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Ronald W. Dudek, Ph.D.
Professor
Department of Anatomy and Cell Biology
Brody School of Medicine
East Carolina University
Greenville, North Carolina

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Preface

The sixth edition of BRS *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 BRS *Embryology* is to provide an accurate and quick review of important clinical aspects of embryology for the future physician. In addition, we have added color to the diagrams. In this regard, I have used the following color scheme. The ectoderm/neuroectoderm and derivatives are colored blue. The neural crest cells and derivatives are colored purple. The mesoderm and derivatives are colored red. When multiple mesodermal structures are involved (e.g., reproductive systems), I used light red and dark red. The endoderm and derivatives are colored yellow.

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 6.6) 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,[1,2] Yoon et al.,[3] Williams et al.,[4] and Hoekstra et al.[5]

I understand that BRS *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 BRS *Embryology* sixth edition, especially after you have taken the USMLE Step 1 examination. Your suggestions will find their way into the seventh edition. You may contact me at dudekr@ecu.edu.

Ronald W. Dudek, PhD

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Contents

chapter 1

Prefertilization Events

I. SEXUAL REPRODUCTION

Sexual reproduction occurs when female and male gametes (oocyte and spermatozoon, respectively) unite at fertilization. Gametes are direct descendants of **primordial germ cells**, which are first observed in **the wall of the yolk sac** at week 4 of embryonic development and subsequently migrate into the future gonad region. Gametes are produced by **gametogenesis** (called **oogenesis** in the female and **spermatogenesis** in the male). Gametogenesis employs a specialized process of cell division, **meiosis**, which uniquely distributes chromosomes among gametes.

II. CHROMOSOMES (FIGURE 1.1)

A single chromosome consists of two characteristic regions called **arms** (**p arm** = **short arm**; **q arm** = **long arm**), which are separated by a **centromere**. During meiosis I, **single chromosomes** undergo DNA replication, which duplicates the arms. This forms **duplicated chromosomes**, which consist of two sister **chromatids** attached at the centromere.

A. **Ploidy and N number.** Ploidy refers to the **number of chromosomes** in a cell. The N number refers to the **amount of DNA** in a cell.

1. **Normal somatic cells and primordial germ cells** contain **46 single chromosomes** and **2N amount of DNA**. The chromosomes occur in **23 homologous pairs**; one member (homologue) of each pair is of maternal origin, and the other is of paternal origin. The term "**diploid**" is classically used to refer to a cell containing 46 single chromosomes. Chromosome pairs 1–22 are **autosomal (nonsex) pairs**. Chromosome pair 23 consists of the **sex chromosomes** (XX for a female and XY for a male).
2. **Gametes** contain **23 single chromosomes** (22 autosomes and 1 sex chromosome) and **1N amount of DNA**. The term "**haploid**" is classically used to refer to a cell containing 23 single chromosomes. Female gametes contain only the X sex chromosome. Male gametes contain either the X or Y sex chromosome; therefore, the male gamete determines the genetic sex of the individual.

B. **The X chromosome.** A normal female somatic cell contains **two X chromosomes (XX)**. The female cell **permanently inactivates** one of the X chromosomes during week 1 of embryonic development. The choice of which X chromosome (maternal or paternal) is inactivated is random. The

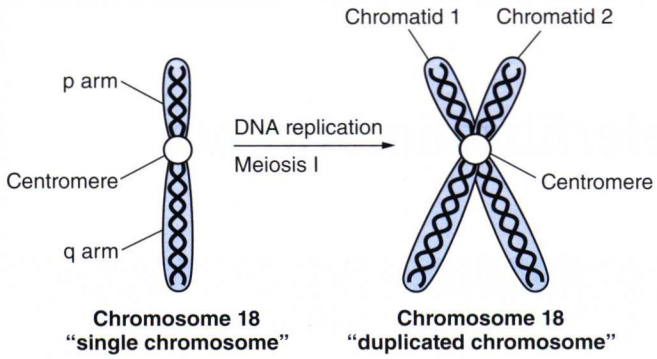

FIGURE 1.1. A schematic diagram of chromosome 18 showing it in its "single-chromosome" state and in the "duplicated-chromosome" state that is formed by DNA replication during meiosis I. It is important to understand that both the "single-chromosome" state and the "duplicated-chromosome" state will be counted as one chromosome 18. As long as the additional DNA in the "duplicated chromosome" is bound at the centromere, the structure will be counted as one chromosome 18 even though it has twice the amount of DNA.

inactivated X chromosome (called the **Barr body**) can be observed by light microscopy near the nuclear membrane.

