BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
Course Code : BM35C7

Unit-III
Principles of Chemotherapy - Part 3

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GENERAL PRINCIPLES IN CHEMOTHERAPY OF CANCER

- In cancer chemotherapy, analogy is drawn with bacterial chemotherapy; the malignant cell being viewed as an invader.
- Bacterial metabolism differs markedly from that of the host, while malignant cells are in fact host cells with deranged regulation of growth and differentiation and only minor other differences.
- Infecting microorganisms are amenable to immunological and other host defence mechanisms. This is absent or minimal against cancer cells.

- A single clonogenic malignant cell is capable of producing progeny that can kill the host.
- To cure, all malignant cells must be killed or removed.
- Survival time is related to the number of cells that escape chemotherapeutic attack.

- In any cancer, subpopulations of cells differ in their rate of proliferation and susceptibility to cytotoxic drugs.
- These drugs kill cancer cells by first order kinetics, i.e. a certain fraction of cells present are killed by one treatment.

- Drug regimens or number of cycles of combined chemotherapy which can effectively palliate large tumour burdens may be curative when applied to minute residual tumour cell population after surgery and/ or irradiation. This is the basis of the combined modality approach

- Whenever possible, complete remission should be the goal of cancer chemotherapy
- Drugs are often used in maximum tolerated doses.
- Intensive regimens used earlier yield better results.

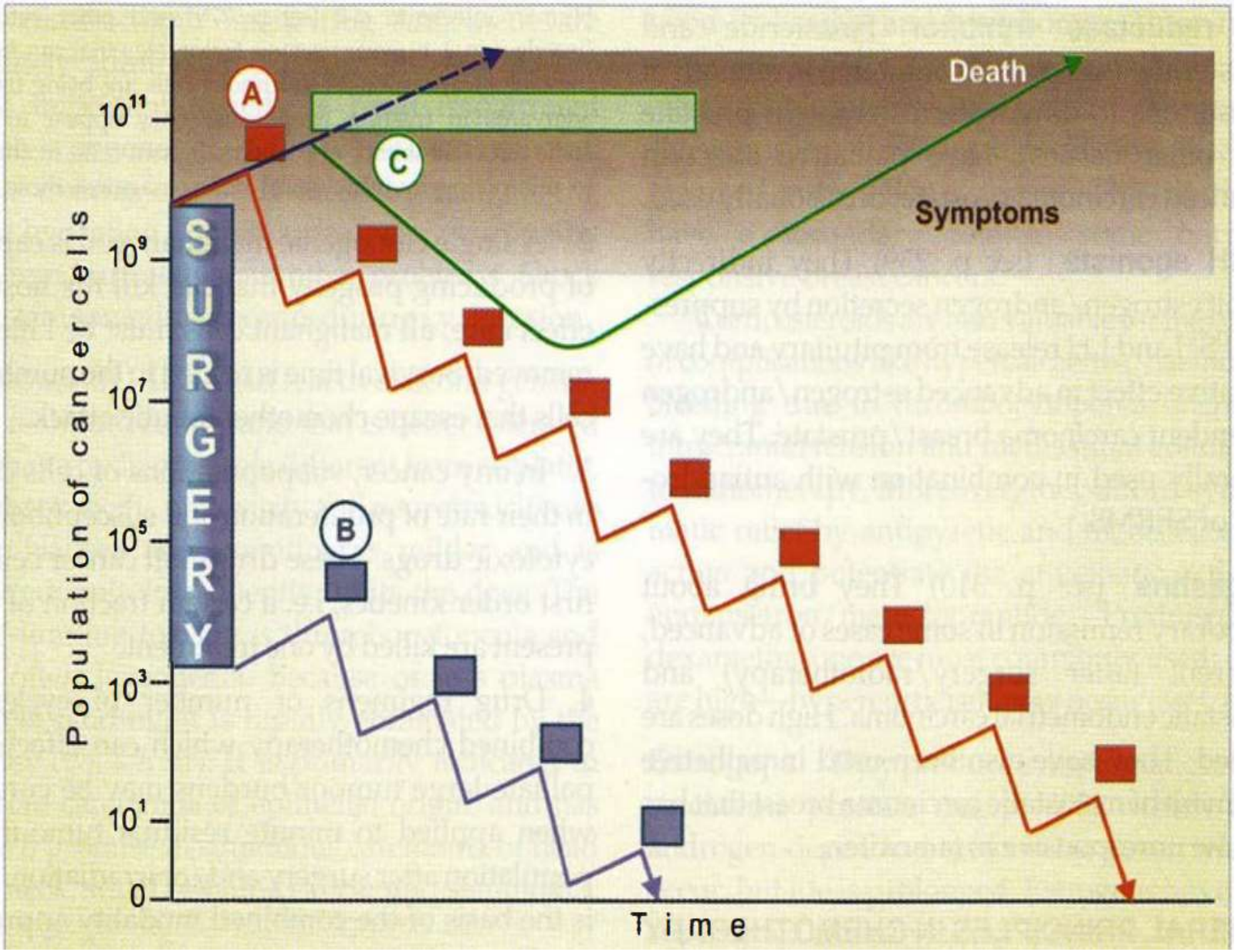
- Formerly cancers were treated with one drug at a time.
- Now a combination of 2-5 drugs is given in intermittent pulses to achieve total tumour cell kill, giving time in between for normal cells to recover.

- A rationally designed combination of 2-5 **chemotherapeutic drugs** (red bar) is given cyclically.
- Each cycle kills **99% tumour cells,** reducing the tumour cell mass by **2 log units** each time.
- Some regrowth occurs during the rest interval, **but the rate of cell kill is more than regrowth** and **resistance does not develop.**
- If the cycles are continued well beyond **all symptoms disappear, cure may be achieved.**
- **Radiation may be used to supplement chemotherapy.**

B. The cancer (in case of solid tumours) is resected **surgically** and the small number of residual cancer cells (at the primary site or in metastasis) are killed by relatively **few cycles of adjuvant combination chemotherapy** (purple bar).

This may be supplemented by radiation (in case of radiosensitive tumours)

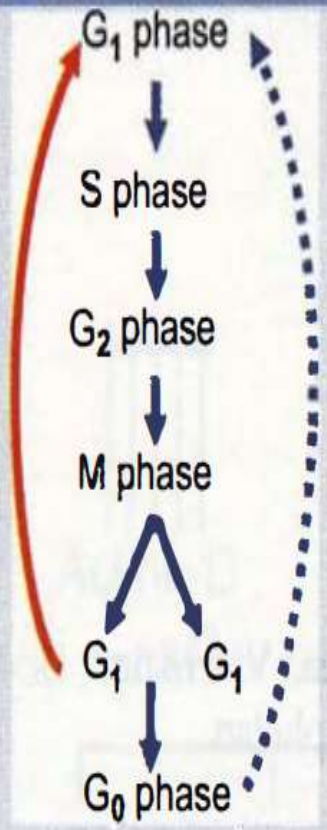
- C. The **chemotherapy is begun relatively late** with a single but effective drug given continuously (blue bar).
- It causes **slower tumour cell kill**, but symptom relief may occur.
- Resistance soon develops, and the tumour starts regrowing even with continued chemotherapy.
- Symptoms reappear and increase in severity. Ultimately failure of therapy and death occur


Death
Symptoms
A
B
C
SURGERY
Population of cancer cells
10^{11}
10^{9}
10^{7}
10^{5}
10^{3}
10^{1}
0
Time

Synergistic combinations and rational sequences are devised by utilizing:

- (a) Drugs which are effective when used alone.
- (b) Drugs with different mechanisms of action.
- (c) Drugs with differing toxicities.
- (d) Empirically by trial and error; optimal schedules are mostly developed by this procedure.
- (e) Drugs with different mechanisms of resistance.
- (f) Drugs with known synergistic biochemical interactions.
- (g) Kinetic scheduling: On the basis of cell cycle specificity /nonspecificity of the drugs and the phase of cell cycle at which the drug exerts its toxicity.

Phases of cell cycle



Pre (nucleic acid) synthesis interval.

Synthesis of DNA occurs.

Post synthetic interval.

Mitosis occurs—two G_1 cells are produced, which either directly re-enter next cycle or pass into the nonproliferative (G_0) phase.

Nonproliferating cells; a fraction of these are clonogenic—may remain quiescent for variable periods, but can be recruited in cell cycle if stimulated later.

(1) G0 (gap 0 or resting) non-proliferative phase.

(2) G1 (gap 1 i.e. presynthetic) phase, during which the cell determines its readiness to commit to DNA synthesis.

(3) S (synthetic) phase, involving DNA synthesis.

(4) G2 (gap 2 i.e. post-synthetic) phase, during which the accuracy of DNA replication is determined, and errors are corrected; and

(5) M (mitotic) phase, during which the replicated chromosomes are separated into two nuclei for the two daughter G1 cells.

These cells may re-enter the cycle or pass into the resting G0 phase.

