Biological Chemistry Department

Biological Chemistry

Transfer of Genetic Information. Protein Biosynthesis in the Cell. Mechanisms of Protein Biosynthesis Regulation. Antibiotics.

Speciality: Pharmacy for foreign students (Language of instructions – English)

Lecturer: ass. prof. Kravchenko G.B.

Lecture Plan

1. Transfer of Genetic Information.
1.1. DNA: Genetic Information, Replication, and Repair.
1.2. RNA metabolism.
1.3. Genetic Code.
2. Protein Biosynthesis in the Cell.
2.1. Structure and functions of Ribosomes.
2.2. The basic steps in protein synthesis.
2.3. Translation. Protein Biosynthesis Stages.
3. Mechanisms of Protein Biosynthesis Regulation.
3.1. Protein Biosynthesis Inhibition. Antibiotics.
3.2. Preparations that Stimulated Protein Biosynthesis.

<u>Individual work</u>

1. Mutations.
2. Molecular Pathology. Principles of Treating.

Information Resources

1. Biological Chemistry: Textbook / A.L. Zagayko, L.M. Voronina, G.B. Kravchenko, K.V. Strel`chenko. – Kharkiv: NUPh; Original, 2011. – 153-182 p.
2. Training Journal for Licensed Exam "KROK-1": Study Material in Biological Chemistry. – Kharkiv: NUPh, 2017. – 109-116 p.
3. DNA Metabolism: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/dna.php.
4. RNA Metabolism: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/rna.php.
5. Translation of Proteins: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/protein-synthesis.php.
6. Protein Modifications and Protein Targeting: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/protein-modifications.php.
https://themedicalbiochemistrypage.org/protein-synthesis.php
7. Protein Synthesis Animation Video – YouTube Available on: https://www.youtube.com/watch?v=Ikq9AcBcohA

Information Pathways

https://lh3.googleusercontent.com/9Xa0OsNekHatvhJIFwZm2dx5IrD4qoiyD_yC91vsATU8p3bDAIeWfC-lL5AR_wgGxKMnag=s85

Biochemical questions raised by the genetic continuity and the evolution of living organisms:

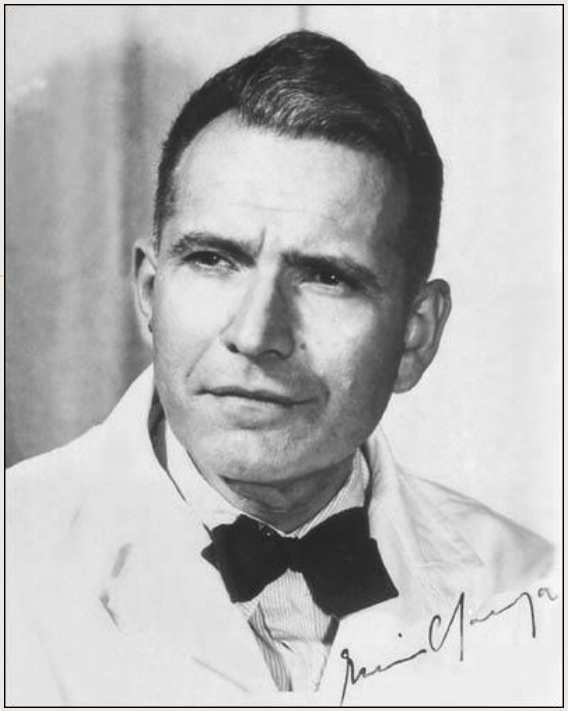
- What is the molecular nature of the genetic material?

- How is genetic information transmitted with such fidelity?

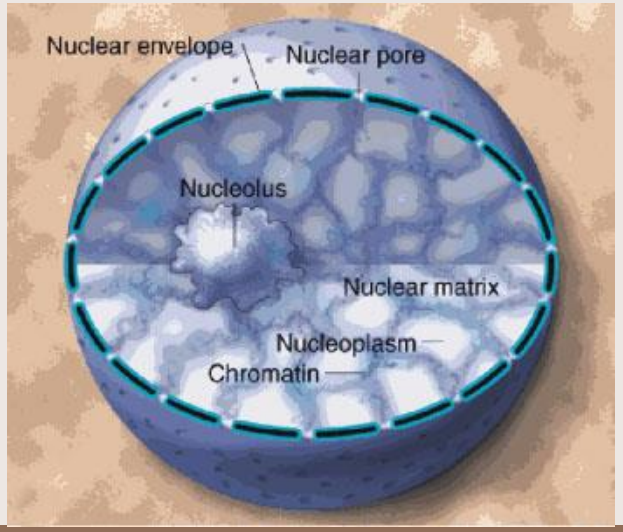
- How is it ultimately translated in the amino acid sequence of protein molecules?

The ability of living organisms to function in the midst of a chaotic environment ultimately depends on the timely flow of information.

Friedrich Miescher



Ervin Chargaff



Chargaff's rules:
[A] = [T]; [C] = [G];
[pyrimidines] = [purines].

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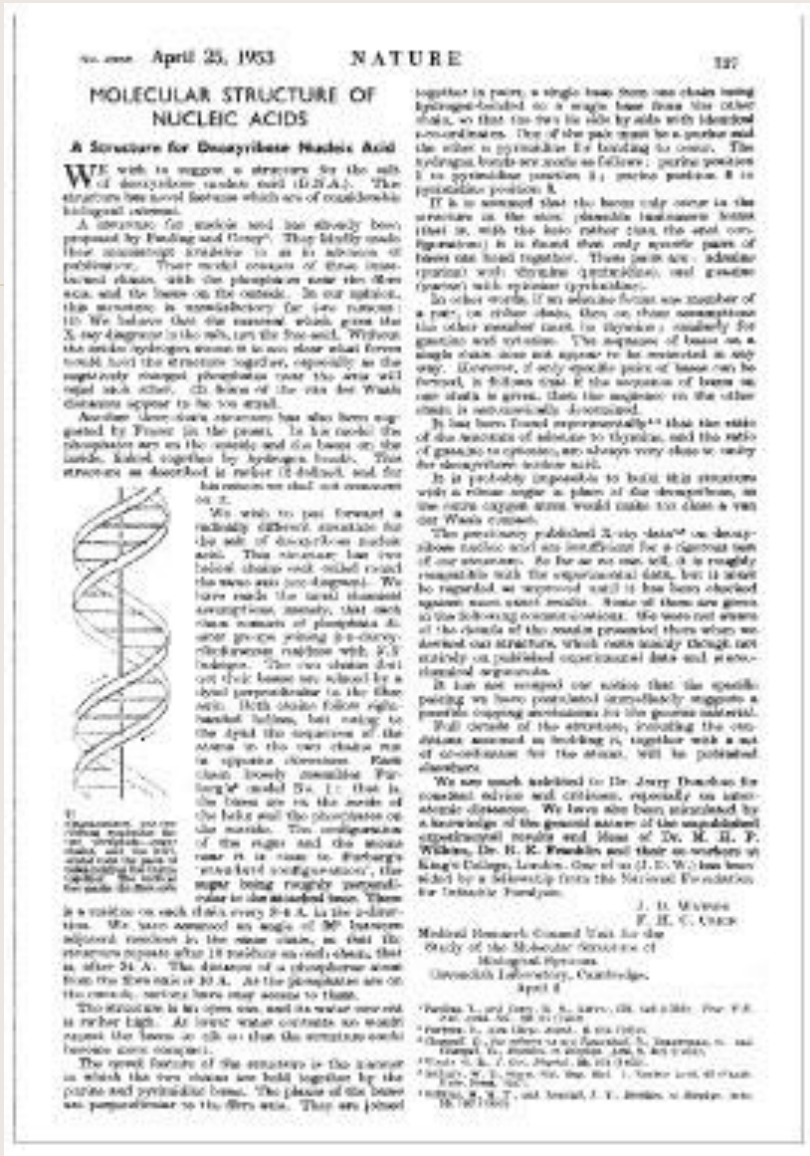


April 25, 1953 NATURE 737

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-coordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can fit together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

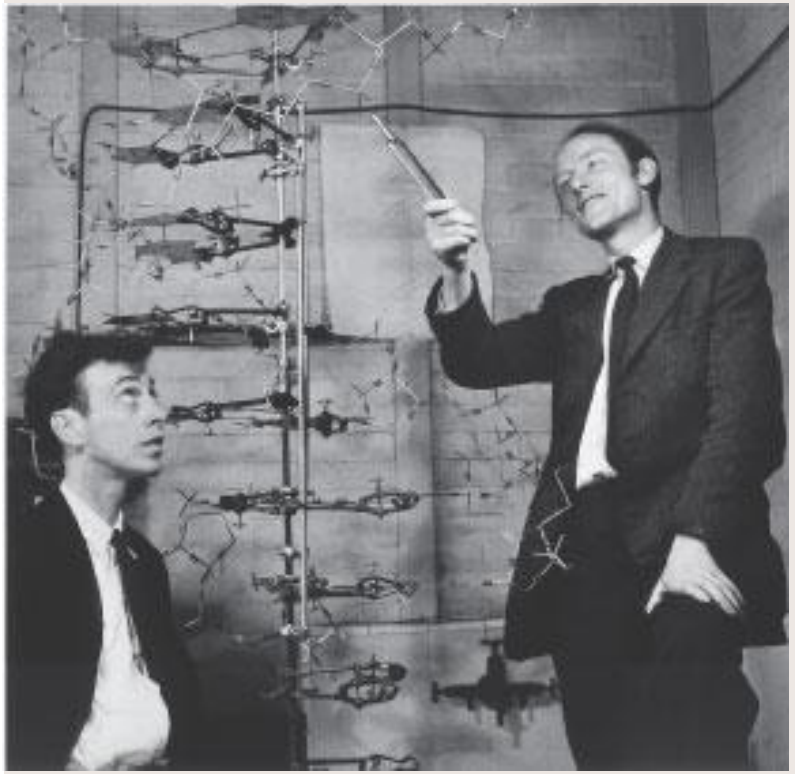
It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2



J.Watson and F.Crick

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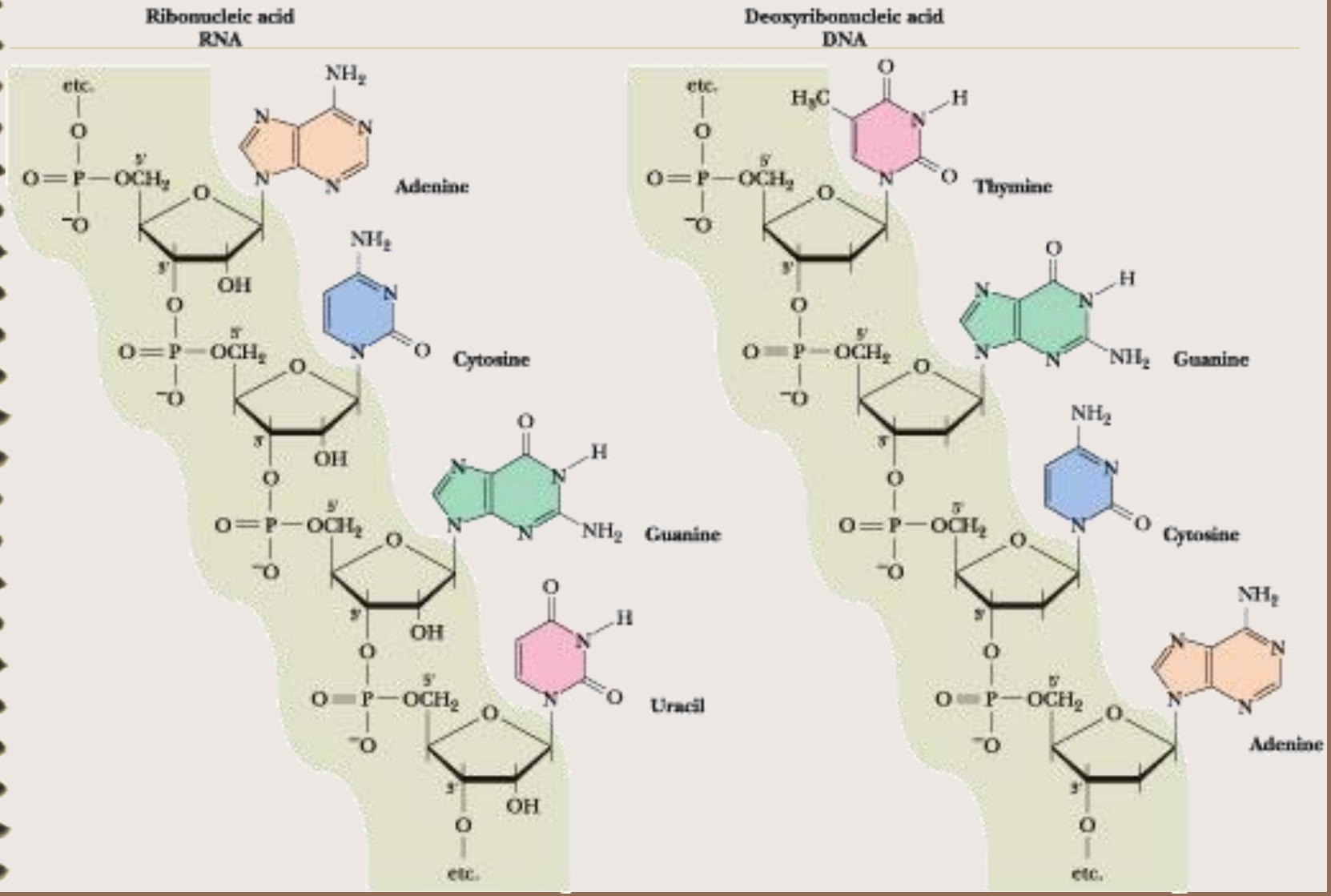
DNA Carries Genetic Information

Genetic information is stored in the sequence of bases along a nucleic acid chain.

The nucleotide sequences of DNA ultimately describe the primary structures of all cellular RNAs and proteins, and through enzymes can indirectly affect the synthesis of all other cellular constituents, determining the size, shape, and function of every living thing.

The structure of DNA is a marvelous device for the stable storage of genetic information.

Nucleic Acids Are Polynucleotides



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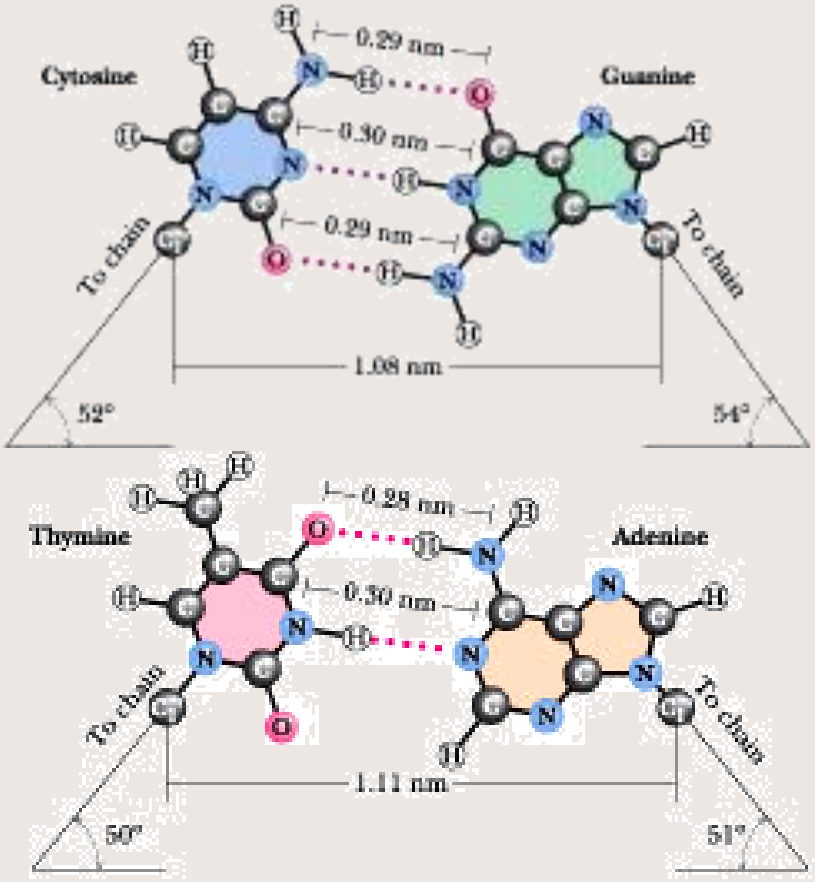
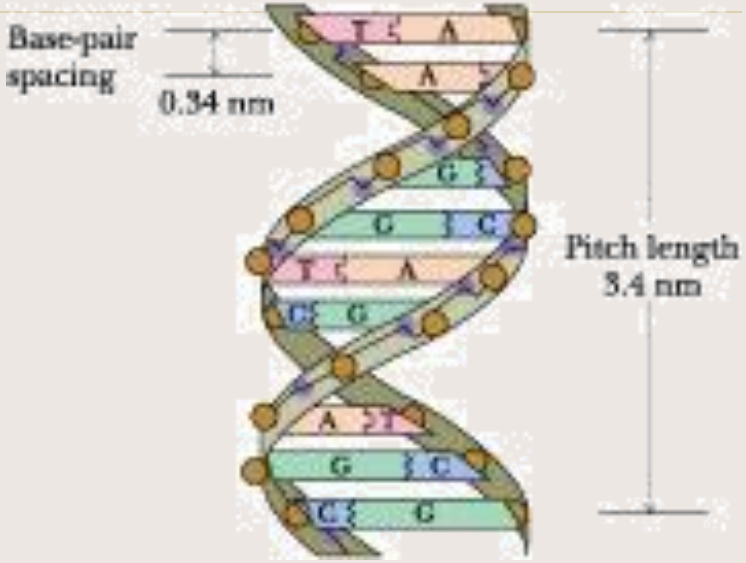
Watson and Crick's Double Helix





These base pairs provide a mechanism for coping the genetic information in an existing nucleic acid chain to form a new chain.

Base pairs A:T and G:C.

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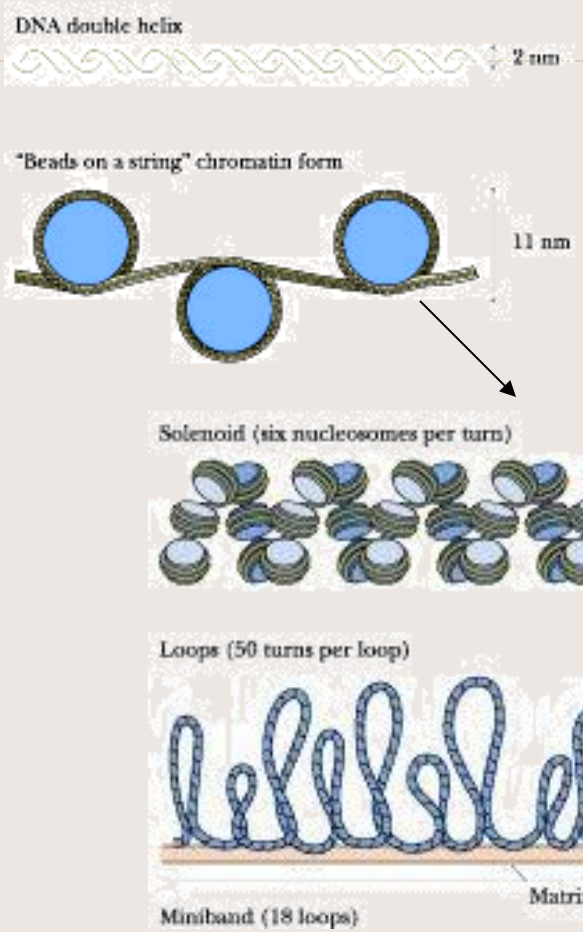
A model for chromosome structure



Histone octamer

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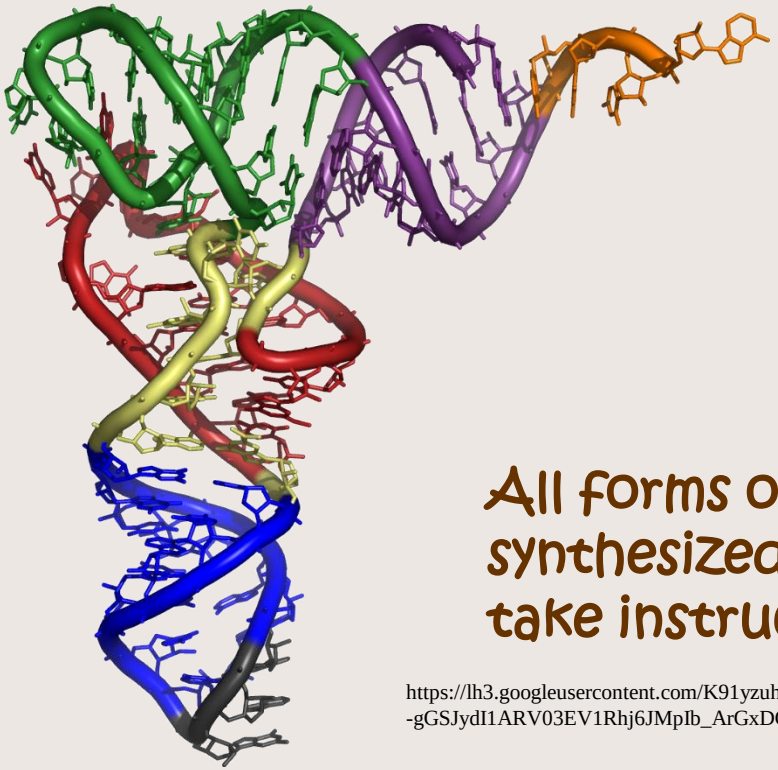
The template for protein synthesis are RNA molecules

Messenger RNA (mRNA) molecules are the information carrying intermediates in protein synthesis.



Transfer RNA (tRNA) and ribosomal RNA rRNA) molecules are part of the protein-synthesizing machinery.

All forms of cellular RNA are synthesized by RNA polymerases that take instructions from DNA templates.

