ND-ND against groups D-ND and ND-D and the control, a significant difference ($P < .05$) indicates greater transfer for the groups that did not have a state change (D-D and ND-ND).

DOUGLAS L. CHUTE
DENNIS C. WRIGHT
Department of Psychology and Space Sciences Research Center, University of Missouri, Columbia 65201

References and Notes

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2. C. A. Pearlman, Jr., S. K. Sharpless, M. E. Jarvik, *J. Comp. Physiol. Psychol.* **54**, 109 (1961).
3. Each animal was anesthetized intraperitoneally with sodium pentobarbital (Nembutal) (30 mg/kg). An incision about 3 cm long, 1 cm from midline, was made in the neck and the underlying tissue layers were teased apart to expose the jugular vein. A heparin-filled (outside diameter, 1.27 mm) polyethylene catheter (Intramedic) was inserted caudally into the jugular vein for approximately 2 cm and secured with sutures around the vein and catheter. The free end of the catheter was then run subcutaneously to the occiput and attached to a 20-gauge hypodermic needle. The corked needle hub was fixed to the skull with dental acrylic anchored to 0.80 stainless steel screws. The catheter was flushed daily with 0.10 ml of a 1000-unit solution of sodium heparin (Liquamin). Four days were allowed for postoperative recovery before training began.
4. R. E. Kirk, *Experimental Design: Procedures for the Behavioral Sciences* (Brooks/Cole, Belmont, Calif., 1968).
5. Supported in part by the Space Sciences Research Center, University of Missouri.

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Behavioral Maintenance of High Concentrations of Blood Ethanol and Physical Dependence in the Rat

Falk *et al.* (*1*) clearly state the criteria for an animal model for alcoholism, claim that their technique satisfies all the criteria, and then describe an experiment which fails to meet them. The criteria, as stated by Falk *et al.* (*1*), are:

> . . . (i) animals should orally ingest ethanol solutions excessively and chronically in a pattern that increases the concentration of blood ethanol analogous to that in the alcoholic; (ii) unequivocal physical dependence on ethanol must be demonstrated; (iii) food and ethanol should be available from sources physically separate so that the factors determining ethanol intake are not inextricably bound to those primarily concerned with meeting nutritional requirements; (iv) the experimental arrangement should retain an elective aspect to the ethanol ingestion by not programming extrinsic reinforcing events (for example, shock avoidance, food pellet delivery) contingent upon drinking ethanol.

Does the experiment satisfy their criterion? The authors state that the rats (initially weighing just over 300 g) were reduced to 80 percent of their weight "by limiting food rations." They were then trained to obtain food, but their total intake of food was limited to maintain the rats' weight at 80 percent. "When the animals began drinking alcohol, additional food supplements were omitted for the remainder of the experiment, as the animal weights were increasing" (*1*). Thus, the animals were chronically and severely hungry, and alcohol intake was producing weight gain. I therefore conclude that factors determining alcohol intake were, in fact, inextricably bound to those concerned with meeting nutritional requirements. No controls are presented that show that the alcohol drinking observed in the experiment is attributable to schedule-induced polydipsia, rather than to simple malnutrition.

The study also fails to meet the first criterion. There is no demonstration that there was a chronic elevation of alcohol consumption analogous to that of the alcoholic. No tests were run to determine preference for alcohol after the conclusion of the experiment. The rats had no fluid available except for the alcohol solution while eating during the period of the experiment, and no tests made afterward are reported. In fact, it has been shown by Senter and Sinclair (*2*) that alcohol preference is not altered by alcohol overdrinking induced by schedule-induced polydipsia. Senter and Sinclair therefore conclude "that excessive drinking of alcohol associated with such treatment is not analogous to alcoholic habituation." This point is linked to the fourth criterion that the "experimental arrangement should retain an elective aspect to the ethanol ingestion." At no time were the rats offered an alternative source of fluid or of deficient calories. The rats had to drink alcohol to remain alive. Falk *et al.* may argue that schedule-induced polydipsia is not due to extrinsic reinforcing effects. This may be true when the rat drinks water beyond its physiological requirement, but it cannot be taken as a demonstrated fact because the causes of normal schedule-induced polydipsia are obscure and remain, as Falk *et al.* state, "the subject of further research and theoretical speculation." While the questions concerning normal schedule-induced polydipsia remain open, extreme reinforcing effects are produced when alcohol is introduced into the situation. To a chronically hungry rat, the drinking of an alcohol solution in the low concentrations used by Falk *et al.* is extremely likely to function as an "extrinsic reinforcing event."

Concerning the second criterion, Falk *et al.* state that they have demonstrated "physical dependence on ethanol in the rat as indicated by withdrawal convulsions." What Falk *et al.* actually present is some poorly controlled and unsystematic evidence concerning audiogenic seizures in rats subjected to the experimental conditions. It is unwarranted to equate audiogenic seizures with withdrawal convulsions caused by alcohol withdrawal. A propensity to audiogenic seizures can be produced by disease or nutritional deficiency (*3*). It seems likely that various types of nutritive deficiency were present in the rats, as a large part of their caloric requirement was satisfied by alcohol. A susceptibility to audiogenic seizures in this case can therefore hardly be viewed as unequivocal evidence for physical dependence on ethanol. A human alcoholic prefers to drink large amounts of alcohol when other nutritional substances are available. Falk *et al.* have demonstrated no change in preference for alcohol, but only an enhanced intake possibly created by hunger and other undetermined factors operating in schedule-induced polydipsia. There are also further cogent criticisms that have already been made of other studies utilizing schedule-induced polydipsia made by Myers and Veale (*4*) in their review. These criticisms, which are unnecessary to repeat here, apply to Falk *et al.*'s study with equal force.

