CHAPTER

6

Alcohol

SOURCE OF ALCOHOL

Alcohol is a chemical term that describes a wide range of substances, very few of which are commonly consumed. Some members of this class are *isopropyl alcohol*, used as rubbing alcohol; *methanol* (*methyl alcohol*) or wood alcohol; and *ethanol* (*ethyl alcohol*), the alcohol we drink. The other alcohols can be consumed and have behavioral effects similar to those of ethanol, but they are rather toxic and are normally consumed only by accident. In this book, as in most others, the term *alcohol* will be used to refer to ethanol. Where other alcohols are discussed, they will be mentioned by name.

Fermentation

The alcohol we drink is made largely by *fermentation*. When sugar is dissolved in water and left exposed to the air, the mixture is invaded by microorganisms called *yeasts*. Yeasts consume the sugars and multiply rapidly. The metabolic processes of the yeasts convert the sugar into ethanol and carbon dioxide (CO_2), which rises to the top in bubbles, and the alcohol remains. More and more yeasts produce more and more alcohol until all the sugar is used up or the yeasts are unable to continue.

The type of beverage resulting from fermentation is determined by the source of the sugar. Almost any vegetable material containing sugar may be used, but the most common are grape juice, which is fermented to make wine, and grains, which are fermented to make beer. Modern fermentation is done with special yeasts rather than the wild variety. Yeasts are living organisms; they have been bred and selected over the centuries for particular types of fermentation. Because yeasts can tolerate only low levels of alcohol, fermented beverages do not have alcohol levels much above 10 to 15%.

Distillation

The Chinese were likely the first to distill alcohol as long ago as 3000 BCE. For a long time, the process, known only to alchemists, was a jealously guarded secret, and little was committed to writing until much later. The process of distillation is quite simple. It starts with ordinary fermentation of a sugary substance. When fermentation is completed, the mixture is heated. Because alcohol has a lower boiling point than water, the vapor or steam given off will have a higher content of vaporized alcohol than the original product. When this vapor is condensed after cooling, the resulting fluid will also contain a higher percentage of alcohol. There is no reason why the condensed spirits cannot be redistilled again and again until the resulting fluid has the desired level of alcohol. The traditional method among moonshiners for determining whether they have distilled their product sufficiently is to take a teaspoon of the stuff and set it on fire. When the fire has burned off all the alcohol, the spoon is tipped, and if more than a drop of water remains, the liquid is distilled again.

Brandy is the result of distilling wine, and whiskey is distilled from fermented grains. Brandy and whiskey were the first popular spirits. Today, we have rum, distilled from fermented molasses, and schnapps, which traditionally is distilled from fermented potatoes. Gin and vodka are made from a mixture of water, flavoring, and pure alcohol distilled from any source. Distilled spirits, or hard liquor, usually have an alcoholic content of about 40 to 50% by volume. In addition to these hard liquors are the liqueurs, which are sweetened and flavored. Some well-known liqueurs are créme de menthe, which is flavored with mint; Cointreau, which has an added flavor of oranges; and the famous Greek drink ouzo, which has an anise flavor.

Midway between the distilled and fermented beverages are the fortified wines, such as sherry, port, madeira, and muscatel, which were developed during the Middle Ages. These are blends of wine with extra alcohol added to boost the alcohol content to about 20%. Vermouth is a flavored fortified wine developed in Turin in the eighteenth century.

ORIGIN AND HISTORY

Alcohol has probably been a part of the human diet and that of our hominin ancestors for millions of years. Many of these ancestors, human and otherwise, consumed fruit, which has a high sugar content and therefore would have been an excellent food. However, because of the sugar and the presence of yeasts, all fruit, even ripe fruit, contains a small amount of alcohol, and as it matures, the alcohol content increases. The taste and smell of alcohol then would have been associated with food and nourishment throughout a significant proportion of our evolutionary history. As we shall see later, this long-term association has probably had a big influence on physiological and behavioral responses to alcohol (Dudley, 2000, 2002).

While people have likely been brewing alcohol since agriculture began about 10,000 years ago, they undoubtedly did so on a small scale, and there is no record of it. The earliest proof of humans fermenting alcohol involves large earthenware jugs found in China that date back 9,000 years. Analysis of the contents has shown that they once stored a wine made from rice, honey, and fruit (McGovern et al., 2004).

The earliest written set of laws, the Code of Hammurabi, written in 2225 BCE in Assyria, sets forth some rules for the keeping of beer and wine shops and taverns. The ancient Egyptians were also known for their drinking. The Egyptian Book of the Dead, from about 3000 BCE, mentions the manufacture of a drink called *hek*, a form of beer made from grain (Bickerdyke, 1971). Herodotus, the Greek historian, narrated how, at a rich man's feast in ancient Egypt, it was the custom to have a man carry around the image of a corpse in a coffin and show it to all the guests saying, "Drink and make merry, but look on this for such thou shalt be when thou are dead" (McCarthy, 1959, p. 66). The ancient Egyptians, as well as the Assyrians and the Babylonians, drank beer primarily (their climate was more suitable for the growing of grains than grapes), but they also drank a great deal of wine.

There is much evidence that the Greeks, who were supposed to be "temperate in all things," may not always have been so temperate where wine was concerned. Plato had much to say about the effects of alcohol. In *The Laws*, Plato wrote:

> When a man drinks wine he begins to be better pleased with himself, and the more he drinks the more he is filled full of brave hopes, and conceit of his powers, and at last the string of his tongue is loosened, and fancying himself wise, he is brimming over with lawlessness and has no more fear or respect and is ready to do or say anything. (Laws I, 649a–b; translation in Jowett, 1931, p. 28)

Although the early Romans had little trouble with wine, there was a great deal of insobriety and debauchery in the declining years of the Roman Empire for which the later Roman emperors, such as Nero, Claudius, and Caligula, became notorious. The fall of the Roman Empire has been blamed on the consumption of wine, not so much as a result of the alcohol, but because wine at the time was fermented and stored in vessels made of lead, and a lead-based additive was put into the wine to enhance flavor and stop fermentation. It is believed that most of the Roman nobility who drank wine suffered from mental instability as a result of lead poisoning (Nriagu, 1983).

Before the Romans brought grapes and wine to the British Isles, the main alcoholic beverages were beer made from barley, mead made from fermented wild

honey, and cider made from fermented apples. The Romans introduced grapes to Britain, but the vines never thrived in the British climate, and wine, as today, was primarily imported. After the Romans left Britain, the Saxons carried on the tradition of heavy drinking with mead, ale, and cider. Taverns and alehouses were established in about the eighth century and quickly acquired a bad reputation.

After the Norman Conquest in 1066, drinking became more moderate, and wine was reintroduced, but the English were still heavy drinkers. "You know that the constant habit of drinking has made the English famous among all foreign nations," wrote Peter of Blois (French, 1884, p. 68).

Although distillation had been known for some time, its presence was not felt in England until the sixteenth century when a number of Irish settlers started manufacturing and distributing *usquebaugh*, which, in English, became known as whiskey. Brandy imported from France was also becoming popular. After the restoration of the monarchy in 1660, distilleries were licensed, and the popularity of gin spread like an epidemic (gin is raw alcohol flavored with juniper berry).

Between 1684 and 1727, the annual consumption of distilled spirits in England increased from about half a million gallons to over 3.5 million gallons (French, 1884). These figures do not include the large quantities of rum and brandy smuggled into the country to avoid paying high duties and tariffs. This epidemic raised such concern that the government passed a desperate series of laws aimed at curtailing the use of liquor, but nothing had much effect.

The English propensity for strong drink was transported across the Atlantic to the colonies. Colonial Americans were hearty drinkers, and alcohol played a large part in their lives.

How highly did the colonies prize strong drink? Their statutes regulating its sale spoke of it as "one of the good creatures of God, to be received with thanksgiving." Harvard University operated its own brewery, and commencements grew so riotous that rigid rules had to be imposed to reduce "the Excesses, Immoralities and Disorders." Workmen received part of their pay in rum, and employees would set aside certain days of the year for total inebriety (Benjamin Rush, quoted in Kobler, 1973).

Before the American Revolution, there had been some success in regulating taverns and drinking, but this control weakened after independence from England was gained. Americans connected liberty from the crown to the freedom to down a few glasses of rum. As a consequence, drinking houses emerged from the war with increased vitality and independence, and the legal regulation of licensed premises waned (Rorabaugh, 1979). Consumption continued to increase to prodigious levels, but a precipitous decline followed between 1830 and 1860. This decline can be attributed to the singular efforts of the temperance movement.

In both England and the United States, there had always been people who openly condemned the use of alcohol, and there were organized movements against drinking and alcohol consumption. In the late 1700s in the United States, the champion of temperance was Dr. Benjamin Rush, a physician who wrote widely about the dangerous physical, social, and moral effects of alcohol and published one of the first influential temperance documents, *An Inquiry into the Effects of Ardent Spirits*.

Although Rush's writings were not heeded at the time, they inspired the American temperance movement of the early nineteenth century, which was more successful than any similar movement before or since. The temperance movement was successful because it was philosophically in tune with the moral tenor and ideals of the new republic. Socially, it filled exactly the same function as drinking. "Some men sought camaraderie at the tavern, others in their local temperance organization" (Rorabaugh, 1979, p. 189). In addition, a religious revival was sweeping the United States at the time. Total abstinence from alcohol provided a symbolic way to express conversion and faith.

The temperance movement was not content to rely on the force of moral persuasion to dry up the country, however. During this period, the movement attracted enough power to have alcohol prohibition laws enacted in 11 states and two territories. Soon, a national Prohibition party was founded, and the temperance reformers set their sights on the federal government. Their vigorous campaign culminated in 1917 with the ratification of the Eighteenth Amendment to the U.S. Constitution. Prohibition was passed with little opposition, as most legislatures had their attention focused on World War I.

Because it did not have widespread public support, the law was virtually unenforceable and provided a vehicle for the rapid development and funding of mobsters and organized crime. Alcohol that was not manufactured

in the United States was smuggled in from Canada and elsewhere in vast quantities. It became apparent to both presidential candidates, Herbert Hoover and Franklin Roosevelt, in the 1932 presidential election that Prohibition did not have popular support. One month after Roosevelt's victory, an amendment to the Constitution was drafted that would void the Eighteenth Amendment. Within 2 months, it was passed by both the House and the Senate, and on December 5, 1933, it was ratified and signed into law. Prohibition had lasted almost 14 years.

After Prohibition ended, alcohol consumption rates increased steadily until they peaked in about 1979. Spurred by movements such as Mothers Against Drunk Driving (MADD), consumption has begun to decline in response to an increasing concern with health and a decreasing public tolerance of drugs in general because of the harm that they do. David Musto, a medical historian at Yale University, is among those who predict that history is likely to repeat itself and that this decline will continue into the early twenty-first century but that it will then be followed by another drinking backlash (Kolata, 1991).

Figure 6-1 shows that American consumption of alcohol appears to go through cycles. Consumption peaks every 60 to 70 years, and these peaks have been followed by declines in use. Historians have pointed out that these periods of decline were accompanied by preoccupation with health and morality and by public concern over the harm that alcohol was doing, but fairly sharp increases in consumption followed. It appears as though the United States is now well into a phase of decreasing alcohol use.

MEASURING ALCOHOL LEVELS IN THE BODY

Alcohol levels are usually measured in terms of the concentration of alcohol in whole blood. This is known as the blood alcohol concentration (BAC), or blood alcohol level (BAL). The BAC may be measured directly by taking a blood sample, but more often a breath sample is taken and analyzed using a device known as a Breathalyzer. It has been established that alcohol concentration in the breath reflects the concentration in the blood fairly reliably, and so the results of a Breathalyzer are reported as "*blood* alcohol concentration" rather than "*breath* alcohol concentration."

Metric Measurements and Percentage

BAC is usually expressed in terms of milligrams (mg) of alcohol per 100 milliliters (ml) of whole blood (a milligram is 1/1,000 gram; a milliliter is 1/1,000 liter; 100 ml

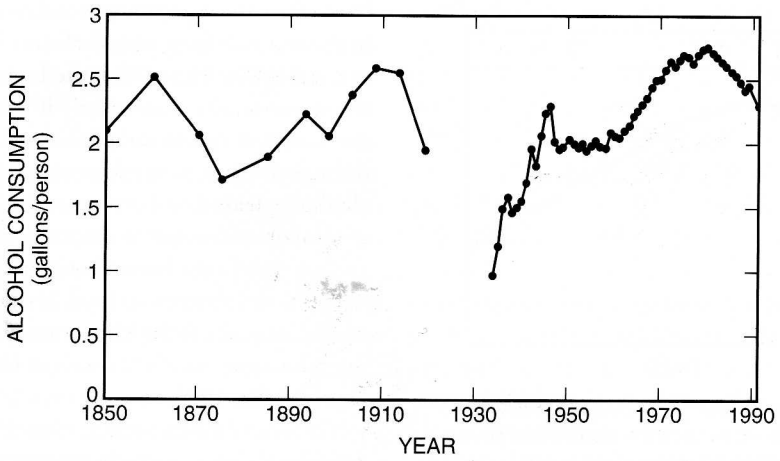

FIGURE 6-1 Yearly alcohol consumption, in gallons per person, of raw alcohol from 1850 to 1990 in the United States. Note that there are three peaks in consumption, about 60 years apart. The gap in the early part of the twentieth century is due to Prohibition. Note the short-lived increase in consumption in the years following World War II. (Williams, Clem, & Dufour, 1993)

is equal to a deciliter [dl]). The BAC may also be reported as a percent of alcohol in the blood. Fortunately, conversion between these measures is not difficult; it involves only moving the decimal point three places to the right or left. For example, a BAC of 80 mg of alcohol per 100 ml of blood (or 80 mg/dl) is equivalent to 0.08%.

