Einleitung
HHR 22.04.2003

DNS-Struktur, Replikation und Expression

Chromosomen und Chromosomenaberrationen

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OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University

***309550**

Link

FRAGILE SITE MENTAL RETARDATION 1 GENE; FMR1

Alternative titles; symbols

FRAGILE X MENTAL RETARDATION PROTEIN; FMRP
FRAGILE X SYNDROME, INCLUDED
FRAGILE X MENTAL RETARDATION SYNDROME, INCLUDED
MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH marXq28, INCLUDED
X-LINKED MENTAL RETARDATION AND MACROORCHIDISM, INCLUDED
MARKER X SYNDROME, INCLUDED
MARTIN-BELL SYNDROME, INCLUDED
FRAGILE SITE, FOLIC ACID TYPE, RARE, FRA(X)(q27.3), INCLUDED; FRAXA, INCLUDED

Gene map locus Xq27.3

TEXT

DESCRIPTION

X-linked mental retardation associated with marXq28, or fragile X syndrome, is characterized by moderate to severe mental retardation

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project Ensembl

The Wellcome Trust Sanger Institute

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About Ensembl

Ensembl is a joint project between EMBL - EBI and the Sanger Institute to develop a software system which produces and maintains automatic annotation on eukaryotic genomes. Ensembl is primarily funded by the Wellcome Trust. Access to all the data produced by the project, and to the software used to analyse and present it, is provided free and without constraints.

Ensembl presents up-to-date sequence data and the best possible automatic annotation for metazoan genomes. Available now are human, mouse, rat, fugu, zebrafish, mosquito, Drosophila, C. elegans, and C. briggsae, Others will be added soon.

For an introduction to the Ensembl project, take the Ensembl tour, and then go through a step-by-step worked example which introduces Ensembl's main functions. For more information read these short papers (Jan 2002, Jan 2003), in Nucleic Acids Research.

For all enquiries, please contact the Ensembl *HelpDesk* (helpdesk@ensembl.org).

Ensembl provides ....

- Easy access to sequence data
- For known genes, predicted structure and location in the genome sequence

Ensembl Species

Human	v. 12.31.1	1 Apr 2003
Mouse	v. 12.3.1	3 Mar 2003
Rat	v. 12.2.1	1 Apr 2003
Zebrafish	v. 12.08.1	3 Mar 2003
Fugu	v. 12.2.1	3 Mar 2003
Mosquito	v. 12.2.1	1 Apr 2003
Fruitfly	v. 12.3.1	3 Mar 2003
C. elegans	v. 12.95.1	3 Mar 2003
C. briggsae	v. 12.25.1	3 Mar 2003

Fast data/sequence retrieval (multi-species) EnsMart

Access to whole genome shotgun data (includes additional species) Trace Server

Help and documentation

- Species-specific documentation is available via the species home pages above.
- Take the Ensembl tour, go through a step-by-step worked example, or read this short paper in Nucleic Acids Research.
- For context-sensitve help on any web page click: Help
- There is also an index of context-sensitive help pages, and a set of guided How do I....? trails.

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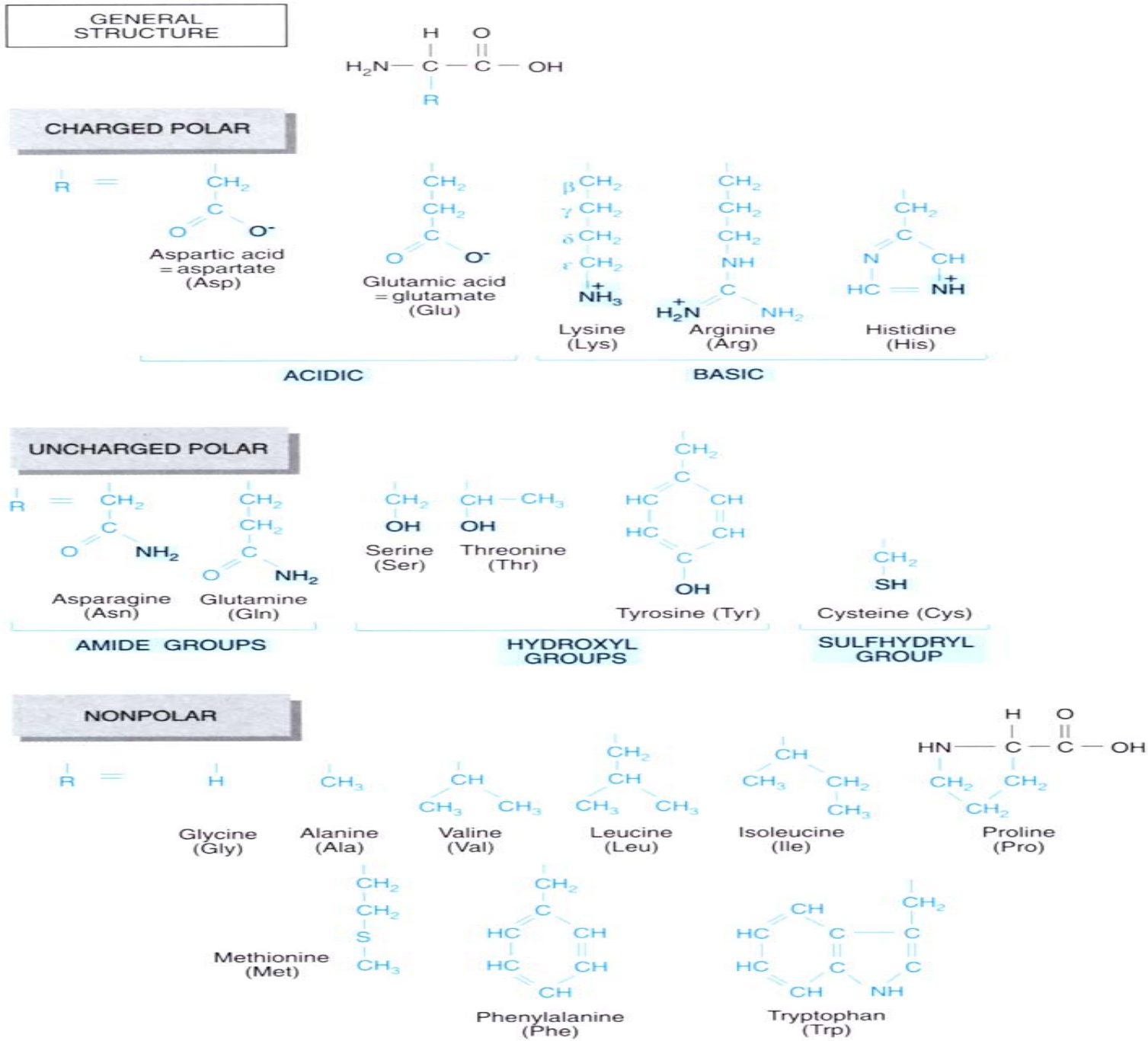


Figure 1.3: Structures of the amino acids.

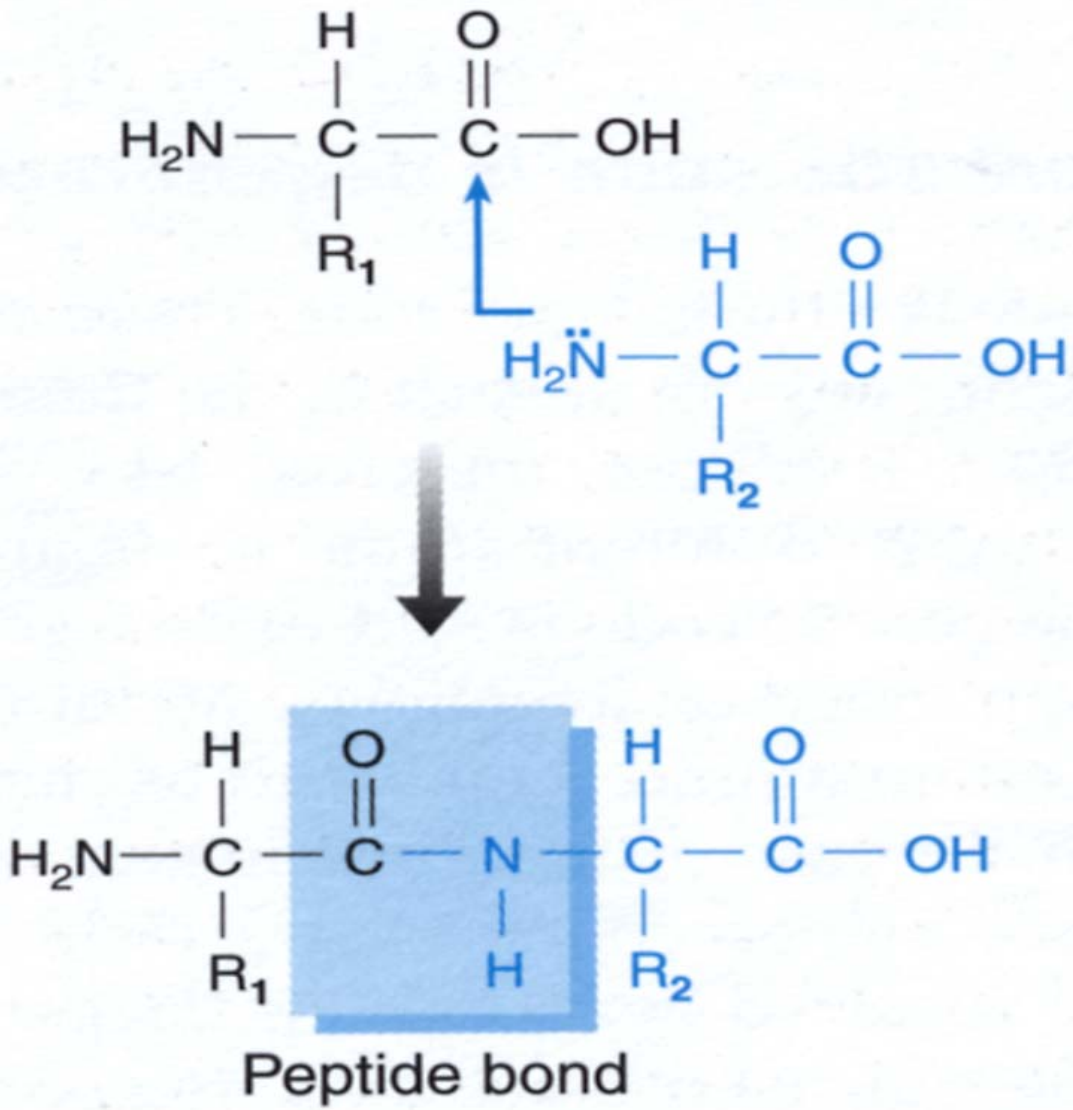
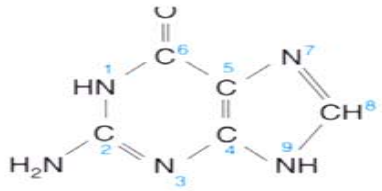
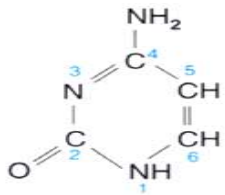


Figure 1.21: Polypeptides are synthesized by peptide bond formation between successive amino acids.

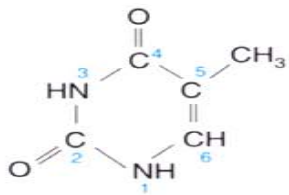
Adenine (A)



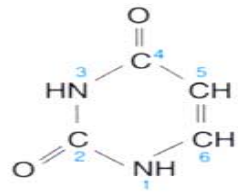
Guanine (G)



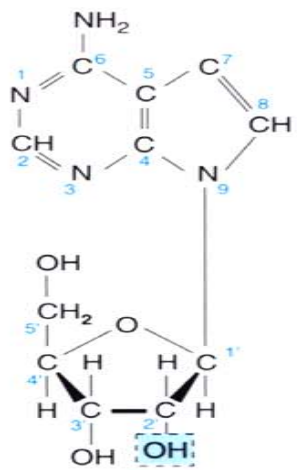
Cytosine (C)



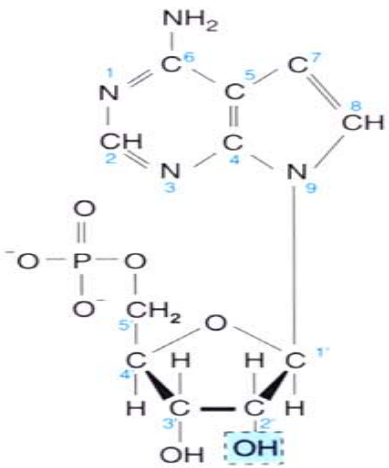
Thymine (T)



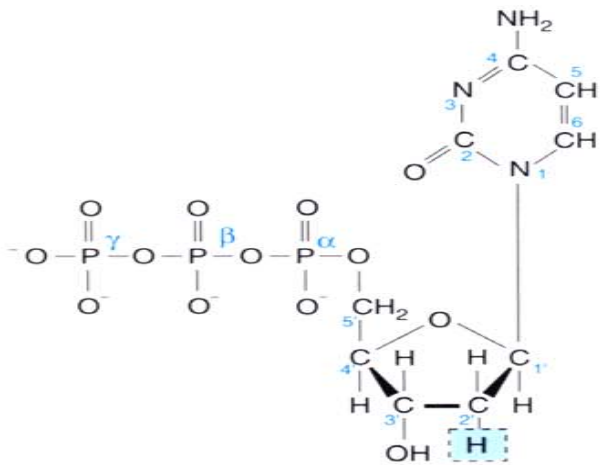
Uracil (U)



Adenosine



Adenosine 5'-monophosphate (AMP)



2'-Deoxycytidine 5'-triphosphate (dCTP)

Figure 1.2: Structure of bases, nucleosides and nucleotides.

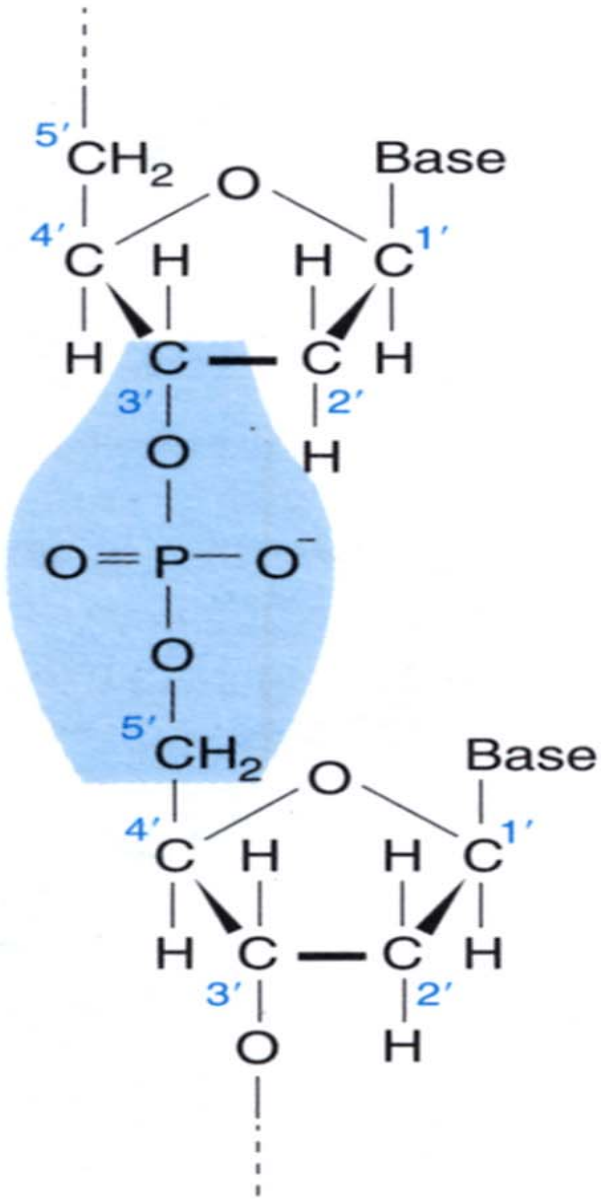


Figure 1.4: A 3′-5′ phosphodiester bond.

Table 1.1: Weak noncovalent bonding

Type of bond	Nature of bond
Hydrogen	Hydrogen bonds form when a *hydrogen atom* is sandwiched between two electron-attracting atoms, usually oxygen or nitrogen. See *Box 1.1* for examples of their importance in nucleic acid and protein structure and function.
Ionic	Ionic interactions occur between *charged groups*. They can be very strong in crystals but in an aqueous environment, the charged groups are shielded by H_2O molecules and other ions in solution and so are quite weak. Nevertheless, they can be very important in biological function, as in the case of enzyme–substrate recognition.
Van der Waals	*Any* two atoms which are very close to each other show a weak attractive bonding interaction due to their fluctuating electrical charges (van der Waals attraction) until they get extremely close, when they repel each other very strongly (van der Waals repulsion). Although individually very weak, van der Waals attractions can become important when there is a very good fit between the surfaces of two macromolecules.
Hydrophobic forces	Water is a polar molecule. When hydrophobic molecules or chemical groups are placed in an aqueous environment they are forced together to minimize their disruptive effects on the complex network of hydrogen bonding between water molecules. Hydrophobic groups which are forced together in this way are said to be held together by *hydrophobic bonds*, even though the basis of their attraction is due to a common repulsion by water molecules.

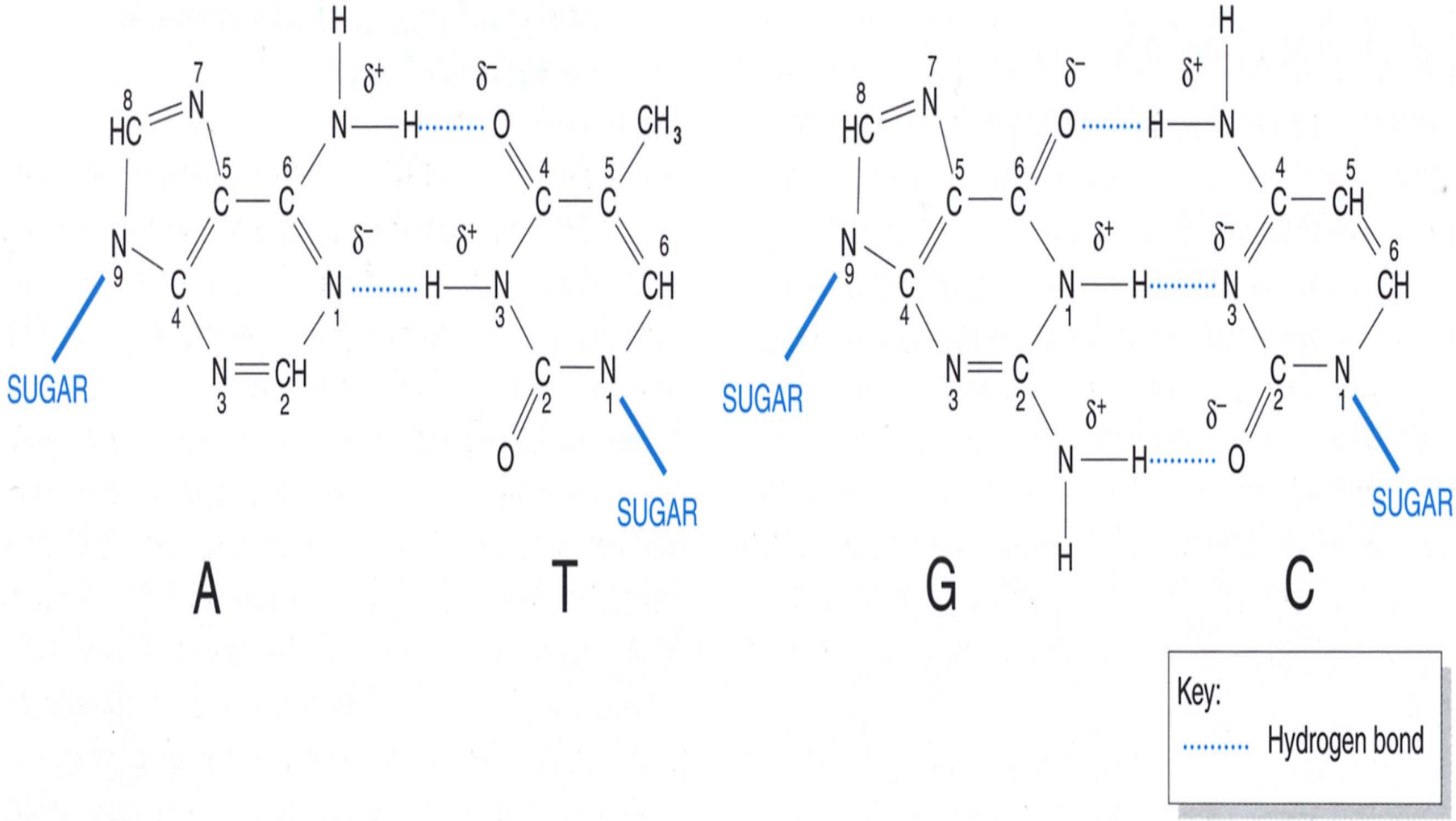


Figure 1.5: A–T base pairs have two connecting hydrogen bonds; G–C base pairs have three.

