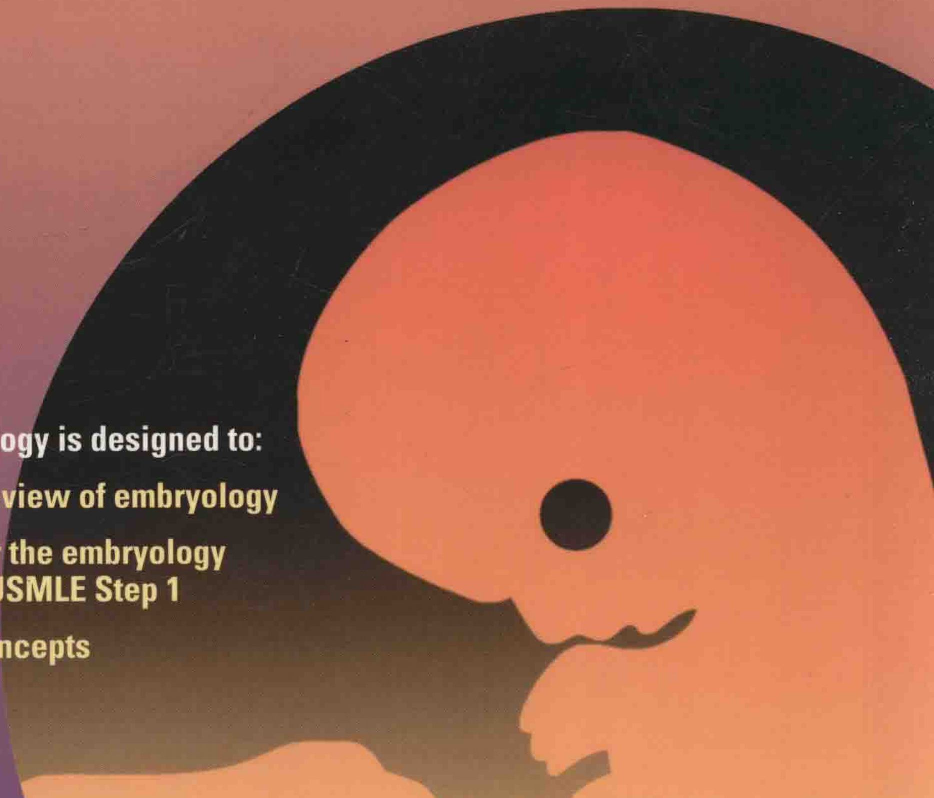
RONALD W. DUDEK

High-Yield™ Embryology

FIFTH EDITION



High-Yield™ Embryology is designed to:

- Provide a quick review of embryology
- Help equip you for the embryology questions on the USMLE Step 1
- Clarify difficult concepts

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Embryology

FIFTH EDITION

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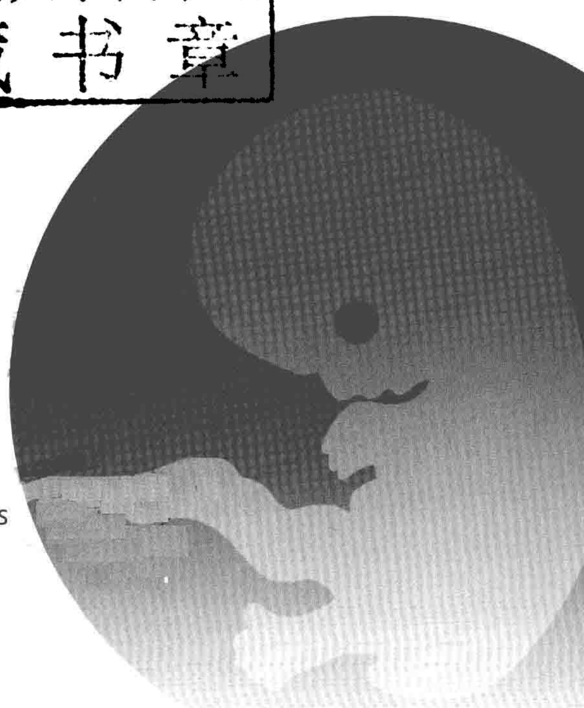

