

# Drive, Incentive, and Reinforcement: The Antecedents and Consequences of Motivation

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The aim of scientific explanation is to characterize the important antecedents of observable (or at least objectively confirmable) events. Explanations of behavior in terms of motivational states are appeals to unobservable, internal events for interpretations of behavior that is variable under apparently constant external stimulus conditions (see, e.g., Brown, 1953; Hinde, 1960). To be identified as the cause of a behavior, the unobservable event or condition must preexist the behavioral event to be explained. A behavior cannot be explained by its consequences, though it may be explained as a consequence of similar events in the animal's history. Scientific explanation involves the sequential identification of what comes first and what follows. To understand correctly what comes first and what follows is to achieve the primary goal of science.

While the teleology of Aristotle's notion of "final causes" encouraged the explanation of what comes first by what comes *after*, the major advance of the scientific revolution was to substitute mechanical causes—necessary and sufficient conditions (the "efficient causes" of Aristotle)—for the "final causes" previously legitimized by Aristotle's teachings (see Aristotle, *Physics*, in Barnes, 1984). Galileo precip-

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itated the culling of Aristotelean teleology from physics; we no longer accept Aristotle's notion that heavy things fall faster than light ones or his teleological suggestion that they do so "in order to reach their natural place." Two centuries after Galileo, Darwin (1859) offered a nonteleological explanation for human evolution; his principles of random mutation and natural selection offered a mechanistic alternative to the Aristotelean notion that human evolution was partly determined by the goal or intention of a creator. Skinner's (1966) parallel suggestion that behavior is generated randomly and selected by its consequences was an attempt to go beyond the rigidity of reflexes while avoiding the teleology inherent in the notion of goal direction. The apparent goal direction of motivated behavior explains nothing; it is the mystery that remains to be explained.

The problem of teleology is the problem of suggesting a consequence—something that follows—as the explanation of its cause—something that came first. A major challenge for psychology is to find mechanistic alternatives to teleological explanations of behavior. For psychology to advance our understanding of behavior within the scientific paradigm it must find the efficient causes—the necessary and sufficient antedating conditions—for behaviors that appear to be controlled by their consequences. This was really the quest of Skinner: the explanation of a given act in terms of its reinforcement history rather than in terms of the animal's presumed intentions. In no sphere of psychology is the temptation to explain an act by its intended consequences stronger than in the field of motivation. Eating is "explained" with the notion that it satisfies the bodily need for energy repletion; sexual behavior is "explained" with the notion that it satisfies the need of the species (or the "need" of the gene) for reproduction. The implication is that sex is initiated in order to reproduce the species and that eating is initiated in order to replenish energy reserves. These are Aristotelian—teleological—explanations. They do not advance our understanding. The task is to impose the step-by-step analysis of linear thinking—the efficient causes of Aristotle (what comes first and what follows)—on the cycles of hunger and satiety that offer our dominant model of motivation.

## The Problem of Definition

As can be seen from a survey of articles from the Nebraska Symposia

of years past, there has never been an adequate scientific definition of motivation. As Beach (1956) once noted on a related topic, "Most writers are satisfied to begin with the uncritical assumption of a mutual understanding between their readers and themselves" (p. 1). Not even in undergraduate textbooks can we find a definition that clearly differentiates motivational from nonmotivational phenomena. Jones, in introducing this symposium in 1955, identified the problem of motivation as the problem of "how behavior gets started, is energized, is sustained, is directed, is stopped, and what kind of subjective reaction is present in the organism while all this is going on" (p. vii). Jones has reserved the whole field of psychology for the motivational specialist. His statement gives us little insight as to an exclusionary rule; what does not fall under the rubric of motivation? In Beck's (1978) text the following was offered in place of a definition: "Motivation is broadly concerned with the contemporary determinants of choice (direction), persistence, and vigor of goal-directed behavior" (p. 24). Beck acknowledged that this is not a definition, apologizing that we cannot "just define motivation; we define a set of variables that are called motivational" (p. 25). The problem, not solved by Beck, is to define the set of such variables in such a way as to define equally the set of nonmotivational variables. Petri's (1981) popular textbook suggests that motivation is "the concept we use when we describe the forces acting on or within an organism to initiate and direct behavior" (p. 3). None of these distinguishes motivation as a subcategory of behavior; none distinguishes motivational theory as distinct from general behavior theory. Most writers have not come to grips with the problem of differentiating motivation from everything else.

Given this serious problem of definition, motivational theory rests on lists rather than principles. The traditional list includes three main motivational variables: drive, incentive, and reinforcement. There is no consensus as to whether these variables are to be invoked merely to explain the intensity of behavior, as argued by some authors (e.g., Brown, 1953; Hebb, 1955; Hull, 1943; Woodworth, 1918), or to explain both the intensity and the direction of behavior as suggested by others (e.g., Bindra, 1974; Teitelbaum, 1966; Toates, 1986; Young, 1949).

## The Variables of Motivation

### DRIVE

Early attempts to explain behavior involved inflexible reflexes and instincts as their basic elements. Reflexes and instincts were too rigid to accommodate instrumental behavior (e.g., Skinner, 1931, 1932), and instincts proved unpalatable because of the conceit that what applied to other animals did not apply to humans. While the instincts that figure in the theories of James and McDougall were not carried forward into more modern theories of behavior, the concept of drive, introduced by Woodworth in 1918, took their place. Woodworth posited multiple drives, the prototypes being hunger and thirst. Woodworth's notion was influenced by Sherrington's (1906) distinction between "preparatory" and "consummatory" (referring to consummation rather than consumption) behaviors. Preparatory or "anticipatory" reactions were seen by Sherrington as responses to distant stimuli that constituted the "attempt either to obtain actual contact or to avoid actual contact with the object" (p. 326). The basic tendencies to approach or withdraw from environmental stimuli were fundamental to Pavlov's early notions of orienting or investigatory reflexes on the one hand and defensive reflexes on the other (see, e.g., Sokolov, 1963). Craig's (1918) Sherrington-like distinction between "appetitive" and consummatory behaviors linked the root of the word "appetite" to the approach behaviors of investigation and manipulation. The tendency to approach or withdraw that was common to Pavlov's and Sherrington's basic reflexes would become the cornerstone of the important theory of motivation developed by Schneirla (1939, 1959) and extended by Glickman and Schiff (1967).

Woodworth characterized the preparatory stage of a reaction as being marked by a state of tension, the strength of which was proportional to the strength of the drive that would see the action through to its consummatory stage (completion). The drive theory first articulated by Woodworth was expanded on by later behaviorists, such as Hull (1943) and Hebb (1955). Inherent in Woodworth's view (as in Hull's and Hebb's) was the postulate that drive was directly responsible for the intensity of behavior but not, directly, for the direction or selection of behavior. By intensifying the responsiveness to food

(by making food-related incentives more salient), however, hunger could indirectly increase the probability of feeding at the cost of play, sex, or some other alternative. The analogy of Hebb (1955) was to the automobile. In his model drive is like the gas pedal, determining how fast the car will go (or whether it will move at all), whereas environmental cues govern the steering function, determining the direction the car will take (when and if it moves). While this distinction has generally not been made in social or personality theory, it has played a major role in behaviorist theories.