SI Units

There has been a recent trend in the scientific literature toward reporting drug concentrations in *SI units* (Système International d'Unités). This measure makes it easy to compare the concentration of different drugs in the blood because it takes into account the molecular weight of the drug. If the concentration expressed in SI units is the same for two different drugs, then there will be the same number of molecules of each drug per liter. The SI unit of concentration is millimoles of alcohol per liter of blood (mmol/l). For example, 80 mg per 100 ml is equivalent to 17.4 mmol/l of blood.

ROUTE OF ADMINISTRATION AND PHARMACOKINETICS

Figure 6-2 shows the theoretical time course for the level of alcohol in the blood after taking a single drink. This curve can be considered as being made up of several phases. The part of the curve labeled A is the absorption phase, during which absorption is taking place much more rapidly than excretion. The plateau phase, labeled B and C, is when absorption tapers off and excretion starts to lower alcohol levels. During this phase, blood alcohol levels peak. If absorption has been rapid, there may also be a brief period, immediately following the peak, when the decline in blood levels is rapid as a result of the distribution of alcohol out of the blood to other parts of the body. In the excretion phase, D, alcohol is eliminated from the body at a constant rate.

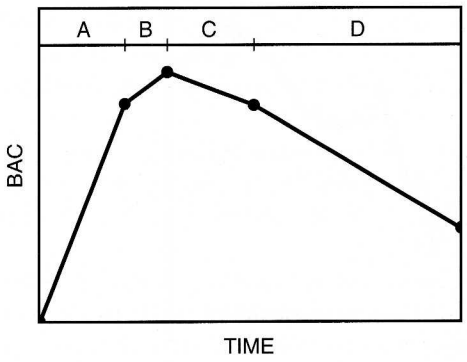

FIGURE 6-2 The theoretical time course for BAC after taking a single drink. Phase A is the absorption phase during which absorption is taking place much faster than elimination. Phases B and C form the plateau phase during which absorption tapers off and elimination starts to lower blood alcohol concentration. During this phase, blood concentration peaks. During the elimination phase, D, absorption is complete, and alcohol is eliminated from the body at a constant rate.

ABSORPTION

Alcohol is normally administered orally, and absorption takes place in the digestive tract. Because the molecules of alcohol cannot be ionized, neither the pH of the digestive system nor the pH of the blood has an effect on absorption.

Alcohol readily dissolves in water, and it may pass into the blood from the stomach, intestines, or colon. However, it is absorbed most rapidly from the small intestine. As long as alcohol stays in the stomach, it is exposed to fairly high levels of *alcohol dehydrogenase*, the main enzyme that breaks down alcohol. The stomach is where *first-pass metabolism* of alcohol occurs, catalyzed by alcohol dehydrogenase. After solid food has been eaten, the digestion process usually keeps the food in the stomach for a period of time before it is released in small quantities. Thus, the longer alcohol stays in the stomach, the more slowly it will be absorbed into the blood. Also, more alcohol will be broken down through *first-pass metabolism*, causing the overall level of alcohol released to be lower. In general, absorption of alcohol is faster on an empty stomach, and more will get into the body. Even though peak blood levels are higher when there is no food in the stomach, the peak will occur at about the same time, and it will take about the same time for blood levels to return to zero (Watkins & Adler, 1993).

Some medicines, such as cimetidine (Tagamet) and ranitidine (Zantac), which are commonly used to reduce stomach acidity, can increase BAC. These drugs, known as *histamine H_2-receptor antagonists*, are widely prescribed for ulcers and heartburn. Zantac 75 is ranitidine in nonprescription strength and is available over the counter. These H_2-receptor antagonists reduce stomach

levels of alcohol dehydrogenase, and this significantly reduces the amount of first-pass metabolism. One study found that the amount of alcohol entering the blood was increased by 17% after a single week of ranitidine treatment (DiPadova et al., 1992). The effect appears even greater with cimetidine. The effects of cimetidine and ranitidine are greatest when alcohol is taken on a full stomach. On an empty stomach (or in the case of alcoholics), there is little first-pass metabolism in the digestive system (DiPadova, Worner, Julkunnen, & Lieber, 1987).

There also appear to be gender differences in first-pass metabolism. Compared to men, women have lower levels of alcohol dehydrogenase in the stomach; consequently, more alcohol enters the blood, resulting in a higher BAC for women than the same amount of alcohol would produce in a man of similar size (Frezza et al., 1990; Whitfield & Martin, 1994).

Interestingly, abstainers appear to reach lower peak BACs than moderate drinkers. The reason for this difference is not clear, but it may have to do with different degrees of first-pass metabolism in people who never drink (Whitfield & Martin, 1994).

The time to reach the maximum blood alcohol level after drinking is highly variable between individuals and situations, but the time to reach the beginning of the plateau (B in Figure 6-2) is usually about an hour, with the peak about 15 minutes later. After a few drinks, however, absorption rates seem to increase, and the peak and plateau will be reached 20 to 25 minutes sooner (Ditmar & Dorian, 1987).

Beer passes out of the stomach more slowly than other alcoholic beverages. For this reason, beer creates lower BACs than the same amount of alcohol consumed in some other beverage. The passage of alcohol through the stomach may also be facilitated by carbonation. Sparkling wines such as champagne and rosé frequently have more "kick" than still wines (Vogel-Sprott, 1992).

The concentration of the alcohol also contributes to the speed of absorption. Diffusion rates increase with increases in concentration; therefore, the alcohol from beverages with high alcoholic content diffuses into the blood faster than the same amount of alcohol mixed in a weaker concentration. There is, however, an upper limit to this effect. High alcohol concentrations slow down the rate at which the stomach empties its contents into the intestine and, thus, can interfere with absorption. It is likely not a coincidence that most rapid absorption occurs at about 40% alcohol, the concentration of most hard liquors.

It has also been suggested that expectancy may have an effect on BAC when drinking. In a recent study, subjects who expected alcohol reached a higher average BAC than subjects who were given alcohol unexpectedly (Cole-Harding & Michels, 2007).

DISTRIBUTION

Because alcohol dissolves much more readily in water than in fat, alcohol is distributed almost entirely in body water. Therefore, individuals with different proportions of body fat, even though they may weigh exactly the same, may reach different BACs after drinking identical amounts of alcohol. Males, for example, have a lower percentage of body fat than females. Thus, if a man and a woman weigh exactly the same and drink the same amount of alcohol, the woman will have a higher BAC (assuming similar first-pass metabolism). The alcohol she drinks will be more highly concentrated in her blood because her body has less water to dilute it.

For males, age also makes a difference, as their body fat percentage generally increases until age 50 or 60. Even though their total body weight may not change, the same amount of alcohol will result in higher BACs as men get older. Women show a much smaller change in body composition with age.

It is possible to calculate the BAC for an individual after the consumption of a given amount of alcohol. Box 6-1 shows how to make these calculations for any individual.

Alcohol is distributed rather evenly throughout body water, and it crosses the blood–brain barrier, as well as the placental barrier, without difficulty. Consequently, alcohol levels in most tissues of the body, including the brain and a fetus (if present), accurately reflect the blood alcohol content of the drinker. Alcohol in the blood circulates through the lungs and vaporizes into the air at a known rate, which is why it is possible to measure the alcohol level in the blood and the rest of the body by measuring the alcohol vapor in exhaled air using a Breathalyzer, as described earlier.

BOX 6-1 Calculating Blood Alcohol Concentrations

Calculating the BAC is relatively simple. You have to know the weight and sex of the individual and the amount of alcohol consumed. To illustrate, let us calculate the BAC of a 175-pound man who has ingested 1 ounce of spirits. Because the BAC is usually given in milligrams per 100 ml of blood, it is easier to do the calculations in metric units rather than in pounds and ounces.

First, we convert the body weight (175 pounds) to kilograms by dividing by 2.2 (1 kg = 2.2 lb). This equals 80 kg. This weight must then be adjusted because not all of the body is capable of absorbing alcohol. The percentage that can absorb alcohol is estimated to be 75% in men and 66% in women. Therefore, an 80-kg man will have 60 kg to absorb alcohol (80 × 0.75 = 60); 60 kg = 60,000 g or 60,000 ml of fluid because 1 ml of water weighs 1 g.

Next, we must convert alcohol to milligrams. One ounce of spirits (100 proof, or 50% by volume) will contain 11.2 g of alcohol (0.5 fluid ounce of water weighs 14 g), and alcohol has a specific gravity of 0.8 (14 × 0.8 = 11.2); 11.2 g is 11,200 mg.

Now we can divide the 11,200 mg of alcohol by 60,000 ml of body fluid and multiply by 100. This calculation yields the BAC: 18.6 mg per 100 ml. Our 175-pound man will raise his BAC by 18.6 mg per 100 ml of blood with every ounce of spirits.

Beer is usually about 5% alcohol by volume and comes in 12-ounce bottles. One such bottle would contain 13.5 g of alcohol, or 13,500 mg. When this is spread around a 60,000-ml body, it gives a concentration of about 22.5 mg per 100 ml. Our 175-pound man would raise his BAC by 22.5 per 100 ml with each beer. The accompanying table gives the alcohol content of various common drinks so that you can do the appropriate calculations for different sources of alcohol.

To calculate how each of these drinks would affect you, take your weight in pounds and convert it to kilograms by dividing by 2.2. Next calculate the body weight (for your sex) that is capable of absorbing alcohol: male, 75%; female, 66%. This figure must then be converted to milligrams (and milliliters) by multiplying by 1,000.

Now calculate the amount of alcohol consumed in milligrams, divide it by your weight in milligrams, and multiply by 100. Because the body metabolizes alcohol at a rate of about 15 mg per 100 ml per hour, you can subtract 15 mg per 100 ml for each hour that has passed since your drinking started. Caution: These estimates of your BAC using this technique are just that—estimates. Two factors in this equation are approximations: the percentage of the body that will absorb alcohol and the rate of alcohol metabolism. Both depend on many factors, such as age, health, build, experience with alcohol, and even other drugs in your system. The figures given here are population averages that might not apply to you. In general, however, this technique tends to overestimate BAC, so it should be reasonably safe for most people most of the time. It is not recommended, however, that you bet your life or your driver's license on it.

Alcohol Contents of Some Beverages

Beverage	Alcohol Content Percent (volume)	Alcohol Content (mg)
Spirits (1 fl. oz.*)		
(100 proof)	50	11,200
(89 proof)	43	9,600
(80 proof)	40	8,900
Beer (12 fl. oz.)	5	13,500
Wine (2.5 fl. oz.)	12	8,400

*A shot is 1.25 oz., so that these figures must be increased by 25% if "shots" are being used to mix drinks.

ELIMINATION

Alcohol may be eliminated in breath, sweat, tears, urine, and feces, but between 90 and 98% of all alcohol consumed is metabolized by the liver (the remaining portion is eliminated by the kidneys, lungs, and through the skin). Because humans have been consuming alcohol throughout a long period of our evolution, we have developed an efficient means of eliminating alcohol and using it as a source of energy. The usual route of metabolism is shown in Figure 1-10. It involves two steps. In the first step, the *rate-limiting step*, alcohol is converted to *acetaldehyde* by the enzyme alcohol dehydrogenase. This is the slowest step in alcohol metabolism. Consequently, the rate at which this conversion takes place limits the speed of the entire process. The rate of conversion of alcohol to acetaldehyde is determined by the amount of alcohol dehydrogenase available and is relatively independent of the concentration of alcohol. The metabolism of alcohol, then, usually takes place at a steady rate throughout most BACs (this rate may vary between individuals and from species to species).

In the second step, the acetaldehyde is converted into *acetyl coenzyme A* by several enzymes, the most common of which is *aldehyde dehydrogenase*. Acetyl coenzyme A is converted mainly into water and carbon dioxide through a series of reactions known as the *citric acid cycle*, during which usable energy is released to the body. Acetyl coenzyme A is also used in a number of bodily processes, such as the production of fatty acids and steroids. As a result, alcohol consumption and its consequent metabolism can alter a great deal of body chemistry.

Between individuals, there is considerable variability in elimination rates. The range found in one study was from 5.9 to 27.9 mg per 100 ml of blood per hour, with a standard deviation of 4.5 (Dubowski, 1985). For the majority of individuals, the range is usually accepted to be between 10 and 20 mg per 100 ml per hour, with a mean of 15. The rate of metabolism of alcohol also seems to be influenced by drinking experience. Nondrinkers metabolize alcohol at a slightly slower rate (12–14 mg/100 ml per hour) than light to moderate drinkers (15–17 mg/100 ml per hour; Goldberg, 1943; Whitfield & Martin, 1994).

It has also been demonstrated that food can have an effect on the rate of alcohol metabolism as well as its absorption. Ramchandani, Kwo, and Li (2001) have shown that eating speeds up the rate of alcohol metabolism from 25 to 45%. The increase does not seem to depend on the type of food eaten and is probably a result of increased blood flow to the liver caused by a food in the stomach.

Although most alcohol is handled by the alcohol dehydrogenase system, another system appears to be in operation as well. This is known as the *microsomal ethanol-oxidizing system* (MEOS). The MEOS normally handles only 5 to 10% of the metabolism of alcohol, but its activity increases at higher levels of blood alcohol. The activity of the MEOS may be doubled or even tripled by continuous alcohol consumption. This increase may account for 50 to 65% of the increased alcohol metabolism induced by heavy drinking, a change that partly accounts for alcohol tolerance. The MEOS is important for another reason: It is also responsible for the metabolism of a number of other drugs, such as barbiturates (see Chapter 7). Therefore, if the MEOS is stimulated by continuous alcohol use, the metabolism of these other drugs will also be speeded up, and vice versa (Leiber, 1977; Leiber & De Carli, 1977). Thus, alcoholics usually have a great deal of resistance to the effects of barbiturates and other drugs.

NEUROPHARMACOLOGY

The neuropharmacology of alcohol is complex and involves a number of systems. One interesting aspect of alcohol intoxication is that a much higher concentration of alcohol is required than most other drugs. Most drugs discussed in this book produce their effects in blood concentrations in the nanomolar (nM) or micromolar range (μM), but effects of alcohol are seen only at the millimolar (mM) range, that is, 1,000 to 1,000,000 times greater than most drugs (these concentrations are given in SI units and reflect the number of drug molecules per liter so that they can be compared with other drugs of different molecular weights). Because its effects seemed to require such high concentrations, alcohol was initially thought to act on the nervous tissue through a physical effect like causing the neural membranes to swell or become distorted. However, it is now known that alcohol works by altering neural transmission at receptor sites and ion channels in a manner similar to other drugs.

