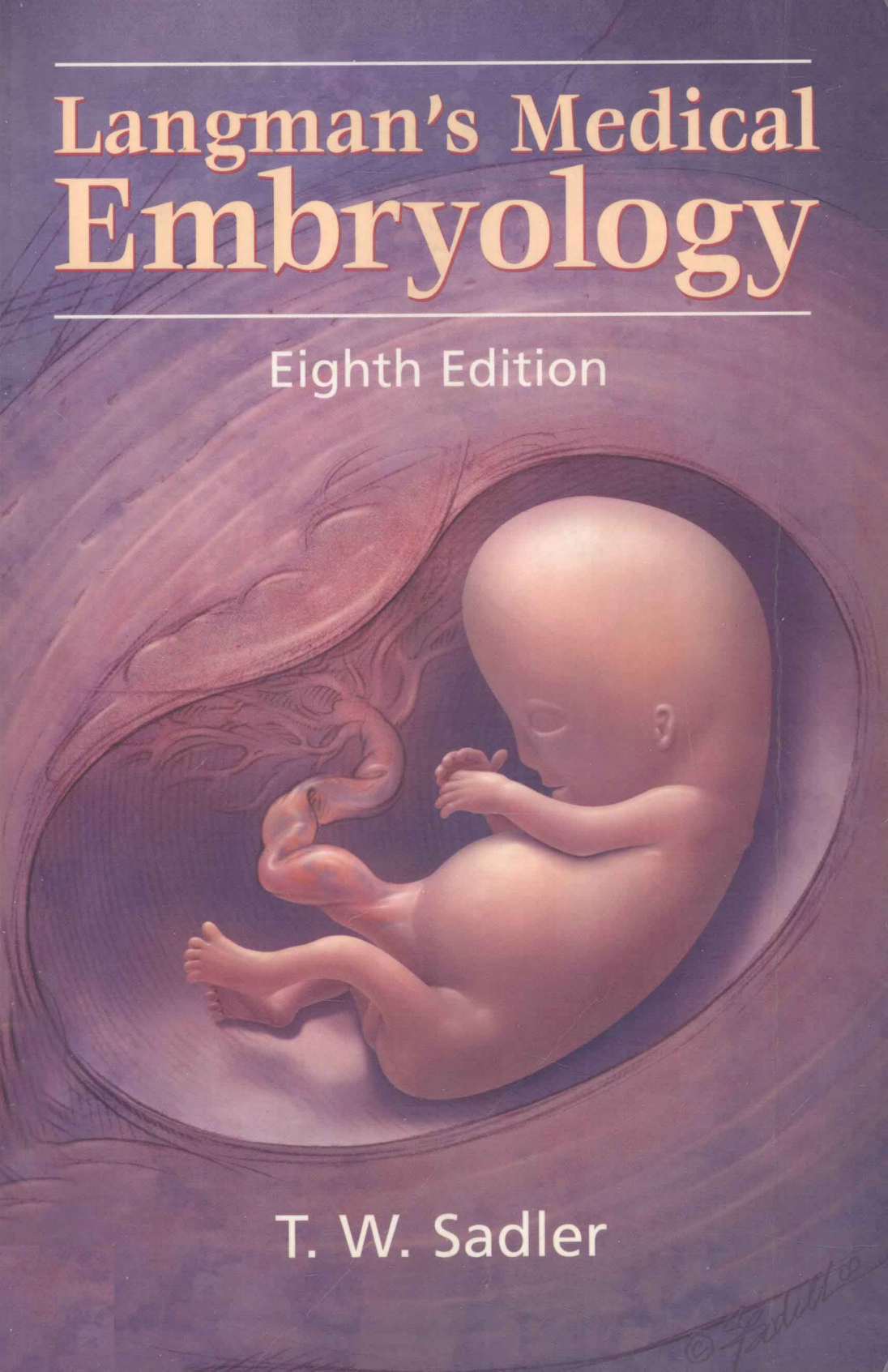
Langman's Medical Embryology

Eighth Edition



T. W. Sadler

Contents

PART III

APPENDIX

PART I

GENERAL EMBRYOLOGY

1 Gametogenesis: Conversion of Germ Cells Into Male and Female Gametes

Development begins with fertilization, the process by which the male gamete, the **sperm**, and the female gamete, the **oocyte**, unite to give rise to a **zygote**. Gametes are derived from **germ cells** that appear in the wall of the yolk sac at the fourth week of development (Fig. 1.1). From this location, these cells migrate by ameboid movement to the developing gonads, where they arrive by the end of the fifth week. Mitotic divisions increase their number during their migration and also when they arrive in the gonad. In preparation for fertilization, germ cells undergo **gametogenesis**, which includes meiosis, to reduce the number of chromosomes and **cytodifferentiation** to complete their maturation.

