9

Tobacco and Nicotine

Tobacco is the only known natural source of *nicotine*, and it is now clear that nicotine is the active ingredient in tobacco. The tobacco plant belongs to the genus *Nicotiana*, of which there are two subgenera, *rustica* and *tabacum*, used for their nicotine content. Both subgenera contain many species and varieties that differ quite widely in physical characteristics. By far the principal source of tobacco today is *Nicotiana tabacum*, which is cultivated in temperate climates all over the world. Species of *rustica* are not grown widely commercially. While it has a higher nicotine content, it is reputedly harder to cultivate. It is interesting to note that cultivated strains of tobacco have a much higher nicotine content than any wild members of the same genus. These facts suggest that the presence of nicotine in tobacco is much more than mere coincidence. The actual nicotine content of the cured tobacco leaf may reach as much as 6.17 percent.

Although some scholars have claimed that tobacco originated in Africa or Asia, it is now certain that its origins are exclusively American and that the aboriginal peoples of North and South America were the first and only users of the drug at the time of the European discovery of the New World. The earliest known illustration of smoking is reproduced in Figure 9-1. This stone carving from a Mayan temple shows a priest smoking what appears to be a cigar or a reed cigarette.

The plants of *N. tabacum* are usually about 2 meters tall and have long, broad, pointed leaves that are harvested two or three at a time from the bottom of the plant as they mature, although for some types of curing the entire plant is cut at one time. In 1809, a French chemist, Louis Nicolas Vauquelin, claimed to have discovered the active ingredient in tobacco (he called it nicotianine), but his extracts were not pure. It was not until 1828 that pure nicotine was isolated by L. Posselt and F. A. Reimann.

PREPARATIONS

The leaves of the tobacco plant are cured and prepared in different ways, depending on the intended use of the tobacco. Tobacco for burning is made into cigars, cigarettes, or pipe tobacco. Tobacco for chewing is specially processed and flavored. Tobacco snuff is made by drying the

Figure 9-1 A priest smoking a cigar or reed pipe; carving found in a Mayan temple. Native American priests and shamans used tobacco in large quantities. Their rituals centered on foretelling the future and curing illness. (From Dunhill, 1954, p. 4)

leaves, grinding them to a very fine powder, and mixing the powder with various aromatic and flavoring agents. The vast bulk of tobacco is consumed as cigarettes or cigars and in pipes, but there has been a resurgence in oral consumption of tobacco, or what is now commonly called smokeless tobacco. This is either the traditional form of chewing tobacco or a product called *moist snuff*, which is not chewed but tucked between the cheek and the gum. Frequent spitting is not required. Smokeless tobacco has the advantage that it can be used in places where smoking is banned or when both hands are busy, for example, when playing baseball.

HISTORY

One aspect of the life of the native peoples of North America was commented on by every early European explorer from Columbus on: their use of tobacco. At San Salvador, the site of Columbus's first landfall in 1492, the local inhabitants presented him with some "dry leaves," which Columbus concluded "must be a thing much appreciated among them." Later members of his expedition went ashore in search of the Great Khan. They found no Khan, but they did observe the natives smoking cigars, something that they did not appreciate or understand. They reported that the natives were "perfuming themselves" and that they "drink smoke." One of these men, Rodrego de Jerez, was later to become all too familiar with the significance of the activity; he took up smoking and was imprisoned by the court of the Inquisition for this "devilish habit."

Jean Nicot, the French ambassador to Portugal, became convinced of the medical usefulness of the plant and sent seeds to the royal family in France. Because of his great interest in this plant, Nicot's name was given to the genus *Nicotiana* and subsequently to the alkaloid nicotine.

Tobacco use spread as a wonder cure, but it did not take long to catch on as a recreation, although many users were quick to point out that they were really using it to prevent diseases, such as the plague. When Samuel Pepys, the British diarist, encountered houses where victims of the Great Plague had perished, he felt "an ill conception of myself and my smell, so that I was forced to buy some roll-tobacco to smell and to chew, which took away the apprehension" (Brooks, 1952, p. 40). This association of tobacco with healing lasted into the Victorian era.

The English were among the last Europeans to take up tobacco. In the late sixteenth century, British sailors and sea captains, among them

Hawkins, Drake, and Raleigh, carried the habit home from the West Indies. Raleigh's name has long been associated with tobacco not only because he is credited with the introduction of smoking to the English court but also because he founded the colony at Virginia that was later to owe its survival and prosperity to tobacco cultivation.

Although the British were late to take to the drug, they made up for their tardiness in the popularity tobacco acquired. By the end of the sixteenth century, the demand for the leaf was beginning to cause concern in some quarters. In 1604, King James I published an antitobacco essay titled *A Counterblaste to Tobacco*, in which he refuted all the arguments claiming medical benefits from smoking. As a matter of fact, James I anticipated most of the modern antismoking campaigns, even to claiming that smoking affects "the inward parts of man, soiling and infecting them with a vicious and oily kind of Soote, as hath been found in some great tobacco takers, that hath after their death opened" (Arber, 1895, p. 111).

The tobacco that the English were smoking all this time (and that so angered the king) was imported from Spain at great expense, but the English colony at Virginia was to change all that. The colonists, under John Rolfe, had gotten off to a very bad start. They suffered shipwreck and starvation and were on the point of quitting when Rolfe decided to try growing some Spanish tobacco seeds (*Nicotiana tabacum*) in the soil of Virginia. The experiment was a great success. The plants prospered, and in 1616 a shipload of Virginia tobacco was sent to Britain. At first, the English were skeptical, but the quality of Virginia tobacco was obvious, and within a decade it had replaced the Spanish imports. In spite of the king's taxes and other attempts to discourage the tobacco trade, the colony flourished and secured the English colonial presence in North America.

Smoking has been the primary means of administering tobacco throughout most of its European history, but for a time, it was eclipsed by snuffing. Powdered tobacco was either pinched between the fingers or placed on the back of the hand and then sniffed into the nostrils. The result was usually a vigorous sneeze. The early use of snuff was associated with the clergy (Pope Urban VII was an ardent snuffer), who preferred it to smoking because it was not outlawed in churches and its use could be better concealed from disapproving parishioners.

Tobacco chewing was a North American contribution. It was first observed as a habit of the American Indian, but chewing was never very popular in Europe. In the early part of the nineteenth century, however, there was a strong nationalist sentiment in the new United States and a deliberate rejection of European habits and fashions; snuff was rejected, and chewing tobacco was adopted with patriotic fervor. Chewing was democratic; snuff was aristocratic. Snuff and the pipe had "filtered down from the leaders of fashion to the common folk, while chewing was a practice which . . . seeped from the common man upward into the higher ranks of society" (Robert, 1967, p. 103). The popularity of chewing prompted one Englishman, Charles MacKay, to suggest that the national emblem of the United States should be a spittoon rather than an eagle.

Like tobacco chewing, cigarette smoking had its beginnings in America. Early Spanish explorers reported that Mexican Indians smoked tobacco through "reeds." These were hollow canes filled with tobacco and lighted so that they "burned themselves out without causing a flame." For centuries, cigarette smoking was confined to the Spanish and Portuguese empires, and, even there, it accounted for only a small part of tobacco use. Quite suddenly, in the 1840s, it became very popular in France, especially among French ladies, and it was chiefly the enthusiasm women showed for this means of smoking that stimulated its general acceptance. It was also about this time that flue-cured, or *bright*, tobacco was discovered in North Carolina. This low-nicotine, sweet, mild smoke was perfectly suited to the cigarette. Some people considered cigarettes a novelty—a fad that would soon pass—but they were wrong.

Tobacco smoking persisted unabated until the 1960s, when tobacco was dealt a severe but not fatal blow. The U.S. Surgeon General's Report of 1964, for the first time, definitely linked smoking

to cancer and other diseases. This was followed in 1971 by a similar report of the Royal College of Physicians of London. The truth could no longer be hidden or ignored: Tobacco smoking was unhealthy. These statements, combined with the environmentalist and naturalist movements, were actually able to stop the growth of smoking and start a decline.

Globally, about one half of the men in the world (47 percent) are smokers, and 12 percent of the women smoke, consuming 15 billion cigarettes a day (American Lung Association, 2004). Although the use of tobacco in the industrialized nations is declining, tobacco consumption has been rising in the developing countries of the world by about 1.4 percent per year. The increase has been most rapid in the western Pacific region. As a result, global cigarette consumption has remained relatively steady at about 1,650 cigarettes per adult throughout the 1980s and early 1990s (World Health Organization, 1996). It appears that tobacco manufacturers, discouraged by the shrinking of their traditional market, turned their attention to populations not so well educated about the health risks of smoking (Fielding, 1985b; Greenlees, 2005). If current trends continue, by the mid-2020s, about 85 percent of the world's smokers will be in poor and developing countries (American Lung Association, 2006).

Legal Status

Even though tobacco contains an active ingredient (nicotine), for various political and economic reasons, tobacco has never been treated as a drug or medicine, and it is not regulated by governments in Western industrialized countries. Tobacco is not even classed as a "consumer product" for purposes of regulation by the U.S. Consumer Product Safety Commission.

In the United Kingdom, tobacco is not governed by the Medicines Act. Until recently, nicotine tobacco products were not regulated by the U.S. Food and Drug Administration (FDA). The FDA is entitled to regulate drugs in the United States, and a drug is defined as a substance intended by its makers (a) to affect the structure or functions of the body or (b) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The tobacco industry had escaped FDA control by claiming that tobacco products were sold for smoking pleasure only and not for the effect of nicotine.

In February 1994, after years of planning, the commissioner of the FDA formally requested that the FDA be given the power to regulate cigarettes as drugs. This request led to a series of hearings before a subcommittee of the U.S. House of Representatives. In the course of the hearings, the commissioner outlined the argument that nicotine was addicting and presented evidence that cigarette manufacturers had knowingly manipulated nicotine delivery of tobacco products (Kozlowski & Henningfield, 1995; Schwartz, 1994) and that, in fact, cigarettes were "nicotine delivery systems." The arguments of the FDA did not convince Congress to give it power to regulate tobacco, but in 1996 the administration of President Clinton gave the FDA authority to reduce access and reduce the appeal of tobacco products to children and adolescents. In 1997, a provision went into effect prohibiting sales of tobacco products to anyone under the age of 18, a measure that was ruled legal by a federal district court decision. However, in 2000, the U.S. Supreme Court ruled in a 5 to 4 decision that the FDA cannot regulate tobacco products until given authority by the Congress. The issue is still unsettled.

