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A Psychomotor Stimulant Theory of Addiction

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The theory is advanced that the common denominator of a wide range of addictive substances is their ability to cause psychomotor activation. This view is related to the theory that all positive reinforcers activate a common biological mechanism associated with approach behaviors and that this mechanism has as one of its components dopaminergic fibers that project up the medial forebrain bundle from the midbrain to limbic and cortical regions. Evidence is reviewed that links both the reinforcing and locomotor-stimulating effects of both the psychomotor stimulants and the opiates to this brain mechanism. It is suggested that nicotine, caffeine, barbiturates, alcohol, benzodiazepines, cannabis, and phencyclidine—each of which also has psychomotor stimulant actions—may activate the dopaminergic fibers or their output circuitry. The role of physical dependence in addiction is suggested to vary from drug to drug and to be of secondary importance in the understanding of compulsive drug self-administration.

Attempts at a general theory of addiction are attempts to isolate—from a variety of irrelevant actions—those drug actions that are responsible for habitual, compulsive, nonmedical drug self-administration. The common assumption of addiction theorists is that general principles of addiction can be learned from the study of one drug and that these principles will have heuristic value for the study of other drugs. Thus far, attempts at a general theory of addiction have failed to isolate common actions that can account for addiction across the range of major drug classes. A major stumbling block has been the psychomotor stimulants—amphetamine and cocaine—which do not readily fit models traditionally based on depressant drug classes. The present article offers a new attempt at a general theory of addiction. It differs from earlier theories (e.g., Collier, 1968; Himmelsbach, 1943; Jaffe & Sharpless, 1968; Jellinek, 1960; Kalant, 1977; Lindsmith, 1947; Solomon & Corbit, 1974) in that it is based on the common denominator of the psychomotor stimulants—amphetamine, cocaine, and related drugs—rather than on the common denominator of the so-called depressant drugs—opiates, barbiturates, alcohol, and others.

We take up two topics before presenting the new theory. First, we briefly discuss the heuristic value of a biological approach and suggest that the biologist's distinction between homology and analogy offers a useful insight. Next we discuss the shortcomings of earlier theories—variants of dependence theory. Then we outline the new theory and review the relevant evidence for its three major assertions: (a) that all addictive drugs have psychomotor stimulant actions, (b) that the stimulant actions of these different drugs have a shared biological mechanism, and (c) that the biological mechanism of these stimulant actions is homologous with the biological mechanism of positive reinforcement.

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Homology and Analogy as Heuristics for Scientific Theory

Any attempt to find a common denominator for such diverse conditions as cocaine addiction, alcohol addiction, and heroin addiction is based on the assumption that knowledge of one of these phenomena may provide insights into the others. The assumption is that a common denominator will have *heuristic* value, that our learning about one addiction will facilitate our learning about another. This assumption need not be valid. In biology there are examples of superficially similar behaviors or organs that have evolved independently, deriving from different ancestors and mechanisms developing out of different embryonic tissue. Such behaviors or organs are termed *analogous,* and successful prediction of something about one side of an analogy from knowledge about the other likely reflects the fact that the independent organs or behaviors have evolved under common environmental pressures rather than from a common ancestral origin (Lorenz, 1974). Analogies do not *necessarily* extend beyond the superficial similarities that were originally noted (Lorenz, 1974). The eye of the octopus and the eye of the vertebrate are examples of analogous organs, and the jealousy of the goose and the jealousy of the human are examples of analogous behaviors; in each case, the analogous details are striking, but there is no commonality of origin and thus no *necessary* commonality of mechanism.

In other cases, different organs or behaviors can derive from common ancestral origins and common embryonic tissue. Such organs or behaviors are termed *homologous:* homology is distinguished from analogy in that homologies result from common biological mechanisms, whereas analogies do not. Since the phyletic or embryonic origins of homologous organs are the same, knowledge of one of a set of homologous organs or behaviors almost necessarily has some degree of heuristic value for

the study of the others, even if the organs or behaviors are superficially dissimilar. Examples of superficially dissimilar but nonetheless homologous organs can be found among the wings of bats, the fins or flippers of whales, and the limbs of dogs and humans. Despite the apparent differences, knowledge of the bones of the bat's wing tells us much about the homologous bones of the whale's flipper. We can predict that this will be the case when we know that the two evolved from a common ancestor.

Homologies are heuristic for the behavioral scientist as well as for the anatomist. Homologous movement rituals in courtship can tell the comparative ethologist that two kinds of birds are ancestrally related despite major differences in their appearance and in the environments where they and their immediate ancestors evolved. Behaviors, like organs, can be homologous even if they are not superficially similar. For example, the females of some species of waterfowl incite their mates to attack other males by using movement patterns that, in related species, have lost this function and appear purely as courtship movements (Lorenz, 1974). From evidence from comparative ethology we can infer that the inciting patterns and the courtship patterns, though seemingly different, are homologous; because they are presumed to be largely under genetic control and derived from a common ancestor, they can be assumed to involve closely related brain mechanisms. Similarly, the panting of dogs, the grooming of rodents, and the sweating of humans are to some degree homologous, because their underlying neural mechanisms appear to have common components. Each is a method of body cooling that seems to be activated by temperature-sensitive cells of the anterior hypothalamus (Bligh, 1966; Hammel, 1968). The fact that the temperature-sensing mechanism that activates the three behaviors is common would seem to result from what Lorenz called "common descent" and thus represents homology rather than analogy.

Attempts to find a common denominator for a number of behaviors are made in the hope that they will yield knowledge that generalizes from one case to others. Clearly, it is homology (commonality of biological mechanism), not analogy (similarity of superficial characteristics), that is the common denominator with greatest heuristic potential. It should be obvious that there is more to be learned about the nursing habits of young porpoises from the homologous feeding patterns of young humans and other young mammals than from the feeding of young fishes. Homology between the known behavior of one species and the unknown behavior of another offers an immediate source of knowledge because common underlying mechanisms necessitate the existence of common underlying principles. Analogy, on the other hand, may often prove to be misleading. If two behaviors are superficially similar but derive from completely different biological mechanisms, then knowledge about one may even impede insight into the other.

In the sections to follow, we will use the distinction between homology and analogy twice. First, we will argue that varied instances of drug dependence syndromes *are not* homologous and that, therefore, there is little heuristic value in continued exploration of dependence as a common denominator of addiction to different drugs. Second, we will argue that the seemingly disparate phenomena of addiction, positive reinforcement, and psychomotor activation *are* homologous, resulting from activation of a common brain mechanism. This homology forms the basis of the theory of addiction that we subsequently develop.

Critique of Earlier Theories

Early Physical Dependence Theories

Most general attempts to isolate a defining property of addiction have focused on one or another form of drug dependence. As might be suspected, the definition of dependence has not proved much easier than the definition of addiction. Dependence is defined as a condition that develops with habitual drug intake and that is revealed by a distress syndrome when habitual intake is discontinued or pharmacologically blocked. The classic physiological dependence syndromes are associated with opiates, alcohol, and barbiturates. The cramps, sweating, nausea, convulsions, and other symptoms associated with withdrawal from chronic, high-dose usage of these agents are dramatic and can be objectively measured; thus dependence on these substances is termed *physiological,* or *physical,* dependence. The concept of physical dependence offers the basis of a theory of addiction that is not circular, because dependence is defined in terms that are separate from the compulsive drug seeking that identifies addition. Identifying physical dependence as the common denominator of addictions to different substances is not merely defining a new word to reflect the same thing. Thus the notion of physical dependence offers a potential explanation of addiction that meets the first criterion for a heuristic theory; it is not merely renaming the phenomenon it attempts to explain.

However, although its lack of circularity gives the concept of physical dependence potential heuristic value, physical dependence has not proved to have actual heuristic value as the foundation of a general theory of addiction. Several facts are inconsistent with the view that physical dependence is either a necessary or a sufficient condition for addiction. One is that the relief of withdrawal distress is minimally effective in treating addictive syndromes (Canada, 1972; Guderman, Shader, & Hemenway, 1972; Hunt & Oderoff, 1962; Jonas, O'Dwyer, Zendel, & Sidel, 1972; Mello & Mendelson, 1972; Moffett, Soloway, & Glick, 1973; Silsby & Tennant, 1974; Tennant, Russell, Casas, & Bleich, 1975; B. K. Wilson, Elms, & Thomson, 1974, 1975; Woods, Ikomi, & Winger, 1971). Another is that the dependence syndromes associated with different drug classes are not homologous. The classic pattern of withdrawal symptoms associated with depressant drugs such as opiates, barbiturates, and alcohol is different from the patterns of withdrawal symptoms that are seen with stimulant drugs such as cocaine, amphetamine, or nicotine (R. T. Jones, 1984; Shiffman, 1979). Indeed, even the withdrawal syndrome seen with the barbiturates is not homologous to that seen with the opiates (Kalant, 1977). In response to these and other problems, dependence theory has gone through a succession of unsuccessful revisions (for a review, see Edwards, Arif, & Hodgson, 1981). The first major attempt to modify dependence theory was an attempt to define a so-called psychic dependence syndrome that would extend to all classes of addictive drugs where physical dependence syndromes had failed to do so (Eddy, Halbach, Isbell, & Seevers, 1965).

The Notion of Psychic Dependence

With the realization that some habit-forming drugs are not associated with a single, classic withdrawal syndrome, attempts have been made to extend the concept of dependence by defining it in terms of drug craving or compulsive drug self-administration, rather than in terms of a syndrome of withdrawal symptoms (see, e.g., Edwards et al., 1981). To distinguish it from the physiological dependence objectively demonstrated in the case of opiates, alcohol, and barbiturates, dependence defined in terms of craving and self-administration is termed *psychic* dependence (Eddy et al., 1965). As will be immediately obvious to those who have thought seriously about the mind–body problem, the dichotomy between psychic and physiologic dependence has proved troublesome. To distinguish psychic dependence from physiologic dependence is to deny the very obvious fact that there is a physiological basis for psychological dependence.

The central problem with this notion is that the concept of psychic dependence is circularly defined; psychic dependence is defined in terms of the very phenomena—craving and compulsive self-administration—that define addiction. Thus the concept of psychic dependence can offer no *explanation* of addiction. Whereas physiologic dependence was defined independently, in terms of physiological *consequences* of habitual intake, psychic dependence is defined circularly, in terms of the intake which it is then argued to cause. Thus the concept of psychic dependence, unlike the concept of physiologic dependence, offers no advantage over the concept of addiction itself; it is no easier to define and it does not advance understanding of the phenomenon. The concept of psychic dependence merely renames the problem; it has no heuristic value whatsoever.

Recent Extensions of the Concept of Physiologic Dependence

In light of the circularity of the concept of psychic dependence, some workers have returned to the notion that all addictive drugs produce dependence syndromes that can be identified by objective physiological consequences of drug withdrawal (e.g., R. T. Jones, 1980, 1984; Shiffman, 1979). Whereas nicotine, amphetamine, cocaine, and caffeine do not produce the classic dependence syndrome associated with opiates, alcohol, and barbiturates, they do produce withdrawal distress and physiological withdrawal symptoms of their own. If we take the production of *any form* of withdrawal distress and *any* physiological withdrawal symptoms as the defining properties of dependence, then it can be said that these drugs are dependence producing. If we take the self-medication of withdrawal distress as a cause of drug self-administration, then dependence can logically serve as a partial explanation of addiction. Inasmuch as the subjectively experienced and subjectively reported withdrawal distress is as unpleasant as many illnesses for which medication is readily prescribed and taken, and inasmuch as physiological withdrawal symptoms—unlike psychic dependence—are demonstrated in ways other than by self-administration itself, the concept of physical dependence offers a noncircular, and thus potentially heuristic, definition of addiction. It is tempting, then, to return to the concept of physical dependence using a broader definition of dependence than was used in early dependence theories.

