10

Caffeine and the Methylxanthines

Coffee is useless since it serveth neither Nourishment nor Debauchery.

—*Anonymous, 1650 (Austin, 1985, p. 236)*

Caffeine is the best-known member of a family of drugs known as the *xanthine stimulants* or the *methylxanthines*. Although there are many methylxanthines besides caffeine, only two others occur naturally and are widely self-administered. These are *theophylline* and *theobromine*. The three have similar molecular structures and similar behavioral and physiological effects. The methylxanthines occur naturally in a number of species of plants belonging to 28 genera and over 17 families, but their most common sources are coffee, tea, and chocolate. Caffeine is also typically added to cola beverages and is an ingredient in many over-the-counter painkillers, cold remedies, and stimulants.

Caffeine was first isolated from coffee in 1820 by Ferdinand Runge, a German chemist, who called it Kaffeebase. It has been suggested that Runge's interest in coffee was stimulated by Wolfgang von Goethe, the author of *Faust*, who was a close friend of Runge's and a great coffee lover. No one is sure where the name *caffeine* came from, but a medical dictionary first used the term in 1823. Theobromine was isolated in 1842 and theophylline in 1888. Most of the basic chemistry of the methylxanthines was worked out and published in 1907 in a book by Emil Fischer, a Nobel prize–winning organic chemist.

SOURCES OF METHYLXANTHINES

Caffeine is available from a wide variety of sources. Table 10-1 gives a summary of some of these sources and an estimate of the amount of caffeine and other methylxanthines they contain.

Coffee

Coffee is made from the fruit of a bush or small tree of the genus *Coffea*. The two most common species are the *arabica* and the *canephora* (also called *robusta*), which together account for 99 percent of the world's coffee. They are native to Ethiopia but are now widely cultivated in Africa and South America and in

TABLE 10-1 Sources of Methylxanthines

Source	Caffeine (mg) Mean	Caffeine (mg) Range	Other Methylxanthines
Coffee (5-oz. cup)			
Instant	60	140	108
Percolated	85	164	124
Drip	112	156	176
Decaffeinated	5	2–5	
Tea (5-oz. cup)			
Bag	40	28–48	Theophylline
Instant	30	24–31	Theophylline
Cola beverages (12 oz.)			
Coca-Cola	45		
Pepsi-Cola	30		
Chocolate (1 oz.)			
Milk	6	11–15	
Sweet	20	15–35	
Baking (bittersweet)	35	18–118	150–300* mg
Chocolate milk (8 oz.)	5	2–7	75–100* mg
Chocolate bar (40–50 g)		40–50	86–240* mg
Over-the-counter analgesics (one tablet)			
Anacin	32		
Dristan	16		
Excedrin	65		
Pre-Mens	66		
Vanquish	32		
Over-the-counter stimulants (one tablet)			
Wake Ups	100		
No-Doz	100		
Ban Drowz	100		
Vivarin	200		

Sources: Barone and Roberts (1984); Gilbert (1976); Mumford et al. (1994); Syed (1976).

* Theobromine.

tropical climates all over the world. The coffee bean is a seed kernel of the coffee berry (or cherry), which grows in clumps along the branches. Each berry contains two seeds within its pulp. Usually, the berry is picked and dried briefly in the sun before the seeds are removed from inside the pulp.

In preparation for making coffee, the beans are roasted. Roasting serves no function other than to enhance the flavor. The roasted beans are then crushed or ground and mixed with boiling water. The caffeine content of a cup of coffee may vary considerably because of a number of factors: the caffeine concentration in the coffee beans (*robusta* has about twice the caffeine content of *arabica*), method of brewing (most brewing methods extract nearly all the available caffeine), and the size of the cup. Actual surveys have shown that the caffeine content of a cup of coffee may range between 40 and 176 mg, but the mean is closer to 85 mg (Barone & Roberts, 1984). However, this estimate is based on a cup size of 5 ounces (150 ml) of coffee. This size may be generally found in restaurants and hospitals, but actual measurements of typical cups used in the home and at work are closer to 7.5 ounces (225 ml). Table 10-1 shows typical sources of caffeine; the 5-ounce cup size is

assumed. These figures can be increased by 50 percent. For the sake of convenience, it is usually presumed that a regular cup of coffee contains 100 mg of caffeine.

Tea

Tea is made from the leaves of *Camellia sinensis*, which in its natural form is a large tree but in its commercial cultivated form is more like a bush. For the best-quality teas, only the bud and the first two leaves of each twig are plucked. Inferior-quality teas are made from the third and fourth leaves. Caffeine content, as well as quality, decreases the farther the leaf is from the bud.

A drink may be made from the raw green leaves, but such concoctions are rather bitter. Most of the tea consumed outside of Asia is *black* or *fermented tea* (the process is not really fermentation but *oxidation*). The green leaves are dried slightly and then crushed and left to oxidize. The crushing or rolling breaks the membrane and releases enzymes that cause the oxidation. This turns the leaf black and gives it a particular taste. In *semifermented* or *oolong tea*, the oxidation process is stopped by roasting before it is completed. In *green Chinese tea* or *unfermented tea*, the leaves are steamed soon after picking and before drying to prevent oxidation. Consequently, green tea has quite a different taste from black tea. In the Orient, teas are frequently scented with flower petals. *Jasmine tea* is an example.

The amount of caffeine in a cup of tea is variable, but it is probably less than in a cup of coffee. One study showed a median of 27 mg per 5-ounce cup with a range of 8 to 91 mg. In addition to caffeine, tea contains *theophylline* and *theobromine* (Gilbert, 1976; Graham, 1984).

Cocoa

Cocoa is made from seeds found in the seedpods of the *cacao tree*, *Theobroma cacao*, which is native to the dense, tropical Amazon rain forest. It is cultivated now mainly in Central and South America, the West Indies, and West Africa. The mature tree grows seedpods from the trunk and main branches. These pods, about 6 to 10 inches long and 3 to 4 inches in diameter, contain 20 to 40 seeds surrounded by pulp. The seeds are removed and put in boxes or piles for fermentation. During this process, which lasts 5 to 6 days, the pulp ferments, becomes very watery, and separates from the seed; fermentation heats the beans, causing them to germinate, and then kills them. The beans are then dried in the sun or in commercial driers. All these things are done on the plantation.

At this stage, the dried beans are shipped to manufacturing plants for further processing. The beans are roasted for enhanced flavor and then crushed, and the husks of the shells are removed. The result is sold as unsweetened chocolate, a product that has a high fat content and is not very appealing. In 1828, in the Netherlands, a Dutchman, C. J. Van Houten, invented a press that could remove most of the fat, or cocoa butter. This turned out to be a major breakthrough in the processing of cocoa. In addition to inventing the press, the Dutch also learned to *alkalize* cocoa, which gives it a stronger flavor and a darker color and makes the powder disperse better in water. (The name *cacao* refers to the tree and its seeds; the term *cocoa* is used to refer to the processed products of the bean. Care should be taken not to confuse either of these terms with *coca*, the bush that is the source of cocaine; see Chapter 11.)

In the production of cocoa powder, the unsweetened chocolate is pressed into cakes. This process removes a large part of the cocoa butter. The cakes are then ground to produce the dry cocoa powder. Chocolate is made by mixing the roasted, alkalized, and refined beans with sugar and cocoa butter and, in the case of milk chocolate, with milk or milk solids. The details of the mixing process are complicated and vary according to the type and proposed use of the chocolate being produced (Minifie, 1970).

Chocolate contains both caffeine and theobromine in varying concentrations. It has been estimated that an ounce of sweet chocolate may

contain between 75 and 150 mg of combined methylxanthines, and a cup of hot chocolate or chocolate milk may contain 150 to 300 mg.

Other Natural Sources of Methylxanthines

Other natural sources of caffeine are the *ilex plant* of the Amazon region of South America and the *cassina* of North America. The ilex plant, *Ilex paraguayensis*, is a holly (related to the Christmas holly) that contains between 1 and 2 percent caffeine. A tea-like drink called *maté* is made from the leaves and is popular in South America. Each morning, men of the Peruvian Achuar Jivaro tribe are reported to drink a strong herbal tea made from the ilex that contains the caffeine equivalent of five cups of coffee, after which they vomit in order to avoid overdose symptoms. It is considered to be part of a macho ritual passed down through the ages (*Science News*, 1992).

Cassina is another type of holly, *Ilex vomitoria*, from which a beverage known as *youpon*, *cassina tea*, or *black drink* is made. Youpon is not used today, but at one time it was widely consumed by native peoples of the southeastern United States. It was considered a noble beverage, and its use was restricted to great men and chiefs. Cassina tea enjoyed a revival during the American Civil War and World War I, when coffee and tea were either not available or very expensive.