The effects of alcohol are not confined to one receptor; alcohol affects many systems at the same time, and

it can have different effects on different systems at different concentrations. The puzzle of how alcohol affects neurophysiology is only now being untangled, and there is a great deal that is still not known. The principal neurotransmitter systems that mediate the behavioral effects of alcohol are GABA and glutamate, but alcohol affects other systems as well, including glycine, serotonin, acetylcholine, dopamine, and the endogenous opioid system.

GABA

GABA is the principal inhibitory transmitter in the brain. PET-detected decreases in brain activity appear to be related to alcohol-induced stimulation of GABA receptors; interestingly, such stimulation is more pronounced in men than in women (Wang et al., 2003). There are two types of GABA receptors: $GABA_A$ and $GABA_B$. Alcohol is known to affect both, but in a different manner. The $GABA_A$ receptor is part of a *receptor–ionophore complex*; it contains a ligand-gated channel permeable to chloride (Cl^-) ions (*ionophore* is sometimes used as a synonym for *ion channel*). $GABA_A$ receptors are *pentameric*—made up of five subunits surrounding the central pore, as can be seen in Figure 7-1 in Chapter 7. Each subunit is a protein or chain of amino acids folded into a complex unit. There is considerable variability in the composition of subunits, each of which is created by a different gene.

There are eight major types of $GABA_A$ receptor subunits, designated alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ϵ), theta (θ), pi (π), and ro (ρ). Some of these subunits are further divided into a number of varieties: There are six varieties of the alpha subunit (α_{1-6}), and three varieties each of beta (β_{1-3}), gamma (γ_{1-3}), and ro (ρ_{1-3}). The remaining four subunits (δ, ϵ, θ, and π) each have only one variety. Every $GABA_A$ receptor complex is made up of five of the possible 19 subunits put together in a variety of combinations, making many different types of $GABA_A$ receptors possible. The most common type of $GABA_A$ receptor is made up of two alpha subunits, two beta subunits, and one gamma subunit, and the most common receptor subunit varieties are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, and $\alpha_3\beta_3\gamma_2$ (Nutt & Stahl, 2010). Different $GABA_A$ receptor subunit configurations are found in distinct areas of the brain, which suggests that both the location and the variety of $GABA_A$ receptor complex may determine its function and how it is affected by alcohol and other GABAergic drugs.

There are two actual receptor binding sites for the GABA transmitter molecule, each located between the interface of an alpha and a beta subunit (see Figure 7-1). These sites are referred to as *orthosteric* sites, where the natural ligand (GABA) binds to its specific receptor site. When an orthosteric site is activated, the ion channel that forms the central pore of the $GABA_A$ receptor complex opens and permits an influx of Cl^- ions, hyperpolarizing the postsynaptic membrane and inhibiting the cell. The $GABA_A$ receptor complex also contains what are called *allosteric* binding sites. When a drug binds to an allosteric site, it is able to alter the function of the receptor complex by creating conformational changes in the receptor that, in turn, affect the functioning of the orthosteric sites. $GABA_A$ receptor complexes contain an allosteric site for benzodiazepines, located between the alpha and gamma subunits, and other allosteric sites for alcohol, barbiturates, neuroactive steroids, picrotoxin, and general anesthetics, all of which are located on the membrane-spanning portion of the receptor complex. In most cases, activation of these allosteric sites does not open the Cl^- ion channel to cause hyperpolarization. Instead, it alters the binding affinity (i.e., the forming of a receptor–ligand complex) and efficacy (i.e., the elicitation of a biological response) of GABA to open the ion channel. Activation of allosteric sites can either enhance the effects of GABA or lessen those effects. If there is an enhancement of GABA, the drug is called a *positive allosteric modulator*; if the effects of GABA are diminished, the drug is a *negative allosteric modulator*. Alcohol is a positive allosteric modulator.

Different configurations of the $GABA_A$ receptor complex are associated with different parts of the brain and mediate different functions (Möhler et al., 2004). In addition, $GABA_A$ receptors made from different subunit combinations are differentially sensitive to different allosteric modulators.

Alcohol is known to act only on $GABA_A$ receptor complexes that contain a delta subunit in combination with alpha 4 or alpha 6 subunits (Tomberg, 2010). Alcohol functions at these receptor complexes as a positive allosteric modulator, enhancing the ability of GABA to open the ion channel. $GABA_A$ receptor complexes with delta subunits are unusual types of $GABA_A$ receptors. They are very sensitive to low levels of GABA

and alcohol and appear to have specialized functions outside synapses. They are believed to be located in two places in relation to the neuron. One is in postsynaptic membranes, but not at a GABA synapse. These receptor complexes are normally activated by spillover GABA that diffuses from a GABA synapse. It is believed that their function is to enhance a tonic or long-term inhibition of the cell (Santhakumar, Wallner, & Otis, 2007; Tomberg, 2010). The other location of these *extrasynaptic* receptors is on a presynaptic membrane where they enhance transmitter release into the cleft, thus intensifying the inhibitory effect of GABA.

Alcohol-sensitive $GABA_A$ receptors containing the delta subunit are located in the cerebellum, a part of the brain responsible for balance, coordination, and motor control. Purkinje neurons, which are responsible for cerebellar output, are stimulated by low concentrations of alcohol, but, at higher doses, alcohol releases GABA from connecting cells, and this inhibits the Purkinje neurons. These alterations in Purkinje cell output cause many of the impairments in motor control caused by alcohol.

Whereas $GABA_A$ receptors maintain an inhibitory tone in the nervous system and are in operation all the time in response to a fairly constant level of GABA, $GABA_B$ receptors are metabotropic. They are not directly linked to an ion channel, but rather use a second messenger and indirectly control the functioning of a K^+ channel (see Chapter 4). There are three varieties of $GABA_B$ receptors that serve different functions. One variety works as an autoreceptor on the presynaptic membrane of GABA synapses where it stimulates GABA release. Another variety, located on postsynaptic membranes, blocks the release of other neurotransmitters by altering calcium channels (Kelm, Criswell, & Breese, 2011). $GABA_B$ receptor activity is also implicated in levels of cyclic AMP, which can alter synaptic plasticity. Alcohol is also known to alter the function of some subtypes of $GABA_B$ receptors, particularly at dopamine synapses stimulating the release of dopamine.

Glutamate

Glutamate is used throughout the brain as an excitatory transmitter, and alcohol blocks glutamate transmission. The level of excitability of the central nervous system (CNS) is maintained by a delicate balance between GABA and glutamate. It has been shown, in several parts of the brain, that acute doses of alcohol at concentrations achieved by normal drinking depress the functioning of the ion channel controlled by glutamate at the NMDA receptor. The NMDA receptor binding site for alcohol is within the ion channel itself, and alcohol molecules have the effect of blocking the ion channel. Just like GABA receptors, the NMDA receptors are composed of many different subunits, and there are specific NMDA subunit configurations that are particularly sensitive to alcohol.

The effects of alcohol on glutamate and GABA converge. GABA stimulation depresses neural activity, and the effect of glutamate diminishes excitability. Together they lead to a suppression of neural activity in particular locations of the CNS. As a result of chronic exposure to alcohol, the brain upregulates NMDA receptor–ion channel functioning; that is, the brain becomes more sensitive to glutamate as a means of compensating for prolonged depression by alcohol. It is believed that this increase in sensitivity to the excitatory transmitter glutamate may be responsible for alcohol withdrawal symptoms that occur when alcohol is no longer being consumed (Sanna & Harris, 1993).

Among many other functions, the hippocampus is responsible for memory formation. The effect of alcohol on NMDA receptors is known to interfere with long-term potentiation, a mechanism necessary for the formation of memories in the hippocampus. In addition, ethanol is known to prevent the formation of new neurons (neurogenesis) in the hippocampus. Both of these effects probably contribute to the effects of alcohol on memory, discussed later in this chapter (Tomberg, 2010).

The prefrontal cortex is responsible for many higher cognitive abilities including impulse control, attention, planning, and problem solving. The effects of alcohol are similar to the effects of brain damage to the prefrontal cortex and include impulsivity and impaired impulse control. The prefrontal cortex consists mostly of glutamatergic pyramidal projection neurons, which send axons throughout the rest of the brain, and inhibitory GABAergic interneurons, which suppress the activity of the pyramidal neurons. Considering the effects of alcohol on glutamatergic and GABAergic functioning, it is not surprising the alcohol can impair many cognitive processes (Tomberg, 2010).

Dopamine

These aforementioned and other changes in neural functioning can explain the effects of alcohol on specific areas of the CNS responsible for many of the behavioral effects of alcohol. The reinforcing effects of alcohol, like most reinforcing drugs, arise from increased activity in the mesolimbic dopamine system, specifically heighted dopamine release in the nucleus accumbens. Under normal conditions, the activity of mesolimbic dopamine neurons is inhibited by GABAergic interneurons synapsing on dopaminergic cell bodies within the ventral tegmental area (see panel B of Figure 12-1). These GABA interneurons are themselves innervated by GABAergic neurons projecting from the nucleus accumbens and ventral pallidum. When alcohol is consumed, nucleus accumbens and ventral pallidum neurons release increased quantities of GABA onto the inhibitory interneurons within the ventral tegmental area, and this decreases their activity. As a result, these interneurons release less GABA, thereby diminishing the inhibition of ventral tegmental dopaminergic neurons—enabling (in a roundabout way) an increase in firing and in the level of dopamine output in the nucleus accumbens (Tomberg, 2010). Glutamate activity likely also plays a role. The nucleus accumbens contains GABAergic medium spiny neurons, a special type of inhibitory cells that integrate the myriad of signals coming into the nucleus accumbens. These neurons receive glutamatergic input from the prefrontal cortex, amygdala, and hippocampus and send output to the nucleus accumbens and ventral pallidum. Ethanol's effects on GABAergic, glutamatergic, and dopaminergic cells converging in the nucleus accumbens are key to its reinforcing effects. Serotonin input is known to further increase activity in ventral tegmental area dopamine neurons (Tomberg, 2010).

ALCOHOL ANTAGONISTS

For thousands of years, people have been searching for a substance that would reverse the effects of alcohol. The ancient Greeks believed that the amethyst, a semiprecious stone, had this property, and the term *amethystics* has been used to describe these supposed agents.

In 1985, researchers at Hoffmann–La Roche reported that they had synthesized a substance called *RO 15-4513*, which seemed to be able to antagonize the effects of alcohol. Careful research has shown that the drug antagonizes only some of the effects of alcohol mediated by GABA (including self-administration; June et al., 1992), because it appears to be a competitive antagonist to alcohol at its allosteric binding site on $GABA_A$ receptors that contain the delta subunit (Hanchar et al., 2006; Wallner & Olson, 2008). There is little likelihood that RO 15-4513 could have any medical use. Although it blocks some of the effects of alcohol, it does not antagonize alcohol's lethal effects, so it cannot be used to treat alcohol overdose. In addition, RO 15-4513 may cause convulsions, making it unsuitable for treating alcoholism.

A common misconception is that coffee can sober someone up; systematic studies have found little evidence to support this belief. An early study suggested that caffeine might reverse some of the impairing effects of low levels of alcohol (less than 100 mg alcohol/100 ml blood) on driving, but could not do so at higher blood alcohol levels (Muskowitz & Burns, 1981). A more recent study examining the effect of 200 to 400 mg caffeine on impairments produced by alcohol (at about 80 mg/100 ml blood) found that caffeine was unable to alter a number of alcohol effects, including the subjective effects. These caffeine doses were able to cause a partial reversal of slowed braking speed caused by alcohol, but did not return braking speed to normal levels (Liguori & Robinson, 2001).

Because alcohol has so many effects on so many different sites within the body, it is unlikely that a single substance could antagonize all of its effects.

EFFECTS OF ALCOHOL

Effects on the Body

Alcohol in low and moderate doses causes dilation of capillaries in the skin. This is why individuals who drink heavily tend to have a flushed face. In addition, drinking alcohol creates a temporary sensation of warmth. A traditional medical use for alcohol was as a remedy for people exposed to cold. However, because alcohol dilates the capillaries, heat is lost from the skin more quickly and the body cools down faster, to the point where core temperature can become dangerously low in extreme cold.

By inhibiting antidiuretic hormone (ADH) secretion, alcohol causes increased urination and loss of water, though this occurs only while BAC is steady or falling.

EFFECTS ON HUMAN BEHAVIOR AND PERFORMANCE

Perhaps an indication of the cultural impact of inebriation is the vast number of synonyms for being drunk. In 1737, Benjamin Franklin compiled 228 terms commonly used for being drunk. The *American Thesaurus of Slang*, published in 1952, lists almost 900 such terms. Most of them suggest some sort of violence or damage, such as *smashed, hammered, crashed, pissed, bombed, loaded, plastered, tanked, paralyzed,* and *wiped out,* to cite just a few. Some terms are very old. *Soused,* for example, dates back to sixteenth-century England, and *cut* was used as long ago as 1770 (Levine, 1981).

What does it mean to be hammered or smashed? The body of literature on this subject, dating back to the time of Aristotle, is so vast that it is almost impossible to characterize it in this short space. Systematic observation of drinkers has shown that at BACs between 50 and 100 mg per 100 ml, people are more talkative, use a higher pitch of voice, and show mild excitement. At about 100 to 150 mg per 100 ml, subjects appear even more talkative and cheerful, and are often loud and boisterous; later, they become sleepy. At BACs above 150 mg per 100 ml, subjects frequently feel nauseous and may vomit. This phase is followed by lethargy and, in some cases, stupor. At doses between 200 and 290 mg per 100 ml, subjects may enter a stupor, experience a loss of understanding, memory blackout, and unconsciousness.

