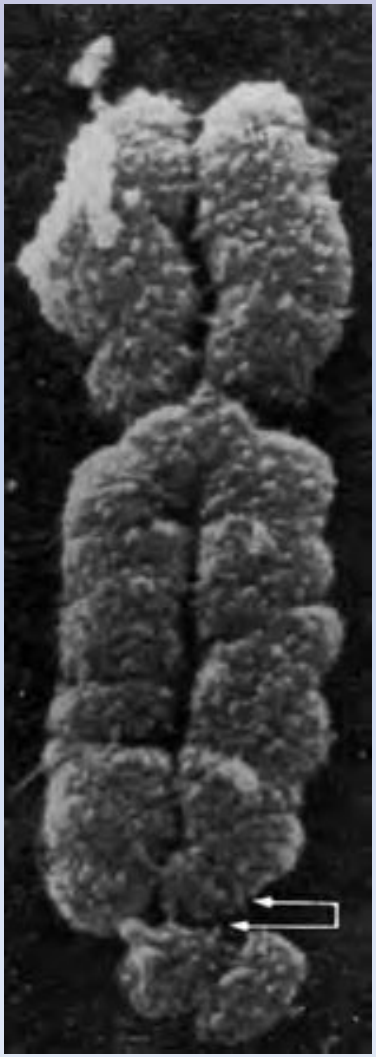
Fragile Sites



Fragile Sites

- Chromosomes of cells sometimes develop constrictions or gaps at particular locations called fragile because they are prone to breakage under certain conditions. More than 100 fragile sites have been identified on human chromosomes
- Fragile sites fall into two groups.
- ***Common fragile sites***
- are present in all humans and are a normal feature of chromosomes. Common fragile sites are often the location of chromosome breakage and rearrangements in cancer cells, leading to chromosome deletions, translocations, and other chromosome rearrangements
- ***Rare fragile sites***
- *are found* in few people and are inherited as a Mendelian trait. Rare fragile sites are often associated with genetic disorders, such as mental retardation. Most of them consist of expanding nucleotide repeats, in which the number of repeats of a set of nucleotides is increased

- One of the most intensively studied rare fragile sites is located on the human X chromosome. This site is associated with mental retardation and is known as the **fragile-X syndrome.**
- Exhibiting X-linked inheritance and arising with a frequency of about 1 in 1250 male births, fragile-X syndrome has been shown to result from an increase in the number of repeats of a CGG trinucleotide.
- Molecular studies of fragile sites have shown that many of these sites are more than 100,000 bp in length and include one or more genes.
- Fragile sites are often late in being replicated. At these places, the enzymes that replicate DNA may stall while unwinding of the DNA continues, leading to long stretches of DNA that are unwound and vulnerable to breakage.

Copy-Number Variations

- Chromosome rearrangements have traditionally been detected by examination of the chromosomes with a microscope.
- Changes in the overall size of a chromosome,
- Alteration of banding patterns revealed by chromosome staining,
- OR the behavior of chromosomes in meiosis
- Microscopy, however, can detect only large chromosome rearrangements, typically those that are at least 5 million bp in length.

- With the completion of the Human Genome Project detailed information about DNA sequences found on individual chromosomes has become available.
- Using this information, geneticists can now examine the number of copies of specific DNA sequences present in a cell and detect duplications, deletions, and other chromosome rearrangements that cannot be observed with microscopy alone.
- Copy-number variations include duplications and deletions that range in size from thousands of base pairs to several million base pairs. Many of these variants encompass at least one gene and may encompass several genes.

- Submicroscopic chromosome duplications and deletions are quite common:
- research suggests that each person may possess as many as 1000 copy-number variations. Many of them probably have no observable phenotypic effects, but some copy-number variations have now been implicated in causing a number of diseases and disorders.
- Janine Wagenstaller and her colleagues studied copy-number variation in 67 children with unexplained mental retardation and found that 11 (16%) of them had duplications and deletions. Copy-number variations have also been associated with osteoporosis, autism, schizophrenia, and a number of other diseases and disorders.

