12

Opiates and Opioids

The patience of a poppy.
He who has smoked will smoke.
Opium knows how to wait.

—*Jean Cocteau (1968, p. 36)*

The drugs in this class are referred to either as *opiates* or *opioids*. These terms refer to any drug, either natural or synthetic in origin, that has properties similar to opium or its main active ingredient, morphine. (Technically, the term *opiate* should be used only to refer to drugs of natural origin, i.e., derived from opium, and *opioid* should be used in reference to all opiate-like drugs, including the opiates and synthetic drugs, but often this distinction is not made.) This text will use the term *opioid* in a generic sense to refer to all drugs in this class.

This family of drugs is also frequently referred to as *narcotic analgesics* or just *narcotics*. Technically, a narcotic is a drug that causes sleep. The narcotic analgesics produce *analgesia* (loss of sensitivity to pain) and make a person sleepy. This name distinguishes these drugs from *nonnarcotic analgesics*, such as aspirin, which do not cause sleep. One difficulty with the word *narcotic* is that over the years, it has acquired a new meaning and is now commonly used to refer to the habit-forming property of a drug. It has also developed a distasteful connotation; calling a drug a *narcotic* immediately conjures up visions of degenerate and depraved addicts who are slaves to the drug and its suppliers. This misuse of the term has been given legal sanction, further increasing the confusion. In the United States, the Harrison Narcotic Act of 1914 defined both marijuana and cocaine as narcotics, along with opiates. In Canada, a so-called Narcotic Control Act regulates the use of many habit-forming drugs, some of which, like marijuana, are not narcotics at all in the sleep-production sense, but in a legal sense they have become "narcotics."

Because it has so many meanings, the term *narcotic* will be avoided here. The term *opioid* will be used instead.

ORIGINS AND SOURCES OF OPIOIDS

Natural and Semisynthetic Opioids

The main natural source of *opium* is a poppy (*Papaver somniferum*). This poppy had its origins in Asia Minor but is now grown in countries with

similar climates throughout the world. On only 10 days in its life cycle, the plant manufactures the drug, which must be gathered then. Opium is the sap that exudes out of scratches made in the seedpods of the poppy after the petals have fallen off. The scratches are made one day; the next day, the sap is scraped off and compressed into cakes. This is *opium*.

There are several active ingredients in opium. The two main ones are *morphine*, which accounts for 10 percent of the weight of opium, and *codeine*, which makes up only 0.5 percent. Morphine was first isolated from opium by the German chemist Frederick Serturner. He called it "morphium" after Morpheus, the Greek god of dreams, and published his findings in 1803. The significance of the finding was not immediately recognized, but in 1831, he was awarded a prize by the Institute of France for his discovery. Also in the 1830s, morphine was first manufactured and sold commercially. Codeine was isolated in 1821 by Pierre J. Robiquet while he was experimenting with a new process for isolating morphine.

Heroin is a semisynthetic opiate made by adding two acetyl groups to the morphine molecule (*diacetylmorphine* or *diamorphine*). Heroin is about 10 times more lipid soluble than morphine and, therefore, gets to the brain faster and in higher concentrations.

Morphine is widely used in medicine and is usually sold as a salt under its generic name *morphine sulfate*. In the United States, morphine and codeine are legally available only on prescription. In Canada, the same is true for morphine, but codeine is available in small quantities, without a prescription, in some over-the-counter painkillers and cough medicines. Heroin is illegal and cannot be prescribed or used in the United States. For some restricted purposes, it may be used in Canada on an experimental basis. It may also be prescribed in the United Kingdom under certain conditions.

Synthetic Opioids

A number of drugs bear little chemical resemblance to morphine but appear to have similar pharmacological and behavioral effects and to work at the same receptor, although they are not all as effective at the receptor as morphine, and some are much more effective. The best known of these is *meperidine*, which is sometimes called *pethidine* (Demerol). It is similar to morphine but shorter acting. *Methadone* (Dolophine) and *LAAM* (l-alpha-acetylmethadol) have a much longer duration of action than morphine and are much more effective when given orally. Other synthetics are *fentanyl* (Sublimaze), *levorphanol* (Levo-Dromoran), *pentazocine* (Talwin), *phenazocine* (Narphen), and *propoxyphine* (Darvon). Another opioid that is widely used both as a medicine and on the street is *oxycodone*. It is sold as Percocet (if it is mixed with acetaminophen) or Percodan (if it is mixed with aspirin). A much more notorious formulation of oxycodone is OxyContin, a tablet that contains many times the oxycodone of a regular tablet but in a slow-release form. It is designed to give long-term pain relief to arthritis sufferers, but if the tablet is crushed, dissolved, and injected, it can create severe addiction and has caused many accidental overdoses. All these drugs are available only on prescription in most countries.

Over the years, clandestine laboratories have synthesized many "designer drugs" based on the fentanyl molecule, *China White* being the best known. Another notorious designer drug was created in an attempt to synthesize pethidine. This resulted in the accidental production of MPTP, which was metabolized into a toxin that destroyed the substantia nigra, part of the extrapyramidal motor system that provides dopamine stimulation of the basal ganglia. The result was what has been called the "frozen addict," a person with severe symptoms of Parkinson's disease.

Another opioid of interest is dextromethorphan, a common ingredient in cough-suppressant medicines like Robitussin. Apart from the ability to suppress coughing, dextromethorphan is a unique opioid in that it does not have an effect on opioid receptors. Instead, it appears to have effects similar to PCP (phencyclidine). For this reason it will be discussed separately in Chapter 16.

Opioid Antagonists and Mixed Agonist-Antagonists

Several synthetic drugs act as antagonists to opioids. One, *naloxone*, is a pure antagonist that will block the action of any other opioid. Others, such as *nalorphine* and *cyclazocine*, have some opioid activity of their own but will antagonize other opioids. (We will return to the neurophysiology of opioids and opioid receptors later.)

HISTORY

It is believed that the opium poppy was being cultivated in the western Mediterranean region in the sixth millennium B.C., and opium capsules found in grass bags in Neolithic burial sites in northern Spain dated to about 4200 B.C. (Rudgley, 1995). The earliest written reference to opium is a Sumerian idiogram that is translated as "joy plant." The use of this symbol has been dated to about 4000 B.C. Opium is also mentioned frequently in Assyrian medical tablets dating from the seventh century B.C. These tablets are probably copies of earlier manuscripts. Originally wild, the opium poppy was being cultivated in Assyria and Babylon by the second century B.C. By this time as well, opium use had spread throughout the Middle East and North Africa. It was mentioned in the Ebers Papyri, early Egyptian medical scrolls dating to 1550 B.C. In these early writings, the poppy is mentioned primarily as a medicine, but the nonmedical properties of the plant were certainly appreciated.

The ancient Greeks knew of opium as well. The Greek physician Hippocrates recommended the use of opium for a number of conditions, as did the Roman physicians Pliny and Galen and the Arabian physician Avicenna, who recommended it for diseases of the eye and diarrhea.

The use of opium spread from the Middle East in every direction with the expansion of the Islamic religion. It was carried east to India by Arab traders in the ninth century and then from India to China, where it was used primarily as a medicine and taken orally. Later, when tobacco smoking was banned by a Chinese emperor in 1644, the Chinese filled their pipes with opium and invented the practice of opium smoking, a very efficient drug delivery system that ensured the popularity of the drug in that country.

The Arabs traded opium, along with spices and other goods, with the merchants of Venice. In the early part of the sixteenth century, Europeans became aware of opium primarily through the efforts of traveling physicians. A Swiss doctor known as Paracelsus traveled throughout Europe and carried opium in the pommel of his saddle. He called it "the stone of immortality." Other physicians quickly adopted the drug and prescribed it in various forms to their patients, with great success. John Sydenham, an English physician, wrote in 1680, "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal or so efficacious as opium."

Throughout the seventeenth and eighteenth centuries, the popular use of opiates grew steadily, but in the nineteenth century, there was a drastic increase in the British consumption of opium. In 1825, the opium consumption rate was between 1 and 2 pounds per 1,000 population, but at its peak in 1875 the rate was greater than 10 pounds per 1,000 population. Opium was available in many formulations from food stores, pubs, and even peddlers on the streets. The most popular form in which opium was sold was tincture of opium, or laudanum, which was opium dissolved in alcohol.

About this time, morphine became available. Morphine, however, remained more under the control of the medical profession and, unlike opium, was never widely sold in shops. This restriction did not hinder its popularity; physicians generally prescribed it when requested. Because the lower classes seldom saw a doctor, morphine was more commonly used by the middle and upper classes.

Although many people were openly addicted to the drug, it was not perceived as a medical or social problem at the beginning of the nineteenth century. Not until the 1830s did all this opium use generate any concern, and not until 1868 was any legislative effort made to control it. The regulatory change was brought about by the development of

social and political ideas rather than medical research or theory.

The availability of the drug was recognized as the main problem. In 1868, the British Parliament passed the Pharmacy Act, which made pharmacists' shops the only legal source of opiates and was the first of several laws that slowly brought the use of opiates under the control of the medical profession and out of the hands of the people. It also marked the start of the belief—a new idea at the time—that addiction was a medical problem and should be handled by physicians.