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I would like to dedicate this book to
my father, Stanley J. Dudek, who died
Sunday, March 20, 1988, at 11 A.M.
It was his hard work and sacrifice
that allowed me access to the finest
educational institutions in the country
(St. John's University in Collegeville, MN;
the University of Minnesota Medical School;
Northwestern University; and the University
of Chicago). It was by hard work and
sacrifice that he showed his love for his wife,
Lottie; daughter, Christine; and grandchildren,
Karolyn, Katie, and Jeannie.
I remember my father often as a good man
who did the best he could.
Who could ask for more?
My father is missed and remembered by many.

Preface

The fifth edition of *High-Yield™ Embryology* includes improvements based on suggestions and comments from the many medical students who have used this book in preparation for the USMLE Step 1 examination and those students who have reviewed the book. I pay close attention to these suggestions and comments in order to improve the quality of this book. The goal of *High-Yield™ Embryology* is to provide an accurate and quick review of important clinical aspects of embryology for the future physician.

Many times in the history of science, certain biological concepts become entrenched and accepted as dogma even though recent evidence comes to light to challenge these concepts. One of these concepts is the process of twinning. Recent evidence calls into question the standard figures used in textbooks on how the process of twinning occurs. In particular, it is becoming increasingly difficult to ignore the fact that dizygotic twins are sometimes monochorionic. Although we by far do not know or attempt to explain exactly how twinning occurs, it seems that the interesting cell and molecular events involved in twinning occur in the first few cell divisions during first three or four days after fertilization. You are not a twin because the inner cell mass splits. The inner cell mass splits because you are a twin. This evidence warrants a new twinning figure (Figure 2-2) that does not comport with the standard figures but tries to embrace recent evidence although many may call it controversial. Progress in our scientific understanding of twinning will never occur if our concept of the twinning process is overly simplistic and reinforced by standard figures repeated over and over in textbooks. Some published references that speak to this twinning issue include Boklage (2009, 2010), Yoon et al. (2005), Williams et al. (2004), and Hoekstra et al. (2008).

I understand that *High-Yield™ Embryology* is a review book designed for a USMLE Step 1 review and that you will not be faced with a question regarding this twinning concept, but I know my readers are sophisticated enough to appreciate the scientific and clinical value of being challenged to question traditional concepts as "grist for the mill" in discussions with your colleagues.

I would appreciate receiving your comments and/or suggestions concerning *High-Yield™ Embryology*, Fifth Edition, especially after you have taken the USMLE Step 1 examination. Your suggestions will find their way into the sixth edition. You may contact me at dudekr@ecu.edu.

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Contents

Chapter 1
Prefertilization Events

I Gametes (Oocytes and Spermatozoa)

A. Are descendants of **primordial germ cells** that originate in the wall of the yolk sac of the embryo and migrate into the gonad region.

B. Are produced in the adult by either **oogenesis** or **spermatogenesis**, processes that involve **meiosis.**

II Meiosis

A. Occurs **only during the production of gametes.**

B. Consists of two cell divisions (**meiosis I and meiosis II**) and results in the formation of gametes containing 23 chromosomes and 1N amount of DNA (23,1N).

C. Promotes the exchange of small amounts of maternal and paternal DNA via **crossover** during meiosis I.

III Female Gametogenesis (Oogenesis) (Figure 1-1)

