# Mutations

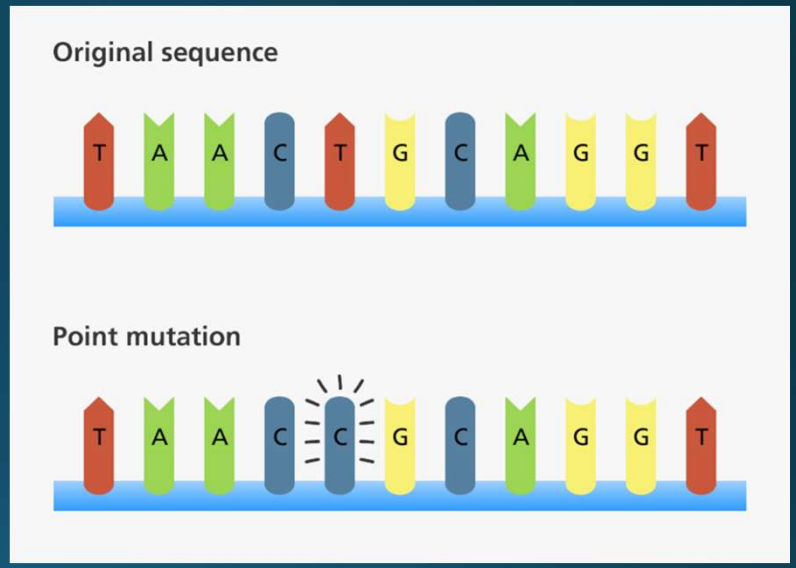
- **Mutation** permanent change to a cell's DNA

- Mutations that occur in the body cells are called ***somatic cell mutations***.
- Mutations that occur in reproductive cells are called ***germ line mutations***.

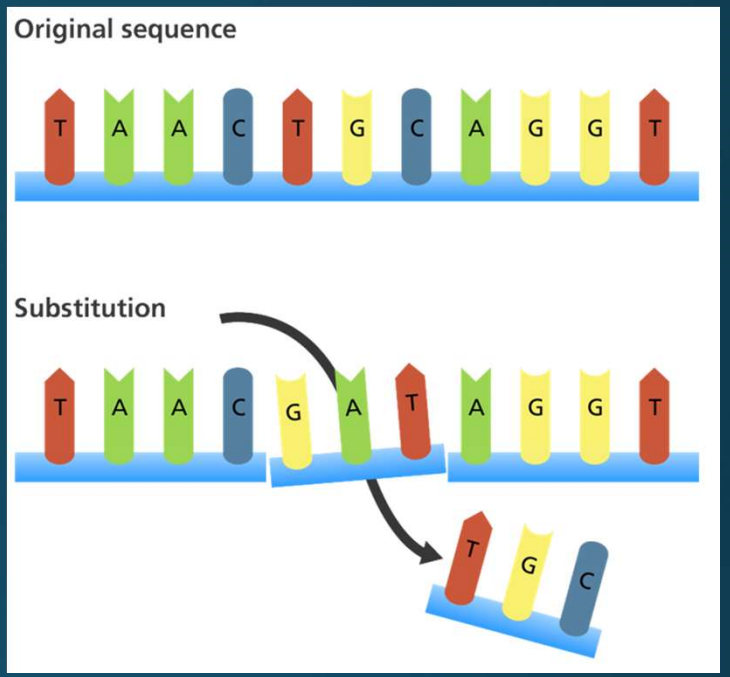
# Types of Mutations

- **point mutation** substitution, insertion, or deletion of one or very few nucleotides

- **A change in the coding sequence of a gene does not always result in a change to the polypeptide product of the gene.**
- For example, a change in the DNA coding strand sequence from **CCT to CCC** will not alter the polypeptide produced, since the associated **mRNA codons (GGA and GGG)** both code for the same amino acid, **glycine.**

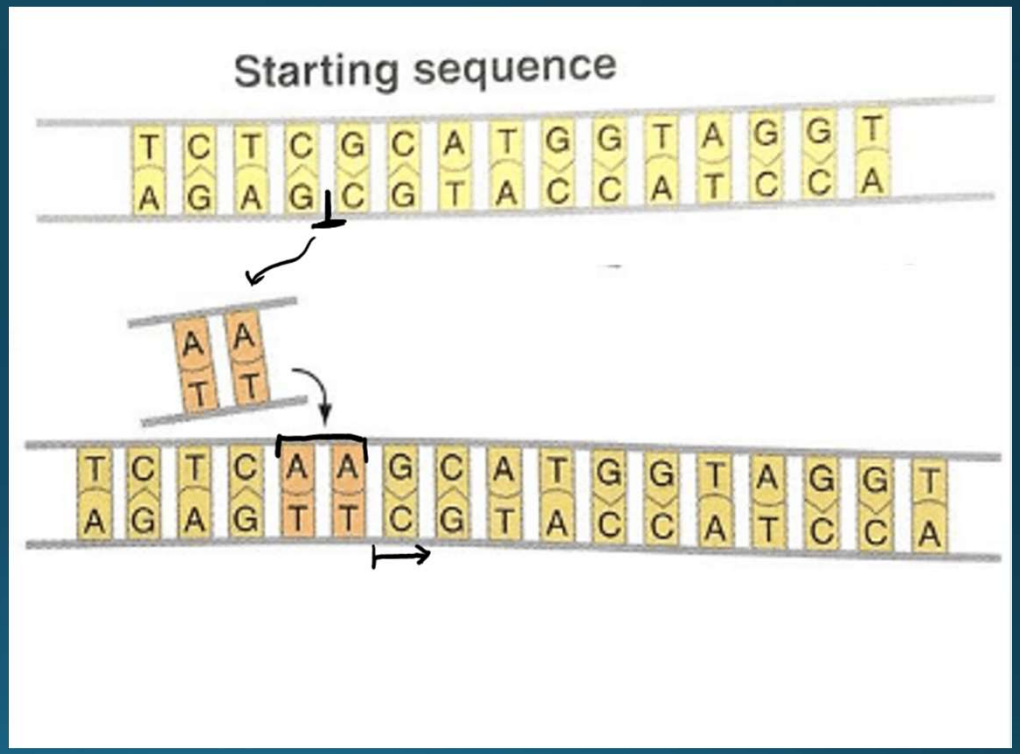


- **Substitution**
- Can be one nucleotide or several.

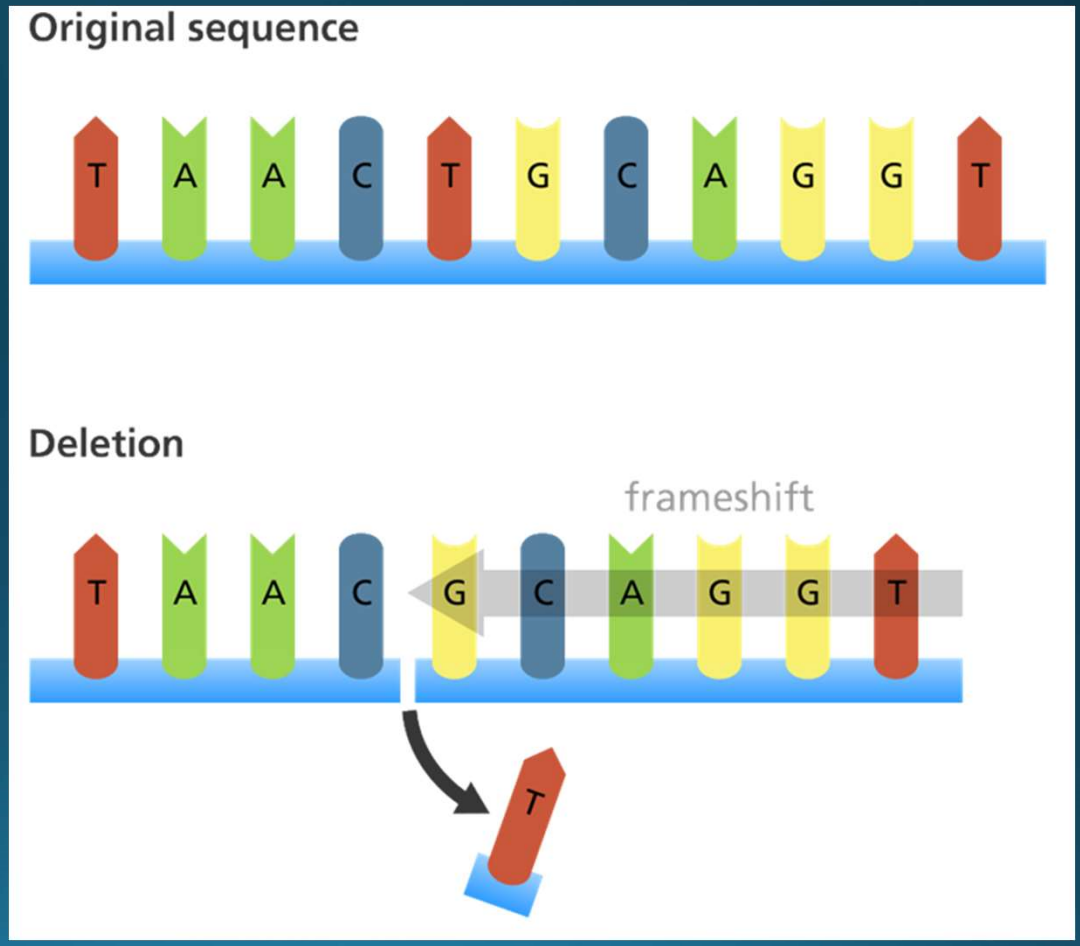



| | |
|---|---|
| Normal | ...GCTATACGCTAGG... |
| Base pair substitution | ...GCTATTCGCTAGG... ↓ G |

- **Insertion**
- An extra nucleotide or several are inserted into the DNA sequence

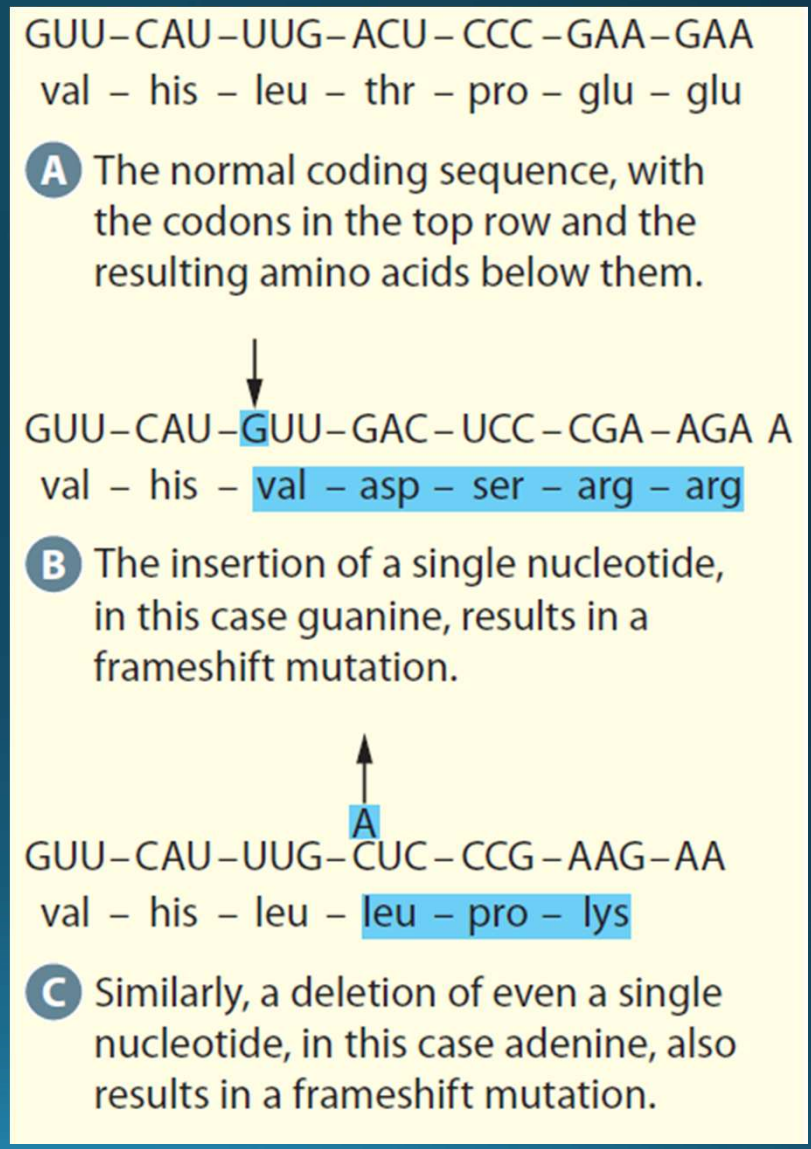


- **Deletion**
- A nucleotide or several are deleted from a DNA sequence



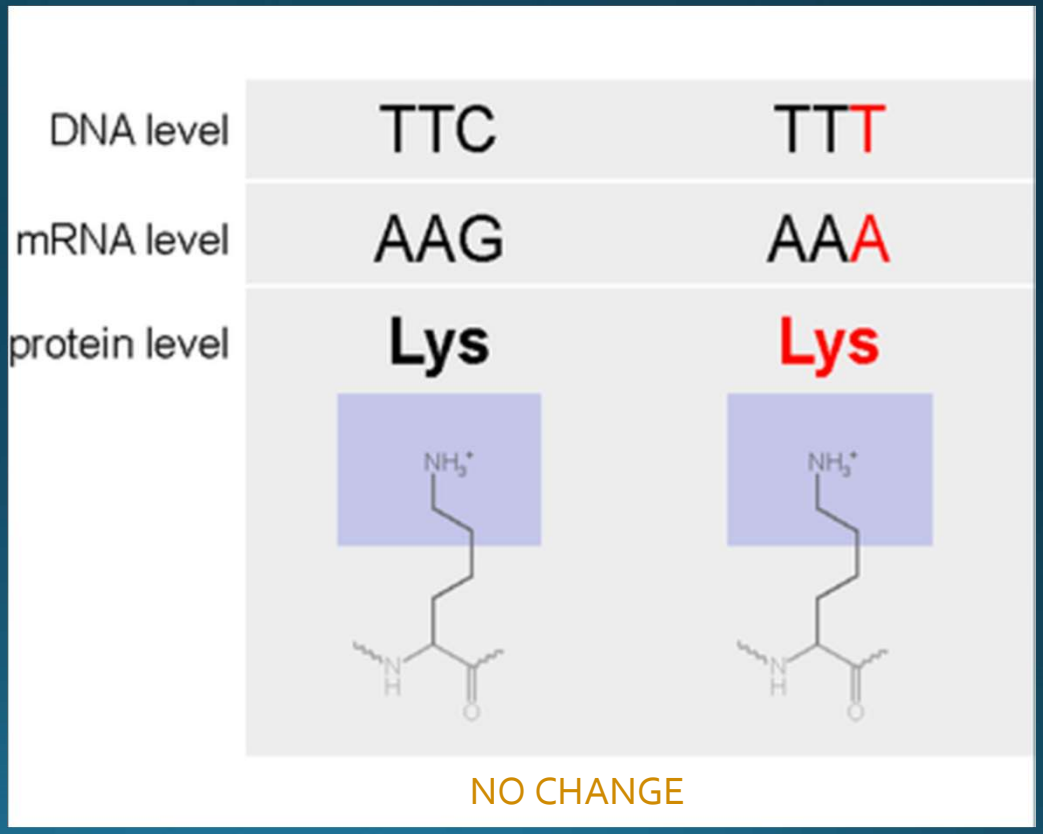
- **frameshift mutation** insertion or deletion that results in a change to the reading frame of a gene
- A frameshift mutation causes the entire reading frame of the gene

Frameshift mutations may be caused by nucleotide insertion or deletion.



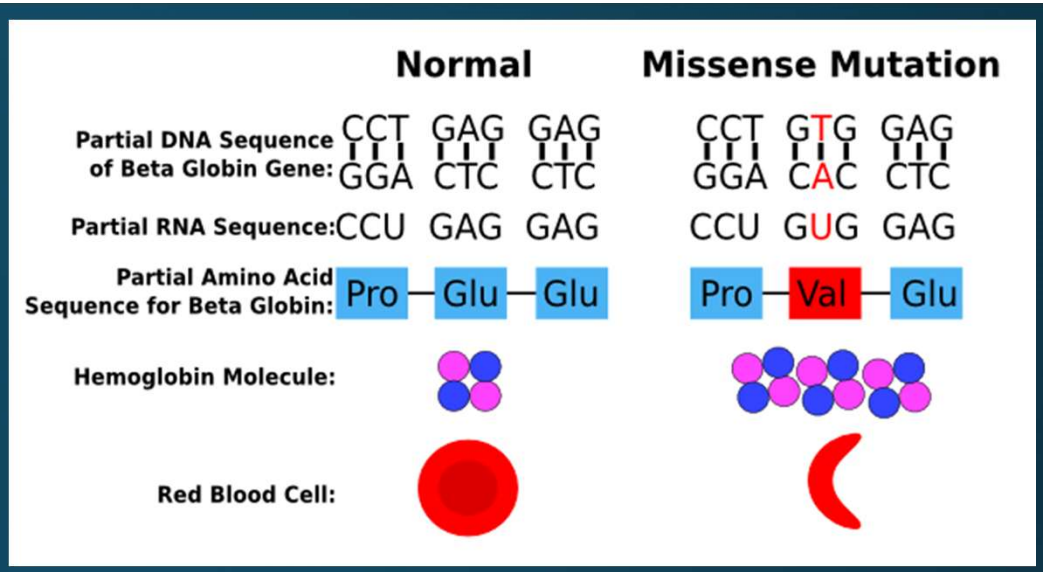
- **silent mutation** has no effect on a cell

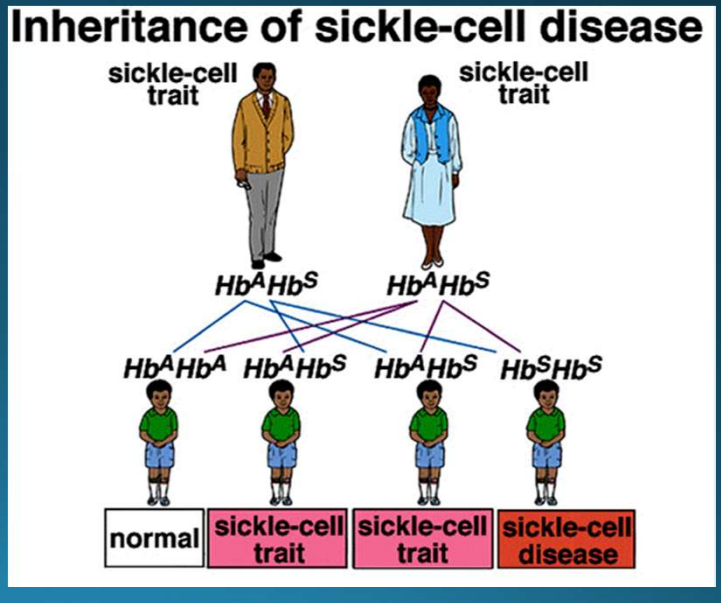
- Even when a point mutation involves the substitution of one amino acid for another, this substitution may not have a significant effect on the final structure or function of the polypeptide produced.



