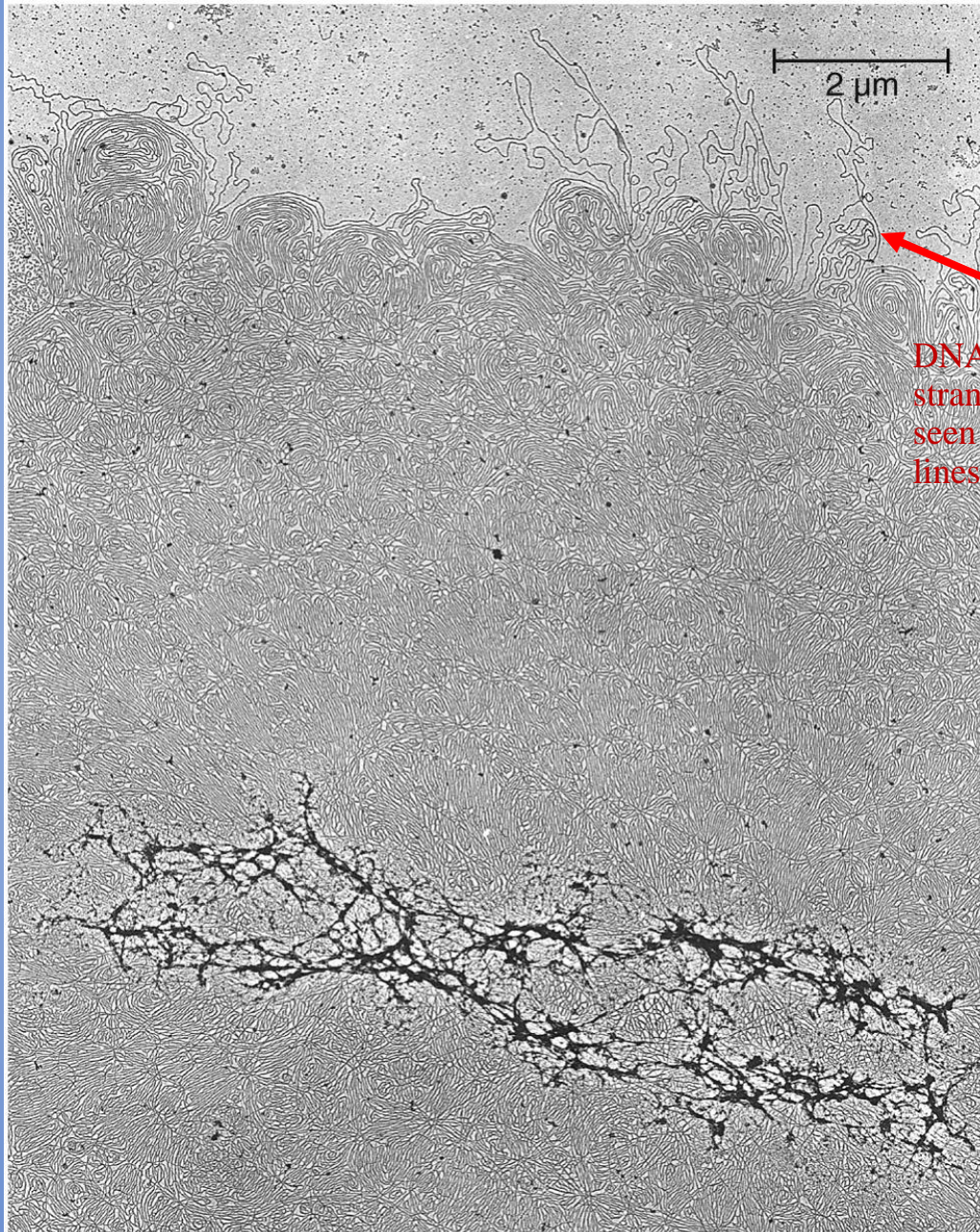


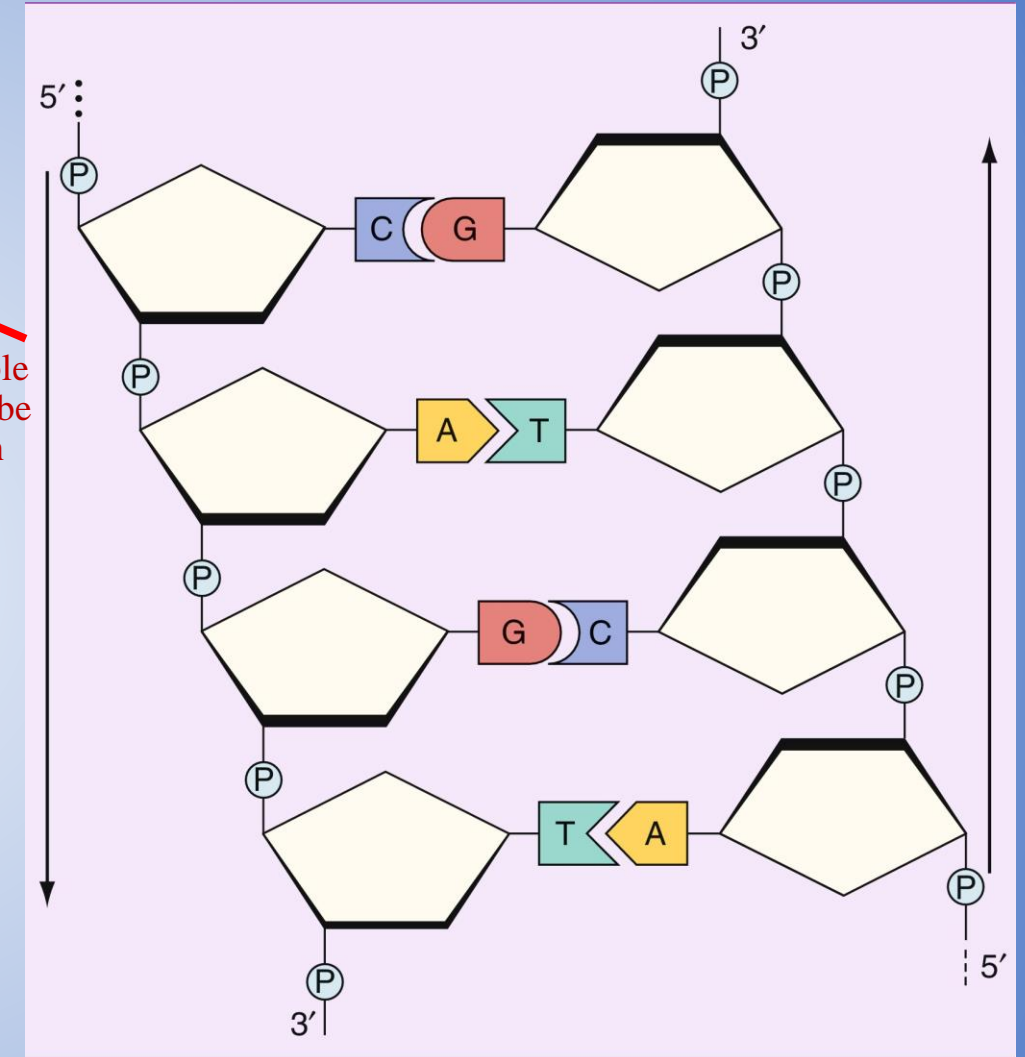
DNA structure and replication



ELECTRON MICROGRAPH OF A CHROMOSOME FROM WHICH MOST PROTEINS WERE EXTRACTED. This allows DNA (thin lines) to spread out from the residual scaffold. Enormous amounts of DNA are packaged in each chromosome. This image shows less than 30% of the DNA of this chromosome.

Book: Cell Biology, Third Edition, 2017, Pollard, Thomas D., MD

