Pathology of male reproductive organs

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General introduction

Diseases and conditions of the male reproductive system are traditionally approached from the perspective of anatomical location, beginning with the scrotal contents, at the site of production of spermatozoa, and ending with the penis and prepuce. This parallels a problems based approach as diseases tend to involve the scrotum and contents, the accessory genital glands and/or the penis and prepuce. If you are interested in one particular species only, the information for other species is still relevant because a disease in one is usually identical to that in another!

The Veterinary Reproductive Pathology website (www.uoguelph.ca/~rfoster/repropath/repro.htm) provides additional information for the dog and cat, as do recently updated pathology textbooks.[1,2]

The Nomina Anatomica Veterinaria[3] (NAV), which establishes the names in anatomy, lists names of reproductive structures. Some differ from commonly used terms. The latest texts in reproductive pathology use the NAV terminology and this overview will use the English version of the Latin name.

Keywords: Male, reproductive, pathology

Scrotal contents

Introduction

The testes are often considered the center of the 'male reproductive universe'. Not every disease of the scrotal contents involves the testes, however. Orchitis is a common clinical diagnosis, but this term can be misleading because inflammation of the testes is a rare event. The inflammation is usually of the vaginal tunics and epididymis. Often times the reaction is to spermatozoa that have leaked into the tissues. The ability of spermatozoa to stimulate a florid inflammatory reaction is overlooked, but is the most important factor when considering prognosis. The testis is recognized as having immune privilege. The development of germ cells occurs long after immune tolerance develops and a constitutive production of anti-inflammatory cytokines in the testis is now recognized. These are directed by local androgens to inhibit proinflammatory cytokines.[4] An alteration of this balance results in immune and inflammatory reactions in the testis.

Spermatic granuloma

The inflammatory and immunologic response to spermatozoa is of critical importance in many diseases and conditions of the male reproductive tract. Any condition that causes leakage of spermatozoa or spermatozoal antigens into the extratubular compartment is potentially complicated by this reaction. Spermatozoa incite a granulomatous and pyogranulomatous reaction known as a spermatic granuloma. Macroscopically, these have an appearance similar to pus. Spermatozoa have a cell wall similar in composition to keratin as they have many sulfur bonds. Spermatozoa produce a foreign body type reaction and the large number of them and their keratin-like composition means that degradation is a slow process. In addition, immune responses are florid with many immunoglobulin producing cells and CD4- and CD8-expressing lymphocytes appear. Upregulation of major compatibility complex (MHC) I in epithelial cells also occurs.[5] The reaction leads to chronic inflammation and fibrosis, and continued disruption and obstruction of tubes and tubules. Spermiostasis, spermatocele and/or further spermatic granulomas are the consequence.

Diseases of the vaginal tunics

Primary diseases of the vaginal tunics are rare. Secondary involvement after epididymitis (see below) is a much more frequent finding. In domesticated species the most well known primary cause of inflammation of the vaginal tunics is feline infectious peritonitis (FIP). Scrotal swelling in the cat is a

presenting sign that should alert the practitioner to consider FIP.[6] Periorchitis is also seen in traumatic events, such as fight wounds in cats, which allow introduction of bacterial pathogens into the vaginal recess. This recess is continuous with the peritoneum; any disease affecting the peritoneum can and will affect this area.

Hydrocele or non-inflammatory fluid within the cavity of the vaginal tunics occurs in ascites in all species and in bulls in conditions of suboptimal nutrition.[7]

Disease of the testis and epididymis

The testes produce spermatozoa and hormones such as testosterone and inhibin. While early research focused on the hypothalamic–pituitary–testicular axis, there is an enormous body of work on local regulation and cellular crosstalk in the testis. Perhaps more complex is the regulation of testicular development and descent as it involves many different hormones, growth factors (including insulin-like growth factors [IGF]) and the interaction of systemic and local factors and their receptors. Not all are well understood.

The regulation of the blood-testis barrier and the effects of inflammation, focusing on the molecular aspects was reviewed recently.[8-10] Germ cell, Sertoli cell and interstitial endocrine cell function is closely interrelated and there is considerable crosstalk among them.[11] Control of programmed cell death and apoptosis is now identified as a critical process in testicular physiology and pathophysiology.[12] It is a normal process that limits potential spermatogenesis by about 25 to 75%. Gonadotrophins and intratesticular androgens act as survival factors, whereas external events such as elevated temperature increase apoptosis of spermatocytes.

Small testes. Small testes mean reduced production of spermatozoa because testicular weight and volume (to name a few) are correlated with daily sperm output. Scrotal circumference in the bull is highly correlated with daily sperm output, but there are few good measures used in the other species. Scrotal circumference can be used in the ram and buck, but the lack of accessible testes for this measurement in the other species means that we must rely on comparing the testes with objects of the same shape and known volume—orchidometers. Testicular size is seldom a selection criterion in non-ruminants.

