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II.1.3 Physiology of Spermatogenesis

M. Bergmann

Summary

Spermatogenesis includes multiplication of spermatogonia, meiosis of spermatocytes and differentiation of spermatids into the male gamete, which is capable of motility and fertilizing an egg. Spermatogenesis occurs within the testicular seminiferous tubules, which consist of peritubular tissue and the seminiferous epithelium. The latter is composed of germ cells and somatic Sertoli cells. Somatic Sertoli cells divide the seminiferous epithelium into basal and adluminal compartments by inter-Sertoli cell junctional complexes protecting spermatocytes and spermatids from the immune system. They support and trigger germ cell development by mediating hormonal stimuli because they are the only cells within the epithelium possessing follicle-stimulating hormone and androgen receptors. Germ cell apoptosis is most important during pubertal establishment of the species-specific ratio of germ cells to Sertoli cells, and is increased together with spermatogenic impairment. There are six different, specific germ cell associations within the seminiferous epithelium: "stages of spermatogenesis". These stages are sequentially arranged along the length of a tubule: "wave of spermatogenesis". The duration of this wave is the "cycle of spermatogenesis". It takes 16 days; the whole process of spermatogenesis from the spermatogonium to the release of the spermatozoon takes about 70 – 75 days.

Spermatogenic efficiency is within the range of other primates and shows that sperm number is not limited by germ cell loss during meiosis but depends on the number of spermatogonia entering meiosis.

Spermatogenic impairment is regularly associated with Sertoli cell maturation deficiency, and incorrect DNA integrity and condensation due to failure in histone to protamine exchange may be an important factor predicting the outcome of assisted reproduction by in vitro fertilization or testicular sperm extraction/intracytoplasmic sperm injection.

II.1.3.1 Spermatogenesis

Spermatogenesis represents the entire process of germ cell development within the seminiferous epithelium of the adult testis. It can be divided into four phases and includes: (1) the proliferation and differentiation of spermatogonia, (2) meiotic divisions of spermatocytes, (3) the transformation of haploid round spermatids arising from the second meiotic division into spermatozoa (spermiogenesis), which (4) are released into the lumen of the seminiferous tubules (spermiation) (Fig. II. 1.8a, b).

II.1.3.2 Seminiferous Tubules

Seminiferous tubules have a diameter of about 180 µm and consist of peritubular tissue (lamina propria) and the seminiferous epithelium. The lamina propria (8 µm) is composed of four to five layers of contractile myofibroblasts and connective tissue. The seminiferous epithelium (80 µm) rests on a basal lamina and consists of germ cells in different developmental stages and the supporting somatic Sertoli cells, which provide an extreme cytoplasmic ramification and surround adjacent germ cells (Fig. II. 1.9a, b).

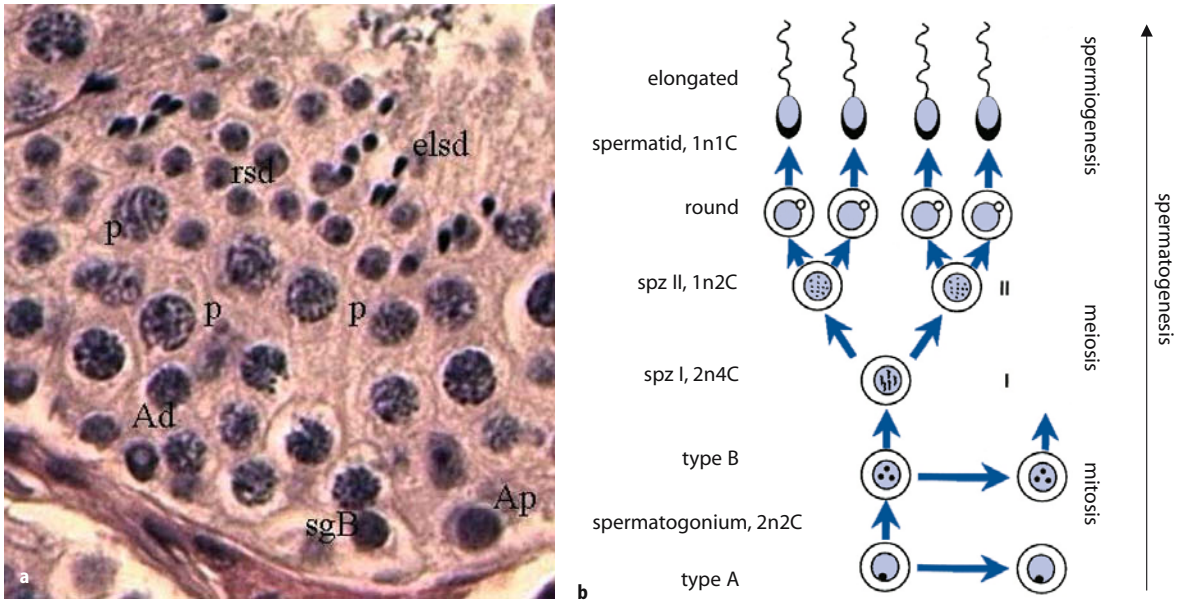

Fig. II.1.8a, b. Seminiferous epithelium and process of spermatogenesis. **a** Normal seminiferous epithelium. [*Ap* Spermatogonium type A (pale), *Ad* spermatogonium type A (dark), *sgB* spermatogonium type B, *P* primary pachytene spermatocyte, *rsd* round spermatid, *elsd* elongated spermatid.] Paraffin section, haematoxylin and eosin, primary magnification, ×40. **b** Process of spermatogenesis

