Chronic Amphetamine Use and Abuse

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INTRODUCTION

The use of stimulant compounds has a long history. Chinese native physicians have been using the drug Ma-huang for more than 5000 years. In 1887, Nagai found the active agent in Ma-huang to be ephedrine. Amphetamine proper was first synthesized in 1887 by Edeleau as part of a systematic program to manufacture aliphatic amines. Early investigations of the properties of amphetamine focused on the peripheral effects and found that amphetamine was a sympathomimetic agent with bronchodilator properties. Oddly, the central nervous system actions were not reported until approximately 1933, and this was closely followed by the first reports of amphetamine abuse. Amphetamines produce feelings of euphoria and relief from fatigue, may improve performance on some simple tasks, increase activity levels, and produce anorexia. The abuse liability of the amphetamines is thought to be primarily related to their euphorigenic effects which leads to high-dose use and the final stage—compulsive abuse. The following sections discuss the basic and clinical research regarding the licit and illicit use of amphetamines and related stimulants.

AMPHETAMINE NEUROPHARMACOLOGY: EFFECTS ON DOPAMINE RELEASE

Several chapters in *The Fourth Generation of Progress* detail catecholamine neurobiology and there are recent reviews of amphetamine neuropharmacology by Kuczenski and Segal (127). Here we present a summary of the acute neuropharmacology and will provide more extensive coverage of the chronic amphetamine effects elsewhere.

Amphetamine has several interactive effects on catecholamine release. We will primarily focus on dopamine (DA) as an example. Amphetamine acts in at least three ways: 1) reversal of the DA uptake carrier, 2) interference with uptake into the DA vesicle, and 3) inhibition (at higher concentrations) of monoamine oxidase. The best known mechanism is binding of extracellular amphetamine to the uptake carrier and its transport into the terminal. It is subsequently dissociated into the cytoplasm, while the carrier binds cytosol DA with its transport out of the terminal (66, 169). More recently, a weak base model (208. 209) proposed that amphetamines, as weak bases, redistribute catecholamines from synaptic vesicles to the cytosol by collapsing the vesicle proton gradient that provides free energy for catechol accumulation. Even non-stimulant weak bases work in this model (208). The excess cytosol DA is thought to promote reverse transport of DA via the membrane transporter (i.e., release). Amphetamine-induced release of DA is accompanied by a decrease in DOPAC, an effect thought to be due to a reduction of monoamine oxidase activity by amphetamine. Direct assessment in vivo suggests that MAO inhibition occurs at relatively high amphetamine concentrations (84, 149).

STIMULANT TOXICITY

Neurotoxic Effects of Stimulant Drugs

Sustained high-dose administration of amphetamines (especially methamphetamine) to experimental animals produces a persistent depletion of DA which is associated with terminal degeneration (62, 182, 195), as well as neuronal chromatolysis in the brain stem, cortex and striatum (42, 182). In contrast, continuous dosing with extremely high doses of cocaine (100–250 mg/kg/day i.v.) did not induce terminal degeneration in frontal cortex and striatum (62, 183). Recently, Cubellis et al. (36) presented evidence that amphetamine, in contrast to cocaine, induces redistribution of DA from the vesicles into the cytosol; thus, the loss of the protection of the vesicles' relatively reducing environment results in cytosolic oxidative stress that may initiate amphetamine neurotoxicity. The DA depletion is reported to be permanent in the caudate of monkeys (196). The main hypotheses for underlying mechanisms have included 1) the conversion of DA into a hydroxy oxidative metabolite (195, 196); and 2) glutaminergic stimulation of toxicity, which can be inhibited by N-methyl-D-aspartate antagonist MK-801 (200).

Methamphetamine toxicity is inhibited by a variety of drug treatments, including: 1) DA synthesis inhibitor alpha-methyl-para-tyrosine; 2) DA receptor antagonists; 3) NMDA receptor antagonists, e.g., MK-801; 4) DA and serotonergic reuptake inhibitors protecting against DA and serotonin toxicity respectively (195). Even though most studies have found that serotonergic and DA reuptake inhibitors specifically protect these two sites, certain reuptake blockers (such as benztropine) do not (195). On the other hand, mazindol, a non-specific blocker, protects against both DA and serotonergic neurotoxicity. Ali et al. (1994) have further demonstrated in mice that a major factor for neurotoxicity is hyperthermia which is highly correlated with the degree of long-term DA depletion (21). Furthermore, haloperidol, diazepam and MK-801, all of which can reduce methamphetamine-induced hyperthermia, protect rats against DA depletion (4). They also demonstrated that reducing the ambient temperature (4°C) reduced neurotoxicity to the same levels found when phenobarbital, diazepam and MK-801 were present to protect the cell. Tolerance to methamphetamine induced by increasing doses also reduces the hyperthermic response and as well protects against neurotoxicity (89, 188).

An important caveat is that not all protective mechanisms act by preventing the hyperthermic effect; the monoamine uptake blockers inhibit neurotoxicity in the absence of inhibition of hyperthermia, e.g., fluoxetine blocks methamphetamine serotonin toxicity without reducing temperature (140). The monoamine protection from neurotoxicity by reuptake inhibition is emphasized by the unexpected discovery that even massive and 24-hour continuous dosing of cocaine, e.g., 100 mg/kg/day, does not result in DA system neurotoxicity (119, 182, 183). Hyperthermia has been well documented to increase amphetamine stereotypy (93, 220). Hyperthermia alone is well known to result in neuronal chromatolysis and has been previously proposed as a significant contributor to amphetamine-induced DA depletion and neuronal damage in clinical as well as experimental animal histopathology (52). Hyperthermia may have been one of the factors resulting in deaths among athletes taking moderate doses of amphetamine in the 1960s and 70s (145). Even in mild hyperthermia, increased body temperature induces a linear decrease in the inhibitory feedback of stimulants on somatodendritic autoreceptors (130). Thus, body temperature changes induced by amphetamine should be considered as one of the contributors to toxicity.

One of the hallmarks of amphetamine-induced neurotoxicity is the loss of DA uptake sites in the striatum and accumbens. These studies of transporters after chronic amphetamine have reported decreases in the range of 30–40% (158). Recently, Silvia et al. (198) addressed the functional significance of changes in transporters on amphetamine's behavioral effects. After seven days of infusion of transporter RNA antisense ODN into the SN/VTA nuclei, mazindol binding was reduced 32% in the caudate. Administration of 2 mg/kg of amphetamine at this time resulted in robust contralateral turning (an increase of 400%); in contrast, 10 mg/kg of cocaine induced no changes in the turning response. The lack of turning response to cocaine after transporter reduction contrasts with the substantial cocaine-induced contralateral turning after unilateral SN/VTA D_2 ODN to reduce D_2 autoreceptors in the striatum (199). Thus, the amphetamine-induced loss of

DA uptake sites could have two consequences: 1) a protective mechanism reducing further neurotoxicity, and 2) reverse tolerance to subsequent amphetamine administration, perhaps resulting in adverse symptoms such as paranoid psychosis (see also the discussion on neurotoxicity in the habenular interpeduncular track and its possible relationship to augmentation amphetamine-induced adverse effects).

Recently, Fleckenstein et al. (68) reported that methamphetamine induced a dose-response sensitive reduction in [^{3}H] DA uptake in washed striated synaptosomes which lasted for at least three hours; at 24 hrs the response had returned to normal. Since the decrease in intake was at maximum as early as 30 minutes after methamphetamine, this decrease in DA uptake is probably augmenting the amphetamine behavioral response and certainly not inducing tolerance. The decrease in DA uptake at doses up to 15 mg/kg could also provide some protection from neurotoxicity due to oxidative species.

These marked neurotoxic effects on the DA systems may underlie the mild Parkinson-like symptoms or "burned out" clinical picture in chronic, high-dose amphetamine abusers. These same individuals have a readily activated stimulant psychosis response. Similar re-activation of psychosis by L-dopa and direct agonists in Parkinson patients raises the question of whether the more severe psychosis resulting from amphetamine vs. cocaine abuse may have a partial basis in the greater toxicity induced by amphetamine.

Fatal Toxicity

Deaths directly attributable to the pharmacological response to amphetamines relate to several phenomena, including: 1) hypertensive cerebrovascular hemorrhage (confirmed pathologically); 2) cardiovascular collapse secondary to ventricular fibrillation (46, 154), with the majority of these cases in individuals less than 30 years of age with no evidence of pre-existing heart disease; 3) hyperpyrexia in the range of 40°C and 4) miscellaneous causes, such as septicemia with bacterial endocarditis or necrotizing angiitis (154). In general, acute fatal drug reactions to amphetamine are more common in the occasional user than in the tolerant, chronic, high-dose abuser. This is particularly true of the hyperthermic and convulsive cascade that precedes many fatalities. This may be related to the observation that experimental animals rapidly develop tolerance to the hyperthermic effects of amphetamine. Although hyperthermic conditions associated with convulsions are seen more frequently with amphetamine, convulsions are more frequent antecedents in acute toxicity from cocaine (76). In contrast to amphetamine, cocaine has the capacity to induce potentially toxic reactions in those tolerant to its use (76). These differences may be related to the differential local anesthetic potency, resulting in arrhythmias, convulsions, and depression of the medullary respiratory center. Although the exact interrelationship of hyperthermia, hypertensive crisis and convulsions, and the sequence of these events in the toxic cascade, is still unknown, both types of stimulants induce a similar fatality (154).

The multifactorial nature of stimulant toxicity requires careful control of experimental conditions in order to study the effects of these agents in the intact animal. When lethality is used as the dependent variable, this endpoint may result from different contributing factors based on the experimental design. For example, aggregation of rodents dramatically increases the toxic and lethal effects, based either on an increase in locomotor activity or hyperthermia (154). Although hyperpyrexia is often fatal to rodents treated with any pharmacological agent, temperature elevation observed in cocaine-treated animals (in contrast to amphetamine-treated ones) is usually not sufficiently high to completely explained the observed mortality. Thus, in experimental studies of toxicity, even in the absence of lethality, control over the acute convulsive as well as the hyperthermic effects of stimulants is a necessary prerequisite. Clearly, catecholamine release and activation of receptors are important in acute toxicity. This statement is supported by the observation that the mortality of amphetamine may be reduced by depletion of catecholamines or by receptor blockade.

CLINICAL USES OF STIMULANTS

Perspectives on Clinical Indications

Since amphetamine-like stimulants have high abuse potential and other adverse toxic consequences, why do we continue to use them? In the US, there are only two Food and Drug Administration (FDA) approved indications for dextroamphetamine and methylphenidate: 1) narcolepsy and 2) attention deficit hyperactivity disorder (ADHD). In Europe, some countries have prohibited any use of stimulants. However, most experts agree that in ADHD and narcolepsy, stimulants have an definitive and uncontroversial therapeutic role when used judiciously. Because of this agreement on specific therapeutic applications for these drugs, their use will not be reviewed here. Rather, we will discuss the use of stimulants for other problems, those for which stimulant administration may be somewhat more controversial.

Utilization of Stimulants as Anorectics

The initial effectiveness of stimulants as anorectics is well documented. In 1972, Scoville (191) found in a meta analysis of the data from 206 anorectic drug trials that these drugs were effective for weight loss at least out to 16 weeks of treatment. The problem with the utilization of anorectics, besides their abuse potential, is that only a small percentage of subjects maintain weight loss for one year after cessation of anorectics (206). Where possible, stimulants with lower abuse potential should be utilized. For example, fenfluramine and chlorpheniramine are amphetamine congeners that appear to work primarily on the serotonergic system without major psychostimulant effects (81).

