

# Alcohol Self-Administration in Monkeys (*Macaca Radiata*): The Effects of Prior Alcohol Exposure<sup>1</sup>

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DENOBLE, V. J. AND H. BEGLEITER. *Alcohol self-administration in monkeys (Macaca Radiata): the effects of prior alcohol exposure*. PHARMAC. BIOCHEM. BEHAV. 8(4) 391–397, 1978. — Responding by 4 monkeys was maintained under a fixed ratio 10 (FR 10) schedule for either food, intravenous sucrose or alcohol. The 20 hr sessions were divided so that food was available during hours 1, 6, 11, 16 and alcohol or sucrose during hours 2–5, 7–10, 12–15, and 17–20. All animals failed to maintain responding for isocaloric sucrose but continued to respond for food during those sessions. Responding under alcohol conditions was positively accelerated in 2 animals that were not previously exposed to alcohol, whereas prior exposure to alcohol produced maximal response rates during the first alcohol test session. The effects of alcohol in all monkeys were to suppress responding maintained by food and this suppression could not be produced with programmed infusions of isocaloric sucrose.

Self-administration    Alcohol    Response suppression    Prior exposure    *Macaca Radiata*

WHILE alcoholism has been shown to be a form of addiction as defined by traditional pharmacological criteria [20], the critical factors that determine alcohol abuse and the relationship between alcohol consumption and diet remain a matter of conjecture. A number of investigators have attempted to devise techniques for inducing preference for alcohol in animals but these have been hampered primarily because of the aversive taste properties of alcohol. Recently, several investigators have succeeded in producing physical dependence upon alcohol in animals using the intravenous route of administration. Deneau *et al.* [4] were the first to demonstrate that monkeys (*Macaca Mulatta*) prepared with an intravenous catheter would self-administer alcohol. Four out of 5 monkeys tested initiated responding for a 200 mg/kg infusion of alcohol via the catheter on a fixed ratio one schedule. The authors reported that the maximum intake for those monkeys that initiated and maintained alcohol self-administration was 8.6 g/kg/day for 7 days. During the periods of self-administration the food intake was decreased and all animals showed substantial weight losses despite ad lib food availability. These authors demonstrated that intravenous alcohol served as a reinforcer and showed that nonphysically dependent animals spontaneously self-infuse alcohol. It is noteworthy that no mention of alcohol's caloric value was made with reference to alcohol's reinforcing properties or in relation to the weight loss observed in all self-injecting animals. Since all alcohols have a high caloric value, the self administration of

alcohol may involve different mechanisms than those related to other psychoactive agents.

In the investigation by Deneau *et al.* [4], it was shown that the monkeys discontinued lever responding following episodes of severe, sustained intoxication. Woods *et al.* [23] confirmed these observations and reported that not all animals immediately initiated intravenous alcohol self-administration, however, following a history of intravenous cocaine or methohexital self-administration these animals initiated and maintained responding for alcohol. Similarly, naive monkeys do not readily initiate intragastric alcohol self-administration. Subsequent programmed infusions of alcohol, 1.0 or 2.0 g/kg per infusions every 3 to 6 hr for 5 to 6 weeks, is not an effective means of initiating self-administration behavior [24]. However, intravenous alcohol self-administration is a sufficient priming procedure, and administration of intragastric doses of ethanol ranging from 2.8–7.5 g/kg/day are observed following a history of intravenous infusions [24]. This would indicate that the critical factor in the initiation of alcohol self-administration is not experience with alcohol per se but experience with the self-injection technique. The pattern of alcohol reinforced responding seems to depend upon the opportunity for self-administration. Monkeys provided with unlimited access (24 hr) will self-terminate alcohol administration following 5 to 7 day periods of high intake, whereas animals maintained on a limited access cycle show few self imposed abstinence periods. It has been suggested

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that the pharmacological effects of alcohol directly alter ethanol reinforced responding and this system produces the self-administration pattern [22].