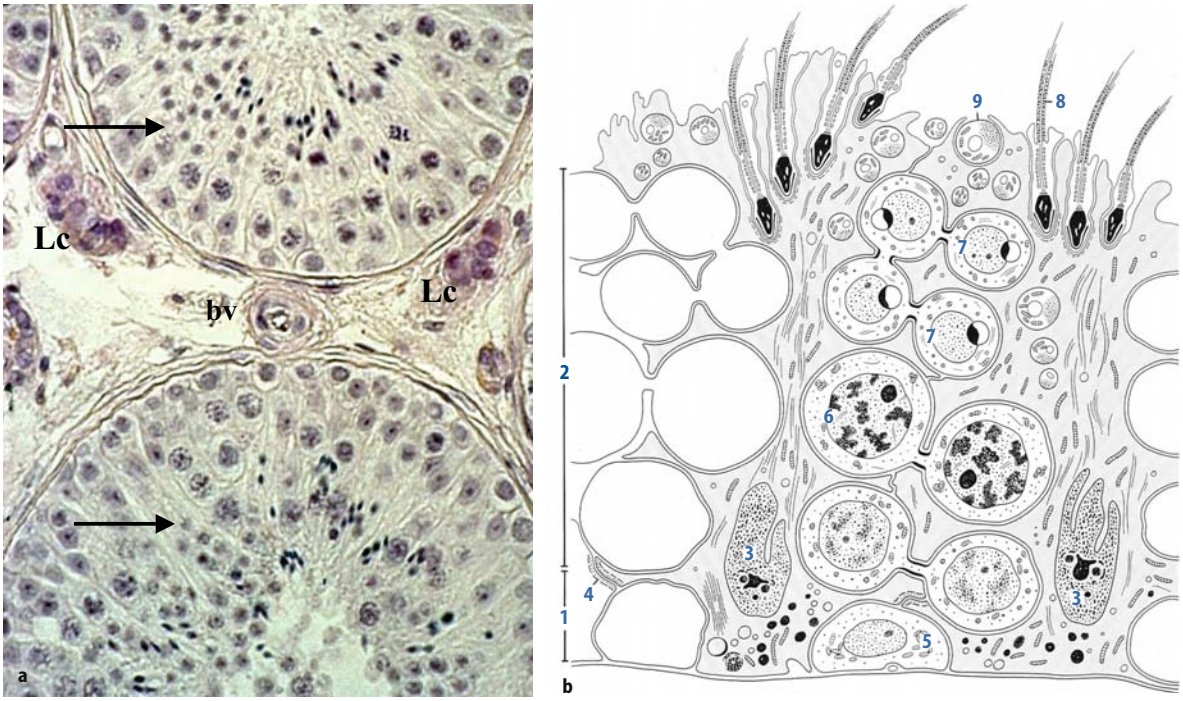

Fig. II.1.9a, b. Normal seminiferous epithelium. **a** Seminiferous tubules with intact seminiferous epithelium (*arrows*) and interstitial tissue containing blood vessels (*bv*), and Leydig cells (*Lc*); paraffin section, haematoxylin and eosin, primary magnification, ×20. **b** Schematic drawing of the seminiferous epithelium. [*1* Basal compartment, *2* adluminal compartment, *3* Sertoli cell nucleus, *4* inter-Sertoli cell junctional complex, *5* type a (pale) spermatogonium, *6* primary pachytene spermatocyte, *7* round spermatid, *8* elongated spermatid, *9* residual body.] From Holstein (1994)

II.1.3.3 Spermatogonia

Spermatogonia are the diploid (2n2 C) stem cells of spermatogenesis, and can be divided into type A and type B. They undergo mitotic divisions and thus represent the renewing stem cell population. The classification is mainly based on differences of nuclear chromatin pattern. Type A spermatogonia have an oval euchromatic nucleus in contrast to type B spermatogonia, which have a round heterochromatic nucleus. In primates including humans, type A spermatogonia are further divided into A pale (Ap) and A dark (Ad) according to their differing nuclear appearance. In contrast to Ap, Ad spermatogonia are characterized by a dark nucleus showing a light halo. A possible functional significance in respect of mitotic activity remains controversial. In non-human primates Ad spermatogonia have no or only weak proliferative activity (Schlatt and Weinbauer 1994), whereas S-phase-specific Ki-67 immunoreactivity indicating mitotic activity was found in both Ap and Ad spermatogonia by Steger et al. (1998) in the human.

It is generally agreed that type B spermatogonia are able to differentiate and enter the process of meiosis. Due to incomplete cytokinesis, type B spermatogonia remain interconnected after the last mitotic division by intercellular bridges forming cellular clones, which allow synchrony of germ cell maturation. These intercellular bridges persist until late spermiogenesis. In spermatogonia, genomic imprinting for parent-of-origin-dependent regulation of gene expression via DNA methylation takes place and is finished before the first meiotic division (Kierszenbaum 2002).

II.1.3.4 Spermatocytes/Meiosis

II.1.3.4.1 Primary Spermatocytes

Meiosis starts with DNA synthesis of type B spermatogonia which lose contact with the basal lamina (preleptotene). After completion of DNA synthesis, each chromosome consists of two chromatids (C). These cells are named primary spermatocytes, and the DNA content is tetraploid (2n4 C). Primary spermatocytes undergo the first meiotic division. The prophase of the first meiotic division takes about 1 – 3 weeks and is divided into several stages: the leptotene, zygotene, pachytene and diplotene stages.