Weintraub et al. (221) clearly demonstrated that, combined with behavioral therapy, sustained dosing of fenfluramine plus the amphetamine-type stimulant, phentermine (Fen-Phen), is effective in initiating and maintaining long-term weight loss. In a study extending beyond three years, fenfluramine (60 mg) and phentermine (15 mg/day) were remarkably effective, compared with placebo, in reducing weight and maintaining weight control, with a small incidence of side effects. (note: fenfluramine-induced pulmonary hypertension needs adequate monitoring. (1, 46) The response to these reports was an overly enthusiastic use of Fen-Phen for weight loss, despite the reported increased incidence of pulmonary hypertension (24). Based on evidence of an increased incidence of cardiac valve leaflet thickening, Fen-Phen has been withdrawn from the US market (33). Pulmonary hypertension following the use of cationic-amphiphilic anorexic drugs has a long history, beginning with the epidemic of aminorex-induced pulmonary hypertension in the 1970s (46). Cationic-amphiphilic drugs accumulate in lung and other tissues especially in cellular organelles with an internal acid pH such as lysosomes, where they bind to acidic enzymes. Lüllmann et al. (136) originally established the connection with lipid enzyme inhibition, lysosomal lipidosis and associated myeloidosis as key processes in the pathological cascade. Since several stimulants and other psychotropic drugs are cationic-amphiphilic compounds that accumulate in lung, brain and other tissues, the variety of pathological mechanisms involved with this group of drugs should be kept in mind with any long-term use of these compounds (94). With any clinical use of psychostimulants, careful history taking for previous drug misuse is warranted. Previous abusers of other stimulants should be obviously excluded from treatment.

Utilization of Stimulants in the Treatment of Atypical Depression and Dysthymic Disorder

One of the underlying symptom profiles that characterizes patients who respond to stimulants is anhedonia, lack of energy, easy fatigability, and low self-esteem. Examples include dysthymic disorder (12), "atypical depression" associated with medical illness [especially post-stroke depression] (185), and more recently HIV-related neuropsychiatric symptoms, including depression (8, 92). Frequently in these patients, the symptomatology is pervasively anergic and apathetic, without sadness, guilt, or more severe depressive mood. Thus, depressed, hospitalized cancer patients, and those with neurological disorders (especially post-stroke) or significant cardiac disorders, all often suffer from difficulties with anergia and easy fatigability and are candidates for stimulant treatment. These syndromes are all similar to the psychiatric diagnosis of atypical depressive mood disorders, which as Quitkin and colleagues (168) have demonstrated in a series of studies,

respond to either psychomotor stimulants or monoamine oxidase inhibitors rather than tricyclic antidepressants.

In psychiatric patients, Rickels et al. (171, 172), found that methylphenidate and pemoline mildly to moderately improved depressed individuals with target symptoms of fatigue, listlessness, apathy, and anorexia. Substantial positive response to methylphenidate has been noted in pathological fatigue or neurasthenia (31, 225). In many of these studies, a positive response was maintained over periods as long as several months. Chiarello & Cole (31) reviewed studies on the use of stimulants in withdrawn, apathetic geriatric patients and concluded that pure senile organic brain syndrome is not improved by stimulant treatment, but those who do not have prominent organic syndromes but were apathetic, mildly depressed, or poorly motivated, did improve significantly.

Willner (229) makes the case that a hypodopaminergic state underlies many of these dysthymic states. Questions are frequently raised as to whether one of the significant side effects of antidopaminergic neuroleptic therapy in schizophrenia is a form of depression. It is difficult to test this directly, but the evidence in normal volunteers indicates that neuroleptics induce feelings of dysphoria, paralysis of volition, and fatigue (17). Based on a series of reports in the 1950s, it was widely accepted that the DA and norepinephrine-depleting drug reserpine induced depression. (Note: the DA depletion from chronic-high dose amphetamine abuse and associated depression will be discussed later). However, Goodwin et al. (80) re-analyzed these data and demonstrated that reserpine-induced depression was a misdiagnosis. The actual syndrome was a ‘pseudodepression' characterized by psychomotor slowing, fatigue and anhedonia but lacking the cognitive features of depression such as hopelessness or guilt (this symptom constellation is similar to that of amphetamine withdrawal). Only 5–10% showed symptoms of major depression, and there was a strong possibility that these patients actually had a prior history of the illness. Similarly, Parkinsonism or pre-Parkinsonism depressions, which respond to treatment with DA agonists, are characterized by decreased motivation and drive but not by feelings of guilt, self-blame and worthlessness (26, 229).

BRIEF HISTORY AND EPIDEMIOLOGICAL ASPECTS OF AMPHETAMINE ABUSE

Amphetamine abuse has been present at least at low endemic levels ever since the introduction of these drugs in the 1930s (116). However, beginning in the 1950s and 60s, amphetamine epidemics appeared in Japan, Sweden, and the United States. Examination of these epidemics indicated that several factors were involved in their development: a) the introduction of large segments of the population to the use of amphetamines for medical, recreational, and anti-fatigue purposes; b) the widespread dissemination of knowledge regarding the amphetamine experience; c) the development of a core of chronic amphetamine users who established a stable illegal market; d) increasing use of rapid routes of administration (iv. and smoking); e) an initial oversupply of amphetamine that affected both the legal and illegal markets; and finally f) the subsequent development of clandestine laboratories for the production and distribution of amphetamine (52). The first amphetamine epidemic in Japan occurred when methamphetamine supplies left over after World War II (originally intended to combat fatigue during war production) became freely available to the general population (25). This epidemic was abruptly halted in a relatively short period of time with social and legal sanctions (153). A second and ongoing methamphetamine epidemic began in Japan in the early 1980s, based almost exclusively on the use of illicitly manufactured methamphetamine. Since then, minor to moderate amphetamine epidemics have occurred in several countries, including Sweden, the United Kingdom, and the United States (especially Hawaii and on the West coast). In the United States, the original epidemic began in the 1960s and was truncated abruptly in the early 1970s by absolute controls on the production of amphetamine, FDA scheduling of the drug and increases in the general knowledge of the potential dangers of amphetamine available both to the medical profession and the lay public. The re-emergence of widespread abuse in the United States, since the mid-80s, has often taken a new form in the guise of "ice," "crank" or

"crystal meth," which can be smoked like crack cocaine. Methamphetamine-related deaths have increased 2–3 fold, but these increases have been mostly limited to areas where supplies are readily available from clandestine laboratories (e.g., in San Francisco, Los Angeles, San Diego and Phoenix) [85]. On the West coast, particularly in San Francisco, methamphetamine abuse for enhancing sexual activity, often in a form of indiscriminate, excessive, bizarre sexual activity among male homosexuals, has led to concern for its substantial contribution to the spread of HIV infection. Another concern has been the significant percentage of truck drivers who have methamphetamine in their blood samples (35, 137). The incidence of traffic accidents or fatalities related to the extended use of amphetamines to the point of exhaustion or loss of mental flexibility and judgment is currently unknown.

STIMULANT ABUSE AND WITHDRAWAL

Definitions of Drug Abuse and Craving

In his textbook chapter on drug addiction and drug abuse, Jaffe, as early as 1980, attempted to define drug abuse without having to use the words ‘addictive' or ‘abuse' which he felt had been used in so many different ways that they had lost specificity (102). Thus, he defined addiction as ". . . a behavioral pattern of drug use characterized by overwhelming involvement with the use of the drug (compulsive use), the securing of the supply and high tendency to relapse after withdrawal." With the use of amphetamine and cocaine, Jaffe (102) states, "In terms of the compulsion to continue to use, the degree to which a drug pervades the life of the user and the tendency to relapse following withdrawal, some compulsive users of amphetamine are addicts." In describing intensity of dependence, Jaffe (101) describes the situation thus, ". . . the intensity of this ‘need' or dependence may vary from mild desire to a 'craving' or 'compulsion' to use the drug and when availability of the drug is uncertain individuals may exhibit a preoccupation with its procurement." Furthermore, Jaffe describes ". . . in its extreme form drug dependence is associated with compulsive drug using behavior and it exhibits the characteristic of a chronic relapsing disorder (45)."

More recently, the term compulsive drug use has given way to a greater utilization of the term craving, which is used to describe both the intense desire for the drug during the period of a drug run or binge as well as the thoughts or urges related to the desire for the drug after complete withdrawal. The two uses of craving appear to be used interchangeably, yet they may be phenomenologically quite different. Craving in the anergic abuser in withdrawal is described more as a memory-triggered conditioned response to appropriate environmental or internal cues, not unlike the desire for water or liquids for an extremely thirsty individual. On the other hand, the craving described during a stimulant binge has the so-called compulsive features of repeated utilization in the face of dramatic tolerance or reduction in the reinforcing properties of the drug, and even the advent of adverse effects. Cocaine is repeatedly administered every 10–30 minutes while, with amphetamines, the interval is moderately longer. The compulsive utilization of stimulants is usually not seen in the early to middle stages of abuse. This abuse pattern develops during the transition to high-dose binges and has an intense, repetitious, stereotyped quality to it, not unlike the compulsive self-administration behaviors in experimental animals given free access to stimulants.

The concept of craving has evolved primarily out of observations with alcohol, where physical dependence is a major factor (105, 142). As Pert et al. (163) has pointed out, more recently incentive motivational concepts have gained prominence as the substrates of stimulant craving (141, 176). Alternatively, stimulant craving is viewed as deficits of an aversive state in withdrawal (i.e., negative reinforcing effects, anergia, dysphoria, and anhedonia) (73, 125). Other researchers have emphasized the incentive motivation mechanisms in the addiction process (141, 176, 223). Incentive motivation is described as the secondary reinforcing properties of stimuli when they follow a specific behavior and which enables them to facilitate and augment performance of the behavior (163). When such stimuli appear prior to a particular behavior, their incentive

motivation properties appear to energize and facilitate the initiation of behavior. Pert (163) makes the point that incentive motivation properties are not initiated until the pharmacological effect is experienced, but later these properties are then conferred to the environmental stimuli associated with the drug. Beginning with Tatum and Seevers (212), many researchers observed that experimental animals developed increased activity, excitement, and eagerness in the presence of situational cues associated with cocaine (163). With amphetamine withdrawal in humans, there is another dimension to reactivation of abuse. When the anergic dysphoric abuser, or even the abuser in long-term withdrawal, attempts to engage in the activities that were once stimulant-associated (e.g., repetitious drawing, hypersexual activity), he no longer experiences the compulsive pleasure. Thus, stimulant-associated activity without its arousal and emotional charge becomes a trigger for relapse.

The Natural History of Stimulant Abuse: Transition from Occasional to Compulsive Abuse

In the 1960s, when amphetamine was used freely for weight loss, only a small percentage of users developed abuse problems. What is the process leading to abuse in either patients or recreational users? In general, stimulants increase alertness, the sense of well-being, and the pleasurable reinforcement experienced with many activities. Early in stimulant use, low-doses often induce positive responses from others to the user's energy, enthusiasm, and productivity complimenting the drug-induced moderate euphoria. Unfortunately, certain individuals, in an effort to intensify the pharmacological euphoria and overcome tolerance, began utilizing larger and larger doses.

With repeated use and higher doses, an increasing search for the intense euphoric sensations ensues. The repeated pursuit of this intense euphoria results in a very stereotyped, repetitive activity centered around drug use and excluding other social activities (27, 74). Abusers often state that the shift to compulsive use begins when access to the drug increases, the doses escalate markedly, or when they switch to more rapid routes of administration (e.g., intravenous or smoking) [107]. Eventually, the pursuit of this high-dose euphoria results in a progression to high-dose binges lasting for days, followed by exhaustion and withdrawal dysphoria (126). This shift into binge-pattern abuse is referred to as the high-intensity transition to compulsive abuse by Gawin and Ellinwood (74).

Humans, like experimental animals, develop stereotyped patterns of self-administration, as well as the patterns of behavior leading up to the acquisition and administration of drugs (49). In fact, Brady et al. (23) and Rosse et al. (180) have described stereotyped compulsive foraging for cocaine (e.g., repetitious stereotyped picking through the pile of a carpet or inspecting the furniture, tracing paths) in more than half of their chronic users. It is well known that in a wide variety of species, stimulants induce stereotyped searching, foraging, and even stalking behavior characteristic of the particular species (53); these properties of stimulants are discussed below in more detail. Apparently, variations of these behaviors in humans become directed toward stimulant acquisition when supplies are sparse.