The story of opiate use in the United States is somewhat different. Americans were just as fond of opiates as the British. In 1870, when British consumption peaked at over 10 pounds per 1,000 population, American consumption rates were greater than 13 pounds per 1,000. Some of this was consumed orally in the form of patent medicines; the majority was refined into morphine and injected by means of the recently developed hypodermic syringe. This route of administration may have become popular because of the wide use of morphine during the Civil War, when morphine addiction became known as "the army disease." In 1914, Congress passed the Harrison Narcotic Act, which, in effect, made it illegal to be an addict and illegal for physicians to prescribe opiates to addicts.

Heroin

Heroin was invented in 1898 by Heinrich Dreser and marketed by the Bayer company of Germany. Dreser was the inventor of aspirin. He had discovered that if he took salicylic acid, an effective but corrosive painkiller, and added an acetyl group to the basic molecule, he could reduce its corrosive properties. The result was acetylsalicylic acid (ASA, originally trademarked as *Aspirin*). Having made a great deal of money with aspirin, Dreser thought he might try the same trick with the morphine molecule and made *diacetylmorphine* (or diamorphine), which the Bayer company marketed as *Heroin*. The name was derived from the German *heroisch*, meaning "heroic," to imply concentrated power. Early tests showed that heroin was more effective as an analgesic than morphine but did not cause as much nausea and vomiting. It was advertised in newspapers and magazines and sold freely as sort of a superior aspirin. Bayer also claimed that heroin was not addictive, and, surprisingly, this was believed by the medical profession for many years.

It did not take long for the morphine users to discover heroin. They soon found that heroin could be sniffed into the nostrils and did not always require injections. This fact and the relative lack of nausea must have enhanced its appeal to casual users. By the 1920s, the newspapers associated heroin with crime, industrial unrest, and a series of Bolshevik bombings, so in 1924 it was banned totally by Congress. It became illegal for doctors to prescribe it for any reason. This law and the Harrison Act are still in effect today in the United States.

Excellent sources of information on the fascinating history of opiates are J. M. Scott (1969), Latimer and Goldberg (1981), and Berridge and Edwards (1981).

ROUTES OF ADMINISTRATION

Morphine is a base with a pKa of about 8. Consequently, it is not rapidly absorbed from the digestive system because most of its molecules are ionized in acid pHs. Even though opium eating (or drinking) is common and morphine is frequently given in oral medications, opiates given by the oral route are much less effective than the same dose given parenterally. In addition to slow absorption, morphine given orally is subject to significant metabolism on its first pass through the liver, before it can get to the brain (Goth, 1984). Opioids are frequently given as analgesics, and the slowness of the absorption from the digestive system is an advantage because by using this route, it is easier to maintain constant drug levels in the blood (Melzack, 1990).

When the drug is administered for its subjective effects, most users prefer parenteral routes, which cause sudden high levels that appear to be the most reinforcing. Heroin, but not morphine, can be taken intranasally in the form of snuff. Many years ago, the Chinese developed a method

of smoking opium in a pipe. More recently, the AIDS epidemic has made many people reluctant to use needles, and a newer form of smoking has been developed, called "chasing the dragon." Oil-rich, relatively pure heroin is heated on metal foil until it vaporizes. The user then inhales it through a tube, chasing the smoke so as not to miss any (Schuckit, 1993). This appears to be an efficient way to get the drug into the body. Anywhere between 17 and 63 percent of heated heroin is vaporized, depending on whether it is a salt or freebase, on the temperature, and on the airflow (Meng, Litchman, Bridgen, & Martin, 1997).

The two most important opioid antagonists, nalorphine and naloxone, are poorly absorbed from the digestive system and are usually administered parenterally. Maximum brain levels are reached in 15 to 60 minutes.

DISTRIBUTION

After absorption into the blood, most opioids are concentrated in the lungs, liver, and spleen, and a large percentage is bound to blood proteins. Opioids readily pass through the placental barrier into the fetus, but most are slow getting through the blood–brain barrier because they have poor lipid solubility.

The heroin molecule is highly lipid soluble and, therefore, gets into the brain quickly and in high concentrations. The heroin molecule is inactive in the brain, but it is rapidly converted into its metabolites, morphine and monoacetylmorphine, in high concentrations. As a result, heroin is about 10 times more potent than morphine (Inturrisi et al., 1983). Codeine also appears to have little direct action on receptors in the brain and has its effect through metabolites, the main one being morphine.

It also appears that the brain is able to eliminate opioids by an active transport mechanism. These two factors combine to keep brain levels of opioid low relative to the levels in other body tissues. Within the brain, opioids are concentrated in the basal ganglia, the amygdala, and the periaqueductal gray, an area closely associated with the sensation of pain. The opioid antagonists enter the brain much more quickly than morphine and reach higher concentrations there.

EXCRETION

About 10 percent of morphine is excreted in the urine unchanged. The remainder is turned into various metabolites that are eliminated in the urine and in the feces through concentration in the bile. The half-life of morphine is about 2 hours; the half-life of codeine is about 3 to 6 hours. Ninety percent of morphine is eliminated within 24 hours of administration (Creasey, 1979).

Meperidine is extensively metabolized in the liver, and the metabolites are eliminated by the kidneys. It has a half-life of 3½ hours. Methadone is not completely metabolized; about 10 percent is eliminated unchanged in the urine. Compared to other opioids, it has an extremely long half-life of 10 to 25 hours because methadone becomes bound extensively to blood proteins and is not available for metabolism. This long duration of action makes methadone ideal for maintenance therapies. At low doses, methadone is excreted primarily in the feces, but at higher doses, more and more methadone is found in the urine. An even longer half-life has been reported for another synthetic opioid, l-alpha-acetylmethadol (LAAM). LAAM itself is not active, but two of its metabolites are.

Naloxone is completely metabolized in the liver and has a half-life of about 1½ hours, although its effects may be shorter than this since the drug is rapidly redistributed to body fat. This may be of concern when naloxone is being used to treat an opioid overdose. Its effects may rapidly disappear, and the opioid overdose effects may unexpectedly return (Clarke, Dargan, & Jones, 2005).

NEUROPHYSIOLOGY

Scientists had been certain for many years that opioids worked at receptor sites because their activity seemed to be related to their molecular configuration, and there was competitive antagonism of their effects. But until the early 1970s, no

one had ever found an opioid receptor in the body, nor had any endogenous substance been found in the brain that might work as an opioid receptor. In 1973, however, three laboratories independently identified specific receptors for opioids in the brains of rats. This discovery stimulated considerable research, and there has been a veritable explosion of data on opioid receptors since that time. Opioid receptors have now been found in the brains of most vertebrates, from hagfish to humans.

If the brain is equipped with receptors for opioids, it is likely that the brain has opiate-like substances of its own. A search for such a substance was begun. Within 2 years of the discovery of opioid receptors, six naturally occurring opioids had been isolated from the brains of several different species of animals, including humans. One of the researchers, Eric J. Simon (1981), proposed the name *endorphins* for these substances. He derived this name from the words *endogenous* and *morphine*. The endogenous opioids are derived from a polypeptide: a string of amino acid molecules. Two of these opioid-acting polypeptides are short strings, five amino acids long, called the *enkephalins*. The longer chains are 16 to 30 amino acids long and are more properly referred to as the endorphins. Many more endorphins have now been isolated, and their molecular structure is now understood (Snyder, 1977). All of these strings of amino acids have been identified as segments of a large molecule called *beta-lipotropin*, 91 amino acids long, which is secreted by the pituitary gland.

In general, endorphins are found in the areas of the brain that are rich in opioid receptors and are known to be stored in synaptic vesicles, so it might be reasonable to suppose that endorphins are neurotransmitters, but other roles have been postulated for them as well. It is known that the presence of an endorphin interferes with the release of other neurotransmitters, such as norepinephrine, dopamine, and acetylcholine, and that opioid receptors are located on presynaptic membranes. These discoveries suggest that the endorphins work as neuromodulators by influencing the presynaptic membranes of other synapses. It is also known that endorphins are released into the blood by the pituitary gland for general distribution around the body, like other pituitary hormones. Opioid receptors are known to exist outside the nervous system in areas such as the intestines; these might be the targets for the endorphins acting as hormones.

Opioid Receptors

There appear to be at least three types of opioid receptors in the brain, referred to as mu (m), kappa (k), and delta (δ). These receptors differ in their distributions and in their affinities for endogenous opioids. The mu receptor has a diffuse distribution throughout the limbic system, including the hippocampus and the amygdala, and throughout the thalamus and the locus coeruleus. The delta receptor is also located in the limbic system, including the hippocampus and the amygdala, but in regions that do not overlap with the mu receptor distribution. Delta receptors are also located in the cortex, the hypothalamus, the nucleus accumbens, and some regions of the medulla. The kappa receptor has a third distinct distribution that includes the nucleus accumbens, the ventral tegmental area, the hypothalamus, and specific regions of the thalamus (Mansour et al., 1994).

