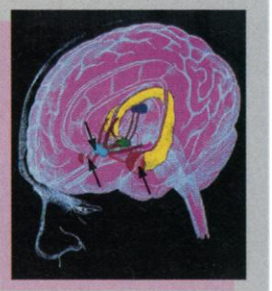
LETTERS

"Reward system"

A reader expresses concern that two neurophysiological studies (and an accompanying Research News article) may not serve a "dispassionate and scientifically objective debate" about the effects of marijuana. In response, the authors agree that "due care" must be taken, but defend the relevance of their findings in laboratory rats to cannabis addiction in humans. [The nucleus accumbens (blue) and the amygdala, two areas of the brain (right) in which cannabis may have addictive effects.] And should "sustainable" harvesting of hawksbill sea turtles in Cuba be "given a chance"?



Marijuana Addiction

The public and professional response to the reports on marijuana by G. Tanda *et al.* (27 June, p. 2048) and F. R. de Fonseca *et al.* (27 June, p. 2050) illustrates a habit that is discouragingly familiar where this drug is concerned: drawing unwarranted conclusions about human behavior and social policy from technical neurophysiological experiments of uncertain significance. It is especially diappointing that *Science* itself has published a commentary (I. Wickelgren, Research News, 27 June, p. 1967) whose tone suggests that we may now have new reasons to bring the law down on marijuana users.

Tanda *et al.* found that tetrahydrocannabinol (THC) affects the dopamine reward system in the nucleus accumbens of rats. Because anything pleasurable activates this reward system, they have not demonstrated a specific affinity between marijuana and heroin, as the commentary on their report implies. De Fonseca *et al.* found that by injecting rats with a cannabinoid antagonist, they could produce a withdrawal syndrome associated with high levels of corticotropin-releasing factor in the amygdala. As they themselves point out, in ordinary use THC leaves the human body so slowly that withdrawal reactions are muted or nonexistent.

Experts who rate the dependence liability of drugs used nonmedically have long placed marijuana at or near the bottom of the list. As a drug of "addiction," it resembles caffeine more than nicotine, alcohol, or heroin, except that the withdrawal reaction is less severe. Because of the present political and legal situation, extreme skepticism should be recommended when we are told that 100,000 people each year seek treatment for marijuana dependence. We are not told how many of these people are under coercion by employers or the courts, and we do not know how many are alcohol, heroin, or cocaine addicts whose incidental marijuana use is bureaucratically recorded as dependence.

It is particularly unfortunate that these technical results are being used to revive the discredited idea that marijuana may be a "gateway" drug that somehow makes its users want to take cocaine or heroin. No real-world evidence of this alleged property has been produced. If anything that affects the dopamine reward system is a gateway to heroin and cocaine, we would have to include sex and chocolate (not to mention alcohol) in that category as well.

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It is heartening to see *Science* giving prominence to the burgeoning field of cannabinoid research with the reports by de Fonseca *et al.* and Tanda *et al.* and the commentary by Wickelgren. However, I fear that the need for dispassionate and scientifically objective debate on cannabis-related issues has not been well served by the commentary or by the speculative conclusions drawn in the reports.

One paramount fact that needs to be recognized is that rats simply do not like

cannabis. There is ample evidence that cannabinoids provoke anxiety in rats, produce conditioned place aversions, and fail to support self-administration (*1*). So the science involved in giving cannabinoids to rats, measuring neurochemical changes, and then extrapolating to issues of addiction in humans is likely to be flawed. Humans might get addicted to cannabis but rats, to the best of our knowledge, do not.

The THC-mediated increase in dopamine efflux in the nucleus accumbens (NAS) reported by Tanda *et al.* and the abolition of this effect by naloxone has been proposed by cannabinoid researchers before (*2*). What is not known is what the effect signifies. Increases in dopamine efflux in the NAS cannot simply be seen as equivalent to drug reward, because aversive stimuli, such as foot shock, and anxiogenic drugs, such as FG 7142 and beta-CCE (which are not self-administered), have exactly the same neurochemical effect (*3*). Thus, increased dopamine efflux in the NAS might equally well reflect drug-induced anxiety as reward.

