Anticancer Drugs

- over 25% of the population of the United States will face a diagnosis of cancer during their lifetime, with more than 1.6 million new cancer patients diagnosed each year.

- Less than a quarter of these patients will be cured solely by surgery and/or local radiation.

- Most of the remainder will receive systemic chemotherapy at some time during their illness.

- In a small fraction (approximately 10%) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission.

- However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death.

- Thus, the overall 5-year survival rate for cancer patients is about 68%, ranking cancer second only to cardiovascular disease as a cause of mortality.

PRINCIPLES OF CANCER CHEMOTHERAPY

- Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cells that can arrest a tumor's progression.

- The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis .

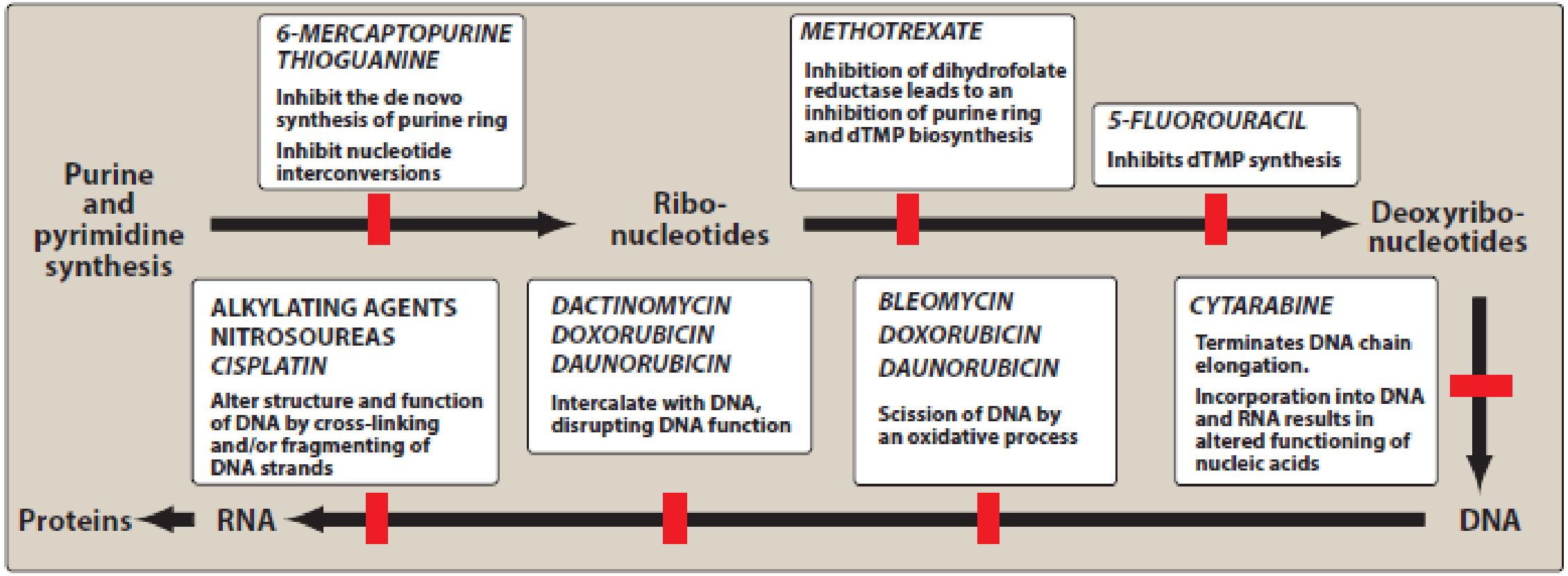


Figure 46.2

Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

- Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells.

- Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells, both normal and abnormal.

- Therefore, almost all antitumor agents have a steep dose–response curve for both therapeutic and toxic effects.

A. Treatment strategies

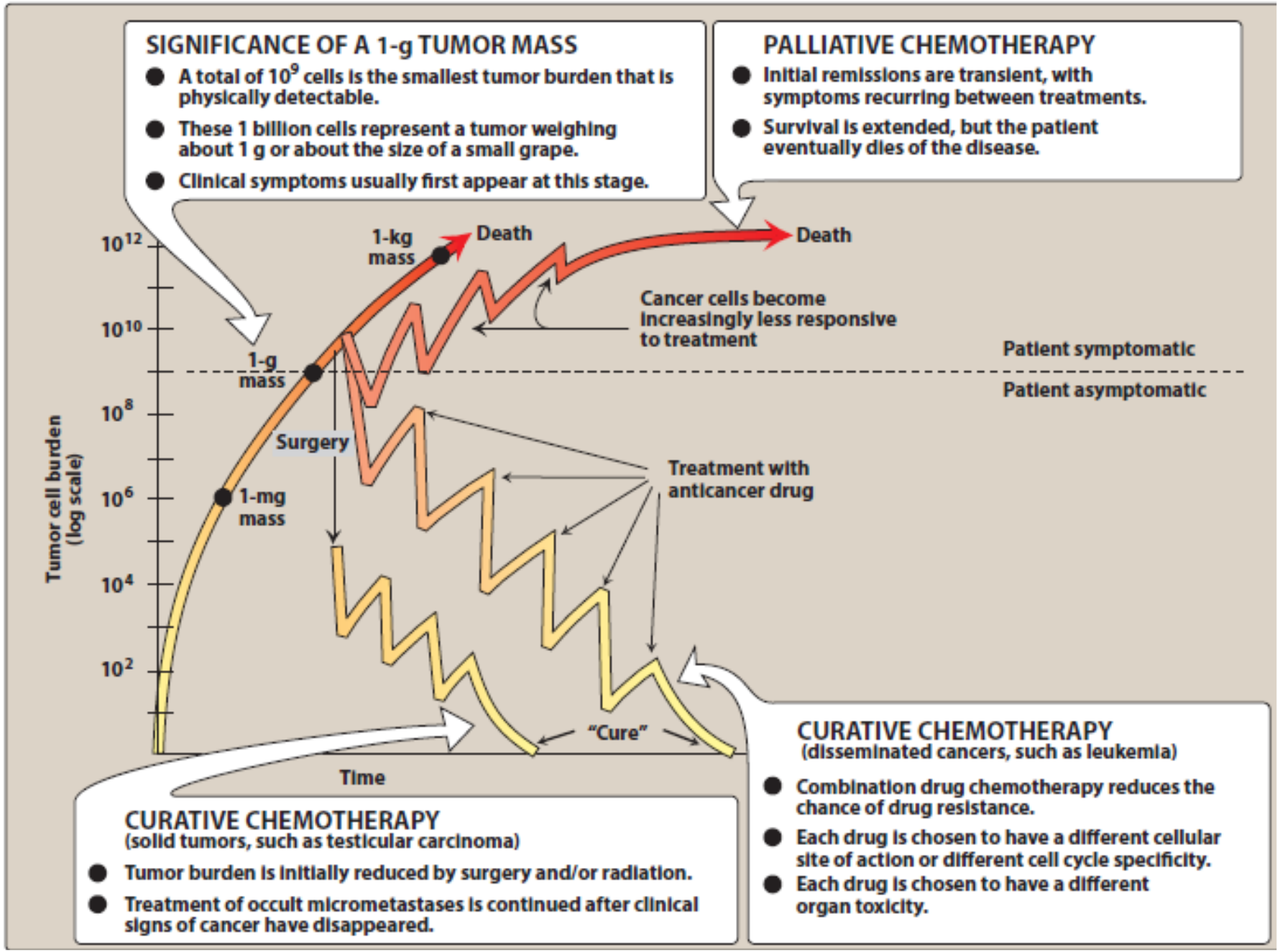
1. Goals of treatment:

- The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival).
- A true cure requires the eradication of every neoplastic cell.
- If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life.
- Thus, the individual maintains a “near-normal” existence, with the cancer being treated as a chronic disease.

- In either case, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by
  - chemotherapy,
  - immunotherapy,
  - therapy using biological modifiers, or
  - a combination of these treatment modalities.

- In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (alleviation of symptoms and avoidance of life-threatening toxicity).

- The goal of treatment should always be kept in mind, as it often influences treatment decisions.


SIGNIFICANCE OF A 1-g TUMOR MASS
A total of 10^9 cells is the smallest tumor burden that is physically detectable.
These 1 billion cells represent a tumor weighing about 1 g or about the size of a small grape.
Clinical symptoms usually first appear at this stage.
PALLIATIVE CHEMOTHERAPY
Initial remissions are transient, with symptoms recurring between treatments.
Survival is extended, but the patient eventually dies of the disease.
Tumor cell burden (log scale)
10^{12}
10^{10}
10^8
10^6
10^4
10^2
1-kg mass
Death
Death
Cancer cells become increasingly less responsive to treatment
1-g mass
Patient symptomatic
Patient asymptomatic
Surgery
Treatment with anticancer drug
1-mg mass
"Cure"
Time
CURATIVE CHEMOTHERAPY
(solid tumors, such as testicular carcinoma)
Tumor burden is initially reduced by surgery and/or radiation.
Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared.
CURATIVE CHEMOTHERAPY
(disseminated cancers, such as leukemia)
Combination drug chemotherapy reduces the chance of drug resistance.
Each drug is chosen to have a different cellular site of action or different cell cycle specificity.
Each drug is chosen to have a different organ toxicity.

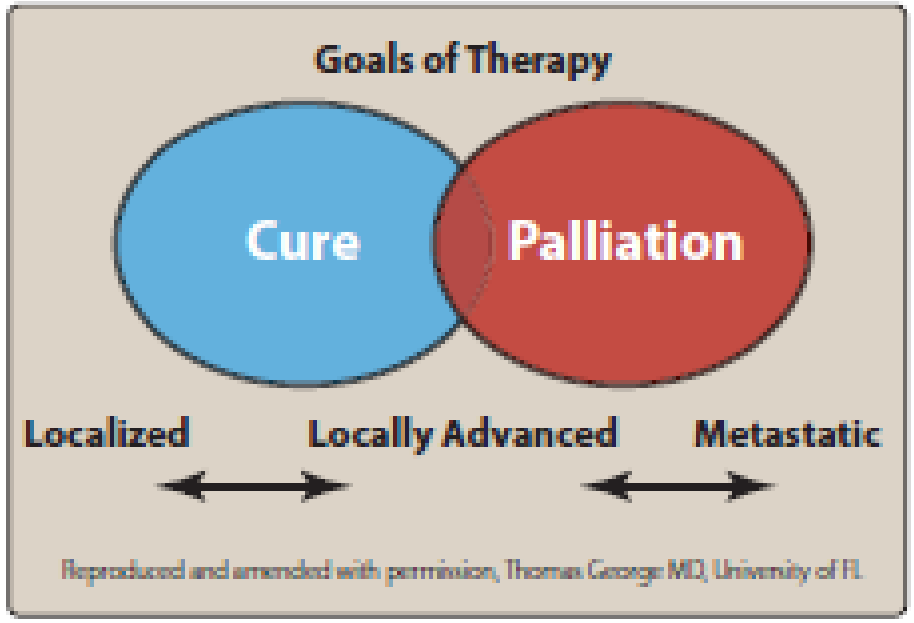


Figure 46.4
Goals of treatment with chemotherapeutic agents.

