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Ethanol and Discriminative Motor Control: Effects on Normal and Dependent Animals[1]

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SAMSON, H. H. AND J. L. FALK. *Ethanol and discriminative motor control: effects on normal and dependent animals.* PHARMAC. BIOCHEM. BEHAV. 2(6) 791–801, 1974. – The effects of ethanol on discriminative motor control were examined in rats using a task in which food pellets were made available if a manipulandum was held within a specified forceband for a fixed period of time. Following performance stabilization, the effects of acute doses of ethanol (1, 2, 3, and 4 g/kg) were determined. Then the animals were placed on a schedule-induced polydipsia regimen to produce chronic ethanol overdrinking. During this chronic ethanol overdrinking, daily performance on the discriminative motor task was measured. Further, the effects of additional acute doses of ethanol upon the task were determined. After various periods of ethanol overdrinking, the effects of short-term (5–10 hr) ethanol withdrawal upon the motor task were evaluated. Following 10 months of chronic ethanol overdrinking, the effects of complete ethanol withdrawal upon the motor task were examined. Prior to chronic ethanol exposure, only doses that produced blood ethanol levels above 120 mg/100 ml blood (3.5–4 g/kg) affected motor performance to any degree. Following chronic ethanol overdrinking, blood levels of over 230 mg/100 ml blood were needed to produce any performance decrements, indicating the development of marked tolerance. Complete ethanol withdrawal was found to disrupt performance for up to 72 hr, which is similar to the time course noted in the human alcoholic abstinence syndrome.

Ethanol Motor control Physical dependence Tolerance Abstinence syndrome Polydipsia

THE EFFECTS of alcohol overindulgence on motor capacities include deficits in coordination, slowed reaction times, and loss of equilibrium as well as other gross motor symptoms [12]. While small to medium doses of ethanol lengthen reaction times and impair motor performance on motor skill tasks in nondrinkers, large ethanol doses are required for similar effects in persons physically dependent upon ethanol [1,11]. It is impossible, however, using human subjects, to assess the changes in performance resulting in the nondrinker after controlled, excessive, chronic ethanol intake.

Operant behavior maintained by food reinforcement in rats [8] and dogs [14] has been examined, and ethanol produced little or no effect until large doses were administered. In other investigations in rats [5,9], maintenance of position on a moving belt was used to evaluate the effect of acute and of short-term chronic ethanol doses. With acute doses, only blood ethanol levels greater than 200 mg/100 ml significantly affected performance. After 14 days of chronic ethanol administration, the dose-effect curve moved to the right, indicating tolerance. Withdrawal resulted in a return to the acute dose-effect relation. Other motor tests have been used with rats, both with acute and chronic ethanol dosage routines [7,13], but for the most part, all tasks have required large doses which produce rather severe motor impairment in order to detect ethanol effects (i.e., gross ataxia).

Until recently, there were no animal preparations that would voluntarily self-ingest large quantities of ethanol to the point of becoming physically dependent while maintaining a positive weight balance (for a review of the problems and preparations, see Mello [10]). We [4] have developed a preparation that will voluntarily ingest large daily amounts of ethanol (13.1 g/kg). After three months of this daily ethanol drinking, these animals show severe withdrawal reactions when water is substituted for the ethanol.

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Falk [2] has described a discriminative motor task in which food is made available when the animal holds a lever within specified force limits for a given period of time. This discriminative motor task was differentially sensitive to various drugs, producing specific dose-response functions for amphetamine, chlorpromazine, pentobarbital, etc. This motor task was used to explore the effects of both acute and chronic ethanol ingestion.

METHOD

Animals

Four male, albino rats (Holtzman strain), weighing 385–405 g were used. Body weights were reduced to 80% of the freefeeding weight by limiting food intake. They were maintained at this level for the first phase of the experiment.

Force Measurement

The basic design of the force apparatus (see Fig. 1) was previously described [2,3]. The animal chamber was made of Plexiglas with stainless steel front and rear panels. On the front panel, the force manipulandum was covered (see Fig. 1, upper left insert) such that the animal's access was limited so that only a single paw could rest upon the manipulandum. On the opposite side of the front panel, a food cup and pellet delivery baffle was mounted. In the center of the front panel, almost at the top, was an audio generator (Sonalert, Mallory), which was used as an audio feedback with respect to performance on the force lever.

The force manipulandum (see Fig. 1, upper right insert) was suspended by a phosphor-bronze leaf spring (0.20 mm thick). Its movement was regulated by a stop on top, and the pressure transducer drive rod connected to the force adaptor unit (Statham, Model UL4) on the bottom. The transducer was a Statham Instruments, Model UC3 strain gauge cell mounted to the Model UL4 load cell accessory. The transducer was coupled to a Statham Model SC1100 bridge amplifier, such that the total transducer output (range 0–50 g) was between 0.040 and 1.00 V DC.

The output of the bridge amplifier was fed directly into an analog input of a Lab-8 digital computer (Digital Equipment Corp.), which was programmed to sample the input once every 12 msec. The sample was analog-to-digital (A/D) converted and processed before the next sample was taken. The digital sample was accurate to 0.196 g (±0.10 g).

The computer was programmed to compare each A/D conversion to a set of upper and lower numerical limits. It then determined when the response force had remained for a predetermined time within those limits and reinforced this response by delivering a food pellet when such criteria had been met. The program allowed for the experimenter to set the upper and lower limits of the force band, to set the length of time the response must remain in-band for reinforcement to occur, and how many pellets were to be delivered per session. At the end of a session the computer returned the following data: total session time, time responding on the lever (a minimum response force of at least 0.5 g was required to be classed as response occurrence), response time in-band, response time above band, and number of band entrances (both from below and above band).

Using these data, the following motor performance measures could be calculated: (1) Efficiency in-band: minimum possible in-band time required to obtain all programmed pellets divided by the actual time spent in-band, (2) Tonic accuracy: time spent in-band divided by total time spent responding, (3) Work rate: total time spent responding divided by session time, (4) Mean in-band time: in-band time divided by the number of band entrances. Also, the total number of band entrances was used alone as a measure of dyskinesia.

The in-band efficiency measure had a fixed numerator, as the session always consisted of 50 pellet deliveries, making the minimum possible time in-band to earn all programmed pellets equal to 75 seconds (50 X 1.5 sec). Thus, if the animal went into band, held in-band for the 1.5 seconds required without leaving, and exited from band exactly at the time of pellet delivery, this ratio measure would approximate 1.00. There were two ways to produce decreases in this measure. First, if the response went into band, but did not remain long enough to obtain a reinforcement, the denominator was increased. Second, if after a reinforcement was delivered, the response continued for a period before dropping out of band, but not long enough to obtain a second pellet, the post-magazine operation in-band time would also produce an increase in in-band time and a resulting decrease in efficiency.

The measure of tonic accuracy approached 1.00 as the total time spent responding approached the time spent in-band. At first it would appear that as accuracy improved, so also should efficiency. However, while in general this appeared to be the case, it did not, in fact, have to occur. While most of the animal's time responding might have been in-band, if he did not hold in-band long enough to meet the requirements for reinforcement, his efficiency could be very low, while maintaining an extremely high tonic accuracy.

Work rate was an independent measure of the amount of time the animal was responding on the lever compared to the time in which he was engaged in other behaviors (i.e., eating, grooming, etc.). While work rate could be either close to 1.00 (the animal was responding during most of the total time in the box) or very close to zero (very little responding while spending a long time in the box to complete the 50 pellet session), the other measures could be close to one or zero completely independent of the work rate.