Hull attempted to tie his drive concept closely to tissue needs. It was easy to accept that hunger was a response to caloric needs and thirst a response to hydrational needs. By tying drive states to physiological need, he offered a definition of drive that was not based on the behavior it was used to explain. By suggesting that the reduction of a need state was the necessary and sufficient condition for reinforcement of learning, he offered a plausible and noncircular theory of how adaptive behavior is learned. However, like many simple, elegant, and testable ideas, his was quickly shown to have major shortcomings. First, rats learn to lever press not only for glucose, which replenishes the energy reserves of the body, but also for saccharin, which is useless as a bodily fuel (Sheffield & Roby, 1950). Second, most drinking in laboratory rats is ancillary to the eating of dry food rather than dictated by dehydration (Kissileff, 1969). Third, and perhaps more fatal than each of these flaws, eating and drinking anticipate (develop prior to) need; we usually eat and drink long before we develop states of tissue need (Fitzsimons, 1972; Le Magnen, 1969). The growing problem of obesity in modern society should make it clear that the feeding behavior can be robust and compulsive in the absence of any serious threat of tissue need. Fourth, Hull's notion that drive is a general state, something akin to an arousal state, and that it energizes all motivated behaviors under a common guiding principle was unworkable. While it sidestepped the triviality of Woodworth's multiple drives (each with its own rules and hence each with little generality), it offered an unsuitable model for sex, play, or even the avoidance of pain (see, e.g. Fiske & Maddi, 1961; Harlow, 1953). As pointed out by Beach (1956, p. 3) "Sexual activity is not, in the biological sense, essential to the well-being of the individual. Despite the fact that arguments to the contrary often provide a convenient rationalization during certain stages of life, no one ever

died for the lack of sex." The argument that, just as hunger and thirst were essential to the survival of the individual, sex was essential to the survival of the species was specious; it is difficult to imagine that a copulating rat has the survival of its species on its mind.

#### INCENTIVE MOTIVATION

The attempt to define motivation in terms of needs and drives failed for a variety of additional reasons. While it is easy to imagine that hunger and thirst are controlled by internal factors reflecting need states, it is difficult to exclude a role for external factors in these—and a dominating role for external factors in other—motivations. Male sexual arousal, for example, is often excited by purely visual or olfactory stimuli. The sight of an attractive female can quickly turn a male's thoughts away from other matters. The smell of a receptive female can awaken a male rodent from sleep, elevate its brain temperature 1° or 1.5° C, and channel its behavior from other activities to the vigorous pursuit of social interaction (E. A. Kiyatkin & R. A. Wise, unpublished observations). While it might be suggested that sexual arousal is controlled by hormones—particularly in lower species—Lehrman's (1965) elegant studies of the reproductive cycles of ring doves illustrate how the hormonal levels that dominate the motivational states of the dove are themselves triggered by external stimulus displays. The feedback from one behavior triggers release of the hormones that induce sensitivity to the stimuli that, in turn, elicit the next behavior in the reproductive sequence. Indeed, even in the case of feeding it proved necessary to modify Hull's model to include what Spence (1956) labeled as "incentive motivation": the energizing of the animal by the food incentive and the otherwise neutral stimuli that become associated with food in the development of food-seeking habits.

Incentive motivation, a drivelike state-variable, was formulated as a contribution to the energizing of behavior rather than to the selection of behavior. A familiar example is the motivational state that results from the tasting of a salted peanut. A weak impulse—arguably elicited by the sight of available nuts—to eat a peanut accounts for the tasting of the first nut. The tasting of the first nut, however—the "sampling" of the incentive—arouses much stronger responsiveness to the remaining nuts. The person will now pursue

with more force the nuts that, at first, elicited a weak attraction. The difference in response strength between reaching for the first nut and reaching for the second is the portion of response strength attributed to the initial contact with the incentive. The subject now has stronger arousal and stronger responsiveness to nuts than existed on the strength of either the physiological state or the stimulus situation that existed a moment earlier. The enhanced arousal and responsiveness is incentive motivation (meaning incentive-induced motivation or arousal rather than incentive-directed motivation or arousal). The increased responsiveness to the second nut suggests that the salience of the stimulus (Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984) has been increased by the tasting of the first nut. It is as if the second nut—as a result of increased appetite induced by the taste of the first nut—is brighter and more fragrant than the first nut. The construct of incentive motivation is normally invoked to explain the arousal associated with conditioned incentive stimuli rather than with the primary incentives themselves.

Bolles (1975) explains how the motivational state—presumably contributing to the strength and not the selection of a response—has what appears to be a response-eliciting power in a food reinforcement task: “when the hungry rat looks to the water side, nothing happens; but when it looks to the food side, it gets excited; thus it is more likely to go to the food side” (p. 294). Thus it is the sight, smell, taste, touch, or sound of the incentive that determines the direction of the behavior, and the combination of any internal drive state plus any incentive-motivational state that determines how strongly the subject is attracted in that direction.

## REINFORCEMENT

Reinforcement, as a motivational topic, is in some ways an unlikely bedfellow for drive and incentive motivation. Reinforcement is more easily related to topics of learning and memory than to the topic of motivation. Reinforcement comes after motivated behavior whereas drive and incentive motivation precede the behavior and energize it. Reinforcement is defined as a mechanism for strengthening the relations between conditioned and unconditioned stimuli (Pavlov, 1928) or for stamping in the associations between stimuli and responses (Thorndike, 1898), not as a mechanism for changing the mo-

mentary state of mind of the animal. The fluctuations in response probability that accompany fluctuations in motivation are phasic, reversible changes like the waxing and waning of hunger and satiety or of sexual arousal and refractoriness. The effects of reinforcement, on the other hand, cause relatively permanent changes in response probability, acting to modify, it is thought, the long-term relations between synapses in the brain rather than the short-term levels of nutrients or hormones in the blood. Nonetheless, reinforcement is part and parcel of the topic of motivation. There are several reasons.

First, the incentives that are primary to incentive motivation are, or lead to, reinforcers (Schnierla, 1939, 1959). The things approached are the things that reinforce exploratory approach patterns, converting them, gradually, into approach habits. The primary reinforcers are things that confer incentive value on the otherwise neutral stimuli that mark the path to food sources, fluid sources, and places of shelter from the elements. It is association with the primary reinforcer—the loved one—that makes special the “street where she lives.”

Second, the reinforcers that stamp in memory traces do so variably as a function of motivational states. Food is ineffective as a reinforcer when the animal is sated; indeed, lever pressing for food progressively extinguishes if the animal is tested when sated (Morgan, 1974). Similarly, the tendency to lever press for intravenous drugs extinguishes under conditions of intoxication. Thus it is not just ongoing behavior that waxes and wanes with motivational state, so too does the reinforcing efficacy of various incentives.

