Molecular Chemistry

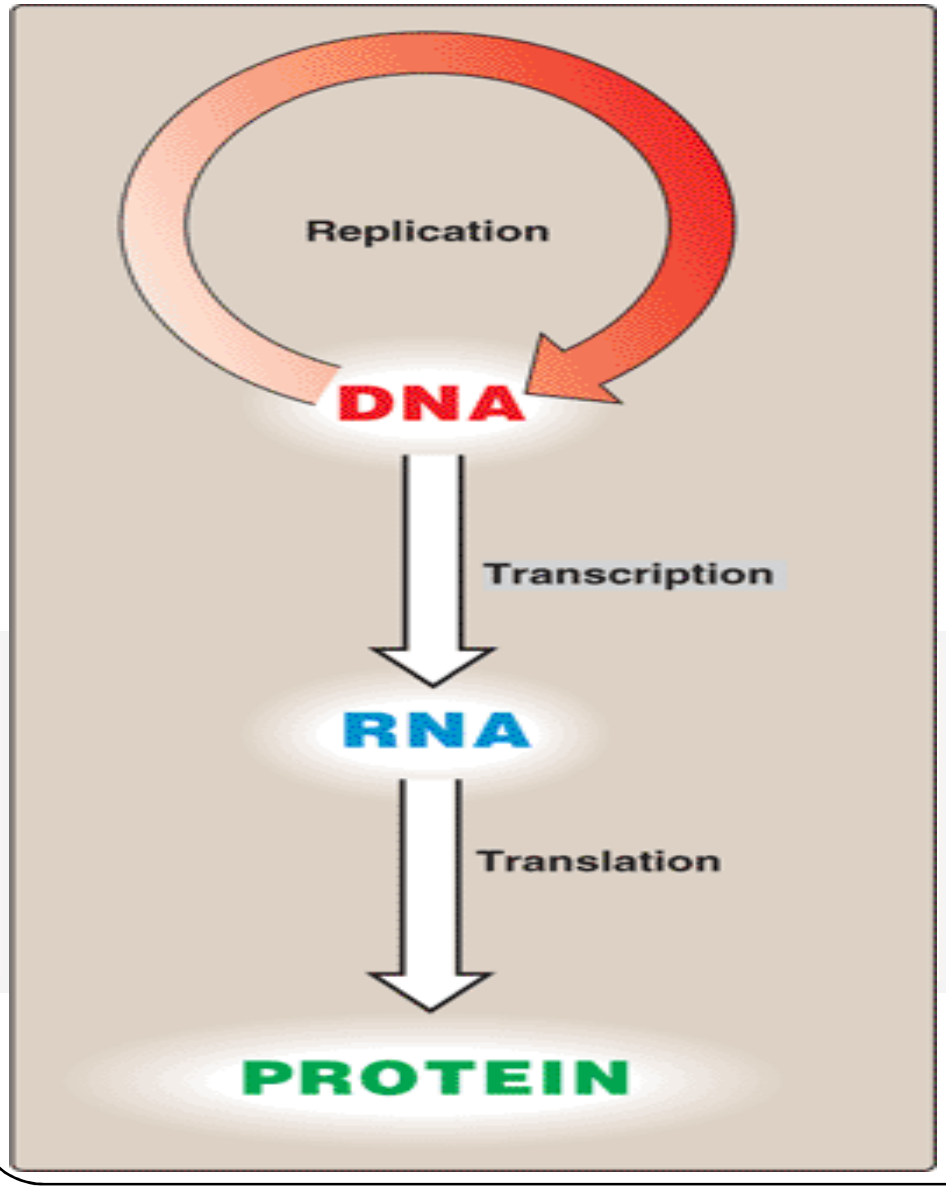
Dr Piyush Tailor

Associate Proffesor

Department of Biochemistry

GMC, Surat

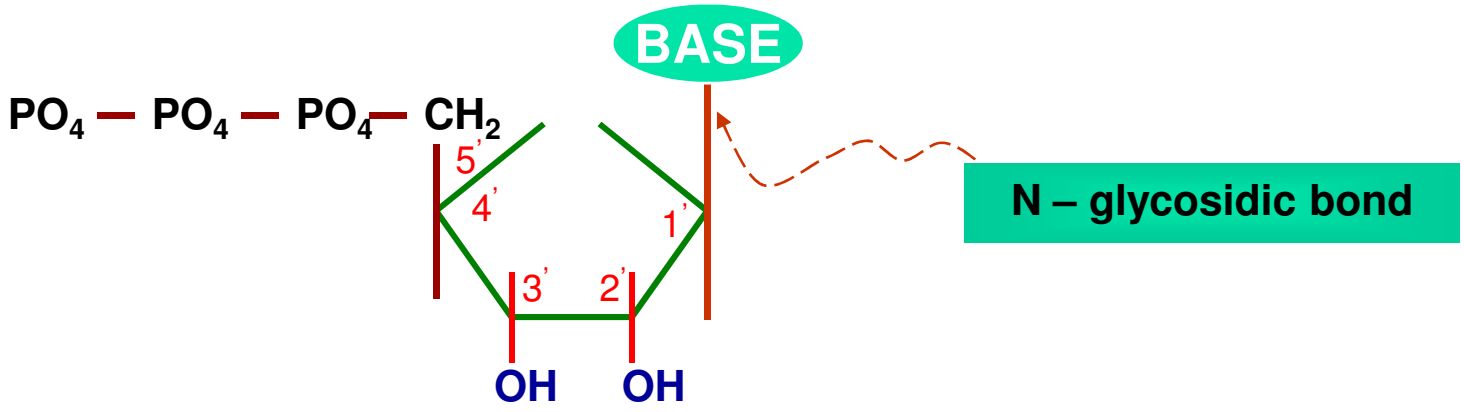
"Central dogma" Of Molecular Biology



- Each cell is specialized, expressing only those functions that are required for it to perform.

- DNA replicate and express only precise information.

STRUCTURE OF NUCLEOTIDES



Nucleoside

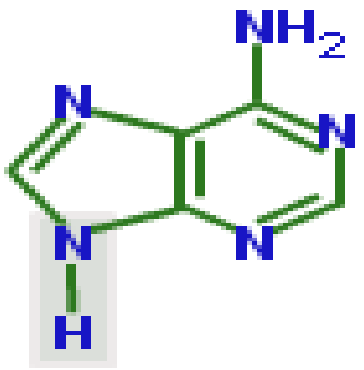
Nucleoside monophosphate

Nucleoside diphosphate

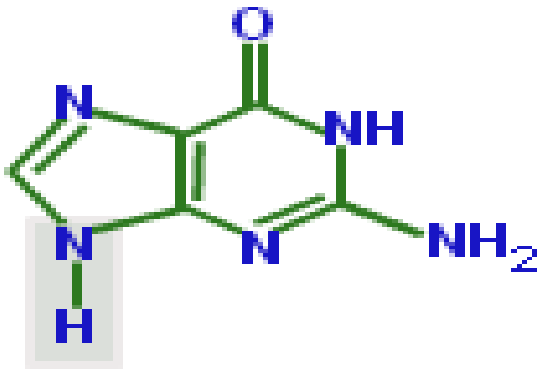
Nucleoside Triphosphate

Nucleotides

Purines

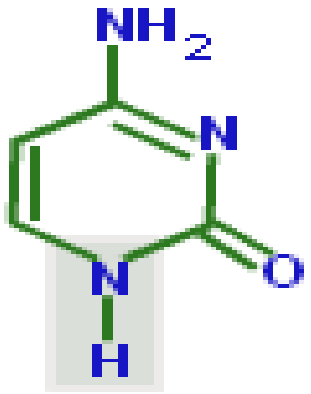


Adenine (A)
DNA
RNA

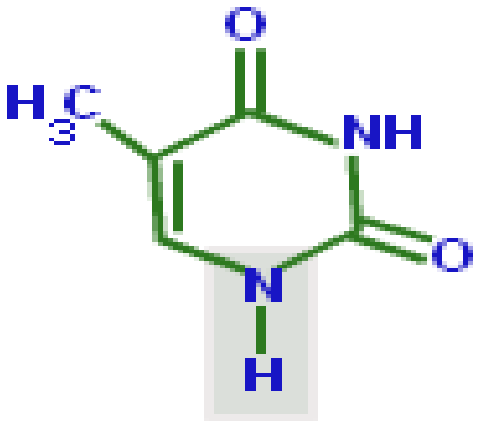


Guanine (G)
DNA
RNA

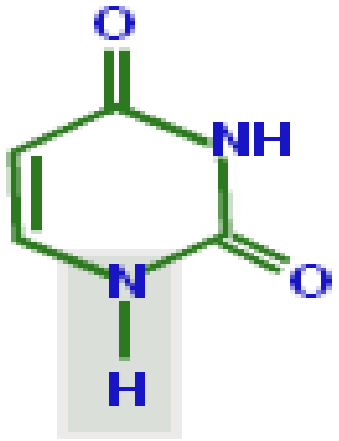
Pyrimidines



Cytosine (C)
DNA
RNA

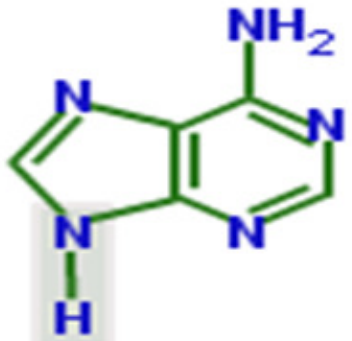


Thymine (T)
DNA

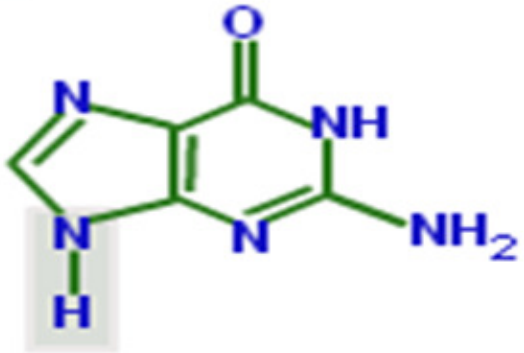


Uracil (U)
RNA

Purines

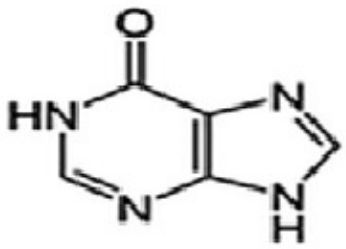


Adenine (A)
DNA
RNA

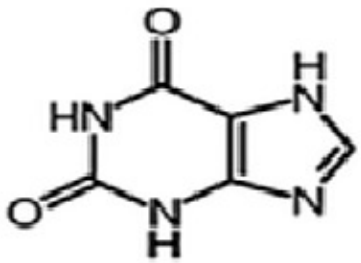


Guanine (G)
DNA
RNA

Modified Purine

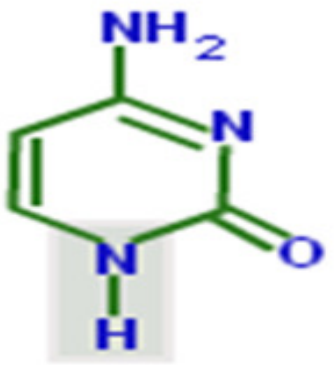


Hypoxanthine

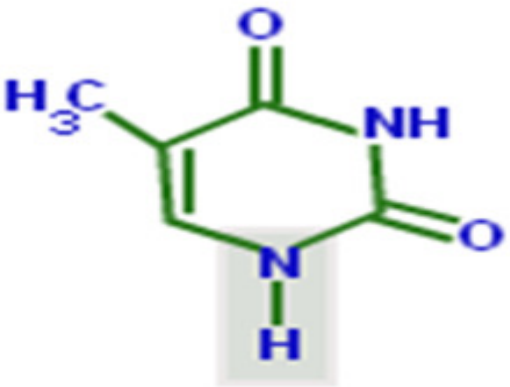


Xanthine

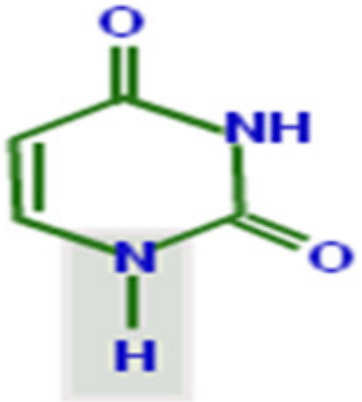
Pyrimidines



Cytosine (C)
DNA
RNA

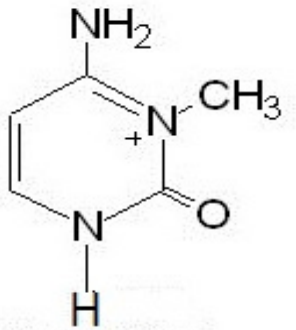


Thymine (T)
DNA

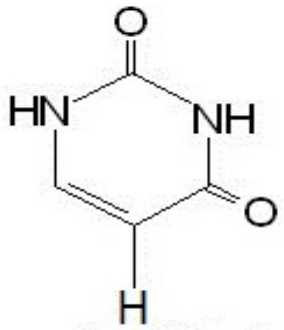


Uracil (U)
RNA

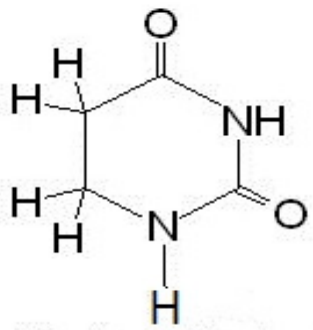
Modified Pyrimidine



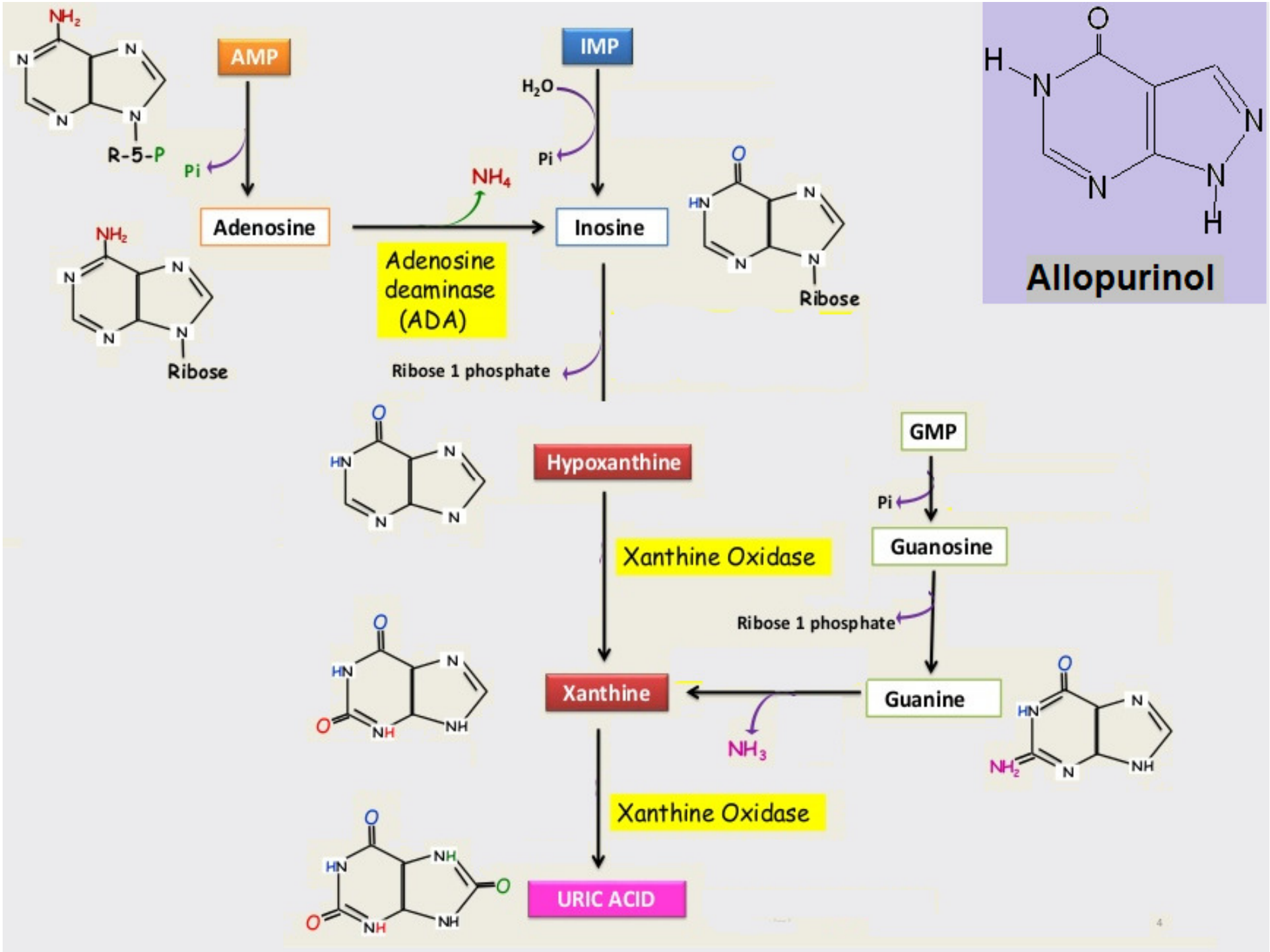
3-methylcytidine



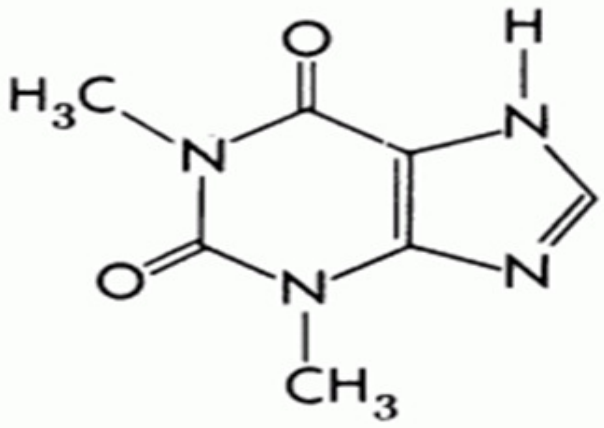
pseudouridine



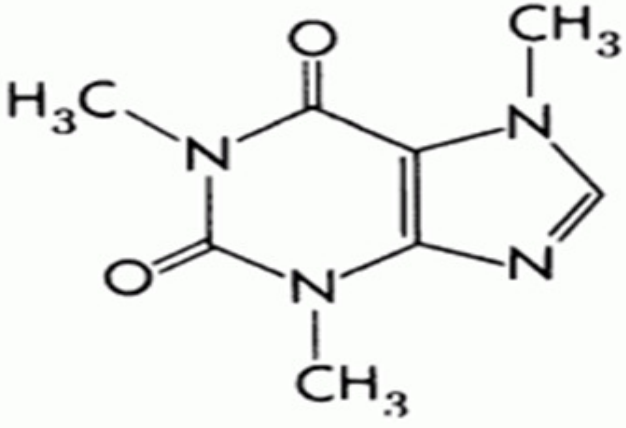
dihydrouridine


AMP
Pi
R-5-P
Adenosine
Ribose
Adenosine deaminase (ADA)
NH4
IMP
H2O
Pi
Inosine
Ribose
Ribose 1 phosphate
Hypoxanthine
Xanthine Oxidase
Xanthine
NH3
GMP
Pi
Guanosine
Ribose 1 phosphate
Guanine
Xanthine Oxidase
URIC ACID
Allopurinol

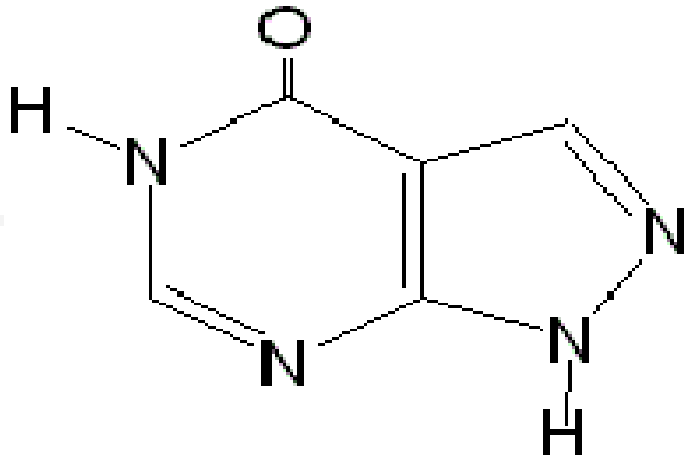
To which molecule is it similar?



