CLINICAL EMBRYOLOGY FOR MEDICAL STUDENTS

THIRD EDITION

RICHARD S. SNELL, M.D., Ph.D.

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Atlas of Clinical Anatomy is coordinated with
Clinical Anatomy for Medical Students. Coordinated with both
is a completely illustrated dissecting room manual
entitled *Gross Anatomy Dissector*.

The other texts by Dr. Snell are
Clinical Neuroanatomy for Medical Students
and *An Atlas of Normal Radiographic Anatomy*
(the latter with Alvin C. Wyman, M.D.).

PREFACE

Embryology provides a basis for understanding gross anatomy and an explanation of many of the congenital anomalies that are seen in clinical medicine. The purpose of this book is to give the student a concise account of the development of the human body. At the end of all pertinent chapters there is a description of the more common congenital anomalies that a practicing physician is likely to encounter. References to embryological literature are included so that students can acquire a deeper knowledge of specific areas of interest, should they so desire.

In this third edition, many of the simple illustrations have been redrawn and color has been included. Photographs of human embryos have been added. Again, clinical problems requiring embryological knowledge for their solution are presented at the end of each chapter. Both the clinical information and the clinical problems have been brought up to date.

The text of this edition has been shortened by eliminating some detail that does not contribute to the understanding of gross anatomy or of the formation of congenital anomalies.

I am grateful to the many students, colleagues, and friends who made valuable suggestions regarding the preparation of this new edition. In particular I would like to thank Dr. Patricia Krupp of the University of Vermont for her helpful comments. I am most grateful to the following clinical colleagues at The George Washington University Medical Center who provided me with photographic examples of congenital anomalies: Dr. John P. Adams, Professor and Chairman of Orthopedic Surgery; Dr. Gordon Avery, Professor of Child Health and Development; Dr. Mervyn Elgart, Professor and Chairman of Dermatology; Dr. David S. Friendly, Professor of Ophthalmology and of Child Health and Development; Dr. Pandit Klug, Associate Professor of Medicine; Dr. Lawrence S. Lessin, Professor of Medicine and of Pathology (Hematology); Dr. Harry Miller, Professor and Chairman, Department of Urology; Dr. Robert J. Neviaser, Professor of Orthopedic Surgery; Dr. Mark M. Platt, Associate Professor of Neurology and of Child Health and Development; Dr. Judson G. Randolph, Professor and Director of Pediatric Surgery; and Dr. Lewis W. Thompson, Professor and Chairman of Plastic Surgery, Child Health and Development.

I am also greatly indebted to Dr. Robert Chase, Emile Holman Professor of Surgery, Stanford University School of Medicine, Stanford, California, for additional photographs illustrating clinical cases. I wish to extend sincere thanks to my artists, Mrs. Terry Dolan and Mrs. Virginia Childs, for the earlier preparation of artwork and to Myra Feldman for the very fine new art in this edition. To Jill Weinstein, the photographer in the Audiovisual Department, George Washington University School of Medicine, acknowledgment is due for her expert skill in taking the photographs of embryos and fetuses. To the librarians of The George Washington University School of Medicine my thanks are due for their help in obtaining much-needed reference material. I am greatly indebted to Miss Sandra Kosha for typing the manuscript.

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GAMETOGENESIS

Gametogenesis is the term used to describe the development of the male and female germ cells or *gametes*. The male germ cell is the *spermatozoon* and its development is known as *spermatogenesis;* the female germ cell is the *oocyte* and its development is called *oogenesis*.

SPERMATOGENESIS

Spermatogenesis takes place in the seminiferous tubules of the testes.

The Testes and Their Ducts

The testes are paired ovoid organs situated in the scrotum (Fig. 1-1). The descent of the testes from the abdominal cavity into the scrotum (Chap. 16) is important, since it has been found that spermatogenesis will take place normally only if the testes are at a lower temperature than that of the abdominal cavity. Each testis has a thick fibrous capsule, the *tunica albuginea* (Fig. 1-2), which is thickened posteriorly to form the *mediastinum testis*. Extending from the inner surface of the capsule to the mediastinum is a series of fibrous septa that divide the interior of the organ into about 250 lobules. Lying within each lobule are one to three coiled *seminiferous tubules*. Each tubule is in the form of a loop, the ends of which are continuous with a *straight tubule*. The straight tubules open into a network of channels within the mediastinum testis called the *rete testis*. Situated within each lobule, between the seminiferous tubules, are delicate connective tissue and groups of rounded *interstitial cells* (Leydig cells) that produce the male sex hormone *testosterone*.

