

Non-Reproductive Long-Term Health Complications of Gonad Removal in Dogs as Well as Possible Causal Relationships with Post-Gonadectomy Elevated Luteinizing Hormone (LH) Concentrations

Khawla Zwida^{1*} and Michelle Anne Kutzler²

¹Department of Animal and Rangeland Sciences, 557 Weniger Hall, College of Agricultural Sciences, Oregon State University, Corvallis, Oregon 97331, USA

²Department of Animal and Rangeland Sciences, 561A Weniger Hall, College of Agricultural Sciences, Oregon State University, Corvallis, Oregon 97331, USA

***Corresponding Author:** Khawla Zwida, Department of Animal and Rangeland Sciences, 557 Weniger Hall, College of Agricultural Sciences, Oregon State University, Corvallis, Oregon 97331, USA; Tel: 541-908-0136; Fax: 541-737-4174; E-mail: zwidak@oregonstate.edu

Citation: Khawla Zwida and Michelle Anne Kutzler (2016) Non-Reproductive Long-Term Health Complications of Gonad Removal in Dogs as Well as Possible Causal Relationships with Post - Gonadectomy Elevated Luteinizing Hormone (LH) Concentrations. J Etiol Anim Health 1: 002.

Copyright: © 2016 Khawla Zwida and Michelle Anne Kutzler. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted Access, usage, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract:

Throughout most of the developed world, surgical sterilization via gonadectomy has become a common tool for combating the overpopulation of unwanted dogs as well as to eliminate the risk of reproductive diseases in pet dogs. However, if a surgical sterilization method is chosen that enables a dog to keep its gonads intact while still preventing reproduction, this may avoid the problems discussed in this article. In the dog as in other normal adult mammals, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone in males and estrogen/progesterone in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively. However, in the gonadectomized mammal, there is no negative feedback, which results in supraphysiologic circulating concentrations of LH. In gonadectomized dogs, LH concentrations are more than thirty times the concentrations found in normal adult dogs. Although the main role of LH is for reproductive functions (e.g. ovulation, corpus luteum formation), there are LH receptors present throughout the body, not just limited to the reproductive tract. The purpose of LH receptors in non-reproductive tissues is not known but may induce cell division and stimulate nitric oxide release. With constant activation following gonadectomy, these receptors are up regulated, further magnifying the effects of the extremely high LH concentrations in non-reproductive tissues. Canine gonadectomy increases the risk of several non-reproductive long-term disorders caused by extremely high LH including obesity, urinary incontinence, urinary calculi, diabetes mellitus, hypothyroidism, hip dysplasia, cranial cruciate ligament rupture, aggressive and fearful behavior, cognitive dysfunction syndrome, prostate adenocarcinoma, transitional cell adenocarcinoma,

osteosarcoma, hemangiosarcoma, lymphosarcoma, and mastocytoma. In this review, the relationship between LH receptor activation in these non-reproductive target tissues will be discussed.

Keywords: Behavior; Cranial Cruciate Ligament Rupture; Diabetes Mellitus; Hip Dysplasia; Hypothyroidism; Longevity; Neoplasia; Obesity; Urinary Incontinence.

Introduction

Throughout most of the developed world, surgical sterilization has become a common tool for combatting the overpopulation of unwanted dogs [1-6] as well as to eliminate the risk of reproductive diseases in pet dogs (e.g. mammary gland cancer and prostate hyperplasia/infection) [7]. In the United States, 64% of dogs have been surgically-sterilized [8]. For the purposes of this review, ovariectomy and ovariohysterectomy (spay) or castration (neuter) will be collectively referred to as gonadectomy, since each of these methods for surgical sterilization include gonad removal (ovaries or testes).

In the normal adult mammal, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone [9]. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone in males and estrogen/progesterone in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively (Figure 1A). However, in the gonadectomized mammal,

there is no negative feedback, which results in supraphysiologic circulating concentrations of LH (Figure 1B). In gonadectomized dogs, LH concentrations are more than thirty times the concentrations found in normal adult dogs [10].

Although the main role of LH is for reproductive functions (e.g. ovulation, corpus luteum formation), there are LH receptors present throughout the body, not just limited to the reproductive tract (Table 1). The purpose of LH receptors in non-reproductive tissues is not known but may induce cell division and stimulate nitric oxide release [11]. With constant activation following gonadectomy, these receptors are up regulated, further magnifying the effects of the supraphysiologic LH concentrations in non-reproductive tissues. In this review, we have summarized several non-reproductive long-term health complications resulting from canine gonadectomy as well as discussed the possibility of how these effects are mediated by LH receptor activation in these non-reproductive target tissues.

Non-Reproductive Tissues	Species	Reference
Adrenal cortex	Dog, human, rat, rhesus macaque	128-130
Blood vessels (endothelial cells, vascular smooth muscle cells)	Human	121; 120; 131
Brain (hippocampus, hypothalamus, cerebellum, brain stem, cortex)	Guinea pig, rat	89; 132
Fibroblasts	Human	131
Gastrointestinal tract (enteric neurons, smooth muscle)	Human, rat	133-135
Lower urinary tract (bladder and urethra)	Dog, human	39, Ponglowhapan, Church, Khalid, 2008; 114
Lymphoid tissues (thymus and lymphocytes)	Hamsters, human	136
Skin (epidermis, hair follicle, sebaceous glands, sweat glands)	Dog, human	36; 125
Striated muscle cells	Human	131
Thyroid gland	Human	62

Table 1: Luteinizing hormone receptors are found in several tissues outside of the reproductive tract. In the dog, activation of these receptors may be responsible for the long-term health complications following gonad removal.

