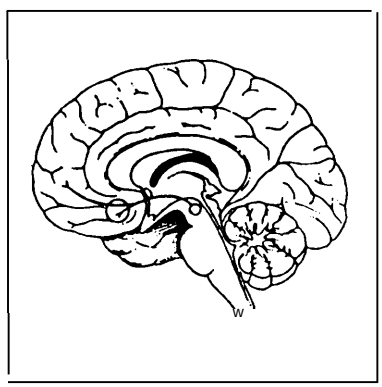
Executive Summary 1

Substance abuse and addiction are complex phenomena that defy simple explanation or description. A tangled interaction of factors contributes to an individual's seeking out, using, and perhaps subsequently abusing 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 psychological makeup (e.g., self-esteem, propensity to take risks, irnpulsivity, depression), biological response to drugs and environmental situation (e.g., peer groups, family organization, socioeconomic status), and the availability of drugs. The exact combination of elements that leads to substance abuse and addiction varies among individuals.

Regardless of the mix of contributing factors, the actions and effects that drugs of abuse exert underlie all substance abuse and addiction. In order to understand substance abuse and addiction one must first understand how drugs work in the brain, why certain drugs have the potential for abuse, and what, if any, biological differences exist among individuals in their susceptibility to abuse drugs. While numerous factors ultimately contribute to an individual's drug-taking behavior, understanding the biological components is crucial to a better comprehension of substance abuse and addiction. In this background paper, the Office of Technology Assessment (OTA) describes the biological components of substance abuse and addiction.



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 former

Box l-A–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 synapse, the gap between two neurons (figure l-l). The molecules of the neurotransmitter move across the synapse and attach, or bind, to proteins called receptors in the outer membrane of an adjacent ceil. Once a neurotransmitteractivates a receptor, it unbinds from the receptor and is removed from the synapse. This is done either by the neurotransmitter being taken backup into the neuron that released it or by its being chemically broken down.

For each neurotransmitter in the brain, there are several specific receptors to which it can attach. Binding by the neurotransmitter activates the receptor. Receptors can be linked to a variety of membrane and cellular mechanisms that are turned on or off by the activation of the receptor. while receptors are specific foa neurotransmitter, there maybe a variety of receptor subtypes, linked to different cellular mechanisms and to different neuronal circuits, that all respond to the same neurotransmitter. In this way one neurotransmitter can have diverse effects indifferent areas of the brain. Many chemicals have been identified as neurotransmitters. Sores are of particular relevance to the rewarding properties of drugs of abuse. These include dopamine, norepinephrine, serotonin, opioids and other neuropeptides, gamma amino butyric add (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). Sometimes a receptor for one neurotransmitter can affect a receptor for another neurotransmitter. In such cases, the 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 neurotransmitter it releases. *Such* receptors are acted on by the neuron's own neurotransmitter to regulate the release of the neurotransmitter. Thus, these so-called autoreceptors act as a feedback mechanism to regulate a neuron's activity. The activity ofa neuron will be determined by the cumulative activity of all of its various receptors.

Drugs that work in the brain, including drugs of abuse, alter normal neuropharmacological activity through a varietyofdifferent mechanisms. They can affect the production, release, or reuptake of a neurotransmitter, they can mimic or block the action of a neurotransmitter 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: office of Technology Assessment, 1993.

relates to the acute mechanisms of action of drugs of abuse 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, which affects that person's response to a drug.

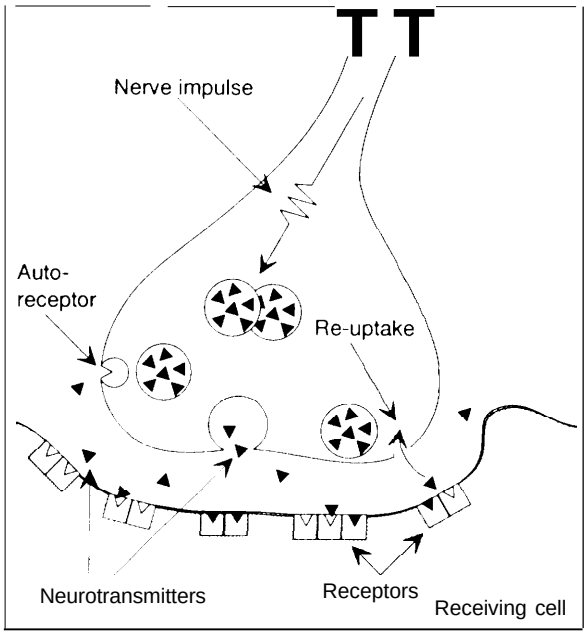
DRUG ACTION

I Acute Actions

Drugs of abuse alter the brain's normal balance and level of biochemical activity (box l-A). What separates drugs of abuse from other psychoactive drugs is that most of these drugs act, at least in part, on those areas of the brain that mediate feelings of pleasure and reward (box l-B).