It is almost impossible to differentiate the cause of small testes in older animals unless the testes have been examined previously. Primary testicular hypoplasia and testicular atrophy cannot be accurately differentiated, in part, because hypoplastic testes undergo degeneration. When animals are examined at puberty, one's confidence in diagnosing hypoplasia is much higher. In general, a hypoplastic testis has a small hypoplastic epididymis attached. The epididymis is usually disproportionately larger in testicular atrophy.

The two main processes resulting in small testes are therefore a failure to develop and a reduction in size. Failure to develop is a 'disorder of sexual development' (DSD)and therefore hypoplasia. A reduction in size is atrophy.

Disorders of sexual development. Testicular hypoplasia exists when the testis remains smaller than expected after puberty. It occurs as an 'uncomplicated' or primary condition in normally descended testes, in cryptorchidism, and in conjunction with other disorders of sexual development such as chromosomal anomalies (detailed below).

Hypoplasia. The failure of one or both testes to grow to a normal size results because of a reduction in the amount of the seminiferous epithelium (lining).[13] There is little written about the molecular mechanisms involved in hypoplasia in domestic animals. It is known to be a genetic disease in many species. Primary hypoplasia can be either unilateral or bilateral. An affected testis is macroscopically similar to normal testis in almost every way—except size. Hypoplasia is the potential end-result of a large number of different abnormalities that may operate at a systemic or local level (in the case of unilateral disease). We are seldom able to identify a cause. It is surprising how little is written

about testicular hypoplasia except in the context of cryptorchidism! This is despite a large percentage of bulls (up to 56% of Belgian Blue bulls) with a scrotal circumference that is too small,[14] and many dogs have histological evidence of hypoplasia.[15]

The reduction in the area of seminiferous epithelium is the result of either some small tubules in the presence of normal ones, or all tubules are small. Theoretically there could be a reduction in the number of tubules, the length of tubules, or the diameter of the tubules, or one or more combinations of these. Germ cells may be absent or present but fail to produce enough spermatozoa. Germ cells may have failed to migrate to the genital ridge *in utero*, failed to migrate in sufficient numbers, failed to survive, have arrested development, undergo excessive apoptosis or undergo degeneration at some stage of spermatogenesis. Hypoplastic testes with a total lack of germ cells are very small and fail to enlarge from their size at birth. Although we are aware of these possibilities, we often lack the tools and finances to determine the molecular mechanisms involved.

A deficiency of gonadotrophins is associated with hypoplasia (hypogonadotrophic hypogonadism) in humans and mice, but studies in domesticated mammals indicate a normal[13] or increased serum concentration of follicle stimulating hormone and luteinizing hormone. Testosterone concentration was lower than normal in some bulls with hypoplasia or degeneration while in sheep, testosterone and inhibin concentrations may be normal.

Kay, et al.[16] reported concurrent branching of the testicular artery on the same side as a hypoplastic testis, regardless of side affected. This abnormal blood supply could be responsible in some cases. This should result in uniform change in the testis—it does not explain those cases where there is a mixture of hypoplastic and normal tubules. This phenomenon should be investigated further.

Recently Borel, et al.[17] identified a bull they considered to suffer from testicular hypoplasia and demonstrated BVD antigen in germ cells, Sertoli cells and blood vessel walls, but not in interstitial endocrine cells. The photographs demonstrated testicular atrophy and degeneration, but the history of 'hypogonadism' suggests this case may be one of hypoplasia with secondary atrophy. A cause and effect was not established. The involvement of BVD in testicular hypoplasia should also be investigated. At the genetic level, hypoplasia is known or suspected to be hereditary in the dog, bull, ram, and buck. The exact genetic abnormality is often not established.

Cryptorchidism. There is much written about cryptorchidism because of the human disease and because it is so common in our domestic animals. It is now classified as a DSD (XY *SRY*+ with testis). There is much discussion about the stages of testicular descent, but there appears to be a consensus emerging (reviewed by Amann and Veeramachaneni[18] and Hughes and Acerini[19]). There are three phases of testicular descent: abdominal translocation, transinguinal migration and inguinoscrotal migration. The first phase involves anchoring of the testis to the inguinal ring by the gubernaculum and relaxation of the cranial suspensory ligament, and this may be controlled by insulin-like peptide 3 (INSL3) and testosterone. Growth and therefore enlargement of the fetus, results in caudal migration. The second phase involves opening of the inguinal ring by an enlarged gubernaculum and intraabdominal pressure. The third phase takes the testis from the subcutaneous location into the scrotum, and is an interaction of androgen, calcitonin gene related protein and the genitofemoral nerve. The exact mechanisms are yet to be elucidated, but they will no doubt be complex and involve an interrelationship of systemic and local factors. The usual locations of the retained testis are adjacent to the inguinal ring, within the inguinal ring, and beneath the inguinal ring in a subcutaneous location, representing failure of one of the phases of migration. Cryptorchidism is the potential end result of genetic, hormonal, structural or other abnormalities. For the genetic causes, a polygenic recessive-hereditary basis has been established or suggested in all species. Recent molecular techniques have identified a mutation in the INSL3 receptor RXFP2 that is strongly associated with the disease in humans.[20] Exposure to endocrine disruptors interfering with hormonal actions, are blamed for some cases. Structural abnormalities such as gonadal splenic fusion are recognized causes. Flock outbreaks in sheep suggest environmental causes can operate as well. Diagnosis and therapeutic intervention to modify or control testicular descent, based on