ROUTE OF ADMINISTRATION

Unlike cocaine from the coca leaf or morphine from opium, nicotine from tobacco was virtually never self-administered in its pure form. Nicotine is a highly toxic poison, and doses must be controlled precisely; too high a dose will have quite unpleasant effects. Because of its diluted concentration in tobacco, precise control of dosage can more easily be achieved when the nicotine is in its natural form.

When tobacco is chewed, the nicotine is absorbed through the membranes of the mouth. It

is only rarely swallowed. Usually, the tobacco juice is spit out, so this process does not represent the usual form of oral administration. Nicotine is a weak base with a pKa of about 8, so it will not have many lipid-soluble molecules when dissolved in solutions with a pH lower than 6. Consequently, nicotine is not quickly absorbed from the acidic digestive system. Oral administration of nicotine has another disadvantage because the blood from the capillaries of the digestive tract must pass through the liver before it achieves general circulation throughout the body. Because the metabolism of nicotine is rather fast in the liver, much of the nicotine taken orally is metabolized during this first pass before it can get to the rest of the body. Although nicotine is not normally self-administered orally, a large number of poisonings occur each year among children who eat tobacco. Fortunately, the nicotine that gets into the blood induces vomiting, and the swallowed tobacco is frequently expelled before the nicotine reaches toxic levels.

Tobacco taken in the form of snuff is sniffed into the nostrils. With this route of administration, most of the nicotine is absorbed through the mucous membranes of the nasal cavity, although some tobacco eventually gets into the stomach and lungs.

When tobacco is burned, nicotine vaporizes and can be found in the smoke and particles of ash that dissolve in the mucous membranes of the inside surface of the lungs. About 90 percent of inhaled nicotine is absorbed into the blood in this way (Pierce, 1941). Studies have shown that the major determinant of nicotine absorption is the volume of smoke inhaled and that increasing the duration of the inhalation does not significantly increase nicotine absorption (Zacny, Stitzer, Brown, Yingling, & Griffiths, 1987).

Nicotine from tobacco smoke may be absorbed through membranes of the mouth in a similar fashion, but this route is more readily influenced by changes in the pH of saliva. In general, cigarettes are made from flue-cured tobacco, which has an acidic smoke, and this lowers the pH of saliva to about 5.3. In acidic saliva, nicotine is ionized and absorption reduced. To be absorbed, the nicotine from cigarette smoke must, therefore, be inhaled into the lungs, which are so efficient that pH has no effect on absorption. By contrast, pipe and cigar tobacco is usually air-cured, and this process results in a more basic or alkaline smoke. Its pH of about 8.5 is well into the range where ionization of nicotine is less than 50 percent, and absorption is facilitated. Consequently, nicotine in the smoke from cigars and pipes can be absorbed from the mouth, and inhalation is not necessary (Armitage, 1973; R. T. Jones, 1987).

Nicotine absorbed from the lungs is carried directly to the heart; from there, much of the blood containing the nicotine goes straight to the brain. Because of this direct route, the nicotine does not get a chance to dissipate, so the high concentration in the lungs after a puff or rapid inhalation of smoke tends to remain in the blood as a nicotine bolus until it reaches the brain (M. A. H. Russell, 1976). Because nicotine is absorbed much more slowly from the capillaries of the mouth and nose, no such bolus occurs if the smoke is not inhaled. The role of the nicotine bolus in nicotine self-administration and dependence will be discussed later in this chapter.

The average cigarette contains 8 to 9 mg of nicotine, of which a typical smoker absorbs 1 mg in the course of taking 10 puffs per cigarette (R. T. Jones, 1987, p. 1592). The amount of nicotine actually delivered to the smoker is determined to a greater extent by the way the cigarette is smoked than by the actual nicotine content of the cigarette; the delivered amount can vary between 0.3 mg and 3.2 mg per cigarette (Benowitz & Henningfield, 1994).

Newer forms of nicotine administration have been developed for the purpose of nicotine replacement therapy in people who have given up smoking. Nicotine chewing gum was the first of these. The fact that nicotine can be absorbed transdermally (through the skin) allowed for the development of the *patch*. Nicotine-containing patches are placed on the skin, and they release nicotine in various concentrations for a period of time. Most recently, a nicotine nasal spray has been tested. Inhalers and lozenges have also been developed.

The patch causes a slow buildup of nicotine in the blood and maintains it at a constant level for hours. The gum will cause rises and falls in blood nicotine levels in response to its use; as a result, it causes patterns in blood nicotine that more closely resemble those caused by smoking, although peak levels reach only one-third that of smoking (Keenan, Henningfield, & Jarvik, 1995). The nasal spray causes the most cigarette-like changes in blood levels. Within 2.5 minutes of administration, nicotine reaches 85 percent of peak levels in the blood (Sutherland et al., 1992). Figure 9-2 shows the blood level of nicotine for 1 hour after administration by these routes.

In 1996, the U.S. FDA approved the use of a nicotine inhaler. It looks like a cigarette and is held between the fingers. It contains small cartridges of vaporized nicotine that is delivered to the mouth and throat when you draw air through it. Absorption is through the membranes of the mouth rather than the lungs and is therefore slow like nicotine gum. It has the advantage, however, of looking very much like a cigarette and permits the user to manipulate something with the fingers and mouth as they would a real cigarette.

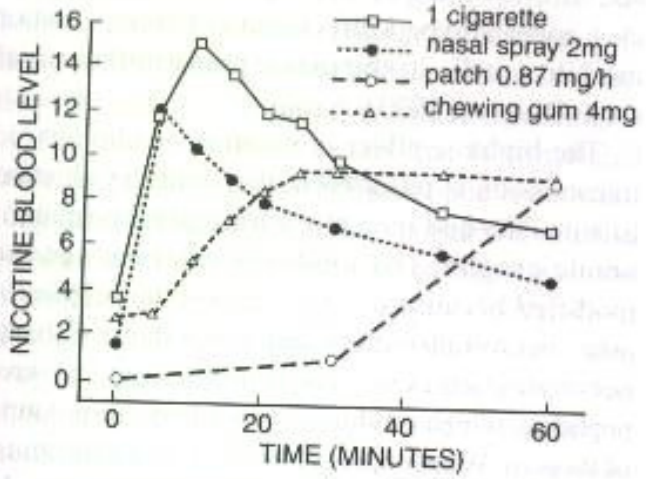


Figure 9-2 Nicotine blood levels for 1 hour after administration of nicotine from various sources. (From de Wit & Zacny, 1995, p. 459)

DISTRIBUTION

The patterns of nicotine distribution in the body depend on the route of administration and the time after administration. When initial high concentrations circulate in the blood, as after inhalation, a high concentration is apparently retained in the brain. After about 30 minutes, the nicotine leaves the brain and is concentrated in the liver, kidneys, salivary glands, and stomach (Schmiterlow & Hanson, 1965).

Nicotine crosses most barriers, including the placenta, and may be found in the sweat, saliva, and milk of nursing women.

EXCRETION

The amount of nicotine excreted by the kidneys depends on the pH of the urine, as described in Chapter 1. Acidic urine (pH less than 7) tends to ionize nicotine and reduce its reabsorption through the nephron wall. Consequently, as much as 30 to 40 percent of administered nicotine may be eliminated in the urine. Reduced ionization at an alkaline pH increases reabsorption into the blood, and the efficiency of the kidneys is reduced, thereby shifting the load of excretion to the enzymes of the liver.

Two pathways in the liver metabolize nicotine to two inactive metabolites, *cotenine* and *nicotine-1'-N-oxide* (Beckett, Gorrod, & Jenner, 1971a). There is evidence that smokers are able to metabolize nicotine faster than nonsmokers and that, among nonsmokers, there may be a difference in nicotine metabolism between males and females (Beckett, Gorrod, & Jenner, 1971b). The half-life of nicotine is variable but is estimated to be about 30 minutes. Nicotine will accumulate in the body of a smoker over the course of a day, but elimination is sufficiently rapid that there will be no day-to-day accumulation (Issac & Rand, 1972).

There appear to be genetic differences in the way people metabolize nicotine. About 16 to 25 percent of the population have a genetic defect in their ability to metabolize nicotine. A given dose of nicotine will reach higher levels and last

longer in those people. This appears to offer some protection from becoming a smoker; people with this genetic defect are less likely to become smokers, and if they do smoke, they consume fewer cigarettes (Pianezza, Sellers, & Tyndale, 1998).

NEUROPHYSIOLOGICAL EFFECTS

There are two basic types of cholinergic receptor sites: (a) *muscarinic* and (b) *nicotinic*. Muscarinic receptors are stimulated by muscarine and blocked by anticholinergics such as atropine (see Chapter 4). Nicotinic receptors may be stimulated by nicotine and blocked by curare, a poison used by South American Indian tribes on the tips of their spears and arrows. Another drug that blocks nicotinic receptors but does not appear to be toxic in effective doses is *mecamylamine*. This drug is useful in research with nicotine because if a nicotine effect can be blocked by giving mecamylamine, it is reasonable to conclude that the nicotine effect was a result of its effect on ACh receptors.

Because nicotine occupies and activates nicotinic cholinergic receptor sites, it has traditionally been classified as a nicotinic cholinergic stimulant, but nicotine has a biphasic effect on cholinergic transmission. In low doses, it stimulates these receptors, but it can also block them at higher doses, so it is more accurate to think of nicotine as both a stimulant and a blocker of cholinergic transmission.

What we know about cholinergic receptors is a result of research on the peripheral nervous system. Although muscarinic receptors have been known to exist in the central nervous system for many years, nicotinic receptors were not discovered in the brain until 1980 (Romano & Goldstein, 1980). This research showed that these receptors are part of cholinergic synapses in the brain and are similar to nicotinic cholinergic receptors in the peripheral nervous system. In addition, many nicotinic receptors are found in the synapses and cell bodies of cells in the brain that use DA and NE, and when they are stimulated, they cause a release of DA and NE. Nicotinic receptors of this nature are found in the cortex, the basal ganglia, the ventral tegmental area, and the nucleus accumbens (Balfour, 1991; Levin, 1992).

In addition to its effect on acetylcholine and the catecholamines, nicotine causes the release of serotonin, beta-endorphin, and numerous hormones, such as vasopressin, growth hormone, and prolactin, all known to have effects on behavior (O. F. Pomerleau & Pomerleau, 1984).