The measure of mean in-band time had several ways in which it could be affected, depending on the manner of the occurring dyskinesia. An animal could, for example, have a high tremor rate and enter and exit the band many times while not building up much in-band time. He could also have the same number of entrances and exits but spend a lot of time in-band. Thus, it is possible to have almost an identical number of band entrances for greatly different mean in-band scores.

Besides processing the force performance online with the computer, the analog output from the force transducer was recorded on magnetic tape (Sony model #TC-366-4) after passing through an FM converter (A.R. Vetters, 0–1000 Hz range). These taped records were then used to make both photographic or polygraphic records to determine if specific tremor change was associated with the behavioral results.

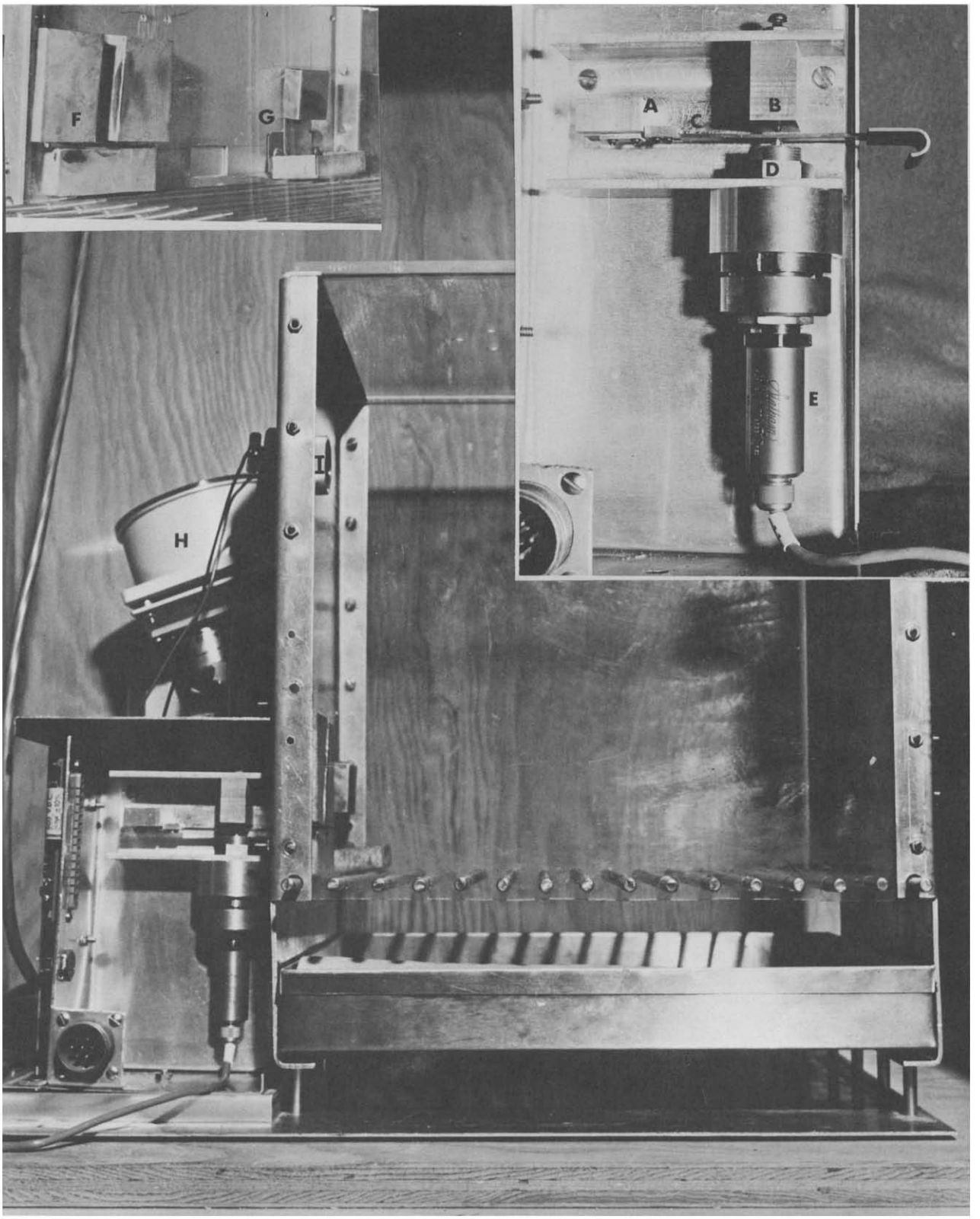

FIG. 1. Force Apparatus. Insert in upper right shows the lever construction. Insert in upper left shows front of animal chamber with manipulandum shield and food cup. (A) Phosphor-bronze spring and housing. (B) Lever stop. (C) Manipulandum. (D) Force transducer converter head. (E) Force transducer. (F) Shield for lever. (G) Food cup. (H) Pellet dispenser. (I) Audio feedback speaker.

Experimental Procedure

The experiment was done in four major phases. Each phase was completed for all animals before the next phase was begun. As far as possible, conditions for all animals remained equal. However, some individual manipulations for specific problems were made, and will be reported in the results.

Phase One. (Initial training and baseline determination.) This phase entailed force response training. The animals were reduced to 80% of their freefeeding body weights. They were housed in individual cages with water available 24 hr a day. Their weights were maintained at 80% by the use of food supplements given after they had completed their daily session on the force task. After shaping the animals to hold the manipulandum for at least 200 msec (for details see [2]), the force limits (the band width) were made smaller than the total output of the force lever and the animals were thus trained to hold the bar with a force greater than 0.5 g and less than 50.0 g for the required time. Each session consisted of 50 reinforcements. Slowly the band width and hold time were changed to make the task more difficult. When the animals reached a difficult performance level, a 10 session baseline was obtained. Then the response criteria were made more difficult, and the baseline was redetermined. This procedure was repeated until it became evident that performance did not improve, but rather deteriorated. The band width and hold time were then set to the immediately preceding level at which stable behavior had been obtained, and 20 days of baseline performance were obtained.

Phase Two. (Acute ethanol dose-effect determination.) Following the 20 day baseline procedure, the effect of acute doses of ethanol were determined. Body weight was maintained as in Phase One. Doses of either 1, 2, 3, or 4 g/kg were administered before a session. Each animal received each dose 3 times. At least two nondrug days occurred between drug sessions. To ensure that blood ethanol concentrations would be at their maxima for the specific dose at the beginning of drug sessions, a pilot study was performed to determine blood alcohol elimination curves for the respective doses. The enzymatic method, as previously described [4], was used to determine blood ethanol levels. These data showed that the 1 g/kg dose produced a peak blood level after 1 hr. For the 2 g/kg dose, 2 hr were required for maximum blood levels to be attained. For 3 g/kg, 2½ hr was the appropriate time, while 3 hr was required for the 4 g/kg dose. Thus, the time from dose administration to session onset was varied according to the above regimen.

All doses were of 15% (v/v) ethanol, given into the stomach by intragastric tube. The tube was inserted while the animal was lightly anesthetized with ether. Both ether and physiological saline (volume equal to the 4 g/kg ethanol dose) control conditions were administered.