Cytotoxic drugs

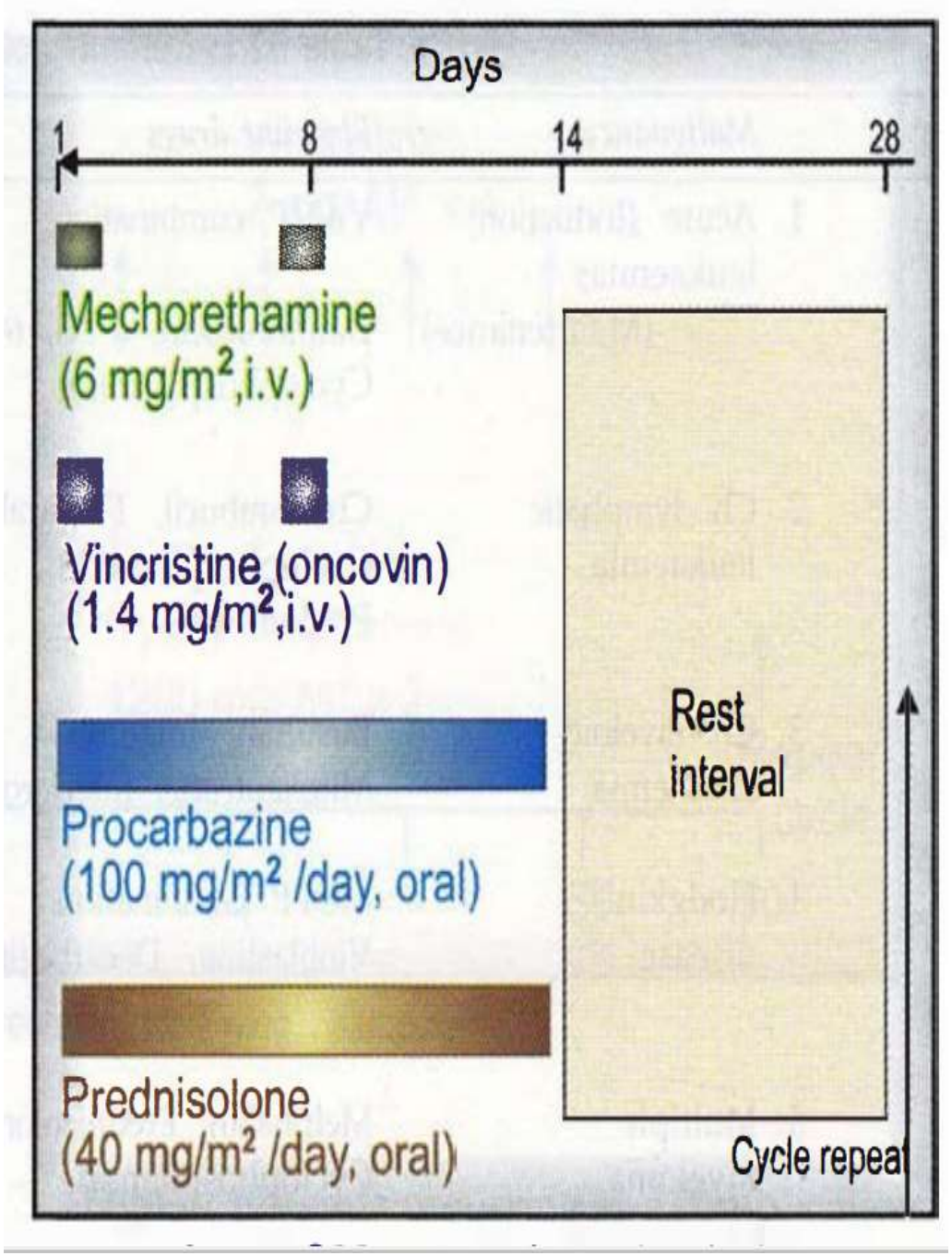
- Cell cycle specific (CCS) Cell cycle specific Kill only actively dividing cells.
- Their toxicity is generally expressed in S phase.
- Phase selectivity,
- G1: Vinblastine.
- S: Mtx, cytarabine, 6-TG, 6-MP, 5-FU, hydroxyurea, mitomycin C, doxorubicin, daunorubicin.
- G2: Daunorubicin, bleomycin, etoposide, topotecan.
- M: Vincristine, vinblastine, paclitaxel, docetaxel

- Cell cycle nonspecific (CCNS)
- (Kill resting as well as dividing cells)
- e.g. **nitrogen mustard, cyclophosphamide, chlorambucil**, carmustine, dacarbazine, busulfan, L-asparaginase, cisplatin, procarbazine, actinomycin D.

- **Topoisomerases I and II** play an important role during DNA replication.
- The cell-cycle transition between G1 and S and that between G2 and M are so well regulated that the cell divides properly with a minimum of errors.
- Check points in G1 and G2 determine whether the cell will enter S and M, respectively.
- These check points are regulated by protein kinases (cyclin-Dependent Kinases cDK) and kinase-associated proteins called cyclins.

- Cell cycle depends balance b/w Positive and Negative regulatory forces.
- Positive: growth factors and a series of cyclins and cDKs.
- Negative: Proteins induced by genes such as tumour suppressor gene p53 (Guardian of genome).
- When there is damage to the DNA, these inhibitors halt the cycle, allowing repair. If repair fails, the cell undergoes degradation of nuclear DNA leading to death called apoptosis (programmed cell death).
- Apoptosis helps to eliminate abnormal cells that have become redundant during development and differentiation.
- First line of defence against mutations and renewal of cells with abnormal DNA that could become malignant.

- MOPP regimen, 80% response rate in Hodgkin's disease.
- For optimum remission 6-11 cycles may be needed.
- Maintenance therapy thereafter does not produce additional benefit.



Cell cycle specific drugs

- It is logical to use cell cycle specific drugs in short courses (pulses) of treatment.
- This allows noncycling cells (which are generally less susceptible to drugs) to re-enter the cycle between drug courses.
- The CCS drugs are generally scheduled after a course of CCNS drug(s) to improve the cell kill.

- CCS - Haematological malignancies and in solid tumours with a small growth fraction
- CCNS – These as well as solid cancers with a small growth fraction

- Tumours often become resistant to any drug that is used repeatedly due to selection of less responsive cells.
- Such selection is favoured if low dose of a single drug is used.