Nature and consequences of altered chromosomal Number

Variation In Chromosome Number

Aneuploidy Is an Increase or Decrease in the Number of Individual Chromosomes

Polyploidy is a change in the number of chromosome sets

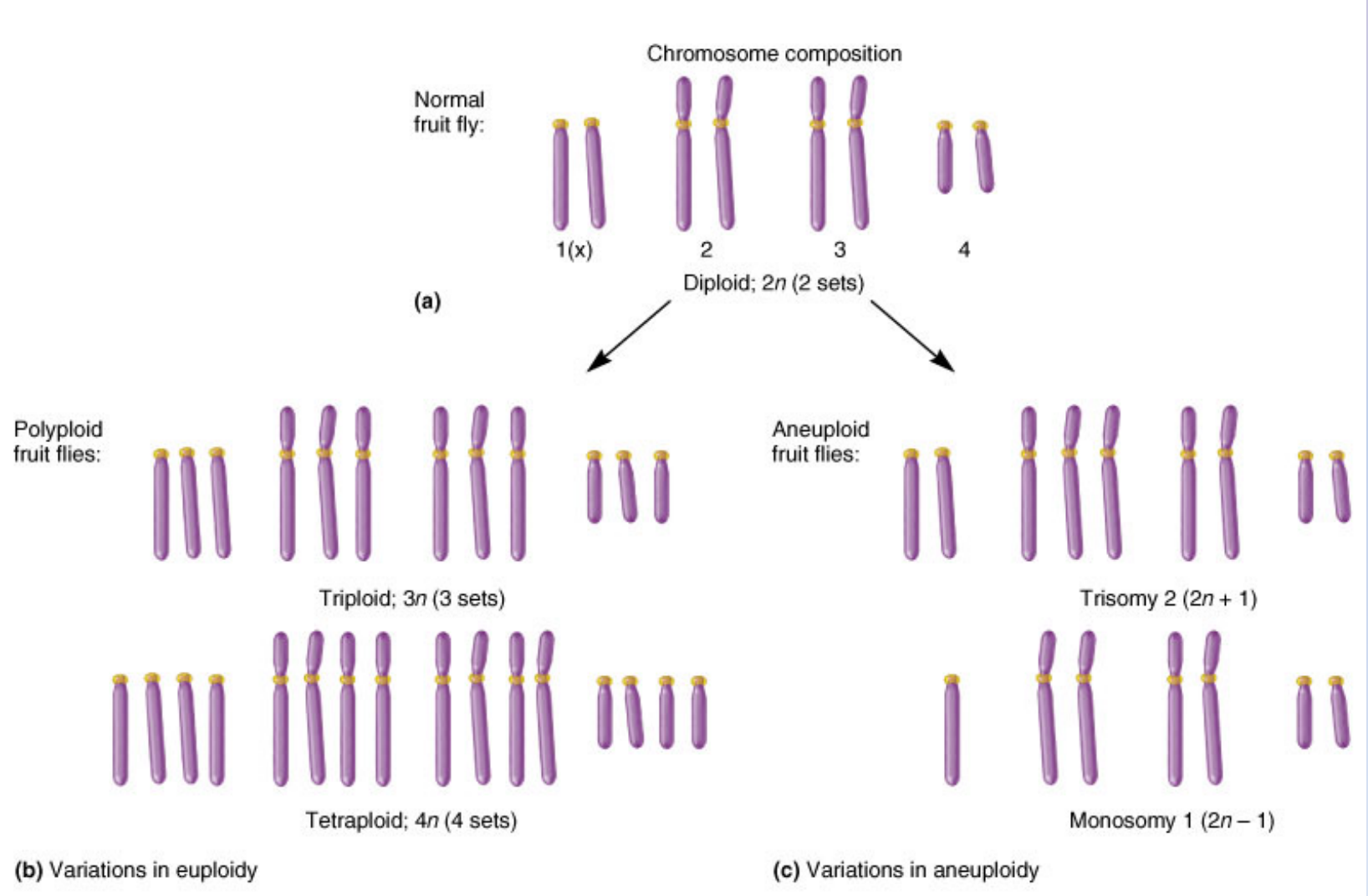
Euploidy

- Normal variations of the number of complete sets of chromosomes
- Haploid, Diploid, Triploid, Tetraploid, etc…

Aneuploidy

- Variation in the number of particular chromosomes within a set
- Monosomy, trisomy, polysomy

Variation In Chromosome Number



- **Aneuploidy** can arise in several ways.
- First, a chromosome may be lost in the course of mitosis or meiosis if, for example, its centromere is deleted.
- Loss of the centromere prevents the spindle fibers from attaching; so the chromosome fails to move to the spindle pole and does not become incorporated into a nucleus after cell division.
- Second, the small chromosome generated by a Robertsonian translocation may be lost in mitosis or meiosis.
- Third, aneuploids may arise through nondisjunction, the failure of homologous chromosomes or sister chromatids to separate in meiosis or mitosis

Types of Aneuploidy

- **Nullisomy**
- is the loss of both members of a homologous pair of chromosomes. It is represented as $2n - 2$, *where n refers to the haploid number of chromosomes. Thus,* among humans, who normally possess $2n = 46$ chromosomes, a nullisomic zygote has 44 chromosomes

- **Monosomy**
- is the loss of a single chromosome, represented as 2*n – 1.*
- *A human monosomic zygote has* 45 chromosomes.
- **Trisomy**
- is the gain of a single chromosome, represented as 2*n + 1. A human trisomic zygote has 47 chromosomes.* The gain of a chromosome means that there are three homologous copies of one chromosome. Most cases of Down syndrome, result from trisomy of chromosome 21.
- **Tetrasomy**
- Gain of two homologous chromosomes, represented as 2*n + 2.*
- *A human* tetrasomic zygote has 48 chromosomes.
- Tetrasomy is not the gain of *any two extra chromosomes, but rather the* gain of two homologous chromosomes; so there will be four homologous copies of a particular chromosome.

Effects of Aneuploidy

- Aneuploidy usually alters the phenotype drastically. In most animals and many plants, aneuploid mutations are lethal. Because aneuploidy affects the number of gene copies but not their nucleotide sequences, the effects of aneuploidy are most likely due to abnormal gene dosage

- A major exception to the relation between gene number and protein dosage pertains to genes on the mammalian X chromosome.
- In mammals, X-chromosome inactivation ensures that males (who have a single X chromosome) and females (who have two X chromosomes) receive the same functional dosage for X-linked genes.
- Extra X chromosomes in mammals are inactivated; so the aneuploidy of the sex chromosomes would be less detrimental in these animals
- Indeed, it is the case for mice and humans, for whom aneuploids of the sex chromosomes are the most common form of aneuploidy seen in living organisms. Y-chromosome aneuploids are probably common because there is so little information in the Y-chromosome.

Aneuploidy in Humans

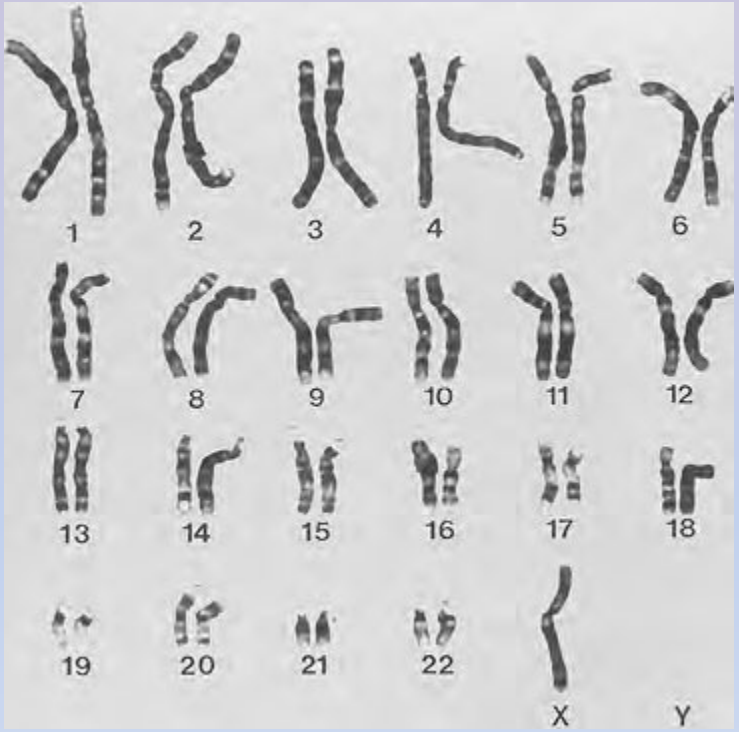
- An incredibly high percentage chromosome abnormalities.
- The rate of chromosome abnormality in humans is higher than in other organisms that have been studied; in mice, for example, aneuploidy is found in no more than 2% of fertilized eggs

- Findings from studies of women who are attempting pregnancy suggest that more than 30% of all conceptions spontaneously abort (miscarry), usually so early in development that the mother is not even aware of her pregnancy.
- Chromosome defects are present in at least 50% of spontaneously aborted human fetuses, with aneuploidy accounting for most of them.
- .Aneuploidy in humans usually produces such serious developmental problems that spontaneous abortion results. Only about 2% of all fetuses with a chromosome defect survive to birth

Sex-chromosome aneuploids

- The most common In living humans has to do with the sex chromosomes.
- As is true of all mammals, aneuploidy of the human sex chromosomes is better tolerated than aneuploidy of autosomal chromosomes.
- Both Turner syndrome and Klinefelter syndrome result from aneuploidy of the sex chromosomes.