C. **The Y chromosome.** A normal male somatic cell contains **one X chromosome** and **one Y chromosome (XY)**.

III. MEIOSIS

Meiosis is a specialized process of cell division that occurs only during the production of gametes within the female ovary or male testes. Meiosis consists of two divisions (meiosis I and II), which result in the formation of four gametes, each containing half the number of chromosomes (23 single chromosomes) and half the amount of DNA (1N) found in normal somatic cells (46 single chromosomes, 2N).

A. **Meiosis I.** Events that occur during meiosis I include the following:
1. **Synapsis:** pairing of 46 homologous duplicated chromosomes.
2. **Crossing over:** exchange of large segments of DNA.
3. **Alignment:** alignment of 46 homologous duplicated chromosomes at the metaphase plate.
4. **Disjunction:** separation of 46 homologous duplicated chromosomes from each other; **centromeres do not split**.
5. **Cell division:** formation of two secondary gametocytes (23 duplicated chromosomes, 2N).

B. **Meiosis II.** Events that occur during meiosis II include the following:
1. **Synapsis:** absent.
2. **Crossing over:** absent.
3. **Alignment:** alignment of 23 duplicated chromosomes at the metaphase plate.
4. **Disjunction:** separation of 23 duplicated chromosomes to form 23 single chromosomes; centromeres split.
5. **Cell division:** formation of four gametes (23 single chromosomes, 1N).

IV. OOGENESIS: FEMALE GAMETOGENESIS (FIGURE 1.2)

A. **Primordial germ cells (46, 2N)** from the wall of the yolk sac arrive in the ovary at **week 6** and differentiate into **oogonia (46, 2N)**, which populate the ovary through *mitotic* division.

B. Oogonia enter meiosis I and undergo DNA replication to form **primary oocytes (46, 4N)**. All primary oocytes are formed by **month 5 of fetal life**. No oogonia are present at birth.

