Chapter 14

Medicinal Chemistry

THE MAIN IDEA

Medicines are like keys that unlock various biological responses.

14.3 Chemotherapy

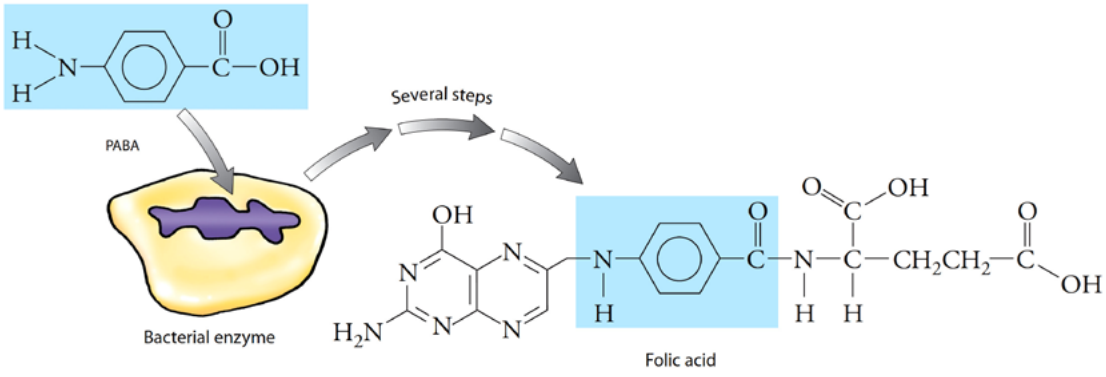
The use of drugs that destroy disease-causing agents without doing excessive harm to the host is known as **chemotherapy**. This approach is effective in the treatment of many diseases, including bacterial and viral infections, as well as cancer. It works by taking advantage of the ways a disease-causing agent is different from the host.

READING CHECK

How does chemotherapy work?

Sulfa Drugs and Antibiotics

Developed in the 1930s, *sulfa drugs* were the first drugs used effectively to treat bacterial infections. They work by taking advantage of a striking difference between humans and bacteria. Both humans and bacteria must have the nutrient *folic acid* in order to remain healthy. While we humans can obtain folic acid from what we eat, bacteria cannot absorb folic acid from outside sources. Instead, bacteria must make their own supply of folic acid. For this, they possess receptor sites that help make folic acid from a simpler molecule found in all bacteria, para-aminobenzoic acid (PABA). The PABA attaches to the specific receptor site and is converted to folic acid, as shown in **Figure 14.6**.



< Figure 14.6

Bacterial enzymes use para-aminobenzoic acid (PABA) to synthesize folic acid.

