Reproduction in Farm Animals

SEVENTH EDITION

E. S. E. Hafez • B. Hafez

Blackwell Publishing

Reproduction in Farm Animals

7th Edition

REPRODUCTION IN FARM ANIMALS

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Edited by

B. Hafez/E.S.E. Hafez

Co-Directors
Reproductive Health Center
IVF/Andrology International
Kiawah Island, South Carolina, USA

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PREFACE

The first edition, published in 1962, covered the basic and comparative aspects of reproductive physiology in a simplified manner to meet the needs of students in reproductive biology, veterinary medicine, and animal sciences. This objective is maintained in the seventh edition, which represents a condensed, concise treatise on the physiology and biochemistry of reproduction of farm animals. The book is divided into major sections and these, in turn, are loosely arrayed into two domains, the components of the reproductive system and the regulation of the reproductive process, from the control of ovulation to the initiation of parturition. The reader will note the profound differences among the various animal species. To address this issue we provided separate coverage of the major species, where this seemed appropriate, so that the student of reproduction could ascertain the similarities and differences among them.

During the past decade there were significant advances in the main concepts of animal reproduction as a result of modern biotechnology, such as the use of gonadotropin releasing hormones and their analogs, assisted reproductive technology/andrology (ARTA), genetics, molecular biology, immunology, toxicology, and pharmacology. Five new chapters have been added to the 7th edition:

1. Reproduction in Llamas and Alpacas
2. Genetic Engineering
3. Pharmacotoxologic Factors and Reproduction
4. Immunology of Reproduction
5. Molecular Biology of Reproduction

Modern techniques of bioengineering of farm animals involve microinsemination, recombination of DNA, and *in vitro* manipulation, transfer, and expression of genes. These techniques were greatly improved with the use of computers, microcomputers, and commercially available diagnostic and analytical kits. A wide variety of techniques have been employed for the evaluation of semen, such as: evaluation of sperm fertilizability using zona-free hamster egg (fresh or frozen); motility pattern as viewed by videotape microscopy; *in vitro* penetrability of sperm in bovine cervical mucus; and cryopreservation of embryos and semen using computerized freezers. Most of the investigations reviewed in this edition are based more on holistic research than on research at the submicroscopic or molecular level. However, the excitement generated by recent advances in molecular biology and development tend to downgrade the value of whole-animal research. No attempt was made to provide a detailed bibliography, but a selected number of classic papers and review articles are listed at the end of each chapter.

This edition could not have been revised without the cooperation of the contributing authors and their willingness to follow the editorial guidelines. The chapters have been concisely edited, and the major concepts have been summarized in tables supplemented by line drawings and scanning electron micrographs. All chapters have been completely revised and condensed. There have been numerous deletions from the sixth edition, as well as integration of new and modern concepts such as "growth factors," molecular biology, genetics, and *in vitro* micromanipulation of gametes and embryos.

Some tabulated appendices include: chromosome numbers and reproductive ability of bovine, caprinae, and equine species and some of their hybrids; preparation of physiologic solutions, sperm stains, tissue culture media, and cryoprotectants. These appendices proved to be helpful for staging demonstrations, laboratory exercises, and training workshops for teachers, laboratory technicians, and students. It is hoped that the seventh edition will be of some help to undergraduate students in animal sciences and veterinary medicine.

B. Hafez/E.S.E. Hafez
Kiawah Island, South Carolina USA
March, 2000

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Contributors

S.E. Abdelgadir
Asst. Professor of Reproduction Endocrinology/Infertility
Director of Andrology/Embryology
Department of OB/GYN
University of Nevada School of Medicine
Las Vegas, Nevada 89102 USA

L.L. Anderson
Department of Animal Science
Iowa State University
11 Kildee Hall
Ames, Iowa 50011 USA

A.E. Archibong
Director of Andrology/Research
Department of OB/GYN and
Asst. Professor
Department of Anatomy/Physiology
Meharry Medical College
Nashville, Tennessee 37208 USA
615-327-6284 (Tel) 615-327-6296 (Fax)

R.L. Ax, Ph.D.
Professor and Head Department of Animal Science
Adjunct Professor
Department of OB/GYN
University of Arizona
Tucson, Arizona 85721-00038 USA
520-621-7623 (Tel) 520-621-9435 (Fax)

M.R. Dally, Ph.D.
Professor of Animal Science
Hopland Research and Extension Center
University of California
Hopland, California 95449 USA

B.A. Didion, Ph.D.
Dekalb Swine Breeders, Inc.
3100 Sycamore Road
Dekalb, Illinois 60115 USA

D.P. Froman
Department of Animal Sciences
Oregon State University
112 Withycombe Hall
Corvallis, Oregon 97331-6702 USA
541-737-5060 (Tel) 541-737-4174 (Fax)

D.L. Garner
Department of Animal Science
School of Veterinary Medicine
University of Nevada
Mail Stop 202, Reno, Nevada 89557-0104 USA
702-784-6135 (Tel) 702-784-1375 (Fax)

R.D. Geisert
Division of Agricultural Sciences and Natural Resources
Department of Animal Sciences
114 Animal Science
Oklahoma State University
Stillwater, Oklahoma 74078-6051 USA
405-744-6077 (Tel) 405-744-7390 (Fax)

B. Hafez
Reproductive Health Center
78 Surfsong Road
Kiawah Island, South Carolina 29455 USA
843-768-5556 (Tel) 843-768-6494 (Fax)

E.S.E. Hafez
Reproductive Health Center
IVF Andrology Laboratory
78 Surfsong Road
Kiawah Island, South Carolina 29455 USA
843-768-5556 (Tel) 843-768-6494 (Fax)
Ivfreprod@aol.com (e-mail)

P.J. Hansen
Department of Dairy/Poultry Sciences
Institute of Food and Agricultural Sciences
University of Florida
Bldg. 499, Shealy Drive
PO Box 110920
Gainesville, Florida 32611-0920 USA
352-393-5590 (Tel) 352-392-5595 (Fax)

M.R. Jainudeen
University Business Centre
University Administration Building
43400 UPM
Serdang, Selangor, Malaysia
603-948-5649 (Tel/Fax)
(Home Address)
60 Jalan SS 19/5B
47500 Subang Jaya, Selangor, Malaysia
603-734-5694 (Tel/Fax)
jain@pop.jaring (e-mail)

R. Juneja
8402 Timberline Court
Monmouth Junction, New Jersey 08852 USA
732-422-8895 (Tel) 732-940-5711 (Fax)
ARJuneja@aol.com (e-mail)

J.D. Kirby
Dept. of Animal Sciences
Oregon State University
112 Withycombe Hall
Corvallis, Oregon 97331-6702 USA
541-737-5060 (Tel) 541-737-4174 (Fax)

S.S. Koide
Population Council
1230 York Avenue
New York, New York 10021 USA
212-327-8731 (Tel) 212-327-7678 (Fax)

R.W. Lenz, Ph.D.
Sire Power, Inc.
R.R.2
Tunkhannock, Pennsylvania 18657 USA

C.C. Love, D.V.M., Ph.D.
Diplomate
American College of Theriogenology
Department of Large Animal Medicine & Surgery
College of Veterinary Medicine
Texas A&M University
College Station, Texas 77843-4475 USA

J.R. Malayer
Division of Agricultural Sciences and Natural Resources
Department of Animal Science
114 Animal Science
Oklahoma State University
Stillwater, Oklahoma 74078-6051 USA
405-744-6077 (Tel) 405-744-7390 (Fax)

C.A. Pinkert
The University of Alabama at Birmingham
Department of Comparative Medicine
227 Volker Hall
1670 University Boulevard
Birmingham, Alabama 35294-0019 USA
205-934-9574 (Tel) 205-975-4390 (Fax)
Pinkert@uab.edu (e-mail)

J.A. Proudman
Research Physiologist
Germplasm and Gamete Physiology Laboratory
Livestock and Poultry Sciences Institute
BARC-East
Building 262
Beltsville, Maryland 20705 USA
301-504-8094 (Tel) 301-504-8546 (Fax)
JohnP@lpsi.barc.usda.gov (e-mail)

J.B. Sumar
Avenida De Los Incas 1412
Wanchaq, Cusco, Peru
51 (84) 224 614 (Tel) 51 (84) 221 632 (Fax)

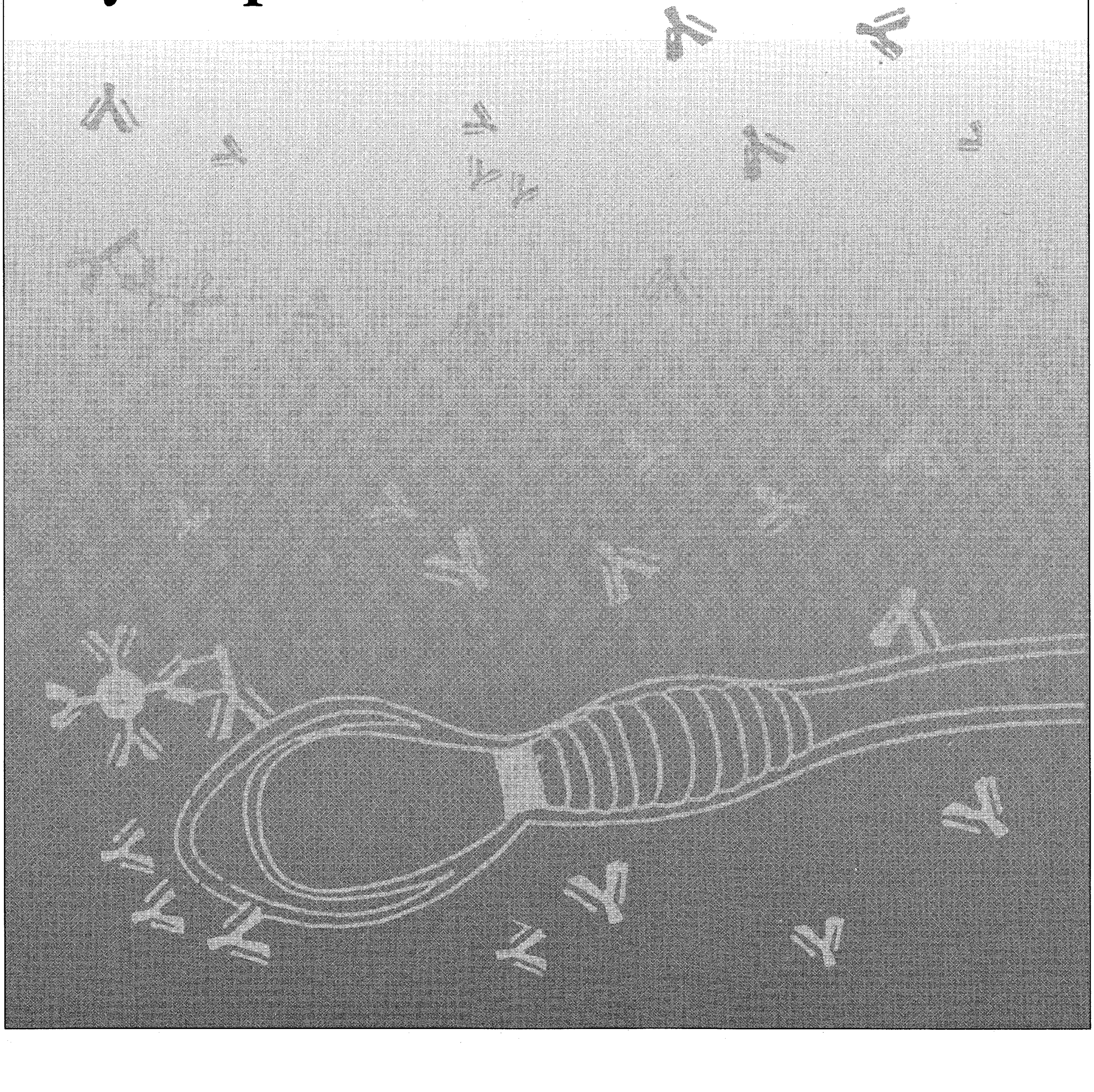
D.D. Varner, D.V.M., M.S.
Diplomate
American College of Theriogenology
Department of Large Animal Medicine & Surgery
College of Veterinary Medicine
Texas A&M University
College Station, Texas 77843-4475 USA

H. Wahid
Department of Veterinary Science
Clinical Studies
University Putra
Malaysia, 43400
Serdang, Selangor, Malaysia
603-948-6101 X1829 (Tel) 603-948-6317 (Fax)
wahid@vet.upm.edu.my (e-mail)

Contents

PART I

Functional Anatomy of Reproduction



Anatomy of Male Reproduction

E.S.E. HAFEZ

The male gonads, the testes, lie outside the abdomen within the scrotum, which is a purselike structure derived from the skin and fascia of the abdominal wall. Each testis lies within the vaginal process, a separate extension of the peritoneum, which passes through the abdominal wall at the inguinal canal. The deep and superficial inguinal rings are the deep and superficial openings of the inguinal canal. Blood vessels and nerves reach the testis in the spermatic cord, which lies within the vaginal process; the *ductus deferens* accompanies the vessels but leaves them at the orifice of the vaginal process to join the urethra. Besides permitting the passage of the vaginal process and its contents, the inguinal canal also gives passage to vessels and nerves supplying the external genitalia.

The spermatozoa leave the testis by efferent ductules that lead into the coiled duct of the epididymis, which continues as the straight ductus deferens. Accessory glands discharge their contents into the ductus deferens or into the pelvic portion of the urethra.

The urethra originates at the neck of the bladder. Throughout its length it is surrounded by cavernous vascular tissue. Its pelvic portion, which is enclosed by striated urethral muscle and receives secretions from various glands, leads into a second penile portion at the pelvic outlet. Here it is joined by two more cavernous bodies to make up the body of the penis, which lies beneath the skin of the body wall. A number of muscles grouped around the pelvic outlet contribute to the root of the penis. The apex or free part of the penis is covered by modified skin—the penile integument; in the resting condition it is enclosed within the prepuce. The topographic features of the organs of the important farm species are shown in Figure 1-1.

The testis and epididymis are supplied with blood from the testicular artery, which originates from the dorsal aorta near the embryonic site of the testes. The internal pudendal artery supplies the pelvic genitalia and its branches leave the pelvis at the ischial arch to supply the penis. The external pudendal artery leaves the abdominal cavity via the inguinal canal to supply the penis, scrotum, and prepuce. Lymph from the testis and epididymis passes to the lumbar aortic lymph nodes. Lymph from the accessory glands, urethra, and penis passes to the sacral and medial iliac nodes. Lymph from the scrotum, prepuce, and peripenile tissues drains to the superficial inguinal lymph nodes.

Afferent and efferent (sympathetic) nerves accompany the testicular artery to the testis. The pelvic plexus supplies autonomic (sympathetic and parasympathetic) fibers to the pelvic genitalia and to the smooth muscles of the penis. Sacral nerves supply motor fibers to the striated muscles of the penis and sensory fibers to the free part of the penis. Afferent fibers from the scrotum and prepuce travel mainly in the genitofemoral nerve.

DEVELOPMENT

Prenatal Development

The testes develop in the abdomen, medial to the embryonic kidney (mesonephros). The plexus of ducts within the testis becomes connected to mesonephric tubules and so to the mesonephric duct, to form the epididymis, ductus deferens, and vesicular gland. The prostate and bulbourethral glands form from the embryonic urogenital sinus and the penis forms by tubulation and elongation of a tubercle that develops at the orifice of the urogenital sinus.

Two agents produced by the fetal testis are responsible for this differentiation and development (1). Fetal androgen causes development of the male reproductive tract. "Müllerian inhibiting substance," a glycoprotein, is responsible for suppression of the paramesonephric (Müllerian) ducts from which the uterus and vagina develop (2). Abnormalities in differentiation and development of gonads and ducts can result in varying degrees of intersexuality (3).

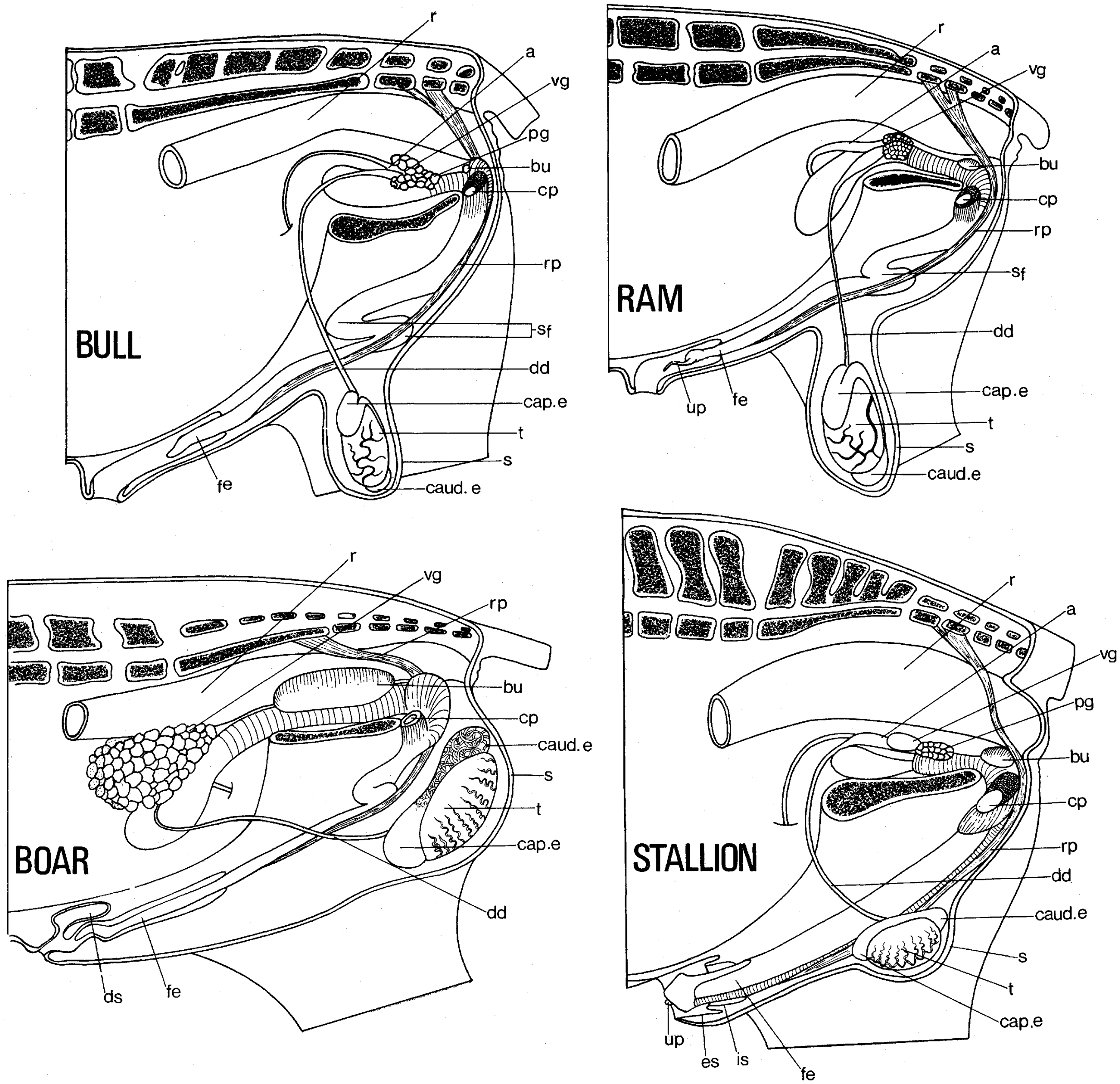


FIGURE 1-1. Diagram of the male reproductive tracts as seen in left lateral dissections. *a*, Ampulla; *bu*, bulbourethral gland; *cap. e*, caput epididymidis, *caud. e*, cauda epididymidis; *cp*, left crus of penis, severed from the left ischium; *dd*, ductus deferens; *ds*, dorsal diverticulum of prepuce; *es*, prepenile prepuce; *fe*, free part of the penis; *is*, preputial fold; *pg*, prostate gland; *r*, rectum; *rp*, retractor penis muscle; *s*, scrotum; *sf*, sigmoid flexure; *t*, testis; *up*, urethral process; *vg*, vesicular gland. (Adapted from Popesko, Atlas der topographischen anatomie der Haustiere. Vol. 3, Jena: Fischer, 1968.)

