Chapter 9

Male Accessory Sex Glands: Structure and Function

Margot Flint, Debra A. McAlister,
Ashok Agarwal and Stefan S. du Plessis

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9.1 Introduction

The accessory sex glands can be regarded as part of the male's reproductive system as they play an integral role in the fertility process. The major male accessory sex glands (Figure 9.1), whose secretions provide the bulk of the semen in varying volumes are the seminal vesicles, prostate glands and Cowper's glands (Dunker and Aumuller 2002; Owen and Katz 2005). Also contributing very small volumes to semen are the ampullary, Littre and Tyson's glands; however, these glands are barely studied and hence are poorly understood (Mortimer 1993). Products of these glands which are secreted at the beginning of the ejaculatory phase serve to nourish and activate the spermatozoa, clear the urethral tract prior to ejaculation, and act as a vehicle of transport for the sperm in the female tract and to plug the female tract after placement of sperm to help ensure fertilisation. The male accessory sex glands
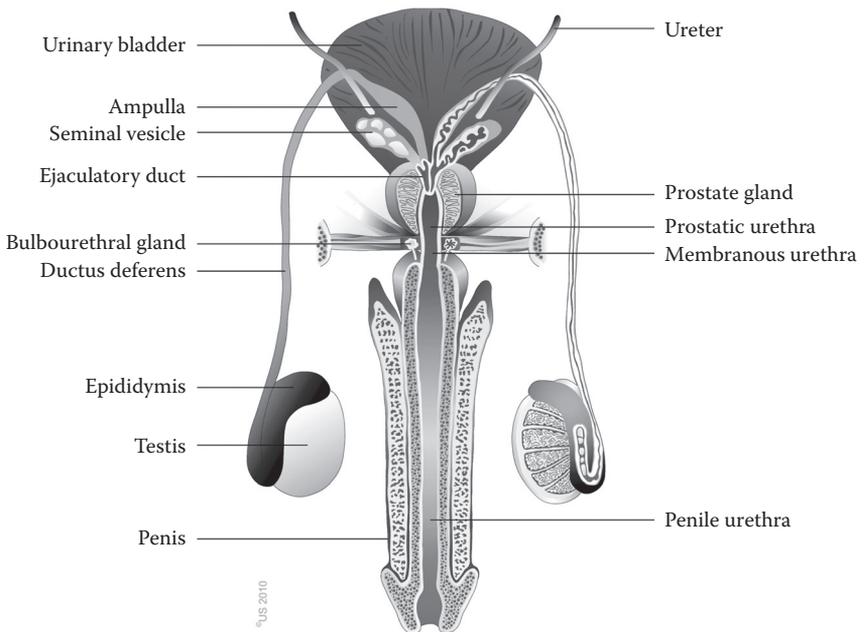

Figure 9.1   (See colour insert.) A posterior view of the adult human male reproductive system to show the location and structure of the major accessory sex glands.

work together in playing an essential role in the reproductive process (Chughtai et al. 2005). The major accessory sex glands will subsequently be discussed in more detail.

9.2 Cowper's Glands

The Cowper's glands, also known as the bulbourethral glands, were discovered in the seventeenth century by an English surgeon, William Cowper (Chughtai et al. 2005). These sex glands, present in the reproductive system of human males, are homologous to Bartholin's glands in females (Woodruff and Friedrich 1985). Although the fluid secreted from the Cowper's glands contributes only a small volume of fluid to the total semen volume in a single ejaculate, it serves an important function prior to ejaculation.

9.2.1 Location

The Cowper's glands exist in pairs and are found in the majority of male mammals. The two Cowper's glands lie side by side and are located beneath the prostate gland in the urogenital diaphragm, posterior and lateral to the membranous urethra. They are positioned between the bulbospongiosus muscles and embedded within the transverse perineal muscle, forming part of the pelvic floor (Dunker and Aumuller 2002). The two glands join the urethra by means of a main duct, to which smaller accessory ducts are attached.

