INTRODUCTION TO NEOPLASTIC DISORDERS

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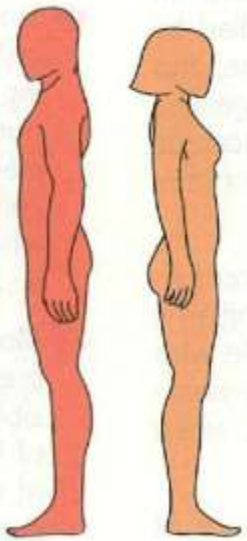
Cancer definition

- A group of diseases by uncontrolled growth and spread of abnormal cells
- Not respond to the normal processes
- Poorly differentiated or immature
- Cannot carry out the physiologic functions
- Ability to metastasize
- ability to angiogenesis

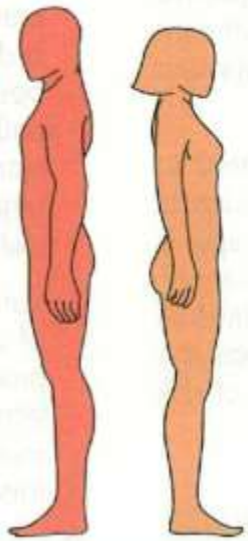
Prevalence

- 1 of 2 American men and 1 of 3 American women will eventually develop cancer
- Approximately 1,529,560 new cases of cancer will be diagnosed in 2010

Estimated new cases*

Males				Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All sites	**789,620**	**100%**		**All sites**	**739,940**	**100%**

Estimated deaths

Males				Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All sites	**299,200**	**100%**		**All sites**	**270,290**	**100%**

Etiology

- An initial "event" causes damage or mutation to the cell's DNA
- These events may include:
  - Lifestyle, environmental, or occupational factors
  - Some medical therapies (e.g., cytotoxic chemotherapy, immunosuppressive or radiation therapy)
  - Hereditary factors

Carcinogenic Risk Factor	Associated Cancer(s)
Environmental	
Ionizing radiation (radon gas emitted from soil containing uranium deposits)	Leukemia, breast, thyroid, lung
Ultraviolet radiation	Skin melanoma
Viruses	Leukemia, lymphoma, nasopharyngeal, liver, cervix
Occupational	
Asbestos	Lung, mesothelioma
Chromium, nickel	Lung
Vinyl chloride	Liver
Aniline dye	Bladder
Benzene	Leukemia
Radiation	Leukemia, thyroid

Lifestyle	
Alcohol	Esophagus, liver, stomach, oropharynx, larynx
Dietary factors	Colon, breast, gallbladder, gastric
Tobacco	Lung, oropharynx, pharynx, larynx, esophagus, bladder
Medical Drugs	
Diethylstilbestrol	Vaginal (in the offspring of the exposed mother), breast, testes, ovary
Alkylating agents	Leukemia, bladder
Azathioprine, calcineurin inhibitors, mycophenolate	Lymphoma
Phenacetin	Bladder
Estrogens, tamoxifen	Endometrial
Cyclophosphamide	Bladder
Etoposide	Leukemia

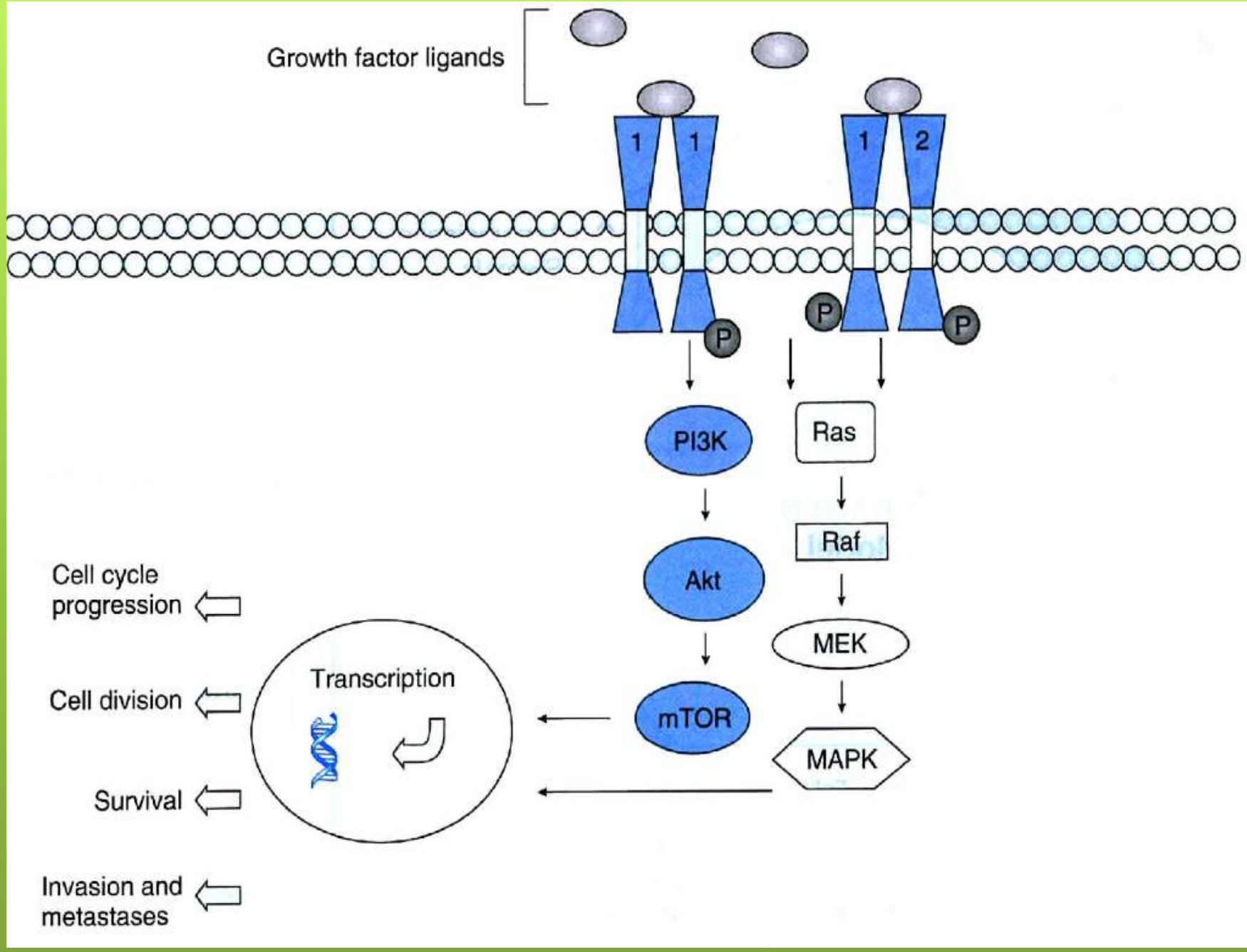
Etiology

- Cancer is a genetic disease
- Two gene classes, oncogenes and tumor suppressor genes, are important in the pathogenesis of cancer
- Oncogenes arise from normal genes called proto-oncogenes
- Proto-oncogenes are responsible for encoding several components of signal transduction pathways, including growth factors, growth factor receptors, signaling enzymes, and DNA transcription factors.

- Tumor-suppressor genes are normal genes that encode for proteins that suppress inappropriate cell division or growth

