ALCOHOLISM IN A SHOT GLASS

ALCOHOL:
CHEMICAL, BEVERAGE, AND DRUG

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Alcohol: Chemical, Beverage, and Drug

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Alcohol: Chemical, Beverage, and Drug

One reason the study of alcoholism is so fascinating is its complexity. The physical sciences, the biological sciences, and the social sciences are needed to help illuminate the strange and baffling phenomenon—the slow, relentless self-poisoning of a human being—that we call alcoholism. Alcohol is a chemical and a drug; it is contained in a vast range of fermented fluids; it is consumed by people; it affects their bodies and their minds, in ways not fully understood. People who drink have personalities, are members of families, live in societies, and are influenced by cultures. To understand the phenomenon of alcoholism, we will need to look at the chemical and drug; its physical and psychological effects; the people who drink it; and the families, societies, and cultures those people live in. This book begins with an examination of the chemical and drug, with alcohol itself.

ALCOHOL AS A CHEMICAL

Alcohol is a chemical. When swallowed, it has pharmacological properties; that is, it acts as a drug, powerfully modifying the functioning of the nervous system. To provide an understanding of the kind of chemical alcohol is and how it works, this chapter begins with a review of some elementary chemistry.

All matter is composed of chemical *elements.* There are 106 of these elements. They vary in the complexity of their structures. These elements are the building blocks of the universe. The qualities of the substances we encounter daily depend on their chemical composition—that is, on the kind and arrangement of elements they contain.

Elements consist of *atoms.* Atoms are basic in that they cannot be further subdivided without losing the very qualities that make an element distinct. Each element consists of atoms that differ in their structure from the atoms of other elements. Atoms consist of a nucleus containing particles called *protons,* which carry positive charges, and rings of *electrons*, which carry negative charges. The nucleus may also contain electrically neutral particles called *neutrons.* Atoms as a whole are electrically neutral. The simplest of the elements is hydrogen; its chemical symbol is H. Its atom consists of one proton and one electron (Figure 1.1). The other elements have progressively more complex atomic structures, but the idea remains the same. In each case there is a nucleus with protons and perhaps neutrons and one or more rings of electrons. The *periodic table* arranges the elements according to their atomic structure.

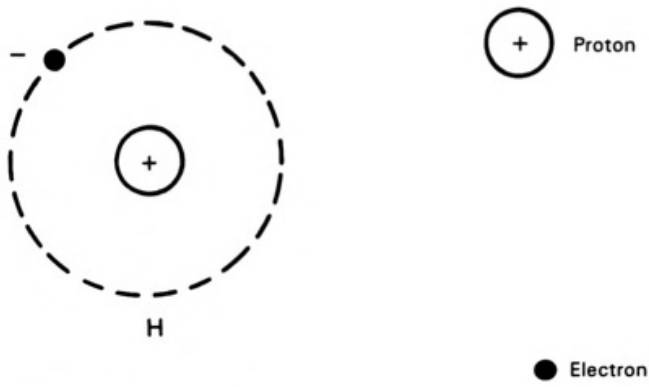

Figure1.1 Hydrogen atom.

In nature, atoms are usually combined into larger units called *molecules.* The number of electrons in the outer ring of an atom determines how readily and with which other atoms it will combine. Atoms are said to seek a stable configuration of electrons in their outermost rings and to enter into chemical reactions to achieve this. Of course, to attribute a desire for stability to an atom is to *anthropomorphize* it—to attribute to it human qualities—but "motivation" aside, that is the way an atom behaves. When two or more atoms combine, the resulting entity is called a molecule.

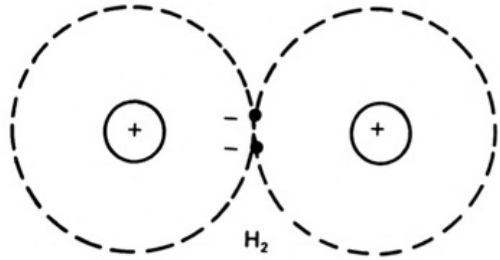

Figure1.2 Hydrogen molecule.

In the hydrogen molecule, shown in Figure 1.2, each atom's outer ring—which in this case is its only ring—contains two electrons. This is a stable configuration for this ring, or shell. The hydrogen atom's ring can hold only two electrons, and as part of a hydrogen molecule it has them.

If the atoms forming a molecule are atoms of different elements, the result is a chemical compound with a definite molecular structure. Just as an element cannot be divided into more ultimate units than atoms without it ceasing to be that element, a compound cannot be divided into more ultimate units than molecules without it ceasing to be that compound.

Atoms combine into molecules in two basic ways. They can share one or more electrons, forming what is called a *covalent bond*, or one of the atoms forming the bond can "donate" one or more electrons to the other atom forming the bond. Thus, one atom becomes positively charged and the other negatively charged. Such bonds are called *ionic bonds*. The hydrogen

molecule, illustrated in Figure 1.2, is an example of a covalent bond. One of the most familiar examples of a compound formed by ionic bonding is ordinary table salt, which consists of one atom of sodium and one atom of chlorine and is symbolized as NaCl. When an atom or a molecule either has more or fewer electrons than it has protons, it has an electrical charge and is called an *ion*. If salt (sodium chloride) is dissolved in water, it forms sodium ions (Na^+) and chloride (Cl^-) ions—charged particles in solution.

Alcohol Is a Compound

The substances known as chemicals are compounds of elements or mixtures of compounds. Alcohol belongs to a class of chemicals called *organic compounds*. Organic compounds contain carbon (C), a unique element that plays an essential role in the chemistry of living things, or organisms—hence the name organic. Carbon is unique because its atomic structure includes an outer ring that can form four bonds with other atoms. The way chemists express this is to say that carbon has a *valence* of four. These bonds are covalent bonds in which the four electrons in carbon's outer shell become linked with four electrons from other atoms. These atoms may be either other atoms of carbon or atoms of other elements that will bond with carbon. Thus, by "sharing" electrons, the carbon atom obtains the use of four additional electrons, allowing it to reach the stable configuration of eight electrons in its outer shell. This allows carbon to combine in variegated and complex ways

into an extraordinary range of substances, including the principal components of all living things.