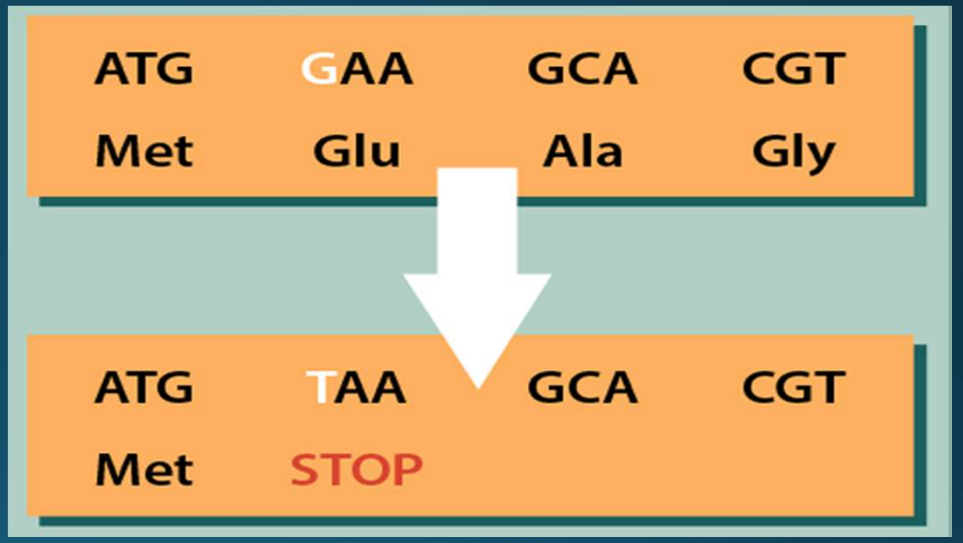
- **mis-sense mutation** mutation that results in an altered but functional protein

- Mis-sense mutations can be harmful.
- A change in a single amino acid in one of the polypeptides that makes up hemoglobin is responsible for the genetic blood disorder known as **sickle cell disease.**
- **Sickle cell is hereditary and can be passed on from one generation to the next**



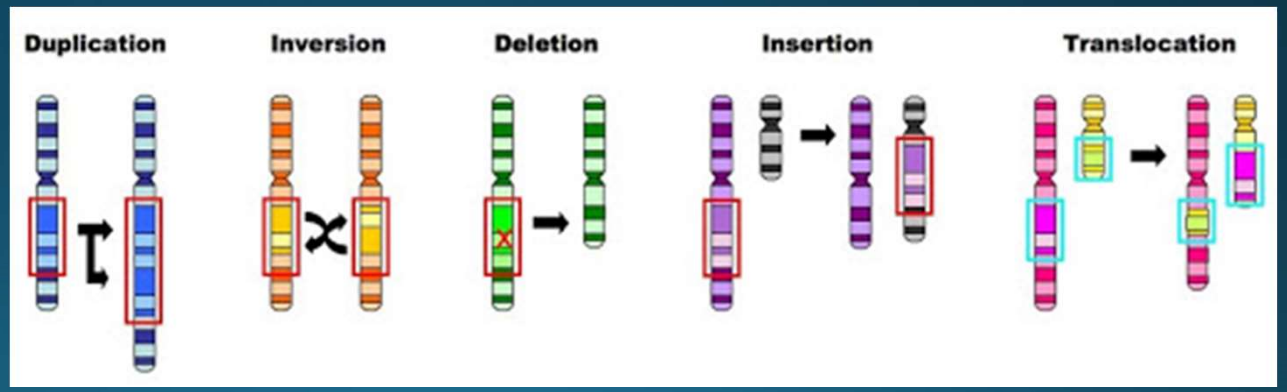
- **nonsense mutation** results in loss of production of a protein
- some substitutions can have severe consequences. If a change in a gene's coding sequence deletes a start signal or results in a premature stop signal, the gene may be unable to produce a functional protein.
- Similarly, a nucleotide substitution that affects a *regulatory sequence* may result in the cell being unable to respond properly to metabolic signals.



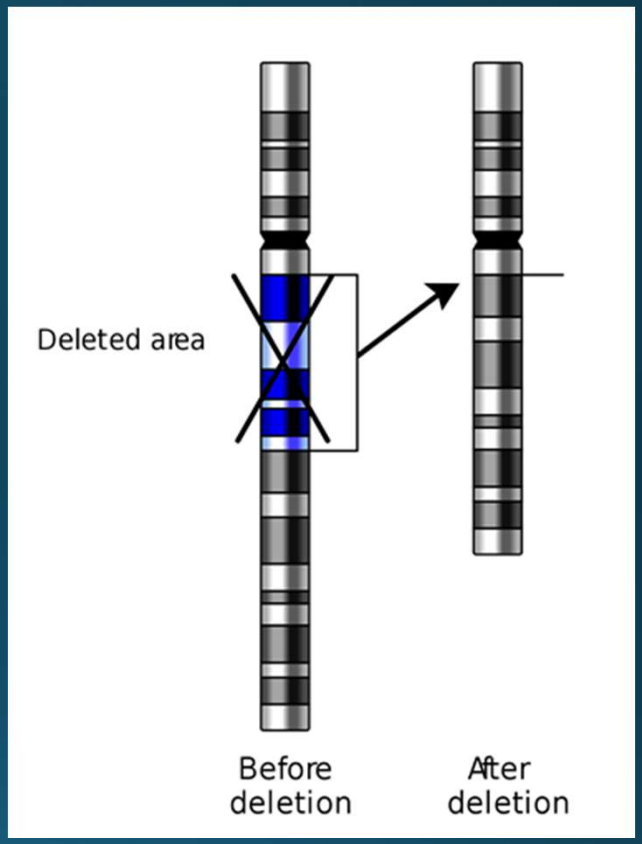
- Worksheet - Mutations

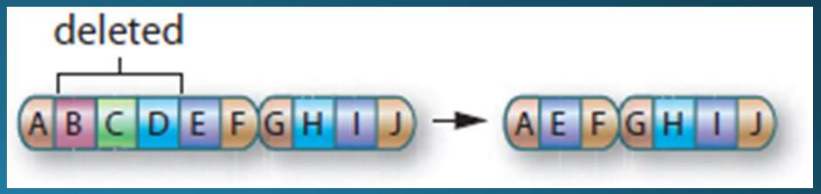
- Exit Card #11

- **Chromosomal Mutations** is the change in the chromosomes as a result of rearranged chromosome parts or changes in the number of individual chromosomes present in the genome.
- Mutations that involve a rearrangement of genetic material.
- These may affect several genes, including genes located on different chromosomes.
- Duplication
- Inversion
- Deletion
- Insertion
- Translocation



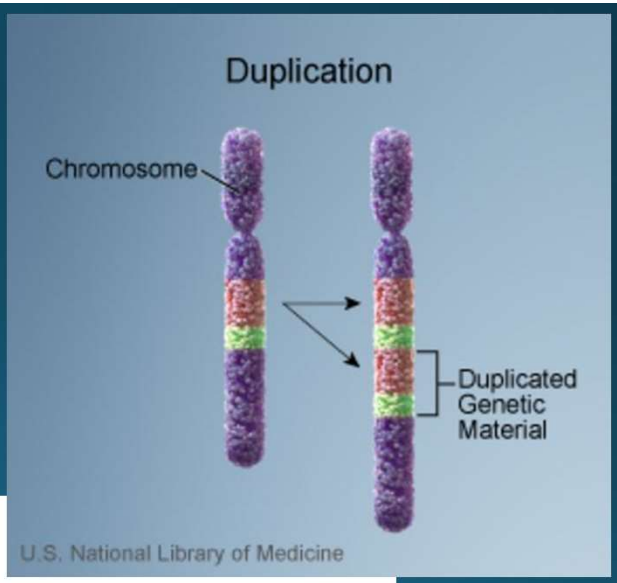
- **Chromosomal Deletion**
- When a section of a chromosome is deleted
- They tend to cause birth defects and limited intellectual development and physical development. In some cases, defects can be severe and affected children die during infancy or childhood.
- **Cri du Chat syndrome is caused by a deletion in chromosome 5.**

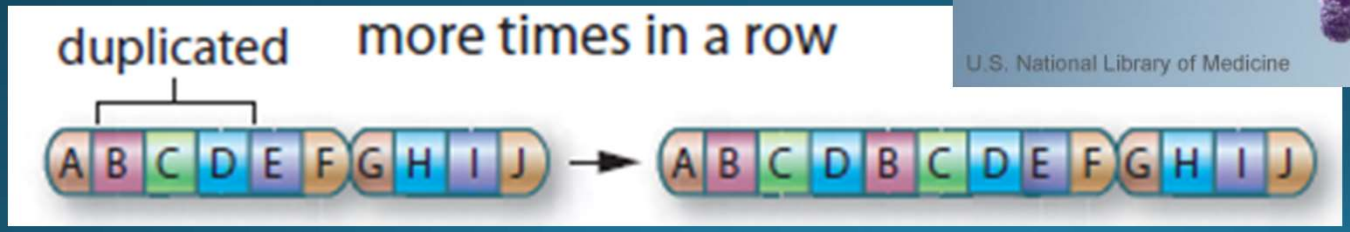


- **Chromosome Duplication**
- is a type of mutation that involves the production of one or more copies of a gene or region of a chromosome.
- a section of a chromosome appears two or more times in a row

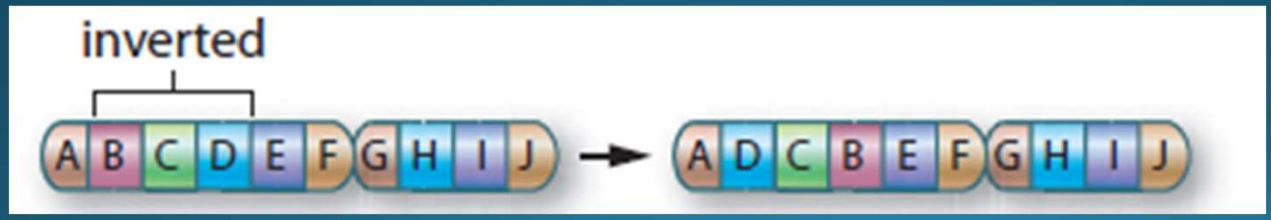
- **Most cases of Charcot-Marie-Tooth disease are caused by duplication of a gene on chromosome 17.**

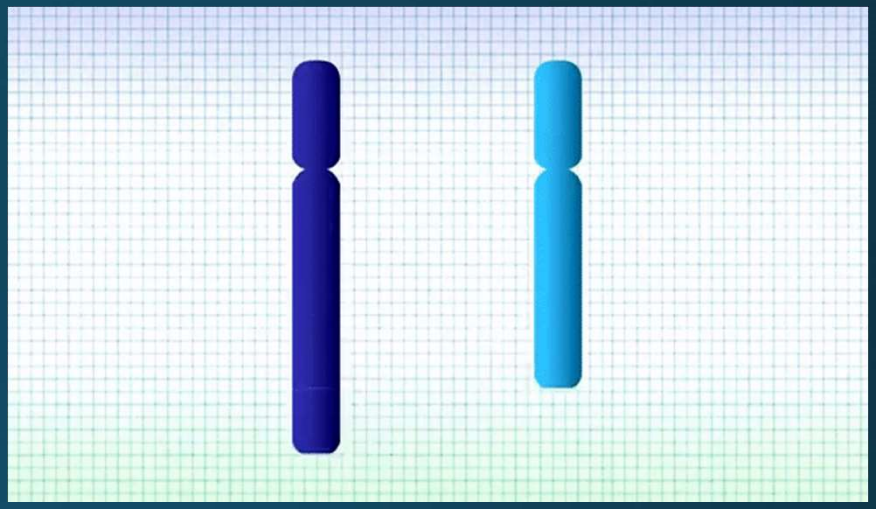



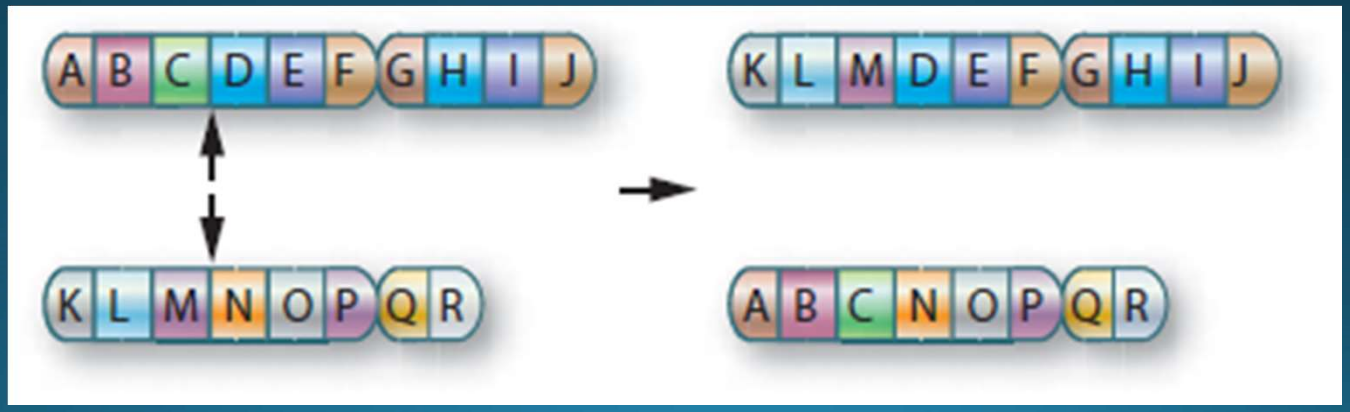
- **Chromosome Inversion**
- If two breaks occur in one chromosome, sometimes the region between the breaks rotates 180 degrees before rejoining with the two end fragments.
- a section of a chromosome is inverted

- **A form of FG syndrome is caused by the inversion of a section of the X chromosome.**

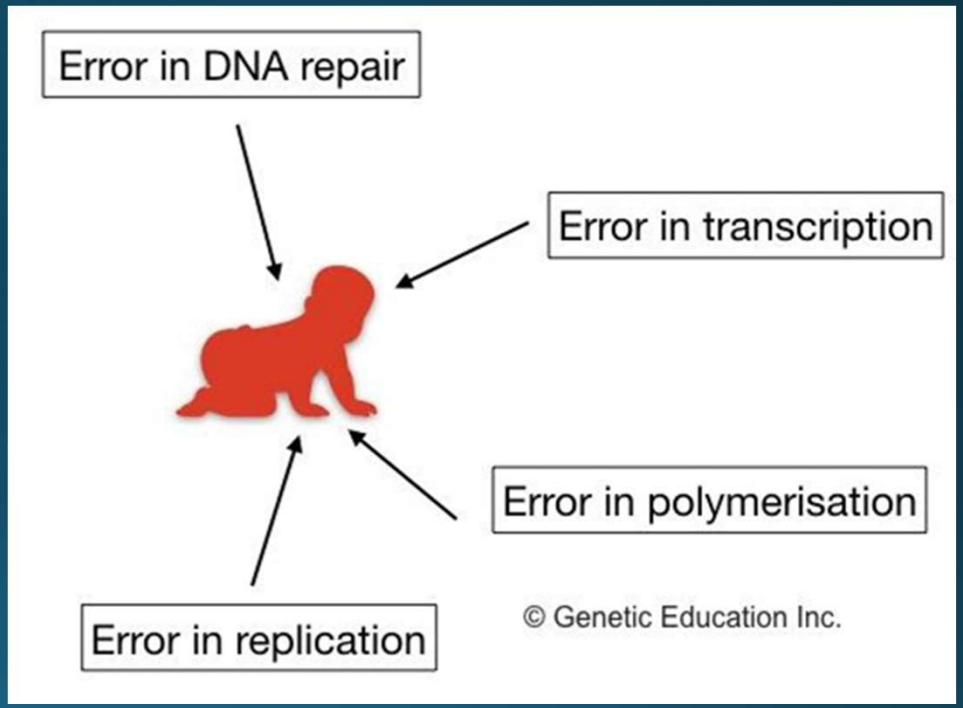
- **Chromosome Translocation**
- a segment of one chromosome becomes attached to a different chromosome
- Most cases of **chronic myelogenous leukemia (CML) are caused by a translocation between chromosomes 9 and 22.**



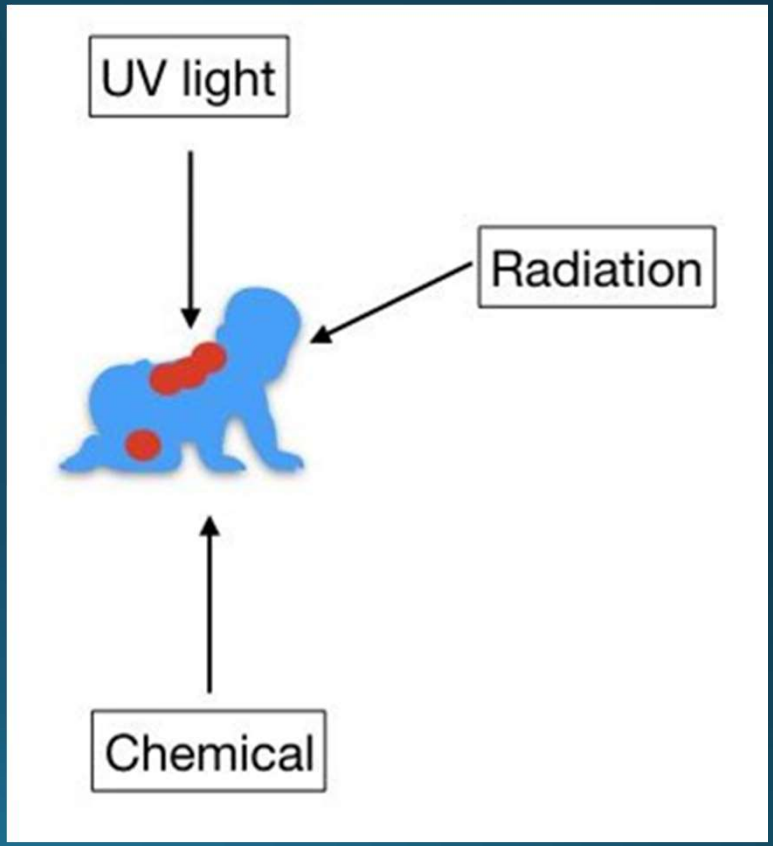


# What causes mutations?

- Many mutations are caused by molecular interactions that take place naturally within cells. These mutations are known as ***spontaneous mutations***.
- One source of spontaneous mutations is incorrect base pairing by DNA polymerase during the process of DNA replication.



- Mutations that are caused by agents outside the cell are said to be ***induced*.**
- **mutagen** causes an increase in mutation rate in an cell



# Physical Mutagens

- Mutagens that cause physical changes in the structure of DNA, they are known **as *physical mutagens*.**

- High-energy radiation, such as that from **X rays and gamma rays**, is the most damaging form of mutagen known. They tear through DNA molecules, causing random changes that range from point mutations to the loss of large portions of chromosomes.

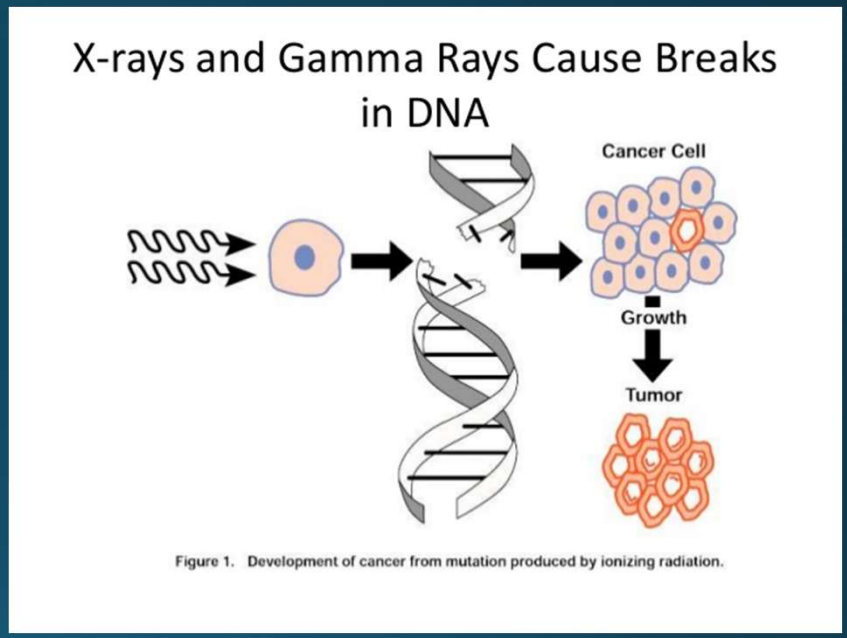
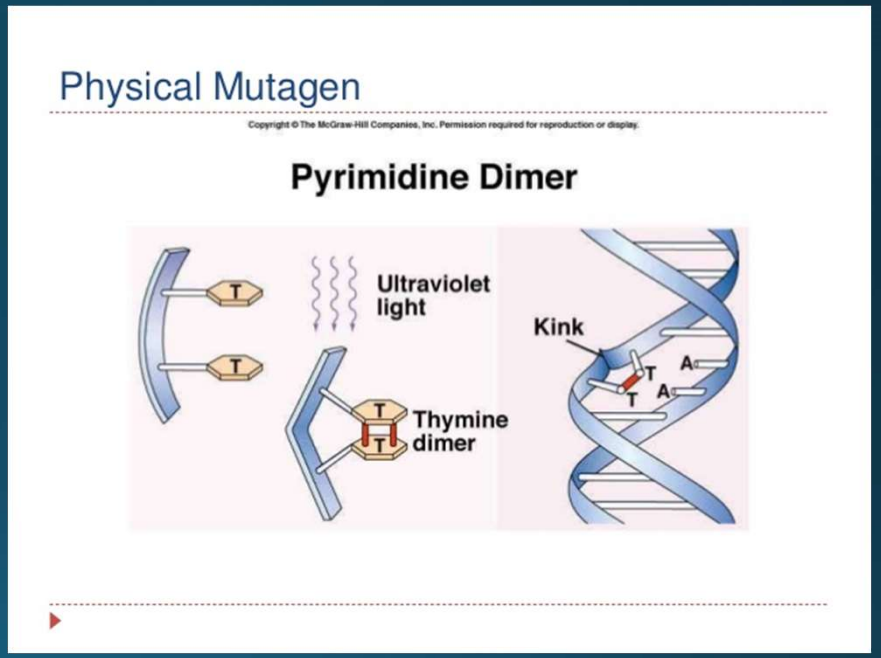


Figure 1. Development of cancer from mutation produced by ionizing radiation.