The rete testis is drained by *efferent ductules* into the long much-coiled duct, the *epididymis* (Figs. 1-1 and 1-2), which is situated on the posterior surface of the testis. The duct of the epididymis becomes continuous with the thick-walled *vas deferens*. This emerges from the lower end or *tail* of the epididymis and passes up through the inguinal canal into the abdomen. On reaching the posterior surface of the bladder, it joins the duct of the *seminal vesicle* to form the *ejaculatory duct*, and this in turn opens into the prostatic part of the *urethra*.

Seminiferous Tubule

The wall of the seminiferous tubule (Fig. 1-2) has a basement membrane lined by an epithelium consisting of a number of layers of cells. The basal layer consists of two types of cells: the scattered, tall pyramid-shaped *Sertoli cells*, which extend from the basement membrane to the lumen of the tubule, and, lying between these cells, the numerous germinal cells, the *spermatogonia*. The spermatogonia are of two types, A and B. Type A spermatogonia are the stem cells, which undergo mitotic division to form additional type A spermatogonia and a more differentiated type B spermatogonia. After this division, type B spermatogonia now divide by mitosis into *primary spermatocytes*. The latter cells migrate toward the middle zone of the seminiferous epithelium and then undergo meiotic division into smaller *secondary spermatocytes*, each containing half the number of chromosomes of the primary cell. The secondary spermatocytes soon divide to form the smallest cells, the *spermatids*, which become embedded in the cytoplasm of the free ends of Sertoli cells. The spermatids now undergo a series of morphological changes, with the ultimate formation of *spermatozoa*. The nucleus of the spermatid condenses and becomes slightly flattened and elongated in shape. It forms most of the sperm head. Granules within the vacuoles of the Golgi apparatus coalesce to form the

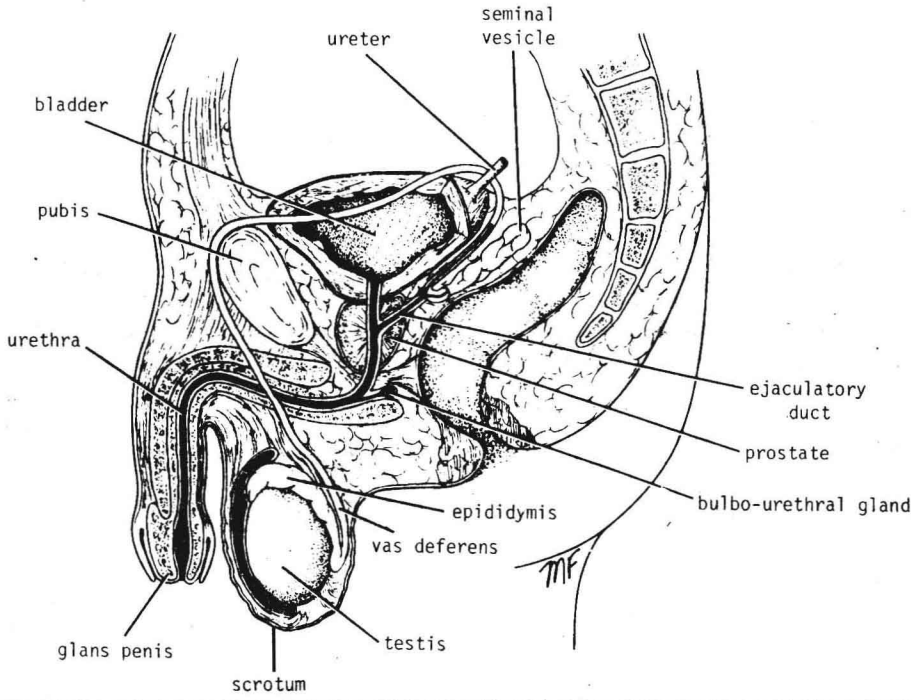

Fig. 1-1. Male reproductive system as seen in sagittal section.

acrosomic granule. This granule then spreads out over the surface of the nucleus as a thin membrane called the *acrosomal cap.* The centrioles move to the side of the nucleus opposite the acrosomal cap. There, one of the centrioles gives rise to an *axial filament* that grows out and penetrates the cell surface. At the same time the mitochondria migrate toward the axial filament and become arranged around it in the form of a sheath or collar. At the distal end of the mitochondrial collar is a ring-like structure, the *terminal ring.* The collar and terminal ring lie within the *middle piece* or *body* of the spermatozoon. The remainder of the cytoplasm is cast off from the developing spermatozoon and degenerates. The fully formed spermatozoon now leaves the Sertoli cell and becomes free within the lumen of the seminiferous tubule. It has been estimated that the total duration of spermatogenesis is 64 days. The spermatozoon moves successively through the straight tubules, rete testis, and efferent ductules to the epididymis. It is believed that smooth muscle in the walls of these tubes is responsible for this movement. While lying within the epididymis, the spermatozoon undergoes further maturation, as seen by the increase in motility and fertilizing power.

