ANTICANCER DRUGS

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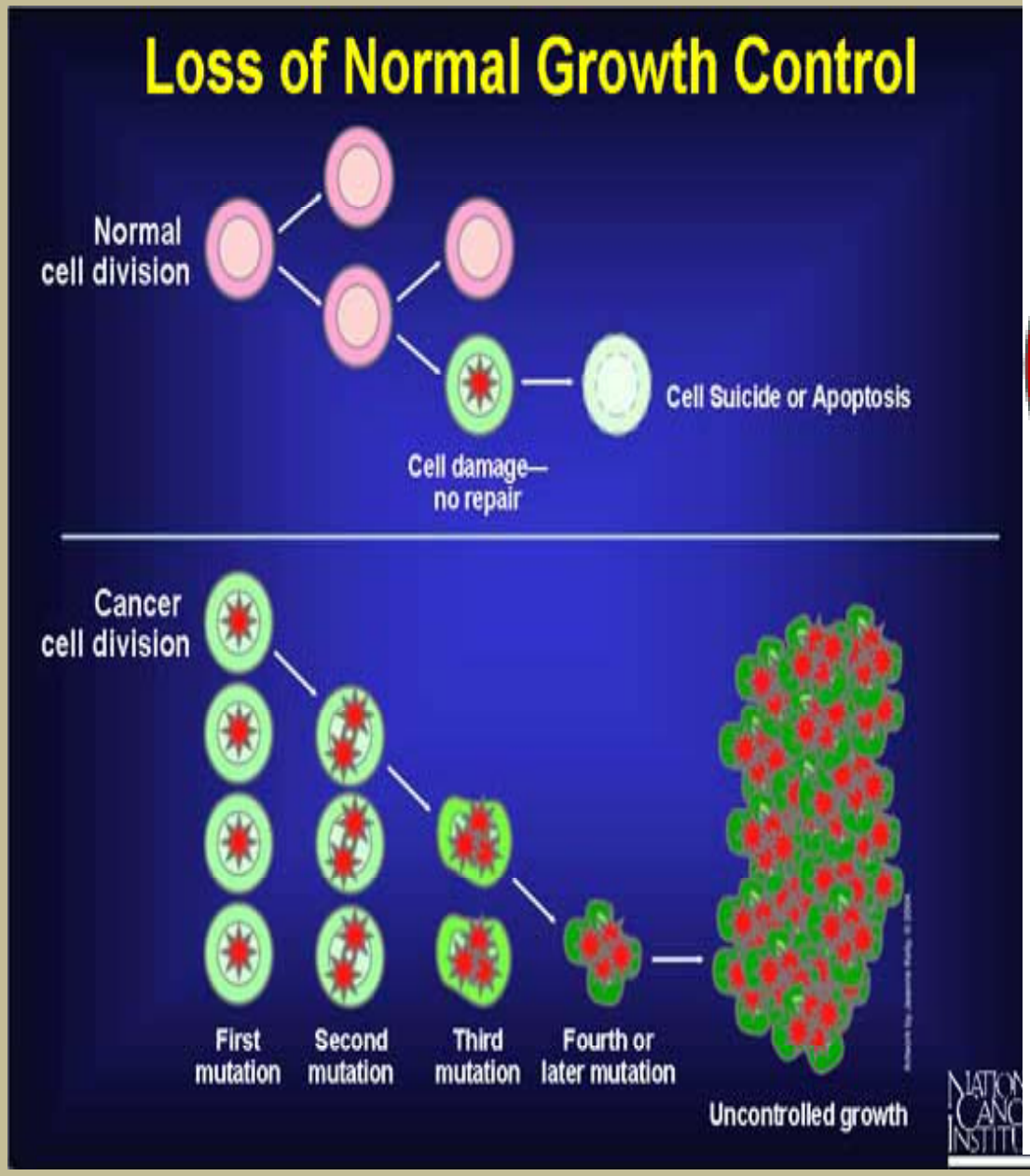
ANTICANCER DRUGS

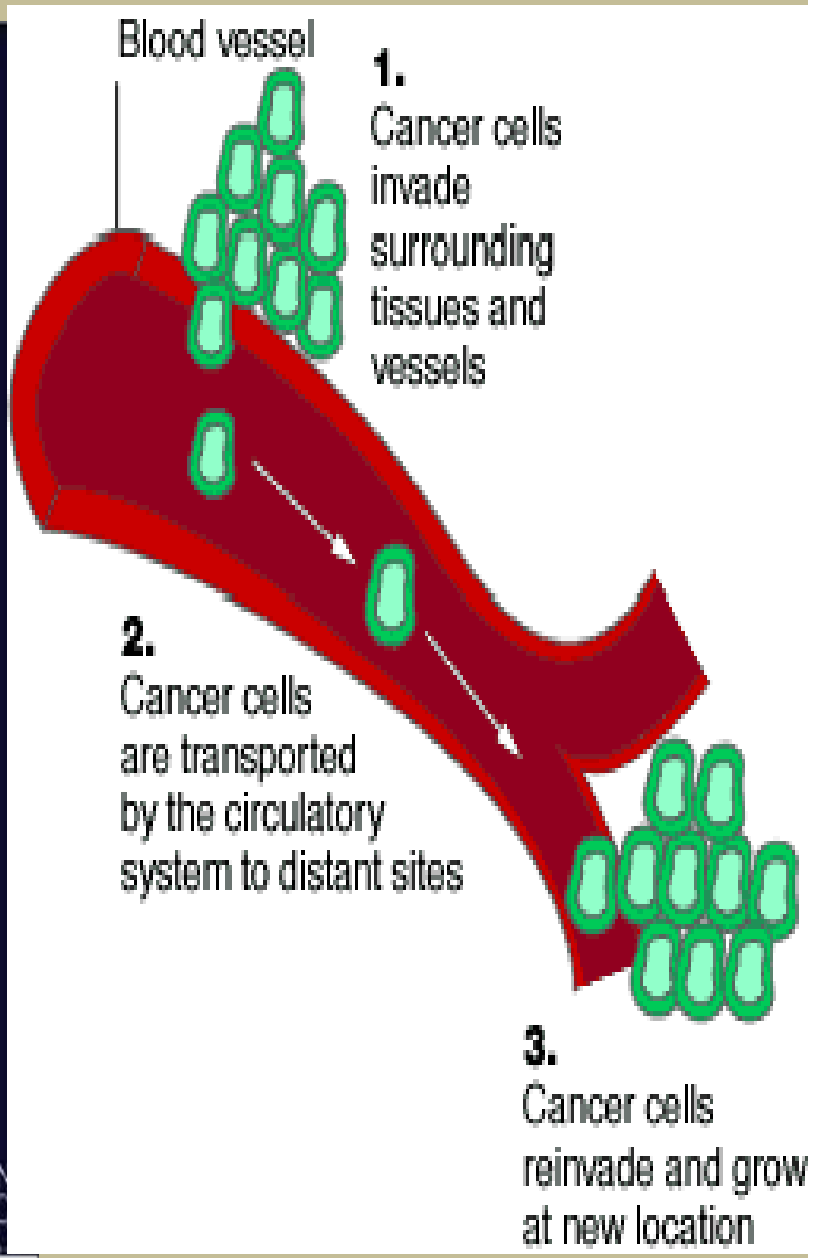
- Drugs used for the treatment of cancer
- Also known as cancer chemotherapy

Cancer

Definition = Uncontrolled division of cells leading to a tumour formation

- Local spread of cancerous tissue cause damage to surrounding blood vessels, nerves, & nearby organs
- Can spread to distant organs by blood & lymphatics =====***Metastasis***
- Cancer, malignant neoplasm & malignant tumour = synonymous (metastasize)
- **Benign tumour**=Non invasive, unable to metastasize


Loss of Normal Growth Control
Normal cell division
Cell Suicide or Apoptosis
Cell damage—no repair
Cancer cell division
First mutation
Second mutation
Third mutation
Fourth or later mutation
Uncontrolled growth


Blood vessel
1. Cancer cells invade surrounding tissues and vessels
2. Cancer cells are transported by the circulatory system to distant sites
3. Cancer cells reinvade and grow at new location

Causes of Cancer

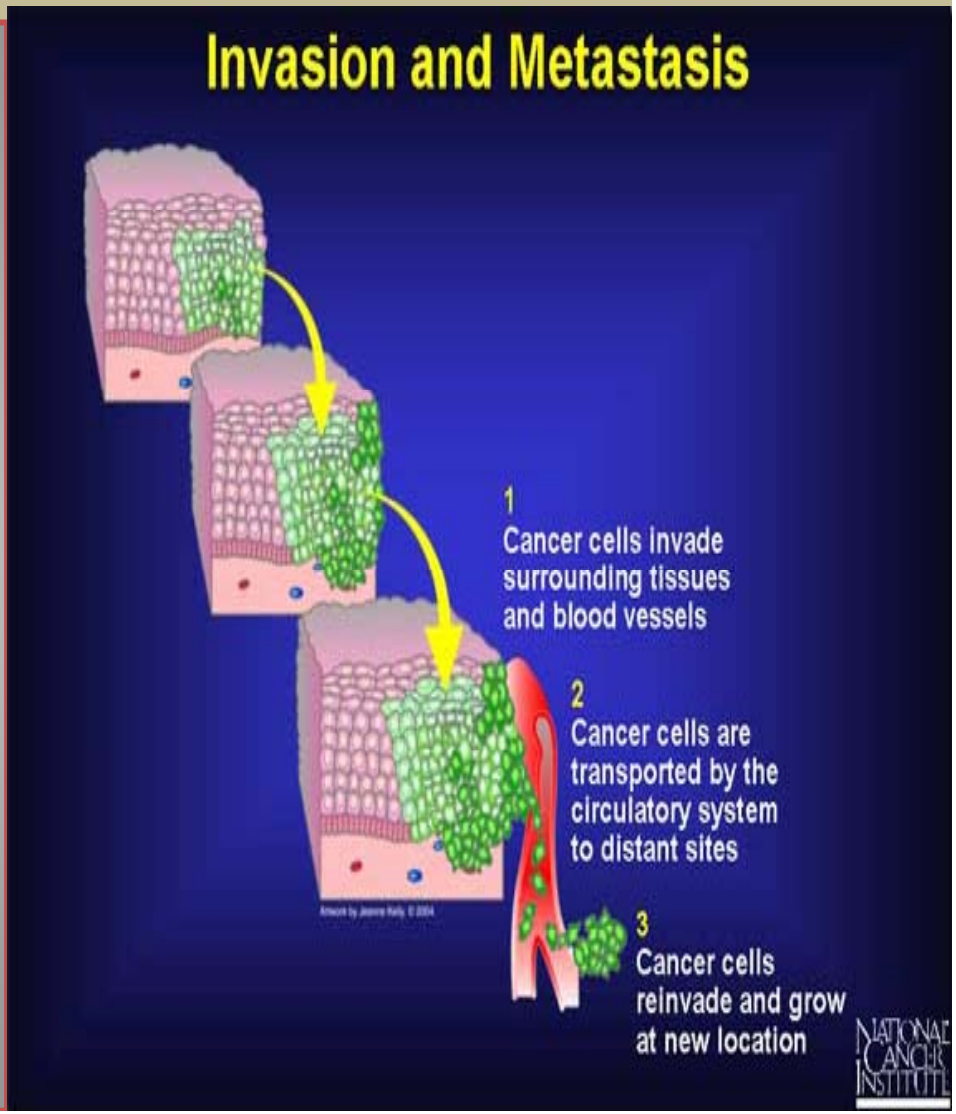
- **Exposure to ionizing radiation** = causing acute leukemias, thyroid cancer, breast cancer, lung cancer & others
- **Viruses** ---expression of viruses induced neoplasm
- **Genetic mutation-**---

i) Inactivation of tumour suppression genes

ii) Activation of proto-oncogenes to oncogenes

Pathogenesis of Cancer

- Uncontrolled proliferation
- Dedifferentiation and loss of function
- Invasiveness
- Metastasis.



Treatment of Cancer

a) Surgery

Removal of tumour

b) Radiation

To kill the remaining cancer cells by radiotherapy

Also kill actively dividing cells (bone marrow, hair follicles & mucosa cells)

c) Chemotherapy

Treatment of cancer with drugs

DRUGS USED IN CANCER

1-Cytotoxic drugs

A-Alkylating agents

B-Antimetabolites

C-Cytotoxic antibiotics

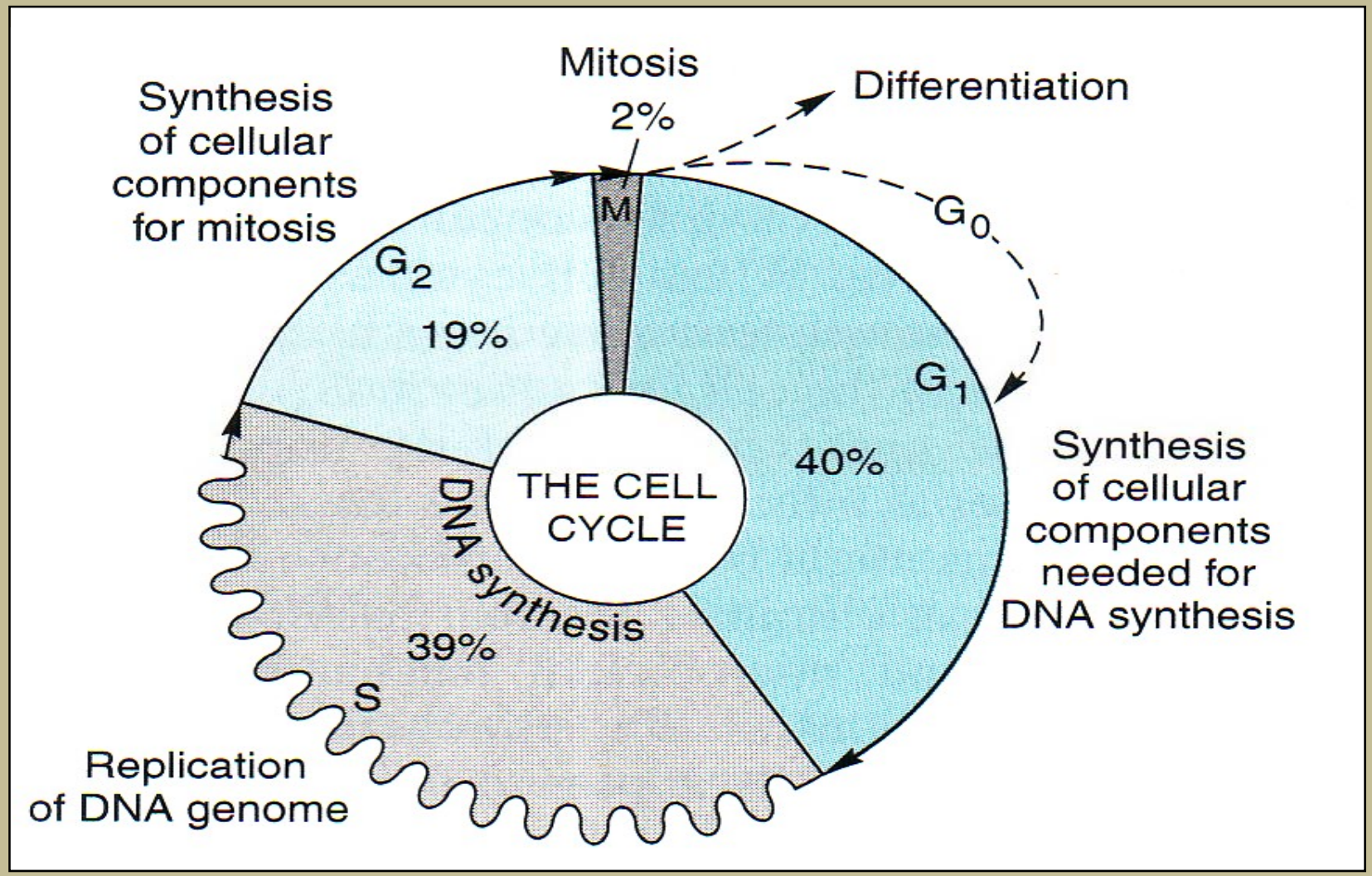
D-Plant derivatives

2-Hormones

3-Enzymes

e.g. L-Asparaginase

CELL CYCLE & CANCER



The Classification of Anticancer Drugs

A) According to chemical structure

E.g., Alkylating Agents, Antimetabolite, Antibiotics, Plant Extracts , Hormones , Others

Cont.