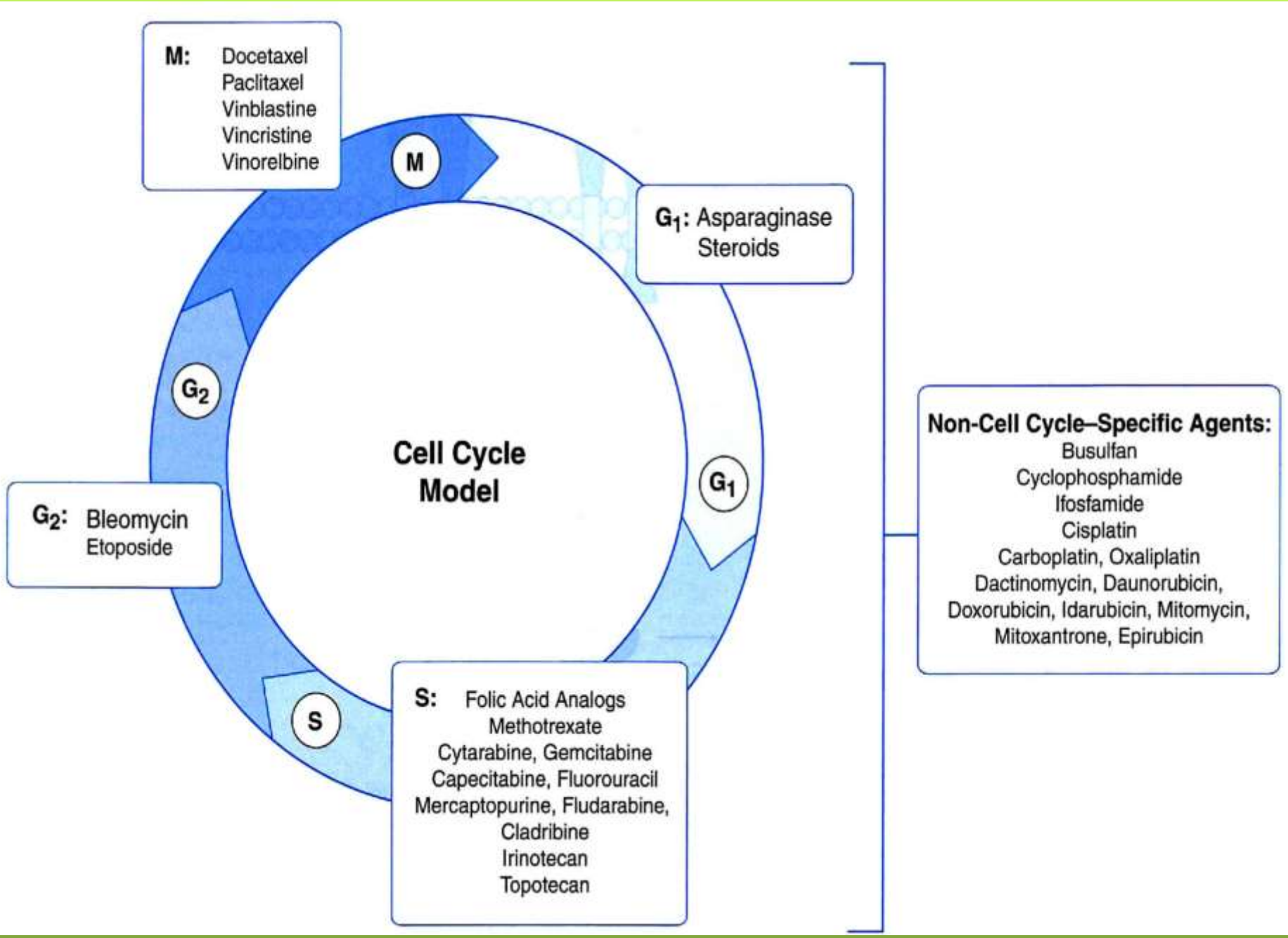
- Gene deletions or mutations can cause these proteins to become inactivated, eliminating the normal inhibition of cell division

- DNA repair genes
  - Correct errors that may arise during DNA duplication


Growth factor ligands
1
1
1
2
P
P
P
PI3K
Ras
Raf
Akt
MEK
mTOR
MAPK
Transcription
Cell cycle progression
Cell division
Survival
Invasion and metastases

Cell cycle

- M phase
  - The cell undergoes mitosis, the process of cell division.
- First gap or resting phase (G1).
  - During the G1 resting phase, the cell makes the enzymes necessary for DNA synthesis.
- S phase
  - The synthesis of DNA occurs during the S phase.
- Second resting phase(G2).
  - RNA and other proteins are synthesized to prepare for cell division during the M phase.


M: Docetaxel
Paclitaxel
Vinblastine
Vincristine
Vinorelbine
M
G1: Asparaginase
Steroids
G2
Cell Cycle
Model
G1
G2: Bleomycin
Etoposide
S
S: Folic Acid Analogs
Methotrexate
Cytarabine, Gemcitabine
Capecitabine, Fluorouracil
Mercaptopurine, Fludarabine,
Cladribine
Irinotecan
Topotecan
Non-Cell Cycle–Specific Agents:
Busulfan
Cyclophosphamide
Ifosfamide
Cisplatin
Carboplatin, Oxaliplatin
Dactinomycin, Daunorubicin,
Doxorubicin, Idarubicin, Mitomycin,
Mitoxantrone, Epirubicin

Metastasis

- The ability of cancer cells to disseminate and form metastases represents their most malignant characteristic
- Tumor metastases have a greater effect than the primary tumor on the frequency of complications and the patient's quality of life
- associated with most cancer-related deaths

- Normally, cells adhere to one another and the extracellular matrix.
- The cell-to-cell adhesion molecules are called *cadherins*
- *the cell-to-extracellular matrix molecules* are called *integrins*.
- *In cancer cells, these molecules are often* absent, allowing tumor cells to easily move away from the primary tumor mass.

- The blood vessels and the lymphatics are the primary pathways by which cells metastasize
- If the primary site drains its blood supply into the vena cava, the cancer cells will reach the capillary bed in the lung.
- Similarly, if the primary site drains its blood supply into the portal circulation, the cancer cells will reach the capillary bed in the liver

Angiogenesis

- In response to low oxygen supply (hypoxia) and other factors, the cancer cells and surrounding tissues secrete growth factors that stimulate the growth of the new blood vessels from existing blood vessels in the surrounding normal host tissue
- Vascular endothelial growth factor (VEGF)
- Platelet-derived growth factor (PDGF)
- Basic fibroblast growth factor

Tumor origin

- Tumors may arise from any of four basic tissue types:
  - Epithelial tissue
  - Connective tissue (i.e., muscle, bone, and cartilage)
  - Lymphoid tissue
  - Nerve tissue
- Carcinomas are malignant growths arising from epithelial cells
- Malignant growths of muscle or connective tissue are called sarcomas.
- An adenocarcinoma is a malignant tumor arising from glandular tissue.

TABLE 135-3 Tumor Classification by Tissue Type

Tissue of Origin	Benign	Malignant
Epithelial		
Surface epithelium	Papilloma	Carcinoma (squamous, epidermoid)
Glandular tissue	Adenoma	Adenocarcinoma
Connective tissue		
Fibrous tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Fat	Lipoma	Liposarcoma
Lymphoid tissue and hematopoietic cells		
Bone marrow elements		
Lymphoid tissue		Hodgkin and non-Hodgkin lymphoma
Plasma cell		Multiple myeloma
Neural tissue		
Glial tissue	"Benign" gliomas	Glioblastoma multi-forme, astrocytoma
Nerve sheath	Neurofibroma	Neurofibrosarcoma
Melanocytes	Pigmented nevus (mole)	Malignant melanoma
Mixed tumors		
Gonadal tissue	Teratoma	Teratocarcinoma

Prevention of Cancer

- TOBACCO
  - lung, head and neck, gastrointestinal, bladder, and cervical cancers
- Chemoprevention
  - breast, colorectal, and prostate cancers
- Human papilloma virus (hpv) vaccines
- Diet
- Sun exposure

Screening and Early Detection of Cancer

- Four basic requirements for screening tests:
  - There must be good evidence that the test is effective in reducing morbidity or mortality (e.g., effective treatment must be available for the screened disease)
  - The benefits of the test should outweigh its risks
  - The costs of the test should be in balance with its presumed benefits
  - The test should be practical and feasible within the existing health care setting.

Diagnosis and Staging of Cancer

- Histologic diagnosis
- the TNM system for staging classification
  - The size of the primary tumor (T)
  - The extent of regional lymph node spread (N)
  - The presence or absence of metastatic spread to distant organs (M)

Clinical presentation

- Depend on the location (including metastases), and the size of the tumor.
- Pain
- Anorexia
- Weight loss
- Fatigue

TABLE 135-5 Cancer's Seven Warning Signs

Change in bowel or bladder habits
A sore that does not heal
Unusual bleeding or discharge
Thickening or lump in breast or elsewhere
Indigestion or difficulty in swallowing
Obvious change in wart or mole
Nagging cough or hoarseness
If YOU have a warning signal, see your doctor!

Complications of Malignancy

- Obstruction of the superior vena cava
- Spinal cord compression
- Brain metastases
- Organ dysfunction and metabolic disturbances

Treatment

- The choice of specific therapy; and the subsequent goal of that therapy, depends on:
  - The histology and stage of the cancer
  - Patient's predicted tolerance of the side effects of the various treatment options
- Curative intent therapy
- Palliative therapy
- Three modality:
  - Surgery
  - Radiation
  - Systemic therapy

Surgery

- To manage both localized and advanced tumors
- Cytoreductive surgery
- Palliative surgery