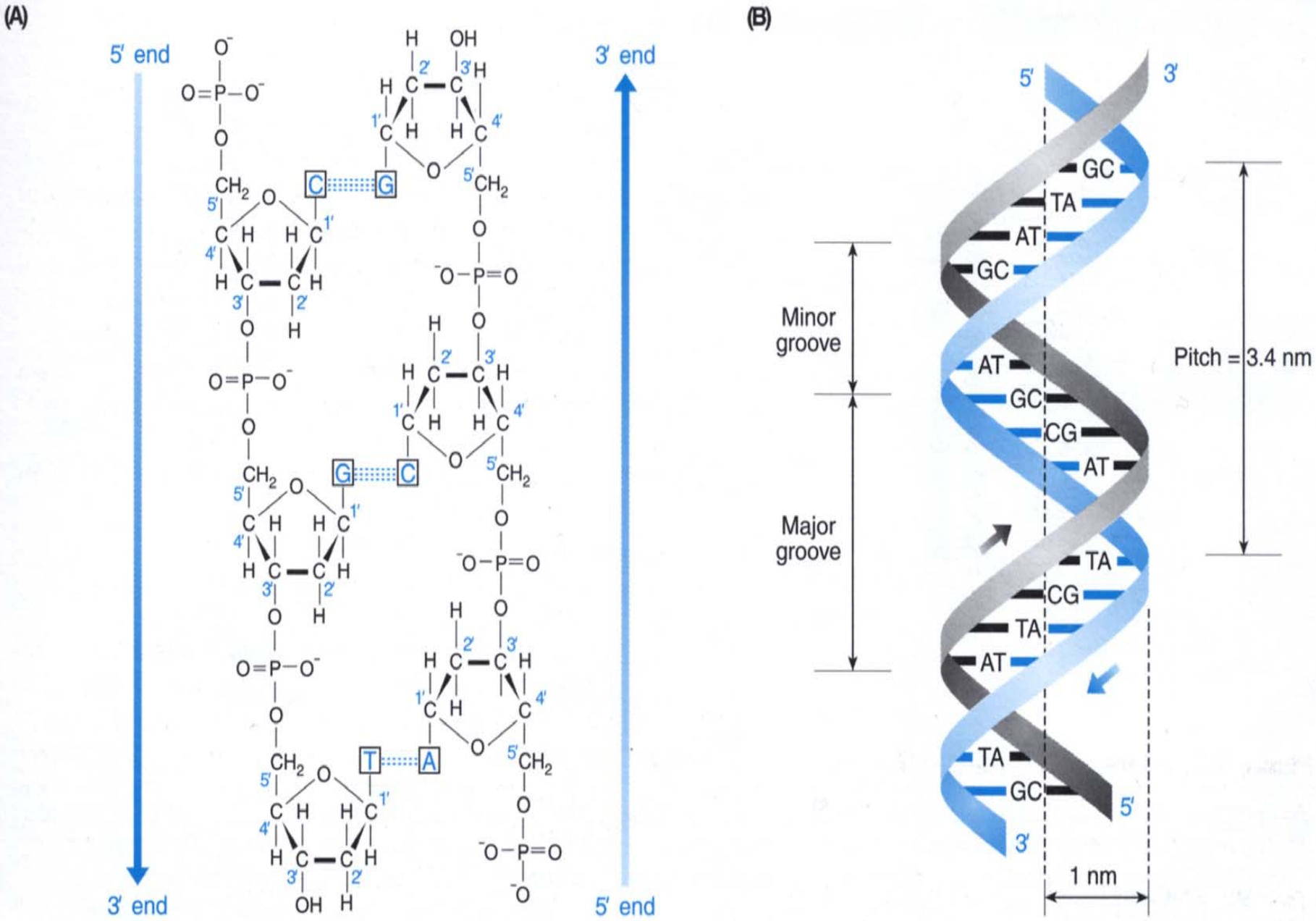


Figure 1.6: The structure of DNA is a double-stranded, antiparallel helix.

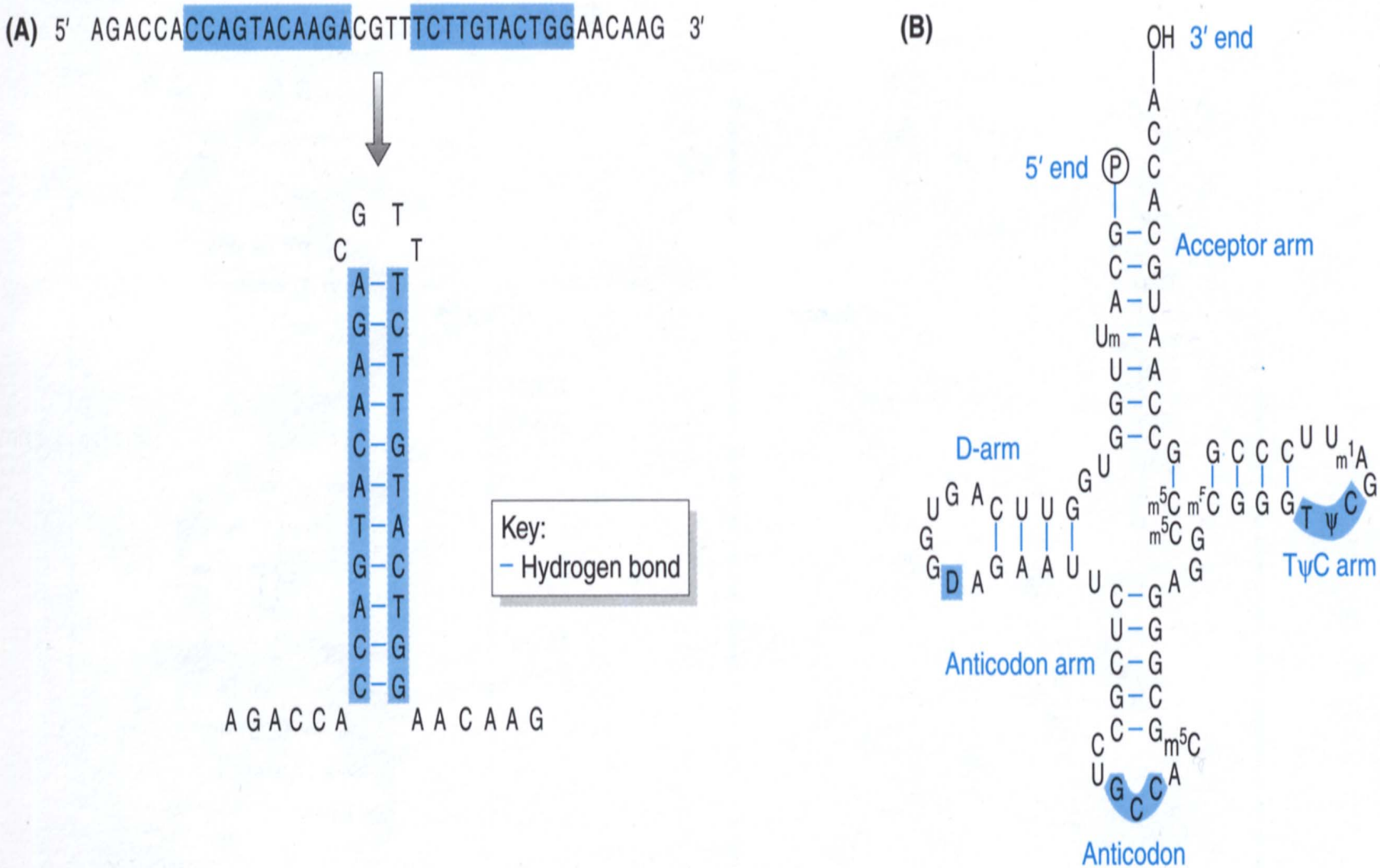


Figure 1.7: Intramolecular hydrogen bonding in DNA and RNA.

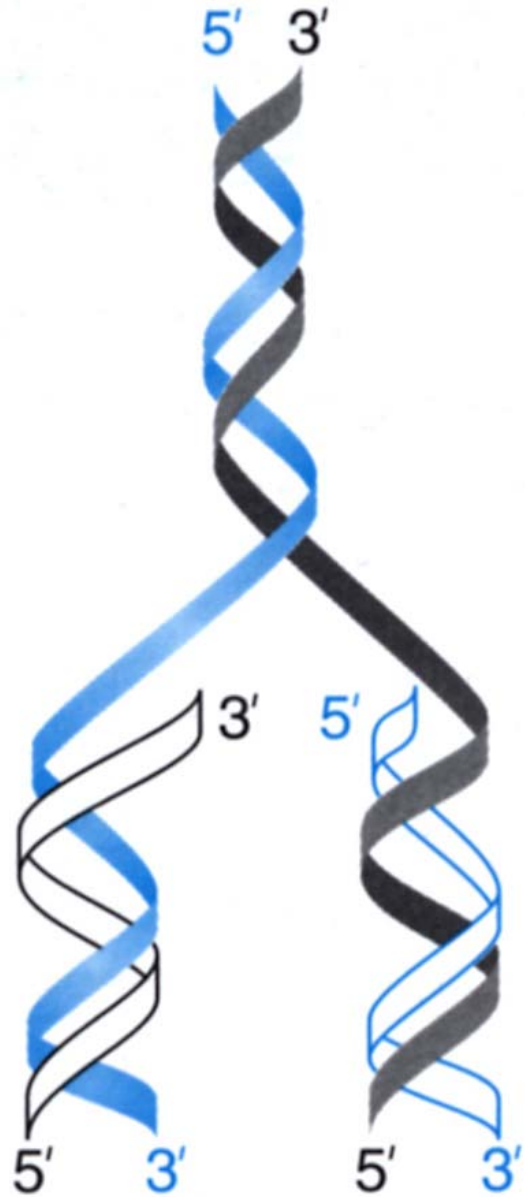


Figure 1.8: DNA replication is semiconservative.

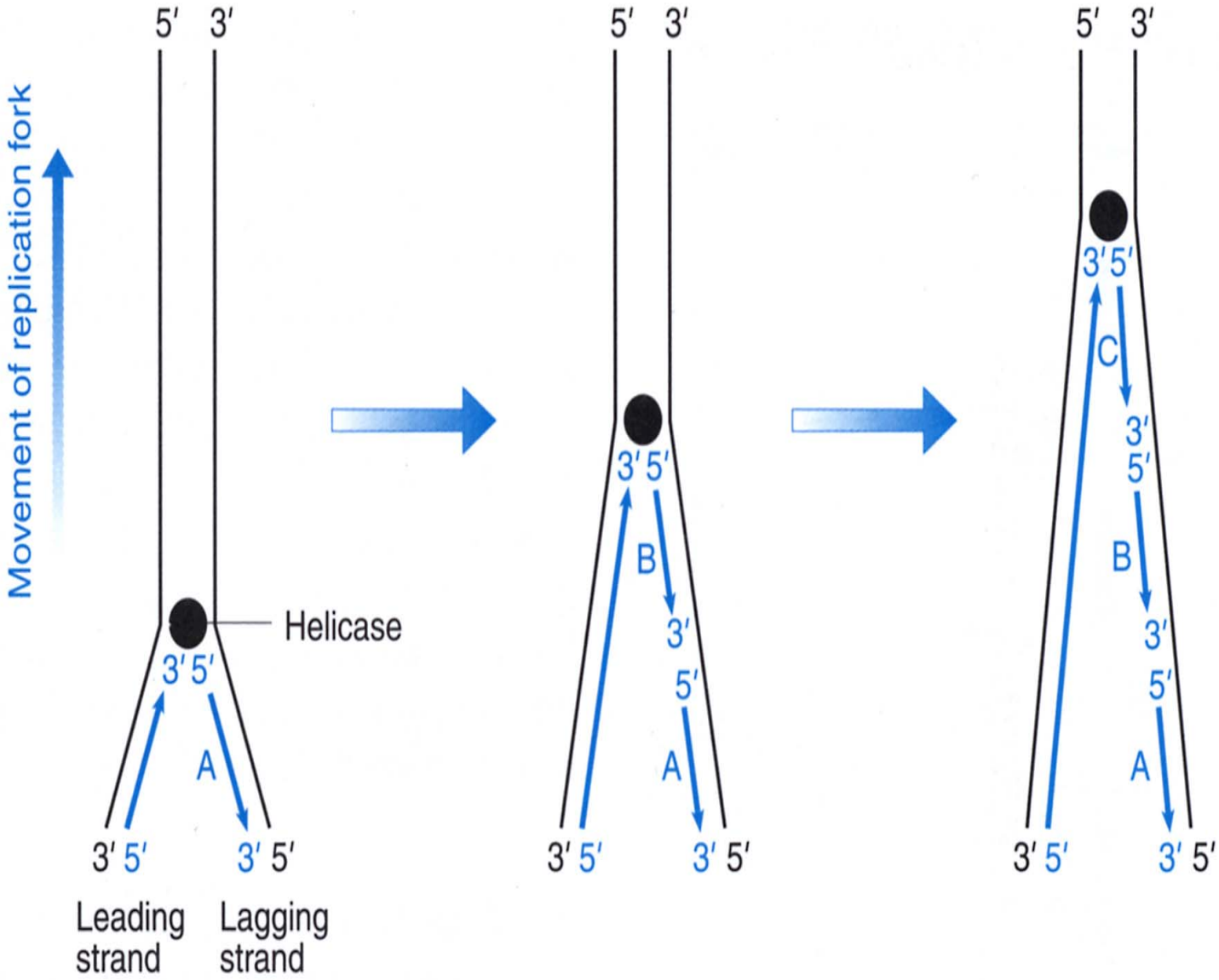


Figure 1.9: Asymmetry of strand synthesis during DNA replication.

Table 1.2: The five classes of mammalian DNA polymerase

	Class				
	α	β	γ	δ	ε
Location	Nuclear	Nuclear	Mitochondrial	Nuclear	Nuclear
Function	Synthesis and priming of lagging strand	DNA repair	Replicates mitochondrial DNA	Synthesis of leading strand	DNA repair
$3' \rightarrow 5'$ exonuclease?	No	No	Yes	Yes	Yes

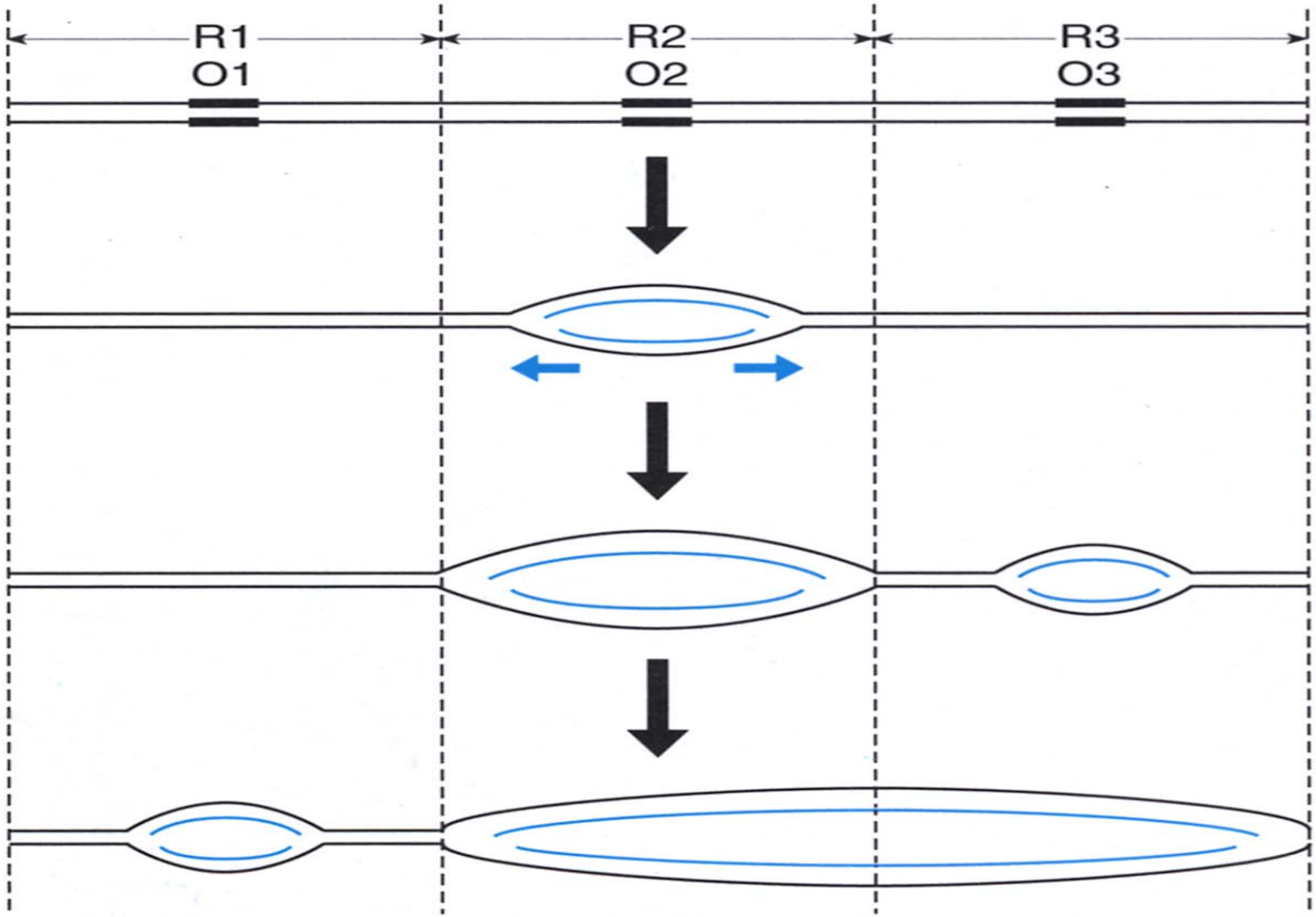


Figure 1.10: The chromosomes of complex organisms have multiple replication origins.

