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Schedule-induced Physical Dependence on Ethanol*

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The intake of ethyl alcohol by man varies all the way from occasional use as a solemn sacrament, through limited recreational drinking, frequent revelry, to chronic abuse. The sources for this wide disparity among individuals in ethanol drinking have been sought in genetic differences, metabolic and nutritional imbalances, personality structures, and environmental determinants. Precious little has been learned about why some individuals overdrink. It would be a help if animals could be induced to overindulge chronically with ethanol so that the resulting state could be studied. But over three decades of research have failed to yield an arrangement under which animals would drink an aqueous ethanol solution so as to become physically dependent (36). Short episodes of overdrinking, as well as modest, long-term increases, have been evoked by various stratagems, but these fall far short of levels sufficient for the production of physical dependence. This seeming reluctance of animals to overindulge could occur for various reasons. (a) It is conceivable that ethanol has qualitatively different effects on animals and man. However, the observable acute effects of ethanol administration, as well as the phenomena of tolerance and physical dependence appear parallel in animals and man (25). (b) It could be that animals differ from man in their taste preferences and simply find ethanol repugnant. But Richter (40) and Richter and Campbell (41) found that rats preferred ethanol to water in low concentrations (1 to 6% ethanol) and this result has been confirmed by subsequent investigators (18, 32–35). (c) It may be argued that only certain individuals with metabolic or personality disorders overindulge and that there exists no animal analogue for these alleged disorders. Similar arguments have been put forth to explain abuse of opioids, barbiturates, central nervous system stimulants *etc.*, but the excessive self-administration of these substances by animals under a variety of conditions makes the notion of a special genetic, metabolic, or personality defect as a necessary precondition most unlikely (see other papers, this conference). (d) Finally, it is conceivable that the excessive drinking observed in some people is catalyzed by certain environmental conditions and that the relevant variables have simply not been manipulated successfully in animal experiments.

With regard to this last alternative, various environmental conditions have been manipulated in attempts to bring about stable, chronic increases in ethanol intake sufficient to induce physical dependence (36). These situational variables may be placed into three general classes. In one type of experiment, situations deemed stressful, aversive, or fraught with uncertainty and conflict are imposed in hopes that they are analogous to conditions producing alcoholism in man. Although some of these attempts have yielded tantalizing increases in ethanol ingestion, they have

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failed to result in large chronic increases or in physical dependence. A second type of experiment forces ethanol consumption by the simple expedient of tying ethanol ingestion to the reinforcing effect of food, *e.g.*, mixing a freely available liquid diet with ethanol (16, 38, 39). Such arrangements have yielded evidence of physical dependence and for that reason are useful research tools. They have, however, two drawbacks: (a) They require the maintenance of a severely reduced body weight which predisposes animals to convulsions and also interferes with the metabolism of alcohol (48). In work reported in 1971, some of these weight-reduction problems seem to have been overcome (17, 49). (b) With food and ethanol mixed into a single source of nutrition, it is impossible to study the effect of variables on ethanol consumption independently of food intake—an entity under severe regulatory constraints of its own. Nevertheless, aside from the intravenous self-administration of ethanol in the rhesus monkey (6, 52), the liquid-food method was, until recently, the only method available whereby animals drank enough ethanol to develop physical dependence. Other methods have required that the experimenter simply impose the ethanol on the animal by gastric intubation (7, 8) or inhalation (20). A third type of environmental arrangement modulates ethanol intake by making either ethanol or food available only intermittently. One of these arrangements consists in presenting ethanol for 2 days, withdrawing it for 2 days, and so on (46, 50). The resulting increased ethanol intake has been called "the alcohol deprivation effect." Again, these increases, while of theoretical interest, are too small to induce physical dependence. Another intermittency arrangement consists of schedules of reinforcement with food pellets. Various schedules of reinforcement have been shown to induce a marked concurrent water polydipsia (9; for a summary see 10). There is no physiological reason why animals exposed to intermittent food delivery should develop the massive overdrinking referred to as "schedule-induced polydipsia." Nevertheless, we reasoned that if rats would abuse water chronically under this arrangement, perhaps they could also be induced to abuse ethanol and become physically dependent if this fluid were made available.

Schedule Induction as a Method for Producing Physical Dependence

In schedule-induced polydipsia studies, it has been a common practice to use sessions of no more than a few hours per day. Under such a regimen, the rat will, for example, drink about one-half its body weight in water in approximately 3 hr while obtaining food (45 mg pellets) on a variable-interval 1-min schedule (9). For month after month, during such daily sessions, animals continue to drink these massive amounts (about 3.4 times their pre-experimental, normal 24-hr water intake level); little water is drunk during the remaining 21 hr per day spent in the home cage although it is freely available. However, we reasoned that if development of physical dependence on ethanol was similar to the barbiturates (53) elevated blood levels would be required for a major portion of each 24-hr cycle. Accordingly, we slowly reduced rats to 80% of their adult free-feeding body weights and then simply fed them individually on an intermittent schedule 24 hr per day. Every 2 min a food pellet was delivered (fixed-time 2-min schedule) during 1-hr feeding periods that were separated by 3-hr intervals. Thus, there were six feeding periods in each 24-hr cycle, delivering a total of 180 pellets. First, water was the available fluid; after schedule-induced polydipsia was established, a gradually-increasing concentration of ethanol was substituted in place of water. Starting with 1% (v/v) ethanol, this concentration was increased every 6 to 8 days in 1% increments to 6% ethanol (13).

