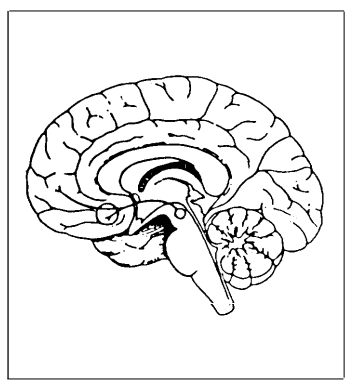
Biology and Pharmacology 3

Substance abuse and addiction are complex phenomena that defy simple explanation or description. A tangled interaction of factors contribute to an individual's seeking out, use, and perhaps subsequent abuse of drugs. Since more individuals experiment with drugs than eventually develop substance abuse problems, great interest persists in understanding what differentiates these groups. Factors that can play a role in drug abuse susceptibility include a person's psychological make-up (e.g., self-esteem, propensity to take risks, impulsivity, depression), biological response to drugs, environmental situation (e.g., peer groups, family organization, socioeconomic status), and the availability of drugs. The exact combination of elements that lead to substance abuse varies among individuals.

Underlying all substance use, abuse and addiction are the actions and effects that drugs of abuse exert. For a complete understanding of drug abuse and addiction one must address how drugs affect the brain, why certain drugs have the potential for being abused, and what, if any, biological differences exist among individuals in their susceptibility to abuse drugs. While many other factors ultimately contribute to an individual's drug-taking behavior, understanding the biological components is crucial in understanding substance abuse, addiction, and dependency.



Two biological factors contribute to substance use, abuse, and addiction: the effects drugs of abuse exert on a person; and the biological status of the individual taking drugs. The former relates to the acute mechanisms of action of drugs in the brain and the long-term effects that occur after chronic exposure. The latter pertains to an individual's biological constitution, most importantly the presence of inherited characteristics that affect that person's response to a drug.

BOX 3–1: Neuropharmacology

Neurons are the cells that process information in the brain. Neurotransmitters are chemicals released by neurons to communicate with other neurons. When a neuron is activated it releases a neurotransmitter into the gap between two neurons (see figure 3-1). The molecules of the neurotransmitter move across the gap and attach to proteins, called receptors, in the outer wall of an adjacent cell. Once the receptor is activated, the neurotransmitter is removed from the gap, either by reabsorption into the neuron that released it or by being broken down chemically.

For each neurotransmitter in the brain, there are specific receptors to which it can attach Receptors and receptor subtypes can activate a variety of membrane and cellular mechanisms. In this way, one chemical can have diverse effects in different areas of the brain. Many chemicals have been identified as neurotransmitters. Some particularly relevant to the reported pleasurable sensations associated with drug abuse include dopamine, norepinephrine, serotonin, opioids and other neuropeptides, gamma ammo butyric acid (GABA), and glutamate.

A neuron can have thousands of receptors for many different neurotransmitters. Some neurotransmitters activate neurons (excitatory neurotransmitters), while others decrease neuron activity (inhibitory neurotransmitters) Some receptors are biochemically coupled the activation of one modulates the function of the other, either increasing or decreasing its activity. A neuron can also have receptors for the chemical it releases, In this way, neurons can regulate their release of a particular neurotransmitter. Thus, these so-called autoreceptors act as a feedback mechanism. The activity of a neuron will be determined by the cumulative activity of all its various receptors.

Drugs that work in the brain, including drugs of abuse, alter normal neuropharmacological activity through a variety of different mechanisms. They can affect the production, release, or reuptake of a chemical, they can mimic or block the action of a chemical at a receptor. or they can interfere with or enhance the activity of a membrane or cellular mechanism associated with a receptor. Prolonged drug use has the potential to alter each of these processes.

SOURCE Off Ice of Technology Assessment, 1994

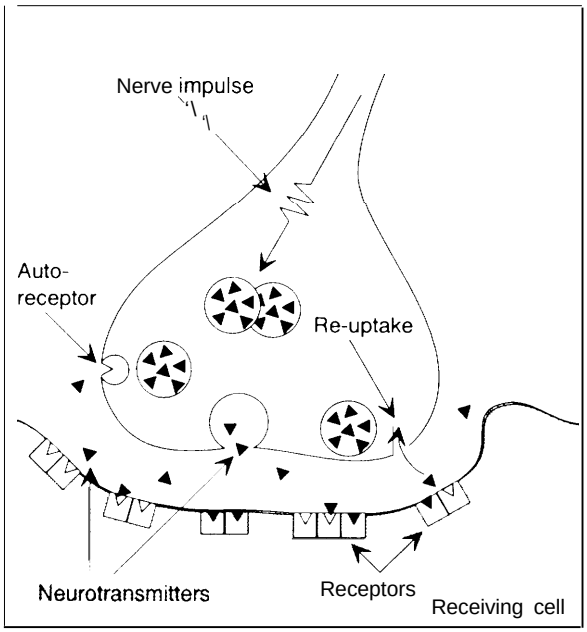
The biological mechanisms of substance abuse are complex and interactive. A previously published background paper by the Office of Technology Assessment (OTA) entitled *Biological Components of Substance Abuse and Addiction* thoroughly discusses the basic concepts, neuropharmacology, and genetics of drug abuse. This chapter is a synopsis of the background paper.