Let us take all due care in cannabinoid science. There is undoubtedly both good and evil lurking in the drug, and the issues involved are of great political and medical significance. Our primary duty as scientists working in this field is to exercise care in interpreting our data so that the continuing debate on cannabis in our communities can be well formed.

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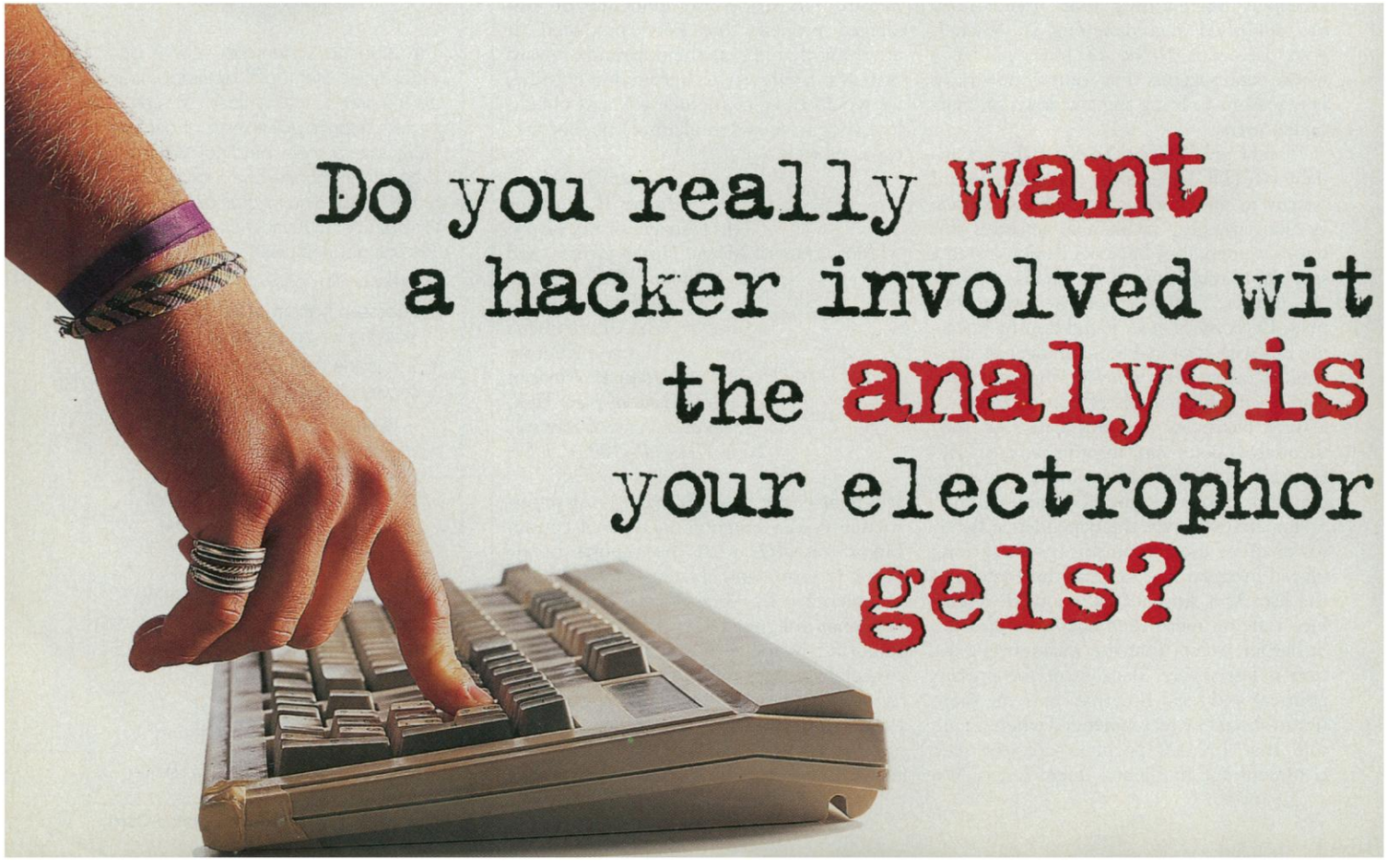
Response: Both letters raise serious doubts about the relevance of our findings to the issue of the addictive liability of marijuana and its alleged property to act as a gateway to heavier drugs (heroin and cocaine). Their main argument is that the property of releasing dopamine in the nucleus accumbens (NAC) cannot be taken as evidence for the addictive liability of marijuana because other rewards (chocolate, sex) and even aversive stimuli do the same. In relation to this, McGregor quotes a report (*1*) that anxiogenic drugs increase dopamine in the NAC. In a later study by our laboratory (*2*), we consistently failed to observe activation of dopamine in the NAC by three different anxiogenic drugs within a range of doses devoid of nonspecific, convulsant effects. Similar considerations apply to the mechanism of the effect of electrical foot shock.