The nature of alcohol's reinforcing properties are not as easily defined as other more conventional reinforcers such as food or water. However, there are 3 distinguishing characteristics of alcohol which may provide some clues to its reinforcing properties. First, alcohol has been reported by man to produce a euphoric feeling; second, alcohol has a high caloric value; and third, alcohol produces physical dependence. There has been a good deal of speculation regarding the relationship between alcohol's reinforcement value, and its caloric content. Previous investigation of alcohol self-administration have used saline self-administration as an indication of the operant level of infusion. An analysis of the pattern of self-administration of an isocaloric sucrose solution and alcohol would provide a basis for determining the importance of the caloric value of alcohol in establishing it as a reinforcer.

A major feature of continued alcohol abuse is a decrease in food consumption and substantial weight loss. While there have been numerous reports of deficient diets resulting from prolonged alcohol consumption in both man and animals there has yet to be a systematic investigation of alcohol self-administration and concomitant food responding in monkeys. Similarly, whether decreases in food and intake are a direct result of the caloric value or an effect of reinforcement strength is as yet unknown. It is therefore the purpose of the present experiment to first, determine whether monkeys would increase their lever pressing behavior when it results in intravenous alcohol infusions; second, to examine the relationship between alcohol self-administration and concurrent response contingent food consumption; third, to determine whether the caloric value of alcohol contributes to its reinforcing properties; and fourth, to assess the effects of prior exposure to alcohol on alcohol reinforced behavior.

#### METHOD

##### *Animals*

Two female (MT15, ML3) and 2 male (MK7, MV29) Bonnett monkeys (*Macaca Radiata*) weighing 4.4, 4.4, 2.3 and 4.3 kg respectively were used. The animals were anesthetized with acepromazine melete (3.0 mg/kg/IM) and sodium pentobarbital (20.0 mg/kg/IV) and were prepared under sterile conditions with indwelling venous catheters made of siliconized rubber (0.025 × 0.047 ID × OD in.). The catheter was anchored in the external jugular vein and passed subcutaneously until it exited through the skin of the animals back. The monkeys wore a close fitting canvas vest which protected the exposed portion of the catheter. To maintain patency the catheter was flushed with a heparin (0.25 ml, 1000 units per ml) and saline (3.0 ml) solution daily. Before behavioral testing the animals were allowed a 3 week recovery period, during which time they were gradually reduced to 90% of their free feeding weights. One male and one female monkey (MT15 and MK7) were exposed to ethanol 4 months prior to the beginning of this study. These two animals received intubations without anesthesia, of a 30% (w/v) ethanol and water solution (5.0 g/kg) every other day for 20 days. The remaining 2 animals were intubated with isocaloric sucrose.

##### *Apparatus*

Each animal was adapted to a BRS/LVE Rhesus chair

(Model pc001) which was located in a BRS/LVE sound attenuated, ventilated cubicle. Stimulus lights, a pellet dispenser, and a response lever were mounted on the back wall of the cubicle. A food reinforcement tray was positioned on the restraint chair and connected to the feeder by rubber tubing. Outside the experimental chamber was a Cole-Parmer variable speed master flex pump which was connected to the intravenous catheter for infusions. Masking noise was present throughout the 20 hr test sessions. Standard electromechanical programming devices controlled the experimental contingencies and data were collected with print-out counters and cumulative recorders.