Descent of the Testis

During testicular descent (4), the gonad migrates caudally within the abdomen to the deep inguinal ring. It then traverses the abdominal wall to emerge at the superficial inguinal ring, which is, in fact, the much-enlarged foramen of the genitofemoral nerve (L3, L4). The testis completes its migration by passing fully into the scrotum. Descent is preceded by the formation of the vaginal process, a peritoneal sac extending through the abdominal wall and enclosing the inguinal ligament of the testis. The inguinal ligament of the gonad is often called the *gubernaculum testis*, and it terminates in the region of the scrotal rudiments. Descent follows the line of the *gubernaculum testis*. The time of descent varies (Table 1-1). In the horse, the epididymis commonly enters the inguinal canal before the testis, and that part of the inguinal ligament connecting testis and epididymis (proper ligament of testis) remains extensive until after birth.

TABLE 1-1. *Development of the Male Reproductive Tract in Farm Animals (weeks)*

	BULL	RAM	BOAR	STALLION
Primary spermatocytes In seminiferous tubules	24	12	10	Variable throughout seminiferous tubules of each testis
Sperm in seminiferous tubules	32	16	20	56
Sperm in cauda epididymidis	40	16	20	60
Sperm in ejaculate	42	18	22	64–96
Completion of separation between penis and penile part of prepuce	32	>10	20	4
Age at which animal can be considered sexually "mature"	150	>24	30	90–150 (variable)

Testicular descent enters scrotum half-way through fetal life (bull, ram), last quarter of fetal life (boar), or just before/after birth (stallion).

Sometimes the testis fails to enter the scrotum. In this condition (cryptorchidism), the special thermal needs of testis and epididymis are not met, although the endocrine function of the testis is unimpaired. Bilaterally cryptorchid males therefore show more or less normal sexual desire but are sterile. Occasionally some of the abdominal viscera pass through the orifice of the vaginal process and enter the scrotum; scrotal hernia is particularly common in pigs.

Postnatal Development

Each component of the reproductive tracts of all farm animals grows in size relative to overall body size and undergoes histologic differentiation. Functional competence is not achieved simultaneously in all components of the reproductive system. Thus, in the bull, the capacity for erection of the penis precedes the appearance of sperm in the ejaculate by several months. In rams, the terminal segment of the epididymis is morphologically "adult" at 6 weeks, but the initial segment is not so until 18 weeks (5). At puberty all the components of the male reproductive system have reached a sufficiently advanced stage of development for the system as a whole to be functional. The period of rapid development that precedes puberty is known as the prepubertal period, although this period is itself sometimes referred to as "puberty." During the postpubertal period, development continues and the reproductive tract reaches full sexual maturity months or even years after the age of puberty. In horses, significant increases in testicular weight, daily sperm production, and epididymal sperm reserves occur at 15 years of age. Some important anatomic changes that occur during postnatal development are summarized in Table 1-1.

TESTIS AND SCROTUM

The testis is secured to the wall of the vaginal process along the line of its epididymal attachment. The position in the scrotum and the orientation of the long axis of the testis differ with the species (Fig. 1-1). The arrangement of tubules and ducts within the testis in the bull is shown in Figure 1-2. The histologic and cytologic characteristics of the cellular components of the seminiferous tubules are summarized in Table 1-2. The rete testis is lined by a nonsecretory cuboidal epithelium.

Testicular size varies throughout the year in seasonal breeders (ram, stallion, camel). Removal of one testis results in considerable enlargement of the remaining gonad (up to 80% increase in weight). In the unilateral cryptorchid, removal of the descended testis may be followed by descent of the abdominal testis as it enlarges.

The interstitial (Leydig) cells, which lie between the seminiferous tubules, secrete male hormones into the testicular veins and lymphatic vessels. The spermatogenic cells of the tubule divide and differentiate to form spermatozoa. Just before puberty, the sustentacular (Sertoli) cells of the tubule form a barrier (6), which isolates the differentiating germ cells from the general circulation. These sustentacular cells contribute to fluid production by the tubule and may

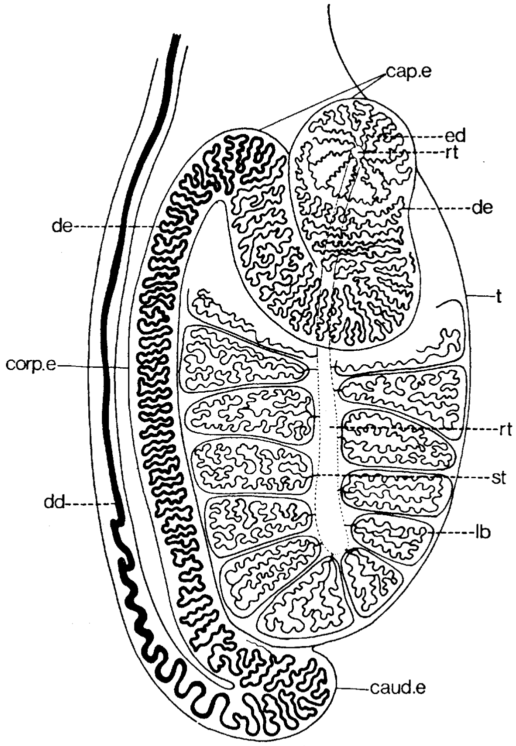


FIGURE 1-2. Schematic drawing of the tubular system of the testis and epididymis in the bull (for clarity the duct system of the rete testis is omitted). *cap. e*, Caput epididymidis; *caud. e*, cauda epididymidis; *corp. e*, corpus epididymidis; *dd*, ductus deferens; *de*, duct of the epididymis; *ed.*, efferent ductule; *lb*, lobule with seminiferous tubules; *rt*, rete testis; *st*, straight tubule; *t*, testis. (Simplified from Blom and Christensen. Nord Vet Med 1968;12:453.)

produce the Müllerian-inhibiting factor found in the rete fluid of adult males (2). The sustentacular cells do not increase in numbers after puberty is attained. This may limit spermiogenesis. Sperm production increases with age in the postpubertal period and is subject to seasonal changes in many species. Castration of prepubertal males suppresses sexual development. Regressive changes in behavior and structure take place following castration of adult males. Castration is a standard procedure in animal husbandry to modify aggressive male behavior and to eliminate undesirable carcass qualities, e.g., boar taint.

Spermatogenesis disorders are monitored by changes in sperm parameters in the ejaculate or by infertility. Turner et al, (7) conducted extensive studies to identify the proteins which play major roles in spermatogenesis and are subsequently transported into the blood stream.

Autonomic innervation of the testis plays a major role in regulating the functions of the male genitourinary tract. Adrenergic, cholinergic, and nonadrenergic noncholinergic (NANC) mechanisms operate in a highly orchestrated fashion to ensure reliable storage and release of urine from the bladder to regulate the transport and storage of sperm in

TABLE 1-2. ***Functional Histology of the Mammalian Testis***

SEGMENT	HISTOLOGIC CHARACTERISTICS
Tunica albuginea	A thick, white capsule of connective tissue surrounding the testis; made primarily of interlacing series of collagenous fiber.
Seminiferous tubules	Appear as large isolated structures, round or oblong in outline; varying appearance due to the complex coiling of the tubules at many different angles and levels. Between the tubules are masses of interstitial (Leydig) cells, which produce the male sex hormones.
Spermatogonia	Lie in the outermost region of the tubule; round nuclei appear as an irregular layer within surrounding connective tissue. Nuclei are small size and dark stain due to presence of large numbers of chromatin granules.
Primary spermatocytes	Located just inside an irregular layer of spermatogonia and Sertoli cells; nuclei are larger than those of the spermatogonia and stain lighter.
Secondary spermatocytes	Maturation divisions and secondary spermatocytes are not seen in the average tubule owing to the short duration of these stages.
Spermatids	Located internally to primary spermatocytes. Layer of spermatids may be several cells in thickness. Sperm lie along the border of the lumen. The sperm heads are lodged in deep indentations of the surface of the Sertoli cell.
Sertoli cells	Large and relatively clear except for the prominent, dark-staining nucleolus. Cytoplasm is diffuse, and its limits are indefinite.

the reproductive tract and coordinate the emission/ejaculation of the sex accessory glands (8).

The adrenergic innervation may play a role in mediating epididymal function. The sympathetic innervation within the epididymis is necessary for neuromuscular events required for the transport of sperm. The neuronal input may play an important role in the maintenance of epididymal function (8).

Thermoregulation of the Testis

For effective functioning, the mammalian testes must be maintained at a temperature lower than that of the body. Anatomic features of the testis and scrotum permit the regulation of testicular temperature. Temperature receptors in the scrotal skin can elicit responses that tend to lower *whole* body temperature and provoke panting and sweating (9). The scrotal skin is richly endowed with large adrenergic sweat glands, and its muscular (dartos) component enables it to alter the thickness and surface area of the scrotum and vary the closeness of the contact of the testes with the body wall. In the horse, this action may be supported by the smooth muscle within the spermatic cord and tunica albuginea, which can lower or raise the testis. In cold conditions, these smooth muscles contract, elevating the testes and wrinkling and thickening the scrotal wall. In hot conditions the muscles relax, lowering the testes within the thin-walled pendulous scrotum. The advantages offered by these mechanisms are enhanced by the special relationship of the veins and arteries.

In all farm animals, the testicular artery is a convoluted structure in the form of a cone, the base of which rests on the cranial or dorsal pole of the testis. These arterial coils are intimately enmeshed by the so-called pampiniform plexus of testicular veins (10). In this countercurrent mechanism, arterial blood entering the testis is cooled by the venous blood leaving the testis. In the ram, blood in the testicular artery falls 4 °C in its course from the superficial inguinal ring to the surface of the testis; the blood in the veins is warmed to a similar degree between the testis and the superficial ring. The position of the arteries and veins close to the surface of the testis tends to increase direct loss of heat from the testis. In the boar, the scrotum is less pendulous (Fig. 1-1) and sweating is less efficient. This may explain the smaller difference between scrotal and rectal temperatures (3.2 °C) (11).

EPIDIDYMIS AND DUCTUS DEFERENS

Three anatomic parts of the epididymis are recognized (Fig. 1-2). The caput epididymidis (head), in which a variable number of efferent ductules (13 to 20) (12) join the duct of the epididymis. It forms a flattened structure applied to one pole of the testis. The narrow corpus epididymidis (body) terminates at the opposite pole in the expanded cauda epididymidis (tail). The middle region of each efferent duct shows marked secretory activity (13). The convoluted duct of the epididymis is very long (bull, 36 m; boar, 54 m). The wall of the duct of the epididymis has a prominent layer of circular muscle fibers and a pseudostratified epithelium of columnar cells. Three segments of the duct of the epididymis can be distinguished histologically; these do not coincide with the gross anatomic regions (14).

There is a progressive decrease in the height of the epithelium and stereocilia and a widening of the lumen throughout the three segments. The first two segments are concerned with sperm maturation, whereas the terminal segment is for sperm storage.

The lumen of the epididymal tubules is lined with epithelium made of a basal layer of small cells and a surface layer of tall columnar ciliated cells.

The mucosa of the ductus deferens is thrown into longitudinal folds. Near the epididymal end, the epithelium resembles that of the epididymis: the nonciliated cells have little secretory activity. The lumen is lined with pseudostratified epithelium. The ampulla of the ductus deferens is furnished with branched tubular glands, which, in the stallion, are highly developed and contribute ergothioneine to the ejaculate. The ejaculatory duct enters the urethra. Fluid uptake and spermiophagy take place in the epithelium of the ejaculatory duct (15). Scanning electron microscopy has been used to evaluate functional ultrastructure of male reproductive organs with emphasis on spermatogenesis (Fig. 1-3). Large volumes of fluid (up to 60 ml in the ram) leave the testis daily, and most of this is absorbed in the caput epididymidis by the initial segment of the duct of the epididymis. Transport of sperm through the epididymis takes about 9 to 13 days. Maturation of sperm occurs during transmit through the epididymis; motility increases as sperm enter the corpus epididymidis. The environment of the sperm in the cauda epididymidis provides factors that enhance fertilizing ability. Sperm from this region give higher fertility than those from the corpus epididymidis (14).

Spermatozoa stored in the epididymis retain fertilizing capacity for several weeks; the cauda epididymidis is the principal storage organ, and it contains about 75% of the total epididymal spermatozoa. The special ability of the cauda epididymidis to store sperm depends on low scrotal temperatures and on the action of male sex hormone (16). Sperm stored in the ampullae constitute only a small part of the total extra-gonadal sperm reserves. Small numbers of nonmotile sperm appear in ejaculates collected weeks or even months after castration.

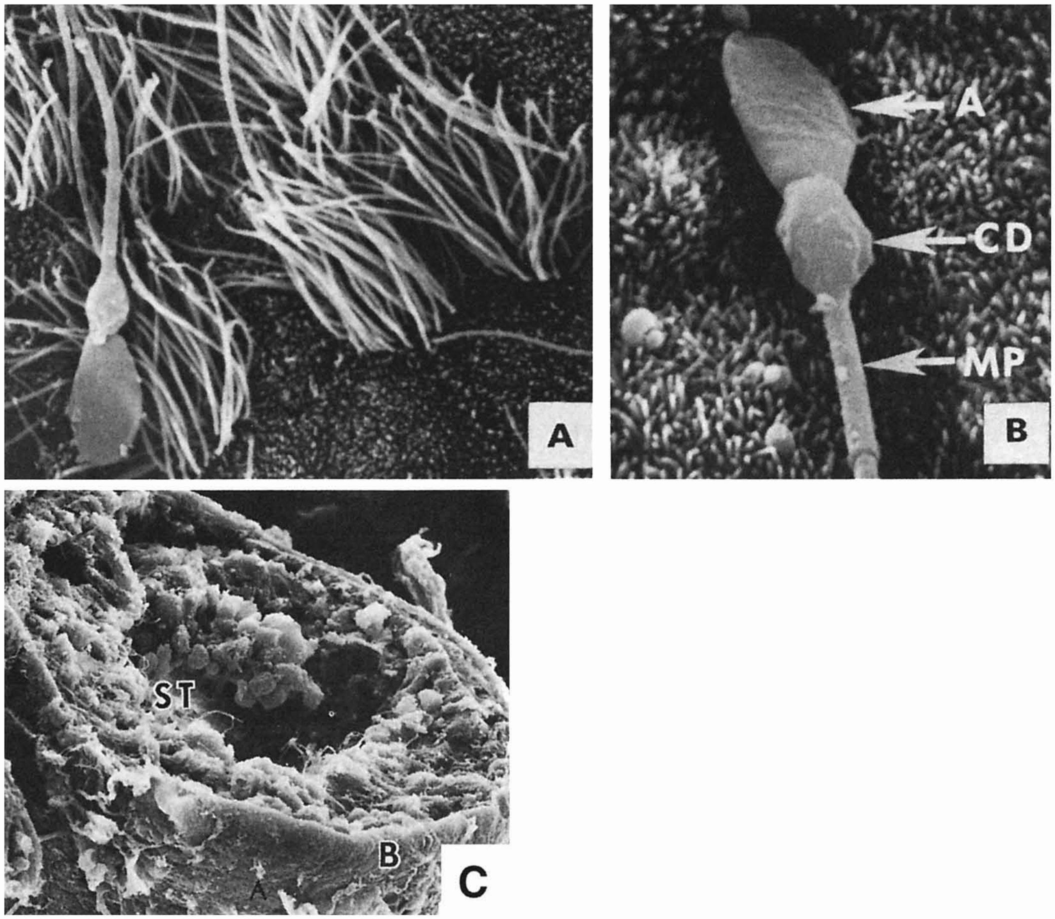


FIGURE 1-3. Scanning electron micrographs (SEM) (**A**) Luminal surface of an efferent duct with ciliated and nonciliated cells and a sperm. (**B**) Short microvilli on the luminal surface of nonciliated cells in the efferent ducts. The spermatozoal cytoplasmic droplet (*CD*), acrosome (*A*), and middle piece (*MP*) are distinguishable (×6,500). (**C**) Cross section of a seminiferous tubule (*ST*). Note several "stages" of spermatogenesis, encased in a muscular boundry tissue. (**A** and **B** from Connell CJ. Spermatogenesis. In: Hafez ESE, ed. Scanning Electron Microscopy of Human Reproduction. Ann Arbor, MI: Ann Arbor Science Pubs, 1978. **C** courtesy of Dr. Larry Johnson, from Johnson L, et al. Am J Vet Res 1978.)

ACCESSORY GLANDS

The prostate and bulbourethral glands pour their secretions into the urethra, where at the time of ejaculation, they are mixed with the fluid suspension of sperm and ampullary secretions from the ductus deferens. Weber et al (17) have demonstrated volumetric changes in the accessory glands of the stallion resulting from sexual stimulation (increased volume) and ejaculation (reduced volume).

