15

Cannabis

At first, a certain absurd, irresistible hilarity overcomes you. The most ordinary words, the simplest ideas assume a new and bizzare aspect. This mirth is intolerable to you; but it is useless to resist. The demon has invaded you . . .

—*Charles Baudelaire*

The hemp plant, or *Cannabis sativa*, was given its name and classification by Linnaeus in 1753. It is not known where the plant originated, but it was probably somewhere in central Asia. There are a great many varieties of cannabis, from small shrubs to bushy 20-foot-high plants. Commonly, the plants can be identified by their distinctive leaves, which are frequently long and slender and have serrated edges. There are male and female plants. The female plants are bushy and may grow quite tall. The male plants are smaller and not as bushy or vigorous. The female plant must be fertilized by pollen from the male flower to produce seeds. To help collect the wind-borne pollen, the female exudes a sticky resin from its flowering top. The resin also protects the seeds from heat and insects.

Since Linnaeus first classified *C. sativa*, there has been speculation about whether there was more than one species. Based on differences in form and potency, some botanists have identified three species: *C. sativa*, *C. indica*, and *C. ruderalis* (Grinspoon & Bakalar, 1993). Otherwise, it is speculated that there is only one species, *C. sativa*, of which there are two phenotypes (subspecies or varieties). One is traditionally cultivated in northerly areas for its fiber. It matures rapidly, has a low content of active ingredients, and is often called *hemp*. The other type is slow maturing, is traditionally cultivated in more southerly and tropical regions for its intoxicating properties, and has a relatively high content of psychoactive ingredients (Small, 1979).

THE CANNABINOIDS

The active ingredient in cannabis is usually reported as *delta-9-tetrahydrocannabinol* (delta-9-THC or Δ^9-THC), but the chemistry of cannabis is much more complex. An entire family of drugs, called the *cannabinoids*, is found exclusively in cannabis, and each may contribute, directly or

indirectly, to the behavioral effects of the cannabis plant. Over 60 cannabinoids have been identified (Grinspoon & Bakalar, 1997). The most common is delta-9-THC. Another cannabinoid is *delta-8-THC*, but there is relatively little delta-8-THC in cannabis compared to the delta-9-THC content. (The numbers in these names refer to the places where different parts of the molecule are attached. Because there are two different conventions for numbering the parts of the molecules, the same chemical can have two names. For this reason, you will sometimes see the active ingredients in cannabis called *delta-1-THC* and *delta-6-THC*. These are exactly the same as delta-9 and delta-8, respectively.) Other cannabinoids are drugs such as *cannabinol* (CBN) and *cannabidiol* (CBD), but by themselves these are not believed to have any important behavioral effects. The story, however, is not quite this simple because the amount of active ingredients appears to depend on preparation and route of administration, and these inactive ingredients may alter the potency or metabolism of more active ingredients.

Cannabis is sometimes taken orally, but usually it is burned and the smoke inhaled. It has been shown that burning changes many of the cannabinoids and appears to create new ones with increased potencies and effects. It is known, for example, that people can get high from smoking marijuana that contains virtually no delta-9-THC but is rich in CBD. Studies have shown that the inactive CBD is converted into delta-9-THC when the plant is burned, and new cannabinoids of unknown potency are also created (Kephalis, Burns, Michael, Miras, & Papidakis, 1976; Salimenk, 1976).

Not only are new cannabinoids created during burning, but more are created during digestion when the drug is taken orally and still more during metabolism. It is still not clear what effects each of these drugs has, how much each contributes to the effect that cannabis has on behavior, or how each of the cannabinoids interacts with the effects of other cannabinoids. Consequently, the effect of a particular cannabis plant cannot be predicted simply on the basis of the results of an analysis of its ingredients. As if things were not complicated enough, the content of marijuana changes over time, especially if exposed to light and air. With time, THC is apparently converted into CBN (Mechoulam et al., 1976). Recent research has shown that the major effects of marijuana smoke on mice—analgesia, hypothermia, and catalepsy—can be explained entirely by the presence of delta-9-THC and that these effects and blood levels of THC are not modified in any way by any of the other ingredients of marijuana smoke (Vavel, et al., 2005).

Cannabis Preparations

All parts of the cannabis plant contain THC, and the plant is prepared for consumption in various ways. The most familiar to North Americans is *marijuana*. The term *marijuana* is a Mexican–Spanish word that originally referred to a cheap tobacco but later came to refer to the dried leaves and flowers of the cannabis plant. Marijuana is usually smoked in a cigarette, cigar, or pipe but is sometimes baked into cookies or brownies.

In India, a distinction is made between *bhang* and *ganja*. Bhang is similar to marijuana. It is the dried leaves of uncultivated cannabis plants or female plants from which the resin has been removed. Generally, bhang is not very potent. Ganja, made from the tops of female plants from which the resin has not been removed, is three to four times more potent than bhang. In the West Indies, cannabis was imported directly from India, and the Indian term *ganja* rather than the North American *marijuana* is used. In Jamaica, *ganja* refers to the entire cannabis plant, and no distinction is made between ganja and bhang.

Hashish, also known as *charas* in India, refers to the dried resin from the top of the female plant. It is a pale yellow sap when harvested but turns almost black when dried. It may be consumed in a number of ways. Frequently, it is smoked, either alone or in a mixture with tobacco, or it may be baked in candies or cookies.

A purified variation of hashish is *hash oil* or *red oil*, which is prepared by boiling the hashish

in alcohol (or some other solvent), filtering out the residue, and then permitting the alcohol to evaporate. The cannabinoids are highly soluble in alcohol, which extracts them from the hashish and concentrates them. Depending on the degree of purity, hash oil may range from black or red to light amber. Hash oil is much more concentrated than hashish. It may contain up to 60 percent cannabinoids, and because it is easier to smuggle, it is becoming more popular. Hash oil may be consumed in several ways. It is common to place a drop on the paper of a regular tobacco cigarette, which may then be smoked inconspicuously. Other ways involve placing a drop on hot tinfoil and inhaling the smoke.

Marijuana samples seized in the 1960s contained, on average, 1.5 percent THC, but the average THC content increased throughout the 1980s to 3.0 to 3.5 percent (U.S. Department of Health and Human Services, 1995). In 1994, it was 3.5 percent THC. Since that time, there appears to have been about a 50 percent average increase in potency. Data from the Potency Monitoring Project indicate that the average THC content of commercial-grade marijuana was 5.03 percent in 2001 and 5.14 percent in 2002. The THC content in crossbred and hydroponically grown marijuana such as *sinsemilla* can be as high as 11.4 percent (National Drug Intelligence Center, 2005a). The increase in average potency is a result of the increased frequency of sinsemilla and high-potency marijuana found in police seizures. Between 1994 and 2002, samples of marijuana testing at higher than 9 percent THC increased more than 600 percent according to data from the Potency Monitoring Project (National Drug Intelligence Center, 2005a).

Extracted and Synthetic Cannabinoids

Pharmaceutical companies have developed cannabinoids for use as medicines. Some of these contain natural cannabinoids extracted and purified from the cannabis plant. One of these is *Sativex*, developed by a British company and granted a license for use in Canada in 2005 for treatment of neuropathic pain associated with multiple sclerosis. It contains THC, which the company calls *tetranabinex*, and cannabidiol, which they call *nabidiolex*. Sativex is administered in the form of a spray squirted under the tongue.

Several synthetic drugs similar to the cannabinoids have been developed, and some are licensed for commercial use. The first was *synhexyl* (called *parahexyl* in Great Britain). *Nabilone* is now used clinically to alleviate nausea and distress in patients receiving chemotherapy for cancer, and a synthetic THC, *dronabinol* (Marinol), is used for the same purpose. Other substances such as *levonantradol* have been developed but not marketed (Consroe & Sandyk, 1992). Another synthetic cannabinoid, *WIN 55212-2*, is now widely used in research. *SR-141716A*, more recently called *rimonabant*, is a synthetic that blocks the main cannabinoid receptor in the central nervous system (CNS) and is an antagonist to cannabinoids (D. Smith, 1998).

HISTORY

It is believed that cannabis originated in central Asia, but its early history is difficult to trace because it was cultivated and widely dispersed long before recorded history. The spread of cannabis appears to have occurred in the middle of the second century B.C. The people responsible were the Scythians, a warlike and mobile Middle Eastern tribe related to the Semites. The word *cannabis* is a Scythian word, and the Greek historian Herodotus described the Scythians as having used cannabis. He explained how the Scythians would enter their tents, throw hemp seeds on heated stones, inhale the vapors, and "howl with joy." This procedure was used as a cleansing ceremony after funerals (Benet, 1975).

The Scythians spread cannabis into Egypt by way of Palestine and northward into Russia and Europe, where the Scythian custom of burning cannabis seeds after funerals still remains (Benet, 1975).

In China, cannabis has been known since Neolithic times, about 6,000 years ago. The Chinese word for hemp, *ma*, has been in use for at

least 3,000 years. The plant was cultivated for its fiber; for its seed, which was a staple grain; for its intoxicating effects; and for its medicinal effects (Li, 1975, p. 56).

Cannabis has been used for centuries in India. Its use spread there directly from China rather than from the Middle East. From India, the drug was introduced to Africa by Arab traders who sailed along the east coast of Africa in the twelfth century. It spread across Africa along with the cultural influence of Islam. In Africa, it is known as *bangi* or *dagga* (Toit, 1975). Hemp was introduced into Russia and Eastern Europe by the Scythians. From there, it spread into Western Europe, where it was grown for centuries without its intoxicating properties being widely recognized. It was grown chiefly for its fiber, from which rope was made. It was also commonly used as a medicine.

