CHROMOSOME ABNORMALITIES

- Chromosome disorders form a major category of genetic disease for example; wastage, congenital malformations, and mental retardation and play an important role in the pathogenesis of malignant disease.
- Specific chromosome abnormalities are responsible for hundreds of identifiable syndromes more common than all the mendelian single-gene disorders together.
- Cytogenetic disorders are present in nearly 1% of live births, in about 2% of pregnancies in women older than 35 years who undergo prenatal diagnosis, and in fully half of all spontaneous first-trimester abortions.

- Abnormalities of chromosomes may be either numerical or structural and may involve one or more autosomes, sex chromosomes, or both simultaneously.
- The most common type of clinically significant chromosome abnormality is **aneuploidy,** an abnormal chromosome number due to an extra or missing chromosome, which is always associated with physical or mental maldevelopment or both.
- **Reciprocal translocations** (an exchange of segments between non-homologous chromosomes) are also relatively common but usually have no phenotypic effect,

there may be an associated increased risk of abnormal offspring.

Abnormalities of Chromosome Number

A chromosome complement with any chromosome number other than 46 is said to be heteroploid. An exact multiple of the haploid chromosome number (n) is called euploid, and any other chromosome number is aneuploid.

Triploidy and Tetraploidy:

- In addition to the diploid (2n) number characteristic of normal somatic cells, two other euploid chromosome complements.

- **Triploid** (3n) and **tetraploid** (4n), are observed in clinical material.
- Both triploidy and tetraploidy have been seen in fetuses, and although triploid infants can be live born, they do not survive long. Triploidy is observed in 1% to 3% of recognized conceptions, and among those that survive to the end of the first trimester, most result from fertilization by two sperm (dispermy).
- Failure of one of the meiotic divisions, resulting in a diploid egg or sperm, can also account for a proportion of cases.

- The phenotypic manifestation of a triploid karyotype depends on the source of the extra chromosome set; triploids with an extra set of paternal chromosomes typically have an abnormal placenta and are classified as **partial hydatidiform moles**, set of maternal chromosomes are spontaneously aborted earlier in pregnancy.
- Tetraploids are always XXXX or XXYY; the absence of XXXY or XYYY sex chromosome constitutions suggests that tetraploidy results from failure of completion of an early cleavage division of the zygote.

Aneuploidy

- Aneuploidy is the most common and clinically significant type of human chromosome disorder, occurring in at least 5% of all clinically recognized pregnancies.

- Most aneuploid patients have either **trisomy** (three instead of the normal pair of a particular chromosome) or, less often, **monosomy** (only one representative of a particular chromosome). Either trisomy or monosomy can have severe phenotypic consequences.

- Trisomy can exist for any part of the genome. The most common type of trisomy in liveborn infants is **trisomy 21** (karyotype 47,XX or XY,+21), the chromosome constitution seen in 95% of patients with Down syndrome (Fig. 5). Other trisomies observed in liveborn include trisomy 18 and trisomy 13. These autosomes (13, 18, and 21) are the three with the lowest number of genes located on them.
- Trisomy for autosomes with a greater number of genes is lethal in most instances. Monosomy for an entire chromosome is almost always lethal; an important exception is monosomy for the X chromosome, as seen in Turner syndrome.

