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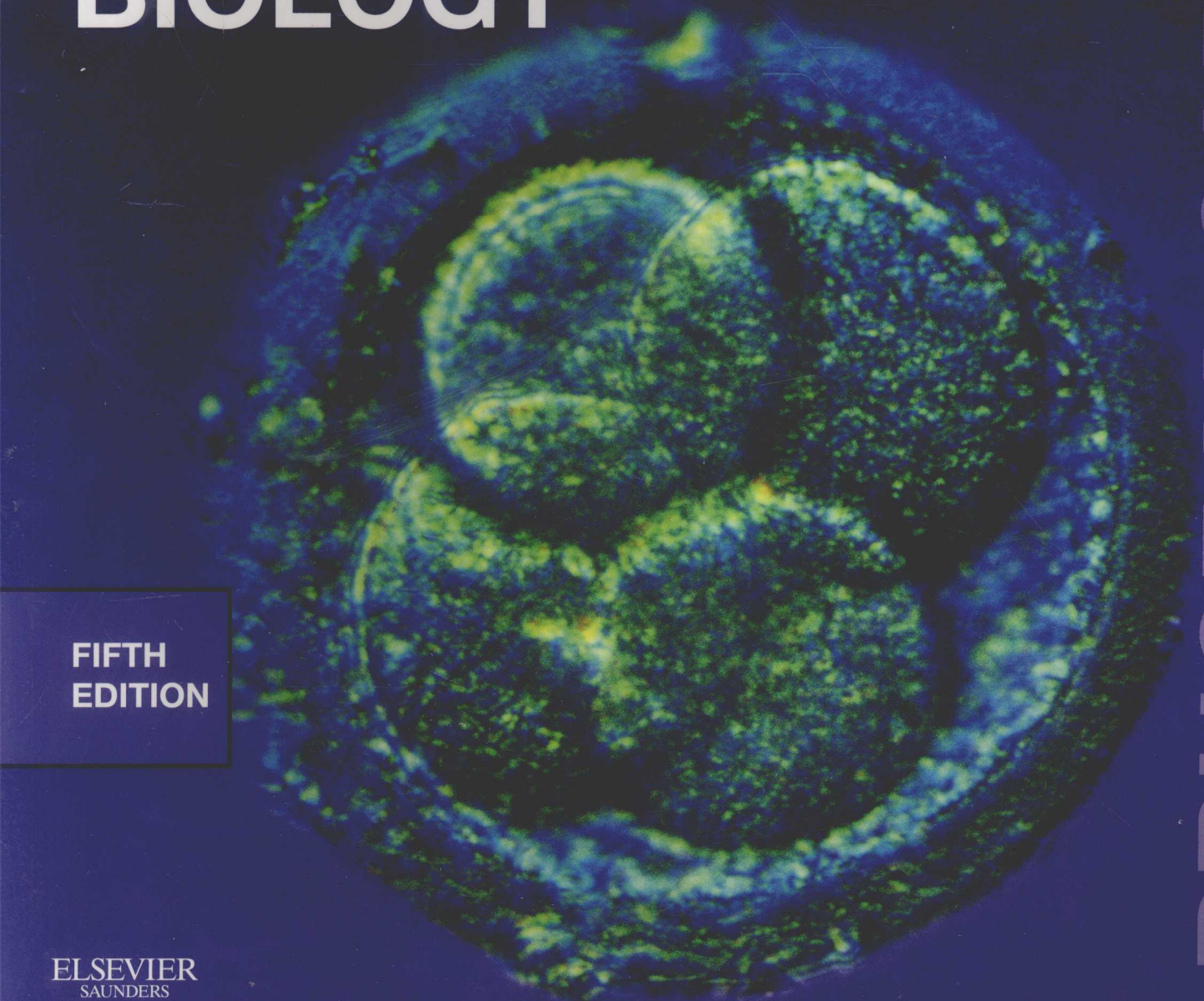
HUMAN EMBRYOLOGY AND DEVELOPMENTAL BIOLOGY



FIFTH EDITION

BRUCE M. CARLSON

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Human Embryology and Developmental Biology

Fifth Edition

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To Jean, for many wonderful years together.

Preface to the Fifth Edition

As was the case in the preparation of the fourth edition (and for that matter, also the previous editions), the conundrum facing me was what to include and what not to include in the text, given the continuing explosion of new information on almost every aspect of embryonic development. This question always leads me back to the fundamental question of what kind of book I am writing and what are my goals in writing it. As a starting point, I would go back to first principles and the reason why I wrote the first edition of this text. In the early 1990s, medical embryology was confronted with the issue of integrating traditional developmental anatomy with the newly burgeoning field of molecular embryology and introducing those already past their formal learning years to the fact that genes in organisms as foreign as *Drosophila* could have relevance in understanding the cause of human pathology or even normal development. This is no longer the case, and the issue today is how to place reasonable limits on coverage for an embryology text that is not designed to be encyclopedic.

For this text, my intention is to remain focused both on structure and on developmental mechanisms leading to structural and functional outcomes during embryogenesis. A good example is mention of the many hundreds of genes, mutations of which are known to produce abnormal developmental outcomes. If the mutation can be tied to a known mechanism that can illuminate how an organ develops, it would be a candidate for inclusion, whereas without that I feel that at present it is normally more appropriate to leave its inclusion in comprehensive human genetic compendia. Similarly, the issue of the level of detail of intracellular pathways to include often arises. Other than a few illustrative examples, I have chosen not to emphasize these pathways.

The enormous amount of new information on molecular networks and interacting pathways is accumulating to the point where new texts stressing these above other aspects of development could be profitably written. Often, where many molecules, whether transcription factors or signaling molecules, are involved in a developmental process, I have tried to choose what I feel are the most important and most distinctive, rather than to strive for completeness. Especially because so many major molecules or pathways are reused at different stages in the development of a single structure, my sense is that by including everything, the distinctiveness of the development of the different parts of the body would be blurred for the beginning student. As usual, I welcome feedback (brcarl@umich.edu) and would be particularly interested to learn whether students or instructors believe that there is too much or too little molecular detail either overall or in specific areas.