Guarana is a paste made from the seeds of *Paullaina cupana*, which, at 2 to 6 percent caffeine, is the most potent of the natural sources of caffeine. The plant grows in the regions of the Amazon, Orinoco, and Negro rivers in South America. The paste is molded into sticks or bars or even sculptures and dried in the sun. For use, it is powdered and mixed with water. Because it has an acrid taste, like chocolate, it is usually sweetened with sugar.

There are a number of species of the genus *Cola*, a small evergreen tree native to southern Nigeria. Its nuts are edible and contain caffeine and theobromine. Kola trees are now cultivated all over western Africa, and chewing the nut is a widespread habit. The nut is sold commercially to the United States, where it is used to flavor cola beverages such as Coca-Cola and Pepsi-Cola. Most of the caffeine in these beverages, however, does not come from the kola nut but is added later.

Medicines and Food Additives

In addition to being added to cola beverages, caffeine is also added in small quantities for flavor to pudding mixes, baked goods, dairy desserts, and candy (Barone & Roberts, 1984).

Caffeine can be found in hundreds of prescription and over-the-counter medicines. Table 10-1 shows a few of these. They include common analgesics such as Anacin, weight control aids, allergy relief compounds, and stimulants.

Both theophylline and caffeine are used as a respiratory stimulant for newborn babies and people suffering from asthma.

HISTORY OF METHYLXANTHINE USE

Coffee

The coffee bush is native to Ethiopia. Its properties were discovered sometime between the twelfth and fifteenth centuries. From Ethiopia, its use spread across Arabia, Egypt, and North Africa, around the Mediterranean into Turkey, and then to Europe.

William Harvey, the first person to describe the circulation of the blood, was one of the first coffee drinkers in England, and he promoted the beverage for its therapeutic benefits. Two of his students believed that it was a cure for drunkenness (Austin, 1985). The first English coffeehouse opened in Oxford in 1650, and the concept soon spread throughout England. The coffeehouses were referred to as "schools of the cultured," and coffee was "the milk of chess players and thinkers." Along with coffee, this intellectual tradition associated with coffeehouses soon spread throughout Europe.

At one time, coffee drinking gained such popularity in England that the consumption of alcoholic beverages, particularly cheap gin, started to

decline. Coffee has remained popular throughout Europe, but in Great Britain it was eventually replaced by tea.

Although tea was the preferred drink in colonial America, coffeehouses were as common as in England and filled the same social function: a meeting place for intellectual and political discussion. Boston coffeehouses such as the Brown, the North End Coffee-House, and the Exchange served as headquarters for Whigs and Tories and were the scenes of much plotting and fighting. One famous coffeehouse, the Green Dragon, is still marked by a plaque at the site where "such adventurous and ardent patriots as Otis, Joseph Warren, John Adams, Samuel Adams, Cushing, Pitts, Molyneux, and Paul Revere met nightly to discuss public affairs" (Cheney, 1925, p. 233).

Tea

There are many legends about the origins of tea. One tale credits the discovery of the beverage to the Chinese emperor Chen Nung. It is known that tea was cultivated and sold commercially in China by 780 A.D., when the book *Ch'a Ching*, or *Tea Classic*, was written. The book was sponsored by a group of merchants, and its purpose was to promote tea drinking (D. Forrest, 1973, p. 16).

Tea was first mentioned in print in Europe in 1559, but it was not until 1606 that the Dutch actually shipped some to Europe. In the 1630s, the Dutch started shipping tea on a regular basis to satisfy a growing demand in their country as well as in Germany and France. Tea was also becoming popular in Portugal, which had an extensive Oriental trade of its own. In the 1640s and 1650s, tea enjoyed a brief phase of popularity in France, but the French turned to coffee in the 1660s.

All this time, tea was not extensively used in England. It did not become fashionable until Charles II married the Infanta Catherine, who brought tea drinking with her from Portugal in 1662. Tea also became popular in the 13 British colonies of North America. In fact, by 1760, tea was the third-largest export from England to the colonies, and this figure represented only a quarter of the total tea imported; the rest was smuggled. The reason for smuggling was the tea tax the English Parliament at Westminster imposed on all tea imported into Britain. When this tea was later shipped to America, the price included this import tax. In 1767, this indirect tax was removed, and a direct tax was imposed. These taxes angered the colonists, and when the British East India Company tried to export a tea surplus to the colonies in 1773, the angry colonists dumped it into Boston Harbor. This "tea party" was the first of many, and it set the stage for the American Revolution.

Cocoa

The Mayas of the Yucatán Peninsula, the Aztecs of Mexico, and the Incas of Peru cultivated the cacao tree long before the European discovery of North America. They believed it to be a gift of the gods. This belief is the origin of the genus name of the cacao bush, *Theobroma*, which is Greek for "food of the gods." Among the Central American Indian tribes, chocolate was a food generally reserved for the wealthy and powerful. It was believed to be an aphrodisiac and was used at wedding feasts and by wealthy noblemen who could afford to support and had to satisfy many wives. It has been reported that Montezuma, emperor of the Aztecs at the time of Cortés, consumed 50 golden goblets of the drink each day. He called it *chocolatl*, but what he downed must have been quite different from modern chocolate. The Aztecs' concoction included maize and spices, such as peppers, but no sugar or milk.

Cortés introduced the drink to the Spanish court in 1520 with the addition of vanilla and sugar, and this sweetened form eventually gained popularity all over Europe. The Spanish managed to keep the source of chocolate secret for 100 years, but eventually the Dutch introduced the plant into the Philippines and Ceylon (now Sri Lanka).

Chocolate was introduced into Europe before coffee and tea and enjoyed a brief popularity, but because it was expensive, its use was restricted to the wealthy and the nobility. In every case, it was

displaced by coffee, which remains the most popular xanthine-containing beverage today. (The exception is in England, where coffee was replaced by tea.) In time, chocolate did become cheaper and more readily available. The first chocolate factory in England was founded by S. J. Fry in 1728, when chocolate had become more plentiful, but by that time, tea was the indisputable beverage of the people.

Even though chocolate did not make it as a popular drink, the development of better processing techniques made it successful as a confection.

Today the bulk of the world's supply of cocoa comes from West Africa rather than South America. It is also grown commercially in Indonesia and Sri Lanka. It is perhaps ironic that cocoa, which is native to South America, is now a more profitable crop in Africa. The South Americans, however, have had their revenge many times over. Coffee, a native African plant, is now grown primarily in South America.

ROUTE OF ADMINISTRATION

When consumed in natural products, the methylxanthines are normally taken orally without difficulty, but when given for medical reasons, the purified drugs sometimes cause nausea and gastric irritation, especially in children. In such cases, the drugs may be given in the form of a rectal suppository or by intramuscular or intravenous routes.

ABSORPTION

Although the methylxanthines are absorbed from the stomach, they are absorbed much more rapidly through the walls of the intestine. Factors that decrease stomach-emptying time, such as the presence of food, will slow methylxanthine absorption. The methylxanthines are bases; consequently, when they are dissolved in the acidic environment of the digestive system, they might be expected to be highly ionized and not lipid soluble. However, these drugs have a very low pKa—about 0.5. Consequently, at the pH of the digestive system and any other pH encountered in the body, the methylxanthines will not be ionized at all and will be free to dissolve in any tissue in accordance with their lipid solubility. The methylxanthines are quite lipid soluble and dissolve poorly in water.

The caffeine in coffee, tea, and chocolate exists and is consumed in its alkaloid form, but for medicinal purposes, the methylxanthines are usually given as salts, which can be absorbed much more readily. Aminophylline is the most widely used methylxanthine preparation. It is a mixture of theophylline and *methylenediamine*. The latter substance is considered therapeutically inert, but it increases the amount of dissolved theophylline 20 times and thereby speeds absorption. *Oxtriphylline* (Choledyl or choline theophylline) is also widely used.

After drinking coffee or tea, a person completely absorbs caffeine from the digestive system, and peak blood levels of caffeine are reached between 30 and 60 minutes later (Arnaud, 1993; Axelrod & Reisenthal, 1953; Marks & Kelly, 1973), although peak absorption may vary between 15 to 120 minutes, depending on the amount of caffeine swallowed and the ingestion of other foods. There is also considerable individual variability in peak blood levels. The same dose may produce a sixfold variation in peak blood levels in different individuals (Dews, 1984). There is no significant first-pass metabolism.

It was once thought that caffeine in cola beverages is absorbed more slowly than caffeine from coffee, but this has been shown not to be the case. Four hundred milligrams of caffeine ingested in either coffee or a cola beverage caused a similar peak caffeine level in saliva at the same time after ingestion. Caffeine absorption from capsules, however, was delayed. There was also no difference in the time course of subjective effects (Liguori, Hughes, & Grass, 1997).

