THE OVARIAN CYCLE AND OESTRUS INDUCTION IN THE BITCH, PROSTATE DISEASES IN THE MALE DOG

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The more we study the bitch hormonal cycle, the more complex it appears.
Indeed, the interest for the bitch reproductive cycle was relatively reduced until some years ago and often associated to extrapolations from studies realized in other species. Since the last 10-20 years, more and more input has been progressively given to the study of reproduction in this species and the peculiarity of canine, among the vast majority of other mammals, slowly arises. Nowadays, dogs are studied per se, but are also used as models for other species of carnivores, particularly for endangered species of wild carnivores. This allows an emerging field of discovery, relative to the physiology of reproduction.
However, it is not the objective of this paper to cover all the aspects of the bitch physiology of reproduction. Many good reviews have been published recently and are certainly worth to read (see further reading advises below). Only some of the most recent information are presented herein.

1. The bitch' estrous cycle.

The bitch is a seasonal monoestral species, with a mean interestrous interval of 7 months. The bitch cycle is characterized by the relatively long duration of each periods of its cycle. Pro-estrus lasts 7-10 days, just as estrus; metestrus/diestrus lasts approximately 2 months, and the cycle ends with an obligatory extremely long anestrus of a mean duration of 4-5 months. However, there are many variations: variation in the duration of the respective periods (proestrus can be as long as 3-4 weeks or as short as a few days), variation in the individual cycle's length (10-25 % of bitches show differences between their successive cycles), variation between individuals (some German Shepherd dogs have a mean cycle length of 4 months, some others have a cycle of 6-7 months) and variation between breeds (classical example is German Shepherd and Basenji which have 4 and 12 months of cycle duration, respectively).
In conclusion, variability is certainly the main characteristic of the bitch's reproductive cycle and this can be applied to any part of the bitch's reproductive life: variations in the hormonal profiles, in the ovarian events, in reproductive behavior…

1.1. The hormonal profile of the bitch

At the end of the obligatory 1-8 months of anestrus, and from early through late proestrus, estradiol concentrations increase to reach a peak value approximately 24-48 hours before the LH surge, then they rapidly decrease throughout estrus. This decrease in estradiol can vary from one bitch to another, and, even if the rule seems to be a return to basal values around days 4-6 of estrus, in some animals estradiol may remain elevated up to the end of estrus and sometime until early metestrus. This explains why some animals may continue to bleed until the very late end of estrus whereas the vast majority of them stop before that. Continuous

estrogen impregnation can also been observed in pathological cases, associated then with follicular cysts and partial/total anovulation.
The reasons why estrogens begin to progressively increase during late anestrus are not yet elucidated, but correspond certainly to the occurrence of a new follicular wave induced by the increase of LH pulsatility, observed 2-4 weeks before behavioral proestrus.