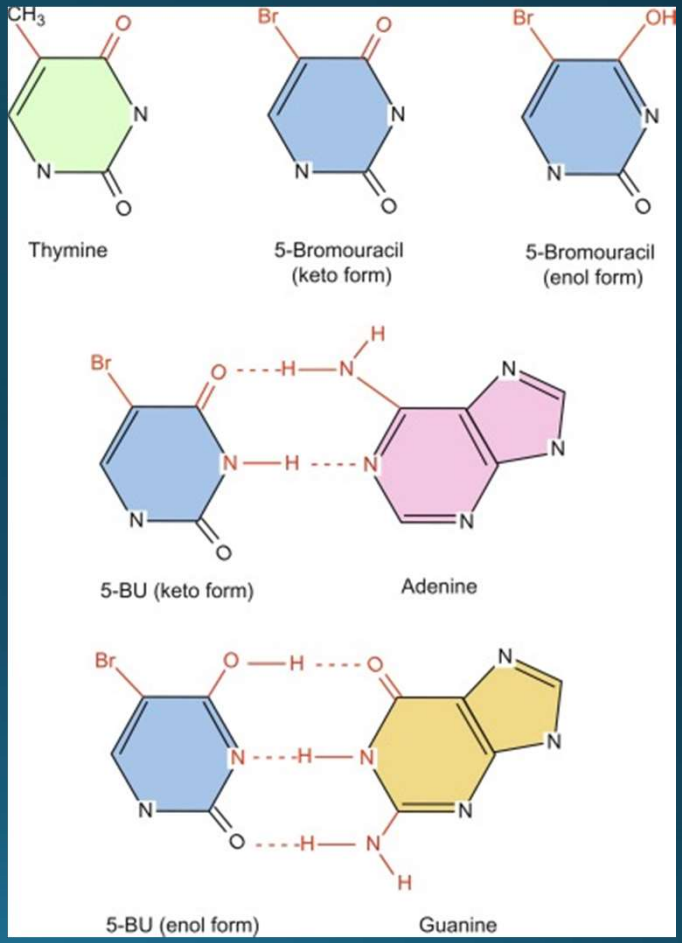
- **Ultraviolet (UV)** radiation, which is present in sunlight, has a lower range of energy levels than X rays, but it is still a powerful mutagen. UV radiation can cause a chemical reaction between **adjacent pyrimidine (C and T)** bases. The result is a distortion in the DNA molecule that interferes with replication.
- Damage from UV radiation, as a result of exposure to **sunlight**, is a known cause of **melanoma**, a form of skin cancer.
- A single sunburn doubles a light-skinned person's chances of developing skin cancer.



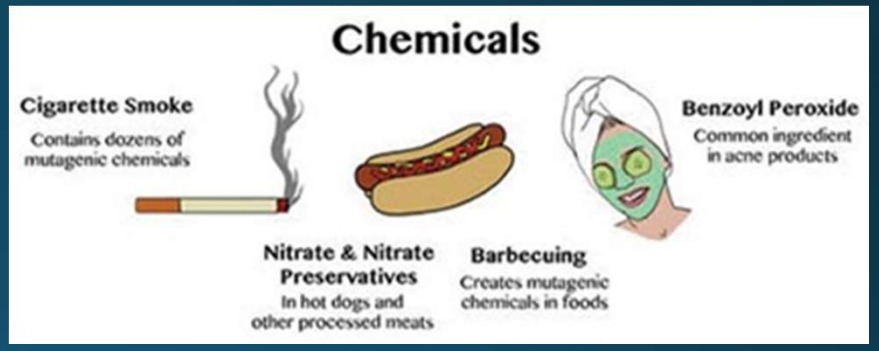
# Chemical Mutagens

- A ***chemical mutagen*** is a molecule that can enter the nucleus of a cell and induce mutations by reacting chemically with the DNA.

- A chemical mutagen may act by **inserting itself into the DNA molecule** in a manner that causes a nucleotide substitution or a frameshift mutation.



- Other chemical mutagens have a structure that is **similar to the structure of ordinary nucleotides but with different base-pairing properties**. When these mutagens are incorporated into a DNA strand, they can cause incorrect nucleotides to be inserted during DNA replication.
- Examples of chemical mutagens include **nitrites** (which are sometimes used as a food preservative), **gasoline fumes**, and more than **50 different compounds found in cigarette smoke.**



- Most chemical mutagens are carcinogens
- **carcinogen** cancer-causing agent

- Cancer is the result of somatic cell mutations that disrupt the expression of genes involved in the regulation of the cell cycle. While carcinogens are present throughout the environment, personal choices can increase or decrease a person's risk of developing cancer.

# CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

THIS GRAPHIC OFFERS A SUMMARY OF A SELECTION OF HAZARDOUS COMPOUNDS IN CIGARETTE SMOKE & THEIR EFFECTS

**ESTIMATED NUMBER OF CHEMICAL COMPOUNDS IN CIGARETTE SMOKE**

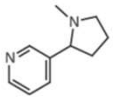
**7,357**

**70**

**NUMBER OF THESE COMPOUNDS WITH CONFIRMED CARCINOGENIC ACTIVITY**

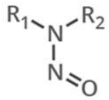
The compounds shown below are all found in cigarette smoke. The mass figures, given in µg, take into account both mainstream (inhaled) and sidestream smoke. 1 µg is equal to 1 millionth of a gram. Amounts of these compounds vary in different brands of cigarettes - these figures are approximate.

## NICOTINE



- Approx. 919µg per cigarette
- Addictive
- Increases heart rate
- Increases blood pressure
- Increases blood glucose
- Lethal dose: around 500-1000mg

## N-NITROSAMINES

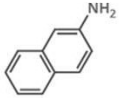


- Large class of compounds
- Several are tobacco-specific
- **Known human carcinogens**
- Most carcinogenic: NNK & NNN
- NNK: approx. 0.3µg per cigarette
- NNN: approx. 2-50µg per cigarette
- May cause reproductive damage

## BENZENE

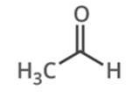
- Approx. 46-272µg per cigarette
- **Known human carcinogen**
- Damages bone marrow
- Lowers red blood cell count
- May harm reproductive organs

## AROMATIC AMINES



- Large class of compounds
- Includes 2-aminonaphthalene:
  - **Known human carcinogen**
  - Linked with bladder cancer
  - Approx. 0.04µg per cigarette

## ACETALDEHYDE

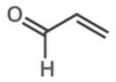


- Approx. 680-1571µg per cigarette
- **Known animal carcinogen**
- **Probable human carcinogen**
- Irritant to skin & eyes
- Irritant to respiratory tract

## 1,3-BUTADIENE

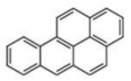
- Approx. 36-191µg per cigarette
- **Known human carcinogen**
- **Suspected human teratogen**
- Irritant to eyes & skin
- Irritant to upper respiratory tract

## ACROLEIN



- Approx. 69-306µg per cigarette
- **Possible human carcinogen**
- **Known DNA mutagen**
- Irritant to skin & nasal passages
- May contribute to heart disease

## POLYAROMATICS



- Large class of compounds
- Includes benzo[a]pyrene:
  - **Known human carcinogen**
  - **Known DNA mutagen**
  - Affects reproductive capacity
  - Up to 0.14µg per cigarette

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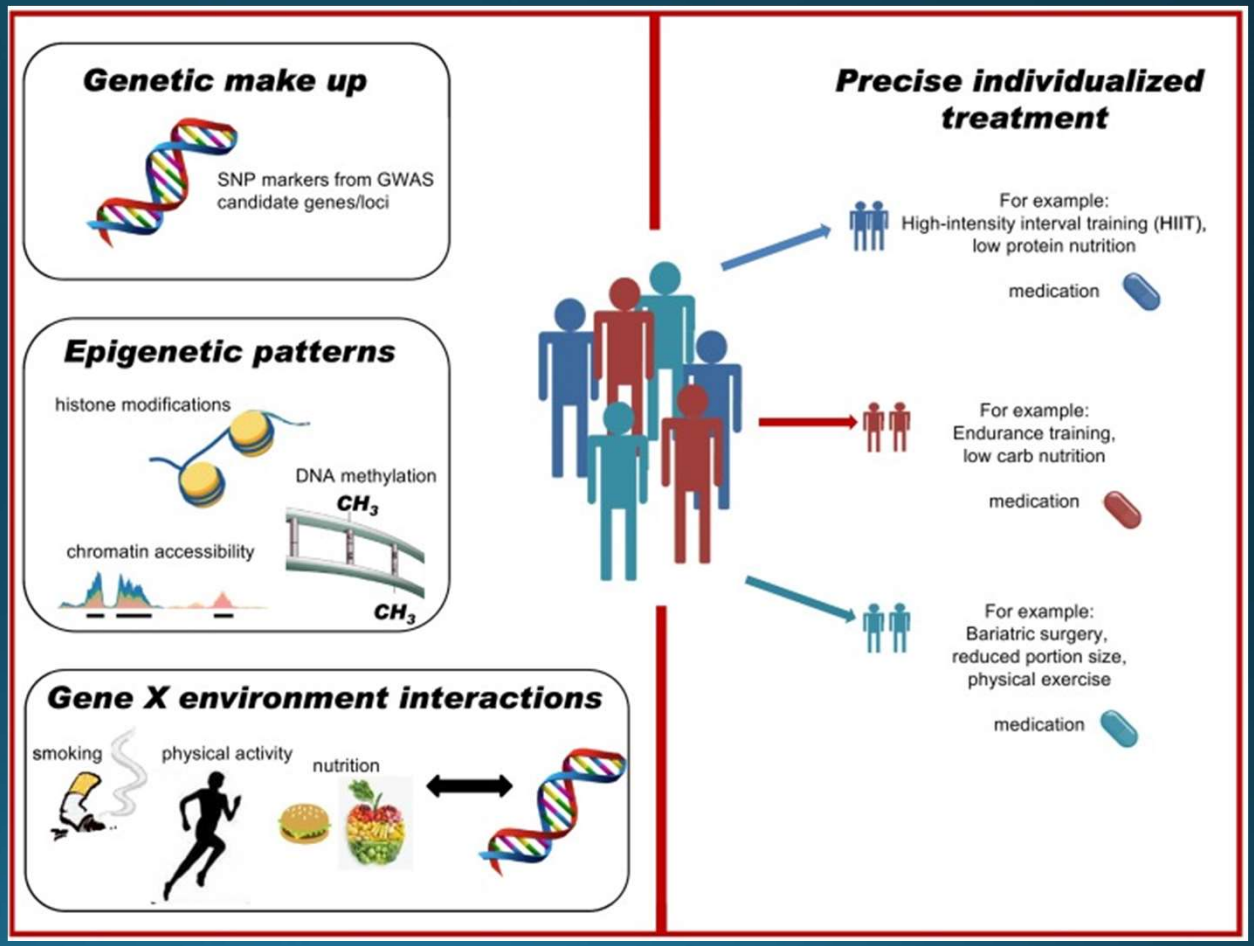
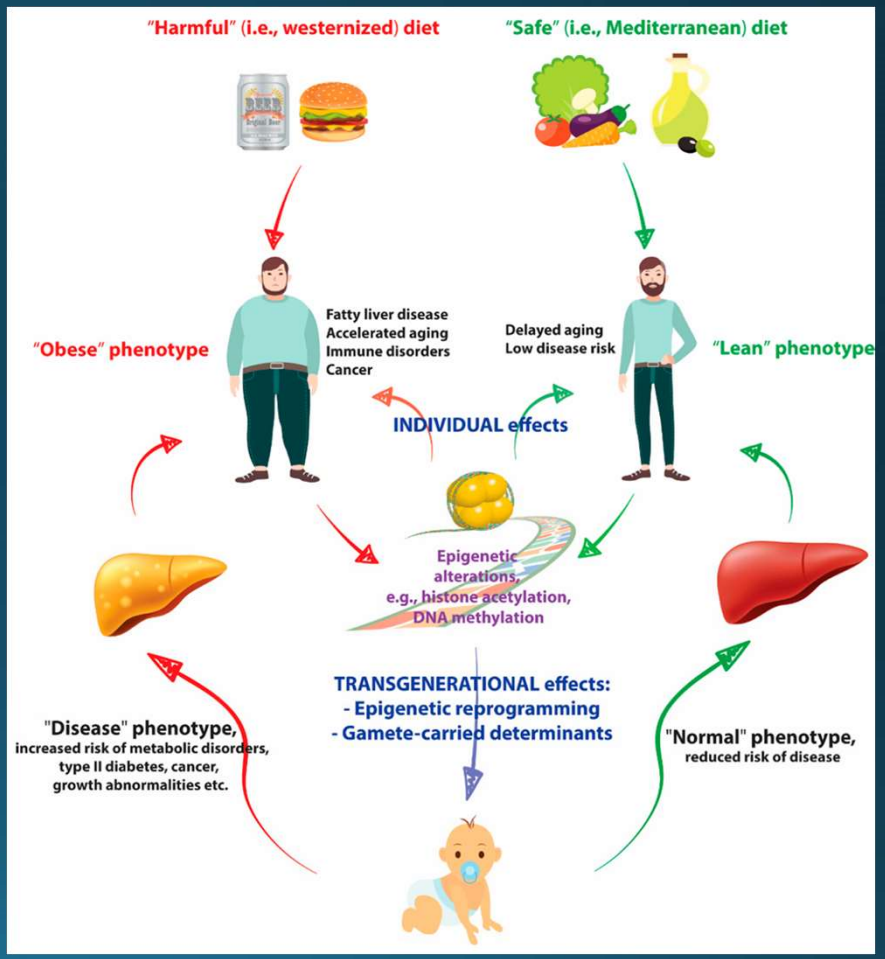
- **Epigenetics** is the study of how your behaviors and environment can cause changes that affect the way your genes work.
- Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence.

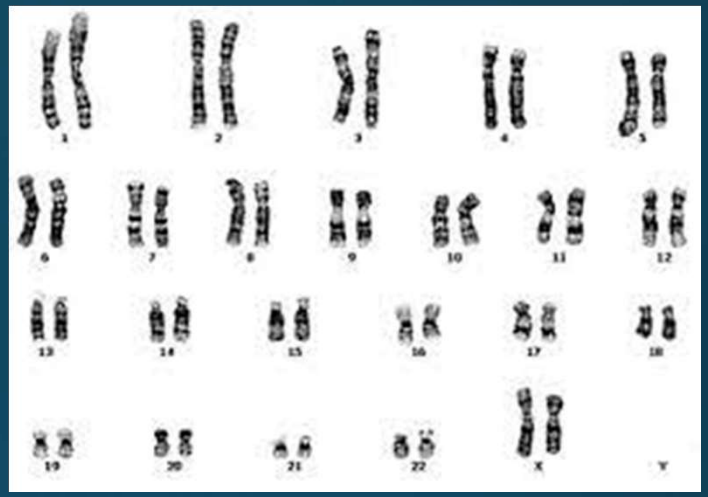


- Gene expression refers to how often or when proteins are created from the instructions within your genes. While genetic changes can alter which protein is made, epigenetic changes affect gene expression to **turn genes "on" and "off."**
- Since your environment and behaviors, such as **diet and exercise**, can result in epigenetic changes, it is easy to see the connection between your genes and your behaviors and environment.

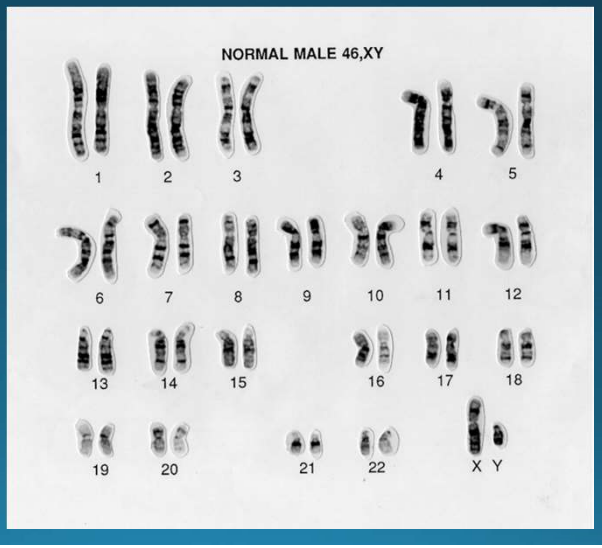


# Genetic Disorders Due to Chromosomal Changes

- **karyotype** an individual's set of chromosomes; often represented as a photo

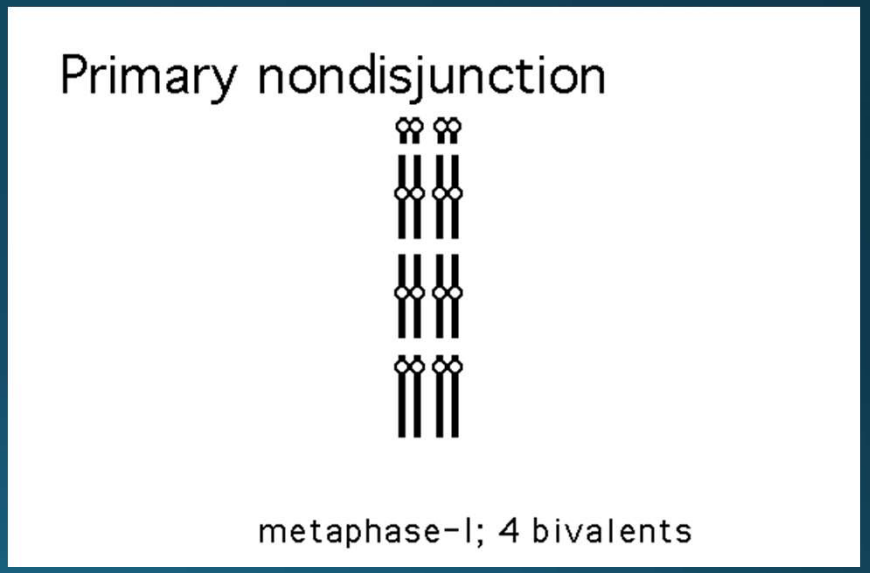


- XX = Female
- XY = Male

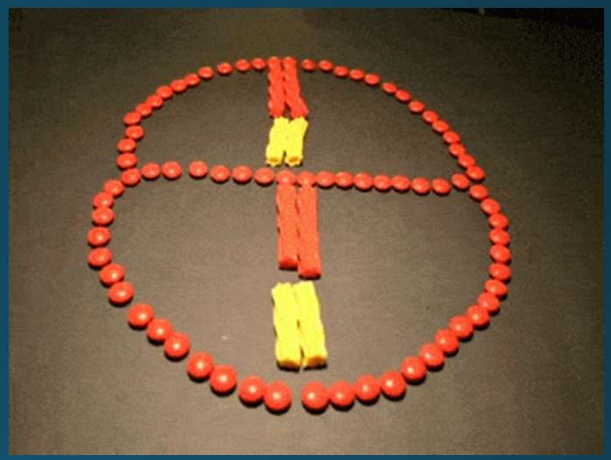


- **nondisjunction** failure of homologous chromosomes or sister chromatids to separate in meiosis

- Genetic disorders that result from an incorrect number of chromosomes are often due to an error that occurs during **Anaphase of meiosis.**



- Nondisjunction can occur in **anaphase I and II of meiosis.**
- In anaphase I, nondisjunction occurs when homologous chromosome pairs do not separate to opposite poles; instead, one entire pair is pulled toward the same pole together.
- In anaphase II, nondisjunction occurs when sister chromatids do not separate to opposite poles; instead, both sister chromatids are pulled toward the same pole together.