DRUG ACTION

Acute Actions

Drugs of abuse alter the brain's normal balance and level of biochemical activity (see box 3-1). In order to have these affects, a drug must first reach the brain. This is accomplished by the drug diffusing from the circulatory system into the brain. The routes of administration, methods by which a drug enters the bloodstream, affect how quickly a drug penetrates the brain. The chemical structure of a drug plays an important role in the ability of a drug to cross from the circulatory system into the brain. The four main routes of administration for drugs of abuse are oral, nasal, intravenous, and inhalation. With oral ingestion, the drug must be absorbed by the stomach or gut which results in a delay before effects become apparent. When the nasal route of administration is used, effects are usually felt within 3 minutes, as the capillary rich mucous membranes of the nose rapidly absorb substances into the bloodstream. Intravenous administration usually produces effects in 1/2 to 2

FIGURE 3–1: The Synapse and Associated Structures



SOURCE Off Ice of Technology Assessment, 1994

minutes and is slowed only by the detour back through the lungs that venous blood must take to reach the brain. Lastly, the inhalation method bypasses the venous system completely because the drug is absorbed into the pulmonary circulation which goes directly from the 1ungs to the heart and then to the brain. As a result, effects are felt within 5 to 10 seconds, making inhalation the fastest route of administration. The route of administration can determine the drug's potency and the efficacy the drug will have on affecting brain activity, thereby contributing to the abuse potential of the drug.

Distinct from other psychoactive agents, drugs of abuse, in part, affect those areas of the brain that mediate feelings of pleasure and reward (see box 3-2). Evidence is accumulating that positive sensations experienced during these activities are mediated by the brain reward system. Studies have shown that direct stimulation of the areas of the brain involved in the reward system, in the absence of any goal-seeking behavior, produces extreme pleasure that has strong reinforcing properties in its own right (48,60). Animals with electrodes implanted in these areas in such a way that electrical impulses produce a pleasurable sensation will repeatedly press a bar, or do any other required task, to receive electrical stimulation. The fact that animals will forego food and drink or will willingly experience a painful stimulus to receive stimulation of the reward system attests to the powerful reinforcing characteristics of the reward system. Most drugs of abuse, either directly or indirectly, are presumed to affect the brain reward system.

Inducing activity in the brain reward system gives drugs of abuse positive reinforcing actions that support their continued use and abuse. Drug reinforcement is defined as increasing the behavior that led to the taking of the drug. Put more simply, individuals who use drugs experience some effect, such as pleasure, detachment, or relief from distress which initially establishes and then maintains drug self-administration. The consequence of taking the drug enhances the probability that it will continue to be used for some real or perceived effect and, hence, tends to lead to continued compulsive self-administration. In fact, the ability of a drug to support self-administration in experimental animals is a measure of the drug's strength as a reinforcer.

While growing evidence suggests that the brain reward system plays a role in the reinforcing properties of most drugs of abuse, the precise mechanisms involved are complex, vary among substances, and have yet to be completely described (41 ,42,43). For example, while some drugs of abuse directly affect the chemical release of dopamine (see box 3-3), the interactions of other neurotransmitters such as gamma amino butyric acid (GABA), opioid peptides, and serotonin may also be important.

Chronic Actions

Chronic, long-term exposure to drugs of abuse can cause changes in the brain that may take weeks,

BOX 3–2: The Brain Reward System

Eating, drinking, sexual, and maternal behaviors are activities essential for the survival of the individual and the species. Natural selection, in order to ensure that these behaviors occur, has imbued them with powerful rewarding properties. The brain reward system evolved to process these natural reinforcers.

The reward system is made up of various brain structures. A key part of this system for drug reward appears to be the mesocorticolimbic pathway (MCLP). The MCLP is composed of the axons of neuronal cell bodies in the middle part of the brain (i.e., ventral tegmental area) projecting to areas in the front part of the brain (I. e., the nucleus accumbens, a nucleus in the limbic system, a network of brain structures associated with control of emotion, perception, motivation, gratification, and memory; medial prefrontal cortex, part of the front of the brain revolved with higher ordered thinking) (see figure 3-2). Ventral tegmental neurons release the neurotransmitter dopamine to regulate the activity of the cells in the nucleus accumbens and the medial prefrontal cortex. Other parts of the reward system include the nucleus accumbens and its connections with other limbic structures, and other regions in the front part of the brain (i.e., substantia innominata-ventral palladium) The nucleus accumbens also sends signals back to the ventral tegmental area, Finally, other neuronal pathways containing different neurotransmitters regulate the activity of the mesocorticolimbic dopamine system and may also be revolved in mediating the rewarding properties of drugs of abuse.

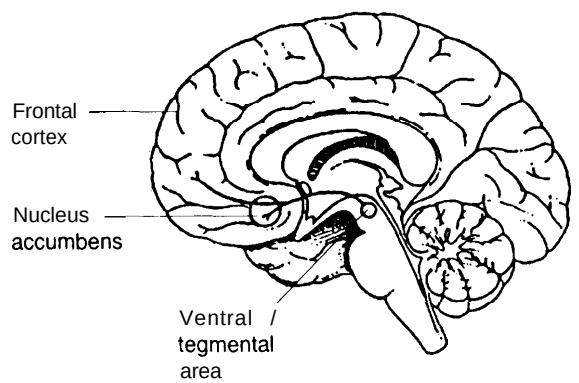
SOURCE Koob, G F, "Drugs of Abuse Anatomy, Pharmacology, and Function of Reward Pathway s," Trends in Pharmacological Sciences 13177-184, 1992, Koob, G F, "Neural Mechanisms of Drug Reinforcement," PW Kalivas and H H Samson (eds), The Neurobiology of Drug and Alcohol Addiction, Annals of the American Academy of Sciences 654171-191, 1992

months, and possibly years, to reverse once drug use has stopped.