However, although it can be argued that there is *some form* of dependence syndrome associated with habitual use of every addicting drug, the *same* dependence syndrome is not common to all drugs. The dependence syndromes associated with different drugs are thus not homologous, but merely analogous. Physical dependence syndromes associated with different drugs differ in their details (Kalant, 1977) and must thus differ in their mechanisms (see, e.g., discussion by Jaffe following Jaffe & Sharpless, 1968). The primary reason for seeking some common denominator of the addictions is that such a common denominator would imply a common underlying mechanism. There does not, however, seem to be a common underlying mechanism for the dependence syndromes associated with stimulants and depressants. The classic dependence syndrome is a syndrome reflecting central nervous system *hyper*excitability that results from chronic depression of major portions of the nervous system by opiates, alcohol, or barbiturates (Jaffe & Sharpless, 1968; Kalant, 1977). The dependence syndromes associated with nicotine, cocaine, and amphetamine are syndromes reflecting general central *hypo*excitability (R. T. Jones, 1984; Shiffman, 1979) that results from chronic activation of many of the same portions of the nervous system as are depressed by the opiates. In general, the dependence syndromes associated with the stimulants are opposite, in their details, to the syndromes associated with the depressants. If the mechanisms of stimulant physical dependence and depressant physical dependence are different—indeed, opposite—then there can be no unitary principle of dependence; stimulant dependence and depressant dependence represent two separate syndromes that require separate names and independent explanations.

Even within the category of depressant drugs, it is now acknowledged that there is no unitary or "classic" mechanism of dependence (Kalant, 1977). Opiates do not fully relieve barbiturate or ethanol withdrawal symptoms, and neither barbiturates nor ethanol fully relieve opiate withdrawal symptoms. The dissimilarities between opiate dependence on the one hand and barbiturate and alcohol dependence on the other were sufficient to lead the Expert Committee of the World Health Organization to suggest differentiation of "dependence of the opiate type" from "dependence of the barbiturate type" (Edwards et al., 1981). This committee, after reviewing decades of presumed progress in defining and uncovering causes of addiction, came to the conclusion that the term *neuroadaptation* might be better than the term *physical dependence* and that the withdrawal syndrome is "a constellation of signs and symptoms" that is "characteristic for the particular drug (or category of drugs) and for the specific biological system or species" (Edwards et al., 1981, p. 239).

Thus there is no homology between dependence of the opiate type and dependence of the barbiturate type. What we know about the mechanism of the one is not necessarily useful in understanding the other. If there is no unity to the concept of physical dependence *even within the class of depressant drugs,* then it seems clear that there can be no unity to the dependence concept as applied *across* various drug classes. Although these are good reasons to turn away from dependence theory, there are

now even stronger reasons to question the utility of physical dependence as a general explanation of addiction.

Dependence and Addiction: The Opiate Model

Of the various problems associated with dependence theory, the most damaging is that dependence does not seem to offer a good or complete explanation of compulsive drug self-administration even when prototypical dependence-producing drugs like opiates or alcohol are considered. Dependence theory attempts to explain drug taking in terms of dependence; drug taking is seen as motivated—once addiction is established—by the need to alleviate withdrawal distress. Dependence theory does not explain why drug self-administration habits get established in initially nondependent subjects (Chein, Gerard, Lee, & Rosenfeld, 1964; Zinberg & Jacobson, 1976); nor does it explain why relapse rates are so high in adequately detoxified ex-addicts (Canada, 1972; Guderman et al., 1972; Hunt & Oderoff, 1962; Jonas et al., 1972; Mello & Mendelson, 1972; Moffett et al., 1973; Silsby & Tennant, 1974; Tennant et al., 1975; B. K. Wilson et al., 1974, 1975; Woods et al., 1971). Dependence theory does not attempt to explain the development of addiction or readdiction; it merely attempts to explain why drug-seeking and drug-taking habits are so strong once they are established.

However, even this aspect of dependence theory has been seriously challenged. For example, alcohol-dependent humans and monkeys will undergo voluntary abstinence periods, failing to initiate alcohol self-administration at times when withdrawal symptoms are strong but subsequently initiating such self-administration at times when withdrawal signs are minimal (Mello & Mendelson, 1972; Woods et al., 1971). Thus withdrawal distress does not necessarily compel an individual to take a drug. Even in the case of opiates, the case where dependence theory was perhaps most firmly rooted (Himmelsbach, 1943; Lindsmith, 1947), dependence and habitual intake can now be clearly dissociated. It has been demonstrated empirically that opiate dependence is not a necessary condition for either establishing or maintaining compulsive opiate self-administration. The data to support this assertion will be discussed in some detail, because if dependence theory fails in the case of opiate self-administration, then it seems clear that the notion of dependence cannot serve as a heuristic explanation of addiction to substances, such as cannabis, nicotine, cocaine, or amphetamine, that produce weak or atypical dependence signs at best (R. T. Jones, 1980, 1984; Shiffman, 1979).

Dependence theory has had as a model or prototype the case of the opiates. It has been variously suggested that heroin addicts initiate their habits through frivolous or neurotic experimentation or through "graduation" from the use of less addictive substances. In the early stages of drug use, the potential addict has generally been viewed as having free choice, being fully capable of resisting any attractive properties of the drug. However, once "addicted"—meaning once physically dependent—the user has been seen as being compelled to maintain drug intake because the distress of drug withdrawal cannot be tolerated. There are two critical assumptions of the most extreme version of this view: (a) that there is no inherent compelling reason—other than peer pressure or personal neurosis—to take opiates prior to the development of physical dependence, and (b) that after the development of physical dependence the compulsion to take the drug is overwhelming.

Neither of these assumptions stands up to current knowledge. The assumption that opiate withdrawal distress is unbearable can be attributed in part to reports of addicts themselves. Under this assumption the addict could perhaps be held responsible for the initial addiction but could not be held responsible for continued use of a drug. Exaggeration of the severity of withdrawal distress was in the short-term interest of the addict attempting to procure more drug (Jaffe, 1975). However, we have no strong objective evidence that the heroin addict has a level of success in discontinuing heroin use that is significantly less than the success of cigarette smokers attempting to discontinue smoking. Nonetheless, many people view the heroin user as having an uncontrollable addiction while viewing the smoker as merely having a distasteful and harmful habit. The addict is not expected to exert self-control, whereas the smoker usually is. It is in the interest of the addict to encourage the popular view that generates these expectations. It is now clear, however, that the intensity of withdrawal distress has been greatly exaggerated (Zinberg, Harding, & Apsler, 1978). Among addicts, it is readily admitted that the distress of opiate withdrawal is similar to the distress sometimes felt with influenza or the separation from a loved one—conditions that are unpleasant, but bearable, for most people.

It is, however, the first assumption—the assumption that opiates are habit forming *only* because they are dependence producing—that has most recently, and most importantly, been shown to be false. It now appears that opiate physical dependence and opiate reinforcement are two independent phenomena involving two independent mechanisms of the brain. Opiates can be powerfully reinforcing—rapidly establishing strong self-administration habits—without necessarily producing any physical dependence syndrome. This has been established clearly from intravenous self-administration studies (Deneau, Yanagita, & Seevers, 1969; B. E. Jones & Prada, 1977; Woods & Schuster, 1968) and has recently been confirmed in two even more convincing paradigms.

First, it has been shown that opiates are reinforcing when injected locally into a brain region uninvolved (or at least minimally involved) in physical dependence, whereas they produce physical dependence when injected locally into a brain region uninvolved in opiate positive reinforcement. Nondependent rats will learn to lever-press for microinjections of morphine into the ventral tegmental area (VTA) but not for injections into surrounding areas and not for injections into the periaqueductal gray (PAG; Bozarth & Wise, 1981b, 1982). Acquisition of this lever-pressing habit is rapid and requires as little behavioral shaping as does acquisition of lever-pressing habits for food or brain stimulation reward. The animals learn to respond for the drug in daily 4-hr sessions, and no dependence signs are seen either at the end of these sessions or when the opiate receptor blocker naloxone is given during the sessions. It should not be surprising that no dependence is seen when the drug is only taken 4 hr per day; however, injections into this region do not produce dependence even if morphine is infused continuously for 72 consecutive hours (Bozarth & Wise, 1983a, 1984). None of the normal rodent withdrawal signs—escape, wet-dog shakes, tooth chattering, diarrhea, and so forth—are seen when

an opiate antagonist is given following 72 hr of morphine infusion into the VTA.

The same 72-hr dosing regimen of morphine is, however, sufficient to produce a strong withdrawal response when it is delivered to the PAG region (Bozarth & Wise, 1983a, 1984). Injections into this region (but not the VTA) are also analgesic (Yaksh & Rudy, 1978). When dependence is established by systemic morphine injections, withdrawal signs can be precipitated by local injections of naloxone into the PAG (Wei, Loh, & Way, 1973). It is not known which cells in the PAG region are responsible for opiate dependence, and it has not been established (indeed, it may well not be the case) that all of the various opiate dependence signs derive from opiate actions in this region. However, it is clear that at least a major part of the opiate dependence syndrome results from opiate action at opiate receptors embedded in the membranes of nerve cells or terminals of this region (Bozarth & Wise, 1983a, 1984; Laschka, Teschemacher, Mahraein, & Herz, 1976; Wei, 1981; Wei & Loh, 1976) and that no obvious portion of the opiate dependence syndrome results from opiate actions at receptors embedded in the membranes of nerve cells in the VTA (Bozarth & Wise, 1983a, 1984).

At least one form of opiate reinforcement does result from opiate actions in the VTA. The opiate receptors responsible for this rewarding action appear to be localized in the membranes either of VTA cell bodies or in the terminals of the inputs to the VTA (Llorens-Cortes, Pollard, & Schwartz, 1979; Pollard, Llorens-Cortes, Bonnet, Constantin, & Schwartz, 1977; Pollard, Llorens-Cortes, Schwartz, Gros, & Dray, 1978). The rewarding VTA action is robust and readily demonstrated even when the drug is restricted, by giving it in minute central injections, so that it does not reach the portion of the brain involved in opiate physical dependence. These data make it clear that opiates can be strongly habit forming even when they do not produce anything approaching the full-fledged opiate withdrawal syndrome.

The self-administration paradigm is, however, a paradigm in which multiple injections are given. How can we be absolutely sure that some undetected form or degree of dependence does not develop with these repeated injections and that relief of some distress, produced as each injection is metabolized, does not account for—or at least contribute to—the rewarding effects of all but the first injection? One can always posit a more subtle form of dependence sign than has been detected in a given paradigm, but a paradigm has been developed in which a reinforcing effect of opiates can be demonstrated with the very first injection the animals ever receive.