Figure 1 shows the amount of ethanol ingested by each of eight rats as a function of the concentration offered. Except for rat no. 6, animals ingested between 11 and

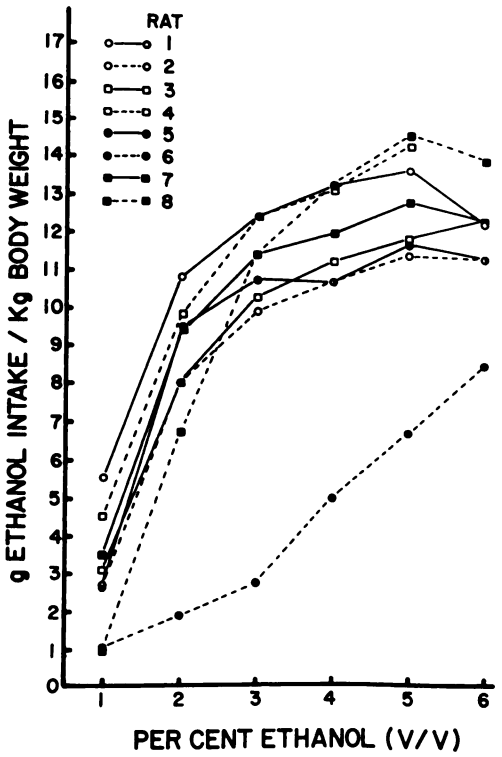

FIG. 1. Mean daily amounts of ethanol drunk by individual rats as a function of the available ethanol concentration.

15 g of ethanol per kg of body weight at 6% ethanol. The change from 5 to 6% ethanol did not lead to an increased consumption of grams of ethanol/kg. Therefore, the concentration was returned to 5% for the ensuing 3 months, after which time the experiment was terminated with a test for the presence of physical dependence. The 180 food pellets per day plus the calories in the ingested ethanol permitted the body weights to increase continuously. At the end of the experiment, the weights had returned to the initial, adult free-feeding level when the test for physical dependence was administered.

During the 2nd month, we measured blood ethanol levels in 50 μl samples from the tail taken 1 hr before and 1 hr after each of the 1-hr feeding periods (fig. 2). The samples were taken serially from 8 A.M. to 7 P.M. Two weeks later the samples between 8 P.M. and 7 A.M. were gathered. Thus, there is a data break indicated between 7 and 8 P.M. in the figure to denote the 2-week interim. For most of the animals, the blood ethanol concentration remained greater than 100 mg/100 ml for most of the time (6 P.M. to 11 A.M.) and often lay between 150 and 300 mg percent. Daily intake of ethanol remained quite constant during the 3-month period on 5% ethanol. For the last 10 days of the experiment, the mean daily intake for the eight animals was 13.1 g of ethanol/kg of body weight.

When these and similarly treated animals in subsequent experiments (43) were withdrawn from ethanol for 8 hr and then subjected to a very brief (less than 5 sec) stimulus consisting of a bunch of keys shaken over them in individual withdrawal cages, severe tonic-clonic seizures resulted, with some animals dying. Prolonged key shaking failed to induce either seizures or preconvulsive activity (tremors, clonic movements, jumping and vocalizing) in control animals, in animals polydipsic on water held to 80% body weight, or in rats held to 80% body weight with free access to 5% ethanol as their sole drinking fluid in a home-cage situation (13, 14, 42). With this method, then, we were able to produce unequivocal physical dependence on ethanol by oral self-administration of an aqueous ethanol solution in animals.

Controlling the Pattern of Daily Blood Ethanol Elevation: Relation to Physical Dependence

One advantage of the schedule-induction method is that the temporal distribution of the polydipsic episodes can be controlled by manipulating schedule parameters while still allowing continuous access to the ethanol solution. Thus, schedule-induced ethanol polydipsia can be arranged to produce not only the fairly continuous elevations described above, but also one or two peaks in blood ethanol level per 24 hr. In our initial experiments, we assumed that physical dependence would

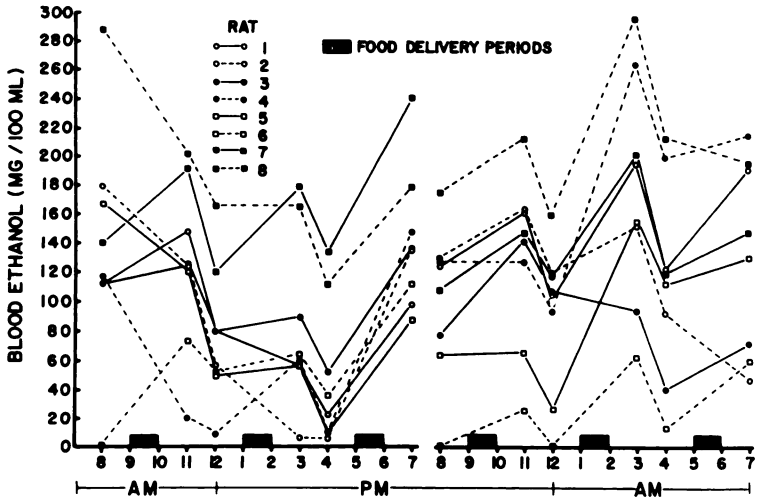

FIG. 2. Blood ethanol concentrations of rats drinking 5% ethanol (v/v). During the indicated 1-hr feeding periods, a food pellet (45 mg) was delivered every 2 min.

be more likely to develop if blood ethanol levels were continuously elevated rather than episodically elevated. To test this assumption, we have used different regimens of food delivery: (a) the usual fixed-time 2-min schedule was in effect for only two 1-hr periods separated by 3 hr each day; (b) the same schedule was used except 12 hr, rather than 3 hr, separated the two feeding periods (45); (c) the full daily food ration was fed all at once as a single feeding (42); (d) the standard six 1-hr fixed-time 2-min feeding periods per day (13). Figure 3 shows the temporal distribution of blood ethanol concentrations (point approximation curves) under these four regimens. After 3 months of intake, only group D showed tonic-clonic convulsions and death when withdrawn from ethanol for about 8 hr and tested with a less than 5-sec shaking of keys. Groups A, B, and C were also tested, but there was no abstinence syndrome nor any increased excitability except for one animal in group C which responded finally to a third prolonged shaking of keys with a very mild tonic-clonic episode. The animal remained standing and the seizure was not comparable to the Group D convulsions in form, intensity, or duration. Although it was not possible to equate the daily ethanol intakes of these groups exactly, these data suggest that blood ethanol concentration must be maintained above some critical level for prolonged periods each day for an unequivocal state of physical dependence to develop.