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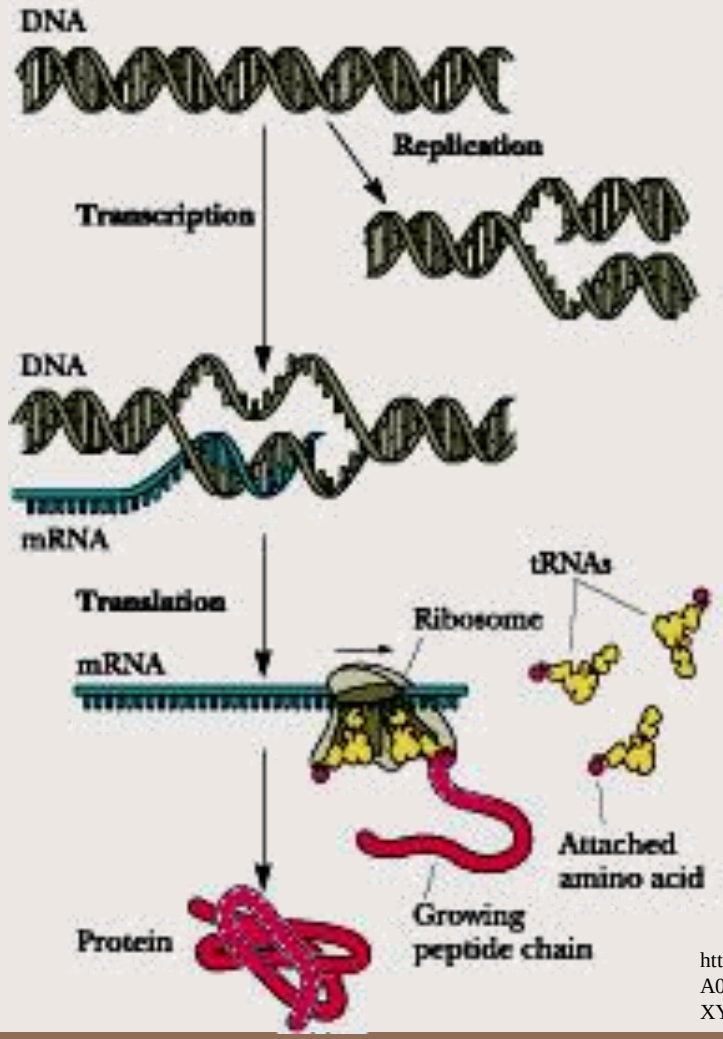
The flow of genetic information, or gene expression



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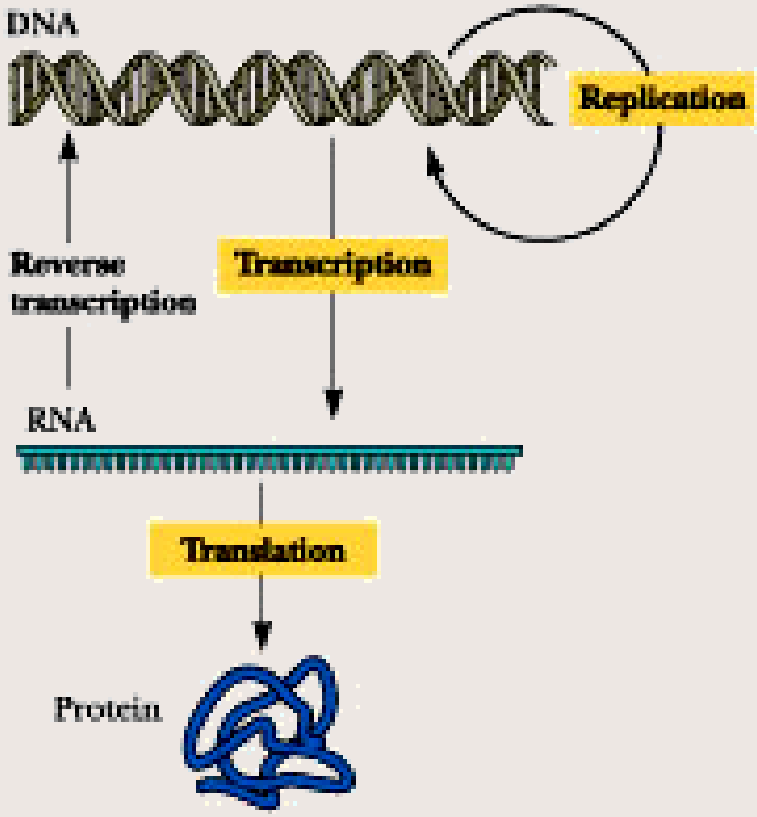
Central Dogma of Molecular Biology

In 1958, Francis Crick enunciated the "central dogma of molecular biology". This scheme outlined the residue-by-residue transfer of biological information as encoded in the primary structure of the informational biopolymers, nucleic acids and proteins.



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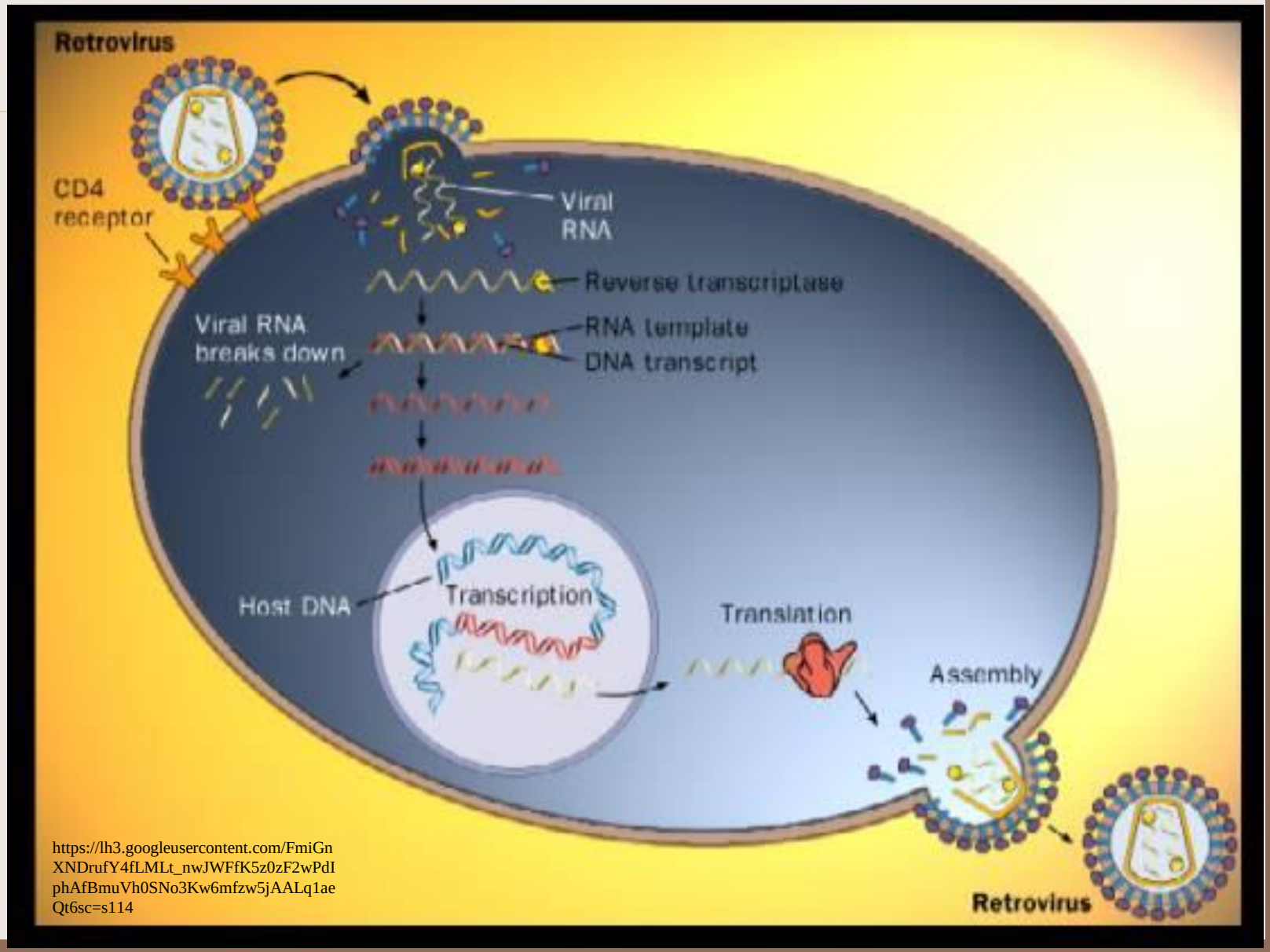
Reverse Transcription



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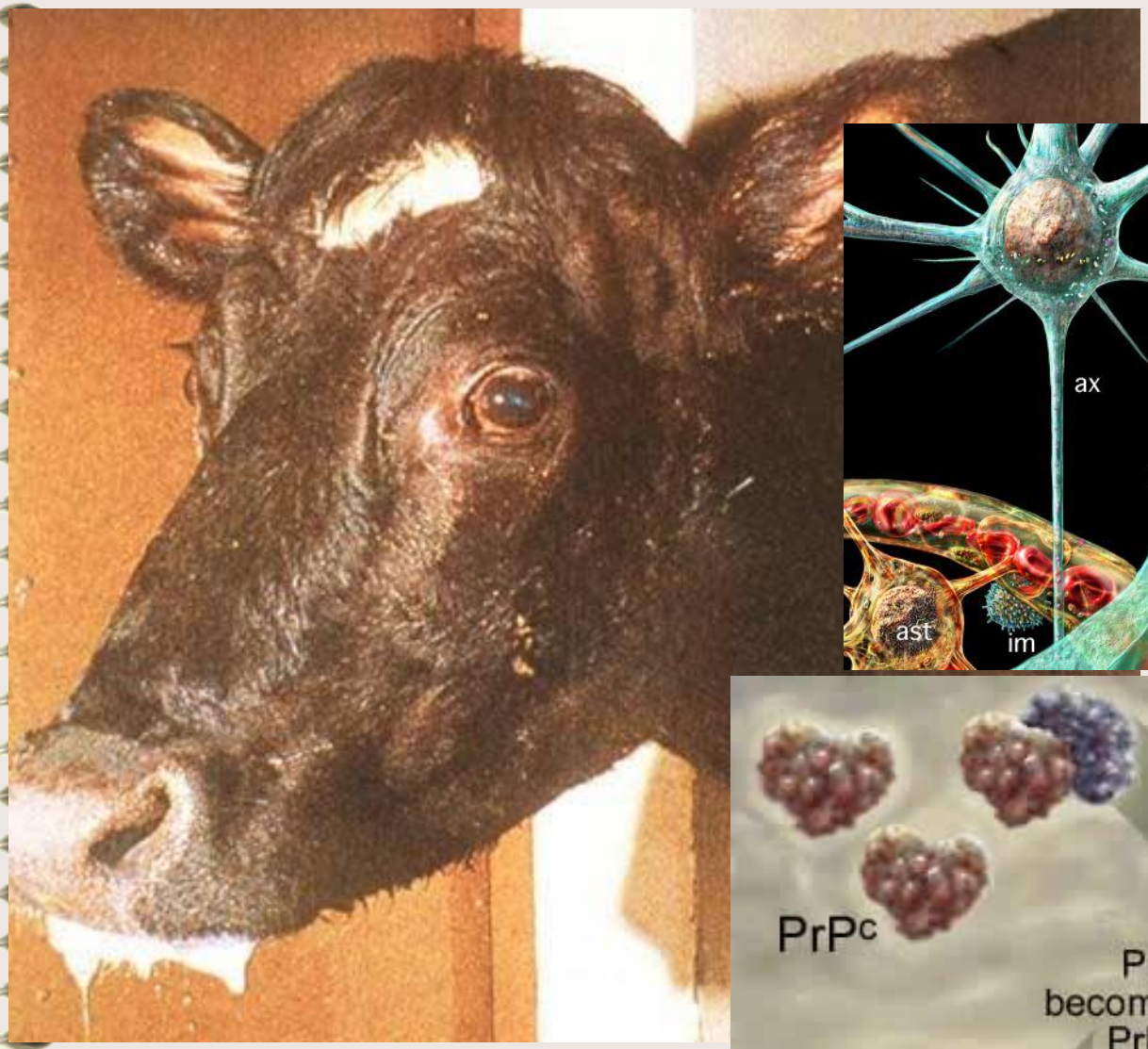
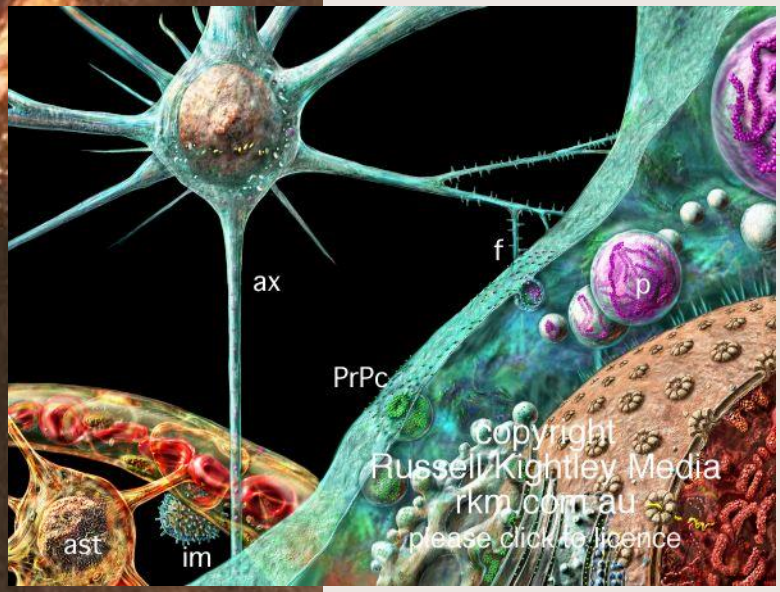
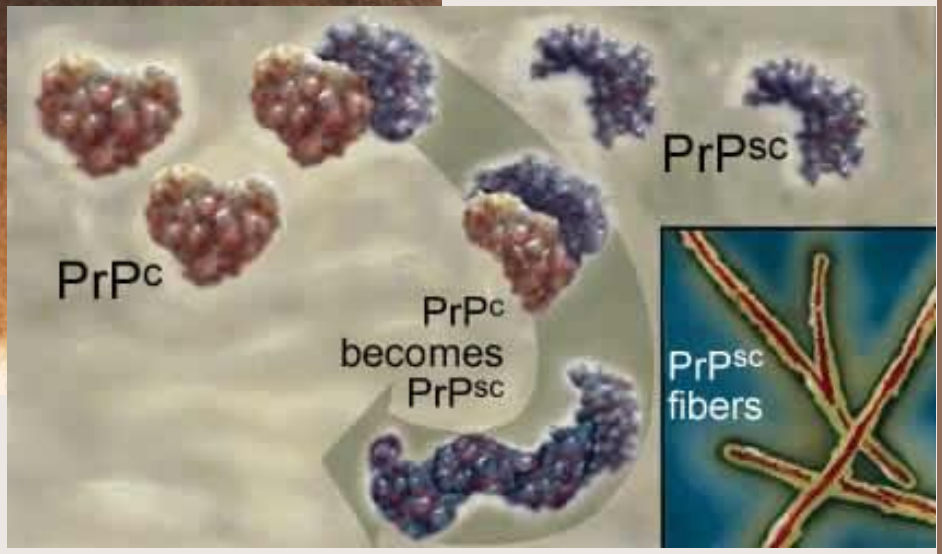
Prions







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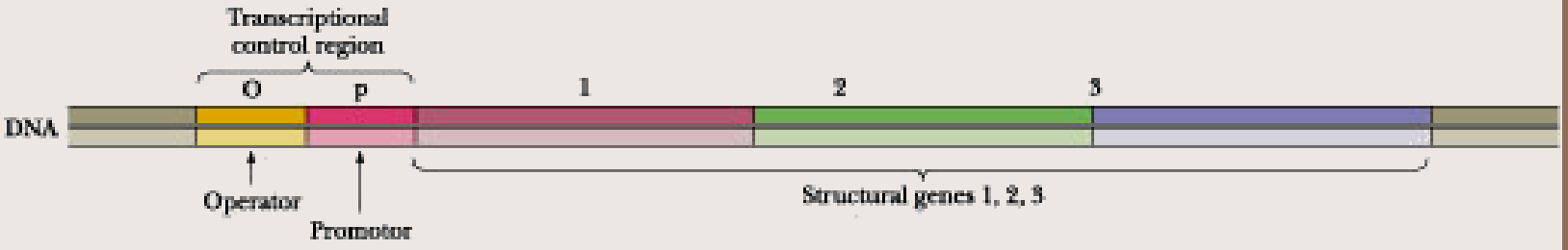
The fundamental unit of information in living systems is the gene.

A gene is defined biochemically as that segment of DNA (or in a few cases RNA) that encodes the information required to produce a functional biological product. This product is most often a protein. However, a gene product can also be one of several classes of RNA molecules.



A protein-coding gene (of prokaryotes) consists of a promoter followed by the coding sequence for the protein and then a terminator.

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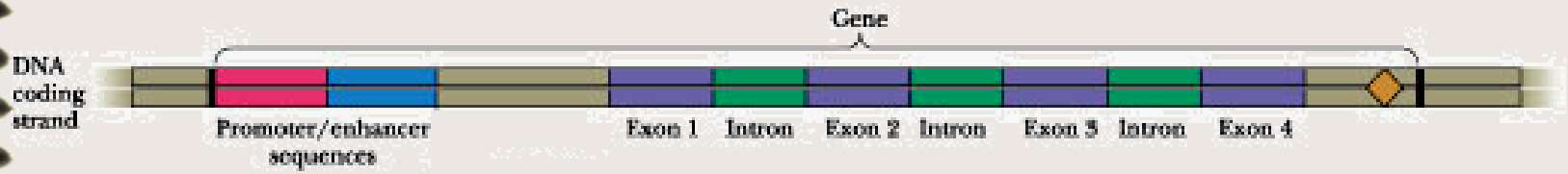
Eukaryotic Gene



Most eukaryotic genes are discontinuous. Noncoding sequences (called introns or intervening sequences) are interspersed between sequences called exons (expressed sequences), which code for a gene product.

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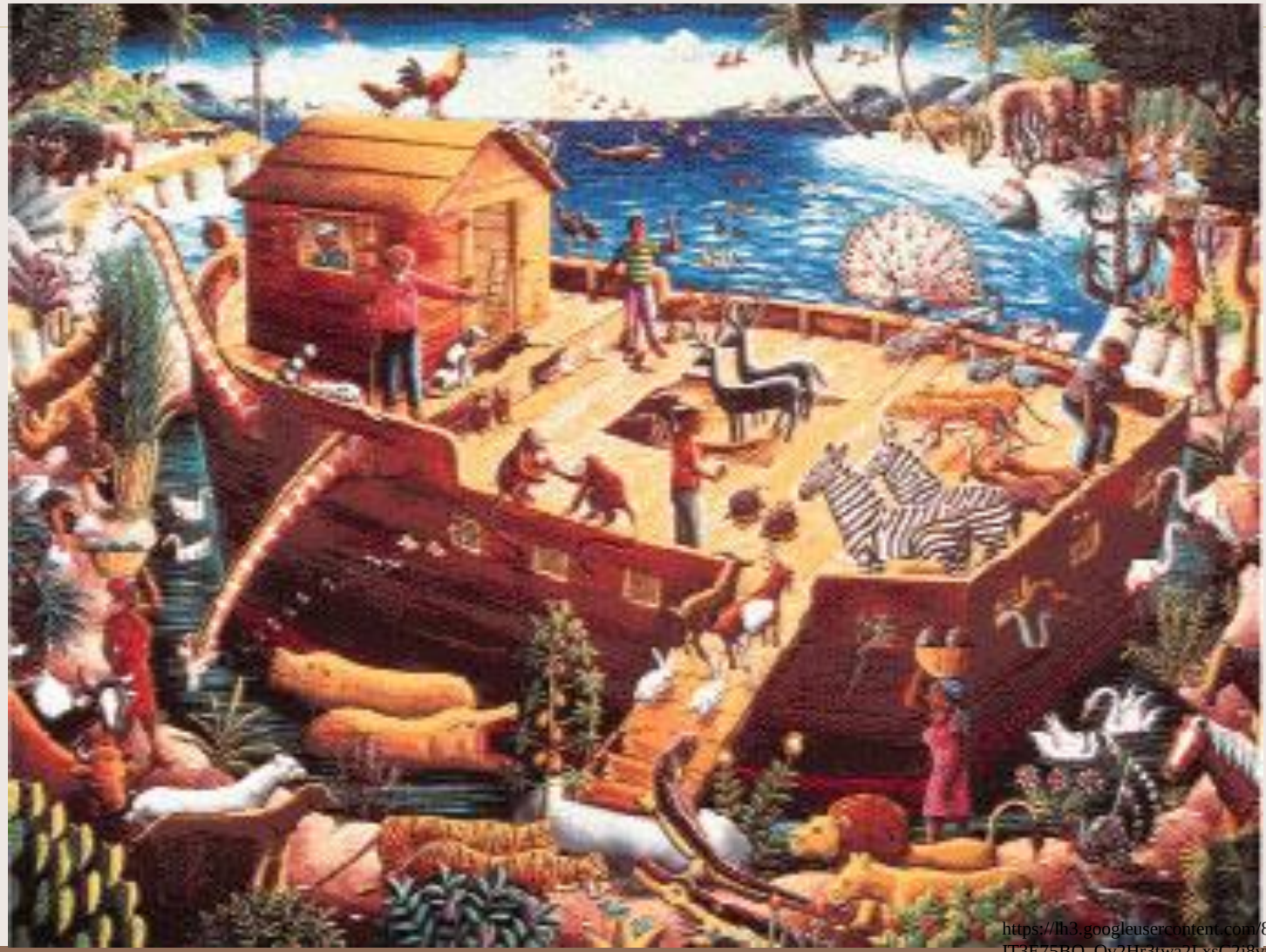
DNA: Genetic Information, Replication, and Repair



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Replication: Synthesis of a daughter duplex DNA molecule identical to the parental duplex DNA.

