

A 28-Year-Old Man Addicted to Cocaine

Steven E. Hyman, MD, Discussant

DR REYNOLDS: Mr R is a healthy 28-year-old man with a 4-year history of cocaine addiction. He lives in Boston with his girlfriend. He has Massachusetts free care insurance coverage and sees his primary care physician, Dr B, at Beth Israel Deaconess Medical Center.

About 4 years ago at a party, Mr R first tried cocaine intranasally. Although he did not seek out more cocaine, about 6 months later, he smoked some cocaine. He has been pursuing smoked cocaine, or crack, ever since. He began using crack several times a day, subsequently losing jobs, apartments, and relationships. He stole a car from his family and money from his friends.

Family and friends have tried to help Mr R. He has been in 2 inpatient treatment programs, first referred by his brother and then by his parents. He stayed for 5 months of a 6-month program, finding its 12-step approach helpful. For about 6 weeks after leaving the program he stayed clean, but one evening gave in to a craving and again started smoking crack. His family disowned him, and he and his girlfriend, who worked at the inpatient treatment center, moved to Boston.

In Boston, Mr R initially was sober for 6 weeks, but has since continued to smoke crack. In the summer of 2000, he came to Beth Israel Deaconess Medical Center requesting treatment. Mr R is enrolled in individual counseling with a social worker and in a weekly group for patients with substance abuse. He has also seen a psychiatrist in consultation. Mr R goes on a "binge" about once every 7 to 10 days, using crack for approximately 24 straight hours. Although his girlfriend holds most of his money, he retains some and panhandles for cash during binges.

Recently, Mr R was admitted to the hospital for cocaine-related chest pain; he had not had a myocardial infarction (MI). In the past, he fractured his right femur and left clavicle in a motor vehicle crash. He once had a kidney stone. Tests for antibodies to human immunodeficiency virus and hepatitis C were negative.

His family history is significant for cancer of unknown type in his father. His mother is an alcoholic who has been sober for the past 20 years.

Mr R does not take medications. His psychiatrist recommended that he try gabapentin to curb his cravings, but this medication is not covered by Massachusetts free care insurance. He has applied for further medical assistance, which

would make him eligible for a more intensive, outpatient, nightly treatment program and for gabapentin.

Mr R wonders if any medications or other treatments might help him achieve his goal of abstinence, marriage, and financial security.

MR R: HIS VIEW

I first started using cocaine about 4 years ago. I don't remember the first time I smoked the crack cocaine. It puts you in another world. I can't explain this euphoric feeling that it gives you, but it's a feeling I had never experienced before. I just want to sit there and enjoy the feeling and not think about anything or do anything. I have to keep doing it constantly to keep up the high.

I actually started staying out all night. I was smoking about 5 times a week and lost my apartment, lost everything. Everything was falling apart with my relationship, and I was starting to miss work a lot. But I just couldn't control it. You know, it overtook me. That's all I thought about and all I wanted to do was to keep smoking. Everything else was secondary.

An intense craving for me is when my heart starts beating fast—actually, I get a little sweaty—and all I think about doing is just going to smoke. That's it. Nothing else—everything that's on my mind just kind of disappears. First you start thinking about it, then your body almost reproduces the feeling that you get from a high.

The treatment center was an inpatient, intensive treatment program. It was a 6-month program and I stuck it out for 5 months. Then I moved into a halfway house and got myself a job. And one night, I wanted to smoke. I just said, "I want to smoke again. I want that feeling again." And I went out and picked up again.

From pretty much then on, I have been using regularly about once a week, once every 2 weeks. Today I have 9 days clean. During the past month, I've used only 2 or 3 times, so I'm curbing it down. I'm getting really sick and tired of

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it, honestly, of the consequences and of the using. And I don't think the high is what it used to be. It's kind of getting monotonous to me. It's getting old. I don't know what it's going to take [for me to stop]. I know I'm the only one who can do it. You know, everyone can tell me to do this and do that, but not until I make that decision that I'm going to get clean 100%.

My concerns are that I will never be able to get this under control and that I'm always going to be struggling with this. I know it's always going to be an issue in my life, but I don't want it to be as persistent as it is. Hopefully when my life is, you know, if it ever comes to that point where I have a family and I have the career that I want, I won't need that escape or need that extra feeling. I'll be high on life, you know, just . . . naturally.

DR B: HER VIEW

I think he's actually quite insightful and well spoken about his drug use. It's a pleasure to work with him, but it's also frustrating. It very clearly shows us the limits of our abilities in terms of substance abuse. It also shows the power that this particular substance can have over people. He wants this high, and he knows he wants this high. I think he knows he wants it regardless of what the fallout is, in part because the fallout has never been so severe for him. He has a big support network, bigger than most people in his situation have. He has a girlfriend, he has a therapist, he has a group, he has friends who continue to employ him. He has a doctor and he has free care. Yet, his life centers around cocaine in a very deeply embedded way. He thinks about it all the time.