In this edition, almost every chapter has been extensively revised, and more than 50 new figures have been added. Major additions of relevant knowledge of early development, especially related to the endoderm, have led to significant changes in Chapters 3, 5, 6, 14, and 15. Chapter 12 on the neural crest has been completely reorganized and was largely rewritten. Chapter 9 (on skin, skeleton, and muscle) has also seen major changes. Much new information on germ cells and early development of the gonads has been added to Chapter 16, and in Chapter 17 new information on the development of blood vessels and lymphatics has resulted in major changes.

For this edition, I have been fortunate in being allowed to use photographs from several important sources. From the late Professor Gerd Steding's *The Anatomy of the Human Embryo* (Karger) I have taken eight scanning electron micrographs of human embryos that illustrate better than drawings the external features of aspects of human development. I was also able to borrow six photographs of important congenital malformations from the extensive collection of the late Dr. Robert Gorlin, one of the fathers of syndromology. This inclusion is particularly poignant to me because while we were students at the University of Minnesota in the early 1960s, both my wife and I got to know him before he became famous. This edition includes a new Clinical Correlation on dental anomalies written by Dr. Pranit N. Kantaputra from the Department of Orthodontics and Pediatric Dentistry at Chiang Mai University in Chiang Mai, Thailand. He has assembled a wonderful collection of dental anomalies that have a genetic basis, and I am delighted to share his text and photos with the readers. Finally, I was able to include one digitized photograph of a sectioned human embryo from the Carnegie Collection. For this I thank Dr. Raymond Gasser for his herculean efforts in digitizing important specimens from that collection and making them available to the public. All these sections (labeled) are now available online through the Endowment for Human Development (www.ehd.org), which is without question the best source of information on human embryology on the Internet. I would recommend this source to any student or instructor.

In producing this edition, I have been fortunate to be able to work with much of the team that was involved on the last edition. Alexandra Baker of DNA Illustrations, Inc. has successfully transformed my sketches into wonderful artwork for the past three editions. I thank her for her patience and her care. Similarly, Andrea Vosburgh and her colleagues at Elsevier have cheerfully succeeded in transforming a manuscript and all the trimmings into a recognizable book. Madelene Hyde efficiently guided the initial stages of contracts through the corporate labyrinth. Thanks, as always, to Jean, who provided a home environment compatible with the job of putting together a book and for putting up with me during the process.

Bruce M. Carlson

Contents

Developmental Tables

Carnegie Stages of Early Human Embryonic Development (Weeks 1 to 8)

Age (days)*	External Features	Carnegie Stage	Crown-Rump Length (mm)	Pairs of Somites
1	Fertilized oocyte	1	0.1	
2-3	Morula (4-16 cells)	2	0.1	
4-5	Free blastocyst	3	0.1	
6	Attachment of blastocyst to endometrium	4	0.1	
7-12	Implantation, bilaminar embryo with primary yolk sac	5	0.1-0.2	
17	Trilaminar embryo with primitive streak, chorionic villi	6	0.2-0.3	
19	Gastrulation, formation of notochordal process	7	0.4	
23	Hensen's node and primitive pit, notochord and neurenteric canal, appearance of neural plate, neural folds, and blood islands	8	1-1.5	
25	Appearance of first somites, deep neural groove, elevation of cranial neural folds, early heart tubes	9	1.5-2.5	1-3
28	Beginning of fusion of neural folds, formation of optic sulci, presence of first two pharyngeal arches, beginning heart beat, curving of embryo	10	2-3.5	4-12
29	Closure of cranial neuropore, formation of optic vesicles, rupture of oropharyngeal membrane	11	2.5-4.5	13-20
30	Closure of caudal neuropore, formation of pharyngeal arches 3 and 4, appearance of upper limb buds and tail bud, formation of otic vesicle	12	3-5	21-29
32	Appearance of lower limb buds, lens placode, separation of otic vesicle from surface ectoderm	13	4-6	30-31
33	Formation of lens vesicle, optic cup, and nasal pits	14	5-7	
36	Development of hand plates, primary urogenital sinus, prominent nasal pits, evidence of cerebral hemispheres	15	7-9	
38	Development of foot plates, visible retinal pigment, development of auricular hillocks, formation of upper lip	16	8-11	
41	Appearance of finger rays, rapid head enlargement, six auricular hillocks, formation of nasolacrimal groove	17	11-14	
44	Appearance of toe rays and elbow regions, beginning of formation of eyelids, tip of nose distinct, presence of nipples	18	13-17	
46	Elongation and straightening of trunk, beginning of herniation of midgut into umbilical cord	19	16-18	
49	Bending of arms at elbows, distinct but webbed fingers, appearance of scalp vascular plexus, degeneration of anal and urogenital membranes	20	18-22	
51	Longer and free fingers, distinct but webbed toes, indifferent external genitalia	21	22-24	
53	Longer and free toes, better development of eyelids and external ear	22	23-28	
56	More rounded head, fusion of eyelids	23	27-31	

*Based on additional specimen information, the ages of the embryos at specific stages have been updated from those listed in O'Rahilly and Müller in 1987. See O'Rahilly R, Müller F: *Human embryology and teratology,* ed 3, New York, 2001, Wiley-Liss, p 490.
Data from O'Rahilly R, Müller F: *Developmental stages in human embryos,* Publication 637, Washington, DC, 1987, Carnegie Institution of Washington.