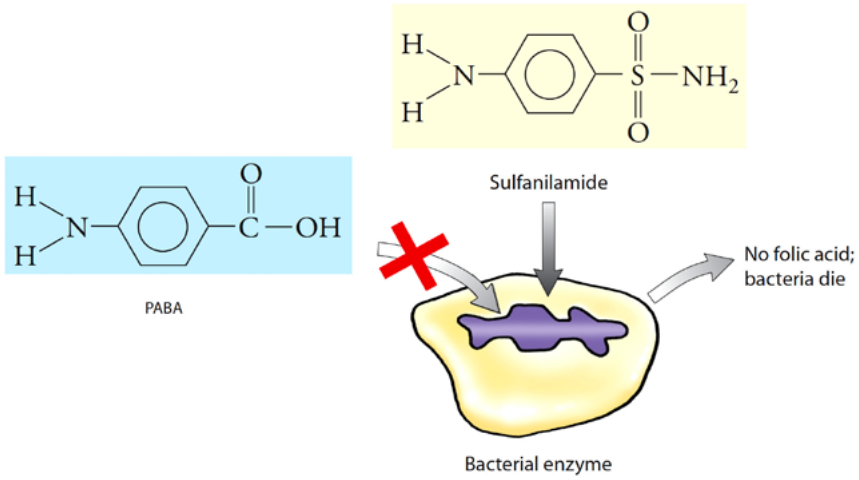


Figure 14.7 >

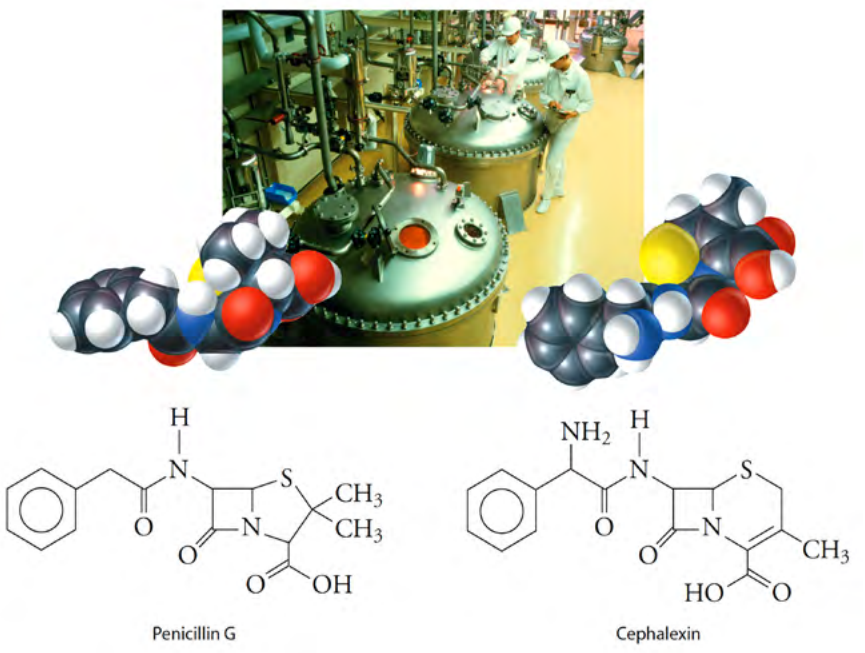
In the body, sulfa drugs are transformed into sulfanilamide, which binds to the bacterial receptor sites and keeps them from doing their job

Sulfa drugs have a close structural resemblance to PABA. When taken by a person suffering from a bacterial infection, a sulfa drug is transformed by the body into the compound *sulfanilamide*, which attaches to the bacterial receptor sites designed for PABA, as shown in **Figure 14.7**. This prevents the bacteria from synthesizing folic acid. Without folic acid, the bacteria soon die. The patient, however, lives on because folic acid is part of their diet.

Microorganisms such as molds, fungi, and even bacteria have evolved to produce chemicals, known as *antibiotics*, that prevent the growth of bacteria. Penicillin was the first antibiotic discovered. Many derivatives of penicillin, such as the penicillin G shown in **Figure 14.8**, have since been isolated from microorganisms as well as prepared in the laboratory. Penicillins and the closely related compounds known as cephalosporins, also shown in Figure 14.8, kill bacteria by inactivating receptor sites responsible for strengthening the bacterial cell wall. With this receptor site inactivated, bacterial cell walls grow weak and eventually burst.

Figure 14.8 >

Penicillins, such as penicillin G, and cephalosporins, such as cephalexin, as well as most other antibiotics, are produced by microorganisms that can be mass-produced in large vats. The antibiotics are then harvested and purified.



CONCEPT **CHECK**

How is sulfanilamide poisonous to bacteria but not to humans?

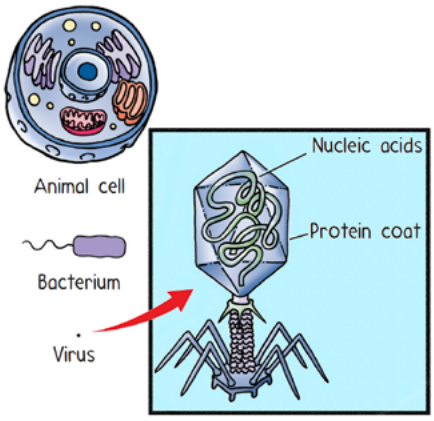
CHECK YOUR ANSWER Sulfanilamide is poisonous to bacteria because it prevents them from synthesizing the folic acid they need to survive. Humans utilize folic acid from their diet, so they are not bothered by sulfanilamide's ability to disrupt the synthesis of folic acid.