He says he wants a house and kids and hopes that life will give him that high. I don't know whether life is ever going to give him the high feeling that he's looking for, because the high that he's talking about is a high that obliterates thinking about anything else.

A couple of weeks ago after a 24-hour binge, he was admitted to the hospital to rule out MI. I hoped that the hospitalization might have been a turning point in his treatment, because I think it probably brought home the fact that cocaine can have serious medical consequences. While he was in the hospital, I told him that I feel like he knows that he's at a point where he can use and get away with it. I don't hear him say, "I really want to be clean." I'd like to hear him say that. I don't know if saying that is adequate, but I think it's necessary to get him really clean.

AT THE CROSSROADS: QUESTIONS FOR DR HYMAN

What are the current patterns of cocaine addiction in the United States? What are the neural pathways of cocaine's action and the mechanisms of addiction? How is smoking crack different from inhaling cocaine? What treatments can we offer? What determines success of rehabilitation? What is the role of the primary care clinician for patients with narcotic addiction? What do you recommend for Mr R?

DR HYMAN: The defining characteristic of addiction is compulsive, out-of-control drug use despite serious negative consequences. The life of the addicted person, in this case Mr R, revolves around obtaining, using, and recovering from the effects of drugs, despite drug-related problems, which for Mr R include a recent bout of chest pain, a car crash, failures in life roles, and serious interpersonal problems. To family, friends, and clinicians alike, the behavior of Mr R may seem incomprehensible. Although there is no specific crisis at this point in the treatment of Mr R, his case can well be considered to be at a crossroads. As is all too common in the treatment of addiction, the hopes of the treating physician are being progressively eroded and the reasonable options for this bright, articulate young man seem progressively fewer. Despite the recent admission to rule out an MI, which seemed a good opportunity for Mr R to comprehend the error of his ways, little has actually changed.

In fact, there is no "magic bullet" to treat addiction to cocaine or other drugs. There is recent documentation that relatively stable patients with drug addiction can be managed successfully in the primary care setting.^{1,2} However, effective management depends on conceptualizing addiction as a chronic, relapsing medical illness.³⁻⁵ Like other medical illnesses, addiction has identifiable risk factors, a typical natural history, and an increasingly well-understood pathophysiology. Nevertheless, the care of addicted individuals in any setting is difficult and often frustrating. It is therefore useful for the treating physician to have a cognitive framework within which to understand compulsion and "loss of control" over drug use,^{3,4} as well as the persistence of relapse risk.^{4,5} Finally, it is useful for the primary care clinician to understand the behavioral as well as the pharmacologic principles that underlie treatment.

Epidemiology

The overall use of illicit drugs for most segments of the US population peaked in approximately 1980 and, after a period of decline, remained relatively stable throughout the 1990s. Within this overall trend, however, there are significant drug-specific patterns. Among 18- to 25-year-olds, the group with the highest rates of illicit substance use, cocaine use peaked in 1979 when 10% of respondents had used the drug during the past month; this rate declined to 2% in 1998.^{6,7} While rates of cocaine use were relatively stable through the 1990s, use of heroin and methamphetamine increased. Recent years have also seen a marked increase in the use of "club drugs" such as methylenedioxy-methamphetamine (ecstasy).⁶ Of the illicit drugs, marijuana remains the most commonly used. Estimates based on survey data from 1997 and 1998 suggest that 23.1% of high school seniors and 8% of youth age 12 to 17 years smoked marijuana during the previous month.⁷ Poly-substance abuse including tobacco, alcohol, and illicit drugs is increasingly common.

The National Comorbidity Survey measured rates of substance use and "dependence" in the noninstitutionalized ci-

vilian population in the 48 contiguous United States.⁸ (In this study dependence was defined by the criteria of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, which like the current fourth edition,⁹ uses the term "dependence" in place of addiction). More than 8000 persons 15 to 54 years of age were interviewed. In this door-to-door survey, 7.5% of individuals were found to be dependent on a psychoactive substance at some time in their lives. Males were significantly more likely than females to have such a lifetime history (9.2% vs 5.9%). This sex disparity in rates of dependence was attributable both to males being more likely to use drugs and, among those who used drugs, being more likely than females to become dependent (16.4% vs 12.6%).⁸ The prevalence of dependence was highest for the group age 15 to 24 years (3.3%) compared with those age 25 to 34 years (1.6%) or those age 45 to 54 years (0.7%). A replication of the National Comorbidity Survey to provide current usage statistics is now under way.

