1 The Adult Male

[See Appendix for a review of male reproductive anatomy.]

1.1 Three Basic Requirements for Fertility in the Male

For a man to be fertile, he must fulfill three basic requirements [1]: produce semen containing sufficient numbers of healthy sperm, achieve an erection of sufficient rigidity to enter the vagina during intercourse, and be capable of ejaculating in a way that deposits semen within the vaginal canal.

Unlike the complex cyclicity of the female, male sexual function is fairly invariant. As in the female, the male reproductive system is regulated and maintained by the endocrine system, specifically the hypothalamic–pituitary–gonadal axis. The key hormones involved include: hypothalamic gonadotropin-releasing hormone (*GnRH*), two gonadotropins (*LH*, *FSH*) secreted from the anterior pituitary (also called the adenohypophysis), and two androgenic sex steroids (testosterone – *T*, and its metabolite dihydrotestosterone, or *DHT*).

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1.2 Endocrinology of the Male Reproductive System

The reproductive system in both sexes is driven by the pulsatile release of GnRH from the hypothalamus. GnRH [2] has a short (less than four minutes) half-life and consists of 10 amino acids that are cleaved off of a larger molecule (pre-proGnRH) whose production is coded for by chromosome 8. Once released, the GnRH decapeptide quickly travels the few millimeters to the anterior pituitary (adenohypophysis) via a specialized capillary portal system, where it binds to pituitary cells called gonadotropes (or gonadotrophs) and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [3] – two gonadotropins named for their actions in the female. Like GnRH, the gonadotropins are also released in pulses and, as the term *trophic* suggests, their function is to "nourish" (Gr), i.e. to maintain the structure and function of the testes and ovaries.

Although pulsatile release [4] of GnRH, and of LH and FSH occurs in both the male and female, the *patterns* of pulsatility differ, and are used by the body to encode their physiological actions. Like a combination of AM and FM radios, their amplitude (how much hormone is released in each pulse) and frequency (time between pulses) vary over time and changes in these parameters allow the body to orchestrate the complexity of the menstrual cycle in nonpregnant women, and to maintain testosterone secretion and reproductive function in the adult male.

Although LH and FSH are structurally different, both are glycoproteins (chains of amino acids linked to sugars). Because these complex and three-dimensional molecules are charged (polar), they are unable to cross the cell membrane and rely instead on cellular recognition via receptors expressed on the plasma membrane.

Gonadotropin binding to the cell membrane is the first messenger [5]. This event activates the receptor and turns on ionic and/or enzymatic pathways inside the cell to generate the

second messengers (e.g. calcium and kinases) that regulate its various functions such as secretion, metabolism, and hormone production.

Leydig cells [6] interspersed between the seminiferous tubules (also called interstitial cells for this reason) are the primary target of LH. The hormone and the cell type having a first letter in common (**L**H-**L**eydig) is an easy way to remember this specificity, and the main action of LH in males [7] is to stimulate the Leydig cells to produce testosterone [8]. Once released, testosterone diffuses into a neighboring seminiferous tubule, within which sperm production occurs, and initiates *paracrine* actions on the Sertoli cells [9] that form the inner lining of each seminiferous tubule to assist in the highly ordered process of spermatogenesis that results in the creation of 100–200 million new sperm daily.

Alternatively, testosterone released from the Leydig cell can be absorbed into the bloodstream via one of the many capillaries that course between the seminiferous tubules and among the Leydig cells. Once testosterone enters the vascular compartment, it travels throughout the body to exert *endocrine* actions on many tissues such as skeletal muscle or the brain.

While there are other androgenic variants and metabolites of this steroid (the most common being DHT), all androgens have 19 carbons. In contrast, progesterone has 21, and estrogen 18. The three main types of sex steroids [10] – progestogens, androgens, and estrogens – are classified by their number of carbons. In addition, there are several steroidal enzymatic pathways by which one steroid may be converted into another. For example, testosterone can be produced from progesterone via 17α-hydroxylation followed by cleavage of two carbons, and estrogen can be made from testosterone via the process of aromatization [11], which involves the appropriately named enzyme *aromatase* (Figure 1.1).