In the above study (*2*), a direct comparison was made of the ability of anxiogenic drugs and of three drugs of abuse (morphine, ethanol, and nicotine) to activate in vivo dopamine transmission in two different target areas of the dopamine system, the prefrontal cortex and the NAC. Although anxiogenic drugs increased dopamine only in the prefrontal cortex, drugs of abuse did not do so at doses that were fully effective in releasing dopamine in the NAC. Therefore, drugs of abuse and aversive (anxiogenic or stressful) stimuli have different patterns of activation of the mesocortical and of the mesolimbic dopamine system; it is specifically the property of ac-



tivating the mesolimbic dopamine neurons projecting to the NAC shell that correlates with the abuse liability of drugs.

However, as pointed out by both letter writers, drugs of abuse resemble rewards (food, sex) in their ability to activate in vivo dopamine transmission in the NAC. Fonzies, a snack food with a corn and cheese taste popular among European adolescents, releases dopamine in the NAC "shell" much like most addictive drugs (3), with one basic difference: even a single exposure to Fonzies results in a long-lasting habituation of dopamine-releasing action in NAC dopamine (3), but this is not the case for drugs of abuse.

The basis for these differences becomes apparent if one considers that food, just like any other natural reward, depends for its action on dopamine neurons from the activation of a long neural chain that starts peripherally from sensory receptors and goes all the way up to the forebrain; drugs, instead, enter the brain and make a direct or very proximate "rendezvous" with dopamine neurons. In the case of natural stimuli, their travel toward dopamine neurons is adaptively modulated to such an extent by previous experience that stimulation of dopamine in the NAC by natural rewards is an exceptional event rather than a matter of everyday life. Once a reward, even an appealing one, becomes known by the subject, it becomes less effective in activating dopamine in the NAC. Therefore, only relatively novel rewards that are of high value for the survival of the self and the species are capable of activating dopamine transmission in the NAC. Drugs, by nonadaptively releasing dopamine, make normal the exceptional, usual the unusual. This, more than anything else, gives the measure of the abnormality of the action of drugs compared with that of natural rewards. We believe (but this is speculation) that it is the nonhabituating property of drugs to release dopamine in the NAC that, by strengthening stimuli and responses related to the drug, leads to craving and compulsive drug use.

A secondary argument made by McGregor is that marijuana is even less addictive than coffee. According to this argument, the lack of addictive properties of marijuana would provide the best proof of the irrelevance of the dopamine-releasing properties for the addictive properties of drugs of abuse. Suffice it to say that 9.2% of individuals who have ever used marijuana meet criteria of dependence (4), and that this prevalence goes to 20 to 30% if one considers the subjects who have used marijuana at least a few times (5).

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Response: The interpretation of our results as suggesting that chronic cannabinoid-induced neuroadaptive processes may enhance vulnerability to future drug abuse has attracted commentaries expressing concern about the relevance of our data for human marijuana addiction.

Our data document that neuroadaptation within brain stress systems—notably the corticotropin-releasing factor system

in the central amygdala and other limbic sites—has taken place after long-term cannabinoid administration. If unmasked by administration of a cannabinoid antagonist, the neuroadaptation can be observed at the cellular, neurochemical, neuroendocrine, and behavioral level. The effects are qualitatively the same as those we have observed during withdrawal from cocaine, ethanol, and opiate use; whether they are quantitatively the same remains to be explored. Nonetheless, these data raise the specter that the same changes are occurring with long-term high-dose cannabinoid receptor activation.