Stimulant Bingeing and Withdrawal

Another component of the binge pattern of amphetamine abuse is the withdrawal symptoms, which may last for as much as 1–2 weeks. Because of sleep deprivation, the individual usually has prolonged hypersomnia, followed by a period of atypical depression. Careful clinical observation has identified a stimulant withdrawal syndrome of depression, lassitude, lethargy, loss of mental energy, interpersonal withdrawal, and even suicide (32, 49, 74, 154). The stimulant withdrawal state of depression or fatigue has been reported many times beginning with the description of the "cocaine blues" at the turn of the century (75). Because cocaine supplies are expensive, and cocaine is very short-acting, perhaps the majority of current abusers cannot sustain a binge over the day or more necessary for the classical withdrawal. This is not the case for the longer acting amphetamines in geographical areas where they are readily accessible. This depressive withdrawal effect is highly dependent not only on individual susceptibility, but also on the duration and the doses of amphetamine

used during the period prior to withdrawal. Many clinicians think that the depression during this period is related to the reports of large and persistent reductions in DA, as well as serotonin, found in animals following chronic treatment with high doses of methamphetamine (See section on neurotoxicity mechanisms) [11, 74, 196, 231]. Methamphetamine is much more neurotoxic to DA and serotonin neurons than cocaine (119). These conclusions are underscored by the hypothesis that DA and serotonin hypofunction plays a significant role in certain depressions (44, 139, 166).

Predisposing Factors to Withdrawal Dysphoria

Are there predisposing factors facilitating the anergic withdrawal syndrome in some individuals? Rounsaville et al. (181) reported that the lifetime rate of major depression diagnosis in cocaine abusers rose from 30.5% to 58.7% when depressive episodes occurring during the period of cocaine withdrawal were no longer excluded. In other words, if cocaine abusers were rated within a 10-day period of withdrawal, they espoused a lifetime history consistent with major depression 58.7% of the time. However, if they were assessed after the withdrawal period, the rate of diagnosis fell to 30.5%, indicating that the depressive or anergic symptomatology during the withdrawal had a strong influence on the lifetime diagnosis based on the history in these patients (average age 27 years) (179). In addition, there was a high rate of current affective disorder (44.3%), although the authors report that this rate was mostly accounted for by chronic mood disorders such as dysthymia. The other major feature of the Rounsaville study was that 35% of the individuals involved had a lifetime history of childhood attention deficit disorder, indicating that judicious therapeutic use of stimulants might be effective in such a group.

Human Stimulant Bingeing: Craving, Compulsion, or Anergia Relief?

Recently, Grant et al. (82) demonstrated that strong stimulant cues induced regional increases in glucose utilization in dorsolateral prefrontal cortex, medial temporal lobe and cerebellum measured by positron emission tomography (PET). All of these areas have well documented relationships to memory mechanisms. Glucose utilization was significantly correlated to the intensity of craving. This response to cue-induced cocaine craving is highlighted by the chronic hypometabolism of glucose, which lasts at least 3–4 months after withdrawal from cocaine (216). In these PET studies, global glucose metabolism was unchanged from control levels, but 16 of the 21 left frontal regions and 8 of the 21 right frontal regions had significant lower metabolic activity. These changes were significantly correlated with years of use and the severity of cocaine abuse. These two studies highlight the considerable evidence for two quite different concepts of withdrawal-related relapse: 1) a memory-related sensitization to responses activated by incentive-motivation and 2) withdrawal-induced anergia and loss of the normal repertoire of motivated behaviors. More likely, both interact to spur relapse (71, 176).

Elucidation of the Hypodopaminergic State: An Analysis of Parkinsonism

Parkinson's disease represents a hypodopaminergic syndrome with cognitive-neuromotor effects that resemble some of the more marginal effects of stimulant withdrawal. The latter effects may be characterized by a hypodopaminergic state. One of the more remarkable changes in Parkinsonism is the loss of executive function, which refers to a group of cognitive skills involved in the initiation, planning, and monitoring of goal-directed behaviors (132). These functions include the ability to: 1) establish and maintain set, shift from one set to another, formulate concepts and reason abstractly; 2) use feedback to monitor behavior, program sequential motor activities; 3) develop strategies to learn and copy complex figures; and 4) exert emotional self-control and maintain socially appropriate behaviors (144). Tests such as the Wisconsin Card Sorting Test (WCST), a task of concept formation and set shifting ability are impaired in Parkinsonism even when psychomotor speed is factored out (144). The executive functions revolving around verbal capacity are not consistently impaired. Visuospatial skills have been the most frequently reported cognitive disturbance (26). Such studies have found that Parkinson patients exhibited deficits in visual analysis and synthesis (e.g.,

imbedded figure task, visual discrimination and matching and pattern completion, constructional praxis) even when the speed component was eliminated (144). Even patients in the early stages of Parkinsonism, before treatment is initiated, have psychomotor slowing, loss of cognitive flexibility and mild reductions in learning and recall (128). If the case can be made that the stimulant withdrawal hypodopaminergic state results in similar mild defects, these changes in the executive functions of monitoring behavior, executing plans, etc. could contribute to the lack of therapeutic engagement and accomplishment noted with many of these patients.

Treatment of Amphetamine Withdrawal with Tricyclic Antidepressants

Symptomatology such as anergia, anhedonia, and apathetic responsiveness have been described as the "cocaine blues" since the turn of the century (75) and more recently for amphetamine (49). In chronic high-dose cocaine (75) or amphetamine abuse (49), energy and euphoria induced by active drug administration is replaced in withdrawal by rebound dysphoric and anergic symptoms that appear to occur whether or not the stimulant abuser meets the diagnostic criteria for a mood disorder (74). This has, in the past, provided the rationale for treatment with tricyclic antidepressants in reducing stimulant "craving" and during the initial phases of abstinence (70); the use of psychomotor stimulants or MAOIs has been avoided because of potentially severe side effects in this patient population.

Gawin et al. (72, 157) reviewed the double-blind studies on the use of tricyclic antidepressants in cocaine abusers. In summary, there as number of positive studies showing a reduction in cocaine use and self-reported craving. These have to be weighed against the negative studies, such as that of Weddington et al. (219). The comparison between positive and negative studies is hampered by lack of information on the type of abuse (e.g., intermittent vs. bingeing abuse) and severity of withdrawal response. Double-blind studies with amphetamine abuse are yet to be published. Gawin et al. (personal communication) have preliminary data of reduced amphetamine use and greater control over craving from a half-sample analysis. Galloway et al. (69) treated 32 amphetamine abusers with either 10 mg/day (controls) or 150 mg/day of imipramine for 180 days. The primary outcome variable, retention in treatment, for the high-dose imipramine group was three times that of the low-dose placebo. However, there were no consistent differences in positive urine samples, Beck Depression Inventory, or craving. Their hypothesis was based on the fact that retention in treatment would provide a basis for engaging the individuals in long-term rehabilitation.

Basic Research Consistent with the Hypothesis that Tricyclic Antidepressant Treatment in the Amphetamine Withdrawal Syndrome Would Be Useful

Recently, Tanda et al. (210) have demonstrated that chronic desipramine treatment increased extracellular norepinephrine and DA by three-fold. In contrast, chronic fluoxetine doubled the extracellular concentrations of serotonin but failed to change the extracellular levels of dopamine, thus indicating a degree of specificity for this tricyclic effect. Kokkinidis and McCarter (121) demonstrated that chronic amphetamine treatment reduced self-stimulation in the substantia nigra following withdrawal. This group had previously demonstrated that amphetamine itself increased self-stimulation in the substantia nigra following an amphetamine injection (122). The post-withdrawal decrease in self-stimulation was restored with amitriptyline, a tricyclic antidepressant (122). Together, these studies showed that tricyclic antidepressants may restore DA function and the reinforcing effects of self-stimulation.

Underlying Distinguishing Features of Atypical vs. Endogenous Depression

Klein (120) makes an interesting argument that there are two main hedonic systems in both humans and lower animals: 1) a series of activities such as foraging, hunting, searching, other pursuit activities and socializing, which generate positive feedback loops and 2) consummatory behaviors such as sexual orgasm, eating, drinking and perhaps sleep, which generate a negative feedback loop, turning off further activity.

Klein (120) indicates that many of the feed-forward, pursuit-acquisition behaviors are sublimated in humans and expressed as the pleasures one might get from sports including running, jogging and other types of play activities, which he sees as a mock hunting activity. The author makes the obvious connection that endogenously depressed patients have decreased consummatory pleasure, whereas dysthymic or atypical depression patients have a loss of energy and interest in pursuit-searching pleasures, yet have an intact consummatory pleasure response. Indeed, the group defined by Quitkin et al. (168) as definite atypical have a weighting of the following symptoms: hyperphagia, hypersomnolence, reversed diurnal variation, and a leaden muscle feeling.

Hyperphagia and hypersomnolence are features of amphetamine withdrawal, along with the loss of energy and pursuit pleasures. Klein (120) points out that the atypical depressed patients respond to amphetamine and to monoamine oxidase inhibitors (including deprenyl) and have only a partial response to tricyclic antidepressants. In contrast, endogenously depressed patients have little, if any, continuing positive response to stimulants but do respond to tricyclic antidepressants. Nunes et al. (157) reported that some subgroups of 113 cocaine abusers had a significant response to imipramine (decreased craving, cocaine euphoria, depression, and, to a lesser extent, cocaine use), with other subgroups having no response. Unfortunately, an MAOI treatment group was not included for comparison. In summary, subtyping of stimulant abusers may, in the future, provide for more selective drug treatment for the earlier phases of stimulant withdrawal in a manner similar to the current treatment of depression.

STIMULANT PSYCHOSIS

The psychosis induced by amphetamine was first reported in 1938 by Young and Scoville, who originally considered it rare. It was only after World War II that large numbers of cases of amphetamine psychosis were summarized by Connell (32). In the 1950s and 60s, the availability of amphetamines and amphetamine-like compounds led to a large number of individuals being initiated into the stimulant and euphoriant effects of amphetamine. This resulted in the subsequent amphetamine addiction epidemics and attendant psychopathology that reached its peak in the 1960s (10, 25, 52, 60, 86, 126, 211).

During the same two decades, the increasing awareness of stimulant-induced psychosis and the advent of DA antagonist neuroleptics provided the twin origins of the DA hypothesis of schizophrenia. Not only has amphetamine psychosis been reported on extensively from case histories, but it has also been studied prospectively under experimental conditions. As Angrist (7) has pointed out, each type of study has strengths and weaknesses. The strengths of the case history are that description of developmental sequences of the psychosis can be obtained from the patient and family, providing insight into the ontogeny of the process. Their weakness is that the premorbid psychiatric status is sometimes not known, and the reported stimulant use history can be unreliable. The experimentally induced studies involved administering amphetamine to individuals under laboratory conditions, where dose and responses are accurately documented. For ethical reasons, these studies, with few exceptions, have been done in experienced abusers. Thus, the prior history of "sensitization" or "tolerance" induced by the previous chronic history of abuse has to be considered (7).

Basic Characteristics

Two distinct clinical thought disorders may be encountered with amphetamine abuse. The term "amphetamine psychosis" should be reserved for the non-confusional paranoid psychosis induced by chronic repeated intoxication. It should not be used to describe the acute clinical picture dominated by delirium and confusion followed by acute administration of very large doses of central stimulants (32, 108). The picture of the chronic non-confusional state has many corresponding symptom profiles which parallel schizophrenia and may not be without a drug history or toxicology, easily distinguishable from the latter. Hallucinations are

frequently described in chronic amphetamine abusers; the incidence is upwards of 81% (32) and 83% (108). Visual hallucinations are seen most frequently, with auditory hallucinations being slightly less common. Paranoid ideation, fears of persecution, hyperactivity and panic are accepted as prominent hallmarks of central stimulant psychosis (32, 60, 103, 108). Following stimulant withdrawal, these patients become gradually cognizant of the delusional quality of their psychoses. However, on re-administration of the drug, the sense of persecution and imminent danger readily returns, and the patient no longer recognizes these feelings as delusions. Often the paranoid phenomena are associated with police and are referred to as the "bull-horrors." Eventually, they becomes accepted as a way of life with those dealing in illegal stimulants.

Dopamine in Stimulant Psychosis

The persistent, sustained increase in the sensitivity to the psychosis-inducing properties of stimulants suggests that chronic consumption of central stimulants induces a permanent alteration in the functional organization of the central nervous system, especially dopaminergic systems. This hypothesis has been presented in reference to amphetamines (111, 117) and indeed similar considerations have been raised for cocaine (167, 205). Arguments for the DA nature of these chronic effects come from studies on L-dopa treatment, which is more easily studied clinically in a prospective manner. In general, psychomotor disturbances are rare in the early phases of L-dopa treatment of Parkinsonism but become increasingly frequent as treatment is continued (117). After two years of treatment, the incidence of such side effects rises to nearly 70% (118). It has also been noted that these side effects (relative to individual doses of L-dopa) tend to increase with chronic administration, such that lower doses are required to elicit psychosis and dyskinesia (117). Thus, a long-lasting hypersensitivity appears to develop, not only to central stimulants but also to L-dopa, such that previously well tolerated doses may later come to induce toxic symptoms.