The estrogen secretion results in vaginal cornification, vulvar swelling and behavioral signs of proestrus. At the end of proestrus, a decline in plasma estradiol content associated with a rise in plasma progesterone (reflecting the preovulatory luteinisation, characteristic of the bitch's estrous cycle) is responsible for the preovulatory LH surge. The change in the estradiol/progesterone ratio initiates the behavioral and physiological changes associated with the estrus period. Among these changes, we have to mention those occurring in vaginal cytology (shift from mostly intermediate cells to keratinized cells) and vaginoscopy (shift from primary/secondary folds to cranulations), acceptation of mating, reduced vulvar blood discharges (shift from bloody to seromucous). At the end of estrus, when estradiol returns to basal level, an abrupt change in vaginal smears is characterized by a decrease in vaginal cornification and reappearance of intermediate/parabasal cells (in general 6 to11 days after the LH surge, referred as day 0). This period, based on the abrupt vaginal changes, is called metestrus (often called "rush of metestrus"). In canine, metestrus does not refer, as in other species, to the period of corpus luteum development. Indeed, the CL development begins in reality at the end of proestrus. That's the reason why metestrus, in canine, refers to vaginal cytological changes rather than to hormonal changes like in other species. Metestrus could be considered as a period lasting a mean of 7 to 10 days and is followed by the period of diestrus, corresponding to a complete and maximal progesterone secretion.
During the luteal phase, the maximal progesterone secretion is observed around days 15-25 after the LH surge and it is then followed by a progressive decline until days 55-70 in non-pregnant cycles; this corresponds to a progressive functional arrest of the corpus luteum function. The apparent termination of the luteal phase (characterized by the inability of the standard assays to detect any circulating progesterone) is considered to be the onset of anestrus. In pregnant bitches, the luteal phase seems remarkably similar to that of the non-pregnant ovarian cycle, but, in fact, the pregnant luteal phase is associated with a huge increase in progesterone production. This different pattern of progesterone secretion is not (or not in a significant way) detected in the plasma circulation, this is probably due to an increased and rapid metabolization of the produced progesterone, leading to a dramatic increase of progesterone metabolites measured in the feces (Gudermuth et al., 1998). This different pattern of progesterone secretion from days 25 and 35 suggests a pregnancy specific stimulation of progesterone production, which may be related either directly to the significant prolactin increase observed during pregnancy or indirectly to the concomitant increase of relaxin in pregnant animals. At whelping, the luteal function ended by an abrupt pre-partum functional arrest (or luteolysis?) induced by the placental prostaglandin PGF2alpha release observed at parturition.
Progesterone then continues to slowly decrease and reach basal concentrations only during the anestrus. In fact, the progesterone decrease is slow and, if plasma concentrations under 1 ng/ml are already observed from days 60-70 after the LH surge (this defines the end of the diestrus period and the beginning of the anestrus period), a deep look into plasma progesterone concentration allows to observe that the lowest plasma levels of progesterone (around 10-50 pg/ml) are achieved only in mid- to late anoestrus. This observation realized a long time ago by Concannon et al as well as by Jöchle who assayed plasma progesterone concentrations with very highly sensitive assays has been recently confirmed, simultaneously by Jeffcoate and by our laboratory where we examined the ovarian progesterone contents in

anestrus. It appears clearly that the ovarian progesterone content is never basal before days 130-160 of the cycle. The role of this continuous progesterone production by the ovarian corpus luteum remains to be determined with regard to the estrous cycle's regulations. Recent data demonstrate a higher basal concentration of LH during the pregnant luteal cycle, associated with low amplitude pulses, in opposition with low basal plasma LH concentration associated with high amplitude pulses in non-pregnant animals. Similarly, FSH was demonstrated to remain basal in non-pregnant animals whereas its plasma concentrations slowly increase from days 20-25 to reach maximal concentrations around parturition. An abrupt decrease is then observed, concomitantly with the progesterone decrease associated with whelping.

1.2. Ovulation and Fertilization

In dogs, the initiation of estrus behavior may be observed as early as 3-5 days before ovulation or as late as 3 days after ovulation. The ovulation occurs about 2 days after the preovulatory LH surge and appears to be simultaneous, while a clear evidence of this has not yet been clearly obtained. In clinical practice, ovulation is timed by using successive serum progesterone assays to detect the rapid preovulatory luteinisation, which occurs during the preovulatory LH surge, or by monitoring the vulvar detumescence and vaginal wrinkling that accompany the preovulatory decline in estradiol. Ovulation has also been timed by ultrasound exams to detect the loss of the anechoic appearance of preovulatory follicular fluid. Ovulation can also been estimated retrospectively as it occurred 5-7 days before the decline in vaginal cornification at the end of estrus or early metestrus. Oocytes are ovulated as primary ovocytes, which undergo a slow maturation over 2 or 3 days in the oviducts. Following ovocytes' maturation, many bitches may remain fertile for 3 days or longer. Recently, the role of cervical closure observed in Beagle dogs in a mean of 6.8 days after the LH surge (from 2 days before up to 1 day after metestrus) has been postulated to be a potential limiting factor for a late mating and fertilization.
The long fertile lifespan of the spermatozoa (from 4-6 days) and also maybe of the mature ovocytes may explain the high fertility rates (>90%) obtained in commercial dogs' breeding facilities. The opportunity to have multiple sires for a single litter is great if mating opportunities are not strictly controlled.

