UNIT -I

ANTINEOPLASTIC AGENTS

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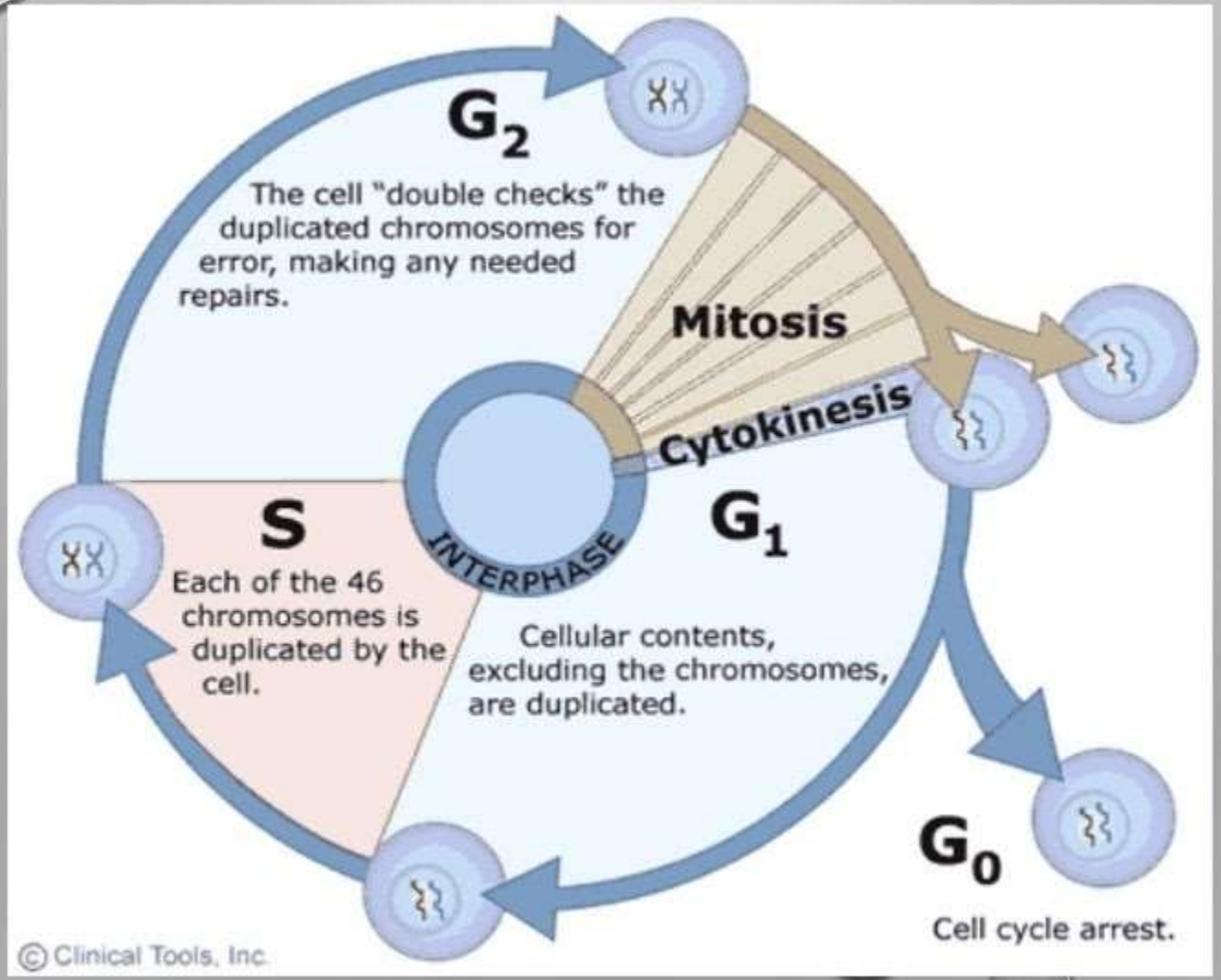
WHAT IS CELL CYCLE???


G2
The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
Mitosis
Cytokinesis
G1
S
Each of the 46 chromosomes is duplicated by the cell.
INTERPHASE
Cellular contents, excluding the chromosomes, are duplicated.
G0
Cell cycle arrest.
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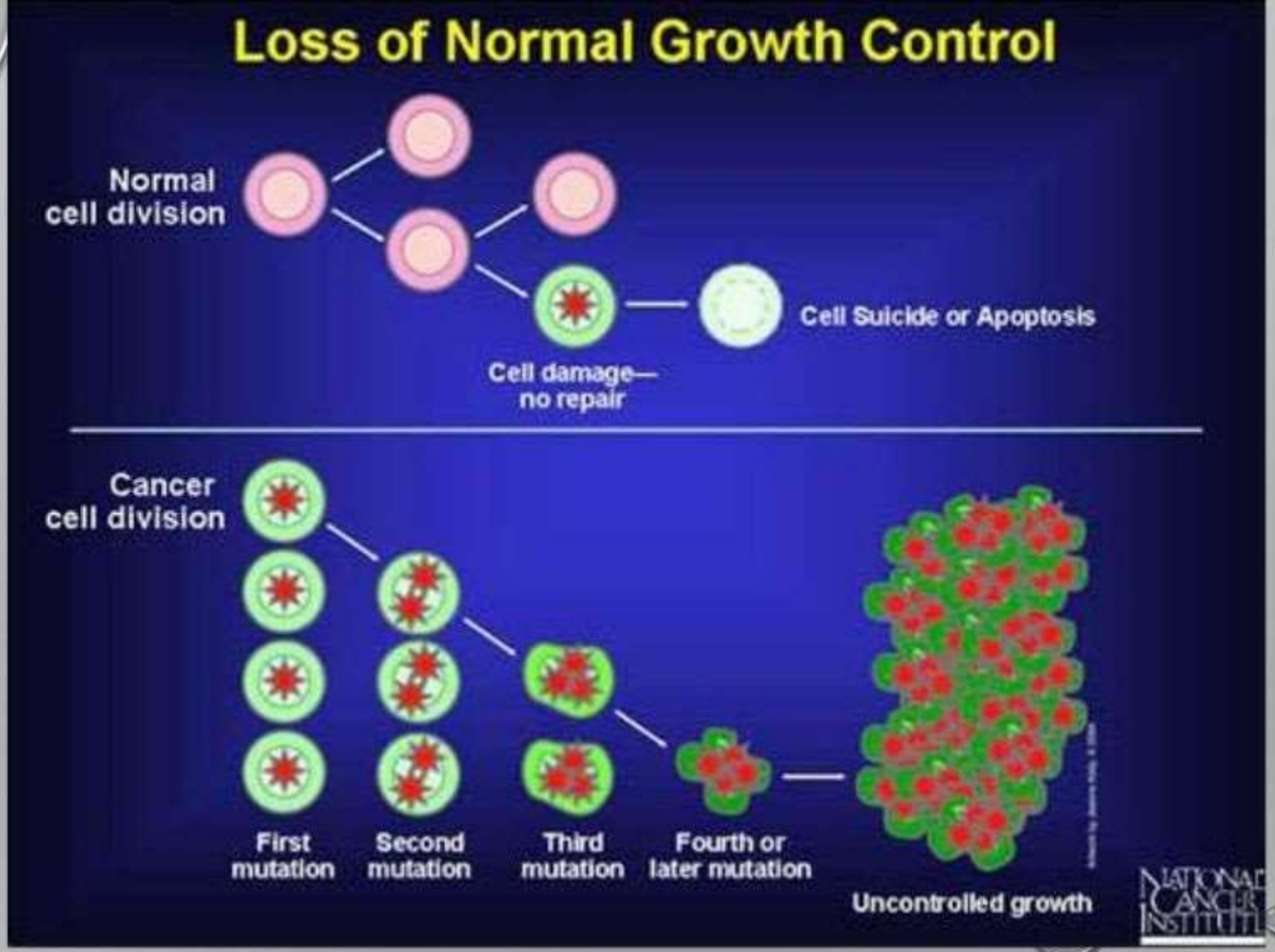
WHAT IS CANCER???

- Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems


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
NATIONAL CANCER INSTITUTE

TYPES OF CANCER

- **Carcinoma** - cancer that begins in the skin or in tissues that line or cover internal organs. There are a number of subtypes of carcinoma, including adenocarcinoma basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.
- **Sarcoma** - cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- **Leukemia** - cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- **Lymphoma and myeloma** - cancers that begin in the cells of the immune system
- **Central nervous system cancers** - cancers that begin in the tissues of the brain and spinal cord.

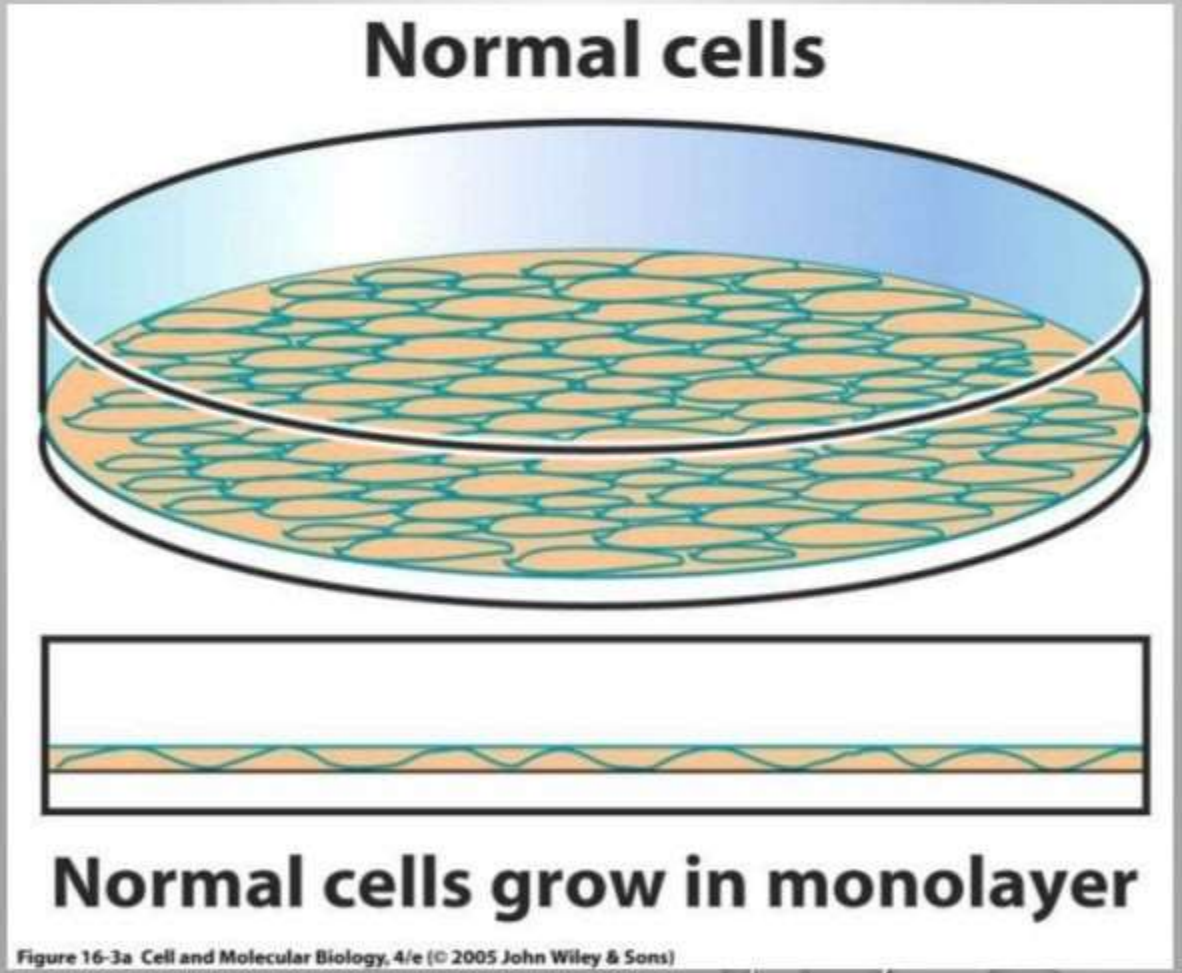
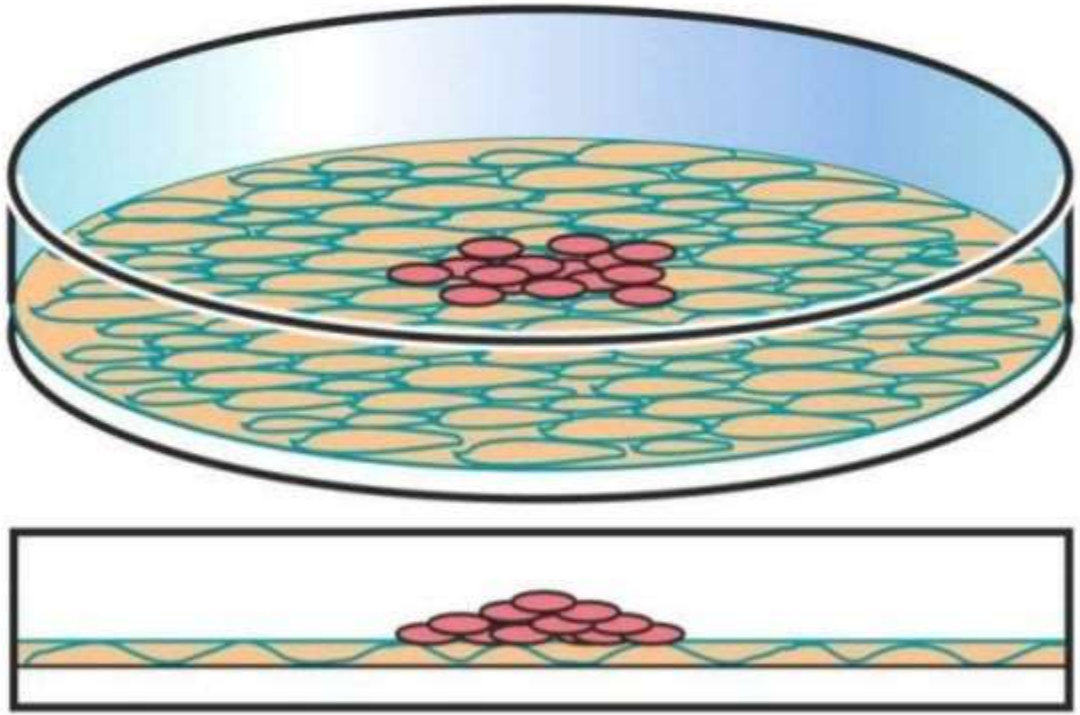