Interestingly, aromatization occurs in some of the neurons of the male brain, so that some of the central actions of testosterone – the male sex hormone – are actually carried out via its conversion into estrogen [12], the female sex hormone. Being small and highly lipid-soluble molecules, all steroids diffuse into

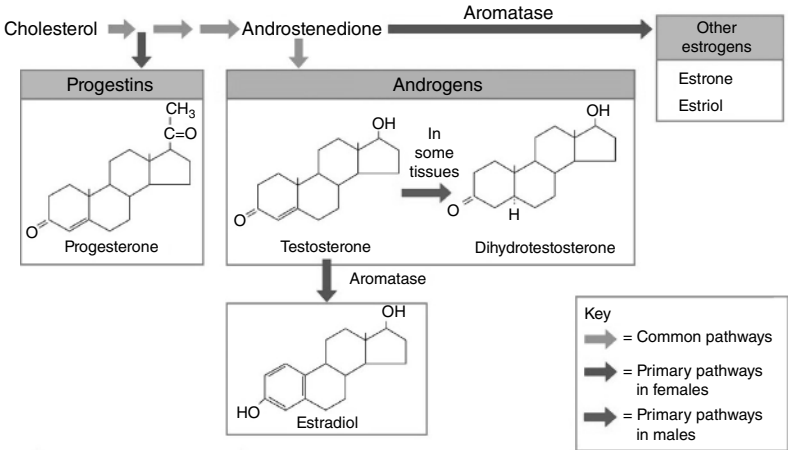

Figure 1.1 Steroidal biochemical pathways.

their target cells and enter the nucleus, where they combine with a nuclear receptor and activate or repress gene transcription. As we learn more about them, however, it is clear that there are also receptors in the cell membrane and, in the case of androgens, these are called membrane androgen receptors, or mARs. The activation of these G-protein-coupled receptors (GPCRs) leads to the generation of second messengers much like that elicited by the binding of the gonadotropins and all other peptide hormones. Acting in concert with promoter elements, testosterone modulates gene transcription to facilitate spermatogenesis and stimulates a range of Sertoli cell metabolic and secretory activities.

Once it reaches the testes, FSH [13], the other pituitary gonadotropin, diffuses from capillary across the connective tissue wall of the seminiferous tubule where it binds to the Sertoli cell membrane and elicits a cascade of second messengers. In response to FSH, Sertoli cells also make a peptide hormone of their own, called inhibin [14], which diffuses out of the tubule, enters the bloodstream and regulates FSH secretion through a negative feedback mechanism (just like testosterone regulates LH).

FSH and testosterone thereby regulate numerous Sertoli cell functions [15] in a cooperative manner. For example, Sertoli cells nurture the developing sperm by secreting nutrients (which is why they are often also called "nurture cells"). They also secrete a fluid into the lumen of the tubule that helps wash the sperm out of the tubules into the epididymis, and produce and secrete a protein called androgen-binding protein, or ABP, into the lumen of the tubule. By continually binding and releasing many testosterone molecules, ABP acts like a testosterone "sponge" and sets up a dynamic equilibrium that allows testosterone concentrations within the tubule to be as much as 50 times higher than those in the systemic circulation.

Sertoli cells also phagocytize the cellular debris shed during spermiogenesis, which we describe later, and produce immunoregulatory molecules that suppress the immune response within the seminiferous tubules. This is important, since the immune system would perceive sperm as being antigenic and mount an autoimmune response by triggering autoantibody production.

A second Sertoli-based anti-immune mechanism is physical: each individual Sertoli cell is connected to its neighbors via tight junctions, which act to "zipper" together the cells into a sheet-like intratubular barrier called the blood–testis barrier [16], preventing the passage of immune and other cells into the immunologically privileged intratubular compartment.

One final consideration related to the spatial relationships between the reproductive cells of the male and the female [17] may be helpful in remembering which hormones act on which cells. We have already considered the tripartite reproductive "unit" of the male as consisting of (i) Leydig cells outside, and (ii) Sertoli cells and (iii) sperm-forming cells inside the seminiferous tubule.

In females, the analogous reproductive units are the mature ovarian follicles. The outer follicular shell (analogous to the Leydig cells in the male) is composed of *theca cells* while the inner one (analogous to Sertoli cells) consists of *granulosa cells*. Like Leydig cells, theca cells bind LH and produce testosterone. On the other hand, the inner granulosa cells that are closest to

the egg (like the Sertoli cells closest to the sperm), bind FSH and take up the testosterone released from the neighboring outer theca cells.

Like Sertoli cells, granulosa cells also secrete the hormone *inhibin*, which enters the circulation and provides a negative feedback on pituitary FSH release. The one important difference is what happens to the testosterone that enters a granulosa cell: because granulosa cells have an abundance of *aromatase,* testosterone (19C) is converted to estrogen (18C) and released to diffuse out of the follicle and into the bloodstream where, and, in addition to exerting many its many endocrine effects on the uterus, brain, breasts, and other organs, the estrogen provides a negative feedback on pituitary LH release. To round out the analogy, note that Sertoli cells also contain some aromatase, and some of the Leydig cell-derived testosterone is converted into 17-beta estradiol to also help direct spermatogenesis.

