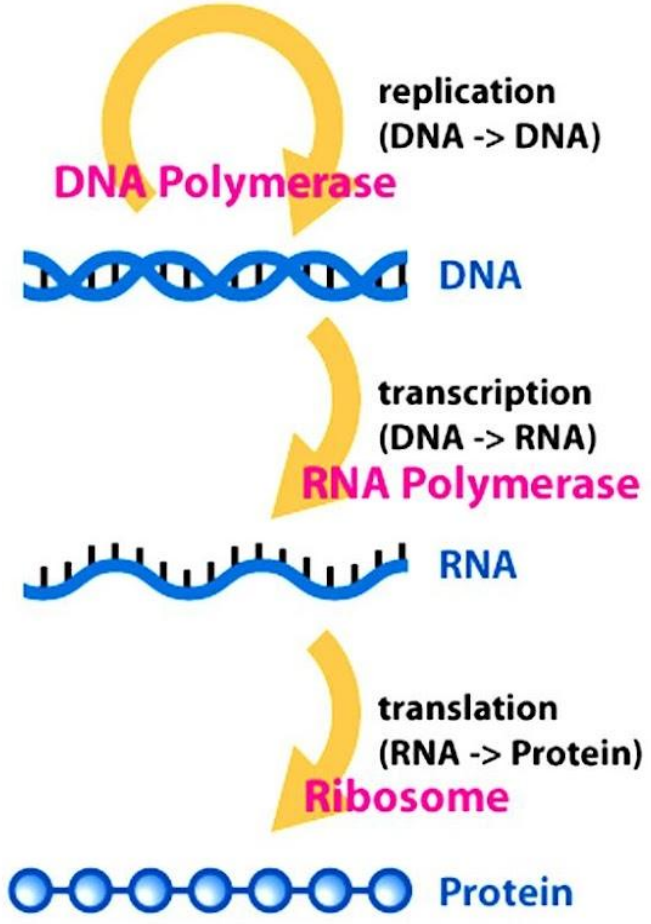
INTRODUCTION TO BIOLOGY
BIO-101

Central Dogma of Life
Lecture 08



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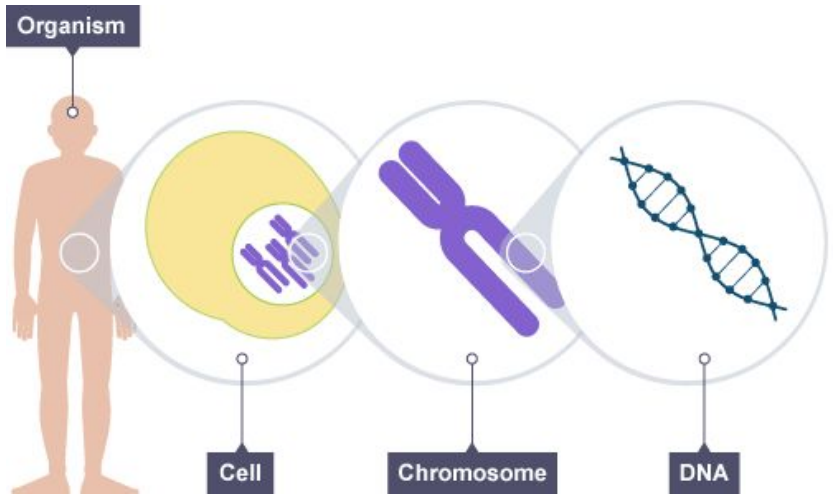
Discovery of Nucleic Acids

- In the 1860s, Friedrich Miescher, a physician by profession, was the first person to isolate **phosphate-rich** chemicals from white blood cells or leukocytes.
- He named these chemicals “nuclein” (which would eventually be known as RNA and DNA) because they were isolated from the nuclei of the cells.

Friedrich Miescher (1844–1895)

Deoxyribonucleic acid (DNA)



- Deoxyribonucleic acid (DNA) is the information-carrying molecule found in all living organisms.
  - In **prokaryotic cells**, DNA is not contained by nucleus, found in an area called the nucleoid.
  - In **eukaryotic cells**, DNA is stored in the nucleus coiled up in thread-like structures called chromosomes.
- For e.g., the nucleus of a human skin cells contains about two meters of DNA. So, a chromosome is a very large molecule compacted into a very small space.
- The information DNA contains is the instruction that the cell uses to make proteins.
- Proteins play a big part in determining the characteristics of specialized cells and whole organisms, e.g., eye color, muscle mass, height and even ability to learn new skills all result from the activity of specific proteins.

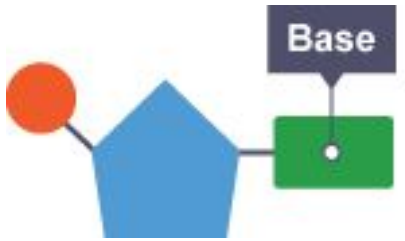
Courtesy: https://www.bbc.co.uk/bitesize/guides/z2qs2nb/revision/1

DNA and RNA Structure

- Both DNA and RNA are nucleic acids, which are long chains (polymers) of chemical units (monomers) called **nucleotides-** the building blocks of DNA and RNA.

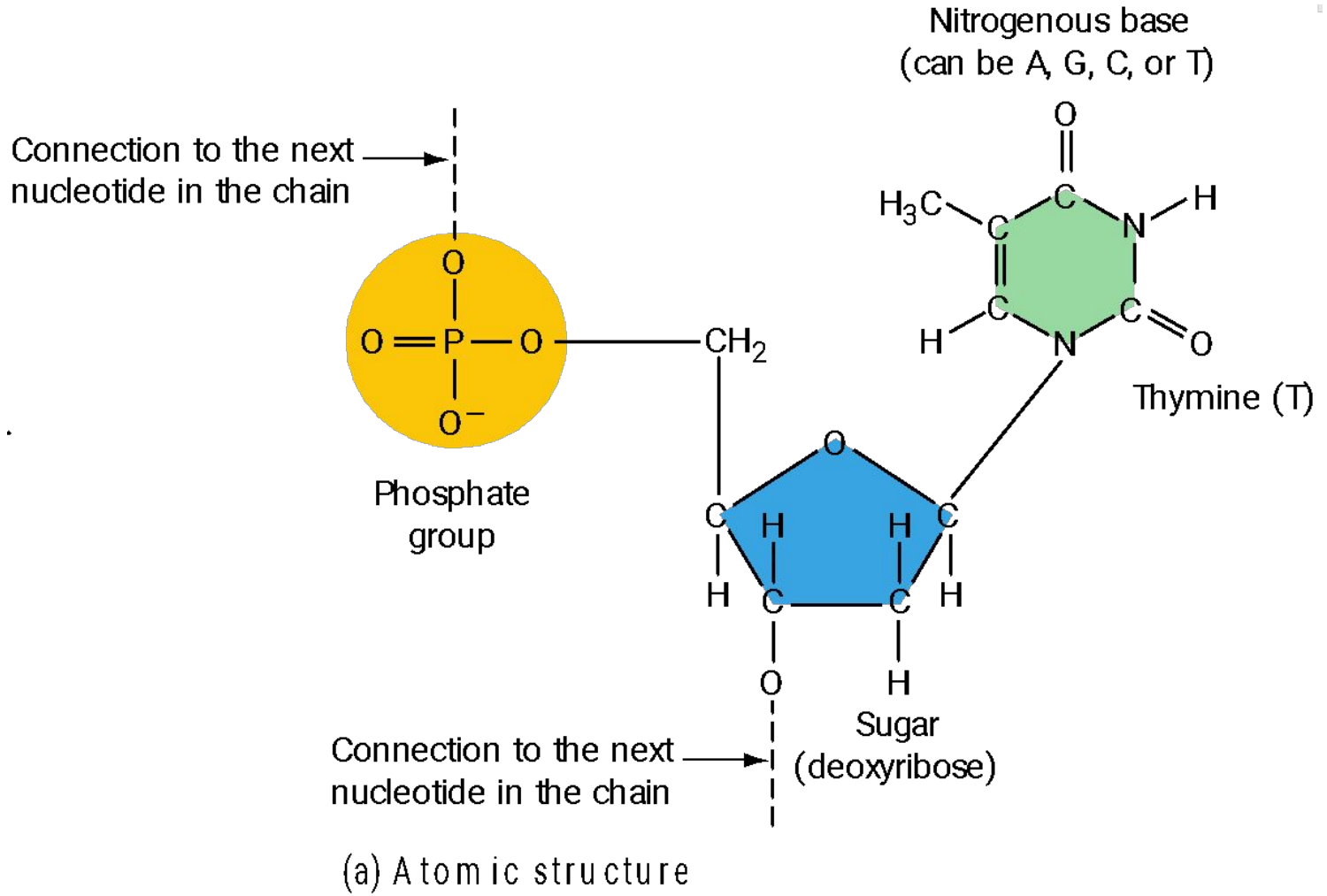
- Nucleotides are joined by covalent bonds between the sugar of one nucleotide and the phosphate of the next. This results in a repeating pattern of sugar-phosphate-sugar-phosphate, which is known as a **sugar-phosphate backbone**.

- There are four different types of nucleotide. The part of a nucleotide that can make it different from others is called the **base**. The nitrogenous bases are arranged like ribs that project from this backbone.



- The bases can be divided into two types.
  - **Thymine (T)** and **cytosine (C)** are single-ring structures and called **Pyrimidines**.
  - **Adenine (A)** and **guanine (G)** are larger, double-ring structures and known as **Purines**.
  - Instead of thymine, RNA has a similar base called **uracil (U)**.

A DNA Nucleotide/ Deoxyribonucleotide



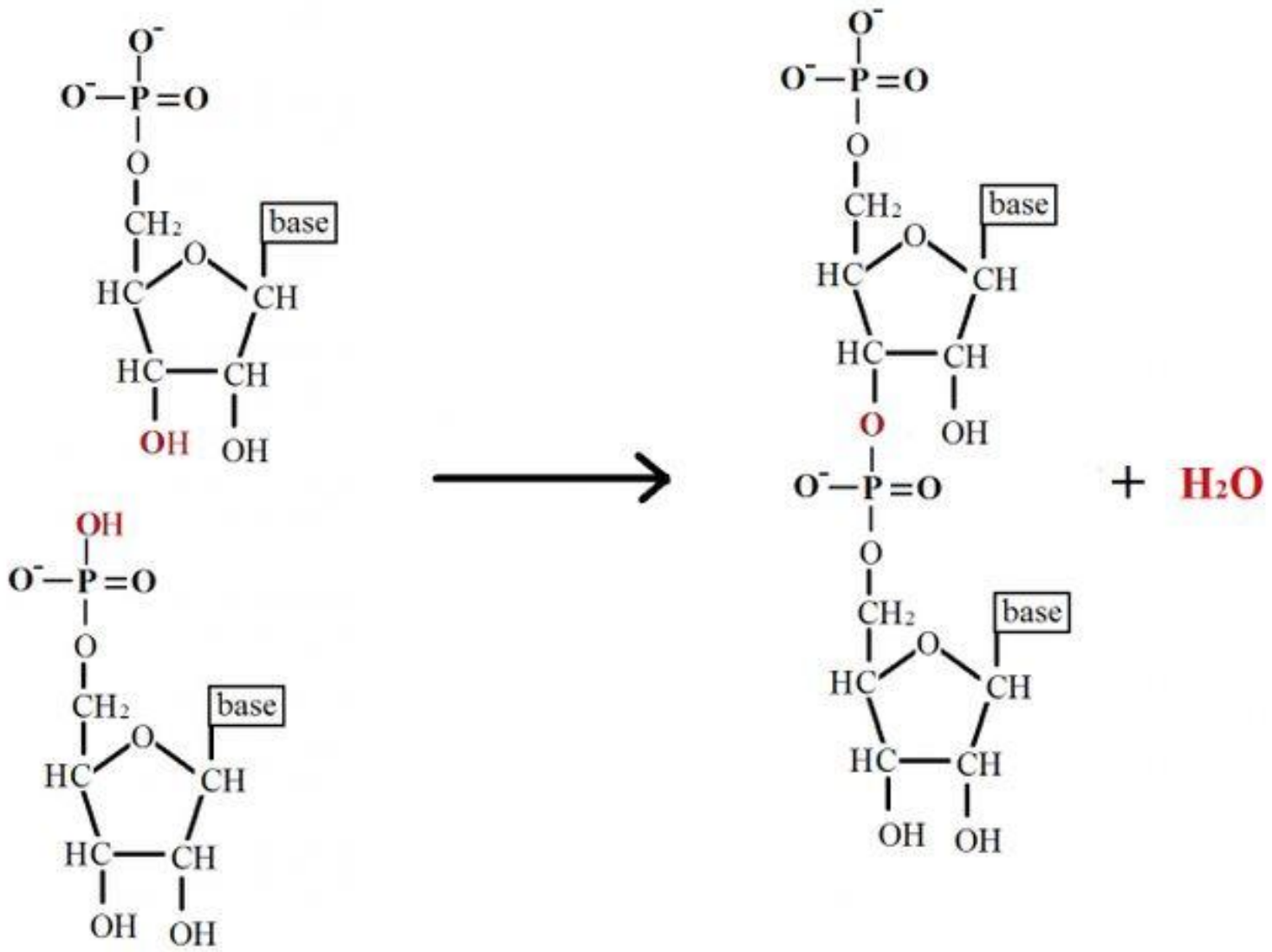
A DNA nucleotide monomer consists of three parts: a sugar (deoxyribose), a phosphate, and a nitrogenous (nitrogen-containing) base.