Comparative Anatomy

THE SEMINAL VESICLES. These lie laterally to the terminal parts of each ductus deferens. In ruminants, they are compact lobulated glands. In the boar, they are large and less compact. In the stallion, they are large pyriform glandular sacs. The duct of the seminal vesicles and the ductus deferens may share a common ejaculatory duct that opens into the urethra.

THE PROSTATE GLAND. A distinct lobulated external part of body lies outside the thick urethral muscle, and a second internal or disseminated part surrounds the pelvic urethra. The disseminate prostate extends caudally as far as the ducts of the bulbourethral glands. The body of the prostate is small in the bull and large in the boar. In the stallion, the prostate gland is wholly external.

THE BULBOURETHRAL GLANDS. These are dorsal to the urethra near the termination of its pelvic portion. In the bull they are almost hidden by the bulbospongiosus muscle. They are large in the boar and contribute the gel-like component of boar semen. In ruminants and the boar, the ducts of the bulbourethral glands open into urethral recesses (18).

The Urethral Glands. The bull lacks urethral glands comparable with those found in man (19). Glands of this name in the horse have been considered comparable to the disseminate prostate of ruminants.

Function

Apart from providing liquid vehicle for the transport of sperm, the function of the accessory glands is obscure although much is known about the specific chemical agents contributed by the glands to the ejaculate (20, 21). Fructose and citric acid are important components of seminal vesicle secretions of domestic ruminants. Citric acid alone is found in stallion seminal vesicle; boar seminal vesicle also contain little fructose and are characterized by a high content of ergothioneine and inositol.

Spermatozoa from the cauda epididymidis are capable of fertilization when inseminated without the addition of

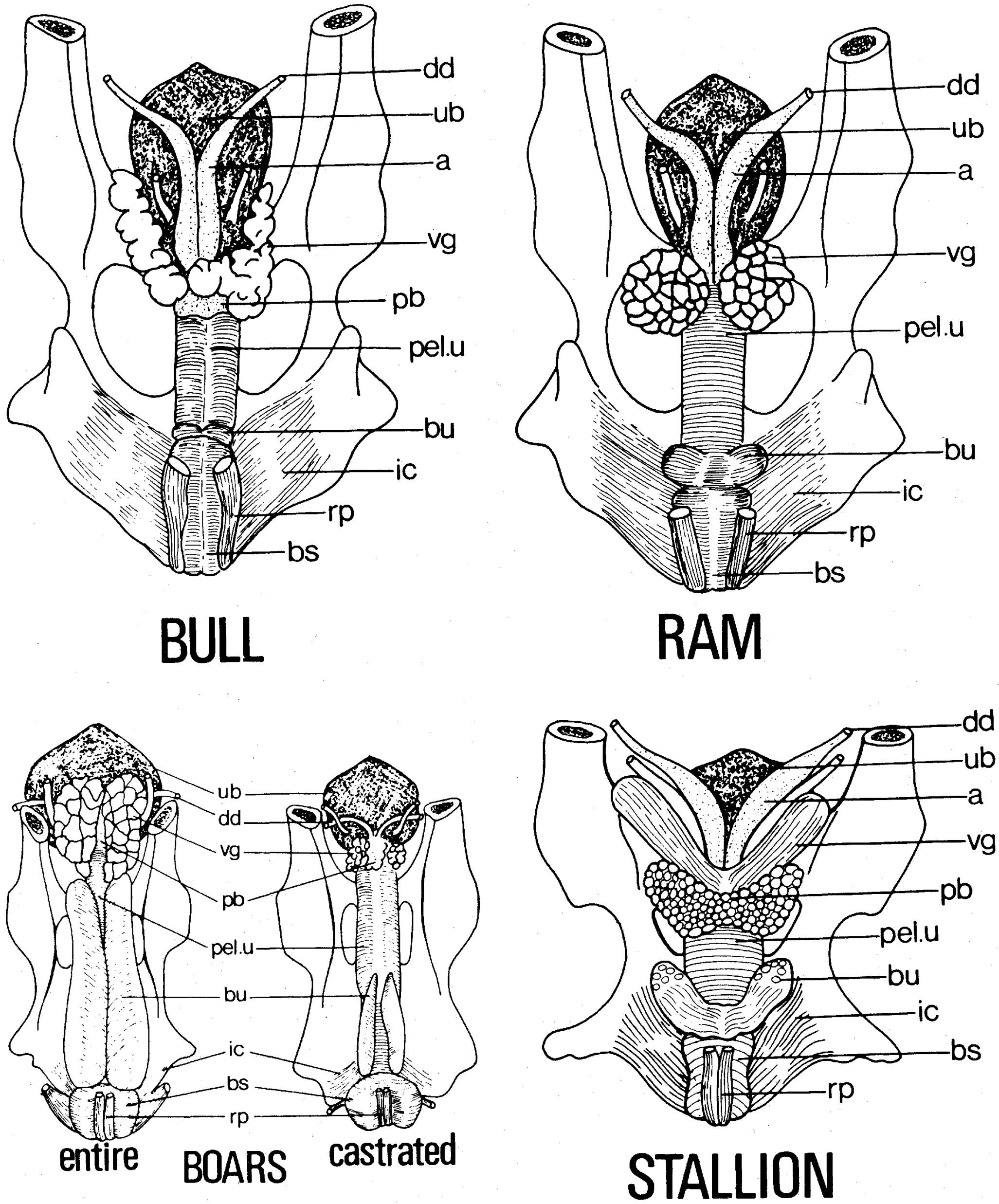


FIGURE 1-4. The pelvic genitalia, within the pelvic bones, as seen from a dorsal view. *a*, ampulla; *bs*, bulbospongiosus muscle; *bu*, bulbourethral gland; *dd*, ductus deferens; *ic*, ischiocavernosus muscle; *pb*, body of prostate gland; *pel. u*, pelvic urethra; *rp*, retractor penis muscle; *ub*, urinary bladder; *vg*, vesicular gland. (Diagrams of bull, boar and stallion redrawn from Nickel R. Tierarztl Umschau 1954;9:386.)

accessory gland secretions. The gel-like fraction of the boar ejaculate forms a plug in the vagina of mated females. In commercial insemination practice, this fraction is removed from the semen by filtration.

In large animals, rectal palpation of some of the accessory glands is possible. The positions of these glands relative to the bony pelvis are shown in Figure 1-4.

In the pig, the size of the bulbourethral glands can be used to differentiate the cryptorchid from the castrated state. After prepubertal castration, the bulbourethral glands are small. In boars with retained testes, the glands are of normal size (22). These differences can easily be felt, ventral to the rectum, with a finger inserted through the anus.

PENIS AND PREPUCE

Structure

In the mammalian penis, three cavernous bodies are aggregated around the penile urethra. The *corpus spongiosum penis*—which surrounds the urethra—is enlarged. This bulb is covered by the striated bulbospongiosus muscle. The corpus cavernosum penis arises as a pair of crura from the ischial arch, which are covered by ischiocavernosus muscles. A thick covering (tunica albuginea) encloses the cavernous bodies. The retractor penis muscles in ruminants and swine control the effective length of the penis by their action on the sigmoid flexure.

In the stallion, the cavernous bodies contain large cavernous spaces; during erection, considerable increases in size result from accumulation of blood in these spaces. In bull, ram, and boar the cavernous spaces of the corpus cavernosum penis is small, except in the crura and at the distal bend of the sigmoid flexure.

In ruminants and swine, the orifice of the prepuce is controlled by the cranial muscle of the prepuce; a caudal muscle may also be present. In the boar there is a large dorsal diverticulum in which urine and epithelial debris accumulate.

Erection and Protrusion

Sexual stimulation produces dilatation of the arteries supplying the cavernous bodies of the penis (especially the crura). Stiffening and straightening of the penis in ruminants is caused by the ischiocavernosus muscle, which pumps blood from the cavernous spaces of the crura into the rest of the corpus cavernosum penis.

Erection failures (impotence) arise from structural defects rather than from psychological causes (23). Rising pressure in the corpus cavernosum penis produces considerable elongation of the ruminant and porcine penis with little dilation (24). When the penis of the bull is protruded,

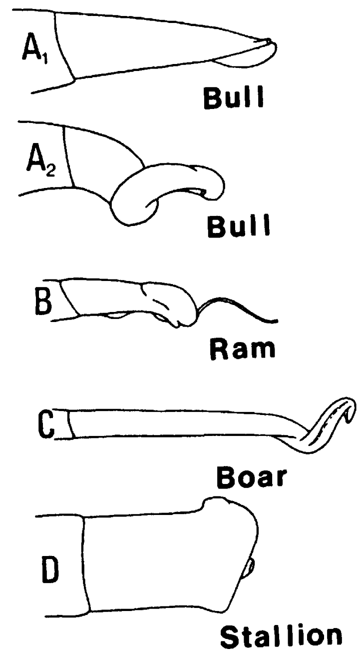


FIGURE 1-5. Diagrams to show the shape of the free end of the penis. (A1) The shape of the penis just before intromission. (A2) The shape after intromission when spiral deviation has occurred. (B) The shape of the penis during natural service. (C) Does not show the full degree of spiralling that occurs during service. (D) Drawn after injection and shows enlargement of the erectile bodies. (A1, A2, and B from photographs. C and D from fixed specimens. Not drawn to scale.)

the prepuce is everted and stretched over the protruded organ.

In normal service, this occurs after intromission. If it occurs before the penis enters the vestibule, intromission cannot be achieved.

Intromission in the bull lasts for about 2 seconds, and straightening of the penis after withdrawal often occurs abruptly as the dorsal apical ligament reasserts its action in keeping the penis straight. Withdrawal into the prepuce follows as the pressure in the cavernous spaces subsides. The fibrous architecture of the corpus cavernosum penis in the region of the sigmoid flexure tends to reform the flexure; this is assisted by shortening of the retractor penis muscle. The terminal 5 cm or so of the boar penis are spiraled (Fig. 1-5), and during erection the whole visible length of the free end of the penis becomes spiraled (24). Intromission lasts for up to 7 minutes, during which time a large volume of semen is ejaculated. Spiral deviation does not occur in the ram or goat, and intromission is of short duration. In the horse intromission lasts for several minutes.

Emission and Ejaculation

Emission consists of movement of the spermatic fluid along the ductus deferens to the pelvic urethra, where it is mixed

TABLE 1-3. *Age and Weight of First Breeding and Semen Characteristics*

SPECIES	BEGINNING OF BREEDING LIFE *Age (months)*	*Body Weight*	*Range*	VOLUME OF EJACULATE *Mean*	*Range*	SPERM CONCENTRATION 10^8 PER ML *Mean*
Cat	9	3.5 kg	0.01–0.3	0.04	1.5–28	14
Dog	10–12	varies	2–25	9.0	0.6–5.4	1.3
Guinea pig	3–5	450 gm	0.4–0.8	0.6	0.05–0.2	0.1
Rabbit	4–12	varies	0.4–6	1.0	0.5–3.5	1.5

From Hamner CE. The semen. In: Hafez ESE, ed. Reproduction and Breeding Techniques for Laboratory Animals. Philadelphia: Lea & Febiger, 1970.

with secretions from the accessory glands. Ejaculation is the passage of the resultant semen along the penile urethra. Emission is brought about by smooth muscles, under the control of the autonomic nervous system. Electrical stimulation of ejaculation in farm animals is a crude imitation of the complex natural mechanisms. During natural service, the sensory nerve endings in the penile integument and the deeper penile tissues are essential to the process of ejaculation.

Passage of semen along the ductus deferens is continual during sexual inactivity. Prinz and Zaneveld (25) suggest that during sexual rest a complex random or cyclic process of sperm removal from the cauda epididymidis may aid the regulation of sperm reserves. Sexual excitement and ejaculation are accompanied by contractions of the cauda epididymidis and ductus deferens, which increase the rate of flow. Overall, the number of sperm passing through the ductus deferens is not increased by sexual activity.

Muscular contraction of the wall of the duct is controlled by sympathetic autonomic nerves of the pelvic plexus derived from the hypogastric nerves. In normal stallions, α-receptor stimulation and β-receptor blockade increase the sperm concentration in the ejaculate (26).

During ejaculation the bulbospongiosus muscle compresses the penile bulb and so pumps blood from the penile bulb into the remainder of the corpus spongiosum penis. Unlike the corpus cavernosum penis, this cavernous body is normally drained by distal veins; peak pressures recorded during ejaculation are much lower than those in the corpus cavernosum penis (27). The waves of pressure passing down the penile urethra may help to transport the ejaculate. Pressure changes in the corpus spongiosum penis during ejaculation are transmitted to the corpus spongiosum glandis; the glans penis enlarges in the ram, goat, and stallion but not in the bull.

LABORATORY ANIMALS

Species differences in the male reproductive organs are shown in Figure 1-1. These organs can move from a wholly scrotal to a wholly abdominal position. Differences in relative size of the accessory glands are reflected in the semen characteristics (Table 1-3).

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Chapter 2

Anatomy of Female Reproduction

B. Hafez and E.S.E. Hafez

The female reproductive organs are composed of ovaries, oviducts, uterus, cervix, uteri, vagina, and external genitalia. The internal genital organs (the first of four components) are supported by the broad ligament. This ligament consists of the mesovarium, which supports the ovary; the mesosalpinx, which supports the oviduct; and the mesometrium, which supports the uterus. In cattle and sheep, the attachment of the broad ligament is dorsolateral in the region of the ileum, so that the uterus is arranged like a ram's horns, with the convexity dorsal and the ovaries located near the pelvis.

Embryology

The fetal reproductive system consists of two sexually nondifferentiated gonads, two pairs of ducts, a urogenital sinus, a genital tubercle, and vestibular folds (Fig. 2-1). This system arises primarily from two germinal ridges on the dorsal side of the abdominal cavity, and it can differentiate into a male or a female system.

The sex of the fetus depends on inherited genes, gonadogenesis, and the formation and maturation of accessory reproductive organs.

Wolffian and Müllerian ducts are both present in the sexually undifferentiated embryo. In the female, the Müllerian ducts develop into a gonaductal system and the Wolffian ducts atrophy. The opposite is true in the male. The female Müllerian ducts fuse caudally to form a uterus, a cervix, and the anterior part of a vagina.

In the male fetus, testicular androgen plays a role in the persistence and development of the Wolffian ducts and the atrophy of the Müllerian ducts.

The Ovary

The ovary, unlike the testis, remains in the abdominal cavity. It performs both exocrine (egg release) and endocrine (steroidogenesis) functions. The predominate tissue of the ovary is the cortex. The primordial germ cells arise extragonadally and migrate through the yolk sac mesentery to the genital ridges. During fetal development, the oogonia are produced by mitotic multiplication. This is followed by the first meiotic division to form several million oocytes, a process that is arrested in the prophase. Subsequent atresia reduces the number of oocytes at the time of birth, a further reduction occurs at puberty, and only a few hundred are present during reproductive senescence.

At birth, a layer of follicular cells surrounds the primary oocytes in the ovary to form the primordial follicles. The shape and size of the ovary vary both with the species and the stage of the estrous cycle (Fig. 2-2). In cattle and sheep, the ovary is almond-shaped, whereas in the horse it is bean-shaped owing to the presence of a definite ovulation fossa, and indentation in the attached border of the ovary. The porcine ovary resembles a cluster of grapes because the protruding follicles and corpora lutea obscure the underlying ovarian tissue.

The part of the ovary that is not attached to the mesovarium is exposed and bulges into the abdominal cavity. The ovary, composed of the medulla and cortex, is surrounded by the superficial epithelium, commonly known as germinal epithelium. The ovarian medulla consists of irregularly arranged fibroelastic connective tissue and extensive nervous and vascular systems that reach the ovary through the hilus. The arteries are arranged in a definite spiral shape. The ovarian cortex contains ovarian follicles and/or corpora lutea at various stages of development of regression (Table 2-1).

The vascular pattern of the ovary changes with different hormonal states. Variations in the architecture of the vessels allow adaptation of the blood supply to the needs of the organ. The intraovarian distribution of blood undergoes remarkable changes during the preovulatory period.

Arterial blood flow to the ovary varies in proportion to luteal activity. Hemodynamic changes seem to be impor-

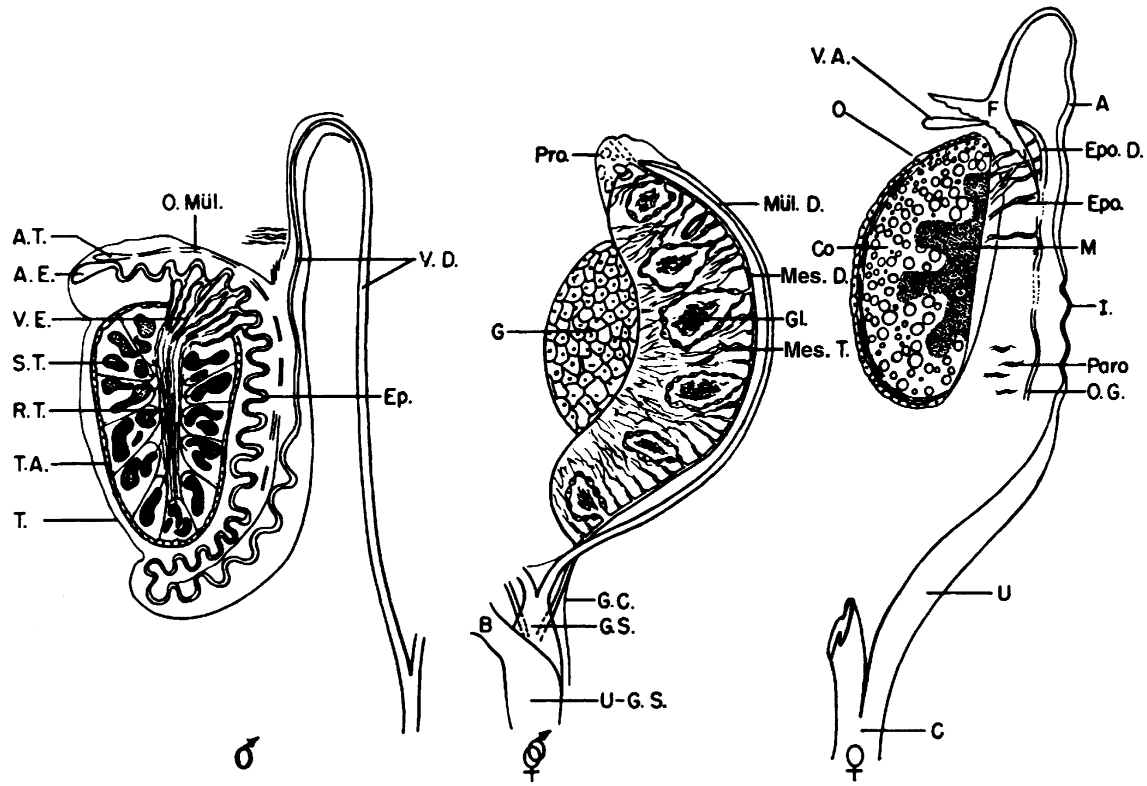


FIGURE 2-1. Simplified scheme of embryonic differentiation of male and female genital systems. (**Center**) The undifferentiated system with its large mesonephros, mesonephric duct, Müllerian duct and undifferentiated gonad. Note that the Müllerian and Mesonephric ducts cross before they enter the genital cords. (**Right**) The female system, in which the ovary and Müllerian ducts differentiate while the remnants of the Mesonephros and Mesonephric ducts atrophy into the epoophoron, paroophoron, and Gartner's duct. (**Left**) The male system in which the testes and Mesonephric (Wolffian) ducts differentiate; the sole remnants of the Müllerian ducts are the testicular appendix and prostatic utricle (vagina masculinus). A, Ampulla; *B*, Bladder; *C*, Cervix; *Co*, Ovarian cortex; *Ep*, Epididymis; *Mul.D.*, Müllerian duct; O, Ovary; *S.T.*, Seminiferous tubules; *T*, Testis; *U*, Uterus; *U-G.S.*, Urogenital sinus; *V.D.*, Vas deferens.