Chemotherapy Can Inhibit the Ability of Viruses to Replicate

So far, chemotherapy has been more successful in treating bacterial infections than in treating viral infections. Perhaps the greatest obstacle to effective viral treatment lies in the nature of viruses. When not attached to a host, a virus is an inert, lifeless bundle of biomolecules—and it's difficult to kill something that's not alive! A typical virus, shown in **Figure 14.9**, consists of only one strand or several strands of either RNA or DNA encapsulated in a protein coat. Some viruses infect the host by attaching to a cell and then injecting their genetic contents. Once inside the cell, the virus's genetic information is incorporated into the host DNA and replicated by the machinery of the host cell. Eventually, the cell bursts because it is overstuffed with a multitude of viral replicates, which then spread to infect other host cells.

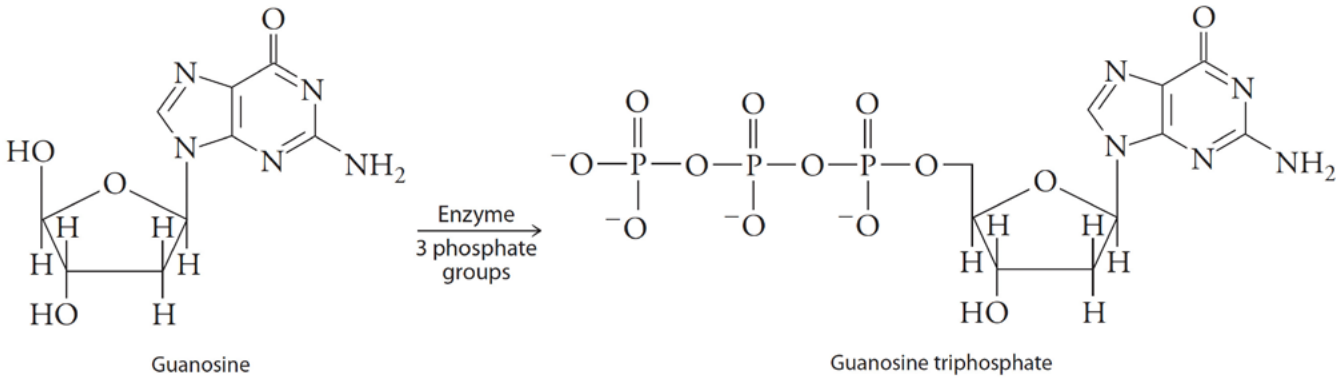
Most common antiviral drugs are derivatives of *nucleosides*, which are similar to nucleotides (Section 13.5) but without a phosphate group. Nucleosides roam freely in all cells and are used by the cells to create RNA or DNA. Before being used, however, the nucleosides must first be primed with three phosphate groups, as shown in **Figure 14.10**.

Various synthetic derivatives of nucleosides are readily primed by virus-infected cells but not by uninfected cells. Two synthetic nucleoside derivatives, both shown in **Figure 14.11**, are acyclovir, sold under the trade name Zovirax®, and zidovudine, sold under the trade name AZT. Once incorporated in the RNA or DNA of a virus-infected host cell, these nucleoside derivatives disrupt protein synthesis, and the infected cell dies before replicating the virus. Proliferation of the virus, although not halted, is thus brought under control.



Λ Figure 14.9

Viruses are much smaller than bacteria and many times smaller than animal cells. (Notice the small dot representing the virus.) The smallest of all pathogens, viruses consist mostly of nucleic acids enclosed in a protein coat.

