BP202T · B.PHARM THEORY

BP202T Biochemistry

Unit V — Nucleic Acid Metabolism & Genetic Information

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit V (8 hours).

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Chapter 17: Biosynthesis of Purine and Pyrimidine Nucleotides

Learning objectives

- Define nucleotide, nucleoside, purine and pyrimidine (from zero).
- Outline de-novo purine synthesis: starting material (PRPP), key donors, end product (IMP).
- Outline pyrimidine synthesis: CPS-II, orotate → OMP → UMP.
- Explain the salvage pathway and its significance (Lesch–Nyhan).
- State the regulation logic.

17.1 From zero: the vocabulary

Concept: Nucleic acids (DNA, RNA) are long chains of **nucleotides**. Each nucleotide = **nitrogenous base + pentose sugar + phosphate**.

- **Nucleoside** = base + sugar (no phosphate). Add phosphate → nucleotide.
- **Bases come in two shapes:**
- **Purines** (double-ring): **Adenine (A), Guanine (G)** — "Pure As Gold" (Purines: Adenine, Guanine).
- **Pyrimidines** (single-ring): **Cytosine (C), Thymine (T)** (DNA), **Uracil (U)** (RNA instead of T).
- Sugars: **ribose** (RNA) vs **deoxyribose** (DNA, one less oxygen).

Analogy: If DNA is a long necklace, each bead (nucleotide) = a coloured stone (base) + a spacer (sugar) + a clasp (phosphate). **Key takeaway:** Nucleotide = base + sugar + phosphate. Purines (A, G) = double ring; pyrimidines (C, T, U) = single ring.

17.2 De-novo purine synthesis (building from scratch)

Concept: The purine ring is built **atom by atom on a ribose-phosphate scaffold** (not made free and then attached). **Starting material: PRPP** (phosphoribosyl pyrophosphate) — the activated ribose foundation. **Atom donors (where the ring atoms come from): glutamine, glycine, aspartate**, plus one-carbon units (from folate) and CO_2. **End product: IMP (inosine monophosphate)** — the parent purine nucleotide, from which **AMP and GMP** are made. **Site:** cytosol (liver mainly). **Regulation:** the first committed step is feedback-inhibited by AMP and GMP (end products switch off their own production) — classic feedback inhibition. **Simple summary:** PRPP + (glutamine + glycine + aspartate + one-carbon units + CO_2) → IMP → AMP / GMP.

17.3 Pyrimidine synthesis

Concept: Opposite strategy to purines — the **pyrimidine ring is built first, then attached to PRPP**. **Steps (simple):**

1. **Carbamoyl phosphate** made by **CPS-II** (cytosolic; uses **glutamine** — contrast with CPS-I of the urea cycle, which uses ammonia in mitochondria).
2. Carbamoyl phosphate + aspartate → … → **orotate** → **OMP** → **UMP** (the parent pyrimidine nucleotide).
3. UMP → UDP → **UTP** → **CTP**; UDP → **dUDP** → **dTMP** (thymidylate) via **thymidylate synthase** (needs folate).

Drug link (awareness): 5-fluorouracil (5-FU), an anticancer drug, inhibits thymidylate synthase — you will study this in medicinal chemistry/pharmacology; here just note the target.

17.4 Salvage pathway

> **Concept:** Instead of building bases from scratch (expensive), cells **recycle** free bases and nucleosides back into nucleotides.

- **Key enzyme: HGPRT** (hypoxanthine-guanine phosphoribosyltransferase) — salvages hypoxanthine → IMP and guanine → GMP.
- **Clinical link: Lesch–Nyhan syndrome** = HGPRT deficiency → no salvage → excess de-novo synthesis → overproduction of uric acid (gout-like features) plus characteristic self-injurious behaviour. Managed by specialists.

> **Analogy:** De-novo synthesis is buying new furniture; salvage is repairing and reusing old furniture — cheaper, so the cell prefers it where possible.

Common confusions

- **Purine ring built ON ribose** (atoms added to PRPP) vs **pyrimidine ring built FIRST, then attached** to ribose — opposite assembly logic, favourite exam trap.
- **CPS-I vs CPS-II:** CPS-I = urea cycle (mitochondria, ammonia); CPS-II = pyrimidine synthesis (cytosol, glutamine).

Common mistakes

- Listing uracil as a DNA base. DNA uses **thymine**; uracil replaces it in **RNA**.
- Saying IMP is the end of purine synthesis — IMP is the *branch point* to AMP and GMP.