2. Indications for treatment:

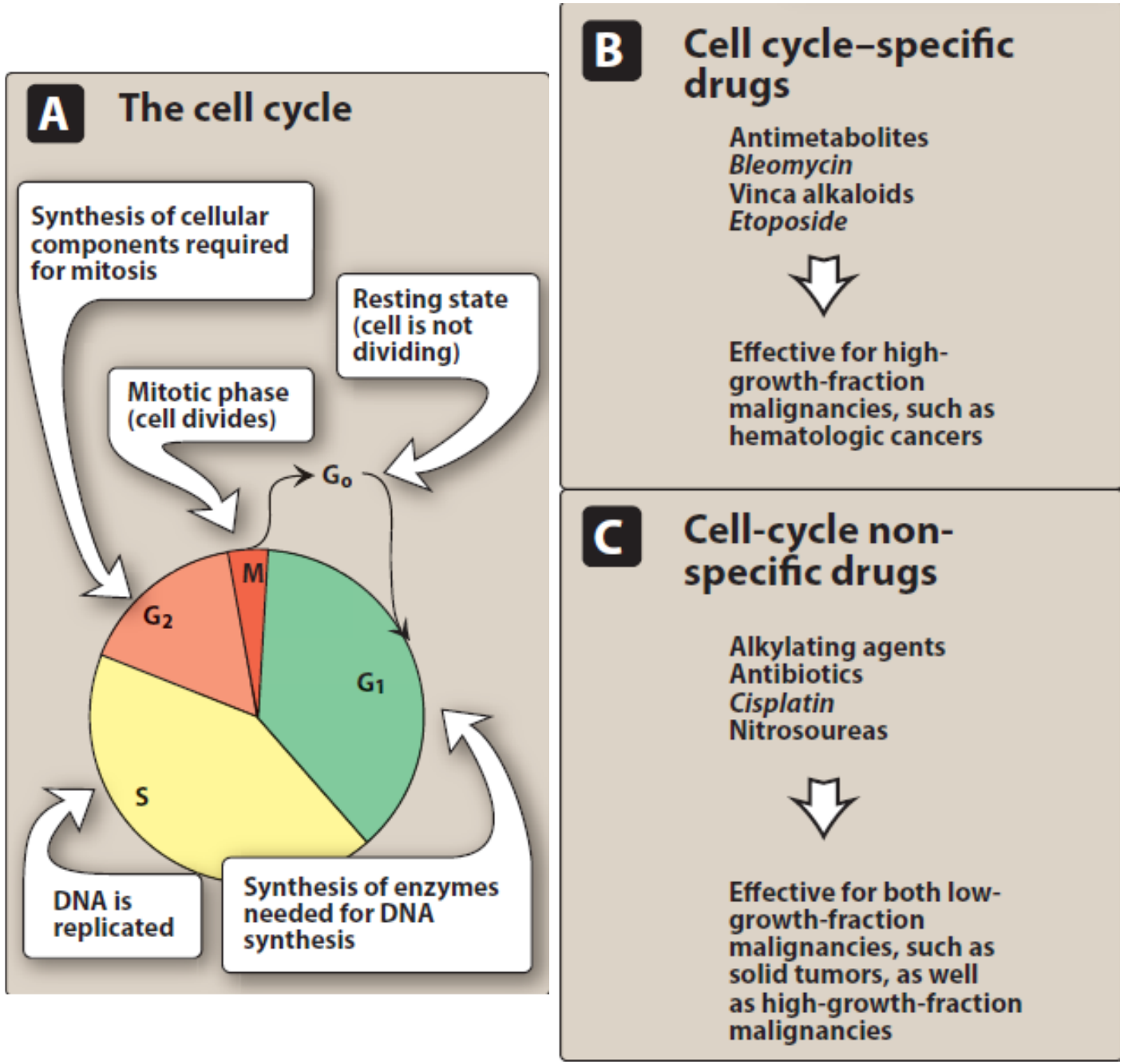
- when neoplasms are disseminated and are not amenable to surgery.
- as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy.
- prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and
- chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

3. Tumor susceptibility and the growth cycle:

- The fraction of tumor cells that are in the replicative cycle ("growth fraction") influences their susceptibility to most cancer chemotherapeutic agents.

- Rapidly dividing cells are generally more sensitive to chemotherapy, whereas slowly proliferating cells are less sensitive to chemotherapy.

- In general, nondividing cells (those in the G0 phase) usually survive the toxic effects of many of these agents.


A
The cell cycle
Synthesis of cellular components required for mitosis
Resting state (cell is not dividing)
Mitotic phase (cell divides)
G_o
M
G_2
G_1
S
DNA is replicated
Synthesis of enzymes needed for DNA synthesis
B
Cell cycle–specific drugs
Antimetabolites
Bleomycin
Vinca alkaloids
Etoposide
Effective for high-growth-fraction malignancies, such as hematologic cancers
C
Cell-cycle non-specific drugs
Alkylating agents
Antibiotics
Cisplatin
Nitrosoureas
Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

a. Cell cycle specificity of drugs:

- Both normal cells and tumor cells go through growth cycles.
- However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues.
- Chemotherapeutic agents that are effective only against replicating cells are said to be cell cycle specific, whereas other agents are said to be cell cycle nonspecific.
- The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells.

b. Tumor growth rate:

- The growth rate of most solid tumors in vivo is initially rapid, but growth rate usually decreases as the tumor size increases.
- This is due to the unavailability of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation.
- Tumor burden can be reduced through surgery, radiation, or by using cell cycle–nonspecific drugs to promote the remaining cells into active proliferation, thus increasing their susceptibility to cell cycle– specific chemotherapeutic agents.

B. Treatment regimens and scheduling

- Drug dosages are usually calculated on the basis of body surface area, in an effort to tailor the medications to each patient.

1. Log kill phenomenon:

- Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells).
- The term “log kill” is used to describe this phenomenon.
- For example, a diagnosis of leukemia is generally made when there are about 109 (total) leukemic cells.
- Consequently, if treatment leads to a 99.999-percent kill, then 0.001% of 109 cells (or 104 cells) would remain.
- This is defined as a 5-log kill (reduction of 105 cells).

- At this point, the patient will become asymptomatic, and the patient is in remission

- For most bacterial infections, a 5-log (100,000- fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells.

- However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.

2. Pharmacologic sanctuaries:

- Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entering.

- Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site.

- Similarly, drugs may be unable to penetrate certain areas of solid tumors.

3. Treatment protocols:

- Combination drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.

a. Combinations of drugs:

- Cytotoxic agents with qualitatively
  - different toxicities, and with
  - different molecular sites and mechanisms of action,
- are usually combined at full doses.

- This results in higher response rates, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities.

- In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

b. Advantages of drug combinations:

1) provide maximal cell killing within the range of tolerated toxicity,

2) are effective against a broader range of cell lines in the heterogeneous tumor population, and

3) may delay or prevent the development of resistant cell lines.

c. Treatment protocols:

- Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state.

- They are usually identified by an acronym.

- For example, a common regimen called R-CHOP, used for the treatment of non-Hodgkin lymphoma, consists of ***r****ituximab,* ***c****yclophosphamide,* ***h****ydroxydaunorubicin (doxorubicin),* ***O****ncovin* (*vincristine*), and ***p****rednisone* or *prednisolone*.

- Therapy is scheduled intermittently (approximately 21 days apart) to allow recovery or rescue of the patient's immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection.

C. Problems associated with chemotherapy

- Cancer drugs are toxins that present a lethal threat to the cells.

- It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1. Resistance:

- Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs.
- Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses.
- The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs.
- Drug combinations are also effective against a broader range of resistant cells in the tumor population.

2. Multidrug resistance:

- Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for “permeability” glycoprotein) is responsible for multidrug resistance.

- This resistance is due to adenosine triphosphate–dependent pumping of drugs out of the cell in the presence of P-glycoprotein.

- Cross-resistance following the use of structurally unrelated agents also occurs.

- For example, cells that are resistant to the cytotoxic effects of the Vinca alkaloids are also resistant to *dactinomycin* and to the anthracycline antibiotics, as well as to *colchicine*, and vice versa.

