

Reproductive system

Article by:

Weichert, Charles K. College of Arts and Sciences, University of Cincinnati, Cincinnati, Ohio.

Wells, Lemen J. Formerly, Professor of Anatomy, University of Minnesota, Minneapolis, Minnesota.

Jost, Alfred Laboratoire de Physiologie du Developpement, Collège de France, Paris, France.

Chang, M. C. Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.

Harper, Michael J. K. Reproductive Biology Division, Center for Research, Department of Obstetrics and Gynecology, University of Texas-Health Science Center, San Antonio, Texas.

Hunter, R. H. F. School of Agriculture, University of Edinburgh, Edinburgh, United Kingdom.

Callard, Ian P. Department of Biology, College of Arts and Sciences, Boston University, Boston, Massachusetts.

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The structures concerned with the production of sex cells (gametes) and perpetuation of the species. The comparative anatomy, human histology, embryology, physiology, endocrinology, and biochemistry of this system are treated in this article.

The reproductive function constitutes the only vertebrate physiological function that necessitates the existence of two morphologically different kinds of individuals in each animal species, the males and the females (sexual dimorphism).

The purpose of the reproductive function is fertilization, that is, the fusion of a male and a female sex cell produced by two distinct individuals. In each sex, the reproductive system comprises a sex gland or gonad, which produces sex cells, or gametes, and ducts, which permit the passage of the gametes. In some animals, such as mammals, copulatory organs permit the male germ cells to be introduced into the female ducts and fertilization is internal, but in many vertebrates, such as anuran amphibians and many fishes, no copulatory organ exists and fertilization is external.

Comparative Anatomy

Egg cells, or ova, and sperm cells, or spermatozoa, are formed in the primary reproductive organs, which are collectively known as gonads. Those of the male are called testes; those of the female are ovaries. Besides giving rise to reproductive cells, both ovaries and testes give off endocrine secretions, or sex hormones, which pass into the blood or lymphatic streams

and are carried to all parts of the body, where they bring about profound effects, not only on the rest of the reproductive system but on several other systems of the body as well. The gonads are paired structures, although in some forms what appears to be an unpaired gonad is the result either of fusion of paired structures or of unilateral degeneration.

The reproductive elements formed in the gonads must be transported to the outside of the body. In most vertebrates, ducts are utilized for this purpose. These ducts, together with the structures that serve to bring the gametes of both sexes together, are known as sex organs. The structures used to transport the reproductive cells in the male are known as deferent ducts and those of the female as oviducts. In a few forms, no ducts are present in either sex, and eggs and sperm escape from the body cavity through genital or abdominal pores. The deferent ducts are usually the mesonephric or Wolffian ducts, which in some cases also serve to carry urinary wastes in those vertebrates in which opisthonephros or mesonephros function either during embryonic or adult life. In vertebrates whose functional adult kidney is the metanephros, the Wolffian duct on each side persists as the ductus deferens. See also: [Kidney \(/content/kidney/364000\)](#)

In most vertebrates, the reproductive ducts in both sexes open posteriorly into the cloaca. In some, modifications of the cloacal region occur and the ducts open separately to the outside or, in the male, join the excretory ducts to emerge by a common orifice. See also: [Animal reproduction \(/content/animal-reproduction/581200\)](#); [Copulatory organ \(/content/copulatory-organ/161360\)](#)

The sex of an individual is dependent upon the chromosomes received from both parents at the time that the egg is fertilized. That the balance between maleness and femaleness is a delicate one, however, is reflected in the fact that environmental factors may assume an influential role in sexual development, and hormonal secretions may modify the extent to which various structures and even behavioral characteristics develop and are maintained.

Ovaries

A typical mammalian ovary is a solid, irregularly shaped structure indistinctly separated into an inner medulla and an outer cortex. The cortex contains numbers of ovarian follicles in various stages of development. See also: [Ovary \(/content/ovary/479400\)](#)

In certain fishes and in amphibians, snakes, and lizards, the ovaries are hollow, saccular structures. The cavity within the teleostean fish ovary is actually a closed-off portion of the coelom (body cavity) into which ripe ova are shed. This is not true of the saccular ovaries of other forms.

Cyclostomes

The adult female lamprey has a single ovary, representing a fusion of two, which runs the length of the body cavity, suspended from the middorsal body wall by a single mesovarium. At the height of the breeding season, it fills the greater part of the body cavity; ripe eggs are shed into the coelom and fertilization is external. The hagfish is hermaphroditic; the anterior part of the single gonad is ovarian and the posterior part is testicular. Usually only one or the other region matures.

Fishes

The ovaries of most fishes are paired, although in some cases they have fused into a single organ. The large eggs of elasmobranchs are discharged from the anteriorly located ovaries directly into the body cavity. In oviparous and ovoviviparous species, following ovulation the ovarian follicles become transformed into corpora lutea, structures which presumably have an endocrine function and may play a role in the extended retention of eggs in the oviducts of oviparous species and of young in the uteri of ovoviviparous forms. Peritoneal folds form in connection with each ovary in teleosts, closing off all connection with the coelom. The anterior end of the ovarian cavity ends blindly, but in most cases continuations of the folds at the posterior

end form an oviduct which opens directly to the outside. Ripe ova, sometimes numbered in the millions, are discharged into the central ovarian cavity, which is actually a part of the body cavity, and thence pass down the oviducts to the outside. The garpike *Lepisosteus* is the only ganoid fish with a saccular ovary. The ovaries are usually solid, flat elongate structures from which mature ova break out into the coelom.

Amphibians

Although the paired amphibian ovaries are saccular structures, ripe ova are liberated into the body cavity through their external walls. The shape of the ovaries varies with the shape of the body. They are long and narrow in caecilians, elongated to a lesser degree in salamanders, and short and more compact in frogs and toads. Fat bodies are associated with amphibian ovaries. They serve for the storage of nutriment and undergo profound changes during the year. A peculiar structure in the male toad, known as Bidder's organ, may under certain conditions develop into a true ovary.

Reptiles

The saccular ovaries of snakes and lizards are similar to those of amphibians, whereas turtles and crocodilians have solid ovaries. In snakes and lizards, they are elongated but not symmetrically disposed. Only the yolk of reptilian eggs is formed in the ovaries, and this represents the true ovum. The size of the eggs is generally in proportion to that of the animal. In certain ovoviviparous snakes and lizards, corpora lutea form from ruptured follicles after ovulation and persist throughout pregnancy. These probably secrete a hormone necessary for maintenance of pregnancy.

Birds

Although both ovaries are present during embryonic development in most birds (except many birds of prey), the right ovary degenerates and only the left is functional. In birds, stalks extend from the surface of the ovary, and each stalk contains many ovarian follicles in various stages of development. A mature ovum escapes from the ovarian follicle through a preformed nonvascular band, the stigma or cicatrix, located on the surface of the follicle opposite the stalk. As in reptiles, only the yolk of the egg represents the true ovum. Increase in the number of hours of daylight stimulates ovarian activity in many birds. Even brief exposure to intense and bright light during hours of sleep increases production of eggs in the domestic fowl. This effect is undoubtedly mediated through stimulation of the pituitary gland. If the functional ovary of the domestic fowl is removed, the rudimentary right gonad will develop into a testislike organ, but without germ cells. See also: [**Sexual dimorphism \(/content/sexual-dimorphism/617800\)**](#)

Mammals

The ovaries of mammals are located in the lumbar or pelvic regions and are small in comparison to the size of the body. The relationship of the microscopic mammalian ovum to the ovarian follicle differs somewhat from conditions in other vertebrates. Follicles in various stages of development, with the youngest near the surface of the ovary, are depicted in **Fig. 1**. At periodic intervals, one or more follicles grow to maturity, rupture, and liberate their ova into the body cavity. In such animals as the rabbit, cat, and ferret, ovulation will not occur unless the animal copulates. Following ovulation, certain cells of the follicle undergo a transformation and the entire structure becomes a more or less solid body, the corpus luteum.

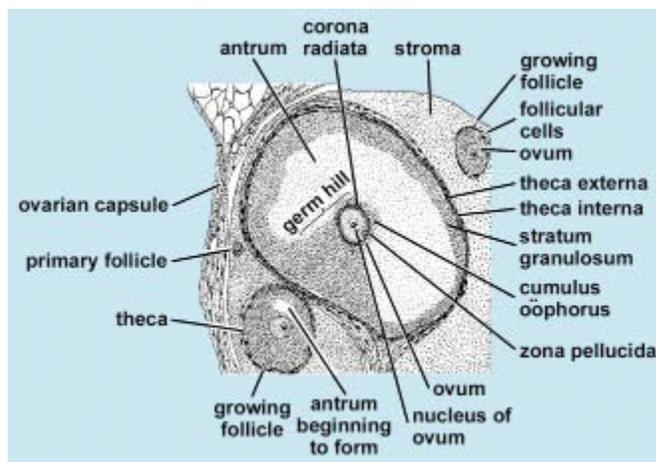


Fig. 1 Section of portion of cortex of rat ovary, showing ovarian follicles in various stages of development, the youngest being near the surface of the ovary. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

If pregnancy does not occur, the corpus luteum persists only for a short time. If pregnancy does ensue, the corpus luteum usually persists throughout pregnancy. In either case, it ultimately degenerates. The corpus luteum is of primary importance as an endocrine gland secreting a hormone called progesterone. See also: [Pregnancy \(/content/pregnancy/543100\)](#)

Oviducts and associated structures

Oviducts, except in teleosts and a few other fishes, are modifications of Müllerian ducts formed early during embryonic development. In most cases, each duct is formed by an invagination of the peritoneum that covers the ventrolateral part of the opisthonephros or mesonephros. The edges of the groove fuse to form a tube which joins the cloaca or forms a uterus posteriorly and remains open anteriorly to become the ostium tubae. Although Müllerian ducts also form in the male, they ordinarily degenerate except for a few vestigial remnants. In some, they persist as prominent but nonfunctional structures.

Cyclostomes

Oviducts are lacking in cyclostomes. Ova pass from the coelom through genital pores into a urogenital papilla and then to the outside.

Fishes

Much diversity exists in the oviducts of fishes. In some teleosts, and in a few other fish, eggs escape from the body cavity through modified abdominal pores. In elasmobranchs, the two Müllerian ducts may fuse at their anterior ends so that only a single ostium tubae connects with the coelom. An enlargement, known as the shell gland, is present in the upper part of each oviduct. Beyond the shell gland, the Müllerian duct enlarges on each side to form a uterus which opens into the cloaca.

The oviducts of most teleosts are short and continuous with the cavities of the saccular ovaries. It is doubtful whether they are true Müllerian ducts because they are formed in a different manner. A cloaca is lacking in teleosts, and the oviducts open independently to the outside. The two oviducts usually fuse, continuing posteriorly as a single structure which may open to the outside through a genital pore or else at the tip of a genital papilla. Most teleosts are oviparous, but many are ovoviviparous. Although the young may develop within the cavities of the ovaries, intrauterine development is more common. The size of the oviducts fluctuates markedly with the seasons. They are naturally largest during the breeding period.

Amphibians

Oviducts in amphibians are paired elongated tubes, each with an ostium tubae situated well forward in the body cavity. The

posterior end of each oviduct is enlarged slightly to form a short uterus which opens into the cloaca. In almost all forms, the uteri serve only as temporary storage places for ova that are soon to be laid. In some toads, the two uteri unite before entering the cloaca by a common orifice. Marked fluctuation in size of the oviducts is apparent at different seasons (**Fig. 2**). During the breeding period, they become elongated and coiled. The glandular lining secretes a clear gelatinous substance (jelly) which is deposited about each ovum as it passes down the oviduct. External fertilization is the general rule in frogs and toads, but in salamanders, with few exceptions, internal fertilization takes place. No copulatory organs are present. A diverticulum, the spermatheca, of the salamander's cloaca serves as a storage place for spermatozoa. The males deposit spermatophores (small packets of spermatozoa) which are taken into the cloaca of the female by muscular movements of the cloacal lips. Internal fertilization occurs in caecilians, the male of which has an eversible cloaca which may serve as a copulatory organ.

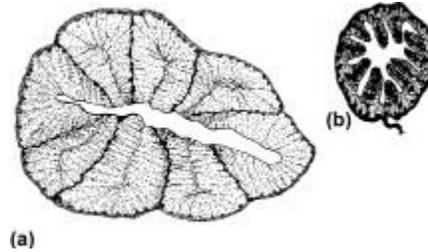


Fig. 2 Cross section of oviduct of the salamander *Eurycea bislineata*. (a) During breeding season. (b) After breeding season. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

Reptiles

The paired oviducts of reptiles open into the coelom through large, slitlike ostia. Each oviduct is differentiated into regions which mediate different functions in forming the layers of materials deposited about the ova prior to laying. The eggshell, which is of parchmentlike consistency, except in some lizards and in crocodylians in which it is hard, is formed in the uterus. Fertilization is always internal in reptiles, copulatory organs being present in the male, with the exception of the primitive *Sphenodon*. Most reptiles are oviparous, but many snakes and lizards are ovoviviparous.

Birds

The right oviduct usually degenerates in birds and only the left one is functional (birds of prey being exceptions). The egg enters the coiled oviduct through the ostium and passes through a glandular region, an isthmus, and a uterus. Two layers of albumen are deposited about the ovum in the glandular region; inner and outer shell membranes and more albumen are laid down in the isthmus; the hard calcareous shell is formed in the uterus. In the hen, these processes take 21–23 h. Fertilization is internal in birds and, in a majority of species, is accomplished by cloacal apposition of the two sexes.

Mammals

Paired Müllerian ducts develop in all mammalian embryos. Each differentiates into an anterior, nondistensible Fallopian tube and a posterior, expanded uterus. In all mammals except monotremes, the uterus leads to a terminal vagina which serves for the reception of the penis of the male during copulation.

The lower part, or neck, of the uterus is usually telescoped into the vagina to a slight degree. This portion is referred to as the cervix.

In the primitive monotremes, a cloaca is present in the adult, and each uterus terminates independently in a urogenital sinus anterior to the region where ureters and bladder enter. Marsupials retain the primitive paired condition, but two vaginas open

into a common urogenital sinus. In some mammals, the kangaroo for example, the vaginas fuse at their upper ends to form a vaginal sinus which extends posteriorly as a blind pocket or tube. It is sometimes referred to as a third vagina and may serve as the birth canal. Its posterior end connects with the urogenital sinus. In the event that this pouchlike structure has no opening, its wall ruptures at the time of delivery, thus permitting the young, lodged in it, to pass directly into the urogenital sinus. Placental mammals have a single vagina which represents a fusion of two; only the pika, which is a lagomorph, has a cloaca in the adult form.

The uterine portions of the Müllerian ducts fuse to varying degrees, resulting in different types of uteri (**Fig. 3**). The simplex type, found in apes and humans, represents the greatest degree of fusion. Only the bilaterally disposed Fallopian tubes indicate the paired origin of this type of uterus. Anomalous uteri of the duplex, bipartite, and bicornuate types are occasionally encountered in the human being.

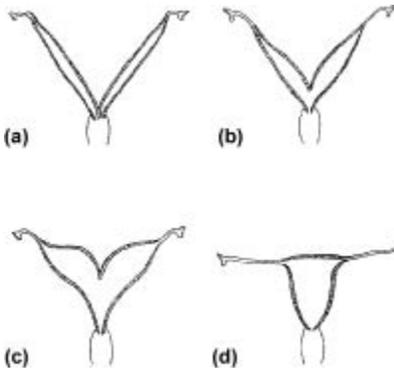


Fig. 3 Degrees of fusion of the uterine portions of the Müllerian ducts in four types of mammalian uteri. (a) Duplex (rat). (b) Bipartite (pig). (c) Bicornuate (horse). (d) Simplex (human). (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

The urethra, coming from the bladder, may join the vagina to form a urogenital sinus, or vestibule, which opens to the outside. Often, a more or less complete fold of mucous membrane, called the hymen, marks the border of the vagina where it opens into the vestibule. The external part of the female reproductive system is called the vulva. In primates, two folds of skin, the labia minora, are located about the margins of the opening of the vestibule. In some apes, and in the human female (**Fig. 4**), two additional outerfolds, the labia majora, make up part of the vulva. A small erectile organ, the clitoris, homologous with the penis of the male, lies ventral to the vaginal orifice. It differs from the penis, however, in that it has no connection with the urethra except in a few forms such as rats and mice.