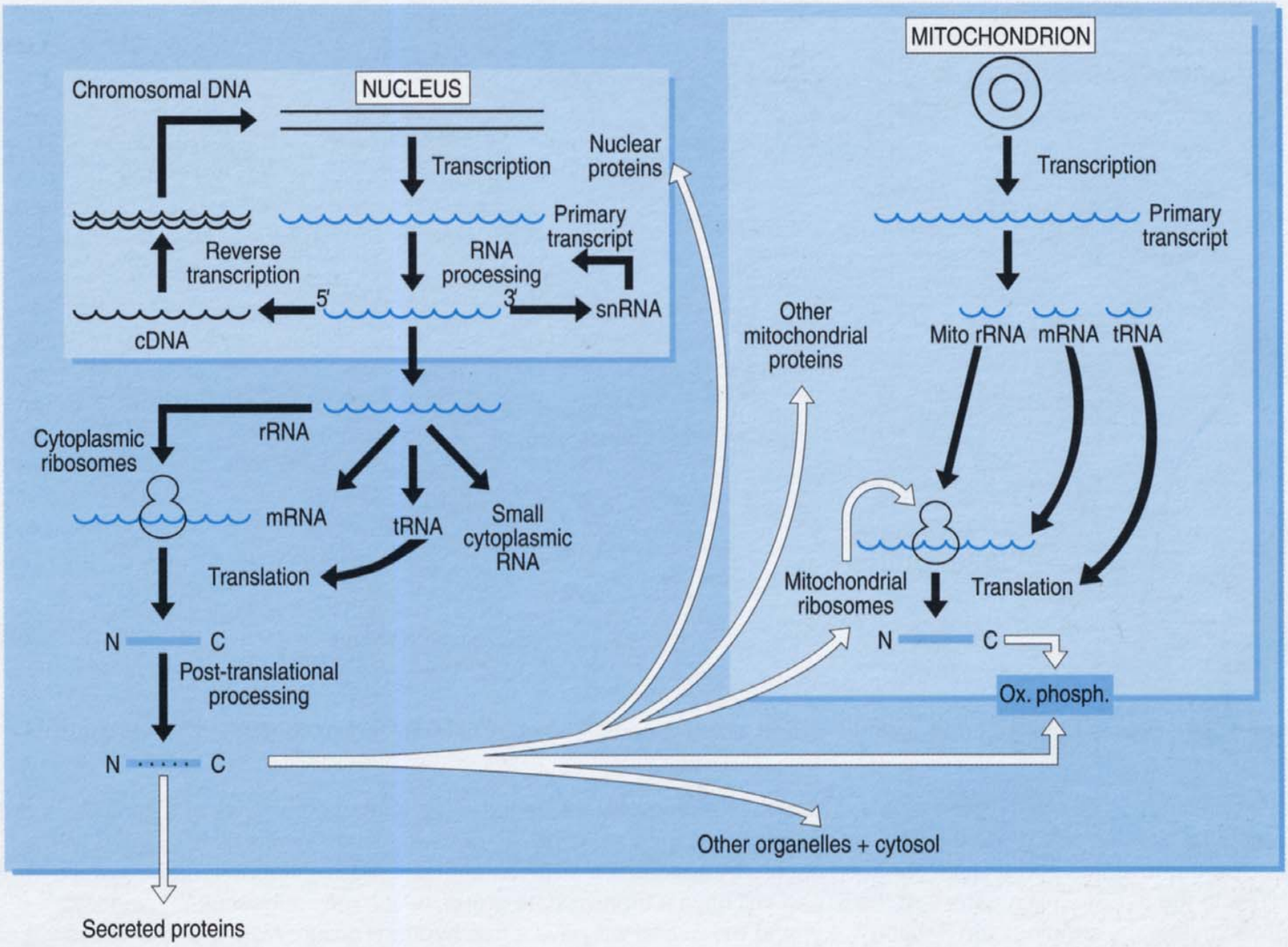
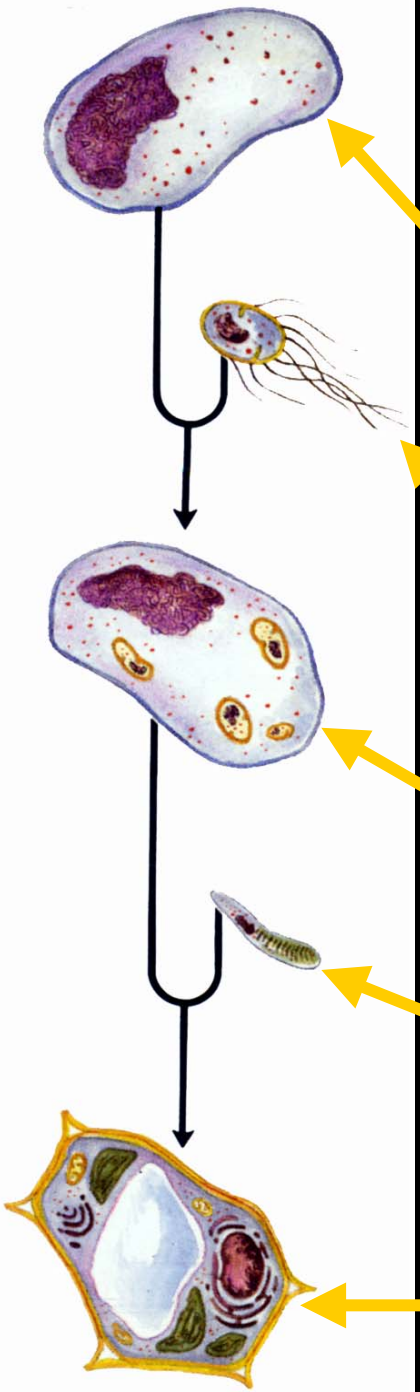


Figure 1.11: Gene expression in an animal cell.

Mitochondrien

Evolution

Endosymbionten-Theorie



anaerobe Urzelle
(anaerobe Glykolyse)

aerobes Bakterium
(oxidative Phosphorylierung)

eukaryontische Tierzelle

Cyanobakterium
(Photosynthese)

eukaryontische Pflanzenzelle

Table 1.3: The three classes of eukaryotic RNA polymerase

Class	Genes transcribed	Comments
I	28S rRNA; 18S rRNA; 5.8S rRNA	Localized in the nucleolus. A single primary transcript (45S rRNA) is cleaved to give the three rRNA classes listed
II	All genes that encode polypeptides; most snRNA genes	Polymerase II transcripts are unique in being subject to capping and polyadenylation
III	5S rRNA; tRNA genes; U6 snRNA; 7SL RNA; 7SK RNA; 7SM RNA	The promoter for some genes transcribed by RNA polymerase III (e.g. 5S rRNA, tRNA, 7SL RNA) is internal to the gene (see *Figure 1.13*) and for others (e.g. 7SK RNA) is located upstream

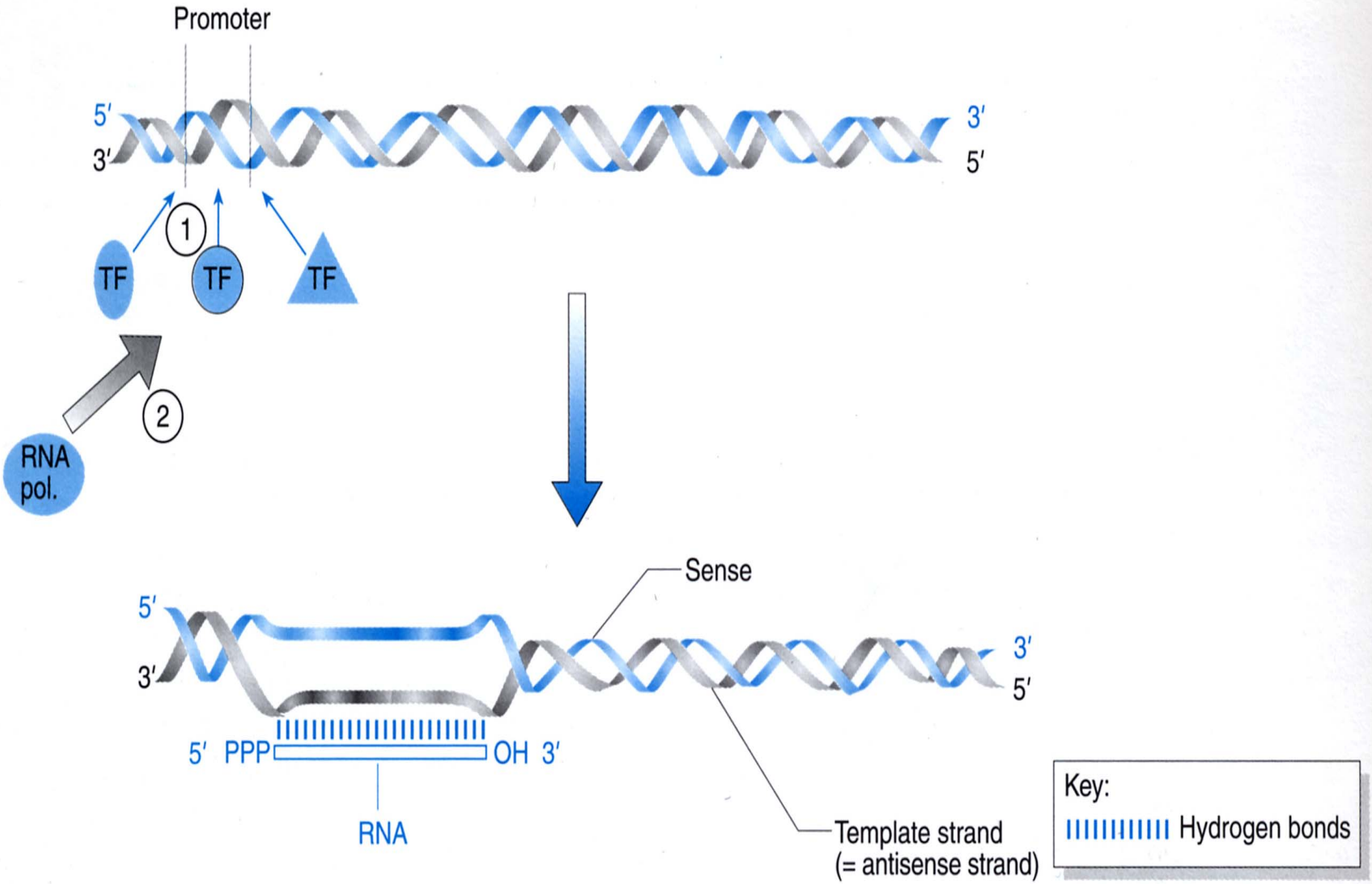


Figure 1.12: RNA is transcribed as a single strand which is complementary in base sequence to one strand (template strand) of a gene.

Table 1.4: Examples of *cis*-acting elements recognized by ubiquitous transcription factors

Cis element	DNA sequence is identical to, or a variant of	Associated *trans*-acting factors	Comments
GC box	GGGCGG	Spl	Spl factor is ubiquitous
TATA box	TATAAA	TFIID	TFIIA binds to the TFIID–TATA box complex to stabilize it
CAAT box	CCAAT	Many, e.g. C/EBP, CTF/NFI	Large family of *trans*-acting factors
CRE (cAMP response element)	GTGACGTA/CAA/G	CREB/ATF family, e.g. ATF-1	Genes activated in response to cAMP

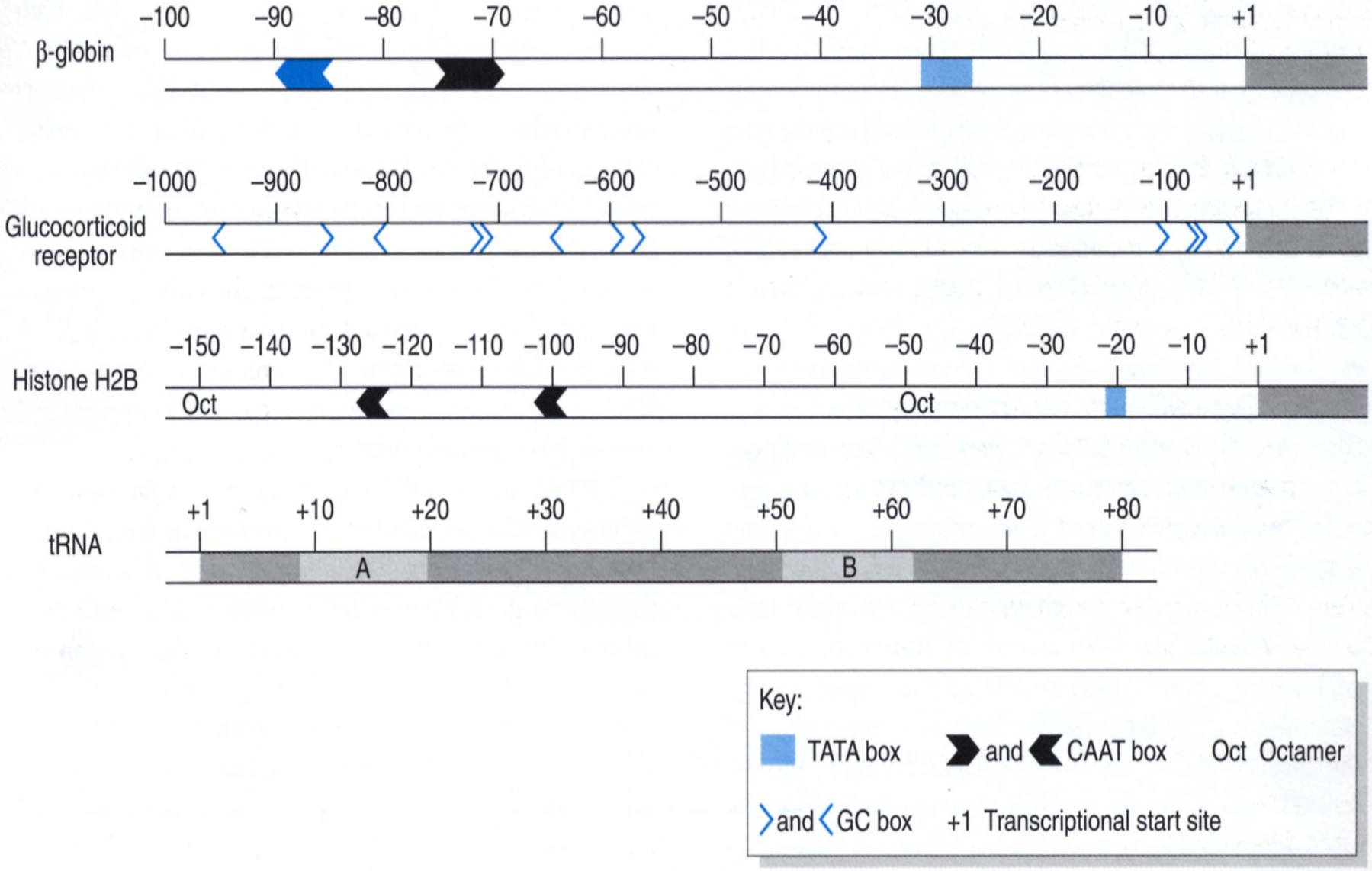


Figure 1.13: Eukaryotic promoters consist of a collection of conserved short sequence elements located at relatively constant distances from the transcription start site.

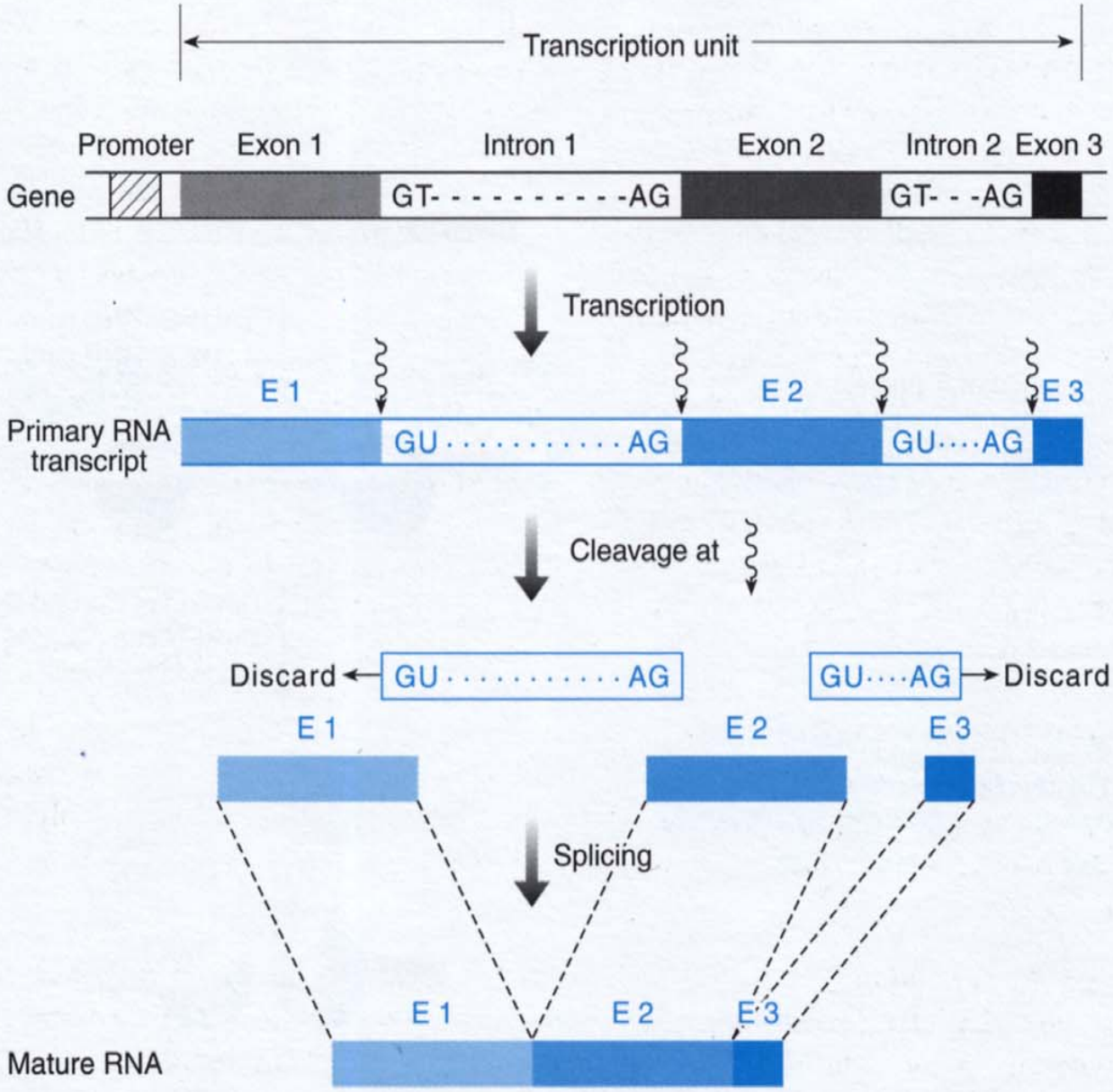


Figure 1.14: RNA splicing involves endonucleolytic cleavage and removal of intronic RNA segments and splicing of exonic RNA segments.

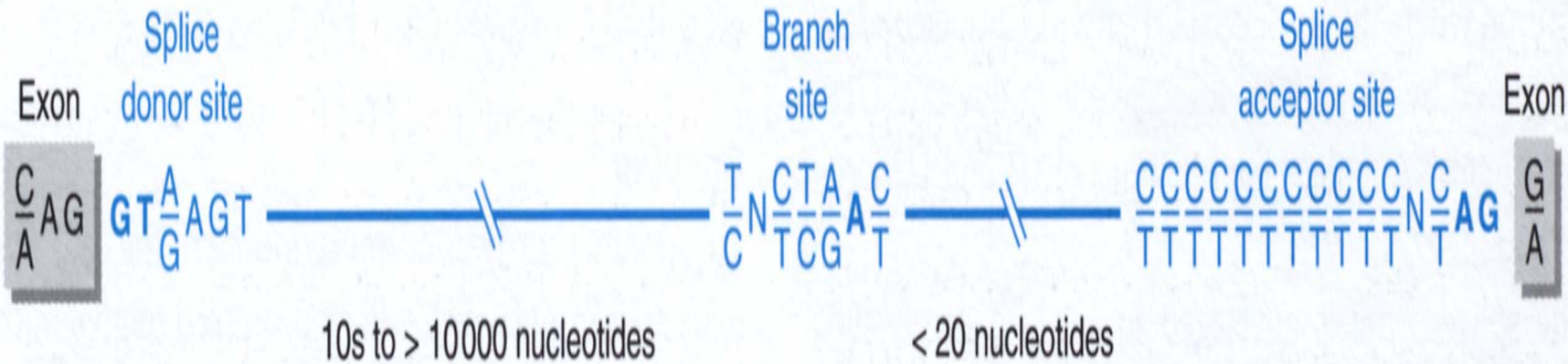


Figure 1.15: Consensus sequences at the DNA level for the splice donor, splice acceptor and branch sites in introns of complex eukaryotes.