An index of positive reinforcement is the degree to which animals learn, through Pavlovian association, to approach more frequently or tarry longer in that portion of the environment in which the reinforcement is given. Indeed, such Pavlovian associations play an important if not critical role in the learning of operant habits (Bindra, 1974; Bolles, 1972). The association of a rewarding drug injection with a particular portion of the environment increases the time an animal will spend in that portion of the environment; Spragg's (1940) addicted chimpanzees attempted to pull the experimenter to the administration room when it was time for an injection. Rats given morphine in a portion of the environment that is normally avoided will come to spend more and more time in that portion as morphine injections are experienced there (Beach, 1957; Rossi & Reid, 1976; Schwartz & Marchok, 1974). Such a shift in the preference for the portion of the environment associated with morphine injections can be demonstrated following a single injection of morphine in animals that, having never received morphine before, could not possibly find it rewarding because it relieves withdrawal symptoms (Bozarth & Wise, 1983a). Thus it now seems well established that the distress caused by discontinuation of habitual opiate intake is not a *necessary* condition for such intake. If physiological dependence is not a necessary condition for opiate addiction, then it is unlikely to provide a common denominator for addiction across other classes of drugs. Attempts to uncover general principles of addiction are most likely to benefit from another frame of reference.

Reinforcement Models

As the proponents of dependence theory failed to resolve these problems (see, e.g., Edwards et al., 1981), a significant number of workers turned to the paradigms and perspective of operant psychology. These workers have been greatly influenced by the teachings of Skinner, who has advocated attention to controlling variables and advised against attempting to identify physiological mechanisms. These workers called attention to the fact that habit-forming agents meet the Skinnerian definition of operant reinforcement. They suggested that drug reinforcement be studied without reference to inferred dependence states just as Skinner (1953, p. 27) suggested that food reinforcement be studied without reference to inferred hunger states. Over the last two decades, workers in this tradition have demonstrated that intravenous injections of a wide range of addictive drugs serve as reinforcers obeying the laws of reinforcement as revealed by studies of food and water reinforcement (see, e.g., Griffiths, Brady, & Bradford, 1979; Johanson, 1978; Kelleher & Goldberg, 1975; Morse, 1975; Schuster, 1970; Schuster & Thompson, 1969; Thompson, 1968; Yanagita, 1973).

This work has not, however, offered an explanatory *theory* of addiction that can be pitted against dependence theory. (Indeed, workers in the operant tradition are advised against any attempt at explanatory theories; Skinner, 1950). To assert that all addictive drugs are reinforcers is to do little more than redefine the phenomenon of addiction; this is probably a step forward, because there is general agreement on the definition of reinforcement, whereas there is little agreement on the definition of addiction. Still, to identify a drug as reinforcing goes no further than to identify the drug as addicting, because it is the common observation of habitual self-administration that serves as the basis for most definitions of both drug reinforcement and drug addiction. A theory of addiction based on the concept of reinforcement would have to identify actions of drugs that are *operationally independent* of self-administration habits in order to offer insight as to *why* drugs are addictive. The only reinforcement theory of addiction that identifies any nonsubjective actions that would meet this requirement is a restatement of dependence theory in terms of negative reinforcement.

Negative reinforcement models. An event is said to be reinforcing if it increases the frequency or probability of the behav-

iors it reliably follows. Negative reinforcers increase response probability by *terminating* a condition or central state that we then infer to be aversive. Termination of footshock is a negative reinforcer. Negative reinforcers are effective because of the central states they alleviate, rather than because of the central states they induce. Dependence theory is an example of negative reinforcement theory in that it postulates the alleviation of an aversive state—withdrawal distress—as the reason that drugs are reinforcing. There have been other negative reinforcement models; the notion has frequently been advanced that drugs are taken to relieve situational anxiety or depression (Alexander & Hadaway, 1982). Such models have never developed much popularity among drug abuse specialists, however, perhaps because most stressed or depressed individuals do not turn to drugs. Indeed, attempts to increase drug intake in laboratory animals by administering uncontrollable stress have proven, for the most part, fruitless (Myers & Holman, 1967; Persensky, Senter, & Jones, 1969).

Positive reinforcement models. Positive reinforcers increase response probability because of the states they *induce* rather than because of the states they alleviate. There has long been controversy as to whether food is a positive or a negative reinforcer: Is food reinforcing because it alleviates hunger (negative reinforcement) or because it produces pleasure independent of hunger (positive reinforcement)? Water and certain foodstuffs can be demonstrated to be reinforcing because of their post ingestional consequences (Epstein, 1960; Le Magnen, 1969), but their sensory properties can also be demonstrated to be reinforcing, independent of any ability to relieve caloric or hydrational deficits. Saccharin is a positive reinforcer; it does not alleviate the biological consequences of food deprivation, but it is reinforcing in proportion to variations in the sweetness it shares with biologically useful sugars (Sheffield & Roby, 1950). Thirsty rats will lick a cool airstream that offers no repletion of hydrational deficits but that shares with water the ability to cool the oral cavity (Mendelson & Chillag, 1970). It would seem, then, that food and water can be reinforcing for both reasons; they have positive reinforcing sensory properties, and they have negatively reinforcing postingestional consequences.

In the case of drugs, there is a similar contrast between positive and negative reinforcement models. Although many workers view addictive drugs—particularly the psychomotor stimulants—as positive reinforcers, the only existing positive reinforcement view of addiction that might qualify as an explanatory theory identifies positive reinforcement with drug euphoria. In this view drugs are addicting (establish compulsive habits) because they produce euphoria or positive affect (Bijerot, 1980; McAuliffe & Gordon, 1974). The notion that addictive drugs have the common ability to produce euphoria is a notion with two unresolved problems. First, many addictive drugs are associated with *dys*phoric effects. Initial interactions with opiates, ethanol, and nicotine, for example, are more likely to be reported as dysphoric than as euphoric. It is difficult to study any euphoric effects of these agents because the dysphoric effects tend to mask and obscure them. Second, euphoria is a condition that cannot be observed but must rather be inferred in lower animals (e.g., Kornetsky, Esposito, McLean, & Jacobson, 1979; Levitt, Baltzer, Evers, Stilwell, & Furby, 1977; Rossi & Reid, 1976). We have no *independent* criteria for euphoria in lower animals above and beyond the evidence that the animals will self-administer the drug or that the drug will increase the self-administration of brain stimulation reward. The fact that humans will self-administer drugs even when they report them to be *dys*phoric must leave us uneasy with inferences of euphoria that are based solely on intake data.

What is needed is a theory of reinforcement that predicts the reinforcing effects of drugs on the basis of some independent set of observations that can be quantified and compared between humans and lower animals. Such a theory of reinforcement is available in the literatures of comparative (Maier & Schneirla, 1935; Schneirla, 1959) and physiological (Glickman & Schiff, 1967) psychology. The theory is, in essence, that any event that elicits approach or forward locomotion will serve as a positive reinforcer. Another way to express this theory is that approach behaviors and positive reinforcement are homologous—they differ in their overt manifestations, but they derive from a common biological mechanism. Critical elements of the mechanism of the homologous phenomena of reinforcement and psychomotor stimulation are found in the medial forebrain bundle as it passes through the lateral hypothalamus (Glickman & Schiff, 1967).

A Psychomotor Stimulant Theory of Addiction

The theory advanced in the present article identifies addiction with the phenomenon known as operant reinforcement. It accepts the Skinnerian definition of reinforcement, but it specifies independent, psychomotor stimulant properties as predictors of whether a given drug or agent will prove reinforcing in an operant situation. The crux of the theory is that the reinforcing effects of drugs, and thus their addiction liability, can be predicted from their ability to induce psychomotor activation. The evidence associating psychomotor stimulant properties with operant reinforcement will first be discussed in the general case and will then be developed for the special case of addictive drugs.

Psychomotor Stimulation and Reinforcement

"Operant reinforcement" is usually defined in relation to the acts that it follows. In operant psychology it is usually either Thorndike's law of effect or Skinner's adaptation of it that is taken as the primary definition of reinforcement. Thorndike (1911) stated his law as follows: "Of several responses made to the same situation, those which are accompanied or closely followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur" (p. 244). Thorndike's use of the poorly defined terms *satisfaction* and *satisfying state of affairs* did not sit well with the movement of behaviorists toward operational definitions, and the term *reinforcer* came to be substituted for the term *satisfier* (Skinner, 1935b).

Skinner was not the first to use the word *reinforcement*, however, and Skinner's definition of the word is not the only viable definition. In his *Conditioned Reflexes*, which appeared in English translation in 1927, Pavlov, or at least his translater, Anrep, used the word *reinforcement* in connection with the pairing of

an unconditioned stimulus with a conditioned stimulus in order to "reinforce" a conditioned reflex that had been weakened by extinction (Pavlov, 1927, p. 59). Skinner (1935b) was aware of Pavlov's usage and, in his early writings, used the notion of reinforcement in relation to his discussion of two types of conditioning. The first—"Type I," later (Skinner, 1937) termed *operant*—involved the type of reinforcement reflected in Thorndike's law of effect. The second—"Type II," later termed *respondent*—involved the type of reinforcement discussed by Pavlov. Skinner used each view of reinforcement in relation to its relevant paradigm, treating each as legitimate and treating the process of conditioning as if the two "types" of reinforcement reflected the same process. Skinner (1935b, 1937) assigned the Pavlovian view of reinforcement and the Pavlovian conditioning paradigm a secondary role in the explanation of goal-directed behavior, but more recent authors have questioned this point of view (e.g., Bindra, 1974; Bolles, 1972).

In the Pavlovian view, any unconditioned stimulus is a potential reinforcer, and the pairing of an unconditioned stimulus with a neutral or a conditioned stimulus constitutes "reinforcement" of the association between the two. The behavioral evidence that a stimulus could serve as a primary reinforcer was, from Pavlov's view, the elicitation of any unconditioned response. In the tradition of operant psychology, largely molded by Skinner's teachings, a reinforcer is identified not by the unconditioned responses it elicits, but rather by its effects on the probability of the "responses" that preceded it. In his earliest writings, Skinner (1935a, 1935b) discussed the notion that there must be some eliciting stimulus for the initial operant response; it was probably for this reason that he chose to term an operant behavior a *response*, rather than simply an *act*. In any case, Skinner (1937) later abandoned the notion of an eliciting stimulus, defining reinforcement in relation to the "response" that preceded the reinforcing event, rather than in relation to the response that followed the reinforcing event. In the operant paradigm, the reinforcer is elicited (from the experimenter or the apparatus) by the response (of the animal); in the Pavlovian paradigm the response is elicited by the reinforcer. In the decades that have followed Skinner's early writings, reinforcement has come to be widely identified with operant behavior, and the Pavlovian usage has largely been restricted to specialists. It is important to remember, however, that even in Skinner's view, a reinforcer is at least potentially capable of eliciting an unconditioned response.

Schneirla (Maier & Schneirla, 1935; Schneirla, 1959) has proposed a theory that, although not couched in the terminology of either operant or respondent traditions, has implications for both views. Schneirla's concern was not conditioned reflexes, but rather the fundamental distinction between approach and withdrawal behaviors. He pointed out that animals at all levels of the evolutionary scale have basic mechanisms of approach and withdrawal, and he suggested that these basic mechanisms are at the root of all motivational phenomena. Although Schneirla did not discuss the concept of reinforcement per se, he did discuss approach and withdrawal mechanisms in relation to various forms of learning and adaptation. He discussed *facilitation*, rather than reinforcement, of approach and withdrawal tendencies, but it is clear in his writings that he considered the stimulus events that Skinner would call positive reinforcers to be the stimulus events that have as their unconditioned effects the elicitation of approach responses.