Mnemonic

Purine donors: "**G**lutamine **G**ives **N**itrogens, **G**lycine **G**ives backbone, **A**spartate **A**dds" — or simply "**G**et **G**ood **A**toms" (Glutamine, Glycine, Aspartate). Salvage: "**S**alvage **S**aves **S**ynthesis-cost" (HGPRT).

Pharmacy relevance

Purine/pyrimidine synthesis is the target of anticancer and immunosuppressant drugs (antimetabolites like 5-FU, methotrexate — folate link). Understanding the pathway explains *why* these drugs harm fast-dividing cells and why folate/B12 counselling matters.

India context

Methotrexate (a folate-pathway drug affecting nucleotide synthesis) is widely used in India for rheumatoid arthritis and cancer — pharmacists counsel on folic-acid supplementation schedules as directed by the doctor.

One-minute revision

Nucleotide = base + sugar + phosphate. Purines (A, G, double ring) built atom-by-atom on PRPP → IMP → AMP/GMP (donors: glutamine, glycine, aspartate). Pyrimidines (C, T, U, single ring): ring first (CPS-II, glutamine) → orotate → UMP → CTP, dTMP. Salvage recycles bases (HGPRT; defect = Lesch–Nyhan).

Practice questions

MCQs

1. The parent purine nucleotide is: (a) UMP (b) IMP (c) CMP (d) TMP — **Answer: (b)**
2. Purine ring atoms come from all EXCEPT: (a) Glutamine (b) Glycine (c) Aspartate (d) Ornithine — **Answer: (d)**
3. HGPRT deficiency causes: (a) Gout only (b) Lesch–Nyhan syndrome (c) PKU (d) Albinism — **Answer: (b)**
4. Pyrimidine synthesis uses CPS-II, which is located in the: (a) Mitochondria (b) Cytosol (c) Nucleus (d) Lysosome — **Answer: (b)**

Short answers: Distinguish nucleoside from nucleotide. Outline purine de-novo synthesis (start, donors, end product). What is the salvage pathway? **Long answer:** Compare the biosynthesis of purine and pyrimidine nucleotides, including regulation and the salvage pathway. **Application-based:** Why do anticancer "antimetabolite" drugs particularly affect fast-dividing cells? Link to nucleotide synthesis. **Viva:** Which base is in RNA but not DNA? What does PRPP stand for and what is its role?

Chapter 18: Purine Catabolism — Uric Acid, Hyperuricemia and Gout

Learning objectives

- Trace purine breakdown to uric acid with the key enzyme.
- Explain why humans excrete uric acid (no uricase).
- Define hyperuricemia and explain gout simply.
- State the drug target (xanthine oxidase) at awareness level.

18.1 The breakdown pathway (from zero)

> **Concept:** Used purine nucleotides (AMP, GMP) are dismantled step by step until only **uric acid** remains, which is excreted in urine. **Steps (simple):** AMP/GMP → (lose phosphate, lose amino groups) → **hypoxanthine** / **guanine** → **xanthine** → **uric acid**.

- **Key enzyme: xanthine oxidase** — converts hypoxanthine → xanthine → uric acid.
- **Human speciality:** most mammals convert uric acid further (via **uricase**) into soluble allantoin — **humans lack uricase**, so uric acid is our end product. Uric acid is poorly soluble, which is why it can cause trouble.

> **Analogy:** Like reducing scrap paper to ash — each step removes more structure until only the final ash (uric acid) is left to throw away. Humans can't dissolve the ash further (no uricase), so it must be flushed out in urine.

18.2 Hyperuricemia and gout

Concept: Hyperuricemia = too much uric acid in blood. **Gout** = the painful joint disease caused when excess uric acid forms **monosodium urate crystals** that deposit in joints. **Simple explanation:** When uric acid exceeds its solubility, it crystallises like sugar crystallising in over-sweetened tea. Crystals in a joint (classically the big toe) trigger sudden, severe inflammation — hot, red, exquisitely painful joint. **Causes (simple):** overproduction (e.g., high cell breakdown, Lesch–Nyhan, excess purine-rich food/alcohol) or underexcretion (kidney issues, some medicines). **Management (general, doctor's domain):** acute attacks treated with anti-inflammatory medicines; long-term control reduces uric acid — e.g., **allopurinol**, which inhibits **xanthine oxidase** (the enzyme from 18.1). Lifestyle: limit alcohol and purine-rich foods, maintain hydration and healthy weight — pharmacist counselling points.