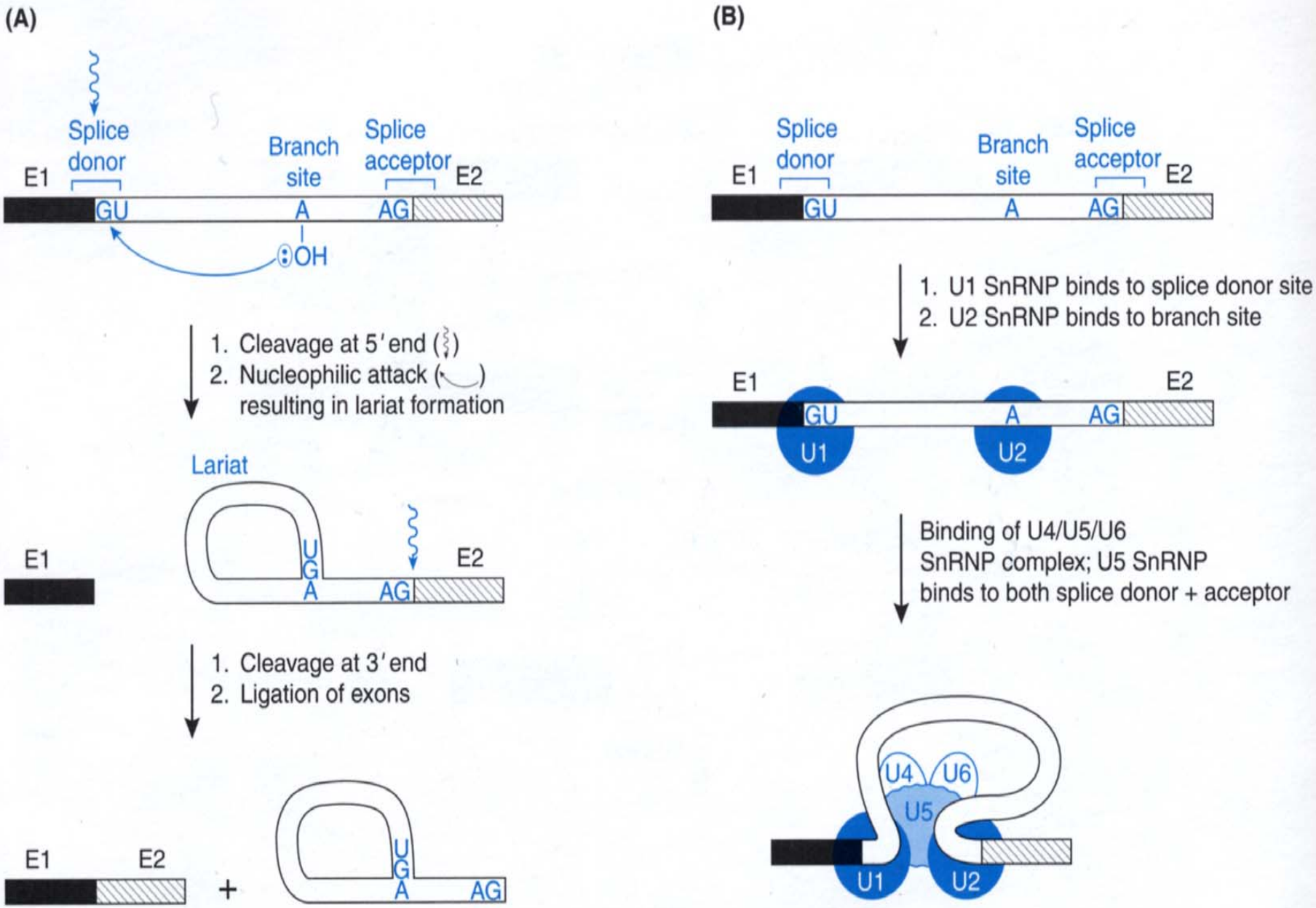


Figure 1.16: Mechanism of RNA splicing (GU–AG introns).

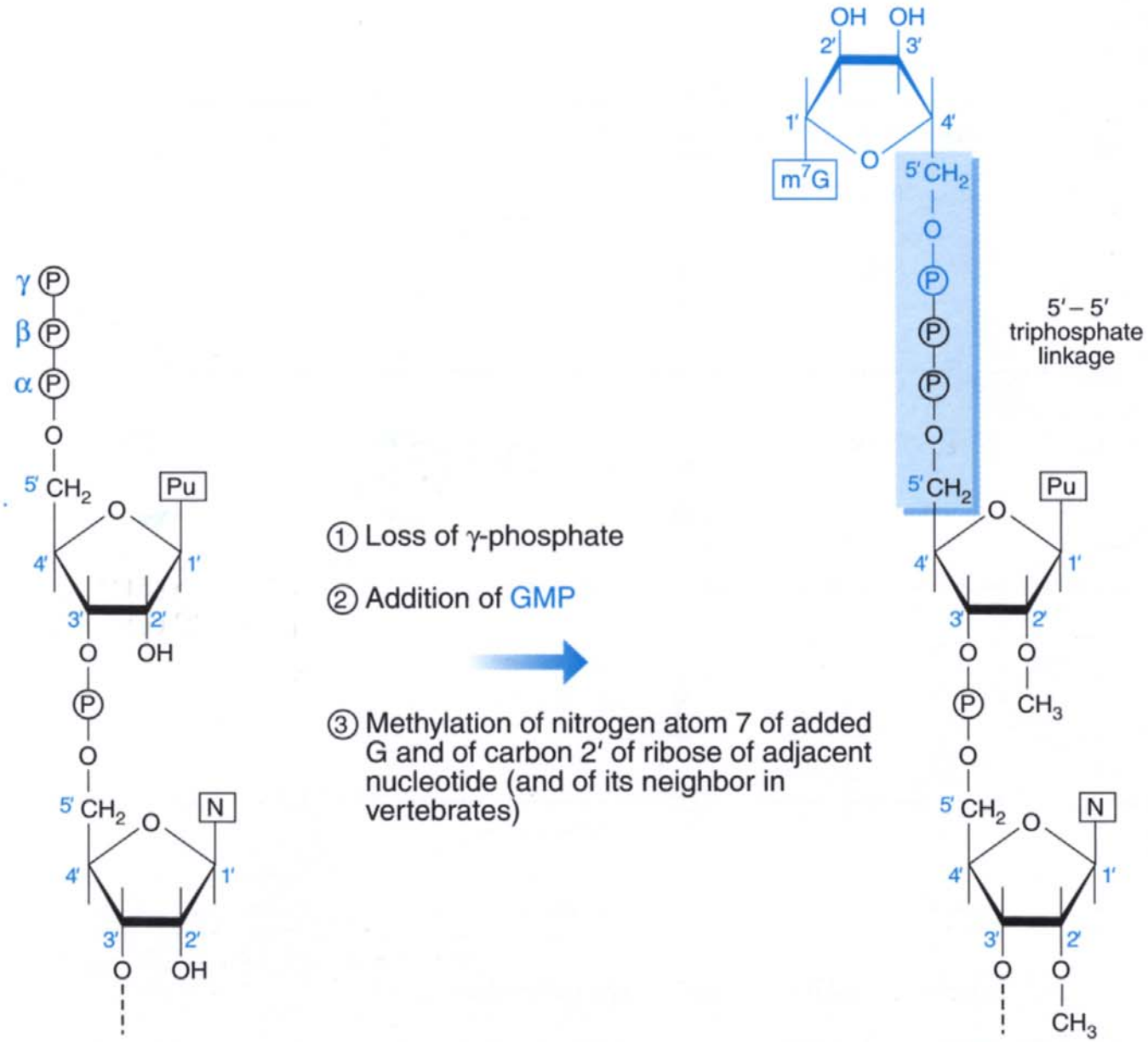


Figure 1.17: The 5′ end of eukaryotic mRNA molecules is protected by a specialized nucleotide (capping).

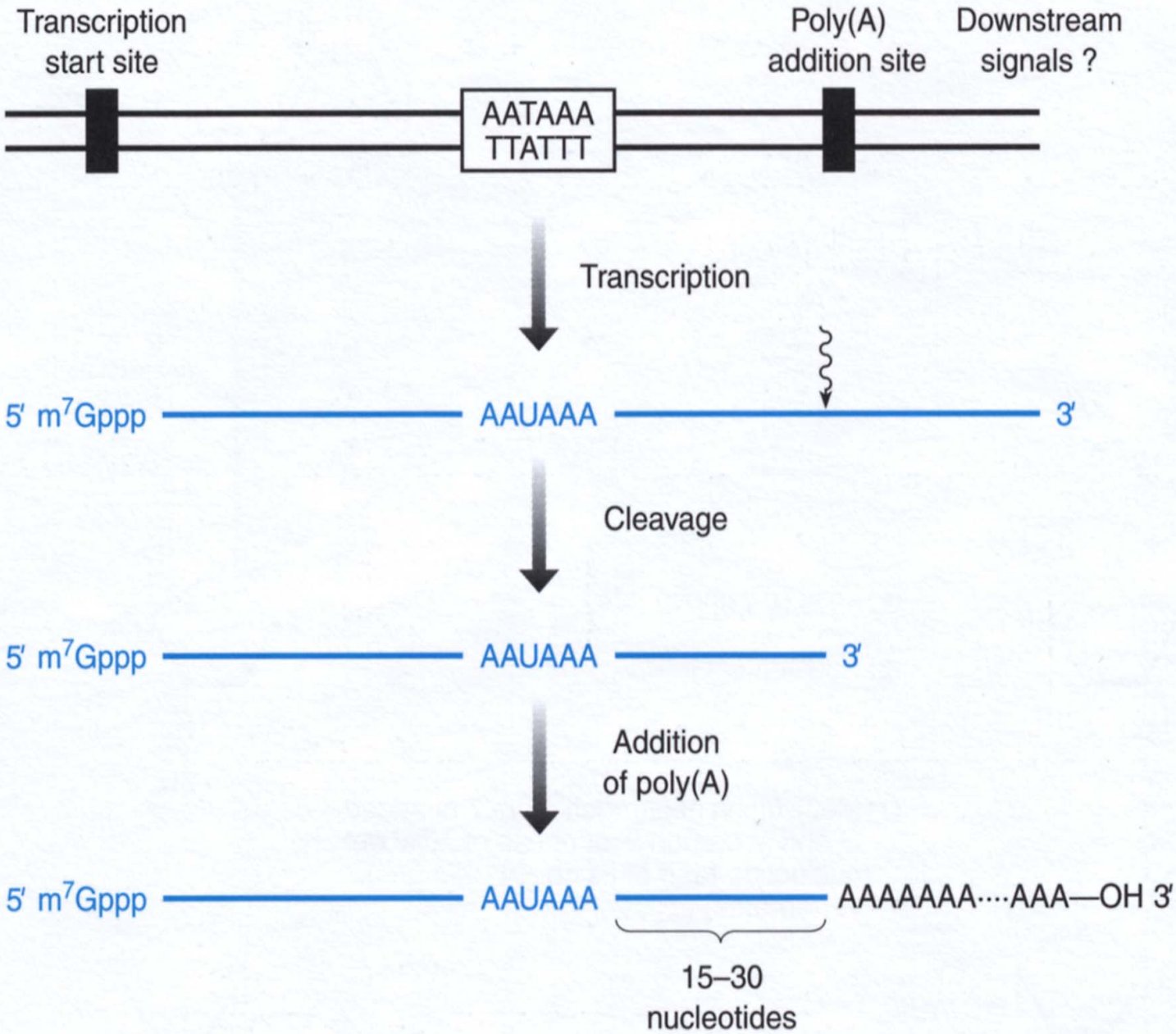


Figure 1.18: The 3′ end of most eukaryotic mRNA molecules is polyadenylated.

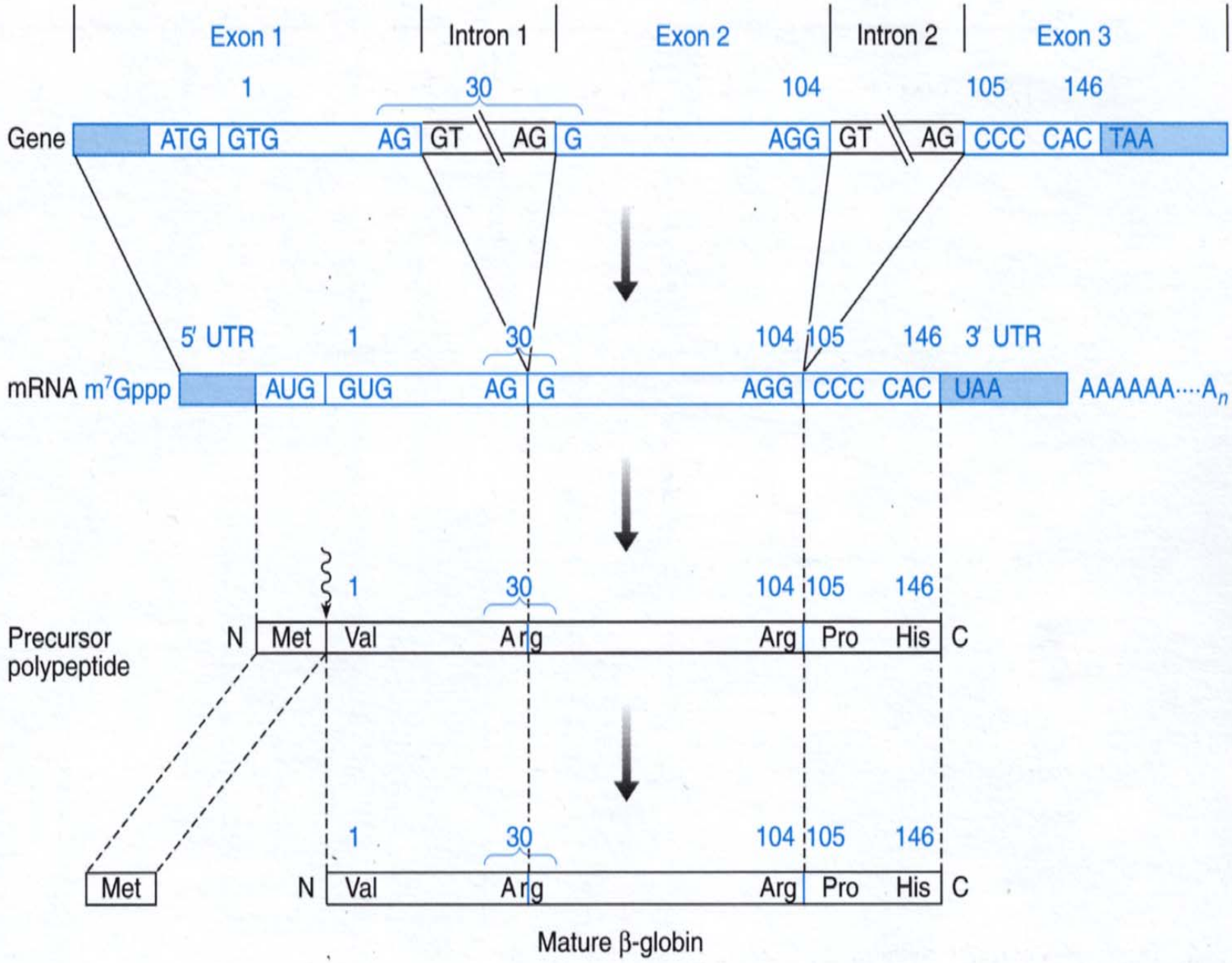


Figure 1.19: Expression of the human β-globin gene.

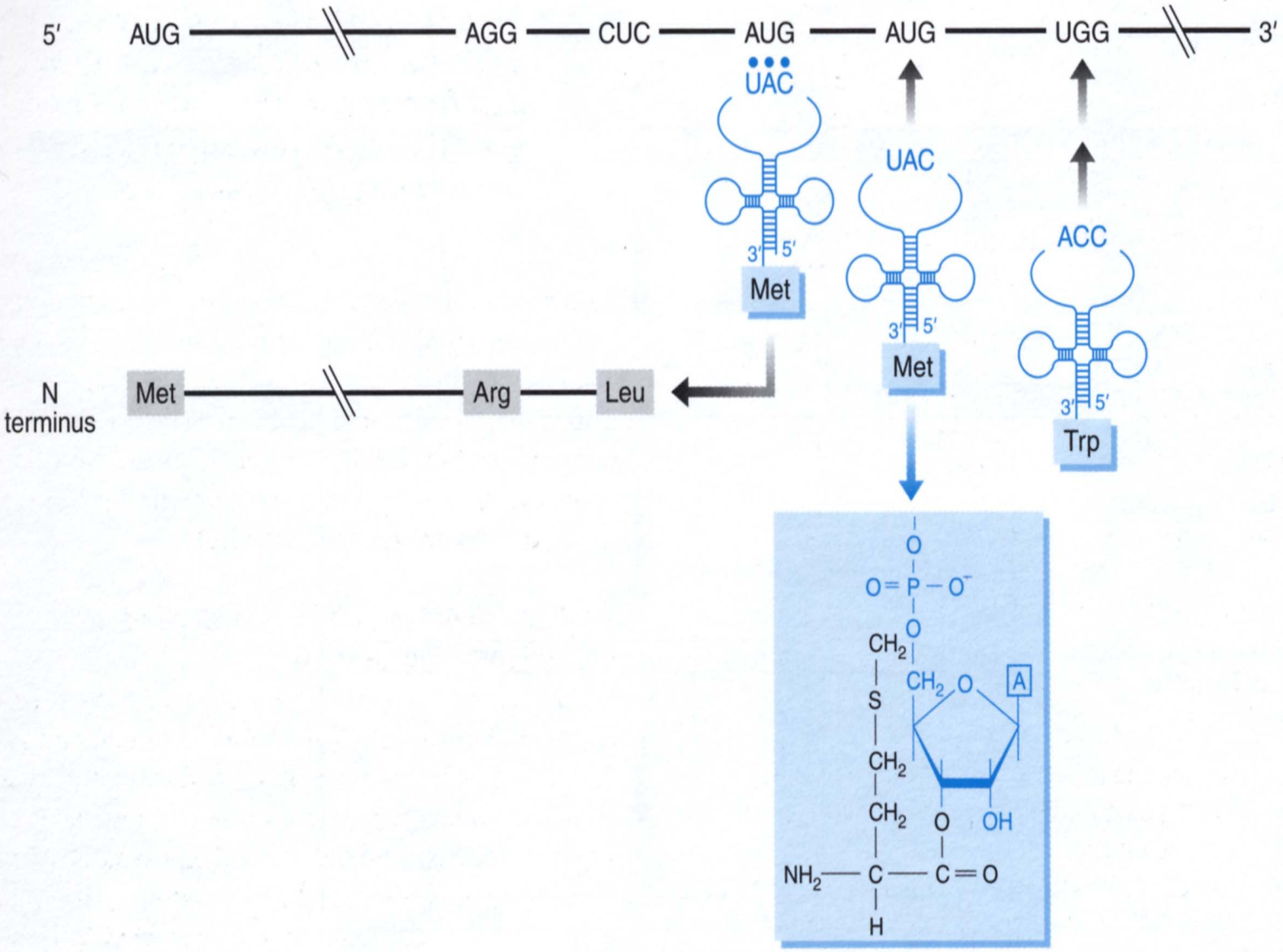


Figure 1.20: The genetic code is deciphered by codon–anticodon recognition.