## The Correlates of Motivation

There is a strong movement to identify the subjective states of motivation, particularly within the field of addiction (see, e.g., Hetherington, 2001; Pickens & Johanson 1992; Tiffany, 1990). While many have argued that they are unknowable, speculations about the subjective states of even the laboratory rat generate considerable interest (Acquas, Carboni, Leone, & Di Chiara, 1989; Koob 1996; Robinson & Berridge, 1993, 2001; Rossetti, Lai, Hmaidan, & Gessa, 1993; Wise, 1982, 2001).

The subjective correlates of drive are craving, hunger, and desire. To illustrate a point about what comes first and what follows, Robinson and Berridge (1993) have introduced “wanting” as a synonym

for craving. Unlike terms like hunger, thirst, and withdrawal distress, which tend to focus on antecedent conditions, such terms focus attention on the subject's state of mind prior to the behavior of interest. For those who posit that we work to reduce drive states (e.g., Dackis & Gold, 1985; Hull 1943; Koob, Stinus, Le Moal, & Bloom, 1989), it is generally assumed that these are, to one degree or another, unpleasant states. Indeed, it is clear that, if they have the choice, animals will avoid the places where they have experienced the conditions associated with such states (Bechara, Nader, & van der Kooy, 1995).

The subjective correlates of incentive motivation—wanting, craving, desire, and the like—are common to the subjective correlates of drive. Lust is perhaps the most obvious model here; for the males of most species lust (inferred craving or desire for sexual interaction) is associated more clearly with external arousing stimuli than with internal hormonal levels or conditions of privation.

The subjective correlates of reinforcement can be identified with much less confidence than the subjective correlates of drive or incentive motivation. The widespread assumption is that reinforcement has positive affective correlates. Pleasure and euphoria are the most frequently suggested correlates of reward (McAuliffe & Gordon, 1974, 1980; Olds, 1956); "liking" has been more recently suggested (Robinson & Berridge, 1993). However, it is not at all clear that pleasure is associated with all rewards; monkeys can be trained to work for aversive shock (Kelleher & Morse, 1968) and various compulsive human activities—such as competitive sports and various forms of thrill seeking—are stressful if not painful. Anecdotal evidence would suggest that even addictive drugs can serve as effective reinforcers in the absence of any associated pleasure or euphoria. First-time heroin users, for example, often report that the drug produces nausea and discomfort (Haertzen, 1966); it is, nonetheless, strongly habit forming. After long exposure to heroin, addicts frequently report that the drug continues to control them despite having lost any ability to cause pleasure or euphoria (Chein, Gerard, Lee, & Rosenfeld, 1964). Thus pleasure is clearly not a necessary correlate of reinforcement. Moreover, animals consistently avoid flavors that have been associated with addictive drugs (Cappell & LeBlanc, 1971; Cappell, LeBlanc, & Endrenyi, 1973) despite the fact that they self-administered those drugs (Wise, Yokel, & de Wit, 1976).

The subjective correlates of the absence of pleasure are dyspho-

ria and anhedonia. While it has been suggested that blocking the synaptic action of brain dopamine causes a state of anhedonia or dysphoria—blunting the hedonic impact of food, water, rewarding brain stimulation, and several drugs of abuse (Wise, 1982)—this suggestion was based on evidence that reinforcement function, not hedonic function per se, was attenuated by dopamine blockers (Wise, 1985). While it is clear that dopaminergic blockade attenuates the rewarding effects of amphetamine (Risner & Jones, 1976; Yokel & Wise, 1975, 1976), it has been reported not to block amphetamine-induced euphoria in humans (Brauer & de Wit, 1997, but see Gunne, Änggard, & Jönsson, 1972; Jönsson, Änggard, & Gunne, 1971). Thus, again, pleasure does not appear to be a necessary correlate of the behavioral control exerted by reinforcers.

## The Etiology of Addiction

The phenomenon of addiction and the animal models used to study it offer heuristic insights into more conventional motivational states. There are two important features of addiction that differentiate it from more traditional motivations. First, to the degree that drugs come to satisfy bodily needs, it is largely acquired bodily needs that they satisfy (Hebb, 1949; Malmö, 1975); thus in addiction we can study the acquisition of need states that parallel the innate need states associated with hunger and thirst. Second, whereas the incentives of food and water are sensed (we can see, hear, taste, touch, or smell them), the incentives of drugs of abuse are unsensed, at least by laboratory animals that are unable to examine the contents of their remote syringes and protected infusion lines. The animal working for intravenous cocaine or heroin detects the drug by only one of its five peripheral senses (taste), and then only after the drug has been consumed and has diffused into the saliva. The traditional definition of an incentive is that of a thing approached; the animal can never approach an intravenous drug injection or a rewarding brain stimulation event in the way that it can approach a food pellet or a sexual partner. Thus animal models of addiction can reveal aspects of drive and incentive motivation that are not evident with more natural rewards like food, water, or potential mates.

Unlike the cases of hunger and thirst, the case of addiction offers no deficit-driven need for drug at the time of the initial drug

reinforcement. What comes first is the first drink, the first puff, the first snort, the first injection. If what is known about reinforcement is valid, the motivation for the second ingestion of a reinforcing dose will be stronger than the motivation for the first. Whatever it is that is stamped in by reinforcers will presumably start strengthening from the very first ingestion. This will include the stamping in of the memory traces of the proprioceptive feedback from the specific responses that led up to the injection, and it will include the stamping in of memory traces associating the drug experience with the various stimuli in the surrounding environment. In some way the reinforcing experience will also decrease the fear of repeating the act. The concerns that accompanied the first ingestion will be weaker with successive ingestions.

What *is* the motivation for the first self-administration of a drug of abuse? This is not easily answered. There are many different motivations—social conformation, peer pressure, status seeking, thrill seeking, relief of boredom, curiosity—so many that we might almost consider the first use of a given drug something akin to the first lever press in an operant chamber: if not an accident, at least not a response that is dependent on any identifiable reinforcement history. However, the motivation for subsequent self-administrations gradually comes under the control of the reinforcement history. Just as natural selection narrows the possibilities for evolution, so does reinforcement narrow the possibilities for future behavior. With each subsequent administration of a reinforcing drug, the freedom of choice—the freedom to accept or decline another administration—is, at least according to reinforcement theory, reduced. In the end, there will be very little freedom of choice for an addict who may have assumed complete freedom during the early stages of drug use; reinforcement is one of the powerful factors that eventually restricts freedom of choice.

Two things change as a subject continues to self-administer a drug. First, there are adaptations of the brain and the gut that occur in the same way and to the same degree whether the subject takes the drug actively or receives it passively. These include adaptations in the autonomic nervous system and changes in the brain circuitry through which the drugs have their rewarding effects. While many of the neuroadaptations—particularly the adaptations of the autonomic nervous system—are unique to the drug or drug class (Kalant, 1977),

some of the neuroadaptations of reward circuitry resulting from repeated treatment are common to such different drug classes as the stimulants and the opiates (Beitner-Johnson & Nestler, 1991; Beitner-Johnson, Guitart, & Nestler, 1992; Berhow et al., 1995). It is widely held that some subset of these neuroadaptations must contribute to the fact that drug taking becomes progressively more compulsive with repeated drug self-administration.

