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CHAPTER

1

What is Addiction?

OUTLINE

DEFINITIONS OF ADDICTION

Drug Use, Drug Abuse, and Drug Addiction

Drug addiction, also known as Substance Dependence (American Psychiatric Association, 1994), is a chronically relapsing disorder that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 1997). The occasional but limited use of an abusable drug clinically is distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic compulsive drug-seeking that characterizes addiction. Modern views have focused on three types of drug use: (1) occasional, controlled or social use, (2) drug abuse or harmful use, and (3) drug addiction. An important goal of current neurobiological research on addiction is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition between occasional, controlled drug use and the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction (Koob and Le Moal, 1997).

The critical nature of the distinction between drug use, abuse and dependence has been illuminated by data showing that approximately 15.6 per cent (29 million) of the U.S. adult population will go on to engage in nonmedical or illicit drug use at some time in their lives, with approximately 3.1 per cent (5.8 million) of the U.S. adult population going on to drug abuse and 2.9 per cent (5.4 million) going on to Substance Dependence on illicit drugs (Grant and Dawson, 1998; Grant *et al.*, 2005). For alcohol, 51 per cent (120 million) of people over the age of 12 were current users, 23 per cent (54 million) engaged in binge drinking, and 7 per cent (16 million) were defined as heavy drinkers. Of these current users, 7.7 per cent (18 million) met the criteria for Substance Abuse or Dependence on Alcohol (see *Alcohol* chapter). For tobacco, 30 per cent (71.5 million) of people aged 12 and older reported past-month use of a tobacco product. Also, 19 per cent (45 million) of persons in the U.S. smoked every day in the past month. From the 1992 National Comorbidity Survey, 75.6 per cent of 15–54-year-olds ever used tobacco, with 24.1 per cent

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TABLE 1.1 Estimated Prevalence Among 15–54-Year-Olds of Nonmedical Use and Dependence Among Users (1990–1992) from The National Comorbidity Survey

	Ever used (%)	Prevalence of dependence (%)	Dependence among users (%)
Tobacco	75.6	24.1	31.9
Alcohol	91.5	14.1	15.4
Illicit Drugs	51.0	7.5	14.7
Cannabis	46.3	4.2	9.1
Cocaine	16.2	2.7	16.7
Stimulants	15.3	1.7	11.2
Anxiolytics	12.7	1.2	9.2
Analgesics	9.7	0.7	7.5
Psychedelics	10.6	0.5	4.9
Heroin	1.5	0.4	23.1
Inhalants	6.8	0.3	3.7

[Reproduced with permission from Anthony *et al.*, 1994.]

meeting the criteria for Dependence (Anthony *et al.*, 1994) (see *Nicotine* chapter).

The number of individuals meeting the criteria for Substance Dependence on a given drug as a function of ever having used the drug varies between drugs. According to data from the 1990–1992 National Comorbidity Survey, the percentage addicted to a given drug, of those people who ever used the drug, decreased in the following order: *tobacco > heroin > cocaine > alcohol > marijuana* (Anthony *et al.*, 1994) (**Table 1.1**). More recent data derived from the National Household Survey on Drug Abuse (Substance Abuse and Mental Health Services Administration, 2003) showed that the percentage addicted to a given drug, of those who ever used, decreases in the following order: *heroin > cocaine > marijuana > alcohol* (**Fig. 1.1**). These more recent data suggest unsettling evidence of an overall trend for a significant increase in Substance Dependence with marijuana (see *Cannabinoids* chapter).

The cost to society of drug abuse and drug addiction is prodigious in terms of both direct costs and indirect costs associated with secondary medical events, social problems, and loss of productivity. In the United States alone, it is estimated that illicit drug abuse and addiction cost society $161 billion (Office of National Drug Control Policy, 2001; see also Uhl and Grow, 2004). It is estimated that alcoholism costs society $180 billion per year (Yi *et al.*, 2000), and tobacco addiction $155 billion (Centers for Disease Control and Prevention, 2004). In France, the total cost of drug use is USD 41 billion (including $22 billion for alcohol, $16 billion for tobacco, and nearly $3 billion for illicit drugs) (Kopp and Fenoglio, 2000).

Addiction and *Substance Dependence* will be used interchangeably throughout this text and will refer to a final stage of a usage process that moves from drug use to abuse to addiction. Drug addiction is a disease and, more precisely, a *chronic* disease (Meyer, 1996). As such, it can be defined by its diagnosis, etiology, and pathophysiology as a chronic relapsing disorder (**Fig. 1.2**). The associated medical, social, and occupational difficulties that usually develop during the course of addiction do not disappear after detoxification. Addictive drugs are hypothesized to produce changes in brain pathways that endure long after the person stops taking them. These protracted brain changes and the associated personal and social difficulties put the former patient at risk of relapse (O'Brien and McLellan, 1996), a risk higher than 60 per cent within the year that follows discharge (Finney and Moos, 1992; Hubbard *et al.*, 1997;

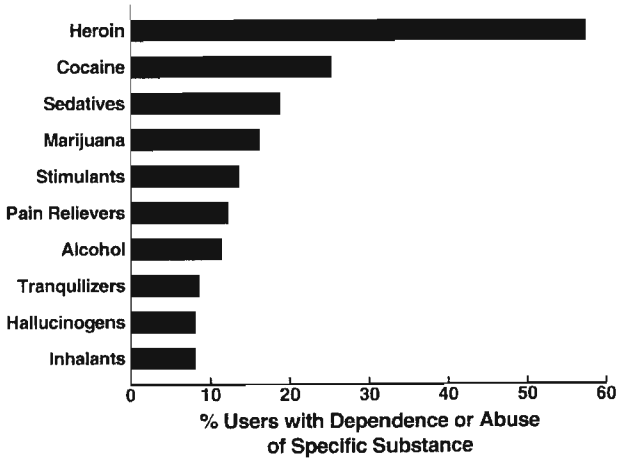

FIGURE 1.1 Dependence or abuse of specific substances among past-year users of substance (Substance Abuse and Mental Health Services Administration, 2003). Heroin: 57.4% (0.2 million), Cocaine: 25.6% (1.5 million), Marijuana: 16.6% (4.2 million).

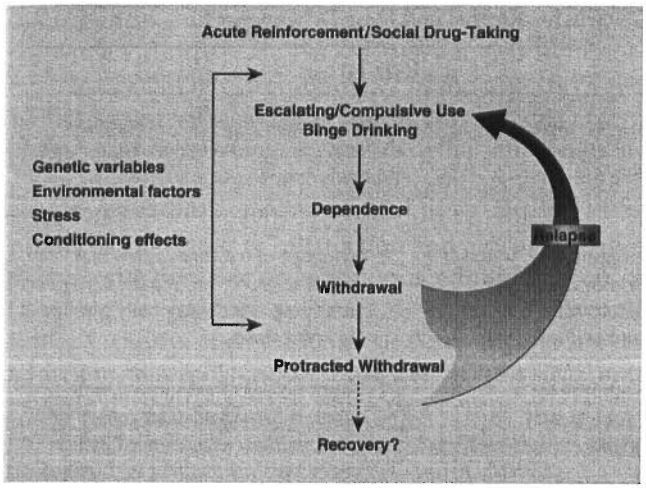

FIGURE 1.2 Stages of addiction to drugs of abuse. Drug-taking invariably begins with social drug-taking and acute reinforcement and often, but not exclusively, then moves in a pattern of use from escalating compulsive use to dependence, withdrawal, and protracted abstinence. During withdrawal and protracted abstinence, relapse to compulsive use is likely to occur with a repeat of the cycle. Genetic factors, environmental factors, stress, and conditioning all contribute to the vulnerability to enter the cycle of abuse/dependence and relapse within the cycle.

McLellan and McKay, 1998; McLellan *et al.*, 2000). While much of the initial study of the neurobiology of drug addiction focused on the acute impact of drugs of abuse (analogous to comparing no drug use to drug use), the focus is now shifting to chronic administration and the acute and long-term neuroadaptive changes in the brain that result in relapse. Cogent arguments have been made which support the hypothesis that addictions are similar in their chronic relapsing properties and treatment efficacy to other chronic relapsing disorders such as diabetes, asthma, and hypertension (McLellan *et al.*, 2000). The purpose of current neuroscientific drug abuse research is to understand the cellular and molecular mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction (Koob and Le Moal, 1997).

Diagnostic Criteria of Addiction

The diagnostic criteria for addiction as described by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994), also have evolved over the past 30 years with a shift from the emphasis and necessary criteria of tolerance and withdrawal to other criteria directed more at compulsive use. In the DSM-IV, tolerance and withdrawal form two of seven potential criteria. The criteria for Substance Dependence outlined in the DSM-IV closely resemble those outlined by the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) (World Health Organization, 1992) (**Tables 1.2** and **1.3**). The number of criteria met by drug addicts vary with the severity of the addiction, the stage of the addiction process, and the drug in question (Chung and Martin, 2001). For example, in adolescents, the most frequently observed criteria are *much time getting or recovering from use* (DSM-IV criteria #5 and #7), *continued use despite problems in social and occupational functioning* (DSM-IV criterion #6), and *tolerance or withdrawal* (DSM-IV criteria #1 and #2) (Crowley *et al.*, 1998) (see *Cannabinoids* chapter).

TABLE 1.2 DSM-IV and ICD-10 Diagnostic Criteria for *Alcohol and Drug Abuse/Harmful Use*

DSM-IV **Alcohol and drug abuse**	ICD-10 **Harmful use of alcohol and drugs**
A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period: 1. recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home. 2. recurrent substance use in situations in which use is physically hazardous. 3. recurrent substance-related legal problems. 4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the drug. B. The symptoms have never met the criteria for substance dependence for the same class of substance.	A. A pattern of substance use that is causing damage to health. The damage may be physical or mental. The diagnosis requires that actual damage should have been caused to the mental or physical health of the user. B. No concurrent diagnosis of the substance dependence syndrome for same class of substance.

