THE YALE JOURNAL OF BIOLOGY AND MEDICINE 61 (1988), 123–136

Evolving Conceptualizations of Cocaine Dependence

FRANK H. GAWIN, M.D.,[a] AND HERBERT D. KLEBER, M.D.[b]

[a]*Assistant Professor of Psychiatry,* [b]*Professor of Psychiatry,*
Yale University School of Medicine, New Haven, Connecticut

Received November 30, 1987

Cocaine was considered incapable of producing dependence in 1980 but was proclaimed the "drug of greatest national public health concern" by 1984. Clinical consensus in 1980 held that cocaine did not produce a withdrawal syndrome, but recent clinical investigations demonstrate that cocaine produces unique abuse and withdrawal patterns that differ from other major abused drugs. Evolving pre-clinical research over the past two decades now suggests that chronic cocaine abuse produces neurophysiological alterations in specific central nervous system systems that regulate the capacity to experience pleasure. These evolving clinical and pre-clinical constructs have led to applications of promising experimental pharmacological treatments for cocaine abuse.

In 1980, cocaine was considered a benign euphoriant [1,2]. Cocaine's popularity was increasing, but broad distribution of cocaine began only in the late 1970s, and little time had elapsed to allow the development of extreme cocaine abuse, so cocaine abusers rarely appeared seeking treatment. By 1982, cocaine abusers had begun to appear at the Substance Abuse Treatment Unit of Yale University and the Addiction Prevention and Treatment Foundation, and the authors founded the Yale cocaine abuse treatment and research program when the number of primary cocaine abusers in the treatment unit reached four (the average census is now over 60 cocaine abusers). The establishment of a unit devoted to cocaine dependence led to a continuing, systematic research effort that has advanced new conceptualizations of cocaine dependence and of the appropriateness of pharmacologic treatment strategies. This article reviews the recent evolution of our understanding of cocaine dependence.

EVOLUTION OF CLINICAL UNDERSTANDING

In 1980, the *Comprehensive Textbook of Psychiatry* stated that "taken no more than two or three times per week, cocaine creates no serious problems" [1]. The *Diagnostic and Statistical Manual*-III (DSM-III) of the American Psychiatric Association reflected the prevailing perception that withdrawal or tolerance to cocaine did not occur and the *Manual* did not list cocaine dependence as a substance abuse problem [3]. Case reports of cocaine dependence from the turn of the century were considered aberrant exaggerations. Experts claimed that cocaine produced, at worst, "minor psychological disturbances" and "psychological" addiction only in some addiction-prone abusers (reviewed in [4]). Moreover, this psychological addiction was considered a relatively minor clinical condition amenable to treatment with psychotherapy, in contrast to the "physiological" addiction associated with narcotics, alcohol, and sedative-hypnotics.

Abbreviations: ICSS: intracranial electrical self-stimulation TCA: tricyclic antidepressant

This clinical consensus existed despite the fact that systematic clinical studies of cocaine abusers had not occurred. Our initial clinical studies were intended, therefore, to reconcile the disparity between the clinical wisdom of the time, that cocaine was not supposed to produce true addiction, and the fact that it was being cited increasingly by patients as the direct cause of compulsive drug taking and seeking treatment.

We employed direct clinical observation of subjects in treatment, using semi-structured interviews as well as structured assessments of cocaine craving and use. These studies showed that cocaine produced a dependence similar, in magnitude and resistance to treatment, to other drugs of abuse such as alcohol and opiates, but that cocaine dependence differed substantially in the pattern of abuse development and in clinical presentation.

Four areas of clinical importance were targeted by these initial investigations: *(1)* details of the progression of dyscontrol over cocaine use [5], *(2)* patterns of cocaine use [6], *(3)* abstinence symptomatology [7], and *(4)* the role played by co-morbid psychiatric disorders [7,8]. Most of these initial observations took place in a very carefully followed subsample of 30 cocaine abusers who were treated between 1982 and 1984. Details of sample characteristics appear elsewhere [6,7,9].

The Progression to Cocaine Dependence [5,11]

Our cocaine abusers related that, as in earlier descriptions of the developing amphetamine dependence [10], dyscontrol over cocaine use occurred gradually, within a social context. Initally, low cocaine doses enhance social enjoyment or vocational performance [5,11]. Few negative consequences of such use were initally apparent; however, lengthening episodes of use, sleep disruption, dosage escalation, and increased social isolation all gradually become accompaniments of cocaine use. Two to five years usually elapsed between initial exposure to cocaine and treatment seeking, explaining the lag between cocaine's initial popularization and the latter appearance of reports of addiction. Compulsive, uncontrolled, binge use began when availability increased (e.g., increased funds, improved supply sources, engaging in cocaine commerce), or on a switch to an administration route of higher intensity, which delivered increased doses to the brain (smoking or intravenous route). The extreme euphoria produced by such binges produced vivid memories that formed the foundation for later stimulant craving.

The human cocaine addicts we studied described binges that paralleled the repeated rapid cocaine self-administration observed in animals provided unlimited access (reviewed in [12]). Thoughts of loved ones, safety, responsibilities, and morality did not enter consciousness during binges. Only thoughts of stimulant effects and supplies persisted. While a similar gradual progression to dyscontrol has been described for other abused drugs, such as opiates and alcohol, the time course for dependence has generally been longer [13], and simple availability of large amounts of the abused drug played a less central role, especially in alcohol abuse, than in cocaine abusers.