The sugar-phosphate backbone is formed by phosphodiester bond between the 3' C of sugar of one ntd. and 5' phosphate of the second ntd.

ntd. = nucleotide

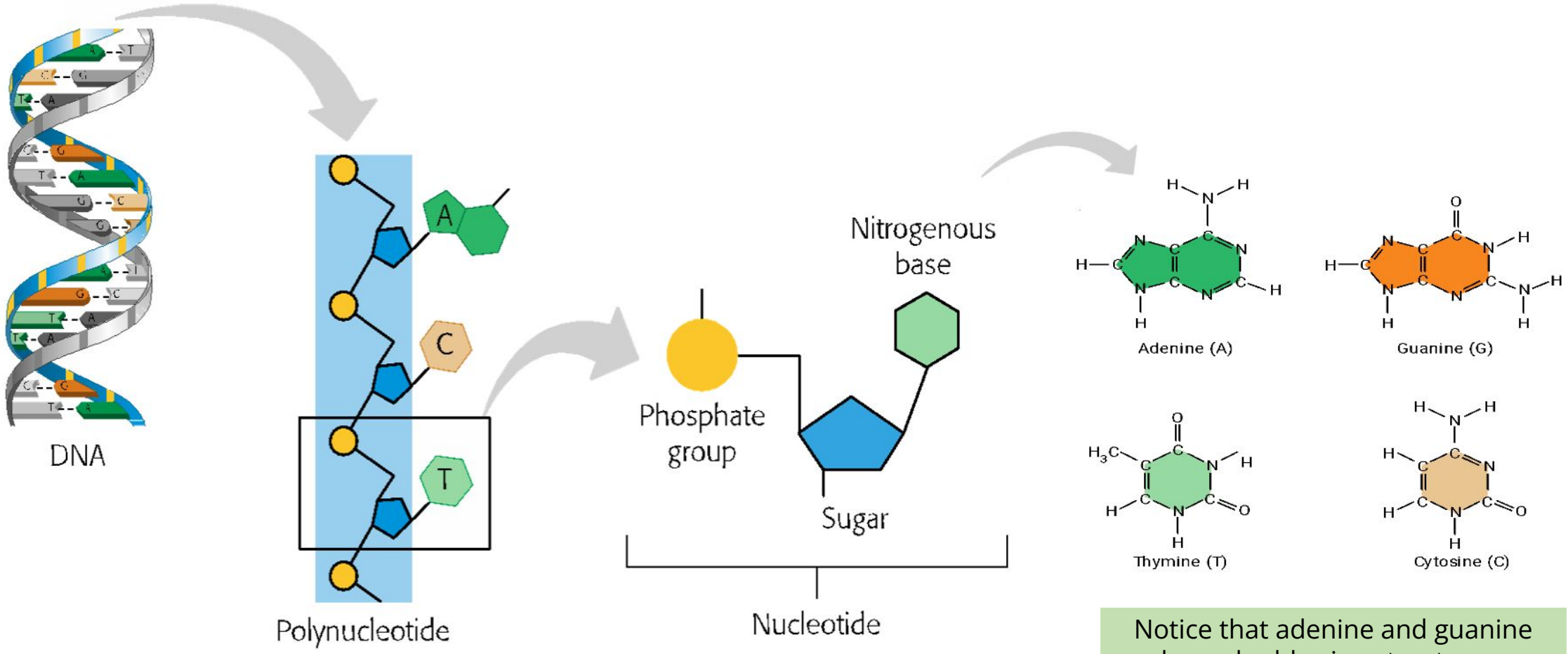
Courtesy: Campbell Essential Biology, Pearson

Phosphodiester Bond Formation



- The sugar-phosphate backbone is formed by phosphodiester bond between the 3’ C of sugar of one ntd. and 5’ phosphate of the second ntd.
- This bond formation releases a molecule of water.

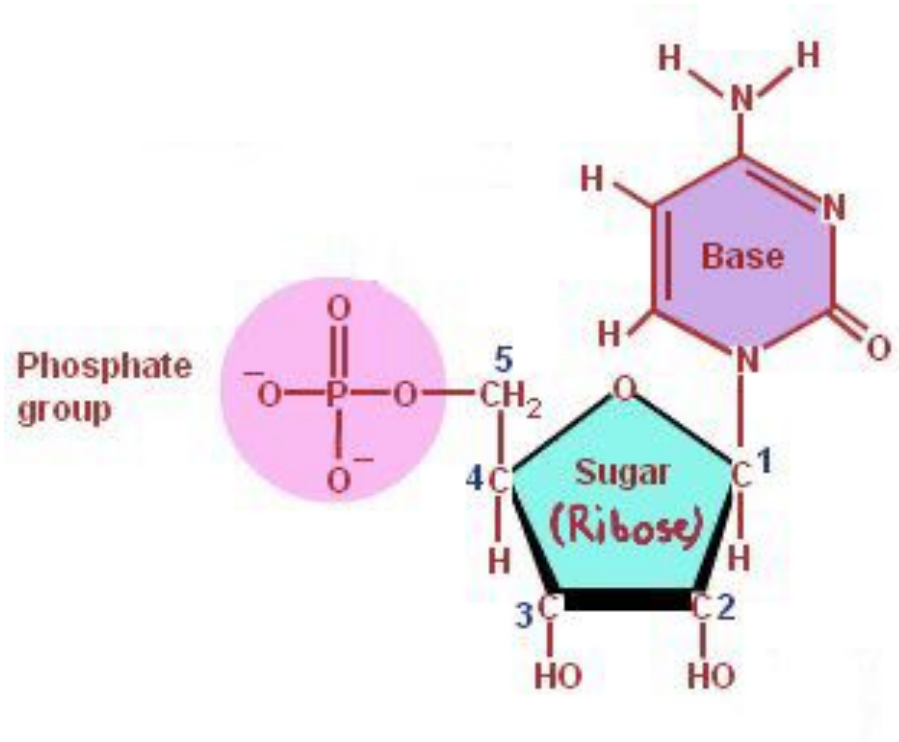
The Chemical Structure of a DNA Polynucleotide



Notice that adenine and guanine have double-ring structures. Thymine and cytosine have single-ring structures.

Courtesy: Campbell Essential Biology, Pearson

An RNA Nucleotide



The RNA nucleotide differs from the DNA nucleotide in two ways:

I. The RNA sugar is ribose rather than deoxyribose

I. The base is uracil (U) instead of thymine (T). The other three kinds of RNA nucleotides have the same bases A, C, and G, as in DNA.

The sugar-phosphate backbone here is formed by the **same phosphodiester bond** between the 3’ C of sugar of one ntd. and 5’ phosphate of the second ntd.

Courtesy: Campbell Essential Biology, Pearson

Double Helix and Complementary Base Pairing

•**Nucleotides** are linked together by **phosphodiester bonds** to form polynucleotide strands.

•DNA consists of two strands of nucleotides twisted around each other to form a shape called a **double helix.**

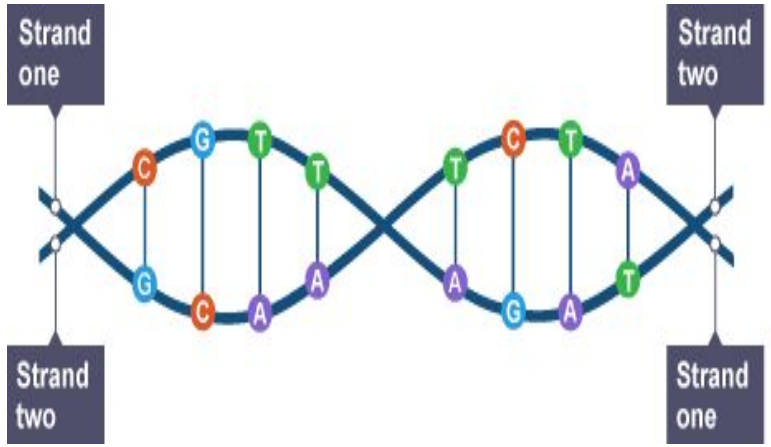
•The **two strands** are held together by weak **hydrogen bonds** between pairs of bases.

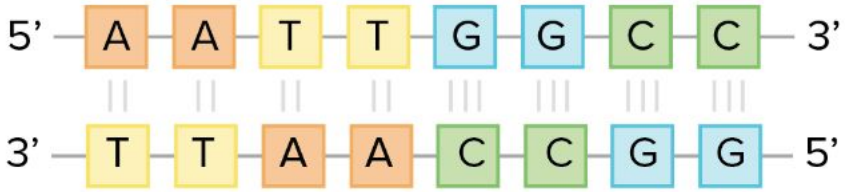
•Only certain pairs of bases have complementary shapes that let them form bonds with each other to make the double helix.

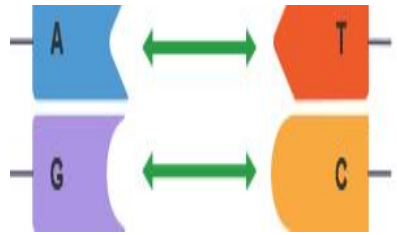
•Base A bonds with base T and base G bonds with base C. These are complementary.

So, The amount of A = always the amount of T

The amount of G = always the amount of C







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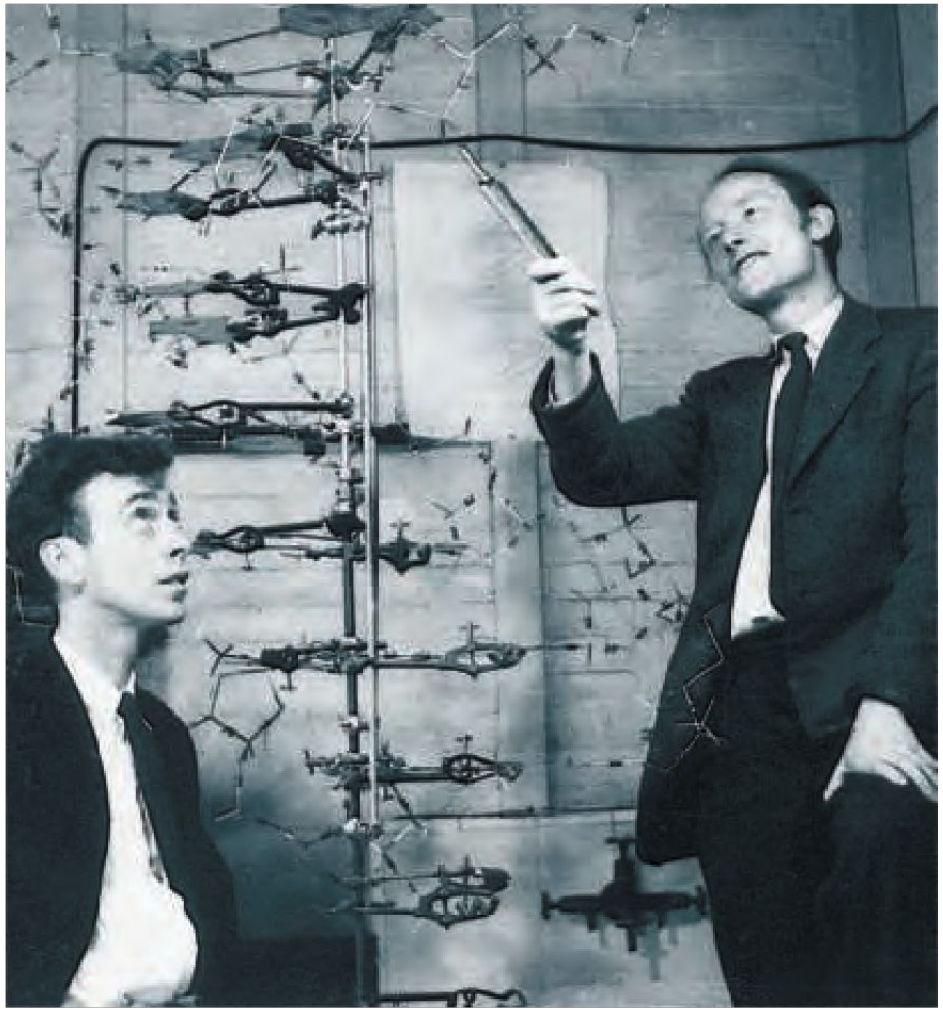
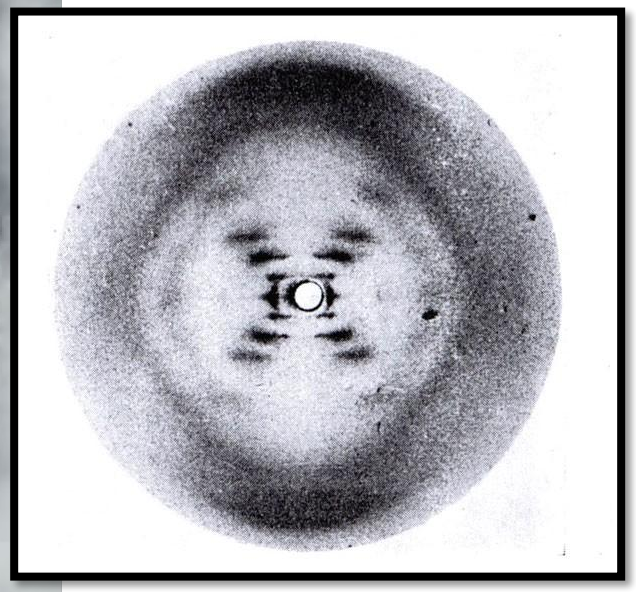
Discoverers of the Double Helix



James Watson (left) and Francis Crick. The discoverers of the structure of DNA are shown in 1953 with their model of the double helix.