(From Paulson JR, Laemmli UK. The structure of histone-depleted chromosomes. Cell . 1977;12:817–828.)



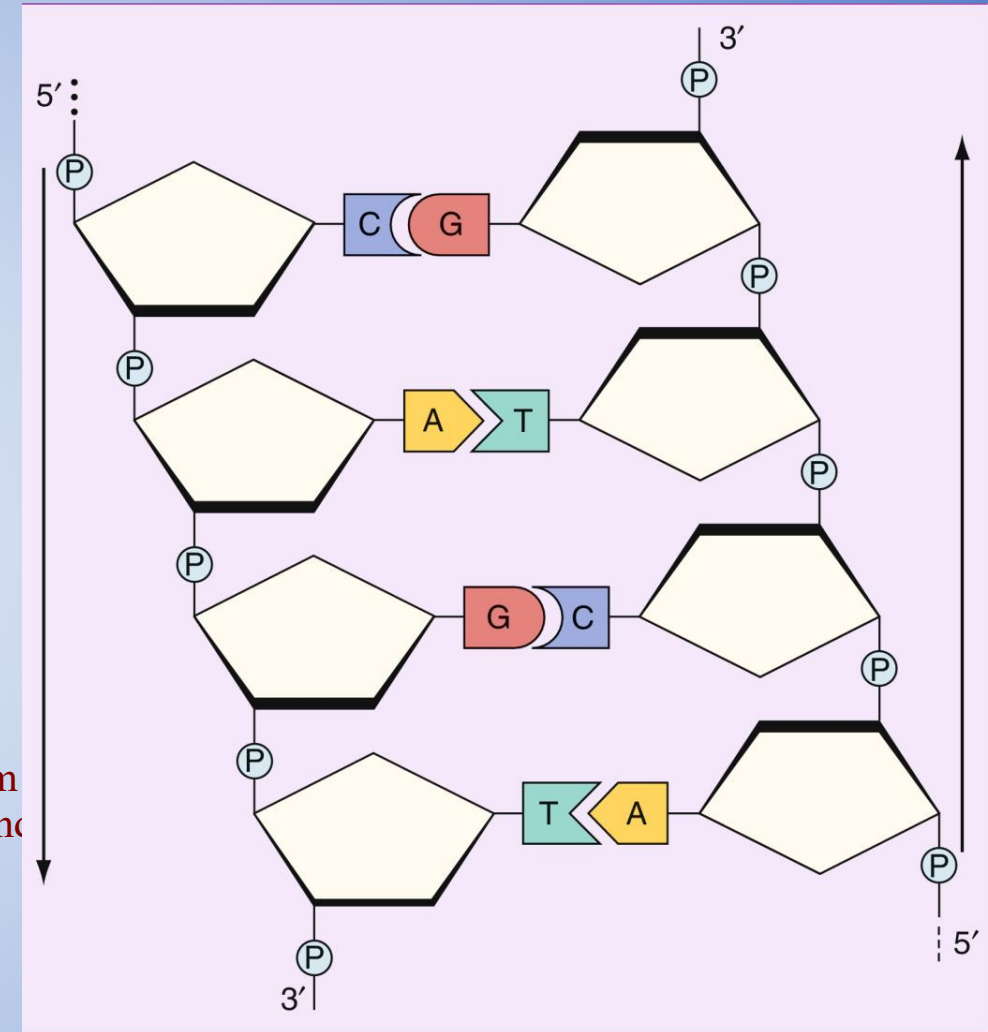
Schematic view of the DNA double strand. Note that the strands are antiparallel and that only A-T and G-C base pairs are permitted. Therefore the base sequence of one strand predicts the base sequence of the opposite strand. A, Adenine; C, cytosine; G, guanine; P, phosphate; T, thymine.