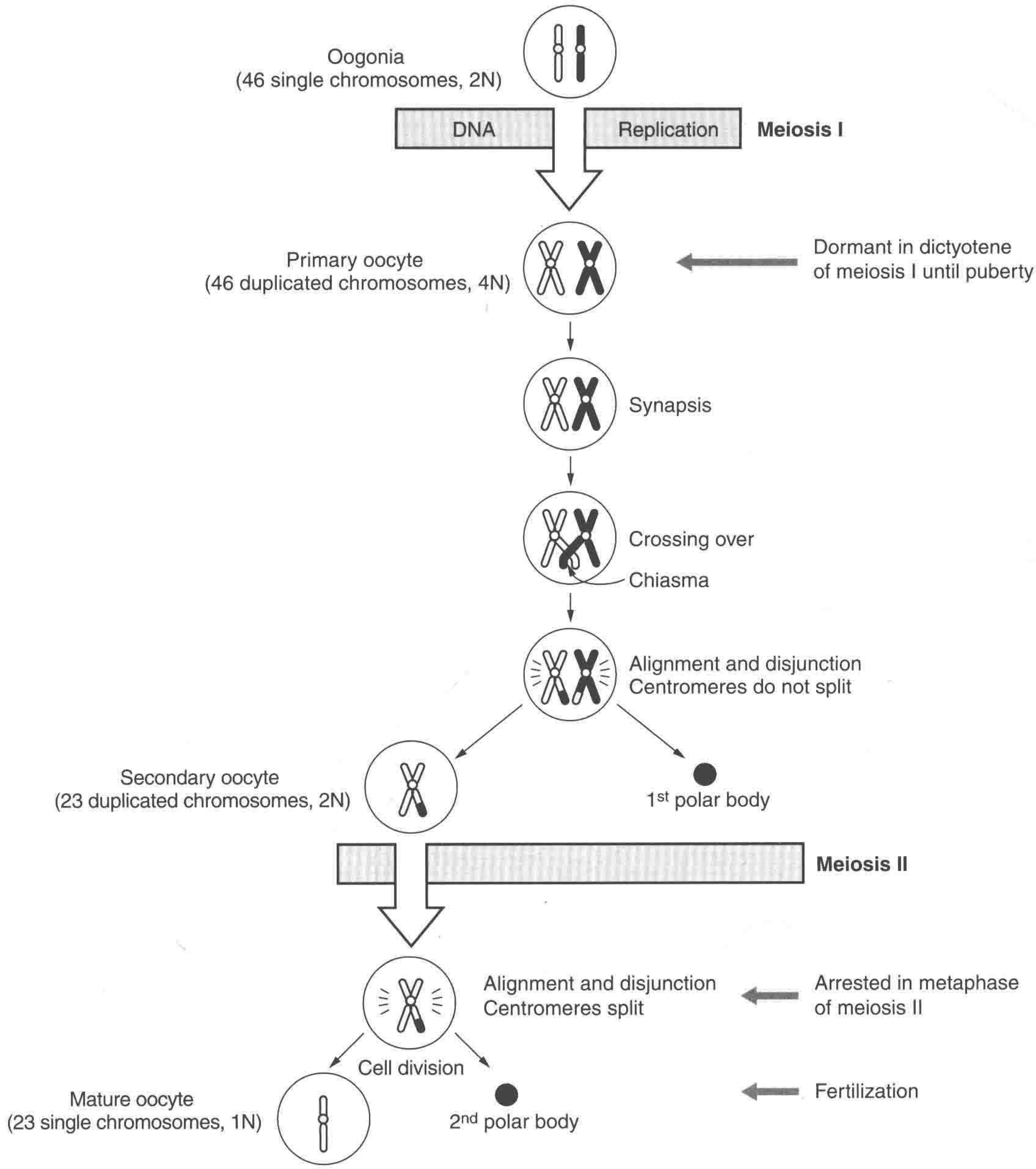
A. PRIMORDIAL GERM CELLS (46,2N) from the wall of the yolk sac arrive in the ovary at week 6 of embryonic development and differentiate into **oogonia** (46,2N).

B. Oogonia enter **meiosis I** and undergo DNA replication to form **primary oocytes** (46,4N). All primary oocytes are formed by the **fifth month of fetal life** and remain dormant in **prophase (dictyotene stage) of meiosis I until puberty.**

C. During a woman's ovarian cycle, a primary oocyte completes meiosis I to form a **secondary oocyte** (23,2N) and a **first polar body**, which probably degenerates.

