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Establishment of Orally Delivered Ethanol as a Positive Reinforcer for Rhesus Monkeys

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Footnotes

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Abstract

Ethanol was established as a positive reinforcer for four food--deprived rhesus monkeys. The monkeys obtained their daily food rations of 1-g pellets during 3-hr sessions. In the presence of the appropriate stimulus each lever press produced a food pellet. Within approximately 20 min after obtaining their food ration, the monkeys drank up to 500 ml of water. In subsequent sessions ethanol in increasing concentrations (0.5, 1, 2, 4, 5.6, 8% w/v) replaced water. When drinking of 8% ethanol stabilized, the availability of food was shifted from within the 3-hr sessions to a period beginning 1 hr after a session ended. Drinking of 8% ethanol persisted following elimination of intrasession access to food. In subsequent sessions 8% ethanol maintained responding under fixed-ratio (FR) schedules. At FR 16 for three monkeys and at FR 32 for a fourth monkey responding at high rates was maintained by 8% ethanol but not by water. Thus ethanol had been established as an effective reinforcer.

Ethanol can function as a positive reinforcer for rhesus monkeys when it is available via the intravenous (Deneau, Yanagita & Seevers, 1969; Woods, Ikomi & Winger, 1971; Winger & Woods, 1973; Carney, Llewellyn & Woods, 1976) or intragastric (Yanagita & Takahashi, 1973; Altshuler, Weaver & Phillips, 1975) routes. A variety of procedures have been used to produce ethanol drinking by monkeys, but when the inducing procedure was terminated, drinking stopped (for reviews see Woods & Winger, 1971; Mello, 1973; Meisch, 1977). Some of the conditions that were neither necessary nor sufficient to establish ethanol as a persisting reinforcer include: a) production of physical dependence by gastric intubation (Myers, Stoltzman & Martin, 1972) or by placing ethanol in a liquid diet (Pieper & Skeen, 1972); b) contingent drinking to avoid electric shock (Mello & Mendelson, 1971a) or obtain food pellets (Mello & Mendelson, 1971b); c) presentation of ethanol during an ongoing shock avoidance program (Clark & Polish, 1960); and d) ethanol as the sole liquid during early development of rhesus monkeys (Mendelson & Mello, 1973). It has been suggested that in principle ethanol should serve as an oral reinforcer but in practice the aversive taste properties and delay of onset of ethanol's interoceptive effects are strong impediments (Mello, 1973; Mello & Mendelson, 1971b).

Preliminary studies (Meisch, Henningfield & Thompson, 1975; Henningfield & Meisch, 1976a) in our laboratory demonstrated that ethanol could be established as an effective oral reinforcer for rhesus monkeys. The basic strategy was developed in studies using rats as subjects (Meisch & Thompson, 1974). According to this procedure, animals are induced to drink large volumes of water by various schedules of food presentation, e.g., schedule-induced polydipsia (Falk, 1971). Then, low concentrations of ethanol (0.5 or 1% w/v), are substituted for the water. The ethanol

concentration is gradually increased across sessions. When the animals reach 8% (w/v) ethanol and are drinking regularly, the inducing schedule of food presentation is discontinued. All rats and monkeys thus far treated continued to drink intoxicating quantities of ethanol in the absence of the food schedule. Since the initial studies involved only two monkeys, it was necessary to both replicate and extend the findings.

In the present studies, four ethanol-naive rhesus monkeys were induced to drink ethanol by a procedure other than schedule-induced polydipsia. This procedure is termed "food-induced drinking" and was developed using rats as subjects (Meisch, 1975). After ethanol drinking was established liquid deliveries were made contingent on fixed-ratio schedules and performance maintained by 8% ethanol was compared to performance maintained by water. The findings support the conclusions that ethanol may serve as a positive reinforcer for rhesus monkeys; that these monkeys will reliably drink intoxicating quantities; and, that resulting patterns of ethanol drinking do not vary as a function of the acquisition procedure.

METHOD

Subjects

Four adult male rhesus monkeys (*Macaca mulatta*) served as subjects. Three monkeys were experimentally naive; the fourth, M-N, had served in a study of second-order schedules of food reinforcement. The monkeys were housed in their experimental chambers in a constantly lighted room. At approximately 80% of their pre-experimental weights, the monkeys weighed: 6.0 kg, M-B; 5.8 kg, M-N; 6.0 kg, M-W; 5.5 kg, M-L. Their weights varied somewhat over time, and their daily food allotment was gradually changed to maintain stable weights. Their daily diets consisted of one-gram Noyes

banana-flavored pellets, a multiple vitamin pill and one fresh fruit.