It was Glickman and Schiff (1967) who formulated Schneirla's (1959) position into an explicit biological theory of reinforcement. Glickman and Schiff reviewed the evidence that approach behaviors and positive reinforcement can each be elicited by electrical stimulation of the fibers of the medial forebrain bundle, and as a result of this evidence they suggested that "it is the activation of these independent paths by whatever means which constitutes what is conventionally described as reinforcement" (p. 85). Glickman and Schiff's theory of reinforcement is noncircular; reinforcement is explained in terms of activation of approach behaviors mediated by medial forebrain bundle mechanisms, and this activation can be assessed by means independent of the observation of operant behavior. Glickman and Schiff, like Pavlov, identified reinforcing stimuli in terms of the responses they elicit, not in terms of the operant responses they follow. By suggesting that approach behaviors and operant reinforcement have a common neural mechanism, they suggested, in effect, that approach behaviors and operant reinforcement are homologous.

Stimulation of the medial forebrain bundle produces a variety of behaviors that involve approach to environmental stimuli (Glickman & Schiff, 1967; Stellar, Brooks, & Mills, 1979). Among these are, for example, eating, drinking, mating behavior, predatory attack, and nest building. Many of these behaviors can be identified as biologically primitive acts that are essential for individual and species survival. Others appear to be merely components of such acts. The common component of each of these behaviors is forward locomotion. Thus the theory of Glickman and Schiff holds that all positive reinforcers should elicit either approach to localized stimuli or some generalized form of forward locomotion. In the case of food, the animal approaches the food; in the case of centrally administered electrical stimulation, the animal merely moves forward, apparently approaching, sequentially, the most salient objects in the environment. It is this view of reinforcement that provides a new perspective on addictive drugs.

Psychomotor Stimulation as the Common Denominator of Addictive Drugs

The major aim of the present article is to extend the theory of Glickman and Schiff (1967) to the case of addictive drugs. According to this view, all drugs that are positive reinforcers should elicit forward locomotion. Evidence will be discussed to indicate that amphetamine, cocaine, and opiates all elicit forward locomotion and that they do so by activating the dopaminergic circuitry of the medial forebrain bundle. The same circuitry is implicated in brain stimulation reward (Wise, 1980). Evidence will also be reviewed that links psychomotor stimulant actions to barbiturates, alcohol, benzodiazepines, and cannabis, although it is not yet so firmly established that *the same* medial forebrain bundle mechanisms are involved in all of these cases. The hypothesis offered here is that the locomotor effects and the positive reinforcing effects of these drugs are homologous; it is suggested that they derive from activation of a common mechanism and that this mechanism is also responsible for the approach and reinforcement associated with more

natural rewards such as food or water for hungry or thirsty animals.

Psychomotor Stimulant Properties of Addictive Drugs

The task of demonstrating that all addictive drugs have psychomotor stimulant properties is complicated by the lack of a widely accepted definition of addiction and of a widely accepted list of addictive drugs. Until a common denominator of addictive drugs is agreed upon, it is not possible to specify which drugs are addictive and which are not. For the purposes of the present article, a broad list will be discussed, including some substances for which addictive actions have been seriously questioned. The intent of the following discussion is to give evidence for psychomotor stimulant properties in all drugs that are generally accepted as addictive, as well as in several borderline cases. The drugs to be included are amphetamine, cocaine, nicotine, caffeine, opiates, barbiturates, alcohol, benzodiazepines, cannabis, and phencyclidine. Although not all of these drugs are universally considered addictive, each has been reported to be compulsively self-administered by at least some individuals, and each has psychomotor stimulant actions.

The Nominal Psychomotor Stimulants

The class of drugs that is labeled *psychomotor stimulants* is not a well-defined class. The term *psychomotor* refers to movement induced by psychic or mental action; the term appears to have originated in the German language and was widely used before the amphetamines were first synthesized. We have not been able to locate the first use of the term in connection with stimulant drugs. "Psychomotor" stimulants are usually distinguished from the general central nervous system stimulants such as strychnine, pentylenetetrazol, and picrotoxin, which have actions so widespread and powerful as to be able to induce fatal convulsions. Unlike the psychomotor stimulants, however, the general central nervous system stimulants fail to increase locomotor activity (in laboratory animals) at doses below those that produce convulsions. The psychomotor stimulants stimulate more subtle "psychomotor" functions in humans; they improve performance in various simple cognitive tasks—reaction time, pursuit rotor, vigilance, and the like (Hindmarch, 1980). (Paradoxically, the psychomotor stimulants have an apparent calming effect on the agitated restlessness of hyperactive children: Knights & Hinton, 1969; Knobel, 1962).

The prototypical psychomotor stimulants are the amphetamines and related sympathomimetics such as methylamphetamine, methylphenidate, ephedrine, and phenylpropinolamine. Cocaine is also classified as a psychomotor stimulant; in addition to its well-known local anesthetic properties (Ritchie, Cohen, & Dripps, 1970), it is also a sympathomimetic (Van Dyke & Byck, 1977), having both similar actions and a related mechanism of action to the amphetamines in both the peripheral and central nervous systems (see, e.g., Ellinwood & Kilbey, 1977).

The mechanisms of action of the amphetamines and cocaine involve the catecholaminergic synapses of the central and peripheral nervous systems. The three principal catecholamines are the transmitters epinephrine, norepinephrine, and dopamine. Amphetamine and cocaine are each stimulants of the sympathetic nervous system; each causes increased sympathetic activation by increasing the synaptic concentrations of adrenergic neurotransmitters. Amphetamine both augments the release and attenuates the synaptic recapture (the main mechanism of inactivation) of catecholamines (Axelrod, 1970; Carlsson, 1970). It may also act as a weak postsynaptic catecholamine agonist (Feltz & de Champlain, 1973; Hoffer, Siggins, Oliver, & Bloom, 1973), and it inhibits the monoamine oxydase enzymes (Axelrod, 1970) that inactivate these transmitters metabolically. Cocaine shares only one of these actions; it attenuates the synaptic recapture mechanism (Heikkila, Orlansky, & Cohen, 1975). Methylphenidate potentiates catecholamine release by facilitating movement of these transmitters from storage pools to functional pools within the nerve ending (Scheel-Kruger, 1971).

The catecholamines are transmitters in the central as well as the peripheral nervous system. The psychomotor stimulants have, for the most part, the same actions in central catecholaminergic synapses as they have in peripheral catecholaminergic synapses. Although some of the subjective effects experienced with these drugs are due to peripheral autonomic activation, the psychomotor effects are presumed to be due to central actions. One source of this inference is the fact that *d*- and *l*-amphetamine are differentially effective in producing psychomotor activation (Alles, 1933; Bradley & Elkes, 1957; Moore, 1963; Roth, Richard, Shemano, & Morphis, 1954) and intravenous self-administration (Yokel & Pickens, 1973, 1974), because *d*- and *l*-amphetamine are differentially potent in some of their central, but not their peripheral, actions. Whereas the amphetamine isomers are equally effective in activating central noradrenergic mechanisms (Bunney, Walters, Kuhar, Roth, & Aghajanian, 1975; Ferris, Tang, & Maxwell, 1972; Heikkila, Orlansky, Mytilineou, & Cohen, 1975; Thornburg & Moore, 1973; Wise & Hoffer, 1977), they are differentially effective in activating central dopaminergic mechanisms (Bunney et al., 1975; Ferris et al., 1972; Heikkila, Orlansky, Mytilineou, & Cohen, 1975; Thornburg & Moore, 1973). As will be documented more fully below, the mechanism of psychomotor stimulation involves a well-identified set of central dopaminergic neurons.

In animal models, two actions have evolved as the identifying mark of the psychomotor stimulants: the enhancement of major movements, or "locomotion," at low doses, and the enhancement of smaller repetitive movements, or "stereotypy," at higher doses. These actions are each due to the enhancement of central dopaminergic activation; the increased locomotion is associated with activation of the mesolimbic dopaminergic projection from the ventral tegmental area to the nucleus accumbens, and the stereotypy is associated with activation of the adjacent dopaminergic nigrostriatal projection from the zona compacta of the substantia nigra to the caudate nucleus (Creese & Iversen, 1975; Kelly, Seviour, & Iversen, 1975). The current view is that the mesolimbic and nigrostriatal fibers should be seen as subdivisions of the same anatomical system, because they derive from common embryonic tissue and develop side by side, with the cell bodies of the ventral tegmental area immediately adjacent to those of the substantia nigra and the terminals of the nucleus accumbens immediately adjacent to those of the nucleus caudatus (Fallon & Moore, 1978; Olson & Seiger, 1972).

Thus the current view is that the two animal manifestations of psychomotor activation involve actions at the synaptic terminals of adjacent subdivisions of the same anatomical structure—the mesocortical (defined to include the "mesolimbic" system; Fallon & Moore, 1978) dopaminergic fiber system.

Why should increased locomotion or stereotyped movements continue to be seen as "psychomotor" and not simply "motor" responses? There are several reasons to characterize the effects of these substances as something more than simple motoric effects. First, lesions or pharmacological blockade of the dopamine systems cause a form of sensorimotor neglect rather than a simple motoric or sensory impairment (Ackil & Frommer, 1984; Carli, Evendon, & Robbins, 1985; Hoyman, 1979; Hoyman, Weese, & Frommer, 1979; Marshall, 1978). Although lesions usually cause total akinesia when all brain dopamine is depleted (Stricker & Zigmond, 1976), it can be seen that certain movements are possible though they are not made in response to the environmental stimuli that normally elicit them (Wolgin, Cytawa, & Teitelbaum, 1976). Similarly, when dopamine systems are blocked pharmacologically, the capability to lever-press or run an alleyway can be demonstrated despite the fact that animals quickly lose interest in performing such responses for normal levels of reinforcement (Fouriezos, Hansson, & Wise, 1978; Fouriezos & Wise, 1976; Franklin & McCoy, 1979; Gallistel, Boytim, Gomita, & Klebanoff, 1982; Liebman & Butcher, 1973; Wise & Colle, 1984; Wise & Raptis, 1986; Wise, Spindler, deWit, & Gerber, 1978). When the lesions are unilateral, the animals generally fail to orient to visual, olfactory, or tactile stimuli contralateral to the side of the lesion (Marshall, 1979). The deficit is, however, clearly one of sensorimotor integration rather than sensory or motor function per se. The animals can demonstrate both contralateral sensory and contralateral motoric capability in selected tests; what the animals consistently fail to do is make contralateral responses to contralateral stimuli (Ackil & Frommer, 1984; Carli et al., 1985; Hoyman et al., 1979; Turner, 1973). The fact that left-lesioned rats can make right-paw responses to left-side stimuli and can make left-paw responses to right-side stimuli makes it clear that the deficit is not a simple sensory or simple motor disability.