TABLE 1.3 DSM-IV and ICD-10 Diagnostic Criteria for *Alcohol and Drug Dependence*

	DSM-IV	ICD-10
Clustering criterion	A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following occurring at any time in the same 12-month period:	A. Three or more of the following have been experienced or exhibited at some time during the previous year:
Tolerance	1. Need for markedly increased amounts of a substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of the substance.	1. Evidence of tolerance, such that increased doses are required in order to achieve effects originally produced by lower doses.
Withdrawal	2. The characteristic withdrawal syndrome for a substance or use of a substance (or a closely related substance) to relieve or avoid withdrawal symptoms.	2. A physiological withdrawal state when substance use has ceased or been reduced as evidenced by the characteristic substance withdrawal syndrome, or use of substance (or a closely related substance) to relieve or avoid withdrawal symptoms.
Impaired control	3. Persistent desire or one or more unsuccessful efforts to cut down or control substance use.	3. Difficulties in controlling substance use in terms of onset, termination, or levels of use.
	4. Substance used in larger amounts or over a longer period than the person intended.	
Neglect of activities	5. Important social, occupational, or recreational activities given up or reduced because of substance use.	4. Progressive neglect of alternative pleasures or interests in favor of substance use; or
Time spent	6. A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance used.	A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance use.
Inability to fulfil roles	None	None
Hazardous use	None	None
Continued use despite problems	7. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use.	5. Continued substance use despite clear evidence of overtly harmful physical or psychological consequences.
Compulsive use	None	6. A strong desire or sense of compulsion to use substance.
Duration criterion	B. No duration criterion separately specified. However, several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g., 'often', 'persistent', 'continued').	B. No duration criterion separately specified.
Criterion for subtyping dependence	*With physiological dependence:* Evidence of tolerance or withdrawal (i.e., any of items A-1 or A-2 above are present). *Without physiological dependence:* No evidence of tolerance or withdrawal (i.e., none of items A-1 or A-2 above are present).	None

Dependence View of Addiction

Historically, definitions of addiction began with definitions of dependence. Himmelsbach defined physical dependence as:

> '... an arbitrary term used to denote the presence of an acquired abnormal state wherein the regular administration of adequate amounts of a drug has, through previous prolonged use, become requisite to physiologic equilibrium. Since it is not yet possible to diagnose physical dependence objectively without withholding drugs, the *sine qua non* of physical dependence remains the demonstration of a characteristic abstinence syndrome' (Himmelsbach, 1943).

Eventually this definition evolved into the definition for physical dependence or 'intense physical

disturbances when administration of a drug is suspended' (Eddy *et al.*, 1965). However, this terminology clearly did not capture many of the aspects of the addictive process where no *physical* signs were observed, necessitating a second definition of *psychic dependence* to capture the more *behavioral* aspects of the symptoms of addiction: 'A condition in which a drug produces "a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort"...' (Eddy *et al.*, 1965). Modern definitions of addiction resemble a combination of physical and psychic dependence with more of an emphasis on the psychic or motivational aspects of withdrawal, rather than on the physical symptoms of withdrawal:

> '*Addiction* from the Latin verb "addicere", to give or bind a person to one thing or another. Generally used in the drug field to refer to chronic, compulsive, or uncontrollable drug use, to the extent that a person (referred to as an "addict") cannot or will not stop the use of some drugs. It usually implies a strong (Psychological) Dependence and (Physical) Dependence resulting in a Withdrawal Syndrome when use of the drug is stopped. Many definitions place primary stress on psychological factors, such as loss of self-control and over powering desires; i.e., addiction is any state in which one craves the use of a drug and uses it frequently. Others use the term as a synonym for physiological dependence; still others see it as a combination (of the two)' (Nelson *et al.*, 1982).

Unfortunately, the word *dependence* has multiple meanings. Any drug can produce dependence if dependence is defined as the manifestation of a withdrawal syndrome upon cessation of drug use, but meeting the DSM-IV criteria for *Substance Dependence* is much more than a manifestation of a withdrawal syndrome, but rather is equivalent to addiction. For the purposes of this book, *dependence* with a lower-case 'little d' will refer to the manifestation of a withdrawal syndrome, whereas *Dependence* with a capital 'big D' will refer to Substance Dependence as defined by the DSM-IV or addiction. The words *Substance Dependence* (as defined by the DSM-IV), *addiction* and *alcoholism* will be held equivalent for this book.

Psychiatric View of Addiction

From a psychiatric perspective, drug addiction has aspects of both impulse control disorders and compulsive disorders. Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act—pleasure, gratification or relief at the time of committing the act—and there may or may not be regret, self-reproach or guilt following the act (American Psychiatric Association, 1994). In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. As an individual moves from an impulsive disorder to a compulsive disorder, there is a shift from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob, 2004) (**Fig. 1.3**). Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity in a collapsed cycle of addiction comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect. Different theoretical perspectives ranging from experimental psychology, social psychology, and neurobiology can be superimposed on these three stages which are conceptualized as feeding into each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997) (**Fig. 1.4**).

Psychodynamic View of Addiction

A psychodynamic view of addiction that integrates well with the neurobiology of addiction is that of Khantzian and colleagues (Khantzian, 1985, 1990, 1997) with a focus on the factors leading to vulnerability for addiction. This perspective is deeply rooted in clinical practice and in psychodynamic concepts developed in a contemporary perspective in relation to substance use disorders. The focus of this approach is on developmental difficulties, emotional disturbances, structural (ego) factors, personality organization, and the building of the self. It is important to note that this contemporary perspective contrasts with a classic but not abundant psychoanalytic literature on the subject which emphasizes the pleasurable aspects of drugs and the regressive aspects of drug use.

Two critical elements (disordered emotions and disordered self-care) and two contributory elements (disordered self-esteem and disordered relationships) have been identified, which have evolved into a modern self-medication hypothesis, where individuals with substance use disorders are hypothesized to take drugs as a 'means to cope with painful and threatening emotions.' In this conceptualization, addicted individuals experience states of subjective distress and suffering that may or may not be associated with conditions meeting DSM-IV criteria for a psychiatric diagnosis (American Psychiatric Association, 1994).

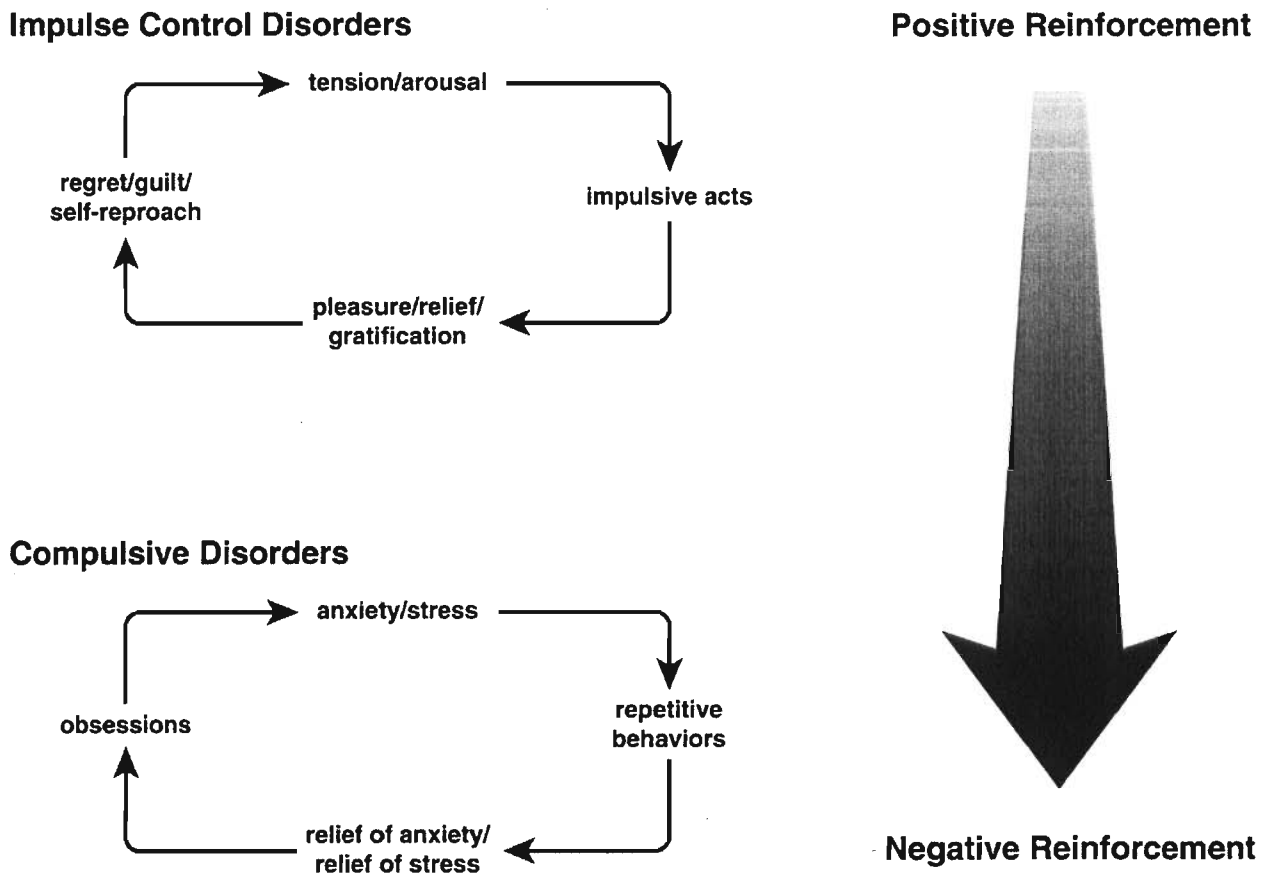

FIGURE 1.3 Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders increasing tension and arousal occur before the impulsive act, with pleasure, gratification, or relief during the act. Following the act there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (American Psychiatric Association, 1994). Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders. [Reproduced with permission from Koob, 2004.]

Addicts have feelings that are overwhelming and unbearable and may consist of an affective life that is absent and nameless. From this perspective, drug addiction is viewed as an attempt to medicate such a dysregulated affective state. The suffering of the patient is deep-rooted in disordered emotions characterized at their extremes either by unbearable painful affect or by a painful sense of emptiness. Others cannot express personal feelings or cannot access emotions and are hypothesized to suffer from alexithymia, defined as 'a marked difficulty to use appropriate language to express and describe feelings and to differentiate them from bodily sensation' (Sifneos, 2000).

Such self-medication may be drug-specific in that patients may have a preferential use of drugs that fits with the nature of the painful affective states that they are self-medicating. Opiates might be effective in reducing psychopathological states of violent anger and rageful feelings. Others suffering from anhedonia, anergia, or lack of feelings, will prefer the activating properties of psychostimulants. Some flooded in their feelings, or cut off from feelings, will welcome repeated moderate doses of alcohol or depressants as medicine to express feelings that they are not able to communicate. Thus, in some cases, the subjects operate to relieve painful feelings, in others, the operative motive is to control or express feelings (Khantzian, 1995, 1997; Khantzian and Wilson, 1993). The common element to this hypothesis is that each class of drugs serves as an antidote to dysphoric states and acts as a 'replacement for a defect in the psychological structure' of such individuals (Kohut, 1971). The paradox is that the choice of drugs to self-medicate such emotional pain will later by itself perpetuate it, thereby continuing a life revolving around drugs.