Neuroadaptations that are simple and direct consequences of the pharmacological action of the drug cannot, however, explain the rituals of drug procurement, drug preparation, and drug taking that form the habit structure of addiction. Nor can the fact that such drug-induced neuroadaptations involve the brain mechanisms responsible for learning and memory (Berke & Hyman, 2000; Nestler, 2001) explain the critical memory traces that distinguish the brains of self-inflicted addicts from the brains of drug-experienced individuals that do not self-administer the drug. The memory traces that are formed uniquely by the specific acts of drug self-administration thus form a second class of neuroadaptation that clearly plays a central role in the increasingly compulsive nature of drug taking. Indeed, the fact that passive receipt of drug injections can result in neuroadaptations within the brain mechanisms of learning and memory creates a special problem for the addiction theorist: How do we differentiate the neuroadaptations that are associated with a drug-taking habit from the neuroadaptations that are associated with a passive drug-receiving history? Woods (1990) has estimated that fewer than 0.01% of those receiving opiates passively go on to become opiate addicts. Another problem for the theorist is how to distinguish neuroadaptations associated with drug-seeking habits from neuroadaptations associated with food-seeking, sex-seeking, thrill-seeking, or other compulsive habits that depend on shared or parallel motivational circuitry (see Bardo & Dwoskin, this volume).

It is the neuroadaptations associated with the drug-seeking habit and drug-associated memories that are most central to the understanding of the compulsive nature of addiction. This is perhaps most clearly evident from animal models of intracranial self-stimulation and intravenous drug self-administration, where the animals never have direct sensory contact with the stimulation or the drug. Whereas the human addict eventually sees, fondles, smells, and perhaps tastes the drug that is ingested, the animal with a brain stimulation reward

habit or an intravenous drug habit has never seen, never touched, never smelled, never tasted its reinforcer. The reinforcer is delivered directly to the brain or to the heart, through wires or infusion catheters that are opaque and ever present. Thus in these cases the reinforcer itself is not the incentive that is approached; only learned incentives—conditioned incentive stimuli—are approached. The things approached are the walls, lights, levers, or nose-poke holes where the animal is able to trigger the hidden mechanisms that deliver the stimulation or the drug. The levers, lights, and holes become learned incentives and secondary reinforcers, as their manipulation or their display becomes associated with time-locked drug delivery. The street corner where drug is purchased (Simon & Burns, 1997), the seller, the pipe or syringe—these are things that become objects of compulsive search and approach. Along with the laying down of learned associations and memories of how to remove the hubcap quietly, how to approach the seller surreptitiously, how to keep the cash safe until the transaction is made, how to slip into the safe house without being noticed by the police or by local freeloaders—along with all these memory traces there accrue, with drug experience, the neuroadaptations associated with the unlearning of various fears. In the case of the laboratory animal, these involve fear of the strange testing situation: the apparatus itself, the handling, the drag of connected stimulating cables or drug lines, the sudden clicks and intravenous pressure or neuronal activation associated with responding. None of these specific memories can be stamped in by the doctor- or experimenter-administered drug injections that produce the neuroadaptations that have been identified to date.

A strong case has been argued for consideration of addiction as a “brain disease” (Leshner, 1997; McLellan, Lewis, O’Brien, & Kleber, 2000). Inasmuch as some drugs of abuse are neurotoxic (Carlson 1977; Schmidt, 1987; Wagner, Ricaurte, Seiden, Schuster, Miller, & Westley, 1980), it is clear that addiction can cause brain disease. What is not yet equally clear, however, is the degree to which brain disease causes addiction. Here we come up against the thorny question of which comes first and which follows. It is often suggested in recent years that mere self-administration of drugs—the self-administration, for example, demonstrated over the last several decades in limited-access animal models—is not tantamount to addiction (e.g., Ahmed & Koob, 1998; Robinson & Berridge, 2000; Tornatzky & Miczek, 2000). With increas-

ing attempts and increasing failure to find an objective, noncircular definition for addiction (Wise, 1987), it has become fashionable to characterize addiction as compulsive drug self-administration, and to look for the event or events that explain the transition from casual to compulsive drug self-administration. The operant psychologist can only wonder how reinforcement itself has come to be seen as insufficient to explain addiction without further postulates. Positive reinforcement is the only explanation sought or offered for the compulsive self-administration of direct electrical stimulation to the lateral hypothalamus, and this is a behavior sufficiently compulsive to lead, like self-administration of cocaine, to self-starvation and death. It has never been suggested that some form of brain disease is required to explain the happy, healthy, long-living (if allowed access to stimulation for only a limited portion of each day), compulsively self-stimulating rat.

The possibility that has status of place in the history of addiction theory is that adaptations to the repeated pharmacological actions of the drug bias the brain and body to such a degree that self-medication becomes necessary for normal mood, function, and homeostasis. Often referred to as dependence theory, this “medical model,” or “self-medication hypothesis,” is best characterized as an opponent-process view of motivation (Solomon & Corbit, 1974) and addiction (Solomon & Corbit, 1973). In early incarnations, dependence models focused on compensatory responses identified largely with the autonomic nervous system (Wei, Tseng, Loh, & Way, 1974) and the withdrawal distress—sweating, cramps, diarrhea, thermoregulatory disturbance—that is experienced when opiate or alcohol use is discontinued. As evidence accumulated against the view that withdrawal distress was a necessary condition for addiction (Deneau, Yanagita, & Seevers, 1969; Jaffe, 1985; McAuliffe & Gordon, 1980; Wise, 1987; Woods & Schuster, 1971), attention shifted from the adaptations of the autonomic nervous system to adaptations within the brain mechanisms of reward themselves, which might desensitize the subjects to various forms of pleasure and reinforcement (Dackis & Gold, 1985; Frank, Martz, & Pommering, 1988; Kokkinidis, Zacharko, & Predy, 1980; Leith & Barrett, 1976; Markou & Koob, 1991; Nestler, 1992). It is clear that there are many neuroadaptations that result from repeated drug use (Nestler, 2001; White & Kalivas, 1998), and that in the neuroadapted state the drug itself can oppose the effects of at least

some of those neuroadaptations: the drug effect, for the moment, shifts the animal back in the direction of normalcy. That is, the drug does “medicate,” by opposing them, some of the neuroadaptations induced by past use of the drug. To what degree such neuroadaptations are causes rather than consequences of addiction, however, is only beginning to be examined in depth (Carlezon et al., 1998; Kelz et al., 1999). The answer depends fundamentally on a very simple issue: which comes first and which after? In addition, it is not clear to what effect the known neuroadaptations are drug-opposite in nature; indeed, most of the known neuroadaptations have been found to result from drug treatments that cause sensitization, not tolerance, to the drug in question.