Radiation

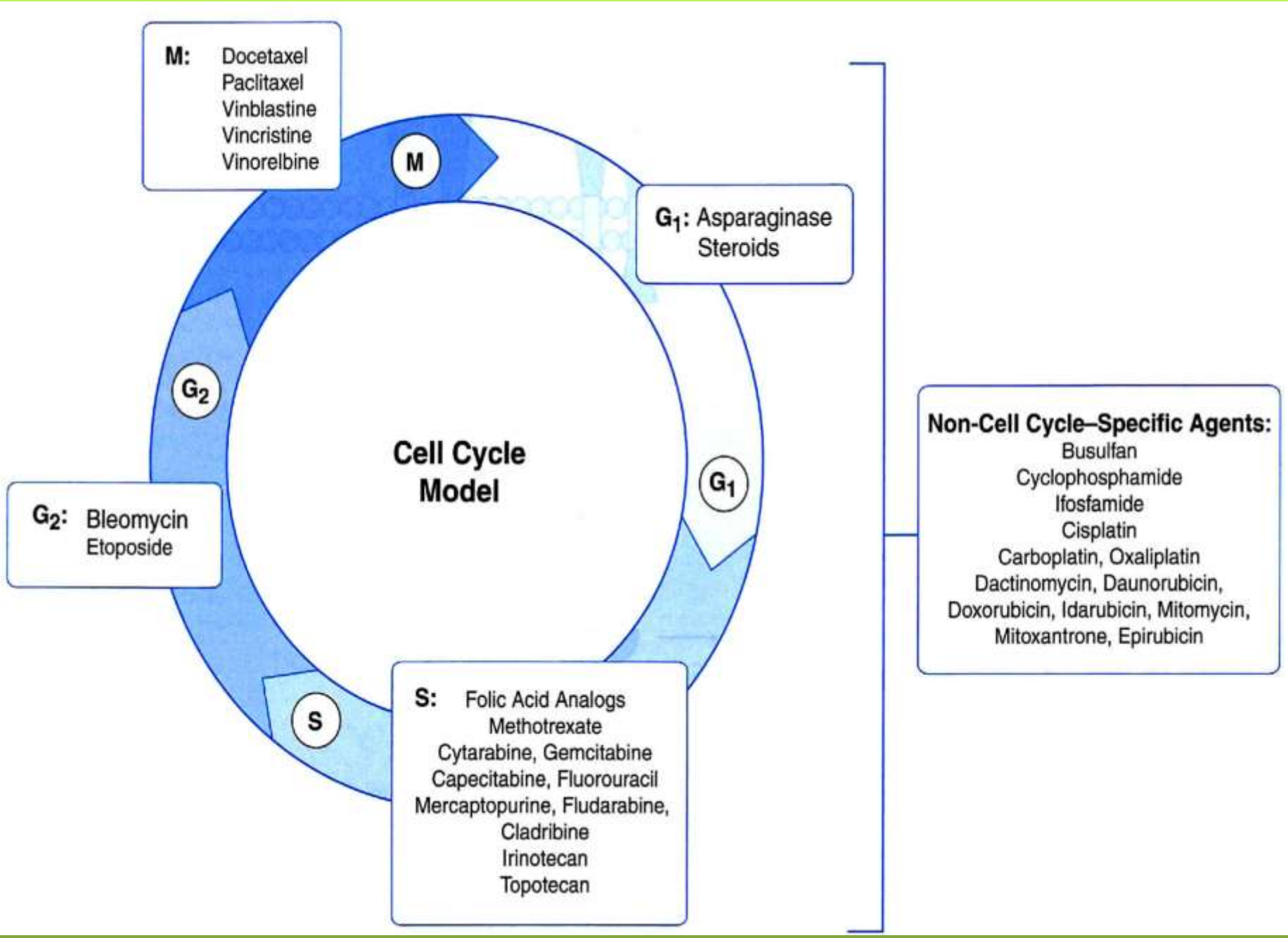
- Curative therapy
- Adjuvant therapy
- Palliative therapy

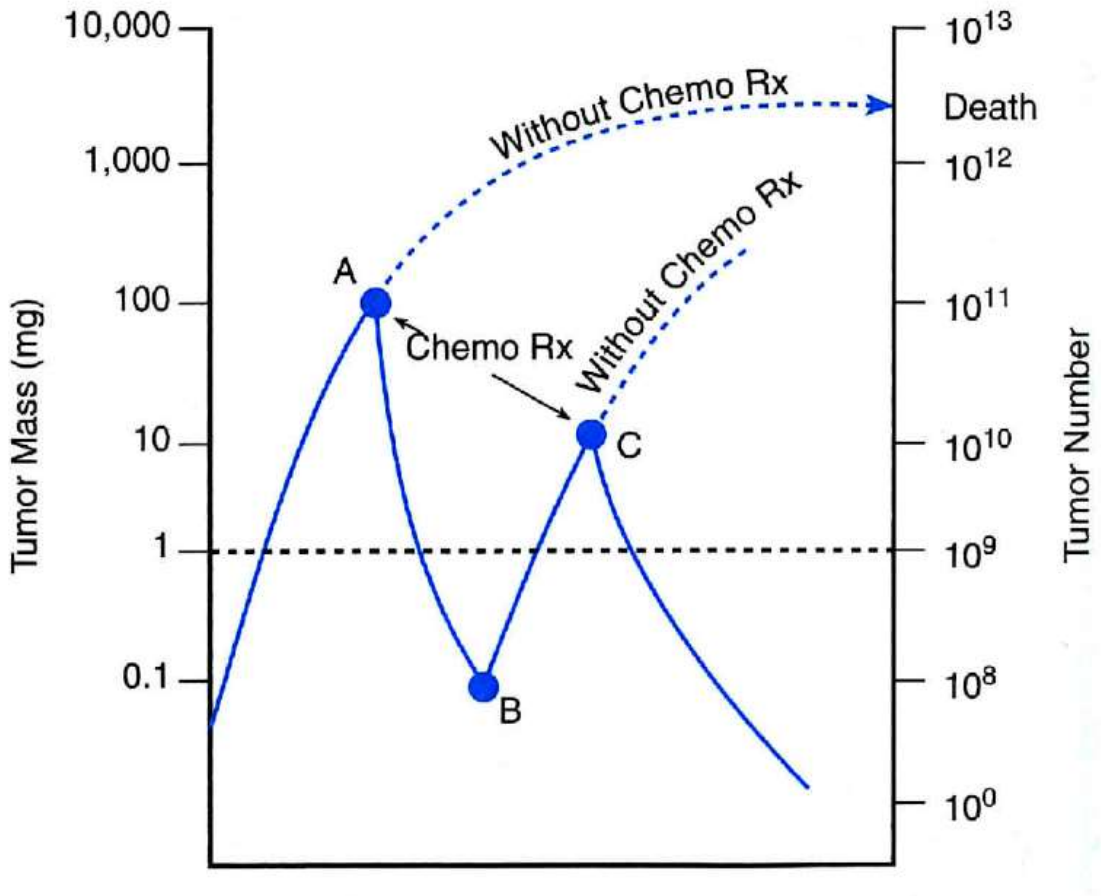
Systemic Therapy

- Chemotherapy
- Targeted therapy
- Endocrine therapy
- Biologic response modifiers

Chemotherapy

- kills cancer cells by damaging DNA, interfering with DNA synthesis, or inhibiting cell division
- phase-specific agents or schedule-dependent agents
- phase-nonspecific agents or dose-dependent agents


M: Docetaxel
Paclitaxel
Vinblastine
Vincristine
Vinorelbine
M
G1: Asparaginase
Steroids
G2
Cell Cycle
Model
G1
G2: Bleomycin
Etoposide
S
S: Folic Acid Analogs
Methotrexate
Cytarabine, Gemcitabine
Capecitabine, Fluorouracil
Mercaptopurine, Fludarabine,
Cladribine
Irinotecan
Topotecan
Non-Cell Cycle–Specific Agents:
Busulfan
Cyclophosphamide
Ifosfamide
Cisplatin
Carboplatin, Oxaliplatin
Dactinomycin, Daunorubicin,
Doxorubicin, Idarubicin, Mitomycin,
Mitoxantrone, Epirubicin


10,000
1,000
100
10
1
0.1
Tumor Mass (mg)
10^{13}
Death
10^{12}
10^{11}
10^{10}
10^{9}
10^{8}
10^{0}
Tumor Number
Without Chemo Rx
Without Chemo Rx
A
Chemo Rx
B
C

Factors that influence response to chemotherapy

- *Dose Intensity*
- *Schedule Dependency*
- *Drug Resistance*
- *Tumor Site*
- *Pharmacogenetics*

Dose Intensity

- The chemotherapy dose per unit time during which treatment is given (e.g., mg/m2/week)

Schedule Dependency

- Chemotherapy is administered in cycles
- can last one or more days
- How often the cycles are repeated depends on the type of cancer being treated and the drugs being used
- The optimal schedule is also influenced by the pharmacokinetics of the agent.

Drug Resistance

- can occur de novo in cancer cells or develop during cell division as a result of mutation
- *multidrug resistance*
  - increase in efflux transporters
  - changes or mutations of drug targets

Tumor Site

- The cytotoxic effects of chemotherapy agents are related to: Concentration X Time
  - The drug dose
  - Infusion rate
  - Route of administration
  - Lipophilicity
  - Protein binding
  - Tumor size and location

Pharmacogenetics

- presence of genetic polymorphisms
  - Dihydropyrimidine dehydrogenase (5_FU)
  - Genetic polymorphisms of UGT1A1(irinotecan)

Combination chemotherapy

- Provides broader coverage against resistant cell lines within the heterogeneous tumor mass
  - Demonstrable single-agent activity against the specific type of tumor
  - Different mechanisms of action
  - Should not have overlapping toxicities
  - All agents should be used in their optimal dose and schedule

Type of chemotherapy

- Primary chemotherapy
  - Curative
  - Palliative
  - Induction therapy
  - Consolidation, intensification, or maintenance chemotherapy
  - Second-line or salvage chemotherapy
- Adjuvant Chemotherapy
- Neoadjuvant Chemotherapy

TABLE 89-11

Adjuvant Chemotherapy: Neoplasms for Which Therapy is Indicated After Surgery

Anaplastic astrocytoma
Breast cancer
Colorectal cancer
Gastric cancer
Melanoma
Non–small-cell lung cancer
Osteogenic sarcoma
Ovarian cancer
Osteogenic cancer
Rectal cancer
Soft tissue sarcoma

TABLE 89-10

Primary Chemotherapy: Neoplasms for Which Chemotherapy is a Primary Treatment Modality

Acute leukemias
Non-Hodgkin lymphoma
Myeloma
Hodgkin lymphoma
Germ cell cancer
Primary central nervous system lymphoma
Ovarian cancer
Small-cell lung cancer
Wilms tumor
Embryonal rhabdomyosarcoma

TABLE 89-12

Neoadjuvant Chemotherapy: Neoplasms for Which Chemotherapy is Indicated for Locally Advanced Disease

Anal cancer
Bladder cancer
Breast cancer
Cervical cancer
Gastroesophageal cancer
Lung cancer
Head and neck cancer
Ovarian cancer
Osteogenic sarcoma
Pancreatic cancer

Clinical pharmacology of chemotherapy

- Alkylating agents exert their effects on DNA and protein synthesis by binding to DNA and preventing the unwinding of the DNA molecule

- Antimetabolites resemble naturally occurring nuclear structural components ("metabolites"), such as the nucleotide bases, or inhibit enzymes involved in the synthesis of DNA and proteins.