Most drugs of abuse have complex actions in the brain and other parts of the body resulting in a variety of behavioral effects. In general, tolerance develops to many of the effects of drugs of abuse and a withdrawal syndrome occurs on cessation after prolonged use. However, the details of these phenomena vary from drug to drug, and the specific details of the biological mechanisms that underlie these phenomena are not completely understood. Recent advances in neuroscience research have begun to unravel how neuroadaptive responses manifest themselves for various drugs of abuse.

Tolerance to a drug develops when, following a prolonged period of use, more of the drug is required to produce a given effect (33,38). This response occurs with many types of drugs. It is a common, but unnecessary, characteristic of drug abuse (see box 3-4). For example, while tolerance develops to some of the effects of cocaine and amphetamines, sensitization can also occur to some of their other effects. Also, while it is unclear from available data whether tolerance develops to cocaine's reinforcing effects, the notion is supported by some experimental evidence and

FIGURE 3–2: The Mesocorticolimbic Pathway



SOURCE Off Ice of Technology Assessment, 1994

BOX 3–3: How Drugs of Abuse Affect the Chemical Release of Dopamine

The rewarding properties of stimulant drugs such as cocaine and amphetamines are due directly to the effects of the chemical dopamine. Opiates, on the other hand, Indirectly stimulate dopamine by activating other chemical pathways, which in turn increase dopamine activity. Similarly, alcohol, barbiturates, and benzodiazepines likely have an Indirect action which Increases dopamine activity All of these drugs have reinforcing properties Phencyclidine (PCP) is also a strong reinforcer but its relationship, if any, to activity in the dopamine pathway has yet to be established. Other drugs are either weak reinforcers or have not been shown to support self -administration in animal experiments. Nicotine stimulates dopamine neurons, however, its effect is modest when compared with cocaine or amphetamine Likewise, caffeine is a weak reinforcer, but the precise mechanisms of its reinforcement are unclear. Finally, cannabis and lysergic acid diethylamide (LSD) also produce positive effects that clearly support their use

SOURCE Office of Technology Assessment 1994

anecdotal reports from cocaine users that the drug's euphoric action diminishes with repeated use. In a recent study, it has been shown that acute tolerance to dopamine response is induced by binge patterns of cocaine administration in male rats (51). Tolerance develops to most of the effects, including the reinforcing properties, of opiates, barbiturates, and alcohol.

Sensitization, the opposite of tolerance, occurs when the effects of a given dose of a drug increase after repeated, but intermittent, administration. Sensitization to a drug's effects can play a significant role in supporting drug-taking behavior.

Dependence is a type of neuroadaptation to drug exposure. With prolonged use of a drug, cells in the brain adapt to its presence such that the drug is required to maintain normal cell function. On abrupt withdrawal of the drug, the cell behaves abnormally and a withdrawal syndrome ensues. Generally, the withdrawal syndrome is characterized by a series of signs and symptoms that are opposite to those of the drug's acute effects. For example, withdrawal of sedative drugs produce excitation and irritability. Conversely, withdrawal of stimulants produces profound depression.

The magnitude of the withdrawal syndrome varies from drug to drug. Although the severity varies, withdrawal is associated with the cessation of use of most drugs of abuse. Opiates, cocaine, amphetamines, barbiturates, alcohol, and benzodiazepines produce pronounced and sometimes severe withdrawal symptoms (20,24,56,68,74) while those for nicotine and caffeine are less intense (1,3 1). A mild withdrawal episode is associated with discontinued cannabis use, while none is associated with lysergic acid diethylamide (LSD) use (12,63). No matter the severity of the physical withdrawal syndrome, its existence can create a craving or desire for the drug and dependence can play a very strong role in recurrent patterns of relapse and maintaining drug-seeking behavior to forestall withdrawal.

At one time, withdrawal was believed to peak within several hours after drug-taking was discontinued and then dissipate; similarly, common knowledge held that tolerance to most drugs was thought to dissipate gradually with time, as the brain readapted to the drug's disappearance. Substantial evidence now indicates that persistent, residual neuroadaptations are present, which can last for months or possibly years, and mayor may not be associated with the pathways that mediate physical dependence (33,44,45,77). An important component of this phenomena maybe the learning which takes place during drug-taking behavior. Moreover, with repeated cycles of abstinence and reinitiation of drug use, the time required to elicit drug dependence grows shorter and shorter. Evidence also indicates that the administration of naloxone, a drug that blocks the actions of opiates, may elicit a withdrawal syndrome in individuals who have abstained from use for extended periods of time. These data indicate the existence of long--lasting, drug-induced neuroadaptive changes that

BOX 3-4: The Two Types of Tolerance

The two types of tolerance are: dispositional (pharmacokinetic) and pharmacodynamic. Dispositional tolerance develops when the amount of drug reaching active sites in the brain is reduced in some way Generally, this arises from an Increased breakdown of the drug or a change in its distribution in the rest of the body Thus, more drug must be taken to achieve the same blood levels or concentrations at the active sites in the brain.