EFFECTS OF TOBACCO

Effects on the Body

Peripheral Nervous System. In the peripheral nervous system, nicotinic receptor sites are located primarily in the neuromuscular junctions of striated or voluntary muscles. The poisonous effects of curare result because the drug blocks these junctions, and the muscles become paralyzed; the victim can no longer breathe and dies of suffocation. Nicotine stimulates these receptors, and muscular tremors result. One British surgeon, H. J. Johnson (1965), was motivated to quit smoking when he noticed that an extra cigarette before surgery caused a fine hand tremor. In addition, there may be an inhibition of some reflexes. There is a decrease in the patellar reflex (knee jerk) after a cigarette. This effect, which is due to a lowering in the tone of voluntary muscles, appears to be a direct result of stimulation of inhibitory cells in the motor pools in the spinal cord (Domino, 1973).

The biphasic effect of nicotine on cholinergic transmission is reflected in the ability of nicotine to stimulate and then block transmission in autonomic ganglia. These two effects, however, are modified because nicotine causes the release of other neurotransmitters that affect the peripheral nervous system. One such neurotransmitter is epinephrine, which produces sympathetic stimulation of its own. When this is combined with neuromuscular and parasympathetic stimulation and blocking, the result is a very complicated array of peripheral nervous system changes.

In general, at doses encountered in tobacco smoking, nicotine produces increases in heart rate and blood pressure and causes a constriction of blood vessels in the skin. This constriction causes a drop in skin temperature and is probably responsible for the cold touch that smokers have and the reason that the skin of smokers tends to wrinkle and age faster than that of nonsmokers (Daniell, 1971). The reduced blood flow to the skin also explains why smokers do not blush easily. This lack of skin color prompted one judge in the 1930s to accuse cigarettes of "deadening the sense of shame" and corrupting the morals of young people.

Nicotine also inhibits stomach secretions and stimulates activity of the bowel. For this reason, especially for someone with little tobacco tolerance, a cigarette can act as a laxative.

Central Nervous System. The effects of nicotine in the central nervous system (CNS) are complicated. Apart from its direct effects on synapses, nicotine also stimulates the release of epinephrine from various sites, including the adrenal glands. This causes a CNS arousal resulting in a decrease in the alpha activity shown in the electroencephalogram (EEG). Arousal is also produced by direct stimulation of the reticular activating system. Respiration is increased because of both direct and indirect stimulation of the medullary respiration centers. Respiratory arrest caused by an overdose of nicotine results from a block of these centers as well as of the neuromuscular junctions that control the muscles used in breathing.

Another brain stem center that is stimulated both directly and indirectly by nicotine is the vomiting center. This effect is most noticeable in naive smokers who have no tolerance and do not have the experience to control dosage appropriately. Their initial experience with tobacco makes most young people nauseous and "green about the gills." This effect is subject to tolerance, but even experienced smokers can feel a bit "green" if they consume more than their accustomed amount of tobacco.

Higher in the brain, nicotine causes a general release of NE and DA and activates systems that use these transmitters. Photon emission tomography (PET) imaging using [^{11}C]raclopride, which binds to D_2 receptors, demonstrates a relationship between the pleasurable effects of smoking and binding potential of the radiotracer. Participants who reported increases in euphoria while smoking their usual brand of cigarette during a PET scanning session also demonstrated significant decreases in [^{11}C]raclopride binding potential in the caudate region of the striatum (Barrett, Boileau, Okker, Pihl, & Dagher, 2004). Decreases in radiotracer binding potential demonstrate that receptor sites are occupied by dopamine. Conversely, participants who reported experiencing smoking-induced decreases in euphoria demonstrated increased [^{11}C]raclopride binding in the caudate.

Recent research has shown that the cells in the ventral tegmental area (VTA) that release DA in the nucleus accumbens contain a subtype of nicotinic receptor. Nicotine is not reinforcing in mice that are genetically manipulated, so they do not have these receptors (knockout mice). When the genes that make these receptors are reintroduced into the VTA, nicotine becomes reinforcing (Maskos et al., 2005). This indicates that nicotine increases dopamine activity in the nucleus accumbens by directly stimulating the neurons in the VTA.

Serotonin systems are also altered by nicotine, particularly the system that runs from the Raphé system to the cortex. This system is the primary site of action of the antidepressant drugs (Chapter 14), and nicotine appears to have an effect similar to that of the antidepressants (Balfour, 1991).

It has also become clear that cholinergic systems, both muscarinic and nicotinic, are important in cognitive functioning. In a later section in this chapter, the cognition-enhancing effects of nicotine are discussed.

Effects on Sleep

There is some evidence that intravenous infusions of nicotine may cause REM sleep in cats (Domino & Yamamoto, 1965), but nicotine given intravenously before bedtime did not have any

effect on sleep stages in healthy humans (Domino, 1967).

In another study, withdrawal from tobacco did disrupt sleep. Smokers undergoing withdrawal were shown to have a moderate increase in REM sleep time. This increase was accompanied by subjective reports of an increase in dreaming and in the vividness of dreams (Kales, Allen, Preston, & Tan, 1970).

EFFECTS ON THE BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

Acute Effects. Smoking is a pleasurable experience for many people (de Wit & Zacny, 1995). In one study, nicotine was administered either by tobacco smoke inhalation or by intravenous infusion to volunteers, and their subjective responses were measured using the Addiction Research Center Inventory. Smokers reported increased liking scores and reported subjective effects similar to those caused by morphine and amphetamine. These effects peaked about 1 minute after administration and were gone within a few minutes. Nonsmokers, however, did not enjoy the experience (Henningfield, Miyasato, & Jasinski, 1985; Jasinski, Johnson, & Henningfield, 1984). These subjective effects were blocked by mecamylamine (Henningfield, Miyasato, Johnson, & Jasinski, 1983). In another experiment, smokers were given cigarettes with different levels of nicotine in the morning after being deprived of smoking since the previous evening. They were permitted to smoke the cigarettes themselves and were asked to push a button when they experienced "a rush, a buzz, or a high." Nineteen of 22 subjects experienced at least one such sensation. Frequency and duration of sensations were related to blood nicotine levels. These sensations lasted for about 11 seconds and occurred with a delay of about 30 seconds after a puff (C. S. Pomerleau & Pomerleau, 1992).

Nesbitt's Paradox. In most studies, nicotine appears to cause an arousal in brain wave activity and a release of epinephrine that arouses the sympathetic nervous system, yet most smokers report that they smoke because smoking a cigarette relaxes them. Even people who have given up smoking for a long time report that they feel the need for a smoke during moments of stress. One researcher (Schachter, 1973) has called this unexpected observation Nesbitt's paradox, after a man who first studied it, and it has been the object of considerable research.

There are a number of explanations of Nesbitt's paradox, and all are related to the question of why people smoke. It may be that lighting and holding a cigarette gives people something to do with their hands, and this act calms the nerves, as pressing worry beads does. In fact, one study showed that the act of smoking causes increases in alpha waves, indicating relaxation, but the nicotine causes arousal (Murphree, Pfeiffer, & Price, 1967). It is also possible that the calmness is a result of relief from the nicotine withdrawal symptoms that smokers may experience in a mild form between cigarettes, or stimulation may be caused by low doses and relaxation by high doses, and the smoker can control the desired effect by altering inhalation of the smoke (O. F. Pomerleau & Pomerleau, 1984; Stepney, 1982). One study showed that the effect of smoking on arousal can depend on the stressfulness of the circumstances in which the cigarette is smoked. When subjects were stressed by noise, smoking reduced arousal as measured by the EEG, but under conditions of low arousal, smoking had an activating effect on EEG (Mangan & Golding, 1978). Another study showed that subjective arousal (although not arousal measured by blood pressure and heart rate) was related to baseline arousal levels. Nicotine nasal spray and cigarette smoking increased arousal in people who had low baseline levels but had little effect on those whose arousal levels were already high (Perkins, Grobe, Epstein, Caggiula, & Stiller, 1992).

Chronic Effects. As we shall see later, one theory of why people smoke is that they are using the nicotine in tobacco to control their response to stress and to create a positive mood. There are, in

fact, few data to support this. A survey in the United Kingdom has shown that smokers have lower levels of psychological well-being than nonsmokers and ex-smokers (West, 1993). In addition, even though it is typically found that mood worsens when a person stops smoking, it slowly returns to the normal smoking level after 3 or 4 weeks. What's more, it then continues to improve even further during the following 10 weeks, so the person's mood becomes even better than it was while he or she was smoking (Hughes, Higgins, & Hatsukami, 1990).

Effects on Performance. There have been many studies of the effects of nicotine on human performance, and the results have not been entirely consistent. The data are further complicated by the fact that the effects of nicotine appear to be different in smokers and nonsmokers. In general, the major effect of smoking is to improve the performance of regular smokers whose behavior has been degraded by withdrawal from nicotine. In a simulated driving task, for example, it was found that the performance of nonsmokers and of smokers who were allowed to smoke was equal, but an impairment in vigilance and tracking was detected in smokers deprived of nicotine (Heimstra, Bancroft, & De Kock, 1967).

Functional magnetic resonance imaging studies provide an illustration of the cognitive impairments caused in chronic smokers by nicotine abstinence. Using BOLD imaging, researchers presented participants with a visual display of constantly changing letters in which the letter X was the target letter. When the letter X appeared, participants were asked to report which letter had been presented either immediately before, two letters before, or three letters before the letter X. Increasing the number of letters that must be remembered increases cognitive load by taxing working memory. If the participants had smoked nicotine within 1.5 hours prior to testing, activity in the dorsolateral prefrontal cortex was significantly lower when reporting which letter had directly preceded the letter X (1-back) compared to when reporting which letter had occurred two or three letters before X (2-back and 3-back). However, following 14 hours of nicotine abstinence when participants were experiencing nicotine withdrawal, BOLD imaging showed that participants exhibited high levels of cognitive activity in the dorsolateral prefrontal cortex, regardless of which letter they were asked to report. In other words during nicotine withdrawal, the previously simple 1-back task required as much brain activity as the 2- and 3-back task. They also found that the participants made more errors on all three tasks during nicotine withdrawal (Xu et al., 2005). These effects are shown in Color Plate B.