THEOPHYLLINE



CAFFEINE

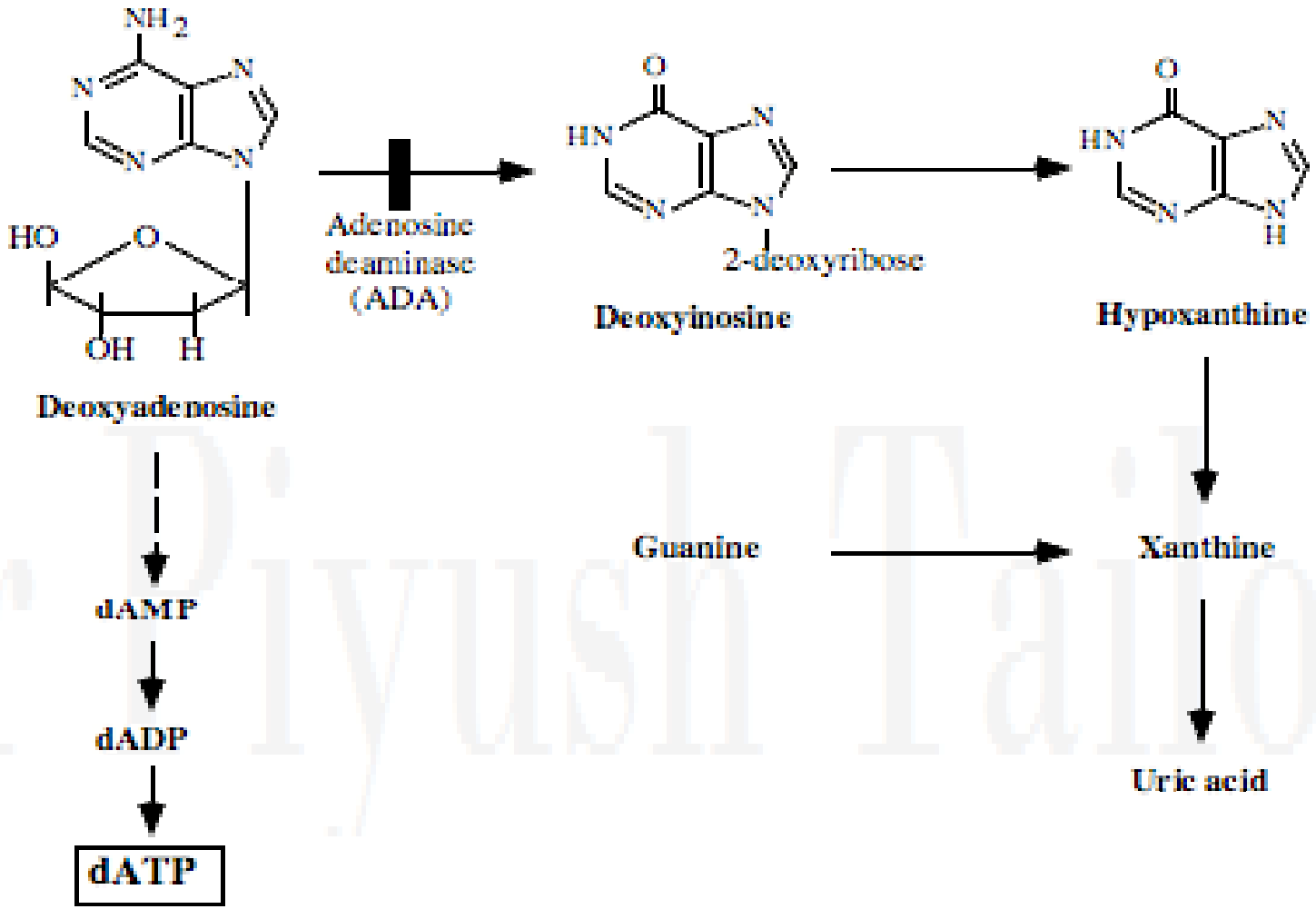


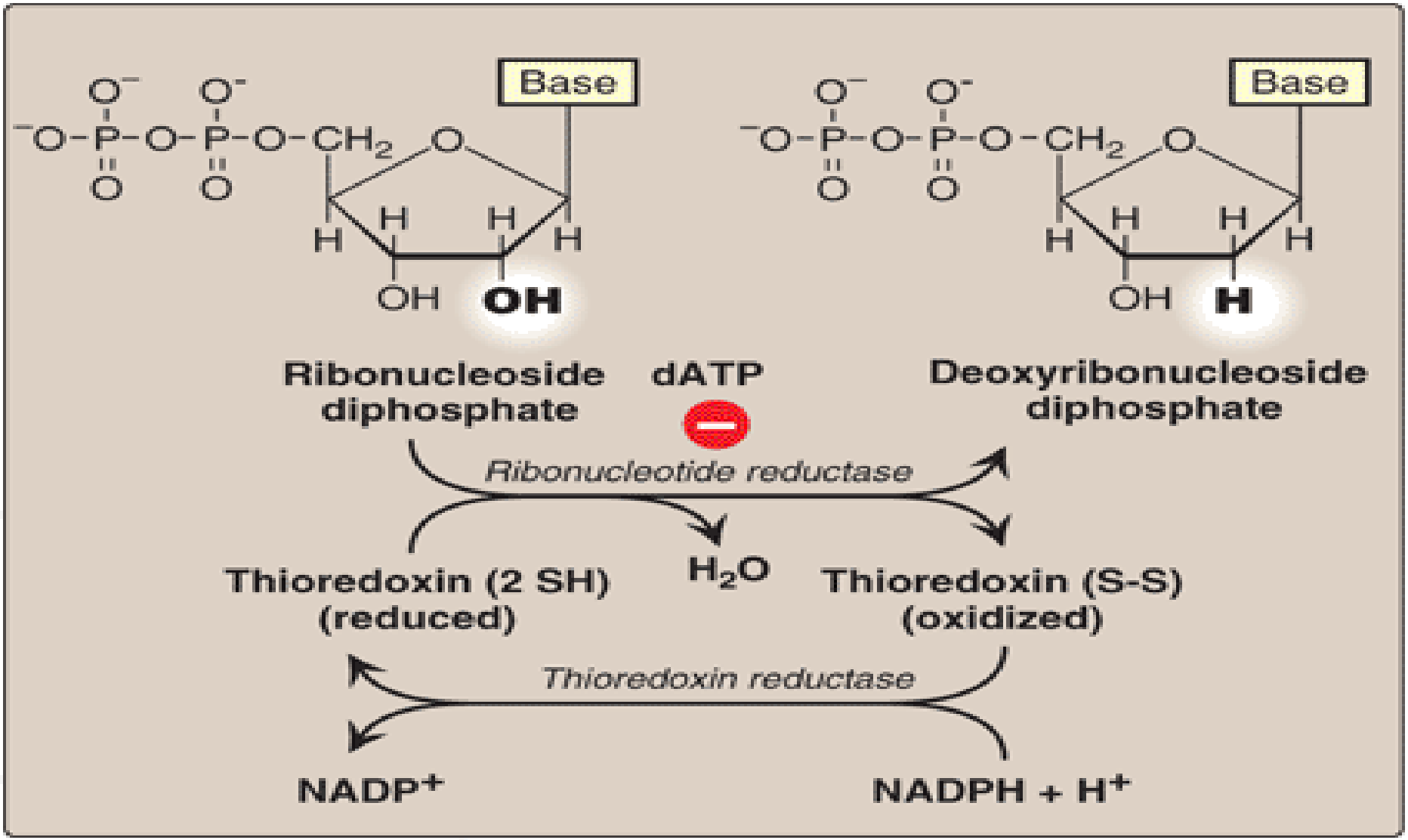
Allopurinol

- Which organ or cell has more concentration of Adenosine deaminase ?
- What is diagnostic important of ADA ?

What can be effect of Adenosine deaminase deficiency

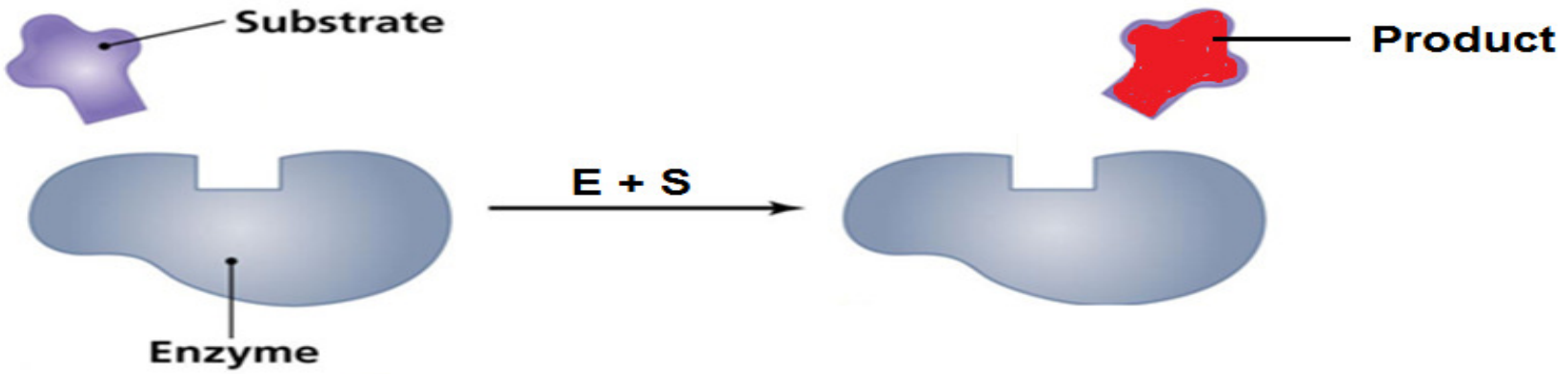
- What get accumulate & deficient ?
  - Substrate or Product ?

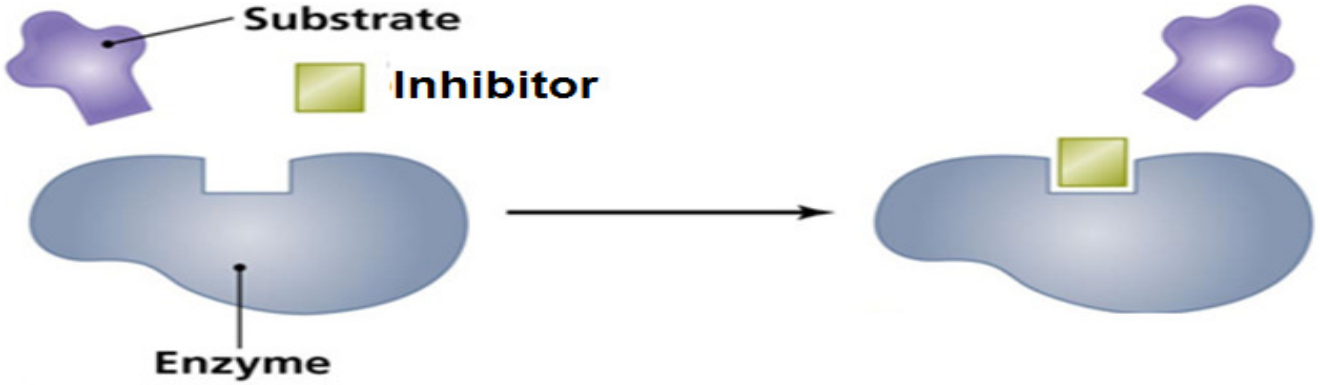


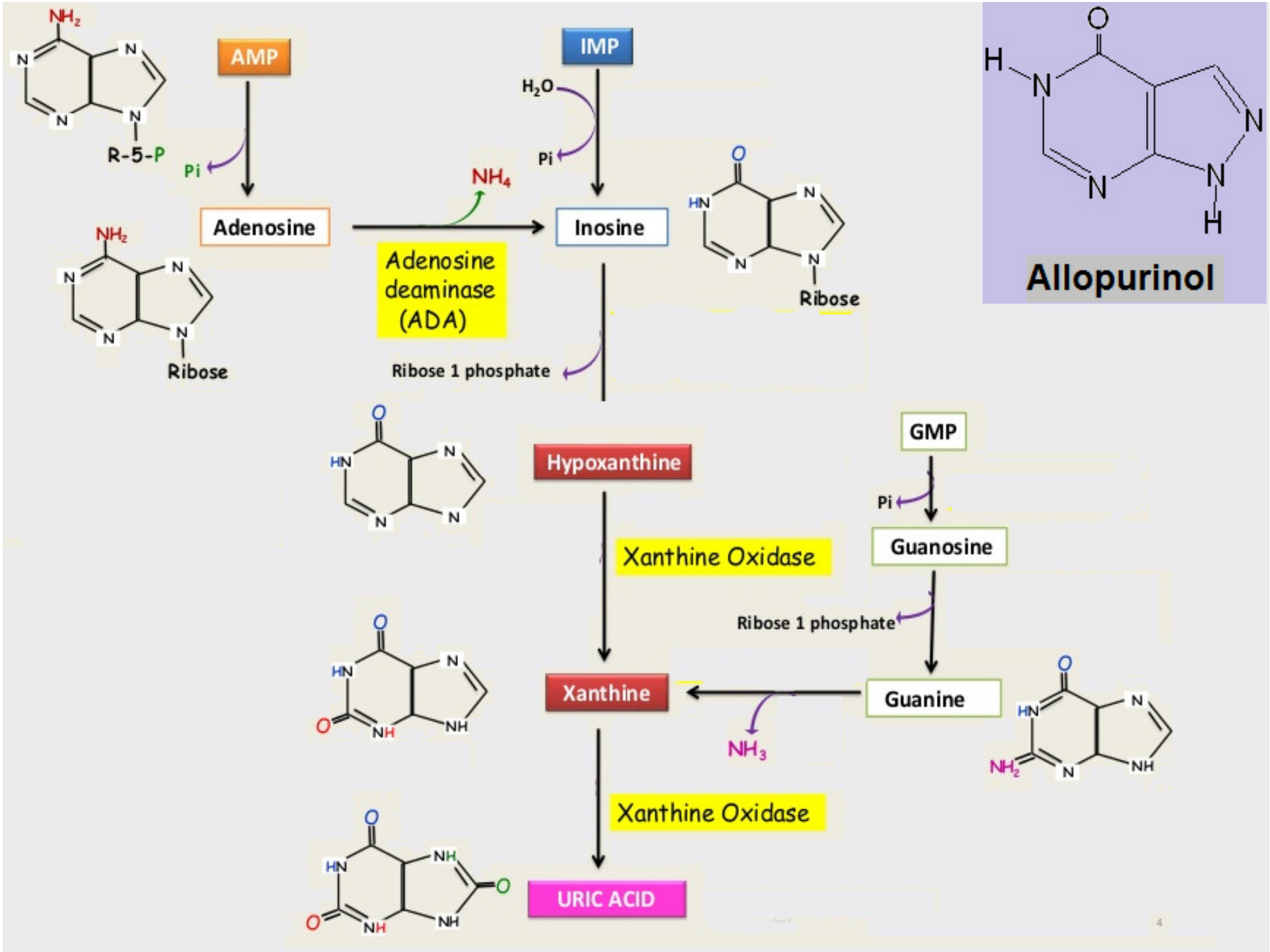

Base
OH
OH
Base
H
Ribonucleoside diphosphate
dATP
Deoxyribonucleoside diphosphate
Ribonucleotide reductase
H2O
Thioredoxin (2 SH) (reduced)
Thioredoxin (S-S) (oxidized)
Thioredoxin reductase
NADP+
NADPH + H+

What can happen to reaction if two structurally similar substrate come to enzyme?

What can happen to reaction if two structurally similar substrate come to enzyme?



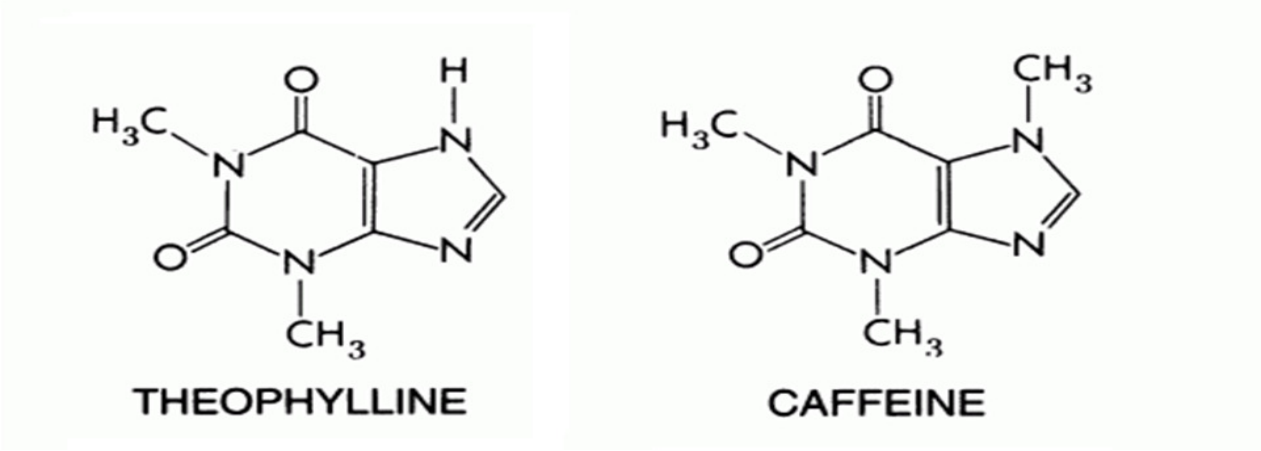


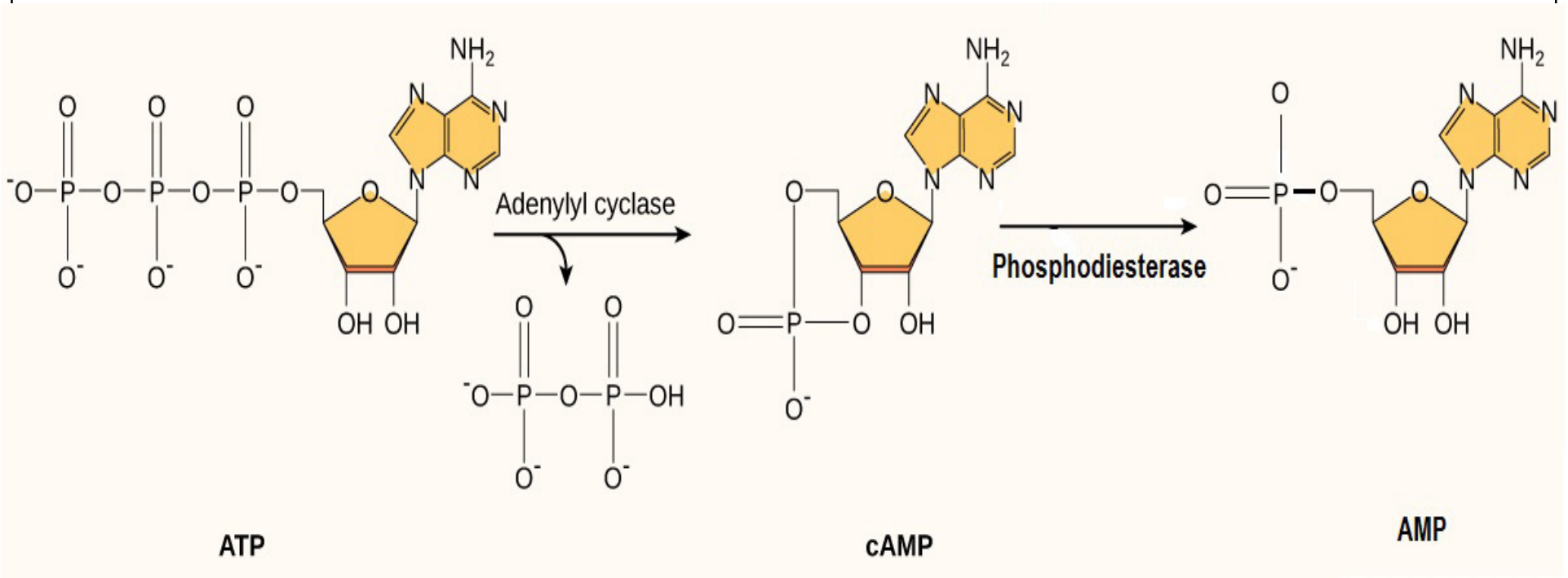

AMP
Pi
R-5-P
Adenosine
Ribose
Adenosine deaminase (ADA)
NH4
IMP
H2O
Pi
Inosine
Ribose
Ribose 1 phosphate
Hypoxanthine
Xanthine Oxidase
Xanthine
NH3
GMP
Pi
Guanosine
Ribose 1 phosphate
Guanine
Xanthine Oxidase
URIC ACID
Allopurinol