Enhancement of Schedule-Induced Ethanol Polydipsia by Saccharin

Increased intakes of ethanol have been reported when ethanol was combined with various flavored solutions, but these increases were modest and not sufficient for the production of physical dependence (36). In hopes of further elevating ethanol intake in our standard chronic polydipsia situation (1-hr sessions of fixed-time 2-min pellet delivery separated by 3-hr intervals), we added saccharin to the 5% ethanol solution usually available (43). To determine whether saccharin addition might have an enhancing effect which was situationally specific, two groups of rats were maintained in standard home cages at 80% body weight and allowed free access to either 5% ethanol (group 1) or a combined 5% ethanol—0.25% saccharin solution (group 2) for 3 months. These groups were compared with another group of animals maintained on our standard, chronic schedule-induced ethanol polydipsia regimen. After 1 month of drinking 5% ethanol, the schedule-induced group was switched

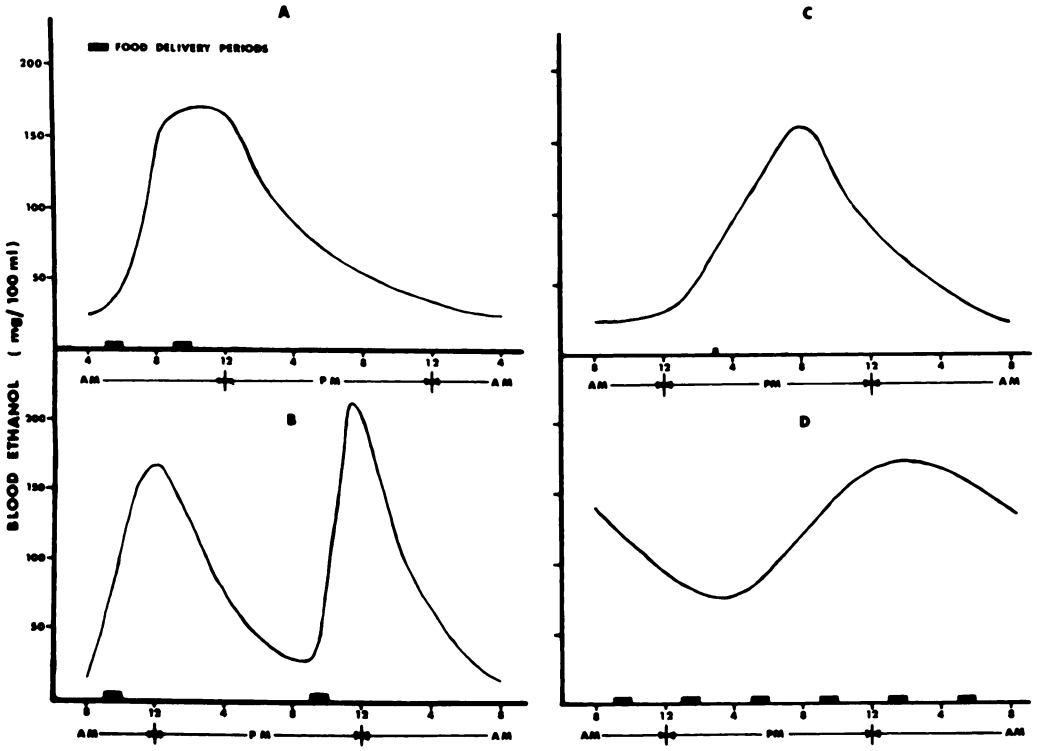

FIG. 3. Temporal distributions of blood ethanol concentrations (point approximation curves) under various daily feeding regimens (see text).

to the ethanol-saccharin solution for 2 months.

As shown in figure 4, there was no significant difference in the grams of ethanol/kg intakes between the two home-cage conditions. However, adding saccharin to the ethanol in the schedule-induced condition markedly increased ethanol intake from 13.1 to 15.1 g of ethanol/kg. Adding saccharin enhanced ethanol intake in the schedule-induced condition but not in the nonschedule-controlled, home-cage condition. Thus, the gustatory component worked only in synergy with the schedule-induced condition which already produced an intake level greater than that of the home-cage condition.

Choice between Ethanol and Other Fluids in Dependent Animals

The experiment described in the previous section demonstrated that ethanol-dependent animals were responsive to an additive which is highly acceptable at the concentration used (0.25% saccharin). In that situation the additive substantially increased an already elevated ethanol intake. Thus, we wished to ascertain whether this and other highly acceptable fluids would compete with 5% ethanol when ethanol-dependent animals were allowed such alternatives. There is an elective aspect to fluid intake in the schedule-induced situation since the animal is not required to overdrink to maintain its caloric or fluid balance; nevertheless, an explicit fluid choice situation would delineate more clearly the dimensions of ethanol acceptance resulting from this situation.

An experiment with our standard, chronic schedule-induction situation was used except that initially 5% ethanol was available from each of two drinking tubes (42). After establishing 5% ethanol polydipsia for 12 days (see fig. 5, early ETOH only), 5% ethanol was in one tube and