All of the opioid receptors have their effects either through second messengers or by being taken inside the cell membrane where they activate kinases directly. The mu receptor is responsible for most of the effects of morphine and the drugs described in this chapter. Solomon Snyder and his colleagues have demonstrated that not all opioids bind to mu receptors with the same affinity; some have a strong attraction for the receptor, and some have a much weaker attraction. In general, those with the weakest attraction at the receptor have the greatest effect on the receptor. Morphine, for example, does not have a strong attachment to mu receptors but has a strong effect when it binds with them. In contrast, nalorphine has only a weak effect on the receptor but is bound strongly to it. When these two drugs are

p 270

mixed together, the nalorphine will be the one to have an effect because it will displace the morphine from the receptor. Because the effect of the nalorphine is only slight, there will be little opioid effect, even though morphine is present. Thus, the nalorphine acts as a competitive antagonist to the morphine, turning off the effect of the morphine and substituting its own mild effect. In this sense, it acts as an antagonist because it blocks the morphine, but it is also an agonist because it stimulates the receptor in a mild, morphinelike way.

An opioid with these properties is known as a *mixed opioid agonist–antagonist*. Nalorphine, pentazocine, and cyclazocine belong to this category. They will terminate the activity of more potent agonist drugs and at the same time have a milder effect of their own (Snyder, 1977).

Naloxone is a pure antagonist. It will displace any other opioid from the mu receptor but has no opioid effect of its own. It is used to treat victims of opioid overdoses because it will immediately terminate the action of all agonists. If naloxone is given to an individual who is physically dependent on opioids, it will immediately cause withdrawal symptoms. Opioid antagonists are used in some forms of treatment of opioid addiction. Naloxone is very important in opioid research because it provides a way of making sure that the effect of a drug is due to its interaction with mu receptors. This can be established simply by giving naloxone and seeing whether the effect is blocked (Garfield, 1983).

Sites of Action in the CNS

The opioids appear to produce their analgesic effects by several mechanisms. They affect areas of the spinal cord that transmit dull, burning pain, and it is believed that they block this incoming sensory information. The periaqueductal or central gray is an area of the brain known to be important in the perception of pain and rich in opioid receptors. When the body undergoes stress and pain, this system is activated, and the pain is reduced. It is believed that opioids cause some of their analgesic effects by stimulating the opioid receptors in this part of the brain.

Pain is a complicated phenomenon. Not only does it have a sensory component, but it has emotional aspects as well. We not only know that a sensation is painful; we also know that we really do not like it.

The sensory component of pain can be broken into several separate sensations. We may experience *thermoceptive pain* (pain caused by extreme heat or cold), *mechanical pain* (pain due to physical damage to the muscles and skin), and *visceral nociception* (pain associated with organ damage). These types of pain can be acute or chronic or may even appear to arise from limbs that have been amputated (*phantom limb pain*). Mu agonists seem to be effective against a broad range of pain, including all the acute types and some chronic types but not phantom pain. Delta agonists are effective against thermal and mechanical pain but are ineffective against visceral pain. Kappa agonists can be used against visceral pain but are effective only against low-intensity thermal and mechanical pain (Millan, 1986, 1990; Schmauss & Yaksh, 1984).

Opioids also reduce the aversive emotional aspect of pain. This effect may be mediated through opioid receptors located in various areas of the limbic system, such as the amygdala. It is believed that in addition to these lower centers, there are opioid systems in the frontal cortex through which opioids relieve pain.

Because of the mu receptors in the ventral tegmental area, opioids also stimulate the mesolimbic dopamine system. Imaging by functional magnetic resonance imaging (fMRI) BOLD in rats has demonstrated heroin-induced increases in signal intensity in the mesolimbic system, amygdala, and hippocampus. These effects are completely prevented by pretreatment with naloxone indicating that they are caused by mu receptors (Xu et al., 2000). This increase in mesolimbic activity is responsible for the reinforcing properties of opioids. Laboratory animals will readily learn to press a lever to deliver minute quantities of morphine directly to the ventral tegmental area.

Opioids depress three important centers in the brain stem. They depress the respiratory center and cause slow, shallow breathing. Death from opioid

overdose is usually a result of respiratory depression. The vomiting center is also depressed, and so is the center that causes us to cough. This suppression of the cough center is one reason why opiates have been included in cough medicines for centuries. At one time, most over-the-counter cough medicines contained codeine, but now they contain dextromethorphan, a synthetic opioid without any analgesic effects (Atweh & Kuhar, 1983).

In addition, repeated injection of morphine into the periventricular gray but not the ventral tegmental area will cause the development of physical dependence (Bozarth & Wise, 1984).

EFFECTS OF OPIOIDS

Effects on the Body

When opioids are first administered, two of their most notable effects are nausea and vomiting. These are caused by the stimulation of an area of the brain known as the chemoreceptor trigger zone, which detects impurities in the blood and stimulates a center that causes vomiting. Opioids also depress this vomiting center, and this action blocks vomiting. The result of these two effects is that nausea and vomiting are usually seen only after the first administration of the drug. With continuing doses, these symptoms decrease.

Because opioids constrict the pupils of the eyes, many opioid users have small pupils, and this effect diminishes only slightly with tolerance. Pinpoint pupils are also a symptom of opioid overdose. Opioids have little effect on the functioning of the heart, but there is some lowering of blood pressure due to dilation of the peripheral blood vessels. This dilation causes the face and neck to become flushed and warm and may cause sweating. Profuse sweating is one of the unpleasant side effects of methadone.

One of the first medical uses of opium was in the treatment of diarrhea and dysentery, and it is still used for this purpose. Opioids do not decrease the overall action of the stomach and intestines, but they seem to disrupt the coordination of digestive activity, causing the food to pass very slowly through the system. This effect stops diarrhea but produces constipation instead, and it can be a serious medical complication of opioid addiction. Opioids also interfere with urination by causing contractions of the bladder sphincter, making it difficult to pass urine.

Opioid use is known to decrease the level of sex hormones in both sexes, and this lowered hormone level is thought to be responsible for males' difficulty in maintaining erection and for the reduced sex drive and diminished fertility of both male and female opioid users. Heavy use may even cause atrophy of secondary sex characteristics in males and stop menstruation in women (Cushman, 1981). It has been suggested that opioid addiction is common among prostitutes because they have historically used opioids as a birth control measure.

Effects on Sleep

In spite of the fact that morphine is named after the god of dreams, opioids do not increase sleep. They cause a sleepy sensation and nodding, under normal circumstances, but acute administration of morphine and heroin actually causes insomnia and does not increase sleeping time (Belleville, Forrest, Shroff, & Brown, 1971). The user may doze off but will soon awaken with a start and will not feel rested. When subjects do sleep, they show increased muscular tension, spend more time in the lighter sleep stages, and experience a decrease in slow-wave and REM sleep (Kay, Eisenstein, & Jasinski, 1969). However, opioids are useful in causing sleep in people who are kept awake by pain.

EFFECTS ON HUMAN BEHAVIOR AND PERFORMANCE

Subjective Effects

Many literary figures were known to be users of opium. One of the first people to write about the effects was Thomas De Quincey, the English essayist, critic, and writer, author of the now famous *Confessions of an English Opium-Eater*,

published in 1821. De Quincey used opium for much of his life and wrote about its effects on his mind and on his life in *Confessions*. Like most people in the nineteenth century, he first took opium as a medicine but quickly appreciated its euphoric effects. After his first dose, his reaction was as follows:

> In an hour, O heavens! What a revulsion! What a resurrection from its lowest depths, of the inner spirit! . . . That my pains had vanished was now a trifle in my eyes; this negative effect was swallowed up in the immensity of those positive effects which had opened before me, in the abyss of divine enjoyment thus suddenly revealed. . . . Here was the secret of happiness, about which philosophers had disputed for so many ages, at once discovered; happiness might now be bought for a penny, and carried in the waistcoat-pocket; portable ecstasies might be had corked up in a pint-bottle and peace of mind might be sent down by the mail. (De Quincey, 1901, pp. 169–170)

De Quincey reported that he had an increased sensitivity in both hearing and vision. The increase was not so much in the loudness of noises and brightness of lights as in the ability of the mind "to construct out of raw organic sound an elaborate intellectual pleasure" (De Quincey, 1901, p. 179).