Rosalind Franklin Using X-rays, Franklin generated some of the key data that provided insight into the structure of DNA.



Rosalind Franklin's
X-ray Diagram of DNA

Watson and Crick brought together data from a number of researchers (including Franklin, Wilkins, Chargaff, and others) to assemble their celebrated model of the 3D structure of DNA.

Courtesy: Campbell Essential Biology, Pearson, Khan Academy

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Watson and Crick's Model of the DNA

This model has the following major features:

•Two long polynucleotide chains are coiled around a central axis, forming a right-handed double helix. The sugar-phosphate backbones make up the outside of the helix.

•The two chains are antiparallel; that is, their C-5'- to-C-3' orientations run in opposite directions.

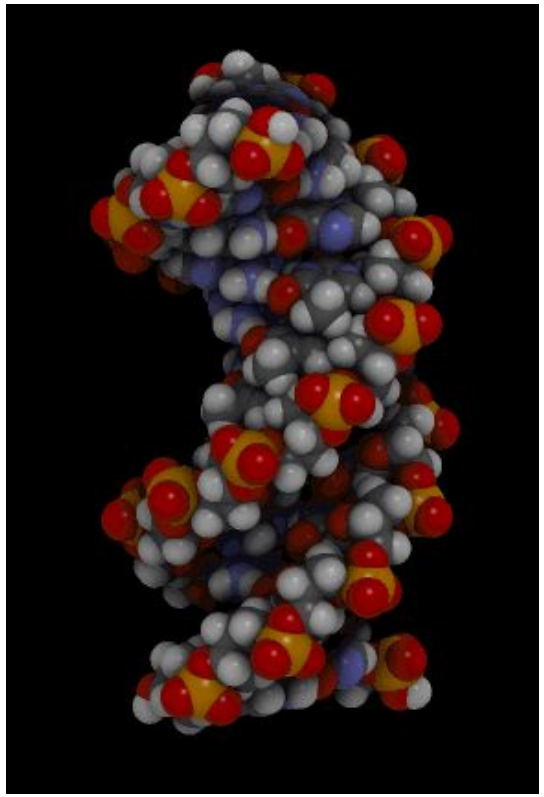
•The bases of both chains are flat structures lying perpendicular to the axis; they are "stacked" on one another, 3.4 Å (0.34 nm) apart, on the inside of the double helix.

•The nitrogenous bases of opposite chains are *paired* as the result of the formation of hydrogen bonds; in DNA, only A,T and G,C pairs occur.

•Each complete turn of the helix is 34 Å (3.4 nm) long; thus, each turn of the helix is the length of a series of 10 base pairs ~ 10 nucleotides.

•A larger major groove alternating with a smaller minor groove winds along the length of the molecule.

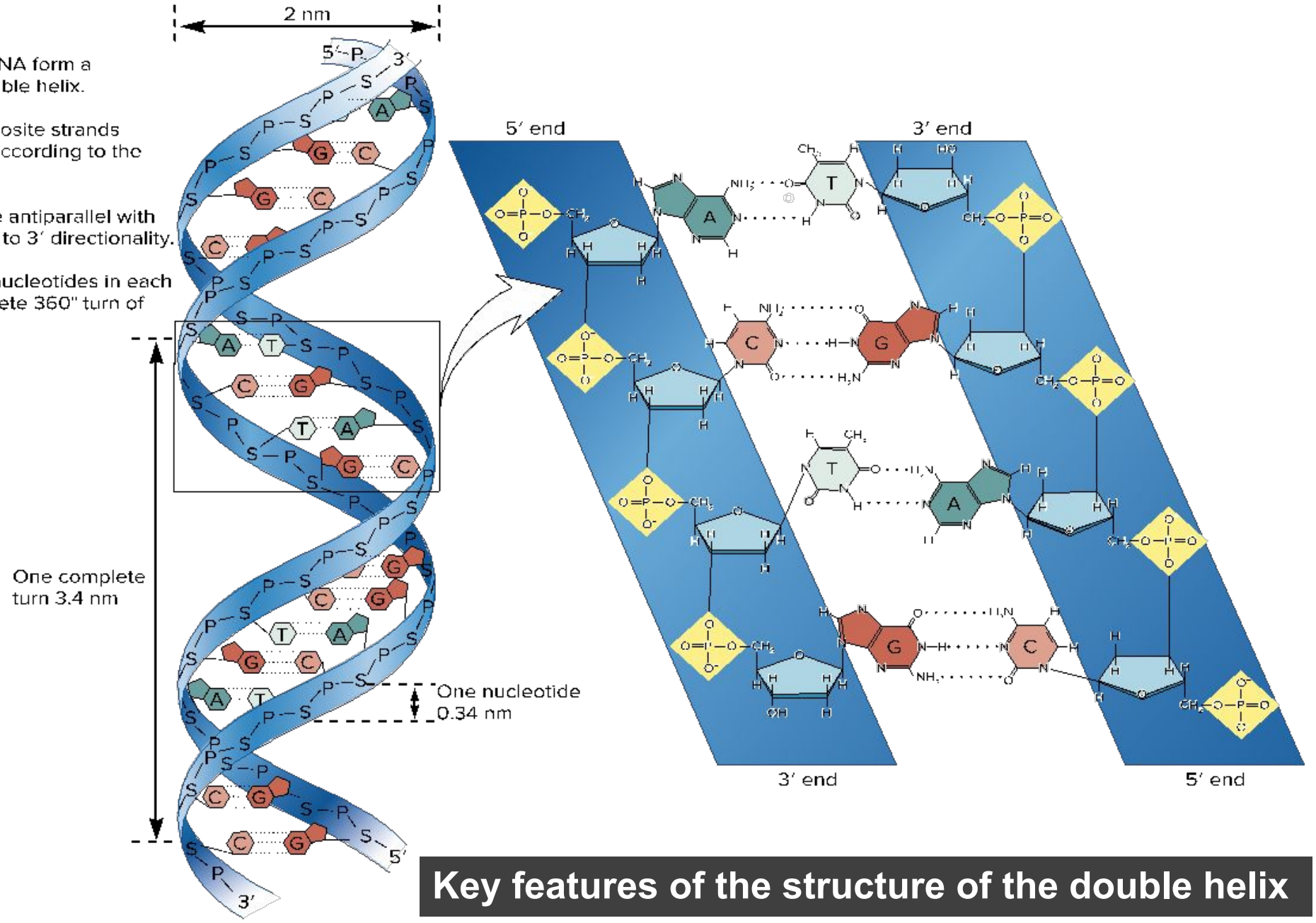
•The double helix has a diameter of 20 Å (2.0 nm).



Courtesy: Khan Academy

Key Features

- Two strands of DNA form a right-handed double helix.
- The bases in opposite strands hydrogen bond according to the AT/GC rule.
- The 2 strands are antiparallel with regard to their 5′ to 3′ directionality.
- There are ~10.0 nucleotides in each strand per complete 360° turn of the helix.



Key features of the structure of the double helix

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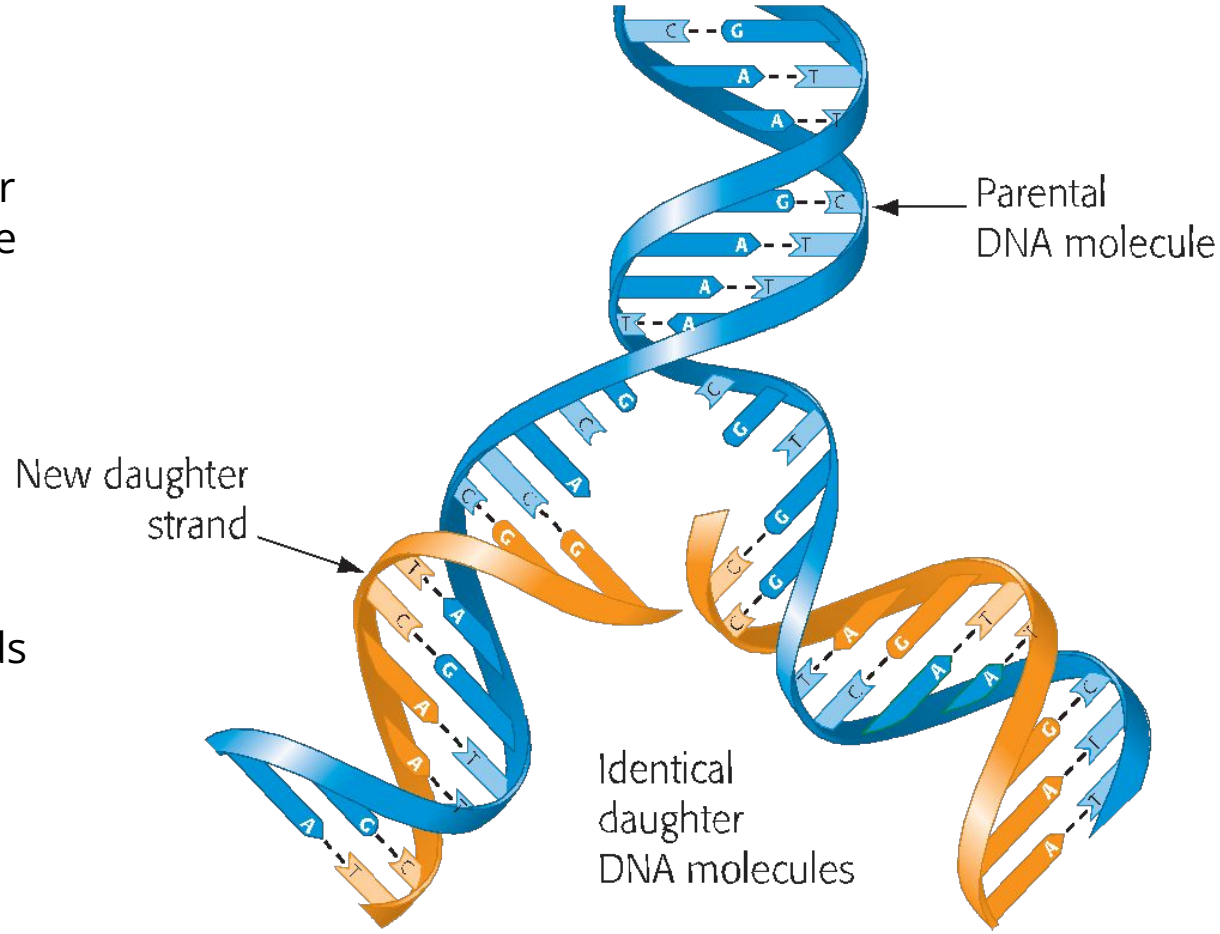
DNA Replication

https://youtu.be/TNKWgcFPHqw?feature=shared

- DNA is the genetic material which bears the hereditary information, passed on from one generation to the next.
- DNA is copied before cell divides, as the daughter cells should have the exact amount of DNA as the parent cell ➡ **DNA replication**
- The two strands of parental DNA separate, and each becomes a template for the new strands: **Semiconservative!**
- The new strands formed from a supply of free nucleotides are complementary to the old strands (parental template strands).
- The parental DNA untwists as its strands separate, and the daughter DNA rewinds as it forms from them. Replication results in **two daughter DNA molecules**, each consisting of one old strand and one new strand.