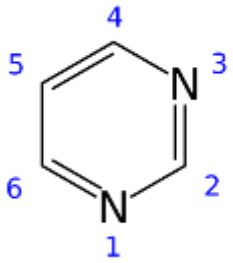
- Antitumor antibiotics derive their name from their source; they are fermentation products of Streptomyces species

Antimetabolites

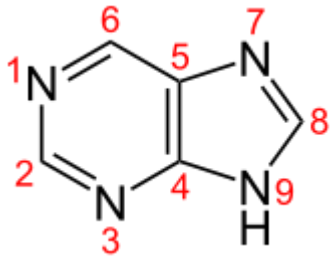
- Similar to the nucleotides that make up DNA and RNA.
- The body metabolizes these drugs as the natural nucleotides.
- Disrupt replication and cell division by interfering with the production of nucleic acids, DNA, and RNA.
- The three major classes:
  - Pyrimidines antagonists
  - Purines antagonists
  - Folate antagonists

Antimetabolites

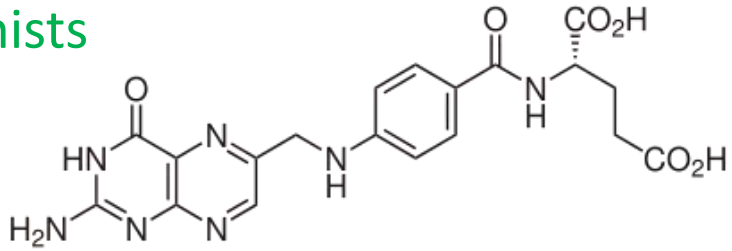
- Pyrimidines antagonists



- Purines antagonists

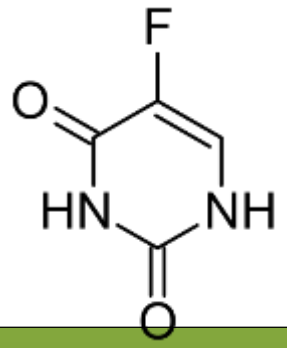


- Folate antagonists

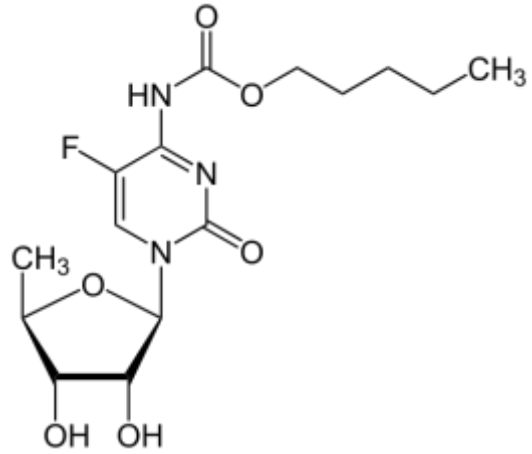


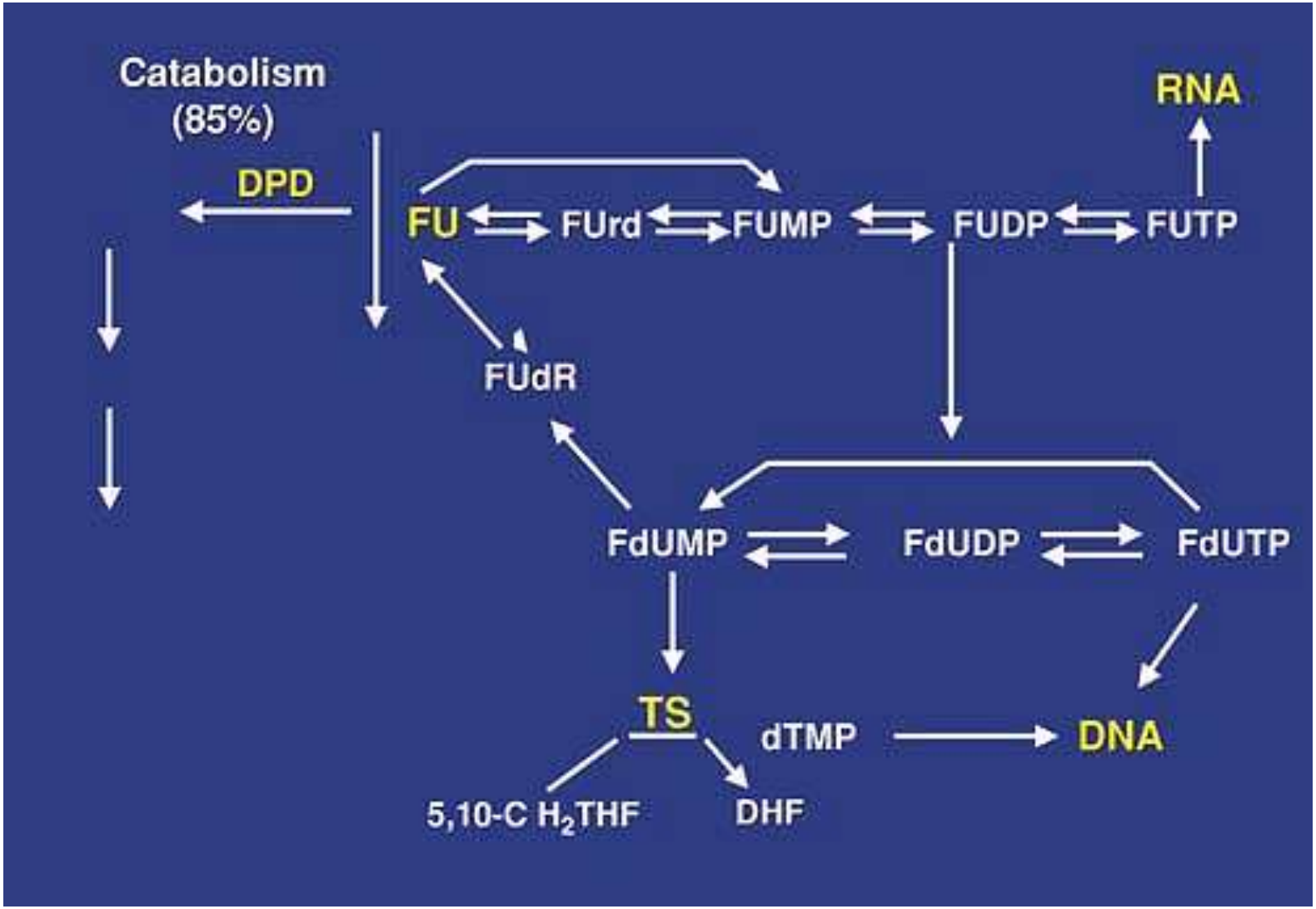
Fluorinated Pyrimidines

- 5-Fluorouracil
  - Interferes with the function of thymidylate synthase.
  - Incorporated into RNA as a false base, and interferes with its function
  - Combination with leucoverin
  - Myelosuppression when administered as an IV bolus administration
  - Hand-foot syndrome and diarrhea when administered as a continuous IV infusion



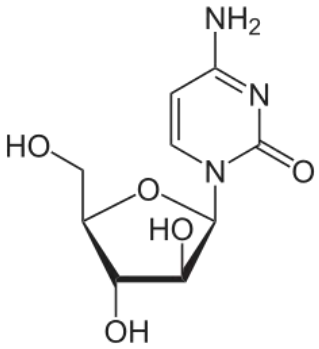
- Capecitabine
  - Orally active pyrimidine analog
  - A prodrug of 5-FU

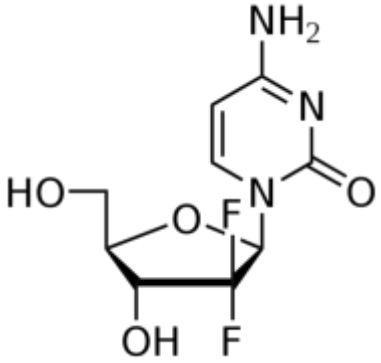



Catabolism
(85%)
DPD
RNA
FU
FUrd
FUMP
FUDP
FUTP
FUdR
FdUMP
FdUDP
FdUTP
TS
dTMP
DNA
5,10-C H2THF
DHF