From: Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

DNA structure

DNA is a polymer of nucleoside monophosphates:

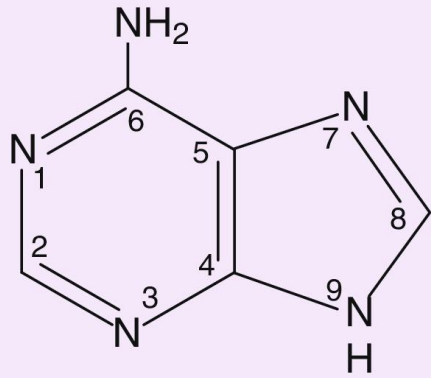
- ▶ Its structural backbone consists of alternating phosphate and 2-deoxyribose residues that are held together by phosphodiester bonds involving carbon-3 and carbon-5 of the sugar
- ▶ Carbon-1 forms a β -N-glycosidic bond with one of the four bases:
 - ▶ Adenine
 - ▶ Cytosine
 - ▶ Guanine
 - ▶ Thymine
- ▶ One end of the DNA strand has a free hydroxyl group at C-5 of the last 2-deoxyribose
- ▶ The other end has a free hydroxyl group at C-3
- ▶ The carbons of 2-deoxyribose are marked by a prime (') to distinguish them from the carbon and nitrogen atoms of the bases; therefore, each strand has a 5' end and a 3' end
- ▶ By convention, the 5' terminus of a DNA (or RNA) strand is written at the left end and the 3' terminus at the right end
- ▶ 2 DNA strands are bound by hydrogen bonds between the inward-facing bases



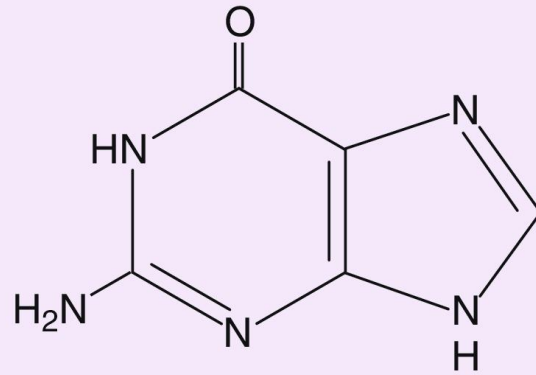
Adenine (A) always pairs with thymine (T) in the opposite strand, and guanine (G) with cytosine (C).

From:
Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

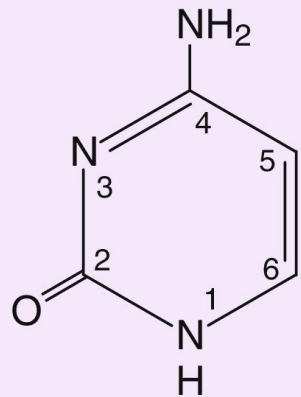
Chemical structure of the bases



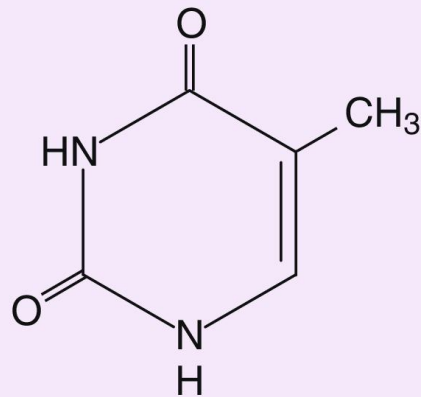
A
Adenine
(A)