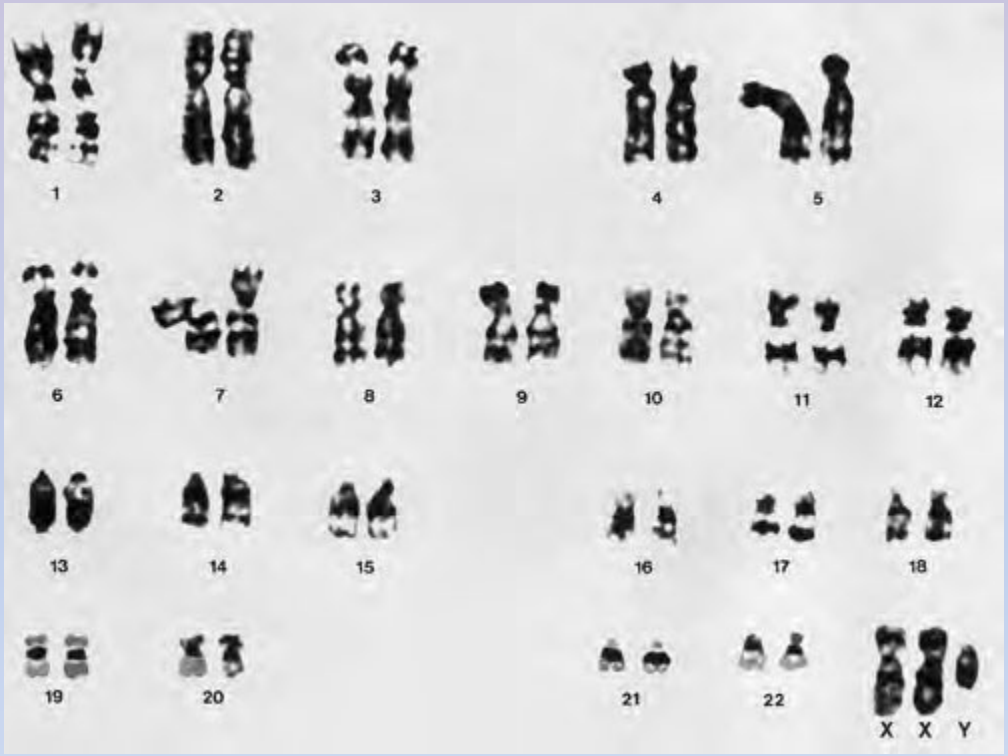
Aneuploidies of the Sex Chromosomes



Persons with Turner syndrome have a single X chromosome in their cells.

45, X

Turner syndrome



Persons with Klinefelter syndrome have a Y chromosome and two or more X chromosomes in their cells