The problem with dose-related descriptions such as these is that there is such variability in the responses of individuals, depending on drinking history, environment, tolerance, and the rapidity of alcohol consumption, that they very seldom describe the behavior of any one individual on any single drinking occasion.

Subjective Effects

Many researchers report that alcohol causes a biphasic effect with regard to time and dose. At low doses and while blood levels are rising, alcohol has a stimulant effect, and people describe elation and euphoria; but at high doses and when the blood levels are falling, subjects report primarily feelings of sedation, anger, and depression (Babor, Berglas, Mendelson, Ellingboe, & Miller, 1983). With regard to aggressive behavior that sometimes ensues in people following high doses of alcohol, laboratory research using mice trained to self-administer alcohol has shown that heightened levels of aggression are due, at least in part, to GABA modulation in the dorsal raphe nuclei (Takahashi, Kwa, Debold, & Miczek, 2010).

Research has also indicated, however, that not everyone experiences the stimulation effect; some subjects experience only the sedating effects. Interestingly, those who describe stimulant-like effects also report a greater *drug liking* for alcohol and show more impairment on the digit symbol substitution test. It has been speculated that such individuals may be at greater risk for alcohol abuse (Holdstock & de Wit, 1998).

Perception

Alcohol has a detrimental effect on vision. It increases both absolute and difference thresholds, but usually only at high doses. A decrease in visual acuity, indicated by a lowering in the critical flicker fusion threshold, is caused by a BAC of about 70 mg per 100 ml. Decreases in peripheral vision have also been reported. Decreases in sensitivity to taste and smell occur at low doses, and a decrease in pain sensitivity is common at BACs above 80 to 100 mg per 100 ml. Changes in visual perception after acute alcohol consumption may be due to a decrease in lateral inhibition wherein an excited neuron reduces that activity of neighboring neurons (Johnston & Timney, 2008). This has the effect of accentuating the contrast between areas of high and low stimulation at edges and boarders. Lateral inhibition is an essential process used by many sensory organs to process incoming information.

Performance

Alcohol slows reaction time by about 10% at BACs of 80 to 100 mg per 100 ml, and large consistent deficits are evident with larger doses. Complex reaction-time tasks that require the subject to scan and integrate stimuli from several sources before responding show that, at lower doses, both the speed and the accuracy of performance decrease. Deficits are also seen in hand–eye coordination tasks, for example, in which the subject is required to maintain a marker over a moving target. PET analyses show that alcohol consumption decreases blood flow to the cerebellum, a region that controls voluntary movement and coordination and that contains $GABA_A$ receptors with the alcohol-sensitive delta

subunit (Volkow, Mullani, Gould, Adler, & Krajeswski, 1988). In general, the more complex the task, the greater the impairment seen at lower doses. Small deficits occur at doses as low as 10 to 20 mg per 100 ml.

Before the Breathalyzer, police used the *Romberg sway test* to detect impairment. The subject is asked to stand with eyes closed and feet together. BACs as low as 60 mg per 100 ml can cause a 40% decrease in steadiness as measured by the amount of swaying. This lack of steadiness makes it difficult for a person to stand on one foot with eyes closed. At higher BACs, the lack of steadiness degenerates into staggering and reeling. The increase in sway appears to be a result of the effect of alcohol on the sensitive organs of balance in the inner ear, which causes *nystagmus*, eye movements responsible for the sensation that the room is spinning around. Alcohol's effect on the cerebellum may also contribute to this effect. Lack of steadiness can also bring on nausea and vomiting (Money & Miles, 1974).

Many people have demonstrated the impairing effects of alcohol on many tasks, but these effects may be dependent upon the expectations and motivations of the individual. Vogel-Sprott (1992) has shown that, at low doses (less than 100 mg/100 ml blood), many response deficits will disappear if subjects are paid or provided with an incentive to overcome the effects of the drug. In addition, subjects who expect that the drug will have an effect are often more impaired than those who do not (Fillmore & Vogel-Sprott, 1998).

Memory

Alcohol is also known to have a detrimental effect on memory. Low and moderate levels of alcohol have been shown to affect attention, encoding, storage, and the retrieval of information, but the storage function seems to be more strongly affected (Birnbaum & Parker, 1977). Rising BACs in the range of 87 mg/100 ml do not increase errors in a short-term (2-minute delay) verbal memory task, but do impair the accuracy of long-term (20-minute delay) verbal memory. Accuracy in both short- and long-term visual memory is not affected by rising BACs, but errors increase during the declining phase of blood alcohol (Schweizer & Vogel-Sprott, 2008).

Working memory was tested by the memory scanning task. In this test, participants are shown an array of two, four, or six items (letters); they are later shown an item; and then they must indicate whether that item was or was not present in the original array. Alcohol at a BAC of 74 mg/100 ml has little effect on recall if two items were used, but alcohol at this dose lengthens reaction time and decreases accuracy when four and six items were tested (Grattan-Miscio & Vogel-Sprott, 2005).

In long-term alcohol abusers, PET analyses using 2-deoxy-2[^{18}F]fluoro-d-glucose show that deficits in verbal and visual memory, as well as attention, correspond with decreased functioning in the dorsolateral prefrontal cortex and the anterior cingulate cortex (Goldstein et al., 2004).

BLACKOUTS. Heavier drinking may also cause periods of amnesia or *blackouts* where people may be unable to remember events that occurred while they were intoxicated. Research indicates that individuals with a BAC of 310 mg per 100 ml blood or greater have a 0.50 or greater probability of experiencing an alcoholic blackout (Perry et al., 2006). There are two different varieties of blackout. The first type is called a *grayout* or a *fragmentary blackout* and is the most common form of alcohol amnesia. When a grayout occurs, the drinker is able to remember only bits and pieces of events that occurred while drinking. The missing memories usually return if the drinker is reminded of these events or if he or she returns to the place where they occurred. This shows that the problem is primarily one of retrieval—the memories were formed and stored in the brain, but the person has trouble accessing them later when the alcohol is gone. Grayouts are thought to result from dissociation (Overton, 1972).

En bloc blackouts are more serious but less frequent. In this type of blackout, the drinker is usually able to remember events of a drinking episode up to a particular time and then remembers nothing until another well-defined point in time, usually when he or she wakes up the next morning. All events that occurred during that block of time are not remembered. In fact, there is no evidence that these memories were ever put into long-term storage because they never return, even when the person is reminded. Interestingly, during the period when a blackout is happening, the drinker's behavior may appear to be perfectly normal. He or she can carry on a conversation and carry out many normal behaviors. They can recall what happened in the past, before they began drinking, but cannot remember what happened 20 minutes ago (Ryback, 1970). They are able to hold

things in short-term storage or working memory, but they are unable to form long-term memories.

Effects on Driving

Studies of the effects of alcohol on driving, in simulators and in real cars on closed tracks, have generally confirmed that alcohol begins to affect performance at about 50 to 80 mg per 100 ml (Mitchell, 1985; Starmer, 1990). At 80 mg alcohol per 100 ml blood, participants in a simulated driving study drove at higher average speeds and exhibited performance deficits, which increased the likelihood of collisions.

More recently, fMRI has been used to simultaneously scan the brains of people in a driving simulation task and assess the effects of alcohol on both driving and brain functioning. Initially, it is necessary to determine the normal patterns of activity and connectivity between different brain areas and establish critical networks that are activated in response to different driving tasks, and then examine the effect of alcohol on those functional networks. Calhoun and Pearlson (2012) have conducted and reviewed such studies and demonstrated that alcohol significantly disrupts most of the brain networks involved in driving in a dose-dependent manner, depending on the specific task involved. They conclude that acute alcohol impairs cognitive control through a decrease in cortical activation and in regions implicated in error monitoring, such as the anterior cingulate and inferior frontal gyrus.

These performance deficits correspond with decreased activation of the orbitofrontal cortex and certain motor regions of the brain (Calhoun, Pekar, & Pearlson, 2004). Unsurprisingly, it is clear that divided attention (i.e., using a cell phone or texting), when coupled with alcohol impairment, causes far more impairment than does alcohol alone (Harrison & Fillmore, 2011). The neural basis of this effect involved alcohol's influence on the hippocampus, anterior cingulate, and dorsolateral prefrontal cortex. These areas are associated with attentional processing and decision making. Consequently, intoxicated drivers are less able to orient and detect novel or sudden stimuli such as road obstacles while driving. The effect of alcohol on the hippocampus is also important as it processes visuospatial memory, which likely underpins the ability to remember the vehicle's spatial location on the road prior to the distracting events (Calhoun & Pearlson, 2012).

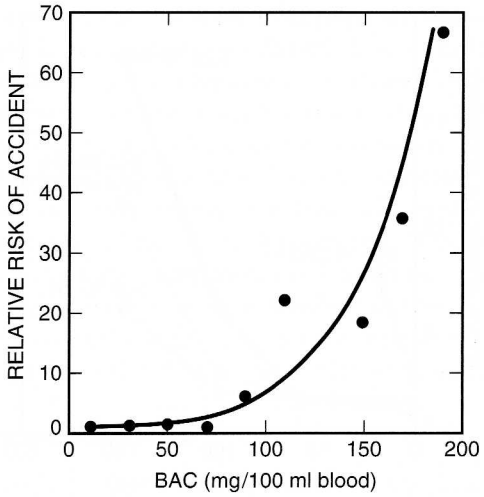

FIGURE 6-3 The relationship between BAC and the relative risk of being involved in a traffic accident. The relative risk of an accident with a BAC of 0.0 is 1.0. (Organization for Economic Cooperation and Development, 1978)

Figure 6-3 shows the relative probability of being responsible for a fatal crash at various BACs. The curve starts to rise between 50 and 100 mg per 100 ml. At 100 mg per 100 ml, the probability of being responsible for a fatal crash is seven times greater than if the BAC had been 0. After this point, the curve rises sharply. At a BAC of 200 mg per 100 ml, a driver is 100 times more likely to cause a fatal crash (Organization for Economic Cooperation and Development, 1978).

Statistics such as these establish the rationale for setting legal limits on BAC for driving. In most jurisdictions, the limit is between 80 and 100 mg per 100 ml of blood, the point at which the curve starts to rise sharply. It is important to remember, however, that these curves underestimate the risk for young inexperienced drivers, older drivers, and people unaccustomed to drinking. Their risk of being involved in an accident is considerably elevated even at BACs below the legal limit. Figure 6-4 shows similar curves for people of different ages (Organization for Economic Cooperation and Development, 1978).

Disinhibition and Behavior Control

One of the common behavioral effects of alcohol is *disinhibition*, a term that refers to the loss of restraint or an inability to withhold behavior under the influence of alcohol.

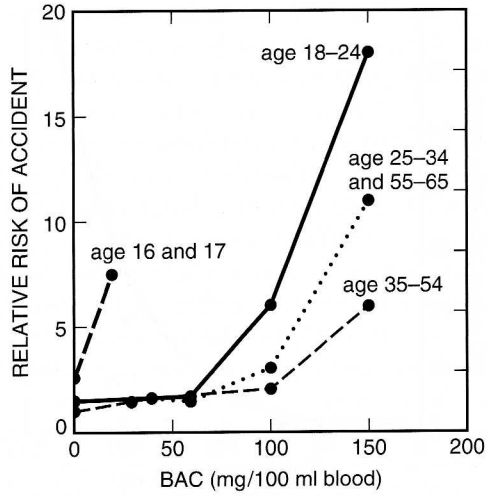

FIGURE 6-4 The relationship between BAC and the relative risk of being involved in a traffic accident for people of different age groups. The relative risk of an accident with a BAC of 0.0 is 1.0. (Organization for Economic Cooperation and Development, 1978)

Intoxication frequently causes disregard for personal risk, social norms, and long-term consequences in favor of short-term gratification. It is interesting that disinhibition may actually improve performance on tasks in which anxiety or conflict is interfering with behavior. In these cases, alcohol in low doses can actually be beneficial to performance.

Studies examining alcohol and behavioral control often use a *go–stop* task. In this task, a subject is required to make a response when a particular signal, the *go* signal, is presented but must withhold that response if the *go* signal is followed by a *stop* signal. Studies have shown that alcohol at moderate doses does not interfere with responding to the *go* signal, but it selectively interferes with the ability of the *stop* signal to inhibit behavior (Schweizer & Vogel-Sprott, 2008). Furthermore, fMRI studies of brain activity during these tasks show that alcohol weakens the connections between the frontal areas of the cortex and the striatum, a motor area of the brain (Vogel-Sprott, Easdon, Fillmore, Finn, & Justus, 2001).

Though disinhibition is usually associated with alcohol's physiological effects, it has been suggested that it may be equally attributed to socially conditioned expectations about alcohol consumption. In a recent study, when participants were exposed to alcohol-related images, they exhibited a tendency to associate images with provocative terms rather than neutral ones. This suggests that even alcohol-related stimuli can cause disinhibition without alcohol being consumed (Freeman, Friedman, Bartholow, & Wulfert, 2010).

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Conditioned Behavior

For various reasons, few studies have been done on the effects of alcohol on positively reinforced behavior, but those that have been done show that the effects are dose dependent. On both fixed interval (FI) and fixed ratio (FR) schedules, alcohol increases the rate of responding at low doses and decreases the rate at higher doses.

The effect of alcohol on punished responding is similar to that of the barbiturates and benzodiazepines (see Chapter 7) but not quite as striking. In an early experiment, Conger (1951) trained rats to run down a runway for food, but gave their paws a shock when they began to eat. He adjusted food deprivation and shock levels until the rats were willing to run partway down the runway but would not touch the food. He found that alcohol would cause the rats to approach and eat the food immediately, but rats given a placebo required many trials. Since then, several researchers have found that ethanol will increase response rates that are suppressed by an administered shock. This result is similar to the finding in humans that alcohol tends to loosen inhibitions and therefore reduces the control of consequences on behavior.

DISCRIMINATIVE STIMULUS PROPERTIES

Animals can be trained very easily to discriminate alcohol from saline. Donald Overton showed that at a dose of 3,000 mg/kg, rats reach criterion discrimination performance in just three trials. Of the drugs tested, the only drugs that were discriminated more quickly were phenobarbital and pentobarbital (Overton, 1982; Overton & Batta, 1977).