Blastocysts enter the uterus around days 9-12, the pre-implantation uterine swellings are grossly detectable around day 16, trophoblast attachment occurs around day 18, and implantation around day 20 after the LH surge. Clinically, pregnancy can be diagnosed by manual palpation of uterine enlargements between days 20 and 35, by ultrasounds after day 20 (embryonic vesicles are detectable between days 16-20, embryonic structures between days 21-23, fetal heartbeats between days 23-25, and the zonary placenta from day 28) and by radiography after days 40-42 after the LH surge. Fetal heart rate can be easily monitored by ultrasonography, beginning at days 25- 28. The average fetal heart rate is around 230 bpm and signs of fetal distress are generally characterized by heartbeats below 200 bpm. Biochemical pregnancy tests are available (detection of protein C reactive, fibrinogen), but are not pregnancy specific and may lead to false positive cases. Serum relaxin assay is pregnancy specific as only the placenta in the canine species secretes relaxin and this allows a pregnancy diagnosis as early as day 25 after the LH surge.

1.3. The Corpus Luteum

The corpus luteum is an ephemeral endocrine gland, appearing after rapid growth and differentiation of both theca and granulosa cells. R. de Graaf, first, described the transformation of the ovarian follicle into a corpus luteum in 1672, but it was only in 1901 that Fraenckel and Cohn recognized the corpus luteum importance for implantation and maintaining of a normal pregnancy. Then, Corner and Allen (1929) identified progesterone as the primary and main endocrine secretory product of the corpus luteum. All the structural and functional characteristics of this gland seem to have only one major objective: the production of progesterone. While the corpus luteum requirement during pregnancy was demonstrated in nearly all species of mammals (Fraenckel, 1903, Drummond and Asdel, 1926, Johnson and Challans, 1930, Hammond, 1953, Sokolowski, 1971), corpora lutea of the cycle, which appear after a cycle without mating or with infertile mating, have a poorly understood function. In canine, several authors have demonstrated that the ovaries are absolutely required during all pregnancy and that ovariectomy or corpus luteum excision is associated with rapid abortion (Sokolowski, 1974, Concannon et al., 1977b, Tsutsui, 1988). Furthermore, some immunocytochemical studies on the canine placenta indicate that there is no, or just in really reduced amount, steroidogenesis in canine placenta (Kiso et Yamauchi, 1984). This observation confirms the necessary role of luteal progesterone in this species. The minimal concentration of progesterone required to maintain pregnancy in bitches appears to be around 1 to 2 ng/ml (Concannon et Hansel, 1977, Vickery et Mc Rae, 1980). A drop of progesterone below this value for more than 24 h is generally associated with abortion.

To survive, the luteal cells are dependent of different substances called “ luteotropins ”. The luteal function is regulated by endocrine, paracrine or autocrine luteotropins. In canine, the main luteotropins are LH and prolactin, both arriving from the pituitary; moreover, temporal variations in CL hormono-dependancy exist. Indeed, it was demonstrated that hypophysectomy induced immediate abortion in pregnant animals and a dramatic decline in plasma progesterone in non-pregnant animals (Concannon, 1980, Okkens et al., 1986). The respective roles of LH and prolactin are still controversial. The administration of one high dose of anti-LH antiserum induced a decline in plasma progesterone in some animals (Concannon et al., 1987), but, in others, it seems to be devoid of any effect (Okkens et al., 1990). Treatments with high doses of a long acting GnRH antagonist, which inhibited LH secretion, induce abortion in bitches, suggesting a luteotropic role of LH in this species (Vickery et al., 1987). However, a treatment with lower doses, still suppressing the circulating LH, was not able to induce similar abortions, except after day 40 (Onclin et al., 2000). LH administration during pregnancy did not prevent the luteolysis resulting from a dopamine agonist treatment, but was able to increase plasma progesterone secretion when administered during the last third of pregnancy. Similarly, the suppression of prolactin secretion by a dopamine agonist induced abortion in pregnant bitches from as early as days 25-30. This suggests a clear luteotropic role of prolactin during that period (Concannon et al., 1987, Post et al., 1987, Wichtel et al., 1987, Onclin et al., 1993). Before that time, the dopamine agonists were not able to induce a continuous progesterone inhibition and an abortion; this demonstrates the reality of a dynamic luteal regulation in the bitch. The relative dependency of the corpus luteum to LH and prolactin is different relative to the periods of pregnancy. Indeed, the corpus luteum is more independent during the first third of pregnancy, and, the closest to the LH surge, the most independent the corpus luteum seems to be. Before day 10, hypophysectomy is unable to induce a corpus luteum functional arrest (Concannon, 1980, Okkens et al., 1986). Similarly, the corpus luteum remains resistant to several indirect luteolytic agents like dopaminergic agonists (bromocryptine: Concannon et al., 1987) or