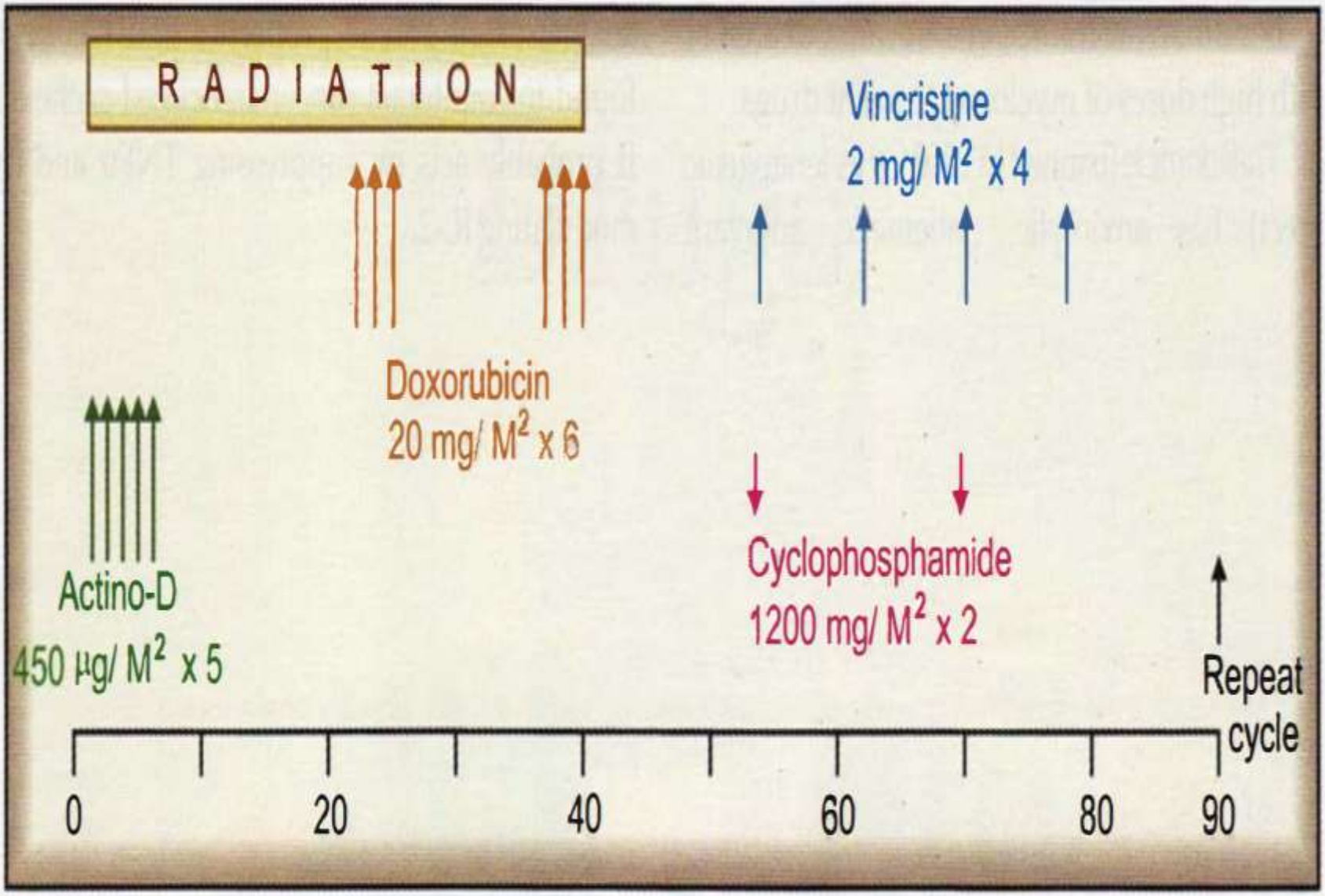


Fig. 62.3: Combined modality treatment for Ewing's sarcoma

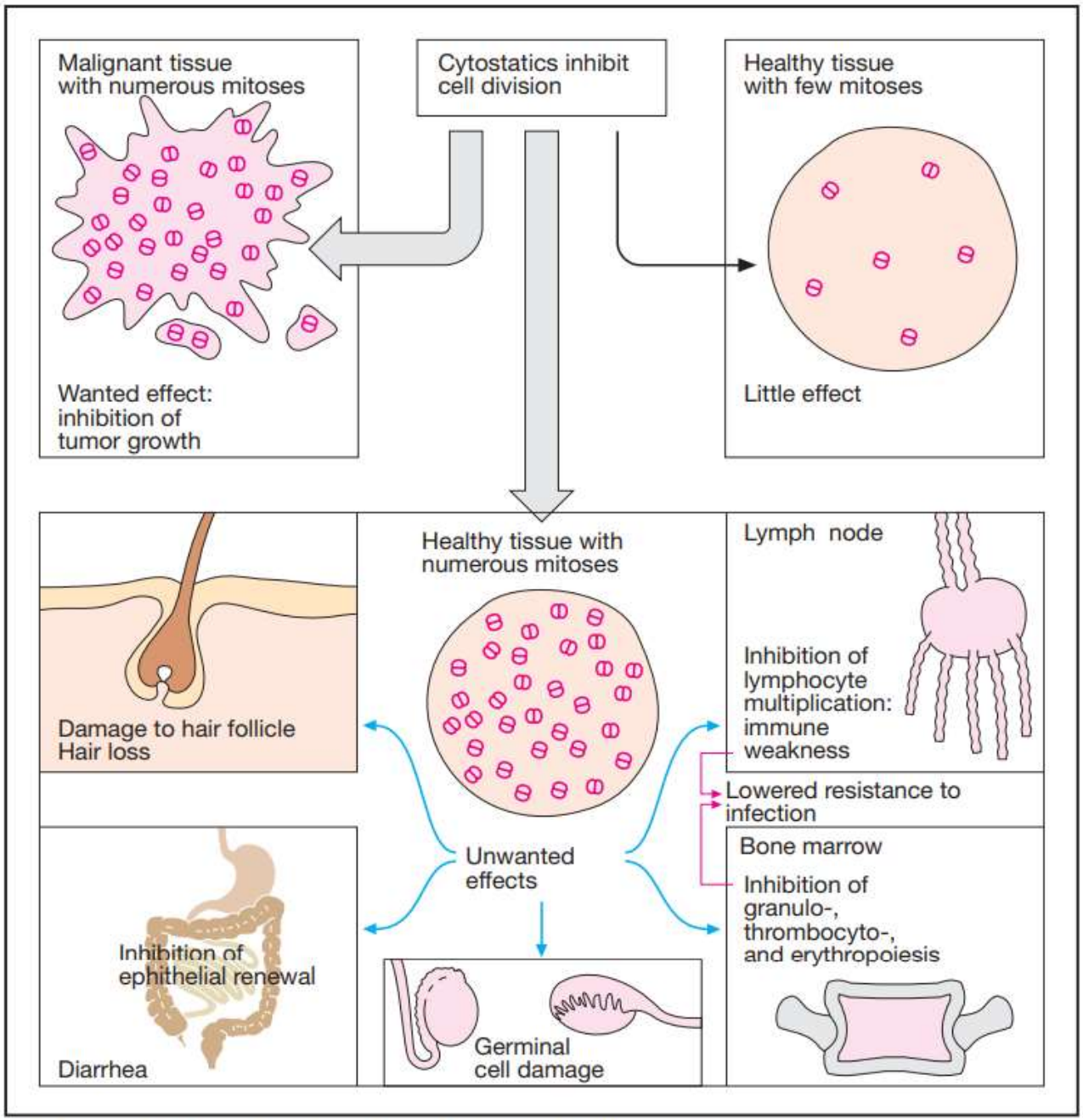
Toxicity amelioration

- Toxicity blocking drugs: Folinic acid rescue has permitted administration of > 100 fold dose of Mtx
- It is professed that normal cells are rescued more than the cancer cells therapeutic index is increased.
- Cystitis caused by cyclophosphamide and ifosphamide can be blocked by systemically administered mesna and by irrigating the bladder with acetylcysteine.
- Both these are -SH containing compounds that combine with and detoxify the toxic metabolites in the bladder.
- Generous fluid intake and frequent bladder voiding also helps.

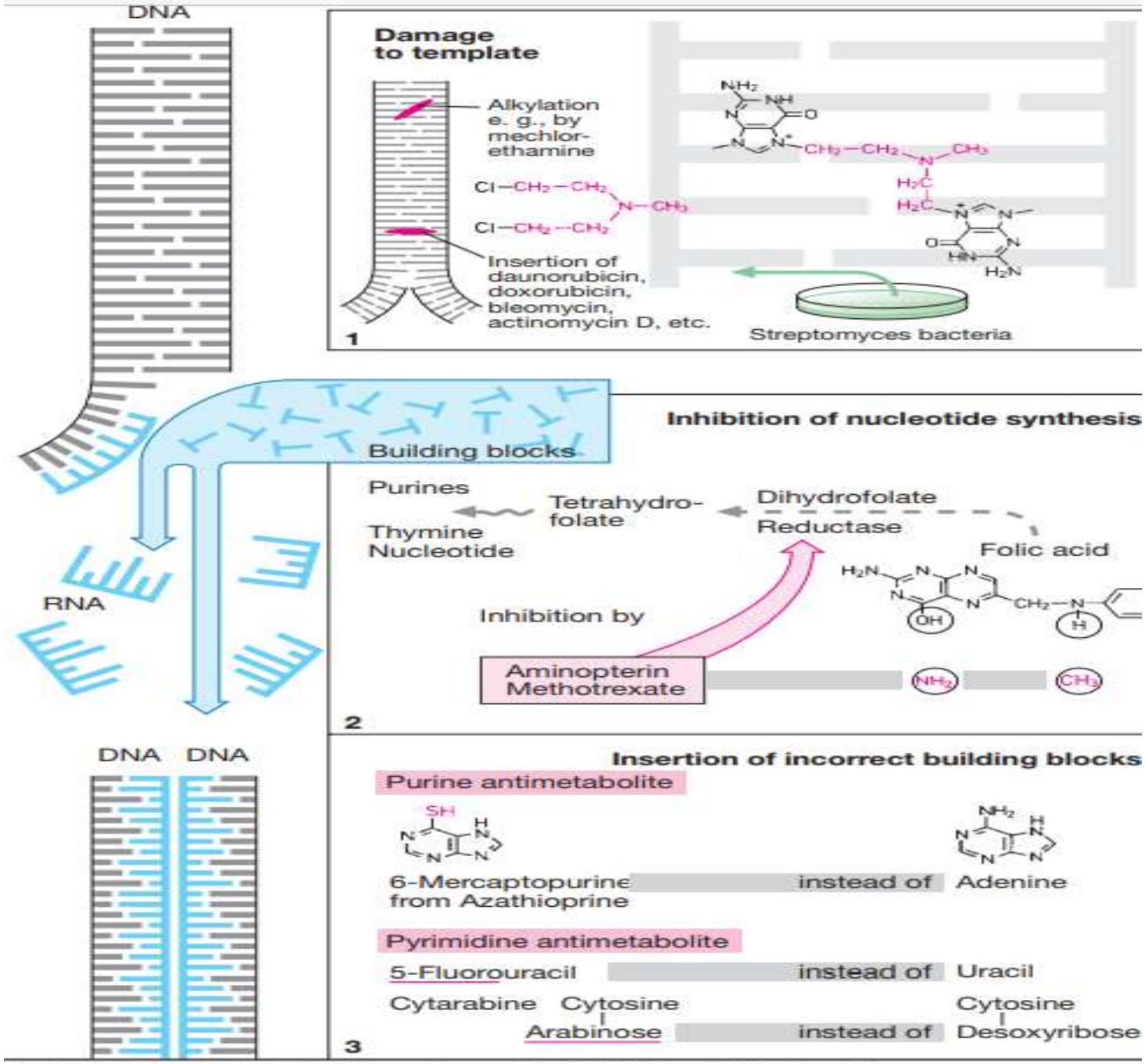
- Hyperuricaemia - destruction of bulky tumour masses and degradation of large amount of purines can be reduced by allopurinol, alkalinization of urine , plenty of fluids. Corticosteroids
- Hypercalcaemia malignancies like myeloma, cancer breast/prostate, etc. may be aggravated by chemotherapy.
- Hydration and i.v. bisphosphonates

- Drugs given in pulses with 2-3 week intervals for normal cells to recover improve the efficacy of therapy: malignant cells recovering more slowly.
- Selective exposure of tumour to the drug by intraarterial infusion into a limb or head and neck;
- intrapleural/ intraperitoneal injection especially for rapidly accumulating pleural effusion or ascitis
- Topical application on the lesion-on skin, buccal mucosa, vagina, etc. may reduce systemic toxicity.

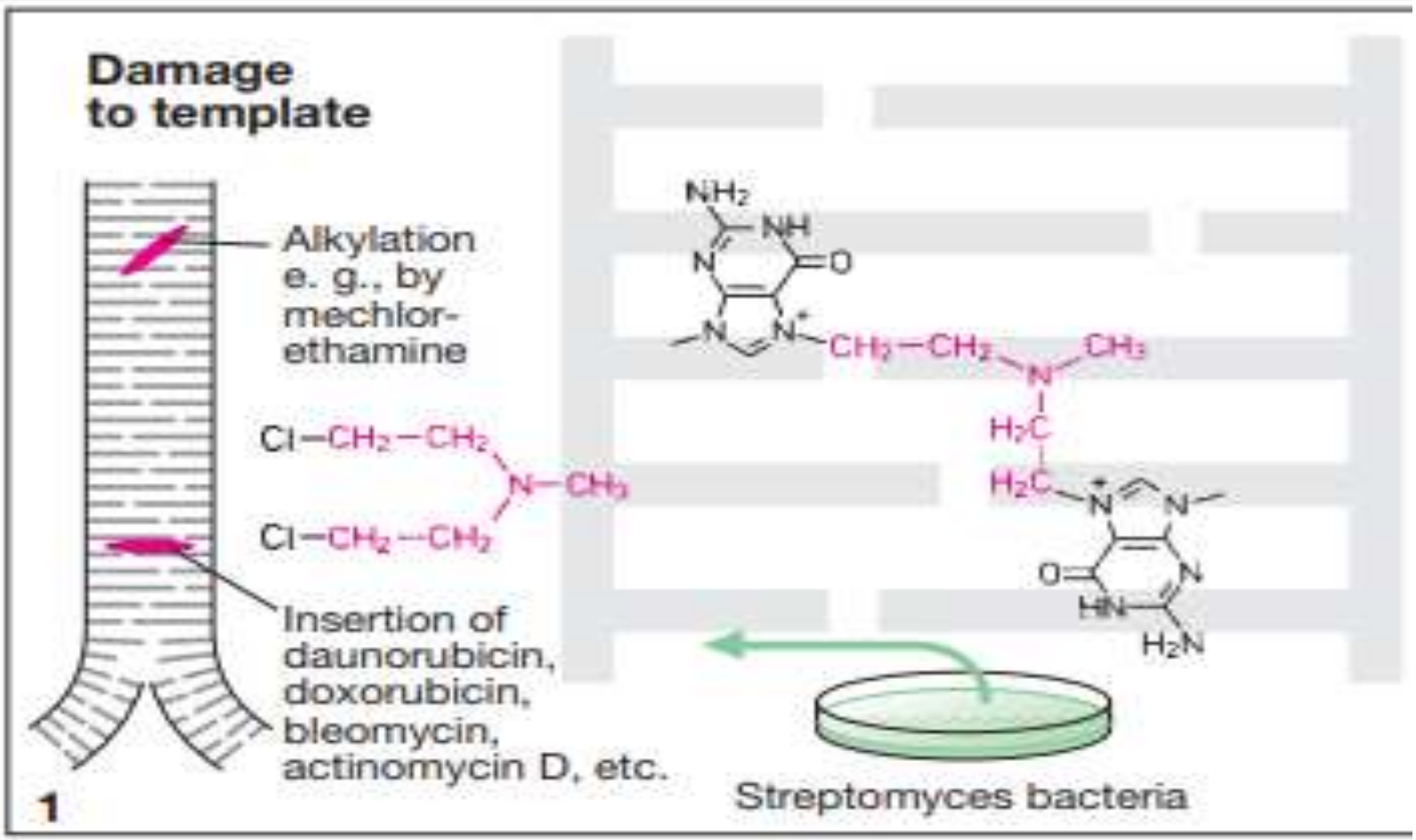
- Platelet and/ or granulocyte transfusion after treatment-to prevent bleeding or infection.
- Use of biological response modifiers like recombinant GM-CSF /G-CSF hastens recovery from cytotoxic drug induced myelosuppression.