Other studies, however, have shown that smoking may do more than just eliminate nicotine withdrawal deficits. On tasks that require vigilance and sustained attention, such as driving, it can enhance performance, even beyond the performance of nonsmokers (Tarriere & Hartemann, 1964; Wesnes & Warburton, 1983). In an extensive review of nicotine and human performance, Wesnes and Warburton (1983) concluded that smoking does help sustain performance on monotonous tasks and improves both the speed and the accuracy of information processing.

In addition to speeded information processing, faster motor reaction speeds produced by nicotine have also been reported for both cigarette smoking and chewing nicotine gum (Pritchard, Robinson, & Guy, 1992; Sherwood, Kerr, & Hindmarch, 1992).

Smoking can also improve performance on learning tasks. The effects of smoking one cigarette on serial anticipation learning of a list of nonsense syllables was determined in an experiment by Anderson (1975). She showed that the effects of the cigarette were similar to any arousing stimulus: The learning of the list was impaired, but recall of the list 45 minutes later was improved. She suggested that this outcome reflects the fact that arousal at the time of learning causes poor immediate recall because of the interfering effect of an increase in nonspecific activity. The increased arousal, however, aids the process of consolidation and improves recall of the list at a later time. Similar effects on consolidation have also been reported in studies on nonhumans, as we shall see.

Other improvements in memory have been noted, and it has now been demonstrated that some of these effects are not attributable to relief of smoking withdrawal in regular smokers (Warburton, 1992).

Interestingly, nicotine has been shown to improve various aspects of cognitive functioning in patients with Alzheimer's disease and in aging laboratory rats and monkeys (Levin, 1992).

In spite of demonstrations that nicotine can improve performance and learning, there are many more reports that it has no effect or may even interfere with cognitive and performance variables (West, 1993). These divergent findings have led to rather heated debates among researchers. A debate that was reviewed in *Addiction* (1993, Vol. 88, pp. 591–600) is particularly interesting because, as we shall see later, one theory of why people smoke is that they find it improves their performance. This theory is advanced as an alternative to the theory that smoking can be considered similar to addiction to other drugs (J. H. Robinson & Pritchard, 1992).

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Unconditioned Behavior

Spontaneous motor activity (SMA) of rats is initially depressed by 0.8 mg/kg of nicotine, but, after 7 days of testing, this dosage produces an increase in SMA that, during repeated testing, gets greater until the increase is similar to that produced by 0.8 mg/kg of amphetamine. It is believed that the initial depression is a result of the effect of nicotine on ACh transmission in the brain, an effect that disappears with tolerance after a few days. Once the ACh effect decreases, the increase in epinephrine causes an increase in SMA in a manner similar to amphetamine (Morrison & Stephenson, 1972b; Stolerman, Fink, & Jarvik, 1973).

Conditioned Behavior

After an initial suppression of all behavior at higher doses, the effects of nicotine on both positively and aversively motivated behavior are similar to amphetamine: The effect is dependent on control rate; high rates are depressed, and low rates are increased (Morrison, 1967; Pradhan, 1970). Like amphetamine, nicotine does not appear to increase responses that have been suppressed by response-contingent shock (Morrison & Stephenson, 1972a).

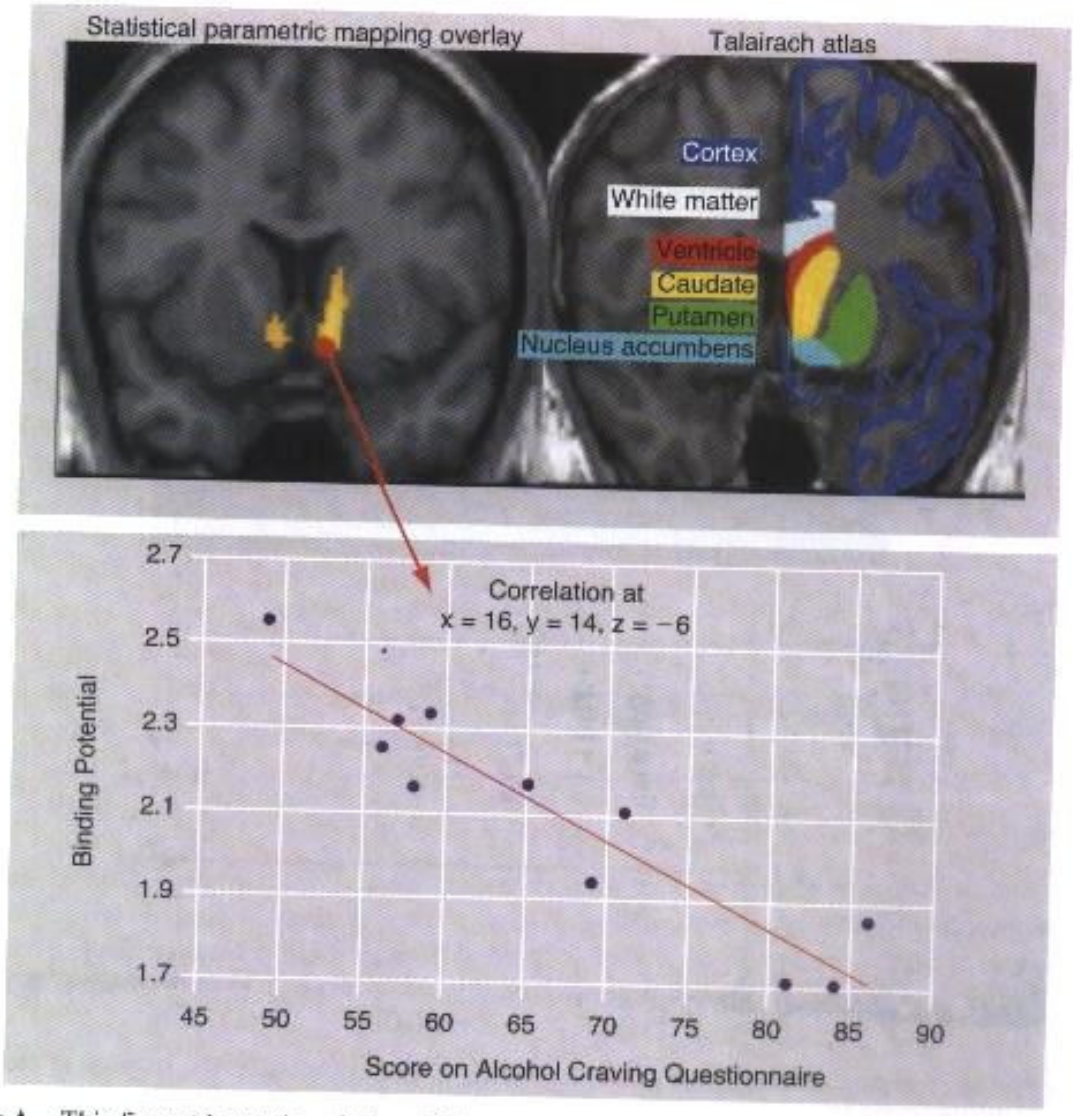
It has also been shown that withdrawal from 0.4 mg/kg of nicotine can disrupt the ability of rats to avoid a shock in the same manner that nicotine withdrawal can interfere with the behavior of humans (Morrison, 1974).

This great similarity between the effects of nicotine and amphetamine on operant behavior suggests that many of these effects are likely brought about by a similar mechanism. Because amphetamine increases activity at catecholamine synapses (see Chapter 11) and nicotine causes the general release of epinephrine and stimulates DA and NE synapses, it is possible that many of these behavioral effects of nicotine are a result of the release of catecholamines (Pradhan, 1970). This increase in catecholamine activity, however, depends on the action of nicotine at its receptor sites because most of these behavioral effects can be blocked by pretreating the animal with mecamylamine, a drug that blocks nicotinic receptor sites (Morrison, 1967).

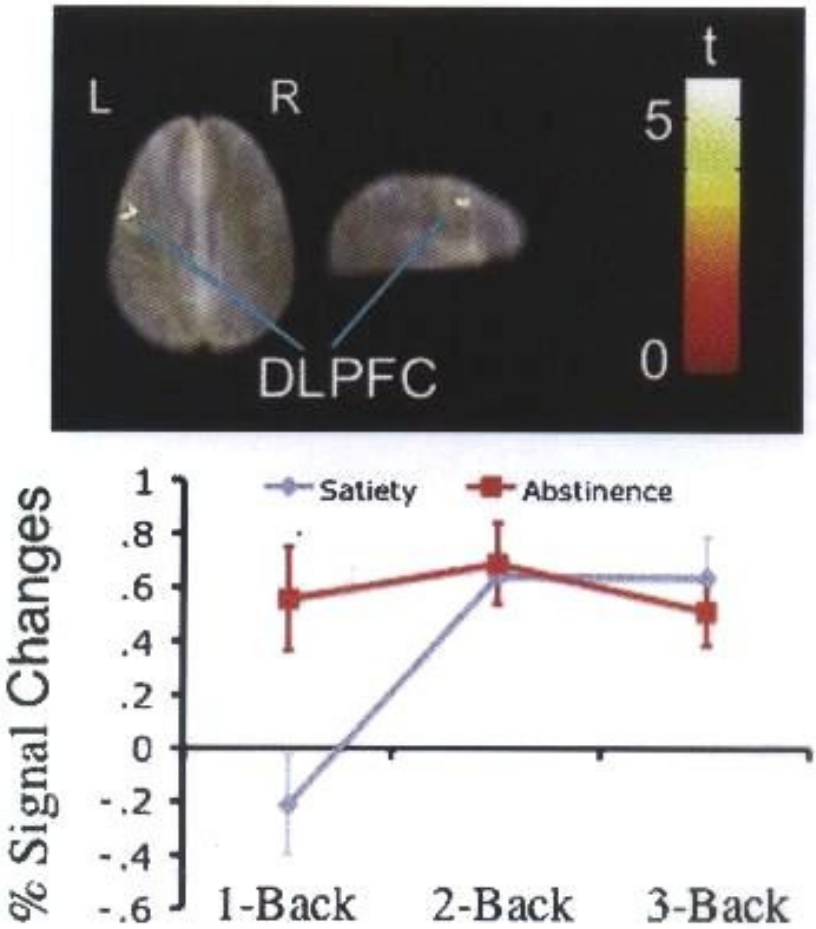
DRUG STATE DISCRIMINATION

Nicotine is an effective cue in a drug state discrimination task in a dosage range similar to one that alters operant behavior. It has been shown that 0.2 mg/kg nicotine can be used as a cue and will not generalize to various doses of epinephrine, pentobarbital, physostigmine, chlordiazepoxide, or caffeine. The stimulus properties of nicotine can be blocked by mecamylamine (Morrison & Stephenson, 1969; Stolerman, Pratt, & Garcha, 1982).