Control of Spermatogenesis

Spermatogenesis begins at about 14 years of age as the result of stimulation of the spermatogonia by the *follicle-stimulating hormone (FSH)* secreted by the anterior lobe of the pituitary gland. It is important to understand that FSH stimulates spermatogenesis only as far as the stage of the formation of secondary spermatocytes. For the complete formation of mature spermatozoa, testosterone must be produced simultaneously by the interstitial cells of the testis. The interstitial cells are stimulated to produce tes-

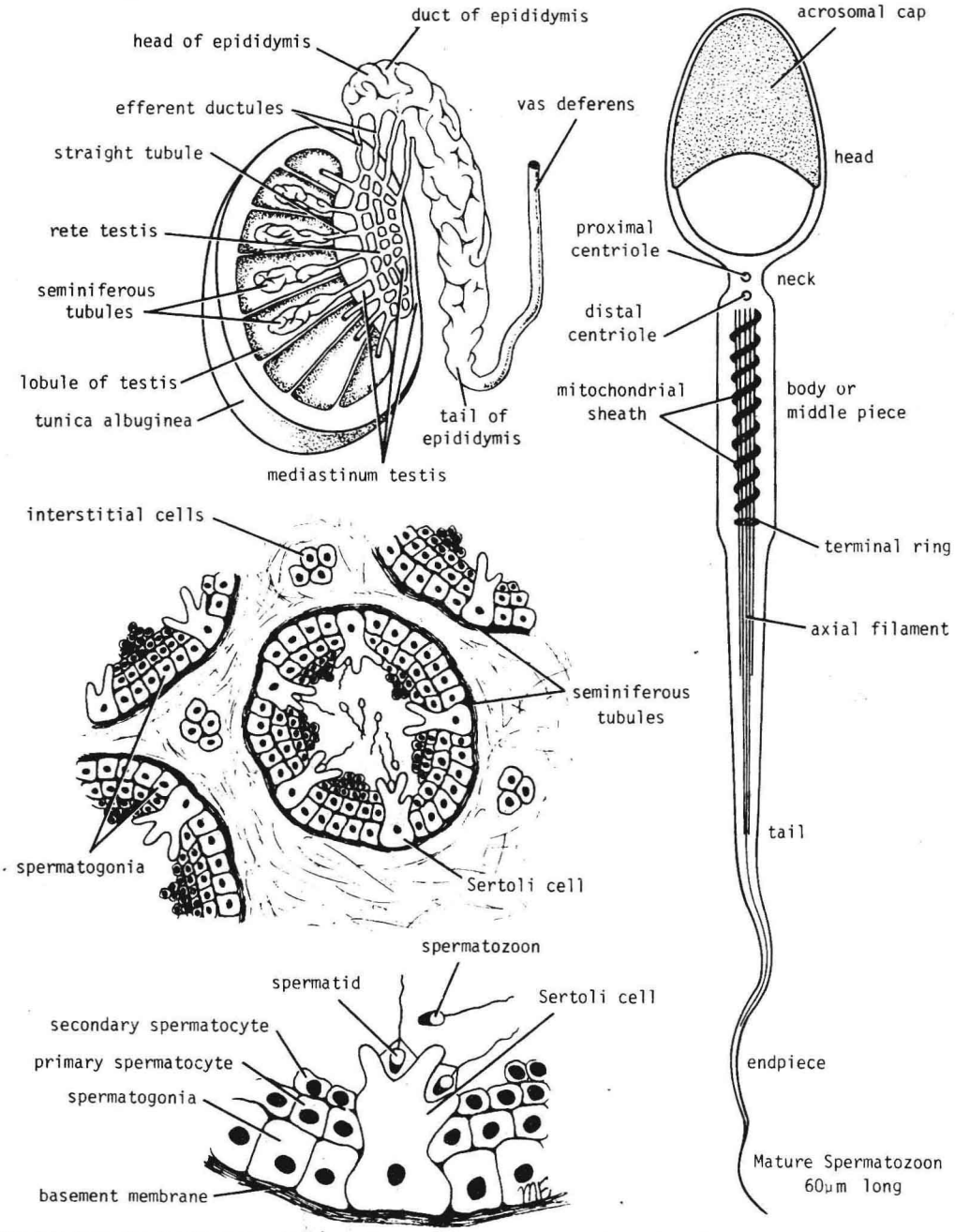

Fig. 1-2. Spermatogenesis.

tosterone by the *interstitial cell–stimulating hormone (ICSH)*, which also is produced by the anterior lobe of the pituitary gland. Thus, the start of spermatogenesis at puberty depends on the following factors: The testis must be at the correct temperature and therefore be in the scrotum, and there must be adequate secretion of FSH and ICSH. Spermatogenesis continues into advanced old age, but after middle age, increasing numbers of atrophic tubules are found.