Pharmacodynamic tolerance represents a reduced response of the brain to the same level of drug It develops during the continued and sustained presence of the drug. It may be that the mechanism of adaptation may differ from drug to drug and depend on the original mechanism of action of a given drug. The net effect is that more drug is required to overcome this new neuronal adaptation to produce an equivalent pharmacologic effect.

Although dispositional tolerance represents a component of tolerance to some drugs (e g., alcohol, barbiturates), in most cases much or all of the tolerance which develops to drugs with significant abuse potential can be attributed to pharmacodynamic tolerance, Tolerance can contribute to drug-taking behavior by requiring that an Individual take larger and larger doses of a drug to achieve a desired effect.

SOURCES Jaffe, J.H "Drug Addiction and Drug Abuse, " The Pharmacological Basis of Therapeutics, A G Gilman, TW Rail, A S Nies, and P Taylor (eds), (New York Pergammon Press, 1990) Kalant, H , "The Nature of Addiction An Analysis of the Problem, " Molecular and Cellular Aspects of the Drug Addictions, A Goldstein, (cd) , (New York, NY Springer Verlag, 1989)

persist for as yet undefined periods of time. Although information explaining this effect is lacking, these changes may help account for the relapses that sometimes occur in long-term abstinent, drug-dependent individuals.

Abuse Liability

The Comprehensive Drug Abuse Prevention and Control Act (Public Law 91-5 13) and the Psychotropic Substances Act of 1978 (Public Law 95-633) gives exclusive authority to the Secretary of the Department of Health and Human Services to determine the abuse liability of substances and to make recommendations concerning substance regulation and other drug policy decisions. Although the Secretary receives advice from the Drug Enforcement Administration (DEA), the Food and Drug Administration (FDA), and various other regulatory agencies, these laws explicitly state that the National Institute on Drug Abuse (NIDA) must provide to the Secretary information relevant to the abuse potential of suspected drugs of abuse and all facts key to an assessment of their abuse potential. On the basis of this information from NIDA, and input from FDA and DEA, the Secretary makes a judgment as to the dependence potential of new drugs. NIDA supports a variety of activities in commercial and private laboratories around the country to provide this information.

A drug's abuse liability is measured by the likelihood that its use will result in drug addiction. Many factors ultimately play a role in an individual drug-taking behavior; nevertheless, the abuse potential of a drug is related to its intrinsic rewarding properties and/or the presumed neuroadaptive motivational effects that result from its prolonged use. Drugs can be tested and screened for their abuse liability in animals. Four criteria can be evaluated to classify a drug as having significant abuse potential:

- pharmacological equivalence to known drugs of abuse,
- demonstration of reinforcing effects,
- tolerance, and
- physical dependence.

The capacity to produce reinforcing effects is essential to any drug with significant abuse potential, whereas tolerance and physical dependence often occur but are not absolutely required to make such a determination.

Testing new pharmaceuticals for their abuse potential is an important step in new drug development. Many major pharmaceutical firms today emphasize the development of new and safer drugs for pain reduction and in the development of psychoactive compounds for treatment of brain disorders. In particular, scientific strides in understanding the brain, neurological disease, psychiatric disturbances, and aging are fueling research into treatment of brain disorders. As psychoactive compounds become available, they must be screened for abuse potential. The abuse liability assessment of new products is not simply at the discretions of the manufacturer. Various federal regulatory laws mandate such testing and federal regulatory agencies are charged with seeing that testing is carried out. The College on Problems of Drug Dependence (CPDD), and, specifically, its Drug Evaluation Committee (DEC), provides the majority of abuse liability testing information to NIDA.

Animal models are generally used to screen for the abuse potential of new drugs in earlier stages of drug development or to evaluate abuse potential in drugs that cannot be readily studied in humans (2). Laboratory methods for abuse potential evaluation in humans are also well developed and is an area of active research (21). However, factors such as the heterogeneity of drug-using populations, the use of multiple drugs, and the other biological, social, and environmental factors involved in human drug use make human studies complex.

In terms of the validity of animal models as a means of studying human drug addiction, an excellent correlation exists between predicting the abuse liability of specific classes of drugs in animals and humans (34). However, it is recognized that animal models are imperfect and, in fact, there are examples of drugs that proved to have significant abuse potential in humans, whereas the preclinical testing in animals revealed relatively minimal abuse potential (9,33,38). The ultimate answer to the issue of whether a drug has significant abuse potential is long-term experience with the drug once it has become available, either legally or illegally. Nevertheless, animal models serve as the only practical means of initially screening drugs for abuse liability and have proven to be the most effective means of detecting whether there is likely to be a problem in humans.

Self-Administration

The predominant feature of all drugs with significant addiction-producing properties is that they are self-administered. In fact, self-administration of a drug to the point when the behavior becomes detrimental to the individual is the primary criterion for classifying a drug as having significant abuse potential for addiction. In addition to self-administration, another contributing factor to abuse liability is the notion of craving (9.33,38). Although craving is a difficult term to quantify, once a drug is voluntarily or involuntarily withdrawn, the increased desire to take the drug can play a role in the relapse to substance abuse. As previously mentioned, the reinforcing properties of the drug may shift the pattern of administration established during the initial, early phase of drug addiction. Specifically, the drug may have initial] y been self-administered for its pleasurable effects but may eventually be self-administered to relieve the discomfort associated with withdrawal.