And finally, the dreams. Opioids at higher doses induce a sleepy, trancelike state called a nod, during which the user sees visions or dreams (hence the expression "pipe dreams"). Unlike the hallucinations from drugs such as LSD, these are more like vivid daydreams:

> Whatsoever things capable of being visually represented I did but think of in the darkness . . . which once traced in faint and visionary colour. . . . They were drawn out by the fierce chemistry of my dreams into insufferable splendor that fretted my heart. (De Quincey, 1901, p. 224)

Nor are the dreams always visual. Samuel Taylor Coleridge always claimed that the words to the famous poem Kubla Khan came to him in a trance after he had taken opium. Users of opium are firmly convinced that the creative processes are helped by the drug. As Jean Cocteau, the French poet, playwright, and artist, said,

> All children possess the magic power of being able to change themselves into what they wish. Poets, in whom childhood is prolonged, suffer a great deal when they lose this power. This is undoubtedly one of the reasons which drives the poet to use opium. (Cocteau, 1968, p. 71)

De Quincey took opium orally, and though he enjoyed the experience well enough, he missed a subjective effect that is usually experienced only by people who inject morphine or heroin or who smoke opium: the rush. This intense momentary feeling of pleasure is experienced after injecting the drug and is a result of the high concentrations delivered suddenly to the brain. Rushes are usually described as sexual, rather like an orgasm in the stomach or in the entire body. As one 17-year-old addict described it, "It's just the most intense wonderful feeling. . . . I worry that I will always be tempted to feel the heroin rush again, because nothing else I've tried comes close to it" (Weil & Rosen, 1983, p. 87).

Systematic Studies of Mood

Many authors who write about the subjective effects of opioids stress the euphoric effects and the "divine enjoyment" that the drug offers. Such writings and other accounts have frequently led theorists to speculate that the origin of the attraction of opioids is the relief of anxiety and depression, but most of the experiments in which mood and emotional behavior are measured objectively find that positive feelings do not last and are replaced with mood changes and emotions that are mostly negative. In one study conducted at the McLean Hospital in Belmont, Massachusetts, by Roger Meyer, Steven Mirin, and their associates (Meyer & Mirin, 1979), male adult heroin addict volunteers were admitted to the hospital and kept in a ward for 42 days. During that time, for a period of 10 days, they were allowed to earn heroin injections. During their entire stay, the ward staff kept track of their aggressive and social behaviors, and they were administered standardized psychological tests and asked to complete mood scales. This study found that during the first few days of heroin administration, before significant tolerance developed, heroin relieved tensions and

produced euphoria. However, as use continued, there was a shift to unpleasant mood states and increased psychiatric symptoms. These unpleasant feelings were relieved for only a brief period of 30 to 60 minutes after each injection. In addition to this deterioration in mood, there was a decrease in physical activity and social interaction and an increase in aggressive behavior and social isolation. These effects diminished when the subjects were maintained on methadone and when the self-administered heroin was blocked by an opioid antagonist.

The effects on mood also differ with whether the drug is given to experienced users or naive subjects. In a classic study, Lasagana and his colleagues at Harvard (Lasagana, Felsinger, & Beecher, 1955) investigated the changes in mood and subjective effects in different populations and found that former addicts were more likely to experience positive feelings after opioids, whereas nonusers reported sedation, mental clouding, and feelings of sickness. In this experiment, 17 out of 30 former users said that they would like to repeat the experience of morphine a second time, whereas only 2 out of 20 nonusers wanted to repeat. Other researchers have not been able to find consistent reports of positive feelings experienced after mu agonists such as heroin (Zacny & Walker, 1998, p. 353).

The subjective effects of morphine are different when given to people experiencing pain. Conley, Toledano, Apfelbaum, and Zacny (1997) gave morphine to subjects who were also experiencing the pain of having their arms immersed in icy water. They found that the pain diminished the feelings of being "spaced out," "high," "sleepy," and "light-headed," which were normally caused by morphine in individuals not experiencing pain.

The mixed opioid agonist–antagonists, like pentazocine, are even more likely to produce unpleasant subjective effects of feeling "confused" and having "difficulty in concentrating" in nondependent opioid users and, to an even greater extent, nonusers. The mixed opioid agonist–antagonists cause withdrawal symptoms in dependent opioid users (Zacny, Hill, Black, & Sadeghi, 1998; Zacny & Walker, 1998).

Some opioids, such as cyclazocine, which have a stronger affinity for kappa receptors, have quite unpleasant subjective effects, including depersonalization, hallucinations, and many symptoms of psychosis in both opioid abusers and nonabusers (Zacny & Walker, 1998).

Performance

In a review of the effects of opioids on human performance (Zacny, 1995), it was concluded that acute administration of opioids to those with little or no experience of the drug can have a moderate effect on performance. In general, performance seems to slow down but does not become more erratic. Partial agonists, or mixed agonist–antagonists such as propoxyphine, cause more impairment than full agonists such as morphine (Zacny et al., 1998). Cognitive performance seems to be less impaired than psychomotor performance.

For most types of tasks, it appears that tolerance develops and that, with moderate dosages of heroin or morphine, addicted individuals can maintain good health and productive work for extended periods. There are numerous cases of individuals who administered opioids in one form or another for years but were still able to pursue successful and even brilliant careers. One such individual was Dr. William Stewart Halstead, one of the founders of Johns Hopkins Medical School and one of the most brilliant surgeons of his day. He pioneered in the development of aseptic surgical techniques and the use of cocaine as a local anesthetic and was known as the "father of modern surgery." Yet during his career, he was addicted to morphine, a fact that he was able to keep secret from all but his closest friends (Brecher & the Editors of *Consumer Reports*, 1972, p. 35).

These observations that tolerance to the detrimental effects of opioids occurs in chronic users have been confirmed. Longtime opioid-dependent users show little, if any, impairment caused by either morphine or the mixed agonist–antagonists. It is still not entirely clear, however, whether this is true for those who use opioids for long-term pain relief, although it has been shown that the detrimental effects of opioids on performance are diminished when given to people experiencing pain (Conley et al., 1997).

Opioid Withdrawal

The only time Dr. Halstead's habit caused him any trouble was when he was attempting to reduce his dosage and started to show withdrawal symptoms. This is similar to the finding by Thompson and Schuster (1964) that food-seeking and shock-avoidance behavior of monkeys was not disrupted while monkeys self-administered morphine but was disrupted when they were not allowed access to morphine and started to experience withdrawal. (This research will be discussed later in this chapter.)

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Unconditioned Behavior

Morphine has a biphasic effect on spontaneous motor activity (SMA). At low doses, there is an increase in movement, but at higher doses, there is a decrease. In mice, this low-dose stimulation causes "running fits," where the mice run blindly and continuously. This effect can be blocked by nalorphine. In rats, low doses cause an increase in SMA. At higher doses, this behavior takes the form of stereotyped responses that differ from the stereotyped behavior caused by amphetamine (see Chapter 11). Morphine-produced stereotyped behavior covers a wide range of behaviors, including social behavior, whereas stereotyped behavior caused by psychomotor stimulants involves only nonsocial behaviors of short duration (Schörring & Hecht, 1979). Still higher doses produce a type of *catalepsy*; the animal's body becomes rigid and can be molded into almost any position, which it will maintain for extended periods. In primates, there does not seem to be an excitatory phase. The main effect is a depression of behavior.

Conditioned Behavior

At low doses, opioids tend to increase response rates of most species of animals responding for positive reinforcers at a low rate, but high doses decrease response rates (Thompson, Trombley, Luke, & Lott, 1970). The rate-decreasing effects of opioid agonists can be blocked by low doses of antagonists, but these antagonists at higher doses have effects very similar to agonists.

As with fixed interval (FI) response rates, there are reports that opioids increased both discrete trials and continuous avoidance of electric shocks at low doses, which is not what might be expected from an analgesic, but at higher doses, opioids slowed avoidance behavior without disrupting escape responding (Heise & Boff, 1962), an effect similar to alcohol and the tranquilizers.

It might be expected that a drug with noted analgesic properties would increase behavior suppressed by punishment, but this is not the case. Opioids usually only decrease response rates already diminished by response-contingent shock (Geller, Bachman, & Seifter, 1963). It would appear that the ability of opioids to diminish pain is not one of the mechanisms by which the drugs change avoidance behavior.

Effects of Self-Administered Opioids

Travis Thompson and Charles Schuster (1964) conducted one of the earliest experiments in which monkeys were maintained on a schedule of self-administered morphine. Monkeys could give themselves intravenous morphine for a brief period every 6 hours. After the self-administration behavior was acquired, Thompson and Schuster placed the monkeys on a fixed ratio (FR) 20 for food and a discrete-trials shock-avoidance schedule between periods of morphine availability. They found that the behavior of the monkeys on these schedules was not impaired by the self-administered drug, even though the doses reached rather high levels. The only time they noticed a deterioration in the avoidance or the FR was when the morphine was no longer available and the monkeys were going through withdrawal. This is similar to the experience of Dr. Halstead, the addicted surgeon described earlier.

DRUG STATE DISCRIMINATION

Opioids are readily discriminated from saline by both rats and monkeys. Morphine is not as discriminable as the barbiturates or marijuana, but it is more easily discriminable than the hallucinogens and the stimulants (Overton, 1973).

Animals trained to discriminate morphine will generalize to all other opioid agonists, such as methadone and codeine, but only partly to mixed opioid agonist–antagonists, such as cyclazocine. In addition, rats can be trained to discriminate between morphine and cyclazocine. Discriminative stimulus control of morphine and cyclazocine can be blocked by opioid antagonists, but cyclazocine requires a dose of antagonist 10 to 30 times higher than morphine. This evidence suggests that these drugs have effects on different populations of opioid receptors (Zacny & Walker, 1998, pp. 349–353). Morphine works at the mu receptor, which can be blocked easily by opioid antagonists, but cyclazocine works at both mu and kappa receptors, so its effects can only be partly blocked by the antagonist.