D. The secondary oocyte enters **meiosis II**, and ovulation occurs when the chromosomes align at metaphase. The secondary oocyte remains **arrested in metaphase of meiosis II** until fertilization occurs.

E. At fertilization, the secondary oocyte completes meiosis II to form a **mature oocyte** (23,1N) and a **second polar body.**



● **Figure 1-1 Female gametogenesis (oogenesis).** Note that only one pair of homologous chromosomes is shown (white = maternal origin; black = paternal origin). Synapsis is the process of pairing of homologous chromosomes. The point at which the DNA molecule crosses over is called the chiasma and is where exchange of small amounts of maternal and paternal DNA occurs. Note that synapsis and crossing over occur only during meiosis I. The polar bodies are storage bodies for DNA unnecessary for the further function of the cell and probably degenerate. There is no evidence that polar bodies divide or undergo any other activity.

IV Hormonal Control of the Female Reproductive Cycle (Figure 1-2)

A. The hypothalamus secretes **gonadotropin-releasing factor** (GnRF).

B. In response to GnRH, the adenohypophysis secretes the gonadotropins, **follicle-stimulating hormone (FSH) and luteinizing hormone (LH).**

C. FSH stimulates the development of a secondary follicle to a Graafian follicle within the ovary.

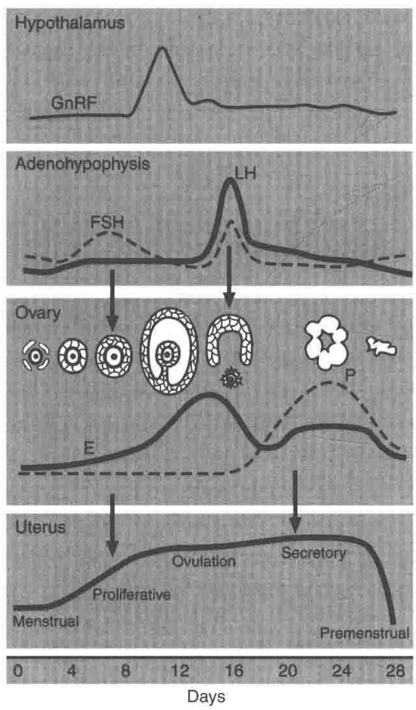
D. Granulosa cells of the secondary and Graafian follicle secrete **estrogen.**

E. Estrogen stimulates the endometrium of the uterus to enter the proliferative phase.

F. LH stimulates ovulation.

G. Following ovulation, granulosa lutein cells of the corpus luteum secrete **progesterone.**

H. Progesterone stimulates the endometrium of the uterus to enter the secretory phase.



● **Figure 1-2 Hormonal control of the female reproductive cycle.** The various patterns of hormone secretion from the hypothalamus, adenohypophysis, and ovary are shown. These hormones prepare the endometrium of the uterus for implantation of a conceptus. The menstrual cycle of the uterus includes the following: (1) The menstrual phase (days 1–4), which is characterized by the **necrosis and shedding** of the functional layer of the endometrium. (2) The proliferative phase (days 4–15), which is characterized by the **regeneration** of the functional layer of the endometrium and a **low basal body temperature** (97.5°F). (3) The ovulatory phase (14–16), which is characterized by **ovulation** of a secondary oocyte and coincides with the LH surge. (4) The secretory phase (days 15–25), which is characterized by **secretory activity** of the endometrial glands and an **elevated basal body temperature** (98°F). Implantation of a conceptus occurs in this phase. (5) Premenstrual phase (days 25–28), which is characterized by **ischemia** due to reduced blood flow to the endometrium. E = estrogen; FSH = follicle-stimulating hormone; GnRF = gonadotropin-releasing factor; LH = luteinizing hormone; P = progesterone.

V Male Gametogenesis (Spermatogenesis) (Figure 1-3) is classically divided into three phases: spermatocytogenesis, meiosis, and spermiogenesis.