Figure 16-3a Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

Cancer cells



Cancer cells grow in clumps (foci)

Figure 16-3c Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

TYPES OF TUMORS

- Not all tumors are cancerous; tumors can be benign or malignant.
- **Benign tumors** aren't cancerous. They can often be removed, and, in most cases, they do not come back. Cells in benign tumors do not spread to other parts of the body.
- **Malignant tumors** are cancerous. Cells in these tumors can invade nearby tissues and spread to other parts of the body. The spread of cancer from one part of the body to another is called metastasis.

Cancer Therapeutic Modalities (classical)

1. Surgery

1/3 of patients without metastasis
Respond to surgery and radiation.

2. Radiation

If diagnosed at early stage,
close to 50% cancer
could be cured.

3. Chemotherapy

50% patients will undergo chemotherapy,
to remove micrometastasis. However,
chemotherapy is able to cure only about 10-15%
of all cancer patients.

GENERAL PRINCIPLES OF CHEMOTHERAPY OF CANCER

1. ANALOGOUS WITH BACTERIAL CHEMOTHERAPY – DIFFERENCES ARE
   - SELECTIVITY OF DRUGS IS LIMITED – BECAUSE "I MAY HARM YOU"
   - NO OR LESS DEFENCE MECHANISM – CYTOKINES ADJUVANT NOW
2. ALL MALIGNANT CELLS MUST BE KILLED TO STOP PROGEMY – SURIVAL TIME IS RELATED TO NO. OF CELLS THAT ESCAPE CHEMO ATTACK
3. SUBPOPULATION CELLS DIFFER IN RATE OF PROLIFERATION AND SUSCEPTIBILITY TO CHEMOTHERAPY
4. DRUG REGIMENS OR COMBINED CYCLE THERAPY AFTER RADIATION OR SURGERY (BASIS OF TREATMENT NOW IN LARGE TUMOUR BURDENS)
5. COMPLETE REMISSION SHOULD BE THE GOAL – BUT ALREADY USED IN MAXIMUM TOLERATED DOSE – SO EARLY TREATMENT WITH INTENSIVE REGIMENS
6. FORMERLY SINGLE DRUG – NOW 2-5 DRUGS IN INTERMITTENT PULSES – TOTAL TUMOUR CELL KILL – COMBINATION CHEMOTHERAPY

COMBINATION CHEMOTHERAPY - SYNERGISTIC

- DRUGS WHICH ARE EFFECTIVE WHEN USED ALONE
- DRUGS WITH DIFFERENT MECHANISM OF ACTION
- DRUGS WITH DIFFERING TOXICITIES
- DRUGS WITH DIFFERENT MECHANISM OF TOXICITIES
- DRUGS WITH SYNERGISTIC BIOCHEMICAL INTERACTIONS
- OPTIMAL SCHEDULE BY TRIAL AND ERROR METHOD
- MORE IMPORTANTLY ON CELL CYCLE SPECIFICITY

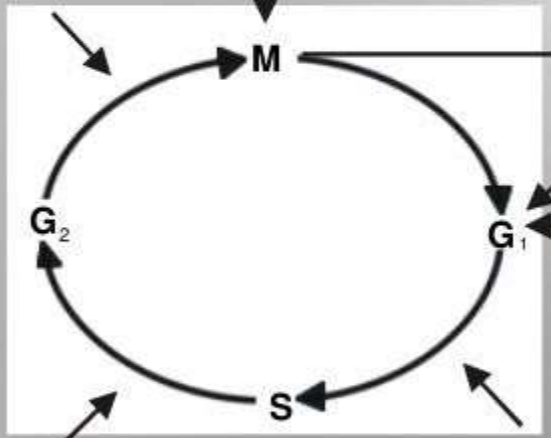
Antineoplastic Agent

a. Cell Cycle Specific (CCS) agents
b. Cell Cycle Non-Specific (CCNS) agents
c. Miscellaneous (e.g., antibodies) agents

Cell cycle specificity of Anti-Neoplastic Agents

Vincristine, Vinblastine
Paclitaxel, Docetaxel

Cyclophosphamide
Bleomycin
Actinomycin D



Hydrocortisone

Purine antagonists
Methotrexate
Cyclophosphamide
5-Fluorouracil
Cytosine arabinoside
Daunomycin

Actinomycin D
5-Fluorouracil
Cytosine arabinoside
Methotrexate
6-Mercaptopurine
6-Thioguanine

G_0 = resting phase
G_1 = pre-replicative phase
G_2 = post-replicative phase
S = DNA synthesis
M = mitosis or cell division

CLASSIFICATION

1. ALKYLATING AGENTS

- A. Nitrogen Mustards: Cyclophosphamide,. Chlorambucil, Melphalan,
- B. Alkyl Sulfonate: Busulfan
- C. Nitrosoureas : Carmustine, Lomustine,semustine
- D. Ethylenimines: Thiotepa
- E. Triazenes : Dacarbazine

2. Antimetabolites

- A. Folate antagonist: methotrexate and gemcitabine
- B. Purine analogues: thioguanine, mercaptopurine, pentostatin
- C. Pyrimidine analogues: fluorouracil, cytarabine

- **3. Plant-derived products :** vinca alkaloids**(** vincristine, vinblastine) epipodophyllotoxins (etoposide) taxanes: (paclitaxel)
- **4. Antibiotics :** doxorubicin , daunorubicin , bleomycin, mitomycin, dactinomycin
- **5. Hormones and related drugs :** tamoxifen estramustine, flutamide , progestins
- **6. Miscellaneous agent :** hydroxyurea, cisplatin , mitoxantrone, levamisole, interferon alfa and aldesleukin.

- **7. Drugs that alters hormonal milieu**
    1. Glucocorticoids: Prednisolon, Prednisone
    2. Estrogen: Diethylstilbestreol
    3. Anti-estrogen: Tamoxifen
    4. Androgen: Testosteron
    5. Progestin: Medroxy Progesteron Acetate

8. **Monoclonal Antibodies**

1. Trantuzumab
2. Rituximab
3. Imatinib

MECHANISM OF ACTION: ALKYLATING AGENT

- Alkylating agents exert their cytotoxic effects via transfer of their alkyl groups to various cellular constituents.
- Alkylations of DNA within the nucleus probably represent the major interactions that lead to cell death.
- The major site of alkylation within DNA is the n7 position of guanine; however, other bases are also alkylated to lesser degrees, including n1 and n3 of adenine, n3 of cytosine, and o6 of guanine

MOA: ANTI METABOLITES

- Antimetabolites are drugs that are structurally related to naturally occurring compounds, such as vitamins, amino acids, and nucleotides. These drugs can compete for binding sites on enzymes or can themselves become incorporated into DNA or RNA and thus interfere with cell growth and proliferation.

ALKYLATING AGENTS

- *ALKYLATING AGENTS* ARE COMPOUNDS THAT ARE CAPABLE OF INTRODUCING AN ALKYL GROUP INTO NUCLEOPHILIC SITES ON DNA , RNA OR ANY ENZYME THROUGH COVALENT BOND .

- THESE AGENTS ARE THOUGHT TO REACT WITH THE 7 POSITION OF GUANINE (OR ANY OTHER NITROGEN BASE) IN EACH OF THE DOUBLE STRANDS OF DNA, CAUSING CROSS-LINKING THAT INTERFERES WITH SEPARATION OF THE STRANDS AND PREVENTS MITOSIS.

- THE EFFECTS OF BASE ALKYLATION INCLUDE MISREADING OF THE DNA CODON AND SINGLE STRAND BREAKAGE OF THE DNA CHAIN. HOWEVER, THE LONGTIME EFFECTS ARE MUTATION AND CELL DEATH.

- THE FAVORED SITE ON DNA IS AT THE N7 POSITION OF GUANINE, ADENINE, CYTOSINE, AND EVEN THE SUGAR PHOSPHATE GROUPS .