DNA replication is governed by a set of fundamental rules:

- DNA replication is semiconservative

- Replication begins at an origin and usually proceeds bidirectionally

- DNA synthesis proceeds in a 5'→3' direction and is semidzseonttnuous

DNA Replication Requires Many Enzymes and Protein Factors

1. DnaA protein: a complex of about 20 DnaA protein molecules that recognizes and successively denatures the DNA in the region, which are rich in A=T pairs.

2. Helicase (DNA B protein): an enzyme that catalyzes the separation of strands in a DNA molecule before replication.

3. Topoisomerases: Enzymes that introduce positive or negative supercoils in closed, circular duplex DNA.

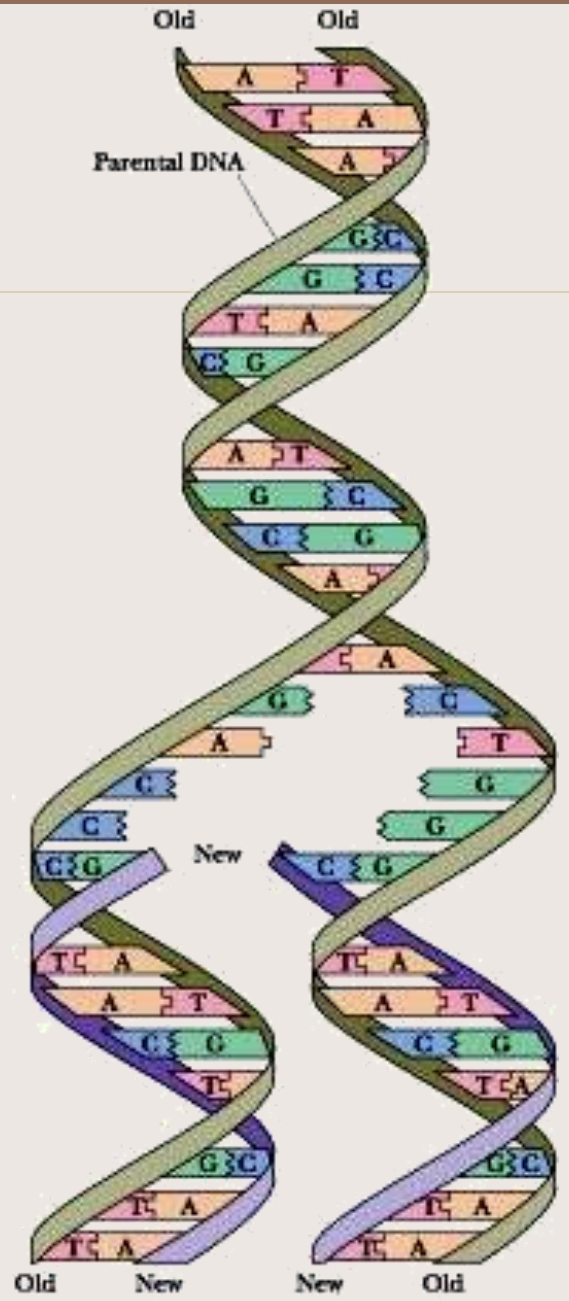
4. Primase: An enzyme that catalyzes the formation of RNA oligonucleotides used as primers by DNA polymerases.

5. DNA polymerase: An enzyme that catalyzes template-dependent synthesis of DNA from its deoxyribonucleoside 5'-triphosphate precursors.

6. DNA ligase: An enzyme that creates a phosphodiester bond between the 3' end of one DNA segment and the 5' end of another.

DNA Replication Is Semiconservative

The mechanism for DNA replication is strand separation followed by the copying of each strand. In the process, each separated strand acts as a template for the synthesis of a new complementary strand whose nucleotide sequence is fixed by the base-pairing rules. Strand separation is achieved by untwisting the double helix. Base pairing then dictates an accurate replication of the original DNA double helix.



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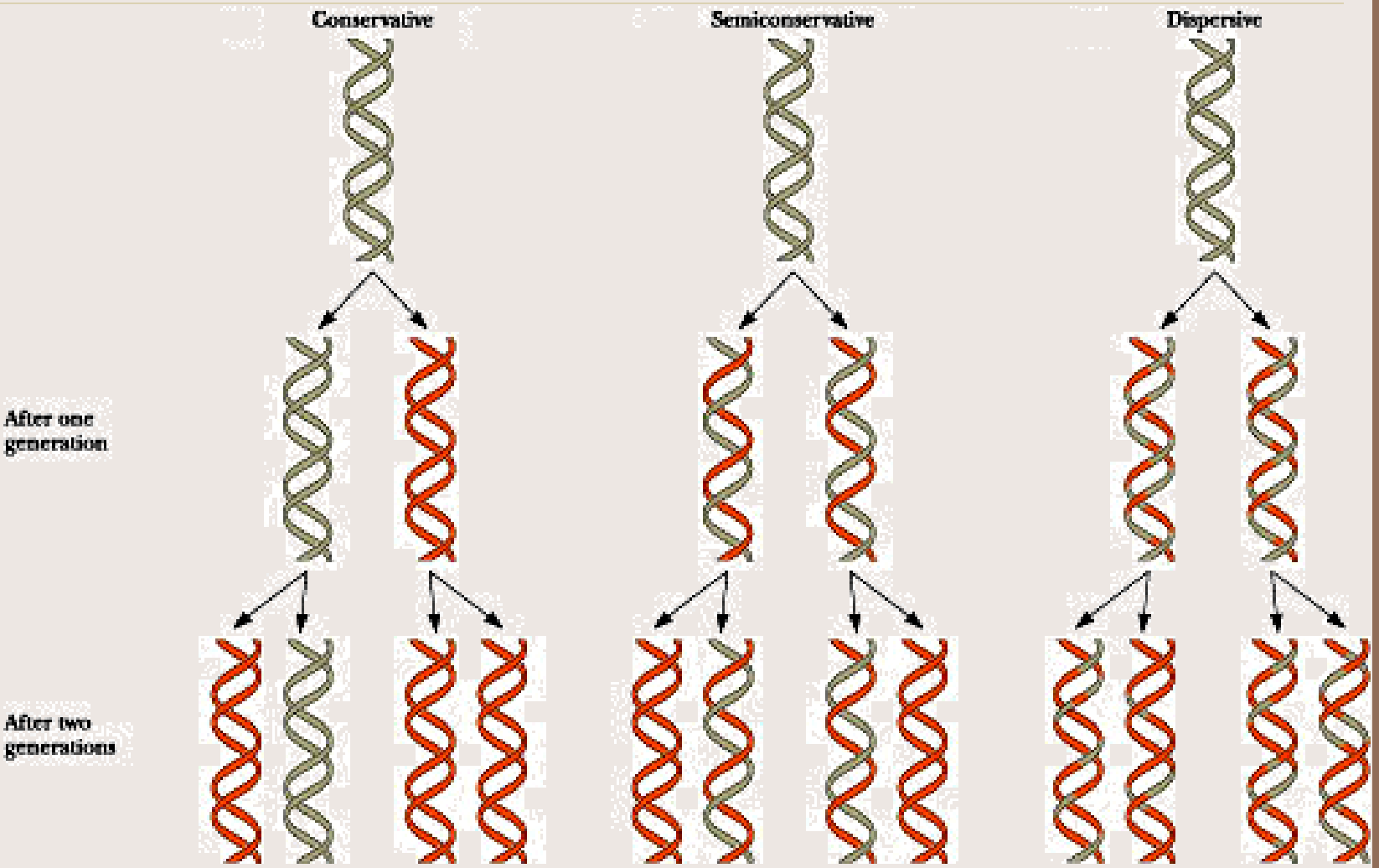
In 1958, Matthew Meselson and Franklin Stahl provided the experimental proof for the semiconservative model of DNA replication.



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Replication Is Bidirectional

Replication of DNA molecules begins at one or more unique sites called origin(s) of replication.

Bidirectional replication involves two replication forks, which move in opposite directions. Unwinding the DNA Helix Semiconservative replication depends on unwinding the DNA double helix to expose single-stranded templates to polymerase action.

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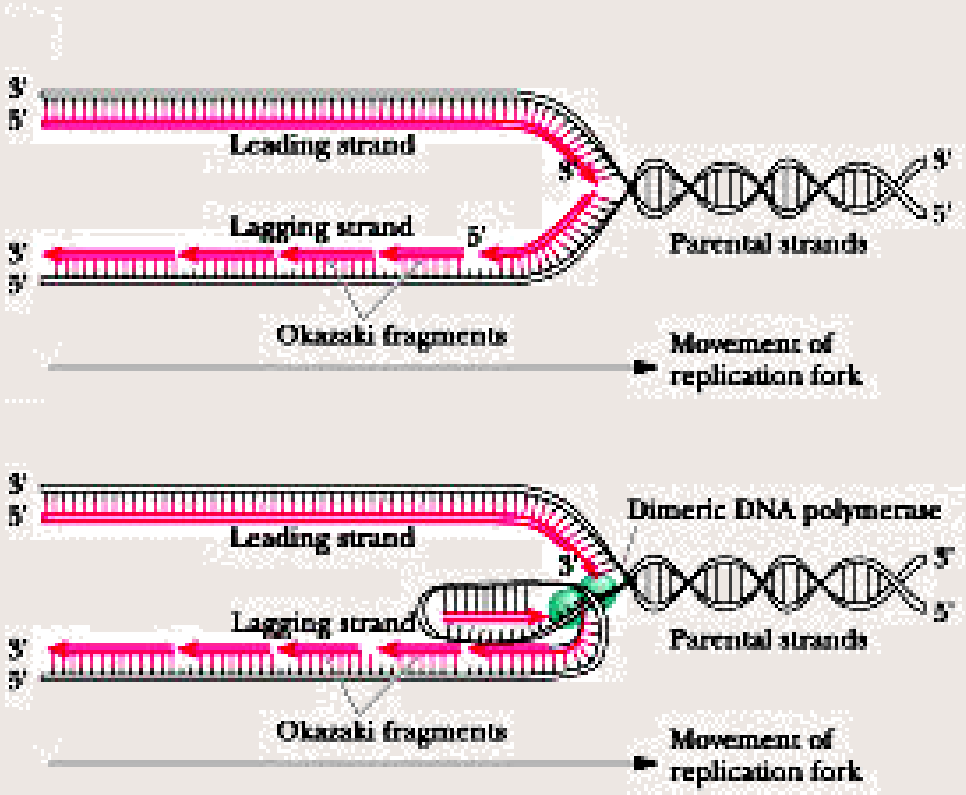
DNA Synthesis Proceeds in a 5'→3' Direction

Replication is semidiscontinuous: because DNA polymerases only polymerize nucleotides 5'→3', both strands must be synthesized in the 5'→3' direction.



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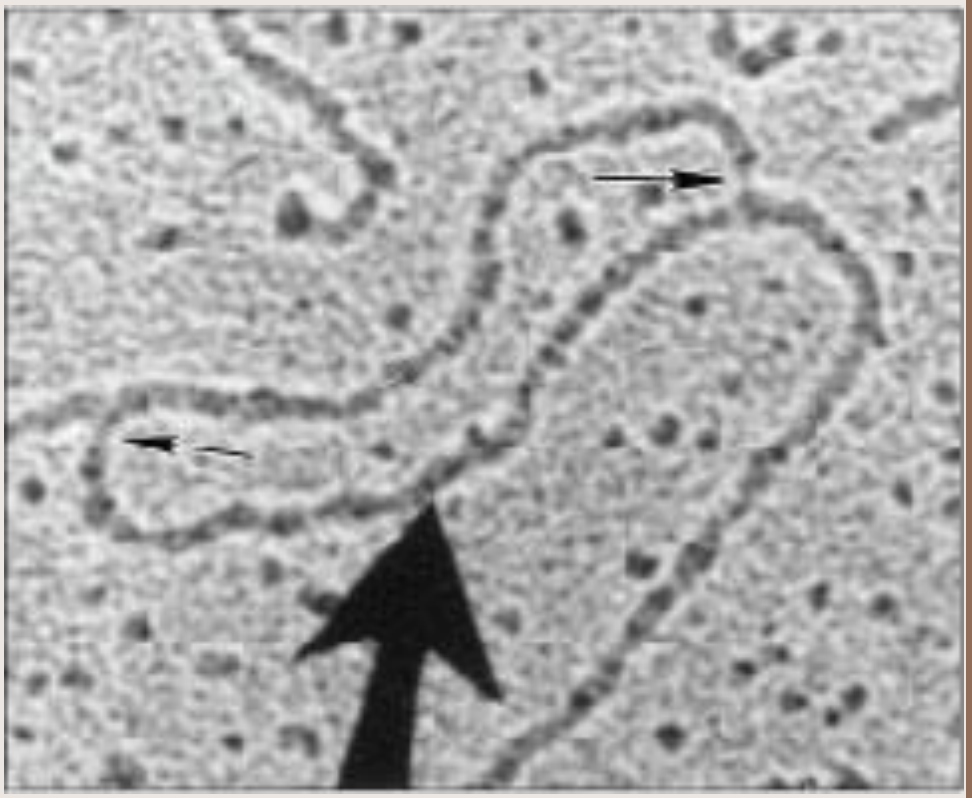
Thus, the copy of the parental 3 '→5' strand is synthesized continuously; this newly made strand is designated the leading strand.

As the helix unwinds, the other parental strand (the 5'→3' strand) is copied in a discontinuous fashion through synthesis of a series of fragments 1000 to 2000 nucleotides in length, called the Okazaki fragments; the strand constructed from the Okazaki fragments is called the lagging strand.

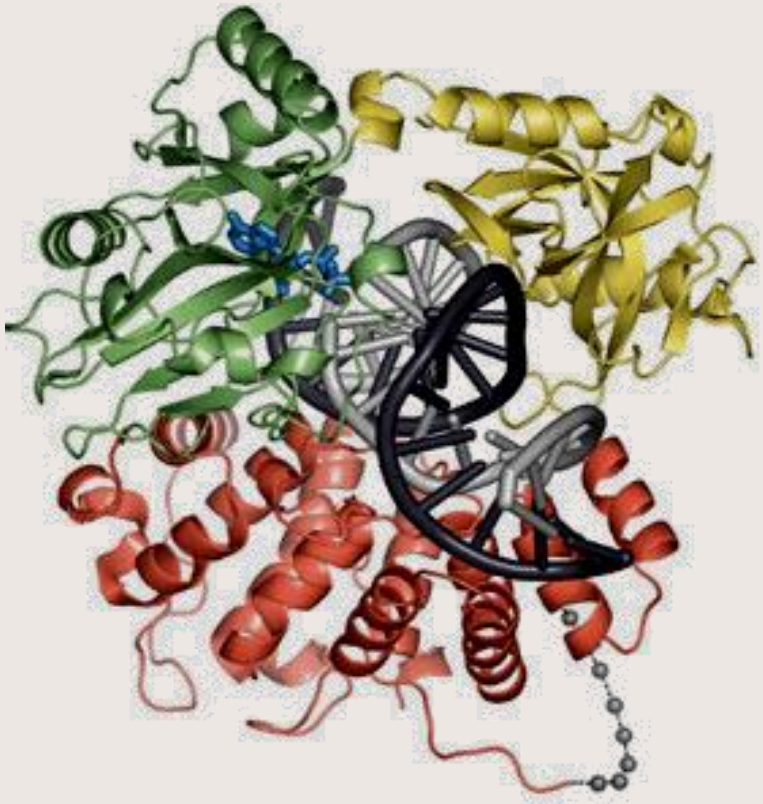
The Lagging Strand Is Formed from Okazaki Fragments



An electron micrograph of DNA replication

DNA Ligase

DNA ligase seals nicks in double-stranded DNA where a 3'-OH and a 5'-phosphate are juxtaposed. This enzyme is responsible for joining Okazaki fragments together to make the lagging strand a covalently contiguous polynucleotide chain.



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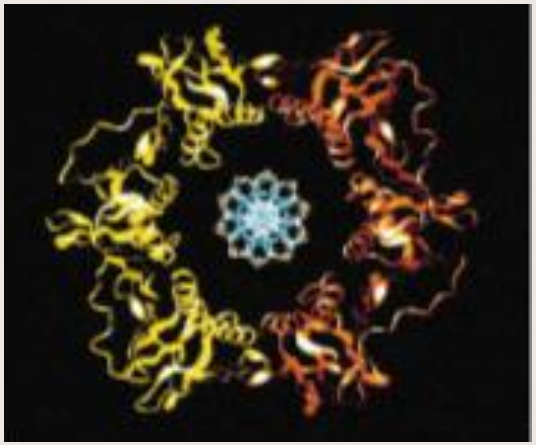
DNA Polymerases—The Enzymes of DNA Replication

The search for an enzyme that could synthesize DNA was initiated in 1955 by Arthur Kornberg and colleagues. This work led to the purification and characterization of DNA polymerase from E. coli cells, a single-polypeptide enzyme now called DNA polymerase I (M_r 103,000).

https://lh3.googleusercontent.com/4iaNpWZIPTSXGRNWrhJcCLU-FJSCrKEnj7QjcSwzj8hyQdrkT_vB6_eTns5MC9-nkhRVxg=s85

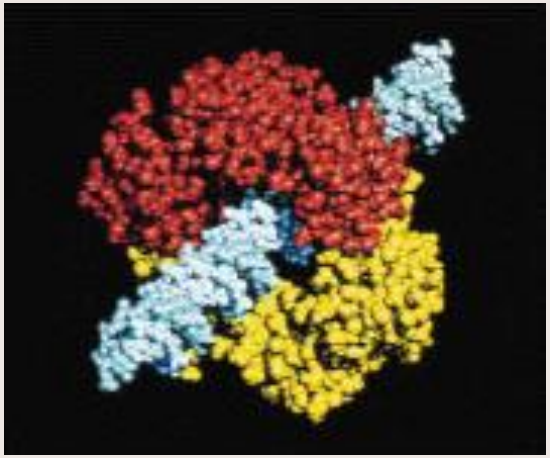
Most cells have several DNA polymerases

In E. coli, DNA polymerase III is the primary replication enzyme. DNA polymerase I is responsible for special functions during replication, recombination, and repair. DNA polymerase II has a specialized replication activity that allows it to replicate past DNA lesions in error-prone DNA repair.



Ribbon diagram of the b subunit dimer of the DNA polymerase III holoenzyme on B-DNA

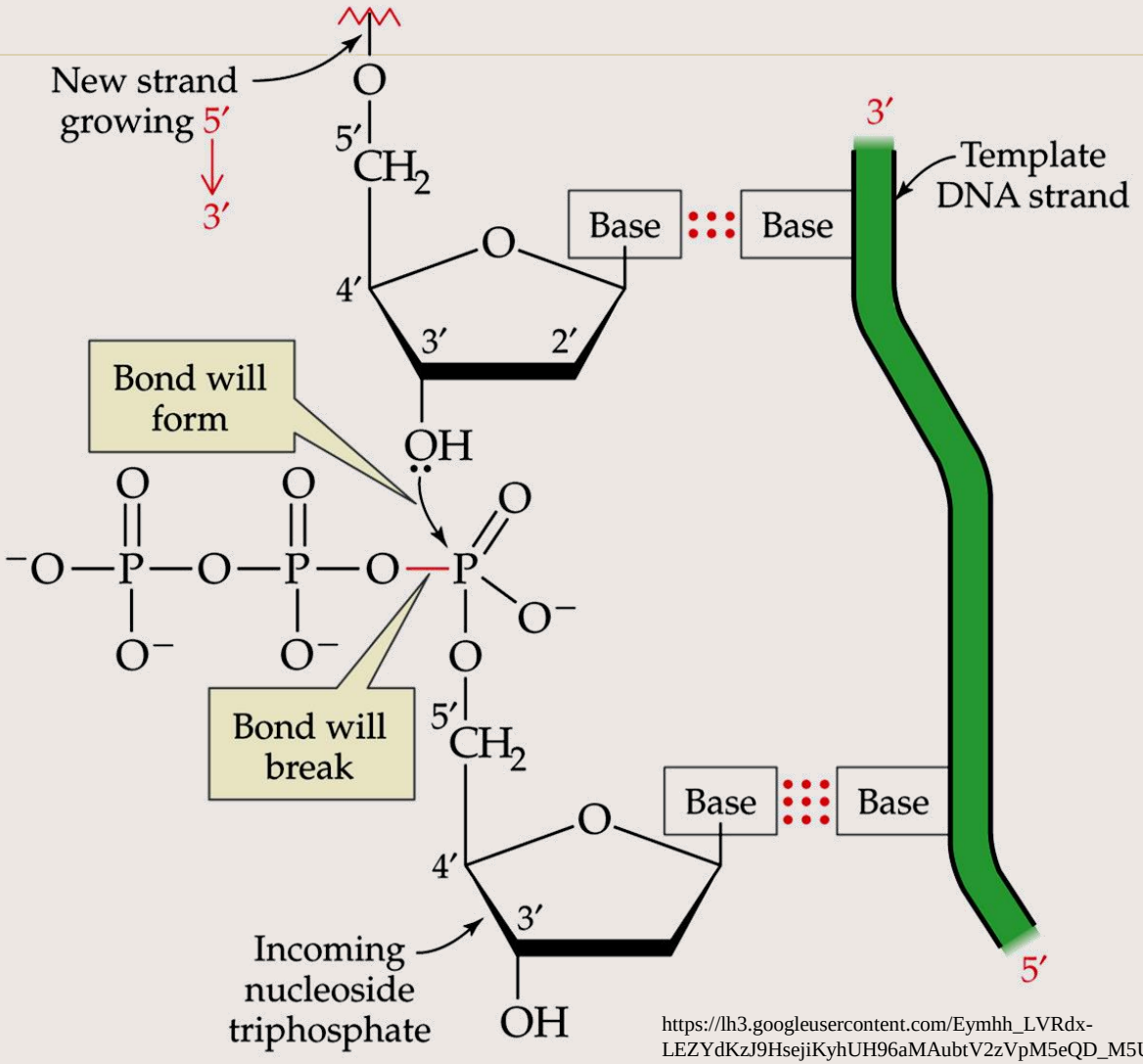
https://lh3.googleusercontent.com/4T1lZVw1C9Tlux6n6eqtB9_LRREXTpO1q4hK0ymddyURyAzhNLf30l28_CwPtw4F1xZKSQ=s103



Space-filling model of the b subunit dimer of the DNA polymerase III holoenzyme on B-DNA.

https://lh3.googleusercontent.com/OwMQDzLmiqspPuC8yv6EQ62dK3PzIEqDv0MiJztpZEG0V1ttqsz9uEJKVCEaoNvXiFU3PA=s102

Bond Formation in DNA Replication



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Topoisomerases

The progression of the replication fork requires that the DNA ahead of the fork be continuously unwound. Due to the fact that eukaryotic chromosomal DNA is attached to a protein scaffold the progressive movement of the replication fork introduces severe torsional stress into the duplex ahead of the fork.