Gar (Hostel)-Kam

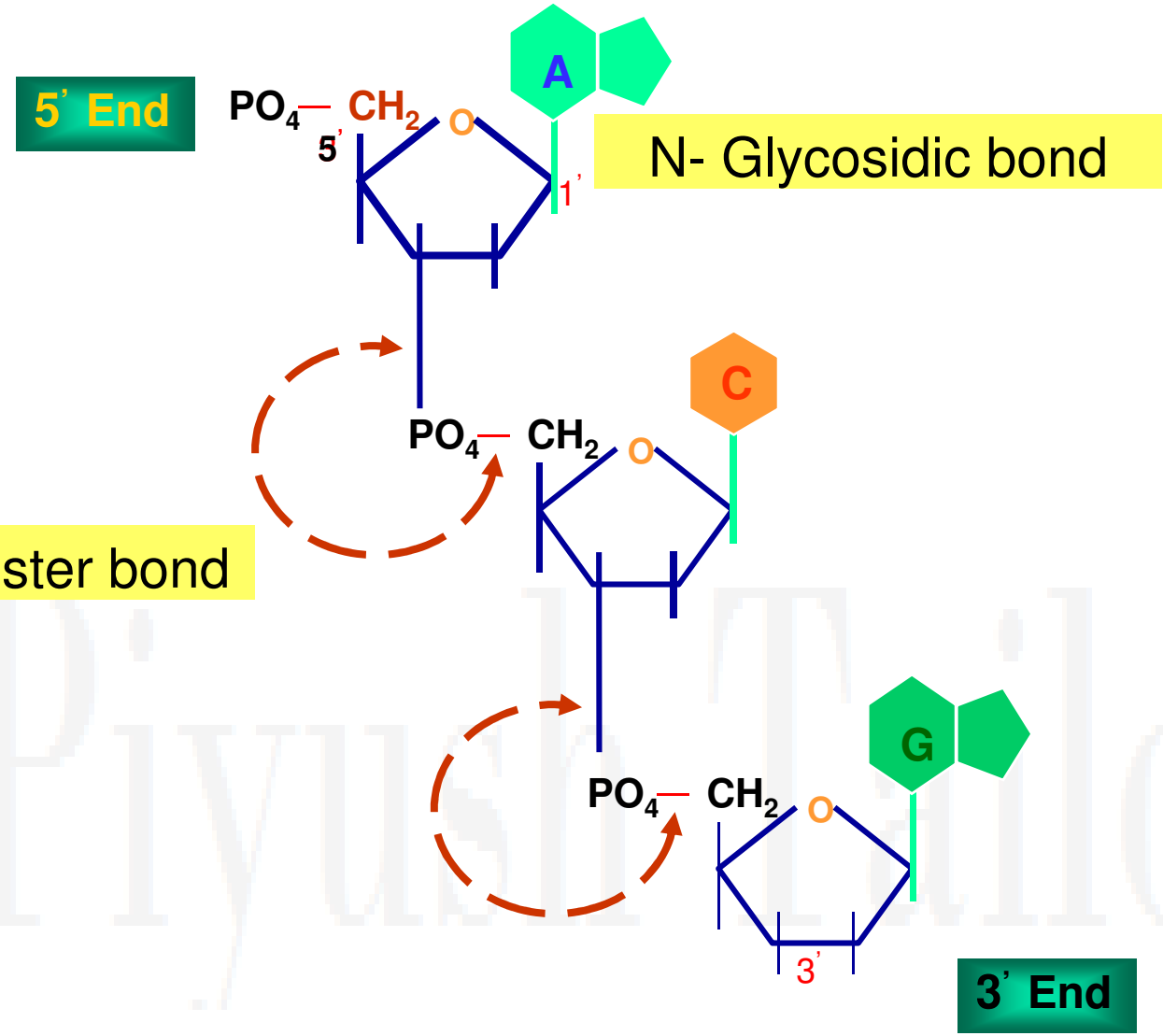
- Name a condition which can happen due to increase serum uric acid level (**Hyperuricemia**).
- What is difference between uric acid and urate crystal?
- Which part of body especially get affected due to hyperuricemia?
- What type of food ingestion can cause hyperuricemia ?
- Which type of condition can increase purine degradation and increase serum uric acid level?
- Which type of condition can decrease excretion of uric acid , which makes increase serum uric acid level?
- What is role of Allopurinol to correct hyperuricemia ?

What can theophylline do with following reaction?

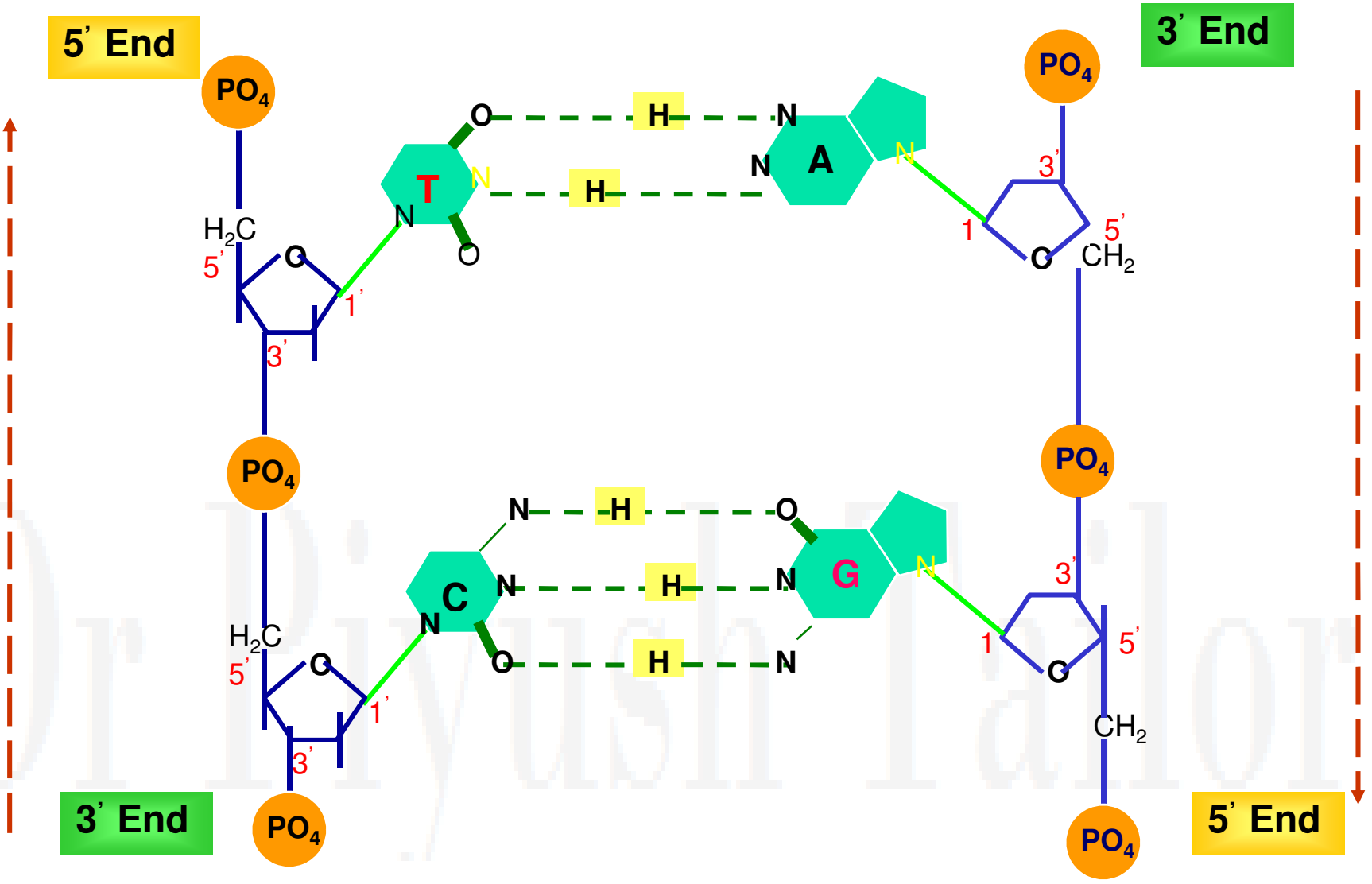




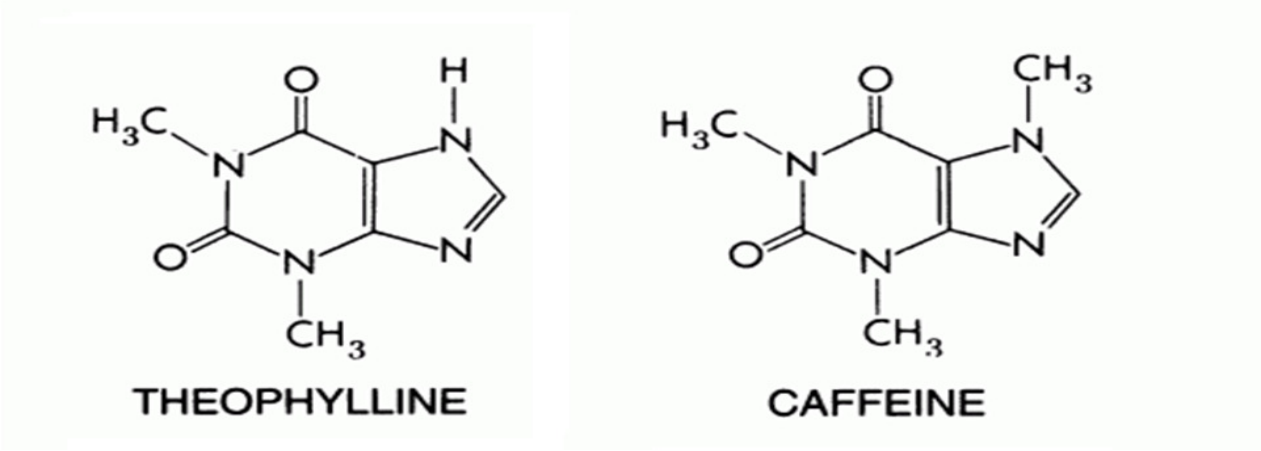
NUCLEIC ACID

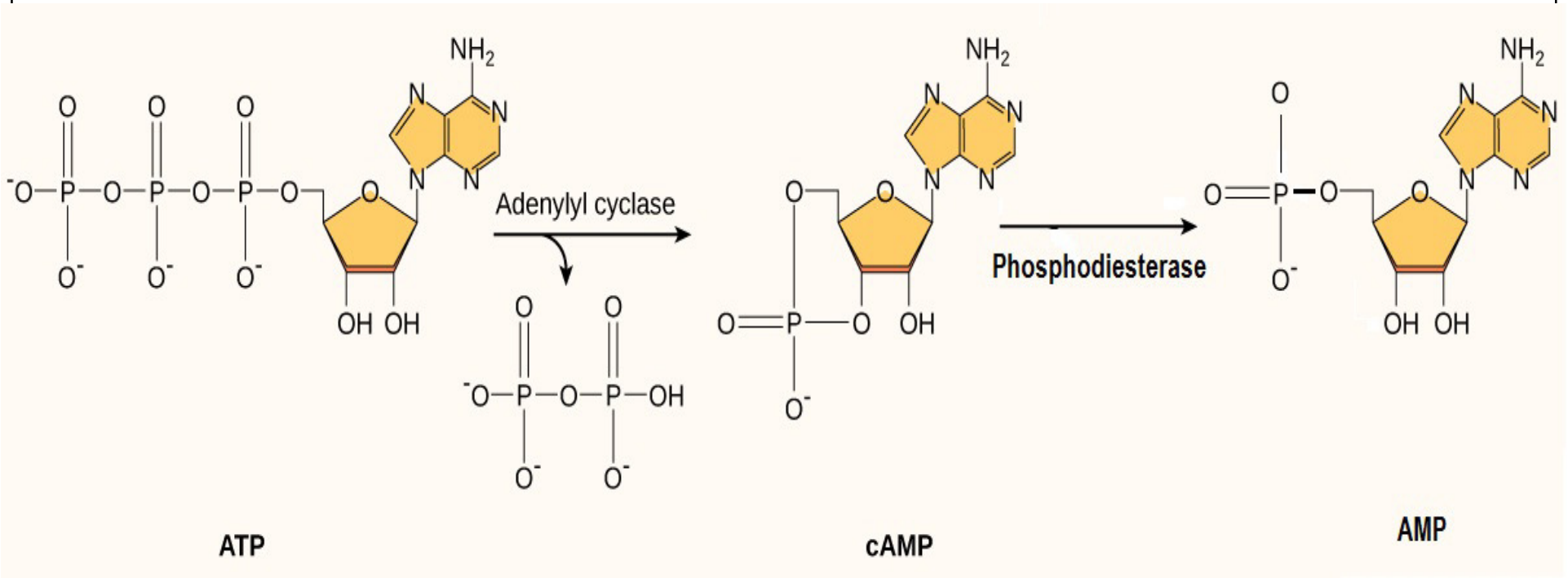


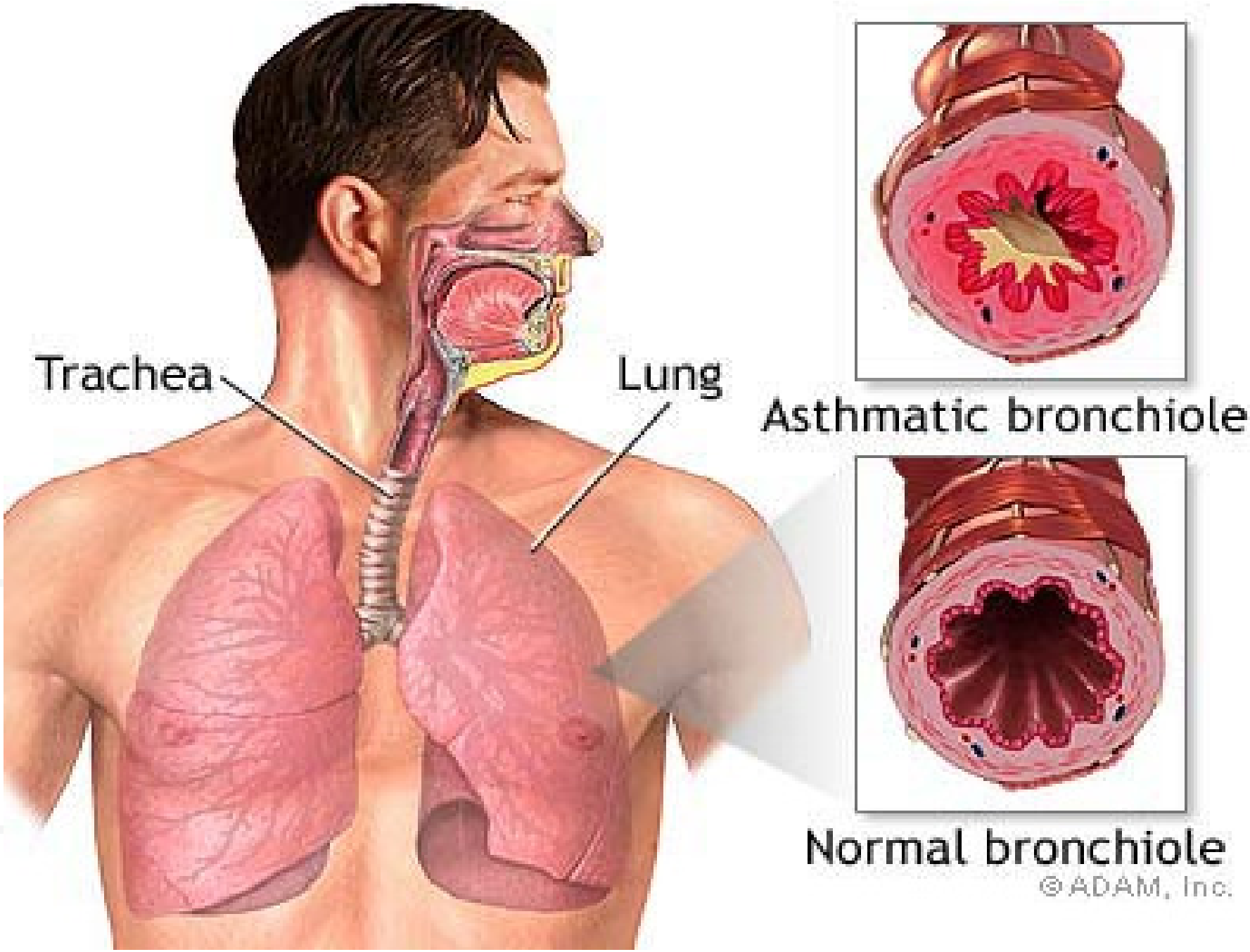
DNA

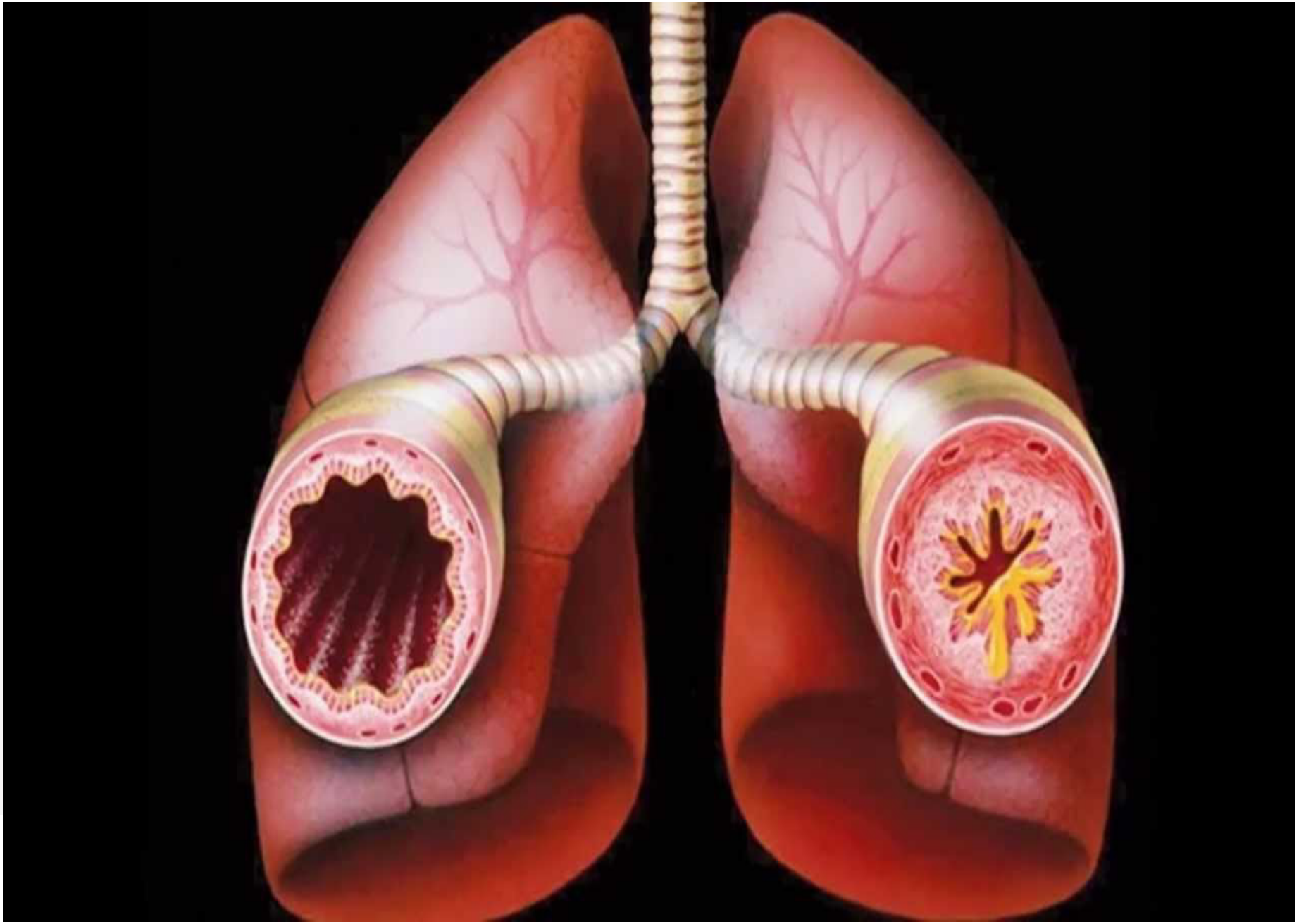


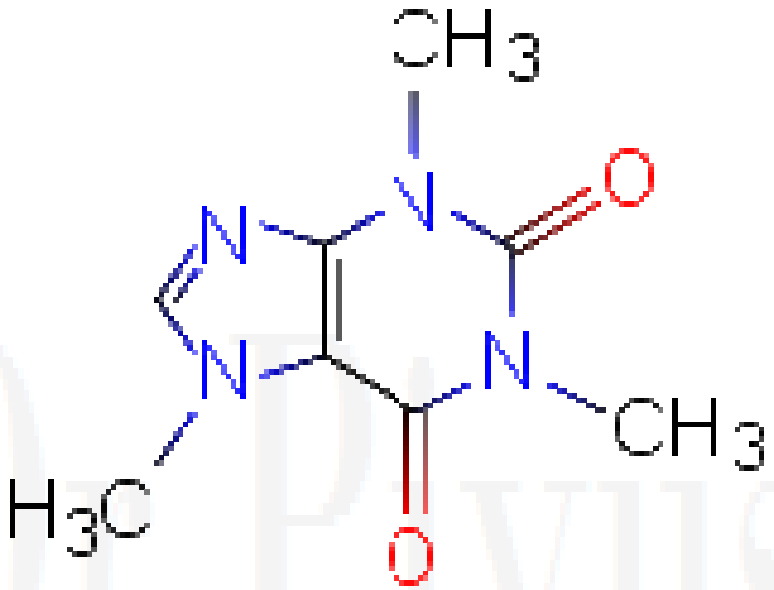
What can theophylline do with following reaction?