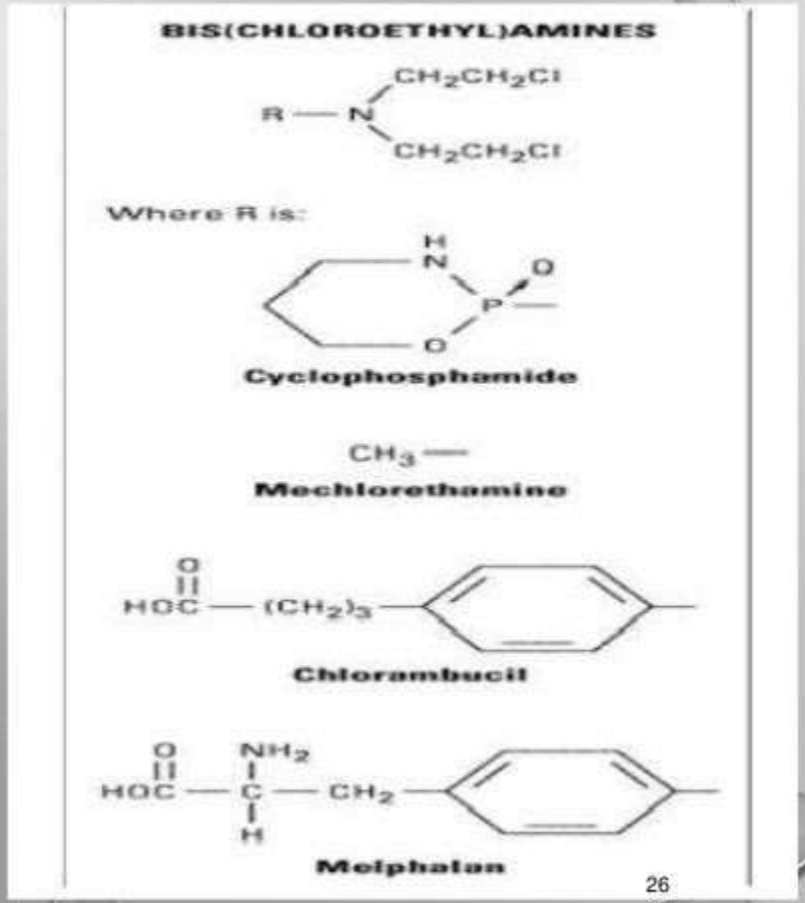
NITROGEN MUSTARDS

- METHCLORETHAMINE
- CYCLOPHOSPHAMIDE
- MELPHALAN
- CHLORAMBUCIL
- IFOSFAMIDE

- THE NITROGEN MUSTARDS ARE CYTOTOXIC CHEMOTHERAPEUTIC AGENTS SIMILAR TO MUSTARD GAS WHICH WAS USED IN WWI AND WWII

- NITROGEN MUSTARDS CONTAIN BIS(2-CHLOROETHYL) GROUP

- MODIFICATION OF THIS GROUP CHANGE STABILITY , REACTIVITY AND LIPOPHILICITY

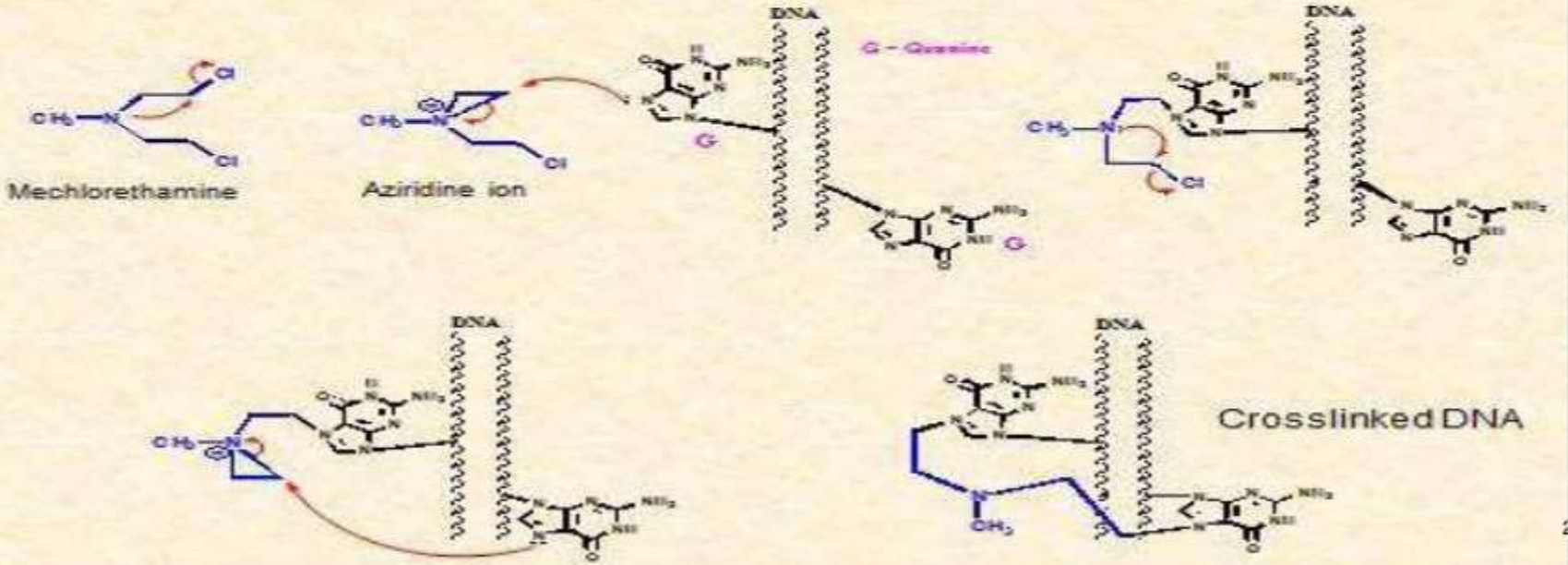


MECHANISM OF ALKYLATION BY

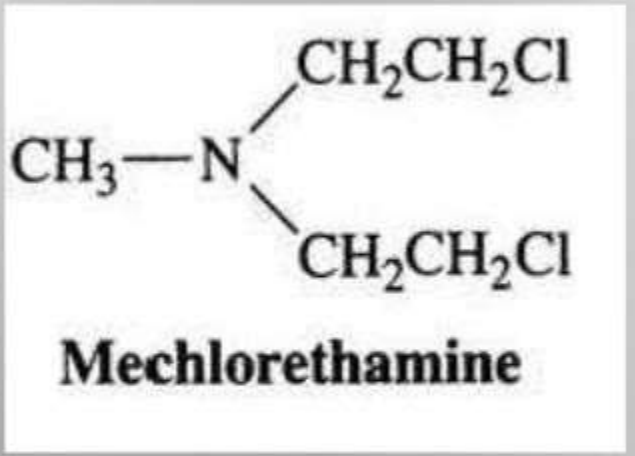
Alkylating agents

Chlormethine

Mechanism of action



- **METHCLORETHAMINE** (2-CHLORO-N-(2-CHLOROETHYL)-N-METHYL-ETHANAMINE)



Mechlorethamine

- A STRONG VESICANT AND IS

TAKEN BY IV INFUSION AND IT USED

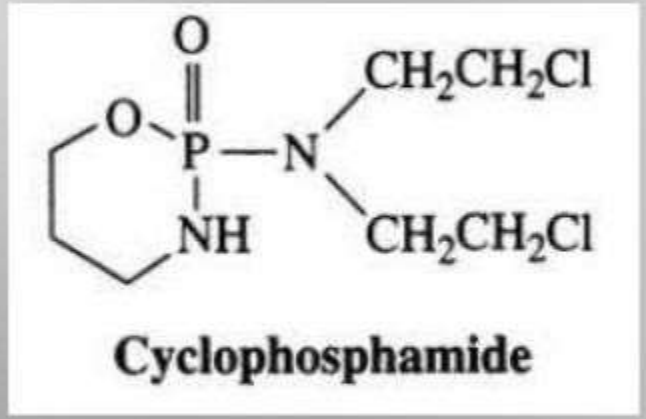
TO TREAT PROSTATE CANCER .

- A MAJOR DISADVANTAGE OF

MECHLORETHAMINE IS THAT IT HAS MUTAGENIC AND CARCINOGENIC EFFECT ON BONE MARROW STEM CELLS.

- CYCLOPHPSPHAMIDE (***CYTOXAN®***)

- **CYCLOPHOSPHAMIDE** (*N*,*N*-BIS(2-CHLOROETHYL)-1,3,2-OXAZAPHOSPHINAN-2-AMINE 2-OXIDE)



Cyclophosphamide

- THIS MOST WIDELY USED ALKYLATING AGENT

- IT IS INACTIVE IN VITRO BUT WHEN IT ADMINISTERED IT IS METABOLIZED BY LIVER INTO PHOSPHORAMIDE MUSTARD (ACTIVE COMPOUND)

CYCLOPHOSPHAMIDE

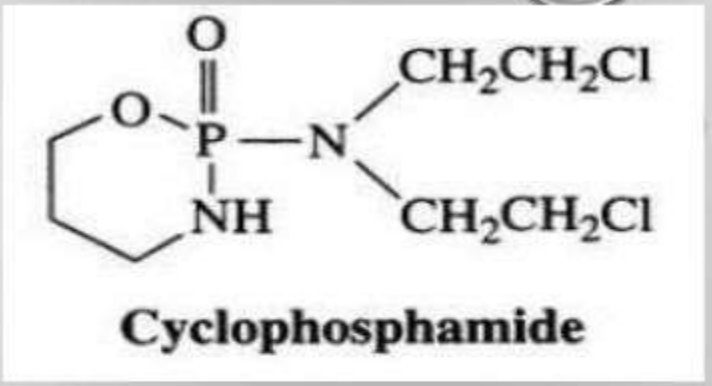
CLINICAL APPLICATIONS:

1. BREAST CANCER
2. OVARIAN CANCER
3. NON-HODGKIN'S LYMPHOMA
4. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
5. SOFT TISSUE SARCOMA
6. NEUROBLASTOMA
7. WILMS' TUMOR
8. RHABDOMYOSARCOMA

CYCLOPHOSPHAMIDE

MAJOR SIDE EFFECTS

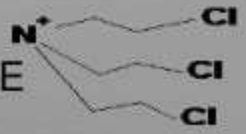
1. NAUSEA AND VOMITING
2. DECREASE IN PBL COUNT
3. DEPRESSION OF BLOOD CELL COUNTS
4. BLEEDING
5. ALOPECIA (HAIR LOSS)
6. SKIN PIGMENTATION
7. PULMONARY FIBROSIS