Alcohol, then, is an organic compound. Actually, there are many alcohols. The alcohol we drink is called *ethyl* alcohol or *ethanol*. A group of chemicals that share certain characteristics and a common structure is called a *family* or *class*. What do the members of the alcohol family have in common? They are organic compounds that contain a certain kind of charged particle, called a *hydroxyl* group. A hydroxyl group consists of an oxygen atom combined with a hydrogen atom. It carries a negative charge and is symbolized as OH^-. In an alcohol, the hydroxyl group, also called the hydroxyl *radical*, is combined with a chain of one or more carbon atoms. The number of carbon atoms determines the type of alcohol. Since carbon "requires" four bonds to complete its outer shell, something must bond with the "unused" positions. In the case of the alcohols, these positions are filled by hydrogen atoms.

Methyl Alcohol The simplest of the alcohols is *methyl* alcohol, or *methanol*. It consists of one carbon atom (C), three hydrogen atoms (H_3), and one hydroxyl group (OH). This can be written as CH_3OH. This is known as its *empirical* formula. It is also possible to draw a picture of the methyl alcohol molecule. Such a picture is called a *structural* formula. Methyl alcohol's structural formula is shown in Figure 1.3. As can be seen in the figure, the

methyl alcohol molecule is built around a carbon atom that forms bonds of shared electrons with the hydrogen atoms and the hydroxyl ion. Methyl alcohol is also called *wood* alcohol. Because it is a poison, it is sometimes added to products containing beverage alcohol to "denature" them, thereby making them undrinkable. Methyl alcohol was the ingredient in the bad hooch of prohibition that caused blindness and death.

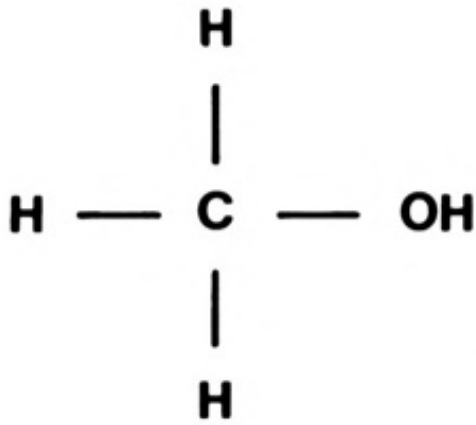

Figure 1.3 Methyl alcohol molecule.
The lines represent covalent bonds between atoms. These bonds consist of shared atoms.

Ethyl Alcohol The alcohol that interests people most—the kind that we drink—is *ethyl* alcohol, or *ethanol*. It is more complex than methanol. The ethanol molecule consists of one hydroxyl ion joined to a chain of two carbon atoms with their associated hydrogen atoms. The empirical formula for ethyl

alcohol is C_2H_5OH. Its structural formula is shown in Figure 1.4. It is with the ethanol molecule and its physiological and subjective effects that we will be concerned in the rest of this chapter.

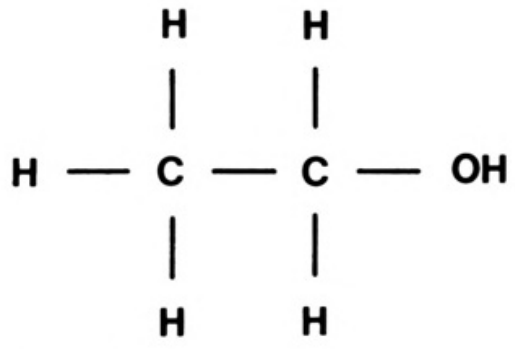

Figure1.4 Ethyl alcohol molecule.

The ethanol molecule is small as organic molecules go, and it is perfectly miscible in water and fairly soluble in fat. Beverage alcohol consists of ethanol, various by-products of fermentation known as *congeners*, flavorings, colorings, and water. Although congeners probably have some biological effects, ethyl alcohol is the active ingredient in beer, wine, and distilled spirits.

Higher Alcohols The "higher" alcohols are simply modifications of methyl or ethyl alcohol in which the hydroxyl ion is combined with longer carbon chains. The next two in the series are propyl and isopropyl alcohol, both of which have the empirical formula C_3H_7OH. Their structural formulas differ, however, in the position of the hydroxyl group. These alternate forms

are called *isomers*. Propyl alcohols are used as rubbing alcohol. Alcohols with four carbon atoms are called *butanols* and are used as industrial solvents. Alcohols with 13 or more carbon atoms are solid at room temperature. The higher alcohols need not concern us further.

We now know something about the *chemical* ethyl alcohol: It is a member of a class of organic compounds called alcohols, which are characterized by carbon chains linked to hydroxyl ions; its empirical formula is C_2H_5OH; and it is a relatively small molecule, perfectly soluble in water and significantly soluble in fat. What about the *drug* ethyl alcohol? Before the chemical can become the drug, it must be present in a beverage, be ingested and absorbed, and then assert its effects on the body. The next section traces this process.

FERMENTATION AND PRODUCTION OF ALCOHOLIC BEVERAGES

Fermentation

Alcohol[1] is produced by the *fermentation* of substances containing sugar by enzymes that are produced by a microorganism yeast. Fermentation is a process of *partial oxidation* in which part of the energy in sugar is released by combining it with oxygen, converting the sugar to alcohol. The alcohol retains some of the chemical energy that was stored in the sugar, and it can be released by further oxidation.

Yeast spores are present in the air. A sugar solution left a few days at room temperature will *ferment*, that is, turn into alcohol and carbon dioxide. Yeast is a *fungus*—a small living plant-like organism[2]—that secretes a substance that forms a wall around the yeast cell. Yeast cells multiply by cell division into units of four to eight cells, which form the yeast spore. When yeast spores come in contact with a nutrient solution, such as a sugar solution, the wall breaks down and the yeast cells become metabolically active. As a result of this metabolic activity, the yeast cells grow and multiply and in the process secrete substances known as *enzymes*. An enzyme is a catalyst produced by a living organism. A *catalyst* is a chemical that changes the rate of a chemical reaction. For all practical purposes the reaction will not take place without the catalyst. Enzymes work by entering into intermediary chemical reactions that facilitate the primary reaction without the enzymes themselves being permanently changed. The primary reaction thereby proceeds to completion, producing the end products of the reaction.