B) According to the cycle or phase specificity of the drug

i) Cell cycle nonspecific agents (CCNSA)

These drugs are active thought cell cycle

e.g. *Alkylating Agent, Platinum Compounds & Antibiotics*

ii) Cell cycle specific agents (CCSA)

Drugs act during a specific phase of cell cycle

E.g., *Antimetabolites, antitumour antibiotics, plant alkaloids*

1-Alkylating Agents

A. Nitrogen mustards

E.g., Cyclophosphamide

B. Nitrosoureas

E.g., Carmustine & Lomustine

C. Alkyl sulfonates

E.g., Busulfan

D. Related Drugs

E.g., Cisplastin

Alkylating Agents

Mechanism of Action

- Drugs contain alkyl group in their chemical structure. The specific type of chemical bonding with DNA occurs ⇒ *alkylation*.
- The N7 of guanine is main target for alkylation in DNA (alkylation of adenosine or cytosine also occurs to lesser degree)
- Bifunctional agent= react with two groups⇒ cause intra- or inter chain cross linking
- Cont.

- After alkylation, DNA is unable to replicate and therefore can no longer synthesize proteins and other essential cell metabolites.

Other Effects= Excision of guanine base or pairing of G with T instead of C occurs

- **Consequently** ⇒ cell reproduction is inhibited and the cell eventually dies
- Alkylating agents=not cell cycle specific but cells are most susceptible to alkylation in late G1 & S phases of cell cycle & express block in G2

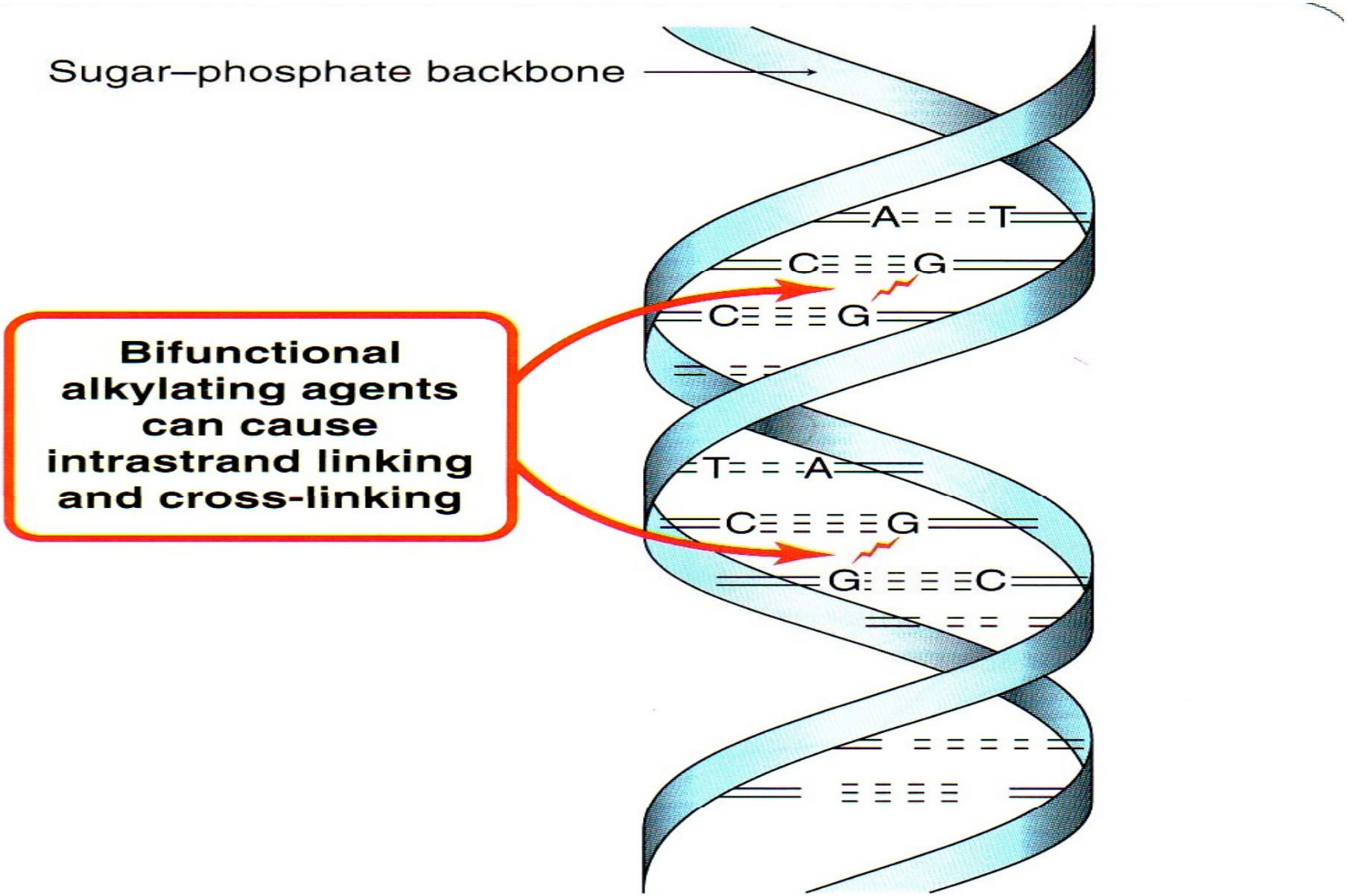


Fig. 50.4 The possible effects of bifunctional alkylating agents on DNA: cross-linking two guanines. (G, guanine; C, cytosine; A, adenine; T, thymine.)

Pharmacological actions of Alkylating agents

- Inhibit the division of rapidly dividing cells including; cancerous cells, normal cells (bone marrow, lymphoid tissue, mucosal surface of GIT, hair follicle, gonads)
- Cause leukopenia, thrombocytopenia, alopecia, sterility, development of vesicles on skin, mucosa & eyes
- Nausea & vomiting

A- Nitrogen Mustard

Cyclophosphamide

- Most commonly used alkylating agent
- It is inactive until metabolized in the liver by the P450 mixed function oxidases.
- It has a pronounced effect on lymphocytes and can be used as an immunosuppressant.

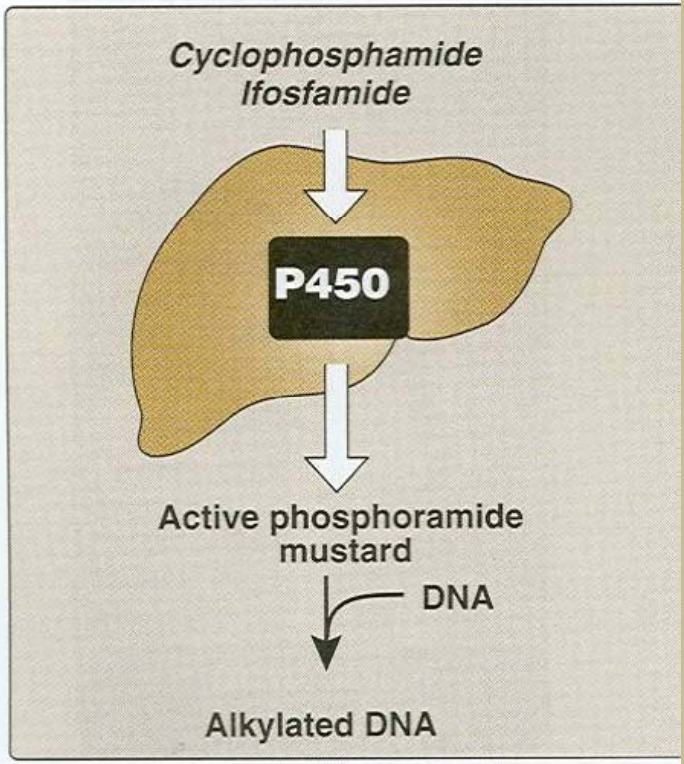


Figure 39.22
Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

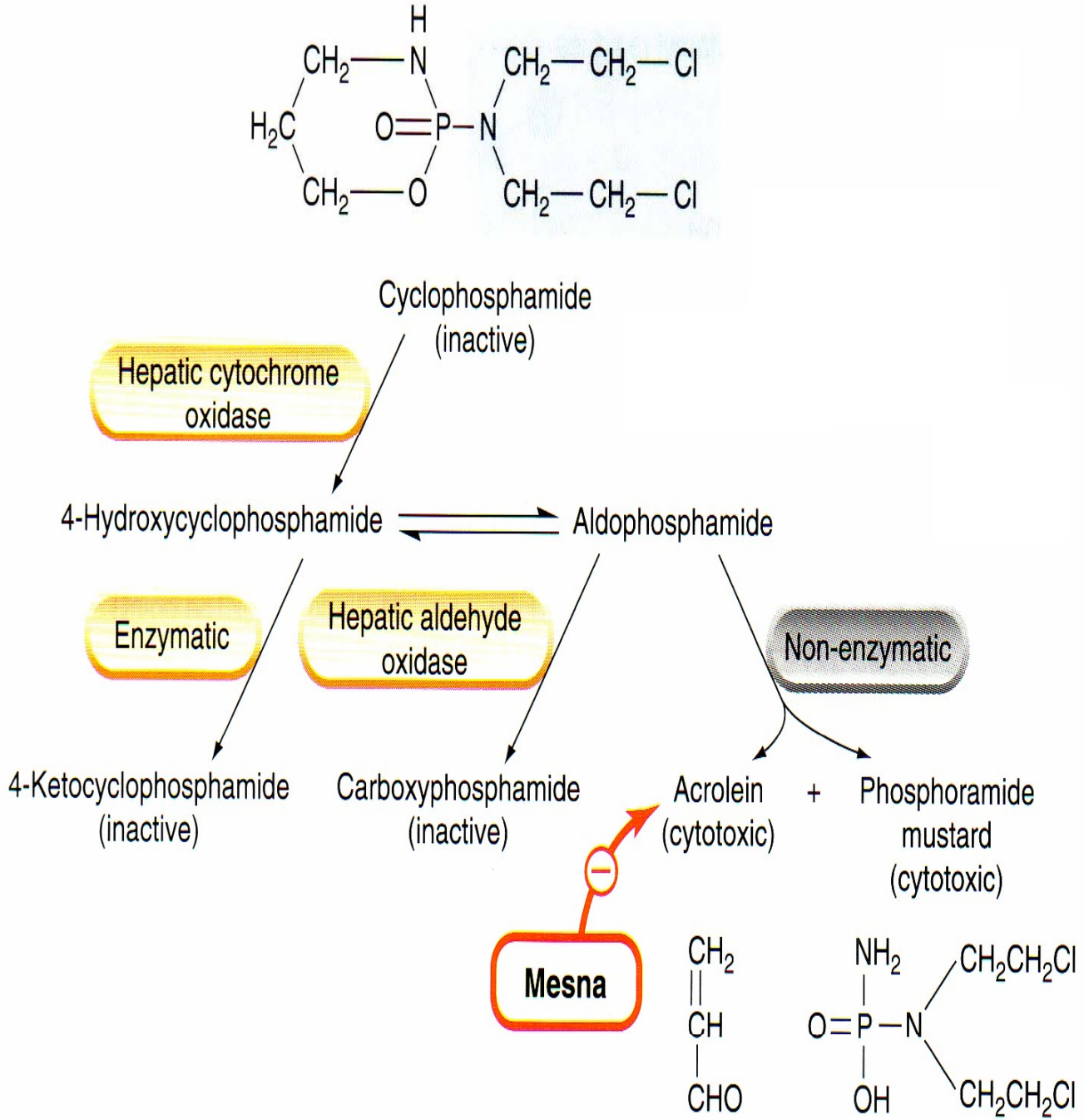


Fig. 50.6 The metabolism of cyclophosphamide.
Cyclophosphamide is inactive until metabolised in the liver by P450 mixed function oxidases to 4-hydroxycyclophosphamide, which forms aldophosphamide reversibly. Aldophosphamide is conveyed to other tissues where it is converted to phosphoramide mustard, the actual cytotoxic molecule, and acrolein, which is responsible for unwanted effects. The part of the cyclophosphamide molecule that gives rise to the active metabolites is shown in the blue box. Mesna (sodium 2-mercaptoethane sulfonate) interacts with acrolein, forming a non-toxic compound.

- Given by orally, i.v, im

Uses

- Used in treatment of lymphomas, ,
- In Burkitt's lymphoma,
- myeloma,
- chronic leukemias.

ADR:- Nausea ,vomiting, bone marrow depression and **haemorrhagic cystitis** (inflammation of urinary bladder)

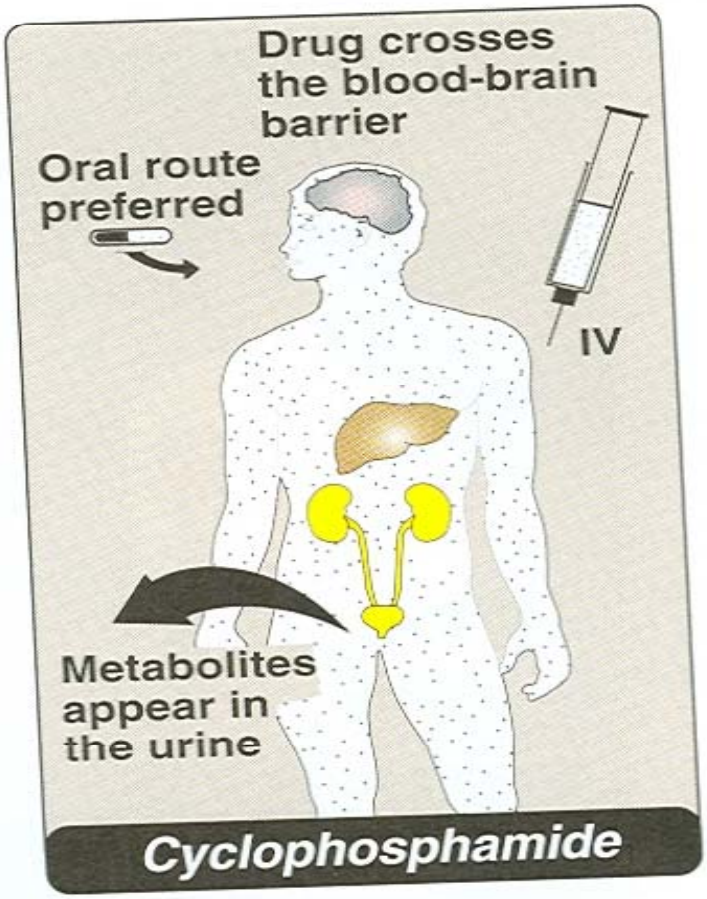
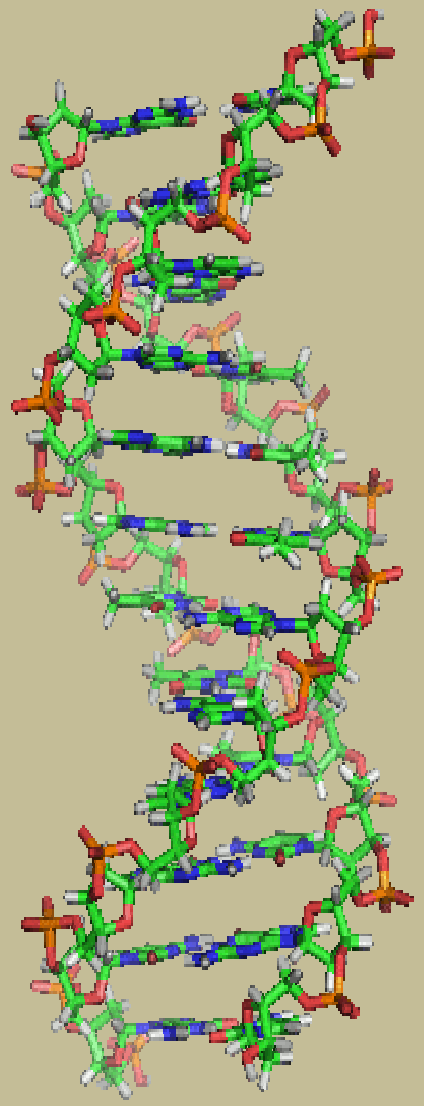


Figure 39.23
Administration and fate of *cyclophosphamide*.