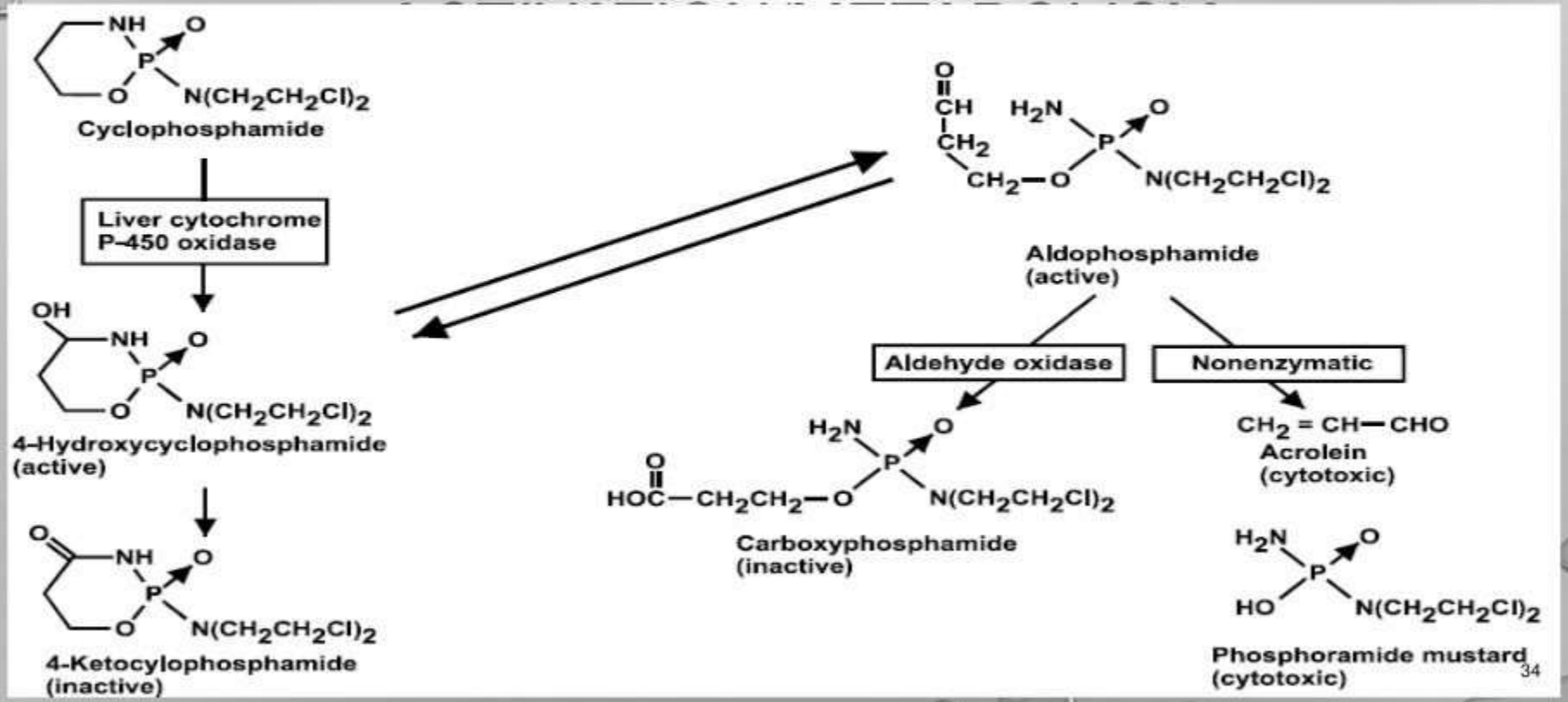
Cyclophosphamide

SAR OF CYCLOPHOSPHAMIDE

- BIS-2-CHLOROETHYLAMINO *GROUP* IS ESSENTIAL
- CHLORO ATOM PROVIDES MAXIMUM ACTIVITY
- LEVO-ISOMER IS INACTIVE
- TRIETHYLENE DERIVATIVE IS INACTIVE



CYCLOPHOSPHAMIDE



- PHOSPHORAMIDE MUSTARD IS CYTOTOXIC TO CANCER CELLS WHILE ACROLEIN IS ***TOXIC TO THE BLADDER***

- CYCLOPHOSPHAMIDE MAY GIVEN ORALLY BUT ITS ABSORPTION INCOMPLETE SO IT IS BETTER TO BE GIVEN I.V

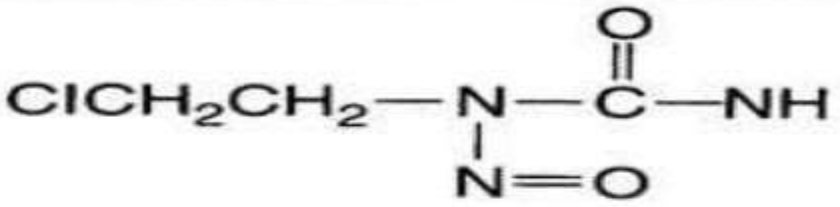
- IT USED TO TREAT MANY TYPES OF CANCER SUCH AS

LYMPHOSARCOMAS , BREAST, OVARIAN, AND LUNG CANCER.

NITROUREAS

- CARMUSTINE *(**GLIADEL®**)*
- LOMUSTINE
- STREPTOZOCIN

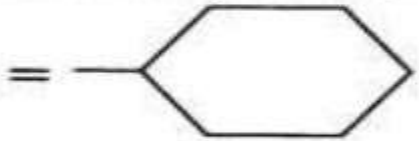
- THEY ARE COMPOUNDS THAT HAVE NITROSO (R-NO) GROUP AND A UREA. THEY HAVE LITTLE CROSS-RESISTANCE WITH OTHER ALKYLATING AGENTS
- THEY CROSS BLOOD-BRAIN BARRIER SO THEY USED AGAINST ***BRAIN TUMORS***



CARMUSTINE (BCNU)

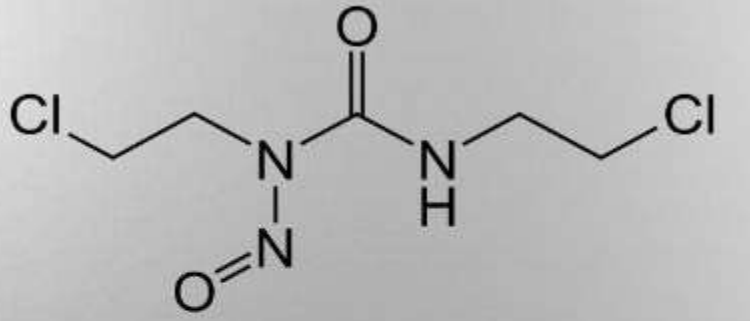
= —CH_2CH_2Cl

LOMUSTINE (CCNU)



SEMUSTINE (METHYL-CCNU)

- **CARMUSTINE (*N*,*N*′-BIS(2-CHLOROETHYL)-*N*-NITROSO-UREA)**



- IT CAUSE ALKYLATION OF DNA AT O-6 POSITION OF GUANINE

- IT MAINLY USED TO TREAT BRAIN CANCER AND LYMPHOMA

- IT CAUSE PULMONARY TOXICITY AND NEPHROTOXICITY

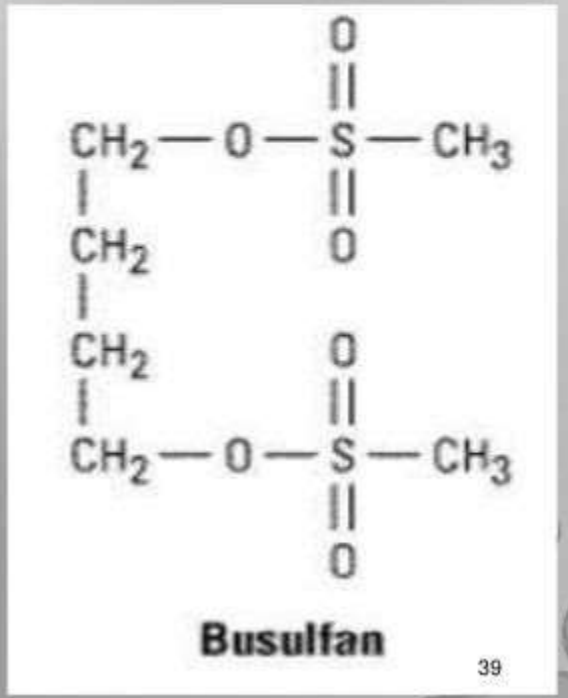
ALKYL SULPHONATES

- BUSULFAN (BUTANE-1,4-DIYL DIMETHANESULFONATE)

(MYLERAN®)

- IT IS USED FOR TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA (CML) IN BONE MARROW TRANSPLANTATION PATIENTS

- MAIN SIDE EFFECT IS SEIZURE



PLATINUM BASED ALKYLATING LIKE AGENTS

- CISPLATIN ***(PLATINOL®)***
- CARBOPLATIN
- OXALIPLATIN

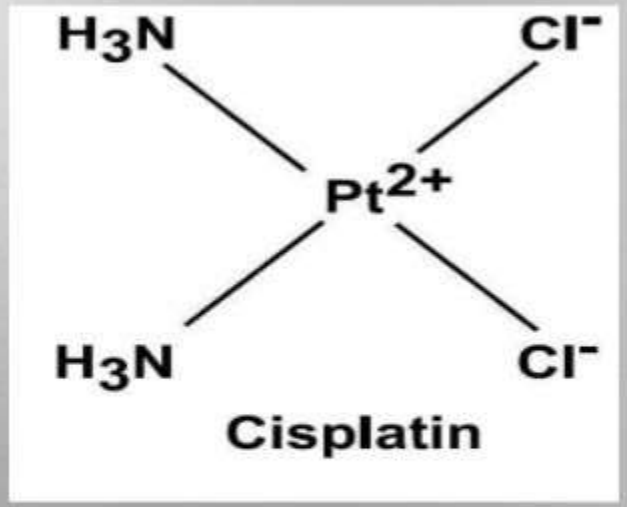
- THESE AGENTS DO NOT HAVE AN ALKYL GROUP, BUT THEY ALSO DAMAGE DNA. THEY PERMANENTLY COORDINATE TO DNA TO INTERFERE WITH DNA REPAIR (THEY TRIGGER *APOPTOSIS*)

- PLATIN IS THE ONLY HEAVY METAL COMPOUND IN COMMON USE AS A CANCER CHEMOTHERAPEUTIC AGENT

- **CISPLATIN** (DIAMMINEDICHLOROPLATINUM)

- IT ACTS AGAINST CELLS THAT ARE ACTIVELY SYNTHESIZING NUCLEIC ACIDS (S PHASE) AND AGAINST CELLS IN MITOSIS (M PHASE)

- THE PREFERRED SITE OF BINDING IS THE N7 POSITION OF GUANIDINE

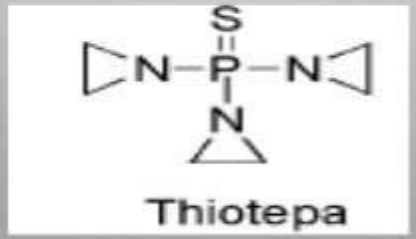


- BECAUSE IT'S BIFUNCTIONAL (HAVING TWO LEAVING GROUPS) CISPLATIN CAN FORM INTER-STRAND DNA CROSS LINKS WHICH CAUSE CYTOTOXICITY

- IT USED IN TREATMENT OF MAN-SEMINOMATOUS TESTICULAR CANCER AND IN OVARIAN CANCER

- IT IS NEPHROTOXIC AGENT

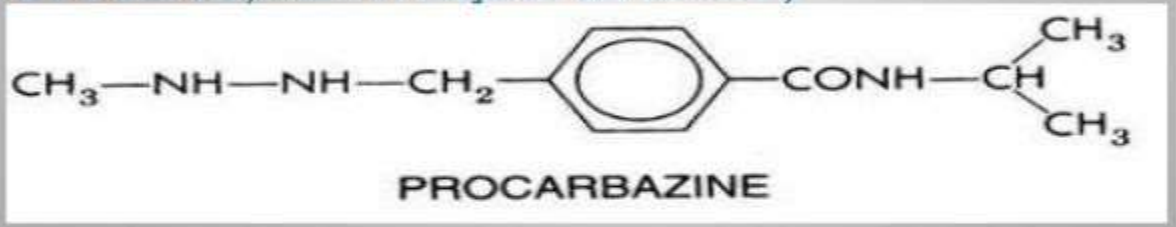
ETHLELYNE IMINE-THIOTEPA



Thiotepa

METHYLHYDRAZINES

- **PROCARBAZINE** (*N*-ISOPROPYL-4-[(2-METHYLHYDRAZINO)METHYL]BENZAMIDE)



PROCARBAZINE

- IT MUST BE CONVERTED INTO AN AZO DERIVATIVE IN VIVO TO BECOME ACTIVE AGAINST TUMOR CELLS.

ALKYLATION OF DNA OR POSSIBLE TRANSMETHYLATION MAY BE THE MODE OF ACTION.

- IT IS A COMPONENT OF THE MOPP (MECHLORETHAMINE, VINCRISTINE , PROCARBAZINE AND PREDINSONE) COMBINATION THAT IS SO EFFECTIVE IN TREATMENT OF HODGKINS DISEASE.