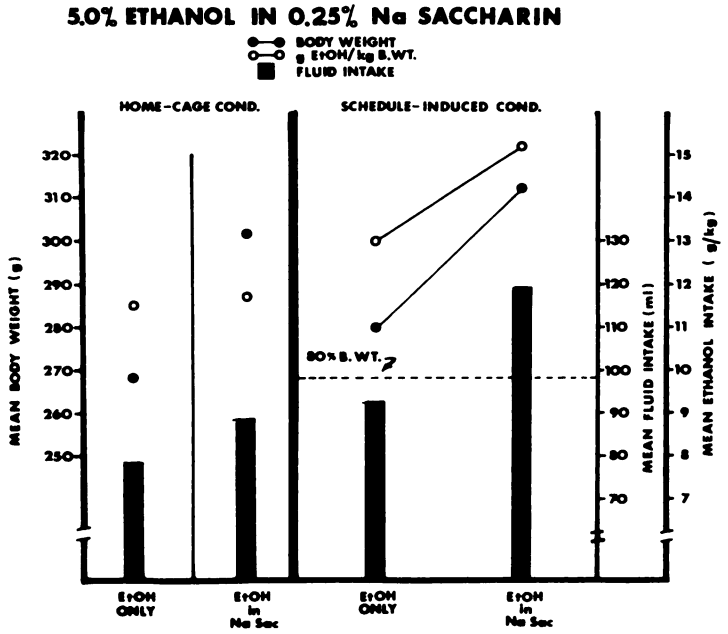

FIG. 4. Effect of addition of sodium saccharin to 5% ethanol intake in both the home-cage and schedule-induced conditions. In the home-cage condition, one group of animals received 5% ethanol as their only drinking fluid (ETOH only; N = 5) while another group received the 5% ethanol-0.25% saccharin mix (ETOH in NaSac; N = 8) for the entire experimental period. In the schedule-induced condition (N = 4), 5% ethanol was available for the first month (ETOH only) and was replaced by the ethanol-saccharin mixture for the following 2 months (ETOH in NaSac). (All data are means for the last 30 days in each condition. The body weights for the two home-cage conditions are the mean 80% weight levels.)

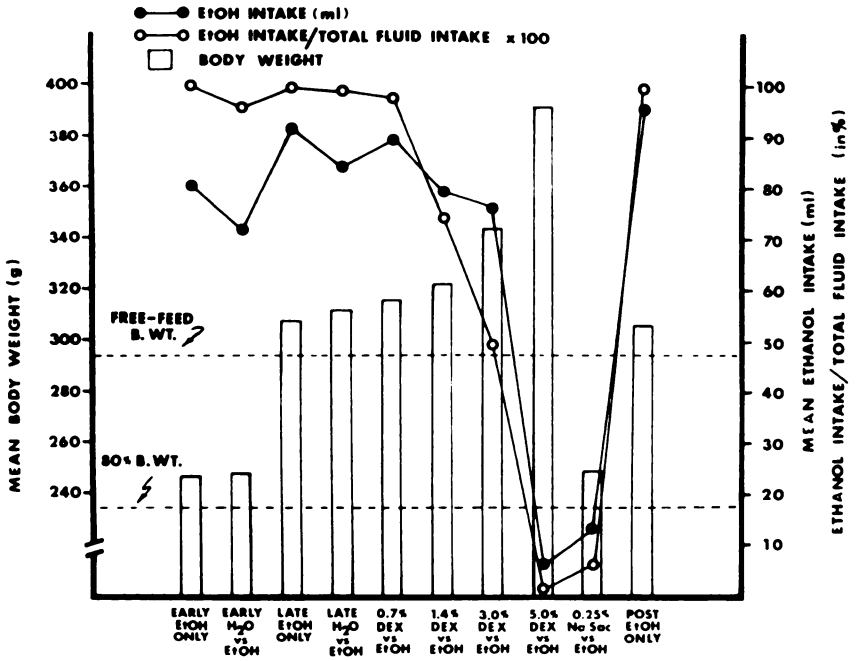

FIG. 5. Preference relation between 5% ethanol and other fluids for rats chronically overdrinking ethanol on the intermittent-food-ration regimen. All values are means.

water in the other tube for 3 days (fig. 5, early H_20 vs. ETOH). Tube positions were switched daily. This test, as well as a similar one on days 76 to 78, indicated that 5% ethanol was preferred to water. In a series of comparisons after this determination, 5% ethanol was in one tube and increasing concentrations of dextrose, commencing with 0.7% (w/v) dextrose, in the other tube. If an animal switched its preference from ethanol to a dextrose solution, the preference test was continued for at least 5 more days. Preference for a particular solution was defined as an intake level of more than 50% of the total fluid intake. After an animal's preference switched from the ethanol solution to a dextrose solution (by the above criterion), a 0.25% sodium saccharin solution (w/v) was substituted for the dextrose solution (0.25 NaSac vs. ETOH). Saccharin was paired with ethanol until the animal either switched back to ethanol (which never happened), or lost so much body weight that general health was compromised. At that point, 5% ethanol was again placed in both tubes and the ethanol drinking levels were redetermined (post-ETOH only).

It is evident from figure 5 that 5% ethanol was preferred to water; however, when the dextrose concentration reached a high enough value, animals switched their fluid preference from ethanol to dextrose. Out of eight rats, one switched at 1.4% dextrose, two rats at 3% dextrose, and the remaining animals at 5% dextrose. All animals preferred the noncaloric saccharin solution even after their weights had declined seriously. Two rats actually died in a state of anorexia, ceasing to eat their scheduled food pellets during the last few days but continuing to drink the saccharin solution. Thus, even with a caloric deficit which progressively developed over a 6-week period, all animals continued to prefer saccharin solution in the presence of a previously preferred ethanol solution which could have provided the calories necessary for body weight maintenance. Similar results were obtained with an additional group of animals which were treated similarly but were given no dextrose solu-