Apparatus

Stainless steel primate cages (Labco #ME1305 and Hoeltge #HB-108) having three solid walls and one barred wall were the experimental chambers. Operanda and stimulus lights were mounted on one solid wall. A primate lever (BRS/LVE #PRL-001/121-07) activated an automatic pellet dispenser (BRS/LVE #PDC-005). Food availability was signalled by the illumination of a red stimulus light mounted above the food lever, and food pellets were delivered to a small tray recessed in the wall. The drinking device was an electrically nonconductive spout, 1 cm in diameter, that protruded 2.7 cm into the cage. Activation of a drinkometer circuit was accomplished when the monkey made lip contact on a small brass plate recessed one centimeter from the tip of the spout. Lip-activation of the drinkometer circuit always illuminated a white stimulus light mounted directly over the spout, thus providing stimulus feedback for responses. Each liquid delivery was approximately 0.5 ml. A green stimulus light mounted above the response feedback light was steadily illuminated when water was present and flashed ten times per second when ethanol was present. Details of the apparatus and drinking device have been reported (Henningfield & Meisch, 1976b; Meisch & Henningfield, 1977). Solid state equipment (Coulbourn Instruments, Inc.) for scheduling and recording events was located in an adjacent room.

Ethanol solutions

Ethanol solutions were prepared using 95% ethanol and tap water. The solutions were prepared at least 20 hr prior to use and kept at room temperature. Concentrations are expressed in grams percent, e.g., 500 ml of

8% (w/v) was prepared by mixing 53 ml of ethanol with enough water to produce a total volume of 500 ml.

General procedure

Daily experimental sessions were 3 hr in duration and were preceded and followed by a 1-hr stimulus blackout during which data were recorded and solutions changed. Water was continuously available during the 19-hr intersession period via the drinking device.

Water Baseline Phase. During these 3-hr sessions, a baseline of water intake was measured. A limited number of food pellets was available at the beginning of the 19-hr intersession period, each contingent upon a lever press response (fixed-ratio schedule or FR 1). The number of 1-g pellets was 50 for M-B; 45 for M-N; 50 for M-W; 55 for M-L.

Food-Induced Drinking Phase. This phase of the experiment is referred to as Food-Induced Drinking since liquid intake was measured in the presence concurrent food. The top frame of Figure 1 shows the scheduling of events during this phase. Daily access to food pellets was shifted from post--session to the beginning of the second hour of the session. The number of food pellets available to each monkey was the same as during the Water Baseline Phase. Availability of food was signalled by the food stimulus light, in the presence of which each lever press was followed by the delivery of one food pellet. After the fixed total allotment of pellets was delivered, the food light was turned off. A protective contingency was programmed to prevent the accidental reinforcement of drinking by access to food pellets: Beginning with the second hour of the session, lip--contact responses delayed food availability by 5 min. Specifically, 1 hr after the beginning of each session, a 5-min clock was started; liquid

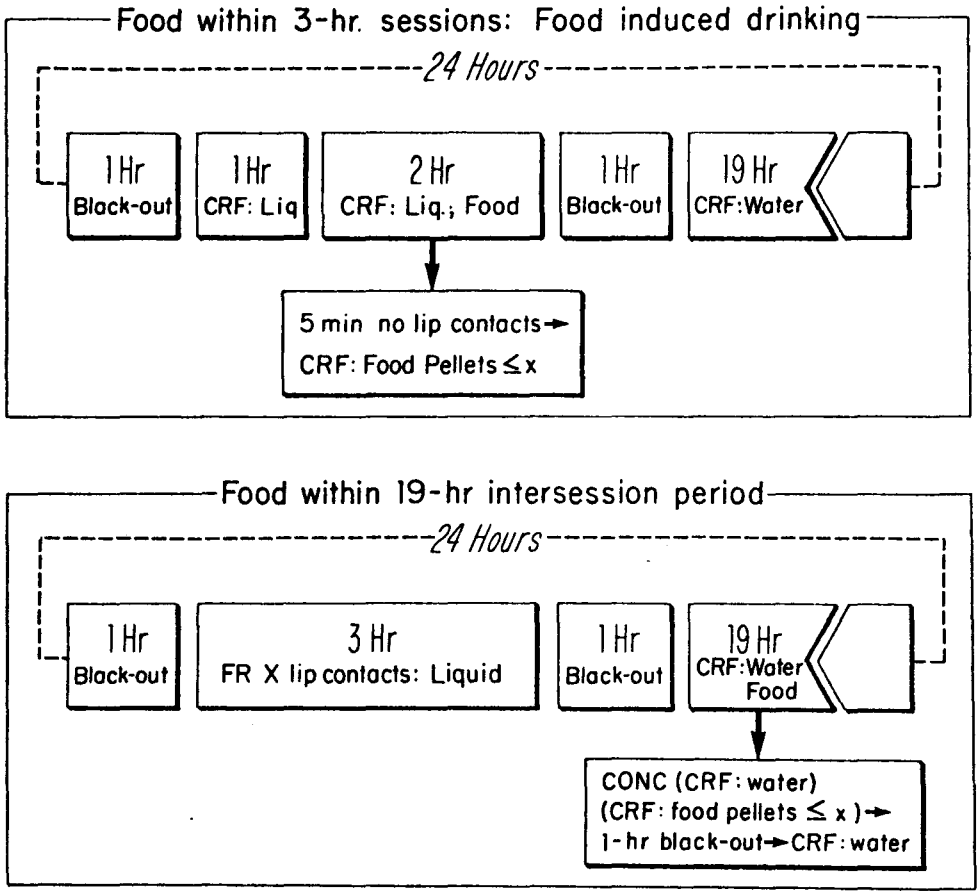

Figure 1. Scheduled activities in 24-hr sequence. CRF:LIQ indicates that each liquid response is reinforced. CONC(crf:liq) (n, FR 1:food) indicates that each liquid response is reinforced and each food response is reinforced until n food pellets are obtained.