Our own studies of drug self-administration in rodents have led me to suspect that drug self-administration becomes compulsive long before the significant development of most of the recently characterized neuroadaptations. We have no scientific standards for the word “compulsive,” but dictionary definitions involve such terms as being compelled, forced, coerced, or constrained: “in psychopathology, an irresistible impulse to perform some irrational act.” One measure of compulsion is the domination of the compelling behavior over less compelling alternatives. Rats or monkeys allowed to lever press for unlimited intravenous amphetamine or cocaine injections will do so to the point of death (Bozarth & Wise, 1985; Johanson, Balster, & Bonese, 1976). Thus we normally do not allow our animals unlimited drug access, but restrict them to sessions of 4 hours or less per day.

A second criterion for compulsion is invariance and predictability. Once a habit is established to the point of no return, the most critical transition toward addiction has already occurred. So long as reinforcement continues, the habit will only become more strongly stamped in. Our experienced animals respond for intravenous cocaine at very constant rates, suggesting strongly established habits; the standard deviation of their inter-response times is close to 20% of their mean inter-response time. When their inter-response intervals reach this level of regularity we can predict with great certainty that they would continue to self-administer the drug compulsively to the point of death if given the opportunity. This level of control is evident in some animals within a single day of training; in 90% of our animals it is reached within five days of training in 4-hour daily

sessions. In the absence of catheter or vein failures, such a habit will always become progressively more compulsive—that is, the standard deviation of the inter-response times will invariably continue to decrease—over the next few weeks. Thus, after as little as one or two days of training it is often clear that a given animal has already reached the stage of compulsive responding. While drug self-administration during 4-hour periods of drug access per day may not establish the escalated (Ahmed & Koob, 1998) or dysregulated (Tornatzky & Miczek, 2000) intake patterns that become typical of animals tested for longer periods with higher doses or unlimited access, testing animals under conditions of limited access is sufficient to establish self-administration habits that are compulsive enough to irrevocably lead, under unrestricted access, to such escalation and dysregulation. Studies of the neuroadaptations to addictive drugs have, for the most part, been based on much longer and stronger drug exposure than is required to establish the point of no return.

I would not argue this for all drugs, nor would I argue it for all doses or routes of administration of even the psychomotor stimulants. However, in the case of intravenous cocaine, amphetamine, and heroin, I think compulsive habits—irrevocably compulsive habits when drug is freely available—are established very early in the animal's exposure, long before we see signs of escalated or dysregulated intake. Most of the neuroadaptations we are currently studying are established after much more severe regimens of repeated drug administration than are necessary to establish sensitized behavioral responses to the drug.

Whatever the strength of the treatments required to produce them, most of the neuroadaptations we are currently studying are not the neuroadaptations associated with the memory traces of the response habit itself. Continued opportunity for drug self-administration extends the stamping in of the response habit and the stimulus associations that sustain the behavior. Inasmuch as the peripheral senses of the animal are exposed to the manipulandum and surrounding stimuli but not the drug itself, the things the animal learns to approach are the features of the test box that, until associated with reinforcement, have only the appeal of novelty. In our paradigm, the most obvious learned incentives are the lever and the light above the lever. We see a form of autoshaping as the habit becomes established. Our light is illuminated whenever the pump is delivering drug; it

gives the signal that the animal has made the required response and that the drug effect will soon be felt. At first the rat just appears to notice the light, glancing at it briefly after each response. In time the animal begins to approach the light, sniff it, lick it, and eventually bite it after each lever press. The approach to the light, like the approach to the lever, becomes highly driven, and the drive is clearly due to the conditioned association between the reinforcing injection and the manipulandum and cue light. As the regularity of approach to the lever increases with each reinforced trial, the incentive value and salience of other environmental stimuli—for example, an identical but ineffective (“inactive”) manipulandum—presumably decrease.

As the animal is repeatedly reinforced for the investigatory reflexes that result in the initial lever presses, the behavior comes under increasing stimulus control. The strong stimulus control that can be established within the first hour of testing results in invigorated approach, sniffing, and facial poking at the lever. In the early stages of this learning, the animal may make several responses during the time-out period when the pump is already delivering an injection. It may also earn two or more injections in rapid succession. This is a learned response pattern, clearly resulting from prior reinforcement. The excitement at the lever is a manifestation of incentive motivation: activation due to the experience of the incentives in the situation. Prior to the first response of the day, the incentives are the learned incentives, the environmental stimuli that, through learning, have become associated with the primary reinforcer. After the first response, the decaying signal from the last reinforcement is a second source of incentive motivation.

The incentive motivation caused by the unconditioned reinforcer itself is often termed a “priming effect.” It is an unlearned response that decays rapidly as soon as the reinforcer is no longer felt. The rapid decay of the priming effect is most obvious with the reward of direct electrical stimulation of the brain, where the reinforcer usually lasts a half-second or less and decays as rapidly as it appears. The running speed of a brain-stimulation-rewarded animal, reinforced at the end of a runway, varies with both the strength of reinforcement in the goal box and also the strength of any “priming” stimulation that is given in the start box. However, it is only the memory of the last reinforcement, not the memory of the last priming stimulation, that is effective after a minute or two delay (Gallistel, Stellar, & Bubis,

1974). Thus the priming that energizes responding leaves no lasting memory trace, whereas the memory of the most recent reinforced trials lasts and can influence subsequent running speed despite the passage of a week or more. Priming stimuli are the effective terminators of periods of abstinence; they are among the most potent stimuli for reinstating temporarily disrupted self-administration habits (de Wit & Stewart, 1981, 1983; Gerber & Stretch, 1975; Stretch & Gerber, 1973).

Priming stimulation is used a good deal by workers in the field of brain stimulation reward and intravenous stimulant self-administration. In an untrained animal, priming stimulation or priming stimulant injections cause the heightened state of arousal that is the hallmark of incentive motivation and psychomotor activation. Even in the untrained animal, priming stimulation is an energizer of behavior. The forward locomotion it induces is initially aimless, increasing the probability of movement but not of any particular movement. Priming stimulation is used in its simplest form to wake or activate the animal. In the trained animal, however, priming stimulation and priming injections selectively energize approach to the reinforcement-associated stimuli in the environment: the side of the cage containing the manipulandum and the manipulandum itself. In experienced animals, priming appears to be a very effective stimulus for craving. Indeed, I believe this is why 12-point rehabilitation programs set total abstinence as their goal; in the wake of the priming effect of a first cigarette, a first drink, or a first snort it becomes much more difficult to resist a second.

Priming injections are often given to animals at the beginning of cocaine self-administration sessions where drug-free animals are more reluctant to initiate cocaine self-administration than might be expected by nonspecialists. The memory of yesterday's cocaine reinforcement apparently carries an ambivalent memory, one tinged, it would seem, with some form of anxiety; when treated with anxiolytic drugs trained rats are much quicker to initiate cocaine self-administration (Ettenberg & Geist, 1991). Priming overcomes this anxiety and shifts the animal's responsiveness to the incentive (approach-inducing) properties of the drug-associated cues.