Public misconception in 1982 often held that intranasal cocaine did not cause addiction; however, 50 percent of the abusers studied were exclusive intranasal users, debunking this perception. The clinical presentation of intranasal abusers did not differ from that of other abusers, with the same severity of dependence [6].

Patterns of Cocaine Use in Dependence [6]

Continuous, daily use of alcohol or opiates is considered the normal pattern in opiate or alcohol dependence. Use is generally repeated within a day of the last use, in order to

ameliorate rapidly appearing withdrawal symptoms. Because many cocaine abusers did not use cocaine daily, the absence of a daily use pattern was considered evidence that cocaine produced a less severe and intractable addiction. While many of the cocaine users we studied described daily use within the year preceding seeking treatment, over 90 percent described a transition to binge abuse on developing dyscontrol. The binge pattern became more pronounced as attempts to curtail use were initiated, and several extra days of abstinence more often separated binges. By the time of treatment seeking, users averaged one to three binges per week, lasting from 8–24 hours. Counterintuitively, abusers described that their earlier *daily* use was associated with some control over cocaine intake—use could be stopped while cocaine supplies remained in order to allow normal sleep to occur. When dyscontrol occurred, users were unable to refrain until supplies were exhausted, and use throughout the night took place, resulting in prolonged binges followed by intervals of abstinence. This observation established that the absence of a daily use pattern in a cocaine abuser did not indicate decreased impairment, and often indicated the opposite, providing a crucial clinical distinction between cocaine addiction and alcohol or opiate dependence.

It should be noted that a pattern of unceasing cocaine bingeing, as described previously by Seigel [14] also occurred, but in less than 10 percent of the sample. In such abuse, brief periods (three to six hours) of sleep interrupt continuous, long-term, high-dose intake [14], but this pattern required almost unlimited access to cocaine (> $100,000/year cocaine expense).

Abstinence Symptoms [7]

We observed a tri-phasic cocaine abstinence pattern that helped dispel the perception that cocaine use produces no withdrawal. The three phases are summarized below.

Crash (Phase 1): Other investigators had emphasized an immediate post-cocaine depression following a binge [14,15]. This "crash" of mood and energy was also described by our patients immediately after cessation of a cocaine binge. Cocaine craving, depression, agitation, and anxiety rapidly intensified. We were intrigued, however, by descriptions that, over approximately one to four hours, cocaine craving was supplanted by mounting fatigue and craving for sleep; further use is then often strongly rejected, *unlike parallel points after several hours of opiate, sedative, or alcohol withdrawal.* The cocaine abusers administered alcohol, anxiolytics, sedatives, opiates, or marijuana to induce sleep. Once sleep occurred, prolonged hypersomnolence followed. The "crash's" length was related to the duration and intensity of the preceding binge. The exhaustion, depression, and hypersomnolence of the crash probably reflect acute neurotransmitter depletion caused by the preceding cocaine binge [16]. Clinical recovery from the "crash" in part depends on sleep, diet, and probably time for neurotransmitter synthesis and repletion. Usual management included nutrition and rest. When the abuser awakens from the hypersomnolence, few crash residua persisted, and the offset of the crash is therefore self-limited.

The crash had sometimes been confused with withdrawal from cocaine by prior investigators [14,17,18]. This confusion had resulted in the erroneous perceptions that *(1)* withdrawal symptoms ended with resolution of the crash; *(2)* no withdrawal treatment was needed, since the crash was self-limited; and *(3)* withdrawal symptoms in cocaine abuse were intense but short. Other investigators questioned whether the crash was even a withdrawal equivalent. Instead they considered it an acute reaction to the massive stimulation of the cocaine binge, concluding that no neurophysiological

adaptation to cocaine occurred and that therefore no withdrawal treatment was necessary [19]. We hypothesized instead that the crash was like the acute withdrawal of the alcohol "hangover" [7,20] and concurred that it does not contribute to long-term abuse. Because of the striking consistency of several-day intervals between cocaine binges, however, we then further evaluated whether other withdrawal symptoms with delayed emergence might be present.

Withdrawal (Phase 2): The usual manifestations of physiological withdrawal symptoms (e.g., hypertension, tachycardia, diaphoresis, piloerection, seizures, cramps) that are produced by abused drugs such as opiates or alcohol are absent in cocaine abusers, which led to the belief that cocaine's addiction was purely "psychological." We observed the gradual onset of a significant protracted dysphoric syndrome, including decreased activation, amotivation, and intense boredom with limited pleasure from the environment (anhedonia), after a variable, brief (one to five days) euthymic interval following the crash. These subtle psychological symptoms were less dramatic than those of the crash and went unrecognized by most early observers. We observed no gross physiological alterations. The symptoms were generally not constant or severe enough to meet psychiatric diagnostic criteria for major mood disorders. Such symptoms nonetheless frequently led to resumption of cocaine use and repetition of a cyclical pattern: binge—crash—euthymic interval—anhedonia—relapse—binge.

Of additional importance was our observation that abusers were often able to withstand the anhedonia of this phase until confronted with classically conditioned cues that evoked memories of cocaine euphoria. Conditioned cocaine cravings were cued by varied, idiosyncratic objects or events that had been temporally paired with cocaine euphoria. Cues included specific persons, locations, or events (e.g., birthdays), or seeing abuse objects (e.g., money, glass pipes, mirrors, syringes, and single-edged razor blades, among many others). Internal cues also evoked craving (e.g., mild alcohol intoxication, or mood states, such as anxiety caused by interpersonal strife which the user had previously soothed by cocaine). When compared to the limited ability to experience pleasure during cocaine withdrawal, cues evoked vivid memories of extreme euphoria, inducing severe stimulant craving, and hence resumption of use. Once abstinence was sustained, however, anhedonic symptoms lifted within two to ten weeks.