9.2.2 Structure

The pea-sized Cowper's glands are about 1 cm in diameter and yellow in colour (Saboorian et al. 1997; Chughtai et al. 2005). This small pair of male accessory glands is arranged in a network of clearly demarcated lobules of compact tubuloalveolar glands (Saboorian et al. 1997; Awakura et al. 2000; Dunker and Aumuller 2002; Chughtai et al. 2005). Tubuloalveolar glands are characterised by possessing both tubular and alveolar secretory units. These units are composed of mucus-like epithelial cells with basal nuclei (King 1993).

The cluster of lobules are separated by and enclosed in a connective tissue capsule of columnar epithelium and secured within fascicles of thick striated skeletal muscle (Hellgren et al. 1982; Saboorian et al. 1997; Dunker and Aumuller 2002; Chughtai et al. 2005). Small accessory ducts extend from each lobule of the gland which joins and enters the bulbourethra separately or as a united duct (Awakura et al. 2000; Bevers et al. 2000). The accessory ducts may therefore drain into the main duct or enter the urethra directly (Chughtai et al. 2005). The main Cowper's duct which is approximately 3 cm in length enters the ventral surface of the bulbourethra near the midline by penetrating the spongiosum, the mass of spongy tissue surrounding the urethra (Hafez 1977).

9.2.3 Secretions and Function

According to Tikva, the male sexual response consists of four phases: excitement, plateau, orgasm and resolution. During sexual excitement and plateau, the Cowper's glands secrete glycoproteins into the bulbous urethra (Tikva 2003). The secretion is a clear, viscous, alkaline mucus-like fluid and is commonly known as *pre-ejaculate,* as it is secreted prior to ejaculation (Riva et al. 1990; Mortimer 1993; Dunker and Aumuller 2002). The amount of pre-ejaculate emitted varies widely between individual men, averaging about 0.2 mL in most men but can be as much as 5 mL in some men depending largely on the duration of the plateau-phase levels of sexual tension (Tikva 2003). Generally the Cowper's secretions make up less than 1% of the semen composition (Riva et al. 1990).

The fluid secreted functions as a lubricant for the seminal fluid containing sperm which is to follow during ejaculation (Riva et al. 1990). Along with acting as a lubricant, this fluid aids in neutralising the acidity of the urine residue in the urethra which may be unfavourable and harmful to sperm (Mortimer 1993). The fluid also assists in neutralising the acidity of the vagina and provides some lubrication for the tip of the penis during sexual intercourse (Chughtai et al. 2005). Along with neutralisation of an acidic environment, the secretion is also well documented for its contribution to coagulation and the characteristic jelly-like appearance of semen (Riva et al. 1990; Brocker 1998).

Moreover, the Cowper's glands have been shown to contribute to the immune defence of the genitourinary tract by secreting many glycoproteins, such as prostate-specific antigens (PSA) (Migliari et al. 1992; Cina et al. 1997; Pedron et al. 1997). Studies have confirmed the presence of a specific distribution of immunocompetent cells in the Cowper's glands, which seems to offer the first immunological barrier against the entry of antigens (Migliari et al. 1992).

It has been long speculated that the fluid from the Cowper's glands may contain sperm, and that coitus interruptus is not a reliable method of contraception. Although it is possible for this fluid to pick up sperm remaining in the urethral bulb from previous ejaculations, the Cowper's gland secretions have been shown to be absent of sperm. In a study by Tikva, it was shown that pre-ejaculatory fluid secreted at the tip of the urethra during sexual stimulation did not contain sperm and therefore cannot be responsible for pregnancies during coitus interruptus (Tikva 2003).

9.2.4 Pathology

The Cowper's glands can be affected by acquired and congenital lesions (Colodny and Lebowitz 1978). Congenital lesions of these glands mainly consist of syringocele (Masson et al. 1979), which tends to be asymptomatic, and may be easily confused with the more serious conditions during diagnostic tests. Like the prostate, acquired

lesions of the Cowper's glands include infection, calcification and neoplasms (Pedron et al. 1997; Chughtai et al. 2005).