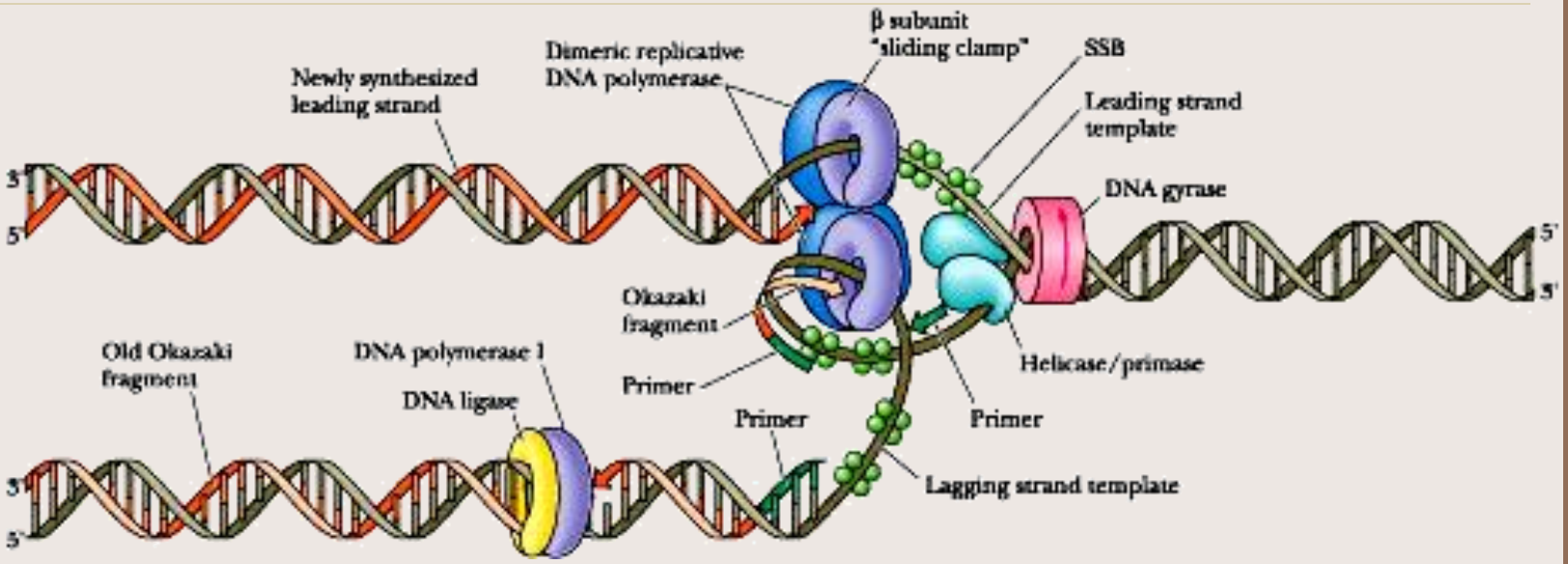
This torsional stress is relieved by DNA topoisomerases Topoisomerases relieve torsional stresses in duplexes of DNA by introducing either double- (topoisomerases II) or single-stranded (topoisomerases I) breaks into the backbone of the DNA.

These breaks allow unwinding of the duplex and removal of the replication-induced torsional strain. The nicks are then resealed by the topoisomerases.

https://lh3.googleusercontent.com/0og1uds7996UJCKbfMDXmeF4iZa9oekDHvwSRtouztl-YyzADhpaq7wg-xmamE35XzIiOg=s119

The DNA would become too tightly supercoiled to allow unwinding of the strands. DNA gyrase, a Type II topoisomerase, acts to overcome the torsional stress imposed upon unwinding by introducing negative supercoils at the expense of ATP hydrolysis.

General Features of a Replication Fork

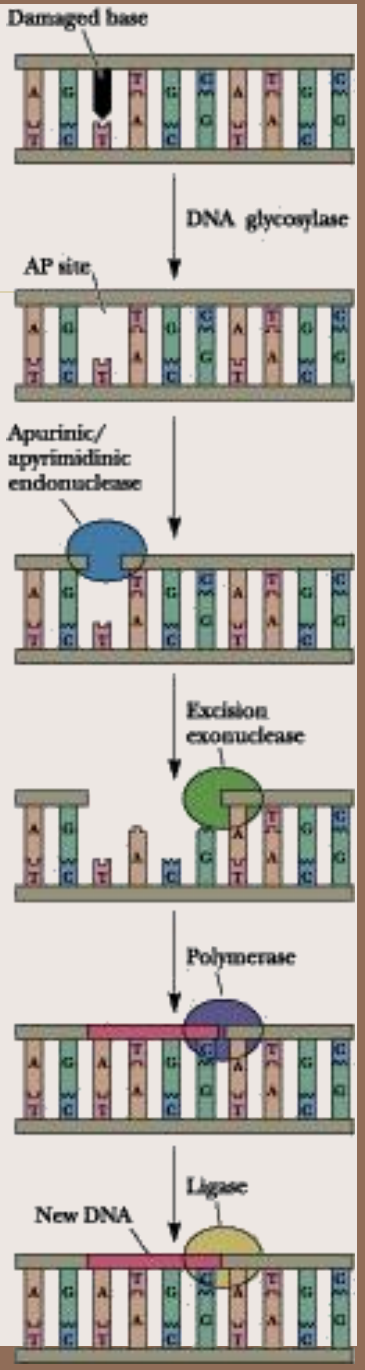


The DNA duplex is unwound by the action of helicase, and the single strands are coated with SSB (ssDNA-binding protein). Primase periodically primes synthesis on the lagging strand. DNA polymerase I and DNA ligase act downstream on the lagging strand to remove RNA primers, replace them with DNA, and ligate the Okazaki fragments.

DNA replication must be highly accurate

The free energies associated with base paring within the double helix suggest that approximately 1 in 10^4 bases incorporated will be incorrect. Yet, DNA replication has an error rate estimated to be 1 per 10^{10} nucleotides.

Two fundamental types of molecular mechanisms for DNA repair can be distinguished: (a) mechanisms that excise and replace damaged regions by replication, recombination, or mismatch repair, and (b) mechanisms that reverse damaging chemical changes in DNA; the latter includes excision repair systems.



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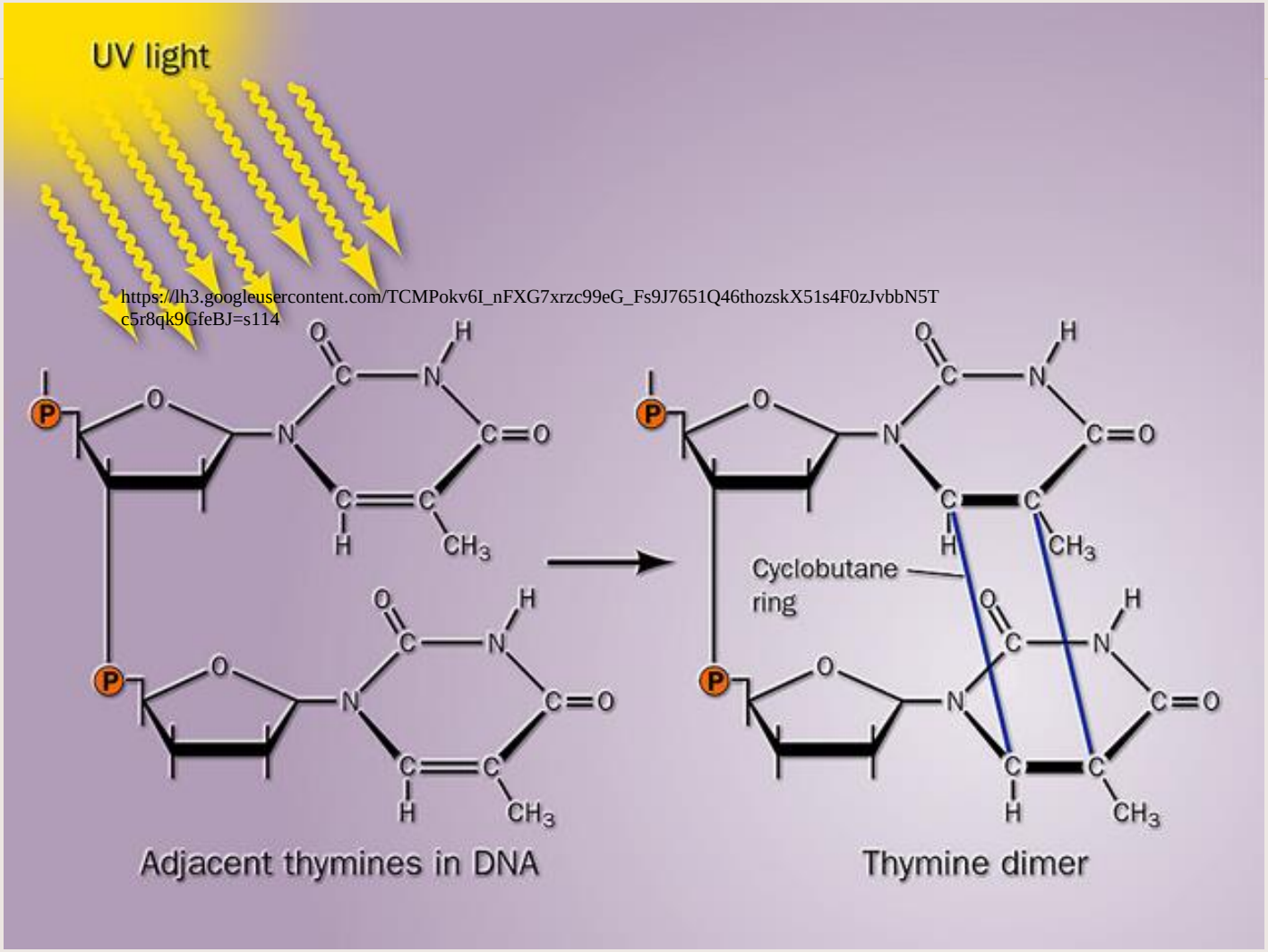
UV irradiation causes dimerization of adjacent thymine bases.



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Chemical carcinogen	Organs affected
Acrylonitrile	Colon, lung
Aniline derivatives	Bladder
Arsenic compounds	Lung and skin
Asbestos	Lung, mesothelium
Cadmium salts	Prostate, lung
Carbon tetrachloride	Liver
Diethylstilbestrol (DES)	Uterus, vagina
Lead	Kidney
Mustard gas	Lung, larynx
α-Naphthylamine	Bladder
Organochloride pesticides	Liver
Radon	Lung
Soot and tars	Skin, lung, bladder
Vinyl chloride	Liver, lung, brain
Wood and leather dust	Nasal sinuses

https://lh3.googleusercontent.com/N5o-F9S2GEXwBJxUjSPgHXT9nEDrnRSUJGfEknJOJ_kbiRx4C5JM5ktnLc8sdlRbl0OBbg=s113

Tobacco smoke, which contains the following:

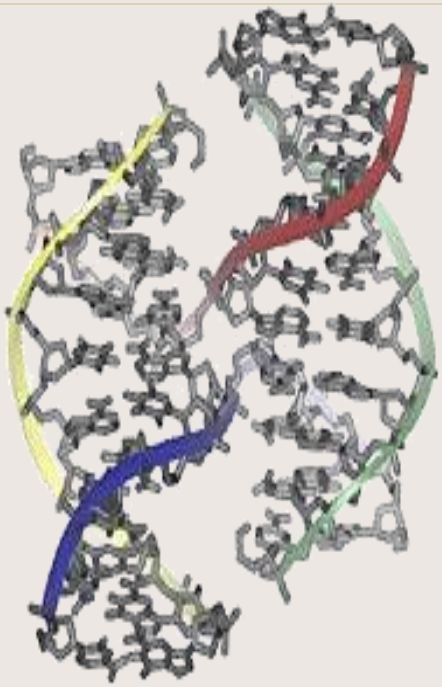
Lung, oral cavity, larynx, esophagus, stomach, pancreas, others

Aminostilbene, arsenic, benz[*a*]anthracene, benz[*a*]pyrene, benzene, µbenzo[*b*]fluoranthene, benzo[*c*]phenanthrene, benzo[*f*]fluoranthene, cadmium, chrysene, dibenz[*a,c*]anthracene, dibenzo[*a,e*]fluoranthene, dibenz[*a,h*]acridine, dibenz[*a,f*]acridine, dibenzo[*c,g*]carbozone, *N*-dibutylnitrosamine, 2,3-dimethylchrysene, indeno[*1,2,3-c,d*]pyrene, S-methylchrysene, S-methylfluoranthene, α-naphthylamine, nickel compounds, *N*-nitrosodimethylamine, *N*-nitrosomethylethylamine, polonium-210, *N*-nitrosodiethylamine, *N*-nitrosoanabasine, *N*-nitrosopiperidine

Chemical carcinogen

https://lh3.googleusercontent.com/PHA_3HHPNht3-qmFypGa1uD_8oxSWItKg1SzoOosEw8kIZWNcUfksbmsKAan4rU72i7i-A=s105

DNA Recombination



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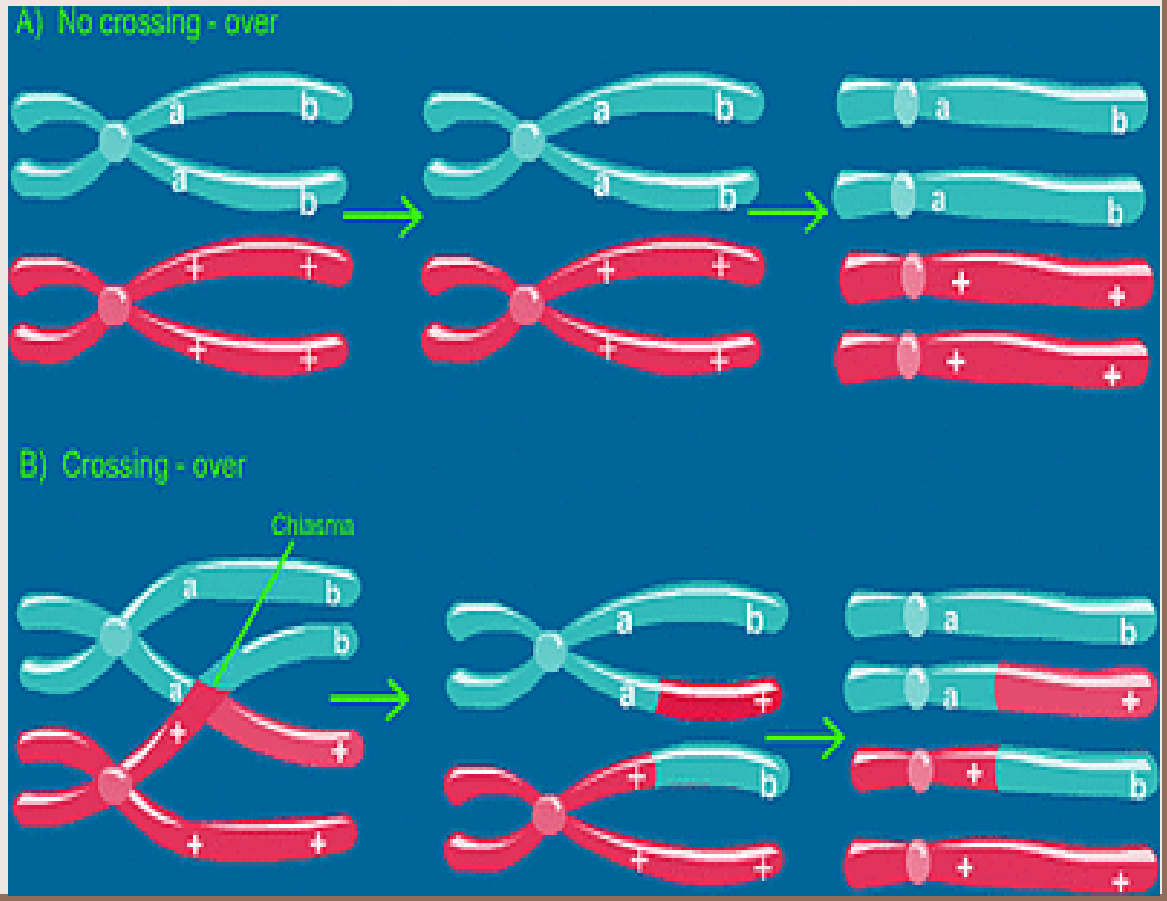

Transcription and the Regulation of Gene Expression

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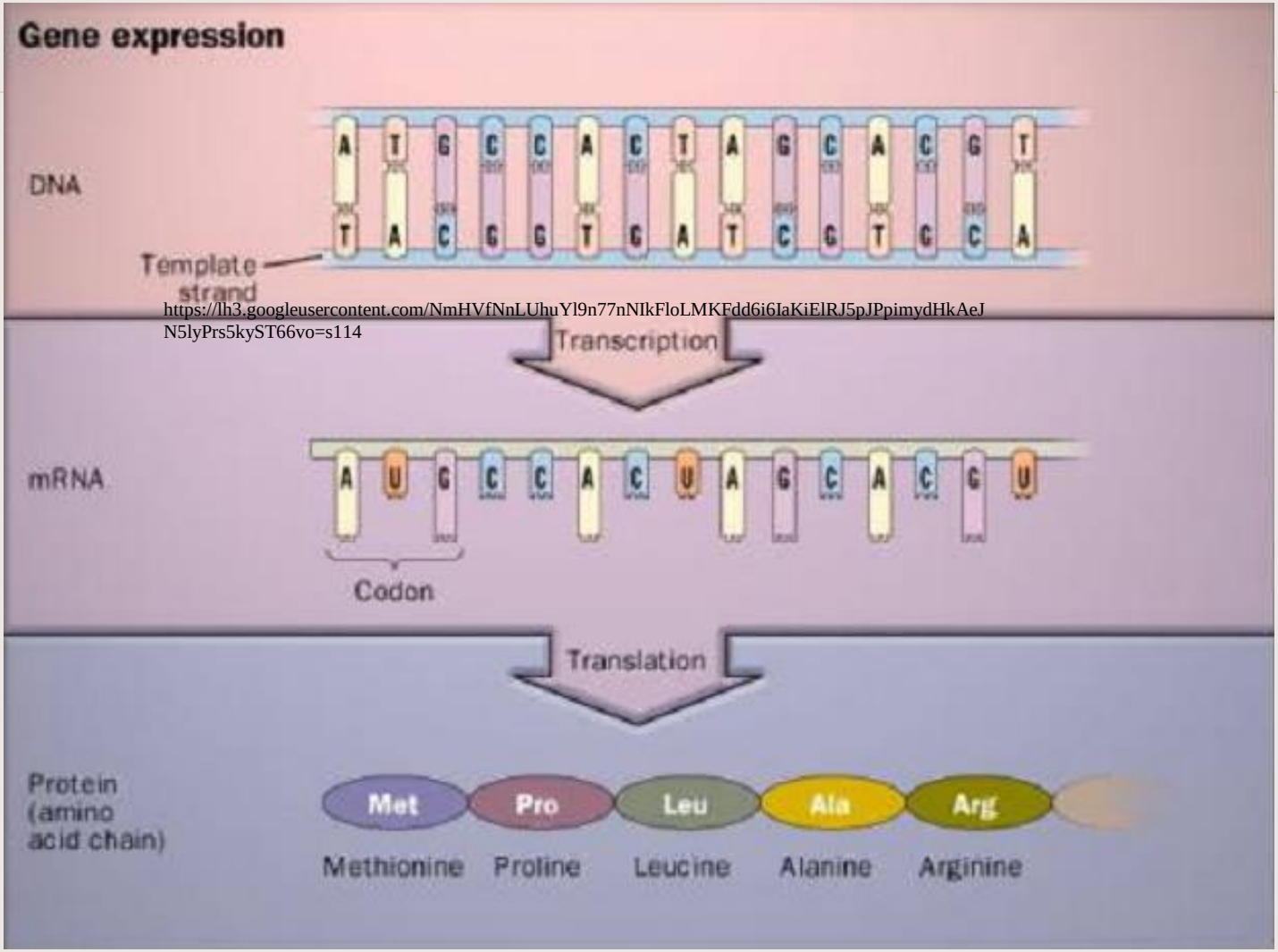
The Flow of Genetic Information



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RNA Metabolism

The expression of the genetic information contained in a segment of DNA always involves the generation of a molecule of RNA.

With the exception of the RNA genomes of certain viruses, all RNA molecules are derived from information permanently stored in DNA. In a process called **transcription**, an enzyme system converts the genetic information of a segment of DNA into an RNA strand with a base sequence complementary to one of the DNA strands. Three major kinds of RNA are produced.