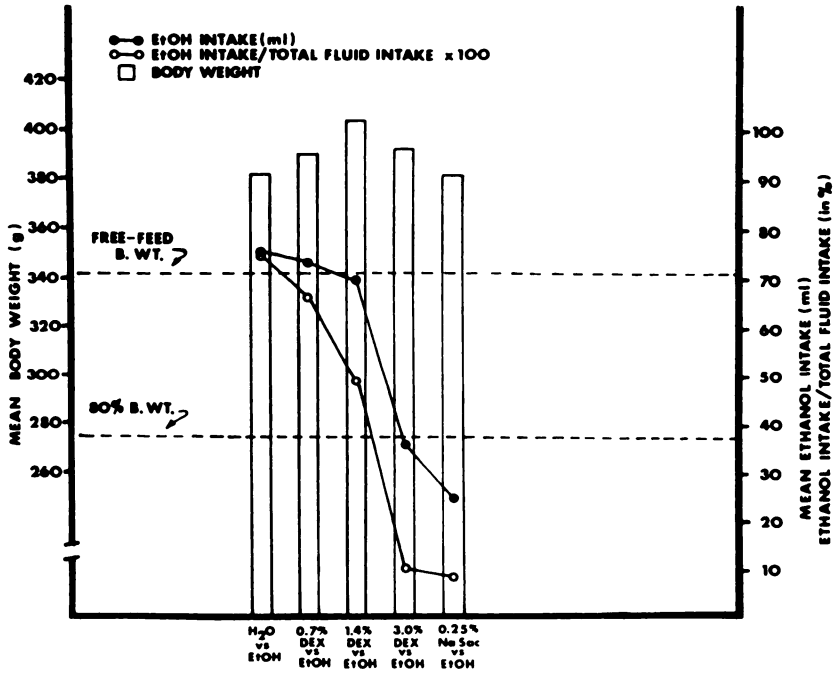

FIG. 6. Preference relation between 5% ethanol and other fluids for rats after chronic ingestion of ethanol in the single food-ration regimen condition, with body weights allowed to increase. All values are means.

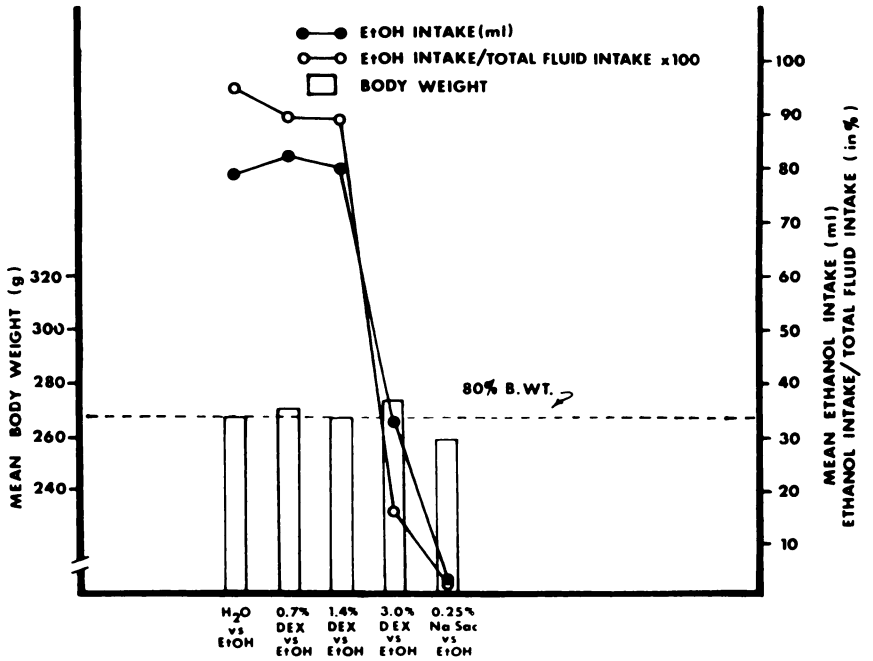

FIG. 7. Preference relation between 5% ethanol and other fluids for rats after chronic ingestion of ethanol in the single food-ration regimen condition, with body weight maintained at 80% of the free-feeding level. All values are means.

tion tests. Thus, the saccharin preference was not a result of any carry over of a preference for a sweet dextrose solution to a sweet saccharin solution.

As noted above, five out of the eight rats switched their preference from 5% ethanol to dextrose only when the dextrose solution concentration was increased to 5%. This result was compared with results from another group of animals maintained with the same fluid choices as the animals described above, but not fed under the intermittent food regimen. Thus, these animals did not have the polydipsic drinking pattern maintaining a continuously elevated blood ethanol level, but they did drink ethanol for the same period as the above group. These animals, then, serve as a control group for long-term adaptation to the ethanol solution. Some of these animals were allowed to increase their body weights, as in the previous experiments, while others were held to the 80% level. All animals preferred 3% dextrose to 5% ethanol (see figs. 6 and 7). They also preferred the saccharin solution to the ethanol. Comparison of figure 5 with figures 6 and 7 indicates that the scheduled-induced, dependent animals still drank a large volume of 5% ethanol during the 3% dextrose choice, while the other animals had decreased their intake of ethanol considerably at that comparison point. For the schedule-induced, ethanol-dependent animals, the acceptability of dextrose was evident only at a higher concentration in competition with 5% ethanol; nevertheless, they did switch to dextrose when the concentration was raised sufficiently. No group chose ethanol in preference to saccharin. For all animals, whether physically dependent on ethanol or not, this last preference change was disastrous in terms of caloric maintenance.

Development of a Drug Abuse Model from Implications of Schedule Induction

Our initial aim in applying a chronic polydipsia technique to ethanol intake was simply to provide a means for the production of physical dependence. Although alternative methods are available for insti-

tuting physical dependence, they are either imposed on the animal (intubation, inhalation) or tied to the intake of liquid food, thereby precluding investigation of the determinants of oral ethanol intake itself. The intravenous method, while allowing the exploration of variables determining intake, uses a route of ethanol administration not chosen by man and involves maintenance problems for small animals, such as the rat, which make lengthy experiments difficult. Long-term experiments are necessary, for the development of the dependence, the behavioral characterization of the dependent state(44), and the evaluation of any slowly developing pathological changes. Schedule-induction seems to be the only method, at present, which results in physical dependence owing to free ingestion from an aqueous ethanol solution.

Now a behavioral method for the production of physical dependence is one thing, but the development of an animal model of alcoholism is quite another matter. A satisfactory method need only induce some specifiable end state or response output; how this terminal state might be produced is of more technical, than theoretical interest. With a model, however, the determining variables are assumed to have the same general structure as the process under study. We hope that, as experiments progress, the schedule-induction technique will change from a method to a model. At this point we will outline the requirements for an alcoholism model and evaluate the status of schedule-induced ethanol polydipsia within this set of requirements.

Requirements for an animal model of alcoholism. We will reiterate four criteria specified previously (13) for an animal model of alcoholism and discuss them in the light of the results presented here.