Stereotypies in Stimulant Psychosis

Integral with the altered behavioral and thinking patterns of chronic abusers are the complex stereotypies referred to as ‘punding' (in Swedish), ‘pung-huvud,' or ‘block-head' (187), ‘knick knacking' or ‘hung-up' (56, 154), which may assume diverse forms. Basally these are small behavioral fragments which are purposefully directed and can be easily be a part of normal daily behavior. However, similar to behaviors in experimental animals, the activity gradually becomes non-goal-directed, socially meaningless, and continually repeated in an often ritualized manner (154). For example, a chronic amphetamine abuser in San Francisco who supported his habit by soliciting money in the streets developed an increasingly stereotyped acquisition behavior. His behavior became ritualized to the point that the subject would no longer wait to receive the monetary reward. Instead, he would spend days walking rapidly from person to person monotonously, asking for loose change but never interacting further with those he encountered. Many other variants of repetitive behavior occur, including disassembly of small machines, repetitious visual analysis, (e.g., puzzles), meaningless listings of automobile license numbers, and repetitive cleaning tasks or sexual acts (60, 126, 187). These repetitious behaviors may include examining, sorting, obsessing over mental puzzles or games, repetitious pattern drawing and drafting (60, 126, 187). The similarity of these repetitious behaviors to the stereotyped behaviors and thinking of chronic schizophrenics is discussed below (20, 203).

Overvalued repetitious behaviors also involve groups of abusers. In the 1960s, certain areas such as Greenwich Village in New York and Haight Ashbury area in San Francisco became the local cultural centers of amphetamine abuse and produced some very interesting crazes. One craze in Greenwich Village was for collecting stones> This illustrates two points: 1) amphetamine-induced hypercathexis of certain objects and 2) the foraging and hoarding behavior associated with this activity. The craze began with one amphetamine abuser obsessively searching parks and elsewhere for stones which he perceived as gems, but he was laughed at by his fellow amphetamine abusers. Later, others became curious and joined in the foraging behavior. Soon some 50 or more people joined in for a three-year period, engaging in the quest for stones which had some magical or at least mystical quality. Stones were hoarded, stolen from one another, bartered along with the

incessant foraging for these objects (65).

Experimental Administration of Amphetamine to Schizophrenics

Lieberman et al. (134) reported that even small doses of stimulants that are subpsychotogenic in non-schizophrenic subjects can provoke psychotic symptoms in schizophrenics, i.e., schizophrenics are supersensitive to stimulants. The phenomenon is described as being state-dependent, occurring mainly during the active, or unstable, stages of the illness (104, 134). That not all schizophrenics respond and only at certain stages of their illnesses thought by Lieberman et al. to reflect the pathological heterogeneity of the illness (134). The more severe psychotic responses include motor symptoms that may be manifest as wildly bizarre and disorganized behavior, catatonia, intense stereotypies, and perseverative self-stimulating behaviors, in addition to the more commonly described affective, cognitive and perceptual disturbances (134). Lieberman et al. (134) further comments that the frequently observed impact of chronic stimulant abuse on schizophrenic pathophysiology has not been well studied and is largely unknown.

Other Amphetamine-induced Psychopathologies

By far, the best documented psychopathological response to chronic amphetamine stimulants is a paranoid schizophrenia-like psychosis in a setting of clear consciousness, in which formal aspects of thought were relatively intact but delusions and hallucinations evoked intense emotions, including intense fear (7, 16, 32, 60, 234). However, as Angrist (7) has outlined, there are several other non-paranoid presentations, including: 1) confusional states, often high-dose delirium in individuals not tolerant to the stimulants; 2) emotional lability syndromes, characterized by a confused, bizarre emotional responsivity (in certain individuals, it takes on the characteristics of a manic episode); 3) bizarre sexual behavior involving autoerotic behavior but also groups of individuals; 4) destructive outbursts that have no readily recognizable provocation; and 5) unmotivated assaults that frequently take the form of repetitive assaultive behavior (described as fugue-like responses). The latter can lead to homicide (58). Thus, although the amphetamine psychosis is usually a fairly distinct syndrome, with the incidence of symptoms having a fair correspondence across various studies, there is marked individual variability. The incidence of other types of psychopathology highlights a similarity with chronic syphilis, in that it can mimic any number of neuropsychiatric disorders (49).

The psychopathology associated with stimulant abuse can take on several forms. Delirium or an organic-like delusional mood can be manifest in individuals who have either taken large doses of amphetamine or in whom the dosing has been repeated over one or two days. The paranoid ideation and hallucinations in these individuals tend to be unorganized, in contrast to the more systematic organized delusions found in cases of chronic amphetamine psychosis. Despite these generalizations, psychotic responses have been reported, although infrequently, after low doses of amphetamine in susceptible individuals (7).

Contribution of Dose and Duration Escalation, Sensitization, and Tolerance to Psychosis

In case studies as well as the experimental studies, the issues of sensitization, tolerance, dose and dose-duration escalation are important for several reasons. Amphetamine psychosis has been induced in experimental studies of amphetamine abusers by doses smaller than those that were originally involved in its gradual development (16, 186). In case studies, Kramer (126), Ellinwood (60) and Ellinwood and Petrie (49) demonstrated that, once an individual has experienced amphetamine paranoia, it readily reappears at lower doses or earlier in a drug run. In the 1991 study by Satel et al. (184), three-fourths of the stimulant abusers who became paranoid said these experiences clearly worsened with continued drug use, and most described a more rapid onset. Similar results were reported by Brady et al. (23). Bartlett and colleagues (15) also described increasing suspiciousness and paranoia but not increased euphoria with repeated cocaine use. In addition to the psychosis being induced by lower doses over time, even stress has been described as capable of inducing psychosis in some patients (186, 214). Sato's case report (186) describes an individual who had

stress-related psychotic behavior even though both he and his wife denied any recent stimulant use by him. Angrist (7) has cogently questioned whether such data can be adequately assessed without some laboratory evidence of the absence of drug use.

Duration of Amphetamine-induced Psychosis

In the post World War II amphetamine epidemic in Japan, Tatetsu (211) noted that a substantial percentage of patients stayed in the hospital because of symptoms extending out beyond a year. He also compared the incidence of schizophrenia in parents and siblings of methamphetamine psychotics, schizophrenics and the general population. Patients with methamphetamine psychosis had a higher incidence of schizophrenia in first-degree relatives than did the general population, but lower than that found in schizophrenics. Both Connell (32) and Bell (16) concluded that uncomplicated amphetamine psychosis cleared rapidly unless subsequent drug utilization ensued, with the exception of schizophrenic patients (16, 32). Iwanami (97) more recently has described 16% of 104 patients with persistent psychotic behavior long after methamphetamine and/or the metabolites had been eliminated from the body. Similarly, another large scale study of 132 methamphetamine-abusing psychiatric patients reported that 28% were hospitalized for over 61 days (152). As Angrist (7) has noted, western investigators have not seen prolonged psychoses with anything near the incidence or duration described by the Japanese. When psychosis was present, most investigators questioned whether latent schizophrenia or actual schizophrenia was involved.

One of the difficulties in assessing the differences between the Japanese experience and the Western experience is that most often an exact description of the persistent psychosis on an individual basis is lacking. When psychosis is induced over longer-term chronic abuse, many patients reported a gradual waxing and waning of their thoughts about their delusional experiences after withdrawal. Some ‘non-psychotic' patients will describe that even 2–3 months after cessation of amphetamine use, "they know that it sounds crazy, that they believe that certain delusional events took place, because it feels like it happened. " Gradually the persistence of the feeling loses any intensity, and the thought itself eventually fades, only to be reactivated by subsequent stimulant dosing. Occasionally, patients who have committed homicide or other drastic actions under the influence of amphetamine delusions will have a more persistent belief that certain psychotic events were ‘real' (58). Thus, subsequent reports of persistent psychotic states would be helped considerably by a description of the type of persistent psychotic symptoms observed. The descriptions might include the type of delusion, e.g., a chronic well-organized delusion, whether there is an indication of pre-existing psychopathology or whether there are environmental contingencies that nurture the continuation of the delusion. For example, if the stimulant abuser is both purchasing as well as selling in the violent drug marketplace and is under potential surveillance by police, it is easy to understand how environmental contingencies may be involved either in sustaining or reactivating paranoid delusional tendencies.

Psychosis and the Role of Stereotypies

In order to understand the development of stimulant psychosis, it is important to examine the pharmacologically induced matrix out of which the residual psychosis evolves. Simply listing symptoms or diagnosis and describing current manifestations of the final psychosis stage or providing surveys of clinicians does not describe the early initiating events and their contribution to the final symptoms. A common phenomenon across all species following moderately high doses of amphetamine is the development of patterns of locomotor exploration, searching and examining at least the motor components of these attending processes. Over time, and/or with increasing doses, these behaviors become increasingly fixed and stereotyped. In humans, one notes this increase not only in stereotyped perceptual motor patterns but also in stereotyped thinking, which involves intense curiosity, searching behavior, and eventually intense suspiciousness (53). Later in the evolution of psychosis, the development of a delusional mood, with objects and environment taking on heightened meaning and significance, leads to delusional misinterpretation. Over time, these delusions become more organized and are elaborated with secondary explanatory delusions not

unlike those of young schizophrenics. In experimental animals, one can observe extremely constricted even bizarre stereotyped behaviors which, like the human stereotyped delusional thinking condition, have gradually evolved with chronic dosing.

Not infrequently, one notes pincer grasp-like cleaning activities such as repetitiously cleaning the mortar cracks in bathroom tiles with toothpicks; cleaning dust from phonograph records grooves with a needle; or painting walls, ceilings and floors with small dots of paint throughout a household. These activities in high-dose stimulant abusers could consume most of the day. In humans, the probing forefinger and pincer grasp is also directed (‘in grooming behaviors') at raised follicles or small irregularities in the skin, resulting in numerous punctuate lesions and scars. The associated cognitive manifestation of this stereotype attitude is the development of delusions of parasitosis. The suspected organism is found not only in the skin, but also in clothes and furniture, all of which undergo detailed examination with magnifying glass or microscope. This pattern of behavior reveals the same attitudinal persistence across different behavioral stereotypies. Paranoid delusions can also ensue from this type of stereotyped attitude, in that the individual examines minute details in the environment to elucidate the underlying nature of their suspiciousness or delusion. For example, one woman examined all of the news periodicals coming into the household to look for secret codes in the period marks behind sentences and discovered secret messages that her paramour was receiving from another girlfriend (60).

Stimulant Sensitization and Tolerance

The biological substrates of these progressive conditions have most often been ascribed to tolerance and/or sensitization. Tolerance is most strongly reflected by the fact that both lower animals and humans can sustain even lethal doses of amphetamine after chronic administration. Sensitization reflects the phenomenon that even though a high dose may have been necessary to induce end-stage behavioral pathology, moderate doses given over a shorter duration are able to activate the behavioral pathology. Both tolerance and sensitization are ‘black box' phenomena for which the initiating, maintaining, and reactivation mechanisms are only partially understood and at times are controversial in the literature. Even the concept of sensitization vs. tolerance and their contribution to the end-stage behaviors continue to be debated. Because sensitization can be induced by much lower doses of stimulants, some have argued that the initiation of stimulant abuse patterns is based more on an early stage of sensitization-like augmentation of conditioned behaviors, whereas the chronic evolution of psychosis more often also requires tolerance-inducing sustained high doses of amphetamine. (74, 134). Lieberman et al. (134) make the case for a tolerance/neurotoxic effects that would explain both the psychosis as well as the withdrawal burnout condition of former ‘speed freaks' (10, Utena et al., 1975). The burnout stage is described similarly to the defect state noted in schizophrenia and would appear to be more of a neurotoxic effect than tolerance. The mechanisms underlying tolerance and sensitization will be discussed below.