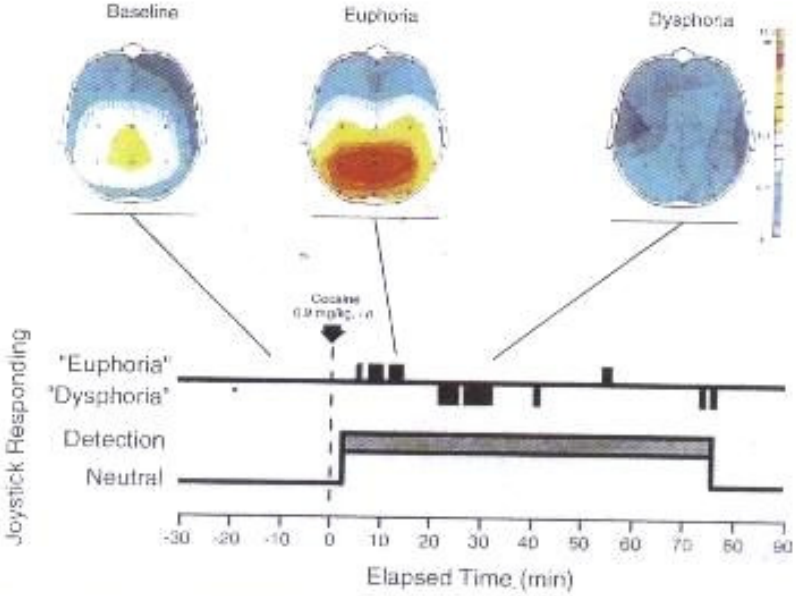
Although it cannot be found consistently, there is some evidence of partial generalization between nicotine and d-amphetamine, and animals trained to discriminate cocaine will sometimes generalize the cocaine response to nicotine (Stolerman,



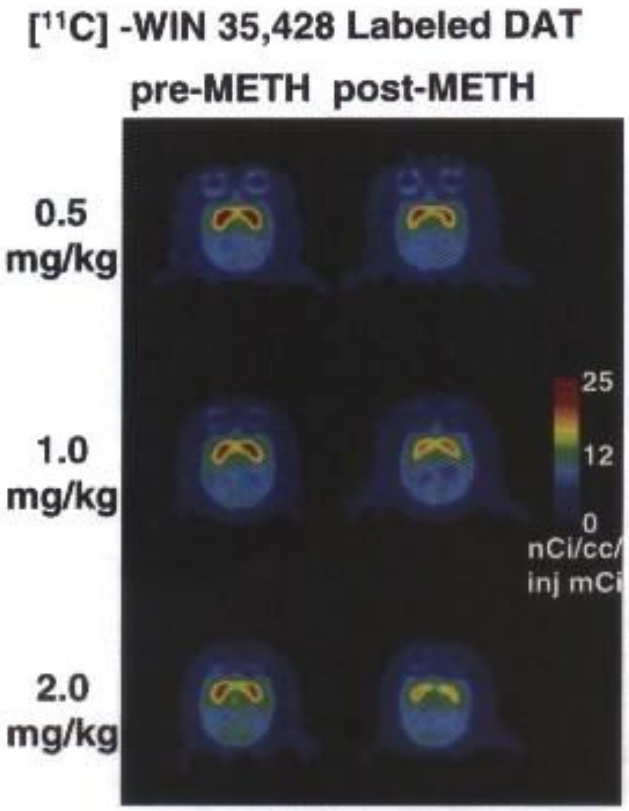
Color Plate A This figure shows the relationship between activity in the ventral striatum (the location of the nucleus accumbens) and craving for alcohol caused by exposure to alcohol-related cues in long-term alcoholics. The yellow brain image at the right shows the area of the brain that was activated when the participants were exposed to the alcohol cues. As you can see, this corresponds to the area of the nucleus accumbens, as shown in the brain image on the left. The lower panel shows the negative correlation between craving and the binding potential for dopamine D_2 receptors in the nucleus accumbens. As you can see, the lower the binding potential at D_2 receptors, the higher the craving induced by the alcohol-related cues. (Heinz et al., 2004; reprinted with permission)



Color Plate B The top panel of this figure shows the BOLD image of the brain. The location of the dorsal lateral prefrontal cortex (DLPC) is indicated. The color bar at the right indicates the level of activity in the DLPC during the task. The lower panel shows the amount of activity in the DLPFC during the 1-, 2-, and 3-back tests when subjects had smoked within the previous 1.5 hours (Satiety) and when they were deprived of nicotine for 14 hours (Abstinence). (Adapted from Xu et al., 2005, fig. 3, p. 147; reprinted with permission)



Color Plate C Behavioral and EEG changes in a participant after receiving a 90 mg/kg cocaine injection. The color bar at the right indicates amount of alpha activity. Euphoria is correlated with increased alpha activity in the occipital and parietal cortex. Below-normal levels of alpha activity occurred when participants reported dysphoria. (Lukas, 1991, chap. 1, fig. 7, p. 14; reprinted with permission)



Color Plate D This figure shows the effect of giving various doses of methamphetamine to baboons four times at 2-hour intervals. These PET images were taken 2 to 3 weeks after the drug treatment. The color bar in the left panel shows the color associated with the amount of binding to the dopamine transporter (DAT), with red showing many transporter molecules and blue showing fewer. The images show the pre- and postmethamphetamine activity in the brain. The yellow and red areas are in the caudate nucleus. You can see a dose-related decrease in DAT binding, indicating that there has been death of some dopamine cells in the area. (Adapted from Villemagne et al., 1998, fig. 1, p. 421; reprinted with permission)

1987). This finding corresponds to the observation made earlier: Humans sometimes describe the effect of intravenous nicotine as being similar to that of cocaine.

It has been shown that humans can discriminate between identical cigarettes that are different only in nicotine content (Kallman, Kallman, Harry, Woodson, & Rosecrans, 1982), although it is not known whether this is done by taste or through a central mechanism.

WITHDRAWAL SYMPTOMS

When most tobacco users attempt to give up their habit, they experience withdrawal symptoms in varying degrees of intensity. If you have ever attempted to quit smoking or have suffered along with someone going through tobacco withdrawal, you are familiar with the symptoms. Withdrawal from nicotine is not as severe physically as withdrawal from heroin, but it is just as stressful psychologically. Indeed, many ex-heroin addicts who have also quit smoking report that they found it harder to give up tobacco than heroin.

Systematic studies of nicotine withdrawal in regular smokers reliably showed the following symptoms: decreased heart rate; increased eating, which caused weight gain; an inability to concentrate; increased awakenings during sleep; craving for cigarettes; and anxiety, anger, aggression, and depression (Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Hughes, Higgins, & Bickel, 1994). Other symptoms that have been reported are nervousness, drowsiness, light-headedness, headaches, dizziness, tremor, and nausea (Jarvik, 1979, p. 27). EEG recordings of nicotine-dependent individuals who abstain from tobacco for 10 to 24 hours show a slowing in the frequency of alpha waves and an increase in theta wave amplitude and frequency, normally seen during drowsiness or light sleep (Herning, Jones, & Bachman, 1983). These effects are immediately reversed on administration of tobacco, suggesting physical dependence on nicotine. Other researchers have also shown that the application of a transdermal nicotine patch during acute nicotine withdrawal increases EEG brain wave as well as P300 amplitudes (Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999).

Most of these symptoms, except for weight gain and craving, are over within a month. For about 25 percent of people, these symptoms may persist as long as 6 months, although there are reports that craving may continue as long as 9 years (Fletcher & Doll, 1969).

Withdrawal symptoms can be relieved by the administration of nicotine from other sources such as gum and transdermal patches. However, unlike withdrawal from many other drugs, the administration of the receptor blocker for nicotine, mecamylamine, does not induce withdrawal in nicotine-dependent smokers (Hughes et al., 1994). Symptoms of nicotine withdrawal can also be reduced, at least temporarily, by the taste and smell of tobacco or the act of smoking itself. One study showed that tobacco withdrawal symptoms were relieved if smokers were allowed to smoke a denicotinized cigarette that delivered no nicotine at all to the smoker (Butschky, Bailey, Henningfield, & Pickworth, 1994).

For a time, nicotine withdrawal can interfere with performance on various cognitive and motor tasks. As we have already seen, nicotine withdrawal interferes with rats' shock avoidance (Morrison, 1974).

Unlike most other drugs that cause physical dependence, withdrawal severity does not seem to be related to dose; heavy and light smokers report equally severe withdrawal. Nor is withdrawal severity related to length of time smoking, previous attempts at quitting, sex, age, education, or alcohol and caffeine use (Hughes et al., 1991).

SELF-ADMINISTRATION IN NONHUMANS

Because self-administration of nicotine in humans is so persistent and widespread, it is surprising that accounts of animal self-administration are rare. There are some anecdotal accounts of tame monkeys smoking. Indeed, Charles Darwin, in *The Descent of Man* (1882), claimed to have seen monkeys "smoke tobacco with pleasure" (p. 7).

Darwin used these observations to support his contention that the sense of taste and the nervous systems of humans and monkeys are similar. Surprisingly, however, systematic research from laboratories has found monkeys to be reluctant smokers (Jarvik, 1973, p. 296). Monkeys have been taught to inhale cigarette smoke, but the procedure involved a period of forced consumption in which the monkeys were reinforced with drinking water for sucking on a tube through which they received tobacco smoke. After this training, some animals seemed to prefer sucking on a tube that delivered tobacco smoke over one that delivered only air. It is doubtful whether this procedure represents a situation similar to human tobacco use. Animals do not normally initiate smoking on their own (Jarvik, 1973).