Cytidine Analogs

- Cytarabine
  - Inhibits DNA polymerase





- Gemcitabine
  - Inhibits DNA polymerase
  - Also inhibits ribonucleotide reductase, which is the enzyme required to convert ribonucleotides into the deoxyribonucleotide forms needed for both DNA synthesis and repair
  - Intracellular concentrations about 20 times higher than does ara-C

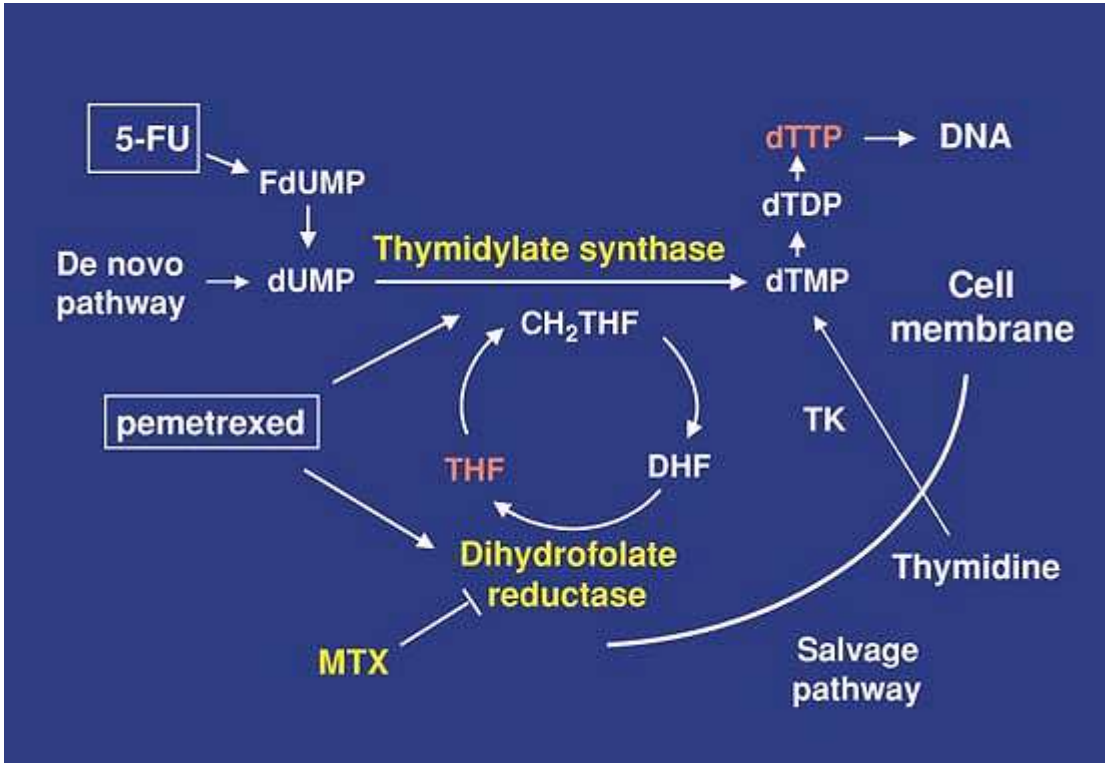
Purines and Purine Antimetabolites

- Mercaptopurine
  - Converted to ribonucleotides that inhibit purine biosynthesis
  - Metabolized by thiopurine methyl transferase(TPMT) and hypoxanthine phosphoribosyl transferase to produce multiple metabolites responsible for the efficacy, hepatic toxicity and myelosuppression

Purines and Purine Antimetabolites

- Fludarabine Monophosphate
  - Interferes with DNA polymerase
  - Incorporates into RNA, resulting in inhibited transcription
  - dose-limiting toxicity is myelosuppression
  - immunosuppressive
    - With associated opportunistic infections resulting from fludarabine's effect on T cells and a subsequent decrease in CD4 counts
    - Prophylactic antibiotics and antiviral medications are recommended and should continue until CD4 counts normalize.

Antifolates



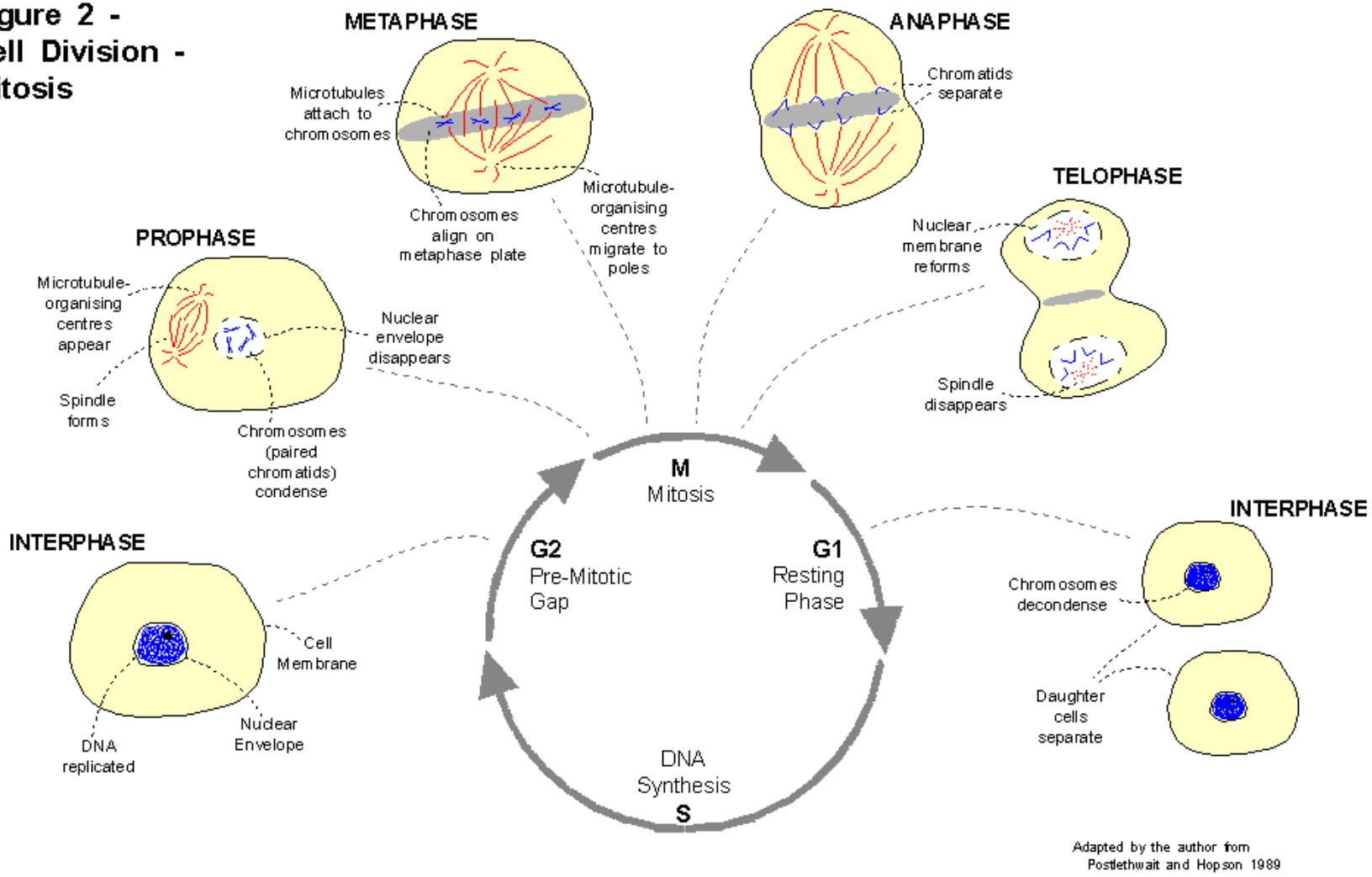
- MTX & Pemetrexed
  - Neutropenia
  - Thrombocytopenia
  - Mucositis
  - Nausea and vomiting

- Renal tubular necrosis with high-dose MTX
- Neutropenic sepsis with Pemetrexed
  - Elevated base-line cystathionine or homocysteine concentrations correlated with this unexpected toxicity.
  - Routine supplementation of folic acid and vitamin B12 lowers levels of these substances and lowers the risk of mortality related to neutropenic sepsis.

