# HMB265: Human & General Genetics

## Lecture 17: **Changes in Chromosome Number**

Prof. Belinda Chang

- Genetics is not biology you can just memorize then forget about it after exams. It's about learning and applications in daily life.

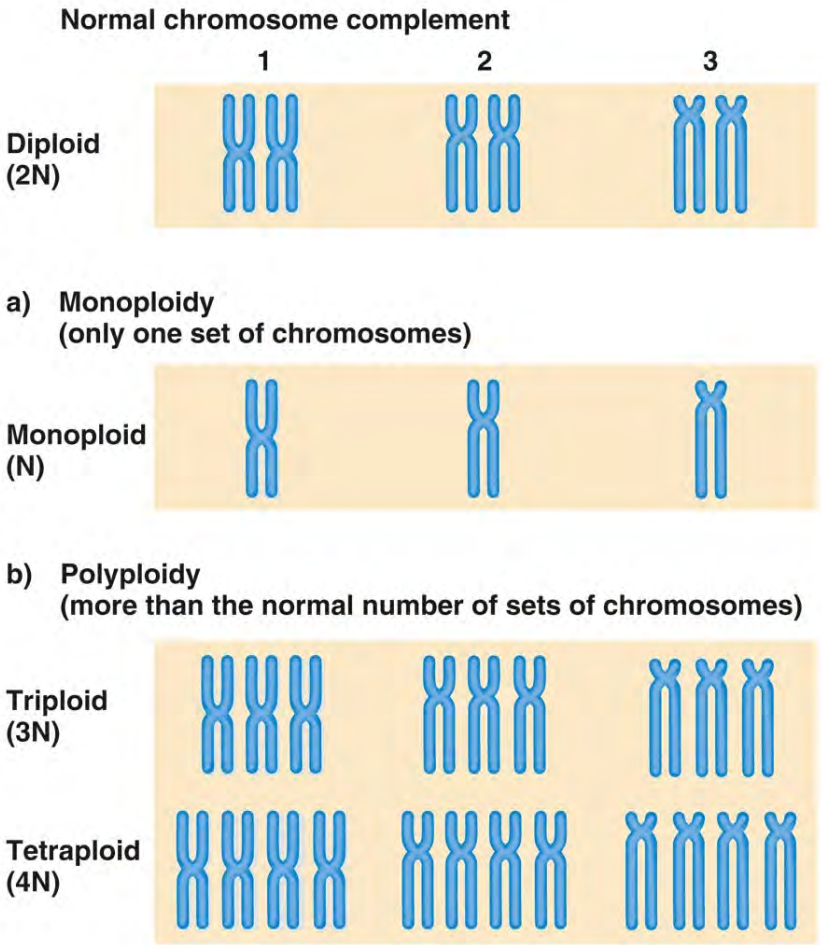
# Lecture Outline

- Euploidy
- Aneuploidy
- Sex chromosomes
- Fetal testing and ethical issues
- Reading:
  - Hartwell *et al*., Canadian ed., Chapter 3 (emphasis on pages 72-79), Chapter 9 (emphasis on 303-313), Chapter 15 (emphasis on 489-90, 511) .

Changing the entire number of chromosomes can lead to detrimental effects, but it can also happen naturally.

# Changes in chromosome number

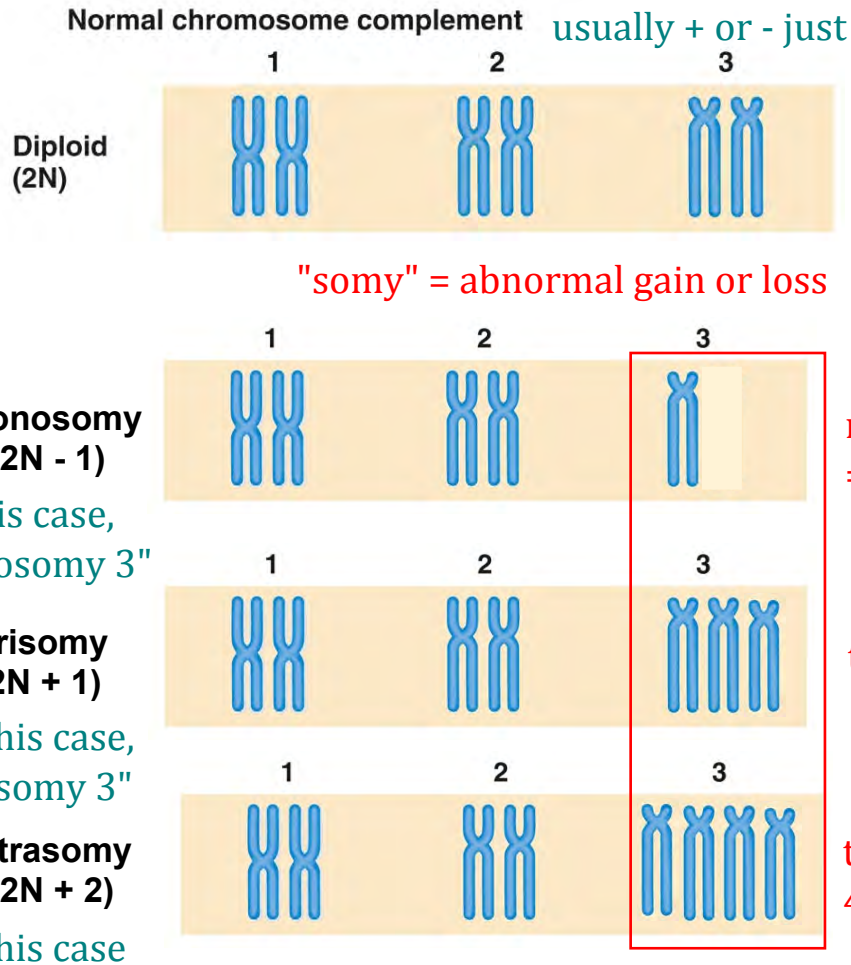
**Euploidy**: complete sets of chromosomes (normal)




Most animals are in diploid state.
It can also be monoploid, or polyploid.

**Aneuploidy**: loss or gain of one or more chromosomes

not across entire set, usually + or - just 1.




"somy" = abnormal gain or loss

**Monosomy (2N - 1)**

in this case, "monosomy 3"

**Trisomy (2N + 1)**

in this case, "trisomy 3"

**Tetrasomy (2N + 2)**

in this case "tetrasomy 3"




mono = 1

tri = 3

tetra = 4

Look at the end result of chromosome number here to figure out the name.

# Monoploidy

it's natural state of their chromosomes

- Male bees, wasps, and ants — Females are diploid
- Parthenogenesis – development of unfertilized egg into an embryo (with no fertilization)
  - single set of chromosomes
  - produce gametes by mitosis

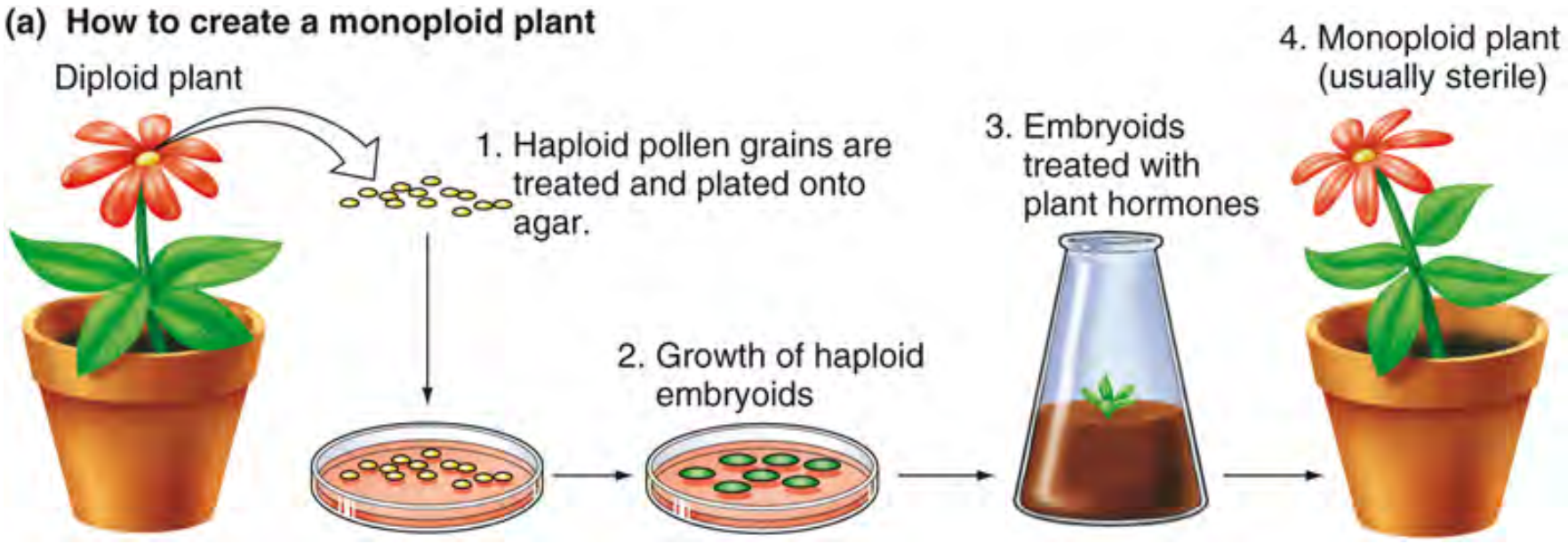
Gametes are naturally haploid from meiosis, but can be induced to develop as well to produce work bees, ants, wasps etc.,

- Usually lethal in other systems
  - unmasks recessive lethals
  - if individual survives to adulthood → no meiosis, sterility

That's why parthenogenesis is not common among animals. Most animals are in fact diploid.