DISTRIBUTION

Caffeine crosses the blood–brain and placental barriers without difficulty and reaches all body organs, although the rates of entering and leaving

the organs may vary. About 10 to 30 percent of caffeine in the blood becomes bound to protein and trapped in the circulatory system (Arnaud, 1993; Axelrod & Reisenthal, 1953). Caffeine is present in all body fluids, including breast milk.

EXCRETION

In humans, less than 2 percent of caffeine is excreted unchanged in the urine (Arnaud, 1993). The remainder is converted to various metabolites (Bonati & Garattini, 1984; Burg, 1975). For a given individual, the half-life of caffeine is fairly constant, but this may vary from 2½ to more than 4½ hours in different individuals, with a mean of 3½ hours. There is evidence that the half-life may be dose dependent; that is, the larger the dose, the longer the half-life (Kaplan et al., 1997). In spite of this long half-life, it has been shown that caffeine does not appear to accumulate in the bodies of normal individuals over days if caffeine is not consumed after 6:00 P.M. (Axelrod & Reisenthal, 1953). In nonhumans, the half-life varies considerably, from 11 to 12 hours in the pig and squirrel monkey to 2 hours in the rat (Kihlman, 1977, pp. 20–21).

Caffeine metabolism is slowed by alcohol and speeded by broccoli, and smokers eliminate caffeine twice as fast as nonsmokers (J. J. James, 1991; Parsons & Neims, 1978). In women, metabolism of caffeine is closely related to hormone levels. The caffeine half-life in women is longer during the luteal phase (after ovulation) than during the follicular phase (before ovulation) of the menstrual cycle (Arnaud, 1993). The half-life in women taking oral contraceptive steroids is twice that of women ovulating regularly (Callahan, Robertson, Branfman, McCormish, & Yesair, 1983). Caffeine elimination is also slowed during pregnancy (Neims, Bailey, & Aldrich, 1979). These changes appear to be due to alterations in enzyme levels.

It has also been shown that newborns cannot metabolize caffeine well. They excrete about 85 percent of it unchanged in the urine, with the result that the half-life is about 4 days. The adult pattern of caffeine metabolism is not developed until 7 to 9 months of age (A. Aldrich, Aranda, & Neims, 1979).

Caffeine is metabolized into numerous metabolites, but no other species metabolizes caffeine the way that humans do. For this reason, one must always approach nonhuman studies of the methylxanthines with caution. Some metabolites created in other species may be more active or toxic than those created in humans (Stavric & Gilbert, 1990), and even in humans, there are differences in metabolic pathways between infants and adults. Not only do newborn babies metabolize methylxanthines more slowly, but they also create different metabolites (A. Aldrich et al., 1979).

NEUROPHYSIOLOGY

The effects of methylxanthines on neural functioning are now fairly well understood (Fredholm, 1995). Most of the effects of the methylxanthines appear to arise from the fact that methylxanthines are *adenosine receptor blockers*. There are four types of adenosine receptors—A_1, A_{2a}, A_{2b}, and A_3—and the methylxanthines appear to be effective blockers of the A_1 and A_{2a} types.

Adenosine functions as a neuromodulator and works presynaptically by inhibiting the release of many neurotransmitters. It also reduces the rate of spontaneous firing of neurons. Its general effect is to inhibit the firing of many neurons in the brain. Methylxanthines prevent adenosine's inhibitory action and cause stimulation (Fredholm, 1995; Nehlig, Daval, & Debry, 1992; Snyder, 1981, 1984).

Adenosine receptors are also known to be involved in the postsynaptic effects of dopamine. They increase the activity of the dopamine D_2 receptor (Garrett & Griffiths, 1997), which is known to play a role in the activity of transcription factors and gene expression in some neurons (Fredholm, 1995).

In addition to their effect on adenosine, caffeine and the methylxanthines are known to block benzodiazepine receptors, but this effect seems to require higher doses of caffeine than those that normally cause behavioral effects. At the dose

equivalent of 10 cups of coffee, as many as 20 percent of benzodiazepine receptors are blocked (Paul, Marangos, Goodwin, & Slotnick, 1980). Among the different methylxanthines, however, there does not seem to be a correlation between the ability to block benzodiazepine receptors and the drug's effects (Snyder, 1984). It is possible that some of the effects of caffeine, particularly the increases in anxiety seen at high doses, are mediated by the ability of the drug to block benzodiazepine receptors.

Caffeine also appears to cause the release of epinephrine and other catecholamines from brain tissues and from the adrenal gland at usual doses. These indirect effects may contribute to the stimulating effects of the drug. It is also known that large doses (in the range of 500 mg), if taken all at once, cause a response similar to the body's reaction to acute stress: The levels of some hormones drop, and corticosteroid and internal opiate (beta-endorphin) levels increase (Spindel & Wurtman, 1984). It is not known whether this effect is mediated by adenosine or benzodiazepine receptors.

Not long ago it was shown that three substances that occur naturally in chocolate resemble anandamide, the endogenous substance that works at cannabinoid receptors (see Chapter 15). In addition, other compounds have been found in chocolate that block the metabolism of anandamide (di Tomaso, Beltramo, & Piomelli, 1996). Although this is not sufficient to cause an obvious high, the presence of these substances could be one reason for the popularity of chocolate beyond the effects predicted by the presence of caffeine.

EFFECTS OF CAFFEINE AND THE METHYLXANTHINES

Effects on the Body

Because the methylxanthines cause the release of epinephrine from the adrenal gland, there is a resultant stimulation of the sympathetic nervous system. However, much of caffeine's effect outside the central nervous system is due to its direct effect on the muscles; smooth muscles tend to relax, and striated muscles are strengthened.

The smooth muscle relaxation results in a dilation of the bronchi of the lungs that decreases airway resistance. Theophylline is the most potent methylxanthine in producing this effect; as a result, it is used clinically in the treatment of asthma. Methylxanthines also reduce the susceptibility of striated (voluntary) muscles to fatigue. The mechanism of this change is probably related to caffeine-caused increases in fatty acids that the muscles can use as fuel (Nehlig & Debry, 1994).

Caffeine has different effects on blood flow in different parts of the body. It causes a constriction of blood vessels in the brain but dilation in the rest of the body. By constricting the blood flow to the brain, caffeine is able to reduce headaches caused by high blood pressure. For this reason, caffeine is found in many over-the-counter headache remedies.

High levels of caffeine stimulate the spinal cord. This is first manifested as an increase in excitability of spinal reflexes. Higher doses lead to convulsions, which are sometimes a cause of death. The regulatory centers of the medulla are also stimulated at high doses, producing an increase in the rate and depth of breathing. This ability of methylxanthines to stimulate respiration makes them useful in the treatment of babies born with breathing difficulties.

Many books suggest that the primary effect of caffeine on the brain is a stimulation of the cortex, but there is little evidence of this effect. Most of the evidence is indirect and based on behavioral studies (Gilbert, 1976).

Effects on Human Performance and Behavior

Textbooks usually give a standard account of the effects of caffeine at low doses (100 to 200 mg). Typically, the following effects are listed: "greater sustained intellectual effort and a more perfect association of ideas" or "a keener appreciation of sensory stimuli" (Ritchie, 1975, p. 367). In reality, there is very little hard evidence that changes of this nature take place. No doubt such accounts are based on subjective experience and the intellectual tradition associated with coffee.

Subjective accounts can be useful in understanding drugs, but they must be interpreted with great caution (see Chapter 2). In an early experiment by A. Goldstein, Kaizer, and Warren (1965), subjects were asked to rate the effects of caffeine on their alertness, physical activity, and wakefulness. Then they were given caffeine and tested on their ability to detect a number in an array of numbers flashed on a screen for 1/32 second. They were also tested on coordination in a line-drawing task. The subjects' assessment of their alertness and physical activeness did not correlate with their real abilities as measured by these various tasks; though all subjects thought they were doing better, caffeine produced no improvement.

There are reports that moderate doses of caffeine can significantly increase visual sensitivity to light, increase the speed of auditory reaction time (Dews, 1984), improve some aspects of driving involving reaction time, and improve performance in a flight simulator (Nehlig et al., 1992). Unfortunately, not all laboratories can replicate these effects, and some find decrements. It seems that the effects of caffeine depend on many factors, including individual susceptibility, dose, time of consumption, and the nature of the task (J. J. James, 1991).

In an extensive review by Weiss and Laties (1962) and another review by Dews (1984), the effects of caffeine on human performance were evaluated. Both reviews concluded that performance on a wide range of activities, with the exception of intellectual tasks, could be enhanced by caffeine. These included athletic activities (see the next section) and perceptual tasks such as monitoring a visual array. It appears, however, that most reports of improved performance occurred only if performance had been degraded by fatigue. The main effect of caffeine was to reduce the effect of drowsiness and boredom. Weiss and Laties also noticed that caffeine caused an improvement in the mood of subjects and in their attitude toward their task, but they were not able to determine whether this improvement in performance caused the mood change. In any case, it appears that coffee breaks may be beneficial, especially for people doing repetitive jobs.