Because the anhedonic state was directly related to craving and resumption of use, it paralleled "withdrawal" from other abused substances, except for the absence of gross physiological changes, and we thus termed it cocaine "withdrawal." As with other drugs of abuse, the withdrawal syndrome from cocaine was an inversion of acute drug effects. Cocaine *acutely* amplifies normal pleasure to produce exaggerated euphoria; cocaine *chronically* produces a withdrawal state of dampened euphoric response to produce anhedonia. The concordance of these symptoms with several types of data on neurophysiological and behavioral alterations after chronic stimulants in animals (reviewed below), and to pharmacotherapy effects (also reviewed below) led us to conceptualize this state as a plausible *psychological manifestation of neuroadaptation to chronic perturbation of brain reward systems by cocaine, and hence to hypothesize that its origins were physiological despite its primarily psychological symptom expression.*

Extinction (Phase 3): Despite resolution of the craving related to withdrawal anhedonia, intermittent cocaine craving was reported to recur by long-abstinent cocaine abusers based on cued memories of cocaine euphoria. As we followed our

sample over time, craving based on conditioned cues was reported months or even years after last cocaine use. The craving was episodic, lasting only hours. Lasting recovery from cocaine dependence appeared to depend on experiencing this intermittent conditioned craving without relapsing. The previous pairing of cues with euphoria would not occur, and, as expected in a classical conditioning phenomenon, extinction of craving gradually followed. Relapse caused by classically conditioned craving and withdrawal had previously been extensively described in opiate and nicotine withdrawal, so their appearance in cocaine abuse was unsurprising. The clinical impression we formed, however, was that evoked cocaine craving was more intense than that occurring with other commonly abused substances, a not unexpected finding given cocaine's extreme potency as a reinforcer in animal models, and the established linkage in animal experiments between strength of reinforcement and magnitude of classical conditioning. This finding led to a substantial appreciation of the importance of managing such cues, and to a focus on techniques to attenuate safely the potency of such cues in psychotherapy treatment and research efforts (reviewed below).

Psychiatric Co-Morbidity [7,8]

Weiss and colleagues [21–22] at MacLean Hospital conducted research on psychiatric disorder in inpatient cocaine abusers at the same time that we conducted similar studies in outpatients at Yale [7,20]. Research from both groups indicated that DSM-III Axis I interview timing and application had to be modified when applied to cocaine abuse and that, while some cocaine abusers suffer primarily from an addictive disorder, substantial proportions might be self-medicating psychiatric disorders such as depression.

Modification of interview timing was needed because "crash" symptoms mimic those of depressed states in affective disorders. In the diagnostic studies cited, DMS-III criteria were applied but clinical assessments were delayed, until crash symptoms should have abated, before diagnostic assessments took place. Significantly, application of this delay resulted in acceptable diagnostic validity [21].

In the two sets of two studies done by Weiss et al. [21,22] and ourselves [7,8], Axis I affective disorders were present in 30–50 percent of cocaine abuse treatment-seeking populations, and attention-deficit disorder-residual type (ADD-RT) was present in 3–5 percent. These findings suggested significant implications regarding predisposition to cocaine abuse. Anxiety or panic disorders and schizophrenia were almost absent, indicating that dysphoric effects of cocaine in these populations may select against the development of abuse. Conversely, the prevalence of cyclical mood disorder (cyclothymic disorder and bipolar disorder) may be ten times higher in cocaine abuse treatment populations compared to opiate and alcohol abuse populations, suggesting preferential selection for cocaine in such individuals.

It should be noted that, because of the coexistence of chronic cocaine abuse, it is impossible to be certain whether these disorders represented pre-abuse psychopathology, psychopathology exacerbated by cocaine, or cocaine-induced disorders. Similarly, the permanence of such states during long-term abstinence has not yet been determined. But, regardless of uncertainties over etiology or stability, the observation of diagnostically discrete sub-populations in cocaine abuse treatment populations has led to important clinical assessments of appropriate pharmacotherapies. In turn, remarkable amelioration of cocaine abuse has been reported in cyclical and attention-deficit disorder cocaine abusers treated appropriately with, respectively, lithium and

stimulant medications, while no response to these agents is found in cocaine abusers without these diagnoses (reviewed in [16]).

Continuing and Future Research on the Clinical Phenomenology of Cocaine Abuse

The studies reviewed created a foundation for investigation of cocaine abuse that helped clarify essential clinical research questions to be addressed in further, more rigorous studies and future research. Numerous investigators are currently examining the clinical characteristics of cocaine dependence. In studies now under way, we and colleagues are evaluating: *(1)* distinctions between cocaine users who have not sought treatment and those in our treatment programs, in order to learn about potential factors creating the transition to dependence and creating the motivation to seek treatment; *(2)* the range of abuse patterns and their development, in order to quantify severity and potentially to predict prognosis, as well as to facilitate development of accurate animal models of cocaine dependence (discussed below); *(3)* whether cocaine abstinence symptoms are amenable to structured, systematic assessment; the findings reviewed thus far have been substantiated by other clinical impressions reported by other investigators but have not yet been subject to structured research evaluations. Investigations are under way that will assess symptom expression in research hospital wards after experimental administration of cocaine. Both behavioral (e.g., ratings of withdrawal symptoms by blind raters) and neurochemical indices of cocaine withdrawal are being investigated. Furthermore, the application of new instruments developed for other psychiatric disorders (such as anhedonia scales developed for depression) to cocaine abusers is being assessed in clinical studies. *(4)* Factors that influence the time course and intensity of abstinence symptoms, such as total cocaine abuse history, recent use, co-use of other substances, and Axis I co-morbidity, are also being assessed in clinical studies. *(5)* The interrelationship of anhedonic craving for cocaine and craving evoked by cues is being explored. In opiate abuse, cues have been demonstrated to evoke not only a desire for opiate euphoria, but also withdrawal symptoms which in turn superimpose additional desire for opiates in order to relieve these symptoms. Whether cocaine cues can evoke or worsen anhedonia, in addition to provoking desire for cocaine euphoria, remains to be assessed.