- IT HAS MONAMINE OXIDASE INHIBITION PROPERTIES (MAOI) , SO IT SHOULD NOT BE TAKEN WITH MOST ANTIDEPRESSANTS AND CERTAIN MIGRAINE MEDICATIONS.

BLOCK NUCLEIC ACID (DNA, RNA) BIOSYNTHESIS

ANTIMETABOLITES:

- **FOLIC ACID ANTAGONIST:** INHIBIT DIHYDROFOLATE REDUCTASE (METHOTREXATE)
- **PYRIMIDINE ANTAGONIST:** INHIBIT THYMIDYLATE SYNTHETASE (FLUOROURACIL) ; INHIBIT DNA POLYMERASE (CYTARABINE)
- **PURINE ANTAGONIST:** INHIBIT INTERCONVERSION OF PURINE NUCLEOTIDE (6-MERCAPTOPURINE AND 6-THIOGUANINE)
- **RIBONUCLEOSIDE DIPHOSPHATE REDUCTASE ANTAGONIST:** (HYDROXYUREA)

INTERFERE PROTEIN SYNTHESIS

- **ANTITUBULIN: VINCA ALKALOIDS (VINCRISTINE AND VINBLASTIN)** AND **TAXANES (PACLITAXEL AND DOCETAXEL)**

BIND TUBULIN, DESTROY SPINDLE AND PRODUCE MITOTIC ARREST

- **INFLUENCE AMINO ACID SUPPLY: L-ASPARAGINASE**

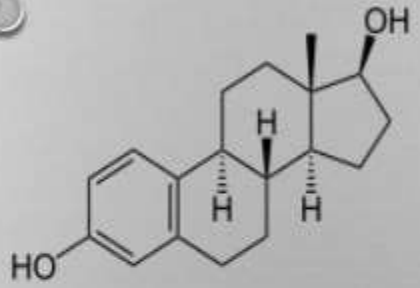
.

INFLUENCE HORMONE HOMEOSTASIS

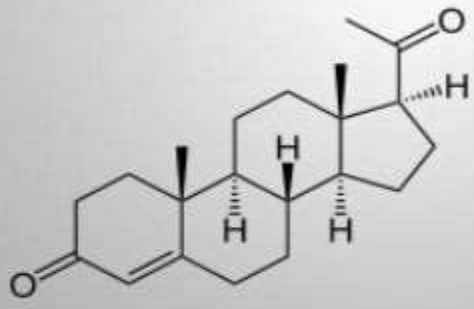
THESE DRUGS BIND TO HORMONE RECEPTORS TO BLOCK THE ACTIONS OF THE SEX HORMONES WHICH RESULTS IN INHIBITION OF TUMOR GROWTH

- ESTROGENS AND ESTROGEN ANTAGONISTIC DRUG (EE, SERM-TAMOXIFENE)
- ANDROGENS AND ANDROGEN ANTAGONISTIC DRUG (FLUTAMIDE AND BICALUTAMIDE)
- PROGESTOGEN DRUG (HYDROXYPROGESTERONE)
- GLUCOCORTICOID DRUG (PREDNISOLONE AND OTHERS)
- GONADOTROPIN-RELEASING HORMONE INHIBITOR: NAFARELIN, TRIPTORELIN
- AROMATASE INHIBITOR: LETROZOLE AND ANASTRAZOLE

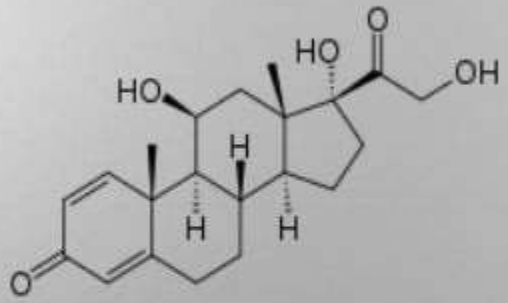
STEROIDAL DRUGS



Estradiol
(estrogen)



Progesterone



Prednisolone
(adrenocorticoids)

Drug Resistance

One of the fundamental issue in cancer chemotherapy is the development of cellular drug resistance. It means, tumor cells are no longer respond to chemotherapeutic agents. For example, melanoma, renal cell cancer,
brain cancer often become resistant to chemo.

A few known reasons:

1. Mutation in p53 tumor suppressor gene occurs in 50% of all tumors. This leads to resistance to radiation therapy and wide range of chemotherapy.

2. Defects or loss in mismatch repair (MMR) enzyme family. E.g., colon cancer no longer respond to fluoropyrimidines, the thiopurines, and cisplatins.

3. Increased expression of multidrug resistance MDR1 gene which encodes P-glycoprotein resulting in enhanced drug efflux and reduced intracellular accumulation. Drugs such as athracyclines, vinca alkaloids, taxanes, campothecins, even antibody such as imatinib.

ANTIMETABOLITES

- FOLIC ACID ANTAGONISTS: MTX
- PURINE ANTAGONISTS: 6MP AND 6TG
- PYRIMIDINE ANTAGONISTS: 5FU AND CYTARABINE

GENERAL CHARACTERISTICS:

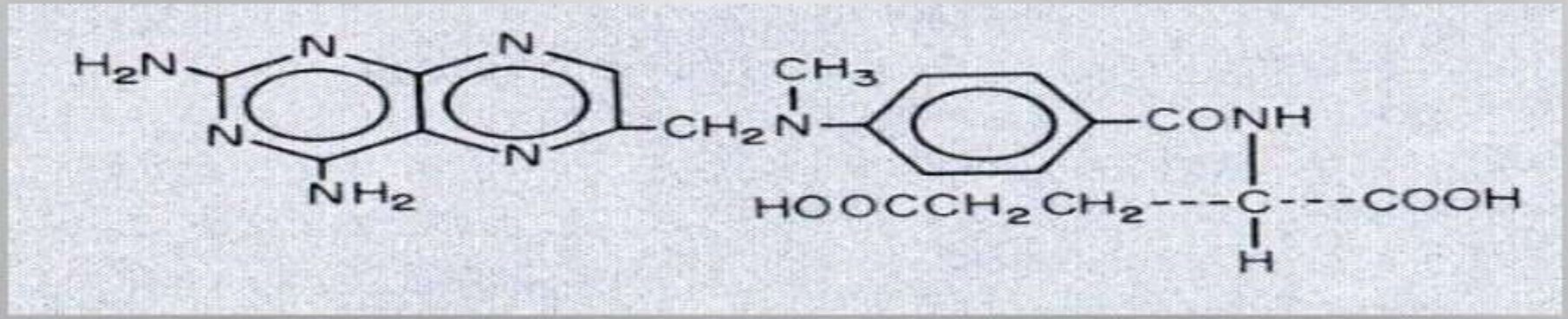
- ANTIMETABOLITES ARE S PHASE-SPECIFIC DRUGS THAT ARE STRUCTURAL ANALOGUES OF ESSENTIAL METABOLITES AND THAT INTERFERE WITH DNA SYNTHESIS.
- MYELOSUPPRESSION IS THE DOSE-LIMITING TOXICITY FOR ALL DRUGS IN THIS CLASS

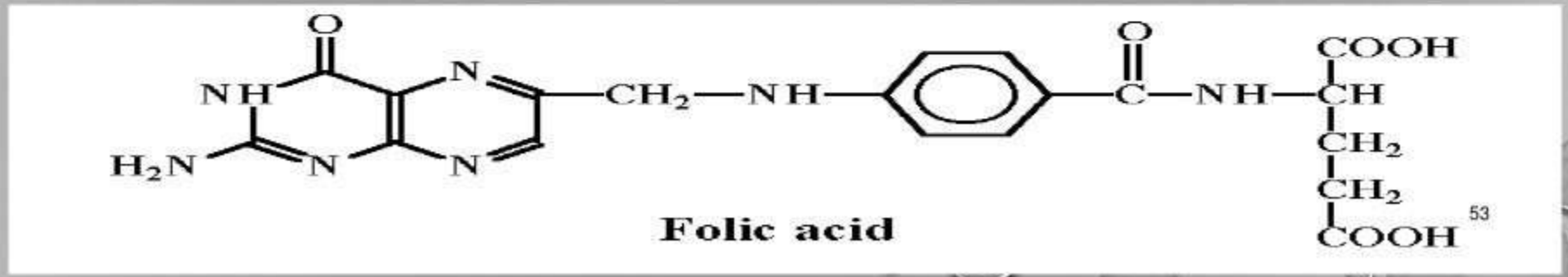
METHOTREXATE – FOLATE ANTAGONIST

- MOA:
  - THE STRUCTURES OF MTX AND FOLIC ACID ARE SIMILAR
  - MTX IS ACTIVELY TRANSPORTED INTO MAMMALIAN CELLS AND INHIBITS DIHYDROFOLATE REDUCTASE
  - THE ENZYME THAT NORMALLY CONVERTS DIETARY FOLATE TO THE TETRAHYDROFOLATE FORM REQUIRED FOR THYMIDINE AND PURINE SYNTHESIS
- LEUCOVORIN RESCUE:
  - ADMINISTERED AS A PLAN IN MTX THERAPY
  - LEUCOVORIN (FOLINIC ACID) IS DIRECTLY CONVERTED TO TETRAHYDROFOLIC ACID - PRODUCTION OF DNA CELLULAR PROTEIN INSPITE OF PRESENCE OF MTX
  - USED TO RESCUE BONE MARROW AND GIT MUCOSAL CELLS
- RESISTANCE:
  - REDUCTION OF AFFINITY OF DHFR TO MTX
  - DIMINISHED ENTRY OF MTX INTO CANCER CELLS
  - OVER PRODUCTION OF DHFR ENZYME

METHOTREXATE (MTX)

- **STRUCTURE:**

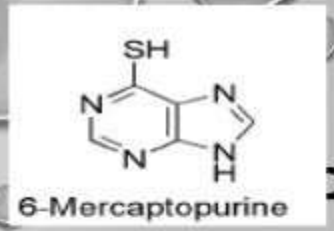




Folic acid

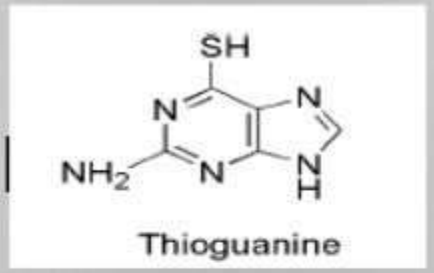
METHOTREXATE – CONTD.