New mutations are usually recessive and you can't see them unless they're in a homozygous state, but monoploid plants can manifest them right away and select desired traits.

# Monoploidy can be produced experimentally




Not all mutations are lethal. Some might result in phenotypes that you'll be interested in, e.g. flower color, leave numbers or structure etc.,

Monoploid plants have many uses

- visualize recessive traits directly
- introduction of mutations

However, you can treat the monoploid plant with chemicals and encourage a diploid state as well.

**Hartwell *et al.* Canadian ed., Fig. 9.33**

In supermarket, we see fruits are getting bigger and bigger, and it's true, because big ones are polyploid, bred more in by farmers, and getting taken advantages for the fruit size.

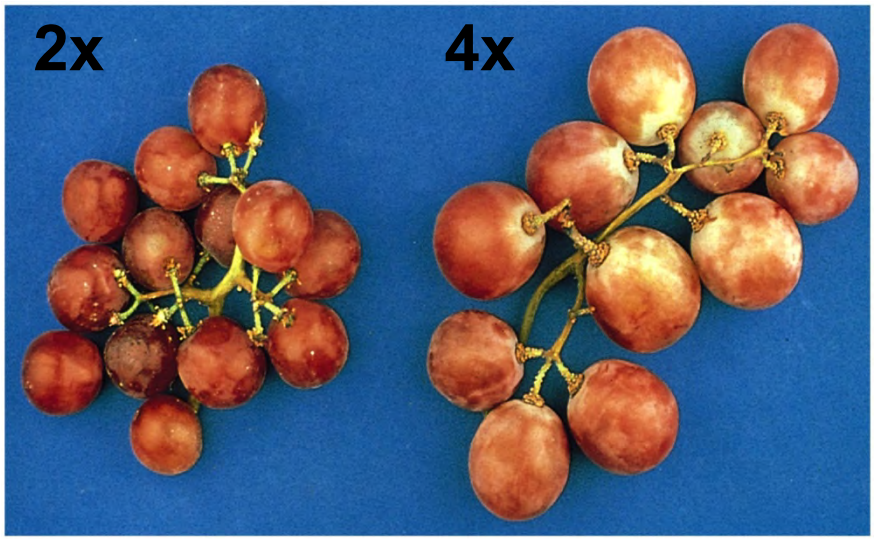
# Polyploidy

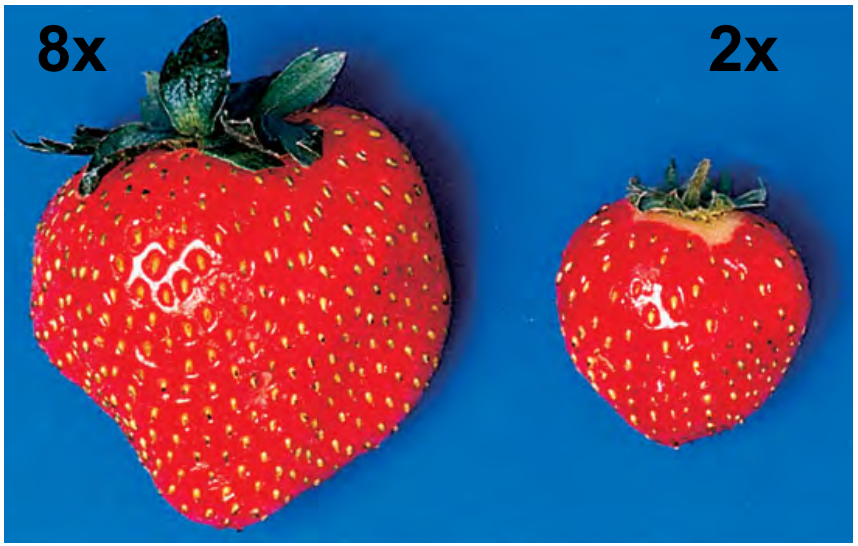
**Very common in plants:** also can be result of breeding sometimes

- associated with origin of new species
- may positively correlate with size and vigor
- eg. alfalfa, coffee, peanuts are tetraploid
- eg large apples, pears, grapes are tetraploid
- eg. large strawberries are octaploid

Polyploid plants can be economically important for agriculture.

vigor = physical strength and good health



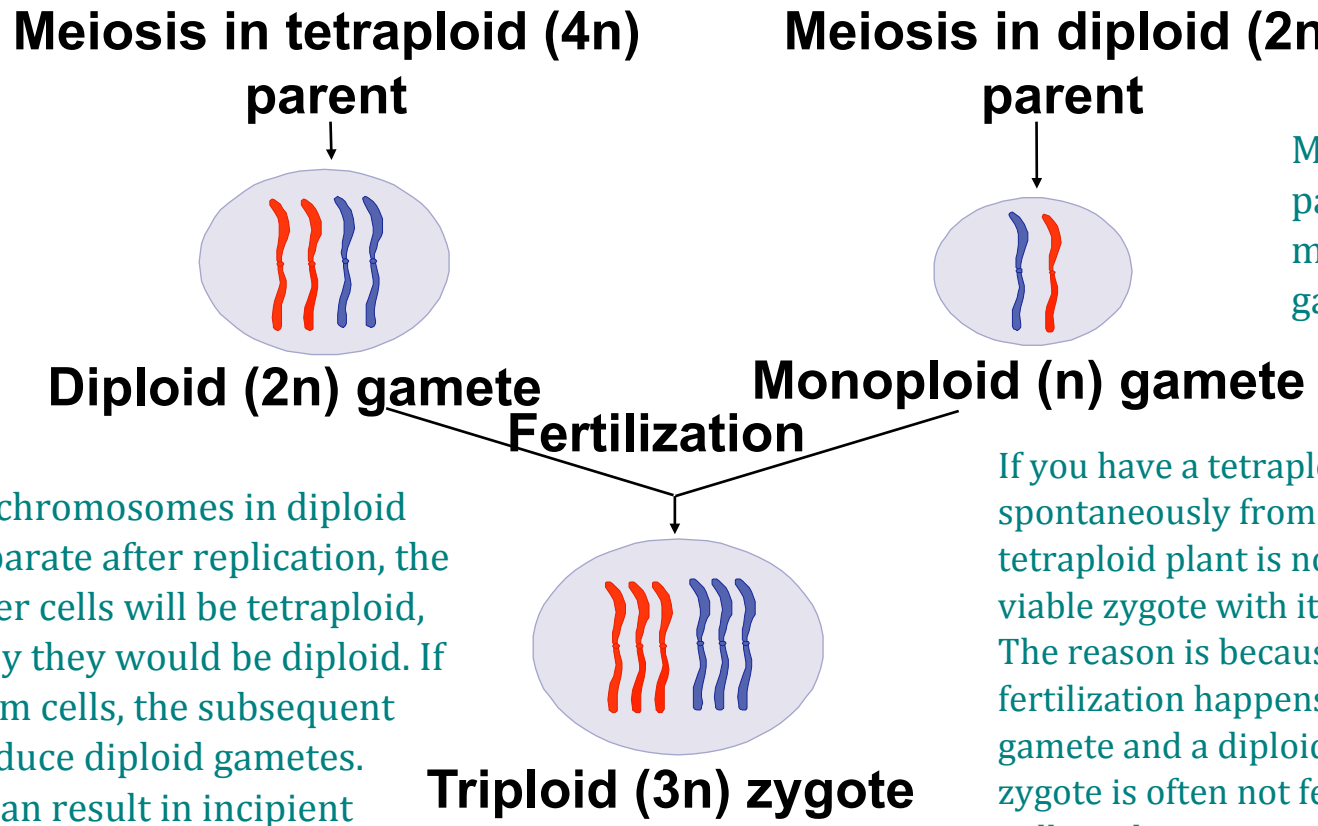

**Hartwell *et al.* (2007) Genetics: From Genes to Genomes**

Incipient speciation: the evolutionary process in which new species form but are still capable of interbreeding; it can be the first part of the larger process of speciation.

# Polyploidy: Autopolyploids

(a normal case that occurs in nature)

## Originate within a species eg. Autotriploid (2n + n = 3n)




Meiosis in the diploid parent will produce monoploid/haploid gametes.