responses reset the clock. When the clock finished timing, i.e., when 5 min had elapsed with no liquid responses occurring, the food stimulus light was illuminated.

Water was available on a fixed-ratio 1 schedule, i.e., each lip--contact response produced 0.5 ml of water during the 3-hr session or until the entire volume of 500 ml had been drunk. The 500 ml limit was a precaution to prevent acute over-hydration during the Food-Induced Drinking Phase. The monkeys were tested daily under these conditions until drinking of water was stable for five consecutive sessions. Behavior was judged stable when visual inspection of the data revealed no systematic trends in either quantity or pattern of responding over five consecutive sessions. After water drinking had stabilized, ethanol was substituted in increasing concentrations (0.5, 1, 2, 4, 5.6, and 8% w/v). Each concentration was presented until five stable sessions were obtained.

Ethanol Drinking in the Absence of Concurrent Food. After drinking of 8% ethanol was stable, session food availability was discontinued, and food pellets were again made available at the beginning of the 19-hr intersession period. The lower frame of Figure 1 shows the scheduling of events. This phase was concluded by obtaining five stable 3-hr sessions of responding for 8% ethanol in the absence of within session access to food pellets. In all subsequent experiments, food was available at the beginning of the intersession period.

Responses and Liquid Deliveries at 8% Ethanol as a Function of Fixed--Ratio Size. Eight percent ethanol solutions were available during daily 3-hr sessions. Responses on the food lever were recorded but produced no scheduled consequence. The fixed-ratio schedule (FR) was imposed by increasing the number of discrete lip-contact responses that were required

per liquid delivery. At least five sessions of stable drinking behavior were obtained at each fixed-ratio value. Fixed-ratio values were increased in the order FR 1, 2, 4, 8, 16; for one monkey, M-B, the additional value of FR 32 was used.

Responses under a Fixed-Ratio Schedule as a Function of Liquid Delivered: Water (0%) or 8% Ethanol. Under the same experimental conditions as described in the preceding experiment, five stable sessions of responding for 8% ethanol were obtained at FR 16 for three of the monkeys and at FR 32 for monkey M-B. Next, water (0%) was substituted for the 8% ethanol. After five stable sessions had been obtained with water, 8% ethanol was reintroduced and five stable sessions were obtained. For each monkey, fixed-ratio values were held constant throughout the experiment.

RESULTS

Food-Induced Drinking of Water. When only water was available during daily 3-hr sessions, the mean volume of water consumed was 107 ml (n = 20; 5 sessions x 4 monkeys). Figure 2 shows that the delivery of a fixed number of 1-g food pellets markedly increased water drinking by all four rhesus monkeys; most of the drinking occurred during the 30 min following access to food. The mean volume consumed when both food and water were present during the daily sessions was 309 ml (n = 20). Typically, the monkeys received all of the available food pellets within 5 min of onset of the food stimulus light. After all available food pellets were obtained, drinking immediately occurred at a high rate. Volume of water consumed was directly proportional to the number of liquid deliveries, with the exception that after receiving food, monkey M-L continued to operate the liquid delivery mechanism when the reservoir was empty. To achieve the stable rates of food-induced drinking shown in Figure 2 required 17