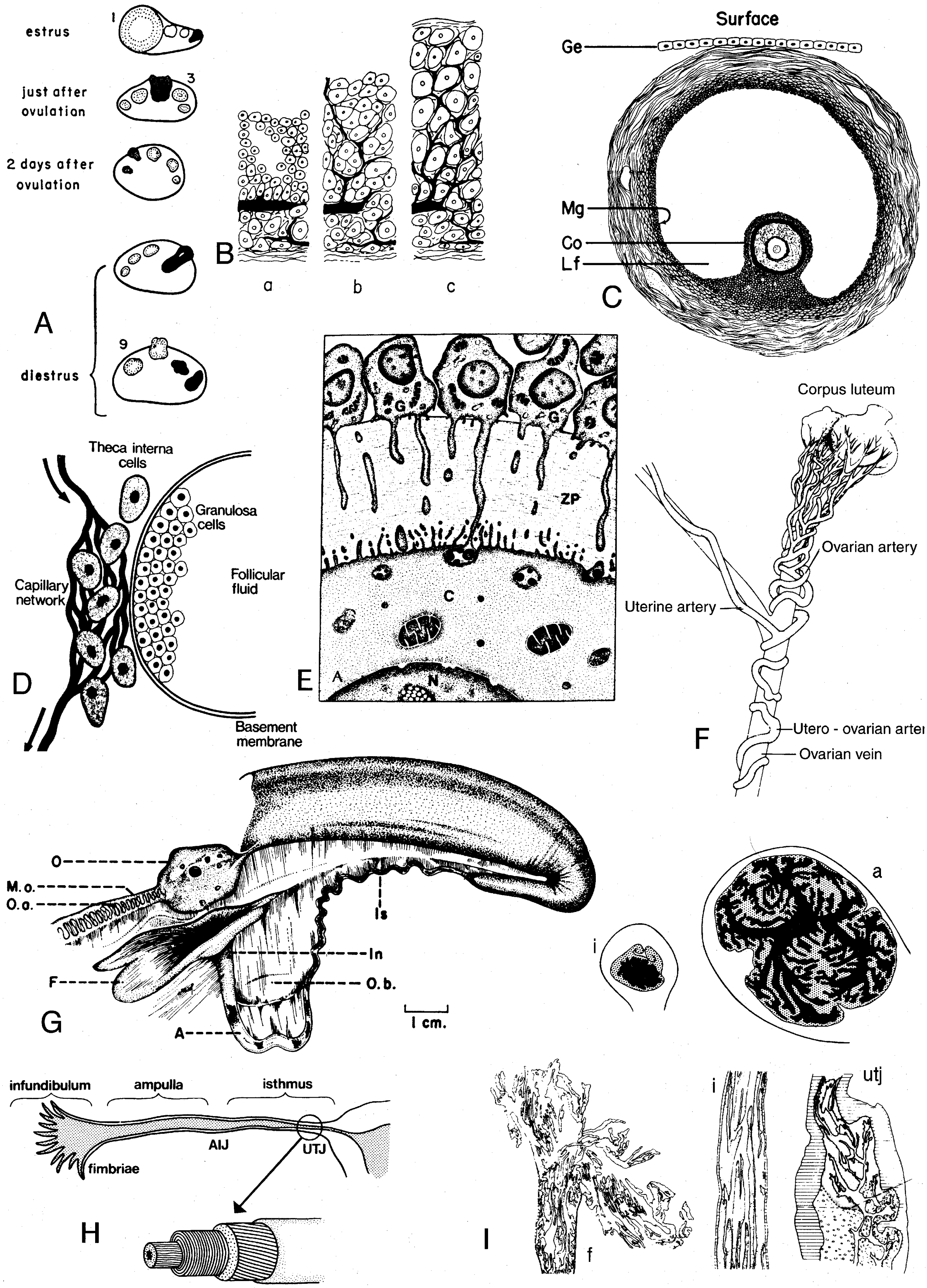
tant in regulating corpus luteum (CL) function and lifespan. Thus, changes in blood flow precede the decline in progesterone secretion, whereas restriction of ovarian blood flow causes premature CL regression. At the time of luteolysis in ewes, there is a reduction in ovarian blood flow (1).

Blood flow to the bovine ovary is highest during the luteal phase, decreases with luteal regression, and reaches a nadir just before ovulation. Ovarian blood flow increases with the newly developing CL. The decline in blood flow seems to follow the abrupt decline at the time of regression of the CL (2).

Corpus Luteum

The CL develops after the collapse of the follicle at ovulation. The inner wall of the follicle develops into macroscopic

FIGURE 2-2. The ovarian/oviductal anatomy of farm animals. (**A**) Changes in estrus cycle of bovine ovary: *1*, ripe follicle; *2*, collapsed follicle surface, wrinkled/walls bloodstained; *9*, corpus albicans (Arthur 1964). (**B**) Organization of cells in estrous ovine corpus luteum: *a*, corpus haemorrhagicum; *b*, corpus luteum of the second day following estrus; *c*, corpus luteum, day 4 after estrus. (**C**) Graffian follicle: *Co*, cumulus oophorus; *Ge*, germinal epithelium; *Lf*, liquor folliculi; *Mg*, membrana granulosa. (**D**) Structure of wall of graafian follicle showing how the granulosa cells are deprived of a blood supply by basement membrane (Baird 1972). (**E**) Fully formed zona pellucida (*ZP*) around an oocyte in a graafian follicle. Microvilli arising from oocyte inter-digitate with processes from granulosa cells (**G**). These processes penetrate into cytoplasm of oocyte (**C**) provide nutrients/maternal protein (*N*) oocuyte nucleus (Baker 1972). (**F**) Anatomy of the bovine ovarian vasculature (J.H. Wise et al, 1982). (**G**)Anatomy of ovine ovary/oviduct. A, ampulla; *F*, fimbriae; *In*, infundibulum; *Is*, isthmus; *M.o.*, mesovarium; O, ovary; *O.a*, ovarian artery; *O.b*, ovarian bursa; *U*, uterus. Note the suspended loop to which the ovarian bursa is attached. The oviduct in the ewe is pigmented. (**H**) Major segments of the oviduct. (**I**) Cross and longitudinal sections of different segments of the oviduct; *1* represents the isthmus; *8* represents the infundibulum. Note the variability in the degree of complexity of the mucosal folds.


estrus
1
just after ovulation
3
2 days after ovulation
9
diestrus
A
B
a
b
c
Surface
Ge
Mg
Co
Lf
C
Theca interna cells
Granulosa cells
Follicular fluid
Capillary network
Basement membrane
D
G
ZP
C
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N
E
Corpus luteum
Ovarian artery
Uterine artery
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A
1 cm.
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a
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TABLE 2-1. ***Functional Histology of the Mammalian Ovary/Ovarian Follicle***

ANATOMIC FUNCTIONAL UNIT	HISTOLOGIC CHARACTERISTICS
Superficial epithelium	Surface layer of flattened epithelium (commonly incorrectly known as germinal epithelium).
Tunica albuginea	Dense, fibrous connective tissue covering the whole ovary just beneath the superficial epithelium.
Ovarian cortex	Contains several primary follicles (with oocytes in a quiescent state) and a few large follicles. During each estrous cycle, variable numbers of follicles undergo rapid growth and development, culminating in ovulation.
Ovarian medulla	Loose connective tissue contains nerves, lymphatics, and tortuous thin-walled blood vessels, collagen and elastic fibers, fibroblasts.
Ovarian stroma	Poorly differentiated, embryonal-mesenchymal-like cells capable of undergoing complex morphologic alterations during the reproductive life; stromal cells can give rise to theca interna cells.
Smooth muscle	Smooth muscle cells throughout the ovary, especially in the cortical stroma. Ovarian myoid cells are similar to smooth muscle cells of other tissues. Large numbers of microfilaments arranged in characteristic bundles. Smooth muscle cells and neural elements directly involved in ovulation. Smooth muscle cells, especially in the perifollicular regions, involved in "squeezing the follicle" during ovulation.
OVARIAN FOLLICLES	
Primary follicle	Oocyte enclosed by a single layer of flattened or cuboidal follicular cells.
Growing follicle	Oocyte with increased diameter/increased number of layers of follicular cells; zona pellucida is present around oocyte.
Secondary follicle	Flattened granulosa cells of the primordial or unilaminar follicle proliferate.
Tertiary (vesicular) follicle	Under the influence of pituitary gonadotrophins, the granulosa cells of multilayered follicles secrete a fluid, liquor folliculi, which accumulates in the intercellular spaces. Continued secretion/accumulation of liquor folliculi result in dissociation of granulosa cells causing formation of a large, fluid-filled cavity—the antrum. Zona pellucida is surrounded by a solid mass of radiating follicular cells, forming the corona radiata.
Graafian follicle	Follicular cells increase in size; antrum filled with follicular fluid. Oocyte pressed to one side, surrounded by accumulation of follicular cells (cumulus oophorus); elsewhere in the follicular cavity an epithelium of fairly uniform thickness called the membrana granulosa has formed.
Preovulatory follicle	Blister-like structure protruding from ovarian surface due to rapid accumulation of follicular fluid/thinning of the granulosa layer. The viscous liquor folliculi is formed from the secretions of granulosa cells and plasma proteins transported into the follicle by transudation. Dramatic changes at subcellular level, particularly in the golgi complex, involved in formation of the zona pellucida. Oocyte, in the prophase of meiosis, resumes several hours before ovulation. First meiotic (maturational) division associated with extrusion of first polar body.

and microscopic folds that penetrate the central cavity. These folds consist of a central core of stromal tissue and large blood vessels, which become distended. The cells develop a few days before ovulation. They regress quickly, and within 24 hours after ovulation all remaining thecal cells are in an advanced stage of degeneration. Hypertrophy and luteinization of the granulosa cells commence after ovulation.

Progesterone is secreted by the luteal cells as granules. In the ewe, this process appears to be maximal at day 10 of the cycle and begins to taper off noticeably at day 12. The secretory activity declines gradually until day 14.

In aged animals, the functions of the CL decline as a result of an inability of follicular cells (granulosa and theca interna) to respond fully to hormonal stimuli, changes in the quantity and/or quality of hormone secretion, and a reduced stimulus for hormone secretion.

DEVELOPMENT. The increase in the weight of the CL is initially rapid. In general, the period of growth is slightly longer than half the estrous cycle. In the cow, the weight and progesterone content of the CL increase rapidly between days 3 and 12 of the cycle and remain relatively constant until day 16, when regression begins. In the ewe and sow, corpora lutea increase rapidly in weight and progesterone content from day 2 to day 8, and remain relatively constant until day 15, when regression begins (3). The diameter of the mature CL is larger than that of a mature graafian follicle except in the mare, in which it is smaller.

REGRESSION. If fertilization does not occur, the CL regresses, allowing other larger ovarian follicles to mature. As these cells degenerate, the whole organ decreases in size, becomes white or pale brown, and is known as the *corpus albicans*. After two or three cycles, a barely visible scar of connective tissue remains. Remnants of the bovine corpus albicans persist during several successive cycles. The bovine CL of the estrous cycle begins to regress 14 to 15 days after estrus, and its size may decrease by half within 36 hours.

LUTEOLYSIS. Estrogen-induced luteolysis, probably mediated through stimulation of uterine prostaglandin during the estrous cycle of the ewe, is responsible for the normal regression of the CL. An embryo must be in the uterus of ewes on days 12 and 13 after mating in order for the CL to be maintained. This time represents the state at which the uterus initiates steps leading to luteolysis.

The main uterine vein and the ovarian artery are the proximal and distal components of a local venoarterial pathway involved in the luteolytic and antiluteolytic effects. Hysterectomy abolishes the luteolytic effect and causes persistence of the CL. Luteolysis in the pig is associated with increased plasma prostaglandin PGF in the uteroovarian vein (4).

The changes in blood flow to the luteal tissue can be attributed to changes in flow to the CL, which receives most of the blood supply. Blood flow to the CL plays a role in the regulation of this gland and in regulating the activity of gonadotropins at the luteal cell level.

CORPUS LUTEUM AND PREGNANCY. Progestogens are necessary for the maintenance of pregnancy. Some progestogens serve as immediate precursors to other steroids that are also necessary during pregnancy. Except in the mare, there is an obligatory requirement for continued secretory activity of the CL throughout pregnancy because the placenta does not secrete progesterone in these species. Overiectomy of the gilt at any time during pregnancy results in abortion within 2 to 3 days. After removing one ovary or the corpora lutea from each ovary on day 40 of gestation, a minimum of five corpora lutea is needed to maintain gestation.

MATERNAL RECOGNITION OF PREGNANCY. Blastocytes must be present by day 12 after ovulation in ewes and day 13 in gilts to extend the lifespan of the CL. Maternal recognition of pregnancy in cattle occurs between day 15 and 17 of gestation. Plasma concentrations of progesterone are higher in pregnant than in nonpregnant cows within 8 days after breeding.

The CL of pregnancy is known as the *corpus luteum vernum* and may be larger than the *corpus luteum spurium* (false yellow body) of the estrous cycle. In cattle it increases in size for 2 to 3 months of gestation, then regresses for 4 to 6 months. Thereafter it remains relatively constant until calving, when it degenerates within 1 week postpartum.

THE OVIDUCT

There is an intimate anatomic relationship between the ovary and the oviduct. In farm mammals, the ovary lies in an open ovarian bursa, in contrast to some species in which it lies in a closed sac (e.g., rat, mouse). This bursa in farm animals is a pouch consisting of a thin peritoneal fold of mesosalpinx, which is attached to a suspended loop at the upper portion of the oviduct. In cattle and sheep, the ovarian bursa is wide and open. In swine it is well-developed, and although open, it largely encloses the ovary. In horses it is narrow and cleft-like and encloses only the ovulation fossa.

Anatomy

The length and degree of coiling of the oviduct vary in farm mammals. The oviduct may be divided into four functional segments: the fringe-like *fimbriae*; the funnel-shaped abdominal opening near the ovary—the *infundibulum*; the more distal dilated *ampulla*; and, the narrow proximal portion of the oviduct connecting the oviduct with the uterine lumen—the *isthmus* (Fig. 2-3). The fimbriae are unattached except for one point at the upper pole of the ovary. This ensures close approximation of the fimbriae and the ovarian surface. In vivo and in vitro techniques used to study the functions of the oviduct are summarized in Table 2-2.

The ampulla, accounting for about half of the oviductal length, merges with the constricted section known as the *isthmus*. The isthmus is connected directly to the uterus; it enters the horn in the form of a small papilla in the mare. In the sow, however, this junction is guarded by long finger-like mucosal processes. In the cow and ewe, there is a flexure at the uterotubal junction, especially during estrus. The thickness of the musculature increases from the ovarian to the uterine end of the oviduct.

Oviductal Mucosa

The oviductal mucosa is made of primary, secondary, and tertiary folds. The mucosa in the ampulla is thrown into high, branched folds that decrease in height toward the isthmus and become low ridges in the uterotubal junction.