Thus, data were gathered for 6 conditions to compare against baseline: (1) ether control (ether anesthesia only), (2) saline, and (3) to (6), doses of 1, 2, 3, or 4 g/kg ethanol. From these data, dose-effect curves for ethanol were determined. While these ethanol doses provide a caloric source which could conceivably attenuate performance on this food-reinforced task, previous results [2] indicated no performance decrement resulting from prefeeding at these caloric levels.

Phase Three. (Ethanol dose-effect determination under chronic ethanol maintenance.) After the determination of the dose-effect curves in Phase Two, the animals were placed into individual Plexiglas cages into which 45 mg food pellets (Noyes Co.) could be automatically delivered from a Gerbrands pellet dispenser. Fluid was available from a stainless steel, ballbearing drinking spout (Ancare #TD-300) which was attached to a 250 ml graduated cylinder. In this phase, the only available fluid was 5% (v/v) ethanol (1 ml of 5% ethanol provides 0.2816 Kcal). Pellets were delivered on a schedule which had previously been shown to induce high, chronic ethanol intake [4]. In this schedule, pellets were automatically delivered every 2 min for 1 hr. Then, a 3 hr period, during which no food was delivered occurred, followed by another 1 hr food delivery period. This 3 hr off–1 hr on regimen was continuous, 24 hr per day. Thus, in each 24 hr period, there were 6 one-hour food delivery periods, spaced 3 hr apart, delivering $6 \times 30 = 180$ food pellets. While on this schedule, the daily force sessions described above were continued. These sessions occurred starting at 11 a.m., during the 10 a.m.–1 p.m. 3 hr off period.

After one month on the above alcohol-drinking schedule, the effects of short-term withdrawal of alcohol on the force performance were determined. Water was substituted for the ethanol on the animals' cages. Both 5 hr and 10 hr ethanol withdrawal periods were tested. These were termed the early, short-term withdrawal tests.

Following these withdrawal tests, the ethanol schedule was maintained for at least 2 more months, with daily sessions on the force task reduced to every other day. Then, a repeat measure of the dose-effect curve for ethanol was performed. The doses were administered in addition to the ethanol intake occurring in connection with the food-schedule regimen. Blood samples were taken 15 min prior to some force sessions to determine blood levels associated with a given performance. This was necessary because of the variable starting blood ethanol levels of the animals. Control blood samples also were taken before some nonethanol sessions to determine resting blood ethanol levels.

Following the redetermination of the dose-effect curves, two more 5 and 10 hr withdrawal sessions were given. These were termed the late, short-term withdrawal tests.

Phase Four. (Ethanol withdrawal.) This was the final phase of the experiment. It consisted of complete ethanol withdrawal. As before, withdrawal was accomplished by substituting water in place of alcohol in the food-delivery schedule situation. Food supplements were given, such that current body weights were maintained. Daily sessions on the force task were administered for the next 14 days, and then every other day for a total of 30 days post-withdrawal.

RESULTS

Phase One: Training and Baseline

All 4 animals were able to hold the force lever in-band for the criterion time of 1.5 sec. Three animals (G24, G25 and G26) could perform this criterion hold-time with a band width of 17 g (18 g–35 g), while the fourth (G23) required a larger band width of 18–39 g (21 g width). The final, 20 day mean baseline values are shown in Fig. 2.

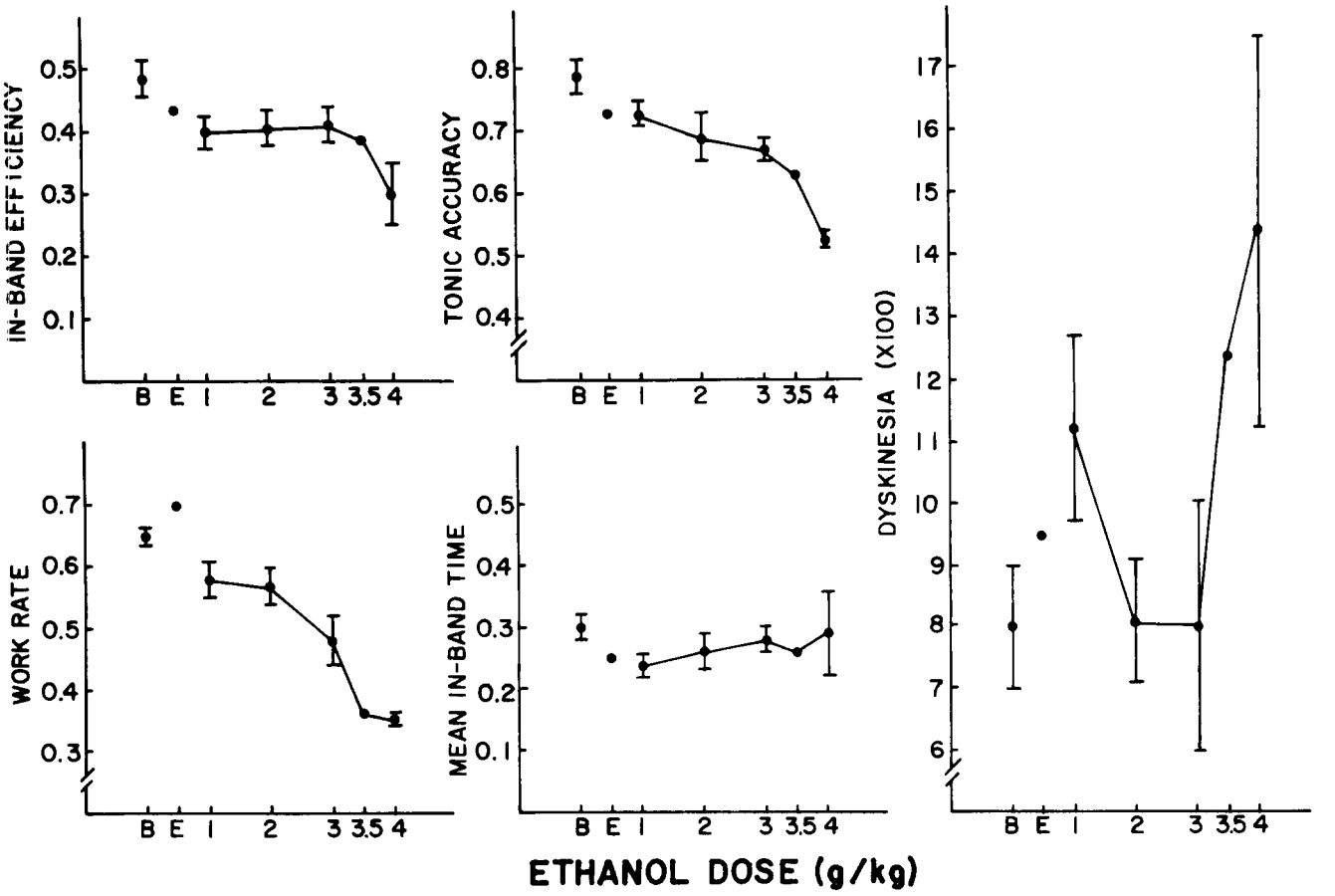

FIG. 2. Force performance measures as a function of acute ethanol dose (IG). (B) Baselines calculated from means of 20 days of performance prior to first ethanol dose. (E) Mean of 4 ether control doses. Values for 3.5 g/kg dose are based on the mean of two observations on one animal.