18.3 Pharmacist's role

Recognise the pattern (sudden single-joint pain in a patient with known high uric acid) and refer; counsel on allopurinol adherence (it prevents attacks, doesn't treat acute pain — a classic counselling confusion), hydration, and avoiding self-medication with painkillers that harm the kidney.

Common confusions

- **Hyperuricemia vs gout:** hyperuricemia is the lab finding; gout is the crystal-deposition disease. Not everyone with hyperuricemia gets gout.
- **Allopurinol** prevents future attacks (lowers uric acid); it does not relieve an acute attack.

Common mistakes

- Saying humans convert uric acid to allantoin. We **lack uricase** — uric acid is the end.
- Confusing xanthine oxidase (purine breakdown) with xanthine in tea/coffee (different context entirely).

Mnemonic

Breakdown: "**H**ypoxanthine → **X**anthine → **U**ric acid" → "**H**e **X**hales **U**ric" (xanthine oxidase does both steps). Gout: "**G**out = **G**lass-like crystals in **G**oints."

Pharmacy relevance

Allopurinol is a staple pharmacy medicine; counselling on its preventive (not painkiller) role is a classic pharmacist intervention. Febuxostat (also a xanthine-oxidase inhibitor) is the alternative — names for awareness.

India context

Gout is increasingly seen in Indian clinics with changing diets and rising metabolic disease; pharmacists counsel on limiting alcohol and organ meats/some seafoods, and on weight management as advised by the doctor.

One-minute revision

Purines → hypoxanthine →(xanthine oxidase)→ xanthine →(xanthine oxidase)→ uric acid. Humans lack uricase → uric acid is the end product. Excess = hyperuricemia; urate crystals in joints = gout (sudden painful joint, classically big toe). Allopurinol inhibits xanthine oxidase (prevention, not acute pain relief).

Practice questions

MCQs

1. The end product of purine catabolism in humans is: (a) Allantoin (b) Uric acid (c) Urea (d) Ammonia — **Answer: (b)**
2. Xanthine oxidase converts: (a) Uric acid to allantoin (b) Hypoxanthine to xanthine to uric acid (c) IMP to AMP (d) Guanine to adenine — **Answer: (b)**
3. Gout is caused by deposition of: (a) Calcium (b) Monosodium urate crystals (c) Cholesterol (d) Oxalate — **Answer: (b)**
4. Allopurinol acts by inhibiting: (a) HGPRT (b) Xanthine oxidase (c) CPS-II (d) Thymidylate synthase — **Answer: (b)**

Short answers: Trace purine catabolism to uric acid. Why can't humans break down uric acid further? Distinguish hyperuricemia from gout. **Long answer:** Describe the catabolism of purine nucleotides and explain the biochemical basis and management principles of gout. **Application-based:** A patient takes allopurinol daily but stops it during a painful gout attack saying "it didn't work." Correct the misunderstanding. **Viva:** Which enzyme is missing in humans for uric-acid breakdown? Classic first joint in gout?

Chapter 19: Organization of the Mammalian Genome

Learning objectives

- Describe how DNA is packaged: from double helix to chromosome.
- Define nucleosome, histone, chromatin, exon, intron, gene.
- State the human genome's scale (chromosomes, approximate size) without inventing precise statistics beyond standard textbook facts.

19.1 The packaging problem (from zero)

Concept: Each human cell contains about 2 metres of DNA, packed into a nucleus only micrometres wide. The **mammalian genome** (all the DNA of the organism) is organised in layers of packaging. **Simple explanation:** Like winding a 2-metre-long thread onto tiny spools, then coiling the spools into thicker ropes, then packing the ropes into 46 neat bundles (chromosomes). **Packaging levels:**

1. **DNA double helix** — the thread itself (two strands, A–T and G–C base pairs).
2. **Nucleosome** — DNA wound around a core of **histone** proteins (like thread on a spool); the "beads on a string" seen under microscopes.
3. **Chromatin** — coiled nucleosome chains; **euchromatin** (loosely packed, genes active) vs **heterochromatin** (tightly packed, genes silent).
4. **Chromosome** — the most condensed form, visible during cell division. Humans have **46 chromosomes** (23 pairs) in each body cell.