Mature Spermatozoon

The mature spermatozoon measures about 60 μm in length. It consists of a *head*, *neck*, *body*, and *tail* (Fig. 1-2). The head is formed largely by the condensed nucleus and is covered by the cell membrane. Covering the anterior two-thirds of the nucleus under the membrane is the acrosomal cap. This contains several enzymes, including hyaluronidase and proteases, which are used in the process of penetration of the ovum. Behind the head, the spermatozoon is slightly constricted to form the neck and this contains the two centrioles. The axial filament arises from the distal centriole and in the body consists of a pair of central fibrils surrounded by two concentric rings of nine fibrils. Outside the concentric rings, another ring of coarse fibrils is present. Mitochondria are arranged spirally around the axial filament within the middle piece or body. The spiral collar of mitochondria ends distally at a terminal ring. The tail forms the greater part of the spermatozoon and is the motile part of the cell. The tail contains the pair of central fibrils surrounded by the two concentric rings of nine fibrils. The outer coarse fibrils are present only at the proximal end of the tail. The spermatozoon is covered by a thin layer of cytoplasm and a cell membrane. Thus it is seen that the head of the spermatozoon contains the structures responsible for the transmission of genetic information and the acrosomal cap contains enzymes that can bring about the penetration of the ovum by the spermatozoon. The mitochondria within the body provide energy for locomotion and the tail is a flagellum that propels the spermatozoon forward.

OOGENESIS

The term *oogenesis* is applied to the development of the oocyte or ovum that takes place within the ovaries.

Ovary

The mature ovaries are paired ovoid organs situated within the pelvis (Fig. 1-3). Each is suspended from the posterior surface of the *broad ligament* of the uterus by a short mesentery, the *mesovarium* (Fig. 1-4). The ovaries are surrounded by a thin fibrous capsule, the *tunica albuginea*. This is covered externally by a single layer of cuboid cells called the germinal epithelium. The term *germinal epithelium* is a misnomer, since this cell layer does not give rise to ova (for further details, see p. 219). The germinal epithelium is a modified area of peritoneum and is continuous with the squamous mesothelial cells of the general peritoneum at the hilum of the ovary where the mesovarium is attached. The ovary has an outer *cortex* and an inner *medulla*, but the division between the two is not clearly defined. Embedded in the connective tissue of the cortex are the *ovarian follicles* in different stages of development and degeneration. The medulla consists of highly vascular connective tissue.

Ovarian Follicles

During early fetal development primordial germ cells migrate from the yolk sac into the developing ovaries. These cells then differentiate into *oogonia*. By the third month after conception, the oogonia start to undergo a number of mitotic divisions within the cortex of the ovary to form the *primary oocytes*. The oocytes now enter the prophase of their first meiotic division, and by the time of birth they are in a late stage of prophase of their meiotic division. The primary oocytes become surrounded by a single layer of flattened cells and are known as *primordial follicles*. The surrounding cells are termed *granulosa cells*. Many oogonia and primary oocytes degenerate during the fifth and sixth months of fetal life (for details, see Chap. 16). The surviving