Animals can be readily trained to self-administer drugs in a variety of settings (9). Animal models of self-administration provide a powerful tool that can give a good indication of the abuse liability of new or unknown drugs. These models also permit examination of the behavioral, physiological, and biological factors leading to sustained self-administration.

Drug Discrimination

Another tool in the assessment of abuse liability of drugs is drug discrimination, which refers to the perception of the effects of drugs (3,9). Specifically, animals or humans trained to discriminate a drug from a placebo show a remarkable ability

to discriminate it from other drugs with different properties. These procedures also permit a determination of whether the subject considers the drug to be the pharmacological equivalent of another drug. Pharmacological equivalence refers to the fact that drugs of particular classes, such as opiates, stimulants, and depressants cause a series of affects on the brain and other organs which collectively constitute their pharmacological profile. Drug discrimination provides a useful measure in animals to assess the subjective effects of drugs in humans.

Dependence and Tolerance

Physical dependence and tolerance to drugs of abuse can readily be induced in animals by chronic administration of these drugs (37,38). Following abrupt cessation of these drugs, a withdrawal syndrome will often develop and, if given the opportunity, self-administration rates will be increased. Furthermore, since the understanding of the biological changes which take place during the development of physical dependence and tolerance are poorly understood in humans, with the possible exception of opiate dependency (45), animal models offer a unique opportunity to carry out experiments designed to address these issues.

GENETIC FACTORS

Why does one person abuse or become dependent on drugs while another, exposed to a similar environment and experiences, does not? To date, the majority of biomedical research has focused on the role, if any, that genetics plays in individual susceptibility to substance abuse and dependence. There is growing interest, however, in researching other factors that effect a person's biological status. For example, nutrition, biological development, in utero experiences, early exposure to environmental lead, head injuries, and other environmental components, can modify individual neurophysiology. Thus, while this section features genetics, there are many other factors that can influence individual biological susceptibility to the effects of a drug.

Progress in understanding the genetics of various conditions and diseases has brought with it a realization that substance abuse and addiction probably involve a genetic component. That is, hereditary biological differences among individuals may make some more or less susceptible to drug dependency than others. However, a genetic component alone is undoubtedly insufficient to precipitate substance abuse and addiction. Unlike disorders such as Huntington's disease and cystic fibrosis that result from the presence of alterations in a single gene, any genetic component of substance abuse is likely to involve multiple genes that control various aspects of the biological response to drugs, individual temperament, and the propensity to engage in risk-taking behaviors, or physiological predisposition to become an abuser. In addition, the involvement of many behavioral and environmental factors indicates that any genetic component acts in consort with other nongenetic risk factors to contribute to the development of substance abuse and addiction. Thus, the presence or absence of a genetic factor neither ensures drug addiction nor precludes it.

Two questions arise when considering a genetic component to substance abuse and addiction. Do inherited factors exist? If so, what are they? To date, most of the work done in this field is related to alcoholism; much less is known about the genetics of other drugs of abuse.

Do Inherited Factors Exist?

Results from family, twin, and adoption studies as well as extensive research on animal models indicate that there are heritable influences on patterns of alcohol use. Animal studies using selective breeding techniques have established that alcohol preference, the reinforcing actions of alcohol, alcohol tolerance, and alcohol physical dependence can be affected by genetic factors. Although fewer studies have examined the genetic component of vulnerability to the addictive properties of other drugs of abuse, evidence from animal studies confirms the role of a genetic influence on the use and abuse of drugs other than alcohol. To study non-

alcoholic drug abuse in humans has been difficult because of substantially lower population prevalence and marked changes in availability and, hence, exposure to these substances. Investigation in this area is further hampered by the complexity of subjects' drug use—most drug abusers have used (and had problems from using) multiple substances. This has led researchers either to concentrate on one class of drug or to treat all illicit drug use as equivalent. The tendency to lump all illicit drugs into one category makes results difficult to interpret or compare.

Family Studies: Alcoholism

References to a familial tendency or hereditary "taint" of alcoholism date back to classical times (23). Family studies have repeatedly confirmed that the risk of alcoholism is higher among first-degree relatives (i.e., parents, siblings, children) of alcoholics as compared with the general population (54). Moreover, while family studies can establish that a disorder (or liability to a disorder) is transmitted, in general they fail to distinguish between biological and environmental transmission. This issue, however, can be evaluated in large family studies by analyzing multiple classes of relatives with differing degrees of genetic relatedness.

Results of numerous family studies indicate that alcoholism segregates within families, with male first-degree relatives of alcoholics having a higher incidence (ranging from 27 to 54 percent) than female first-degree relatives (6 to 17 percent) as compared to first-degree relatives of nonalcoholics (20 percent of males, 4 percent of females) (26,66,76). In fitting models of inheritance to family data, researchers concluded that observed patterns of inheritance were consistent with the hypothesis that familial factors predisposing to alcoholism were the same in men and women, but that nonfamilial environmental factors exerted more influence in the development of alcoholism in women (14). However, a review of drug abuse research on women presented several comparative studies of men and women showing that alcoholism among some women appeared more highly correlated with a family history of alcohol problems. Compared to alcoholic men in various studies, alcoholic women had a greater likelihood of having an alcoholic father and/or parents, as well as alcoholic siblings (47). Additionally, while perhaps not genetically influenced, familial alcoholics (those with at least one relative with alcoholism) appear to have earlier onset, more antisocial symptoms, more social complications of alcohol use, and worse treatment outcome than nonfamilial alcoholics (22,62,70).