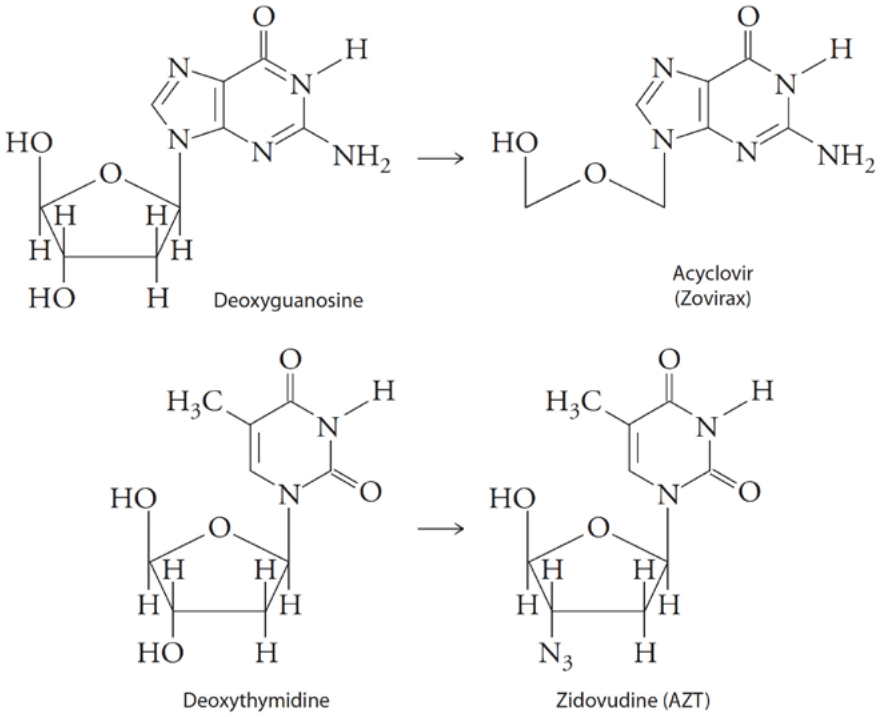


Λ Figure 14.10

Before a nucleoside such as guanosine can be incorporated into RNA or DNA, it must be activated through the attachment of three phosphate groups.

Figure 14.11 >

Acyclovir (Zovirax®) is a derivative of the nucleoside deoxyguanosine, and zidovudine (AZT) is a derivative of the nucleoside deoxythymidine.

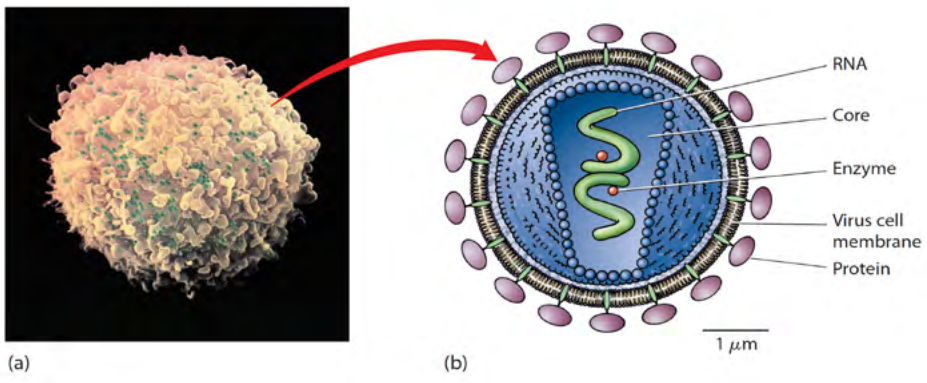


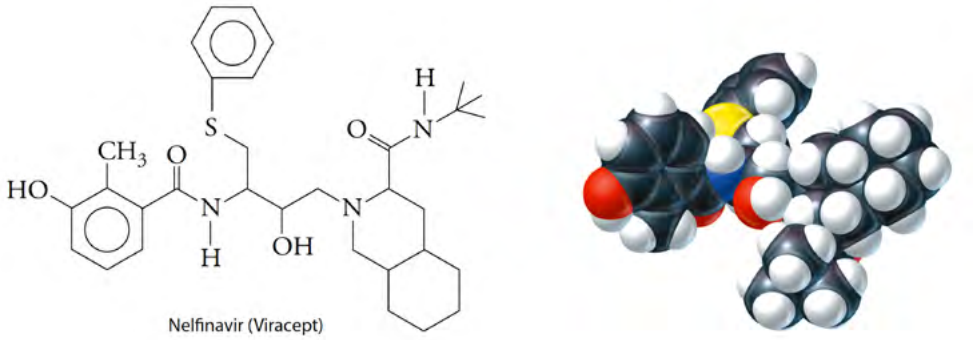
Acyclovir is useful in the treatment of herpes. Oral herpes is caused by the herpes simplex virus 1 (HSV-1), and genital herpes is caused by the herpes simplex virus 2 (HSV-2). More than 90 percent of the world's population is infected with the oral herpes virus, although many infected people do not exhibit symptoms. Genital herpes is the most prevalent non-curable sexually transmitted disease. In the United States, about 30 million people are infected with HSV-2 and an estimated 200,000 to 500,000 new cases are seen each year. Zidovudine is used to suppress the replication of the human immuno-deficiency virus (HIV), which is responsible for acquired immune deficiency syndrome, AIDS (**Figure 14.12**). According to the World Health Organization, as of 2020, about 38 million people were living with an HIV infection.