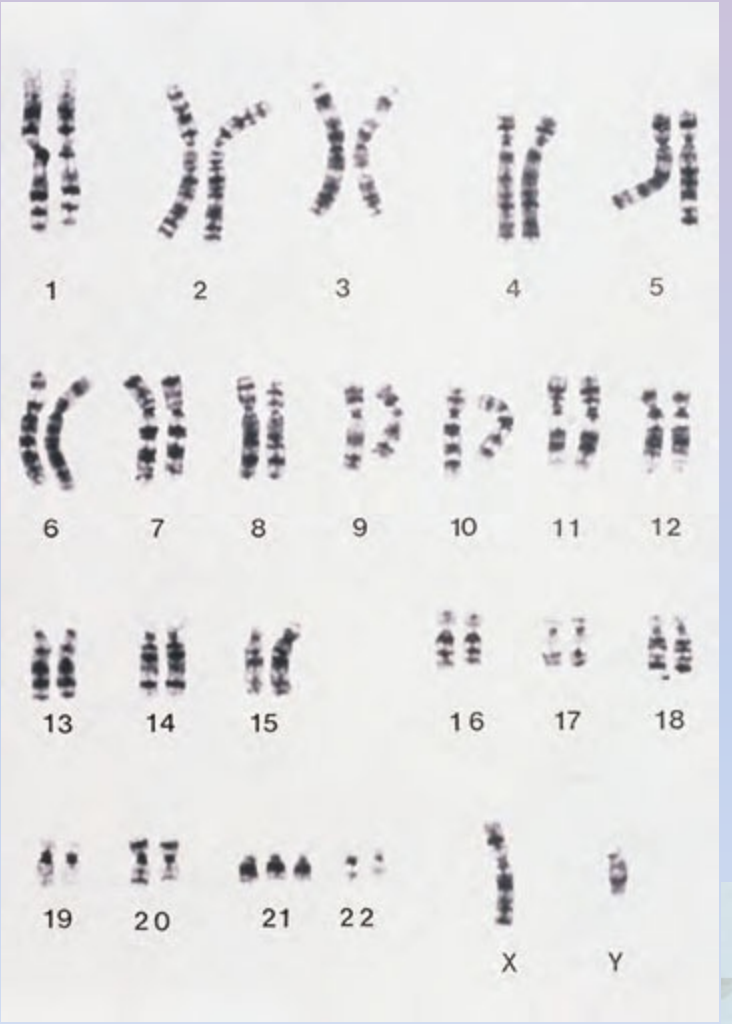
47, XXY

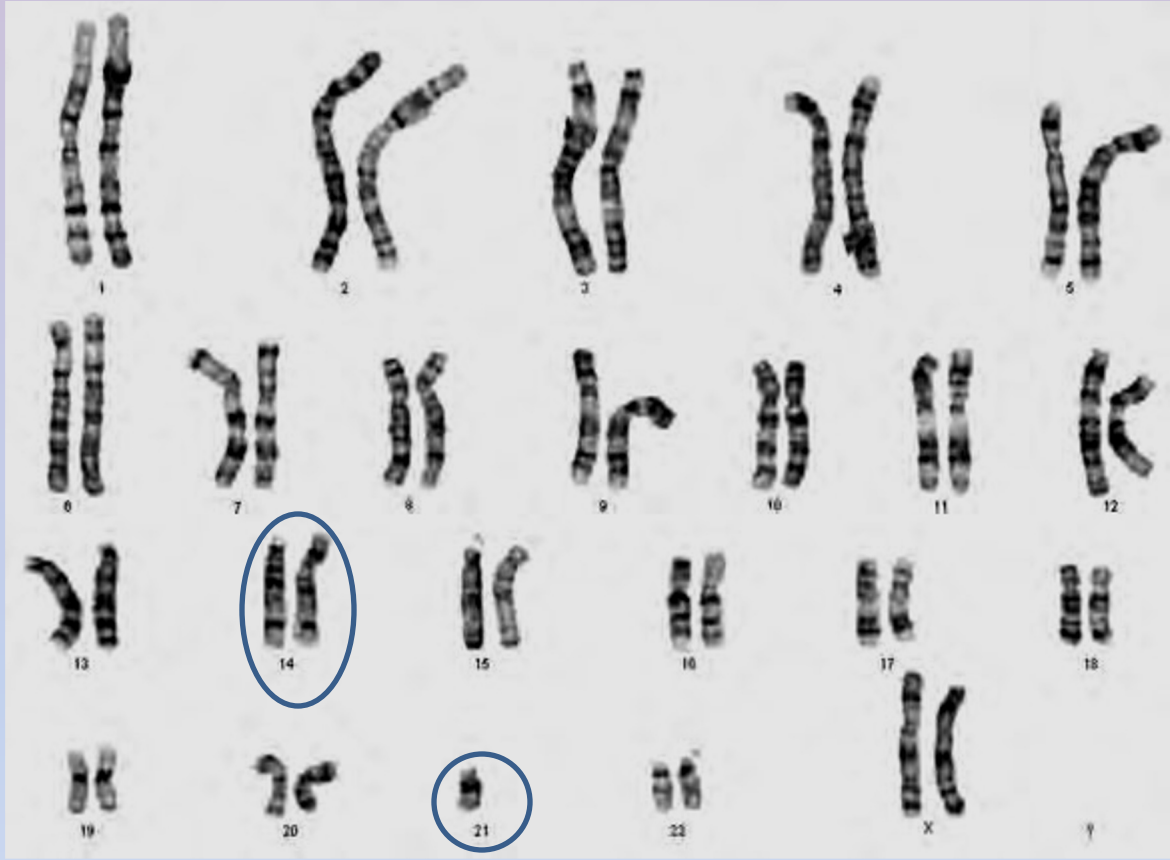
Klinefelter syndrome

Autosomal aneuploids

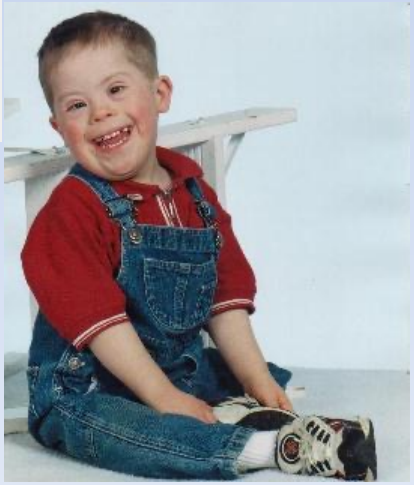
- in live births are less common than sex-chromosome aneuploids in humans, probably because there is no mechanism of dosage compensation for autosomal chromosomes.
- Most autosomal aneuploids are spontaneously aborted, with the exception of aneuploids of some of the small autosomes such as chromosome 21. Because these chromosomes are small and carry fewer genes, the presence of extra copies is less detrimental than it is for larger chromosomes

- The most common autosomal aneuploidy in humans is **trisomy 21,** also called Down syndrome
- Approximately 92% of those who have Down syndrome have three full copies of chromosome 21
- Primary Down syndrome usually arises from spontaneous nondisjunction in egg formation: about 75% of the nondisjunction events that cause Down syndrome are maternal in origin, most arising in meiosis I.
- Most children with Down syndrome are born to normal parents, and the failure of the chromosomes to divide has little hereditary tendency.
- About 4% of people with Down syndrome are not trisomic for a complete chromosome 21. Instead, they have 46 chromosomes, but an extra copy of part of chromosome 21 is attached to another chromosome through a translocation. This condition is termed **familial Down syndrome** because it has a tendency to run in families





Primary Down syndrome is caused by the presence of three copies of chromosome 21

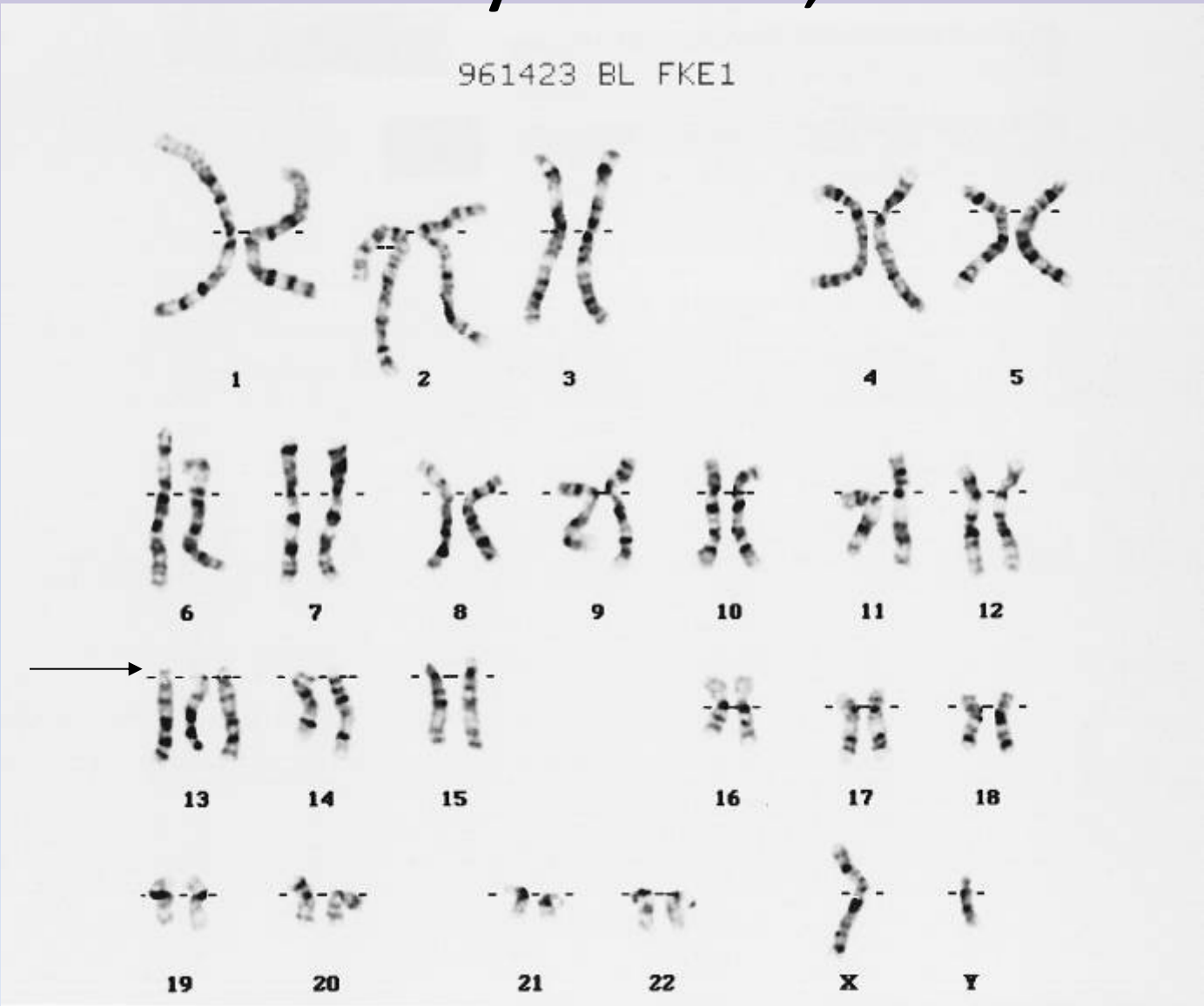


The translocation of chromosome 21 onto another chromosome results in familial Down syndrome

Other human Trisomies

- **Trisomy 18**
- also known as **Edward syndrome,** arises with a frequency of approximately 1 in 8000 live births.
- Babies with Edward syndrome are severely retarded and have low-set ears, a short neck, deformed feet, clenched fingers, heart problems, and other disabilities
- **Trisomy 13 Patau syndrome**
- has a frequency of about 1 in 15,000 live births and produces
- Characteristics of this condition include severe mental retardation, a small head, sloping forehead, small eyes, cleft lip and palate, extra fingers and toes, and numerous other problems.
- Rarer still is **trisomy 8,** which arises with a frequency ranging from about 1 in 25,000 to 1 in 50,000 live births. This aneuploid is characterized by mental retardation, contracted fingers and toes, low-set malformed ears, and a prominent forehead. Many who have this condition have normal life expectancy.