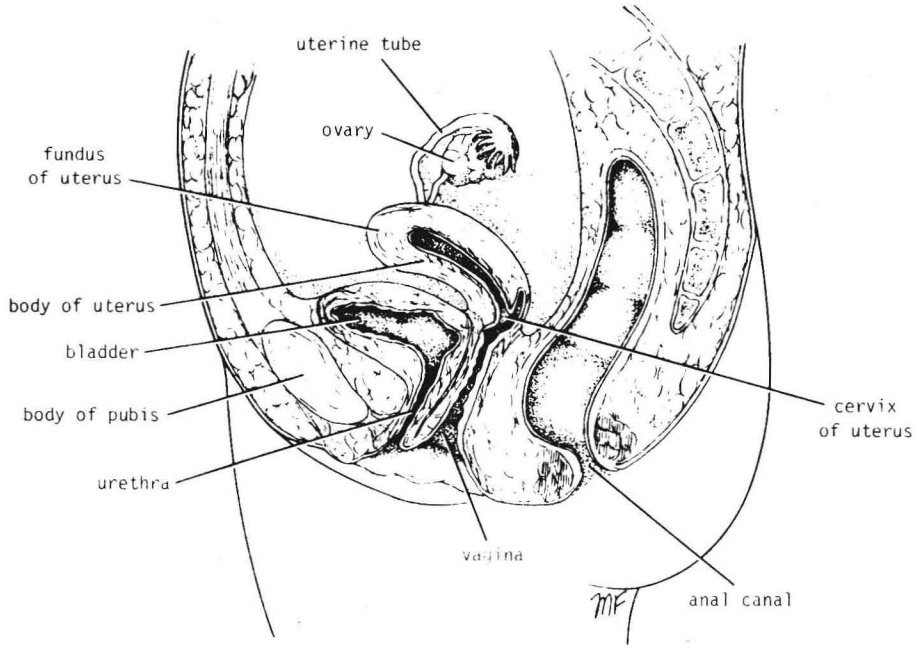

Fig. 1-3. Female reproductive system as seen in sagittal section.

primordial follicles mainly occupy the periphery of the cortex. The nucleus of the oocyte is large, pale, and centrally placed. Little chromatin is seen, but the nucleolus is prominent. The cytoplasm is pale and yolk granules are evenly dispersed throughout it. At birth there may be more than 700,000 follicles present in the two ovaries. The number diminishes with age, so that about 40,000 survive to puberty.

At puberty, the hypothalamic neurosecretory cells start secreting the *FSH releasing factor*. This stimulates the cells of the anterior lobe of the pituitary to produce FSH, which in turn stimulates the ovarian follicles so that the ovarian cycles begin. With each cycle, many follicles in both ovaries start to enlarge, but gradually only one follicle gains ascendancy and reaches maturity, while the remainder degenerate and become *atretic follicles*. As a result, one ovum normally ovulates during each ovarian cycle. It has been estimated that during a woman's reproductive life only 300 to 400 follicles come to full maturity and liberate ova from the ovaries.

The primordial follicles increase in size after puberty in response to the FSH of the pituitary. The granulosa cells become cuboid in shape and begin to divide, so that the oocyte is surrounded by a number of layers of granulosa cells. These cells now secrete around the oocyte a hyaline material consisting of glycoproteins. This material forms the *zona pellucida*. As the oocyte increases in size, irregular spaces filled with clear fluid, the *liquor folliculi*, appear among the granulosa cells. These spaces later coalesce to form a single cavity, the *follicular antrum*. The granulosa cells that line the cavity make up the *membrana granulosa*. The oocyte, still surrounded by granulosa cells—the *cumulus oophorus*—projects into the antrum from one side. At this stage of development the follicle is known as a *graafian follicle*. While the follicle has been increasing in size, the surrounding stroma has been differentiating into an inner vascular layer of secretory cells, the *theca in-*