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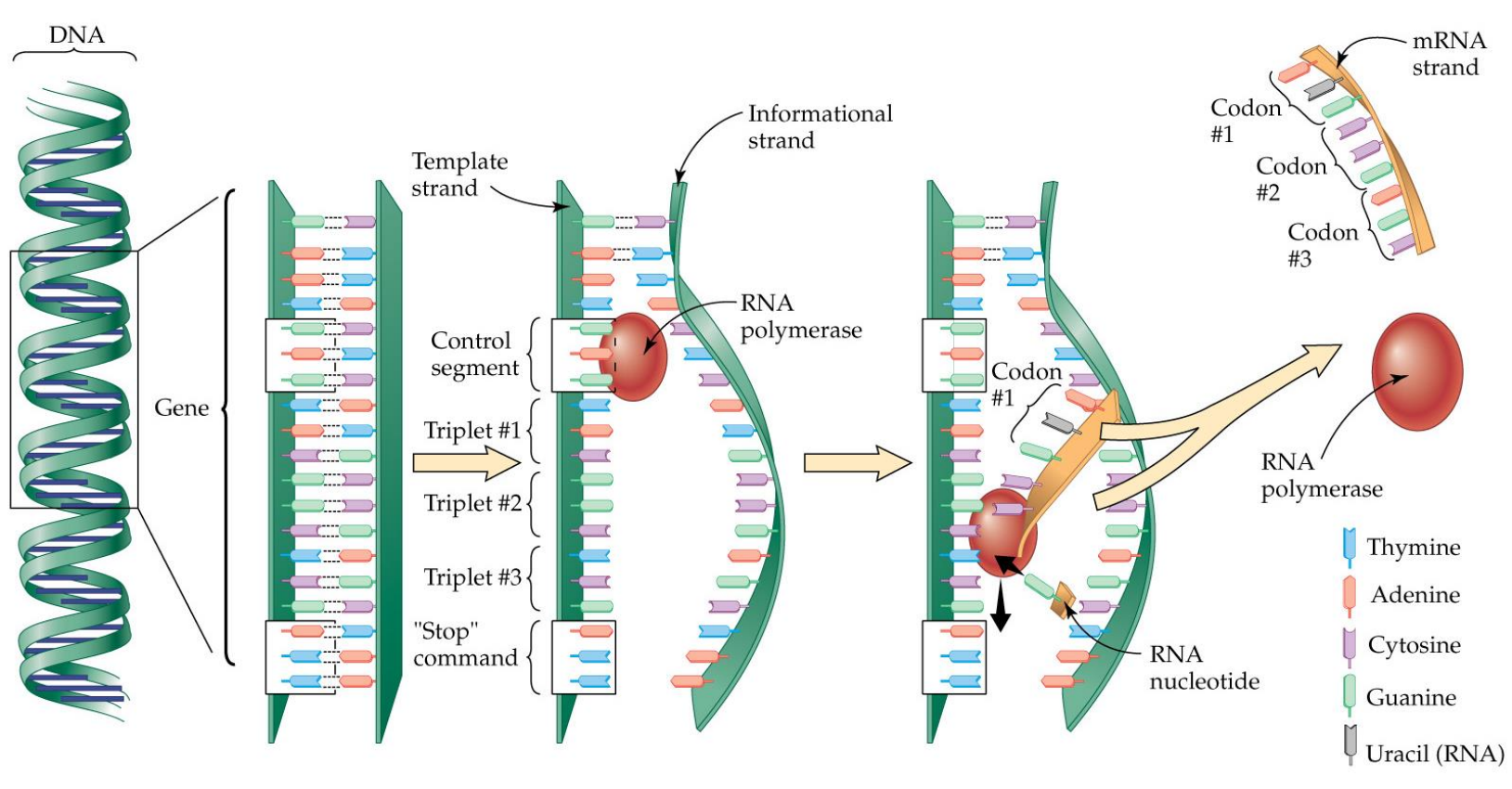
Transcription, whether prokaryotic or eukaryotic, has three main events.

- **Initiation** - binding of RNA polymerase to double-stranded DNA; this step involves a transition to single-strandedness in the region of binding; RNA polymerase binds at a sequence of DNA called the promoter. **Initiation is the most important step in gene expression!!!**

- **Elongation** - the covalent addition of nucleotides to the 3' end of the growing polynucleotide chain; this involves the development of a short stretch of DNA that is transiently single-stranded.

- **Termination** - the recognition of the transcription termination sequence and the release of RNA polymerase.

Transcription



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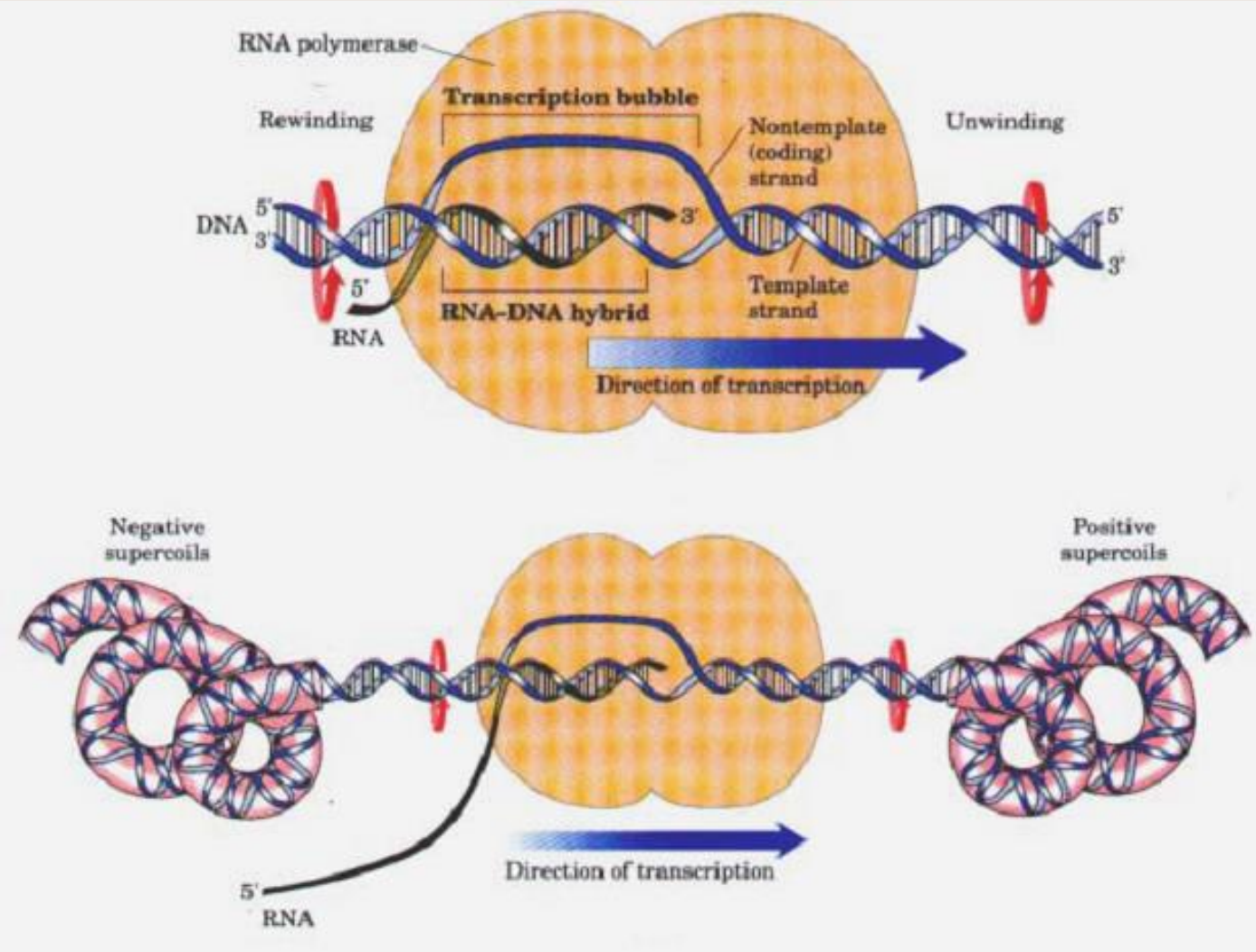
Transcription by RNA polymerase in E. coli.



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Eukaryotic transcription

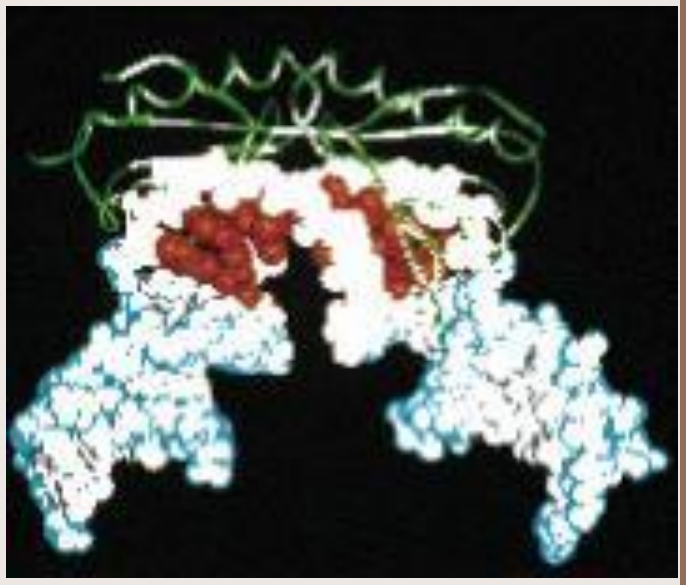
Eukaryotes have evolved much more complex transcriptional regulatory mechanisms than prokaryotes. For instance, in eukaryotes the genetic material (DNA), and therefore transcription, is localized to the nucleus, where it is separated from the cytoplasm (where translation occurs) by the nuclear membrane. This allows for the temporal regulation of gene expression through the sequestration of the RNA in the nucleus, and allows for selective transport of RNAs to the cytoplas, where the ribosomes reside.

Adding to this complexity, eukaryotes have three RNA polymerases.

Classes of RNA Polymerases

In prokaryotic cells, all 3 RNA classes are synthesized by a single polymerase. In eukaryotic cells there are 3 distinct classes of RNA polymerase, ***RNA polymerase I, II and III***. Each polymerase is responsible for the synthesis of a different class of RNA.

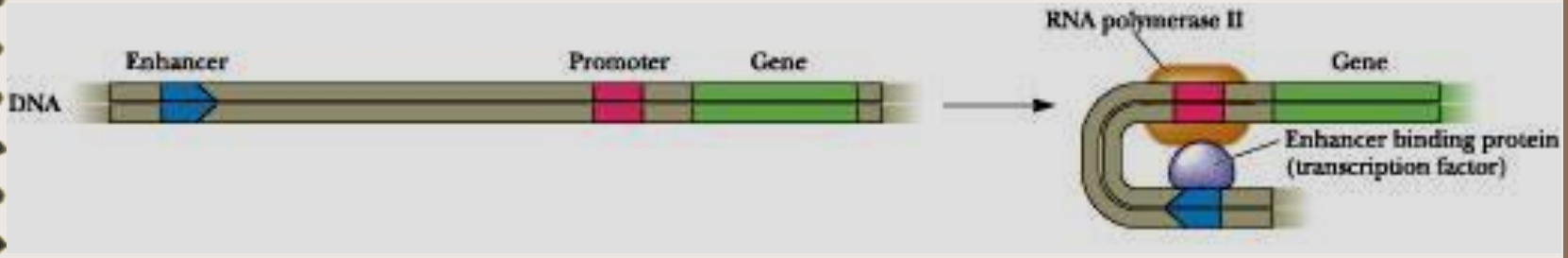
RNA pol I is responsible for rRNA synthesis. RNA pol II synthesizes the mRNAs and some of the small nuclear RNAs (snRNAs) involved in RNA splicing. RNA pol III synthesizes the tRNAs, and some snRNAs.



RNA polymerase II

https://lh3.googleusercontent.com/19_xdKspxx8m75_j6K270Tdp7lfA1ZTFyX0rvrCkWLeQe8V-aFY1EUNwTzGz4pQ7XyTT2g=s100

The basal eukaryotic transcription complex includes the RNA polymerase and additional proteins that are necessary for correct initiation and elongation.

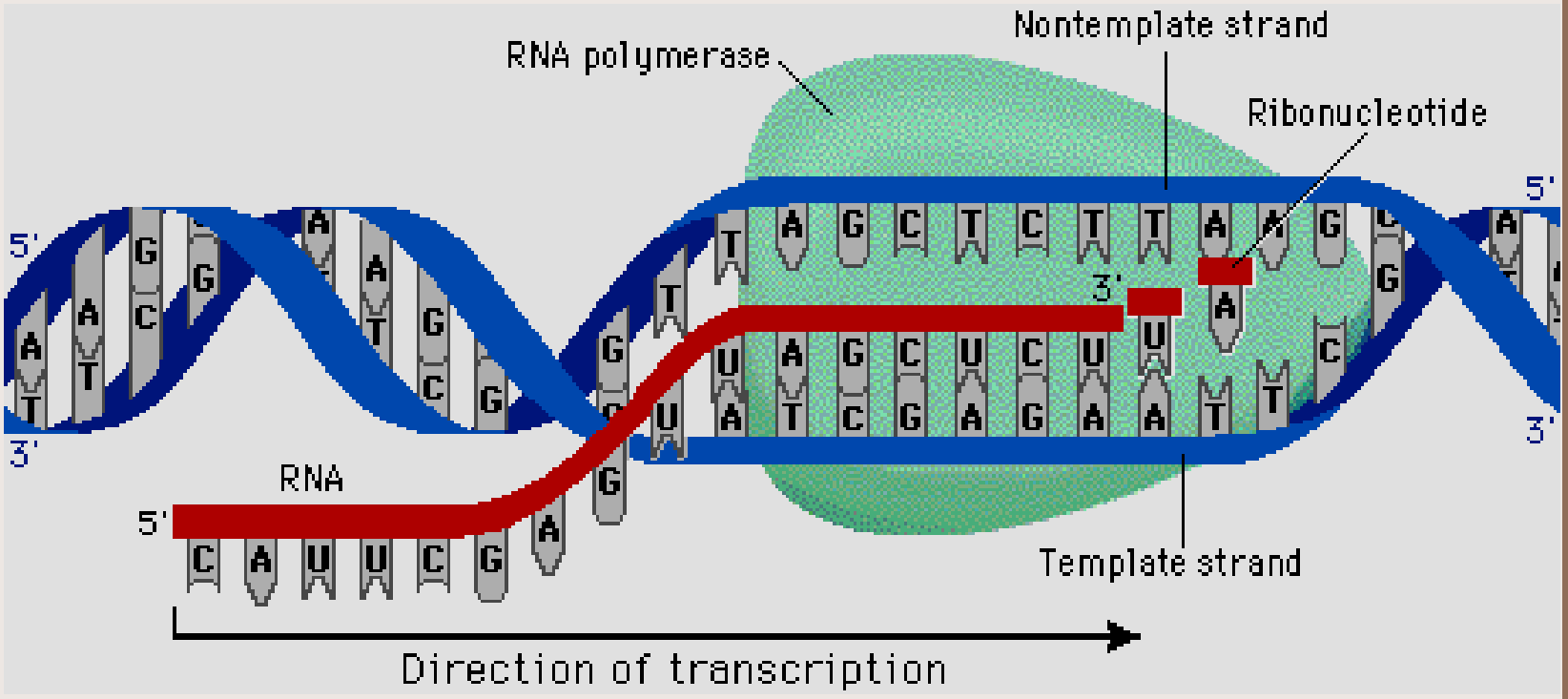


Enhancers are sequence elements located at varying positions and orientation relative to the promoter that act to enhance transcription initiation. Transcription factors (proteins) bind to enhancers and stimulate RNA polymerase II binding at a nearby promoter.

Transcriptional promoter and enhancer elements are important sequences used in the control of gene expression.

https://lh3.googleusercontent.com/wjm6JYRgfvpXuoiOTPvBXXRLWOMFGTWJHlnsTC9YItvo_IF8l7z99-2x059UD3vZSp5fVw=s170

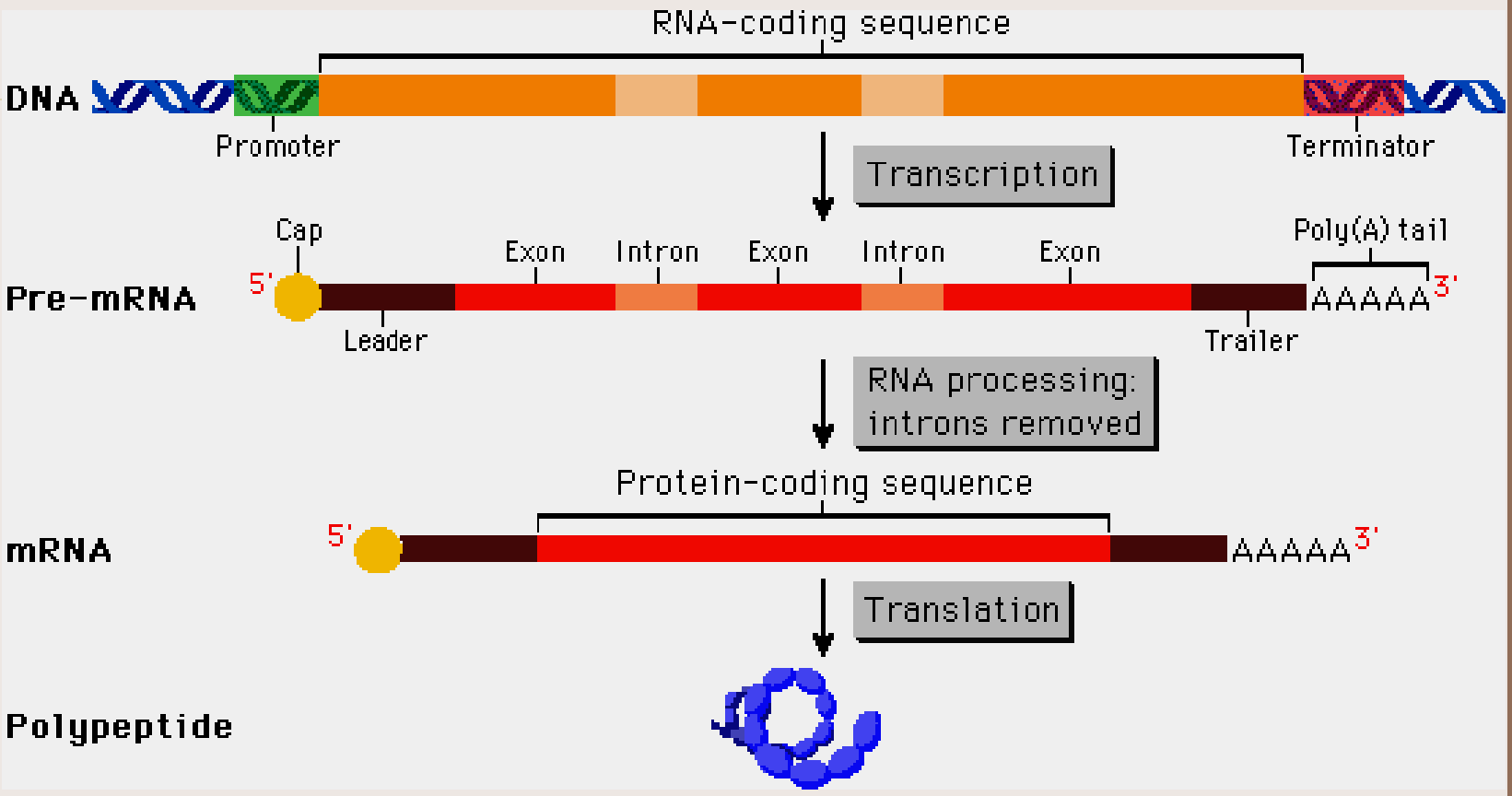
The Transcription Process



RNA synthesis involves separation of the DNA strands and synthesis of an RNA molecule in the 5' to 3' direction by RNA polymerase, using one of the DNA strands as a template.

https://lh3.googleusercontent.com/lQvTTbfoAxCRGbjBCTOqdOaBOQ9J_u_D0Bqqb6DGKw_ObFNAUybovZ4noy0xFID6a5VQ044=s170