9.2.4.1 Congenital Lesions

9.2.4.1.1 Syringocele

Obstruction to the orifice of the Cowper's duct gives rise to dilatation of the duct, a consequence of stasis and pressure changes (Merchant et al. 1997), commonly known as syringocele. Syringocele assumes a cystic appearance (Merchant et al. 1997; Kickuth et al. 2002; Chughtai et al. 2005) and is an uncommon deformity usually diagnosed in male infants and children presenting with urinary tract infection, macrohematuria and voiding symptoms (Awakura et al. 2000; Bevers et al. 2000). Cowper's syringocele may be closed or open, which is a distended cyst-like swelling in the wall of the urethra or an opening enabling urine reflux into the syringocele respectively. Bacterial colonisation in the pool of mucus or urine that stagnates within the syringocele is inevitable. Although most cases are asymptomatic and may go unnoticed, syringocele may present in adults as urinary tract infections with frequency, pain and discharge, symptoms of urethral obstruction, or chronic post-void incontinence (Chughtai et al. 2005).

Treatment of Cowper's syringocele usually consists of a short outpatient procedure such as marsupialisation, which involves the surgical removal of the cyst. This is performed by opening the Cowper's syringocele transurethrally with a Collins knife (Bevers et al. 2000; Kickuth et al. 2002).

9.2.4.2 Acquired Lesions

9.2.4.2.1 Cowperitis

Cowperitis refers to the bacterial infection and inflammation of the Cowper's gland which may be chronic or acute. The infections are generally found to be caused by the same organisms that cause urinary tract infections, such as *Escherichia coli*, *Neisseria gonorrhoea* and *Chlamydia trachomatis* (Birnstingl et al. 1957; Dunker and Aumuller 2002; Chughtai et al. 2005).

Acute cowperitis presents as fever, malaise, sever pain in the perineum with frequency, urgency, painful defecation and sometimes acute urinary retention. Acute cowperitis is usually treated successfully with a suitable anti-biotic (Chughtai et al. 2005).

Chronic cowperitis is usually associated with an underlying defect such as syringocele which causes the bacterial infection as a result of the bacteria-ladened urine and mucus collecting in the area (Birnstingl et al. 1957). Treatment for a pathology of this nature requires the removal of the defect and subsequent treatment with

antibiotics, yet antibiotics have not always been found to be successful (Chughtai et al. 2005).

9.2.4.2.2 Stones

Cowper's gland calcifications are found more commonly in elderly patients. Patients with these Cowper's stones usually experience blockages of secretions and infection. The calcifications usually consist of phosphate salts of calcium, magnesium, potassium, calcium carbonate or calcium oxalate and can be detected through pelvic ultrasound. These stones are rarely infected or cause abscesses. The treatment in the case of large stones usually involves the removal of the Cowper's gland, however in asymptomatic cases, the stones may be observed closely without treatment (White et al. 1983; Chughtai et al. 2005).

9.2.4.2.3 Neoplasms

Adenocarcinoma of the Cowper's gland exhibits irregular-shaped glands lined with anaplastic cells. Symptoms usually include the abnormal narrowing of the urethra with or without a bloody discharge and no increase in PSA. Carcinoma of the Cowper's gland is rare, and may be treated with chemotherapy, radiation therapy or surgical removal. In the few reported cases of this pathology, the most appropriate treatment was the combination of radiation and surgical therapy (Saboorian et al. 1997; Chughtai et al. 2005).

9.3 Prostate Gland

The prostate in a healthy young adult male is a walnut-size gland that weighs up to 20 g and contributes approximately 30% to the total seminal volume (Honda et al. 1988; Lalani et al. 1997). The combinations of compounds that are secreted by the prostate enhance the chances of successful oocyte fertilisation and the gland is of clinical importance due to the link between an increase in age and pathological changes in the prostate (Rui et al. 1986; Sherwood 2007).

9.3.1 Location

The prostate gland is located between the urogenital diaphragm and the neck of the bladder, and connecting the prostate and the bulbourethral glands is the urogenital sinus (Wilson et al. 1997). The prostate completely surrounds both the ejaculatory ducts as well as the urethra and begins its journey at the neck of the bladder and ends by merging with the ejaculatory ducts (Pienta and Esper 1993; Sherwood 2007).