It has been shown that tolerance to the discriminative effects of morphine in rats can develop in 1 to 3 days and increases with higher doses (Young, Steigerwald, Makhay, & Kapitsopoulos, 1991).

TOLERANCE

As we have seen with many of the behavioral effects of opioids in humans, there is rapid and extensive tolerance to most of their effects. Figure 12-1

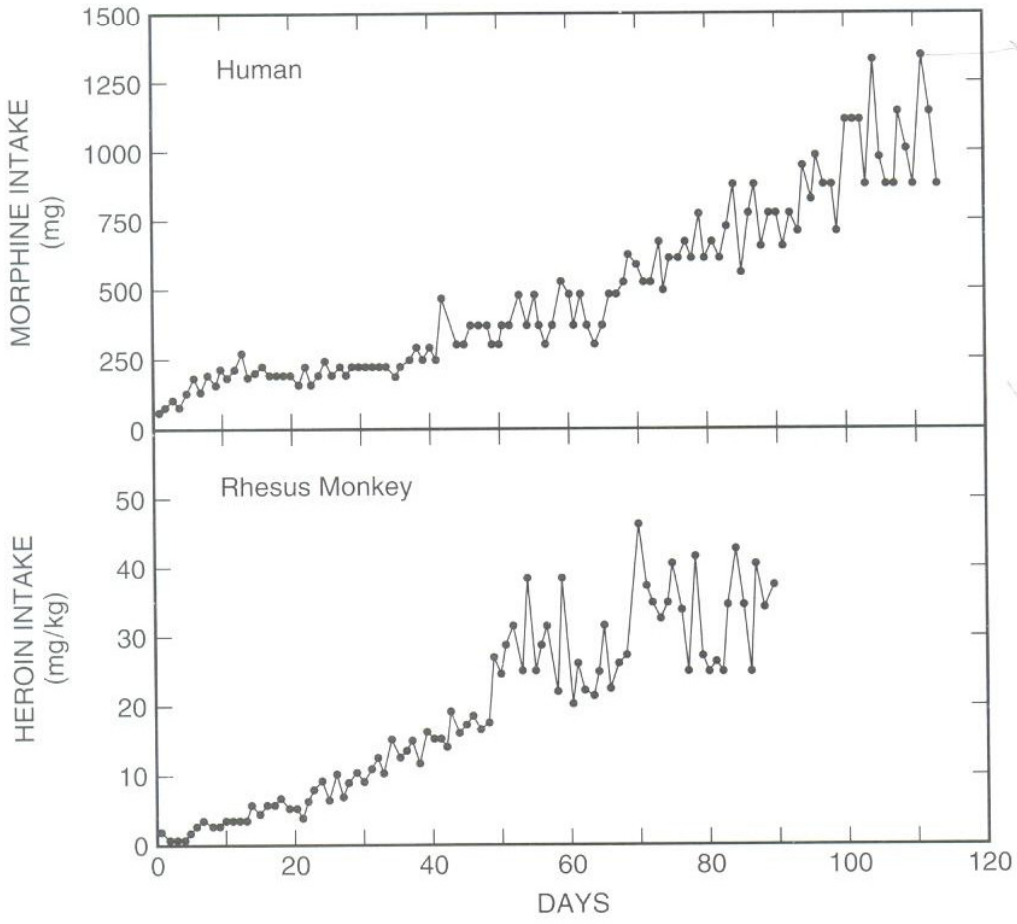

Figure 12-1 Daily intake of morphine and heroin in a human and a rhesus monkey when allowed free access to the drug. In both species, intake slowly increases over time, and there are no periods of abstinence or voluntary withdrawal. (Adapted from Griffiths et al., 1980)

shows the increasing dose self-administered by two species. Within 3 or 4 months of regular use, consumption will increase tenfold or more. In fact, doses taken by a regular user may be sufficiently high to kill a nontolerant individual several times over. Tolerance to different effects develops at different rates and disappears at different rates. For example, complete tolerance to the analgesic and positively reinforcing effects may develop, but the constriction of the pupils only partially disappears with continued opioid use, and the constipating effects never go away.

Some tolerance is due to changes in opioid metabolism, and some is the result of changes in the properties of the opioid receptors. Another likely mechanism of tolerance is learning since tolerance seems, to some extent, to be dependent on the environment in which the drug is given (S. Siegel, 1983). (See the discussion of tolerance in Chapter 3.)

Cross-Tolerance

Generally, when tolerance has developed to any opioid drug, there will be tolerance to all others. This cross-tolerance does not extend to the depressants, stimulants, or hallucinogens, but there is some degree of cross-tolerance between opioids and alcohol.

WITHDRAWAL

Opioid withdrawal is probably one of the most misunderstood aspects of drug use, largely because of the images of withdrawal that have been portrayed in the movies and popular literature for many years. The popular notion of the severity of heroin withdrawal probably came about in the 1920s and 1930s, when heroin addicts had easier access to cheaper sources of the drug and took it in much greater quantities than are common now. Few addicts these days are able to take enough drug to cause the severe withdrawal symptoms that are shown in the movies. Even in its most severe form, however, opioid withdrawal is not as dangerous or terrifying as withdrawal from barbiturates or alcohol. In fact, withdrawal from alcohol can be fatal, but withdrawal from heroin or any other opioid is never fatal.

Classic heroin withdrawal proceeds in predictable stages. It starts 6 to 12 hours after the last administration of the drug, peaks at 26 to 72 hours, and, for the most part, is over within a week. The first signs are restlessness and agitation. Yawning soon appears and may become quite violent. The person is able to stay still only briefly and paces about with head and shoulders stooped over. The user experiences chills, with an occasional hot flash, and breathes with short, jerky breaths. During this time, goose bumps appear on the skin, which takes on the appearance of the skin of a plucked turkey (this is the origin of the expression "going cold turkey"). At this point, the addict becomes drowsy and will often fall into a deep sleep known as the *yen sleep*, which may last 8 to 12 hours. After awakening, there are cramps in the stomach, back, and legs; vomiting; and diarrhea. There may also be twitching of the extremities, which causes the hands to shake, and a kicking of the legs (this is the origin of the expression "kicking the habit"). There is also profuse sweating; the person's clothes and bed may become saturated with sweat. These symptoms become progressively less severe and soon disappear altogether.

The severity of the withdrawal depends on the daily dose of the addict and is seldom as drastic as this description. For most individuals, withdrawal resembles a bad case of the flu. Even though heroin withdrawal is not life threatening, it is extremely uncomfortable and is not undertaken lightly.

Withdrawal is similar for all opioids, although it is usually less severe with the less potent opioids such as codeine or propoxyphine. The withdrawal symptoms can be stopped almost instantly, at any stage, by the administration of any of the opioid drugs. Opioid withdrawal symptoms can also be reduced by alcohol (Ho & Allen, 1981). Withdrawal in a physically dependent individual can be

generated almost instantly by the administration of an opioid antagonist.

SELF-ADMINISTRATION IN HUMANS

We tend to think of all heroin users as addicts, but this assumption is certainly not true. Many people appear to be able to maintain what is called an "ice cream habit" or "*chipping*," in which heroin is taken occasionally when the drug and the opportunities to take it are available. Chipping is a reality, but its extent is unknown because chippers are difficult to detect. They appear to be able to maintain a normal lifestyle and seldom require treatment.

We know a great deal more about the pattern of addicted heroin use, which has been extensively studied. In this pattern, the user is often (though not always) physically dependent and attempts to consume sufficient heroin to experience the rush and to avoid withdrawal—usually at least one injection a day. The addict is preoccupied with "taking care of business" or "scoring"—obtaining and taking the drug. This usually requires most of the addict's attention and money, leaving little time and resources for anything else. A heroin addict typically chooses friends and associates who are also heroin users.

The first exposure to heroin is usually motivated by curiosity and approached with caution. Frequently, the new user is introduced to the drug by someone he or she trusts. Surveys show that the majority of addicts were first given the drug by a friend. Very few were given the drug by a "pusher" or someone unknown to them. It is extremely unlikely that someone could be made into an addict, against his or her will, by an unscrupulous pusher trying to develop new markets.

We have already seen that the initial experience with heroin is considered unpleasant by the majority of first-time users, and it probably requires considerable persistence to acquire a physical dependence. It is not known how many people exposed to opioids do not become addicts and avoid the addicted lifestyle.

At the other end of addiction, there appears to be a *maturing out* of heroin use. Studies have indicated that many addicts spontaneously discontinue use of the drug (Winick, 1962). These addicts usually reach this point in their 30s or 40s after some 5 to 10 years of heroin use. The longer a person has used heroin, the less the chance of maturing out. It is difficult to estimate the number of addicts who eventually mature out; estimates range from more than two-thirds (Winick, 1962) to less than a quarter (Ball & Snarr, 1969). A great many heroin addicts never do manage to leave the habit behind and survive into old age still using heroin. Addiction workers are reporting an increasing number of heroin-addicted seniors (C. Jones, 2005).