Put more simply, enzymes are biological agents that facilitate chemical reactions. In the case of yeast and sugar solutions, the enzymes involved include *zymase, invertase,* and *maltose*. Each enzyme is specific in its action. Invertase and maltase facilitate the conversion of the complex sugars sucrose (cane sugar) and maltose (malt sugar) into, respectively, the simple sugars glucose and fructose. These simple sugars are in turn acted on by the enzyme zymase in such a way that the glucose or fructose is converted into alcohol,

carbon dioxide, and heat. The chemical equation for this reaction is as follows:

$$\underset{\text{Glucose or Fructose}}{C_6H_{12}O_6} \xrightarrow{\text{Zymase}} \underset{\text{Alcohol}}{2C_2H_5OH} + \underset{\text{Carbon dioxide}}{2CO_2} + \underset{\text{Heat}}{20\ \text{kg/cal}}$$

Thus, if the juice of grapes or another sweet solution is kept at room temperature, it will change into wine as yeast spores settle into the juice and begin to produce their enzymes. Bubbles of gas (carbon dioxide) will rise to the surface, and a scum of yeast will collect. Primitive peoples probably discovered this by accident, and in this sense man's use of alcohol is serendipitous. However, this serendipity soon resulted in planned production. The development of reliable and replicable techniques for the production of beverage alcohol is one of man's earliest technological achievements. Almost every known culture discovered or developed a form of alcohol production, and every substance that can be fermented has been made into a beverage. Perhaps this early development of techniques for the production of alcohol, with its inherent potential for both beneficent and malignant consequences, is emblematic of the double-edged nature of all subsequent technological advance. From this point of view, human ambivalence toward alcohol is a manifestation of ambivalence toward technology.

Distillation

Distillation, which became popular in the fifteenth century, is a way of removing water from the fermented product, thereby increasing the concentration of alcohol. Put simply, alcohol boils at a lower temperature than water; therefore, heating a fermented product will result in the alcohol boiling off first. This gaseous alcohol is then cooled as it passes through coiled tubes. The cooling produces condensation, and the resulting distillate is collected. Brandy is the distillate from fermented grapes; bourbon is the distillate from fermented com; rye whiskey is the distillate from fermented rye; vodka is the distillate from fermented potatoes; and sake is the distillate from fermented rice. The concentration of alcohol in distilled products is measured in *proof*. A proof is half a percent by volume. Pure or absolute alcohol is 200 proof. The alcohol content of beer and wine is generally reported as a percentage of alcohol by volume.

By-Products of Fermentation

Fermentation results not only in alcohol but also in a variety of byproducts known as *congeners*. Congeners give a particular form of beverage alcohol its unique quality. Chemically, congeners mostly fall into three groups: alcohols other than ethanol, members of a class of chemicals known as *aldehydes*, and members of a class of chemicals known as *esters*. Aldehydes differ from alcohols in that their hydroxyl group is replaced by a double bond to an oxygen atom. As we will see, one of these aldehydes is produced by the

metabolism of alcohol in the body. Esters have two carbon chains separated by an oxygen atom. Esters give a beverage its characteristic aroma. The chemical structure of aldehydes and esters is illustrated in Figure 1.5. Although some researchers believe that congeners contribute to a hangover and may have long-term effects, congeners are present in very small amounts and do not play a major role in the effects of alcoholic beverages on people. They will not be considered further here.

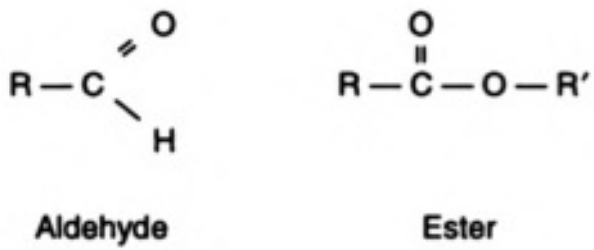

Figure1.5 Structure of by-product molecules. R and R' are carbon chains.

Now we know what is in the bottle and how it got there: ethyl alcohol; other alcohols; aldehydes; esters; possibly flavorings, as in the case of juniper berries added to gin; possibly colorings; possibly carbon dioxide, as in the bubbles of beer; and water. The next section looks at what happens when the contents of the bottle are ingested.

INGESTION AND ABSORPTION OF ALCOHOL

Ingestion

From the bottle, alcohol usually goes into the glass, although "serious" drinkers may omit this step. From the glass, alcohol goes into the mouth and is swallowed. Although alcohol can be absorbed by the mucous membranes of the mouth, it is rarely retained there long enough for this route of absorption to be of much practical importance. Nonetheless, part of the enjoyment drinkers derive from drinking comes from the gustatory and olfactory sensations that accompany the passage of alcohol past the lips and through the mouth. Alcohol can also be absorbed by the lungs, but this too is of little practical importance. From the mouth alcohol passes through the pharynx, is swallowed, descends the esophagus, and enters the stomach. It is important to note that alcohol irritates the tissues with which it comes in contact. This may also be true of congeners. Prolonged, heavy, particularly abusive alcohol consumption is associated with an increased risk of disease in these tissues. It is believed that prolonged, heavy drinking may be an etiological—that is, causal—factor in cancers of the lips, mouth, pharynx, esophagus, and stomach.

Absorption

Alcohol requires no digestion; that is, no physical or chemical processes need intervene between the ingestion of alcohol and its absorption from the digestive tract. It is absorbed into the body and asserts its influence there

without undergoing any change. Along with its small molecular size, this makes alcohol readily and rapidly absorbable. The actual rate of absorption depends on the concentration of alcohol in the stomach and bloodstream and on the contents of the stomach. Drinking on an empty stomach "hits" the drinker much harder than drinking with a meal or after eating.