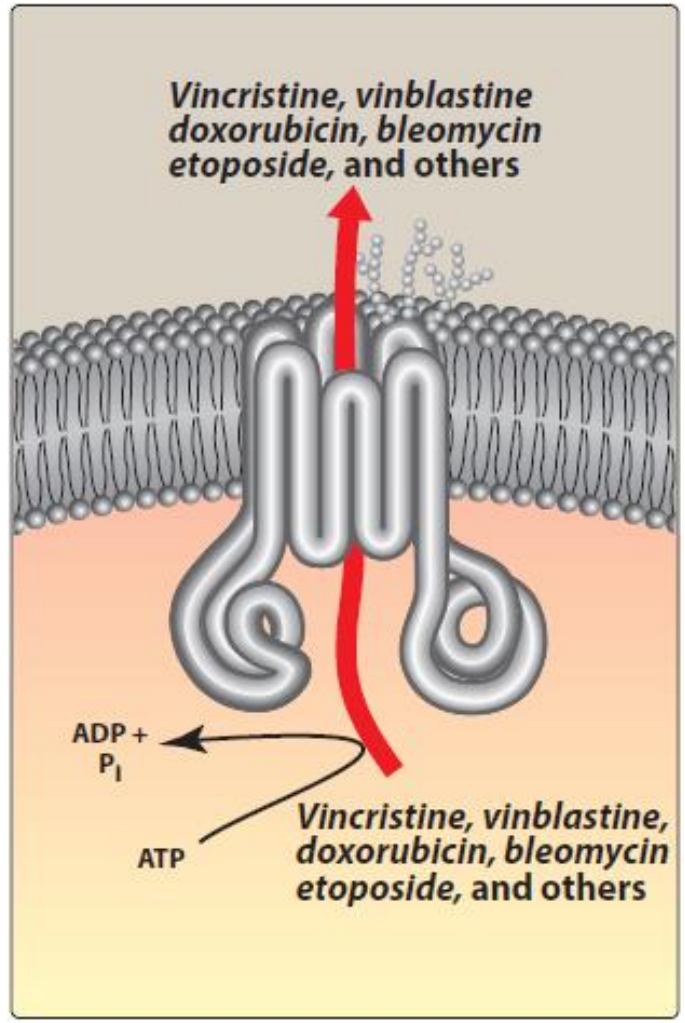


Figure 46.6

The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

- [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the
  - kidney,
  - liver,
  - pancreas,
  - small intestine,
  - colon, and
  - adrenal gland.

- Certain drugs at high concentrations (for example, *verapamil*) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent.

- However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought.

3. Toxicity:

- Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the
  - buccal mucosa,
  - bone marrow,
  - gastrointestinal [GI] mucosa, and
  - hair follicles),

contributing to the toxic manifestations of chemotherapy.

a. Common adverse effects:

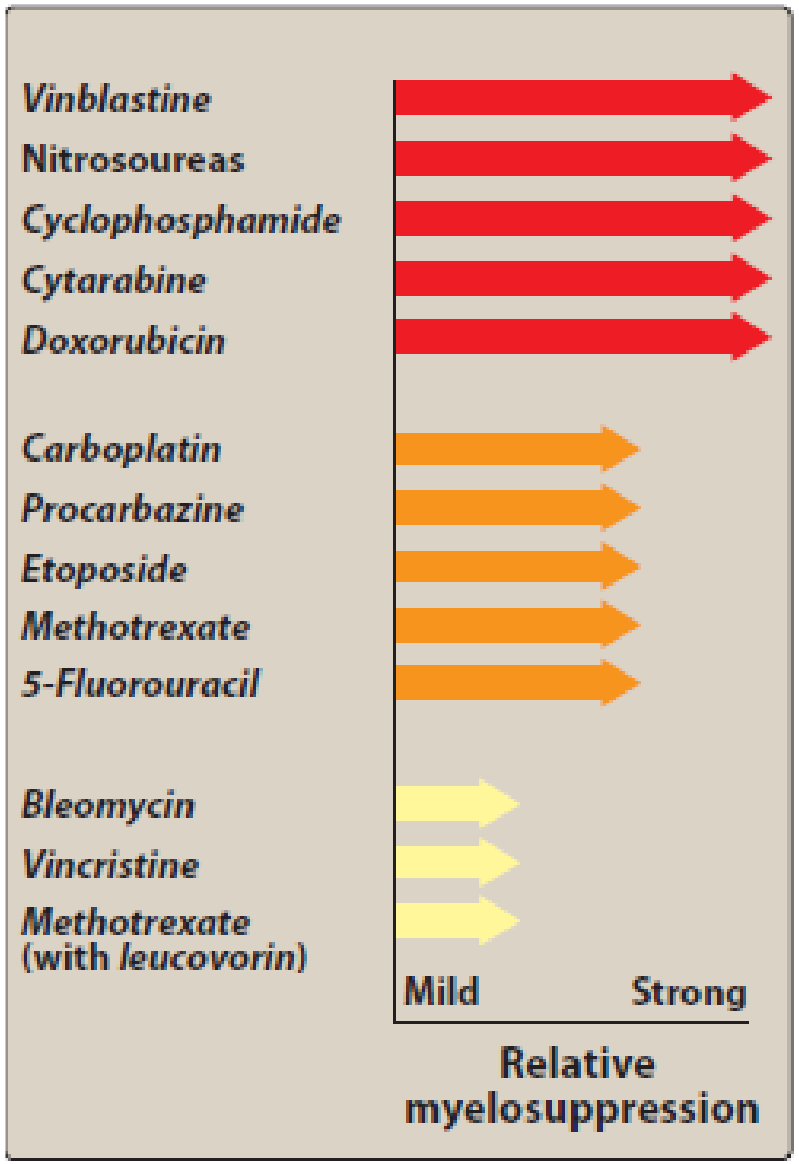
- Most chemotherapeutic agents have a narrow therapeutic index.
- Severe vomiting,
- stomatitis,
- bone marrow suppression, and
- alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents.

- Vomiting is often controlled by administration of antiemetic drugs.

- Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents,

- whereas other adverse reactions are confined to specific agents, such as bladder toxicity with *cyclophosphamide*,
- cardiotoxicity with *doxorubicin, and*
- *pulmonary* fibrosis with *bleomycin*.

- *The duration of the side effects varies* widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities can be irreversible.


Vinblastine
Nitrosoureas
Cyclophosphamide
Cytarabine
Doxorubicin
Carboplatin
Procarbazine
Etoposide
Methotrexate
5-Fluorouracil
Bleomycin
Vincristine
Methotrexate (with leucovorin)
Mild
Strong
Relative myelosuppression

b. Minimizing adverse effects:

- Some toxic reactions may be ameliorated by interventions, such as the use of
  - cytoprotectant drugs,
  - perfusing the tumor locally (for example, a sarcoma of the arm),
  - removing some of the patient's marrow prior to intensive treatment and then reimplanting it, or
  - promoting intensive diuresis to prevent bladder toxicities.

- The megaloblastic anemia that occurs with *methotrexate can be effectively counteracted* by administering *folinic acid (leucovorin).*

- *With the availability* of human granulocyte colony–stimulating factor (*filgrastim*), *the* neutropenia associated with treatment of cancer by many drugs can be partially reversed.

4. Treatment-induced tumors:

- Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured.

- [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.]

Most tumors that develop from cancer chemotherapeutic agents respond well to treatment strategies.

III. ANTIMETABOLITES

- Antimetabolites are structurally related to normal compounds that exist within the cell.

- They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.

- Their maximal cytotoxic effects are in S-phase and are, therefore, cell cycle specific.

A. Methotrexate, pemetrexed, and pralatrexate

- The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication.

- *Methotrexate* (*MTX), pemetrexed , and pralatrexate* are antifolate agents.

1. Mechanism of action:

- ***MTX is structurally related to folic acid and*** acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4) (Figure 46.9).

- The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH2), or by administration of *leucovorin, which bypasses the blocked enzyme and replenishes* the folate pool (Figure 46.9).

- [Note: *Leucovorin, or folinic acid, is* the N5-formyl group–carrying form of FH4.]
- *MTX is specific for the* S-phase of the cell cycle.

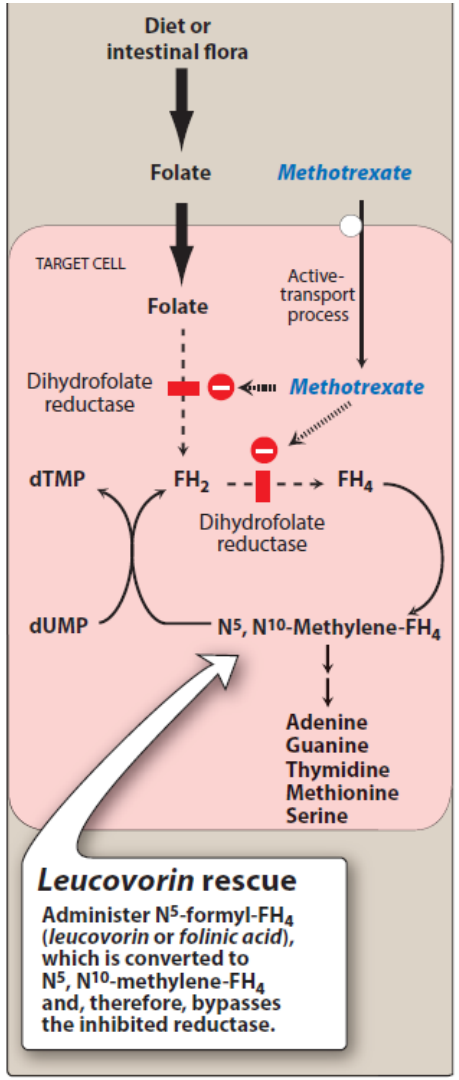


Figure 46.9
Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*. FH_2 = dihydrofolate; FH_4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate.

2. Therapeutic uses:

- ***MTX, usually in combination with other drugs,*** is effective against
  - acute lymphocytic leukemia,
  - Burkitt lymphoma in children,
  - breast cancer,
  - bladder cancer,
  - and head and neck carcinomas.

- In addition, low-dose *MTX is effective as a single agent* against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease.

- All patients receiving *MTX require close monitoring for possible toxic effects.*

3. Resistance:

- Nonproliferating cells are resistant to *MTX*
- Decreased levels of the *MTX* polyglutamate have been reported in resistant cells and may be due to its decreased formation or increased breakdown.
- amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme.
- The enzyme affinity for *MTX may also be* diminished.

- Resistance can also occur from a reduced influx of*MTX, apparently caused by a change in the carrier-mediated* transport responsible for pumping the drug into the cell.

4. Pharmacokinetics:

- MTX is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes .

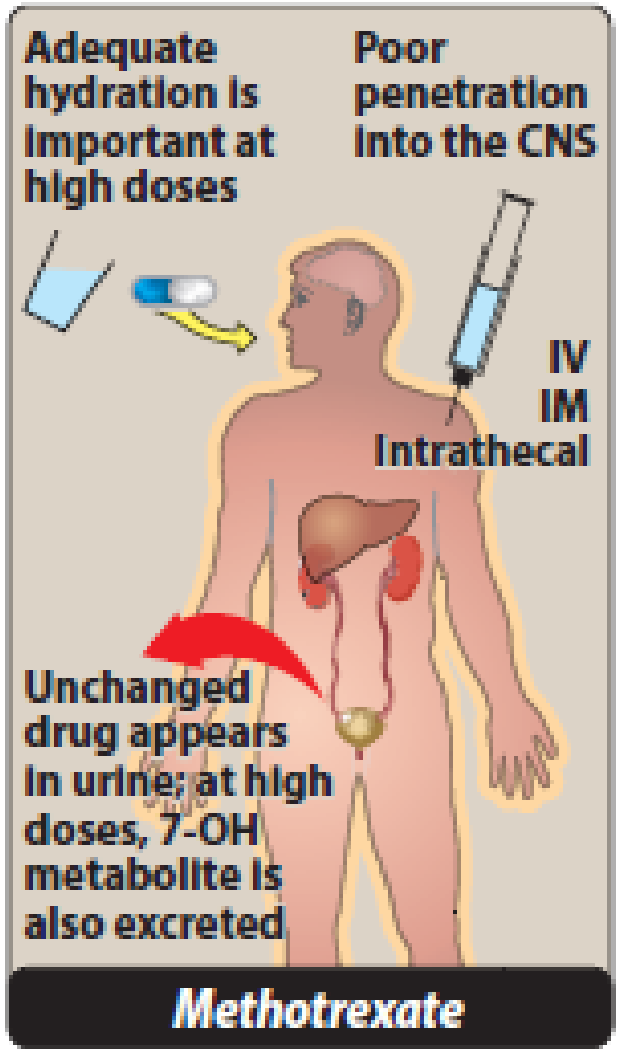
- Because *MTX* does not easily penetrate the blood–brain barrier, it can be administered intrathecally to destroy neoplastic cells that are thriving in the sanctuary of the CNS.

- *High* doses of *MTX undergo hydroxylation at the 7 position and become* 7-hydroxymethotrexate.

- This derivative is much less active as an antimetabolite.

- It is less water soluble than *MTX and may lead to* crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity.

- Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine,
- although some of the drug and its metabolite appear in feces due
- to enterohepatic excretion.


Adequate hydration is important at high doses
Poor penetration into the CNS
IV
IM
Intrathecal
Unchanged drug appears in urine; at high doses, 7-OH metabolite is also excreted
Methotrexate

5. Adverse effects:

- *Pemetrexed* should be given with folic acid and vitamin B12 supplements to reduce hematologic and GI toxicities.
- It is also recommended to pretreat with corticosteroids to prevent cutaneous reactions.
- One of the more common side effects of *pralatrexate* is mucositis.
- Doses must be adjusted or withheld based on the severity of mucositis.
- *Pralatrexate* also requires supplementation with folic acid and vitamin B12.

B. 6-Mercaptopurine

- *6-MP* and *6-thioguanine* were the first purine analogs to prove beneficial for treating neoplastic disease.

- [Note: *Azathioprine,* an immunosuppressant, exerts its cytotoxic effects after conversion to *6-MP*.]

- *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia. *6-MP* and its analog, *azathioprine,* are also beneficial in the treatment of Crohn disease.

1. Mechanism of action:

- *6-MP* must penetrate target cells and be converted to the nucleotide analog, 6-MP-ribose phosphate (better known as 6-thioinosinic acid or TIMP
- The addition of the ribose) phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine– guanine phosphoribosyltransferase (HGPRT).

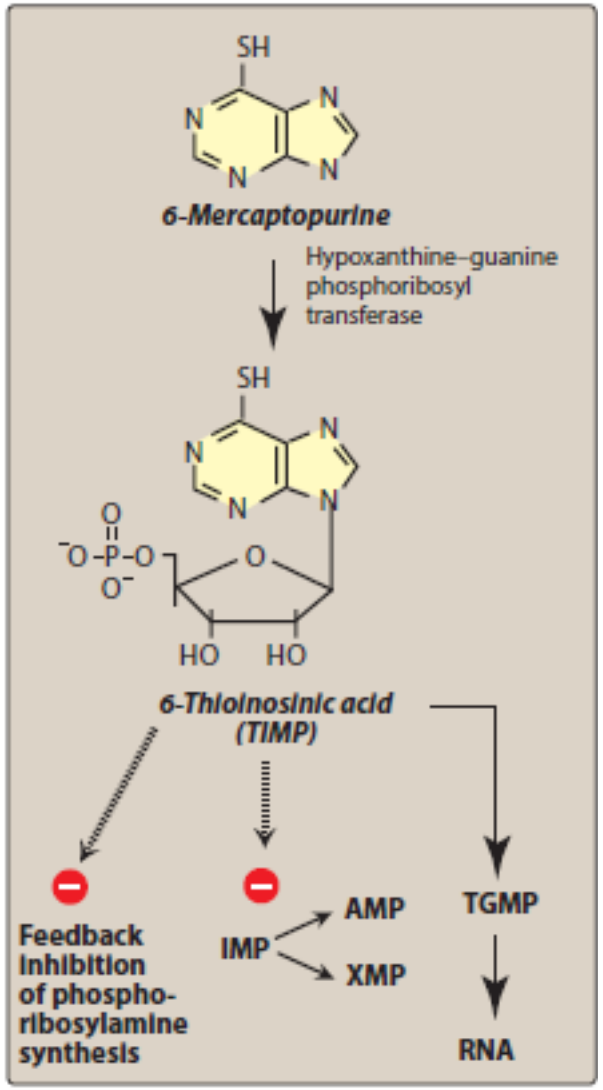


Figure 46.11
Actions of *6-mercaptopurine*. GMP = guanosine monophosphate; AMP = adenosine monophosphate; XMP = xanthosine monophosphate.

- A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP.
- TIMP is converted to thioguanine monophosphate, which after phosphorylation to di- and triphosphates can be incorporated into RNA.
- The deoxyribonucleotide analogs that are also formed are incorporated into DNA.
- This results in nonfunctional RNA and DNA.

Pharmacokinetics:

- Oral absorption is erratic and incomplete.
- the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF).
- The bioavailability of *6-MP* can be reduced by first-pass metabolism in the liver.
- *6-MP* is converted in the liver to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite).
- The parent drug and its metabolites are excreted by the kidney.

C. Fludarabine

- a purine nucleotide analog.
- It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma.
- Mechanism of action ◦ Not quite known ◦ The triphosphate is uptaken into DNA and RNA decreasing their synthesis in the S phase
- *Fludarabine* is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite.
- Urinary excretion accounts for partial elimination.

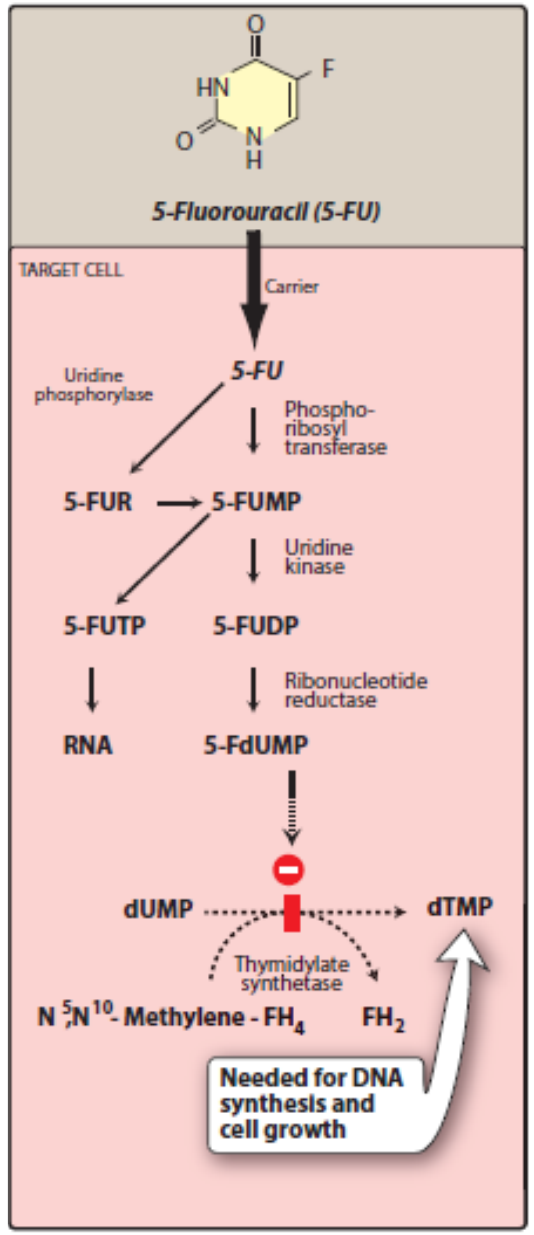
5-Fluorouracil

- a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring.

- The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the
- essential precursors for DNA synthesis.

- *5-FU* is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas).

- When applied topically, *5-FU* is also effective for the treatment of superficial basal cell carcinomas.


5-Fluorouracil (5-FU)
TARGET CELL
Carrier
5-FU
Uridine phosphorylase
Phospho-ribosyl transferase
5-FUR
5-FUMP
Uridine kinase
5-FUTP
5-FUDP
Ribonucleotide reductase
RNA
5-FdUMP
dUMP
dTMP
Thymidylate synthetase
N 5,N 10- Methylene - FH4
FH2
Needed for DNA synthesis and cell growth

3. Pharmacokinetics:

- Because of its severe toxicity to the GI tract, *5-FU* is given IV or, in the case of skin cancer, topically.

- The drug penetrates well into all tissues, including the CNS.

- *5-FU* is rapidly
- metabolized in the liver, lung, and kidney.

- The dose of *5-FU* must be adjusted in impaired hepatic function.

F. Capecitabine

- *Capecitabine* is a novel, oral fluoropyrimidine carbamate.
- It is used in the treatment of colorectal and metastatic breast cancer.
- After being absorbed, *capecitabine,* which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to *5-FU*.
- This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors.
- Thus, the cytotoxic activity of *capecitabine* is the same as that of *5-FU* and is **tumor specific**.
- The most important enzyme inhibited by *5-FU* is thymidylate synthase.