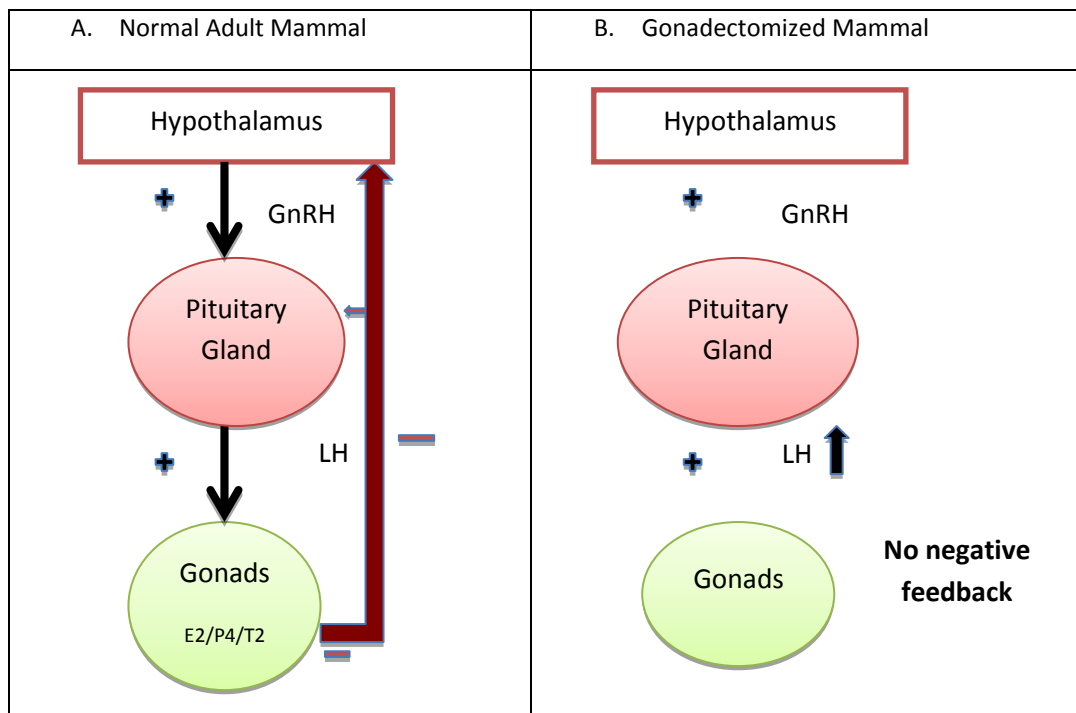


Figure 1: A: In the normal adult mammal, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone (T2) in males and estrogen (E2)/progesterone (P4) in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively. B: In the gonadectomized mammal, there is no negative feedback, which results in supraphysiologic circulating concentrations of LH.

Obesity:

Obesity is serious medical problem defined as an excessive accumulation of fat beyond the physical and skeletal limits [12]. Gonadectomy is the single largest risk factor for the development of obesity in dogs [7, 13]. Up to 68% of gonadectomized dogs are obese [14 – 19]. Gonadectomy induces obesity through two main mechanisms: increased appetite and decreased metabolic rate. Gonadectomy stimulates food intake [20] and increases indiscriminate appetite [21]. In unaltered dogs, food intake suppresses the secretion of gastrointestinal hormones (cholecystokinin and glucagon) resulting in satiety (alleviation of hunger)[22]. However, within 1 week following gonadectomy, food intake increases by 20% and then persists [23, 24]. It is possible that stimulation of LH receptors present in the gastrointestinal tract following gonadectomy suppresses cholecystokinin and/or glucagon release. It is also possible that LH receptors in the hypothalamus are involved in the increase in [25] as lesions within the ventromedial hypothalamus result in hyperphagia [26].

Gonadectomy also results in a 30% decrease in daily energy requirements [24]. The underlying mechanism for decreased energy requirements is not known but is likely due to decreased physical activity [27-30]. Within the first

90 days after gonadectomy, dogs will gain a significant amount of weight [23]. Weight gain results from a decrease in activity without a corresponding decrease in food intake [23]. Of course, with an increased appetite from gonadectomy, decreasing food intake leaves the dog in an unpleasant and perpetual state of hunger.

Urinary System:

Urinary incontinence: Urinary incontinence is an involuntary leakage of urine resulting from either a weakened or complete loss of urinary sphincter control. The association between urinary incontinence and gonadectomy in female dogs was first described by Jo [31]. Urinary incontinence is a common long-term health complication of gonadectomy in female dogs with a reported incidence ranging from 5-30% [32-35]. Early age gonadectomy (under 5 months of age) may further increase the risk of occurrence of urinary incontinence [35-37]. LH receptors are expressed in all regions the canine lower urinary tract, from the body and neck of the bladder to the proximal and distal urethra [38, 39]. Gonadectomized female dogs with urinary incontinence have a significantly higher number of LH receptors in the lower urinary tract compared to unaltered females[40]. Urinary continence can be restored in gonadectomized females by reducing circulating LH concentrations using estrogens [34, 41-44], GnRH agonists [45, 46] or GnRH immunization [47,48].

Urinary calculi: Urinary calculi are solid particles (concretions) in the urinary system, usually composed of mineral salts that can form in any part of the urinary tract [49]. Urinary calculi may be large enough to obstruct the flow of urine or small enough to be passed with the urine. After evaluating records from more than two million dogs, Banfield Pet Hospital found that all urinary calculi (urine crystals, kidney stones, and bladder stones), occurred at a rate three times higher in gonadectomized dogs compared to unaltered dogs [50]. Under normal circumstances, there is a balance of urinary calculi promoters and inhibitors. However, this balance appears to be disrupted under the influence of an abundant LH environment.

Endocrine System:

Diabetes Mellitus: Diabetes mellitus results from the impaired secretion of insulin with variable degrees of peripheral insulin resistance leading to hyperglycemia. In dogs, the incidence of diabetes mellitus is 0.4-1.2% [51] and has been increasing over the past 30 years [52,53]. Gonadectomy doubles the risk for developing diabetes mellitus in dogs [53]. Although gonadectomy increases the risk for obesity, the increased prevalence for diabetes mellitus in gonadectomized dogs is unrelated to obesity [54, 55] and may be a direct effect of LH on the pancreas.

Hypothyroidism: Hypothyroidism is a common endocrine disorder in which the thyroid gland does not produce sufficient quantities of thyroid hormone (thyroxin, T4) [56, 57]. Gonadectomy has a profound effect on thyroid function [58] and is the most significant cause for the development of hypothyroidism in dogs [59]. Thirty percent more gonadectomized dogs develop hypothyroidism compared to unaltered dogs [60]. Women who have undergone gonadectomy are also at an increased risk for developing hypothyroidism [61]. LH receptors are expressed in normal and adenomatous human thyroid glands [62] and presumably also present in the canine thyroid gland. Because thyroid stimulating hormone concentrations remain similar for both gonadectomized and unaltered dogs [63], research is needed to determine the effects of LH receptor activation in unaltered and gonadectomized dogs.

Musculoskeletal System

Hip Dysplasia: Canine hip dysplasia is associated with the abnormal joint structure and laxity of the muscles, connective tissue, and ligaments that would normally support the hip [25, 64, 65]. As hip joint laxity increases, the articular surfaces between the pelvic tubar coxae and head of the femur lose contact with each other, resulting in subluxation. Over time, subluxation results in a significant change in the size and shape of both articular surfaces and varying severity of osteoarthritis. It is important to note that

most dogs with hip dysplasia are born with normal hips but then develop hip dysplasia secondary to intrinsic and/or extrinsic factors. The incidence of hip dysplasia can be as high as 40-83% in giant and large breed dogs [64-68]. Independent of the occurrence of obesity, gonadectomy significantly increases the incidence of canine hip dysplasia [68]. Compared to unaltered dogs, gonadectomy increases the by 1.5 [64] to 2 times [69] the occurrence in unaltered dogs. The mechanism for the increased incidence is not known but possibly results from an increase in LH receptor expression and/or activation in the structural support tissues within the hip joint.