Using the electrified T-maze, Overton found that rats trained to discriminate alcohol from saline generalized the alcohol response when given a barbiturate and vice versa, indicating that the two drugs produce

a similar subjective state. However, in a later series of experiments, he was able to train rats to discriminate between the two, showing that although the effects of barbiturates and alcohol are similar, they can be discriminated. It has been found that the alcohol response is not generalized to chlorpromazine, amphetamine, or atropine (Barry & Kubina, 1972) though it can be generalized to several anesthetics.

The stimulus properties of alcohol can be blocked by serotonin 5-HT_3 receptor blockers but not by haloperidol, a dopamine D_2 blocker—an indication that serotonin rather than dopamine may mediate the subjective effects of alcohol (Grant & Barrett, 1991). The discriminative effects of alcohol can be blocked by mu-selective doses of the opioid receptor blocker naltrexone, showing that the opioid system is also involved in the subjective effects of ethanol. Alcohol is known to increase the release of endogenous opioids (Platt & Bano, 2011).

More recent research has shown that the alcohol stimulus is complex and made up of several elements shared with other drugs. Porcu and Grant (2004) used a three-choice discriminative task to separate these elements. They trained rats to discriminate between water, ethanol, and the benzodiazepine midazolam (a positive $GABA_A$ modulator). Because ethanol is also a positive $GABA_A$ modulator, this forced the rats to discriminate ethanol on the basis of some other property. In this situation, the alcohol cue generalized to dizocilpine, an NMDA receptor blocker, showing that the effects of ethanol on both GABA and NMDA glutamate receptors have separate stimulus effects that can be differentiated experimentally.

TOLERANCE

Acute Tolerance

Several studies have shown that many of the effects of alcohol are more pronounced while the BAC is rising than later when the BAC is falling. The phenomenon of acute tolerance, when tolerance develops during a single administration, is illustrated in Figure 3-1. In the first study of this type, done many years ago, it was shown that while the BAC was rising, subjects first appeared intoxicated at 150 mg per 100 ml, but while the BAC was falling, they appeared sober at 200 mg per 100 ml (Mirsky, Piker, Rosebaum, & Lederer, 1945). Many effects of alcohol also show acute tolerance, but some do not. Schweizer and Vogel-Sprott (2008) found that the speed of cognitive performance usually recovers from impairment to drug-free levels during declining BACs, whereas alcohol-increased errors fail to diminish.

Acute tolerance of alcohol effects on cognitive functioning vary depending on many factors. Some of these include dose and prior alcohol exposure (Hiltunen, 1997). A genetic component has been implicated in acute tolerance as well. Hu and colleagues (2008) isolated several possible genes in mice that may be responsible for the similar effects of acute tolerance in humans.

Chronic Tolerance

Chronic tolerance to alcohol appears to develop fairly rapidly in both nonhumans and humans. The extent and speed of observed tolerance depends on the species studied and the effect measured. Maximal tolerance develops in a few weeks in humans and reaches a point at which dose increases of 30–50% are required to attain similar effects. Tolerance disappears in rats after 2 or 3 weeks of abstinence but develops again more quickly with repeated exposure (Kalant, LeBlanc, & Gibbins, 1971).

Metabolic Tolerance

One effect of heavy drinking is the stimulation of both alcohol dehydrogenase, the major enzyme responsible for the breakdown of alcohol, and the MEOS, a secondary pathway for ethanol metabolism. As described in the section on Absorption, light to moderate drinkers are able to metabolize alcohol somewhat faster than abstainers (Goldberg, 1943; Whitfield & Martin, 1994). Also, it appears that metabolic tolerance develops over time in adult rats, but not in adolescent rats (Broadwater, Varlinskaya, & Spear, 2011). It is unknown whether this difference also exists in adolescent and adult humans.

Behavioral Tolerance

Repeated exposure and practice seem to be important in the development of tolerance to the behavioral effects of alcohol. In one experiment, a group of rats was given alcohol and placed on a treadmill. The rats quickly developed tolerance to the disruptive locomotor effects of the drug, presumably due to practice. Those given a similar amount of alcohol without the treadmill sessions did not

show any tolerance when tested on the treadmill later under the influence of alcohol (Wenger, Tiffany, Bombardier, Nicoins, & Woods, 1981).

Tolerance also depends on expectancy. In one experiment, two groups of participants received equal doses of alcohol, either in the familiar form of beer, or in an unfamiliar drink (a blue peppermint mixture). Participants who received the alcohol in the unfamiliar drink showed poorer performance on cognitive and motor tasks and rated themselves as more intoxicated than participants who received beer (Remington, Roberts, & Glautier, 1997).

It has been suggested that voltage-gated calcium and potassium channels may be partly responsible for behavioral tolerance. Mice that have had the genes for these ion channels *knocked out* through experimental manipulation develop much more rapid tolerance at the cellular and behavioral levels than mice with active channels. It is apparent that the action of ethanol on calcium and voltage-gated potassium channels has a direct effect on behavior, though the mechanism is not clear (Martin et al., 2008).

WITHDRAWAL

As with most of the depressant drugs, chronic consumption of alcohol can cause withdrawal symptoms. Although the distinction may not always be appropriate, it is customary to think of two separate stages of alcohol withdrawal: (a) the early minor syndrome and (b) the late major syndrome, also known as *delirium tremens* or the *DTs*. The early minor symptoms usually appear about 8 to 12 hours after the end of a drinking bout, although many aspects of withdrawal may be seen during the latter part of long drinking sessions even while the drinking is still going on. Withdrawal starts in the form of agitation and tremors; other symptoms, such as muscle cramps, vomiting, nausea, sweating, vivid dreaming, and irregular heartbeat, may also be seen. This stage is usually over within 48 hours.

Studies of patients admitted to the ER with alcohol withdrawal syndrome indicate a 2% mortality rate overall and an 8% mortality rate for those patients who develop delirium (Ferguson, Suelzer, Eckert, Zhou, & Dittus, 1996). Fewer than 5% of patients hospitalized for alcohol withdrawal go on to show the late major withdrawal symptoms. After 2 days of the minor symptoms, patients show increasing agitation, disorientation, confusion, and hallucinations. Seizures may also occur (Wolfe & Victor, 1972). These major symptoms may last as long as 7 to 10 days. Alcohol withdrawal hallucinations do not usually take the form of the proverbial pink elephant. They frequently involve smaller animals, such as rats, bats, or insects, and can be quite terrifying.

In general, the most effective treatment of alcohol withdrawal is a combination of supportive care and the administration of another depressant drug such as diazepam, which suppresses the withdrawal symptoms and has a long duration of action. Other specific symptoms may also be treated with other drugs; for example, hallucinations can be controlled with haloperidol, an antipsychotic. Effective supportive care consists of measures such as reducing sensory stimulation by placing the patient in a dimly lit, quiet room; providing adequate food and water to prevent dehydration; keeping the patient warm and comfortable; and providing reassurance (Naranjo & Sellers, 1986).

SELF-ADMINISTRATION IN NONHUMANS

Oral Self-Administration

When alcohol is freely available to rats and monkeys, they will drink the alcohol but not in quantities sufficient to cause obvious intoxication or physical dependence. This type of drinking resembles typical human drinking patterns, but the thrust of this research has been to provide a model of human alcoholism. Because alcoholics tend to consume much more alcohol than these moderate amounts, there has been considerable research over the years to find what factors can cause this consumption to increase. Research using oral administration has been hampered because alcohol has a disagreeable taste that most nonhuman species prefer to avoid, and the effects on the CNS are somewhat delayed because of slow absorption from the digestive system (Meisch, 1977).

One way to increase intake is to subject the animal to a period of forced consumption when its only source of food or water is laced with alcohol. After a rat has been forced to consume the alcohol, its voluntary intake may increase. Depriving the animal of food or water will also induce it to consume higher levels of alcohol. Intake will

sometimes remain high even after the food or water is returned (see Chapter 5). Other induction methods include putting the alcohol in water sweetened by sucrose and then *fading* the sucrose and delivering single small food pellets at regular intervals.

The animal will learn to press a lever on a reinforcement schedule for access to oral alcohol. Although some reports claim that food deprivation and other induction procedures are not necessary, they are often used.

The genetic basis for alcohol use has been studied by breeding rat and mice strains that will either prefer or avoid the free consumption of alcohol. This research, however, presents problems because it is not clear that the behavior system being selected has anything to do with alcoholism. For example, it may be that oral consumption is normally suppressed by a learned aversion to alcohol, a phenomenon called *conditioned taste aversion* (CTA). By selectively breeding alcohol-preferring rats, you may be selecting rats that are unable to learn the CTA, rather than ones who have a genetic disorder similar to alcoholism in humans (Green & Grahame, 2008).

Intravenous Self-Administration

Induction procedures are generally not necessary when alcohol is administered through a cannula implanted in the bloodstream. Providing alcohol this way avoids the issues of bad taste, CTA, and slow CNS effects, and most mice and monkeys rapidly learn to self-administer. Rats, however, are difficult to train to self-administer alcohol intravenously, but do readily learn to press a lever to receive access to water containing alcohol in various concentrations which they can drink.

When alcohol infusions are freely available, the pattern of self-administration is somewhat erratic. Periods of high-level intake are followed by self-imposed abstinence lasting 2 to 4 days, when withdrawal symptoms may occur. These periods do not seem to follow any regular pattern. (Compare this with stimulants such as cocaine; see Figure 10-6). Figure 5-2 (bottom panel) shows the intake of a rhesus monkey pressing a lever for intravenous alcohol over a period of 90 days in the laboratory of Jim Woods and his colleagues (Griffiths et al., 1980). The similarity of this pattern to human alcohol intake has already been noted.

SELF-ADMINISTRATION IN HUMANS

Laboratory Studies

In the laboratory, the pattern of alcohol self-administration is fairly consistent when alcohol is freely available. Alcohol is consumed at high levels for several days. It is then followed by a self-imposed period of low consumption lasting 2 or 3 days. During this time, withdrawal symptoms may appear. Figure 5-2 (top panel) shows the drinking pattern of alcoholic volunteers who worked on an operant schedule of button pushing to earn drinks. This pattern is very similar to that of a rhesus monkey under similar conditions, and to the typical pattern of many chronic alcoholics under natural conditions (Griffiths et al., 1980).

Factors That Affect Consumption

CULTURE. Cross-cultural studies in numerous societies in which alcohol is consumed have revealed some interesting patterns that appear to be consistent across cultures, including our own. Alcohol consumption is generally a male activity that is practiced socially outside the home among peer groups and not in the company of family members or people of higher status. Drinking is generally more acceptable among those who engage in physical labor and must grapple with the environment than among individuals who are charged with preserving tradition, such as priests, mothers, and judges (Robinson, 1977).

But differences also exist—among individuals and cultures, many drinking patterns have been identified. The spree drinker, common in Finland, binges occasionally but stays relatively sober otherwise. In France, on the other hand, it is more common for individuals to consume a fixed amount of alcohol every day steadily over the course of the day and exhibit few symptoms of intoxication. Such differences in national drinking patterns do not seem to influence certain consequences of consumption, such as rate of alcoholism or alcohol-related diseases. However, the difference may be significant when acute intoxication is important; for example, one beer a day may not ever cause a traffic accident, but the same quantity of beer, if consumed on one occasion every 2 weeks, could easily be responsible for traffic accidents.

GENDER. In a survey of nearly 300 undergraduate students, men reported a mean of 7.27 drinking occasions per month during which they consumed an average of 6.82 drinks per occasion. Woman reported a mean of 5.77 drinking occasions per month and an average of 5.05 alcoholic beverages per occasion (Balodis, Potenza, & Olmstead, 2009). Although heavy drinkers are more likely to be male, this fact does not mean that women reach a lower level of intoxication than men. Studies have shown that women do consume less alcohol than men; however, when adjustments are made for differences in body size and the ability to absorb alcohol, it turns out that women social drinkers achieve the same BACs as men (McKim & Quinlan, 1991; Vogel-Sprott, 1984).

AGE. A number of studies have shown that, although people drink just as frequently as they age, they tend to drink less on each occasion (Vogel-Sprott, 1984), so their total consumption declines. Unlike the difference in consumption between genders, this age-related decline in consumption per occasion cannot be explained by changes in body composition with age (McKim & Quinlan, 1991).

ALCOHOLISM

When the social reform movement of the nineteenth century was campaigning for better treatment of people who drank too much, it adopted the position that excessive drinking was a disease. Previously, alcohol intoxication was known by such terms as *inebriety* or *intemperance*, but more medical-sounding terms were developed, including *alcoholism*, *dipsomania*, and *narcomania*. *Alcoholism* survived and is now used widely (Barrows & Room, 1991). It is, however, not used by the current *DSM*. The *DSM-IV-TR* (2000) defines substance dependence and substance abuse using established criteria listed in Chapter 5 (see Box 5-1). These are the same criteria no matter which substance is being discussed. If the substance is alcohol, the diagnosis would be "substance abuse or dependence of the alcohol type" not "alcoholism."

As discussed in Chapter 5, alcoholism was the first form of drug addiction accepted as a disease, and theories of alcoholism have had a considerable influence on how we understand addiction in general. Also, the Alcoholics Anonymous movement has adopted and widely endorses the original disease theory of alcoholism that was proposed by E. M. Jellinek in the 1950s and 1960s.