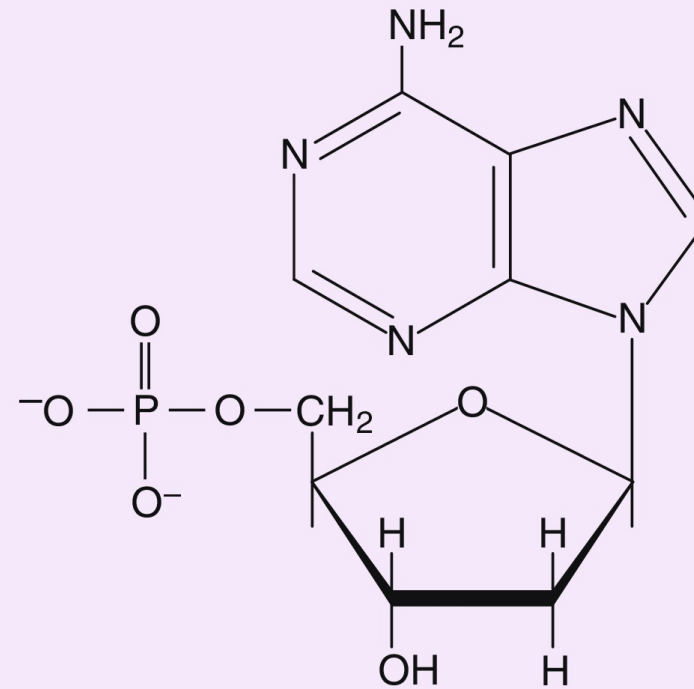
Guanine
(G)



Cytosine
(C)



Thymine
(T)



B

2-deoxy-AMP
(dAMP)

B, Structure of 2-deoxy-adenosine monophosphate (dAMP), one of the four 2-deoxyribonucleoside monophosphates (also called 2-deoxynucleotides) in the repeat structure of DNA. Note that a nitrogen atom of the base is bound by a β -N-glycosidic bond to C-1 of 2-deoxyribose, whereas C-5 forms a phosphate ester bond.

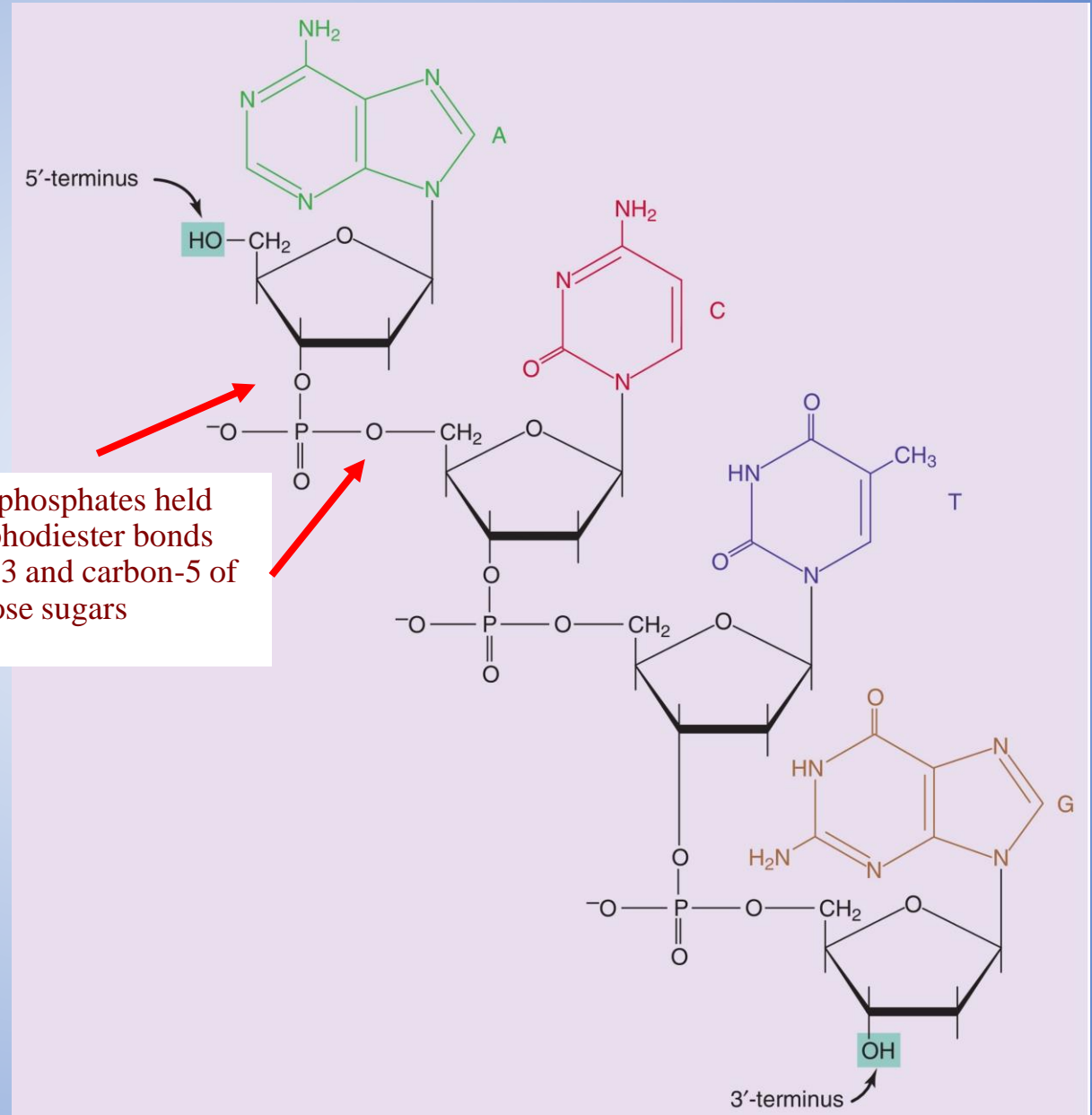
From:
Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

The building blocks of DNA. A, Structures of the four bases, 2-deoxyribose, and phosphate. The bases A and G are purines, and C and T are pyrimidines.