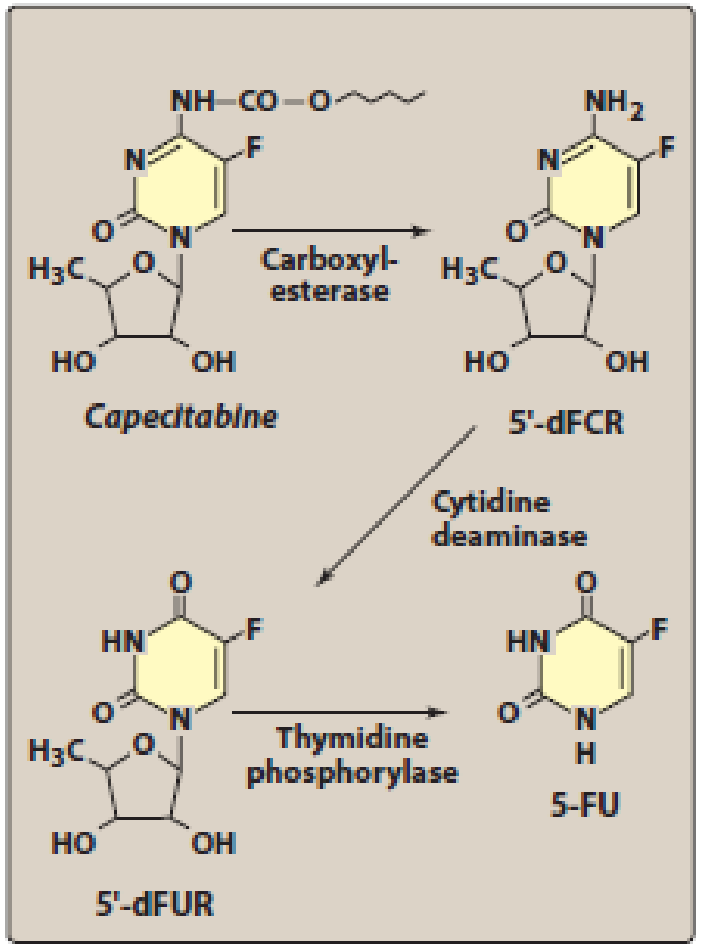


Figure 46.13
Metabolic pathway of *capecitabine* to *5-fluorouracil* (*5-FU*). 5′-dFCR = 5′-deoxy-5-fluorocytidine; 5′-dFUR = 5′-deoxy-5-fluorouridine.

G. Cytarabine

- *Cytarabine* acts as a pyrimidine antagonist.
- The major clinical use of *cytarabine* is in acute nonlymphocytic (myelogenous) leukemia (AML).
- *Cytarabine* enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form to be cytotoxic.
- , S-phase (and, hence, cell cycle) specific.

2. Pharmacokinetics:

- *Cytarabine* is not effective when given orally, because of its deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver.

- Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts.

- Therefore, it may also be injected intrathecally.

- *Cytarabine* undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite.
- Both *cytarabine* and ara-U are excreted in urine.

H. Azacitidine

- is a pyrimidine nucleoside analog of cytidine.
- It is used for the treatment of myelodysplastic syndromes and AML.
- *Azacitidine* undergoes activation and gets incorporated into RNA to inhibit RNA processing and function.
- It is S-phase cell cycle specific.

I. Gemcitabine

- is an analog of the nucleoside deoxycytidine.
- It is used most commonly for pancreatic cancer and non– small cell lung cancer.
- Resistance to the drug is probably due to its inability to be converted to a nucleotide, caused by an alteration in deoxycytidine kinase.
- In addition, the tumor cell can produce increased levels of endogenous deoxycytidine that compete for the kinase, thus overcoming the inhibition.
- *Gemcitabine* is infused IV.

IV. ANTIBIOTICS

- cytotoxic action due to interactions with DNA, leading to disruption of DNA function.

- In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect.

- They are cell cycle nonspecific with *bleomycin* as an exception.

A. Anthracyclines:

- **Doxorubicin,**
- **daunorubicin**
- **idarubicin,**
- **epirubicin, and**
- **mitoxantrone**

- Applications for these agents differ despite their structural similarity and their apparently similar mechanisms of action.

- *Doxorubicin* is one of the most important and widely used anticancer drugs.

- It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas.

- *Daunorubicin* and *idarubicin* are used in the treatment of acute leukemias, and *mitoxantrone* is used in prostate cancer.

Carcinoma

- Carcinoma refers to a malignant neoplasm of epithelial origin or cancer of the internal or external lining of the body.
- Carcinomas, malignancies of epithelial tissue, account for 80 to 90 percent of all cancer cases.
- Carcinomas are divided into two major subtypes:
- adenocarcinoma, which develops in an organ or gland, and squamous cell carcinoma, which originates in the squamous epithelium.

- Most carcinomas affect organs or glands capable of secretion, such as the breasts, which produce milk, or the lungs, which secrete mucus, or colon or prostate or bladder.
-

Sarcoma

- Sarcoma refers to cancer that originates in supportive and connective tissues such as
  - bones,
  - tendons,
  - cartilage,
  - muscle, and
  - fat.

- Generally occurring in young adults, the most common sarcoma often develops as a painful mass on the bone.
- Sarcoma tumors usually resemble the tissue in which they grow.

Mechanism of action:

- cytotoxicity through several different mechanisms.

- For example, *doxorubicin*-derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines

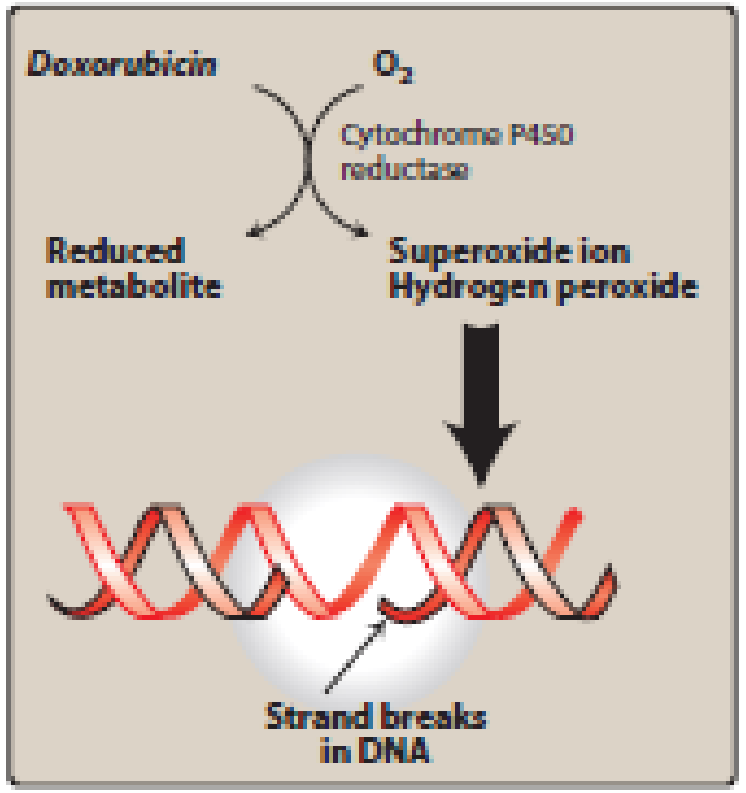


Figure 46.16

Doxorubicin interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

2. Pharmacokinetics:

- All these drugs must be administered IV, because they are inactivated in the GI tract.
- Extravasation is a serious problem that can lead to tissue necrosis.
- They bind to plasma proteins as well as to other tissue components, where they are widely distributed.
- They do not penetrate the blood–brain barrier or the testes.

- These agents undergo extensive hepatic metabolism, and dosage adjustments are needed in patients with impaired hepatic function.

- Biliary excretion is the major route of elimination.

- Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.

Adverse effects:

- Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction

- Addition of *trastuzumab* to protocols with *doxorubicin* or *epirubicin* increases congestive heart failure.

- There has been some success with the iron chelator *dexrazoxane* in protecting against the cardiotoxicity of *doxorubicin*.

- The liposomal-encapsulated *doxorubicin* is reported to be less cardiotoxic than the usual formulation.

B. Bleomycin

- *Bleomycin* cause scission of DNA by an oxidative process.

- *Bleomycin* is cell cycle specific and causes cells to accumulate in the G2 phase. It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma.

Mechanism of action:

A DNA–*bleomycin*–Fe^{2+} complex appears
to undergo oxidation to *bleomycin*–Fe^{3+}.

The liberated electrons
react with oxygen to form superoxide or hydroxyl radicals, which, in
turn, attack the phosphodiester bonds of DNA, resulting in strand
breakage and chromosomal aberrations (Figure 46.17).

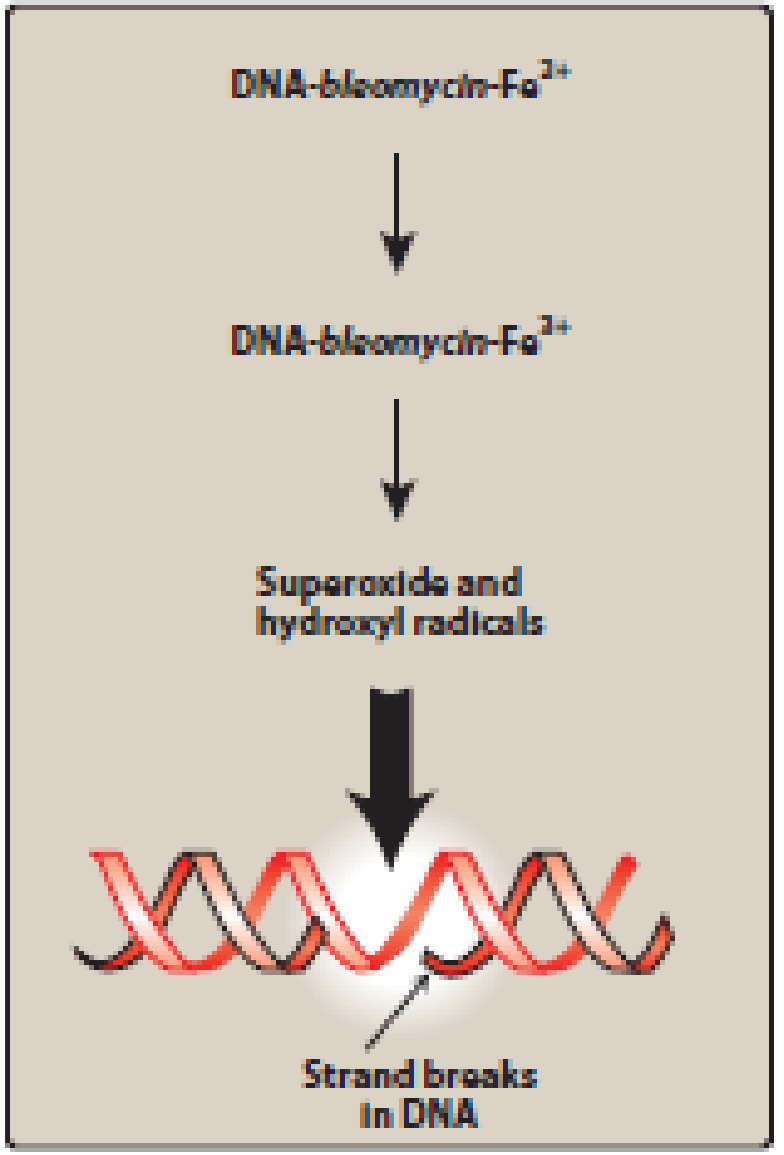


Figure 46.17
Bleomycin causes breaks in DNA by an oxidative process.

