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REPRODUCTIVE TOXICOLOGY

EDITOR: **Donald R. Mattison**

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REPRODUCTIVE TOXICOLOGY

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Preface: Reproductive Toxicology

Donald R. Mattison, MD

Reproductive toxicology holds in its purview the development and function of the male and female reproductive systems, including fertilization, implantation, embryonic and fetal development, parturition, and postnatal adaptation. This broad perspective—encompassing reproductive and developmental biology, toxicology, teratology, and pharmacology as well as epidemiology, occupational and environmental health and medicine—may seem overwhelming to the health scientist interested in learning about (or participating in) this fascinating science. This volume represents an attempt to review and synthesize these diverse sciences. The need for conciseness and the pressures of editorial deadlines have inevitably produced gaps. Fortunately, knowledge and understanding continue to grow and in time this volume will be supplanted by one which is more complete and lucid.

The basic stimulus for this symposium was derived from efforts to synthesize the sciences of reproductive biology and toxicology. These began while I was a Clinical Associate in the National Institute of Child Health and Human Development (NICHD). This synthesis has been fostered by scientists within several of the Institutes as well as several individuals within NICHD. Those individuals have shared unselfishly of their time, knowledge, laboratory space and budgets.

Like other aspects of science, the development of this volume rests on several previous events. Two deserve special acknowledgment. The Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) of the Scientific Committee on Problems of the Environment (SCOPE)—sponsored by the World Health Organization—convened a Workshop on Methodologies for the Assessment of the Effects of Chemicals on Reproductive Function in Ispra, Italy, in the spring of 1981. The broad perspective of that meeting was incredibly stimulating and strengthened my resolve to attempt this volume. The other stimulus was the International Course on Occupational Hazards and Reproduction, sponsored by the Finnish Institute of Occupational Health and held outside Helsinki in the summer of 1981. This second meeting (coupled with the legendary hospitality of the Finns and the stimulus of the sauna) removed the last impediments to this volume. The opportunity to meet other scientists at both meetings and discuss a broad range of topics concerned with reproductive toxicology was enormously useful for me.

The first section of this volume reviews the biology of the male and female reproductive systems, early embryonic development and genetics. The second section briefly reviews some aspects of toxicology, including the sensitivity of reproductive events to interference by xenobiotic compounds, and methods for monitoring exposures to genotoxicants. The third section focuses on specific forms, sites, or mechanisms of reproductive toxicity. The fourth section reviews aspects of prenatal, perinatal and postnatal

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toxicity. Authors contributing to the fifth section have focused on isssues relating to surveillance for adverse reproductive effects of occupational, environmental or drug exposures. And the final section addresses some of the important and difficult—but frequently ignored—issues relating to the social impact of reproductive toxicity.

I would like to thank Dr. Irving J. Selikoff and the American Journal of Industrial Medicine for the opportunity to present this "Journal Symposium on Reproductive Toxicology." My wife, Margaret, deserves special thanks for tolerating my forgetfulness and my other less desirable characteristics. Ms. Maria S. Nightingale deserves thanks for keeping my laboratory functioning while I attended to the tasks associated with this volume. And finally I would like to thank the participating authors who have spent valuable time in the preparation of manuscripts designed to summarize specific facets of this field. It is hoped that this volume will be a useful and stimulating resource for health scientists interested in the broad discipline of reproductive toxicology.

REPRODUCTIVE BIOLOGY

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The Biology of Human Male Reproduction: An Overview

James W. Overstreet, MD, PhD, and William F. Blazak, PhD

In this overview, the focus is on the biology of human male reproduction. The structure and function of the testis are described, and the endocrine control of spermatogenesis is discussed. The formation of spermatozoa during spermatogenesis and their maturation in the epididymis are reviewed. The physiology of ejaculation and sperm transport in the female tract are discussed. Sperm capacitation, the acrosome reaction, and fertilization of human gametes are also reviewed.