From:
Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

Example of a single DNA strand

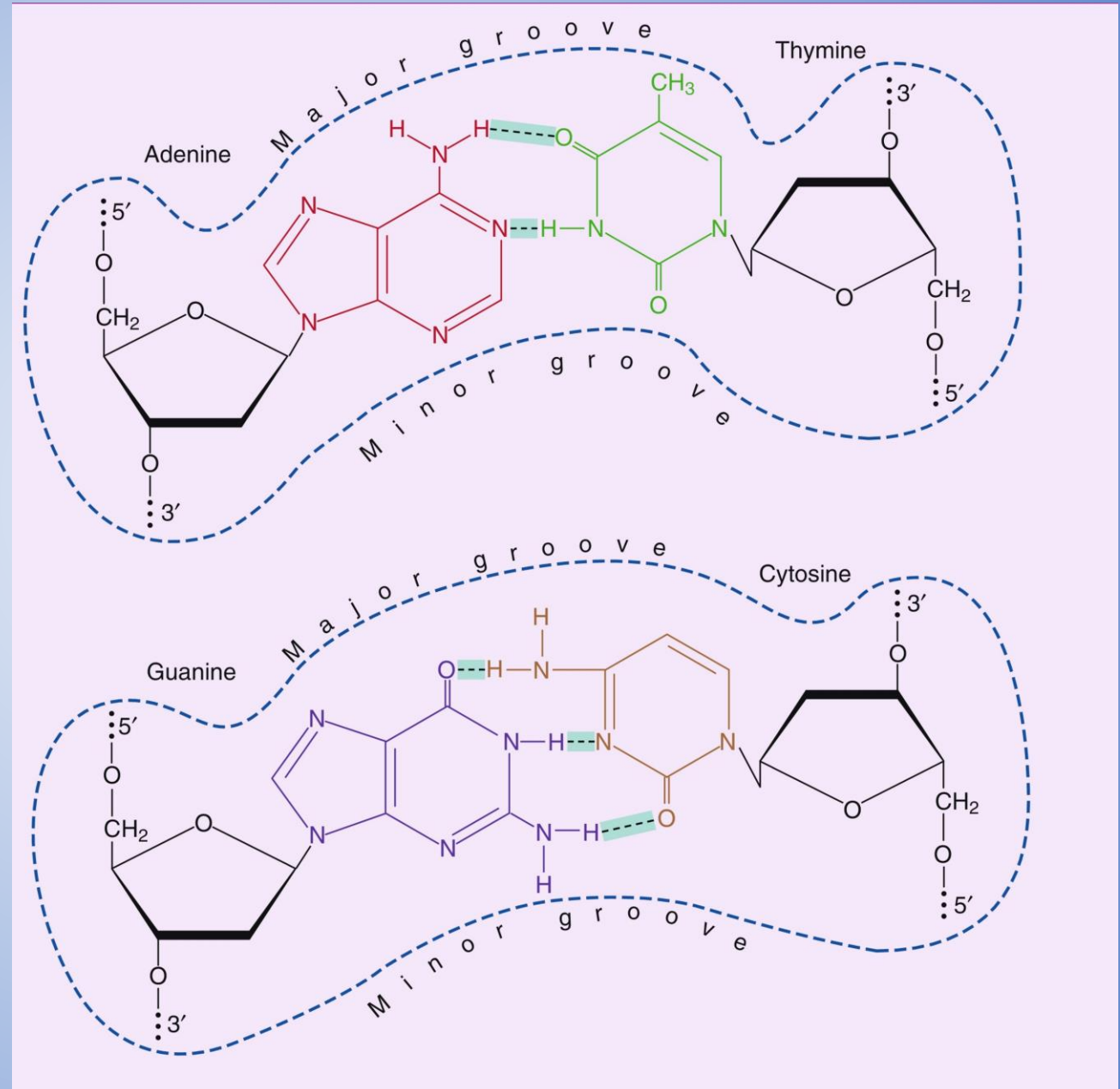
Nucleoside monophosphates held together by phosphodiester bonds involving carbon-3 and carbon-5 of the two deoxyribose sugars



Structure of the (2-deoxy-)tetranucleotide ACTG. The DNA strands in chromosomes are far larger, with lengths of many million nucleotide units. A, Adenine; C, cytosine; G, guanine; T, thymine.

From:
Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

Hydrogen bonds holding together double stranded DNA



Cross-sections through an adenine-thymine (A-T) and a guanine-cytosine (G-C) base pair in the DNA duplex. The A-T base pair is held together by two hydrogen bonds [—] and the G-C base pair by three.