The Relationship of Chronic Stimulant-induced Behavior in Animals to the Development of Psychosis in Humans

In animals models, even after 2–3 moderately high doses of amphetamine, there is an evolution of a specific behavioral sequence, or series of sequences, that pervades the stimulant-induced state. With chronic, single-dose daily administration of a stimulant, this behavior gradually develops into an extremely intense, constricted behavioral pattern. The behavior may take the form of a stereotypy with bizarre postural dysjunction between body movements. The behavior frequently is highly specific for a directed attitude and behavior towards a specific area of the experimental chamber (not often emphasized in the literature on behavioral stereotypies). There is a perseverative attitude by the animal. In fact, the attitude may be constant even though the motor performance changes over time, e.g., a dog given amphetamine in an open space might continue to follow another dog despite many intervening obstacles in which he has to jump, dodge, speed up or slow down to continue the persistent attitudinal activity of following (see Video 1of following

dog). In higher animals (e.g., cats, dogs and monkeys), persistent attitude change is often more prominent than motor stereotypy. In higher animals, the two most prominent attitudes are: 1) an abnormally intense investigation and 2) hyper-reactivity. The investigatory attitude is found more frequently in the early stage of chronic intoxication and is operationally defined as actively reaching out to or approaching restrictive elements of the environment with persistent excessively compulsive demeanor. At later stages, the reactive attitude is prominent and is described as sudden disproportionate startle or reactive reactions with a jumpy, agitated quality (51). These attitudes in animals may reflect similar perseveration of perceptual-cognitive-attitudinal sets in human amphetamine abusers. We have hypothesized that a common postural attitudinal mechanism may subserve both the motor stereotypies as well the constricted perceptual and cognitive patterns (55). These specific behaviors and attitudes induced by amphetamine are latently maintained for months of total abstinence and activated by subsequent acute stimulant administration.

Even though single daily doses induce this enduring reaction to stimulant drugs, dosing patterns that prolong the drug state over most of the 24-hour period of the day, e.g., bingeing patterns, induce even more constricted and bizarre behaviors. Chronic extended daily duration dosing (e.g., 18 hr/day) first induces the extremely constricted stereotyped behavior but then progresses to a different drug-induced state, i.e. ‘hyper-reactivity' (51, 61). The stimulant-induced hyper-reactivity is characterized by a short period of stereotypy followed by repetitive hyper-reactive behaviors. The hyper-reactive behaviors include 1) hyper-startle responses; 2) jerking or reactive orienting movements to unseen stimuli; 3) hyper-reactive movement to the animals own bodily functions such as salivation; 4) hyper-reactive side-to-side looking movements; and 5) reactive behaviors that are also associated with disjunctive postures. Similar hyper-reactive states with attendant fear following chronic stimulant dosing were also noted in unpublished human research in the Lexington Narcotic Hospital in the 1950s and by several research groups in the 1960s (7). Case studies of amphetamine psychosis also revealed a progression of behavioral attitudes from heightened curiosity, repetitious examining, searching, sorting, to sustained pleasurable suspiciousness and search for underlying meanings, to a more severe stage of hallucination, ideas of reference persecutory delusions and fearful panic-stricken, agitated hyper-reactivity (51). The late stage of hyper-reactive fear has not received attention in the more recent clinical research literature. Angrist (7) describes such cases, e.g., "he jumped at every movement and misinterpreted the investigator's gestures as signals to the gang," all of which was within the context of hallucination and delusional visual and auditory misinterpretation. Given this type of clinical research presentation, it is difficult to understand why current animal research on stimulant-induced models of psychosis rarely extends dosing schedules to explore the hyper-reactive stage of chronic intoxication.

Is the progression of behavioral states resulting from chronic stimulant dosing (especially single daily doses) a form of sensitization? Typically, reverse tolerance or sensitization is defined as the activation of a pharmacodynamic response at a lower dose than the initial dose. Alternatively, sensitization is described as a shift to the left in the dose response curve. For the initial acute dosing, the higher the amphetamine dose, the more constricted the behavioral state. The dose-response curve for rodents begins with a mild arousal, then hyperactivity with locomotion, then more intense sniffing or oral stereotypies gradually leading to extremely constricted stereotypies. Arousal and locomotion is induced by acute low doses of 0.25–1.0 mg/kg, whereas higher doses ({ewc MVIMG, MVIMAGE,!greateq.bmp}2.5 mg/kg) induce intense stereotypies after a brief period of locomotion. Lower test doses are needed for activation of each of these stages in the chronic dosing model, compared with controls. Thus, by the usual criteria, reverse tolerance or sensitization has taken place after repeated daily administration. However, the usual definition of sensitization does not explain the enduring underlying latency to respond to subsequent stimulant doses with a specific, fixed reaction pattern. Lower doses than originally needed to develop the fixed pattern can activate the stereotyped pattern. In higher animals, including humans, quite different and unique patterns of stereotyped behavior develop in different individuals. The extent to which this represents the maintenance for a specific memory process and especially the specific underlying neurological mechanisms is not known.

STIMULANT SENSITIZATION AND TOLERANCE

Time-dependent Interaction of Sensitization and Tolerance

Sensitization is a robust, extremely long-lasting effect of repeated, especially intermittent, stimulant administration. The rapidity of the establishment of sensitization is influenced by many factors, including dosing parameters, negative influence of male gonadal hormones, and the time after the last dose of amphetamine (177). With intermittent stimulant administration, there is progressive enhancement of locomotor hyperactivity and/or stereotyped behavior (194, 205). In contrast, continuous administration of amphetamine or cocaine induces a tolerance to subsequent injections for at least a week after chronic dosing, while intermittent dosing induces a reverse tolerance (30, 115, 223). Yet, high-dose (10–30 mg/kg/day), continuous administration or multi-day dosing eventually induces bizarre hyper-reactive and fragmented behavior, including fearful responsivity, which is more easily reactivated after withdrawal in a manner similar to other sensitization responses to stimulants. The characteristic presentation of this behavior after amphetamine dosing is an initial induction of stereotypy followed by a rapid fade of stereotypy and the emergence of the hyper-reactive fearful state (51). Similar findings were reported by Nielsen et al. (155) using continuous amphetamine administration for 4.5 days, followed by a reactivating low dose of amphetamine after a drug-free period. These studies in the rat demonstrated an augmented response of ‘wet dog shakes,' episodes of parasitotic-like abortive grooming, and limb flicks. All of these behaviors are more similar to the effects of hallucinogenic amphetamines. In the primate, these late-stage behaviors include hallucinatory-like behaviors, fearful repetitious startle-like orienting movements, reactive grooming and Awet dog shakes: (50, 53, 61) (see Video 2 of hyper reactive monkey). When animals are repeatedly dosed for weeks, these behaviors become quite readily re-induced with subsequent dosing. The reactivation of these hyper-reactive behaviors by low to moderate doses of amphetamine following continuous dosing regimes is difficult to reconcile with the current notions and proposed underlying mechanisms involved with the sensitization of locomotion and stereotypy induced by intermittent dosing. However, they need to be considered when discussing augmentation of stimulant-induced behaviors. Neurotoxicity induced by high-dose continuous dosing as well as even higher levels of intermittent dosing may well contribute to the so-called end-stage behaviors. With continuous dosing, neurotoxicity appears at doses above 20 mg/kg/day in rats (182).

The half-life of methamphetamine in humans is 12–14 hours at physiological pH (6). In fact, laboratory-based half-life calculations in humans may be much shorter than the actual half-life in abusers on large repeated doses, in whom the very high plasma levels exceed the enzymatic capacity for metabolism (cytochrome P450). The much shorter methamphetamine half-life in rats (1 hour or less; ref. 146) does not reflect the potential for neurotoxicity seen in humans; therefore, continuous dosing models in rats may be necessary to reflect the long half-life in humans. Once or twice a day dosing regimens in rats do not adequately model the sustained plasma levels in human abusers.

Continuous (in contrast to intermittent) dosing with either cocaine or amphetamine induced tolerance to subsequent challenges for 7–14 days after withdrawal (114, 129). In addition, amphetamine pretreatment induced neurotoxicity in a dose-dependent manner, while cocaine, even at very high doses, did not. Following continuous methamphetamine or amphetamine infusion via Alza pumps, Ricuarte et al. (173) and Ryan et al. (182) found silver staining histopathological evidence for caudate neurotoxicity at doses above 16–20 mg/kg/day; no significant toxicity was observed at lower doses.

Thus, the continuous dosing regimens may induce either tolerance or toxicity or both. The continuous dosing regime is particularly relevant to the clinical amphetamine binge abuser. In contrast to cocaine, amphetamine has a much longer half-life, and binges take very large doses over days of abuse (100). At the extreme, some individuals take as much as 2 gm/day or more of methamphetamine, which is 100 times the clinical dose or approximately 30 mg/kg/day. For example, Kramer et al. (126), reported that some individual intravenous

methamphetamine abusers would administer as much as 1 gm every 2 hr (126). Because of the longer half-life and it's lower cost, amphetamine abusers can more easily extend binges out to several days resulting in complete exhaustion after withdrawal (126).

The anergia, including dysphoria, lack of mental energy associated with withdrawal from high-dose methamphetamine abuse, may wax and wane for months after withdrawal (46, 49). This extended period of intermediate- to long-term withdrawal is rarely found after cocaine bingeing (74). The extended period of methamphetamine recovery raises the question whether neurotoxicity (173), or at least some long-term functional change, has been superimposed on the usual stimulant tolerance associated with withdrawal characterized by 1–2-week period of anergia and psychasthenia. The latter symptomatology is more frequently found in cocaine binges and lower-dose methamphetamine abusers.

A recent postmortem study (227) reported that chronic methamphetamine users had significantly decreased levels of DA, tyrosine hydroxylase (TH), and DAT (measured by [^{3}H] WIN 35428 and [^{3}H] GBR 12935 binding and immunological staining for DAT) in the caudate and putamen. In contrast, DOPA decarboxylase (DDC) and the VMAT2 levels showed no changes between controls and chronic methamphetamine abusers. The authors commented that the loss of DA nerve terminals as a consequence of such toxicity would be expected to reduce all of the presynaptic DA markers examined, as has been shown to occur in idiopathic Parkinson's disease (228),. To the extent that DDC and VMAT2 levels provide reasonable estimates of DA innervation density, normal levels of these two indices indicate that the methamphetamine abusers in their study did not suffer permanent loss of striatal DA nerve terminals. However, Lieberman et al. (134) made a case for the extended tolerance/neurotoxic effects that would explain the ‘burn out' condition in former speed freaks (10, 213). Wilson et al. (227) also suggested that decreased DA levels (up to 50% of control), even if not indicative of neurotoxicity, are consistent with motivational changes reported by methamphetamine abusers in the intermediate withdrawal period. These different types of changes, functional vs. more extended neurotoxic following methamphetamine bingeing, may have important implications in formulating the type and duration of medication treatment after withdrawal. The duration of treatment for the withdrawal phase being currently explored for cocaine may not apply for neurotoxic conditions found in a segment of amphetamine abusers.

One other phenomenon that occurs with certain high-dose amphetamine dosing is the first week post-withdrawal coexistence of tolerance to amphetamine effects and a nocturnal hypo-activity state coexisting with an ‘inhibited' but latent sensitization that reemerges later. The sensitization reexpresses itself two weeks after withdrawal and is preceded by 7–10 days of hypoactivity (160). In this study, the doses of amphetamine were given twice a day with an 8-hour interval and were escalated over 42 days from 1 to 10 mg/kg. Thus, the escalation of doses in the lower range would have been sufficient to establish sensitization, whereas the higher doses (20 mg/kg/day) would probably have had sufficiently extended blood concentration throughout most of the 24-hour period sufficient for a continuous dosing model of tolerance. That the same dosing parameters induce both stimulant tolerance and withdrawal hypoactivity raises the question of whether these phenomena have a similar biological basis. In a subsequent study, Paulson and Robinson (160) found this withdrawal nocturnal hypoactivity was associated with a significant decrease in DA and metabolites (microdialysis) in dorsolateral caudate, but no changes were found in the accumbens. These studies also imply that, once sensitization is induced, it has an enduring quality that reemerges after a period of 7–10 days of hypoactivity/tolerance. In bingeing humans, a similar withdrawal pattern is noted in the hypo-activity and anergic responsivity which lasts for only approximately seven days to two weeks in moderately high-dose users. Other investigators (218) demonstrated that high-dose amphetamine resulted in an increasing number of foot slips on the balance beam task in rats, which lasted up to one month after dosing. Other features of amphetamine withdrawal syndrome that may be related to behavioral depression include changes in motivational and affective states, demonstrated by decreases in electrical self-stimulation reward (121, 122, 131).

