Integration of chemotherapy and radiation therapy

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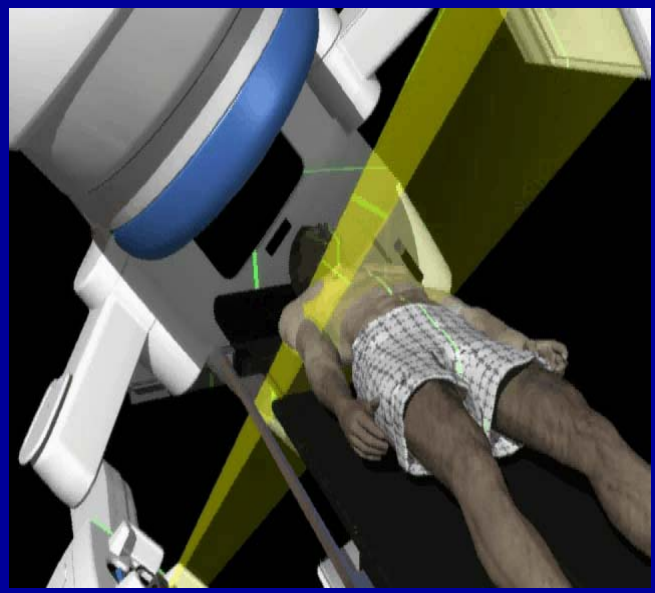
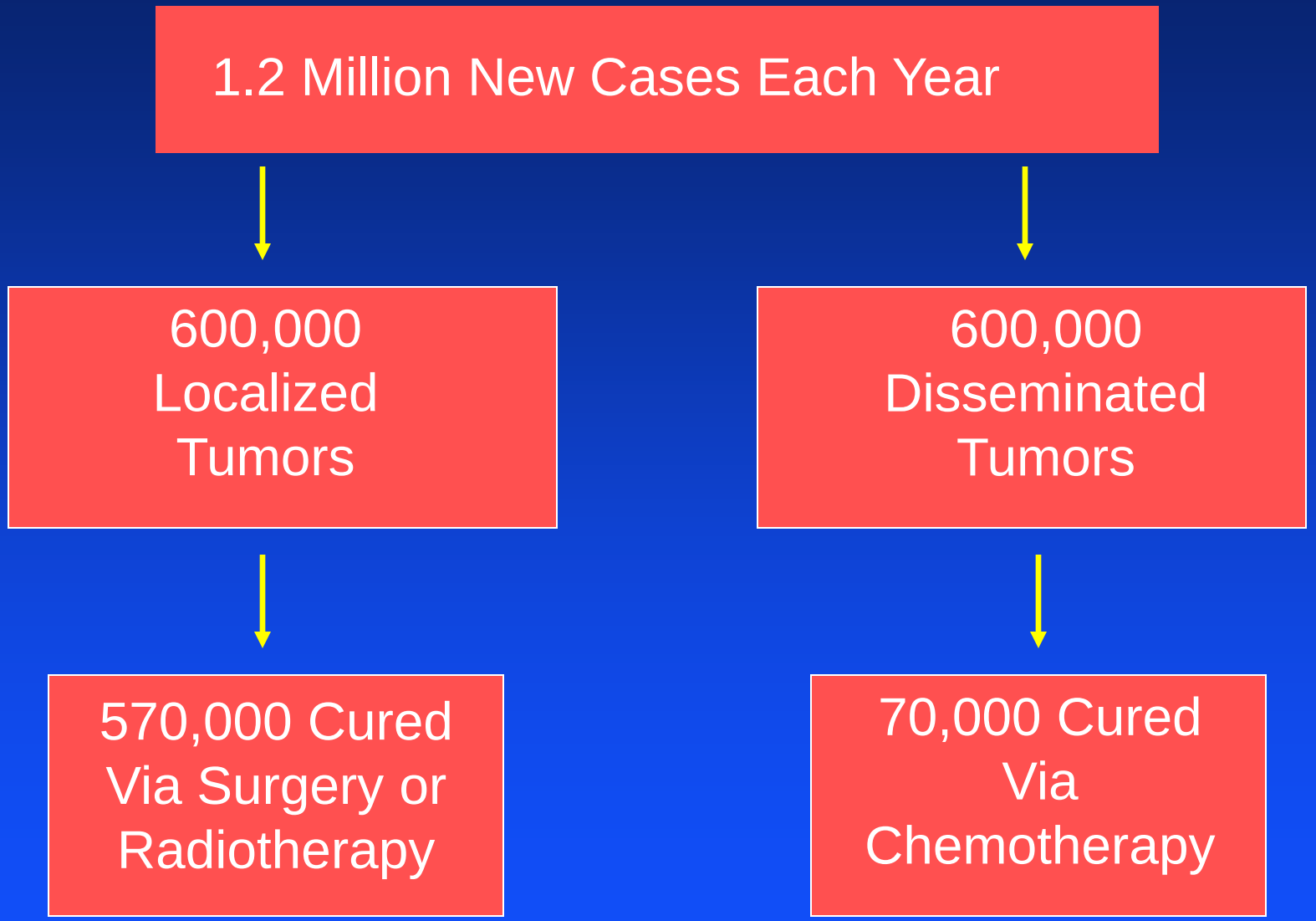


No Disclosures

U.S. Cancer Statistics - 1998



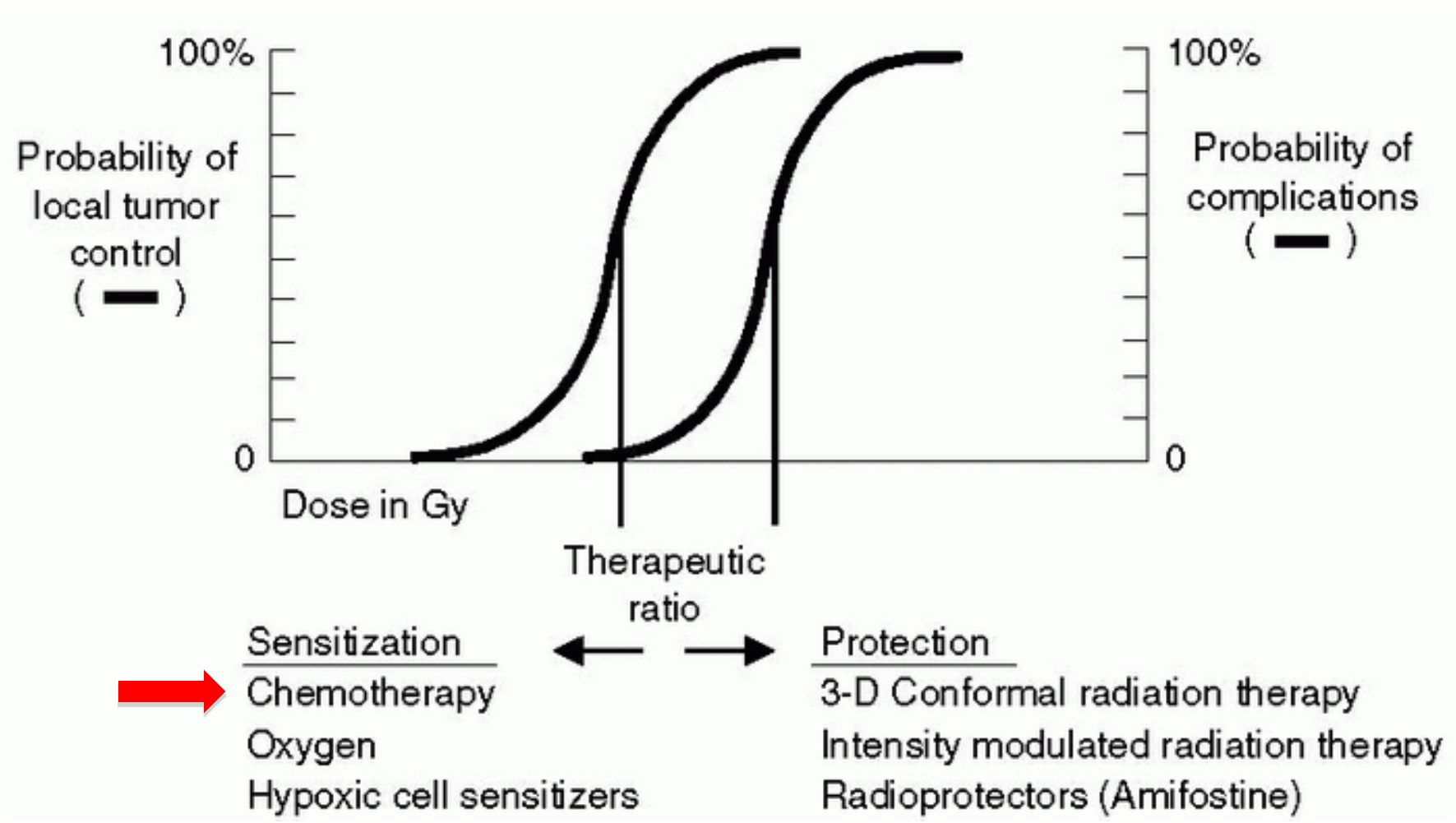
Outline

- Current Status
- Rationale for combination of chemotherapy with Radiation
- Mechanism of action and resistance
- Disease sites and toxicity of combination therapies
- New targets

The past decade

- Radiotherapy has Improved & will Improve Further
- Most Recent Advances Relate to Imaging & Planning
- Future Advances will be in New Delivery Approaches
- RT Dose and Fractionation Paradigms will Shift
- RT Target Volume “Rules” will Also Shift
- RT/Drug Interactions Could Dictate Dose & Fractionation

Therapeutic Ratio Curves



Reasons to use Chemoradiation

- Sterilize **micrometastases** outside of the XRT portal
- Tumor cell sensitization
- Improved nutrition and reoxygenation to hypoxic tumor cell (decrease tumor burden)
  - Better blood supply to remaining tumor cells
- Cells cycle into a more radiation sensitive phase
- Inhibit cell division between radiation doses
- Inhibit cellular repair of damage between therapies

Rationale for combined chemotherapy and radiotherapy

- Spatial cooperation
- Toxicity independence
- Action as a radiosensitizer (possible synergism)
- Eliminate need for surgical procedure.
  - Not all patients able to undergo anesthesia.
- Addresses systemic and locoregional disease.
  - Neoadjuvant chemotherapy delays local control component of surgery.

Spatial Cooperation

- Cytotoxic agents active against tumor cells located in areas not radiated.
- Radiation delivered to areas of sanctuary from chemotherapy
  - Idea used in treatments for Ewing's sarcoma, Wilm's tumor, rhabdomyosarcoma, ALL, breast cancer and small cell lung cancer
  - First use in practice is childhood ALL with cranial radiation
  - May cause need to decrease doses for tolerance of therapy

Rationale for combined chemotherapy and radiotherapy

- Improved functional/cosmetic outcome.
- Surgical salvage remains an option.
- Landmark studies
  (chemo-radiotherapy $\rightarrow$ surgery)
  suggest long term survivors have
  no tumor in resection specimen.