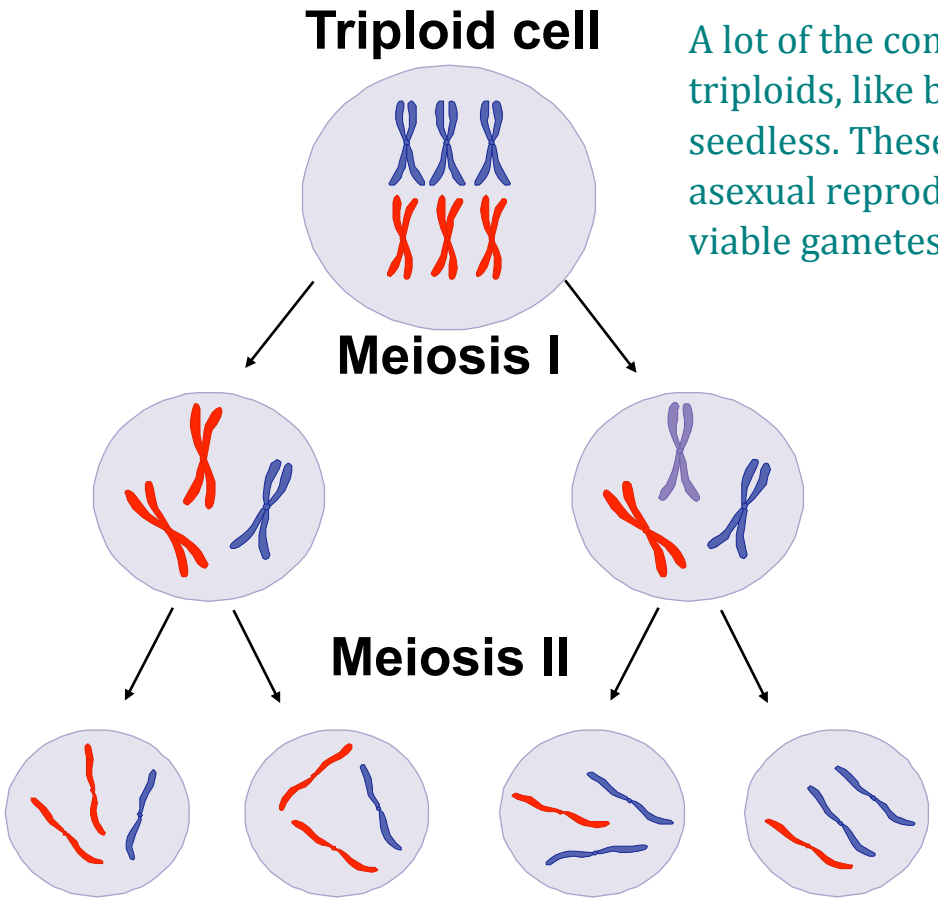
If in mitosis, the chromosomes in diploid tissues fail to separate after replication, the resulting daughter cells will be tetraploid, whereas normally they would be diploid. If it happens in germ cells, the subsequent meioses will produce diploid gametes. Autopolyploids can result in incipient speciation.

If you have a tetraploid plant that arises spontaneously from a diploid parent, that tetraploid plant is no longer able to produce viable zygote with its diploid parent species. The reason is because when you have fertilization happens between a monoploid gamete and a diploid gamete, the triploid zygote is often not fertile. The triploid zygote will produce unusual, unblanaced gametes during meiosis that will be sterile.

**Hartwell *et al.* (2007) Genetics: From Genes to Genomes**

# Autotriploids are sterile

## Due to formation of aneuploid gametes eg. bananas




A lot of the commercial crops are sterile triploids, like bananas or watermelons. They are seedless. These plants are propagated via asexual reproduction. They cannot produce viable gametes, so it leads to sterility.

Hartwell *et al.* (2007) Genetics: From Genes to Genomes

# Autotetraploids

chromosomal doubling within a species

- Doubling of **2n** chromosome complement to **4n**
  - spontaneous doubling
  - induced by a drug such as colchicine
  - often the source of a new species

The process can happen naturally in nature, but there are also artificial ways to assist it to induce a new species or new strength, e.g. colchicine is applied to mitotic cells to disrupt the spindle fiber formation during metaphase and anaphase.

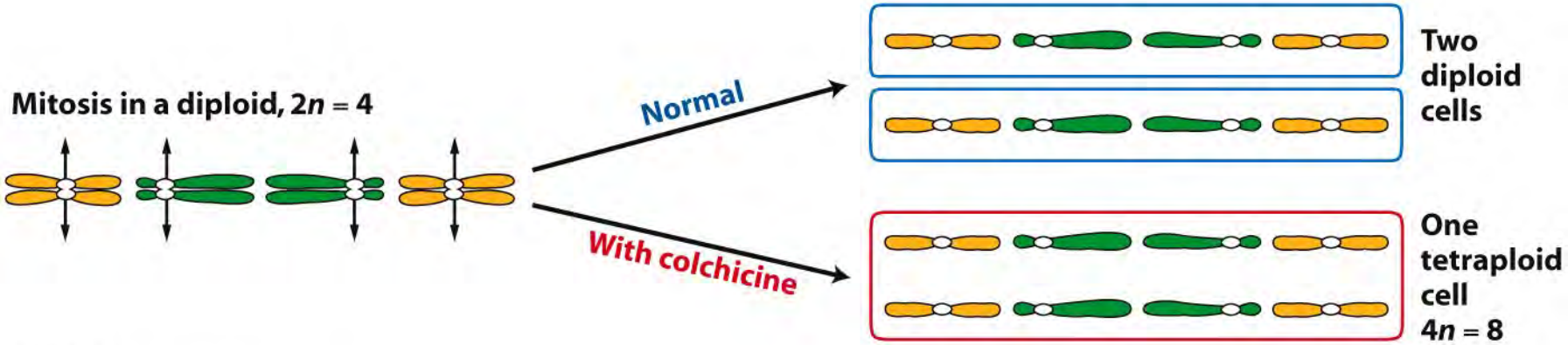



**Figure 17-5**
*Introduction to Genetic Analysis*, Tenth Edition


As a result, chromosomes aren't pulled apart to the poles appropriately. Therefore, one of the daughter cells gets all of the chromosomes and the other one gets none. The one that gets all of the chromosomes become tetraploid. Preventing the migration of chromatids after the centromeric split can give rise to autotetraploids.

# Polyploidy: Allopolyploids

- hybrid of two or more closely related species

It's not a doubling within a species.

- partially homologous chromosomes (**homeologous**)
- **amphidiploid** --doubled diploid: doubling in germ cells

e.g. breeding a cabbage "Brassica" with a radish "Raphanus". They are closely related, but F1 is sterile. Then there was a spontaneous doubling that happened and made it fertile.

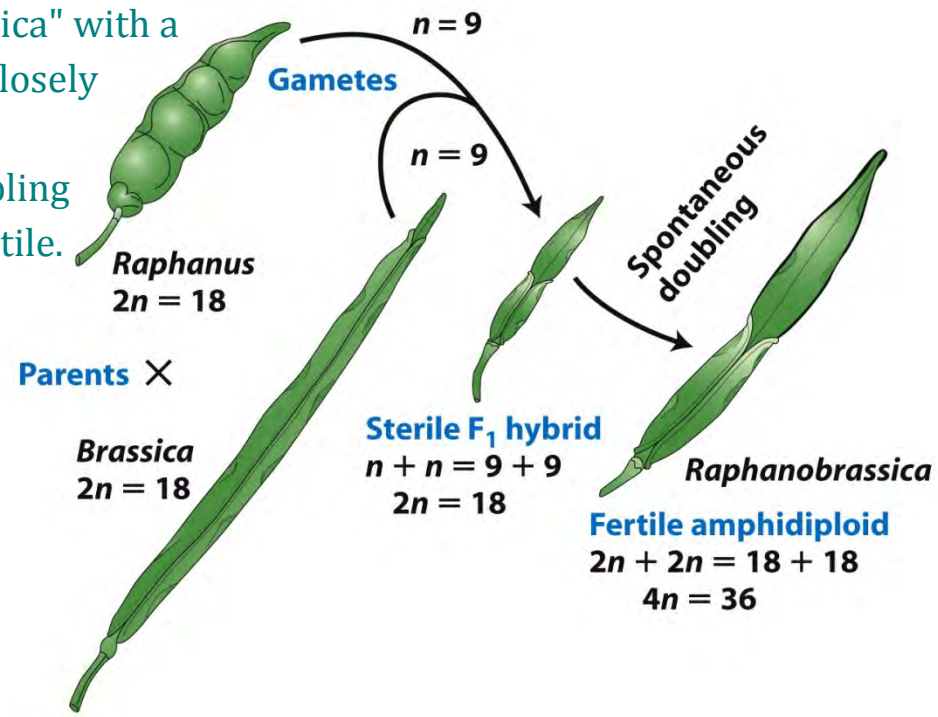



Figure 17-7
*Introduction to Genetic Analysis*, Tenth Edition
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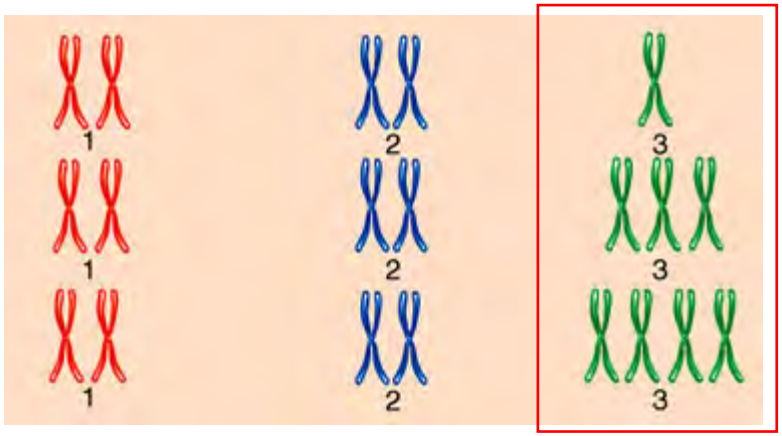
The result of this cross gave rise to a whole new species. The breeders wanted to get the root of the radish and the leaf of the cabbage to breed a better commercial crop, but as a result, they got the leaf of the radish and the root of the cabbage, the exact opposite.