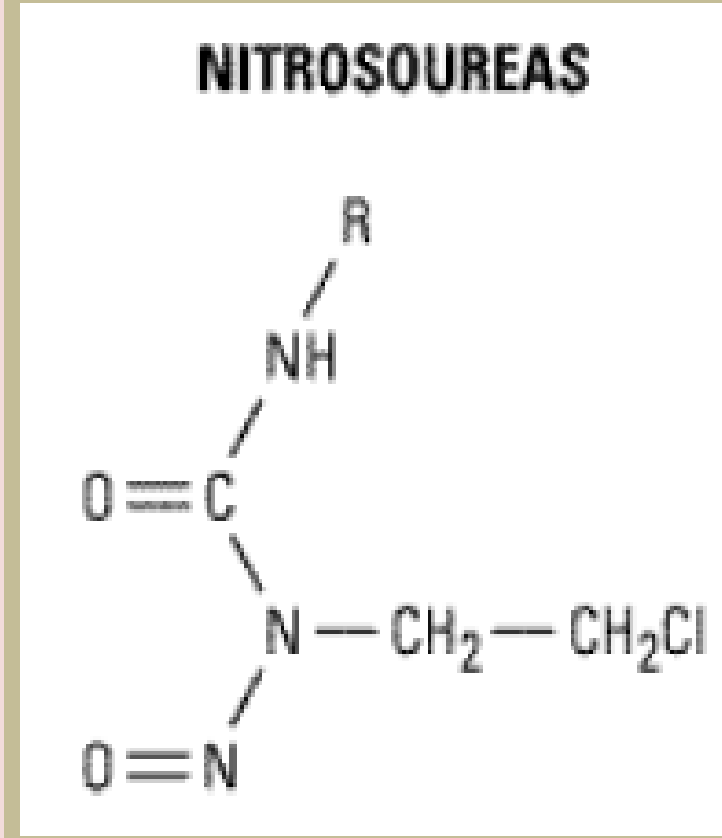
- **Haemorrhagic cystitis** → is due to acrolein (metabolite)
- ameliorated by ↑fluid intake and by taking sulfhydryl donors such as
- sodium-2-mercaptoethane sulfonate, or **mesna**

- Mesna + acrolein = non toxic compound
- **Mesna** = used during treatment with cyclophosphamide to ↓ its toxicity



B-NITROSOURES

- e.g. **Lomustine** and **Carmustine**
- They are **CCNSA**
- They are lipid soluble and can, therefore, cross the blood-brain barrier,



- B/c of their excellent penetration they can be used against tumours of the brain and meninges.
- Severe cumulative depressive effect on the bone marrow.

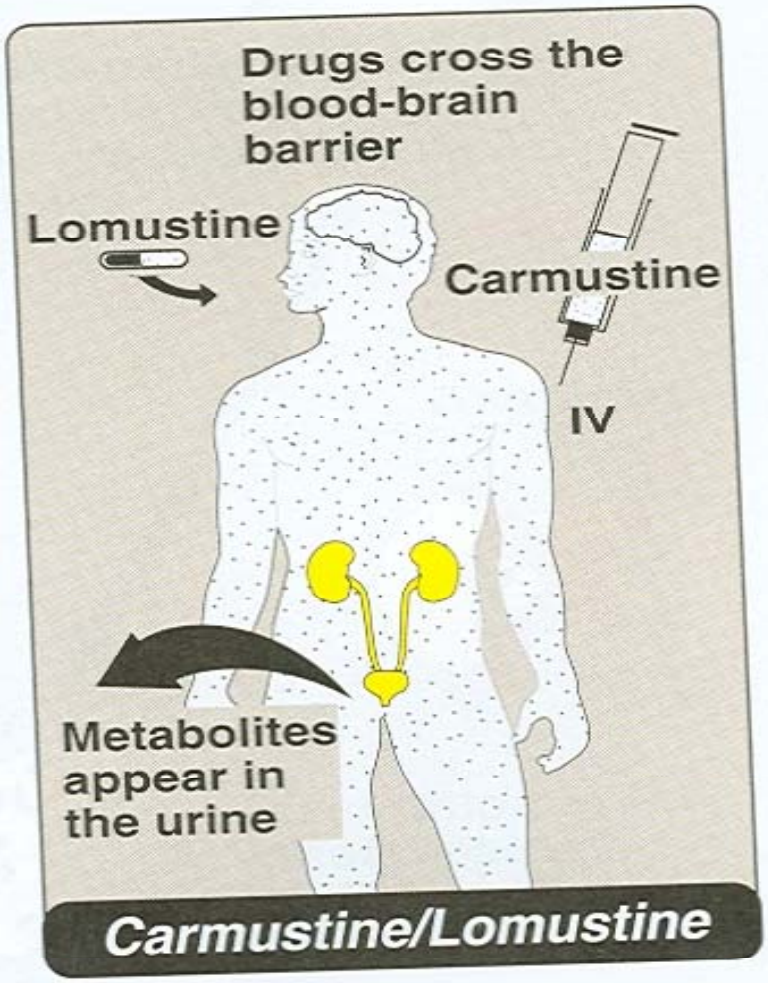


Figure 39.24
Administration and fate of *carmustine/lomustine*.

C- Alkyl sulfonates

Busulphan

- It has selective effect on bone marrow, depresses the formation of granulocytes and platelets in low dosage and red cells in higher dosage. In high doses, it produces a rare but sometimes fatal pulmonary fibrosis, ”busulfan lung”.
- No effect on lymphoid tissue or the gastrointestinal tract.
- It is used in chronic **granulocytic leukemia**.

D- Other related drugs

Cisplastin

Water soluble complex=central Pt

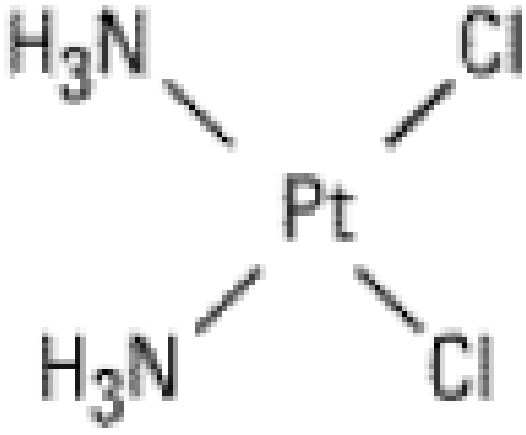
Actions= similar to alkylating agent

On entering into cell, Cl- ion dissociate

Complex reacts with water & then

With DNA

Causes intrastrand cross linking==breaking of H bonds b/w G & C bases ⇒ denaturation of DNA chain



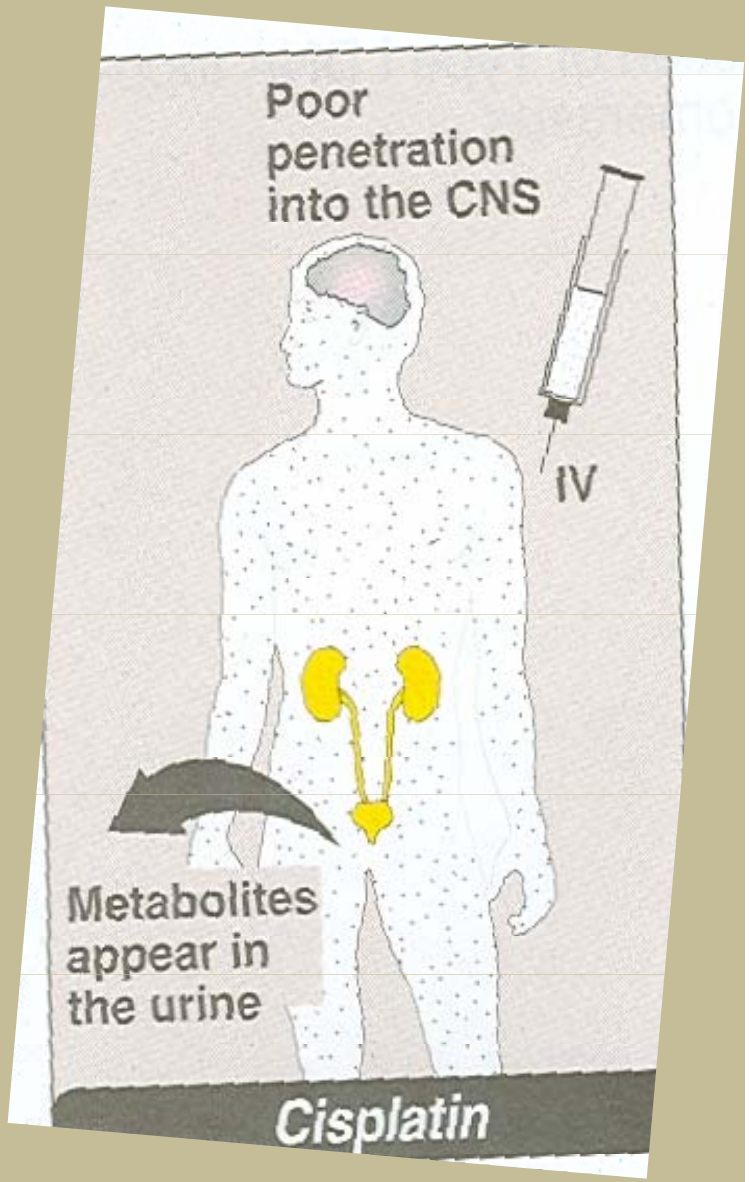
Cisplatin

Pharmacokinetics

- Cisplastin is given by slow intravenous injection or infusion.

Clinical uses (solid tumours)

Lung cancer, esophageal & gastric cancer, head & neck cancer & genitourinary cancers (testicular, ovarian & bladder)



Adverse Effects

- It is seriously nephrotoxic
- It has low myelotoxicity , very severe nausea and vomiting.
- **Ondansetron** (5HT3 antagonist)=effective to reduce nausea & vomiting
- Tinnitus and hearing loss in the high frequency range, peripheral neuropathies, hyperuricaemia and anaphylactic reactions.

2- Antimetabolites

- **S phase-specific** drugs (CCSA) that are structural analogs of essential metabolites & that interfere with DNA synthesis

Classification of Antimetabolites

a) **Folic acid antagonists** e.g. ***Methotrexate***

b) **Pyrimidine Analogues** e.g. ***Fluorouracil & Cytarabine***

c) **Purine Analogues** e.g., ***Fludarabine, pentostatin & mercaptopurine***

a) Folic acid antagonist

- E.g., **Methotrexate** (most widely used anticancer drug)
- The structures of methotrexate and folic acid are similar.
- Folates are essential for the synthesis of purine nucleotides and thymidylate ⇒DNA
- Folates consist of three elements: a **pteridine ring, *p*-aminobenzoic acid (PABA) and glutamic acid**
-

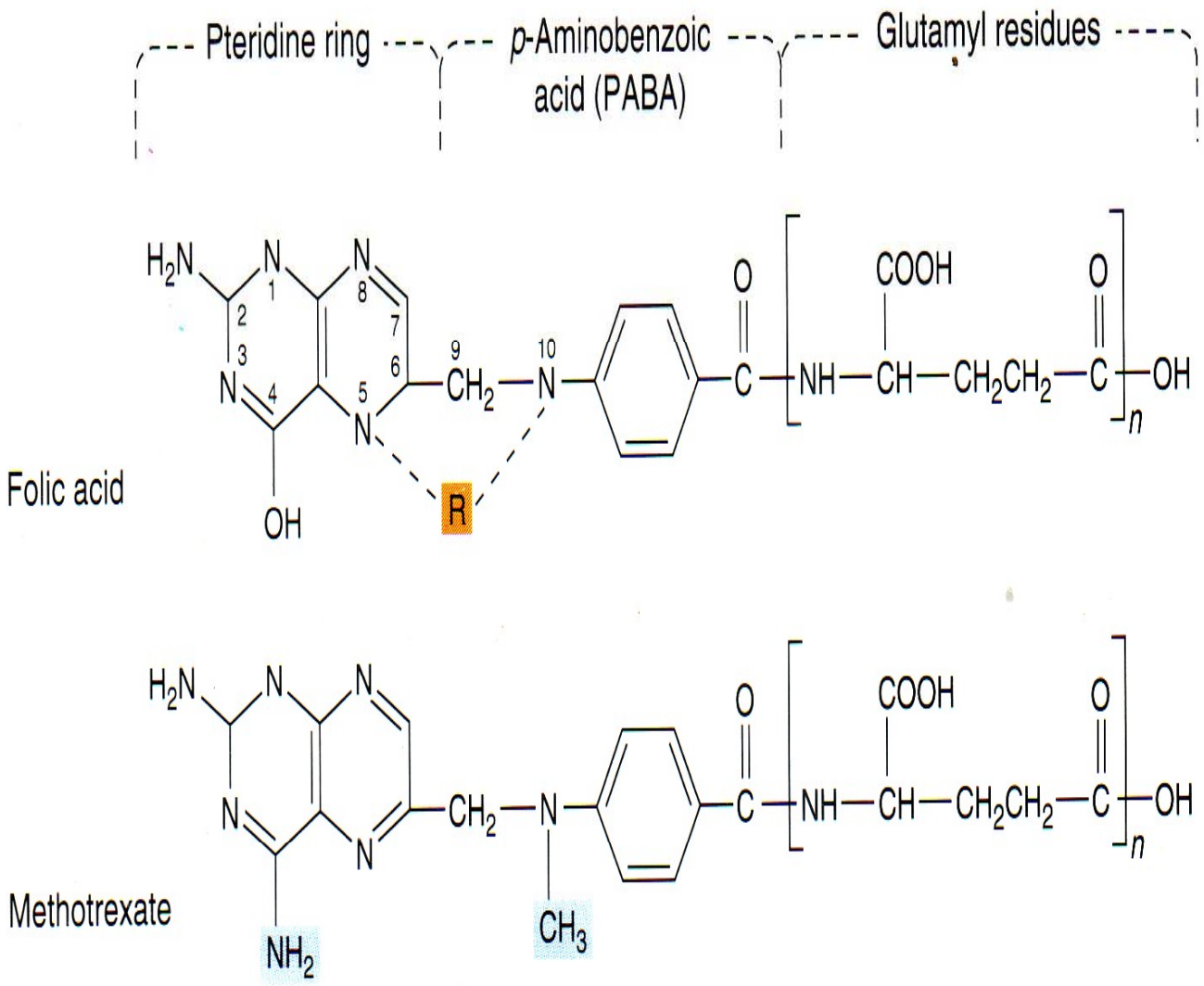


Fig. 50.7 Structure of folic acid and methotrexate. Both compounds are shown as polyglutamates. In tetrahydrofolate, one-carbon groups (R, in orange box) are transported on N5 or N10 or both (shown dotted). (See Figs 21.2 and 21.3.) The points at which methotrexate differs from endogenous folic acid are shown in the blue boxes.