Disordered self-care is hypothesized to combine with a disordered emotional life to become a principal

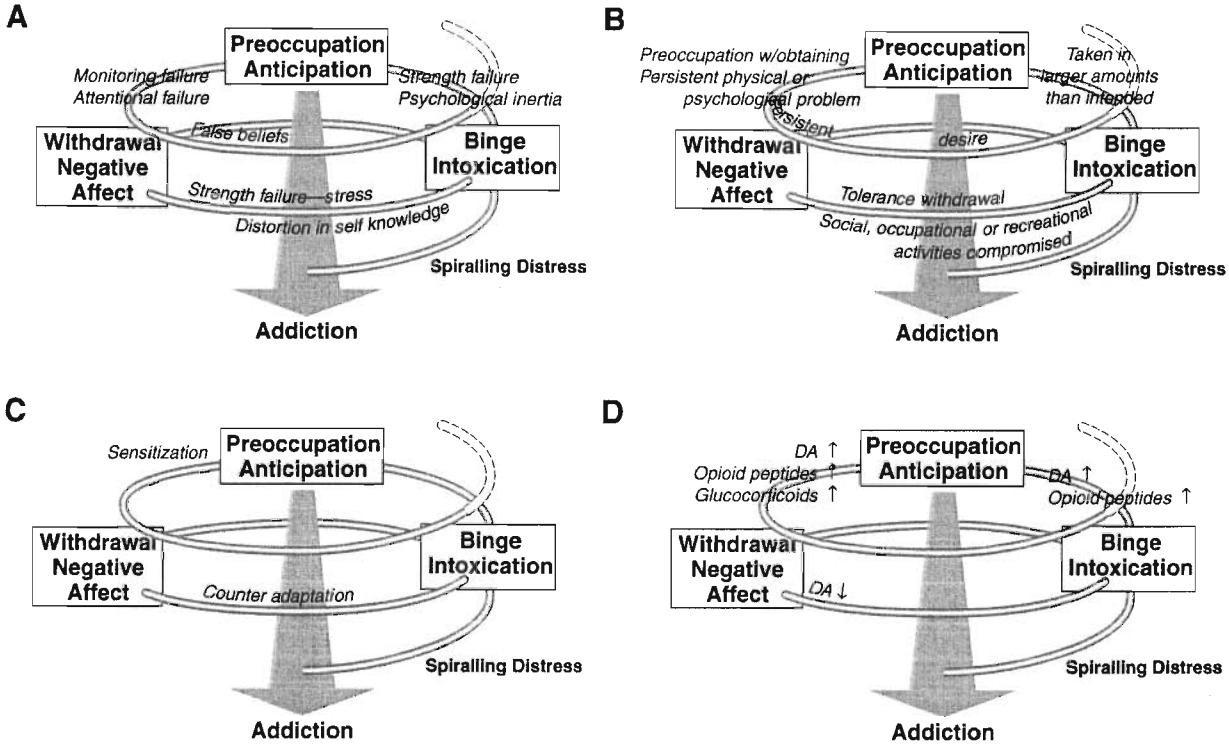

FIGURE 1.4 Diagram describing the spiraling distress—addiction cycle from four conceptual perspectives: social psychological, psychiatric, dysadaptational, and neurobiological. Note that the addiction cycle is conceptualized as a spiral that increases in amplitude with repeated experience, ultimately resulting in the pathological state known as addiction. **(A)** The three major components of the addiction cycle—preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect—and some of the sources of potential self-regulation failure in the form of underregulation and misregulation. **(B)** The same three major components of the addiction cycle with the different criteria for substance dependence incorporated from the DSM-IV. **(C)** The places of emphasis for the theoretical constructs of sensitization and counteradaptation. **(D)** The hypothetical role of different neurochemical and endocrine systems in the addiction cycle. Small arrows refer to increased functional activity. DA, dopamine; CRF, corticotropin-releasing factor. [Reproduced with permission from Koob and Le Moal, 1997.]

determinant of substance use disorders. Self-care deficits reflect an inability to ensure one's self-preservation and are characterized by an inability to anticipate or avoid harmful and dangerous situations, and an inability to use appropriate judgment and feeling as guides in the face of danger. Thus, self-care deficits reflect an inability to appropriately experience emotions and appreciate the consequences of dangerous behaviors, and the core element of this psychodynamic perspective is a dysregulated emotional system or systems in individuals vulnerable to addiction.

This psychodynamic approach integrates well with a growing amount of evidence for a critical role of dysregulated brain reward and stress systems, from studies on the neurobiology of addiction using animal models that have developed from a physiological framework (see chapters that follow). However, from a neurobiological perspective, there is the additional insult to the personality produced by the direct effects of the drugs themselves to perpetuate, and actually *create*, such character flaws (Koob, 2003).

Social Psychological / Self-regulation View of Addiction

At the social psychology level, self-regulation failure has been argued as the root of the major social pathology in present times (Baumeister *et al.*, 1994). From this perspective there are important self-regulation elements that may be involved in the different stages of addiction to drugs, as well as in other pathological behaviors such as compulsive gambling and binge eating (Baumeister *et al.*, 1994). Such self-regulation failures ultimately may lead to addiction in the case of drug use or an addiction-like pattern with nondrug behaviors. Underregulation as reflected in strength deficits, failure to establish standards or conflicts in standards, and attentional failures as well as misregulation (misdirected attempts to self-regulate) can contribute to the development of addiction-like patterns of behavior (**Fig. 1.4**). The transition to addiction can be facilitated by lapse-activated causal patterns. That is, patterns of behavior that contribute to the transition from an

initial lapse in self-regulation to a large-scale breakdown in self-regulation can lead to spiraling distress (Baumeister *et al.*, 1994). In some cases, the first self-regulation failure can lead to emotional distress which sets up a cycle of repeated failures to self-regulate and where each violation brings additional negative affect, resulting in spiraling distress (Baumeister *et al.*, 1994). For example, a failure of strength may lead to initial drug use or relapse, and other self-regulation failures can be recruited to produce an entrance to, or prevent an exit from, the addiction cycle.

At a neurobehavioral level, such dysregulation again may be reflected in deficits of information-processing, attention, planning, reasoning, self-monitoring, inhibition, and self-regulation, many of which involve functioning of the frontal lobe (Giancola *et al.*, 1996a,b) (see chapters that follow). Executive function deficits, self-regulation problems, and frontal lobe dysfunctions or pathologies constitute a risk factor for biobehavioral disorders including drug abuse (Dawes *et al.*, 1997). Deficits in frontal cortex regulation in children or young adolescents predict later drug and alcohol consumption, especially for children raised in families with drug and biobehavioral disorders histories (Dawes *et al.*, 1997; Aytaclar *et al.*, 1999).

Vulnerability to Addiction

Drug abuse is a far more complex phenomenon than previously thought, and it is now recognized that drug abusers represent a highly heterogeneous group, and the patterns leading to dependence are diverse. Individual differences in temperament, social development, comorbidity, protective factors, and genetics are areas of intense research, and a detailed discussion of these contributions to addiction are beyond the scope of this book. However, each of these factors presumably interacts with the neurobiological processes discussed in this book. A reasonable assertion is that the initiation of drug abuse is more associated with social and environmental factors, whereas the movement to abuse and addiction are more associated with neurobiological factors (Glantz and Pickens, 1992).

Temperament and personality traits and some temperament clusters have been identified as factors of vulnerability to drug abuse (Glantz *et al.*, 1999) and include disinhibition (behavioral activation) (Windle and Windle, 1993), negative affect (Tarter *et al.*, 1995), novelty- and sensation-seeking (Wills *et al.*, 1994), and 'difficult temperament' (conduct disorder) (Glantz *et al.*, 1999).

From the perspective of comorbid psychiatric disorders, some of the strongest associations are found with mood disorders, anxiety disorders, antisocial personality disorders, and conduct disorders (Glantz and Hartel, 1999). Data from the International Consortium in Psychiatric Epidemiology (representing six different sites in the United States, Germany, Mexico, The Netherlands, Ontario, and Canada) and the National Comorbidity Study (United States; approximately 30 000 subjects) have revealed that approximately 35 per cent of the sample with drug dependence met lifetime criteria for a mood disorder. About 45 per cent met criteria for an anxiety disorder, and 50 per cent met criteria for either conduct or antisocial personality disorder (Merikangas *et al.*, 1998). More recent data on 12-month prevalence of comorbidity from the National Institute on Alcohol Abuse and Alcoholism's National Epidemiologic Survey on Alcohol and Related Conditions represents over 43 000 respondents and shows similar results (21–29 per cent for comorbidity of mood disorders; 22–25 per cent comorbidity for anxiety disorders; 32–70 per cent comorbidity for personality disorders) (Grant *et al.*, 2004a,b,c) (**Table 1.4**). The association of Attention Deficit Hyperactivity Disorder (ADHD) with drug abuse can be explained largely by the higher comorbidity with conduct disorder in these children (Biederman *et al.*, 1997). Independent of this association, there is little firm data to support a risk due to treatment of ADHD with stimulants (Biederman *et al.*, 1999), and no preference for stimulants over other drugs has been noted (Biederman *et al.*, 1997).

Developmental factors are important components of vulnerability, with strong evidence developing that adolescent exposure to alcohol, tobacco, or drugs of abuse leads to significant vulnerability for alcohol

TABLE 1.4 12-Month Prevalence of Comorbid Disorders Among Respondents with Nicotine Dependence, Alcohol Dependence, or Any Substance Use Disorder

	Mood	Anxiety	Personality
Alcohol	27.6%	23.5%	39.5%
Nicotine	21.1%	22.0%	31.7%
Substance Dependence (including alcohol but not nicotine)	29.2%	24.5%	69.5%

[Data from Grant *et al.*, 2004a,b,c.]