1.3 Physiological Actions of Testosterone and Related Androgens

The testosterone that passes into the capillaries of the testis and circulates throughout the body has multiple and diverse endocrine actions [18] in a number of tissues. As described above, it provides a negative feedback signal to the pituitary to control LH secretion. It also regulates and maintains the structure and function of all of the associated secondary sex organs which include the various ducts (e.g. vas deferens), glands (e.g. seminal vesicles and prostate), and organs (e.g. penis, testes). Within the testis, the process of spermatogenesis would be abrogated without testosterone, and the individual would likely have a low sperm count and be infertile. A male lacking or deficient in testosterone might also experience different feelings and emotions, since testosterone is important in central nervous system (CNS) function, and would likely have a less masculine appearance and a reduced sex-drive.

Some of the most impactful actions of testosterone occur in utero [19], well before birth. If a child is destined to be a boy, testosterone production is initiated by factors derived from the Y chromosome quite early in pregnancy (weeks 6–8). Its action at this time, along with other factors secreted from the testes, is to shunt the process of sexual differentiation [20] toward the male sex by stimulating the growth of primordial male gonads and accessory ducts and glands. We initially have primitive gonads and ducts that can develop either into male or female sex organs. The Wolffian duct develops into the male; the Mullerian duct into the female. Without testosterone, the Wolffian ducts atrophy and the reproductive organs of the individual become female (default). In a male embryo, however, the female vestiges (Mullerian ducts) involute due to the secretion of anti-Mullerian hormone (secreted from the testes), while the Wolffian ducts are stimulated to grow and differentiate under the influence of testosterone, and develop into the reproductive structures of the male. This process of sexual differentiation is normally completed by week 15 of gestation.

The action of testosterone and its related androgens during and after puberty [21] is to promote growth of the secondary sexual organs like the penis and scrotum, stimulate the growth and secretory activity of the epididymis and accessory glands, and facilitate the initiation of spermatogenesis. Androgens also effect changes in the pitch of the voice (via growth of the larynx and thickening of the vocal cords), stimulate skeletal muscle development, and the development of facial, chest, and axillary hair. Testosterone stimulates protein anabolism and bone growth, although it also hastens epiphyseal closure. In the case of testosterone excess, a boy may experience accelerated growth, but end up being shorter than he would have been otherwise. In genetically prone individuals, androgens may also lead to loss of hair on the head (male pattern baldness).

After puberty, the Leydig cells of the adult male produce 6–7 mg of testosterone per day. As he passes from youth to middle, and then old age, this amount slowly declines, so that daily production is halved by the seventh or eighth decade of life.

As might be expected, this is mirrored by a similar reduction in circulating concentrations. Because this process is very gradual, however, an aging male does not undergo a sudden cessation of sex steroid production (as women do after menopause), and can remain fertile well into old age.

In the adult male, testosterone stimulates the production of red blood cells (erythropoiesis), which is why men tend to have hematocrit values that are several points higher than those of women. At the same time, as circulating concentrations decrease, its physiological effects begin to wane, resulting in a slowing of metabolism, reduction in libido, and a loss of muscle mass.

Once it is absorbed into the bloodstream, testosterone circulates bound to plasma proteins, so that the effective (or "free") concentration is only 2–3% of the total hormone present in the blood. Within many tissues, testosterone functions as a prohormone, and is converted into DHT [22], an active metabolite that may be several times more potent than testosterone in its actions. The importance of DHT becomes evident when one considers the fate of individuals who lack 5α-reductase [23], the enzyme that converts T into DHT. DHT is critical for directing the normal development of the male external genitalia during embryonic life and, without it, the female structures may predominate, even though the sex is male, and underdeveloped and undescended testes may be present in the inguinal region. Hence, the individual is a genetic male (has a Y chromosome), but has the phenotypic appearance of a female.

A variation of this is the rare syndrome called androgen-insensitivity syndrome (AIS, [24]), formerly called *testicular feminization syndrome* in which a genetic male is unable to respond to testosterone due to defects on the X chromosome that result in a nonfunctional androgen receptor. When the Y chromosome stimulates the production of testosterone *in utero* during mid-pregnancy, the testosterone cannot activate its receptor and the individual will develop into a phenotypic female, e.g. he will have a vagina but no cervix or uterus, may develop breasts during

puberty, and will likely be raised as a female. This individual will not be able to menstruate due to an absence of the uterus, and may only be diagnosed as an AIS patient during puberty, when the failure to menstruate becomes manifest.