# Aneuploidy

we are not talking about sets of chromosomes

- Loss or gain in the number of individual chromosomes
  - **For autosomes:**
    - **nullisomy**: 2n – 2
    - **monosomy**: 2n – 1
    - **trisomy**: 2n + 1
    - **tetrasomy**: 2n + 2




- For sex chromosomes, list copies of each chromosome:

  eg. **XXY, XXX, XO, XYY** since sex chromosomes have different names, we can just write it out.

**See Table 17-1 in Griffiths**

The effect can be detrimental due to complete deletion or abnormal state of chromosomes in some cells. Even though there aren't any new genes introduced, problem with dosage compensation exists, i.e. genes can be expressed at inappropriate levels.

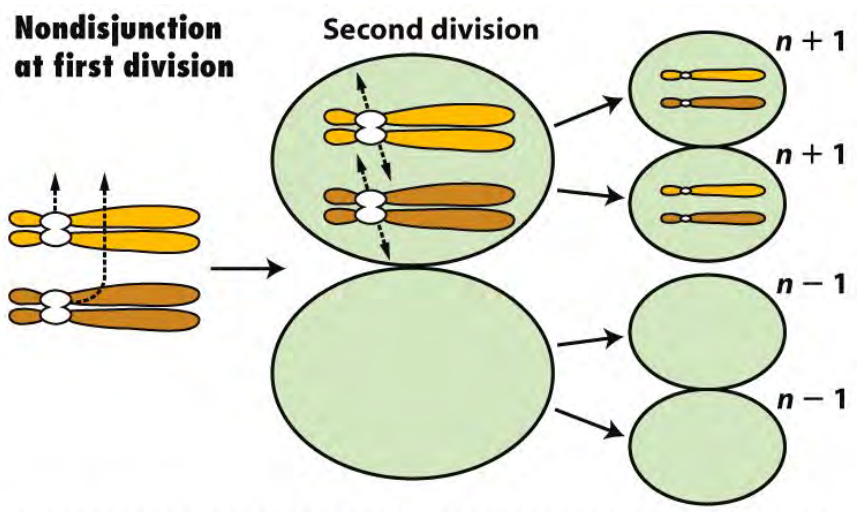
# Cause: Nondisjunction

in meiosis I or II

All the other sets segregate properly, except this pair.

## Meiotic nondisjunction

abnormal, aneuploidy



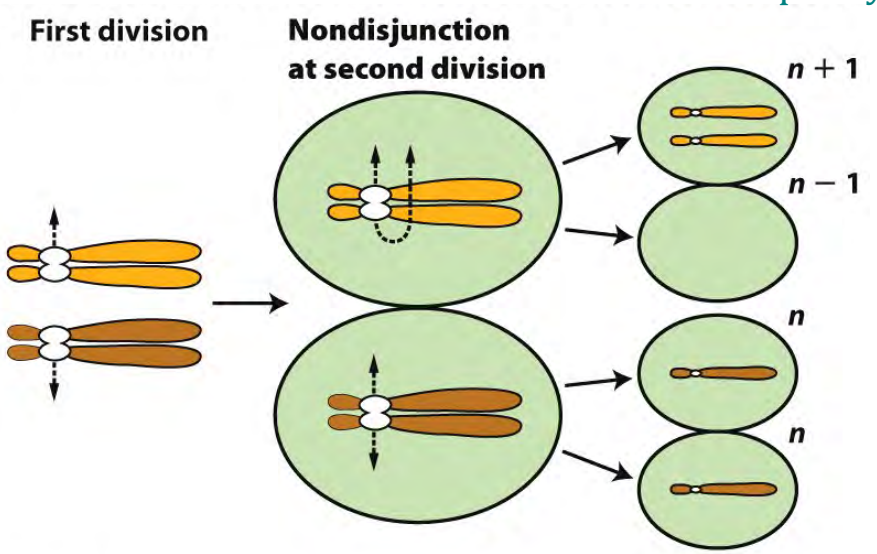




Figure 17-12
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In this case, after non-disjunction at meiosis I, both chromosomes went into one daughter cell, then divide again at meiosis II. All gametes exhibit aneuploidy.

In the case of non-disjunction at meiosis II, some are normal, and some are not.

- OR, mitotic nondisjunction
  - results in a mosaic

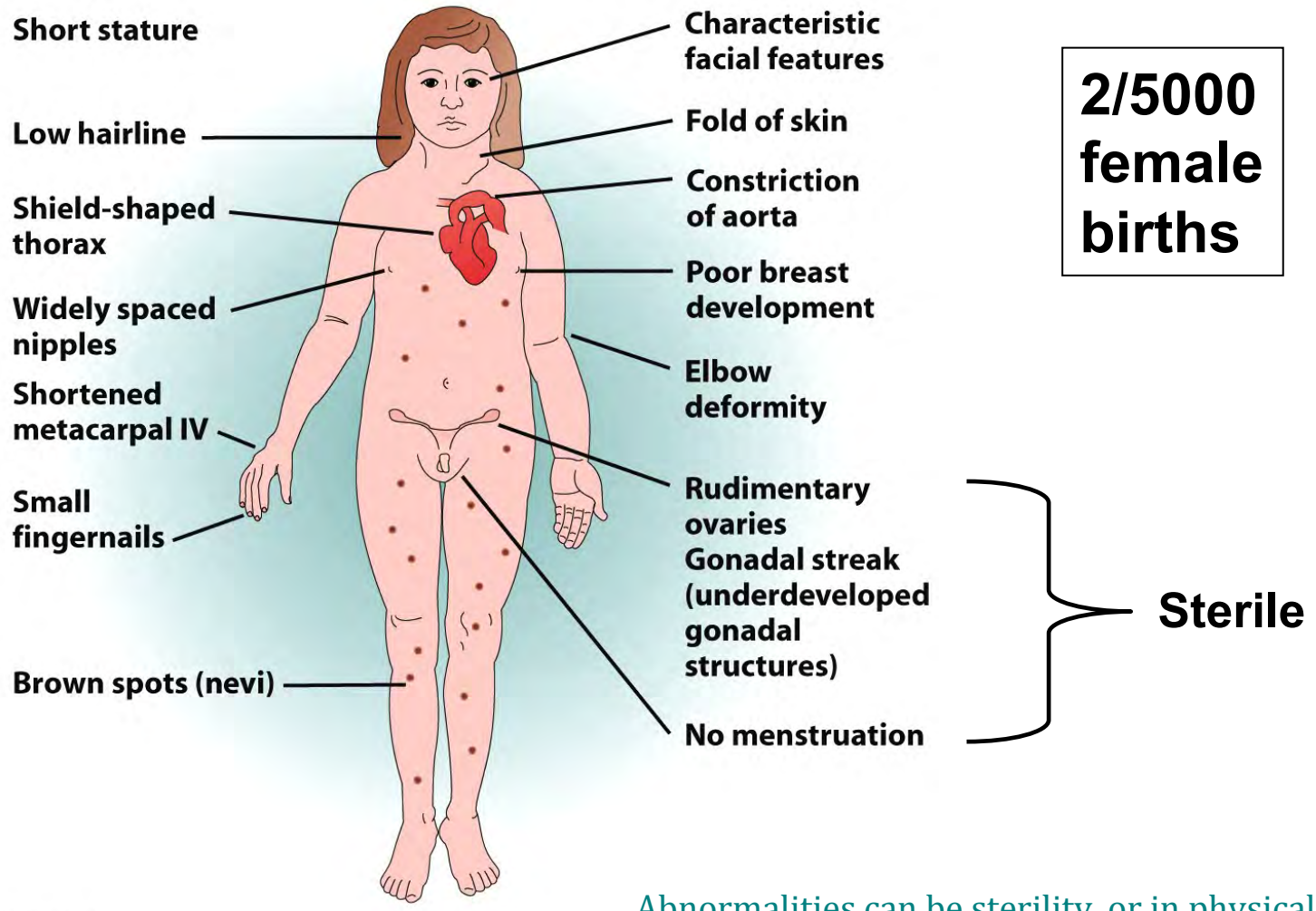
See also Hartwell *et al.*, Fig. 9.31

# Monosomy

- **2*n* - 1** can delete an entire chromosome, or can be epigenetic effect where that gene is not even turned on, completely lacking that gene.
- Usually lethal *in utero* in humans Fetuses with loss of an entire chromosome will be aborted in the uterus, won't even make it to birth.
- **Examples:** Some of them do make it to birth, but with abnormalities.
  - **Monosomy 21**: born with severe multiple abnormalities but die shortly after birth

    Chromosome 21 if duplicated can result in Down syndrome.
  - **Turner syndrome (XO):** 99% of affected fetuses are not born. Those who are born have developmental abnormalities. 2 out of 5000 can have it, very high rate of incident, very severe effect

# Turner syndrome (XO)




**2/5000 female births**

Figure 17-13
*Introduction to Genetic Analysis*, Tenth Edition


Abnormalities can be sterility, or in physical or developmental features.

# Question: X inactivation occurs in XX individuals. Why are there abnormalities in XO individuals?

- X inactivation does not occur until the 100-cell stage in development It only occurs at a fairly late stage of development.

- Some of the genes on the "inactivated" X chromosome are expressed Mostly inactivated, but not entirely activated. The expressed genes are actually critical for normal functions.