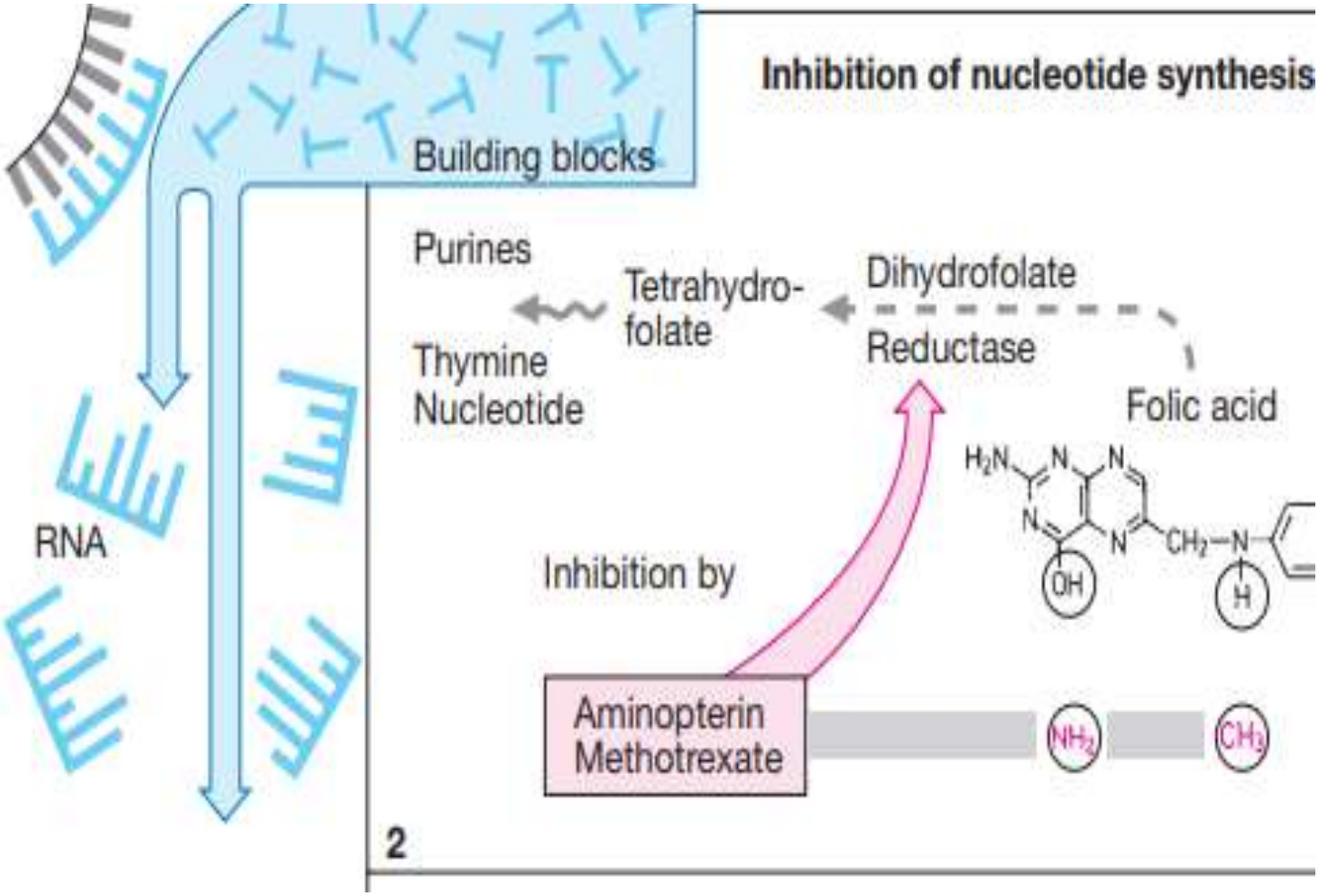


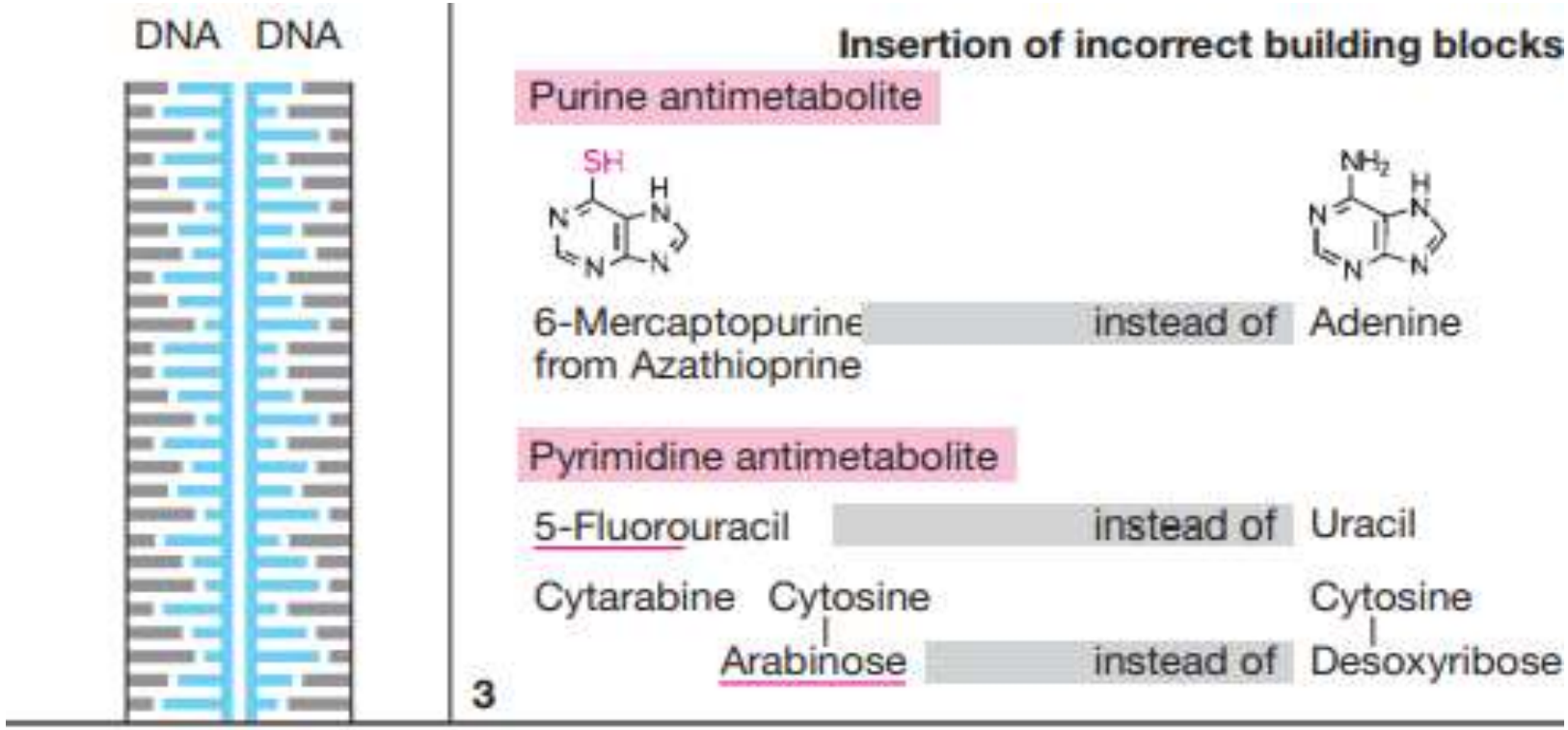
A. Chemotherapy of tumors: principal and adverse effects