Key words: spermatogenesis, spermatozoa, epididymis, sperm transport, fertilization

STRUCTURAL AND FUNCTIONAL ASPECTS OF THE TESTIS

The mammalian testis consists of two principal functional components: the seminiferous tubules and the interstitial tissue. Spermatozoa are produced within the seminiferous tubules, which are long, extensively convoluted tubular structures whose ends open into the rete testis. In humans, the tubules in each testis are arranged in about 300 lobules, with each lobule containing one to four tubules. The boundary tissue, or lamina propria, of the tubules has a clearly defined structure consisting of multiple layers of adventitial cells. The seminiferous tubules contain germ cells at various stages of maturity and Sertoli cells. The Sertoli cells extend from the basal lamina propria to the lumen of the seminiferous tubule. These cells, which do not divide after puberty, fulfill a number of important functions. These include participation in the formation of the blood–testis barrier, facilitation of release of spermatozoa from the germinal epithelium, synthesis of specific proteins (eg, androgen-binding protein), secretion of fluid into the lumen of the seminiferous tubule, as well as providing a sustentacular function for germ cells during the later stages of spermiogenesis. The Sertoli cells also

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serve important functions in the endocrine control of testicular function. The male germ cells will be discussed in some detail in a later section.

The testicular interstitial tissue, which is located exterior to and between the seminiferous tubules, contains blood and lymph vessels, nerves, and the interstitial or Leydig cells. The Leydig cells normally produce testosterone, estradiol and 17-OH progesterone. In normal men, about 7 mg of testosterone are produced per day mainly by the Leydig cells. The functions of testosterone, as well as the role of Leydig cells in the endocrine control of spermatogenesis, are discussed in the following section.

The testis of the adult human male serves two main functions: (1) production of male gametes—spermatozoa, and (2) production of male hormones or androgens, principally testosterone. These two functions of the testis are highly interrelated in that androgen production is necessary for sperm production, and successful male reproduction requires normal sexual behavior and the development of the secondary sexual characteristics (male accessory organs such as the prostate and seminal vesicles, external genitalia, etc), which are also androgen dependent. It is clear that perturbations in either of these testicular functions will result in reduced reproductive capacity.

ENDOCRINE CONTROL OF ADULT TESTICULAR FUNCTION

The endocrine control of testicular function is a remarkably complex subject, which has been extensively reviewed [cf, Steinberger and Steinberger, 1974; Steinberger et al, 1977; Setchell, 1978; diZerega and Sherins, 1981]. Our purpose here is to outline the salient features of this control briefly; the reader is referred to the referenced reviews for a more detailed discussion and introduction to the original literature.

Adult testicular function is largely under the influence of the two gonadotropic hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [see Table I]. These hormones are glycoproteins that are synthesized and released by the anterior pituitary under the influence of blood-borne gonadotropin-releasing factors from the hypothalamus. Both hormones bind to specific receptors on the membranes of their respective target cells and stimulate cellular metabolism via increases in adenylate cyclase activity, cyclic AMP, and protein kinase activity. LH binds to the Leydig cells and promotes steroidogenesis. The primary product is the androgen testosterone, with smaller amounts of estradiol and 17-OH progesterone also being synthesized. Testosterone is required for normal spermatogenesis, the integrity of the male accessory sex glands, male secondary sexual characteristics, and is also involved in the regulation of LH secretion via a negative feedback system on the hypothalamus and anterior pituitary. Increased concentration of testosterone in the blood will inhibit the release of LH from the anterior pituitary. Estradiol also inhibits the release of LH.

FSH acts on the Sertoli cells within the seminiferous tubules resulting in an increase in general protein synthesis as well as the synthesis of a number of specific proteins. One such protein, androgen-binding protein (ABP), is synthesized by the Sertoli cells in response to FSH and acts to bind testosterone in the interstitial tissues and facilitate its entry into the seminiferous tubules where it is required in high local concentration for normal spermatogenesis. FSH also enhances the LH stimulation of testosterone production by Leydig cells, perhaps by increasing the number of LH receptors. Experimental evidence also indicates that FSH may be required for the maturation of spermatids into spermatozoa (spermiogenesis).