Analogy: DNA = thread; histones = spools; nucleosomes = wound spools; chromatin = coiled rope; chromosome = packed suitcase. **Key takeaway:** Genome packaging: DNA → nucleosome (histones) → chromatin → chromosome (46 in humans).

19.2 Genes, exons and introns

- **Gene:** a DNA stretch that carries the instruction for one protein (or functional RNA).
- **Exons:** the *expressed* coding parts — kept in the final message.
- **Introns:** the *intervening* non-coding parts — cut out before the message is used.

Mnemonic: "**Ex**ons **Ex**it to expression; **Int**rons **Int**errupt and are removed."

19.3 Scale and surprises (standard textbook facts, cautious)

- Human body cells carry **46 chromosomes**; the genome is roughly **3 billion base pairs** long (textbook order of magnitude).
- Only a small fraction of the genome codes for proteins; much is regulatory or structural DNA — the exact functional annotation remains an active research area, so precise percentages are not memorised here.
- **Mitochondria** carry their own tiny circular DNA (maternal inheritance) — relevant to mitochondrial disorders.

Common confusions

- **Chromatin vs chromosome:** chromatin is the loose packaged material in a resting nucleus; chromosome is the super-condensed form during division — same material, different packing.
- **Gene vs genome:** a gene is one instruction; the genome is the complete instruction set.

Common mistakes

- Saying humans have 48 chromosomes (that's the old error; correct = 46).
- Calling introns "junk" — they have regulatory roles; "non-coding" is the accurate term.

Pharmacy relevance

Genome organisation underlies pharmacogenomics — why the same drug dose affects people differently (e.g., drug-metabolising enzyme variants). Pharmacists will increasingly use genetic test results in personalised medicine.

India context

India's GenomeIndia initiative is cataloguing Indian genetic diversity — pharmacogenomic differences matter because drug-response variants differ across populations.

One-minute revision

2 metres of DNA per cell packed as: double helix → nucleosomes (DNA + histones) → chromatin (euchromatin active, heterochromatin silent) → 46 chromosomes. Gene = instruction; exons kept, introns spliced out. Mitochondria have their own small DNA.

Practice questions

MCQs

1. DNA is wound around: (a) Ribosomes (b) Histones (c) Tubulin (d) Keratin — **Answer: (b)**
2. The "beads on a string" structure is the: (a) Chromosome (b) Nucleosome (c) Exon (d) Plasmid — **Answer: (b)**
3. Human body cells contain: (a) 23 chromosomes (b) 46 chromosomes (c) 48 chromosomes (d) 44 chromosomes — **Answer: (b)**
4. Introns are: (a) Coding regions kept in mRNA (b) Non-coding regions removed before use (c) Promoters (d) Telomeres — **Answer: (b)**

Short answers: Describe the levels of DNA packaging. Distinguish euchromatin from heterochromatin. Define exon and intron. **Long answer:** Describe the organization of the mammalian genome from DNA to chromosome. **Application-based:** Why can two patients need different doses of the same drug? Link to genome variation in one line. (Genetic variants in drug-metabolising enzymes.) **Viva:** Which base pairs with adenine? Where is mitochondrial DNA inherited from? (Mother.)

Chapter 20: DNA Replication, Transcription and Translation — the Central Dogma

Learning objectives

- State the central dogma in one line.
- Describe replication (semi-conservative) with key enzymes.
- Describe transcription: template, RNA polymerase, mRNA/tRNA/rRNA.
- Describe translation: ribosome, codons, tRNA, steps (initiation, elongation, termination).

20.1 The central dogma (from zero)

> **Concept:** The **central dogma** = **DNA → RNA → protein**. Genetic information flows from DNA (archive) to RNA (working copy) to protein (the worker). **Simple explanation:** DNA is the master recipe book locked in the library (nucleus); transcription photocopies one recipe (mRNA); translation is the chef (ribosome) cooking the dish (protein) from the photocopy. **Key takeaway:** Replication copies DNA; transcription copies DNA → RNA; translation reads RNA → protein.

20.2 DNA replication

> **Concept:** Before a cell divides, it must copy its DNA exactly. Replication is **semi-conservative** — each new DNA keeps one old strand and one new strand. **Simple explanation:** Unzip the DNA zipper; each half-zipper acts as a template to build its matching half. **Key enzymes (one-line roles):**

- **Helicase:** unzips the double helix.
- **Topoisomerase:** relieves the twisting tension ahead of the fork.
- **Primase:** lays a short RNA primer (DNA polymerase can't start from nothing).
- **DNA polymerase:** builds the new strand 5′→3′, proofreading as it goes.
- **Ligase:** glues the fragments (Okazaki fragments on the lagging strand) together.