HIV research has led to a new class of antiviral agents known as *protease inhibitors*. The life cycles of many viruses, including HIV, depend on the actions of enzymes known as proteases, which break down proteins. A protease, for example, might be used by a virus to penetrate the proteins on the cell membrane of a host cell or to break down the host's polypeptides to create a supply of amino acids necessary for viral replication. Drugs that block the action of proteases control viral proliferation. Nelfinavir, sold under the trade name Viracept®, is an example of an effective protease inhibitor

Figure 14.12 >

(a) The small green bodies covering this white blood cell are human immunodeficiency viruses. (b) The anatomy of HIV. After the initial infection, the infected person's immune response eliminates most of the virus. Some of the virus, however, remains dormant in infected cells and evades the immune response. Over a period of years, HIV reactivates itself, the immune system collapses, and the person succumbs to opportunistic diseases such as cancer and pneumonia.





< Figure 14.13

The protease inhibitor nelfinavir.

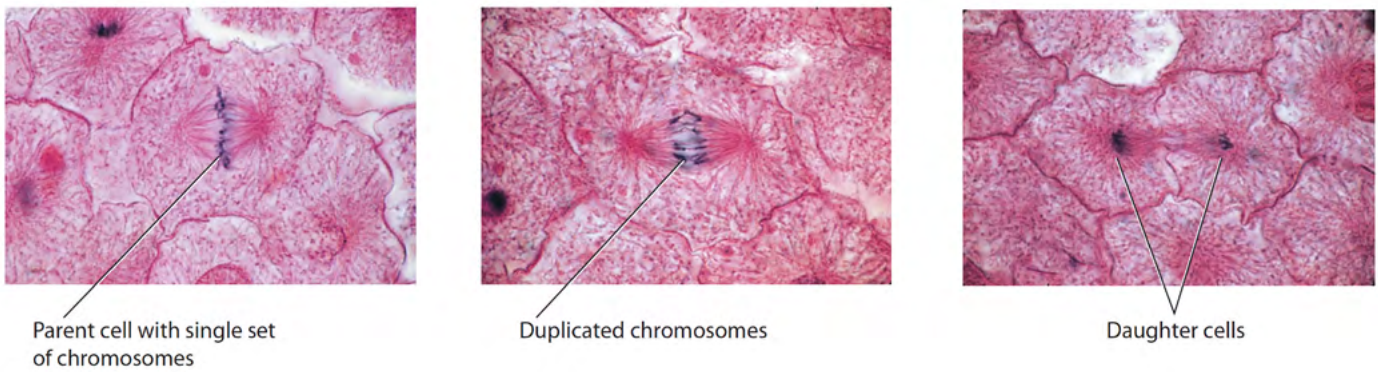
and is shown in **Figure 14.13**. Patients receiving a "cocktail" of a protease inhibitor and nucleoside antiviral agents may have their HIV counts brought below detectable levels. Although it is unlikely that this regimen can totally eliminate HIV from an infected person, the highly reduced viral counts tend to significantly delay or prevent the onset of AIDS and reduce the patient's infectiousness to others.

Protease inhibitors used to fight HIV infection have been developed also to fight Covid-19 infections. This is particularly the case with the Pfizer drug Paxlovid®, which contains the protease inhibitor ritonavir. When taken soon after an infection, this chemotherapy has been shown to reduce the need for hospitalization.

Cancer Chemotherapy Targets Rapidly Growing Cells

Cells periodically lose the ability to control their own growth and begin multiplying faster than they should. Normally, the immune system recognizes these renegade cells and destroys them. Occasionally, however, they escape this line of defense and continue to multiply unchecked. The result can be a mass of tissue, called a *tumor*, that deprives healthy cells of oxygen and nutrients or causes other problems. Cells from a tumor may break away and be carried to other sites in the body, where they lodge and continue to multiply, forming additional tumors. As tumors multiply, more and more healthy cells are damaged and eventually die. Ultimately, the whole body may die. This is the process of cancer, the second leading cause of death in most developed nations. At present mortality rates, one in six of us will die of this disease.

Chemotherapy is most effective at the early stages of cancer, because drugs work best on cells that are in the process of dividing, a process called *cellular mitosis*, shown in **Figure 14.14**. When a tumor is young, most of



Λ Figure 14.14

During cellular mitosis, DNA and certain cellular proteins bundle together into chromosomes, which are visible under a microscope. These chromosomes duplicate themselves and then divide evenly into two separate cells called "daughter cells."

