[R.B.: $t(84) = 4.01$, $P < .001$; L.E.L.: $t(78) = 3.10$, $P < .001$; M.S.: $t(124) = 9.32$, $P < .001$] and interocular [R.B.: $t(87) = 2.28$, $P < .025$; L.E.L.: $t(86) = 3.76$, $P < .001$; M.S.: $t(127) = 9.68$, $P < .001$] adaptation conditions. Subject R.B. showed a significant difference in the strength of the illusion in the interocular and direct adaptation conditions [R.B.: $t(55) = 2.47$, $P < .02$].

9. D. C. Burr, *Vision Res.* **20**, 391 (1980); K. K. DeValois, *ibid.* **17**, 209 (1977); L. E. Arend and R. V. Lange, *ibid.* **19**, 1089 (1979); C. F. Stromeyer, A. F. Lange, L. Ganz, *ibid.* **13**, 2345 (1973); L. Maffei and A. Fiorentini, *ibid.* **13**, 1255 (1973).

10. This research was supported by NIH grant EY01596, NSF grant BNS7817948, a career development award to R.B., and NIH postdoctoral fellowship EY05436 to L.E.L. We thank J. Zacks, A. Arditi, and W. Martens for helpful comments and assistance and M. Banks for earlier discussion.

6 November 1980; revised 19 January 1981

Electroencephalographic Tolerance and Abstinence Phenomena During Repeated Alcohol Ingestion by Nonalcoholics

Abstract. *Certain measures of the auditory average evoked response are sensitive to alcohol and provide evidence for abstinence and tolerance during and after 10 days of alcohol consumption by nonalcoholics. Electroencephalographic techniques provide a single sensitive measure for the study of the etiology of tolerance and abstinence with particular reference to a new area of investigation with nonaddicted humans.*

Mendelson (*1*) proposed that the pharmacological criteria of alcoholism most amenable to systematic investigation are tolerance and physical dependence. The study of these phenomena and the relationship between them has been extensive, but largely limited to infrahuman species or to humans already suffering from a long history of chronic alcoholism. A further restriction on such investigations has been the relative absence of techniques whereby both tolerance and physical dependence are assessed by comparable response indices. This led Begleiter and Porjesz to conclude that "to choose one technique to measure tolerance and another to assess physical dependence will continue to produce incomprehensible findings" (*2*, p. 356). They proposed the use of electroencephalography (EEG) as a remedy, since the same objective and quantifiable response measurements can be used to assess the effects on central nervous system excitability of both exposure to ethanol (*3*) and its removal (*4*). Our investigation is, to our knowledge, the first attempt to use quantitative EEG measures in a study of both tolerance and withdrawal in nonalcoholic humans.

Eight male volunteers (*5*) were informed of the purpose and risks of the study before consenting to participate. Subjects remained on our clinical research unit for the 16 days of the study. A battery of electrophysiological and psychological tests, administered twice daily, included spontaneous occipital EEG; vertex auditory average evoked potentials (AEP's) following 0-, 20-, 50-, and 90-dB tone stimuli; heart rate; hand tremor; postural sway; smooth pendular pursuit eye movements; verbal recall; and intoxication self-rating in that order. The order of testing remained constant throughout the study. The 16 days of the study were divided into three phases; the first 3 days were a preliminary baseline (baseline 1), followed by a 10-day alcohol phase, and a 3-day final baseline (baseline 2). On each day of the investigation, the test battery was administered twice, once before and once 20 minutes after the subject drank a beverage. During the baseline periods, the beverage was 500 ml of orange juice, and during the alcohol phase, alcohol (1 g per kilogram of body weight) mixed to a 10 percent solution with an orange juice vehicle. During the alcohol phase, breath alcohol was tested by a standard breath analysis machine immediately after the measurement of the auditory evoked responses. For six subjects, the beverage was consumed at 1400 hours, and for two, at 1000 hours. During the alcohol phase, after completing the second test battery, subjects consumed additional alcohol (0.9 g/kg) over 2 to 3 hours to keep blood alcohol concentrations elevated over a significant portion of each day. For these days, before-beverage testing occurred approximately 19½ hours after the completion of the previous day's alcohol ingestion.