Timing of Chemotherapy Administration

- **Neoadjuvant**
  - May be give 2 months prior to XRT for micrometastasis sterilization
  - Used to reduce the number of clonogens in XRT portal
    - ability to decrease portal size
  - Could leave resistant cells or allow for proliferation during a break in XRT needed for toxicity
- **Concurrent**
  - Alternating
    - Chemotherapy alternates weekly with XRT
      - Lymphomas and small cell CA has some data
  - Simultaneously
    - Chemotherapy and XRT given at the same time
      - Most commonly used mode
- **Adjuvant**
  - Given after XRT finished

Clinical Results of Radiation Therapy and Chemotherapy

- **Combined radiation therapy and chemotherapy may improve local control or survival**
  - Rectal cancer (local control, survival)
  - Limited -stage small cell lung cancer (survival)
  - Hodgkin's disease (local control)
  - Limited-stage non- Hodgkin's lymphoma (local control, survival)
  - Rhabdomyosarcoma (local control, survival)
  - Anaplastic astrocytoma (local control, survival)
  - Esophageal cancer, Melanoma
  - Cervix cancer, Gastric cancer
- **Combined radiation therapy and chemotherapy avoids debilitating surgery without compromising survival**
  - Anal cancer
  - Bladder cancer
  - Head and neck cancer
  - Extremity sarcoma
  - Breast cancer

Combination of radiation and systemic agent (level I evidence)

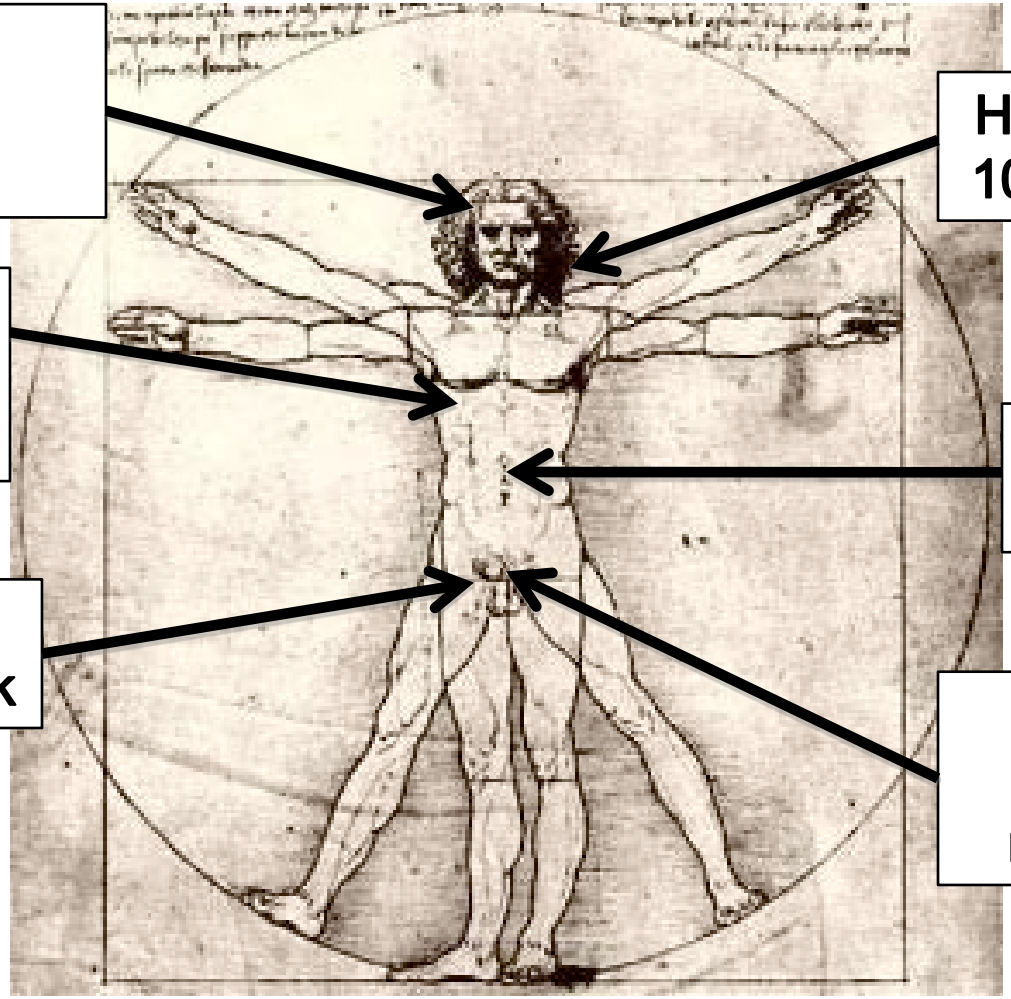
Primary	Systemic agent	Abs. improvement in Overall Survival
Glioblastoma (Brain)	Temozolomide	14% at 2 yr
Head and neck	Cisplatin, cetuximab	20% at 2 yr
Lung	Cisplatin	7% at 2 yr
Esophagus	5FU + cisplatin	26% at 5 yr
Stomach	5FU + leucovorin	?
Rectum	5FU	15% at 5 yr
Anus	5FU + mitomycin	Improve local control
Cervix	Cisplatin	14% at 5 yr

Dose limiting toxicity of Gemcitabine + RT

Site	Non-hematological toxicity	ref
Pancreas	Vomit and nausea, anorexia, fatigue, abdominal pain	Wolf CCR 2001
Head and neck	Mucositis, pharyngitis, skin	Eisenbruch JCO 2001
Cervix	Diahorrhea, cystitis, nausea and vomit	Umazon GynOnc 2006
Lung	Esophagitis, pneumonitis, skin	Trodella JCO 2002
Brain	neurotoxicity	Huan ChMJ 2007

When Gemcitabine is combined with RT, toxicity is *site dependant*

Maximal tolerated dose of Gemcitabine when combined with full dose RT



Brain
100-600
mg/m^2/week

Head and neck
10 mg/m^2/week

NSCLC
200
mg/m^2/week

Pancreas
50 mg/m^2/week

Bladder
100 mg/m^2/week

Cervix
100
mg/m^2/week

ONCOLOGY
Principles of chemotherapy

Electron micrograph of mitotic cell

Biological Basis of Chemotherapy

- Most anticancer drugs work by affecting DNA synthesis or function
- Effectiveness depends on the **growth fraction** of the tumor
  - i.e. fraction of cells actively cycling
- **Cell cycle specific agents** are active during a particular phase of the cell cycle
  - i.e. S-phase specific drugs
- **Cell cycle non-specific agents**

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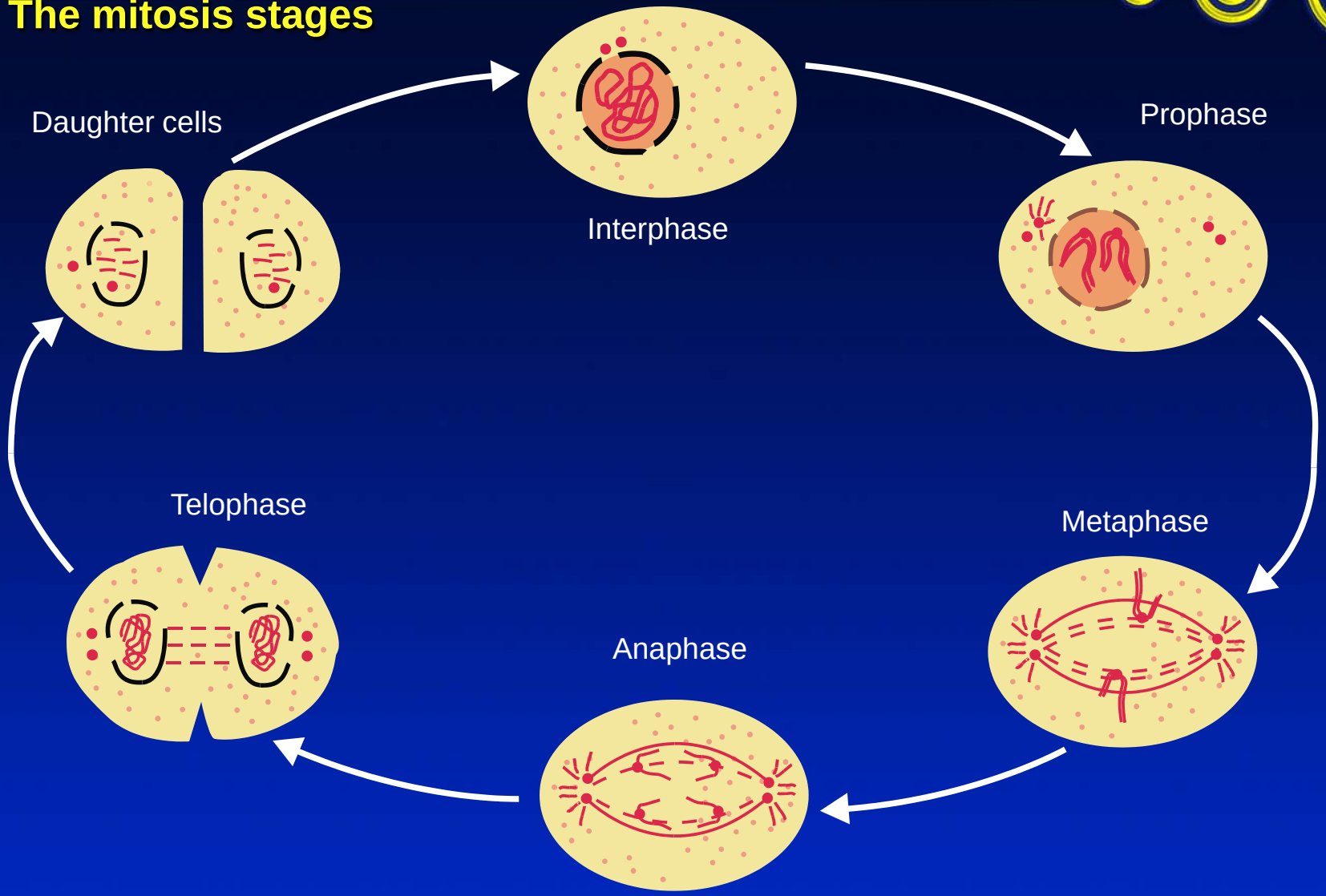
Principles of chemotherapy

The mitosis stages



ONCOLOGY
Principles of chemotherapy

Classification of cytotoxic agents

Alkylating Agents	Anti-Metabolites	Mitotic Inhibitors	Antibiotics	Others
Busulfan	Cytosine	Etoposide	Bleomycin	L-asparaginase
Carmustine	Arabinoside	Teniposide	Dactinomycin	Hydroxyurea
Chlorambucil	Floxuridine	Vinblastine	Daunorubicin	Procarbazine
Cisplatin	Fluorouracil	Vincristine	Doxorubicin	
Cyclophosphamide	Mercaptopurine	Vindesine	Mitomycin-c	
Ifosfamide	Methotrexate	Taxoids	Mitoxantrone	
Melphalan	Gemcitabine		Plicamycin	

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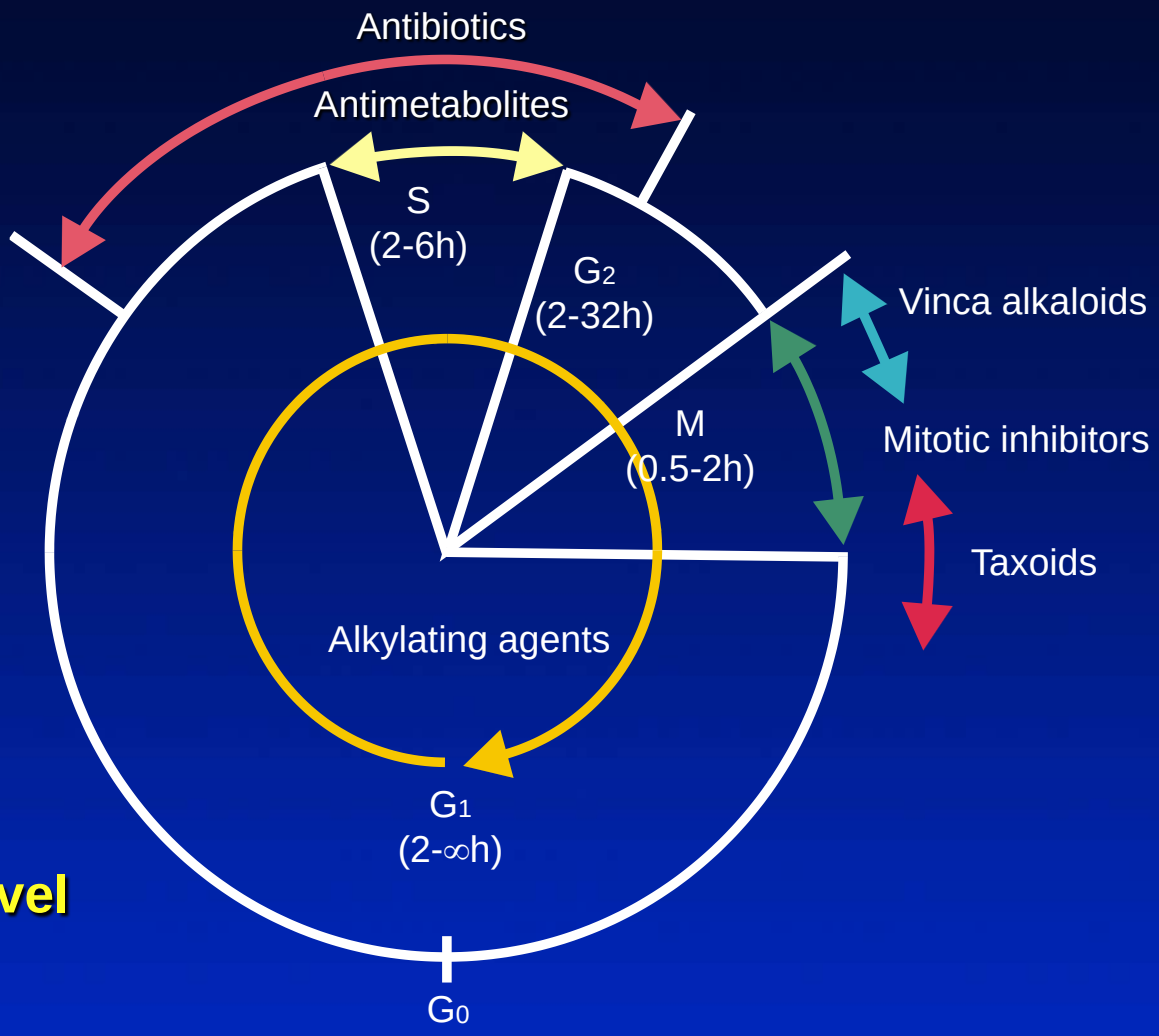
Principles of chemotherapy

