more evaluative language, both positive and negative (for example, right-wrong, good-bad) ($t = 2.86$, $P < .01$) than controls did. In addition, they differed significantly ($z = 5.00$, $P < .001$) from the controls in their greater use of positive evaluative language. Experimental subjects reported feeling no more suspicious than did control subjects. These last two findings weaken the possible criticism that the results were based simply on anger induced by the experimental manipulation.

Both groups experiencing a hearing deficit reported, as expected, that their hearing was not keen, but reported no other sensory difficulties. Those who were partially deaf without being aware of the source of the deafness did experience greater confusion, which is likely to have motivated an active search for an appropriate explanation. Over time, however, if their delusional systems were allowed to become more coherent and systematized, the paranoid reaction would be less likely to involve confusion. Ultimately, there is so much confidence in the proposed paranoid explanatory system that alternative scenarios are rejected.

Despite the artificiality of our laboratory procedure, functionally analogous predicaments occur in everyday life. People's hearing does deteriorate without their realizing it. Indeed, the onset of deafness among the elderly is sometimes actively denied because recognizing a hearing deficit may be tantamount to acknowledging a greater defect—old age. Perhaps self-deception about one's hearing deficit may even be sufficient, in some circumstances, to yield a similar response, namely, a search for a more personally acceptable alternative that finds fault in others rather than in oneself. When there is no social or cultural support for the chosen explanation and the actor is relatively powerless, others may judge him or her to be irrational and suffering from a mental disorder. Although our subjects were young and had normal hearing, these findings have obvious bearing on a possible cognitive-social mechanism by which deafness may lead to paranoia among the middle-aged and elderly.

PHILIP G. ZIMBARDO
SUSAN M. ANDERSEN*
Department of Psychology,
Stanford University,
Stanford, California 94305
LOREN G. KABAT
Health Sciences Center,
State University of New York,
Stony Brook 11794

References and Notes

1. B. Pritzker, *Schweiz. Med. Wochenschr.* **7**, 165 (1938).
2. F. Houston and A. B. Royse, *J. Ment. Sci.* **100**, 990 (1954).
3. M. Vernon, *J. Speech Hear. Res.* **12**, 541 (1969).
4. K. Z. Altshuler, *Am. J. Psychiatry* **127**, 11 and 1521 (1971).
5. Personal communication from J. D. Rainer (14 July 1980), who has studied the psychiatric effects of deafness for the past 25 years at the New York State Psychiatric Institute.
6. E. Kraepelin, *Psychiatrie* **8**, 1441 (1915).
7. D. W. K. Kay, *Br. J. Hosp. Med.* **8**, 369 (1972).
8. F. Post, *Persistent Persecutory States of the Elderly* (Pergamon, London, 1966).
9. H. A. McClelland, M. Roth, H. Neubauer, R. F. Garside, *Excerpta Med. Int. Congr. Ser.* **4**, 2955 (1968).
10. A. F. Cooper, R. F. Garside, D. W. K. Kay, *Br. J. Psychiatry* **129**, 532 (1976).
11. A. F. Cooper, A. R. Curry, D. W. K. Kay, R. F. Garside, M. Roth, *Lancet* **1974-II**, 7885 (1974).
12. A. F. Cooper and R. Porter, *J. Psychosom. Res.* **20**, 107 (1976).
13. A. F. Cooper, *Br. J. Psychiatry* **129**, 216 (1976).
14. D. W. K. Kay, A. F. Cooper, R. F. Garside, M. Roth, *ibid.* **129**, 207 (1976).
15. B. Maher, in *Thought and Feeling*, H. London and R. E. Nisbett, Eds. (Aldine, Chicago, 1974), pp. 85–103.
16. G. Reed, *The Psychology of Anomalous Experience* (Houghton Mifflin, Boston, 1974).
17. E. M. Lemert, *Sociometry* **25**, 2 (1962).
18. L. Festinger, *Hum. Relat.* **7**, 117 (1954).
19. N. A. Cameron, in *Comprehensive Textbook of Psychiatry*, A. M. Freedman and H. I. Kaplan, Eds. (Williams & Wilkins, Baltimore, 1967), pp. 665–675.
20. A. Beck, in *Thought and Feeling*, H. London and R. E. Nisbett, Eds. (Aldine, Chicago, 1974), pp. 127–140.
21. W. W. Meisner, *The Paranoid Process* (Jason Aronson, New York, 1978).
22. R. E. Shor and E. C. Orne, *Harvard Group Scale of Hypnotic Susceptibility, Form A* (Consulting Psychologists Press, Palo Alto, Calif., 1962).
23. A. M. Weitzenhoffer and E. R. Hilgard, *Stanford Hypnotic Susceptibility Scale, Form C* (Consulting Psychologists Press, Palo Alto, Calif., 1962).
24. A fuller presentation of procedures is available by request.
25. W. G. Dahlstrom, G. S. Welsh, L. F. Dahlstrom, *An MMPI Handbook*, vol. 2, *Research Applications* (Univ. of Minnesota Press, Minneapolis, 1975).
26. We derived this scale specifically for this study; it consisted of 15 self-declarative statements responded to on 7-point rating scales. The scale was drawn from a clinical study of paranoia (*14*).
27. L. Ross, M. R. Lepper, M. Hubbard, *J. Pers. Soc. Psychol.* **35**, 817 (1977).
28. W. L. Hays, *Statistics for Psychologists* (Holt, Rinehart & Winston, New York, 1965), p. 465.
29. This report is dedicated to Neal E. Miller as part of a commemoration by his former students of his inspired science teaching. We wish to acknowledge the expert and reliable research assistance of Harry Coin, Dave Willer, Bob Sick, James Glanzer, Jill Fonaas, Laurie Plautz, Lisa Carrol, and Sarah Garlan. We thank Joan Linsenmeier and David Rosenhan for critical editing of the manuscript.
* Present address: Department of Psychology, University of California, Santa Barbara 93106.