These days, a natural question is whether gender identity is related to sex hormone signaling and, although the field is in its infancy in terms of our understanding of its physiologic basis, there are some recent studies that have associated gender dysphoria with overrepresentation of alleles and genotypes that regulate sex-hormone signaling and responsiveness.

1.4 Spermatogenesis and Spermiogenesis

The production of healthy sperm in sufficient quantities is essential for fertility in the male. According to the World Health Organization's (WHO) latest guidelines, sperm counts [25] below 15 million/ml of semen are considered abnormal. Many men have sperm counts on the order of 50–200 million/ml of semen; therefore, it is not unusual for the total ejaculate, which has a volume of 3–5 ml, to contain more than half a billion sperm. The process of spermatogenesis is active, ongoing throughout adult life in the male, and largely genetically determined although it is also subject to influence by chemical and physical environmental factors (e.g. BPA, an estrogenic molecule found in some plastics, or heat and radiation).

Sperm produced within the seminiferous tubules [26] are transported through a series of ducts (rete testis; efferent ductules) into the epididymis. They may be stored in the epididymis or vas deferens for a considerable period of time (weeks) before passing into the urethra prior to ejaculation. The challenge of spermatogenesis is to create a sufficient number of cells that are haploid, motile, capable of penetrating the cumulus and zona pellucida of the egg, and have the ability bind to the plasma membrane of the oocyte (the oolemma).

Each testis contains hundreds of tightly packed seminiferous tubules ranging from 150 to 250 μm in diameter, and having a combined length of 30–70 cm (1–2 ft). The tubules are packed into distinct lobules, each containing one convoluted seminiferous tubule whose ends empty into a collecting region of the testes called the *rete testis*. The interior of the seminiferous tubule is lined with Sertoli cells and avascular. Sertoli cells are connected to each other by tight junctions that effectively divide each tubule into a basal (outer) and an adluminal (inner) compartment. By virtue of the blood–testis barrier, the luminal compartment is an immunologically privileged compartment free of any cells derived from the circulation. Following testicular injury or vasectomy, or in some autoimmune diseases, the production of antisperm antibodies may destroy the sperm and render the male infertile.

The progenitor cells for the production of sperm are the spermatogonia [27]. These non-differentiated cells are found in the basal compartment of the seminiferous tubules, and constantly undergo mitotic division, continually replenishing themselves. The process of spermatogenesis is initiated when some of the spermatogonia grow into primary spermatocytes [28], and migrate across the tight junctional complexes into the adluminal compartment. The mechanism involves the opening of a junction to allow a developing primary spermatocyte through, followed by its rapid closure to restore the integrity of the barrier. Once a primary spermatocyte is formed, it embarks on a spermatogenic path in which it will undergo two meiotic divisions that result in the creation of four separate haploid cells.

In the first meiotic division (*reduction division*), one primary spermatocyte forms two secondary spermatocytes [29]. Each of the two secondary spermatocytes will thus contain only 23 chromosomes, but with two copies of each due to DNA replication. The secondary spermatocyte is therefore haploid from a genetic standpoint (*n* rather than 2*n*); however, its DNA mass is equal to that of a regular diploid cell.

Because maternal and paternal chromosomes align [30] in a random way during the first meiotic division, the chromosome

present in a particular secondary spermatocyte has an equal chance of it being of either maternal or paternal origin. This presumably random event alone results in potentially more than 8 million (2^{23}) different genetic combinations just as there would be if one laid 23 coins out on a table in various heads vs. tail combinations. In addition, there is a certain degree of chromosomal mutation and translocation that occurs, particularly in prophase of the first meiotic division, resulting in an individual spawning even greater genetic diversity during spermatogenesis in the male (and, similarly, during oogenesis in the female).

Each secondary spermatocyte undergoes a second meiotic division called an *equatorial division*, in which the two secondary spermatocytes form four spermatids [31] with only one copy of each of the 23 genes per cell, i.e. haploid in terms of both genetics and DNA mass.

Once the second meiotic division is completed, the rather undistinctive appearance of each spermatid begins to undergo a morphologic change that transforms it into what we would easily recognize as a sperm. The nucleus condenses (increases in its density), and the cytoplasm is shed. The acrosome [32], a lysosome-like structure unique to spermatozoa buds from the Golgi apparatus, flattens, and comes to rest on top of the head of the sperm like a cap. The centrioles migrate to the caudal pole and form the tail by producing a long axial filament composed of nine peripheral microtubule doublets arranged around a central pair called the axoneme [33]. The axoneme is surrounded by a fibrous sheath, conferring some rigidity to the tail and is an evolutionarily conserved structure that is identical to any cilium or flagellum.