Priming is confounded with reinforcement in lever-pressing tasks where no time-out is imposed. When time-outs or low-density reinforcement schedules are used, the inter-response time can exceed

the period of effective priming that is established by the previous reinforcement. When animals are allowed to earn reinforcement at their own preferred frequency, the varying strength of the priming effect largely determines when craving will again arise and when the next response will be made. I will return to this topic in the section on regulation of drug intake.

With sufficient drug experience, animals undergo a number of the neuroadaptive changes mentioned earlier (Nestler & Aghajanian, 1997; White & Kalivas, 1998). Many of these known adaptations are within the circuitry of the brain that is essential for the reinforcing actions of drugs of abuse. While most of the known neuroadaptations last less than a week or two, they may prove important in the development of more long-lasting changes. The craving-associated memory traces of the addict are themselves long-lasting; thus it is the long-lasting neuroadaptations—probably most importantly those associated with learning and memory for past drug experience—that offer the possibility of an explanation for the problems of relapse and compulsion that plague the addict. The most interesting long-lasting changes are perhaps the dendritic branching of neurons in the reward pathway (Robinson & Kolb, 1997, 1999). Such changes can be produced by self-administered cocaine experience of as little as 1 hour per day (although such exposure has been maintained for many days in the work thus far: Robinson, Gorny, Mitton, & Kolb, 2001).

It is clear that some changes in the brain must distinguish the addicted brain from the nonaddicted brain. One thing that remains to be determined is whether any of the known changes—changes induced, for the most part, by high doses of experimenter-administered drugs—is a significant contributing cause of addiction and not just a consequence of addiction. That is, must any of these known neuroadaptations occur prior to the transition from voluntary to compulsive drug self-administration? Or must there already be compulsive drug self-administration before there is sufficient drug exposure to produce the known neuroadaptations and make them stand out from the everyday neuroadaptations that result from the various stresses and pleasures of normal life? A second thing to be determined is the relative importance of differences between the drug-naïve and the drug-addicted brain and differences between the brains of experienced subjects that have self-administered the drug and experienced subjects that have received the drug passively.

## The Regulation of Drug Intake

Hunger and thirst are the prototypical drive states of motivational theory. Motivation for food and water wax and wane, and behavior makes a major contribution to the maintenance of homeostatic balance. Fluctuations in water seeking and food seeking are periodic and periods of satiety determine when water and food will be ineffective as reinforcers (Smith, 1982). The behavioral contribution to fluid and energy balance has been termed "behavioral homeostasis."

Thirst is the simplest model because the category of water is well defined while the category of food includes a wide variety of substances and varies between cultures and environments. Fluid balance is controlled in part by the function of the kidney, which extracts water from the blood when blood pressure is high and ceases to do so when pressure (and its usual correlate, extracellular fluid volume) is low. Fluid balance is also influenced by body temperature; the evaporation of perspiration and saliva are major sources of cooling in a hot environment and after exertion. Finally, fluid balance is controlled by behavior; when blood pressure is low or when salt concentration in cells of the hypothalamus is high thirst is experienced and the probability of water seeking and drinking is increased.

It is of interest to inquire just how water seeking and drinking are triggered. The traditional view is the drive hypothesis. Epstein (1973) summarized the thirst literature of the time with the suggestion that "(a) thirst goes on in the brain, (b) the neurological machine for thirst integrates multiple inputs, and (c) from these inputs a specific motivational state arises and drives the animal to seek water and ingest it" (p. 316). This summary is useful for those who are interested in the sensation and perception of thirst, but it offers no explanation of the motivational consequences of thirst. Rather, the research has focused on the sensing of deficit, not the control of behavior by deficit. The research, valuable as it has been in identifying the sources of thirst, deals with the sensory physiology, not the motivation, of drinking behavior. The drive hypothesis always fails to suggest a mechanism for the initiation and energizing of the seeking and ingesting acts. An incentive-motivational hypothesis, in contrast, offers at least the outline of a mechanism. It suggests that the state of dehydration increases probability of water seeking and drinking by increasing the salience—the Siren Cry<sup>1</sup>—of water-associated incentives in the

environment, and that these learned incentives—with their stronger valences the closer they are to the goal—lead the animal from point to point along the learned path to water. The drive hypothesis suggests that it is the reduction of the need state or reduction of the associated drive that accounts for the reinforcing effects of water for a thirsty animal, whereas incentive-oriented studies suggest it is enhanced responsiveness to the lure of the incentive that is critical. The issue is whether the drive causes a push stimulus to action or rather the environmental cue causes a pull to action. The latter hypothesis is the stronger one, because it can account for the direction the animal takes; the animal that is responsive to drive and ignores the environment has little chance of getting on the right path, whereas the animal that is more and more strongly attracted to water-associated environmental stimuli is very likely to be drawn to water once thirst makes the animal sufficiently sensitive to such cues.

Drive states clearly modulate the motivational effectiveness of environmental stimuli. Studies of air licking in thirsty rats suggest that it is the cooling sensation in the oral cavity that accounts for the reinforcing effects of ingested fluids, and that such cooling sensations are reinforcing only if the animal is dehydrated (Freed & Mendelson, 1974; Mendelson & Chillag, 1970; Ramsauer, Mendelson, & Freed, 1974). Thirsty animals will not only drink water; they will lick at air streams that cool the oral cavity. They will lick at cool airstreams and they will lick at warm airstreams if the warm air is dry enough to evaporate saliva from the oral cavity (Freed & Mendelson, 1974). Air licking is an act that becomes compulsive in fluid-deprived rodents despite the fact that this behavior increases, through evaporation, the bodily need for water. The incentive motivational hypothesis is that behavior of the thirsty animal becomes controlled by the thirst-enhanced salience of stimuli that have, in the animal's reinforcement history, been associated with oral cooling. The reinforcing action of oral cooling in thirsty rodents is a sufficient mechanism to guarantee that few individuals fail to meet their hydrational needs except under conditions of extreme drought, since few rodents outside the laboratory ever find means of oral cooling that fail to involve the ingestion of fluids.

In a similar way, the reinforcing property of sweet taste is a sufficiently powerful stimulus to guarantee that animals do not starve to death in the presence of fruit. That sweet things become more

attractive during states of privation (Cabanac, 1971) guarantees consumption of sweet things, which, except in laboratory conditions (Sheffield & Roby, 1950), tend to provide for much of an animal's nutrient need. Reinforcement by sweet taste provides a mechanism that makes intake of caloric foods highly probable in the wild. Drive-induced modulation of the salience of sweetness makes such intake more probable during states of privation. Control by sweetness usually accomplishes these things without the direct intervention of actual need reduction. However, the more an animal needs glucose, the more it can be seduced by the sweet taste of a non-nutritive substance (Jacobs & Sharma, 1969). Thus drive reduction is a seemingly inadequate and, indeed, seemingly incorrect explanation of why food and water are reinforcing.