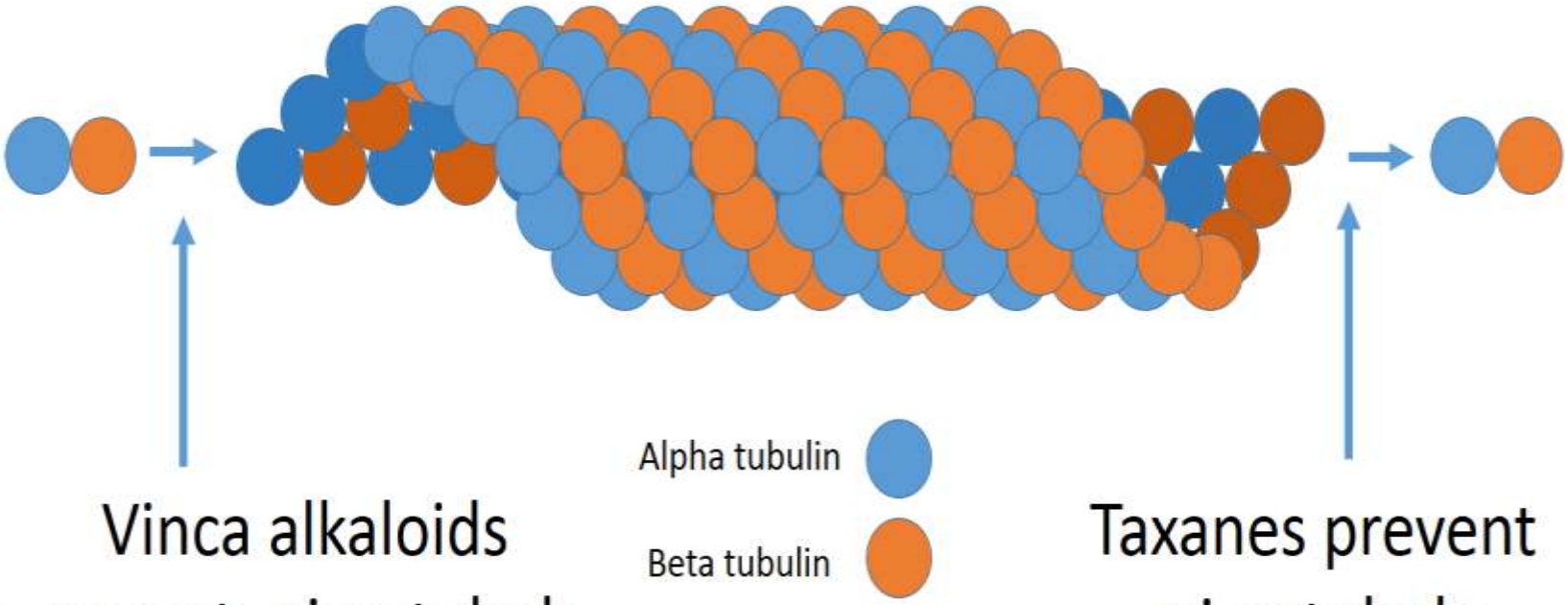
Microtubule-targeting drugs

- Vinca Alkaloids
  - Vincristine, vinblastine, and vinorelbine
    - Mitotic inhibitors
    - Different activities and patterns of toxicity
    - Vinorelbine and vinblastine with dose-limiting myelosuppression
    - Vincristine is more neurotoxic
- Taxanes
  - Paclitaxel and docetaxel
    - Mitotic inhibitors and Inhibition of angiogenesis
    - Myelosuppression is common with both agents
    - Increased fluid retention with docetaxel, increased neurotoxicity and hypersensitivity reactions with paclitaxel.

Figure 2 - Cell Division - Mitosis



Adapted by the author from Postlethwait and Hopson 1989

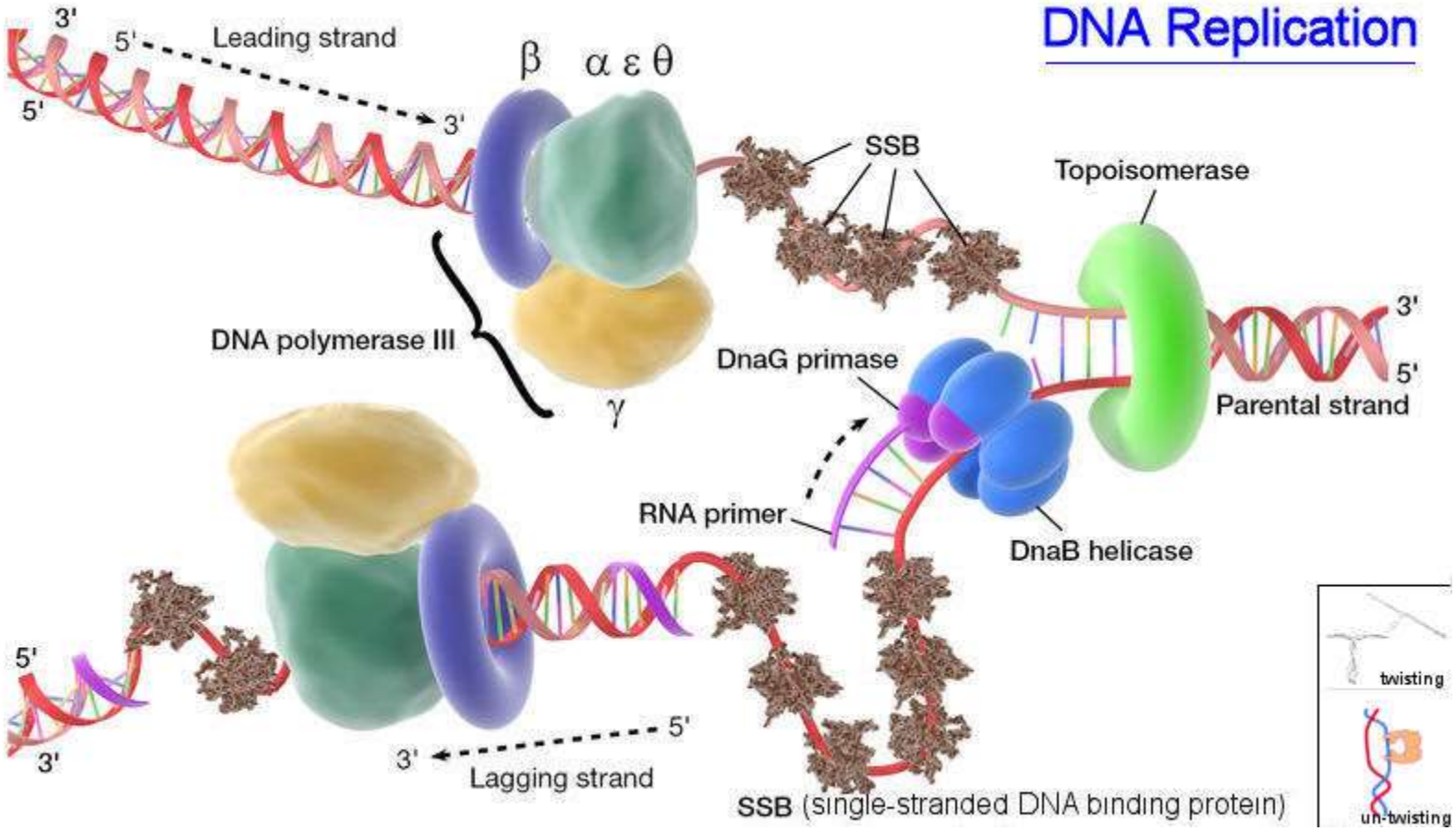


Vinca alkaloids prevent microtubule assembly.

Taxanes prevent microtubule disassembly.

Topoisomerase inhibitors

- Camptothecin Derivatives
  - Topotecan and irinotecan
  - Inhibit topoisomerase I enzyme activity
  - diarrhea and myelosuppression are the most common toxicities with irinotecan
- Etoposide and Teniposide
  - bind to tubulin and interfere with microtubule formation.
  - topoisomerase II inhibitors
  - dose-limiting toxicity is myelosuppression


DNA Replication
3'
5'
Leading strand
5'
3'
β α ε θ
SSB
Topoisomerase
DNA polymerase III
γ
DnaG primase
3'
5'
Parental strand
RNA primer
DnaB helicase
5'
3'
3'
5'
Lagging strand
SSB (single-stranded DNA binding protein)
twisting
un-twisting