Phase Two: Acute Ethanol Effects

Dose-effect relations are presented in Fig. 2. With a load of 1 g/kg, a slight decrease in in-band efficiency was found. In general, there was also a decrease in tonic accuracy and work rate, as seen in the overall data, but only 2 of the 4 animals actually decreased. Three out of four animals decreased in mean in-band time. The measure of dyskinesia (band entrances) went up overall, with three animals showing increases.

At dose levels of 2 and 3 g/kg, in-band efficiency was affected the same as with a 1 g/kg dose, a slight decrease. Tonic accuracy showed a progressive decrease as the dose was increased, as did work rate. Mean in-band time showed little difference from a 1 g/kg dose, with a slight return towards baseline. Perhaps the most striking and unexpected effects were seen on dyskinesia, with all animals returning to baseline or even below baseline at these doses.

At a dose of 4 g/kg, only 2 of the 4 animals responded. The animals which failed to respond were later tested at a dose of 3.5 g/kg. Only 1 of the 2 would respond at this dose. His data show effects between those at 3 g/kg and 4 g/kg.

At the 4 g/kg dose, force performance was greatly affected. In-band efficiency, tonic accuracy, and work rate were greatly reduced. Interestingly, mean in-band time was basically the same as baseline. This is a result of both a decrease in efficiency and increased dyskinesia, with the increased dyskinesia as the more influential effect.

Figure 3 shows sample force records for one animal (G24) to demonstrate the patterns of force-responding at the dose levels of ethanol administered. Since all animals showed individual, characteristic, normal response patterns, the observed effects on response pattern were somewhat different for the various doses in each animal. Prior to the start of baseline determination (11/2/71), a great amount of band search responding occurs. However, at the completion of baseline (12/27/71) and during the determination of the acute, ethanol dose-effect curves (1/3/72), entrance into band was fairly direct. The lever was held in-band until pellet delivery and was then immediately released.

With a dose of 1 g/kg, the response pattern is more like prebaseline behavior (11/2/71) than that observed 24 hr prior to the dose (12/27/71). However, a dose of 2 g/kg resulted in response patterns similar to baseline performances.

With loads of 3 and 4 g/kg, the response patterns indicate great difficulty in maintaining response force in-band.

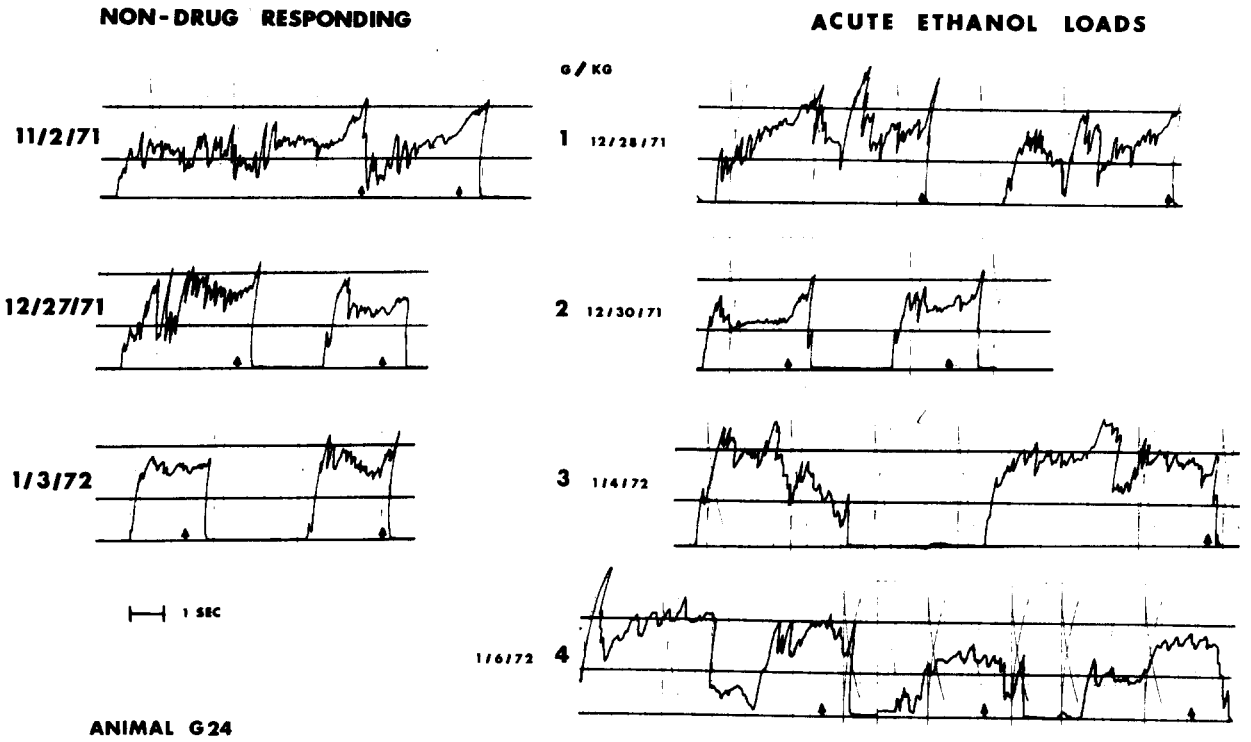

FIG. 3. Sample force performance records for Rat G24 prebaseline, baseline, and acute ethanol load (1–4 g/kg, IG) conditions. (Arrows indicate pellet delivery. Lower line indicates zero force level; middle and upper lines mark off limits of the required force band.)

TABLE 1

CHRONIC MONTHLY VALUES (MEANS) FOR BODY WEIGHT, 5% ETHANOL INTAKE AND g ETHANOL/kg BODY WEIGHT*

	Rat G23			Rat G24			Rat G25			Rat G26		
month	wt	intake (ml)	g/kg	wt	intake (ml)	g/kg	wt	intake (ml)	g/kg	wt	intake (ml)	g/kg
1	308	94	12.07	323	96	11.73	309	59	7.63	324	104	12.70
2	315	112	14.11	336	112	13.22	308	72	9.28	323	120	14.72
3	333	111	12.26	358	102	11.27	311	75	9.53	339	128	14.93
4	351	110	12.39	367	93	10.05	315	69	8.70	338	121	14.22
5	370	104	11.16	404	67	6.62	334	72	8.53	384	117	12.15
6	346	99	11.37	374	92	9.72	325	76	9.23	376	114	12.10
7	364	106	11.57	383	94	9.75	356	75	8.37	386	112	11.52
8	380	106	11.04	397	95	9.50	359	78	8.58	395	115	11.61
9	392	107	10.82	403	95	9.37	369	76	8.18	399	116	11.56
10	397	112	11.16							394	122	12.25

*One ml of 5% ethanol provides 0.2816 Kcal

Phase Three: Chronic Ethanol Administration

Ethanol intake. In Table 1, the average monthly weights, intake of 5% ethanol (ml), and g/kg of absolute ethanol taken are shown for the 9–10 month period in which the animals chronically ingested ethanol, 24 hr per day. Three of the 4 animals showed intakes during the first 3 months that were equal to those reported by Falk *et al.* [4]. One animal (G25) failed to drink over 10 g/kg at any time.