3 December 1980; revised 23 February 1981

Exposure of Rats to Alcohol in utero Alters Drug Sensitivity in Adulthood

Abstract. *Pregnant rats were intubated with alcohol (ethanol, 3 grams per kilogram) twice daily throughout gestation. Control animals received solutions of isocaloric sucrose. At birth, offspring were placed with untreated surrogate dams. Beginning at 6 months of age, the offspring were tested for their thermogenic responsiveness to various drugs and to cold. Prenatal exposure to alcohol resulted in tolerance to alcohol and cross-tolerance to pentobarbital and diazepam but did not result in cross-tolerance to chlorpromazine, morphine, and* d*-amphetamine and did not affect responsiveness to cold. This pattern of effects suggests that prenatal exposure to alcohol produces specific long-term effects on the neural mechanisms underlying drug tolerance.*

Fetal alcohol syndrome refers to a pattern of anomalies—growth retardation, morphological abnormalities, and behavioral disorders—in the offspring of female chronic alcoholics (*1*). Nearly all of these anomalies have also been produced in animals prenatally exposed to alcohol (*2*), supporting the validity and utility of animal models of this syndrome.

We report that, in rats, prenatal exposure to alcohol modifies adult responsiveness to alcohol and to drugs for which alcohol causes cross-tolerance but does not alter responsiveness to drugs for which alcohol does not induce cross-tolerance. This pattern of effects suggests that alcohol exposure in utero alters specific cellular mechanisms underlying tolerance in the brain. Because of its sensitivity as an indicator of drug action, temperature regulation was used to assess tolerance (*3*). Considerable information is available concerning the neuroanatomical and neurochemical bases of thermoregulation (*4*), which could provide foci for further studies.

Twenty-five Long-Evans rats (Blue Spruce Farms), pregnant and about 100 days old, were divided into two groups. Group A rats ($N = 15$) were intubated with 3 g of ethanol (8 percent by volume) per kilogram twice daily throughout pregnancy, beginning on day 1 of gestation. This dose is behaviorally teratogenic in rats (*5*). Group C rats ($N = 10$) were intubated with a solution of isocaloric sucrose. The group C animals were given the same amount of food (Teklad 10 percent) and water as received by the group A animals. All animals were individually housed in Plexiglas cages in a

0036-8075/81/0626-1531$00.50/0

room with 14 hours of light and constant temperature (22° ± 1°C) and humidity (45 percent). On day 20 of gestation, five animals from group A were killed 1 hour after intubation and 25 μl of blood was removed and analyzed by gas chromatography (*6*) for blood alcohol concentrations. Isopropanol was used as an internal standard. The remaining animals were allowed to deliver their litters.