The leptotene stage is characterized by DNA condensation resulting in the appearance of thin filaments within the nucleus. In the zygotene stage, condensation of chromosomes proceeds, and pairing of homologous chromosomes takes place due to the formation of the "synaptonemal complexes" which are only visible using an electron microscope. In the pachytene stage, there is an exchange of genetic material derived from maternal and paternal sources between sister chromatids of homologous chromosomes involving DNA breakage and repair in autosomes but not in the heterosomes "x" and "y". The pairing of chromosomes leads to a "crossover" of adjacent sister chromatids. When the chromosomes start to separate in the pachytene stage, these sites become visible and are termed "chiasmata". In the diplotene stage, chromosomes separate with the exception of the chiasmata sites. The end of the meiotic prophase is recognized as "diakinesis", when chromosomes shorten and the four separate chromatids become visible. Finally, the nuclear membrane disappears and chromosomes are subsequently arranged in the metaphase plate. After formation of the spindle apparatus, chromosomes move to opposite poles, but, in contrast to mitotic division, chromatids remain interconnected. Thus the number of chromosomes in resulting secondary spermatocytes is haploid, but the DNA content is still diploid (1n2 C).

II.1.3.4.2 Secondary Spermatocytes

Secondary spermatocytes undergo the second meiotic division after a short interphase of about 6 h in the human without DNA synthesis. By this division, chromatids are finally separated leading to round spermatids with a haploid number of chromosomes and DNA content (1n1 C).

II.1.3.5 Spermatids/Spermiogenesis

Early round spermatids are postmitotic cells, exhibit a nucleus with a homogenous chromatin pattern and can be identified by the perinuclear acrosome vesicle, which can easily be seen after periodic acid Schiff (PAS) reaction on formalin, or Bouin-fixed paraffin-embedded sections or at the ultrastructural level.

The transformation of conventional round cell spermatids into spermatozoa with the capacity for motility and fertilization of an egg includes a complex sequence of events: (1) formation of the acrosome, (2) condensation of the nucleus, (3) development of the sperm tail, (4) reorganization of cellular organelles such as mitochondria and centrioles and (5) reduction of the cytoplasm.

The synthesis of many acrosome-specific proteolytic enzymes starts as early as in pachytene spermatocytes. These proteins, such as proacrosin, are packed into electron-dense vesicles: proacrosomal granules (PAGs) derive from the trans-Golgi complexes. They start to fuse after completion of meiotic divisions in

step1 spermatids. The growing acrosome forms a cap-like structure that covers about 30–50% of the nuclear surface (Bermudez et al. 1994).

Nuclear condensation in the human is due to replacement of about 85% of the DNA-associated lysine-rich histones by transition proteins, and finally by arginine-rich protamines. In contrast to histones, which form a loop-like association with DNA (nucleosomes), protamines are associated with the grooves of the DNA helix, leading to extreme condensation and finally to a reduction to about 10% of the original nuclear size. Transition proteins are believed to be involved in DNA repair mechanisms during histone to protamine exchange (Fig. II.1.10). Associated with the increased exchange of nuclear proteins is a decrease in and cessation of gene transcription. Thus, in spermatids gene transcription and protein translation are temporally uncoupled (for review see Steger 1999, 2001), together with the temporal storage of mRNA in spermatid-specific nucleoprotein complexes, which were described at the ultrastructural level by Holstein and Roosen-Runge (1981). The fertilization capacity of spermatozoa depends on the protamine content being adequate and the ratio of the two protamines PRM1 and PRM2 being correct (Steger et al. 2003).

The formation of the tail (flagellum) starts early in spermiogenesis. The axoneme shows the typical "9+2" structure of microtubules. This is the common pattern of eukaryotic cilia and derives from one of the pair of centrioles. These centrioles are placed in a nuclear fossa opposite the acrosome. The distal centriole gives rise to the flagellum. The other structures of the flagellum, the fibrous sheet and outer dense fibres are developed when spermiogenesis takes place.

Mitochondria from the periphery of the spermatid aggregate around the proximal part of the flagellum in a helical manner forming the latter's mid-piece. At the end, the spermatid's cytoplasm is shed by active involvement of the adjacent Sertoli cell, and this "residual body" is phagocytosed by Sertoli cells.

The events described occur either simultaneously or with a degree of overlap. For practical reasons, depending on the development and formation of the acrosome, the whole process of spermiogenesis can be divided as follows:

- Golgi phase
  Development of the acrosome vesicle
- Cap phase
  Formation of the acrosomal cap together with the start of nuclear condensation and development of the flagellum
- Acrosome phase
  Differentiation of the acrosome, and elongation of the nucleus and cell body