This transformation from a morphologically nonremarkable cell to the sleek and specialized motile spermatozoon (*spermatozoa* plural) is called sper*mio*genesis [34]. The oval head of the human sperm is only a few microns in diameter, and can exceed 50 μm in length. The acrosome capping each spermatozoon contains a variety of proteolytic enzymes such as hyaluronidase, acrosin, neuraminidase, phospholipase A, and esterases. The head of the sperm contains the

tightly packed haploid DNA, and, at its caudal end, narrows to form the neck, which transitions into the midpiece. The midpiece has the axoneme in its center, and a well-organized spiral sheath of mitochondria wound around the central filament. These produce ATP to fuel locomotion via the beating of the tail, and produce energy from nutrients present in the fluid within which they are suspended. The tail propels the sperm by a twisting motion derived from interactions between tubulin fibers and dynein side arms, a process that utilizes a magnesium-dependent ATPase.

Because each spermatogonium has one X chromosome and one Y chromosome, two of the four spermatids will have a single X chromosome that will combine with the egg's X chromosome to form a genetic female, XX, and two will contain a Y chromosome which, combined with the X egg will produce a male XY genotype. The proper names for these X or Y containing sperm are gymnosperm vs. androsperm [35] based on their ability to determine the sex of the offspring. Because the Y chromosome is quite small, androsperm (Y) sperm are lighter than gymnosperm (X) and may be separated by differential centrifugation and used in assisted reproductive technology to create a baby of either sex. The sperm therefore determines the sex of the offspring.

The process of spermatogenesis is synchronized and carried out in close physical association with the Sertoli cells. The entire process is under the direct regulation of the Sertoli cell which is, in turn, guided by the combination of FSH from the pituitary, and testosterone from neighboring Leydig cells. For sperm to be functionally mature, they must pass through the epididymis, which is about an inch and a quarter in length and consists of a tightly packed, highly convoluted tube which is some 15″ in length in humans. Prior to entering the epididymis, sperm are immotile, while those exiting from the tail of the epididymis have acquired motility. A second thing of note is that sperm become decapacitated during their passage through the epididymis [36] due to the absorption of various lipids (such

as cholesterol) secreted by the epididymal epithelium onto the head of the spermatozoa. This process stabilizes their membrane and is protective during ejaculation but it also renders them incapable of fertilizing the egg. Capacitation normally occurs only after ejaculation and involves a washing off of the lipids by the fluids within the female reproductive tract. Spermatozoa spend two to four weeks in the epididymis, and the entire spermatogenic process (beginning with the formation of a primary spermatocyte, two meiotic divisions, spermiogenesis, and passage through the epididymis) takes approximately 10 weeks to complete in humans.

1.5 Production of Seminal Plasma

Although the number of sperm produced daily may be staggering, spermatozoa only comprise a small fraction (about 5%) of the total ejaculate. The remaining 90–95% is composed of fluids derived from the seminal vesicles (approximately 60%), the prostate (30%), and accessory glands called the bulbourethral (or Bartholin's) glands (<5%). There are also urethral glands sprinkled along the urethra that secrete a lubricating mucus, making the walls or the penile urethra slippery and providing less resistance during ejaculation.

Prostatic secretions [37] are milky, thin, and alkaline. They contain prostate-specific antigen (PSA) which is often elevated in prostate cancer, and can therefore be used as a marker for prostatic malignancy. Prostatic secretions also contain other enzymes, most notably spermine phosphate or phosphatase, which are used as markers for semen in forensic investigation.

The secretions of the seminal vesicles [38] are sticky and rich in mucus, and contain fructose (the principal energy substrate for glycolysis in ejaculated sperm), ascorbic acid, and prostaglandins. Prostaglandins can induce smooth muscle contractility, and aid sperm ascending the female reproductive tract by inducing reverse peristalsis. They were first isolated

from semen and assumed to originate in the prostate (a fact that was subsequently found not to be true), but the name has remained in use.

Finally, it is worth noting that there is also a complete clotting/declotting system [39] present in semen derived from clotting enzymes in prostatic fluid, and fibrinogen in seminal vesicle fluid. Their coordinated action during ejaculation results in the semen quickly forming a gel, affording sperm some physical protection. It also allows time for the diffusion of buffers and antibacterial substances from the coagulum into the vagina, keeps semen from leaking out of the vagina, and facilitates its ascent into the uterus and Fallopian tubes, since the reverse peristalsis is more effective against a gel than a liquid. The gel structure of semen is maintained for 15–20 minutes following ejaculation, at which time it reverts to a liquid form through a process of liquefaction [40].