Action sites of cytotoxic agents



Cell cycle level

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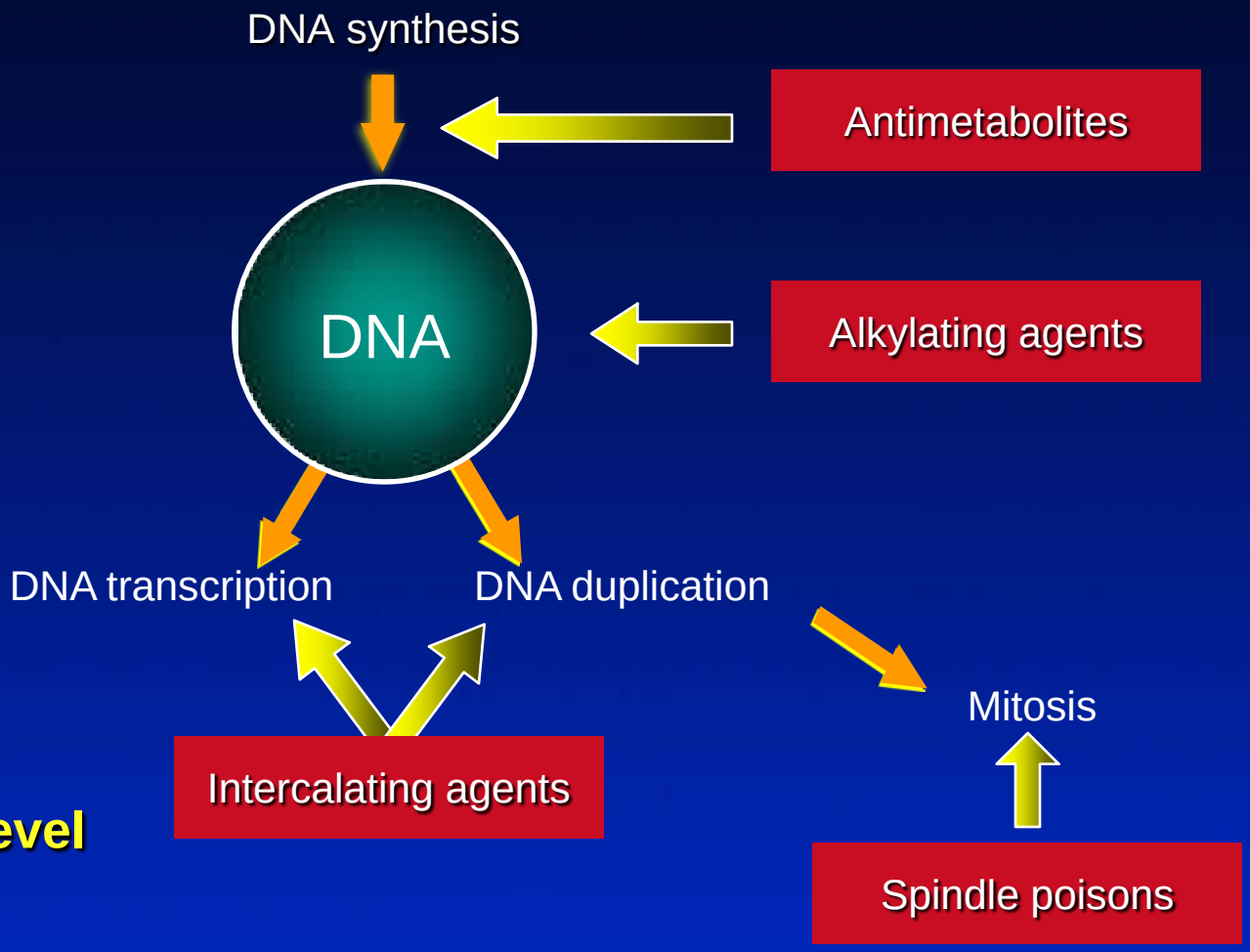
Action sites of cytotoxic agents



Cellular level

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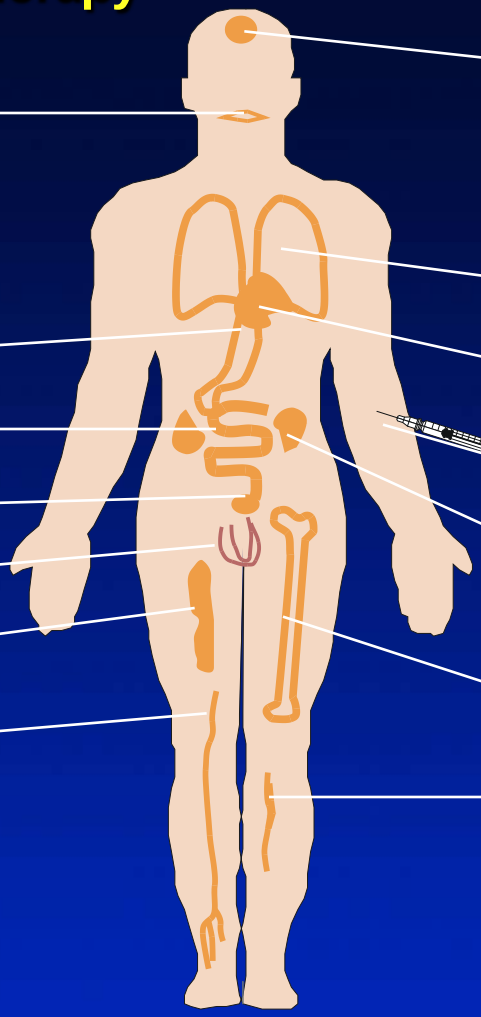
Side effects of chemotherapy



Mucositis

Alopecia

Pulmonary fibrosis

Nausea/vomiting

Cardiotoxicity

Diarrhea

Local reaction

Cystitis

Renal failure

Sterility

Myelosuppression

Myalgia

Phlebitis

Neuropathy

Anti-Metabolites

- Most **inhibit nucleic acid synthesis** either directly or indirectly - tend to be **active mainly against proliferating cells**
- Most are **cell-cycle specific**
- **Toxicity**-reflects effect on proliferating cells; primarily seen in bone marrow cells GI mucosa

Anti-Metabolites (cont.)

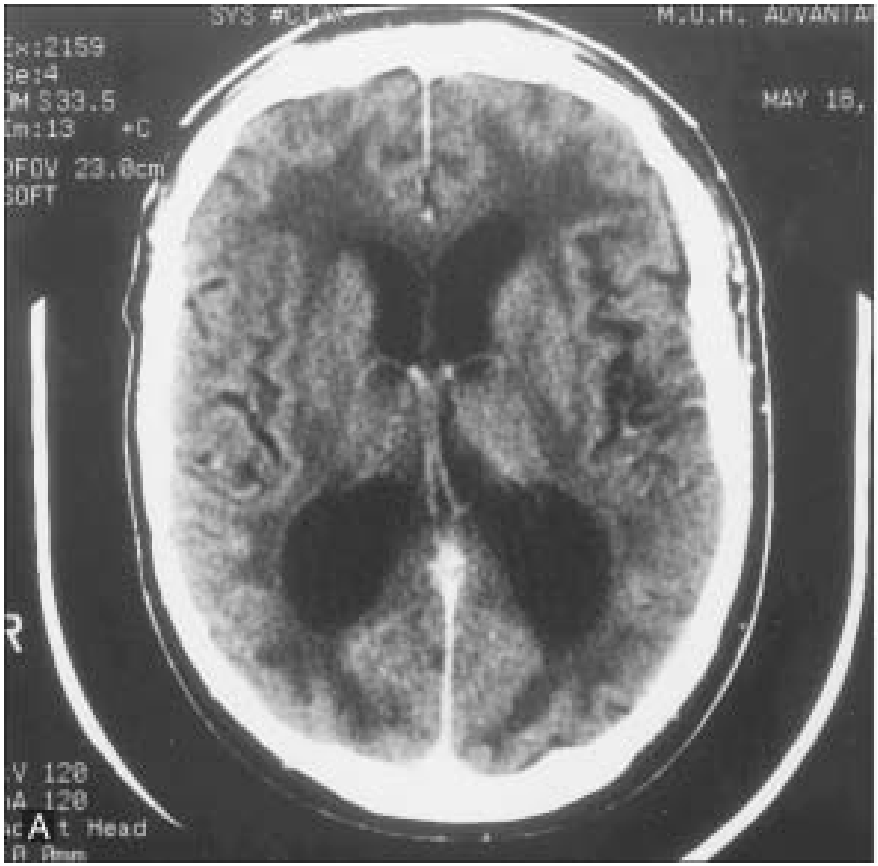
- **Methotrexate**
  - Analog of vitamin, **folic acid**
  - Prevents the formation of reduced folate which is required for DNA synthesis; is a competitive inhibitor of **DHFR** (dihydrofolate reductase)
- **5-fluorouracil**
  - Closely resembles uracil and thymine bases
  - Interferes with both RNA and DNA metabolism, in particular **inhibits the enzyme thymidylate synthetase**
- **Cytidine Analogs**
  - **Cytosine arabinoside (ara-C)**
    - Competitive inhibitor of DNA polymerase, enzyme necessary for DNA synthesis; **causes death of S phase cells**

Anti-metabolites

- Enhances through altering cell kinetics of surviving cells
  - Mitotic cells have 3X response to XRT compared with late S-phase cells
    - **Methotrexate** kills s-phase cells leaving XRT resistant cells behind. Prior XRT leaves S-phase cells behind and allows for enhanced killing with MTX
      - Whole Brain XRT and High dose oral/IT MTX enhances late CNS damage. Especially if XRT precedes the MTX.

Leukoencephalopathy

Widespread destruction of white matter and diffuse atrophy



The patient was a 63-year-old man with meningeal lymphoma who underwent whole-brain radiation therapy. Several months later, his meningeal lymphoma recurred and was treated with intrathecal methotrexate. Progressive dementia developed.

Abeloff: Abeloff's Clinical Oncology, 4th ed.

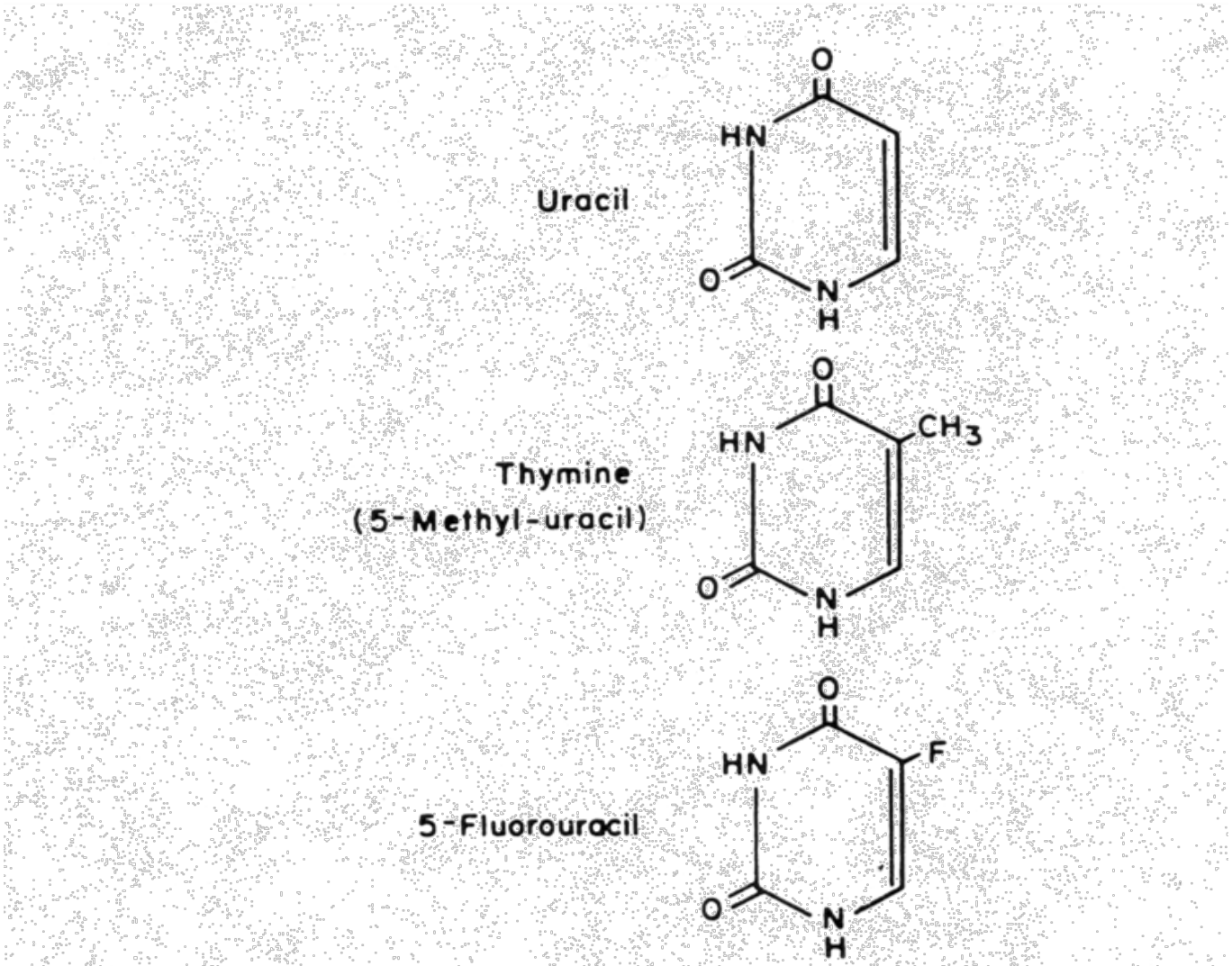


Figure 16.9. Structures of uracil, thymine, and the analogue 5-fluorouracil.