Within 12 hours after birth, all litters were removed from their biological mothers, culled to ten pups, and given to untreated foster mothers to avoid possible artifacts resulting from alcohol-induced impairment of maternal behavior or lactation (*7*). Offspring were weaned at 22 days of age and placed in cages with two to three littermates of the same sex. Beginning at 6 months of age, ten females and ten males from each group were given intraperitoneal injections of ethanol (2 or 3 g/kg), sodium pentobarbital (5 or 20 mg/kg), morphine (5 or 20 mg/kg), diazepam (5 or 20 mg/kg), chlorpromazine (5 or 20 mg/kg), and *d*-amphetamine (5 mg/kg). At least 4 days separated the injections received by each rat. Rectal temperatures were obtained with a Yellow Springs Telethermometer before injection and at hourly intervals after injection. The last injection was given when the rat was 10 months old. Two weeks later, baseline rectal temperatures were again obtained for females. These animals were then placed in a cold (4°C) chamber for 8 hours to determine temperature regulation in response to cold stress.

The effects of alcohol exposure in utero on blood alcohol levels, weight at birth, and postnatal mortality have been reported elsewhere (*8*). Mean blood alcohol level 1 hour after intubation was 204 ± 11 mg per 100 ml. At 6 months of age, experimental males and females had mean weights of 499 ± 16 and 270 ± 8 g, respectively, compared to 553 ± 15 and 302 ± 5 g for male and female controls ($P < .05$, Student's *t*-test). Litter size was not significantly affected.

The effects of prenatal exposure to alcohol on drug responsiveness in females are presented in Fig. 1. Baseline temperatures before drug administration were identical for groups A and C on each day of testing. The changes in body temperature were dose-related. Morphine and *d*-amphetamine produced slight hyperthermia in addition to hypothermia. The hypothermia produced by 2 or 3 g of alcohol per kilogram was significantly ($P < .02$ and $P < .001$, respectively) less in females that had been exposed to alcohol prenatally (group A). Group A females also experienced a significantly smaller decrease in body temperature in response to pentobarbital (20 mg/kg; $P < .05$) or diazepam (20 mg/kg; $P < .005$). [The treatment × trials interaction but not the main treatment factor was significant in the pentobarbital study. However, replication with this dose did result in a significant main treatment effect ($P < .05$), with group A animals exhibiting less hypothermia than group C animals.]

Differences between the responses of control and experimental rats to morphine (5 or 20 mg/kg), chlorpromazine (5 or 20 mg/kg), or *d*-amphetamine (5 mg/kg) were not significant. Between-group differences in sensitivity to cold in the absence of drug treatment were also not significant. Compared to control males, group A males exhibited significantly less hypothermia only in response to the lower dose of alcohol ($P < .05$). Differences in sensitivity to the other drugs were not significant.

Previous studies have also shown that tolerance to alcohol can result in cross-tolerance to pentobarbital and diazepam (*9*). Cross-tolerance between morphine and alcohol does not generally occur [however, see (*10*)], nor does cross-tolerance occur between alcohol and chlorpromazine or *d*-amphetamine (*11*).

The present results demonstrate that prenatal exposure to alcohol can produce long-lasting tolerance not only to alcohol but also to drugs for which alcohol stimulates cross-tolerance. These observations, together with the nonsignificant between-group differences in sensitivity to drugs for which alcohol does not stimulate cross-tolerance (morphine, chlorpromazine, or *d*-amphetamine) or in senstivity to cold, suggest that prenatal exposure to alcohol affects some specific mechanism underlying responsiveness to alcohol and related drugs rather than a general temperature-regulating mechanism. Since these drugs are metabolized by different hepatic mechanisms, the observed tolerance is probably the result of functional changes in the central nervous system. The absence of comparable effects for male animals, however, suggests that the effect is sex-specific. The greater sensitivity of females to the effects of alcohol given in utero has been noted in other contexts (*5*).

Although pre- and postnatal exposure to alcohol have been reported to induce tolerance to alcohol (*7, 12*), the observations were noted in relatively young offspring. Our demonstration of tolerance to alcohol and related drugs occurring as long as 6 months after the last exposure is remarkable, since loss of tolerance in alcohol-treated animals generally occurs within days (*13*). Interestingly, long-term tolerance to the hypothermic effects of phenobarbital has also been observed in animals prenatally exposed to phenobarbital (*14*), suggesting that in utero exposure to drugs may irreversibly affect cen-