Cranial Cruciate Ligament Rupture

The cranial cruciate ligament serves to prevent cranial displacement of the tibia relative to the femur, to limit internal rotation of the tibia relative to the femur, and to prevent stifle hyperextension [70, 71]. Cranial cruciate ligament rupture is another musculoskeletal disorder that initially involves the degeneration of the cranial cruciate ligament, which leads to a partial rupture and then progresses to a complete rupture following an unspectacular traumatic event [72, 73]. Similar to hip dysplasia, most dogs with cranial cruciate ligament ruptures are born with normal stifle joints but then develop the tendency for cranial cruciate ligament rupture secondary to intrinsic and/or extrinsic factors. Gonadectomy significantly increases the prevalence of cranial cruciate ligament rupture [74], doubling the occurrence reported for unaltered dogs [75]. With an incidence as high as 5.1% and 7.7% in males and females, respectively [69]. Prepubertal gonadectomy delays tibial growth plate closure [76], which extends the length of tibia and the steepness of the tibial plateau [77,78]. Increased steepness of the tibial plateau can increase the cranial tibial thrust, which is a risk for cranial cruciate ligament rupture [79, 80]. Despite the skeletal deformations that occur with pre-pubertal gonadectomy, even dogs post-pubertally gonadectomized have an increased risk for cranial cruciate ligament rupture [69]. There is some evidence that hormones (estrogen and relaxin) may play a role in altering cranial cruciate ligament laxity and may be modifiable risk factors in humans [81, 82]. The role for LH and its receptor in the etiopathogenesis of canine cruciate ligament rupture should not be overlooked.

Behavior and Cognition

The role of gonadectomy on behavior is complex and evidence for benefits as well as detriments following gonadectomy has been reported. Reproductive-related behaviors (such as urine marking in house, mounting, and roaming) are all reduced or eliminated following gonadectomy [83, 84, 30]. However, fear and aggression tend to be exacerbated [85].

Fear of storms, fear of gunfire, fear of noises, fear biting, timidity, separation anxiety, and submissive urination all increase significantly following gonadectomy. Gonadectomized females are also more reactive to the presence of unfamiliar humans and dogs [86]. Although some dogs may become less aggressive following gonadectomy [84], dominance aggression [87] and owner-directed aggression [21, 88] occur with a significantly higher frequency in gonadectomized dogs compared to unaltered dogs. The hippocampus and hypothalamus both play important roles in controlling behaviors, especially those pertaining to fear and aggression. Luteinizing hormone receptors are abundant in hippocampus and hypothalamus [89-91]. In addition, administration of supraphysiologic concentrations of LH to gonadectomized animals can induce aggression and other behavioral changes [92-94].

Cognitive dysfunction syndrome is a neurodegenerative disorder of senior dogs, which is characterized by both cognitive changes and neurophysiological pathologies [95, 96]. Memory impairment, poor problem solving skills, social disconnect, confusion, and day-night reversal may occur as the condition progresses. Gonadectomy significantly increases the development and progression of cognitive dysfunction syndrome in dogs. Increases in luteinizing hormone are associated with declines in cognitive performance [97]. In addition, elevated LH concentrations increase beta amyloid plaque formation and are implicated in the development of Alzheimer's syndrome in humans [98, 99]. Male sex hormones and systemic inflammation in Beta amyloid plaques are also involved in the pathogenesis of cognitive dysfunction syndrome in dogs [100, 51]. Therefore, it is possible that LH and its receptor are important in the development of cognitive dysfunction syndrome in gonadectomized dogs.

Neoplasia

Prostate Adenocarcinoma

Unlike the condition in men, the aggressive nature of the canine prostate adenocarcinoma and the lack of a screening test make the identification of dogs with early-stage prostate cancer extremely problematic [101]. In dogs, gonadectomy is the largest risk factor for the development of prostate adenocarcinoma [102, 103]. Luteinizing hormone receptors are abundant in the prostate gland and increase in expression following gonadectomy [104, 105]. Prostate carcinomas in dogs are associated with a high rate of metastasis at presentation and too poor of a prognosis to recommend aggressive local therapies [101]. Prostatectomy is associated with significant postoperative morbidity, in particular urinary incontinence, without significantly extending survival times [106, 107].

Transitional Cell Carcinoma

Transitional cell carcinomas can arise from the

bladder or urethra, including the prostatic urethra [108-112]. Even with surgical removal, radiation treatment and chemotherapy, the prognosis for dogs with transitional cell carcinomas is poor with only 16% of treated dogs surviving for over one year [113]. Gonadectomized dogs have a significantly higher risk of developing a transitional cell carcinoma compared with unaltered dogs [113]. Luteinizing hormone receptors are widely distributed throughout the bladder and urethra [39, 105, 114] and increase in expression following gonadectomy [115].

Osteosarcoma

Osteosarcoma is a highly metastatic cancer of bone tissue. Despite many advances over the past 20 years, survival times for dogs diagnosed with osteosarcoma have not changed, with the principal cause of mortality being the development of pulmonary metastases [116]. Osteosarcoma occurs with significantly higher frequency in gonadectomized dogs [117]. The incidence of osteosarcoma in gonadectomized dogs is 1.3-2.0 times higher than in unaltered dogs [118]. It is not known if LH receptors exist in the bone or if LH could be using an indirect mechanism to mediate the increased incidence of osteosarcoma.

Hemangiosarcoma

Hemangiosarcoma is a rapidly growing, highly invasive cancer arising from the lining of blood vessels and occurring almost exclusively in dogs. Primary tumors can arise in any vascular tissue but the spleen and heart are the most common locations for hemangiosarcoma to develop. Even with surgical removal, the mean life expectancy is 86 days (range, 10-202 days) without adjunctive chemotherapy and 189 days (range, 118-241 days) with adjuvant chemotherapy [119]. Many studies have confirmed the presence of LH receptors in vascular endothelial and smooth muscle cells [120, 121]. Gonadectomized female dogs have two times the risk for developing splenic hemangiosarcoma and five times the risk for developing cardiac hemangiosarcoma compared to unaltered females [122, 85]. Research is needed to determine if canine hemangiosarcomas possess LH receptors and if adjunctive therapy targeting these receptors would extend life expectancy.

Lymphosarcoma

Lymphosarcoma is a cancer of lymphocytes and/or lymphoid tissues. Lymphosarcoma is the most common cancer diagnosed in dogs accounting for up to 24% of all canine cancers. LH receptors are present in lymphocytes and lymphoid tissue (medulla of thymus) [123]. Gonadectomy increases the incidence of lymphosarcoma [85]. Gonadectomized males are three times more likely to develop lymphosarcoma than unaltered males and about 1 in 10 neutered males will develop lymphosarcoma [69].

Mastocytoma

Mastocytomas are the most common skin tumor in dogs [124]. Luteinizing hormone receptors are abundant in the skin [38, 125]. Several studies have documented an increased risk for developing mastocytoma following gonadectomy in dogs [69, 126,85].