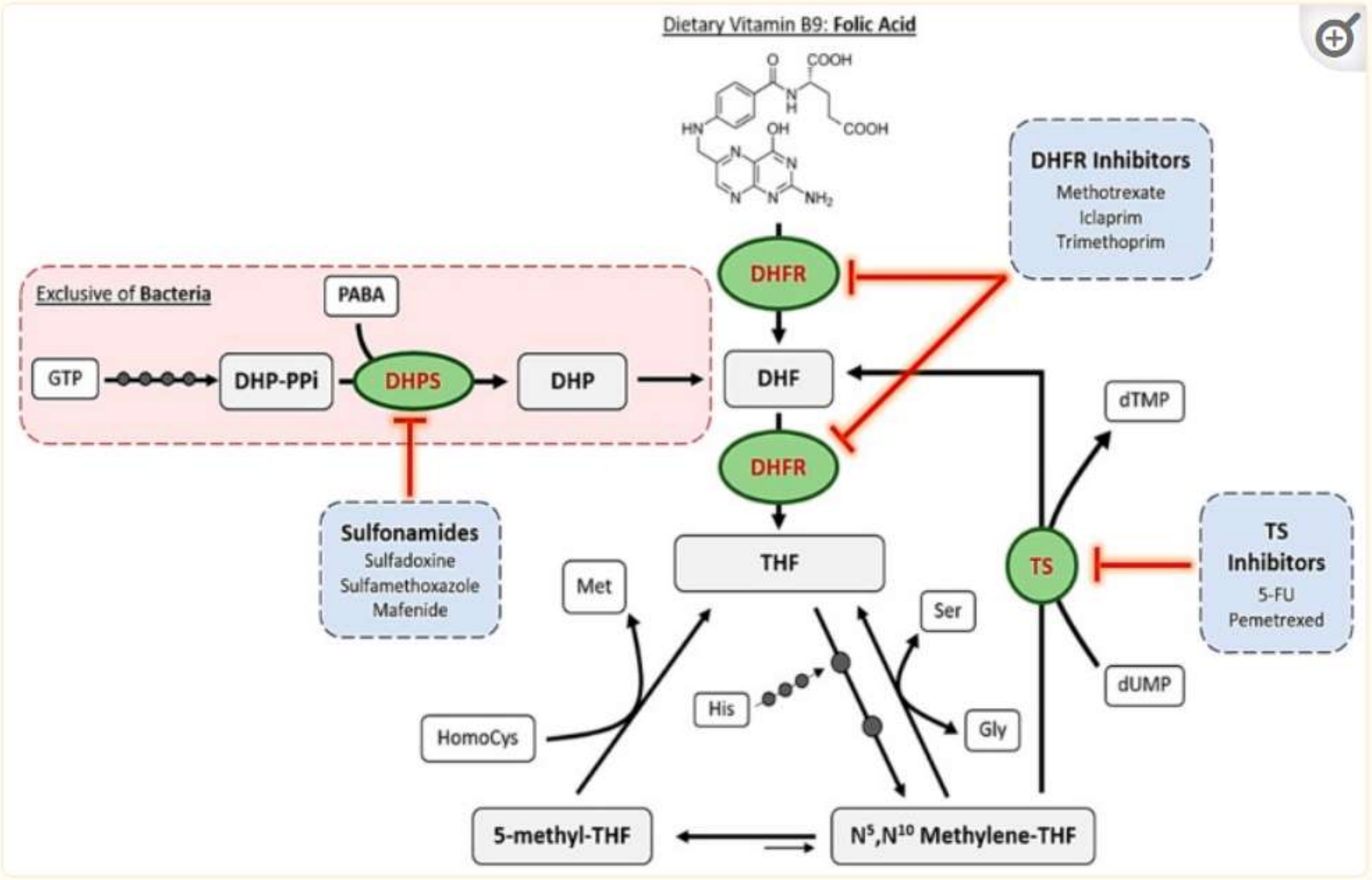
A. Cytostatics: alkylating agents and cytostatic antibiotics (1), inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)

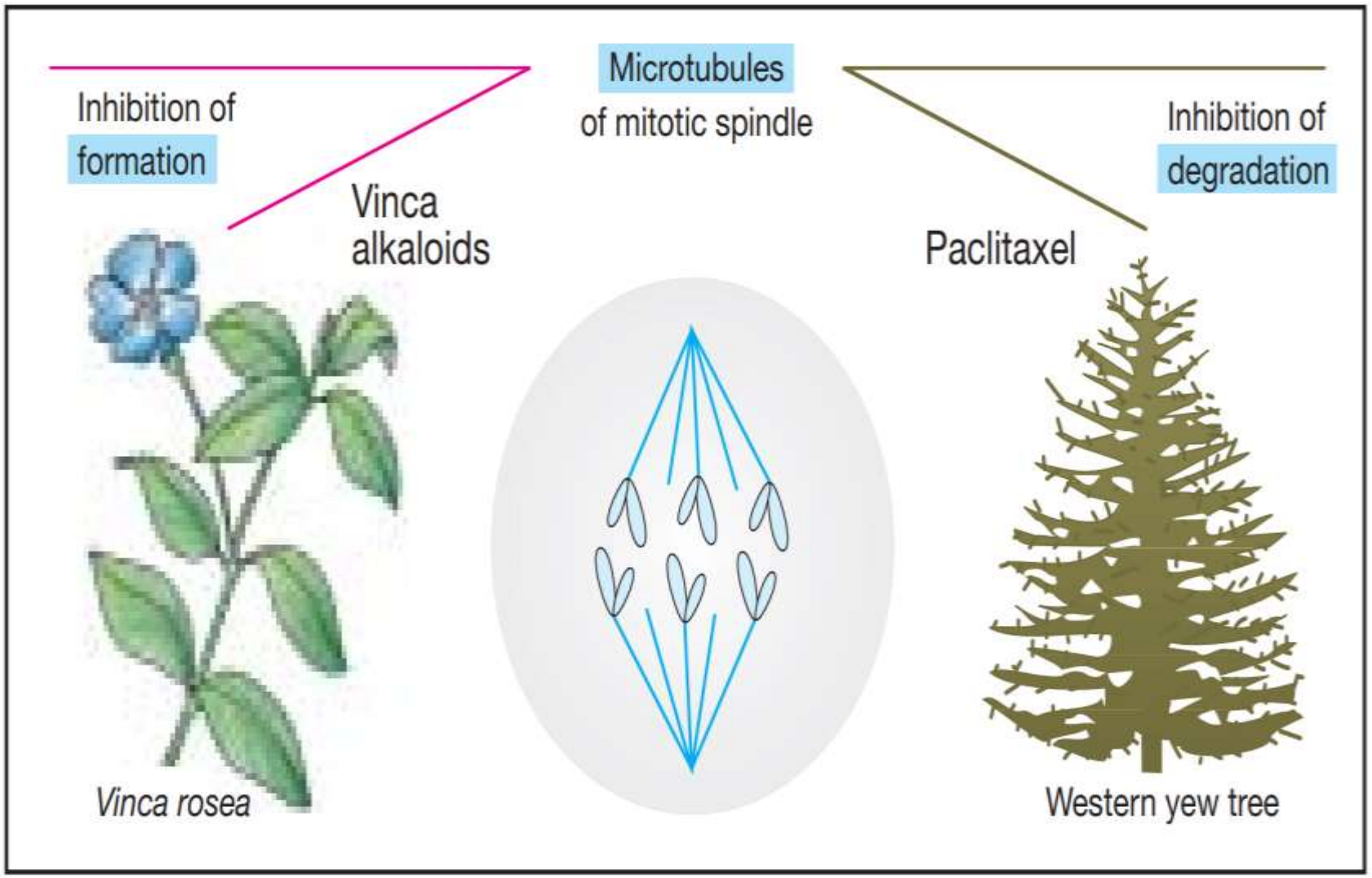

Damage to template
Alkylation e. g., by mechlor-ethamine
Cl–CH2–CH2
N–CH3
Cl–CH2–CH2
Insertion of daunorubicin, doxorubicin, bleomycin, actinomycin D, etc.
1
NH2
NH
N
O
N
N+
CH2–CH2
N
CH3
H2C
H2C
N+
N
O
HN
N
H2N
Streptomyces bacteria


Inhibition of nucleotide synthesis
Building blocks
Purines
Tetrahydro-
folate
Dihydrofolate
Reductase
Thymine
Nucleotide
Folic acid
RNA
Inhibition by
Aminopterin
Methotrexate
2



A. Cytostatics: alkylating agents and cytostatic antibiotics (1), inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)


Dietary Vitamin B9: Folic Acid
DHFR Inhibitors
Methotrexate
Iclaprim
Trimethoprim
Exclusive of Bacteria
PABA
GTP
DHP-PPi
DHPS
DHP
DHFR
DHF
DHFR
THF
Sulfonamides
Sulfadoxine
Sulfamethoxazole
Mafenide
dTMP
TS
TS Inhibitors
5-FU
Pemetrexed
dUMP
Met
Ser
His
Gly
HomoCys
5-methyl-THF
N5,N10 Methylene-THF