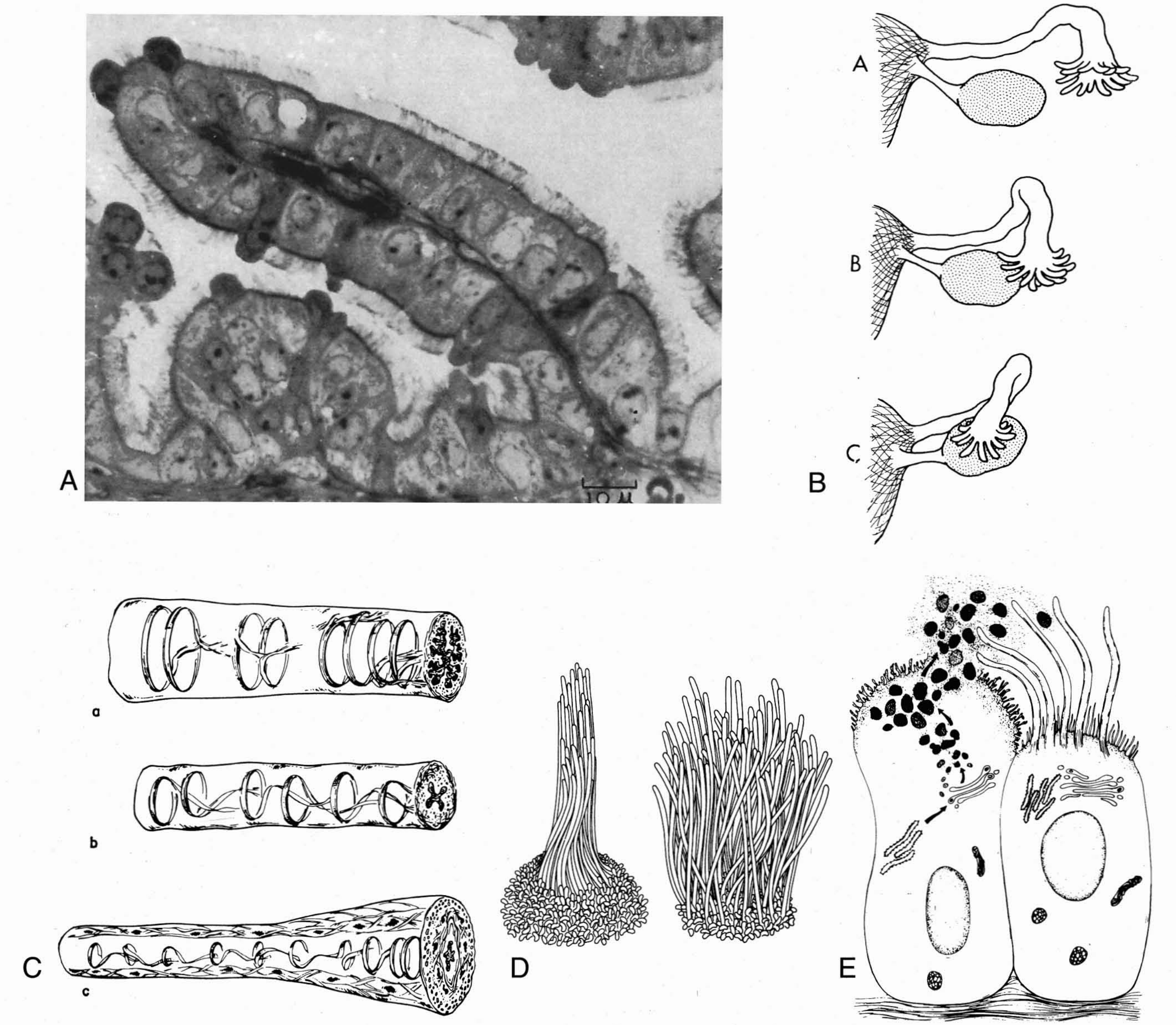

FIGURE 2-3. Physiology, histology, and cytology of the oviduct. (**A**) Oviductal epithelium. *A*, secretory cells with bulging secretory material/ciliated cells with kinocilia (Photo by Professor S. Reinius). (**B**) Contraction of fimbria in relation to ovarian surface, a mechanism by which eggs are picked up into the infundibulum. (**C**) The musculature in the oviduct of ungulates. *A*, ampulla: the musculature consists of spiral fibers arranged almost circularly; *B*, isthmus: note difference in morphology of muscle fibers; *C*, uterotubal junction: note the longitudinal muscle coat of uterine origin, as well as peritoneal fibers (Schilling. Zentralbl Veterinaermed 1962;9:805). (**D**) Ciliated cells from the oviduct (*right*) and uterus (*left*). Note the presence of microvilli on the apical surface of the cell. (**E**) Secretory cells showing the biosynthesis, packaging, storage, release, and distribution of secretory material, which is the main component of the luminal fluid in the oviduct and uterus. The action of kinocilia facilitates the release of secretory granules from the surface cells.

The complex arrangement of these mucosal folds in the ampulla almost completely fills the lumen so that there is only a potential space. Fluid is at a minimum; thus, the cumulus mass is the intimate contact with the ciliated mucosa (Fig. 2-4). The mucosa consists of one layer of columnar epithelial cells. The epithelium contains ciliated and nonciliated cells.

CILIATED CELLS. The ciliated cells of the oviductal mucosa have a slender motile cilia (kinocilia) that extend

TABLE 2-2. *In Vivo and In Vitro Techniques Used to Study Functions of the Oviduct*

FUNCTION UNDER STUDY	TECHNIQUES
Structure and ultrastructure of epithelium, secretory activity, and cilia	Scanning and transmission electron microscopy Culture of fragments of oviductal mucosa Histochemical observations of frozen section
Identification of adrenergic or cholinergic receptors	Fluorescence histochemical technique Physiopharmacology of oviductal contractility (e.g., response to drugs)
Contractility of oviductal musculature	Visual observation of oviduct through abdominal wall or abdominal window
Biochemical composition of oviductal fluid	Extra-abdominal or intra-abdominal device to collect fluid
Detection of protein uptake in oviductal epithelium	Immunofluorescence Pharmacology/neuropharmacology
Egg transport in oviduct	Effects of prostaglandins, steroid hormones Segmental flushing of oviduct Use of surrogate eggs Recovery of eggs from uterus in vivo
Sperm transport in oviduct	Segmental flushing of oviduct at intervals following artificial insemination Flushing of oviduct from fimbriae, by laparoscopy, at intervals following breeding or A.I.
Kinetics of cilia beat	High-speed cinematography

into the lumen. The rate of beat of cilia is affected by the levels of ovarian hormones, activity being maximal at ovulation or shortly afterward when the stroke of the cilia in the fimbriated portion of the oviducts is closely synchronized and directed toward the ostium. The action of ciliary beat seems to enable the egg within the surrounding cumulus cells to be stripped from the surface of the collapsing follicles toward the ostium of the oviduct. The percentage of ciliated cells decreases gradually in the ampulla toward the isthmus and reaches a maximum in the fimbriae and infundibulum. Ciliated cells are noted in large numbers at the apices of the mucosal folds. Variations in the percentage of ciliated and secretory cells along the length of the oviduct have some function significance. Ciliated cells are most abundant where the egg is picked up from the ovarian surface, whereas secretory cells are abundant where luminal fluids are needed as a medium for the interaction of eggs and sperm.

The cilia beat toward the uterus. Their activity, coupled with oviductal contractions, keeps oviductal eggs in constant rotation, which is essential to bring egg and sperm together (fertilization) and preventing oviductal implantation. Ciliation of the oviduct is hormonally controlled in the rhesus monkey: cilia disappear almost completely after hypophysectomy and develop in response to administration of exogenous estrogens. The oviducts atrophy and deciliate during anestrus, hypertrophy and become reciliated during proestrus and estrus, and atrophy and deciliate during pregnancy.

Infections of the female reproductive tract are associated with dramatic changes in cell morphology. Infection is usually associated with the loss of ciliated cells. A decrease in the number of cilia may lead to the accumulation of tubal fluid and inflammatory exudate, which contributes to the agglutination of tubal plicae and subsequent development of salpingitis.

NONCILIATED CELLS. The secretory cells of the oviductal mucosa are nonciliated and characteristically contain secretory granules, the size and number of which vary widely among species and during different phases of the estrous cycle. The apical surface of the nonciliated cells is covered with numerous microvilli. Secretory granules accumulated in epithelial cells during the follicular phase of the cycle are released into the lumen after ovulation, causing a reduction in epithelial height.

The oviductal fluid has several functions, including sperm capacitation, sperm hyperactivation, fertilization, and early preimplantation development. The oviductal fluid is composed of a selective transudate of serum and secretory products of the granules from the secretory cells of the oviductal epithelium (5). Oviductal secretions are regulated by steroid hormones.

Several protein components are common to oviductal fluid and serum. Some of these, however, are present in different proportions in these two body fluids; for example, the quantity of a transferrin and prealbumin in oviductal fluid is far greater relative to albumin than is the quantity of these proteins in the serum. Many serum proteins have

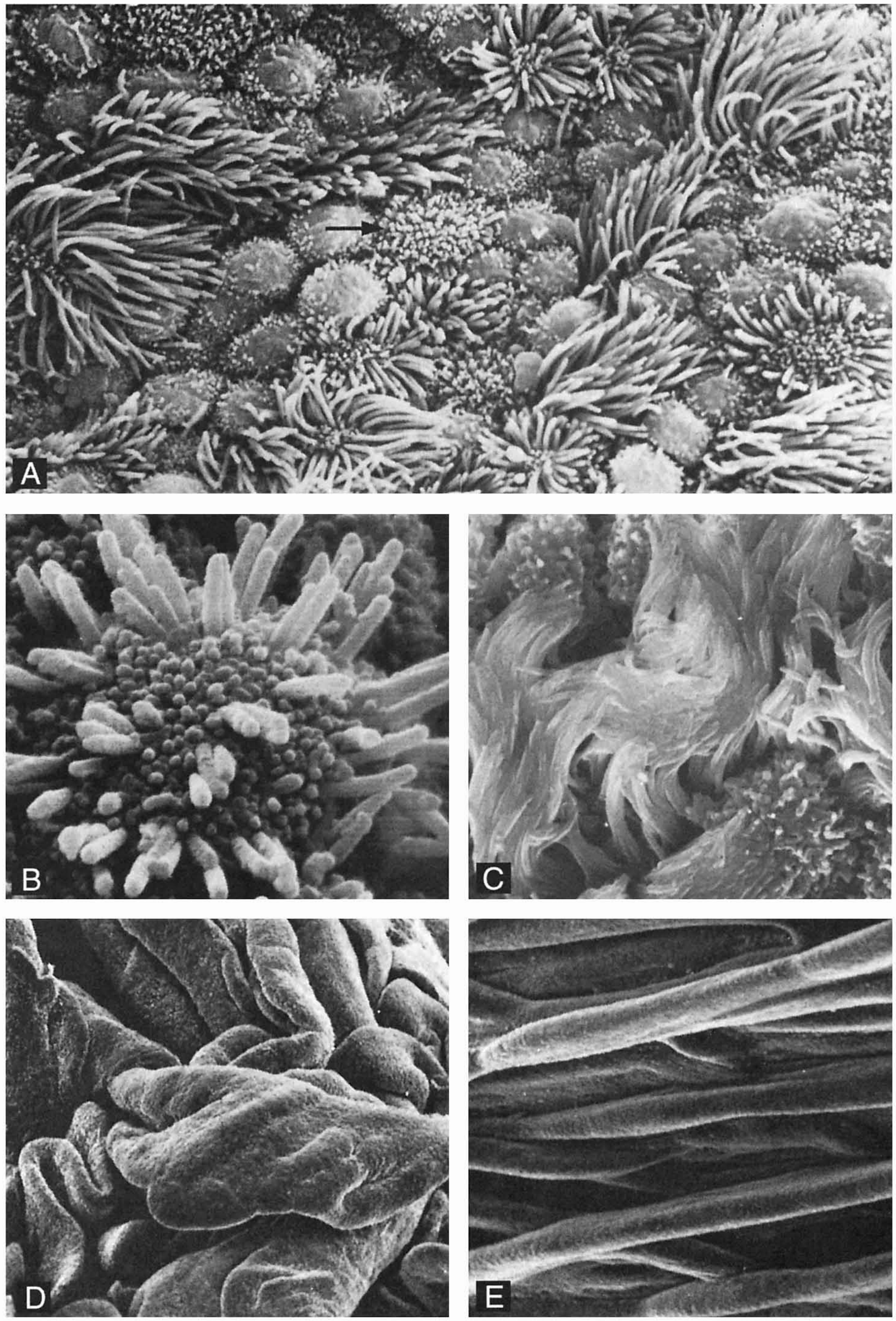

FIGURE 2-4. Scanning electron micrographs of the oviduct. (**A**) The oviductal epithelium showing secretory (*arrow*) cells heavily coated with microvilli and ciliated cells. Note that some cells are fully ciliated while others have cilia on the periphery. (**B**) Rosette-like structure of a ciliated cell ciliogenesis, a process that occurs at random, culminating in complete ciliation as shown in here. (**C**) Fully ciliated cells in the fimbriae that assist in the pick-up of ova after its release from the Graafian follicle. (**D**) *E*, oviductal epithelium. Mucosal folds which protrude in the lumen of ampulla (37™). (**E**) Mucosal folds that protrude in the lumen of the isthmus (40™).

no counterparts in oviductal fluid and conversely, several proteins are unique to oviductal fluid.

Oviductal Musculature and Related Ligaments

Oviductal contractions facilitate mixing of oviductal contents, help to denude the ova, promote fertilization by increasing egg-sperm contact, and partly regulate egg transport. Unlike intestinal peristalsis, oviductal peristalsis tends to delay slightly the progression of the ovum instead of transporting it.

PATTERNS OF OVIDUCTAL CONTRACTIONS. The oviductal musculature undergoes various types of complex contractions: localized peristalsis-like contractions originating in isolated segments or loops and traveling only a short distance; segmental contractions; and worm-like writhings of the entire oviduct. Contractions in an abovarian direction are more common than those in an adovarian direction. In general the ampulla is less active than the isthmus. Additional complicating factors are the contractile activities of the mesosalpinx, the myometrium and the supporting ligaments, and ciliary movement.

Oviductal muscular contractions are stimulated by contractions of two major membranes that contain smooth musculature and are attached to the fimbriae, ampulla, and ovary: the mesosalpinx and the mesotubarium superius. The frequency and amplitude of spontaneous contractions vary with the phase of the estrous cycle. Before ovulation, contractions are gentle with some individual variations in the rate and pattern of contractility. At ovulation, contractions become most vigorous. At ovulation, the fringe-like folds contract rhythmically and "massage" the ovarian surface.

The pattern and amplitude of contraction vary in different segments of the oviduct. In the isthmus, peristaltic and antiperistaltic contractions are segmental, vigorous, and almost continuous. In the ampulla, strong peristaltic waves move in a segmented fashion toward the midportion of the oviduct.

UTERO-OVARIAN AND RELATED LIGAMENTS. The utero-ovarian ligament contains smooth muscle cells arranged primarily in longitudinal bundles, which continue into the myometrium but not into the ovarian stroma. The smooth muscles in the mesovaria and the various ligaments of the mesenteries attached to the ovaries and the fimbriae contract intermittently. These rhythmic muscular contractions ensure that the fimbriae remain in a constant position relative to the surface of the ovaries.

THE UTERUS

The uterus consists of two uterine horns (cornua), a body, and a cervic (neck) (Fig. 2-5). The relative proportions of each, as well as the shape and arrangement of the horns, vary according to species. In swine, the uterus is of the bicornuate type (uterus bicornis). The horns are folded or convoluted and may be as long as 4 to 5 feet, while the body of the uterus is short (Fig 2-6). This length is an anatomic adaptation for successful litter bearing. In cattle, sheep, and horses, the uterus is of the bipartite type (uterus bipartitus). These animals have a septum that separates the two horns and a prominent uterine body (the horse has the largest). In ruminants the uterine epithelium has several caruncles. Both sides of the uterus are attached to the pelvic and abdominal walls by the broad ligament.

Endometrial Glands and Uterine Fluid

The endometrial glands are branched, coiled, tubular structures lined with columnar epithelium. They open onto the endometrial surface, except in the caruncular areas (in ruminants). The glands are relatively straight at the time of estrus; they grow, secrete, and become more coiled and complex as the level of progesterone produced by the developing CL rises. They begin to regress when the first signs of luteal regression are also noted. The endometrial epithelial cells are relatively tall during estrus; following a period of active secretion during estrus, they become low and cuboidal at 2 days postestrus.

The volume and biochemical composition of the uterine fluid show consistent variation during the estrus cycle. In sheep the volume of the fluid in the uterus exceeds that of the oviduct during estrus, whereas during the luteal phase, the reverse is true.

UTERINE PROTEINS. The endometrial fluid contains mainly serum proteins and small amounts of uterine-specific proteins. The ratio and amounts of these proteins vary according to the reproductive cycle. Differences in concentration as well as distribution of components in the uterine fluids compared to the blood serum provide evidence that secretion as well as transudation occurs. In the rabbit, a protein named *blastokinin* (uteroglobulin) can influence blastocyst formation from morulae. The uterine fluid in the mouse contains a factor that initiates implantation. Uterine secretions provide an optimal environment for the survival and capacitation of spermatozoa and the cleavage of the early blastocyst before implantation.

Specific proteins of uterine and/or conceptus origin have been characterized during early pregnancy in the ewe. One of the proteins, a purple-colored, iron-containing glycoprotein named *uteroferin* has been purified (6). Uterine secretions play a part in the control of embryonic growth and the implantation.

UTERINE CONTRACTION. The contraction of the uterus is coordinated with the rhythmic movements of the oviduct and ovary. There is considerable variation in the origin, direction, amplitude degree, and frequency of contractions in the reproductive tract.

During the estrous cycle the frequency of myometrial contractions is maximal at and immediately after estrus. At estrus, uterine contractions originate in the posterior part of the reproductive tract and more predominantly toward the oviduct. During the luteal phase, the frequency of contractions is reduced and only a small percentage moves toward the oviducts. Estradiol increases the frequency of uterine contractions in ovariectomized ewes, where the progesterone reduces the frequency. High levels of progesterone are noted when contractile activity is relatively quiescent.