correcting the exact abnormality, is currently a theoretical possibility only. Because of prolonged exposure to increased temperature, the cryptorchid testis is hypoplastic and will eventually degenerate.

Chromosomal disorders of sexual development. Animals with chromosomal abnormalities that affect sexual development result in dysgenesis, hypoplasia and or cryptorchidism. There are many recent reviews of disorders affecting sexual development, with the most recent being from Meyers Wallen.[21] The terminology of DSD includes hermaphrodism, intersex, and ambiguous development. This overview uses the recommendations of Hughes[22] in naming DSD. Briefly the DSD are categorized according to the genotype, presence of the SRY gene, the gonadal type and phenotype. For example, at the chromosomal level, XXY *SRY* positive testicular DSD (Klinefelter's-like syndrome) is recognized. Affected cats, bulls, dogs, pigs, horses and sheep have an XXY genotype or a mosaicism with XXY chromosomes. The most famous of these is the male tortoiseshell or calico cat. XX *SRY* negative testicular DSD occurs in goats of the Saanen breed with the gene for polledness and in dogs. A variety of other DSD have been identified as being associated with hypoplasia and or cryptorchidism including the persistent Müllerian duct syndrome (XY *SRY* positive testicular DSD) in schnauzers and bassets.

Testicular atrophy and degeneration. Testicular atrophy is defined as the macroscopic reduction in size of the testis after it has attained its post-pubertal size. Degeneration is the histological term. The germinal epithelium reduces in amount and eventually all spermatogenesis stops. There is often spermiostasis, and mineralization of the tubular content. Spermatic granulomas may develop.

Testicular degeneration usually occurs because of external influences (cf. hypoplasia) that interfere with any of the three main cell types of the testis—Sertoli cells, interstitial endocrine cells and germ cells. There is a seemingly endless list of potential causes (Table 1). The close interrelationship of the Sertoli cells, interstitial endocrine cells and germ cells means that insults to any one or several of them eventually affect them all. The manifestation in the testis is not always bilateral or uniform and in some species has a distinct pattern. The testes of bulls frequently degenerate from the ventrum, and rams from the dorsum. Mineralization, a common sign of degeneration, may involve whole or part of one seminiferous tubule, or whole regions. Testicular biopsies could miss affected areas.

Maintenance of normal testicular function requires a normal hypothalamic pituitary gonadal axis, and maintenance of the normal paracrine and autocrine functions of the testis.[8] Any factor that interrupts the endocrine control (such as endocrine disruptors), or interferes with the cytokine milieu will alter spermatogenesis and or induce apoptosis. At the cellular level, the basic mechanisms of degeneration are similar to that of other cells and tissues. The more we learn about the mechanisms involved in other tissues, the more will be identified in the testis.[23] For example, a recent review highlighted the effect of oxidative stress on cells of the testis.[24]

Neoplasms. Testicular neoplasms are most commonly found in the dog. There is no satisfactory explanation for this, but intact dogs are allowed to live as long as they are able, and they tend to be watched closely. Male cats tend to be castrated early and fewer of those that are intact live to old age. Neoplasms arise in all species sporadically and, with the exception of the dog, it is possible to predict the histologic type of neoplasm based on species and age. Seminoma is the common tumor of the aged, and teratoma is more common in young horses. Cats, rams and bucks get neoplasms rarely, and both seminoma and Sertoli cell tumor are reported. Bulls are more likely to have interstitial cell tumors, but Sertoli cell tumors are also reported.

Three main testicular neoplasms of dogs are the Sertoli cell tumor, the interstitial cell tumor and the seminoma. These are reviewed in detail at www.uoguelph.ca/~rfoster/repropath/repro.htm. Multiple types of neoplasia may be found in one testis. Most primary testicular neoplasms in dogs are benign. Exceptions are extremely rare. Identification of metastasis is the only way to determine that the neoplasm is malignant; there are no good cytological or histologic markers. Recently, an unusual presentation of testicular tumors was reported.[25] These occurred in dogs that were previously castrated, and the tumors

developed in the spermatic cord and incision site. Sertoli cell tumors were most common in dogs and interstitial cell tumors in cats. Implantation of testicular tissue during surgery is believed to be the cause.