All animals gained weight over the intake period, and as weight increased, the g/kg decreased somewhat, not because of a decrease in ml intake, but rather because of

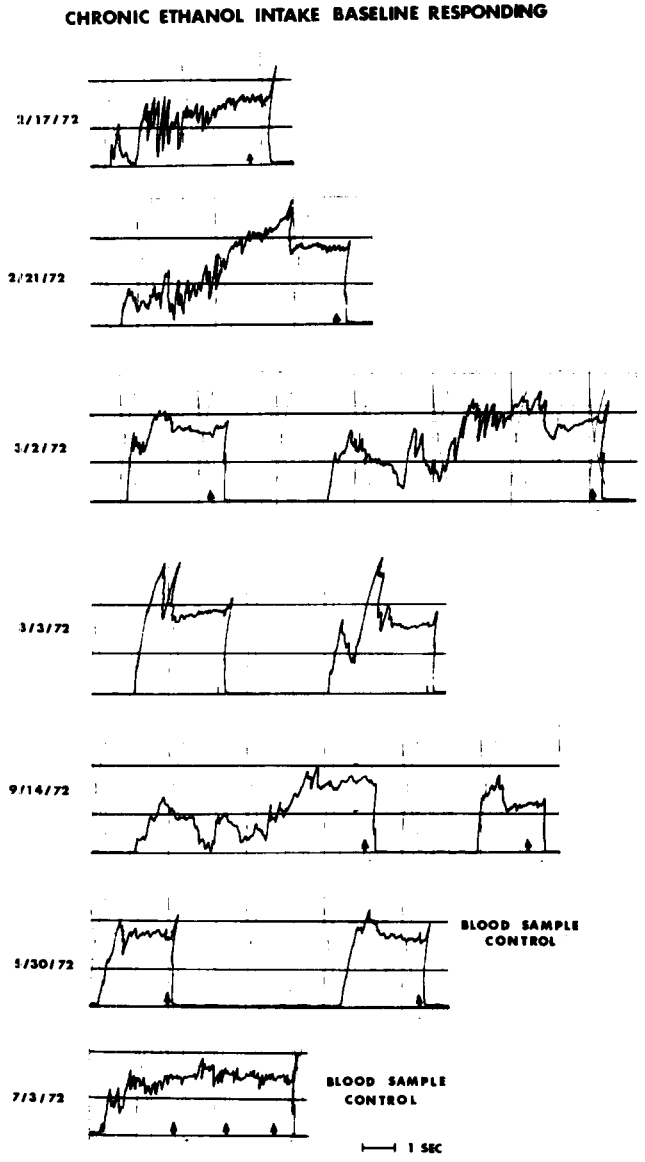

FIG. 4. Sample force performance records for Rat G24 at various dates during chronic ethanol ingestion. (Blood sample controls: blood sampled 15 min prior to session.)

the increased weight. Intake volumes remained stable after the second month.

During the fifth month, because of the large weight increases, a decrease in the number of programmed pellets was instigated. Food pellets were omitted every second day for a 10 day period. This succeeded in producing a mild body weight loss, as shown in the decreased mean weights of the sixth month.

Force performance. For the first 7–10 days of chronic ethanol intake, only a slight disruption in force performance occurred. Pausing behavior increased which led to moderately decreased work rates. A slight increase in dyskinesia occurred, but this was within the normal range. As has been previously noted [4], animals under schedule-induced ethanol intake conditions are slightly ataxic during the first week on this procedure. But no great degree of motor impairment occurred.

Over the 10 month drinking period, the only major effect seen on the daily control performance was a decrease in work rate which was coupled with body weight gain. All other measures of force performance remained stable during the entire 10 month, chronic-ingestion period. Figure 4 presents the response patterns for the same animal as Fig. 3. The figure illustrates some of the variability observed in response patterns during the alcohol ingestion. However, similar variability was noted before the animal was placed in the chronic ethanol intake situation.

The effects of the early withdrawal tests performed at the end of the first month of chronic ingestion are presented in Table 2. Following 5 hr without alcohol, all measures were affected. However, the major effects were seen in a greatly decreased work rate and an increased dyskinesia score. The animals showed some preconvulsive behaviors when handled, and were obviously hyperactive, which led to more time exploring the experimental chamber instead of responding, resulting in lower work rate. Blood samples showed that 5 hr of withdrawal reduced the blood ethanol levels to below 30 mg/100 ml.

The 10 hr withdrawal produced less effect on the force parameters than the 5 hr withdrawal. Blood alcohol levels were at normal, base level (<5 mg/100 ml). The only measure affected was the dyskinesia score, which remained above baseline.

The redetermination of the dose-effect curve under chronic ethanol intake conditions was complicated in that

TABLE 2

CHANGES IN MEAN (±S.E.) FORCE PERFORMANCE MEASURES AS A FUNCTION OF ETHANOL WITHDRAWAL

	baseline	chronic ethanol ingestion baseline	5 hr withdrawal	10 hr withdrawal
Inband Efficiency	0.49 ± 0.02	0.47 ± 0.04	0.38 ± 0.05	0.42 ± 0.04
Tonic Accuracy	0.79 ± 0.03	0.75 ± 0.04	0.65 ± 0.10	0.72 ± 0.04
Work Rate	0.65 ± 0.02	0.51 ± 0.04	0.33 ± 0.11	0.48 ± 0.05
Mean Inband Time	0.30 ± 0.02	0.28 ± 0.04	0.24 ± 0.03	0.28 ± 0.04
Dyskinesia	800 ± 98	762 ± 118	1347 ± 291	1112 ± 276

any administered dose was in addition to an existing variable blood level. With a resting blood level of between 70 and 150 mg/100 ml, an IG dose of 4 g/kg generally brought blood levels over the 350 mg/100 ml level, which placed the animal in a partially anesthetized state, making the force performance impossible. Because of the blood level variability, each individual animal's mean scores are presented, rather than the overall means.

Table 3 presents mean blood ethanol concentrations for various dose levels at which samples were taken. The resting blood ethanol level while in the chronic ethanol intake condition was appro..imately the same as that following a dose of 4 g/kg in the prechronic condition (cf., 150 and 160 mg/100 ml). However, in the chronic, ethanol intake condition, no changes from prechronic baseline performance measures occurred. Thus, tolerance to ethanol was apparent by the end of the first month, as similar blood ethanol levels before chronic ingestion (i.e., a dose of 4 g/kg) produced severe disruption of force performance as reported above.

The individual dose-effect curves are presented in Fig. 5. None of the 4 animals responded on the force task after a dose of 4 g/kg given in addition to the normal chronic, daily ethanol intake. Therefore, only doses of 1, 2 and 3 g/kg are presented. In-band efficiency, in two animals (G24 and G25), showed a decrease at all dose levels. For Animal G26, at all dose levels there was a slight increase in efficiency, while for G23, no change from baseline occurred.

TABLE 3

MEAN BLOOD ETHANOL LEVELS BEFORE AND DURING CHRONIC ETHANOL INTAKE AFTER VARIOUS ACUTE DOSES OF ETHANOL (ALL VALUES EXPRESSED AS mg/100 ml BLOOD)

		doses (g/kg)			
	Resting level	1	2	3	4
Before chronic ethanol intake	Less than 5.0	*	*	100	160
During chronic ethanol intake	150	*	230	280	350

*No blood samples taken under these conditions.