The ability to induce activity in the so-called brain reward systems gives drugs of abuse positive reinforcing actions that provoke and support their continued use and abuse. *Reinforcement* is defined as the likelihood that the consequences of taking the drug will increase the behavior directed toward seeking that drug. Put more simply, individuals who use drugs experience some effect, such as pleasure, detachment, or relief from distress, that initially establishes and then maintains drug self-administration. The **con-**

Figure I-I—The Synapse and Associated Structures



SOURCE: Office of Technology Assessment, 1993.

sequence of taking the drug enhances the prospect that it will continue to be used for some real or perceived effect and eventually compulsive self-administration. In fact, the capacity of a drug to support self-administration in experimental animals is a measure of the drug's strength as a reinforcer.

While growing evidence indicates that the brain reward system likely plays a role in the reinforcing properties of most drugs of abuse, the precise mechanisms involved in all drugs of abuse have yet to be completely described. The rewarding properties of stimulant drugs such as cocaine and amphetamines are due to a direct increase in the activity of the neurotransmitter dopamine in the mesocorticolimbic dopamine pathway (see box l-B). Opiates, on the other hand, indirectly stimulate dopamine activity by activating other neurotransmitter pathways, which in turn increase dopamine activity in the mesocorticolimbic pathway (MCLP). Similarly, alcohol, barbiturates, and benzodiazepines also indirectly activate MCLP. All of these drugs have strong reinforcing properties. Phencyclidine (PCP) is also a strong reinforcer but its relationship, if any, to activity in MCLP has not been established. Other drugs are either weak reinforcers or have not been shown to support self-administration in animal experiments. Nicotine activates dopamine neurons in the mesocorticolimbic system. However, when compared with cocaine or amphetamine, this effect is modest. Likewise, caffeine is a weak reinforcer, but the precise mechanisms of its reinforcement are unclear. Finally, while cannabis and lysergic acid diethylamide (LSD) produce positive effects that clearly support their use, there is currently little empirical evidence that they act as reinforcers in controlled experiments.

Chronic Actions

Changes occur in the brain when it is exposed to drugs. Beyond their immediate, rewarding properties, drugs of abuse, when used on a chronic, long-term basis, can cause either permanent changes in the brain or alterations that may take hours, days, months, even years to reverse on drug cessation. These changes are adaptive responses related to the pharmacological action of a given drug that occur in the brain to counter the immediate effects of a drug.

Tolerance develops to a drug when, following a prolonged period of use, more of the drug is required to produce a given effect. Tolerance occurs with many types of drugs and is a common, but not necessary, characteristic of drugs of abuse. Tolerance can contribute to drug-taking behavior by requiring that an individual take progressively larger doses of a drug to achieve a desired effect.

Dependence occurs when, with prolonged use of a drug, neurons in the brain adapt to the drug's presence such that the use of the drug *is* now required to maintain normal function in the cells. On abrupt withdrawal of the drug, the neuron behaves abnormally and a "*withdrawal syn*drome" ensues, Generally, the withdrawal syn-

Box 1-B—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) (figure 1-2). MCLP is made up 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[1] in the limbic system, a network of brain structures associated with control of emotion, perception, motivation, gratification, and memory; medial prefrontal cortex, the front part of the brain involved with higher ordered thinking). 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 involved in mediating the rewarding properties of drugs of abuse.

1 A nucleus is a collection of cells in the brain that share the same anatomical region and, to varying degrees, the same function.

SOURCE: G.F. Koob, "Drugs of Abuse: Anatomy, Pharmacology, and Function of Reward Pathways," *Trends in Pharmacological Sciences* 13:177-184, 1992; G.F. Koob, "thud Mechanisms of Drug Reinforcement," P.W. Kalivas, and H.H. Samson (eds.), *The Neurobiology of Drug and Alcohol Addiction, Annals of the American Academy of Sciences* 654:171-191, 1992.

drome is characterized by a series of signs and symptoms that are opposite to those of the acute effects of the drug. Withdrawal creates a craving or desire for the drug and plays a very strong role in recurrent patterns of relapse, in maintaining drug-seeking behavior to forestall the withdrawal syndrome, and in the need to reestablish some sense of normalcy.