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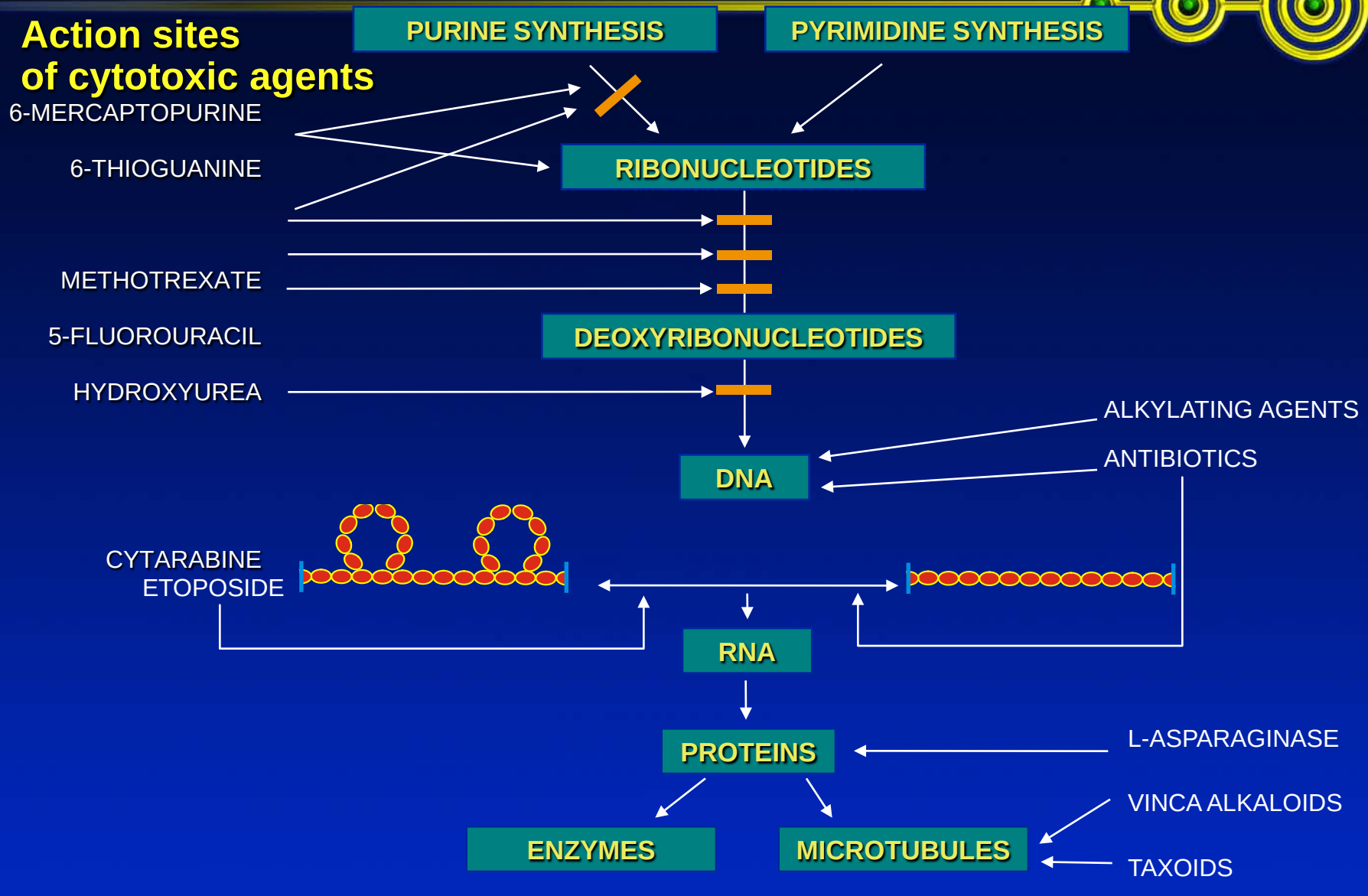
Principles of chemotherapy



XELODA- capecitabine

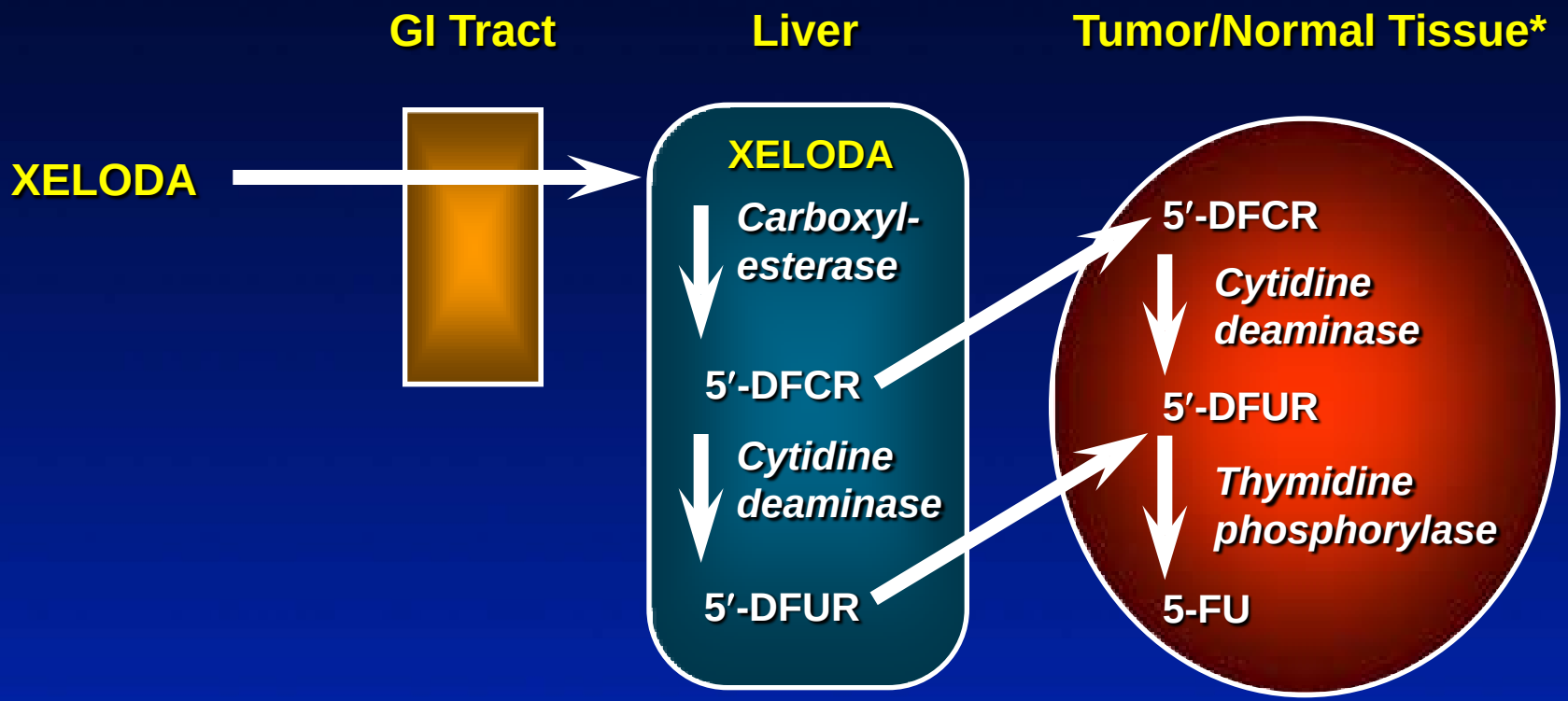
XELODA (capecitabine) is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumor tissues. The clinical significance is unknown.

Capecitabine Chemical Structure

XELODA

5-FU

XELODA® Enzymatic Activation



* Some human carcinomas express thymidine phosphorylase in higher concentrations than surrounding normal tissues

Thymidine Phosphorylase (TP)

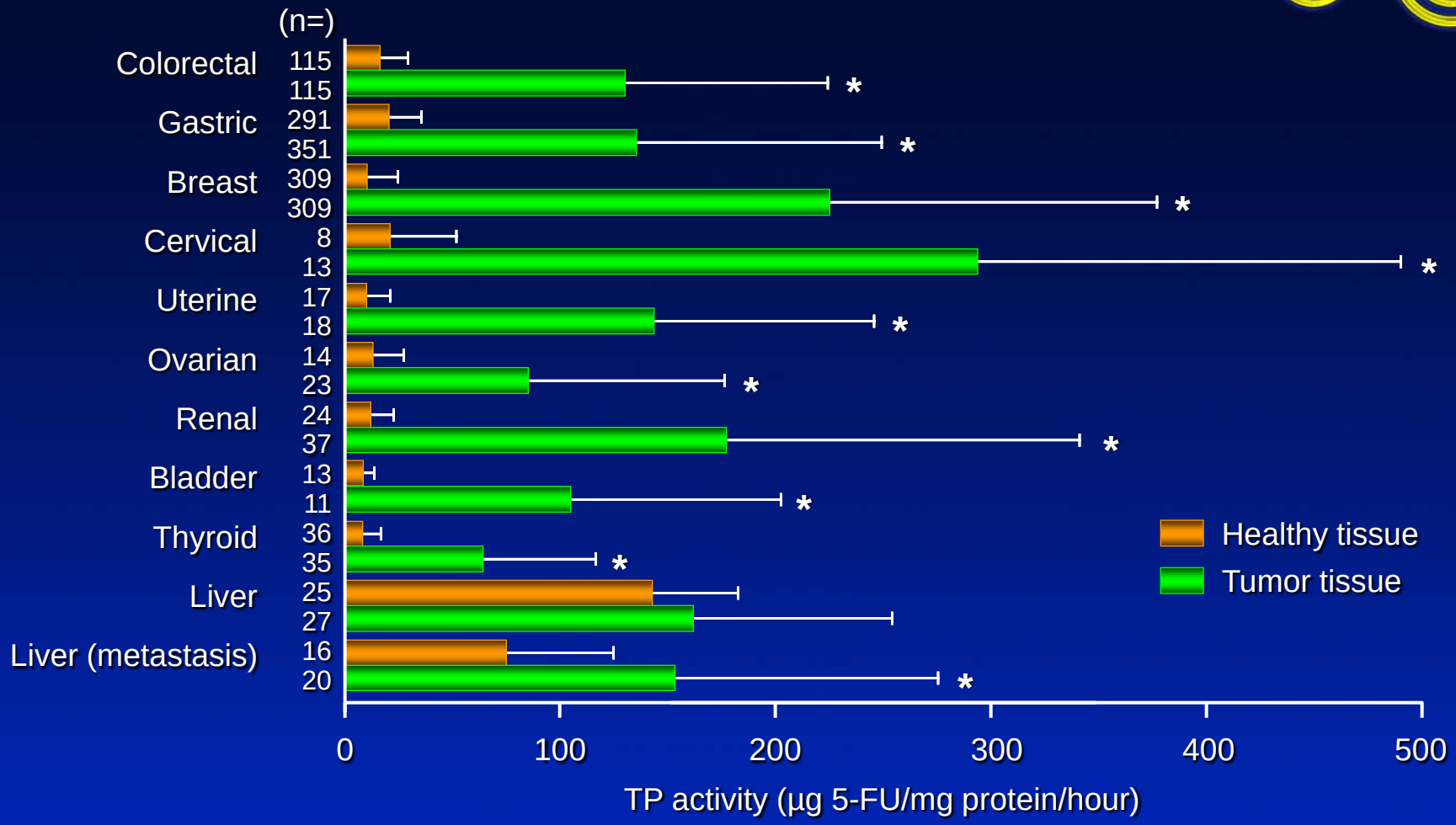
- TP is known as tumor-associated angiogenic factor or platelet-derived endothelial growth factor (PD-EGF)
- Promotes neovascularisation and inhibits apoptosis [1,2]
- Correlates with aggressive malignant growth and poor patient prognosis [3]