The release of FSH from the anterior pituitary appears to be modulated by the testosterone concentration of the blood, as described for LH. As with LH, estradiol

TABLE I. The Endocrine Control of Adult Testicular Function*

Hormone	Source	Major target(s)	Direct or indirect effect on target(s)
Luteinizing hormone (LH)	Anterior pituitary	Leydig cells	Stimulate steroidogenesis (testosterone production)
Follicle-stimulating hormone (FSH)	Anterior pituitary	Sertoli cells	Stimulate protein synthesis (eg, androgen-binding protein)
		Sertoli and/or germ cells	Maturation of spermatids into spermatozoa (spermiogenesis)
Testosterone	Leydig cells	Male accessory glands	Maintain structure and function
		Hypothalamus, pituitary	Negative feedback control on release of FSH and LH
Estradiol	Leydig cells[a]	Anterior pituitary	Negative feedback control on release of FSH and LH
Inhibin	Sertoli cells	Anterior pituitary	Negative feedback control on release of FSH

*Adapted from Setchell [1978] and diZerega and Sherins [1981].

[a]About 30% of the estradiol is secreted by the testis; the remainder is derived from the peripheral aromatization of testosterone.

also inhibits FSH release. Unlike that of LH, however, a seminiferous tubule protein termed inhibin is also involved in the regulation of FSH. Inhibin is produced by the Sertoli cells and is believed to operate as a negative feedback control of FSH release at the anterior pituitary.

In addition to the gonadotropic regulation of testicular function, recent studies provide evidence for the existence of an intratesticular Leydig cell–Sertoli cell interaction. Sertoli cells are capable of converting androgen precursors into estrogen, and estrogen inhibits testosterone secretion by the Leydig cells. These events can occur independently of LH and suggest a local hormonal control of testicular testosterone production mediated by the Sertoli cells.

SPERMATOGENESIS

Germ Cells of the Seminiferous Epithelium

Aside from spermatozoa, three distinct types of male germ cells can be distinguished in human seminiferous epithelium: spermatogonia, spermatocytes, and spermatids. Spermatocytes are large, diploid cells, which lie against the basal lamina propria within the seminiferous tubules. Clermont [1963, 1966] described three types of spermatogonia in the human testis, type A-dark (Ad), type A-pale (Ap), and type B. Type Ad spermatocytes undergo numerous mitotic divisions and some of these cells differentiate into Ap spermatogonia; Ap spermatogonia likewise proceed through mitotic divisions, eventually differentiating into type B spermatogonia. The type B spermatogonia divide mitotically and eventually become preleptotene spermatocytes. One characteristic feature of male germ cells is that the cytoplasm does not completely separate upon nuclear division. Such incomplete cytokinesis results in a cohort of cells, held together by cytoplasmic bridges, which develop synchronously. The type Ad spermatogonia, therefore, are thought to be the most primitive spermatogonial cells and represent a class of renewing stem cells [Clermont, 1970]. These stem cells continue to provide Ap spermatogonia for entry into the spermatogenic cycle and eventual transformation into spermatozoa.

The cells resulting from the last mitotic division of the type B spermatogonia are a class of primary spermatocytes termed pre-leptotene spermatocytes. The chromatin in these cells undergoes visual organization into thin filaments resulting in leptotene spermatocytes. Chromosome replication has already occurred, and leptotene spermatocytes contain a tetraploid amount of DNA. Homologous chromosomes then synapse, synaptinemal complexes are formed between pairs of chromosomes, and the nucleoli become more visible; primary spermatocytes at this stage are termed zygotene spermatocytes. In the next stage of prophase of the first meiotic division, pachytene, crossing-over occurs, the chromosomal bivalents become more condensed and thicker, and each chromosome divides longitudinally (except at the centromere) into two sister chromatids. The following stage, diplotene, is characterized by the formation of chiasmata between homologous chromosomes, and the chromosomes appear even more condensed. In the final stage of meiotic prophase, diakinesis, the chiasmata are in the process of moving laterally toward the ends of the chromatids, and the chromosomes display maximal condensation. The chiasmata continue to terminalize and the homologous chromosomes then segregate from one another during anaphase of the first meiotic division. This division results in secondary spermatocytes that contain a diploid amount of DNA. After a short interphase, each secondary spermatocyte divides in a mitotic fashion (without interphase chromosome replication, however) to yield two spermatids, each containing a haploid amount of DNA.