9.3.2 Structure

The prostate is a heterogeneous, multilobulated gland consisting of four morphologically different zones (Figure 9.2): the transition, central and peripheral zone, as well as the anterior fibro-muscular stroma (Rui et al. 1986; Fritjofsson et al. 1988; Lalani et al. 1997). The central zone surrounds the ejaculatory ducts and constitutes approximately 25% of the gland. The peripheral zone is the main contributor of glandular tissue, making up 70% of the prostate volume. The transition zone encircles the proximal prostatic urethra and is a minor supplier of glandular tissue occupying only 5% of the volume of the prostate. Lying anteriorly is the fibro-muscular stroma, which contains no glandular tissue but consists of smooth muscle fibres, dense collagen and fibroblasts (Wilson et al. 1997). The central and peripheral zones are collectively termed the outer or cortical prostate. The inner or periurethral prostate consists of the anterior fibro-muscular stroma and the transition zone (Lalani et al. 1997). Penetrating the posterior surface of the prostate are two ejaculatory ducts (Hafez 1977), and encircling the entire organ is a vascular capsule consisting of an inner layer of smooth muscle and outer fibrous shell (Lalani et al. 1997).

The prostate consists of tubuloalveolar glands which open into the prostatic urethra. Together with the epithelium, the prostatic glands form folds that produce a papillary appearance (Hafez 1977). This irregular shape is to facilitate fluctuations
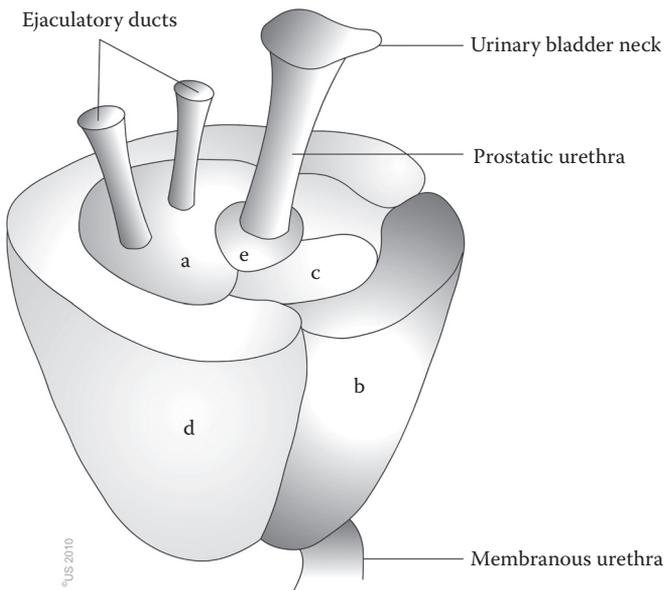

Figure 9.2 (See colour insert.) Schematic representation of the different zones of the prostate gland. a = central zone; b = fibro-muscular zone; c = transitional zone; d = peripheral zone; e = periurethral gland region.

in the gland's size that occurs when the secretions are produced. The epithelial layer of the prostate consists of a double layer of cells: the basement membrane cells and the upper layer of columnar secretory cells. Dividing the two is an intermediate layer of flattened basal cells (Lalani et al. 1997).

9.3.3 Secretions and Function

The prostate secretes a thin, milky, alkaline fluid which is typically low in proteins yet it contains a wide variety of various proteolytic enzymes and electrolytes. The accessory glands supply their secretions in an ordered sequence to the ejaculate. The prostate secretions are released directly after the bulbourethral glands release their secretions (WHO 1992; Nieschlag and Behre 2000). The main compounds secreted by the prostate gland are citric acid and hydrolytic enzymes (Heath and Young 2000). In addition, the following compounds are also secreted: zinc, spermine, cholesterol, magnesium, phospholipids, muramidase, fibrinolysin, fibrinogenase and acid phosphatase (Hafez 1977; Ganong 1981).