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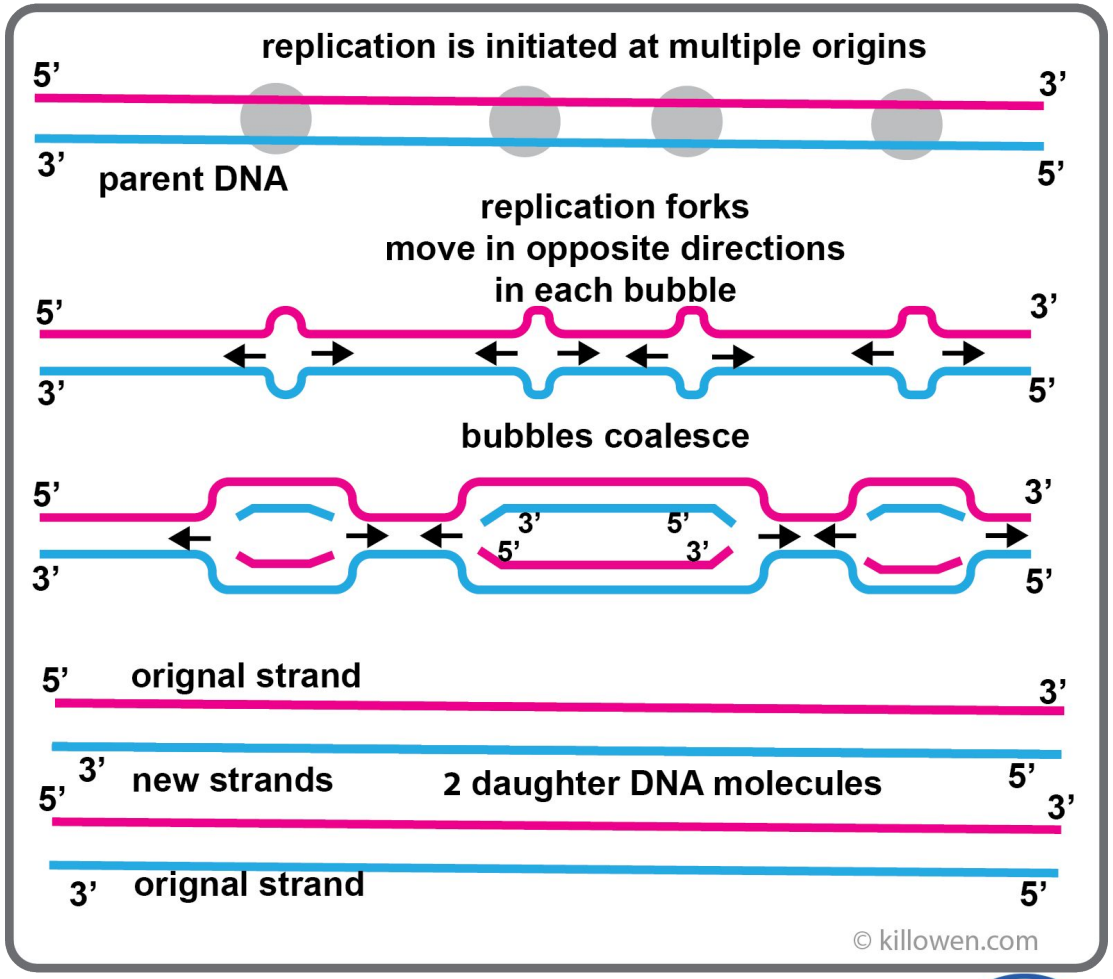
Origin of Replication

- DNA replication begins on a double helix at specific sites, called **origin of replication**.
- Specialized proteins recognize the origin site, bind to it and help open the DNA up. This leads to the formation of 2 **replication forks** (Y-shaped structure).
- Replication then proceeds in both directions, creating what are called **replication "bubbles".**
- The replication forks move in opposite directions, elongating daughter strands on both sides of each bubble.
- The DNA molecule of a typical eukaryotic chromosome has many origins where replication can start simultaneously, shortening the total time needed for the process. Eventually, all the bubbles merge, yielding two completed double-stranded daughter DNA molecules.

Multiple "bubbles" in replicating DNA



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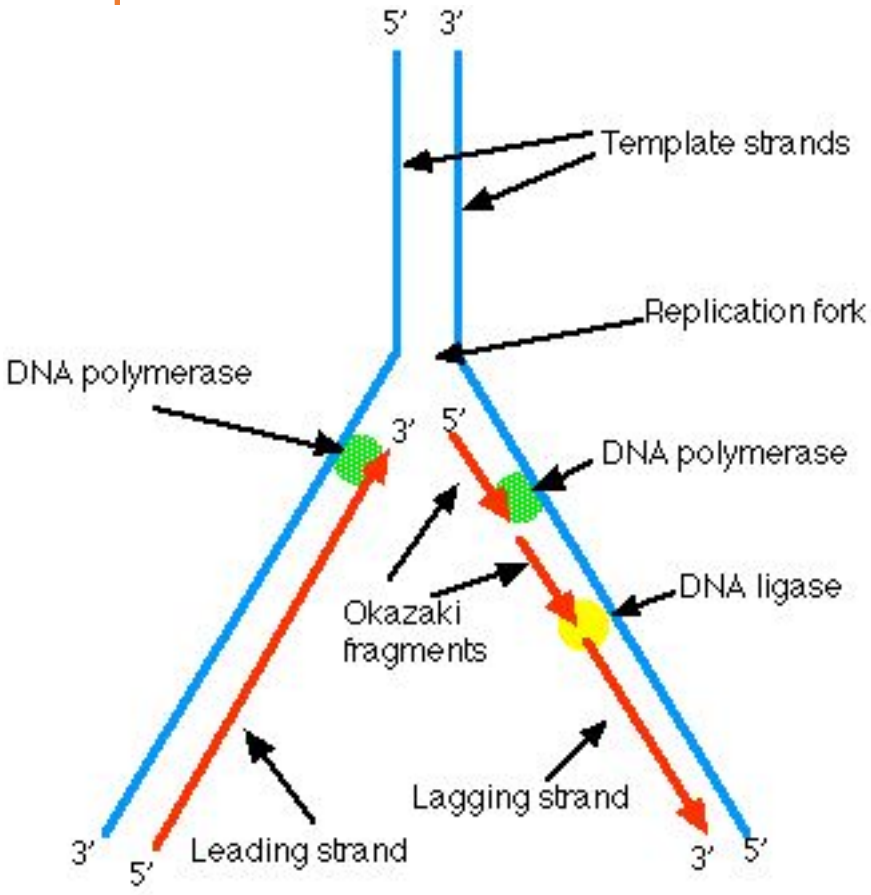
DNA Replication: The steps



- After the DNA separates at the origin, an enzyme called **Helicase** help move the replication fork by unwinding the DNA.
- Another enzyme, **Primase** comes and provides starting point (primer) from where the new DNA strand would be synthesized.
- The enzyme **DNA polymerase** starts synthesizing the new strands from the primer: adds nucleotides one by one that are complementary to the template.
- DNA polymerase basically forms the covalent phosphodiester bonds between the incoming nucleotides. The ntd.s also pair with the complementary bases of the template strand by forming hydrogen bonds.
- DNA pol. can only synthesize DNA in the **5' to 3' direction** but since DNA double helix is antiparallel, the 2 new strands are synthesized in 2 different ways.
  - One new strand synthesized continuously: **leading strand**
  - The other new strand synthesized in Okazaki fragments: **lagging strand**
- When the whole parental DNA is replicated, the primers are removed and replaced by ntd.s with help of DNA pol.
- The remaining gaps are sealed by another enzyme called **DNA ligase.**

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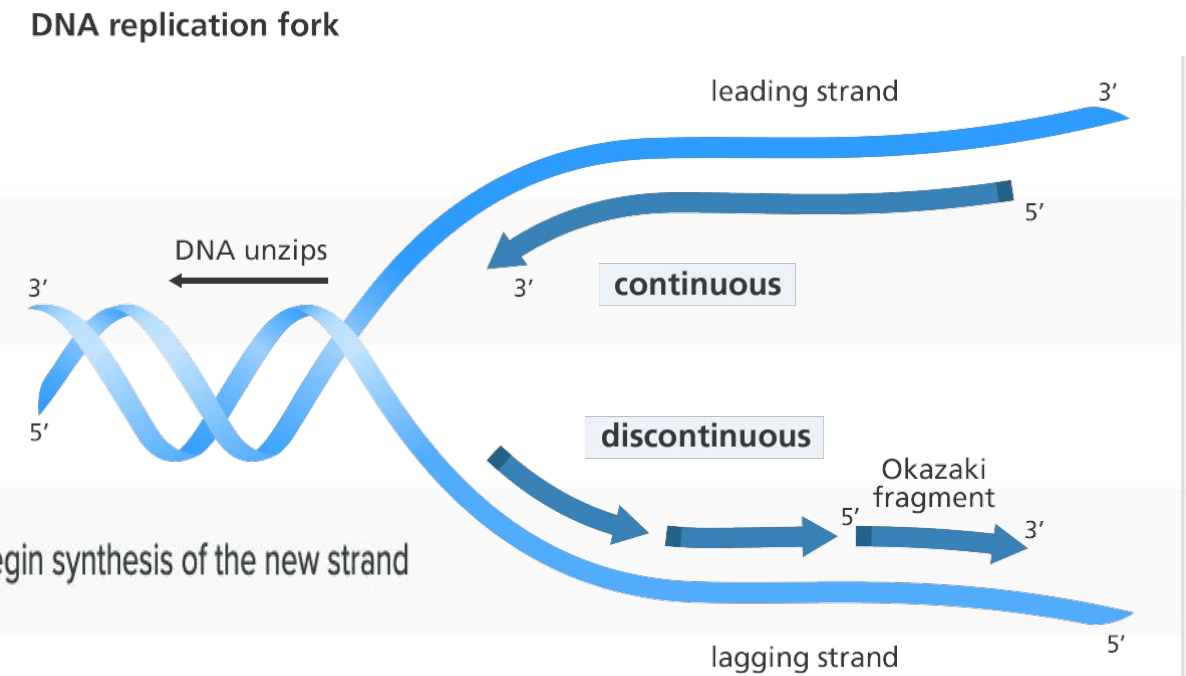
Important Enzymes in DNA Replication

Enzyme	Function
Topoisomerase	Relaxes the super-coiled DNA
DNA helicase	Unwinds the double helix at the replication fork
Primase	Provides the starting point for DNA polymerase to begin synthesis of the new strand
DNA polymerase	Synthesizes the new DNA strand; also proofreads and corrects some errors
DNA ligase	Re-joins the two DNA strands into a double helix and joins Okazaki fragments of the lagging strand



Animation on replication: https://www.youtube.com/watch?v=9EwNHIMfKR8

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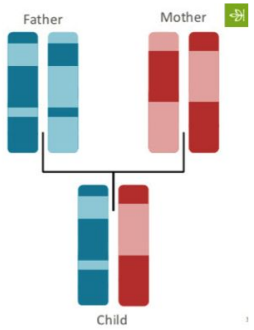
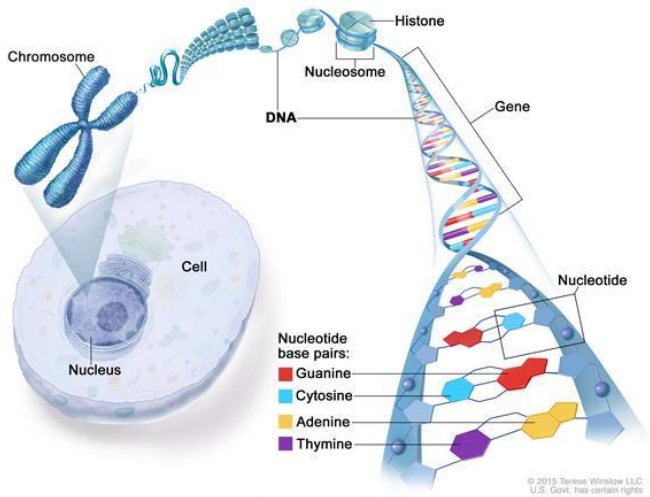
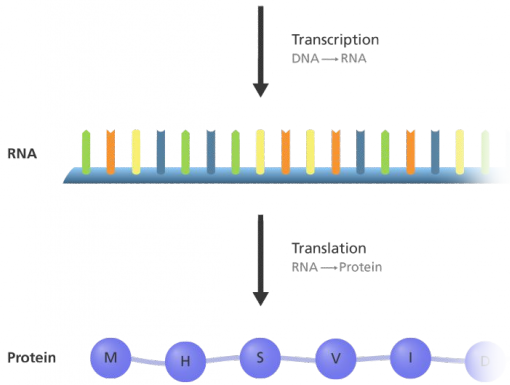
How does an organism's genotype determine its phenotype?







- DNA: The genetic material that holds the inheritable information within the nucleotide sequence. An organism's genetic make up is known as **"Genotype".**
- But how does the sequence of DNA (genotype), determine the observable characteristics which is known as **"Phenotype"** of an organism?
- DNA is not just stretch of nucleotides, but it contains areas of functional units, which are called **"genes".**
- Each gene holds the instructions for a functional product, a protein (polypeptide) molecule with specific purpose in the organism's system.
- The process of how DNA directs the formation of polypeptide can be divided into **2 important steps**:

1. **Transcription:** The transfer of genetic information from DNA into an RNA molecule.
2. **Translation:** The transfer of the information from RNA into a polypeptide (amino acid chain).