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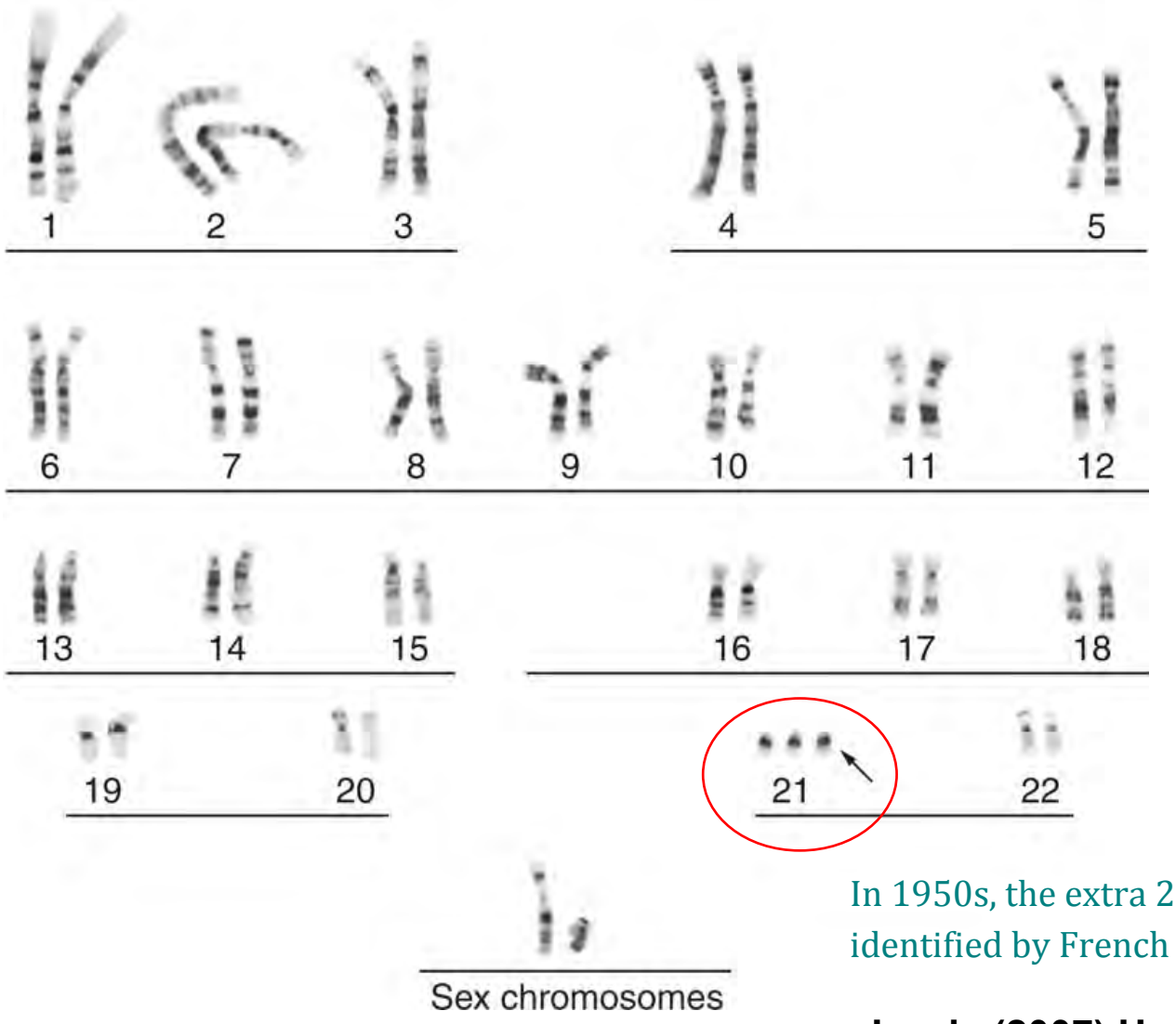
# Trisomy

- **$2n + 1$** an extra chromosome leads to gene dosage problem
- Often lethal in animals owing to chromosome imbalance
- **Examples:** most of them are lethal mutations in animals, but some can make it to birth
  - Trisomy 21: Down syndrome — 3 copies of chromosome 21, with highest incident rate and fairly famous
  - Trisomy 18: Edward syndrome — A lot of them are fatal in early stage in life.
  - Trisomy 13: Patau syndrome
  - Klinefelter syndrome: XXY
  - Trisomy XYY
  - Trisomy XXX

It was named after British physician Dr. Down in 1966.

# Down syndrome karyotype




In 1950s, the extra 21 chromosome was identified by French researchers.

**Lewis (2007) Human Genetics**

# Down syndrome (trisomy 21)

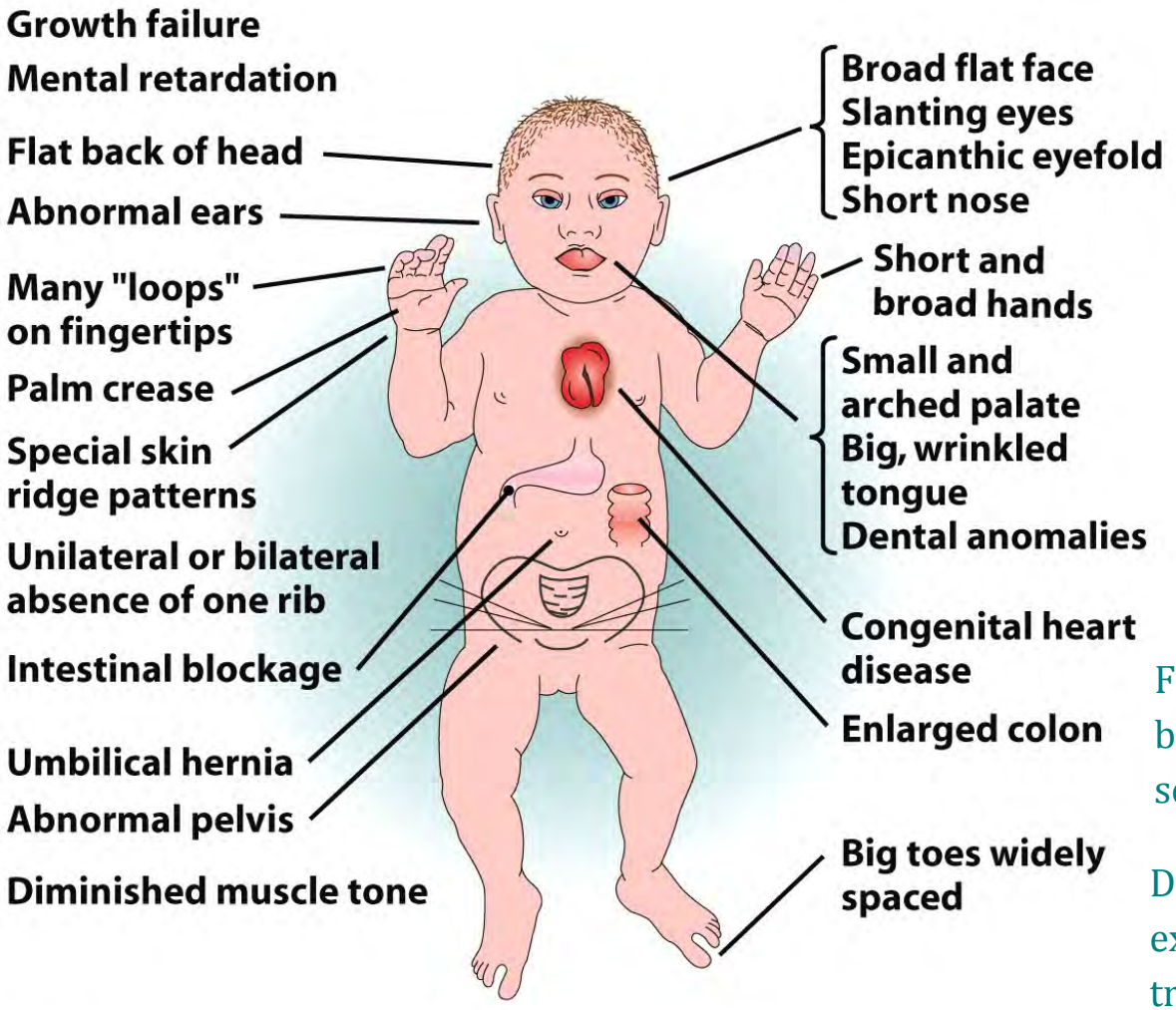



**Figure 17-16**
*Introduction to Genetic Analysis*, Tenth Edition


- **Females can be fertile**
- **Males infertile**
- **Average life expectancy ~40-60 years**

Frequency of incident: 1 in 700~1000 live births. It is a lot lower now due to genetic screening (used to be 1 in 500).

Down syndrome patients have longer life expectancy than most cases of other types of trisomy. Other trisomies' fetuses won't even be born.

# Risk of having a baby with Down syndrome rises with maternal age

The mechanism behind this phenomenon is not entirely clear, but it has to do with oocytes sitting in prophase I. Oocytes don't resume action until menstruation, and will start to age after that. Oocytes are aging as the mothers are aging.

Now they are different types of screening processes used in medicine.