[1] Matsuura T et al. Cancer Res 1999;59:5037–40

[2] Kitazono M et al. Biochem Biophys Res Commun 1998;253:797–803

[3] Koukourakis M et al. Br J Cancer 1997; 75:477-81

Increased TP Activity in Tumor *vs.* Normal Human Tissues



Miwa M et al. Eur J Cancer 1998;34:1274–81

***p<0.05**

Five Classes of Alkylating Agents

1. Nitrogen Mustard and derivatives
   - Cyclophosphamide, chorambucil, melphalancyclophosphamide are in widest clinical use for many cancers – dose limiting toxicity is myelosuppresion
2. Ethylenimine derivatives
   - i.e. thiotepa
3. Alkyl slufonates
   - i.e. bisulfan
4. Triazene derivatives
   - i.e. dicarbazine
5. Nitrosureas
   - i.e. BCNU, CCNU, methyl CCNU
     - Lipid soluble, penetrate into CNS-used for treatment of brain tumors

ONCOLOGY
Principles of chemotherapy

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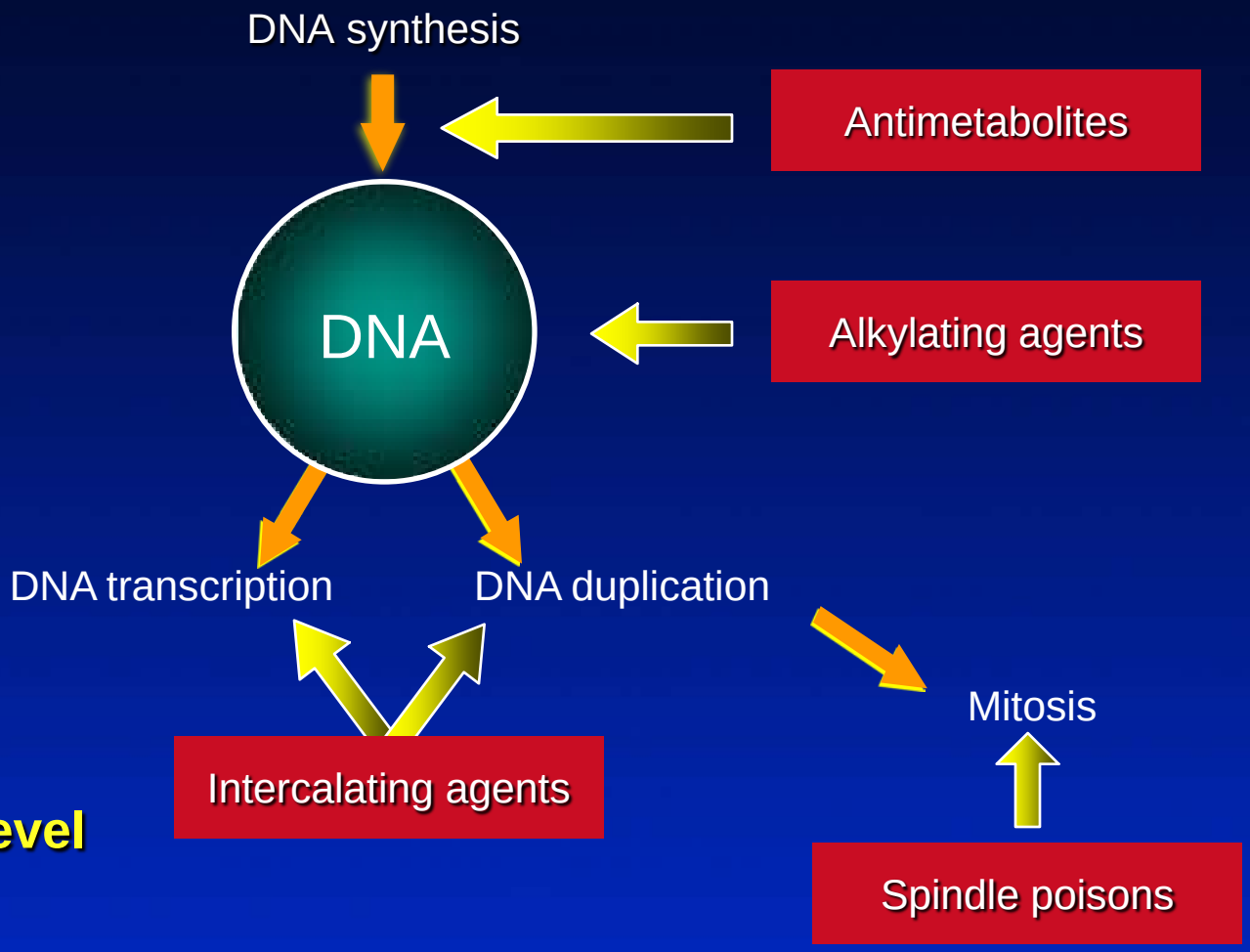
Cisplatin	Fluorouracil	Vincristine	Doxorubicin	
Cyclophosphamide	Mercaptopurine	Vindesine	Mitomycin-c	
Ifosfamide	Methotrexate	Taxoids	Mitoxantrone	
Melphalan			Plicamycin	

ONCOLOGY
Principles of chemotherapy

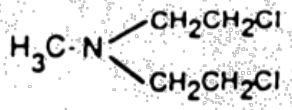
Action sites of cytotoxic agents



Cellular level

Classes of Agents and Mode of Action

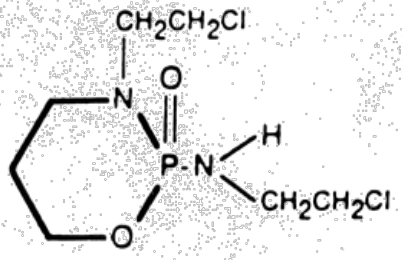
- **Alkylating Agents**
  - Act through covalent boding of alkyl –**CH_2Cl** to intracellular groups
    - E.g. macromolecules
  - May be **monofunctional or bifunctional**
    - i.e. can form cross-links; alkylation of DNA bases are major cause of lethal toxicity
  - **Cell-cycle nonspecific**
    - There are five classes of alkylating agents



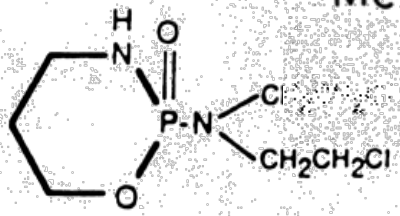
Nitrogen Mustard
(Mechlorethamine)

Chlorambucil

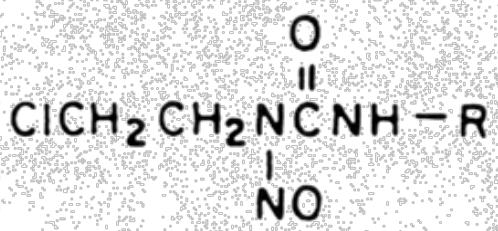
Melphalan
(L-Phenylalanine Mustard)



Ifosfamide

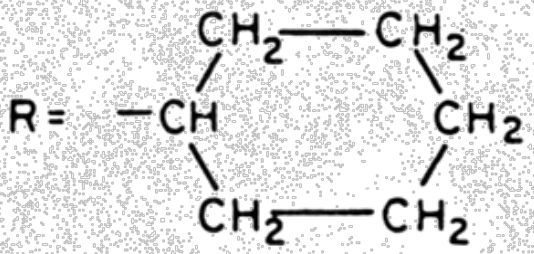


Cyclophosphamide

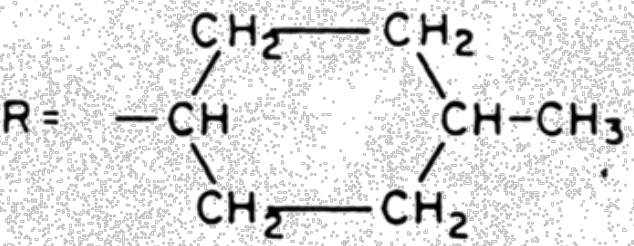


BCNU R = CH_2CH_2Cl

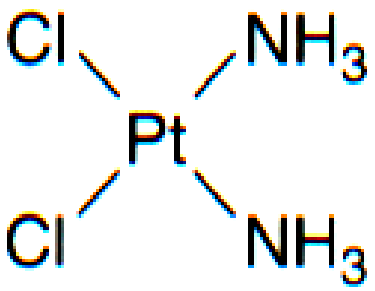
CCNU



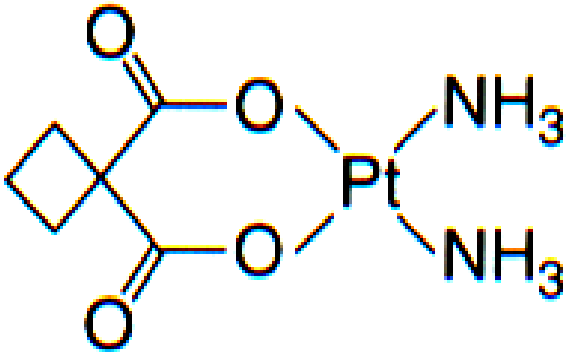
Methyl-CCNU



Platinum Coordination Complexes



CISPLATIN



CARBOPLATIN

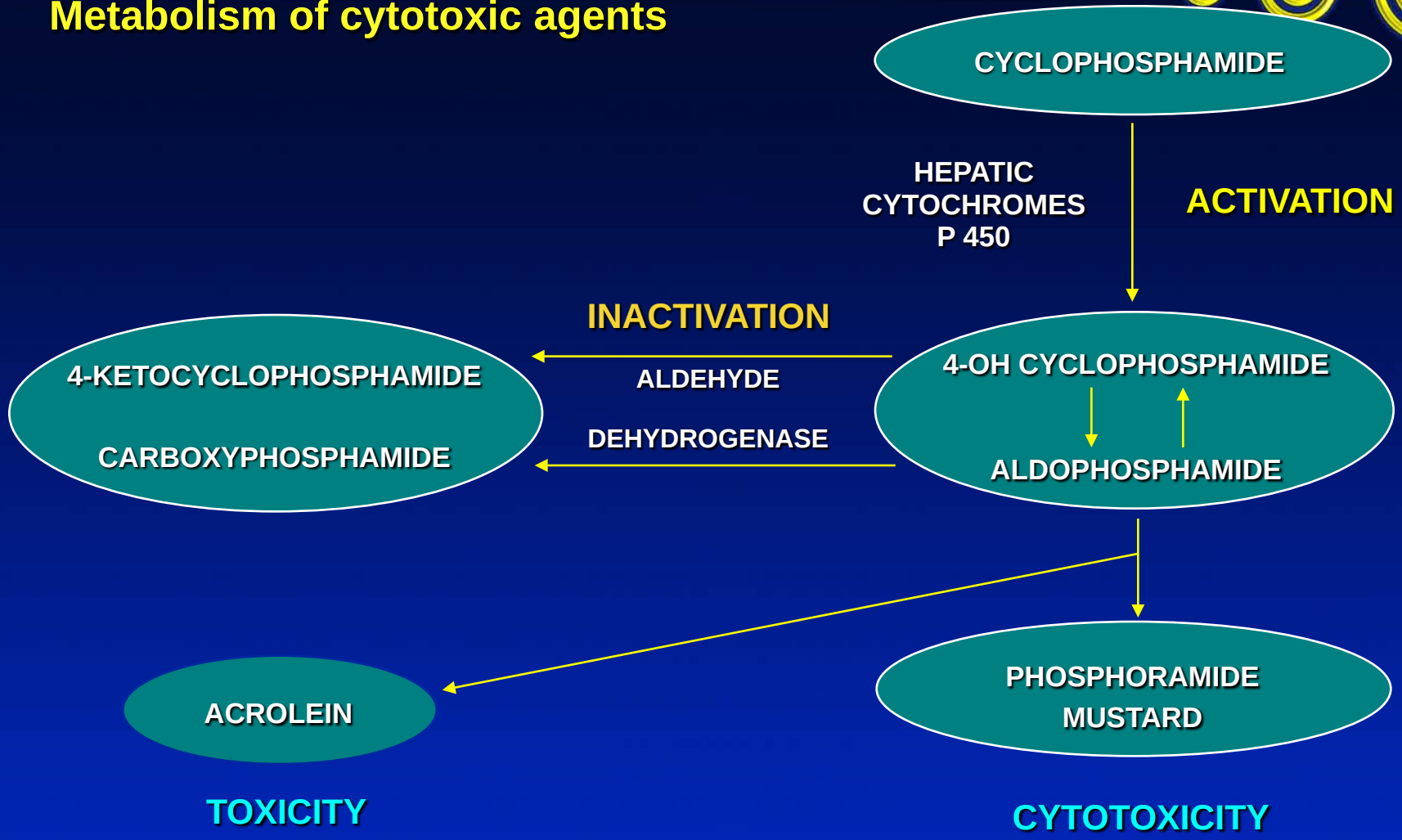
-These compounds alkylate N7 of **guanine**.
-They cause nephro- and ototoxicity. To counteract the effects of nephrotoxicity, give mannitol as an osmotic diuretic or induce chloride diuresis with 0.1% NaCl.