Uterine Metabolism

The endometrium metabolizes carbohydrates, lipids, and proteins to supply the necessary requirements for cell nutri-

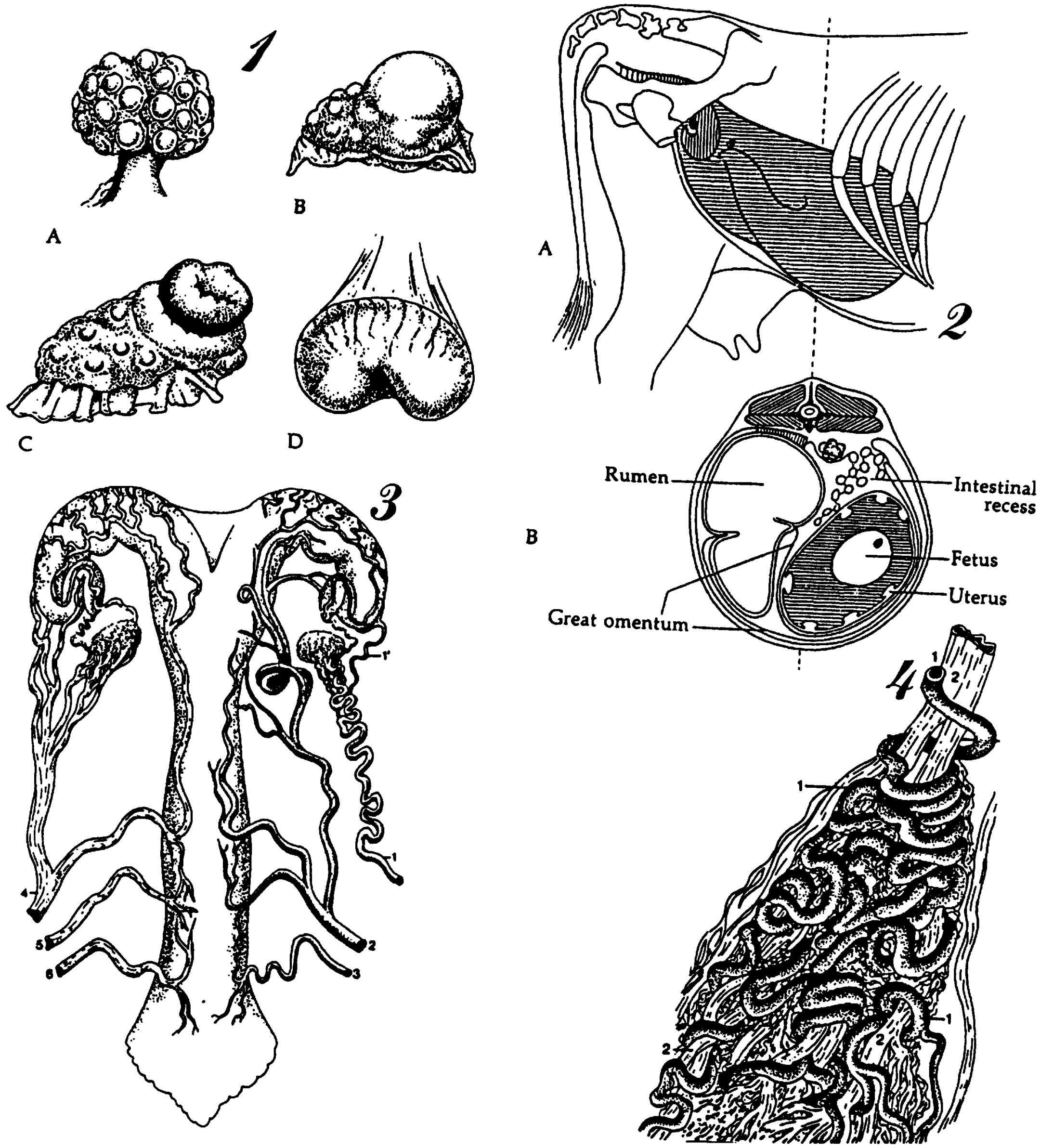

FIGURE 2-5. Comparative parameters of female reproductive anatomy. (**1**) Ovarian differences resulting from species morphology and functional changes. *A*, sow ovary (berry-shaped); *B*, cow ovary (almond-shaped) with ripening follicle; *C*, cow ovary with fully developed corpus luteum; *D*, mare ovary (kidney-shaped) with ovulation fossa (identation) (Dyce KM, Sack WO, Wensing CJG. Textbook of veterinary anatomy. Philadelphia: W.B. Saunders, 1987). (**2**) Position of the cow's uterus at the third and sixth months of pregnancy. *A*, superimposed uterus and ovary (*left*) (vertical striping, uterus; blackened circle, ovary) represents the uterus at the third month of pregnancy; *B*, cross section of uterus at sixth month of pregnancy with its contained fetus relative to adjoining abdominal viscera (rumen on left/uterus on right side of abdomen) (Dyce KM, Wensing CJG. Essentials of bovine anatomy. Philadelphia: Lea & Febiger, 1971). (**3**) Blood supply to the reproductive tract of the cow. The arteries are shown on the right side and the veins on the left. *1*, ovarian artery; *1'*, uterine branch; *2*, uterine artery; *3*, vaginal artery; *4*, ovarian vein; *5*, uterine vein; *6*, vaginal vein (Dyce KM, Sack WO, Wensing CJG. Textbook of veterinary anatomy. Philadelphia: W.B. Saunders, 1987). (**4**) Relationship of the ovarian artery of a ruminant and its branches; *1*, to those of the uterine vein; *2*, the intertwining ensures a large area of contact (Dyce KM, Sack WO, Wensing CJG. Textbook of veterinary anatomy. Philadelphia: W.B. Saunders, 1987).

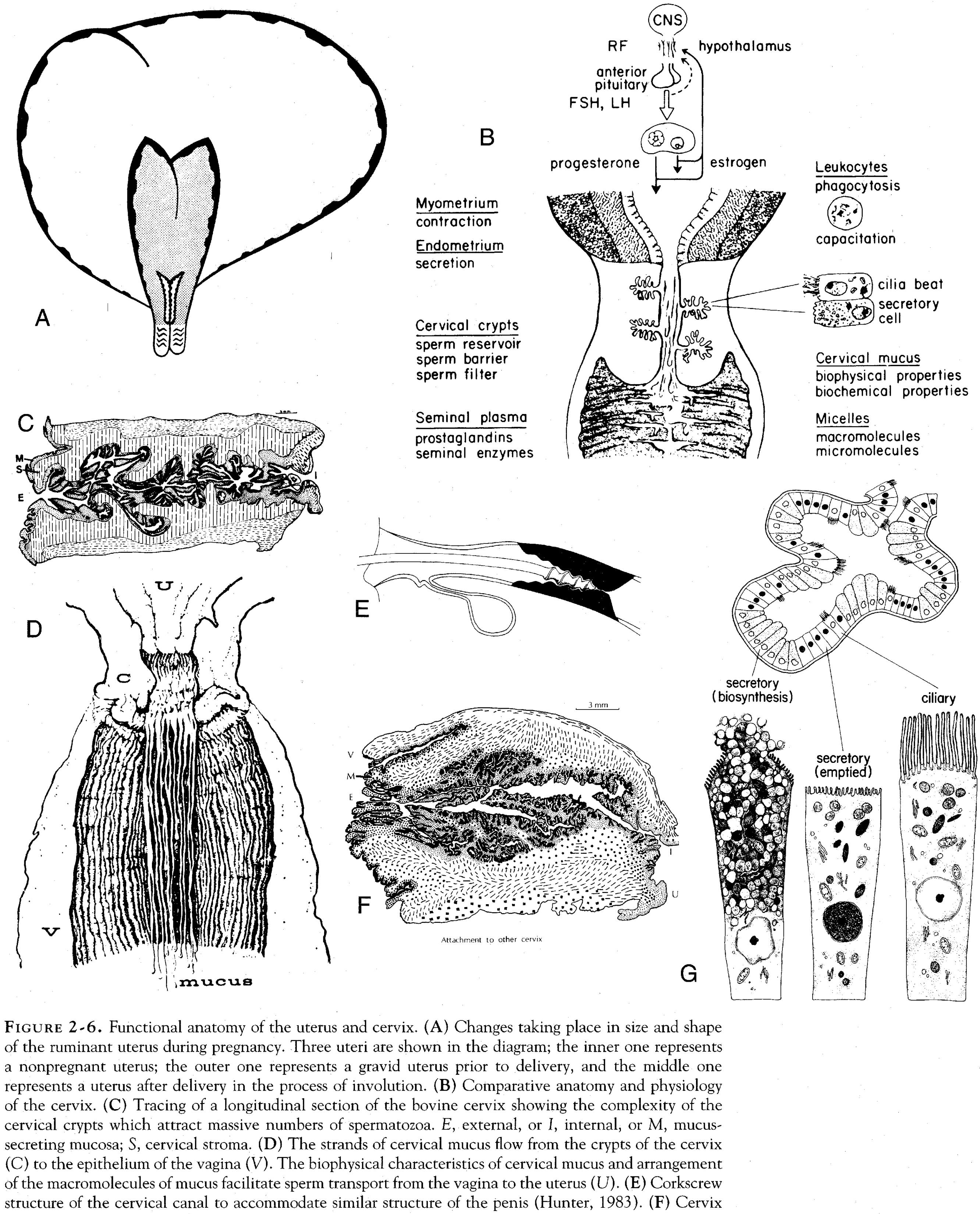

Figure 2-6. Functional anatomy of the uterus and cervix. (A) Changes taking place in size and shape of the ruminant uterus during pregnancy. Three uteri are shown in the diagram; the inner one represents a nonpregnant uterus; the outer one represents a gravid uterus prior to delivery, and the middle one represents a uterus after delivery in the process of involution. (B) Comparative anatomy and physiology of the cervix. (C) Tracing of a longitudinal section of the bovine cervix showing the complexity of the cervical crypts which attract massive numbers of spermatozoa. *E*, external, or *I*, internal, or *M*, mucus-secreting mucosa; *S*, cervical stroma. (D) The strands of cervical mucus flow from the crypts of the cervix (C) to the epithelium of the vagina (*V*). The biophysical characteristics of cervical mucus and arrangement of the macromolecules of mucus facilitate sperm transport from the vagina to the uterus (*U*). (E) Corkscrew structure of the cervical canal to accommodate similar structure of the penis (Hunter, 1983). (F) Cervix of the rabbit. Note the complexity of cervical canal of the double cervix. (G) Cervical crypt (*top*) and secretory cells before and after secretion of mucus (*bottom*).

tion, rapid proliferation of the uterine tissue, and development of the conceptus. These reactions depend on four phenomena: (a) the enzymatic reactions involved in glucose metabolism; (b) the increase in circulation through the spiral arterioles; (c) the morphologic changes that occur in the endometrium and myometrium; and (d) the stimulating action of the ovarian and other hormones.

Ovarian hormones play a substantial role in regulating uterine metabolism. Growth of the uterus (both protein synthesis and cell division) is induced by estrogen. A rapid change occurs in the metabolism of the endometrium about the time the egg passes through the uterotubal junction.

Function of the Uterus

The uterus serves a number of functions. The endometrium and its fluids play a major role in the reproductive process: (a) sperm transport from the site of ejaculation to the site of fertilization in the oviduct; (b) regulation of the function of the CL; and (c) initiation of implantation, pregnancy and parturition.

SPERM TRANSPORT. At mating, the contraction of the myometrium is essential for the transport of sperm from the site of ejaculation to the site of fertilization. Large numbers of sperm aggregate in the endometrial glands. As sperm are transported through the uterine lumen to the oviducts, they undergo "capacitation" in endometrial secretions.

LUTEOLYTIC MECHANISMS. There is a local utero-ovarian cycle whereby the CL stimulates the uterus to produce a substance that in turn destroys the CL. The uterus plays an important role in regulating the function of the CL. Corpora lutea are maintained in a functional state for long periods following hysterectomy of cattle, sheep, and swine. If small amounts of uterine tissue remain in situ, luteal regression occurs and cycles are resumed after variable periods. Following unilateral hysterectomy, corpora lutea adjacent to the excised uterine horn are usually better maintained than those adjacent to the remaining horn.

Intramuscular or intrauterine administration of prostaglandin causes complete luteal regression in the cow and ewe. The gravid uterine horn exerts an antiluteolytic effect at the level of the adjacent ovary. This effect is exerted through a local utero-ovarian venoarterial pathway.

IMPLANTATION AND GESTATION. The uterus is a highly specialized organ that is adapted to accept and nourish the products of conception from the time of implantation until parturition. Uterine "differentiation" is governed by the ovarian steroid hormones. This process must evolve to some critical stage when the uterus is prepared to selectively accept the blastocyst. Unless such differentiation occurs, the uterus is unsuited to permit implantation.

After implantation, the embryo depends on an adequate vascular supply within the endometrium for its development. Throughout gestation, the physiologic properties of the endometrium and its blood supply are important for the survival and development of the fetus. The uterus is capable of undergoing tremendous changes in size, structure, and position to accommodate the needs of the growing conceptus.

PARTURITION AND POSTPARTUM INVOLUTION. The contractile response of the uterus remains dormant until the time of parturition, when it plays the major role in fetal expulsion. Following parturition, the uterus almost regains its former size and condition by a process called *involution.* In the sow, the uterus continuously declines in both weight and length for 28 days after parturition; thereafter it remains relatively unchanged during the lactation period. However, immediately after the young are weaned, the uterus increases in both weight and length for 4 days.

During the postpartum interval, the destruction of endometrial tissue is accompanied by the presence of large numbers of leukocytes and the reduction of the endometrial vascular bed. The cells of the myometrium are reduced in number and size. These rapid and disproportional changes in the uterine tissue are a possible cause of low postpartum conception rate. Neither the presence of suckling calves nor anemia delays uterine involution. Caruncular tissues are sloughed off and expelled from the uterus 12 days after calving.

EFFECTS OF FOREIGN BODIES AND IUDs. The stimulation of the uterus during the early stages of the estrous cycle hastens regression of the CL and causes precocious estrus. Uterine stimulation can be initiated by placing a small foreign body in the lumen. The subsequent estrous cycle will be either shortened or prolonged, depending on when the foreign body was inserted and on the nature and size of the material introduced. The fact that the estrous cycle is unaffected when the uterine segment containing the foreign body is denervated implies that the nervous system is responsible for this effect.

Although intrauterine devices (IUDs) have an antifertility effect in several domestic animals, their apparent mode of action varies widely. The major antifertility effect of IUDs seems to be exerted between the time the embryo enters the uterus and the time of implantation. The insertion of large-diameter IUDs in sheep and cattle alter the estrous cycle by shortening the functional lifespan of the CL. In sheep, large-diameter IUDs inhibit sperm transport and fertilization.

CERVIX UTERI

The cervix is a sphincter-like structure that projects caudally into the vagina (Fig. 2-7). The cervix is a fibrous organ

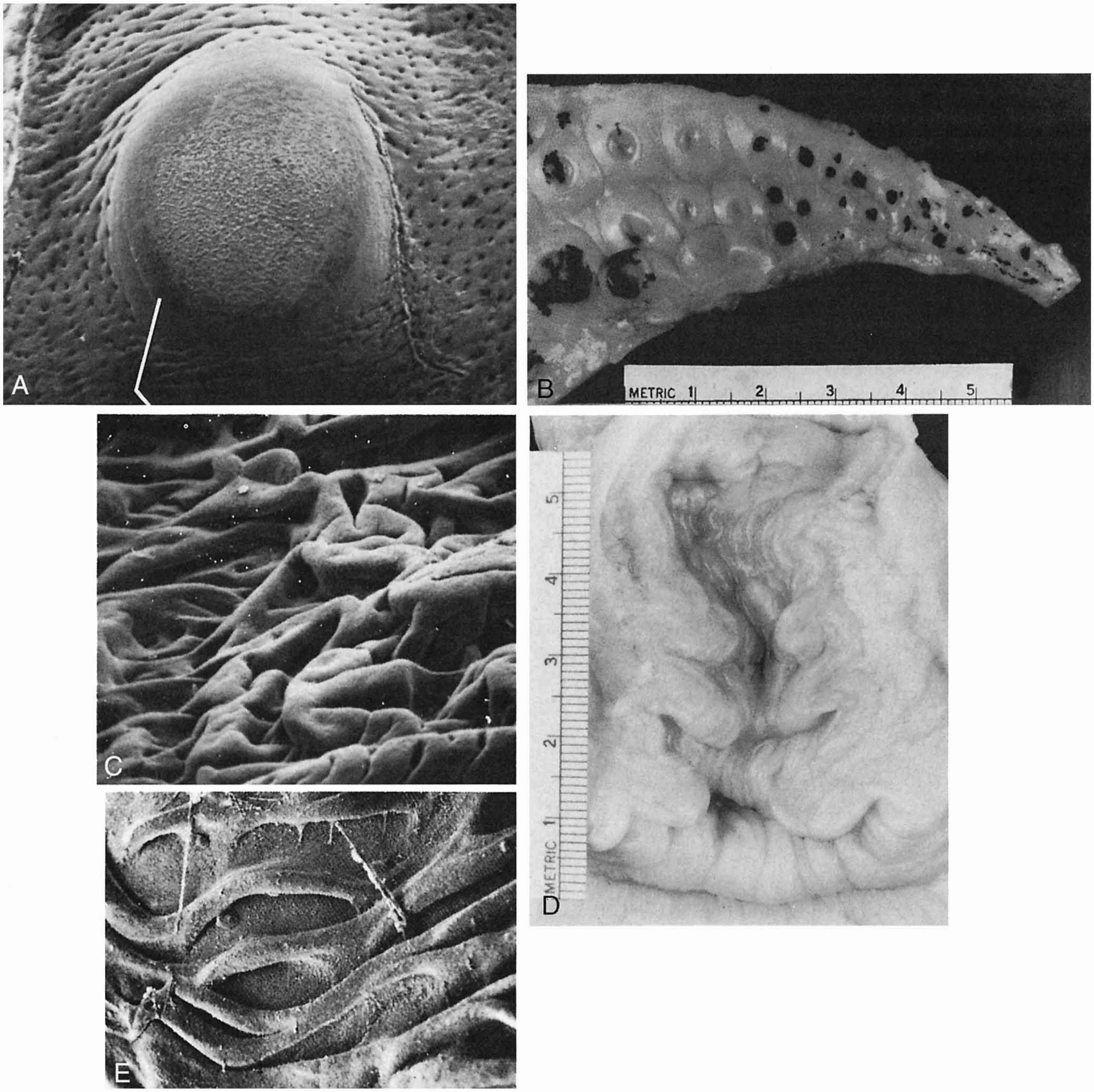

Figure 2-7. Scanning electron micrographs (SEM) of female reproductive organs. (A) Ovine endometrium: caruncle surrounded by openings of endometrial glands. (B) Mucosa of uterine horn of the nonpregnant ewe. Note caruncles and pigmentation of the endometrium. (C) Rabbit vagina showing the rugae of the vaginal epithelium for expansion during copulation and parturition. (D) Morphology and histology of the cervix (cut open) of a heifer four days after estrus. Note the annual rings around the cervical canal. (E) Bovine cervix showing complexity of cervical crypts (59™).

composed predominantly of connective tissue with only small amounts of smooth muscle tissue present. The cervix is characterized by a thick wall and constricted lumen. Although the structure of the cervix differs in detail among farm mammals, the cervical canal has various prominences. In ruminants these are in the form of transverse or spirally interlocking ridges known as *annular rings*, which develop to varying degrees in the different species. They are especially prominent in the cow (usually four rings) and in the ewe, where they fit into each other to close the cervix securely. In the sow, the rings are in a corkscrew arrangement that is adapted to the spiral twisting of the tip of the boar's penis. Distinguishing features of the mare's cervix are the conspicuous folds in the mucosa and the projecting folds into the vagina.

The cervix is tightly closed except during estrus, when it relaxes slightly, permitting sperm to enter the uterus. Mucus discharged from the cervix is expelled from the vulva.

Cervical Stroma and Physiologic Changes

The connective tissue of the cervical stroma is made of ground substance, fibrous constituents, and cellular elements. The ground substance contains proteoglycan, and hyaluronic acid, chondroitin-4,6-sulfate, dermatan sulfate, heparan sulfate, and keratan sulfate associated with proteins. The fibrous constituents include collagen, elastin, and reticulin. Cellular elements comprise mast cells, fibroblasts, and wandering cells. Collagen is made of chains of several amino acids such as glycine, proline, hydroxyproline, lysine, or hydroxylysine. The patterns of reticulin, elastin, and interfibrous ground substances facilitate the dilation of the cervix at delivery. The dissociation of the collagen fibers, which become widely separated from one another, causes the loosening of cervical tissues and increases clear spaces between collagen bundles.