##### *Procedure*

Three weeks following surgery the animals were adapted to the restraint apparatus and shaped to lever press for a 190 mg Noyes banana flavored pellet. Each animal received 100 reinforcements on a fixed ratio 1 (FR 1) schedule for each of 3 days. After FR 1 training the reinforcement contingency was gradually changed to a FR 10 with a 1 min time out (TO 1 min) following each reinforcement. During the TO all lights were extinguished and responses had no scheduled consequence. Following 7 daily 2 hr test sessions on the FR 10 TO 1 min schedule the animals were tested during a 20 hr test session which began at 1300 hr daily. The first hour of the session was signalled by a white light and responding reinforced with banana flavored pellets. During the next 4 hr the white light was extinguished and a red stimulus light was illuminated. Responding during this block of 4 hr resulted in either a 0.1 g/kg infusion of a 15% w/v solution of ethanol in sterile distilled water or a 0.1 g/kg infusion of isocaloric sucrose, both delivered at a rate of 0.05 ml/sec. All infusions began during the TO when the lights were extinguished. The sequence of 1 hr of food availability followed by 4 hr of alcohol or equicaloric sucrose infusions was repeated 4 times totaling a 20 hr session. Following 20 hr of testing the animals were removed from the restraint apparatus, weighed and returned to their home cage where they received food supplements to maintain their body weight at 90%. During the 10 baseline sessions, responding in the presence of the red stimulus resulted in an isocaloric sucrose infusion. Following the 10 baseline sessions, alcohol (15% w/v solution) was substituted in the infusion pump for sucrose. Following 13 consecutive days of response contingent alcohol infusions, sucrose was substituted for alcohol. Then, a sequence of 5 days in which sucrose was available followed by 5 alcohol days was repeated until the catheters became inoperative or until 58 days. The total number of food reinforcements, alcohol and sucrose infusions were recorded each day.

To determine the effects of the caloric value of alcohol on food directed behavior a sucrose probe was administered 2 days prior to each second alcohol test block. This consisted of sucrose being infused periodically through the 20 hr test session with a total volume equaling the equivalent of a 6.5 g/kg dose of alcohol. This procedure was repeated every isocaloric sucrose test block 2 days prior to alcohol substitution.

#### RESULTS

Figure 1 presents the number of alcohol or sucrose infusions and food reinforcements taken daily across conditions for the two animals previously exposed to