Risk Factors

For drug abuse and addiction, the best-validated risk factors are family history and male sex. In one family study, first-degree relatives of affected probands exhibited an 8-fold increase in risk of substance use disorders involving a wide range of substances.¹⁰ The general familial risk factors for substance use disorders appear to be partly independent of factors involved in selection of a substance of choice.¹⁰⁻¹² This is relevant to Mr R, who is addicted to cocaine, but has a family history of addiction to another substance in that his mother has been treated for alcoholism. Twin studies^{12,13} suggest that familial risk of substance use disorders is due to genes rather than shared familial environment. Multiple adoption studies, which more clearly distinguish the ef-

fects of genes and environment, have been performed for alcoholism. The risk of alcoholism in early adoptees shows concordance with the biological not the adoptive parents.^{14,15} Analysis of the segregation of risk of alcoholism and other substance use disorders within families suggests that the influence of genes is complex, reflecting the interaction of multiple genes and nongenetic factors.

Significant environmental risk factors include drug availability and peer cultures that see drug use as desirable. Other risk factors for substance use disorders include certain psychiatric disorders,^{16,17} most notably conduct disorder in adolescents and antisocial personality disorder in adults. Attention-deficit hyperactivity disorder may also increase risk of substance use disorders.¹⁸ Pharmacologic treatment of attention-deficit hyperactivity disorder, including treatment with methylphenidate, reduces subsequent risk of drug abuse,¹⁸ even though methylphenidate itself can be abused. Other psychiatric disorders that may increase risk of substance use disorders are bipolar disorder, unipolar depression, and anxiety disorders.¹⁹ Mr R does not have any apparent comorbid psychiatric disorders.

Acute Actions of Cocaine and Other Addictive Drugs

Addictive drugs (TABLE)²⁰ are both rewarding (ie, interpreted by the brain as intrinsically positive) and reinforcing (ie, behaviors associated with such drugs tend to be repeated).²¹ Because they are rewarding, individuals use these substances to alter their mood or mental state. Because they are reinforcing, individuals tend to take them repetitively. Herein lies the central danger of addictive drugs: when they are used repetitively, molecular changes occur in the brain that promote continued drug taking in a manner that becomes increasingly difficult to control.^{4,5,22} In people who are vulnerable as a result of

Table. Addictive Drugs*

Class	Molecular Target	Examples
Opioids	Mu opioid receptor (agonist)	Heroin Hydromorphone (Dilaudid) Oxycodone (Percodan, Percocet, Oxycontin) Methadone (Dolophine) Meperidine (Demerol)
Sedative-hypnotics	GABA(A) receptor (agonist)	Barbiturates Methaqualone (Quaalude) Meprobamate (Miltown) Glutethimide (Doriden) Ethchlorvynol (Placidyl)
Psychomotor stimulants	Dopamine transporter (antagonist)	Cocaine Amphetamine derivatives
Phencyclidinlike drugs	NMDA glutamate receptor channel (antagonist)	Phencyclidine (PCP, or "angel dust") Ketamine
Cannabinoids	CB1 cannabinoid receptors (agonist)	Marijuana Hashish
Nicotine	Nicotinic acetylcholine receptor (agonist)	Tobacco products
Ethyl alcohol	GABA(A) receptor (agonist), NMDA glutamate receptor (antagonist), and multiple other targets	Multiple beverage products

*Caffeine can produce mild physical dependence, but does not produce addiction. Illegal drugs that are abused, but do not produce compulsive use, include anabolic steroids and hallucinogens such as lysergic acid diethylamide (LSD), mescaline, and psilocybin. GABA(A) indicates γ -aminobutyric acid receptor type A; NMDA, N-methyl D-aspartate. Table adapted from Hyman.²⁰

genetic and developmental risk factors¹⁰⁻¹⁴ and as a result of their current context (including drug availability), a transition to addiction may occur. Once addiction has taken hold, it tends to follow a chronic course³⁻⁵ in which periods of abstinence are followed by relapse to active drug use, most often caused by drug-related cues²³ or stress.²⁴