Despite the fact that cannabis has been used as a folk remedy wherever it has been grown, scientific medical attention was not directed toward the drug until 1839 when W. B. O'Shaughnessy, a young chemistry professor at the University of Calcutta, tried it out on various ailments. He reported that hemp was an effective anticonvulsant and an appetite stimulant. There followed a series of papers that expounded the usefulness of hemp in the treatment of a number of disorders, including tetanus, neuralgia, dysmenorrhea, asthma, gonorrhea, and migraine. It was also reported to be useful in treating addiction to alcohol, opium, and chloral hydrate, and there were claims that hemp might be useful in the treatment of mental illness. One of the earliest of these claims was made in 1845 by the French physician J. J. Moreau de Tours, who used it to treat melancholia, hypomania, and other forms of mental illness (Moreau, 1973). In England, Sir John Russell Reynolds, president of the Royal College of Physicians and physician to Queen Victoria, used marijuana extensively in the treatment of neurological disorders (Consroe & Sandyk, 1992).

In general, the intoxicating effects of the drug remained unnoticed by Europeans until the publication of *Le Club des Hachichins* by the French writer Théophile Gautier in 1846. Gautier was a romantic and flamboyant writer who once offered a reward to anyone who could invent a new pleasure. The reward was earned (but we do not know whether he ever collected) by J. J. Moreau de Tours, the physician just mentioned. Dr. Moreau introduced Gautier to Le Club des Hachichins and gave him his first hashish with the words, "This will be subtracted from your share in Paradise." Gautier's account of the effects is now a classic description of the drug experience.

The drug that Gautier used was imported from the Middle East and North Africa. No one made the association between hashish and the quantities of hemp that were being grown at that time all over Europe to make rope. Even though he recognized that the two plants were related, Moreau believed that hemp and hashish were different. (What the members of the club received was not cannabis resin or what we now call hashish. Moreau used the term *hashish* to refer to a product made by boiling the plant in butter.)

In the era of European imperialism, rope was a very important item. Empires were built on naval strength, and ships could not sail without rope. Hemp did not grow well in England, so its production was encouraged in the American colonies. Sir Walter Raleigh was ordered to grow hemp in his Virginia colony, and consequently a crop was planted alongside tobacco in 1611, the colony's first season. American hemp proved to be of good quality, and hemp became a staple crop of the American colonies for more than 200 years. One of the better-known hemp growers was George Washington.

It is believed that the use of the cannabis plant for smoking and the word *marijuana* were introduced into the United States by Mexican laborers in the early twentieth century. Marijuana smoking spread slowly through the United States, but only among racial minorities and jazz musicians. This association did much to shape the perceptions of white legislators and to motivate opponents. In the 1920s, marijuana started to attract the attention of the authorities and the public, which

almost universally condemned it. Alarmist stories appeared in newspapers attributing criminal activity to the drug, especially crimes of violence.

Because there was a shortage of reliable scientific data to the contrary, these accusations went unchallenged. By 1937, most states had laws against marijuana, and the U.S. government had passed the Marijuana Tax Act, which imposed prohibitive taxes on possession and use, effectively eliminating the legitimate medical use of marijuana, and driving recreational users underground. Soon, most other Western countries had antimarijuana laws. In Canada, marijuana is classed as a "narcotic" and included in the Narcotic Control Act with the opiate drugs (and cocaine).

The medical profession, represented by the American Medical Association, has always supported the position of the U.S. government. In 1970, one result was the Controlled Substances Act, which ignored the previous century of accumulating medical evidence and declared that marijuana had no potential medical use but had a high potential for abuse.

In spite of these laws (or perhaps because of them), the popularity of marijuana continued to grow until it reached its peak in the 1970s and started to level off. Throughout the 1980s and early 1990s, use in the United States declined considerably, but that decline may be coming to an end (see the discussion later in this chapter).

ABSORPTION

Oral Administration

THC is a weak acid with a pKa of 10.6; consequently, it is not ionized at body pHs. The cannabinoids are extremely lipid soluble—in fact, they will hardly dissolve in water. When marijuana is taken orally, the cannabinoids are absorbed from the digestive system rather slowly. Oral absorption may be aided by adding oil to the plant material before consumption. This is often done by baking it in a food, such as cookies or brownies. When THC is taken orally in the form of a pill (Marinol is a synthetic THC dissolved in sesame oil), absorption is also incomplete and erratic, and there is considerable first-pass metabolism (D. Smith, 1998, p. 128). For this reason, the dose must be doubled or tripled to have the same effect as when inhaled (Institute of Medicine, 1982, p. 21).

The peak effects after oral administration usually occur 1 to 3 hours after ingestion and may last 5 hours or longer (Agurell, Lindgren, Ohlsson, Gillispie, & Hollister, 1984; Paton & Pertwee, 1973). Oral administration is also more likely to cause nausea or vomiting (Grinspoon, 1969).

With an interest in the use of cannabinoids for medicinal purposes, pharmaceutical companies are developing ways of delivering cannabis preparations that have more rapid absorption. Sativex, for example, is delivered as a spray under the tongue, but absorption is still not as fast as with inhalation. Cannabis inhalers are being developed, but none are commercially available.

Inhalation

Smoking cannabis plant material is an efficient route of administration. Usually the material is hand-rolled in a paper and the *joint* consumed in the manner of a tobacco cigarette. Hashish is often mixed with tobacco and smoked as a joint, but more often it is smoked in a pipe. A water pipe known as a *bong* is often used. It cools the smoke and prevents the loss of the drug through sidestream smoke. Hash oil is placed on joints or tobacco cigarettes or heated on tinfoil, and the fumes are inhaled.

Normal smoking causes about 10 to 25 percent of the cannabinoids in a marijuana cigarette to enter the lungs, and virtually all of that enters the body (Agurell et al., 1986). Blood levels of THC peak within 15 minutes. Effects may begin to be felt within a few minutes and reach a peak after 30 to 60 minutes.

Because of a widespread belief that absorption increases with the duration of each puff, experienced marijuana smokers will take a deep draw on

the marijuana cigarette and then hold the smoke in the lungs for 10 to 20 seconds. Actually, holding the smoke in the lungs may not contribute much to absorption of THC. It appears that the depth of an inhalation is much more important than duration in determining THC absorption (Azorlosa, Greenwald, & Stitzer, 1995).

DISTRIBUTION

Because of their high lipid solubility, the cannabinoids are distributed to all areas of the body according to blood flow but tend to become concentrated in the lungs, the kidneys, and the bile of the liver. Only about 1 percent of the administered dose at peak blood concentrations actually enters the brain. This amounts to 2 to 44 micrograms (Adams & Martin, 1996).

Figure 15-1 shows the rated "high" produced by different doses of THC administered by different routes. This peak high lags behind the peak blood levels of THC (Adams & Martin, 1996). The effect may be delayed because THC levels in the brain continue to increase for several hours after the drug has been consumed.

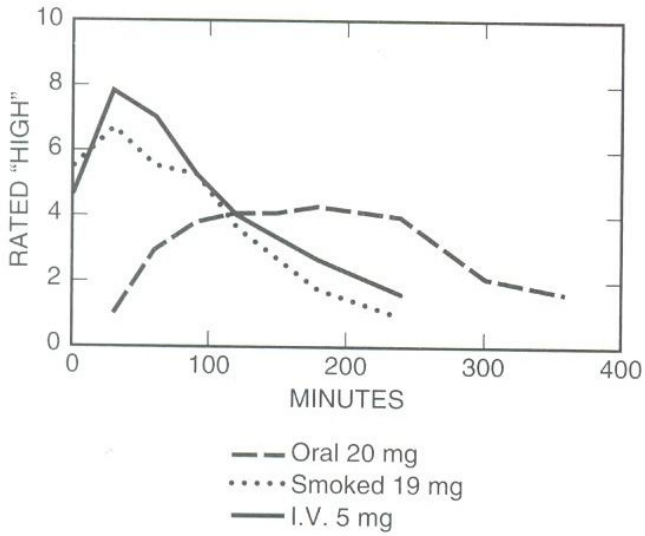

Figure 15-1 The time course for intensity of a subjective "high" after consuming various doses of THC via different routes of administration. (Adapted from Agurell et al., 1986)

EXCRETION

Metabolism starts as soon as the cannabinoids enter the body. There is some metabolism in the lungs if the drug is inhaled and some in the intestines if the drug is taken orally, but most of the metabolism takes place in the liver. Delta-9-THC is converted primarily into *11-hydroxy-delta-9-THC*, a substance that is believed to be more active than delta-9 and that penetrates the blood–brain barrier more easily (Adams & Martin, 1996). These substances are then rapidly converted into numerous other metabolites, some of which may have effects of their own. Some of these effects may be similar to those of THC, but others may be different. Most of these metabolites are less lipid soluble and are more easily excreted (Mechoulam et al., 1976).

CBD is thought to have only a slight effect of its own, but it appears to have a direct effect on the metabolism of THC. It blocks the enzyme that metabolizes delta-9-THC, slows its metabolism, and prolongs its duration of action. By contrast, CBN may speed the metabolism of THC (Mechoulam et al., 1976). It is also possible that CBD and CBN interact with THC in other ways. For example, these substances may alter the distribution of THC by displacing it from binding sites in the blood and increasing the amount of THC available for distribution to the brain (Siemens, Kalant, & Nie, 1976).

Blood levels of delta-9-THC and its main metabolites fall rather rapidly at first. This initial decline, due to redistribution, has a half-life of about 30 minutes in humans, but this is followed by a phase with a much slower rate of decline and a half-life of 20 to 30 hours (Agurell et al., 1986). During this phase, the rate of metabolism is limited by the rate at which the THC is released from body fat into the blood, which is quite slow. Traces may be detected in the body as long as 30 days later (Institute of Medicine, 1982, p. 20; Smith-Kielland, Skuterud, & Mørland, 1999).