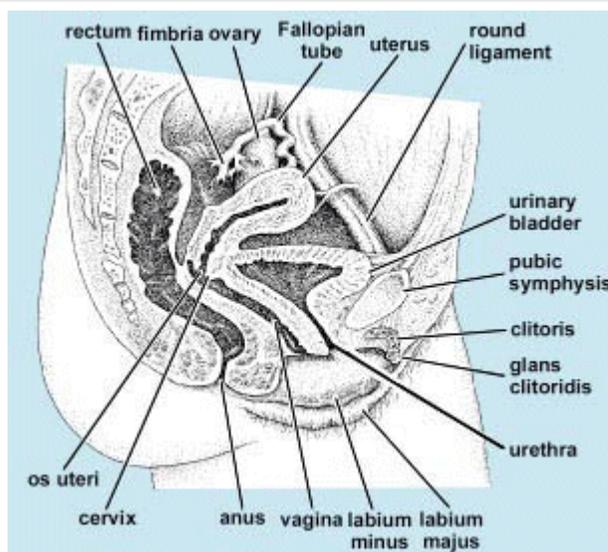


Fig. 4 Urogenital system of the human female. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

In addition to the above structures, certain glands, as well as rudiments remaining from the degenerated mesonephros, are associated with the female reproductive system. Glands of Bartholin correspond to Cowper's glands (bulbourethral glands) of males. They open into the vestibule near the hymen and secrete a clear, viscid fluid under sexual excitement. This serves as a lubricant during copulation. Paraurethral glands (of Skene), corresponding to the prostate glands of males, are occasionally encountered in females but are inconstant in appearance and of doubtful function. Small, mucus-secreting, vestibular glands, homologous with the glands of Littre of the male, are located around the opening of the urethra and on the clitoris. Among the remnants of the degenerated mesonephros that are associated with the reproductive organs of the female is the epoophoron, a complex of degenerate anterior mesonephric tubules connecting to a persistent portion of the Wolffian duct. The paraoophoron, a similar group of more posterior tubules, is located farther caudad. Both epoophoron and paraoophoron are situated in the broad ligament near the ovaries. A canal of Gärtner, located in the wall of the uterus or vagina, represents a vestige of the Wolffian duct proper. None of these structures is functional.

The epithelium that lines the Fallopian tube consists of two kinds of cells: ciliated cells, which are most numerous on the fimbriated funnel surrounding the ostium tubae, and others of a glandular nature. No true glands are present here, however. The beat of the cilia is abovarian in direction, and this, together with the peristaltic muscular contractions, serves to transport ova down the Fallopian tube. In most species of mammals, it takes 3 or 4 days for fertile ova to pass down the Fallopian tube to the uterus. If fertilization does not occur, the ova die and probably disintegrate before they have even reached the uterus.

Testes

The typical testis is a compact organ which varies greatly in shape in different groups of vertebrates. In all but a few primitive forms, each testis is composed of numbers of seminiferous ampullae or seminiferous tubules which connect by means of ducts to the outside. Spermatozoa are formed within the tubules or ampullae. See *also*: [Testis \(/content/testis/686100\)](#)

In seasonal breeders, the size of the testes fluctuates with the seasons, being largest just before the breeding season. After this period, they shrink to only a fraction of their former size. Each testis is suspended from the middorsal body wall by a membrane, the mesorchium.

Cyclostomes

The gonad of the male lamprey differs little in general appearance from that of the female. It is a single organ, representing a fusion of two, and is suspended from the middorsal body wall by a single mesorchium. Even when fully developed the testis does not become as voluminous as does the ovary in the female. Spermatozoa are discharged into the body cavity from which they escape via genital pores through a urogenital papilla. The hermaphroditic gonad of the hagfish has already been mentioned.

Fishes

In elasmobranchs, the paired testes are relatively small compact structures located at the anterior end of the coelom. In most other fishes, they are elongated and often lobulated. Ducts transport spermatozoa to the outside. Male gonads vary greatly in size and are extremely large at the breeding season. In some teleosts, interstitial cells lie in spaces among the seminiferous ampullae or tubules; in others, they form part of the walls of ampullae and show seasonal variation in appearance and activity.

Amphibians

The shape of the testes of amphibians is roughly correlated with that of the body. Thus, in caecilians, each testis is elongated

and resembles a string of beads. The enlargements consist of masses of seminiferous ampullae connected by a longitudinal collecting duct. In salamanders, the testes are shorter and irregular in outline; in frogs and toads, they are small, oval, compact structures. A pronounced difference in size is apparent during the breeding season. Fat bodies are associated with the gonads of male as well as of female amphibians.

Reptiles

Reptilian testes are round, oval, or pyriform in shape and contain seminiferous tubules that are long and convoluted. In snakes and lizards, one testis usually lies farther forward in the body cavity than the other. Periodic fluctuations in size of the testes are typical.

Birds

The round or oval shape of bird testes is characteristic. In the domestic fowl, the testes function throughout the year and no periodic variations in size are obvious. Most birds, however, are seasonal breeders, the testes enlarging conspicuously at the approach of the breeding season. Increase in the number of hours of daylight stimulates spermatogenesis in certain birds and hence brings about testicular enlargement, this generally occurring in spring.

Mammals

In all mammals except monotremes, the oval-shaped testes move from their place of origin to the pelvic region, where they may remain permanently, or they may descend farther into a pouchlike scrotum. In many seasonal breeders, the testes are located in the scrotum only during the breeding period. The scrotum serves as a temperature regulator, providing an environment for the testes several degrees below that of the body. This seems to be a requirement for normal development of spermatozoa. In marsupials the scrotum lies anterior to the penis but in other mammals it is posterior to that organ. In several species, a relation between the number of hours of daylight and testicular activity has been demonstrated.

Male ducts

The ducts which in most vertebrates serve to transport spermatozoa to the outside of the body are the archinephric ducts or Wolffian ducts formed in connection with the opisthonephros or mesonephros, respectively. Their original function is elimination of urinary wastes. In some fishes and amphibians, certain modified kidney tubules are employed in carrying spermatozoa from the testis to the archinephric duct. The tubules are known as efferent ductules, and the duct is termed the ductus deferens. The male ducts undergo profound changes in size in seasonal breeders (**Fig. 5**). Reproductive ducts are lacking in cyclostomes.

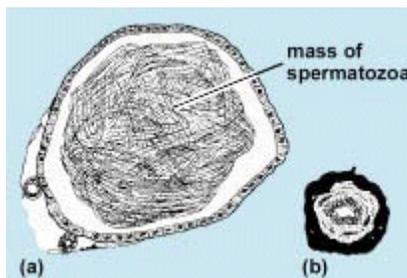


Fig. 5 Cross section of ductus deferens of male salamander *Eurycea bislineata*. From specimen obtained (a) just prior to breeding season; (b) several weeks after breeding season. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

Fishes

A variety of conditions is encountered in the reproductive system of male fishes. In elasmobranchs, small efferent tubules course from the testis through the mesorchium, connecting with some anterior kidney tubules along the medial border of the opisthonephros. The kidney tubules lead to the archinephric duct, which now serves almost entirely as a ductus deferens. The ductus deferens courses along the ventral side of the opisthonephros. In young specimens, it is a straight tube with a urinary function; in older individuals, it is highly convoluted. The posterior end is markedly dilated to form a seminal vesicle. The two seminal vesicles open into a common urogenital sinus which enters the cloaca through an aperture at the tip of a urogenital papilla. A pair of blind sperm sacs projects forward from the ventral wall of the urogenital sinus. These sacs may be remnants of the Müllerian ducts which persist in the male.

In most other fishes, the kidney ducts serve only for the passage of urinary wastes. The sperm duct, which is not a true ductus deferens because it is formed in a different manner, may be entirely independent of the kidney duct, although the two may have a common opening to the outside.

Amphibians

The arrangement of the male ducts in amphibians rather closely resembles that of elasmobranch fishes. In salamanders, the ductus deferens courses outside the lateral border of the kidney (**Fig. 6**). Small efferent ductules from the testis join Bidder's canal, a duct lying medial to the kidney. This in turn connects to the ductus deferens by means of modified kidney tubules. In frogs and toads, both Bidder's canal and the ductus deferens lie within the opisthonephros. A Bidder's canal is also present in the female, but its function, if it has any, is obscure. In caecilians, the longitudinal collecting duct, which connects the lobules of the testis, gives off small, transverse canals between successive lobules. These pass to the kidney to join another longitudinal duct which runs along the lateral edge of the opisthonephros. Spermatozoa then pass through a second series of transverse canals to join kidney tubules which transport them to the archinephric duct which joins the cloaca posteriorly. In males of several species of frogs and toads, a dilation of the archinephric duct, or ductus deferens, as it nears the cloaca, forms a seminal vesicle in which spermatozoa may be stored temporarily. Ductus deferens, and seminal vesicles when present, undergo striking seasonal variations in size, being controlled by changes in the level of testosterone, the hormone secreted by the testes. The cloacal glands of male urodeles, which secrete a jellylike material used in forming the spermatophores deposited by the male, become markedly enlarged as the breeding season approaches.

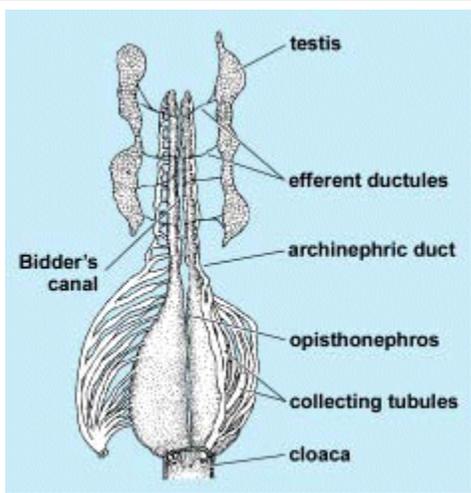


Fig. 6 Urogenital organs of male salamander, ventral view. The collecting ducts on the right side are shown detached from the cloaca and spread out for clarity. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

Reptiles

When the embryonic mesonephros degenerates in male reptiles, its duct (archinephric or Wolffian duct) persists as the

reproductive duct. The end near the testis becomes greatly convoluted and is called the epididymis. This connects with the testes by means of a few persistent mesonephric tubules which serve as efferent ductules. The remainder is the ductus deferens, sometimes straight and sometimes convoluted. In snakes and lizards, this joins the ureter of the metanephros before entering the cloaca. In turtles and crocodylians, these ducts open at the proximal end of a groove which carries spermatozoa to the free end of the penis. Seasonal variations under endocrine control are obvious in the epididymides and deferent ducts of most reptiles. In many, some of the posterior urinary tubules of the metanephros enlarge during the breeding season, producing an albuminous secretion which contributes to the seminal fluid. Glandular secretions from the cloacal walls in snakes and lizards pass into the grooves of the hemipenes. Nonfunctional Müllerian ducts, usually much reduced in size, commonly persist in male reptiles.

Birds

The reproductive ducts of male birds are essentially similar to those of reptiles but open independently into the cloaca. In the few birds that possess a penis, a groove on the upper surface carries spermatozoa to the apex. In some passerine birds, a nodule, composed of a tightly coiled portion of the ductus deferens, protrudes into the cloaca. The temperature of the nodule is somewhat lower than body temperature. This may be of importance in the maturation of spermatozoa.

Mammals

A few persistent mesonephric tubules connect the seminiferous tubules of each testis to a compactly coiled epididymis which is continuous with the ductus deferens. In man, the portion of the Wolffian duct included in the epididymis averages 20 ft (6 m) in length. Experiments have demonstrated that, during their passage through the epididymis, spermatozoa, although remaining quiescent, acquire the capability of becoming fully motile. In mammals having scrotal testes, the ductus deferens enters the body cavity lying between the peritoneum and the body wall. It crosses in front of the ureter, loops over that structure, and then courses posteriorly for a short distance before joining the urethra (**Fig. 7**). This peculiar arrangement is the result of the descent of testes from their original abdominal location. In many mammals, the ductus deferens enlarges at its posterior end to form an ampulla. A glandular seminal vesicle may arise on each side as a saccular diverticulum of the ductus deferens. It does not store spermatozoa, but its secretion contributes to the seminal fluid in which spermatozoa are suspended. Seminal vesicles are absent in monotremes, marsupials, carnivores, and whales. The lower portion of the ductus deferens, between seminal vesicle and urethra, is often called the ejaculatory duct. The urethra, coming from the bladder, extends the length of the penis, opening at the tip of that organ through a small meatus. It serves both for passage of urine and seminal fluid. Accessory glands associated with the urethra include the prostate gland, which contributes to the seminal fluid; Cowper's glands, which secrete a clear, viscid fluid during sexual excitement; and small, mucus-secreting urethral glands. In some mammals, as in the rat, when the secretions of the seminal vesicles and prostate gland are intermingled, they coagulate, so that just after mating a so-called copulation plug is present in the vagina. This aids in retaining spermatozoa in the reproductive tract of the female. The development and functioning of the accessory sex organs in mammals are clearly under control of the hormone testosterone. A few remnants of the mesonephros may persist in male mammals in close relation to the reproductive systems. Among these are the paradidymis, a few aberrant ductules, and the appendix of the epididymis. Persistent homologs of the Müllerian ducts may also be present in males. The small appendix of the testis and the prostatic utricle represent such remnants.

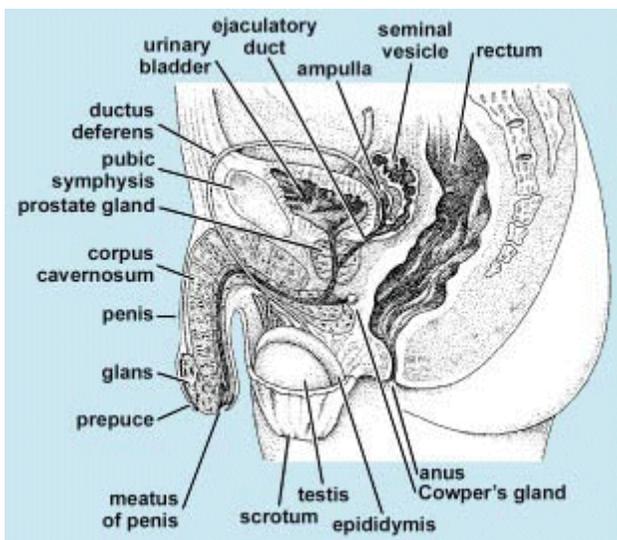


Fig. 7 Urogenital system of the human male. (After C. K. Weichert, *Elements of Chordate Anatomy*, 3d ed., McGraw-Hill, 1967)

Copulatory organs

Fertilization always takes place in a fluid medium. In many aquatic vertebrates, external fertilization takes place, with water furnishing the medium in which sperm travel to gain access to ova. Terrestrial forms and even numerous aquatic species have internal fertilization. Secretions supplied by both sexes furnish the necessary fluid medium. In a number of terrestrial vertebrates, spermatozoa are transferred from male to female by cloacal apposition. In most, however, as well as in many aquatic species, intromittent, or copulatory, organs are employed to deposit spermatozoa, suspended in seminal fluid, within the reproductive tract of the female.

Fertilization usually takes place in the upper part of the oviduct. In forms in which the egg is surrounded by a shell, fertilization must take place before the shell has been formed about the ovum.

Fishes

In those fishes having internal fertilization, the copulatory organs are modifications of fins, pelvic fins in elasmobranchs and anal fins in teleosts. Claspers, which are modifications of pelvic fins, are used as intromittent organs by male elasmobranchs. Each clasper is essentially a scroll-like tube through which seminal fluid may be ejected with some force into the cloaca of the female. It is probable that only one clasper is inserted at a time. In teleosts having internal fertilization, the anterior border of the anal fin is elongated posteriorly to form an intromittent organ, the gonopodium. In some teleosts, modifications of the hemal spines of certain caudal vertebrae form a copulatory organ.

Amphibians

Although internal fertilization occurs in most salamanders, copulatory organs are lacking. By muscular action of the cloacal lips, the female is able to pick up spermatophores, or packets of spermatozoa, deposited by the male. The eversible and protrusible cloaca of some male caecilians may be used as a copulatory organ when the cloacae of both sexes are in apposition.

Reptiles

Sphenodon is the only reptile lacking copulatory organs. In others, two types of structures are evident. Snakes and lizards employ paired hemipenes, which are saclike structures, devoid of erectile tissue, lying under the skin adjacent to the cloaca.

Each bears a groove for the passage of spermatozoa. These organs are everted during copulation and spermatozoa are deposited in the cloaca of the female. Hemipenes are not homologous with the single penis of turtles and crocodilians, which is basically similar to that of mammals, and contains erectile tissue which becomes distended with blood during sexual excitement. A homologous structure, the clitoris, is present in rudimentary form in females. Paired, thickened ridges in the anterior and ventral walls of the cloaca are called corpora cavernosa. They are composed of connective and erectile tissue. A groove along the dorsal surface provides for the passage of spermatozoa. During the act of mating, the corpora cavernosa are filled and distended with blood and the penis is firm and greatly enlarged. It is then said to be erect. This property of erectile tissue makes it possible for the penis to serve as an intromittent organ. Without erection, copulation is impossible. During erection, the veins which normally drain blood from the erectile tissue become compressed. There is an increased supply of arterial blood supply accompanied by an impeded venous drainage. Return of the penis to its flaccid state after erection is termed detumescence.