There are few accounts of animals' working for intravenous infusions of nicotine. Most studies show that if nicotine is self-administered, responding is not robust and is rather slow (Stolerman, 1987). In one study (Deneau & Inoki, 1967), monkeys were given the opportunity to self-administer nicotine through an intravenous cannula. After being given hourly infusions of nicotine for 2 to 5 days, some animals reliably responded for nicotine, but response rates were low, and the pattern was not consistent from day to day. In a later study, S. R. Goldberg, Spealman, and Goldberg (1981) were able to demonstrate reliable intravenous self-administration in monkeys. Using a second-order schedule, they found that if the nicotine infusion was preceded by a colored light, monkeys would respond at a high rate for the light alone, even if it was paired with the nicotine infusion only occasionally. It appears that the stimuli associated with the delivery of nicotine make a very important contribution to the effectiveness of nicotine as a reinforcer. Goldberg and his associates also demonstrated that injections of the nicotine antagonist mecamylamine reduced responding to saline control levels.

In another study, Risner and Goldberg (1983) demonstrated that dogs would self-administer nicotine on a fixed ratio (FR) 10 schedule when a 4-minute time-out was imposed after each infusion. Progressive ratio schedules showed that some nicotine doses would support ratios as high as 510 responses per infusion, much higher than saline but considerably lower than cocaine.

It appears, then, that nicotine infusions do have reinforcing properties in laboratory animals under a restricted range of conditions. Conditions that support nicotine infusion are a period of forced consumption, stimuli paired with the infusion, and a fixed interval or second-order schedule that imposes an abstinence period between opportunities to self-administer.

Intravenous nicotine can also serve as a punisher. In one study, food-reinforced behavior of monkeys was suppressed if it was followed by an infusion of nicotine (S. R. Goldberg & Spealman, 1983). This suppression occurred at the same dose that served as a positive reinforcer for monkeys in other experiments conducted in the same laboratory. It is not clear what might make nicotine a reinforcer under some circumstances and a punisher in others.

SELF-ADMINISTRATION IN HUMANS

There is little doubt that nicotine is a reinforcer in human smokers. In one study, human smokers were attached to an intravenous catheter and could self-administer infusions of nicotine by pressing a lever on an FR 10 schedule. Responding increased on this lever when the nicotine was available and was extinguished when saline infusions were substituted. It was also shown that when larger doses were used, subjects administered fewer infusions, and they increased infusions when the dose was decreased (Henningfield et al., 1987, pp. 582–585; Henningfield, Lucas, & Bigelow, 1986).

Delivery of nicotine is clearly a reinforcer in humans, and humans are capable of adjusting nicotine doses, but the nature of the change in blood nicotine levels that is responsible is not clear. One possibility is that smokers are trying to maintain a constant level of nicotine in the blood, another is that they are trying to achieve

sudden high doses delivered to the brain, and a third is that smokers manipulate dose depending on situational factors and the effects that they expect the drug to have on their mood and behavior.

Constant Blood Level Theory

There is evidence that the smoker is trying to maintain a constant level of nicotine in the blood, that is, a dose high enough to avoid withdrawal symptoms but below a level that has toxic or aversive effects.

For some time, it had not been clearly established that nicotine is the ingredient in tobacco that is responsible for tobacco consumption. To show that it is, researchers used the strategy of changing the nicotine content of cigarettes and noting whether the amount of smoking changed as a consequence. Would smokers titrate their dose to achieve a constant level?

Early studies had trouble demonstrating dose compensation when they measured dose by simply counting the number of high-and low-nicotine cigarettes a person smoked. They soon learned that people control nicotine intake not by changing the number of cigarettes they smoke but by changing their smoking behavior; that is, they compensate for low-nicotine cigarettes by taking deeper and more frequent puffs on the cigarette. These variables can be measured precisely by having subjects smoke through a special cigarette holder connected to a computer that monitors total smoke inhalation. Using these techniques, it has been demonstrated that smokers will compensate for increased or reduced doses by increasing and decreasing their puffing behavior, but the compensation is not as complete as when intravenous infusions are used.

One of the predictions of this theory is that the first few puffs on a cigarette will be rapid and deep as the smoker tries to raise blood nicotine levels that have fallen since the previous cigarette was smoked. As the nicotine level increases, the puff rate will decrease, and few puffs will be taken near the end of the cigarette. This change in puff rate has been recorded by several researchers (Chait & Griffiths, 1982). In addition, the theory predicts that people will be highly motivated to smoke when their blood levels are low and that the lowest levels occur after a night of sleeping. A British study showed that 14 percent of smokers light up within 5 minutes of waking in the morning, and 50 percent do so within 30 minutes.

In an elaboration of this theory, Stanley Schachter, at Columbia University, has suggested why smoking increases in times of stress. During stress, the urine becomes acidic. Because nicotine is a weak base, it becomes highly ionized in the acidic urine and, consequently, cannot be reabsorbed into the blood. As a result, the kidneys are very efficient in excreting nicotine, and the blood levels drop rapidly. Schachter (1978) suggested that this rapid drop in blood nicotine is the signal that another cigarette is necessary. In other words, "the smoker's mind is in the bladder." Consequently, smoking increases in times of stress.

Human smokers attempt to prevent their nicotine blood level from falling to the point where withdrawal symptoms occur. Smokers also can make adjustments for the amount of nicotine delivered by their cigarette, but they are unable to compensate completely. Their blood levels then become higher than normal when nicotine content is increased and lower than normal when it is decreased. In addition, increasing blood nicotine levels with nicotine chewing gum will decrease smoking but does not eliminate it. Factors other than constant blood level are controlling nicotine intake as well.

Nicotine Bolus Theory

The *nicotine bolus theory* has been proposed by M. A. H. Russell of the Maudsley Hospital in London to explain some aspects of smoking behavior. Careful observation of a cigarette smoker will show that when smoke is inhaled into the lungs, it is frequently done with one rapid inhalation rather than gradually, as with a normal breath. This sudden filling of the lungs with smoke tends to saturate the blood in the

capillaries of the lungs with nicotine at the moment of inhalation. This concentration of nicotine in the blood, known as the *nicotine bolus,* stays together as the blood returns to the heart and is pumped to the brain. This theory suggests that the sudden high level of nicotine in the brain acts as a positive reinforcer and keeps the smoker smoking. It has been established that nicotine stimulates the mesolimbic dopamine system like most other reinforcing drugs, and this is likely responsible for the reports of positive mood and euphoria after its administration. Because the bolus is so pleasurable, it is responsible for the intense craving for tobacco (M. A. H. Russell, 1976). A similar theory has been proposed to explain the addictive nature of intravenous injections of heroin (Dole, 1980) and is consistent with the general finding that the reinforcing properties of drugs can be greatly enhanced by delivering them to the brain rapidly in high concentrations.

Because a nicotine bolus can be achieved only by smoking, this theory explains why the craving for the drug is worse in smokers than in those who take tobacco by other means, but it cannot account for the great popularity of tobacco in its other forms throughout history.

Psychological Tool Theory

Another explanation of smoking is related to Nesbitt's paradox described earlier. It suggests that a smoker uses nicotine as a tool to help cope with daily tasks by manipulating levels of arousal and other psychological functions. As we have seen, nicotine can subjectively both increase and decrease levels of arousal, depending on dose and circumstances. The *psychological tool theory* suggests that the smoker uses smoking as a tool to decrease arousal in times of stress and to increase arousal during fatigue and boredom and, thus, is able to maintain an optimal level of arousal. Changing arousal levels allows performance on tasks to be enhanced as well. Together, these factors increase the psychological comfort of the smoker and provide the motivation for smoking (Balfour, 1982; Hutchison & Emley, 1973; J. H. Robinson & Pritchard, 1992; Stepney, 1982, pp. 193–196).

This idea has considerable intuitive appeal, and there is some evidence to support it, but most of this evidence is indirect. It has been shown that nicotine can enhance performance on some tasks and can reduce the effects of stress, but these effects are disputed and not easily replicated. In addition, it is difficult to show that beneficial effects of nicotine, even if they do occur, are responsible for nicotine self-administration. Recent studies with amphetamines and sedatives have shown that people will sometimes choose to use a drug that either stimulates them or sedates them, depending on the demands of a task they will be performing (K. Silverman, Mumford, & Griffiths, 1994), but this has not been shown for nicotine. Moreover, many other studies (described in Chapter 5) indicate that, in general, drugs are seldom self-administered for their therapeutic effects. We know that smoking increases in times of stress, but this observation can be explained more simply by other mechanisms, as Schachter has done. In addition, stress-reducing agents such as the benzodiazepines (Librium and Valium) do not appear to be effective in helping people to stop smoking (Jaffe, 1987).

Comparing Theories

These three explanations—the constant blood level theory, the nicotine bolus theory, and the psychological tool theory—are not mutually exclusive. They may all be correct to some extent. Nicotine can act as a positive reinforcer. Constant blood levels that avoid withdrawal may well be reinforcing, and so may the nicotine bolus and the ability to alter arousal and performance. Smokers may be trying to achieve any one or all three at the same time. A combination of all ideas can explain more of the data than a single theory alone. It is also possible that one theory may not be appropriate for all smokers. Different people may smoke for different reasons. Tobacco smoking is a complicated activity.

The debate on the nature of smoking has taken on a political significance since the 1988 U.S. Surgeon General's Report and the 1994 U.S. House of Representatives hearings on whether the tobacco industry in the United States should be regulated by the FDA. The FDA and the surgeon general argue that smoking is addicting in the same sense that cocaine and heroin are; that is, it stimulates reward centers in the brain and is a positive reinforcer. Defenders of the tobacco industry claim that this is not the case. Smoking, they say, is motivated by a desire to control mood and performance; that is, it is a behavior enhancer (J. H. Robinson & Pritchard, 1992). The debate has not been settled on either the scientific or the political front, but the behavior enhancer argument seems to be losing ground on both fronts (Kozlowski & Henningfield, 1995).

Smoking Behavior of Humans

North American native peoples, who were the first to use tobacco, tended to use it as a hallucinogen, and they consumed it irregularly in fairly high doses. It was associated with ceremonies and was often used by shamans. Modern use is quite different. Most cigarette smokers space cigarettes out fairly evenly throughout their waking hours, but a careful analysis shows that there is a regular daily pattern. Smoking is usually greatest in the early afternoon, right after lunch, and after supper (between 7:00 and 10:00 P.M.). Throughout the course of a week, Wednesday and Sunday are the lightest smoking days, and Saturday is the heaviest (Meade & Wald, 1977).

Although the pattern of cigarette smoking is fairly regular over the course of a day or a week for any individual, cigarette intake may increase in particular circumstances. One factor is the presence of cigarettes or of other smokers. Experiments have shown that if smokers are asked to wait in a room, they will light up a cigarette much sooner if other people in the room are smoking (Glad & Adesso, 1976). People are also more likely to smoke if a pack of cigarettes is left in a conspicuous place in the room (Herman, 1974).