Conclusion

Unrelated to any particular disease or major cause of death, years of gonad exposure prolong longevity [127]. Based upon the review of the literature, it becomes clear that canine gonads are not merely reproductive organs but critical to endocrine, musculoskeletal, behavior, and anti-neoplastic health. Among the non-reproductive functions of gonads, suppression of LH secretion and resulting LH receptor over expression appear necessary in maintaining homeostasis. Therefore, a surgical sterilization method that enables the dog to keep gonads intact while still preventing reproduction is likely to prolong its health.

References

1. Salmeri KR, Olson PN, Bloomberg MS (1991) Elective gonadectomy in dogs: a review. *J Am Vet Med Assoc.* 198(7). P 1183-92.
2. Totton SC, Wandeler AI, Zinsstag J, Bauch CT, Ribble CS, Rosatte RC, McEwen SA (2010) Stray dog population demographics in Jodhpur, India following a population control/rabies vaccination program. *Prev Vet Med.* 97(1). P 51-57.
3. Voslárová E, Passantino A (2012) Stray dog and cat laws and enforcement in Czech Republic and in Italy. *Ann Ist Super Sanita.* 48(1) P 97-104.
4. Domingues LR, Cesar JA, Fassa AG, Domingues MR (2015) Responsible pet animal guardianship in the urban area of the municipality of Pelotas in the state of Rio Grande do Sul, Brazil. *CienSaude Colet.* 20 (1). P185-192.
5. Downes MJ, Devitt C, Downes MT, More SJ (2015) Neutering of cats and dogs in Ireland; pet owner self-reported perceptions of enabling and disabling factors in the decision to neuter. *PeerJ.* 20. 3:e1196.
6. Vanderstichel R, Forzán MJ, Pérez GE, Serpell JA, Garde E (2015) Changes in blood testosterone concentrations after surgical and chemical sterilization of male free-roaming dogs in southern Chile. *Theriogenology.* 83(6),p 1021-7.
7. Kustritz MVR. (2012) Effects of surgical sterilization on canine and feline health and on society. *Reproduction in Domestic Animals.* 47. P 214-222.
8. Trevejo R, Yang M, Lund EM. (2011) Epidemiology of surgical castration of dogs and cats in the United States. *Journal of American Veterinary Medical Association.* 238(7). P 898-904.
9. Meethal VS, Atwood CS (2005) The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. *Cellular and Molecular Life Sciences.* 62(3). P 257-70.
10. Beijerink NJ, Buijtel JJ, Okkens AC, Kooistra HS, Dieleman SJ. (2007) Basal and GnRH-induced secretion of FSH and LH in anestrus versus ovariectomized bitches. *Theriogenology.* 67(5): p 1039-45.
11. Greene JM, Ginther OJ (2015) Circulating nitric oxide metabolites during luteolysis and the effect of luteinizing hormone on circulating nitric oxide metabolites in heifers. *Theriogenology.* 83(2). P 213-21.
12. German AJ. The growing problem of obesity in dogs and cats. (2006). *J Nutr.* 136(7 Suppl). 1940S-1946S.
13. Martin LJ, Siliart B, Dumon HJ, Nguyen PG. (2006) Hormonal disturbances associated with obesity in dogs. *J AnimPhysiolAnimNutr (Berl).* 90(9-10). P 355-60.
14. Anderson RS. Obesity in dogs and cats in GrunsellCS, Hill FWG(ed). *The veterinary Annual.* Bristol, Weight, 1973, pp 183-186.
15. Mason E. (1970). Obesity in pet dogs. *Vet Rec.* 86(21). P 612-6.
16. David G, Rajendran EI. (1980) The aftereffects of spaying in bitches and cats. *Cheiron.* 9. P 193-195.
17. Lefebvre SL, Yang M, et al. (2013) Effect of age at gonadectomy on the probability of dogs becoming overweight. *Journal of American Veterinary Medical Association.* 243. P 236-243.
18. Lewis LD. Obesity in the dog. *J Am AnimHospAssoc* 1978;14:402-409.
19. Norris MP, Beaver BV (1993) Application of behavior therapy techniques to the treatment of obesity in companion animals. *J Am Vet Med Assoc.* 202. P 728-730.
20. Houpt KA. Feeding and drinking behavior problems. (1991) *Veterinary Clinical of North America Small Animal Practice.* 21. P 281-298.
21. O'Farrell, V. Peachy, E. (1990) Behavioural effects of ovariohysterectomy on bitches. *Journal of Small Animal Practice.* 31. P 595-598.