Birds

Most birds copulate by cloacal apposition. A penis is present only in ducks, geese, swans, and ostriches. It is a single structure of the same type as that of turtles and crocodilians. A clitoris is present in females of these species. In many other birds, a rudimentary penis can be identified.

Mammals

In monotremes, the single penis lies on the floor of the cloaca. It is similar to the organ in turtles, crocodilians, and birds except that the groove on the dorsal side has become a closed tube. This is surrounded by another mass of erectile tissue known as the corpus spongiosum. The canal in monotremes possibly carries only seminal fluid since the urethra has a separate opening into the cloaca. The monotreme urethra thus differs from that of all other mammals. Marsupials lack a cloaca. The marsupial penis is covered by a sheath which opens to the outside of the body just beneath the anus. It may be protracted and retracted. The scrotum in marsupials is anterior to the penis. There are two erectile corpora cavernosa, separated by a septum, and a single erectile corpus spongiosum surrounding the urethra. Usually in marsupials, three pairs of Cowper's glands open into the urethra at the base of the penis.

In higher mammals, there is a tendency for the penis to be directed forward; and in all forms possessing a scrotum, the penis is located anterior to the scrotum. In most mammals, it lies within a sheath from which it can be protracted and retracted. In primates, the penis is permanently exerted. Its distal end bears a sensitive, swollen glans. Among mammals, there are many variations in shape and structure of the glans, which contains erectile tissue continuous with the corpus spongiosum. In some forms, as in the cat, the glans bears numerous horny papillae or spines on its surface; these undoubtedly function as a sexual irritant. The glans is covered by a sheath, the prepuce, or foreskin, which may be retracted. Preputial glands secrete a sebaceous material called smegma about the base of the glans underneath the prepuce.

A bone is present in the penis of many rodents, carnivores, bats, whales, and lower primates. It is situated in the connective tissues between the corpora cavernosa and corpus spongiosum. In whales, there is but a single corpus cavernosum. Anomalous development of the vertebrate penis is occasionally encountered. The most common anomalies are referred to as hypospadias and epispadias, in which the urethra opens on the under or upper sides, respectively, of the penis, rather than being continued to the tip of the glans.

Charles K. Weichert

Histology in Humans

The human reproductive system comprises many different organs, and therefore all the primary types of tissue are identified.

Male reproductive system

In the following sections, the histological features of the testes, scrotum, excretory ducts, and auxiliary glands are discussed.

Testes

The testes have two important structural elements, the contorted seminiferous tubules and the interstitial cells which are situated between the tubules. The contorted seminiferous tubules have two kinds of cells, nutrient cells, which also serve as supporting cells (the cells of Sertoli), and germinal cells, which develop into spermatozoa by the process of spermatogenesis. The interstitial cells of the testis are seemingly modified connective-tissue cells. They resemble epithelial cells and hence are correctly designated epithelioid cells. They produce testosterone, the male sex hormone, which chemically is a steroid compound, in mammals and perhaps in other vertebrates. See also: [Spermatogenesis \(/content/spermatogenesis/643700\)](#)

Scrotum

The scrotum consists of skin, smooth muscle, and connective tissue. The scrotal skin is rich in sweat glands; it is thus able to act as a thermoregulator for the testes. The human scrotal temperature is about 13°F (7°C) lower than that of the abdominal cavity. The smooth muscle is a “skin muscle” called the dartos tunic; its relaxation lengthens the scrotum and promotes loss of heat, whereas its contraction shortens the scrotum and reduces loss of heat. See also: [Sweat gland \(/content/sweat-gland/672200\)](#); [Thermoregulation \(/content/thermoregulation/691600\)](#)

Excretory ducts

The excretory ducts which convey spermatozoa from the contorted seminiferous tubules to the urethra are either intratesticular (tubuli seminiferi recti and rete testis) or extratesticular (epididymis, ductus deferens, and ejaculatory duct). From the seminiferous tubules, spermatozoa enter the epididymis, a tubular structure consisting of head, body, and tail. The head of the epididymis has 12 or more efferent ductules (ductuli efferentes testis), the epithelium of which bears cilia, or little hairlike projections, which assist in moving sperm into the coiled part of the epididymis. The body and tail of the epididymis constitute the ductus epididymis, a coiled tube which, when uncoiled, is about 15–20 ft (4.5–6 m) long. The ductus deferens in humans is about 18 in. (45 cm) when uncoiled. Its proximal end is dilated to form the ampulla ductus deferentis.

Auxiliary glands

The auxiliary glands in humans include two seminal vesicles, one prostate, and two bulbourethral glands. Their secretions together with spermatozoa and the small amount of secretion from the excretory ducts constitute the semen. In the male, one ejection of semen, known as ejaculation, has a volume of 3–5 ml, and each milliliter contains about 6×10^7 spermatozoa. The seminal vesicles, named in accordance with the erroneous belief that they are receptacles for spermatozoa (after death, sperm may be found in the vesicles), are hollow glands which lie along the back wall of the prostate. They are about 2 in. (5 cm) in length, and, developmentally, each gland is an outgrowth of the ampulla of the ductus deferens. The right and left seminal vesicles open into the prostatic urethra via the ejaculatory ducts. The prostate is a solid gland which surrounds the urethra (prostatic urethra) at its origin from the urinary bladder. It is about 1–1.5 in. (2.5–4 cm) in diameter, and has several small ducts which open individually into the prostatic urethra. The bulbourethral glands, or glands of Cowper, are about 0.25 in. (6 mm) in diameter. Each opens into the urethra at a site slightly below the prostate.

In such species as the rat, guinea pig, and rhesus monkey, the mixture of the secretions from the auxiliary glands coagulates, as in the case of ejaculated semen. In the mating of rats and guinea pigs, the coagulated semen produces the vaginal plug which temporarily partly occludes the vagina of the female partner.

Female reproductive system

The histological discussion of the female system includes the ovaries, uterine tubes, uterus, vagina, and external genitalia.

Ovary

The ovary (ovarium), or egg producer, is largely covered by peritoneum; it has follicles with egg cells (ova), a stroma of connective tissue, and, in maturity, corpora lutea.

Maturation of the ovum

The process of the origin, growth, and formation of the ovum in its preparation for fertilization is known as oogenesis. The young sex cell is an oogonium. Growth produces the primary oocyte; only the beginning of the first maturation division occurs before ovulation. After ovulation, the primary oocyte divides to produce two unequal elements: a secondary oocyte and a smaller body, the first polar body. Then the secondary oocyte divides to yield the mature ovum (rarely called ootid) and the second polar body. The mature ovum has the haploid number of chromosomes; the two polar bodies eventually disintegrate.

See also: **[Oogenesis \(/content/oogenesis/469500\)](/content/oogenesis/469500)**

Corpus luteum

The corpus luteum is a yellow endocrine body which originates at the site of a ruptured Graafian follicle and which produces progesterone, one of the female sex hormones. It originates by the metamorphosis of granulosa cells and thecal cells into lutein cells which are epithelioid. The corpus luteum of ovulation persists about 14 days, whereas the corpus luteum of pregnancy lasts several months. The degeneration of a corpus luteum produces a white, fibrous scar in the ovary, the corpus albicans.

Fallopian tube

The human Fallopian tube is a muscular structure about 4.5–5 in. (11.4–12.7 cm) long, and has three regional subdivisions: a funnellike upper part, the infundibulum (infundibulum tubae uterinae); a dilated part below the infundibulum, the ampulla; and a constricted part near the uterine junction, the isthmus. The mouth of the tube, or ostium, communicates with the peritoneal cavity, and is guarded by a fringe, the fimbriae tubae. Fertilization of the ovum occurs in the tube.

Uterus

The uterus is covered in part by peritoneum. It has an outer layer of smooth muscle, the myometrium, and an inner layer of connective tissue and epithelium, the endometrium. Thickness of the endometrium varies during the menstrual cycle. See also: **[Menstruation \(/content/menstruation/415000\)](/content/menstruation/415000)**

Vagina

The musculomembranous organ situated between the cervix uteri and the external genitalia is the vagina. During copulation, it ensheathes the penis. Ventrally and dorsally, the anterior and posterior fornices, respectively, overlap the uterine cervix. In youth, the lower end of the vagina is constricted a bit by a membranous shelf of mucosa, the hymen vaginae.

External genitalia

The external genitalia include the clitoris, vestibule of the vulva (fossa vestibuli vaginae), paired lips of the vulva (labium majus pudendi and labium minus pudendi), and a pair of small vestibular glands (glandulae vestibulares minores). The large lips of the vulva are essentially folds of skin, whereas the small lips are covered with a mucous membrane. The vestibular glands secrete mucus, and, in cases of gonorrhea, may become inflamed and then form large cysts.

Embryology

The embryology of the reproductive system shows great similarities in all vertebrates, with the exception of teleost fishes, in which it is less specialized. It proceeds by three steps: sex determination; organogenesis of gonads; and later, during development, differentiation of the genital tract.

Sex determination

At the time of fertilization, the sex of each individual is genetically determined by certain genes carried by the sex chromosomes contained in the gametes. If both the male and the female germ cells have an identical X chromosome, the egg, upon fertilization, receives two X chromosomes (homozygous egg). If one parent germ cell contains an X and the other contains a Y chromosome, the egg cell receives an XY assortment (heterozygous egg). In mammals and in frogs, for instance, the male is the heterozygous XY sex. In birds and several urodeles, the condition is reversed and the female sex is the heterozygous XY sex.

Sex determination should be considered as the first step in sexual differentiation of each individual. Techniques have been developed which permit direct study of the chromosomes, particularly the sex chromosomes, in dividing cells of any tissue. Chromosomal anomalies, such as the absence of one chromosome (for example, XO) or the presence of one or more supplementary chromosomes (for example, XXY), can be recognized in humans or in animals. Mosaicism results from the presence of two or more types of cells, for instance, cells with XX and cells with XY chromosomes, in the same individual. In such individuals, the genetic basis of sex is disturbed, and embryological anomalies may occur. See *also*: [Chromosome \(/content/chromosome/134900\)](#); [Sex determination \(/content/sex-determination/617400\)](#)

Role of urinary system

The development of the genital tract is intimately correlated with development of the urinary system ([Figs. 8–11](#)); the urinary system itself is derived from successive excretory organs. The first pair of kidneys, the pronephroi of the early embryo, develops mainly in the future neck region. The excretory (drainage) duct of the pronephros grows posteriorly and reaches the cloaca. Shortly afterward, the second pair of excretory organs, the mesonephroi, differentiates approximately in the middle of the trunk, in connection with the primitive pronephric duct. The pronephros then retrogresses, and its duct becomes the mesonephric duct, also called the Wolffian duct. In higher vertebrates (birds and mammals), the mesonephroi are later replaced by a third pair of kidneys, the metanephroi.

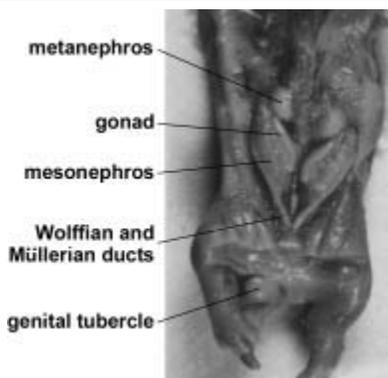


Fig. 8 Dissection of a 19-day-old rabbit fetus showing the undifferentiated condition of the genital tract.

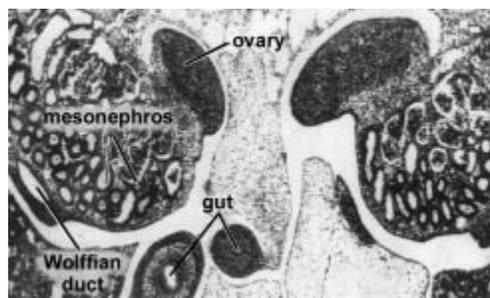


Fig. 9 Section through the body of a 17-day-old rabbit fetus, showing the ovaries at an early stage of differentiation located on the internal side of the mesonephroi.

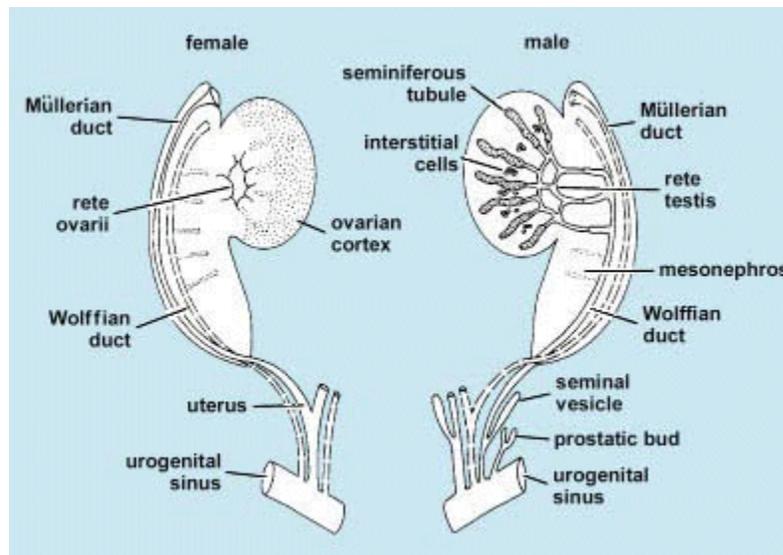


Fig. 10 Homologies in the development of the male and female genital tract of mammals. The gonads are shown on the inner side of the mesonephroi, and the ducts on their outer border. (After A. Jost, *General outline about reproductive physiology and its developmental background*, in H. Gibian and E. J. Plotz, eds., *Mammalian Reproduction*, pp. 4–32, Springer, 1970)

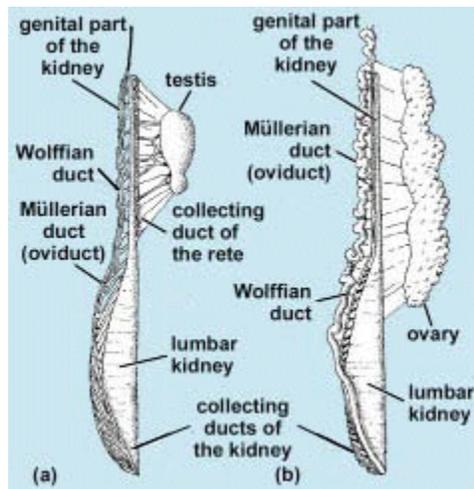


Fig. 11 Drawings of the right half of the reproductive system of the newt *Triton (Triturus) cristatus*. (a) Male. (b) Female. (After J. de Beaumont, *Wilhelm Roux Arch. Entwicklungsmech. Organ.*, 129:120, 1933)

Among the vertebrates, except for the teleost fishes, the sex glands differentiate in connection with the mesonephros. They retain these connections in male amphibians, in which the mesonephros remains the adult kidney (**Fig. 11**). The testicular tubules are connected with specialized mesonephric tubules. An adult male frog displays conditions which are similar to those

found in the early bird or mammalian embryo. See also: [Urinary system \(/content/urinary-system/724000\)](#); [Urogenital system \(/content/urogenital-system/724300\)](#)

Development of gonads

The development of the gonads is a progressive process, which may be divided into three main phases: (1) appearance of a genital ridge, (2) organization of an undifferentiated gonadal anlage, and (3) sexual differentiation of this primordium.

Genital ridge

The genital ridge appears on the mesolateral side of the mesonephros as a thickening of the coelomic epithelium covering the mesonephros. In reptiles, birds, and mammals, it consists of a layer of enlarged coelomic cells, which at first is two or three cells thick. This contrasts with the flat cells of the other parts of the mesonephric coelomic wall. Primordial germ cells, the cells which will give rise to the germ cells, come in close contact with the so-called germinal epithelium and even penetrate between its cells. These primordial germ cells have an extragonadal origin.

Extragonadal origin of germ cells

In the chick embryo, the primordial germ cells are first seen as large undifferentiated cells, located in the germinal crescent, a part of the extraembryonic area of the blastoderm situated anteriorly to the embryo's future head. They reach the level of the gonadal anlage by way of the bloodstream. In sauropsidians and mammals, their extragonadal origin has also been established. They originate in the primitive gut and usually migrate through the dorsal mesentery toward the gonadal area. In mammals, and in human embryos, they can be traced with histochemical techniques, showing their high content of alkaline phosphatase. In the frog, the primitive germ cells have been traced from the very beginning of the cleavage of the egg; their early destruction led to the development of sterile gonads.