Leading vs lagging strand: one strand is built continuously (leading); the other in short pieces (Okazaki fragments, lagging) — because polymerase only works in one direction. **Mnemonic:** "**H**elicase **H**alf-opens, **P**rimase **P**rimes, **P**olymerase **P**roduces, **L**igase **L**inks" — "**H**urry, **P**lease **P**ack **L**unch."

20.3 Transcription

> **Concept:** Transcription = making an RNA copy of a gene. Enzyme: **RNA polymerase**. **Simple steps:**

1. RNA polymerase binds the **promoter** (start signal on DNA).
2. It unwinds DNA and builds RNA 5′→3′ using one DNA strand as template (A–U, G–C pairing; **uracil** replaces thymine in RNA).
3. The three RNA types: **mRNA** (message — carries the recipe), **tRNA** (transporter — brings amino acids), **rRNA** (ribosomal — builds the ribosome machine).
4. In eukaryotes, the raw transcript is processed: **introns removed (splicing)**, cap and tail added → mature mRNA leaves the nucleus.

> **Key takeaway:** Transcription = DNA → RNA (mRNA message, tRNA carriers, rRNA machine parts).

20.4 Translation

> **Concept:** Translation = reading mRNA to build a protein. Machine: the **ribosome** (rRNA + proteins). Dictionary: the **genetic code** — each 3-letter **codon** on mRNA = one amino acid; **tRNA** molecules with matching **anticodons** deliver the amino acids. **Steps:**

1. **Initiation:** ribosome assembles on mRNA at the **start codon (AUG)** with the first tRNA.
2. **Elongation:** tRNAs arrive, codons are read one by one, amino acids are linked by **peptide bonds** — the chain grows.
3. **Termination:** a **stop codon (UAA, UAG, UGA)** is reached; the finished protein is released.

> **Analogy:** mRNA is a Telegram message in 3-letter code words; tRNAs are delivery boys each carrying one specific grocery item (amino acid); the ribosome is the cook assembling the thali in order.

Summary table

Process	Template → product	Enzyme/machine	Site
Replication	DNA → DNA	DNA polymerase (+ helicase, ligase…)	Nucleus
Transcription	DNA → RNA	RNA polymerase	Nucleus
Translation	mRNA → protein	Ribosome + tRNAs	Cytoplasm (ribosomes)

Common confusions

- **Transcription vs translation:** transcription *transcribes* the same language (nucleic acid → nucleic acid); translation *translates* into a new language (nucleic acid → protein).
- **Codon vs anticodon:** codon is on mRNA; anticodon is on tRNA — they pair up.

Common mistakes

- Saying translation happens in the nucleus. It happens on **ribosomes in the cytoplasm** (mRNA travels out of the nucleus).
- Putting thymine in RNA. RNA uses **uracil**.

Pharmacy relevance

Most antibiotics target bacterial transcription/translation (next chapter) — this chapter explains *why* they kill bacteria but spare us (mostly). Protein-synthesis knowledge underlies biotech drugs (insulin, vaccines) made by engineered cells.

India context

India's biotech and vaccine industry (a global vaccine supplier) runs on engineered transcription/translation — every recombinant protein drug is made by cells reading engineered mRNA.

One-minute revision

Central dogma: DNA → RNA → protein. Replication: semi-conservative DNA copying (helicase, primase, DNA polymerase, ligase; Okazaki fragments on lagging strand). Transcription: RNA polymerase makes mRNA/tRNA/rRNA from a DNA template (U for T). Translation: ribosome reads mRNA codons; tRNAs deliver amino acids; start AUG, stop UAA/UAG/UGA.