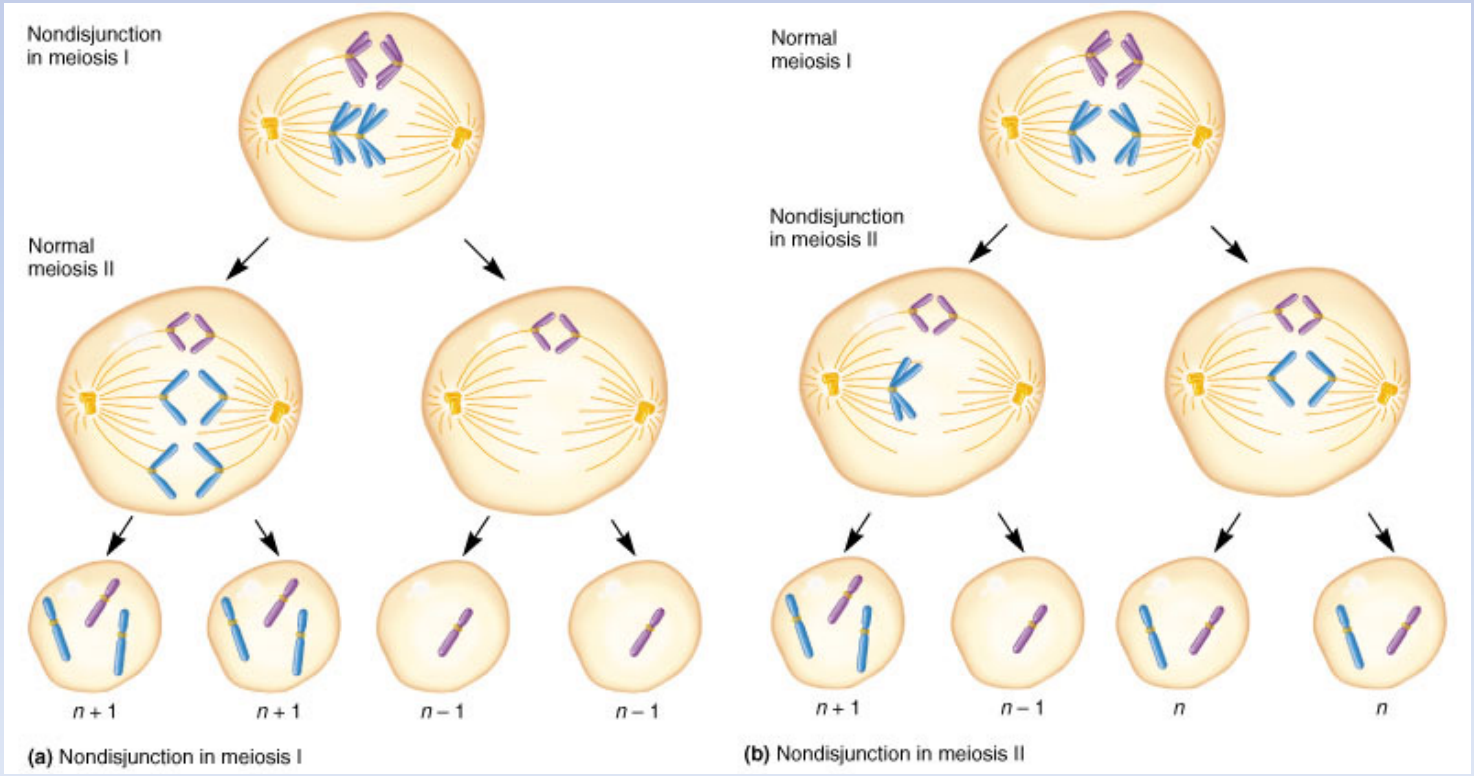
Trisomy 13: 47, 13+

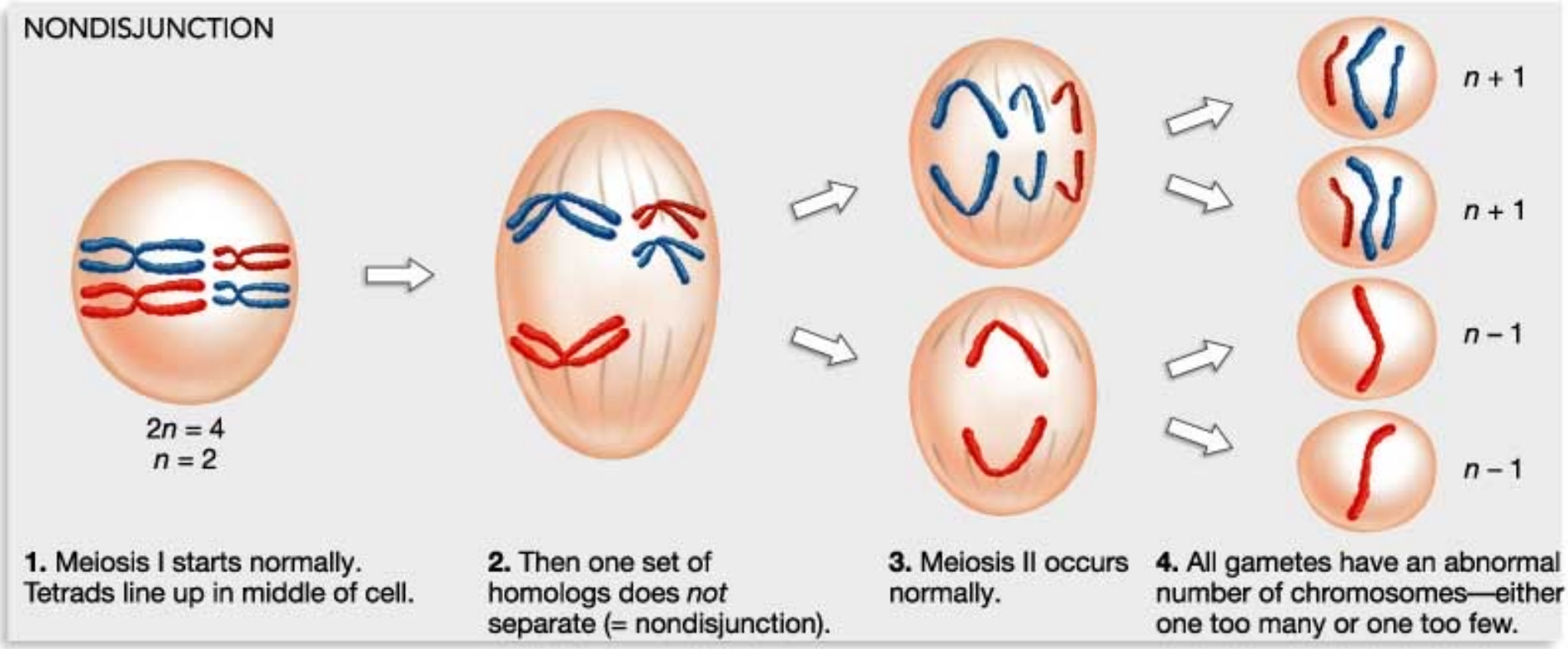


Nondisjunction

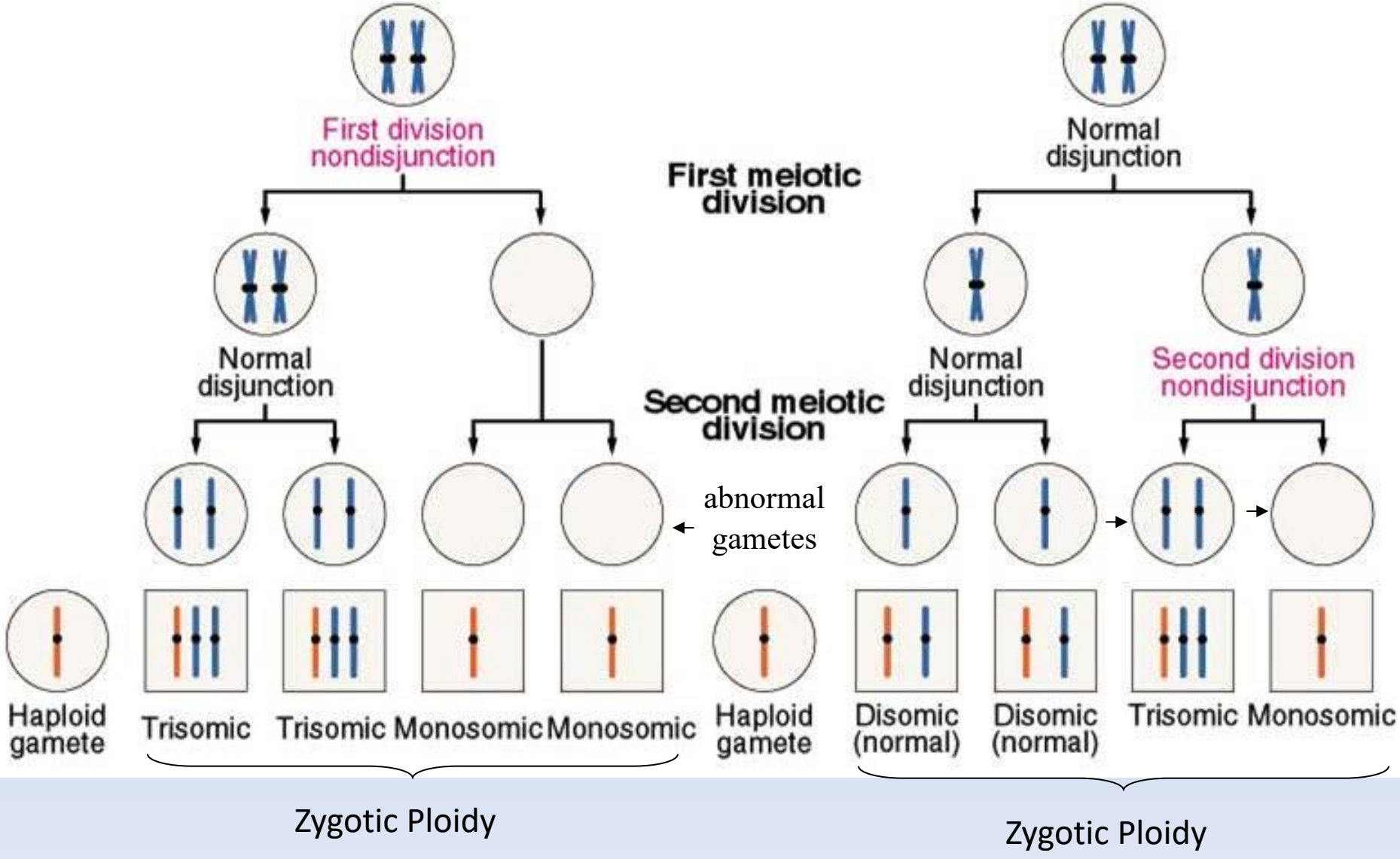
- **Failure** of chromosomes **to separate** during meiosis
- Causes gamete to have **too many** **or** **too few** **chromosomes**
- **Disorders:**
  - **Down Syndrome – three 21st chromosomes**
  - **Turner Syndrome – single X chromosome**
  - **Klinefelter's Syndrome – XXY chromosomes**

- Meiotic nondisjunction
  - Can occur during meiosis I
    - All resulting gametes are aberrant (aneuploid)
  - Can occur during meiosis II
    - Half of the resulting gametes are aberrant (aneuploid)




NONDISJUNCTION
2n = 4
n = 2
n + 1
n + 1
n – 1
n – 1
1. Meiosis I starts normally. Tetrads line up in middle of cell.
2. Then one set of homologs does not separate (= nondisjunction).
3. Meiosis II occurs normally.
4. All gametes have an abnormal number of chromosomes—either one too many or one too few.

Meiotic Nondisjunction Generates Aneuploidies



Anueploidy and cancer

- Many tumor cells have extra or missing chromosomes or both; some types of tumors are consistently associated with specific chromosome mutations, including aneuploidy and chromosome rearrangements.