Mechanism of Action of Methotrexate

- In order to act as coenzymes, folate must be reduced to tetrahydrofolate (FH4).
- **Methotrexate** has a higher affinity for dihydrofolate reductase than FH2
- Methotrexate is actively transported into mammalian cells and inhibits dihydrofolate reductase, (enzyme converts folate to tetrahydrofolate) & depletes intracellular FH4

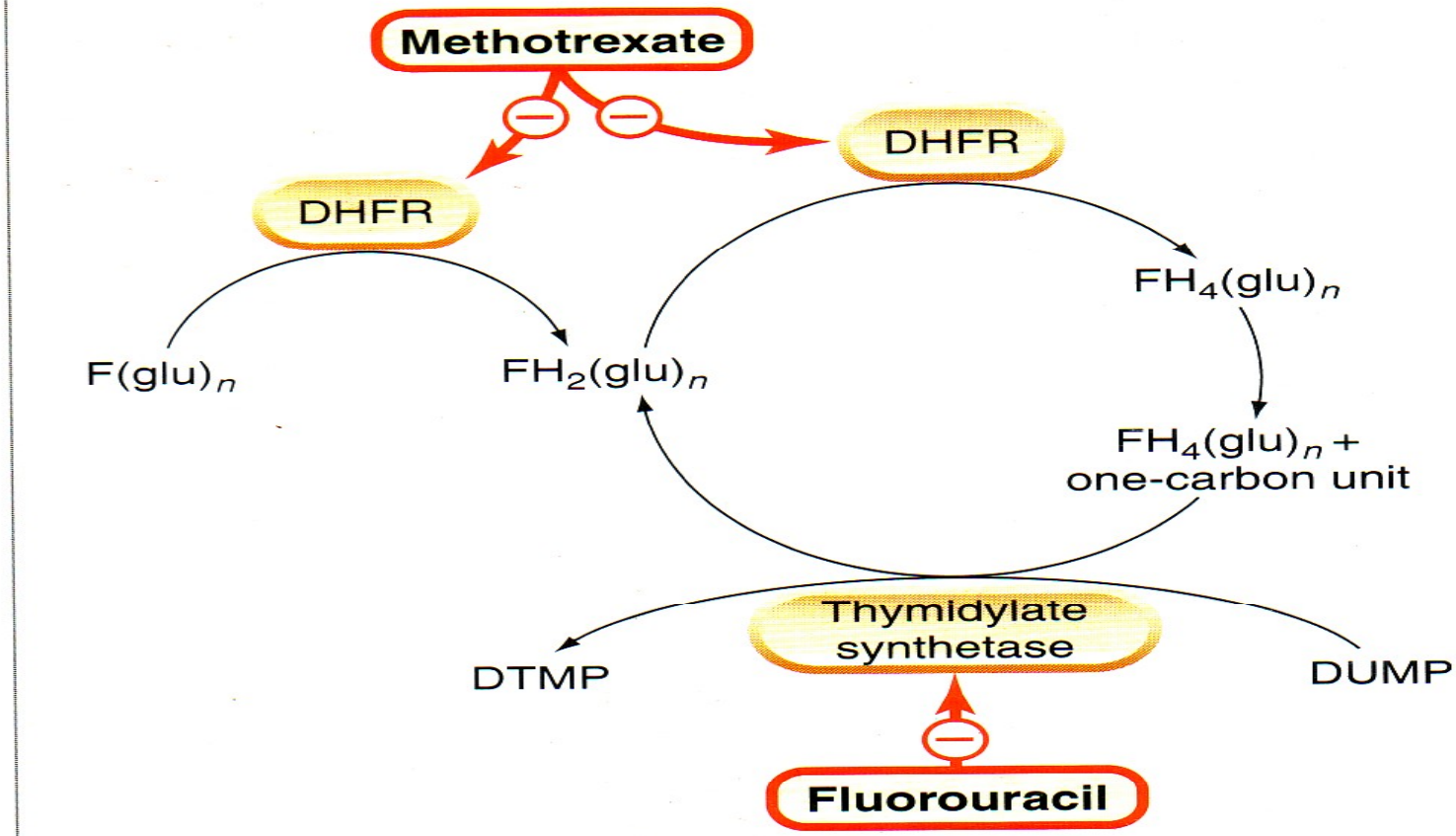


Fig. 50.8 Simplified diagram of action of methotrexate and fluorouracil on thymidylate synthesis. Tetrahydrofolate polyglutamate $FH_4(glu)_n$ functions as a carrier of a one-carbon unit, providing the methyl group necessary for the conversion of 2′-deoxyuridylate (DUMP) to 2′-deoxythymidylate (DTMP) by thymidylate synthetase. This one-carbon transfer results in the oxidation of $FH_4(glu)_n$ to $FH_2(glu)_n$. Fluorouracil is converted to FDUMP, which inhibits thymidylate synthetase. (DHFR, dihydrofolate reductase.)

- Given –oral, IV, IM, intra-thecal

Low lipid solubility===poor

Penetration into brain

- It is actively taken up into cells by the transport system used by folate and is metabolized to polyglutamate derivatives, which are retained in the cell for weeks.

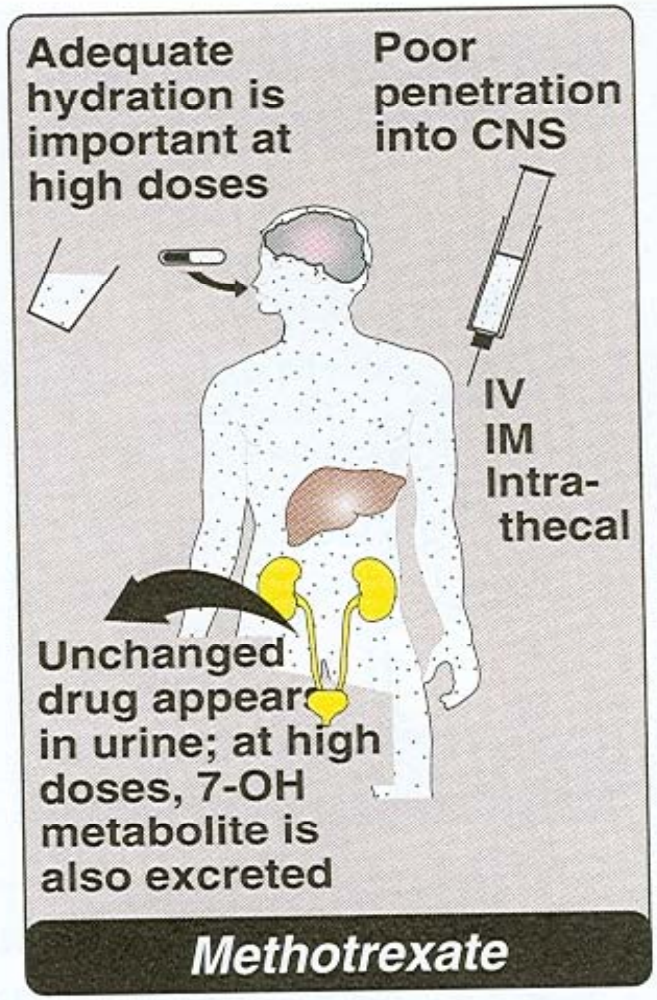


Figure 39.8
Administration and fate of *methotrexate*.

- ***Clinical uses:***-acute lymphoblastic leukemias, Burkitt's lymphoma, in adjuvant therapy of breast carcinoma; in the palliation of metastatic breast, head, neck, cervical, and lung carcinomas
- *ADR:-* depression of the bone marrow, damage to the epithelium of the GIT, pneumonitis.
- At high-dose regimens → nephrotoxicity.

- High-dose regimens, must be followed by 'rescue' with **leucovorin** (a form of FH4) or **folinic acid** to treat folic acid deficiency

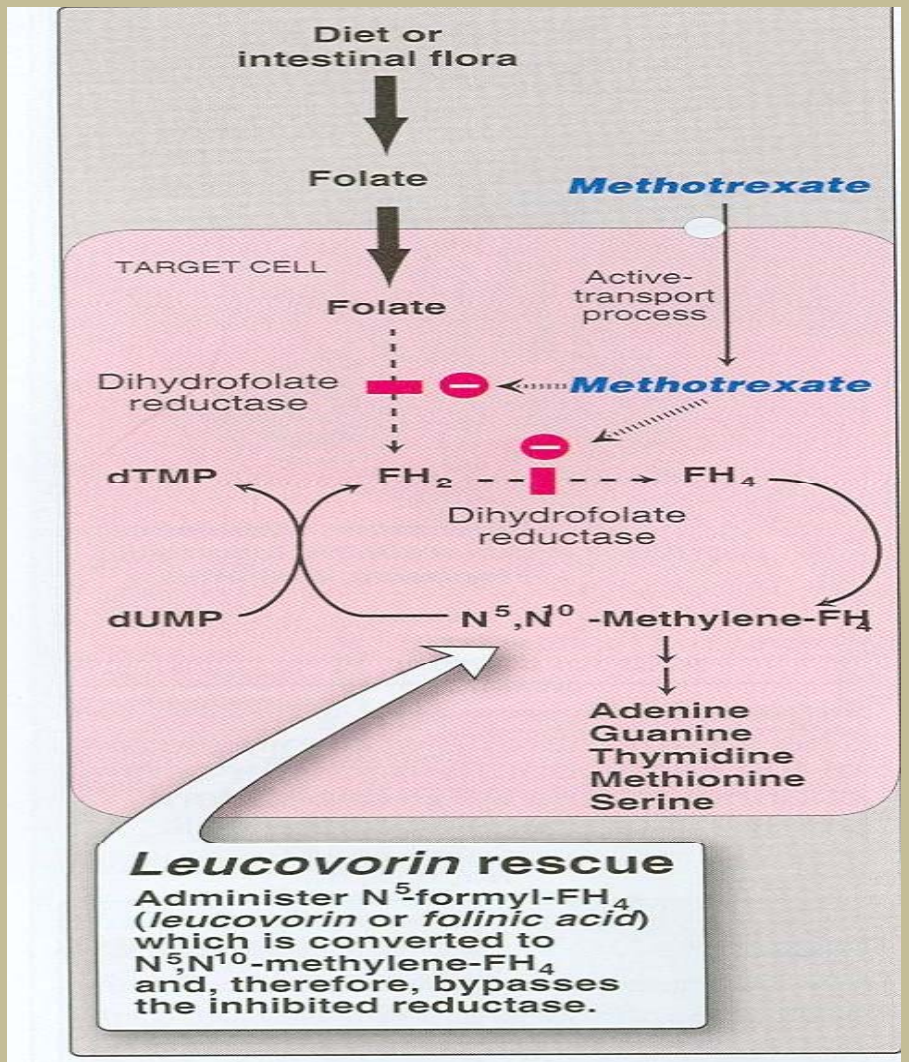


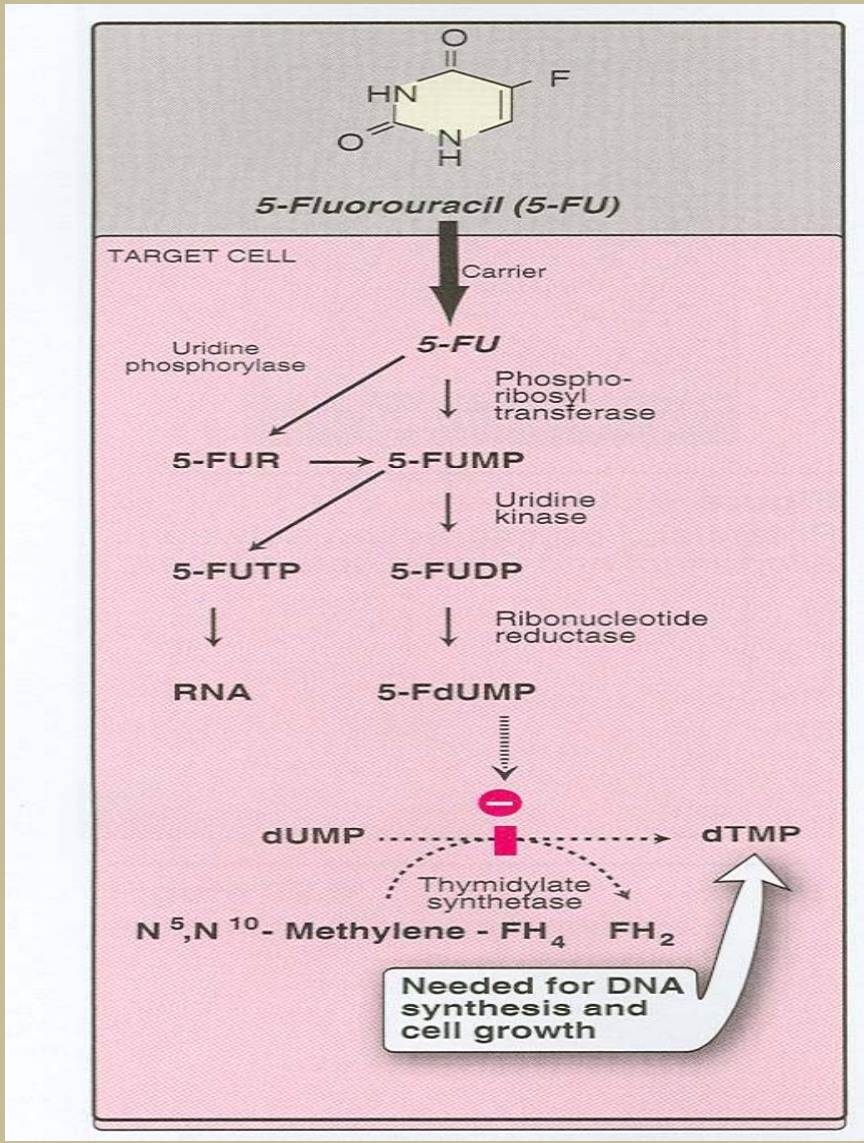
Figure 39.7
Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*. FH_2 = dihydrofolate; FH_4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine mono phosphate.

Pyrimidine Analogues

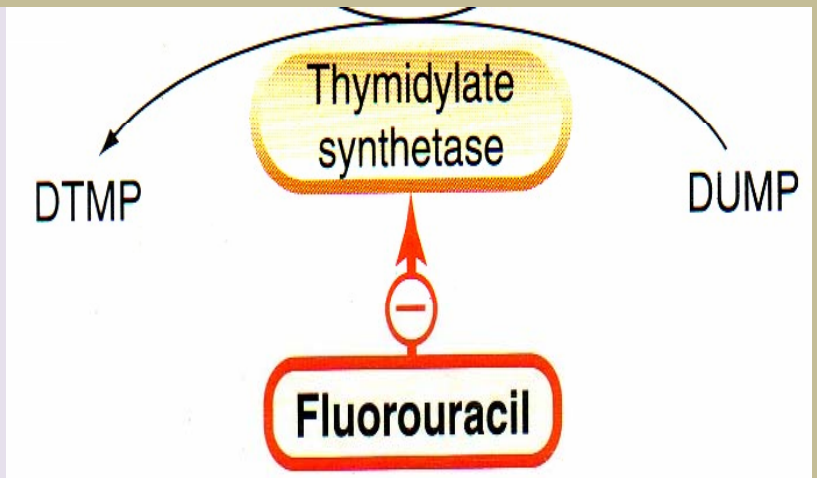
i) Fluorouracil

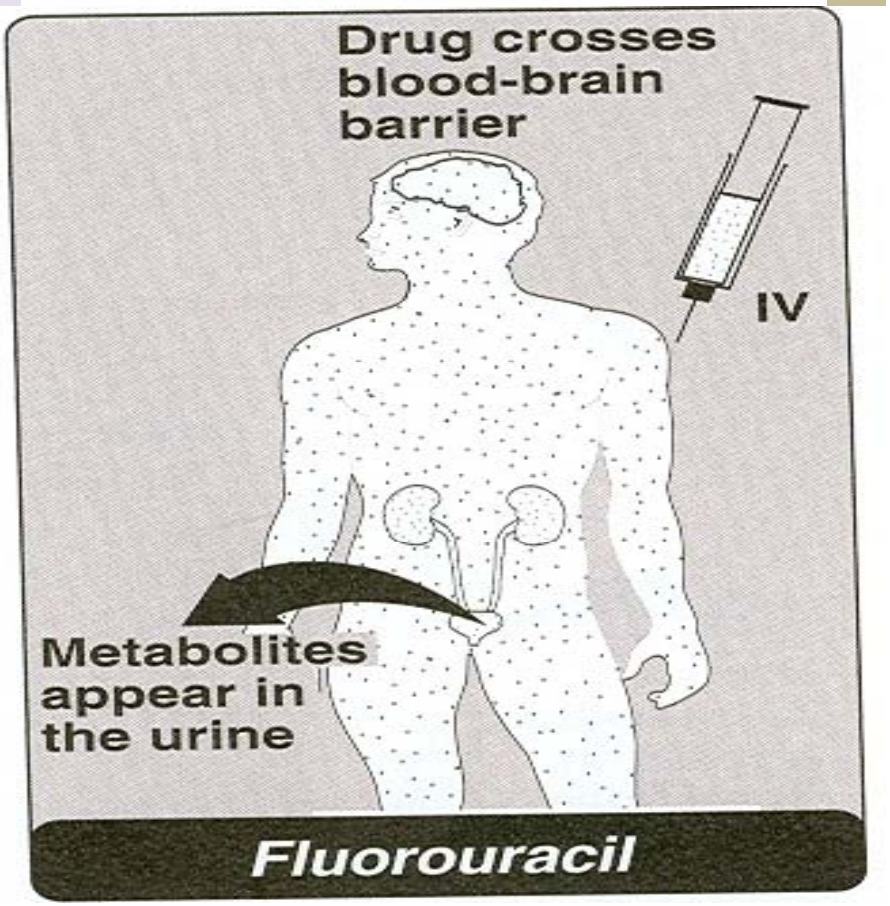
An analogue of uracil

It is converted into metabolite fluorodeoxyuridine monophosphate (FDUMP,) ⇒inhibits **thymidylate synthetases** and prevents the synthesis of **thymidine**



- Fluorouracil is usually given parenterally.
- **Clinical uses:-** combination regimens in the treatment of breast cancer, palliative treatment of gastrointestinal adenocarcinomas.
- **ADR:-** GIT epithelial damage , myelotoxicity.