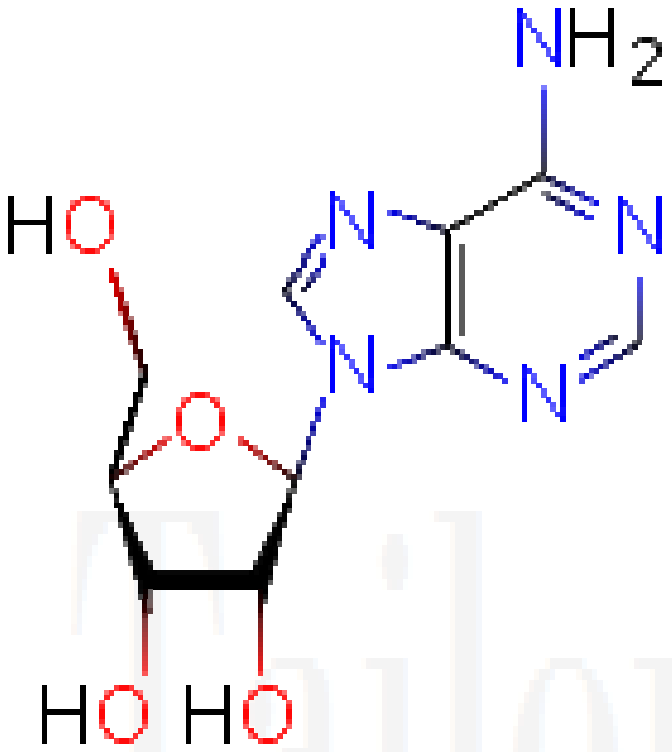



Trachea
Lung
Asthmatic bronchiole
Normal bronchiole
©ADAM, Inc.

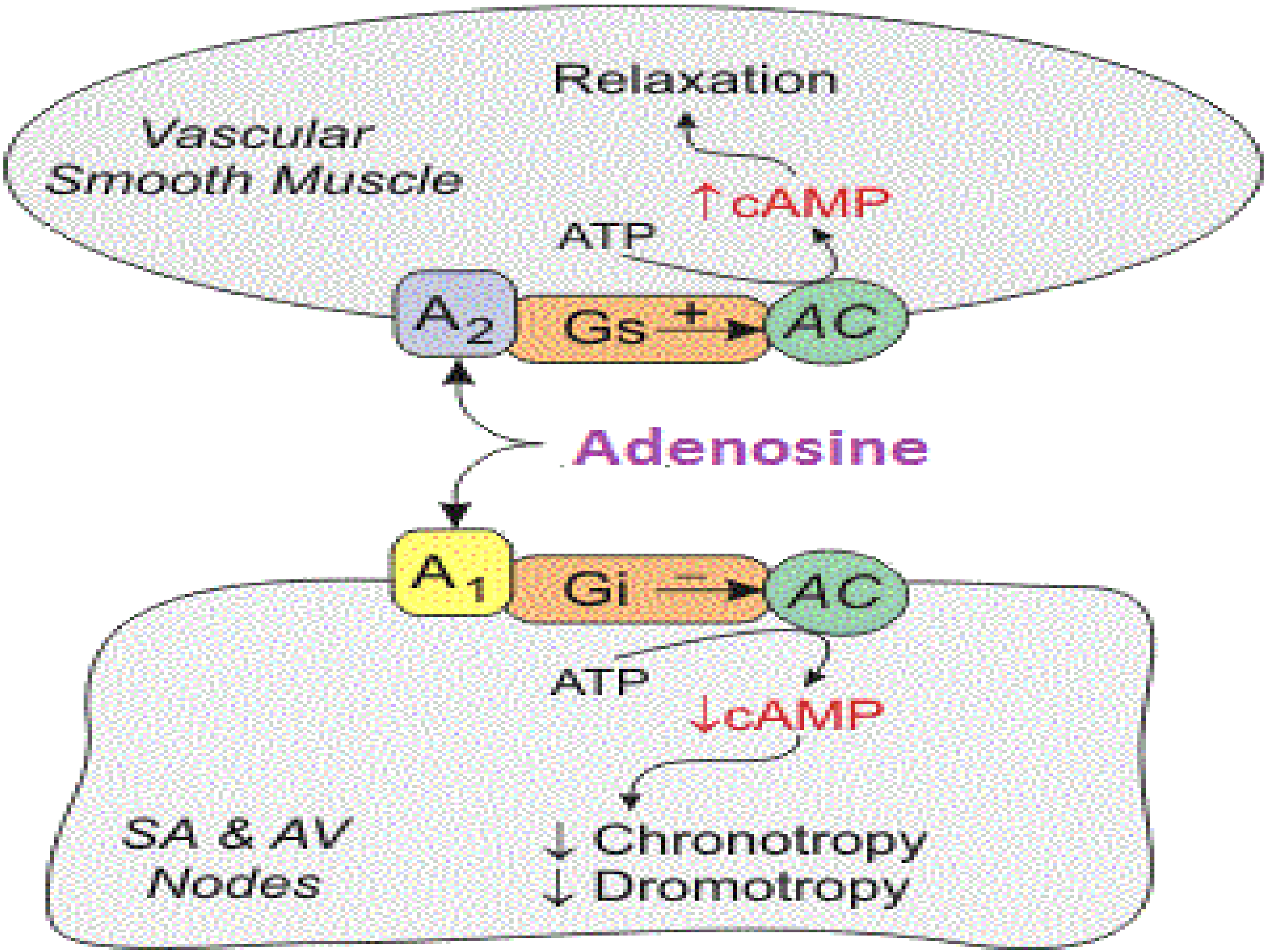




Caffeine



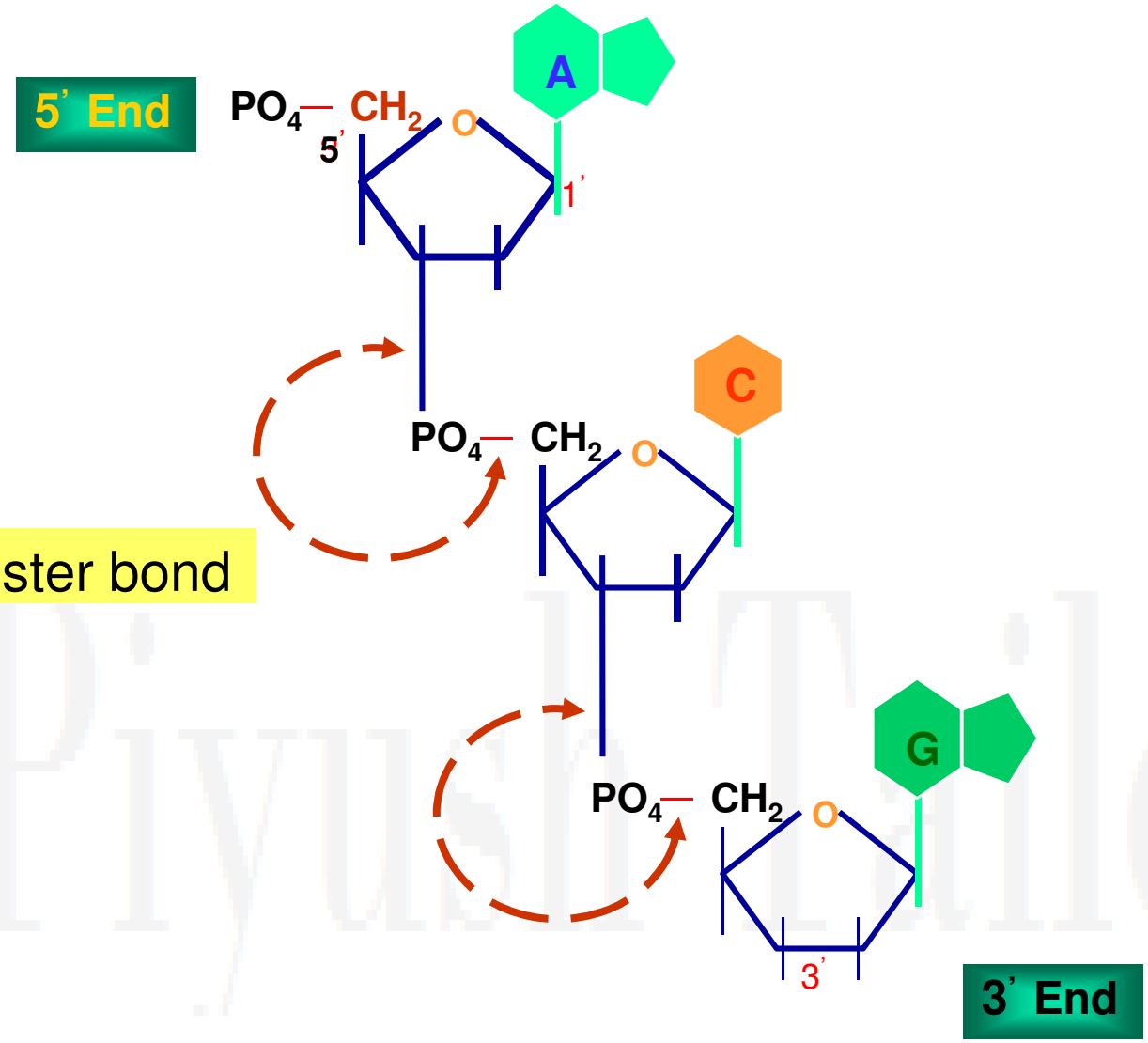
Adenosine


Relaxation
Vascular
Smooth Muscle
↑cAMP
ATP
A2
Gs
+
AC
Adenosine
A1
Gi
AC
ATP
↓cAMP
SA & AV
Nodes
↓ Chronotropy
↓ Dromotropy

Digetion of Nucleic acid

- Pancreatic & Intestinal Juice contain
  - Ribonuclease , Deoxyribonuclease
- Nucleotidase liberate phosphate from nucleotides.
- Resulting nucleoside are hydrolysed by nucleosidase forming free nitrogen base & pentose sugar.
- Dietary nitrogen base are never utilized for nucleic acid synthesis.
- They directly catabolised.

NUCLEIC ACID

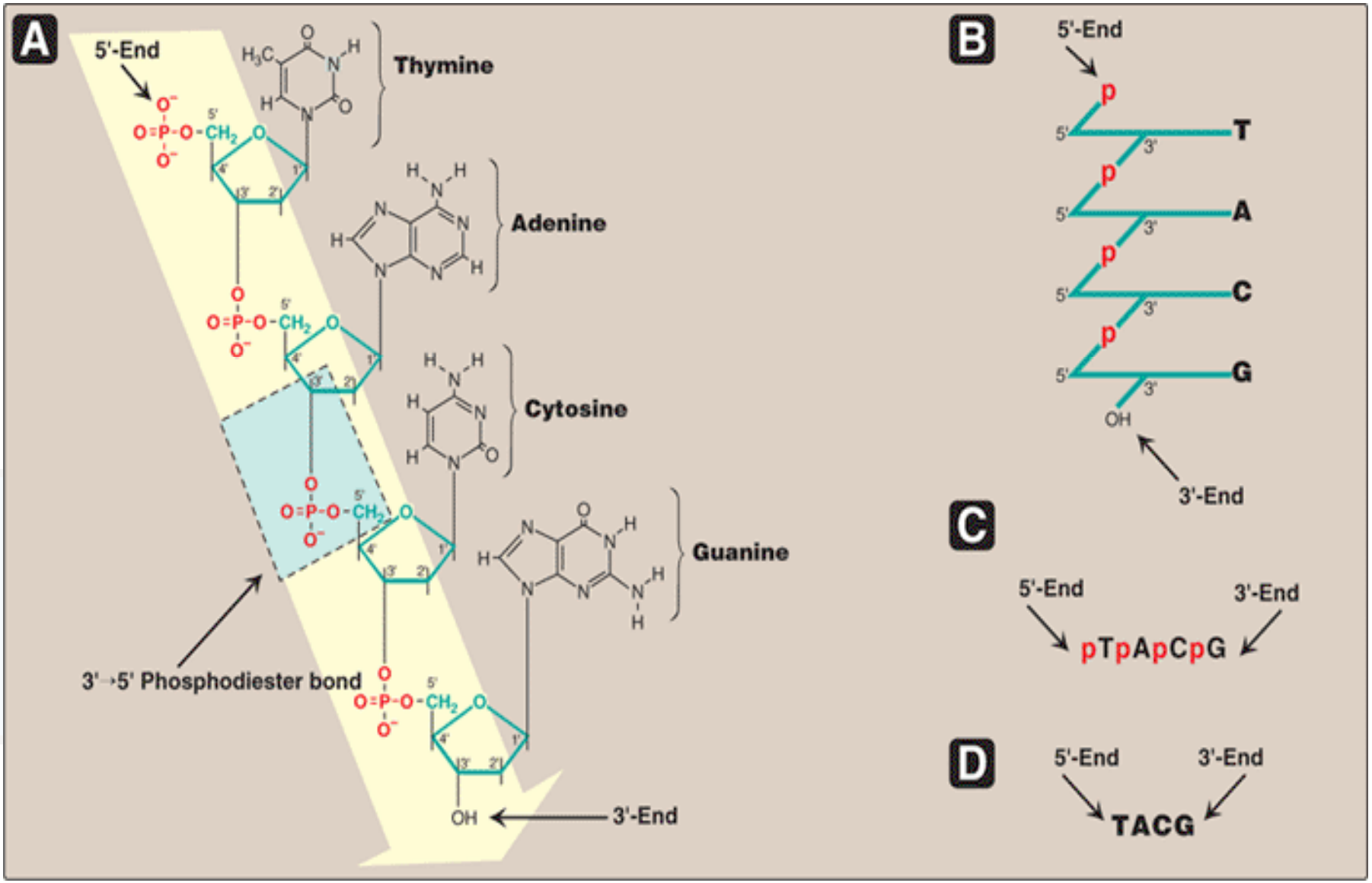


Phosphodiester bond

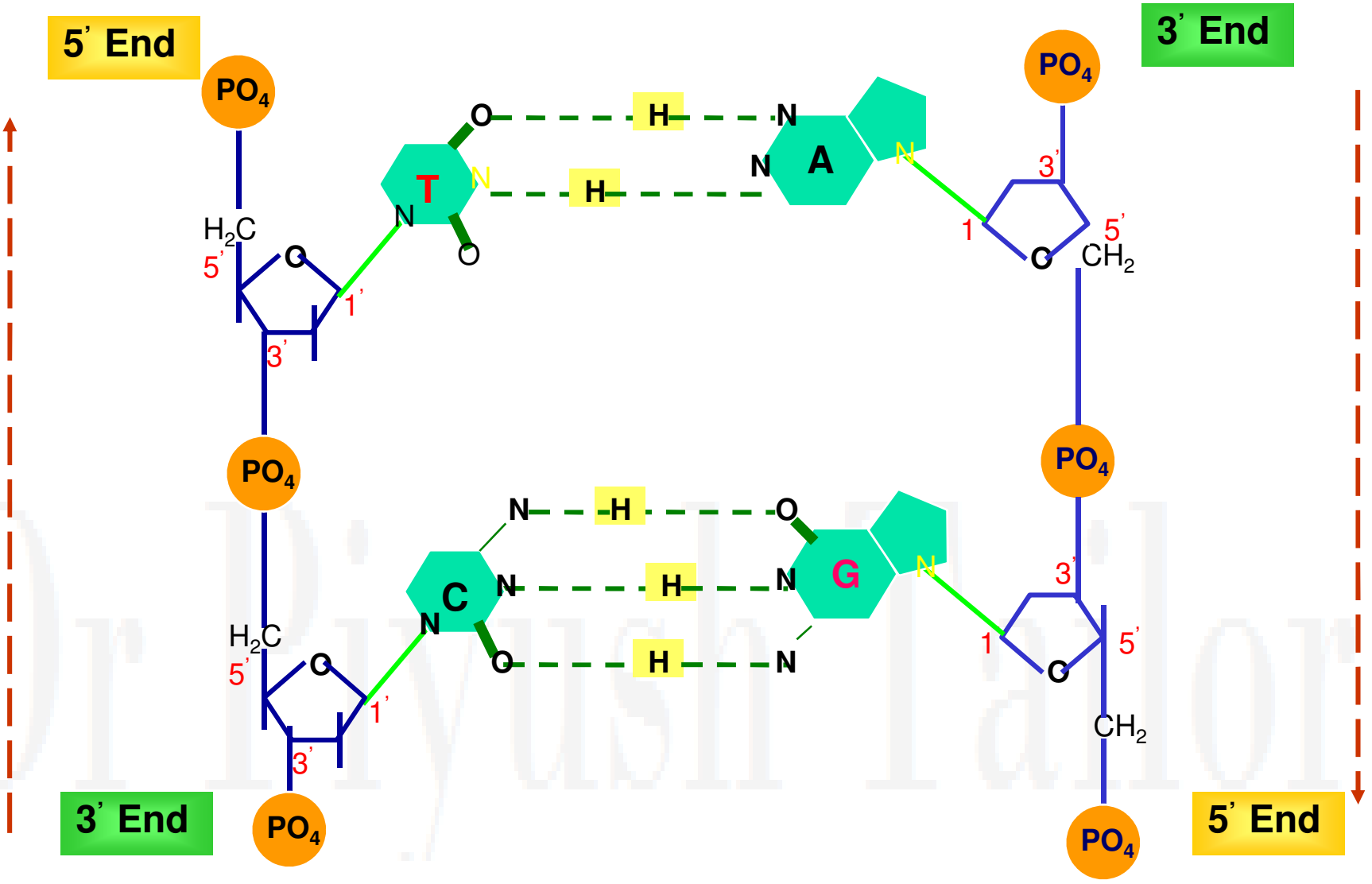
Phosphodiester bonds

- Phosphodiester bonds join
  the 3′-OH group of the deoxypentose of one nucleotide to
  the 5′-OH group of the deoxypentose of an adjacent nucleotide
  through a phosphate group
- The resulting unbranched chain with two ends.
- 5′-end (the end with the free phosphate) and 3′-end (the end with the free hydroxyl)
- Ends are not attached to other nucleotides.

Nucleotide sequence of DNA read in 5′ → 3′ direction.