A second reason to stress that the locomotor and stereotypy responses of lower animals are *psycho*motor in nature is that the response components are not so motorically stereotyped as has been commonly assumed. The stereotypic behavior of the laboratory rat usually consists of licking, chewing, and lateral head movements associated with sniffing. When observed in traditional testing conditions this behavior appears motorically driven, but when conditions are varied it is clear that the behavior is flexible. For example, rats have been shown to be capable of lever-pressing several thousand times per hour during periods of intense amphetamine stereotypy (Wise, Yokel, Hansson, & Gerber, 1977); thus amphetamine stereotypy does not disrupt the ability to respond in an integrated fashion to environmental stimuli. Another example is the case of apomorphine stereotypy; apomorphine produces stereotyped movements similar to those induced by amphetamine and is known to do so by a common behavioral mechanism (Ernst, 1967). However, apomorphine-induced stereotyped behavior takes the form of head-wagging sniffing movements only if the animals are tested on a horizontal surface. When tested in narrow or wire cages, the same animals will rear or climb. The common denominator of these motorically distinct responses is the maintenance of surface–snout contact—contact with the floor in one case and with the walls of the cage in the other (Szechtman, Ornstein, Teitelbaum, & Golani, 1982). The head wagging of the rat thus seems to be an exaggerated and nonhabituating form of the "orienting" or "investigatory" response (Pavlov, 1927; Sokolov, 1963) and not a simple motoric compulsion. Consistent with this view is the fact that amphetamine stereotypy of the cat does not involve the chewing, sniffing, and licking typical of the rat. Cats given amphetamine develop sniffing stereotypies if tested in a closed environment, but if tested in an open environment they develop a pattern of response involving rapid head movements and changes in visual fixation (Ellinwood & Escalante, 1970). That the response is not a driven motoric response is clear from the fact that the head movements cease when the cat is blindfolded (J. R. Stevens, personal communication, January 25, 1981). Thus, again, psychomotor stimulant stereotypy appears to involve a sensorimotor integration rather than the simple activation of a fixed motor program.

It is even more clear in the case of the locomotor response that amphetamine-induced behavior reflects exaggerated responsiveness to environmental stimuli rather than the simple driving of the motor system. The clearest evidence is seen in the behavior of animals that have their dopaminergic systems activated unilaterally; in such conditions the animals usually locomote with a directional bias, turning consistently away from the side of higher dopaminergic activation (Ungerstedt, 1971). Thus when animals with dopaminergic lesions in the left hemisphere are tested in round test chambers, they generally circle toward the left when the undamaged right side is activated by amphetamine. Some animals circle spontaneously; in this case the direction of circling reflects the side of the brain with highest dopaminergic turnover (Glick, Jerussi, & Fleisher, 1976). Thus the circling of animals with more dopaminergic activation on one side of the brain is a directionally biased manifestation of the simple locomotion seen when the two sides are activated equally. Several facts make it clear, however, that the circling locomotion is a complex, psychomotor response and not a simple, purely motor reaction.

The simplest (motoric) models of the rotation produced by asymmetrical dopamine activation suggest either that locomotor mechanisms are asymmetrically activated—resulting in circling much as a boat circles when one oar is pulled harder than the other—or that postural mechanisms are asymmetrically activated—resulting in a curved spine that imposes a curved path on the animal. Neither of these models is adequate. First, although animals with unilateral lesions of the nigrostriatal system show a curved spine (Ungerstedt, 1971), neither spontaneous circlers nor animals with one dopaminergic mechanism stimulated by central morphine injections do (Holmes & Wise, 1985; Pisa & Szechtman, 1984). Each of these latter types of animal can walk in a straight line for several meters, but each tends to turn away from the activated side when an obstacle is encountered. The size of the circles thus depends more on the size of the testing environment than on the degree of dopaminergic imbalance (Holmes & Wise, 1985; Wise & Holmes, 1986). Moreover, the direction of circling can be reversed, in these animals, by environmental manipulations. For example, animals

that spontaneously circle clockwise around the edge of a tabletop will circle counterclockwise around a circular hole in the center of the table (Pisa & Szechtman, 1984). Animals that circle clockwise around the inside of a test box in response to unilateral pharmacological dopaminergic activation will circle counterclockwise around the outside of the same box (Wise & Holmes, 1986). The locomotion seems to be an exaggeration of the rat's orientation toward, or exploration of, environmental stimuli. It does not reflect an activation of hard-wired motor programs. The stronger circling that can be seen in animals with unilateral nigrostriatal damage, on the other hand, does seem more marked by motoric asymmetry (Ungerstedt, 1971), but this may be more a difference in degree of effect than a difference in the nature of the effect.

The fact that psychomotor stimulants exaggerate orienting or exploratory reactions to environmental stimuli is even more obvious in higher animals; in dogs, for example, the locomotor response to systemic amphetamine takes very different forms, depending on what the animal is doing when the drug takes effect. If the dog is following another dog, it may continue to follow the same animal for hours (Ellinwood & Kilbey, 1975). The pattern of specific movements is, in such cases, determined by the leading dog, not the amphetamine-treated follower. Thus the form of the response, both in the case of stereotypy and in the case of locomotion, is often influenced by the environment and is thus, in these cases at least, truly "psychomotor" and not simply "motor."

The nominal psychomotor stimulants are thus identified with increased responsiveness to environmental stimuli, rather than with reflexive activation of central motor programs. The principal indices of psychomotor stimulant action in lower animals are increased locomotor and orienting responses, and the mechanism of these responses involves, as critical central elements, forebrain dopamine systems. It will be seen that other addictive drugs also produce these and related behaviors and also activate the forebrain dopamine systems.

The De Facto Psychomotor Stimulants

The classifications of drugs have evolved under a variety of pressures, and there is no exhaustive and widely accepted classification scheme. Most drugs meet the defining requirements for membership in more than one drug class, and some drugs fail to fit comfortably into any major drug class. Nicotine and caffeine are cases in point; each has stimulant properties, but each has some characteristics in common with "classic" central nervous system stimulants—stimulating the central nervous system at multiple levels, for example—and each has some characteristics in common with the "psychomotor" stimulants. It is the latter characteristics that are of most interest here.

Nicotine. Nicotine is readily self-administered by humans and lower animals (Cox, Goldstein, & Nelson, 1984; Dougherty, Miller, Todd, & Kostenbauder, 1981; Henningfield & Goldberg, 1983; Spealman & Goldberg, 1982). Although nicotine is not traditionally categorized as either a psychomotor stimulant or a central nervous system stimulant, both animal and human data suggest that nicotine has amphetaminelike properties. Nicotine stimulates noradrenergic fibers of the sympathetic nervous system as well as cholinergic fibers of the parasympathetic system; thus it has sympathomimetic actions. It also has central stimulant effects (Aceto & Martin, 1982); nicotine causes increased locomotor activity and stereotypy in rats (Iwamoto, 1984). Both humans and lower animals respond to nicotine in discrimination tests as if it were more similar to amphetamine than to saline (Henningfield & Jasinski, 1983; Schechter, 1981). Nicotine improves psychomotor performance in humans, particularly when fatigue and boredom are factors in performance (Wesnes & Warburton, 1983; Wesnes, Warburton, & Matz, 1983). Thus nicotine has amphetaminelike properties in humans and lower animals and should be considered a psychomotor stimulant whatever its distinguishing "side effects."

If nicotine is to be considered a psychomotor stimulant, however, it must be considered a weak one, at least in its *net* behavioral effects. Nicotine causes minimal increases in rat locomotor activity (Iwamoto, 1984; Morrison & Stephenson, 1973; Pradhan, 1970; Schlatter & Battig, 1979) and stereotyped head movements (Iwamoto, 1984); the effects are weak in comparison to those of amphetamine. Similarly, the stimulus properties of nicotine, although weakly amphetaminelike, are not so similar as to be confused with amphetamine (Henningfield & Goldberg, 1985). The significance of these facts is not clear, however, because nicotine may have discriminative properties *in addition to* amphetaminelike stimulus properties, and these additional properties might account for the discrimination of nicotine from amphetamine despite major, but masked, psychomotor stimulation effects. The apparent weakness of nicotine effects on locomotion and stereotypy may also reflect nicotinic "side effects." As will be seen in the case of morphine, a drug can have multiple actions, some of which obscure evidence of the others. Thus although the behavioral evidence does not suggest strong central psychomotor stimulant actions of nicotine, neither does it rule out this possibility. All that can be said at the present time is that nicotine does have some degree of psychomotor stimulant action.

There is some evidence to suggest that nicotine acts on the mechanism associated with the psychomotor stimulant effects of amphetamine; nicotine does seem to activate the ventral tegmental dopaminergic neurons (Arqueros, Naquira, & Zunino, 1978; Giorguieff-Chesselet, Kemel, Wandscheer, & Glowinski, 1979; Lichtensteiger et al., 1982; Svennson, Grenhoff, & Aston-Jones, 1986; Yoon et al., 1986), though it has not been demonstrated directly that nicotine's behavioral actions depend critically on such dopaminergic activation.

Caffeine. Caffeine is self-administered by humans (Gilbert, 1976), though it is not a potent reinforcer in lower animals Deneau et al., 1969). Caffeine is generally classified as a general central nervous system stimulant (Ritchie, 1970), though it is widely used for psychomotor stimulant purposes by humans. Caffeine increases locomotor activity in rodents, and this effect is at least partially antagonized by dopamine receptor blockers (Estler, 1979; Waldeck, 1973). Caffeine stimulates mesolimbic dopamine turnover (Govoni et al., 1984). Thus caffeine has amphetaminelike psychomotor stimulant actions, and these actions appear to depend at least partially on a brain mechanism homologous with that of amphetamine's psychomotor stimulant actions.

The Nominal CNS Depressants

Several drugs of abuse—opiates, barbiturates, and alcohol, for example—are generally considered to be central nervous

system (CNS) depressants. It may seem paradoxical to propose that depressant drugs are addictive because of their stimulant actions, yet this is the central assertion of the proposed theory. There is no question that CNS depression is the dominant effect of these drugs—at least when high doses are given. The hypothesis advanced here is critically dependent on evidence that these drugs, despite their depressant properties, also have important psychomotor stimulant properties and that these stimulant properties are mediated by the same brain mechanism as mediates the stimulant properties of amphetamine and cocaine. These drugs will each be discussed in turn. Because the present hypothesis rests heavily on the demonstrated psychomotor stimulant properties of opiates, this case is described first and in greatest detail.

Opiates. When given systemically, opiates have biphasic effects on locomotor behavior, stimulating it at low doses and inhibiting it at high doses (Babbini, Gaiardi, & Bartoletti, 1979; Fog, 1970; Martin, Wikler, Eades, & Pescor, 1963; Vasko & Domino, 1978). Even when high doses are given, the low-dose effect is evident shortly after injection, when the full dose is only partially absorbed. The high-dose effect—sedation—follows the early period of stimulation; the low-dose effect then reappears as the drug is metabolized to low levels. It is now clear that the stimulant and depressant effects of opiates derive from independent actions at different brain mechanisms. The earliest evidence came from the fact that tolerance develops to the sedative actions but not to the stimulant actions; after several repeated tests, the stimulant actions are unmasked by the tolerance to sedation (Adams, Lorens, & Mitchell, 1972; Bush, Bush, Miller, & Reid, 1976).

More recently, it has been possible to confirm separate mechanisms and to identify the different anatomical sites of sedative and stimulant actions of opiates by injecting them directly into relatively localized regions of the brain. Opiates inhibit behavior because of low-dose actions at a site in the brainstem (Broekkamp, LePichon, & Lloyd, 1984) and perhaps also because of additional, high-dose actions in the striatum (Havemann, Winkler, & Kuschinsky, 1982). Opiates elicit locomotor activity, on the other hand, because of low-dose actions on or near the dopaminergic cells of the ventral tegmentum and substantia nigra (Broekkamp et al., 1976; Holmes, Bozarth, & Wise, 1983; Holmes & Wise, 1985; Iwamoto & Way, 1977; Joyce & Iversen, 1979) and because of higher-dose actions in the nucleus accumbens (Kalivas, Widerlov, Stanley, Breese, & Prange, 1983).