1.6 Testicular Thermoregulation; Varicocoele

The human testes do not function normally at body temperature and are therefore maintained at 35 °C (~95 °F) rather than 37 °C (98.6 °F). This is accomplished by several concurrent mechanisms for testicular thermoregulation [41].

The initial event – testicular descent into the scrotum through the inguinal canal – normally occurs *in utero*, during the last trimester of pregnancy through a combination of hormonal and mechanical mechanisms. Failure of testicular descent is termed cryptorchidism (or cryptorchism; [42]), a condition that occurs in 2–3% of male infants. Failure to do so in the first few months of life warrants corrective surgery (orchiopexy) because undescended testes are associated with a 4- to 10-fold increase in the risk of developing testicular cancer, and with reduced fertility. In the adult, both testes lie within the scrotum and each is connected to the body via the spermatic cord which

contains nerves, blood vessels, and the vas deferens which exit the abdominal cavity in the inguinal region. The anatomy of the inguinal region creates an area of weakness in the abdominal wall that can become herniated in response to increased intra-abdominal pressure (e.g. from straining during the Valsalva maneuver, or from lifting heavy objects). Although they can occur in women as well, 90% of the time, inguinal hernias occur in men.

Once testicular descent has occurred, the distance of the testes from the body can be regulated by a thin, sheet-like skeletal muscle called the cremaster (mechanism 1, [43]) that relaxes in a warm environment, allowing the testes to drop away from the body.

The second protective thermoregulatory mechanism involves evaporative cooling, since the scrotum is well-endowed with sweat glands (mechanism 2, [44]).

A third mechanism is countercurrent heat exchange (mechanism 3, [45]) between the testicular arteries and the veins. Blood flows down to each testis via the testicular artery, which ramifies within the testis into smaller arteries and capillaries that course between the seminiferous tubules. Blood returns from the testis via a specialized tangle of veins called the pampiniform plexus [46]. Tightly wrapped around the spermatic artery, this anatomic arrangement facilitates a countercurrent exchange of heat in which warm blood flowing to the testis is cooled by the cooler venous blood within the pampiniform plexus; conversely, the cooler venous blood returning to the body is rewarmed by the heat given up by the arterial blood within the testicular artery.

The pampiniform plexus sometimes becomes varicosed, slowing the normal flow of blood and altering testicular hemodynamics. This condition is called a varicocele [47], is not uncommon (one in six men have it to some degree) and usually (>90% of the time) occurs in the left testis. As with most varicosities, the cause is overdistension of the vein from excessive intravenous pressure.

The mechanism underlying the "sidedness" is related to an asymmetry in vascular anatomy [48]: while the right testis drains into the inferior vena cava – a large, low-pressure vessel that returns blood to the heart – the left testicular vein enters the left renal vein. Being somewhat longer than the right, and having several additional venous branches emptying into it, the left renal vein has a vigorous flow and this, in itself, creates a rheological (flow-induced) obstruction. In addition, intravenous pressure tends to be a few millimeters of mercury higher in the left vs. right renal vein because of its proximity to the superior mesenteric artery, which may compress it and impede the venous flow. This combination of high flow and increased pressure creates a backpressure that is transmitted into the pampiniform plexus, over-distending the testicular veins and resulting in permanent varicosity. Varicocele is graded based on severity and can be diagnosed by palpation, which has been likened to feeling a "bag of worms." In severe cases, it results in a softening and shrinking of the left testicle and in reducing spermatogenesis. Thus, varicocele is associated with infertility, especially if a man has a borderline sperm count. When this is a concern, varicocele can be surgically corrected by vein removal (varicocelectomy) or percutaneous embolization.

1.7 Penile Erection

Sexual arousal from physical and/or psychic stimuli results in an increase in parasympathetic drive to the reproductive organs, particularly the penis, which is largely composed of lacunar erectile tissue that is sponge-like in structure and capable of filling with blood. The efferent nerve impulses are carried to the penis by parasympathetic nerves emerging in the sacral (S2–S4) region of the spinal cord via the cavernous nerve branches of the prostatic plexus.

The penis is composed of three cords of erectile tissue [49] – the basocentral *corpus spongiosum* (which also forms the glans, or head of the penis and contains the urethra) and

two *corpora cavernosa* situated in a horizontal plane above the corpus spongiosum. Note: the corpus spongiosum is sometimes referred to as the *urethral corpus cavernosum*.

The neurovascular mechanism of erection [50] during arousal involves an increased frequency of efferent parasympathetic neural impulses eliciting a release of vasodilatory neurotransmitters, particularly nitric oxide (NO) from nerves located around the small, muscular penile helicene arteries. These vessels are normally under sympathetic influence and operate in a partially constricted state (tone) that restricts the amount of blood flowing into the flaccid penis via the internal pudental artery.