Most neoplasms cause enlargement of the testis. In general, seminomas are white, soft and usually bulge on cut section. Sertoli cell tumors tend to contain a lot of fibrous tissue so they are white in color and are firm. The interstitial cell tumor is soft, tan or yellow in color, and often contains areas of hemorrhage.

Sertoli cell tumors, but rarely interstitial cell tumors, can produce a hyperestrogenism-like syndrome and feminization. This is usually manifested by attractiveness to other male dogs, gynecomastia, and alopecia. Some develop bone marrow aplasia. Affected animals return to normal after removal of the neoplasm. The signs are not always associated with estrogen production and not all dogs will have increased serum estrogen concentrations. In these instances inhibin secretion by the neoplastic Sertoli cells inhibits the secretion of follicle stimulating hormone and luteinizing hormone by the pituitary, which in turn, inhibits testosterone production. The imbalance between testosterone and estrogen is responsible for the relative increase in estrogen and feminization. Extratesticular signs are much more common when the neoplasm is larger, and therefore is more common in cryptorchid dogs. It is also in these dogs that an unfortunate sequel of testicular torsion can occur.

Testicular torsion..With the exception of stallions, torsion of the testis is very rare unless there is incomplete descent. A testicular neoplasm is often also present to provide sufficient weight to maintain the torsion. The usual clinical presentation is acute abdominal pain, and the offending mass is blackened due to venous infarction and is sometimes indistinguishable as testis. Spontaneous torsion of the cryptorchid testis of boars is seen commonly at slaughter.

There are many publications about testicular torsion in humans and rodent models. Torsion results in testicular ischemia, and reperfusion results in the release of proinflammatory cytokines by testicular macrophages, Sertoli cells, interstitial endocrine cells, and germ cells and they bind to receptors on the same cell types thus having autocrine and paracrine effects.[26] Oxidative injury also occurs[24,27] and is very important.

Orchitis. Apart from bulls in areas endemic for *Brucella abortus*, orchitis is a rare and sporadic disease in domesticated animals. The vast majority of cases in domestic species diagnosed clinically as orchitis are really epididymitis. Foci of lymphocytes are occasionally seen in the testes of most species and suggest a subclinical disease.

Orchitis as the primary manifestation occurs sporadically and is reported in cats with FIP, rams and bucks with *Corynebacterium pseudotuberculosis*, pigs with *Brucella suis* or *Burkholderia pseudomallei* and stallions with migrating larvae of *Strongylus* spp. nematodes. Sporadic infection with other bacteria will no doubt occur from time to time. The isolated position of the testis suggests that infection with the various agents is hematogenously derived, or occurs by direct traumatic penetration. The growth of bacteria is no doubt aided by the immune privilege of the testis.

Experimental studies particularly of autoimmune orchitis are numerous and have helped to unravel the molecular mechanisms. The cytokines that are important in the normal regulation of the testis are also involved in immune and inflammatory reactions. As well as the direct effects of effector cells on the testicular cells, there is upregulation of chemokines such as CCL2, 3 and 4, toll-like receptors (TLR) and release of proinflammatory cytokines IFNγ, IL-6 and TNFα result in germ cell apoptosis and disrupt spermatogenesis.[8]

Developmental epididymal disease. There are many different developmental diseases that affect the epididymis, but only two that we will deal with specifically here. They are segmental aplasia and spermatic granuloma of the epididymal head.

The first of these, segmental aplasia, occurs when a portion is missing. Usually it is the tail of the epididymis. As can be expected, the affected side is sterile. Although this occurs in all species, it is known to have a hereditary basis in bulls.

The second disease is called spermatic granuloma of the epididymal head. In this condition not all efferent ductules attach to the epididymal tube—some end blindly. In the blind ending ductules, spermiostasis develops and subsequently becomes a spermatic granuloma. This disease is recognized as the granulomas only occur in the region of the epididymal head. Every case of azoospermia with normal testicular production of spermatozoa, based on biopsy or unilateral castration that I have investigated, had this condition. I now regard the diagnosis of testicular sperm resorption as a cause of azoospermia with great suspicion.

Infectious epididymitis. Bacteria cause most infections of the epididymis. Viruses, such as equine arteritis virus and others are reported to induce epididymitis. Primary infection with *Brucella spp*. in each species results in epididymitis. *B. ovis, B. canis, B. melitensis* and *B. suis* are especially virulent for the epididymis. It is assumed that the infection is systemic and the bacterium localizes in the epididymis.