- This flow of genetic information from DNA to RNA to Protein is known as **"Central Dogma".**

Courtesy of Khan Academy

From Nucleotides to Amino Acids: The Flow of Chemical Language of DNA

Transcription

- DNA (gene) ⟶ RNA (messenger RNA or mRNA)
- The sequence of deoxyribonucleotides of DNA rewritten (transcribed) in a sequence of ribonucleotides of RNA

  Molecule: **Nucleic acid**

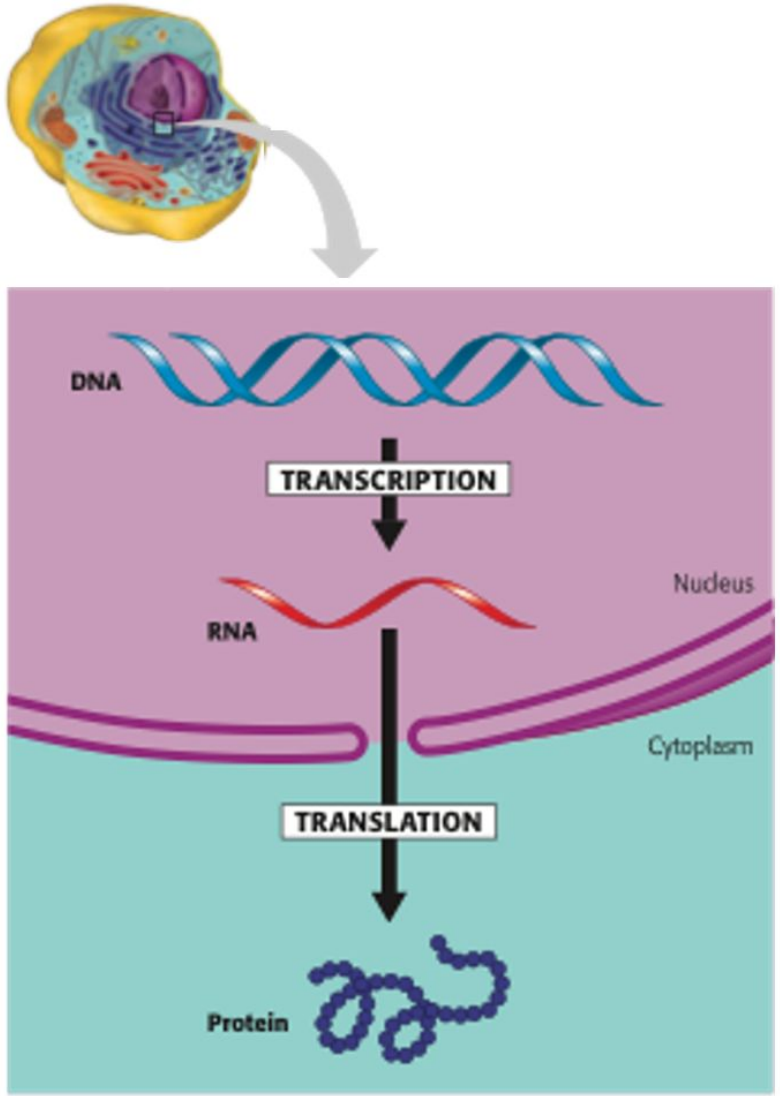
  Location: **Cell's nucleus**

Translation

- RNA (mRNA) ⟶ Polypeptide chain
- The sequence of ribonucleotides of RNA translated to sequence of amino acids of polypeptide chain
- Polypeptides are polymers of amino acid monomers

  Molecule: from **Nucleic acid to Protein/ Polypeptide**

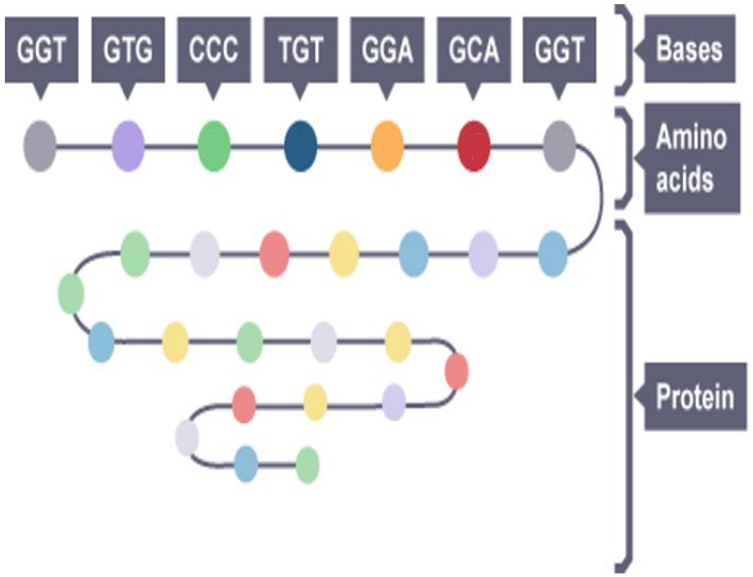
  Location: **Cell's cytoplasm**



The Genetic Code

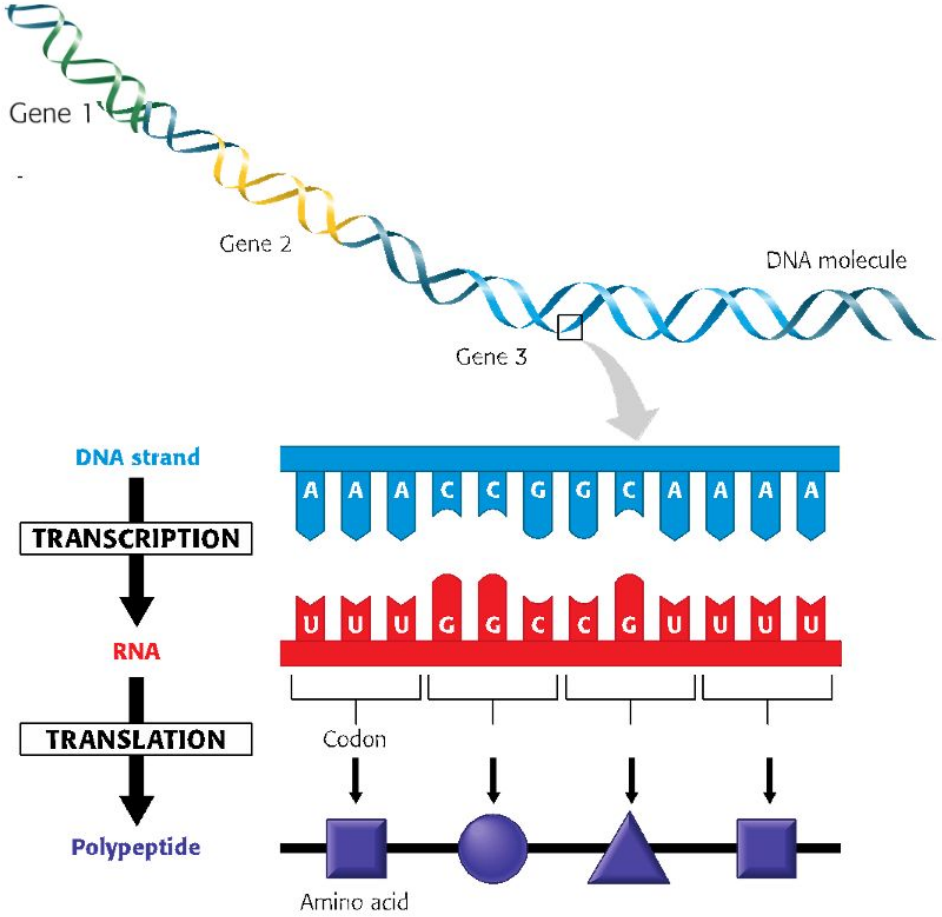
How does the DNA sequence of a gene, determine the sequence of amino acids?

- The DNA must contain **codes**!
- The **sequence of nucleotides** in a DNA molecule can determine the sequence of amino acids in a protein molecule. **Groups of three nucleotides: triplets** represent different amino acids.
- This is the basis of the genetic code. The triplet codes within the DNA and then RNA hold the instructions for the amino acid sequence. Thes codes are known as **codons.**
- The nucleotides are identified by their bases and there are 4 bases. So possible codon number = $\mathbf{4^3 = 64}$; more than enough to specify the 20 amino acids.



The Genetic Code

- Every living organism is built with this **same set of 20 amino acids**.
- So, the codons or triplet codes are **universal** for all living organisms on planet Earth.
- The codons, written in DNA are first transcribed to mRNA.
- Each codon within the mRNA similarly consists of 3 ribonucleotides. With several exceptions, each codon usually specifies *one* amino acid.
- The standard genetic code is represented as an **RNA codon table**, as proteins are directly made from mRNA.

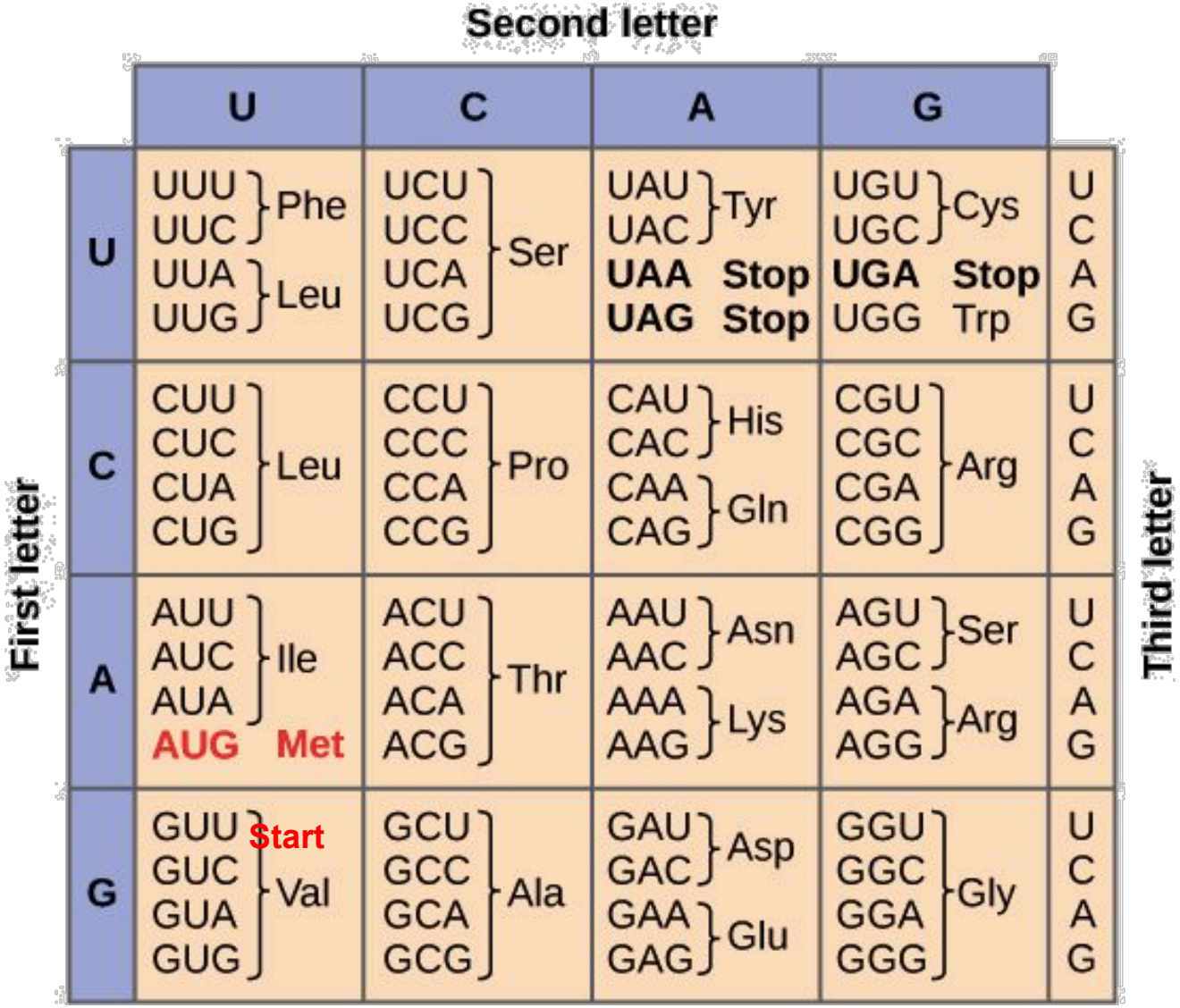


The Genetic Code

- There is **1 "start codon"** & **3 "stop codons"** which **initiate** and **terminate** translation, respectively.

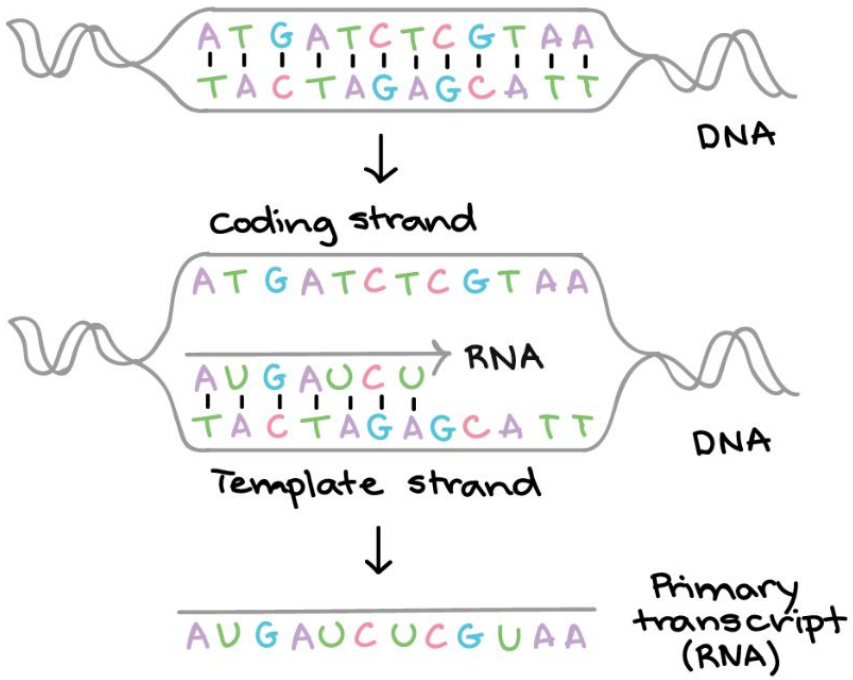
- **Start codon: AUG** codes for amino acid **methionine**. So, methionine initiates most polypeptide chains.
- **Stop codon: UAA, UAG, and UGA** are termination signals and do not encode any amino acids.