From:
Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

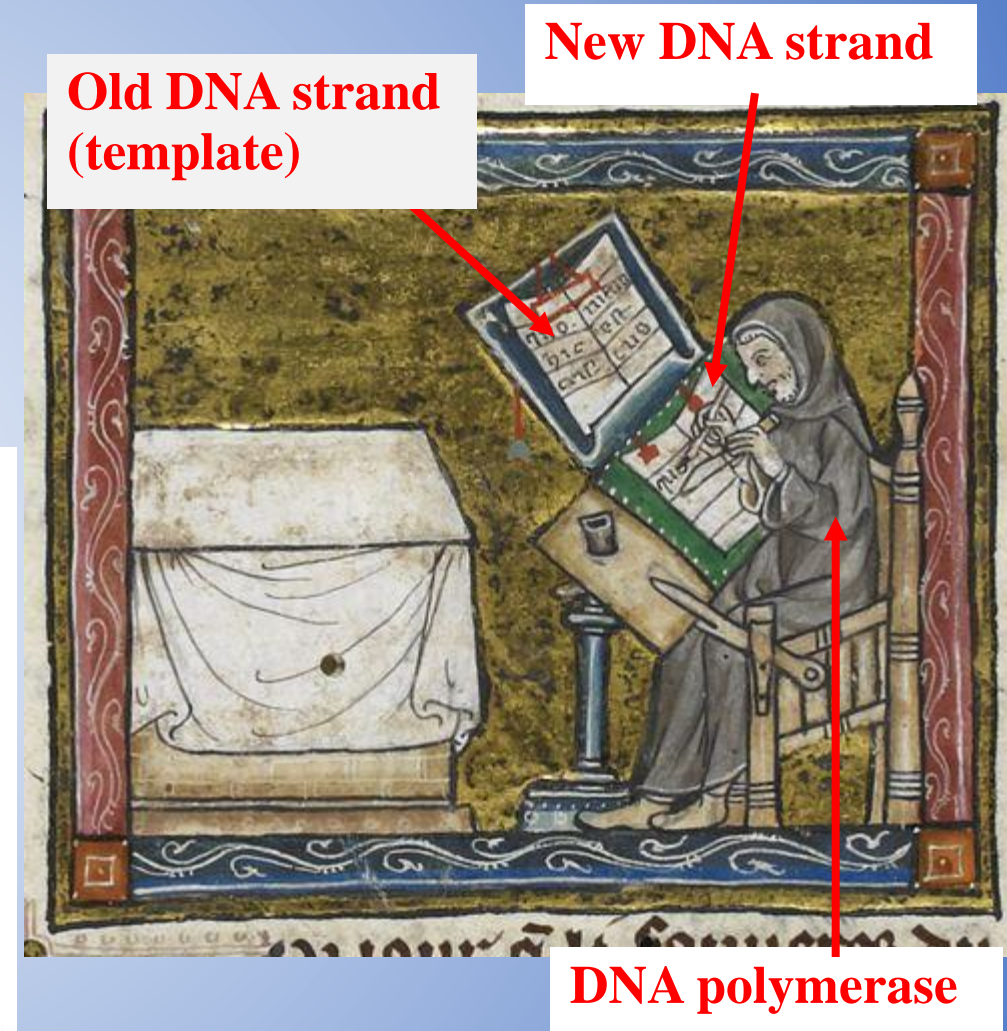
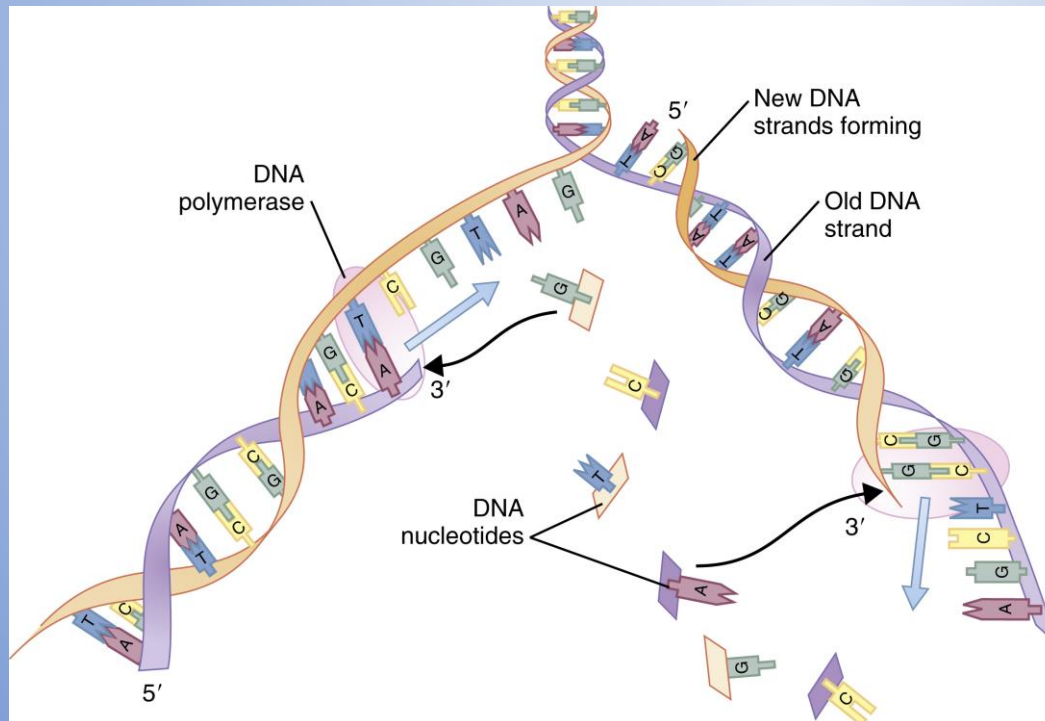
DNA polymerase