GnRH antagonists (Vickery et al., 1987, 1988), and to direct luteolytic agents like prostaglandin F2alpha (Concannon et Hansel, 1977). The reasons for this relative and apparent independence of CL during the first third and maybe the first half of pregnancy are not yet elucidated. This appears to be independent of LH or prolactin receptor variations as Fernandes et al. (1987) observed a constant expression of both receptors during luteal phases of non-pregnant animals.
In clinical studies on bitches, Conley & Evans (1982), Concannon et al. (1987), Post et al. (1987), Wichtel et al. (1987), as well as Verstegen & Ballabio (1992) have demonstrated that administration of a dopamine agonist was able to inhibit progesterone secretion and to induce abortion during late pregnancy.

In conclusion, if prolactin appears to be the essential luteotropin in canines, the role of LH is far from being clear, but does not appear to be essential. The conclusions of some of our recent works (Onclin et al., 2000) were that, "(a) LH immunoneutralisation does not impair CL function, (b) GnRH antagonists induced dose and time dependent effects. Only high doses result in a progesterone decrease, and, later is the pregnancy, longer is this decrease. Continuous GnRH antagonist administration, even if associated with a complete LH inhibition, is not associated with detectable effects on progesterone and (c) LH administration does moderately stimulate progesterone and may modify prolactin in the last third of pregnancy."
During a pregnant diestrus, a concomitant or closely related increase of relaxin and prolactin is observed. The role of relaxin, essentially produced by the placenta in this species, is not yet clear. Relaxin may play a major role directly at the corpus luteum level or indirectly through prolactin or progesterone secretions. Indeed, in non-pregnant animals, no increase of prolactin nor neither relaxin nor progesterone synthesis and metabolism is observed.

The role and plasma pattern of secretion of estradiol during the luteal phase are not yet clearly elucidated. Some recent data from our laboratory show a parallel evolution of estradiol and progesterone. Plasma 17beta-estradiol increases when corpus luteum develops and decreases when CL functional arrest is observed. Estrogens may participate in the progesterone secretion, maybe by increasing LH receptor numbers at the CL levels.
The pregnancy causes a resistance to exogenous insulin in diabetic bitches, and appears to cause mild insulin resistance in some normal bitches. This increase in insulin resistance is also associated with an increased production of GH; both phenomenons lead to subclinical to clinical hyperglycemia. The GH increase observed in pregnant as well as in non pregnant animals in relation to the progesterone increase appears to be related to a de novo synthesis of GH by the mammary gland, and not by an increase of the pituitary secretion of GH.

