normally located on different chromosomes (see Chapters 6 and 15).

CHROMOSOME ABNORMALITIES

Abnormalities of chromosomes may be either numerical or structural and may involve one or more autosomes, sex chromosomes, or both simultaneously. The overall incidence of chromosome abnormalities is approximately 1 in 154 live births (Fig. 5-8), and their impact is therefore substantial, both in clinical medicine and for society. By far the most common type of clinically significant chromosome abnormality is **aneuploidy,** an abnormal chromosome number due to an extra or missing chromosome. An aneuploid karyotype is always associated with physical or mental abnormalities or both. **Structural abnormalities** (rearrangements involving one or more chromosomes) are also relatively common (see Fig. 5-8). Depending on whether or not a structural rearrangement leads to an imbalance of genomic content, these may or may not have a phenotypic effect. However, as explained later in this chapter, even balanced chromosome abnormalities may be at an increased risk for abnormal offspring in the subsequent generation.

Chromosome abnormalities are described by a standard set of abbreviations and nomenclature that indicate the nature of the abnormality and (in the case of analyses performed by FISH or microarrays) the technology used. Some of the more common abbreviations and examples of abnormal karyotypes and abnormalities are listed in Table 5-1.

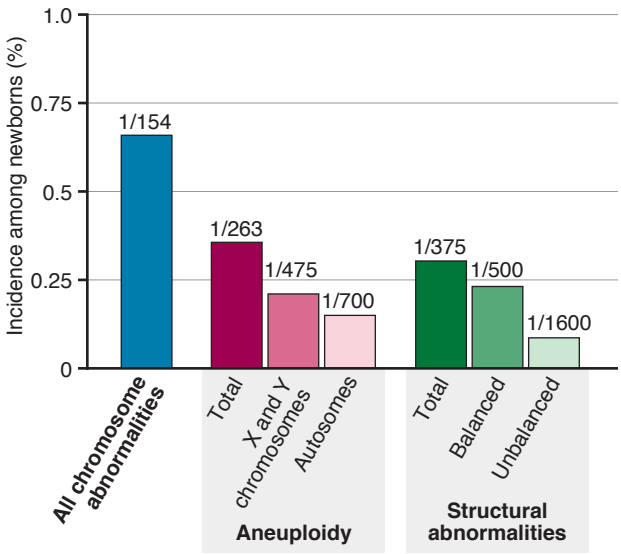

Figure 5-8 Incidence of chromosome abnormalities in newborn surveys, based on chromosome analysis of over 68,000 newborns. *See Sources & Acknowledgments.*

TABLE 5-1 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities, with Representative Examples

Abbreviation	Meaning	Example	Condition
		46,XX	Normal female karyotype
		46,XY	Normal male karyotype
cen	Centromere		
del	Deletion	46,XX,del(5)(q13)	Female with terminal deletion of one chromosome 5 distal to band 5q13
der	Derivative chromosome	der(1)	Translocation chromosome derived from chromosome 1 and containing the centromere of chromosome 1
dic	Dicentric chromosome	dic(X;Y)	Translocation chromosome containing the centromeres of both the X and Y chromosomes
dup	Duplication		
inv	Inversion	inv(3)(p25q21)	Pericentric inversion of chromosome 3
mar	Marker chromosome	47,XX,+mar	Female with an extra, unidentified chromosome
mat	Maternal origin	47,XY,+der(1)mat	Male with an extra der(1) chromosome inherited from his mother
p	Short arm of chromosome		
pat	Paternal origin		
q	Long arm of chromosome		
r	Ring chromosome	46,X,r(X)	Female with ring X chromosome
rob	Robertsonian translocation	rob(14;21)(q10;q10)	Breakage and reunion have occurred at band 14q10 and band 21q10 in the centromeric regions of chromosomes 14 and 21
t	Translocation	46,XX,t(2;8)(q22;p21)	Female with balanced translocation between chromosomes 2 and 8, with breaks in bands 2q22 and 8p21
+	Gain of	47,XX,+21	Female with trisomy 21
–	Loss of	45,XY,–22	Male with monosomy 22
/	Mosaicism	46,XX/47,XX,+21	Female with two populations of cells, one with a normal karyotype and one with trisomy 21

Abbreviations from Shaffer LG, McGowan-Jordan J, Schmid M, editors: *ISCN 2013: an international system for human cytogenetic nomenclature*, Basel, 2013, Karger.

Gene Dosage, Balance and Imbalance

For chromosome and genomic disorders, it is the *quantitative* aspects of gene expression that underlie disease, in contrast to single-gene disorders, in which pathogenesis often reflects *qualitative* aspects of a gene's function. The clinical consequences of any particular chromosome abnormality will depend on the resulting imbalance of parts of the genome, the specific genes contained in or affected by the abnormality, and the likelihood of its transmission to the next generation.

The central concept for thinking about chromosome and genomic disorders is that of **gene dosage** and its balance or imbalance. As we shall see in later chapters, this same concept applies generally to considering some single-gene disorders and their underlying mutational basis (see Chapters 7, 11, and 12); however, it takes on uniform importance for chromosome abnormalities, where we are generally more concerned with the dosage of genes within the relevant chromosomal region than with the actual normal or abnormal sequence of those genes. Here, the sequence of the genes is typically quite unremarkable and would not lead to any clinical condition except for the fact that their dosage is incorrect.

Most genes in the human genome are present in two doses and are expressed from both copies. Some genes, however, are expressed from only a single copy (e.g., imprinted genes and X-linked genes subject to X inactivation; see Chapter 3). Extensive analysis of clinical cases has demonstrated that the relative dosage of these genes is critical for normal development. One or three doses instead of two is generally not conducive to normal function for a gene or set of genes that are typically expressed from two copies. Similarly, abnormalities of genomic imprinting or X inactivation that cause the anomalous expression of two copies of a gene or set of genes instead of one invariably lead to clinical disorders.