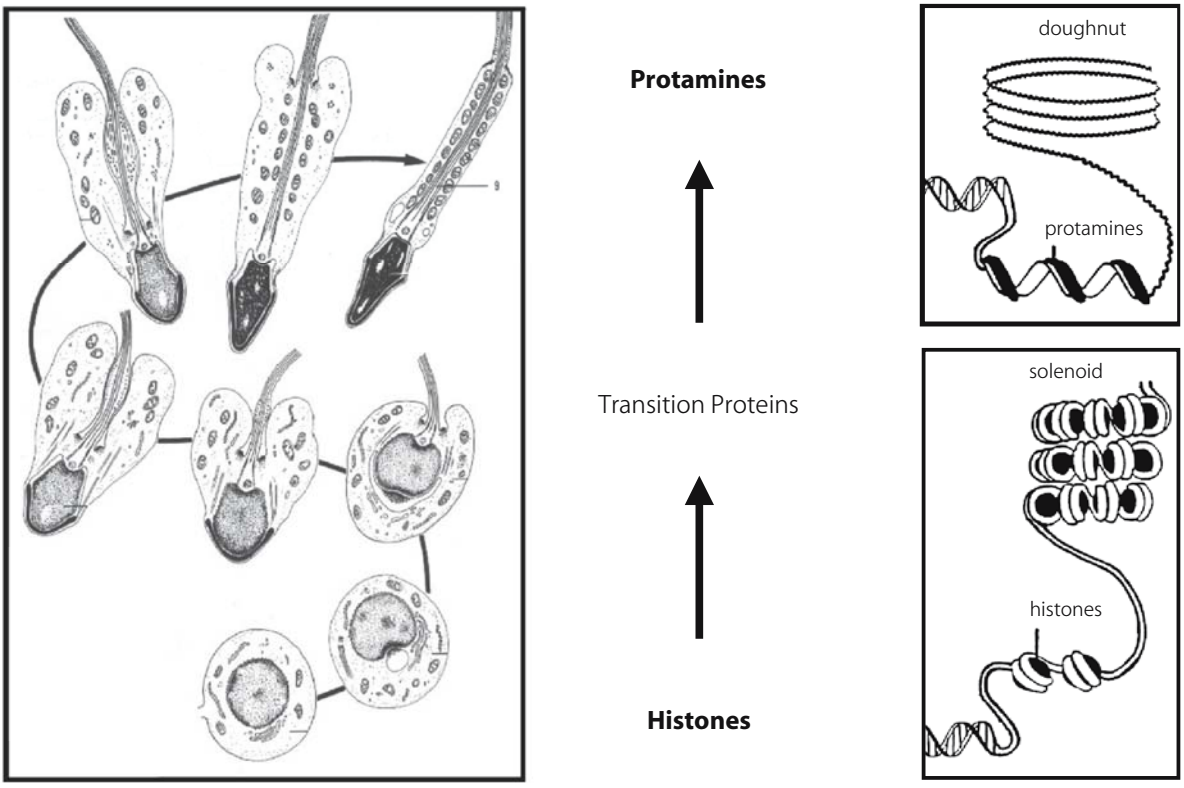

Fig. II.1.10. Schematic presentation of histone to protamine exchange

- Maturation phase
  Differentiation of the species-specific form of the acrosome and sperm head; completion of nuclear condensation, and the reduction of cytoplasm.

The release of fully differentiated spermatids into the lumen of the seminiferous tubule, which is triggered by the Sertoli cell, is termed "spermiation".

The haploid germ cell within the seminiferous epithelium is termed the "spermatid" (round, elongating, elongated). The haploid germ cell after spermiation is a "spermatozoon" (sperm).

II.1.3.6 Spermatozoon (Fig. II.1.11)

The length of the human spermatozoon measures about 60 µm. The flat and oval head (diameter: 3 µm, length: 5 µm) consists of the acrosome and the extremely condensed nucleus. The acrosome covers the head surface, and contains numerous proteolytic enzymes, i.e. hyaluronidase, collagenase, neuraminidase, phospholipase A, acrosin and others. The release of these enzymes, the so-called acrosome reaction, enables the spermatozoon to penetrate the "corona radiata" of follicle cells and the zona pellucida of the egg. Some nuclear vacuoles are common.

The flagellum measures about 55 µm in length. It possesses the central axoneme and is divided into:

- The neck/connecting piece (1 µm). It contains the basal and striated bodies and is the point of articulation between the sperm head and the flagellum.
- The mid-piece (6 µm). It contains the mitochondria and the nine doublets of microtubules, which are associated with outer dense fibres, each consisting of at least 14 polypeptides with a molecular mass ranging from 11 to 87 kDa (Henkel et al. 1994). Outer dense fibres are believed to maintain the passive elastic structure for flagellar bending and also to protect it from shearing forces during epididymal transit and ejaculation (Baltz et al. 1990). Hinsch et al. (2004) detected the voltage-dependent anion-sensitive channels VDAC2 and VDAC3 in bovine outer dense fibres, indicating their functional role in the regulation of sperm motion or sperm structural integrity.
- The principal piece (45 µm). In addition to the outer dense fibres, the flagellum contains a fibrous sheet.
- The end-piece (5 µm) only contains microtubules.

Spermatozoa acquire motility during epididymal passage and their competence for fertilization during the passage of the female genital tract (capacitation).