A. SPERMATOCYTOGENESIS

1. **Primordial germ cells (46,2N)** from the wall of the yolk sac arrive in the testes at week 6 of embryonic development and remain dormant until puberty.
2. At puberty, primordial germ cells differentiate into **type A spermatogonia** (46,2N).
3. Type A spermatogonia undergo **mitosis** to provide a continuous supply of stem cells throughout the reproductive life of the male (called spermatocytogenesis).
4. Some type A spermatogonia differentiate into **type B spermatogonia** (46,2N).

B. MEIOSIS

1. Type B spermatogonia enter meiosis I and undergo DNA replication to form **primary spermatocytes** (46,4N).
2. Primary spermatocytes complete meiosis I to form two **secondary spermatocytes** (23,2N).
3. Secondary spermatocytes complete meiosis II to form four **spermatids** (23,1N).

C. SPERMIOGENESIS

1. Spermatids undergo a **postmeiotic series of morphological changes** (called spermiogenesis) to form **sperm** (23,1N).
2. Newly ejaculated sperm are incapable of fertilization until they undergo **capacitation**, which occurs in the female reproductive tract and involves the unmasking of sperm glycosyltransferases and removal of proteins coating the surface of the sperm.

VI Clinical Considerations

A. OFFSPRING OF OLDER WOMEN

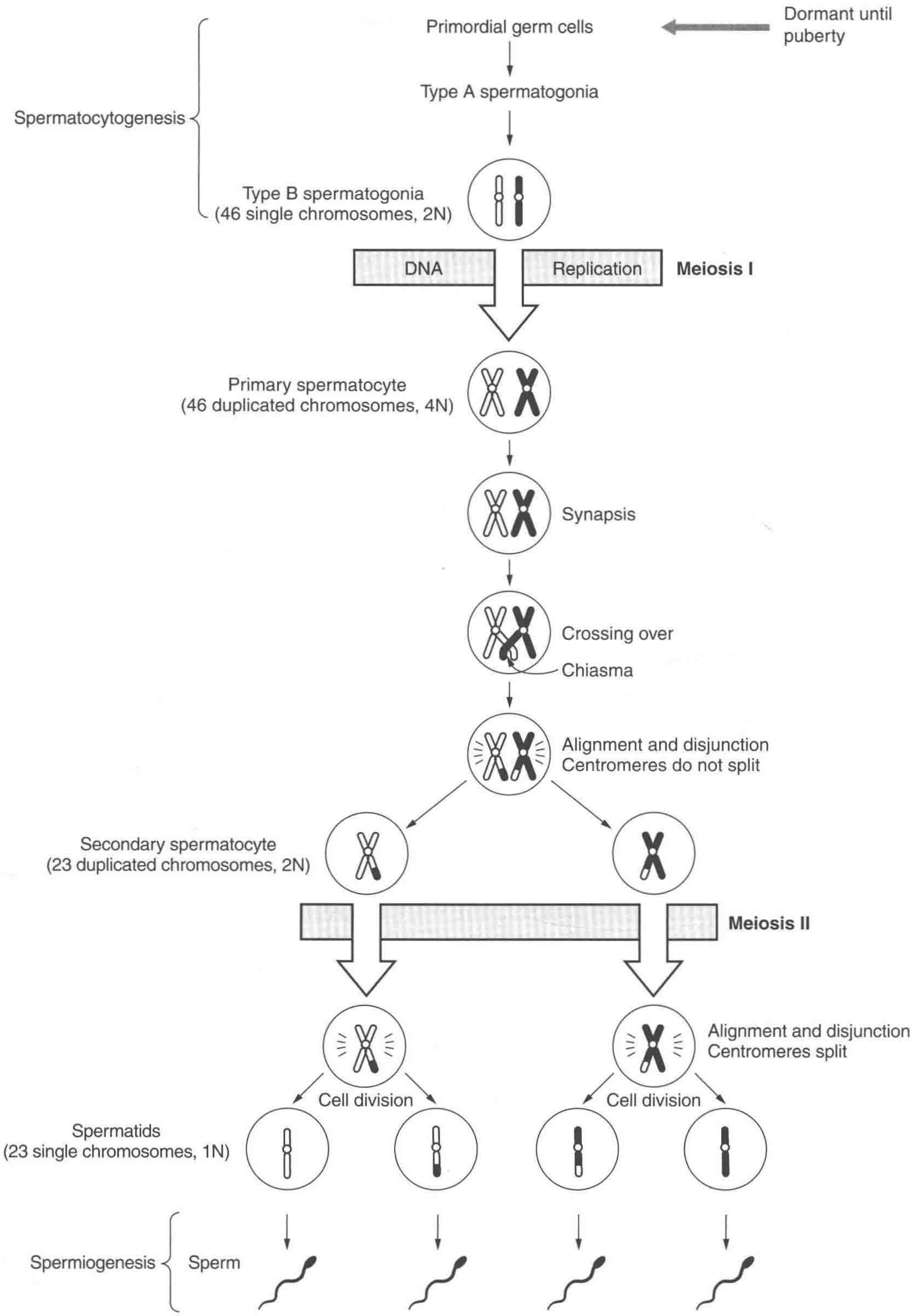
1. Prolonged dormancy of primary oocytes may be the reason for the high incidence of chromosomal abnormalities in offspring of older women. Since all primary oocytes are formed by month 5 of fetal life, a female infant is born with her entire supply of gametes. Primary oocytes remain dormant until ovulation; those ovulated late in the woman's reproductive life may have been dormant for as long as 40 years.
2. The incidence of **trisomy 21 (Down syndrome)** increases with advanced age of the mother. The primary cause of Down syndrome is maternal meiotic nondisjunction. Clinical findings include severe mental retardation, epicanthal folds, Brushfield spots, simian creases, and association with a decrease in α-fetoprotein.