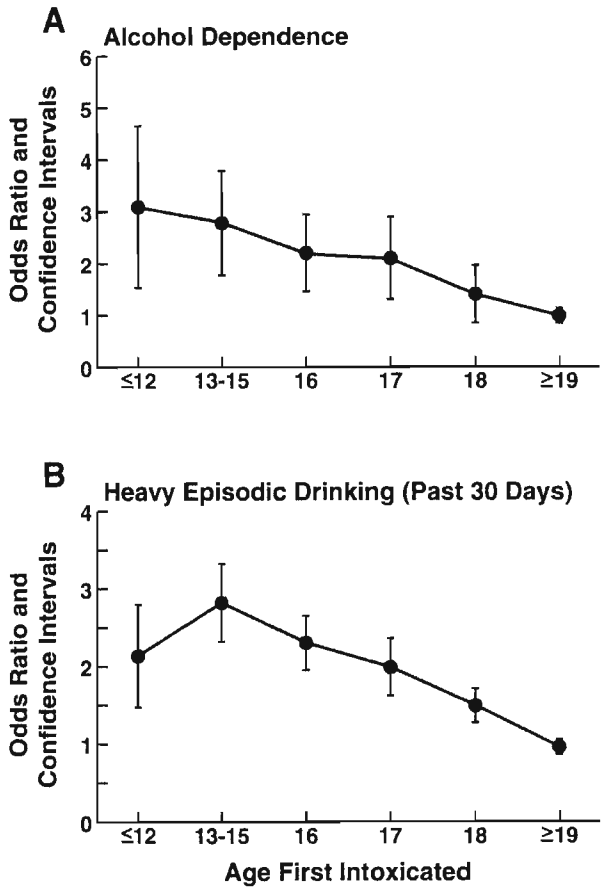

FIGURE 1.5 1999 College Alcohol Survey. **(A)** Alcohol Dependence according to age first intoxicated. **(B)** Past 30 days heavy episodic drinking according to age first intoxicated. After controlling for personal and demographic characteristics and respondent age, the odds of meeting alcohol dependence criteria were 3.1 times greater for those first drunk at or prior to age 12 compared with drinkers who were first drunk at age 19 or older. The relationship between early onset of being drunk and heavy episodic drinking in college persisted even after further controlling for alcohol dependence. Respondents first drunk at or prior to age 12 had 2.1 times the odds of reporting recent heavy episodic drinking than college drinkers first drunk at age 19 or older. [Reproduced with permission from Hingson *et al.*, 2003.]

dependence and alcohol problems in adulthood. Persons first intoxicated at 16 or younger were more likely to drive after drinking, to ride with intoxicated drivers, to be injured seriously when drinking, to be more likely to become heavy drinkers, and to be 2–3 times more likely to develop substance dependence on alcohol (Hingson *et al.*, 2003) (**Fig. 1.5**). Similarly, persons who smoked their first cigarette during 14–16 years of age were 1.6 times more likely to become dependent than those who initiated at a later age (Breslau *et al.*, 1993; Everett *et al.*, 1999). Others have argued that regular smoking during adolescence raises the risk for adult smoking by a factor of 16 compared to nonsmoking during adolescence (Chassin *et al.*, 1990). Most smoking initiation occurs in the United States during the transition from junior high school to high school (14–15 years of age) (Winkleby *et al.*, 1993). The age at which smoking begins influences the total years of smoking (Escobedo *et al.*, 1993), the number of cigarettes smoked in adulthood (Taioli and Wynder, 1991), and the likelihood of quitting (Ershler *et al.*, 1989; Chassin *et al.*, 1990) (**Fig. 1.6**). When prevalence of lifetime illicit or nonmedical drug abuse and Substance Dependence was estimated for each year of onset of drug use from ages 13 and younger to 21 and older, early onset of drug use was a significant predictor of the subsequent development of drug abuse over a lifetime (Grant and Dawson, 1998) (**Fig. 1.7**). Drugs included sedatives, tranquilizers, opioids other than heroin, amphetamines, cocaine and crack cocaine, cannabis, heroin, methadone, hallucinogens, and inhalants. Overall, the lifetime prevalence of

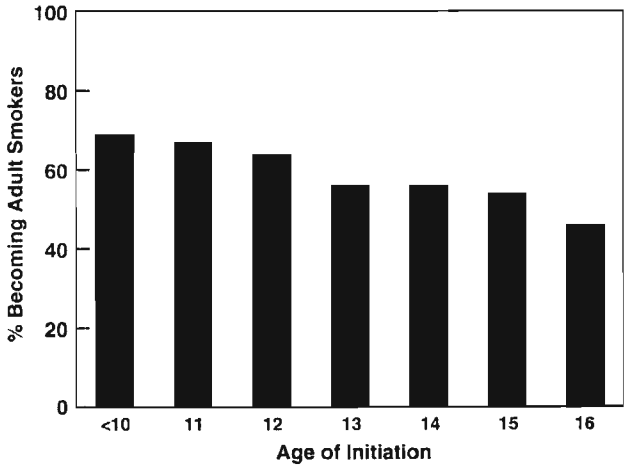

FIGURE 1.6 Percentages of adolescent regular smokers who became adult regular smokers as a function of grade of smoking initiation. Subjects consisted of all consenting 6th to 12th graders in a Midwestern county school system who were present in school on the day of testing. All 6th to 12th grade classrooms (excluding special education) were surveyed annually between 1980 and 1983. There was a potential pool of 5799 individuals who had been assessed at least once during their adolescence between 1980 and 1983. At the time of follow-up, 25 of these subjects were found to be deceased, and 175 refused participation. 4156 provided data (72%). The subjects were predominantly Caucasian (96%), were equally divided by sex (49% male; 51% female), and were on an average 21.8 years old. 71% had never been married, and 26% were currently married. 58% had completed at least some college by the time of follow-up. 32% were still students. 43% had a high school education. For nonstudents, occupational status ranged from 29% in factory, crafts, and labor occupations, to 39% in professional, technical, and managerial occupations. At follow-up, the overall rate of smoking at least weekly was 26.7%. [Reproduced with permission from Chassin *et al.*, 1990.]

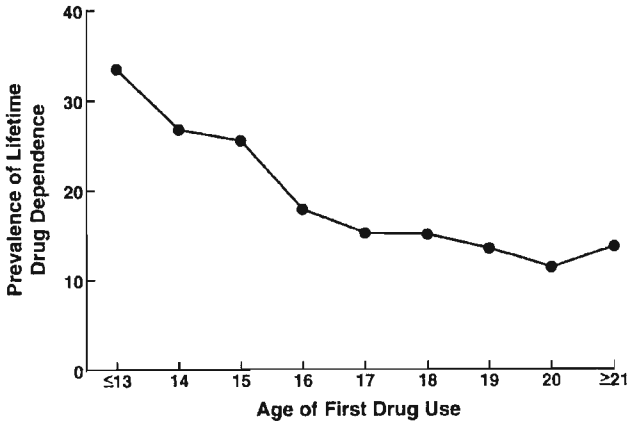

FIGURE 1.7 Prevalence of lifetime drug dependence by age at first drug use. The prevalence of lifetime dependence decreased steeply with increasing age of onset of drug use. Overall, the prevalence of lifetime dependence among those who started using drugs under the age of 14 years was about 34%, dropping sharply to 15.1% for those initiating use at age 17, to about 14% among those initiating use at age 21 or older. [Reproduced with permission from Grant and Dawson, 1998.]

dependence among those who started using drugs under the age of 14 years was 34 per cent; this percentage dropped to 14 per cent for those who started using at age 21 or older (Grant and Dawson, 1998).

In adolescents, it has been proposed that there are stages and pathways of drug involvement (Kandel and Jessor, 2002). There is considerable support for the hypothesis that initiation begins with legal drugs, alcohol and tobacco, and involvement with illicit drugs occurs later in the developmental sequence, marijuana often being the bridge between licit and illicit drugs. However, although this sequence is common, this does not represent an inevitable progression. Only a very small percentage of youths progress from one stage to the next and on to late stage illicit drug use or Dependence.

Genetic contributions to addiction have long been postulated and can result from complex genetic differences that range from alleles that control drug metabolism to hypothesized genetic control over drug sensitivity and environmental influences. Complex genetic influences are those that are genetic but are not due to single-gene effects that produce Mendelian inheritance patterns, as stressed by Uhl and Grow (2004). The classical approaches to complex trait genetics have been the examination of co-occurrence or comorbidity for the trait in monozygotic versus dizygotic twins, reared together or apart, and in analogous family studies with other sorts of biological relatives. Twin and adoption studies can provide researchers with estimates of the extent of genetic effects, termed *heritability* (the

TABLE 1.5 Heritability Estimates for Drug Dependence

	Males	Females
Cocaine	44%	65%
Heroin (opiates)	43%	—
Marijuana	33%	79%
Tobacco	53%	62%
Alcohol	49% (40–60%)	64%
Addiction overall	40%	

Male cocaine, heroin, marijuana: Tsuang *et al.*, 1996. *Male nicotine:* Carmelli *et al.*, 1990. *Female cocaine:* Kendler and Prescott, 1998b. *Female marijuana:* Kendler and Prescott, 1998a. *Female nicotine:* Kendler *et al.*, 1999. *Male alcohol:* Liu *et al.*, 2004; Prescott and Kendler, 1999; McGue *et al.*, 1992. *Female alcohol:* McGue *et al.*, 1992. *Addiction overall:* Uhl and Grow, 2004.

proportion of observed variation in a particular trait that can be attributed to inherited genetic factors in contrast to environmental factors). Using such estimates, genetic studies have demonstrated that genetic factors can account for approximately 40 per cent of the total variability of the phenotype (**Table 1.5**). Twin studies suggest significant overlap between genetic predisposition for Dependence on most classes of addictive substances (Karkowski *et al.*, 2000). Clearly, in no case is heritability 100 per cent, which argues strongly for gene–environment interactions, including the stages of the addiction cycle, developmental factors, and social factors.

It also should be emphasized that genetic and environmental factors can convey not only vulnerability, but also protection against drug abuse. Certain Asian populations missing one or more alleles for acetaldehyde dehydrogenase show significantly less vulnerability to alcoholism (Goedde *et al.*, 1983a,b; Mizoi *et al.*, 1983; Higuchi *et al.*, 1995). There is also similar evidence developing for individuals with a genetic defect in metabolizing nicotine (Tyndale and Sellers, 2002; Sellers *et al.*, 2003). Clearly, there are also protective factors within the social environment that can promote competent adaptation and as a result prevent drug abuse (Dishion and McMahon, 1998).