Major Developmental Events during the Fetal Period

External Features	Internal Features
8 WEEKS	
Head is almost half the total length of fetus	Midgut herniation into umbilical cord occurs
Cervical flexure is about 30 degrees	Extraembryonic portion of allantois has degenerated
Indifferent external genitalia are present	Ducts and alveoli of lacrimal glands form
Eyes are converging	Paramesonephric ducts begin to regress in males
Eyelids are unfused	Recanalization of lumen of gut tube occurs
Tail disappears	Lungs are becoming glandlike
Nostrils are closed by epithelial plugs	Diaphragm is completed
Eyebrows appear	First ossification begins in skeleton
Urine is released into amniotic fluid	Definitive aortic arch system takes shape
9 WEEKS	
Neck develops and chin rises from thorax	Intestines are herniated into umbilical cord
Cranial flexure is about 22 degrees	Early muscular movements occur
Chorion is divided into chorion laeve and chorion frondosum	Adrenocorticotropic hormone and gonadotropins are produced by pituitary
Eyelids meet and fuse	Corticosteroids are produced by adrenal cortex
External genitalia begin to become gender specific	Semilunar valves in heart are completed
Amniotic fluid is swallowed	Fused paramesonephric ducts join vaginal plate
Thumb sucking and grasping begin	Urethral folds begin to fuse in males
10 WEEKS	
Cervical flexure is about 15 degrees	Intestines return into body cavity from umbilical cord
Gender differences are apparent in external genitalia	Bile is secreted
Fingernails appear	Blood islands are established in spleen
Eyelids are fused	Thymus is infiltrated by lymphoid stem cells
Fetal yawning occurs	Prolactin production by pituitary occurs First permanent tooth buds form Deciduous teeth are in early bell stage Epidermis has three layers
11 WEEKS	
Cervical flexure is about 8 degrees	Stomach musculature can contract
Nose begins to develop bridge	T lymphocytes emigrate into bloodstream
Taste buds cover inside of mouth	Colloid appears in thyroid follicles Intestinal absorption begins
12 WEEKS	
Head is erect	Ovaries descend below pelvic rim
Neck is almost straight and well defined	Parathyroid hormone is produced
External ear is taking form and has moved close to its definitive position in the head	Blood can coagulate
Yolk sac has shrunk	
Fetus can respond to skin stimulation	
Bowel movements begin (meconium expelled)	
4 MONTHS	
Skin is thin; blood vessels can easily be seen through it	Seminal vesicle forms
Nostrils are almost formed	Transverse grooves appear on dorsal surface of cerebellum
Eyes have moved to front of face	Bile is produced by liver and stains meconium green
Legs are longer than arms	Gastric glands bud off from gastric pits
Fine lanugo hairs appear on head	Brown fat begins to form

Major Developmental Events during the Fetal Period—cont'd

External Features	Internal Features
Fingernails are well formed; toenails are forming	Pyramidal tracts begin to form in brain
Epidermal ridges appear on fingers and palms of hand	Hematopoiesis begins in bone marrow
Enough amniotic fluid is present to permit amniocentesis	Ovaries contain primordial follicles
Mother can feel fetal movements	
5 MONTHS	
Epidermal ridges form on toes and soles of feet	Myelination of spinal cord begins
Vernix caseosa begins to be deposited on skin	Sebaceous glands begin to function
Abdomen begins to fill out	Thyroid-stimulating hormone is released by pituitary
Eyelids and eyebrows develop	Testes begin to descend
Lanugo hairs cover most of body	
6 MONTHS	
Skin is wrinkled and red	Surfactant begins to be secreted
Decidua capsularis degenerates because of reduced blood supply	Tip of spinal cord is at S1 level
Lanugo hairs darken	
Odor detection and taste occur	
7 MONTHS	
Eyelids begin to open	Sulci and gyri begin to appear on brain
Eyelashes are well developed	Subcutaneous fat storage begins
Scalp hairs are lengthening (longer than lanugo)	Testes are descending into scrotum
Skin is slightly wrinkled	Termination of splenic erythropoiesis occurs
Breathing movements are common	
8 MONTHS	
Skin is pink and smooth	Regression of hyaloid vessels from lens occurs
Eyes are capable of pupillary light reflex	Testes enter scrotum
Fingernails have reached tips of fingers	
9 MONTHS	
Toenails have reached tips of toes	Larger amounts of pulmonary surfactant are secreted
Most lanugo hairs are shed	Ovaries are still above brim of pelvis
Skin is covered with vernix caseosa	Testes have descended into scrotum
Attachment of umbilical cord becomes central in abdomen	Tip of spinal cord is at L3
About 1 L of amniotic fluid is present	Myelination of brain begins
Placenta weighs about 500 g	
Fingernails extend beyond fingertips	
Breasts protrude and secrete "witch's milk"	

Part I

Early Development and the Fetal-Maternal Relationship

Chapter 1

Getting Ready for Pregnancy

Human pregnancy begins with the fusion of an egg and a sperm within the female reproductive tract, but extensive preparation precedes this event. First, both male and female sex cells must pass through a long series of changes (**gametogenesis**) that convert them genetically and phenotypically into mature **gametes**, which are capable of participating in the process of fertilization. Next, the gametes must be released from the gonads and make their way to the upper part of the uterine tube, where fertilization normally takes place. Finally, the fertilized egg, now properly called an **embryo**, must enter the uterus, where it sinks into the uterine lining (**implantation**) to be nourished by the mother. All these events involve interactions between the gametes or embryo and the adult body in which they are housed, and most of them are mediated or influenced by parental hormones. This chapter focuses on gametogenesis and the hormonal modifications of the body that enable reproduction to occur.

Gametogenesis

Gametogenesis is typically divided into four phases: (1) the extraembryonic origin of the germ cells and their migration into the gonads, (2) an increase in the number of germ cells by mitosis, (3) a reduction in chromosomal number by meiosis, and (4) structural and functional maturation of the eggs and spermatozoa. The first phase of gametogenesis is identical in males and females, whereas distinct differences exist between the male and female patterns in the last three phases.