From the spontaneous EEG, power spectral analysis techniques were used to derive estimates of the percentage of alpha, beta, and theta powers in addition

Table 1. Auditory evoked response means and standard deviations associated with 90- and 50-dB stimulus levels for the three phases of the experiment. Significance levels are for comparisons of before- and after-beverage scores (analysis of variance).

Measure	Baseline 1 (days 1 to 3)	Alcohol (days 4 to 13)	Baseline 2 (days 14 to 16)
	90-dB stimulus		
Variance $(\mu v)^2$			
Before	1.13 ± 0.52	1.41 ± 0.49****	1.17 ± 0.43
After	1.08 ± 0.63	0.98 ± 0.40	1.39 ± 0.44
ANR (dB)			
Before	−14.75 ± 2.34	−13.97 ± 2.30***	−14.54 ± 2.50
After	−15.63 ± 3.43	−15.97 ± 2.56	−14.02 ± 2.12
N_1 latency (msec)			
Before	111.25 ± 13.38	104.53 ± 8.79***	103.58 ± 11.23
After	107.63 ± 9.68	109.17 ± 10.10	105.00 ± 13.26
P_2 latency (msec)			
Before	182.54 ± 16.11	176.53 ± 15.29*	173.91 ± 14.35
After	175.08 ± 11.17	172.33 ± 14.31	175.67 ± 13.74
N_1P_2 amplitude (μV)			
Before	9.06 ± 2.63	10.20 ± 2.46***	9.13 ± 2.74
After	8.71 ± 2.82	7.72 ± 4.34	9.87 ± 2.88
	50-dB stimulus		
Variance			
Before	0.62 ± 0.32	0.71 ± 0.32***	0.64 ± 0.26
After	0.67 ± 0.33	0.53 ± 0.27	0.69 ± 0.29
ANR			
Before	−17.38 ± 2.46	−17.22 ± 2.30***	−17.37 ± 1.98
After	−17.82 ± 2.36	−18.76 ± 2.19	−17.18 ± 1.92
N_1 latency			
Before	120.58 ± 16.55	120.75 ± 14.32	118.75 ± 14.23
After	121.46 ± 11.91	124.81 ± 17.72	115.43 ± 13.37
P_2 latency			
Before	195.88 ± 16.04	191.69 ± 15.98	186.42 ± 16.05
After	190.71 ± 20.81	192.79 ± 21.19	188.87 ± 22.60
N_1P_2			
Before	5.59 ± 1.95	6.34 ± 1.87**	6.31 ± 1.54
After	5.63 ± 2.02	5.01 ± 1.89	6.51 ± 1.68

*$P < .05$. **$P < .01$. ***$P < .005$. ****$P < .001$.

0036-8075/81/0605-1175$00.50/0

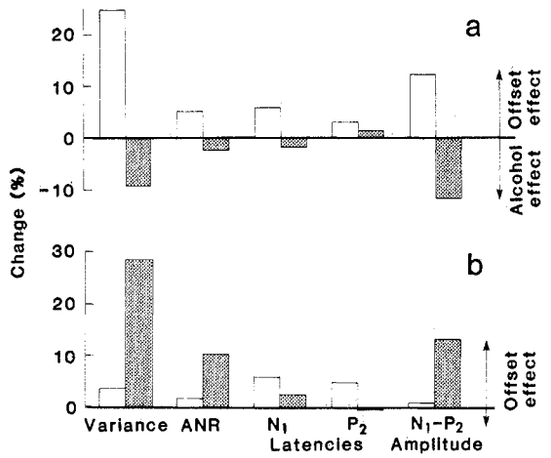

Fig. 1. (a) Percentage change in EEG measures in response to a 90-dB tone for the 10-day alcohol administration period compared with the initial 3-day baseline period. Before-beverage changes are with respect to the before-beverage baseline, and after-beverage changes are with respect to the after-beverage baseline. Changes have been adjusted so that the alcohol effect is negative and offset effect is positive. (b) Percentage change of baseline 2 from baseline 1.

to alpha peak frequency (*6*). The auditory AEP was the source of the following statistics: variance of the AEP, average-to-noise ratio (ANR) (*7*), N_1 and P_2 latencies, and magnitude difference (in microvolts) between the N_1 and P_2 peaks. The EEG variables were submitted to an analysis of variance on days, subjects, and session. The interaction of the main effect with subjects was used as an error term.