During arousal, NO binds to and stimulates the enzyme *guanylate cyclase* within penile arterial smooth muscle, resulting in the conversion of *guanosine triphosphate (AGTP)* into *cyclic guanylate* monophosphate (cGMP [51]). By inducing calcium extrusion from the cell, and sequestration to intracellular organelles, cGMP reduces cytosolic calcium concentrations in arterial smooth muscle cells, decreasing force production, and leading to their relaxation and vasodilation. Blood flow increases secondary to vasodilation and the erectile tissues become engorged with blood (the filling phase, [52]), causing the penis to elongate and become tumescent.

As the erectile tissues expand secondary to the increased arterial inflow, they compress the veins, which are located peripherally, allowing maximal (nearly systemic) pressure to develop within the cavernosa and spongiosum (the tumescent phase, [53]).

Being a neurovascular process rather than a reflex (like ejaculation), erection is not all-or-none, i.e. a man may achieve partial or full erection, depending on the degree of sexual stimulation and psychological arousal. Although NO derived from nerves initiates the process, endothelial NO contributes to its maintenance. In both cases, the increase in NO results from the activation of nitric oxide synthase 3 (NO-3), which converts the amino acid arginine into citrulline, liberating NO as a byproduct.

1.8 Cellular Mechanism of PDE-5 Inhibitors in Treating Erectile Dysfunction

As with many other physiological systems, the intracellular concentration of cGMP in vascular smooth muscle reflects a summation of production (anabolism) vs. breakdown (catabolism). The breakdown of cGMP is primarily carried out by an enzyme called phosphodiesterase (PDE), and penile helicene arteries are particularly rich in the PDE-5 isoform. Inhibition of PDE-5 slows the breakdown of cGMP, favoring an increase in its cytosolic concentrations derived from NO influence. This, in turn leads to calcium extrusion from vascular smooth muscle cells and results in vasodilation.

Because drugs like sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) are relatively specific PDE-5 inhibitors [54], they enhance the process of penile vasodilation and erection but do not cause it by themselves, and have much weaker effects on blood vessels in nonreproductive organs. This has some obvious practical benefits, especially for a drug like tadalafil, whose half-life is on the order of 17 hours (the half-lives of vardenafil and sildenafil are much shorter: 4–6 hours).

At the same time, some decrease in systemic blood pressure may occur because resistance arteries normally operate in a partially constricted state (tone), and their relaxation lowers peripheral resistance and blood pressure. The spillover effect is normally insignificant unless a man has very low blood pressure, or is on antihypertensive medicines, in which case PDE-5 inhibitors should be used cautiously and at the lowest dose that produces a satisfactory effect. Blood vessels of the eye have the PDE-6 isoform, which is also partially affected by PDE-5 inhibitors, and one of the less intuitive side effects of taking PDE-5 inhibitors is a change in and, very rarely, loss of vision due to nonarteritic ischemic optic neuropathy (NAION).

1.9 Emission and Ejaculation

If appropriate in pattern and of sufficient intensity, penile stimulation leads to the ejaculatory reflex [55], in which semen is expelled from the penile urethra via a sympathetic neuromuscular mechanism. Once it is triggered, ejaculation is no longer under voluntary control and is therefore most appropriately classified as a reflex.

Its efferent arc originates at the L3–L4 level where a spinal ejaculatory generator in the lumbar spinal cord stimulates a secretory center (T10–L2) that induces sequential contractions of the epididymis, vas deferens, seminal vesicles, and prostate gland.

Sperm and associated fluids from the epididymis and vas deferens are propelled into the urethra by peristaltic contractions of the vas. At the same time, the capsules of the seminal vesicles and prostate contract, increasing intraglandular pressure and forcing their secretions into the urethra. This results in the mixing of testicular/epididymal fluid containing sperm with the glandular secretions and is called the emission phase [56].

The filling of the urethra initiates sensory afferents via the pudental nerves which travel to the mechanical center in the sacrospinal (S2–S4) region of the spinal cord and triggers the ejaculatory phase [57]. The spinal reflex mechanism induces rhythmic contractions of the striated bulbospongiosus and bulbocavernosus and ischiocavernosus muscles, propelling the semen out of the tip of the penis in spurts roughly a second apart.

Several other muscular events [58] are coordinated by the sympathetic nervous system during ejaculation. These include contraction of the neck of the bladder to prevent retrograde ejaculation, and contraction of pelvic skeletal muscles – particularly, the *ischio- and bulbo-cavernosus, and perineal muscles*, all which contribute to the pleasurable sensation of orgasm. While its occurrence is normally concurrent with ejaculation, male orgasm [59] is a physiologically distinct event which involves CNS activation, tachycardia, and acutely increased blood pressure and respiration.