Jellinek's (1960) theory was published in his book *The Disease Concept of Alcoholism*. Jellinek was associated with the *Alcoholics Anonymous* movement, which, along with Jellinek's arguments, was effective in convincing both the American Medical Association and the World Health Organization to declare alcoholism a disease. One of the more important assumptions of this disease theory is that alcoholism is not caused by alcohol. Alcoholism is a genetic disease, and people are alcoholics from the time they are born. Everyone, both alcoholic and nonalcoholic, starts drinking in the same way, in a moderate, social manner. But there are some who progress to drink more and more heavily, and, eventually, they enter the *prodromal phase* of alcoholism, which is characterized by frequent blackouts. Many such people are not *alcoholics*. They are *problem drinkers* who either stay that way or eventually stop drinking. Some individuals progress to become *gamma alcoholics* (Jellinek's term). The change from being a problem drinker to a gamma alcoholic is marked by two symptoms: (a) a loss of control over drinking, and (b) physical dependence indicated by high levels of tolerance and withdrawal symptoms such as seizures, hallucinations, and the delirium tremens. It is worth noting that the distinction between problem drinkers and alcoholics is the presence or absence of physical dependence and loss of control, not the amount consumed. Problem drinkers may actually consume more than alcoholics, but they are not considered alcoholics, and they do not have the disease. Any research on the disease of alcoholism, therefore, must be done on alcoholics, not on problem drinkers. This distinction is responsible for many arguments over data between supporters and opponents of the disease model.

Genetics of Alcoholism

Jellinek's insistence that alcoholism is a genetic disease stimulated a great deal of research in the hope that the nature of the disease could be more precisely defined. Evidence is clear that the risk of becoming an alcoholic is increased as much as fourfold if a close relative (mother, father, or sibling) is an alcoholic. It is known that the amount of drinking of identical twins (who are, genetically, clones) is more similar than the drinking behavior of fraternal twins (who have the same genetic similarity

as normal siblings). Thus, the closer the genetic makeup, the more similar the drinking pattern. It is clear from years of research that genetic factors can explain about half of the variance in vulnerabilities leading to heavy drinking and associated problems (Li, Hewitt, & Grant, 2004; Schuckit, 1992, 2009).

There appear to be four characteristics under genetic control that contribute to such vulnerabilities: (a) a flushing response to alcohol; (b) a low level of response to alcohol; (c) personality characteristics that include impulsivity, sensation seeking, and neuronal and behavioral disinhibition; and (d) psychiatric symptoms. It is clear that there is no single alcoholism gene; however, genome linkage studies have identified several chromosome regions that are associated with each of these four factors. Genes encoding enzymes associated with the metabolism of alcohol are the most well-established genes that have polymorphisms associated with alcohol dependence (Kimura & Higuchi, 2011). For example, the flushing response is a result of a genetically controlled inability to metabolize acetaldehyde.

While genetics clearly plays a major role, additional factors cannot be neglected, as a person with an identical twin who is an alcoholic has only a 60% chance of being alcoholic. Genetics controls physiological factors including aspects of body chemistry, personality, and brain function that increase the probability that a person will drink in an alcoholic manner in a particular environment. A variety of genetic susceptibilities to alcohol may cause problems only in particular environments. The right combination of environment and genetics is necessary to make a person drink in an alcoholic manner.

FHP Versus FHN

One method that could be useful in understanding the nature of the disease of alcoholism might be to compare alcoholics with nonalcoholics on a number of measures; any consistent difference in the biochemistry, personality, or response to alcohol could give a clue as to the nature of alcoholism. A problem with this approach is that any differences found might be caused by the alcohol consumed, not the alcoholism. One widely used strategy to avoid this difficulty is to compare people who are likely to become alcoholics with those less likely, before they start drinking, and to note the differences (remember that, according to Jellinek's theory, an alcoholic is an alcoholic before he or she starts drinking). We know that people who come from families in which there is a history of alcohol problems (*family history positive* [FHP]) are at a greater risk of becoming alcoholic than those who have a family history without alcohol problems (*family history negative* [FHN]). One interesting line of research has attempted to compare high-risk (FHP) and low-risk (FHN) individuals to see whether it is possible to detect differences in these groups that might be able to identify potential alcoholics or shed some light on what makes people drink excessively and become alcoholics.

Although early studies were encouraging, there appear to be few consistent differences between FHP and FHN individuals in terms of pharmacokinetics and metabolism of alcohol, and no clear-cut differences have been established in cognitive and neuropsychological measures of personality (Searles, 1988) or in alcohol preference, alcohol-liking scores, BACs, or alcohol-induced impairment (de Wit & McCracken, 1990).

Some studies, however, have detected differences between FHN and FHP subjects in electroencephalographic responses, and in some experiments, FHP subjects may show a greater sensitivity to the subjective and motor-impairing effects of alcohol than FHN subjects (Porjesz & Begleiter, 1987; Schuckit, 1987, 1992). As well, researchers using fMRI have demonstrated that FHP individuals differ in their sensitivity of the reward circuit (Andrews et al., 2011). In a meta-analysis, Quinn and Fromme (2011) found confirming evidence that the overall subjective effect of alcohol is less in FHP males than FHN males demonstrating the "low level of response" characteristic proposed by Schuckit (2009).

Loss of Control

According to the disease model, one of the defining characteristics of alcoholism is *loss of control*. It is assumed that exposure to even one or two drinks of alcohol will cause, in the alcoholic, an uncontrollable craving to drink more and more. For this reason, it was considered that someone who was an alcoholic could never be a moderate or social drinker, and therefore the only therapy for alcoholism must be total and complete abstention from alcohol, forever.

Since the time it was proposed, the loss-of-control theory has never received significant experimental

support. In fact, most research has disconfirmed the basic notion (Finagrette, 1988). A number of studies in England (Davis, 1962) and the United States (Armor, Polach, & Stambul, 1978) have found many cases of alcoholics who have reverted from excess drinking to moderate social drinking and have maintained that level for years. These studies caused a storm of controversy, and many alcoholism experts denounced them as unscientific and attacked them on various grounds.

Some have argued that most of these studies were done with problem drinkers, not with populations of gamma alcoholics, as defined by other characteristics such as physical dependence. In addition, it has been argued that most studies showing that alcoholics can return to controlled drinking do not allow enough time to detect whether controlled drinking is possible (Maltzman, 1994).

In addition to the research with alcoholics in treatment, laboratory studies have repeatedly shown that alcoholics are perfectly capable of moderating their alcohol intake in response to such manipulations as increased cost, and they virtually never lose control (Mello & Mendelson, 1972). Such laboratory studies are also challenged on the grounds that the laboratory is too artificial and irrelevant to alcohol use in a natural setting.

As Schuckit (2009) suggested, it is also likely that lack of impulse control is a major factor under genetic control in the development of alcoholism.Rogers, Moeller, Swann, and Clark (2010) demonstrated recently that many individuals who develop alcohol dependence also have neurological problems which lead to poor impulse–behavior control. For people with such problems, it is probably best that they avoid even social drinking, but there is little evidence that *loss of control* is the inevitable consequence of taking even one drink.

Related to the concept of loss of control is the phenomenon of reinstatement or priming (see Chapter 5). Reinstatement is when a learned drug self-administration response is extinguished to the point where all responding has stopped, and administration of a noncontingent dose of the drug causes the drug self-administration response to resume. de Wit and Chutuape (1993) have shown that social drinkers are much more likely to choose an alcoholic drink and report an increased craving for alcohol after they have been given a dose of alcohol. This study was later replicated (Chutuape, Mitchell, & de Wit, 1994), but a later study was able to show that a drink of alcohol increased only desire for alcohol; it did not increase choice of alcohol among social drinkers (Kirk & de Wit, 2000). Reinstatement has also been demonstrated in laboratory animals. While reinstatement looks like loss of control, it is not clear whether it is analogous to what Jellinek's theory would call loss of control. Reinstatement is a fairly universal phenomenon that can be seen in many species with many different reinforcers, while loss of control as described by Jellinek is seen only for alcohol and only in alcoholics.

HARMFUL EFFECTS OF AN ACUTE ADMINISTRATION

On July 23, 2011, English singer/songwriter Amy Winehouse was found dead in her London home. The coroner's report, released in late October, ruled that her death had been due to alcohol poisoning. It stated that Winehouse's blood alcohol content was 416 mg per 100 ml blood at the time of her death (*The Guardian*, 2011). There was no evidence of any other drug present in the singer's body. Unfortunately, alcohol-related deaths are not uncommon. Thousands of people are admitted to hospital, and hundreds die each year from acute alcohol poisoning. University students appear to be a particularly vulnerable population, perhaps largely because of a drinking culture that encourages binge drinking at institutes of higher learning. Between 1999 and 2008 in the United States, hospitalization rates for alcohol overdoses, in young adults alone, increased 25% reaching 29,412 cases in 2008 (Oster-Aaland, Lewis, Neighbors, Vangsness, & Larimer, 2009; White, Hingson, Pan, & Yi, 2011).

A single dose of alcohol, if large enough, can be lethal. A BAC of about 300 to 400 mg per 100 ml of blood will usually cause loss of consciousness. In a study of alcohol poisonings, Kaye and Haag (1957) reported that without therapeutic intervention, people whose BACs reached 500 mg per 100 ml of blood died within an hour or two. The world record for high BAC is thought to be 1,500 mg per 100 ml, reported in a 30-year-old man whose life was saved by vigorous medical intervention. Later, he reported that he had drunk 4.23 liters of beer and an undetermined number of bottles of liquor in the space of 3 hours (O'Neil, Tipton, Prichard, & Quinlan, 1984).

As with most depressant drugs, death by alcohol usually results from respiratory failure. Alcohol is a toxic substance, and the lethal dose is uncomfortably close to

the usual social dose. A 150-pound male would have to drink 7.5 ounces of liquor to have a BAC of 150 mg per 100 ml of blood. These numbers are at the upper levels of an acceptable social high. Around 25 ounces of liquor would produce a BAC of 500 mg per 100 ml of blood, probably a lethal dose for most people. Thus, the therapeutic index for alcohol is about 3.3 (25 ÷ 7.5).

Fortunately, alcohol has built-in safety features: Vomiting or unconsciousness will usually occur before death. People who die from alcohol poisoning usually have to drink a large amount quickly and in high concentrations in order to get a lethal dose into their bodies before they lose consciousness.

Hangover

The problem of how to avoid a hangover from alcohol has occupied some of history's best minds, as this passage from Plato's *The Dialogues* illustrates:

> They were about to commence drinking, when Pausanias said, "And now, my friends, how can we drink with the least injury to ourselves?" I can assure you that I feel severely the effect of yesterday's potations, and must have time to recover; and I suspect that most of you are in the same predicament, for you were of the party yesterday. Consider then: "How can the drinking be made easiest?" (Symposium 176a–b, translation in Jowett, 1931)

Like the ancient Greeks, most drinkers have, at some time, suffered the next day for having had too much the night before. There are several explanations for a hangover. They suggest that hangover results from alcohol-produced effects, such as low blood sugar levels, dehydration, and irritation of the lining of the digestive system. There is no doubt that most effects of alcohol contribute to discomfort the next day, but it is probably best to think of a hangover as a miniature withdrawal from alcohol—a rebound excitation of an alcohol-depressed nervous system.

For most drinkers, hangovers are not physiologically serious, but for people with epilepsy, heart disease, or diabetes, hangovers can have serious medical consequences (Gauvin, Cheng, & Holloway, 1993).

The Greeks never did answer Pausanias's question "How can the drinking be made easiest?" apart from concluding that "drinking deep is a bad practice." But over the centuries, a number of cures have been suggested, including eating a spoonful of sugar or drinking lots of water. To the extent that a hangover can be thought of as a withdrawal from alcohol, one cure is to take a "hair of the dog that bit you." Consuming more alcohol relieves the hangover by depressing this rebound excitability in the same way that other depressant drugs are used to treat withdrawal. A small amount could be effective, but if too much is consumed it will only postpone the withdrawal.

Alcohol-Induced Behavior

Apart from the self-inflicted physical harm that can be done by an acute administration of alcohol, the drug can be responsible for changes in behavior that cause untold social, psychological, financial, and physical harm to the drinker and others. It is not possible to catalog all the manifestations of harm, but most people have been made aware of them in some form. They include accidents caused while drunk or hung over not only while driving but also in industry and at home (Gutjahr, Gmel, & Rehm, 2001), crimes committed under the influence of alcohol, and damage done to families and social relationships. All these effects are difficult to quantify, and some may not be a direct result of alcohol. They are nonetheless real and must be included in any assessment of the harmful effects of alcohol.

Reproduction

A well-known quote from Shakespeare's *Macbeth* states that drink "provokes the desire, but takes away the performance" in matters sexual. The bard's analysis is essentially correct. Acute alcohol consumption may increase interest by diminishing inhibitions, but, in higher doses, it reduces sexual arousal in both males and females. In males, lower doses (BAC less than 100 mg/100 ml) may increase the duration of erections and thus provide increased opportunities for fulfillment of the partner. This fact may explain why alcohol is often perceived as enhancing sexual performance (Mello, 1978; Rubin & Henson, 1976). As well, it has been found that males experience a decreased sensitivity to female social cues and that they are less able to differentiate between friendliness and sexual interest (Farris, Treat, & Viken, 2010). In females, higher doses of alcohol (100 mg/100 ml blood) reduced genital arousal, but moderate levels (80 mg/100 ml blood) did not (George et al., 2011).

One study using rats showed that increasing doses of alcohol caused increasing disruptions of copulation of male rats with receptive females. In addition, low doses of alcohol that disrupted copulation with receptive females caused male rats to attempt to copulate with unreceptive females, something they would not normally attempt. These findings support the speculation that low doses of alcohol adversely affect uninhibited sexual performance but can stimulate sexual behavior that is normally inhibited (Pfaus & Pinel, 1988).

HARMFUL EFFECTS OF CHRONIC CONSUMPTION

The Liver

Prolonged drinking of alcohol damages the liver. The damage usually starts with a buildup of fatty acids in the liver cells, or *steatosis*. Alcoholics frequently contract alcoholic hepatitis, which usually develops into *cirrhosis*, which means *scarring*. The liver cells swell and experience cellular hardening, membrane damage, and eventually cell death. Once the liver becomes filled with scar tissue and is no longer able to function, the condition is often fatal, especially if alcohol consumption is not stopped.

Cirrhosis occurs in approximately 8% of chronic alcoholics; among nonalcoholics, the condition affects only 1%. Alcohol consumption accounts for somewhere between 40 and 90% of liver cirrhosis deaths in the United States. Generally, alcohol consumption of more than five drinks a day for at least 5 years is necessary for the development of cirrhosis.