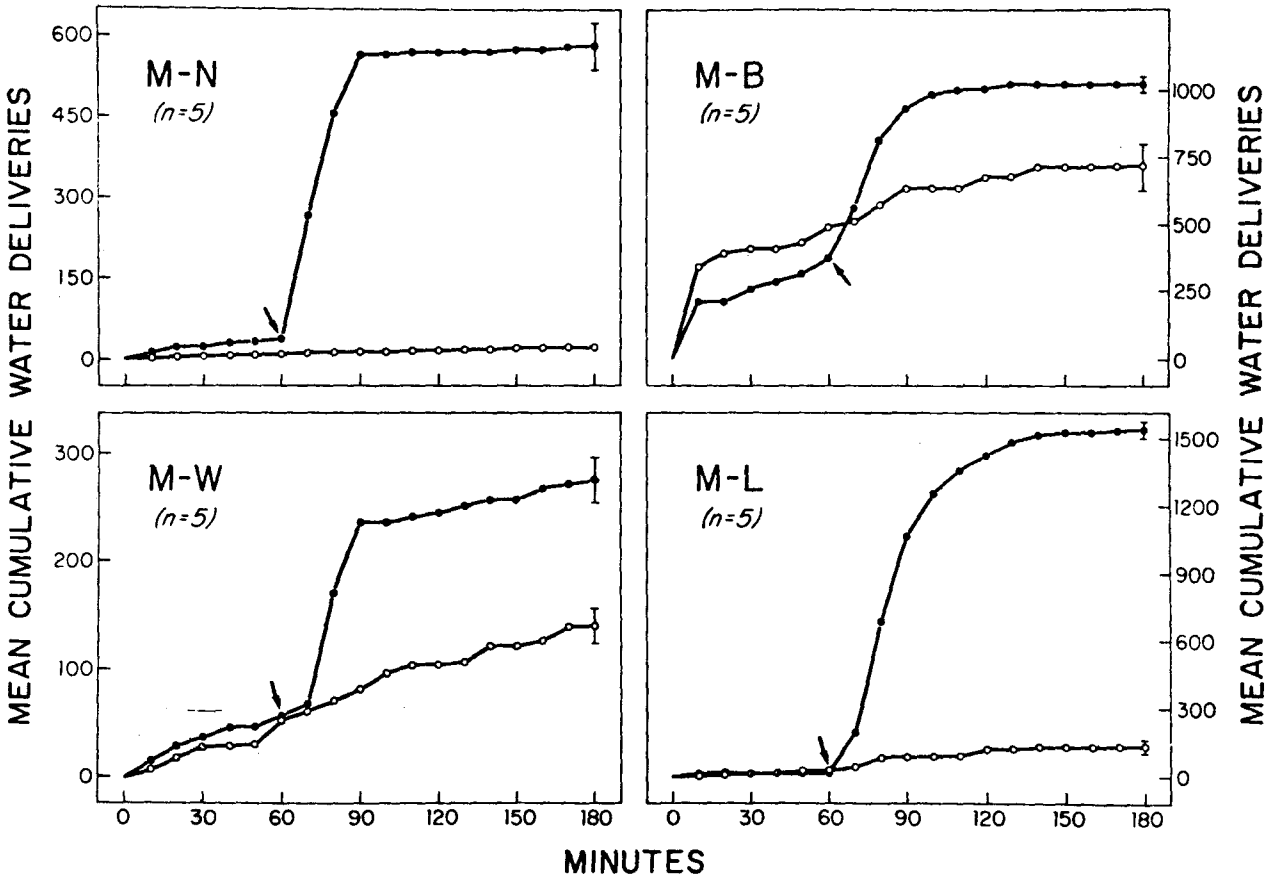

Figure 2. Cumulative means (n = 5) of liquid deliveries at 10-min intervals during 3-hr sessions. Filled circles indicate water deliveries during sessions when food pellets were available. Unfilled circles indicate water deliveries during sessions when food was not concurrently available. Brackets show the standard error of the mean. Absence of brackets indicate that the standard error value fell within the area occupied by the plotted point. Arrows mark the first interval during which food pellets were available.

sessions for M-B, 12 sessions for M-N, 9 sessions for M-W, and 21 sessions for M-L.

Food-Induced Drinking of Ethanol. Figure 3 shows that for each monkey the number of liquid deliveries was an inverted U-shaped function of ethanol concentration. The concentration at which the greatest number of liquid deliveries occurred varied with different monkeys but was less than 5.6%. For M-B and M-L, the peak of the function was higher than would have been predicted from the total volumes consumed. This apparent anomaly resulted from the monkeys' continuing to operate the liquid delivery system after the reservoir had been emptied. Functionally, the reservoirs were empty when 485-490 ml had been consumed. At 0.5 to 2% each of the monkeys occasionally drank all available liquid in his reservoir. Thus, the relatively constant volumes consumed at these concentrations were partially due to the 500 ml limit. Though the volume consumed decreased at 5.6% and further decreased at 8%, the g/kg body weight of ethanol consumed generally increased as the ethanol concentration increased (Table 1). When food was present during sessions, most ethanol deliveries occurred immediately following food presentation.

Ethanol Drinking in the Absence of Concurrent Food. Figure 3 shows that when food availability was shifted from within the 3-hr session to the beginning of the 19-hr intersession period, deliveries of 8% ethanol decreased for M-L and were unchanged for M-N, M-B and M-W. When food was no longer presented during sessions, the temporal pattern of ethanol deliveries changed markedly. Most drinking occurred at the beginning of the session, whereas when food had been present the highest rate of drinking was in the middle third of the session.