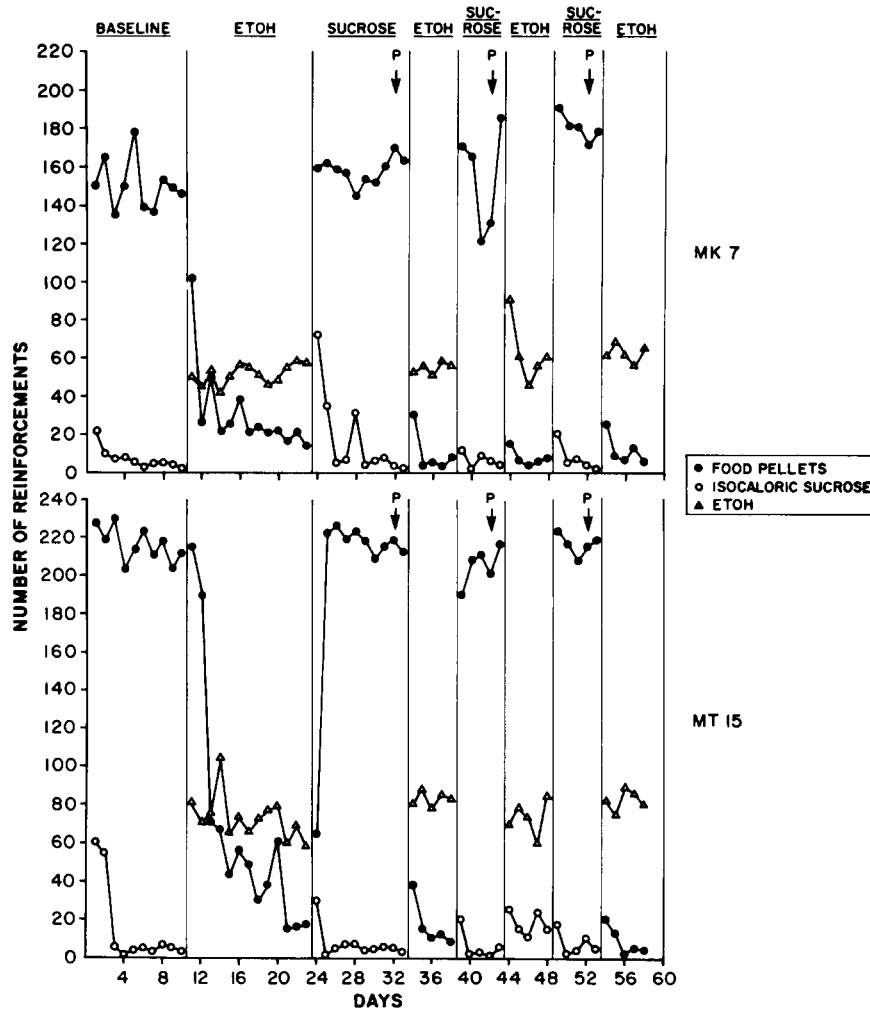


FIG. 1. The total number of reinforcements, both food and alcohol, for each session for the 2 male animals previously exposed to alcohol (MT15, MK7). Filled circles show the number of food reinforcers, open circles show the number of sucrose infusions and the triangles show the number of alcohol infusions. The symbols CD = catheter dislodged and P = a probe day during which a volume of isocaloric sucrose equivalent to 6.5 g/kg of alcohol, was infused into the animal.

alcohol (MK7, MT15). While the number of food reinforcements during each baseline session is different, both animals' data shows a relatively stable reinforcement rate. During the baseline session responding in the presence of the red stimulus light resulted in an infusion of isocaloric sucrose. It can be seen that following an initial elevation in sucrose infusions (2 days) the self-administration behavior decreased and sucrose infusions did not exceed seven in any of the remaining baseline sessions. When alcohol was substituted for sucrose the number of infusions increased in these two animals to a mean 69.1 per session. The number of food pellets responded for dropped when alcohol was available from a mean of 176.8 during the baseline to 28.1 reinforcements per session. When sucrose was substituted for ethanol in the infusion pump the number of food reinforcements increased to baseline levels and the number of sucrose infusions decreased. This pattern of baseline food responding during sucrose availability and food response suppression during alcohol availability was characteristic for both these animals across the seven solution

substitutions. For both monkeys previously exposed to alcohol the sucrose probe failed to produce any observable changes in the number of food reinforcements.

The 2 graphs in Fig. 2 present the number of alcohol or sucrose infusions and the number of food reinforcements per session for the 2 animals that had not been previously exposed to alcohol (ML3, MV29). During the baseline session the number of food pellets each day remained stable for both monkeys and the number of sucrose infusions decreased to less than 6 per session after the fourth baseline day. The major difference between the exposed and non-exposed groups can be seen in the first block of days during which alcohol was substituted for sucrose. With the exception of the first two days of the block there was no significant difference in the number of alcohol infusions between the groups ( $p < 0.01$  students  $t$ -test). On the first 2 days of the first alcohol self-injection block the mean number of infusions for the exposed group was 61.7 whereas the mean number of infusions for the unexposed group was 19.5. For both groups the sucrose probes did not