The Nervous System

Some alcoholics and heavy drinkers may show a cluster of symptoms that includes a loss of memory for past events, an inability to remember new material, and disorientation and confusion. These symptoms are collectively known as *Korsakoff's psychosis, Wernicke's disease,* or *Wernicke–Korsakoff syndrome*. They are a result of damage in certain parts of the brain first noted by Carl Wernicke. The condition seems to result from deficiency of thiamin (vitamin B1), which is common among many alcoholics (Victor, Adams, & Collins, 1971). Many of the conditions suffered by alcoholics can be traced to vitamin deficiencies, chiefly because people who drink large quantities of alcohol do not normally have a balanced diet. In addition, alcohol can damage the digestive system and interfere with the normal absorption of some nutrients.

The Wernicke–Korsakoff syndrome is not the only neurological damage associated with heavy drinking. A number of other disorders of both the central and peripheral nervous systems are attributable, either directly or indirectly, to excessive alcohol use and do not appear to involve dietary deficiencies. These include epilepsy, cerebellar syndrome, and alcoholic dementia (Marsden, 1977). In alcoholic dementia, patients show a gradual progressive decline in cognitive functions involving much more than just memory. Alcohol-related dementia probably accounts for more than 10% of all cases of dementia (Gupta & Warner, 2008). It is diagnosed after alcohol consumption of 35 drinks per week for males and 28 for females for more than 5 years and seems to be associated with binge drinking.

MRI analysis of chronic alcohol users shows decreases in cerebral blood flow (Demir, Ulug, Lay Ergun, & Erbas, 2002) and widespread reduction in brain tissue, including loss of glial cells and neurons in the prefrontal cortex, hypothalamus, cerebellum, and hippocampus (Brust, 2010; Gazdzinski, Durazzo, & Meyerhoff, 2005; Mann et al., 2001). Neurodegeneration occurs primarily during intoxication, due to the increased oxidative stress and proinflammatory proteins, which are neurotoxic (Crews & Nixon, 2009). It may also arise from glutamate excitotoxicity, in which high levels of glutamate lead to cell death. Alcohol itself can protect the brain from glutamate excitotoxicity through blockade of NMDA receptors and glutamate activity, but frequent alcohol use causes an upregulation of glutamate transmission and excessive glutamine release during hangover and withdrawal. These changes are partially reversed with prolonged abstinence from alcohol, with the greatest increases in brain volume noted within the first month of withdrawal (Gazdzinski et al., 2005).

You do not have to drink heavily for years to show evidence of neurotoxic effects of alcohol. In a study of drinking by university students (18 to 20 years old), students whose intake was characterized by sporadic consumption of large quantities of alcohol in short periods (binge drinking) had problems on a battery of memory tests, showing a deficit in declarative verbal memory. Such findings are characteristic of damage to the hippocampus (Parada et al., 2011).

Cancer

The use of alcohol is causally related to cancers of the mouth, throat, colon, and liver—parts of the body that are directly exposed to high alcohol concentrations and susceptible to alcohol damage (Boffetta & Hashibe, 2006). This may be a result of the acetaldehyde molecule, which is a first metabolite of alcohol and is thought to have a *genotoxic* effect. That is, it can cause damage to the genetic code, which in turn may lead to cancer. The role of alcohol as a solvent for tobacco carcinogens, and the *reactive oxygen species*, which are chemically reactive byproducts of alcohol metabolism, may also contribute to alcohol's carcinogenic effects.

There is conflicting evidence relating alcohol consumption with breast cancer in women. In general, there appears to be a weak association, but alcohol does appear to increase breast cancer incidence in populations that are otherwise at risk, such as those who have a family history of breast cancer or those postmenopausal women taking estrogen replacement therapy (Gunzerath, Faden, Zakhari, & Warren, 2004). Increased estrogen and androgen levels in women who consume alcohol appear to be significant factors in the development of breast cancer. However, alcohol cannot be exclusively blamed in many cases, as genetic predisposition, dietary choices, and lifestyle habits all contribute to the development of any type of cancer (Singletary & Gapstur, 2001).

Reproduction

In males, chronic alcohol consumption is known to cause impotence, shrinking of the testicles, and a loss of sexual interest. Although there have been few studies of the effects of chronic alcohol consumption in females, there is evidence that it can cause menstrual dysfunctions, such as amenorrhea, dysmenorrhea, and premenstrual discomfort (Mello, 1987).

Since ancient times, people believed that alcohol might be teratogenic (responsible for birth defects). In ancient Carthage, drinking on wedding days was forbidden; it was believed that it might cause an abnormal child to be born (Jones & Smith, 1975). Aristotle warned against drinking during pregnancy, and later, at the time of the gin epidemic in England, it was noted that there was an increase in infant deaths. Similar effects associated with alcohol consumption have been reported in the medical literature, and the extent of the problem is now fully appreciated. It is now recognized that the use of alcohol during pregnancy can harm the developing fetus and may result in a number of behavioral, anatomical, and physiological irregularities, which are known as *fetal alcohol syndrome* (FAS), in their more severe form, or *fetal alcohol effects* (FAE), *alcohol-related birth defects* (ARBD), or *alcohol-related neurobehavioral disorder* (ARND) if only a few behavioral or neurological symptoms are present. In 1983, the term *fetal alcohol spectrum disorder* (FASD) came into use as an umbrella term identifying the wide range of outcomes from prenatal alcohol exposure (Riley, Infante, & Warren, 2011).

The manifestations of FAS are mental retardation, poor coordination, loss of muscle tone, low birth weight, growth deficiency, malformation of organ systems, and characteristic facial features, such as small eyes, smooth philtrum (the area between the nose and the upper lip), and a thin upper lip (see Figure 6-5; NIAAA, 2004). These symptoms do not always appear together, but the chances for development of any or all of these effects increase according to the amount of alcohol consumed during pregnancy.

The incidence of FAS depends on the criteria used to diagnose it. Using strict diagnostic guidelines, FAS prevalence is believed to be between 0.5 and 2.0 cases per 1,000 live births in the United States, but the incidence of FASD has been estimated to be as high as 10/1,000 live births and, in some places in the world, 68 to 89/1,000 live births (Riley et al., 2011).

The mechanism by which alcohol affects the developing fetus is not precisely known, but studies with nonhumans have shown that in the developing brain alcohol

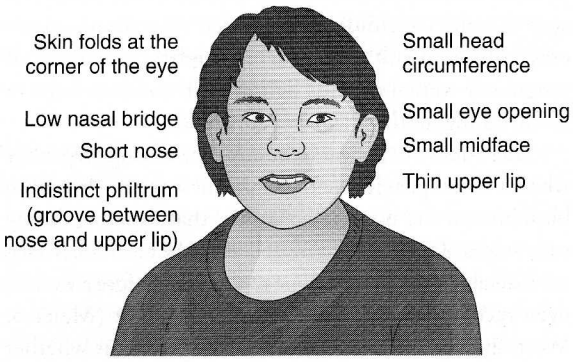

FIGURE 6-5 Typical facial characteristics of a child with fetal alcohol syndrome. (Adapted from National Institute on Alcohol Abuse and Alcoholism, 2004)

can disrupt neurogenesis, cell migration, cell adhesion, neuron survival, axon outgrowth, synapse formation, and neurotransmitter function (Brust, 2010). As we have seen in Chapter 4, all these processes are vital to the proper development of the central nervous system. Functional disruption of neural organization may occur particularly in the formation of the cortex. It appears that alcohol disrupts cell migration during cortical development; only four layers, rather than the usual six layers, are formed. In addition, neurons may end up migrating to the wrong layer (Abel & Sokol, 1989). Structural abnormalities are seen in other brain regions including the corpus callosum, basal ganglia, hippocampus, and cerebellum (Niccols, 2007).

Many normal, healthy children are born to women who have drunk heavily during pregnancy, so alcohol alone cannot be entirely responsible. As Abel and Sokol (1989) suggest, alcohol is a necessary but not sufficient condition for FAS or FAE. Other factors that have been associated with the likelihood of FAS or FAE include (a) having previous children, (b) being black, (c) having a high score on an alcohol screening test, and (d) having a high percentage of drinking days. It also seems clear that occasional high levels of consumption do more damage than the same amount of alcohol consumed at chronic low levels (Abel & Sokol, 1989; Maier & West, 2001).

Apart from FAS, maternal alcohol consumption can affect other aspects of fetal development, including growth. Mothers who consumed greater than 12 grams of alcohol (approximately the equivalent of one standard drink) per day had a greater risk of having a low-birthweight baby, whereas lower consumption on weekends produced the opposite effect (Mariscal et al., 2006). At ages 10 and 14, children of women who drank an average of one drink a day during the first 3 months of pregnancy were 4 pounds lighter than children born to nondrinking mothers (Day et al., 2002).

There does not appear to be any time during pregnancy when it is completely safe to drink, but it seems clear from both human and nonhuman studies that drinking during early stages of pregnancy is most likely to be harmful. In fact, considerable harm can be done to the fetus before a woman even recognizes that she could be pregnant (Maier & West, 2001). There is also no clear agreement whether there is a safe level of alcohol consumption during pregnancy. The Surgeon General of the United States and the British Department of Health recommend complete abstinence from alcohol during pregnancy (and during times when becoming pregnant is possible) as the only way to be certain of avoiding ill effects.

Heart Disease

Degeneration of the heart muscle, known as *alcoholic cardiomyopathy*, results directly from the chronic consumption of alcohol. This condition most likely arises from the effect alcohol has on the metabolism of the membrane of the cells of the heart muscle. The result is very similar to cirrhosis of the liver and was once described as "cirrhosis of the heart" (Myerson, 1971, p. 183). It appears that moderate consumption of alcohol can reduce the risk of developing heart disease, but binge and irregular heavy drinking seems to be correlated with an increased risk (Bagnardi, Zatonski, Scotti, La Vecchia, & Corrao, 2008). Based on these findings, patterns of alcohol consumption seem to be a major consideration in terms of health risks and benefits.

Other Effects

Chronic use of alcohol may also be responsible for a number of other pathologies. These include diseases of the digestive system such as ulcers and cancer, inflammation and other disorders of the pancreas, pneumonia and other diseases of the lungs and respiratory system, abnormalities of the blood, and malnutrition.

It has been observed for some time that alcoholics are more susceptible to many infectious diseases and less responsive to treatment. The reasons for this susceptibility include differences in lifestyle, nutrition, liver functioning, and the adverse effects of excessive consumption of alcohol on many aspects of the immune system.

That being said, a low to moderate dose of certain alcoholic drinks, such as beer and wine, may trigger a sort of protective effect on the immune system in healthy adults (Romeo et al., 2007). The cause of this protective effect is difficult to attribute to alcohol, however, as it may be due to other compounds present in the wine or beer.

BENEFITS OF ALCOHOL CONSUMPTION

It is not unusual for substances that are physiologically stressful and toxic at high doses to be beneficial at low doses. This effect is called *hormesis* (Dudley, 2002).

It may reflect an evolutionary adaptation to substances that an organism is naturally exposed to at low doses. The sort of exposure to alcohol experienced by our frugivore ancestors may have favored the evolution of metabolic adaptations to alcohol that maximize its benefits and minimize its harm.

Historically, alcohol has been used as a medicine. Avicenna, the tenth-century Persian physician, recommended wine for his older patients, although he cautioned his younger patients to drink it in moderation. Arnaud de Villeneuve, who reputedly invented brandy in the thirteenth century, hailed it as the water of immortality and called it *aqua vitae*, "water of life." He was convinced that it would increase longevity and maintain youth (McKim & Mishara, 1987).

Generally speaking, there is a U-shaped relationship between alcohol consumption and mortality among adults over the age of 45. There has been a great number of epidemiological studies that have plotted daily dose of alcohol against the *relative risk* of one health problem or another. Relative risk is calculated by dividing the incidence of a disease in people who use a given amount of alcohol by the incidence of that disease in people who do not consume any alcohol at all. Thus, if 5% of alcohol abstainers get cancer and 10% of heavy drinkers get cancer, then the relative risk for heavy drinkers is 2.0; that is, they are twice as likely to get cancer as abstainers. The relative risk of abstainers is always 1.0, and numbers less than 1.0 indicate a reduced risk of the disease. Figure 6-3 shows a plot of the relative risk of having an automobile accident against various BACs.

When alcohol consumption is plotted against relative risk of coronary heart disease, the result is in the form of a "J" curve or a "U" curve, depending on the range of doses reported; that is, relative risk drops to numbers less than 1.0 for moderate consumption (usually defined as one or two drinks a day) but increases to higher numbers as daily consumption increases (Brust, 2010; Gunzerath et al., 2004). The relative risk of myocardial infarction (heart attack) is reduced by 25% in men who consume up to two drinks a day. In fact, it has been suggested that if all drinking of alcohol ceased, there would be about 80,000 more deaths from coronary heart disease each year in the United States (Pearson & Terry, 1994). This protective effect of alcohol is likely a result of the ability of alcohol to lower levels of low-density cholesterol and increase high-density cholesterol. The type of alcoholic beverage consumed may also be a factor as red wine and dark beers have been found to provide more protection than liquor (Mann & Folts, 2004).

Another J-shaped risk curve with alcohol consumption has been reported for diabetes. Most studies indicate that moderate drinking reduces the incidence of type 2 diabetes and is associated with improved glycemic control in those with the disease. One study showed a 60% reduction associated with two drinks a day, but at three drinks a day this protective effect disappeared. And the incidence of diabetes increased as alcohol consumption increased above that level (Gunzerath et al., 2004).