Table 1.5: Codon–anticodon pairing admits relaxed base-pairing (wobbles) at the third base position of codons

Base at 5′ end of tRNA anticodon	Base recognized at 3′ end of mRNA codon
A	U only
C	G only
G	C or U
U	A or G

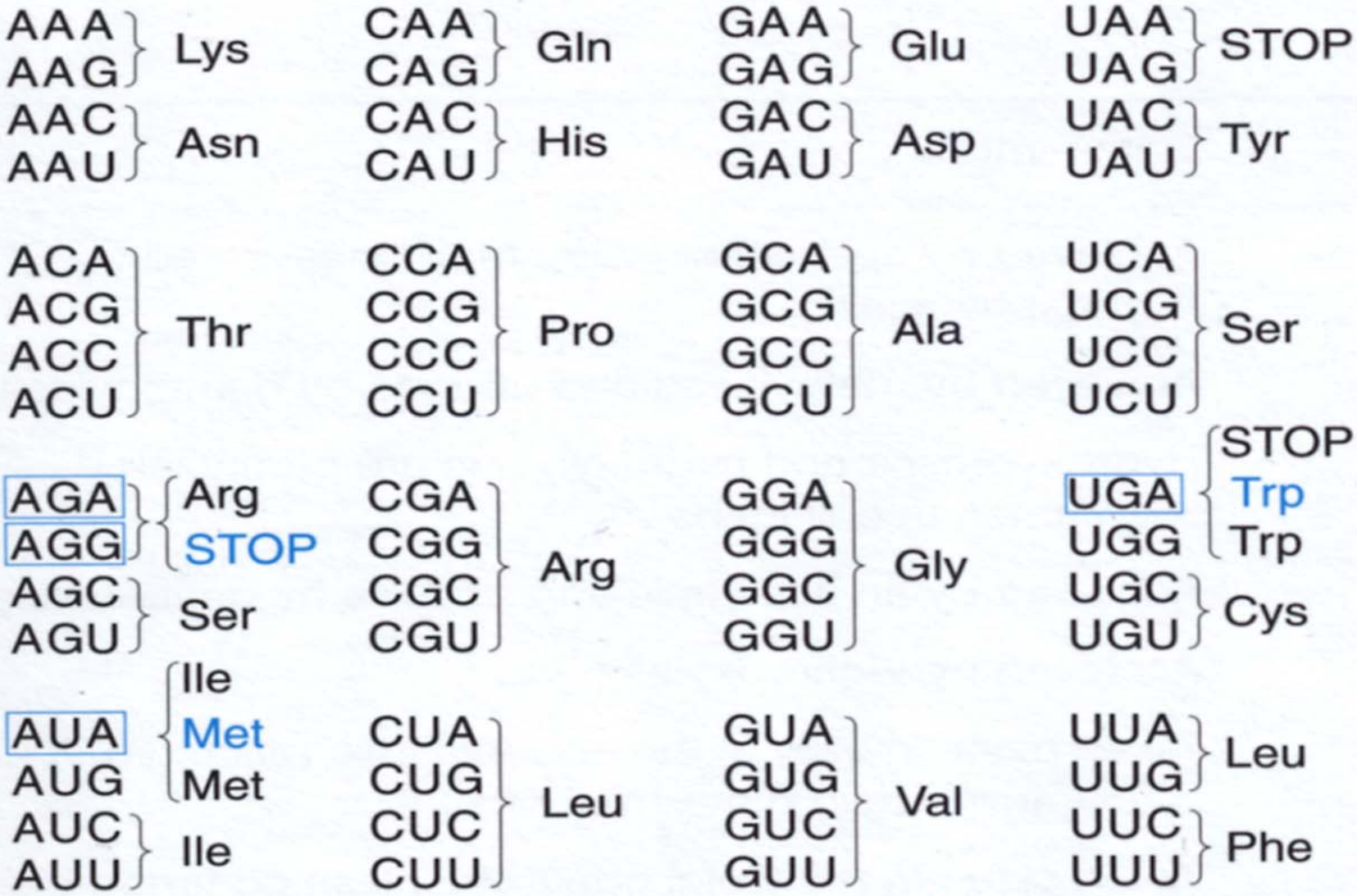


Figure 1.22: The nuclear and mitochondrial genetic codes are similiar but not identical.

Table 1.6: Major types of modification of polypeptides

Type of modification (group added)	Target amino acids	Comments
Phosphorylation (PO_4^-)	Tyrosine, serine, threonine	Achieved by specific kinases. May be reversed by phosphatases
Methylation (CH_3)	Lysine	Achieved by methylases and undone by demethylases
Hydroxylation (OH)	Proline, lysine, aspartic acid	Hydroxyproline and hydroxylysine are particularly common in collagens
Acetylation (CH_3CO)	Lysine	Achieved by an acetylase and undone by deacetylase
Carboxylation (COOH)	Glutamate	Achieved by γ-carboxylase
N-glycosylation (complex carbohydrate)	Asparagine, usually in the sequence: **Asn**–X–Ser/Thr	Takes place initially in the endoplasmic reticulum; X is any amino acid other than proline
O-glycosylation (complex carbohydrate)	Serine, threonine, hydroxylysine	Takes place in the Golgi apparatus; less common than *N*-glycosylation
GPI (glycolipid)	Aspartate at C terminus	Serves to anchor protein to *outer* layer of plasma membrane
Myristoylation (C_{14} fatty acyl group)	Glycine at N terminus (see text)	Serves as membrane anchor
Palmitoylation (C_{16} fatty acyl group)	Cysteine to form S-palmitoyl link.	Serves as membrane anchor
Farnesylation (C_{15} prenyl group)	Cysteine at C terminus (see text)	Serves as membrane anchor
Geranylgeranylation (C_{20} prenyl group)	Cysteine at C terminus (see text)	Serves as membrane anchor

Table 1.7: Examples of protein localization sequences

Destination of protein	Location and form of signal	Examples
Endoplasmic reticulum and secretion from cell	N-terminal peptide of 20 or so amino acids; very hydrophobic	Human insulin – 24 amino acids, highly hydrophobic signal peptide: N–Met–Ala–Leu–Trp–Met–Arg–Leu–Leu–Pro–Leu–Leu–Ala–Leu–Leu–Ala–Leu–Trp–Gly–Pro–Asp–Pro–Ala–Ala–Ala
Mitochondria	N-terminal peptide; α-helix with positively charged residues on one face and hydrophobic ones on the other	Human mitochondrial aldehyde dehydrogenase – N-terminal 17 amino acids: N–Met–Leu–**Arg**–Ala–Ala–Ala–**Arg**–Phe–Gly–Pro–**Arg**–Leu–Gly–**Arg**–**Arg**–Leu–Leu
Nucleus	Internal sequence of amino acids; often a string of basic amino acids plus prolines; may be bipartite	SV40 T antigen – continuous: Pro–Pro–**Lys**–**Lys**–**Lys**–**Arg**–**Lys**–Val p53 – bipartite: **Lys**–**Arg**–Ala–Leu–Pro–Asn–Asn–Thr–Ser–Ser–Ser–Pro–Gln–Pro–**Lys**–**Lys**–**Lys**
Lysosome	Addition of mannose 6-phosphate residues	

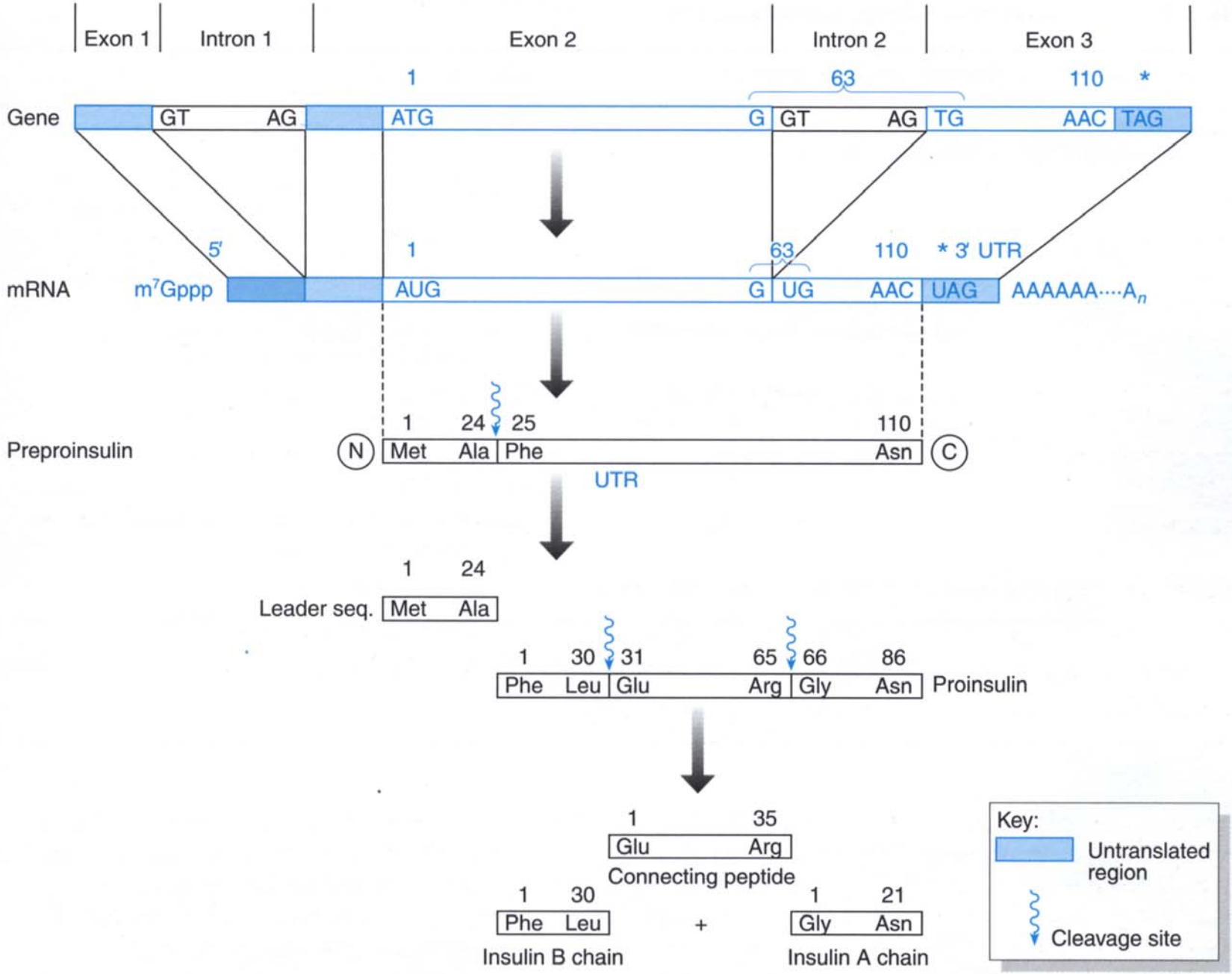


Figure 1.23: Insulin synthesis involves multiple post-translational cleavages of polypeptide precursors.

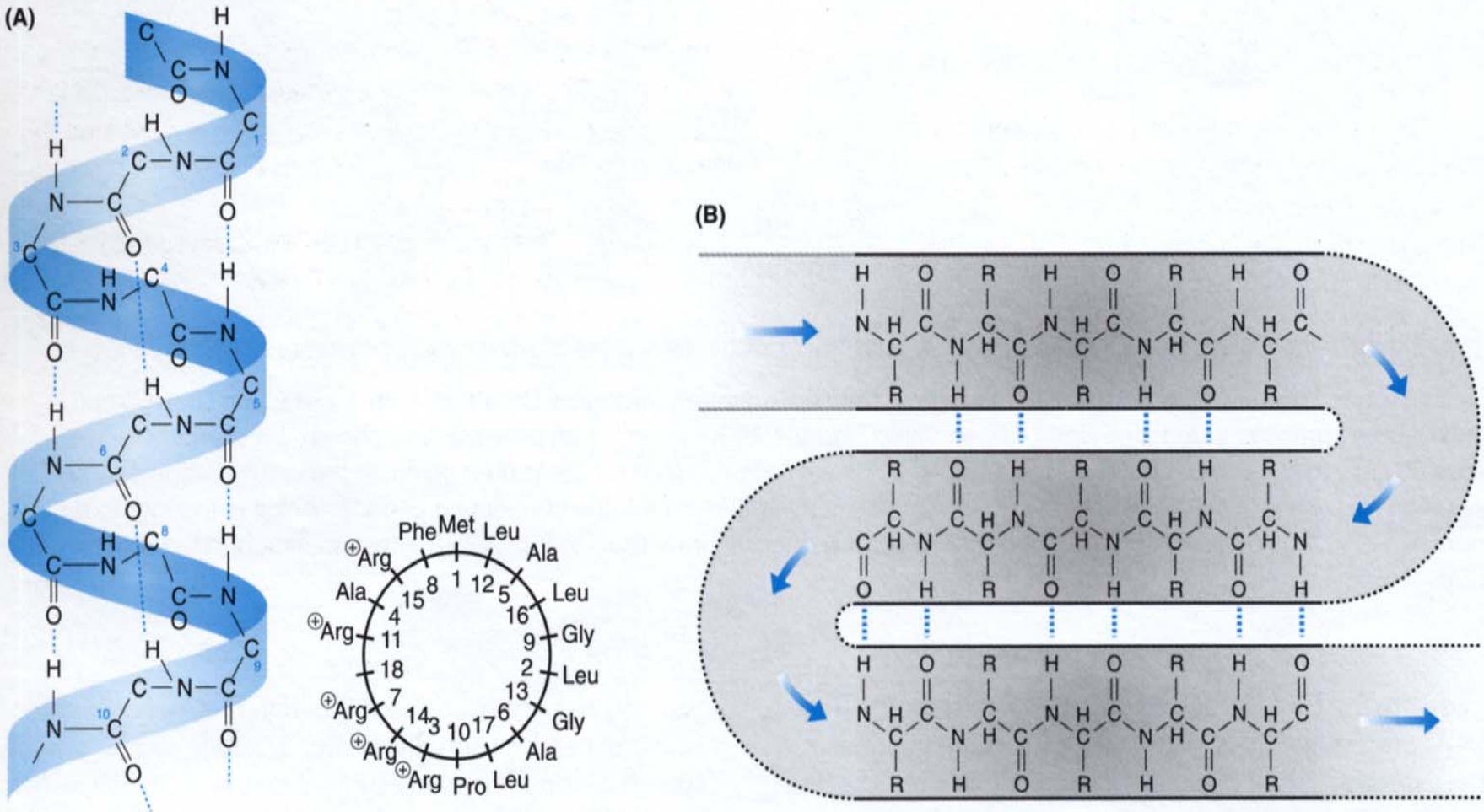


Figure 1.24: Regions of secondary structure in polypeptides are often dominated by intrachain hydrogen bonding.

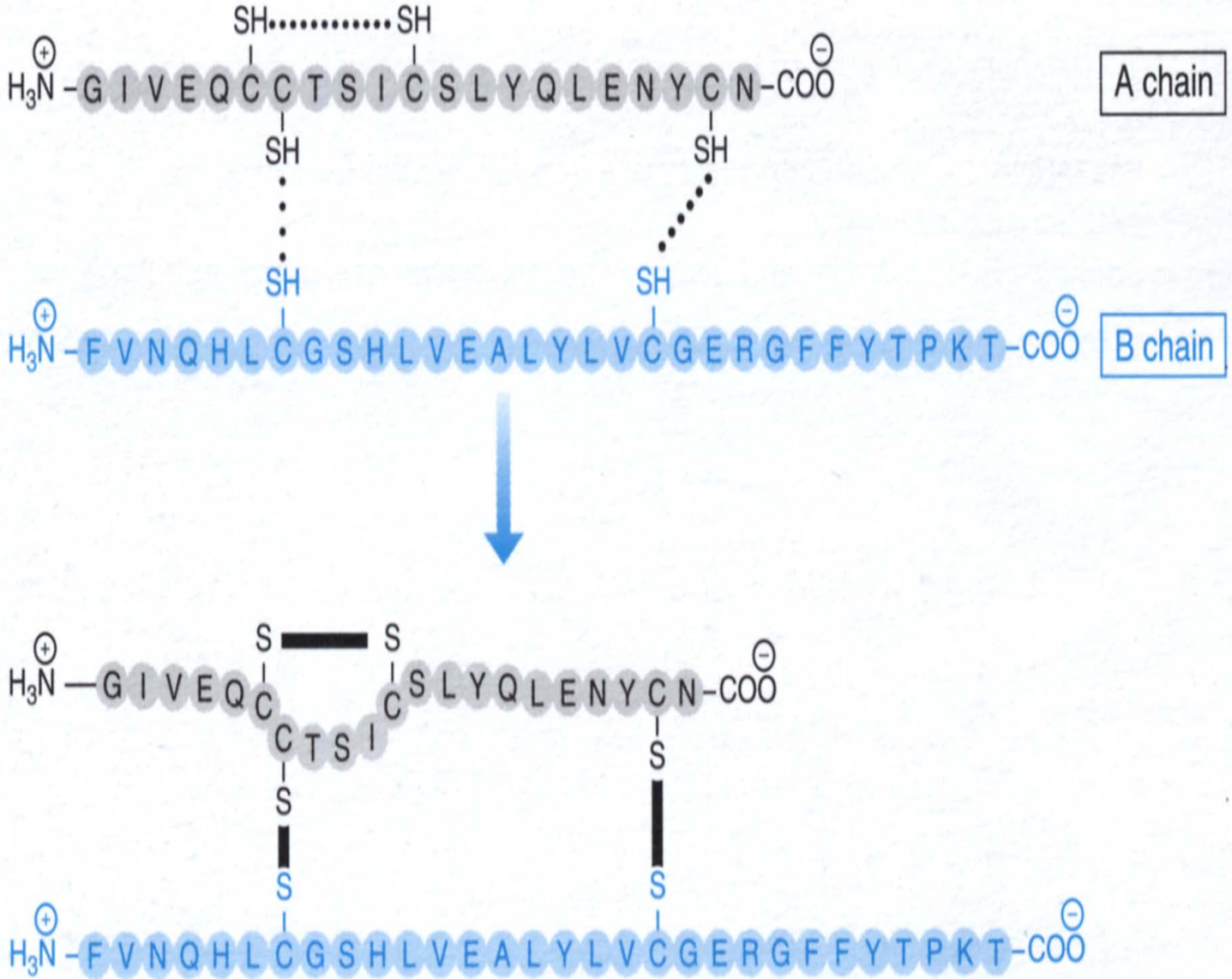


Figure 1.25: Intrachain and interchain disulfide bridges in human insulin.

Table 1.8: Levels of protein structure

Level	Definition	Comment
Primary	The linear sequence of amino acids in a polypeptide	Can vary enormously in length from a small peptide to thousands of amino acids long
Secondary	The path that a polypeptide backbone follows in space	May vary locally, e.g. as α-helix or β-pleated sheet, etc.
Tertiary	The overall three-dimensional structure of a polypeptide	Can vary enormously, e.g. globular, rod-like, tube, coil, sheet, etc.
Quaternary	The overall structure of a multimeric protein, i.e. of a combination of protein subunits	Often stabilized by disulfide bridges and by binding to ligands, etc.

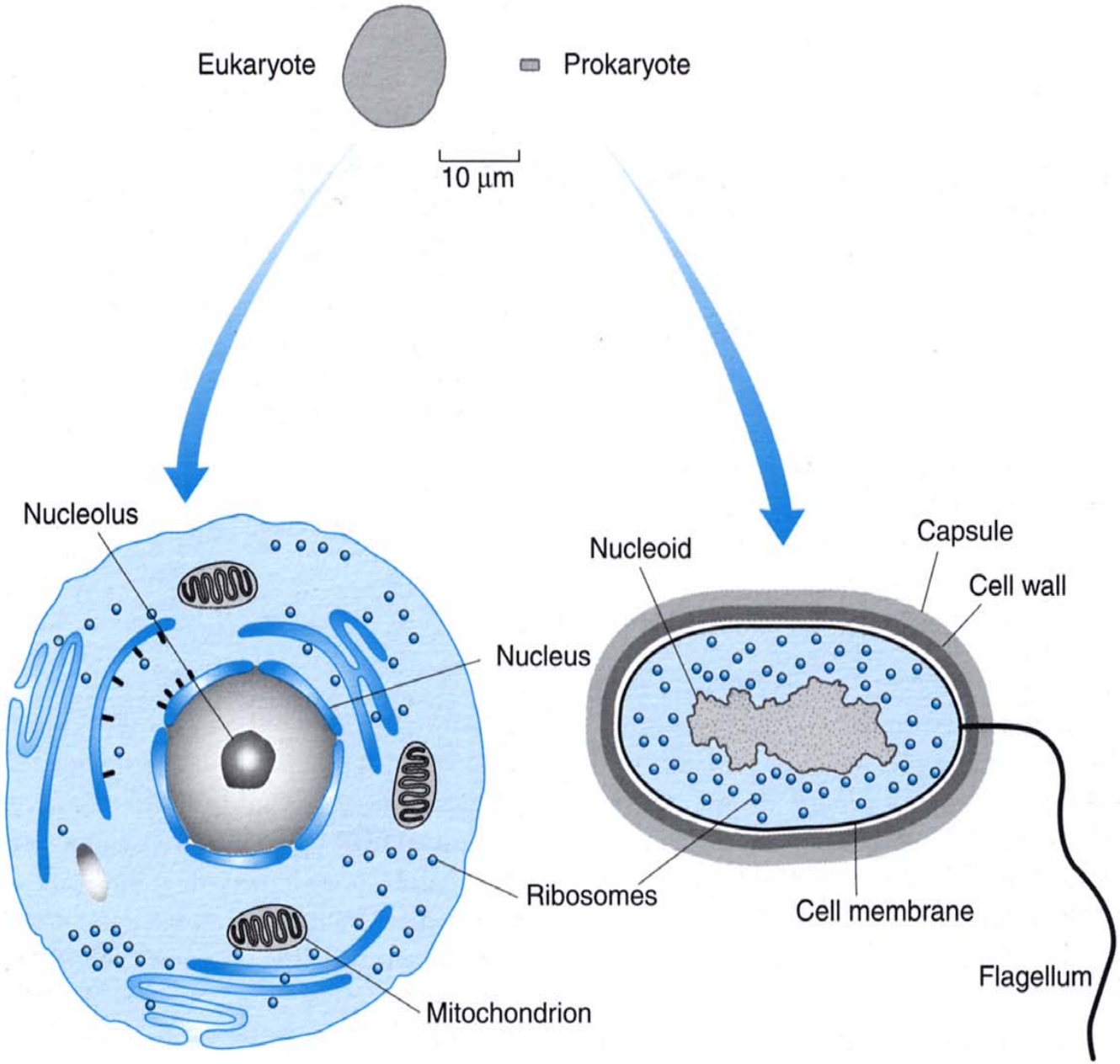


Figure 2.1: Prokaryotic and eukaryotic cell anatomy.