EVOLVING APPLICATIONS OF PRE-CLINICAL RESEARCH TO CLINICAL PROBLEMS

When our studies began, it was assumed that neuroadaptation did not occur in human cocaine abuse and that cocaine was only "psychologically" addicting. Nonetheless, the brain's prototypical response to persistent, drug-induced neurochemical perturbation is homeostatic compensatory neuroadaptation. We consequently evaluated available pre-clinical data to determine if the abstinence symptomatology we observed might be based in neurophysiological adaptations to chronic cocaine administration.

Substantial pre-clinical research (reviewed in [23–25]) had established that cocaine and amphetamine facilitate activity of a central nervous system reward system, presumably by increasing neurotransmission in mesolimbic and/or mesocortical dopaminergic tracts. In humans, activation of these pathways would produce sensations of euphoria. Lesions in these pathways block cocaine effects in animal experiments. Dopamine receptor blockers, which should disrupt transmission in these pathways, also attenuate cocaine effects in animals. Furthermore, electrical self-

stimulation using electrodes placed in these pathways produces behavior identical to that observed in cocaine self-administration experiments.

Although less pre-clinical research on chronic cocaine administration had taken place than on acute cocaine effects, most reports described neurophysiological alteration from chronic administration of cocaine or the very similar abused stimulant, amphetamine. A crucial concordance existed between animal models of pleasure and our clinical observations of cocaine withdrawal. Intracranial electrical self-stimulation (ICSS) in animals, of the same dopaminergic reward pathways that are activated by acute cocaine administration, had previously been used as a model for human pleasure. Chronic stimulants decrease ICSS reward indices (reviewed in [11]). These ICSS decrements implied that chronic cocaine abuse could produce a neurophysiological downregulation of the brain reward regions activated by acute cocaine use. Such downregulation would be consistent with our clinical observations of protracted anhedonia in abstinent stimulant abusers. Complementary findings existed in neuroreceptor adaptation studies. Central dopaminergic, α-adrenergic, and β-adrenergic receptor supersensitivity were demonstrated after chronic cocaine administration (reviewed in [26]), but pre-synaptic and post-synaptic receptor changes were not differentiated in these studies. We hypothesized that relative autoreceptor supersensitivity would decrease dopaminergic neurotransmission and might provide a foundation both for the ICSS changes demonstrated in animals and the anhedonia observed in humans [7].

The concordance of clinical and pre-clinical data provided a foundation for the new hypothesis that clinical cocaine dependence was associated with sustained neurophysiological changes, but in brain systems that regulate only psychological processes—particularly, hedonic responsivity or pleasure—and therefore involved a true *physiological addiction* and withdrawal, but one *whose clinical expression appears primarily psychological.*

Despite the compelling concordance and parsimony of generalizing between pre-clinical findings and clinical findings on cocaine, the existence of a neuroadaptive withdrawal state in cocaine abusers remains a not yet proven working hypothesis. Before this hypothesis can be considered proven or disproven, not only will broader investigations of cocaine's consequences be needed, but also advances in research methodology: in particular, two fundamental research areas, both the foci of ongoing work, will require exploration.

The first area of investigation concerns whether the administration conditions in animal studies generalize to human abuse. Prior chronic animal paradigms have employed administration patterns that do not reflect human abuse patterns [27]. The chronic stimulant studies in animals involve daily intraperitoneal drug administration that may not accurately reflect the consequences of multi-dose binges and the multiple-day, cocaine-free intervals that characterize human abuse. Administration duration is also usually only one to three months in such experiments and may not accurately reflect the consequences of multiple years of cocaine abuse. Hence, more accurate reproductions of human drug self-administration are needed in future pre-clinical research.

Second, does evidence of neuroadaptation exist in human beings who abuse cocaine? While we [9,28] and others [18,29] have conducted studies of neuroendocrine indices and neurotransmitter metabolite levels, as indices of dopaminergic function, that appear to be consistent with animal data, such indirect peripheral indices can be

confounded by multiple sources. For example, other drugs abused, altered sleep cycles, concurrent medical or psychiatric disorder, and diet might all alter peripheral indices of central neurotransmitter function, as might duration of abstinence, intensity of abuse, and genetic heterogeneity, among many others [9]. These confounds caused by differences in antecedent history can, at present, only be resolved by chronic cocaine studies in animals that control for all variables other than cocaine administration. Advances in imaging, particularly *in vivo* imaging of humans, may soon obviate the problems of examining animals or peripheral indices in humans, by directly evaluating metabolism and neurochemistry in the brains of cocaine abusers. The spatial resolution of current positron emission tomographic scanning and magnetic resonance spectroscopic imaging are currently insufficient to demarcate brain function in the dopaminergic reward regions of principal interest in cocaine abuse studies, but rapid advances in these imaging technologies may make such studies possible in the near future. Preliminary imaging studies of cocaine abusers in withdrawal have already been done [30,31].