Before and after measures of spontaneous EEG and 0- and 20-dB evoked EEG did not differ statistically during either of the baseline periods or during the alcohol phase. In contrast, significant differences were found between before and after measures of 50- and 90-dB AEP's (Table 1). Alcohol is associated with reductions in N_1P_2 amplitude and increases in N_1 latency (*3*). During the alcohol period, a number of before-beverage values underwent changes in direction opposite to that of the after-beverage values and were in a direction consistent for withdrawal (*8*) or "offset" effects (Table 1). The signs of such changes are adjusted so that offset effects are positive in Fig. 1. Except for the latency of P_2 (*9*), changes in the before-beverage measures were in a different direction from those in the after-beverage measures. This difference in direction of change was responsible for significant differences between a number of before- and after-beverage values during the alcohol period (Table 1). The 50-dB stimulus showed a similar pattern, although some differences were not significant. Therefore, compared with the before-beverage baseline means (*10*), before-beverage variance, ANR, and N_1P_2 amplitude increased during the alcohol period, and N_1 latency decreased. These before-beverage offset effects did not increase gradually during the entire alcohol ingestion period, but were typically apparent by the second or third day of the alcohol phase and remained fairly stable throughout the remainder of this phase. Compared with the after-beverage baseline, after-beverage variance, ANR and N_1P_2 amplitude decreased while N_1 latency increased. The size of the before-beverage change was greater than that of the after-beverage change for all measures (Fig. 1a). During the final 3-day baseline period all measures tended to change in the offset direction (Fig. 1b). A set of typical responses is shown in Fig. 2.

Although offset effects opposite to alcohol effects were readily apparent (Fig. 1), tolerance associated with the after-beverage responses during the alcohol period was not demonstrated when strict criteria were applied to each evoked EEG measure (*11*). We considered tolerance present for a particular index if there was, over the alcohol period, a statistically significant trend or slope, indicating a progressive reduction of the alcohol effect relative to the before-beverage responses. Such a significant trend was found for verbal recall indices (*12*) but not for other measures (*13*), including AEP variables. For a number of measures, there was an apparent trend for the reduction of the alcohol response with repeated alcohol administration, but the slopes were not statistically significant. Slopes were greatest for the measures that showed the greatest initial alcohol effect; verbal recall indices were associated with the largest initial alcohol effect. Such an observation is consistent with the suggestion (*14*) that the rate of development of tolerance is related to the size of the alcohol-induced disturbance. Under such a hypothesis, only when responses are large would the trend due to tolerance be large enough to be detected by conventional statistical techniques. For smaller effects with the same variability, tolerance would develop more gradually and the trend would not likely be statistically significant.

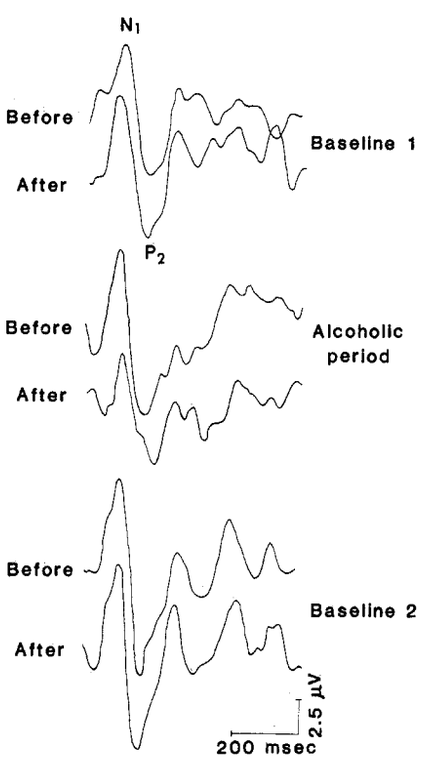

Fig. 2. Typical evoked responses.