Because alcohol reduces blood clotting and levels of low-density cholesterol that can clog arteries, it might be expected that alcohol would be able to reduce the risk of ischemic strokes (caused by clots blocking arteries in the brain). In fact, a J-shaped curve has been shown for risk of ischemic strokes in the elderly, with two drinks a day giving the best protection but seven drinks a day increasing relative risk to 3.0 (Gunzerath et al., 2004; Reynolds et al., 2003). Figure 6-6 illustrates the relative risk of stroke for men and women (and overall risk) related to daily alcohol consumption. Data are plotted according to the number of grams of alcohol consumed per day. A standard drink (12 oz of beer, 5 oz of wine, 1.5 oz of 80-proof distilled spirits of liquor such as gin, rum, vodka, or whisky) generally contains about 12.0 to 14.0 grams (0.4 to 0.5 oz) of pure alcohol. The risk of stroke decreases at low levels of consumption (one to three or so drinks per day), but increases rapidly at high levels (five or more drinks per day). Notice that this effect is most evident in women than in men (Reynolds et al., 2003). Low levels of alcohol consumption appear to offer protection only against ischemic stroke (where an artery to the brain is blocked), not from hemorrhagic stroke where the blood vessels rupture and bleed into the brain.

Alcohol, in low doses, may also offer some protection against age-related dementias. One meta-analysis found that small amounts of alcohol reduce incidence of dementia (risk ratio 0.63) and Alzheimer's disease (risk ratio 0.57), but not vascular dementia and cognitive decline (Peters, Peters, Warner, Beckett, & Bulpitt, 2008).

In general, it appears that there are some beneficial effects of low and moderate levels of alcohol consumption, but it seems that most of the conditions where alcohol is beneficial are those associated with aging. Young people are at relatively low risk of coronary heart disease,

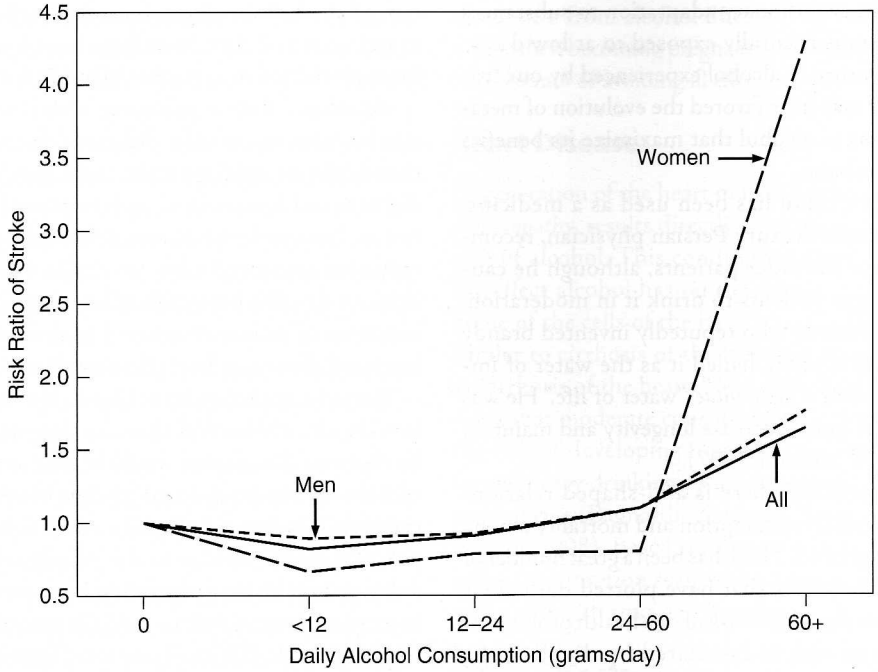

FIGURE 6-6 The relative risk of stroke for men and women related to average daily alcohol consumption. This is an example of a "J" curve mentioned in the text. The risk of stroke decreases at low levels, but increases rapidly at high levels. Note that this effect appears much more pronounced in women than in men. (Data from Reynolds et al., 2003)

ischemic stroke, and diabetes. Therefore, they are not likely to gain from any of the beneficial effects of alcohol but are exposed to all the risks of alcohol consumption, whereas older people are more likely to get some benefit. Research has shown that for those under 60, increased alcohol consumption is related to increased risk of dying from any cause (no J curve), but for those over 60, the relative risk of dying was less for light and moderate drinkers than for heavy drinkers and abstainers. This relationship was the same for both sexes (Rehm & Sempos, 1995). It is possible that all this was foreseen a thousand years ago by Avicenna when he recommended wine for his older patients.

If alcohol has so many health benefits, should it be *prescribed* to abstainers? One article summed up the dilemma this way: "Nowhere in medicine is the double edged sword so sharp on both sides" (Sandridge, Zylstra, & Adams, 2004, p. 670). These authors believe that the beneficial effects could be offset by the risks of addiction, especially in people with a family history of alcoholism. They believe that patients should be informed of all the pros and cons and then be allowed to make an informed decision.

It must also be remembered that all this research is correlational, not experimental. It is possible that there is some third factor, such as general health or sociability, that correlates with alcohol consumption. It may be, for example, that people who are healthy tend to drink and abstainers may not drink because they do not feel well. This would make it look like moderate drinking makes you healthy. Timothy Naimi and his colleagues at the Centers for Disease Control and Prevention in Atlanta, Georgia, analyzed the findings of a large-scale population health study and found many factors that correlated with both moderate alcohol consumption and reduced risk of cardiovascular disease. They point out that many of these confounding factors are not measured in studies indicating that moderate alcohol consumption is associated with a lowered risk of cardiovascular disease, so there is no way of assessing their involvement in the relationship (Naimi et al., 2005). On the other hand, most modern studies attempt to avoid this criticism by

measuring general health and accounting for its effects. Another criticism is that the group of abstainers used to establish the relative risk may contain former alcoholics who have stopped drinking, but may have increased their risk in the past by drinking heavily. This would not give an accurate picture of the risk of true lifetime abstainers. Many recent studies have addressed this criticism by excluding former drinkers from the abstinent group.

TREATMENTS

Because there has been little agreement about what alcoholism really is and why people drink, many types of treatments have been developed to help those who want to reduce their alcohol intake. It is generally agreed upon that the first step must be to eliminate physical dependence if it is present. This is usually done in a hospital or a detoxification center where the alcoholic goes through withdrawal under medical supervision until all withdrawal symptoms are over. Following detoxification, an active treatment phase may or may not be followed by a long-term program to prevent relapse.

The nature of the therapy and its outcome goals are determined by how the therapist defines alcoholism. If alcoholism is considered a genetic disease, as described by Jellinek, no *cure* is possible, and the aim of therapy should be complete and total lifetime abstinence. On the other hand, if excessive drinking is a result of environmental factors interacting with genetic vulnerabilities, it may be possible to moderate drinking without eliminating it altogether.

In Chapter 5, various behavioral and social approaches to the treatment of addictions (including alcoholism) were discussed. These include cognitive behavioral therapy, contingency management, motivational enhancement, and family therapy, and can involve individual or group therapeutic techniques. One technique, Alcoholics Anonymous (AA), was initially developed as a method to help alcoholics stay sober. The AA approach, also known as the 12-step approach, has been adapted by many other support groups for people who have problems controlling gambling, overeating, and the use of other drugs.

Because of its prominence and its influence on the treatment of all addictions, we will take a brief look at the history and philosophy of AA.

Alcoholics Anonymous

Alcoholics Anonymous was founded in 1935 by Dr. Bob Smith and Bill Wilson. It grew out of the Oxford Movement, a popular Protestant religious movement in which small groups met weekly for prayer, worship, and discussion, with the aim of self-improvement. One Oxford group meeting in Akron, Ohio, was attended by an alcoholic stockbroker and an alcoholic physician, both of whom were seriously but unsuccessfully trying to stop drinking. They found that their fellowship and that of the group helped them to stop drinking. They brought other alcoholics into the group, and many had similar success. In fact, helping other alcoholics to stay sober seemed to be making an important contribution to the maintenance of their own sobriety. As the meetings got bigger, new groups were formed, and eventually they broke away from the Oxford Movement and became AA (Alcoholics Anonymous, 1980).

The organization has grown rapidly and spread around the world. In 1982, there were 20,000 groups in 100 countries, and the estimated world membership was well over 1 million (Maxwell, 1984). Currently, AA estimates that there are almost 116,000 groups and a membership of over 2 million, half of which are in the United States (Alcoholics Anonymous, 2012). Although AA broke away from the Oxford Movement, it has retained many of the elements that seemed to be responsible for its effectiveness, including spirituality, although this aspect can be moderated to suit each individual.

At every meeting of AA, someone reads the 12 steps and the 12 traditions that explain the basic principles and processes the organization has found to be effective over the years. Most AA members believe that to control drinking, the individual must first admit to being "powerless over alcohol" and unable to control drinking without help. AA members believe that drinking can be controlled only by relying on a greater power, often identified as "God" or "God as we have come to understand Him" (or Her) for people who are uncomfortable with the concept. They feel that there is no cure; there are only alcoholics who drink and alcoholics who do not drink. For this reason, members are expected to attend regular meetings for extended periods of time. It is not unusual for new members to attend more than six meetings a week (in fact, there is a tradition of new members doing "90 meetings in 90 days"). In addition to attending meetings, members often see each other

socially outside of meetings and frequently talk on the phone, especially if stress or desire for alcohol is threatening a member's resolve (Maxwell, 1984). For many people, AA is not a treatment at all; it is a long-term commitment and a way of life. It has been estimated that AA is currently helping as many alcoholics in the United States as all medical facilities combined. It has been estimated that about 5% of all alcoholics are affiliated with AA (Finagrette, 1988).

Although AA has reported that 64% of participants drop out of the program within their first year, there is no doubt that AA is effective for many drinkers. In fact, it has been claimed that participation in AA is the most effective treatment, but this is a difficult claim to test, largely because AA does not permit itself to be subjected to the same close scientific evaluation that other treatment techniques must undergo. In addition, the people who try and stick with AA are most likely to have a high socioeconomic status and a stable social situation, are highly motivated to quit, are between ages 40 and 45, and have spouses who help with the treatment (Baekeland, 1977). These are the best candidates for help, no matter what the treatment (Ogbourne & Glaser, 1981).

Vaillant has suggested that one reason why AA works is that it provides alternative sources of reinforcement and keeps the alcoholic busily engaged in activities that are incompatible with drinking alcohol. AA provides a busy schedule of social and service activities with supportive former drinkers, especially at times of high risk (e.g., holidays). AA requires members to "work the program" and encourages returning again and again to group meetings and to sponsors who provide an external conscience (Vaillant, 1992, p. 52).

Pharmacotherapies for Alcoholism

The U.S. Food and Drug Administration has approved only four agents for the treatment of alcoholism, which are usually used in conjunction with other behavioral and social therapies. These pharmacotherapies are disulfiram, acamprosate, and oral and extended-release naltrexone. Numerous other drugs are being tested as well.

ANTABUSE (DISULFIRAM). The effect of disulfiram was described in Chapter 1. As shown in Fig 1-10, it blocks the action of aldehyde dehydrogenase, the enzyme which breaks down acetaldehyde. Drinking alcohol without this enzyme leads to a buildup of acetaldehyde in the body and makes a person feel very sick. Thus, taking disulfiram regularly prevents people from drinking because, if they do, they will become very ill. Extensive clinical trials with disulfiram have shown that it offers some protection from unplanned or spontaneous drinking, but a patient who wants to drink can simply stop taking the drug. There is, in fact, a very high rate of noncoherence in patients—up to 80% do not take Antabuse as directed (Garbutt, 2009). People who are motivated enough to take disulfiram regularly are also motivated enough to avoid alcohol without taking disulfiram. However, the drug does appear to be effective if it is taken under some sort of supervision, usually in conjunction with another therapy. The supervisor needs to be trained in supervisory techniques and educated in evasion behaviors used by patients with alcohol dependence (Brewer, 1992).

ACAMPROSATE. Acamprosate (Campral) is effective in suppressing glutamate activity, which is hyperactive in the postwithdrawal phase of alcoholics. The major goal of this therapy is to reduce the aversiveness of withdrawal and thereby diminish the motivation to resume drinking (Rosner et al., 2010). Results of acamprosate clinical trials have been mixed, with trials in Europe showing that the drug is effective, while trials in the United States show no such effect. The difference may be due at least in part to a difference in procedure. In the U.S. trials, patients were tested a short time after detoxification, whereas in the European trials a longer period of time had elapsed between detoxification and the drug trial (Garbutt, 2009).

NALTREXONE. Naltrexone is an opioid receptor antagonist (see Chapter 11). Two formulations have been approved by the FDA for use in the United States. They are oral naltrexone and an extended-release injection that remains effective for a month. Naltrexone blocks activity in the opioid system and has been shown to reduce the normal *high* or level of intoxication after alcohol consumption. It is also reported to reduce craving for alcohol in abstinent heavy drinkers. There have been numerous studies that show that oral naltrexone is modestly effective in reducing the likelihood of relapse to heavy drinking and enhances the possibility of complete abstinence from alcohol. While the therapeutic effects are generally modest, clinical experience has shown

that some patients have a strong therapeutic response. It has not been clearly established which patients respond well to naltrexone, but they seem to be patients with a positive family history of alcoholism and a higher baseline rate of craving for alcohol (Garbutt, 2009). It has also been shown that patients who reliably take their naltrexone are also more likely to show improvement. For this reason, an extended-release formulation has been developed and tested. The extended-release injection has undergone several clinical trials and been shown to be effective, particularly in men and patients who are abstinent for 4 or more days before receiving the naltrexone (Garbutt, 2009).

Naltrexone may cause side effects, which include vomiting, diarrhea, and somnolence. The extended-release injection has been reported to cause nausea, decreased appetite, dizziness, and some injection-site pain. These are generally well tolerated, but may contribute to some noncompliance.

OTHER PHARMACOTHERAPIES. Tiapride is a D_2 dopamine receptor blocker approved for use in France. It has been shown to be effective in a limited number of clinical trials, but may have serious side effects, particularly in young people. Other dopaminergic agents have been used, particularly antipsychotic drugs such as clozapine, aripiprazole, and olanzapine. These appear to be especially effective in patients with schizophrenia and bipolar disorder. Other drugs that have been tested, and that have shown some promising results, are anticonvulsants such as topiramate and valproic acid/divalproex (Depakote or Depakene) (Garbutt, 2009).