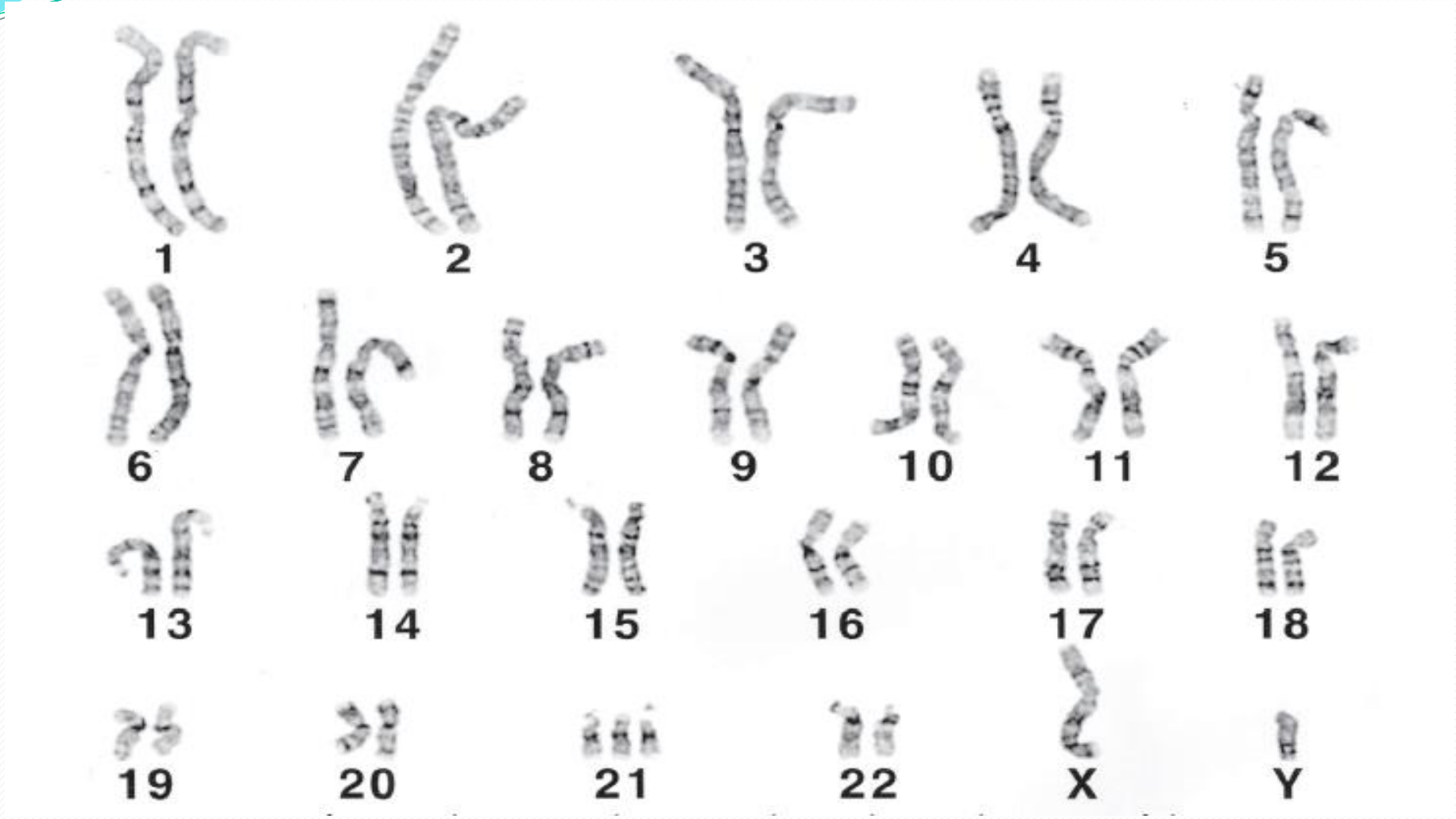

Figure 5. Karyotype from a male patient with Down syndrome, showing three copies of chromosome 21.

Although the causes of aneuploidy are not well understood, it is known that the most common chromosomal mechanism is meiotic **nondisjunction.** This refers to the failure of a pair of chromosomes to disjoin properly during one of the two meiotic divisions, usually during meiosis I. The consequences of nondisjunction during meiosis I and meiosis II are different (Fig. 6). If the error occurs during meiosis I, the gamete with 24 chromosomes contains both the paternal and the maternal members of the pair. If it occurs during meiosis II, the gamete with the extra chromosome contains both copies of either the paternal or the maternal chromosome.