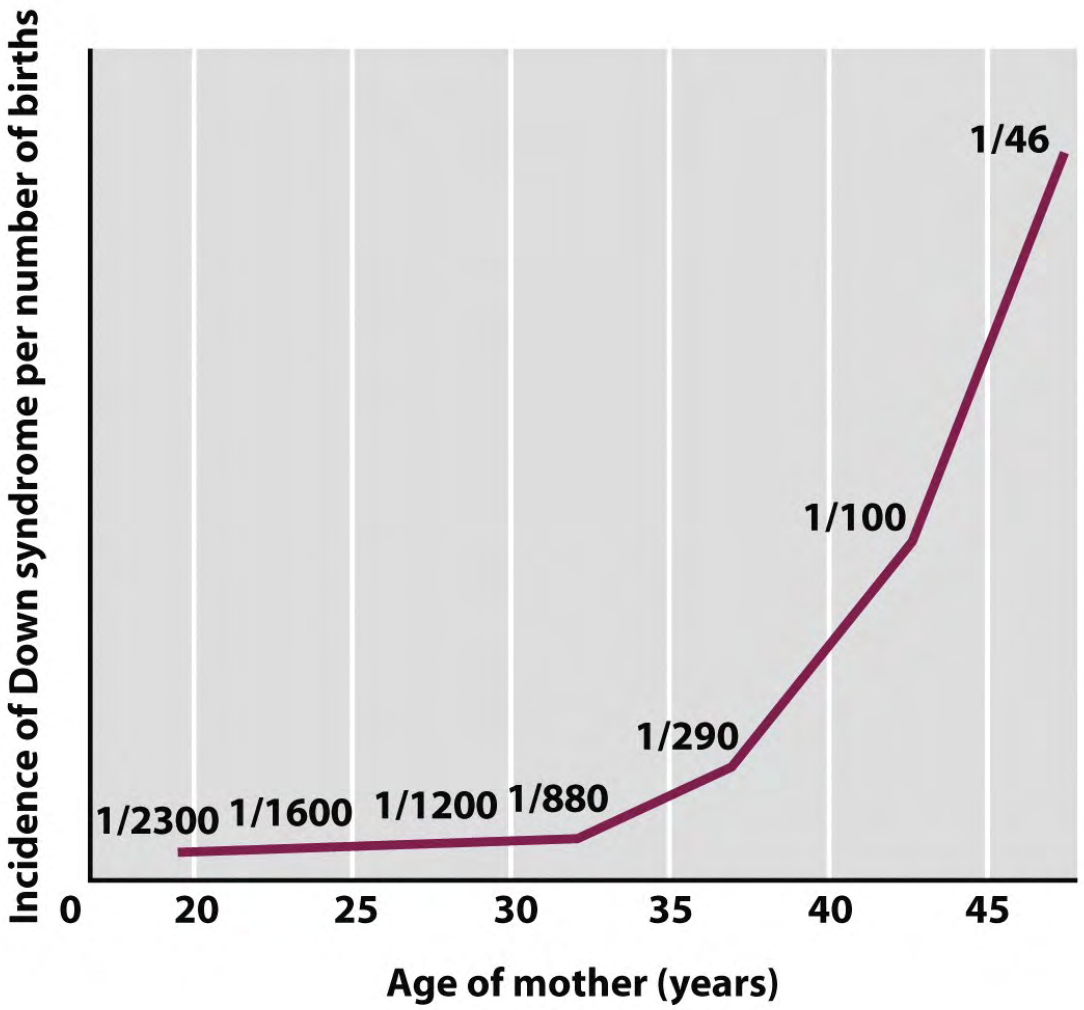



**Figure 17-17**
*Introduction to Genetic Analysis*, Tenth Edition


Older mothers have a much higher risk of having a child with Down syndrome than younger mothers.

After the age of 35, the chance for a mother to have a kid with Down syndrome increases quickly.

Father's age is associated as well but not as manifested as mother's age.

# Edward syndrome (trisomy 18)

much more severe than trisomy 21

- Severe physical and mental abnormalities
  - Eg. heart defects, growth retardation, “faunlike” ears, small jaw, kidney abnormalities, narrow pelvis, “rocker bottom” feet, oddly clenched fists
- Average life expectancy of a few weeks
- 1/6,000 to 1/10,000 live births

incident is much lower than Down syndrome


**Lewis (2007) Human Genetics**

# Trisomies XXX and XYY

more common but less severe

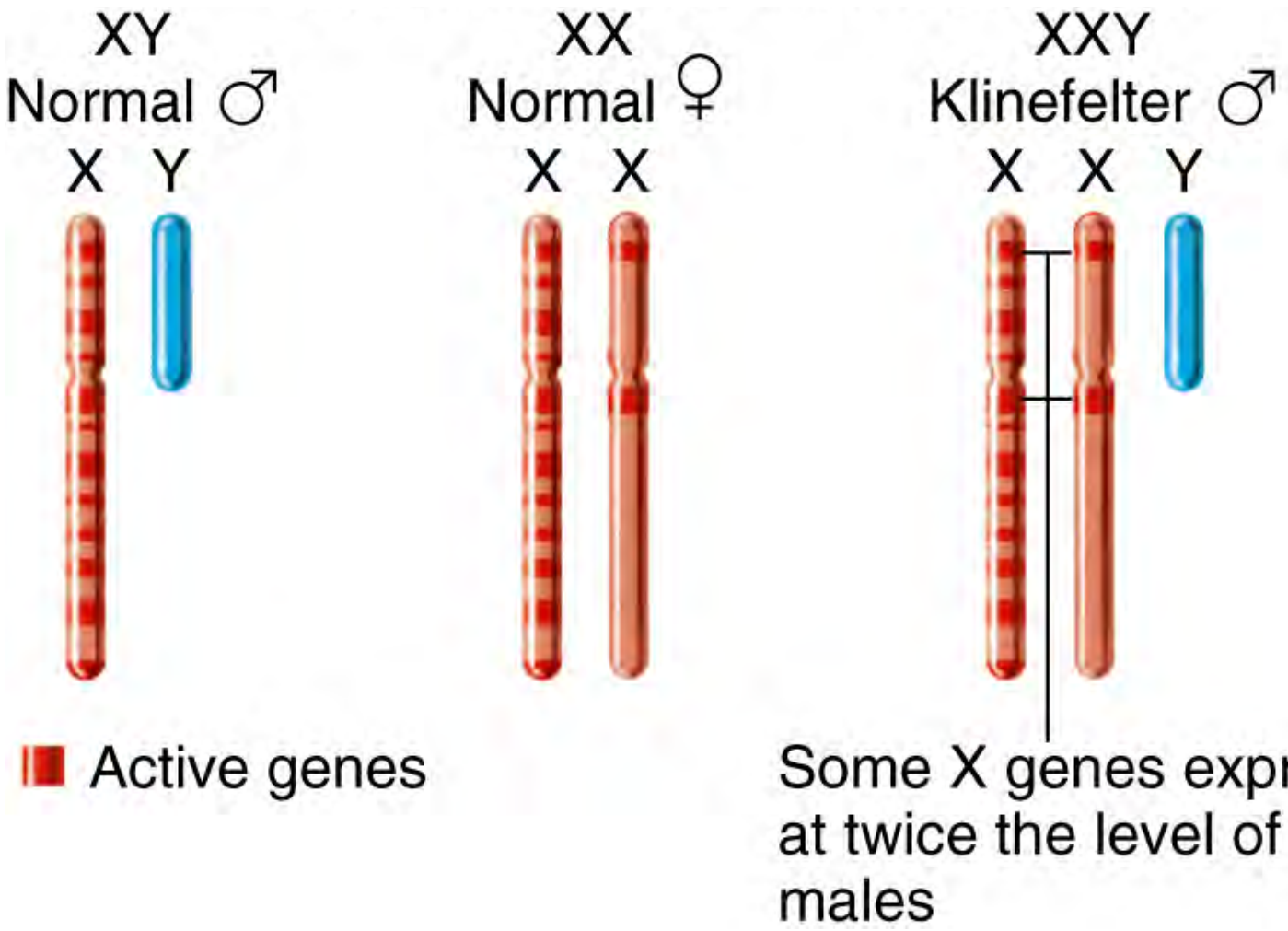
- XYY: Usually fertile – **X** pairs with one **Y**; other **Y** does not pair and is not transmitted to gametes
  - i.e. **X** or **Y** gametes, not **XY** or **YY**

Linkage to violence with an extra Y chromosome was suspected in the past, but is not proven.

- XXX: Usually fertile - Two **X chromosomes** pair; third does not pair and is not transmitted
  - i.e. only **X** gametes, not **XX**
- Thus, conditions are not passed on to progeny

Having two Y chromosomes and three X chromosomes are not detrimental, but having XXY is a different story.

# XXY: One X is inactivated in Klinefelter syndrome




You'd think that having two X chromosomes is okay because of random X inactivation, but that's not true, because the few genes can get expressed doubled the amount due to two X chromosomes than normal males. It can result in sterility.

**Hartwell *et al.* Canadian ed., Fig. 9.30**

# Sex determination across organisms

all work differently

| Table 3.2 | Mechanisms of Sex Determination | |
|---|---|---|
| | ♀ | ♂ |
| Humans and *Drosophila* | XX | XY |
| Moths and *C. elegans* | XX (hermaphrodites in *C. elegans*) | XO |
| Birds and Butterflies | ZW | ZZ |
| Bees and Wasps | Diploid | Haploid |
| Lizards and Alligators | Cool temperature | Warm temperature |
| Tortoises and Turtles | Warm temperature | Cool temperature |
| Anemone Fish | Older adults | Young adults |

- Many different mechanisms of sex determination
- Some are based on sex chromosomes, some on other factors

Heterogametic (the other sex) effect can be dosage-dependent, environment-dependent etc.,.