Direct infection of the epididymis by penetrating injury is a rare event. Secondary infection from periorchitis, or peritonitis is an occasional possibility. Almost all species develop infection of the epididymis by the ascending route. This has been studied in the ram where *Actinobacillus seminus* and *Histophilus somni* are common isolates. While the exact mechanism is not known, the work of Jansen[28] in South Africa during the 1980's indicated that preputial organisms migrate to the accessory genital glands (AGG) and infect the epididymis by retrograde movement. The privileged environment of the lumen of the epididymal duct allows the organisms to infect the organ and incite damage. The formation of spermatic granulomas means that the reproductive potential of the affected side is lost. Complete return to normal is rare. In the dog, the sequel of self-trauma of the scrotum and systemic affects of infection with endotoxin producing bacteria such as *Escherichia coli* further complicates epididymitis by causing systemic illness.

The epididymis relies on innate immune mechanisms to prevent infection. The isolation of the epididymal duct and its narrow and long course must provide a challenge to ascending organisms. The one-way flow of spermatozoa and strong muscular contractions are also detrimental to bacterial passage. Antimicrobial molecules such as TLRs are found in the rat epididymis[29] and granulocyte chemotactic protein (GCP-2/CXCL6) is present in human epididymis,[30] thus microbial pattern recognition molecules are present to prevent infection. The epididymis has no natural local immune system of antigen receptors, recirculation of immunocytes and no local plasma cell population. Some aggregates of lymphocytes are occasionally seen in otherwise normal animals. After infection, the epididymis must develop a local immune system, but alas, the damage is usually so extensive, and the sequelae so severe that immunity is too late. Even so, the epithelial cells have the ability to express MHC I and II and lymphocytes and plasma cells can be recruited after challenge.[5]

Spermatic cord

The spermatic cord is composed of the deferent duct (ductus deferens), pampiniform plexus, muscle and nerve. There are many diseases that affect this area. The principal ones we will deal with are varicocele and inguinal hernia.

When palpating the region of the spermatic cord and the inguinal ring, all of the structures of this area can usually be identified. The deferent duct may have indications of a previous vasectomy, the lymph node may be enlarged with lymphoma, and a large inguinal hernia will be palpated as a sack-like structure that may contain intestines. It is particularly important in the horse to palpate the scrotum of animals that have colic.

Varicocele is a disease that particularly affects old rams. It can be a cause of subfertility of both testes because of the effects of reduced blood flow that is involved with the formation of varicocele. The bilateral nature of the effects suggests that a failure to thermoregulate is probably simplistic. Varicocele is a common disease in humans[31] where up to 15% percent of individuals are affected. Most are on the left side because the left testicular vein empties into the left renal vein at a right angle, rather than obliquely into the caudal vena cava as occurs in the right testicular vein. The higher pressure in the left

testicular vein combined with less effective venous valves results in dilation of the vein and varicocele. Except in the ram, where varicocele is more common, most cases of varicocele in animals occur secondary to scaring or other obstruction of the testicular veins. Varicocele is usually only recognized in domestic animals when thrombosis develops. There is considerable discussion about the effects of varicocele on fertility. In humans, varicocele can cause failure of testicular development and if the condition develops after puberty, infertility. Infertility is thought to be the result of increased scrotal temperature, greater oxidative stress and reduced blood flow resulting in greater Fas ligand activity[32] which is involved in apoptosis of germ cells. The semen of men with varicocele contains higher levels of oxidants and reduced levels of antioxidants compared to that of unaffected individuals.[33] Intersititial cell dysfunction from interstitial fibrosis may also be involved.

Accessory genital glands

The AGG include the ampullae, vesicular glands (seminal vesicles), prostate, and bulbourethral glands. They are frequently overlooked during necropsy examination, unless there are specific indicators of disease.

Diseases of the AGG are sporadic in most of the species and tend to be incidental findings. Disease of the prostate of the dog, and vesicular glands (seminal vesicles) of bulls, are common and important.

Prostatic disease in the dog

The prostate is the only genital gland of the dog and it is prone to diseases that can be difficult to differentiate. The gland is relatively inaccessible and signs of prostatic disease are not always specific to that organ.

Prostatic hyperplasia. The prostate gland has been the focus of much research, especially in the area of prostatic hyperplasia. Canine prostates progressively enlarge with age. A prepubertal dog has a very small prostate, and with puberty, it increases in size to 'normal'. The size tends to reflect body size although the Scottish terrier is reported to have a prostate that is about four times the size of dogs of a similar size.[34] About 63% of dogs develop progressive enlargement of the prostate with age after puberty.[34] The gland can become large enough to cause clinical signs or fecal obstruction rather than urinary obstruction (as occurs in humans). The enlarged prostate hangs over the pelvic brim when the dog is in its normal quadrapedal position, but when the position for defecation is assumed, the prostate is pulled by gravity into the pelvic inlet and with an increase in intraabdominal pressure, forms a 'ball valve' and compresses the colon. The increase in size is reported to be the result of increased interstitial tissue with the overall amount of epithelium not increasing in amount. The lumen of glands, however, increases in diameter with age.[35,36] Shain and Boesel[37] examined the androgen receptor content of canine prostates and found that hyperplastic glands had a higher receptor content than normal, but there was no difference in the receptor content per cell and there was no increase in testosterone. Moore,et al.[38] found that estradiol enhanced androgen effects on the prostate by enhancing an androgen binding protein in the cytoplasm. Castration of juveniles results in a failure of prostatic development and reduces the number of prostatic diseases to one–carcinoma (see below).