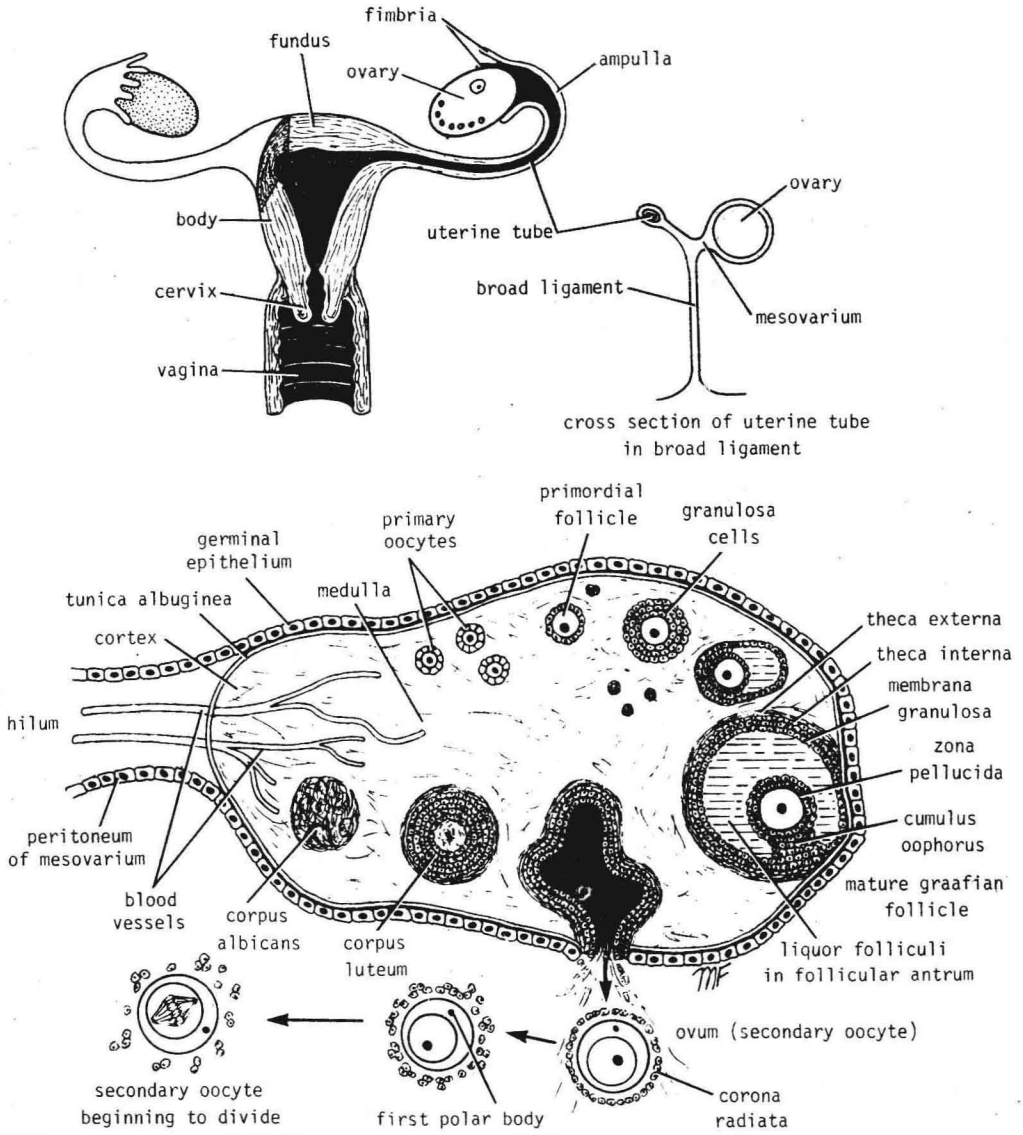

Fig. 1-4. The ovary and the maturation of an ovarian follicle.

terna, and an outer connective tissue layer, the *theca externa*. After 10 to 14 days of growth, the follicle measures about 10 mm in diameter and bulges slightly from the free surface of the ovary.

As the ovarian follicles mature under the influence of the FSH of the anterior lobe of the pituitary, the ovary begins to elaborate large amounts of *estrogens*. It is believed that the theca interna cells secrete most of the estrogens.

Ovulation

Ovulation in a normal woman who has a 28-day sexual cycle occurs 14 days after the onset of menstruation.

The meiotic division of the primary oocyte, which began during the third month of fetal development, finally is completed a few hours before ovulation occurs, and the *secondary oocyte* and the *first polar body* are formed. The first polar body, which receives only a little cytoplasm, lies between the zona pellucida and the cell membrane of the secondary oocyte (Fig. 1-4). As a result of the continued accumulation of liquor folliculi, the tense graafian follicle now ruptures, and the secondary oocyte, the zona pellucida, and the cumulus oophorus (now known as the *corona radiata*) escape into the peritoneal cavity. Immediately after ovulation the secondary oocyte (Fig. 1-5) undergoes the second meiotic division to form the *mature ovum* and the *second polar body;* however, this division is not completed until after fertilization has taken place. When the second polar body is formed, the first and second polar bodies break down rapidly and disappear. The mature ovum has a diameter of about 120 μm.

Following ovulation, the walls of the follicle collapse and the cells of the membrana granulosa are thrown into folds. Blood from the ruptured capillaries of the theca interna fills the remains of the antrum and clots. The cells of the membrana granulosa and the theca interna are stimulated by the *luteinizing hormone* (LH) of the pituitary. They enlarge and their cytoplasm accumulates lipid. Later a yellow pigment appears in the cytoplasm. These modified cells are known as *luteal cells*, and together they form the *corpus luteum*. The luteinized theca interna cells continue to produce estrogens, and the luteinized granulosa cells start to produce large amounts of progesterone and estrogens. As the result of continued hormonal stimulation from the pituitary, the corpus luteum enlarges for about 10 days after ovulation, reaching a diameter of about 2 cm, when it may be seen on the surface of the ovary as a yellowish projection surrounded by an area of hyperemia. If fertilization does not occur, the LH of the pituitary decreases in amount and the corpus luteum begins to involute. The secretion of progesterone and estrogens diminishes, and the corpus luteum finally is converted into a fibrous scar, the *corpus albicans*.

The administration of progesterone will inhibit the process of ovulation. This finding has led to the preparation of contraceptive compounds that contain progesterone and may be taken orally to completely arrest the process of maturation of the follicles. It is of clinical interest to note that the ovaries may be artificially stimulated to ovulate by the administration of the pituitary FSH followed by the chorionic gonadotropic hormone or by treatment with the synthetic nonsteroid *clomiphene citrate.* This may be of value in cases of sterility resulting from anovulation.