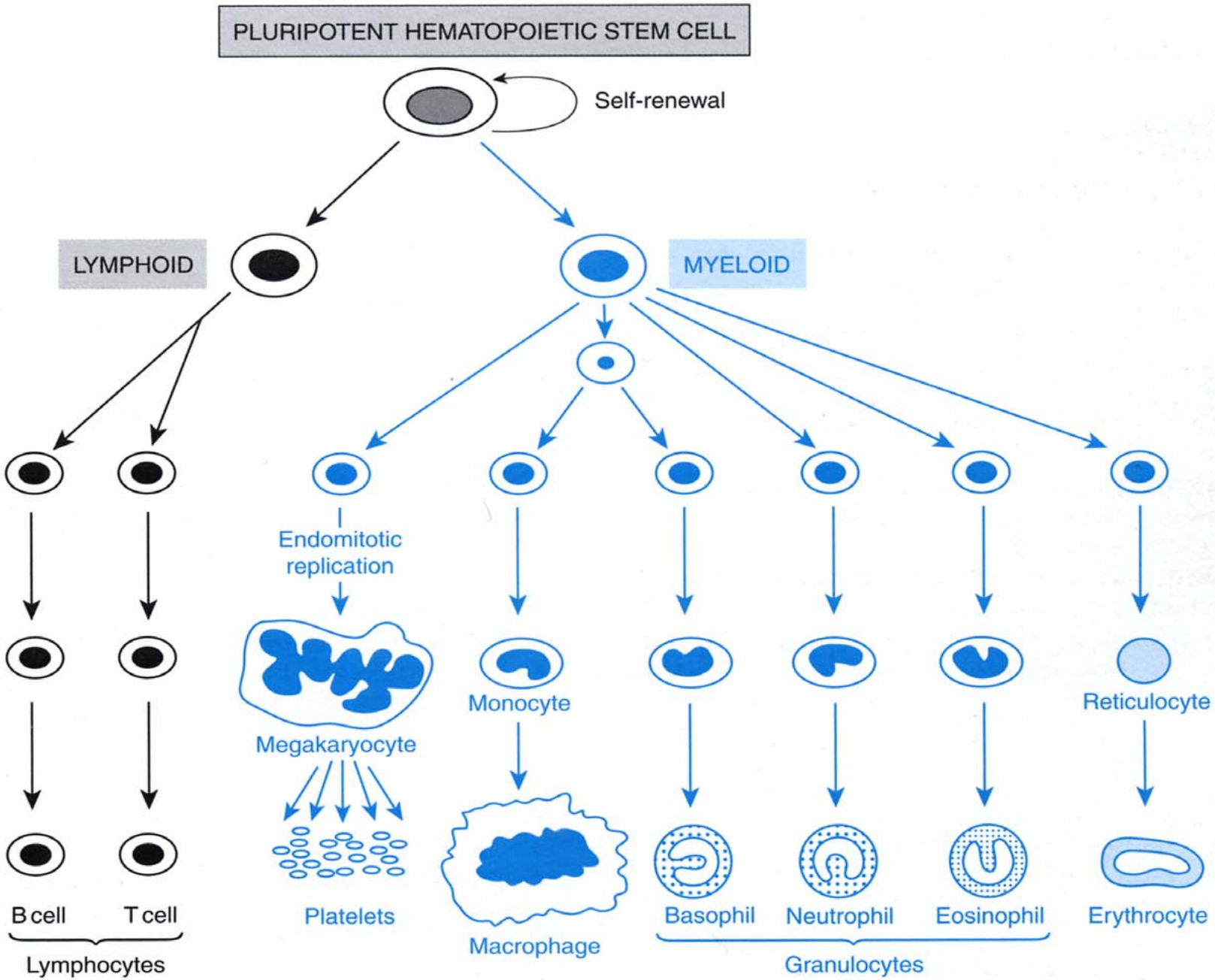
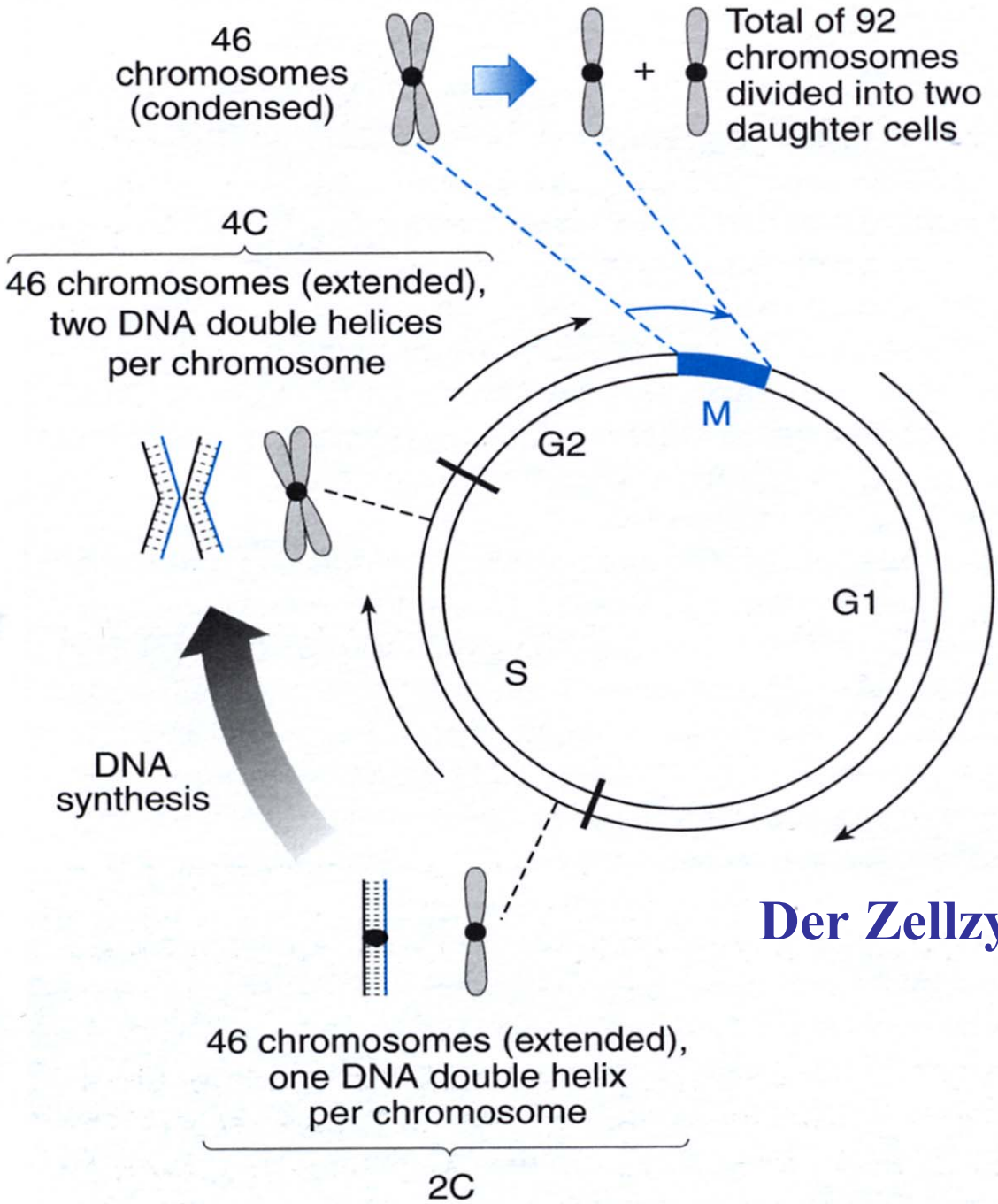


Figure 2.5: Commitment and differentiation in a cell lineage.

Table 2.1: Variation in chromosome number and genome size

Species	Haploid chromosome number	Haploid genome size (Mb)
Saccharomyces cerevisiae (yeast)	16	14
Dictyostelium discoideum (slime mold)	7	70
Caenorhabditis elegans (nematode)	11/12	100
Drosophila melanogaster (fruit fly)	4	170
Gallus domesticus (chicken)	39	1200
Mus musculus (mouse)	20	3000
Xenopus laevis (toad)	18	3000
Homo sapiens (human)	23	3000
Zea mays (maize)	10	5000
Allium cepa (onion)	8	15000



Der Zellzyklus

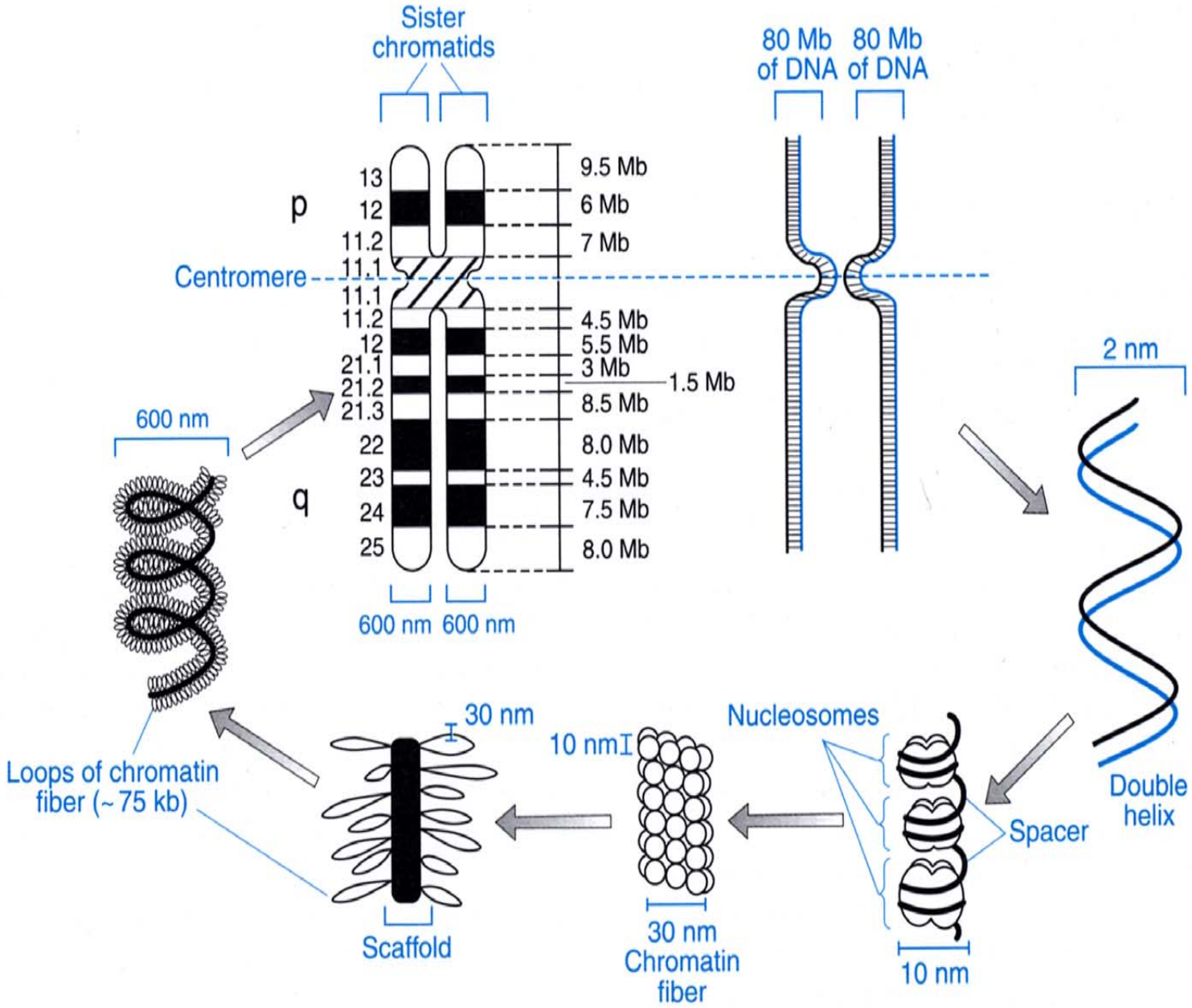


Figure 2.7: From DNA duplex to metaphase chromosome.

Centromere

TCACATGAT AGTGTACTA	80–90 bp > 90% (A+T)	TGATTTCCGAA ACTAAAGGCTT
I	II	III

Telomere

Tandem repeats based on the general formula

$(TG)_{1-3}\,TG_{2-3}/C_{2-3}\,A(CA)_{1-3}$

e.g.

5′....TGTGTGGGTGTGGTGTGTGTGG....3′
3′....ACACACCCACACCACACACACC....5′

Autonomous replicating sequence

Contains an 11-bp core consensus that is AT-rich, plus some imperfect copies of this sequence spanning an approximately 50-bp region of DNA

Imperfect copies

Core consensus =

ATTTAT(A/G)TTTA
TAAATA(T/C)AAAT

Figure 2.8: The functional elements of a yeast chromosome.

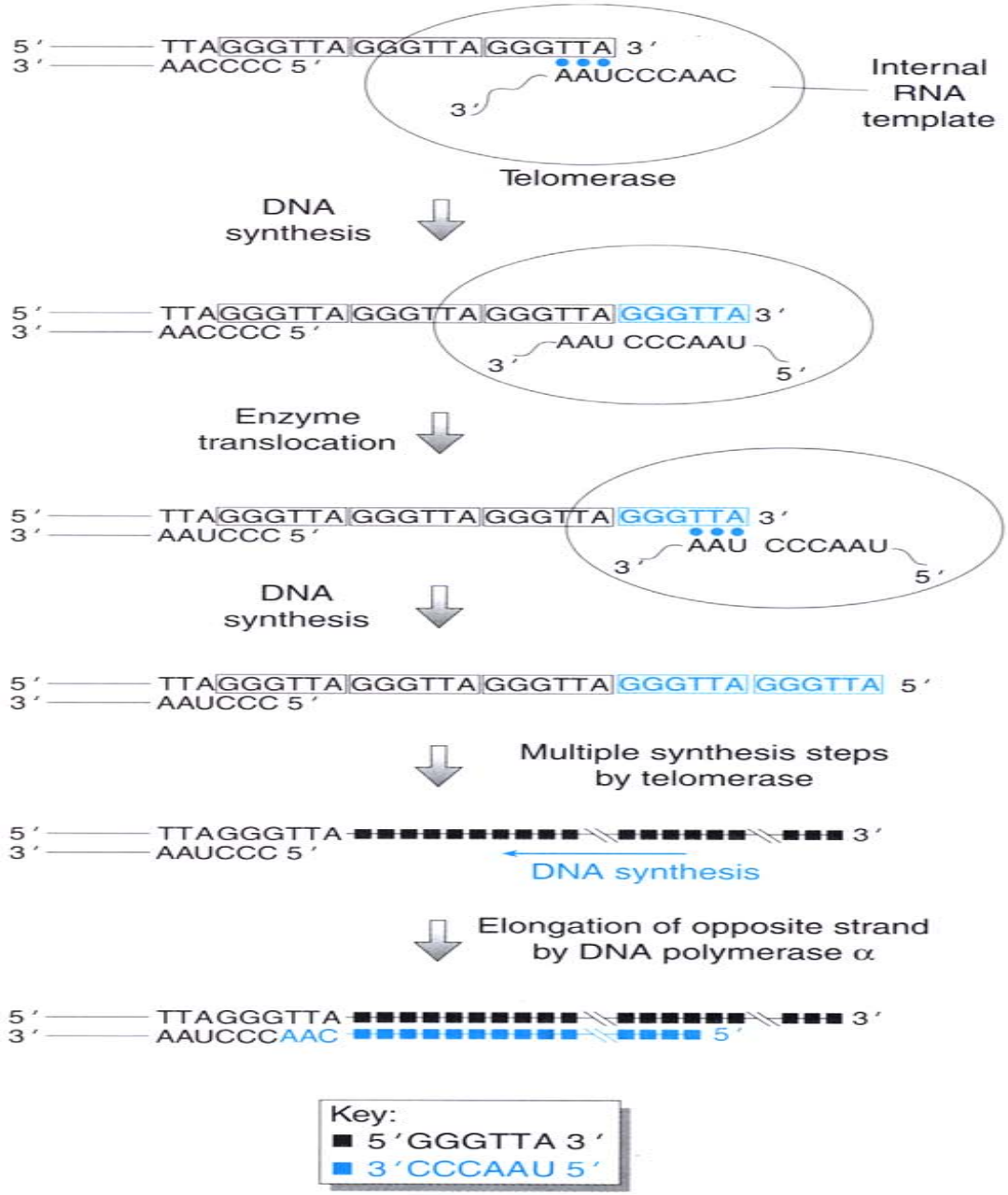


Figure 2.9: Telomerase extends the TG-rich strand of telomeres by DNA synthesis using an internal RNA template.

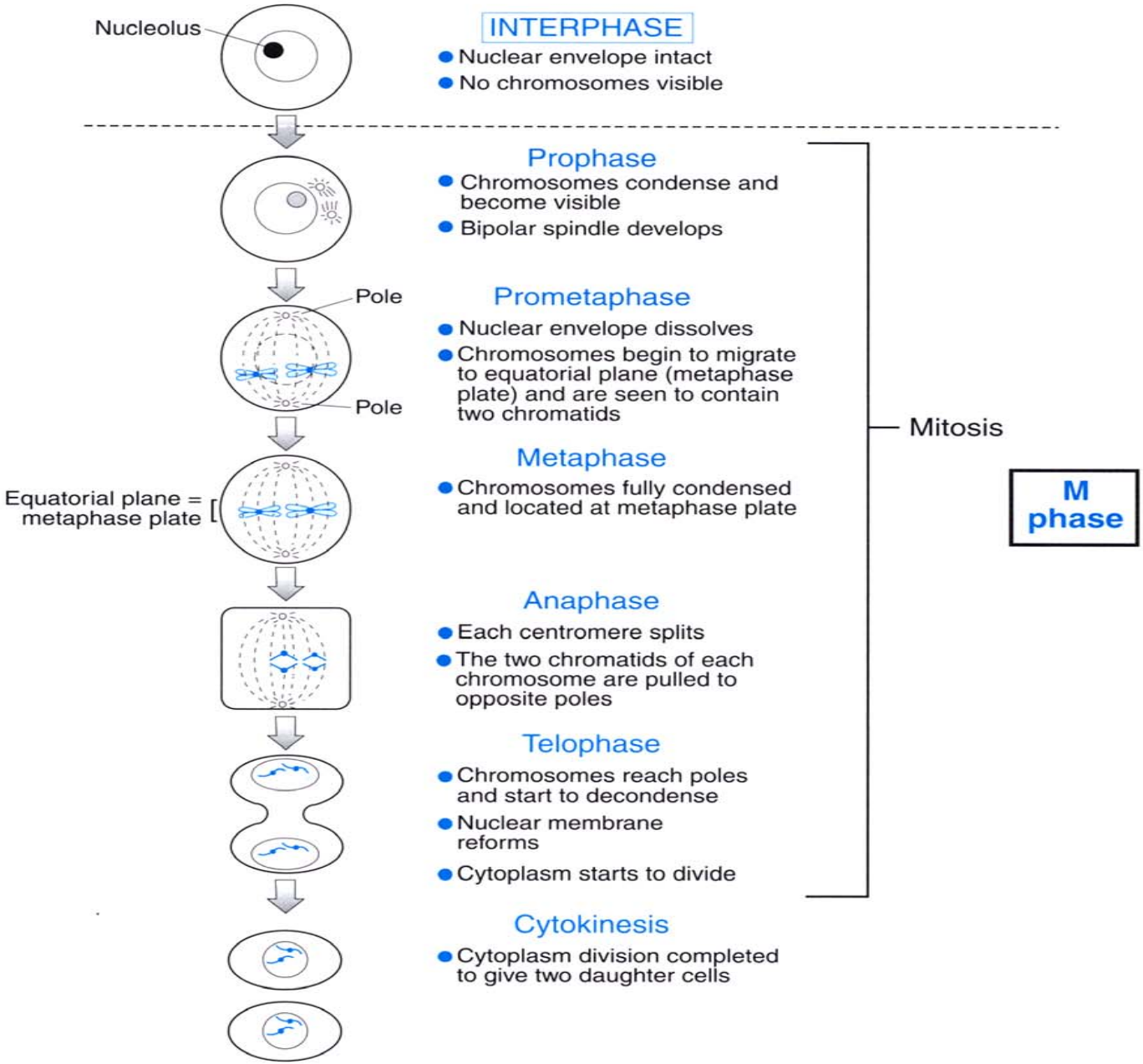


Figure 2.10: Cell division by mitosis.