TABLE 8.1
Aneuploid Conditions in Humans

Condition	Frequency	Syndrome	Characteristics
Autosomal			
Trisomy 21	1/800	Down	Mental retardation, abnormal pattern of palm creases, slanted eyes, flattened face, short stature
Trisomy 18	1/6,000	Edward	Mental and physical retardation, facial abnormalities, extreme muscle tone, early death
Trisomy 13	1/15,000	Patau	Mental and physical retardation, wide variety of defects in organs, large triangular nose, early death
Sex Chromosomal			
XXY	1/1,000 (males)	Klinefelter	Sexual immaturity (no sperm), breast swelling
XYY	1/1,000 (males)	Jacobs	Tall
XXX	1/1,500 (females)	Triple X	Tall and thin, menstrual irregularity
X0	1/5,000 (females)	Turner	Short stature, webbed neck, sexually undeveloped

Polyploidy

- Polyploidy Is the Presence of More Than Two Sets of Chromosomes.
- Most eukaryotic organisms are diploid (2*n) for most of their* life cycles, possessing two sets of chromosomes.
- Occasionally, whole sets of chromosomes fail to separate in meiosis or mitosis, leading to polyploidy, the presence of more than two genomic sets of chromosomes

- Polyploids include
- *triploids (3n),*
- *tetraploids (4n),*
- *pentaploids (5n),*
- *and even higher* numbers of chromosome sets.