Absorption begins when the differential concentration of alcohol in the stomach and bloodstream sets up a pressure gradient that moves the alcohol across the *gastric muccsa* (the lining of the stomach). This diffusion across a membrane is called *osmosis*. Most nutrients are not so readily absorbed. It has recently been discovered that the enzymes that metabolize alcohol are present in the stomach and that they are capable of breaking down low concentrations of alcohol before it can be absorbed into the bloodstream. It is believed that heavy drinking exhausts these enzymes, so the liver must metabolize all the alcohol consumed. The remaining alcohol passes through the *pyloric valve* at the bottom of the stomach and enters the small intestine, where it is then absorbed. Approximately 20% of the alcohol consumed is absorbed by the stomach. The remaining 80% is absorbed by the small intestine, whose mucosa is specialized for the task of absorption by the presence of tiny tubes called *villi*. Little, if any, alcohol normally descends lower in the digestive tract than the *duodenum* (the first part of the small intestine). Thus, alcohol rapidly enters the bloodstream from the stomach and small intestine.

Once alcohol enters the bloodstream it is transported throughout the body. The distribution of alcohol to various organs and tissues is understood, but for our purposes it is sufficient to know that it is distributed to and affects every cell in the body. Alcohol's small molecule and its solubility make it readily transportable across cell membranes, and its resulting ubiquity in the body is the reason that alcohol abuse can harm so many different organs.

Of all the actions of alcohol on cells and tissues, its action on the nervous system is by far the most important. Alcohol's effect on nerve tissue produces both the objective, observable changes in behavior that follow its consumption and the inward, subjective changes in thought and feeling that the drinker experiences. It is the action of alcohol on the nervous system that makes one "high."

EFFECT OF ALCOHOL ON THE NERVOUS SYSTEM: WHAT PRODUCES THE HIGH

The Neuron

In order to understand the effects of alcohol on the nervous system, it is necessary to have some understanding of how that system works. The nervous system is composed of specialized cells called *neurons*, which conduct electrical impulses. The information that it is the business of the nervous system to transmit is encoded in the pattern and frequency of these impulses. The typical neuron consists of a cell body, called the *soma*, which

contains the nucleus of the cell; the *dendrites*, which are projections that receive impulses from other neurons; and the *axon*, which transmits the impulse to the next neuron. The neuron, like all cells, is separated from the surrounding extracellular fluid by a semipermeable barrier known as the *cell membrane*. This membrane's semipermeability allows some, but not other, molecules and ions to cross it.

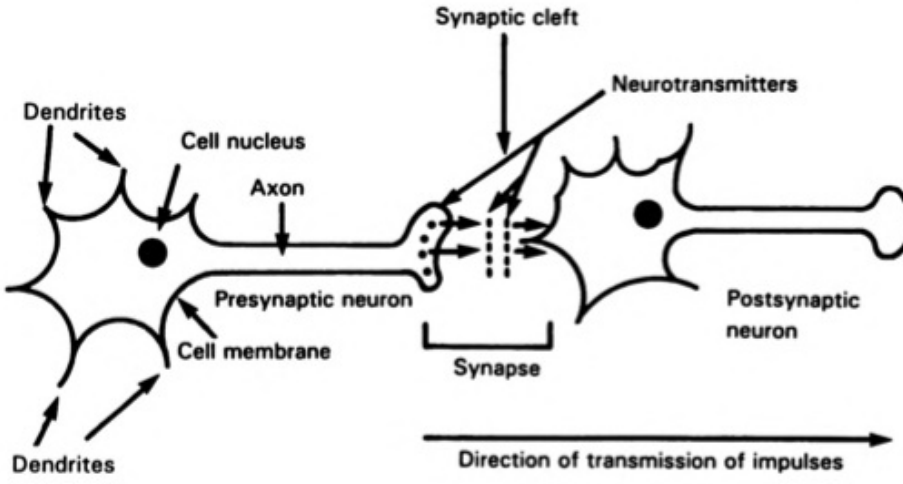

Figure 1.6 Neurons.

Neurons do not quite touch each other, and the gap between them—between the axon of one neuron and the dendrites of the next—is the *synapse*. Two neurons and their synapse, or junction, are shown in Figure 1.6. The electrical impulses in the *presynaptic neuron* are transmitted across the *synaptic cleft*, by chemicals known as *neurotransmitters*. Neurotransmitters

induce an electrical impulse in the *postsynaptic neuron*. Thus the electrical impulse travels from neuron to neuron. A neuron may junction with many other neurons, thereby being *polysynaptic*. Further, synaptic transmissions, which can be either *excitatory* or *inhibitory*, can be combined or *summed* either spatially or temporally by the receiving neuron. Excitatory neurons do just that—they excite, or increase the activity of, the neurons with which they communicate. Inhibitory neurons inhibit the nerve cells to which they send messages. *Spatial summation* means that a given neuron may receive impulses from two or more contiguous neurons simultaneously and combine their messages into one. Nerve impulses arriving sequentially can be combined in the same way; this is *temporal summation*. This arrangement allows the nervous system to encode and fine tune highly complex information and provides for exquisite control of the functions of the organism.

The electrical activity of the neuron is called an *action potential*. In the neuron, as in all cells, there is an electrical charge, a difference in potential, across the cell membrane. This electrical potential is caused by differences in the type and concentration of ions within the cell and without the cell. Normally there is a greater concentration of negatively charged ions within the cell, intracellularly. More explicitly, large negatively charged organic ions (A^-) are found inside the cell, while positively charged sodium ions (Na^+) are found in greater concentration in the extracellular fluid, that is, outside the

cells. Potassium ions (K^+) are found in greater concentration intracellularly, and chloride ions (Cl^-) are found in greater concentration extracellularly. This results in a *negative* voltage differential between the inside and outside of the cell. The uniqueness of the neuron consists in the ability of its cell membrane to undergo a sudden change in permeability, which allows the sodium ions to cross the membrane and enter the cell. As the sodium ions move in, some of the potassium ions move out. This sudden influx of sodium ions results in an abrupt change in the electrical potential of the cell from approximately 70 millivolts of negativity to a slight positivity. This change is the action potential. We speak of the neuron "firing." This is an all or none phenomenon; it has no degrees; it occurs or it does not. The number and pattern of these action potentials encode the information that is transmitted. The process is illustrated in Figure 1.7.