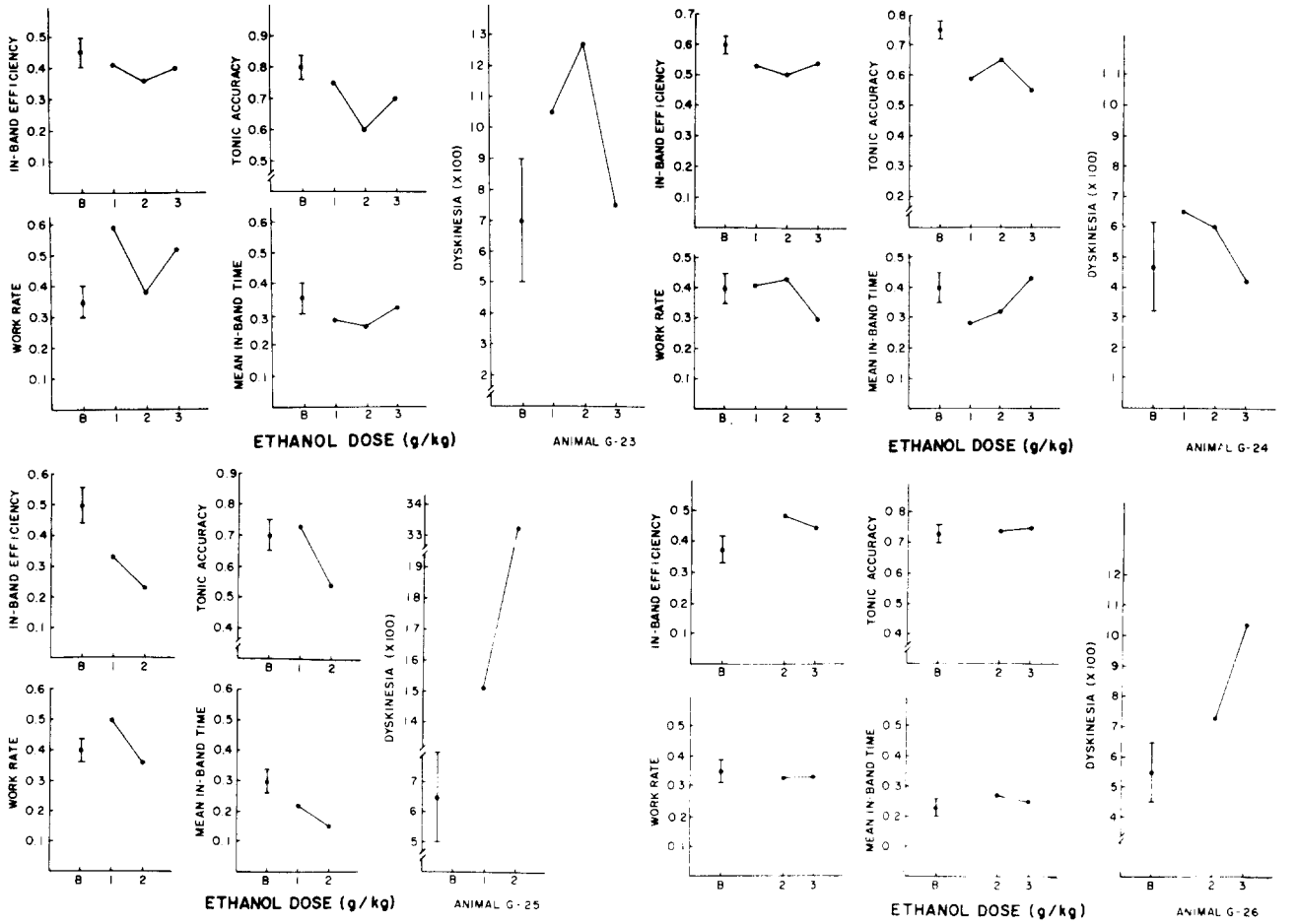

FIG. 5. Force performance measures as a function of acute ethanol doses after 3 months of chronic ethanol overdrinking (all animals). (B) Baselines calculated from means of 20 days of performance prior to first ethanol dose.

Tonic accuracy decreased at the 2 and 3 g/kg dose levels in all animals except G26, who showed no change.

Work rate was extremely variable across dose levels, as was the mean in-band time measure.

At doses of 1 and 2 g/kg, Animals G23, G24 and G25 had increases in dyskinesia scores, with a drop towards baseline for Animals G23 and G24 at the 3 g/kg dose level, while G25 failed to respond after this dose. For Animal G26, both 2 and 3 g/kg doses increased the dyskinesia score.

The effects of acute loads during chronic ethanol ingestion on response patterns are shown in Fig. 6. The variability of response patterns to equal ethanol loads was considerable. Blood ethanol levels prior to the sessions confirmed that because of daily variability in existing blood ethanol levels, the range in preforce session blood ethanol levels following acute loads could be as great as 100 mg/100 ml (from 200 to 300 mg/100 ml). This factor could account for the observed differences in force performance.

The late, short-term withdrawal effects are presented in Table 4. The major effect was found in the dyskinesia scores. The effects of short-term withdrawal on response patterns are shown in Fig. 7.

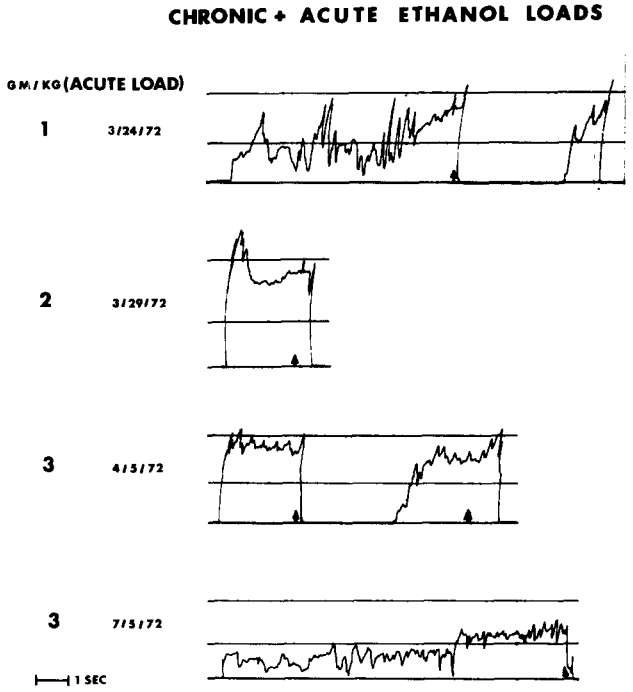

FIG. 6. Sample force performance records for Rat G24 with acute ethanol doses in addition to self-ingested, chronic ethanol levels.

Phase Four: Complete Withdrawal

Complete withdrawal of ethanol affected two measures significantly, in-band efficiency and dyskinesia. In-Band efficiency (Fig. 8) showed a decrease in efficiency during the first 48 hr, with a greater decrement at 24 hr than at 48 hr. There was a parallel increase in dyskinesia (Fig. 9) lasting for 72 hr. It should be noted that the dyskinesia scores for 24 hr of complete withdrawal were essentially

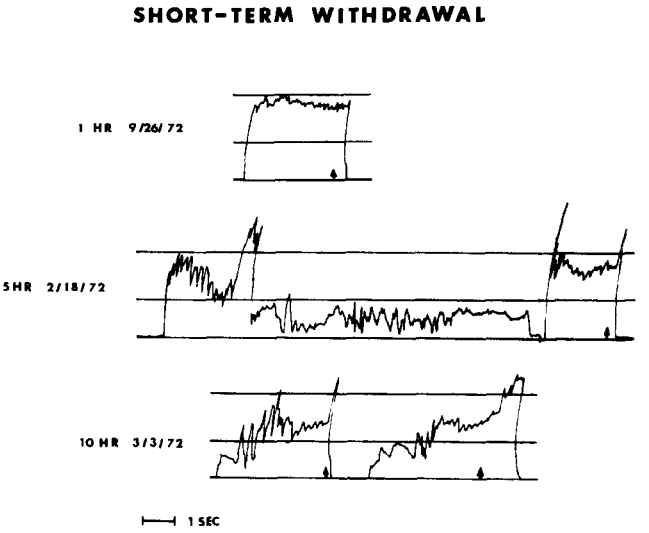

FIG. 7. Sample force performance records for Rat G24 following 1, 5, or 10 hr of ethanol withdrawal after at least 3 months of chronic overdrinking.