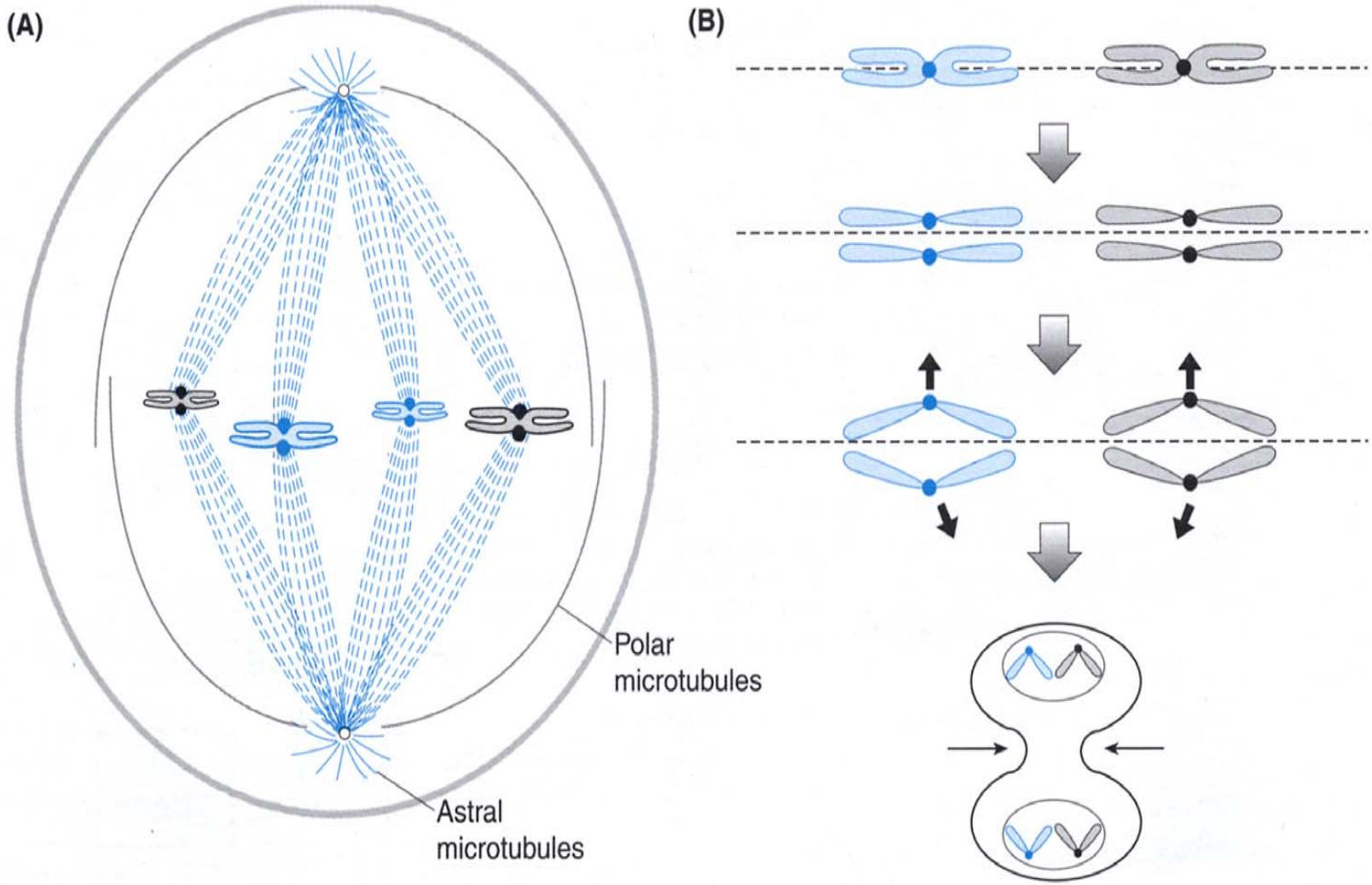


Figure 2.11: Mitosis: homologous chromosomes align independently on the metaphase plate and spindle fibers then pull the separated sister chromatids to opposite poles.

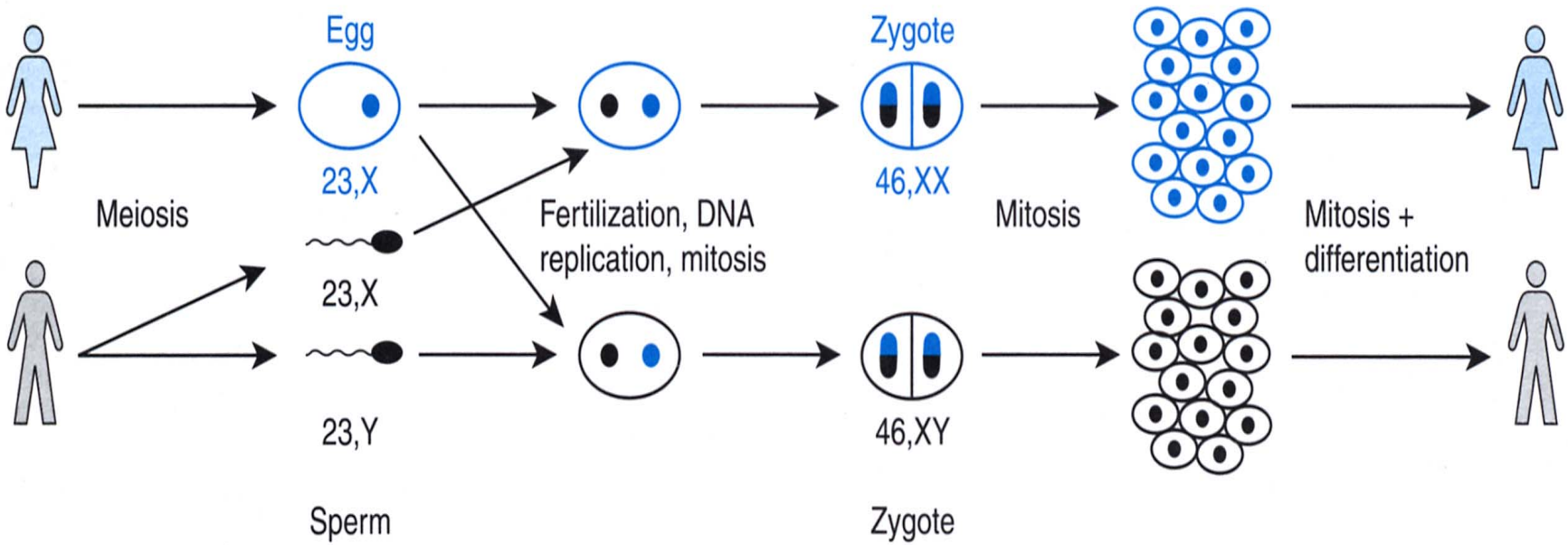


Figure 2.3: Human life, from a chromosomal viewpoint.

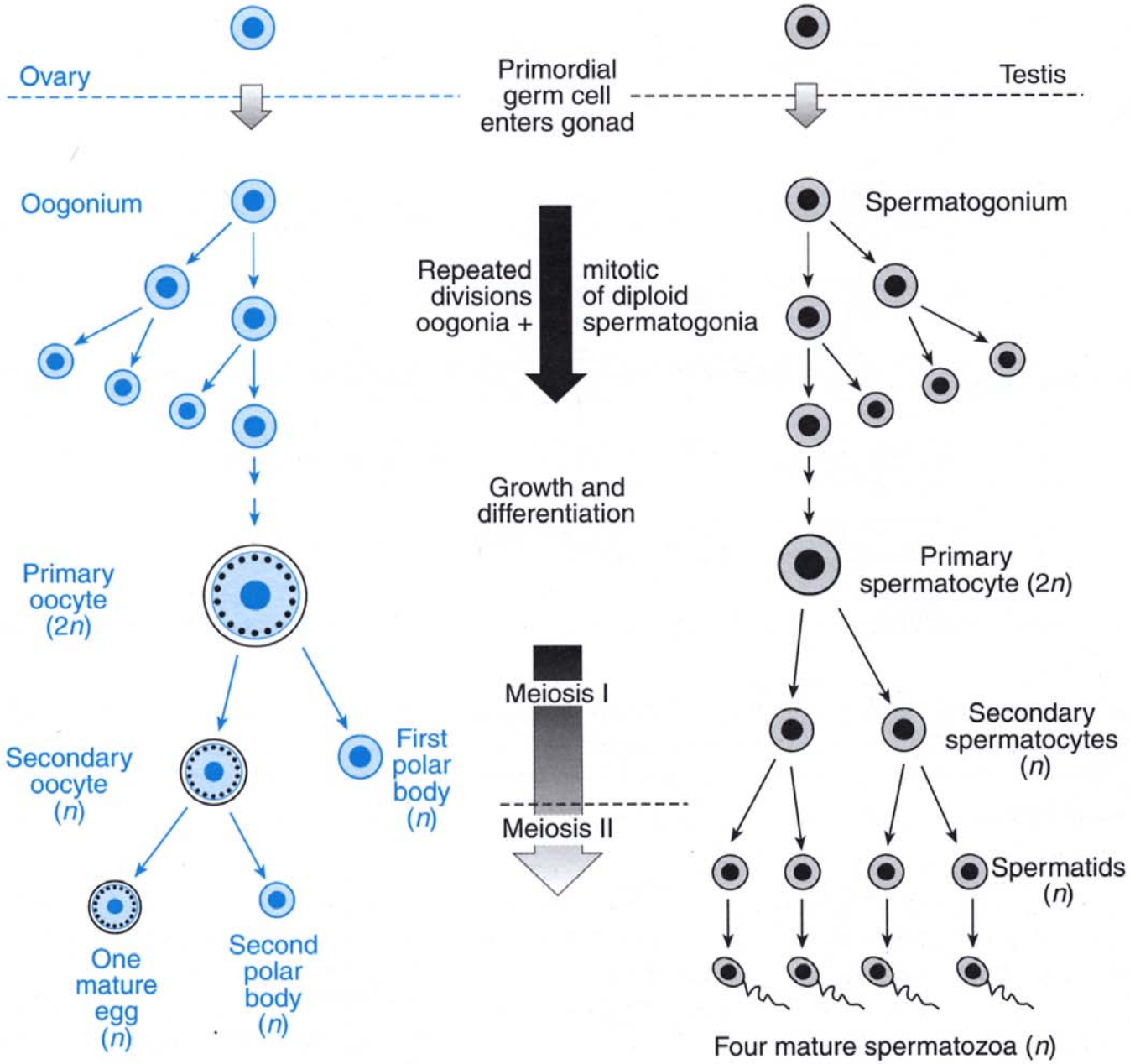


Figure 2.12: Development of the germ line.

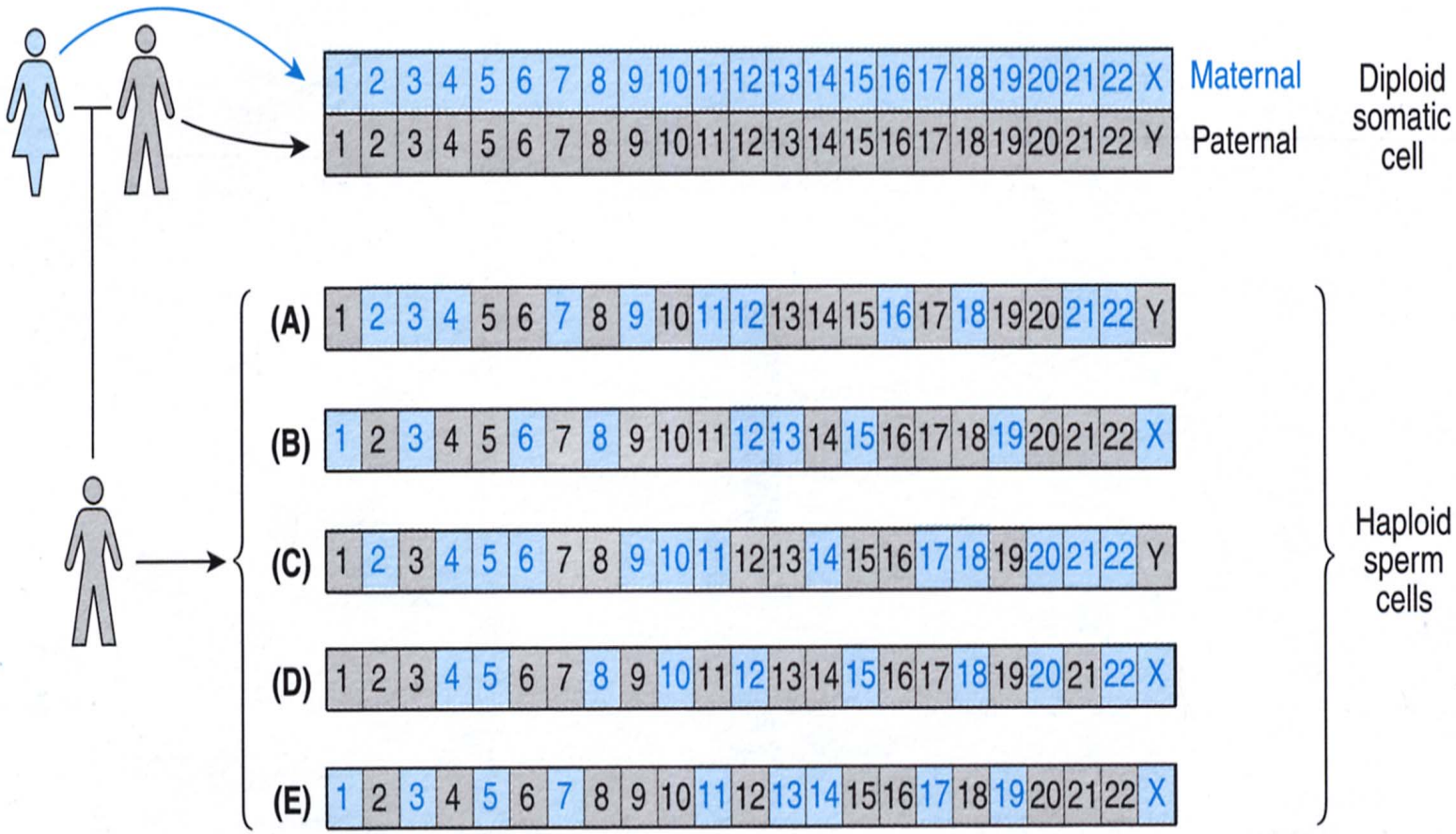
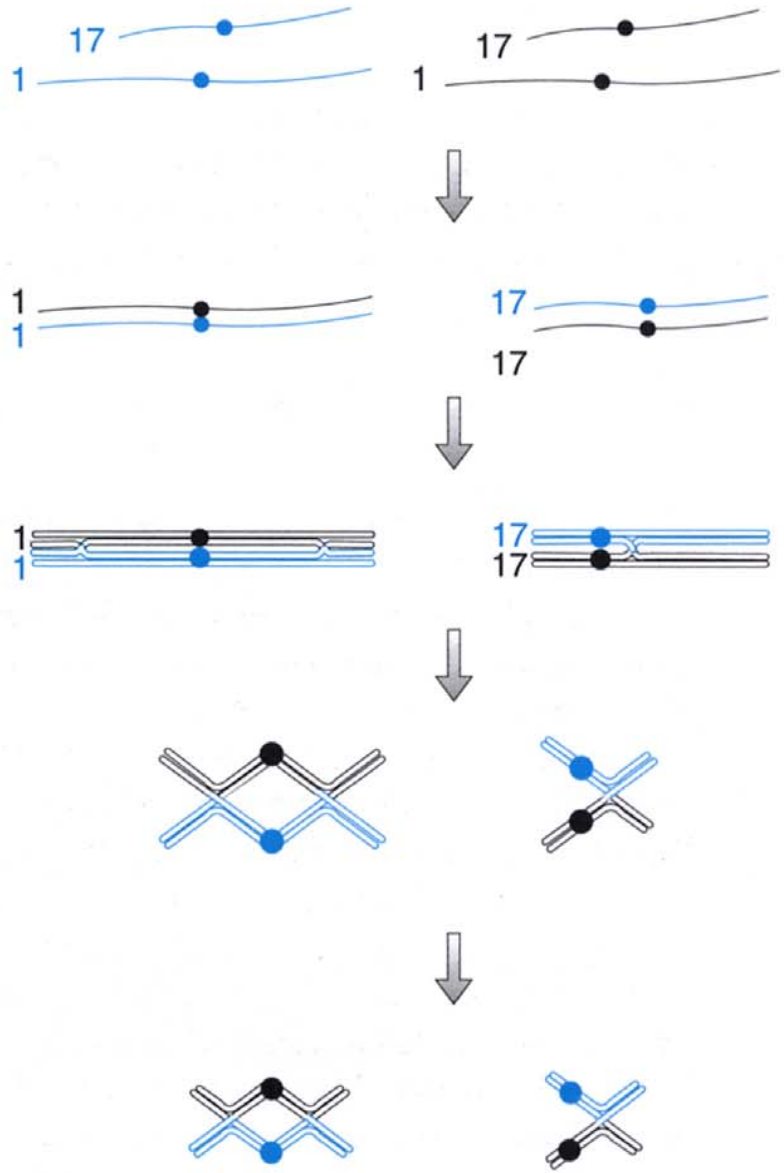


Figure 2.13: Meiosis: independent assortment of maternal and paternal homologs at meiosis I produces the first level of genetic diversity.



Leptotene

Chromosomes are unpaired fine threads consisting of two tightly bound sister chromatids

Zygotene

Maternal and paternal homologs pair together to form bivalents

Pachytene

Chromosomes thicken
Crossing-over occurs

Diplotene

Homologs separate but are held together by chiasmata

Crossovers can be counted and positions recorded

Diakinesis

Bivalents more contracted

Figure 2.14: Meiosis: the five stages of prophase in meiosis I.