Tobacco Chippers. As with other drugs, the amount of nicotine consumed varies considerably among individuals. The average regular smoker consumes about 25 cigarettes a day and shows signs of physical dependence on nicotine, but about 10 percent of regular smokers consume fewer than five cigarettes a day and are clearly not physically dependent. These smokers have been called *tobacco chippers* because their pattern of occasional use without physical dependence resembles a pattern of heroin use called "chipping" (Shiffman, 1989; see also Chapter 12).

Who Smokes?

Tobacco is not used by everyone. Studies of smokers and nonsmokers have revealed some interesting differences. Like drinking, smoking appears to have a genetic component. Studies of twins have shown that identical twins are more likely to have similar smoking habits than fraternal twins. Even when they are not reared together, the smoking behavior of identical twins is highly correlated (Eysenck & Eaves, 1980; Hughes, 1986).

Smokers are more likely than nonsmokers to use other drugs such as caffeine and, especially, alcohol. In addition, smokers are more likely to change their jobs, get married and divorced, have more traffic accidents, be more rebellious, achieve less academically, and be more sexually active than nonsmokers (Ashton & Stepney, 1982, p. 121; Jarvis, 1994).

Before smoking peaked at nearly 80 percent in the middle of the twentieth century, there was no relation between social class, education, and smoking, but now that smoking rates have fallen, distinct effects of social class and economics have become apparent. People who are unemployed, work in unskilled and manual labor jobs, or have less than a high school education are much more likely to smoke than people who work at professional jobs and have a college degree.

Typically, people start to smoke when they are teenagers. At this stage, social class does not

seem to have an effect; however, having parents who smoke, a significant other who is a smoker, or poor academic achievement will predict, albeit weakly, who will start smoking. Few people become smokers after the age of 20.

Behavioral Economics

Numerous attempts have been made to determine the price elasticity of cigarettes. Estimates range from −0.4 to −1.3, but the figure is generally accepted to be about −0.7. This indicates a relatively inelastic demand. Further analyses, however, have shown that this inelasticity is not the same for different segments of the population or for different measures of demand. Teenage smokers are more susceptible to price increases than older smokers in terms of both the number of cigarettes smoked and the number of smokers. The slope of the demand curve of participation (number of smokers) was shown to be −1.20 for smokers 12 to 17 years old in the United States, and the quantity (cigarettes smoked per smoker) was −0.25, with a combined demand of −1.40. In this study, the slope of the demand curve for smokers over 20 was −0.42. These figures indicate that demand in young smokers is elastic—that is, increasing the price of cigarettes will have a considerable impact on the initiation rate of young smokers, but it may not have a large effect on the smoking behavior of older, established smokers. Because most people become smokers before the age of 20, price increases will have a considerable effect. They will decrease cigarette consumption not only at the time they are put into effect but also far into the future (Lewitt, 1989).

Another study of demand elasticity for cigarettes has shown that elasticities are greater if long-term effects are measured. A study of cigarette prices in the United States from 1955 to 1985 found that a permanent increase of 10 percent in price had an immediate effect of reducing consumption by 4 percent. In the long term, however, there was a decrease in consumption of 7.5 percent. In addition, elasticities were much smaller if the price increase was temporary rather than permanent (Becker, Grossman, & Murphy, 1988).

HARMFUL EFFECTS

Heart Disease

Heart disease caused by tobacco smoke appears to be due largely to the combined action of nicotine and carbon monoxide. Nicotine increases the workload of the heart, and carbon monoxide reduces the oxygen-carrying capacity of the blood and, consequently, the oxygen supply to the heart itself. These effects are further complicated by the fact that other constituents in the smoke reduce the lungs' ability to absorb oxygen, so the heart must work even harder to pump more blood through the lungs and satisfy the oxygen needs of the body. In addition, there is a relationship between atherosclerosis and the number of cigarettes smoked per day. Atherosclerosis is a disease wherein plaques, or deposits, build up in blood vessels and eventually stop the circulation of blood. When the blood flow to the heart itself is stopped in this manner, the heart muscle dies, and a heart attack occurs. Atherosclerosis is caused in part by high cholesterol levels in the blood, but smoking doubles the risk of heart attack both in people who have normal cholesterol levels and blood pressure and in those who have raised cholesterol and high blood pressure. Figure 9-3 summarizes how smoking cigarettes contributes to heart disease.

Lung Disease

When tobacco smoke is inhaled, the ash and tars are deposited on the moist membranes on the inside surface of the lung, through which oxygen and carbon dioxide must pass to and from the blood. Normally, particles are cleared from the lungs by small hairs called *cilia*, which agitate and work the pollutants upward until they are ejected by coughing. Another line of defense against inhaled particles is the action of *phagocytes*. The phagocytes attack, surround, and destroy foreign matter in the lungs. Smoking reduces the actions of both the cilia and the phagocytes, leaving the lungs more vulnerable to the toxic effects of inhaled pollutants and infections by bacteria and viruses. As a result, smokers are more susceptible to chronic bronchitis and emphysema.

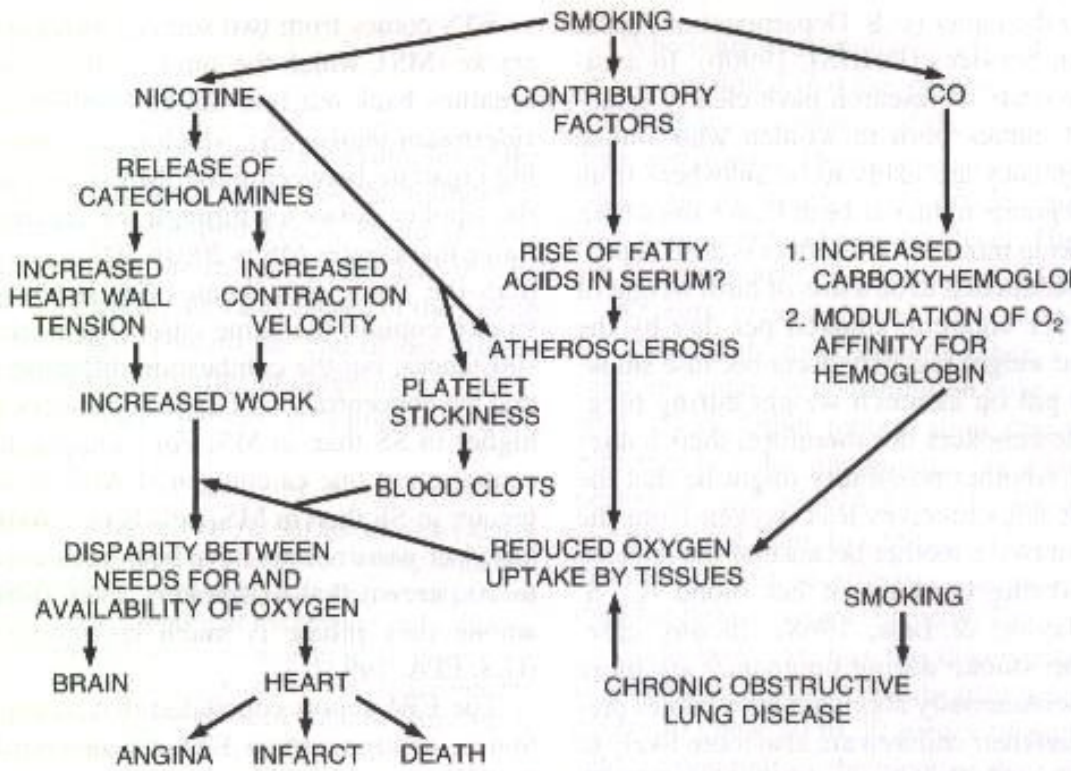


Figure 9-3 The mechanisms by which smoking contributes to heart disease. Smoking increases the demand on the heart by increasing its workload while at the same time decreasing the oxygen the heart muscle receives by increasing carboxyhemoglobin and causing atherosclerosis and lung diseases. (From Van Lancker, 1977, p. 252)

Cancer

The causal link between smoking and cancer is less well established. It is known that smoking greatly increases the risk of cancer of the mouth, lungs, and bladder, but the mechanism by which tobacco smoke actually causes cancer is not entirely understood. A number of substances in tobacco smoke could produce cancerous cells by altering the DNA in normal body cells, but whether this process is what actually takes place in humans has not been conclusively demonstrated. What is known is that smoking greatly increases the risk of cancers produced by other known carcinogens, such as pollutants, asbestos, and alcohol. For example, the risk of smokers getting cancer of the mouth and pharynx is two to six times greater in heavy drinkers than in nondrinkers (Rothman & Keller, 1972).

The risk of lung cancer can be greatly decreased by quitting smoking, and the risk lessens considerably over time after a person stops (Halpern, Gillespie, & Warner, 1993).

Reproduction

There is some debate whether women who smoke are more likely to be infertile than nonsmokers, but the bulk of evidence to date suggests that they are and that the effect is dose related. Women who smoke more than 20 cigarettes per day are 1.7 to 3.2 times more likely to be infertile than nonsmokers. It also appears that the effect is reversible: Fertility returns to normal after cessation of smoking (Baird, 1992).

There is now some evidence that smoking during pregnancy may cause birth defects. Such defects are associated with smoking of both the

mother and the father (U.S. Department of Health and Human Services [DHHS], 1990b). In addition, many years of research have clearly established that babies born to women who smoke during pregnancy are likely to be anywhere from 150 to 200 grams lighter at birth than babies born to nonsmoking mothers. This effect is dose dependent and is estimated to be a loss of birth weight of 11 grams per cigarette smoked per day by the mother. The weight loss may occur because smokers do not put on as much weight during pregnancy as nonsmokers do; therefore, their babies are lighter. Another possibility might be that the developing fetus receives less oxygen from the body of a smoking mother because of the reduced oxygen-carrying capacity of her blood (C. S. Russell, Taylor, & Law, 1968). In any case, women who smoke during pregnancy are more likely to spontaneously abort and have babies prematurely, and their children are also more likely to be ill and die (M. S. Kramer, 1987; U.S. DHHS, 1989, 1990a).