1.4. The Post-Partum Anestrus and the Interestrous Intervals

Factors regulating the duration of anestrus, and thus the interestrous interval, have not been extensively studied in dogs. Heritability seems likely since many bitches of at least one breed (German Shepherd) have characteristically short (4-5 months) interestrous intervals, and a few breeds appear to have average cycles' lengths longer than the 7 months commonly seen in Beagles and other breeds. The cycle length increases with age over 8 years in Beagles. Prolactin is most likely inhibitory for the termination of anestrus and initiation of proestrus. Indeed, the suppression of prolactin with a dopamine agonist from as soon as mid-dioestrus up to late anoestrus can result in a precocious onset of proestrus, within 10-50 days, resulting in an interestrous interval of about 100-170 days and 40-120 days less than normal. The resulting induced estrus is fertile, except when the treatment is given in diestrus, this period is probably associated with a poor uterine regeneration and this prevents an implantation to occur. The normal physiology of anestrus includes the presence of elevated levels of serum FSH (Kooistra 2000, Onclin & Verstegen 2001) and relatively low levels of LH. Increased LH pulsatility, as a result of increased GnRH pulse frequency, stimulates ovarian activity at the end of anestrus. The key element in the transition from anestrus to proestrus is probably LH as suggested by the fact that administration of only highly purified LH, three times a day for one week, induced proestrus in all treated bitches. Even if FSH levels are high during late anoestrus, administration of FSH alone is not associated with consistent estrus induction (Verstegen et al.).

1.5. Anoestrus Termination and Estrus Induction

For many reasons, it is sometimes necessary to induce a fertile estrus in bitches. Indications may include possible missed breeding opportunities, failure to conceive on the previous cycle, limited availability of a specific male, etc... Some control of the bitches' cycle is also necessary if artificial breeding technologies have to be applied (dogs and non-domestic carnivores). Unfortunately, the success rate has been rather limited up to date, and several drugs that have been used are not actually available in the USA.

Reliable fertile estrus induction protocols have been difficult to define in the bitch, because of the lack of understanding of the hormonal events preceding folliculogenesis and responsible for the termination of anestrus (see before). Anestrus is characterized by a slow and progressive decline in plasma progesterone concentrations, with basal levels obtained around days 120-160, by a progressive increase of FSH with a maximum observed just before the proestrus, and by an increase of LH pulsatility and surge amplitude during the last third of anestrus. Similarly, prolactin concentrations slowly decrease to reach basal levels only on the beginning of the new estrous cycle. LH is certainly essential for the initiation of the folliculogenesis in dogs, but prolactin, directly or indirectly, is actually thought to play a major role in the inhibition of the cycle or in the initiation of the new estrous cycle.

Estrous induction in bitches may be considered as a treatment for primary anestrus (lack of estrous cycling by 24 months of age) or secondary anestrus (lack of estrous cycling within 12 months from the previous cycle) for which no underlying cause was found. Owners of working dogs or exhibition dogs may request induction of estrus to allow pregnancy and whelping at a more convenient time than that offered by the bitch's natural cycle. Estrous induction is also useful for breeders, who are usually dealing with the problem of excessive natural estrous synchronization of their bitches, which may result in a lack of available puppies in certain periods of the year. Drugs' protocols that have been described for induction of estrus in bitches include the use of gonadotropins (Equine Chorionic Gonadotropin: eCG, FSH, LH, Human Chorionic Gonadotropin: hCG) alone or in associations, estrogens (diethylstilbestrol: DES, estradiol benzoate) alone or in associations, GnRH and its analogues, and the dopamine agonists (bromocryptine, cabergoline) or the serotonine antagonists (metergoline).
Unfortunately, many of the proposed protocols are unreliable or associated with side effects (superovulation, supra-physiologic estrogen production, antibodies induction, poor ovulation rates or short luteal phases,…). Furthermore, the comparison of different protocols is often difficult, this is due to the unknown history of the bitches used and to the various criteria used to assess the success of the treatment (e.g.: induction of behavioral estrus, evidence of ovulation, full-term pregnancies,...). Finally, control groups are rarely associated to the treated groups even if this is the only clear demonstration of the treatment's efficacy. A

recent study from England et al. (2000) demonstrated, using ultrasonography and histology, that, except for the dopamine agonist treatments, in all hormonal protocols, the follicular dynamics differed widely from those of spontaneous estrus.