Predicting clinical outcomes for chromosomal and genomic disorders can be an enormous challenge for genetic counseling, particularly in the prenatal setting. Many such diagnostic dilemmas will be presented throughout this section and in Chapters 6 and 17, but there are a number of general principles that should be kept in mind as we explore specific types of chromosome abnormality in the sections that follow (see Box).

UNBALANCED KARYOTYPES AND GENOMES IN LIVEBORNS: GENERAL GUIDELINES FOR COUNSELING

- ***Monosomies are more deleterious than trisomies.*** Complete monosomies are generally not viable, except for monosomy for the X chromosome. Complete trisomies are viable for chromosomes 13, 18, 21, X, and Y.
- ***The phenotype in partial aneuploidy depends on a number of factors***, including the size of the unbalanced segment, which regions of the genome are affected and which genes are involved, and whether the imbalance is monosomic or trisomic.
- ***Risk in cases of inversions depends on the location of the inversion with respect to the centromere and on the size of the inverted segment.*** For inversions that do not involve the centromere (paracentric inversions), there is a very low risk for an abnormal phenotype in the next generation. But, for inversions that do involve the centromere (pericentric inversions), the risk for birth defects in offspring may be significant and increases with the size of the inverted segment.
- ***For a mosaic karyotype involving any chromosome abnormality, all bets are off!*** Counseling is particularly challenging because the degree of mosaicism in relevant tissues or relevant stages of development is generally unknown. Thus there is uncertainty about the severity of the phenotype.

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 occasionally observed in clinical material. Both triploidy and tetraploidy have been seen in fetuses. Triploidy is observed in 1% to 3% of recognized conceptions; triploid infants can be liveborn, although they do not survive long. Among the few that survive at least to the end of the first trimester of pregnancy, most result from fertilization of an egg by two sperm (dispermy). Other cases result from failure of one of the meiotic divisions in either sex, resulting in a diploid egg or sperm. The phenotypic manifestation of a triploid karyotype depends on the source of the extra chromosome set; triploids with an extra set of maternal chromosomes are typically aborted spontaneously early in pregnancy, whereas those with an extra set of paternal chromosomes typically have an abnormal degenerative placenta (resulting in a so-called **partial hydatidiform mole**), with a small fetus. Tetraploids are always 92,XXXX or 92,XXYY and likely result 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, but trisomy for a whole chromosome is only occasionally compatible with life. By far the most common type of trisomy in liveborn infants is **trisomy 21,** the chromosome constitution seen in 95% of patients with **Down syndrome** (karyotype 47,XX,+21 or 47,XY,+21) (Fig. 5-9). Other trisomies observed in liveborns include trisomy 18 and trisomy 13. It is notable that these autosomes (13, 18, and 21) are the three with the lowest number of genes located on them (see Fig. 2-7); presumably, 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** (Case 47). These conditions are considered in greater detail in Chapter 6.

Although the causes of aneuploidy are not fully understood, 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 genomic consequences of nondisjunction during meiosis I and meiosis II are different (Fig. 5-10). 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. (Strictly speaking, these statements refer only to the paternal or maternal centromere, because recombination between homologous chromosomes has usually taken place in the preceding meiosis I, resulting in some genetic differences between the chromatids and thus between the corresponding daughter chromosomes; see Chapter 2.)

Proper disjunction of a pair of homologous chromosomes in meiosis I appears relatively straightforward (see Fig. 5-10). In reality, however, it involves a feat of complex engineering that requires precise temporal and spatial control over alignment of the two homologues, their tight connections to each other (synapsis), their interactions with the meiotic spindle, and, finally, their release and subsequent movement to opposite poles and to different daughter cells. 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, which are critical for maintaining proper synapsis. 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 some cases, aneuploidy can also result from 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.

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 (see later section). In some malignant cell lines and some cell cultures, mitotic nondisjunction can lead to highly abnormal karyotypes.

Abnormalities of Chromosome Structure

Structural rearrangements result from chromosome breakage, recombination, or exchange, followed by reconstitution in an abnormal combination. Whereas rearrangements can take place in many ways, they are together less common than aneuploidy; overall, structural abnormalities are present in approximately 1 in 375 newborns (see Fig. 5-8). Like numerical abnormalities, structural rearrangements may be present in all cells of a person or in mosaic form.

Structural rearrangements are classified as **balanced,** if the genome has the normal complement of chromosomal material, or **unbalanced,** if there is additional or missing material. Clearly these designations depend on the resolution of the method(s) used to analyze a particular rearrangement (see Fig. 5-1); some that appear balanced at the level of high-resolution banding, for example, may be unbalanced when studied with chromosomal microarrays or by DNA sequence analysis. Some rearrangements are stable, capable of passing through mitotic and meiotic cell divisions unaltered, whereas others are unstable. Some of the more common types of structural rearrangements observed in human chromosomes are illustrated schematically in Figure 5-11.

Unbalanced Rearrangements

Unbalanced rearrangements are detected in approximately 1 in 1600 live births (see Fig. 5-8); the phenotype is likely to be abnormal because of deletion or duplication of multiple genes, or (in some cases) both. Duplication of part of a chromosome leads to **partial trisomy** for the genes within that segment; deletion leads to **partial monosomy**. As a general concept, any change that disturbs normal gene dosage balance can result in abnormal development; a broad range of phenotypes can result, depending on the nature of the specific genes whose dosage is altered in a particular case.