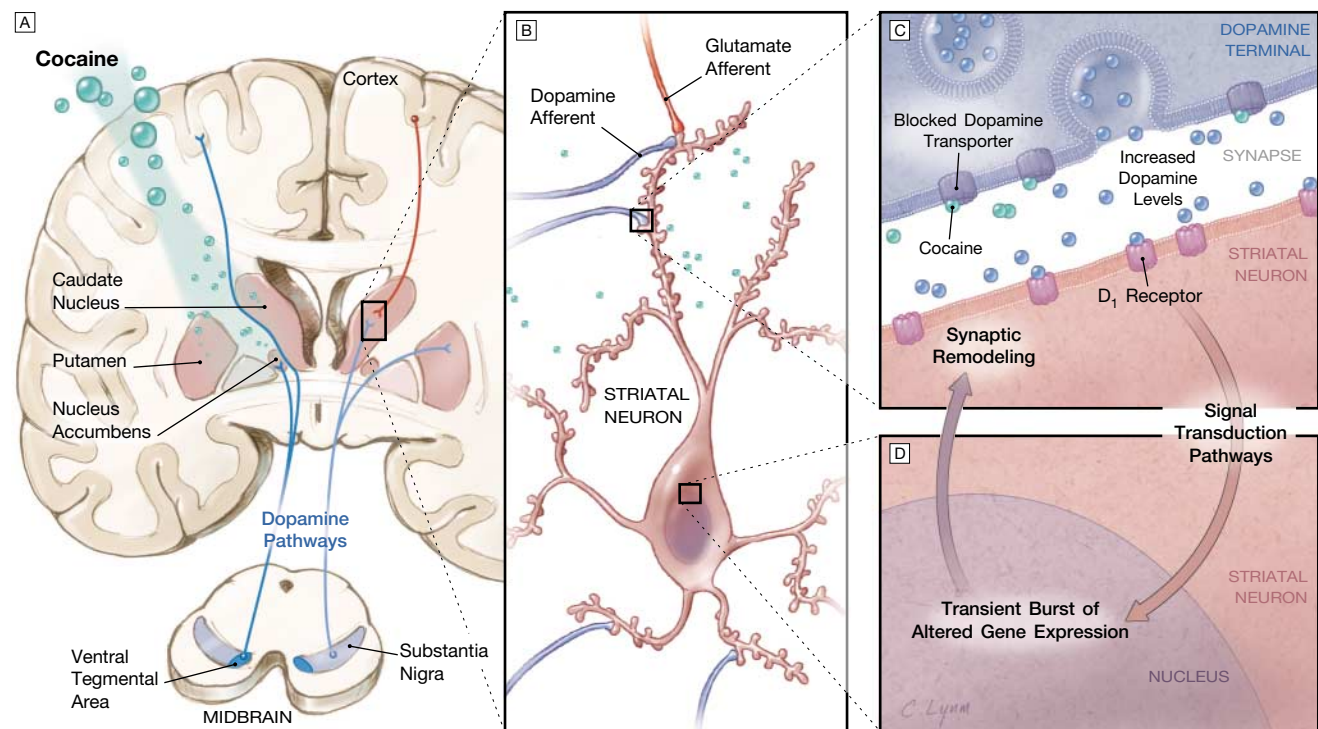
The critical circuit in the brain that underlies reward and reinforcement extends from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc) and uses dopamine as its major neurotransmitter (FIGURE). The drugs listed in the Table are addictive largely because of their shared ability to produce marked increases in levels of synaptic dopamine in this brain reward circuit.²⁵ Under normal circumstances, this circuit is a critical substrate for the rewarding and reinforcing effects of positive natural stimuli associated with survival, such as food and reproductive opportunities.^{4,5,21,26} The powerful control over behavior exerted by addictive drugs is thought to result from the brain's inability to distinguish between the activation of reward circuitry by drugs or by natural survival behaviors.^{21,27} Whether related to drug taking or survival, any behavior that activates this circuitry tends to be repeated.^{4,5,21,27} Our patient described a subjective correlate of

activating brain reward circuitry—his experience of intense euphoria. The neurotransmitters involved in the subjective aspects of drug taking are not yet certain.

In addition to shared effects on brain reward circuitry that makes them addictive, each class of drugs listed in the Table also has drug-specific properties. This is because receptors for these drugs are also found outside the VTA-NAc projection system on diverse neuronal populations. Thus, both morphinelike opiates (eg, heroin) and cocaine are addictive; but morphinelike opiates are analgesic and sedating, whereas cocaine is a psychomotor stimulant. Mr R's drug of choice, cocaine, increases synaptic dopamine by blocking the transporter that normally terminates dopamine action by taking it back up into presynaptic terminals.²⁶

Mr R first used cocaine nasally and found that he could "take it or leave it." However, once he began smoking cocaine, he became addicted. The route of administration of a drug has a marked impact on its addictive potential. The more rapid the rate of increase of drug levels in blood and brain, the greater the relative risk. Smoking is a particularly efficient way to produce a rapid increase in drug levels as lipophilic substances are exposed to the enormous sur-

Figure. Cocaine Addiction: Neural Pathways and Molecular Mechanisms



The neural substrates of cocaine action are shown at 3 levels: A, neural pathways on which cocaine acts; B, medium spiny neurons in the nucleus accumbens (ventral striatum) and dorsal striatum (caudate nucleus and putamen), which receive dopamine afferents from the ventral tegmental area and substantia nigra, respectively; and C and D, molecular level, including the synapse (C) between the dopamine terminal and the medium spiny neuron in which cocaine acts to increase dopamine levels, and (D) altered gene expression in the nucleus of the medium spiny neuron that is hypothesized to yield transcripts and eventually proteins that act to remodel synapses. Synaptic remodeling is thought to consolidate addiction-related behaviors.

face area of the lungs. As a result, intravenous and smoked cocaine are more addictive than intranasal use (snorting), which is in turn more addictive than the traditional Andean practice of chewing coca leaves. Conversely, the constant low levels of nicotine produced by the nicotine patch are not experienced by smokers as fully replacing the rapid elevation of nicotine levels produced by smoking.²⁶