Undifferentiated gonad

In Amphibia, the primordial germ cells are first disposed in clumps near the inner border of the mesonephros. The genital ridge is formed when these primordial germ cells protrude into the abdominal cavity with some connective tissue and the covering coelomic epithelium. The anlage is invaded by clusters of cells coming from the mesonephric blastema. The gonadal anlage has then attained a stage known as the indifferent stage, which is the same irrespective of the genetic sex of the animal.

The indifferent sex gland consists of the coelomic epithelium at the periphery, the cells of which are flat and scattered and cover the voluminous primitive germ cells. Some connective tissue surrounds the central mass of small cells which came from the mesonephric blastema. The outer zone is often called cortex, and the inner part is called medulla. Both constituents participate in the formation of the definitive sex glands.

In mammals and birds, the undifferentiated primordia of the gonads are also composed of three major components: a superficial epithelium, inner cell masses, and germ cells. The limit between the superficial layer and the inner cells usually disappears and becomes poorly defined. Therefore, the origin and the significance of the constituents of the indifferent gonad gave rise to various interpretations which still prevail. In order to understand the issue, it must be kept in mind that in the mature female animal the ova are released from the ovary through its surface, into the abdominal cavity, in a centrifugal way, and that they are then collected by the tubes. Accordingly, in the development of the ovary, the superficial layers play the major part. On the contrary, in males the sperm cells are released into an intratesticular and complex system of channels derived from the mesonephros, in a centripetal way. Accordingly, the seminiferous tubules develop in the center or in the depth of the organ (**Fig. 10**).

This explains why embryologists more than a century ago introduced the concept that the undifferentiated gonadal primordium was hermaphroditic. It was supposed to comprise a superficial female component and a central male component, the latter originating from the mesonephric renal structures. Only one of these sexually specialized parts was assumed to differentiate in each sex, while the other degenerated. Another long-lived classical theory assumed that the superficial epithelium of the genital ridge proliferated so-called sex cords into the underneath undifferentiated mesenchyme. A first set of these cords was held to constitute the male medullary cords, while in females the superficial epithelium, the cortex, proliferated a second set of sex cords, which developed in an ovarian cortex, after the involution of the medullary cords.

It is still difficult to assess the exact history of the various cell types involved in the development of the sex glands, since no cellular markers are available. In any case, there is no indication of a hermaphroditic constitution of the primordium, since no separate male or female component can be distinguished.

Sexual differentiation of the gonads

Testes differentiate earlier than ovaries, and for a while female embryos can be recognized only because they do not develop testes.

The initial step of testicular differentiation consists of the appearance of a new type of cells in the undifferentiated gonad, the primordial Sertoli cells. These cells aggregate together, and with germ cells they delineate the early testicular seminiferous cords. (In the adult testis, the Sertoli cells support the germ cells in the seminiferous tubules.) In the meantime, at the surface of the testis, the cells become rarefied, flatten, and form the albuginea of the testis. A second crucial step in testicular differentiation is the differentiation of the Leydig cells, between the seminiferous cords. These cells produce the steroid male hormone. See also: [Hormone \(/content/hormone/323000\)](/content/hormone/323000); [Steroid \(/content/steroid/655700\)](/content/steroid/655700)

At the same time that these events occur in males, the presumptive ovaries in females maintain a morphologically undifferentiated condition. The first clear-cut sign of ovarian differentiation is the onset of the meiotic prophase. In fetal ovaries, the germ cells enter the preparatory phases of chromosomal reduction (or meiosis), a nuclear process which will be completed during adulthood when oocytes are released from the ovary. A long phase of nuclear quiescence takes place between the fetal preliminaries and their completion at the time of ovulation in adulthood. See also: [Meiosis \(/content/meiosis/413500\)](/content/meiosis/413500)

Meiosis seems to be a critical phase of ovarian development. Many germ cells entering meiosis degenerate; a few of them survive and become surrounded by follicular cells. The primary ovarian follicles are constituted in that way. It seems very likely that the follicular cells are homologous to the testicular Sertoli cells. The question as to why the ovarian germ cells enter the meiotic prophase, whereas in males of the same age they do not, is not yet solved, though it has been suggested that a meiosis-inhibiting substance is produced by the testis and a meiosis-inducing substance by the ovary. The reason why so many germ cells degenerate at incipient meiosis also remains unknown.

Gonadal differentiation is well established in reptiles or birds before hatching, or in placental mammals at birth. In the marsupials, such as the opossum, intrauterine pregnancy is very short and is followed by a period of development in the marsupial pouch. Sexual organogenesis takes place after birth during pouch life.

Exceptions to general scheme

Many animals have developmental patterns that deviate from the scheme outlined above. In a great number of birds, only one ovary becomes functional in the adult. In the female chick embryo, for instance, dissymmetry of the gonads is conspicuous at an early stage, because the left anlage is much larger than the right one. The right gonad, composed of some vestigial medullary tubules, remains, and is a nonfunctional rudiment in the hen. It may develop as a small testis if the left ovary is

removed.

In toads of either sex, the anterior part of the gonadal anlage acquires the structure of a persistent rudimentary ovary, Bidder's organ, above the functional gonad. In adult animals, Bidder's organ may develop into a functional ovary when the actual gonads are surgically removed. Males deprived of their testes undergo a slow feminization and may lay eggs.

In frogs, there are racial differences. In animals living in cold countries or at high altitude, males and females both differentiate early. In most frogs from temperate climates, the process of sexual differentiation is different. During the months before metamorphosis, in all individuals, whatever their genetic sex, the gonads first differentiate in a feminine way, since testicular differentiation takes place and several germ cells increase in size and enter the meiotic prophase. However, at metamorphosis, in half the individuals the largest germ cells degenerate and testes differentiate, while the other animals follow the normal feminine line. Thus, males suffer from a delayed testicular organogenesis. Animal species or strains which show such a transitory feminine phase of the male gonads are known as indifferent strains. Several amphibians, teleosts, and cyclostomes also develop indifferent strains.

Control of gonadal differentiation

In mice and in humans, evidence that the presence of a Y chromosome is a prerequisite for morphological differentiation of testes has accumulated. Thus, exceptional XO mice are females and XXY mice are males. The problem of how the sex genes control gonadal organogenesis has not yet been fully explained on cellular or biochemical bases.

The effects of administering hormones to developing embryos are profound, but vary among organisms (**Table 1**). Such experiments do not, however, warrant the generalization that sex hormones control sex differentiation. In lower vertebrates, sex differentiation may be influenced by external factors. Experiments made on turtles, alligators, and the newt *Pleurodeles* showed that breeding the eggs at different temperatures resulted in the development of young which were all of the same sex, depending on the temperature. Genetically, male *Pleurodeles* which were sex-reversed into functional females by breeding at high temperature could be mated with normal males and the progeny could be studied.

TABLE 1. Effect of administered sex hormones on developing gonads

Animal	Estradiol (on males)	Testosterone (on females)
Fishes		
<i>Lebistes</i>	Feminization	Masculinization
Amphibians		
Frogs, various species	Feminization (low dosage) Masculinization (high dosage), paradox effect	Masculinization
<i>Alytes</i>	Feminization	No effect
<i>Xenopus</i>	Complete feminization	No effect
<i>Bombina</i>	No effect	No effect
<i>Amblystoma</i>	Complete feminization	Feminization, paradox effect
<i>Pleurodeles</i>	Complete feminization	Feminization, paradox effect
Birds		
Chick	Feminization	Slight masculinization
Duck	Slight feminization	No effect
Marsupials		
Opossum	Feminization	No effect
Placental mammals		
Several species	No effect	No effect

Sex differentiation of the gonads is controlled by genetic factors and the question arises of how and in which cells these genetic factors express themselves. As mentioned above, the gonadal primordium has long been assumed to be hermaphroditic, and it was accepted that the genetic factors gave prevalence to one sex component over the other, possibly via the dominance of one of the two antagonistic sex inductors produced by the sexually opposed gonadal components. In 1965, Alfred Jost introduced the concept that the sex glands were programmed to develop according to the homogametic sex (female in mammals, male in birds) and that in the heterogametic sex a special triggering mechanism imposes alternate sexuality on the primordium. This scheme was largely accepted, but the trigger has yet to be identified. A theory propounded in 1975 by Stephen Wachtel and others had some success. It proposed that the HY-histocompatibility antigen (discovered by grafting male skin in female mice and characteristic of individuals possessing the Y chromosome) was a triggering protein responsible for the differentiation of the sex gland in the heterogametic sex. This concept does not, however, fit with Humphrey's fundamental experiments mentioned above or with other observations. The chemical control of gonadal sex differentiation remains to be definitively elucidated.

Gonadal abnormalities

Important abnormalities include absence of the gonad, hermaphroditism, and sex reversal.

Absence of the gonad

The entire gonad may fail to develop or may regress at very early stages, leaving only some indistinct remnants which are impossible to recognize as testes or as ovaries. This condition, called gonadal agenesis or gonadal dysgenesis, is known among humans and other animals. In humans, gonadal dysgenesis is a part of the polymorphic Turner syndrome, which occurs in patients having the abnormal chromosomal formula XO. Since it also occurs in patients who have other normal or abnormal chromosomal formulas, the exact correlation between the sex chromosomes and gonadal dysgenesis is not yet clear.

Hermaphroditism

The presence of male and female gonadal tissue in the same individual is not normal among vertebrates except in some species of fishes. It can occur as an abnormal condition more or less frequently among other vertebrates. It is rather frequent in some frogs and toads, and was considered to be the result of an incomplete dominance of either the cortex or the medulla of the indifferent gonad. It might also, however, result from incomplete expression of the testicular determining system. In humans, several cases of true hermaphroditism have been reported in sterile individuals. Several cases have been correlated with chromosomal abnormalities such as XX/XY mosaicism, and in one case it was observed that the ovarian tissue contained mainly XX cells and the testicular tissue XY cells.

Genital tract development

The sex ducts become sexually specialized some time after the sexual differentiation of the sex glands. The male or female conditions develop from an indifferent condition which is identical in both sexes in early stages.

Indifferent stage

The gonads are already recognizable as presumptive ovaries or testes and are located on the anterior part of the mesonephros. The mesonephric or Wolffian duct is the ureter, and opens posteriorly into the cloaca in lower vertebrates or into the urogenital sinus in mammals. Another duct, the oviduct or Müllerian duct, parallels the mesonephric duct. The oviduct arises from a funnel which opens into the coelomic cavity. The blind end of this primordium proliferates and extends progressively caudally.

In selachians and urodeles, the funnel from which the Müllerian duct originates corresponds to a pronephric nephrostome, the coelomic opening of the primitive urinary tubules. Because the pronephros is located near the neck of the larva, and because the ostium of the oviduct retains this position, the oviducts open into an anterior part of the body cavity (**Fig. 11**).

In birds and mammals, the origin of the oviduct from pronephric remnants is not as clear, but it is obvious that the oviduct develops in the region of the nephric field. The early funnel is located on the top of the mesonephros, and the ostia tubae open above the ovaries.

Differentiation of female genital tract

The Müllerian ducts differentiate into the female ducts. Depending upon the animal species, either a simple secretory oviduct (amphibians) or a more complicated structure develops from this simple unicellular layered duct. It is divided into several specialized sections involved in the secretion of albumen or shell, as in selachians, reptiles, and birds. In those birds in which the female has only one functional ovary, only one oviduct develops (**Fig. 12**).

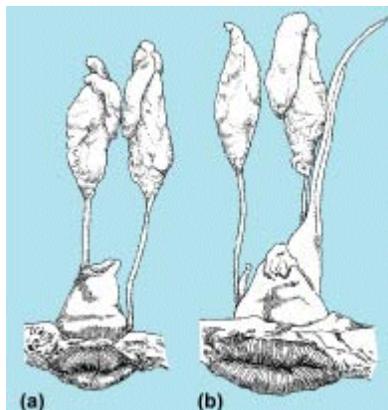


Fig. 12 Reproductive system of normal chick embryos, shortly before hatching. (a) Male (two testes present). (b) Female (sole left ovary and left oviduct). (After E. Allen, ed., *Sex and Internal Secretions*, 3d ed., Williams and Wilkins, 1961)

In mammals, the Müllerian ducts give rise to the oviduct, or tube, and the uterus. Usually the embryonic Müllerian ducts fuse posteriorly, but the extent of fusion is variable. In humans and monkeys, a single uterus is formed from the fused part of the ducts; the tubes correspond to the nonfused part. In rodents, the two Müllerian ducts fuse only in the upper vagina, and form two uterine horns and two tubes. In ruminants, an intermediary condition is realized in which the uterus is composed of an inferior stem and two horns which largely communicate (**Fig. 3**).

The posterior part of the mammalian female genital tract is constituted by the vagina. The embryology of this organ displays great variability from one animal species to the other, and this makes an accurate interpretation difficult.

In the undifferentiated stage, the Müllerian ducts terminate blindly at the wall of the urogenital sinus (or embryonic urethra), between the two Wolffian ducts which open into the urogenital sinus. They may retain this primitive connection, as is the case in the rabbit (**Fig. 13a**), and the urogenital sinus then becomes a urethrovaginal duct.

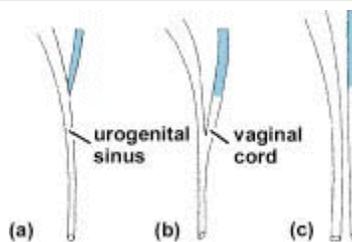


Fig. 13 Schematic interpretation of vaginal organogenesis in three species. Müllerian ducts are shaded. The three conditions are explained in the text.

In other animals, a cord of cells, the vaginal cord, may detach from the dorsal wall of the urogenital sinus and grow progressively caudally below the end of the Müllerian parts (**Fig. 13b**). In the rat or the mouse, this sinusary vagina finally opens independently of the definitive female urethra in a vaginal opening (**Fig. 13c**). In other animals, such as the mare, the vaginal cord remains connected with the posterior part of the urogenital sinus. The vestibulum then remains as a common opening to both the vagina and urethra.

Comparative embryology of the vagina helps in understanding abnormalities of the human genital tract. Absence of the vagina and opening of the female ducts into the urethra may result from the preservation of the primitive connections.

The Wolffian or mesonephric duct of the female embryo is never incorporated into the genital tract. In animals that keep their mesonephros as a functional kidney in adulthood (selachians and amphibians), the mesonephric duct remains as the excretory channel (**Fig. 11**). In female birds and mammals, the mesonephric duct, as well as the mesonephros, disappears, leaving only some minor vestiges.

Differentiation of male genital tract

The male sex ducts are derived from the mesonephric or Wolffian ducts. In selachians and amphibians, the mesonephros remains the functional kidney, and the mesonephric ducts function as pathways for urine as well as for sperm. Even in such animals, however, the anterior part of the kidney often becomes specialized as the sexual part. The posterior part of the kidney then produces urine, and several excretory tubes may bring this urine directly to the cloaca. In such cases, the Wolffian duct of the male is only a genital canal, as in the newt *Triton cristatus* (**Fig. 11**).

The Wolffian ducts of birds differentiate into an undulated vas deferens, whereas in mammals the ducts differentiate into the

epididymis at one end and the seminal vesicles at the other (**Fig. 10**).

The Müllerian duct has no function in males, and as a rule it disappears. In some amphibians, such as newts and toads, the oviducts persist in a rudimentary condition (**Fig. 11**); they may be activated under appropriate hormonal stimulation in adult males.

In male mammals, the urogenital sinus becomes the definitive male urethra. Several accessory glands, such as the prostatic glands, bud from it, and display great variations from one animal species to another, but all open into the urethra (**Fig. 10**).

Copulatory organs

Copulatory organs are well developed in mammals and reptiles. In selachians, they are often a specialized part of the fins, the claspers. As a rule, no copulatory organ is present in amphibians and birds; only a few male birds, such as the duck, possess a penis.

In mammals, the copulatory organ develops from an undifferentiated genital tubercle which is identical in both the male and female embryos and lies above the opening of the urogenital sinus. The male penis encloses the penile urethra and increases in size, whereas the homologous female clitoris remains more like the primitive tubercle.

Hormonal control

The genital tract differentiates after sexual differentiation of the sex glands, and time relationships support the view that sexual specialization of the genital tract is controlled by hormones produced by the developing sex glands. This has been shown experimentally by depriving embryos or young animals of their gonads. It was established that, in the gonadless body, the genital tract becomes identical whatever the genetic sex of the individual. This means that in the absence of the sex glands, sexual dimorphism, which is a characteristic feature of almost all vertebrate species, does not appear. This identical, hormoneless aspect of the body is known as the neutral form. However, the gonadless sexual type is not the same in mammals and birds.