One difficulty with these experiments is that they are usually done on subjects who are regular caffeine consumers and who have been deprived of caffeine for some period of time before the experiment. Under these circumstances, it is difficult to determine whether improvements in performance are a result of relief of withdrawal deficits in performance or net improvements in performance. One recent paper suggests that most reports of improvements can be attributed to relief of caffeine withdrawal (Rogers & Dernoncourt, 1998; Rogers et al., 2005).

Effects on Athletic Performance

Caffeine, in doses of about 6.5 mg/kg (450 mg in a 155-pound person), has been shown to improve some types of athletic performance. It does not seem to improve performance in events that require muscle strength, such as weight lifting, nor does it improve performance that requires intense output over a short duration, such as sprinting and throwing. It does, however, improve performance in tasks that require submaximal output for an extended period of time, such as cross-country skiing, running, or cycling (Nehlig et al., 1992; Ryu et al., 2001). However, even in these events, results are far from consistent, and the effect is moderated by other factors such as body composition. The most likely reason for improved performance on these tasks is that caffeine increases blood levels of fatty acids that can be used as fuel by the muscles. As a result, the muscles use less glycogen, their normal fuel; it is kept in reserve, so the muscles are not fatigued as quickly in endurance events (Tarnopolsky, 1994). These effects are subject to tolerance, and there is a delay between maximal blood levels of fatty acids and caffeine blood levels. For this reason, athletes wanting to take advantage of this effect need to abstain from taking caffeine for 4 days before the event and consume caffeine 3 to 4 hours before the event (Nehlig & Debry, 1994).

Because of the possibility that caffeine is an athletic performance enhancer, for many years caffeine was banned by the International Olympic

Committee (Lombardo, 1986) in urine in concentrations higher than 12 mg per liter (Tarnopolsky, 1994). Only one athlete has ever been disqualified from Olympic competition for exceeding the caffeine limit—a member of the Australian pentathlon team in the 1988 Summer Olympics at Seoul (J. J. James, 1991). The World Anti-Doping Agency lifted this restriction in January 2004, and there are now no legal restrictions on caffeine.

Effects on Sleep

There is little doubt that the methylxanthines can produce insomnia (A. Goldstein, 1964). Their effect seems to be in increasing the "stability of wakefulness" by increasing the length of time it takes to fall asleep and reducing total sleeping time. In one study, 300 mg of caffeine caused an increase in the latency of sleep onset, normally 18 minutes to 66 minutes, and reduced total sleeping time from 475 minutes to 350 minutes compared to control subjects (Brenesova, Oswald, & Loudon, 1975). As can be seen in Table 10-1, caffeine is the major ingredient in many over-the-counter stimulant pills. Most such tablets contain 100 mg of caffeine.

In general, people who take caffeine before going to bed report sleeping less soundly and feeling less rested. Caffeine also lowers the acoustic arousal threshold while sleeping; people wake up more easily in response to a sound in the night. This effect is variable among individuals; habitual coffee drinkers are less affected than coffee abstainers. Recently, it was shown that this difference is probably due to tolerance rather than a preexisting difference between coffee drinkers and coffee abstainers. After 7 days of exposure to a 400-mg dose, measures such as total sleep time and awakenings had returned to baseline levels (Bonnet & Arand, 1992).

It has also been demonstrated that caffeine can counteract the sleep-inducing effects of pentobarbital. A usual sleep-inducing dose of pentobarbital, 100 mg, when given in combination with 250 mg of caffeine, produces the same effect on sleep as a placebo (W. H. Forrest, Bellville, & Brown, 1972).

Effects on Behavior of Nonhumans

Unconditioned Behavior. Caffeine will increase spontaneous motor activity of mice in an open field. Maximum increases are 20 to 40 mg/kg. A dose of 80 mg/kg will greatly decrease spontaneous motor activity. Increases in activity are also produced by theophylline at similar doses, but there is some evidence that theophylline may be slightly more potent than caffeine (C. C. Scott & Chen, 1944). Interestingly, chronic, long-term treatment with caffeine results in a depression of spontaneous activity (Fredholm, 1995).

The LD_{50} of caffeine for both rats and mice is in the neighborhood of 250 mg/kg by intraperitoneal administration (Barnes & Elthrington, 1973). Death may be due to convulsions. Convulsive effects are another example of how chronic treatment has effects opposite to acute treatment. After chronic treatment, there is a decrease in seizure sensitivity (Fredholm, 1995).

Some animals die at lower doses from bleeding as a result of attacking themselves. Automutilation has been observed in rats when caffeine was given at a dose of 185 mg/kg for 14 days. The rats bit their tails and paws, even though they seemed to retain their normal sense of pain. When a ball of wire was placed in their cage, they temporarily attacked it but soon returned to biting themselves. When picked up, they did not bite the hand of the experimenter, but they did attack other rats placed with them in a cage (Peters, 1967).

Operant and Respondent Conditioned Behavior. The first person to experiment with the effects of caffeine on conditioned behavior was Pavlov (1927). He showed that the drug could disrupt conditioned discriminations by increasing responses to the negative stimulus. After ingesting caffeine, the animals responded to stimuli that did not signal food in the same way that they had responded to stimuli that did signal food. He concluded that the drug produced "an increase in excitability of the Central Nervous System."

The profile of effects of caffeine on operant behavior is very similar to but not exactly the

same as the profile caused by the psychomotor stimulants (W. A. McKim, 1980). This similarity is probably a result of the increased catecholamine release and dopamine activity caused by caffeine (Garrett & Griffiths, 1997).

There is some evidence that caffeine at 30 mg/kg in a rat will increase food-reinforced responding that has been suppressed by punishment with an electric shock (Morrison, 1969). If this observation is true, it makes this effect of caffeine more similar to the barbiturates than to amphetamine. In general, caffeine appears to increase avoidance responding. Increases were seen on nondiscriminated avoidance responding of squirrel monkeys at a dosage of 1 to 30 mg/kg of caffeine; these increases were almost as great as those seen with amphetamine (T. R. A. Davis, Kensler, & Dews, 1973).

Although the effects of caffeine and the other methylxanthines on conditioned animal behavior have not been extensively investigated, it appears that they are very different from the effects of amphetamine on some types of behavior and very similar to amphetamine on others. These data clearly show that caffeine cannot be thought of as a mild amphetamine; its behavioral properties are quite distinctive and difficult to classify with any other category of drug.

DISCRIMINATIVE STIMULUS PROPERTIES

At a dose of 32 mg/kg, rats can be trained to discriminate between caffeine and saline in a two-lever Skinner box. Rats generalize the state produced by caffeine to lower doses of caffeine and higher doses of theophylline, but there is no generalization to nicotine (Modrow, Holloway, & Carney, 1981).

As with human subjective effects, caffeine appears to share some of the subjective effects of cocaine and amphetamine, at least at low doses. There is partial generalization to cocaine and amphetamine in rats trained to discriminate low but not high doses of caffeine and vice versa. Caffeine will increase the discriminative effects of low doses of cocaine. Dopamine receptor blockers will block the discriminative effects of low but not high doses of caffeine (Garrett & Griffiths, 1997, p. 536).

For some time, there has been a concern over what are known as *look-alike* or *turkey drugs*. These preparations look, in all regards, like controlled psychoactive drugs, such as amphetamine, but instead contain a drug or a combination of drugs that are not prescribed or controlled substances. Turkey drugs designed to mimic amphetamine or cocaine often contain caffeine in combination with other substances such as *ephedrine* and *phenylpropanolamine*. One study has shown that, in rats at least, this combination of drugs can mimic the discriminative stimulus effects of 10 mg/kg of cocaine (Gauvin, Harland, Michaelis, & Holloway, 1989).

Although there is considerable individual variability, humans can discriminate the presence of caffeine in capsules in very low doses. In one experiment, a dose of 1.8 mg of caffeine was detected by one subject, although two others detected a dose of 10 mg, and one subject needed 178 mg. In the same experiment, the same subject who was able to detect 1.8 mg of caffeine detected a dose of 100 mg of theobromine, but two subjects out of seven were unable to discriminate 1,000 mg of theobromine (Mumford et al., 1994).