Tolerance, Dependence, and Addiction

Compulsive, out-of-control use is the central feature of addiction, but it is not the only long-term effect of addictive drugs. Addictive and many nonaddictive drugs alike may produce tolerance and dependence. Tolerance, dependence, and addiction are thought to result from 2 major classes of molecular processes stimulated by drugs of abuse in the brain: homeostatic adaptations, or “neuroadaptations” as they are often called,^{28,29} and associative learning mechanisms.^{4,5,30} Homeostatic adaptations represent compensatory physiologic responses to excessive stimulation, and in diverse forms are exhibited by all cell types in the body. Associative learning mechanisms are brain-specific and are thought to remodel synaptic connections in response to salient experiences and thus consolidate new patterns of information processing and behavioral programs. Homeostatic processes in the brain tend to be reversible after drug cessation over days to weeks, depending on the cells and circuits involved. By physically remodeling synapses and circuits, associative learning mechanisms may produce permanent changes in brain function.

Tolerance refers to the diminishing effect of a drug after repeated administration at a constant dose, or to the need for increasing doses to produce a constant effect. Homeostatic compensations to excess stimulation are thought to underlie tolerance. For some drugs, such as alcohol, metabolic clearance is increased with chronic use, giving rise to pharmacokinetic tolerance, but pharmacodynamic tolerance is far more significant.²⁶ At a behavioral level, tolerance may result in higher and more frequent drug doses in an attempt to maintain the desired subjective effects. Mr R said that he had to “keep [smoking cocaine] constantly, to keep up the high.” Such dosage acceleration serves to drive further molecular changes in the brain. Dependence represents an adapted physiological state that develops as a homeostatic response to repeated bombardment of neurons by drugs. Dependence may be unmasked on cessation of drug taking, resulting in withdrawal symptoms.

Although many responses to cocaine and the similarly acting amphetamines exhibit tolerance, these drugs can also produce sensitization (progressive increases) of other responses. In humans, sensitization may be responsible for the paranoid state that may develop with chronic cocaine or amphetamine use.³¹ Whether sensitization might also underlie some aspects of compulsive use is a current matter of research.³²

To a great degree, the traditional distinction between “physical” and “psychological” dependence represents a vestige of a time prior to modern investigations of addiction and the brain.

What is called “physical dependence” results when adaptations occur in brain circuits that control directly observable bodily functions, such as heart rate or blood pressure. Among the addictive drugs, ethanol and opiates produce physical dependence, which is manifested by somatic withdrawal symptoms such as hypertension, tremor, and seizures for ethanol, or such as hypertension and abdominal cramps for opiates. The basis of physical dependence on opiates is particularly well understood and has been shown to occur because mu opiate receptors, the major molecular target of heroin and related morphinelike opiates, are expressed by neurons in the locus coeruleus²⁸ and related brainstem nuclei that regulate autonomic function. In addition, opiate receptors are expressed on enteric neurons that regulate bowel function, making opiates constipating and leading to severe abdominal cramps on withdrawal.

The term “psychological dependence” is often applied vaguely, but generally refers to compulsive use of a substance—the very core of addiction. Compulsive use results from both neuroadaptations and associative learning mechanisms that control emotion, motivation, and behavior, but may not control readily measurable peripheral physiological functions. Initial neuroimaging reports have appeared that identify neural correlates of craving for cocaine.³³⁻³⁵ While these approaches are a long way from clinical relevance, they may help provide a demonstrable physical basis for what has too often been dismissed as a “merely psychological” phenomenon.

In contrast to ethanol and opiates, cocaine and amphetamines do not have receptors on neurons that regulate peripheral physical function and therefore do not produce physical dependence or a physical withdrawal syndrome.²⁶ Rather, the major adaptations produced by cocaine appear to occur within brain reward pathways in response to excess dopamine levels. A cocaine withdrawal syndrome is not universally observed, but may include mild to moderate depressionlike symptoms, periods of diminished arousal, anhedonia, and drug craving.³⁵

Tolerance and dependence are neither necessary nor sufficient for addiction. Indeed, withdrawal symptoms from cessation of addictive drug use tend to resolve within days to weeks and therefore cannot account for the profound persistence of relapse risk,^{4,5} which has been well documented in addicted populations.⁵ Because reversible homeostatic effects cannot account for the persistent tendency of addicted individuals to relapse, attention has turned to the possibility that addictive drugs usurp normal associative learning mechanisms in the brain.^{4,5,30}

Both humans and animal models readily learn to self-administer addictive drugs. This requires the specific recognition of drug-associated cues and their association with the performance of complex action sequences. Cues associated with drug administration acquire intense motivational significance,³² as befits the involvement of a dopaminergic circuit that normally functions to consolidate survival behaviors.²⁷ Relapse risk is highest on reexposure

to cues associated with drug use, consistent with an important role for associative learning.^{4,5,23,30}