1. 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. Blood ethanol concentration should remain at a high level for the major portion of the day to reproduce the levels found in human alcoholics (29, 37). This was accomplished in our chronic ethanol polydipsia situation (fig. 2), and in further work it was shown that daily episodic elevations in blood ethanol concentration (fig. 3, A, B, and C) failed to generate physical dependence.

2. Unequivocal physical dependence on ethanol must be demonstrated. We regarded the production of a full tonic-clonic convulsion after withdrawal of ethanol as proof of physical dependence. Furthermore, it should be triggered by weak stimulation; in our studies less than 5 sec of jingling keys. This is a rather stringent criterion and we have no doubt that not all investigators would wish to limit the notion of physical dependence to such a weak stimulus and strong a response. We judged that it was important to use a clearly defined and reliable end-point. Other investigators have used criteria such as withdrawal irritability, extreme tremor of the extremities, severe hyperreflexia, salivation, mydriasis (7, 39) and changes in startle thresholds to shock (19) to good advantage. With similar, less demanding, criteria it is possible to use dependence induction times of less than 3 months, especially if stimuli of greater intensity and duration are used to trigger the withdrawal reaction. For example, Lieber and DeCarli (26) used weanling rats raised on a liquid diet containing ethanol as 36% of the total calories. Within a few weeks, the sound of a fire bell delivering 84 decibels to the test cage for 2 min produced seizures in these animals, but not in controls 18 to 24 hr after ethanol withdrawal. No comparative growth curves for these immature animals were given, nor were blood ethanol levels presented. However, it is evident that by using very young animals and a very strong stimulus, physical dependence was demonstrated to have developed in a short time. The purposes of the experimenter will obviously govern exactly what criteria will be considered adequate for the presence of a dependence state and how severe a state is required. At this stage of the research, we

prefer to work with a severe dependence state.

We have tested various control groups to be sure that no nutritional feature of our technique predisposed the animals to seizures. The Holtzman strain rats used in our experiments are not prone to audiogenic seizures. In normal rats, or in animals in the chronic ethanol polydipsia condition before ethanol withdrawal, prolonged key shaking did not elicit either seizures or preconvulsive signs. Two other groups of rats were reduced to 80% of their adult, free-feeding weights and subjected to a prolonged key-shaking test. One group was simply maintained in their home cages; the others were on a chronic water polydipsia regimen. No seizures could be evoked. These last two groups were more reduced in body weight when tested than were the chronic ethanol polydipsia group which had returned to their starting body weights at the time of withdrawal testing. Therefore, it was not the nutritional status nor the prolonged exposure to ethanol which disposed these animals to convulse. It was the withdrawal of ethanol.

3. 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. This requirement stems from the evident lack of a relation between drinking and eating in human alcoholism. It is possible to force the development of physical dependence in animals by mixing ethanol with food, but food consumption is not the reinforcing relation which sustains chronic drinking in the human alcoholic.

Since our animals were allowed only a limited amount of food (180 pellets or 8.1 g), it might be maintained that increased ethanol intake was merely a feeding response. The interrelations among food intake, ethanol intake and weight status are important to consider in relation to the model. The animals were started on the chronic ethanol polydipsia regimen at 80% body weight, but their weights increased slowly so that they had returned to the initial free-feeding weight by the time of the test for physical dependence. A group of animals allowed continuous, free access to 5% ethanol were reduced to 80% body weight and subsequently returned to free-feeding weights by adjusting their single daily food ration over a 3-month period. They averaged an ethanol intake of a little over 10 g/kg per day, rather than the 13.1 found for animals under the same weight gain conditions fed on the intermittent food regimen which generates polydipsia (42). Another group of animals limited to 8.1 g of food as a single ration per day and given free access to 5% ethanol as their sole drinking fluid lost weight continuously and their ethanol intake did not increase. Obviously, the chronic ethanol polydipsia was not simply a response to caloric need but was induced by the dipsogenic nature of the food-delivery regimen. But perhaps the strongest evidence against a caloric interpretation of the ethanol overdrinking is that 0.25% saccharin solution was drunk almost to the exclusion of 5% ethanol when both were available and the ethanol had previously been preferred to water and drunk in large volumes (fig. 5; see also ref. 42 for a more complete treatment of these and related data). This preference persisted despite a disastrous weight loss.

When chronic ethanol overdrinking occurred as a function of the schedule-induction procedure, the steady weight gain observed was clearly due to the considerable caloric load contributed by the ethanol. The percentage of the total caloric intake which was ingested as ethanol was 44.8%. The human alcoholic selects close to 50% of his daily calories as ethanol (30). The schedule-induction technique, then, reproduces this caloric selection pattern of the alcoholic, which supports the validity of the model.

4. 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. The schedule-induction procedure does not reinforce drinking by making food delivery contingent upon it. Yet it induces a chronic polydipsia as long as the schedule remains in effect. The level of drinking is far beyond physiologically defined body water requirements. In this sense, overdrinking, even when only 5% ethanol is present, remains elective. However, a stronger case for the elective aspect of the overindulgence can be made in the cases where there was an alternative second fluid available in the situation. As previously described, 5% ethanol was preferred to water and to dextrose solutions up to and including 3% dextrose. Nondependent animals preferred 5% ethanol over dextrose concentrations only up to 1.4%. While this difference illustrates that physical dependence biases the choice of fluid toward ethanol, it also shows that there are gustatory reinforcers which can displace the reinforcing effect of 5% ethanol to the dependent animal, *viz.*, 5% dextrose or 0.25% saccharin. This agrees with the recent findings of several investigators indicating that "craving" or "loss of control" as explanations of alcoholic drinking are unsatisfactory (1, 4, 21, 22, 27, 28, 31). Additional work has shown that specific environmental manipulations suppress drinking in chronic alcoholics (2). When 10 or 15 min of physical and social isolation was the consequence of each drink, alcohol intake decreased about 50%. When the consequence of each drink was a 40-min time-out from social interactions, drinking was suppressed to very low levels when alternate sources of reinforcement (television, games, *etc.*) were not available (23). Such results are strong evidence against a "craving" driven by a biochemical need as the mechanism which maintains an inexorable course of drinking in the alcoholic. The contingent withdrawal of social interaction is sufficient to markedly attenuate drinking. Thus, while an organism may overindulge in ethanol as a function of certain environmental conditions, alternate reinforcing possibilities, such as 5% dextrose or 0.25% saccharin for the rat, or the contingent withdrawal of social interactions for man, are sufficient to practically eliminate drinking in spite of physical dependence.