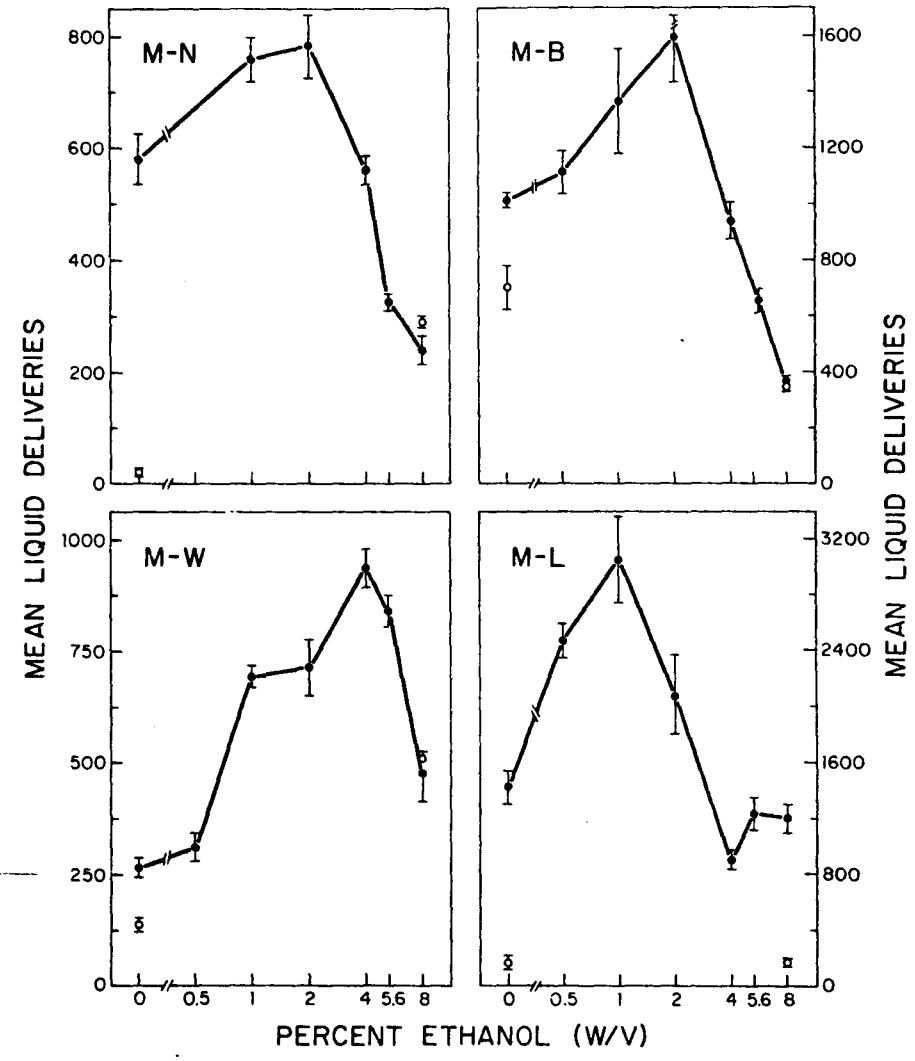

Figure 3. Mean liquid deliveries (n = 5) per 3-hr sessions as a function of ethanol concentration. Filled circles indicate that food was available during the sessions (food-induced drinking procedure). Open circles indicate that food was available at the beginning of the inter-session period and only liquid was available during the sessions. Brackets show the standard error of the mean. Note the different scales of the ordinates.

Table 1

G of ethanol consumed per kg of body weight (means of five sessions ± S.E.) during 3-hr sessions

	Ethanol Concentration (w/v)						
Monkey	0.5%	1%	2%	4%	5.6%	8%	8%*
M-B	0.37(.00)	0.72(.00)	1.19(.05)	2.36(.10)	2.35(.15)	2.00(.12)	1.77(.14)
M-N	--------	0.78(.04)	1.57(.05)	2.04(.07)	1.50(.04)	1.50(.17)	1.68(.08)
M-W	0.15(.01)	0.66(.04)	1.31(.03)	2.77(.14)	3.27(.15)	3.31(.24)	2.69(.11)
M-L	0.41(.00)	0.81(.01)	1.62(.02)	1.54(.19)	4.23(.38)	5.76(.18)	0.99(.04)
Group Means	0.31	0.74	1.42	2.18	2.84	3.14	1.78

*Food was not available during sessions.

The number of experimental sessions and thus number of days from 0.5 to 8% ethanol was 142 days for M-B; 116 days for M-N; 43 days for M-W; 93 days for M-L. During this time the monkeys' body weights decreased a mean of 0.5 kg. Specifically, body weight decreased from 6.6 to 6.0 kg, M-B; from 7.2 to 6.7 kg, M-N; from 6.4 to 6.3 kg, M-W; and from 6.0 to 5.3 kg, M-L. Thus, during this acquisition phase the monkeys were in negative caloric balance.

Responses and Liquid Deliveries at 8% Ethanol as a Function of Fixed--Ratio Size. Figure 4 shows that for each monkey the number of lip contact responses was directly related to the FR requirement, whereas the number of liquid deliveries remained relatively constant. The mean volumes consumed at FR 1 and FR 16 were 139 ml and 138 ml, respectively (n = 20; 4 monkeys x 5 sessions). Thus, mean volume consumed paralleled liquid deliveries. Mean grams of ethanol consumed per kilogram of body weight during the 3-hr sessions were 1.90 at FR 1 and 1.96 at FR 16. Fixed--ratio responding, when it occurred, was similar to that maintained by more commonly studied reinforcers such as food and water. Response rate was high and constant, and occasional pauses occurred after liquid delivery (Fig. 6 presents cumulative records that show FR performance).

