune system.

3. The Pituitary Gland – Cushings Disease

According to a 2009 study,[73] *"Cushing's disease (CD) is a common endocrinological disorder in dogs… in contrast to humans in whom CD is rare. The clinical presentation of CD, however, is highly similar between dogs and humans, with characteristic signs, such as abdominal obesity, weight gain, fatigue, muscle atrophy and skin changes. Canine CD may therefore serve as an animal model for human CD."*

In neutered (castrated) male dogs we are seeing an increased incidence of overproduction of cortisol purportedly due to a pituitary tumor (microadenoma), or to enlargement (hyperplasia) of the pituitary gland, and diagnosed as Cushings disease.

In studies among ancient human civilizations which practiced castration of males at a very early age, the bone structure in the brain which houses the pituitary gland was enlarged, consistent with pituitary enlargement.[81] More recently, a 1979 study [100] conducted on patients with diseases that caused them to have low gonadal sex hormones (e.g. testosterone), the authors noted, *"…results suggest that hyperplasia or microadenoma of the pituitary gland* ***may occur secondary to gonadal failure…lack*** *of awareness may result in inappropriate surgical management of what may appear to be primary pituitary tumor."*

We believe the veterinary community is, as discussed above, mistakenly focusing upon the abnormalities in the pituitary. Surgery is rarely attempted as the pituitary is difficult to access, and microadenomas may not be reliably visualized on a scan, whereas the hyperplasia may be diffuse and hard to remove in its entirety. Consequently, the treatment to date has generally been the utilization of drugs to destroy a portion of the adrenal gland, so as to diminish its ability to produce cortisol.

However, if the historical studies[81,100] on human males are correct, **Cushings of a pituitary origin in neutered male dogs should be treated by testosterone injections, rather than drugs that destroy a normal adrenal gland**. Researchers have long observed the presence of adequate levels of cortisol along with normal circulating levels of sex hormones serve to "turn off" the signal (ACTH) coming from the pituitary which stimulates the adrenal gland to produce more cortisol. The precise interactions are unclear, however a series of studies in the late '90s evaluated the cortisol production of castrated male animals provided with subcutaneous implants supplying various levels of testosterone replacement. As the level of testosterone replacement increased (up to normal physiological levels), the cortisol production decreased.[129] Certainly additional clinical studies could/should be conducted at this time to confirm or deny the efficacy of testosterone replacement as a treatment modality for Cushings of pituitary origin in male dogs.

The pituitary gland also produces Growth Hormone, which can be compromised when the pituitary and adrenal glands are excessively stressed. Lack of growth hormone can cause altered glucose metabolism (precursor to diabetes), abdominal obesity, diminished muscle tone and function, and reduced vitality and energy. Because these symptoms seem so much like those of the other endocrine maladies we are discussing here, it serves as an example as to why it is so difficult to identify and remedy hormone imbalance.

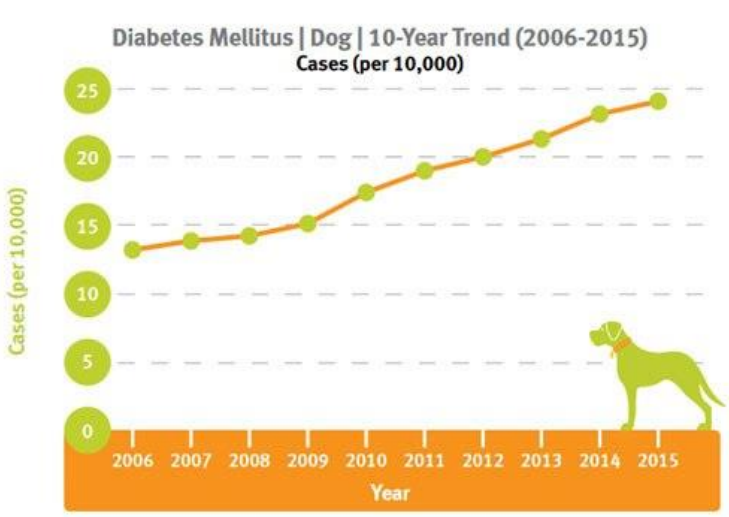
4. Hyperestrinism – Atypical Cushings

Atypical Cushings is defined in veterinary literature as overproduction of other adrenal steroids known as "sex steroids" [76] with no excess cortisol (e.g. hyperestrinism). Atypical Cushings does not exist as a disease entity in humans. Hyperestrinism (excess estradiol) without elevated cortisol, as Billy experienced, is an emerging disease entity in canines, with a side effect of insulin resistance in male dogs which can lead to type 2 diabetes.