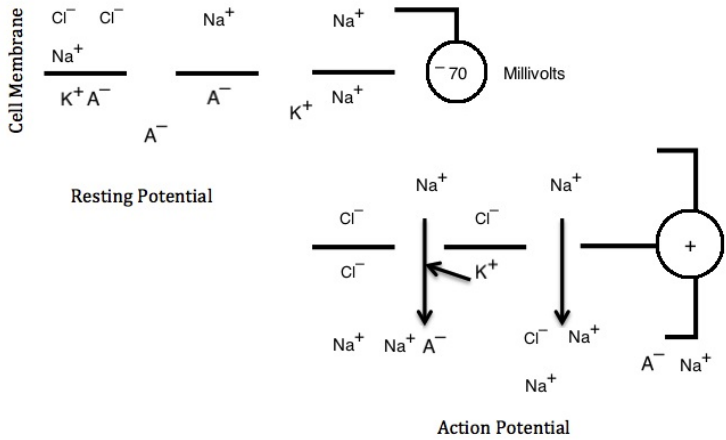

Figure 1.7 Firing of a neuron.

Alcohol and the Neuron

Before the neuron can fire again, the *resting potential*—the negative voltage differential across the cell membrane—must be restored. The gun must be cocked, so to speak, before it can be fired again. The resting potential is reestablished by an active metabolic (living chemical) process within the cell membrane, which transports the sodium ions outward across the membrane and the potassium ions inward across the membrane, reestablishing a negative potential between the intra- and extracellular fluids, restoring the ionic status quo ante, and permitting the neuron to fire again. It is postulated that alcohol interferes with this active transport of sodium ions

by disrupting the membrane. In other words, alcohol slows, or depresses the functioning of the neuron by interfering with the reestablishment of its resting potential.

Ethanol not only interferes with the active transport of sodium ions across the neuron membrane but also *disturbs membrane phenomena* in general and retards the transport of numerous, variable metabolites—the products of metabolism—through the cell membrane. Cell membranes consist of lipids (fats) and proteins. Because it is soluble in fat, ethanol penetrates the neuronal membrane, swelling it and disrupting the lipids. This in turn alters the function of the membrane proteins, contributing to the depression of neural activity.

Ethanol is a "dirty little molecule" (R. Maslansky, personal communication, 1988) that not only penetrates every system, organ, tissue, and cell in the body but also, once it penetrates the cell, intrudes on and disrupts a wide variety of biochemical reactions on the molecular level. Unlike a drug such as morphine, which reacts with a specific receptor at a definite site in particular cells, ethanol's dirty little molecule has no one specific receptor upon which it acts. Instead, it becomes involved in numerous pharmacological actions, which is one reason it is so toxic. Thus, ethanol's action is *multimodal*, that is, it asserts its pharmacological action through a variety of mechanisms. It is likely that further research will

establish the primacy of one or two of these effects, but at present all are considered significant.

The current "hot" biochemical research focus is ethanol's effect on the *second messenger system*. Once metabolites such as amino acids and proteins cross the cell membrane, they not only perfuse the *cytoplasm*— the fluid part of the cell—and *organelles*—substructures within the cell— by diffusion but they are also directed and transported—sort of piggybacked—to the sites of their metabolic actions by second messengers, the most prominent of which is *cyclic adenosine monophosphate* (cAMP). cAMP tells the neuron to engage in various metabolic processes, including the synthesis of proteins from amino acids that enter the cytoplasm. Alcohol's dirty little molecule gets into the neuron and disrupts the interaction of cAMP with various proteins. This depresses cell activity. Calcium ions (Ca^{2+}), for example, open and close channels to receptor sites used by second messengers as well as carrying information and signaling by modifying the microelectrical environment of various biochemical transactions. Researchers believe that ethanol acts on the calcium-second messenger system and that disruption of the second messenger system by ethanol is one of the primary ways that alcohol affects the central nervous system. The hypothesized mechanism of this action is complex. Neurons contain receptors for the various neurotransmitters in a sort of lock and key arrangement. One of these receptors is *N methyl D aspartate* (NMDA), which is the receptor site for the amino acid

neurotransmitter *glutamate*. When glutamate binds to the NMDA receptor, it activates a system that permits CA^{2+} to enter the cell turning on cellular processes, some of which involve cAMP, and thereby exciting the neuron. If ethanol binds to the NMDA site, as hypothesized, then it acts as a glutamate *agonist* (an imitator that blocks an action), slowing the flow of Ca^{2+} and thereby decreasing neural activity.

The neuron is constructed so that the action potential travels rapidly down the axon to the synapse. Here it brings about the release of a neurotransmitter, which diffuses across the synaptic cleft and changes the permeability of the postsynaptic membrane. If the transmitter is excitatory, the postsynaptic neuron will fire. It is believed that alcohol interferes, in unclear but complex ways, with this process. Thus, alcohol decreases the frequency of the action potential by disturbing the membrane, slowing the active transport of sodium ions and retarding the transmission of impulses across the synapse. The higher the dose of alcohol, the greater the retardation. The net effect of alcohol on the nervous system, and its primary physiological effect, is this *graded depression of synaptic transmission*. Graded depression means that parts of the central nervous system are more sensitive to the effects of alcohol than others, and their rates of synaptic transmission will become depressed at lower doses. It is the parts of the nervous system with the most synapses—the greatest number of junctions—that are the most easily affected by alcohol.

The pharmacology of ethanol is extremely complex and at present only partly understood. Some researchers (Cloninger, 1987b) believe that in very low doses ethanol has an excitatory rather than an inhibitory effect on neurons in the tegmental area of the midbrain and that this stimulation is pleasurable to some people. Cloninger also postulates that such an individual difference in reaction to ethanol may help account for some forms of predisposition to alcoholism. Wise (1987) goes further and postulates a common excitatory (reward-center stimulating) mechanism for all addicting drugs, including alcohol, mediated through the action of these drugs on a part of the midbrain called the *nucleus accumbens*. In his view, the main pharmacological effect of alcohol, its stimulation of the pleasure center, is masked by its overwhelming "side effect," sedation. This has interesting clinical implications suggesting that while some people may become addicted to alcohol because of their strong attraction to its stimulating effects, others become addicted because of their attraction to alcohol's sedating effects.