CYTARABINE

- Cytosine arabinoside.
- Analogue of 2'deoxy cytidine
- Cytarabine **enters the target cell and undergoes phosphorylation reactions to give the cytosine arabinoside trisphosphate→ ↓DNA polymerase by its triphosphate**

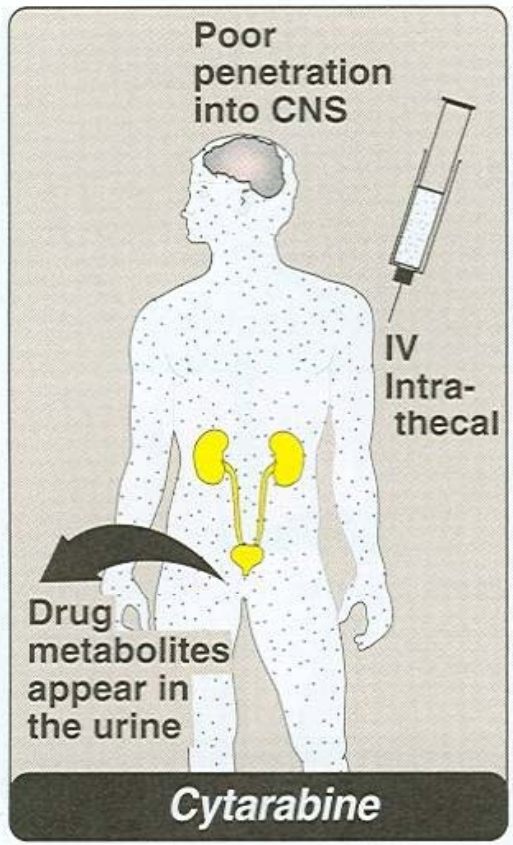


Figure 39.15
Administration and fate of *cytarabine*.

- **Clinical uses:-**is used in the chemotherapy of acute myelogenous leukemia, it has been used intrathecally in the treatment of meningeal leukemias and lymphomas as an alternative to methotrexate.
- ADR:- GIT epithelial damage , myelotoxicity , nausea and vomiting.

Purine Analogues

- The main anticancer purine analogues include **fludarabine,** pentostatin **, 6-**mercaptopurine.
- **Mercaptopurine** is used in the maintenance therapy of acute lymphoblastic leukemia.
- **Fludarabine** is metabolized to the trisphosphate and inhibits DNA synthesis by actions similar to cytarabine .
- Highly active in the treatment of chronic lymphocytic leukemia.
- It is **myelosuppressive**.

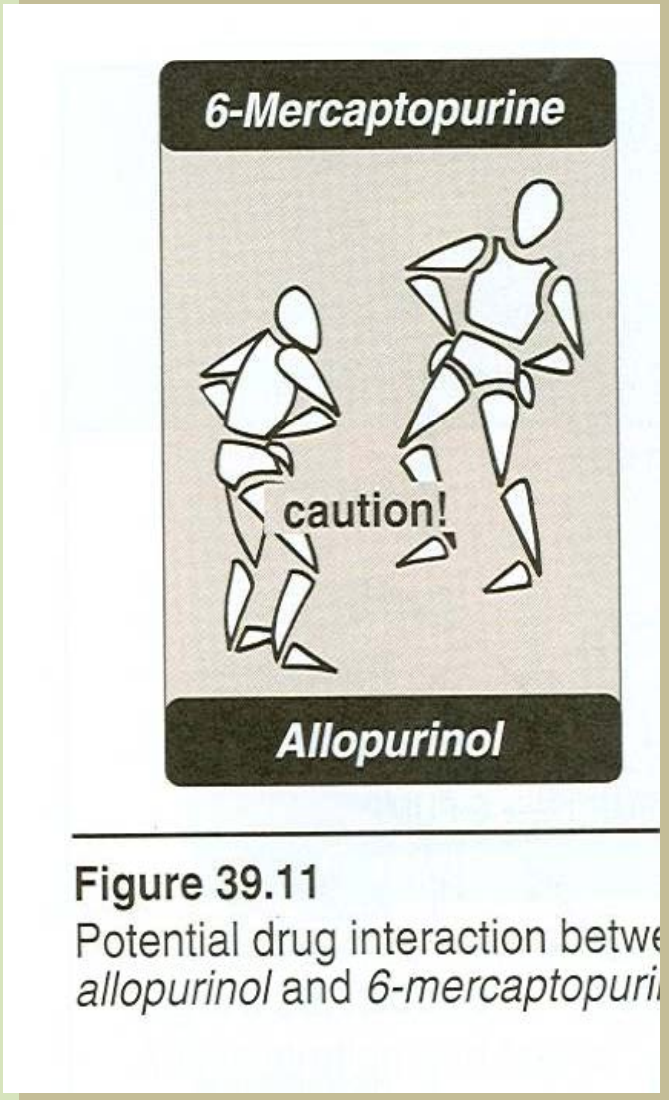


Figure 39.11
Potential drug interaction betwe
allopurinol and *6-mercaptopuri*

- **Pentostatin** inhibits **adenosine deaminase**.
- interfere with critical pathways in purine metabolism , on cell proliferation.
- Pentostatin is effective in the therapy of hairy cell leukemia.

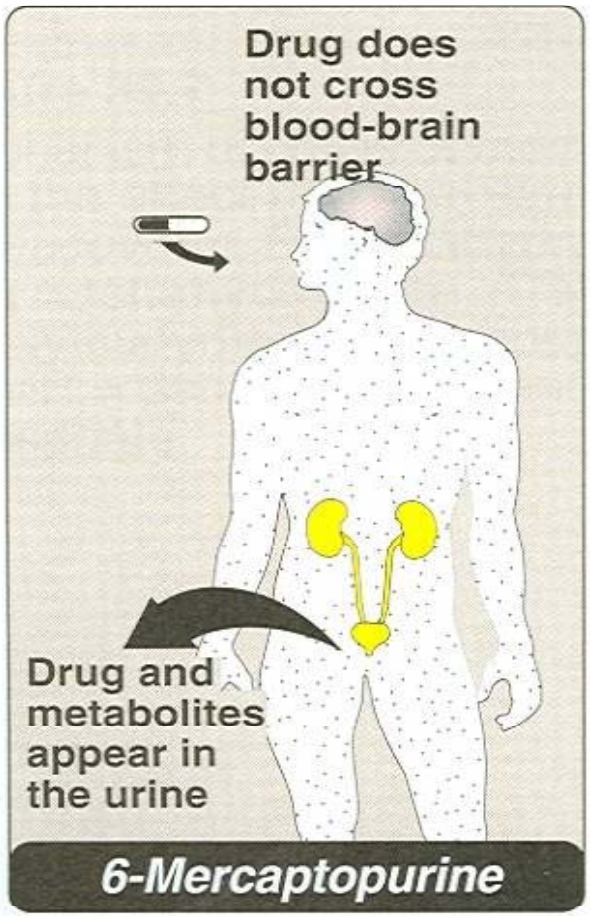


Figure 39.10
Administration and fate of *6-mercaptopurine*.

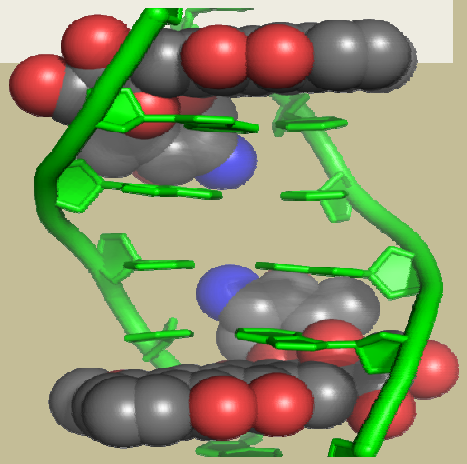
3) Cytotoxic Antibiotics

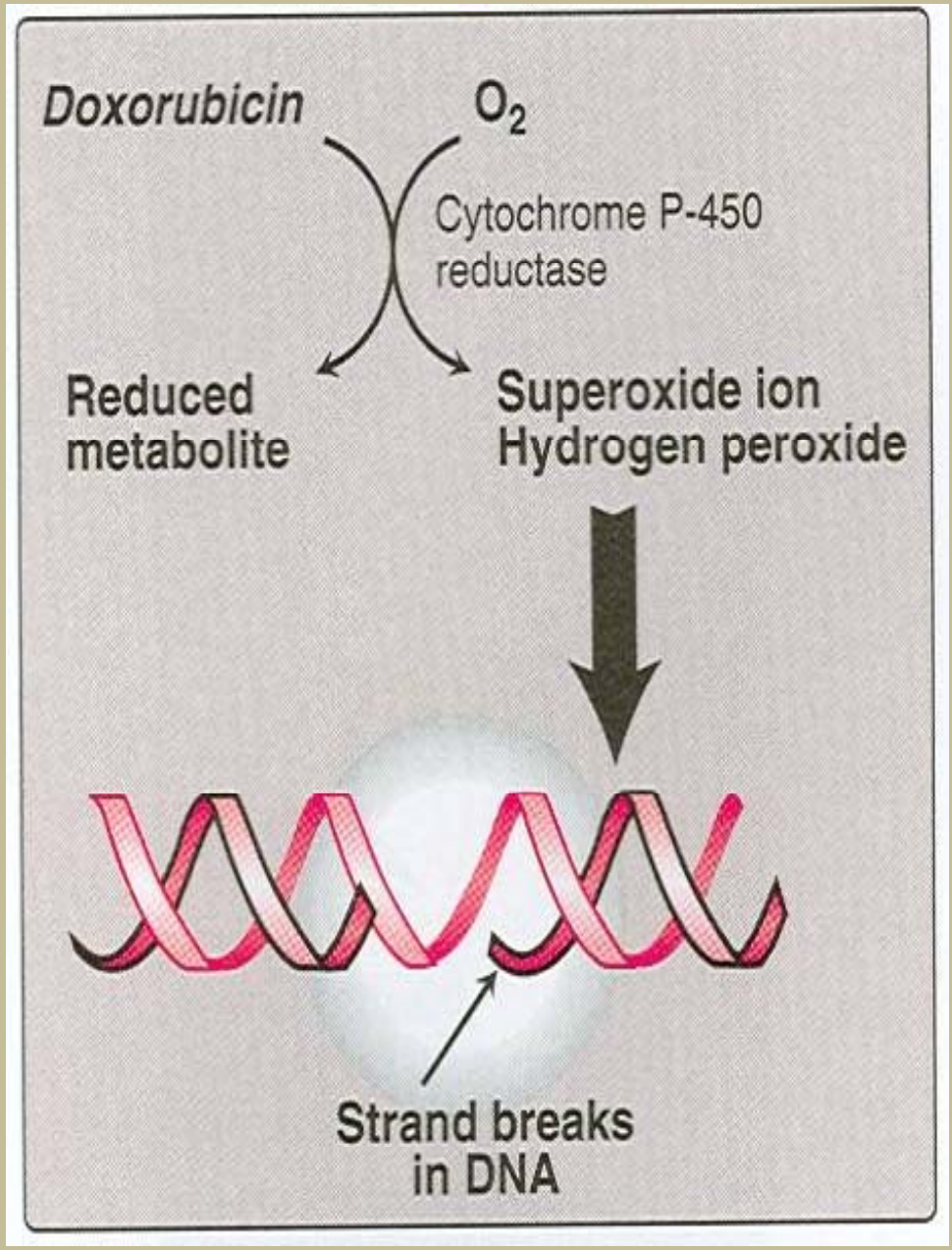
- Antitumour antibiotics produce their effects mainly by direct action on DNA
- **A. Anthracyclines**
- E.g., Doxorubicin hydrochloride.
- **B. Dactinomycin**
- **C. Bleomycins**

Doxorubicin

- **Doxorubicin** [anthracycline] has several cytotoxic actions.
- 1-It binds to DNA and inhibits both DNA and RNA synthesis.
- **2-Its main cytotoxic action is mediated through an effect on topoisomerase II (a DNA gyrase).**

- 3-Doxorubicin interacts with molecular oxygen , producing superoxide ions and hydrogen peroxide , which cause single strand breaks in DNA.
- 4-Binds cell membrane & alter fluidity & ion transport





PK=

IV route

Metabolized extensively

- Doxorubicin can cause cumulative, **dose-related cardiac damage**, leading to dysrhythmias and heart failure.