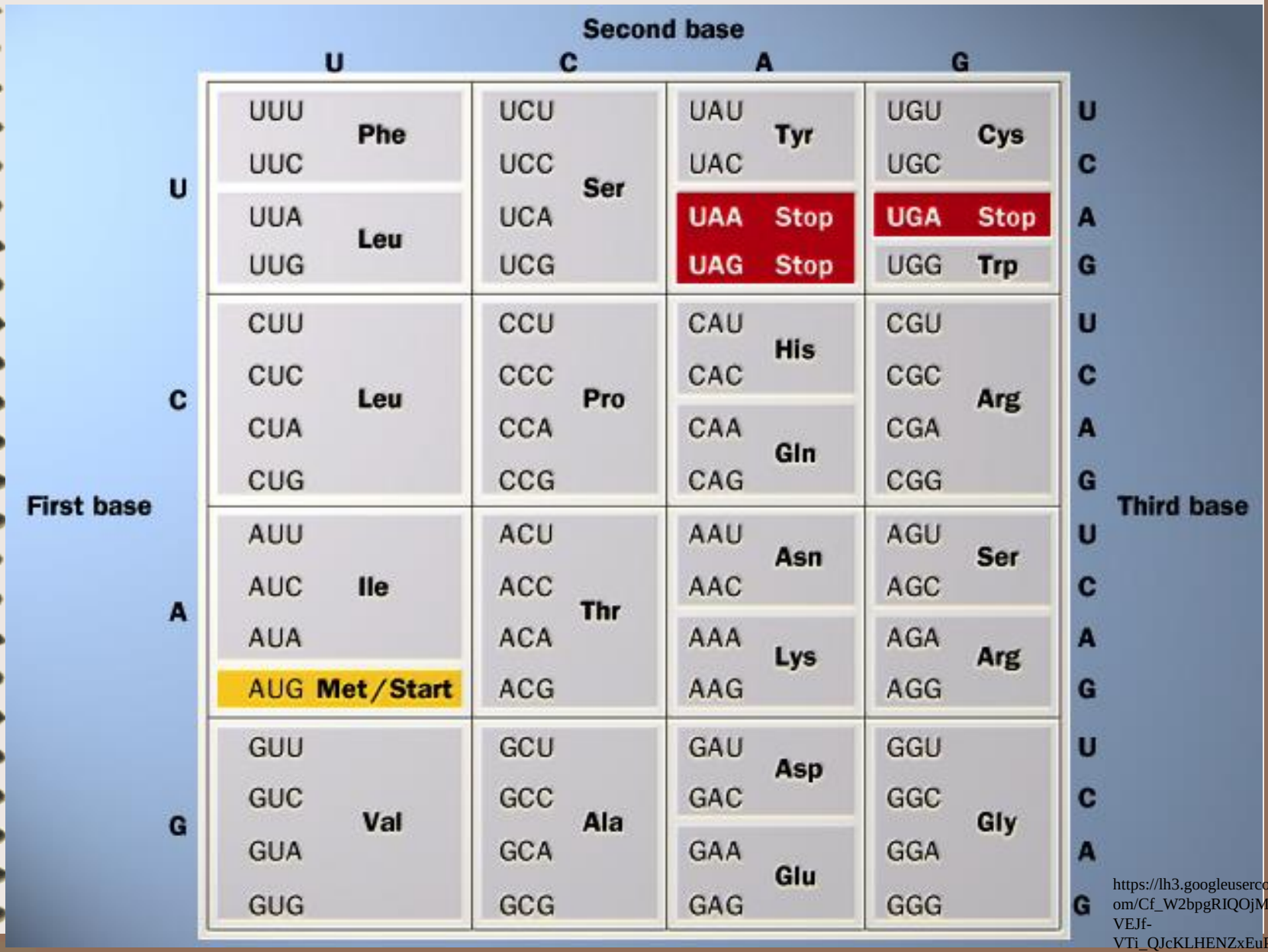
Posttranscriptional Processing of RNAs



The process of intron removal is called **RNA splicing**. Additional processing occurs to mRNAs. The 5' end of all eukaryotic mRNAs are **capped** with a unique 5' --> 5' linkage to a 7-methylguanosine residue.

https://lh3.googleusercontent.com/Br6LYVma4u2MnMSAGQmIiGx2M9ZkY_mn4h-RZMbGkSrN__kAiG0qKeR0_W0TGc_lh1i_qA=s164

Genetic Code



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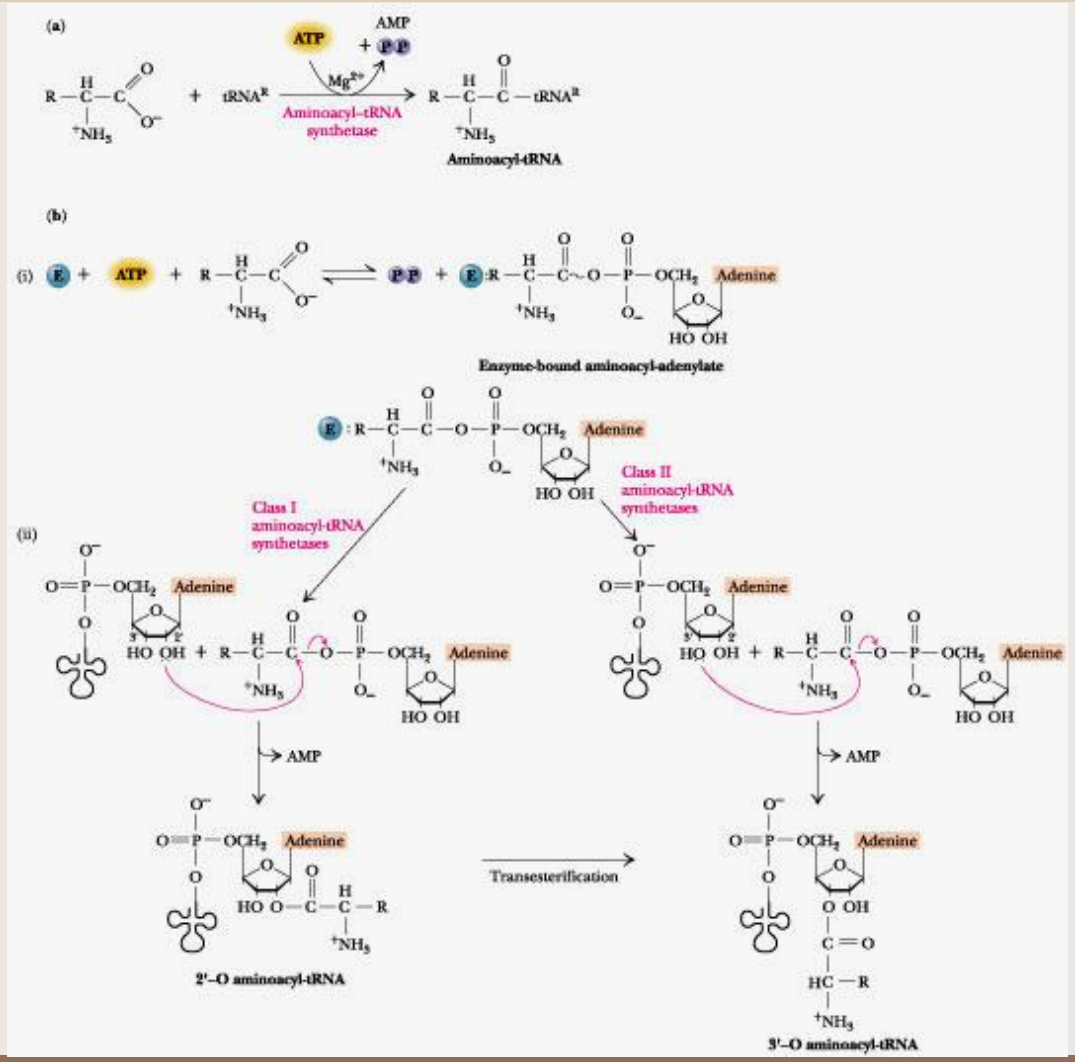
The Nature of the Genetic Code

1. All the codons have meaning.
2. The genetic code is unambiguous.
3. The genetic code is degenerate.
4. Codons representing the same amino acid or chemically similar amino acids tend to be similar in sequence.
5. The genetic code is "universal."

The Aminoacyl-tRNA Synthetase Reaction



The aminoacyl-tRNA synthetase reaction. (a) The overall reaction. (b) The overall reaction commonly proceeds in two steps.

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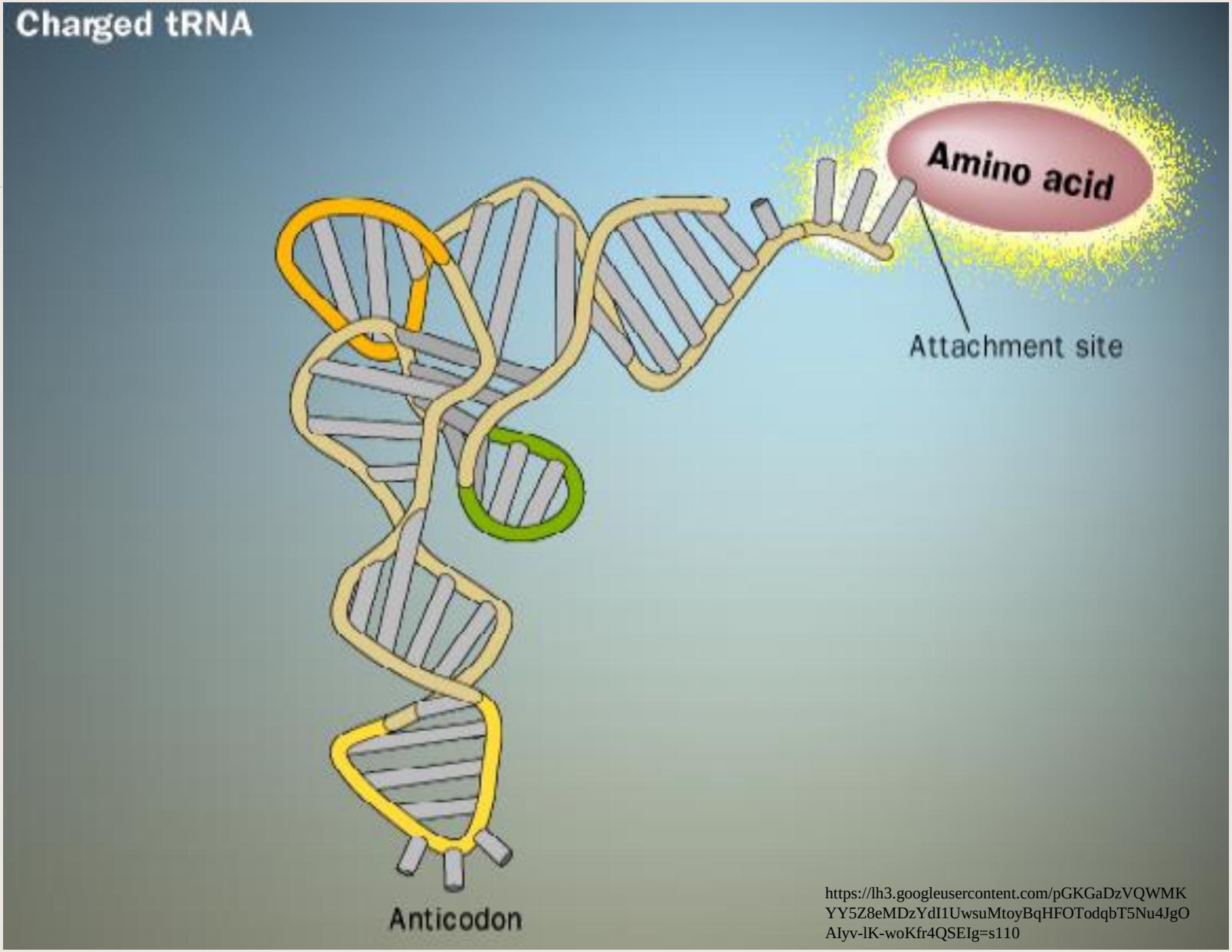

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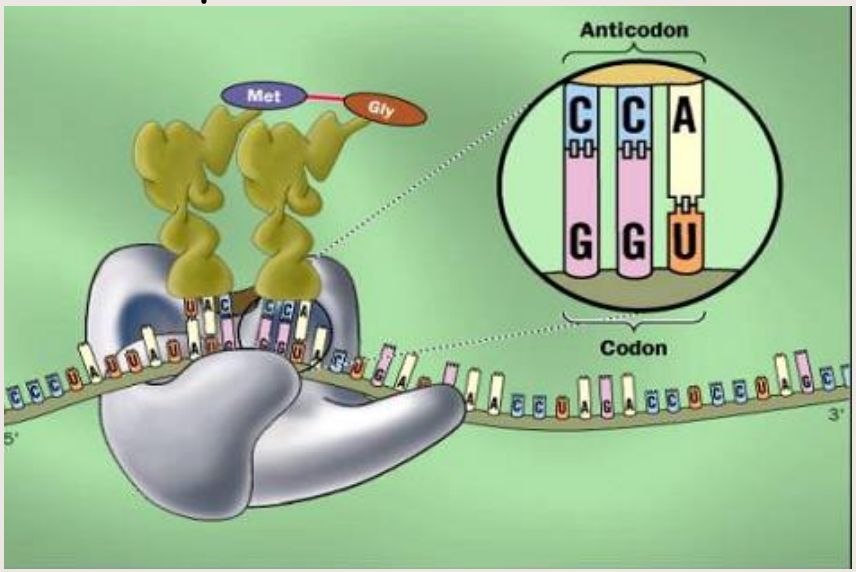
Protein Synthesis

Braille is a system of raised dots for translating written words into tactile word signs.

https://lh3.googleusercontent.com/NpnK951OkGpGrZW3K4JaGYBw17zcB8SXoXQ6whpzmQRo9UM5HRhWIFY8ROjoo7RIJWamUQ=s112

Protein biosynthesis is achieved by the process of **translation.**

Translation converts the language of genetic information embodied in the base sequence of a messenger RNA molecule into the amino acid sequence of a polypeptide chain.
During translation, proteins are synthesized on ribosomes by linking amino acids together in the specific linear order stipulated by the sequence of codons in an mRNA.



Ribosomes are the agents of protein synthesis

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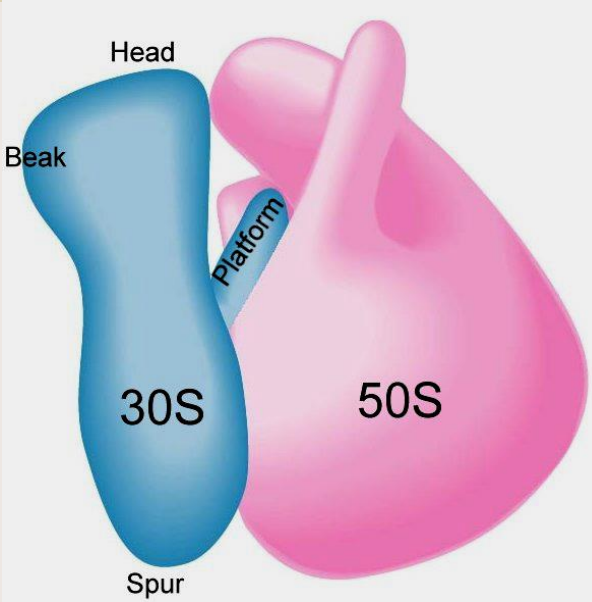
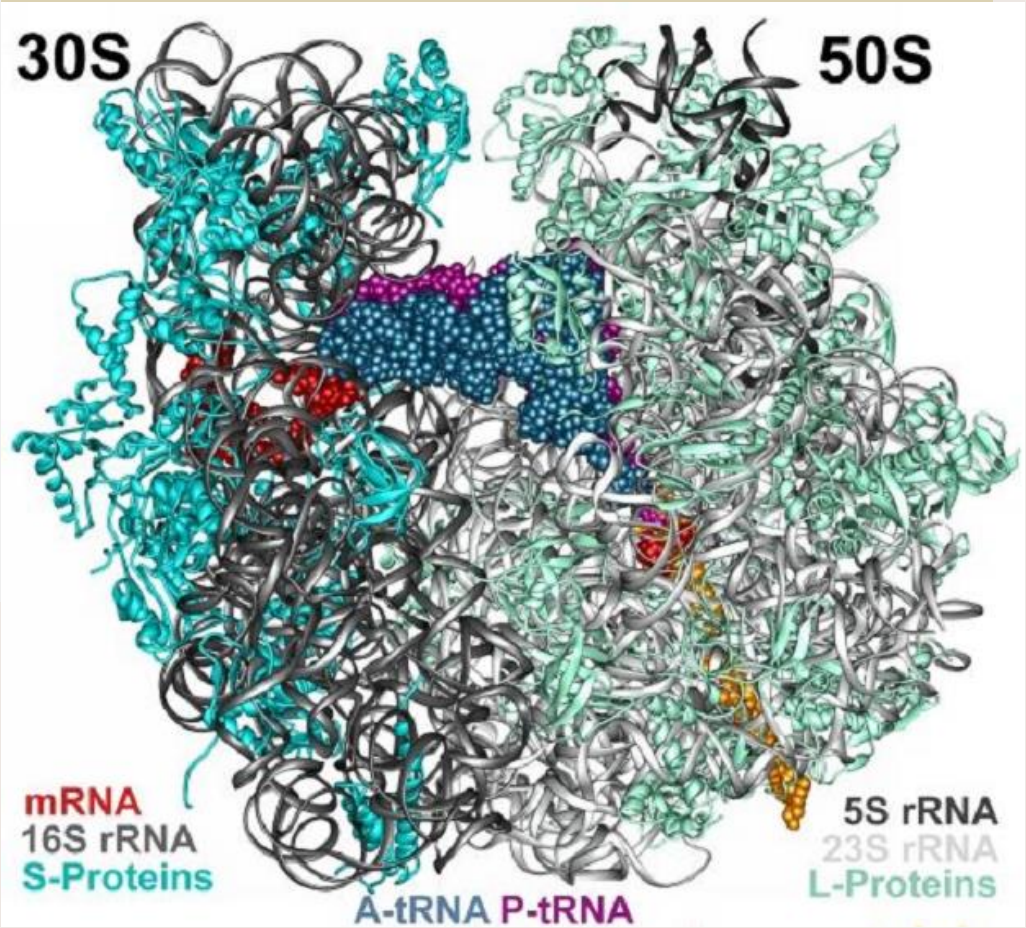
Ribosome Structure





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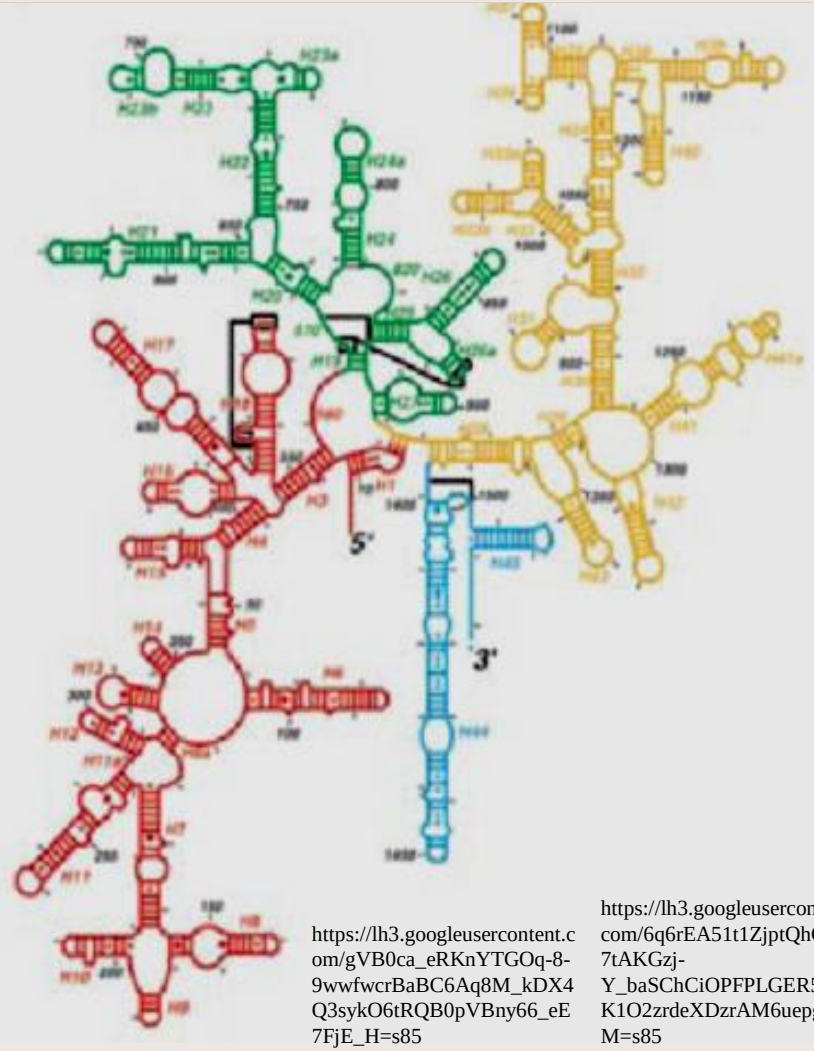
rRNA



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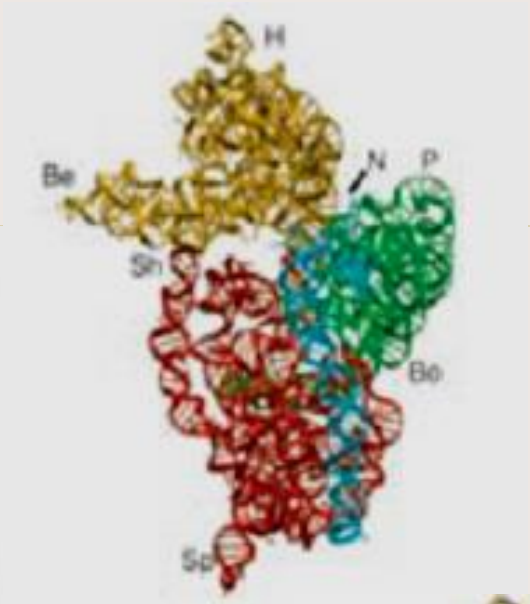

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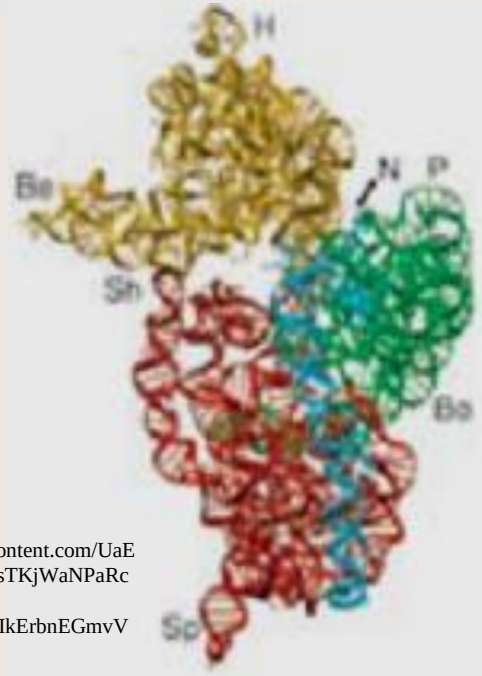