In mammals, gonadless sexual organization has been studied in rabbit fetuses which were surgically castrated in utero. It was found that the neutral condition is essentially feminine. This means that no embryonic gonad is necessary to produce the feminine sexual structures. In males, the testes prevent persistence and development of the female structures (tube and uterus) and impose masculinity on the whole genital apparatus (**Fig. 14**).

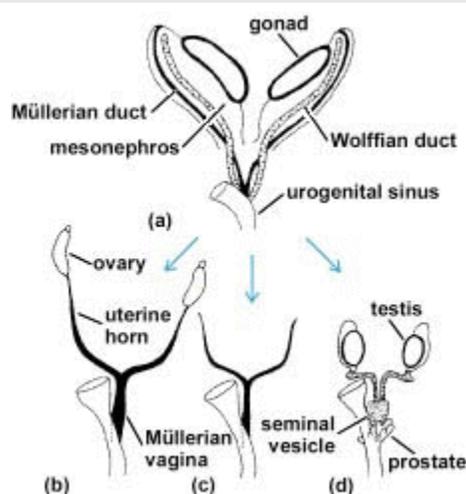


Fig. 14 Sexual differentiation of the genital tract of the rabbit fetus: (a) undifferentiated condition; (b) female; (c) castrate;

(d) male. (After A. Jost, *Mem. Soc. Endocrinol.*, no. 7, 1960)

In a duck embryo castrated by a beam of x-rays, E. Wolff noticed masculine differentiation of such sex characters as the penis or the voice organ (syrinx). During normal sexual differentiation, the embryonic ovary prevents such characters from becoming masculine. In addition, the neutral aspect of the genital tract is also characterized by the presence of oviducts. These structures are normally absent in males in which they are inhibited by an embryonic testicular hormone (Fig. 15). A similar trend toward maleness was observed in young newts, *Triturus cristatus*, castrated before sex differentiation. In that species, females are heterozygous, as in birds.

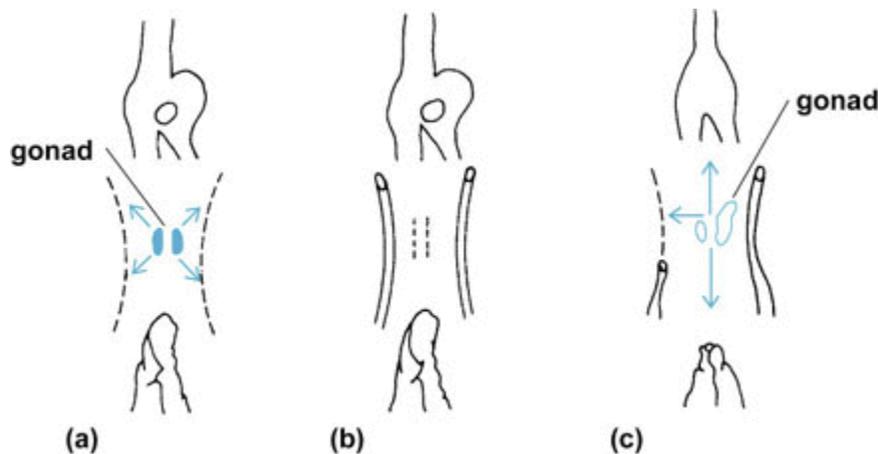


Fig. 15 Evolution of sex characters in the duck embryo: (a) male, (b) castrate, (c) female. Top sketch, voice organ or syrxinx, well developed in males. Middle sketch, Müllerian duct (compare with Fig. 13); arrows symbolize inhibiting gonadal actions. Bottom sketch, genital tubercle. (After E. Wolff, *Compt.Rend.*, 229:428, 1949)

It appears that in some vertebrates the neutral type is feminine (mammals) and in others it is predominantly masculine (birds and newts). In the absence of gonadal hormones, a basic developmental program prevails that corresponds to the homozygous sex, female in mammals, and male in birds and newts. In the heterozygous sex, the gonads counteract this program and impose respectively maleness or femaleness in mammals and in birds and newts.

As mentioned above, in some amphibians, complete sexual reversal of the gonads can be obtained under hormonal influences (testes developing in genetic females or ovaries in genetic males). In such animals, the genital tract develops in agreement with the actual sexual structure, and function of these gonads and fertility are ensured.

Such a complete sexual reversion has not yet been produced in higher vertebrates. The condition prevailing for placental mammals deserves special attention. Sex hormones administered to the pregnant mother animal or injected into the fetus itself modify the development of the genital tract with the exception of the gonads themselves. The young thus become intersexes and definitely abnormal. Estrogenic hormones given to pregnant rats or mice feminize the male fetuses to a large extent. In addition to unaltered testes, large parts of the Müllerian ducts can be retained and a vagina and feminine external genitalia develop. Under the influence of androgenic hormones, female fetuses acquire several masculine structures, such as male external genitalia, urethra, accessory sex glands, vasa deferentia, and seminal vesicles. But they retain their ovaries, tubes, and uterus. Similarly, in castrated rabbit fetuses given testosterone or similar hormones, masculine organs develop but the Müllerian ducts are not suppressed. Androgenic steroid hormones do not inhibit the Müllerian ducts. This suggests that the fetal testis produces two kinds of substances, one stimulating the development of masculine characters, and another inhibiting the female ducts. The dual nature of the hormonal control of the differentiation of the genital tract is now established. In addition to steroidal androgens such as testosterone, the fetal testis produces a Müllerian inhibitor called anti-Müllerian hormone or Müllerian-inhibiting substance. This hormone, as produced by the fetal calf testis in cell cultures, was shown to be a glycoprotein of a molecular weight of 124,000. The two fetal testicular hormones are produced by two different

cell types, the Sertoli cells for the anti-Müllerian factor and the Leydig cells for androgens.

Another line of important facts concerns the target cells for androgens. It is established that androgens can masculinize undifferentiated primordia only if the cells are provided with appropriate androgen receptors. Moreover, in several target organs, testosterone has to be converted into dihydrotestosterone by the intracellular enzyme, 5 α -reductase, before it acts in the nucleus. Absence of receptors or of proper conversion of testosterone results in the same effect as absence of hormone. A partial cellular defect produces an intermediary degree of masculinization.

Abnormalities of genital tract

Many types of genital developmental abnormalities are known in animals and humans. Genetically female fetuses may be partially virilized (masculine or ambiguous intermediary aspect of the external genitalia) under the influence of androgenic substances either given to their pregnant mother or produced by their own abnormal adrenals (adrenogenital syndrome).

Genetically male fetuses may suffer from incomplete masculinization by their own testes. The discovery of a dual hormonal control of the differentiation of the genital tract and of the necessity of hormonal receptors in target tissues gave explanations for many sex abnormalities. Males can be incompletely masculinized in the following cases:

1. The testes are absent. In this case, the genital tract is completely feminine, but remains infantile because no ovarian hormones are produced. This condition resembles that of castrated rabbit fetuses.
2. The testes do not produce testosterone, or not enough. Several enzymes are involved in the synthesis of testosterone from acetate or cholesterol, and several enzymatic defects depending on discrete genes are known. This results in a condition of pseudohermaphroditism.
3. The target cells lack androgen receptors. Since androgens are not effective, no male sex duct (vas deferens) and no male organs are present, except endocrinologically normal testes. Since the Müllerian inhibitor is produced, the tubes and uterus do not persist. This condition prevails in the syndrome called testicular feminization in humans or in animals.
4. The target organs lack 5 α -reductase, a defect that does not permit appropriate masculinization (such as at the level of external genitalia). This is another type of pseudohermaphroditism.
5. The testes fail to produce the Müllerian inhibitor (or possibly the Müllerian ducts lack receptors). In these subjects, testes and male sexual characters are well developed, but a set of female organs persists (persistent Müllerian ducts).
6. In true hermaphrodites, when testicular tissue is present only on one side of the body, masculinization of the internal genital structures may be limited to the same side.

In conclusion, multiple causes of genital abnormalities are known. In females, they usually result from androgens that should not be present. In males, partial or total lack of masculinization may be due to lack of androgen secretion or action, lack of Müllerian inhibitor secretion or action, or both.

Alfred Jost

Physiology

The physiological process by which a living being gives rise to another of its kind is considered one of the outstanding characteristics of plants and animals. It is one of the two great drives of all animals: self-preservation and racial perpetuation.

In contrast to other physiological processes, reproduction in vertebrates can be achieved only by participation of two individuals, the male and the female. Each produces germ cells called gametes. The male produces spermatozoa and the female produces ova, which carry the biochemical information arranged as genes in the chromosomes for the transmission of inherited characters. No matter how discrepant the pairing gametes may be in size and in form within a species, they contribute the same number of chromosomes. Although reproductive devices are quite different from one species to another, all serve one end, the bringing together of the spermatozoon and the ovum, each containing half the number of chromosomes of the parent cells. After the union of the chromosomes at fertilization, the newly constituted embryo possesses the number of chromosomes of its race and then divides, differentiates, grows, and develops into an individual either outside the mother (oviparity) or inside the mother (viviparity). The obvious advantage in bisexual reproduction lies in the fact that young produced from the mingled genes of two ancestral lines will not be a direct copy of either parent, but will represent different combinations of ancestral traits with great potential for the survival of the fittest. Reproduction is facilitated or inhibited by environmental and nutritional factors as well as by all the other physiological activities, but it is controlled predominantly by the endocrine system and mediated at least in part by the nervous system.

Breeding season

The season when animals perform their overt reproductive functions is known as the breeding season. This sexual periodicity is a general phenomenon common to plants and animals. In general, sexual periodicity is predominant in lower vertebrates, but all birds and wild mammals are seasonal breeders. As nutritional and environmental conditions improve, the reproductive season is not so restricted; cattle, the domestic rabbit, and humans all illustrate this fact; nevertheless their fertility is higher in spring than in winter. Males of many mammalian species are capable of sperm production and copulation at any time and rarely experience a true sexual period such as rut in the deer. In mice and rats, the testes do not descend to the scrotum until puberty and in certain other rodents they descend only during the breeding season. Most vertebrates breed only in spring or summer at the time when food, temperature, and light are optimal; they are then in the best physiological condition for reproduction. Others, for example, sheep, breed at a time which allows parturition to occur at the season of year most suitable for successful survival of the young. See also: [**Reproductive behavior \(/content/reproductive-behavior/581400\)**](#)

All environmental factors play a part, but an increase of temperature for lower vertebrates and an increase or decrease of daylight for mammals play a major role in determining the onset of their breeding seasons. For instance, most fish and amphibians breed when temperature increases. The mink and horse breed at the time of increase of daylight, in the spring, and their offspring are born in the summer or the spring, respectively, of the following year. The armadillo, deer, goat, and sheep breed during the decrease of daylight in the autumn and their offspring are born the next spring. Transportation of sheep from the Northern to the Southern Hemisphere changes their breeding season to accord with the seasons of the new environment. The testes of the cottontail rabbit return to a completely immature condition in the fall and their germ cells are all of the spermatogonial type. In late November, the testes begin to grow; in early spring, they reach 50–100 times their weight in the inactive stage and the growth of accessory glands follows that of the testes. Although artificial increase of daylight brings wild rabbits and ferrets into breeding condition in midwinter, permanent short-day lighting does not entirely prevent breeding in the spring. Furthermore, artificial increase of daylight has so far failed to show any definite effect in advancing the breeding season of the domestic rabbit, guinea pig, hedgehog, or ground squirrel.

Among fishes, the duration of the breeding season varies considerably according to the group to which they belong and where they live. The ova of the elasmobranchs are deposited singly or in pairs at varying intervals throughout a great part of the year, but some species appear to have regular recurrent breeding seasons. Most bony fishes, producing millions of ova, breed only in the spring, and most of them migrate to a suitable locality for the deposition of their gametes. In the frog and many other amphibians, the ova are produced during the winter hibernation when the animals eat very little. Similarly, the genital organs of salmon develop during migration, when the fishes cease to feed. The spermatogenesis of the amphibian

Rana temporaria is determined by the gonadotropic activity of the pituitary and by the sensitivity of the germinal epithelium to gonadotropin during the spring; this activity and sensitivity are influenced by temperature rather than light. In the autumn and winter, their testes are not sensitive to gonadotropin under natural conditions. Reptiles that hibernate usually begin to breed shortly after the beginning of the warm weather that terminates the hibernating period. Spring and summer are the seasons when most birds pair, build their nests, and incubate their eggs. The migration of some birds is invariably associated with an increase in the size of ovaries and testes.

Estrous and menstrual cycles

The cyclic changes of reproductive activities in mammalian females are known as estrous or menstrual cycles (**Table 2**). Most mammalian females accept males only at estrus (heat). The follicles in the ovaries grow at a rather constant rate before estrus. Just before or at estrus, the follicles grow rapidly, resulting in a higher output of estrogen, a female hormone. During or toward the end of estrus, the follicle, or group of follicles in animals producing litters, ruptures and releases the ovum (ovulation). The follicle is transformed into the corpus luteum, a glandular tissue which produces another female hormone, progesterone. If fertilization occurs, the corpus luteum persists during all or most of the gestation period according to the species. Without mating or fertilization, the corpus luteum persists for a relatively short time and then degenerates. The growth of the next crop of follicles begins again.

TABLE 2. Average length of the ovulatory cycle of some familiar mammals

Animal	Length
Opossum	28 days
Guinea pig	16 days
Rat	5 days
Mouse	5 days
Sheep	16 or 17 days
Pig	20–22 days
Cow	21 days
Horse	21 days
Macaque monkey	24–26 days
Human	28 days
Chimpanzee	37 days

Estrus

Estrus in mammals can occur several times in one breeding season; the mare, ewe, and rat come to estrus every 21, 16, and 5 days respectively if breeding does not take place. This condition is called polyestrus. The bitch is monestrous; she has only one heat, or estrus, to the breeding season and, if not served then, she does not come into heat again for a prolonged interval, 4–6 months according to different breeds. The duration of estrus varies according to the species, such as 4–9 days in the mare, 16–18 h in the cow, and 14 h in the rat. In the ferret, estrus is shown by predominant swelling of the vulva and lasts several weeks unless copulation takes place.

In monestrous and seasonally polyestrous species, the period of sexual quiescence between seasons is called anestrus. In sheep and deer this occurs in the summer, while in the ferret and mink it is restricted to the winter. Proestrus denotes a short period just before the time of coming in heat. It is very marked in the bitch; the genital organs swell and become congested, and there is bleeding from the uterus. Following estrus, the ensuing period in which sexual activity declines is called metestrus. After metestrus, a relatively longer period of diestrus occurs and occupies the bulk of the estrous cycle before proestrus recurs. Most females ovulate spontaneously, and shed their ova close to the end of estrus: about 2–4 days before

the end of estrus in the mare, 13 h after the end of estrus in the cow, and 10 h after the beginning of estrus in the rat. Some species, such as the rabbit, ferret, and cat, ovulate following the stimulation of copulation. If fertilization takes place, pregnancy occurs. If mating is unsuccessful, pseudopregnancy, a physiological condition very similar to pregnancy but which lasts a relatively short period, may occur in some species, particularly the dog and the rabbit. See also: [Estrus \(/content/estrus/242700\)](#)

Menstruation

The reproductive cycle of the female in the primate and human is well marked by menstruation, the period of blood flow from the vagina. Menstruation does not correspond to estrus but occurs between the periods of ovulation at the time the corpus luteum declines precipitously. As a result of the collapse of the superficial capillaries in the endometrium, blood is extravasated in quantity and about two-thirds of the endometrium is desquamated, or shed. After menstruation, there is a period in which the uterus is replenished under the influence of estrogens by the growth of the epithelium and its capillaries. This is known as the proliferative stage and is equivalent to proestrus and estrus in other mammals. It is accompanied by growth of the vaginal epithelium and some cornification, but these changes are gradual and are not as well defined as in many other mammals. The Graafian follicle ruptures near the midcycle, about 15 days before the beginning of the next menstruation. Ovulation is spontaneous and is followed by the formation of the corpus luteum, whose secretion of progesterone causes great glandular growth of the endometrium. This is known as the luteal or secretory phase and is equivalent to diestrus in other mammals. In New World monkeys, menstruation is confined to the appearance in the vaginal lavage of a few red blood cells. Tissue destruction and hemorrhage in the uterus of the elephant shrew *Elephantulus* of South Africa at the end of diestrus has been described, but the bleeding at proestrus in the bitch, at metestrus in the heifer 14 h after ovulation, and at metestrus occasionally in the guinea pig is due to intensive congestion of blood vessels in the uterus or in the upper part of the vagina and is not true menstruation.