The Chromosome Theory of Inheritance

Traits of a new individual are determined by specific **genes** on **chromosomes** inherited from the father and the mother. Humans have approximately 100,000 genes on 46 chromosomes. Genes on the same chromosome tend to be inherited together and so are known as linked genes. In somatic cells, chromosomes appear as 23 **homologous** pairs to form the **diploid** number of 46. There are 22 pairs of matching chromosomes, the **autosomes**, and 1 pair of **sex chromosomes**. If the sex pair is XX, the individual is genetically female; if the pair is XY, the individual is genetically male. One chromosome of each pair is derived from the maternal **gamete**, the **oocyte**, and one pair from the paternal gamete, the **sperm**. Thus each gamete contains a **haploid** number of 23 chromosomes, and the union of the gametes at **fertilization** restores the diploid number of 46.

MITOSIS

Mitosis is the process whereby one cell divides, giving rise to two daughter cells that are genetically identical to the parent cell (Fig. 1.2). Each daughter cell receives the complete complement of 46 chromosomes. Before a cell enters mitosis, each chromosome replicates its deoxyribonucleic acid (DNA). During this replication phase the chromosomes are extremely long, they diffusely spread through the nucleus, and they cannot be recognized with the light microscope. With the onset of mitosis the chromosomes begin to coil, contract, and condense; these events mark the beginning of prophase. Each chromosome

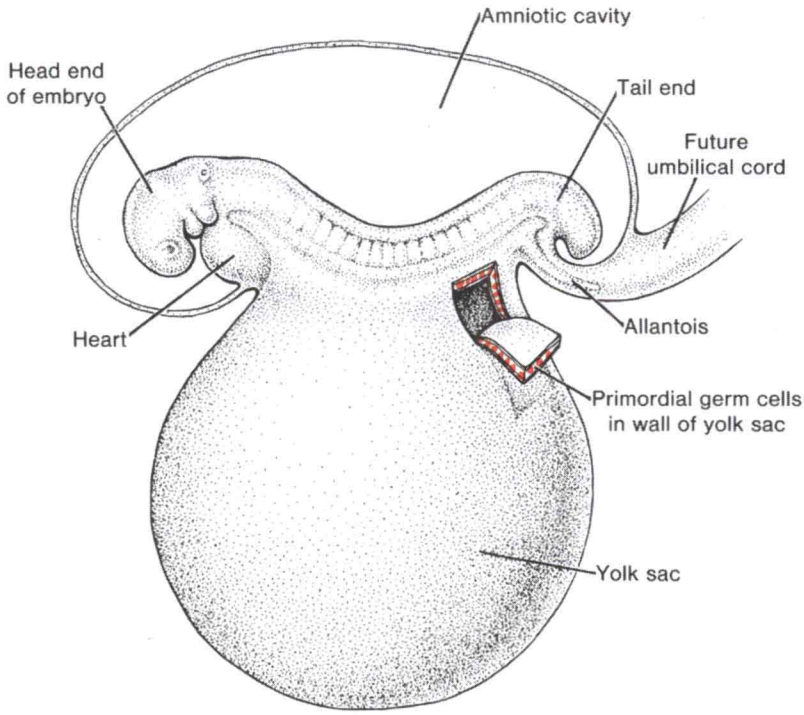


Figure 1.1. An embryo at the end of the third week, showing the position of primordial germ cells in the wall of the yolk sac, close to the attachment of the future umbilical cord. From this location these cells migrate to the developing gonad.

now consists of two parallel subunits, **chromatids**, that are joined at a narrow region common to both called the **centromere**. Throughout prophase the chromosomes continue to condense, shorten, and thicken (Fig. 1.2*A*), but only at prometaphase do the chromatids become distinguishable (Fig. 1.2*B*). During metaphase the chromosomes line up in the equatorial plane, and their doubled structure is clearly visible (Fig. 1.2*C*). Each is attached by **microtubules** extending from the centromere to the centriole, forming the **mitotic spindle**. Soon the centromere of each chromosome divides, marking the beginning of anaphase, followed by migration of chromatids to opposite poles of the spindle. Finally, during telophase, chromosomes uncoil and lengthen, the nuclear envelope reforms, and the cytoplasm divides (Fig. 1.2, *D* and *E*). Each daughter cell receives half of all doubled chromosome material and thus maintains the same number of chromosomes as the mother cell.