B. Cytostatics: inhibition of mitosis

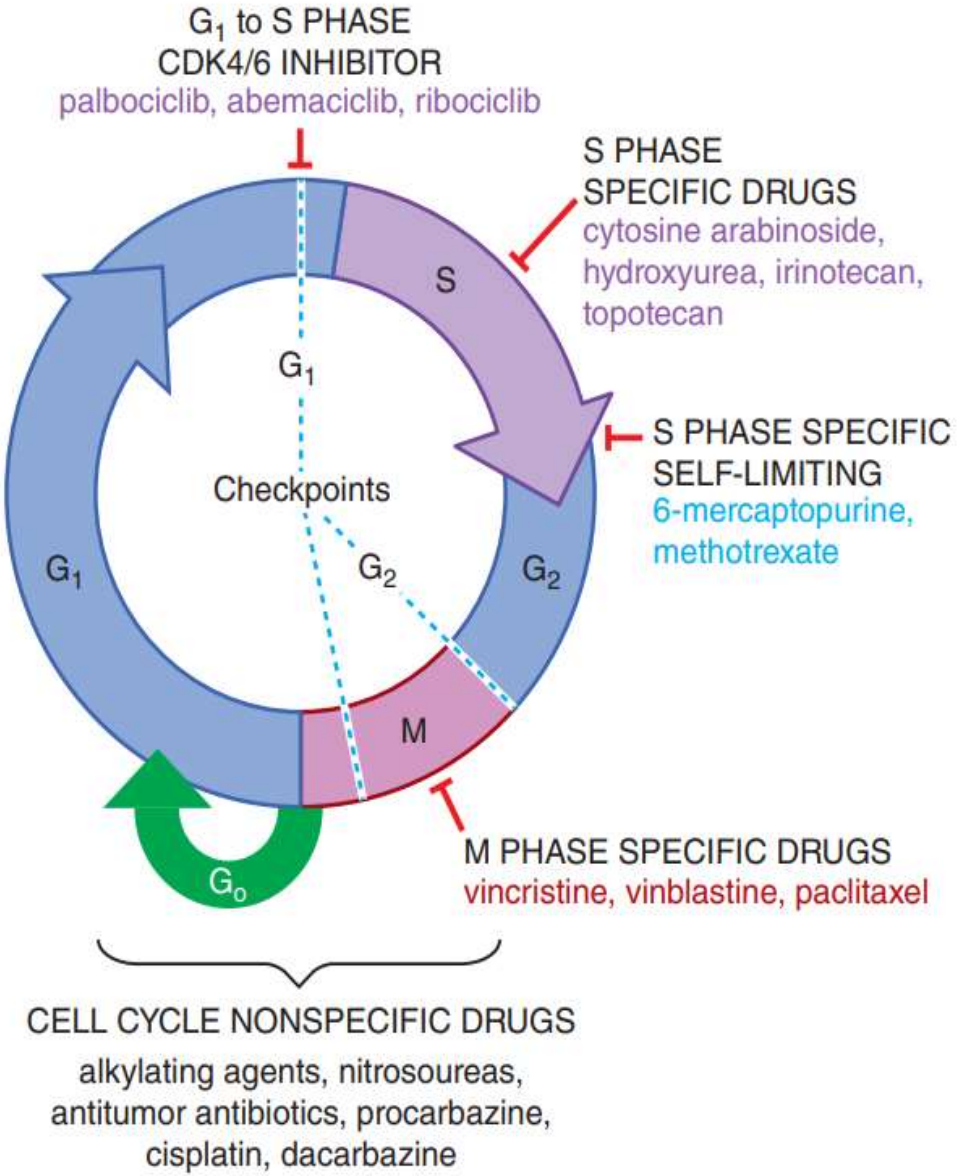
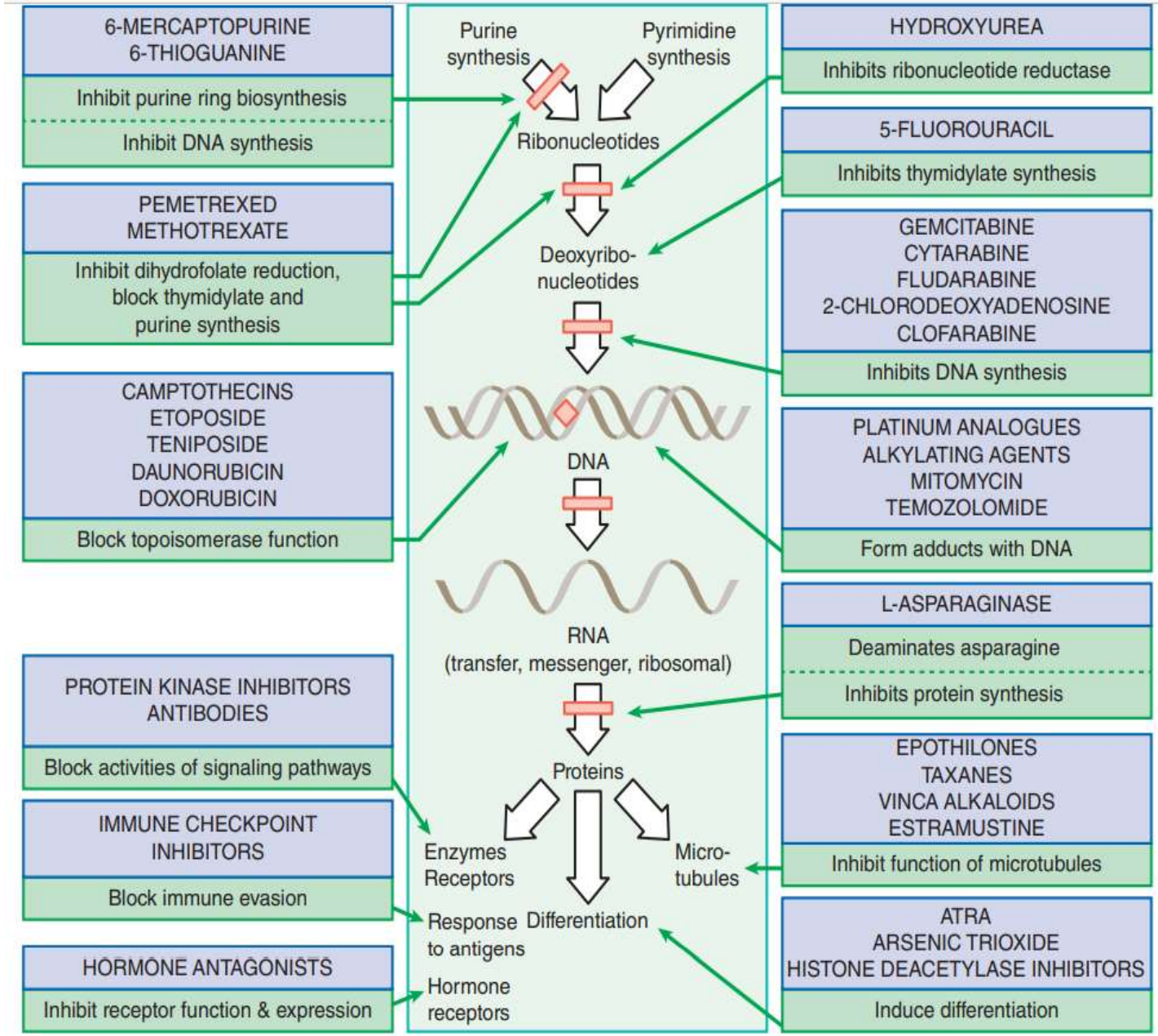
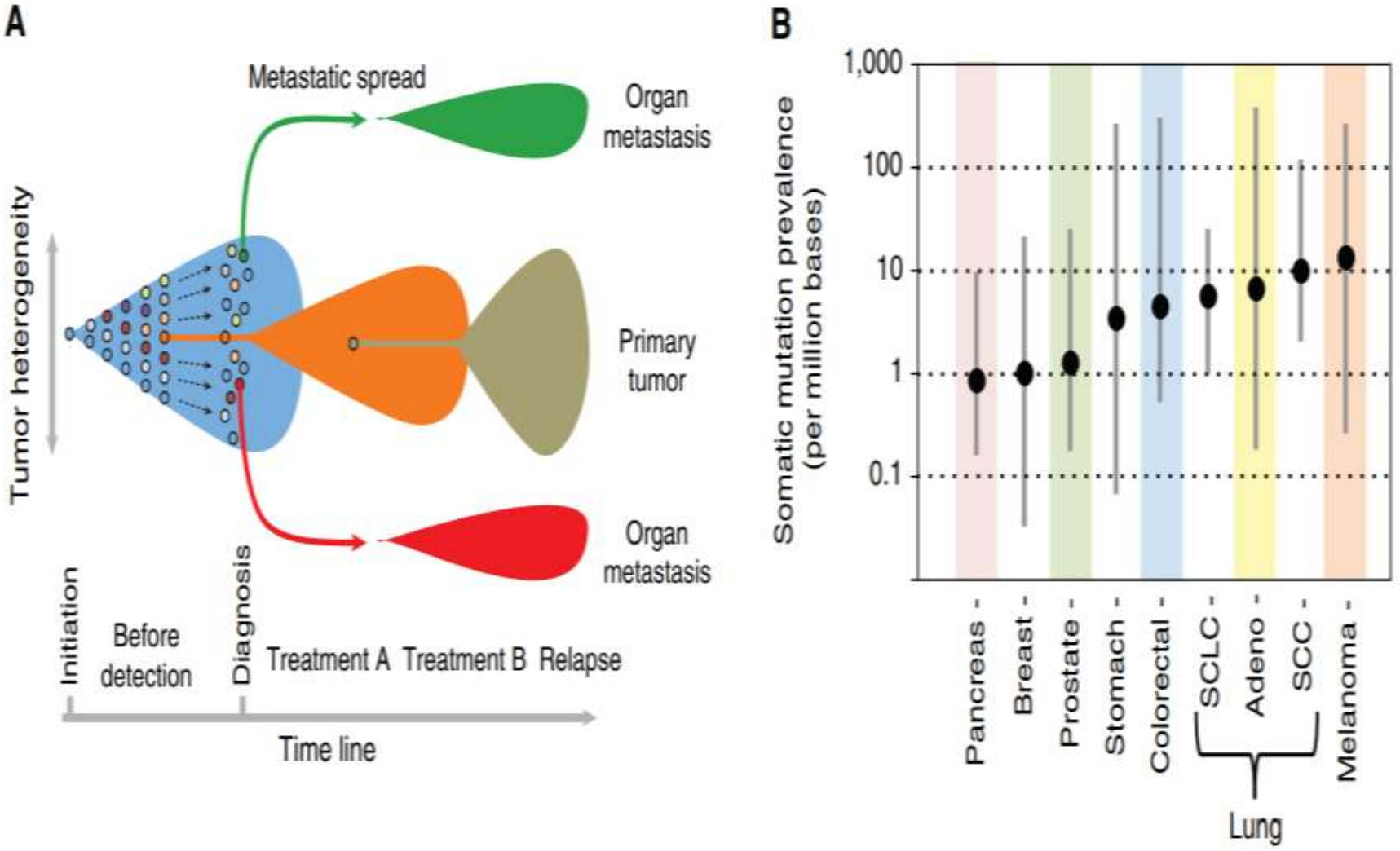


Figure 65–2 *Cell cycle specificity of drugs used in the treatment of cancer.*



Mechanisms and sites of action of some of the drugs used in the treatment of cancer.


A
Metastatic spread
Organ metastasis
Primary tumor
Organ metastasis
Tumor heterogeneity
Initiation
Before detection
Diagnosis
Treatment A
Treatment B
Relapse
Time line
B
Somatic mutation prevalence (per million bases)
1,000
100
10
1
0.1
Pancreas
Breast
Prostate
Stomach
Colorectal
SCLC
Adeno
SCC
Lung
Melanoma

- In the cancer cell, deregulation of the cell cycle control occurs by: • Abnormal growth factor function.
- Abnormal cDK function.
- Abnormal DNA synthesis; and Abnormal decreases in negative regulatory forces due to mutation in the tumour suppressor gene.

Anticancer Drugs - Classification

- I Phase-specific, cell-cycle active e.g. Antimetabolites, Bleomycin, Taxane, Epipodophylotoxin and Vinca alkaloids.
- II Phase non-specific e.g. Alkylating agents, Antitumour antibiotics Camptothecins and Platinum analogues. These can injure DNA at any phase of the cell cycle but appear to block the check points before the cell division.
- III Hormones and antihormone; and
- IV Miscellaneous eg Immunological agents Monoclonal antibodies (mAb).