Further research has shown that the effects of maternal smoking can last for some time. At 7 years of age, the children of mothers who smoked during pregnancy have lower spelling and reading scores, have shorter attention spans, and are more often hyperactive than children of mothers who did not smoke during pregnancy (Naeye & Peters, 1984). It is not clear, however, whether these effects are due entirely to smoking or to some other factor that correlates with smoking.

It has been estimated that if maternal smoking could be eliminated altogether, the overall infant death rate could be reduced by 10 percent (Haglund & Cnattingius, 1990).

Environmental Tobacco Smoke

Smoking is unhealthy not only for smokers but also for those who work and live with them. In 1992, the U.S. Environmental Protection Agency (U.S. EPA) released a document reviewing what was known at that time about the dangers of being exposed to environmental tobacco smoke (ETS).

ETS comes from two sources: (a) *mainstream smoke* (MS), which the smoker inhales and then breathes back out into the atmosphere, and (b) *sidestream smoke* (SS), which issues from a burning cigarette between puffs. MS is created when the smoker draws air through the cigarette. The flame that creates MS is 200 to 300 degrees hotter than the flame that creates SS. Both types of smoke contain the same carcinogens and toxic substances, but the combustion differences mean that the concentration of these substances is much higher in SS than in MS. For example, the concentration of one carcinogen, 4-ABP, is 30 times greater in SS than in MS. Levels of 4-ABP in the blood of nonsmokers have been measured at 10 to 20 percent that of smokers, even though the smoke they inhale is much less concentrated (U.S. EPA, 1992).

The EPA report concluded that in the United States, carcinogens in ETS are responsible for 3,000 lung cancer deaths per year among nonsmokers. Even though the health dangers of ETS are present for all age-groups, children are particularly vulnerable. The report also concludes that ETS is responsible for between 150,000 and 300,000 cases of bronchitis and pneumonia in infants up to 18 months of age and that ETS exposure worsens the severity of asthma symptoms in 200,000 to 1 million children per year (Spitzer et al., 1990; U.S. EPA, 1992). The report also finds a strong link between ETS and sudden infant death syndrome (SIDS; infants die suddenly and unexpectedly between the ages of 1 month and 1 year). The risk of dying of SIDS is between 1.6 and 7.7 times greater for babies of smoking mothers than for babies of nonsmokers. The risk is also dose dependently higher for babies in homes where the mother smokes more than 20 cigarettes per day (Nicholl & O'Cathain, 1992; U.S. EPA, 1992). It has been estimated that there would be a 27 percent decrease in SIDS if maternal smoking were eliminated (Haglund & Cnattingius, 1990).

The low birth weights created by smoking while pregnant can also occur in nonsmoking women if they are exposed to several hours of ETS daily (U.S. EPA, 1992).

TREATMENTS

Compulsion to Smoke

Perhaps one of the most tragic examples of the strength of the tobacco habit was the founder of psychoanalysis, Sigmund Freud. Freud smoked cigars most of his life in spite of the fact that he suffered from heart pains and cancer of the mouth as a direct result. Toward the end of his life, he was in constant pain after undergoing 33 operations for his cancer yet was still unable to quit. One report concludes,

> Freud died of cancer in 1939, at the age of eighty-three. His efforts over a forty-five-year period to stop smoking, his repeated inability to stop, his suffering when he tried to stop, and the persistence of his craving and suffering even after fourteen continuous months of abstinence—a "torture . . . beyond human power to bear" make him the tragic prototype of [the tobacco addict]. (Brecher & Editors of *Consumer Reports*, 1972, p. 215)

Freud, of course, is not alone. In his Statement on Nicotine-Containing Cigarettes in 1994 before the House Subcommittee on Health and the Environment, David Kessler, the commissioner of the FDA, made the following points: (a) Two-thirds of adults who smoke say that they wish they could quit, and (b) 17 million try to quit each year, but fewer than 1 out of 10 succeed. Three out of four adult smokers say they are addicted. By some estimates, as many as 74 to 90 percent are. Eight out of 10 smokers say they wish they had never started.

Tobacco smoking can be a difficult habit to break. Nevertheless, up to 90 percent of former tobacco smokers have quit without the benefit of any treatment. For those who need help, a great variety of therapies is available. One of the most common and most effective is nicotine replacement therapy.

Nicotine Replacement Therapy

This treatment is based on the same strategy as methadone maintenance with heroin addicts (see Chapter 12). It substitutes a relatively safe source of the drug, such as a nicotine patch, gum, or nasal spray, for the more harmful source, tobacco.

When this treatment was originally developed, it was assumed that the primary motivation for smoking was avoidance of the symptoms of nicotine withdrawal. Delivery systems—the nicotine patch and chewing gum—were designed to maintain a constant nicotine blood level. These systems are quite effective, as can be seen in Figure 9-1.

Reports on the use of nicotine gum show that it is significantly more effective than a placebo in reducing cigarette consumption over a period of 2 to 3 weeks. Other reports show that the gum is effective in reducing smoking for a much longer period of time, provided that the smoker continues to use the gum. In addition, it appears that the gum may be more effective for heavy smokers than for light smokers (Stepney, 1982, p. 201).

Gum, however, has the disadvantage that it is difficult to maintain an adequate dose. It is necessary to chew 20 to 30 pieces of gum a day to achieve one-half of the nicotine dose of cigarette smoking (Keenan et al., 1995). The transdermal patch does not have this problem and is also effective. A combination of the patch and the gum is better than either alone (Fagerström, Schneider, & Lunell, 1993).

The nicotine bolus theory has suggested that smokers may not be smoking only to avoid withdrawal; they may be obtaining positive reinforcement by delivering high levels of nicotine in the brain. It follows, then, that a nicotine delivery system that mimics this natural pattern of smoking is a more effective substitute. Consequently, a nicotine nasal spray has been developed (Sutherland et al., 1992) and is currently being considered for approval by the FDA (de Wit & Zacny, 1995).

Nicotine replacement may not always lead to smoking cessation, but even if it succeeds only in reducing the number of cigarettes smoked, as it often does, it will have achieved partial success (Keenan et al., 1995). Nicotine replacement therapy should continue for several months with a gradual weaning of dose, although many people continue to use it for a much longer period of time. Those who stop may find it necessary to revert to use of the gum or a patch in circumstances where relapse is likely.

TABLE 9-1 Preference for Different Methods of Smoking Cessation and Success Rates

Method	*Preference (%)*	*Success Rate (%)*
Cold turkey/self-help	90.4	<10
Counseling/behavioral	1.3	15
Nicotine patch	4.2	17.7
Nicotine gum	1.6	23.7
Nicotine inhaler	<1	22.8
Nasal spray	0	30.5
Buproprion (Zyban)	1.2	30.5
Other	3.1	Not available

Source: American Lung Association (2006).

Buproprion is another pharmacological treatment but is not a nicotine replacement therapy. Buproprion is an antidepressant drug sold as Zyban (see Chapter 14). It is not clear why it helps people stop smoking, but it appears to be effective. Table 9-1 shows the relative success rates and popularity of different methods of smoking cessation (American Lung Association, 2006).

Immunization

Two pharmaceutical companies, one in England and the other in the United States, have developed and have started clinical trials of a tobacco vaccine. The vaccine, known as TA-NIC or NicVAX, stimulates the body's immune system to create antibodies for molecules of nicotine. The antibodies then block the ability of nicotine to cross the blood–brain barrier. This should greatly diminish the ability of nicotine to act as a reinforcer and should cause smoking behavior to extinguish. The vaccine would need to be given in four or five doses and require a booster shot every few months.

A clinical trial has shown that the vaccine is effective in helping people quit smoking in those where the vaccine was able to create high levels of nicotine antibodies, but this was only one-third of those tested. Before more trials can be conducted, it will be necessary to find a way to increase the ability of the drug to create nicotine antibodies in more people (Maugh, 2005).

CHAPTER SUMMARY

- Nicotine is a drug found exclusively in the tobacco plant, which is consumed either by smoking or chewing or as snuff. It may also be administered in the form of a transdermal patch, nicotine chewing gum, or nasal spray.
- Nicotine is absorbed best from the lungs and is distributed rapidly throughout the body. It is excreted unchanged by the kidneys and metabolized by the liver. It has a half-life of about 30 minutes.
- Nicotine stimulates and then blocks nicotinic cholinergic receptors as dose increases. It has effects on both the central and the peripheral nervous system. It causes elevated levels of catecholamines, and it stimulates dopamine in the mesolimbic dopamine reinforcement system.
- Brain imaging studies show that pleasure reported by people who are smoking is correlated with increased dopamine receptor activation in the striatum, where the nucleus accumbens is located.
- Intravenous nicotine causes euphoric feelings in smokers but may cause unpleasant symptoms in nonsmokers. Even though nicotine increases the arousal level in the brain, smokers report that nicotine causes a feeling of relaxation.
- Some studies have shown that nicotine has little effect on performance, but others have concluded that nicotine at certain levels can enhance performance on some tasks.
- Nicotine's unpleasant withdrawal symptoms include irritability, weight gain, and sleep disturbances. Withdrawal can interfere with performance and has been shown to increase brain activity normally associated with drowsiness.
- Although nicotine is not self-administered by nonhumans as readily as many other drugs, tobacco is a powerful reinforcer for humans. One possible source of the reinforcing effect of nicotine is the sudden high concentration of nicotine that the brain receives after a puff on a cigarette; this is the nicotine bolus theory. Another theory, the psychological tool theory, claims that smokers use nicotine to increase and decrease level of arousal so as to enhance performance. Another theory suggests that smokers try to maintain a constant blood level in order to avoid nicotine withdrawal.

- Population studies show that the demand for cigarettes is inelastic in established smokers. In young smokers, price increases are effective in decreasing the number of smokers and the number of cigarettes they smoke.
- Smoking is not healthy. Tobacco smoking has been linked to heart disease, lung diseases such as emphysema and lung cancer, and cancer of the mouth and bladder. Smoking during pregnancy causes increases in the rate of stillbirths and illness in the newborn. Environmental tobacco smoke—both mainstream smoke (smoke inhaled and expelled by smokers) and sidestream smoke (uninhaled smoke from a burning cigarette)—have been shown to present health hazards to nonsmokers.
- As an aid to quitting, nicotine replacement therapy has been developed. The transdermal patch, nicotine gum, and nicotine nasal sprays are used to replace nicotine normally delivered by smoking. Nicotine replacement therapy appears to improve the success rate of people who quit smoking. Other drugs such as buproprion are also effective.