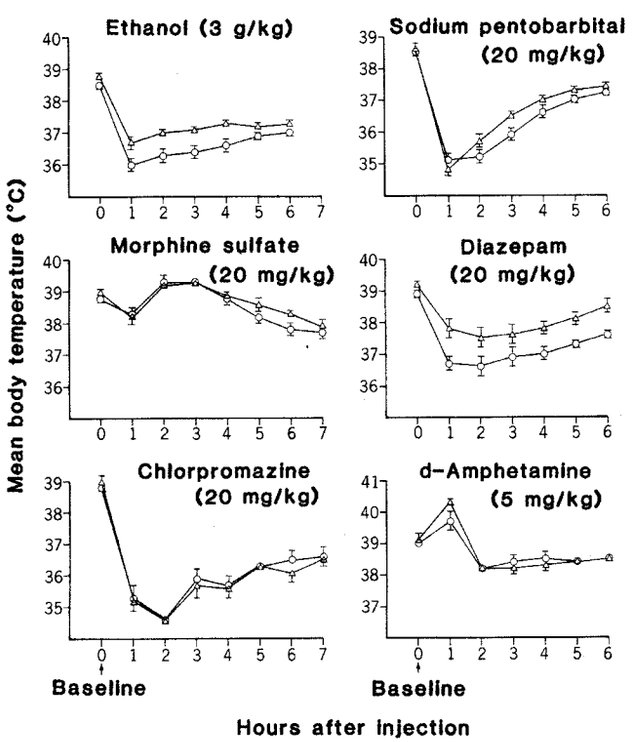

Fig. 1. Drug-induced hypothermia in female rats prenatally exposed to alcohol (△) and in controls (○).

tral neural mechanisms underlying drug tolerance. In several instances, the behavioral effects of prenatal exposure to alcohol tended to dissipate with age (*15*). The long-lasting effects reported here and previously by our laboratory with regard to learning deficits (*5*) suggest that permanent functional changes in the central nervous system result from in utero exposure to alcohol.

ERNEST L. ABEL
RENEE BUSH
BARBARA A. DINTCHEFF
Research Institute on Alcoholism, Buffalo, New York 14203

References and Notes

1. K. L. Jones and D. W. Smith, *Lancet* **1973-II**, 999 (1973); S. Clarren and D. W. Smith, *N. Engl. J. Med.* **298**, 1063 (1978).
2. E. L. Abel and B. Dintcheff, *J. Pharmacol. Exp. Ther.* **207**, 196 (1978); C. L. Randall, W. J. Taylor, D. W. Walker, *Alcoholism* **1**, 219 (1977); E. P. Riley, E. A. Lochry, N. R. Shapiro, *Psychopharmacology (Berlin)* **62**, 47 (1979).
3. R. F. Ritzmann and B. Tabakoff, *J. Pharmacol. Exp. Ther.* **199**, 158 (1976).
4. R. D. Myers, *Drug and Chemical Stimulation of the Brain* (Van Nostrand Reinhold, New York, 1974), pp. 237–301.
5. E. L. Abel, *Pharmacol. Biochem. Behav.* **10**, 239 (1979); W. F. Caul, G. L. Osborne, K. Fernandez, G. I. Henderson, *Addict. Behav.* **4**, 311 (1979).
6. H. Greizerstein and C. M. Smith, *J. Pharmacol. Exp. Ther.* **187**, 319 (1973).
7. E. L. Abel, *Arch. Int. Pharmacodyn. Ther.* **210**, 121 (1974); *Behav. Neurol. Biol.* **25**, 411 (1979).
8. ———, B. A. Dintcheff, R. Bush, *Teratology*, in press.
9. A. Barnett and R. Fione, *Eur. J. Pharmacol.* **13**, 239 (1971); G. Redmond and G. Cohen, *Science* **171**, 387 (1971).
10. J. M. Kharma, A. D. Le, H. Kalant, A. E. LeBlanc, *Eur. J. Pharmacol.* **59**, 145 (1979).
11. D. B. Goldstein, *J. Pharmacol. Exp. Ther.* **193**, 14 (1972).
12. N. Anandam, T. Strait, J. M. Stern, *Teratology* **21**, 25 (Abstr.) (1980).
13. A. E. LeBlanc, H. Kalant, R. J. Gibbins, N. D. Berman, *J. Pharmacol. Exp. Ther.* **168**, 224 (1969); A. E. LeBlanc, H. Kalant, R. J. Gibbins, *Psychopharmacology (Berlin)* **48**, 153 (1976).
14. J. Yanai and B. Tabakoff, *Psychopharmacology (Berlin)* **64**, 325 (1979).
15. N. W. Bond and E. L. DiGiusto, *ibid.* **52**, 311 (1977); M. H. Lee, R. Haddad, R. Rabe, *Neurobehav. Toxicol.* **2**, 189 (1980); B. A. Shaywitz, J. H. Klopper, J. W. Gordon, *Pediatr. Res.* **10**, 451 (1976).
16. This work was supported by New York State health planning grant 9–014. We thank H. Greizerstein for blood alcohol analysis and critical comments.