5. Diabetes

Epidemiological studies indicate that the increased presence of endocrine disrupting chemicals (EDCs) in the environment may also play an important part in the incidence of metabolic diseases.[122] Among these compounds, polychlorinated biphenyls (PCBs), dioxins, phthalates and bisphenol-A (BPA), have been correlated with alterations in blood glucose homeostasis in humans…this altered blood glucose homeostasis may enhance the development of type 2 diabetes.[123] The data linking EDCs with obesity, metabolic syndrome and diabetes are strong and the number of studies finding positive association is growing.[124] If spay/neuter acts in the manner of endocrine disruptors, as we assert, you would expect to see an increase in type 2 diabetes in dogs.

The incidence of diabetes has been increasing **rapidly** per Banfield Veterinary Hospitals (see above graph). In their "State of Pet Health 2016 Report" it states:



"The prevalence of diabetes mellitus in dogs increased from 13.1 cases per 10,000 in 2006 to 23.6 cases per 10,000 in 2015—a 79.7 percent increase."

The veterinary community is finally acknowledging the emergence and rapid rise of diabetes in dogs, however they generally fail to classify it as type 2 diabetes, which is an important distinction to make. Low thyroid, Cushings, hyperestrinism, and low testosterone are all increasing in incidence due to the endocrine disruption brought on by spay/neuter, and all are associated in some manner with an increased likelihood of developing type 2 diabetes.

EDCs can disrupt the thyroid's normal processes, and therefore, can disrupt day to day metabolism. Recent (2016) studies in human populations have linked low thyroid hormones to type 2 diabetes. In one study it was found that low thyroid function is associated with a 1.2-fold increased risk of type 2 diabetes.[93] In another study, it was concluded that there appears to be a correlation between serum thyroid hormone levels and the prevalence of type 2 diabetes in the general population.[121]

Type 2 diabetes is often associated with Cushing's syndrome in the human environment. A review [97] published in *Trends in Endocrinology & Metabolism* suggests that 36% of human patients with overt Cushing's syndrome and 22% of patients with subclinical Cushing's syndrome had diabetes while another 17% to 23% have impaired glucose tolerance.

Our dog Billy had type 2 diabetes. He had normal pancreatic function as evidenced by normal pancreatic enzymes and normal levels of insulin in his blood, yet he was hyperglycemic. This is the hallmark of type 2 diabetes – normal amounts of insulin are unable to move glucose from the blood to the cells of the body because the cells have insulin resistance. Low thyroid, subclinical Cushing's, hyperestrinism and low/no testosterone all factored into his development of type 2 diabetes.

With the emergence of these endocrine diseases, new tests have been devised to diagnose these illnesses as well as explore avenues of treatment. Steroid hormone profiling in veterinary medicine started at the University of Tennessee Clinical Endocrinology Service. The adrenal gland is central to most of these endocrine diseases, and the hormone profile test evolved on the premise that multiple steroid hormone analyses would increase the diagnostic accuracy of adrenal-function tests.[76]

However, it is clear from the scientific reviews/studies over time that there was little or no appreciation in the veterinary community or among the "experts" at the University of Tennessee for the hormonal chaos spay/neuter was creating. Once a dog has been spayed or neutered, their endocrine system has been forever altered. There is no going back to optimal health; spay/neuter permanently damages your dog's ability to respond to physical and/or psychological stress; leaving your dog increasingly susceptible to cancer, metabolic disease including diabetes, immune-related disease, infection and anxiety.[85] **The damage of spay/neuter to the endocrine system of your dog is permanent, and no dog is immune**.