Phase 1: Origin and Migration of Germ Cells

Primordial germ cells, the earliest recognizable precursors of gametes, arise outside the gonads and migrate into the gonads during early embryonic development. Human primordial germ cells first become readily recognizable at 24 days after fertilization in the endodermal layer of the yolk sac (**Fig. 1.1A**) by their large size and high content of the enzyme alkaline phosphatase. In the mouse, their origin has been traced even earlier in development (see p. 390). Germ cells exit from the yolk sac into the hindgut epithelium and then migrate* through the dorsal mesentery until they reach the primordia of the gonads (Fig. 1.1B). In the mouse, an estimated 100 cells leave the yolk sac, and through mitotic multiplication (6 to 7 rounds of cell division), about 4000 primordial germ cells enter the primitive gonads.

Misdirected primordial germ cells that lodge in extragonadal sites usually die, but if such cells survive, they may develop into **teratomas**. Teratomas are bizarre growths that contain scrambled mixtures of highly differentiated tissues, such as skin, hair, cartilage, and even teeth (**Fig. 1.2**). They are found in the mediastinum, the sacrococcygeal region, and the oral region.

Phase 2: Increase in the Number of Germ Cells by Mitosis

After they arrive in the gonads, the primordial germ cells begin a phase of rapid mitotic proliferation. In a mitotic division, each germ cell produces two **diploid** progeny that are genetically equal. Through several series of mitotic divisions, the number of primordial germ cells increases exponentially from hundreds to millions. The pattern of mitotic proliferation differs markedly between male and female germ cells. **Oogonia**, as mitotically active germ cells in the female are called, go through a period of intense mitotic activity in the embryonic ovary from the second through the fifth month of pregnancy in the human. During this period, the population of germ cells increases from only a few thousand to nearly 7 million (**Fig. 1.3**). This number represents the maximum number of germ cells that is ever found in the ovaries. Shortly thereafter, numerous oogonia undergo a natural degeneration called **atresia**. Atresia of germ cells is a continuing feature of the histological landscape of the human ovary until menopause.

*Considerable controversy surrounds the use of the term "migration" with respect to embryonic development. On the one hand, some believe that displacements of cells relative to other structural landmarks in the embryo are due to active migration (often through ameboid motion). On the other hand, others emphasize the importance of directed cell proliferation and growth forces in causing what is interpreted as apparent migration of cells. As is often true in scientific controversies, both active migration and displacement as a result of growth seem to operate in many cases where cells in the growing embryo appear to shift with respect to other structural landmarks.

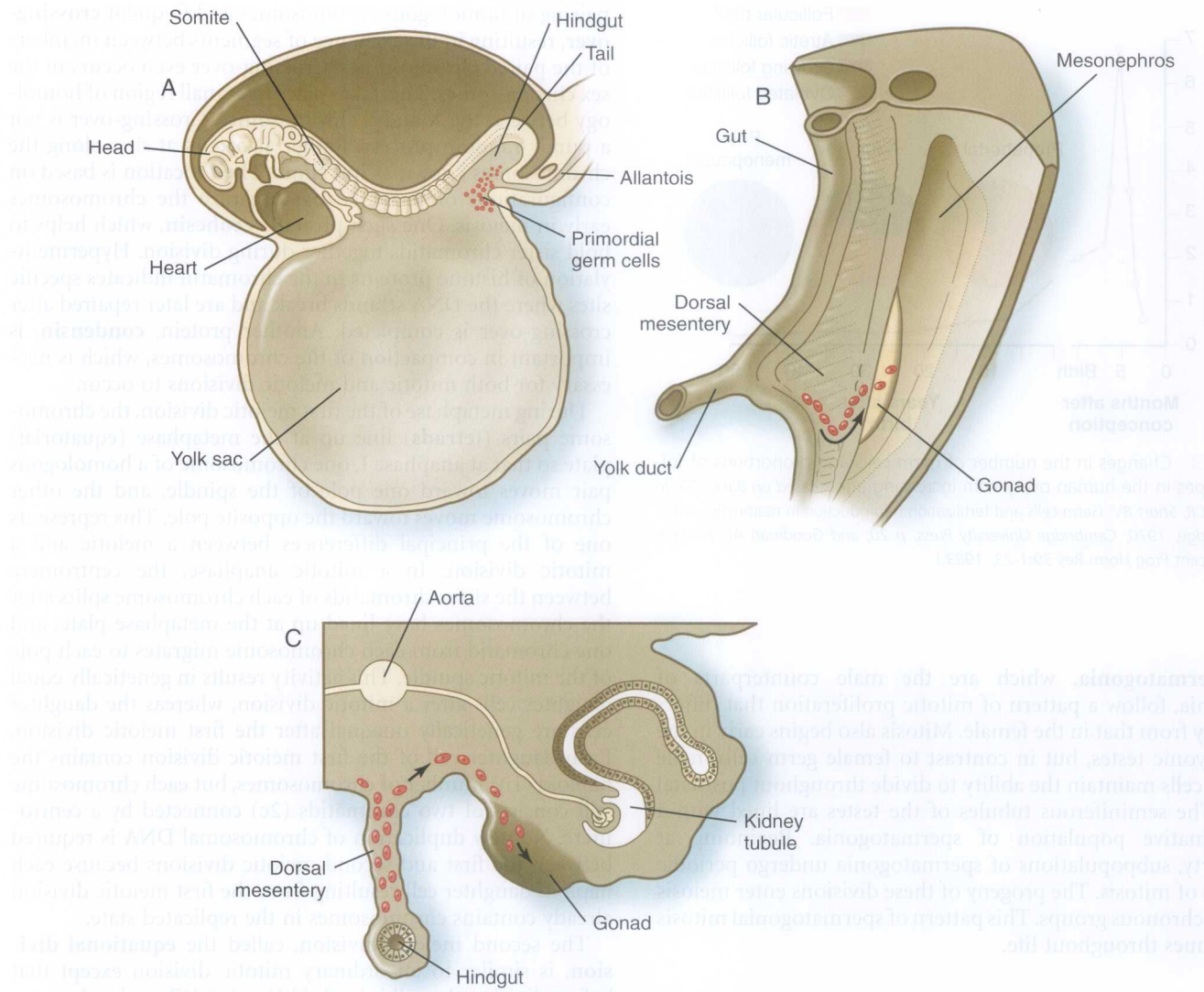


Fig. 1.1 Origin and migration of primordial germ cells in the human embryo. **A,** Location of primordial germ cells in the 16-somite human embryo (midsagittal view). **B,** Pathway of migration *(arrow)* through the dorsal mesentery. **C,** Cross section showing the pathway of migration *(arrows)* through the dorsal mesentery and into the gonad.