TOXICITY

- Bone marrow and immuno-lymphoreticular system suppression.
- Damage to GI mucosa (enteritis and ulceration), nausea and vomiting.
- Loss of hair (Alopecia).
- Specific organ damage e.g. gonads, lungs.
- Impaired wound healing.
- Growth inhibition in children; and
- Teratogenicity.

ANTIBIOTICS

- These are products obtained from microorganisms and have prominent antitumour activity.
- Practically all of them intercalate between DNA strands and interfere with its template function.

Daunorubicin (Rubidomycin), Doxorubicin

- They are capable of **causing breaks in DNA strands by activating topoisomerase II** and generating **quinone** type free radicals.
- They have mutagenic and carcinogenic potential.
- Maximum action is exerted at **S phase**, but toxicity is usually exhibited in **G2 phase.**

MISCELLANEOUS CYTOTOXIC DRUGS

- These drugs (except L-asparaginase) have been developed by random synthesis and testing for antitumour activity.

Hydroxyurea

- It blocks the conversion of **ribonucleotides to deoxyribonucleotides** by inhibiting the enzyme **ribonucleoside diphosphate reductase**
- Interferes with DNA synthesis;
- Exerts S-phase specific action.

Procarbazine

- After metabolic activation (it is inactive as such), **procarbazine depolymerizes DNA** and causes chromosomal damage.
- Inhibition of nucleic acid synthesis also occurs.

Imatinib

- Inhibits the tyrosine protein kinases in chronic myeloid leukaemia (CML) cells

HORMONES

- They are not cytotoxic, but modify the growth of hormone-dependent tumours.
- All hormones are only palliative.

Glucocorticoids

- They have marked lympholytic action-are primarily used in acute childhood leukaemia and lymphomas

Estrogens

- They produce symptomatic relief in carcinoma prostate which is an androgen-dependent tumour

- Selective estrogen receptor modulators

(tamoxifen)

- Selective estrogen receptor down regulators

(fulvestrant)

- Aromatase inhibitors

(letrozole)

Antiandrogen

- Flutamide and bicalutamide
- Antagonise androgen action on prostate carcinoma and have palliative effect in advanced/metastatic cases

5-a. reductase inhibitor

- Finasteride and dutasteride
- Inhibit conversion of testosterone to dihydrotestosterone in prostate
- Palliative effect in advanced carcinoma prostate;

GnRH agonists

- They indirectly inhibit estrogen/ androgen secretion by suppressing FSH and LH release from pituitary
- Palliative effect in advanced estrogen/ androgen dependent carcinoma breast/prostate.

Antibiotics

- Produced by microorganisms
- suppress the growth of or kill other microorganisms at very low concentrations.
- The two major groups are penicillins and cephalosporins

- These are antibiotics having a β-lactam ring.

PENICILLINS

- First antibiotic to be used clinically in 1941.
- Obtained from the fungus *Penicillium notalum, but the* present source is a high yielding mutant of *P. chrysogenum.*

Chemistry and properties

- **The penicillin** nucleus consists of fused **thiazolidine and B-lactam** rings to which side chains are attached through an **amide linkage**
- Penicillin G (PnG), having a benzyl side chain at R (benzyl penicillin)

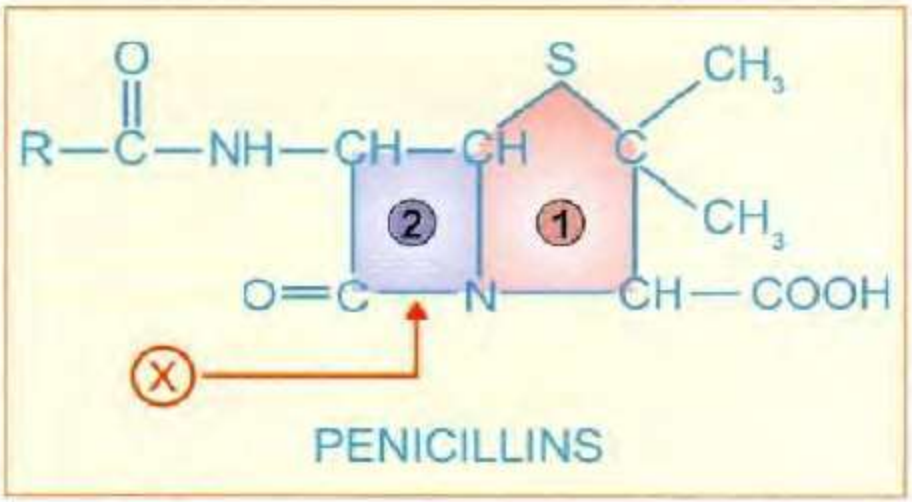


Fig. 52.1: Chemical structure of penicillins. (1) Thiazolidine ring; (2) β-lactam ring; (X) Bond which is broken by penicillinase (a β-lactamase)

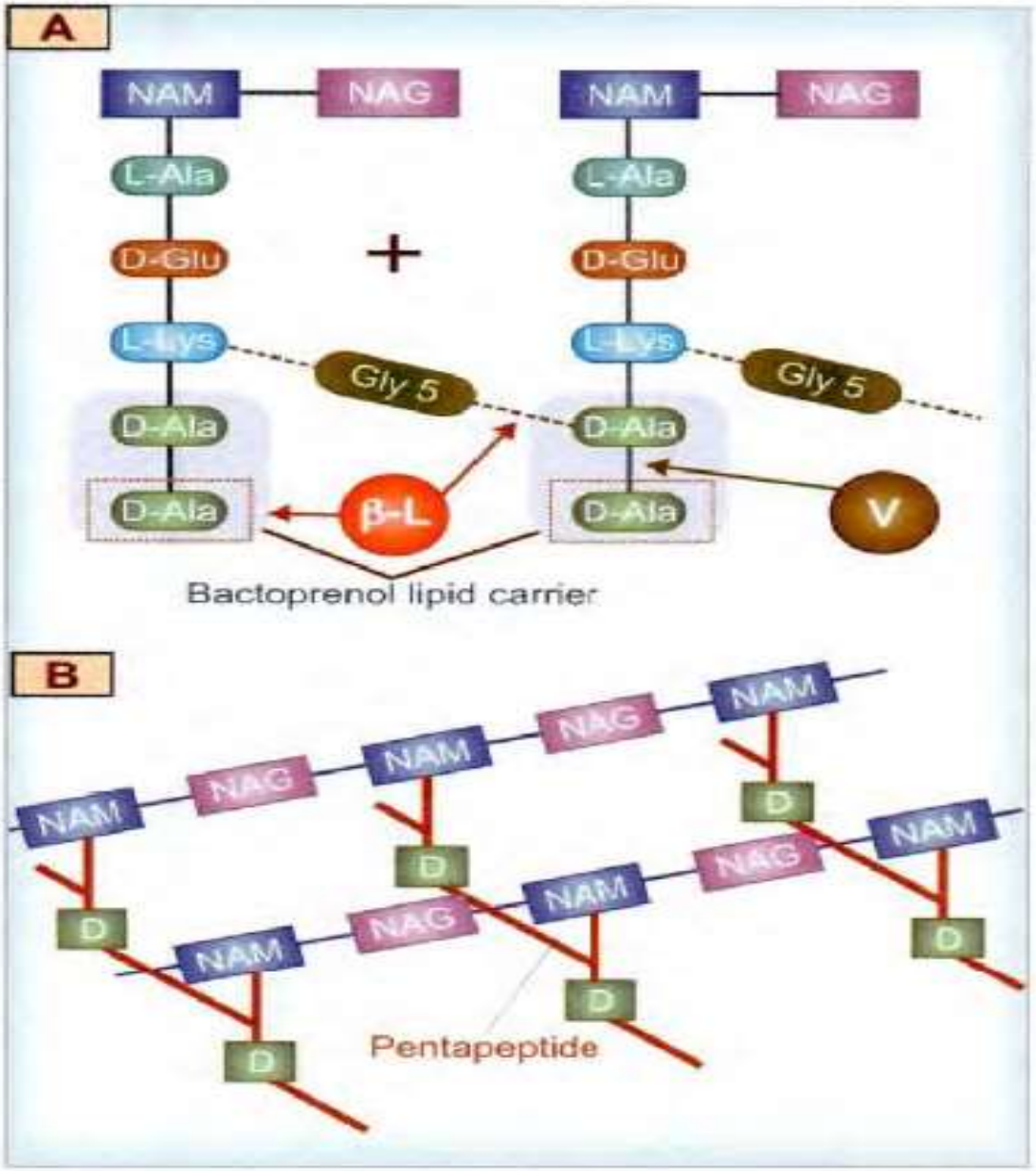
Mechanism of action

- B-lactam interfere with the synthesis of bacterial cell wall.
- The bacteria synthesize **UDP- N-acetylmuramic acid** pentapeptide, called ' Park nucleotide‘ and **UDP-N-acetyl glucosamine.**
- The peptidoglycan residues are linked together forming long strands and **UDP is split off.**
- The final step is cleavage of the terminal **D-alanine of the peptide chains by transpeptidases;** the energy so released is utilized for establishment of **cross linkages between peptide chains of the neighbouring strands**
- This cross linking provides stability and rigidity to the cell wall.

B-lactam antibiotics

- Inhibit the transpeptidases so that cross linking does not take place.
- These enzymes and related proteins constitute the *penicillin binding proteins (PBPs)* which have been located in the bacterial cell membrane.
- Each organism has **several PBPs, and PBPs obtained from different species** differ in their affinity towards different B-lactam antibiotics.
- Differing sensitivity to the various B-lactam antibiotics.

- When susceptible bacteria divide in the presence of a B-lactam antibiotic
- Cell wall deficient (CWD) forms are produced.
- Because the interior of the bacterium is hyperosmotic, the CWD forms swell and burst
- Bacterial lysis occurs- Bactericidal action.


A
NAM
NAG
L-Ala
D-Glu
L-Lys
Gly 5
D-Ala
D-Ala
β-L
V
Bactoprenol lipid carrier
B
Pentapeptide

Gram-positive bacteria

- Cell wall is almost entirely made of peptidoglycan, which is >50 layers thick and extensively cross linked, so that it may be regarded as a single giant mucopeptide molecule.