NEUROADAPTATIONAL VIEWS OF ADDICTION

Behavioral Sensitization

Repeated exposure to many drugs of abuse results in a progressive and enduring enhancement in the motor stimulant effect elicited by a subsequent challenge. The phenomenon of *behavioral sensitization* has been thought to underlie some aspects of drug addiction

(Vanderschuren and Kalivas, 2000). Behavioral or psychomotor sensitization, as defined by increased locomotor activation produced by repeated administration of a drug, is more likely to occur with intermittent exposure to drugs, whereas tolerance is more likely to occur with continuous exposure. This phenomenon was observed and characterized in the 1970s and 1980s for various drugs (Babbini *et al.*, 1975; Eichler and Antelman, 1979; Bartoletti *et al.*, 1983a,b; Kolta *et al.*, 1985). Another intriguing aspect is that it has been suggested that the sensitization grows with the passage of time (Antelman *et al.*, 1983, 1986, 2000). Moreover, stress and stimulant sensitization effects show cross-sensitization (Antelman *et al.*, 1980). Psychomotor sensitization is linked invariably to a sensitization of the activity of the mesolimbic dopamine system (Robinson and Berridge, 1993).

A conceptualization of the role of psychomotor sensitization in drug addiction has been proposed where a shift in an incentive-salience state described as *wanting*, as opposed to *liking*, was hypothesized to be progressively increased by repeated exposure to drugs of abuse (Robinson and Berridge, 1993) (**Fig. 1.8**). The transition to pathologically strong *wanting* or craving was proposed to define compulsive use.

The theory posits that there is no causal relationship between the subjective pleasurable effects of the drugs (drug *liking*) and the motivation to take drugs (drug *wanting*). The brain systems that are sensitized do not mediate the pleasurable or euphoric effects of drugs, but instead they mediate a subcomponent of reward termed *incentive salience* (i.e., motivation to take drug or drug *wanting*). It is the psychological process of incentive-salience specifically that is responsible for instrumental drug-seeking and drug-taking behavior (*wanting*) (Robinson and Berridge, 2003). When sensitized, this incentive-salience process produces compulsive patterns of drug use. By means of associative learning, the enhanced incentive value becomes oriented specifically toward drug-related stimuli, leading to escalating compulsion for seeking and taking drugs. The underlying sensitization of neural structures persists, making addicts vulnerable in the long-term to relapse.

The theory posits:

> '... it is specifically sensitization of incentive salience attribution to representation of drug cues and drug-taking that cause the pursuit of drugs and persisting vulnerability to relapse and addiction ... Individuals are guided to incentive stimuli by the influence of Pavlovian stimulus-stimulus (S-S) associations on motivational systems, which is psychologically separable from the symbolic cognitive systems that mediate conscious desire, declarative expectancies of reward, and act-outcome representations' (Robinson and Berridge, 2003).

Counteradaptation–Opponent-Process

Counteradaptation hypotheses have long been proposed to explain tolerance and withdrawal and the motivational changes associated with the development of addiction. Here, the initial acute effect of the drug is opposed or counteracted by homeostatic changes in systems that mediate primary drug effects (Solomon and Corbit, 1974; Siegel, 1975; Poulos and Cappell, 1991). The origins of such counteradaptive hypotheses can be traced to some of the earlier work on physical dependence (Himmelsbach, 1943), and the counteradaptive changes associated with acute and chronic opioid administration on physiological measures.

Martin (1968) proposed a homeostatic and redundancy theory of tolerance and dependence to opioids that had a striking resemblance to what was to follow as a more general *opponent process* theory by other researchers (see below). Based on studies of acute tolerance and physical dependence produced in dogs by infusing 8 mg/kg of morphine per hour for 7–8 h, and subsequently precipitating abstinence with 20 mg/kg of the mixed agonist/antagonist nalorphine, a regular sequence of changes in physiological parameters such as temperature took place over time. Martin argued that the following sequence of events transpired in the development of *acute tolerance* (**Fig. 1.9,** left side). Morphine lowered the homeostat—that is, lowered the thermoregulatory set point (A). The difference between the homeostatic level and the level of the internal environment or existing state (B) gave rise to an error force (C) which in turn drove a physiological system (D) to rectify the error. In the case of a temperature change, this was effected by panting in the dog. As the error force was diminished, the level of function of the physiological system rectifying the error also diminished, and acute tolerance developed.

A similar scheme explained *acute physical dependence* except that initially, nalorphine rapidly reversed the effects of morphine on body temperature (A), restoring the homeostat to a control level. However, a new error force of the opposite valence was established by the nalorphine (C) which recruited heat-generating mechanisms (D) (**Fig. 1.9**). These error forces remained until a new equilibrium state was achieved (D).

Similar shifts in the homeostatic level of control were hypothesized for signs of withdrawal and precipitated abstinence in *chronically dependent subjects*. The mechanism involved was the same, except that with chronic physical dependence, chronic

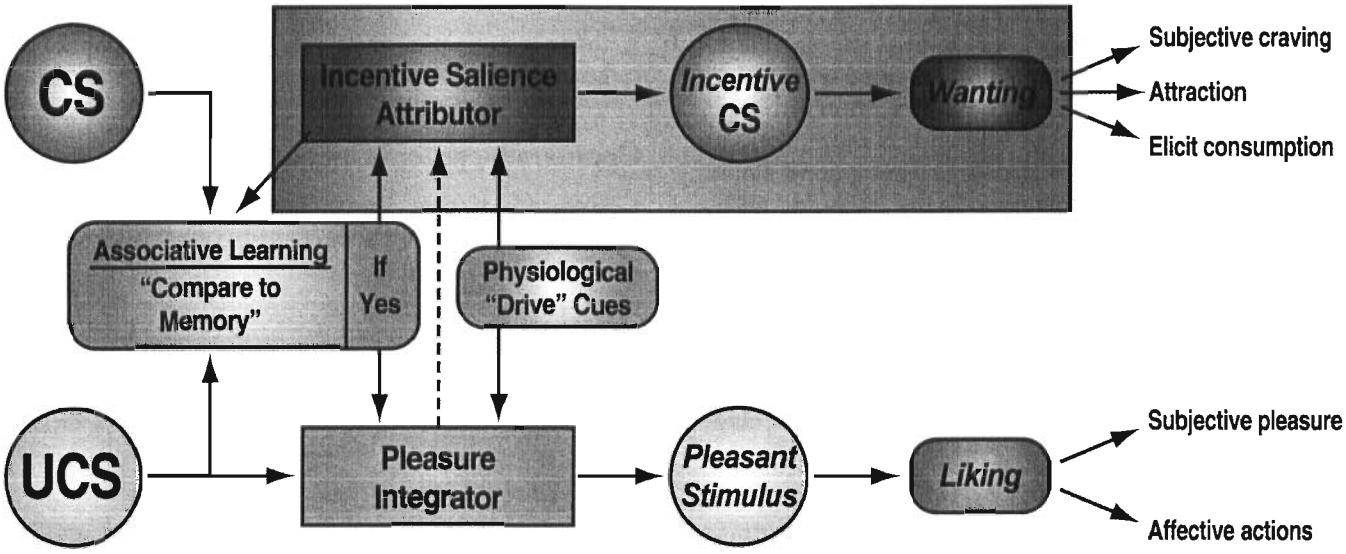

FIGURE 1.8 A schematic illustration of a model which proposes a process of incentive salience and accounts for the consequences of drug-induced sensitization. In this modified model of incentive motivation, the psychological process (and neural substrate) for pleasure (*liking*) is separate from the psychological process (and neural substrate) responsible for incentive salience (*wanting*). Robinson and Berridge (1993) proposed that the activation of esotelencephalic dopamine systems plays a *direct* role only in the process of *wanting* via the attribution of incentive salience to the perception and representation of conditioned stimuli (CS). This portion of the model (i.e., the psychological process) is sensitized by repeated drug administration. It is the hyperactivation of this specific psychological process (incentive salience), due to sensitization of its neural substrate by drugs, that results in the excessive attribution of incentive salience to drug-related stimuli. Whereas normal levels of incentive salience attribution results in normal *wanting*, hyperactivation of this system is hypothesized to result in excessive incentive salience attribution, which is experienced as craving. Craving is pathologically intense *wanting*. The major difference between this model of incentive motivation and the traditional model is that psychological processes and neural substrates responsible for pleasure (*liking*) are separate from those for incentive salience (*wanting*). Thus, natural incentives (unconditioned stimuli [UCS]) produce pleasure directly, but produce incentive salience and elicit goal-directed approach behavior only indirectly (as indicated by the dashed arrow from 'pleasure integrator' to the 'incentive salience attributor'). The direction of incentive salience attribution to stimuli that preceded or accompanied incentive salience activation is determined by associative learning. Thus, activation of the incentive salience attributor by an unconditioned stimulus results in incentive salience being assigned to the perception of conditioned stimuli that were originally neutral (such as the sight of a syringe) and to their mental representations. This is what makes conditioned stimuli attractive and 'wanted' and able to elicit approach. Conditioned stimuli (and unconditioned stimuli) are always compared against past associative memories. Without the direction provided by associative learning, incentive salience could not be focused on any single target. Although diffuse attribution of incentive salience would be both psychologically and behaviorally activating, without associative direction it would not be sufficient to guide behavior toward a specific goal. Familiar conditioned stimuli that have been paired with incentive salience attribution in the past are the target of incentive salience when encountered again, especially when an animal is in particular physiological states (indicated by the arrow from *Physiological 'Drive' Cues*). Incentive salience assigned to conditioned stimuli must be further 'reboosted' each time they are paired again with salience activation (indicated by the dashed arrow from the incentive salience attributor to associative learning). Disruption of this reboosting, by neuroleptics for example, can produce 'extinction mimicry' or decay of incentive value. Ordinarily, incentive salience is assigned only to stimuli that have been paired with pleasure. But brain manipulations (such as drugs or electrical brain stimulation) may circumvent pleasure, by activating the neural substrate of incentive salience directly. This will result in the attribution of incentive salience to associated stimuli and actions and result in their becoming 'wanted,' even in the absence of pleasure. This can be considered a kind of 'sham reward.' Sensitization of the neural substrate for incentive salience will lead to pathological *wanting* (craving) for stimuli associated with its excessive activation (e.g., those involved in drug taking), even if this produces little or no pleasure. As mentioned, the direction of incentive salience by associative learning is the primary determinant of exactly which stimuli become craved. Thus, in the addict, drug-paired stimuli which have been experienced repeatedly in association with the excessive stimulation of dopamine systems become the nearly exclusive targets for the attribution of incentive salience. Other contributions of associative learning are also possible in this model. For example, the pleasure elicited by an unconditioned stimulus can change with repeated experience, as when one develops an appreciative palate for Scotch whiskey (this is indicated in the model by the arrow from learning to the 'pleasure integrator'). Also, a conditioned stimulus that has been repeatedly paired with pleasure can itself come to elicit subjective pleasure, as in the example of a conditioned 'high' reported by 'needle freaks' (arrows from the conditioned stimulus to the 'pleasure integrator' via associative learning). But these effects are separate from the attribution of incentive salience, and they have only a relatively weak influence on motivated behavior compared to the craving produced by the attribution of excessive incentive salience. Finally, none of the psychological processes described in this model, except for subjective *wanting* (craving) and subjective pleasure, are apparent to conscious awareness. The interaction among incentive salience, pleasure and associative learning is not available to introspection. Only the final products of the interaction are interpreted by cognitive mechanisms as subjective *wanting* and *liking*. For an addict whose neural substrates of incentive salience have been sensitized, the subjective product is dominated by the intense experience of drug craving. [Reproduced with permission from Robinson and Berridge, 1993.]