The spermatids that result from the second meiotic division are initially small, round cells containing a moderate amount of cytoplasm. These cells then undergo a remarkable transformation into spermatozoa, a process termed spermiogenesis. This transformation includes nuclear condensation, formation of an acrosome, elimination of most of the cytoplasm, development of a tail, and the arrangement of mitochondria into the sperm middle piece. It is during this transformation that the nucleus of the spermatid assumes the shape characteristic of the spermatozoa of the species.

Upon completion of spermiogenesis, the elongated nucleus of the spermatid is embedded in the cytoplasm of a Sertoli cell, with the tail projecting into the lumen of the seminiferous tubule. The spermatid is extruded into the lumen of the tubule largely through the activity of the Sertoli cell. This extrusion process leaves the majority of the cytoplasm of the spermatid embedded in the cytoplasm of the Sertoli cell.

Dynamics of Human Spermatogenesis

Before a type B spermatogonium becomes a spermatozoon, many other spermatogonial cells will have entered the spermatogenic cycle. This results in several superimposed generations of germ cells in any cross-section of a seminiferous tubule. Owing to the regularity of this process, certain germ cells in the seminiferous epithelium are always found in association with one another, and never with certain other types of germ cells. Thus, the various generations of germ cells are not associated at random but form cellular associations of fixed composition. It follows that only a limited number of such cellular associations will exist in various cross-sections of a seminiferous tubule. Each such association of cells is termed a stage of the cycle of the seminiferous epithelium; a cycle of the seminiferous epithelium is formed by the series of successive cellular associations that occurs along a seminiferous tubule between two successive appearances of the same cellular association. In man, Clermont [1963] described six different stages based on nuclear morphology and the topographical arrangement of the cells. The length of time required for one complete cycle of the seminiferous epithelium in man was shown to be 16 days [Heller and Clermont, 1964].

The spermatogenic cycle extends from the time a type B spermatogonium differentiates into a pre-leptotene spermatocyte until this same cell is released into the lumen of the seminiferous tubule as a spermatozoon. The duration of the spermatogenic cycle, therefore, is the amount of time required for the production of a sperm cell from a pre-leptotene spermatocyte. The duration of the spermatogenic cycle in man was determined by Heller and Clermont [1964] using intratesticular injections of tritiated thymidine, and following the most advanced, labeled cells in testicular biopsies obtained at various times after injection. They concluded that the duration of the human spermatogenic cycle was 74 days, with a possible variation of 4 or 5 days. This represents the time required for about 4.6 cycles of the seminiferous epithelium. The duration of the spermatogenic cycle in other mammalian species is approximately equivalent to this number of cycles of the seminiferous epithelium, but differs in the amount of time required because of differing durations of the cycle of the seminiferous epithelium among species [Ortavant et al, 1977].

Rate of Sperm Production

The rate of production of spermatozoa by men has been assessed in a few studies. By enumerating the spermatozoa in human ejaculates collected every 3 days, mean daily sperm production rates of 95×10^6 to 155×10^6 cells have been reported [Freund, 1962, 1963; Zimmerman et al, 1965]. In a recent report, Amann and Howards [1980] calculated the daily rate of production of spermatozoa in 23 men after enumerating the number of elongated spermatids in homogenates prepared from the testes of these men. The mean number of spermatozoa produced daily by these men was $123 \pm 18 \times 10^6$, with a range of 21 to 374×10^6 cells per day. These rates are equivalent to 4.45×10^6 sperm per day per gram of testis. As discussed by Amann and Howards [1980], daily sperm production by humans is considerably below that of other mammalian species, owing mainly to a paucity of germ cells within the seminiferous tubules.

THE EPIDIDYMIS AND SPERM MATURATION

Upon release of spermatozoa from the seminiferous epithelium, sperm pass through the rete testis and enter the epididymis via the ductuli efferentes. The cells at this stage are immature and are virtually immobile, incapable of fertilizing ova, and often bear a remnant of cytoplasm (cytoplasmic droplet) in the neck and middle piece region. Final maturation of the cells occurs during transit through the epididymis, a convoluted duct located on the posterior surface of the testis. The epididymis is divided anatomically into three segments: the caput, corpus, and cauda epididymidis. The epididymis is dependent upon testicular androgen for the maintenance of its structural and functional properties.