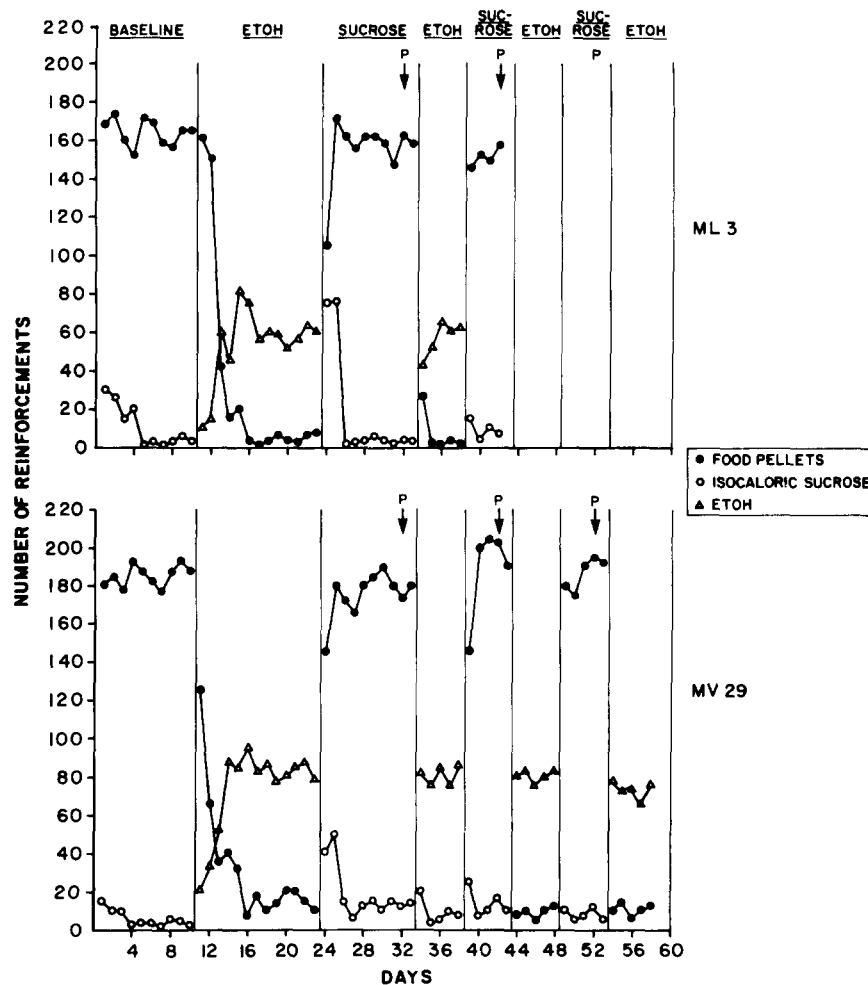


FIG. 2. The total number of reinforcers both food and alcohol for each session for the 2 animals unexposed to alcohol (ML3, MV29). The meanings of the symbols are the same as that described in Fig. 1.

produce a suppression in the number of food reinforcements. Other than the difference in the first 2 days of alcohol infusions the pattern of self-administration and food responding was similar for all 4 animals across days. When sucrose was substituted for alcohol the number of infusions was elevated somewhat on the first day and then decreased to baseline levels for the remaining days. The elevation in sucrose infusions during the first day of each block successively decreased across blocks. There was no specific pattern of responding for either male or female animals.

The top graph in Fig. 3 shows that the number of food reinforcements, for each of the 4 hr it was available, was stable across baseline and sucrose days, however, when response contingent alcohol was infused the number of food reinforcements responded for decreased. Typically, the first hr of each session either alcohol or sucrose, resulted in the largest number of food reinforcements. During hours 6, 11 and 16 the number of food reinforcements was decreased to near zero levels. The bottom portion of Fig. 3 shows the number of infusions (alcohol or sucrose) during the 16 hr each session infusions were available. The largest number of sucrose infusions were taken during the first 4 hr of any sucrose session.

Thereafter, in all sessions in which sucrose was available, the number of infusions progressively decreased. The opposite result can be seen when response contingent alcohol is available. All animals increase the number of infusions and each 4 hr rate of infusion remains stable throughout each session and across each session.

Figure 4 shows the mean number of responses occurring during the time out. During the baseline session the mean number of TO responses for the hours when food was available was  $17.0 (\pm) 4.7$  SD. The mean number of TO responses during the baseline sessions when sucrose was available was  $12.8 (\pm) 11.22$  SD. The figure shows that during all sessions when sucrose was available the TO responding was lower than that of the TO response following a food reinforcer. The opposite trend can be seen when alcohol was available. The mean number of TO responses following infusions of alcohol for all sessions was  $72.6 \pm 28.3$  SD and during those sessions the mean number of TO responses following each food reinforcement was  $4.6 \pm 2.7$  SD. The sucrose probes had no observable effect on TO responses occurring after food or sucrose infusions.

