Heroin ``Overdose'' Death: Contribution of Drug-Associated Environmental Cues

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conditioned response to an aversive US—is impaired by morphine. It may be that conditioned aversiveness or fear is an essential component of learning and memory in this task. Considerable evidence implicates morphine as acting on conditioned fear (*10, 11*).

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Heroin "Overdose" Death: Contribution of Drug-Associated Environmental Cues

Abstract. *A model of "overdose" deaths among heroin addicts is proposed which emphasizes recent findings concerning the contribution of drug-associated environmental cues to drug tolerance. Results of animal experiments performed to evaluate this model suggest that conditioned drug-anticipatory responses, in addition to pharmacological factors, affect heroin-induced mortality.*

Substantial tolerance generally develops to the effects of opiates; the drug-experienced individual can survive a dose many times greater than that which would kill the drug-inexperienced individual (*1*). Despite such tolerance, about 1 percent of U.S. heroin addicts die each year, mostly from the so-called overdose (*2*). In urban areas with substantial numbers of addicts, drug overdose is among the leading causes of death in people aged 15 to 35 (*3*). Postmortem examination of these victims routinely reveals pulmonary edema (*4*), which usually is attributed to hypoxia resulting from drug-induced respiratory depression (*5*).

Although mortality attributed to drug overdose is a major public health problem, its mechanisms are unclear. Some fatalities result from pharmacological overdose (*6*), but many experienced drug users die after a dose that should not be fatal in view of their tolerance (*7, 8*). Indeed, some die following a heroin dose that was well-tolerated the previous day (*8*). Some fatalities may result from a synergism between the opiate and other drugs concomitantly administered or from adulterants (especially quinine) in the heroin, but many do not result from such drug interactions (*7, 8*).

We suggest that drug "overdose" may frequently result from a failure of tolerance. That is, the opiate addict, who can usually tolerate extraordinarily high doses (*4, 9*), is not tolerant on the occasion of the overdose. A recently proposed model of tolerance based on the principles of Pavlovian conditioning (*10*) suggests conditions that favor such a failure of tolerance. The model is based on Pavlov's (*11*) suggestion that drug administration constitutes a conditioning trial, with the conditioned stimulus consisting of environmental cues present at the time of administration and the unconditioned stimulus consisting of the systemic effects of the drug. According to this interpretation of tolerance, as the drug is administered with increasing frequency, with the same environmental cues signaling each pharmacological stimulation, an association is established between these cues and the central effects of the drug. This association may be revealed in a subject with a history of drug abuse by administering a placebo in the drug administration environment. Conditioned pharmacological responses revealed in this manner are often the converse of the unconditioned drug effects (*10, 12*). Such anticipatory responses attenuate the drug effects and contribute to tolerance. Accordingly, environmental signals of impending pharmacological stimulation are important because they enable the organism to make compensatory conditioned responses in anticipation of the unconditioned effects.

Table 1. Rat mortality after the injection of heroin at 15 mg/kg.

Group	Number of rats	Mortality (%)
ST	37	32.4
DT	42	64.3
Control	28	96.4

On the basis of this model, a failure of tolerance should occur if the drug is administered in an environment that has not, in the past, been associated with the drug. Indeed, several studies have demonstrated such dependence of opiate tolerance on environmental cues. For example, if the last of a series of morphine injections is given in the presence of cues that have not previously signaled the drug, rats and humans display less tolerance than if this injection were given in the presence of the usual drug-associated cues (*13*). Although these studies establish a role for learning in morphine tolerance, primarily small drug doses were used. There is evidence, however, that the conditioning model of tolerance applies to the pernicious effects of very high doses of opiate (*14*). Thus, one contributing factor in death from the so-called opiate overdose might be the absence of a conditioned compensatory pharmacological response.

The results of the study described below indicate that heroin-induced mortality in heroin-experienced rats is higher when the drug is injected in an environment not previously associated with the drug than when it is injected in the usual drug-administration environment. The experimental design used provided a methodologically rigorous demonstra-

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tion of the contribution of contextual stimuli to tolerance (*10, 15*).