The maturation of spermatozoa in the human epididymis has been studied by Bedford et al [1973]. These authors demonstrated a number of maturational changes in human spermatozoa as they progressed from the caput to the cauda epididymidis including (1) loss of the cytoplasmic droplet, (2) structural maturation of the nucleus and tail organelles through the formation of disulfide bonds between protein sulfhydryl groups, (3) acquisition of progressive motility, and (4) changes in the surface of the spermatozoal plasma membrane. The nature of these changes indicated that human spermatozoa, like those of other mammals, gained the capacity to fertilize ova after maturation in the epididymis. In a recent report, Hinrichsen and Blaquier [1980] found that human spermatozoa collected from the cauda epididymidis were capable of under-

going capacitation and entering the ooplasm of the zona pellucida-free hamster ovum in vitro, whereas those collected from the corpus and caput segments of the epididymis failed to penetrate ova. These findings provide further evidence that human spermatozoa gain the capacity to fertilize ova after transit through the epididymis.

In contrast to other mammalian species, the transit time of spermatozoa through the human epididymis is very short and highly variable. Rowley et al [1970] found that the rate of transport varied from 1 to 21 days within an individual. Amann and Howards [1980] identified transit times of 0.72 ± 0.11, 0.71 ± 0.10, and 1.76 ± 0.24 days in the caput, corpus, and cauda segments, respectively, of the human epididymis. This relatively short and variable transit time may be a significant factor in the structural and functional heterogeneity of spermatozoa in the human ejaculate [Bedford et al, 1973].

EJACULATION

The normal sequence of sexual functions in the human male includes erection, emission, and ejaculation. Emission of spermatozoa into the prostatic urethra is effected by the sympathetic hypogastric nerves innervating the epididymis, the vas deferens, and the prostate gland [Hotchkiss, 1970]. Preceding emission, there is an initial movement of spermatozoa from the distal epididymis toward the ampulla of the vas deferens [Mitsuya et al, 1960]. During emission, the vas deferens and its ampulla become narrowed and the ampulla becomes less cavernous. The contents of the ampulla and the prostatic secretions first enter the prostatic urethra. This is followed by contraction of the seminal vesicles during which about one-tenth of their contents is emptied into the urethra. These events of emission are followed by ejaculation, which is a reflex action mediated by afferent impulses in the pundendal nerves and efferent impulses along the same nerves, causing contraction of the pelvic and perineal muscles. As pressure builds in the prostatic urethra, its contents are propelled into the penile urethra. Additional prostatic secretions then enter the prostatic urethra and further contractions of the seminal vesicles occur, the cycle being repeated an average of six additional times [Mitsuya et al, 1960].

MALE ACCESSORY SECRETIONS

The human ejaculate is composed of spermatozoa from the vas deferens and cauda epididymidis, together with accessory fluids from the prostate gland, the seminal vesicles and Cowper's gland [Mann, 1964]. The role of the accessory gland secretions in relation to sperm physiology is poorly understood. One recognized function of the seminal plasma is its buffering effect on the vaginal environment. In women, the vaginal acidity is usually pH 5 or less, but the buffering capacity of the seminal plasma can raise the vaginal pH to more than 7 within 8 sec after ejaculation [Fox et al, 1973].

The semen is usually ejaculated in a specific sequence. The first fraction of the ejaculate characteristically contains the majority of the spermatozoa and the prostatic secretion, whereas the second portion is composed of seminal vesicle secretion and relatively fewer spermatozoa. When these fractions are mixed in vitro or within the vagina, the semen spontaneously coagulates. The clot-like material that is formed liquefies spontaneously within the next 20 min. It has been suggested that the seminal vesicles may provide specific proteins involved in formation of the coagulum and that the prostate may be the source of hydrolytic enzymes required for its liquefaction, but the biochemistry of these processes is very complicated and not well understood [Tauber et