Responses Under a Fixed-Ratio Schedule as a Function of Liquid Delivered: Water (0%) or 8% Ethanol. Figure 5 shows that mean liquid deliveries decreased when water was substituted for 8% ethanol. When 8% ethanol was reinstated, drinking values returned to their former levels. For example, mean volume consumed decreased from 135 ml to 17 ml when water replaced 8% ethanol, and volume consumed increased to 116 ml when 8% ethanol replaced water (n = 20; 4 monkeys x 5 sessions). For monkey M-B, water was substituted for 8% ethanol at FR 16. However, his responses and liquid intake increased in the presence of water; thus, the FR value was increased

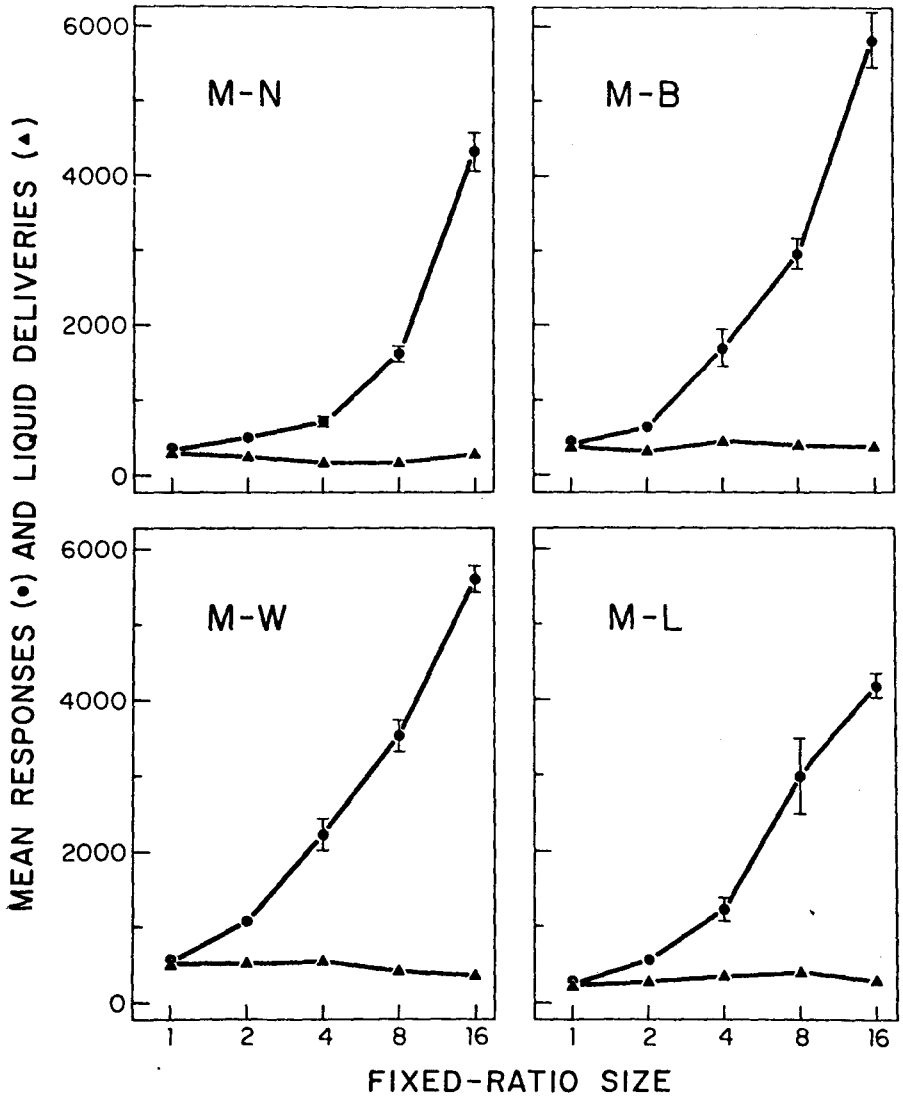

Figure 4. Mean responses and 8% ethanol deliveries (n = 5) as a function of fixed-ratio size. Brackets show the standard error of the mean. Absence of brackets indicates that standard error values fell within an area occupied by the plotted point.