MEIOSIS

Meiosis is the cell division that takes place in the **germ cells** to generate male and female gametes, sperm and egg cells, respectively. Meiosis requires two

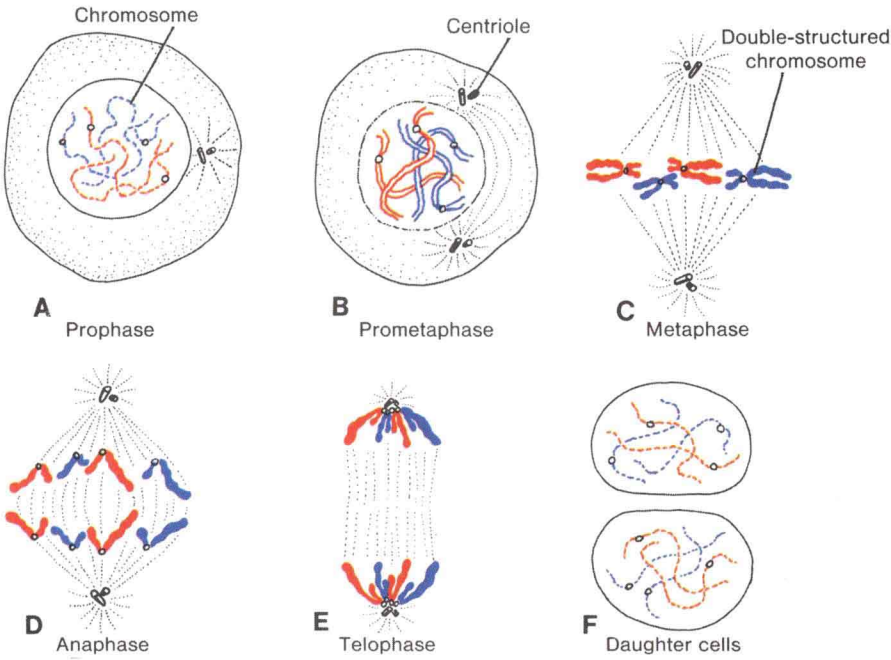


Figure 1.2. Various stages of mitosis. In prophase, chromosomes are visible as slender threads. Doubled chromatids become clearly visible as individual units during prometaphase. At no time during division do members of a chromosome pair unite. *Blue*, paternal chromosomes; *red*, maternal chromosomes.

cell divisions, **meiosis I** and **meiosis II**, to reduce the number of chromosomes to the haploid number of 23 (Fig. 1.3). As in mitosis, male and female germ cells (**spermatocytes** and **primary oocytes**) at the beginning of meiosis I replicate their DNA so that each of the 46 chromosomes is duplicated into sister chromatids. In contrast to mitosis, however, **homologous chromosomes** then align themselves in **pairs**, a process called **synapsis**. The pairing is exact and point for point except for the XY combination. Homologous pairs then separate into two daughter cells. Shortly thereafter meiosis II separates sister chromatids. Each gamete then contains 23 chromosomes.

Crossover

Crossovers, critical events in meiosis I, are the **interchange of chromatid segments** between paired homologous chromosomes (Fig. 1.3*C*). Segments of chromatids break and are exchanged as homologous chromosomes separate. As separation occurs, points of interchange are temporarily united and form an X-like structure, a **chiasma** (Fig. 1.3*C*). The approximately 30 to 40 crossovers (1 or 2 per chromosome) with each meiotic I division are most frequent between genes that are far apart on a chromosome.