From dependence method to alcoholism model. Thus far, the chronic schedule-induced ethanol polydipsia situation seems to satisfy the requirements we have formulated for an animal model of alcoholism. But the congruence of data with formal tenets is only the first phase in the investigative process which must occur before models attain acceptance. A model also is required to reproduce within its framework the phenomena already known to occur within the area of inquiry. Therefore, it is worth considering briefly whether the present model yields data which aligns with what is known about alcoholism.

As we have described above, the blood ethanol concentration levels are chronically elevated under the schedule-induced regimen as they are in chronic alcoholism. The regimen yields unequivocal physical dependence by oral self-administration from an aqueous ethanol solution separate from the major food source. This ingestion is not sustained by any contingent relation to the delivery of food, intracranial stimulation, or avoidance of shock. The ingestion is elective in the sense that it is not tied to body water requirements and is chosen in preference to certain other available fluids, including water. The chronic ethanol overindulgence is likewise not reducible to a caloric regulatory response. All of these characteristics square with the circumstances of chronic alcoholism. The preference for ethanol over other fluids in the dependent rat finally can be overcome when the alternate fluids reach certain concentrations (5% dextrose or 0.25% saccharin), just as Cohen *et al.* (5) showed that 7-day abstinence in human alcoholics could be purchased with money when the payment was high enough.

With continued drinking, alcoholics show considerable tolerance to the disruptive effects of ethanol on motor coordina-

tion (27). We found similar relations in chronic schedule-induced ethanol polydipsic rats which were required to hold a force-transducer manipulandum within a specified force band for a fixed period of time (44). Before chronic ethanol exposure, doses producing ethanol levels greater than 120 mg/100 ml of blood affected discriminative motor control. But after chronic ethanol overdrinking, blood levels greater than 230 mg/100 ml of blood were required, indicating the development of marked tolerance.

Experimental work has shown that chronic alcoholics divide their daily caloric intake approximately equally between food and ethanol (27, 30). Similarly, our chronic polydipsic animals ingested 44.8% of their calories in the form of ethanol (13).

Alcoholics do not drink in an uncontrolled manner nor do they drink every day (27, 28, 37). Several days of drinking are typically interrupted by one or more days of abstinence. We have noted that some animals on the saccharin enhancement of ethanol polydipsia regimen, where ethanol intake averaged 15.1 g/kg per day, reduced their intakes on occasion for a 3- to 4-day period to approximately 35% of their typical daily intake (43). The occurrence of periodic self-withdrawal was also a feature of intravenous self-administration of ethanol in monkeys (52).

Finally, alcoholics may show two phases to the abstinence syndrome (47, 51). There is an initial stage of tremors and seizures which occurs just after intoxication subsides and usually lasts from 6 to 48 hr, although it can persist for 72 hr. A second phase, occurring in a small proportion of patients, is characterized by psychomotor and autonomic nervous system overactivity and has its onset 48 to 96 hr after withdrawal. Ellis and Pick (7) found that the convulsive stage in monkeys was also of relatively short duration (17 to 24 hr after the final ethanol dose), but various signs of hyperexcitability subsided only after 2 or 3 days. In dogs, all but one of the convulsions occurred between 18 and 21 hr after withdrawal, but tremors persisted for 36 to 124 hr (8).

We found with our testing method that the susceptibility to seizures occurred between 8 and 10 hr after withdrawal (12, 43). Dyskinesia was measured daily by our discriminative motor control technique and found to persist for 72 hr, with a return to normal motor behavior occurring by 96 hr postwithdrawal (44). In figure 8 is shown this relation in which dyskinesia was measured by the number of times the applied force entered the required force band during a session, and was an indication of the lack of steadiness. A similar 72-hr time course of motor hyperactivity in the rat was noted after withdrawal with open-field activity (3) and responsiveness to electric shock (15). In general, the animal research agrees with observations on the first phase of the abstinence syndrome in man. There is a relatively short-term susceptability to seizures followed by motor hyperactivity and dyskinesia persisting up to 72 hr.

The schedule-induction situation as a model for the reinforcing effects of drugs. The heading for this final section may seem strange since the reinforcing effect

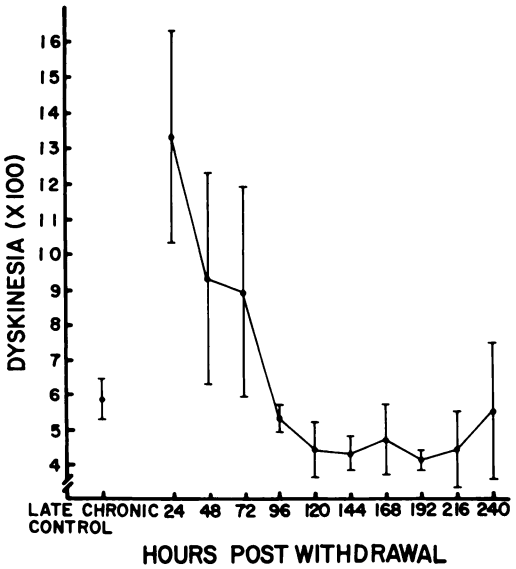

FIG. 8. Effects of complete ethanol withdrawal on dyskinesia (number of force band entrances). Means ± S.E., N = 4.

of a drug is usually considered as principally a function of the direct pharmacological action of the drug. However, there is ample evidence from behavioral studies that the reinforcing efficacy of an agent is greatly dependent upon the environmental circumstances under which it occurs. This is less evident with a powerful reinforcing agent such as intravenous cocaine than in the case of a more marginal agent such as ethanol where various environmental influences play a more important role in determining its reinforcing efficacy. Not much is known concerning the dimensions of these environmental determinants. The effects of several kinds of conditions, such as stress, avoidance, punishment, escape and extinction schedules, crowding, and conflicts on ethanol consumption have been, for the most part, disappointingly modest. But, the relatively simple expedient of imposing a chronic, intermittent feeding schedule generates chronic overdrinking of ethanol.