1.6 Conclusion

The ovarian cycle of the bitch is slowly discovered. Many recent studies have demonstrated some similarities, but mainly numerous differences with the cycle of other domestic animal species. Dogs deserve to be studied per se and the extrapolation of data from other mammals is certainly no longer valid anymore. The hormonal profiles are characteristic and the variations observed are responsible for many tissular changes that can be used by the veterinarian to improve breeding results.
However, even if there are new developments and an increased knowledge about the bitch' estrous cycle, there are still many points which deserve further studies.

2. Prostate and Prostate Diseases

The prostate is the only accessory sexual gland in the dog and is responsible for many clinical troubles in the entire adult male dogs during the second half of their life.

2.1. Investigation Techniques

The diagnosis of prostate diseases is never easy; indeed, none of the clinical signs are really specific and the clinical expression of the prostate disease is often highly variable. However, the development of small animal clinical sciences during the last recent years has led to the development of numerous techniques of investigation allowing an easier characterization of the prostate diseases. Among the most interesting techniques, we find the ultrasonography, semen/prostate fluid collection and analysis, radiography, biopsies and laparoscopy.
The different diagnostic tools available don't have the same clinical value and interests. Abdominal and rectal palpation are easy to realize, but they generally give poor indications about the possible existence of a prostate disease, without a real diagnosis. Radiography is also often limited as for other soft tissues examinations, except when a prostate tumor is suspected; in this case, the radiography of the caudal abdomen may reveal the presence of lymph nodes or bones metastasis.
On the contrary, ultrasonography associated with a prostatic fluid analysis can be considered as two essential techniques. The first one allows a correct evaluation of the size, the location, and the structure of the prostate. It's the only non-invasive technique that can show clearly cysts, abscesses, cavities, edema, fibrosis, calcification,… The second technique allows a distinction between acute and chronic inflammatory, infectious, degenerative or tumorous processes. Moreover, the prostatic fluid collected can be used for the realization of a bacterial analysis and antibiogram. Biopsy is easily realized under ultrasonographic guidance, but can also be performed by laparoscopy or laparotomy. The histological investigation will allow a precise and complete diagnosis. An ideal prostate investigation should at least include abdominal and rectal palpations, ultrasonographic exam and prostatic fluid analysis. If a prostate tumor is suspected following those exams, a complementary radiography can be realized to detect metastasis. The differential diagnosis with low urinary tract diseases always requires a urinary analysis to be performed.

The diagnostic methodologies available today are various and numerous. A progressive and logical approach in their selection is needed to allow for a clear and precise diagnosis, leading finally to the establishment of the prognosis and to the selection of the best treatment.

2.2. Prostate Pathologies and Treatments

2.2.1. Symptoms

Several diseases can affect the prostate gland, they are quite common in adult mature dogs and consist in acute or chronic infections, or may have a hormonal, anatomical or embryological origin. An increase in the incidence of prostate diseases is observed in relation with age and could be related to the physiological hyper-development of the gland, due to the androgens. The prostate pathologies may sometimes be asymptomatic or life threatening, but no symptoms are really pathognomonic of a specific disease. Indeed, many clinical signs associated with prostate disease are non-specific. They are often first attributed to other organs such as bladder, digestive tract, or orthopedic problems.
In all entire male animals of more than 5-6 years where one or several of the following clinical signs are observed, the prostate should always be carefully investigated.

Urinary symptoms: These include haematuria which is not necessarily associated with urination, urinary incontinence with a full bladder, dysuria, stranguria and anuria.

Digestive symptoms: These are not constant, but are sometimes the only clinical signs related to prostatic disease. They are caused by the hypertrophy of the prostate in the pelvis, inducing constipation with sometimes characteristic flat feces.

Locomotor symptoms: Stiffness, posterior lameness paresis and edema of the legs can sometimes be observed in dogs with prostatic disease. These symptoms may appear suddenly (abscesses or acute prostatitis) or progressively (hyperplasia, tumors) and are related to local compression due to the enlargement of the prostate gland, to the presence of pain or of local metastasis.

General systemic signs of no specific origin: General signs such as fever, pain, prostration, anorexia, emesis and septicemia may be associated with the pathological condition. They may be the only symptoms detected by the owner, the more specific signs such as haematuria being more discrete. In all entire adult male dogs presented with systemic clinical signs of no specific origin, a careful complete investigation of the prostate should be carried out.