For example, a 2003 University of Tennessee study [77] was conducted to determine steroid hormone concentration profiles in healthy intact and neutered male and female dogs. The study states:

"Results from this study will enhance interpretation of suspected adrenal and/or gonadal disorders of dogs. Because estradiol concentrations were similar in all groups of dogs, ***measuring estradiol may not be a useful diagnostic test."***

Several years later, the University of Tennessee was forced to admit that they were completely wrong in their assessment of the hormonal response to spay/neuter. From a 2007 presentation [76] given by Dr. Jack W. Oliver, also an author of the aforementioned 2003 study:

*"**Hyperestrinism in dogs may be a new and emerging disease entity.** In sample submissions to the Clinical Endocrinology Service (2005) at The University of Tennessee, **40% of adrenal panels had elevated estradiol levels present.**..Effective treatment options for hyperestrinism in dogs is limited at the present time…"*

In 2005, the Tennessee veterinarians were recommending 12 mg./day of melatonin (an aromatase inhibitor) to reduce the estradiol in dogs with hyperestrinism. Unfortunately, outside research on melatonin seems to have largely been ignored by the Tennessee veterinarians. As early as 1996, melatonin was found to be a hormone with such global effects in the bodies of people (and animals) that it was termed a "master hormone".[96]

In 2005, researchers associated with UC Berkeley published a study in Science Daily which concluded:

"…It [melatonin] is a powerful hormone… It could have a multitude of effects on the underlying physiology of an organism, but we know so little about how it interacts with other hormone systems."

In 2012, another study published in Science Daily stated, "**the release of insulin, which regulates blood sugar levels, is known to be regulated by melatonin**."

Yet, in 2013 when we received Billy's hormone panel results, the University of Tennessee "experts" provided a recommendation regarding Billy's hyperestrinism. It stated:

*"Where positive test results of increased adrenal activity are present, consider the need for: Melatonin. Often used as a first treatment, especially if alopecia [fur loss] is present, since it is cheap, **has few side effects** and is available in health food stores or via nutrient suppliers on the Internet. Typically…**a dose of 6 mg. is given q12 hrs. (BID) for dogs over 30 lbs**."*

In 2009, Billy had developed alopecia, and a skin biopsy in the bald areas indicated the cause was hormonal. Our vet consulted with endocrine "experts" then and consequently Billy had been taking 12 mg. of melatonin daily since 2009 to address his alopecia. In 2013, Billy had lost even more fur, his estradiol levels were six times normal, and he was an uncontrolled Type 2 diabetic with routine blood glucose readings at or near 400 (normal being 80-100), despite injections of insulin. This is a classic example where "juggling" hormones was not only ineffective, but harmful. It appears that with spay/neuter, there are no "fixes" for the hormonal chaos. In Billy's case, the "experts" had no answers for us except dogs do not have type 2 diabetes, and stay on that large dose of melatonin because it has ***"few side effects".***

Even in 2016, the veterinarians at the University of Tennessee are still recommending 12 mg./day of melatonin and have now added lignans to combat excess estradiol – with no mention that melatonin could raise blood glucose levels. In early 2016, a study of humans showed that insulin-producing cells respond to a 4 mg. dose of melatonin/day by reducing the amount of insulin they release – thereby raising blood glucose. This begs the question:

If a person weighing 150 pounds has a significant increase in blood glucose while taking only 4 mg. melatonin/day, what would you expect for a 50 pound dog taking 12 mg. of melatonin/day?

In 2013, based upon the failure of the "experts" to provide us any guidance as to how to control Billy's blood glucose levels, we began our own research. We had already established that diet, exercise and injections of various types and combinations of insulin was entirely ineffective. We were left to address the other documented anomaly–hormonal imbalance. We looked to see if there was any evidence that the hormonal imbalance (presumably created at least in part by neuter due to the absence of testosterone) can lead to the development of hypothyroidism, Cushing's, Atypical Cushing's, hyperestrinism, and diabetes. We were forced to research studies on humans as the veterinary community does not acknowledge the causal relationship and has not conducted studies to prove/disprove the thesis. Initially, the most helpful study we found, "Induction of insulin resistance,"[79] states:

"We conclude that sex hormone administration, i.e. testosterone treatment in females and ethinyl estradiol treatment in males, can induce insulin resistance in healthy subjects."