Practice questions

MCQs

1. The central dogma is: (a) RNA → DNA → protein (b) DNA → RNA → protein (c) Protein → RNA → DNA (d) DNA → protein → RNA — **Answer: (b)**
2. Okazaki fragments occur on the: (a) Leading strand (b) Lagging strand (c) mRNA (d) tRNA — **Answer: (b)**
3. The start codon is: (a) UAA (b) AUG (c) UAG (d) AAA — **Answer: (b)**
4. Translation occurs on the: (a) Nucleus (b) Ribosome (c) Lysosome (d) Golgi — **Answer: (b)**

Short answers: State the central dogma. List the key enzymes of replication with one-line roles. Name the three RNA types and their jobs. **Long answer:** Describe DNA replication, transcription and translation, highlighting the enzymes and key signals (promoter, start/stop codons). **Application-based:** A new drug "blocks bacterial RNA polymerase." Which process does it stop, and why might human cells be less affected? (Stops transcription; bacterial and human RNA polymerases differ — selective toxicity.) **Viva:** What does semi-conservative mean? Which base replaces thymine in RNA?

Chapter 21: The Genetic Code and Inhibitors of Transcription and Translation

Learning objectives

- List the properties of the genetic code.
- Name key inhibitors of transcription and translation with their targets (antibiotics and toxins).
- Explain selective toxicity in one line.

21.1 Properties of the genetic code (from zero)

> **Concept:** The **genetic code** is the dictionary mapping each 3-letter mRNA **codon** to an amino acid (or stop). **Properties (must-know):**

1. **Triplet:** 3 bases = 1 codon (4^3 = 64 possible codons).
2. **Degenerate/redundant:** most amino acids have more than one codon (e.g., leucine has 6).
3. **Unambiguous:** one codon = one amino acid (no confusion).
4. **Universal:** (nearly) the same code in all organisms — why human genes work in bacteria (basis of biotechnology).
5. **Non-overlapping:** codons are read in sequence, one after another, no sharing of letters.
6. **Start and stop signals: AUG** = start (methionine); **UAA, UAG, UGA** = stop.
7. **61 sense codons** (code for amino acids) + **3 stop codons** = 64.

Mnemonic: "**T**riplet, **D**egenerate, **U**nambiguous, **U**niversal, **N**on-overlapping" → "**T**hree **D**octors **U**se **U**niversal **N**otes." Stops: "**U**AA, **U**AG, **U**GA" → "**U** Are **A**way, **U** Are **G**one, **U** Go **A**way" (all start with U).

21.2 Inhibitors of transcription

Inhibitor	Target	One-line mechanism
Rifampicin (antibiotic)	Bacterial RNA polymerase	Blocks RNA chain initiation in bacteria (anti-TB drug)
Actinomycin D (antibiotic/anticancer)	DNA template	Binds DNA and blocks RNA polymerase movement
α-Amanitin (toxin, from death-cap mushroom)	Eukaryotic RNA polymerase II	Shuts down mRNA synthesis — fatal in mushroom poisoning

21.3 Inhibitors of translation

Inhibitor	Target	One-line mechanism
Tetracyclines	Bacterial 30S ribosomal subunit	Block tRNA entry (aminoacyl site)
Aminoglycosides (e.g., streptomycin, gentamicin)	Bacterial 30S	Cause misreading of codons
Chloramphenicol	Bacterial 50S	Blocks peptidyl transferase (peptide-bond formation)
Macrolides (e.g., erythromycin)	Bacterial 50S	Block translocation (ribosome movement)
Puromycin	Ribosome (both)	Mimics tRNA — causes premature chain termination
Cycloheximide	Eukaryotic 60S	Blocks eukaryotic translation (lab tool, too toxic as a drug)
Diphtheria toxin	EF-2 (elongation factor)	ADP-ribosylates EF-2 — halts elongation (bacterial toxin)

Why antibiotics spare us (selective toxicity): bacterial ribosomes are **70S** (30S + 50S) while human ribosomes are **80S** (40S + 60S) — different enough that drugs like tetracycline and chloramphenicol prefer the bacterial machine. This one difference is the basis of many antibiotics.

Common confusions

- **Rifampicin vs streptomycin:** rifampicin blocks *transcription* (RNA polymerase); streptomycin disrupts *translation* (30S misreading).
- **Puromycin vs cycloheximide:** puromycin terminates chains (both systems); cycloheximide blocks only eukaryotic translation.

Common mistakes

- Saying chloramphenicol acts on the 30S subunit — it acts on **50S** (peptidyl transferase).
- Mixing up which toxin hits which polymerase — α-amanitin hits **RNA polymerase II** (mRNA).

Mnemonic

30S blockers: "**T**etracyclines **T**ake the **T**hirty" and "**A**minoglycosides **A**lter reading at **3**0S." 50S blockers: "**C**hloramphenicol **C**uts peptide bonds, **M**acrolides **M**ove-block" (translocation).