22. Levine AS, Sievert CE, Morley JE, Gosnell BA, Silvis SE. (1984) Peptidergic regulation of feeding in the dog (*Canis familiaris*). *Peptides*. (4). p 675-9.
23. Houpt KA, Coren B, Hilderbrant JE. (1979) Effects of sex and reproductive status on sucrose preference, food Intake, and body weight of dogs. *Journal American Veterinary Medical Association*. 174. P 1083-1085.
24. Jeusette I, Detilleux J, Cuvelier C, Istasse L, Diez M (2004) Ad libitum feeding following ovariectomy in female Beagle dogs: effect on maintenance energy requirement and on blood metabolites. *J AnimPhysiolAnimNutr (Berl)*. 88(3-4). P 117-21.
25. Daniel JA, Foradori CD, Whitlock BK, Sartin JL(2013) Hypothalamic integration of nutrient status and Dassler CL. (2003) Canine hip dysplasia: diagnosis and nonsurgical treatment, in Slatter D (ed): *Textbook of small animal surgery* (ed 3). Philadelphia, PA, Saunders. P 2019–2020
26. Rozkowska E, Fonberg E (1973) Salivary reactions after ventromedial hypothalamic lesions in dogs. *ActaNeurobiolExp (Wars)*. 33(3). P 553-62.
27. LeRoux, P. H. (1983)Thyroid status, oestradiol level, work performance and body mass of ovariectomised bitches and bitches bearing ovarian auto transplants in the stomach wall.*J. S. Afr. Vet. Assoc.* 54, 115.
28. Sibley KW. (1984) Diagnosis and management of the overweight dog. *Br. Vet. J.* 140, 124-131.
29. Sloth, C. (1992) *J. Small Anim. Pract.* 33, 178.
30. Maarchalkerweerd, RJ., Endenburg, N., Kirpensteijn J., and Knol, BW. (1997) Influence of orchietomy on canine behavior". *Veterinary Record*. 140. P 617-619.
31. Joshua Jo. (1965) The spaying of Bitches. *Vet Rec.* 77. P 642-6.
32. Arnold S. Urinary incontinence in castrated bitches. (1997) Part 1: Significance, clinical aspects and etiopathogenesis. *Schweiz Arch Tierheilkd.*139(6). P 271-6.
33. Stocklin-Gautschi NM, Ha` ssg M, Reichler IM, Hubler M, Arnold S. (2001) The relationship of urinary incontinence to early spaying in bitches. *Journal of Reproduction and Fertility*. 57 (Suppl.) p 233–6.
34. Angioletti A, De Francesco I, Vergottini M, Battocchio ML. (2004)Urinary incontinence after spaying in the bitch: incidence and oestrogen therapy. *Veterinary Research Communication*. 28 (Suppl. 1): p153–5.
35. Spain CV, Scarlett JM, Houpt KA. (2004) Long-term risks and benefits of early-age gonadectomy in dogs. *Journal American Veterinary Medical Association*. 224. P 380–7.
36. Mckenzie B. (2010) Evaluating the Benefits & Risks of Neutering. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources*. 5(045).p 1-18.
37. Thrusfield MV. (1985) Association between urinary incontinence and spaying in bitches. *Veterinary Record*.116. P 695.
38. Welle MM, Reichler IM, Barth A, Forster U, Sattler U, Arnold S. (2006) Immunohistochemical localization and quantitative assessment of GnRH-, FSH-, and LH-receptor mRNA Expression in canine skin: a powerful tool to study the pathogenesis of side effects after spaying. *Histochemistry Cell Biology*. 126 (5). P 527-35.
39. Ponglowhapan S, Church DB, Scaramuzzi RJ, Khalid M. (2007) Luteinizing hormone and follicle-stimulating hormone receptors and their transcribed genes (mRNA) are present in the lower urinary tract of intact male and female dogs.*Theriogenology*.67 (2). P 353-66.
40. CoitVA, Dowell FJ, Evans NP. (2009) Neutering affects mRNA expression levels for the LH- and GnRH-receptors in the canine urinary bladder. *Theriogenology*. 71(2). P 239-47.
41. Rosin AE, Barsanti JA. (1981) Diagnosis of urinary incontinence in dogs: role of the urethral pressure profile.*J Am Vet Med Assoc*. 178, P 813-822.
42. Hill K, Jordan D, Ray J, Mays AA, Griffin K. (2012) Medical therapy for acquired urinary incontinence in dogs. *Int J Pharm Compd*. 16(5). P 369-75.
43. Veronesi MC, Rota A, Battocchio M, Faustini M, Mollo A. (2009) Spaying-related urinary incontinence and oestrogen therapy in the bitch. *Acta Vet Hung*.57(1). P 171-82.
44. Mandigers RJ, Nell T. (2001) Treatment of bitches with acquired urinary incontinence with oestriol. *Vet Rec*. 22-29. 49(25). P 764-7.
45. Reichler IM, Hubler M, Jöchle W, Trigg TE, Piché CA, Arnold S. (2003)The effect of GnRH analogs on urinary incontinence after ablation of the ovaries in dogs. *Theriogenology*. 60(7). P 1207-16.
46. Reichler IM, Barth A, Piché CA, Jöchle W, Roos M, Hubler M, Arnold S.(2006) Urodynamic parameters and plasma LH/FSH in spayed Beagle bitches before and 8 weeks after GnRH depot analogue treatment. *Theriogenology*. 66(9). P 2127-36.
47. Donovan CE, A Weston and MA Kutzler. (2013) Gonadotropin-Releasing Hormone Immunization to Treat Urethral Sphincter Mechanism Incompetence in a Bitch that Experienced an Adverse Reaction to Phenylpropanolamine. *J Vet Sci Med Diagn*. 2:3.
48. Donovan CE, Gordon JM, Kutzler MA. (2014) Gonadotropin-releasing hormone immunization for the treatment of urethral sphincter mechanism incompetence in ovariectomized bitches. *Theriogenology*. 81(2): p 196-202.
49. Bartges JW, Callens AJ. (2015)Urolithiasis. *Vet Clin North Am Small AnimPract*. 45(4). P 747-68.
50. Grauer FG. (2015) Prevalence of Uninary Calculi in Dogs and Cat. *Today's veterinary practice*. 5(5). P 13.