Squamous metaplasia will cause a prostate to be larger. It occurs after administering estrogens and in Sertoli cell tumors. In all animals, paracrine signals from the stroma define the epithelial type that will develop. It will also define the arrangement of the epithelium, including whether the epithelium will form a gland or a cavity. This whole interaction involves epithelial feedback and regulation (reviewed by Cunha, et al.[39]). Steroid hormones regulate this interaction and in the normal prostate, AR is an important factor. In estrogen-induced squamous metaplasia, estrogen stimulates estrogen receptor (ER)α, which is especially important in the stroma (the main ER of the epithelium is ERβ). In ER knockout mice, both stromal ERα and epithelial ERα must be present and stimulated to induce both proliferation and metaplasia. The stratified squamous cells acquire cyclooxygenase 2 activity as a result of estrogen stimulation.

Prostatitis. Prostatitis is a common finding, even in asymptomatic dogs.[40] It is reported to occur in canine brucellosis.[41] Many dogs have foci of inflammatory cells in the interstitial tissues,[35] suggesting that subclinical infection may be common. Ten percent of dogs had these at six months but 45% had them at seven years of age.

Sequential studies of prostatitis are lacking, so much is assumed from studies in other animals. It is assumed that prostatitis occurs mostly by ascending infection—organisms travel from the penis and prepuce via the urethra to the prostate. The bacteria isolated from cases of prostatitis include *Escherichia coli*, *Proteus*, *Klebsiella*, *Staphylococcus*, and *Streptococcus* sp., but there is little information on prevalence. Hematogenous spread and localization in the prostate is probably the way that infection with *Brucella canis* reaches the prostate, but infection from epididymitis is also possible. There is also the theoretical possibility of infection of the prostate from the bladder and urine.

Once bacteria infect the prostate, they proliferate within the lumen of the glands, and from there either elicit an inflammatory response or invade. Thus there is an acute intraacinar or glandular phase and later an interstitial phase. Neutrophils and the contents of their granules contribute to the chemotactic factors of the bacteria to incite an inflammatory response. Bacteria are usually Gram negative and therefore release endotoxin. With time, the interstitial response will become more obvious, and lymphocytes and plasma cells predominate. This interstitial phase will also be accompanied with fibrosis. Abscessation of the prostate is also an outcome of prostatitis.

Paraprostatic cysts and pseudocysts. The most common 'cyst' attached and external to the prostate is the paraprostatic pseudocyst. Some can be 30 cm in diameter or larger and form a space-occupying mass in the abdomen.[42] It is not known how or from what they arise. Some cysts, particularly the smaller ones, are lined by epithelium and they may communicate with prostatic cysts and acini. Many prostates have projections of glands from the prostate into and through the capsule—they extend between bundles of the discontinuous smooth muscle of the capsule. Many paraprostatic cysts are therefore an extension of cysts in prostatic hyperplasia. Other possible origins for paraprostatic cysts are the serosal inclusion cyst and hematomas. Those that are in the dorsal midline region of the prostate are probably derived from a cystic uterus masculinus, a remnant of the paramesonephric duct. The structure of the cysts make determining their origin impossible as the inner lining is seldom lined by epithelium. The term pseudocyst is more precise in this instance. The lining is often either fibrous or granulation tissue with an appearance similar to a 'seroma'. The wall is usually of compressed fibrous tissue and the outer lining is mesothelium (serosa). It is not unusual for the pseudocysts to have mineralization of the wall, although the literature is scant.[43,44]

Prostatic neoplasia. Prostatic carcinoma is a term with several meanings. The convention is that carcinomas of the prostate are actually adenocarcinomas (from the prostate glandular tissue), and although this is reasonable in humans, it is not necessarily the case in dogs. There are several types of carcinoma in dogs, including adenocarcinoma (presumably from the glands), transitional cell carcinoma (from the prostatic ducts), mixed carcinomas and squamous cell carcinomas. There is disagreement as to which is the most common and this is because subclassifying carcinomas is subjective. Prognostically, there is little difference as virtually every dog develops metastasis.[45]

Prostatic carcinomas occur in sexually intact and neutered dogs.[46,47] Carcinomas in castrated dogs tend to have pulmonary metastasis when diagnosed and transitional cell differentiation is more common than adenocarcinoma. Intact dogs have an equal prevalence of transitional cell and glandular differentiation.[34,48]

Prostatic carcinomas occur in sexually intact and neutered dogs.[46,47] Tumors in castrated dogs tend to have pulmonary metastasis when diagnosed. Those carcinomas with transitional cell differentiation tend to occur more commonly in castrated dogs whereas neutered dogs are evenly split between those with and those without transitional differentiation.[34,48]

The phenotype of carcinomas in the prostate was debated for many years. Attempts to separate them morphologically,[49] using immunohistochemistry for cytokeratin 7 and arginine esterase,[50] and

protein expression profiling[51] were fruitless as prostatic glandular epithelium and normal bladder epithelium are identical in their expression. It seems reasonable to call all carcinomas of the prostate the generic term 'carcinoma of the prostate' or 'prostatic carcinoma'.