Opiate-inexperienced male rats (Wistar-derived, 90 to 110 days old) with permanent jugular cannulas (*16*) were intravenously injected with diacetylmorphine hydrochloride (heroin) 15 times, one injection every other day. The dose was increased according to the following schedule: first injection, 1 mg/kg; second and third injections, 2 mg/kg; fourth through seventh injections, 4 mg/kg; and eighth through fifteenth injections, 8 mg/kg. Each rat also received one volumetrically equated injection of the vehicle (5 percent dextrose solution) on days when it was not injected with heroin.

The injections were given in two different environments. One was the colony, where the rats were individually housed. The animal was removed from its cage, injected, and returned to its cage. The other environment was a different room with constant white noise (60 dB SPL). Rats were injected 15 minutes after being transferred to this room and were kept there for an additional 2 hours. One group of rats received heroin in the distinctive room and dextrose in the colony; a second group received heroin in the colony and dextrose in the distinctive room. Finally, the subjects in each group were placed in one of the two environments and injected with 15 mg of heroin per kilogram. This procedure permitted evaluation of the effects of a high dose of heroin in the context of cues that had previously signaled lower doses of the drug [similarly tested (ST) rats] and in the context of cues not previously associated with the drug [differently tested (DT) rats]. It should be emphasized that, throughout the study, both experimental groups were injected an equal number of times with the same doses of heroin at the same intervals between injections [results obtained from the two counterbalanced conditions were not significantly different (*17*)]. A third group received 30 daily injections of dextrose in each of the two environments on an alternating schedule and then an injection of heroin (15 mg/kg) in one of the two environments. Thus the control rats had no experience with the opiate before the final session.

Chi-square analysis indicates that mortality differed significantly among groups ($P < .001$) (*18*). Both groups with pretest experience with sublethal doses of heroin were more likely to survive the highest dose than control animals ($P < .002$), suggesting that tolerance resulted from the sublethal heroin injections independent of the environment associated with those injections. However, mortality was significantly higher in DT than in ST rats ($P < .001$), indicating that identical pretest pharmacological histories do not necessarily result in the display of equivalent tolerance to the lethal effect of heroin. The experiment was conducted in six replications (three involving testing in each of the two environments), and in every replication a greater proportion of DT than ST rats died ($P < .02$, binomial test). The combined results for all replications are summarized in Table 1.

In conclusion, groups of rats with the same pharmacological history of heroin administration can differ in mortality following administration of a high dose of the drug: rats that received the potentially lethal dose in the context of cues previously associated with sublethal doses were more likely to survive than animals that received the dose in the context of cues not previously associated with the drug.

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16. The cannula was a modified version of that described by R. J. Brown and C. B. Breckenridge [*Biochem. Med.* **13**, 280 (1975)]. Subjects were cannulated 1 week before the experiment. The rate of injection was controlled by infusing the injected substance at a rate of 0.005 ml/sec through the intravenous cannula with a Harvard model 902 infusion pump. The concentration of heroin (in sterile 5 percent dextrose) was 3.125, 6.250, 12.500, 25.000, and 50.000 mg/ml for the doses of 1, 2, 4, 8, and 15 mg/kg, respectively. Thus the duration of the infusion for all rats at all dose levels was equivalent (about 1 min/kg).
17. Of the 37 ST rats, 17 were injected with heroin in the distinctive room and 20 were injected with heroin in the colony. Half of the 42 DT rats were injected with heroin in each of the environments.
18. For subjects that died as a result of the injection of heroin at 15 mg/kg, the median times for the start of the injection until death (as determined by lack of heartbeat) in ST, DT, and control groups were 187, 174, and 164 seconds, respectively. Thus these animals died soon after the start of the lethal injection (differences between groups were insignificant), as is frequently the case with human victims of drug overdose (*7, 8*).
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Tumor Rejection in Rats After Inescapable or Escapable Shock

Abstract. *Rats experienced inescapable, escapable, or no electric shock 1 day after being implanted with a Walker 256 tumor preparation. Only 27 percent of the rats receiving inescapable shock rejected the tumor, whereas 63 percent of the rats receiving escapable shock and 54 percent of the rats receiving no shock rejected the tumor. These results imply that lack of control over stressors reduces tumor rejection and decreases survival.*

Psychological states involving the loss of control, such as helplessness, bereavement, and depression, are associated with an increased incidence of cancer (*1*). The influence that psychological variables may have on the development and maintenance of malignancies is difficult to determine from correlational studies of humans: the psychological states may have preceded cancer onset, resulted from it, or occurred at the same time. Therefore, animal studies in which psy-

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