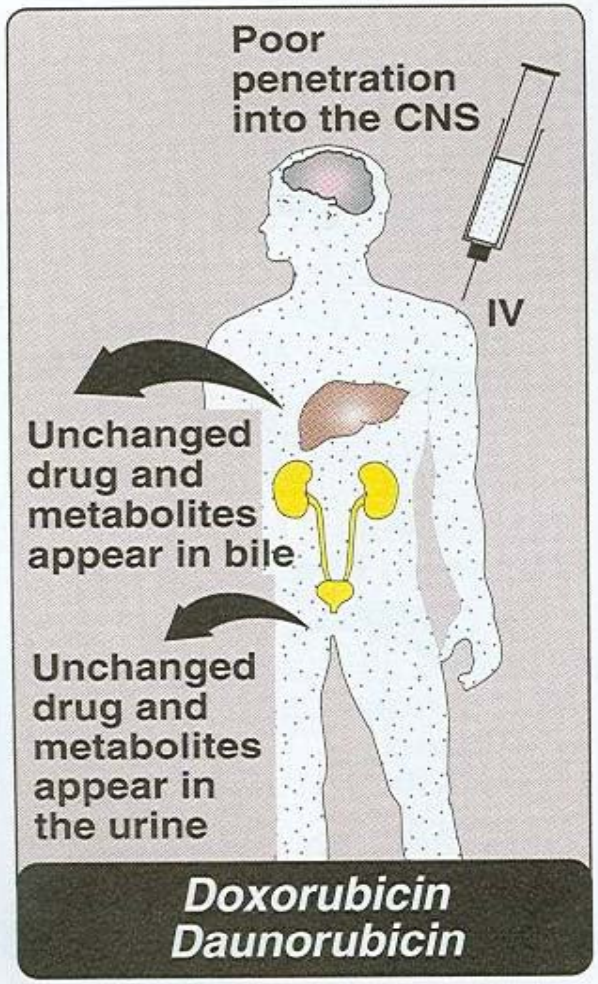
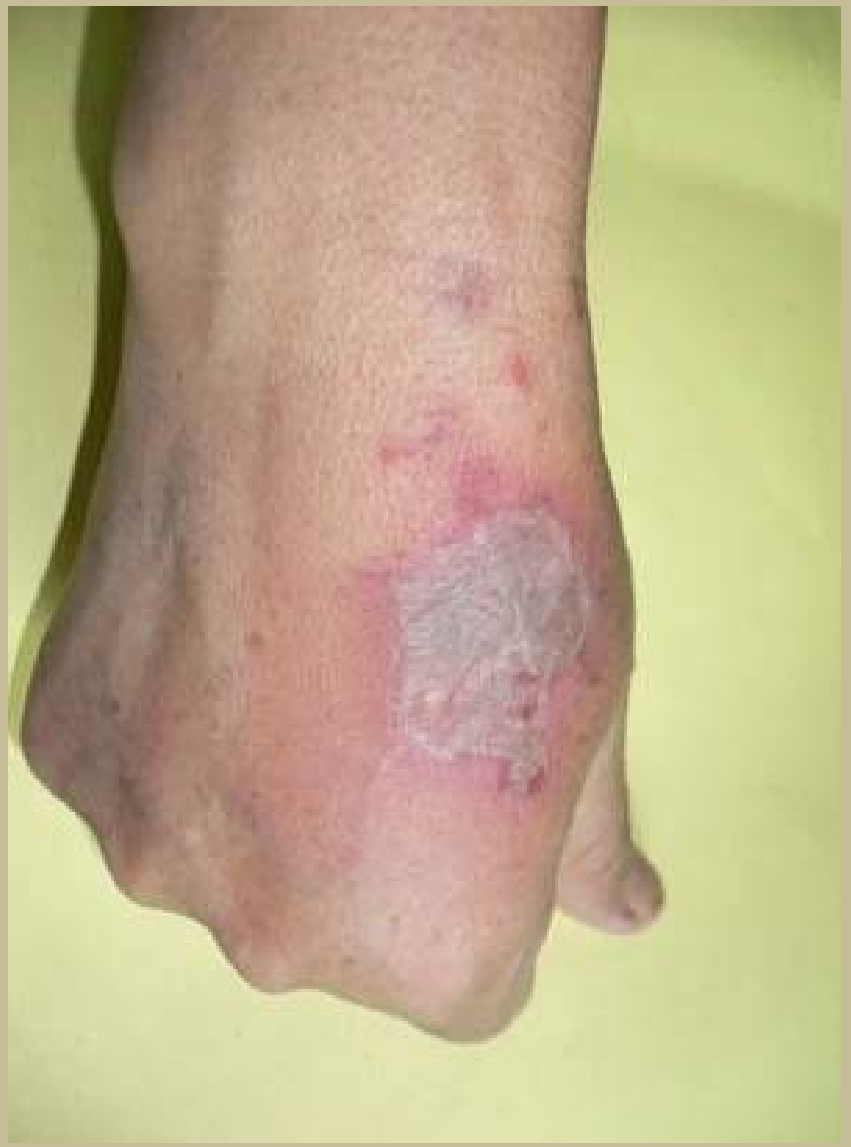


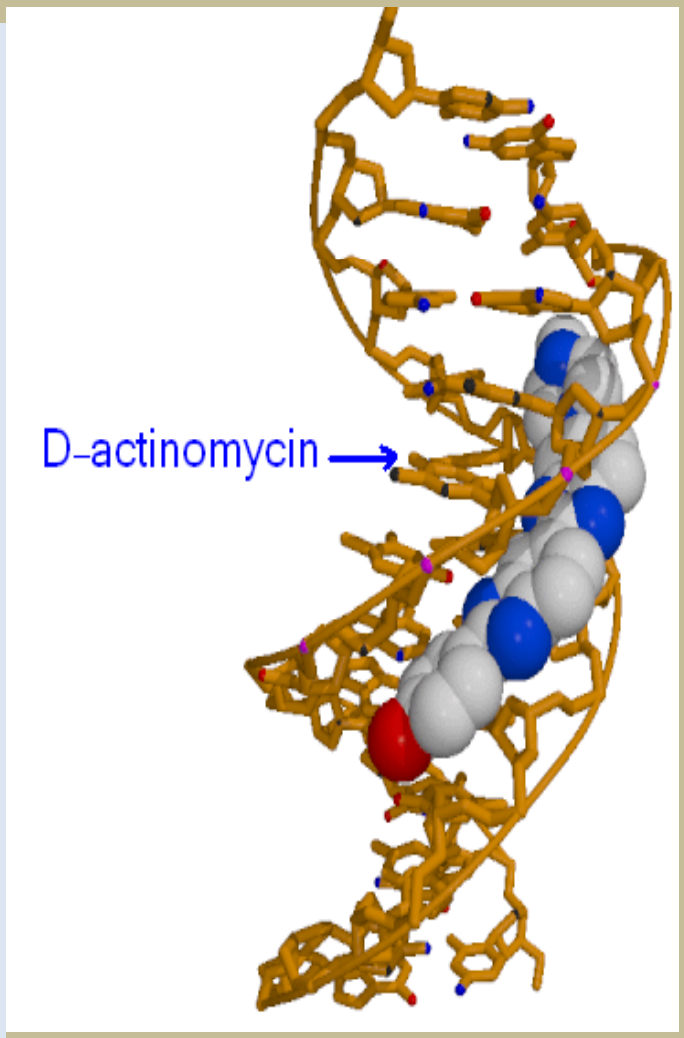
Figure 39.19
Administration and fate of *doxorubicin* and *daunorubicin*.

- Extravasation → ***local tissue necrosis.***
- Marked hair loss
- **<u>Clinical uses:-</u>** carcinomas of the breast, ovary, endometrium, bladder, and thyroid ,it is included in several combination regimens for lymphomas and Hodgkin's disease.



Dactinomycin

- **Dactinomycin** intercalates in the minor groove of DNA between adjacent guanosine-cytosine pairs, interfering with the movement of **RNA polymerase** along the gene and thus preventing transcription.



- has a similar action to the anthracyclines on topoisomerase II.
- **Clinical uses**:- gestational choriocarcinoma, testicular tumors, lymphomas, melanomas, and sarcomas.

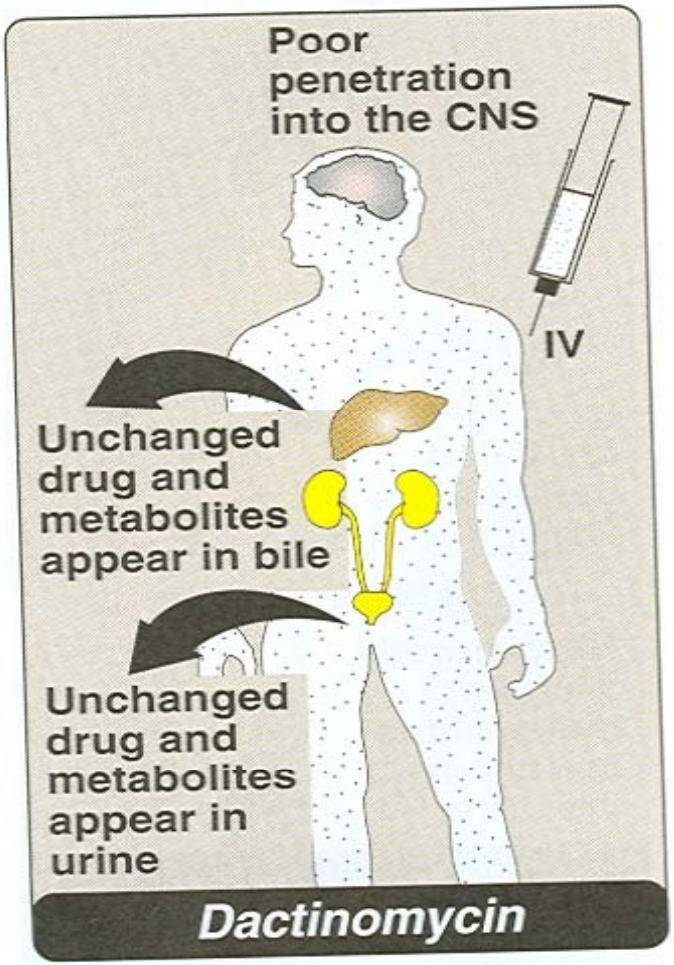


Figure 39.17
Administration and fate of *dactinomycin*.

Adverse Effects

- Myelosuppression, immunosuppression, elevated liver function tests, hepatitis, extravasation →necrosis.

Bleomycins

- The bleomycins are a group of metal-chelating glycopeptide antibiotics that degrade preformed DNA, causing chain fragmentation and release of free bases.

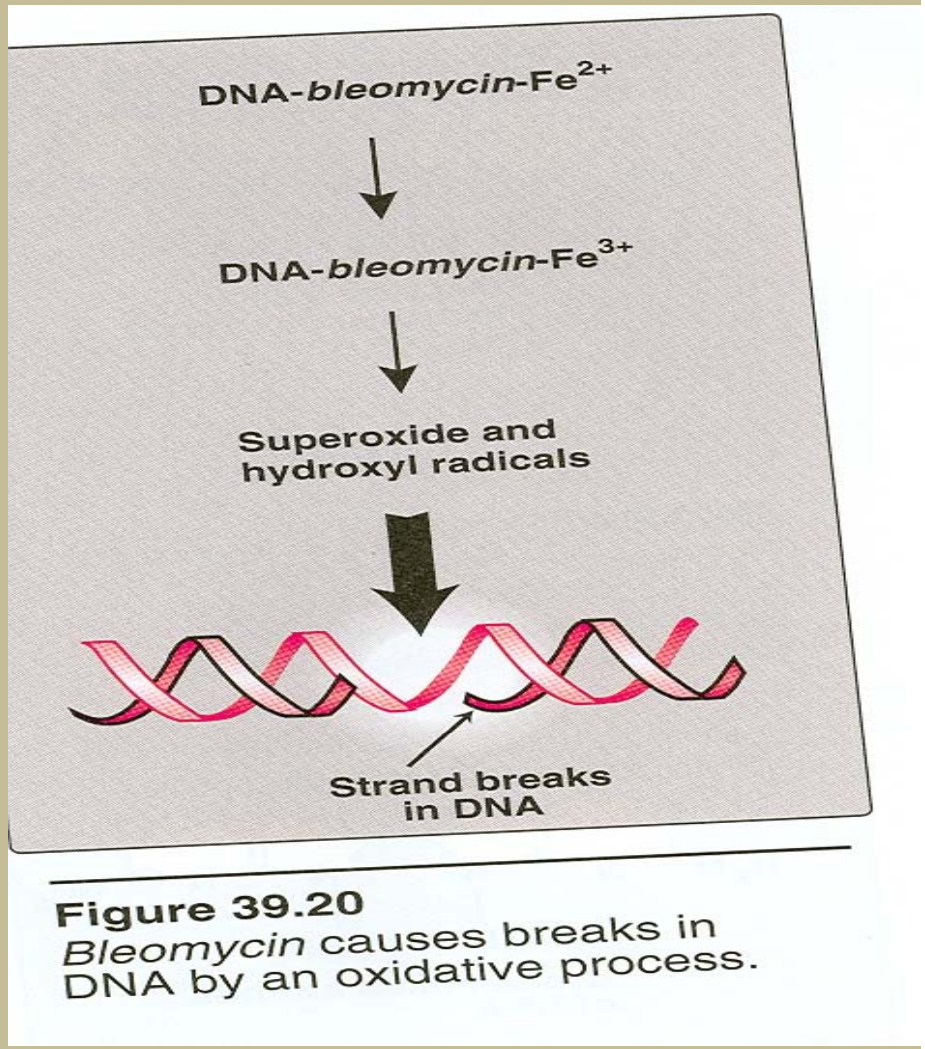


Figure 39.20
Bleomycin causes breaks in DNA by an oxidative process.

- Bleomycin is most effective in the **G2** phase of the cell cycle and mitosis, also active against non-dividing cells
- Causes little **myelosuppression**

Clinical uses:-

- Advanced testicular carcinomas, Hodgkin's and non-Hodgkin's lymphomas.
- ADR= Its most serious toxic effect is **pulmonary fibrosis.**
- Allergic reactions .
- Mucocutaneous reactions and may develop hyperpyrexia.

Plant Alkaloids

A. Vinca alkaloids

E.g., Vincristine & Vinblastine

B. Epipodophyllotoxins

E.g., Etoposide & Teniposide

C. Taxanes

E.g., Paclitaxel

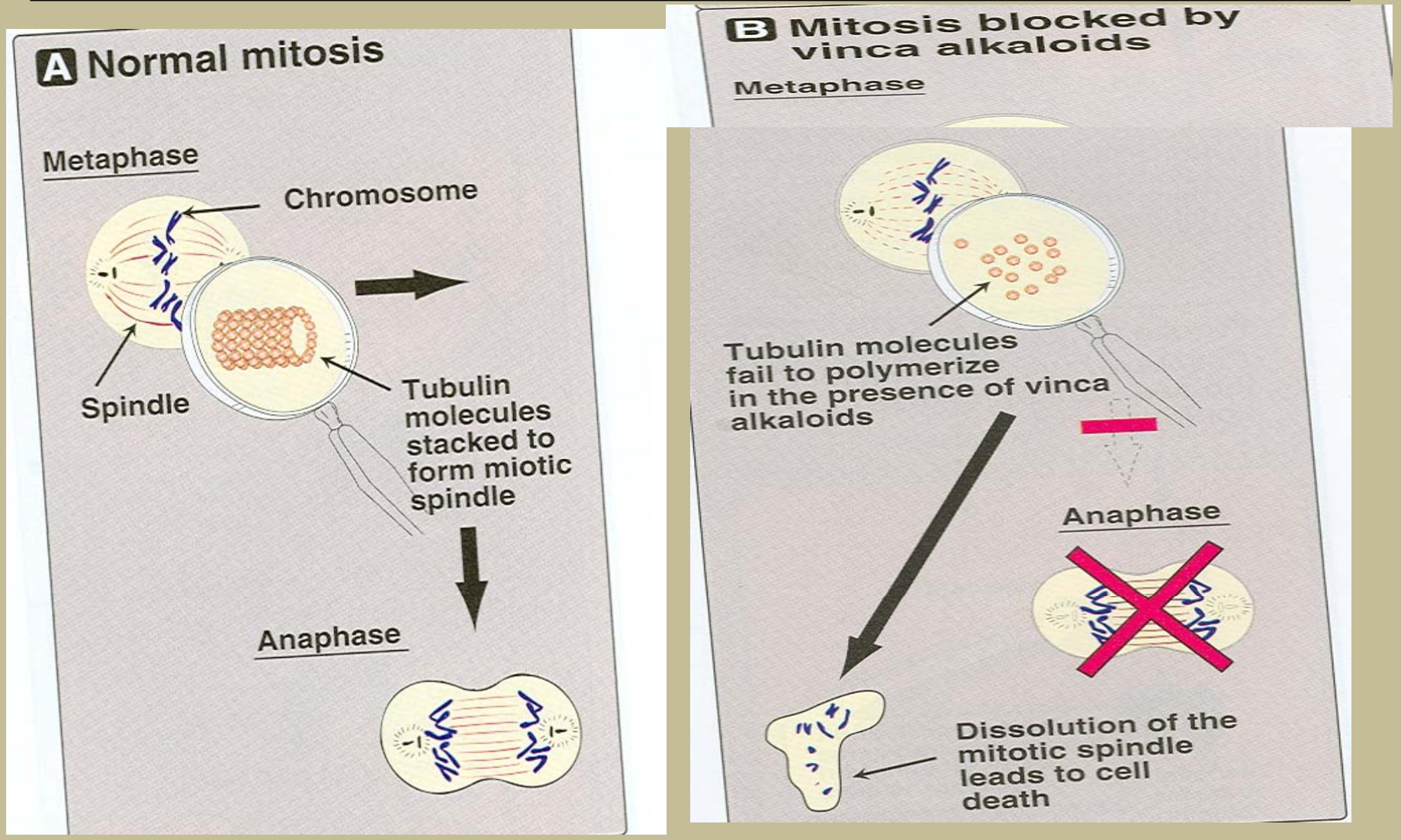
A-Vinca Alkaloids

- Main alkaloids; **Vincristine, Vinblastine**
- Both alkaloids are cell-cycle specific & phase specific, b/c they block mitosis in metaphase (M phase)

Mechanism of action

They act by binding *to tubulin* & inhibits its polymerization into microtubules (microtubule assembly), causing cells to arrest in the late G2 phase by preventing spindle formation

Mechanism of action of microtubule inhibitors



- Vinca alkaloids derived from **periwinkle** plant
- Extensively bound to tissues.
- Biliary excretion.