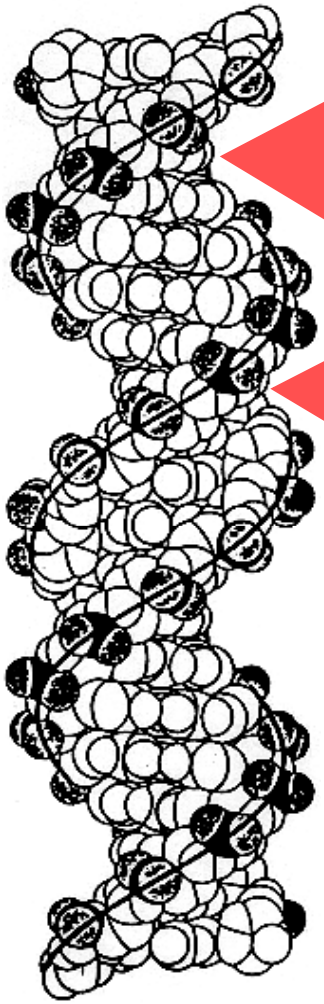
DNA



DNA double helix

- **Look like “twisted ladder”.**
- **Outside = Hydrophilic = Deoxyribose–phosphate .**
- **Inside = Hydrophobic = Nitrogen Bases .**
- **Between the two strands in the helix major (wide) and minor (narrow) groove.**
- **These grooves provide**
  - access for the binding of regulatory proteins to their specific recognition sequences along the DNA chain.
  - Anticancer drugs = Dactinomycin (Actinomycin D)
  - interact into the narrow groove of the DNA double helix
  - Thus inhibit with DNA replication and RNA synthesis.

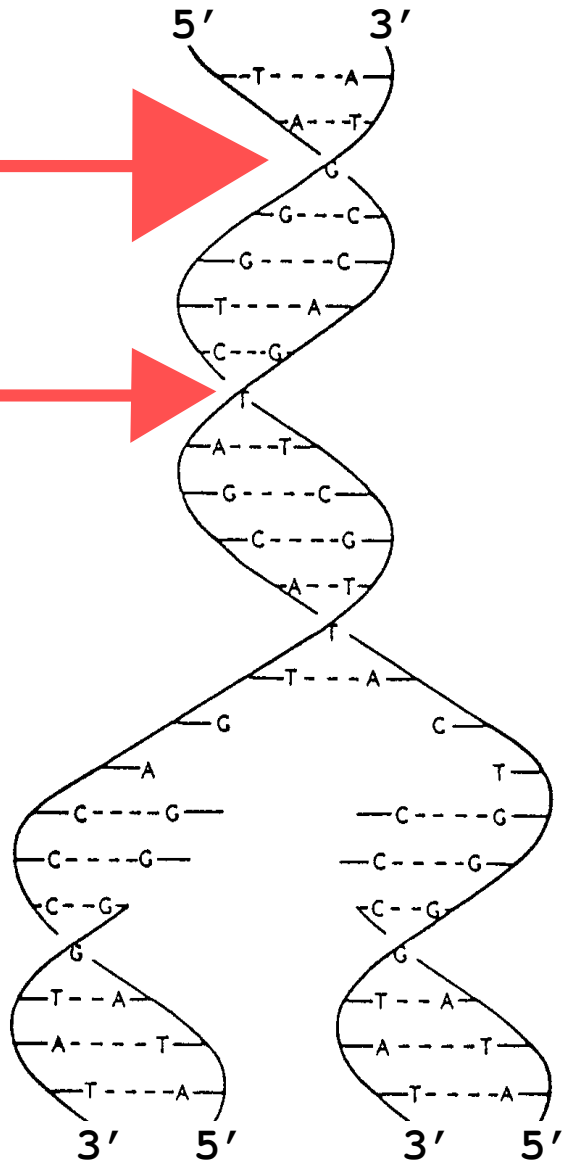
Double-stranded DNA



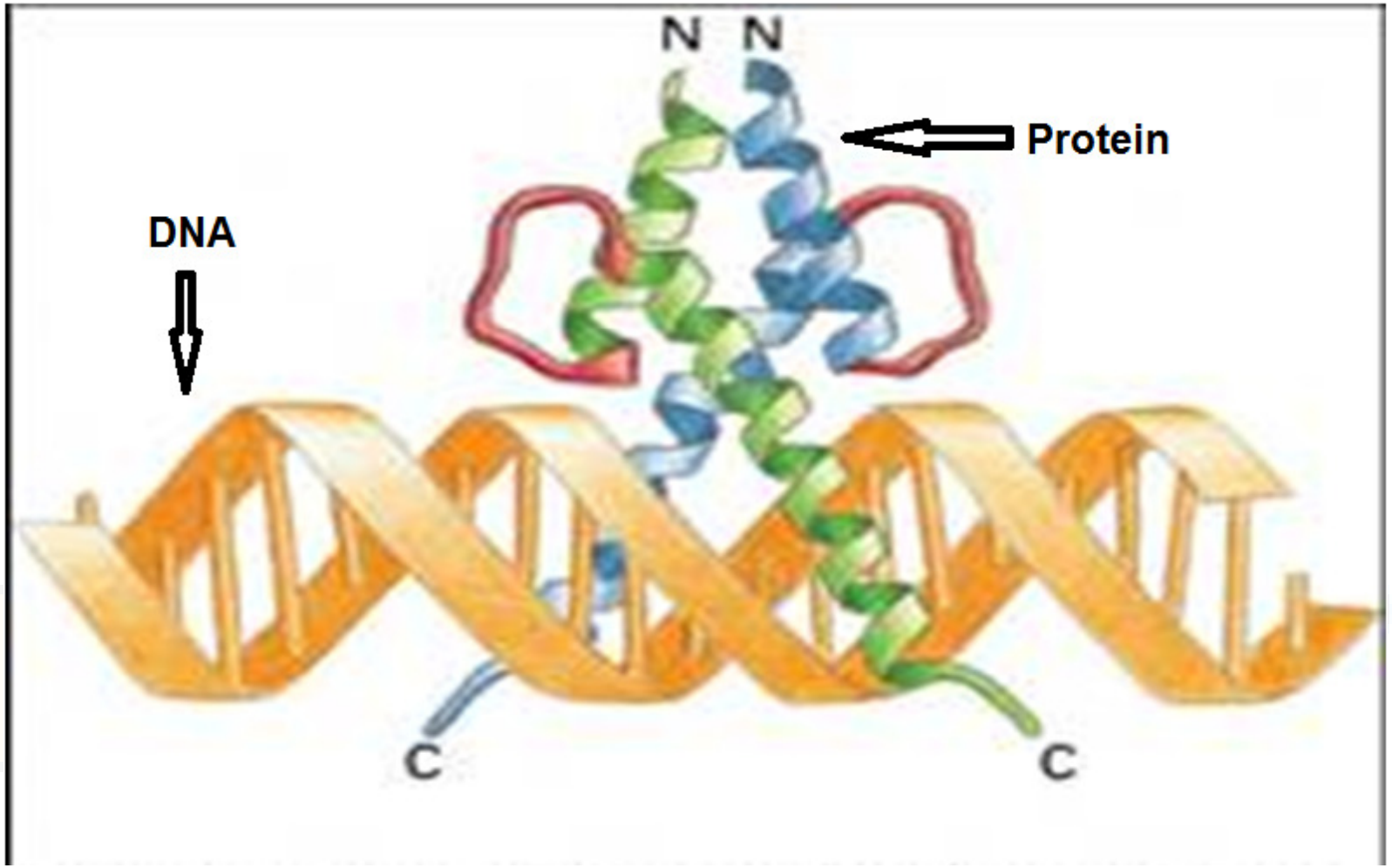
"B" DNA

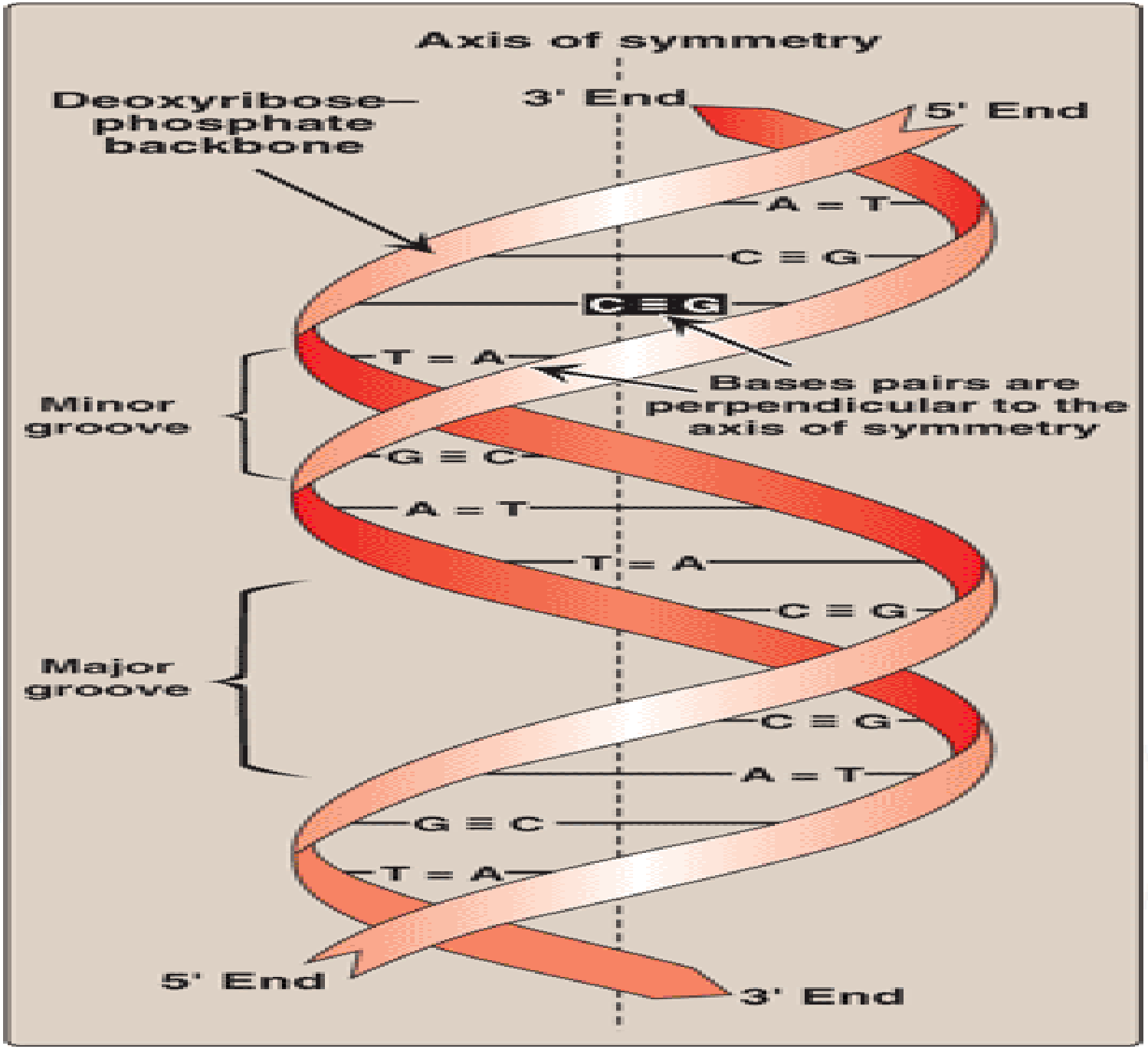
Major groove

Minor groove



What can be effect this protein binding to replicating DNA?




Axis of symmetry
Deoxyribose—
phosphate
backbone
3' End
5' End
A = T
C ≡ G
C ≡ G
T = A
Bases pairs are
perpendicular to the
axis of symmetry
Minor
groove
G ≡ C
A = T
T = A
C ≡ G
Major
groove
C ≡ G
A = T
G ≡ C
T = A
5' End
3' End

DNA = Watson-Crick Model

- **Right handed Double – helix**
  - Hydrogen bonding between nitrogenous bases
    - Base pairs (A with T & C with G)
  - Complementary strands
  - Antiparallel
- **Composed of a sugar- phosphate backbone**
- **Sugar is deoxyribose**
- **Each Spiral = 3.4 nm & 10 Base pairs**
- **Diameter of helix = 1.9 – 2.0 nm**
- **Two type of groow = Major & Minor**
- **Chargaff Rule**
  - No. of Adenine is equal to No. of Thymine
  - No. of Guanine is equal to No.of Cytosine

Type of DNA

Type	Shape	Helix	Base pairs per Turn	Width	Base angle
A	Broad	Right Handed	11	2.3 nm	20 Degree tilt from perpendicular line
B	Inter-mediate	Right Handed	10	1.9 nm	Perpendicular
Z	Elongate d	Left Handed	12	1.8 nm	

Nuclear DNA

- Present in almost every cell
- Nuclear DNA is larger in size

Mitochondrial DNA

- Each cell contains thousands of mt,
- Mt DNA is in larger quantities in a cell

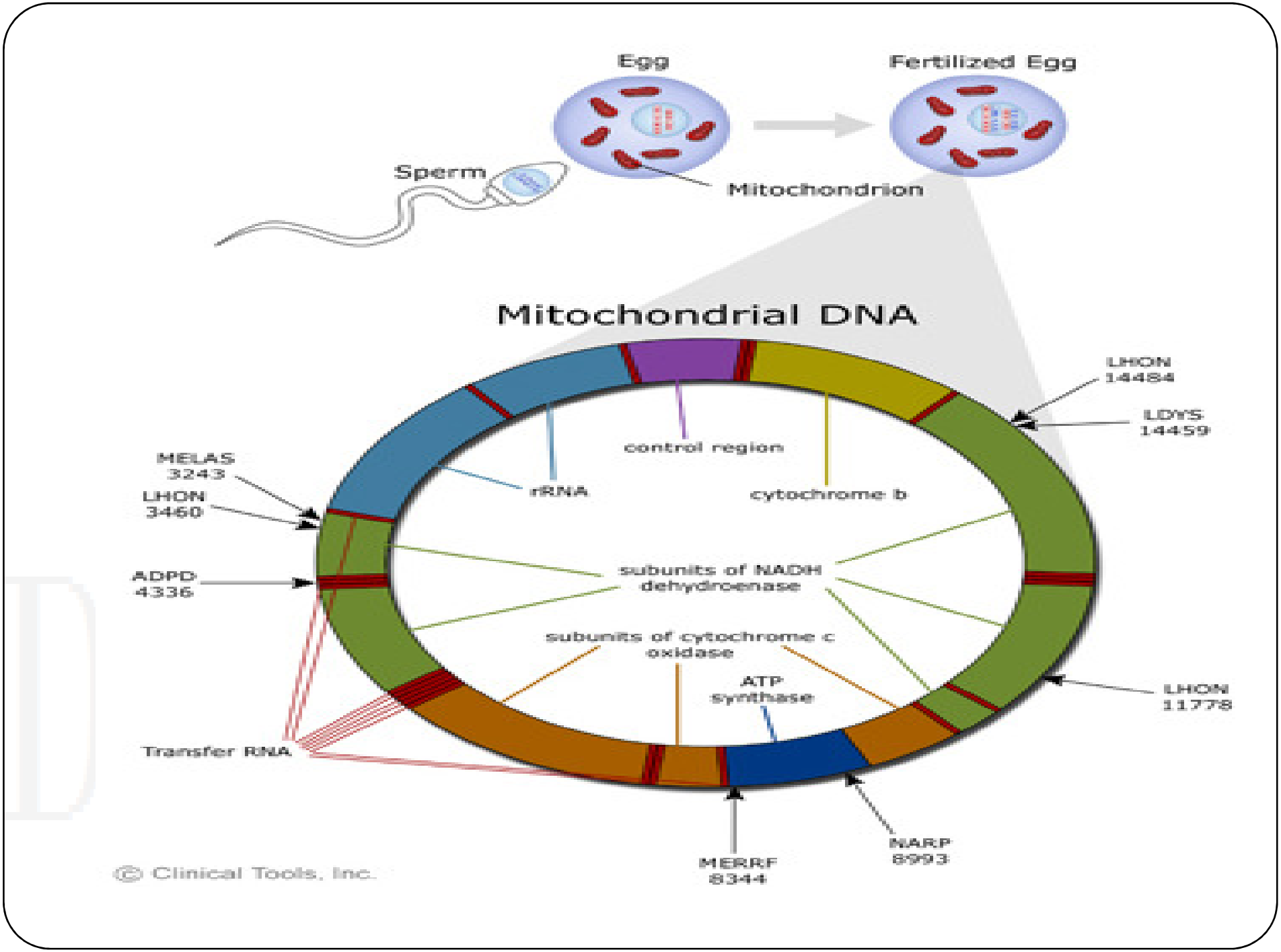
Mt DNA = 16,569 bases in length

- It's Code for
  - 13 proteins of respiratory chain
  - 22tRNAs,
  - 2rRNAs needed for cell respiration
  - This region has very little variability
  - So everyone's DNA in this region will be nearly the same sequence of TGCAs

5 – 10 times high mutation rate than nuclear

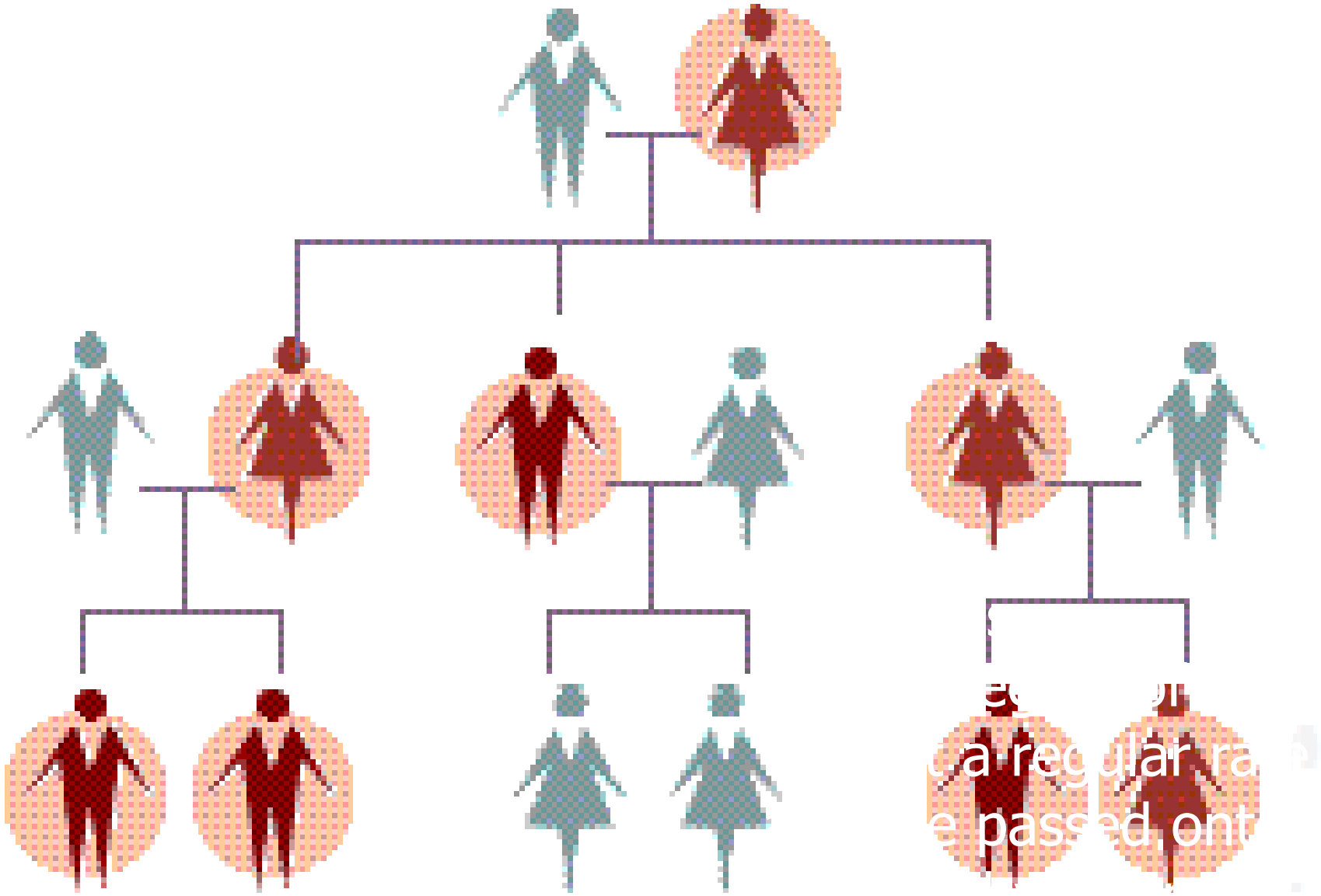
Mt DNA is inherited from mom

- **Every sibling will get their mt DNA from their mother**
- **Why?**
- **During fertilization, When egg and sperm join ,only female mitochondria survive. So Mother mitochondrial DNA are passed onto to new baby.**


Egg
Fertilized Egg
Sperm
Mitochondrion
Mitochondrial DNA
LHON
14484
LDYS
14459
control region
MELAS
3243
LHON
3460
rRNA
cytochrome b
ADPD
4336
subunits of NADH
dehydroenase
subunits of cytochrome c
oxidase
ATP
synthase
LHON
11778
Transfer RNA
MERRF
8344
NARP
8993
© Clinical Tools, Inc.