Be this as it may, alcohol's usual pharmacological action is inhibitory. Although the mechanism of this inhibition remains unclear, one additional possibility is that ethanol facilitates the action of an inhibitory neurotransmitter called *gamma aminobutyric acid* (GABA). Most neurotransmitters are excitatory in their actions; they increase the rate of firing of the postsynaptic neuron. The family of neurotransmitters called the *catecholamines*, which includes *epinephrine* (adrenaline) and the

neurotransmitter *acetylcholine*, which plays an important role in muscle contraction, are excitatory; GABA is not. It is, so to speak, the nervous system's "brake"; it decreases the rate of firing in the postsynaptic neuron. The *anxiolytics* ("minor" tranquilizers) Librium and Valium, which are also central nervous system depressants, work primarily by helping GABA do its work, facilitating its action on the neuron by enabling GABA's bonding to its receptor. Ethanol may do the same. Prolonged heavy drinking depresses the level of GABA in the brain, seriously disturbing the normal balance of neurotransmitters required for optimal functioning of the central nervous system. It apparently does this by reducing the number of GABA receptor sites, which may be the mechanism of seizure vulnerability during withdrawal.

In summary, apart from its possible action as a psychomotor stimulant of parts of the mid-brain, alcohol's primary pharmacological action is depression of the central nervous system. It apparently brings about this depression through three mechanisms: (1) disruption of membrane phenomena; (2) blocking of the NMDA receptor, thereby depressing the flow of the second-messenger calcium ions; and (3) potentiating—that is, augmenting—the action of the inhibitory neurotransmitter GABA.

Alcohol as a Sedative-Hypnotic Drug

Chemically, the classification of ethanol as an alcohol is based on its molecular structure. Pharmacologically, ethanol belongs to the class of *sedative-hypnotics*. This classification is based on its effect on the nervous system. Sedative-hypnotics are central nervous system depressants; they are not necessarily similar in chemical structure, but rather in their pharmacological function. As their dosage increases, their sedative effects progress. The sedative-hypnotics family includes barbiturates, the so-called minor tranquilizers such as Valium, and general anesthetics.

The initial effect of sedative-hypnotics, including alcohol, is to depress the inhibitory synapses of the brain. Since the negation of a negative is a positive, the depression of the inhibitory synapses is excitatory. This is one reason why alcohol is sometimes misclassified as a stimulant, rather than as a depressant. Behaviorally, this disinhibition may manifest itself in high spirits and a "devil may care" attitude. Subjectively, it may be experienced as euphoria. There is often a concomitant reduction in anxiety, especially in inhibited people. It is for this reason that the superego—Freud's term for the conscience—has been defined as that part of the psyche that is soluble in alcohol. The sensation of euphoria and feeling carefree are what many drinkers seek. However, excitatory synapses are soon depressed, and the behavioral and experiential effects of alcohol catch up with its pharmacological effect, which has been primarily depressive all along. The progressive effects of sedative-hypnotics, including alcohol, are depicted in

Figure 1.8. There is another, not quite as scientific, way to conceptualize the effect of progressively greater doses of ethanol on the drinker: jocose, bellicose, lachrymose, comatose!

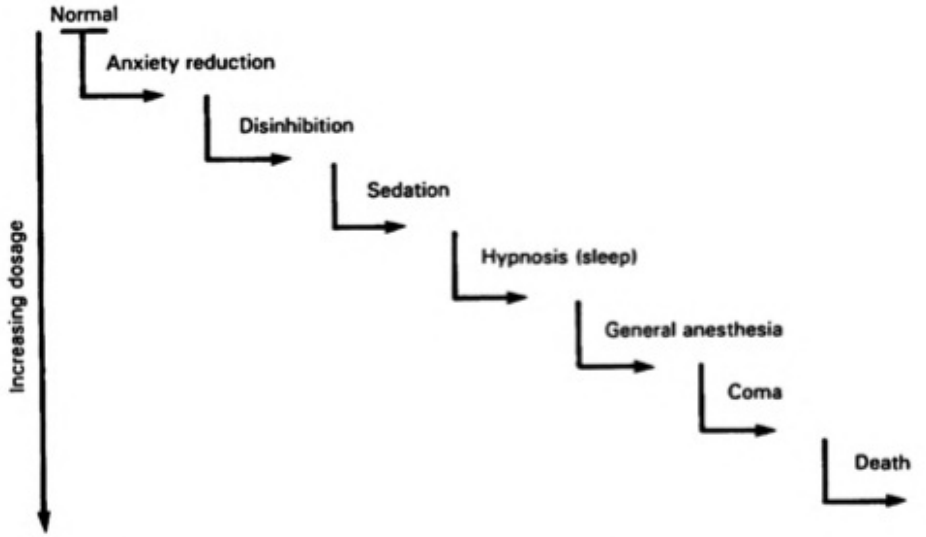

Figure 1.8 Progressive effects of sedative-hypnotics.

As will be discussed in more detail later, alcohol is addictive in that the drinker develops a tolerance to it, requiring more and more to get the same effect, and in that withdrawal symptoms are experienced after cessation of heavy and/or prolonged drinking.

METABOLISM OF ALCOHOL

Metabolism is the sum total of the chemical processes and energy exchanges that take place within an organism. Metabolic processes include the *anabolic*, in which more complex substances are built from simpler ones (as when the constituents of protoplasm are built from the amino acids derived from ingested proteins) and the *catabolic*, in which more complex substances are converted into simpler ones, usually with the liberation of energy (as when the glucose derived from ingested carbohydrates is converted into carbon dioxide, water, and energy). Life is dynamic; building up and tearing down, construction and destruction, anabolism and catabolism ebb and flow ceaselessly.