Vincristine

- Effectively combined with **prednisone** for remission induction in acute lymphoblastic leukemia in children, also in Hodgkin's & non Hodgkin's lymphoma

- **The periwinkle plant**

- **Vinblastine** → testicular carcinomas, Hodgkin's disease, breast cancer, and renal cell carcinoma.

Adverse effects

- Neurological toxicity → **vincristine**.
- Bone marrow toxicity → **vinblastine.**
- tissue necrosis if extravasated.

EPIPODOPHYLLOTOXINS

- Two compounds, ***etoposide & teniposide*** are semi-synthetic derivatives of podophyllotoxin extracted from mayapple root (*Podophllum pellatum*)

Podophyllum

MOA

Block cell division in late S- and G2-phases of the cell cycle

Inhibition of topoisomerase II, which results in DNA damage through strand breakage

- Useful against testicular and ovarian germ cell cancers, lymphomas, and acute myelogenous and lymphoblastic leukemia.
- ADR:- mild nausea, alopecia, allergic reaction, phlebitis at the injection site, and bone marrow toxicity.

- complexes with topoisomerase II, which results in a single-strand breakage of DNA.

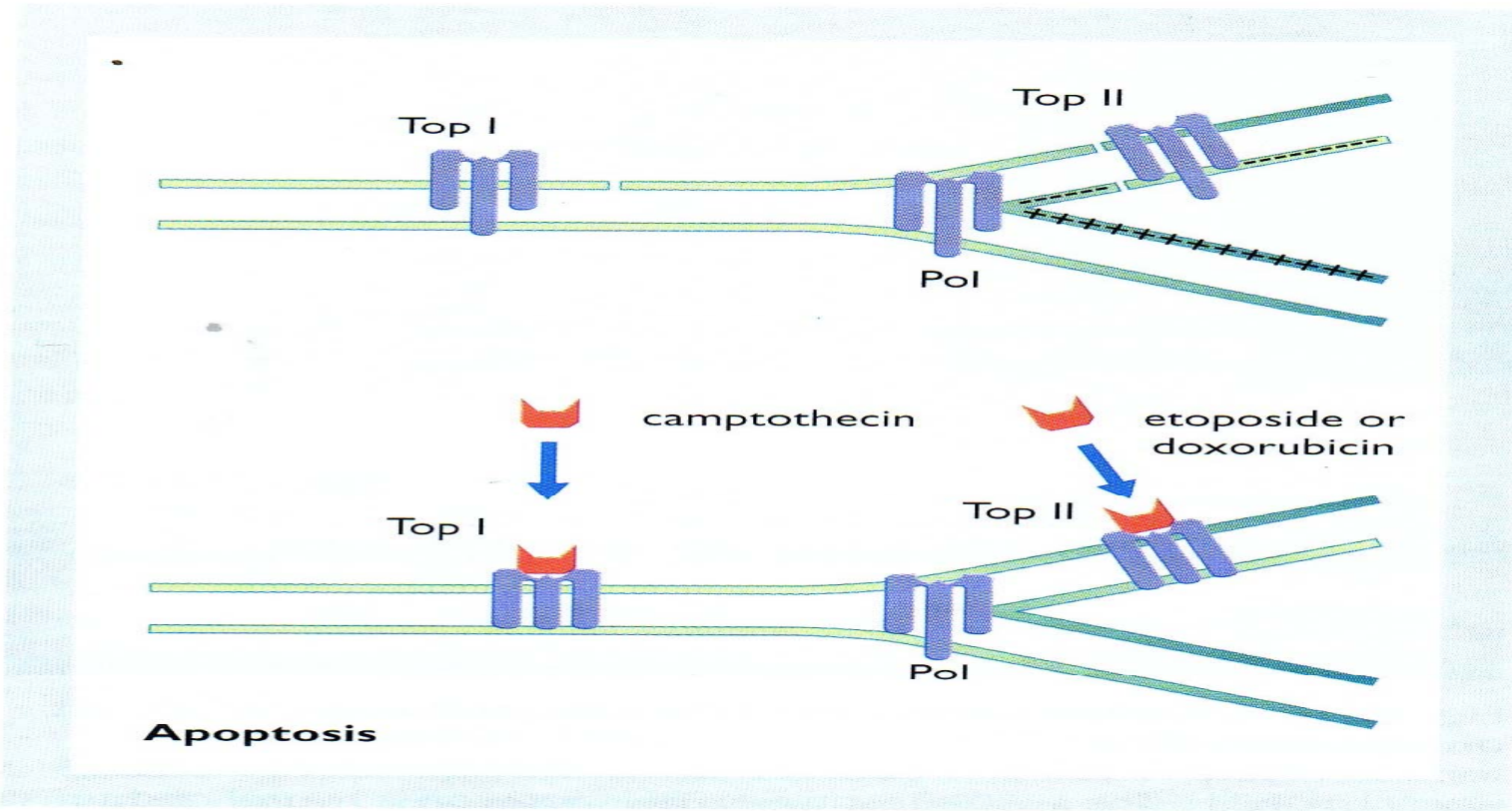


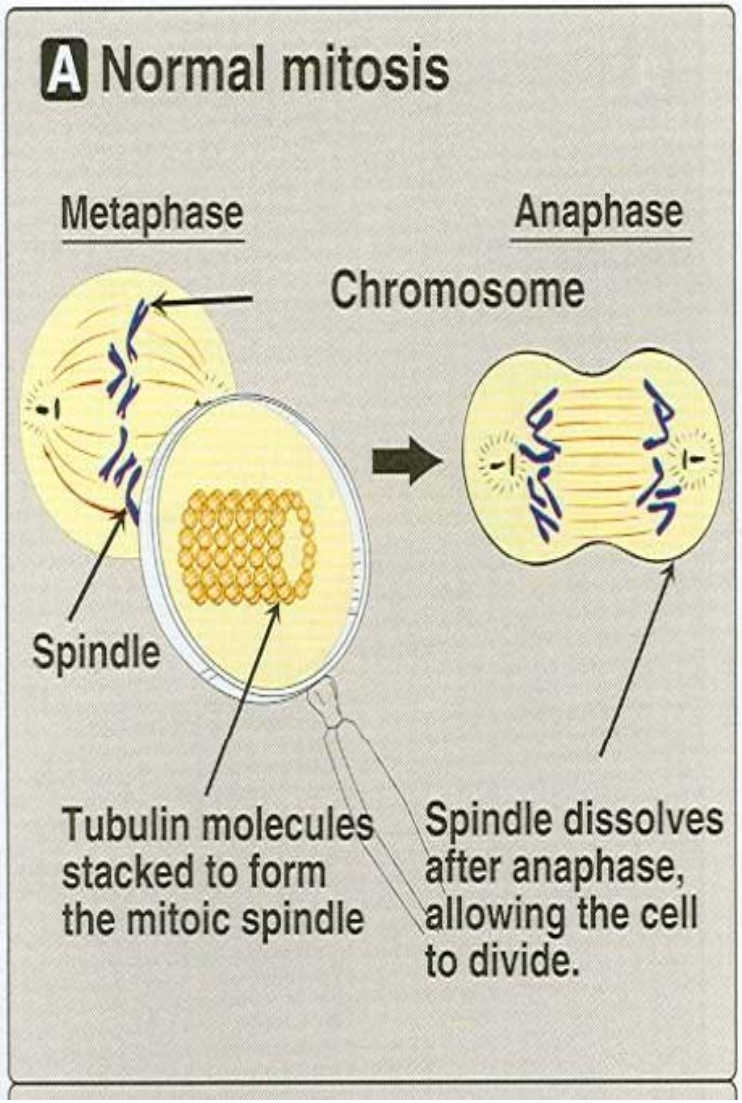
Fig. 12.15 Sites of action of camptothecin and etoposide or doxorubicin. They stabilize the normally transient covalent cleavage in replicating DNA produced by topoisomerase I (Top I) and/or topoisomerase II (Top II), which produces a double-strand DNA break by collision with the DNA replication apparatus of DNA polymerase a (leading strand 5′⟶3′) and polymerase d (lagging strand 3′⟶5′) (Pol).

Taxanes

- **E.g., Paclitaxel (Taxol)**→ Alkaloid ester derived from bark of the Pacific yew tree (*Taxus bravifolia)*

MOA

- Mitotic spindle poison ; High affinity binding to microtubules with enhancement of tubulin polymerization



- Large volume of distribution, highly metabolized in the liver.
- Used in carcinomas of the breast, ovary, lung, head, and neck.
- **+ cisplatin** → ovarian and lung carcinomas
- **+doxorubicin** → breast cancer.
- ADR:- myelosupression, alopecia, numbness & tingling sensation

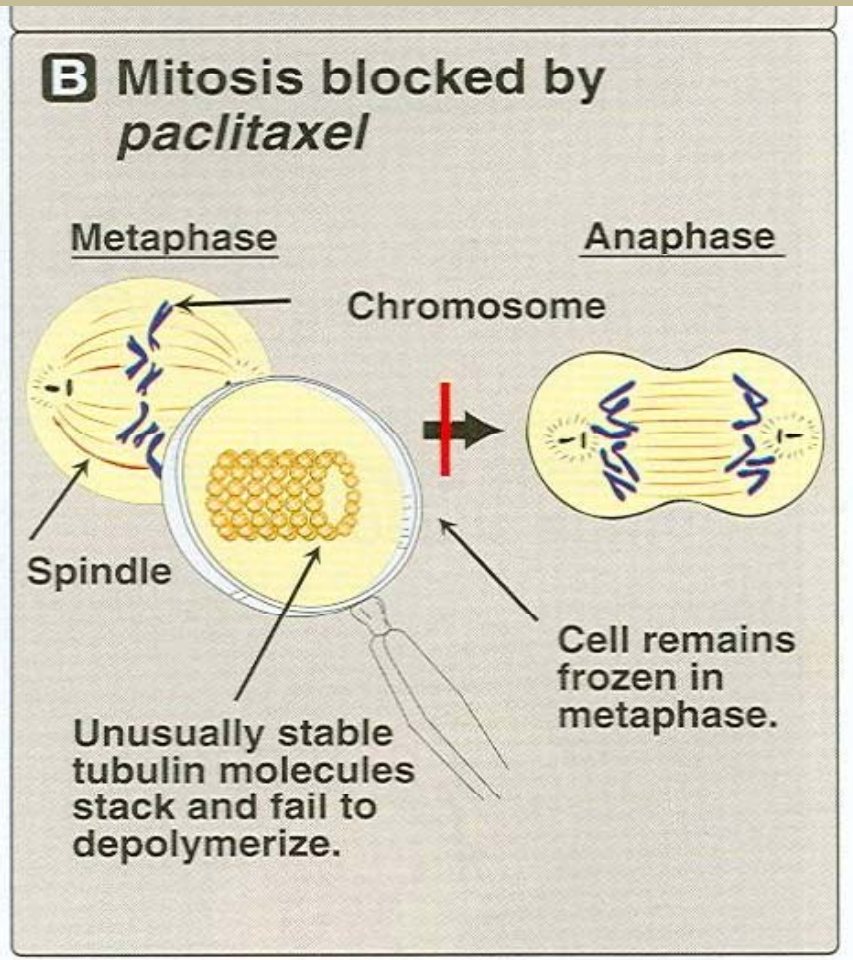


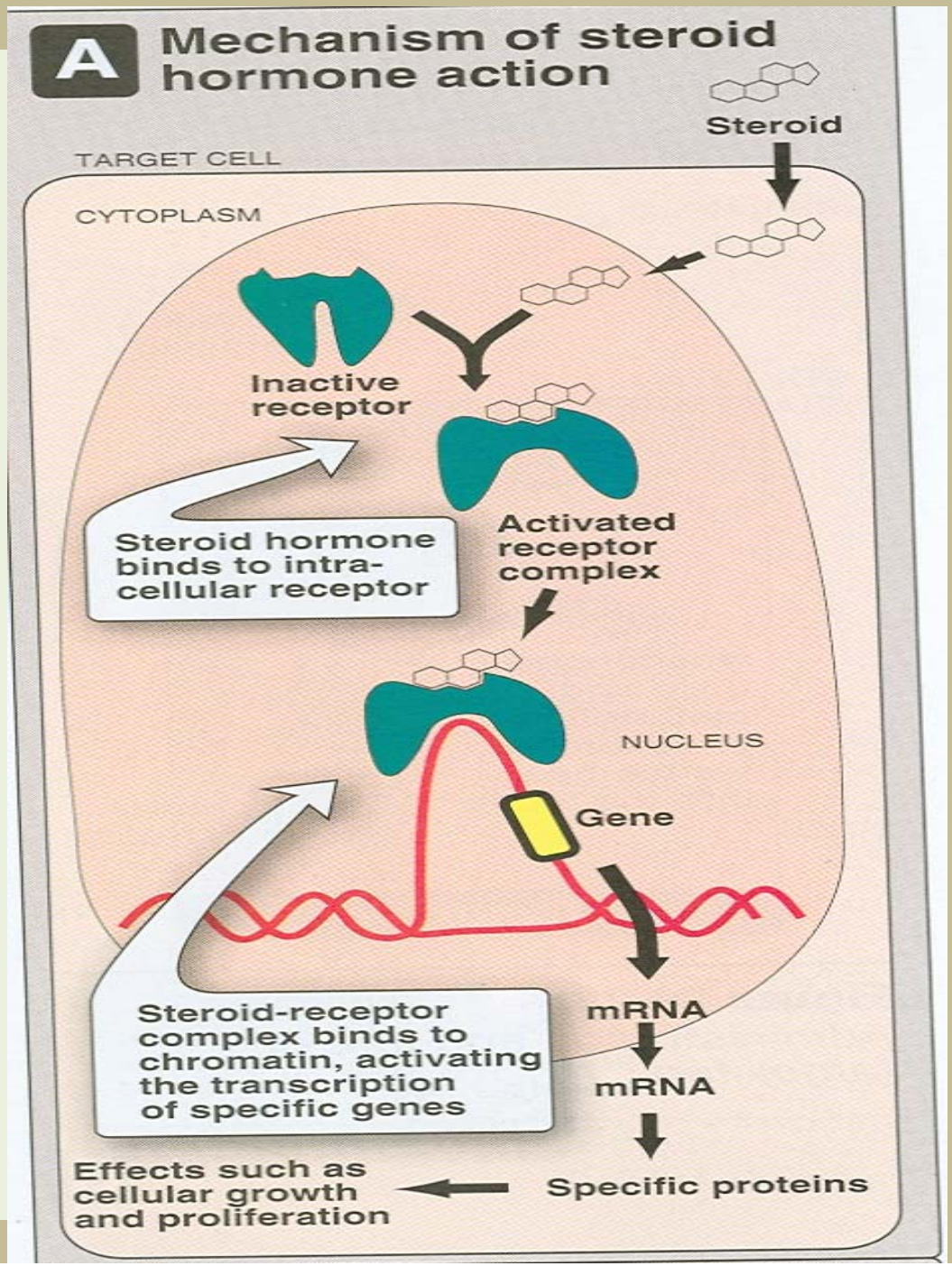
Figure 39.27
Paclitaxel stabilizes microtubules, rendering them nonfunctional.

Hormones

- Several types of hormone-dependent cancer (especially breast, prostate, and endometrial cancer) respond to treatment with their corresponding hormone antagonists.
- **Estrogen** antagonists are primarily used in the treatment of breast cancer, whereas **androgen** antagonists are used in the treatment of prostate cancer. **Corticosteroids** are particularly useful in treating lymphocytic leukemias and lymphomas.