1.10 Infertility

Male infertility [60] which accounts for approximately 40% of total infertility, can arise from problems with: (i) sperm number, structure, or function, (ii) obstructive disease that blocks normal emission and/or ejaculation, and (iii) disorders of sexual function.

If a male does not produce sperm in sufficient concentrations, and has a low sperm count [61] (<15 million/ml of semen), he will be infertile. Similarly, if sperm are not viable, structurally abnormal, or immotile, the male may be able to achieve erection and ejaculate, but be infertile. The causes should be considered as being either pre-testicular (problems with the hypothalamo–pituitary axis or other endocrinopathies that interfere with GnRH-LH/FSH production) or testicular (e.g. a congenital absence of Sertoli cells, immune damage). Low sperm counts are the largest single cause of male infertility, and have been suggested to be responsible for up to 90% of cases.

Semen analysis [62] is a useful tool for evaluating sperm number, viability, motility, and frequency of morphologic defects. The man is asked to refrain from sexual activity for at least 48 hours, as repeated ejaculations reduce both sperm number and ejaculate volume, potentially yielding a false-positive diagnosis. Although the acrosome is not readily apparent through a light microscope, specialized stains can be applied to selectively stain for the presence of acrosomal enzymes and an intact acrosomal membrane. If problems are discovered, the cause is often endocrine in nature since spermatogenesis is ultimately dependent on the hypothalamus, pituitary, and normal Leydig and Sertoli cell function. A defect in any part of this endocrine/cellular system may be responsible for low sperm count and male factor infertility. Finally, epididymal defects that result in immotile sperm and structural defects (two heads, bent tails; absence of an acrosome; defective genetic material) may all contribute to reducing the viability of sperm and, hence, male fertility.

Parameters for semen analysis [63] are currently based on 2010 WHO guidelines, and include the 15 million/ml reference value for sperm count (39 million per total ejaculate, and a volume of at least 1.5 ml), along with >40% total motility (32% for forward progressive motility), and 58% viability. Their values are remarkably forgiving for one parameter in particular: morphology; for a semen sample to be considered normal, only 4% of sperm have to appear normal.

The second broad cause of male infertility is obstruction. This may be due to a congenital absence of vas deferens, for example, from scarring following trauma or infection, or from a voluntary surgical procedure such as vasectomy. A variant, hypospadias [64], is due to an anatomical anomaly in which the urethra exits the penis at its base rather than tip. In this case, there is no obstruction, *per se* – rather, the inability to deposit sperm in the vaginal canal, precluding normal insemination.

The third category of male infertility is *sexual dysfunction*, e.g. an inability to produce an erection or to ejaculate. The underlying causes are numerous, and may be psychological, neural, vascular, or muscular in origin. The older term – *impotence* – has been replaced in recent years by erectile dysfunction (ED, [65]), defined as *the inability of a male to produce an erection of sufficient rigidity to deposit semen intravaginally.* As already discussed, these days, ED is most often aided by oral PDE-5 inhibitors such as sildenafil. Neural or vascular damage may also lead to sexual dysfunction, in which case PDE-5 inhibition may be of limited use. ED be due to many different causes, including spinal cord injury, autonomic and peripheral neuropathy, endocrine disorders, psychogenic disorders (e.g. performance anxiety and depression), atherosclerosis (yes, it can occur there too), and drug-induced effects. Anything that affects the neurovascular pathway we already discussed may affect sexual function, even physical compression (as in poorly designed bicycle seats). Ironically, while depression can lower libido, so can antidepressant drugs (such as Prozac).

One last word on impotence vs. infertility [66]. The former term is narrower than the latter, and is defined as "the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse". A summary of causes of male infertility can be found in Table 1.1, below.

Table 1.1 Causes of Male Infertility

I. Disorders of spermatogenesis
   A. Pre-testicular (e.g. pituitary and endocrine disorders, tumors)
   B. Testicular (e.g. varicocele, cryptorchidism)

II. Obstruction of the efferent ducts
   A. Congenital (e.g. absence of the vas deferens)
   B. Acquired (e.g. vasectomy)

III. Disorders of sperm motility
   A. Congenital (immotile Cilia syndrome, epididymal dysfunction)
   B. Acquired (antisperm antibodies)

IV. Sexual dysfunction
   A. Congenital (immotile Cilia syndrome, epididymal dysfunction)
   B. Impotence
   C. Ejaculatory abnormalities (e.g. retrograde ejaculation)