It is still not clear whether regular cannabis users metabolize and excrete the cannabinoids faster than nonusers (Adams & Martin, 1996; Agurell et al., 1986). Research with laboratory

animals has not shown that the development of tolerance is related to any change in cannabinoid absorption, distribution, or metabolism (Agurell et al., 1986; Dewey, Martin, & Harris, 1976).

NEUROPHARMACOLOGY

Until the late 1980s, the mechanism by which cannabinoids alter neural functioning was a mystery. There was plenty of evidence that they work at a receptor site, but receptor sites for cannabinoids had never been identified. In 1990, an announcement was made that a receptor for cannabinoids had been identified by two scientists at the National Institute of Mental Health in Bethesda, Maryland. The scientists had been working on different problems independently in adjacent labs in the same building.

Researchers in the laboratory of Miles Herkinham had been working with the synthetic cannabinoid levonantradol, which had been made radioactive so that its location could be mapped in the brain of rats. Using this technique, the scientists in Herkinham's lab were creating a map of where levonantradol ended up in the brain and presumed that it was binding to a cannabinoid receptor at these sites.

In the neighboring laboratory of Tom I. Bonner, Linda Matsuda had discovered a gene that would make a receptor. The goal was to find a receptor for substances that modulate pain, but their receptor did not bind any known pain neurotransmitter; in fact, it did not seem to bind any known neurotransmitter. Matsuda knew, however, exactly where in the brain these receptors were found. She had made a map. When Matsuda heard of Herkinham's map, she went down the hall, and they compared maps. It was apparent in an instant that the two maps were similar; the mystery receptors were in exactly the same place in the brain where the radiolabeled levonantradol ended up. It did not take long for the two researchers to confirm that Matsuda's receptor was in fact a cannabinoid receptor (Restak, 1993).

Subsequent work has isolated at least two types of receptors, both of which are coupled to second-messenger systems that use cyclic AMP as the second messenger. The CB_1 receptor, the one identified by Herkinham and Matsuda, is found primarily in the CNS; the CB_2 receptor is located mainly outside the nervous system altogether (B. Martin, 2000; Munro, Thomas, & Abu-shaar, 1993).

The maps of Herkinham and Matsuda showed that CB_1 cannabinoid receptors are concentrated primarily in the cortex, hippocampus, cerebellum, and basal ganglia but occur also in the hypothalamus, brain stem, and spinal cord (Howlett, Evans, & Houston, 1992). CB_2 receptors are found in the spleen and the immune system (Mechoulam, Hanus, & Martin, 1994). These receptors are structurally different from those found in the brain, and they seem to be associated with the effects of cannabinoids on immune functions. This peripheral cannabinoid receptor also appears to be affected by CBN. These discoveries raise the possibility that there may be many other types of cannabinoid receptors, as there are with the receptors for other neurotransmitters and neuromodulators. Different types of cannabinoid receptors could mediate different cannabinoid effects and make it possible to develop medicines that selectively produce medically useful cannabinoid effects with a minimum of side effects.

Like the discovery of the opioid receptor, the discovery of the cannabinoid receptor has stimulated research into the nature of the endogenous ligand, the substance (or substances) that occurs naturally in the body and acts as the receptor. Such endogenous substances have been referred to as *endocannabinoids* (Di Marzo, Melck, Bisogono, & Di Petrocellis, 1998). The first endocannabinoid was identified by William Devane and Raphael Mechoulam at the Hebrew University of Jerusalem. They called it *anandamide* after the Sanskrit word *ananda*, meaning "internal bliss" (Mechoulam et al., 1994; Restak, 1993). These researchers have also found two more. One of these is *2-arachidonylglycerol*, more conveniently referred to as *2-AG*. THC is longer lasting and had a much greater effect on the cannabinoid receptors than the endocannabinoids.

These discoveries stimulated an explosion of research. Its full impact has yet to be felt, but it will likely lead to new drugs and medicines as well as a better understanding of where and how THC and the cannabinoids alter the functioning of the brain and change behavior.

Cannabinoid receptors and their endogenous ligand appear to function more as neuromodulators of many different neurotransmitters than as neurotransmitters themselves. CB_1 receptors are located mostly in neurons on the terminal boutons. That is, they are presynaptic, and the enzyme that destroys the endocannabinoids is located in the cell body and dendrites of the postsynaptic cell. This indicates that the endocannabinoids are a signaling mechanism between the postsynaptic cell and the presynaptic cell. What seems to be happening is that when the membrane of the postsynaptic cell is depolarized, this triggers the release of an endocannabinoid that acts at the CB_1 receptors on the presynaptic membrane, causing ion channels to open and consequently blocking the action potentials as they arrive. The result is that the presynaptic neuron is disabled. Thus, the postsynaptic neuron is able to shut down the presynaptic neuron. If the neurotransmitter released by the presynaptic neuron is inhibitory, this effect is called *depolarization-induced suppression of inhibition* or (DSI). If the transmitter is excitatory, it is called *depolarization-induced suppression of excitation* (DSE). This effect lasts for tens of seconds and affect other synapses in the area.

When THC is administered, it would have the same effect of shutting down both excitatory and inhibitory transmission in neurons that have these CB_1 receptors in the entire brain for a much longer period of time.

DSI and DSE operate on neurons that use many different neurotransmitters, including norepinephrine (NE), dopamine (DA), serotonin (5-HT), acetylcholine (ACh), histamine, opioid peptides, gamma-aminobutyric acid (GABA), and prostaglandins. In addition, cannabinoids are known to increase synthesis of NE, DA, 5-HT, and GABA. They can potentiate the actions of NE, ACh, GABA, and opiate peptides, and they can alter the functioning of receptors for NE, DA, and ACh. Not all of these effects, however, are likely to be mediated via the cannabinoid receptor; some may be achieved directly by other means (Pertwee, 1992).

Cannabinoid receptors are found in the nucleus accumbens, and it is clear that the THC increases DA levels and activity in the mesolimbic DA reward system. They perform this function by potentiating the effects of endogenous opioid peptides, which in turn function as neuromodulators of DA transmission. This effect appears to be responsible for the reinforcing effects of cannabinoids (Gardner, 1992; Tanda, Pontieri, & Chiara, 1997).

Cannabinoid receptors are also found in the cerebellum and basal ganglia, other parts of the extrapyramidal motor system, and the hippocampus. These anatomical findings correspond to what we know about the effects of cannabinoids on movement and memory.

The endocannabinoid system within the nervous system appears to contribute to many functions, particularly those involved in stress recovery. One review article concluded, "Thus, 'relax, eat, sleep, forget and protect' might be some of the messages that are produced by the actions of endocannabinoids, alone or in combination with other mediators" (Di Marzo et al., 1998, p. 528). There is also evidence that CB_1 receptors are important to the reinforcing effects and the development of physical dependence on opiate drugs such as morphine and heroin (Ledent et al., 1999).

Few cannabinoid receptors are found in the medulla in the brain stem. This is not surprising since we know that they have little effect on the breathing reflex (B. Martin, 2000).

EFFECTS OF CANNABIS

Effects on the Body

Low and moderate doses of marijuana have predictable physiological effects on most people. The most common effect is bloodshot eyes, caused by dilation of the small blood vessels in

the whites of the eyes. This effect, which reaches a peak about an hour after smoking, causes no discomfort to the user. Heavy marijuana use can sometimes be detected because the user looks stoned—an appearance marked by a slight droop in the eyelids (Domino, Rennick, & Pearl, 1974).

Another effect is the sensation of having a dry mouth and a compulsion to drink, which frequently induces some users to drink alcoholic beverages while smoking marijuana. An intense feeling of hunger, known as the *munchies*, is strongest about 3 hours after smoking, when other effects have declined. This increase in appetite eventually appears to show tolerance; after a few weeks of continuous marijuana use, appetite is actually depressed.

Smoking marijuana also causes a reliable increase in heart rate, which can go as high as 160 beats per minute in some individuals. There are also unpredictable fluctuations in blood pressure and body temperature. Nausea and vomiting sometimes result, especially after the user has been moving around. At higher doses, headaches are sometimes reported (Paton & Pertwee, 1973).

Effects on Sleep

Marijuana causes drowsiness and increases sleeping time in humans, but higher doses interfere with sleep, causing restlessness and insomnia (Tart & Crawford, 1970). Habitual users may have difficulty getting to sleep (Paton & Pertwee, 1973). Low doses of marijuana cause slight changes in sleep-stage patterns, and many studies have found no effect on sleep. At higher doses, marijuana disrupts normal sleep stages, but when marijuana is discontinued, this does not cause the poor quality of sleep, frequent wakening, or nightmares often seen with barbiturate withdrawal (Feinberg, Jones, Walker, Cavness, & Floyd, 1975).

Medically Useful Effects

Some effects on the body that are not normally noticed have some medical usefulness. For example, THC reduces the pressure of the fluid in the eyeball. *Glaucoma*, a condition in which pressure in the eyes is too high, has been successfully treated with marijuana. In a rather famous case in the United States, a young man with glaucoma was prosecuted for growing marijuana but won his case by arguing that it was necessary to break the law in order to treat his glaucoma (Grinspoon, 1971, p. 397; Grinspoon & Bakalar, 1993, 1997, pp. 48–58).

THC can act as an *antiemetic* (a drug that stops nausea and vomiting). Nabilone and Marinol are now frequently used to treat the nausea and sickness of people receiving chemotherapy for cancer.