Why Mother?

- Egg contains
  - 23 chromosomes
  - cell cytoplasm which contains thousands of maternal mitochondria.
- Sperm contains
  - 23 chromosomes
  - very little cytoplasm



Mitochondrial DNA Inheritance

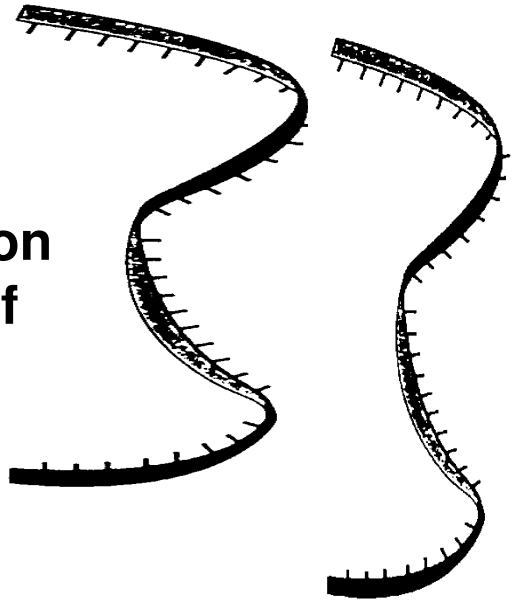
Mitochondrial Disease

- Mitochondrial myopathy
- Leber's hereditary optic neuropathy
- Leigh syndrome,
- Neuropathy
- Ataxia
- Retinitis pigmentosa
- Myoneurogenic gastrointestinal encephalopathy
- Myoclonic Epilepsy with Ragged Red Fibers Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS)
- mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Denaturation of DNA

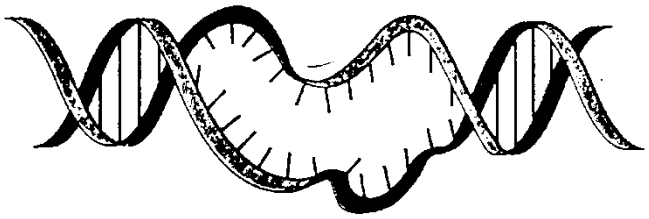
Double-stranded DNA

Strand separation and formation of single-stranded random coils

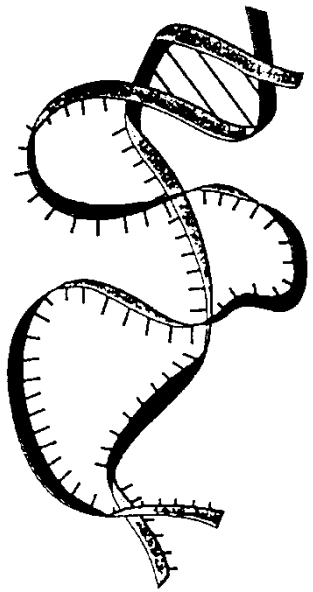


Extremes in pH or high temperature

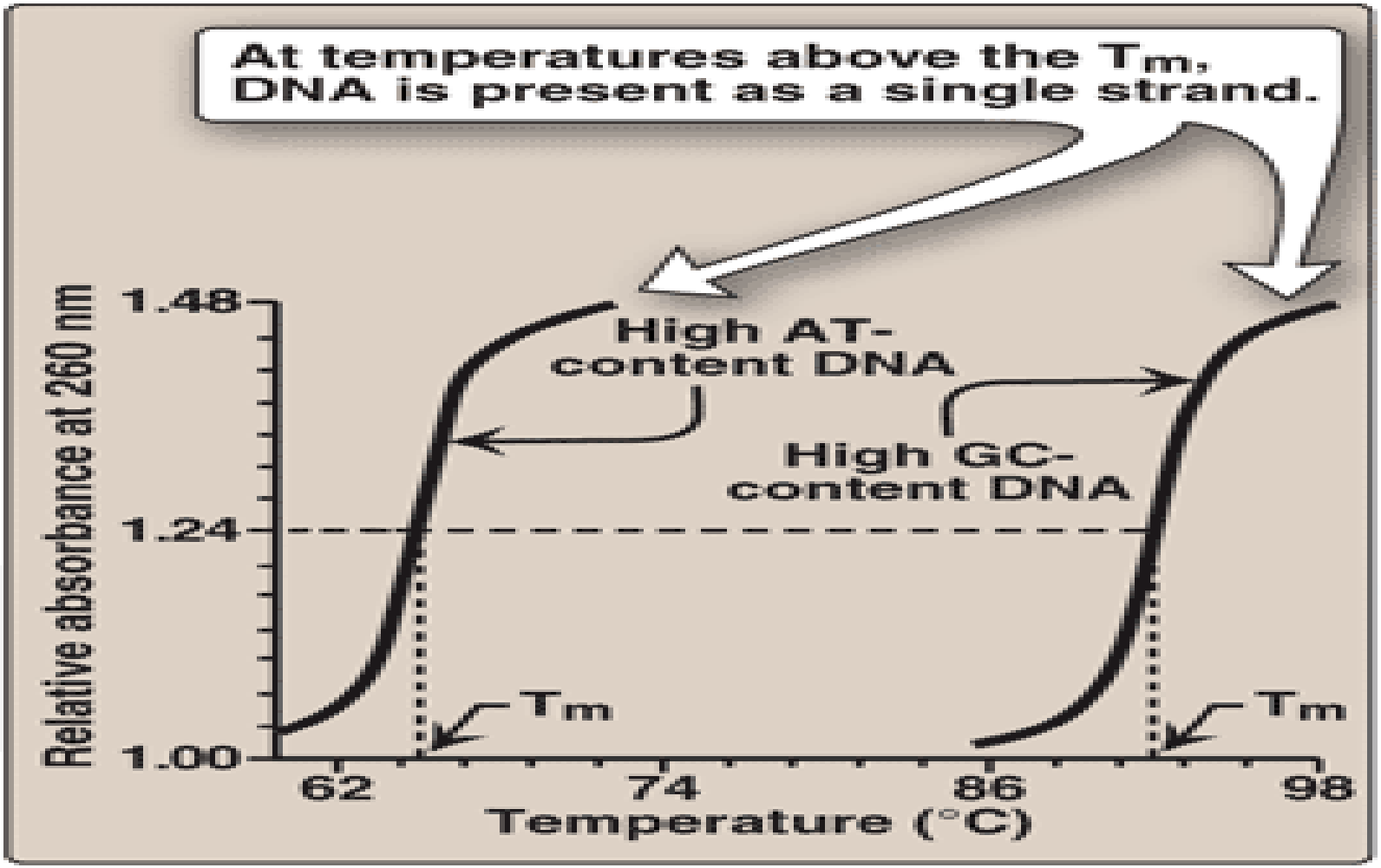
A-T rich regions denature first



Cooperative unwinding of the DNA strands

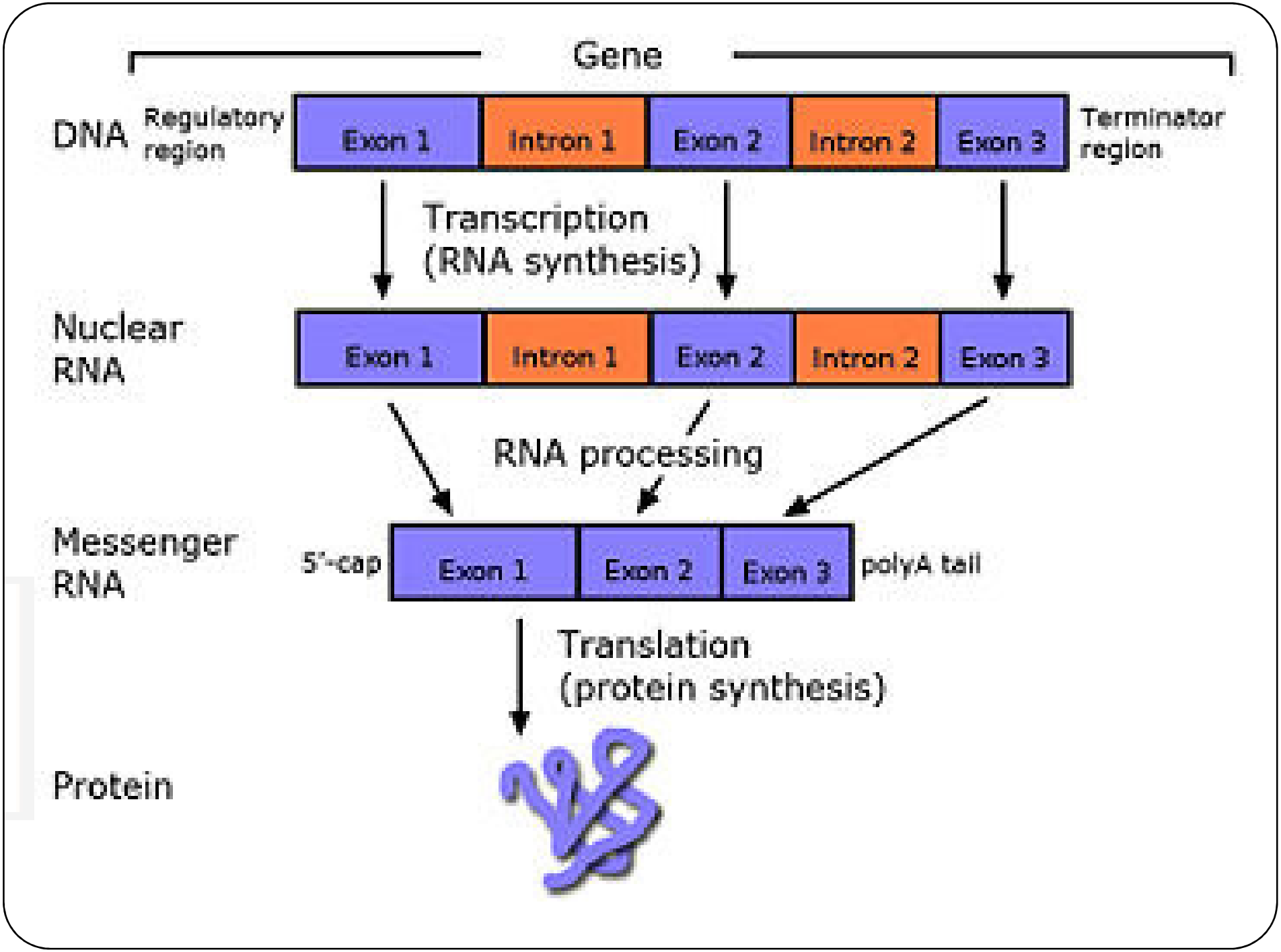


Tm for DNA Denaturation



Intron ,Exon & Cistron

- Only 10% of the human DNA contain gene
- **Exon**
- Segments of gene coding for protein.(Expressed region)
- **Intron**
- Nonfunctional (Not Expressed for Protein)
- Interspaced in the DNA with silent areas.
- Serve as basis for future genes.
- For evolution of new genes
- **Cistron**
- The unit of genetic expression
- One Cistron will code for one polypeptide chain.


Gene
DNA
Regulatory region
Exon 1
Intron 1
Exon 2
Intron 2
Exon 3
Terminator region
Transcription (RNA synthesis)
Nuclear RNA
Exon 1
Intron 1
Exon 2
Intron 2
Exon 3
RNA processing
Messenger RNA
5'-cap
Exon 1
Exon 2
Exon 3
polyA tail
Translation (protein synthesis)
Protein

The (exon-intron-exon)$_n$ structure of various genes

histone

total = 400 bp; exon = 400 bp

β-globin

total = 1,660 bp; exons = 990 bp

HGPRT (HPRT)

total = 42,830 bp; exons = 1263 bp

factor VIII

total = ~186,000 bp; exons = ~9,000 bp

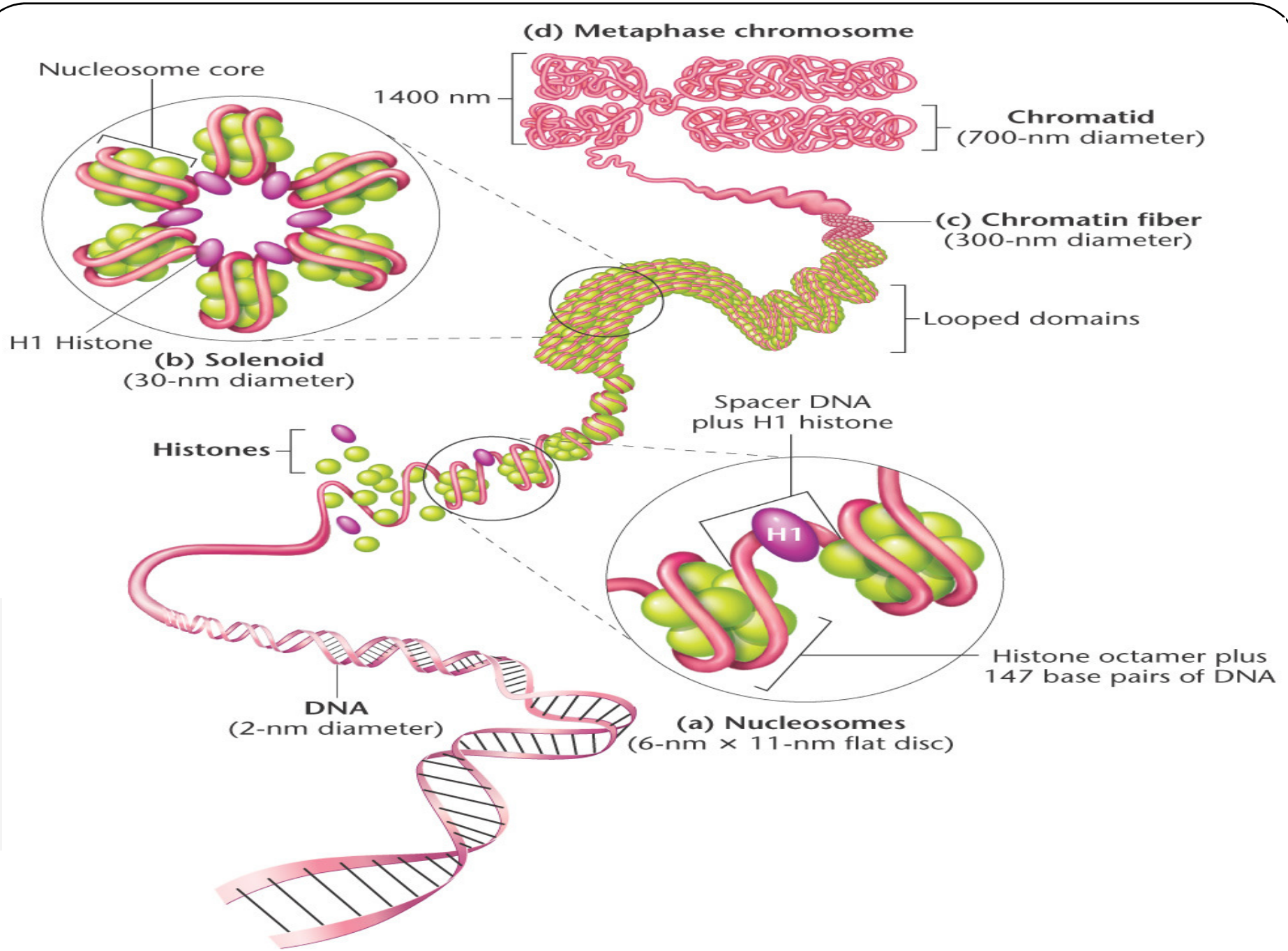
Human genome

- ~3 X 10^9 bp of DNA
- 30,000 to 40,000 genes
- Any Genes can have 1 to >75 exons
- Genes can be = in length from <100 to >2,300,000 bp