**Hartwell *et al.* Canadian ed., p. 78**

# Human chromosome mutations

**Table 9.2 Aneuploidy in the Human Population**

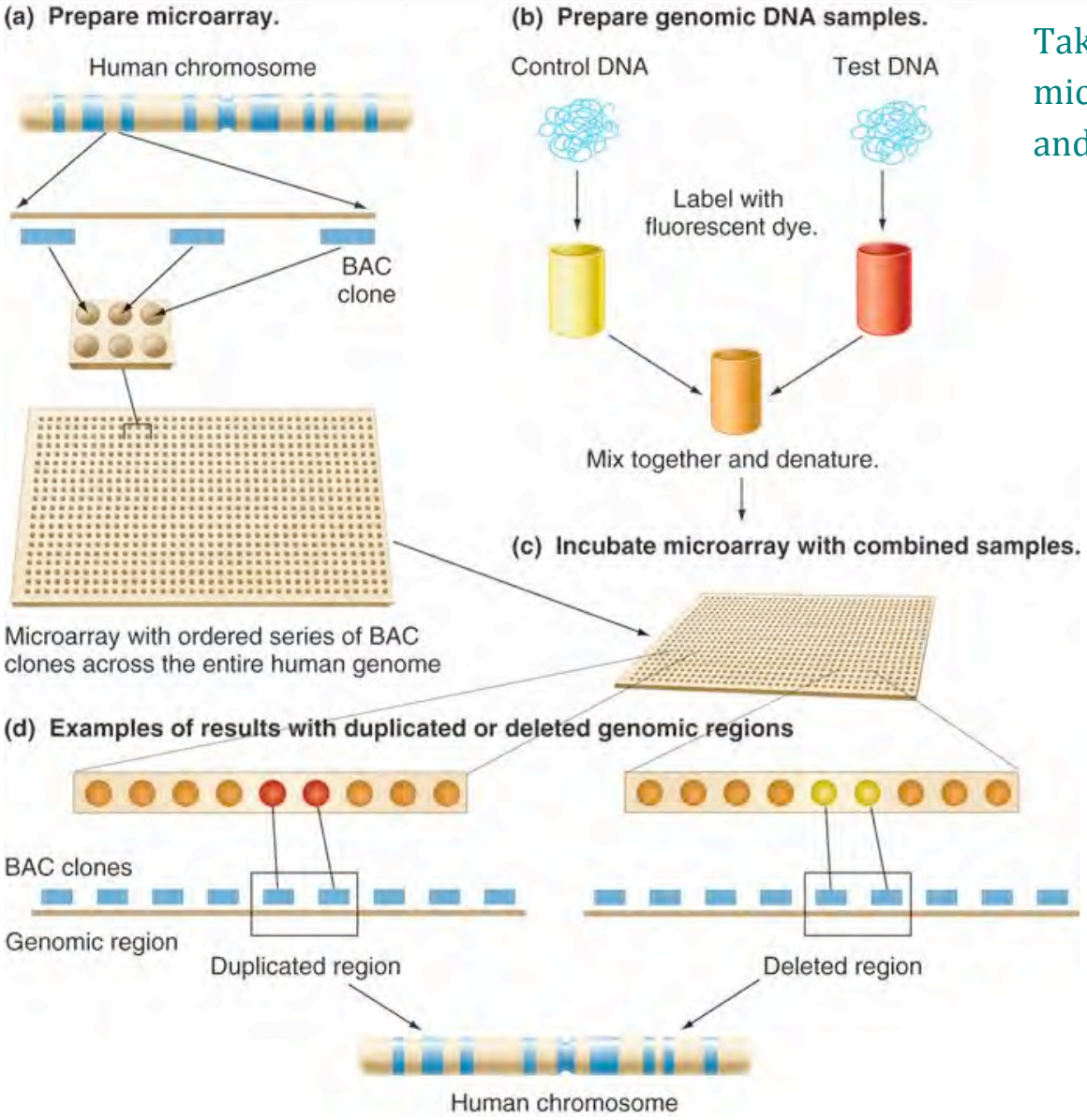
| Chromosomes | Syndrome | Frequency at Birth |
|---|---|---|
| ***Autosomes*** | | |
| Trisomic 21 | Down | 1/700 |
| Trisomic 13 | Patau | 1/5000 |
| Trisomic 18 | Edwards | 1/10 000 |
| ***Sex chromosomes, females*** | | |
| XO, monosomic | Turner | 1/5000 |
| XXX, trisomic | | |
| XXXX, tetrasomic | | 1/700 |
| XXXXX, pentasomic | | |
| ***Sex chromosomes, males*** | | |
| XYY, trisomic | Normal | 1/10 000 |
| XXYY, tetrasomic | | |
| XXY, trisomic | Klinefelter | 1/500 |
| XXXY, tetrasomic | | |
| XXXXY, pentasomic | | |
| XXXXXY, hexasomic | | |

About 0.4 percent of all babies born have a detectable chromosomal abnormality that generates a detrimental phenotype.

Most of them end up in spontaneous abortions, except trisomy 21 and trisomy in sex chromosomes.

Hartwell *et al*., p. 313

# Genomic hybridization: microarrays




Take parts of the genome and spot it on the microarray, then prepare DNA genomic samples and see where they hybridize.

Microarray-based methods for detecting duplication/deletions of at least 50 Kb

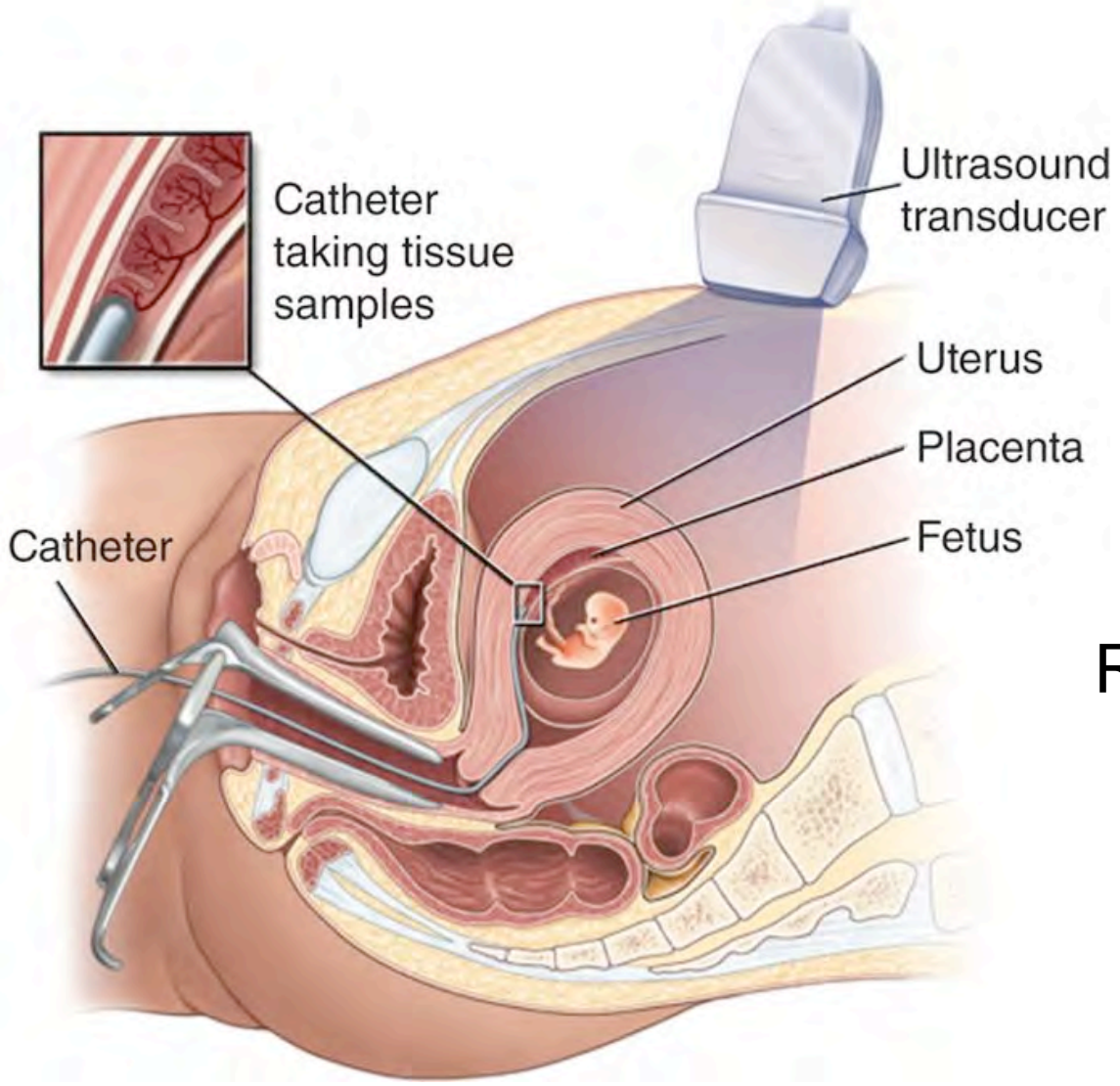
Lack of hybridization indicates deletion or duplication.