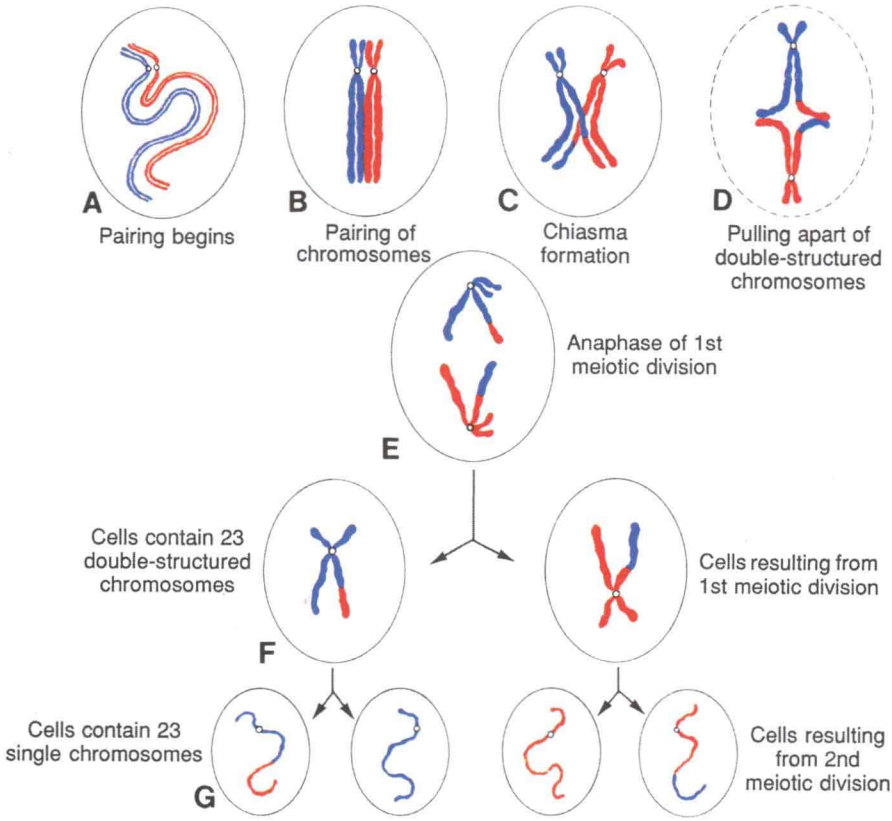


Figure 1.3. First and second meiotic divisions. **A.** Homologous chromosomes approach each other. **B.** Homologous chromosomes pair, and each member of the pair consists of two chromatids. **C.** Intimately paired homologous chromosomes interchange chromatid fragments (crossover). Note the chiasma. **D.** Double-structured chromosomes pull apart. **E.** Anaphase of the first meiotic division. **F** and **G.** During the second meiotic division, the double-structured chromosomes split at the centromere. At completion of division, chromosomes in each of the four daughter cells are different from each other.

As a result of meiotic divisions (*a*) genetic variability is enhanced through crossover, which creates new chromosomes, and through random distribution of homologous chromosomes to the daughter cells; and (*b*) each germ cell contains a haploid number of chromosomes, so that at fertilization the diploid number of 46 is restored.

Polar Bodies

Also during meiosis one primary oocyte gives rise to four daughter cells, each with 22 plus 1 X chromosomes (Fig. 1.4*A*). However, only one of these

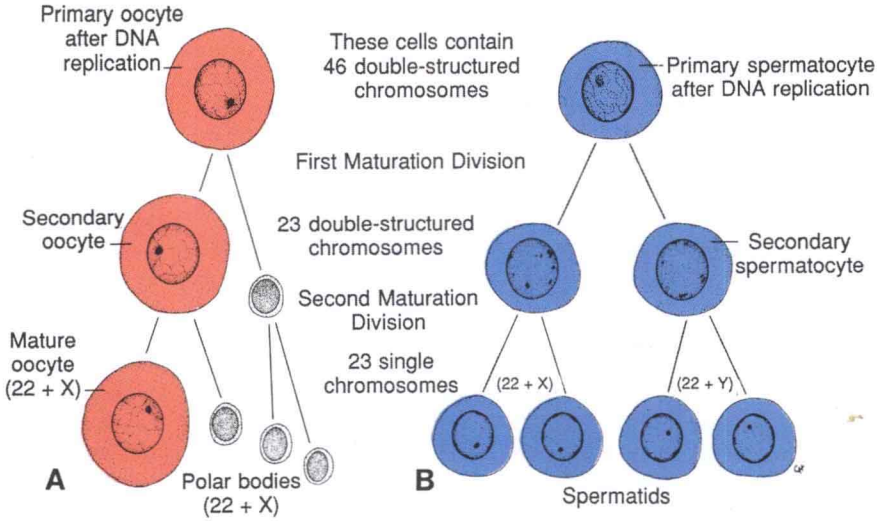


Figure 1.4. Events occurring during the first and second maturation divisions. **A.** The primitive female germ cell (primary oocyte) produces only one mature gamete, the mature oocyte. **B.** The primitive male germ cell (primary spermatocyte) produces four spermatids, all of which develop into spermatozoa.

develops into a mature gamete, the oocyte; the other three, the **polar bodies**, receive little cytoplasm and degenerate during subsequent development. Similarly, one primary spermatocyte gives rise to four daughter cells, two with 22 plus 1 X chromosomes and two with 22 plus 1 Y chromosomes (Fig. 1.4*B*). However, in contrast to oocyte formation, all four develop into mature gametes.

CLINICAL CORRELATES

Birth Defects and Spontaneous Abortions: Chromosomal and Genetic Factors

Chromosomal abnormalities, which may be **numerical** or **structural**, are important causes of birth defects and spontaneous abortions. It is estimated that 50% of conceptions end in spontaneous abortion and that 50% of these abortuses have major chromosome abnormalities. Thus approximately 25% of conceptuses have a major chromosomal defect. The most common chromosome abnormalities in abortuses are 45,X (Turner syndrome), triploidy, and trisomy 16. Chromosome abnormalities account for 7% of major birth defects, and **gene mutations** account for an additional 8%.