22 December 1980; revised 18 March 1981

Morphine-Induced Attenuation of Morphine Tolerance

Abstract. *Rats experienced both morphine and an environmental cue, but the cue always signaled a drug-free period. They were subsequently administered morphine in the presence of the cue, and the development of analgesic tolerance was assessed. The prior experience retarded such tolerance. The finding that a procedure of opiate administration can retard opiate tolerance suggests that an association between cues preceding the drug and the drug itself contributes to tolerance.*

Several investigators have suggested that learning contributes to opiate tolerance, and recent analyses of tolerance emphasize the principles of Pavlovian conditioning (*1*). Pavlov (*2*) suggested that the administration of a drug normally constitutes a conditioning trial. The conditional stimulus (CS) consists of environmental cues uniquely present at the time of drug administration, and the unconditional stimulus (UCS) consists of the systemic effects of the drug. The development of an association between the environmental and pharmacological stimuli is revealed if the subject is administered a placebo. Drug conditional responses (CR's) are often opposite in direction to the unconditional effects of the drug (*1, 3*). These anticipatory responses, antagonistic to the effects of the drug, should attenuate the effect of the drug and may contribute to tolerance.

The conditioning analysis of tolerance is supported by demonstrations that a variety of nonpharmacological manipulations similarly affect CR formation and morphine tolerance (*1*). Thus, if placebo injections are presented either before, interspersed among, or after morphine injections, the acquisition of morphine tolerance is attenuated, much as presentations of the CS before, during, or after paired CS-UCS presentations attenuate CR strength [so-called "latent inhibition," partial reinforcement, and extinction effects, respectively (*4, 5*)]. Such results demonstrate that tolerance can be diminished by presenting without the drug the cues that normally signal the drug. The conditioning account of tolerance suggests an even more dramatic and counterintuitive demonstration of the contribution of learning to tolerance—morphine tolerance should be retarded by the administration of the drug itself in the absence of environmental cues.

Consider the situation in which the analgesic effect of morphine is tested, in subjects experienced with the drug, in the context of a distinctive CS. Subjects who, before the test, receive morphine paired with the CS (paired morphine group, PM) should, on the basis of the conditioning model, display tolerance—that is, the effect of the drug should be partially canceled by the drug-compensatory CR. In contrast, subjects with the same exposure before the test to morphine and the cue, but in an explicitly unpaired manner (explicitly unpaired morphine group, EUM) should be retarded in the subsequent acquisition of tolerance when the distinctive cue is paired with morphine. This prediction is based on evidence from a variety of classical conditioning studies indicating that an explicitly unpaired procedure imbues the CS with inhibitory properties (*6*). Such inhibition is evidenced by retarded learning when the explicitly unpaired cue is subsequently paired with the UCS. If Pavlovian conditioning contributes to morphine tolerance, such tolerance should be subject to inhibitory learning. The results of our experiment demonstrate that an initial series of explicitly unpaired presentations of environmental CS and morphine retard the analgesic tolerance subsequently developed when the CS is arranged to signal the drug.

Throughout the experiment, Wistar-derived rats (90 to 110 days old) were each housed in a translucent cage located in one drawer of a filing cabinet. There was no illumination in the drawers, and a ventilation fan at the rear of each drawer provided 70 dB of background noise. Subjects were placed in the drawers and left undisturbed for 5 days before the first experimental session. The purpose of housing the subjects in this manner was to allow the presentation of a conveniently manipulated environmental CS, which consisted of a 1-hour period during which the filing cabinet drawers were opened, exposing the rats to illumination provided by the overhead room lights, and the ventilation fans were turned off, reducing background noise.

During the initial phase of the experiment, which consisted of 15 daily sessions, five groups of rats differed in their experience with the CS, morphine, or both. Group PM ($N = 12$) received explicit pairings of the CS and morphine: Morphine was injected 15 minutes after the drawers were opened. The drawers then remained open for 45 minutes, after which time the cabinet was closed and the fans turned on (*7*). Group EUM ($N = 12$) received the same experience with the CS and morphine, but the two were explicitly unpaired: morphine was injected 4 hours after each presentation of the CS. These explicitly unpaired morphine injections were given while a dim red light provided the only illumination, and the ventilation fans remained on (the drawer was opened, the animal injected, and the drawer immediately closed). A third group received daily

0036-8075/81/0626-1533$00.50/0