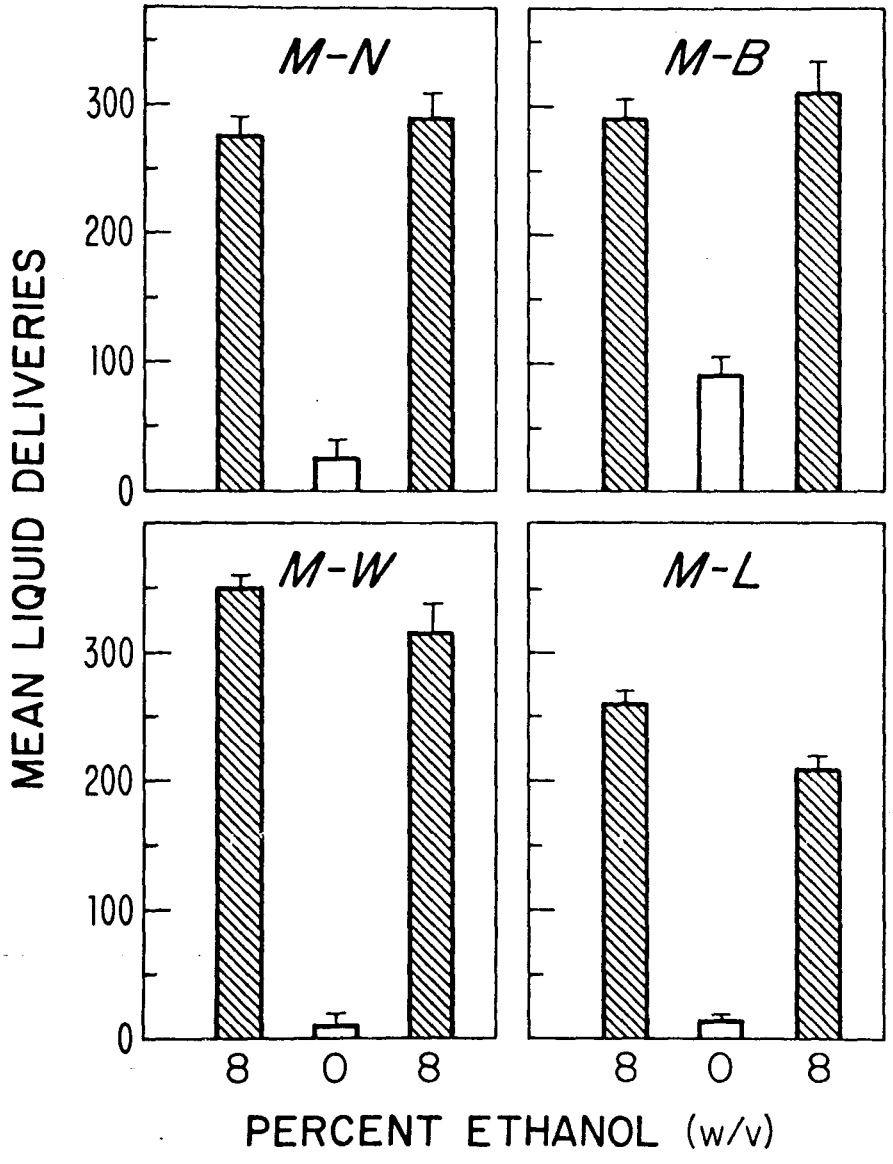

Figure 5. Mean liquid deliveries (n = 5) per 3-hr session when either 8% ethanol (striped bars) or water (open bars) was present. Brackets show the standard error of the mean. Liquid deliveries for monkey M-B were contingent on FR 32 whereas liquid deliveries for the other 3 monkeys were contingent on FR 16.