By no means does the lack of cannabinoid self-administration in rats invalidate these data. Many behavioral and pharmacological properties of a drug contribute to abuse liability, none of which is predictive by itself. Moreover, as was the case with ethanol and nicotine, valid animal models of self-administration often take a long time to develop. Neither does the argument that rats "do not like cannabis" hold up to close scrutiny. While anxiogenic and aversive effects are indeed common after high doses, low doses of psychoactive cannabinoids not only activate brain reward mechanisms, but can produce conditioned place preference and induce anxiolysis in rats (*1*). In fact, two of the common neurobiological elements associated with addiction—activation of the brain reward system upon short-term administration and activation of brain stress systems during withdrawal from long-term administration—have been demonstrated with cannabinoids. In particular, the convergence of the effects of stress and drugs of abuse (*2*) is highly informative for the understanding of factors that maintain drug addiction or lead to relapse. Enhanced behavioral and neuroendocrine reactivity to stress is not only a reliable index of vulnerability to psychostimulant self-administration in laboratory animals (*3*), but approximately 75% of relapse in human drug abuse takes place in situations of stress, conflict, and social pressure (*4*). It must be of concern, therefore, that in vulnerable individuals continuous high-dose use of THC can engage stress systems and thereby augment susceptibility to future drug abuse.

Statistics show that 9% of THC users become substance dependent using DSM-IIIR criteria (*5*), and a recent study revealed the same incidence (9%) of presentation of a withdrawal syndrome in a large sample of users (*6*). That study confirms that despite the slow elimination of THC, a distinct behavioral cannabinoid withdrawal syndrome can be observed in humans. In the history of drug abuse research, significant motivational signs of withdrawal have often been overlooked because of a preoccupation with physical withdrawal symptoms that may be largely irrelevant (*7*). When vulnerable populations are explored, cannabis dependence becomes more apparent. In a recent structured assessment of 229 substance-dependent adolescent patients who had serious conduct problems, more than 70% met criteria for cannabis dependence. More than two-thirds of the cannabis-dependent individuals complained of withdrawal, and one-fourth of the cannabis-dependent persons reported using cannabis to relieve withdrawal symptoms (*8*).

Because of the substantial political, social, and public health implications, we could not agree more with admonishments to "let us take all due care in cannabinoid science." However, this goes for those on either side of the issue. Inflammatory rhetoric invoking visions of law enforcement "crackdowns" on marijuana users as a result of this research does not serve the need for dispassionate and scientifically objective debate about cannabis. The conclusions drawn by us follow from the data and stand independent of the issue of marijuana's legal status. There is an urgent need to advance the scientific understanding of both the "good and evil" that may be lurking in this drug. In this endeavor, clinical, epidemiological, and neurobiological studies all have their rightful place.

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Hawksbill Turtles in Cuba

In his article "Turtle project can't outrun bureaucracy" (News & Comment, 20 June, p. 1785) Jeffrey Mervis states that Cuba is seeking limited trade of hawksbill sea turtles on the grounds that its population is self-contained. The Cuban proposal at the 10th meeting of CITES (Convention on International Trade in Endangered Species of Flora and Fauna) in Harare did not say that hawksbills in Cuban waters were a closed population; it argued that the data were consistent with some hawksbills being relatively residential in those waters.

The main grounds for the Cuban proposal were that hawksbills in its waters were well managed and that the proposed quota for trade was conservative, almost a tenth of the harvest levels that had been sustained for more than two decades. These are more important matters than whether some turtles cross international boundaries. However, to the extent that such movements do occur, one would think that other Caribbean nations would give Cuba some credit for having reduced its harvest by about 90%. And, in fact, although the Cuban proposal did not obtain the two-thirds majority necessary for CITES approval, more parties voted for it than against it.

Sustainable use as a conservation method has been effective with vicunas and crocodiles; it should be given a chance with sea turtles.

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Letters to the Editor

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