B. OFFSPRING OF OLDER MEN.

An increased incidence of **achondroplasia** (an autosomal dominant congenital skeletal anomaly characterized by retarded bone growth in the limbs with normal-sized head and trunk) and **Marfan syndrome** are associated with advanced paternal age.

C. MALE INFERTILITY

1. **Sperm number and motility:** Infertile males produce less than 10 million sperm/mL of semen. Fertile males produce from 20 to more than 100 million sperm/mL of semen. Normally up to 10% of sperm in an ejaculate may be grossly deformed (two heads or two tails), but these sperm probably do not fertilize an oocyte owing to their lack of motility.



● **Figure 1-3 Male gametogenesis (spermatogenesis).** Note that only one pair of homologous chromosomes is shown (white = maternal origin; black = paternal origin). Synapsis is the process of pairing of homologous chromosomes. The point at which the DNA molecule crosses over is called the chiasma and is where exchange of small amounts of maternal and paternal DNA occurs. Note that synapsis and crossing over occur only during meiosis I.

2. **Hypogonadotropic hypogonadism** is a condition where the hypothalamus produces reduced levels of GnRF leading to reduced levels of FSH and LH and finally reduced levels of testosterone. **Kallmann syndrome** is a genetic disorder characterized by hypogonadotropic hypogonadism and anosmia (loss of smell).
3. **Drugs:** Cancer chemotherapy, anabolic steroids, cimetidine (histamine H_2-receptor antagonist that inhibits stomach HCl production), spironolactone (a K^+-sparing diuretic), phenytoin (an antiepileptic drug), sulfasalazine (a sulfa drug used to treat ulcerative colitis, Crohn's disease, rheumatoid arthritis, and psoriatic arthritis), and nitrofurantoin (an antibiotic used to treat urinary tract infections).
4. **Other factors:** Klinefelter syndrome, seminoma, cryptochordism, varicocele, hydrocele, mumps, prostatitis, epididymitis, hypospadias, ductus deferens obstruction, and impotence.