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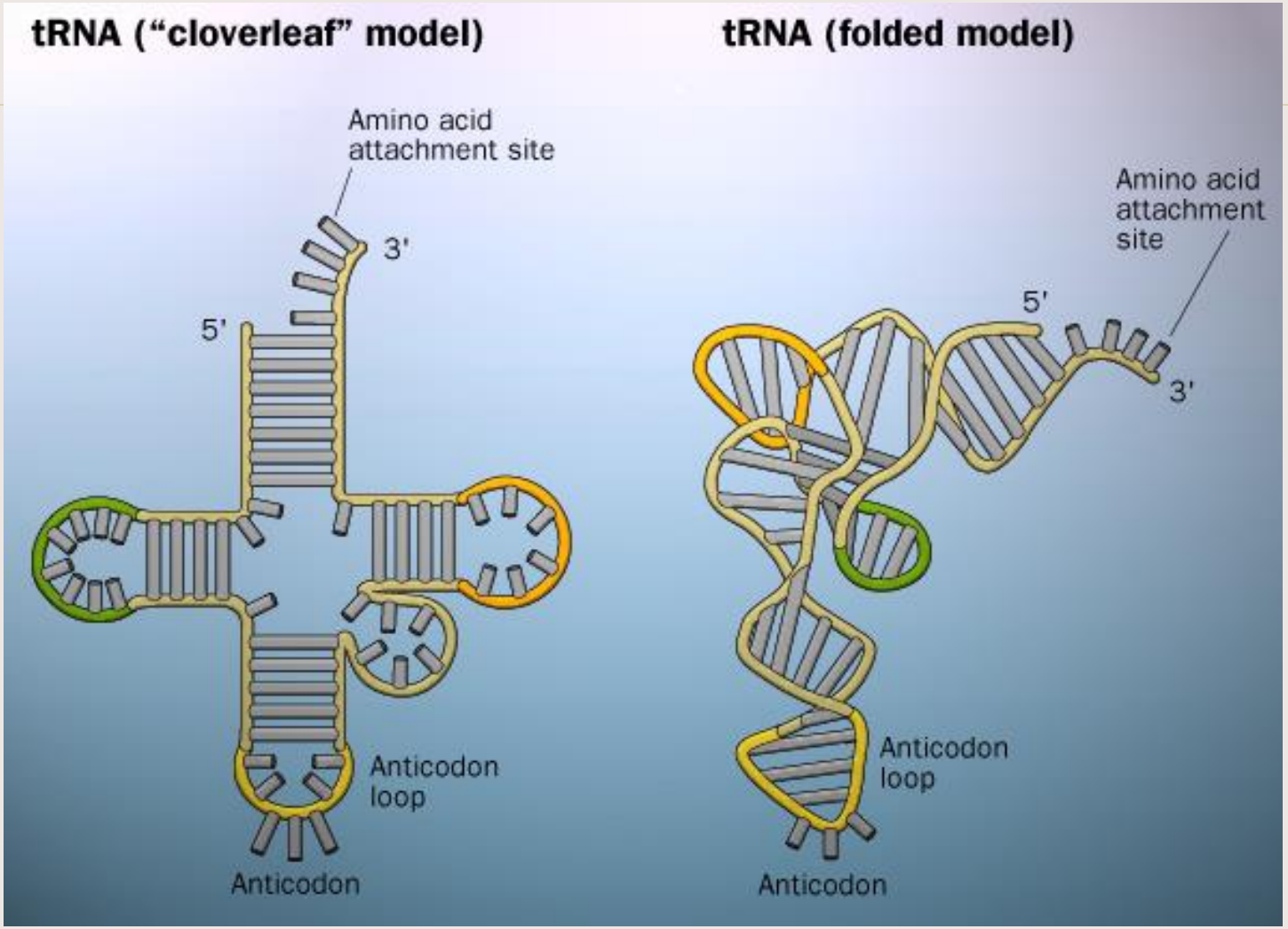
tRNA



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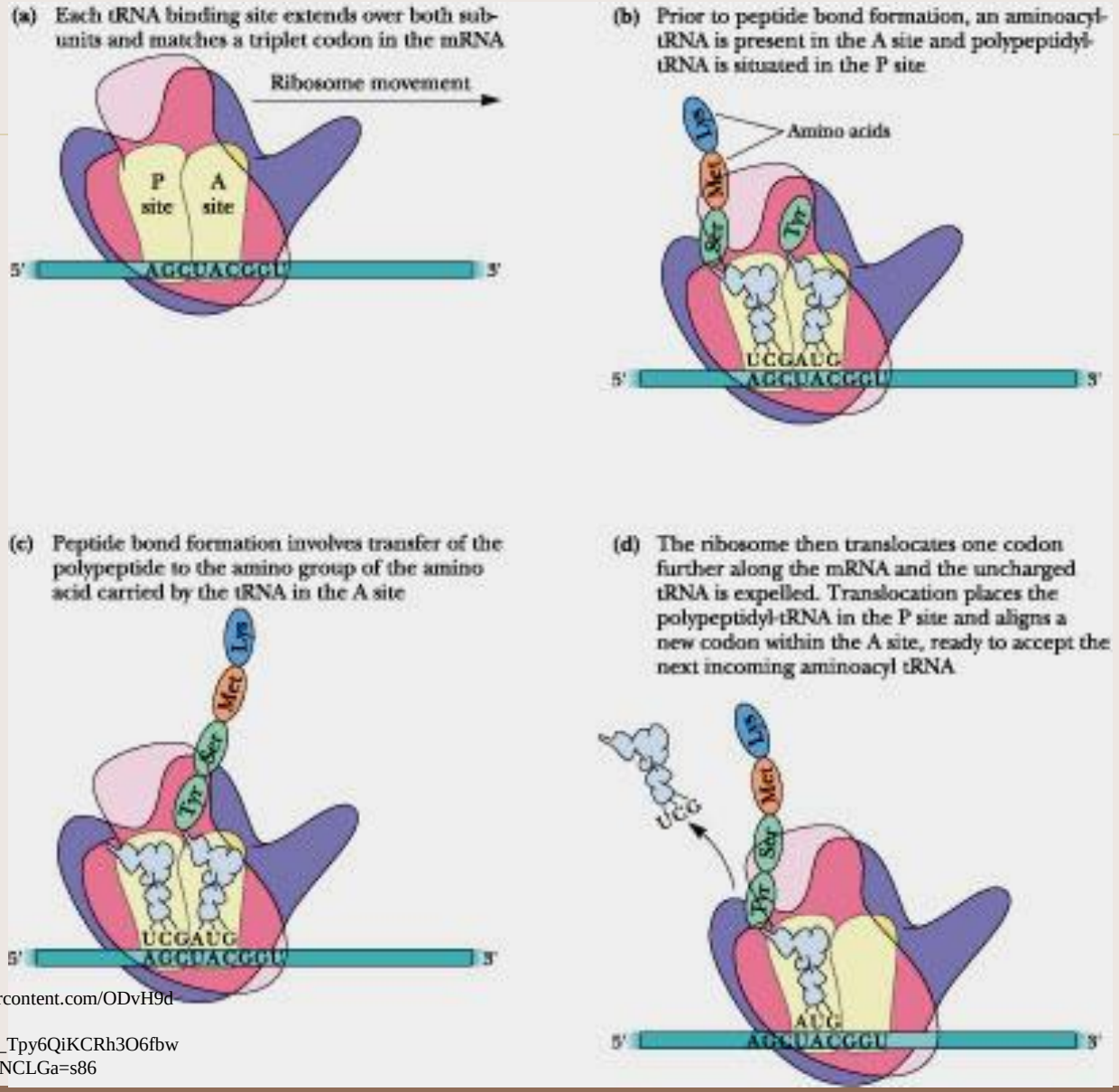
The basic steps in protein synthesis



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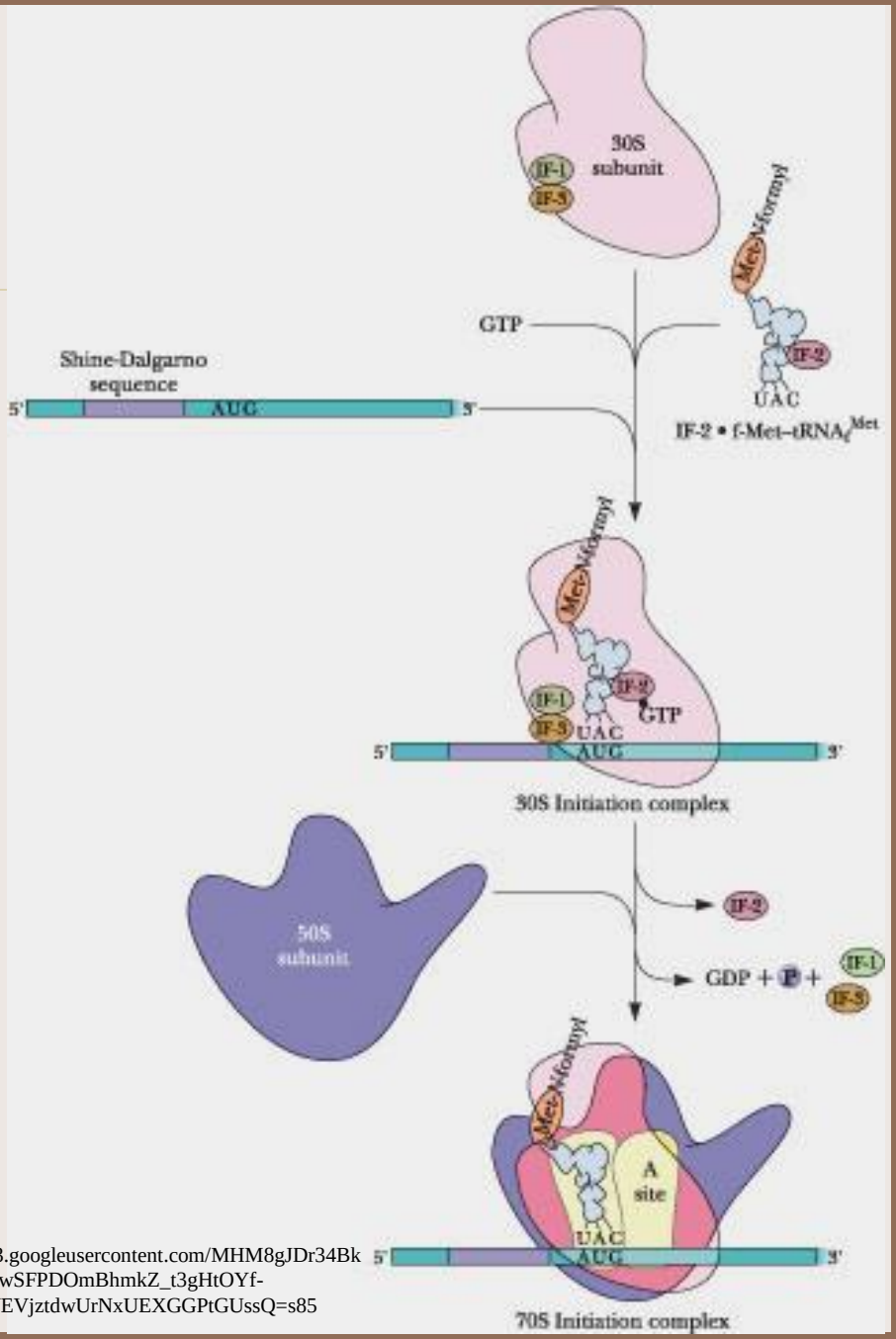
Initiation involves binding of mRNA by the small ribosomal subunit, followed by association of a particular **initiator aminoacyl-tRNA** that recognizes the first codon. This codon often lies within the first 30 nucleotides or so of mRNA spanned by the small subunit. The large ribosomal subunit then joins the initiation complex, preparing it for the elongation stage.



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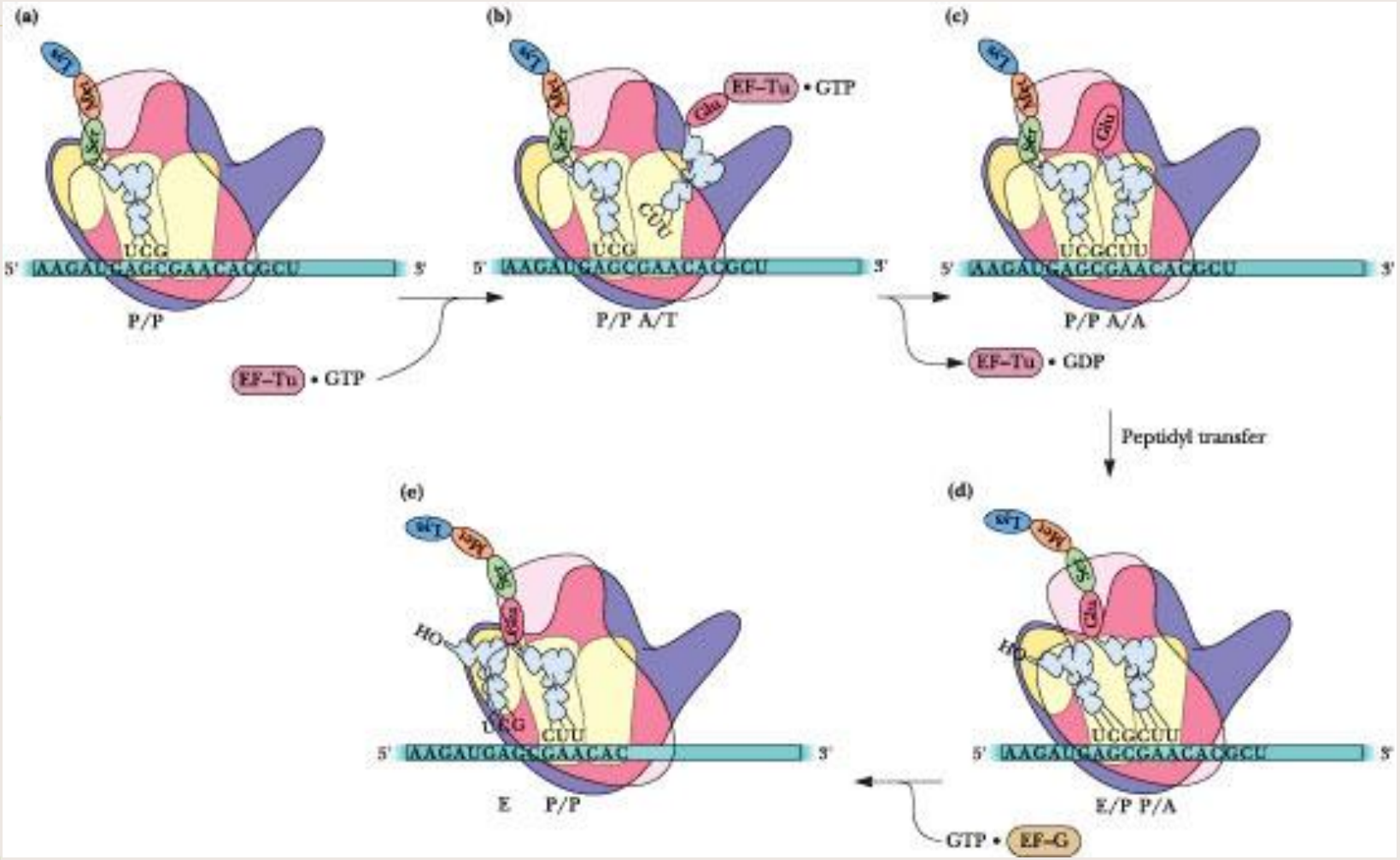
Elongation includes the synthesis of all peptide bonds from the first to the last. The ribosome remains associated with the mRNA throughout elongation, moving along it and translating its message into an amino acid sequence. This is accomplished via a repetitive cycle of events in which successive aminoacyl-tRNAs add to the ribosome:mRNA complex as directed by codon binding, and the polypeptide chain grows by one amino acid at a time.



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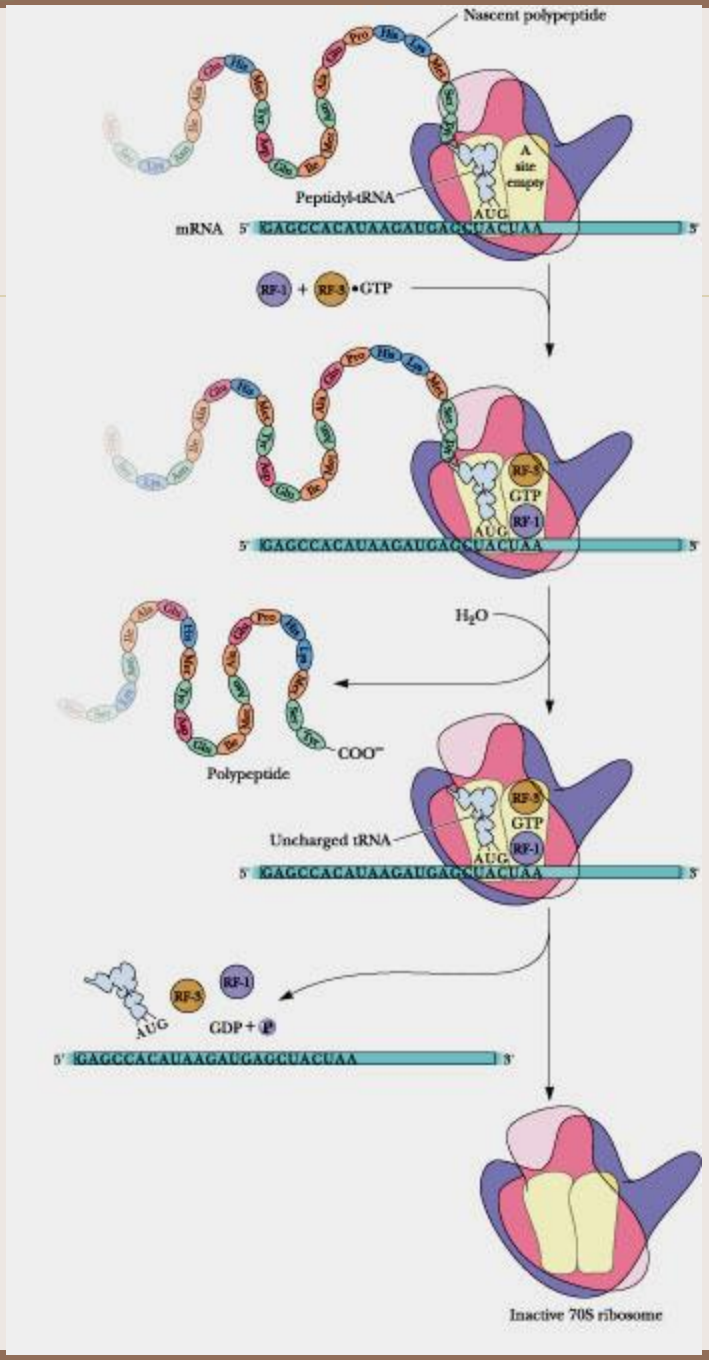
Termination is triggered when the ribosome reaches a "stop" codon on the mRNA. At this point, the polypeptide chain is released, and the ribosomal subunits dissociate from the mRNA.

Protein synthesis proceeds rapidly. In vigorously growing bacteria, about 20 amino acid residues are added to a growing polypeptide chain each second. So an average protein molecule of about 300 amino acid residues is synthesized in only 15 seconds. Eukaryotic protein synthesis is only about 10% as fast.