#### DISCUSSION

The principal finding was that intravenous alcohol

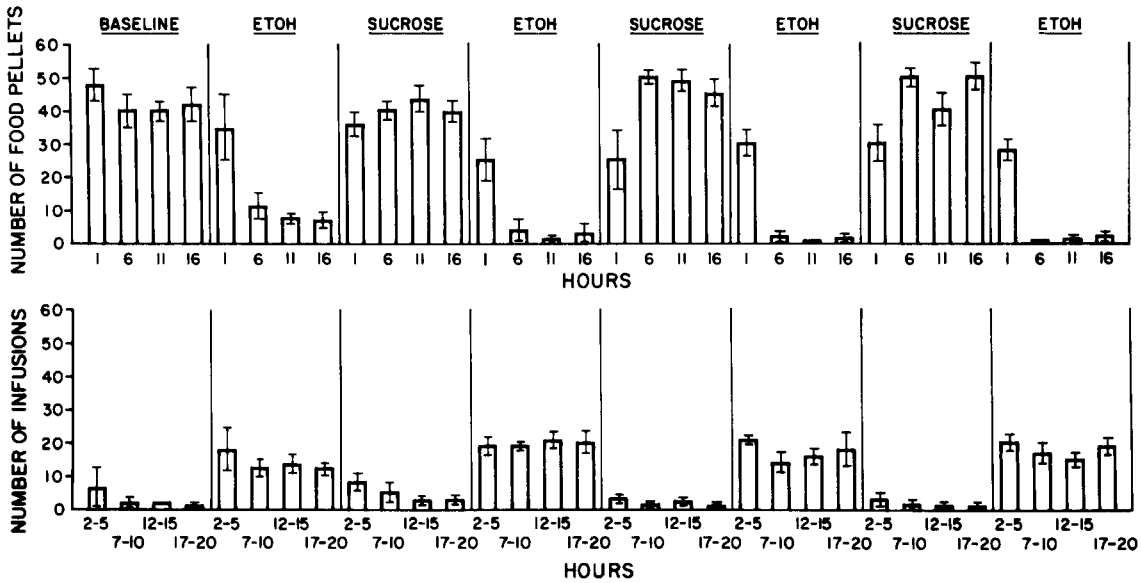


FIG. 3. The top graph in Fig. 3 shows the mean number of food reinforcements during baseline, ethanol and sucrose sessions as a function of the hours of food availability in each session. The bottom graph in Fig. 3 shows the mean number of infusions during baseline, alcohol and sucrose sessions combined with blocks of four hours within each session. The vertical lines represent the SD. The N for the SD varies depending upon the number of days in each condition.