- All the amino acids are represented by two to six codons except for methionine (AUG) and tryptophan (UGG).



The dictionary of the genetic code

Transcription: From DNA to RNA



- Before transcription, the DNA unwinds and exposes its two strands. But **only one of the DNA strands serves as a template** to synthesize the complementary RNA molecule ⟹ single stranded RNA
- The other strand remains unused.

- Participants:

1. - The **DNA molecule** with the template strand
2. - An enzyme called **RNA polymerase**
3. - Free **ribonucleotides**

- Product:
- **RNA molecule** also called primary transcript/ pre-mRNA

- The process of transcription can be divided into 3 stages:
- - Initiation
- - Elongation of RNA
- - Termination

Transcription: The steps

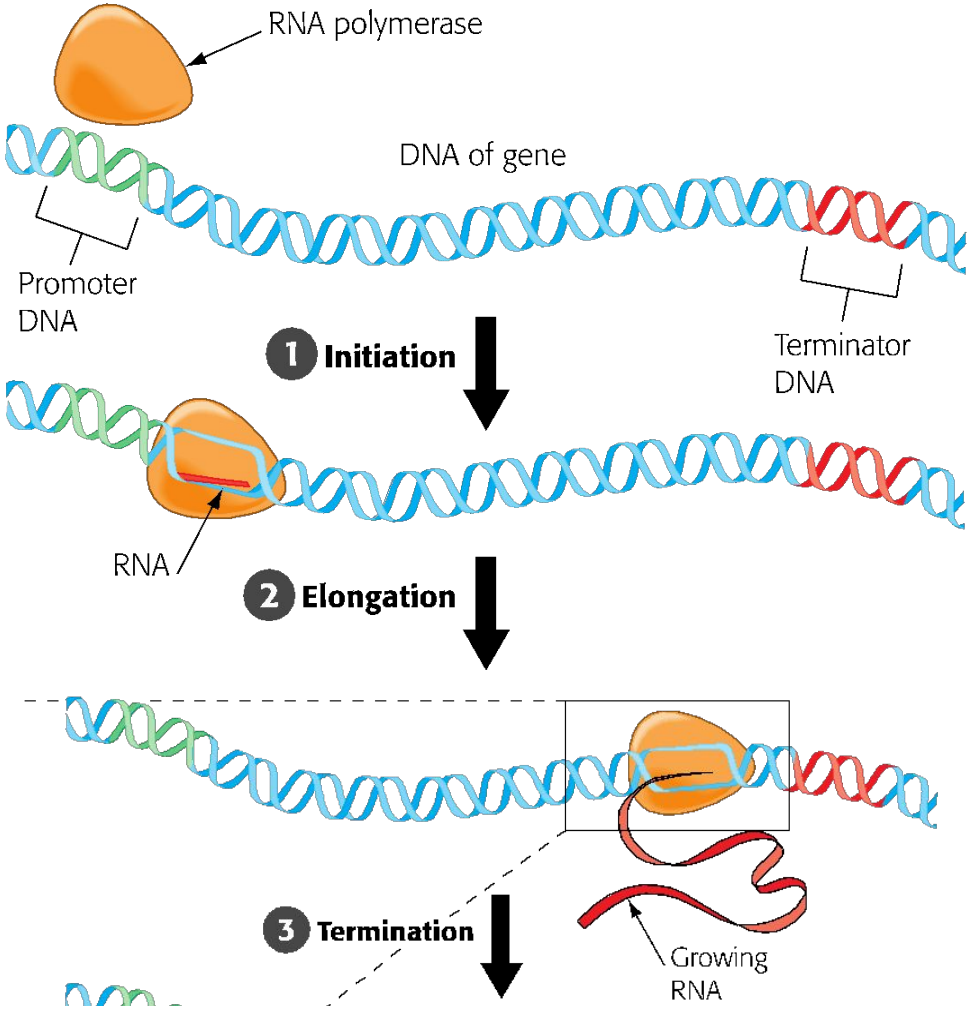
1. Initiation of transcription

- **In the DNA**, there is a nucleotide sequence which signals the **start of transcription**: **"Promoter".** The promoter is located at the beginning of a gene, and this is where the **RNA polymerase attaches**. The first step of transcription is the attachment of RNA polymerase to the promoter which initiates RNA synthesis.

2. RNA Elongation

- During this stage, RNA is synthesized.
- The ribonucleotides that make up the new RNA take their place one at a time along the complementary DNA template strand by forming **hydrogen bonds** with the deoxyribonucleotide bases of the **DNA**. The usual base-pairing rules are followed, except that **U pairs with A**.
- The ribonucleotides are linked to each other by the transcription enzyme **RNA polymerase** through forming **phosphodiester bonds**.

- As RNA synthesis continues, the RNA strand peels away from its DNA template, allowing the two separated DNA strands to come back together in the region already transcribed.

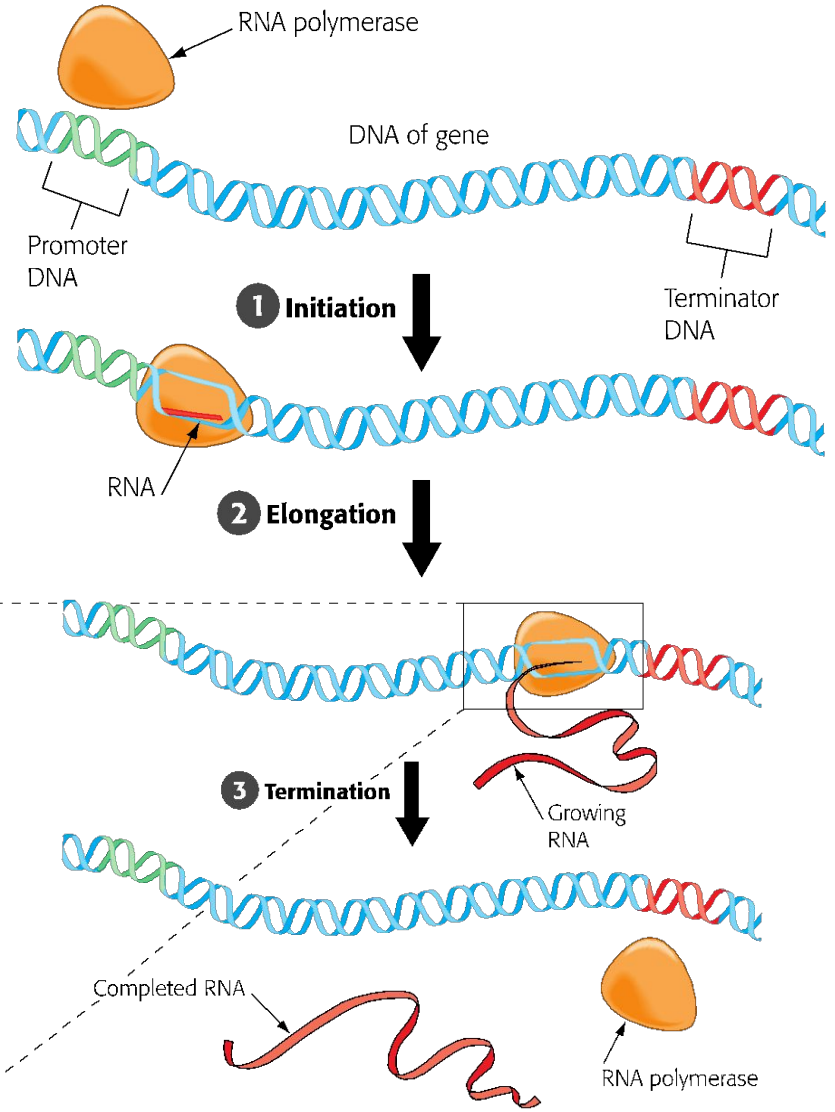


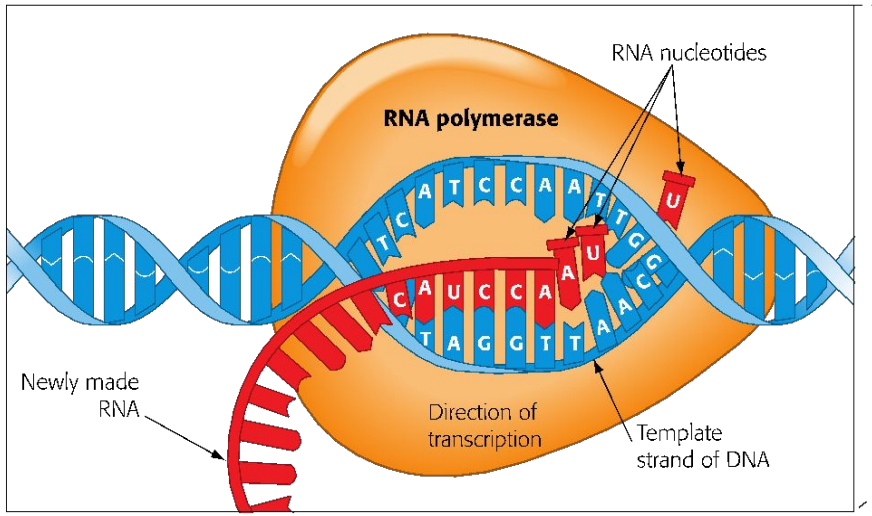
Transcription: The steps

3. Termination of transcription

- As the RNA polymerase moves along the DNA, the DNA unwinds to continue transcription.
- This continues until the **terminator sequence** is reached. This sequence in the DNA signals **the end of the gene**, meaning transcription should be terminated here.

- At this point, the RNA polymerase molecule detaches from the RNA molecule and the gene, and the DNA strands rejoin.





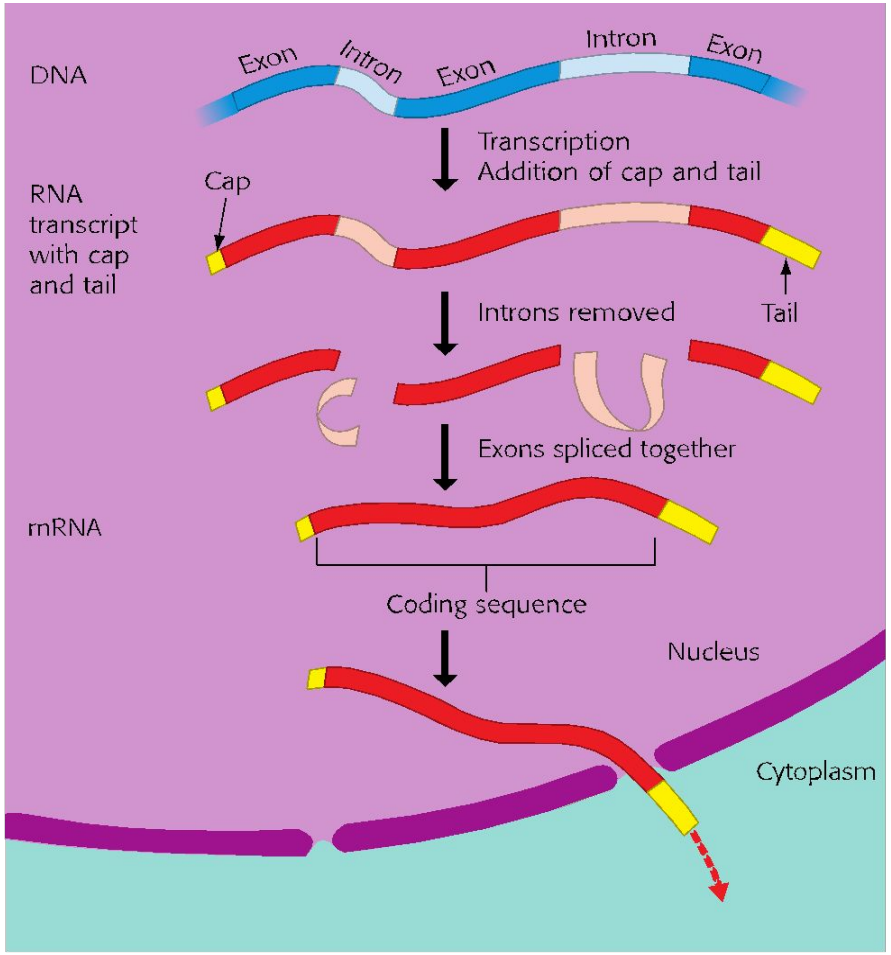
The Processing of Eukaryotic mRNA

- In eukaryotes, the RNA transcribed from DNA has to go through some modifications, before it can be translated to polypeptide chain. This "pre-mature" RNA is called: **pre-mRNA/ primary transcript/ RNA transcript**

- There are 3 ways to process this pre-mRNA and make it ready for translation:

1. Capping (5' end): addition of chemical group at 5' end of transcript
2. Tailing (3' end): addition of chemical group at 3' end of transcript
Both capping and tailing protect the transcript, help it get exported from the nucleus to cytoplasm to be recognized by ribosome.