The exact diagnosis needs a combination of several investigation techniques. The treatments are numerous, but depend on the exact cause of the problem. They can be hormonal for endocrine related diseases such as benign hyperplasia or squamous metaplasia, or surgical or even a combination of both approaches for the other conditions.

The prostatic secretions have an acidic pH and play a bactericidal role during rest, preventing ascending bladder infections. They have a major role during ejaculation in the production of the seminal fluid. Indeed, in dogs, the prostate is responsible for most of the volume of the ejaculate produced.

During the dog's life, the development of the prostate can be divided into three periods. The first one corresponds to the period of embryogenesis and immediate post-natal development; this period ends when the animal is around 2-3 years. The second period is one of exponential hypertrophic development. This phase is clearly androgen-dependent and terminates when the animal is approximately 12-15 years old. The last period is a senile involution and begins when, in geriatric animals, the production of androgens slowly begins to decrease. The clear distinction between the different periods is difficult to make and is indeed highly subjective, with variations between animals. However, it is generally accepted that, after 5-6 years of age, nearly all dogs have a certain degree of prostatic hypertrophy, which may continue to develop, leading in some animals to the pathological features known as the benign prostatic hyperplasia (BPH) disease. This clinical condition is observed in 60% of dogs older than 5 years and in nearly 100% of dogs over 10-12 years old. The position of the prostate changes slowly as it increases in size. Indeed, from being in the pelvis in young animals, the prostate slowly becomes more abdominal and, finally, after 8-12 years, the gland becomes fully abdominal, this process can also be more rapid in some individuals.

2.2.2. Prostate Diseases

The prostate gland may be affected by infection (acute and chronic prostatitis and abscess), endocrine dependent diseases (prostatic hyperplasia and metaplasia) or tumorous processes (adenocarcinoma). Cysts are also described, they are congenital (paraprostatic cysts), primary (prostatic cysts) or secondary ones (due to other diseases, particularly benign prostatic hyperplasia and squamous metaplasia).

Prostatic diseases are often complex, with different types of lesions observed simultaneously. Different etiological agents can occur independently or simultaneously. Furthermore, the ‘haemato-prostatic barrier' reduces a medical treatment penetration and efficacy.

<u>Infectious prostatic diseases</u>:

Bacterial prostatitis is probably the second most common prostatic disorder in dogs after benign prostatic hyperplasia. Infection’s causes of canine prostatitis include *E. coli, Proteus spp., Pseudomonas spp., Brucella Canis, Mycobacterium spp., Staphylococci, Streptococci* and occasionally the *Distemper virus* and *Blastomyces Dermatidis.* Microscopic examination of centrifuged prostatic fluid allows the observation of normal prostatic cells with numerous polymorphonuclear cells in acute infections or macrophages and lymphocytes in chronic phenomenons, red blood cells and sometimes bacteria. Acute prostatitis can be associated with many and varied clinical signs, while chronic prostatitis can be more discrete.

<u>Endocrine prostatic diseases:</u>

<u>*Benign prostatic hyperplasia*</u>:**b**enign prostatic hyperplasia is observed in entire adult males or animals that have been treated with androgenic hormones. The prostate is usually homogeneously enlarged. The exact etiology of this condition in the dog is not established yet, but the condition is closely related to the effects of testosterone after transformation into dihydrotestosterone by the 5-alpha reductase enzyme. Some effects of estrogens have also been proposed. Prostatic hyperplasia is considered to be normal in animals older than 5-7 years and is only considered as a disease when clinical signs are present. Prostatic hyperplasia may be present in some animals without any clinical signs, but may be associated with mild to acute symptoms in others. The symptoms were previously described.

Prostatic metaplasia: exogenous estrogens administered as therapeutic agents (this is no longer accepted nowadays!) or endogenous estrogens from Sertoli Cells' tumors may cause a prostatic squamous metaplasia. The prostate is no longer homogeneous in shape and often cysts or abscesses may develop. Numerous squamous cells are observed in the prostatic fluid.