Laboratory Studies

Laboratory studies of human opioid self-administration show that opioids act as reinforcers in opioid abusers by a number of different routes of administration. Different drugs have different reinforcing potential. Morphine appears to be more reinforcing than codeine, and both are more reinforcing than propoxyphine. Propoxyphine would be self-administered only in situations where it was available at little or no cost. Not surprisingly, heroin does not function as a reinforcer in opioid abusers when they are pretreated with an opioid antagonist. A study by Lamb et al. (1991) showed that nondependent drug users would self-administer intramuscular morphine at doses so low that the drug had no detectable subjective effect.

There are few studies of self-administration in non–drug-abusing populations. One such study of fentanyl showed that it would not be self-administered unless the subject was experiencing pain from immersing his or her arm in cold water. Thus, it appears that in non–drug users, opioids function as reinforcers only in the presence of pain. This is not surprising given the results of the Lasagana et al. (2005) study mentioned earlier, but more research needs to be done with this population (Zacny & Walker, 1998, pp. 346–349).

Patterns of Use

Studies of nonhumans and humans have shown very similar patterns. In both cases, when the drug is freely available, the amount of self-administered drug is carefully regulated. The daily dose increases gradually and regularly until it reaches a peak and then remains steady. There are no intake–abstinence cycles as with alcohol and stimulants, and withdrawal symptoms are not seen. Figure 12-1 shows data from similar studies. In one study, a human heroin addict self-administered morphine intravenously; in the other, a rhesus monkey gave himself heroin via the same route (Griffiths, Bigelow, & Henningfield, 1980). For the most part, this pattern is similar to that of the opioid addict who attempts to maintain a fairly constant blood level and avoids withdrawal when it is at all possible to do so.

It is tempting to speculate that the gradual increase in dose is a result of tolerance, but this may not be the case. As we have seen in Chapter 3, the reinforcing effects of many drugs, including heroin, become sensitized with repeated rather than diminished administrations. The increase in self-administered drug may be a result of increased reinforcing properties of the drug since it has been shown that up to a point, larger doses are more reinforcing than smaller doses.

SELF-ADMINISTRATION IN NONHUMANS

Morphine was the first drug for which intravenous self-administration was demonstrated in nonhumans. We have already discussed one of the first experiments of this type, conducted by Travis Thompson and Charles Schuster and published in 1964. At the time this research was done, it was assumed that physical dependence was an essential aspect of addiction, so Thompson and Schuster used squirrel monkeys that had been made dependent on morphine by injections four times a day for 30 days. The monkeys were then given the opportunity to bar press for morphine four times a day. The monkeys were placed on an FI–FR chain schedule; to receive the drug, the monkeys were on an FI 2-minute schedule while a tone was turned on. The first response made after 2 minutes turned off the tone and turned on a white light. While the white light was on, the animals were required to make 25 responses. When this requirement was completed, a red light came on, and an infusion of morphine was given through an intravenous catheter.

The monkeys readily learned this response, and they performed on these schedules in the same manner as they would for any other reinforcer. Thompson and Schuster (1964) also demonstrated that both deprivation from morphine and injections of nalorphine would increase the amount of morphine the monkeys would administer. In later research, they demonstrated that nondependent monkeys would also self-administer morphine (Schuster & Thompson, 1969).

As shown in Figure 12-1, when morphine is freely available, it is self-administered by laboratory animals with great regularity on a daily basis, and the dose slowly increases.

All the mu receptor agonists are self-administered by laboratory animals, although the mixed agonist–antagonists do not seem to be as reinforcing as morphine and heroin. The reinforcing effects of the opioids can be blocked by mu antagonists. The antagonists naloxone and naltrexone are not self-administered. In fact, laboratory animals will learn to respond to avoid administrations of antagonists (Zacny & Walker, 1998, p. 344).

Drugs such as cyclazocine, which stimulate kappa receptors, are not self-administered, and there are reports that laboratory animals will respond to avoid infusions of them. There are also reports that kappa agonists can block the reinforcing effects of both morphine and cocaine, suggesting that the kappa receptor system may interact with the mu system where reinforcement is concerned (Glick, Maisoneuve, Raucci, & Archer, 1995). Delta agonists do not appear to have reinforcing properties.

In humans, heroin is often administered in conjunction with cocaine in what is called a *speedball*. One study with monkeys self-administering

vaporized heroin showed that the reinforcing effect of the heroin was enhanced when it was administered in conjunction with vaporized cocaine (Mattox, Thompson, & Carroll, 1997).

HARMFUL EFFECTS

Acute Effects

At very high doses, opioids produce a comatose state with pinpoint pupils and severe depression of breathing, which eventually causes death. Unlike barbiturates, opioids lower the seizure threshold and may also cause convulsions at high doses. Opium has been used historically as a poison, so it is not surprising that people die from time to time from accidental overdoses of opioids. Box 12-1 describes how a derivative of fentanyl was used by the Russian security forces on Chechen rebels who seized a Moscow theater in 2002. The drug killed both the hostage takers and many hostages.

Heroin overdose is the leading cause of death among heroin users. In fact in some communities, it is the leading cause of death in males between the ages of 25 and 54. In Australia, it has been estimated that every year about 2 percent of heroin users die, and the majority of these deaths are due to overdose (Gerostamolous, Staikos, & Drummer, 2001). Most heroin overdose deaths occur in people with 5 to 10 years of experience with using the drug; only about 17 percent are new users. These deaths do not seem to be related to changes in the purity of street heroin (Sporer, 2003).

One mystery related to heroin overdose is that many times, the victim has not used more heroin than usual or more heroin than other people using the drug at the time (Brecher & the Editors of *Consumer Reports*, 1972).

If these deaths were not overdoses, what could be killing so many addicts? There are several explanations. One possibility is quinine, a drug used to cut or dilute the heroin before it is sold on the streets. Quinine can be lethal when given intravenously, and these overdose victims frequently show signs of quinine poisoning, such as froth oozing from the nose and mouth. Another explanation is the mixing of heroin with other drugs. One study showed that 85 percent of those dying from heroin overdose were using another central nervous system depressant, 45 percent were using benzodiazepines, and 36 percent were using alcohol (Gerostamolous et al., 2001). These drugs potentiate the effects of heroin and may make an otherwise normal dose of heroin lethal. Janis Joplin, the rock singer, died of a heroin overdose after some hard drinking with her friends at a nearby bar.

Another possible cause of an unexplained overdose is a loss of tolerance to the drug. Often this loss is due to a period of abstinence. Addicts have seven times the risk of overdose during their first 2 weeks after their release from residential treatment (Sporer, 1999). During treatment, they have lost their tolerance to the lethal effects of the drug, so their usual dose is now fatal.

Another possible reason for the loss of tolerance may be due to conditioned tolerance effects. As described in Box 3-1 in Chapter 3, some tolerance may depend on the specific environment in which the drug is normally given. If the drug is used in a new environment, tolerance is diminished, and what is a normal dose for an addict may suddenly be transformed into a lethal dose.

Chronic Effects

Health. Surprisingly few medical problems arise as a direct result of chronic heroin use. One of these is constipation. Somewhat more serious is a direct link between opioids and cancer. Opioids interfere with the body's ability to repair damaged DNA molecules, and this effect makes them cancer promoters; they enhance the cancer-causing effects of other substances that damage DNA. Like alcohol use, heroin use greatly increases the chance of bladder cancer caused by smoking (Falek, Madden, Shafer, & Donahoe, 1982).

CNS Effects. Opioids do not appear to alter the structural anatomy of the brain. However, SPECT data suggests that chronic heroin use is

BOX 12-1 What Was the Mysterious Gas Used by the Russians to End the Moscow Theater Hostage Taking?

On October 23, 2002, at about 9:00 P.M., 41 Chechen terrorists invaded a popular Moscow theater. They took over 800 people hostage and demanded that the Russians withdraw their troops from Chechnya. The terrorists threatened to start shooting their hostages and blow up the theater with explosives strapped to their bodies. The Russian government refused to negotiate. The standoff lasted 57 hours. Early on the morning of October 27, the Russian Federal Security Service pumped a gas into the theater and then stormed it and took it by force. The gas was effective—it knocked the terrorists out so fast that they were not able to detonate their explosives. Unfortunately, the gas proved lethal to many; 129 of the hostages and all but two of the terrorists were killed by the gas.

At the time, the Russians would not say what gas they had used, but in response to international pressure they announced several days later that the gas had been a fentanyl derivative, but questions still remain. There are several derivatives of fentanyl that could have been used, but the most likely would have been carfentanil, which is more than 30 times more potent than fentanyl and 10,000 times more potent than morphine. Potency would have been an important consideration. Fentanyl and its derivatives like morphine are not normally a gas at room temperature, so the carfentanil must have been nebulized and made into an aerosol, that is, turned into very fine particles and dispersed into the air—a complicated process. The more potent the drug, the less nebulization would have been needed.