Large structural rearrangements involving imbalance of at least a few megabases can be detected at the level of routine chromosome banding, including high-resolution karyotyping. Detection of smaller changes, however, generally requires higher resolution analysis, involving FISH or chromosomal microarray analysis.

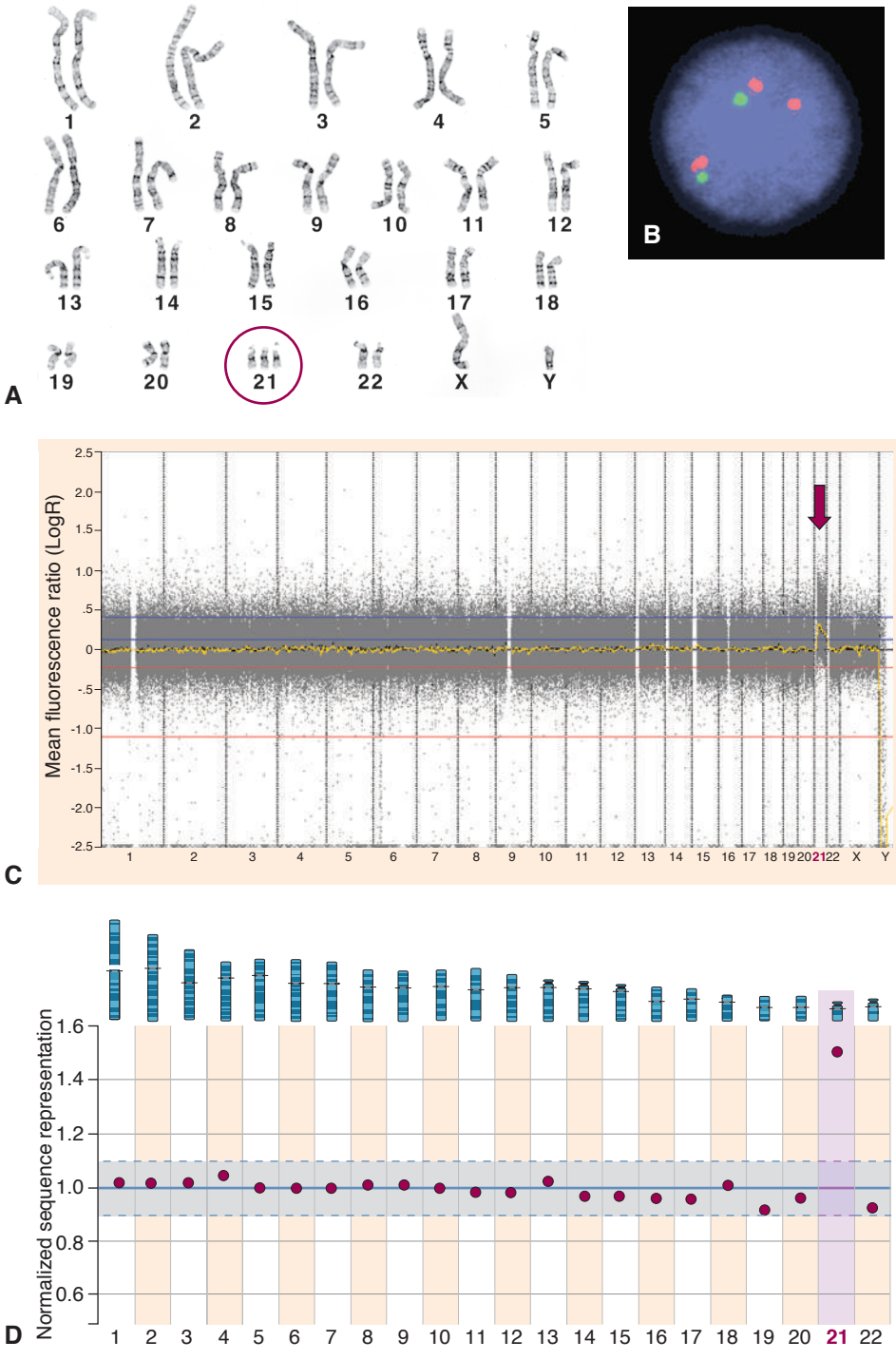

Figure 5-9 **Chromosomal and genomic approaches to the diagnosis of trisomy 21. A,** Karyotype from a male patient with Down syndrome, showing three copies of chromosome 21. **B,** Interphase fluorescence in situ hybridization analysis using locus-specific probes from chromosome 21 (*red*, three spots) and from a control autosome (*green*, two spots). **C,** Detection of trisomy 21 in a female patient by whole-genome chromosomal microarray. Increase in the fluorescence ratio for sequences from chromosome 21 are indicated by the *red arrow*. **D,** Detection of trisomy 21 by whole-genome sequencing and overrepresentation of sequences from chromosome 21. Normalized sequence representation for individual chromosomes (± SD) in chromosomally normal samples is indicated by the *gray shaded region*. A normalized ratio of approximately 1.5 indicates three copies of chromosome 21 sequences instead of two, consistent with trisomy 21. *See Sources & Acknowledgments*.