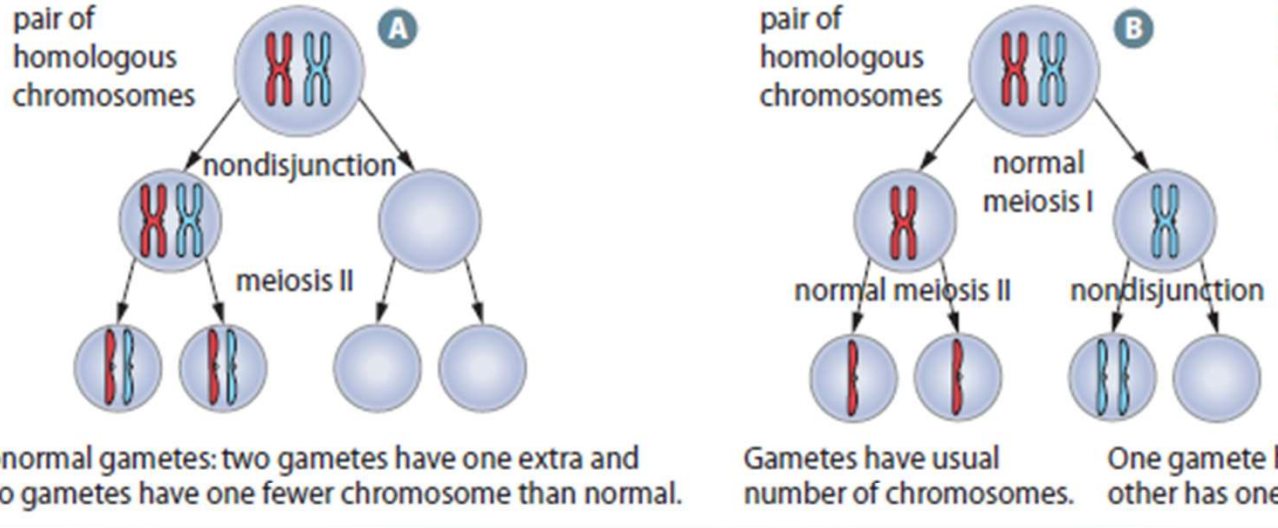
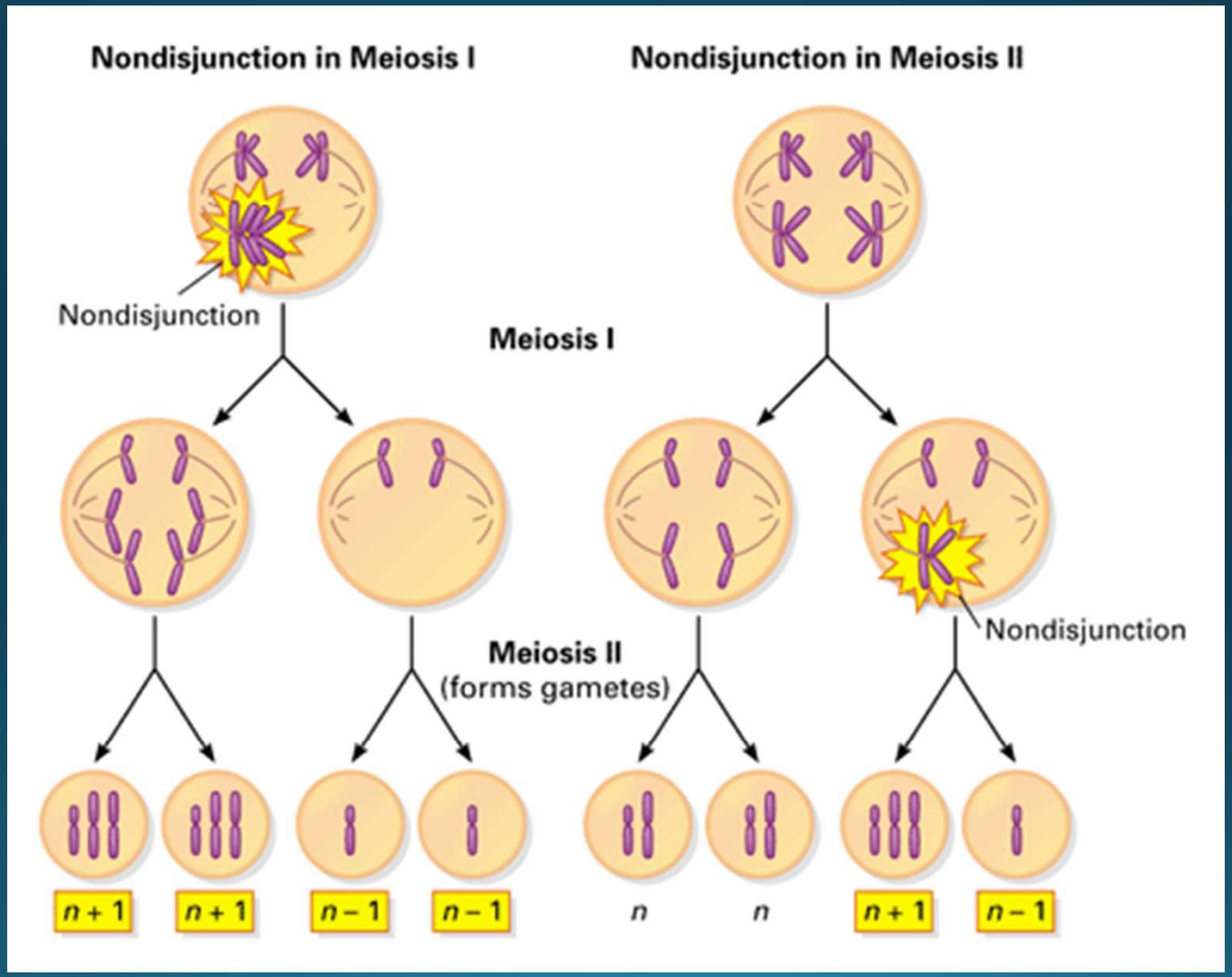


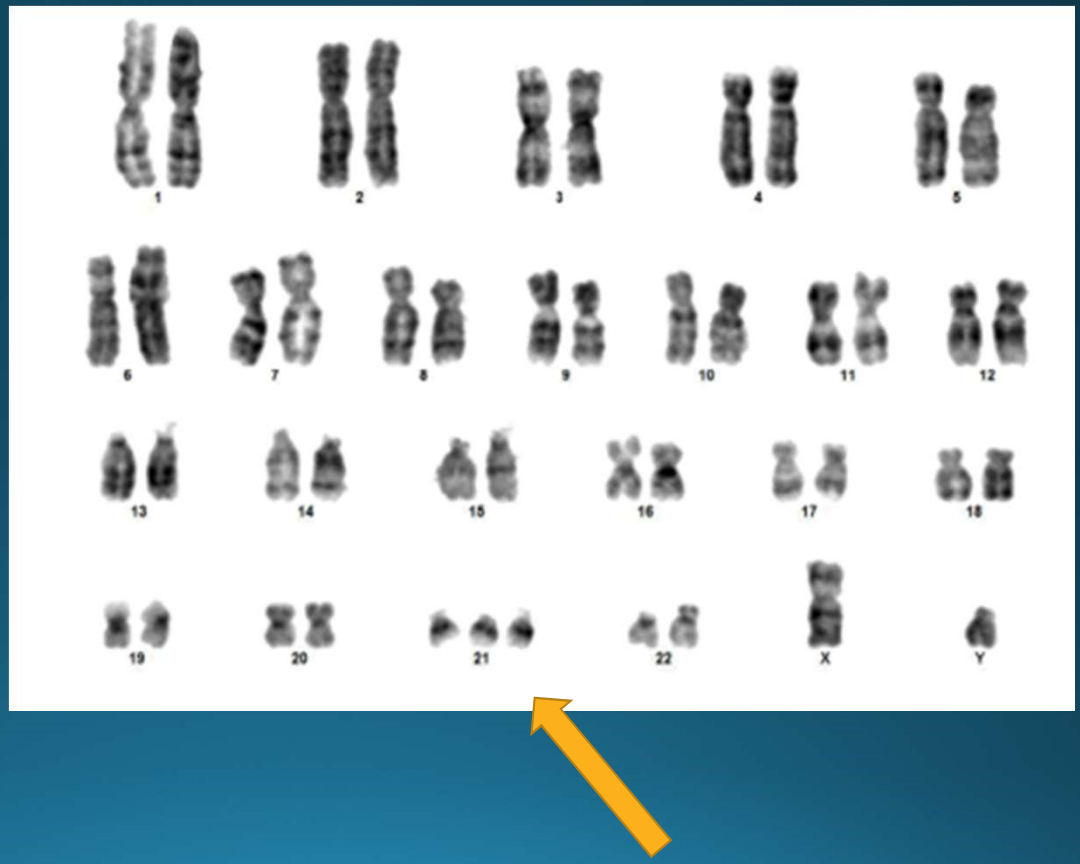

**Figure 14.30**
Nondisjunction may take place during anaphase I (**A**) or anaphase II (**B**).


Nondisjunction in Meiosis I
Nondisjunction in Meiosis II
Nondisjunction
Meiosis I
Meiosis II
(forms gametes)
Nondisjunction
n + 1
n + 1
n – 1
n – 1
n
n
n + 1
n – 1

# Down Syndrome

- What is wrong with this Karyotype?

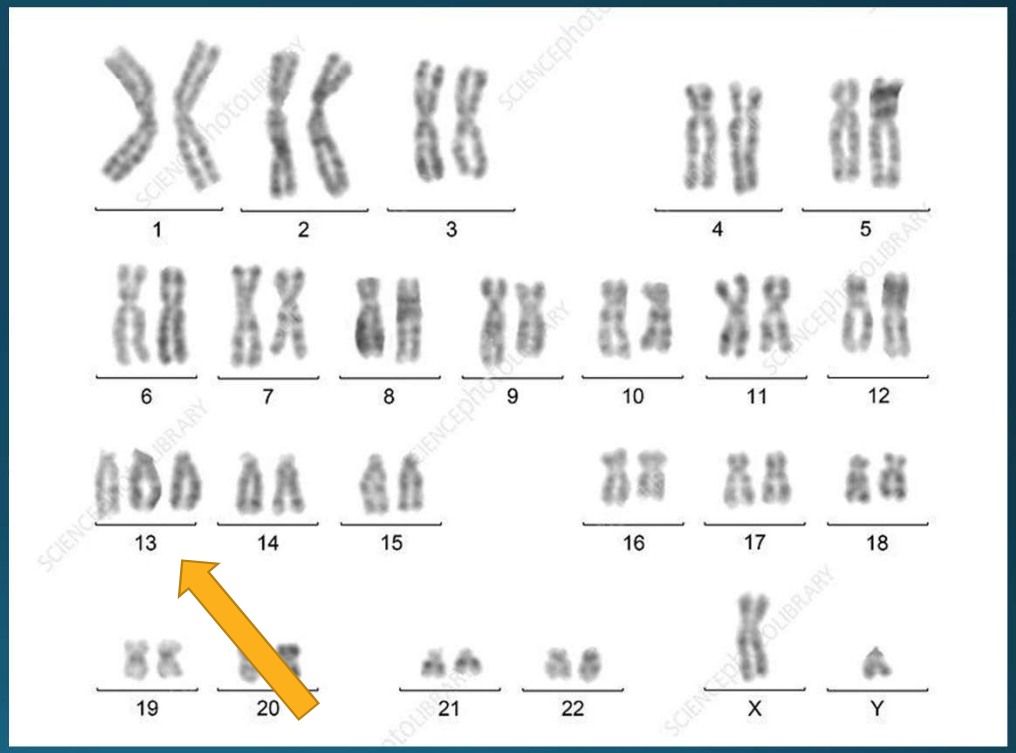
Three copies of chromosome 21
**trisomy 21**



# Patau Syndrome

- What is wrong with this Karyotype?

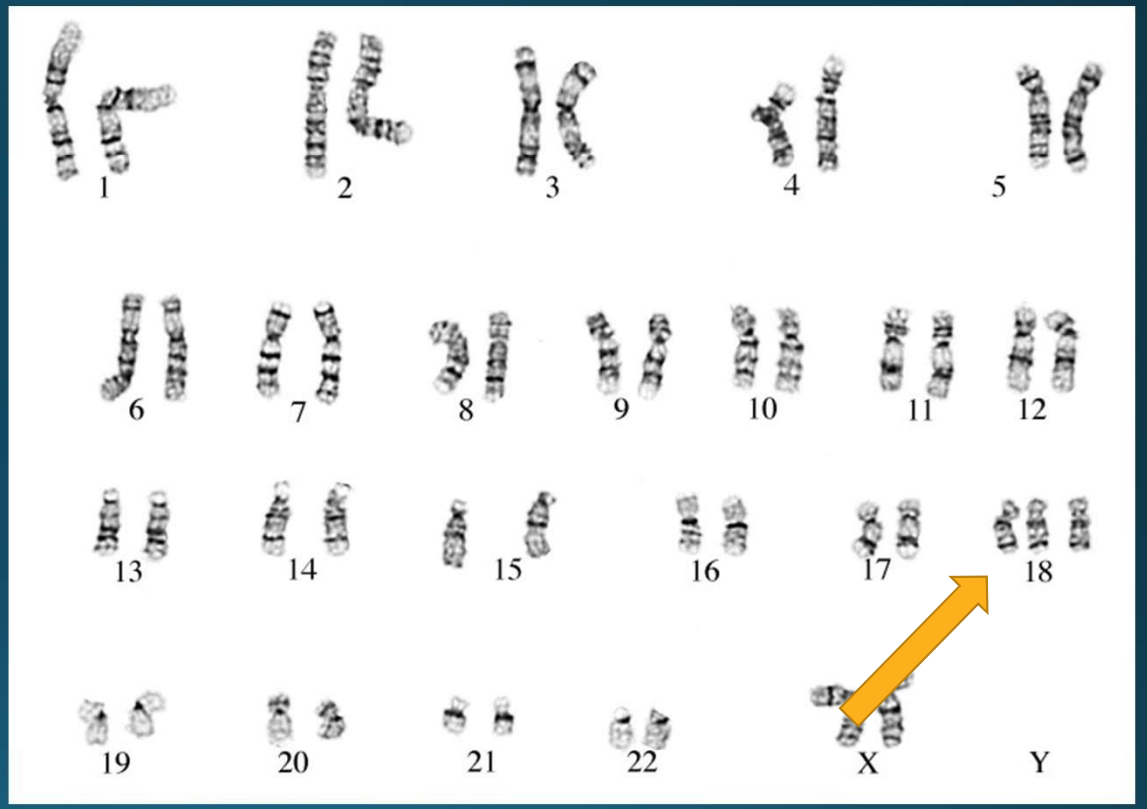
Three copies of chromosome 13
**trisomy 13**



# Edward Syndrome

- What is wrong with this Karyotype?

Three copies of chromosome 18
**trisomy 18**



# Turner Syndrome

- What is wrong with this Karyotype?

Only one sex chromosome
a single X
**Monosomy X**

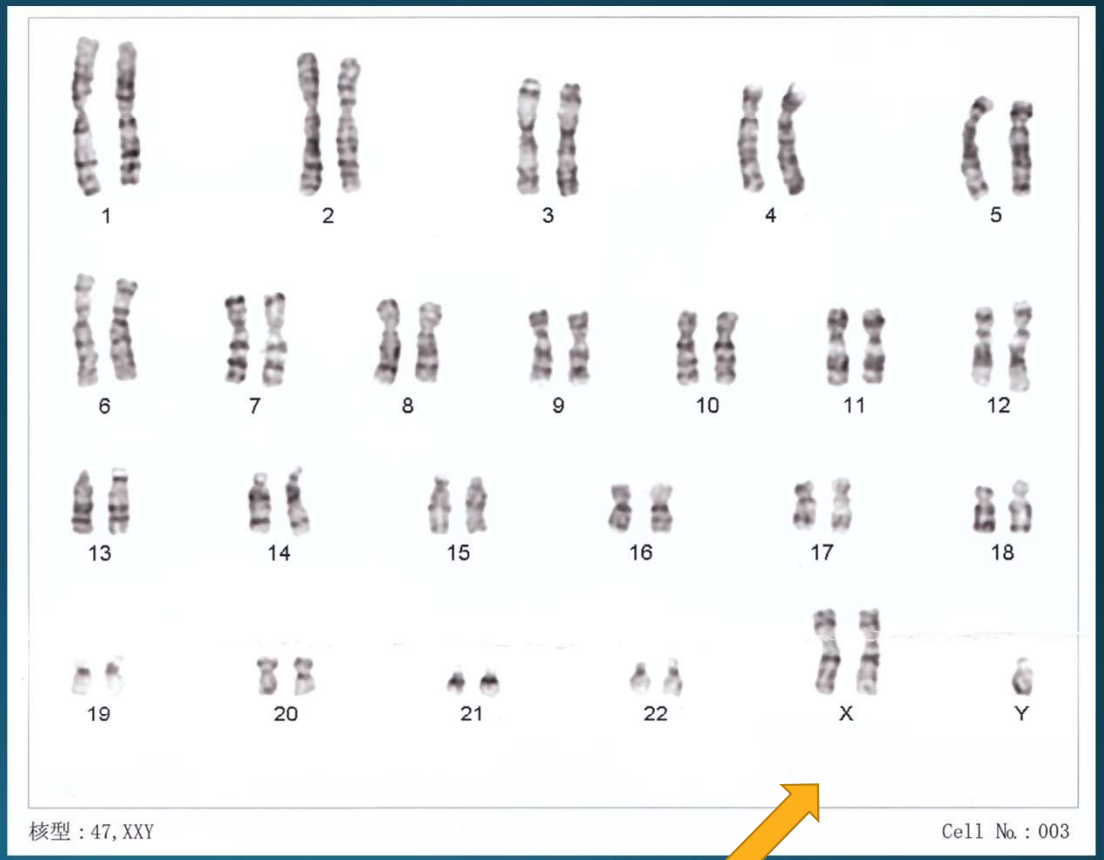
# Klinefelter Syndrome

- What is wrong with this Karyotype?

Two copies of the X chromosome and one copy of the Y

**A form of trisomy**

**XXY**



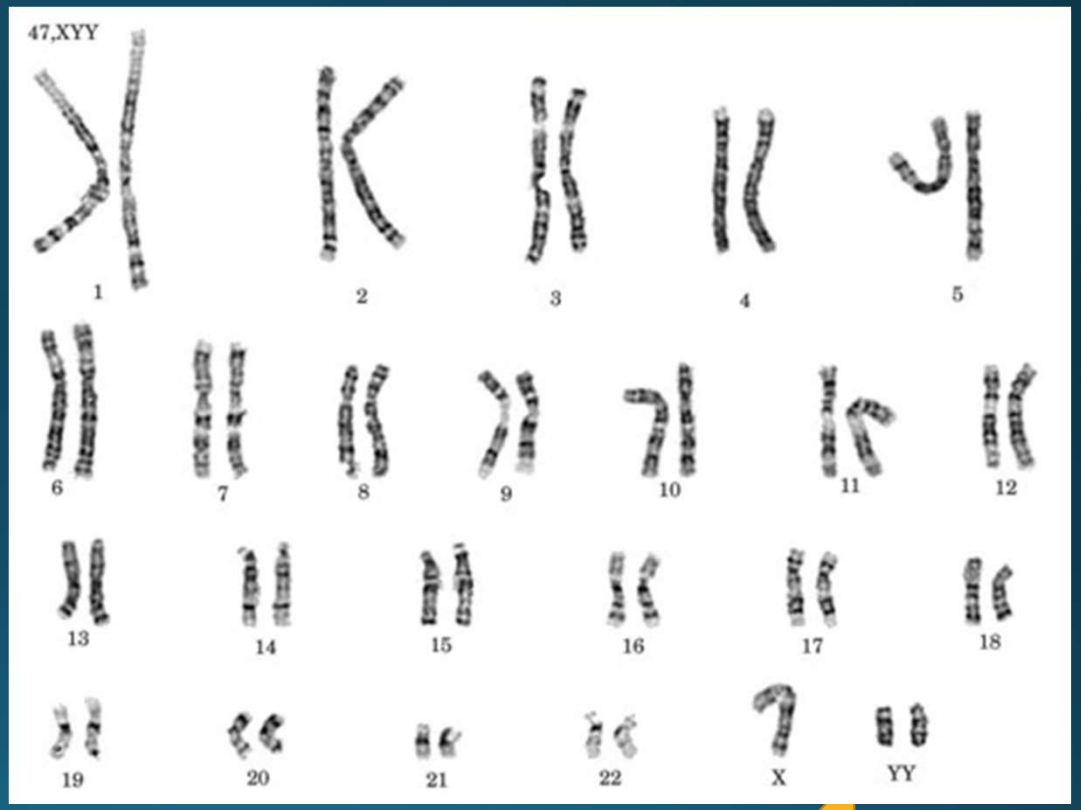
# XYY Syndrome

- What is wrong with this Karyotype?