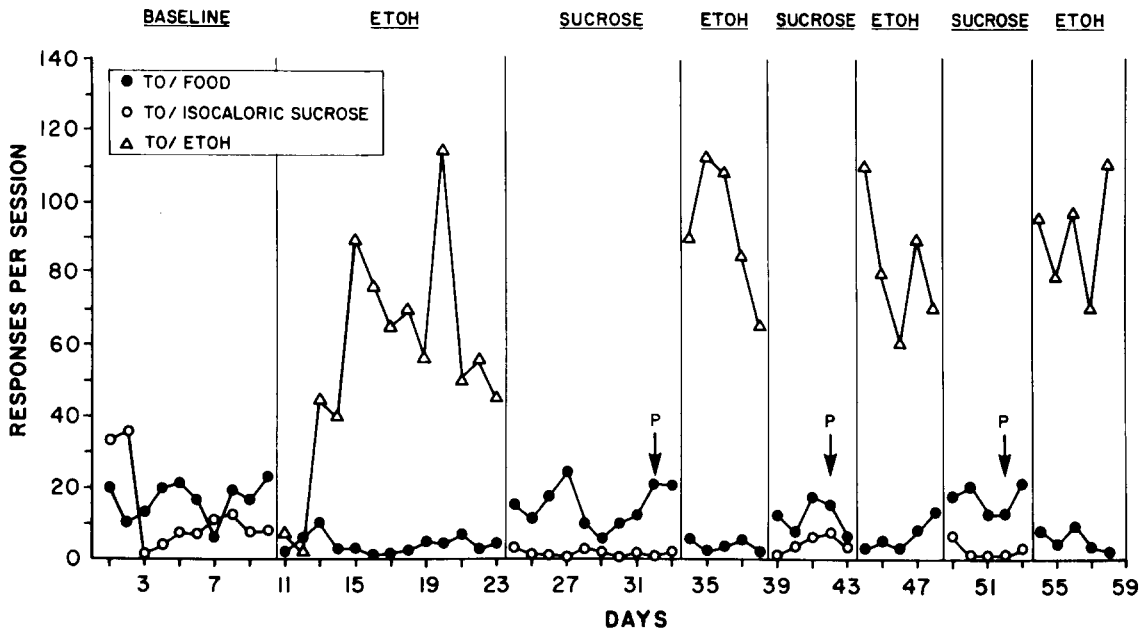


FIG. 4. The mean number of responses occurring during the TO following each food reinforcement (filled circles), ethanol (triangles) and sucrose infusions (open circles) combined across animals. The symbol P = a sucrose probe.

maintained operant responding and isocaloric sucrose did not. The data also show that there was no difference in total daily volume of alcohol infused between exposed and non-exposed animals. Furthermore, the behavior maintained by food reinforcement was suppressed during alcohol sessions and unchanged during isocaloric sucrose sessions. The present results confirm and extend previous reports showing that intravenous alcohol infusions increase the frequency of responding when that responding results in an infusion of alcohol [4, 22, 23]. The present study compared the number of alcohol infusions to the number of isocaloric sucrose infusions and the data clearly show

that isocaloric sucrose did not serve as a reinforcer, suggesting that the reinforcing characteristics of alcohol are not caloric in nature.

It has been suggested that prior exposure to alcohol may result in an increased sensitivity to the drug which may lead to the development of alcohol addiction [11]. While the data show no significant difference between the exposed animals and the non-exposed animals in relation to the total daily intake, there was a significant difference between the total volume self-injected during the first 2 alcohol test days. This is of particular interest because it has been shown that exposure to alcohol produces persistent long

term central nervous system changes [3, 5, 6, 7, 8, 16], and it has been suggested that the differential effects to alcohol in previously dependent individuals may stimulate the alcoholic to drink. More recently [3,16] it has been shown that exaddicted rats given a challenge dose of alcohol two weeks post withdrawal, display brain hyperexcitability whereas the same challenge dose produces a depression of brain activity in controls. The present data combined with previous studies from our laboratory suggest that long term changes in the central nervous system's response to alcohol, may be of importance in the susceptibility of the exaddict to readdiction rather than determining the absolute volume consumed. The prior exposure of our animals to alcohol occurred 4 months before the beginning of this experiment and was administered by nasogastric intubation. The likelihood of a reinforcement association between the intubation and self-administration is tenuous. It could also be argued that the rate of ethanol metabolism was different in exposed vs nonexposed animals and this difference resulted in the initial differential reinforcer effects. Recent studies in both man [12] and animal [15] have shown that there is no difference in the rate of alcohol metabolism between the alcoholic and the non-alcoholics when both groups have abstained for a minimum of 3 weeks. Therefore, it seems reasonable that the difference in the acquisition of lever pressing reinforced by intravenous alcohol infusions reflects addiction susceptibility and indications from other studies suggest that this increased susceptibility may be correlated with central nervous system changes during initial alcohol exposures.