The increased locomotor activity appears to result primarily from the activation of the dopaminergic cells of the ventral tegmental area (Holmes & Wise, 1985); these are the same dopaminergic cells that are thought to be responsible for the locomotor effects of amphetamine (Creese & Iversen, 1975; Kelly et al., 1975). It is not clear whether the relevant opiate receptors are embedded in the membranes of the dopaminergic cells themselves or are rather localized on afferents to the dopaminergic cells; opiate receptors are present at both locations (Llorens-Cortes et al., 1979; Pollard et al., 1977). Current electrophysiological evidence confirms that systemic and local opiate injections activate dopaminergic neurons (Finnerty & Chan, 1981; Gysling & Wang, 1983; Matthews & German, 1984; Ostrowski, Hatfield, & Caggiula, 1982); Hu and Wang (1984) have reported intracellular recording evidence suggesting that morphine has a direct action on the dopaminergic cells themselves.

The locomotor effects of morphine appear to depend critically on activation of the dopamine system whether or not the action is direct; neuroleptics block the locomotor responses to morphine at doses that do not block similar locomotion elicited by injections of muscimol, a central nervous system convulsant (Holmes & Wise, 1985). Because neuroleptics themselves increase dopamine turnover (Carlsson & Lindqvist, 1963) and accelerate the firing of dopaminergic cells (Bunney, Walters, Roth, & Aghajanian, 1973), it may seem paradoxical that these agents should block the locomotion induced by stimulating these cells by morphine; the explanation is that although neuroleptics do stimulate the dopamine system itself (by blocking the dopamine-mediated self-inhibition of activity in these cells; Groves, Wilson, Young, & Rebec, 1975), they block expression of such autoreceptor-mediated disinhibition by blocking dopamine receptors on the target neurons to which the dopaminergic cells project (Seeman, 1980). By blocking the access of dopamine to receptors on the target neurons, neuroleptics counteract their own dopaminergic activating effects along with those of morphine and other stimulants. It is the postsynaptic action of neuroleptics that is thought to account for the blockade of morphine-induced locomotion (Holmes & Wise, 1985).

In addition to facilitating locomotor activity, the opiates also facilitate other approach behaviors elicited by rewarding medial forebrain bundle electrical stimulation. The two such behaviors that have been widely studied are feeding and drinking. Morphine facilitates both freefeeding and feeding induced by lateral hypothalamic electrical stimulation (Wise, Jenck, & Raptis, 1986), whereas the opiate antagonists naloxone and naltrexone attenuate both behaviors (Jalowiec, Panksepp, Zolovick, Najam, & Herman, 1981; Lowy, Starkey, & Yim, 1981; Mello, Mendelson, & Bree, 1981; Ostrowski, Rowland, Foley, Nelson, & Reid, 1981; Wise, Jenck, & Raptis, 1986). Endogenous opioid peptides seem to be involved in these behaviors (Morley, Levine, Gosnell, Kneip, & Grace, 1983; Morley, Levine, Grace, & Kneip, 1982). The facilitatory effects of opioids on feeding are not very robust because the high-dose sedative effects usually mask feeding effects; however, they, like the rewarding and locomotor effects of opiates, can be clearly seen in animals given local central injections in the ventral tegmental area (Wise, Jenck, Gratton, & Quirion, 1986). Injections into the periaqueductal gray area—where morphine has sedative (Broekkamp et al., 1976) and dependence-producing actions (Bozarth & Wise, 1984; Wei et al., 1973)—inhibit this behavior and inhibit deprivation-induced eating (Carr & Simon, 1983; Wise, Jenck, Gratton, & Quirion, 1986; Wise, Jenck, & Raptis, 1986). The effects of central injections thus make it clear that there are both sedative and stimulant actions of opiates and that they involve independent mechanisms localized in different brain structures. This fact has not been fully appreciated from studies of systemic opiate injections, because such injections activate both mechanisms, allowing the sedative effect to mask expression of the stimulant effects.

Thus, despite the fact that opiates have major depressant or sedative effects, they also have important, amphetaminelike, psychomotor stimulant effects. Although the opiates must continue to be classified as depressant drugs, they should also be

considered psychomotor stimulants, having effects in common with other drugs in the stimulant class and producing these effects by activating the same dopaminergic brain mechanism. It is troublesome to have to consider a drug as both a stimulant and a depressant, notwithstanding the fact that most drugs are acknowledged to have multiple effects. It is one of our goals in the present article to call attention to the stimulant effects that are common to opiates and other drugs of abuse but that are usually ignored. These effects have received too little attention because they have been overshadowed, in the literature as in the brain, by the depressant effects that are also, and more obviously, characteristic of the opiates and several other addictive substances.

Barbiturates. Barbiturates are readily self-administered in humans and lower animals (J. D. Davis, Lulenski, & Miller, 1968; J. D. Davis & Miller, 1963; Woods & Schuster, 1970). Just as the opiates have biphasic effects on behavior, so do the barbiturates (Domino, 1962; Jacobs & Farel, 1971; Mori, Winters, & Spooner, 1968; Winters, Mori, Spencer, & Bauer, 1967). Again, behavioral activation is seen at low doses, but behavior is inhibited by high doses (Jacobs & Farel, 1971; Winters et al., 1967). Barbiturates increase eating and drinking (Jacobs & Farel, 1971; Watson & Cox, 1976) as well as locomotor activity. Again, the stimulant effects are usually seen in the early period when high doses are first being absorbed, and they are seen again for a longer period as the drug is metabolized to low levels once more (Jacobs & Farel, 1971). It is not known whether the mechanism of the low-dose stimulant action involves the dopaminergic system implicated in opiate, amphetamine, and cocaine stimulant effects.

Alcohol. Alcohol is readily self-administered by humans and lower animals, though reinforcing effects and significant self-administration are demonstrated with some difficulty in laboratory animals (Lester & Freed, 1973; Meisch & Beardsley, 1975; Mello, 1973; Sinclair, 1974). Alcohol, like barbiturates and opiates, has biphasic effects on locomotor activity (Friedman, Carpenter, Lester, & Randall, 1980; Frye & Breese, 1981; Strombom & Liedman, 1982). Alcohol activates ventral tegmental dopaminergic neurons (Gessa, Muntoni, Collu, Vargiu, & Mereu, 1985), and the locomotor-stimulant effects appear to be dopamine dependent (Dudek, Abbott, Garg, & Phillips, 1984; Liljequist & Carlsson, 1978; Strombom & Liedman, 1982); thus it seems likely that alcohol has low-dose psychomotor stimulant actions involving the same dopaminergic mechanism implicated in the psychomotor stimulant actions of opiates, amphetamine, and cocaine.

Benzodiazepines. Though their abuse liability in humans might be questioned (deWit, Johanson, & Uhlenhuth, 1984; Griffiths & Ator, 1981), benzodiazepines are self-administered by humans and lower animals (Griffiths, Bigelow, Liebson, & Kaliszak, 1980; Griffiths, Lukas, Bradford, Brady, & Snell, 1981). The benzodiazepines, too, have biphasic effects on locomotor behavior; again, the low-dose effect is stimulation and the high-dose effect is sedation (Margules & Stein, 1968). The high-dose sedative effect shows tolerance over repeated injections, whereas the low-dose stimulatory effect on locomotion and on feeding (Cappell, LeBlanc, & Endrenyi, 1972; Cooper, 1980; Margules & Stein, 1968; Poschel, 1971; Randall, Schallek, Heise, Keith, & Bagdon, 1960; Wise & Dawson, 1974) shows no tolerance but is rather unmasked as tolerance develops to the sedative effect (Margules & Stein, 1968; Wise & Dawson, 1974). Diazepam facilitates eating induced by lateral hypothalamic electrical stimulation at the doses that facilitate free feeding and locomotor stimulation (Soper & Wise, 1971).

Cannabis. Cannabanoids are self-administered by humans but are not readily self-administered by lower animals (Harris, Waters, & McLendon, 1974). Cannabis, again, is sedative at high doses but has locomotor stimulant properties at low doses (Glick & Milloy, 1972). It is reported to enhance the taste of food in humans (Abel, 1971; Hollister, 1971) and, at low doses, enhances feeding in animals (Drewnowski & Grinker, 1978; Glick & Milloy, 1972). The mechanism of neither the stimulant nor the depressant effect is understood in any detail.

Phencyclidine. Phencyclidine is another drug of potential abuse; it is self-administered by humans (Siegel, 1978) and by rhesus monkeys (Balster, Johanson, Harris, & Schuster, 1973). It has actions in common with a wide range of psychoactive drugs, including anesthetics, opiates, and psychomotor stimulants (Johnson, 1978). Its psychomotor stimulant actions include locomotion and stereotypy (Boren & Consroe, 1981; Castellani & Adams, 1981; Murray & Horita, 1979; Schlemmer et al., 1978); dopamine-antagonists attenuate these actions (Castellani & Adams, 1981; Murray & Horita, 1979; Schlemmer et al., 1978). Phencyclidine causes an increase in synaptic concentration of dopamine, and it has been suggested that phencyclidine is a dopamine releaser (Vickroy & Johnson, 1982). It is difficult, however, to discriminate between increased dopamine concentrations caused by increased release and those caused by attenuation of reuptake (Heikkila, Orlansky, & Cohen, 1975); more recent work suggests that phencyclidine does not cause dopamine release, but rather blocks its reuptake (Gerhardt & Rose, 1985).

Homology Between Psychomotor Stimulation and Positive Reinforcement

Evidence reviewed thus far indicates that the major drugs that are widely considered as addictive all have psychomotor stimulant actions even if they also have sedative actions that can override the behavioral manifestation of psychomotor arousal. The important question for the proposed theory, however, is whether these psychomotor stimulant actions bear any causal relation to the habit-forming or addictive properties of these substances. The central argument of the theory is that a common biological mechanism plays homologous roles in psychomotor stimulation and in positive reinforcement. Psychomotor stimulation is argued to be the Pavlovian manifestation of the Skinnerian process of response reinforcement. This suggestion is supported by reasonably convincing evidence only in the cases of the nominal psychomotor stimulants—amphetamine and cocaine—and the opiates. It is here argued, however, that the same biological mechanism is likely to play homologous roles not only in amphetamine, cocaine, and opiate psychomotor stimulation but in barbiturate, alcohol, benzodiazepine, and cannabis psychomotor stimulation as well. The next task, then, is to develop the evidence that psychomotor stimulation and positive reinforcement are homologous—that they derive from common or at least overlapping neural mechanisms.

As mentioned earlier, it has been proposed by Schneirla (1959) and by Glickman and Schiff (1967), among others, that forward locomotion—the common denominator of psychomotor stimulants—is the unconditioned response to all positive reinforcers. The argument of Glickman and Schiff hinged on the question of whether the same medial forebrain bundle circuitry mediates the forward locomotion induced by hypothalamic stimulation and the rewarding effects produced by similar—but not identical—stimulation at the same sites (Glickman & Schiff, 1967; Hoebel, 1969). This question is not entirely resolved and is beyond the scope of the present article. It seems clear, however, that the rewarding effects of hypothalamic stimulation depend critically upon the activation, either directly or indirectly (Wise, 1980; Yeomans, 1982), of a dopaminergic mechanism, because blocking dopamine receptors with neuroleptics attenuates the rewarding impact of hypothalamic stimulation (Esposito, Faulkner, & Kornetsky, 1979; Fenton & Liebman, 1982; Fouriezos et al., 1978; Fouriezos & Wise, 1976; Franklin, 1978; Franklin & McCoy, 1979; Gallistel et al., 1982; Liebman & Butcher, 1973; Zarevics & Setler, 1979).