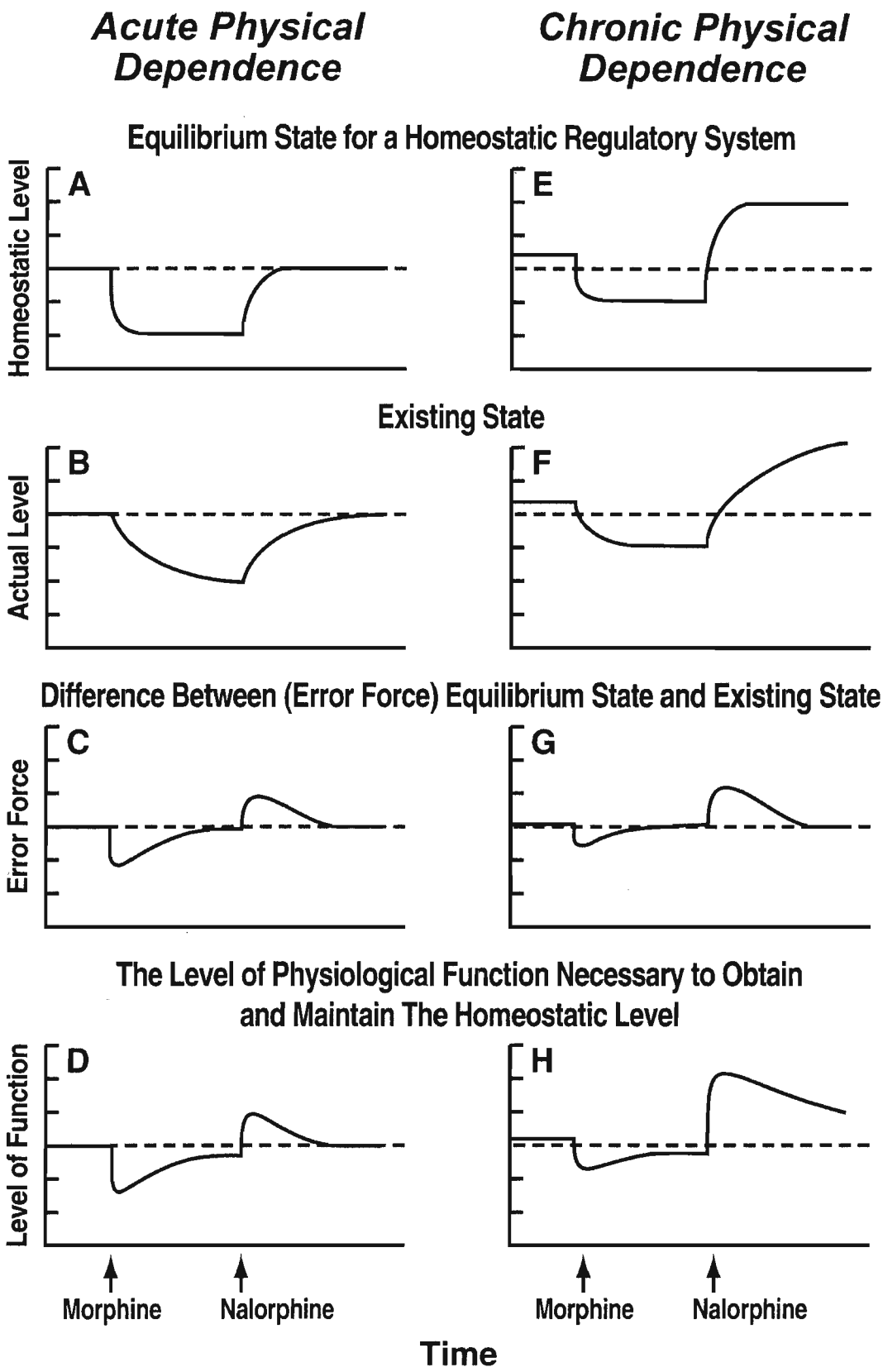

FIGURE 1.9 A general and theoretical formulation of the homeostatic theory of acute and chronic tolerance and physical dependence (see text for details). [Reproduced with permission from Martin, 1968.]

morphine elevated the homeostatic level above the pre-addiction level. In other words, at the time when morphine was administered, the animal was already in early abstinence and the homeostatic level was already slightly above the control level (E) (**Fig. 1.9**). When morphine was administered, the level to which the homeostat was depressed was smaller than it was in the nondependent state. Martin hypothesized that it proceeded from an elevated baseline and the absolute magnitude of the depression was smaller. As a consequence, the error force was smaller (G) (**Fig. 1.9**), and the level of function of the restorative system was lower (H) (**Fig. 1.9**). When nalorphine was administered, a very large error force was generated (G) (**Fig. 1.9**) revealing the true level of the hypersensitized homeostat.

Martin (1968) went on to speculate that the changes observed in homeostatic set point could be explained by redundancy theory where two separate neurochemical systems mediate a given function (Martin and Eades, 1960). When applied to tolerance and dependence, it is assumed that morphine interrupts one of the redundant systems (pathway B) but does not disrupt the other (pathway A). Eventually, pathway A will develop hypertrophy and take over the previous function of pathway B. The tolerance that develops is a consequence of the hypertrophy of the redundant pathway A, not a decrement in the effect on pathway B. When the drug is withdrawn, pathway B returns to its normal level of excitability, but the total system functions at a much higher level because of the contribution of the hypertrophied pathway A. One means of integrating the redundancy theory with the original contra-adaptive theory of Himmelsbach (1942) was to argue that there exists a negative feedback mechanism on pathways A and B that is diminished when pathway A is hypertrophied.

The views of Martin (1968) significantly predate *opponent process* theory (Solomon and Corbit, 1974) and within-system (hypertrophy of pathway A) and between-system (decreased negative feedback of pathway A) neuroadaptations (Koob and Bloom, 1988), but certainly contained elements of both. In addition, as we will see later in the book, Martin's concepts of acute tolerance and acute dependence apply not only to temperature regulation but also to analgesia and the hedonic effects of drugs in humans and animals.

Opponent-process theory was developed during the 1970s by Solomon and colleagues (Solomon and Corbit, 1973, 1974; Hoffman and Solomon, 1974; D'amato, 1974). Since then, it has been applied by many authors to various situations such as drugs (opiates, nicotine, alcohol) to adjunctive drinking, fear conditioning, tonic immobility, ulcer formation, eating disorders, jogging, peer separation, glucose preference, and parachuting (Solomon and Corbit, 1973, 1974; Hoffman and Solomon, 1974; Solomon, 1980).

The theory assumes that the brain contains many affect control mechanisms, working as though they were affect immunization systems that counter or oppose all departures from affective neutrality or equilibrium, whether they be aversive or pleasant (Solomon and Corbit, 1974). The theory is a negative feedforward control construct designed to keep affect in check even though stimulation is strong. The device is composed of three subparts organized in a temporal manner. Two opposing processes control a summator, which determines the controlling affect at a given moment. First, an unconditional arousing stimulus triggers a primary affective process, termed the *a-process*. It is an unconditional reaction that translates the intensity, quality, and duration of the stimulus (for example, a first opiate intake). Second, as a consequence of the *a-process*, and inherently linked to it on a biological basis, the *b-process* is evoked after a short delay, an opponent process. Empirically, the *b-process* feeds a negative signal into the summator, subtracting from the impact on the summator the already existing *a-process*. The two responses are consequently and temporarily linked (*a* triggers *b*) but were hypothesized to depend on different neurobiological mechanisms. The *b-process* has a longer latency, but some data show that it may appear soon after the beginning of the stimulus in the course of the stimulus action (Larcher *et al.*, 1998). The *b-process* also has more inertia, a slower recruitment, and a more sluggish decay. At a given moment, the pattern of affect will be the algebraic sum of these opposite influences and the dynamics reveal, with the passage of time, the net product of the opponent process (Solomon, 1980) (**Fig. 1.10**).

In this opponent-process theory from a drug addiction perspective, tolerance and dependence are inextricably linked (Solomon and Corbit, 1974). Solomon argued that the first few self-administrations of an opiate drug produce a pattern of motivational changes where the onset of the drug effect produces a euphoria that is the *a-process*, and this is followed by a decline in intensity. Then, after the effects of the drug wear off, the *b-process* emerges as an aversive craving state. The *b-process* gets larger and larger over time, in effect contributing to or producing more complete tolerance to the initial euphoric effects of the drug (**Fig. 1.10**).

What is important to understand is that the dynamics, with the repetition of the stimulus, is the result of a progressive increase in the *b-process*. In other words, the *b-process* sensitizes through drug use, appears more and more rapidly after the unconditional stimulus onset, lasts longer and longer (the conditional effect), and masks the unconditional effect (*a-process*), resulting in