Mitochondrial genome

- Circular genome of ~17,000 bp
- Contains <40 genes

Condesation of DNA



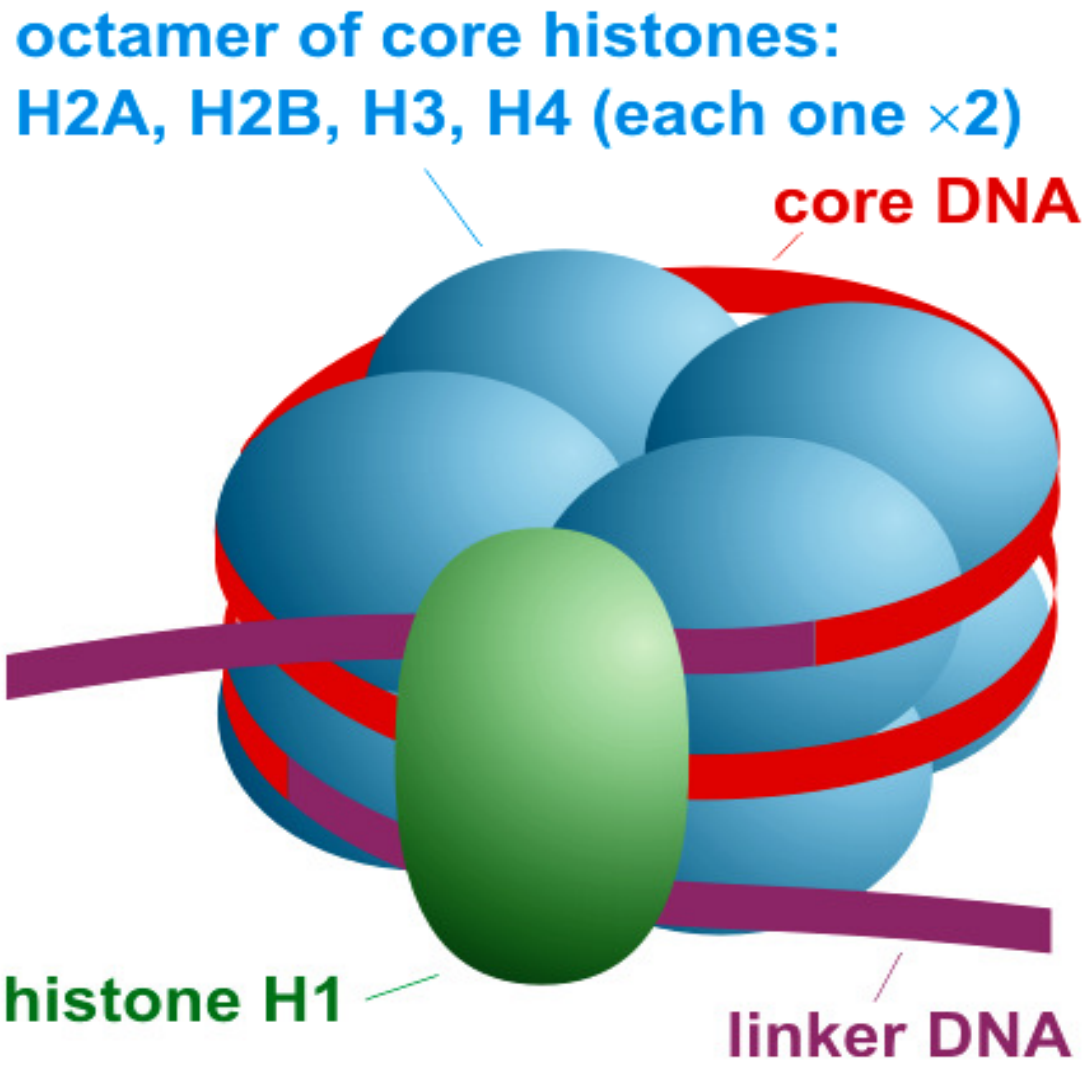
Mathematic behind Condensation

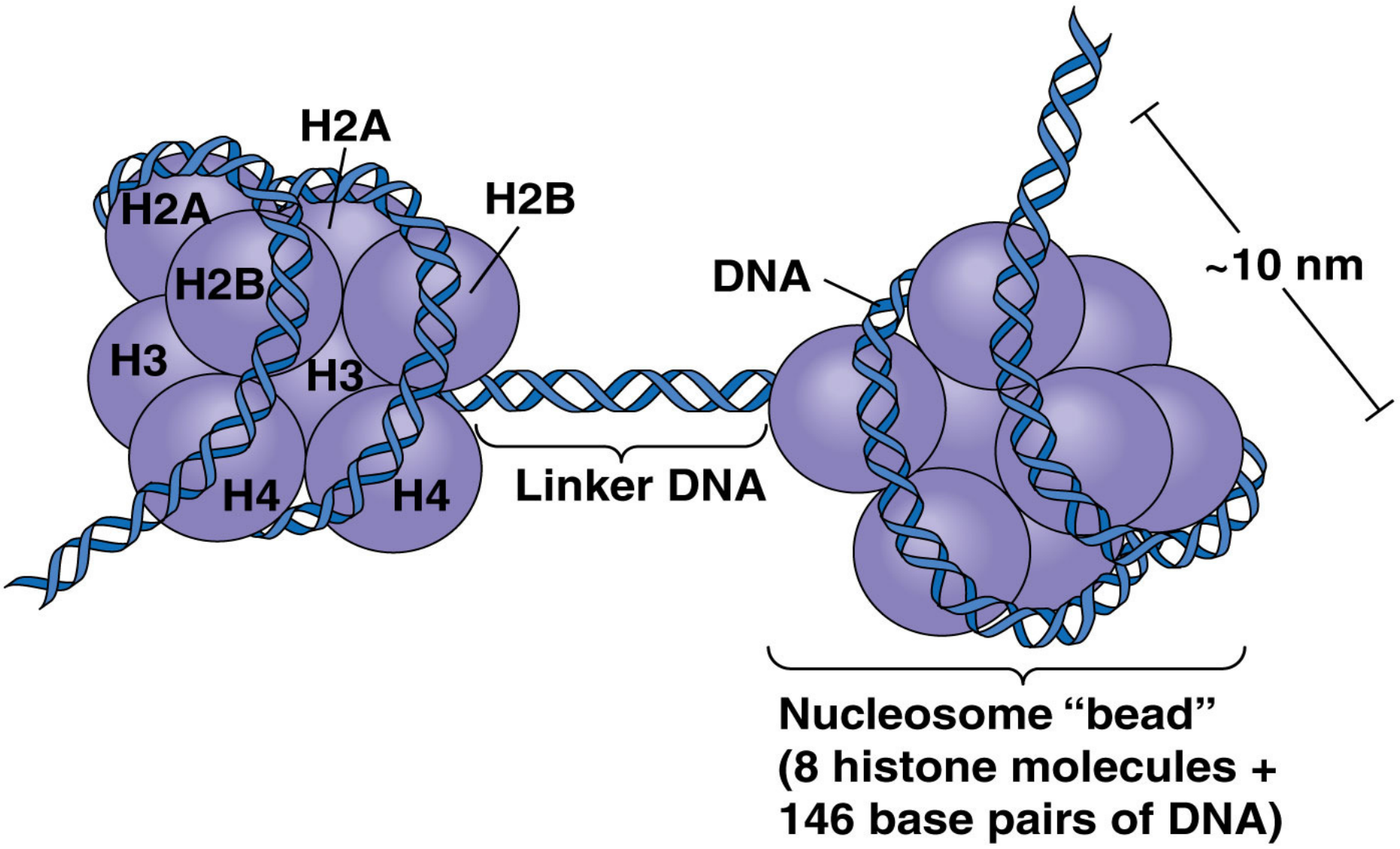
- Human genome (in diploid cells) = 6×10^9 bp
- 6×10^9 bp X 0.34 nm/bp = 2.04×10^9 nm = 2 m/cell
- Very thin (2.0 nm), Extremely fragile
- Diameter of nucleus = 5-10 mm
- DNA must be packaged to protect it,
- But it must still be accessible to allow gene expression and cellular responsiveness

HISTONES

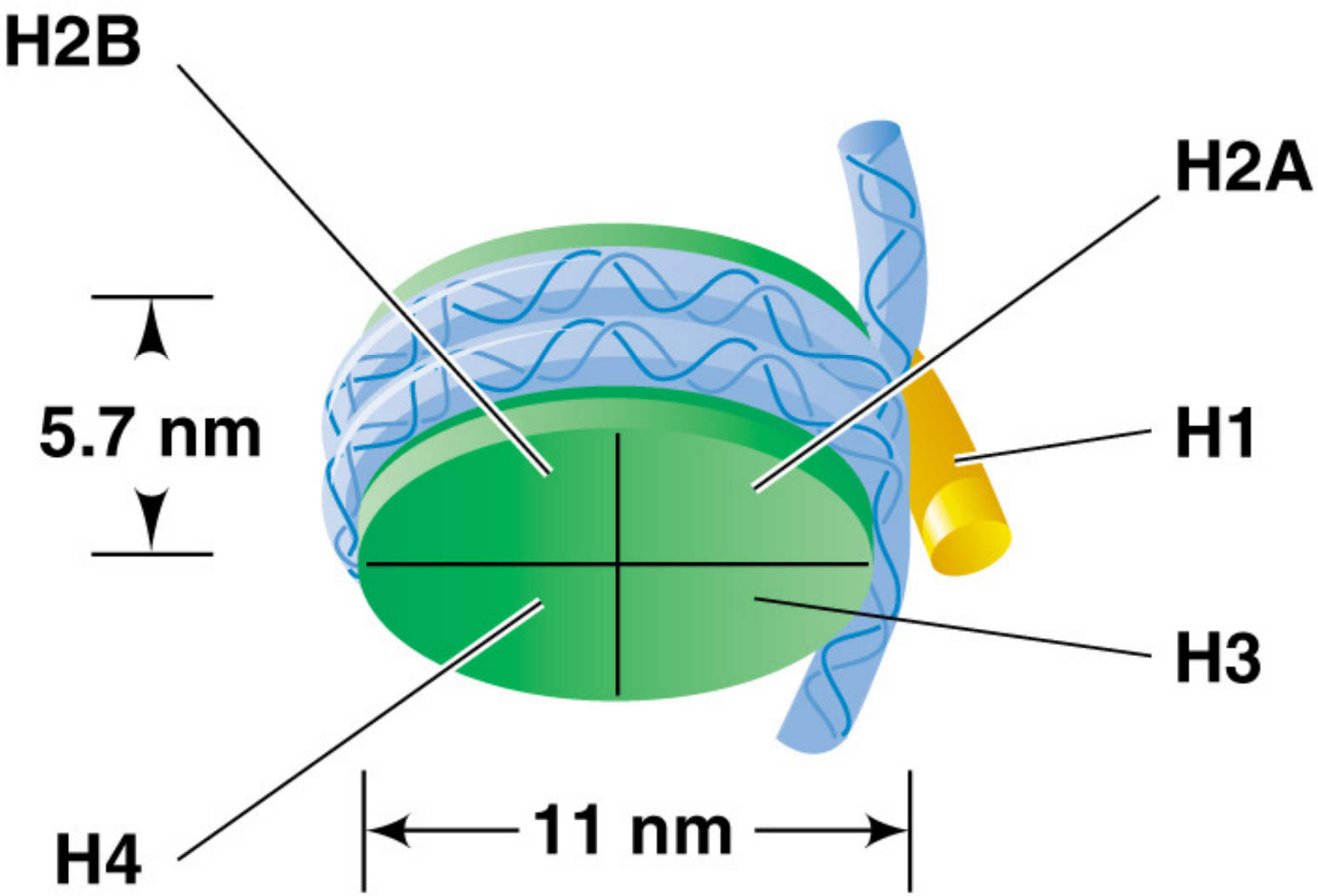
- Main packaging proteins
- 5 classes: H1, H2A, H2B, H3, H4.
- Rich in Lysine and Arginine
- DNA wraps around it 1 3⁄4 times for a 7-fold condensation factor.

Nucleosome


octamer of core histones:
H2A, H2B, H3, H4 (each one ×2)
core DNA
histone H1
linker DNA