Finally, future research supporting the hypothesis of a neuroadaptive withdrawal state should also be able to quantify the extent of neuroadaptation. Our preliminary clinical observations indicate that both symptom severity and duration were related to the length and intensity of the preceding chronic abuse. Predisposing psychiatric disorders also amplified withdrawal [7]. Conversely, in infrequent "recreational" cocaine users without psychiatric disorders, withdrawal may not occur. High-intensity "binge" cocaine use and coinciding neuroadaptation might be required before withdrawal occurs. Basic research is thus needed to determine how to "stage" neurophysiological alterations produced by cocaine abuse, and to determine the extent to which inter-individual differences exist in susceptibility to and recovery from cocaine neuroadaptation. Such information would aid in providing a precise scientific foundation for a cocaine abuse treatment design.

EVOLVING TREATMENT STRATEGIES

As cocaine abusers began to appear for treatment throughout the United States, available drug treatments, usually alcohol or opiate abuse psychotherapies, were applied without adaptation for the unrecognized specific problems, such as anhedonia or conditioned craving, in cocaine dependence [5,32].

Cocaine abuse treatment, like other substance abuse treatment, can be subdivided into two phases, abstinence initiation and relapse prevention. These correspond to the withdrawal and extinction phases of cocaine abstinence [27].

Abstinence Initiation Strategies

Continued cycles of stimulant binges or of daily use are likely as long as anergic and anhedonic symptoms are present. Hospitalization, group and individual psychotherapy, and treatment contracts involving aversive contingencies for continued drug use have long been employed to facilitate abstinence in varied substance abuse populations and have been routinely employed in cocaine abuse treatment. Of these, only hospitalization has the advantage of ensuring abstinence. Hospitalization, however, also has the simultaneous disadvantage of isolation from the cue-rich environment, precluding extinction during an inpatient stay.

We and others considered these approaches either inadequate or too costly and sought new alternatives to treatment of cocaine anhedonia, exploring pharmacological

treatments aimed at reversing the hypothesized deficits in dopaminergic reward systems.

Anhedonia is a common symptom in multiple psychiatric disorders, especially unipolar and bipolar depression. Tricyclic antidepressants (TCAs), while having broad effects on numerous depressive symptoms, also effectively reverse the anhedonia of severe depression. While only 10 percent of cocaine abusers in treatment samples met criteria for severe depression, most cocaine abusers report anhedonic symptoms, and we reasoned that such agents might have specific anti-anhedonic effects in this population. Pre-clinical data strengthened this possibility. Chronic TCA effects on neurophysiology are generally opposite to those of chronic cocaine: they induce receptor subsensitivity rather than supersensitivity. In particular, TCAs produce autoreceptor subsensitivity in dopaminergic systems and increase dopaminergic transmission, which would oppose the dopaminergic autoreceptor supersensitivity we hypothesized to underlie cocaine anhedonia. More important, in a little-noticed study done in 1974, Simpson, investigating whether stimulant-induced ICSS deficits might provide a useful model for severe depressive disorders, demonstrated that chronic desipramine treatment increased sensitivity to electrical stimulation in ICSS animals pre-treated with stimulants, thereby reversing the chronic effect of the stimulants [33]. The same findings were later extended to other closely related tricyclic antidepressants [34]. These results had implications not only as a model for affective disorder but also had direct implications for stimulant abuse treatment. Regardless of whether autoreceptor changes in dopaminergic tracts are responsible for ICSS changes and their reversal by TCAs, or some other mechanism, is responsible, these data implied that cocaine anhedonia could be reversed by TCAs.

Despite the presence of significant suggestive animal data from electrophysiology and neurochemistry research, a decade passed before clinicians began to explore the possible utility of tricyclic antidepressants in human stimulant abusers. Shortly after establishing the cocaine clinic in 1982, we began a series of pharmacotherapy pilot trials in cocaine abusers. In addition to evaluating the efficacy of a TCA, desipramine, we studied two other agents. Methylphenidate was evaluated because of the possibility that it might rapidly restore dopaminergic reward functioning, analogous to methadone treatment for heroin abusers, and lithium was evaluated because of anecdotal accounts that it had benefitted some stimulant abusers.

The first two trials were open-label comparisons. Subjects in both open trials were psychotherapy-resistant, outpatient cocaine abusers. The first study [26] compared desipramine plus psychotherapy, lithium carbonate plus psychotherapy, and psychotherapy alone in chronic cocaine abusers who had failed to stop cocaine abuse with the help of psychotherapy alone. Six desipramine patients (200 mg/day) uniformly decreased and ultimately ceased their cocaine use during the 12-week trial. Craving did not change from pre-treatment until the third week of pharmacotherapy, consistent with the delayed efficacy of TCAs in depression and the delay before receptor changes take place in TCA animal studies [35]. By the end of week three, craving scores were reduced to one-third of their pre-treatment value. Declines in cocaine use paralleled the craving scores. Decreases in use and craving occurred regardless of other coexisting psychiatric disorders. Subjects without depressive disorders appeared to benefit from a subtle but consistent increase in the ability to respond to pleasurable stimuli. Desipramine was uniformly well-tolerated. In addition to these six patients who were being studied in the formal pilot trial, we reported on an additional six cocaine abusers

treated with desipramine, and the results were essentially the same. Taken collectively, the pilot study found that desipramine decreased cocaine craving and resulted in abstinence in 11 out of 12 chronic cocaine abusers (92 percent).