Hartwell *et al.*, Canadian ed., Fig. 9.38

# Prenatal testing

- **Screening tests:**
  - eg. First trimester screening test (11 to 13 weeks)— ultrasound (nuchal translucency) and maternal blood test [pregnancy associated plasma protein-A (PAPP-A) and human chorionic gonadotrophin (hCG)] levels of hormones associated with pregnancy
- **Diagnostic tests:** at different stages of fetal development
  - Chorionic villi sampling (10 to 13 weeks)
  - Amniocentesis (16+ weeks)

# Chorionic villi sampling




take tissue cells from placenta as sample with catheter

done in 10~13 weeks

Risk of miscarriage due to the procedure: 1%

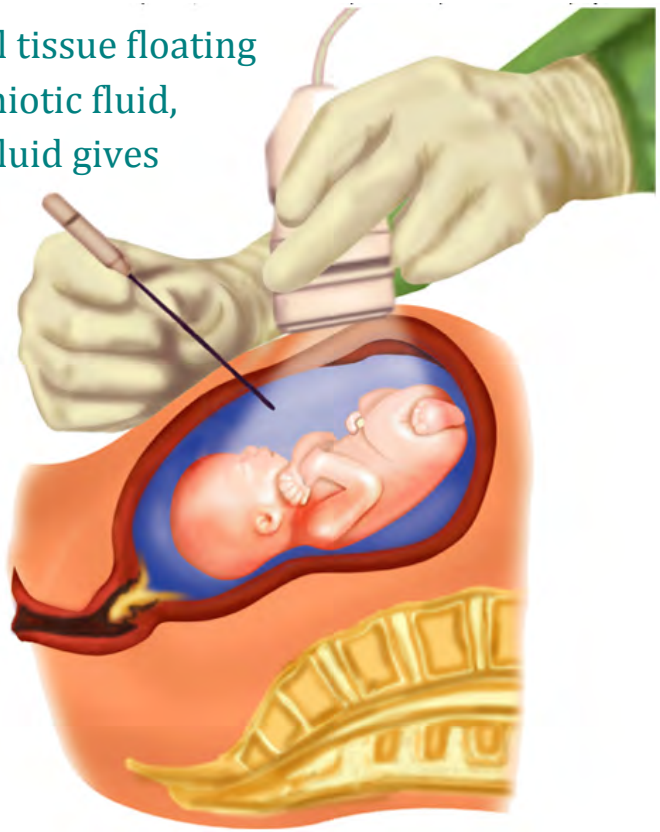
still fairly low, but the risk of infection still exists. It can be used to test Down syndrome or other aneuploidy.

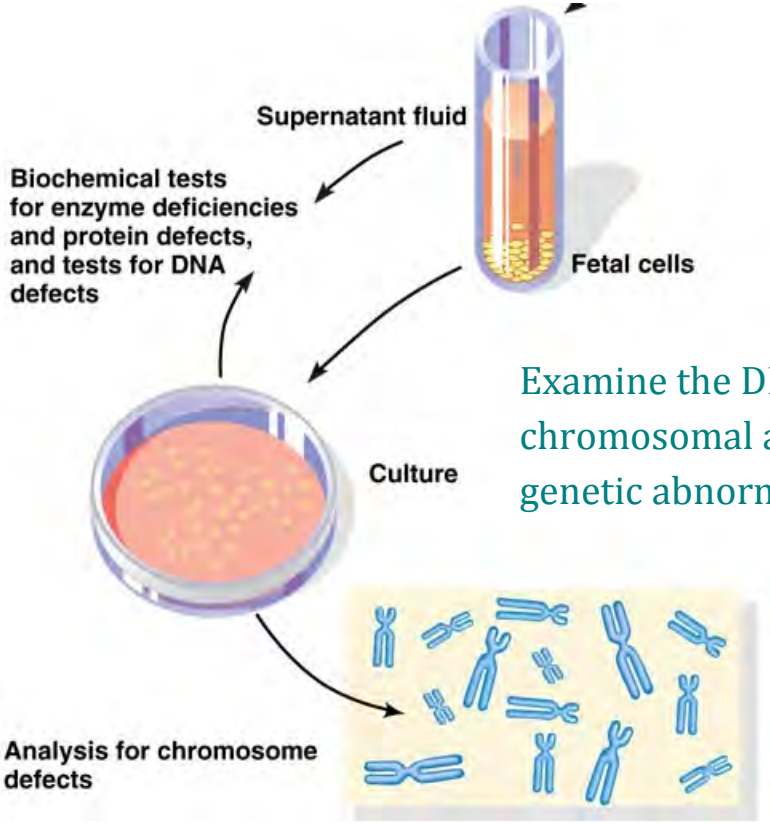
Hartwell, Fig. B, p. 76

# Amniocentesis

done in 15~18 weeks.

There are fetal tissue floating around in amniotic fluid, so taking the fluid gives sample.






Examine the DNA for chromosomal and genetic abnormalities.

**Test results available 1 to 3 weeks later**

**Risk of miscarriage due to the procedure: 0.5%**

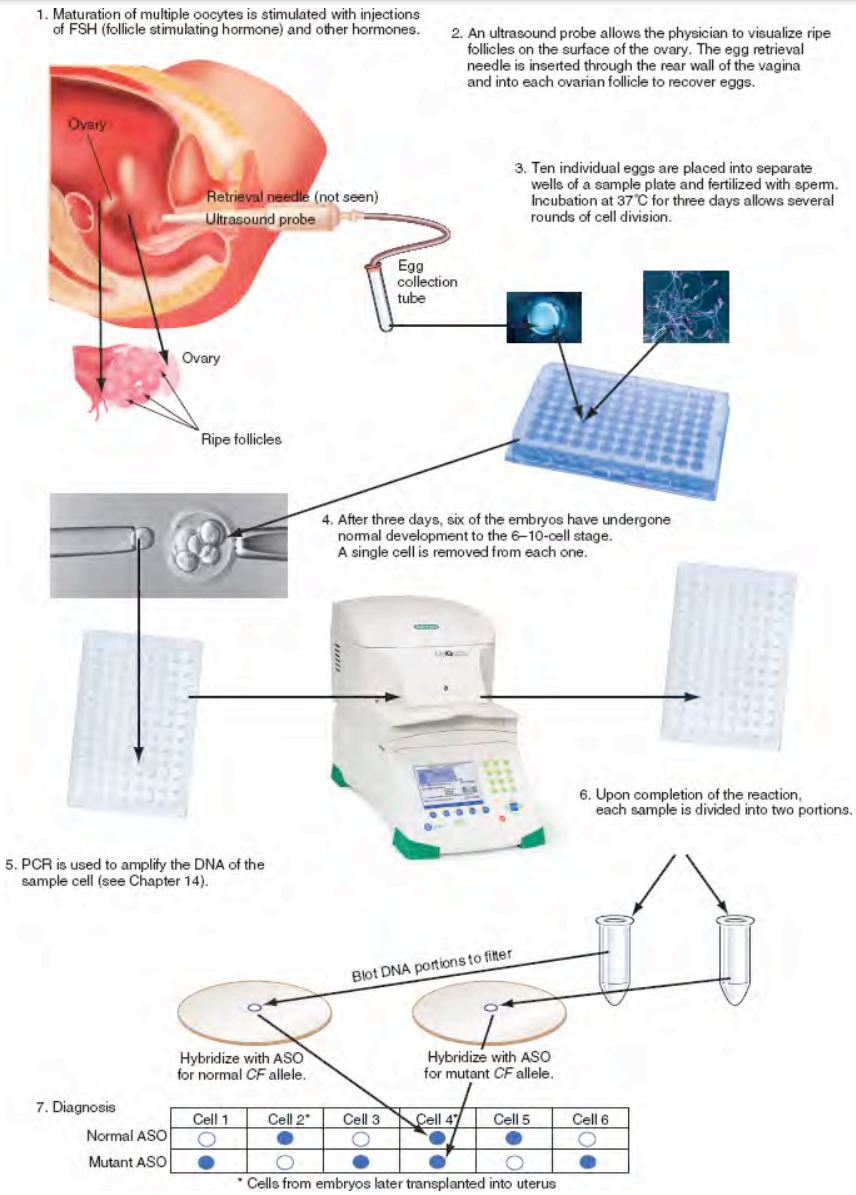
**Hartwell, Canadian ed., Fig. A, p. 76; Lewis (2007) Human Genetics**

# Fetal testing (cont)

- Look for abnormal karyotypes use PCR to look for chromosomal or genetic defects
- Possible to screen for biochemical and molecular disorders
- Tests are done in combination with blood tests for certain fetal proteins and maternal hormones, and with ultrasound tests

There is also in vitro fertilization (IVF) to deal with infertility issues.

# Preimplantation embryo diagnosis




- Screen for mutant alleles prior to implantation
- First used for CF allele (cystic fibrosis)

Soon we can do whole genome sequencing (within our life time). It's not available at the moment because it's still too expensive.

**Hartwell *et al.*, Canadian ed., Fig. 15.1**

# Ethical considerations

- Which genetic variants should be screened?
- Who should have access?
- Should parents have the right to make any genetic decision? Parents get to make decision of the embryo lives or not, if found with genetic defect? At what age of the embryo?
- Who should have access to test results?

# Ethical considerations

Down syndrome should not be the obstacle of living a long and fulfilling life.

**Hartwell *et al.*, Canadian ed., Fig. 3.1**