Accordingly, reducing Billy's estradiol should diminish his insulin resistance, thereby improving his blood glucose. We researched the connection between Cushings and Type 2 diabetes and found further helpful references. One was excerpted from a presentation at the International Congress of Endocrinology and the Endocrine Society in 2014 [97]:

"Undiagnosed Cushing's syndrome is common in type 2 diabetics. There are a substantial number of patients with type 2 diabetes who have Cushing's syndrome as a contributing factor to their diagnosis. You can substantially improve their diabetes and possibly eliminate it, if they are treated for their Cushing's syndrome…"

It was generally suspected because Billy had most symptoms of Cushings, yet did not test positive for Cushings, that Billy had subclinical or Atypical Cushings. If this was true, our only remaining option to treat his diabetes seemed to be normalization of Billy's hormones. We searched to find effective medications that would reduce Billy's estradiol and we discovered anastrozole.[96,98] Anastrozole is an aromatase inhibitor tested on dogs and subsequently utilized for women with estrogen sensitive breast cancer, with no significant side effects reported. We took Billy off melatonin and were able to convince the veterinary Internal Medicine specialist to prescribe anastrozole for Billy. It reduced his estradiol levels and we were able to bring his average daily blood glucose readings with both insulin injections and anastrozole from 400 to just under 300.

There were many studies which associated low testosterone with insulin resistance in men, and in 2010, the *Endocrine Society's Clinical Practice Guideline* recognized the need for testosterone replacement therapy in adult men with Type 2 diabetes and low testosterone. Since Billy was a male and had **no** testosterone at all, we asked for testosterone replacement therapy. The Internal Medicine specialist refused to prescribe testosterone for Billy, as she insisted it may make Billy aggressive and perhaps make him dangerous to other people and dogs. Thankfully, although expressing strong reservations due to potential aggression, our primary care veterinarian gave Billy testosterone injections to bring him to a normal level of testosterone. Almost immediately, with insulin injections, anastrozole, and testosterone supplements, Billy's blood glucose levels came down from 300 to the low 200s. Over the last year of Billy's life, his average daily blood glucose readings continued to drop until they were in the mid 100s. **There is now accumulating evidence that low serum testosterone level is associated with type 2 diabetes**.[78,95]

It is difficult to explain why the veterinary community continues to treat testosterone as a hormone only relevant to reproduction. In fact, if you do not intend to breed your dog, the veterinary community contends testosterone can only create problems for your male dog. On the other hand, it is no exaggeration to say that in modern human medicine and endocrinology testosterone is no longer a marginal hormone. Neither is it a lifestyle hormone for those men seeking eternal youth. Its deficiency leads to a serious deterioration of the health of men expressing itself in the metabolic syndrome and its sequels: diabetes mellitus type 2 and atherosclerotic disease, osteoporosis and sarcopenia, all strongly limiting physical independence in old age and accelerating morbidity and mortality.[128]

Behaviorally, the vets were again in error, as the effects of the testosterone proved to be positive. Billy was now no longer afraid of new people or dogs, or loud noises like fireworks.

More research needs to be undertaken to confirm the specifics of endocrine disruption as well as the exact mechanism by which failure to respond to stress appropriately has resulted in the emergence of hypothyroidism, Cushings, Atypical Cushings, hyperestrinism and Type 2 diabetes in dogs.

However, there would be great value in moving immediately to tubal ligation and vasectomy for canine population control. Studies affirm benefits would include elimination of sex-hormone related orthopedic problems, reduced incidence of certain types of cancer and resolution of behavior problems spay/neuter has been shown to create in dogs. Further, we fully expect the preservation of the endocrine balance will greatly reduce the incidence of the metabolic diseases discussed here.

https://healthyandhappydog.wordpress.com/hormones-and-the-endocrine-system by Dr. Suzanne Valente