Pharmacy relevance

This chapter *is* antibiotic pharmacology's foundation — pharmacists must know why these drugs work and their signature toxicities (e.g., aminoglycoside kidney/ear toxicity, chloramphenicol blood effects — detail in pharmacology). Diphtheria-toxin knowledge reinforces why vaccination matters.

India context

Rifampicin is the backbone of India's TB treatment programme; pharmacists are central to DOTS adherence counselling — understanding its transcription-blocking mechanism strengthens patient education.

One-minute revision

Genetic code: triplet, degenerate, unambiguous, universal, non-overlapping; AUG start; UAA/UAG/UGA stop; 61 + 3 = 64. Transcription blockers: rifampicin (bacterial RNA pol), actinomycin D (DNA), α-amanitin (eukaryotic RNA pol II). Translation blockers: tetracyclines/aminoglycosides (30S), chloramphenicol/macrolides (50S), puromycin (chain termination), cycloheximide (eukaryotic 60S), diphtheria toxin (EF-2). Selective toxicity: 70S bacterial vs 80S human ribosomes.

Practice questions

MCQs

1. The start codon is: (a) UAA (b) AUG (c) UGA (d) GUG only — **Answer: (b)**
2. Rifampicin inhibits: (a) DNA polymerase (b) Bacterial RNA polymerase (c) Ribosome (d) DNA ligase — **Answer: (b)**
3. Chloramphenicol acts on the: (a) 30S subunit (b) 50S subunit (c) RNA polymerase (d) DNA gyrase — **Answer: (b)**
4. Diphtheria toxin inactivates: (a) EF-2 (b) RNA polymerase (c) DNA polymerase (d) Ligase — **Answer: (a)**

Short answers: List five properties of the genetic code. Name two transcription inhibitors with targets. Why do many antibiotics target the 70S ribosome? **Long answer:** Describe the properties of the genetic code and the major inhibitors of transcription and translation, with their targets. **Application-based:** A patient asks why antibiotics don't damage human cells the way they kill bacteria. Answer using ribosome differences. **Viva:** How many codons are there in total? Which toxin comes from the death-cap mushroom?

Chapter 22: DNA Damage, Repair Mechanisms and Disorders of Faulty Repair

Learning objectives

- List types of DNA damage with one cause each.
- Describe the main repair mechanisms in simple words.
- Name disorders of faulty repair (xeroderma pigmentosum as the key example).
- Explain why repair failure leads to cancer in general terms.

22.1 Types of DNA damage (from zero)

> **Concept:** DNA is constantly damaged by internal and external agents. Common types:

- **UV radiation → thymine dimers** (two adjacent thymines fused — the classic sunburn lesion).
- **X-rays/ionising radiation** → strand breaks.
- **Chemicals** (e.g., smoke components) → bulky adducts stuck to bases.
- **Spontaneous errors** → base loss, deamination (C → U), and replication mismatches.

Simple explanation: DNA is a precious manuscript; sunlight fades it, chemicals stain it, and copying introduces typos. **Key takeaway:** Damage is inevitable and constant — survival depends on repair crews.

22.2 Repair mechanisms (simple words)

Mechanism	What it fixes (simple)	One-line how
Base excision repair (BER)	Small damaged single bases	Removes the bad base, fills the gap
Nucleotide excision repair (NER)	Bulky lesions, thymine dimers	Cuts out a short patch around the damage, resynthesises
Mismatch repair (MMR)	Copying typos after replication	Proofreads the new strand, corrects mismatches
Double-strand break repair	Broken both strands (serious)	Rejoins ends or copies from the sister copy

> **Analogy:** BER = correcting one wrong letter with an eraser; NER = cutting out a stained sentence and rewriting it; MMR = the spell-checker after typing; double-strand repair = rebinding a torn page.

22.3 Disorders of faulty DNA repair

- **Xeroderma pigmentosum (XP):** defective **nucleotide excision repair** → cannot fix UV-induced thymine dimers → extreme sun sensitivity, freckle-like skin changes in childhood, very high skin-cancer risk. Management: strict sun avoidance, specialist dermatology care.
- **Ataxia telangiectasia:** defective response to double-strand breaks → radiation sensitivity, immune and neurological features.
- **Bloom syndrome:** defective DNA unwinding → growth failure, cancer predisposition.
- **General principle:** faulty mismatch repair → hereditary colon-cancer predisposition (Lynch/HNPCC concept, awareness level).