Two copies of the Y chromosome and one copy of the X

**A form of trisomy**

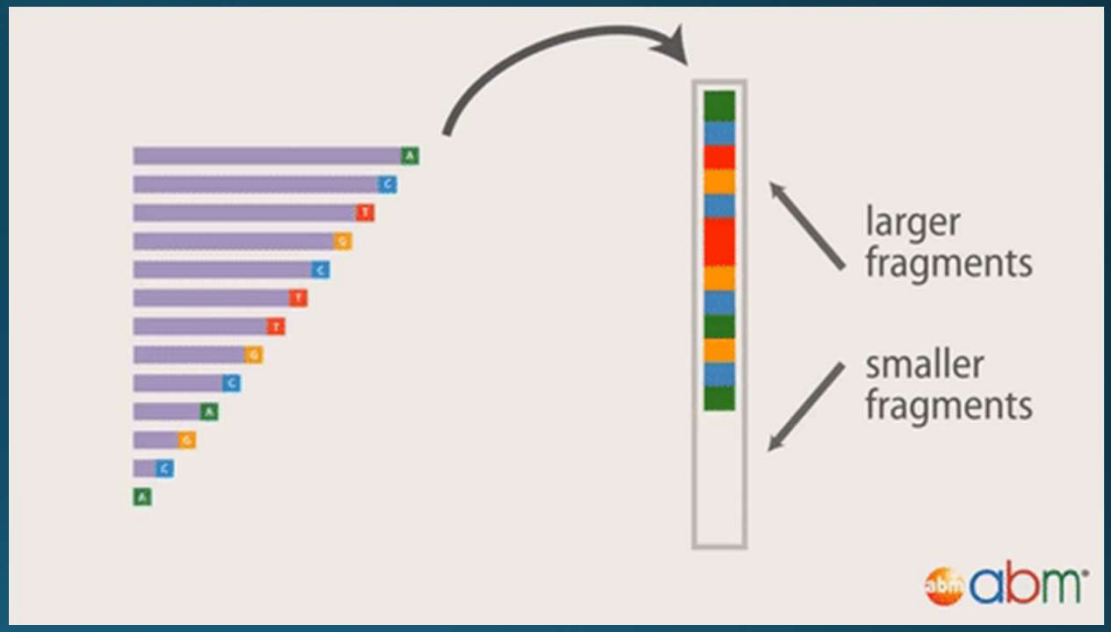
**XYY**



# Sequencing Genomes

- **DNA sequencing** process of identifying the nucleotide sequence of a DNA fragment

- In 1977, the genome of the virus X174 became the first entire genome to be sequenced. At that time, the sheer size of eukaryotic genomes made it impossible for scientists to sequence these genomes using the same techniques.



# The Human Genome Project

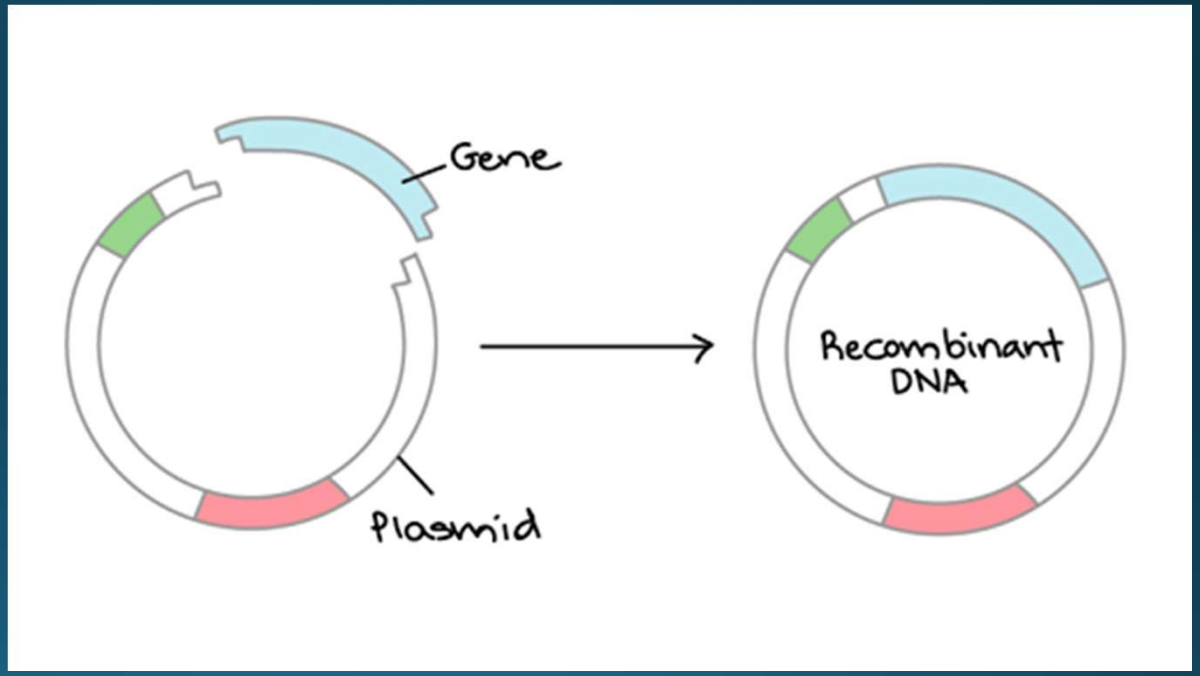
- In 2003, an international team of researchers completed the ***Human Genome Project***, monumental effort to sequence the entire human genome.
- The Human Genome Project is a landmark in the field of human genetics, and it has **important applications in medicine and other sciences.**

- CONNECTIONS + SCIENCE AND TECHNOLOGY
- The Human Genome Project
- P 594

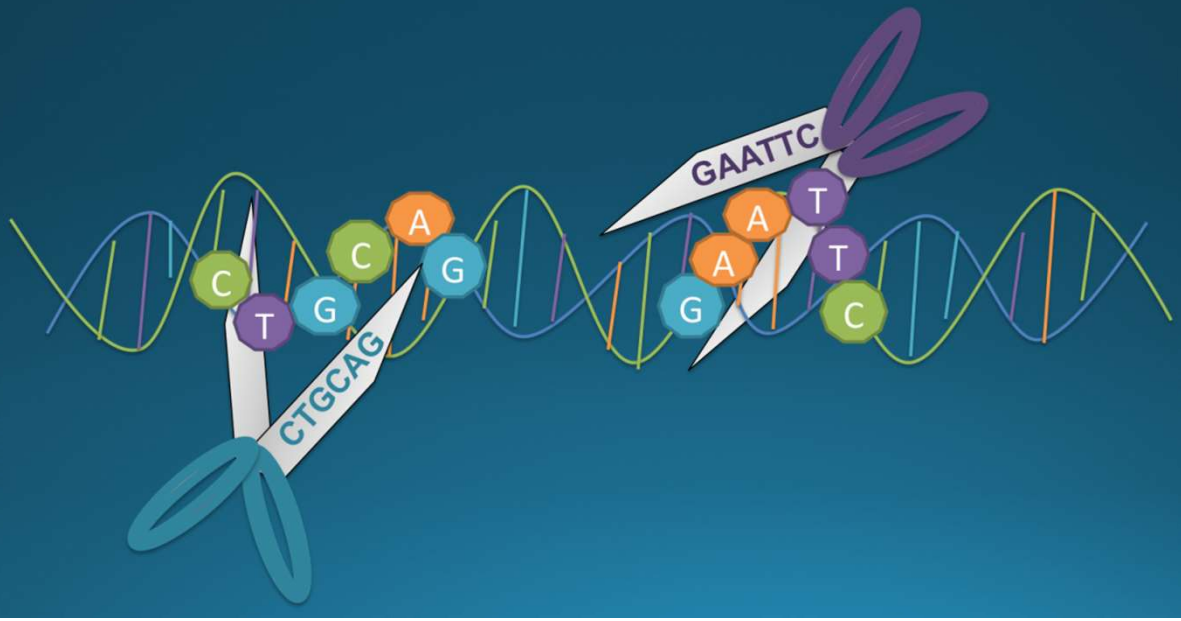
# Genetic Technologies

- **genetic engineering** manipulation of genetic material to alter genes and blend plant, animal, and bacterial DNA

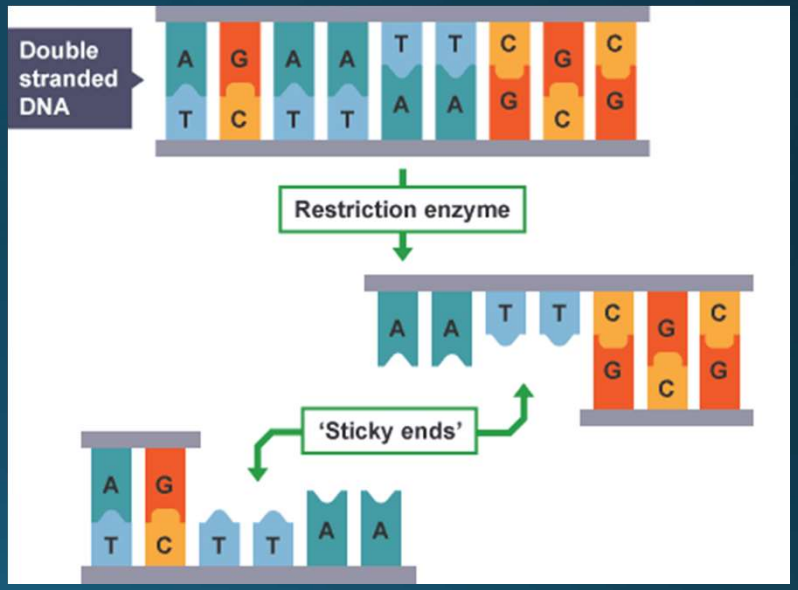
- **recombinant DNA** a molecule of DNA that includes genetic material from different sources



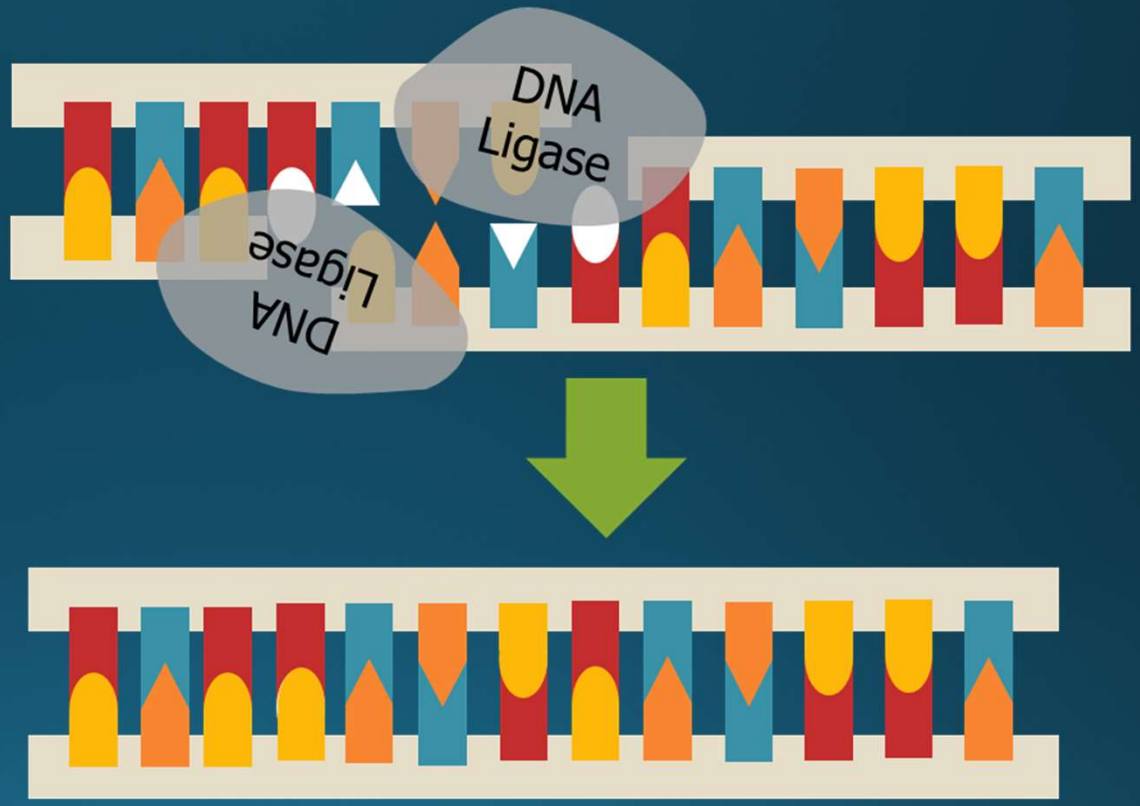
- **restriction enzyme**
  enzyme that catalyzes the cleavage of DNA at specific nucleotide sequences



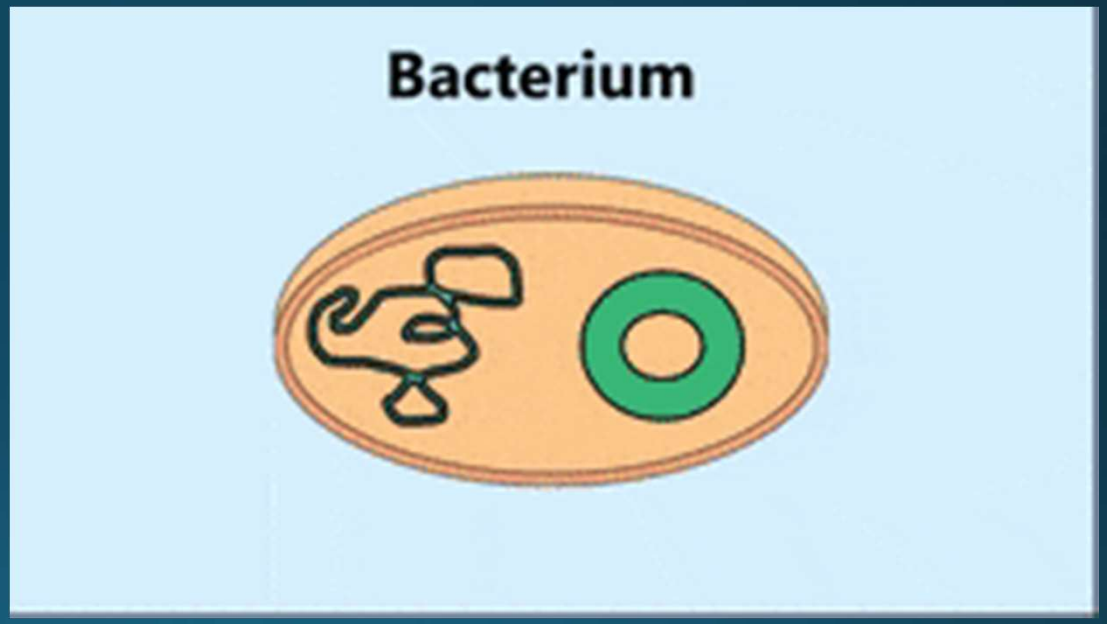
- Two characteristics of restriction enzymes:
- **Specificity:** The cuts made are specific and predictable. That is, the same enzyme will cut a particular strand of DNA the same way each time, producing an identical set of small DNA fragments.
- **Staggered cuts:** Most produce a staggered cut that leaves a few unpaired nucleotides on a single strand at each end of the restriction fragment.
- These short strands, often referred to as **sticky ends,** can then form base pairs with other short strands that have a complementary sequence.



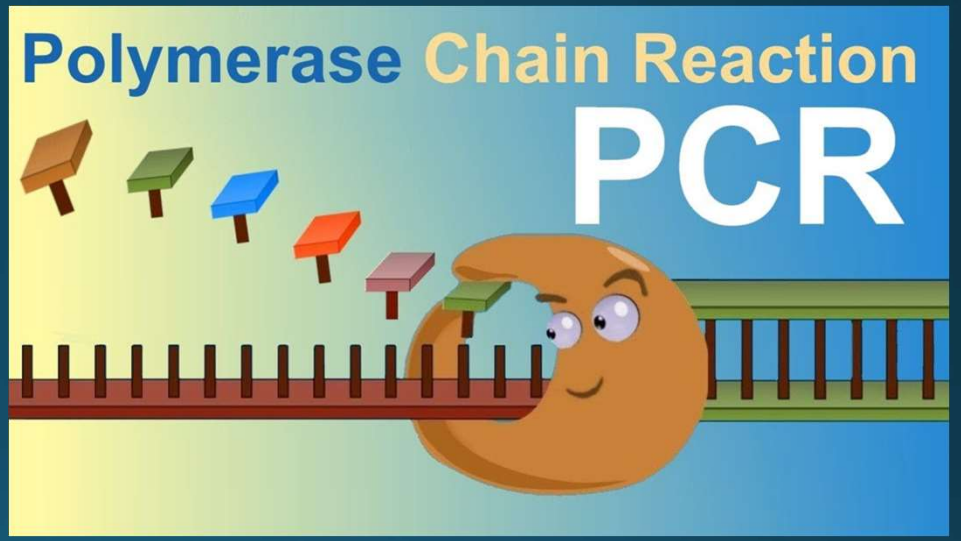
- Once the sticky ends have formed base pairs with one another, the action of another enzyme, ***DNA ligase,*** joins them together. The result is a stable recombinant DNA molecule.



- The human insulin gene can be combined with a type of **bacterial DNA** called a ***plasmid***. The recombinant DNA molecule can be introduced into bacteria where it will replicate numerous times and produce the human insulin protein, which can then be isolated and used medicinally.