Peptide Chain Termination



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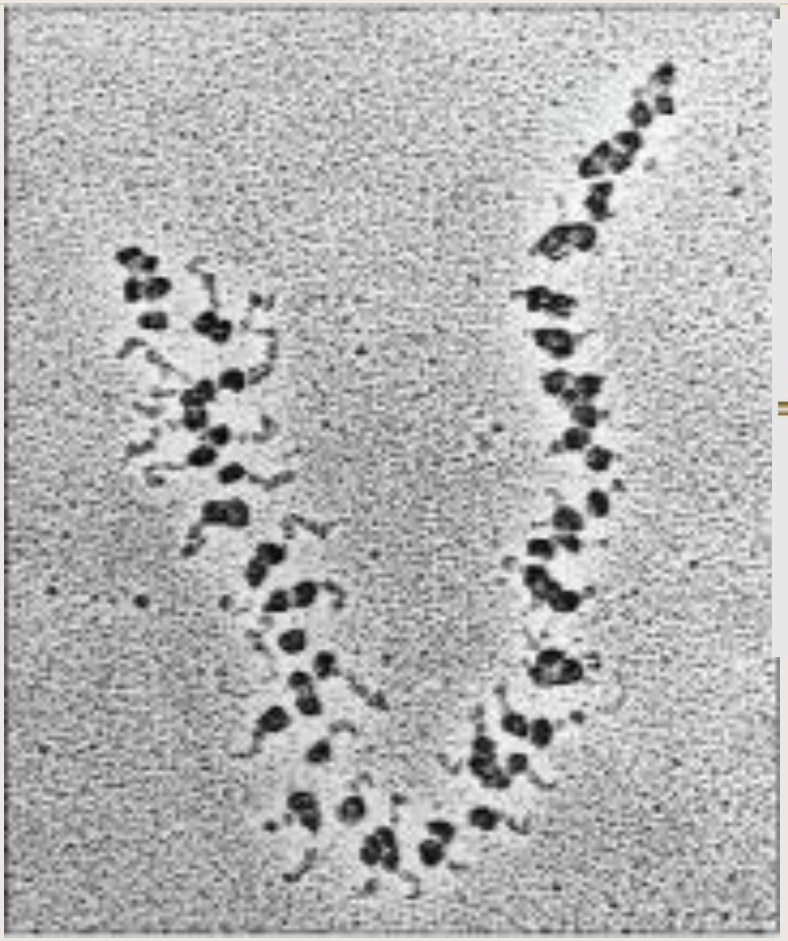
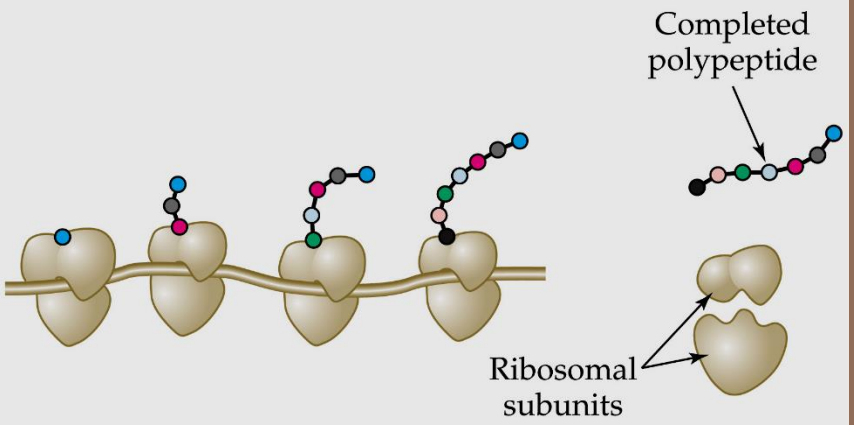
Polyribosomes Are the Active Structures of Protein Synthesis





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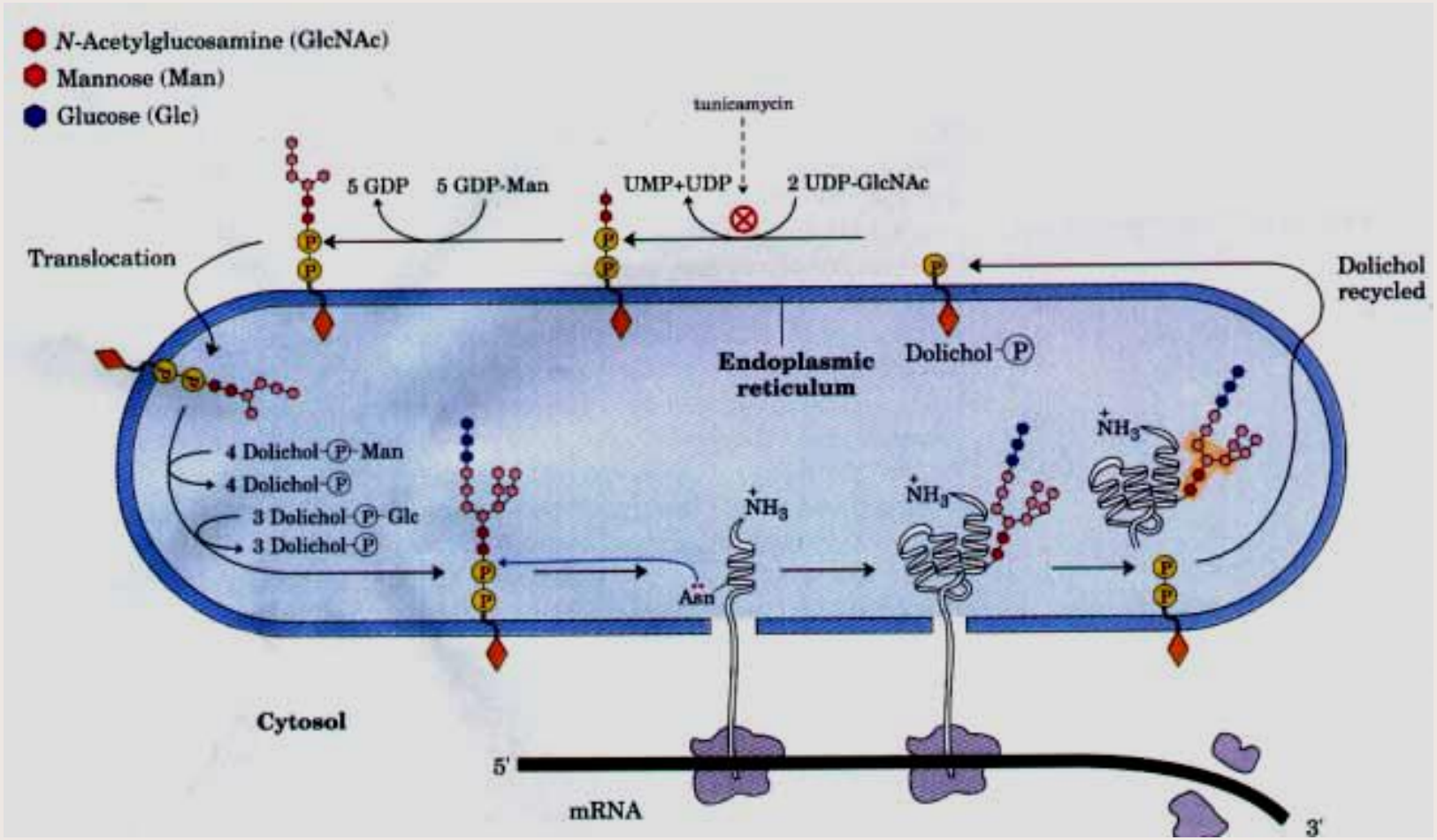
Electron micrograph of polysomes: multiple ribosomes translating the same mRNA.

Post-Translational Processing of Proteins



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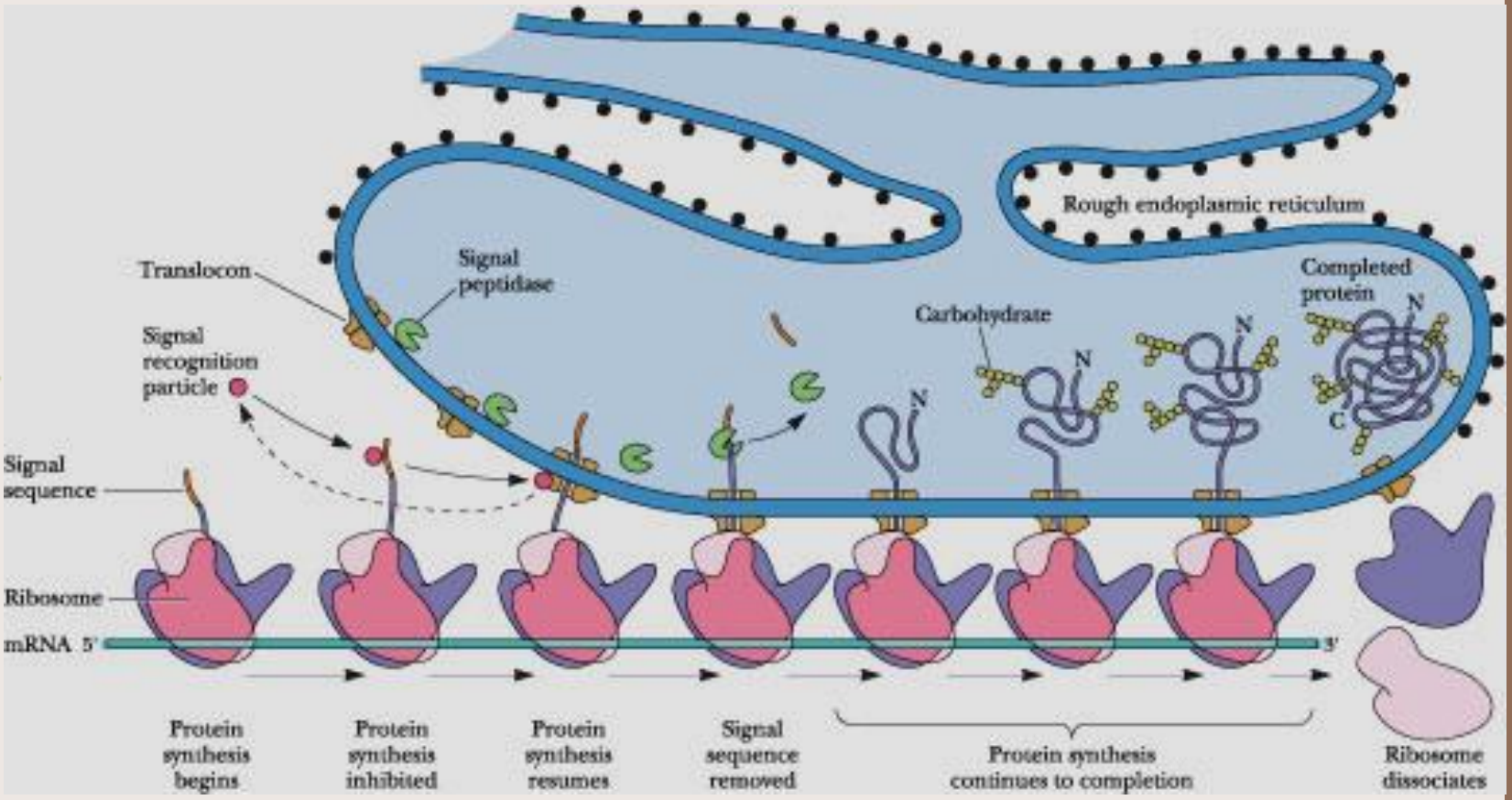
Eukaryotic Protein Sorting and Translocation



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Inhibitors of Protein Synthesis

Protein synthesis inhibitors have served two major, and perhaps complementary, purposes.

First, they have been very useful scientifically in elucidating the biochemical mechanisms of protein synthesis.
Second, some of these inhibitors affect prokaryotic but not eukaryotic protein synthesis and thus are medically important antibiotics.

Selected Antibiotic Inhibitors of Protein Synthesis

Chloramphenicol – Inhibits prokaryotic peptidyl transferase

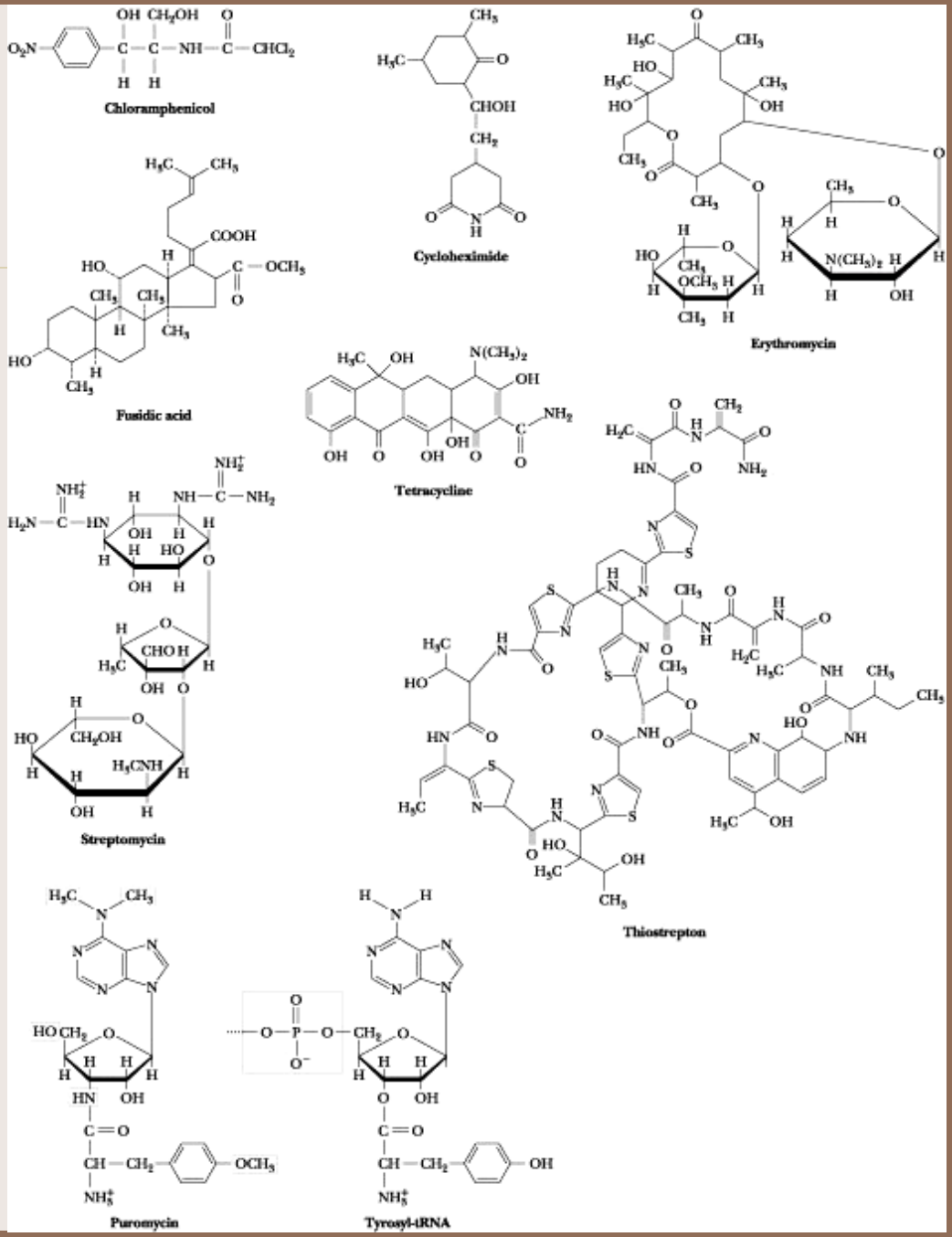
Cycloheximide – Inhibits eukaryotic peptidyl transferase

Erythromycin – Inhibits prokaryotic peptide chain elongation

Streptomycin – Binding to 30S subunit causes mRNA misreading

Tetracycline – Binding to 30S subunit interferes with aminoacyl-tRNA binding

The structures of various anti-biotics that act as protein synthesis inhibitors.



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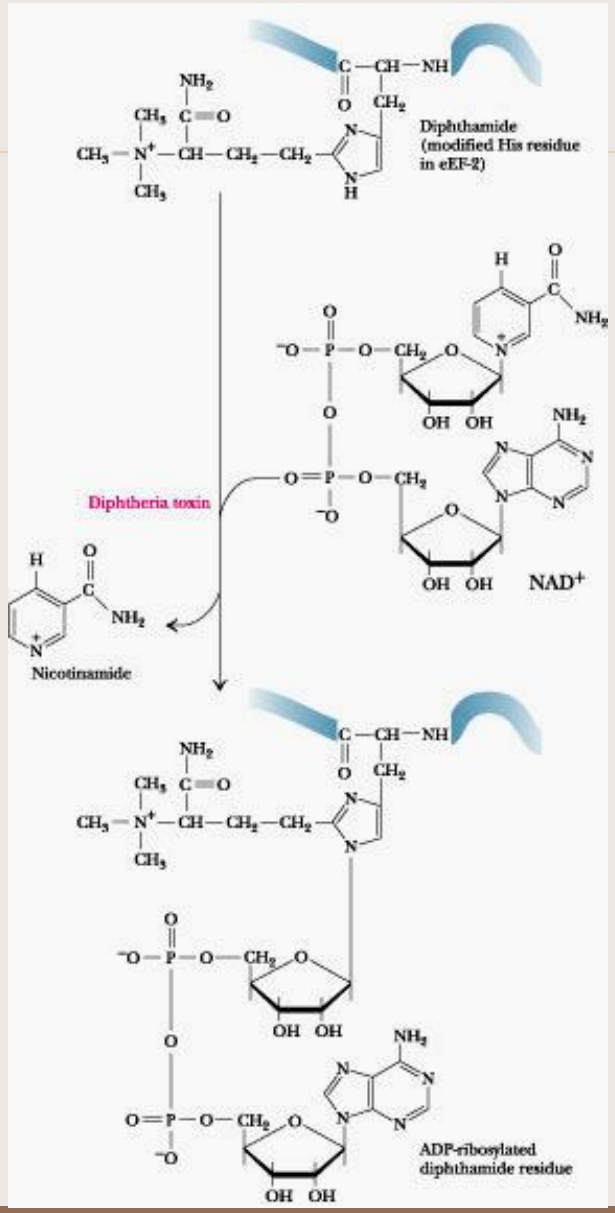
Diphtheria Toxin

Diphtheria arises from infection by *Corynebacterium diphtheriae*.



Diphtheria toxin is an enzyme secreted by these bacteria that is capable of inactivating a number of GTP-dependent enzymes through covalent attachment of an ADP-ribosyl moiety derived from NAD^+. One target of diphtheria toxin is the eukaryotic translocation factor, EF2.

ADP-ribosylated EF2 retains the ability to bind GTP but is unable to function in protein synthesis. Because diphtheria toxin is an enzyme and can act catalytically to modify many molecules of its target protein, just a few micrograms suffice to cause death.

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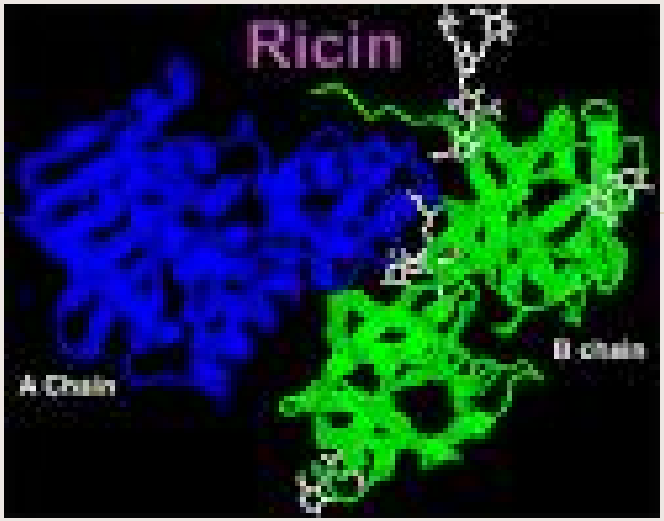
Ricin



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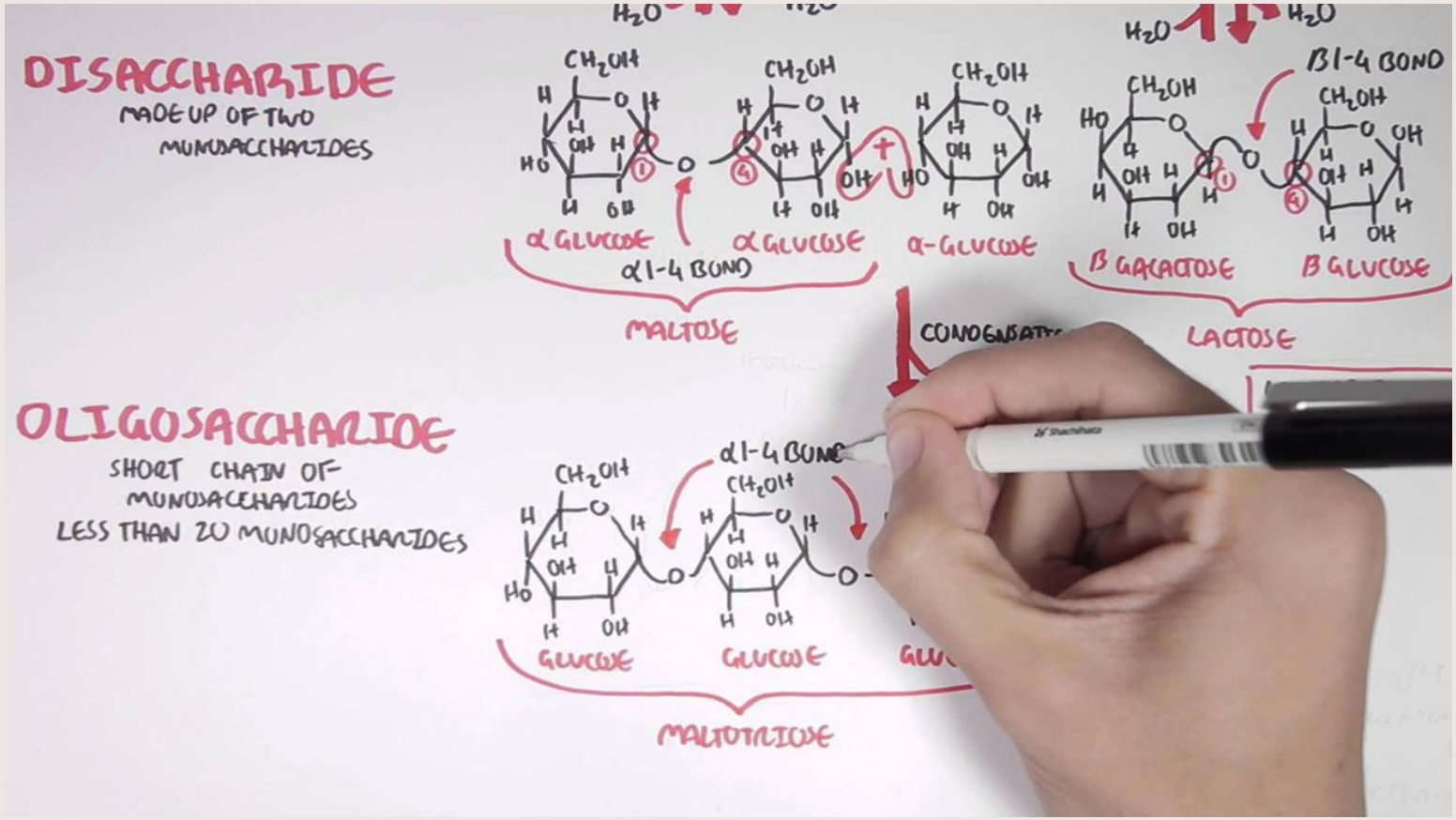
Ricin is an extremely toxic glycoprotein produced by the plant *Ricinus communis* (castor bean). The protein is a disulfide-linked, ab heterodimer of roughly equal subunits. The A subunit is an enzyme and serves as the toxic subunit; it gains entry to cells because the B subunit is a lectin. (Lectins form a class of proteins that bind to specific carbohydrate moieties commonly displayed by glycoproteins and glycolipids on cell surfaces.) Endocytosis of ricin catalytically inactivates eukaryotic large ribosomal subunits. A single molecule of ricin A chain in the cytosol can inactivate 50,000 ribosomes and kill a eukaryotic cell!

Conclusions

1. Todays understanding of information pathways as arisen from the convergence of genetics, physics, and chemistry in modern biochemistry.
2. DNA replication is governed by a set of fundamental rules.
3. All cells have multiple DNA repair systems.
4. Three major kinds of RNA are produced.
5. RNA is synthesized by RNA polymerases.
6. All RNA molecules in eukaryotes are processed after they are synthesized.
7. Genetic code is the set of triplet code "words" in DNA or mRNA) coding for the amino acids of proteins.
8. Translation is the process in which the genetic information present in mRNA molecular specifies the sequence of amino acids during protein synthesis.

Do you have any questions?

Thank you for your attention!



https://www.youtube.com/watch?v=JxK5rZxbyQY