Alkylating Agents

- **Cyclophosphamide (also ifosfamide)**
  - Injury to cells is the same as radiation effect
  - Alternating cytoxan and XRT produces a maximum killing response
  - Limiting toxicities:
    - Bladder injury
      - concurrent administration with XRT not recommended
      - seen 1 week post administration and can persist for 1 year
      - seen with XRT 5 months after treatment
    - Increased injury seen in CNS, lung, esophagus, small bowel and skin
    - XRT and cytoxan interaction can be seen up to 9 months after either is given.

ONCOLOGY
Principles of chemotherapy

Metabolism of cytotoxic agents



Reaction with DNA Bases

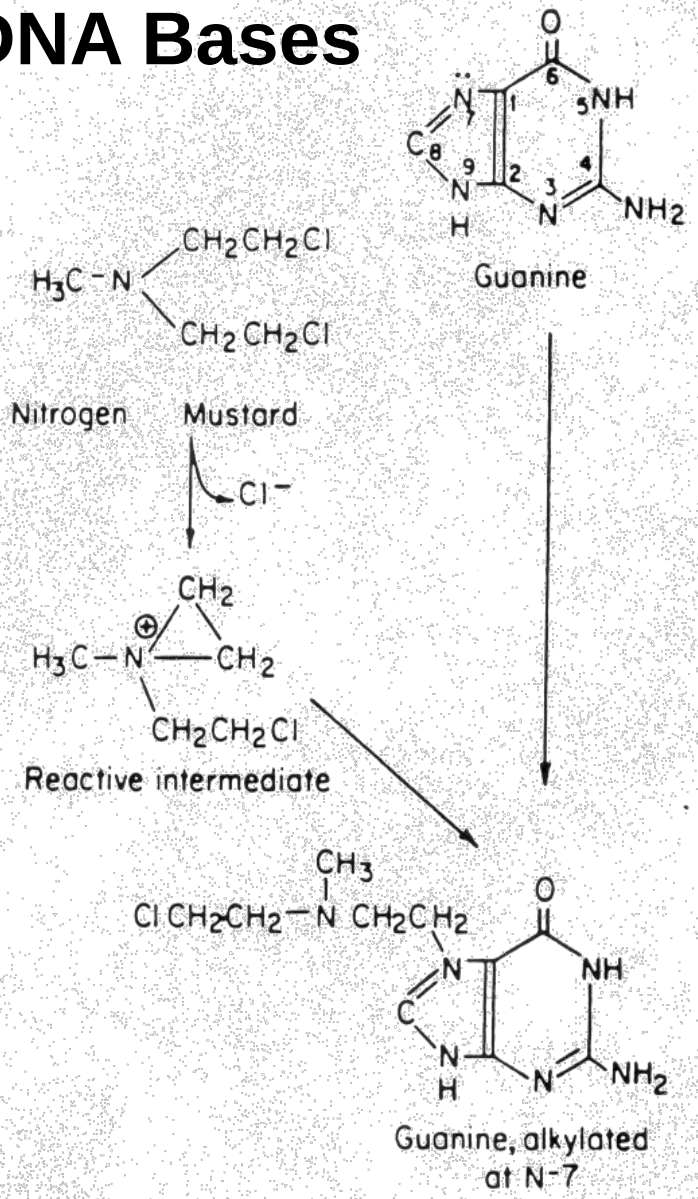


Figure 16.3. Reactions leading to alkylation at the N-7 position of guanine by nitrogen mustard.

Alkylating Agents

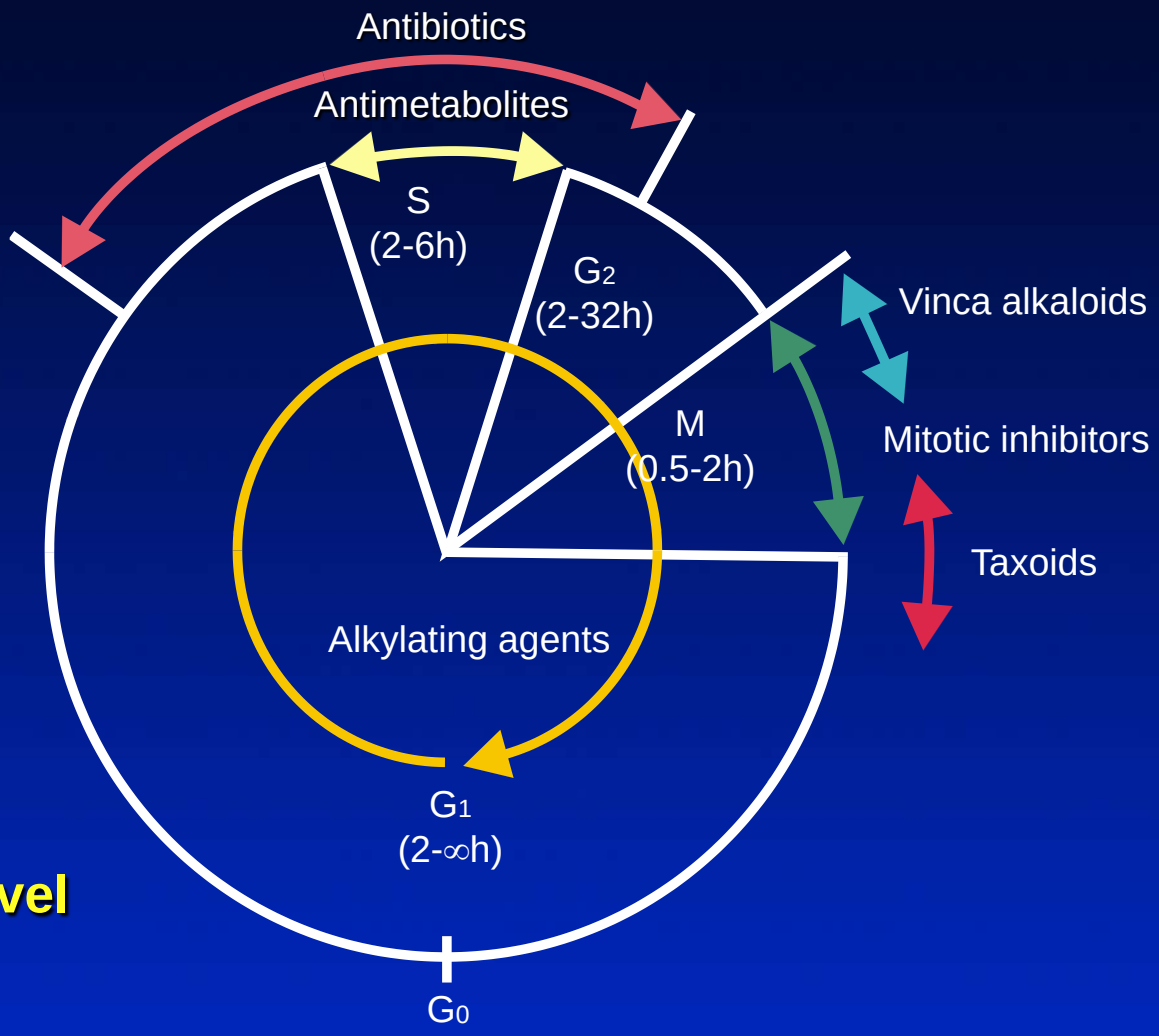
- **Cisplatin and carboplatin**
  - Supra-additive effect with XRT
  - Impairs sub-lethal damage repair
    - works by free-radical related mechanism and biochemical mechanism
  - Hypoxic cell sensitizer at very high doses
    - not clinically achievable in humans
  - Hyperthermia increases the effects of the drug
  - Limiting toxicities:
    - kidney toxicity seen if given within 6 months prior to XRT but not seen if given after XRT

Natural Products

- **ANTIBIOTICS**
  - Anthracyclines – are planar multi-ring structures
    - Example doxorubicin (Adriamycin), daunorubicin – major limiting toxicity is cardiac damage
  - Doxorubicin – one of the most active anticancer drugs in clinical practice
    - Mechanisms of action
      - Can intercalate between turns of the double helix in DNA
      - Inhibit topoisomerase 11 (catalyzes the orderly breaking of DNA strands, unwinding of DNA, and relegation of DNA fragments during synthesis)
      - Formation of free radicals

ONCOLOGY
Principles of chemotherapy

Action sites of cytotoxic agents



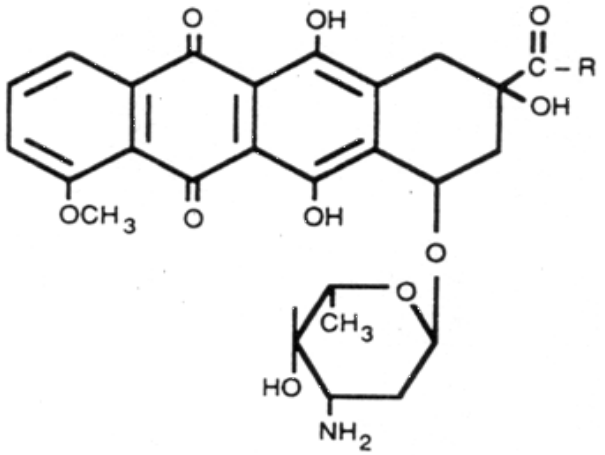
Cell cycle level

Antibiotics

- Dactinomycin (actinomycin D)
  - Intercalates with DNA binding noncovalently between purine and pyrimidine base pairs
  - Inhibits sublethal damage repair in some studies
    - With daily XRT drug can cause the enhancement of lung damage
  - Can cause radiation pneumonitis, acute skin and mucosal reactions, hepatic damage and late fibrosis
    - Recall reaction seen if drug is given after XRT. The portal outline is seen.
  - Enhances distant metastasis control in many tumors
    - Still used in pediatric tumors
      - Ewing's Sarcoma
      - Wilm's Tumor
      - Rhabdomyosarcoma

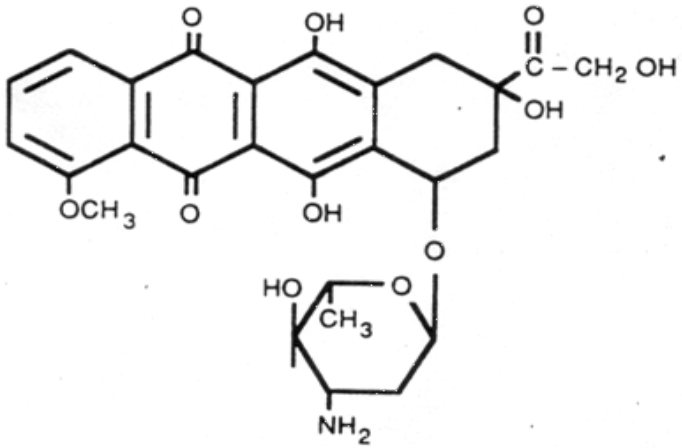
Antibiotics

- Doxorubicin
  - Intercalates between base pairs in DNA
  - Double strand break repair is inhibited
    - drug exposure before XRT gives maximal enhancement
  - Marked mucosal (esp. esophagus) and skin reaction is seen
    - increased delayed fibrosis and necrosis
  - Cardiac tolerance is reduced in people receiving XRT prior to chemotherapy
  - CONCURRENT USE IS AVOIDED



R = CH_2 OH, doxorubicin

= CH_3 daunorubicin



Epirubicin

Figure 16.16. Structure of doxorubicin (Adriamycin), daunorubicin, and epirubicin.