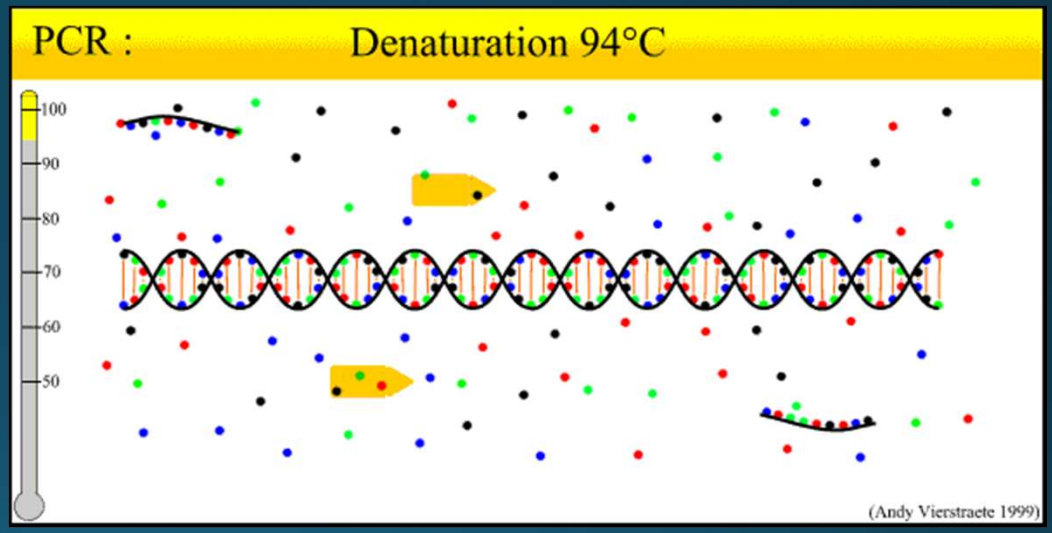


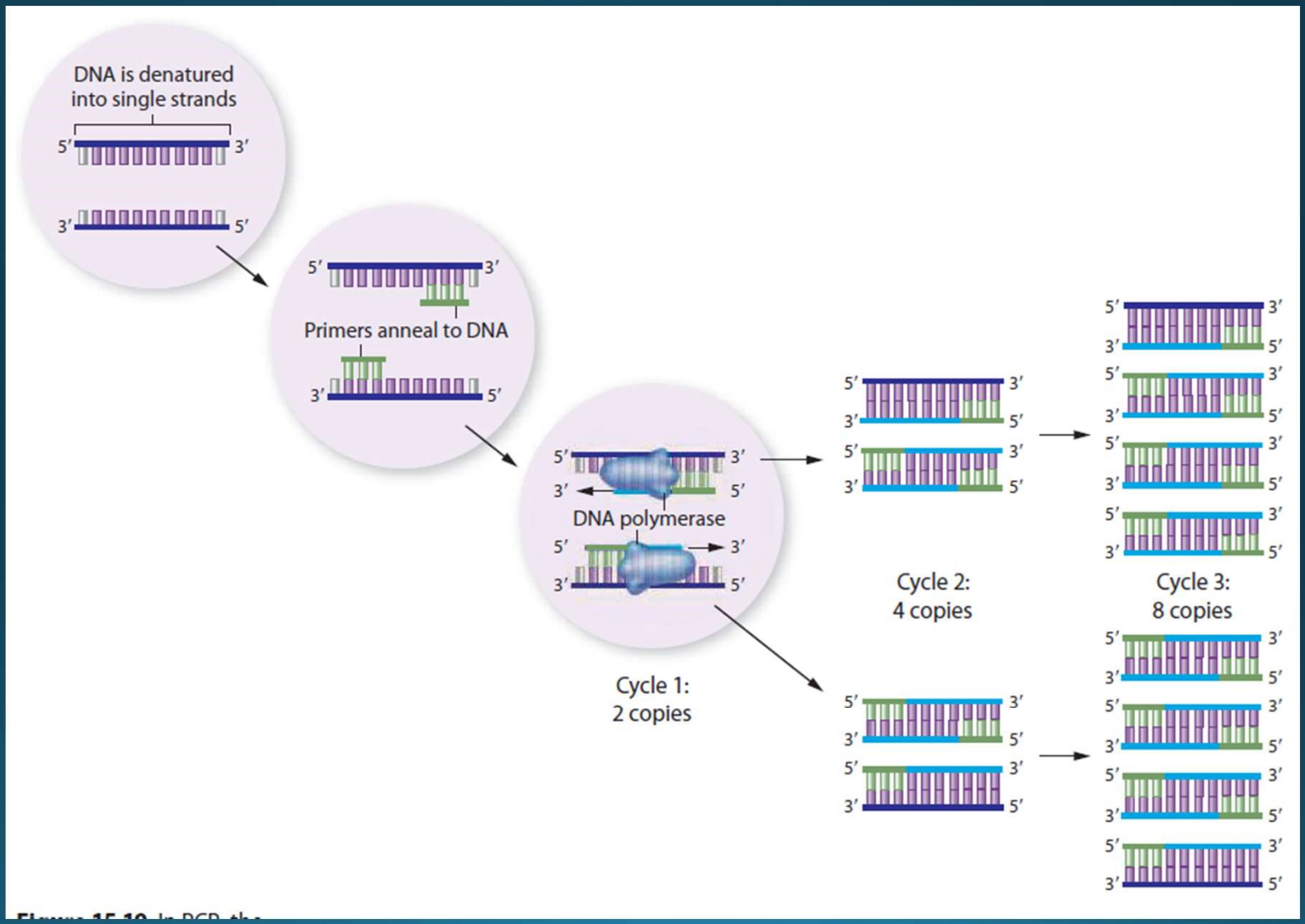
- **Polymerase chain reaction (PCR)** is a method widely used to rapidly make millions to billions of copies (complete copies or partial copies) of a specific DNA sample, allowing scientists to take a very small sample of DNA and amplify it to a large enough amount to study in detail.



# DNA Amplification

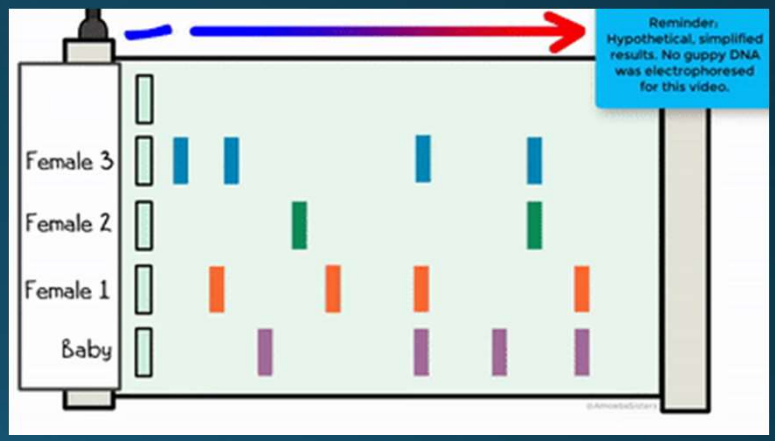
- PCR uses **DNA replication** and a special type of **DNA polymerase** that adds nucleotides onto **primers** that bind to each end of the region to be amplified.
- **After the first round, or cycle, of PCR two new double stranded DNA molecules are formed.**
- The same cycle is typically repeated 20 to 30 times. This results in sufficient amounts of DNA



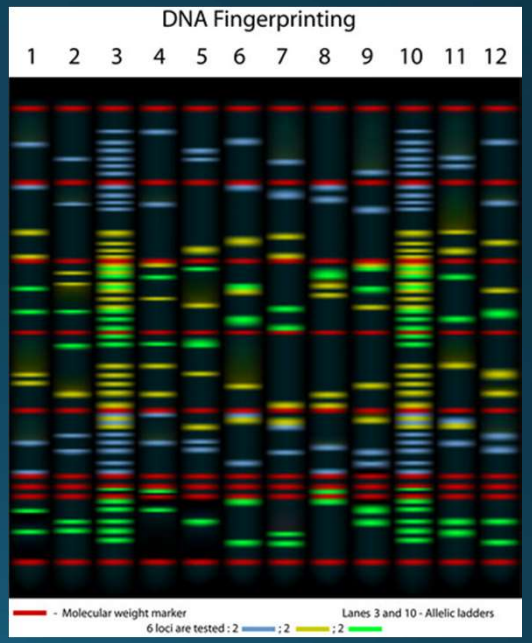

DNA is denatured into single strands
5′
3′
3′
5′
5′
3′
Primers anneal to DNA
3′
5′
5′
3′
3′
5′
DNA polymerase
5′
3′
3′
5′
Cycle 1:
2 copies
Cycle 2:
4 copies
Cycle 3:
8 copies

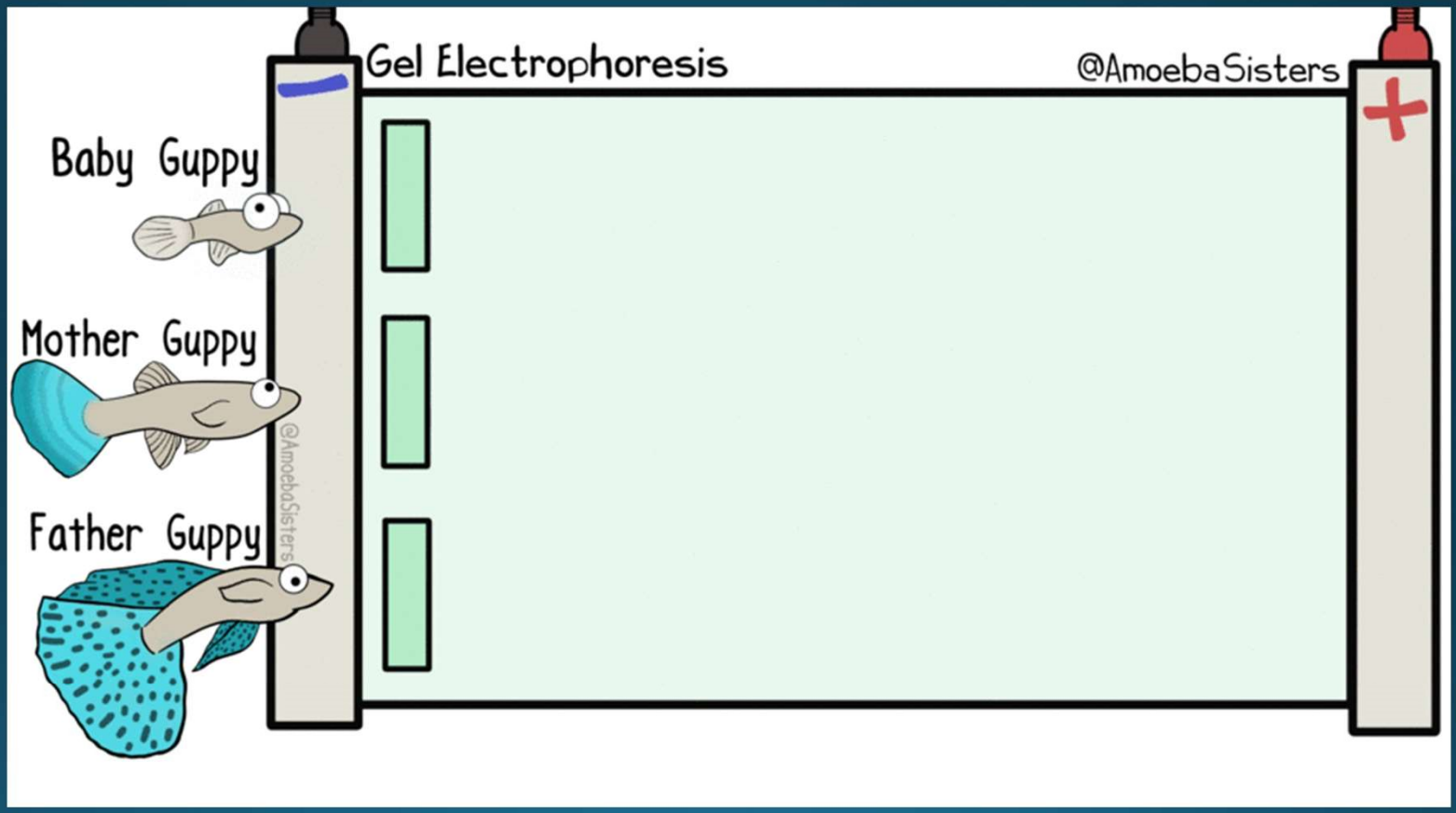
# Sorting and Analyzing DNA

- **Gel electrophoresis** tool used to separate molecules according to mass and charge
- To begin, a solution that contains DNA fragments is applied at one end of a gel. An electric current is then passed through the gel.
- This causes one end of the gel to develop a positive electric charge and the other end to develop a negative electric charge.
- Because DNA has a negative charge, the DNA fragments tend to move toward the gel's positive end**. The smaller fragments move more quickly.**

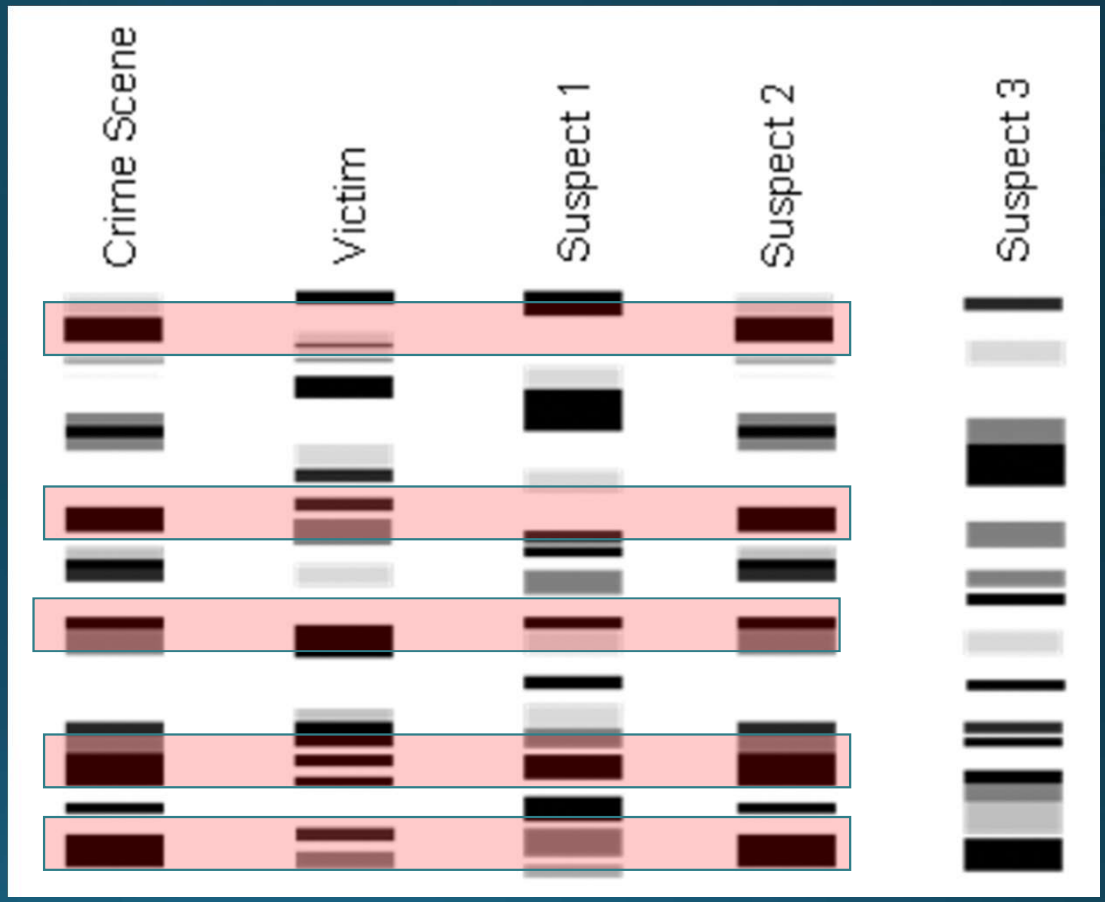


- **DNA fingerprinting** uses gel electrophoresis to distinguish between samples of the genetic material.
- Since no two people (other than identical twins) have the same DNA, a person's DNA fingerprint is unique and can be used for identification purposes.
- A DNA fingerprint of a sample from a crime scene can be compared with the DNA fingerprint of a suspect. A match is very strong evidence that the suspect was present at the crime scene.
- Similarly, DNA fingerprints can be used to solve disputes over parentage. DNA is inherited equally from both parents, a child's DNA fingerprint will show some matches with the DNA fingerprint of each parent.



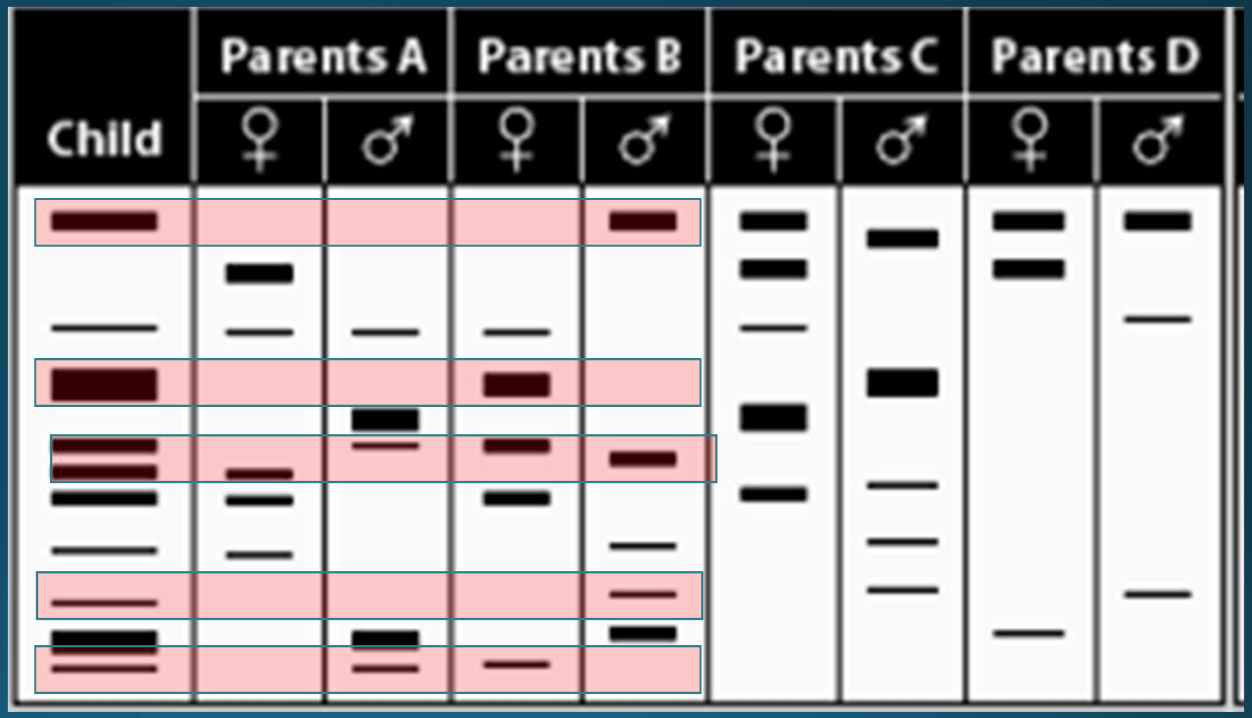

Gel Electrophoresis
@AmoebaSisters
Baby Guppy
Mother Guppy
Father Guppy
@AmoebaSisters
+

- Who committed the crime?



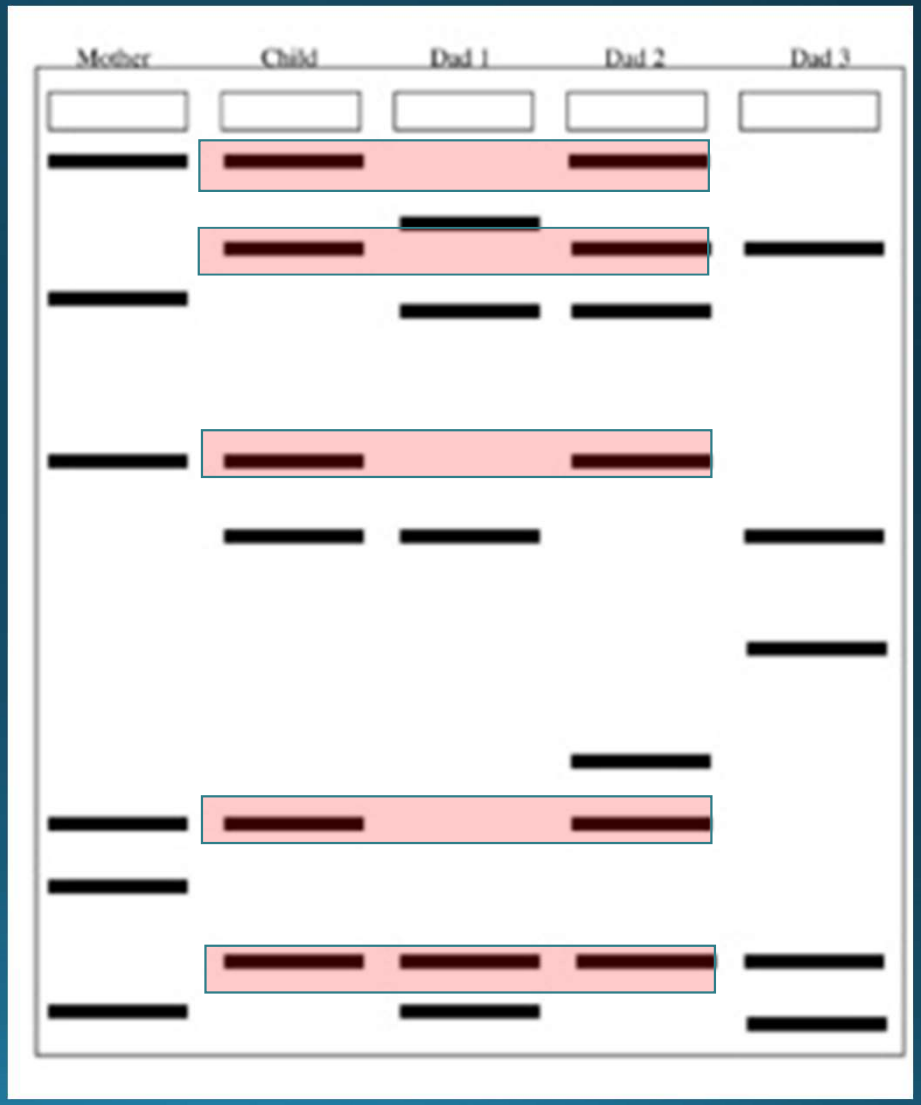

**Suspect 2!**

- Which parents own the child?