Numerical Abnormalities

The normal human somatic cell contains 46 chromosomes; the normal gamete contains 23. Normal somatic cells are **diploid**, or 2*n*; normal gametes are **haploid**,

or ***n***. **Euploid** refers to any exact multiple of ***n***, e.g., diploid or triploid. **Aneuploid** refers to any chromosome number that is not euploid; it is usually applied when an extra chromosome is present (**trisomy**) or when one is missing (**monosomy**). Abnormalities in chromosome number may originate during meiotic or mitotic divisions. In **meiosis** two members of a pair of homologous chromosomes normally separate during the first meiotic division so that each daughter cell receives one member of each pair (Fig. 1.5*A*). Sometimes, however, separation does not occur (**nondisjunction**), and both members of a pair move into one cell (Fig. 1.5, *B* and *C*). As a result of nondisjunction of the chromosomes, one cell receives 24 chromosomes, and the other receives 22 instead of the normal 23. When at fertilization a gamete having 23 chromosomes fuses with a gamete having 24 or 22 chromosomes, the result is an individual with either 47 chromosomes (trisomy) or 45 chromosomes (monosomy). Nondisjunction, which occurs during either the first or the second meiotic division of the germ cells, may involve the autosomes or sex chromosomes. In women the incidence of chromosomal abnormalities, including nondisjunction, increases with age, especially at 35 and older.

Occasionally nondisjunction occurs during mitosis (**mitotic nondisjunction**) in an embryonic cell during the earliest cell divisions. Such conditions produce **mosaicism**, with some cells having an abnormal chromosome number and oth-

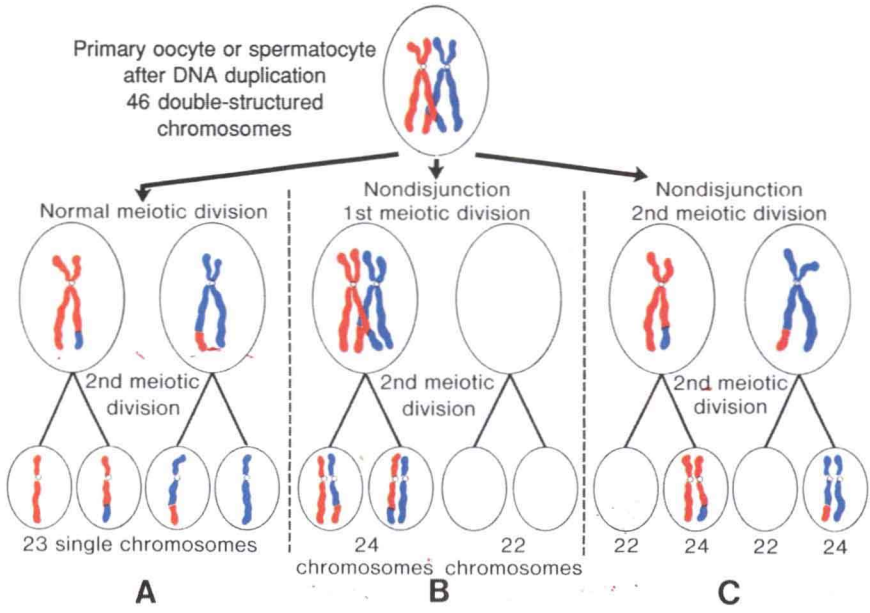


Figure 1.5. **A**. Normal maturation divisions. **B**. Nondisjunction in the first meiotic division. **C**. Nondisjunction in the second meiotic division.

ers being normal. Affected individuals may exhibit few or many of the characteristics of a particular syndrome, depending on the number of cells involved and their distribution.

Sometimes chromosomes break, and pieces of one chromosome attach to another. Such **translocations** may be **balanced**, in which case breakage and reunion occur between two chromosomes but no critical genetic material is lost and individuals are normal; or they may be **unbalanced**, in which case part of one chromosome is lost and an altered phenotype is produced. For example, unbalanced translocations between the long arms of chromosomes 14 and 21 during meiosis I or II produce gametes with an extra copy of chromosome 21—one of the causes of Down syndrome (Fig. 1.6). Translocations are particularly common between chromosomes 13, 14, 15, 21, and 22 because they cluster during meiosis.

Trisomy 21 (Down Syndrome)

Down syndrome is usually caused by an extra copy of **chromosome 21** (**trisomy 21**, Fig.1.7). Features of children with Down syndrome include growth retardation; varying degrees of mental retardation; craniofacial abnormalities, including upward slanting eyes, epicanthal folds (extra skin folds at the medial corners of the eyes), flat facies, and small ears; cardiac defects; and hypotonia (Fig. 1.8). These individuals also have relatively high incidences of leukemia, infections, thyroid dysfunction, and premature aging. Furthermore, nearly all develop signs of Alzheimer's disease after age 35. In 95% of cases the syndrome is caused by trisomy 21 resulting from meiotic nondisjunction, and in 75% of these instances, nondisjunction occurs during oocyte formation. The incidence of Down syndrome is approximately 1 in 2000 conceptuses for women under age 25. This risk increases with maternal age to 1 in 300 at age 35 and 1 in 100 at age 40.