51. Nelson RW, Reusch CE. (2014) Animal models of disease: classification and etiology of diabetes in dogs Neus Bosch M, Pugliese M, Andrade C, Gimeno-Bayón J, Mahy N, Rodriguez MJ. (2015). Amyloid- β immunotherapy reduces amyloid plaques and astroglial reaction in aged domestic dogs. *Neurodegener Dis.* 15(1). P 24-37.
52. Marmor M, Willeberg P, Glickman LT, Priester WA, Cypess RH, Hurvitz AI. (1982) Epizootiologic patterns of diabetes mellitus in dogs. *American Journal Veterinary Research.* 43. P 465–470.
53. Guptill L, Glickman L, Glickman N. (2003) Time trends and risk factors for diabetes mellitus in dogs: analysis of veterinary medical data base records (1970-1999). *Vet J.* 165(3). P 240-7.
54. Rand JS, Fleeman LM, Farrow HA, Appleton DJ, Lederer R.(2004) Canine and feline diabetes mellitus: nature or nurture? *J Nutr.*134(8 Suppl). P 2072S-2080S.
55. Krook L, Larsson S, Rooney JR.(1960) The interrelationship of diabetes mellitus, obesity, and pyometra in the dog. *Am J Vet Res.* 21. P 120-7.
56. Mooney CT. (2011) Canine hypothyroidism: a review of etiology and diagnosis. *N Z Vet J.* 59(3). P 105-14.
57. Scott-Moncrieff JC. (2007) Clinical signs and concurrent diseases of hypothyroidism in dogs and cats. *VetClin North Am Small AnimPract.* 37. P709-722.
58. Dixon R.M., Mooney C.T. (1999) Canine serum thyroglobulin autoantibodies in health, hypothyroidism and nonthyroidal illness. *Res. Vet. Sci.* 66. P 243–246.
59. Panciera DL. (1994) Hypothyroidism in dogs: 66 cases (1987-1992). *J Am Vet Med Assoc.* 204(5). P 761-7.
60. Milne KL, Hayes HM Jr. (1981) Epidemiologic features of canine hypothyroidism. *Cornell Vet.* 71(1). P 3-14.
61. De Leo V, D'Antona D, Lanzetta D. (1993) Thyrotropin secretion before and after ovariectomy in premenopausal women. *GynecolEndocrinol.* 7(4). p 279-83.
62. Liu J, Chen G, Meng XY, Liu ZH, Dong S. (2014) Serum levels of sex hormones and expression of their receptors in thyroid tissue in female patients with various types of thyroid neoplasms. *Pathol Res Pract.* 210(12). P 830-5.
63. GünzelApel A.R., Seefeldt A., Eschricht F.M., Urhausen C., Kramer S., Mischke R, Hoppen H.O., Beyerbach M., Koivisto M., Dieleman S.J. (2009) Effects of gonadectomy on prolactin and LH secretion and the pituitarythyroid axis in male dogs. *Theriogenology*, 15. P 746–753.
64. Van Hagen MA, Ducro BJ, van den Broek J, Knol BW.(2005) Incidence, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of boxers”. *American Journal Veterinary Resources.* 66(2). P 307-312.
65. Demko, J; McLaughlin R. (2005) Developmental orthopedic disease. In Renberg, WC (ed). *Veterinary Clinics of North America Small Animal Practice: General Orthopedics.* WB Saunders Co, Philadelphia, PA. 35(5). P 1111-1135.
66. Martin SW, Kirby K, Pennock PW. (1980) Canine hip dysplasia: breed effects. *Can Vet J.* 21(11). P 293-6.
67. Priester, W A. (1972). Canine hip dysplasia: relative risk by sex, size, and breed, and comparative aspects. *Journal of American Veterinary Medical Association.* 160. P 735-739
68. Witsberger TH, Villamil JA, Schultz LG, Hahn AW, Cook JL. (2008) Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. *Journal of the American Veterinary Medical Association.* 232(12). P 1818-1824.
69. Torres de la Riva G, Hart BL, Farver TB, Oberbauer AM, Messam LL, Willits N, Hart LA. (2013) Neutering dogs: effects on joint disorders and cancers in golden retrievers. *The Public Library of Science One.* 8(2): e55937.
70. Grierson J, Asher L, Grainger K. (2011) An investigation into risk factors for bilateral canine cruciate ligament rupture. *Vet Comp OrthopTraumatol.* 24(3). P 192-6.
71. De Rooster H, De Bruin T, and van Bree H (2010) Morphology and Function of the Cruciate Ligaments. In: Muir P (Ed), *Advances in the Canine Cranial Cruciate Ligament.* Wiley-Blackwell. P 5-12.
72. Knebel J, Meyer-Lindenberg A. (2014) Etiology, pathogenesis, diagnostics and therapy of cranial cruciate ligament rupture in dogs. *TierarztPraxAusg K KleintiereHeimtiere.* 42(1):36-47.
73. Vasseur PB, Pool, RR, Arnoczky SP, Lau RE. (1985) Correlative biomechanical and histologic study of the cranial cruciate ligament in dogs. *Am J Vet Res.* 46, P 1842-1954.
74. Duval JM, Budsberg SC, Flo GL, Sammarco JL.(1999) Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs. *Journal of the American Veterinary Medical Association.* 215(6); p 811-814.
75. Whitehair, JG. Vasseur, PB. Willits, NH. (1993) Epidemiology of cranial cruciate ligament ruptures in dogs”. *Journal of the American Veterinary Medical Association.* 203(7). P 1016-1019.
76. Salmeri KR, Bloomberg MS, Scruggs SL, Shille V. (1991) Gonadectomy in immature dogs: effects on skeletal, physical, and behavioral development. *Journal of American Veterinary Medical Association.* 198 (7). P 1193-203.
77. Osmond CS, Marcellin-Little DJ, Harrysson OL, Kidd LB. (2006) Morphometric assessment of the proximal portion of the tibia in dogs with and without cranial cruciate ligament rupture. *Vet Radiol Ultrasound.* 47. P 136–141.
78. Griffon DJ. (2010) A review of the pathogenesis of canine cranial cruciate ligament disease as a basis for future preventive strategies. *Vet Surg.* 39. P 399–409.
79. Slocum B, Devine T. Cranial tibial thrust: A primary force in the canine stifle. *J Am Vet Med Assoc* 1983;183:456–459.
80. Morris E, Lipowitz AJ. (2001) Comparison of tibial plateau angles in dogs with and without cranial cruciate ligament injuries. *J Am Vet Med Assoc.* 218. P 363–366.

81. Prodromos CC, Han Y, Rogowski J, Joyce B, Shi K. (2007) A meta-analysis of the incidence of anterior cruciate ligament tears as a function of gender, sport, and a knee injury-reduction regimen. *Arthroscopy*.23(12). P 1320-1325.
82. Dragoo JL, Castillo TN, Braun HJ, Ridley BA, Kennedy AC, Golish SR. (2011) Prospective correlation between serumrelaxin concentration and anterior cruciate ligament tears among elite collegiate female athletes. *Am J Sports Med*. 39(10). P 2175-80.
83. Hopkins SG, Schubert TA, Hart BL. (1976) Castration of adult male dogs: effects on roaming, aggression urine spraying, and mounting. *Journal of the American Veterinary Medical Association*. 168. P 1108–10.
84. Neilson, J. C., Eckstein, R. A., & Hart, B. L. (1997) Effects of castration on problem behaviors in male dogs with reference to age and duration of behavior. *Journal of the American Veterinary Medical Association*. 211(2). P 180-182.
85. Zink MC, Farhooody P, Elser SE, Ruffini LD, Gibbons TA, Rieger RH. (2014) Evaluation of the risk and age of onset of cancer and behavioral disorders in gonadectomized Vizslas. *J Am Vet Med Assoc*. 244(3). P 309-19.
86. Kim HH, Yeon SC, Houpt KA, Lee HC, Chang HH, Lee HJ. (2006) Effects of ovariectomy on reactivity in German Shepherd dogs. *Vet J*. 172(1). P 154-9.
87. Borchelt, P.L. (1983) Aggressive behavior of dogs kept as companion animals: classification and influence of sex, reproductive status and breed. *Appl. Anim. Ethol*. 10. P 45-61.
88. Reisner, IR. Houpt, KA. Shofer, FS. (2005) National survey of owner-directed aggression in English Springer Spaniels". *Journal of American Veterinary Association*. 227(10). P 1594-1603.
89. Lei ZM, Rao CV, Kornyei JL, Licht P, Hiatt ES. (1993) Novel expression of human chorionic gonadotropin/luteinizing hormone receptor gene in brain. *Endocrinology*. 132(5). P 2262-70.
90. Croxatto H, Arrau J, Croxatto H. (1964) Luteinizing hormone-like activity in human median eminence extracts. *Nature*. 204. P 584-5.
91. Bagshawe KD, Orr AH, Rushworth AG. (1968) Relationship between concentrations of human chorionic gonadotrophin in plasma and cerebrospinal fluid". *Nature*. 217(5132).p 950-1.
92. Emanuele NV, Tentler J, Scanlon S, Reda D, Kirsteins L. (1991) Intracerebroventricular luteinizing-hormone (LH) depresses feeding in male-rats. *Neuroendocrinology Letters*. 13. P 413–418.
93. Kawakami M, Sawyer CH. (1959) Induction of behavioral and electroencephalographic changes in the rabbit by hormone administration or brain stimulation. *Endocrinology*. 65. P 631–643.
94. Telegdy G, Rozsahegyi G. (1971) Effect of gonadotropins on extinction of an avoidance conditioned reflex and exploratory behaviors in the rat". *Acta Physiologica Academiae Scientiarum Hungaricae*. 40. P 209–214.
95. Oates SM. (2014) Uncovering cognitive decline: the emergence of canine cognitive dysfunction in veterinary medicine and its implications for understanding Alzheimer's disease. *Vet Herit*. 37(2). P 47-51.
96. Schütt T, Toft N, Berendt M. (2015) Cognitive Function, Progression of Age-related Behavioral Changes, Biomarkers, and Survival in Dogs More Than 8 Years Old. *J Vet Intern Med*. 29 (6). P 1569-77.
97. Casadesus G, Milliken EL, Webber KM, Bowen RL, Lei Z, Rao CV, Perry G, Keri RA, Smith MA. (2007) Increases in luteinizing hormone are associated with declines in cognitive performance. *Mol Cell Endocrinol*.269(1-2). P 107-11.
98. Verdile G, Laws SM, Henley D, Ames D, Bush AI, Ellis KA, Faux NG, Gupta VB, Li QX, Masters CL, Pike KE, Rowe CC, Szeoke C, Taddei K, Villemagne VL, Martins RN; AIBL Research Group.(2014) Associations between gonadotropins, testosterone and β amyloid in men at risk of Alzheimer's disease. *Mol Psychiatry*. 19 (1). P 69-75.
99. Butchart J, Birch B, Bassily R, Wolfe L, Holmes C. (2013) Male sex hormones and systemic inflammation in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 27 (2). P 153-6.
100. Schmidt F, Boltze J, Jäger C, Hofmann S, Willems N, Seeger J, Härtig W, Stolzing A. (2015) Detection and Quantification of β -Amyloid, Pyroglutamy A β , and Tau in Aged Canines. *J NeuropatholExp Neurol*. 74(9). P 912-23.
101. Leroy BE, Northrup N.(2009) Prostate cancer in dogs: comparative and clinical aspects. *Vet J*. 180(2). P 149-62.
102. Cornell KK, Bostwick DG, Cooley DM, Hall G, Harvey HJ, Hendrick MJ, et al. (2000) Clinical and pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases". *Prostate*. 45(2): p 173–83.
103. Leav I, Ling GV. (1968) Adenocarcinoma of the canine prostate gland. *Cancer*. 22: 1329–45.
104. Reiter E, McNamara M, Closset J, Hennen G. (1995) Expression and functionality of luteinizing hormone/chorionic gonadotropin receptor in the rat prostate. *Endocrinology*. 136(3). P 917-23.
105. Ponglowhapan S, Church DB, Khalid M. (2012) Expression of luteinizing hormone and follicle-stimulating hormone receptor in the dog prostate. *Theriogenology*.78(4). P 777-83.
106. Hardie, E.M., Barsanti, J.A., Rawlings, C.A. (1984) Complications of prostatic surgery. *Journal of the American Animal Hospital Association*. 20. p 50–56.
107. Basinger, R.R., Rawlings, C.A., Barsanti, J.A., Oliver, J.E. (1989) Urodynamic alterations associated with clinical prostatic diseases and prostatic surgery in 23 dogs. *Journal of the American Animal Hospital Association*. 25, p 385–392.
108. Osborne CA, Low DG, Perman V, Barnes DM. (1968) Neoplasms of the canine and feline urinary bladder: Incidence, etiologic factors, occurrence, and pathological features. *Am J Vet Res*. 29. P 2041- 2055.
109. Straffuss AC, Dean MJ. "Neoplasms of the canine urinary bladder". *Journal American Veterinary Medical Association*, 1975: 166:1161-1163.