Other prostatic conditions:

Prostatic tumors: prostatic tumors (mainly adenocarcinoma) are, fortunately, rare in dogs. They may be observed in both young adults or old animals and they are not directly androgen-related in this species. Their appearance and subsequent growth are rapid and, in general, metastases are already present when a diagnosis is achieved. Multinucleate cells can sometimes be observed in the prostatic fluid. Adenocarcinoma tends to metastasize through the external and internal iliac lymph nodes, to the vertebral bodies as well as to the lungs. The pelvic musculature, the pelvis and urethra may also be invaded by direct extension of the tumor. The prognosis is poor and no satisfactory treatment has been found yet.

Prostatic cysts: these are often the consequence of prostatic gland obstruction related to calculi, cellular desquamation in metaplasia, or hyperplasia. They are of no clinical significance as long as their size is small and infection does not occur.

Paraprostatic cysts: Paraprostatic cysts are found laterally, outside of the prostate and the urinary bladder. Some of them may become confluent and contain large amounts of fluid. The origin of the cysts remains unclear, but suggests vestigial abnormalities (Mullerian ducts of the female).

Prostatic calculi and calcification are sometimes observed, but they are of no clinical significance if no complications such as cysts, abscesses or infection are observed.

2.2.3. Treatments of prostatic diseases

During acute prostatitis, the haemato-prostatic barrier is no longer functional and antibiotic therapy has a good chance of being effective. A broad-spectrum antibiotic should be used until antibiotic sensitivity has been assessed. Chronic prostatitis is always more difficult to cure, due to the haemato-prostatic barrier, a reduced blood supply and the organ fibrosis. The antibiotic choice has to be made taking into account the results of antibiotic sensitivity and the pH of the prostatic secretions. High dosages and prolonged (minimum 4-6 weeks) treatments are the keys to success. Since other conditions such as BPH or metaplasia are often observed simultaneously, castration as well as anti-androgen drugs, progestogens or 5-alpha reductase inhibitors can be used concurrently. When abscesses are present, antibiotics should be used alone or in combination with an omentalization and a prostatic curettage if cavities of more than 1 cm in diameter are detected. For the cystic conditions, as for abscesses, omentalization of the cavity is the best treatment and has replaced drainage or marsupialization.

Castration for all endocrine related diseases is generally an efficient treatment if the animal is not required for breeding. However, castration can also be beneficial for all other prostatic diseases. Indeed, by the glandular atrophy induced, castration often permits a rapid improvement of the clinical signs. By reducing the volume of the target tissue submitted to the disease, it reduces the risk of future reoccurrence of the pathology. In valuable breeding animals, the use of anti-androgens or specific inhibitors induces a significant reduction of the prostate without major effects on spermatogenesis, reproductive behavior and fertility. Unfortunately, these treatments have to be applied everyday for the rest of the reproductive life of the concerned animals to prevent the symptoms reoccurrence. Estrogen administration, even at very low doses, is certainly contra-indicated, mainly because of the multiple side effects associated with this hormone in canines.

Surgery has recently gained more importance and favor with the development of omentalization. Indeed, this technique allows a clear improvement in the treatment of abscesses, cysts, and chronic prostatitis as it is devoid of the major complications previously observed with marsupialization, mono or multiple drainage techniques or total resection of the prostate tissue.

2.3. Conclusions

Prostate diseases have to be suspected and researched in all entire male dogs over 5-6 years old, where this gland can be the target of many endocrine or infectious or degenerative processes. The clinical pattern is variable and prostate has to be investigated in all cases where an entire male dog over 5-6 years old present either urinary, digestive, locomotor or systemic signs. A systematic approach has to be developed, including a complete history, abdominal and rectal palpation and the development of special investigation techniques including sonography, radiography, cytology and bacteriology. This systematic approach is the only one that can lead to a clear diagnosis, to the selection of the best treatment and to the establishment of a correct prognosis.

3. Further Readings

A full reference list is available upon request for those who either provide an e-mail address or a self-addressed, stamped envelope.