THC has been shown to be effective in treating movement disorders and *spasticity* (Braude & Szara, 1976, vol. 2; S. Cohen & Stillman, 1976; Institute of Medicine, 1982). People with damaged spinal cords and people suffering from diseases like multiple sclerosis often experience uncontrollable muscle spasms, loss of motor control, and pain. Clinical studies clearly show that cannabinoids are an effective treatment for this spasticity (Earleywine, 2000).

The cannabinoid system has recently been implicated in the modulation of pain responses. Synthetic cannabinoids can decrease the amount of glutamate released by neurons in culture (Shen, Piser, Seybold, & Thayer, 1996). CNS neurons in pain centers become less responsive to pain-inducing stimuli after administration of synthetic cannabinoids (W. R. Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Finally, blockade of CB_1 receptors in the spinal cord increases sensitivity to pain as measured by the hot plate test (J. D. Richardson, Aanonsen, & Hargreaves, 1998). Together, these results suggest that endocannabinoids play a role as a natural analgesic by shutting off pain signals. Natural or synthetic cannabinoids may mimic this effect.

In a review of the literature on medical marijuana, Earleywine (2002) concluded that cannnabinoid drugs have been proven effective for the following conditions: glaucoma (although alternative treatments work better), nausea (although alternative methods work better but cost more), pain, spasticity, and diminished appetite and weight

loss experienced by people with cancer and AIDS. Cannabinoids have a potential for use as a treatment for anxiety, arthritis, dystonia, insomnia, microbial infections, seizures, Tourette's syndrome, and tumors.

Many people who use cannabis for medicinal purposes inhale cannabis smoke. The rapid absorption of the cannabinoids allows them to get rapid effects and to titrate the dose they receive so that they can get maximum medicinal effect without side effects (for medicinal purposes, getting high is usually considered an undesirable side effect). Commercially manufactured cannabinoids such as Nabilone and Marinol are taken as pills and absorbed slowly, and have a delayed effect, making titration difficult. This is one reason why many users of medicinal cannabis prefer smoking marijuana to taking pills. In an effort to overcome this problem, newer medicinal cannabinoid preparations like Sativex are administered as a spray under the tongue and are absorbed much faster, making titration easier. Cannabinoid inhalers that would have much faster effects are also being developed.

Now that cannabinoid receptors have been identified, an increased understanding of how the cannabinoids produce their various effects may soon make it possible to isolate specific medically useful effects and design cannabinoids that will produce them without side effects (Consroe & Sandyk, 1992).

EFFECTS ON BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

The first European writer to describe the effects of cannabis was Théophile Gautier, who was a member of Le Club des Hachichins of Paris in the middle of the nineteenth century (Gautier, 1966). Gautier's accounts must be considered with some skepticism because they were written primarily to entertain rather than inform. Gautier was an artist, not a scientist, and a rather creative and romantic artist at that. And again, the drug that Gautier and the other club members took was not what we know as hashish but the very potent *dawamesc*, made by boiling the cannabis plant in oil or butter. In addition, dawamesc contains *cantharis* (a supposed aphrodisiac also known as *Spanish fly*), which has unpredictable toxic effects (Grinspoon, 1971, p. 58). Gautier's experiences are, therefore, not typical of contemporary North American use, but much of what he reports is characteristic of the hallucinogenic effects of cannabis intoxication at high doses. Gautier's account is a classic, and in spite of its embellishments and inaccuracies, it has shaped the expectancies and prejudices of users and opponents through the years.

Later, Charles Baudelaire, another member of the club, published his accounts of the hashish experience. Other classical descriptions were written by Fitzhugh Ludlow, the American son of an abolitionist minister and friend of Mark Twain, and the American traveler and diplomat Baynard Taylor (Ebin, 1961; Solomon, 1966).

Mood Changes and Getting High

A more typical experience with marijuana is characterized by swings of mood from euphoric gaiety with hilarious laughter to placid dreaminess. The experience is nearly always pleasant—a feeling of well-being and joyfulness is usually referred to as being high—but occasionally there are feelings of anxiety and foreboding, even at low doses in hospitable surroundings.

When cannabis is consumed socially, as it often is, there is frequent laughing and good humor. Almost anything seems funny, and the most innocent event or statement may ignite gales of contagious laughter. If the drug is taken alone or in a quiet setting, the user may spend time predominantly in a dreamy state getting off, or concentrating on, the subjective experience. It is frequently felt that perceptions are keener and that sensory effects are more intense and are enjoyed more. Just as slightly funny things seem hilarious, mundane thoughts and insights may take on great significance and importance. Artists

and musicians frequently feel that their creativity is enhanced.

Although physical activity sometimes increases and users feel that their actions are effortless, they generally avoid tasks requiring effort and prefer instead to remain passive.

In spite of consistent reports from users that marijuana elevates mood, when subjective changes in feelings are measured systematically by a test like the POMS, findings are not at all clear-cut. Both positive and negative changes in mood have been reported (de Wit, Kirk, & Justice, 1998; R. T. Jones & Benowitz, 1976; Rossi, Babor, Meyer, & Mendelson, 1974), and the pattern of responding to mood scales appears to be unique. For example, in one study, smoking marijuana caused an increase in scales indicating stimulation and at the same time increased scores on scales associated with sedation. There were no changes in scales indicating euphoria or positive mood states (Chait et al., 1988). The subjective effects of smoked marijuana and oral THC are similar, except for their time course (Chait & Zacny, 1992) (see Figure 15-1).

Many researchers believe that the reason for variability in subjective ratings between studies is that environment can have a considerable influence on how the drug changes mood. The effects of surroundings on mood have been investigated, but differences such as smoking in a neutral as opposed to a psychedelic environment or while watching television, listening to rock music, or carrying on a conversation had no effect on subjective self-ratings. One factor that does seem to be important, however, is the mood of others. In an experiment in 1978, mood self-ratings were not correlated with ratings of intoxication, but after subjects took marijuana, mood ratings were highly correlated with the mood of the other subjects in the experiment, whether they were high or not. Thus, it would seem that after smoking marijuana, a person becomes more susceptible to being influenced by the mood of others (Rossi, Kuehnle, & Mendelson, 1978).

Mood changes have been studied extensively in experienced users, but almost no attempts have been made to study the subjective effects of marijuana in naive subjects, even though one's first experience with the drug seems to be an important determinant of later use. One study of college students showed that those who reported positive effects at first experience were more likely to use the drug sooner the second time and use it regularly later (Davidson & Schenk, 1994).

Perception

One of the subjective effects of the cannabinoids is an increased sensory sensitivity, but subjective testing of sensory thresholds has found only decreases in sensitivity or no change in auditory, visual, and tactile thresholds (R. T. Jones, 1978). The cannabinoids also cause a loss of sensitivity to pain, which indicates that the drug has analgesic properties.

The time-distorting effect of cannabis has been demonstrated experimentally (Domino, Rennick, & Pearl, 1976). Weil, Zinberg, and Nelson (1968) found that three subjects out of nine judged a 5-minute speech to be 10 minutes long. Increases in subjective time rate (people experience time passing more quickly) is one of the most reliable behavioral effects of cannabis (Chait & Pierri, 1992).

Memory

Marijuana appears to have no effect on the ability to recall material already well learned or on recognition memory (the ability to recognize words or figures), but it does disrupt the ability to recall words or narrative material (Chait & Pierri, 1992). The problems occur primarily in short-term memory, in which information is held actively in the brain for short periods. While intoxicated with cannabis, people frequently show what has been called *temporal disintegration*—they lose the ability to retain and coordinate information for a purpose. If they are required to hold information in the brain for any length of time, it frequently gets lost before it can be used. It is not unusual, for example, for people under the influence of cannabis to start a sentence and then stop

halfway through because they forgot what they started to say. When such things happen, others who have been using the drug are not likely to remember the initial idea either, and some very disjointed conversations result (Weil & Zinberg, 1969). Some users have described this inability to hold things in short-term storage by saying that thoughts come so quickly that it is difficult to keep from being distracted by them. It is quite likely that the deficits in short-term memory and the distorted time sense are related since memory helps with judging the passage of time.

It has been pointed out that the effects of cannabis on memory are similar to the symptoms of Korsakoff's psychosis, a neurological disorder seen in long-term alcoholics (see Chapter 6). Among the symptoms of Korsakoff's psychosis are a memory disorder and a disorientation in time that is caused by damage to the limbic system and hippocampus. This similarity has led to speculation that cannabis affects memory by blocking the functions of the hippocampus (L. L. Miller & Drew, 1974). This is a likely hypothesis in light of the fact that cannabinoid receptors are found in high concentrations in the hippocampus.

Attention

There also appears to be a deficit on tasks requiring vigilance or sustained attention, particularly if the task takes more than 50 minutes (Chait & Pierri, 1992). Just as cannabis creates an inability to retain thoughts, it also appears to make attention more distractible. Many researchers report that subjects are not able to concentrate on the tasks they are doing after being given marijuana. They are easily distracted, usually by events in their own minds. Being easily distracted can interfere with many different types of tasks (De Long & Levy, 1974).

Creativity

One of the subjective effects of cannabis is that it helps to improve appreciation of art, even art produced by the user. The widespread belief that the drug increases the creativity of artists may have arisen largely because the drug was widely used by musicians and artists. Nevertheless, there is no consistent evidence from objective research that creativity is enhanced (Chait & Perri, 1992) or that artists who use marijuana are more successful than artists who are not users (Grinspoon, 1971, p. 157).

Performance

Any attempt to summarize the effects of cannabis on the various measures of performance is nearly impossible. There is no doubt that certain tasks are impaired by high doses of the drug, but results are so variable that it is difficult to be specific. As we have seen, variability among experimental findings can arise from differences such as experience of subjects, instructions, motivation, setting, and dosage. These are only a few of the factors that can contribute to the confusion—and no doubt have done so (Chait & Pierri, 1992).