But another question remains. Why did so many people die? It turns out that carfentanil and other fentanyl derivatives have a fairly high therapeutic index (TI) compared to morphine. The TI of morphine is about 70, while the TI of carfentanil is 10,600. These numbers suggest that these drugs should have been quite safe. There are two possible answers to this question. The first is that the dose received by each individual would have varied greatly, depending on where each person was. The aerosol was introduced into the theater by the ventilation system, and those close to the air vents would have received a much higher dose. This inability to control the dose is an inherent problem with using gases and aerosols in this manner. But there is another possibility: Another agent may have been mixed with the fentanyl derivative.

One advantage of using an opioid drug is that there is a very effective and fast-acting antidote available, naloxone. After the raid, many victims were treated in nearby hospitals that had been warned to stock up on their supplies of naloxone; unfortunately, the doctors were not told that the gas was an opioid, so many did not use the naloxone. In many cases, however, when it was used, it did not seem to be effective. This has led many to speculate that another agent had been mixed with the fentanyl derivative. Many suspect that it might have been the gaseous anesthetic halothane (see Chapter 8). Many survivors reported a sweet smell as the gas took effect. This is a property of halothane. In addition, a toxicological analysis of a German survivor after returning to Germany showed traces of halothane. If halothane were mixed with the fentanyl derivative, it might explain why there were so many deaths. Halothane has a very low therapeutic index, and, additionally, it does not have any antidote.

In these days of terrorism and hostage taking, there is little doubt that many militaries around the world are developing "calmative" or rapidly acting agents that can incapacitate a person rapidly but not be lethal. Normally such research is never made public, so this incident provides us with a speculative glimpse of where this field may be going (Wax, Becker & Curry, 2003).

associated with widespread reductions in cerebral blood flow to the frontal, parietal, and temporal lobes of patients with the first week of heroin withdrawal. These effects may not be long lasting since perfusion deficits show marked improvement following 3 weeks of heroin abstinence (Rose et al., 1996). Opioid users and former users do show abnormal brain activation patterns during decision making on the *Cambridge risk task*. This task involves choosing among two computer-based decks of cards, one associated with an unlikely high reward and one associated with a likely low reward. As is the case with stimulant addicts, imaging by photon emission tomography (PET) and fMRI completed during the task demonstrate that opioid addicts show reduced activation of the anterior cingulate cortex during errors made on the task (Forman et al., 2004). It is not clear whether this difference was caused by the drug or whether it is a preexisting condition in opioid addicts.

Lifestyle Effects. Although opioids cause some direct health problems, most of the harm done by opioids is indirect and arises from the addicted lifestyles most addicts are forced to adopt. Heroin is expensive, and it may take several hundred dollars a day to support the habit. Because getting the drug takes such priority, housing and nutrition suffer, and so does health. Added to these difficulties is the greatly increased exposure to disease caused by the practice of "shooting up" the drug. These injections are seldom done with clean needles and syringes; many people often use the same equipment, providing direct access into the body for diseases such as hepatitis and HIV/AIDS. Being a heroin addict is not healthy.

In a 33-year study of 581 heroin-addicted criminal offenders admitted to the California Civil Addict Program between 1962 and 1964, it was found that by 1997, nearly half the group had died. This represents a death rate 50 to 100 times the death rate among the general population of men the same age. Accidental poisoning and drug overdose were the most common cause of death (21.6 percent). Nineteen and a half percent were homicide, suicides, and accidents. Liver disease, cancer, and cardiovascular disease accounted for the remaining deaths (Hser, Hoffman, Grella, & Anglin, 2001). Nearly 40 percent of those surviving used heroin within the past year, and nearly 10 percent were in methadone treatment.

Reproduction. In males, chronic opioid use reduces levels of the male sex hormone testosterone. This effect leads to a decrease in sex drive and fertility and may also cause changes in secondary sex characteristics. In women, alteration in hormone levels causes menstrual irregularities, amenorrhea, and a consequent decrease in fertility.

Pregnancies are also complicated by direct and indirect effects of opioids and opioid withdrawal. During pregnancy, the ability of the body to eliminate opioids is increased. The subsequent reduction in circulating levels of opioids leads to increased demand for the drug, and the probability of withdrawal is greater if the drug supply is irregular or uncertain. It is believed that opioid withdrawal during pregnancy can harm the fetus because it causes a decrease in blood oxygen levels. Numerous other medical complications during the pregnancies of addicted women may arise from the problems of the addicts' lifestyle. These complications, which occur in 40 to 50 percent of pregnant addicts, include anemia, cardiac disease, swelling, liver disease, hypertension, pneumonia, tuberculosis, and infections of the urogenital system, such as bladder infections and venereal disease (Kreek, 1982).

Babies born to addicted mothers have low birth weights and are more likely to be premature and to experience illness and complications after birth. In general, these problems are less likely in methadone-maintained mothers than in those using street heroin.

One big problem for babies born to dependent mothers is that right after birth, they have to go through withdrawal because they are no longer exposed to the opioid in the mother's blood. Withdrawal in neonates is similar to adult withdrawal. The symptoms include irritability,

respiratory distress, yawning, sneezing, tremors, difficulty in sucking and swallowing, and a peculiar high-pitched cry. Some may even experience seizures. These symptoms start within 72 hours of birth and may last 6 to 8 weeks (Finnegan, 1982).

TREATMENT

Maintenance Therapies

The British System. Maintenance therapies are based on the philosophy that the real harm done by opioids arises from the fact that they are expensive and illegal. It follows that if addicts have a cheap, reliable source of the drug, they will remain healthy, be free to pursue careers and normal lives, and not be forced into a criminal way of life. In England, this approach has been followed for years. An addict can obtain a prescription from a special clinic and have it filled at public expense at any druggist's shop. This approach is known as the *British System*, and it appears to be modestly effective in preventing new cases of heroin addiction, decreasing the death rate in addicts, reducing criminal behavior, and improving the functioning of addicts. It has the added advantage of bringing addicts into regular contact with health professionals and is effective in stopping the spread of AIDS (Bewley, 1974; O'Mara, 1993).

One British writer has suggested that treating addiction as a medical problem in a clinic reduces the glamour of drugs; after all, "Sickness is generally less attractive than sin" (Bewley, 1974, p. 160).

Methadone Maintenance. In the United States, various laws made it impossible for doctors to prescribe heroin to addicts, so methadone has been used to prevent withdrawal (Nyswander, 1967). Methadone has several advantages over heroin as a maintenance drug: (a) It can be taken orally, (b) it prevents withdrawal symptoms for 24 hours, and (c) it acts as an antagonist to heroin. Because it can be taken orally, it is easy to administer and does not have all the associations of shooting up. The fact that it lasts for 24 hours means that it can be administered once a day in a clinic, and the user does not need to take it home. And because it blocks the effects of heroin, addicts on methadone will experience few euphoric effects or rushes if they decide to try heroin. This is probably because methadone occupies mu receptors and blocks mu agonists like heroin. Methadone continues to occupy mu opioid receptors in the thalamus, caudate, anterior cingulate cortex, and middle temporal and frontal cortices at 22 hours postadministration in former heroin users on maintenance therapy. PET imaging with [^{18}F]cylcofoxy, which binds to mu receptors, suggests that receptor availability is reduced by 19 to 32 percent in these regions (Kling et al., 2000). It is also likely that the lack of sensitivity to heroin arises from cross-tolerance between methadone and heroin.

Substitution of methadone for heroin is not considered a therapeutic end in itself. Methadone is always used in conjunction with psychological or social treatments. In fact, the success of methadone treatments depends heavily on the addict's having a good, trusting relationship with a well-trained staff (Weddington, 1995).

In a typical methadone maintenance clinic, patients are screened to ensure that they really are physiologically dependent on heroin. Then, over a period of several weeks, a dosage of methadone is worked out that will maintain the patients free from withdrawal symptoms. Typically, patients must return to the clinic every day for a drink of methadone. In some programs, addicts who demonstrate that they have been free of heroin and other problems are permitted to take the drug home and are required to attend only two or three times a week.

Over the years when methadone has been used as a maintenance drug in the United States, it has been demonstrated that it reduces sickness and death associated with illicit drug use (Sporer, 2003), normalizes disruptions of immune and endocrine functions, reduces the transfer of HIV/AIDS, and reduces criminal activity (Ling, Rawson, & Compton, 1994).

Many addicts choose to stay maintained on methadone indefinitely, but as normal lifestyles

develop, there are pressures to detoxify altogether. Methadone patients are discriminated against in insurance, licensing, employment, and housing, and the pressures to attend clinics regularly interfere with travel and vacations. Then, too, methadone has uncomfortable side effects, such as sweating, sexual dysfunction, and constipation. When patients appear ready and motivated to discontinue the drug, doses of methadone are slowly decreased over a period of no less than 6 months, so that withdrawal is minimized. This process is best accomplished at a very gradual rate that is decided on by the user. Even when the methadone reduction is gradual, detoxification becomes difficult when the dosage gets low.