Subjective Effects

Early studies on the subjective effects of caffeine were confusing. In some studies, subjects reported increased anxiety, jitteriness, and nervousness, but other studies reported no subjective effects at all. Recent studies have found increasingly that subjects experience an array of positive effects, such as increases in feelings of well-being, alertness, energy, motivation for work, and self-confidence. Griffiths and Mumford (1995; Rush, Sullivan, & Griffiths, 1995) report that positive effects are more reliably detected under a restricted set of conditions. First, they are seen when caffeine is administered to people who are not caffeine users or to caffeine users who have been deprived at least overnight. The fact that positive effects are seen in

coffee abstainers indicates that these effects are not simply a matter of alleviating caffeine withdrawal (N. J. Richardson, Rogers, Ellman, & O'Dell, 1995). Second, positive effects are more likely to be seen at low doses (from 20 to 200 mg). The higher the dose, the more likely that unpleasant effects will be reported. Finally, positive effects are most likely to be reported by individuals for whom caffeine acts as a positive reinforcer (see the next section).

In a study by Mumford and associates (1994), subjects were given 178 mg of caffeine, and responses to a mood scale were determined at various times afterward. The drug caused increases in well-being, magnitude of drug effect, energy, affection for loved ones, motivation to work, self-confidence, social disposition, alertness, and concentration and decreases in "sleepy" and "muzzy" feelings. These changes were evident within 30 minutes and remained higher than placebo levels for at least 8 hours.

The same study also examined the subjective effects of theobromine. A dose of 100 mg produced positive changes in energy, motivation to work, and alertness but to a much smaller extent than caffeine. The time course for these changes was similar to caffeine, but 5 to 10 hours after ingestion, subjects reported unpleasant effects such as headache and lethargy.

In another experiment, subjects with experience with street drug use, including cocaine, were given intravenous doses of caffeine, and the subjective effects were measured. There was a dose-related increase in ratings of "liking," "drug effect," "high," and "good effects." These occurred 2 minutes after injection and decreased over the following 60 minutes. At high doses, caffeine was identified as "a stimulant (like cocaine or amphetamine)." Most subjects were reasonably certain that they had been given cocaine (Rush et al., 1995).

Tolerance

Studies of adenosine receptors have shown that chronic administration of caffeine causes an increase in the number of adenosine receptors, presumably an attempt to restore the influence of adenosine prior to caffeine (Hirsh, 1984).

Tolerance to the behavioral effects of caffeine has been shown to develop in rats. One study (Wayner, Jolicoeur, Rondeau, & Baron, 1976) showed that bar pressing on an FI schedule could be depressed to about 40 percent saline control rates by a 100-mg/kg injection of caffeine. After eight injections of caffeine, this dose could only depress responding to 75 percent of baseline. It has also been demonstrated, in a study of operant responding in rats, that chronic treatment with caffeine shifted the caffeine dose–response curve to the right by a factor of 6. This means that after exposure to caffeine, a sixfold increase in dose was required to produce the same effect as before the exposure (Carney, 1982).

A number of studies using human subjects have shown that caffeine has less effect on heavy drinkers of coffee than on nondrinkers of coffee. In one experiment (Goldstein et al., 1969), 150 to 300 mg of caffeine produced complaints of jitteriness, nervousness, and upset stomach in nonusers, but users reported increased alertness, decreased irritability, and a feeling of contentedness. It should be pointed out that studies like these, while probably demonstrating tolerance, may simply be showing that individuals who are resistant to the effects of caffeine are the ones who become heavy coffee drinkers.

To demonstrate tolerance to a drug effect, an experimenter must give the drug to one group of subjects and a placebo to a second group for a period of time. The effect must diminish in the drug-exposed group. Furthermore, the placebo group must show the effect when switched to the drug. Tolerance to several effects of caffeine has been demonstrated using this design. Different effects of caffeine at normal doses show tolerance at different rates; for example, cardiovascular effects fade within 2 to 5 days, but caffeine-induced increases in urination may take considerably longer or never show complete tolerance. Similarly, tolerance to various physiological effects has been demonstrated (Griffiths & Mumford, 1995). We have seen that the sleep-disrupting effects of

400 mg of caffeine show tolerance within 7 days. The subjective effects of 300 mg are tolerated within 4 days (Evans & Griffiths, 1992). In general, many effects of caffeine seem to disappear within a week at usual levels of consumption. As was pointed out earlier, some acute effects of caffeine—the effect on spontaneous motor activity and susceptibility to convulsions—actually reverse with chronic treatment.

WITHDRAWAL

Laboratory animals appear to suffer from caffeine withdrawal, although the main symptom is a decrease in locomotor activity and a disruption of ongoing operant responding. In humans, there have been a number of documented cases of caffeine withdrawal dating back to 1833. The most common symptom is a headache. In addition, people report drowsiness, decreased energy, and fatigue that can be described as weakness, letdown, or lethargy. People also report decreased motivation for work and impaired concentration, decreased feelings of well-being and self-confidence, increased irritability, and flu-like feelings such as aches and muscle stiffness, hot and cold spells, heavy feelings in the limbs, and nausea (Griffiths & Mumford, 1995). The severity of symptoms is directly related to dose. In one study, deprivation of normal caffeine consumption in the morning (12 to 28 hours of deprivation) produced withdrawal symptoms at lunchtime testing (e.g., decreased feelings of vigor and well-being and increased feelings of fatigue and lightheadedness). No changes in psychomotor performance or reaction time were detected, however (J. D. Lane, 1997; Phillips-Bute & Lane, 1998).

Doses as high as 600 mg per day can cause physical dependence after only 6 to 14 days of exposure. Withdrawal symptoms can also be seen at daily exposures of as little as 100 mg per day over a longer period of time (Griffiths & Mumford, 1995).

Withdrawal symptoms usually start within 12 to 28 hours of the last coffee intake, peak at 20 to 51 hours, and last 2 to 9 days (Griffiths & Mumford, 1995; Griffiths & Woodson, 1988; Juliano & Griffiths, 2004). Figure 10-1 shows the time-course incidence of headache and scores on an "energy/active" scale of subjects maintained on 100 mg of caffeine and switched to a placebo. As you can see, it took nearly 2 weeks for these scores to return to normal (Griffiths & Mumford, 1995).

Studies have shown that among coffee consumers in the United States who have gone without coffee for 24 hours, 27 to 52 percent report experiencing headaches. Estimates of the number of people who are exposed to caffeine withdrawal (i.e., the number who consume more than 100 mg a day) is enormous. Caffeine withdrawal is often overlooked as a possible diagnosis when people report headache, fatigue, and mood disturbances in circumstances where normal diet, including caffeine, is disrupted. Such circumstances might include fasting before various laboratory tests, operations, or procedures such as endoscopies.

On a more mundane level, caffeine withdrawal may well be responsible for the behavior of people who are grouchy and impossible to get along with until they have had their first cup of coffee in the morning. It is probably also responsible for illnesses and headaches that occur during holidays or weekends or when people interrupt normal routines that include coffee drinking.

In the *DSM-IV-TR*, a revision of the *DSM-IV* put out in 2000 (American Psychiatric Association, 2000), caffeine withdrawal was included on an experimental basis to encourage research into its clinical significance. It has also been included as an official diagnosis in the *ICD-10* (World Health Organization, 1993). However, in 2002, it was suggested that withdrawal symptoms from caffeine could be explained by nonpharmacological factors such as expectations or placebo effects, as described in Chapter 2 (Dews, O'Brien, & Bergman, 2002). This possibility was investigated in 2004 by Juliano and Griffiths (2004), who reviewed the current literature to that date. They pointed out that most of the studies that have found clinically significant withdrawal from caffeine were double-blind studies where the participants did not know that they were experiencing caffeine withdrawal; expectancy and