Antibiotics

- Bleomycin
  - Radiomimetic
  - Causes single and double stranded DNA breaks
    - intercalation is partially the MOA
    - oxygen free-radicals are generated by bleomycin-oxygen-iron complexes
    - enhanced effects with dactinomycin
    - major effects are in the G2 and M phases
      - creates a G2-M blockade helping synchronize cells

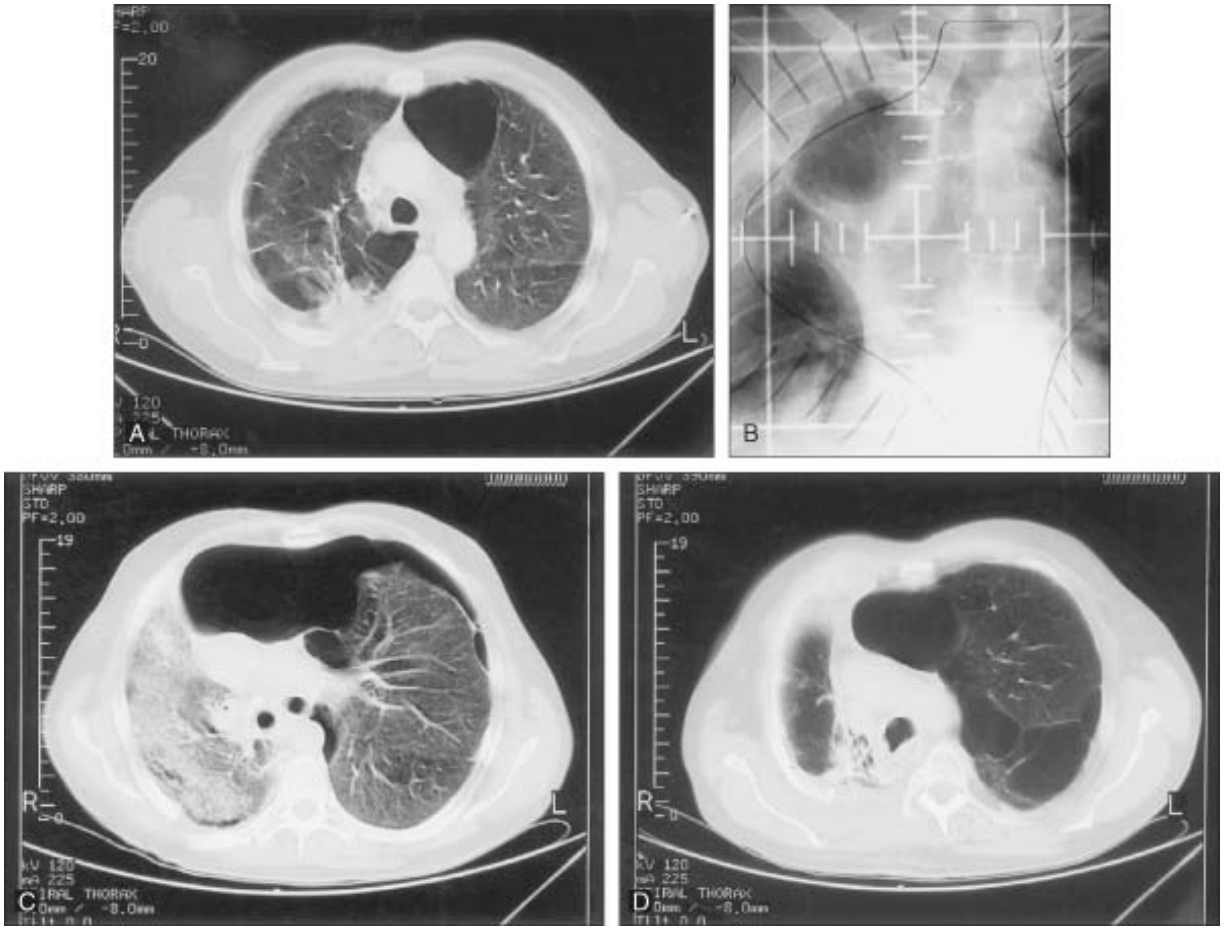
Antibiotics

- Bleomycin
  - Lung damage is most enhanced
  - Skin and mucosal damage is also enhanced
  - Drug given before XRT is most enhancing esp 6 hours prior to therapy
    - prolonged exposure increases damage

Antibiotics

- Mitomycin C
  - Alkylating agent which cross-links DNA strands and halts DNA synthesis
  - Interacts with XRT by killing hypoxic cells
  - Enhances XRT reaction in the skin and soft tissues
  - Used in cancers of
    - anus
    - head and neck
    - esophagus

Radiation Pneumonopathy



The patient was treated with steroids, antibiotics, and a Pleurx catheter. CT scan approximately 1 year later, the patient's condition was stable with no evidence of recurrent cancer. The patient had discontinued steroid therapy but needed intermittent oxygen therapy for radiation fibrosis of the right lung.

Abeloff: Abeloff's Clinical Oncology, 4th ed.

Natural Products (cont.)

- VINCA ALKALOIDS
  - Vincristine, Vinblastine
    - Bind to tubulin and inhibit its polymerization into microtubules that form the mitotic spindle
- TAXANES
  - Paclitaxel, docetaxel
    - Semisynthetic derivative
    - Act by stabilizing microtubules
      - i.e. inhibit microtubular disassembly thereby preventing cell division
  - Radiosensitizes cells in the G1-S phase, G2-M blockade, commonly used in Lung, H&N, Bladder
  - Enhances XRT with nontoxic doses

Drug Resistance

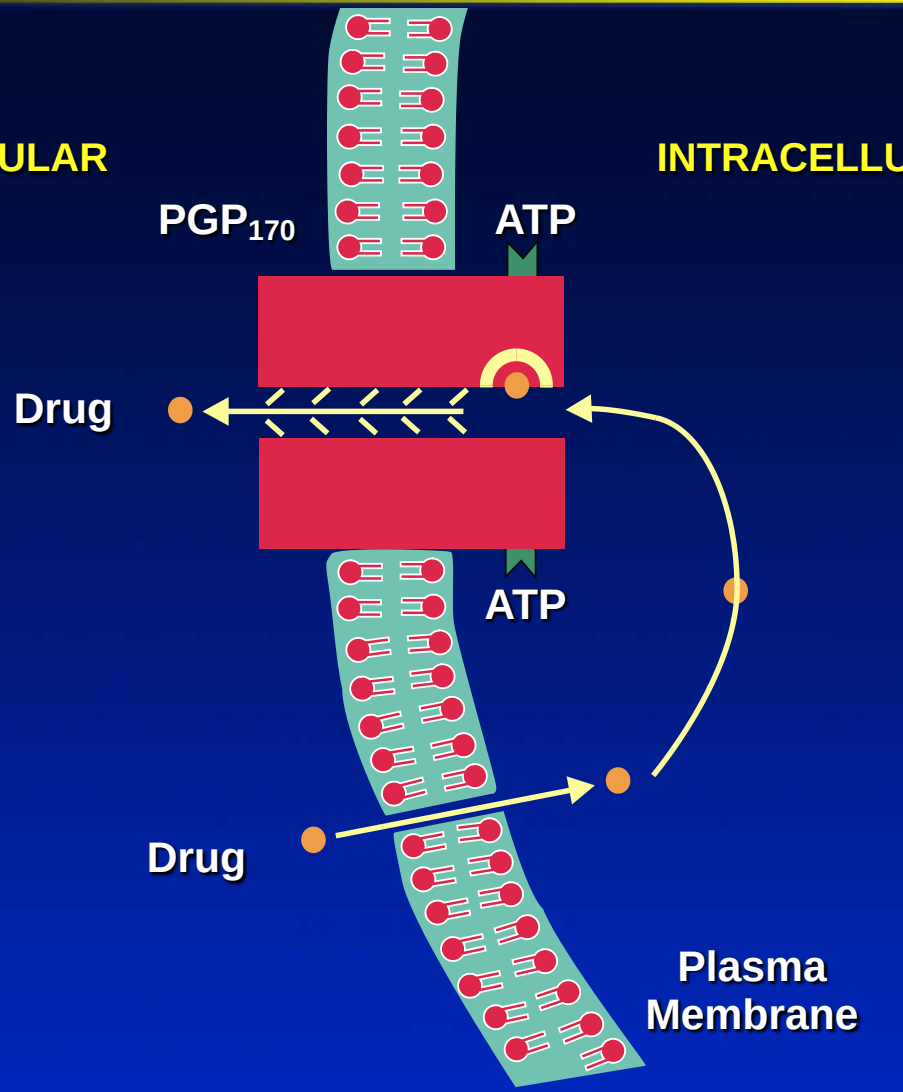
- Factors influencing resistance to chemotherapy
  - Proliferative state of cells
    - i.e. cell cycle effects
  - Limited diffusion due to solid tumor environment
    - i.e. limited vascular access
  - Intrinsic resistance of tumor cells themselves, most important factor
    - i.e. drug therapy results in the selection or induction of this drug-resistant subpopulation with a tumor

Mechanisms of Intrinsic Resistance

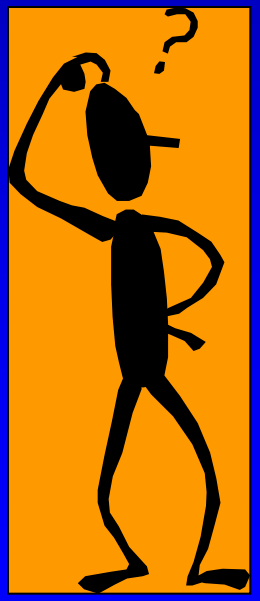
- Decreased cellular uptake
- Reduced drug activation
- Binding of alkylating species to sulfhydryl cpds such as glutathion, followed by transport out of cell
- Increased removal of drug adducts from DNA
- Increased repair of DNA damage
- Increased efflux by MDR protein pumps

ONCOLOGY
Principles of chemotherapy

Drug resistance



Does resistance to chemotherapy translate into resistance to radiotherapy?



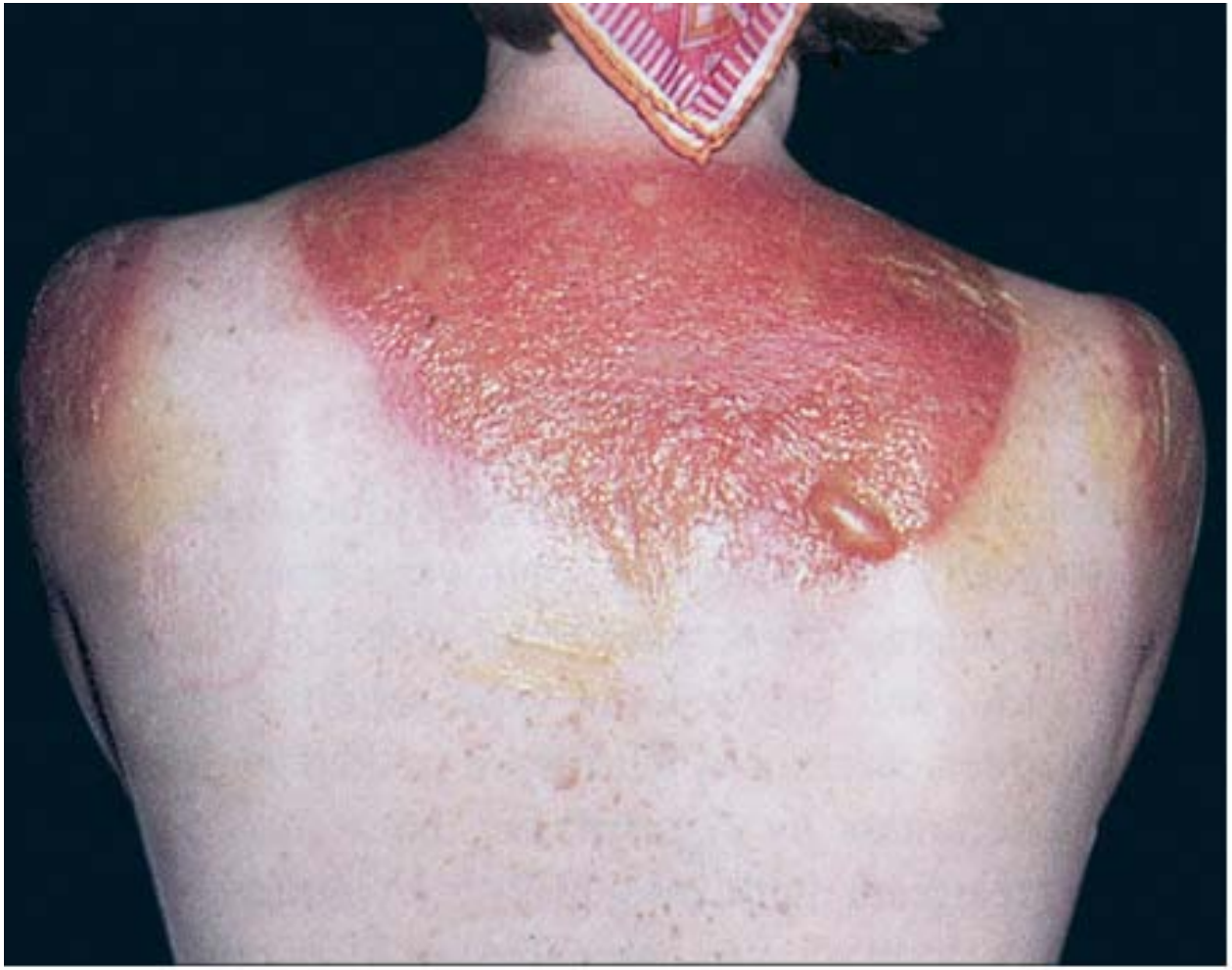
NO!