3. Splicing: deals with the two regions of a gene- **intron (non-coding) and exon (coding).** Both exons and introns are transcribed from DNA into RNA. The noncoding stretches of nucleotides interrupt the nucleotides that code for amino acids. So, the introns need to be removed before the RNA leaves the nucleus for translation. After removing introns, the exons are joined to produce an mRNA molecule with a continuous coding sequence.



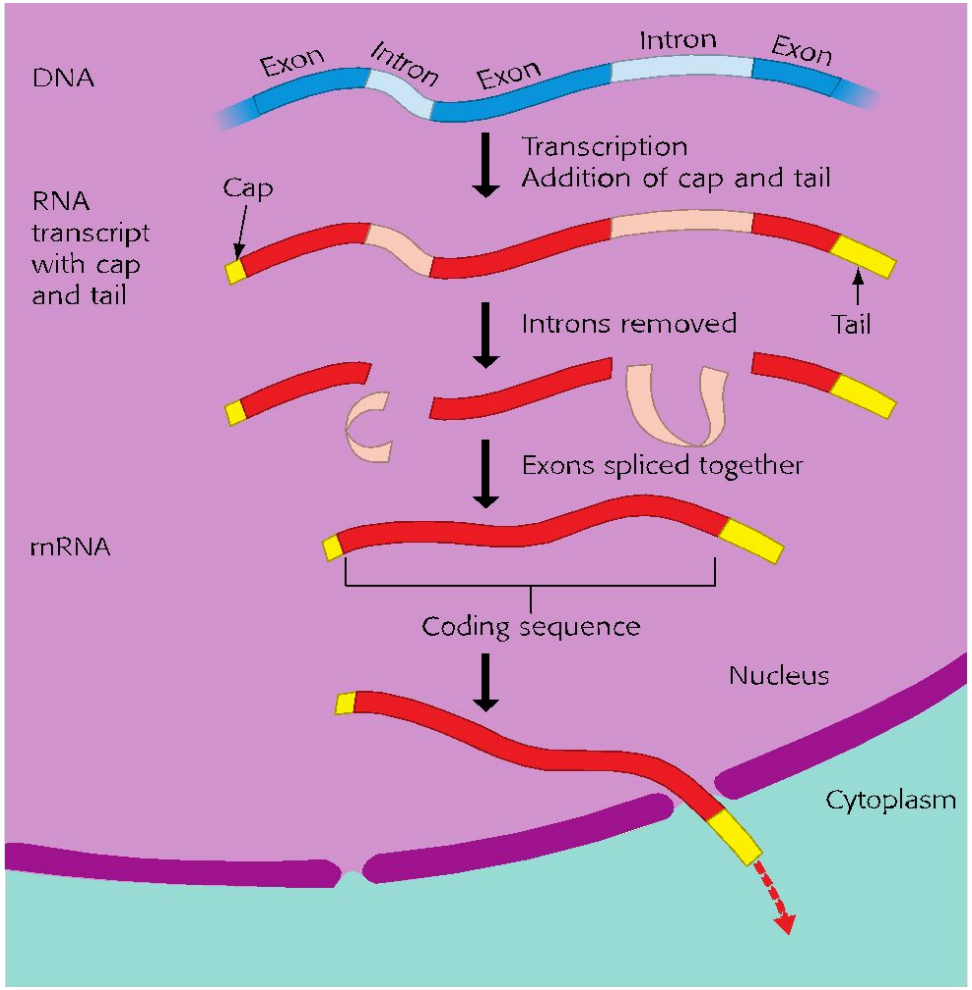
Courtesy of Khan Academy

The Processing of Eukaryotic mRNA

- **Significance of splicing:** RNA splicing is believed to play an important role in humans in allowing our approximately 21,000 genes to produce many thousands more polypeptides. This is accomplished by varying the exons **(different exon combinations from a single gene)** that are included in the final mRNA – **alternative splicing**.

- The mRNA that leaves the nucleus is substantially different from the RNA that was first transcribed from the gene.

- In the cytoplasm, the coding sequence of the final **mature mRNA** will be translated with the help of protein-synthesizing machinery.



Translation: From RNA to Protein

- In cytoplasm, the mature mRNA is now ready for protein synthesis.
- The codons of the mRNA are read one by one to synthesize the polypeptide chain.

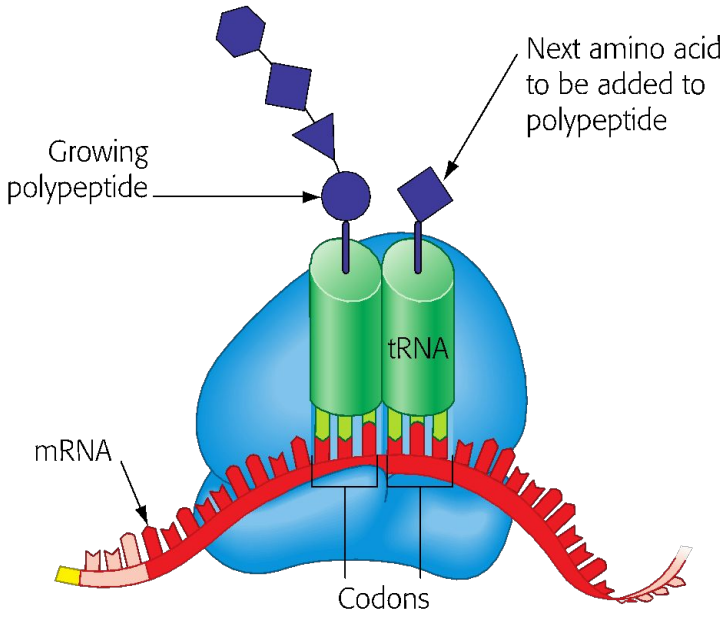
- Participants:

- **Messenger RNA (mRNA):** synthesized in nucleus from DNA

- **Transfer RNA (tRNA):** molecules that connect mRNA to amino acids. Has 2 parts. One end of a tRNA has a sequence of three nucleotides called an **anticodon**, which can bind to complementary **mRNA codons**. The other end of the tRNA carries the **amino acid** specified by the codons.

- **Ribosome:** structure where the polypeptide chain is made. Has 2 subunits which come together for translation.

- **Amino acids:** monomers that build the polypeptide chain. Found freely in the cytoplasm.



During polypeptide synthesis, a ribosome holds one molecule of mRNA and two molecules of tRNA. The growing polypeptide is attached to one of the tRNAs.

Courtesy of Khan Academy

Translation: The steps

- Translation can be divided in 3 stages, similar to transcription.

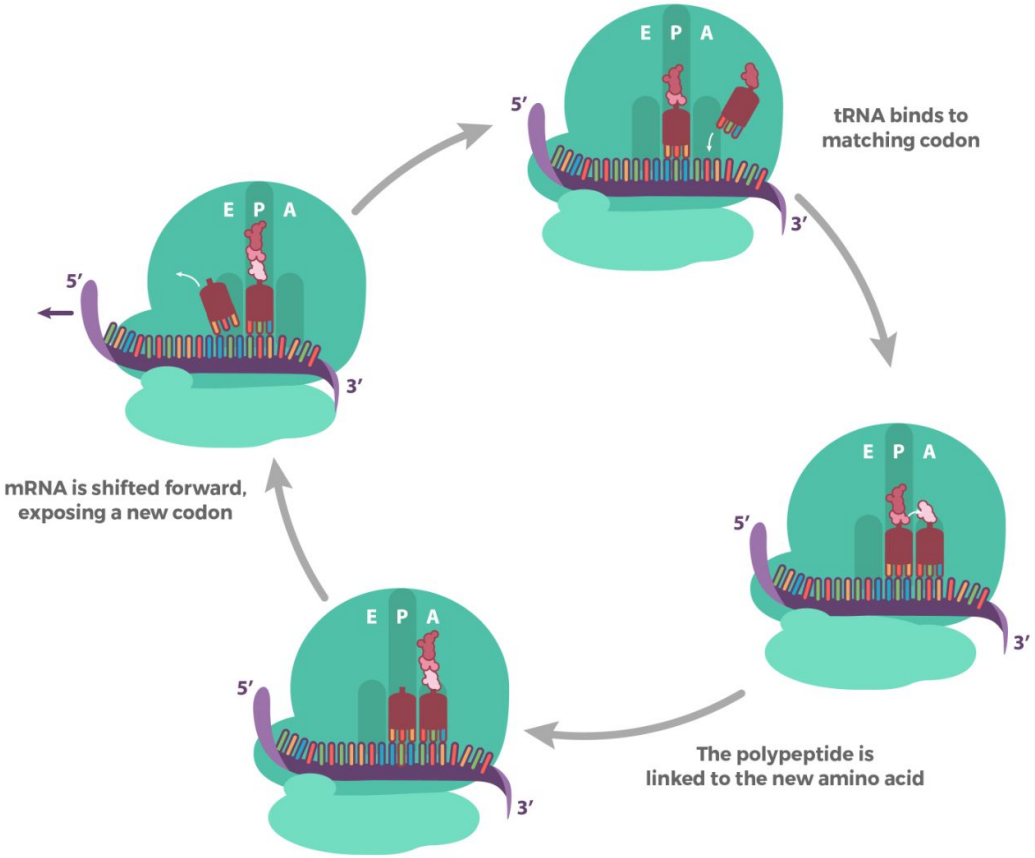
1. **Initiation:** The ribosome assembles with the mRNA and the first tRNA which brings the first amino acid (met) encoded by the start codon.

2. **Elongation of polypeptide chain:** During this stage, the amino acid chain is extended. The mRNA is read, one codon at a time.

When a codon is read:

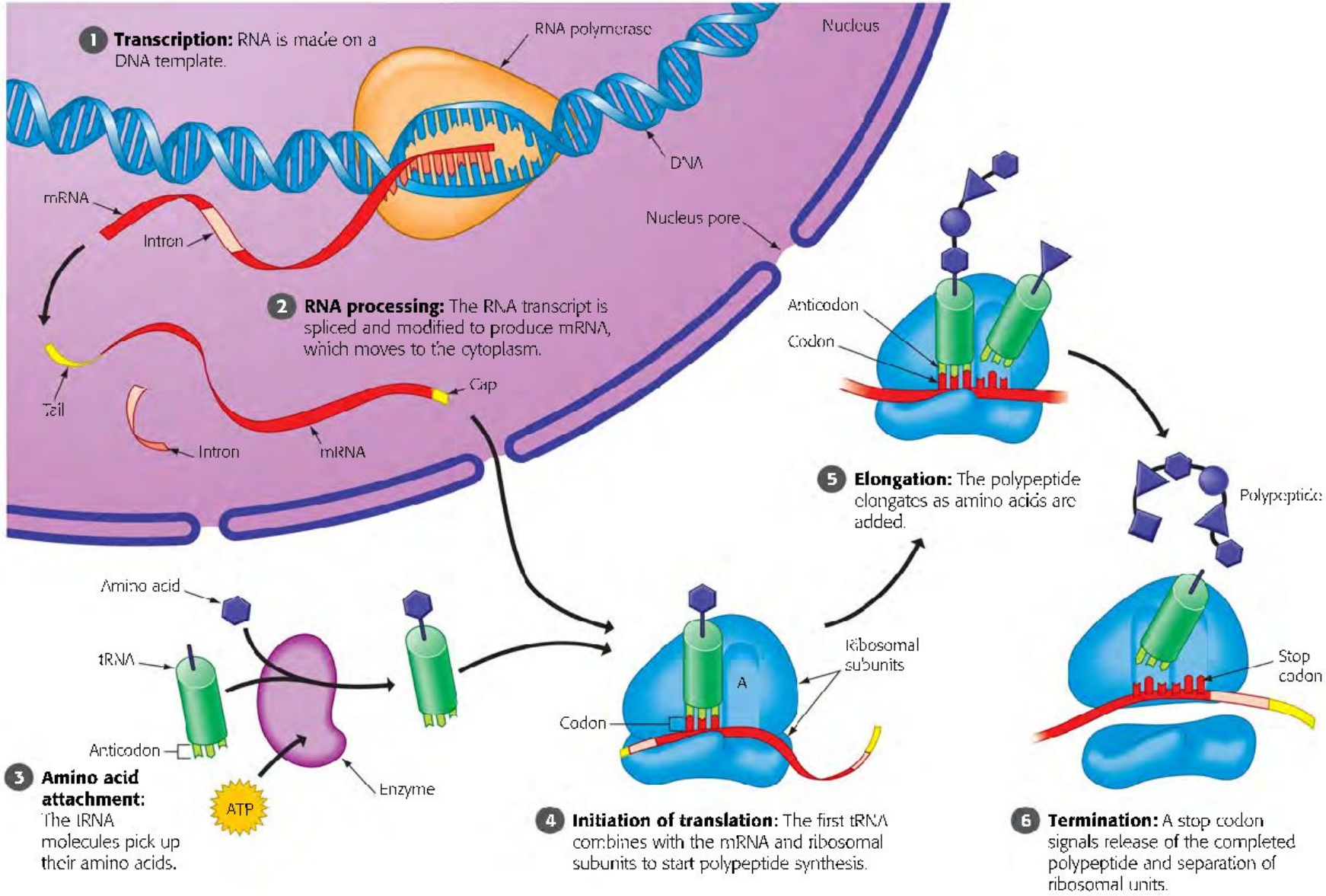
- A matching tRNA binds to the codon (A site)
- The existing growing chain binds to the new amino acid brought by the tRNA (from P to A site)
- The mRNA moves one codon forward in ribosome (new codon in A site)
- Empty tRNA is released (from E site)

3. **Termination:** When a stop codon reaches the A site of ribosome, translation is terminated. The completed polypeptide is released.