FOR YOUR INFORMATION

An unusual feature of the herpes viruses is their preference for nerve cells. Stress to the nervous system, such as emotional stress or sunburn, can cause the virus to replicate, which leads to an outbreak through the skin. When they are not replicating, these viruses remain in nerve cells, where they are not detected by the body's immune system, which has little activity in nerve cells. While remaining dormant in the nervous system, the viruses evade not only the immune system but also antiviral drugs.

CONCEPT **CHECK**

A virus is so much simpler than a bacterium. Why then are viruses so much more difficult to target with chemotherapeutics?

CHECK YOUR ANSWER Chemotherapeutics act by interfering with one or more of the chemical reactions a pathogen needs in order to exist. The more complex a pathogen, the more ways there are to interfere with its life cycle. The fact that viruses are so simple means we have few avenues for a chemotherapeutic approach.

its cells are undergoing mitosis. As the tumor ages, however, the fraction of cells in this growth phase decreases, reducing drug sensitivity. Drugs also have a difficult time destroying all cells in a large tumor. A 100-gram tumor, for example, may contain about 100 billion cells. Killing 99.9 percent of these cells would still leave 100 million cells—too many for the patient's immune response to control. The same treatment against a 50-milligram tumor containing about a million cells would leave only about 1000 cells, which can be controlled by the immune system. Survival rates from cancer are therefore greatly increased by early diagnosis. Hence, you are advised to keep close watch on your body for unusual signs and schedule regular checkups with your physician.

Unfortunately, cancerous cells are not the only cells in the body that divide. Normal cells divide periodically, and some types of cells, such as those in the gastrointestinal tract and in hair follicles, are always in a state of cellular division. As a consequence, many cancer chemotherapeutics are noted for their toxicity; patients undergoing treatments often experience gastrointestinal problems and hair loss.

DNA is the target of many anticancer compounds, because during cellular mitosis, strands of DNA are unwound and therefore susceptible to chemical attack. A variety of chemicals may be used to selectively kill cells that are in the process of dividing. The compound 5-fluorouracil, for example, shown in **Figure 14.15**, is mistaken by a cell for the nucleotide base uracil. Once incorporated into the DNA of the cancerous cell, 5-fluorouracil's non-nucleotide structure interferes with the normal DNA workings, and the cell dies. Harsher agents, such as cyclophosphamide and cisplatin, also shown in Figure 14.15, destroy DNA's ability to function by chemically

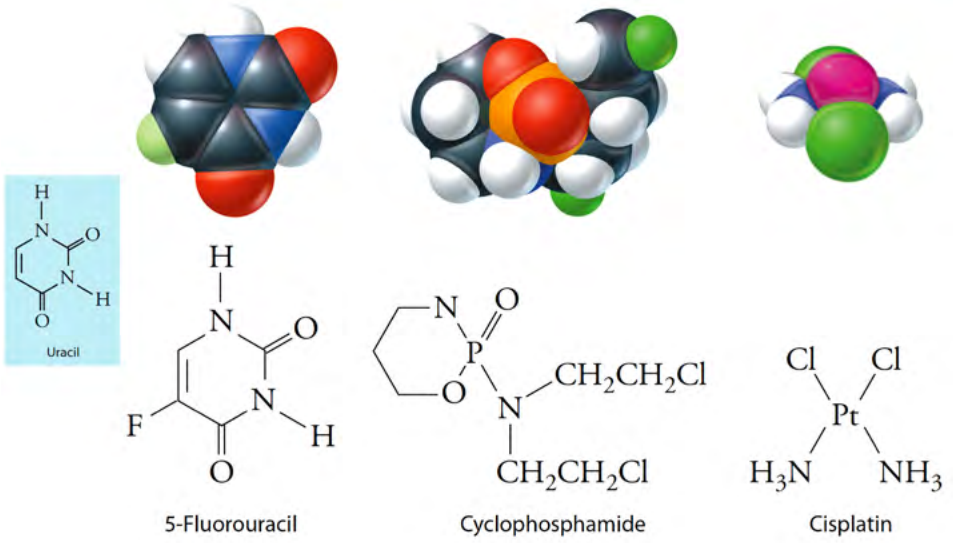
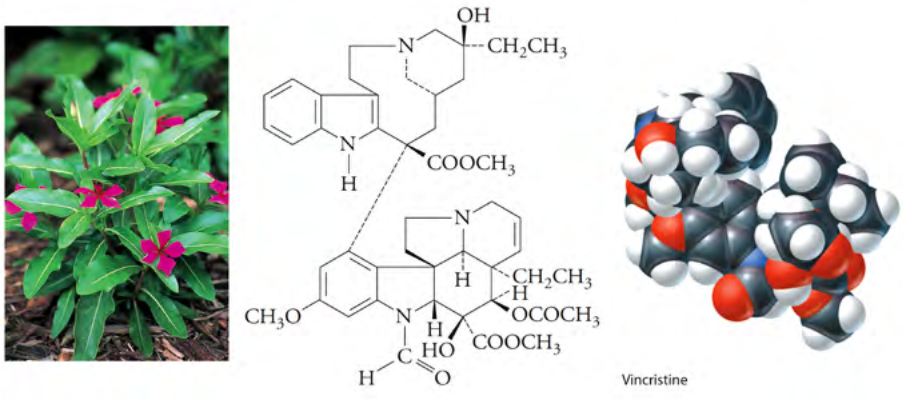