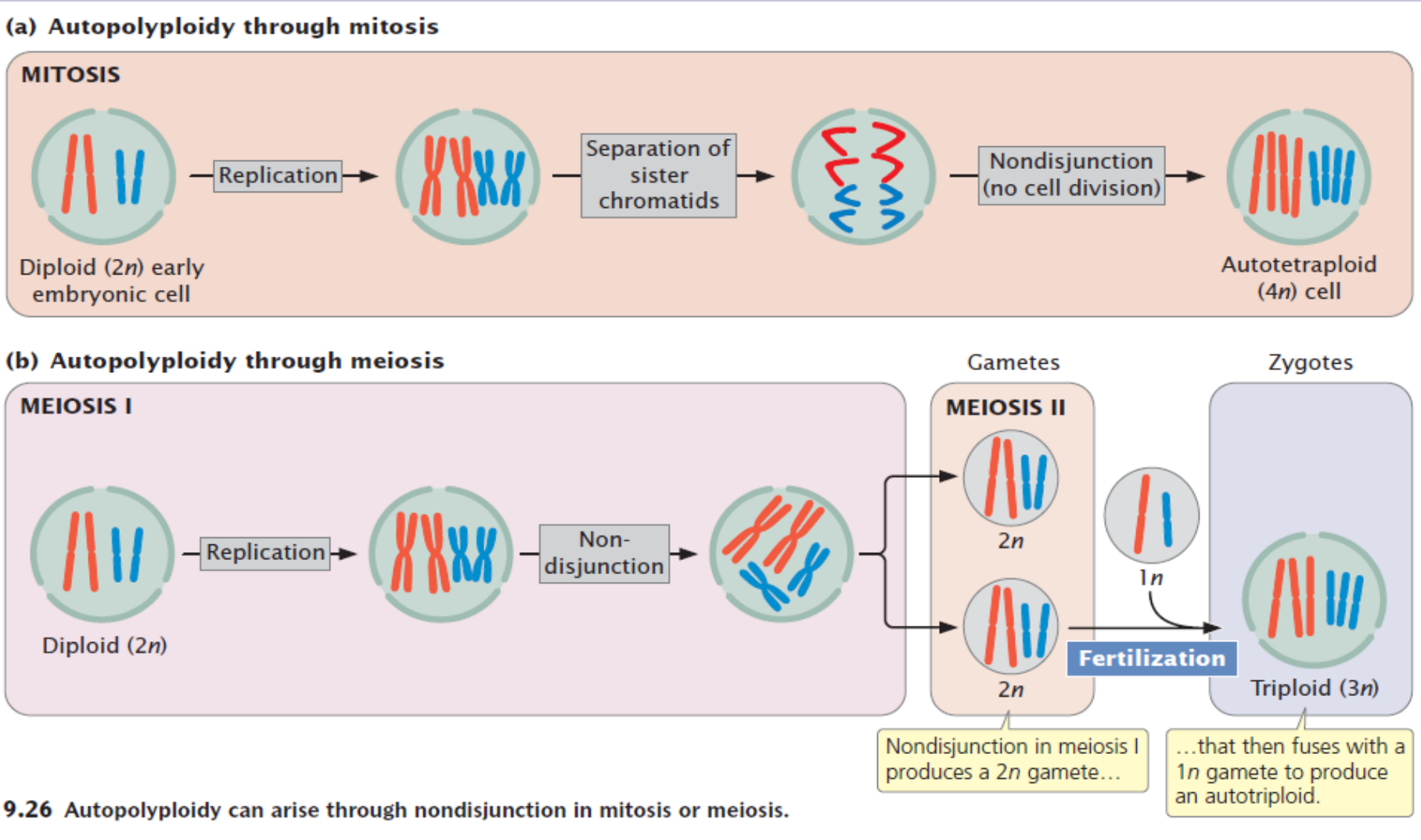
- Polyploidy is common in plants and is a major mechanism by which new plant species have evolved.
- Approximately 40% of all flowering-plant species and from 70% to 80% of grasses are polyploids. They include a number of agriculturally important plants, such as wheat, oats, cotton, potatoes, and sugar cane.
- Polyploidy is less common in animals but is found in some invertebrates, fishes, salamanders, frogs, and lizards.
- No naturally occurring, viable polyploids are known in birds, but at least one polyploid mammal—a rat in Argentina—has been reported

Major types of polyploidy:

- **autopolyploidy,**
- in which all chromosome sets are from a single species;
- and **allopolyploidy,**
- in which chromosome sets are from two or more species

Autopolyploidy

- Autopolyploidy is due to accidents of meiosis or mitosis that produce extra sets of chromosomes, all derived from a single species.
- Nondisjunction of all chromosomes in mitosis in an early 2*n embryo, for example, doubles the* chromosome number and produces an autotetraploid (4*n)*
- An autotriploid (3*n) may arise* when nondisjunction in meiosis produces a diploid gamete that then fuses with a normal haploid gamete to produce a triploid zygote