An example of this confusion can be found in experiments on hand–eye coordination, using a pursuit rotor wherein subjects are required to track a moving target manually. One experiment found that marijuana impaired this ability in novice subjects, but the performance of experienced subjects actually improved with marijuana (Weil et al., 1968). Findings like these are not unusual.

Another factor complicates the findings in performance tasks: Deficits in performance may not indicate a loss of the specific ability being measured. Many (but not all) experiments show an increase in mean reaction time. A careful analysis of the data, however, shows that the slowing is a result of a few rather long reaction times in an otherwise normal performance. These occasional long latencies appear to be due to lapses in attention and an inability to concentrate on the task rather than an inability to move the hand. In another experiment, subjects were required to pursue a moving dot on an oscilloscope screen with another dot that they could control by hand. Marijuana interfered with performance, but the interfering factor was a lack of motivation and interest in the task, not a lack of coordination.

One subject stopped following the moving dot and drew patterns on the screen with the dot that he controlled (Manno, Manno, Kiplings, & Forney, 1974).

Simple reaction time appears to be unaffected by marijuana. In complex and choice-reaction-time tests, accuracy but not speed is likely to be affected. Marijuana is often reported to impair hand–eye coordination tasks such as the pursuit rotor and tasks that measure both psychomotor and memory tests (e.g., the digit symbol substitution test) (de Wit et al., 1998).

Driving

Numerous studies have been conducted on the effects of marijuana on driving and flying, and most have reported impaired performance, although such effects are not reported for all individuals (Chait & Pierri, 1992; Klonoff, 1974).

Studies in a driving simulator have shown that marijuana has little effect on the ability to control a car, but it impairs the driver's ability to attend to peripheral stimuli. Thus, marijuana-intoxicated drivers might be able to stop a car as fast as they normally could, but they may not be as quick to notice things that they should stop for, probably because they are attending to internal events rather than to what is happening on the road (Moskowitz, Hulbert, & McGlothlin, 1976). One recent study of the effects of THC on driving in real traffic showed significant impairment caused by low doses of THC (100 and 200 micrograms/kg body weight). These effects were greatly amplified when small doses of alcohol were consumed as well (Ramaekers, Robbe, & O'Hanlon, 2000).

Performance Screening Tests

One concern raised about marijuana and driving is that it is not possible to do a roadside screening test for THC in the same manner as a breathalizer test for alcohol. The State Police of Victoria in Australia have been developing a performance screening test for marijuana intoxication based on the test developed for alcohol in the 1970s called the *Standardized Field Sobriety Test*. It consists of tests of *gaze nystagmus* (eye movements as someone follows a moving object with their eyes), the *walk and turn test* (where the subject walks heel to toe up and down a line), and a one-leg stand (where the subject stands on one leg and counts out loud). Performance on all these tasks is scored using objective criteria. This test was administered to three groups. One had been given a placebo, and the other two had smoked marijuana with low and high THC content. The test identified 2.5 percent of the placebo group as being intoxicated and 38.5 percent of the low-THC group and 56.4 percent of the high-THC group as being intoxicated. These results suggest that it should be possible to develop a reliable screening test for THC intoxication (Papafotiou, Carter, & Strough, 2005).

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Unconditioned Behavior

THC has a biphasic effect on spontaneous motor activity (SMA); in many species, there is an increase in activity followed by a depression in behavior. The depressant effect is more powerful, appears in more species, lasts longer, and is more resistant to tolerance. Interestingly, the stimulatory effects appear to be an exaggerated response to environmental stimuli rather than a general increase in activity (de Wit et al., 1998). At high doses, the decrease in motion is called *ataxia* and is accompanied by a loss of motor control and by fine tremors. Laboratory animals assume one posture without moving for long periods. Monkeys stare into space or look at their hands and occasionally appear as though they are hallucinating (Paton & Pertwee, 1973).

One effect was noticed early in animal experimentation: a taming effect, or a reduction in aggression. Animals that were normally aggressive and hard to handle became tame and placid after receiving THC. THC will reduce the attack behavior of the dominant member of a pair of rats and will also diminish the ability of a submissive

rat to defend itself in a fight. Predatory attack behavior of several species is also reduced.

In rats, THC causes a decrease in food intake and a subsequent weight loss. THC is about half as potent as amphetamine in suppressing food intake, but unlike amphetamine, THC causes an increased preference for sweet sugar solutions. This may be related to the munchies effect in humans (Sofia, 1978).

THC is as potent as morphine in reducing the response of laboratory rats to painful stimuli, as measured by a number of tests. CBN also has analgesic effects but is only as potent as aspirin. No analgesic effects were found for CBD (Sofia, 1978). The metabolites of THC are probably more potent than the parent compound. At one time, it was believed that these effects were dependent on interactions with the opiate system, but now it has been shown that the analgesic effects are mediated through systems in the brain and spinal cord and are independent of opiate pain control (de Wit et al., 1998).

Conditioned Behavior

As with humans, THC appears to interfere with tasks that require short-term memory, such as the radial maze and the *matching-to-sample test*, in which the animal is required to remember a stimulus for a brief period of time. These deficits in memory are correlated with suppression of firing of cells in the rat's hippocampus and can be caused by direct injection of THC into the hippocampus (Heyser, Hampson, & Deadwyler, 1993). THC has also been reported to interfere with schedules and tasks that require timing. Performance on other tasks appears normal until higher doses, which suppress all behavior, are reached.

Like the barbiturates and the benzodiazepines, THC decreases avoidance responding at doses that do not alter escape responding in a discriminated avoidance task, an effect it shares with the tranquilizers, anesthetics, and alcohol. One might expect that a drug that has both antianxiety and analgesic effects would increase punished behavior, but neither delta-9-THC nor delta-8-THC appears to increase behavior suppressed by punishment with electric shock (McMillan & Leander, 1976). In this regard, THC is very unlike the tranquilizers, anesthetics, and alcohol.

DISSOCIATION

Both delta-9-THC and delta-8-THC cause dissociation of an avoidance task in rats. Rats were unable to transfer to a nondrug state what they had learned in a drug state, and there was a symmetrical inability to transfer to the drug state what they had learned in the nondrug state (Henricksson & Järbe, 1971). Dissociation has also been demonstrated in humans using marijuana. In one study, subjects were asked to learn a list of words after taking a placebo and then to recall the list after smoking marijuana and vice versa. When the subjects acquired information in one state, they had difficulty transferring it to the other state. This effect was not very powerful because the loss of recall could be overcome by prompting and cuing the subjects by reminding them of word categories (Stillman, Eich, Weingartner, & Wyatt, 1976). In another study, only *asymmetrical dissociation* was found. Information acquired while the subjects were not intoxicated was remembered after smoking marijuana, but information acquired during marijuana intoxication was not remembered when sober (Darley & Tinklenberg, 1974).

Dissociation has not been demonstrated for motor skill and perceptual tasks such as card sorting, or on the pursuit rotor task or signaled avoidance, even though marijuana impaired performance on those tasks (Järbe & Mathis, 1992).

DRUG STATE DISCRIMINATION

Rats are easily able to discriminate THC from placebo when it is administered intravenously, intraperitoneally, or orally. The stimulus properties are evident as early as 7½ minutes after injection and peak at 30 minutes but are still reliable at 60 minutes. A training dose of delta-9-THC would generalize to delta-8-THC and the 11-hydroxy metabolite but would not generalize to CBD

(Balster & Ford, 1978), although some generalization occurs to CBN (Järbe & Mathis, 1992). Interesting interactions have been noted with these other naturally occurring cannabinoids; in some experiments, CBD has been shown to enhance and prolong the stimulus effects of THC (Järbe & Mathis, 1992).

Many other drugs have been tested to learn whether the THC response generalizes to them. There appears to be partial generalization to sedative drugs and no generalization to drugs of any other class, including stimulants, hallucinogens, and opiates. Cannabinoid discriminations can be blocked by the cannabinoid receptor antagonist SR-414716A. Interestingly, animals trained to discriminate THC generalized poorly to anandamide and then only when anandamide was given in high doses (de Wit et al., 1998).

Experienced marijuana smokers can easily learn to distinguish marijuana cigarettes containing 0 percent THC from marijuana cigarettes containing 2.7 percent THC. In one study, they were able to make the discrimination within 90 seconds of taking the first puff. They were successful in identifying marijuana containing 1.7 percent THC, but they identified a sample with 0.09 percent THC as a placebo (Chait et al., 1988).

TOLERANCE

In laboratory animals, tolerance to the effects of THC on operant behavior develops rapidly. Depending on the dose and the route of administration, complete tolerance may develop after 5 or 6 days of repeated injections of THC (Abel, McMillan, & Harris, 1974). This tolerance lasts for more than a month, and there is cross-tolerance between delta-9-THC and its 11-hydroxy metabolite (Kosersky, McMillan, & Harris, 1974). Tolerance also develops within a few days to increases in motor activity, but the progress is much slower for the depression in activity. There is no tolerance at all to the anorexia effects or the discriminative stimulus effects. There is also tolerance to the lethal effects in pigeons; a dose of 180 mg/kg had no effect on tolerant animals but was lethal in naive pigeons (B. Martin, 2000). Tolerance does not appear to be due to alterations in absorption, metabolism, or distribution of the drug (Dewey et al., 1976). Instead, it is known that tolerance is associated with a decrease in the number of cannabinoid receptors in selected brain areas (B. Martin, 2000).