Gross changes in the biochemical composition of the cervix during pregnancy indicate that the cervix during pregnancy is preparing for a change in its functional properties by alterations in the parameters that regulate the physical properties of connective tissue matrices. Morphologically, these pregnancy-related changes do not become apparent until quite late during gestation, when tissue breakdown and destruction of the collagen network become apparent.

During the course of pregnancy, the cervix may show as much as eightfold increase in mass. The enhanced growth and the decreased concentrations of the matrix components may be a consequence of several factors, including increased vascularization and increased concentrations of glycoproteins.

Cervical softening and ripening are not due exclusively to enzymatic activity involving only matrix degradation. The dynamic nature of the cervix at the time of parturition may provide an anabolic basis by which a new matrix with altered physical properties is produced. The major characteristics of the parturient cervix include (a) increased rates of proteoglycan and hyaluronate synthesis with a concomitant decrease in hexuronate concentration, (b) the appearance of a new type of proteoglycan, and (c) a breakdown in the structure and organization of the collagen network.

Cervical Mucus

Cervical mucus consists of macromolecules of mucin of epithelial origin which are composed of glycoproteins (particularly of the sialomucinous type) that contain about 25% amino acids and 75% carbohydrates. The mucin is composed of a long, continuous polypeptide chain with numerous oligosaccharide side chains. The carbohydrate portion is made of glactose, glucosamine, fucose, and silic acid. The proteins of cervical mucus include prealbumin, lipoprotein, albumin, β-globulins, and γ-globulins. The cervical mucus contains several enzymes, including glucuronidase, amylase, phosphorylase, esterase, and phosphatases.

Owing to its unique biophysical characteristics, the cervical mucus has several rheologic properties such as ferning, elasticity, viscosity, thixotrophy, and tack (stickiness). The cervical mucus during estrus shows a fern pattern of crystallization on drying on a glass slide. This fern pattern, associated with the high chloride content of the mucus, does not occur with drying of mucus obtained at stages of the cycle when progesterone levels are high or during pregnancy. The phenomenon may have some value, when combined with other observations, for early pregnancy diagnosis. The secretion of cervical mucus is stimulated by ovarian estrogen and inhibited by progesterone.

Cyclic qualitative changes in the cervical mucus throughout the estrous cycle and cyclic variations in the arrangement and viscosity of these macromolecules cause periodic changes in the penetrability of spermatozoa in the cervical canal. Optimal changes of cervical mucus properties—such as an increase in quantity, viscosity, ferning, and pH, and decrease in viscosity and cell content—occur during estrus and ovulation, and these are reversed during the luteal phase when sperm penetration in the cervix is inhibited. Under the influence of estrogens, the macromolecules of glycoprotein of the mucus are oriented so that the spaces between them measure 2 to 5μm. In the luteal phase, the spaces of the meshwork of macromolecules become increasingly smaller. Thus, at the time of estrus and ovulation, the larger size of the meshes allows the transport of sperm through the meshwork of filaments and through the cervical canal.

Functions

The cervix plays several roles in the reproductive process: (a) it facilitates sperm transport through the cervical mucus to the uterine lumen; (b) it acts as sperm reservoir; and (c) it may play a role in the selection of viable sperm, thus preventing the transport of nonviable and defective sperm.

SPERM TRANSPORT. Upon ejaculation, sperm are oriented toward the internal os. As the flagellum beats and vibrates, the sperm head is propelled forward in the channels of least resistance. The macrorheologic and microrheologic properties of cervical mucus play a major role in sperm migration. Sperm penetrability increases with the cleanliness of mucus, since cellular debris and leukocytes delay sperm migration. The aqueous spaces between the micelles permit the passage of sperm as well as diffusion of soluble substances. Proteolytic enzymes may hydrolyze the backbone protein or some of the crosslinkages of the mucin and reduce the network to a less resistant mesh with more open channels for the migration of sperm. When cervical mucus and semen are placed in apposition *in vitro*, phase lines immediately occur between the two fluids. Sperm phalanges soon appear and develop high degrees of arborization, the terminal aspects of which consist of channels through which one or two sperm can pass.

After mating or artificial insemination, massive numbers of sperm are lodged in the complicated cervical crypts. The cervix might act as a reservoir for sperm, thus providing the upper reproductive tract with subsequent releases of sperm. It is also possible that sperm that are trapped in the cervical crypts are never released, thus preventing excessive numbers of sperm from reaching the site of fertilization.

In ruminants prolonged survival of sperm in the cervix relative to other parts of the reproductive tract suggest that the cervix acts as a sperm reservoir. In the cervices of cattle and goats, most sperm are not randomly distributed but are located between cervical crypts. Penetration of sperm to these sites in the cervix depends on sperm viability and on the structure and, consequently, the rheologic properties of the cervical mucus.

THE CERVIX DURING PREGNANCY. During pregnancy, a highly viscid, nonferning, thick, and turbid mucus occludes the cervical canal, acting as an effective barrier against sperm transport and invasion of bacteria in the uterine lumen, thus preventing uterine infections. The only other time the cervix is open is before parturition. At this time the cervical plug liquefies and the cervix dilates to permit the expulsion of the fetus and fetal membranes.

THE VAGINA

The vaginal wall consists of surface epithelium, muscular coat, and serosa. The muscular coat of the vagina is not as well developed as the outer parts of the uterus. It consists of a thick inner circular layer and a thin outer longitudinal layer; the latter continues for some distance into the uterus. The muscularis is well supplied with blood vessels, nerve bundles, groups of nerve cells, and loose and dense connective tissue. The cow is unique in possessing an anterior sphincter muscle in addition to the posterior sphincter found in the other farm mammals.

There are species differences in vaginal changes during the estrous cycle. These differences probably reflect different secretion rates for estrogen and progesterone and ultimately for the gonadotrophins. Vaginal smears, however, are not useful in diagnosing the stage of the cycle or hormonal abnormalities.

The surface of the vaginal cells is made of numerous microridges that run longitudinally or in circles. In this multilayered stratified epithelium, the cells are wedged on each other by interlocking opposed microridges, thus forming a firm surface. The morphology and pattern of these microridges, which affect the firmness of the epithelium, vary throughout the reproductive cycle.

Physiologic Responses

VAGINAL CONTRACTIONS. Vaginal contractility plays a major role in psychosexual responses and possibly sperm transport. The contraction of the vagina, uterus, and oviducts is activated by fluid secreted into the vagina during precoital stimulation.

IMMUNOLOGIC RESPONSES. The vagina appears to be one of the major sites for sperm antigen-antibody reaction since the vagina is more exposed to sperm antigen than are the uterus and oviduct. Local production of antibodies to sperm antigens may occur within the vaginal tissue.

Immature and mature plasma cells, located beneath the epithelium, seem to be under endocrine control since these cells increase in number during the luteal phase, following ovariectomy and during the postmenopausal stage. These plasma cells seem to be involved in the secretion of immunoglobulins A and G, which seem to prevent bacterial infection and produce antibodies against spermatozoa.

VAGINAL FLUID. The vaginal fluid is composed primarily of transudate through the vaginal wall, mixed with vulvar secretions from sebaceous glands and sweat glands and contaminated with cervical mucus, endometrial, and oviductal fluids and exfoliated cells of the vaginal epithelium. As estrus approaches, the vascularity of the vaginal wall increases and the vaginal fluid becomes thinner.

A specific and distinct odor is present in the urogenital tract of cows during estrus. This odor apparently disappears or is greatly attenuated during diestrus. Dogs can be trained to detect and respond to the odors associated with estrus in cattle (7).

MICROBIOLOGIC FLORA. The vaginal flora is made of a dynamic mixture of aerobic, facultatively anaerobic, and strictly anaerobic microorganisms with new strains constantly being introduced. The flora of microorganisms varies throughout the life cycle. The various populations of microorganisms are equipped enzymatically to survive and replicate under a given vaginal environment. During periods of high glycogen content, acidophilic organisms predominate, but other organisms are present among the heterogeneous group making up the normal flora.

Functions of the Vagina

The vagina has multiple functions in reproduction. It is a copulatory organ in which semen is deposited and coagulated until sperm are transported through the macromolecules of the cervical mucus column. The dilated bulbous vagina provides a postcoital semen pool to supply sperm for cervical reservoirs. The rugae vaginales and the fence-like, rhomboidshaped arrangement of the musculature allow distention of the vagina during mating and parturition. Although the vagina contains no glands, its walls are moistened by transudates through the vaginal epithelium (incorrectly called *mucosa*), by cervical mucus, and by endometrial secretions.

Following ejaculation, the seminal plasma is not transported into the uterus; most of it is expelled or absorbed through the vaginal walls. Some of the biochemical components of the seminal plasma, when absorbed in the vagina, exert physiologic responses in other parts of the female reproductive tract.

The pH of the vaginal secretion is unfavorable to sperm. A complex interaction of the cervical mucus, vaginal secretion, and seminal plasma induces a buffering system that protects sperm until they are transported through the micelles of cervical mucus. Pathologic conditions resulting in insufficient buffering of the seminal pool (e.g., low volume of ejaculate, scanty amounts of thick cervical mucus, and leakage of semen) may cause rapid immobilization of spermatozoa. The vagina serves as an excretory duct for secretions of the cervix, endometrium, and oviduct; it also serves as the birth canal during parturition. These functions are accomplished through various physiologic characteristics, namely, contraction, expansion, involution, secretion, and absorption.

EXTERNAL GENITALIA

The vestibule, the labia majora, the labia minora, the clitoris, and the vestibular glands compose the external genitalia.

Vestibule

The junction of the vagina and vestibule is marked by the external urethral orifice and frequently by a ridge (the vestigial hymen). In some cattle, the hymen may be so prominent that it interferes with copulation.

The vestibule of the cow extends inward for approximately 10 cm, where the external urethral orifice opens into its ventral surface. Gartner tubes (remnants of the Wolffian ducts) open into the vestibule posteriorly and laterally to Gartner's ducts. The glands of Bartholin, which secrete a viscid fluid, most actively at estrus, have a tuboalveolar structure similar to the bulbourethral glands in the male.

Labia Majora and Labia Minora

The integument of the labia majora is richly endowed with sebaceous and tubular glands. It contains fat deposits, elastic tissue, and a thin layer of smooth muscle. It has the same outer surface structure as the external skin. The labia minora have a core of spongy connective tissue.

Clitoris

The ventral commissure of the vestibule conceals the clitoris, which has the same embryonic origin as the male penis. It is composed of erectile tissue covered by stratified squamous epithelium, and it is well-supplied with sensor nerve endings. In the cow, the greater part of the clitoris is buried in the mucosa of the vestibule. In the mare, however, it is well developed, and in the sow it is long and sinuous, terminating in a small point or cone.

Extensive investigations have been conducted on comparative anatomy of female reproductive organs of farm mammals (8–12).

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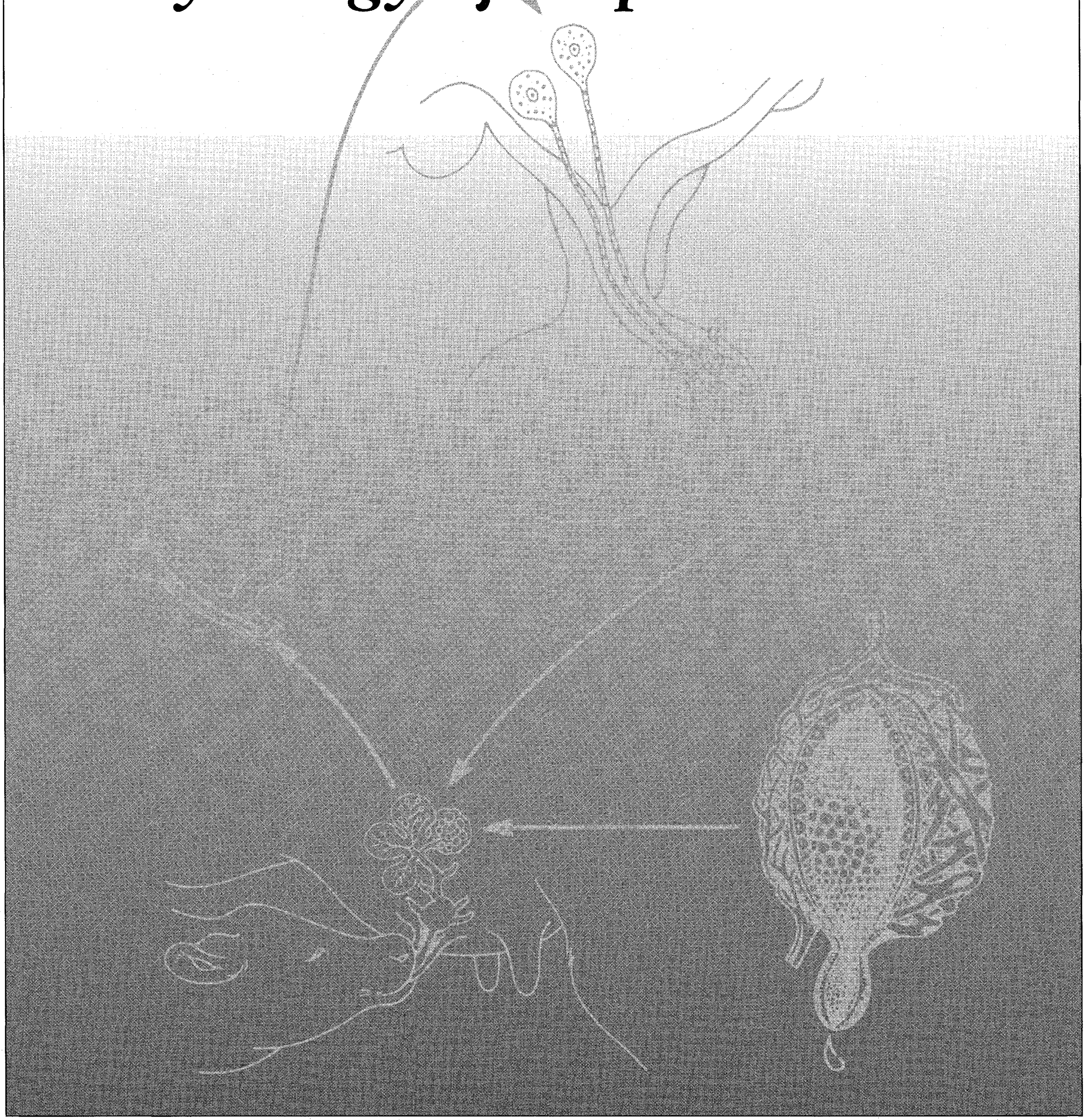
PART II

Physiology of Reproduction



Hormones, Growth Factors, and Reproduction

E.S.E. HAFEZ, M.R. JAINUDEEN, AND Y. ROSNINA

Over the passage of time, the control of mammalian reproduction has shifted from the central nervous system (CNS) to regulation by two separate systems, the CNS and the endocrine systems (Fig. 3-1). Then followed the discovery that the hypothalamus linked the two systems through the hypothalamo-hypophyseal portal system to coordinate the functions of the gonads. However, many phenomena could not be explained solely on neuroendocrine control. Therefore, the past decade has witnessed the discovery of chemical messengers (growth factors) and the presence of regulatory autocrine/paracrine systems within the gonads. These advances have helped to unravel phenomena that hitherto could not be explained solely on neuroendocrine control.

Both the endocrine and nervous systems function to initiate, coordinate, or regulate the functions of the reproductive system. Unlike the nervous system, which controls body function through rapid, electric nerve impulses e.g., musculoskeletal system, the endocrine system uses chemical messengers or hormones to regulate slow body processes, e.g., growth and reproduction.

The classic definition of a hormone is a physiologic, organic, chemical substance synthesized and secreted by a ductless endocrine gland, which passes into the circulatory system for transport. Hormones inhibit, stimulate, or regulate the functional activity of the target organ or tissue. However, organs like the uterus and the hypothalamus produce hormones, which do not meet the classic definition of a hormone.

Besides hormones from the endocrine glands, extensive investigations during the last decade have revealed the role of peptide growth factors, commonly known as "Growth Factors" in reproduction. Growth factors are hormone-related substances controlling the growth and development of several organs, tissues, and cultured cells. Unlike hormones, growth factors are produced and secreted by cells from different tissues to diffuse into target cells.

This chapter is presented in two sections. The first deals with the biochemical structure, modes of communication, and function feedback mechanisms of the major reproductive hormones in farm animals. The second section reviews Growth Factors, their mode of communication and roles in the reproductive process in farm animals. More details are found in later chapters.

ENDOCRINE GLANDS

Before discussing the hormones of reproduction, it is worthwhile to review briefly the functional anatomy of the hypothalamus, the pituitary, and the gonads.

Hypothalamus

The hypothalamus occupies only a very small portion of the brain. It consists of the region of the third ventricle, extending from the optic chiasma to the mammillary bodies (Fig. 3-2). There are neural connections between the hypothalamus and the posterior lobe through the hypothalamic-hypophyseal tract and vascular connections between the hypothalamus and the anterior pituitary lobe (Fig. 3-3). Arterial blood enters the pituitary by way of the superior hypophyseal artery and inferior hypophyseal artery. The superior hypophyseal artery forms capillary loops at the median eminence and pars nervosa. From these capillaries, blood flows into the hypothalamo-hypophyseal portal system, which begins and ends in capillaries without going through the heart. Part of the venous out flow from the anterior pituitary is by way of a retrograde back flow, which exposes the hypothalamus to high concentrations of anterior pituitary hormones. This blood flow provides the pituitary gland the negative feedback mechanism of regulating the functions of the hypothalamus. This type of feedback has been termed the short-loop feedback.