Figure 14.15 >

These anticancer agents kill dividing cells by targeting the cells' DNA.



< Figure 14.16

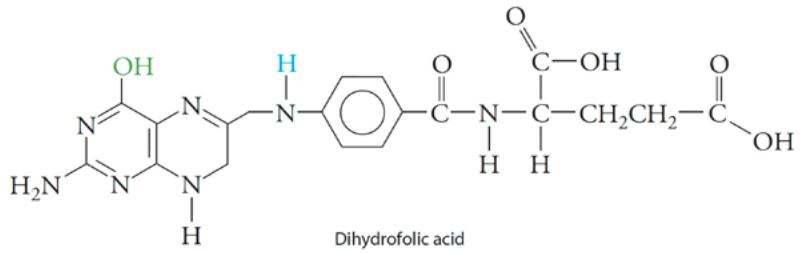
Vincristine is a naturally occurring alkaloid that shows significant anticancer activity. It is isolated from a plant closely related to the periwinkle, a common ornamental plant of tropical and temperate regions.

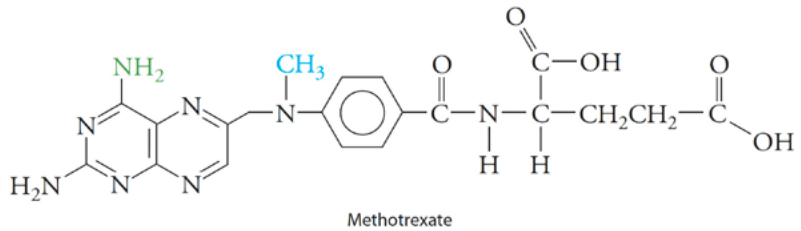
bonding to the DNA or by cross-linking the two strands of the double helix.

Some anticancer drugs kill cancerous cells without acting on DNA. Certain alkaloids, such as vincristine, shown in **Figure 14.16**, and paclitaxel of Figure 14.4, kill dividing cells by preventing the formation of cellular microstructures they need for division.

As another point of attack, cancerous cells have high metabolic rates, which means they rely heavily on biochemical nutrients, such as the dihydrofolic acid shown in **Figure 14.17**. The anticancer agent methotrexate is structurally very similar to dihydrofolic acid and works by binding to dihydrofolic acid receptor sites in the cancerous cells, thereby interfering with metabolic reactions in the cells.

The high metabolism of cancer cells means they also need to be fed an adequate supply of blood—a source of both nutrients and oxygen. The growth of a tumor, therefore, requires that new blood vessels be allowed to grow alongside new tumor cells. The growth of new blood vessels is called *angiogenesis*. Drugs blocking the growth of new blood vessels are called *angiogenesis inhibitors*. Some powerful angiogenesis inhibitors have been developed that selectively bind to a protein that cancer cells need to promote angiogenesis. Upon binding, the inhibitor deactivates the protein. This shuts down the growth of new blood vessels into the tumor, which begins to shrink as cancer cells die from a lack of blood. Importantly, angiogenesis inhibitors are also being developed to inhibit angiogenesis in fat cells to help treat people with obesity.