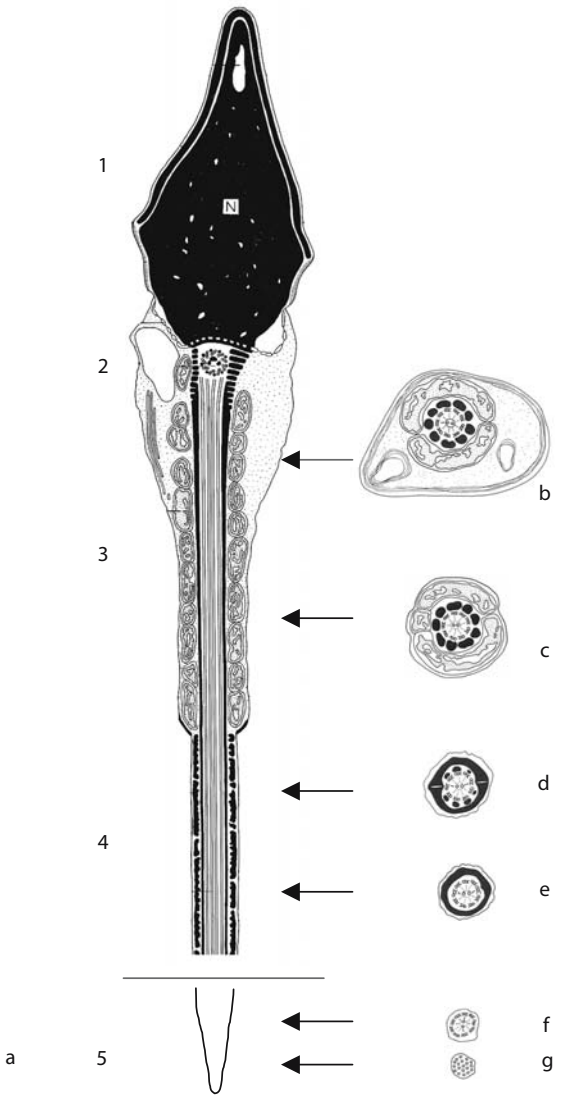

Fig. II.1.11. Schematic drawing of the human spermatozoon according to Holstein and Roosen-Runge (1981). **a** Longitudinal section showing *1* head with acrosome, *2* neck, *3* mid-piece and *4* principal piece, and *5* end-piece. **b–f** Flagellar cross sections through the **b, c** mid-piece, **d, e** principal piece, and **f** end-piece

II.1.3.7 Sertoli Cell

Sertoli cells are postmitotic somatic cells, which extend from the basement membrane of the seminiferous tubule to the lumen, providing an extreme cytoplasmic ramification, and surround adjacent germ cells (Figs. II.1.9b, II.1.12a). They are responsible for the establishment of the blood–testis barrier (BTB) within the seminiferous epithelium by inter-Sertoli cell junctional complexes. These complexes are located between the level of spermatogonia and primary spermatocytes and consist of tight junctions and gap junctions, which are

associated with actin filaments and cisternae of the endoplasmic reticulum. The latter bears ribosomes on the cytoplasmic site. Tight junctions prevent diffusion through the intercellular space, which can be demonstrated by tracer application such as lanthanum or horseradish peroxidase (Bergmann et al. 1989). By this, Sertoli cells divide the seminiferous epithelium into a basal compartment (blood milieu) and an adluminal compartment (milieu of the intratubular fluid created by Sertoli cells) (Figs. II.1.9a, II.1.12b–d). The functional significance is: (1) as an immunological barrier to protect spermatocytes and spermatids from the immune system preventing autoimmune orchitis and (2) to create a specific milieu for germ cell development that differs from the normal intercellular blood-borne milieu. The BTB has to be considered as a highly dynamic structure undergoing disintegration and reconstruction during the passage of developing germ cells from the basal to the adluminal compartment.

Intercellular communication within the seminiferous epithelium occurs via inter-Sertoli cell and Sertoli-germ cell gap junctions (Fig. II.1.12d). The most important gap-junction protein is connexin 43 (Cx43) and to a lesser extent connexin 26 (Cx26), which are first expressed during puberty at the same time as the onset of spermatogenesis and the formation of the BTB (see Brehm et al. 2002).

Sertoli cells support and trigger germ cell development and differentiation by mediating the hormonal stimuli. They are known to be the only cell type within the seminiferous epithelium to express both the membrane-bound follicle-stimulating hormone (FSH) receptor (FSHR) (Böckers et al. 1994), and the nuclear androgen receptor (AR) (Van Roijen et al. 1995; Suarez-Quian et al. 1999). However, FSH and FSHR mRNA were later found in germ cells, from spermatogonia to round spermatids, by Baccetti et al. (1998). FSH expression is regulated by the steroid hormone inhibin pro-