This conclusion must be tempered by the statement that it has not yet been directly demonstrated that rewarding hypothalamic stimulation activates dopamine systems. Indeed, attempts to detect increased metabolic activity in the dopaminergic neurons or their target cells have been unsuccessful to date (Gallistel, Gomita, Yadin, & Campbell, 1985; Gomita & Gallistel, 1982). Thus far, however, such attempts have been based on between-animal or between-hemisphere comparisons of the average glucose utilization in the region of dopaminergic fibers or their terminals. This methodology is likely to be insensitive to the critical events. First, comparisons of the stimulated hemisphere with the unstimulated hemisphere are based on the assumption that the dopamine system is not crossed; this assumption is not well-founded, because the dopamine pathways project bilaterally (Fass & Butcher, 1981; Pritzel & Huston, 1981; Pritzel, Sarter, Morgan, & Huston, 1983) and contralateral nucleus accumbens injections of neuroleptics attenuate (though to a lesser extent than ipsilateral injections) medial forebrain bundle brain stimulation reward (Colle & Wise, 1986).

Second, it is quite possible that it is the momentary pattern of dopaminergic discharge, rather than the total number of impulses in the dopaminergic system, that determines the net effectiveness of dopamine output (Freeman, Meltzer, & Bunney, 1985). It must be remembered that it is the effects at dopamine receptors on postsynaptic target neurons, not the activation of dopaminergic neurons themselves, that determine the rewarding impact of dopaminergic activation (Colle & Wise, 1986; Stellar, Kelley, & Corbett, 1983). Third, although the postsynaptic effect is ultimately to activate locomotor activity, there has been (and still is) controversy as to whether this behavioral activity results from the activation (Kitai, Sugimori, & Kocsis, 1976) or inhibition (Siggins, 1978) of postsynaptic target neurons.

Finally, the measurement of glucose utilization reflects the *average* glucose use of a variety of cell types in a given area. It is possible that the change in glucose utilization of the dopamine neurons following rewarding stimulation is minimal compared to the utilization or change in utilization of other cells in the same brain regions. Thus, confirmation that rewarding events activate the dopamine system awaits the development of measures that are sensitive to moment-to-moment fluctuations in local dopamine concentration or in activity specific to dopaminergic target neurons. The most promising methods are just nearing the stage of development that would make such measurements possible (Gerhardt, Oke, Nagy, Moghaddam, & Adams, 1984; Hoffer, Rose, Gerhardt, Stromberg, & Olson, 1985).

Just as it seems clear that activation of postsynaptic dopamine receptors is critical for the rewarding impact of hypothalamic brain stimulation, so is it clear that such activation is critical for the rewarding effect of the psychomotor stimulants and at least some other addictive drugs. Our understanding of the biological mechanisms of addiction is far from complete in the case of any drug class and is almost nonexistent in the case of some drug classes. Nonetheless, in the cases where the mechanisms are partially understood, there is good reason to believe that the psychomotor stimulant and the reinforcing actions derive from actions on a common biological substrate—the forebrain dopamine systems and one or more of their efferent connections.

Psychomotor stimulants. It has already been stated that the psychomotor stimulant effects of amphetamine and cocaine derive from activation of a mechanism having mesencephalic dopamine neurons as a critical synaptic link. The locomotor effects of these drugs seem to derive from increased concentrations of dopamine in synapses of nucleus accumbens, and the stereotypy seems to derive from increased concentrations of dopamine in synapses of the caudate nucleus (Creese & Iversen, 1975; Kelly et al., 1975). The fact that amphetamine decreases the activity of the dopamine-containing neurons themselves is not incompatible with this conclusion; amphetamine inhibits dopaminergic neurons by increasing dopamine concentration at presynaptic dopamine autoreceptors (Groves et al., 1975), presumably by blocking reuptake of dendritic dopamine released near the cell body (Cheramy, Leviel, & Glowinski, 1981; Groves & Linder, 1983). Several lines of evidence implicate the same nucleus accumbens synapses in the mechanism of amphetamine and cocaine reinforcement. This evidence has been reviewed in detail elsewhere (Fibiger, 1978; Wise, 1978, 1980, 1982, 1984) and will only be summarized here.

The psychomotor stimulants have long been known to activate central and peripheral catecholamine mechanisms (Axelrod, 1970; Carlsson, 1970; Heikkila, Orlansky, & Cohen, 1975). That such activation plays a causal role in the reinforcing effects of amphetamine and cocaine was established by studies of central catecholamine blockade or depletion (Pickens, Meisch, & Dougherty, 1968; M. C. Wilson & Schuster, 1972). The reinforcing effects of amphetamine and cocaine are blocked by selective dopamine receptor blockers but not by selective noradrenergic blockers (W. M. Davis & Smith, 1975; Risner & Jones, 1976, 1980; Yokel & Wise, 1975, 1976). Amphetaminelike reinforcement is also caused by selective dopamine agonists (Baxter, Gluckman, Stein, & Scerni, 1974; W. M. Davis & Smith, 1977; Risner & Jones, 1976; Wise, Yokel, & deWit, 1976; Woolverton, Goldberg, & Ginos, 1984; Yokel & Wise, 1978) but not by selective noradrenaline agonists (Risner & Jones, 1976; Yokel & Wise, 1978, but see W. M. Davis & Smith, 1977, who reported *opiate*like reinforcing effects of the noradrenergic agonist, clonidine). Selective pharmacological blockade of dopa-

mine, but not noradrenaline, receptors also attenuates amphetamine euphoria in humans (Gunne, Anggard, & Jonsson, 1972). The psychomotor stimulants increase dopamine concentration both at autoreceptors that play a role in negative-feedback regulation of dopamine synthesis and cell firing (thus decreasing the firing rate of the dopaminergic cells) and also at postsynaptic receptors that normally transmit the consequences of dopaminergic activation to the subsequent neurons in the circuit. It is the amplification of the dopamine effects at the postsynaptic receptors, and not the amplification of autoreceptor-mediated self-inhibition, that accounts for the rewarding effects of psychomotor stimulants (Baxter, Gluckman, & Scerni, 1976).

Lesion studies suggest that it is the dopaminergic projection to nucleus accumbens that plays the most significant role in stimulant self-administration. Neurotoxin lesions of dopamine terminals in nucleus accumbens (which may also damage dopamine fibers continuing on to frontal cortex) impair ongoing stimulant self-administration and impair learning of self-administration in naive animals (Lyness, Friedle, & Moore, 1979; Roberts, Corcoran, & Fibiger, 1977; Roberts, Koob, Klonoff, & Fibiger, 1980); neurotoxin lesions of the cells of origin of this system have similar effects (Roberts & Koob, 1982). Neurotoxin lesions of the output cells of nucleus accumbens also attenuate stimulant self-administration (Zito, Vickers, & Roberts, 1985), as do nucleus accumbens microinjections of dopamine-specific antagonists (Phillips & Broekkamp, 1980); neither of these treatments would affect the cortical dopamine projections that pass near nucleus accumbens. Lesions of the caudate nucleus are relatively ineffective unless they are accompanied by damage to nucleus accumbens. Rats have been reported to work for direct injections of amphetamine (Hoebel et al., 1983) or dopamine (Guerin, Goeders, Dworkin, & Smith, 1984), but not cocaine (Goeders & Smith, 1983), into the nucleus accumbens. The cocaine finding is surprising because rats will work for cocaine injections into the frontal cortex (Goeders & Smith, 1983).

It has been suggested that frontal cortex dopamine plays the important role in cocaine self-administration, whereas nucleus accumbens dopamine plays the important role in amphetamine self-administration, though it is difficult to imagine how the two dopaminergic terminal fields discriminate the two drugs—which are each thought to act at both places. Thus, while dopamine clearly plays a role in the reinforcing effects of the psychomotor stimulants, it is not yet clear which of the various forebrain dopamine terminals are involved. Current evidence implicates nucleus accumbens strongly and suggests the frontal cortex as another possible site of reinforcing stimulant interactions with dopaminergic circuitry.

Opiates. Evidence has been reviewed above to indicate that at least one of the psychomotor stimulant actions of the opiates is associated with activation of the ventral tegmental dopaminergic cells. It is now believed that opiates can activate locomotor activity at a second central site as well; the second site is the nucleus accumbens itself (Almaric & Koob, 1985; Kalivas et al., 1983; Pert & Sivit, 1979). Inasmuch as nucleus accumbens is the synaptic target of many of the ventral tegmental dopamine neurons, it appears that opiates can activate the same locomotor mechanism at two synaptic loci: at the synapse of afferents onto the dopamine cells and at the synapse of dopamine fibers onto their efferent target cells. The ventral tegmental site of action seems to be the more sensitive, responding to lower doses of intracranial opioids (Kalivas et al., 1983). As in the case of the psychomotor stimulants, it appears that opiates have their reinforcing actions through the same mechanism as mediates their psychomotor stimulant actions. Moreover, the same dopaminergic mechanism appears to mediate the psychomotor stimulant and the reinforcing properties of both the nominal psychomotor stimulants and the opiates.

Clear-cut and powerful reinforcing effects of opiates have been demonstrated when they are injected in the region of the dopamine-containing cells of the VTA (Bozarth & Wise, 1981b, 1982; Phillips & LePiane, 1980; van Ree & de Wied, 1980). VTA injections of naloxone and quaternary nalorphine block and attenuate, respectively, the reinforcing effects of intravenous heroin (Britt & Wise, 1983), and pimozide and haloperidol block the shift in conditioned place preference caused by opiate injections (Bozarth & Wise, 1981a; Spyraki, Fibiger, & Phillips, 1983). Although both neuroleptics and opiates increase dopamine turnover, it must be remembered that neuroleptics, unlike opiates, block the postsynaptic expression of that increase in turnover. Thus, despite their common effect on dopamine turnover, opiates and neuroleptics have very dissimilar—in this case, opposite—effects on behavior. Even in the case of the gross sedation that can be caused by opiates and neuroleptics, the behavioral effects are different and reflect independent mechanisms of action (De Ryck, Schallert, & Teitelbaum, 1980; Segal, Browne, Bloom, Ling, & Guillemin, 1977).

Reinforcing effects of opiates have also been demonstrated with injections into nucleus accumbens (Goeders, Lane, & Smith, 1984; Olds, 1982; van der Kooy, Mucha, O'Shaughnessy, & Bucenieks, 1982). Nucleus accumbens injections of quaternary naloxone—like VTA injections of the same compound—attenuate the reinforcing effects of intravenous heroin (Vaccarino, Bloom, & Koob, 1985). Thus opiate actions at nucleus accumbens opiate receptors offer a secondary site of rewarding opiate action. It appears that the cells of the nucleus accumbens—targets, in all probability, of dopaminergic synaptic terminals—are involved, because neurotoxic lesions of the nucleus accumbens or of the VTA attenuate intravenous opiate reinforcement (Bozarth & Wise, 1986; Zito et al., 1985).