Oxytocin, a neurohypophysical hormone produced by the hypothalamus and stored in the posterior pituitary, has also been shown to be synthesised locally in various tissues within the male reproductive system, including the prostate (Robbins and Kumar 1987; Sherwood 2007). Research has shown that the peptide exerts a paracrine effect upon the prostate, stimulating contraction of the gland during ejaculation as well as playing a role in the regulation of the growth of the prostate (Robbins and Kumar 1987).

Prostatic secretory products produce an alkaline fluid with a high pH ranging from about 7.2 to 8.0 which protects the spermatozoa from the acidic cervical mucus and vaginal secretions. This neutralising effect is important as sperm function more advantageously in an alkaline environment and require a buffer from the hostile environment of the female reproductive tract (WHO 1992; Sherwood 2007).

The prostate secretes certain enzymes that interact with the fibrinogen secreted from the seminal vesicles (Lwaleed et al. 2004). This interaction produces the insoluble compound fibrin. Fibrin is a protein which forms the meshwork of a clot and is responsible for the coagulation of semen in the female reproductive tract directly after ejaculation. However, in order to allow for the quick release of motile sperm, the clotted semen needs to be broken down. Fibrinolysin, a proteolytic enzyme produced by the prostate, acts to degrade the fibrin, which liquefies the congealed semen within 5–15 min. Subsequently, spermatozoa are free to now travel through the cervix to reach their target (Heath and Young 2000; Sherwood 2007).

9.3.4 Pathologies

The functional integrity and maintenance of the prostate, as with the other accessory sex glands, is dependent on androgens. The growth of normal prostate epithelium is reliant upon testosterone (Pienta and Esper 1993). However, it is often observed

in the category of men over the age of 50 that prostate growth becomes deregulated and the activity of dihydrotestosterone (DHT), a derivative of testicular testosterone, generates a state of hypertrophy (Pienta and Esper 1993). Cases of glandular dysfunction are seldom encountered in men under the age of 40 and this state of malfunctioning results in either benign or malignant overgrowth (Thackare et al. 2006). Inflammation, benign prostatic hypertrophy and carcinoma are the three pathological conditions observed in the prostate (Robbins and Kumar 1987).

9.3.4.1 Prostatitis

Infection of the prostate, prostatitis, is observed in young men and is a focal infection whereby certain areas of the prostate become infected whilst the other zones may not. Prostatitis can be an acute or chronic inflammation of the prostate and is classified in four groups: acute bacterial prostatitis, chronic bacterial prostatitis, achronic bacterial prostatitis and asymptomatic inflammatory prostatitis (Nieschlag and Behre 2000). The condition has a scientifically proven negative impact on the functioning of the reproductive system and is often the common cause for recurrent urinary tract infections (Robbins and Kumar 1987; Jennet 1989). A decrease in sperm motility, semen volume and prostatic secretions is observed in patients presenting with chronic bacterial prostatitis. The predominant organisms responsible for the infection are the bacteria *Ureaplasma urealyticum* and the gram-negative bacteria *Escherichia Coli* (Robbins and Kumar 1987), which reach the prostate either via the blood stream or the urethra. Chronic prostatitis may be responsible for infertility either by its negative influence on spermatozoa motility and viability or through its relation to prostatic secretions (Hafez 1977). The diagnosis of prostatitis is achieved by a digital rectal examination as well as an examination of the urine and glandular secretions to detect the presence of pathogens. The route of treatment for the inflammatory condition is a course of antibiotics (Ullmann 2009).

9.3.4.2 Prostatic Hypertrophy

During a male's reproductive cycle, a common physio-anatomical event when a man reaches reproductive senescence is the enlargement of the prostate (Hafez 1977). This is a result of the non-malignant condition known as benign prostatic hypertrophy which occurs when the mucosal and submucosal glands become enlarged without undergoing cell division (Silverthorn 2009). Benign prostatic hypertrophy most commonly arises in the transitional and central prostatic zones (Pienta and Esper 1993) and difficulty experienced when passing urine is a common symptom (Nieschlag and Behre 2000). This is due to the fact that the prostatic gland completely encircles the urethra, if the gland is swollen; it will impinge on the portion of the urethra that passes though the prostate. Patients present with frequent bouts of urination due to the fact that the wall of the bladder thickens and contraction of the muscular wall of the bladder occurs even with a small amount of urine present

in the bladder (Sherwood 2007). The presence of blood in the urine as well as frequent bladder infections can also be used in diagnosing the condition (Jennet 1989). Depending on the severity, there are several ways in which the glandular enlargement can be treated. In the case of partial urinary obstruction, medication is available. However, in severe cases where a patient presents with complete urinary obstruction, surgery is required to relieve the symptoms.