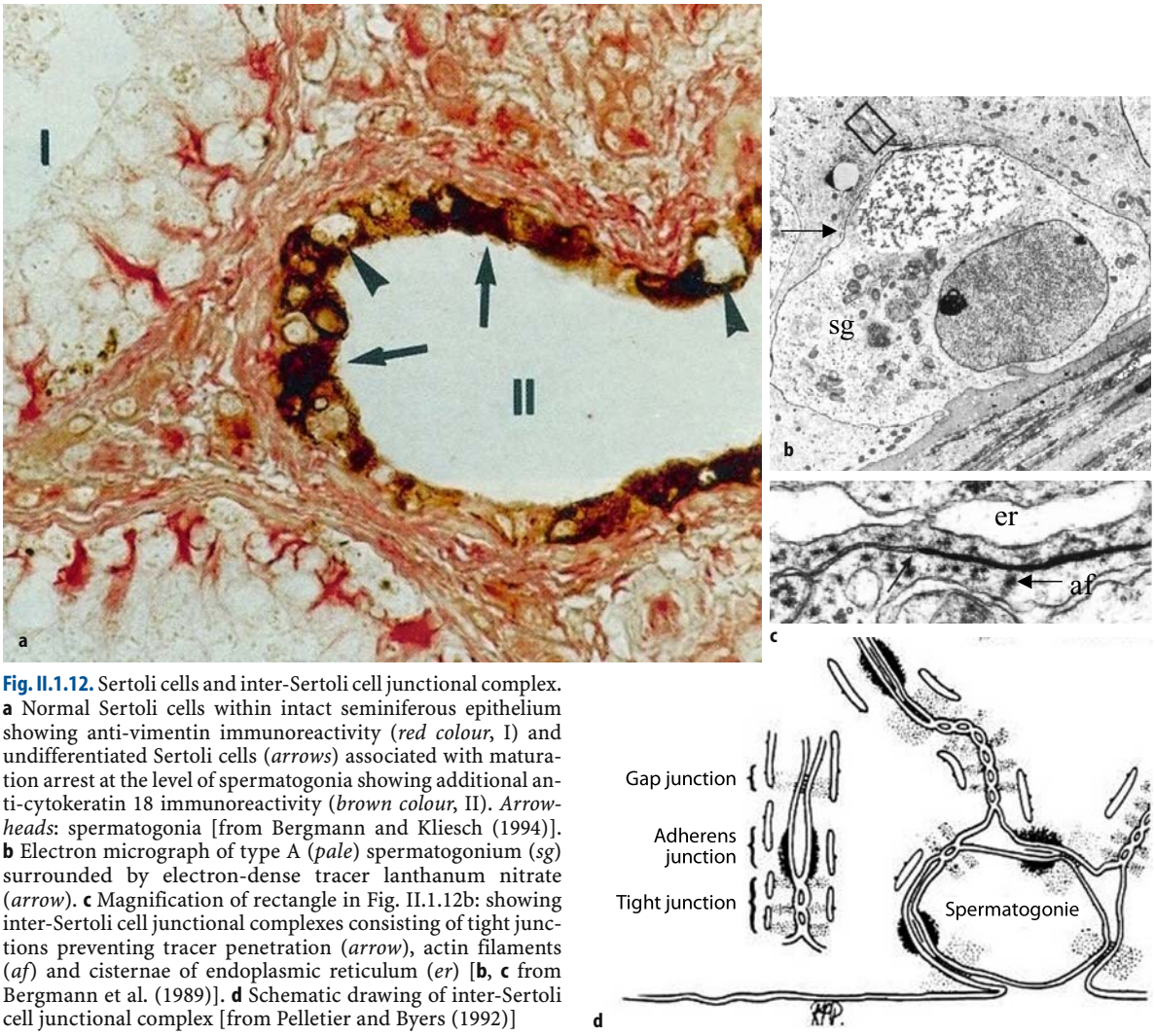

Fig. II.1.12. Sertoli cells and inter-Sertoli cell junctional complex. **a** Normal Sertoli cells within intact seminiferous epithelium showing anti-vimentin immunoreactivity (*red colour*, I) and undifferentiated Sertoli cells (*arrows*) associated with maturation arrest at the level of spermatogonia showing additional anti-cytokeratin 18 immunoreactivity (*brown colour*, II). *Arrowheads*: spermatogonia [from Bergmann and Kliesch (1994)]. **b** Electron micrograph of type A (*pale*) spermatogonium (*sg*) surrounded by electron-dense tracer lanthanum nitrate (*arrow*). **c** Magnification of rectangle in Fig. II.1.12b: showing inter-Sertoli cell junctional complexes consisting of tight junctions preventing tracer penetration (*arrow*), actin filaments (*af*) and cisternae of endoplasmic reticulum (*er*) [**b**, **c** from Bergmann et al. (1989)]. **d** Schematic drawing of inter-Sertoli cell junctional complex [from Pelletier and Byers (1992)]

duced by Sertoli cells. The typical cytoplasmic skeletal elements are microtubules and vimentin intermediate filaments which are responsible for Sertoli cell shape (Fig. II.1.12a) (see Bergmann and Kliesch 1994).

Sertoli cells produce numerous factors such as androgen-binding protein (ABP), which ensures high levels of testosterone in the seminal fluid within the adluminal compartment, rete testis, efferent ductules and epididymis, the iron-binding protein "transferrin" and copper-binding protein "ceruloplasmin", both necessary for germ cell differentiation (for review see De Kretser 2003). They trigger spermatogonial proliferation via the FSH-dependent stem cell factor (SCF), which binds to the tyrosine kinase receptor c-kit which is expressed by spermatogonia (Rossi et al. 2000). Their metabolism is influenced by germ cells and vice versa.

II.1.3.8 Apoptosis and Spermatogenesis

Apoptotic cell death is a prerequisite for continuous spermatogenesis, and limits the germ cell population in physiological conditions. It is most important to establish a species-specific ratio between germ cells and Sertoli cells during prespermatogenesis and especially around puberty (Heiskanen et al. 1996; Rodriguez et al. 1997). In the adult human seminiferous epithelium, apoptosis occurs at the level of spermatogonia, spermatocytes and spermatids, as a rare event (Brinkworth et al. 1997), and shows possible ethnic differences between Caucasian and Chinese men. These differences may help to explain the greater efficacy of testosterone-induced spermatogenic suppression observed in Asian compared to non-Asian men (SinhaHikim et al. 1998). However, apoptosis is increased in patients with impaired spermatogenesis (Lin et al. 1997), especially in primary spermatocytes and round spermatids associated with incomplete spermiogenic failure (Tesarik et al. 1998). Regulation of apoptosis within the seminiferous epithelium depends on the Fas/FasL system. FasL is expressed by Sertoli cells and Fas only by degenerating germ cells (Francavilla et al. 2000). The proteins of the Bcl2 family prevent apoptosis (for review see Print and Loveland 2000). It seems to be inhibited by testosterone (Singh et al. 1995) and FSH (Tesarik et al. 2000). Apoptosis of Sertoli cells under physiological conditions has not yet been reported.