TABLE 4

LATE SHORT-TERM WITHDRAWAL EFFECTS (MEAN VALUES ± S.E.)

	chronic baseline	5 hr withdrawal	10 hr withdrawal
Inband Efficiency	0.48 ± 0.05	0.41 ± 0.05	0.44 ± 0.04
Tonic Accuracy	0.74 ± 0.02	0.62 ± 0.08	0.74 ± 0.05
Work Rate	0.38 ± 0.02	0.32 ± 0.08	0.41 ± 0.04
Mean Inband Time	0.32 ± 0.04	0.23 ± 0.03	0.29 ± 0.05
Dyskenesia	592 ± 60	1289 ± 226	1030 ± 306

the same as at 5 and 10 hr of short-term withdrawal. The response patterns for complete withdrawal are presented in Fig. 10. Little effect on responding pattern is evident after 72 hours.

DISCUSSION

The effects of acute doses of ethanol suggest that little impairment of motor discrimination occurs in the non-dependent animals with doses of 3 g/kg and below (blood ethanol levels of 100 mg/100 ml or less). There is the possibility that very small doses (i.e., 1 g/kg and less) produce a slight motor excitability that is reflected in an increased dyskinesia. Doses of 3.5 g/kg and greater show marked reduction of the animal's performance, with a greatly increased dyskinesia and corresponding decreased tonic accuracy and in-band efficiency. This dose level produces blood ethanol levels between 120 and 150 mg/100 ml, suggesting that in the nondependent animal, blood ethanol levels below 100 mg/100 ml have a mild sedative effect with little to no major disruption of motor

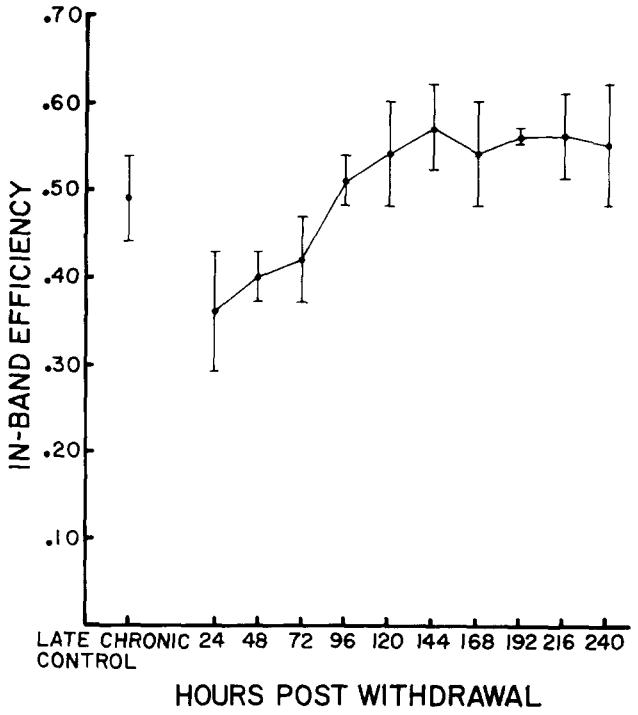

FIG. 8. Effect of complete ethanol withdrawal on in-band efficiency. Means (± S.E.) for all animals.

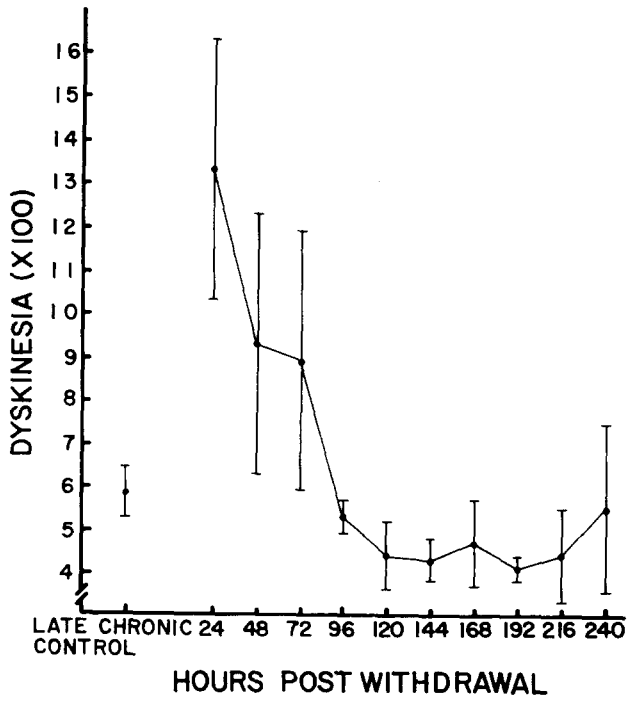

FIG. 9. Effects of complete ethanol withdrawal on dyskinesia (band entrances). Means (± S.E.) for all animals.

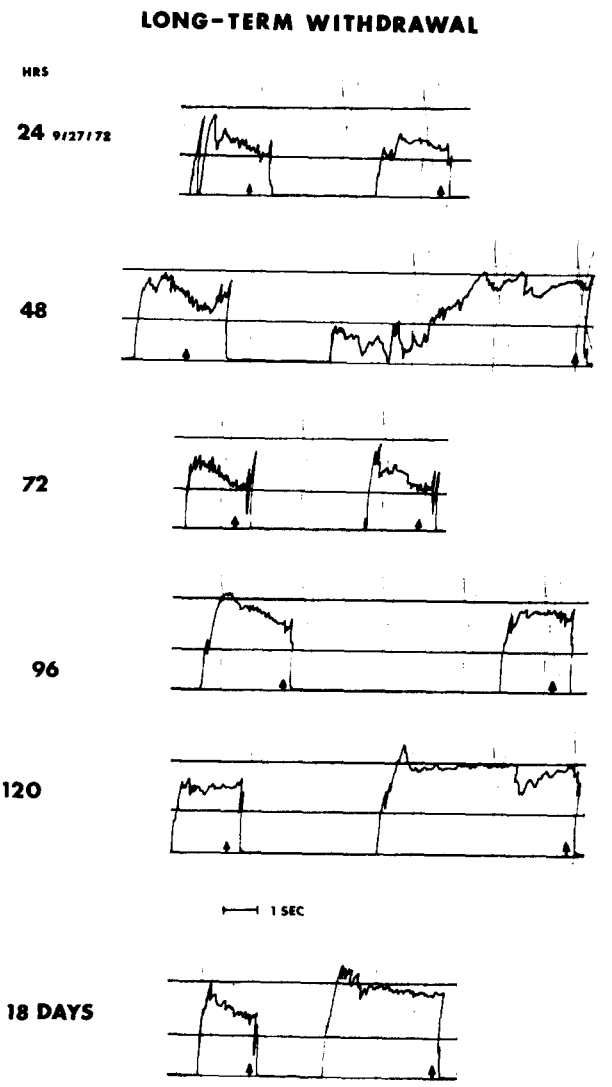

FIG. 10. Sample force performance records for Rat G24 during complete ethanol withdrawal.

discrimination. The effects of ethanol could be compared to the effects of pentobarbital [2] on most measures. However, the relation of dose to the dyskinesia measure shows a somewhat U-shaped function for ethanol, while the barbiturate gives a more linear dose-effect curve. Thus, the basic drug response to ethanol in the nondependent animal could be described as basically similar to that of the barbiturates.