9.3.4.3 Prostate Cancer

Cancer of the prostate has fast become a growing concern in the medical community due to both the increasing incidence of diagnosis, as well as mortality rate in men over the age of 50 years. Although the reason behind the phenomenon remains unclear, the frequency of the condition displays an almost exponential rise in this particular age group and is now the most common form of cancer in men (Pienta and Esper 1993). The disease is most often found in the peripheral zone and manifests itself in two forms: histological and clinical (Pienta and Esper 1993). Researchers have suggested that disturbances in hormonal metabolism may result in the disease progressing from the one state to the other. The initial stages of the disease have been linked to hormonal stimuli, notably the anabolic steroid, testosterone (Pienta and Esper 1993). Increased concentrations of testosterone are present in men who have undergone vasectomies and these men have an increased predisposition for developing the disease (Honda et al. 1988). A rectal examination is used to detect an enlargement of the prostate, as well as an ultrasound examination to obtain a more comprehensive idea of the shape and size of the gland. Prostatic acid phosphatase and PSA are phenotypically expressed by the luminal secretory cells of the prostate into the seminal fluid (Lalani et al. 1997) and the enzyme plays a role in the degradation of the coagulated semen following ejaculation. However, in men with prostatic cancer, the concentrations increase. This makes PSA a sensitive serum marker for detecting the disease and screening for PSA can be used as an alternative diagnostic method (Stenman et al. 1999). Once malignancy is detected, the size of the tumour dictates the line of treatment. For larger tumours, hormone therapy can be used. The aim of hormone treatment is to disable the growth-stimulating influence of the male hormones on the prostate. For smaller tumours, surgery is the first line of treatment. Surgical removal of a tumour involves the removal of the entire prostate gland, the seminal vesicle behind the prostate, a section of the ureter as well as the neighbouring lymph nodes (Ullmann 2009).

9.4 Seminal Vesicles

Seminal fluid is a complex assortment of various substances, which ultimately are responsible for optimising spermatozoa functioning. The seminal vesicles are a pair of accessory sexual glands, which provide a variety of secretions vital to the

overall composition of semen. The seminal vesicles are an important part of the male reproductive system as they are the main and final contributors towards the seminal plasma, together supplying up to 85% of the total volume of semen (Heath and Young 2000).

9.4.1 Location

Anatomically, the sac-like seminal vesicles are found in the space between the rectum and the posterior surface of the bladder (Wilson et al. 1997). The glands lie on either side of the last section of the ductus deferens. The ductus deferens is part of the extra-testicular pathway and is two tube-like structures which extend out of the scrotal sac from the epidymis and empties at the base of the bladder into the urethra. This last section of the ductus deferens is where the seminal vesicles deposit their secretions. After this point, the duct continues onto what becomes the ejaculatory duct, which then empties into the urethra (Nieschlag and Behre 2000).

9.4.2 Structure

The seminal vesicles are a pair of two membranous pouches, approximately 7.5 cm in length. Each of the glands is comprised of a tube which is coiled upon itself, creating an irregular glandular diverticulum (Hafez 1977; Heath and Young 2000; Sherwood 2007). Surrounding the glands is a muscular wall organised into an outer longitudinal and an inner circular layer (Heath and Young 2000). Short adrenergic neurons that originate from the pelvic ganglia are found innervating the muscular wall of the seminal vesicles. During the emission phase of ejaculation (Nieschlag and Behre 2000) sympathetic impulses result in sequential contraction of the smooth muscles (Heath and Young 2000). As a result, the secretions of the seminal vesicles are delivered to the urethra in preparation for expulsion from the penis.