Familial is not identical to genetic, and in the case of alcoholism, the familial patterns of inheritance are not consistent with those of a purely genetic condition (36,79). In addition, researchers suggest that the transmissibility of alcoholism has increased over time (65). Thus, any genetic factors promoting the development of alcoholism are significantly moderated by nongenetic influences.

Family Studies: Other Drugs

Although fewer family studies have been conducted on the genetic transmission of liability to other drugs of abuse, researchers suggest that, as in the case of alcohol, addiction to other psychoactive substances appears to run in families.

One study found evidence of drug use running in families, based on family history obtained from individuals admitted for substance abuse treatment (53). However, this study combined use of all illicit drugs into one category and relied on self-reports by the subject on his or her drug use as well as that of family members. A large family interview of opiate addicts found that the relatives of opiate users had elevated rates of drug addiction as compared with the controls (67). In addition, an association was found between opiate use and the presence of antisocial personality disorder (ASPD). Further analysis of these data revealed that the incidence of both drug abuse and ASPD was higher among the siblings of the opiate subjects than among their parents (49,50).

A familial association between opiate addiction and alcoholism has been noted in some studies (46). However, another family history study found that while both opiate addiction and alco-

holism clustered within families, co-occurrence of the disorders within families occurred only as frequently as expected by chance, thus supporting the hypothesis of independent transmission (29).

Little has been done to test hypotheses regarding familial transmission of liability to addiction to specific substances other than opiates or alcohol. One study examining treated drug abusers and their relatives found that alcoholism was equally common among relatives of individuals who preferentially abused opiates, cocaine, or sedative-hypnotics (27 percent, 31 percent, and 24 percent of male relatives, respectively), whereas relatives of sedative-hypnotic users were subject to diagnoses of other substance abuses (2 percent of male relatives, versus 11 percent of male relatives of opiate abusers and 16 percent of male relatives of cocaine abusers) (55).

Twin and Adoption Studies

Twin and adoption studies provide information to distinguish between biological and cultural transmission. Twin studies observe siblings raised in the same environment, but compare how often identical twins, who are genetically identical, and fraternal twins, who have the genetic similarity of nontwin siblings are concordant for a trait. A high concordance rate for a trait among identical twins versus fraternal twins usually indicates a genetic component for the trait. Adoption studies, by contrast, compare the presence of a trait among biological versus adoptive family members or other control groups. In this way individuals sharing the same environment but having different genetic heritages, or vice versa, can be compared.

Evidence from **twin studies** suggests genetic influences on drinking patterns as well as alcohol-related problems. Results from twin studies demonstrate genetic influences on measures of alcohol consumption such as abstention, average alcohol intake, and heavy alcohol use (28,39,61). Twin studies also indicate an inherited risk for smoking (16).

When evaluating the development of alcoholism, twin studies have generally supported the existence of genetic influences over the disorder's development. One early study found a higher concordance rate for alcohol abuse between identical twins (54 percent) than in fraternal twins (28 percent) (35), while two other studies did not find such a relationship (25,61). A 1991 study examined male and female identical twin pairs, and male and female fraternal twin pairs, with one member of the pair meeting the criteria for alcohol abuse or dependence (64). Researchers found that identical male twins differed from fraternal male twins in the frequencies of both alcohol abuse and dependence as well as other substance abuse and/or dependence. On the other hand, female identical and fraternal twins were equally likel y to abuse alcohol and/or become dependent on other substances, but identical female twins were more likely to become alcohol dependent. Another study of 356 twin pairs also found higher identical than fraternal rates of concordance for problems related to alcohol and drug use as well as conduct disorder (52). The same study also noted that among men, heritability played a greater role in the early rather than late onset of alcohol problems, whereas no such effect was seen among women. However, a study of 1,030 female twin pairs found evidence for substantial heritability of liability to alcoholism, ranging from 50 to 60 percent (40).

Thus, twin studies provide general agreement that genetic factors influence certain aspects of drinking. Most twin studies also show genetic influence over pathological drinking, including the diagnosis of alcoholism, which appears (like many other psychiatric disorders) to be moderately heritable. Whether genetic factors operate comparably in men and women, and whether severity of alcoholism influences twin concordance is less clear. How psychiatric comorbidity may affect heritability of alcoholism also remains to be clarified.

Adoption studies have supported the role of heritable factors in risk for alcoholism (6,1 1,71). The results from a series of studies conducted in Denmark during the 1970s are typical. Researchers studied male adoptees, later comparing them with nonadopted brothers; female adoptees, later

comparing them with nonadopted daughters of alcoholics, comparisons were also made with matched control adoptees. Sons of alcoholic and nonalcoholic parents who were put up for adoption were compared for the development of alcoholism. Sons of alcoholic parents were found to be four times as likely as sons of nonalcoholic parents to have developed alcoholism; evidence also suggested that the alcoholism in these cases was more severe. The groups differed little on other variables, including prevalence of other psychiatric illness or "heavy drinking." Being raised by an alcoholic biological parent did not further increase the likelihood of developing alcoholism; that is, rates of alcoholism did not differ between the adopted-away children and their nonadopted brothers. In contrast, a study of daughters of alcoholics revealed no elevated risk of alcoholism (23).