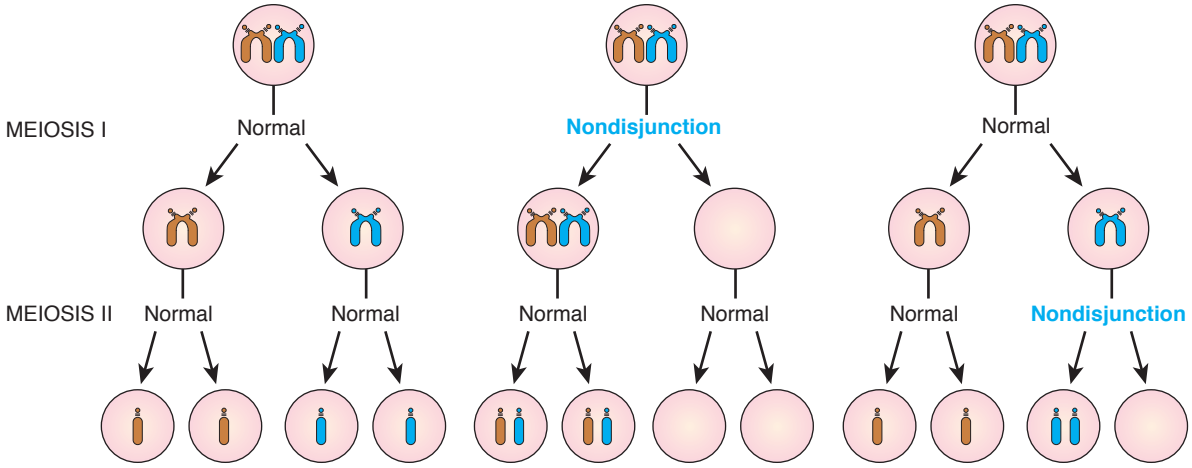

Figure 5-10 The different consequences of nondisjunction at meiosis I (*center*) and meiosis II (*right*), compared with normal disjunction (*left*). If the error occurs at meiosis I, the gametes either contain a representative of both members of the chromosome 21 pair or lack a chromosome 21 altogether. 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.

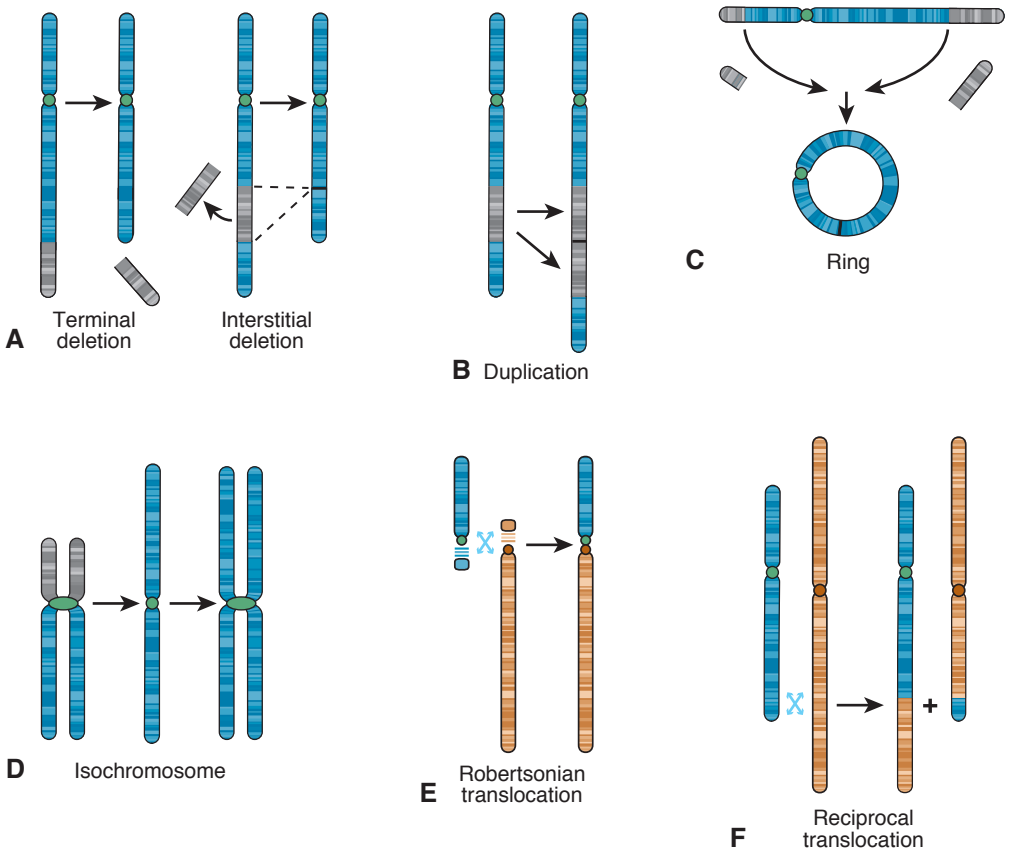

Figure 5-11 **Structural rearrangements of chromosomes, described in the text. A,** Terminal and interstitial deletions, each generating an acentric fragment that is typically lost. **B,** Duplication of a chromosomal segment, leading to partial trisomy. **C,** Ring chromosome with two acentric fragments. **D,** Generation of an isochromosome for the long arm of a chromosome. **E,** Robertsonian translocation between two acrocentric chromosomes, frequently leading to a pseudodicentric chromosome. Robertsonian translocations are nonreciprocal, and the short arms of the acrocentrics are lost. **F,** Translocation between two chromosomes, with reciprocal exchange of the translocated segments.

Deletions and Duplications. Deletions involve loss of a chromosome segment, resulting in chromosome imbalance (see Fig. 5-11). A carrier of a chromosomal deletion (with one normal homologue and one deleted homologue) is monosomic for the genetic information on the corresponding segment of the normal homologue. The clinical consequences generally reflect **haploinsufficiency** (literally, the inability of a single copy of the genetic material to carry out the functions normally performed by two copies), and, where examined, their severity reflects the size of the deleted segment and the number and function of the specific genes that are deleted. Cytogenetically visible autosomal deletions have an incidence of approximately 1 in 7000 live births. Smaller, submicroscopic deletions detected by microarray analysis are much more common, but as mentioned earlier, the clinical significance of many such variants has yet to be fully determined.