9.4.3 Secretion and Function

The seminal vesicles secrete a fluid which is yellowish in colour, viscid and alkaline in nature (Heath and Young 2000). A wide range of compounds are produced by the secretory cells found in the epithelial lining of the glands (Heath and Young 2000). The predominant compounds are fructose, proteins and prostaglandins. Other secretory products include fibrinogen, ascorbic acid, flavins, phosphorylcholine and ergothioneine (Hafez 1977).

The seminal vesicles play no role in the storage of sperm but are however responsible for the final contribution to the seminal plasma. This assists in expelling and diluting the spermatozoa into the urethra and helping them to become mobile. The alkalinity of the secretions functions as a buffer against the acidic environment that spermatozoa will encounter in the female reproductive tract (WHO 1992; Sherwood 2007). However, the primary role of the seminal vesicles is to provide

high concentrations of fructose to the seminal plasma. The normal value of fructose is 13 μmol or more per ejaculate and is vital to the functional integrity of spermatozoa as it is the major source of glycolytic energy in order to maintain motility (WHO 1992).

Another function of the seminal vesicles is to secrete fibrinogen, a precursor of the molecule fibrin. Fibrinogen interacts with enzymes produced by the prostate, ultimately resulting in the 'clotting' of semen. This ensures that following coitus and the extraction of the penis, the semen remains in the female reproductive tract (Sherwood 2007).

An important role of the seminal vesicles is to produce prostaglandins. Prostaglandins were first discovered in semen and are found in abundance in human seminal plasma. Originally, the prostate was believed to be responsible for producing acidic lipids known as prostaglandins, hence how the name is derived. However, it is now known that prostaglandins originate from the seminal vesicles. Prostaglandin F2α (PGF2α) is the predominant form of prostaglandins in semen and males presenting with infertility display significantly decreased concentrations of PGF2α (Hafez 1977). Prostaglandins are one of the most biologically active compounds known with numerous pharmacological effects, including the stimulation of smooth muscle. The prostaglandins produced by the seminal vesicles influence both the female and male reproductive systems and are responsible for promoting the transport of sperm. Prostaglandins stimulate the smooth muscle of the male reproductive tract during the process of ejaculation and the resultant contractile action promotes the movement of sperm (Hafez 1977; WHO 1992). In the female reproductive system, seminal prostaglandins cause the uterus and vagina to contract following sexual intercourse which also facilitates the transport of sperm towards the site of fertilisation (Hafez 1976; Sherwood 2007).

9.4.4 Pathologies

Certain abnormalities in semen parameters can be indicative of dysfunctional or overactive seminal vesicles. Sex gland secretions play a vital role in providing spermatozoa with nourishment and a suitable environment, and alterations in the secretory patterns can be detrimental to viability and motility. Conditions such as raised concentrations of zinc and fructose as well as an increase in the volume (>6 mL) of semen are symptomatic of a glandular dysfunction in the seminal vesicles. Diabetic men who often suffer from infertility present semen which can have a fructose concentration that is almost double that of a non-diabetic ejaculate (Hafez 1976, 1977).

The seminal vesicles are androgenic dependent and the primary androgen responsible for maintaining the normal function of the seminal vesicles is a derivative of testosterone: dihydrotestosterone (DHT). The absence of the anabolic steroid can be detrimental to the reproductive system, possibly even causing the condition of aspermia (ejaculation failure). This is a result of the deterioration of the secretory epithelia within the seminal vesicles (Hafez 1977; Nieschlag and Behre 2000).

Patients who present with the condition of hypogonadism can undergo testosterone treatment. This form of therapy can result in the seminal vesicles as well as the prostate enlarging and hence normal functioning of the glands is resumed.

9.5 Conclusions

The male gametes are produced in the testis, but ultimately released during the process of ejaculation in order to enter the female reproductive tract. During this stage it is vital that the male accessory sex glands release their secretions in an orderly manner, allowing for the facilitation of sperm movement, nourishment and protection, which may eventually lead to the successful fertilisation of the oocyte.

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