Anthracene Derivatives

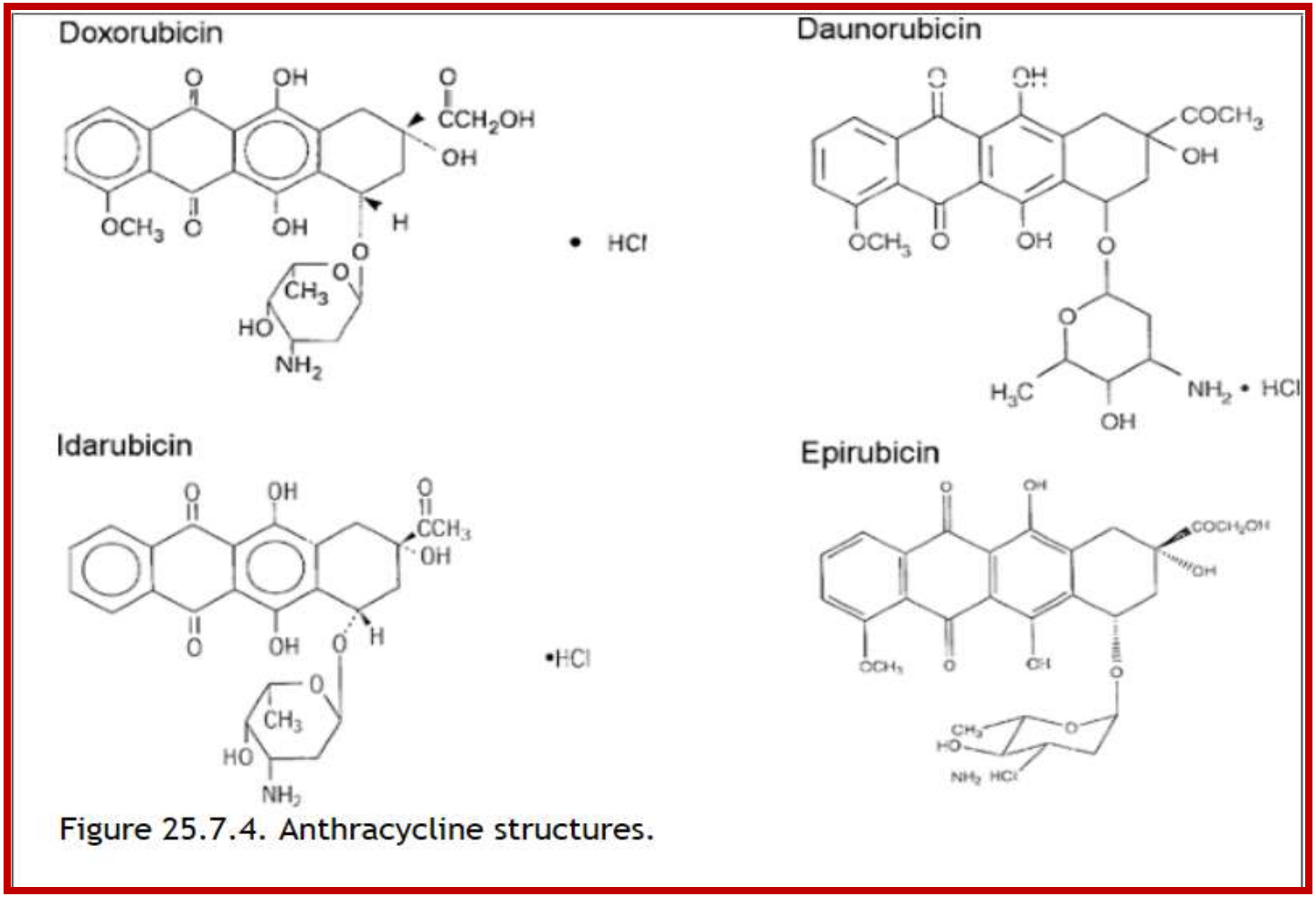


Figure 25.7.4. Anthracycline structures.

- Anthracyclines
- topoisomerase II inhibitors
- also undergo electron reductions to reactive compounds that can damage DNA and cell membranes
- free-radical formation is firmly established as a cause of cardiac damage and extravasation injury
- Mitoxantrone
  - Less cardiac toxicity

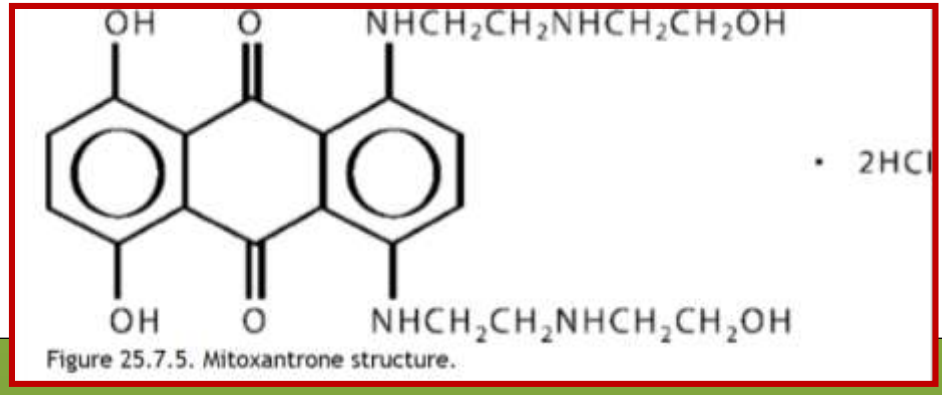
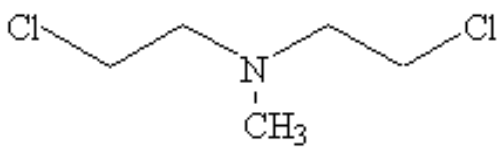


Figure 25.7.5. Mitoxantrone structure.

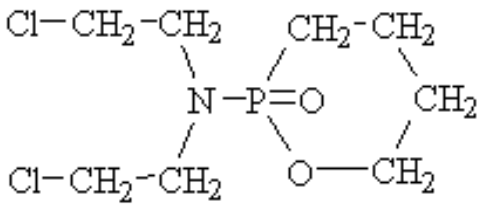
Alkylating agents

- Covalent bonding of highly reactive alkyl groups or substituted alkyl groups with nucleophilic groups of proteins and nucleic acids and inhibition of DNA replication
- not cell-cycle phase-specific.
- Nitrogen Mustards
  - Cyclophosphamide and ifosfamide
  - Bendamustine
- Nitrosoureas
  - Carmustine
  - Lomustine

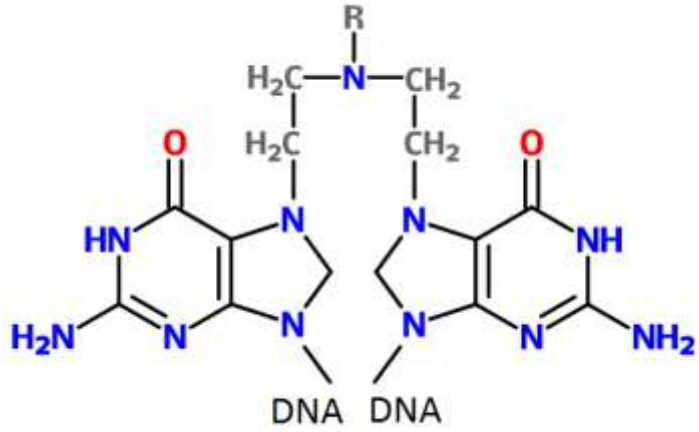
Alkylating Agents

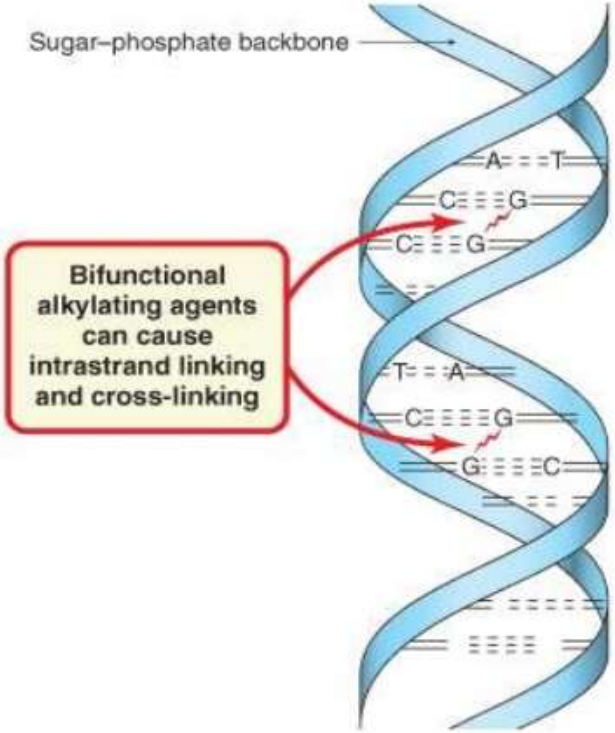


Nitrogen Mustard - Mechlorethamine



Cyclosporamide



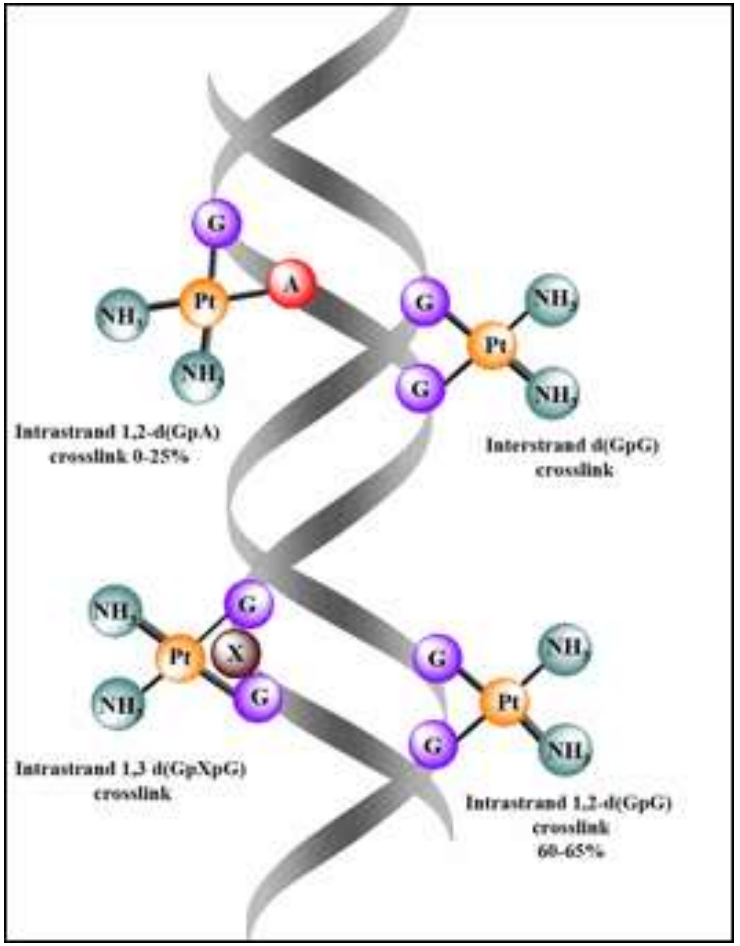


Nonclassic Alkylating Agents

- Dacarbazine and Temozolomide
  - interrupts DNA replication by causing methylation of guanine
- Important pharmacokinetic differences
  - Dacarbazine is poorly absorbed, and must be administered by intravenous infusion
  - Temozolomide is rapidly absorbed after oral administration & crosses the blood-brain barrier