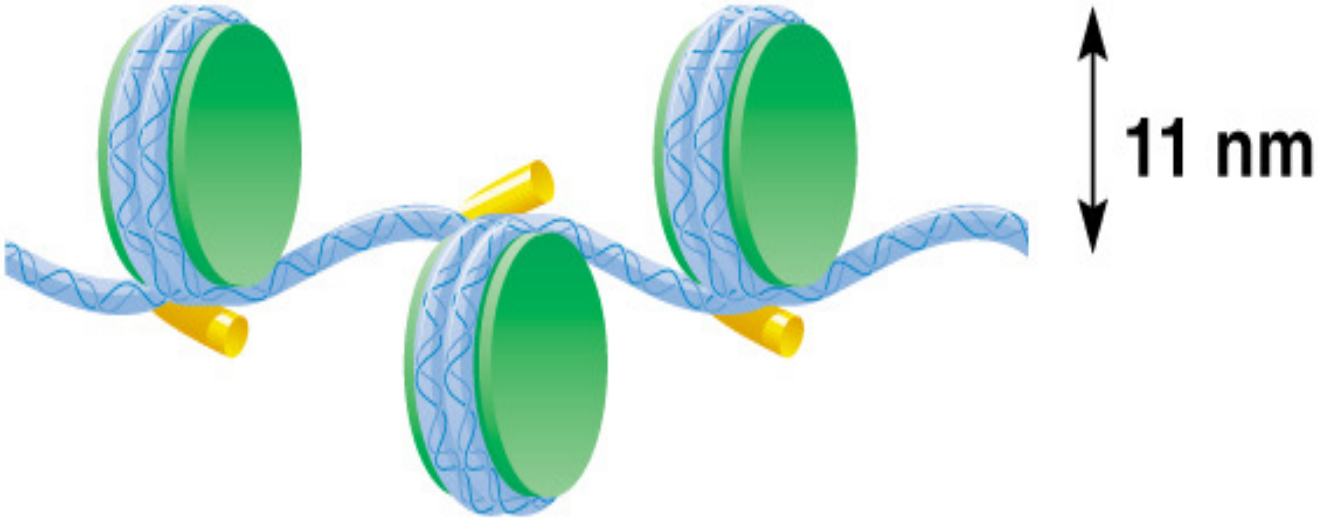


Nucleosome

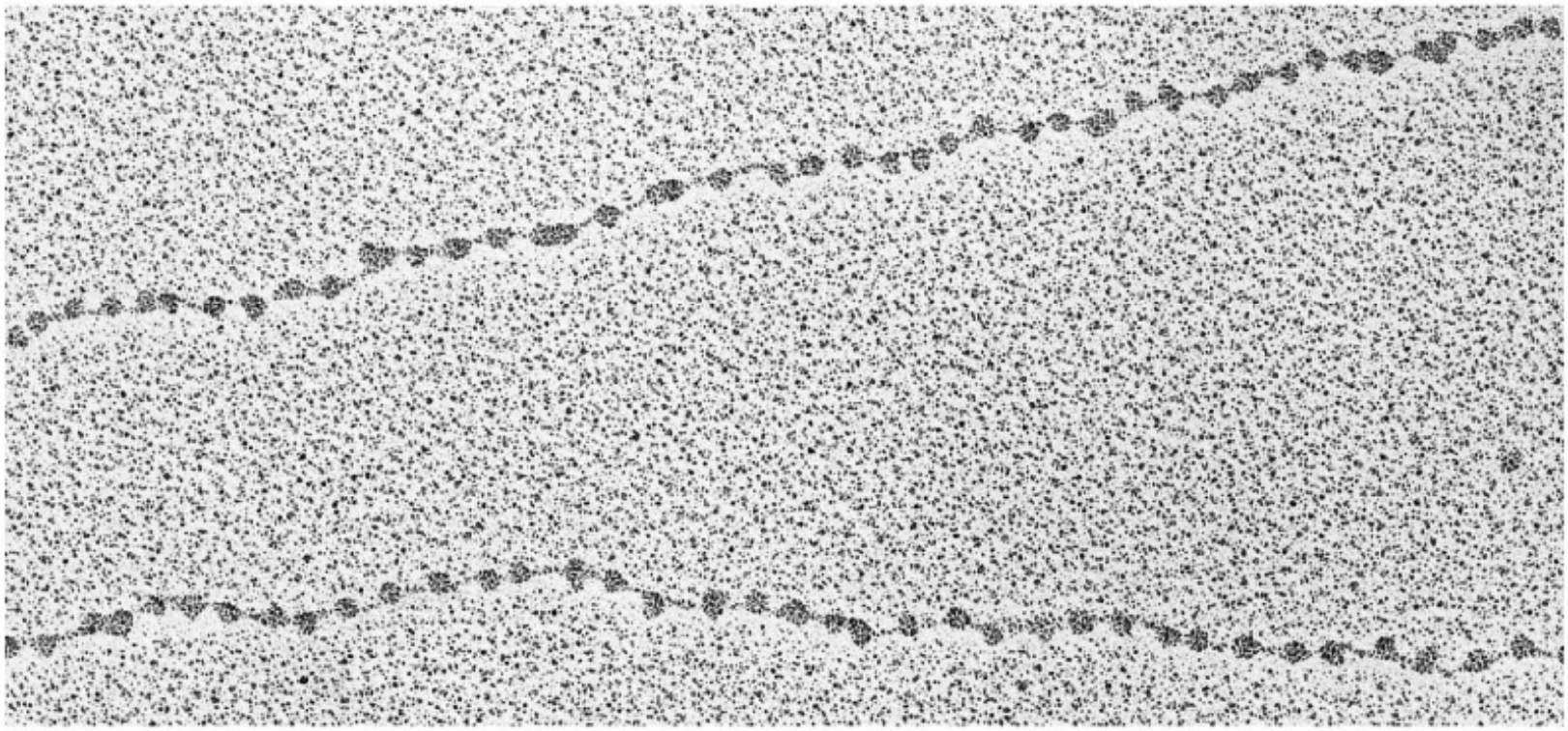


Chromatin fibril

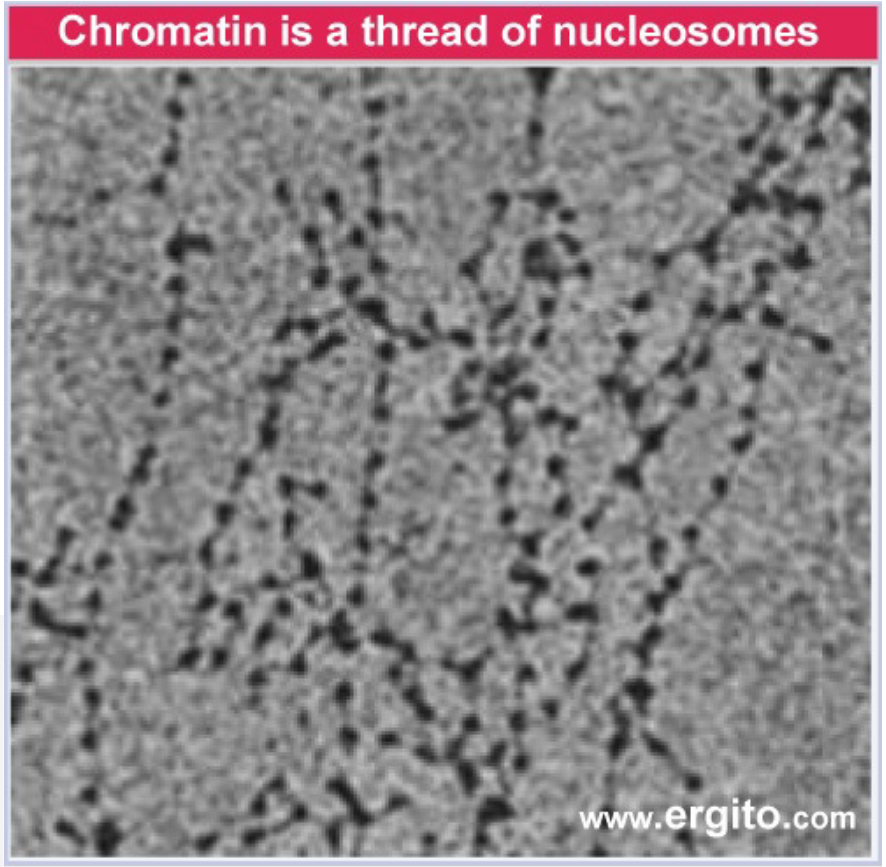
Beads-on-a-string form of chromatin

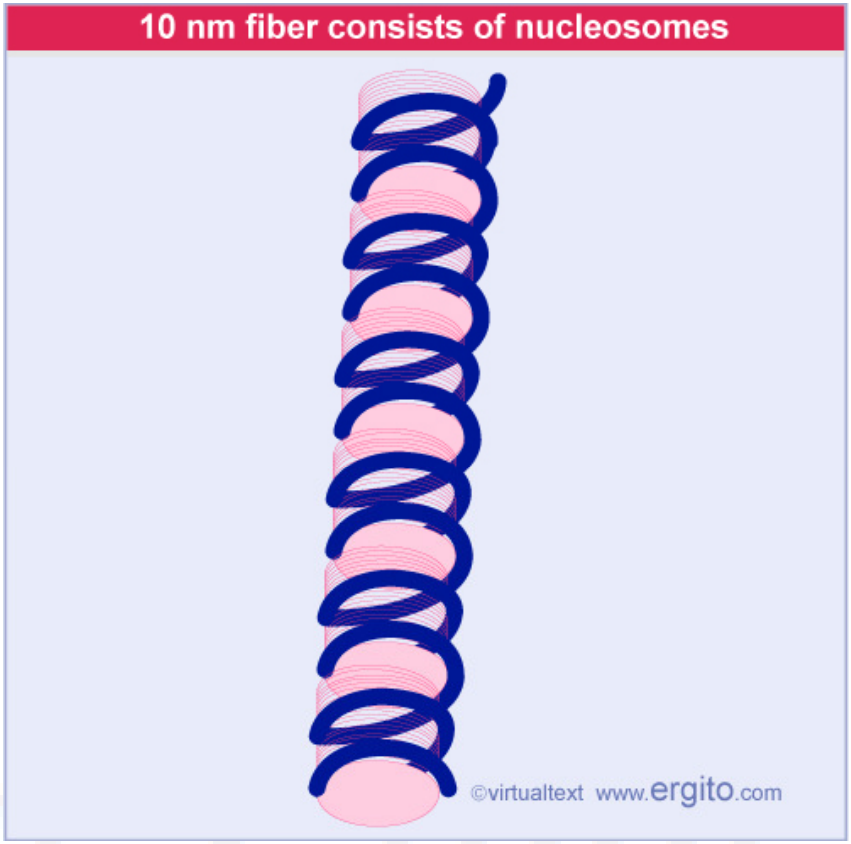


Beads on a String—10 nm Fiber

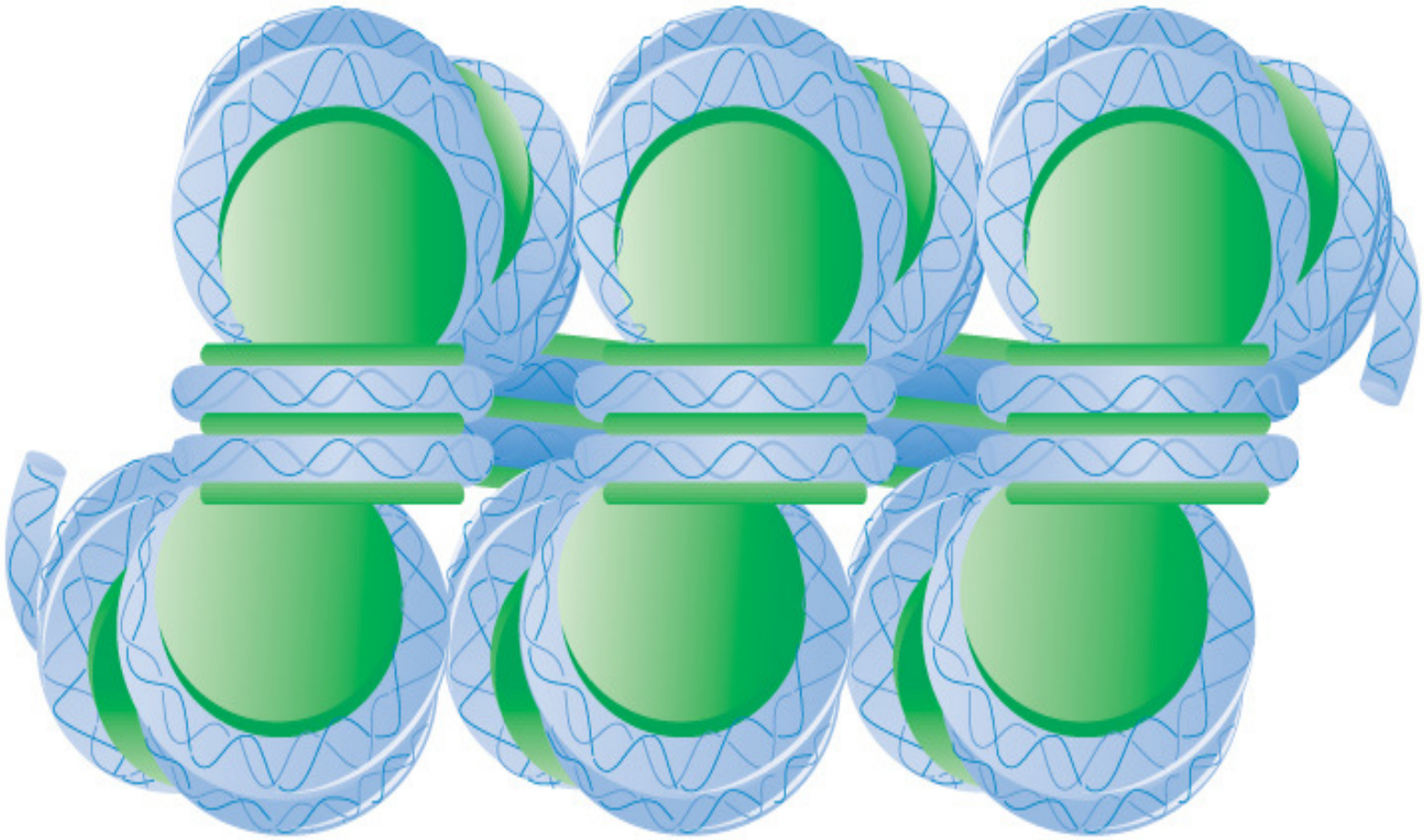


10 nm Fiber



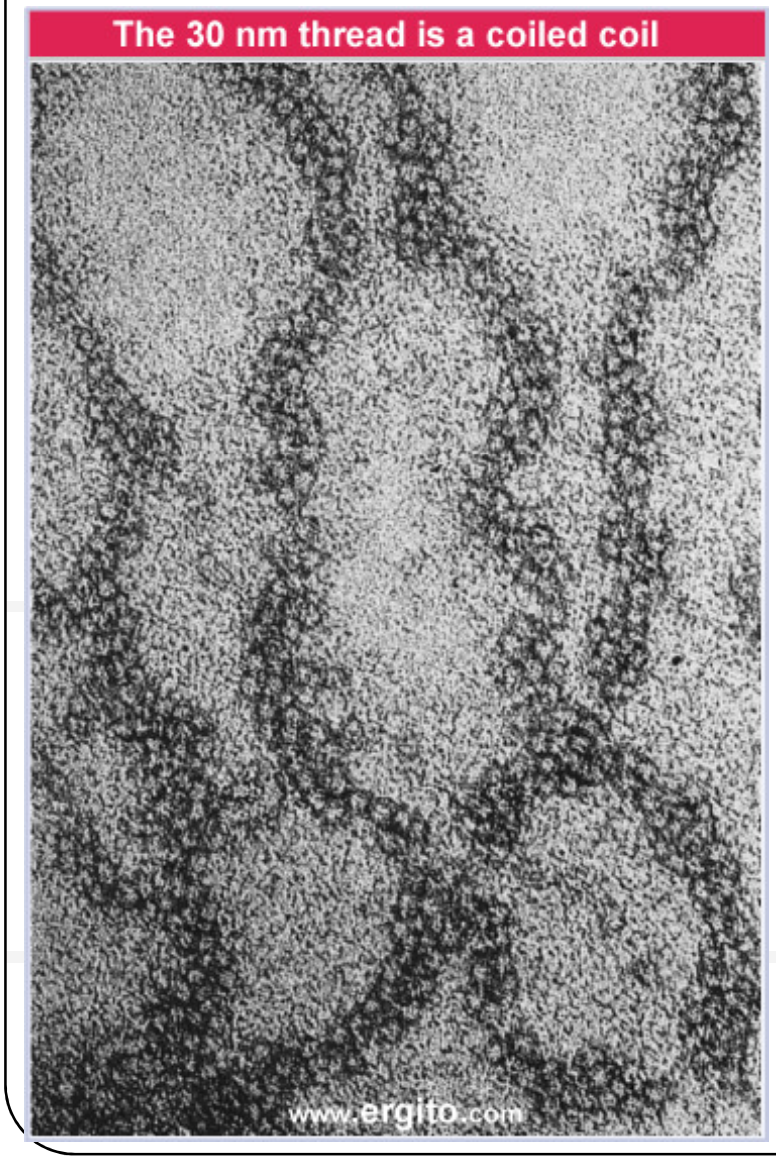


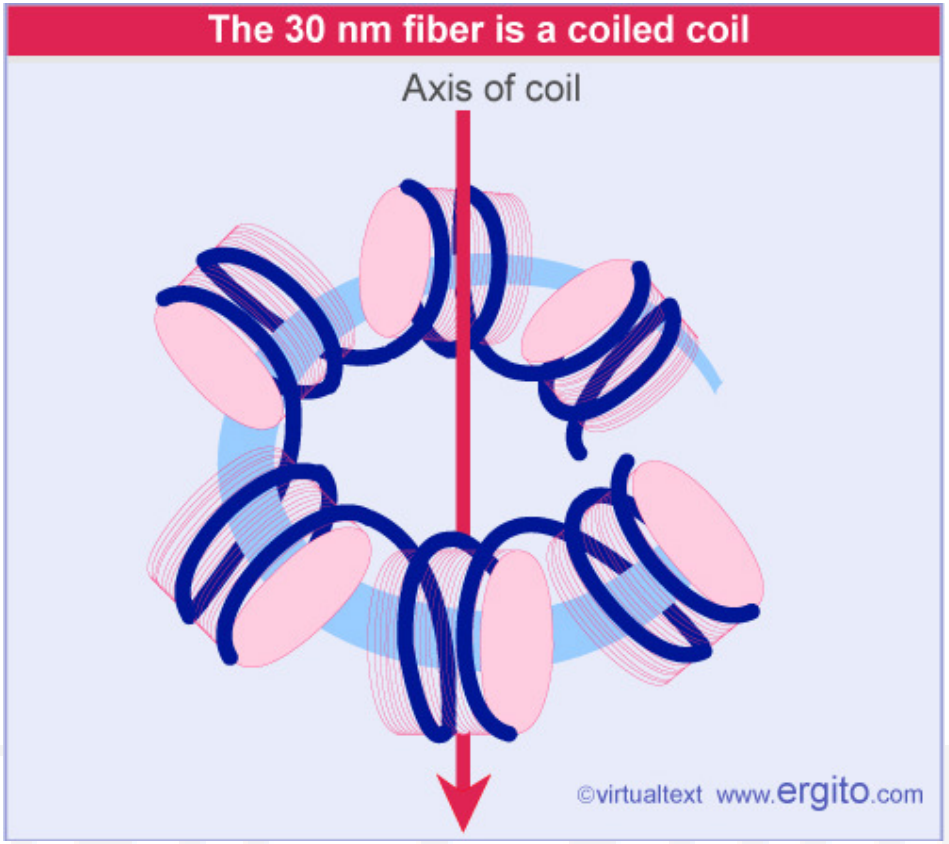
- A string of nucleosomes is seen under EM as a 10 nm fiber



b)

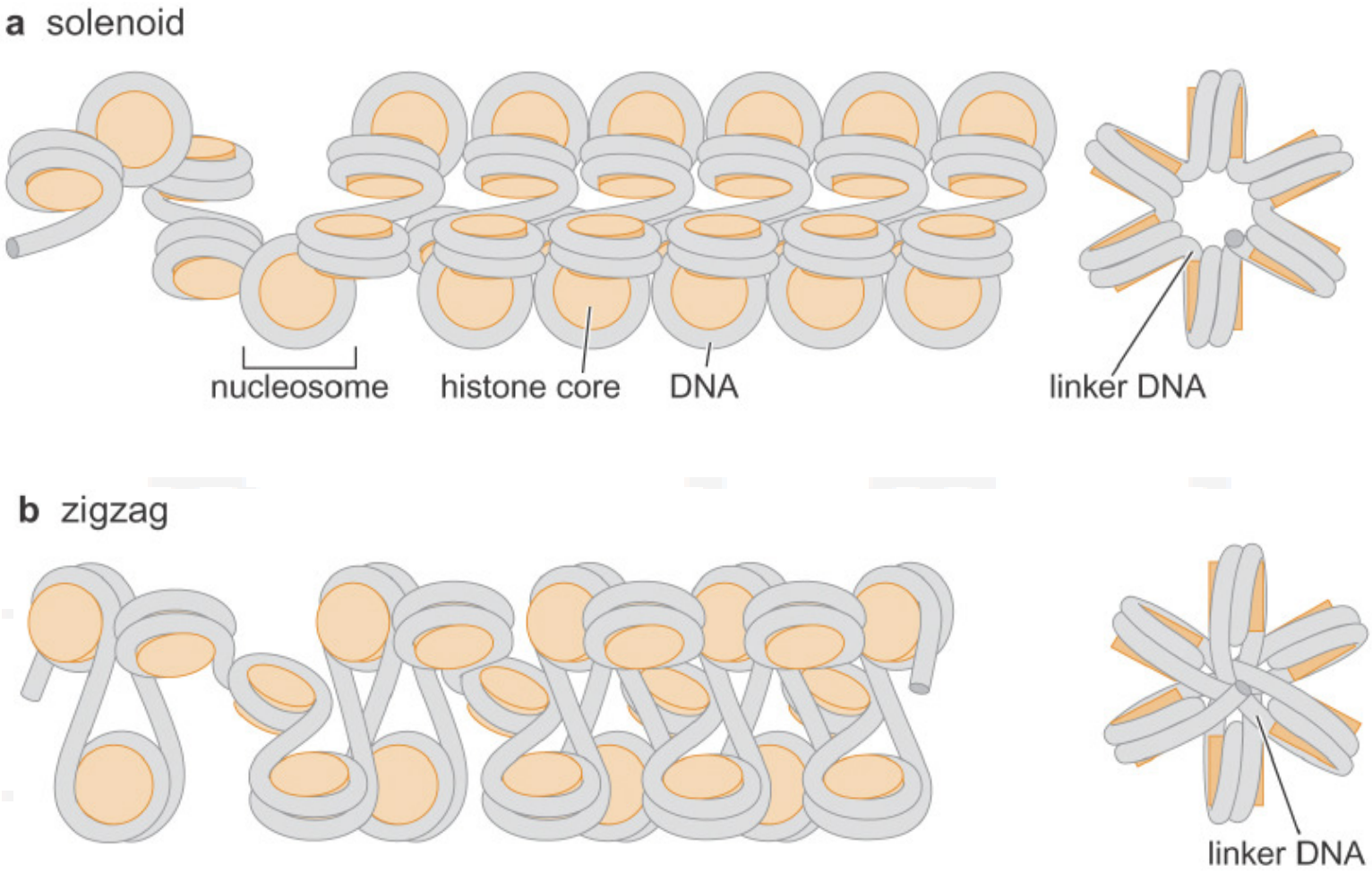
30 nm Chromatin Fibril





- 30 nm fiber is coil of nucleosomes with 6/turn

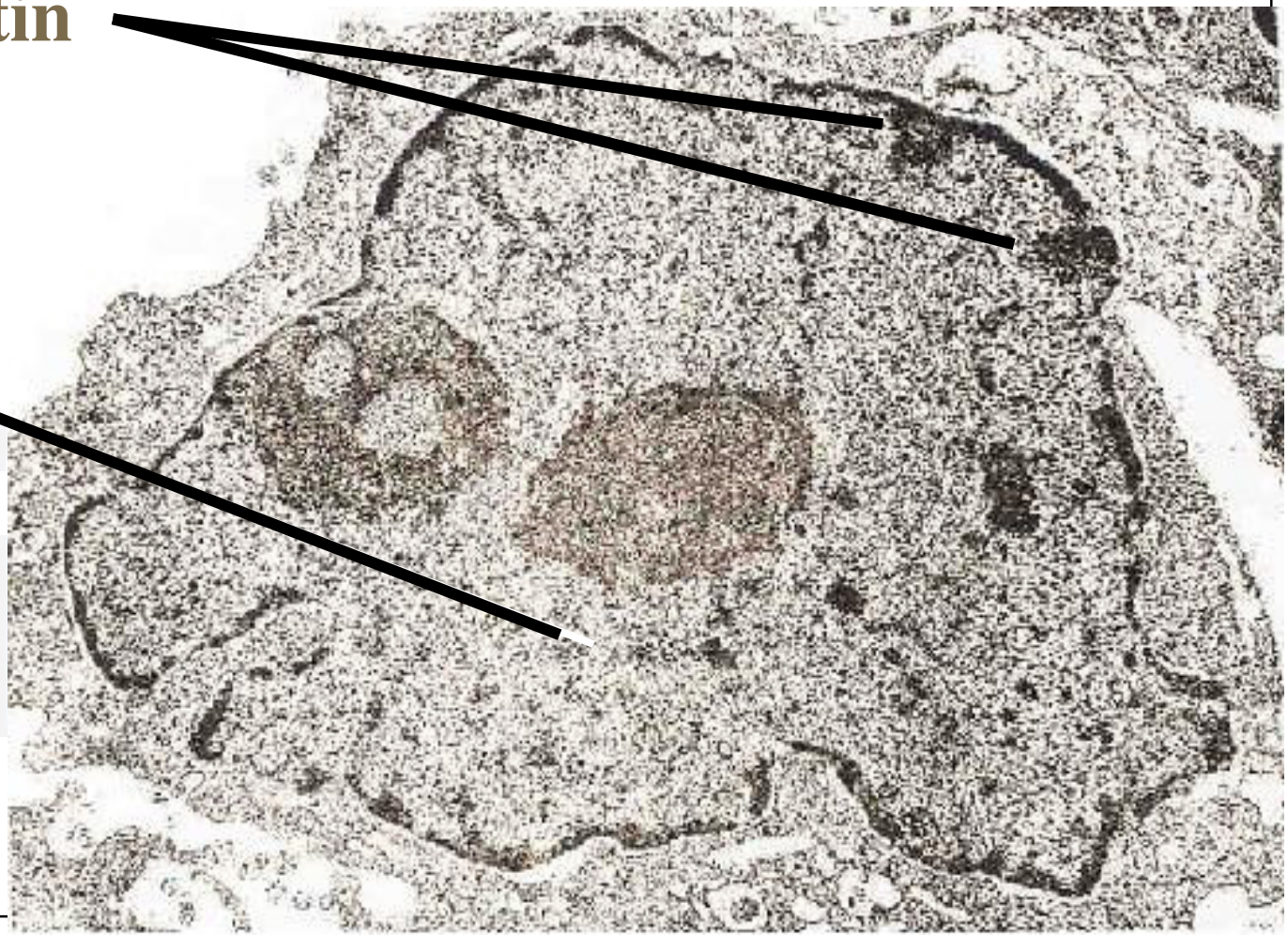
The 30 nm Fiber
(Compacts DNA 7X more)



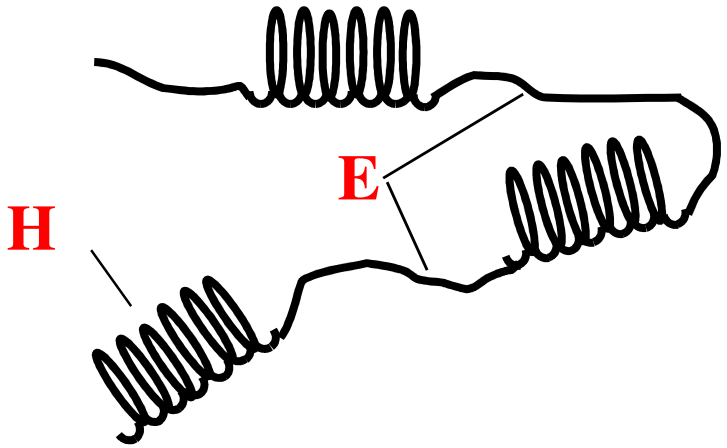
Different forms of chromatin show differential gene activity

Heterochromatin

Euchromatin

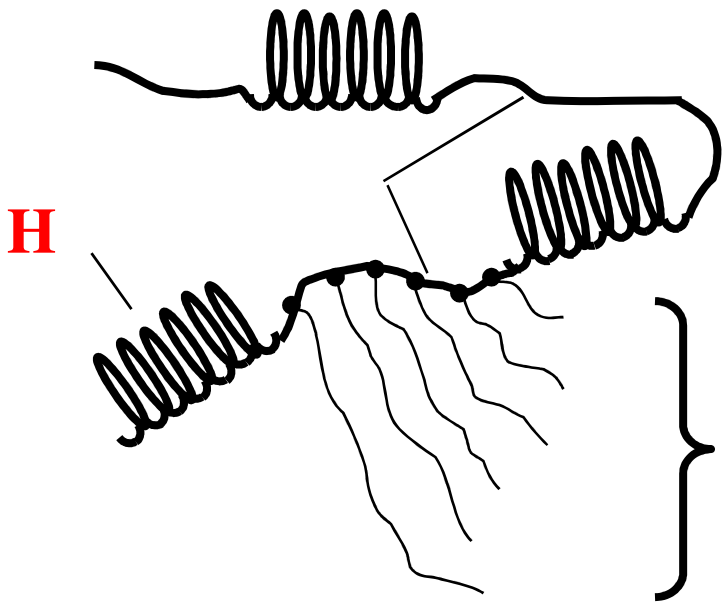


Euchromatin (E) *vs* Heterochromatin (H)



DNase

Heterochromatin = More condensed
=(tightly packed)
= Resistant to DNase digestion.



Transcriptionally active DNA (an active gene) is in *euchromatin*.

Histones (H1, H2A, H2B, H3, H4)

- Small nucleio-proteins
- Arginine or Lysine rich: positively charged
- Interact with negatively (due to phosphate) charged DNA
- Following modification decrease positive charge of DNA
  - ✓Phosphorylation
  - ✓Poly(ADP) ribosylation
  - ✓Methylation
  - ✓Acetylation
    - ***Hypoacetylation***
      associate with transcriptional repression
    - ***Hyperacetylation***
      associate with transcriptional activation

- **Modified Nucleiotide & it's significant.**
- **DNA replication is semi-conservative.**

Gar (Hostel)-Kam

- Name a condition which can happen due to increase serum uric acid level (**Hyperuricemia**).
- What is difference between uric acid and urate crystal?
- Which part of body especially get affected due to hyperuricemia?
- What type of food ingestion can cause hyperuricemia ?
- Which type of condition can increase purine degradation and increase serum uric acid level?
- Which type of condition can decrease excretion of uric acid , which makes increase serum uric acid level?
- What is role of Allopurinol to correct hyperuricemia ?

- **If a section of DNA has 13% thymine and 37% guanine, then there is _____ adenine.**
  - 13%
  - 26%
  - 37%
  - 74%

- **The percentage of A + G equals _____.**
  - 26 %
  - 50 %
  - 80 %
  - 100 %

- **The sequence of one strand of DNA is 5’ TCGATC 3’. The sequence of the complementary strand would be**
  - 5’ AGCTAG 3’
  - 5’ CTAGCT 3’
  - 5’ GCTAGC 3’
  - 5’ GATCGA 3'

- **DNA has antiparallel two nucleotide chain, which is held together by**
  - **phosphodiester bond.**
  - **hydrogen bond.**
  - **N-glycosidic bond**
  - **O-glycosidic bond**

- **All of Following, which has similar structure like purine and use drug for treatment of gouty arthiritis,**
  - **Hypoxanthine**
  - **Xanthine**
  - **Uric acid**
  - **Allopurinol**

- **Adenosine deaminase deficiency cause, except**
  - **increase uric acid level**
  - **increase of adenosine**
  - **increase of d-ATP**
  - **All of above**

- Uric acid is breakdown product of purine base.
- So Which of following condition can increase uric acid level
  - chemotherapy
  - radiotherapy
  - leukemia
  - All of above

- **Mitochondrial DNA is , except**
  - **circular**
  - **maternal inheritance**
  - **very lengthy**
  - **very large in amount**

- **What is incorrect about Histone?**
  - **Positive charged & base in nature**
  - **Contain abundant arginine & lysine**
  - **Help in condensation of DNA**
  - **All are cylindrical in shape**

- Euchromatine part of chromosome is
  - highly condense with nucleosome
  - active transcription gene
  - seen darkly stained in electron-microscopy
  - All of Above