In approximately 4% of cases of Down syndrome there is an unbalanced translocation between chromosome 21 and chromosome 13, 14, or 15 (Fig. 1.6). The final 1% are due to mosaicism resulting from mitotic nondisjunction. These individuals have some cells with a normal chromosome number and some that are aneuploid. They may exhibit few or many of the characteristics of Down syndrome.

Trisomy 18

Patients with trisomy 18 show the following features: mental retardation, congenital heart defects, low-set ears, and flexion of fingers and hands (Fig. 1.9). In addition, patients frequently show micrognathia, renal anomalies, syndactyly, and malformations of the skeletal system. The incidence of this condition is about 1 in 5000 newborns. The infants usually die by age 2 months.

Trisomy 13 = Cleft lip

The main abnormalities of trisomy 13 are mental retardation, holoprosencephaly, congenital heart defects, deafness, cleft lip and palate, and eye defects, such as microphthalmia, anophthalmia, and coloboma (Fig. 1.10). The incidence of this abnormality is about 1 in 5,000 live births. Most of the infants die by age 3 months.

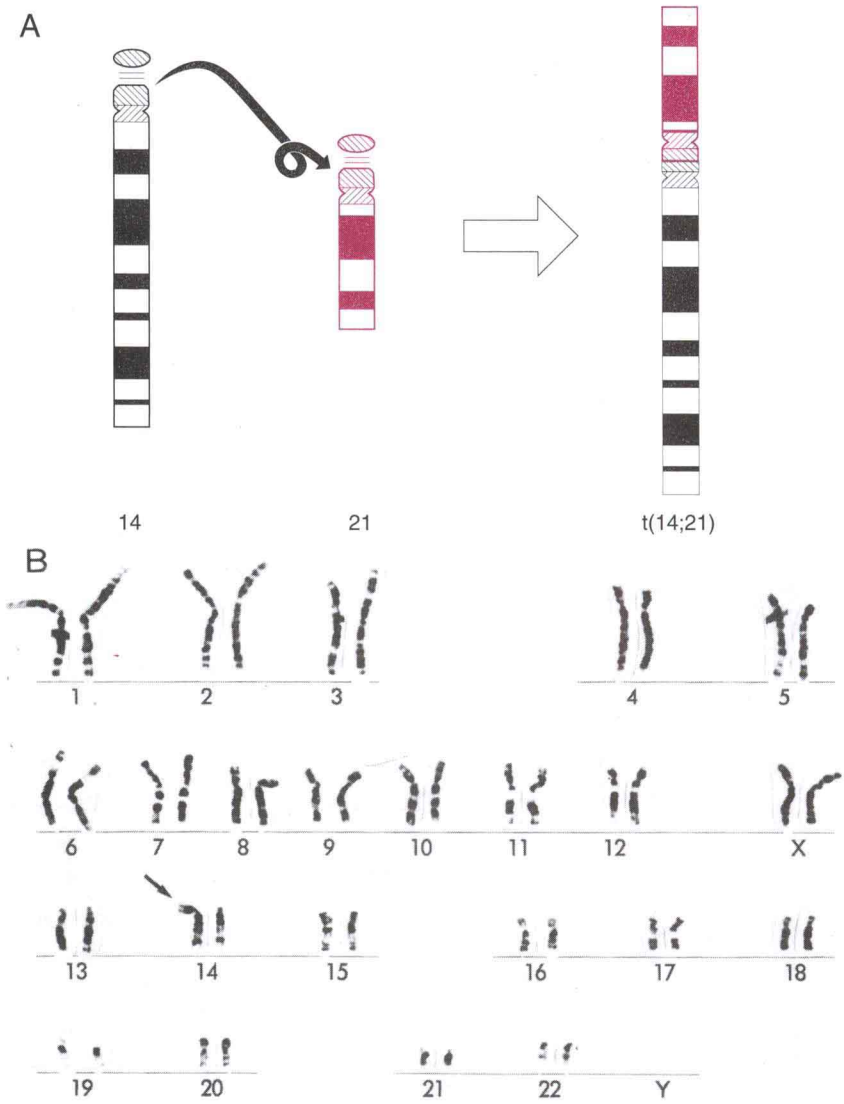


Figure 1.6. **A**. Translocation of the long arms of chromosomes 14 and 21 at the centromere. Loss of the short arms is not clinically significant, and these individuals are clinically normal, although they are at risk for producing offspring with unbalanced translocations. **B**. Karyotype of translocation of chromosome 21 onto 14, resulting in Down syndrome.