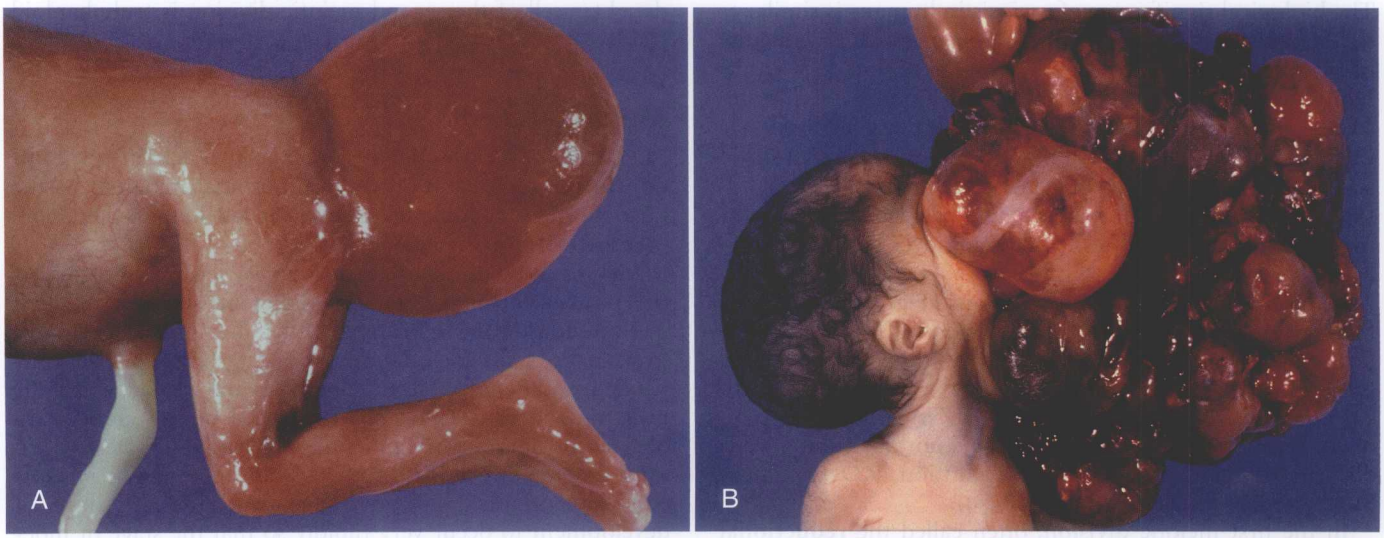


Fig. 1.2 **A,** Sacrococcygeal teratoma in a fetus. **B,** Massive oropharyngeal teratoma. *(Courtesy of M. Barr, Ann Arbor, Mich.)*

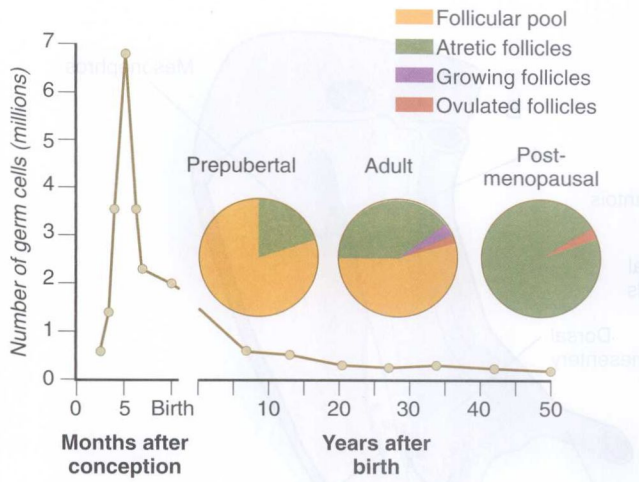


Fig. 1.3 Changes in the number of germ cells and proportions of follicle types in the human ovary with increasing age. *(Based on Baker TG: In Austin CR, Short RV:* Germ cells and fertilization (reproduction in mammals), *vol 1, Cambridge, 1970, Cambridge University Press, p 20; and Goodman AL, Hodgen GD:* Recent Prog Horm Res *39:1-73, 1983.)*

Spermatogonia, which are the male counterparts of oogonia, follow a pattern of mitotic proliferation that differs greatly from that in the female. Mitosis also begins early in the embryonic testes, but in contrast to female germ cells, male germ cells maintain the ability to divide throughout postnatal life. The seminiferous tubules of the testes are lined with a germinative population of spermatogonia. Beginning at puberty, subpopulations of spermatogonia undergo periodic waves of mitosis. The progeny of these divisions enter meiosis as synchronous groups. This pattern of spermatogonial mitosis continues throughout life.

Phase 3: Reduction in Chromosomal Number by Meiosis

Stages of Meiosis

The biological significance of meiosis in humans is similar to that in other species. Of primary importance are (1) reduction of the number of chromosomes from the diploid (2n) to the **haploid** (1n) number so that the species number of chromosomes can be maintained from generation to generation, (2) independent reassortment of maternal and paternal chromosomes for better mixing of genetic characteristics, and (3) further redistribution of maternal and paternal genetic information through the process of crossing-over during the first meiotic division.