There is some disagreement about the development of tolerance in humans. Many marijuana users have reported a sensitization or *reverse tolerance* to the drug—they become more sensitive to the effects, rather than less sensitive, with repeated use. Reverse tolerance has never been shown in laboratory studies with nonhumans or humans. For several reasons, reverse tolerance is observed only outside the laboratory. One likely reason is a matter of dosage. In laboratory studies, dosage is carefully measured. Outside the laboratory, users calculate their consumption in terms of the number of joints they smoke. With experience, users learn to inhale more efficiently so that they are able to get more drug into their bodies from a given amount of marijuana. Therefore, they will require fewer joints to get high. In addition, experience may be required to learn not only how to get high but also the activities, situations, and company that contribute to the high. All these factors could contribute to the observation that over time, fewer joints are needed to get high.

Early experiments showed that tolerance to the subjective effects of THC and marijuana would develop only if the drug was given in high doses for an extended period of time (Frank, Lessin, Tyrrell, Hahn, & Szara, 1976; R. T. Jones & Benowitz, 1976), but more recent studies have shown that the subjective effects of both high and low doses of orally administered THC and high-potency smoked marijuana administered four times a day showed a considerable drop over 4 consecutive days (Haney, Ward, Comer, Foltin, & Fischman, 1999a, 1999b). In the same experiment, no tolerance to increased food consumption was seen.

WITHDRAWAL

Withdrawal symptoms have been seen after prolonged administration of high doses in nonhumans. These symptoms are not severe and frequently

appear as an increase in motor behavior. Recently, it has been reported that cessation of chronic cannabinoid injection causes a marked withdrawal in rodents, but this withdrawal is usually masked by the long half-life of THC and its metabolites. If animals receive high doses of a synthetic cannabinoid for 2 weeks, no withdrawal is seen after administration stops. If the animals receive an injection that blocks cannabinoid receptors, however, withdrawal does occur as measured by release of stress hormones (de Fonseca, Carrera, Navarro, Koob, & Weiss, 1997).

Withdrawal symptoms, without the use of cannabinoid blockers, have been reported with humans. In an early study, human volunteers took high doses of oral THC every 4 hours for 12 days. When the drug was stopped, the subjects reported a sense of "inner unrest" after 6 hours. By 12 hours after the last dose of THC, subjects reported a variety of symptoms, including hot flashes, sweating, runny nose, loose stools, hiccups, and loss of appetite. Other symptoms that were noticed by the experimenters were irritability, restlessness, and insomnia (R. T. Jones & Benowitz, 1976).

More recent research, however, has shown withdrawal symptoms to smoked marijuana and oral THC after four doses per day for only 4 days. During the withdrawal period, subjects reported increased anxiety and irritability and decreased food intake and quality and quantity of sleep (Haney et al., 1999a, 1999b).

SELF-ADMINISTRATION IN HUMANS AND NONHUMANS

THC is self-administered by humans, but until recently there have been no demonstrations of nonhuman self-administration (Griffiths, Bigelow, & Henningfield, 1980). Tanda, Manzar, & Goldberg (2000) trained squirrel monkeys to give themselves low does of THC, but it was necessary to train them to self-administer cocaine first. The problem seems to be that THC is not readily soluble in water, and this makes it difficult to administer just the right dose intravenously. After all, humans never inject THC. More success has been achieved with water-soluble synthetic cannabinoids like WIN55212-2, which is self-administered by mice (Lident et al., 1999). THC has also been shown to create a conditioned place preference in rats (Lepore, Vorel, Lowinson, & Gardner, 1995).

It is seldom difficult to get humans to take cannabis. In a hospital ward setting, Mendelson and his associates (H. H. Mendelson, Kuehnle, Greenberg, & Mello, 1976) conducted an experiment in which subjects were required to press a button to gain points with which they could buy marijuana cigarettes. A joint could be earned for about 30 minutes of work. Extra points could be saved for money at the end of the experiment. In this experiment were two groups of subjects: casual users and heavy users of marijuana. The number of joints smoked by each group was far less than the number available but showed a slight increase over the 26 days of the experiment. Casual users smoked about two joints per day at the beginning and increased to three by the end of the experiment. Heavy users started at four a day and ended at about seven. Apart from this slight increase, the amount consumed was fairly stable from day to day; no cyclic patterns or periods of abstinence were noted, although there was a big increase on the last day that marijuana was available. No evidence of withdrawal was seen when use was stopped. In this study, there seemed to be a level of high that most users tried to achieve, and they stopped when they achieved it. In other words, they appeared to titrate the dose.

Marijuana self-administration in humans in experimental settings has been demonstrated a number of times since then, but, curiously, it has not yet been shown that THC content is important. In one recent experiment (Kelly, Foltin, Mayr, & Fishman, 1994), marijuana cigarettes with 0 and 2.3 percent THC were smoked with equal frequency, even though self-reports of "high," "potency," and "liking" were higher for the THC-containing marijuana.

Titration

The ability of users to titrate the dose was studied in another experiment. Experienced marijuana users were given joints of different potencies and asked to smoke until they achieved a "nice high." To some extent, these experienced users did smoke fewer high-potency joints than low-potency joints before they stopped, but the compensation was far from perfect. The subjects smoked 60 percent more of the weak marijuana than the strong marijuana, but even after this compensation, they administered a 250 percent higher dose to themselves when the strong joints were available (Cappell & Pliner, 1974). On the basis of this experiment, even experienced users seem unable to adjust their intake accurately in the face of variations in the potency of the marijuana they are smoking. Doubt is also cast on the notion that there is such a thing as a "social high" that can be determined on the basis of an administered dose. Factors other than dosage must control marijuana intake.

Even though people in experiments will smoke an equal number of marijuana cigarettes with 0 percent THC and with 2.4 percent THC (Kelly et al., 1994), choice experiments have shown that the reinforcing effect of marijuana increases with higher THC content. In a preference study, experienced users sampled marijuana of two different potencies (0.63 and 1.95 percent THC). During the choice phase of the experiment, subjects chose the high-potency marijuana much more often than the low-potency marijuana (Chait & Burke, 1994).

EPIDEMIOLOGY

In North America, cannabis is a social drug. In the 1970s, most marijuana was smoked in groups. On some occasions, it may have been consumed in large public gatherings such as rock concerts or large parties, but most of the gatherings were of close friends and acquaintances. The drug was consumed in an almost ritualistic manner. A pipe or joint was passed from one person to another in a circle. Each person took a drag or, if already sufficiently high, passed it along. More recently, solitary use of the drug has become more common, and the ritualism has declined.

The social nature of marijuana may also be responsible for initiation to marijuana use. A very small percentage of users first smoke marijuana alone. There can be no doubt that the strong social reinforcement and the feelings of shared pleasure and intimacy contribute considerably not only to the start of drug use but to its continuation as well.

In some countries where cannabis is a traditional drug with a long history, the pattern and extent of use are quite different than in Europe and North America, where cannabis use is comparatively recent. In countries such as India, Egypt, Greece, Morocco, and Jamaica, the majority of cannabis users take extensive doses every day, and there is little casual use. In the United States, the vast majority of users are casual, and only a small percentage use it daily. Compared with other countries, relatively small amounts are consumed in North America. It has been estimated that a casual cannabis user can get "stoned" on 5 to 6 mg of THC, and the average daily user in the United States consumes about 50 mg of THC per day. The average daily user in Eastern countries consumes 200 mg per day. In addition, marijuana use is not as persistent in the United States as in other countries. Most westerners who start using cannabis eventually decrease their use and stop. In countries where use is more extensive, it may persist for 20 to 40 years.

According to the National Household Survey on Drug Abuse, between 1985 and 1992 the number of marijuana users in the United States declined from 9.3 percent of the population to 4.3 percent, and the number of frequent marijuana users (once a week or more) dropped from 4.6 to 2.4 percent (U.S. Department of Health and Human Services, 1994). This decline bottomed out between 1992 and 1994 (U.S. Department of Health and Human Services, 1995). While marijuana did not substantially increase between 1995 and 2000, marijuana disorders of abuse and dependence as diagnosed by the *DSM-IV* has increased