Why repair failure → cancer (general): unrepaired mutations accumulate in growth-control genes; damaged cells that should stop dividing don't — the foundation of carcinogenesis. (Cancer biology detail belongs to later courses.)

22.4 Pharmacist's angle (recognise and refer)

Unusual childhood sun sensitivity with skin changes → refer to dermatology/paediatrics; do not dismiss as ordinary sunburn. Counsel XP families on rigorous photoprotection as advised by the doctor. Note that some anticancer drugs work by *damaging* DNA — repair pathways are also drug targets (awareness level).

Common confusions

- **Damage vs mutation:** damage is a physical lesion (fixable); mutation is a permanent sequence change (if unrepaired damage is copied).
- **XP vs ordinary sunburn:** XP is a genetic repair defect with extreme sensitivity from minimal sun — not "bad sunburn."

Common mistakes

- Saying all DNA damage causes cancer. Most damage is repaired; cancer needs specific unrepaired mutations plus failed safeguards.

Mnemonic

Repairs: "**B**ase (small), **N**ucleotide (bulky), **M**ismatch (typos), **D**ouble-strand (breaks)" → "**B**ig **N**urses **M**end **D**amage." XP: "**X**eroderma = **X**-tra sun sensitivity, **N**ER defect."

Pharmacy relevance

Sunscreen counselling has a biochemical basis (UV → thymine dimers); pharmacists advising on photoprotection for photosensitive patients apply this chapter directly. DNA-damaging anticancer drugs (alkylating agents, etc.) are understood through these pathways.

India context

India's high UV index makes photoprotection counselling relevant for all, and critical for XP and other photosensitive patients; pharmacists guide on sunscreen selection and reapplication as per product directions.

One-minute revision

DNA damage: UV → thymine dimers; X-rays → strand breaks; chemicals → adducts; spontaneous → base loss/mismatches. Repairs: BER (single base), NER (bulky/dimers), MMR (typos), double-strand break repair. Faulty NER = xeroderma pigmentosum (extreme sun sensitivity, skin-cancer risk). Unrepaired mutations → cancer risk.

Practice questions

MCQs

1. UV radiation typically causes: (a) Strand breaks (b) Thymine dimers (c) Base loss only (d) Chromosome gain — **Answer: (b)**
2. Xeroderma pigmentosum is a defect in: (a) Base excision repair (b) Nucleotide excision repair (c) Mismatch repair (d) Urea cycle — **Answer: (b)**
3. Mismatch repair corrects: (a) UV dimers (b) Replication typos (c) Double-strand breaks (d) Chemical adducts — **Answer: (b)**
4. XP patients must mainly avoid: (a) Cold (b) Sunlight/UV (c) Protein (d) Exercise — **Answer: (b)**

Short answers: List four types of DNA damage with causes. Name the four repair mechanisms and what each fixes. What is xeroderma pigmentosum? **Long answer:** Describe DNA damage types and repair mechanisms, with an overview of disorders caused by faulty repair. **Application-based:** A child develops severe blistering after brief sun exposure, far beyond normal sunburn. What should the pharmacist advise? (Urgent dermatology/paediatric referral — possible XP; strict sun avoidance meanwhile.) **Viva:** Which repair handles bulky lesions? What is a thymine dimer?

Combined References (Units III–V)

As per the BP202T syllabus — Recommended References (preferably latest editions):

1. Nelson, D.L., Cox, M.M. and Hoskins, A., *Lehninger Principles of Biochemistry*. New York: W.H. Freeman.
2. Kennelly, P.J., Rodwell, V.W., Bender, D.A., Botham, K.M. and Weil, P.A., *Harper's Illustrated Biochemistry*. New York: McGraw-Hill Education.
3. Murray, R.K., Bender, D.A., Botham, K.M., Kennelly, P.J., Rodwell, V.W. and Weil, P.A., *Harper's Biochemistry*. New York: McGraw-Hill.
4. Voet, D. and Voet, J.G., *Biochemistry*. New York: John Wiley & Sons.
5. Devlin, T.M., *Textbook of Biochemistry with Clinical Correlations*. New York: Wiley-Liss.
6. Satyanarayana, U. and Chakrapani, U., *Biochemistry*. Kolkata: Books and Allied (P) Ltd.
7. Stryer, L., *Biochemistry*. New York: W.H. Freeman.