Another analysis examined factors promoting drug abuse as well as alcoholism (10). In this study, all classes of illicit drug use were categorized into a single category of drug abuse. Most of the 40 adopted drug abusers examined had coexisting ASPD and alcoholism; the presence of ASPD correlated highly with drug abuse. Among those without ASPD, a biological background of alcoholism (i.e., alcoholism in a biological parent) was associated with drug abuse. Also, turmoil in the adoptive family (divorce or psychiatric disturbance) was associated with increased odds for drug abuse in the adoptee.

Finally, results from other adoption studies suggest two forms of alcohol abuse (7,13). The two forms were originally classified by C.R. Cloninger as "milieu-limited" or type 1 alcohol abuse and "male-limited" or type 2 alcohol abuse (15). Type 1 alcohol abuse is characterized by moderate alcohol problems and minimal criminal behavior in the parents, and is generally mild, but occasionally severe, depending on presence of a provocative environment. Type 2 is associated with severe alcohol abuse and criminality in the biological fathers. In the adoptees, it is associated with recurrent problems and appears to be unaffected by postnatal environment.

While the appropriateness of the biological and environmental parameters used in the Cloninger study have been challenged, the discriminating characteristics used to classify individuals as type 1 or 2 alcohol abusers have not been-until recently. A new study of familial and nonfamilial male alcoholics has investigated the type 1 and 2 classifications by analyzing the importance of age differences and cohort distributions (19). The researchers showed that among the male alcoholics, there was not a clear distinction between familial and nonfamilial based alcohol abuse problems and type 1 or 2 characteristics, as reported in previous studies. Additionally, another recent publication discusses the absence of paternal sociopathy in the etiology of severe alcoholism, and the possibility of a type 3 alcoholism (30). This type of research raises obvious questions as to the validity of the discriminating characteristics originally outlined by Cloninger and currently used in the classification of individual alcohol abusers.

In summary, adoption studies of alcoholism clearly indicate the role of biological, presumably genetic, factors in the genesis of alcoholism. They do not exclude, however, a possible role for nongenetic, environmental factors as well. Moreover, researchers have suggested more than one kind of biological background may be conducive to alcoholism. In particular, one pattern of inheritance suggests a relationship between parental antisocial behavior and alcoholism in the next generation. Thus, adoption studies, like other designs, suggest that even at the genetic level, alcoholism is not a homogeneous construct.

What Is Inherited?

While study results indicate a probable genetic component to alcoholism and probably other drug abuse, they lack information about what exactly is inherited. For example, do individuals with a family history of drug abuse have an increased susceptibility or sensitivity to the effects of drugs with reinforcing properties? If a susceptibility exists, what are its underlying biological mechanisms? To understand what might be inherited, both indi-

viduals who have a substance abuse problem and animals models of substance abuse are studied. Various types of information can be derived from these studies. As with family, twin, and adoption studies, much more information is available about alcoholism as compared with other drugs of abuse.

First, it maybe possible to identify specific inherited risk markers for alcoholism and other substance abuse. A risk marker is a biological traitor characteristic associated with a given condition. Thus, if an individual is found to have an identified marker for substance abuse, he or she is at risk for developing a drug dependency. To date, no biological characteristic has been clearly identified as being a risk marker for either alcoholism or substance abuse, although evidence suggests some possible candidates. The identification of a valid and reliable risk marker could provide important information about the fundamental mechanisms underlying substance abuse and addiction and would be an invaluable aid in diagnosis and treatment.

Second, inherited differences in biochemical, physiological, and anatomical processes related to differences in drug responses might be identified and studied. Animal models of substance abuse allow thorough biological assays to be carried out. Animal genetic models of substance abuse consist of strains of animals (usually rodents) that have been selectively bred to either exhibit a preference for taking or refusing a drug, or to differ in some way in their behavioral or physiological response to a drug. In the case of alcohol, studies suggest that low doses of alcohol are more stimulating and produce a stronger positive reward in rats bred to have a high preference for alcohol as compared with normal rats. Experimental data indicate that this may be due to inherited differences in the dopamine, GABA, and serotonin systems (27,32, 57,73). These differences represent inherited traits related to drug taking behavior, and these animals can be examined to determine what biological mechanisms are involved in the expression of these traits.

Third, the genetic technique of linkage analysis can narrow the area on a chromosome where a gene may be located. It can lead to the identification of the gene itself which in turn can improve the understanding of the molecular events that underlie the expression of the gene. There have been few genetic linkage studies related to substance abuse since few specific biological traits associated with drug dependency have been identified. Some studies in humans have been carried out related to alcoholism but the findings of these studies are contradictory and inconclusive.

Several studies have reported an association between alcoholism and a gene that regulates the number of a type of dopamine receptor in the brain; other studies have found no such link (4,5,8,18,58). The reason for this discrepancy is unclear. One study revealed a relationship between the presence of the gene not only in alcoholics, but in other disorders such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome (17). Thus, the presence of this particular gene, while not uniquely specific for alcoholism, may cause an alteration in the brain's dopamine system that somehow exacerbates or contributes to alcohol abuse.