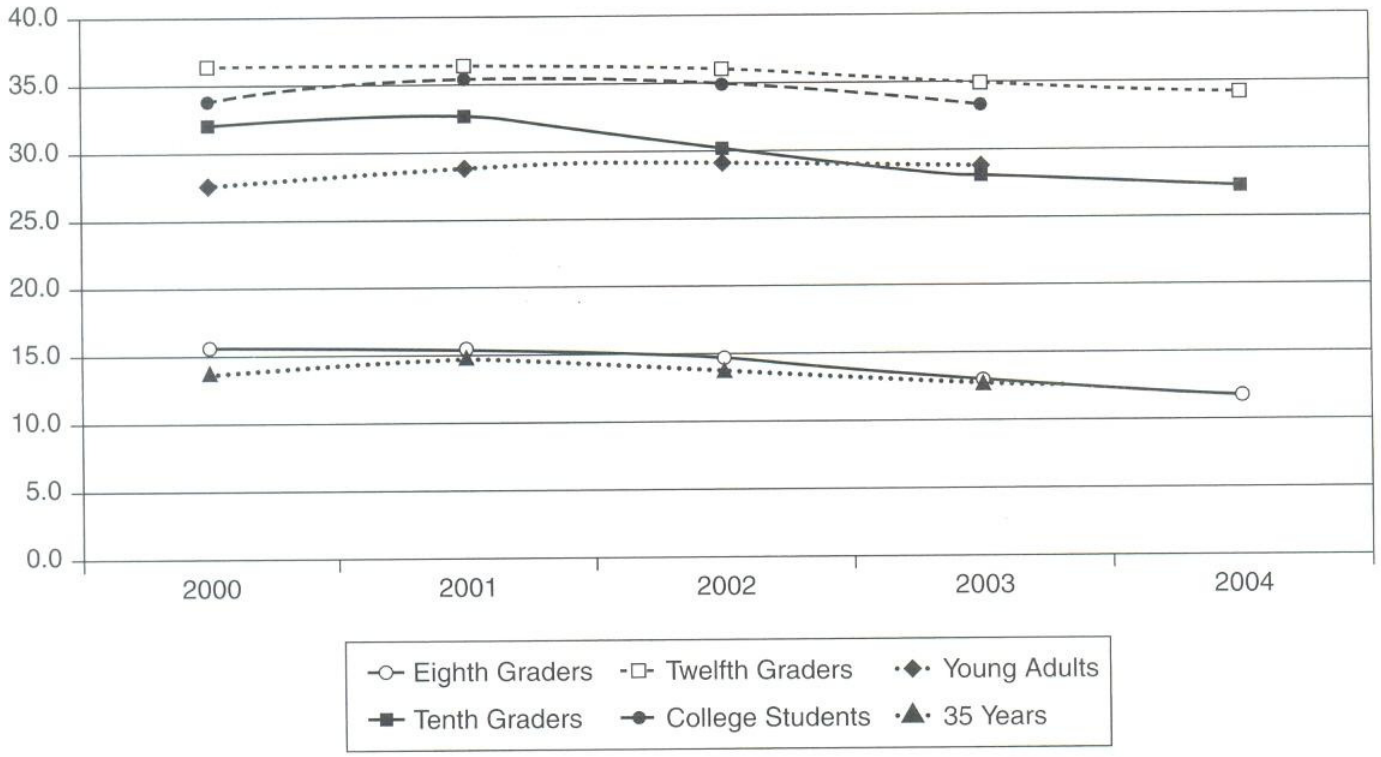

Figure 15-2 Trends in marijuana use in the United States for different age-groups between 2000 and 2004. (Adapted from National Drug Intelligence Center, 2005b)

(Compton et al., 2004). Marijuana was also increasingly involved in hospital emergency room cases during that time. The Drug Abuse Warning Network reported a 126 percent increase in marijuana-related incidents between 1995 and 2000 (NIDA, 2001). The increased potency of marijuana described earlier may have been causing problems for those who continue to use the drug.

Figure 15-2 shows changes in the percent of people in different age-groups in the United States who report using marijuana in the past year from 2000 to 2004. As can be seen, there appears to be a gradual but steady decrease since 2001.

HARMFUL EFFECTS

Cannabis is a drug of great controversy. Probably no other drug in recent times has generated more public concern and debate or stimulated more research into its safety (or lack of it). This body of scientific literature is highly specialized, confusing, and often contradictory, and it is often misrepresented in the popular media, which have tended to publicize only selected research findings and to ignore others. Nonexperts have had difficulty keeping track of it all. People generally are confused, and those with particular biases have no trouble supporting their position.

The debate on the harmful effects of cannabis products has taken on a new dimension in recent times with the move to use cannabis as a medical treatment for numerous diseases and the tendency to "decriminalize" its use in countries like Holland and Canada.

Marijuana has been accused of having many harmful effects, some of which we shall discuss. It will be obvious to anyone who has read this section that cannabis, like any other drug, has a great number of effects on many systems of the body, some of which have the potential for great harm. It should also be obvious that even though the potential for harm exists, especially at high

doses, there are very few hard data to show that the drug really does any harm. The lack of data may mean that there is no harm, but it may also mean that reliable data are difficult to collect.

Violence and Aggression

One of the oldest beliefs about cannabis is that it directly causes violence and aggression and is associated with crime, but there are absolutely no systematic data to support the myth. In long-term studies where marijuana was given to individuals in controlled hospital ward settings, increases in violence were never reported. In addition, mood rating scales generally showed decreases in feelings of hostility and increases in friendliness.

Numerous surveys and field studies, using a variety of techniques, have compared criminal behavior and crimes of violence in groups of marijuana users and nonusers, and in the vast majority of these studies no connection has been found. In fact, if there was a correlation, it was with a decrease in violence. For example, one study showed that among a certain population of young criminal males, marijuana was used specifically to reduce aggression rather than to increase it (Tinklenberg, 1974). Although there may be isolated cases of idiosyncratic or unusually violent reactions among some individuals after taking marijuana, these ordinarily occur in people with a prior psychiatric disturbance or when other drugs are used at the same time.

Mental Disturbance

When the drug is taken in larger doses than usual, the user may be overcome with overwhelming anxiety and paranoid feelings. Such a state often leads to a trip to a hospital emergency department. At higher doses, another reaction to cannabis is an *acute psychotic reaction*, a panic that arises from hallucinations and perceptual distortions. This effect is commonly referred to as a *freak-out*. Users lose touch with reality and feel that they may be going insane, and they panic. Freak-outs usually occur when the drug is taken in unusual and stressful circumstances, if more drug is consumed than the user is accustomed to, or if the cannabis is mixed with other drugs. Freak-outs are much more common with hallucinogens such as LSD than with cannabis. Patients usually can be effectively treated by being quietly "talked down," but in severe cases, a benzodiazepine tranquilizer can be effective (Dinwiddie & Farber, 1995).

What is not so clear is whether cannabis use can cause psychotic or schizophrenia-like illness in later life. A number of studies have shown that heavy cannabis users have an increased risk of suffering from schizophrenia in later life, but later research has suggested that this trend can be explained by the fact that cannabis may precipitate or speed up the emergence of schizophrenic symptoms in people who would have developed the disease in any case (Iverson, 2005). There is little evidence that cannabis use will generate psychoses in users unless they have a predisposing tendency to become schizophrenic. In fact, a study in Australia over a 30-year period has shown that the incidence of schizophrenia did not increase in spite of a drastic increase in cannabis use during that time (Degenhardt, Hall, & Lynskey, 2003).

Permanent Intellectual Impairment and Brain Damage

It is known that long-term heavy use of alcohol results in brain damage and a loss of mental functions; recently, there have been reports that the same outcomes might occur with marijuana. In North Africa and other places where cannabis is used for long periods at high doses, there are reports of *cannabis dementia*. One British study has even reported evidence of a shrinking of the brain, along with the loss of functions seen in alcoholics.

There is conflicting evidence from laboratory studies and experiments with nonhuman animals that exposure to high levels of cannabis might cause damage to nerve cells (Chan, Hinds, Impey, & Storm, 1998; Collins, Pertwee, & Davies, 1994; Silkker, Paule, Ali, Scarlett, & Baily, 1992), but there is no evidence that heavy cannabis use causes any irreversible damage to humans.

In an exhaustive review of the literature, Solowij (1998) concluded that in humans there is little evidence that long-term heavy use produces any severe or grossly debilitating impairment of cognitive functioning. However, the long-term use of cannabis may produce more subtle impairments in the higher cognitive functions of memory, attention, and the organization and integration of complex information. The nature and extent of these problems are related to the duration and extent of use. It is still not known the extent to which these deficits are reversible after abstinence (Solowij, 1998, p. 9).

Most of the research showing that cognitive effects of marijuana are reversible have been conducted in adults, but because so much marijuana is being consumed by teenagers and preteens, there is concern that marijuana use may have irreversible effects on a developing brain. One study suggests that these effects may be reversible. Fried, Watkinson, James, & Gray (2002), compared the IQ of a group of young people when they were 9 years old with their IQ at ages 17 to 19. Those who were using cannabis at the later time showed a decline in IQ, but there was no decline in IQ in people who had been heavy users and had stopped taking the drug. The IQ measure used, however, may not have been able to detect the subtle deficits described by Solowij. This is one area that requires further research.

Amotivational Syndrome

It has sometimes been observed that when a young person starts smoking marijuana, systematic changes occur in that person's lifestyle, ambitions, motivation, and, possibly, personality. These changes have been collectively referred to as the *amotivational syndrome*. Its symptoms are apathy, loss of effectiveness, and a diminished capacity or willingness to carry out complex long-term plans, endure frustration, concentrate for long periods, follow routines, or successfully master new material. Verbal facility is often impaired in both speaking and writing.

Such individuals exhibit greater introversion, become totally involved with the present at the expense of future goals, and demonstrate a strong tendency toward regressive, childlike, magical thinking (McGlothlin & West, 1968, p. 372).

There is no doubt that many young individuals have changed from clean, aggressive, upwardly mobile achievers into the sort of person just described at about the same time as they started smoking marijuana. What is not clear, however, is a causal relationship between the loss of middle-class motivations and cannabis. There is considerable evidence showing that users of cannabis is correlated with reduced educational achievement (Macleod et al., 2003).

Evidence for the existence of an amotivational syndrome has been found in an experiment in which rhesus monkeys were exposed to the smoke from marijuana cigarettes every day for a year (Silkker et al., 1992). These monkeys pressed a lever for banana-flavored food pellets on a progressive ratio schedule. Each time the pellet was received, the ratio requirement increased, and more presses were required (see Chapter 2). Silkker and associates found that during exposure to marijuana smoke, breaking points were considerably lower than they were for controls, and they returned to normal when exposure to the smoke was discontinued. Thus, the monkeys exposed to marijuana smoke were not as willing to work hard for an attractive food as nonexposed monkeys. Because the animals responded normally on other tasks for the same food pellets, the researchers argued that this result was analogous to the amotivational syndrome seen in humans and was not a result of either loss of the ability to respond or loss of appetite.

Laboratory studies with humans have found conflicting effects of cannabis on motivation. In an early experiment by Mendelson, Kuehnle, Greenberg, & Mello (1976), hospitalized volunteers worked on an operant task to earn money and marijuana for 26 days. Smoked marijuana did not influence the amount of work done by either the casual-user group or the heavy-user group; all remained motivated to earn and take home a significant amount of money in addition to the work they did for the marijuana. However, a more recent

experiment by Cherek, Lane, & Dougherty (2002) found that cannabis did have a detrimental effect on the motivation of participants to earn money.