Pituitary Gland

The pituitary gland is located in the sella turcica, a bony depression at the base of the brain. The gland is subdivided

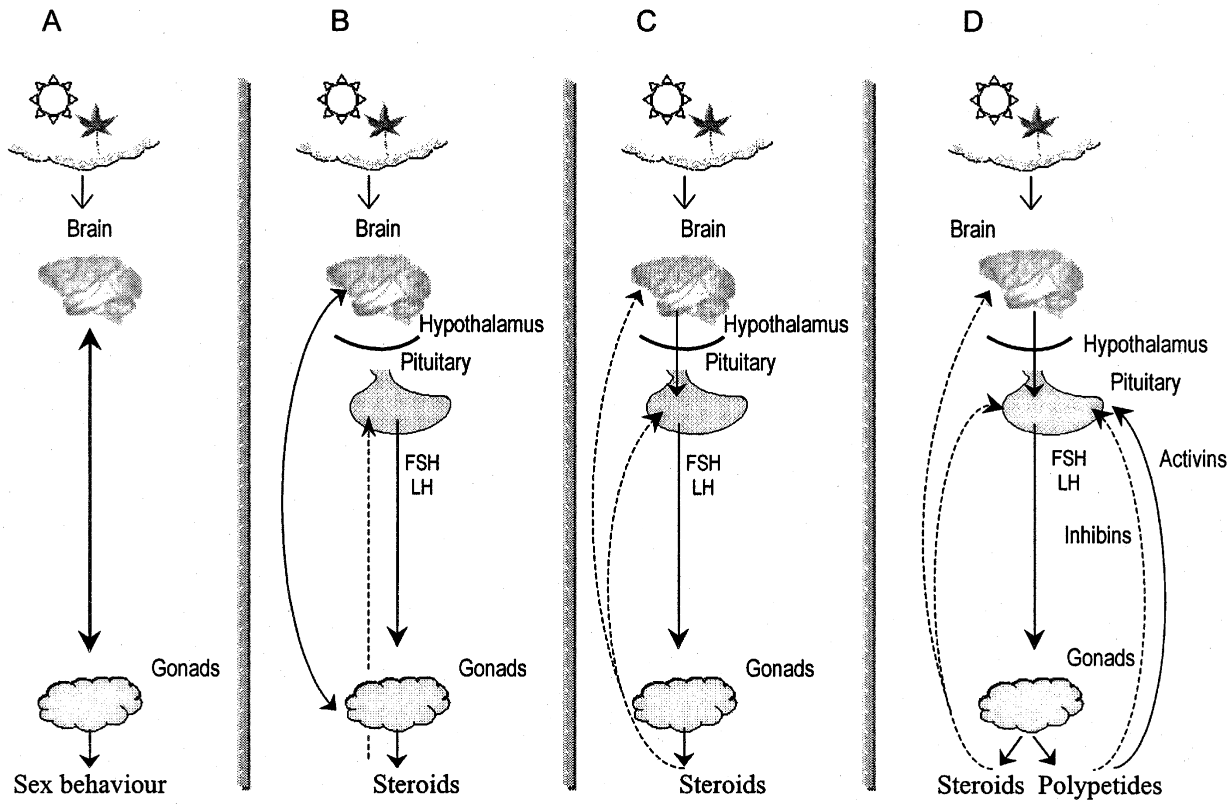


FIGURE 3-1. Chronology of the changing concepts on regulation of mammalian reproduction. (A) Central nervous system acts via nerve pathways (neural control). (B) The discovery of the endocrine system (ES) shifted the emphasis from the CNS to ES (endocrine control). The gonadotropic hormones from the anterior pituitary controlled gonadal hormone secretion (steroids). The steroids through a negative feedback mechanism decreased/increased hormone output from the anterior pituitary gland. (C) Later, the recognition of the hypothalamus-hypophyseal portal system provided the route for hypothalamic hormones to control the anterior pituitary gland (neuroendocrine control). (D) The intragonadal regulators or "growth factors" acting via autocrine/paracrine mechanisms modulate the secretion of pituitary gonadotropic hormones.

into three distinct anatomic parts: anterior, intermediate, and posterior lobes. There are remarkable species variations in the anatomy of the pituitary gland. For example, the pars intermedia is well developed in the hypophysis of cattle and horses.

The cell types in the anterior pituitary have traditionally been classified on their staining characteristics into agranular and granular chromophils. The chromophils are divided into acidophils and basophils. This classification has been revised with the advent of immunochemistry and electron microscopy. The anterior pituitary has five different cell types secreting six hormones. By cell type, the somatotropes secrete growth hormone, corticotropes secrete adenocorticotropic hormone (ACTH), mammotropes secrete prolactin, thyrotropes secrete thyroid stimulating hormone (TSH), and gonadotropes which secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Gonads

In both sexes, the gonads play a dual role: the production of germ cells (gametogenesis) and the secretion of gonadal hormones. The interstitial cells that are located among the seminiferous tubules are named the Cells of Leydig. The Leydig cells secrete testosterone in the male whereas the theca interna cells of the Graafian follicle are the primary source of circulating estrogens. Following rupture of the follicle (ovulation), the granulosa and thecal cells are replaced with the corpus luteum (CL) that secretes progesterone.

Pineal Gland

The pineal gland (epiphysis) originates as a neuroepithelial evagination from the roof of the third ventricle under the posterior end of the corpus callosum. The pineal gland of

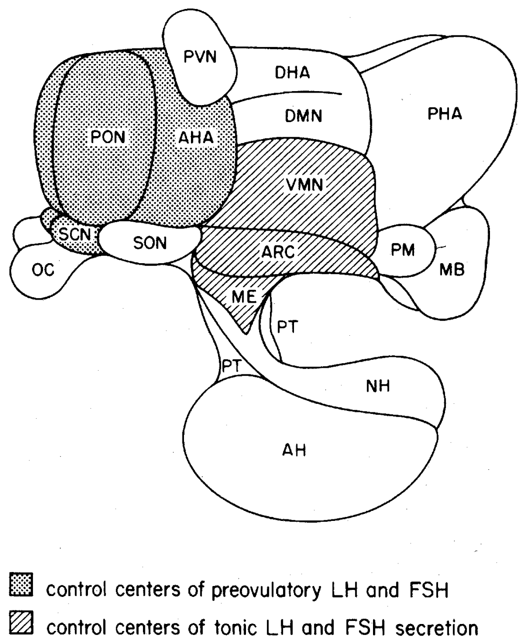


FIGURE 3-2. Schematic drawing of hypothalamic nuclei and pituitary. *AH*, adenohypophysis; *ARC*, arcuate nucleus; *AHA*, anterior hypothalamic area; *DHA*, dorsal hypothalamic area; *DMN*, dorsal medial nucleus; *ME*, median eminence; *NH*, neurohypophysis; *MB*, mammillary body; *PM*, premammillary nucleus; *OC*, optic chasm; *PVN*, paraventricular nuclei; *PON*, preoptic nuclei; *PHA*, posterior hypothalamic area; *PT*, pars tuberalis; *SCN*, suprachiasmatic nucleus; *SON*, supraoptic nuclei; *VMN*, ventromedial nucleus.

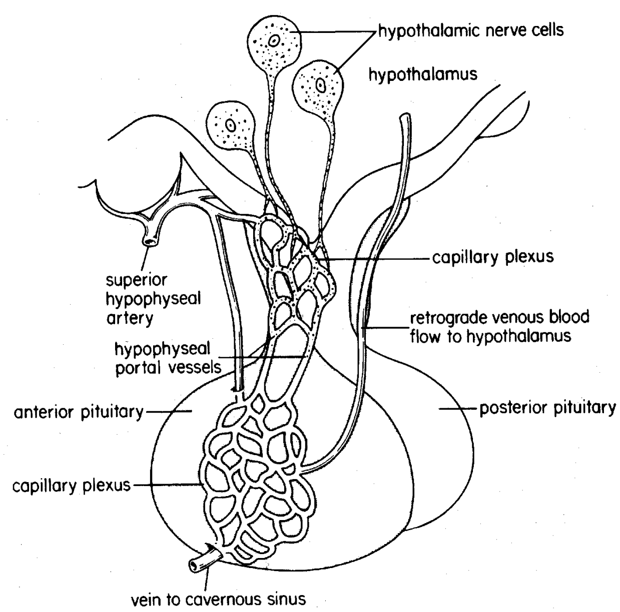


FIGURE 3-3. Hypothalamus-pituitary-gonadal complex. Hypothalamic nerve cells releasing neurohormones into the portal vessels for transport to the anterior pituitary via the hypothalamopypophyseal vessels. Solid particles in nerve cells represent neurohormones. Blood is transported by the retrograde venous system back to the hypothalamus.

the amphibian is a photoreceptor that sends information to the brain, whereas the mammalian pineal is an endocrine gland.

The hormonal activity of the pineal gland is influenced by both the dark-light cycle and the seasonal cycle, causing it to play an important role in the neuroendocrine control of reproduction. The gland converts neural information from the eyes about daylight length into an endocrine output of melatonin, which is secreted into the blood stream and cerebrospinal fluid.

Hormones

Hormones may be classified according to either their biochemical structure or mode of action. The biochemical structure of hormones includes glycoproteins, polypeptides, steroids, fatty acids, and amines.

Structure of Hormones

According to their chemical structure, the hormones of reproduction are divided into four groups:

Proteins: These are polypeptide hormones ranging from a molecular weight of 300 up to 70,000 daltons, e.g., oxytocin, FSH, and LH.

Steroids: These are derived from cholesterol and have a molecular weight of 300 to 400 daltons, e.g., testosterone.

Fatty acids: These are derived from arachidonic acid and have a molecular weight of about 400 daltons.

Amines: These compounds are derived from tyrosine or tryptophan, e.g., melatonin.

Modes of Intercellular Communication

The CNS was considered to be the coordinator of all body systems until the discovery of endocrine glands. Then the view became that regulation of reproduction was shared by two separate systems with the hypothalamus as the interface between the two systems. Currently, chemical messengers that do not fit either system—Growth Factors—are being discovered that play a role in the control of reproduction.

Cells communicate with each other via chemical messengers such as amines, amino acids, steroids, and polypeptides. Thus, there are four modes of intercellular communications:

Neural communication, in which neurotransmitters are released at synaptic junctions from nerve cells and act across narrow synaptic clefts between as neurotransmitters.

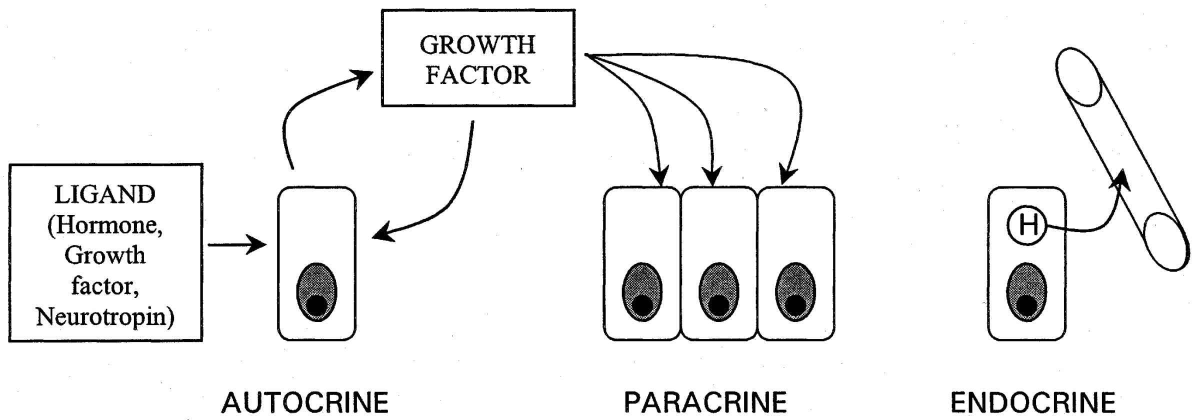


FIGURE 3-4. Modes of intercellular communication. Locally produced growth factors acting in an autocrine/paracrine manner mediate endocrine action in target cells.

Endocrine communication, in which hormones transported through blood circulation, typical of most hormones.

Paracrine communication, in which the products of the cells diffuse through extracellular fluid to affect neighboring cells that are at a distance., e.g., prostaglandins.

Autocrine communication, in which cells secrete chemical messengers that bind to receptors on the same cell that secreted the messenger (Fig. 3-4).

Regulation of Hormone Secretion

The nervous system plays an essential role in the regulation of gonadal activity by means of endocrine feedback mechanism, neural pathways, and immunoendocrine control.

ENDOCRINE FEEDBACK

Gonad. A target gland hormone (e.g., estrogen) can influence the secretion of the tropic stimuli that caused its own release (e.g., FSH). The feedback control occurs at the level of the hypothalamus and the pituitary gland (Fig. 3-3). Depending on their concentration in the blood, steroid hormones may exert a stimulatory (positive) or an inhibitory (negative) feedback.

Inhibitory or negative feedback. This system involves reciprocal interrelationships between two or more glands and target organs. For example, as stimulation of the ovary increases estrogen secretion, FSH levels decline. Similarly, when pituitary hormones reach a certain level, some hypothalamic nuclei respond by decreasing the production of their particular releasing hormone, a decline in secretion of pituitary tropic hormone, and a lower level of target gland function.

Stimulatory or positive feedback. In this system, an increasing level of hormone(s) causes subsequent increase of another hormone. For example, increasing levels of estrogen during the preovulatory phase trigger an abrupt release of pituitary LH. These two events are precisely synchronized, because a LH surge is necessary for the rupture of ovarian follicle.

Hypothalamic hormones. Both pituitary and steroid hormones regulate the synthesis, storage, and release of hypothalamic hormones through two feedback mechanisms: a long and a short loop. Long feedback involves interaction among the gonad, pituitary, and hypothalamus while the short feedback system permits pituitary gonadotropins to influence the secretory activity of the releasing hormones without mediation of the gonads (see Hypothalamus—retrograde back flow in the hypothalamus).

NEUROENDOCRINE REFLEX. Apart from the feedback mechanisms mentioned above, the nervous system may control release of hormones through neural pathways, e.g., oxytocin in milk-let down and LH release following copulation, as will be pointed out later.

IMMUNOENDOCRINE CONTROL. The endocrine and immune systems interact extensively to regulate each other. Several endocrine organs are involved in some aspect of this regulatory process: hypothalamus, pituitary, gonads, adrenals, pineal, thyroid, and thymus. Many of these organs are themselves affected by immune function.

Hormone Receptors

Each hormone has a selective effect on one or more target organs. This effect is achieved through two mechanisms:

Each target organ has a specific method of binding that hormone not found in other tissue.

The target organs have certain metabolic pathways capable of responding to the hormone-metabolic pathways not shared by nontarget tissue.

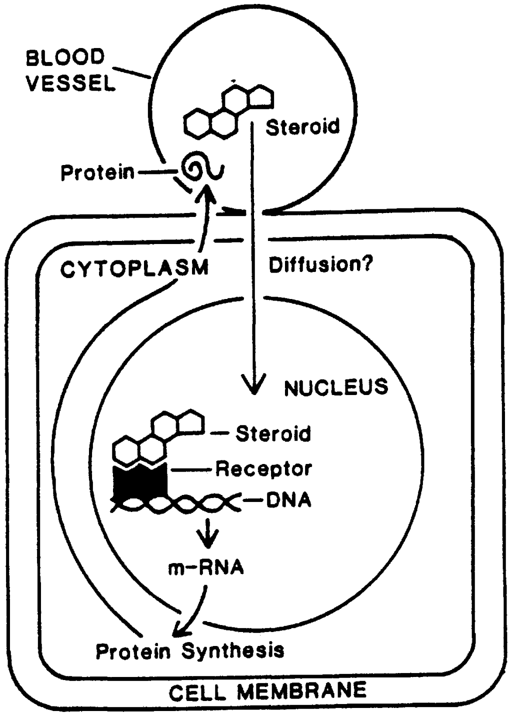


Figure 3-5. Schematic mechanism of action of steroid hormones. The steroid passes through the cell membrane and into the nucleus to bind to its receptor.

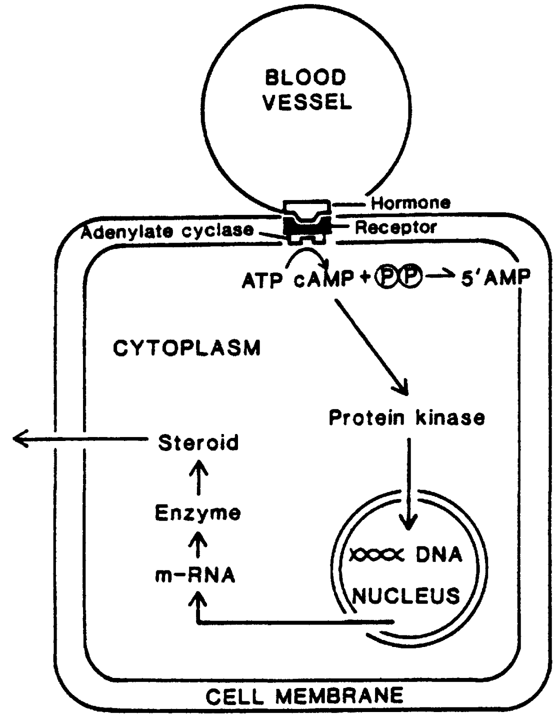


Figure 3-6. Schematic mechanism of action of protein hormones. The sequence of cellular events that occur following binding of a protein hormone to a receptor in the membrane of a target cell is shown.

Specific binding is the usual mechanism. For example, all target tissues that respond to steroid hormones contain a receptor protein within the cell, which specifically binds the activating hormone. Within the target cell, the steroid hormone is found in the cytoplasm, bound to a relatively large protein (molecular weight, 200,000 daltons). Binding results in transformation or activation of the steroid protein complex, allowing it to move (translocate) into the cell nucleus. At the nuclear site the steroid complex binds to specific receptor and causes a sequence of physiologic responses specific for that cell (Fig. 3-5).

The target cells of the anterior pituitary possess cell membrane receptors that recognize and selectively bind the protein hormones, including gonadotropins (Fig. 3-6). The binding phenomenon triggers the synthesis and secretion of the pituitary hormone via the cyclic AMP-protein kinase system of the cell. Estrogen levels, in turn, influence the gonadotropin receptors (1).

Hormone Assays

Several techniques are used to study endocrinology: ablation of a gland, organ replacement therapy, and isolation of hormones. Quantitative at measurements of hormones are based on bioassays, immunologic assays, and radioimmunoassays (RIAs).

Biologic assays have been used to measure activity of all hormones. The hormone is administered to the animal to induce a measurable biologic response. The RIA, one of the major advances in analytic endocrinology, allows rapid measurement of large numbers of samples containing low concentrations of hormones. The principle of the RIA is based on the theory that in the absence of unlabeled antigen or hormone (H), the labeled radioactive hormone (H*) has maximal opportunity to react with a limited number of antibody-binding sites (Ab).

Primary Hormones of Reproduction

Primary hormones regulate the various reproductive processes, whereas secondary or metabolic hormones indirectly influence reproduction. The latter hormones are not discussed in this chapter. The primary hormones are involved in many aspects of reproductive processes—spermatogenesis, ovulation, sexual behavior, fertilization, implantation, maintenance of gestation, parturition, lactation, and maternal behavior.

Reproductive hormones are derived primarily from four major systems or organs: various areas of the hypothalamus, anterior and posterior lobes of the pituitary gland, gonads (testis and ovary including their interstitial tissues and corpus luteum), and the uterus and placenta.