110. Travin G, Patnai A, Greene R. (1978) Primary urethral tumors in dogs. *J Am Vet Med Assoc.* 172. P 931-933.
111. Wilson GP, Hayes HM, Casey HW. (1979) Canine urethral cancer. *Journal American Animal Hospital Association.* 15. P 741-744.
112. Esplin DG. Urinary fibromas in dogs: 51 cases (1981-1985). (1987). *Journal American Veterinary Medical Association.* 190. P 440-444.
113. Norris AM, Laing EJ, Valli VE, Withrow SJ, Macy DW, Ogilvie GK, Tomlinson J, McCaw D, Pidgeon G, Jacobs RM. (1992) Canine bladder and urethral tumors: A retrospective study of 115 cases (1980-1985). *Journal of Veterinary Internal Medicine.* 6(3). P 145-153.
114. Schwalenberg T, Stolzenburg JU, Ho TP, Mallock T, Hartenstein S, Alexander H, Zimmermann G, Hohenfellner R, Denzinger S, Burger M, Horn LC, Neuhaus J. (2012) Enhanced urothelial expression of human chorionic gonadotropin beta (hCG beta) in bladder pain syndrome/interstitial cystitis (BPS/IC). *World J Urol.* 30. P. 411-417.
115. Reichler IM, Welle M, Sattler U, Jöchle W, Roos M, Hubler M, Barth A, Arnold S. (2007) Comparative quantitative assessment of GnRH- and LH-receptor mRNA expression in the urinary tract of sexually intact and spayed female dogs. *Theriogenology.* 67(6). P 1134-42.
116. Wycislo KL, Fan TM. (2015) The immunotherapy of canine osteosarcoma: a historical and systematic review. *J Vet Intern Med* 29. P 759-769.
117. Cooley DM, Beranek BC, Schlittler DL, Glickman NW, Glickman LT, Waters DJ. (2002) Endogenous gonadal hormone exposure and bone sarcoma risk. *Cancer Epidemiology, Biomarkers, and Prevention.* 11. P 1434-40.
118. Ru G, Terracini B, Glickman LT. (1998) Related risk factors for canine osteosarcoma. *Veterinary Journal.* 156. P 31-39.
119. Yamamoto S, Hoshi K, Hirakawa A, Chimura S, Kobayashi M, Machida N. (2013) Epidemiological, clinical and pathological features of primary cardiac hemangiosarcoma in dogs: a review of 51 cases. *J Vet Med Sci.* 75. P 1433-1441.
120. Lei ZM, Rao CV, Pridham D. (1993) Novel coexpression of human chorionic gonadotropin/luteinizing hormone receptors and their ligand hCG in human fallopian tubes. *The Journal of Clinical Endocrinology and Metabolism.* 132. P 2262-70.
121. Reshef E, Lei ZM, Rao CV, Pridham DD, Chegini N, Luborsky JL. (1990) The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. *J Clin Endocrinol Metab.* 70(2). P 421-30.
122. Ware WA, Hopper DL. (1999) Cardiac tumors in dogs: 1982-1995. *Journal Veterinary Internal Medicine.* 13. P 95-103.
123. Su S, Fang F, Liu Y, Li Y, Ren C, Zhang Y, Zhang X. (2013) The compensatory expression of reproductive hormone receptors in the thymus of the male rat following active immunization against GnRH. *Gen Comp Endocrinol.* 185. P 57-66.
124. Shoop SJ, Marlow S, Church DB, English K, McGreevy PD, Stell AJ, Thomson PC, O'Neill DG, Brodbelt DC. (2015) Prevalence and risk factors for mast cell tumours in dogs in England. *Canine Genet Epidemiol.* 26;2:1. doi: 10.1186/2052-6687-2-1.
125. Venencie PY, Méduri G, Pissard S, Jolivet A, Loosfelt H, Milgrom E, Misrahi M. (1999) Luteinizing hormone/human chorionic gonadotrophin receptors in various epidermal structures". *British Journal of Dermatology.* 141(3). P 438-46.
126. White CR, Hohenhaus AE, Kelsey J, Procter-Gray E. (2011) Cutaneous MCTs: associations with spay/neuter status, breed, body size, and phylogenetic cluster. *Journal American Animal Hospital Association.* 47(3). P 210-6.
127. Waters DJ, Kengeri SS, Clever B, Booth JA, Maras AH, Schlittler DL, Hayek MG. (2009) Exploring mechanisms of sex differences in longevity: lifetime ovary exposure and exceptional longevity in dogs". *Aging Cell.* 8(6). P 752-5.
128. Papadopoulos V, Berkovich A, Krueger KE. (1990) The role of diazepam binding inhibitor and its processing products at mitochondrial benzodiazepine receptors: regulation of steroid biosynthesis. *Neuropharmacology.* 30(12B). P 1417-23.
129. Nicolini G, Balzan S, Morelli L, Iacconi P, Sabatino L, Ripoli A, Fommei E. (2014) LH, progesterone, and TSH can stimulate aldosterone in vitro: a study on normal adrenal cortex and aldosterone producing adenoma. *Horm Metab Res.* 46(5). P 318-21.
130. Lasley B, Conley A, Morrison J, Rao CV. (2015) Identification of Immunoreactive Luteinizing Hormone Receptors in the Adrenal Cortex of the Female Rhesus Macaque. *Reprod Sci.*
131. Bukovsky A, Indrapichate K, Fujiwara H, Cekanova M, Ayala ME, Dominguez R, Caudle MR, Wimalsena J, Elder RF, Copas P, Foster JS, Fernando RI, Henley DC, Upadhyaya NB. (2003) Multiple luteinizing hormone receptor (LHR) protein variants, interspecies reactivity of anti-LHR mAb clone 3B5, subcellular localization of LHR in human placenta, pelvic floor and brain, and possible role for LHR in the development of abnormal pregnancy, pelvic floor disorders and Alzheimer's disease. *Reprod Biol Endocrinol.* 3.1. p 46.
132. Wahjoepramono EJ, Wijaya LK, Taddei K, Bates KA, Howard M, Martins G, deRuyck K, Matthews PM, Verdile G, Martins RN. (2011) Direct exposure of guinea pig CNS to human luteinizing hormone increases cerebrospinal fluid and cerebral beta amyloid levels. *Neuroendocrinology.* 94(4). P 313-22.
133. Hammar O, Veress B, Montgomery A, Ohlsson B. (2012) Expression of luteinizing hormone receptor in the gastrointestinal tract in patients with and without dysmotility. *DTI.* 6. P 13-18.
134. Sand E, Bergvall M, Ekblad E, D'Amato M, Ohlsson B. (2013) Expression and distribution of GnRH, LH, and FSH and their receptors in gastrointestinal tract of man and rat. *Regul Pept.* 10. P 24-28.