DNA is synthesized by DNA polymerases:

- ▶ DNA polymerases are literate enzymes, they are like the scribe monks in medieval monasteries, who worked day and night copying old manuscripts without understanding their content
- ▶ DNA replication is semiconservative, 2 strands of a DNA double helix are used as templates for 2 new strands (each having 1 old and 1 new strand in the helix)
- ▶ DNA polymerase adds new new complementary nucleotides to the strand in a stepwise fashion and in the 5' → 3' direction

DNA replication. The hydrogen bonds between the two original strands are broken, allowing the bases in each strand to undergo complementary base pairing with free bases. This process, which proceeds in the 5' to 3' direction on each strand, forms two new double strands of DNA.

From:
Medical Genetics, Sixth Edition, 2020, Jorde, Lynn B., PhD



A scribe at work, from an illuminated manuscript from the Estoire del Saint Graal, France (Royal MS 14 E III c. 1315 – 1325 AD. From <http://britishlibrary.typepad.co.uk/>)

Literature:

Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD
Medical Genetics, Sixth Edition, 2020, Jorde, Lynn B., PhD

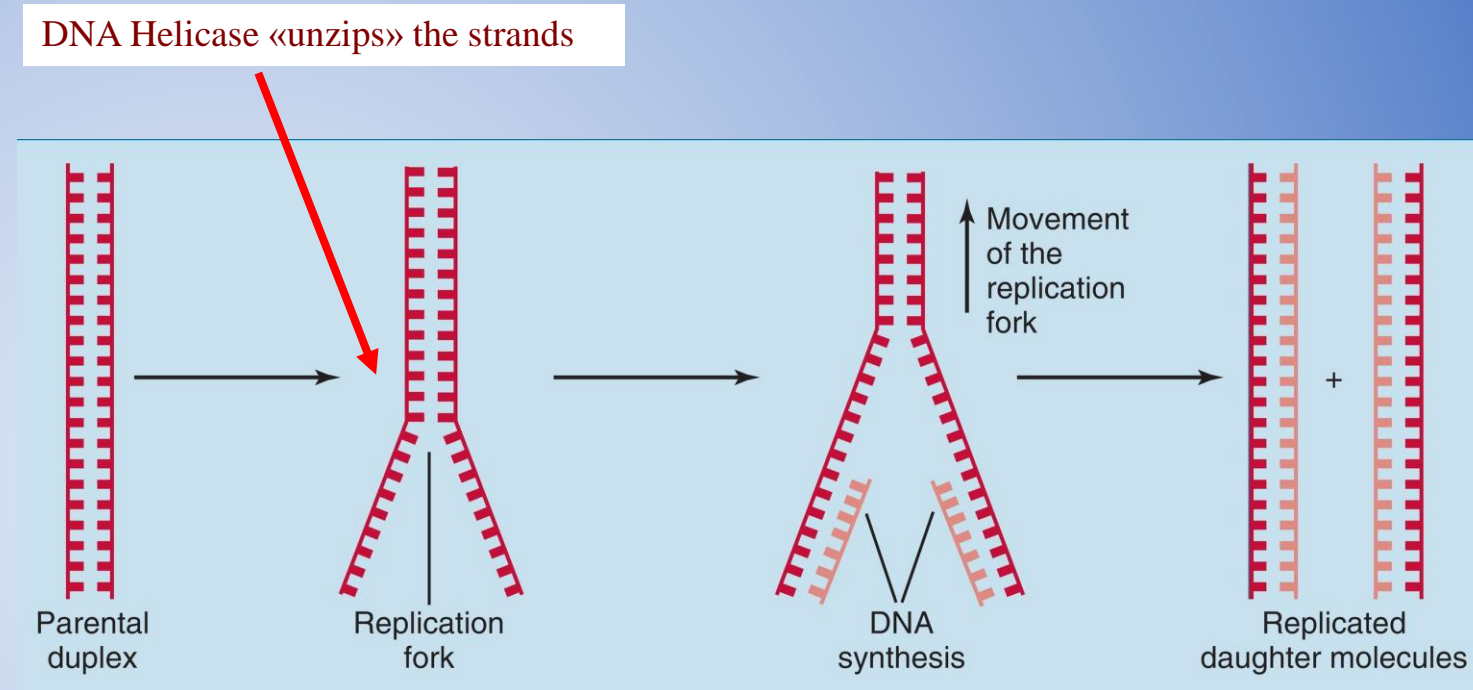
DNA polymerase

DNA is synthesized also is involved in proof reading of added nucleotides:

- ▶ Added nucleotide is checked to make certain that it is in fact complementary to the template base
- ▶ If it is not, the nucleotide is excised and replaced with a correct complementary nucleotide base
- ▶ When a DNA replication error is not successfully repaired, a mutation has occurred which can lead to diseases

DNA replication steps

- ▶ DNA double spiral cannot be replicated while both strands are bound by hydrogen bonds
- ▶ The double helix is unwinded to produce two single strands and this is done by ATP-dependent enzymes to break the hydrogen bonds between bases (DNA helicase)
- ▶ DNA unwinding creates two replication forks
- ▶ DNA on the other side of the fork gets wound more tightly and this would create tension that would impede unwinding the double helix above the fork
- ▶ Topoisomerases I enzymes produce transient nicks in the DNA back-bone, which temporarily release the tension (II more complex mechanism)
- ▶ Once strands have been separated, they are kept in the single-stranded state by associating loosely with a single-stranded DNA binding protein (SSB protein)
- ▶ A new complementary strand is synthesized for each of the two old strands by 2 DNA polymerases from the 2 old (template) DNA strands



Semiconservative mechanism of DNA replication.