- KINETICS:
  - GIVEN ORALLY/IM /IV AND ALSO INTRATHECALLY AND GOOD ORAL ABSORPTION
  - CSF ENTRY - INTRATHECAL
- INDICATIONS:
  - CHORIOCARINOMA - WAS THE FIRST DEMONSTRATION OF CURATIVE CHEMOTHERAPY
  - TUMORS OF HEAD AND NECK
  - BREAST CANCER
  - ACUE LYMPHATIC LEUKEMIA
  - MENINGEAL METASTASES OF A WIDE RANGE OF TUMORS
- ADRS: 1) MYELOSUPPRESSION - SEVERE LEUKOPENIA, BONE MARROW APLASIA, AND THROMBOCYTOPENIA 2) GIT DISTURBANCES 3) RENAL TOXICITY (CRYSTALLURIA)



6-Mercaptopurine

PURINE ANTAGONISTS – 6MI



Thioguanine

6-MERCAPAPURINE (6-MP) AND OTHERS

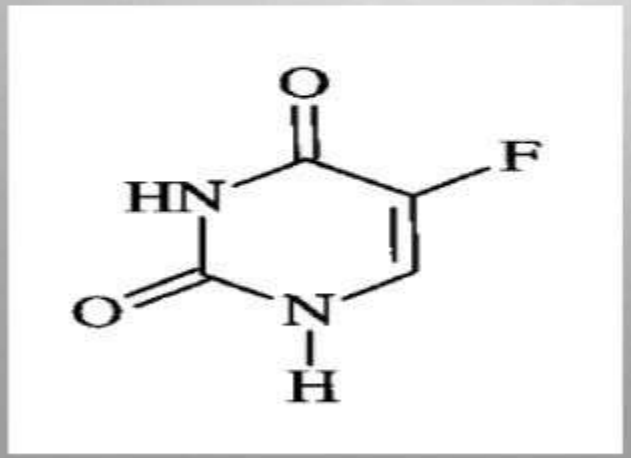
- EXACT MECHANISMS OF ACTION ARE STILL UNCERTAIN – INHIBIT PURINE BASE SYNTHESIS
- USED IN CHILDHOOD ACUTE LYMPHATIC LEUKAEMIA FOR MAINTENANCE AND REMISSION AND MAY ALSO BE IN COMBINATION WITH MTX IN CHORIOCARCINOMA
- METABOLIZED BY XANTHINE OXIDASE (INHIBITED BY ALLOPURINOL) AND ALLOPURINOL DOSE HAS TO BE ADJUSTED TO $\frac{1}{2}$ OR $1/4^{TH}$
- WELL TOLERATED, MILD MYELOSUPPRESSION AND HEPATOTOXICITY ON LONG TERM ADMINISTRATION

ANTIMETABOLITES (PYRIMIDINE ANTAGONISTS) - 5 FU

- MOA:
  - FLUOROURACIL IS AN ANALOGUE OF THYMINE
  - CONVERTED TO 5-FLUORO-2DEOXY-URIDINE MONOPHOSPHATE (5-FDUMP)
  - 5-FDUMP INHIBITS THYMIDYLATE SYNTHASE AND BLOCKS CONVERSION OF DEOXYURIDILIC ACID TO DEOXYTHYMIDYLIC ACID - FAILURE OF DNA SYNTHESIS
- INDICATIONS: SOLID TUMORS, ESPECIALLY BREAST, COLORECTAL, AND GASTRIC TUMORS AND SQUAMOUS CELL TUMORS OF THE HEAD AND NECK
- ADRS:
  - NAUSEA AND VOMITING, MYELOSUPPRESSION, AND ORAL AND GASTROINTESTINAL ULCERATION. NAUSEA AND VOMITTING ARE USUALLY MILD
  - MUCOSAL DAMAGE AND MYELOSUPPRESSION

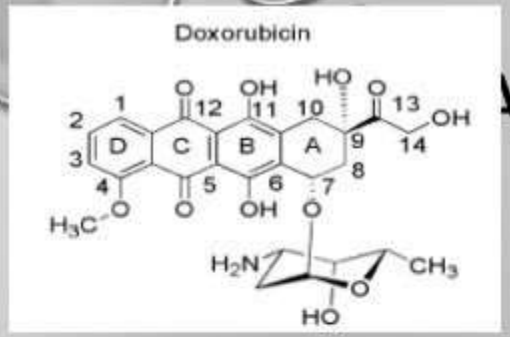
FLUROURACIL (5-FU)

- STRUCTURE:

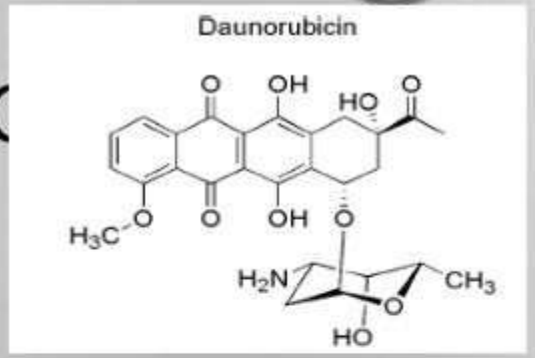


ANTIBIOTICS

- ANTHRACYCLINES (DOXORUBICIN AND DAU NORUBICIN), DACTINOMYCIN, BLEOMYCIN, AND MITOMYCIN
- ANTHRACYCLINES:
  - ENTERS THEMSELVES INTO DNA AND CAUSES DNA BREAK
  - ACTIVATES TOPOISOMERASE II AND CAUSE BREAK IN DNA STRANDS
  - GENERATES EXCESS FREE RADICALS CAUSING PRODUCTION OF SUPEROXIDE – DAMAGE TO DNA
  - KNOWN TO DAMAGE CARDIAC CELLS ALSO (UNIQUE)
  - RESISTANCE DEVELOPES DUE TO INCREASED EFLUX OF DRUG
  - USES: DOXO- BREAST, OVARY, LUNG, [PROSTATE AND ACUTE LYMPHATIC LEUKAEMIA
  - DAUNO- ALL AND AML

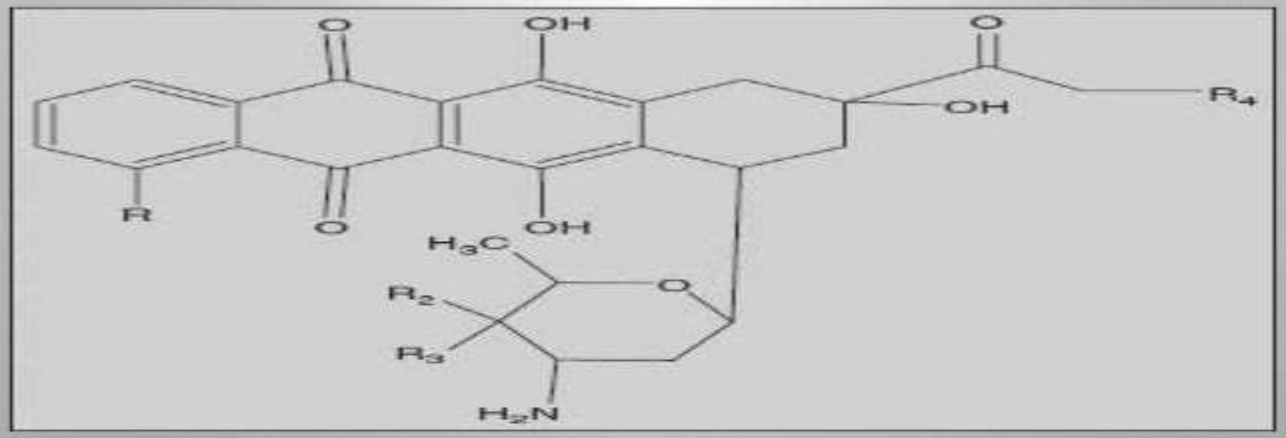


ANTICANCER ANTIBIOTIC



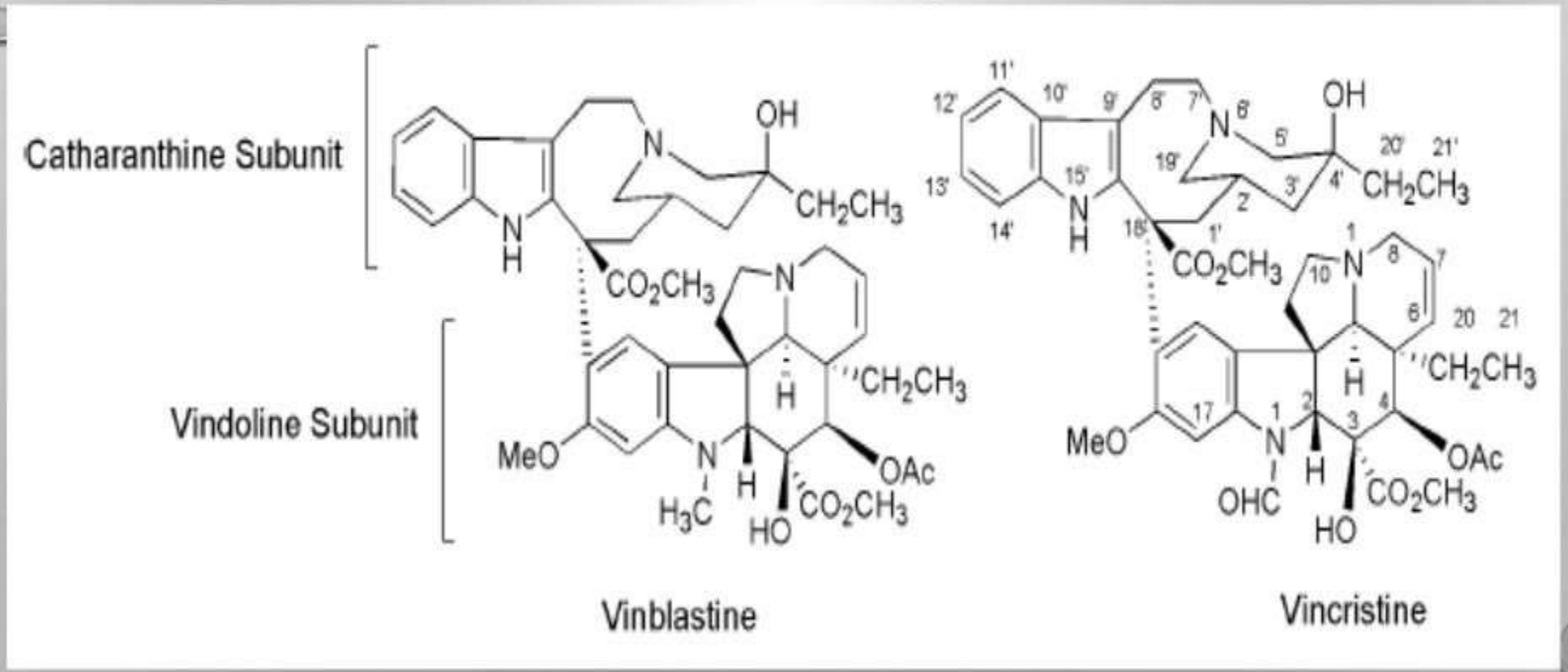
- **ANTHRACYCLINE ANTIBIOTICS:** ANTHRACYCLINES OCCUR AS GLYCOSIDES OF THE ANTHRACYCLINONE. THE GLYCOSIDIC LINKAGE USUALLY INVOLVES THE 7-HYDROXYL GROUP OF THE ANTHRACYCLINONE AND THE B-ANOMER OF A SUGAR WITH L-CONFIGURATION. ANTHRACYCLINONE REFERS TO AN AGLYCONE CONTAINING THE ANTHRAQUINONE CHROMOPHORE WITHIN A LINEAR HYDROCARBON SKELETON. THE ANTHRACYCLINES DIFFER FROM EACH OTHER IN THE NUMBER AND LOCATION OF THE PHENOLIC HYDROXYLGROUPS, THE DEGREE OF OXIDATION OF THE TWO CARBON SIDE-CHAINS AT POSITION 9, AND THE PRESENCE OF CARBOXYLIC ACID ESTER AT POSITION 10