Mechanisms Underlying Sensitization and Tolerance

Stimulant-induced psychosis can be much more severe with amphetamine than cocaine. In contrast to cocaine, amphetamine has a much longer half-life, and binges take very large doses over days of abuse. At the extreme, some individuals take as much as two grams a day: 100 times the usual clinical daily dose. As Peat et al. (162) have demonstrated, amphetamine non-toxic daily doses, when extended over 18 hours a day (e.g. continuous dosing) led to a marked depletion of DA and other neurotransmitters, unlike cocaine, which frequently produces neurotoxicity (11, 196). Thus, tolerance and perhaps even neurotoxicity may be intervening mechanisms leading to at least some aspects of the psychosis induction. Continuous administration of both cocaine and amphetamine over the 24-hour period of the day when given chronically leads to a residual state of tolerance to subsequent stimulants, in contrast to the intermittent model of sensitization. For both cocaine and amphetamine, continuous dosing is also associated with both somatodendritic and terminal autoreceptor supersensitivity seven days after withdrawal (47, 98, 106, 114, 129, 237). That behavioral tolerance develops to both cocaine and amphetamine provides evidence that tolerance and neurotoxicity are separable phenomena, since very high doses of cocaine do not induce neuronal damage (119, 183). Furthermore, the fact that cocaine induces tolerance in the absence of neurotoxicity provides one perspective on evaluating whether mechanisms altered by chronic amphetamine are due to tolerance or neurotoxicity. Although no neurotoxicity is found with high-dose cocaine, DA in the basal ganglia and limbic system is decreased during intermediate withdrawal as measured by microdialysis (159) and with amphetamine in animals given non-neurotoxic doses (160).

Alterations in mechanisms associated with sensitization are more frequently cited in the literature as possible mechanisms leading to psychosis. Daily intermittent dosing with stimulants induces reverse tolerance or sensitization (41). Dose-response curves are shifted to the right and/or the same dose induces a behavioral syndrome only seen with higher doses prior to the sensitization process. The mechanisms maintaining sensitization (to a subsequent stimulant challenge) over weeks and months after chronic intermittent administration are basically unknown. If one examines mechanisms prior to approximately 2–3 days after withdrawal, there is still a marked fluctuation of unstable, changing mechanisms. Since no mechanism associated with sensitization appears to be consistently maintained over the long course of sensitization, it is difficult to ascribe one specific mechanism to the expression of sensitization (223).

Based on their studies of sensitization induced by the direct DA agonist quinpirole, as well as by amphetamine, Muscat et al. (151) have reasoned that one single presynaptic mechanism cannot explain sensitization induced by different DA agonists. Zahniser and Peris (235) pointed out that initiation of sensitization to amphetamine occurs if amphetamine is locally injected into the cell bodies of the substantia nigra compacta or VTA, but not if it is locally injected into the terminal regions (39, 110, 204). (note: Yet, tolerance can be induced by continuous infusion of amphetamine into the terminal regions (39), and Kalivas and Duffy (109), reviewed the evidence that D_1 activation of mechanisms in the substantia nigra and ventral tegmental area play a central role in the sensitization of phenomena, especially the role of facilitating glutamate release and increasing DA cell firing.)

Zahniser and Peris (235) also pointed out that reactivation of sensitization is dependent on both D_2 and the entirely post-synaptic D_1 mechanisms. Since D_1 receptors activate cyclic AMP production, whereas D_2 receptors have no effect or inhibit the cyclase, recent attention has focused on the stimulant-induced phosphorylation of cAMP response element binding protein (CREB) in the DA terminal regions (124). Phosphorylated CREB protein binds to the CRE in the promoter regions of several genes to induce their transcription. Fitzgerald and Nestler (156) showed that chronic stimulant treatment led to the formation of persistent early gene expression that lasts for at least seven days after withdrawal. Recent evidence indicates that differential effects of D_1 and D_2 stimulation are important for the reactivation of self-administration in chronic stimulant-treated animals (197). These researchers found that a priming effect for markedly increased self-administration was selectively induced by D_2-like but, not D_1-like DA agonists in rats. Secondly, D_1

agonists inhibited cocaine seeking behavior induced by cocaine, whereas D_2-like agonists enhanced that behavior.

In animals sensitized to intermittent amphetamine or cocaine, there is an associated increase in the release of DA in the axon terminal regions, as demonstrated both by *in vitro* and *in vivo* methods. Slices of the nucleus accumbens or caudate putamen from animals sensitized to amphetamine demonstrated that DA was more readily released following exposure to amphetamine in vitro (28, 123). Similarly, microdialysis studies demonstrate that intermittent doses of amphetamine or cocaine result in increased extracellular release of DA after subsequent stimulant injections (2, 109, 178, 215). In contrast, Segal and Kuezenski (192, 193) reported using microdialysis that repeated amphetamine or cocaine administration, while inducing behavioral sensitization, resulted in reduced DA release following subsequent stimulant challenges.

Insofar as one explores the autoreceptor control of DA release within the first three days of withdrawal from intermittent dosing, the results are quite variable. Yi and Johnson (223) provided data suggesting a desensitization of D_2 autoreceptors was responsible for the increase release of dopamine. In contrast, Dwoskin et al. (43) reported that intermittent cocaine treatment caused an increase in the sensitivity of terminal D_2 autoreceptors. Utilizing in vitro voltammetry, Muscat et al. (151) found no evidence following chronic sensitizing amphetamine dosing that autoreceptors were controlling DA efflux in electrically stimulated nucleus accumbens slices. In contrast, fast-cyclic voltammetry studies of intermittent or continuous chronic cocaine demonstrated respectively subsensitive or supersensitive autoreceptor responses to quinpirole (106).

One of the questions pertinent to the effects of sensitization is what mechanisms are not necessary for the induction of, in contrast to the maintenance of, sensitization. This type of question arises since many reported studies involve correlations between a neurobiological mechanism and the induction of behavioral sensitization, not a causation link. Thus, we know sensitization to stereotyped behavior can occur in the absence of: 1) release of DA and/or its later neurotoxic effects of oxidative DA radicals, since direct agonists such as bromocriptine or quinpirole induce sensitization; 2) Pre-seizure activity (or induction of kindling) found with high doses of cocaine and amphetamine would not appear necessary since high potency apomorphine and quinpirole (at doses lacking local anesthetic, seizure inducing, effects) induce sensitization; 3) A specific effect acting through DA transporters does not seem necessary since L-dopa and direct agonists induce sensitization; 4) Peripheral systemic effects of stimulant-released catecholamines, activation of the HPA axis, or drugs acting directly at the DA terminal sites would appear unnecessary since VTA infusions can induce sensitization (110). Similarly, infusions into the terminal DA region does not induce sensitization (40, 110). The foregoing conclusion that certain mechanisms are not necessary for the induction of sensitization does not preclude their contribution to sensitization.

Alterations in Presynaptic Autoreceptor Function

The sulfhydryl alkylating agent N-ethylmaleimide inactivates G-protein G1 to uncouple DA D_2 receptor activation (91) and blocks the regulation of noradrenergic release by a_2-adrenoceptors (5). Recently, it was reported that chronic treatment with cocaine decreases the levels of G-protein subunits Gia and Goa in the A10 region (156). Furthermore, the inactivation of the G1 protein in the A10 area by microinjection of pertussis toxin produced behavioral sensitization to cocaine (202). Yamada et al. (232) recently reported that N-ethylmaleimide as well as forskolin enhanced stimulation-evoked DA release in striatal slices in a concentration-dependent matter. Furthermore, N-ethylmaleimide prevented the inhibitory effects of DA receptor agonist, as well as the stimulatory effect of DA receptor antagonists. Thus, their results strongly suggest that N-ethylmaleimide inactivates the GTP binding proteins to block DA autoreceptor regulation of evoked DA release. Furthermore, a methamphetamine pretreatment paradigm resulting in behavioral sensitization attenuated the stimulatory effects of N-ethylmaleimide on evoked DA release, thus raising the hypothesis that sensitization to methamphetamine may include a mechanism inhibiting GTP binding protein.

Do Chronic Therapeutic Doses of Amphetamine Induce Sensitization to Adverse Effects?

The issue of ‘sensitization' to adverse effects following repeated low to moderate doses of stimulants is a critical issue in the treatment of attention deficit hyperactivity disorders (ADHD) in children as well as adolescents and adults. Is there sensitization to drug reinforcement or potential for psychosis? The suggested dose range for methylphenidate and dextroamphetamine dosing in most children is 0.3– 2.0 mg/kg daily and slightly lower doses for adolescents and adults. The dose for dextroamphetamine is cited as being approximately half that for methylphenidate (226). Even without considering the rodent to man correction, 0.25–1.0 mg/kg/day is clearly within the dose range quoted in most paradigms of locomotion sensitization in experimental animals. Studies in adolescents generally indicate that the stimulants are efficacious and safe in the treatment of ADHD (226). There are no reported differences in the incidence of substance abuse in medicated vs. unmedicated adolescents (90); this is based on a review of eight outcome studies comprising 580 adolescents previously treated with stimulants for six months to five years. Looney (135) suggested that adequate treatment of ADHD children and adolescents with stimulants may indeed have a protective effect against the development of substance abuse. There have been no systematic studies on the risk for development of substance abuse in ADHD adults treated with stimulants, and such a study would have difficulties based on the high comorbidity of adult ADHD and stimulant abuse.

With regard to the development of psychosis in children, an extensive review on stimulant treatment of ADHD (100 studies which included 4,200 patients) reported only six cases of psychosis (14). There are, however, 20 case reports in the literature of stimulant-induced psychosis in children treated with stimulants for ADHD (226). Considering that psychosis is thought to be a dose-related phenomena primarily occurring at higher doses, along with the potential difficulty in mg/kg/day dosing in children, these incidences are really quite low given the magnitude of the incidence of ADHD and its stimulant treatment. Rounsaville et al. (181) has reported that upwards of 40% of stimulant abusers have a comorbid diagnosis of ADHD. There has been some reflection that stimulant abuse is an effort by the patient to self-medicate. Recently, Biederman et al. (19) reported that adults with ADHD also have high rates of comorbid antisocial, depressive and anxiety disorders providing a different perspective from the drug abuse clinic patient. Moreover, recent evidence (201) indicates that adult attention deficit disorder requires stimulant treatment (methylphenidate) in doses similar to those in childhood ADHD (i.e., 1.0 mg/kg/day). This raises the question whether some of the abuse potential in ADHD adults may be inappropriate self-medication in the search for a higher effective dose even with illegal stimulants.

Another clinical problem treated with amphetamine and other stimulants is narcolepsy, a condition treated over many years at amphetamine doses ²40 mg/day or methylphenidate ²60 mg/day (although higher doses than this have been used by many clinicians). Concerns regarding tolerance, undesirable side effects and drug dependency are reasons most frequently cited for limiting the use of stimulants for treating narcolepsy symptoms. However, a systematic review of the literature on the use of these agents revealed that there was no evidence from prospective randomized studies for these dependence phenomena in patients treated for sleep disorders (150). Mitler (150) further stated that " . . . we know of no published data showing that patients with narcolepsy or other primary sleep disorders either abuse or become physically dependent on stimulants." They comment that the case reports of adverse effects primarily come from studies of drug abuse populations or from retrospective studies. For a 70 kg person, 40 mg would certainly be within the dose that, in rats, induces sensitization. The lack of evidence for increasing sensitivity to drug abuse or psychosis in a carefully managed medical population would indicate that lower dose sensitization animal models may not be readily applicable to sensitization models of abuse reinforcement and psychosis.

In contrast to stimulant treatment of narcolepsy, the treatment of Parkinsonism with L-dopa and direct DA agonists not infrequently results in hallucinations and delusions. In the latter case, doses of DA agonists are frequently increased, and/or given at more frequent intervals and over an extended period of the day in attempts to overcome treatment resistance with ‘on-off' episodes. Parkinson patients not infrequently have

disturbed sleep and hallucinatory episodes during the night indicating there has been an extension, a duration of daily dosing and drug blood levels affecting most of the 24-hour period.