From:

Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

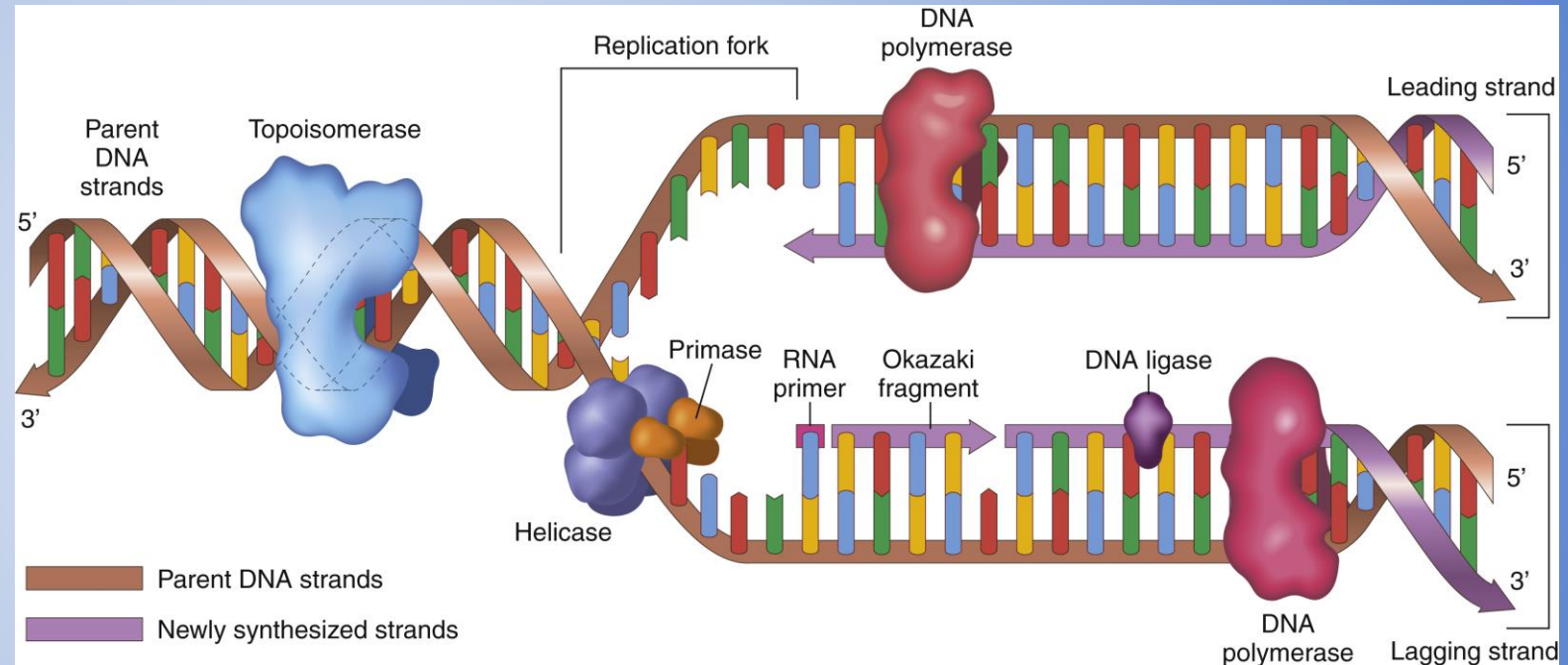
Literature:

Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD

Essential Cell Biology, 2014, Bruce Alberts; Dennis Bray; Karen Hopkin; Alexander Johnson; KE Roberts

DNA replication steps

- ▶ Before a new DNA strand can be created a short piece of RNA called an RNA primer binds to the 3' end of the leading strand
- ▶ Primers are generated by the enzyme DNA primase and always bind as the starting point for DNA replication
- ▶ The lagging strand begins replication by binding with multiple primers that are only several bases apart
- ▶ DNA polymerase then adds pieces of DNA, called Okazaki fragments (100 to 200 nucleotides long), to the strand between primers and those fragments are not connected at this point
- ▶ DNA ligase, joins the Okazaki fragments to form a single unified strand
- ▶ After the leading and lagging strands are both formed, the enzyme exonuclease removes the RNA primers from the original strands, and the primers are replaced with appropriate DNA bases



DNA replication, showing the replication fork and leading and lagging strands of DNA.

From:
Guyton and Hall Textbook of Medical Physiology Fourteenth Edition, 2021

Literature:

Principles of Medical Biochemistry Fourth Edition, 2017, Meisenberg, Gerhard, PhD
Guyton and Hall Textbook of Medical Physiology Fourteenth Edition, 2021