In general, relapse rates in addicts weaned from methadone are similar to those with other methods—80 to 90 percent—but some reports have been quite impressive (Meritz, Kleber, Riordan, & Solbetz, 1978; D. D. Simpson, Joe, & Bracy, 1982; Weddington, 1995). It is estimated that of the 500,000 to 1,000,000 people in the United States who are addicted to heroin, 100,000 receive methadone maintenance therapy in the 750 to 800 clinics across the country (Ling et al., 1994).

LAAM. Like methadone, this new maintenance drug can be taken orally and blocks the effects of heroin, but its effects last longer than methadone (up to 72 hours) and it needs to be taken only three times a week. The addict need not come to the clinic as often, and the clinic need not send any of the drug home with the addict. After many years of extensive testing, LAAM was formally approved in the United States in 1993 as a maintenance drug for heroin addicts.

LAAM appears to work better than methadone for addicts who are unable to get to a clinic on a daily basis because of difficulties with employment, child care, or transportation. Some addicts also have problems stabilizing on a dose of methadone, and some simply refuse to enter methadone treatment. Many of these people report that LAAM "holds" better than methadone (Ling et al., 1994).

Some people believe that LAAM has the capacity to change the face of heroin maintenance therapy. Methadone may still be used for primary treatment in specialized clinics in inner-city areas, where heroin use flourishes and users require the intensive support of daily clinic visits, but as addicts establish more stable lifestyles, employment, and family lives, it would be more appropriate to switch to LAAM and make it available in a general health care setting (Ling et al., 1994).

Buprenorphine. Buprenorphine has been used as an analgesic and is still used experimentally for heroin dependence. It can be taken orally and has a long half-life, although its effects do not last as long as those of LAAM. Buprenorphine is a mixed agonist–antagonist. Thus, it will block the effects of heroin and causes only mild physical dependence itself. Therefore, it is much easier to stop taking buprenorphine than methadone or LAAM, and it is easier to switch to antagonist therapies without experiencing withdrawal (Ling et al., 1994). In normal circumstances, buprenorphine is given every day, but recently it has been shown that buprenorphine is just as effective when given three times a week (Schottenfield et al., 2000). One problem with buprenorphine pills is that they are sometimes crushed and injected for a more intense effect. To prevent this, naloxone is added to the oral buprenorphine pills, which are administered sublingually (under the tongue). This way, the buprenorphine is absorbed, but the naloxone is not. If crushed and injected, the naloxone blocks the effect of the buprenorphine.

Antagonist Therapies

As mentioned, one of the advantages of methadone over heroin for maintenance is that methadone works as an antagonist to the effects of heroin. In the presence of methadone, the effect of heroin is greatly diminished. This aspect of methadone is considered beneficial, but it is not the main reason why methadone is used. Methadone prevents withdrawal. An implicit assumption of maintenance therapies is that the

primary motivation for taking heroin is the fear of withdrawing. Addicts are, therefore, maintained on the drug so that they will not be compelled to use heroin from the streets to prevent withdrawal. As we have seen in Chapter 3, this assumption may not be correct. We know from studies of self-administration with laboratory animals that physical dependence is not necessary to maintain opioid self-administration. Nondependent monkeys will self-administer opioids at a high rate even though they have never experienced withdrawal. This type of research has shown that drug taking is motivated by the positively reinforcing effects of drugs, not the fear of withdrawal. It is little wonder, then, that drug-seeking behavior persists during and after maintenance. It is likely that the heroin-blocking effect of methadone is more important than its ability to avoid withdrawal.

If the reinforcing effect of the heroin is responsible for its use, there is no need to maintain a person in a physiologically dependent state, but it is important to keep the reinforcing effect of heroin blocked. This is where the antagonists can play a role. They are very effective heroin blockers and have only minimal agonist properties.

Patients are first withdrawn from heroin and kept abstinent for 7 to 10 days; otherwise, the antagonist would precipitate withdrawal symptoms. This stage can be difficult, and the dropout rate is very high. As early as possible, addicts are given daily doses of an antagonist—naloxone, naltrexone, or cyclazocine—when they come for therapy, which is usually at an outpatient day program where they also have educational seminars, recreational activities, and group therapy. The best way to get rid of positively reinforced responses is to extinguish them by allowing the responses to occur but removing the reinforcement. The antagonist accomplishes this purpose by blocking the rewarding effects of heroin when it is used so that the heroin is no longer a reinforcer. Because the patients in the antagonist therapy treatment are outpatients who are free to spend their evenings and weekends with their friends, they inevitably attempt to use heroin, but this behavior quickly extinguishes and soon disappears.

Early experimental antagonist programs report success in keeping addicts in treatment. At the end of one year, 70 percent were still in the day program, and fewer than half of these were still taking the antagonist. Urine tests for heroin showed that fewer than 2 percent of the patients used heroin (Kleber, 1974). The results of programs such as these suggest that maintenance on antagonists may be more beneficial than maintenance on agonists.

Even though results have been encouraging (Kleber, 1974), an unexpected difficulty has arisen. When drug users know that they are getting an antagonist, they seldom try to shoot up heroin because they know that it will not have an effect. When they start taking the antagonist, they usually stop using heroin so suddenly that the positive reinforcing effects of the heroin on heroin-seeking behavior never get a chance to extinguish. Consequently, once the antagonist is discontinued, relapse rates will be high (W. R. Martin, Eades, Thompson, Huppler, & Gilbert, 1976). In addition, compliance is also a problem with antagonist therapies—patients often discontinue the antagonist when they want to use heroin. In spite of this problem, research has shown that if a person stays in antagonist therapy for 2 to 3 months or longer, chances of staying heroin free after treatment are considerably increased. Success rates with antagonist therapies are much better with people who are highly motivated to quit, have strong family support, and have legitimate professional careers to pursue or have been ordered by a court to discontinue heroin use (Jaffe, 1987). Antagonist therapy is beneficial, probably because it gives users a chance to decide to remove themselves from the temptation to relapse and permits them to develop other, more socially acceptable sources of reinforcement (Wikler, 1980).

To help overcome the compliance problem, a slow-release implant has been developed that will maintain effective levels of the antagonist on the body for weeks at a time.

CHAPTER SUMMARY

- The opioids are a class of natural and synthetic drugs. Opium, derived from the opium poppy, is the source of morphine and codeine. Heroin is made by slightly altering the morphine molecule to make it more lipid soluble and, consequently, more potent. Synthetic opioids such as pentazocine, methadone, and LAAM have a different chemical structure but have the same site of action and similar physiological effects. These drugs are sometimes referred to as narcotics or narcotic analgesics.
- Opium has been used for centuries in the Middle East. It was spread by Arab traders from there to Africa, China, and Europe, where in the sixteenth and seventeenth centuries it was widely used as a medicine. Its popularity grew until the middle of the 1800s, when legal restrictions were placed on its use in England. In the United States, all opioids were banned by the Harrison Narcotic Act of 1914.
- Most opioids are not well absorbed from the digestive system; they need to be inhaled or injected for full effect. The opioids are metabolized primarily in the liver and have a half-life of 2 to 4 hours, except for some synthetics such as methadone or LAAM, which have much longer half-lives.
- The body uses endogenous opiate-like chemicals called endorphins or enkephalins as both neurotransmitters and neuromodulators. There are several opioid receptors—mu, kappa, and delta. The mu receptor is responsible for reinforcing and many analgesic effects.
- One opioid system involves the spinal cord and a part of the brain known as the periaqueductal or central gray. It is thought that some of the analgesic properties of the opioids are mediated by this mechanism. Opioids also activate the nucleus accumbens and depress the respiratory center.
- Opioids cause a sleepy, dreamy state. When taken intravenously, they cause rushes, or feelings of intense pleasure resembling orgasm.
- Mu agonists cause feelings of pleasure and rushes at high doses in experienced users but often have unpleasant effects on inexperienced subjects.
- Chronic opioid use causes constipation and diminished sex drive and sexual performance, but if doses are not too high, chronic use does not interfere with intellectual or physical abilities.
- The opioids slow the behavior of nonhumans responding on both positively and negatively reinforced schedules. They slow avoidance responding at doses that do not affect escape but do not increase punishment-suppressed behavior.
- Tolerance to the different effects of opioids develops at different rates. Withdrawal symptoms occur after chronic opioid use, and the severity of withdrawal increases with higher chronic doses. These symptoms may last for about 3 days, and although very unpleasant, they are not life threatening.
- Humans and nonhumans will readily self-administer mu agonists whether they are physically dependent or not. The typical pattern is to start at low doses and increase dosage as tolerance develops. Once a stable pattern has been achieved, daily doses seldom change, and there is little variability from day to day. Intake is not cyclic, and voluntary withdrawal symptoms are seldom seen.
- Although chronic opioid use has few serious direct physical effects, the indirect effects of using the drug and the addicted lifestyle can be serious.
- Most attempts to treat chronic heroin use have a very high relapse rate—about 90 percent. The most popular current treatment is maintenance on a long-acting opioid such as methadone or LAAM or buprenorphine.