A deletion may occur at the end of a chromosome (**terminal**) or along a chromosome arm (**interstitial**). Deletions may originate simply by chromosome breakage and loss of the acentric segment. Numerous deletions have been identified in the course of prenatal diagnosis or in the investigation of dysmorphic patients or patients with intellectual disability; specific examples of such cases will be discussed in Chapter 6.

In general, duplication appears to be less harmful than deletion. However, because duplication in a gamete results in chromosomal imbalance (i.e., partial trisomy), and because the chromosome breaks that generate it may disrupt genes, duplication often leads to some phenotypic abnormality.

Marker and Ring Chromosomes. Very small, unidentified chromosomes, called **marker chromosomes,** are occasionally seen in chromosome preparations, frequently in a mosaic state. They are usually in addition to the normal chromosome complement and are thus also referred to as **supernumerary chromosomes** or **extra structurally abnormal chromosomes**. The prenatal frequency of de novo supernumerary marker chromosomes has been estimated to be approximately 1 in 2500. Because of their small and indistinctive size, higher resolution genome analysis is usually required for precise identification.

Larger marker chromosomes contain genomic material from one or both chromosome arms, creating an imbalance for whatever genes are present. Depending on the origin of the marker chromosome, the risk for a fetal abnormality can range from very low to 100%. For reasons not fully understood, a relatively high proportion of such markers derive from chromosome 15 and from the sex chromosomes.

Many marker chromosomes lack telomeres and are **ring chromosomes** that are formed when a chromosome undergoes two breaks and the broken ends of the chromosome reunite in a ring structure (see Fig. 5-11). Some rings experience difficulties at mitosis, when the two sister chromatids of the ring chromosome become tangled in their attempt to disjoin at anaphase. There may be breakage of the ring followed by fusion, and larger and smaller rings may thus be generated. Because of this mitotic instability, it is not uncommon for ring chromosomes to be found in only a proportion of cells.

Isochromosomes. An isochromosome is a chromosome in which one arm is missing and the other duplicated in a mirror-image fashion (see Fig. 5-11). A person with 46 chromosomes carrying an isochromosome therefore has a single copy of the genetic material of one arm (partial monosomy) and three copies of the genetic material of the other arm (partial trisomy). Although isochromosomes for a number of autosomes have been described, the most common isochromosome involves the long arm of the X chromosome—designated i(X)(q10)—in a proportion of individuals with Turner syndrome (see Chapter 6). Isochromosomes are also frequently seen in karyotypes of both solid tumors and hematological malignant neoplasms (see Chapter 15).

Dicentric Chromosomes. A dicentric chromosome is a rare type of abnormal chromosome in which two chromosome segments, each with a centromere, fuse end to end. Dicentric chromosomes, despite their two centromeres, can be mitotically stable if one of the two centromeres is inactivated epigenetically or if the two centromeres always coordinate their movement to one or the other pole during anaphase. Such chromosomes are formally called **pseudodicentric**. The most common pseudodicentrics involve the sex chromosomes or the acrocentric chromosomes (so-called Robertsonian translocations; see later).

Balanced Rearrangements

Balanced chromosomal rearrangements are found in as many as 1 in 500 individuals (see Fig. 5-8) and do not usually lead to a phenotypic effect because all the genomic material is present, even though it is arranged differently (see Fig. 5-11). As noted earlier, it is important to distinguish here between *truly* balanced rearrangements and those that *appear* balanced cytogenetically but are really unbalanced at the molecular level. Because of the high frequency of copy number polymorphisms around the genome (see Chapter 4), collectively adding up to differences of many megabases between genomes of unrelated individuals, the concept of what is balanced or unbalanced is subject to ongoing investigation and continual refinement.

Even when structural rearrangements are truly balanced, they can pose a threat to the subsequent generation because carriers are likely to produce a significant frequency of unbalanced gametes and therefore have an increased risk for having abnormal offspring with unbalanced karyotypes; depending on the specific

rearrangement, that risk can range from 1% to as high as 20%. There is also a possibility that one of the chromosome breaks will disrupt a gene, leading to mutation. Especially with the use of whole-genome sequencing to examine the nature of apparently balanced rearrangements in patients who present with significant phenotypes, this is an increasingly well-documented cause of disorders in carriers of balanced translocations (see Chapter 6); such translocations can be a useful clue to the identification of the gene responsible for a particular genetic disorder.

Translocations. Translocation involves the exchange of chromosome segments between two chromosomes. There are two main types: reciprocal and nonreciprocal.

Reciprocal Translocations. This type of rearrangement results from breakage or recombination involving nonhomologous chromosomes, with reciprocal exchange of the broken-off or recombined segments (see Fig. 5-11). Usually only two chromosomes are involved, and because the exchange is reciprocal, the total chromosome number is unchanged. Such translocations are usually without phenotypic effect; however, like other balanced structural rearrangements, they are associated with a high risk for unbalanced gametes and abnormal progeny. They come to attention either during prenatal diagnosis or when the parents of a clinically abnormal child with an unbalanced translocation are karyotyped. Balanced translocations are more commonly found in couples who have had two or more spontaneous abortions and in infertile males than in the general population.