Metabolic processes usually either require or release energy. Metabolic processes take place in every cell and tissue of the human body, but the liver is a specialized organ designed to do metabolic work. The liver performs most specialty metabolic processes, such as the metabolism of drugs and of some hormones. It is, among other things, a very complex and efficient "chemical factory." Since the liver has a uniquely arranged blood supply, the *hepatoportal circulatory system*, that conveys substances absorbed by the gastrointestinal tract directly to and through it, any substance that is absorbed from the gut and enters the bloodstream can be readily acted on by the liver. This is true of alcohol, which is largely metabolized by the liver. The metabolism of alcohol entails its chemical conversion into metabolites and energy. The metabolites, or breakdown products, are then eliminated from

the body.

The metabolism of alcohol—its conversion into waste products and energy—is to be distinguished from its pharmacological effects, discussed earlier. The metabolism of alcohol is a process by which it is changed and eliminated from the body; its pharmacological action is the result of the effects of the intact alcohol molecule on the functioning of the neuron. The two are often confused.

The Normal Pathway

The metabolism of alcohol by the liver takes places in several steps. These steps occur in the individual liver cells, the *hepatocytes*, which contain the "ingredients" necessary for these metabolic transactions to take place. Essentially, there must be (1) something with which the alcohol can react and (2) an enzyme to facilitate that reaction. The hepatocyte has both, dissolved in its cytoplasm. The first is *nicotinamide adenine dinucleotide* (NAD), and the second is *alcohol dehydrogenase* (ADH). The first is a *cofactor*, the second is an enzyme. The first "reacts" with alcohol; the second facilitates that reaction. In the reaction, alcohol "loses" a hydrogen ion, which is "gained" by the NAD. Thus, the cofactor, or *coenzyme*, serves as a *hydrogen receptor*. In this reaction alcohol is converted into an aldehyde, *acetaldehyde*. This is illustrated by structural formulas in Figure 1.9.

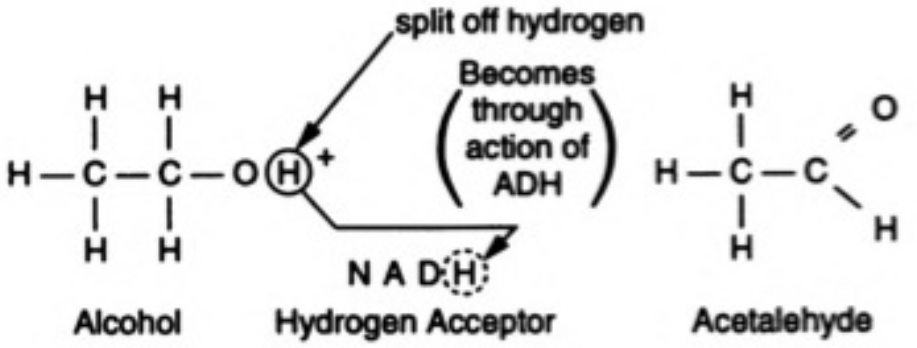

Figure 1.9 Alcohol is metabolized to acetaldehyde.

When alcohol is converted into acetaldehyde, the hydrogen ion circled in the figure is split off and transferred to the NAD, with which it combines to form NADH. Simultaneously, the carbon attached to the hydroxyl radical (OH) of the alcohol molecule forms a double bond with the oxygen. The alcohol has now become acetaldehyde. This process takes place only in the presence of a specific enzyme. Since this enzyme facilitates the removal of a hydrogen atom from the alcohol molecule, it is called alcohol dehydrogenase. It is primarily found in the hepatocytes. This is why alcohol metabolism is almost entirely a liver function. The kidney and stomach contain some ADH, so they too have a role in the metabolism of alcohol, but it is a minor one. The amount of ADH, which is fixed, sets the maximum rate at which alcohol is normally metabolized. This rate is independent of the concentration of alcohol in the blood and is approximately the alcohol contained in one drink per hour. This first step in the metabolism of alcohol can be symbolized as follows:

Ethanol			ADH	Acetaldehyde
C_2H_5OH	+	NAD	⇒	C_2H_4O + NADH

Acetaldehyde is then converted by the enzyme *aldehyde dehydrogenase* (AldDH) into acetate. NAD again acts as a hydrogen acceptor. The reaction is as follows:

Acetaldehyde		AldDH		
C_2H_4O + NADH		⇒	Active acetate	+ NADH

The drug *disulfiram*, sold under the trade name *Antabuse*, blocks the conversion of acetaldehyde to acetate, leading to accumulation of acetaldehyde, which is highly toxic, in the body. This property of disulfiram has led to its use in the treatment of alcoholism. The Antabuse user cannot drink alcohol without becoming acutely and severely ill. Depending on the dosage of Antabuse, its reaction with alcohol ranges from unpleasant to potentially lethal.

Acetaldehyde can react with a number of neurotransmitters, including *dopamine*—which plays a vital role in both normal and pathological brain function—to produce a class of chemicals known as *tetrahydrosioquinolines* (TIQs). TIQs are similar in structure to opiates, such as morphine, and have similar effects. Morphine is, of course, addictive. When TIQs are injected into certain parts of animal brains, the animals develop an addiction to alcohol. It is speculated that a similar mechanism, the production of TIQs from the reaction of acetaldehyde with various neurotransmitters in chronic heavy

drinkers, is implicated in alcohol addiction in humans. In animals, addictive drinking continues whenever they have access to alcohol, once their brains have been exposed to TIQs. If this animal model has relevance to humans, it would have important implications for the treatment of alcoholism—namely, that total abstinence from alcohol would necessarily be the treatment of choice for neurochemical reasons, quite apart from psychological factors. However, this is a theory and not a fact about the development of alcohol addiction.

Acetate, which is the end product of the second stage of alcohol metabolism, in turn undergoes a complex series of metabolic reactions known as the *Krebs cycle*, or *tricarboxylic acid cycle*. The Krebs cycle is the final common pathway for the conversion of sugars, fatty acids, and amino acids into energy. Thus, it is not unique to the metabolism of alcohol. The Krebs cycle is the means by which energy is derived from alcohol. The acetate is burned, so to speak, in this cycle. Since energy is derived from it, alcohol is, in this limited sense, a food—one that consists of empty calories. Alcohol provides nothing that the body can use to build new tissue—no vitamins, minerals, or amino acids; it is simply used as a fuel in the series of steps described above.