All of the subjects being treated with psychotherapy alone reported persistent subjective cravings for cocaine. Only one of the six (17 percent) was able to abstain totally from cocaine, and only half the group showed any improvement. Six patients received a combination of lithium plus psychotherapy. Only subjects with cyclothymic disorder became abstinent in this group.

We continued evaluating TCAs in a second open pilot trial [8,36] in which the subjects consisted only of individuals without diagnoses of affective disorders, in order to assess further whether TCA responses occurred in subjects who did not meet criteria for depression. Twenty-six patients without major affective disorders were selected. The methods employed were otherwise the same as in the first trial. Six patients declined pharmacotherapy and were used as a non-medication comparison group. Open pharmacological treatment was added to the psychotherapy treatment regimen in the remaining 20 patients, who were randomly assigned to desipramine, or a comparison active treatment (lithium or methylphenidate).

Desipramine hydrochloride produced abstinence in over 80 percent of a desipramine group, compared to less than 40 percent in comparison groups who were given other agents (lithium and methylphenidate) or continued in psychotherapy without medication. As in our first study, craving and cocaine use decreased in the desipramine group after a typical tricyclic time lag. Methylphenidate produced rapid reductions in craving during the first week that then reversed. As methylphenidate tolerance developed, subjects described conditioned craving as a result of mild methylphenidate stimulation. The methylphenidate trial was stopped after five subjects had been treated for four weeks because all five deteriorated clinically [37]. Subsequent subjects were given lithium.

Similarly promising results occurred in an independent, simultaneous open trial in an unselected population using another tricyclic, imipramine, conducted by Rosecan and colleagues [38]. Tennant and colleagues [39] assessed short-term, low-dose desipramine courses, which do not produce the neurophysiological changes of longer courses [35], and found that these did not facilitate abstinence. By 1985, four groups had reported open-trial data that TCAs facilitated recovery from cocaine abuse.

These promising early results led to a substantial effort to evaluate these findings using double-blind methods. Gianinni et al. recently completed the first double-blind trial in 24 cocaine abusers, contrasting desipramine to an active placebo, diphenhydramine [40]. Ongoing, double-blind, placebo-controlled studies by ourselves and O'Brien et al. have also reported mid-point data; these investigations have confirmed that desipramine produces statistically and clinically significant increases in abstinence rates [36,41] and decreases in cocaine use, craving, and symptom scores [36,40–41].

While these findings remain tentative, since two of the studies require completion, they imply that a generally effective pharmacotherapy to facilitate abstinence initiation exists. Three additional groups have recently initiated double-blind TCA trials, and a complete assessment of the value of TCAs in the abstinence initiation phase of cocaine abuse treatment will shortly exist. If proven effective by this collective research, an extremely important, new, effective, inexpensive, and expedient modality for cocaine abuse treatment will be available for the first time.

Other experimental pharmacological research strategies, all based on a rationale of increasing reward transmission in dopaminergic reward systems, are also in preliminary stages of investigation. Most are attempts to increase dopaminergic neurotransmission directly using dopamimetic agents like amantidine [42], bromocriptine [43], tyrosine [44], and, as described above, methylphenidate [37]. These agents have all been reported to produce acute decreases in cocaine craving in small, short-term open trials, lending further substantiation to the hypothesis that cocaine produces a neuroadaptation that can be affected pharmacologically. The clinical utility of these treatments, however, is less clear than for TCAs. Tennant and colleagues conducted a double-blind comparison of amantidine and bromocriptine in 14 cocaine abusers [42], but 71 percent of the bromocriptine subjects dropped out because of side effects, rendering the amantidine findings difficult to interpret. Giannini has reported double-blind reductions in symptom scores in bromocriptine-treated subjects compared to those given placebo but did not report abstinence or craving data.

Relapse Prevention Strategies

While relapse prevention pharmacotherapies exist for opiate and alcohol abuse (naltrexone and disulfiram, respectively), no similar pharmacotherapy has yet emerged for cocaine dependence (possible stimulant blockade has also been tried using lithium [26], trazodone [45], imipramine, and neuroleptics [25], but these experiments have not yet demonstrated a clinically useful blockade of cocaine effects for any pharmacotherapy).

Beginning studies are now under way in our treatment programs to elucidate which psychotherapeutic techniques best preclude relapse in cocaine abusers. The approaches under study are generally comparable to those used after withdrawal in other substance abuse treatments [46]. The goal of relapse prevention is gradually to decrease the external controls placed on the abuser, by family and therapist, during initiation of abstinence, and gradually to facilitate development of the abuser's internal controls. Relapse prevention techniques include extinguishing conditioned cues, reducing external dysphoria and stress, developing drug-free socialization networks, predicting situations of high relapse risk, rehearsing avoidance strategies, and connecting memories of negative consequences of cocaine abuse to positive memories of cocaine in order to counteract evoked memories of cocaine euphoria. Idiosyncratic needs in the addict's life that the stimulant may have met, albeit dysfunctionally, are also explored and constructive alternatives to meeting these needs are pursued [47].