ANTICANCER ANTIBIOTICS

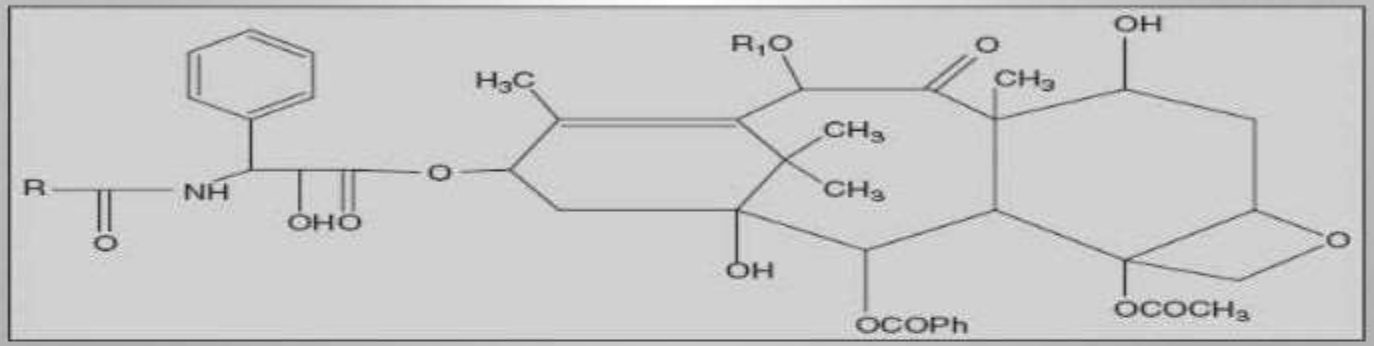


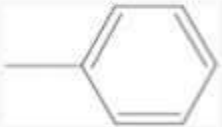
	R_1	R_2	R_3	R_4
Daunorubicin	—OCH_3	H	OH	H
Doxorubicin	—OCH_3	H	OH	OH
Carminomycin	OH	H	OH	OH
Idrabucin	H	H	OH	H
Epirubicin	—OCH_3	OH	H	OH

Plant derived anticancer Agents-Vinca Plant

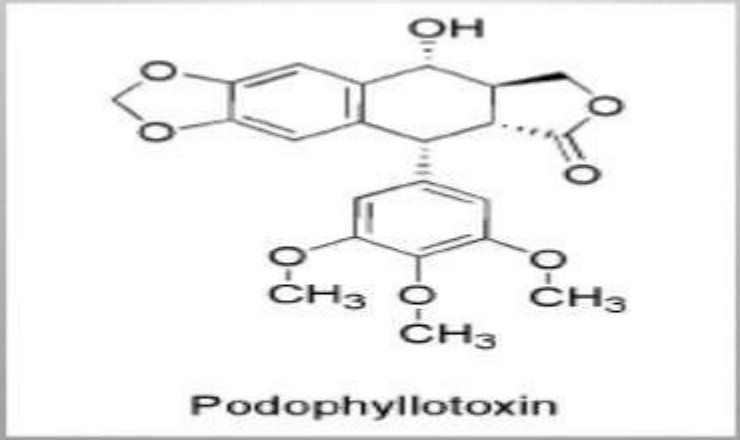


ANTICANCER PLANT PRODUCTS



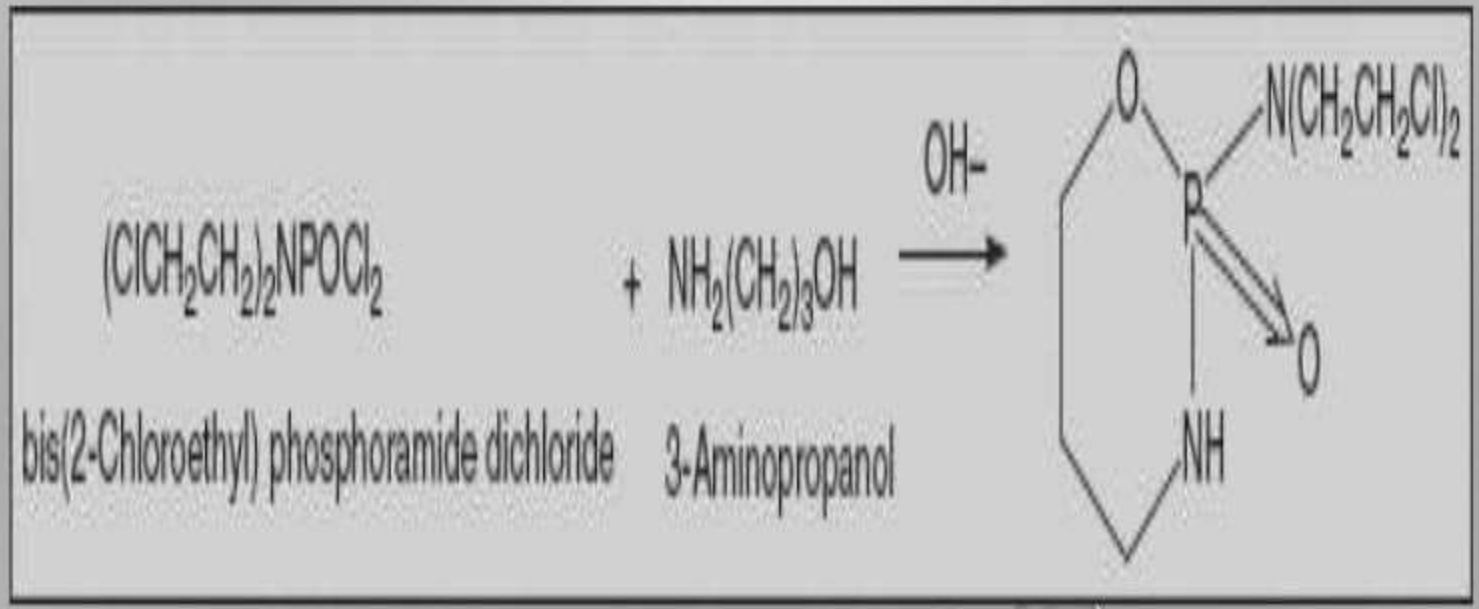
	R	R_1
Paclitaxel		— $COCH_3$
Docetaxel	$(CH_3)_3CO$—	H

Plant derived-Podophyloroxin

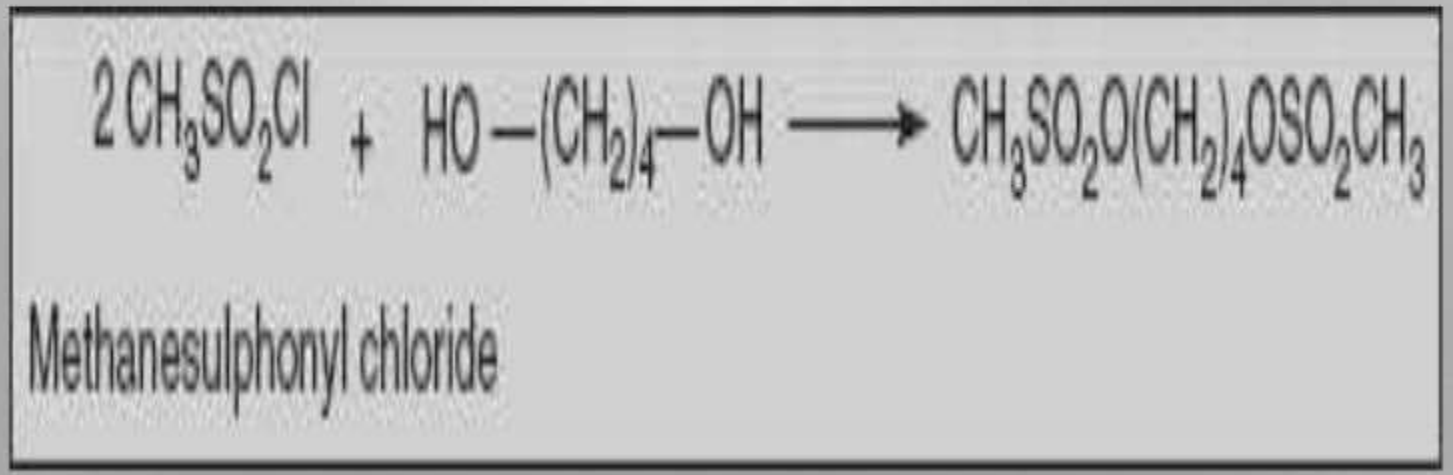


Podophyllotoxin

SYNTHESIS OF CYCLOPHOSPHAMIDE



SYNTHESIS OF BUSULFAN



A. Alkylating agents

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
a. Nitrogen Mustards				
A. Mechlorethamine	DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Must be given Orally	Nausea and vomiting, decrease in PBL count, BM depression, bleeding, alopecia, skin pigmentation, pulmonary fibrosis
B. Cyclophosphamide	Same as above	Breast, ovarian, CLL, soft tissue sarcoma, WT, neuroblastoma	Orally and I.V.	Same as above
C. Chlorambucil	Same as above	Chronic lymphocytic leukemia	Orally effective	Same as above
D. Melphalan	Same as above	Multiple myeloma, breast, ovarian	Orally effective	Same as above
E. Ifosfamide	Same as above	Germ cell cancer, cervical carcinoma, lung, Hodgkins and non-Hodgkins lymphoma, sarcomas	Orally effective	Same as above

A. Alkylating agents

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
b. Alkyl Sulfonates				
A. Busulfan	Atypical alkylating agent.	Chronic granulocytic leukemia	Orally effective	Bone marrow depression, pulmonary fibrosis, and hyperuricemia

c. Nitrosoureas	**1. Mechanism of Action**	**2. Clinical application**	**3. Route**	**4. Side effects**
A. Carmustine	DNA damage, it can cross blood-brain barrier	Hodgkins and non-Hodgkins lymphoma, brain tumors, G.I. carcinoma	Given I.V. must be given slowly.	Bone marrow depression, CNS depression, renal toxicity
B. Lomustine	Lomustine alkylates and crosslinks DNA, thereby inhibiting DNA and RNA synthesis. Also carbamoylates DNA and proteins, resulting in inhibition of DNA and RNA synthesis and disruption of RNA processing. Lomustine is lipophilic and crosses the blood-brain barrier	Hodgkins and non-Hodgkins lymphoma, malignant melanoma and epidermoid carcinoma of lung	Orally effective	Nausea and vomiting, Nephrotoxicity, nerve dysfunction
C. Streptozotocin	DNA damage	pancreatic cancer	Given I.V.	Nausea and vomiting, nephrotoxicity, liver toxicity

A. Alkylating agents

d. Ethylenimines	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Triethylene thiophosphoramide (Thio-TEPA)	DNA damage, Cytochrome P450	Bladder cancer	Given I.V.	Nausea and vomiting, fatigue
B. Hexamethylmelamine (HMM)	DNA damage	Advanced ovarian tumor	Given orally after food	Nausea and vomiting, low blood counts, diarrhea

d. Triazenes	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Dacarbazine (DTIC)	Blocks, DNA, RNA and protein synthesis	Malignant Melanoma, Hodgkins and non-Hodgkins lymphoma	Given I.V.	Bone marrow depression, hepatotoxicity, neurotoxicity, bleeding, bruising, blood clots, sore mouths.

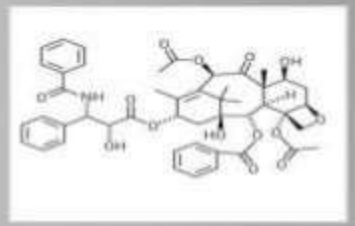
B. Natural Products

1. Antimitotic Drugs

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Vincristine	Cytotoxic: Inhibition of mitotic spindle formation by binding to tubulin. M-phase of the cell cycle.	Metastatic testicular cancer, Hodgkins and non-Hodgkins lymphoma, Kaposi's sarcoma, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Bone marrow depression, epithelial ulceration, GI disturbances, neurotoxicity
B. Vinblastine	Methylates DNA and inhibits DNA synthesis and function	Hodgkins and non-Hodgkins lymphoma, brain tumors, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Nausea and vomiting, neurotoxicity, thrombocytosis, hyperuricemia.