It has been suggested that stable alcohol infusion rates result from experience with the self-injection apparatus [11] or progressive increases in dosage [22]. Our data are somewhat divergent in that all animals initiated and maintained alcohol self-injection (0.1 g/kg/injection) at daily volumes which were grossly intoxicating ( $x = 6.91$  g/kg SD 1.06) without prior experience with the self-injection apparatus and at an infusion volume which has been shown to be minimally effective in producing stable self-injection behavior. One possible explanation of the different results is that the manipulanda on which the animal produced response contingent alcohol infusion was the same that produced food reinforcement under different stimulus conditions, or the different acquisition results between studies may reflect species differences.

In all animals response contingent alcohol infusions suppressed food responding. This suppression cannot be attributed to the caloric value of alcohol because on sucrose probe days the number of food reinforcements were at baseline levels. This indicates that the suppression in food directed behavior involved more complex mechanisms than that of caloric equivalence. It has been long known that chronic alcohol consumption is accompanied by brain degeneration [18,19]. Similarly, it has been demonstrated that the neurophysiological activity in the lateral hypothalamus changes following intravenous alcohol infusions [21]. It would seem then that changes in food directed behavior may result from alcohol's direct effect on central mechanism involved with the regulation of eating and drinking, specifically, an alteration in the hypothalamic system mediating reward. However, there is the possibility that the suppressed food consumption may be a secondary effect of intoxication.

Since red stimulus light signalled the availability of

infusions, both alcohol and sucrose and there was no external stimulus particular to each the discrimination between alcohol and sucrose appears to be based upon interoceptive stimulation. In the present study the interoceptive discrimination between alcohol and sucrose led to differential rates of infusion. Recent studies [1, 9, 17] indicate that most drug discrimination tests are concerned with the distinctiveness rather than the strength of the pharmacological effects. The present investigation suggests that part of the distinguishing characteristics of a drug may arise from the potential reinforcing actions.

Both human [10,14] and animal [23] provided with the opportunity to work for alcohol alternate drinking episodes of 3 to 6 days followed by abstinence periods of 2 to 3 days and these abstinence periods are characterized by partial withdrawal symptoms. Results from animal experiment indicate that self-termination results from high levels of ethanol intake (6.0 g/kg) under unlimited access conditions. The present results show that the rate of alcohol infusion is stable between blocks of 4 hr in each session. This suggests that the rate of alcohol self-administration may depend upon the blood alcohol concentration and is consistent with the hypothesis that alcoholics may drink to maintain a stable blood alcohol concentration, one which is optimal for producing an intoxication effect. These data, considered in conjunction with previous investigations, suggest that dietary changes may result from both the alcoholic's effort to manipulate the intoxication level from alcohol's direct effect on neuronal systems involved with eating and drinking.

The differential rate of responding during the TO between food and alcohol days is due primarily to the reduction in the number of food reinforcements during alcohol sessions. With the exception of the first 2 days of baseline the number of time out responses following sucrose infusions were consistently low. The first 2 days of baseline responding during the red stimulus, resulted in sucrose infusions and the withholding of food reinforcement, a procedure which temporarily increases instrumental behavior [13].

While the responding during the time out following food or sucrose conditions did not seem to undergo any major changes, the total number of responses following the alcohol infusion was accelerated. There seems to be several possible explanations of this data. Baum [2] has shown that alcohol produces greater resistance to extinction in rats on an avoidance task. Our results would appear to confirm Baum's studies; however, it was during this time out period that alcohol was being infused. Changes in the level of responding during the time out may reflect reinforcement strength. Another alternative explanation is the accidental pairing of time out responses and the effects of alcohol. If this accidental contingency existed then the reinforcer (alcohol) exerted discrimination control over time out responses, evidenced by lack of responding during other time out conditions.

The results show that intravenously self-administered alcohol serves as a reinforcer in monkeys and the reinforcing properties of alcohol are not dependent upon its caloric value. Further, the relationship between previous exposure to alcohol and subsequent intake was not reflected in daily dose but was shown to affect the rate of acquisition of self-administration behavior.

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