Meiosis involves two sets of divisions (**Fig. 1.4**). Before the first meiotic division, deoxyribonucleic acid (DNA) replication has already occurred, so at the beginning of meiosis, the cell is 2n, 4c. (In this designation, **n** is the species number of chromosomes, and **c** is the amount of DNA in a single set [n] of chromosomes.) The cell contains the normal number (2n) of chromosomes, but as a result of replication, its DNA content (4c) is double the normal amount (2c).

In the first meiotic division, often called the **reductional division**, a prolonged prophase (see Fig. 1.4) leads to the pairing of homologous chromosomes and frequent **crossing-over**, resulting in the exchange of segments between members of the paired chromosomes. Crossing-over even occurs in the sex chromosomes. This takes place in a small region of homology between the X and Y chromosomes. Crossing-over is not a purely random process. Rather, it occurs at sites along the chromosomes known as **hot spots**. Their location is based on configurations of proteins that organize the chromosomes early in meiosis. One such protein is **cohesin**, which helps to hold sister chromatids together during division. Hypermethylation of histone proteins in the chromatin indicates specific sites where the DNA strands break and are later repaired after crossing-over is completed. Another protein, **condensin**, is important in compaction of the chromosomes, which is necessary for both mitotic and meiotic divisions to occur.

During metaphase of the first meiotic division, the chromosome pairs (**tetrads**) line up at the metaphase (equatorial) plate so that at anaphase I, one chromosome of a homologous pair moves toward one pole of the spindle, and the other chromosome moves toward the opposite pole. This represents one of the principal differences between a meiotic and a mitotic division. In a mitotic anaphase, the centromere between the sister chromatids of each chromosome splits after the chromosomes have lined up at the metaphase plate, and one chromatid from each chromosome migrates to each pole of the mitotic spindle. This activity results in genetically equal daughter cells after a mitotic division, whereas the daughter cells are genetically unequal after the first meiotic division. Each daughter cell of the first meiotic division contains the haploid (1n) number of chromosomes, but each chromosome still consists of two chromatids (2c) connected by a centromere. No new duplication of chromosomal DNA is required between the first and second meiotic divisions because each haploid daughter cell resulting from the first meiotic division already contains chromosomes in the replicated state.

The second meiotic division, called the **equational division**, is similar to an ordinary mitotic division except that before division the cell is haploid (1n, 2c). When the chromosomes line up along the equatorial plate at metaphase II, the centromeres between sister chromatids divide, allowing the sister chromatids of each chromosome to migrate to opposite poles of the spindle apparatus during anaphase II. Each daughter cell of the second meiotic division is truly haploid (1n, 1c).

Meiosis in Females

The period of meiosis involves other cellular activities in addition to the redistribution of chromosomal material. As the oogonia enter the first meiotic division late in the fetal period, they are called **primary oocytes**.

Meiosis in the human female is a very leisurely process. As the primary oocytes enter the diplotene stage of the first meiotic division in the early months after birth, the first of two blocks in the meiotic process occurs (**Fig. 1.5**). The suspended diplotene phase of meiosis is the period when the primary oocyte prepares for the needs of the embryo. In oocytes of amphibians and other lower vertebrates, which must develop outside the mother's body and often in a hostile environment, it is highly advantageous for the early stages of development to occur very rapidly so that the stage of independent locomotion and feeding is attained as soon as pos-