Gram-negative bacteria

- Cell wall consists of alternating layers of lipoprotein and peptidoglycan (each layer 1- 2 molecule thick with little cross linking).
- This may be the reason for higher susceptibility of the gram-positive bacteria to PnG.

Bacterial resistance

- **Many bacteria are** inherently insensitive to PnG because in them the target enzymes and **PBPs are located deeper under lipoprotein** barrier where PnG is unable to penetrate or have low affinity for PnG.
- The primary mechanism of acquired resistance is production of penicillinase.

Pharmacokinetics

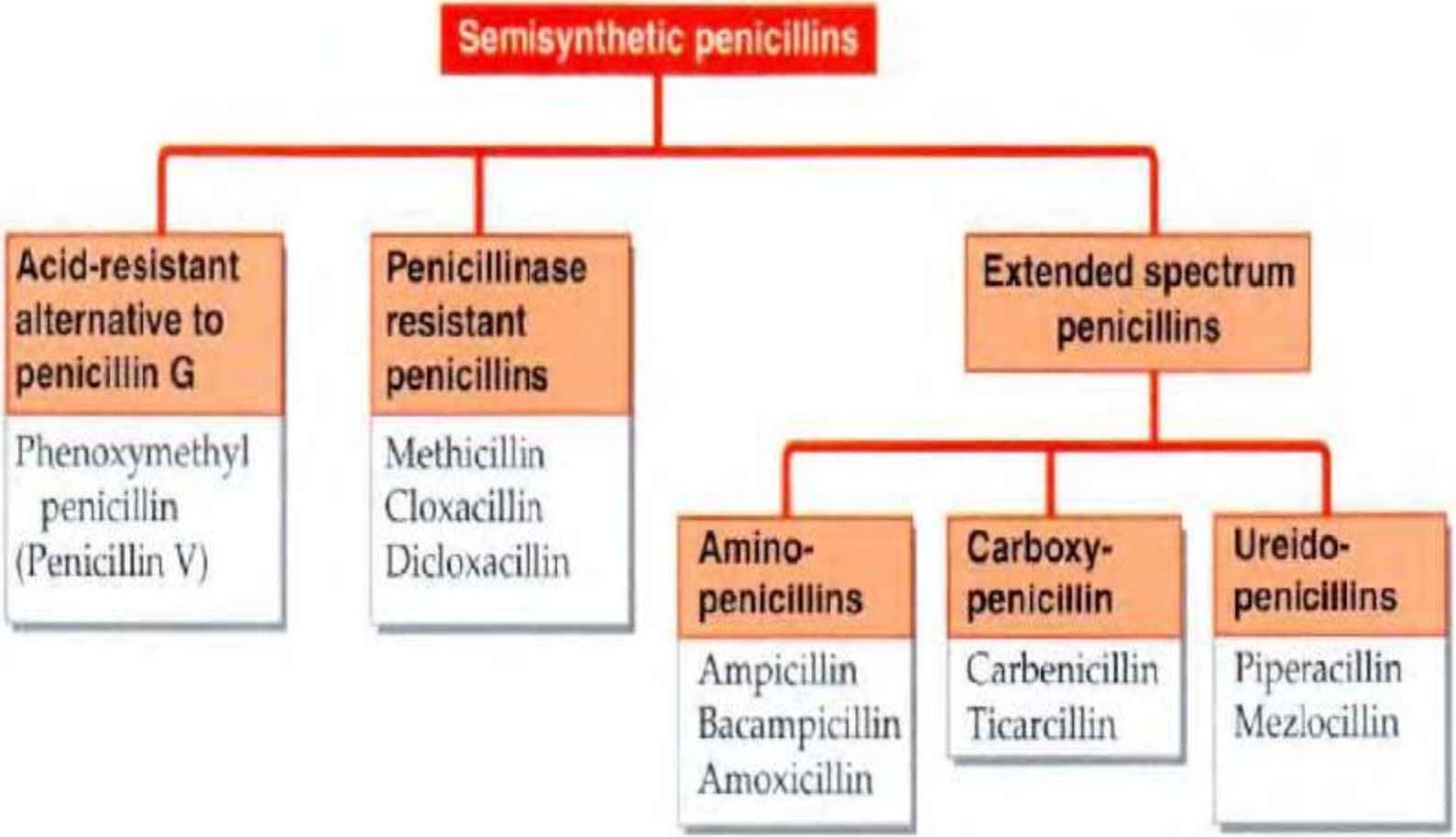
- Penicillin G is acid labile, therefore destroyed by gastric acid.
- Less than 1/3"' of an oral dose is absorbed in the active form.
- Absorption of sod. PnG from i.m. site is rapid and complete; peak plasma level is attained in 30 min.
- It is distributed mainly extracellularly; reaches most body fluids
- Penetration in serous cavities and CSF is poor.
- However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites.
- About 60% is plasma protein bound.
- It is little metabolized because of rapid excretion.
- I 0% by glomerular filtration

Hypersensitivity

- An incidence of 1- 10% is reported.
- Individuals with an allergic diathesis are more prone to develop ppenicillin allergy are-rash, itching, urticaria and fever.
- Wheezing, angioneurotic edema, serum sickness and exfoliative dermatitis are less common.
- Anaphylaxis is rare (I to 4 per l 0,000 patients), but may be fatal

- History of penicillin allergy must be elicited before injecting it.
- A scratch test or intradermal test (with 2- 10 U) may be performed first.

- *Sypillis*
- *Leprospirosis:*
- *Diphtheria Antitoxin*
- *Tetanus and gas gangrene Antitoxin*
- Rheumatic fever
- Bacterial endocarditis


Semisynthetic penicillins
Acid-resistant alternative to penicillin G
Phenoxymethyl penicillin (Penicillin V)
Penicillinase resistant penicillins
Methicillin
Cloxacillin
Dicloxacillin
Extended spectrum penicillins
Amino-penicillins
Ampicillin
Bacampicillin
Amoxicillin
Carboxy-penicillin
Carbenicillin
Ticarcillin
Ureido-penicillins
Piperacillin
Mezlocillin

CLASSIFICATION

1. ***Acid-resistant alternative to penicillin G*** Phenoxymethyl penicillin (Penicillin V).
2. ***Penicillinase-resistant penicillins*** Methicillin, Cloxacillin.
3. ***Extended spectrum penicillins***
   (a) *Aminopenicillins*: Ampicillin, Bacampicillin, Amoxicillin.
   (b) *Carboxypenicillins*: Carbenicillin, Ticarcillin.
   (c) *Ureidopenicillins*: Piperacillin, Mezlocillin.

β-lactamase inhibitors Clavulanic acid
Sulbactam, Tazobactam

ACID-RESISTANT ALTERNATIVE TO PENICILLIN-G

- Phenoxymethyl penicillin (Penicillin V)
- It differs from PnG only in that it is acid stable.
- Oral absorption is better; peak blood level is reached in 1 hour and plasma tllz is 30-60 min.
- Streptococcal pharyngitis, sinusitis, otitis media, prophylaxis of rheumatic fever

Cloxacillin- PENICILLINASE-RESISTANT PENICILLINS

- It has an isoxazolyl side chain
- Highly penicillinase as well as acid resistant.
- It is more active than methicillin against penicillinase producing Staph, but not against MRSA.

EXTENDED SPECTRUM PENICILLINS

- These semisynthetic penicillins are active against a variety of gram-negative bacilli as well

Ampicillin

- It is active against all organisms sensitive to PnG; in addition, many gram-negative bacilli, e.g. H. influenzae, E. coli, Proteus, Salmonella and Shigella are inhibited.

Carboxypenicillins

- Carbenicillin
- The special feature of this penicillin congener is its activity against Pseudomonas aeruginosa and indole positive Proteus which are not inhibited by PnG or aminopenicillins.

Ureidopenicillins

- Piperacillin
- This antipseudomonal penicillin is about 8 times more active than carbenicillin.
- It has good activity against **Klebsiella** and is used mainly in neutropenic / immunocompromised patients having serious gram-negative infections, and in burns.

BETA-LACTAMASE INHIBITORS

- BETA-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate
- BETA-lactam antibiotics by opening the BETA lactam ring

Clavulanic acid

- Obtained from Streptomyces clavuligerus, it has a □-lactam ring but no antibacterial activity of its own.
- It inhibits a wide variety (class II to class V) of □-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria.

- Clavulanic acid is a 'progressive' inhibitor
- binding with □ -lactamase is reversible initially, but becomes covalent later-inhibition increasing with time.
- Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme.
- It permeates the outer layers of the cell wall of gram negative bacteria and inhibits the periplasmically located □ -lactamase.

CEPHALOSPORINS

- Semisynthetic antibiotics derived from a fungus *Cephalosporium.*

CEPHALOSPORIN

- All cephalosporins are bactericidal and have the same mechanism of action as penicillin,
- i.e. inhibition of bacterial cell wall synthesis.
- However, they bind to different PBPs than those which bind penicillins.
- This may explain differences in spectrum, potency and lack of cross resistance.

First generation cephalosporins

Parenteral	*Oral*
Cefazolin	Cephalexin
	Cefadroxil

Second generation cephalosporins

Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil
	Cefprozil

Third generation cephalosporins

Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	Ceftamet pivoxil

Fourth generation cephalosporins

Parenteral

Cefepime

Cefpirome

Fifth generation cephalosporins

Parenteral

Ceftaroline fosamil

Ceftobiprole medocaril

*Not available in India

FIRST GENERATION CEPHALOSPORINS

- These were developed in the 1960s, have high activity against gram-positive but weaker against gram-negative bacteria.

Cefazolin

- Streptococci, gonococci, meningococci, C. diphtheriae, H. influenzae, clostridia and Actinomyces.
- Activity against Klebsiella and E. coli is relatively high, but it is quite susceptible to staphylococcal lactamase.
- It can be given i.m. (less painful) as well as i.v. and has a longer tlh (2 hours) due to slower tubular secretion; attains higher concentration in plasma and in bile.
- It is the preferred parenteral first generation cephalosporin, especially for surgical prophylaxis.

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