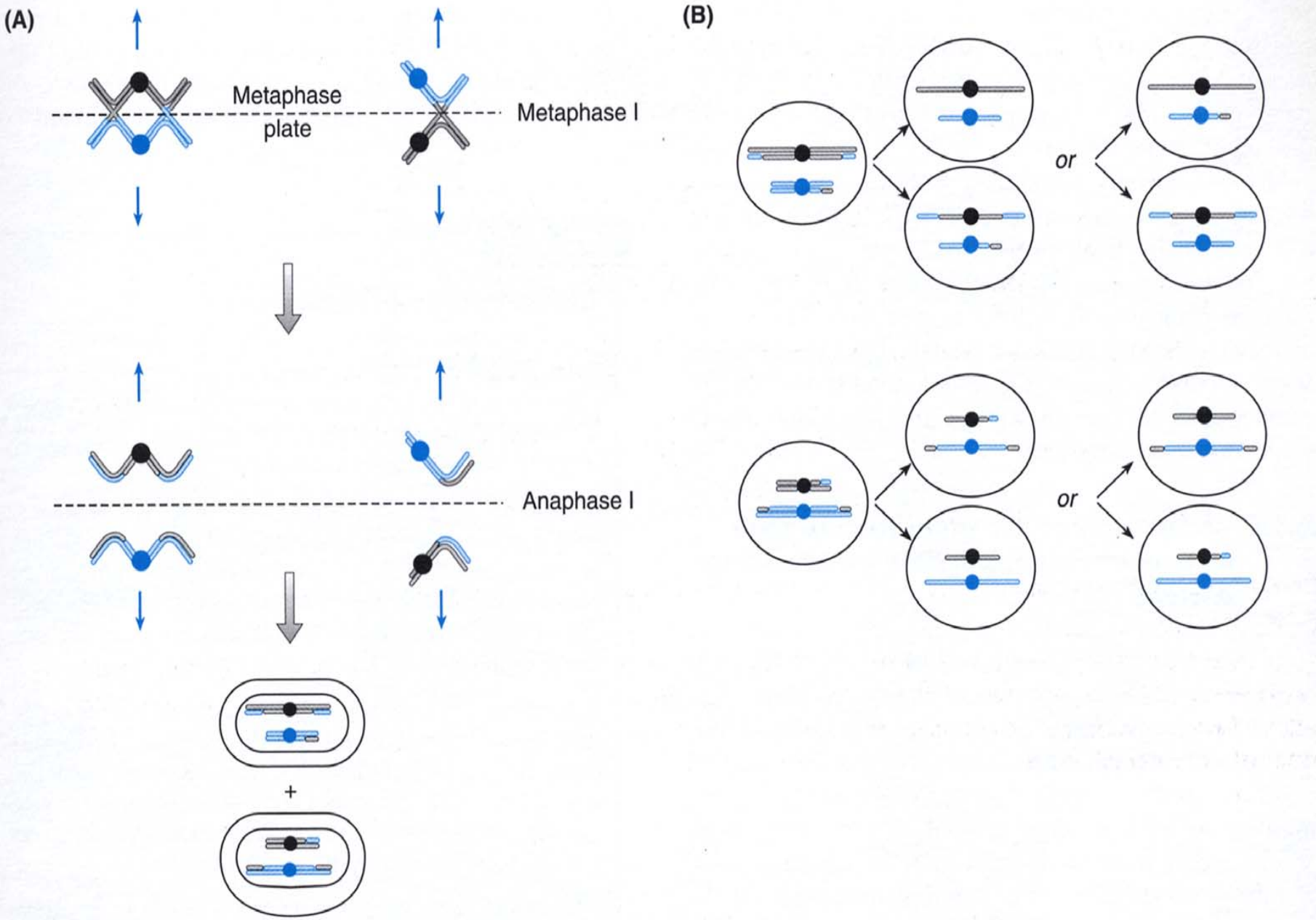


Figure 2.15: Meiosis: from metaphase I to the gametes.

Table 2.3: Human chromosome groups

Group	Chromosomes	Description
A	1–3	Largest; 1 and 3 are metacentric but 2 is submetacentric
B	4,5	Large; submetacentric with two arms very different in size
C	6–12,X	Medium size; submetacentric
D	13–15	Medium size; acrocentric with satellites
E	16–18	Small; 16 is metacentric but 17 and 18 are submetacentric
F	19,20	Small; metacentric
G	21,22,Y	Small; acrocentric, with satellites on 21 and 22 but not on the Y

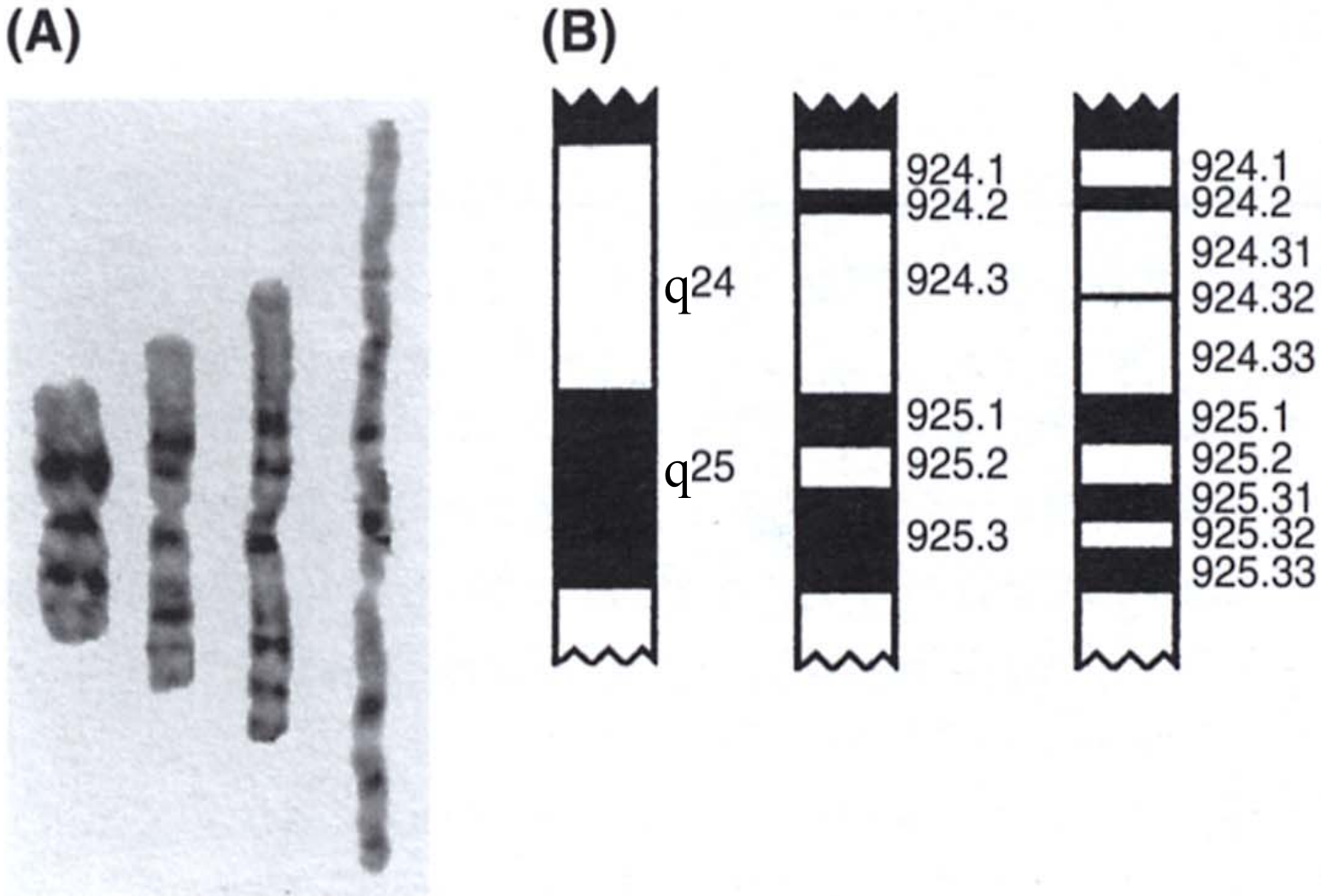


Figure 2.16: Different chromosome banding resolutions can resolve bands, sub-bands and sub-sub-bands.

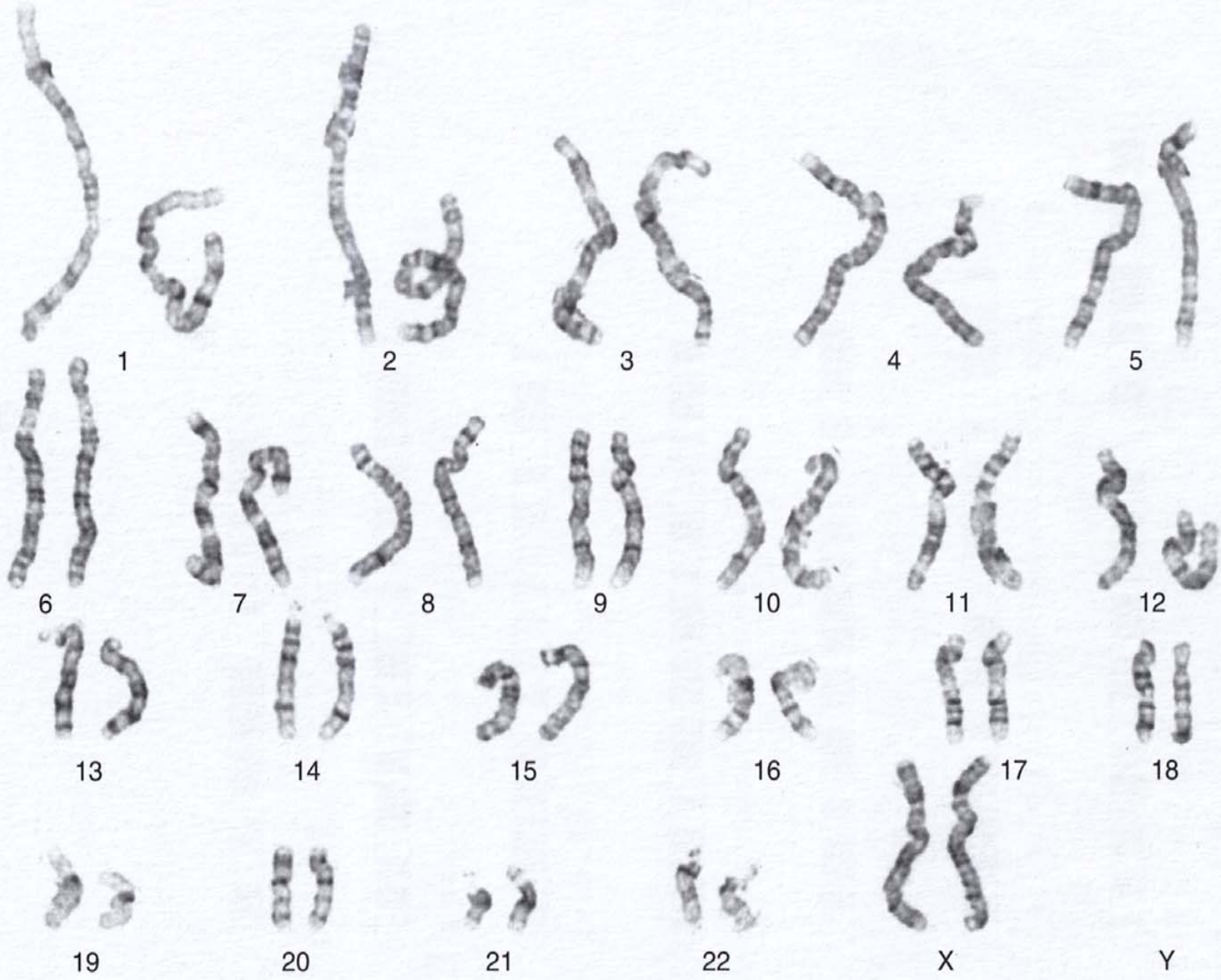


Figure 2.17: G-banded prometaphase karyogram of mitotic chromosomes from lymphocytes of a normal female.

1
2
3
4
5
6
7
X
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Y
Key:
Centromere
rDNA
Noncentromeric heterochromatin

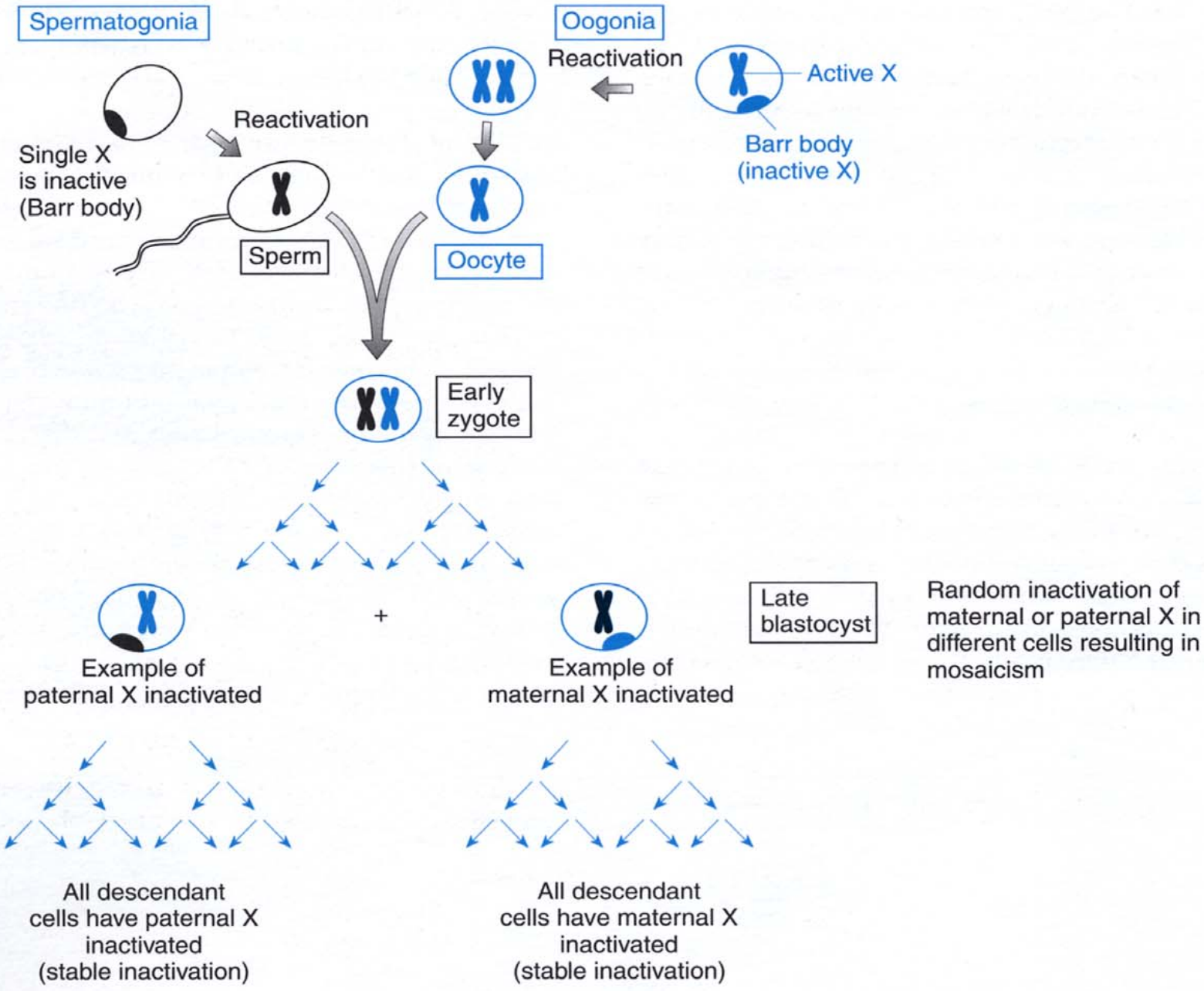


Figure 2.6: The process of X chromosome inactivation in mammals.

Table 2.4: Consequences of numerical chromosomal abnormalities

Polyploidy		
Triploidy	(69,XXX, XXY or XYY)	1–3% of all conceptions; almost never liveborn; do not survive
Aneuploidy		
Autosomes	**nullisomy** (missing a pair of homologs)	Preimplantation lethal
	monosomy (one chromosome missing)	Embryonic lethal
	trisomy (one extra chromosome)	Usually embryonic or fetal lethal
		Trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) may survive to term
		Trisomy 21 (Down syndrome) may survive to age 40 or longer
Sex chromosomes		
	XXX, XXY, XYY	Relatively minor problems, normal lifespan
	45,X	Turner syndrome – 99% abort spontaneously; survivors are of normal intelligence but infertile and show minor physical signs

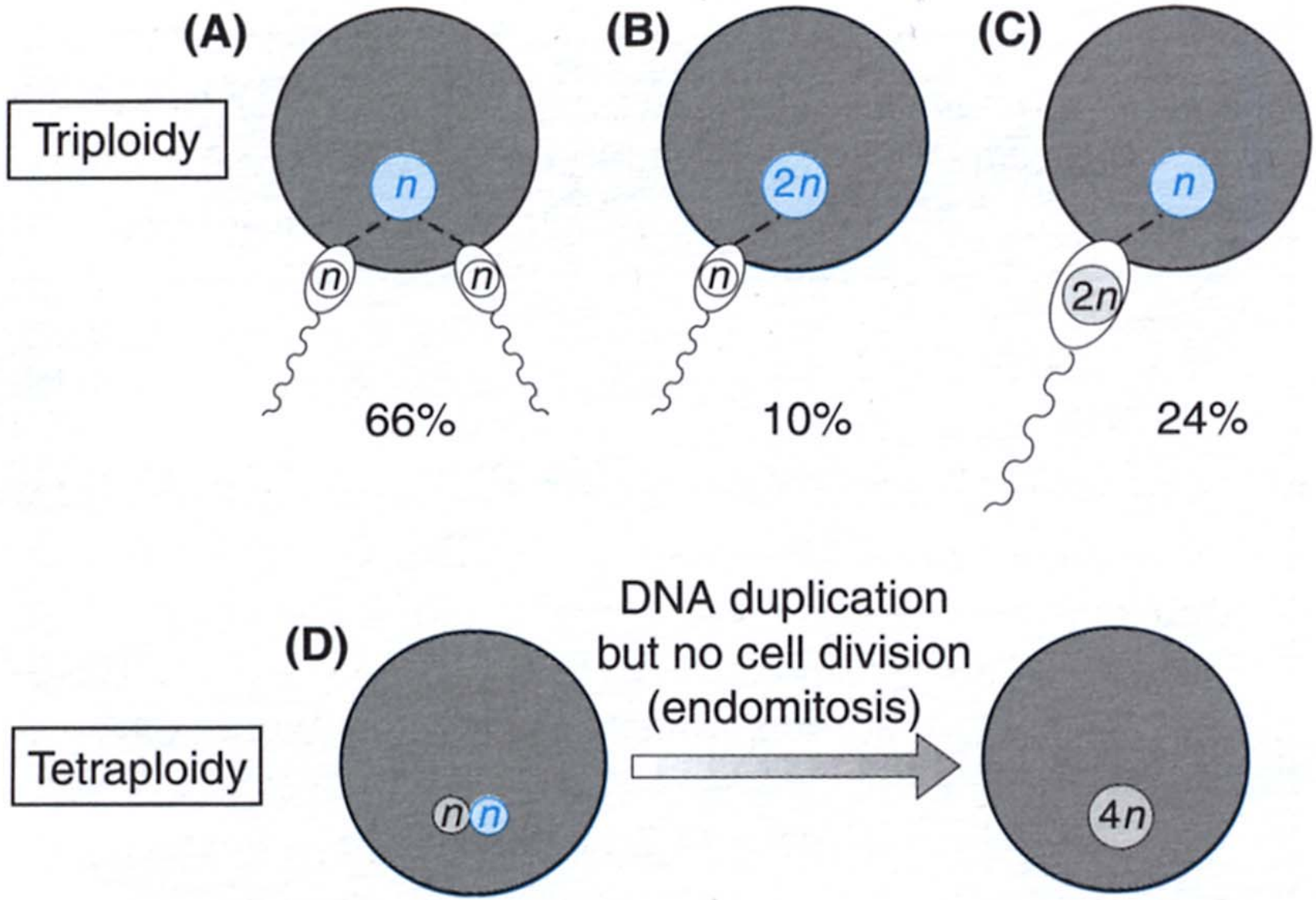


Figure 2.19: Origins of triploidy and tetraploidy.

Table 2.5: Structural abnormalities resulting from misrepair of chromosome breaks or recombination between nonhomologous chromosomes

	One chromosome involved	Two chromosomes involved
One break	Terminal deletion (healed by adding telomere)	–
Two breaks	Interstitial deletion; Inversion; Ring chromosome (*Figure 2.20*) Duplication or deletion by unequal sister-chromatid exchange (*Figure 9.7*)	Reciprocal translocation (*Figure 2.21*) Robertsonian translocation (*Figure 2.21*) Duplication or deletion by unequal recombination (*Figure 9.7*)
Three breaks	Various rearrangements, e.g. inversion with deletion, intrachromosomal insertion	Interchromosomal insertion (direct or inverted)

Entstehung von Trisomien und Monosomien:

Chromosomenfehlverteilung während der Meiose
(--> Keimzellen mit einem Chromosom zu viel oder zu wenig)

Ursache von Mosaiken (z.B. 46,XX/45, X0 = Turner-Mosaik):
- Mitotische Chromosomenfehlverteilung während der frühen Keimesentwicklung ('somatic nondisjunction')
- oder 'Reparaturversuch' eines meiotischen Fehlers (Verlust eines überzähligen Chromosoms in einem Teil der Körperzellen bei Trisomie)

Sonderfall 'uniparentale Disomie': euploider Karyotyp (z.B. 46,XX), beide Chromosomen eines Chromosomenpaares stammen jedoch vom gleichen Elternteil (z.B. beide Chromosomen 15 von der Mutter --> Prader-Willi-Syndrom). Ursache meist wie oben (hier: Verlust des einzigen väterlichen #15 nach (letaler) Trisomie 15)