J. A. DEUTSCH
Department of Psychology, University of California, San Diego, P.O. Box 109, La Jolla 92037

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We are pleased to learn that Deutsch (*1*) accepts the four behavioral criteria we described (*2*) for an animal model of alcoholism. The criticism that we do not satisfy these criteria in the experimental preparation we presented for the use of those interested in long-term sequelae of physical dependence on ethanol revolves, in essence, around four major alleged points. (a) The experimental arrangement does not satisfy criterion (i) [see start of paragraph 3 (*1*)]. (b) The animals were reduced in weight, starving, and therefore forced to drink ethanol for its caloric content. (c) The animals were not shown to prefer ethanol over other solutions as a result of the procedure. (d) Withdrawal convulsions were not demonstrated, see criterion (ii).

(a) Criterion (i) requires ingestion of ethanol so that the *concentration* of blood ethanol is analogous to the pattern observed in alcoholics. In paragraph 2, Deutsch rewords this to state that there was no chronic elevation of alcohol *consumption*. In fact, what is required by the model is not just an increased consumption of ethanol, a result which can be accomplished by various techniques, but rather, blood ethanol concentrations must remain at high levels for the major portion of each 24-hour cycle in order to reproduce the human condition (*3*). This is demonstrated in our figure 2 (*2*), showing the 24-hour-cycle blood ethanol concentration values for all animals. The pattern of intake which determines this chronic elevation is induced by the schedule condition in which the ethanol consumption is distributed over the complete 24-hour cycle, rather than being concentrated into one or two short periods. The total 24-hour ingestion level is also chronically high, 13.1 g of ethanol per kilogram of body weight [figure 1 in (*2*)], a value for long-term consumption beyond any we have found reported. We maintain that this preparation, then, satisfies all the requirements of criterion (i) and that this is clearly evident in our published report.

(b) The interrelations among food intake, ethanol intake, and weight status are important. Animals received a programmed 8.1 g of food per 24 hours while having free access to ethanol. Their weights progressively increased by approximately 20 percent, thereby returning to their initial, free-feeding, adult body weights. This continuous period of positive energy balance can hardly constitute the "chronically and severely hungry" state Deutsch claims. Of course ethanol contributed to the weight gain; it is a caloric source. The technique was developed to reproduce the situation of the human alcoholic who divides his caloric intake approximately evenly between food and ethanol. The animals did show this pattern, which adds to the validity of the model. Food intake simply cannot be maintained at a prealcoholic level with the necessarily huge ethanol caloric load added to it.

The ethanol intake was not just a function of its caloric content. First, intake occurs mainly during the six spaced, 1-hour feeding periods and not in the 3-hour interperiods. This can be observed by noting the consistent elevations in blood ethanol concentrations occurring after the feeding periods [figure 2 in (*2*)]. Therefore, the elevated and sustained concentration was produced by the dipsogenic nature of the food-delivery regime and not simply by the calories in the ethanol. Second, owing to space limitations, we could not present data on various control conditions. For example, when animals simply were limited to 8.1 g of food per day and allowed free access to 5 percent ethanol, they lost weight continuously, and their ethanol intake did not increase. The large ethanol consumption in our reported experiment, then, was not simply a response to caloric need.

(c) Our criteria do not state that animals should prefer ethanol after the conclusion of the experiment. A preference change outlasting the environmental arrangements which generate a high level of ethanol consumption is not a requirement of the criteria for ethanol dependence. That preferences do change as a function of ethanol acclimation, and the like, is known. The notion that a stable, environment-independent change in preference is a requirement for demonstrating dependence is reminiscent of the discredited notion of "craving" or "loss of control" drinking (*4*).

(d) Holtzman rats are not a strain prone to audiogenic seizures. As stated in our report, prolonged key-shaking failed to elicit seizures or preconvulsive signs in normal animals. Other seizure controls involved similar attempts to obtain convulsions in animals under the ethanol polydipsia condition prior to ethanol withdrawal, in animals reduced to 80 percent of their normal weights, and in similarly weight-reduced animals under a water polydipsia condition. No seizures could be evoked. The last two of these groups were more reduced in weight (80 percent) when tested than were the animals described in our report (*2*). Therefore, neither the nutritional status of the animals nor their prolonged exposure to ethanol per se resulted in a disposition to convulse to key-shaking. But withdrawal from ethanol with a very brief (less than 5 seconds) key-jingling stimulus yielded death from tonic-clonic seizures, as reported.

There are other, more minor misinterpretations embedded in Deutsch's comments. Our animals were not "trained to obtain food"; they were simply fed. The ethanol intake was not maintained by any extrinsic reinforcing events, nor was ethanol drinking itself an "extrinsic reinforcing event" as stated by Deutsch. It is obviously an intrinsic one.

Finally, the Myers and Veale review is cited as containing "cogent criticisms" of the schedule-induced ethanol polydipsia technique which apply "with equal force" to our study. This excellent review in fact correctly criticizes the pharmacological significance of short-duration, daily ethanol polydipsia sessions yielding small values for intake (grams of ethanol per kilogram of body weight). Their criticism obviously is not applicable to our technique.

JOHN L. FALK
HERMAN H. SAMSON
Department of Psychology,
Rutgers University,
New Brunswick, New Jersey 08903
GAIL WINGER
Department of Psychiatry,
State University of New York,
Downstate Medical Center,
Brooklyn, New York 11203

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