- *Bleomycin* is administered by a number of routes.

- The *bleomycin*-Inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in the lung and is absent in skin (accounting for the drug's toxicity in those tissues).

- Most of the parent drug is excreted unchanged in the urine, necessitating dose adjustment in patients with renal failure.

Adverse effects:

- Mucocutaneous reactions and alopecia are common.
- Hypertrophic skin changes and hyperpigmentation of the hands are prevalent.
- There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions.
- Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis.
- The pulmonary fibrosis that is caused by *bleomycin* is often referred as
- "bleomycin lung." *Bleomycin* is unusual in that myelosuppression is rare.

V. ALKYLATING AGENTS

- Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents.

- Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells.

- Alkylating agents do not discriminate between cycling and resting cells, even though they are most toxic for rapidly dividing cells.

- They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers.

- In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

Cyclophosphamide and ifosfamide

- They are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450).

- These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as
  - non-Hodgkin lymphoma,
  - sarcoma, and
  - breast cancer.

Mechanism of action:

- *Cyclophosphamide* is the most commonly used alkylating agent.
- They are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system .
- Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.
- The parent drug and its metabolites are primarily excreted in urine.

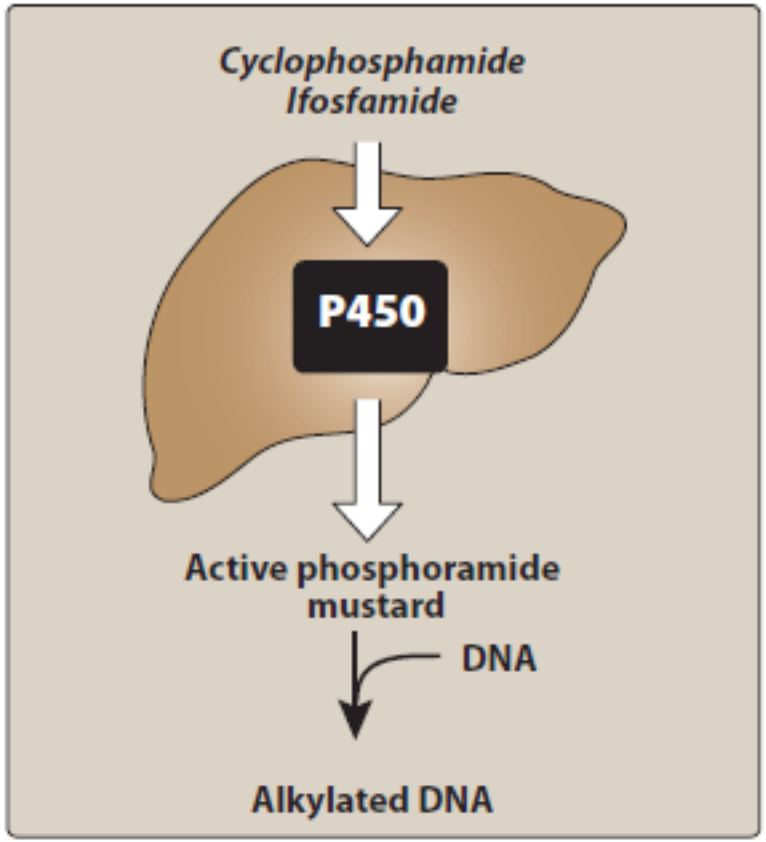


Figure 46.19
Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

Pharmacokinetics:

- *Cyclophosphamide* is available in oral or IV preparations, whereas *ifosfamide* is IV only.

- metabolized in the liver to active and inactive metabolites, and
- minimal amounts are excreted in the urine as unchanged drug.

Resistance:

- Resistance results from
  - increased DNA repair,
  - decreased drug permeability, and
  - reaction of the drug with thiols (for example, glutathione).

Adverse effects:

- A unique toxicity of both drugs is hemorrhagic cystitis, which can lead to fibrosis of the bladder.

- Adequate hydration as well as IV injection of mesna (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem.

- A fairly high incidence of neurotoxicity has been reported in patients on high-dose *ifosfamide*

B. Nitrosoureas

- *Carmustine* and *lomustine* are closely related nitrosoureas.

- Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

1. Mechanism of action:

- The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis.

- Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing.

2. Pharmacokinetics:

- **In spite of the similarities in their structures,** *carmustine is administered IV and as chemotherapy wafer* implants, whereas *lomustine is given orally.*

- *Because of their lipophilicity,* they distribute widely in the body, but their most striking property is their ability to readily penetrate the CNS.

- The kidney is the major excretory route for the nitrosoureas

VI. MICROTUBULE INHIBITORS

- The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells.

- The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin.

- The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides.

- Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized
- forms of the microtubules, thereby causing cytotoxicity.

A. Vincristine and vinblastine

- *Vincristine (VX) and vinblastine* (*VBL) are structurally related compounds derived from the periwinkle* plant, Vinca rosea.

- They are, therefore, referred to as the Vinca alkaloids.

- Although the Vinca alkaloids are structurally similar to one another, their therapeutic indications are different.

- *VX is used in the treatment of* acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas

- [Note: *VX (former trade* name, Oncovin) is the “O” in the R-CHOP regimen for lymphoma.

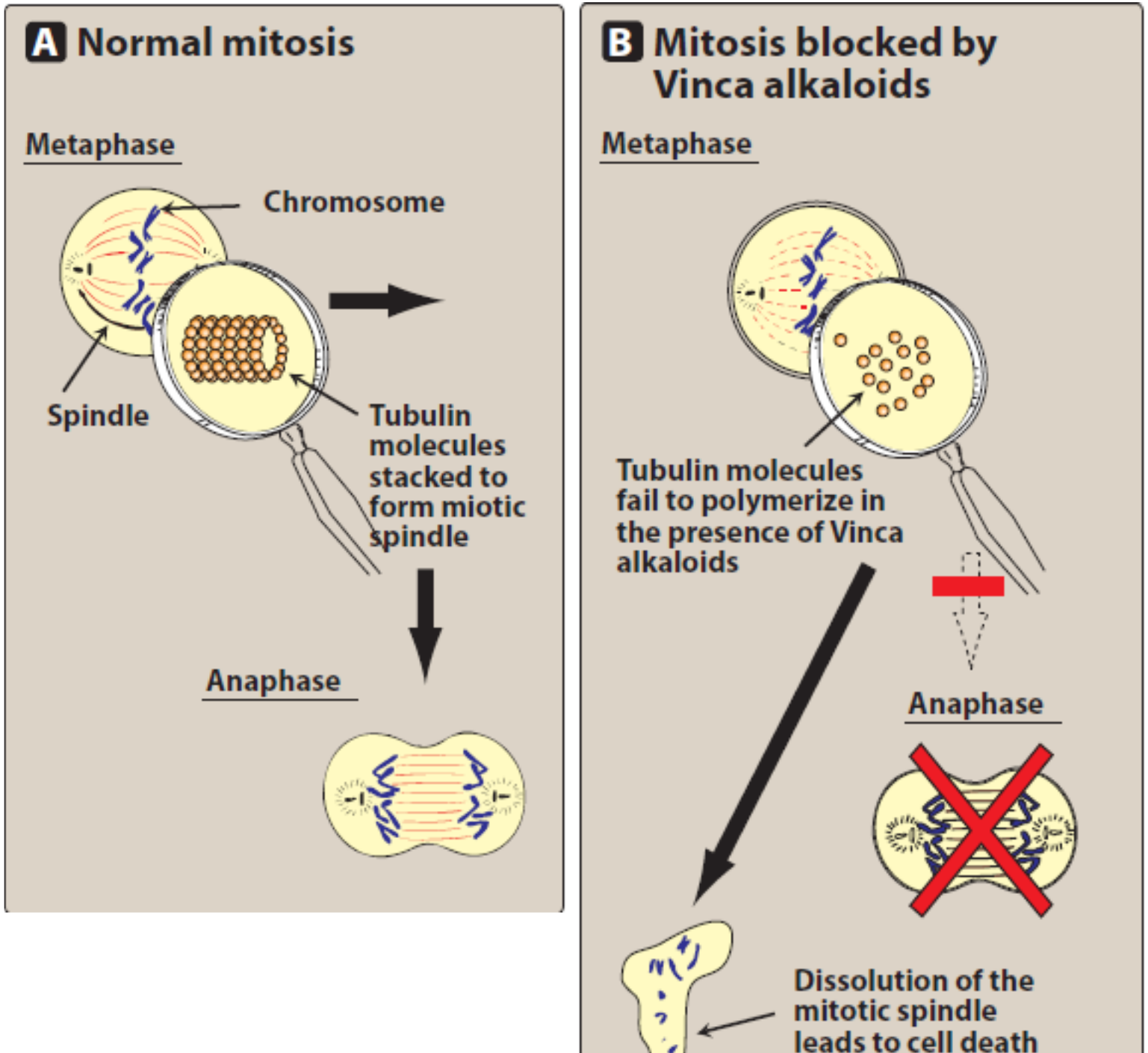
- Due to relatively mild myelosuppressive activity, *VX is used in a number of* other protocols.]

- *VBL is administered with bleomycin and cisplatin for* the treatment of metastatic testicular carcinoma.

- It is also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas.