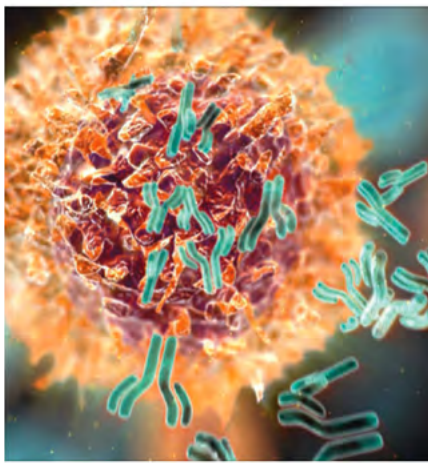


< Figure 14.17

Methotrexate disturbs the metabolism of cancerous cells by substituting for dihydrofolic acid at dihydrofolic acid receptor sites

FOR YOUR INFORMATION

The microorganism, Bugula neritina, is a common marine fouling agent that coats surfaces such as the hull of a boat. This species also produces small quantities of a structurally complex molecule, Bryostatin, which shows much biological activity. This includes awakening HIV from its defensive dormant phase and thus making this virus susceptible to antivirals. Bryostatin's toxicity, however, is limiting. Further, this molecule is difficult to isolate and difficult to synthesize in the laboratory. That said, this is a classic example of where nature has given us a valuable head start in our search for effective chemotherapeutics.



∧ Figure 14.18

Antibodies are Y-shaped macromolecules that are a frontline defense in a person's immune system. Once an antibody binds to a pathogen, a cascade of events leads to the destruction of the pathogen.

fyi FOR YOUR INFORMATION

There are over 200 different types of cancer, which can affect nearly any type of body tissue. Of all the forms of cancer, about half of the newly diagnosed cases each year in the United States are non-melanoma skin cancers. Lung cancer is next in frequency, with over 200,000 new cases in the United States each year. The deadliest form of cancer is pancreatic cancer, which has a 1-year survival rate of about 3 percent. One of the main reasons for this low survival rate is that it is often asymptomatic until it has reached a late, or "advanced," stage. Regular health check ups are the best defense.

Figure 14.19 >

The amino acid chains of a renegade protein that causes a cancerous proliferation of blood cells are shown in blue and pink. This protein is formed from a certain mutation of DNA. The Gleevec® molecule, shown in gold, binds to receptor sites of this protein, rendering it defunct.

The angiogenesis inhibitors just described are examples of monoclonal antibodies, which have much potential in treating many different kinds of cancer. An antibody is a protein macromolecule the body produces to identify and then destroy an infectious agent, such as a bacterium or virus and even a cancer cell (**Figure 14.18**). Antibodies specific for certain cancer cells, called *monoclonal antibodies*, can be created in the laboratory. The term monoclonal means these antibodies are identical clones of each other, which means they can be produced in quantities sufficient for clinical use. The monoclonal antibody rituximab, for example, is effective at killing cancerous cells of certain lymphomas. Although not a cure, the rituximab helps to maintain a state of remission.

Cancer chemotherapy combined with radiation therapy and/or surgery can be effective in minimizing the growth of or even curing many forms of cancer. As our understanding of cellular mechanics continues to grow, so will our ability to increase the overall survival rates of cancer patients. A case in point lies with chronic myeloid leukemia, CML, a form of cancer in which certain blood cells proliferate because of an abnormal protein produced by a DNA mutation. From a mapping of the receptor sites on this protein, scientists were able to design a molecule, called Gleevec®, that binds to these receptor sites, as shown in **Figure 14.19,** and inhibits their functioning. Although not a cure for this once very deadly cancer, Gleevec® stops the progression of this disease and related diseases, with remarkable 5-year survival rates of around 95 percent. There are many forms of cancer, each with its own unique biochemistry. As Gleevec® demonstrates, our best hope lies not with a single magic bullet, but in our ability to learn the details of each cancer's biochemistry. From what we learn, we are then empowered to develop targeted treatments. Much progress is being made in this arena of what is sometimes called "targeted chemotherapy." As further examples, search online for information on BTK inhibitors, BCL-2 inhibitors, CAR-T Cell Therapy, CAR-NK Cell Therapy, and bispecific antibodies. Many of the recent agents are stunning in their curative capabilities. That's good chemistry.