2. Antimitotic Drugs

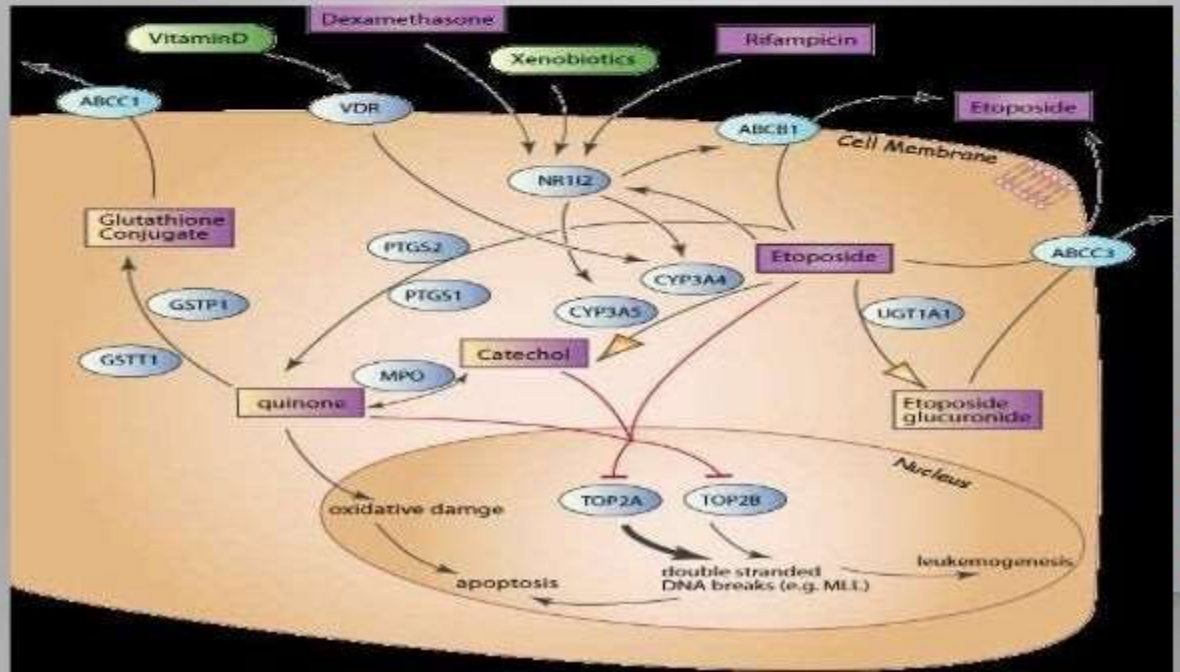
	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
Paclitaxel (Taxol) 	Cytotoxic: binds to tubulin, promotes microtubule formation and retards disassembly; mitotic arrest results	Melanoma and carcinoma of ovary and breast	I.V.	Myelodepression and neuropathy



3. Epipodophyllotoxins (These are CCS)

Act on Topoisomerase II

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Etoposide	Binds to and inhibits Topoisomerase II and its function. Fragmentation of DNA leading to cell death, apoptosis.	Testicular cancer, small-cell lung carcinoma, Hodgkin lymphoma, carcinoma of breast, Kaposi's sarcoma associated with AIDS	I.V.	Myelosuppression, alopecia
B. Teniposide	Same as above	Refractory acute lymphocytic leukemia	I.V.	Myelosuppression,



Accumulation of single- or double-strand DNA breaks, the inhibition of DNA replication and transcription, and apoptotic cell death.

Etoposide acts primarily in the G_2 and S phases of the cell cycle

4. Antibiotics (CCS)

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
a. Dactinomycin (ACTINOMYCIN D)	It binds to DNA and inhibits RNA synthesis, impaired mRNA production, and protein synthesis	Rhabdomyosarcoma and Wilm's tumor in children; choriocarcinoma (used with methotrexate	I.V.	Bone marrow depression, nausea and vomiting, alopecia, GI disturbances, and ulcerations of oral mucosa
b. Daunorubicin (CERUBIDIN)	inhibit DNA and RNA synthesis	Acute lymphocytic/granulocytic leukemias; treatment of choice in nonlymphoblastic leukemia in adults when given with cytarabine	I.V.	Side effects: bone marrow depression, GI disturbances and cardiac toxicity (can be prevented by dexrazoxane)
Doxorubicin (ADRIAMYCIN)	inhibit DNA and RNA synthesis	Acute leukemia, Hodgkin's disease, non Hodgkin's lymphomas (BACOP regimen), CA of breast & ovary, small cell CA of lung, sarcomas, best available agent for metastatic thyroid CA	I.V.	Cardiac toxicity, Doxorubicin mainly affects the heart muscles, leading to tiredness or breathing trouble when climbing stairs or walking, swelling of the feet .
c. Bleomycin (BLENOXANE)	fragment DNA chains and inhibit repair	Germ cell tumors of testes and ovary, e.g., testicular carcinoma (can be curative when used with vinblastine & cisplatin), squamous cell carcinoma	Given I.V. or I.M.	Mucosocutaneous reactions and pulmonary fibrosis; bone marrow depression much less than other antineoplastics

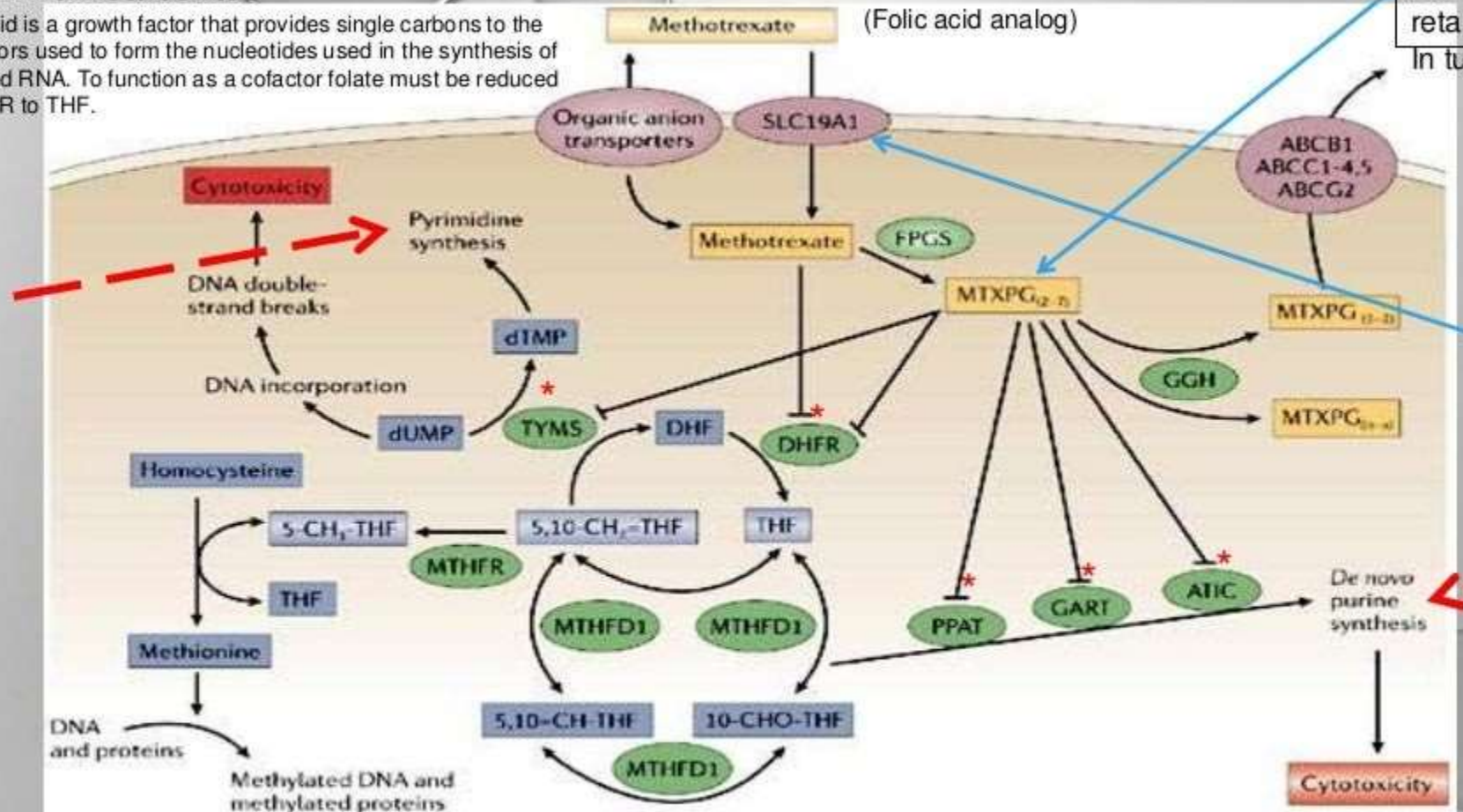
Inhibit DNA and RNA syntheses

5. Enzymes: L-asparaginase

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
L-asparaginase	Hydrolyzes L-asparagine (to L-aspartic acid) an essential amino acid to many leukemic cells	Acute lymphocytic leukemia, induction of remission in acute lymphoblastic leukemia when combined with vincristine, prednisone, and anthracyclines	I.V. or I.M.	Nausea and vomiting, Poor appetite, Stomach cramping, Mouth sores, Pancreatitis. Less common: blood clotting

C. Antimetabolites

Folic acid is a growth factor that provides single carbons to the precursors used to form the nucleotides used in the synthesis of DNA and RNA. To function as a cofactor folate must be reduced by DHFR to THF.



MTX polyglutamates Are selectively retained In tumor cells.

Reduced Folate Carrier protein

MTX Kills cells during S-phase

Cancer Chemotherapy
Chapter 55. B.G. Katzung

C. Antimetabolites

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
1. Methotrexate	inhibits formation of FH4 (tetrahydrofolate) from folic acid by inhibiting the enzyme dihydrofolate reductase (DHFR); since FH4 transfers methyl groups essential to DNA synthesis and hence DNA synthesis blocked.	Choriocarcinoma, acute lymphoblastic leukemia (children), osteogenic sarcoma, Burkitt's and other non-Hodgkin's lymphomas, cancer of breast, ovary, bladder, head & neck	Orally effective as well as given I.V.	bone marrow depression, intestinal lesions and interference with embryogenesis. Drug interaction: aspirin and sulfonamides displace methotrexate from plasma proteins.

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
2 Pyrimidine Analogs: Cytosine Arabinoside	inhibits DNA synthesis	most effective agent for induction of remission in acute myelocytic leukemia; also used for induction of remission acute lymphoblastic leukemia, non-Hodgkin's lymphomas; usually used in combination chemotherapy	Orally effective	bone marrow depression

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
2 Purine analogs: 6-Mercaptopurine (6-MP) and Thioguanine	Blocks DNA synthesis by inhibiting conversion of IMP to AMPS and to XMP as well as blocking conversion of AMP to ADP; also blocks first step in purine synthesis. Feedback inhibition blocks DNA synthesis by inhibiting conversion of IMP to XMP as well as GMP to GDP; also blocks first step in purine synthesis by feedback inhibition	most effective agent for induction of remission in acute myelocytic leukemia; also used for induction of remission acute lymphoblastic leukemia, non-Hodgkin's lymphomas; usually used in combination chemotherapy	Orally effective	bone marrow depression,

REFRENCES

- **FOY'S PRINCIPLES OF MEDICINAL CHEMISTRY, CHAPTER 42, SIXTH EDITION.*
- ***FOY'S PRINCIPLES OF MEDICINAL CHEMISTRY, CHAPTER 6, SIXTH EDITION*
- *GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS , ELEVENTH EDITION*
- *CANCER CHEMOTHERAPY--THE FIRST TWENTY-FIVE YEARS BY* R. B. SCOTT
- *HANDBOOK OF CANCER CHEMOTHERAPY* (6TH EDITION)