Mechanism of action

- **They** are all cell cycle specific.
- Their binding to the microtubular protein, tubulin, blocks the ability of tubulin to polymerize to form microtubules.
- Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed.
- The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation


A Normal mitosis
Metaphase
Chromosome
Spindle
Tubulin molecules stacked to form miotic spindle
Anaphase
B Mitosis blocked by Vinca alkaloids
Metaphase
Tubulin molecules fail to polymerize in the presence of Vinca alkaloids
Anaphase
Dissolution of the mitotic spindle leads to cell death

Pharmacokinetics:

- IV injection of these agents leads to rapid cytotoxic effects and cell destruction.

- The Vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway and eliminated in bile and feces.

- Doses must be modified in patients
- with impaired hepatic function or biliary obstruction.

3. Adverse effects:

- phlebitis or cellulitis, if the drugs extravasate during injection, as well as
- nausea, vomiting, diarrhea, and alopecia.

- *VBL* is a more potent myelosuppressant than *VX*, whereas
- peripheral neuropathy is associated with *VX*.

- Constipation is more frequently encountered with *VX*.

- These agents should not be administered intrathecally.
- This potential drug error can result in death, and special precautions
- should be in place for administration.

B. Paclitaxel and docetaxel (taxanes)

- *Paclitaxel* was the first member of the taxane family to be used in cancer chemotherapy.
- A semisynthetic *paclitaxel* is now available through chemical modification of a precursor found in the needles of Pacific yew species.
- Substitution of a side chain has resulted in *docetaxel*, which is the more potent of the two drugs.
- *Paclitaxel* has shown good activity against advanced ovarian cancer and metastatic breast cancer.
- Favorable results have been obtained in non–small cell lung cancer when administered with *cisplatin*.
- *Docetaxel* is commonly used in prostate, breast, GI, and non–small cell lung cancers.

Mechanism of action

- Both drugs are active in the G2/M-phase of the cell cycle, but unlike the Vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly, leading to the accumulation of microtubules. The
- overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur.

- This results in death of the cell.

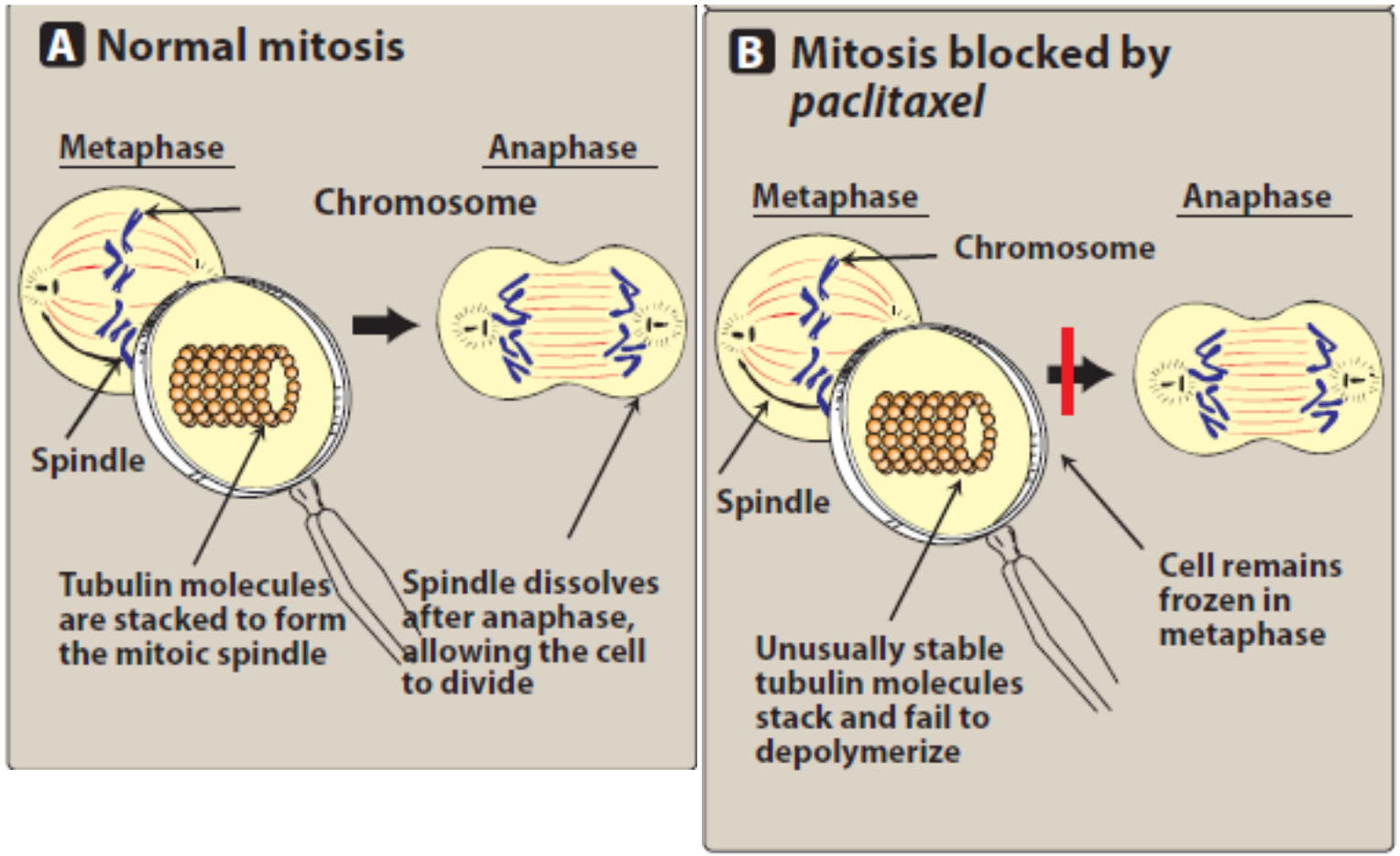


Figure 46.24

Paclitaxel stabilizes microtubules, rendering them nonfunctional.

Pharmacokinetics:

- These agents undergo hepatic metabolism by the CYP450 system and are excreted via the biliary system.

- doses should be reduced in patients with hepatic dysfunction.

3. Adverse effects:

- The dose-limiting toxicities of *paclitaxel* and *docetaxel* are neutropenia and leukopenia.

- Alopecia occurs, but vomiting and diarrhea are uncommon.

- [Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), patients who are treated with *paclitaxel* should be premedicated with *dexamethasone* and *diphenhydramine*, as well as with an H2 blocker.]

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Vincristine	IV	Neurotoxicity, constipation	*Phenytoin, phenobarbital, carbamazepine*, azole antifungal drugs	CBC, hepatic function, peripheral neuropathy	Vesicants, IT administration may result in death.
Vinblastine	IV	Myelosuppression, neurotoxicity		CBC, hepatic function	
Vinorelbine	IV	Granulocytopenia			
Paclitaxel	IV	Neutropenia, neurotoxicity, alopecia, N, V	*Repaglinide, gemfibrozil, rifampin* (CYP2C8)	CBC, hepatic function, peripheral neuropathy	Hypersensitivity reactions (dyspnea, urticaria, hypotension), require premedications
Docetaxel	IV	Neutropenia, neurotoxicity, fluid retention, alopecia, N, V, D	*Ketoconazole, ritonavir* (CYP3A4)		

IV= intravenous; IT=intrathecal; N=nausea; V=vomiting; D=diarrhea; CBC=complete blood count.

VII. STEROID HORMONES AND THEIR ANTAGONISTS

- Tumors that are steroid hormone sensitive may be either
  - 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; or
  - 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or
  - 3) both.

- Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by
  - surgery (for example, in the case of orchiectomy—surgical removal of one or both testes—for patients with advanced prostate cancer) or by
  - drugs (for example, in breast cancer, for which treatment with the antiestrogen *tamoxifen* is used to prevent estrogen stimulation of breast cancer cells;

- For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone

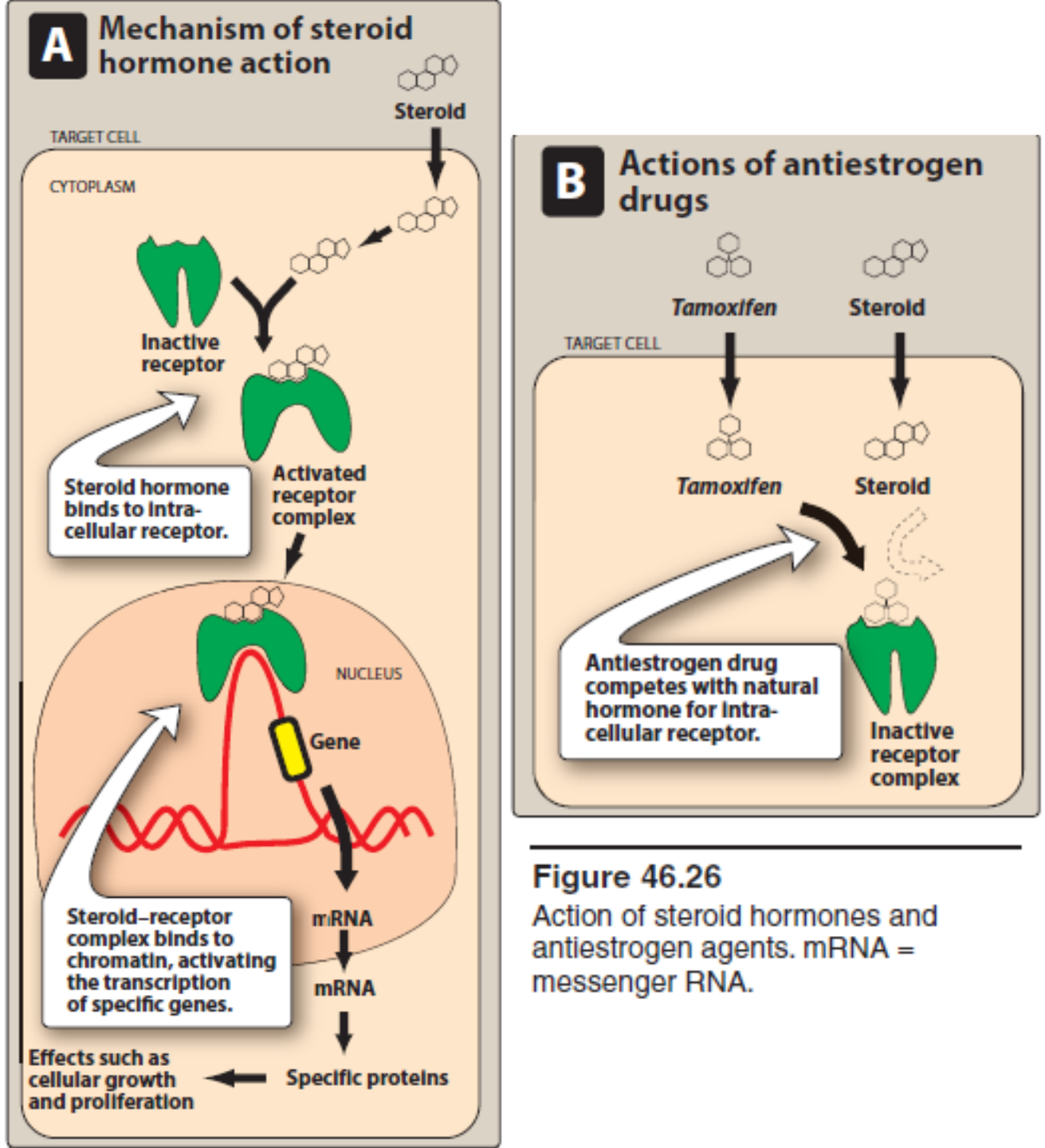


Figure 46.26
Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA.