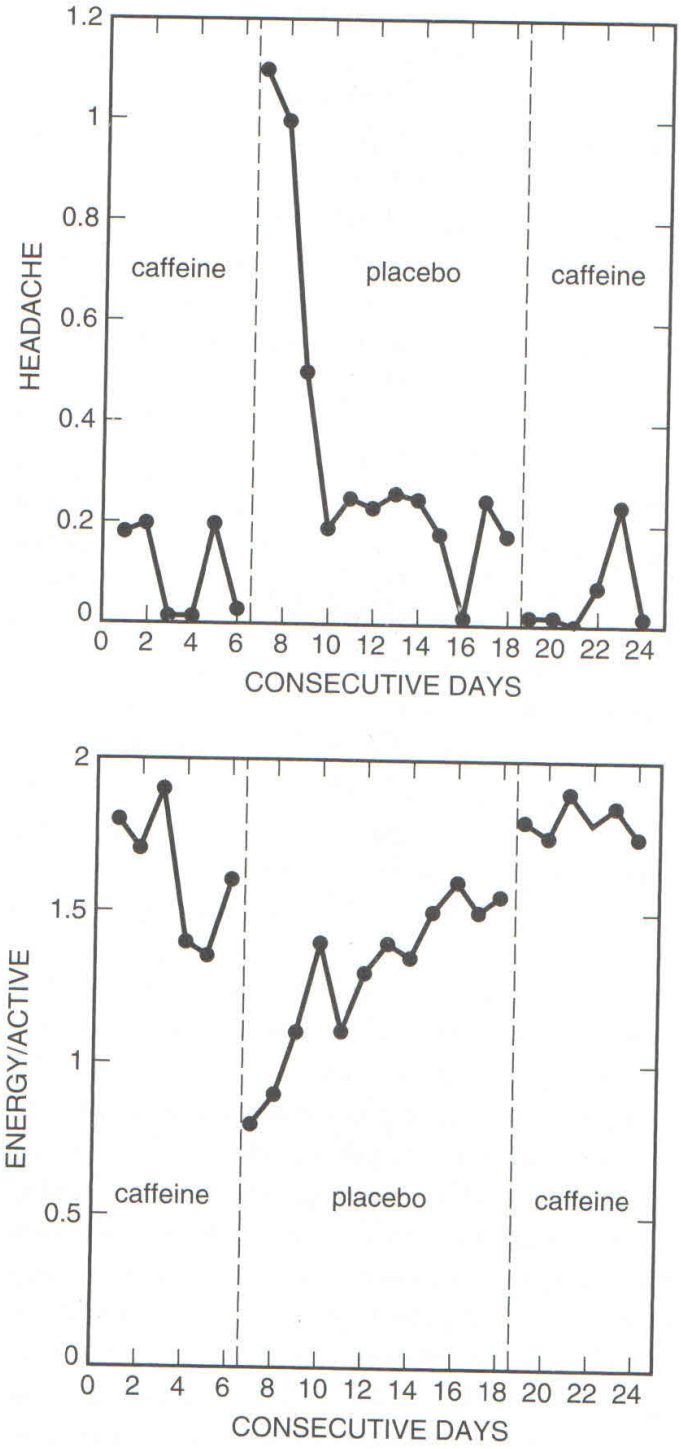

Figure 10-1 Changes in frequency of reported headaches and scores on an "energy/active" scale of subjects for 24 days while they consumed 100-mg caffeine capsules, then a placebo, and then switched back to caffeine. Caffeine withdrawal caused increases in reported headaches and a decrease in energy and activity that lasted as long as a week. (From Griffiths et al., 1990)

placebo effects were not likely to have caused the withdrawal symptoms. In fact, in some studies, participants did not know that the experiment involved caffeine at all.

SELF-ADMINISTRATION IN NONHUMANS

In laboratory animals, caffeine is not a robust reinforcer. It can serve as a reinforcer but only in a limited number of circumstances, and it does not seem to be able to support a lot of behavior. In one study where bar pressing delivered an intravenous caffeine infusion, only two out of six monkeys self-administered the caffeine spontaneously. The four monkeys that did not give themselves caffeine were then given automatic infusions of caffeine for a period of time. This procedure succeeded in establishing caffeine as a reinforcer in three of the four remaining monkeys (Deneau, Yanagita, & Seevers, 1969). The pattern of self-administration was irregular; there were periods of voluntary abstinence. There was no tendency to increase the dose over time. Other researchers have also demonstrated modest reinforcing effects with caffeine, but they were limited to specific doses and particular animals (Griffiths, Bigelow, & Lieberson, 1979). Other studies have not been able to demonstrate reinforcing effects of caffeine at all, although these studies used only one dose of caffeine or tested for only a short time (Hoffmeister & Wuttke, 1973).

Figure 10-2 shows the pattern of caffeine self-administration in a baboon (Griffiths & Mumford, 1995). This animal is typical of most. Caffeine is administered erratically, and irregular periods of abstinence occur. The reinforcing nature of caffeine is demonstrated, however, because rates of responding decline to near zero when a placebo is substituted.

Similar results have been found when rats have been given the opportunity to consume caffeine orally. Few spontaneously consume caffeine orally, and some period of forced consumption is usually required before caffeine is self-administered (M. V. Vitiello & Woods, 1975).

Even though it may not be a robust reinforcer on its own, caffeine has been shown to potentiate

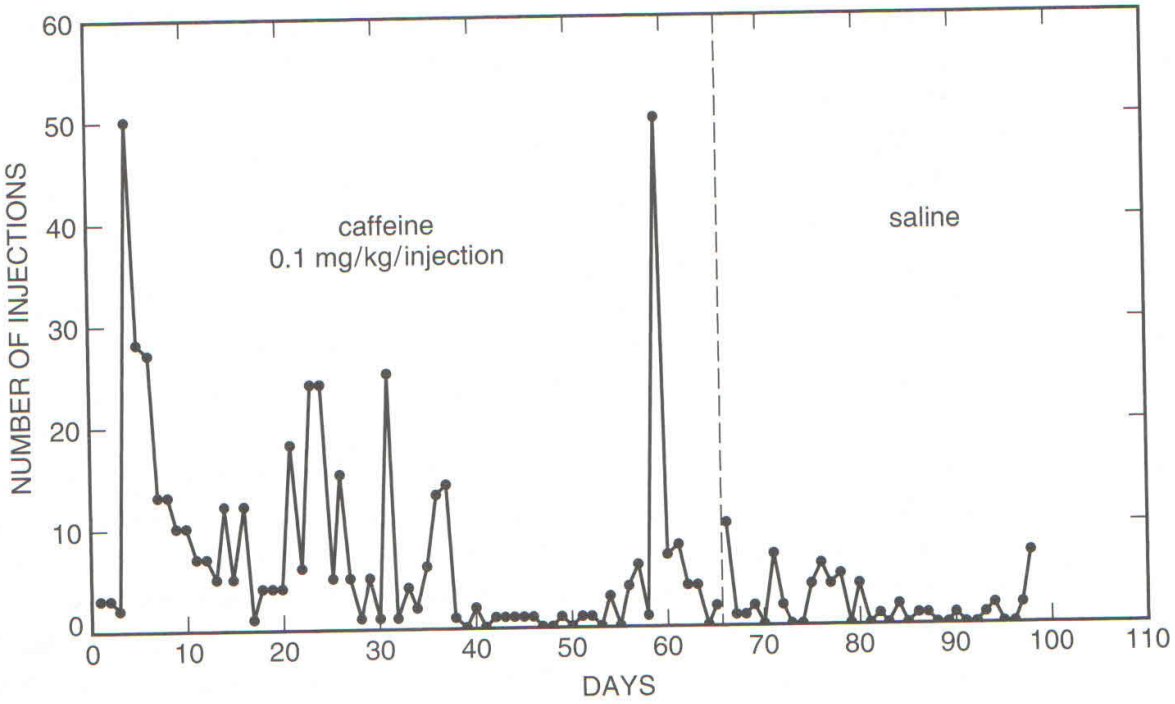

Figure 10-2 Intravenous self-injection rates of caffeine for a baboon with a history of self-administering numerous sedative and stimulant drugs. Caffeine was available on an FR 2 schedule, and a maximum of 50 administrations were available each session. The dotted line indicates that a saline placebo injection was substituted for the caffeine. (From Griffiths & Mumford, 1995)

the reinforcing effects of cocaine (Horger, Wellman, Morien, Davis, & Schenk, 1994), and it will act as a primer for cocaine; that is, an injection of caffeine will reinstate previously extinguished cocaine self-administration in rats (Worley, Valdez, & Schenk, 1994), an effect that can be blocked by the administration of dopamine receptor blockers.

SELF-ADMINISTRATION IN HUMANS

A number of human self-administration preference studies have shown that both caffeinated coffee and capsules containing caffeine will serve as reinforcers in humans. People who have been permitted to consume caffeine freely for 1 week before the test reliably preferred caffeinated coffee, but people who were not permitted to have any caffeine for 1 week and were presumably not physically dependent on caffeine showed considerable individual variation in caffeine preference (Griffiths & Woodson, 1988). In later research, subjects were given a choice between capsules containing caffeine and a placebo. Of 12 subjects, four showed a clear-cut preference for caffeine. Coffee consumption prior to the experiment did not seem to be related to caffeine preference (Griffiths & Woodson, 1988). Another study, conducted with moderate coffee drinkers, showed that they had a distinct preference for caffeinated coffee over decaffeinated coffee. This preference could be detected in some people at doses as low as 25 mg per cup and was greatest when the subjects reported caffeine withdrawal (Hughes, Higgins, Bickel, & Hunt, 1989; Hughes, Higgins, Gulliver, & Mireault, 1987).

These and other studies (Schuh & Griffiths, 1997) show that the preference for caffeine may be determined by the state of physical dependence on caffeine. In one study (Garrett & Griffiths, 1998), subjects were maintained for 9 to 12 days on a daily dose of caffeine (300 mg/70 kg/day; caffeine dependent) or a placebo (caffeine nondependent).