II.1.3.9 Kinetics of Spermatogenesis

II.1.3.9.1 Cycle of the Seminiferous Epithelium

The seminiferous epithelium in a given cross-section shows characteristic germ cell association at different developmental stages. The type of spermatogonium is specific to the stage of meiosis and spermatid development. The series of different germ cell associations between the two appearances of the same stage was first described in the rat by LeBlond and Clermont (1952) and later by Clermont (1963) in the human as the cycle of the seminiferous epithelium. In the rat, XIV stages were defined based on 19 different steps of spermiogenesis as identified by the PAS reaction of the acrosome. The number of stages was found to differ according to the species: XII stages in the mouse or in non-human primates; VIII stages in the bull, stallion, or dog; and VI stages including eight steps of spermiogenesis in the human and great apes (Fig. II.1.13) (see Wistuba et al. 2003).

Whatever the case, stage I is defined by the occurrence of early round spermatids showing an acrosome vesicle after the second meiotic division. The last stage (VI, VIII, XII, or XIV, according to the species) is characterized by the presence of secondary spermatocytes.

In human spermatogenesis, in stage II residual bodies derived from spermatid cytoplasm are found within Sertoli cells. After stage II, spermiation takes place. Stage III is characterized by the beginning of spermatid nuclear condensation and the entry of type B spermatogonia into meiosis.

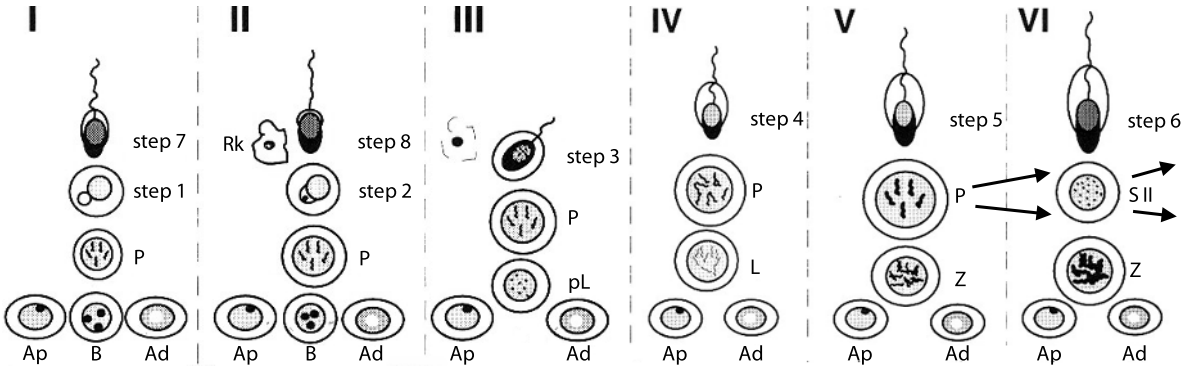

Fig. II.1.13. VI stages of spermatogenesis [from Bergmann (1998)]

Stages IV and V exhibit ongoing condensation of spermatid nuclei, and can be distinguished by the presence of leptotene primary spermatocytes in stage IV and zygotene primary spermatocytes in stage V. After stage V, pachytene primary spermatocytes undergo diakinesis and the first meiotic division takes place. The second meiotic division of secondary spermatocytes at the end of stage VI gives rise to round spermatids in stage I. In stage I, type A spermatogonia differentiate into type B spermatogonia.

These stages are arranged sequentially along the length of a tubule resulting in a "wave of spermatogenesis" in space. In contrast to most mammals investigated so far, in humans, as in the great apes, a given seminiferous tubule cross-section contains more than one stage of spermatogenesis (multi-stage arrangement vs. single-stage arrangement, i.e. in the rat) (Fig. II.1.14). This was explained by Schulze and Rheder (1984) to be the result of a helical orientation of several spirals of spermatogenic waves, but Johnson et al. (1996) demonstrated a random distribution of different stages within a given cross section. The difference between single-stage and multi-stage arrangements most likely depends on differences in the size of germ cell clones, being smaller in species with a multi-stage arrangement (for review see Luetjens et al. 2005).

The duration of this wave in time is the "cycle of spermatogenesis". In the human, this cycle takes about 16 days and the progression from spermatogonia to spermatozoa about 70 – 75 days, i.e. four and a half cycles (Heller and Clermont 1964).

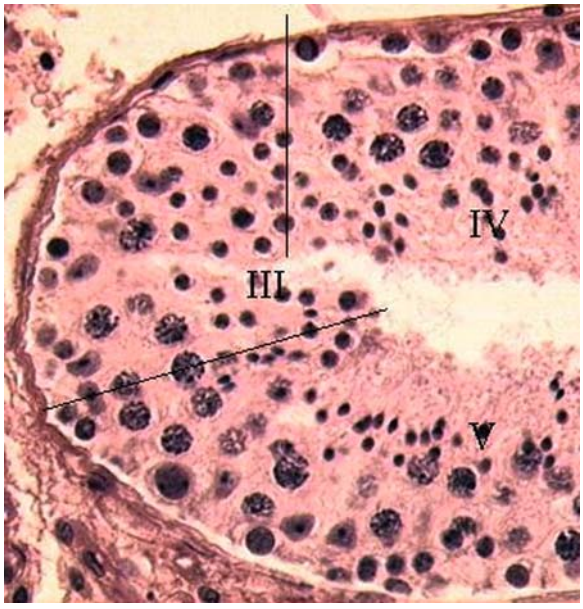

Fig. II.1.14. Multi-stage arrangement (stages II, IV, V) of normal human seminiferous epithelium, paraffin section, HE, primary magnification, ×40