To test the hypothesis that a relationship exists between the size of the initial effect of alcohol and the rate tolerance develops, 15 measures derived from the entire battery of electrophysiological and behavioral tests [except P_2 latency (*9*)] for both 50- and 90-dB stimuli were selected for a regression analysis of the slope of recovery and the initial size of the alcohol effect (*15*). Consistent with the hypothesis, the slopes of the various functions toward baseline over the 10-day alcohol period were significantly (*16*) related to size of the initial alcohol effect ($r = -.87$, d.f. = 14, $P < .008$). Moreover, the slope toward baseline was steeper for the EEG measures obtained with the 90-dB than with the 50-dB stimulus; the initial alcohol effect was greater with the louder stimulus. What was true for individual measures was paralleled among individual subjects; subjects with the greatest initial response to alcohol also tended to return to the before-alcohol baseline most rapidly. (For variance at 50 dB, $r = -.83$; at 90 dB, $r = -.77$, $P < .05$. For N_1 latency at 90 dB, $r = -.94$, $P < .001$. For ANR at 90 dB, $P < .10$; N_1P_2 amplitude, 90 dB, $P < .10$.)

In summary, larger initial alcohol ef-

fects were associated with more rapid adaptation to these effects. This result with human subjects is consistent with the general hypothesis of Kalant *et al.* (*14*) and in line with the view that tolerance had developed. Therefore, the absence of statistically significant tolerance in EEG measures, may not reflect a refractoriness of the alcohol-induced disturbance to the development of tolerance, but rather the small alcohol effect on the EEG at the dose studied.

The observation of both abstinence and tolerance in the EEG's of nonalcoholic volunteers supports the proposal of Begleiter and Porjesz (*2*) that EEG techniques are sufficiently sensitive to provide an assessment of the effects of both alcohol and its removal on brain activity. More important, however, the results suggest the possibility that human tolerance and abstinence can be studied in an experimental setting where severe physical dependence (as evidenced by the appearance of an acute withdrawal syndrome) need not be produced. The regimen of alcohol ingestion in this investigation was intermediate between a single exposure and long-term exposure associated with the development of dependence. Whether the tolerance and offset phenomena produced by this much exposure lie at the lower end of a continuum for their expression, or whether the events recorded are unique to subclinical exposure, cannot be answered without further investigation.

DUANE H. ZILM*
HOWARD L. KAPLAN
HOWARD CAPELL†

Human Responses and Biomedical Engineering Laboratory, Addiction Research Foundation, Toronto, Ontario, Canada M5S 2S1