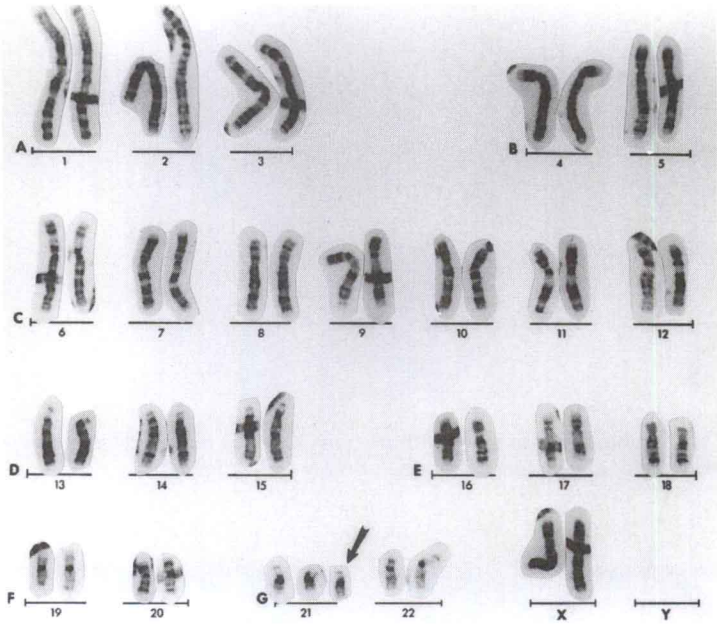


Figure 1.7. Karyotype of trisomy 21 (*arrow*), Down syndrome.

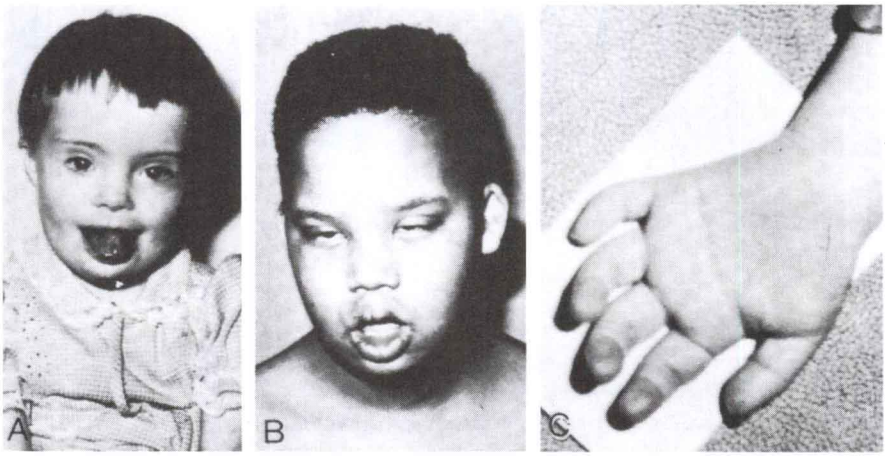


Figure 1.8. **A** and **B**. Children with Down syndrome, which is characterized by a flat, broad face; oblique palpebral fissures; epicanthus; and furrowed lower lip. **C**. Another characteristic of Down syndrome is a broad hand with single transverse or simian crease. Many children with Down syndrome are mentally retarded and have congenital heart abnormalities.

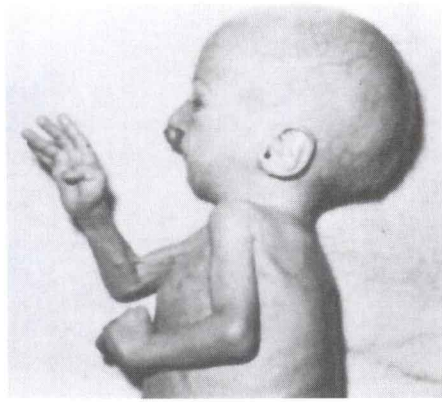


Figure 1.9. Photograph of child with trisomy 18. Note the prominent occiput, cleft lip, micrognathia, low-set ears, and one or more flexed fingers.

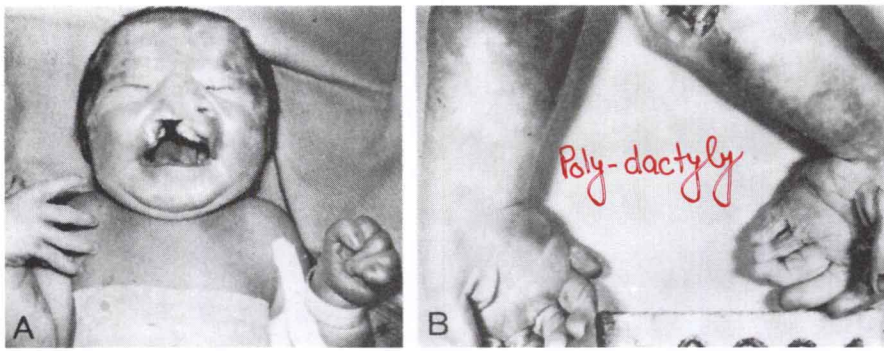


Figure 1.10. **A**. Child with trisomy 13. Note the cleft lip and palate, the sloping forehead, and microphthalmia. **B**. The syndrome is commonly accompanied by polydactyly.