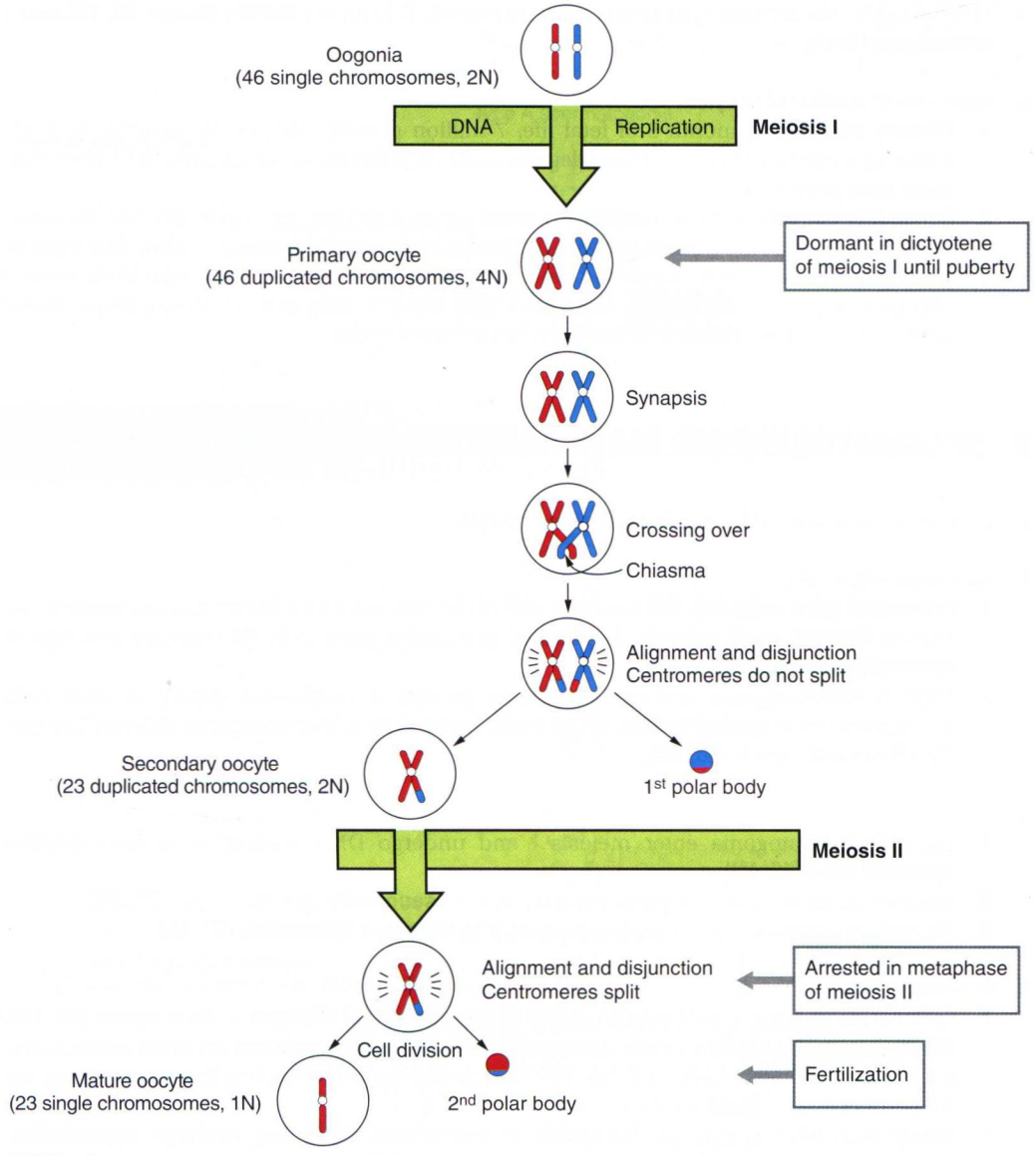

FIGURE 1.2. Oogenesis: female gametogenesis. Note that only one pair of homologous chromosomes is shown (*red*, maternal origin; *blue*, paternal origin). Synapsis is the process of pairing of homologous chromosomes. The point at which the DNA molecule crosses over is called the chiasma and is where exchange of small segments 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.

C. Primary oocytes remain **dormant in prophase (dictyotene) of meiosis I** from month 5 of fetal life until puberty. After puberty, 5 to 15 primary oocytes begin maturation with each ovarian cycle, with usually only 1 reaching full maturity in each cycle.

D. During the ovarian cycle and triggered by the **luteinizing hormone (LH) surge,** a primary oocyte completes meiosis I to form two daughter cells: the **secondary oocyte (23, 2N)** and the **first polar body**, which degenerates.

E. The secondary oocyte promptly begins meiosis II but is **arrested in metaphase of meiosis II** about 3 hours before ovulation. The secondary oocyte remains arrested in metaphase of meiosis II until fertilization occurs.

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

G. Approximate number of oocytes

1. **Primary oocytes:** At month 5 of fetal life, 7 million primary oocytes are present. At birth, 2 million are present (5 million have degenerated). At puberty, 40,000 are present (1.96 million more have degenerated).
2. **Secondary oocytes:** Twelve secondary oocytes are ovulated per year, up to 480 over the entire reproductive life of the woman (40 years × 12 secondary oocytes per year = 480). This number (480) is obviously overly simplified since it is **reduced** in women who take birth control pills (which prevent ovulation), in women who become pregnant (ovulation stops during pregnancy), and in women who may have anovulatory cycles.

V. SPERMATOGENESIS: MALE GAMETOGENESIS (FIGURE 1.3)

Spermatogenesis is classically divided into three phases:

A. Spermatocytogenesis

1. **Primordial germ cells (46, 2N)** from the wall of the yolk sac arrive in the testes at **week 6** and remain **dormant until puberty**. At puberty, primordial germ cells differentiate into **type A spermatogonia (46, 2N)**.
2. Type A spermatogonia undergo mitosis to provide a continuous supply of stem cells throughout the reproductive life of the male. 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 **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** to form **sperm (23, 1N)**. These changes include the (a) formation of the acrosome, (b) condensation of the nucleus, and (c) formation of head, neck, and tail. The total time of sperm formation (from spermatogonia to spermatozoa) is about 64 days.
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 the removal of adherent plasma 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 the 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