The existence of translocations presents challenges for the process of chromosome pairing and homologous recombination during meiosis (see Chapter 2). When the chromosomes of a carrier of a balanced reciprocal translocation pair at meiosis, as shown in Figure 5-12, they must form a **quadrivalent** to ensure proper alignment of homologous sequences (rather than the typical bivalents seen with normal chromosomes). In typical segregation, two of the four chromosomes in the quadrivalent go to each pole at anaphase; however, the chromosomes can segregate from this configuration in several ways, depending on which chromosomes go to

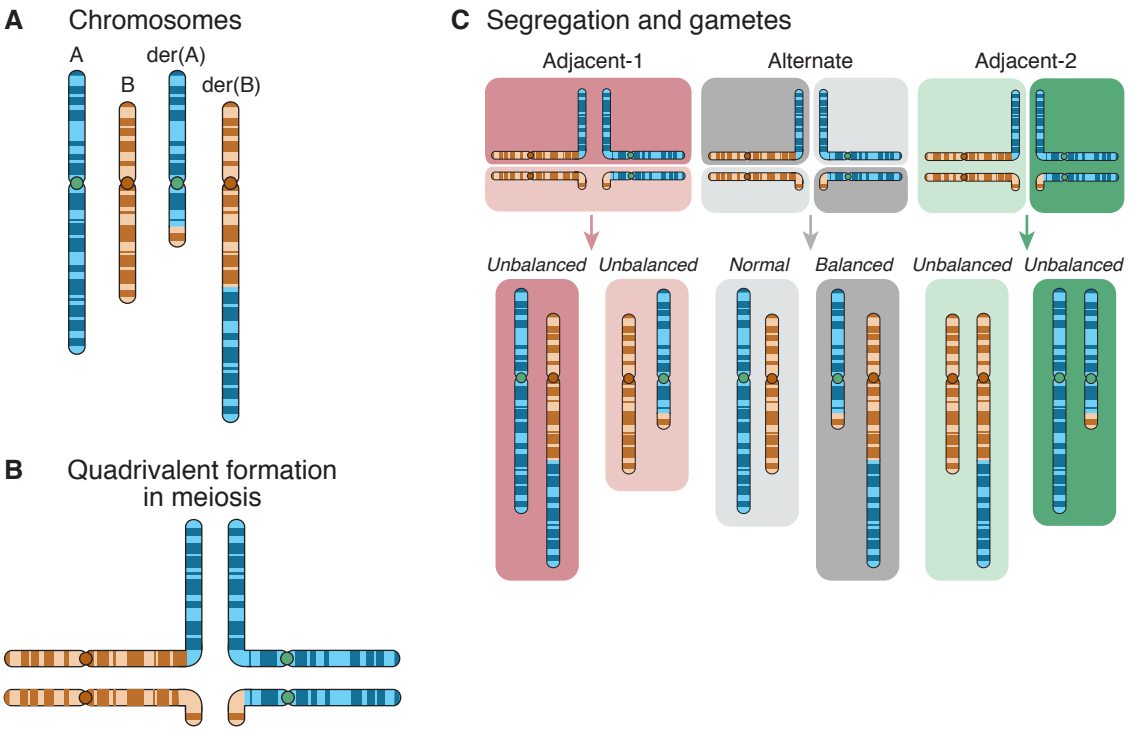

Figure 5-12 **A,** Diagram illustrating a balanced translocation between two chromosomes, involving a reciprocal exchange between the distal long arms of chromosomes A and B. **B,** Formation of a quadrivalent in meiosis is necessary to align the homologous segments of the two derivative chromosomes and their normal homologues. **C,** Patterns of segregation in a carrier of the translocation, leading to either balanced or unbalanced gametes, shown at the bottom. Adjacent-1 segregation (in *red,* top chromosomes to one gamete, bottom chromosomes to the other) leads only to unbalanced gametes. Adjacent-2 segregation (in *green,* left chromosomes to one gamete, right chromosomes to the other) also leads only to unbalanced gametes. Only alternate segregation (in *gray,* upper left/lower right chromosomes to one gamete, lower left/upper right to the other) can lead to balanced gametes.

which pole. **Alternate segregation,** the usual type of meiotic segregation, produces balanced gametes that have either a normal chromosome complement or contain the two reciprocal chromosomes. Other segregation patterns, however, always yield unbalanced gametes (see Fig. 5-12).

Robertsonian Translocations. Robertsonian translocations are the most common type of chromosome rearrangement observed in our species and involve two acrocentric chromosomes that fuse near the centromere region with loss of the short arms (see Fig. 5-11). Such translocations are nonreciprocal, and the resulting karyotype has only 45 chromosomes, including the translocation chromosome, which in effect is made up of the long arms of two acrocentric chromosomes. Because, as noted earlier, the short arms of all five pairs of acrocentric chromosomes consist largely of various classes of satellite DNA, as well as hundreds of copies of ribosomal RNA genes, loss of the short arms of two acrocentric chromosomes is not deleterious; thus, the karyotype is considered to be balanced, despite having only 45 chromosomes. Robertsonian translocations are typically, although not always, pseudodicentric (see Fig. 5-11), reflecting the location of the breakpoint on each acrocentric chromosome.

Although Robertsonian translocations can involve all combinations of the acrocentric chromosomes, two—designated rob(13;14)(q10;q10) and rob(14;21)(q10;q10)—are relatively common. The translocation involving 13q and 14q is found in approximately 1 person in 1300 and is thus by far the single most common chromosome rearrangement in our species. Rare individuals with two copies of the same type of Robertsonian translocation have been described; these phenotypically normal individuals have only 44 chromosomes and lack any normal copies of the involved acrocentrics, replaced by two copies of the translocation.

Although a carrier of a Robertsonian translocation is phenotypically normal, there is a risk for unbalanced gametes and therefore for unbalanced offspring. The risk for unbalanced offspring varies according to the particular Robertsonian translocation and the sex of the carrier parent; carrier females in general have a higher risk for transmitting the translocation to an affected child. The chief clinical importance of this type of translocation is that carriers of a Robertsonian translocation involving chromosome 21 are at risk for producing a child with translocation Down syndrome, as will be explored further in Chapter 6.