The issue is not settled, but even if there is no specific motivational effect, it is clear that cannabis affects attention and memory, and these are intellectual capacities usually considered necessary for success in educational institutions. Achievement motivation must be high indeed in any individual who combines high levels of cannabis use with a successful academic career or job.

Progression to Other Drugs

There are claims that marijuana is a *gateway drug* or a stepping-stone toward the use of more dangerous drugs. In support of this gateway theory are studies that show that virtually all heroin users had used marijuana before they adopted heroin (Golub & Johnson, 1994). In addition, studies have shown that the more a person uses marijuana, the greater is the probability that the person will use other drugs as well (Mullins, Vitola, & Michelson, 1975).

These data suffer from the same difficulty as the research on the amotivational syndrome: No causal relationship can be established. The fact that marijuana is used before heroin does not mean that marijuana use caused heroin use. Most people drink soda pop before they drink alcohol, but this fact does not mean that soda pop causes alcohol drinking.

At the heart of the progression hypothesis is the idea that users develop tolerance to "mild" drugs, become bored with their effects, and escalate to more powerful drugs. If this were true, we might expect that users would abandon marijuana when they progress to other drugs, but this does not appear to be the case. Marijuana is seldom abandoned in favor of other drugs. Instead, the usual pattern is to adopt the use of other drugs along with marijuana.

Even though a causal relationship cannot be proved, we cannot dismiss the correlation between the use of marijuana and other drugs; there must be an explanation, and, like the amotivational syndrome, it probably has more to do with sociology than with pharmacology. Heavy marijuana use provides the social settings, motivation, and opportunity to use other drugs. In addition, the personality traits of curiosity and risk taking that might motivate a person to use marijuana are also likely to motivate the use of other drugs as well.

As was described in Chapter 5, experience with one drug can sensitize the mesolimbic dopamine system and increase the reinforcing value of another drug. Although specific experiments have not been attempted with THC, we know that THC increases dopamine levels, and it is possible that its use could act to increase use of other drugs.

Reproduction

Although not all researchers have been able to replicate the finding, marijuana seems to lower the levels of the male sex hormone testosterone in both human and nonhuman males. However, it is not yet apparent whether this finding has any biological significance. The levels of testosterone vary greatly from one individual to another and within the same individual throughout the course of a day. We do not know as yet whether a marijuana-induced suppression of testosterone will make any difference in the face of this great natural variability.

There has been some speculation on problems that might be caused by low testosterone levels. These effects include a reduction in fertility (Hembree, Zeidenberg, & Nahas, 1976) and a disruption in the sexual differentiation of males during embryonic development (Kolodny, 1975). In general, little reliable data have been collected to show that these effects occur more frequently among chronic cannabis users.

Studies in mice have shown that anandamide is a chemical messenger between the embryo and the uterus during implantation of the embryo in the uterine wall. It is, in fact, the first communication that occurs between the mother and the child. It is possible that THC might block cannabinoid receptors and interfere with this signal and prevent

this process from occurring (Wang, Paria, Dey, & Armant, 1996).

In a large-scale study between 1984 and 1989, more than 7,000 pregnant women in the United States were studied, and their drug use histories were recorded. Eleven percent of these women reported using marijuana during pregnancy. Marijuana use was not associated with low birth weight or prematurity. By comparison, 35 percent of the women smoked tobacco, and this history was associated with low birth weight (Shiono et al., 1995).

Some functional differences, however, have been detected in children exposed prenatally to cannabinoids through maternal marijuana smoking. One study showed abnormal sleep patterns in newborns that persisted at least until the age of 3 years in cannabis-exposed children (Dahl, Scher, Williamson, Robles, & Day, 1995). There is some evidence that prenatal exposure to cannabis may have effects that do not show up for several years. These effects include hyperactivity, impulsiveness, and learning disorders. These effects are small, however, and it is impossible to demonstrate any causal connection to marijuana use (Earleywine 2002, p. 162).

Immunity

It has been clearly established that marijuana reduces activity in the body's immune system, which fights invading microorganisms and disease. This reduction has even caused speculation that THC might be effective in stopping the body's rejection of tissue after transplant operations. Again, the clinical significance of this effect has not been determined. We might suspect that marijuana users would be more susceptible to disease than nonusers, but adequate statistical data on this issue are difficult to obtain and have not been collected (Munson, 1975).

Cancer

Evidence is clear that tobacco smoke is associated with cancer. What about marijuana smoke? Even though marijuana users typically inhale much less smoke than tobacco users, the smoke from marijuana contains 50 to 70 percent more carcinogenic material than tobacco smoke, and marijuana smokers typically inhale more deeply and hold the smoke in the lungs longer than tobacco smokers. Surprisingly, little research has been done in this area, and results are frequently confounded by the fact that most marijuana smokers also smoke tobacco. It seems likely that marijuana accelerates the carcinogenic effects of tobacco smoke. Even though the median age for developing cancer is between 55 and 65, one study of people under age 45 with lung cancer found that almost all smoked both tobacco and marijuana (Sridhar et al., 1994). On the other hand, there are reports that cannabidiol and delta-9-THC are potent antioxidants (Hampson, Grimaldi, Axelrod, & Wink, 1998). Antioxidants are compounds that neutralize free radicals that damage DNA, which, in turn, can lead to cancer. A lot more work needs to be done in this area.

EPILOGUE

Psychopharmacological McCarthyism?

When Lester Grinspoon began studying marijuana in 1967, he claimed that he had no doubt that he would find it was a harmful drug used by more and more foolish people. He took as his job the task of revealing the dangers of marijuana. Instead, after 3 years of study, he concluded that he had been wrong and that his belief that the substance was dangerous was unfounded. In 1971, he wrote a book titled *Marihuance Reconsidered* (Grinspoon, 1971) in which he said so. He naively believed that people would come to understand that marijuana was much less harmful than legal drugs such as alcohol and tobacco and, consequently, that marijuana would be legal within 10 years.

Not only was he wrong, but in another book published in 1993, he comments that there is something special about illicit drugs: "If they don't always make the user behave irrationally, they certainly cause many nonusers to behave that way" (Grinspoon & Bakalar, 1993, p. ix). Grinspoon

points out that instead of legalization, the climate has deteriorated so seriously that we are now in a period of what he calls "psychopharmacological McCarthyism"; it is not even acceptable to state in public that a drug like marijuana might have beneficial effects. He points to the widespread public condemnation of published research that found that adolescents who had engaged in some drug experimentation with marijuana were better adjusted than those who had not.

As another example of psychopharmacological McCarthyism, Grinspoon points to mandatory drug testing. In the McCarthy era, people were forced to take loyalty oaths or else risk losing their jobs or reputations. Grinspoon calls drug testing a "chemical loyalty oath." Just as loyalty oaths did little to enhance the national security of the United States, mandatory drug testing is of little use in preventing or treating drug abuse; instead, Grinspoon claims that it is little more than shotgun harassment designed to enhance outward conformity.

CHAPTER SUMMARY

- There may be three species of cannabis plant, although many believe that there is only one species, *Cannabis sativa*, with two distinct phenotypes. One, widely called hemp, has low levels of active ingredient. The other phenotype grows in warmer climates, has a high content of active ingredient, and is used primarily as an intoxicant.
- Although there are a great many cannabinoids, the primary active ingredient in cannabis is delta-9-tetrahydrocannabinol (THC). A number of synthetic cannabinoid-like drugs have also been developed for medical applications.
- Marijuana is made from the dried leaves and flowers of the cannabis plant and is not very potent. Hashish is the resin from the flowering tops of the female plant and is 10 times more potent than marijuana. Hashish can be refined and concentrated into a liquid called hash oil or red oil.
- THC is absorbed very poorly from the digestive system and is usually inhaled in the form of smoke, which is a much more efficient system of administration. After inhalation, effects may begin in 30 to 60 minutes. The effects disappear within an hour or so.
- In the late 1980s, a receptor for THC was isolated and located in many parts of the brain. Later, an endogenous cannabinoid, anandamide, was discovered. Cannabinoid receptors are located on presynaptic neurons and serve to modulate neurotransmitter release in response to endogenous cannabinoids released from the postsynaptic neuron.
- THC has several physiological effects. It causes bloodshot eyes, decreases the pressure in the eyeball, increases appetite and heart rate, and can act as an antiemetic and an anticonvulsant.
- At high doses, cannabis acts like a hallucinogen, but at the low doses common in North American use, the drug is reported to cause a pleasurable high. Cannabis causes temporal disintegration; that is, the user loses the ability to store information in the short term and is easily distracted.
- Cannabis can interfere with driving performance. Roadside screening tests for marijuana intoxication are being developed.
- THC has distinctive stimulus properties and will cause dissociation in both humans and nonhumans. The stimulus properties will generalize to other cannabinoids but not to any other drug.
- Tolerance develops to most of the effects of the cannabinoids.
- Withdrawal symptoms have been reported in humans and nonhumans but are usual only after continuous administration of fairly high doses. Some of the withdrawal symptoms reported are hot flashes, runny nose, loose stools, and sweating.
- Cannabinoids are self-administered by nonhumans. Humans will work to earn marijuana and will titrate dosage, though not very accurately. The use of marijuana in the United States has been steadily decreasing in recent years.
- The belief that cannabis causes violence and aggression has no support in research. It is known to interfere with immune processes and to lower the levels of testosterone in males, but the exact clinical significance of these findings for reproduction and susceptibility to disease in marijuana users is not known.