Over the 10 months during which the animals chronically overdrank ethanol daily, there was no detectable change in motor discrimination provided that the animals drank the ethanol daily. During most of this time, the blood ethanol levels were between 150 and 200 mg/100 ml blood, which is as high or higher than the blood levels which in the nondependent state produced marked impairment on the required task. Thus, a marked tolerance to ethanol occurred following a short period of chronic ethanol overdrinking. A slight impairment of performance was noted during the first few days of the

chronic ingestion phase, but since this corresponded to a shift in living quarters, feeding regimen, and daily handling procedures, no direct relation can be attributed to ethanol drinking and/or tolerance.

The acute ethanol doses during the chronic ingestion period produced various results which can be accounted for by the variability of the baseline blood ethanol levels upon which the additional doses were administered. Overall, marked tolerance to ethanol was shown, as little performance change occurred with blood levels as high as 280 mg ethanol/100 ml blood, a blood level almost twice that which severely affected performance before chronic overdrinking.

Ethanol withdrawal effects were seen following one month of chronic drinking. The short-term withdrawal produced an increase in the dyskinesia measure, but was not particularly severe as shown by the other performance measures. Little difference in the short-term withdrawal effects were seen after 3 months. However, long-term withdrawal showed marked impairment in performance for 72 hr following ethanol removal, which corresponded to the general withdrawal syndrome pattern of the human alcoholic [15]. During this period, the animals were hyperactive, with marked increases in dyskinesia scores. Efficiency and accuracy were also significantly reduced.

Overall, three major points are clear. First, in nondependent animals, blood ethanol levels less than 100 mg/100 ml produced no major effects on motor discrimination. Second, marked ethanol tolerance occurred following 3 months of chronic ethanol overdrinking. Third, for the first 72 hr of ethanol abstinence, animals that had been chronically overdrinking ethanol for 10 months showed a severe decrement in discriminative motor control.

These data suggest that the effects of low to medium doses of ethanol that result in blood levels of less than 100 mg/100 ml have little effect upon motor discrimination in nondependent animals and may, in fact, act as mild sedatives and improve performance to a small degree. The implication is not difficult to accept, as the resulting decreased motor tremor from the minor sedative effects of these doses should, in fact, not be disruptive to performance.

In animals that were physically dependent on ethanol [4], the marked tolerance to blood ethanol levels demonstrated by lack of impairment in motor discrimination, fits well with the data of Talland *et al.* [11]. Very high blood levels were needed in human alcoholics to produce a noticeable impairment on motor skill tasks, which, while not the same as the motor discrimination task used in these experiments, still involved some of the same components of motor discrimination. Such marked tolerance in dependent animals suggests that blood levels alone are not satisfactory indicants of motor capabilities without knowledge of the past history of ethanol exposure.

The effects of ethanol withdrawal in physically dependent animals were quite pronounced on motor discrimination. The increased motor tremors which were associated with the abstinence syndrome were, of course, a major reason for the observed decrement; but besides these tremors, the animals in these studies seemed to have motor coordination problems (as reflected in their accuracy and efficiency scores). The general appearance of the animals suggested that the withdrawal resulted in a behavioral disruption beyond that of simple motor function. This disruption could be implicated in some of the performance decrement seen during the 72 hr following ethanol removal. The animals were hyperreactive to incidental tactile and auditory stimuli (i.e., handling, laboratory noises, etc.). In some instances it appeared that the motor discrimination was not only hampered by the increased resting tremor but also by an inability to coordinate band-searching motor function.

One postulated mechanism for the withdrawal syndrome is that ethanol blocks normal synaptic transmission, resulting in a functional state of partial denervation. When ethanol is removed from the system, denervation supersensitivity results [6]. The general motor performance disruption during withdrawal that was found in these studies suggested that fine motor control was severely impaired at several levels of neuromuscular control. This impairment could possibly be attributed to an increased hypersensitivity resulting in loss of coordinated motor function.

REFERENCES

1. Carpenter, J. A. Effects of alcohol on some psychological processes. *Q. Jl Stud. Alcohol* **23:** 274–314, 1962.
2. Falk, J. L. Drug effects on discriminative motor control. *Physiol. Behav.* **4:** 421–427, 1969.
3. Falk, J. L. and W. O. Hass, III. The control and recording of response force. *J. exp. Analysis Behav.* **8:** 195–197, 1965.
4. Falk, J. L., H. H. Samson and G. Winger. Behavioral maintenance of high blood ethanol and physical dependence in the rat. *Science* **177:** 811–813, 1972.
5. Gibbins, R. J., H. Kalant and A. E. LeBlanc. A technique for accurate measurement of moderate degrees of alcohol intoxication in small animals. *J. Pharmac. exp. Ther.* **159:** 236–242, 1968.
6. Jaffe, J. H. and S. K. Sharpless. Pharmacological denervation supersensitivity in the central nervous system: a theory of physical dependence. In: *Addictive States.* Ass. Res. Nerv. Ment. Dis. Res. Publ. 46, edited by A. Wikler. Baltimore: Williams, 1968, pp. 226–246.
7. Kinaid, F. W. and M. G. Hay. Effect of ethanol administration on brain and liver enzyme activities. *Am. J. Physiol.* **198:** 657–658, 1960.
8. Laties, V. G. and B. Weiss. Effects of alcohol on timing behavior. *J. comp. physiol. Psychol.* **55:** 85–91, 1962.
9. LeBlanc, A. E., H. Kalant, R. J. Gibbins and N. D. Berman. Acquisition and loss of tolerance to ethanol by the rat. *J. Pharmac. exp. Ther.* **168:** 244–250, 1969.
10. Mello, N. K. A review of methods to induce alcohol addiction in animals. *Pharmac. Biochem. Behav.* **1:** 89–101, 1973.
11. Talland, G. A. and R. Kasschau. Practice and alcohol effects on motor skill and attention. *Q. Jl Stud. Alcohol* **26:** 393–401, 1965.
12. Wallgren, H. and H. Barry, III. *Actions of alcohol.* Amsterdam and New York: Elsevier, 1970.
13. Wallgren, H. and R. Lindbohm. Adaptation to ethanol in rats with special reference to brain tissue respiration. *Biochem. Pharmac.* **8:** 423–424, 1961.
14. Weiss, B. and V. G. Laties. Effects of amphetamine, chlorpromazine, pentobarbital, and ethanol on operant response duration. *J. Pharmac. exp. Ther.* **144:** 17–23, 1964.
15. Wolfe, S. and M. Victor. The physiological bases of the alcohol withdrawal syndrome. In: *Recent advances in studies of alcoholism,* edited by N. K. Mello and J. H. Mendelson. Washington: U.S. Government Printing Office, Publication #(HSM) 71-9045, 1971.