**Parents B!**

- Which dad owns the child?

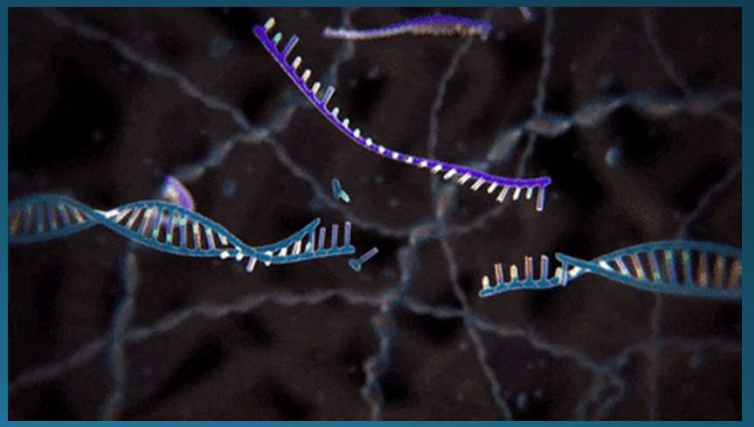



**Dad 2!**

- Exit Card #12

# CRISPR

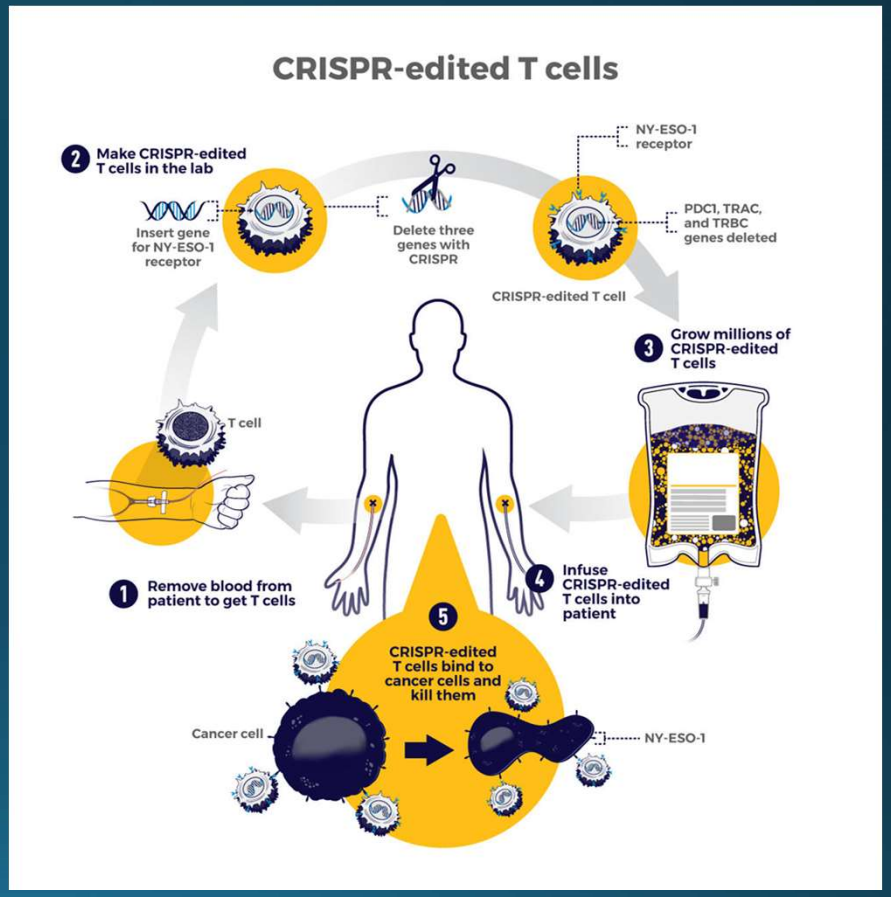
- **CRISPR** a genetic engineering tool that uses a CRISPR sequence of DNA and its associated protein to edit the base pairs of a gene.
- The essence of CRISPR is simple: it's a way of **finding a specific bit of DNA inside a cell.** After that, the next step in CRISPR gene editing is usually to **alter that piece of DNA.**

# How it works

- CRISPR uses a type of bacteria protein (Cas) to find a section of RNA/DNA, cut it and then modify it with alternate nucleotides.

- 1.) Design - Ensure that you select the optimum guide RNA and other components for your experiment
- 2.) Edit - Introduce the CRISPR components into cells to allow the genome engineering to occur
- 3.) Analyze - Verify the effectiveness of your experiment and move on to the next steps



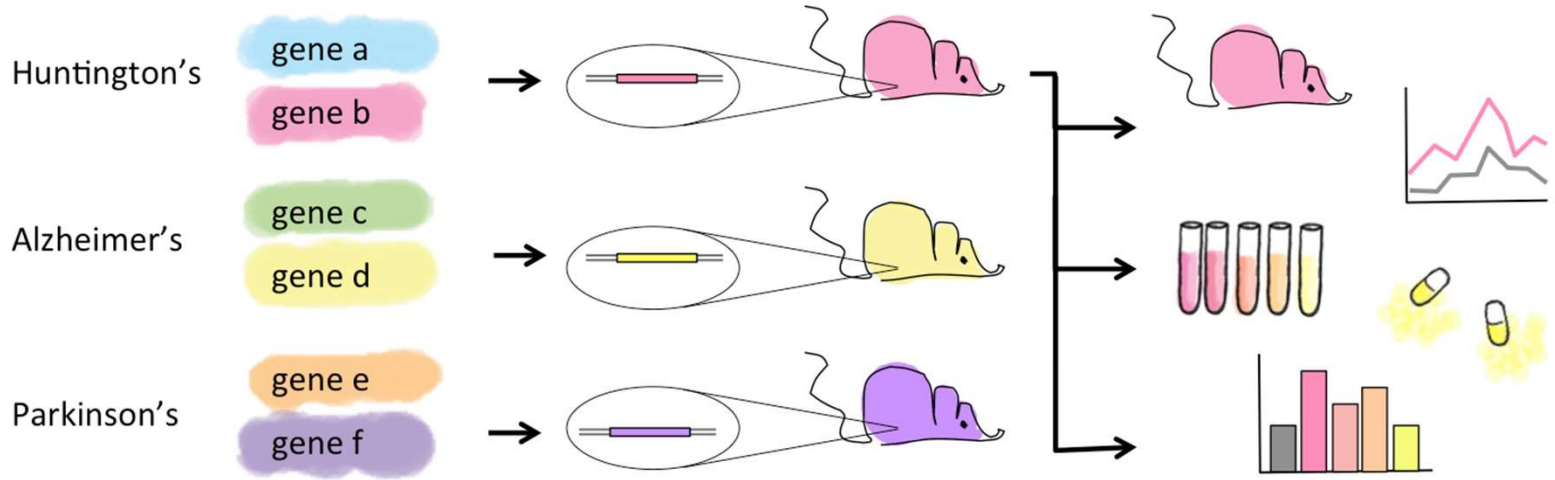
# How is it being used/can it be used right now?

- 1. Turning pigs into organ donors
- 2. Making new and improved fruit
- 3. Changing flowers from violet to white
- 4. Modifying human embryos
- 5. Halting muscular dystrophy in dogs
- 6. Creating new treatments for cancer and blood disorders
- 7. Eliminating mosquitoes

Genetic studies identify human gene mutations linked to neurologic diseases.

CRISPR is used to disrupt or introduce targeted mutations in the disease-linked genes in mice.

These mice are studied to learn how each gene and mutation affects disease, and used to test new drugs.



# DNA microarray

- **DNA microarray** tool for analysis of gene expression levels using cDNA probes
- A DNA microarray is a chip (usually a glass microscope slide or a polymer membrane) that contains a grid of thousands of microscopic cells.
- Each cell contains a nucleic acid sequence that can bind with one of the mRNA molecules transcribed during gene expression.

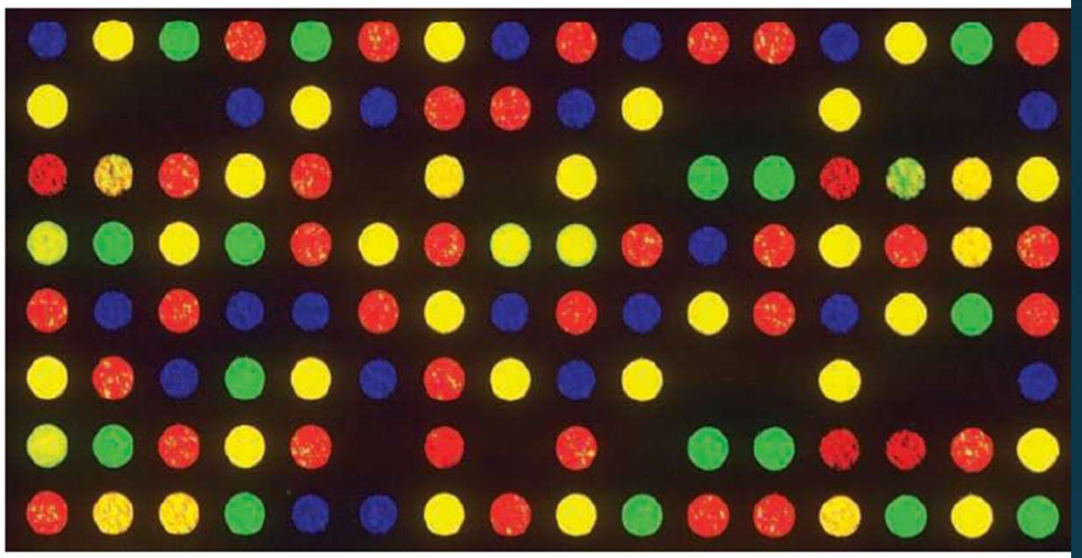
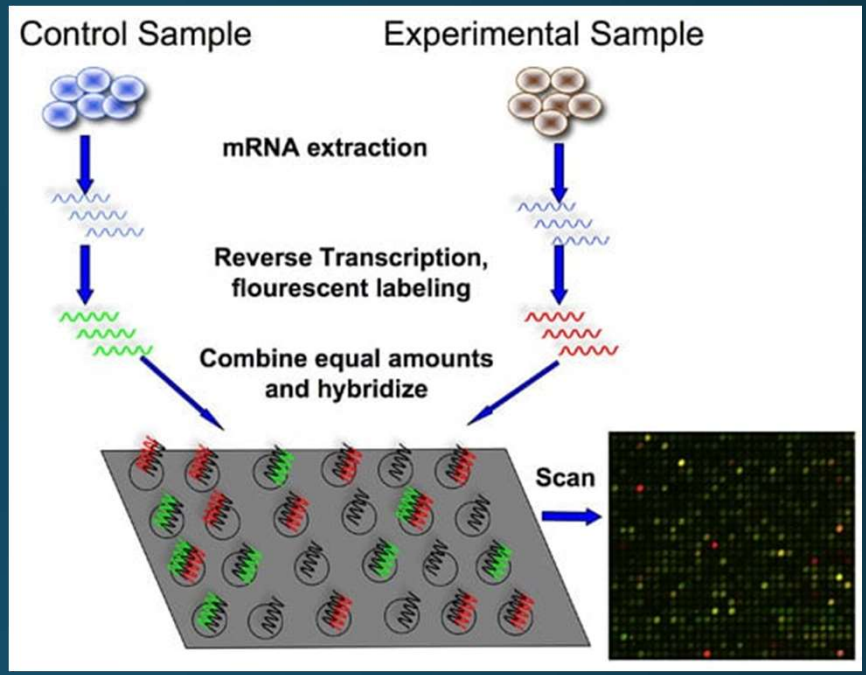
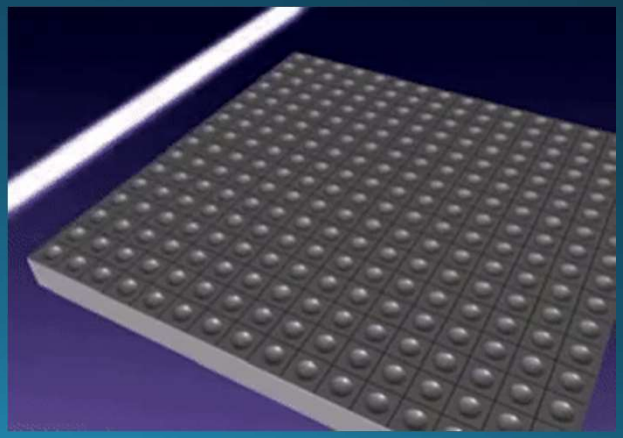


**Figure 15.21** The results of a DNA microarray analysis comparing gene expression in two different cell samples. The red spots indicate genes that are expressed only by cells in the first sample, and the green spots indicate genes that are expressed only by cells in the second sample. The yellow spots indicate genes that are expressed by cells in both samples.

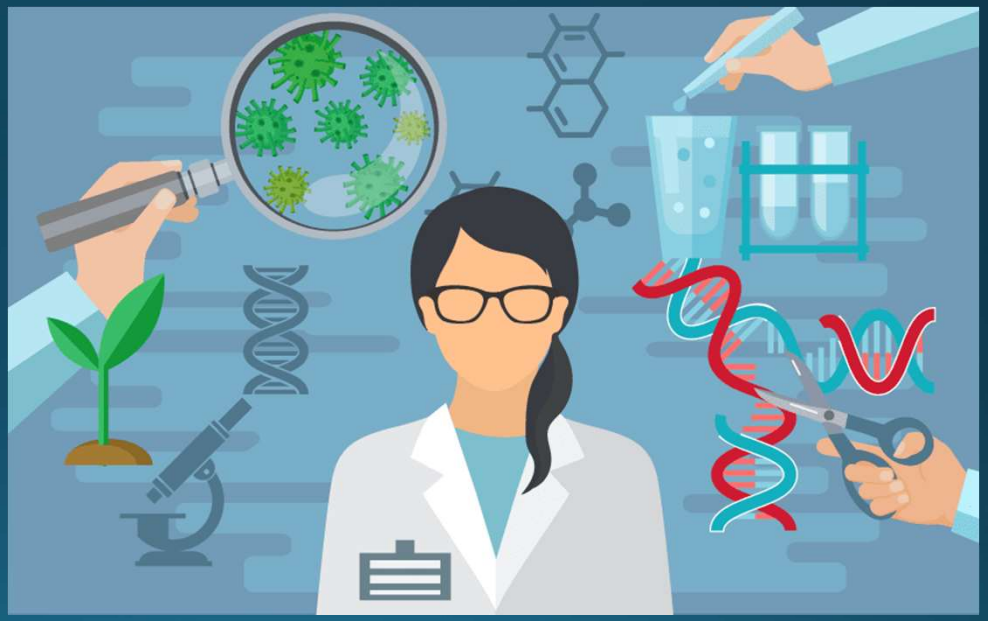
- A typical microarray experiment includes the following steps:
- **1.** **mRNA is extracted** from the cell or cells to be studied.
- **2.** mRNA from each cell sample is used as a template to **synthesize** an **artificial** form of DNA, called ***copy DNA*** (*cDNA*). The cDNA from each sample is marked by a fluorescent tag for later identification.
- **3.** The labelled cDNA samples are **incubated** with the microarray. The cDNA binds to the microarray at locations that correspond to individual genes in the cell genome.
- **4.** The microarray is scanned and analyzed to **compare the patterns** of gene expression in each cell sample.



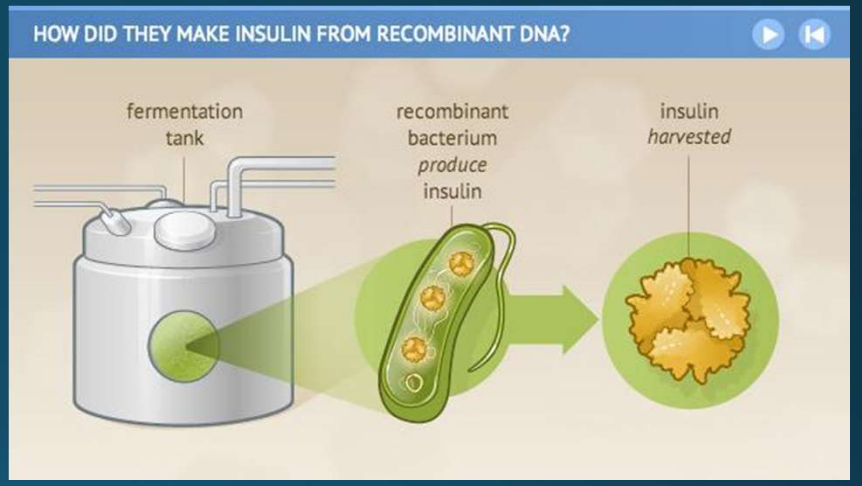
# Biotechnology

- **biotechnology** use of biological systems to create new technologies and products



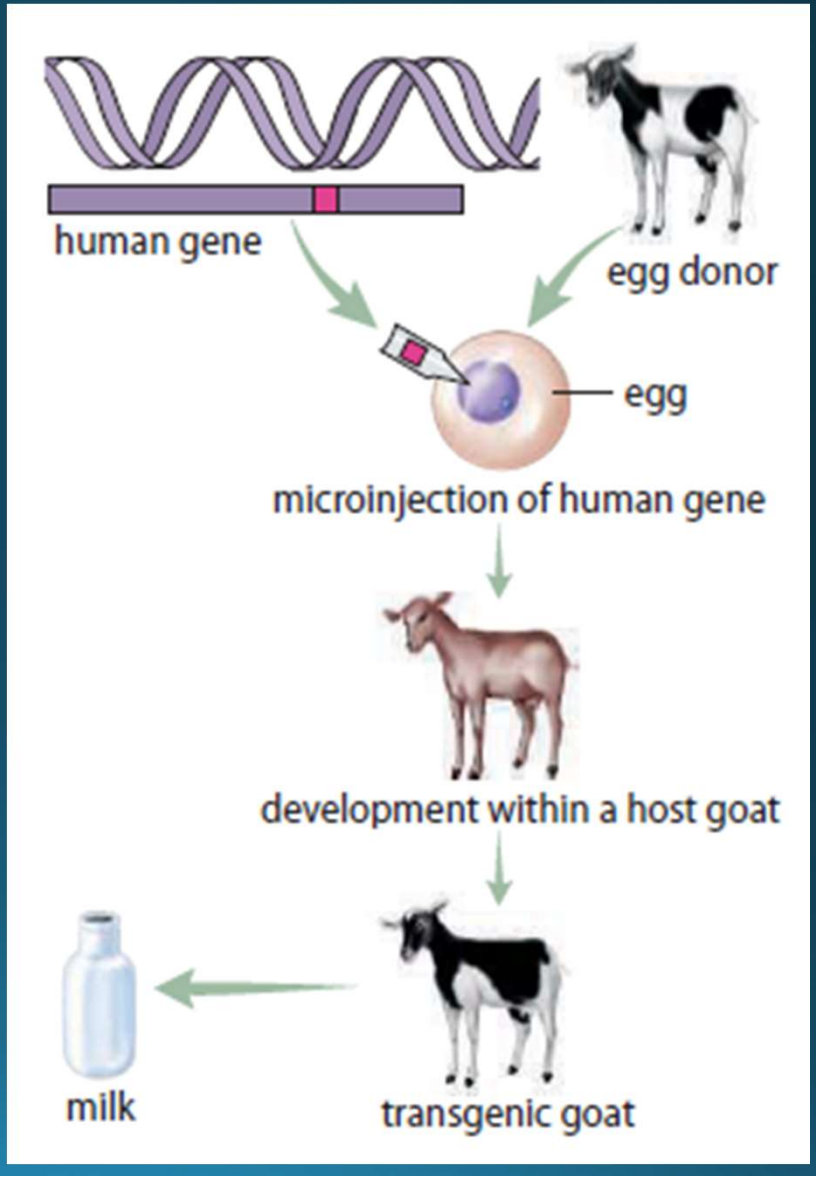
# Biotechnology Products

- **Medicinal Bacteria** bacteria are used to produce antibiotics, vaccines, and medically-useful enzymes.
- In 1982, human insulin synthesized by transgenic bacteria was approved for medical use in the United States.
- Some bacteria naturally degrade toxic substances, such as polychlorinated biphenyls (PCBs).
- The use of living cells for environmental remediation is known as ***bioremediation***.
- Clean up oil spills, to filter air from factory smokestacks, or to remove heavy metals from water.