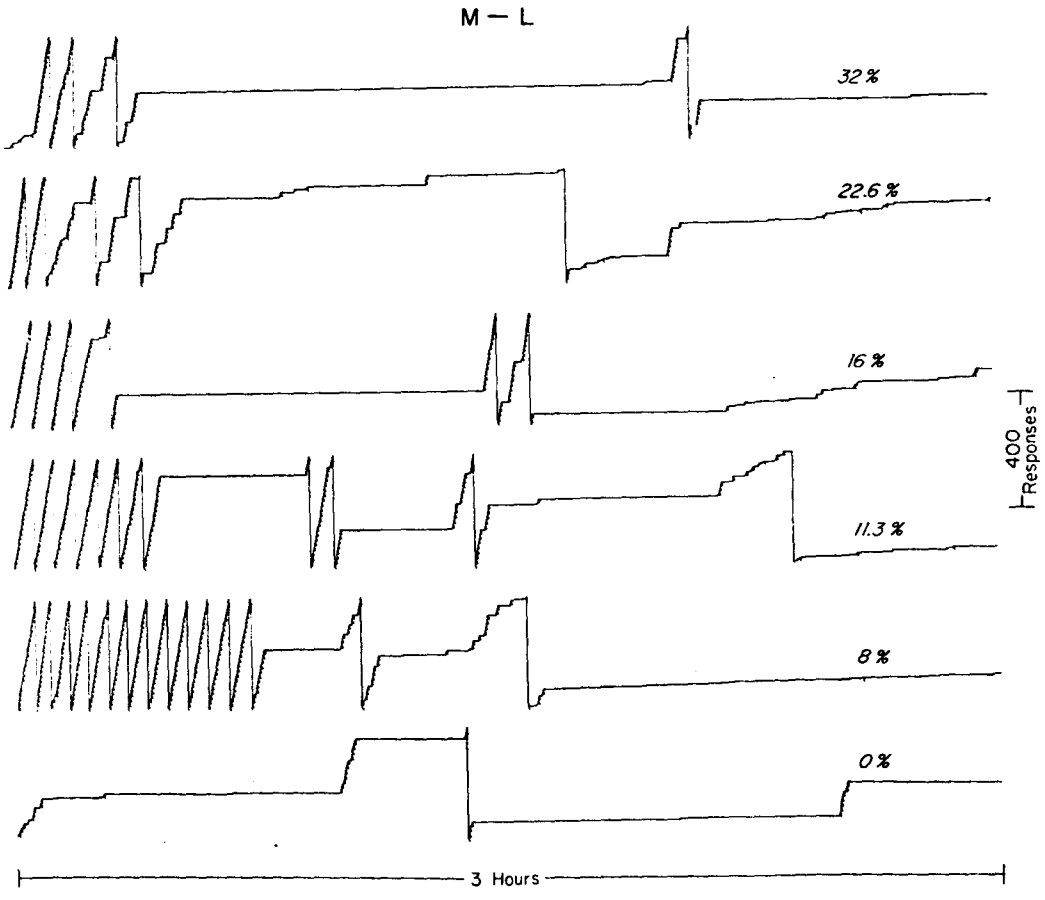

Figure 6. Cumulative records of monkey M-L were chosen on the basis of being closest to the mean data that were obtained during the last five sessions at each concentration. Responses are indicated on the ordinate and time is indicated on the abscissa. The diagonal hatch marks indicate liquid deliveries.

to FR 32. As shown in Figure 5, at FR 32 water maintained substantially less responding than did 8% ethanol. Cumulative response records (Fig. 6) show that the temporal pattern of drinking was different for ethanol than for water: Ethanol drinking occurred in a negatively acclerated pattern over the 3-hr session. Following the initial burst of responding at the beginning of a session was a period of no responding. Frequently another shorter burst of ethanol responding occurred before the end of a session. Occasionally, toward the end of a session, responses were emitted at a slow, irregular rate. This change may reflect the effects of the ethanol consumed earlier in the session.

DISCUSSION

Eight percent ethanol maintained fixed-ratio performance that was distinct in both quantity and temporal pattern from that of the control vehicle, water. Fixed-ratio performance was similar to that of more commonly studied reinforcers, such as food, in that responding occurred at high and constant rates with occasional pauses following ethanol delivery. The negatively acclerated temporal pattern of ethanol deliveries was similar to that found when ethanol served as a reinforcer for rats via the oral route (Meisch & Thompson, 1974; Meisch & Beardsley, 1975) and monkeys via parental and oral routes (Deneau et al., 1969; Woods et al., 1971; Winger & Woods, 1973; Yanagita & Takahashi, 1973; Altshuler et al., 1975; Meisch et al., 1975; Carney et al., 1976; Henningfield & Meisch, 1976a). The pattern of drinking was similar to that obtained when schedule-induced polydipsia was used to initiate ethanol drinking (Meisch et al., 1975). Thus, ethanol served as a positive reinforcer for these rhesus monkeys.

In the present study, ethanol drinking was initiated by a food reinforcement schedule that differed from the schedule we used in our pilot study (Meisch et al., 1975). Here, each lever press produced a food pellet, while in the earlier study food pellets were intermittently available. The difference in schedules is important, since schedule-induced polydipsia (SIP) occurs under conditions of intermittent pellet delivery (Falk, 1971). Thus, in this study, the term "food-induced drinking" (FID) is a more appropriate description of the procedure than schedule-induced polydipsia. Comparisons of intake at identical concentrations show that the two procedures, FID and SIP, engendered consumption of similar quantities of ethanol (compare present results with Meisch et al., 1975). Regardless of the procedure used to induce drinking, ethanol intake persisted when food pellets were not presented within the sessions. These results are also similar to those obtained with rats: Different procedures may be used to establish ethanol as a reinforcer (Meisch, 1975).

Two alleged difficulties in the establishment of ethanol as a reinforcer are its aversive taste and the delay in the effects because of the time required for absorption (Mello & Mendelson, 1971b; Mello, 1973). The aversive taste of ethanol is indicated by studies demonstrating that rhesus monkeys prefer water to low concentrations of ethanol (Myers, Stoltzman & Martin, 1972), and that several months of exposure does not result in increased preference for ethanol (Mello & Mendelson, 1971b). That delay in onset of effects is probably another factor as indicated by the earlier noted findings that intravenously administered ethanol usually serves as a reinforcer without special procedures to initiate its self-administration. Difficulties of aversive taste and delay of effects

were circumvented by the present procedure. High water consumption reliably occurred after monkeys ate a fixed amount of food; then in place of water, ethanol in increasing concentrations was presented, and considerable time was allowed for adaptation at each concentration. The use of food--deprived monkeys helped to minimize the delay in absorption, and the taste of ethanol was paired daily with the effects that occur following its absorption.

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