CHROMOSOMAL CHANGES DURING SPERMATOGENESIS AND OOGENESIS

In the human somatic cell there are 46 chromosomes, consisting of 22 pairs of *autosomes* and one pair of *sex chromosomes* (XY or XX). The different pairs of autosomes vary in size, but the two members of any given pair of autosomes are identical. The sex chromosomes in the female (XX) also are identical, but in the male there is one X and a much shorter Y chromosome. The spermatogonia and oogonia possess 46 chromosomes. When mitotic division of these cells occurs, resulting in the formation of the primary spermatocytes and oocytes, respectively, each chromosome splits longitudinally so that each daughter cell receives the identical number of chromosomes as the mother cell (Fig. 1-5). When

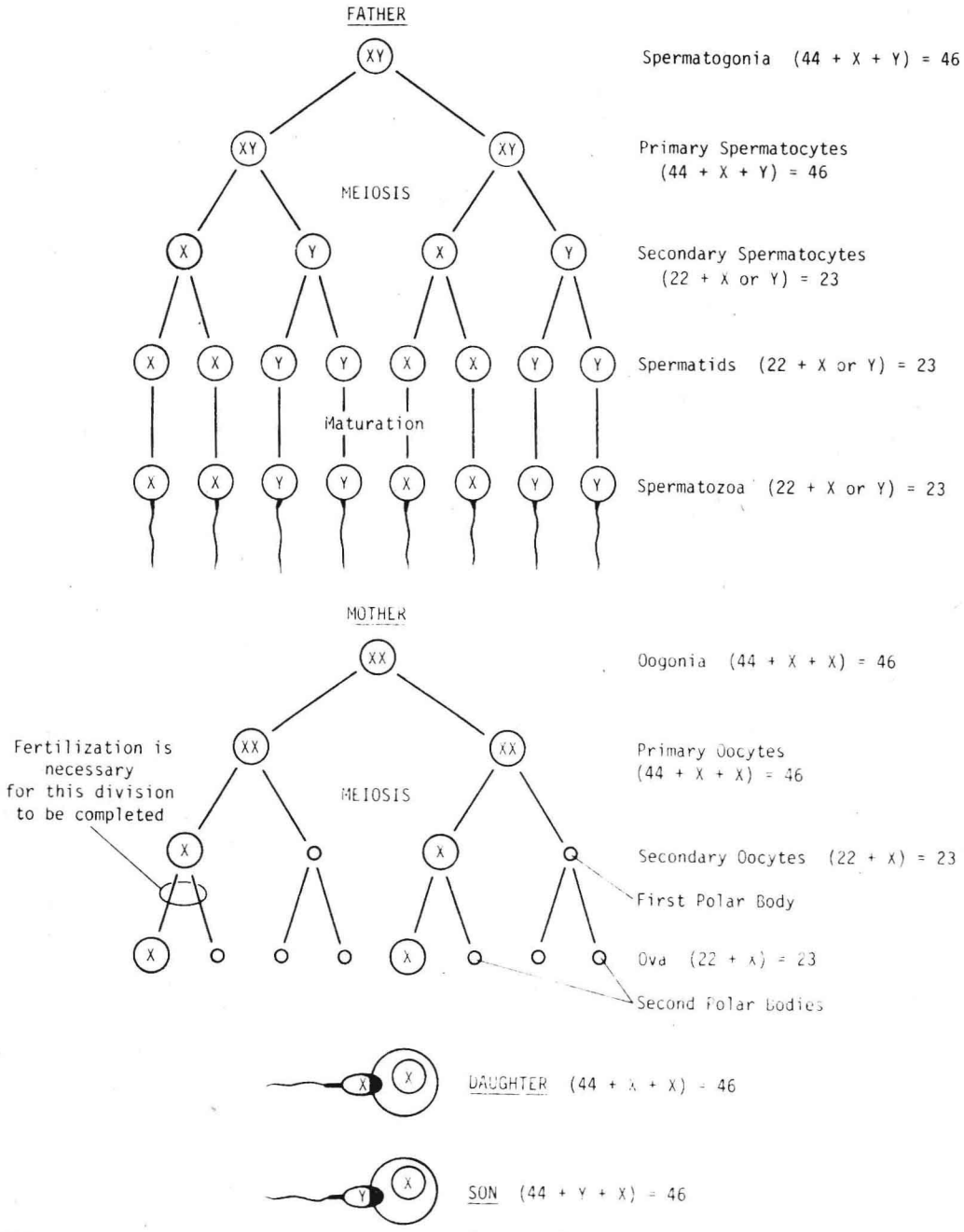

Fig. 1-5. Chromosomal changes during spermatogenesis and oogenesis, with ultimate formation of zygote.

the primary spermatocytes and oocytes divide meiotically, the secondary spermatocytes and oocytes receive only half (haploid) the number of chromosomes, i.e., 23. In the male, 22 + X chromosomes go to one secondary spermatocyte and 22 + Y chromosomes pass to the other. In the female, 22 + X chromosomes pass to the secondary oocyte and 22 + X chromosomes go to the first polar body. The term *first polar body* is given to the very much smaller of the two daughter cells, which receives very little cytoplasm from the mother cell.