A diagnosis of prostatic carcinoma in a dog carries an extremely poor prognosis. Metastasis to the lung is most common but about 14% have metastasis to bone, especially the lumbar vertebrae and pelvis.[45,48,52]

There are no known causes, although there is a slightly increased risk in castrated dogs.[47] As already indicated, castration is not protective so the systemic hormonal environment does not appear to be important. Lai, et al.[53] found that androgen receptors were less common in neoplastic prostatic tissue than in normal prostate. Positive staining was in the cytoplasm rather than the nucleus and there were no detectable mutations to DNA coding for the AR. There are numerous studies outlining the distribution of ERs in canine prostates, and the intranuclear receptors are found in stromal cells and in the epithelial cells. Hyperplastic prostates have a similar distribution. Grieco, et al.[54,55] found a loss of ERs in the stromal of all prostates including those with carcinoma. The main ER in the epithelium is ERβ. In the more 'differentiated' tumors, ER was present but with less intense staining. Staining was reduced with the less differentiated tumors. The significance of this is yet to be established. Gallardo, et al.[56] examined AR, ER α and β, and progesterone receptor expression in prostatic specimens from dogs with prostatic hyperplasia, prostatitis and neoplasia. Expression of these was less common in disease except for progesterone receptor, where more animals had expression in disease conditions.

It is widely believed that precursor lesions, such as low grade prostatic intraepithelial neoplasia, do not occur in dogs, although Matsuzaki, et al.[57] believe they do. High grade prostatic intraepithelial neoplasia however is reported in clinically normal dogs[58] and in dogs with carcinoma.[59,60]

Some prostatic carcinomas have cytogenetic abnormalities and of particular interest is one with an abnormality similar to human prostatic carcinoma. The carcinoma studied had trisomy of chromosome 13, which is similar to chromosome 8 of humans and which also has cytogenetic anomalies in some human prostatic carcinomas.[61,62]

Vesicular adenitis (seminal vesiculitis) in bulls

Vesicular adenitis occurs commonly as a subclinical disease in ruminant species. In bulls it is recognized as an important clinical disease and a cause of infertility and poor freezibility of semen. It is a disease of young bulls predominantly—those less than two years of age. The pathogenesis has not been proven, but it is commonly believed that hematogenous infection is important. This would certainly be the case with *Brucella abortus* or *Mycoplasma bovis* infection. Abnormalities of the seminal colliculus are implicated also. Ascending infection in a similar mechanism to the pathogenesis of epididymitis in rams[28] seems to have been overlooked by many. *Arcanobacterium pyogenes* and *Histophilus somni* are common isolates in North America[63] but many bacteria and some mycoplasmas were recovered from clinical cases.[64-66]

Two forms of vesicular adenitis in the bull are recognized, an acute fibrinopurulent form where there are the typical signs of acute inflammation—swelling, pain on palpation and neutrophils in the semen. Some bulls may have systemic signs. A chronic interstitial form is the second type and there is a considerable increase in size, excessive fibrosis, firm consistency and loss of lobulation.[64-66]

Penis and prepuce

Diseases of the penis and prepuce are common in all species. Many of the congenital or developmental diseases are part of the DSD. Congenitally short penis, lack of sigmoid flexure in ruminants, hypospadias, deviations and other obvious and less obvious anomalies may be seen from time to time. The epithelium of the penis and prepuce are fused until puberty, when there is separation of the epithelium. Failure of complete separation will result in a persistent membrane (called a persistent preputial band) or frenulum that may cause deviation of the penis when it is erect.

Trauma and related diseases[67] occur in all species but eversion of the preputial mucosa is very important and common in bulls of the *Bos indicus* and in polled breeds of the *Bos taurus* species.

Eversion is normal but inadequate preputial muscles and injuries to the everted epithelium are the cause. Trauma and desiccation lead to edema, inflammation, and persistent preputial prolapse. Mating injuries occur in dogs and horses especially, and the constricting effects of hair (and 'hair ring') occur in cats, sheep and goats.