135. Ducker TE, Boss JW, Altug SA, Mehrabian H, Dekeratry DR, Clench MH, Mathias JR. (1996) Luteinizing hormone and human chorionic gonadotropin fragment the migrating myoelectric complex in rat small intestine. *NeurogastroenterolMotil.* 8(2). P 95-100.
136. Seiki K, Sakabe K, Kawashima I, Fujii-Hanamoto H. (1990) Hormone and immune response, with special reference to steroid hormone 1. A short review. *The Tokai journal of experimental and clinical medicine.* 15(2-3). P 191-9.
137. Appel SL, Lefebvre SL, Houston DM, Holmberg DL, Stone JE, Moore AE, Weese JS. (2008) Evaluation of risk factors associated with suture-niduscystoliths in dogs and cats: 176 cases (1999-2006). *Journal American Veterinary Medical Association.* 233(12).p 1889-95.
138. Cooley DM, Schlittler DL, Glickman LT, Hayek M, Waters DJ. (2003) Exceptional longevity in pet dogs is accompanied by cancer resistance and delayed onset of major diseases. *Journal Gerontology A Biological Sciences Medical Sciences.* 58(12). P 1078-84.
139. Galac S, Kars VJ, Klarenbeek S, Teerds KJ, Mol JA, Kooistra HS.(2010) Expression of receptors for luteinizing hormone, gastric-inhibitory polypeptide, and vasopressin in normal adrenal glands and cortisol-secreting adrenocortical tumors in dogs. *DomestAnimEndocrinol.* 39(1). P 63-75.
140. Hart BL. (2001) Effect of gonadectomy on subsequent development of age-related cognitive impairment in dogs. *Journal American Veterinary Medical Association.* 219(1). P 51-6.
141. Hess RS, Kass PH, Ward CR.(1998) Association between hyperadrenocorticism and development of calcium-containing uroliths in dogs with urolithiasis. *Journal American Veterinary Medical Association.* 212(12). P 1889-91.
142. Jochle W. (1991) Pet population Control. *Journal Veterinary Medical Association.* 198. P 1225-1230.
143. Kawakami E, Kobayashi M, Ikeda A, and Hori T.(2014) Occurrence of Prostatic Adenocarcinoma in Castrated Dogs and Prostatic Superoxide Dismutase Activity of Healthy dogs before and after Castration. *Asian Journal of Animal and Veterinary Advances.* 9(6). P 362-366.
144. Lukacs H., Hiatt E. S., Lei Z. M. and Rao CV (1995) Peripheral and intracerebroventricular administration of human chorionic gonadotropin alters several hippocampus-associated behaviors in cycling female rats. *Hormones and Behavior.* 29. P 42-58.
145. Olson PN, Kustritz MV, Johnson SD. (2001) Early-age neutering of dogs and cats in the United States (a review). *Journal Reproduction and fertility supplement.* 57. P 223-232.
146. Prymak, C. et al. (1988) Epidemiologic, clinical, pathologic, and prognostic characteristics of splenic hemangiosarcoma and splenic hematoma in dogs: 217 cases (1985). *Journal of American Veterinary Medical Association.* 193(6). P 706-712.
147. Rao CV, Li X, Toth P, Lei ZM, Cook VD. (1993) Novel expression of functional human chorionic gonadotropin/luteinizing hormone receptor gene in human umbilical cords. *The Journal of Clinical Endocrinology and Metabolism.* 77(6). P 1706-14.
148. Richter KP, Ling V. (1985) Clinical response and urethral pressure profile changes after phenylpropanolamine in dogs with primary sphincter incompetence. *Journal of American Veterinary Association.* 187. P 605-611.

Please Submit your Manuscript to Cresco Online Publishing

<http://crescopublications.org/submitmanuscript.php>