Heavy metal compounds

- Cisplatin, Carboplatin, and Oxaliplatin
- The cytotoxicity of the platinum derivatives depends on platinum binding to DNA and the formation of intrastrand cross-links or adducts between neighboring guanines.
- Carboplatin & Cisplatin
  - A similar spectrum of clinical activity and cross-resistance
  - Different toxicity
  - Nephrotoxicity, ototoxicity, peripheral neuropathy, emesis, and anemia for cisplatin
  - Hematologic toxicity for carboplatin


G
A
Pt
NH3
NH3
Intrastrand 1,2-d(GpA)
crosslink 0-25%
G
Pt
NH3
NH3
G
Interstrand d(GpG)
crosslink
NH3
G
Pt
X
NH3
G
Intrastrand 1,3 d(GpXpG)
crosslink
G
Pt
NH3
NH3
G
Intrastrand 1,2-d(GpG)
crosslink
60-65%

Heavy metal compounds

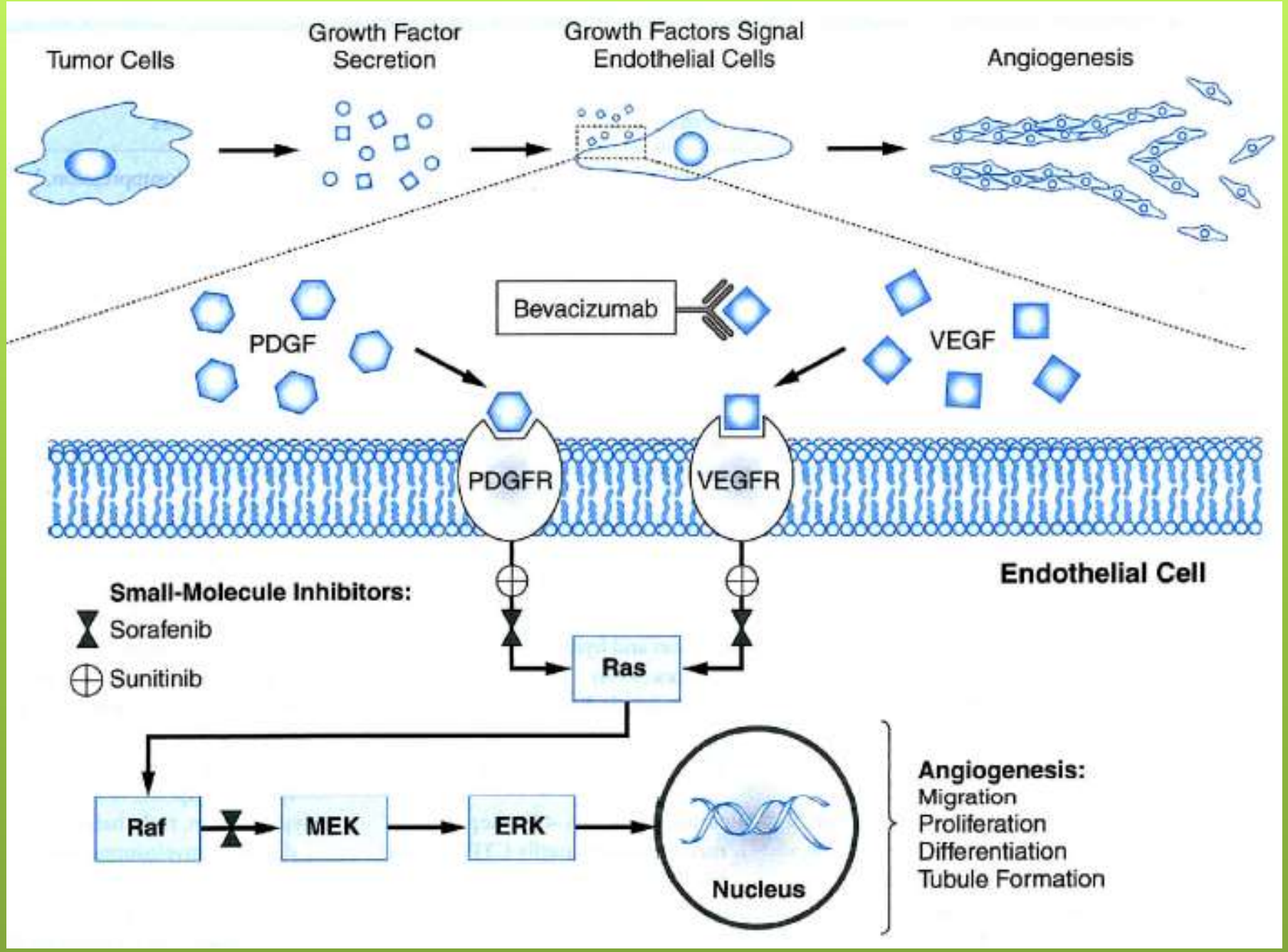
- Oxaliplatin
  - Is not nephrotoxic or ototoxic
  - Is moderately emetogenic
  - Can cause peripheral neuropathies and unique cold-induced neuropathies

Endocrine Therapy

- Can be used to treat several common cancers which arise from hormone-sensitive tissues
  - Breast, prostate, and endometrial cancers
  - Selective estrogen receptor modulators
  - Aromatase inhibitors

Targeted agents

- Monoclonal antibodies
  - The EGFR, HER2/neu, and VEGF signaling pathways can be blocked
  - Inhibit receptor tyrosine kinase activation by binding to the extracellular domain.
- Tyrosine kinase inhibitors
  - Inhibit tyrosine kinase activation by competing with ATP for binding to the intracellular tyrosine kinase domain


Tumor Cells
Growth Factor Secretion
Growth Factors Signal Endothelial Cells
Angiogenesis
PDGF
Bevacizumab
VEGF
PDGFR
VEGFR
Endothelial Cell
Small-Molecule Inhibitors:
Sorafenib
Sunitinib
Ras
Raf
MEK
ERK
Nucleus
Angiogenesis:
Migration
Proliferation
Differentiation
Tubule Formation

Biologic Response Modifiers (Immunotherapy)

- substances that either boost or restore the ability of the immune system to fight cancer, infections, or other diseases
  - Vaccines
  - INTERFERON-α
  - INTERLEUKIN 2
  - checkpoint inhibitors

Administration

- Intravenous route
  - Bolus injection
  - Short infusion
  - Continuous infusion
- Oral route
- Regional and local

TABLE 89-17
Local or Regional Routes of Chemotherapy Administration

Route of Administration	Cancer Managed With Alternative Route
Intrathecal or intraventricular	Leukemia, lymphoma
Intravesicular	Bladder
Intraperitoneal	Ovarian
Intrapleural	Malignant pleural effusions
Intra-arterial	Melanoma, sarcoma
Hepatic artery	Liver metastases
Chemoembolization (intra-arterial or intravenous)	Colon, rectal, carcinoid, liver metastases

Assessing Response to Therapy

- Antitumor and toxic effects
- Effect on the patient's overall quality of life and survival

Response Evaluation Criteria in Solid Tumors RECIST

- Complete Response :
  - Disappearance of all target lesions.
- Partial Response:
  - At least a 30% decrease in the sum of diameters of target lesions
- Progressive Disease:
  - At least a 20% increase in the sum of diameters of target lesions
- Stable Disease:
  - Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease
- Diseasefree Survival:
  - Time from documentation of complete response until disease relapse or death.
- Overall Survival:
  - Time from treatment until time of death.

- National Cancer Institute Common Toxicity Criteria for Adverse Events
- Quality of life
  - Reduced pain
  - Decreased use of analgesics
  - Weight gain
  - Improved performance status

Tumor markers

- Substances that may be found in tumor tissue or released from a tumor into the blood or other body fluids
- Should be produced and released at levels proportional to the tumor mass.
- Should be detectable at very low levels

TABLE 89-19
Clinically Useful Tumor Markers

Tumor Marker	Cancers Commonly Associated With Increased Markers
CA-19-9	Pancreatic
CA-15-3	Breast
CA-27-29	Breast
Neuron-specific enolase	Neuroblastoma, small-cell lung cancer
α-Fetoprotein (AFP)	Liver
CA-125	Ovarian, testicular—nonseminoma
Carcinoembryonic antigen (CEA)	Colon, lung
Human chorionic gonadotropin (hCG)	Trophoblastic, testicular
β_2-Microglobulin	Multiple myeloma
Prostate-specific antigen (PSA)	Prostate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- Medication Errors
  - The use of abbreviations
  - Verbal orders
  - Multiple-day regimens
  - Incorrect references and protocols
  - Illegible medication orders