Mating

Mating, also called copulation or coitus, is the synchronized bodily activity of the two sexes which enables them to deposit their gametes in close contact. It is essential for successful fertilization because sperm and ovum have a very limited life span; as examples, the fertilizing capacity of trout and salmon sperm lasts about 30 s in freshwater, and that of rabbit sperm lasts about 30 h in the female tract. Trout and frog ova become nonfertilizable soon after contact with water, whereas rabbit ova remain fertilizable for 6–8 h after ovulation. Human spermatozoa have a fertilizing life span of about 72 h, and ova have a fertilizable life of about 24 h. Mating behavior is a very common phenomenon in the animal kingdom. Even in the primitive vertebrate, the lamprey, some sort of mating takes place. The female is seized by the male, who winds his tail around her and discharges his sperm over the ova as they extrude from her body. In the dogfish, which practices internal fertilization, contact between male and female is necessary for the claspers of the male to convey his sperm into the cloaca of the female. In the majority of the bony fish, physical contact may be slight, yet the male follows the female closely or presses his body to hers and deposits his sperm over the ova either soon after they are laid or at the same time. Certain salamanders walk slowly ahead of the female and deposit spermatophores which the female straddles and secures with the lips of her cloaca. In other low vertebrates, a rudimentary penis exists either as a single intracloacal organ (crocodile, turtle, and duck) or as a paired structure placed behind the cloaca (snake and lizard) and sperm are deposited into the female's cloaca at mating. In mammals, the copulatory organs are well developed, varying a great deal in structure. Patterns of mating are different; the time required for mating varies from 3 h (ferret) to a few seconds (sheep and rabbit), and the number of intromissions varies from 1 (bull) to 50 (hamster).

Mating in many birds and cold-blooded vertebrates is the culminating event of a more or less complicated series of love antics. It is quite probable that these sexual displays have a direct bearing upon ovulation and that in many species ovulation would not occur in the absence of such sexual experiences. Sexual excitement and violent physical exertions of both partners

may also be essential for a fertile mating.

Ovulation

Ovulation can be considered as the culmination of a series of events in the process of oogenesis, which begins in the embryo and continues into adult life. Oogenesis is the formation, growth, and maturation of the oocyte within the ovary. The time of first ovulation at puberty varies among species, occurring as early as 30 days after birth in mice and as late as 11+ years in humans. The stages in the development of the ovum are, however, similar in most mammals. By birth, most of the primordial germ cells have become oogonia and developed into primary oocytes. Most of these oocytes remain in this stage until, under the stimulation of gonadotropic hormones (especially follicle-stimulating hormone), one or more (depending on the species) follicles containing the primary oocytes begin to enlarge and differentiate into Graafian follicles. During this process, the primary oocyte undergoes a first meiotic division, in which the chromosome number is halved from the diploid to haploid state with the extrusion of the unwanted chromosomal material in the first polar body via unequal cytoplasmic division, and commences the second meiotic division. This secondary oocyte is released when the follicle is stimulated to rupture under the influence of the gonadotropin, known as luteinizing hormone. Ovulation has been likened to an inflammatory process, and it is thought that certain mediators of inflammation, such as prostaglandin $F_{2\alpha}$ 12-HETE, may be involved in the final rupture of the follicle wall, thus permitting release of the ovum. The ovum remains arrested at metaphase II of the second meiotic division until sperm activation. It is surrounded at ovulation by two cellular layers, the bulky and sticky cumulus oophorus and the corona radiata, the highly adherent radially arranged three-deep layer of cells with connective processes joined to the vitelline membrane. See also: [**Endocrine mechanisms \(/content/endocrine-mechanisms/231700\)**](#)

Sperm transport in mammals

The logistics of sperm transport to the site of fertilization in the oviduct present many interesting features in mammals, but it is important to distinguish between passive transport of sperm cells in the female genital tract and sperm migration, which clearly attributes significance to the intrinsic motility of the cell. The rapidity (a few minutes in most mammals) with which spermatozoa reach the upper portions of the oviduct after mating or artificial insemination has emphasized that sperm motility alone could not have made a major contribution to passage over the relatively long distances involved. It is generally accepted that the role of sperm motility becomes critical only in certain regions of the tract such as the cervix and uterotubal junction and during penetration of the egg membranes. The journey for the spermatozoa is largely dependent upon contractions in the smooth-muscle layers of the tract, which may be enhanced by the action of oxytocin released after coital stimulation. Smooth-muscle stimulants in the semen, such as prostaglandins of the E series, may also contribute to the process of sperm transport in species where semen is deposited in the anterior vagina (for example, humans and sheep). Nonetheless, in animals in which the duration of estrus is long and mating takes place early in the receptive period, migration of spermatozoa from storage regions such as the lower oviduct must be of physiological significance, especially since the excited state of the uterus and oviducts promoted by coitally released oxytocin would long since have ceased.

In comparison with the number of spermatozoa deposited in the female at mating, there is a massive reduction in sperm numbers toward the upper portions of the oviduct. This sperm gradient reduces the chances of polyspermy by restricting the numbers of spermatozoa that achieve the site of fertilization. During this marked diminution in sperm numbers, the cells are progressively removed from the seminal plasma, and they become strongly influenced by the uterine and tubal fluids. This situation increases the metabolic activity of ejaculated spermatozoa, and may also be directly associated with development of the capacitated state, discussed below.

Explanations for the fact that spermatozoa "ascend" the oviducts while the eggs are "descending" arise in part from viewing the isthmus as a compartment functioning in a manner different from the ampulla, a view that is emphasized by the results of intraperitoneal insemination. However, viable spermatozoa are actively motile; and although myometrial contractions play a

major role in sperm transport through the uterus, progressive motility does contribute to migration into and within the oviducts. Waves of peristaltic contraction in the isthmus proceed principally toward the ampullary-isthmic junction, and this activity should therefore assist transport of sperm cells. These waves of contraction are propagated through the circular muscle, and may be sufficiently powerful to occlude the lumen and, for example, to transport droplets of oil or Indian ink upward to the peritoneal cavity, but the contractions tend to fade beyond the ampullary-isthmic junction. Whether the relatively high concentration of 19-hydroxyprostaglandin E₁ or other prostaglandins of the E series in primate semen benefit sperm transport by means of some alteration in the myosalpinx remains to be clarified.

Cilia in the rabbit and pig isthmus may beat actively toward the ampullary-isthmic junction at the time of ovulation, thereby creating local currents of fluid. However, such ciliary currents have not been detected in the isthmus of cat, cow, sheep, monkey, or human.

The rate and efficiency of transport of spermatozoa are influenced by the timing of coitus relative to the moment of ovulation. Transport of cells as far as the tubal isthmus usually follows semen deposition shortly before ovulation, but it is uncertain whether sufficient viable spermatozoa would have reached the ampulla before the actual time of ovulation to be immediately available for penetration of the freshly ovulated egg or eggs. Spermatozoa may be largely sequestered in the isthmus in the preovulatory interval, only to be released for further proovarian transport when ovulation has occurred and the products of ovulation have entered the tube. The inference here is that there may be some synchrony between release of the egg from the Graafian follicle and a redistribution of spermatozoa from the constricted lumen of the isthmus.

Even though a specific attractant substance for spermatozoa has not yet been demonstrated to be released from mammalian eggs or their investments, some form of chemotaxis may contribute to the final phase of sperm transport and orientation toward the egg surface. Alternatively, maturation of the spermatozoa within the oviduct may induce intrinsic motility, which is then responsible for further progression of the spermatozoa along the oviduct to the site of fertilization.

Capacitation of spermatozoa

Although in most mammalian species the oocyte is shed from the Graafian follicle in a condition suitable for fertilization, ejaculated spermatozoa must undergo some form of physiological change in the female reproductive tract before they can penetrate the egg membranes. The interval required for this change varies from about 1.5 to 6 h according to species, and the process is referred to as capacitation. The precise changes that constitute capacitation remain unknown, although there is strong evidence that they are—at least in part—membrane-associated phenomena, particularly in the region of the sperm head, that permit release of lytic acrosomal enzymes with which the spermatozoon gains access to the vitelline surface of the egg. However, increased respiratory and flagellar activities are also noted after capacitation, the changes in motility being presumed to facilitate sperm penetration of egg membranes.

Capacitation is now understood to precede and permit a coordinated acrosome reaction, thus being an essential preliminary to activation or release of inner acrosomal enzymes and penetration of the zona pellucida; it may involve some adjustment in the distance separating the plasma and outer acrosomal membranes to permit the vesiculation reaction to proceed.

An understanding of the posttesticular changes occurring in spermatozoa in the male reproductive tract has provided some insight into the possible nature of capacitation. During passage along the epididymal duct, spermatozoa undergo a series of modifications that confer increased stability on the head, including a compaction of the nuclear chromatin and a tighter application of the plasma and acrosomal membranes to the sperm nucleus. Secretions within the epididymal duct also influence the maturing spermatozoa, for the antigenic nature of the sperm surface changes during the 1 to 2 weeks spent in epididymal transit. There is good evidence that enzyme inhibitors are “added” to the spermatozoa while still in the male, although whether the principal phase of addition occurs in the epididymis, during the preejaculatory mixing with whole seminal

plasma, or in the initial passage of spermatozoa within seminiferous and rete testis fluid remains to be clarified. Neutralization or removal of inhibitors of acrosomal enzymes in the female tract would seem a logical stage in the capacitation process, or an immediate sequel to it, and could explain how the enzymes of fundamental importance in fertilization are stabilized in the sperm head until spermatozoa are within reach of the eggs.

Although capacitation seemingly involves both membranous and metabolic changes in the sperm cell, evidence suggests that modification in the glycoprotein and other moieties of the plasma membrane is a critical step. For example, as uterine incubation of ejaculated rabbit spermatozoa proceeds, the ability of the cell surface to bind lectins disappears progressively from the tip of the sperm head, suggesting that carbohydrate-containing moieties are being removed progressively from the plasma membrane. This alteration in the cell surface would be expected to prepare it for fusion with the outer acrosomal membrane, possibly by reducing net negative charges or by increasing membrane fluidity. As a sequel to the acrosome reaction, at least in hamster spermatozoa, there is a modification in the postnuclear cap which facilitates sperm head incorporation by the egg plasmalemma.

Although conventional descriptions of the acrosome reaction emphasize that membrane fusion occurs as a means of releasing proteolytic enzymes critical for sperm penetration of the egg investments, there is evidence that hyaluronidase may escape from viable sperm cells before membrane vesiculation can be detected in the electron microscope. A second point concerning acrosomal enzymes is that acrosin—the putative zona lysin—is apparently packaged in zymogen form and needs to be activated from proacrosin during the capacitation process.

There is evidence from at least three mammalian species (rabbit, hamster, pig) that different compartments of the female tract act synergistically to promote capacitation, and that sequential exposure to the uterus and then oviduct accelerates the process of capacitation. A specific action of the oviducal environment is therefore suggested and, in the golden hamster, the effects on stimulated respiration and achievement of the capacitated state are so distinct that they can be seen through the thin wall of the ampulla in terms of a massive increase in sperm motility; even though hamster sperm reach the oviducts in under 1 h, another 3 h are required for this dramatic change to be accomplished. Precise evidence for the capacitation of primate spermatozoa is not available; if it occurs it must be rapid, since human ejaculated spermatozoa after washing, but without any exposure to female reproductive tract fluids, can penetrate matured oocytes in culture within 4 h.

The evolutionary significance of capacitation can be viewed in two ways. Physiologically, it can be regarded as a process whereby the sperm cell becomes competent to undergo an orderly sequence of membrane changes, collectively termed the acrosome reaction, to permit release of the lytic enzymes. Biologically, capacitation probably evolved to meet requirements associated with internal fertilization in mammals, and might best be regarded as an effective means of gamete selection during sperm transport through the different regions of the female reproductive tract; only spermatozoa at the optimal stage of their maturation process are able to penetrate the egg.

Fertilization

Fertilization is a process that begins with penetration of the ovum surface layer (zona pellucida) and binding to the vitelline membrane by the fully matured and acrosome-reacted spermatozoon, followed by incorporation of the spermatozoon into the ovum cytoplasm and activation of the ovum. The haploid chromosome complements of the sperm nucleus and ovum are then transformed into male and female pronuclei, respectively. The pronuclei migrate to the center of the ovum, permitting the joining of the two sets of chromosomes, or syngamy, which is the final stage of the fertilization process. The ovum, now known as a zygote, begins to develop by cell division, or mitosis. Normally, after penetration of the vitelline membrane by one spermatozoon, the fertilizing sperm, the entry of additional spermatozoa is prevented by the cortical reaction, the breakdown of cortical granules that underline the membrane. See also: [Fertilization \(animal\) \(/content/fertilization-animal/254900\)](http://accessscience.com/content/reproductive-system/581500)

Even if the processes of gamete transport succeed in bringing capacitated spermatozoa and recently ovulated eggs into functional contact in the appropriate portion of the oviduct, a viable zygote may still not be formed. Anomalies of fertilization such as digyny (retention of the second polar body) or polyspermy (penetration of the egg cytoplasm by more than one sperm) are pathological in the higher mammals, and nearly always associated with very early embryonic death. Digyny or polyspermy arises especially following postovulatory aging of the egg, a situation in which control of the numbers of spermatozoa passing through the isthmus to the site of fertilization is also less effective.

Regulation of early embryonic development and transport

As noted above, fertilization takes place in the oviducts of mammals, usually in the region of the ampullary-isthmic junction, and the fertilized eggs or embryos do not descend to the uterus for some 3 to 4 days in most species. During this interval, the embryo undergoes a series of mitotic divisions until it comprises a sphere of 8 or 16 cells and is termed a morula. Formation of a blastocyst occurs when the cells of the morula rearrange themselves around a central, fluid-filled cavity, the blastocoele. As the blastocyst develops within the uterine environment, it sheds its protective coat, the zona pellucida, and undergoes further differentiation before developing an intimate association with the endometrium, which represents the commencement of implantation or nidation. Early development of embryos in most species is largely under the control of the maternal genome, with sequential activation and utilization of oocyte components. Expression of the embryonic genome does not occur until after the two-cell stage in mice, four-cell stage in cattle, four- to eight-cell stage in humans, and eight-cell stage in sheep zygotes.

During this preimplantation period, whose duration is approximately 4 days in small laboratory species, 7 days in humans, and 2 to 3 weeks in pigs and sheep, respectively, metabolic support of the embryo depends partially on its own cytoplasmic reserves of lipids and other substrates, but to a far greater extent on constituents of oviducal and uterine secretions. The nature and volume of the secretions are known to be closely regulated by the prevailing balance of ovarian hormones, estrogen and progesterone; and since the corpus luteum is developing during this period, it follows that the secretion of progesterone will also be increasing. Thus, the dynamic situation in the pattern of ovarian steroid secretion will be reflected in a changing pattern of oviducal and uterine fluids, which is critically adjusted to meet the nutritional requirements of the developing embryo. Many experiments show that the nature of the substrate available in oviducal fluid is closely regulated by the prevailing balance of ovarian hormones and is therefore changing to match the embryo's requirement for and ability to utilize the substrates. Mouse one-cell zygotes require pyruvate or oxaloacetate as an energy source, but at the two-cell stage can also utilize phosphoenolpyruvate and lactate; only after the eight-cell stage can glucose be utilized. Human zygotes appear much less dependent on a critical composition of the surrounding medium for growth and development, since many media, both simple and complex, have been used for culture of oocytes prior to the successful replacement of the resulting zygotes into the oviduct or uterus of the infertile woman.

In nonprimate species, when developing zygotes are delayed in the oviduct beyond the time of normal tubal transport, they fail to implant; similarly, when they reach the uterus too early, subsequent development can be compromised. In primates, however, a zygote reaching the blastocyst stage in the oviduct can implant, resulting in an ectopic pregnancy. This condition is rare in nonhuman primates but not uncommon in humans, accounting for about 1% of all pregnancies. The reason for the occurrence of this condition, which is potentially life-threatening because of hemorrhage and shock subsequent to tubal rupture, is unknown; in nonprimates, oviducal secretions may be hostile to continued zygote development after the normal period of tubal transport, approximately 72 h. See also: **[Pregnancy disorders \(/content/pregnancy-disorders/543200\)](#)**

Coincident with their influence upon secretory activity, the ovarian hormones also regulate muscular activity in the oviducts, and so control passage of the embryo into the uterus. Any interference with the ratio of estrogens to progesterone during the free-living, preimplantation stages of the embryo will adversely influence fertility through dual effects on transport and nutrition

of the embryo. Administration of suitable preparations of ovarian steroid hormones, such as those contained in the contraceptive pill, thereby provides potent means of regulating fertility even when taken after coitus. In fact, in some instances, the principal mechanism whereby ovarian steroidal hormones regulate fertility is not by blocking ovulation via steroidal feedback mechanisms, but by upsetting the delicate relationship between the egg and the reproductive tract, leading to failure of fertilization or degeneration of the egg.