D. FEMALE INFERTILITY

1. **Anovulation** is the absence of ovulation in some women due to inadequate secretion of FSH and LH and is often treated with **clomiphene citrate** (a fertility drug). Clomiphene citrate competes with estrogen for binding sites in the adenohypophysis, thereby suppressing the normal negative feedback loop of estrogen on the adenohypophysis. This stimulates FSH and LH secretion and induces ovulation.
2. **Premature ovarian failure (primary ovarian insufficiency)** is the loss of function of the ovaries before age 40, resulting in infertility. The cause is generally idiopathic, but cases have been attributed to autoimmune disorders, Turner syndrome, Fragile X syndrome, chemotherapy, or radiation treatment. The age of onset can be seen in early teenage years, but varies widely. If a girl never begins menstruation, the condition is called **primary ovarian failure**. Clinical findings include: amenorrhea, low estrogen levels, high FSH levels, and ultrasound may show small ovaries without follicles.
3. **Pelvic inflammatory disease (PID)** refers to the infection of the uterus, uterine tubes, and/or ovaries leading to inflammation and scar formation. The cause is generally a sexually transmitted infection (STI), usually Neisseria gonorrhea or Chlamydia trachomatis. However, many other routes are possible (lymphatic spread, hematogenous spread, postpartum infections, postabortal [miscarriage or abortion] infections, or intrauterine device infections). Clinical findings include: some cases that are asymptomatic, fever, tenderness of the cervix, lower abdominal pain, discharge, painful intercourse, or irregular menstrual bleeding.
4. **Polycystic ovarian syndrome** is a complex female endocrine disorder defined by oligo-ovulation (infrequent, irregular ovulations), androgen excess, multiple ovarian cysts (by ultrasound). The cause is uncertain, but a strong genetic component exists. Clinical findings include: anovulation, irregular menstruation, amenorrhea, ovulation-related infertility, high androgen levels or activity resulting in acne and hirsutism, insulin resistance associated with obesity, and Type II diabetes.
5. **Endometriosis** is the appearance of foci of endometrial tissue in abnormal locations outside the uterus (e.g., ovary, uterine ligaments, pelvic peritoneum). The ectopic endometrial tissue shows cyclic hormonal changes synchronous with the cyclic hormonal changes of the endometrium in the uterus. Clinical findings include: infertility, dysmenorrhea, pelvic pain (most pronounced at the time of menstruation), dysuria, painful sex, and throbbing pain in the legs.

Chapter 2

Week 1 (Days 1–7)*

I Overview.

Figure 2-1 summarizes the events that occur during week 1, following fertilization.

II Fertilization

A. Occurs in the **ampulla of the uterine tube.**

B. The sperm binds to the zona pellucida of the secondary oocyte arrested in metaphase of meiosis II and triggers the **acrosome reaction**, causing the release of acrosomal enzymes (e.g., **acrosin**).