Insertions. An insertion is another type of nonreciprocal translocation that occurs when a segment removed from one chromosome is inserted into a different chromosome, either in its usual orientation with respect to the centromere or inverted. Because they require three chromosome breaks, insertions are relatively rare. Abnormal segregation in an insertion carrier can produce offspring with duplication or deletion of the inserted segment, as well as normal offspring and balanced carriers. The average risk for producing an abnormal child can be up to 50%, and prenatal diagnosis is therefore indicated.

Inversions. An inversion occurs when a single chromosome undergoes two breaks and is reconstituted with the segment between the breaks inverted. Inversions are of two types (Fig. 5-13): **paracentric,** in which both breaks occur in one arm (Greek *para*, beside the centromere); and **pericentric,** in which there is a break in each arm (Greek *peri*, around the centromere). Pericentric inversions can be easier to identify cytogenetically when they change the proportion of the chromosome arms as well as the banding pattern.

An inversion does not usually cause an abnormal phenotype in carriers because it is a balanced rearrangement. Its medical significance is for the progeny; a carrier of either type of inversion is at risk for producing abnormal gametes that may lead to unbalanced offspring because, when an inversion is present, a loop needs to form to allow alignment and pairing of homologous segments of the normal and inverted chromosomes in meiosis I (see Fig. 5-13). When recombination occurs within the loop, it can lead to the production of unbalanced gametes: gametes with balanced chromosome complements (either normal or possessing the inversion) and gametes with unbalanced complements are formed, depending on the location of recombination events. When the inversion is paracentric, the unbalanced recombinant chromosomes are acentric or dicentric and typically do not lead to viable offspring (see Fig. 5-13); thus, the risk that a carrier of a paracentric inversion will have a liveborn child with an abnormal karyotype is very low indeed.

A pericentric inversion, on the other hand, can lead to the production of unbalanced gametes with both **duplication** and **deficiency** of chromosome segments (see Fig. 5-13). The duplicated and deficient segments are the segments that are distal to the inversion. Overall, the risk for a carrier of a pericentric inversion leading to a child with an unbalanced karyotype is estimated to be 5% to 10%. Each pericentric inversion, however, is associated with a particular risk, typically reflecting the size and content of the duplicated and deficient segments.

Mosaicism for Chromosome Abnormalities

When a person has a chromosome abnormality, whether numerical or structural, the abnormality is usually present in all of his or her cells. Sometimes, however, two or more different chromosome complements are present in an individual; this situation is called **mosaicism**. Mosaicism is typically detected by conventional karyotyping but can also be suspected on the

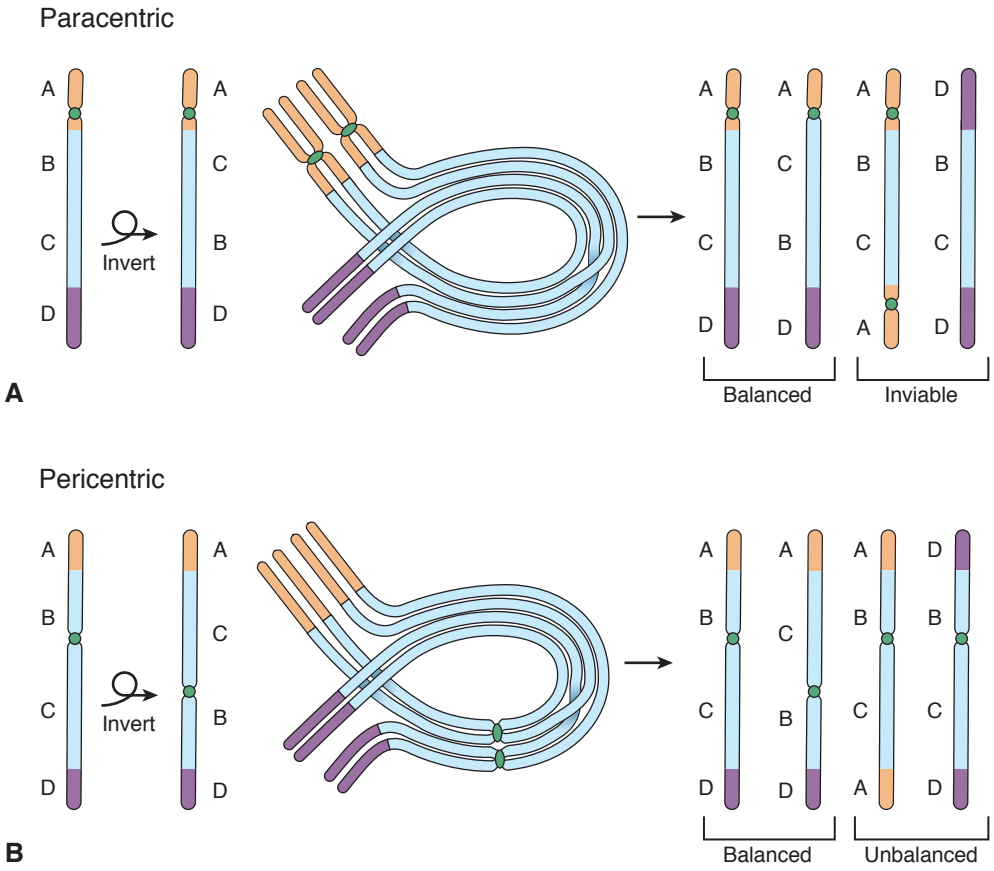

Figure 5-13 **Crossing over within inversion loops formed at meiosis I in carriers of a chromosome with segment B-C inverted (order A-C-B-D, instead of the normal order A-B-C-D). A,** Paracentric inversion. Gametes formed after the second meiosis usually contain either a normal (A-B-C-D) or a balanced (A-C-B-D) copy of the chromosome because the acentric and dicentric products of the crossover are inviable. **B,** Pericentric inversion. Gametes formed after the second meiosis may be balanced (normal or inverted) or unbalanced. Unbalanced gametes contain a copy of the chromosome with a duplication or a deficiency of the material flanking the inverted segment (A-B-C-A or D-B-C-D).

basis of interphase FISH analysis or chromosomal microarrays.