At the molecular level, high levels of synaptic dopamine produced by addictive drugs stimulate dopamine D1 receptors in the multiple brain regions, including the NAc and dorsal striatum. D1 receptor stimulation activates signaling pathways that extend to the cell nucleus and produces a transient burst of altered gene expression.³⁶ An important goal of current research is the identification of genes that are transiently induced by addictive drugs, which produce proteins that remodel synapses.³⁷ Synaptic remodeling (plasticity) in the NAc would alter information processing in the brain in a way that increases the motivational significance of drug-associated cues. Plasticity within the dorsal striatum would lead to automatization of complex behavioral sequences in response to drug-related cues.^{4,5} Such behavioral sequences might include foraging for and self-administration of drugs. The long-term or permanent encoding of specific information that permits drug-related cues, internal states, or stress to control behavior and thus maintain addiction, may be represented in an altered pattern of synaptic connections in the brain.^{4,5}

Treatment

For Mr R, previous treatments provided only temporary help for his cocaine addiction. The goals of treatment for addiction are 3-fold: achievement of abstinence, prevention of relapse, and rehabilitation.³ Treatments exist that can help the addicted person attain those goals, although more effective treatments are needed, including effective pharmacologic therapies for cocaine addiction. Tragically, access to existing treatments is often extremely limited. In comparison to treatment for general medical disorders, treatment for addictive disorders is often less well covered by insurance in the private sector. In the public sector, funding of treatment is often limited as are treatment "slots" in both outpatient and inpatient programs.

For people addicted to opiates who are unable to achieve abstinence, maintenance therapy with long-acting oral opiate agonists such as methadone or levomethadyl acetate is an effective alternative.³⁸ Recent evidence suggests that it is feasible for stable opioid-dependent patients to receive methadone maintenance in primary care.² Maintenance therapy facilitates improved social and occupational functioning while decreasing heroin use with its attendant risks, which include potential use of nonsterile needles.³⁹ In contrast, there is no safe and effective cocaine replacement therapy as an alternative to abstinence. Indeed, there are no robustly effective pharmacologic therapies for any stage of treatment for cocaine addiction, whether for detoxification, early relapse prevention when emotional withdrawal symptoms may be present, or for late relapse prevention. A variety of antidepressant drugs, including desipramine, selective serotonin reuptake inhibitors, and bupropion have been tried as have several anticonvulsant drugs, including carbamazepine and more recently gabapentin, but convinc-

ing efficacy has not been demonstrated.^{38,40} One of Mr R's clinicians has recommended a trial of gabapentin; early adoption of innovative treatments prior to well-conducted clinical trials data demands well thought-out end points and close interaction with the patient throughout the empirical trial.

Advances in neurobiology provide cause for hope, however. Based on increased understanding of neural mechanisms, clinical trials of the long-acting opioid antagonists naltrexone and nalmefene have been performed in alcoholism.^{41,42} Both of these drugs decrease the rewarding properties of alcohol; their major clinical effect appears to be decreasing the likelihood that "slips" (ie, occasional deviations from abstinence) will become full relapses. Acamprosate, a drug that acts on the glutamate neurotransmitter system, also appears promising in the treatment of alcoholism. Similar mechanisms may also prove useful for cocaine. Experimental approaches to treatment for cocaine have focused on receptors within the brain reward pathway including mu and kappa opiate receptors and D1 dopamine receptors.²⁶ In addition, there are promising early experiments with vaccines that block the psychoactive effects of cocaine.⁴³

As described, associative learning mechanisms appear to play a critical role in addiction, including late relapses, which may be triggered by drug-related cues.^{23,44} Cognitive and behavioral therapies have been designed to prevent relapse by helping patients to minimize exposure to drug cues and to modify their responses to cues that are encountered.⁴⁴ For Mr R, as for many addicted individuals, money has become a drug-related cue. As an example of a relapse prevention strategy, arrangements can be made to minimize the likelihood that an individual will have free cash to buy drugs, but such strategies require greater determination to become abstinent than Mr R exhibits. Other forms of behavioral therapy, based on operant and social learning principles, offer incentives for positive behavioral change. One such form of behavioral therapy, contingency management, provides vouchers redeemable for goods and services contingent on performance of desired behaviors.⁴⁵ Because money can initiate cue-dependent relapse, vouchers must not be redeemable for cash. Contingency management appears to have its greatest efficacy if it is part of a more comprehensive treatment program, and has been used, for example, among opioid-addicted individuals to increase adherence to pharmacologic treatments. A naturalistic study of 1605 patients treated in 11 different cities demonstrated that current cognitive and behavioral treatments for cocaine addiction improve outcomes as measured by a decrease in weekly cocaine use at 1 year from 73.1% to 23.5%. Conclusions are limited by lack of a control condition.⁴⁶ For patients with the most severe problems, relatively long stays in residential programs were associated with better outcomes.⁴⁶ Twelve-step programs, such as the one Mr R attended, are in wide use, although they have not been studied enough for cocaine addiction to answer questions of efficacy. Twelve-step programs for cocaine and other drugs

are self-help groups based on the principles of Alcoholics Anonymous, which include a commitment to abstinence.⁴⁷