The factors that control muscular activity of the oviduct, and hence modulate the transport of the developing zygotes to the uterus at the correct time, have not been defined. However, it is known that oviducal motility can be influenced by prostaglandins, catecholamines, peptides (such as vasoactive intestinal peptide, neuropeptide Y, substance P, oxytocin, and vasopressin), cyclic nucleotides, and gamma aminobutyric acid. Flow of oviducal fluid and ciliary activity of epithelial cells lining the oviducts are also thought to be involved in the transport process.

Implantation

Association of the embryo with the uterine epithelium, by either superficial attachment or specific embedding in or beneath the endometrium, leads in due course to the formation of a placenta and complete dependence of the differentiating embryo upon metabolic support from the mother. Implantation and placentation exhibit a variety of forms, but in all instances the hormonal status of the mother is of great importance in determining whether or not implantation can proceed. In several species of rodent such as rats and mice, implantation is held in abeyance during lactation; while in other mammals such as roe deer, badger, and certain bears, there is an obligatory period of delayed implantation known as embryonic diapause; the inappropriate endocrine conditions associated with delayed implantation render the blastocyst metabolically dormant. Ovariectomy shortly before the expected time of implantation can prevent implantation, whereas ovariectomy plus replacement therapy with a suitable ratio of progesterone and estrogen permits implantation.

Despite this dominance by maternal hormonal factors, studies have indicated that the embryo itself may be modifying the local environment between its trophoblastic surface and the endometrium by means of steroid hormone, prostaglandin, and platelet-activating factor secretion and perhaps also by production of carbon dioxide (CO₂). The cells of the trophoblast possess enzymes capable of synthesizing ovarian hormones, and embryonic membranes supplied in culture with suitable biochemical substrates will secrete estrogens and progesterone. Such a pattern of synthetic activity in the late preimplantation embryo, which has also been indicated by histochemical studies, may explain in part the regional changes in the endometrium corresponding specifically to the future implantation sites, and also the local changes in capillary permeability of the uterus as demonstrated by the pontamine-blue reaction.

The physical relationship between the implanting embryo and the uterus is best summarized according to whether the embryo remains in the lumen of the uterus, referred to as central implantation, as in cattle, sheep, and pigs, or colonizes the glandular crypts and maternal tissues leading to eccentric or interstitial implantation, as in rodents and humans. The process of invasion by the embryonic trophoblast in the mouse, for example, promotes characteristic changes in the uterine stroma termed the decidual reaction. This cellular proliferation occurs on the fourth day of pregnancy in mice in response to the presence of a blastocyst, but the precise physiological nature of the stimulus leading to these changes is not understood.

One other feature of the implantation process that influences the form of the placenta is whether maternal cell layers are bypassed during development of the implantation association. In species where the embryo is invasive and penetrates the maternal tissues to reach the wall or lumen of the blood vessels, this gives rise to an endotheliochorial (carnivores) or hemochorial (rodents, primates) form of placenta. In other words, cells of the maternal epithelium no longer interpose between the maternal vascular supply and the developing embryo, a situation which facilitates transfer of nutrients to the fetus.

Prevention of implantation

It should be apparent that the process of implantation is susceptible to interference by hormonal or physical means, and provides a major avenue for the regulation of human fertility. Apart from contraceptive treatment with steroid hormones that disturb the oviducal transport of eggs or embryos (as described above) and hence the time relationships essential to implantation, the application of intrauterine devices (IUDs) in a variety of forms has also been used to prevent implantation and development of the embryo. Such devices consist of threads; plastic coils; and T- or 7-shaped plastic devices that release copper or T-shaped devices that release progesterone or a more potent progestational steroid, levonorgestrel; they are inserted into the uterus via the cervical canal.

Their mechanism of action in inhibiting implantation remains to be clarified; but whatever form it takes, it does not prevent the rapid restoration of fertility upon loss or removal of the device from the uterus. A component of their action is almost certainly mechanical, disturbing the spatial relationship between the blastocyst and endometrium, but recent studies on laboratory and farm species indicate that the abnormal uterine fluids produced in the presence of IUDs must also play a role directly or indirectly in preventing development of the embryo and its subsequent implantation. The observation that the addition of copper or progesterone to inert IUDs markedly increases their contraceptive efficiency suggests the occurrence of toxic or inflammatory effects in the uterus acting on the blastocyst as well as on the endometrium itself. While systematic research continues to clarify the basic mechanisms involved, particularly the manner whereby uterine prostaglandins may mediate the observed effects, the use of IUDs by many women in Western societies and in developing countries continues to give substantial protection against pregnancy, without resort to daily or weekly regimes of pill taking. In the United States, the availability of IUDs has been greatly restricted because of potential legal liability.

The most widely used method of fertility control is sterilization—vasectomy in the male and tubal ligation, resection, or cauterization in the female. In general, sterilization is nonreversible. Various plastic devices (capsules, IUDs, vaginal rings) or long-acting injectable biodegradable formulations that release potent progestational agents such as levonorgestrel, alone or in combinations with an estrogen, are possible alternatives to conventional oral contraceptives. Such devices and formulations are especially suitable for use in developing countries. The most advanced method available in certain countries comprises six silastic capsules that release levonorgestrel and are inserted under the skin of the forearm of the woman. They can provide effective contraception for up to 5 years. Methods to inhibit male fertility, other than condoms and sterilization, are not well advanced.

Much research has been devoted to the development of contraceptive vaccines. The most advanced method involves using the beta subunit of human chorionic gonadotropin (hCG) or a portion joined to a foreign protein to induce antibodies to hCG, which is required to maintain luteal function (secretion of progesterone) during early pregnancy in the human. Other antigens under consideration as the basis for a contraceptive vaccine involve proteins or glycoproteins isolated from spermatozoa or the zona pellucida (the outer coating) of the ovum. Antibodies to such antigens would prevent fertilization. Difficulties involved in development of contraceptive vaccines include risks of irreversibility, induction of autoimmune diseases, risk of teratological damage at low antibody titers, and the need to make each vaccination effective for at least 1 year.

Fertility regulation after implantation

Research is also attempting to develop a means of regulating fertility subsequent to the process of implantation. The luteotrophic support required for the early maintenance of pregnancy may be vulnerable to immunological blockade; however, in treatments requiring antibody administration, the shortcomings mentioned above must be taken into account. The alternative approach to this form of hormonal regulation is the use of compounds that are directly luteolytic in nature or block the action of progesterone at the uterine receptors and that rapidly terminate the endocrine support of pregnancy. The prostaglandin $F_{2\alpha}$ is effective as a luteolytic agent in animals but not in primates. However, administration of prostaglandins

alone during the first 49 days of pregnancy can terminate the pregnancy by directly stimulating uterine contractility with expulsion of the fetus. Side effects with this treatment are common and, although in general not life-threatening, make the method less acceptable. More promising is a potent progesterone antagonist, mifepristone, which combined with a low dose of a prostaglandin is very effective in terminating early pregnancy (up to 49 days) with minimal side effects. However, this method is available in only a few countries.

Endocrine function in reproduction

The endocrine glands secrete certain substances (hormones) which are necessary for growth, metabolism, reproduction, response to stress, and various other physiological processes. The endocrine glands most concerned with the process of reproduction are the pituitary and the gonads. Other contributions to the proper functioning of the reproductive system are provided by the thyroid, pineal, and adrenal glands. The hypothalamus is also an important organ for regulating reproduction.

See also: **[Endocrine system \(vertebrate\) \(/content/endocrine-system-vertebrate/231900\)](#)**; **[Estrogen \(/content/estrogen/242600\)](#)**; **[Pituitary gland \(/content/pituitary-gland/520400\)](#)**

The formation of gametes (spermatogenesis and oogenesis) is controlled by anterior pituitary hormones. The differentiation of male and female reproductive tracts is influenced, and mating behavior and estrous cycles are controlled, by male or female hormones. The occurrence of the breeding season is mainly dependent upon the activity of the anterior lobe of the pituitary, which is influenced through the nervous system by external factors, such as light and temperature. The ratio of light to dark during the daily cycle affects the secretion of melatonin by the pineal gland in the brain. Melatonin can be either stimulatory or inhibitory for reproductive activity in a wide variety of mammals, especially those with defined periods of estrus and anestrus (for example, sheep and many rodents). Its role in human reproduction is still uncertain, but it can inhibit ovulation in certain circumstances. The transportation of ova from the ovary to the Fallopian tube and their subsequent transportation, development, and implantation in the uterus are controlled by a balanced ratio between estrogen and progesterone. Furthermore, it is known that estrogens, androgens, and progesterone can all have the effect of inhibiting the production or the secretion, or both, of gonadotropic hormones, permitting the cyclic changes of reproductive activity among different animals.

Mammary glands are essential for the nursing of young. Their growth, differentiation, and secretion of milk, and in fact the whole process of lactation, are controlled by pituitary hormones as well as by estrogen and progesterone. Other glands and physiological activities also influence lactation, although this is largely via the trophic support of other pituitary hormones.

M. C. Chang
Michael J. K. Harper
R. H. F. Hunter

Nonmammalian species

The successful radiation of recent vertebrates has depended upon the adaptation of their reproductive cycles to the environments in which they have evolved. Since almost all environments show some degree of fluctuation (water, food supplies, temperature, light), control of the reproductive cycle of males and females of a species is essential if young are to be born at a time of year that is advantageous to survival. Such control is brought about through the brain-pituitary-gonadal axis. In this system, information about the external environment is detected by appropriate sensory structures (for example, the lateral eyes) and released to the basal hypothalamus of the brain, which regulates pituitary production of gonadotropic hormones and thus synchronizes gonadal development with environmental cues. Evidence is available for all vertebrate groups (except the degenerate hagfishes, or lampreys) to suggest that control of the gonad by the brain-pituitary system exists. This involves a brain peptide, gonadotropin-releasing hormone, that stimulates the release of two pituitary

gonadotropins. One of these, the homolog of mammalian follicle-stimulating hormone, is concerned with gamete production; the other, a homolog of mammalian luteinizing hormone, is primarily concerned with gonadal hormone production and ovulation in conjunction with follicle-stimulating hormone. With few exceptions, the known testicular and ovarian steroids that are synthesized and secreted by nonmammalian gonads are identical to the major gonadal steroids of mammals. These are progesterone and testosterone and their oxygenated and hydroxylated derivatives and the estrogens, of which the most important is estradiol-17 β . The testicular and ovarian sites of synthesis and secretion of these hormones appear to be similar, if not identical, at least down to the elasmobranch level of vertebrate gonadal organization. Plasma levels of the gonadal steroids of both sexes reflect the stage of germ cell development and correlated steroidogenic cell function. The plasma steroids thus undergo marked fluctuations associated with the gonadal cycle and ensure proper central nervous function and development of the peripheral structures of the reproductive tract so that behavioral responses and internal (elasmobranchs, reptiles, and birds) or external (teleosts and amphibia) fertilization occur.

Spermatogenesis

Throughout the Vertebrata, the cytological sequence of changes from immature, round germ cells through mature, flagellated spermatozoa is virtually identical. From early stages, germ cells form part of an anatomically and functionally related clone of cells, all derived from the same stem cell and synchronized through development. In addition to the germ cells, the primary spermatogenic units (spermatocysts) include somatic elements (the Sertoli cells) that provide structural and nutritive support and in all ways mediate between the soma and the developing germ cell. The spermatogenic process begins with a number of premeiotic spermatogonial divisions. These mitotic stages are followed by meiosis (spermatocyte stage), during which the $2n$ (diploid) number of chromosomes is reduced to the round spermatid stage. The spermatids enter a metamorphic stage during which they are transformed into elongate, flagellated spermatozoa.

The primary unit of testicular structure is the spermatoblast or spermatocyst, which consists of germ cell clones plus associated Sertoli cells. In anamniote species, germ cell clones are anatomically discrete spherical units. In contrast, in amniotes (reptiles, birds, and mammals), the spermatocyst is not closed or spherical but irregular in form and open to other clones and the tubular lumen. The individual Sertoli cells of amniotes, unlike those of anamniotes, are shared by four or five germ cell clones in succeeding generations. These nonrandom cellular associations signify functional relationships that are the basis for the cycle of the seminiferous epithelium and the spermatogenic wave of amniotes. Apart from the differences in clonal association of the Sertoli cells of the amniotes compared to anamniotes, the Sertoli cells of some anamniotes (such as fish or urodele amphibians) proliferate, and they remain associated and develop synchronously with a given germ cell clone throughout spermatogenesis; at spermiation, they degenerate or are otherwise lost into the semen. By contrast, Sertoli cells of reptiles, birds, and mammals are permanent elements of the seminiferous epithelium, nurturing generation after generation of developing germ cells. In these groups, Sertoli cell mitoses are thought to be restricted to prepubertal development.

The secondary germinal compartment is delineated by a boundary wall and composed of blind-ended sacs (lobules) or open-ended lobules, both of which are continuous with the intratesticular collecting duct system and surrounded by the endocrine Leydig cells. In the elasmobranchs, however, definitive Leydig cells appear to be absent; the spermatocysts are embedded in connective tissue stroma and joined to collecting ducts via a short stalk patent only at spermiation. In some teleosts and in urodele amphibians, a secondary germinal compartment can be identified in mid-late developmental stages, with stem cells and spermatogonial stage spermatocysts embedded directly in connective tissue stroma. The secondary germinal units are continuously formed adjacent to the germinal region and then regress after spermiation. Leydig cells are limited to lobular-tubular regions. In some teleosts and anuran amphibians and in all amniotes, Sertoli cells and germ cells are permanent components of the adult testis, containing germinal elements at all developmental stages. Interstitial Leydig cells are present.

In all species, there is a strict temporal and spatial relationship among the different germ cell stages. Species variation is

evident, however, in the timing and anatomical organization of cells in the spermatogenic sequence. The unique developmental sequence of spermatogenesis is regulated at several levels: at the organismal level, by circulating gonadotropic hormones; at the organ level, by local (paracrine-autocrine) factors; and at the cellular level, by direct cell–cell interactions. Comparative studies suggest that the Leydig cells evolved primarily for the secretion of steroids into the peripheral circulation. Although of secondary importance to the Leydig cell in the supply of steroid hormones, the nonmammalian Sertoli cell has a steroidogenic capacity that is quantitatively more important than that of mammals in providing the steroidal needs of germ cell production; in elasmobranchs, Sertoli cells are the primary steroidogenic component of the testis throughout the year. The elasmobranch testis is of particular interest, inasmuch as germ cell–Sertoli cell units can be harvested at specific stages of development, and it is possible to correlate steroidogenic function with specific stages. Androgen production is correlated with the more mature stages of sperm development, and androgen synthesis and specific estrogen receptors are significantly correlated with earlier spermatogenic stages. Studies with the mud puppy, *Necturus*, support a role for estrogen in the proliferation of early germinal elements because both androgen and estrogen receptors are found in testicular zones with immature germ cells. As in mammals, gonadal steroid hormones in nonmammals are transported within the testis and blood by androgen-binding proteins, as demonstrated in trout and shark.

Oogenesis

As in mammals, oogonial proliferation in nonmammalian vertebrates is characterized by the presence of intercellular bridges, probably important in synchronizing of mitosis. Oogonial proliferation may be limited to the embryonic (larval) period (in lampreys, elasmobranchs, some bony fishes, and birds) or to the adult (in most teleosts, amphibians, and reptiles). Little is known of the role of hormones in the regulation of oogonial proliferation, but some evidence suggests that gonadotropins and possibly gonadal steroids increase oogonial division in some adult fish, amphibians, and reptiles. Primary oocyte growth appears to be gonadotropin-independent in cyclostomes; in contrast, in amphibians and reptiles, the process is gonadotropin-dependent, and atresia of primary oocytes in hypophysectomized amphibians and reptiles is prevented by gonadotropins. Folliculogenesis, or the investment of the primary oocyte with follicle cells to form a primordial follicle, is similar in all nonmammalian vertebrates. As in mammals, the trigger for folliculogenesis is not known, but considerable evidence suggests that at least the vitellogenic stages of follicular growth in all nonmammalian species are dependent upon pituitary gonadotropins. In amphibia and teleost fish, the resumption of meiosis at the onset of oocyte maturation and subsequent ovulation is gonadotropin- and progestin-dependent, as in mammals. Although all nonmammals produce yolky eggs, the lampreys, teleosts, and amphibians generally produce large numbers of small yolky oocytes, and the elasmobranchs, reptiles, and birds produce fewer, larger yolky eggs. A hierarchical arrangement of follicles or cohorts of follicles is readily seen in some reptiles and birds. Smaller ovarian follicles represent future generations of oocytes to be ovulated sequentially.