Other sites of opiate reinforcing action have been reported (Olds, 1979; Olds & Williams, 1980; van der Kooy et al., 1982) but not yet confirmed (Bozarth & Wise, 1982; Britt & Wise, 1981). Whether or not there exist multiple sites of opiate reinforcing action, the two major sites identified thus far are also sites of opiate stimulant action. In addition, these two sites appear to be but one synapse removed from one another within a common neuronal circuit. Thus the current evidence suggests that the positive reinforcing effects and the psychomotor stimulant effects are homologous. Moreover, the mechanism of the stimulant and reinforcing actions of opiates involves the same dopaminergic elements as are implicated in the stimulant and reinforcing actions of amphetamine and cocaine. Thus the current evidence suggests that opiate and amphetamine stimulant actions are homologous and that opiate and amphetamine reinforcing actions are homologous. The current evidence further suggests that the stimulant and positive reinforcing effects of

opiates, amphetamine, and cocaine all derive from activation of the midbrain dopamine neurons or their target neurons in the forebrain.

Nicotine, caffeine, barbiturates, alcohol, benzodiazepines, cannabis, and phencyclidine. Strong evidence has been marshalled for the view that a common brain mechanism mediates the reinforcing and the psychomotor stimulant properties of the nominal psychomotor stimulants and the opiates. This evidence suggests homology between the psychomotor stimulant and reinforcing actions of these agents; a common biological mechanism can account for both effects of both drug classes. Except for some preliminary evidence in the case of phencyclidine (Giovino, Glimcher, Mattei, & Hoebel, 1983), similar evidence is not available for the other drugs under discussion, though some evidence has been mentioned linking the psychomotor stimulant actions of alcohol and the benzodiazepines to the dopaminergic mechanisms associated with the rewarding and psychomotor stimulant actions of amphetamine, cocaine, and the opiates. It seems likely however, that just as the psychomotor stimulant and the reinforcing effects of amphetamine, cocaine, and the opiates are homologous, so will the stimulant and reinforcing effects of these other drugs prove to be homologous. Just as the psychomotor stimulant effects of opiates are homologous to the psychomotor stimulant effects of amphetamine and cocaine, so is it likely that the psychomotor stimulant effects of other drugs will be homologous to the psychomotor stimulant effects of opiates, amphetamine, and cocaine.

The central postulate of the present theory is that a common biological mechanism mediates the psychomotor stimulant properties and the positive reinforcement properties of a wide variety of environmental stimuli, central manipulations, and drugs of abuse. The prediction of the present theory is that when the mechanism of the psychomotor stimulant actions and the reinforcing actions of each of these drugs is fully understood, it will be seen to involve the same dopaminergic system or systems involved in amphetamine, cocaine, and opiate stimulant and reinforcing actions.

Testing the Theory

The theory is that all addictive drugs have psychomotor stimulant properties and that the biological mechanism of the psychomotor stimulant properties is the same as, or has common elements with, the biological mechanism of the reinforcing effects of these drugs. A weak prediction of the theory would be that, for a given drug or drug class, there exists a common mechanism for stimulant actions and for reinforcing actions. The strong prediction of the theory is that for all addictive drugs, regardless of class, a common mechanism, or at least elements of a common mechanism, mediates both psychomotor stimulant actions and reinforcing actions. Evidence on some of these points has been reviewed and represents the *foundation* of the theory; this evidence cannot be considered a *test* of the theory. Some specific elements of the theory have been formulated for a few years, however, and have been "tested." This literature will be briefly summarized, and a few potential tests that have not yet been undertaken will be sketched.

The view that opiates and psychomotor stimulants activate a common reinforcement mechanism, and evidence suggesting the role of dopamine in this mechanism, was first forcefully advanced in the mid-1970s by Broekkamp and his collaborators. These workers used microinjection techniques to localize amphetamine's facilitation of brain stimulation reward to a mechanism in or near the nucleus accumbens (Broekkamp, Pijnenburg, Cools, & Van Rossum, 1975) and to localize morphine's facilitation of brain stimulation reward to a mechanism in or near the ventral tegmental area (Broekkamp et al., 1976). The notion that facilitation of brain stimulation reinforcement reflected activation of the same mechanism as direct drug reinforcement was a notion implicit in the work of several early groups (Adams et al., 1972; Bozarth, Gerber, & Wise, 1980; Bush et al., 1976; Kornetsky et al., 1979; Levitt et al., 1977; Marcus & Kornetsky, 1974), but the first test of the notion was the demonstration that morphine had direct rewarding effects (Bozarth & Wise, 1981b; Phillips & LePiane, 1980) when microinjected into the same region where its effects on brain stimulation reward had been demonstrated by Broekkamp et al. (1976). Each of these two groups predicted that opiates would have direct reinforcing actions in the ventral tegmental area based on Broekkamp's demonstrations (Broekkamp et al., 1976; Broekkamp, Phillips, & Cools, 1979) that opioids facilitated brain stimulation reward when injected into this region. The theory that a common mechanism underlies psychomotor stimulant and opiate self-administration has subsequently been stated (Bozarth & Wise, 1983b; Wise, 1980, 1982; Wise & Bozarth, 1982, 1984) in several contexts.

With the exception of workers in the laboratories where it has been proposed, the theory that opiates and psychomotor stimulants activate a common reinforcement mechanism has been put to major test only by Koob (in press) and his coworkers. Ettenberg, Pettit, Bloom, and Koob (1982), on the grounds of their failure to block heroin self-administration with dopamine antagonists and their failure to block cocaine self-administration with opiate antagonists, argued that separate neural systems mediate opiate and stimulant reinforcement. They drew the same conclusion from their failure to disrupt heroin self-administration with selective damage to nucleus accumbens dopamine terminals (Pettit, Ettenberg, Bloom, & Koob, 1982). These recent findings thus require careful consideration.

It is not surprising that opiate antagonists have no effect on stimulant self-administration, because the site of opiate receptors in the proposed circuit (Wise & Bozarth, 1982, 1984) is afferent to the site of stimulant interaction with that circuit. However, the fact that intravenous heroin self-administration and opiate conditioned place preference (Mackey & van der Kooy, 1985) can still be demonstrated in animals treated with dopamine receptor blockers appears, on the surface, to discredit the theory. This problem seems resolved, however, when it is realized that opiates have two independent sites of access to the system (Vaccarino et al., 1985). Opiates can activate the dopaminergic neurons at their cell bodies, as discussed earlier, and they can act at the cells of nucleus accumbens, efferent to or parallel to the dopaminergic synapse (Kalivas et al., 1983; Pert & Sivit, 1979). There is disagreement as to the relative importance of the two sites (Britt & Wise, 1983; Vaccarino et al., 1985), but it now seems clear that opiate actions in the nucleus accumbens, efferent to the dopaminergic link in the system, can account for intravenous heroin self-administration in dopa-

mine-blocked or dopamine-depleted animals (just as stimulant actions in nucleus accumbens, efferent to the opiate synapse in the ventral tegmental area, can account for intravenous cocaine self-administration in naloxone-treated animals). Thus the recent data that seemed, at first, to challenge the notion of a common mechanism for stimulant and opiate reinforcement can readily be viewed as consistent with that notion. Although Koob (in press) continues to argue for separate mechanisms of cocaine and heroin reinforcement, he and his coworkers (Vaccarino et al., 1985) agree that there is a common mechanism of opiate and stimulant locomotor activation.

There has also been some controversy as to whether a common reinforcement mechanism might mediate stimulant and alcohol reinforcement (Amit & Brown, 1982). The psychomotor stimulant properties of alcohol are thought to depend on a dopaminergic mechanism, as discussed earlier, but oral intake of ethanol is argued not to be dopamine dependent. There are, however, reasons for questioning whether the amounts of ethanol typically consumed by laboratory rats reflect pharmacologically reinforcing actions of ethanol. The demonstration that rats will lever-press for oral ethanol appears to require either very careful selection of rats (Sinclair, 1974) or manipulations of food deprivation during training (Meisch & Beardsley, 1975). It would be useful to have data on the effects of dopaminergic manipulations on lever-pressing for ethanol, but such data are not available. Unlike the notion that dopamine plays a role in the mechanism of alcohol's reinforcing properties, the notion that dopamine plays a role in the mechanism of alcohol's locomotor stimulant actions is not in question.

The theory makes several testable predictions. It predicts that all addictive drugs will have psychomotor stimulant effects, and it is based on literature which suggests that they do. It predicts that the psychomotor stimulant actions of these drugs will be mediated by dopaminergic neurons or their efferents, and with the exception of the benzodiazepines and barbiturates, the evidence suggests that the drugs discussed have this action also. Benzodiazepines and barbiturates may activate dopamine efferents, as suggested above. The theory implies that the strength of the psychomotor stimulant properties of a drug should predict the strength of the reinforcing action of that drug, but this prediction should only be expected to hold if the stimulant strength and the reinforcing strength can be isolated from sedative and other interfering side effects. If stimulant and unwanted side effects of ethanol, benzodiazepines, and cannabinoids could be separated, drugs of these classes might be found to be more addictive, as well as more stimulating, than they currently seem. The most testable predictions of the theory are (a) that the psychomotor stimulant and reinforcing actions of any addictive drug should both be disrupted by any lesion or treatment that disrupts either one of these actions, (b) that dopaminergic lesions or pharmacological blockade should have such effects in all classes of drugs that have actions restricted to mechanisms afferent to the dopamine synapse, and (c) that lesions of efferent pathways should disrupt both the rewarding and psychomotor stimulant actions of all addictive substances. This last prediction offers the most stringent test of the theory; this test awaits identification of the final common path of psychomotor stimulant action.

The theory relates the reinforcing effects of drugs and brain stimulation to unconditioned psychomotor stimulant effects of those agents that result from activation of dopaminergic fibers of the medial forebrain bundle, its inputs, or its outputs. A serious problem for the ultimate success of the theory is the fact that dopamine receptor blockade does not have immediate effects on the psychomotor activation caused by a click that has been paired with food in a free-feeding task (Wise & Colle, 1984) despite its having immediate and potent effects on the psychomotor activation caused by similar cues in a partial-reinforcement operant task (Gray & Wise, 1980; Tombaugh, Anisman, & Tombaugh, 1980). Moreover, dopamine blockers have no appreciable effects on the "priming" effects of stimulation in animals that have been trained to run an alley and lever-press (Wasserman, Gomita, & Gallistel, 1982) or simply to run in a running wheel (Gallistel et al., 1982) for such stimulation. It seems that the *conditioned* psychomotor stimulant effects of reinforcers can be maintained for a significant period without the support of the dopamine system (Beninger & Hahn, 1983; Beninger, Phillips, & Fibiger, 1983). The relation between unconditioned and conditioned psychomotor actions of reinforcing drugs is not addressed by the present theory but has major significance for both the understanding and the treatment of addiction (Stewart, deWit, & Eikelboom, 1984).

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Gallup Appointed Editor of the *Journal of Comparative Psychology,* 1989–1994

The Publications and Communications Board of the American Psychological Association announces the appointment of Gordon G. Gallup, Jr., State University of New York at Albany, as editor of the *Journal of Comparative Psychology* for a 6-year term beginning in 1989. As of January 1, 1988, manuscripts should be directed to

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Manuscript submission patterns for the *Journal of Comparative Psychology* make the precise date of completion of the 1988 volume uncertain. The current editor, Jerry Hirsch, will receive and consider manuscripts until December 31, 1987. Should the 1988 volume be completed before that date, manuscripts will be redirected to Gallup for consideration in the 1989 volume.