Glucocorticoids →↓
lymphocyte proliferation, used in leukaemias and lymphomas.

- Used in a supportive role in other cancers on basis of effect on raised intracranial pressure.



- **Estrogens**, **fosfestrol** (**a pro-drug**→ prostatic tumours
- Estrogens inhibit the effects of endogenous androgens and androgen-dependent metastatic prostatic carcinoma

Progestins

Useful in endometrial neoplasm & also used in renal tumors

Hormone Antagonists

- **Anti-estrogens**
- **Tamoxifen** → hormone-dependent breast cancer.
- It competes with endogenous E for E receptor
- Chemopreventive in women at high risk for breast cancer.
- can cause **Endometrial cancer**

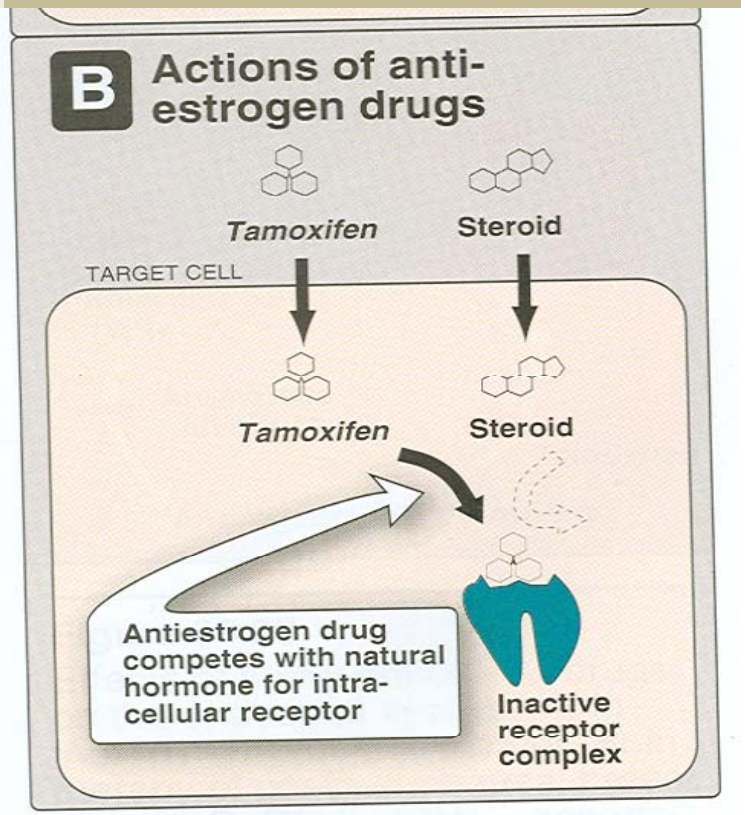


Figure 39.28
Action of steroid hormones and antiestrogen agents.

- Tamoxifen is cardioprotective
- Given orally , well absorbed, maximum plasma levels 4-6h.
- ADR:-Menopausal symptoms, fluid retention ,edema, thromboembolic events,

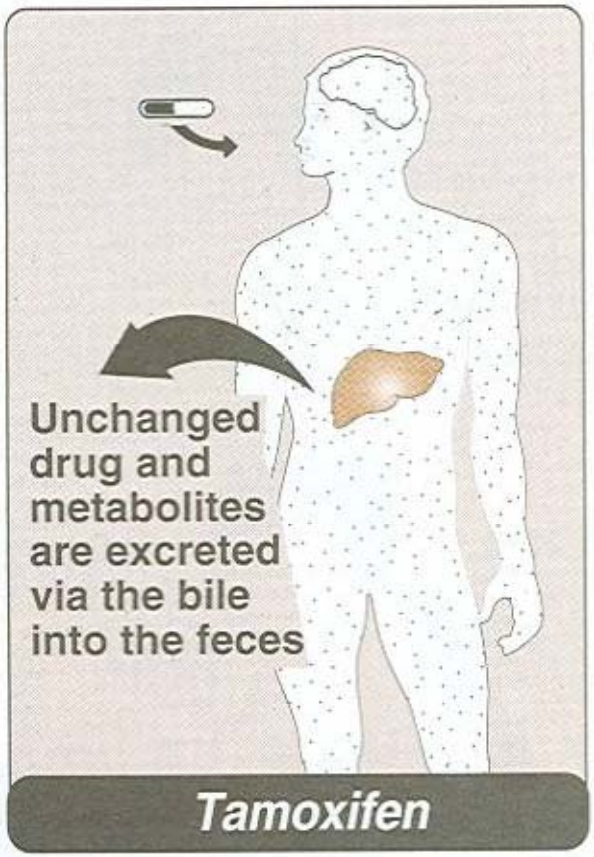
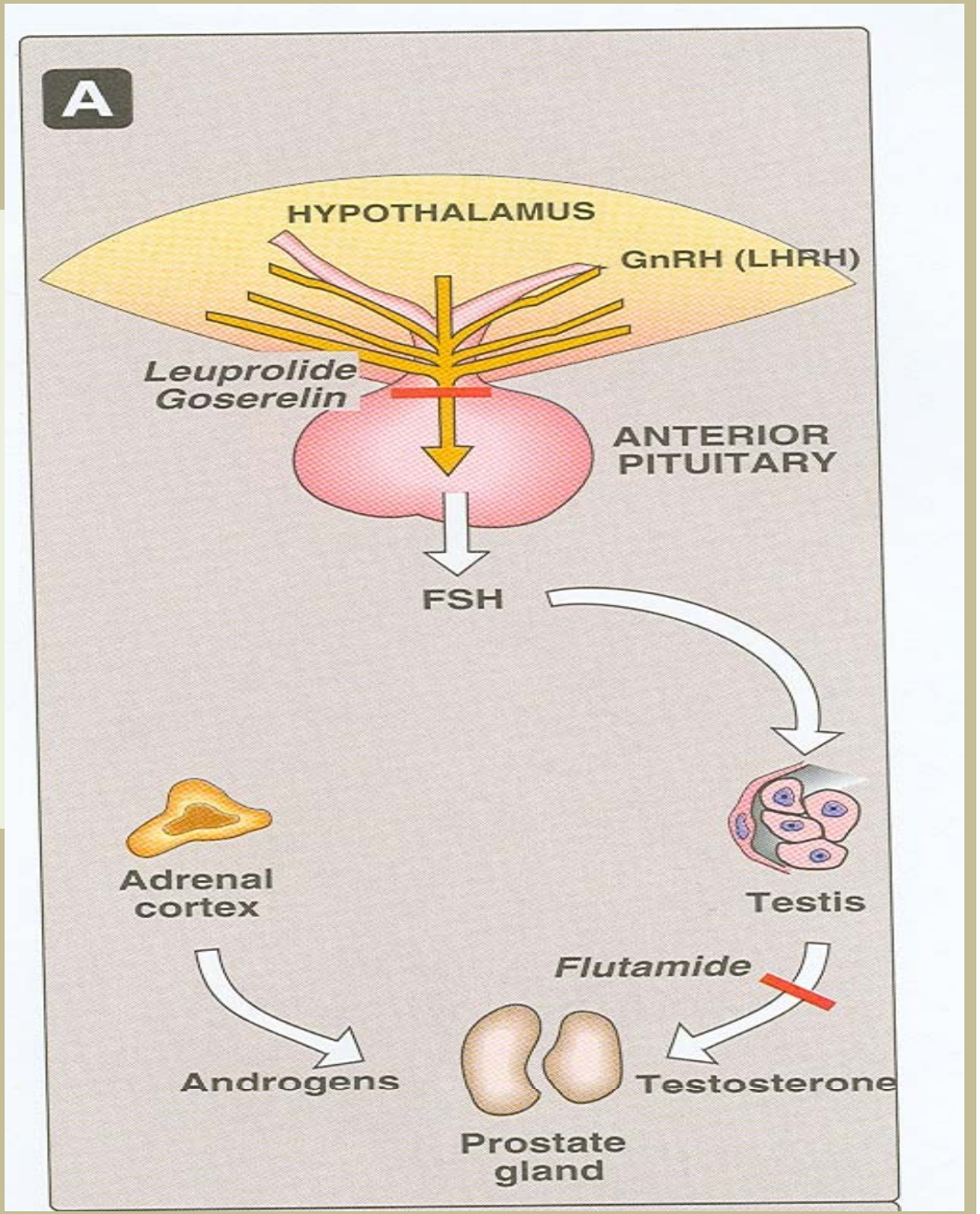


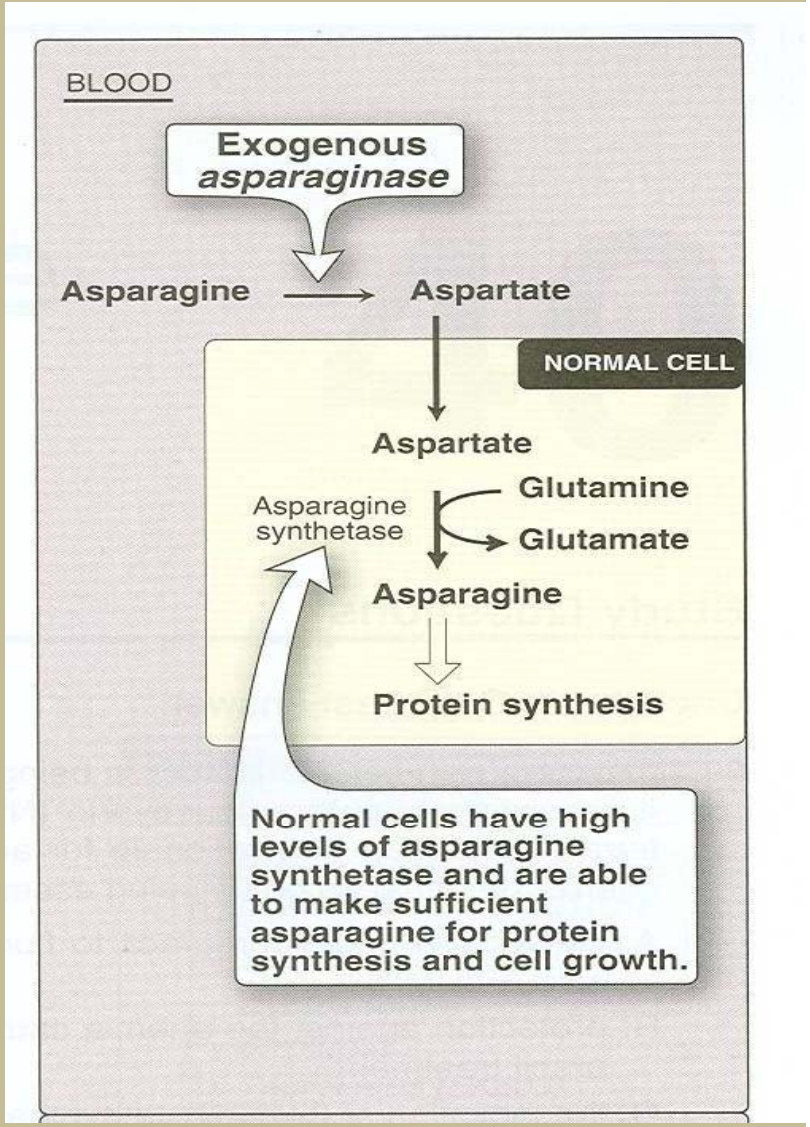
Figure 39.29
Administration and fate of *tamoxifen*.

- **Anti-androgens,** **flutamide** and **cyproterone**, are used in prostate tumours.

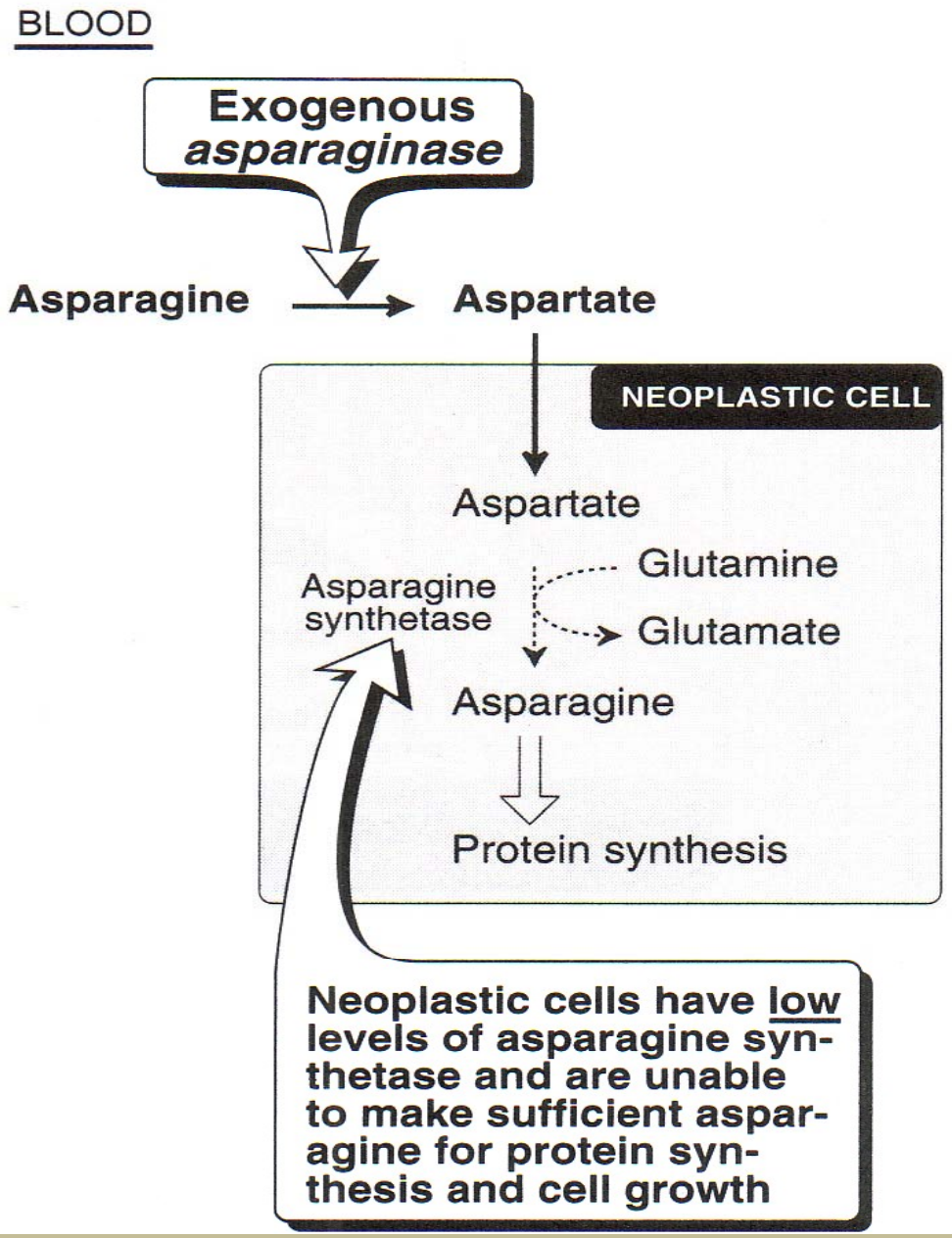


Asparaginase

- **L-asparaginase**
  →obtained from *Escherichia coli* and *Erwinia carotovora.*
- Catalyzes the deamination of asparagine (required for protein synthesis) to aspartic acid & ammonia.



- Tumor cells sensitive to L-asparaginase are deficient in the enzyme asparagine synthetase lack asparagine
- Remains primarily in the intravascular space.



- Little appears in the CSF.
- Used for childhood acute lymphoblastic leukemia & certain types of lymphoma.
- ADR:-may produce hypersensitivity reactions, urticarial skin rashes and severe anaphylactic reactions, pancreatitis .
- *Lacks toxicity to bone marrow, gastrointestinal tract, and hair follicles.*

THANKS

&

GOOD LUCK

FOR YOUR

EXAMINAITON