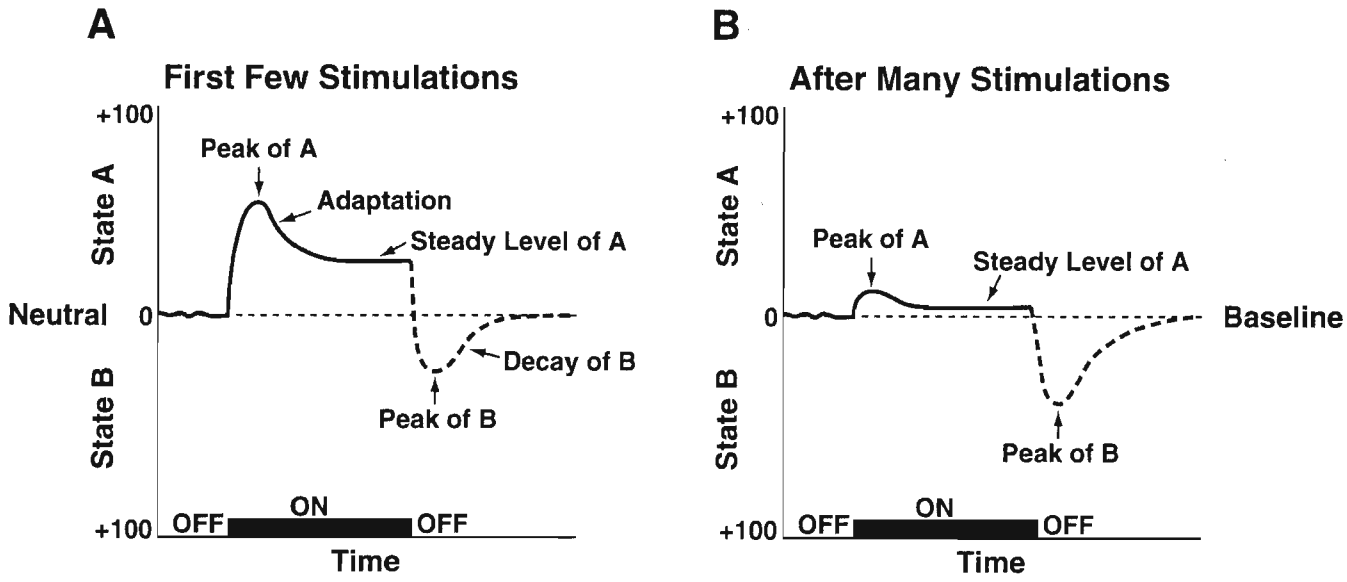

FIGURE 1.10 **(A)** The standard pattern of affective dynamics produced by a relatively novel unconditioned stimulus. **(B)** The standard pattern of affective dynamics produced by a familiar, frequently repeated unconditioned stimulus. [Reproduced with permission from Solomon, 1980.]

an apparent tolerance (Laulin *et al.*, 1999). Experimental data show that if the development of the *b-process* is blocked, no tolerance appears. The unconditioned effect of the drug does not change with repeated drug administration. The development of the *b-process* equals the development of a negative affective state and withdrawal symptoms, in opposition to the hedonic quality of the unconditioned stimulus. Importantly, the nature of the acquired motivation is specified by the nature of the *b-process*, that is, an aversive affect in the case of drug abuse. The subject will work to reduce, terminate, or prevent the negative affect.

Motivational View of Addiction

Rather than focusing on the *physical* signs of dependence, our conceptual framework has focused on *motivational* aspects of addiction. Emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 2001), has been associated with this transition from drug use to addiction. Indeed, some have argued that the development of such a negative affective state can define dependence as it relates to addiction:

> 'The notion of dependence on a drug, object, role, activity or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc.' (Russell, 1976).

A key common element that has been identified in animal models is the dysregulation of brain reward function associated with removal from chronic administration of drugs of abuse, and this observation lends credence to the motivational view (see subsequent chapters).

Rapid acute tolerance and opponent process-like effects to the hedonic effects of cocaine have been reported in human studies of smoked coca paste (Van Dyke and Byck, 1982) (**Fig. 1.11**). After a single smoking session, the onset and intensity of the 'high' are very rapid via the smoked route of administration, and a rapid tolerance is manifest in that the 'high' decreases rapidly despite significant blood levels of cocaine. Even more intriguing is that human subjects also actually report a subsequent 'dysphoria', again despite significant blood levels of cocaine. Intravenous cocaine produced similar patterns of a rapid 'rush' followed by an increased 'low' in human laboratory studies (Breiter *et al.*, 1997) (**Fig. 1.12**).

The hypothesis that compulsive use of cocaine is accompanied by a chronic perturbation in brain reward homeostasis has been tested in an animal model of escalation in drug intake with prolonged access. Animals implanted with intravenous catheters and allowed differential access to intravenous self-administration

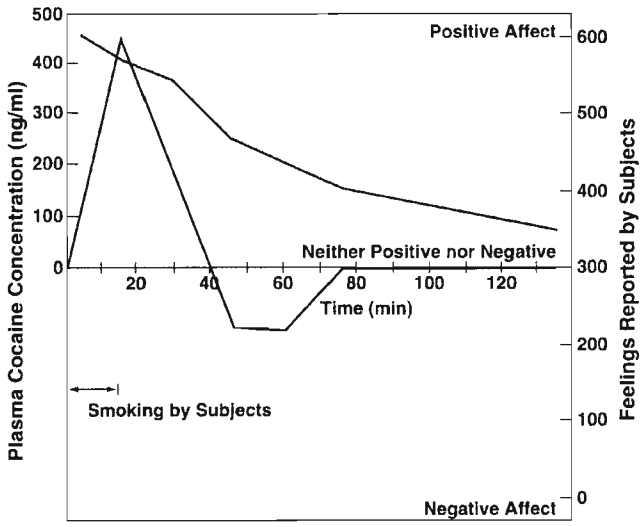

FIGURE 1.11 Dysphoric feelings followed the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration of cocaine in the plasma of the blood remained relatively high. The dysphoria is characterized by anxiety, depression, fatigue, and a desire for more cocaine. The peak feelings for the subjects were probably reached shortly before the peak plasma concentration, but the first psychological measurements were made later than the plasma assay. Hence, the temporal sequence of the peaks shown cannot be regarded as definitive. [Reproduced with permission from Van Dyke and Byck, 1982.]

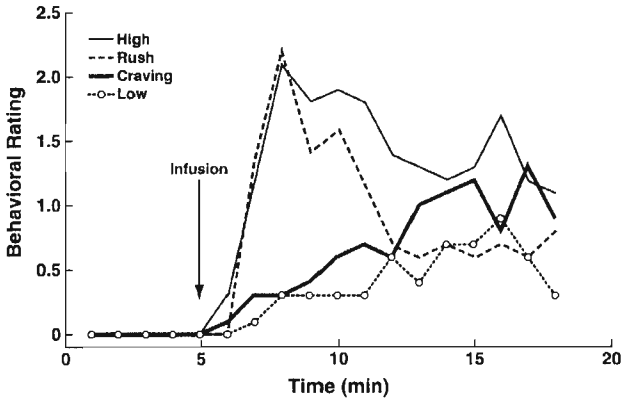

FIGURE 1.12 Average behavioral ratings after an infusion of cocaine (0.6 mg/kg over 30 s; $n = 9$). The rush, high, low, and craving ratings were averaged within each category for the subjects who had interpretable cocaine functional magnetic resonance imaging data after motion correction and behavioral ratings time-locked to the scanner. Both peak rush and peak high occurred 3 min post-infusion. Peak low (primary reports of dysphoria and paranoia) occurred 11 min post-infusion. Peak craving occurred 12 min post-infusion. No subject reported effects from the saline infusion on any of the four measures. Ratings obtained for rush, high, low, and craving measures were higher in subjects blinded to the 0.6 mg/kg cocaine dose compared to subjects unblinded to a 0.2 mg/kg cocaine dose. [Reproduced with permission from Breiter *et al.*, 1997.]

of cocaine show increases in cocaine self-administration from day to day in the long-access group (6 h; LgA) but not in the short-access group (1 h; ShA) (Ahmed and Koob, 1998; Deroche-Gamonet *et al.*, 2004; Mantsch *et al.*, 2004). The differential exposure to cocaine self-administration had dramatic effects on intracranial self-stimulation (ICSS) reward thresholds. ICSS thresholds progressively elevated for LgA rats, but not for ShA or control rats across successive self-administration sessions (Ahmed *et al.*, 2002) (see *Psychostimulants* chapter). Elevation in baseline ICSS thresholds temporally preceded and was highly correlated with escalation in cocaine intake. Post-session elevations in ICSS reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby deviating more and more from control levels. The progressive elevation in reward thresholds was associated with the dramatic escalation in cocaine consumption that was observed previously. After escalation had occurred, an acute cocaine challenge facilitated brain reward responsiveness to the same degree as before but resulted in higher absolute brain reward thresholds in LgA when compared to ShA rats.

With intravenous cocaine self-administration in animal models, such elevations in reward threshold begin rapidly and can be observed within a single session of self-administration (Kenny *et al.*, 2003) (**Fig. 1.13**), bearing a striking resemblance to human subjective reports. These results demonstrate that the elevation in brain reward thresholds following prolonged access to cocaine failed to return to baseline levels between repeated, prolonged exposure to cocaine self-administration (i.e., residual hysteresis), thus creating a greater and greater elevation in 'baseline' ICSS thresholds. These data provide compelling evidence for brain reward dysfunction in escalated cocaine self-administration that provide strong support for a hedonic allostasis model of drug addiction.

Allostasis and Neuroadaptation

More recently, opponent process theory has been expanded into the domains of the neurocircuitry and neurobiology of drug addiction from a physiological perspective. An allostatic model of the brain motivational systems has been proposed to explain the persistent changes in motivation that are associated with vulnerability to relapse in addiction, and this model may generalize to other psychopathology associated with dysregulated motivational systems. Allostasis from the addiction perspective has been defined as the process of maintaining apparent reward

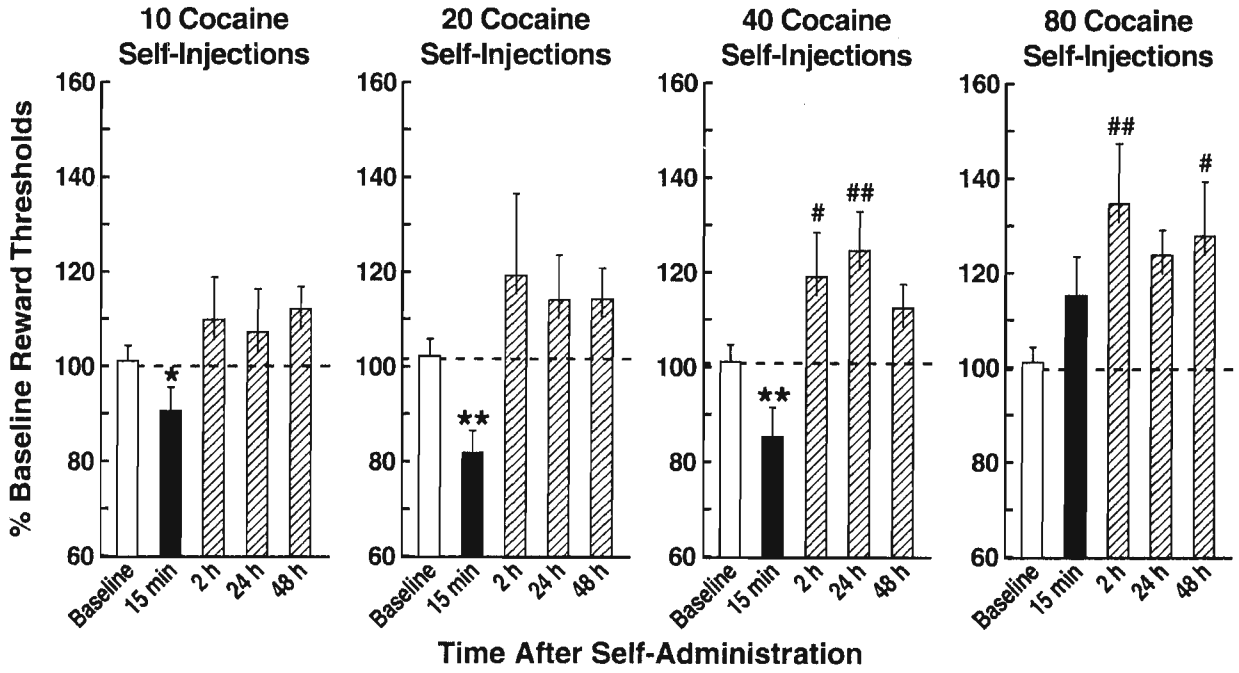

FIGURE 1.13 Rats (n = 11) were allowed to self-administer 10, 20, 40, and 80 injections of cocaine (0.25 mg per injection), and ICSS thresholds were measured 15 min and 2, 24, and 48 h after the end of each intravenous cocaine self-administration session. The horizontal dotted line in each plot represents 100% of baseline levels. All data are presented as mean + SEM percentage of baseline ICSS thresholds. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to baseline; paired t-test. $\#p < 0.05$, $\#\#p < 0.01$ compared to baseline; Fisher's LSD test after a statistically significant effect in the repeated-measures analysis of variance. [Reproduced with permission from Kenny *et al.*, 2003.]