When dependent on caffeine, subjects showed typical withdrawal symptoms (fatigue and so on) when given a placebo. They were also willing to forfeit money to avoid placebo administration and to pay more money for caffeine than when they were nondependent. When dependent, they were twice as likely to take a dose of caffeine versus a placebo as when they were nondependent. This study shows clearly that people were actively avoiding the caffeine withdrawal as well as seeking the effects of caffeine.

In both humans and nonhumans, the reinforcing properties of caffeine seem to vary considerably from individual to individual, and several factors have been identified as contributing to choosing caffeine. Being physically dependent is one. Another is that the people who usually report positive subjective effects from caffeine also show a caffeine preference, and people who report adverse effects usually avoid it (Griffiths & Woodson, 1988). But these characteristics are not essential. In one experiment, a person who was otherwise a coffee abstainer showed a definite preference for caffeine over a placebo (Griffiths & Mumford, 1995).

Higher doses are not as reinforcing as lower doses. Increasing doses beyond 100 mg usually decreases the rate of self-administration, and doses in the 400- to 600-mg range are usually avoided.

Studies have also shown that caffeine preference may be related to task requirements after ingestion. All subjects, in an experiment in which they were required to participate in a computer vigilance task after taking a capsule, showed a preference for caffeine-containing capsules, but only two of seven subjects had a preference for caffeine when the capsule was followed by a relaxation activity (K. Silverman, Mumford, et al., 1994).

Caffeine Dependence Syndrome?

In Chapter 5, the *DSM-IV* criteria for "substance dependence" were discussed. These criteria are used to make a clinical diagnosis of dependence on a variety of drugs, such as cocaine and heroin. Is it possible to be clinically diagnosed as "dependent" on caffeine? Evidence from case histories suggests that it is. One study, published in the *Journal of the American Medical Association* in 1995, reported on clinical interviews with a number of people recruited through newspaper notices who thought that they were dependent on caffeine. These people were interviewed using a structured clinical interview by a psychiatrist, and 16 were identified as meeting the *DSM-IV* criteria of caffeine "dependence." Of these 16, 94 percent reported withdrawal, 94 percent reported use continuing despite knowledge of persistent or recurrent physical or psychological problems likely to have been caused or exacerbated by caffeine use, 81 percent reported persistent desire or unsuccessful attempts to cut down or control use, and 75 percent reported tolerance. These people reported daily doses of caffeine that ranged between 129 and 2,548 mg per day, and three people diagnosed as dependent had daily doses less than the average daily consumption in the United States. Seven of the 16 primarily consumed soft drinks, one drank tea, and the remainder drank coffee (Strain, Mumford, Silverman, & Griffiths, 1995).

In a laboratory study, coffee and cigarettes were made available to subjects on a fixed ratio (FR) schedule of 100, and then the FR requirement was increased to 1,000 and 2,500 independently for each reinforcer. Coffee demand was relatively inelastic (elasticity index -0.26 and -0.51), meaning that coffee consumption did not decrease in proportion to the price increases. As the price of cigarettes increased, the consumption of both coffee and cigarettes decreased, but as the price of coffee increased and coffee consumption fell, the consumption of cigarettes did not change. This finding suggests that changes in smoking behavior can influence coffee consumption, but people will smoke whether they are drinking coffee or not (Bickel, Hughes, DeGrandpre, Higgins, & Rozzuto, 1992).

Population Studies

It is surprising that nonhumans are reluctant caffeine consumers and that humans do not show a more avid and compelling preference in the laboratory. Caffeine and the other methylxanthines

are probably the most widely self-administered drugs in the world. After oil, coffee is the world's most valuable traded commodity.

The Scandinavian countries have the world's greatest partakers of coffee. Their per-capita consumption is about twice that in the United States. Canada ranks quite a bit below the United States, and countries such as Iraq, Sudan, and Japan are at the bottom of the list of coffee consumers. Where tea is concerned, Ireland and Great Britain outconsume Canada by about 4 to 1 and the United States by about 12 to 1. European countries, including the Scandinavian countries, are at the bottom of the tea list.

The average caffeine consumption of the world's population is about 70 mg per person per day, 90 percent of which is consumed in the form of coffee and tea. North American consumption is probably over 200 mg per person per day (Barone & Roberts, 1984). About 60 percent of caffeine consumption is in the form of coffee, 16 percent as tea, 16 percent as soft drinks, and less than 2 percent as chocolate (Gilbert, 1984). Elsewhere, it is estimated that the total consumption of methylxanthines in the United States is more than 230 mg per day. Caffeine accounts for 84 percent, theobromine 17 percent, and theophylline less than 1 percent (Hirsh, 1984).

HARMFUL EFFECTS

Reproduction

At high enough levels, caffeine will damage chromosomes, but it appears that such effects do not occur at the concentrations normally found in the human body, and caffeine is generally considered safe in this regard, although there is some speculation that it might enhance the chromosome-damaging activity of other agents, such as X-rays (Kihlman, 1977, pp. 414–415). Even though it does not damage chromosomes, caffeine can affect the fetus via other mechanisms. For example, caffeine raises the levels of circulating catecholamines, which could affect the unborn child by reducing blood flow to the fetus. Studies in animals have shown that low levels of caffeine retard both embryonic and neonatal growth in animals (Dunlop & Court, 1981). One study has shown that daily consumption of three cups of coffee moderately increases the risk of miscarriage. It is not clear, however, that this was a result of caffeine because it was not the case for women consuming an equivalent amount of caffeine in the form of caffeinated soft drinks (Dlugosz et al., 1996).

There is now some evidence that caffeine consumption retards fetal growth and lowers birth weight in humans, especially if caffeine consumption exceeds 300 mg per day (Santos, Victoria, Hutty, & Morris, 1998). In addition, it has been shown that caffeine will potentiate the effect that smoking has on reducing birth weight (see Chapter 9; for a review, see E. M. McKim, 1991). In addition, heavy caffeine use during pregnancy (more than four cups of coffee per day) increases the risk of SIDS (sudden infant death syndrome) in infants (Ford et al., 1998). Remember that the rate of caffeine metabolism is considerably delayed during pregnancy, and women who maintain usual consumption will experience higher and higher blood levels of caffeine as their pregnancy progresses, and so will their unborn child.

Methylxanthines are also found in considerable concentrations in breast milk. Considering that the rate of methylxanthine metabolism in newborns is extremely slow, even small amounts acquired in breast milk could accumulate, possibly to toxic levels.

Some claim that there is no reason why pregnant women should be concerned about caffeine consumption during pregnancy, but the majority of expert opinion suggests that until a safe level of consumption can be established, it is probably wiser for pregnant women (and nursing mothers) to abstain from caffeine-containing beverages and medicines (J. J. James, 1991).

Cardiac Disease

Some studies show that caffeine increases blood pressure (e.g., Kaminsky, Martin, & Whaley, 1998), and others do not (e.g., Hofer & Battig, 1994). Even

studies that show blood pressure increases report considerable variation among individuals.

The epidemiological evidence linking caffeine consumption to heart disease is still equivocal. In the early 1970s, the Boston Collaborative Drug Surveillance Program published two studies that showed that drinking more than six cups of coffee a day doubled the risk of heart attack. Since that time, numerous studies have failed to replicate the finding. Contradictory results abound. For example, one study of more than 85,000 women in the United States concluded that coffee was not an important cause of heart attacks (Willett et al., 1996); another study of more than 800 women in Boston found that heavy coffee consumption (more than five cups per day) did increase the risk of heart attack (Palmer, Rosenberg, Rao, & Shapiro, 1995).

Factors that may contribute to these divergent findings might be that exposure to caffeine is usually not measured accurately, and, as a result, risk is consistently underestimated (J. J. James, 1991). Another reason might be related to the manner in which coffee is prepared. One study has shown that boiled coffee contains a substance that raises cholesterol levels, but filtered coffee does not contain this factor (Pirich, O'Grady, & Sinzinger, 1993). Even though many have assumed that coffee consumption is not a risk factor in heart disease (Robertson & Curatolo, 1984), the issue is far from settled.

Cancer

Studies with caffeine in laboratory animals have failed to show clearly that caffeine causes cancer. Some studies have found that caffeine may enhance the effect of other cancer-causing agents by inhibiting the ability of the cell to repair damaged DNA. Other studies have actually found that caffeine may inhibit some cancers (J. J. James, 1991).