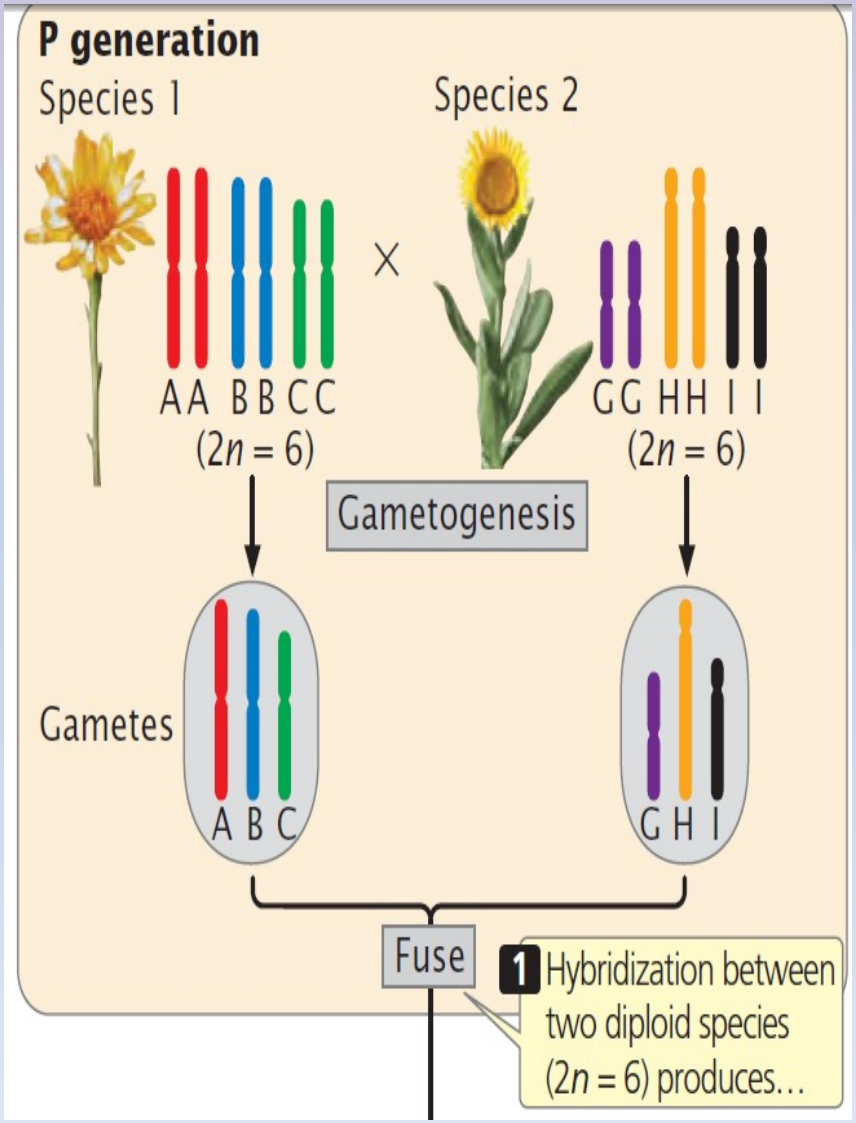


9.26 Autopolyploidy can arise through nondisjunction in mitosis or meiosis.

Because all the chromosome sets in autopolyploids are from the same species, they are homologous and attempt to align in prophase I of meiosis, which usually results in sterility.

Allopolyploidy

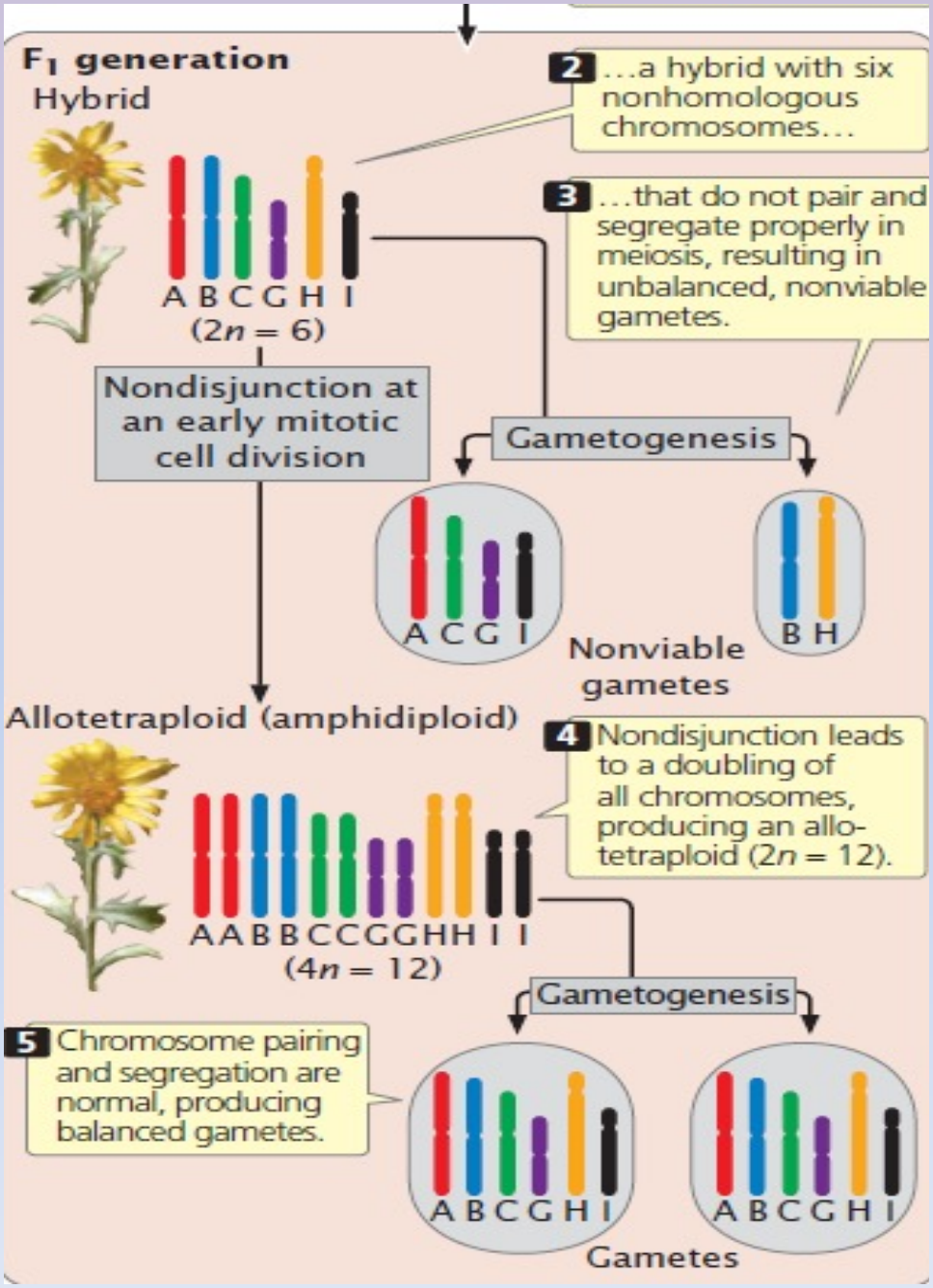
- Allopolyploidy arises from hybridization between two species; the resulting polyploid carries chromosome sets derived from two or more species
- Species 1 (AABBCC, 2*n* = 6) *produces haploid gametes with chromosomes* ABC,
- and species 2 (GGHHII, 2*n* = 6) *produces* gametes with chromosomes GHI.
- If gametes from species 1 and 2 fuse, a hybrid with six chromosomes (ABCGHI) is created.



The hybrid has the same chromosome number as that of both diploid species; so the hybrid is considered diploid. However, because the hybrid chromosomes are not homologous, they will not pair and segregate properly in meiosis; so this hybrid is functionally haploid and sterile.

The sterile hybrid is unable to produce viable gametes through meiosis, but it may be able to perpetuate itself through mitosis (asexual reproduction).

On rare occasions, nondisjunction takes place in a mitotic division, which leads to a doubling of chromosome number and an allotetraploid with chromosomes AABBCCGGHHII.
This type of allopolyploid, consisting of two combined diploid genomes, is sometimes called an **amphidiploid**



Euploidy Variations

- Plants commonly exhibit polyploidy
  - 30-35% of ferns and flowering plants are polyploid
  - Many of the fruits & grain are polyploid plants

- Polyploid strains often display desirable agricultural characteristics
  - wheat
  - cotton
  - strawberries
  - bananas
  - large blossom flowers

(a) A hexploid species

Diploid

Tetraploid

(b) A comparison of diploid and tetra

- Variations in euploidy
  - Occur naturally in a few animal species
    - e.g., Honeybees
      - Females are diploid
      - Males (drones) are haploid (monoploid)
        - » Produced from unfertilized eggs

- Variations in euploidy
  - Common in plants
    - 30 – 35% of ferns and angiosperms are polyploid
  - Important in agriculture
    - Many food plants are polyploid
      - e.g., Fruits and grains
    - Often display outstanding agricultural characteristics
      - Often larger and more robust
- Variations in euploidy
  - Sterility is generally a detrimental trait
  - Can be desirable agriculturally
    - e.g., Seedless bananas and watermelons are triploid