It remains possible, however, that sweet taste becomes reinforcing through experience with need reduction. Le Magnen (1959) has shown that rats adjust their intake of a given food, after four or five days, on the basis of the caloric value of the food but also the caloric value of intragastric glucose that is given as a supplement. The animal's approach to the food is adjusted to compensate for the amount of glucose in the associated stomach load. Thus it is possible that even sweet taste is an acquired incentive, one that is reinforcing because of prior conditioning, prior need reduction, associated with sweet tastes in the past (Le Magnen, 1959; Myers and Sclafani, 2001a, 2001b). Mammals gain experience with sweet taste—and, indeed, have their needs met in association with the sweet taste of mothers' milk—from the time of birth; such experience results from the consequences of the expression of the neonatal suckling reflex. Sweet taste is an instrumental reinforcer very early in life; rats can learn on the first day of life to lever press for intra-oral milk infusions (Johanson & Hall, 1979). However, rats do not show deprivation-enhanced approach to either food or water stimuli until much later in life (Changizi, McGehee, & Hall, 2002). Thus the modulation of ingestive reflexes may itself be learned. In any case, whether or not need reduction contributes to the reinforcing effects of such things as oral cooling or sweet taste, it is the sensory events of oral cooling and sweet taste that come to control motivated behavior. They do so to the point that oral cooling or sweet taste in the absence of need reduction can become compulsive and dominate other behaviors (Jacobs & Sharma, 1967).

Just as drinking and eating are cyclic behaviors, characterized

by periods of drive and satiety, so is drug seeking a cyclic behavior in animal models of intravenous drug self-administration. Well-trained animals respond about once every five minutes for 1 mg/kg injections of cocaine (Wise, Newton, Leeb, Burnette, Pocock, & Justice, 1995), about once every 20 minutes for 0.1 mg/kg injections of heroin (Gerber & Wise, 1989), and about once every 30 minutes for 0.25 mg/kg injections of amphetamine (Yokel & Pickens, 1973, 1974). Such injections cause, each by its own pharmacological mechanism, elevations of brain dopamine in nucleus accumbens. This elevation is essential to the reinforcing effects of amphetamine (Lyness, Friedle, & Moore, 1979; Yokel & Wise, 1975) and cocaine (de Wit & Wise, 1977; Roberts, Corcoran, & Fibiger, 1977) and, arguably, heroin (Bozarth & Wise, 1986; Wise, 1989). At the beginning of each test session, the trained animal responds frequently; this phase of the session is termed the "loading phase" and is seen as a period when the behavior of the animal is establishing some level of drug satiety. After a pause in which much of the previous injection is metabolized, the animal then settles down to slower and more regular responding termed the "maintenance phase" of the session. It is in the maintenance phase that the animal appears to regulate its drug intake with some kind of homeostatic precision.

In the maintenance phase of responding, the animal makes each response for additional cocaine (Wise, Newton, Leeb, Burnette, Pocock, & Justice, 1995), amphetamine (Ranaldi, Pocock, Zereik, & Wise, 1999), or heroin (Wise, Leone, Rivest, & Leeb, 1995) long before dopamine levels return to normal baseline. The dopamine level at the time of response may differ somewhat between animals, ranging between two and three times the normal basal level of nucleus accumbens dopamine. While there is variability of trigger level between animals, the level within a given animal is quite consistent. It is as if the animal is "hungry" for drug whenever dopamine levels fall below about 200% of normal and as if they are sated whenever dopamine levels surge above about 300% of normal. One may question whether this is a true case of homeostatic regulation, but it is not really clear what constitutes "true" regulation even in the case of food or fluid intake. We know that many humans take in more food than they need to maintain body weight, and they do so despite significant penalties, gradually increasing their weight and their health risks over the course of their lifetime. Similarly, we know that there is

little penalty for taking in more fluid than we need, as, for example, when drinking beer on a hot day; excess is simply excreted. Thus the term "regulation" has wide application and is descriptive rather than explanatory; the appearance of regulation is evident in many things and is always a phenomenon to be understood rather than to be used as an explanation. Whether apparent regulation depends on reward in states of depletion or penalties or nonreward during states of satiety must be determined individually for each incentive that is capable of establishing compulsive behavior.

The apparent regulation of drug intake involves a rate of intake that matches, reasonably well, the rate of metabolism. Once the animals have loaded their system with drug, each subsequent injection is taken when the drug level in blood (Yokel & Pickens, 1973, 1974) and the dopamine level in nucleus accumbens (Ranaldi et al., 1999; Wise, Newton, Leeb, Burnette, Pocock, & Justice, 1995; Wise, Leone, Rivest, & Leeb, 1995) have been metabolized to within 10% or so of the levels at which the last injection was taken. The hypothesis that the drug intake is somehow regulated by drug level in the blood, dopamine level in the brain, or some correlate of the two is self-evident and confirmed by the finding that supplemental experimenter-administered infusions of the drug postpone the animal's next response by just enough to compensate for the supplement (Gerber & Wise, 1989; Tsibulsky & Norman, 1999). The mechanics of how this level of regulation is achieved remain to be determined.

The issue of regulation revolves around the question of why, if the drug is powerfully reinforcing, the animals do not take drug more frequently than they do. Why, if food is powerfully reinforcing, do we not overeat? Of course we often do, but food loses at least some of its reinforcing efficacy—its incentive salience—in periods of satiety (Cabanac, 1971). Is the same true for cocaine? The control of subsequent drug intake by drug in the blood, dopamine in the brain, or some correlate of the two could reflect either active or passive regulation. That is, the animals might be conjoined against taking more drug, just as a full stomach and its hormonal consequences is one of the factors that actively inhibits food intake (Smith & Gibbs, 1994), by some performance impairing or aversive effects of high drug or transmitter levels. Neither of these possibilities would seem to be the case. First, we know from two-lever tests offering the choice between drug and brain stimulation reinforcement that rats remain

capable of lever pressing at high rates between normal responses for amphetamine (Wise, Yokel, Hansson, & Gerber, 1977) or heroin (Gerber, Bozarth, Spindler, & Wise, 1985). Second, we know that the animals do not find higher levels of drug or dopamine to become, on balance, aversive. If they did, they would choose between two levers the one associated with smaller doses, keeping low the peak drug and dopamine levels resulting from each injection (but compensating by taking the low dose more frequently). Instead, if anything, rats and monkeys, while taking them less frequently, prefer the higher of two doses offered concurrently (Iglauer, Llewellyn, & Woods, 1976; Manzardo, Del Rio, Stein, & Belluzzi, 2001; Yokel, 1987).

It appears most likely that the intake of stimulants, at least, is passively regulated; as in the case of water intake, there is apparently no significant penalty for taking more than satiating levels of drug, but neither, it appears, is there any significant benefit. Thus, the tendency of animals to respond soon after the previous injection, which is seen in the first few days of training, appears to gradually disappear because there is no added reward value of drug once dopamine levels are elevated. As the animal learns this fact there is decreased incentive salience associated with the response lever—the animal stops responding to it—when dopamine levels are above about 300% normal. The gradual extinction of the tendency to respond before the last injection has been metabolized suggests a model of cycles of incentive motivation (induced by the priming effects of the last injection) and satiety (induced by *d*-amphetamine concentrations above 0.2 g/ml of blood or dopamine concentrations higher than 300% of normal).