Few studies have examined possible inherited biological mechanisms associated with the abuse of other drugs. For example, strains of rats and mice that differ in their sensitivity to the reinforcing effects of cocaine and in their cocaine-seeking behavior have been observed to also have differences in the actual number of dopamine-containing neurons and receptors in certain brain areas. Also, a comparison of one strain of rat that self-administers drugs of abuse at higher rates than another strain, found that the higher self-administering strain exhibited differences in the intracellular mechanisms that control activity in some of the neurons in the brain reward system (see box 3-2) as compared with the low self-administering strain. Additional studies exploring the role of genes in drug response are needed to more fully understand the full range of biological factors associated with drug abuse. The recent develop-

ment of new and more sensitive techniques to analyze brain activity and processes will facilitate these studies.

ROLE OF LEARNING

The learning that occurs during drug-taking activities is an important force in the continued use and craving of drugs (59,72). Drugs of abuse often produce feelings of intense pleasure in the user. In addition, such drugs produce changes in numerous organ systems (e.g., cardiovascular, digestive, endocrine). Both the behavioral and physiological effects of a drug occur in the context of the individual's drug-seeking and drug-using environment. As a result, environmental cues are present before and during an individual drug use that are consistently associated with a drug's behavioral and physiological effects. With repetition the cues become conditioned stimuli, that on presentation, even in the absence of the drug, evoke automatic changes in organ systems and sensations that the individual reports as drug craving. This is analogous to Pavlov's classical conditioning experiments in which dogs salivated at the cue of a bell following repeated pairing of food presentation with a ringing bell. Evidence for this effect is seen in numerous studies showing that animals seek out places associated with reinforcing drugs and that the physiological effects of drugs can be classically conditioned in both animals and humans (72).

Conditioning also occurs in relation to the withdrawal effects of drugs (75). It was observed that opiate addicts who were drug free for months and thus should not have had any signs of opiate withdrawal, developed withdrawal symptoms (e.g., yawning, sniffling, tearing of the eyes) when talking about drugs in group therapy sessions. This phenomenon, termed conditioned withdrawal, results from environmental stimuli acquiring the ability, through classical conditioning, to elicit signs and symptoms of pharmacological withdrawal. Conditioned withdrawal can also play a role in relapse to drug use in abstinent individuals. The emergence of withdrawal symptoms as a result of exposure to conditioned cues can motivate an individual to seek out and use drugs.

These associations are difficult to reverse. In theory, repeated presentation of the environmental cues, without the drug should extinguish the conditioned association. Animal studies indicate that stopping the conditioned response is difficult to achieve and does not erase the original learning. These types of studies examining drug conditioning have found that various aspects of extinguished responses can either be reinstated with a single pairing of the drug and environmental cue, can be reinstated with a single dose of drug in the absence of the environmental cue, or can spontaneously recover (72).

Thus, exposure to environmental cues associated with drug use in the past can act as a stimulus for voluntary drug-seeking behavior. If the individual succeeds in finding and taking the drug, the chain of behaviors is further reinforced by the drug-induced, rewarding feelings and the effects of the drug on other organ systems (59). The effects of the environmental stimuli can be similar to the priming effects of a dose of the drug.

The complexity of human responses to drugs of abuse, coupled with the number of drugs that are abused, complicates understanding of the role of biology in drug use and abuse. Nevertheless, scientists know the site of action of many drugs in the brain, and sophisticated new devices are expected to improve that understanding. A genetic component to drug use and abuse is likely, but it has not been fully characterized.

SUMMARY

Underlying all alcohol and drug problems are the actions and effects that drugs of abuse exert. It is important to understand how drugs work in the brain, why certain drugs have the potential for being abused, and what, if any, biological differences exist among individuals in their susceptibility to abuse drugs.

Two biological factors contribute to substance abuse and addiction: the effects drugs of abuse exert on the individual, and the biological status of

the individual taking drugs. The effects the drugs exert can be either acute or chronic and will vary depending on the drug and its route of administration. Most drugs of abuse influence the brain's reward system. The pleasurable sensations that drug use can produce reinforce drug-seeking and -taking behaviors. These actions differ with different drugs: and, thus, some substances have greater potential for abuse and addiction than others.

Prolonged or chronic use of a substance or substances can produce both biological and behavioral changes (some long-lasting). Biological changes can include sensitization and/or tolerance and, if use is discontinued, withdrawal. The behavioral changes from continued drug use are directly related to these biological changes. An individual's drug-craving, -seeking, and -taking behaviors are amplified through the neuroadaptive changes in the brain reward system that occur with chronic administration.

Environmental cues also play a large role in drug-seeking and -taking behavior. On encountering certain environmental stimuli (i.e., specific locations, smells, tastes), drug-craving and drug withdrawal symptoms have been reported by former drug users who have been drug-free for months, even years.

Through family, twin, and adoption studies, most researchers agree that genetic factors play some part in the heritability of alcohol problems and, although less clear, other drug problems. No conclusive evidence has been found to explain precisely what is inherited or the overall importance of this inherited material. It has been hypothesized that there are probably numerous genes (as opposed to one) that interact in complex ways, and whose expressions are affected by a myriad of environmental factors. Thus, the presence or absence of a genetic factor neither ensures nor protects against drug dependency.