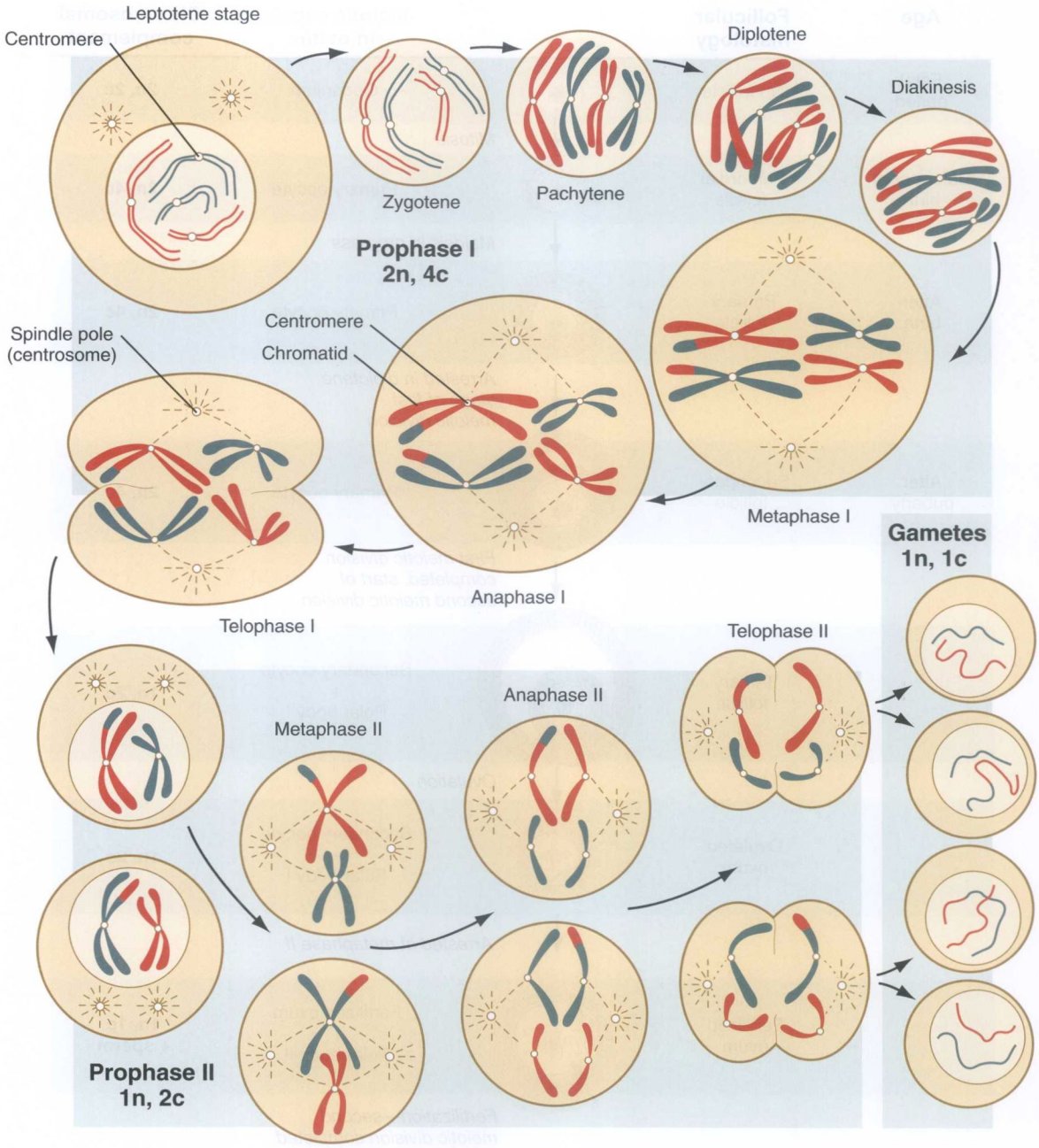


Fig. 1.4 **Summary of the major stages of meiosis in a generalized germ cell.**

sible. These conditions necessitate a strategy of storing up the materials needed for early development well in advance of ovulation and fertilization because normal synthetic processes would not be rapid enough to produce the materials required for the rapidly cleaving embryo. In such species, yolk is accumulated, the genes for producing ribosomal ribonucleic acid (rRNA) are amplified, and many types of RNA molecules are synthesized and stored in an inactive form for later use.

RNA synthesis in the amphibian oocyte occurs on the lampbrush chromosomes, which are characterized by many prominent loops of spread-out DNA on which messenger RNA (mRNA) molecules are synthesized. The amplified genes for producing rRNA are manifested by the presence of 600 to 1000 nucleoli within the nucleus. Primary oocytes also prepare for fertilization by producing several thousand cortical granules, which are of great importance during the fertilization process (see Chapter 2).

The mammalian oocyte prepares for an early embryonic period that is more prolonged than that of amphibians and that occurs in the nutritive environment of the maternal reproductive tract. Therefore, it is not faced with the need to store as great a quantity of materials as are the eggs of lower vertebrates. As a consequence, the buildup of yolk is negligible. Evidence indicates, however, a low level of ribosomal DNA (rDNA) amplification (two to three times) in diplotene human oocytes, a finding suggesting that some degree of molecular advance planning is also required to support early cleavage in the human. The presence of 2 to 40 small (2-μm) RNA-

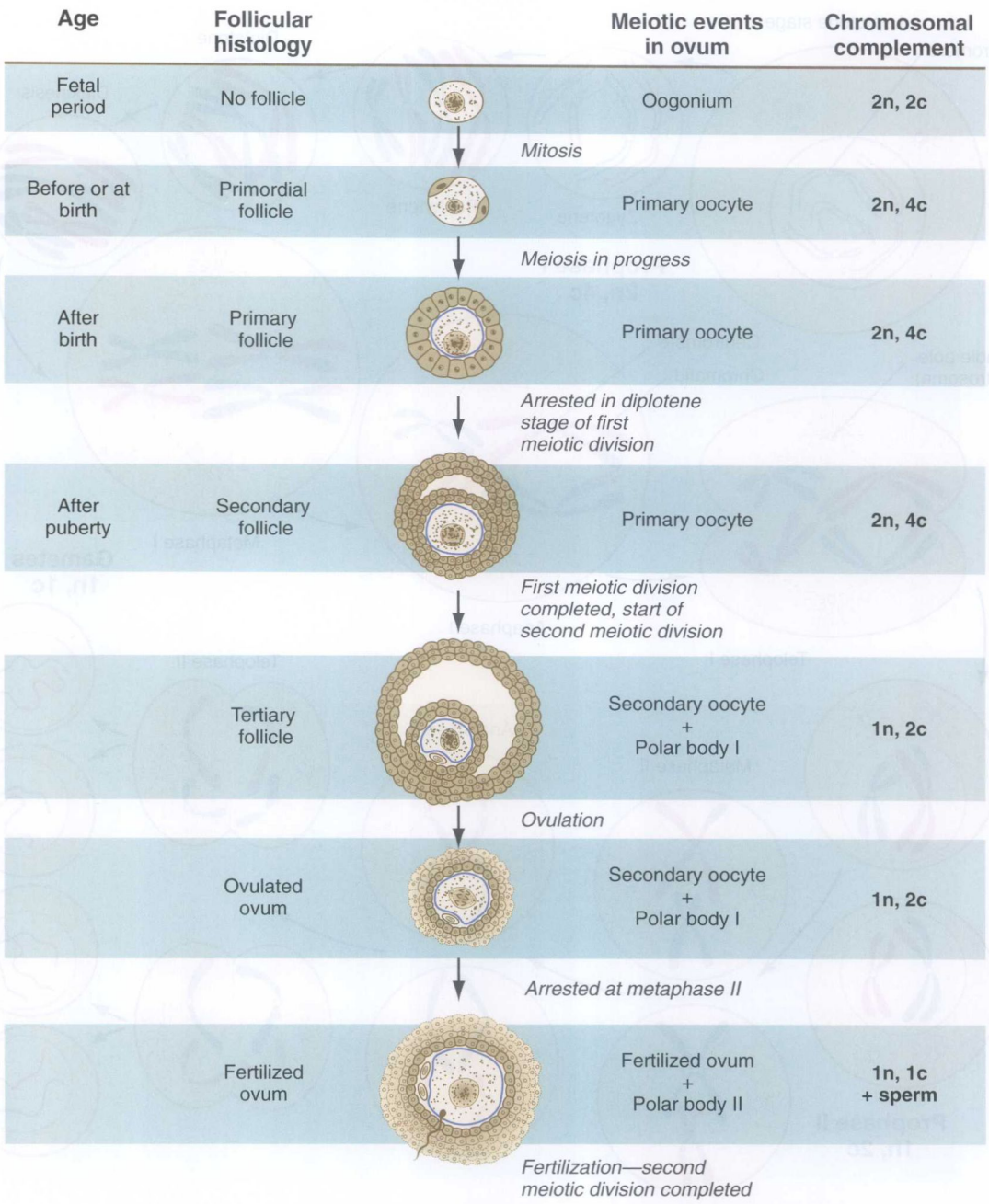


Fig. 1.5 **Summary of the major events in human oogenesis and follicular development.**

containing micronuclei (miniature nucleoli) per oocyte nucleus correlates with the molecular data.