The conversion of NAD, which plays an important role as a hydrogen acceptor in many metabolic processes, into NADH during the metabolism of

alcohol significantly changes the chemical environment of the liver. There is now less NAD available for the other work of the liver. NADH is ultimately changed back to NAD by the *mitochondria*, an organelle in the cell that does specialized metabolic work; however, this process requires both time and the expenditure of energy. When alcohol consumption is heavy, the mitochondria cannot keep up and the NAD/ NADH ratio remains altered. These changes in hepatocyte chemistry impair the normal biochemical activities of the liver, which can result in a variety of disease processes. Explicitly, the metabolism of both carbohydrates and fats in the liver is affected by the altered NAD/NADH ratio, with its resultant reduction in the availability of a basic hydrogen acceptor. These processes and their resulting pathologies will be discussed in more detail in the next chapter.

ADH and AldDH, like all enzymes, have complex molecular structures involving many constituent atoms and ionic groups. These atoms and groups can be put together in more than one way. Variations in the structure of the constituents of a molecule are called isomers. An example we have already encountered is propyl alcohol, the alcohol that contains three carbon atoms. Its empirical formula is C_3H_7OH, but it can have different forms depending on where the OH group is attached. Propyl alcohol is shown in Figure 1.10 and its isomer, isopropyl alcohol is shown in Figure 1.11. In the case of enzymes whose molecules are far bigger and more complex than alcohol molecules, the structural variants are called *isoenzymes*. Isoenzymes are also known as

atypical enzymes. Both ADH and AldDH have isoenzymes. The amount of atypical ADH and atypical AldDH is genetically determined and is an individual variation. The presence or absence of atypical forms of these liver enzymes affects alcohol metabolism. Some researchers postulate that such variations in liver enzymes affect susceptibility to alcoholism and may be a predisposing factor. Being a genetically determined trait, this lends credence to theories of the heritability of alcoholism. The precise mechanisms by which the atypical enzymes would predispose to alcoholism, if this is indeed the case, are unknown.

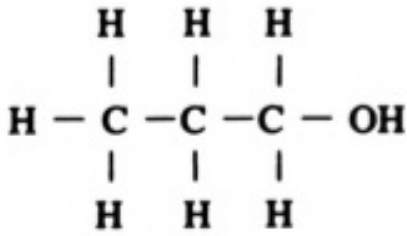

Figure 1.10 Structural formula of propyl alcohol.

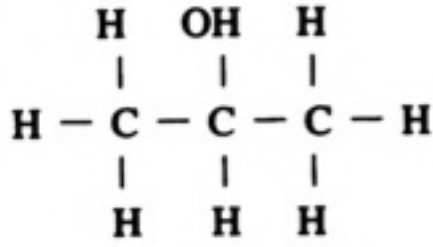

Figure 1.11 Structural formula of isopropyl alcohol.

Other Pathways

There are other enzymes in the hepatocytes that can facilitate conversion of alcohol to acetaldehyde. They normally play a minor role in the metabolism of alcohol. However, with prolonged heavy drinking, these "alternate pathways" come to play a more significant role. They are "overflow valves," called into play when the primary valve, metabolism by ADH, is overburdened. There are two alternate pathways: the metabolism of alcohol by the enzyme *catalase*, in which the cofactor is hydrogen peroxide, and metabolism by the *microsomal ethanol oxidizing system* (MEOS). Both change alcohol to acetaldehyde. Microsomes are organelles that have explicit metabolic functions. The MEOS is involved in the metabolism of many drugs as well as various naturally occurring substances, including some hormones. Repeated heavy drinking "induces" (that is, produces more of) the enzymes involved in the MEOS. This is not true of ADH. The buildup of microsomes, thread-like particles in the cytoplasm of the hepatocytes, can be seen under the microscope. This induction of the MEOS means that alcohol is metabolized more rapidly by a heavy drinker, and this is one of the bases of the development of tolerance for alcohol by the heavy drinker. The other is accommodation of the neurons themselves to alcohol. Since the MEOS also metabolizes other drugs, *cross-tolerance* is built, and more of these other drugs become necessary for them to achieve the same effect. *Cross-addiction and cross-tolerance* are terms that are often confused. Cross-addiction means

addiction to more than one drug—alcohol and cocaine, for example. Cross-tolerance means that the tolerance a person has acquired for a given drug, so that more of that drug is needed to get the same effect, makes that person more tolerant of other drugs in the same pharmacological class. For example, increased tolerance for one sedative-hypnotic drug, such as alcohol, results in increased tolerance for other such drugs (such as Quaalude). Barbiturates and general anesthetics are among the drugs to which cross-tolerance is built by heavy drinking. This can be of considerable practical importance, as when an active alcoholic requires emergency surgery and normal levels of anesthetics are ineffective because of cross-tolerance.

ELIMINATION OF ALCOHOL

Approximately 95% of the alcohol ingested is absorbed and metabolized as described above. What is eliminated are the end products of that metabolic process: carbon dioxide and water. Carbon dioxide is eliminated by the lungs and water by the kidneys. The increased urinary frequency observed after drinking is due partly to fluid intake, partly to the direct effect of alcohol on the kidneys, and partly to alcohol's suppression of the antidiuretic hormone produced by the pituitary gland. Five percent of the alcohol is eliminated unmetabolized, primarily in the urine and respired air. (This active exhalation of unchanged alcohol is the reason breath mints do little to conceal alcohol consumption.) If alcohol consumption has been heavy

and prolonged, some of the alcohol will be excreted in the sweat.

About the Author

Jerome D. Levin, Ph.D., has treated addictions for over thirty years. He is the author of eleven previous books and has taught at Suffolk Community College, Marymount Manhattan College, St. Joseph's College, and the New School for Social Research, where he directed a program to train addiction counselors for over twenty-five years. He practices psychotherapy in Manhattan and Suffolk County, New York. You can contact Dr. Levin at jeromedlevin@gmail.com or (212) 989-3976.

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Notes

[1] Henceforth the word alcohol, unless otherwise noted, will be used to mean ethyl alcohol.

[2] Some biologists classify the fungi as a phylum of plants, others consider the fungi a separate "kingdom.