- Chemoresistance is usually due to a target
  - MDR, thymidylate synthase, topoisomerase I or II
- Radioresistance is multifactorial
  - Free radical formation, DNA repair, oxygen status

Radiation Recall Reaction

- The chemotherapy drugs that have been reported to cause radiation recall in more than 10 percent of patients include:
- Cosmegen® (actinomycin)
- Adriamycin® (doxorubicin)
- Rheumatrex® (methotrexate)
- 5-FU (fluorouracil)
- Hydrea® (hydroxyurea)
- Taxol® (paclitaxel)
- Doxil® (liposomal doxorubicin)

Recall Phenomena

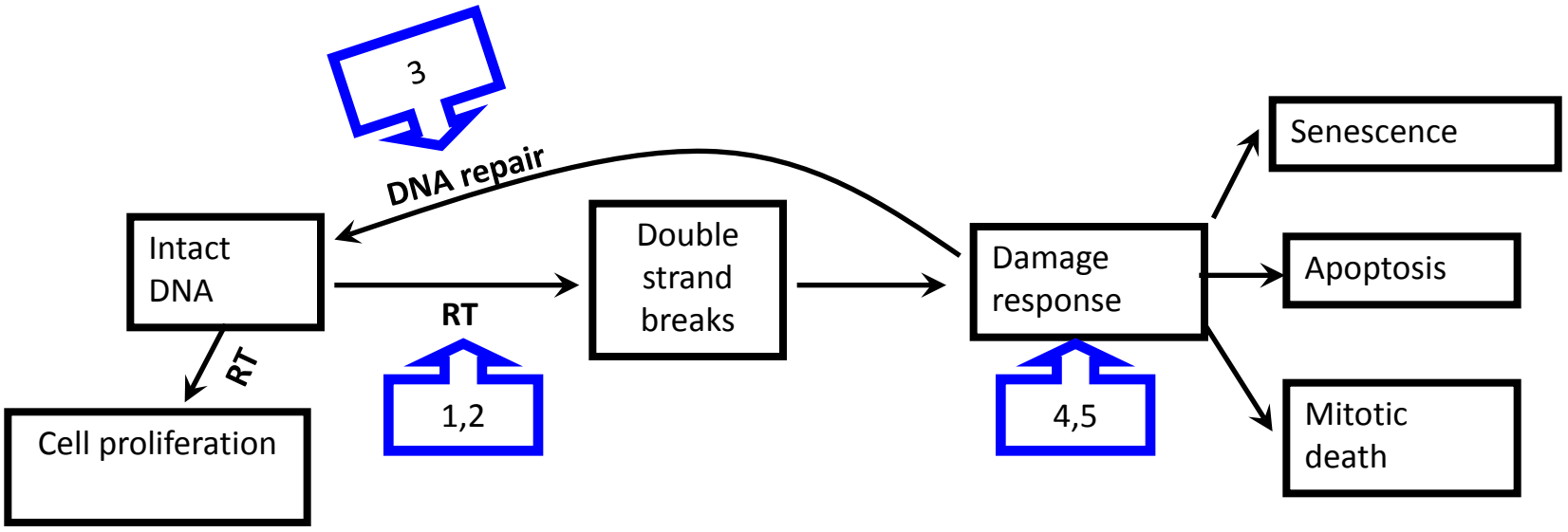


Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Phase I Medical Oncology	Phase I Radiation Oncology
Escalate dose until maximal tolerated (MTD)	
First in humans	Significant human exposure
Toxicity - unpredictable	Toxicity - predictable
- systemic	- local
- acute	-medium / long term
Range of cancer types	Organ specific
Patients have failed multiple treatments	May be treatment naive
Pharmacokinetic studies	Not needed

Mechanisms of Radiosensitization

1. Cell cycle effects
2. Expose DNA to free radical damage
3. Inhibit DNA repair
4. Influence cell's response to DNA damage, promote apoptosis
5. Spindle checkpoint removal, leading to mitotic death

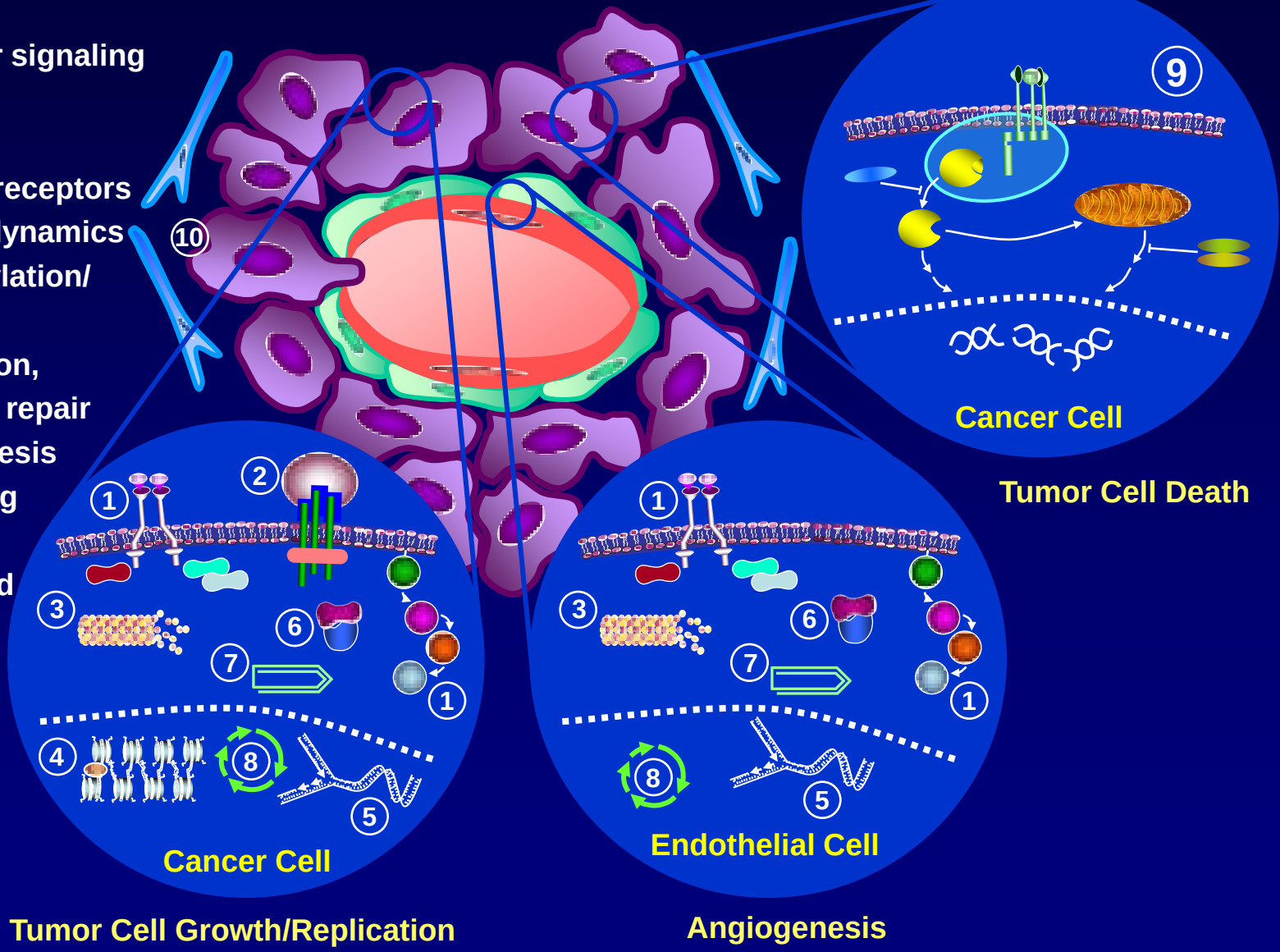


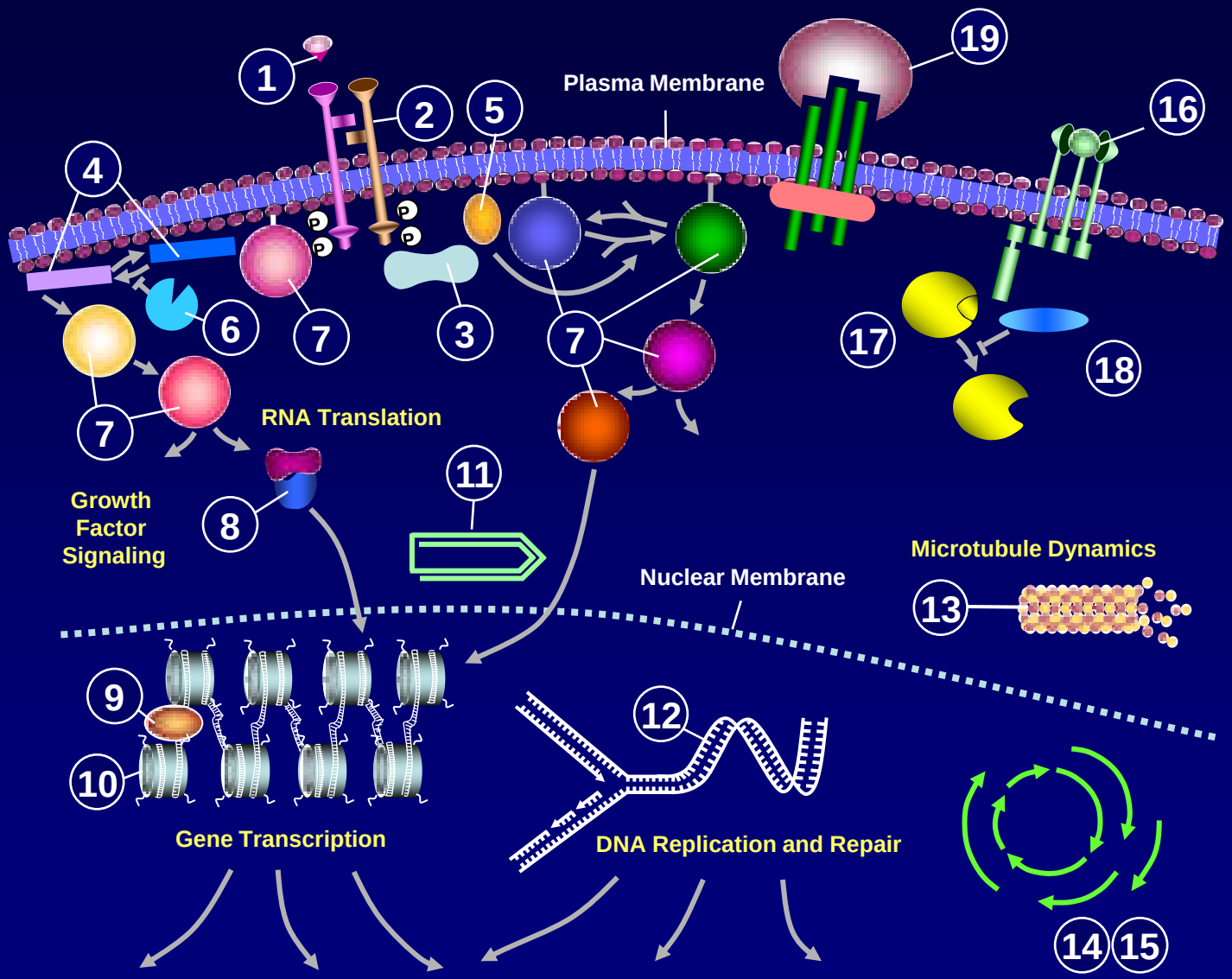
Signaling Pathways

Therapeutic Targets in Cancer

Targeting the Tumor and Its Microenvironment

1. Growth factor signaling
2. Other growth stimulating/ suppressing receptors
3. Microtubule dynamics
4. Histone acetylation/ deacetylation
5. DNA replication, transcription, repair
6. Protein synthesis
7. Protein folding
8. Cell cycle
9. Activators and inhibitors of apoptosis
10. Metastasis





1. Growth factors
2. Growth factor receptors
3. Adaptor proteins
4. Docking proteins/ binding proteins
5. Guanine nucleotide exchange factors
6. Phosphatases and phospholipases
7. Signaling kinases
8. Ribosomes
9. Transcription factors
10. Histones
11. Molecular chaperones
12. DNA
13. Microtubules
14. Cyclins
15. Cyclin-dependent kinases
16. Cell death receptors
17. Apoptosis-effector caspases
18. Caspase inhibitors
19. CD40-CD40L

Thank you