While conceptually attractive and clinically expedient, such techniques have not yet been systematically evaluated. Using precisely applied, research psychotherapy methodologies, fundamental questions are now being assessed as to whether systematic application of these straightforward relapse prevention techniques improves outcome compared to less directive psychotherapy. Examples of questions being addressed by current studies include: *(1)* What is the relative value of each of the relapse techniques listed above? *(2)* Can internal cues (e.g., those evoked by mood states or interpersonal strife) be extinguished as readily as external cues (e.g., locations where cocaine was used) that are more easily reproduced and controlled? *(3)* When should return to the cue-rich environment be avoided, and when should it be advocated? *(4)* Do such treatments have additive or interactive effects when combined with pharmacotherapies? While this research is in its infancy, it promises guided, rational application of psychotherapy to prevent relapse.

CONCLUSION

The advent of cocaine dependence as a drug-dependence disorder without gross physiological withdrawal symptoms forces reconceptualization of "classic" drug abuse constructs such as dependence, tolerance, and withdrawal. These constructs have been based on gross physiological measures and have been unchanged for decades. There exist for benzodiazepines, alcohol, and opiates excellent anti-withdrawal agents that reverse gross physiological withdrawal symptoms, but these agents have not solved the problem of addiction to these drugs. This implies that other symptoms contribute to unrelenting abuse. These symptoms may be of the same order as the psychological symptoms expressed in cocaine withdrawal and may also be neurophysiological in origin. The lack of broad clinical applicability of "classic" constructs of withdrawal, tolerance, and dependence based on gross physiological parameters has led the World Health Organization to discard old terms in favor of the more physiologically precise "neuroadaptation" [48], and recently led the American Psychiatric Association to define drug dependence in behavioral rather than gross physiological terms for the first time [49].

The concept of cocaine dependence has evolved, within one decade, from a non-existent disorder to a complexly regulated disorder with interwoven behavioral, psychological, and neurophysiological components. It is unlikely that a shift of similar magnitude will result from our or other's research efforts during the next decade; instead, future research, at Yale's cocaine abuse clinic and elsewhere, will provide increasingly precise depictions of the details of the development, expression, and management of cocaine abuse.

REFERENCES

1. Grinspoon L, Bakalar JB: Drug dependence: non-narcotic agents. In Comprehensive Textbook of Psychiatry, 3rd edition. Edited by HI Kaplan, AM Freedman, BJ Sadock. Baltimore, Williams and Wilkins, 1980
2. National Commission on Marihuana and Drug Abuse: Drug Use in America: Problems in Perspective. Second Report of the National Commission on Marihuana and Drug Abuse. Washington, DC, National Institute on Drug Abuse, March 1973
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders—III (DSM-III). Washington, DC, American Psychiatric Association Press, 1980
4. Gawin FH, Kleber HD: Medical Management of Cocaine Withdrawal. New York, Weber/Myrstad, 1986
5. Kleber HD, Gawin FH: The spectrum of cocaine abuse and its treatment. J Clin Psychiat 45:18–23, 1984
6. Gawin FH, Kleber HD: Cocaine use in a treatment population: Patterns and diagnostic distinctions. Natl Inst Drug Abuse Monogr Ser 61. Washington, DC, U.S. Government Printing Office, 1985, pp 182–192
7. Gawin FH, Kleber HD: Abstinence symptomatology and psychiatric diagnosis in chronic cocaine abusers. Arch Gen Psychiat 43:107–113, 1986
8. Gawin FH: New uses of antidepressants in cocaine abuse. Psychosomatics 27:s24–s29, 1986
9. Gawin FH, Kleber HD: Neuroendocrine findings in chronic cocaine abusers. Brit J Psychiat 147:569–573, 1985
10. Ellinwood EH, Petrie WM: Dependence on amphetamine, cocaine and other stimulants. In Drug Abuse: Clinical and Basic Aspects. Edited by SN Pradhan. New York, CV Mosby, 1977, pp 248–262
11. Gawin FH, Ellinwood EH: Stimulant abuse treatment. In Psychiatric Treatment Manual: Substance Abuse. Edited by HD Kleber. Washington, DC, American Psychiatric Association Press, in press
12. Johanson CE: Assessment of the dependence potential of cocaine in animals. Natl Inst Drug Abuse Res Monogr Ser 50. Washington, DC, U.S. Government Printing Office, 1984, pp 54–71