Epidemiological studies have suffered from the same problems as described for cardiac disease; that is, the ability to measure exposure to caffeine is imprecise. Many studies find increased cancer risk for coffee users as opposed to nonusers but no difference in risk between those who use different amounts of caffeine. Some have suggested that this failure to find a dose effect means that the link between coffee and cancers is circumstantial rather than causal. Nevertheless, it has been pointed out that studies may be examining the wrong measure of coffee exposure. In one study, it was found that the risk of ovarian cancer was 3.4 times greater in women who had drunk coffee for more than 40 years than in women who had never drunk coffee. Among those who did drink coffee, the risk of cancer remained the same no matter how much was consumed. Possibly, the crucial variable is duration of use rather than amount of use—a measure seldom taken in epidemiological studies.

A study in the early 1980s claimed to have found an association between caffeine and pancreatic cancer. This caused considerable concern, but there were methodological flaws in the study, and the effect cannot be consistently replicated. Nevertheless, recent work seems to indicate that caffeine may interact with smoking in causing pancreatic cancer; that is, the risk of cancer for smokers is increased by the consumption of coffee, but coffee has no effect in nonsmokers. Interestingly, the cancer risk for smokers was increased by both regular coffee and decaffeinated coffee. This finding may mean that the important agent was not caffeine, or it may indicate that current drinkers of decaffeinated coffee may have been regular coffee users in the past (J. J. James, 1991).

Inconsistent associations have also been reported between caffeine use and kidney cancer, bladder cancer, testicular cancer, fibrocystic breast disease, and breast cancer (J. J. James, 1991).

Bone Density

Of increasing concern is the effect of caffeine on the rate of bone density in postmenopausal women. One study showed that a daily consumption of two to three cups of coffee accelerated bone loss in the spine and body of postmenopausal women who consumed less than the recommended daily dietary source of calcium (S. Harris & Dawson, 1994).

Abnormal Behavior

At doses of 5 to 10 cups per day, caffeine can cause sensory disturbances, such as ringing in the ears and flashes of light, as well as mild delirium and excitement. These are symptoms of a disorder called *caffeinism*, which is very similar to anxiety neurosis and is frequently diagnosed as such. Caffeinism is usually seen at doses above 1,000 mg per day. Patients report a low-grade fever of about 100 degrees Fahrenheit, which is a result of the drug's action on the body's heat-regulating mechanism in the hypothalamus. Other symptoms include flushing, chilliness, insomnia, irritability, irregular heartbeat, and loss of appetite. Unlike anxiety neurosis, these symptoms do not respond to treatment with tranquilizers. The only cure is to eliminate caffeine from the diet (Greden, 1974).

It has also been shown that caffeine will cause panic attacks and increase anxiety in people with panic and anxiety disorders, but it does not generate them in normal individuals unless used excessively (Carroll, 1998, p. 102).

The psychological basis for these effects appears to lie in the fact that, at high doses, caffeine blocks benzodiazepine receptors. The benzodiazepines are the family of tranquilizers to which chlordiazepoxide (Librium) and diazepam (Valium) belong (see Chapter 7). The benzodiazepines act at a particular type of receptor in the brain that appears to be the site of action of an endogenous form of benzodiazepine that has similar antianxiety properties. The reason caffeine produces anxiety-like symptoms at higher doses is that it blocks these benzodiazepine receptors, and the body's natural benzodiazepine cannot function. When these receptors are blocked, the therapeutic effectiveness of an administered benzodiazepine is also diminished.

There is also evidence that caffeine reduces the effectiveness of the major family of antipsychotic drugs, the phenothiazines, including chlorpromazine (Kulhanek, Linde, & Meisenberg, 1979).

Not only does caffeine interfere with the effectiveness of many psychotherapeutic drugs, but it may also make the symptoms of both neurotic and psychotic patients worse (Greden, Foutaine, Lubetsky, & Chamberlin, 1978). In one experiment (De Freitas & Schwartz, 1979), patients in a psychiatric hospital who were switched to decaffeinated coffee for 3 weeks without their knowledge showed a decrease in anxiety, hostility, irritability, tension, and psychotic symptoms. During a 3-week period after caffeine was restored, all the improvements were reversed. This study, however, has not been replicated (Mayo, Falkowski, & Jones, 1993).

Lethal Effects

Six deaths due to caffeine overdose have been reported (Syed, 1976). The lethal dose in humans has been estimated at between 3 and 8 g (30 to 80 cups of coffee or stay-awake pills) taken orally. Death results from convulsions and respiratory collapse.

EPILOGUE

What Do We Really Know About Caffeine?

Caffeine is big business—even bigger than the tobacco business. You can be sure that any threat to the profits of the coffee industry would be met with resources similar to those that the tobacco industry has put forward in defending itself against the increasing public awareness of the dangers of smoking. Perhaps that threat already has been met.

In an editorial in the British journal *Addiction*, one of the world's foremost caffeine researchers, Jack James of La Trobe University in Bundoora, Australia, warned that the coffee industry has been subtly directing caffeine research away from areas of health problems and manipulating the dissemination of health information about caffeine for many years (J. J. James, 1994). The coffee industry established something called the International Life Sciences Institute (ILSI). This sounds as though it should be a scholarly organization with lofty aims, but in reality it was established to make sure that caffeine

retained its status as "generally recognized as safe" by the U.S. Food and Drug Administration. In this regard, it has been successful. Despite increasing numbers of studies that have provided reason to doubt it, caffeine is still considered a "safe" food additive.

How does the ILSI work? Its influence may be seen in the pages of this book. According to James, the ILSI sponsors international conferences attended by prominent scholars by invitation only and then publishes the results. According to James, however, in the publications that deal with the health hazards of caffeine, "evidence is consistently interpreted in a way that is favourable to the interests of the book's sponsors." This approach is given credibility because other publications that do not deal with health issues are balanced, erudite, and scholarly.

In addition, the caffeine industry sponsors research but is careful to sponsor research in "safe" areas, such as the study of compounds in coffee other than caffeine. As James says, "Under the guise of public interest, the industry actively supports continuing research on noncaffeine constituents of coffee, knowing fully that nothing untoward (and nothing of particular interest to the public) is likely to be revealed" (J. J. James, 1994, p. 1579).

CHAPTER SUMMARY

- The three commonly used methylxanthine drugs are caffeine, found mainly in coffee; theophylline, found in tea; and theobromine, found in chocolate. Caffeine is also added to some cola beverages, headache medications, and over-the-counter stimulants.
- Beverages that contain methylxanthines have been used in Europe and North America since the 1600s, and their popularity has made them important commodities. Their trading and taxation have played an important role in commerce and history.
- The methylxanthines are readily absorbed orally and distributed throughout the body. After its oral administration, caffeine reaches peak blood levels in 30 to 60 minutes. It is metabolized in the liver and eliminated slowly, with a half-life of about 3½ hours.
- The main neurophysiological effect of the methylxanthines is that they block receptors of the inhibitory neuromodulator adenosine. They also cause the release of epinephrine and catecholamines.
- Caffeine improves performance on boring and tiring tasks. There are some circumstances in which caffeine can improve athletic performance in endurance events.
- Caffeine can delay sleep. Sleep after caffeine is lighter, and people are more easily awakened.
- In nonhumans, caffeine stimulates spontaneous activity and can cause automutilation at larger doses. Operant analysis of the effects of caffeine has shown that its effects are similar to those of amphetamine, with some important differences.
- Caffeine can act as a discriminative stimulus and will generalize partially to cocaine. Humans can also detect the presence of caffeine in low concentrations.
- Doses of 100 to 200 mg of caffeine administered to people who are not tolerant to caffeine are experienced as pleasant, and when it is given intravenously, people report a "high" similar to cocaine. Higher doses are often reported to be unpleasant.
- Tolerance develops to many of the effects of caffeine in both humans and nonhumans. Withdrawal symptoms, consisting of headaches and restlessness, have been reported at doses as low as 100 mg a day. Withdrawal peaks between 20 and 48 hours and may last as long as a week.
- Although humans consume vast quantities of caffeine, it is not a robust reinforcer in laboratory animals. It usually requires a period of forced administration before it will serve as a reinforcer. Humans will choose beverages and capsules containing caffeine if they report pleasant subjective effects and are physically dependent on caffeine.
- It is possible to meet the *DSM-IV* criteria for "substance abuse" with caffeine.
- The average caffeine consumption in North America is over 200 mg per person per day. Most caffeine is consumed in the form of coffee.

- There is evidence of a detrimental effect of caffeine on reproduction and a possible association with heart disease and cancer. It has not yet been clearly established that there is a link because of difficulties with measuring caffeine consumption and separating its effects from the use of other drugs, such as tobacco.
- At higher doses (10 to 15 cups a day), the drug can cause caffeinism, with symptoms indistinguishable from anxiety neurosis. Even at low doses, caffeine may worsen the symptoms of neurosis and psychosis and diminish the effectiveness of some psychotherapeutic drugs.