function stability through changes in brain reward mechanisms (Koob and Le Moal, 2001). The allostatic state represents a chronic deviation of reward set point that often is *not* overtly observed while the individual is actively taking the drug. Thus, the allostatic view is that not only does the *b-process* get larger with repeated drug taking, but the reward set point from which the *a-process* and *b-process* are anchored gradually shifts downward creating an allostatic state (Koob and Le Moal, 2001) (**Fig. 1.14**).

The allostatic state is fueled not only by dysregulation of neurochemical elements of reward circuits per se, but also by the activation of brain and hormonal stress responses (see *Neurobiological Theories of Addiction* chapter). From the perspective of a given drug, it is unknown whether the hypothesized reward dysfunction is specific to that drug, common to all addictions, or a combination of both perspectives. However, from the data generated to date, and the established anatomical connections, the manifestation of this allostatic state as compulsive drug-taking and loss of control over drug-taking is hypothesized to be critically based on dysregulation of specific neurotransmitter function in the central division of the extended amygdala (a basal forebrain macrostructure comprised of the central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition area in the region of the shell of the nucleus accumbens) (Koob *et al.*, 1998) (see *Neurobiological Theories of Addiction* chapter). Decreases in the function of γ-aminobutyric acid, dopamine, serotonin, and opioid peptides, as well as dysregulation of brain stress systems such as corticotropin-releasing factor and neuropeptide Y are hypothesized to contribute to a shift in reward set point. Thus, a chronic elevation in reward thresholds as elaborated in Koob and Le Moal (2001) is viewed as a key element in the development of addiction and as setting up other sources of self-regulation failure and persistent vulnerability to relapse (protracted abstinence).

It is hypothesized further that the pathology of this neurocircuitry is the basis for the emotional dysfunction long associated with drug addiction and alcoholism in humans. Some of this neurocircuitry pathology persists into protracted abstinence, thereby providing a strong motivational basis for relapse. The view that drug addiction and alcoholism are the pathology that results from an allostatic mechanism that usurps the circuits established for natural rewards provides a realistic approach to identifying the

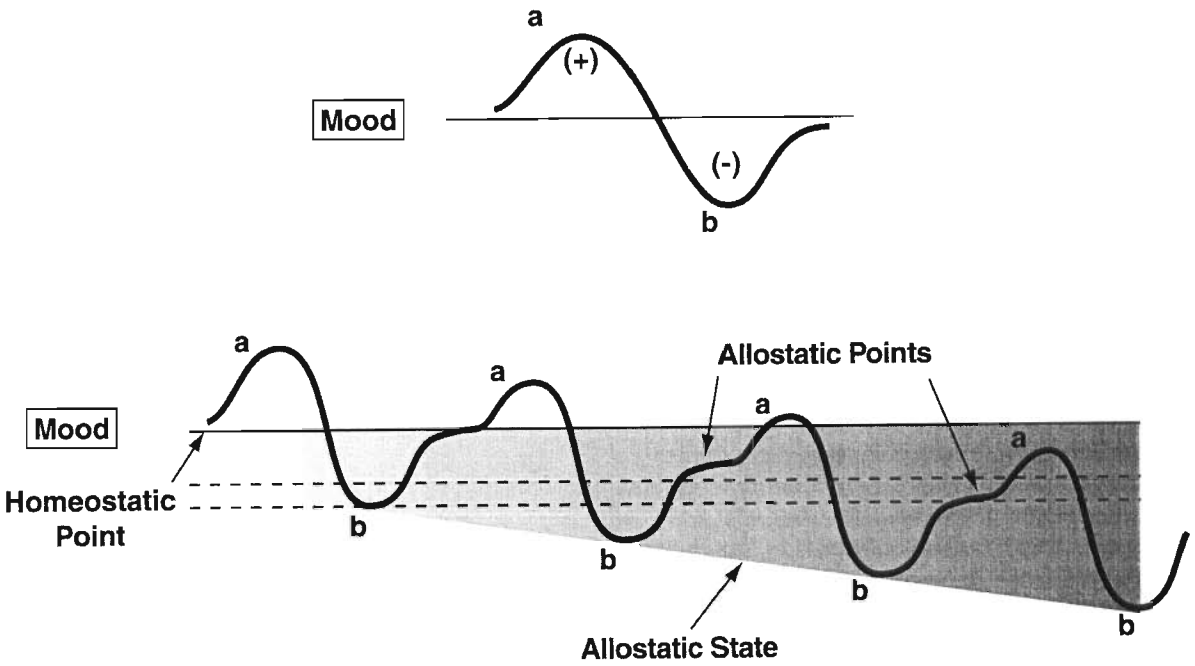

FIGURE 1.14 Diagram illustrating an extension of Solomon and Corbit's (1974) opponent-process model of motivation to outline the conceptual framework of the allostatic hypothesis. Both panels represent the affective response to the presentation of a drug. (Top) This diagram represents the initial experience of a drug with no prior drug history. The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be a sum of both an *a-process* and a *b-process*. An individual experiencing a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the *a-process*. In other words, an appropriate counteradaptive opponent process (*b-process*) that balances the activational process (*a-process*) does not lead to an allostatic state. (Bottom) The changes in the affective stimulus (state) in an individual with repeated frequent drug use that may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Note that the apparent *b-process* never returns to the original homeostatic level before drug-taking is reinitiated, thus creating a greater and greater allostatic state in the brain reward system. In other words, the counteradaptive opponent process (*b-process*) does not balance the activational process (*a-process*) but in fact shows a residual hysteresis. While these changes are exaggerated and condensed over time in the present conceptualization, the hypothesis here is that even during post-detoxification, a period of protracted abstinence, the reward system is still bearing allostatic changes. In the nondependent state, reward experiences are normal, and the brain stress systems are not greatly engaged. During the transition to the state known as addiction, the brain reward system is in a major underactivated state while the brain stress system is highly activated. The following definitions apply: *allostasis*, the process of achieving stability through change; *allostatic state*, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; *allostatic load*, the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases, pathological states and accumulation of damage. [Reproduced with permission from Koob and Le Moal, 2001.]

neurobiological factors that produce vulnerability to addiction and relapse.

The neurobiological view of drug addiction presented in this book represents a neuroadaptational perspective that is shared by most current neurobiological theories. Controversies exist, however, over the importance of the phenomenon of psychomotor sensitization associated with the mesolimbic dopamine system (see *Neurobiological Theories of Addiction* chapter). According to the psychomotor sensitization conceptual framework, the *wanting* and *liking* of drugs are separate phenomena with separate neurobiological substrates, and a shift in an incentive-salience state described as *wanting* was hypothesized to be progressively increased by repeated exposure to drugs of abuse (Robinson and Berridge, 1993). However, the allostatic-neuroadaptational position is that locomotor sensitization may play a role in initial sensitivity to a drug, but that it disappears or becomes irrelevant with the development of motivational dependence. Intertwined with the psychomotor sensitization hypothesis is a prominent or even critical role for dopamine in the motivational effects of drugs of abuse. The allostatic- neuroadaptational position is that dopamine has a role in addiction, particularly for psychomotor stimulants, but is not critical nor sufficient for the development of addiction to many drugs of abuse such as opiates, alcohol, phencyclidine, and others. An extension of the psychomotor sensitization and dopamine theories of addiction is the dismissal of drug withdrawal as a motivating factor in drug addiction. The allostatic-neuroadaptational position is that

drug withdrawal is largely misunderstood by the neurobiology of drug addiction research community. The focus should not be on *physical* withdrawal, which for the allostatic-neuroadaptational position is largely a marker for dependence, but rather on *motivational* withdrawal which allostatic-neuroadaptational hypotheses hold as one of the key elements of drug addiction (see *Drug Addiction: Transition from Neuroadaptation to Pathophysiology* chapter).

SUMMARY

This chapter defines addiction as a chronic relapsing disorder characterized by compulsive drug seeking, a loss of control in limiting intake, and emergence of a negative emotional state when access to the drug is prevented. The definition of addiction is derived from the evolution of the concept of dependence and the nosology of addiction diagnosis, and a distinction is made between drug use, drug abuse, and drug addiction. Addiction affects overall a large percentage of society, including illicit drugs, licit drugs, alcohol, and tobacco, and has with it enormous monetary costs. Addiction is further conceptualized as a condition that evolves, moving from impulsivity to compulsivity, and ultimately being comprised of three major stages: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation. Motivational, psychodynamic, social psychological, and vulnerability factors all contribute to the etiology of addiction, but the focus of the conceptualization for this book is placed on the neuroadaptational changes that occur during the addiction cycle. A theoretical framework is described that derives from early homeostatic theories and subsequent opponent process theories that provides a heuristic framework for understanding the neurobiology of addiction. This framework is followed in each subsequent major drug class, each covered by a separate chapter (*Psychostimulants, Opioids, Alcohol, Nicotine, and Cannabis*) and is tied together in the *Imaging, Neurobiological Theories of Addiction* and *Drug Addiction: Transition from Neuroadaptation to Pathophysiology* chapters.

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