Sensitization occurs when the effects of a given dose of a drug increase after repeated administration. Thus, sensitization is the opposite of tolerance. Sensitization to a drug's behavioral effects could play a significant role in supporting drug-taking behavior.

For example, while tolerance to some of the effects of cocaine and amphetamines develops, sensitization to other of their effects can also occur. Also, while it is unclear horn available data whether tolerance develops to cocaine's reinforcing effects, the notion is supported by some experimental evidence and anecdotal reports born cocaine users that the drug's euphoric actions diminish with repeated use. Tolerance also develops to the effects, including the reinforcing properties, of opiates and alcohol.

A withdrawal syndrome of varying severity is associated with most drugs of abuse. Barbiturates, alcohol, stimulants, opiates, and benzodiazepines produce pronounced and sometimes severe withdrawal symptoms, while those for nicotine and caffeine are less intense. **A mild withdrawal is** associated with cannabis use, while there is no evidence of a withdrawal syndrome related **to** LSD.

I Abuse Liability

The abuse liability of a drug is a measure of the **likelihood that its use will result in drug addic**tion. Many factors ultimately play a role in an individual's drug-taking behavior; nevertheless, the abuse potential of a drug is related to its intrinsic rewarding properties and/or the neu-

roadaptive responses that result from its prolonged use. Drugs can be tested and screened for their abuse liability using animals as models. The criteria that can be evaluated to classify a drug as having significant abuse potential are 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 most commonly occur but are not absolutely required to make such a determination.

SELF-ADMINISTRATION

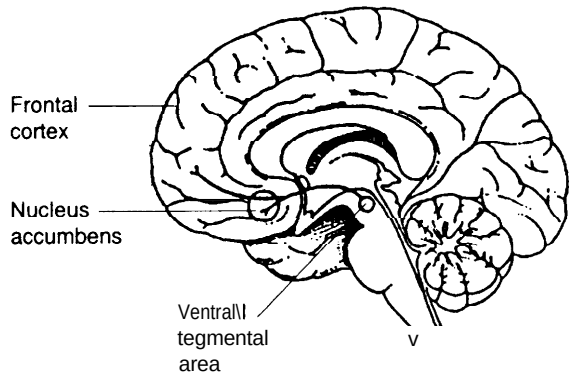
The predominant feature of all drugs with significant abuse potential properties is that they are self-administered. In fact, self-administration of a drug to the point when the behavior becomes obsessive and detrimental to the individual is the primary criterion that must be met to classify a drug as having significant potential for addiction. In addition to self-administration, another contributing factor to abuse liability is the notion of craving and the tendency of individuals to relapse to drug use during withdrawal. Although craving is a difficult term to quantify, once a drug is voluntarily or involuntarily withdrawn, the desire to take the drug can play a role in the relapse to substance abuse.

Animals can be readily trained to self-administer drugs. 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 an examination of the behavioral, physiological, and biological factors that lead 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. Specifically, animals or humans trained to discriminate

Figure 1-2—The Mesocortlcolimbic Pathway



The mesocorticolimbic pathway from the ventral tegmental area to **the nucleus accumbens and the frontal cortex is a key component of the brain reward system for drug reinforcement.**
SOURCE: Office of Technology Assessment, 1993.

a drug from a placebo show a remarkable ability to distinguish that drug 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 a particular class, such as opiates, stimulants, and depressants, cause a series of effects on the brain and other organs that collectively constitute their pharmacological profile.

DEPENDENCE AND TOLERANCE

Dependence and tolerance can readily be induced in animals by chronic administration of drugs. Following abrupt withholding of a drug, a withdrawal syndrome will often develop and the motivation for self-administration of the drug may be increased. Thus, the capacity of a drug to induce neuroadaptive motivational changes can be assessed. Furthermore, since the understanding of the neuroadaptive changes that take place during the development of physical dependence and tolerance are poorly understood in humans, animal models offer a unique opportunity to carry out experiments designed to address these issues.

GENETIC FACTORS

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 make some individuals either more or less susceptible to drug dependency than others. While it seems likely that inherited differences exist, a genetic component alone is insufficient to produce substance abuse and addiction.