The process of hepatic yolk protein synthesis, vitellogenesis, is regulated by the ovarian hormone 17(β)-estradiol and thus indirectly by the pituitary gland. The action of estradiol on the induction of yolk protein synthesis by the liver has been well studied. The process is steroid receptor–mediated and involves the hormonal induction of specific vitellogenin genes in liver cells. Vitellogenin, a complex phospholipoglycoprotein, is secreted into the blood by hepatic cells and is sequestered from the blood by developing oocytes under the influence of gonadotropin. In reptiles, it appears that hormones other than estradiol are involved in vitellogenesis. Growth hormone is synergistic with estrogen and required for the full expression of the estradiol effect. In contrast, progesterone, testosterone, and prolactin appear to be inhibitory to vitellogenin synthesis. Of these hormones, the progesterone is of particular interest in the vertebrate groups in which viviparity (live-bearing) is a common reproductive strategy (as opposed to egg laying, such as in elasmobranchs or squamate reptiles).

The evolution of live-bearing from the primitive egg-laying mode of reproduction has occurred in parallel in all vertebrate groups except birds. Physiologically, this process requires the retention of eggs, loss of the outer eggshell membranes, and the ultimate development of a placental mechanism. The placenta, when present, is involved in fetal nutrition and ultimately

supplants the process of vitellogenesis. In elasmobranchs and reptiles, species have been described in which the dependency of the nutrition of intrauterine young upon the placenta has reached a near-mammalian condition. A corollary of this development is the reduction or elimination of yolk from the eggs. Some evidence suggests that the ovarian hormone progesterone is responsible for the switch from oviparity to viviparity through an inhibitory action on the smooth muscle of the reproductive tract. This tends to favor egg retention and thus viviparity. In mammals, progesterone is of primary importance for the maintenance of a quiescent uterus during gestation. Since even elasmobranch corpora lutea (formed from follicles after ovulation) synthesize and secrete progesterone, which inhibits uterine muscle activity, it appears that many of the endocrine mechanisms associated with reproduction and reproductive tract adaptations for egg, embryo, and fetal care were evolved early in vertebrate evolution. Coincident with the effect of progesterone on the reproductive tract and egg retention, the function of the hormone to switch off cyclic vitellogenesis is extended during evolution to a progressive inhibition of vitellogenesis as placentation takes on the role of embryo-fetal nutrition.

In general, the two layers of the ovarian follicle wall (theca and granulosa) cooperate to carry out the enzymatic conversions from cholesterol through progesterone and androgens to estrogens. However, the two components have different roles in different species. Thus, androgens are converted to estrogens by the granulosa cells of fish and mammals, but this function is performed by the theca in birds. Conversely, androgens are produced by the mammalian theca, but by the avian granulosa. In elasmobranchs, the granulosa elements are the primary steroidogenic components, being able to synthesize estrogens from cholesterol. In a squamate reptile (snake), thecal synthesis of estradiol is low in the absence of substrate in the form of progesterone supplied by the granulosa. This pattern of enzymatic activities in the snake ovarian follicle is unique in vertebrates. In all vertebrate groups, ovarian follicular steroid synthesis and secretion is gonadotropin-dependent. In at least elasmobranchs and reptiles, corpora lutea formed from the ovulated follicle are steroidogenic and produce progesterone in response to gonadotropins in the living organism and in cell culture. In general, in all vertebrates, gonadal steroids have been identified in plasma, and cyclic fluctuations of plasma levels of the principal ovarian steroids—progesterone, testosterone, and estradiol—correlate well with ovarian follicular development and ovulation. There is evidence that the circulating hormones have extensive actions on the peripheral target tissues that are important in the synchronization of the reproductive process in nonmammalian species.

Ian P. Callard

Neuroendocrine function

The associated physiological activities of the nervous system and of the endocrine system that influence animal reproduction are briefly dealt with here to illustrate the intrinsic mechanism involved. In the lower forms of life, especially in those forms without a nervous system, the rhythm of reproduction may be controlled metabolically by the direct action of environmental factors—food, temperature, light, humidity, and chemical composition of the environment. In the higher forms, certain external factors act through the intermediation of the nervous system. In the bird, the number of eggs in a clutch is generally constant within narrow limits; if the eggs are withdrawn shortly after they are laid, many birds will go on laying, making an attempt to lay the right number. In the pigeon, ovulation often is induced by courtship with another pigeon. The number of eggs laid has been reported to be increased if a mirror is placed in front of a pigeon cage. These instances illustrate the influence of the nervous system on reproduction. See also: [**Neurosecretion \(/content/neurosecretion/450200\)**](#)

Stimuli

Experimental study on birds and on ferrets has shown that breeding can be induced in midwinter by artificial light. Hypophysectomized and blind ferrets do not ordinarily react to light as expected, and it is obvious that the stimulus must be passed through the eye, optic nerve, or some receptors in the pineal gland or brain region, and via changes in secretion of melatonin or other indoles, and thence to the anterior pituitary. Moreover, the rabbit, ferret, and ground squirrel normally

ovulate in response to the stimulation of copulation. Since this stimulation to switch from the follicular phase to the luteal phase cannot be effected in the absence of the pituitary but can be brought about by injecting pituitary extracts or pituitarylike extracts, pregnant woman's urine (PU) or pregnant mare serum (PMS), it would seem that this stimulus is normally due to nervous reflexes mediated through the hypothalamus and pituitary. The stimulus, however, may be carried by several nervous paths, because local anesthesia of vagina and vulva, complete thoracosympathectomy, absence of any nerve pathway to the ovaries, or cervical sympathectomy will not inhibit ovulation after coitus. Because stimulation of the brain, of the lumbosacral part of the spinal cord, of the cervical sympathetic ganglion, or of the hypothalamus will induce ovulation to a certain extent, it seems that more than one nervous path and more than one mechanism for the initiation of ovulation must be involved. Furthermore, the rat, unlike the rabbit, ovulates spontaneously, but a prolongation of the life of the corpora lutea with subsequent pseudopregnancy can be induced by sterile mating, mechanical stimulation of the cervix, or electrical stimulation of the brain. Pseudopregnancy in the rat also seems to be mediated by the pituitary through nervous pathways. There is additional evidence to show that the stimulus for luteinizing hormone release in a spontaneously ovulating animal is controlled by nervous mechanisms employing cholinergic and adrenergic components.

Lesions

It is well established that lesions in the basal tuber or median eminence induce ovarian atrophy in the cat, dog, and rabbit. The role of the nervous system in establishing cyclic pituitary activity has also been emphasized. Localization of an erection center and of an ejaculation center in the hypothalamus has been reported. Appropriately placed hypothalamic lesions in the female guinea pig sometimes result in anestrus or prolonged estrous periods with sexual behavior in keeping with the gross changes of the cycle. In the male guinea pig, similar lesions induce sexual impotence, without genital regression. Hypothalamic production of oxytocin and the derivation of vasopressin from neurosecretory process have been postulated. As for mating behavior, it is assumed that advancing evolutionary status is accompanied by a progressive dominance of the nervous system and a corresponding reduction of endocrine control. To interpret the effect of sex hormones on mating behavior, it has been suggested that their activity may increase the excitability of the central excitatory mechanism.

Fertility and sterility

The ability or inability to produce offspring is termed fertility or sterility. Fertility and sterility occur in different grades among various species and among individuals of the same species. Absolute sterility is rare, but infertility of all degrees is very common, especially among higher vertebrates. The rate of reproduction in any species depends upon the average number of young born in each litter, the frequency of recurrence of breeding season, the duration of the reproductive period, and the age at which the animal starts to breed. The age as a general rule is earlier in small species than in large ones. In general, the number of young in a litter of mammals is inversely proportional to the size of the animal. For instance, a cow rarely produces twins, whereas the rat occasionally bears as many as 16 young. A theory of fertility has been proposed that states that individuation and genesis vary inversely; that is, the power to sustain individual life and the power to produce new individuals are inversely proportional. Where there is abundant food supply and a favorable environment, and the necessary expenditure of energy is relatively slight, the cost of individuation is much reduced and the rate of genesis is correspondingly increased.

See also: [Infertility \(/content/infertility/343450\)](http://accessscience.com/content/infertility/343450)

Factors controlling fertility

J. Hammond proposed that three factors control fertility:

1. The number of ova shed. In accordance with the genetic constitution of the species and the nutritional status, the number of ova shed is controlled by gonadotropic hormones through the pituitary gland, but influenced by external factors. Before puberty, at old age, and during pregnancy, pseudopregnancy, and early lactation, very few mammals ovulate. Although by

administering gonadotropic hormones the possibility of increasing the number of ova shed in mammals was demonstrated, the actual number of young produced was rather low, probably as a result of limitations to support excessive embryos.

2. The number of ova fertilized. This depends upon the number of spermatozoa produced by the male, and the morphological and physiological integrity of the gametes. It also depends upon the probability of meeting between gametes provided by the male and female in the lower vertebrates, the efficiency of sperm transport to the site of fertilization, and the time of mating in the higher vertebrates. Aging phenomena in gametes have a deleterious influence on fertility.

3. The number of embryos developing into self-sustaining individuals. The probability of normal development depends upon where ova are deposited and the protection that the parents give to the zygotes in the lower vertebrates. In the higher animals, it depends upon the transportation of zygotes to the prepared uterus at the right time, and the physiological activities of embryo and of mother for proper implantation, for the maintenance of pregnancy, and for proper parturition.

Control of reproduction

The topic of controlling fertility, for example, the regulation of implantation in humans described above, should not be left without portraying the considerable technology available to modify fertility in domestic animals.

While artificial breeding of cattle, and to a lesser extent pigs, sheep, and goats, by means of insemination of deep-frozen or diluted semen samples has been extensively applied in recent years, enabling the exploitation of males of superior genetic merit, other features of contemporary reproductive technology are less widely known; attention will be devoted to two of these. The first can be termed controlled breeding, as seen in the various techniques of synchronization of estrus. There are obvious advantages in being able to decide when an animal is to be bred, not only for convenience at the time of artificial insemination or mating, but also because the time of birth, weaning, and marketing of the offspring can be predicted quite accurately. The key to controlled breeding lies in reprogramming the ovary, and treatments attempt to modify, in the short term, the influence of the secretions of the corpus luteum and the Graafian follicle expressed, respectively, in the luteal and follicular phases of the cycle. Inducing synchronized estrus in a population of animals is achieved most effectively by causing regression of the corpus luteum so that animals enter the follicular phase and estrus approximately synchronously.

The demonstration in the late 1960s that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was almost certainly the luteolytic factor in domestic species, informing the ovary that the uterus did not contain a viable embryo and inducing regression of the corpus luteum, has caused this hormone to become the basis of extensive estrous synchronization programs, replacing the progestagenic compounds previously used to simulate and extend the luteal phase prior to a synchronized follicular phase. Potent synthetic analogs of $PGF_{2\alpha}$ are now available that cause luteolysis following a single intramuscular injection. However, the corpus luteum in cattle is only susceptible to injected $PGF_{2\alpha}$ between days 5 and 15 of the 21-day estrous cycle; thus, to achieve synchronization in all animals in a herd, two injections are given 10 days apart. Nearly all animals will be in estrus within 48–72 h of the second injection, when they can be inseminated as a group. Prostaglandins are being used in this manner extensively.

Another area of reproductive technology in domestic animals receiving attention is that of storage and transplantation of embryos, particularly in the context of exploiting rare or exotic breeds of cattle after procedures of superovulation to increase egg numbers. Transplantation of embryos is, of itself, not a new technique, for it was successfully performed in rabbits before the turn of the century, and since about 1950 embryo transfer has been a leading experimental tool in reproductive physiology. Two of the biological facts permitting such manipulations of the embryo are the relatively long period during which the blastocyst is free-living in the uterine lumen before implantation, especially in pigs, sheep, and cattle (ungulates), and also the fact that the embryo is not rejected as foreign material from the host uterus.

Apart from the care needed during handling and storage of embryos in the culture medium, many experiments have indicated that the single most important factor determining the success of a transfer operation is the degree of synchronization of estrous cycles between the donor and recipient animals. In cattle and sheep, there is some degree of tolerance in the timing; but once development of the embryo is more than 24 h out of phase with that of the recipient uterus, the pregnancy rate commences to decline sharply. Transfer of single, freshly recovered embryos by a surgical means involving an incision to expose the uterus can lead to 90% of the transferred embryos developing into calves. Transfer of two embryos, one to each horn of the uterus, has been used to induce twinning in cattle, although here the success rate is closer to 70%. Nonsurgical transfer of embryos, that is, their introduction into the uterus from the vagina by means of a suitable pipette, has been much less satisfactory, rarely giving pregnancy rates of greater than 20–40%. Apart from the greater risk of introducing infection by this approach, there is also the problem of ejection of embryos which usually follows manipulation of the cervix during the luteal phase. Nevertheless, now that bovine embryos can be preserved at -321°F (-196°C), as has been the case for spermatozoa for many years, the emphasis is on overcoming the problems of nonsurgical transplantation. With synchronization of estrus being a practical proposition, and deep-frozen banks of embryos in the offing, the attraction of breeding programs involving this technically straightforward means of propagation is considerable, although it can be economically justified only for valuable animals with desirable genetic traits.

In several species of farm animals (sheep, cattle, and pigs), zygotes up to the 8–16-cell stage can be halved or quartered. The separated clumps of cells can then be placed in homologous zonae, from which all cytoplasmic material has been removed, and can develop into normal young after retransfer to a suitable recipient. Not only does this technology rapidly create additional copies of the traits of a particular mother or father, or both, but it also provides for identical twins, triplets, and so forth for studies of the impact of environmental and nutritional factors on the same genetic background. Such a technique will be useful primarily as a research tool rather than for production purposes, where transgenic animals will be more useful.

Such advances in control of animal reproduction have given rise to the application of these techniques to humans for the alleviation of infertility. Men with low sperm counts or poor spermatozoal motility can be assisted by collection of the semen specimen and concentration of the spermatozoa. The chance of pregnancy can be improved if the female partner undergoes artificial insemination with such treated sperm samples at the time of midcycle ovulation.

Infertile women can be induced to mature larger numbers of follicles by treatment with hormones. Ova from such follicles can then be recovered and placed in the oviduct with a prepared sperm sample; matured and fertilized in a culture dish and replaced in the oviduct; or matured, fertilized, and cultured in a dish and then replaced into the uterus. Many thousands of children have been born worldwide following such procedures.

In addition, zygotes can still develop normally after removal of one or more blastomeres. Through the use of polymerase chain reaction amplification of gene sequences from such a blastomere, prenatal diagnosis of genetic defects can be detected prior to replacement of an externally fertilized embryo in the mother. Such techniques can revolutionize the field of prenatal diagnosis, and have been used to detect a number of hereditary disorders. See *also*: **[Polymerase chain reaction \(PCR\) \(/content/polymerase-chain-reaction-pcr/900192\)](/content/polymerase-chain-reaction-pcr/900192)**; **[Prenatal diagnosis \(/content/prenatal-diagnosis/543350\)](/content/prenatal-diagnosis/543350)**

In animals, research has focused on the production of transgenic animals. Most experiments have been conducted in mice, although the techniques developed are being tried in farm animals. Genetic material with desirable characteristics can be isolated with the techniques of molecular biology, and the deoxyribonucleic acid (DNA) can be microinjected into the ovum, or inserted into embryonic stem cells in a culture dish; then, the cells can be microinjected into the cavity of a blastocyst and become commingled with the cells of the host inner cell mass. The foreign DNA can integrate into the host chromosomal DNA and can be carried into both germ and somatic cells. The transgenic animal passes the foreign DNA to its offspring in a

mendelian manner. After introduction of genes that are normally expressed in a tissue-specific manner, the location of DNA sequences important in developmental programming of each gene can be determined. The gene for rat growth hormone injected into mouse ova gave rise to mice that grew much larger than their noninjected siblings.

Other areas in which contemporary reproductive technology is attempting to increase animal productivity include induction of ovulation at a precise time, increasing the numbers of eggs shed (superovulation), extending the breeding season of sheep and goats, and, perhaps most important of all, regulating the time of parturition to avoid perinatal losses. In the future, this technology will doubtless also include the application of pheromones to modify in diverse ways the reproductive activity of farm livestock, and the possibility of predetermining the sex of offspring by insemination of X- or Y-bearing spermatozoa in fractionated semen samples. See also: [Genetic engineering \(/content/genetic-engineering/285000\)](#); [Reproductive technology \(/content/reproductive-technology/581625\)](#)

M. C. Chang
Michael J. K. Harper
R. H. F. Hunter

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