Now there are two possible objections to considering schedule-induced ethanol overindulgence as a model for alcoholism. One is that the overdrinking is not specific to ethanol, and the other is that whatever the etiology of human alcoholism might be, it certainly does not spring from intermittent feeding schedules. To answer these possible objections first requires a short discussion of "adjunctive behavior." It has been shown that not only is polydipsia generated by certain intermittent feeding schedules, but also aggression, pica, wheel-running, air-licking, and escape from positive reinforcement schedules (for a review, see ref. 11). The particular behavior manifested is a function of the environmental situation. All of these behaviors are engaged in excessively, and can be generated chronically as stable, exaggerated behaviors as long as the inducing schedule conditions remain in effect. They are not new responses elicited by the schedule conditions, but are large increases in the rate of a behavior already present as a response to the existing situation. For an animal on a deprivation regimen, the interruption of consummatory behavior imposed by feeding intermittency induces excessive engagement in some other behavior present in that situation. Adjunctive behavior, then, "is behavior maintained at a high probability by stimuli whose reinforcing properties in the situation are derived primarily as a function of schedule parameters governing the availability of another class of reinforcers" (11). Thus, under certain intermittent food schedule values, water or ethanol solutions become powerful reinforcers maintaining excessive drinking.

Intermittently scheduled presentations of various environmental commodities can lead to, among other things, chronic and excessive indulgence in other commodities. The overindulged entities already possess reinforcing properties in the situation; the schedule only serves to exaggerate greatly this process. Thus, while various behaviors could be facilitated by the generator schedule, ones that are already occurring or are the preferred alternative will dominate. Therefore, while schedule-induced polydipsia is certainly not specific to ethanol, a 5% ethanol solution is preferred to concurrently available water (18, 32–35, 40) and its ingestion is more likely to be increased by the intermittent schedule of food presentation. We have already described how this ethanol overindulgence, in turn, can be displaced by preferred fluids in the rat or by money in man. That schedule-induced polydipsia is not specific to ethanol solutions only emphasizes the continuity between excessive ethanol ingestion and other behaviors which have the potential of being exaggerated and substituting for ethanol.

While intermittent food schedules constitute an important determining condition for adjunctive behavior in animals (rats, mice, monkeys, and chimpanzees), the scheduling of other events may be more important in controlling the excessive behavior of people not deprived of food. Kachanoff *et al.* (24) demonstrated both schedule-induced polydipsia and schedule-

induced pacing as a function of delivering pennies under fixed-interval schedules to schizophrenic subjects not deprived of either food or water. Thus, certain environmental contexts in which people live may constitute appropriate schedules for generating inordinate amounts of adjunctive behavior. While some of these behaviors may be as inconsequential as scratching, talking, or gesticulating, others may have more serious consequences such as smoking, drinking alcoholic beverages, or self-administering drugs. Intermittent food schedules can induce a wide variety of adjunctive behaviors. This generality may apply not only to the behaviors generated, but also to the generating conditions. The intermittent scheduling of commodities other than food may also induce adjunctive behaviors. If this is correct, excessive drug-taking in people might be induced by schedules of reinforcement in ways analogous to the generation of polydipsia and aggression in animals. Applying the relations obtained from the generation of adjunctive behavior by food schedules, certain predictions are possible concerning drug-taking behavior. For example, one would expect that only a limited effective range of schedule parameter values would yield excessive drug-taking; in the case of food schedules, polydipsia is not evident when the time between pellet deliveries is either very short (less than several seconds) or long (greater than several minutes) (11). Furthermore, it should be possible with a food generator schedule to increase the reinforcing efficacy of a drug solution of marginal efficacy. This follows from the definition of adjunctive behavior. Thus, perhaps a concentration of morphine which is self-injected by monkeys at rates not much greater than saline would command greater rates when available concurrently with an appropriate generator food schedule.

The experiment (43) in which the ethanol-saccharin solution was ingested more than the plain ethanol solution under the chronic schedule-induced polydipsia regimen, while there was no difference between the ingestion levels under home-cage conditions, can be viewed as a case wherein saccharin enhancement of ethanol intake is marginal under normal conditions and is synergized by the schedule. This effect added to the already enhanced ethanol intake level produced by the schedule regimen itself (fig. 4).

It may be enlightening, then, to view excessive drug-taking within the general framework of variables generating adjunctive behavior. The commonly abused drugs can function to reinforce self-administration just as water can reinforce drinking in a normal feeding situation. Reinforcing efficacy can be greatly increased by certain generator schedules. At present, the most well documented case of enhancing the reinforcing efficacy of a drug is that of schedule-induced ethanol polydipsia with the ensuing development of physical dependence. But the paucity of alternate reinforced lines of endeavor in the lives of many chronic drug abusers suggests the possibility that such conditions both precipitate and maintain excessive drug-taking for two reasons initially. First, appropriately intermittent reinforcement schedules enhance the reinforcing efficacy of an available drug. Second, these schedules not only generate adjunctive drug-taking but also cannot compete with the drug as an alternative to it. The response rates on schedules of reinforcement generating adjunctive behavior are typically much lower than rates seen on such schedules when adjunctive alternatives are not available. Initially then, the process would seem to work like a push-pull amplifier. Later, with the maintenance of the drug-taking behavior, physical dependence can develop to certain abused agents. This state can operate to produce preference changes, as we have shown in the case of ethanol, which yield further behavioral maintenance of the drug-taking. When the generator schedule is either eliminated or its values changed appropriately, or alternate strong reinforcers are provided, ex-

cessive drug-taking no longer occurs in spite of the presence of physical dependence.

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