Unlike disorders, such as Huntington's disease and cystic fibrosis, that result from the presence of alternations in a single gene, a genetic component of substance abuse is likely to involve multiple genes that control various aspects of the biological response to drugs or physiological predisposition to become an abuser. In addition, the complex nature of drug dependency, involving 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 of a genetic factor does not ensure drug addiction nor does its absence guarantee protection from drug addiction.

Two questions arise when considering a genetic component to substance abuse and addiction: Do inherited factors exist? And, if so, what are they? To date, much of the work done in this field relates to alcoholism. Less is known about the genetic aspects of the abuse of other drugs.

I Do Inherited Factors Exist?

Results from family studies, twin studies, and adoption studies as well as extensive research on animal models indicate that heredity influences normal as well as pathological use of alcohol. Animal studies have established that genetic factors contribute to alcohol preference, the reinforcing actions of alcohol, alcohol tolerance, and alcohol physical dependence. While few 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. The study of nonalcoholic drug abuse in humans has been difficult due to substantially lower population prevalence and differences in availability and, hence, exposure to these agents. Investigation in this area is further hampered by the complexity of subjects' drug use: most drug abusers have used multiple agents. 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.

I What Is Inherited?

While study results support the role of a genetic component in alcoholism and probably other drug abuse, they provide no 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? Information about inherited biological mechanisms is most easily derived from studies of animals bred to have differing responses to various drugs. However, in humans, few studies have examined the relationship between inherited behavioral traits and the inherited biological mechanisms that might underlie them.

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 mesocorticolimbic dopamine system (see box l-B) and an inherited increased response of this system when exposed to alcohol. Also, alcohol-preferring rats have been found to have different levels of activity in other neurotransmitter systems that modulate activity in the mesocorti-

colimbic system. In humans, studies of college-aged individuals indicate that low initial sensitivity to alcohol may be a predictor for alcoholism later in life.

Studies using the technique of genetic linkage analysis[1] have attempted to identify genes that might be associated with alcoholism in humans. However, the findings of these studies are inconclusive. While some studies have reported a link between alcoholism and a gene that regulates the number of a type of dopamine receptor in the brain, others have not. The reason for this discrepancy is unclear, but one study has found a relationship between the presence of the gene not only in alcoholism, but also in other disorders such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome. Thus, the presence of the gene may cause an alteration in the brain dopamine system that somehow exacerbates or contributes to alcohol abuse, but is not uniquely specific for alcoholism.

Fewer studies have focused on 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 also been observed to have differences in the 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 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 development of new and more sensitive techniques to analyze brain activity and processes will facilitate these studies.

ROLE OF LEARNING

The learning that occurs when an individual takes drugs is an important contributing force in the continued use and craving of drugs. Drugs of abuse produce positive or pleasurable feelings in the user and have reinforcing properties. In addition to these effects, drugs of abuse produce changes in numerous organ systems such as the cardiovascular, digestive, and endocrine systems. Both the behavioral and physiological effects of a drug occur in the context of an individual's drug-seeking and drug-using environment. As a result, environmental cues are present before and during an individual's 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 behavioral sensations that the individual experiences as drug craving. These associations are difficult to reverse. In theory, repeated presentation of the environmental cues, absent the drug, should extinguish the conditioned association. Animal studies indicate that extinction is difficult to achieve and does not erase the original learning, As a result, even once established, the extinction is readily reversed.

Also, it has long been known that conditioning occurs in relation to the withdrawal effects of drugs. This phenomenon, termed conditioned withdrawal, results from environmental stimuli acquiring the ability, through classical conditioning, to elicit signs and symptoms of pharmacological withdrawal. The emergence of withdrawal symptoms as a result of exposure to conditioned cues can contribute to drug use relapse by

[1] Genetic linkage studies establish an association between an area of a specific chromosome and the expression of a trait. Linkage analysis uses specific markers that identify the area on a chromosome that might contain the gene of interest. If the marker consistently occurs in association with the expressed trait, then it is likely that the gene of interest is in that chromosomal region.

motivating an individual to seek out and use drugs.

Thus, exposure to environmental cues associated with drug use in the past can act as a priming force to motivate voluntary drug-seeking behavior. Drug conditioning can help explain the fact that many drug abusers often return to environments associated with drug use, even after being counseled not to. The effects of the environmental stimuli can be similar to the priming effects of a low dose of the drug or result in withdrawal symptoms. In either case these stimuli can occasion further drug use even after successful detoxification.

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.