In the male, the second meiotic division of the secondary spermatocytes to form spermatids takes place so that two spermatids are produced with 22 + X chromosomes and two with 22 + Y chromosomes (Fig. 1-5). In the female, the secondary oocytes divide in a similar manner so that one ovum is formed with 22 + X chromosomes and a *second polar body* is formed (resulting from unequal distribution of cytoplasm from the mother cell) with 22 + X chromosomes. At the same time, the first polar body may divide to form two additional secondary polar bodies. By this means, in the male one spermatogonium with 44 autosomes and one pair of XY chromosomes eventually gives rise to eight spermatozoa. Four of the spermatozoa have 22 autosomes and one X sex chromosome and four have 22 autosomes and one Y sex chromosome. In the female, one oogonium with 44 autosomes and one pair of XX chromosomes eventually gives rise to two ova with 22 autosomes and one X sex chromosome.

If fertilization should occur and a spermatozoon with 22 + Y chromosomes enters an ovum with 22 + X chromosomes, a male child will result. If, on the other hand, a spermatozoon with 22 + X chromosomes enters an ovum, a female child will result. These chromosomal changes are summarized in Figure 1-5.

MALFORMATION OF SPERMATOZOA AND OVA

Abnormal spermatozoa are found frequently in the *semen* (see page 13). Spermatozoa may have abnormally small heads or abnormally large heads, or the heads may be tapering or narrow. Spermatozoa with two or more tails or with one tail and two heads may be present. Although they have a normal morphological appearance, spermatozoa may lack normal motility. Normal spermatozoa move rapidly and progress in a straight line, whereas abnormal forms are sluggish and tend to move in a circle or in an irregular pattern. It is difficult to estimate accurately what percentage of spermatozoa may be abnormal without loss of fertility, although it is believed to be as many as 10 percent.

The formation of abnormal ova is extremely rare. More than one oocyte may be seen in a developing follicle, but these usually degenerate before ovulation takes place.

CLINICAL PROBLEMS *Answers on page 409*

1. A 75-year-old man visited his physician and asked his advice about marrying a 28-year-old woman. He said that they were very fond of one another and wanted to have children. He was concerned that his advanced age might interfere with his ability to have intercourse and produce viable spermatozoa. Using your knowledge of anatomy and physiology, what advice would you give this patient?

2. A concerned mother consulted a pediatrician about her 14-year-old son. He was starting to date girls and return home late after school dances. When he was a 2-year-old, she had noticed that when he was being bathed he often fondled his penis and displayed erections. She thought he might be "oversexed" and might get a "nice girl into trouble." Using your knowledge of anatomy and physiology, what advice would you give this mother?

3. A 26-year-old male intern at a children's hospital was surprised to see, on looking in the shaving mirror, that his right parotid and right submandibular regions were swollen. He also was experiencing a slight headache and malaise and noted some discom-

fort in the parotid region on opening and closing his mouth. The diagnosis of mumps was made and he was sent home to bed. One week later he developed severe pain in the left testicle. On examination, the right testis was seen to be normal, but the left one was tense, acutely tender, and slightly swollen. The intern had a pyrexia of 101° F. A diagnosis of left-sided orchitis was made secondary to the mumps infection. Using your knowledge of anatomy and physiology, do you think that sterility will follow this infection?

4. An 18-year-old man was examined medically prior to entering the army. On physical examination he was found to have bilaterally undescended testes (cryptorchism). Based on your knowledge of anatomy and physiology, what advice would you give this patient?

5. A mother asked her physician to explain what is meant by the terms *puberty, menarche, adolescence,* and *menopause.* She also asked if her daughter could become pregnant once she had started to menstruate. What would you tell this mother?

6. An 18-year-old woman visited her physician for a premarital examination and to discuss conception control. Can you explain the action of contraceptive drugs?

7. A fourth-year medical student was asked in an examination what therapeutic methods exist for the treatment of anovulation associated with secondary amenorrhea. The student also was asked if there were any complications associated with the treatment. How would you have answered these questions?

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