13. Kleber HD: Drug abuse. In A Concise Handbook of Community Mental Health. Edited by L Bellak. New York, Grune and Stratton, 1974
14. Seigel RK: Cocaine smoking. J of Psychoactive Drugs 14:321–337, 1982
15. Anonymous: Adverse effects of cocaine abuse. Med Lett Drugs Ther 26:51–52, 1984
16. Gawin FH, Kleber HD: Pharmacological treatment of cocaine abuse. Psych Clin N Am 9:573–583, 1986
17. Khantzian EJ: Cocaine dependence, an extreme case and marked improvement with methylphenidate treatment. Am J Psychiat 140:784–785, 1983
18. Dackis CA, Gold MS, Sweeney DR: The physiology of cocaine craving and 'crashing' [letter]. Arch Gen Psychiatr 44:298–300, 1987
19. Anker AL, Crowley TJ: Use of contingency in speciality clinics for cocaine abuse. Natl Inst Drug Abuse Res Monogr Ser 41. Washington, DC, U.S. Government Printing Office, 1982, pp 452–459
20. Kleber HD, Gawin FH: Cocaine withdrawal [reply]. Arch Gen Psychiatr 44:298–299, 1987
21. Weiss RD, Mirin SM, Michael JL, Sollogub AC: Psychopathology in chronic cocaine abusers. Amer J Drug Alcohol Abuse 12:17–29, 1986
22. Weiss RD, Mirin SM, Michael J, Griggin M, Sollogub A: Psychopathology in drug abusers and their families. Presented at the 140th meeting of the American Psychiatric Association, Chicago Illinois, May 12, 1987
23. Wise R: Neural mechanisms of the reinforcing action of cocaine. Natl Inst Drug Abuse Res Monogr Ser 50. Washington, DC, U.S. Government Printing Office, 1984, pp 15–53
24. Spyraki C, Fibiger HC, Phillips AC: Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6 hydroxydopamine lesions. Brain Res 253:195–203, 1982
25. Gawin FH: Neuroleptic reduction of cocaine-induced paranoia but not euphoria? Psychopharmacology 90:142–143, 1986
26. Gawin FH, Kleber HD: Cocaine abuse treatment: open pilot trial with desipramine and lithium carbonate. Arch Gen Psychiatr 42:903–910, 1984
27. Gawin FH, Kleber HD: Issues in cocaine abuse treatment research. In Cocaine: Clinical and Biobehavioral Aspects. Edited by S Fischer, B Raskin, R Uhlenhuth. New York Oxford University Press, 1986, pp 169–187
28. Kleber HD, Gawin FH: The physiology of cocaine craving and 'crashing' [reply]. Arch Gen Psychiat 44:300–301, 1987
29. Giannini AJ, Malone DA, Loiselle RH, Price WA: Blunting of TSH response to TRH in chronic cocaine and phencyclidine abusers. J Clin Psychiatry 48:25–26, 1987
30. Baxter LR: Localization of the neurochemical effects of cocaine and other stimulants in the human brain. Presented at the North American Conference on Cocaine Abuse and Its Treatment, Washington, DC, September 16, 1987
31. Gawin FH, Gore JC, Byck R: Cocaine abuse: Central neuropathology detected with MRI? Submitted for publication
32. Kleber HD, Gawin FH: Cocaine abuse: a review of current and experimental treatments. Natl Inst Drug Abuse Res Monogr Ser 50. Washington, DC, U.S. Government Printing Office, 1984, pp 111–129
33. Simpson DM, Annau Z: Behavioral withdrawal following several psychoactive drugs. Pharmacol Biochem Behav 7:59–64, 1977
34. Kokkinidis L, Zacharko RM, Predy PA: Post-amphetamine depression of self-stimulation responding from the substantianigra; reversal by tricyclic antidepressants. Pharmacol Biochem Behav 13:379–383, 1980
35. Charney DS, Menkes DB, Heninger GR: Receptor sensitivity and the mechanism of action of antidepressant treatment. Arch Gen Psychiat 38:1160–1180, 1981
36. Gawin FH, Byck R, Kleber HD: Desipramine augmentation of cocaine abstinence: initial results. Presented at the 15th Collegium Internationale Neuropharmacologicum, San Juan, Puerto Rico, December 15, 1986; proceedings in Clin Neuropharmacol 9(Supplement 4):202–204, 1986
37. Gawin F, Riordan C, Kleber HD: Methylphenidate use in non-ADD cocaine abusers—a negative study. Amer J Drug Alcohol Abuse 11:193–197, 1985
38. Rosecan J: The treatment of cocaine abuse with imipramine, L-tyrosine, and L-tryptophan. Presented at the VII World Congress of Psychiatry, Vienna, Austria, July 14–19, 1983
39. Tennant F: Double-blind comparison of desipramine and placebo in withdrawal from cocaine dependence. Natl Inst Drug Abuse Res Monogr Ser. Washington, DC, U.S. Government Printing Office, in press

40. Giannini AJ, Malone DA, Giannini MC, Price WA, Loiselle RH: Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. J Clin Pharmacol 25:211–214, 1986
41. O'Brien C: Controlled studies of pharmacologic and behavioral treatments of cocaine dependence. Presented at the North American Conference on Cocaine Abuse and Its Treatment, Washinton, D.C., September 16, 1987
42. Tennant FS Jr, Sagherian AA: Double-blind comparison of amantidine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch Intern Med 147:109–112, 1987
43. Dackis CA, Gold MS: Bromocriptine for cocaine withdrawal [letter]. Lancet i:1151–1152, 1985
44. Gold MS, Pottash ALC, Annitto WD: Cocaine withdrawal: efficacy of tyrosine. Presented at the Society for Neuroscience, 13th annual meeting, Boston, MA, November 7, 1983
45. Rowbotham M, Jones RT, Benowitz N, Jacob P: Trazodone-oral cocaine interactions. Arch Gen Psychiat 41:895-899, 1984
46. Marlatt GA, Gordon JR: Determinants of relapse: Implications for the maintenance of behavior change. In Behavioral Medicine: Changing Health Lifestyles. Edited by PO Davidson, SM Davidson. New York, Brunner/Mazel, 1980, pp 410–452
47. Rounsaville BJ, Gawin FH, Kleber HD: Interpersonal psychotherapy (IPT) adapted for ambulatory cocaine abusers. Am J Drug Alcohol Abuse. 11:171–191, 1985
48. World Health Organization, WHO Expert Committee on Addiction-Producing Drugs: Nomenclature and classification of drug and alcohol-related problems. Bull WHO 39:225–242, 1981
49. Rounsaville BJ, Spitzer RL, Williams JB: Proposed changes in DSM-III substance use disorders: Description and rationale. Am J Psychiatry 143:463–468, 1986