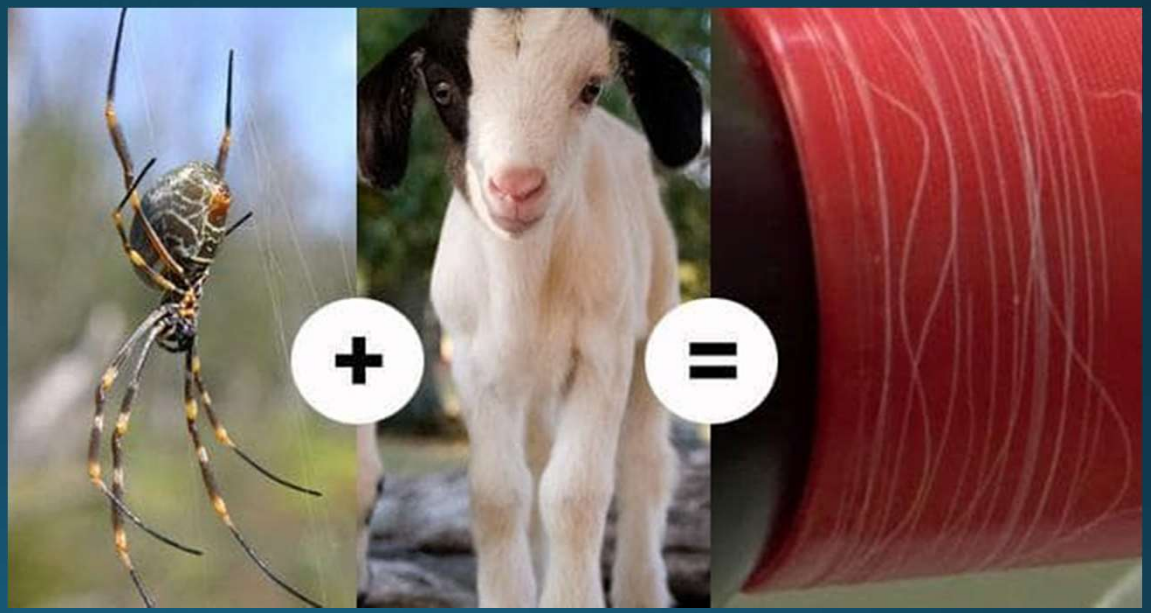


- **Transgenic Animal** animal genetically engineered to contain DNA from another organism

- Researchers have been able to create new varieties of animals with useful traits. For example, **transgenic milk-producing** animals, such as **goats**, are being used to produce pharmaceutical products.



- Similar steps have been used by a Canadian research company to insert a spider gene into goats. The transgenic goats secrete **spider silk in their milk.**
- The silk can be extracted and spun into lightweight, strong fibres with many uses.



- Another area of research involves developing **transgenic animals** that can serve as **organ donors for humans.**

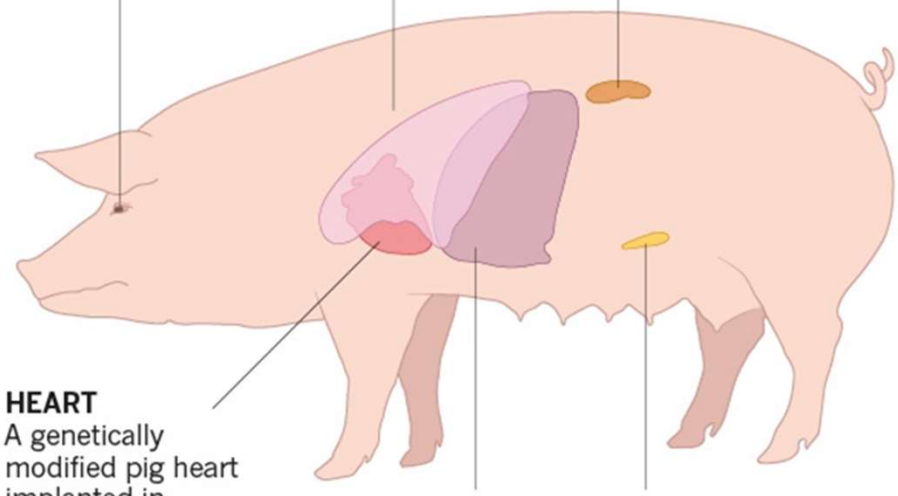
- Usually, the transplantation of organs from animals, such as pigs, into human patients has limited success
- Pigs could become a source of organs that are more compatible to the human body.

Researchers are looking to source an increasing variety of living tissues, including solid organs, from pigs. Many are attempting to genetically engineer the animals to reduce the risk of rejection and infection in humans.

**CORNEA**
Pig corneas were approved for marketing in China in April.

**LUNG**
A factory farm is being designed to produce 1,000 pig lungs per year.

**KIDNEY**
A kidney with six genetic modifications supported a baboon's life for 4 months.



**HEART**
A genetically modified pig heart implanted in a baboon's abdomen survived for 2.5 years.

**LIVER**
Livers could be engineered to produce their own antibodies against primate immune cells.

**PANCREAS**
Phase III clinical trials of insulin-producing islet cells are under way.

- **Transgenic Plant** plant genetically engineered to contain DNA from another organism
- Crop plants that contain recombinant DNA now account for over half the corn and canola produced in North America.
- Many of these plants have been modified to increase their resistance to herbicides, insect pests, or viruses.
- **Golden Rice** is genetically modified to contain nutrients otherwise not found in rice.

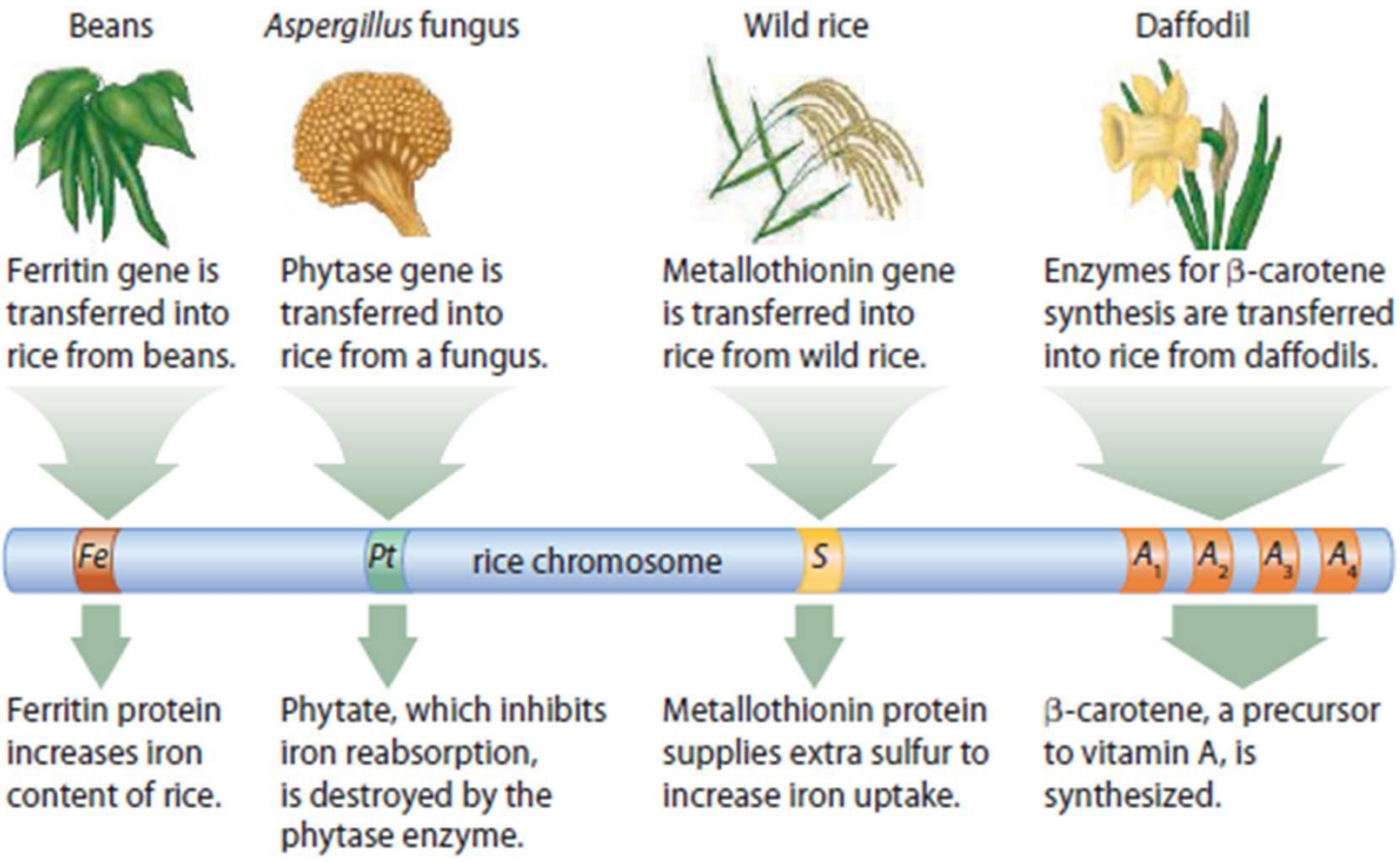
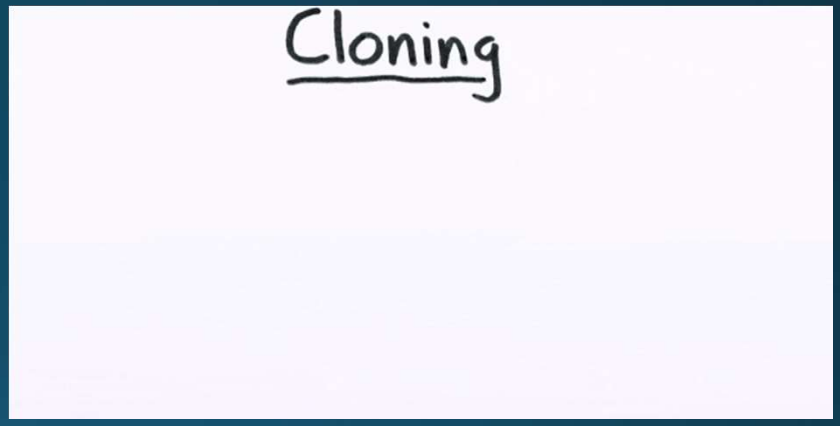



**Figure 15.24** The transgenic product, golden rice, contains four different foreign genes. Three of these genes come from other plants and one comes from a fungus.

- **clones** genetically identical organisms

- Cloned offspring suffer from a high mortality rate, however, as well as a high incidence of disease. Many also show signs of metabolic disorders, such as premature aging. Outcomes such as these reflect the need for ongoing research into the complexities of gene expression in animals.
- **Dolly** the sheep



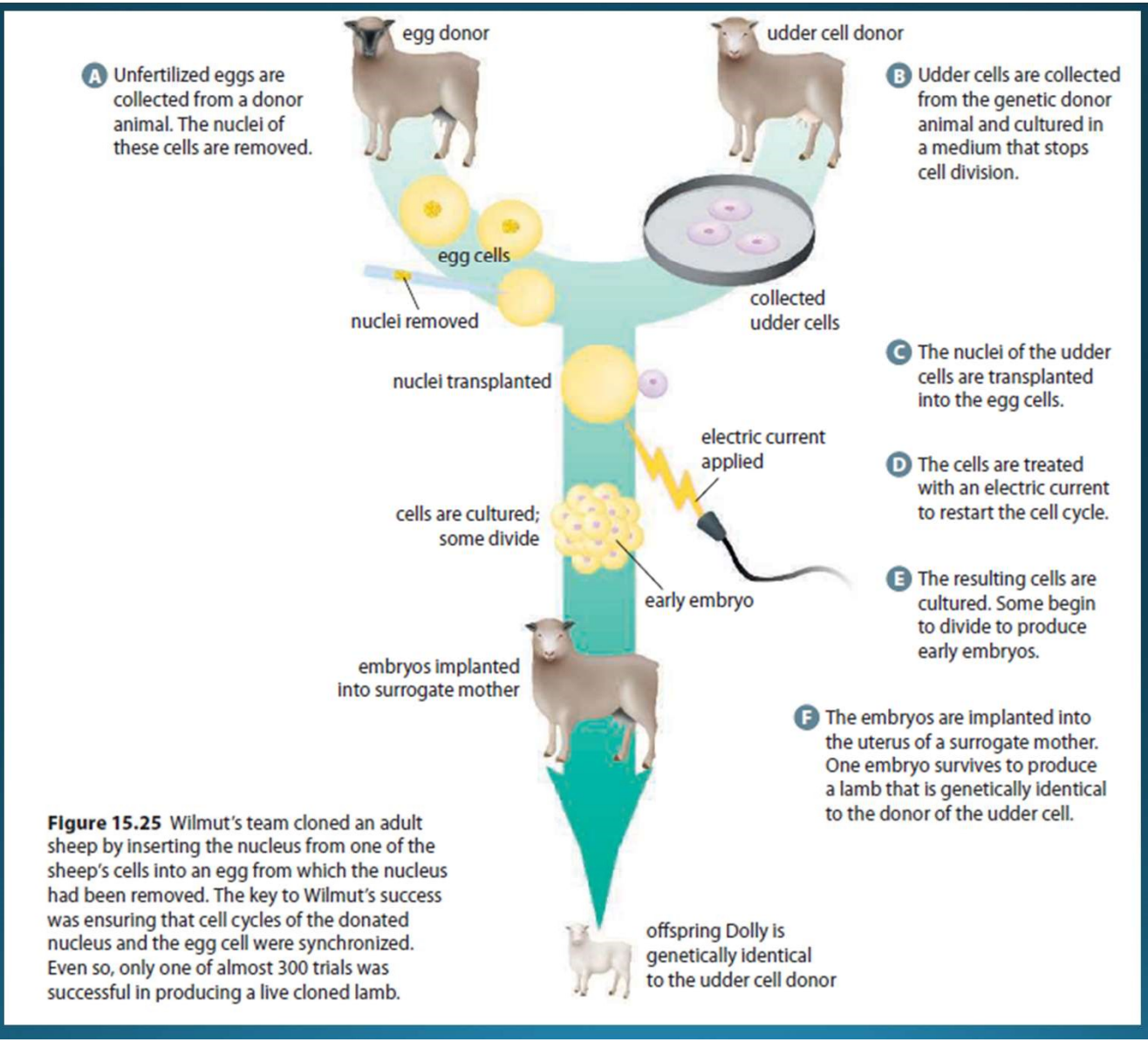


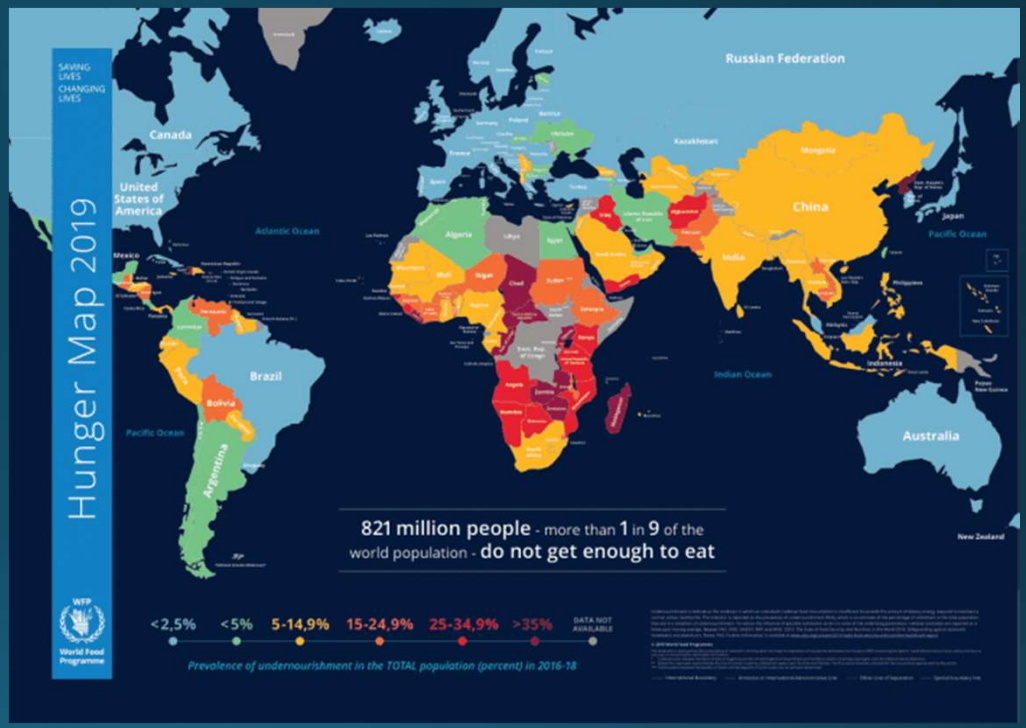

**Figure 15.25** Wilmut's team cloned an adult sheep by inserting the nucleus from one of the sheep's cells into an egg from which the nucleus had been removed. The key to Wilmut's success was ensuring that cell cycles of the donated nucleus and the egg cell were synchronized. Even so, only one of almost 300 trials was successful in producing a live cloned lamb.

# Assessing the Benefits and Risks

- **Environmental threats:** The use of herbicide-resistant plants could encourage farmers to use higher levels of herbicides.
- This, in turn, could lead to a **buildup of herbicide chemicals in water supplies and neighbouring ecosystems.** As well, there is evidence that engineered genes can be transferred to wild plants and other organisms, raising concerns about the emergence of **"superweeds"** and **"superbugs."**
- More generally, ecosystems involve complex and delicate balances among many different organisms.
- The introduction of transgenic bacteria, plants, or animals could **upset these ecosystems**

- **Health effects:** Many consumer groups **argue that not enough is known** about the long-term effects of consuming transgenic products, including genetically modified foods and medicines. The complex processes of gene regulation are not well understood, so it is difficult to predict potential health risks.

- **Social and economic issues:** Advocates of genetically modified foods argue that these foods will help to improve human health and **alleviate world hunger.**
- Their opponents argue that genetic research absorbs millions of dollars, which would be better spent directly helping people in need.
- Many people are concerned about the growing influence of private corporations over global food production.
- The treatment of plants and animals as commodities to be manipulated and patented also raises questions about our relationships with—and responsibilities to—other living organisms.



# Research Poster Project

- Students are expected to research social, environmental, and ethical issues associated with application of a specific genetic technology (e.g., human gene therapy, genetically modified foods, personal genomics). They should take a position on the use of a specific genetic technology and construct arguments to support and defend their position.
- SCOs 25.0 should be assessed as part of this activity. Additionally, teachers may assess skill outcomes 7.0, 8.0, and 26.0. Refer to the *Integrated Skills* unit for elaboration of these outcomes.
- Readdress SCO 43.0; identifying and describing careers related to genetics (e.g., genetic counsellor, animal breeder, bioethicist, biotechnologist, forensic laboratory assistant, geneticist).

- Complete the STSE case study (*NL Biology*, pp. 574-575) to analyze the risks and benefits to society of gene therapy applications.