A. Prednisone

- *Prednisone* [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than *cortisol*.
- [Note: At high doses, *cortisol* is lymphocytolytic and leads to hyperuricemia due to the breakdown of lymphocytes.]
- *Prednisone* is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin and non-Hodgkin lymphomas.
- *Prednisone* itself is inactive and must first undergo 11-β-hydroxylation to *prednisolone* in the liver.
- *Prednisolone* is the active drug.

B. Tamoxifen

- *Tamoxifen* is an estrogen antagonist with some estrogenic activity, and it is classified as a selective estrogen receptor modulator (SERM).
- It is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer.
- It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk.
- However, because of possible stimulation of premalignant lesions due to its estrogenic properties, patients should be closely monitored during therapy.

1. Mechanism of action:

- *Tamoxifen* binds to estrogen receptors in the breast tissue, but the complex is unable to translocate into the nucleus for its action of initiating transcriptions.

- That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 46.26B).

- The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed.

- [Note: Estrogen competes with *tamoxifen*. Therefore, in premenopausal women, the drug is used with a gonadotropin releasing hormone (GnRH) analog such as *leuprolide,* which lowers estrogen levels.]

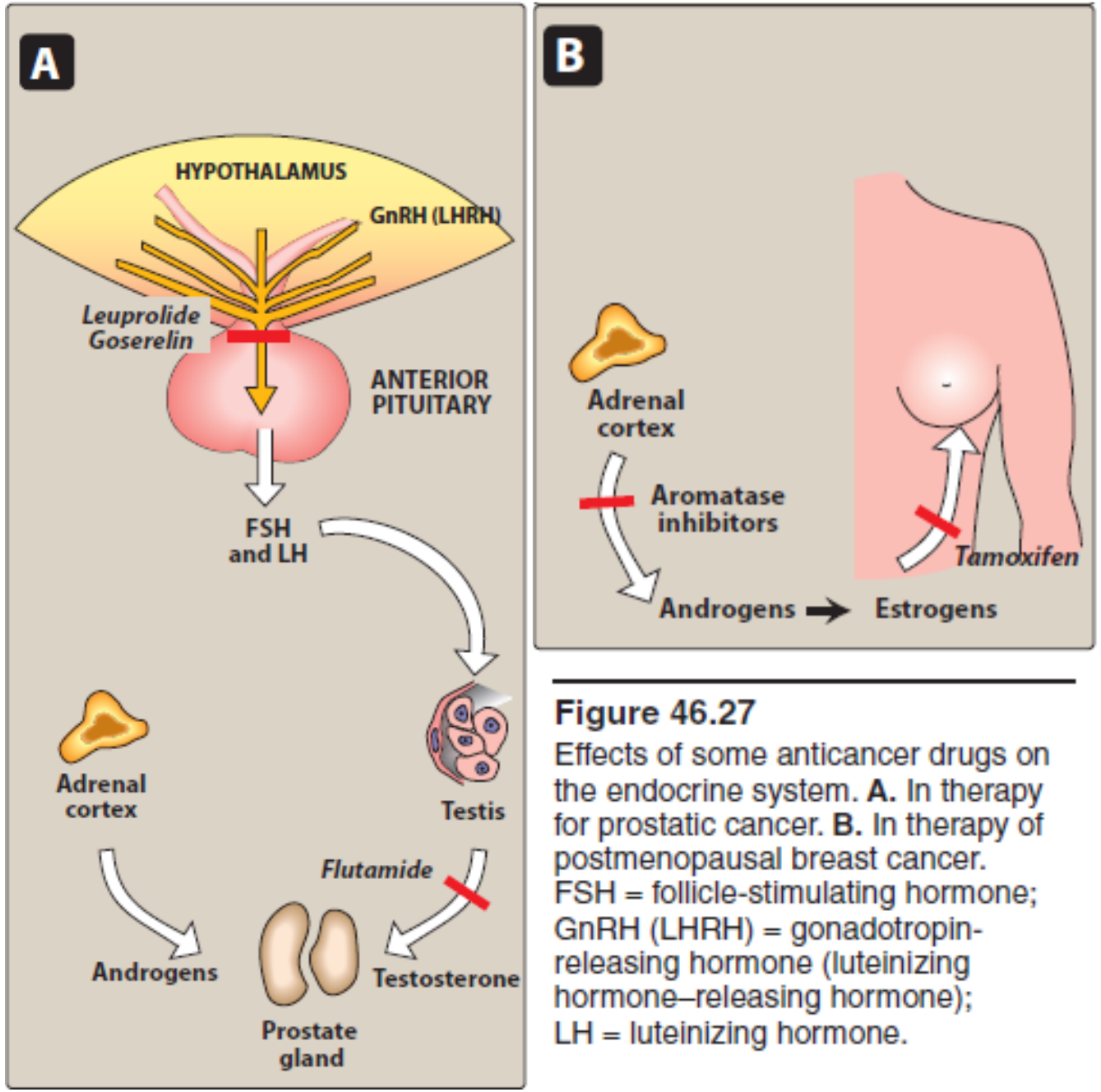


Figure 46.27

Effects of some anticancer drugs on the endocrine system. **A.** In therapy for prostatic cancer. **B.** In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH (LHRH) = gonadotropin-releasing hormone (luteinizing hormone–releasing hormone); LH = luteinizing hormone.

2. Pharmacokinetics:

- *Tamoxifen* is effective after oral administration.
- It is partially metabolized by the liver.
- Some metabolites possess antagonist activity, whereas others have agonist activity.
- Unchanged drug and metabolites are excreted predominantly through the bile into the feces.
- *Tamoxifen* is an inhibitor of CYP3A4 and P-glycoprotein.

3. Adverse effects:

- Side effects caused by *tamoxifen* include hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites).

- Hypercalcemia may occur, requiring cessation of the drug.

- *Tamoxifen* can also lead to increased pain if the tumor has metastasized to bone. *Tamoxifen* has the potential to cause endometrial cancer.

- Other toxicities include thromboembolism and effects on vision. [Note: Because of a more favorable adverse effect profile, aromatase inhibitors are making an impact in the treatment of breast cancer.]

D. Aromatase inhibitors

- The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies.

- Peripheral aromatization is an important source of estrogen in postmenopausal women.

- Aromatase inhibitors decrease the production of estrogen in these women.

1. Anastrozole and letrozole:

- nonsteroidal aromatase inhibitors.
- They do not predispose patients to endometrial cancer
- Although *anastrozole* and *letrozole* are considered second-line therapy after *tamoxifen* for hormone dependent breast cancer in the United States, they have become first-line drugs in other countries for the treatment of breast cancer in postmenopausal women.
- They are orally active and cause almost a total suppression of estrogen synthesis.
- Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

2. Exemestane:

- A steroidal, irreversible inhibitor of aromatase, *exemestane* is orally well absorbed and widely distributed.
- Hepatic metabolism is by the CYP3A4 isoenzyme.
- Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure.
- Its major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

E. Progestins

- *Megestrol acetate is a progestin that was widely used* in treating metastatic hormone-responsive breast and endometrial neoplasms.

- It is orally effective.

- Other agents are usually compared to it in clinical trials; however, the aromatase inhibitors are replacing it in therapy.

F. Leuprolide, goserelin, and triptorelin

- GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones:
  - 1) luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and
  - 2) follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen

- *Leuprolide ,goserelin*, and *triptorelin are synthetic analogs of* GnRH.

- they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH.

- Thus, both androgen and estrogen syntheses are reduced.

- Response to *leuprolide in prostatic cancer* is equivalent to that of orchiectomy with regression of tumor and relief of bone pain.

- These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer.

- *Leuprolide is available as*
  - *1) a* sustained-release intradermal implant,
  - 2) a subcutaneous depot injection, or
  - 3) an intramuscular depot injection to treat metastatic carcinoma of the prostate.

- *Goserelin acetate is a subcutaneous implant,* and *triptorelin pamoate is injected intramuscularly.*

- *Levels of androgen* may initially rise but then fall to castration levels.

- The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

G. Estrogens

- Estrogens, such as *ethinyl estradiol, had been used in the treatment* of prostatic cancer.
- However, they have been largely replaced by the GnRH analogs because of fewer adverse effects.
- Estrogens inhibit the growth of prostatic tissue by blocking the production of LH, thereby decreasing the synthesis of androgens in the testis.
- Thus, tumors that are dependent on androgens are affected.
- Estrogen treatment can cause serious complications, such as thromboemboli, myocardial infarction, strokes, and hypercalcemia.Men who are taking estrogens may experience gynecomastia and impotence.

H. Flutamide, nilutamide, and bicalutamide

- *They are synthetic, nonsteroidal* antiandrogens used in the treatment of prostate cancer.
- They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus.
- These antiandrogens are taken orally and are cleared through the kidney.
- Side effects include gynecomastia and GI distress. Rarely, liver failure has
- occurred with *flutamide. Nilutamide can cause visual problems.*