Forced deviation of the penis (hematoma of the penis, broken penis) is a disease of bulls mostly. Deviation of the penis during coitus causes the extremely high pressure generated by the coital thrust to result in rupture of the penis at the level of the insertion of the retractor penis muscle. A hematoma develops and it may be large enough to cause hypovolemic shock. Most are not so immediately life-threatening and will heal with scarring and phimosis.[68]

Paraphimosis is a complication of tranquilizing horses, especially if phenothiazines are used. It also occurs in debilitated horses.[69] Affected horses are unable to retract the penis, and engorgement and trauma result. Dogs frequently develop paraphimosis as a 'spontaneous' lesion.

Most species, but especially cats and ruminants, develop urolithiasis and the stones lodge in the penile urethra. Penile necrosis, and 'water belly' with bladder and/or urethral rupture, occurs.

Inflammation and or infection of the prepuce (posthitis) mostly occur as a nonspecific event. Inflammation of the penis and prepuce is called balanoposthitis but should more accurately be called phalloposthitis except in the dogs where the head of the penis is the portion of the penis from the bulb to the tip; balanoposthitis is the appropriate term.

As with any external site, the prepuce has a normal flora that contains potential pathogens. Sexually transmitted organisms are usually found in the prepuce and may not be a cause of disease in males. Organisms of importance include the herpesviruses, mycoplasmas and ureaplasmas of most species. Specific agents include *Tritrichomonas foetus*, *Campylobacter fetus*, *Corynebacterium renale* and *Ureaplasma diversum* in bulls, and *Eubacterium suis* in pigs. A nonspecific preputial discharge is seen frequently in male dogs. Geldings tend to extrude their penis less often than stallions, and they urinate in their sheath. The buildup of smegma and or the effect of urine allow secondary organisms to flourish.

Outbreaks of posthitis are recorded in wethers, and rarely in rams. There is a combination of factors in this disease. The animals are usually on a high protein diet thus producing abundant urea. The causative agent is *Corynebacterium renale*, a urease-producing organism that breaks down urea to ammonia. It is believed that the ammonia causes ulceration adjacent to the preputial orifice. Further damage and infection results in a severe posthitis then preputial obstruction, scarring and eventually death.[70,71] Boars develop preputial diverticulitis with ulcers and abundant necrotic debris.

Canine transmissible venereal tumor (CTVT) in endemic areas is common, and diagnosis of masses around the prepuce can usually be made on either fine needle aspiration or incision or excisional biopsy. Canine transmissible venereal tumor was the first naturally occurring neoplasm that is spread by the transferring of cells from an affected dog to another. It happens to be venereally transmitted. The second neoplasm to be spread in a similar fashion is the oral facial tumor of Tasmanian devils, called devil facial tumor disease. They are therefore allographs. There are several reviews written about the CTVT.[72-74] The cells of CTVT have a chromosomal number of 57, 58 or 59. Murgia, et al.[75] used molecular techniques to demonstrate that neoplasms from different continents and collected decades apart are clonal, and, while there are two subtypes, they have a common origin. The DNA of the CTVT is closely related to DNA of wolves and East Asian dog breeds. The cells of a CTVT are able to avoid detection by the immune cells. They downregulate class I molecules and there is no class II activity because they secrete inhibitory cytokines (TGFβ1 and IL 6).[75,76] In the initial proliferative phase of CTVT, they express little MHC Class I or II. After about 12 weeks in an experimental model, lymphocytes stimulated MHC expression and subsequent regression of the tumors.[77] Most transmissible venereal tumors are exquisitely sensitive to vincristine.

Squamous cell carcinoma of the penis of the horse is a relatively common condition of older animals. The head of the penis is mostly affected, and about 10% metastasize to the superficial inguinal lymph nodes.[78,79] The cause is not known and smegma is no longer considered a likely candidate.

Young bulls commonly develop fibropapillomas. The papilloma virus, bovine papilloma virus type 2, causes these exophytic lesions. They often occur during the first mating season, and they are fleshy lesions that become ulcerated and cause hemorrhage and pain.[80]

Table 1. Some of the known causes of testicular degeneration in mammals, including rodents.

- Advancing age
- Chlorinated naphthalenes
- Epididymitis
- Chemicals
  - Chemotherapy
  - Halogenated compounds including hexachlorophene
- Nitrogen containing compounds including
  - Benzimidazoles
  - Nitrofurans
- Heat
- Hormones
  - Dexamethasone
  - Estrogen
  - Testosterone
  - Zeranolone
- Metal compound toxicity
- Neoplasia
  - Pituitary tumors
  - Sertoli cell tumors
  - Nutritional disorders
  - Negative energy balance
  - Fatty acid deficiency
  - Hypovitaminosis A
  - Hypervitaminosis A
  - Hypovitaminosis B
  - Hypovitaminosis E
  - Hypovitaminosis C
  - Protein and amino acid deficiency
  - Zn deficiency
- Oxidative stress
- Plants
  - Locoweed (Astragalus)
  - Lysine seeds
- Radiation
- Stress/Corticosteroid therapy
- Trauma
- Ultrasound
- Viral infection
  - PRRS virus

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