II.1.3.9.2 Efficiency of Human Spermatogenesis

The efficiency of spermatogenesis depends on many factors, i.e. the absolute number of germ cells and Sertoli cells, the Sertoli cell/germ cell ratio, duration of the seminiferous cycle, germ cell loss during spermatogenesis, as well as on anatomical parameters such as the length of the seminiferous tubules or testis size resulting in different species-specific values for daily sperm production. In primates, the absolute number of germ cells is within a low range of 100 – 300 ml/g testis weight compared to about 530 ml/g testis weight in the rat. However, in the human, the conversion ratio from pachytene spermatocytes to round spermatids was found to be 3.5, and from round spermatids to elongated spermatids to be about 0.9 almost reaching theoretical levels of 4 and 1 respectively. These values are within the range of those for other primates as well as the rat (3.85/1.33), indicating that the efficiency of spermatogenesis in the human does not differ from that in other mammals (for review see Wistuba et al. 2003; Luetjens et al. 2005). These data also show that sperm production is not limited by germ cell loss during meiosis or spermiogenesis, but depends on the number of spermatogonia entering meiosis.

II.1.3.10 Pathophysiology of Spermatogenesis and Infertility

Impairment of spermatogenesis leading to infertility is associated with the histological appearance of hypospermatogenesis, partial or complete maturation arrest at the level of early round spermatids, primary spermatocytes or spermatogonia, to a complete loss of germ cells (Sertoli cell only syndrome = SCO) or even all cells (tubular shadows) within the seminiferous epithelium. The latter are often described as "hyalinized tubules". SCO and hyalinized tubules are often found in Klinefelter syndrome. In addition, numerous alterations of germ cell differentiation, i.e. meiotic arrest (megalospermatocytes) or impairment of spermiogenesis (multinucleated spermatids), are described (for review see Holstein et al. 1988). Interestingly, any spermatogenetic impairment is associated with a population of Sertoli cells showing signs of differentiation deficiency, including the persistence of undifferentiated nuclei, anti-Müllerian hormone secretion or the (re-) expression of foetal cytokeratin 18 intermediate filaments (Bruning et al. 1993; Bergmann and Kliesch 1994; Steger et al. 1999; Maymon et al. 2000, for review see Sharpe et al. 2003) (Fig. II.1.12a).

Impairment of spermatogenesis influences ejaculate parameters leading to a reduction of sperm density (oligo-), motility (oligo-astheno-), and an increase of

abnormal morphology (oligo-astheno-teratozoospermia = OAT syndrome). There is now increasing evidence that incorrect DNA integrity and condensation due to failure during spermiogenesis (histone to protamine exchange) seems to be an important factor predicting the outcome of assisted reproduction with morphologically normal spermatozoa (Blanchard et al. 1990; Ankem et al. 2002; Steger et al. 2003) or even in globozoospermia with germ cells missing an acrosome (Vicari et al. 2002).

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II.1.4 Physiology of Sexual Function

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Summary

The parasympathetic nervous system provides the primary pro-erectile innervation of the penis. Originating from the sacral nerve roots (S2–S4) the nerves provide vasodilating innervation to the cavernosal tissue. The parasympathetic nerves release a cocktail of pro-erectile neurotransmitters, of which the most important is nitric oxide (NO), which acts on the smooth muscle cell via a second messenger system involving cyclic GMP. The sympathetic innervation mediates detumescence and originates within the thoraco-lumbar cord (T11–L2) via release of noradrenaline. Our knowledge of the pharmacology of erection has recently provided us with a number of therapeutic approaches to the treatment of erectile dysfunction. The pudendal nerve represents the somatic innervation of the penis carrying both afferent impulses from the genitalia and motor fibres to the muscles of the pelvic floor.

The erection itself is a vascular event during which the degree of erection depends upon the balance between the arterial inflow and venous outflow of the penis. Parasympathetic stimulation (with an accompanying reduction in sympathetic stimulation) results in smooth muscle relaxation in the penile arteries, relaxation of the cavernosal (trabecular) smooth muscle and closure of the venous outflow from the penis.

Ejaculation has two phases, emission and ejection, the latter usually being accompanied by orgasm. Emission involves the sequential contraction of the epididymis, vas deferens, seminal vesicles and prostate, with ejaculatory fluid being "emitted" into the posterior urethra. Ejection is accompanied by tight closure of the bladder neck, with contraction of the prostatic musculature together with a sequence of variably coordinated contractions of the bulbocavernosus, ischiocavernosus and other pelvic floor muscles. The ejaculate is propelled into the anterior urethra and beyond.

The foreskin or the prepuce is a specialized, junctional mucocutaneous tissue that marks the boundary between mucosa and skin. It may have a number of functions including one as a sensory erogenous area and there may be others, but little is actually known.

Male sexual function can be thought of as having four phases, namely desire, arousal, orgasm and resolution. This chapter will deal with the physiology of the second and third of these phases, namely arousal and orgasm. In men, the most obvious manifestation of arousal is penile erection while ejaculation usually occurs with orgasm, although they are actually separate events. This chapter will deal initially with the physiology of erection, moving on to the physiology of ejaculation and orgasm, before finishing with a brief résumé of what we know about the physiology of the foreskin.