References and Notes

1. J. H. Mendelson, in *The Biology of Alcoholism*, vol. 1, *Biochemistry*, B. Kissin and H. Begleiter, Eds. (Plenum, New York, 1971), p. 513.
2. H. Begleiter and B. Porjesz, *Drug Alcohol Depend.* **4**, 353 (1979).
3. G. Holmberg and S. Martens, *Q. J. Stud. Alcohol* **16**, 411 (1955); H. B. Murphree, R. E. Schultz, A. G. Jusko, *Q. J. Stud. Alcohol Suppl.* **5**, 50 (1970); R. F. Docter, P. Naitoh, J. C. Smith, *Psychosom. Med.* **28**, 605 (1966); H. Fruhstorfer and P. Soveri, *Acta Physiol. Scand.* **74**, 26A (1968); A. Salamy and H. L. Williams, *Electroencephalogr. Clin. Neurophysiol.* **35**, 3 (1973); J. R. Wolpaw and J. K. Penry, *ibid.* **44**, 458 (1978); H. J. Krogh, M. A. Khan, L. Fosvig, K. Jensen, P. Kellerups, *ibid.*, p. 1; B. S. Kopell, W. T. Roth, J. R. Tinklenberg, *Psychopharmacology* **56**, 15 (1978).
4. H. Begleiter, B. Porjesz, C. Yerre-Grubstein, *Psychopharmacologia* **37**, 15 (1974); R. W. Coger, A. M. Dymond, E. A. Serafetinides, I. Lowenstam, D. Pearson, *Biol. Psychiatry* **11**, 435 (1976); A. M. I. Wagman, R. P. Allen, R. Funderburk, D. Upright, *ibid.* **13**, 719 (1978).
5. Subjects were 26.5 years old (standard deviation, 5.1 years); their mean weekly alcohol consumption was less than the equivalent of approximately 190 g per week, and their mean consumption per occasion was the equivalent of 36 g. None had a history or record of alcohol abuse.
6. D. H. Zilm, L. Huszar, P. L. Carlen, H. L. Kaplan, D. A. Wilkinson, *Clin. Toxicol.* **16**, 345 (1980).
7. The vertex EEG (Cz referred to A_1) was digitized at 1 kHz for 650 msec after the presentation of a 1-kHz tone burst. The AEP was typically computed from responses to 128 stimuli. The ANR was computed from the variance of the average and the variance of the 650-msec EEG ensembles. The ANR is a measure of the contribution of the average response to the evoked response. The N_1 peak is the negative peak at approximately 100 msec, and P_2 is the positive peak at approximately 180 msec in the AEP. These peaks are ones of intermediate latency in the average response.
8. Withdrawal effects here refer to changes of the EEG in a direction opposite to that produced by alcohol. The withdrawal is not that associated with established physical dependence since we sought to avoid exposing nonalcoholics to amounts and durations of alcohol associated with the production of physical dependence. Rather than refer to withdrawal, we prefer "offset" effects to underline their association with a state intermediate between that produced by a single exposure and truly long-term exposures. Whether such offset effects reflect anticipation of receiving alcohol each day, an interaction between such anticipation and increased central nervous system excitability, or a partially developed hyperexcitability with the relatively modest alcohol exposure cannot be answered from these results. The presence of offset effects was not unique to the evoked EEG; mean before-beverage hand tremor increased significantly over the 10-day alcohol phase ($r = .70$, $P < .05$).
9. The effect of alcohol on P_2 latency was equivocal, increasing with the 90-dB stimulus and decreasing with the 50-dB stimulus. The response of P_2 latency to alcohol has been equivocal in the literature as well; therefore this measure was omitted in subsequent analyses of the data.
10. No significant difference was found between before- and after-beverage means during the initial baseline period. They were not combined for the computation of changes during the alcohol and baseline-2 periods because conditions for before and after measurements were not equivalent. Not only were the EEG measures approximately 2 hours apart, but the conduct of additional elements of the measurement battery and the consumption of a beverage took place in the interval between the two.
11. D. H. Zilm, H. L. Kaplan, H. Cappell. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **39**, 597 (1980).
12. L. Wolff, D. H. Zilm, C. X. Poulos, H. L. Kaplan, H. Cappell, paper presented to the annual meeting of the Eastern Psychological Association, Hartford, Conn., 9 to 11 April 1980.
13. Mean breath alcohol concentrations measured 35 minutes after the subject drank the alcohol ranged from 75 to 85 mg per 100 ml on each of the ten alcohol days. The concentrations showed no evidence of metabolic tolerance.
14. H. Kalant, A. E. LeBlanc, R. J. Gibbins, in *Biological Bases of Alcoholism*, Y. Israel and J. Mardones, Eds. (Wiley, New York, 1971), p. 235.
15. The size of the alcohol effect for each variable was computed as the fractional change of the first three alcohol days from the initial 3-day baseline. The slope was computed from the regression of the mean daily responses over the alcohol period divided by the baseline mean. The slope was expressed in units of reciprocal days and was therefore comparable between measures. No practice effects or habituation were found either in the first three baseline days or in the before-beverage values for the alcohol period with the exception of eye movements. In this case, the before-beverage slope was used to correct after-beverage values during the alcohol period.
16. The initial alcohol effect and slope are not statistically independent; if a response attributed to the alcohol effect happens, by chance, to be above (or below) its expected value (its baseline), there would be an expected negative (or positive) slope over the next 10 days. Our observed correlation ($-.87$) lies at the extreme points on a Monte-Carlo distribution generated under the null hypothesis, and the P value reported is based on such a distribution arrived at by simulation.
17. We thank L. Ramsay and L. Wolff for helping us conduct the investigation and analyze the data.

* Present address: Regional Biomedical Engineering, Kelowna, B.C., Canada V1Y 1T2.
† Reprint requests should be sent to H.C.

8 August 1980; revised 10 December 1980