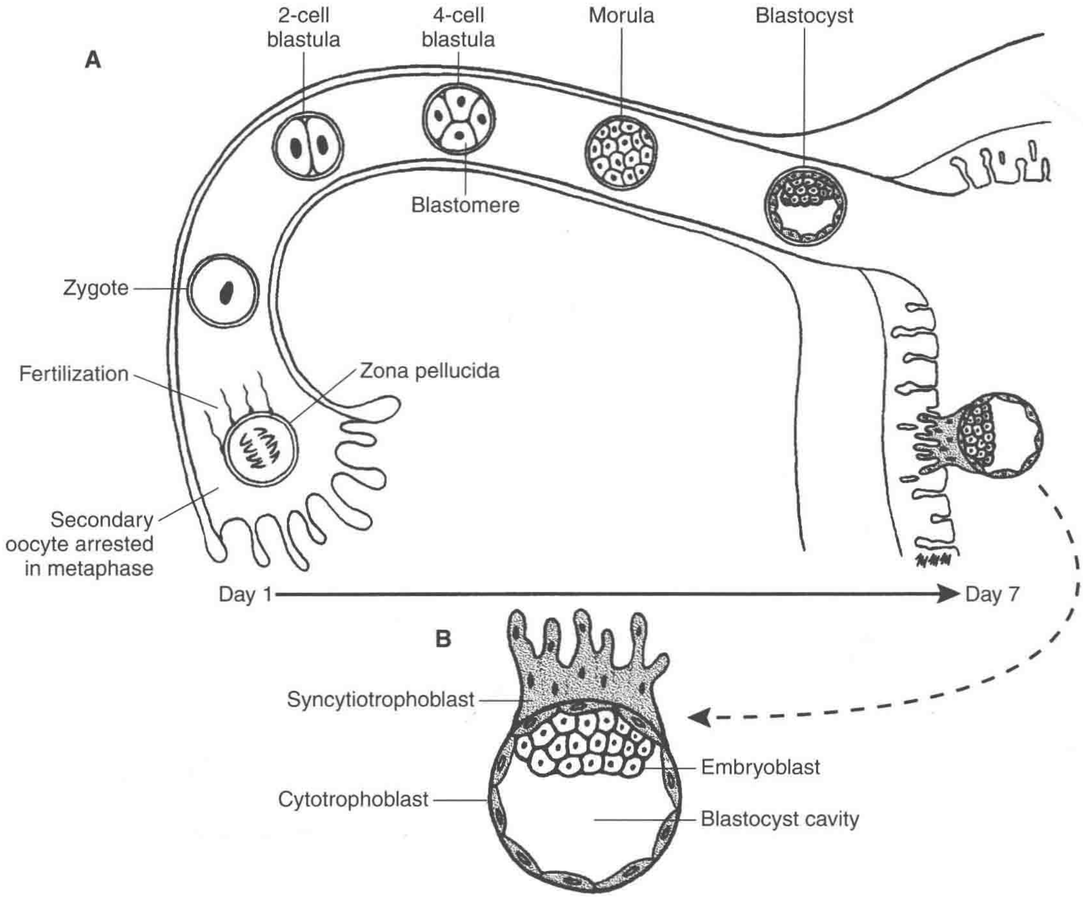
C. Aided by the acrosomal enzymes, the sperm penetrates the zona pellucida. Penetration of the zona pellucida elicits the **cortical reaction**. The cortical reaction is the release of lysosomal enzymes from cortical granules near the oocyte cell membrane that changes the oocyte cell membrane potential and inactivates sperm receptors on the zona pellucida.

D. These changes are called the **polyspermy block**, which is thought to render the secondary oocyte impermeable to other sperm. However, we know that polyspermy block does not work very well since diandric triploidy (an embryo with three sets of chromosomes, two of which come from the father) is quite common.

E. The sperm and secondary oocyte cell membranes fuse. The nuclear contents and the centriole pair of the sperm enter the cytoplasm of the oocyte. The sperm nuclear contents form the **male pronucleus**. The tail and mitochondria of the sperm degenerate. Therefore, all mitochondria within the zygote are of maternal origin (i.e., **all mitochondrial DNA is of maternal origin**). The oocyte loses its centriole pair during meiosis so that the establishment of a functional zygote depends on the sperm centriole pair (a cardinal feature of human embryogenesis) to produce a microtubule organizing center (MTOC).

F. The secondary oocyte completes meiosis II, forming a mature **ovum**. The nucleus of the ovum is the **female pronucleus**.

*The age of the developing conceptus can be measured either from the estimated day of fertilization (fertilization age) or from the day of the last normal menstrual period (LNMP). In this book, ages are presented as fertilization age.



● **Figure 2-1 (A)** The stages of human development during week 1. **(B)** A day 7 blastocyst.

G. **Syngamy** is a term that describes the successful completion of fertilization, that is, the formation of a **zygote**. Syngamy occurs when the male and female pronuclei fuse and the cytoplasmic machinery for proper cell division exists.

H. The life span of a zygote is only a few hours because its existence terminates when the first cleavage division occurs.

III Cleavage

A. Cleavage is a series of **mitotic** divisions of the zygote, where the plane of the first mitotic division passes through the area of the cell membrane where the polar bodies were previously extruded.

B. In humans, cleavage is **holoblastic**, which means the cells divide completely through their cytoplasm. Cleavage is **asymmetrical**, which means the daughter cells are unequal in size (i.e., one cell gets more cytoplasm than the other) at least during the first few cell divisions. Cleavage is **asynchronous**, which means only one cell will divide at a time;