Mr R's longest period of abstinence was 5 months. Achieving and maintaining stable abstinence depends not only on the specific treatment for the addiction, but also on detection and effective treatment of comorbid psychiatric and general medical disorders such as anxiety disorders, depression, and bipolar disorder. In addition, helping patients manage stress may be instrumental in reducing relapse, as stress, like drug-conditioned cues, may activate drug craving and drug-seeking behaviors.⁴⁸

Recommendations

Mr R is bright, articulate, and charming. He is very involved in his treatment and is working hard to find funding for an additional evening rehabilitation program. Why, then, does he continue to use cocaine regularly? As the foregoing discussion has emphasized, addiction to cocaine exerts a tenacious hold over human behavior. Cocaine mimics a critical neurotransmitter, dopamine, in a brain circuit that controls survival behaviors and produces progressive and potentially permanent alterations in that and related circuits. Thus, return to drug use is characteristic of the natural history of addiction. Given the current state of treatment, no modality, whether pharmacologic, behavioral, or rehabilitative, should be seen by the physician or patient as a panacea. When addicted patients relapse, as is the rule,^{1,5} physicians are too ready to give up. An "all or nothing" model does not work with addiction any more than it works with many cancers. Initial treatment may fail or work only for a time; relapses may occur before a stable remission is achieved. However, many patients ultimately can achieve long periods of stable abstinence and productive life.

Mr R appears to enjoy his treatment and his interactions with caregivers, but in truth, he has greater allegiance to cocaine. The primary care clinician has particular challenges with a patient such as Mr R, who comes to treatment and says things that sound promising, but who nonetheless fails to improve. For such a patient, exploratory or insight-oriented therapies should be avoided. There is a substantial risk that such therapies will only provide additional rationales for his addiction. What matters for Mr R is his behavior. Cognitive and behavioral approaches can be effective if the patient is committed. The physician must assume a confrontational stance, not against the patient, but with the patient, against the disease. Attendance at therapy sessions and physician appointments is important and to be encouraged, but Dr B must keep her eye firmly on measures of cocaine use. We hope that powerful medications can be developed that will interrupt the relapsing course of this illness. Currently, however, such treatments do not exist. Thus, Dr B as well as Mr R's companion and social supports must be prepared to press on through his denial, rationalizations, and relapses to help him use what he has learned in treatment to achieve and maintain abstinence.

QUESTIONS AND DISCUSSION

A PHYSICIAN: Are there any useful analogies between addiction to substances like cocaine, alcohol, or nicotine, and addiction to food, which is probably even more of a health hazard in the United States?

DR HYMAN: The term "addiction" has been applied to compulsive involvement with food, gambling, and sex, as well as drugs. There are some commonalities among these—all are rewarding and probably engage similar brain circuitry to an extent. But there are also differences relevant to treatment of eating disorders vs substance use disorders. One important behavioral difference is that human beings can abstain entirely from alcohol, nicotine, or cocaine. If they can do this, they eliminate a trigger for relapse. In contrast, people must continue to eat. Therefore, for eating disorders and obesity, people have a different kind of management problem. At the brain level, eating depends not only on reward pathways, but also on a complex network of hypothalamic peptides that regulate feeding behavior and energy balance. Thus, food is rewarding and activates some of these same circuits as drugs of abuse, but there are also many important differences.

A PHYSICIAN: If physical changes occur in the brain with cocaine, what happens in people who have stopped cocaine successfully? What adaptive mechanisms might have occurred to keep someone successful in staying off the drug?

DR HYMAN: Many homeostatic adaptations do reverse over days to weeks or months. Different adaptations have different time courses. People who have been alcoholic, for example, may suffer with insomnia for longer than a year, which creates an important risk of relapse. However, such symptoms ultimately remit. Associative learning mechanisms that permit reminders of drug use to control behavior do not seem to reverse as readily over time. This scenario is not hopeless. In some sense, the patient has to use one part of the brain to overcome trouble in another part of the brain. Patients must learn to identify the cues or situations that cause trouble, avoid them ahead of time, and learn how to manage should a situation arise that may trigger use. Metaphorically, we can compare it with what happens after a stroke in some people who recover because another part of the brain picks up certain functions. A different kind of learning must compensate for long-term changes in drug-affected brain circuits.

A PHYSICIAN: What about people with Parkinson disease?

DR HYMAN: People with Parkinson disease, who lack dopamine, would take cocaine without any positive effect. In some ways, Parkinson disease has the opposite features of drug addiction.