A common cause of mosaicism is nondisjunction in an early postzygotic mitotic division. For example, a zygote with an additional chromosome 21 might lose the extra chromosome in a mitotic division and continue to develop as a 46/47,+21 mosaic. The effects of mosaicism on development vary with the timing of the nondisjunction event, the nature of the chromosome abnormality, the proportions of the different chromosome complements present, and the tissues affected. It is often believed that individuals who are mosaic for a given trisomy, such as mosaic Down syndrome or mosaic Turner syndrome, are less severely affected than nonmosaic individuals.

When detected in lymphocytes, in cultured cell lines or in prenatal samples, it can be difficult to assess the significance of mosaicism, especially if it is identified prenatally. The proportions of the different chromosome complements seen in the tissue being analyzed (e.g., cultured amniocytes or lymphocytes) may not necessarily reflect the proportions present in other tissues or in the embryo during its early developmental stages. Mosaicism can also arise in cells in culture *after* they were taken from the individual; thus, cytogeneticists attempt to differentiate between **true mosaicism,** present in the individual, and **pseudomosaicism,** which has occurred in the laboratory. The distinction between these types is not always easy or certain and can lead to major interpretive difficulties in prenatal diagnosis (see Box earlier and Chapter 17).

Incidence of Chromosome Anomalies

The incidence of different types of chromosomal aberration has been measured in a number of large population surveys and was summarized earlier in Figure 5-8. The major numerical disorders of chromosomes observed in liveborns are three autosomal trisomies (trisomy 21, trisomy 18, and trisomy 13) and four types of sex chromosomal aneuploidy: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XYY,

TABLE 5-2 Outcome of 10,000 Pregnancies*

Outcome	Pregnancies	Spontaneous Abortions (%)	Live Births
Total	10,000	1500 (15)	8500
Normal chromosomes	9,200	750 (8)	8450
Abnormal chromosomes	800	750 (94)	50
Specific Abnormalities			
Triploid or tetraploid	170	170 (100)	0
45,X	140	139 (99)	1
Trisomy 16	112	112 (100)	0
Trisomy 18	20	19 (95)	1
Trisomy 21	45	35 (78)	10
Trisomy, other	209	208 (99.5)	1
47,XXY, 47,XXX, 47,XYY	19	4 (21)	15
Unbalanced rearrangements	27	23 (85)	4
Balanced rearrangements	19	3 (16)	16
Other	39	37 (95)	2

*These estimates are based on observed frequencies of chromosome abnormalities in spontaneous abortuses and in liveborn infants. It is likely that the frequency of chromosome abnormalities in all conceptuses is much higher than this, because many spontaneously abort before they are recognized clinically.

and 47,XXX (see Chapter 6). Triploidy and tetraploidy account for only a small percentage of cases, typically in spontaneous abortions. The classification and incidence of chromosomal defects measured in these surveys can be used to consider the fate of 10,000 conceptuses, as presented in Table 5-2.

Live Births

As mentioned earlier, the overall incidence of chromosome abnormalities in newborns has been found to be approximately 1 in 154 births (0.65%) (see Fig. 5-8). Most of the autosomal abnormalities can be diagnosed at birth, but most sex chromosome abnormalities, with the exception of Turner syndrome, are not recognized clinically until puberty (see Chapter 6). Unbalanced rearrangements are likely to come to clinical attention because of abnormal appearance and delayed physical and mental development in the chromosomally abnormal individual. In contrast, balanced rearrangements are rarely identified clinically unless a carrier of a rearrangement gives birth to a child with an unbalanced chromosome complement and family studies are initiated.

Spontaneous Abortions

The overall frequency of chromosome abnormalities in spontaneous abortions is at least 40% to 50%, and the kinds of abnormalities differ in a number of ways from those seen in liveborns. Somewhat surprisingly, the single most common abnormality in abortuses is 45,X (the same abnormality found in Turner syndrome), which accounts for nearly 20% of chromosomally abnormal spontaneous abortuses but less than 1% of chromosomally abnormal live births (see Table 5-2). Another difference is the distribution of kinds of trisomy; for example, trisomy 16 is not seen at all in live births but accounts for approximately one third of trisomies in abortuses.

CHROMOSOME AND GENOME ANALYSIS IN CANCER

We have focused in this chapter on constitutional chromosome abnormalities that are seen in most or all of the cells in the body and derive from chromosome or regional mutations that have been transmitted from a parent (either inherited or occurring de novo in the germline of a parent) or that have occurred in the zygote in early mitotic divisions.

However, such mutations also occur in somatic cells throughout life and are a hallmark of cancer, both in hematological neoplasias (e.g., leukemias and lymphomas) and in the context of solid tumor progression. An important area in cancer research is the delineation of chromosomal and genomic changes in specific forms of cancer and the relation of the breakpoints of the various structural rearrangements to the process of oncogenesis. The chromosome and genomic changes seen in cancer cells are numerous and diverse. The association of cytogenetic and genome analysis with tumor type and with the effectiveness of therapy is already an important part of the management of patients with cancer; these are discussed further in Chapter 15.

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