Human diplotene chromosomes do not appear to be arranged in a true lampbrush configuration, and massive amounts of RNA synthesis seem unlikely. The developing mammalian (mouse) oocyte produces 10,000 times less rRNA and 1000 times less mRNA than its amphibian counterpart. Nevertheless, there is a steady accumulation of mRNA and a proportional accumulation of rRNA. These amounts of maternally derived RNA seem to be enough to take the fertilized egg through the first couple of cleavage divisions, after which the embryonic genome takes control of macromolecular synthetic processes.

Because cortical granules play an important role in preventing the entry of excess spermatozoa during fertilization in human eggs (see p. 31), the formation of cortical granules (mainly from the Golgi apparatus) continues to be one of the functions of the diplotene stage that is preserved in humans. Roughly 4500 cortical granules are produced in the mouse oocyte. A higher number is likely in the human oocyte.

Unless they degenerate, all primary oocytes remain arrested in the diplotene stage of meiosis until puberty. During the reproductive years, small numbers (10 to 30) of primary oocytes complete the first meiotic division with each menstrual cycle and begin to develop further. The other primary

oocytes remain arrested in the diplotene stage, some for 50 years.

With the completion of the first meiotic division shortly before ovulation, two unequal cellular progeny result. One is a large cell, called the **secondary oocyte**. The other is a small cell called the **first polar body** (see Fig. 1.5). The secondary oocytes begin the second meiotic division, but again the meiotic process is arrested, this time at metaphase. The stimulus for the release from this meiotic block is fertilization by a spermatozoon. Unfertilized secondary oocytes fail to complete the second meiotic division. The second meiotic division is also unequal; one of the daughter cells is relegated to becoming a second polar body. The first polar body may also divide during the second meiotic division. Formation of both the first and second polar bodies involves highly asymmetric cell divisions. To a large extent, this is accomplished by displacement of the mitotic spindle apparatus toward the periphery of the oocyte through the actions of the cytoskeletal protein **actin** (see Fig. 2.7).

Meiosis in Males

Meiosis in the male does not begin until after puberty. In contrast to the primary oocytes in the female, not all spermatogonia enter meiosis at the same time. Large numbers of spermatogonia remain in the mitotic cycle throughout much of the reproductive lifetime of males. When the progeny of a spermatogonium have entered the meiotic cycle as **primary spermatocytes**, they spend several weeks passing through the first meiotic division (**Fig. 1.6**). The result of the first meiotic division is the formation of two **secondary spermatocytes**, which immediately enter the second meiotic division. About 8 hours later, the second meiotic division is completed, and four haploid (1n, 1c) **spermatids** remain as progeny of the single primary spermatocyte. The total length of human spermatogenesis is 64 days.

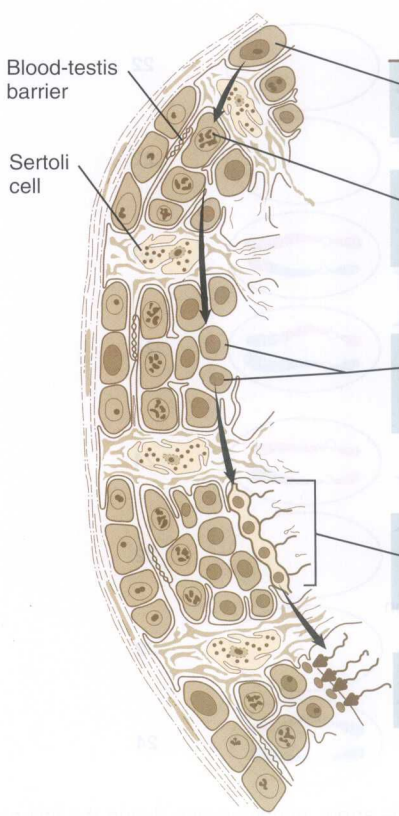
Disturbances that can occur during meiosis and result in chromosomal aberrations are discussed in **Clinical Correlation 1.1** and Figure 1.7.

Phase 4: Final Structural and Functional Maturation of Eggs and Sperm

Oogenesis

Of the roughly 2 million primary oocytes present in the ovaries at birth, only about 40,000—all of which are arrested in the diplotene stage of the first meiotic division—survive until puberty. From this number, approximately 400 (1 per menstrual cycle) are actually ovulated. The rest of the primary oocytes degenerate without leaving the ovary, but many of them undergo some further development before becoming atretic. Although some studies suggested that adult mammalian ovaries contain primitive cells that can give rise to new oocytes, such reports remain controversial.

The egg, along with its surrounding cells, is called a **follicle**. Maturation of the egg is intimately bound with the development of its cellular covering. Because of this, considering the



Cell types	Meiotic events	Chromosomal complement
Spermatogonium (type B)	DNA replication	2n, 4c
Primary spermatocyte	First meiotic division in progress	2n, 4c
First meiotic division completed		
Two secondary spermatocytes	Second meiotic division in progress	1n, 2c
Second meiotic division completed		
4 Spermatids	Immature haploid gametes	1n, 1c
Spermiogenesis		
4 Spermatozoa	Haploid gametes	1n, 1c

Fig. 1.6 **Summary of the major events in human spermatogenesis.**