Courtesy of Khan Academy

A Summary of Transcription & Translation



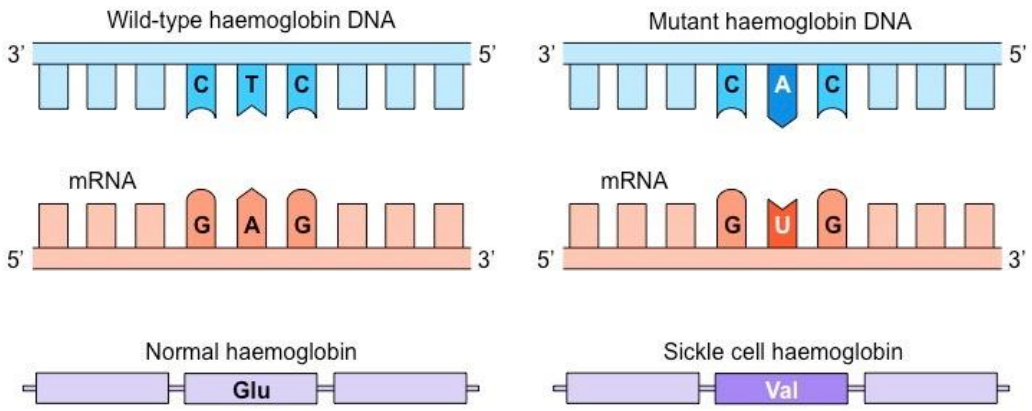
Animation on transcription & translation: https://www.youtube.com/watch?v=gG7uCskUOrA

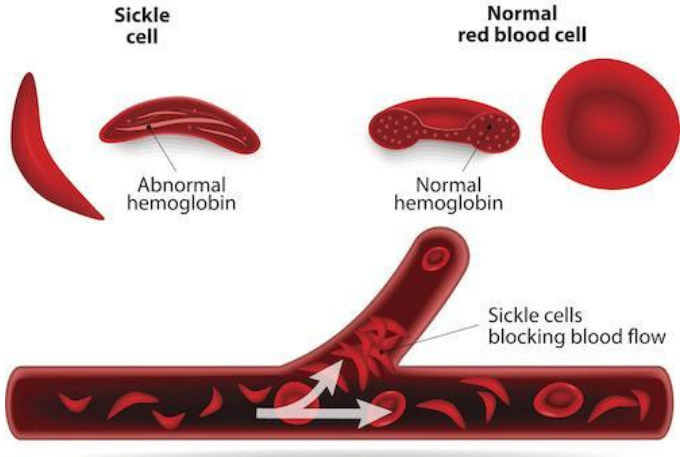
Mutation

- Mutations are changes in the **DNA sequence**, may lead to abnormal protein production.
- Affected region can vary: large regions of a chromosome or just a single nucleotide pair.

- Usually, mutations don't have major effects, as
  - can be repaired quickly by repairing machineries
  - mostly occur in somatic cells which are not passed on to next generation.

- But can have larger effects when mutations occur in **germline cells (eggs, sperms).**
- For e.g. sickle cell disease is a genetic condition inherited from parents. The mutation involved affects only a single nucleotide pair. The sickle-cell allele differs from its normal counterpart, a gene for hemoglobin, by only one nucleotide. This difference changes the mRNA codon from one that codes for the amino acid glutamic acid (Glu) to one that codes for valine (Val).





Types of Mutation

Mutations within a gene can be divided into two general categories: nucleotide substitutions and nucleotide insertions or deletions

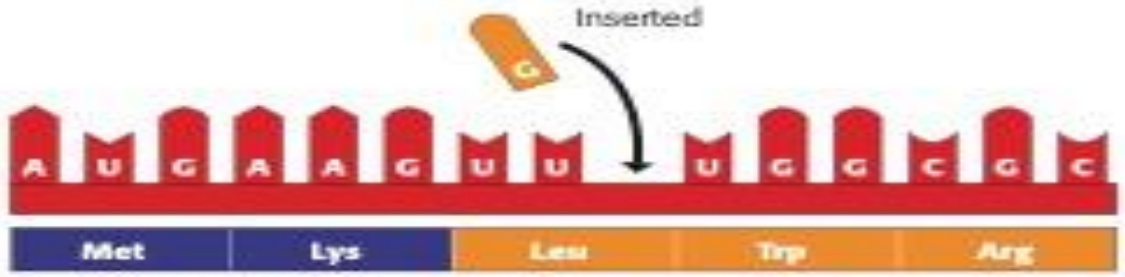
Type of Mutation	Effect
Substitution of one DNA base for another	**Silent** mutations result in no change to amino acids.
	Missense mutations swap one amino acid for another.
	Nonsense mutations change an amino acid codon to a stop codon.
Insertions or **deletions** of DNA nucleotides	Frameshift mutations can alter the triplet grouping of codons and greatly change the amino acid sequence.

Three Types of Mutations and Their Effects

mRNA and protein from a normal gene

(a) Base substitution. Here, an A replaces a G in the fourth codon of the mRNA. The result in the polypeptide is a serine (Ser) instead of a glycine (Gly). This amino acid substitution may or may not affect the protein's function.

(b) Nucleotide deletion. When a nucleotide is deleted, all the codons from that point on are misread. The resulting polypeptide is likely to be completely nonfunctional.



(c) Nucleotide insertion. As with a deletion, inserting one nucleotide disrupts all codons that follow, most likely producing a nonfunctional polypeptide.

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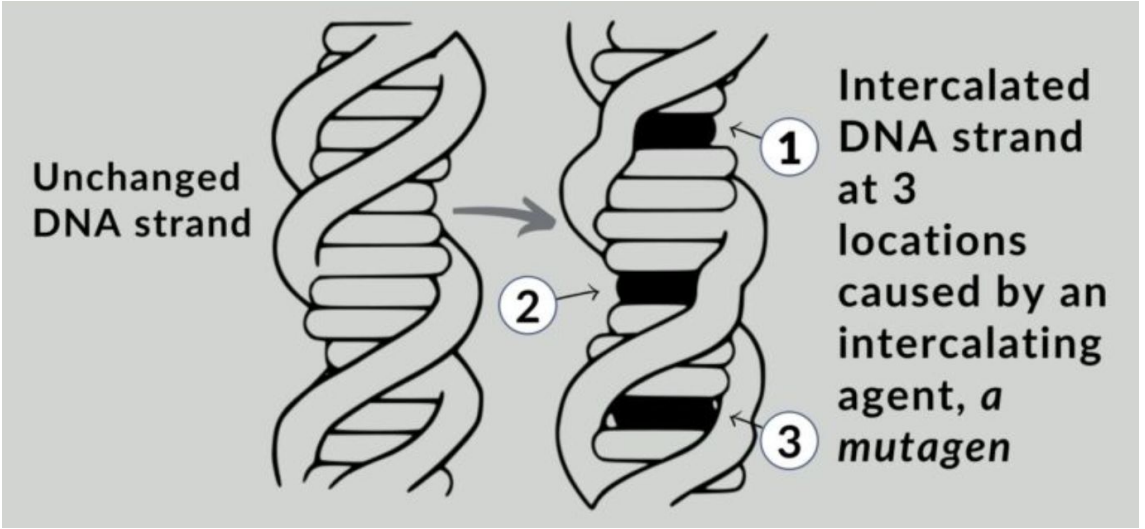
Mutagens

- Mutations can occur in several ways. Spontaneous mutations result from random errors during DNA replication or recombination.

- Other sources of mutation are mainly physical, chemical & biological agents known as **mutagens**.



- **Physical mutagen** examples could be high- energy radiation, such as X-rays and ultraviolet (UV) light.

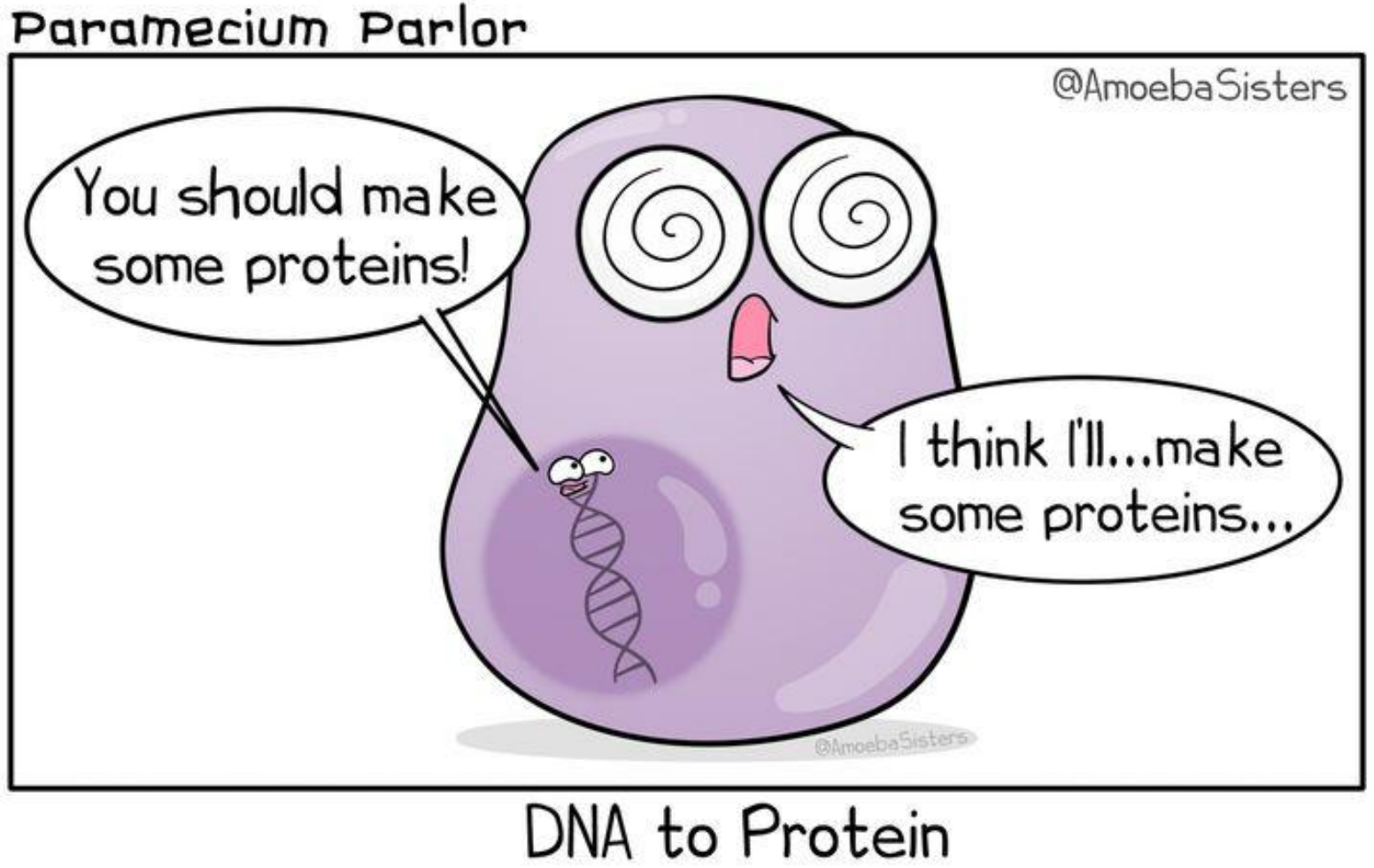
- **Chemical mutagens** are of various types. One type, for example, consists of chemicals (base analogs) that are like normal DNA bases but they base-pair incorrectly when incorporated into DNA.

- **Biological agents** could be viruses that incorporate their DNA into host DNA sequence (HIV).

- Mutagens can act as carcinogens (agents that cause cancer).

Courtesy of Biology Online

Thank You!



Courtesy of Amoeba Sisters