Klinefelter Syndrome 47 chro XXY

The clinical features of Klinefelter syndrome, found only in males and usually detected at puberty, are sterility, testicular atrophy, hyalinization of the seminiferous tubules, and usually gynecomastia. The cells have 47 chromosomes with a sex chromosomal complement of the XXY type, and a sex chromatin body is found in 80% of cases (Fig. 1.11). The incidence is about 1 in 500 males. Nondisjunction of the XX homologues is the most common causative event. Occasionally patients with Klinefelter syndrome have 48 chromosomes: 44 au-

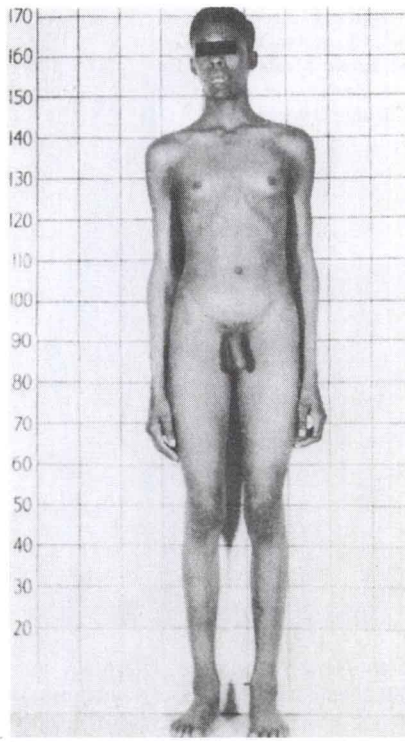


Figure 1.11. Patient with Klinefelter syndrome showing normal phallus development but gynecomastia (enlarged breasts).

tosomes and 4 sex chromosomes (XXXY). Although mental retardation is not generally part of the syndrome, the more X chromosomes there are, the more likely is some degree of mental impairment.

Turner Syndrome 45 44+X

Turner syndrome, found in women with an unmistakably female appearance (Fig. 1.12), is characterized by the absence of ovaries (**gonadal dysgenesis**) and short stature. Other common associated abnormalities are webbed neck, lymphedema of the extremities, skeletal deformities, and a broad chest with widely spaced nipples. Approximately 55% of affected women are monosomic for the X and chromatin negative due to nondisjunction. In 80% of these women nondisjunction in the male gamete is the cause. In the remainder of women, structural abnormalities of the X chromosome or mitotic nondisjunction resulting in mosaicism is the cause.

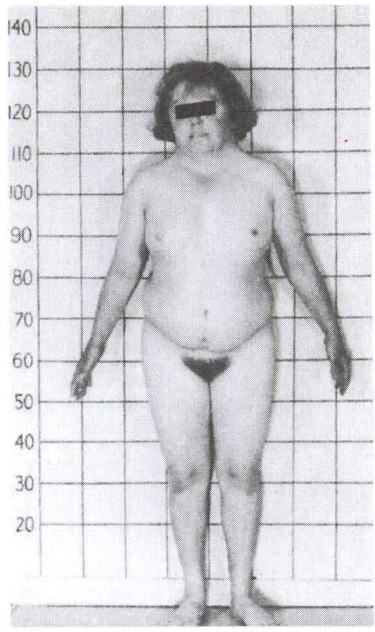


Figure 1.12. Patient with Turner syndrome. The main characteristics are webbed neck, short stature, broad chest, and absence of sexual maturation.

Triple X Syndrome

Patients with triple X syndrome are infantile, with scanty menses and some degree of mental retardation. They have two sex chromatin bodies in their cells.

Structural Abnormalities

Structural chromosome abnormalities, which involve one or more chromosomes, usually result from chromosome breakage. Breaks are caused by environmental factors, such as viruses, radiation, and drugs. The result of breakage depends on what happens to the broken pieces. In some cases the broken piece of a chromosome is lost and the infant with partial **deletion** of a chromosome is abnormal. A well-known syndrome caused by partial deletion of the short arm of chromosome 5 is the **cri-du-chat syndrome**. Such children have a catlike cry, microcephaly, mental retardation, and congenital heart disease. Many other relatively rare syndromes are known to result from a partial chromosome loss.

Microdeletions, spanning only a few **contiguous genes**, may result in **microdeletion syndrome** or **contiguous gene syndrome**. Sites where these deletions occur, called **contiguous gene complexes**, can be identified by **high-resolution chromosome banding**. An example of a microdeletion occurs on the long arm of chromosome 15 (15q11–15q13). Inheriting the deletion on the maternal chro-