What is the mechanism by which drug intake becomes regulated? Our examination of the progression from investigatory lever pressing to regulated lever pressing within binges of limited-access drug self-administration suggest an incentive motivational view rather than a drive interpretation. It is clearly the place cues in the environment that are the determinants of the left turn or the right turn that takes the animal to the lever. It is clearly the spatially localized lever, not the spatially ambiguous drug, that the animal approaches. Once the animal is away from the lever, it is only environmental cues that give information as to which way to turn. The behavior is clearly dependent in some way or another on a correlate of drug concentration in the body. Our working hypothesis is that dopamine

levels influence behavior as occasion-setters, not as eliciting stimuli, determining on a moment-to-moment basis the incentive salience—the drawing power—of the lever.

In this view, drug-associated environmental stimuli have maximum incentive salience when dopamine levels are somewhere between normal and twice normal. Elevating dopamine levels by giving a priming injection will increase the probability that the animal in a lever-pressing task will notice, approach, and manipulate the lever. In a two-lever task, the words of Bolles (1975), slightly modified, best illustrate the point: when the rat with slightly elevated dopamine levels happens to look to the “inactive” lever side, nothing happens; but when it happens to look to the “active” lever side, it gets excited; thus it is more likely to notice the active lever, approach it, and press it. When it does so, the drug will serve as a reinforcer just as food does when the animal is food deprived. However, when the dopamine level is elevated, the animal is unresponsive to the active lever, unmoved by it just as is the sated animal that looks at a food-associated lever. Now, the dopamine level is out of the optimal range and does not serve as an occasion-setter. Should the animal occasionally press the lever in this condition the drug injection and its associated dopamine bolus will not be reinforcing. High dopamine levels signal to the investigator, and presumably to the animal, that while another drug injection may prolong the rewarding effects of the previous injection, the second injection will not intensify the reward resulting from the previous injection, and will thus not serve as an effective reinforcer; high dopamine levels reduce the incentive value of the drug-associated cues so that the animal learns to no longer respond.

## Dysregulation of Intake

If drug intake is maintained for prolonged periods at high doses, the apparent regulation that is typical of limited access experiments deteriorates. The point of dysregulation suggests yet another transition in the etiology of addiction that should be associated with neuroadaptations of one sort or another, and in this case neuroadaptations in the brain mechanisms of drug reward are suggested. Animals given unlimited access to intravenous cocaine or amphetamine come to take the drugs erratically and to the point of death (Bozarth & Wise,

1985; Johanson et al., 1976). The most obvious result is weight loss; most deaths occur when the animals approach death by starvation (Bozarth & Wise, 1985). Loss of sleep is also evident. In the initial opportunity for unlimited drug access, the animals frequently respond regularly for one to three days without interruption (Pickens & Harris, 1968). The behavior then becomes sporadic, with binges and abstinence periods of irregular length (Pickens & Harris, 1968) that give the appearance of periodicity to group averages (Bozarth & Wise, 1985). If, instead of continuous drug access, animals are given intermittent access in long (6 hour or longer) sessions, dysregulation can take another form. In such circumstances the animals tend to respond more and more strongly during the initial, "loading," phase of each session (prior to establishing the elevated drug or transmitter levels that provide regulatory feedback), thus increasing their total drug intake for each session (Ahmed & Koob, 1998). The fact that the animals return to escalated intake even after long periods of withdrawal is reminiscent of the way that obese humans, once they have undergone a period of overfeeding, tend to return to a pattern of excess following periods of diet and weight loss (Levin, 2000). The degree to which these dysregulations depend on known neuroadaptations is unclear, however. The irregular intake that develops after prolonged continuous intoxication (Bozarth & Wise, 1985; Tornatzky & Miczek, 2000) is associated with a dosing regimen that should be associated with the development of drug tolerance (Emmett-Oglesby & Lane, 1992; Li, Depoortere, & Emmett-Oglesby, 1994), whereas the escalated early intake that develops after repeated periodic intoxication is associated with a regimen associated with drug sensitization or "reverse tolerance" (Downs & Eddy, 1932; Kilbey & Ellinwood, 1977; Segal & Mandell, 1974). Thus the two forms of dysregulation are probable consequences of independent mechanisms and opposite neuroadaptations.

## Contrasts between Sensed and Unsensed Incentives

What unique insights can be gained from comparing the motivations for sensed and unsensed rewarding incentives? Perhaps the most obvious has to do with the role of learning in the control of behavior by sensed incentives. In the case of drug reward and brain stimulation reward, the sensed incentives are the cues and manipulanda

that have learned motivational significance and cue value and are the objects of attention at or just prior to the time of drug delivery. In these cases the click of the relay or the flash of the cue light is the sensory message of receipt of reward. Similarly, in a well-trained animal the click of the latch on the door hiding the food may simply be the sound of receipt of reward. Consider the person who wins a lottery: Is not the moment of the receipt of reward—the moment of celebration, of motivational excitation—the moment the winning number is announced? Don't the subsequent events of the receiving of the check, the cashing of the check, the trading of the cash for food, and the eating of the food constitute progressively weaker rewarding events than the first message announcing the inevitability of reward? Separating the motivational importance of the sensory information that predicts reward from the sensory information that constitutes reward is not so straightforward as might first be assumed.

Another important insight is that in addition to behavior controlled by drugs or brain stimulation, behavior controlled by rewards of sweet taste or oral cooling can become compulsive. In the case of air-licking or compulsive saccharin drinking there seems no obvious reason to invoke neuroadaptations or brain disease to explain compulsive behavior. It seems self-evident that the variety of compulsive behaviors forms a continuum, differing more in degree than in kind, and from this perspective it seems more heuristic to look for commonalities between the habits established by various incentives than to look for unique properties that set addiction, for example, apart from the rest. Inasmuch as drug seeking and food seeking appear to be controlled by the same motivational substrates (see, e.g., Ettenberg & Camp, 1986; Wise, 1982), it might well prove to be the case that drug-induced brain pathology is a consequence, rather than the precipitating cause, of compulsive behavior. It seems unlikely that brain pathology plays a significant role in the variety of nondrug compulsions—such as compulsive self-stimulation—that accompany a wide range of motivated behaviors.

## Note

1. I use here a metaphor from C. R. Gallistel, likening the attraction of an incentive to the seductive come-hither songs of the sea nymphs of Greek and Roman myth. The idea is that each object in the animal's environment

has a degree of allure that sometimes exceeds and sometimes fails to exceed the animal's threshold for approach responses. A given drive state is seen to increase the probability that an individual is responsive to the appropriate incentive stimuli, enhancing their allure (their salience as attractants).

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