STEREOTYPED BEHAVIORS IN NON-HUMAN SUBJECTS

The Nature of Stereotypies

Stimulant-induced stereotypy was first reported for cocaine by Caldwell (29). Dose response curves for stereotyped behavior can be established using predetermined parameters or rating scales (145). Initial arousal, in lower species, and exploratory locomotion (noted at lower doses) are usually included in the bottom of rating scales. However, some species, e.g., cat and monkey, do not appear to have a locomotor response. Locomotor responsiveness as the only dependent variable only allows an assessment at constricted low-dose range and precludes a complete dose-response curve description of sensitization, a phenomenon discussed above. Briefly, for most authors, sensitization essentially refers to a shift in the dose-response curve to the left with repeated intermittent dosing. The more intense stereotypies are repetitious, purposeless patterns of behavior that often resemble a fragment of the animal's normal behavior disassociated from its usual behavioral context. Most of the stereotypies involve arousal and exploratory patterns of examining or searching that depend on the normal repertoire of species-specific behaviors. Thus, sniffing, gnawing and licking movement are predominant in rodent species, cats have a sniffing or search/looking behavior, whereas primates have searching/looking behavior often with forefinger pincer grasp, eye-hand coordinated searching patterns (54).

Based on observations of amphetamine-induced behavior (138) stereotypy was defined as "higher rates of activity but in decreasing number of response categories." Ridley (174) refers to stereotypy as "the excessive production of one type of motor act or mental state which necessarily results in repetition." He makes the distinction with perseveration, which is a restriction of choices of action such that the behavior is repetitive but, not excessive. For example, mental states that are slow to change are perseverative, while those that are demanding, preoccupying, or intrusive would be described as stereotyped. In order to understand the relationship between motor stereotypy and mental stereotypy, it is necessary to highlight the nature of persistent attitude. For example, for dogs in an open kennel compound, the most conspicuous effects of amphetamine on one dog that had been following another dog at the time of onset was a continuous pursuit and chase of the other dog in spite of the fact that it required jumping over, going around, and changing his speed. Thus, one can frequently note, even in lower animal, the persistent attitude of the animal even though there may be considerable variation in the motor acts.

Even in the initial stages of amphetamine intoxication, components of behavior in animals become relatively fixed over time and demonstrate a loss of cohesive flow among initiatives and their relative priorities. We have found that there are not only fixed postures and movement patterns, but also fixed attentional emotive attitudes; animals would continue to maintain set attitudes even after accompanying motor stereotypy has subsided (52). These fixed attitudes are quite similar to the phenomenon observed in speed freaks, who become ‘hung up' in puzzles, in examining/sorting compulsions for hours, or in the intense grossly suspicious or fearful attitudes that are so commonly associated with repetitious scanning eye movements. We have previously postulated that in many species perseveration and distortions of postural-motor-attitudinal sets are common in the amphetamine intoxication syndromes. As an illustrative example, one of the main stereotyped behaviors induced by amphetamine in primates is repetitive use of the probing forefinger and pincer grasp to explore different objects. In both humans and monkeys, the pincer grasp shows up as stereotyped picking phenomena: both picking the body and grooming patterns or picking at various segments of the environment (see examples of picking stereotypes (see Video 3) in a schizophrenic and experimental monkey (see Video 4). In tracing the ontogeny of the pincer grasp in humans, Gessell (77) noted that, at birth, the tonic neck

reflex turns the head in relationship to the outstretched hand; later, at approximately nine months of age, the head turns in relationship to the outstretched hand but now with the probing forefinger and pincer grasp. At this stage of development, the infant is enthusiastically and repetitiously attentive to small details in his environment; crumbs, specks of dust, and any number of small objects increasingly become his/her main ‘perceptual hang-ups.' Just prior to this stage of development, the infant completely disregarded minute objects. Thus, we see an energized ‘telekinetic' postural mechanism leading to a predominant perceptual mode or attitude. In fact, it is more than just attention to details, it is the perseverative attitude of searching out small details in the environment. Over time, of course, this developmental perceptual-motor mode is integrated and fades into the background repertoire of attention examining mechanisms. We question whether high-dose stimulants can reactivate a sustained involvement with these perceptual-motor attitudes.

Posturomotor attention mechanisms are thought to be largely subserved by the basal ganglia circuits, yet much of drug abuse as well as psychosis research is focused on the mesolimbic circuits, relegating the basal ganglia to motor function (133). Much recent research argues for a more relevant role for the basal ganglia circuits. The basal ganglia are organized into a number of primarily, separate cortical-striatal-ophthalmo-cortical circuits. Alexander and Crutcher (3) described five pathways through the basal ganglia, each organized in parallel and innervating different regions of the thalamus and frontal cortex. These include ‘a motor' circuit, centered on the supplementary motor area and regions of the motor cortex; the ‘oculomotor' circuit, centered on the frontal eye fields; the other circuits, e.g., limbic, orbital-frontal and dorsal-lateral-prefrontal, each appear to be processing different kinds of information. Groves et al. (87) hypothesize a ‘switch' that allows passage of preferential information within the basal ganglia. Such a focusing mechanism would not only allow facilitated input to produce the strongest modulation but also permit, if needed, a substitution between alternative types of information. That only selected and limited cortical-striatal input may be facilitated while the rest may be suppressed has been proposed in reviews and theoretical papers on basal ganglia functions several times over the years (37, 8, 113). Jackson and Houghton (99) marshal considerable experimental evidence favoring a basal ganglia model that, once a behavioral sequence or event has been selected, it may function as an attentional zoom lens or amplifier, enhancing behaviorally relevant cortical signals. Further, it operates to maintain focal attention by suppressing the activity of irrelevant signals. Schultz et al. (189) also make the point that DA neurons respond to the most important salient external stimuli. Salient stimuli are described as unconditioned rewards, aversive stimuli, conditioned stimuli, conditioned stimuli predicting rewards or punishment, and high intensity surprising, novel stimuli. These stimuli alert the subject, which interrupts this ongoing behavior, orients it to the stimulus, and processes it with high priority (190). On the other hand, most DA neurons respond best to a subset of salient stimuli, specifically primary rewards, and conditioned reward predicting stimuli. Schultz et al. (189) further discuss data consistent with the hypothesis that the DA neuron triggered DA release in the striatum results in a general reduction of cortical-striatal processing, thus focusing the striatal activity onto the strongest inputs whereas the weaker activity is lost. Given that basal ganglia activity fosters the intent to act either cognitively or behaviorally, one could reason that an ongoing preferred activity, if artificially activated by DA agonists (stimulants), would continue in an even more focused manner. The DA agonist would also inhibit the firing of DA neurons by activating autoreceptors, thus precluding other salient stimuli reaching the basal ganglia. This would be at least a partial basis for the ever more focused and constricting nature of stereotyped thinking and behavior. In the repeated sensitization model of chronic stimulant intoxication, it would be reasonable to assume that the same nigrostriatal pathways involved intensely in the rewarding stereotypy phase of stimulant administration would also be supersensitive to the salient internal or external cues associated with either drug administration or acquisition behaviors preceding administration. The prefrontal cortex and hippocampus, as well as other parts of the mesolimbic system, are anatomically closely interconnected with the basal ganglia. They may well form the interrelated system initiating and mediating context-dependent stimulant behavior. The limbic system's interrelationship is noted in the striatum's expectation-related responses, as well as the ability of the structure to access stored information (189). Graybiel and Imura's (83) observation that patterns of anatomical connectivity indicate that the limbic system has primary access to the striatum fits well with the striatum mediating the interpretation of the saliency of information.

In summary, amphetamine-induced stereotypies are quite often comprised primarily of the postural-motor components of attending and examining patterns (53). We hypothesize that these components represent the underlying postural basis of perceptual cognitive behaviors. We conceive of the normal process as an intrinsic scaffolding of behavior with a fluid capacity to switch between postural expectancies based on cognitive or sensory feedback. Although other anatomical sites such as frontal eye fields and temporal lobe contribute, the mesolimbic-striatal DA complex with its extensive cortical projections is conceived of as a major switching station. This is not unlike the striatal behavioral filter proposed by Stevens (203; see also refs. 87, 148, 190). Qualitatively, the nature of these mechanisms might fall somewhere between posture, attitude and the initiation of movement, or indeed thinking. These mechanisms would appear to coordinate many of the modes of attention. The mechanisms might be seen as the leading edge of attention searching and orientation to the outside world. Conversely, these mechanisms might switch attention among various external and internal cognitive sets. Thus, stereotyped thinking could be conceived of as being very similar to motor stereotypies.

Recently, Geyer and Markou (78) argued that locomotion not stereotypy is a better model of psychosis, since low-dose amphetamine locomotion is a hallmark of the mesolimbic system, whereas the striatal system mediates the high-dose stereotypies. The reasoning is based on the notion that the mesolimbic system underlies psychosis whereas the striatal system is involved in motor dyskinesias. Elsewhere, we point out that ‘low-dose' in experimental animal models of locomotion and its sensitization are well within the therapeutic dose range for amphetamine treatment of narcolepsy and ADHD, which would be a questionable model for psychosis.

Neuroanatomical Substrates of Stereotypy

The neuroanatomical substrates of stereotypy have been known for many years, in that infusion of DA into the caudate nucleus of rats produced stereotyped oral behaviors (i.e., grooming and gnawing), while dopamine-blocking drugs infused in the same area can prevent amphetamine-induced stereotypies (34). In contrast, DA infused into the adjacent nucleus accumbens induces locomotion as well as sniffing stereotypy (95, 165).

Unilateral frontal or temporal lobe lesions can lead to increased ipsilateral striatal activity and, indeed, unilateral frontal lesions in rats result in amphetamine increased contralateral turning (79). In humans, spontaneous contraversion turning is also noted in old frontal strokes as well as a large subgroup of schizophrenics who have turning and unilateral spacial neglect; Bracha (22) hypothesized that this was a manifestation of a unilateral striatal hyperdopaminergic state induced by lack of inhibitory frontal lobe control of the striatum. Volkow (1988, 1992) reported reductions in glucose metabolism and frontal lobe cerebral blood flow weeks to months after withdrawal from cocaine abuse. Furthermore, CT scans of long-term abusers show frontal lobe atrophy. Certain schizophrenic symptoms (e.g., delusions) have been thought to result from right fronto-parietal dysfunction (22, 147). If stereotyped perceptual and cognitive forms are based on unilateral attention-switching mechanisms, then some forms of amphetamine-induced psychosis could result from overactivity in one hemisphere, especially the right (59).

Patients with frontal lobe lesions exhibit perseveration behaviors but not intense energized stereotypies. However, frontal lesions with subsequent amphetamine stimulation of the DA system exacerbate stereotypies in monkeys (174) and in rats (96). Thus, descending frontal projections may exert an inhibitory effect on striatal activity in DA projections or facilitate switching between behavioral alternatives. Increased stimulated stereotyped behavior has also been noted with hippocampal lesions (38). Thus, the realization that stereotypy can be a complex response reflecting a disruption of coordinated function not only within the basal ganglia but also between striatal and other forebrain areas, provides insight into neural sites interacting to induce schizophrenic-like dysfunction (38). Such a conceptualization provides for a more comfortable marriage of the hypofrontality and DA hyperfunction hypothesis of schizophrenia.

Interaction of Environment with Species-specific Behaviors

Examples of environmental modification of amphetamine stereotypy are well known and have been described by Ellinwood and Kilbey (50) and Robbins and Sahakian (175). In fact, conditioning of ongoing behavior at the time of the initial reinforcing effects of amphetamine can literally provide the basis for accidental conditioning of this behavior, as well as later remnants of this behavior found in chronically treated animals (57). Yet, the behavior entrained must be compatible with one of the more prepotent behaviors of the particular species in order to be sustained with high dosing over time. An example is demonstrated in the video of a cat with a looking stereotypy, but with the postural components of groin grooming, a phenomena we have termed postural dysjunction (see Video 5). The initial groin grooming stereotypy was inadvertently triggered by a few drops from the first amphetamine injection wetting the groin. Gradually, over days, the grooming stereotypy was superseded by a more prepotent looking behavioral stereotypy. In another example, cats trained to paw press for stimulants will repetitiously paw press initially but, this is soon replaced by intermittent sniffing movements that activate the drug levers and finally by repetitious sniffing around the lever to the point of overdosing fatalities (50). Robbins and Sahakian (175) have similar comments that stereotyped behavior would then become reinforcing ‘in itself' and therefore of itself, suggesting that stereotypy is driven by sensitive internal motivation states even if these are not related to the environment in the usual adaptive purposeful way (see also discussion on incentive-motivation).