A PHYSICIAN: In terms of the physiological and learning changes in the brain with cocaine use, can you comment on the effects on the developing brain? Are adolescents at more risk for long-term changes?

DR HYMAN: The issue of development is very significant. Recently, medical opinion has lurched from believing that children exposed to cocaine in utero were irretrievably harmed

to a far more benign view.⁴⁹ It is certainly not time to be complacent.⁵⁰ For example, a recent report demonstrated very serious disorganization of the cerebral cortex in rhesus macaques exposed to cocaine during their equivalent of the second trimester.⁵¹ The relevance of such a finding to humans is not clear, but what is clear is that we must continue to learn what happens to drug-exposed human infants at the brain and behavioral levels. Throughout childhood and adolescent life our brains undergo remarkable developmental changes as a result of an unfolding genetic program interacting with diverse environmental influences, including family and peer interactions, education, illness, injury, and drugs. We know that drugs such as cocaine can alter gene expression in the brain and probably the wiring of brain circuitry. It is therefore likely that drug-induced perturbations are more serious early in life because they can derail normal brain development. It's also important to recognize that, at a behavioral level, use of intoxicating drugs impairs the ability of children and youth to utilize their schooling effectively and develop healthy relationships with family members and peers. For example, drug-using youth tend to aggregate with antisocial peer groups, creating risk of further deviancy. Thus, there is both a brain problem and an enormous psychosocial developmental problem, which together may create a terrible downward spiral.

A PHYSICIAN: As a distinguished physician, you are talking about addiction as an illness. As an appointed public official, you are talking about criminal activity. Where does the physician fit into that?

DR HYMAN: Too often the roles of the physician and the criminal justice system have opposed each other in addressing drug abuse and addiction. In fact, our society has evolved to permit different professional roles that, if managed better than they often are, can converge to fight drug abuse and addiction. One important experiment is the emergence of drug courts in several jurisdictions. Nonviolent drug offenders may be diverted to such courts that have substantial experience in dealing with drug cases. Typically, such courts mandate treatment as an alternative to incarceration. Successful outcomes seem to depend on close monitoring of offenders with appropriate sanctions for failures in compliance. Successful outcomes also appear to depend on close cooperation between treatment and law enforcement personnel.

One other point deserves mention here. Much is often made of the distinction between the legal drugs, nicotine and alcohol, and the illegal drugs, such as cocaine and heroin. There is no biological or medical basis for this distinction. It is based on historical and social rather than scientific factors.

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CLINICAL CROSSROADS

UPDATE

A 25-Year-Old Woman With Bipolar Disorder, 1 Year Later

IN APRIL 2000, AT PSYCHIATRY GRAND ROUNDS, GARY Sachs, MD, discussed the epidemiology, natural history, diagnosis, and treatment of bipolar disorder.¹ Ms G, a 25-year-old woman, exhibited pressured speech, tangential thinking, and labile affect prior to her 2 psychiatric admissions. Due to her concern about weight gain with lithium carbonate, she was treated with divalproex and olanzapine. As an outpatient, Ms G was taking divalproex (750 mg, twice daily) and bupropion hydrochloride (150 mg, twice daily). She recognized the ongoing need for medications, but hoped to get off them over time. She wondered what other treatment modalities might be available to her.

Dr Sachs noted that Ms G, if untreated for bipolar disorder, faced a 15% risk of death by suicide. Without treatment, he predicted an almost 100% chance of a recurrence. Dr Sachs suggested that she would benefit from treatment with lithium if her illness occurred again on her current regimen. He noted that psychotherapy appears to augment the beneficial effects of medications. He pointed out that patients such as Ms G benefit from simple "harm-reduction strategies," such as writing out a plan to use in case of an acute episode and restricting access to credit cards, firearms, and motor vehicles. Dr Sachs suggested that Ms G see her psychiatrist monthly.

DR Z, THE PATIENT'S PSYCHIATRIST

As a result of listening to the Grand Rounds, Ms G decided to switch to lithium. Because she exhibited some hypomanic behavior, I increased her lithium dose. She did fairly well for several months and kept her appointments with me. Unfortunately, her father became ill and this stress contributed to Ms G's next acute episode and subsequent psychiatric hospitalization. She has since moved out of state to be closer to her family.

MS G, THE PATIENT

I felt pretty well after starting on lithium. I did need to be hospitalized for about 6 days because I wasn't sleeping well. They adjusted my medications and I am doing fine now. I am sleeping 10 hours per night, and in general, my mood is pretty good. I am taking 600 mg of lithium twice per day and 200 mg of Seroquel [quetiapine fumarate] at bedtime. I did break up with my boyfriend and moved to Virginia. I am currently living with my father and stepmother and that feels very supportive to me. I am waitressing at a local restaurant and that seems OK for now.

Richard A. Parker, MD
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