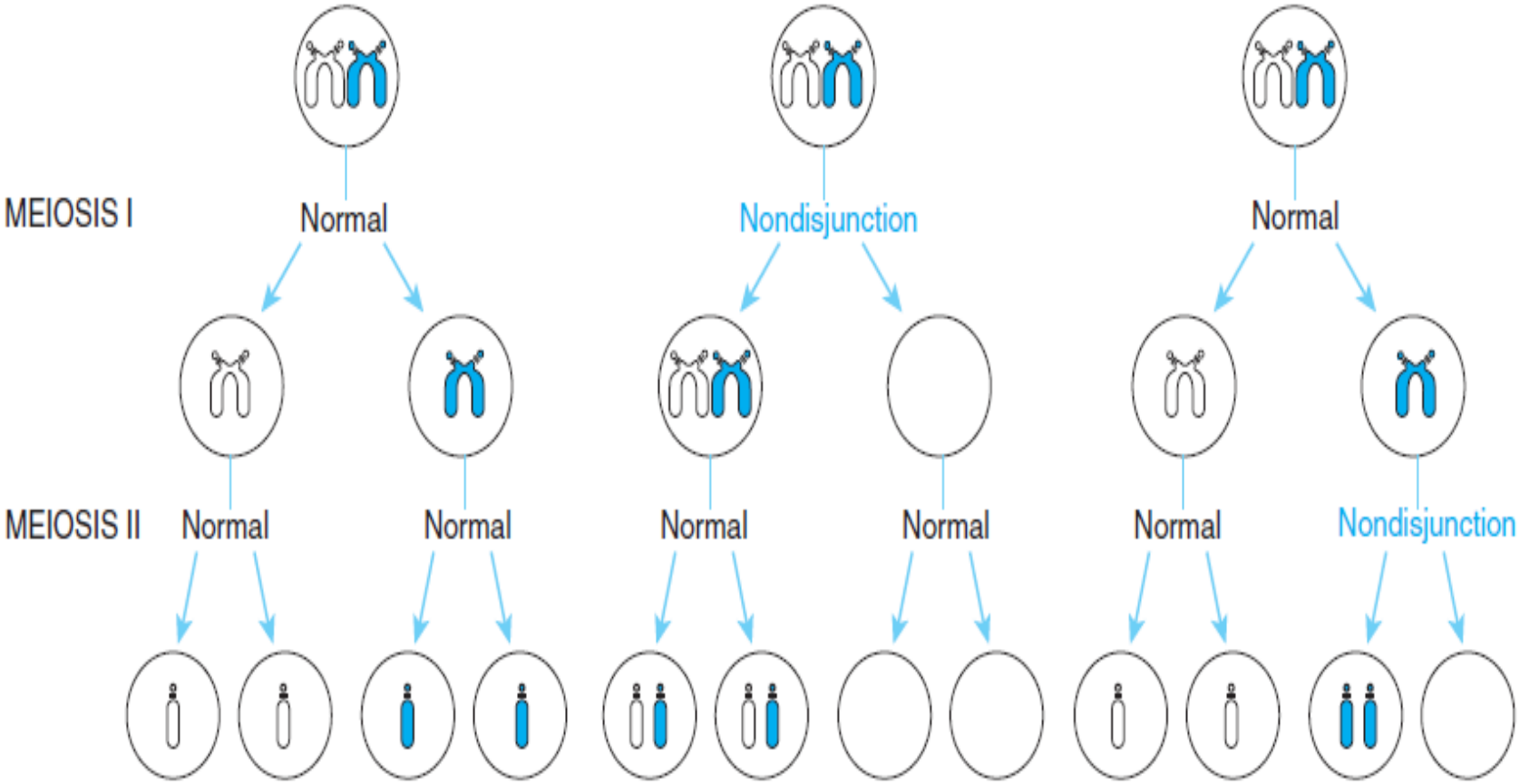

Figure 6. The different consequences of nondisjunction at meiosis I (center) and meiosis II (right), compared with normal disjunction (left). If the error occurs at meiosis I, the gametes either contain a representative of both members of the chromosome 21 pair or lack a chromosome 21 altogether. If nondisjunction occurs at meiosis II, the abnormal gametes contain two copies of one parental chromosome 21 (and no copy of the other) or lack a chromosome 21.

The propensity of a chromosome pair to nondisjoin has been strongly associated with aberrations in the frequency or placement, or both, of recombination events in meiosis I. A chromosome pair with too few (or even no) recombinations, or with recombination too close to the centromere or telomere, may be more susceptible to nondisjunction than a chromosome pair with a more typical number and distribution of recombination events. In addition to classic nondisjunction, in which improper chromosome segregation is the result of the failure of chromosomes either to pair or to recombine properly, or both,

another mechanism underlying aneuploidy involves premature separation of sister chromatids in meiosis I instead of meiosis II. If this happens, the separated chromatids may by chance segregate to the oocyte or to the polar body, leading to an unbalanced gamete.

More complicated forms of multiple aneuploidy have also been reported. A gamete occasionally has an extra representative of more than one chromosome. Nondisjunction can take place at two successive meiotic divisions or by chance in both male and female gametes simultaneously, resulting in zygotes with unusual chromosome numbers, which are extremely rare except for the sex chromosomes

Nondisjunction can also occur in a mitotic division after formation of the zygote. If this happens at an early cleavage division, clinically significant mosaicism may result. In some malignant cell lines and some cell cultures, mitotic nondisjunction can lead to highly abnormal karyotypes.