Evolution of Acquisition Behaviors in Self-administration Paradigms

Ellinwood and Kilbey (50), animals taught to paw-press for milk, which was then substituted with a stimulant infusion, rapidly increases the paw-pressing activity to reach a high sustained dose resulting in the activation of a species-specific prepotent behavior, e.g. sniffing. The sniffing in and around the lever evolves to subject-directed sniffing movements becoming the operant resulting in massive doses of stimulant. Thus, the emergence of these species-specific prepotent behaviors in conjunction with large increases in the underlying natural activator, i.e., dopamine, provides for synergistic potentiation. As the prepotent behavior emerges to become an acquisition operant, sensitization as a mechanism underlying the operant conditioning becomes more apparent; preacquisition, exploring, hunting and foraging behaviors typically get sensitized. Unfortunately, unlike the usual consummatory objects of acquisition, i.e., food, water, sex, etc., which result in consumption-induced reduction in behavior, stimulants generally motivate further escalation of the acquisition behavior at the cost of reducing any other motivated behaviors in the natural repertoire. The behavior becomes increasingly intense and constricted, which might be interpreted as an increasing craving. In humans, when there is a readily available amphetamine supply or when the experimenter gives non-contingent intermittent doses to experimental animals, other compulsive behaviors ensue which have no relationship to drug acquisition. This does not preclude the ‘ready access abusers' from repeatedly reinitiating bingeing episodes to experience both the initial intense rush as well as the ensuing sensitized motivated behavior. Certainly, ‘punding' stimulant abusers seek out activation of these behaviors with another drug run in the full knowledge that the drug run will end up in aversive, fearful panic-like psychosis.

The sensitized non-contingent behaviors more than likely are initially activated and sustained by an accidental conditioning process (57). In laboratory settings, the investigator-administered stimulant initially activates arousal, investigatory-type (non-contingent) behavior through dopaminergic mechanisms. As the higher DA concentrations ensue, the reinforcement results in this particular behavior becoming accidentally conditioned and evolving into bizarre constricted stereotypies over time. In humans, an increase in particular activities related closely to the drug taking experiences occur over time in individuals with fairly ready stimulant access.

Shifts in Behavior from Contingent to Non-contingent Stereotypy

Animals taught to paw press for food while being injected repeatedly with amphetamine will continue to bar

press but will not eat the food so acquired. This observation suggests that stereotypy drives the bar-pressing behavior rather than the food reward. Similarly, rats trained to bar press to maintain the temperature of their cage continue to respond under the influence of amphetamine even though hyperthermia occurs (224). Species-specific stereotypies under continuing self-administration become the operant, and stereotyped compulsive behavior can lead to lethal overdosing (50). In humans, compulsive drug acquisition and administration behavior is also described by high-dose stimulant binges.

OVERVIEW

The initial low-dose effects of central stimulants induces at least two concomitant effects. One effect is to induce arousal-attentive mechanisms, a general energizing effect noted in rodents as exploratory locomotion. In humans, this effect is primarily expressed as an activation of attentive mechanisms and energizing/focusing of ongoing activities, coupled with secondary, generalized feeling of well-being. The focusing effect accounts for the therapeutic use of stimulants in ADHD, while in adults even therapeutic doses can induce various mild degrees of euphoria. An example of the focusing mechanism was described by Mattay et al. (143), who showed that a cognitive task specific activation of topographically distinct CNS sites is enhanced by amphetamines at therapeutic doses. Thus, in the Raven Progressive Matrices Test, which usually activates the hippocampus, amphetamine further augmented blood flow in this area but decreased it in the frontal cortex. The exact opposite effect on blood flow occurred with the Wisconsin Card Sort Test, known to activate the frontal cortex. This would imply that CNS mechanisms, which are involved in switching and intensifying focus on activated sites, are further enhanced by stimulants. Thus, these drugs can facilitate the continuation of ongoing site-specific activity while reducing other CNS activity.

What happen to these mechanisms when doses at 10–200 times the therapeutic dose are abused? Secondly, what happens when these doses are used repeatedly over time? If the initial arousal behaviors at the beginning of low-dose amphetamine dosing are not only maintained but also become more constricted during the subsequent high-dose abuse, does this represent an increased channelization of behavior at the expense of a massive reduction in a flexible behavioral repertoire? Since striatal-cortical interrelations are reported to be topographically specific (148), one might hypothesize that a specific neural network of striatal-cortical complexes are activated while others are relatively inhibited (87, 99). In this vein, the so called ‘hyperdopaminergic hypothesis of psychosis' might better be termed a ‘selective hyperdopaminergic state.' The relation of constricted, stereotyped behavior in schizophrenic syndromes has a long history. Bleuler (20) described stereotyped posture, attitude, thinking (talking, etc.), movement and mannerisms as pervasive, constricted elements in schizophrenia, which resulted in an overall limitation of the behavioral repertoire in schizophrenics.

Animals administered low stimulant doses often engage in the specific exploratory behaviors; when the exact same series of behaviors are repeated over multiple administrations, the phenomena takes on the characteristics of accidental conditioning, i.e., the initial ongoing arousal behavior become accidentally conditioned to the reinforcing effects of low-dose stimulants. As the dose is increased, behavior becomes more and more constricted, and reduced, often to a fragment of the original behavior. However, unless the original behavior is compatible with one of the dopamine-activated, species-specific behaviors, the conditioned behavior fades away and is replaced by a species-specific stereotypy, e.g., repetitious sniffing, licking, or gnawing in the rodents. The low-dose effects of stimulants are consistent with activation of the VTA mesolimbic system and its well known arousing reinforcing properties (176). The increasingly constricted stereotypies are more consistent with activation of both the mesolimbic and striatal systems.

What are the species-specific behaviors and their place in the natural repertoire of an animal's behavior? In the rodent in the natural environment the exploratory sniffing, licking and gnawing are acquisition behaviors

often lasting over long periods of time before the actual search object is obtained. Thus, these behaviors must be maintained by a sustained activation over long periods (even days) if the object, e.g., food, is not readily available. Food is the main object of hunting/foraging in lower animals, but primates explore a large variety of objects. Interestingly, instillation of DA or DA agonists into parts of the mesolimbic and caudate nuclei in rodents activates these behaviors even after food-consumption satiation (note: even though the main purpose of these acquisition-search behaviors are oriented toward food, these prepotent behaviors are adapted to carry out a variety of functions, e.g., rodents gnawing for nest building or beavers gnawing trees for dams and dens. Thus, it is thought that the DA systems underlie the sustained activation of these behaviors. In the absence of any contingent relationship, as with experimenter-administered high doses of stimulants, the behaviors become increasingly stereotyped and totally non-contingently related to objects. The behavior itself becomes more and more constricted and, at times, fragmented over time; the process has been called sensitization, but this is probably an oversimplification.

If the experimental animal is required to activate a manipulandi to obtain the stimulant, the behavior around the manipulandi, as drug accumulates, increasingly takes on some form of a species-specific stereotyped pattern. For example, sniffing around the manipulandi may become the operant substituting for the trained original paw-press. Thus, the species-specific behavior, which is an acquisition behavior in the animal's natural behavioral repertoire, now becomes drug acquisition operant behavior with a compulsive nature. Whether contingently or non-contingently related, the repetitious, compulsive behaviors in humans are described as being very pleasurable; stimulant abusers often state that they will take the stimulants in order to engage in these activities. For example, methamphetamine addicts take the drug to activate their drawing or painting compulsions which indeed sometimes results in works of art, or they engage in taking machines apart, repairing them, and sometimes actually putting them back together. They may also compulsively play video games for days. Thus, the behavior may be productive, but productivity is not necessary for the enjoyment of behavior. It is important to remember that drug acquisition and administration behaviors are often admixed with non-contingent drug behaviors. In humans, as well as animals, especially with short-acting stimulants such as cocaine, one sees very compulsive drug acquisition and administration behaviors, where the individual repeatedly administers drugs often in the face of mounting adverse effects such as agitation, fear and paranoia.

Gradually, over time and increasing doses, especially with high-dose utilization, there is a transition to the high-dose platform of drug abuse. With these higher doses, massive tolerance develops to the energizing and reinforcing effects of the drugs as well as to the neurotoxic (but not to the psychogenic) adverse effects. For example, fatal hyperthermia and hypertensive crises are reduced to a point that individuals can be taking as much as a gram of methamphetamine at a time. Associated with the mechanisms underlying high-dose tolerance, the period following withdrawal increasingly becomes one of loss of energy, anhedonia, loss of focus of attention. These symptoms can last for 10 days to two weeks (particularly with amphetamines) and the anergia may wax and wane for weeks thereafter (perhaps aggravated by neurotoxicity). The interrelationship of tolerance vs. chronic neurotoxicity, especially in the DA systems, needs consideration when assessing the more persistent withdrawal symptoms. During the withdrawal period, drug craving appears most intense during the first two weeks, yet reappears periodically for weeks afterwards. Drug craving has been described as activated by various stimulant cues, e.g., white powder, etc. resulting in automatic acquisition behaviors coming into play—often with little consciousness of the process. This relative lack of consciousness of craving in the presence of compulsive acquisition behaviors requires phenomenological redefinition of craving. This is especially important in treatment of abusers, in that bringing the cue responsive crave\acquire automatic behaviors into the forefront of consciousness is one of the important objectives in gaining control of abuse. Craving usually is more pronounced in individuals who have an underlying anergic and anhedonic mood substrate, especially when the individual has had a prolonged abuse history with a marked reduction in the repertoire of often reinforced behaviors such as social engagement, recreation etc.

An important difference between cocaine and amphetamine is the well documented neurotoxicity of amphetamine in high continuous dosing regimes. Neurotoxicity of DA and serotonin terminals compounds any tolerance or short-term depletion that may have been induced in these systems. Thus, any withdrawal anergia would be compounded. In addition, neurotoxicity in cortical areas that provide inhibitory control over the DA systems adds complicity to our notions of sensitization of amphetamine behavioral effects. Based on research in Parkinson patients, loss of executive functions with DA system neurotoxicity could also contribute to the problems with therapeutic engagement.

Sensitization to intermittent stimulant dosing is generally recognized as inducing stereotyped behaviors that are reactivated by lower doses than were required to activate them initially. Quite reasonably, it has been proposed as a mechanism underlying stimulant-induced psychosis. Yet, continuous dosing induces perhaps even more bizarre hyper-reactive behaviors in animal models that can be reactivated by test doses even months later. This warrants some reconsideration of our formulations and our perspective of sensitization or reverse tolerance and their contributions to psychopathology. Also, in higher animals including humans, the unique idiosyncratic behavior reactivated does not fit well with pharmacological concepts, as well as with a neural adaptation concept.

Despite the numerous adverse effects of high-dose amphetamine abuse, amphetamines have a definite place in the FDA-recognized treatment of attention deficit disorder and narcolepsy. In addition, there are other conditions where amphetamine has a therapeutic utility in the treatment of weight reduction and the atypical depression found with many medical illnesses. The atypical depressions are thought to be responsive both to amphetamine-like drugs as well as to monoamine oxidase inhibitors. The dramatic similarity of the anergia anhedonic loss of mental energy associated with both atypical disorders as well as the stimulant withdrawal syndrome raises the questions of whether a less potent amphetamine-like drug or MAOI would prove efficacious in treating the stimulant withdrawal syndrome.

Therapeutic dosing for narcolepsy and attention deficit disorder has a very low liability for either stimulant abuse or induction of psychosis. The doses used, therapeutically, are in the same range as doses used to induce locomotor sensitization in animal models. These animal models of locomotion are often cited as paradigms to explore both drug abuse as well as psychosis. Given the low incidence of these disorders in humans at therapeutic doses, there are cautions about the validity of these models. In contrast, with therapeutic dosing with DA agonists and L-dopa in Parkinsonian patients (who often dose throughout much of the day), there is a reasonable incidence of psychosis, particularly occurring during the nighttime period. This argues for a careful consideration of duration of daily dosing as well as the higher doses of agonists used in Parkinsonism as a model in animals, at least, for induction of psychosis. Finally, stimulant-induced psychopathology provides a mirror that elucidates a segment of human behavior. Stimulant abusers are performing pharmacological experiments that, while offensive, nonetheless provide insights into the biological nature of emotionally cathected thinking; psychosis; obsessional and compulsive behaviors; and violence.

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