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CHAPTER 10

The Effects of Alcohol on the Central Nervous System in Humans

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INTRODUCTION: RESEARCH QUESTIONS AND METHODOLOGICAL PROBLEMS

Although gross changes in personality and behavior are readily apparent during acute alcoholic intoxication, these changes have only become the subject of systematic study within the past 100 years. Miles (1932) has summarized the different stages of clinical intoxication in the form of a scale relating the subjective states and typical behavioral changes seen with increasing blood alcohol levels. The earliest effects, tingling sensations in the mucous membrane of the mouth and throat, may appear with a blood alcohol level as low as 10 mg%. At the upper extreme (300 mg%) the subject passes into a stuporous condition, and at still higher levels (400 mg%) falls into a state of deep anesthesia which may end in death. This description of successive stages in clinical intoxication represents the typical or modal response commonly seen with a given blood

alcohol level. The association between blood alcohol concentration and stages of clinical intoxication is not a clear one-to-one relationship. As with other psychotropic drugs, there are large individual differences in response to a given dosage as well as considerable variability in the subject's response at different times or in different settings.

The Miles scale summarizes the changes in subjective states and social behavior induced by drinking. More recently Carpenter (1962) has reviewed the experimental literature dealing with the effects of alcohol on sensory functions and different measures of motor performance. Since the various changes in subjective states, personality characteristics, and changes in sensory and motor functioning are mediated by alterations in the activity of the central nervous system under alcohol, considerable research effort has been devoted to uncovering possible electrophysiological correlates of these psychological changes. An extensive literature has accumulated on the effects of alcohol on the neural functioning in animals using implanted electrodes to study single unit and mass activity in different brain structures. Human studies have been largely limited to scalp-recorded measures of brain activity. The raw electroencephalogram yields a number of frequency and associated amplitude characteristics which may be scored separately, or combined in the form of a spectrum analysis showing percent time or amount of energy plotted as a function of wave frequency. For clinical purposes and for evaluating toxic drug effects, the amount of EEG abnormality is frequently evaluated by means of relatively standard criteria on a 4- or 5-point pathology scale.

The EEG provides an ongoing record of the neuroelectric activity of the brain, either in the resting state or under different activation procedures (hyperventilation, repetitive photic stimulation, drug ingestion, etc.). The neural response to stimulation in different sensory modalities may also be examined by time locking the recording to successive presentations of a repetitive stimulus. Such summated measures of neural activity as the average evoked response and the recovery function show the neural response to specific stimulation which is frequently hard to detect or to analyze in the ongoing EEG record.

Although admittedly the scalp-recorded EEG is a gross measure of brain activity, it provides the best and most direct measure currently available for assessing the functional state of the central nervous system, and detecting abnormal or impaired functioning found in certain pathological states. (The pneumoencephalograph will frequently provide confirmatory evidence when EEG abnormalities are related to structural changes or brain damage.)

The ability to monitor ongoing brain activity makes it possible for researchers to examine the relationship between subjective states, behavioral changes, and the electrophysiological activity of the central nervous system. In the field of alcoholism early interest was focused primarily on investigating whether the ingestion of alcohol affected the EEG and whether chronic alcoholics show

increased evidence of EEG abnormalities. Of particular interest is the question whether alcohol-induced changes in the EEG closely parallel the more or less stepwise changes in subjective state and behavior during drinking. Unfortunately a parametric dosage study showing changes in the EEG as a function of increasing blood alcohol level over the full range of values has not yet been systematically done. This is the counterpart of the Miles scale of subjective and behavioral changes commonly found at given concentrations of blood alcohol and is needed to determine the degree of correspondence between psychological changes and changes in the electrophysiological activity of the brain during intoxication.

The second question has a more practical goal. If distinctive EEG signs are characteristic of the chronic alcoholic, these may point to possible neural mechanisms underlying alcohol-related symptomatology and provide some basis for the diagnosis and treatment of the alcoholic during the course of the disease.

As is true in most research areas, what appeared to be easily answered questions—does alcohol affect the EEG and do chronic alcoholics show distinguishing EEG characteristics—turned out to be difficult to investigate. These questions break down into a series of questions requiring investigation, some of which present difficult methodological problems which make clear-cut answers hard to obtain. The review of the literature will be organized around these basic questions:

The Effects of Alcohol on the Electroencephalogram

1. Does alcohol affect the electrical activity of the brain as measured by the EEG?
2. Are alcohol-induced changes in the EEG either quantitatively or qualitatively different in the chronic drinker as compared to the nonalcoholic?
   a. Do alcoholics show EEG differences reflecting tolerance effects due to the prolonged use of alcohol or differences related to impaired efficiency of alcohol metabolism due to liver damage, etc.?
3. Does the EEG change progressively during extended periods of drinking?
   a. Is there evidence for either tolerance or sensitization effects on CNS activity during sustained high blood alcohol levels?
4. Is alcohol a central nervous system depressant, or does it have both a stimulant and depressant action depending upon dose level and time of testing, as some investigators have suggested (see Mello and Mendelson, 1968)?

Comparison of EEG Recordings in Alcoholics *vs.* Nonalcoholics

1. Are the EEG's of chronic alcoholics between drinking bouts different from those of nonalcoholics?

2. Do alcoholics have a higher incidence of abnormal recordings (persistent arrhythmias and dysrhythmias, paroxysmal spiking, etc.) than normal controls?
   a. To what extent does the impairment in cerebral functioning reflect underlying structural pathology or brain damage?
3. If EEG abnormalities are more frequent in alcoholics, do these abnormalities appear in the resting EEG or only under activation procedures?
   a. Is the cerebral dysfunction widespread or predominately localized in specific brain areas?
4. Do differences in the EEG precede the development of alcoholism or only occur following several years of sustained drinking?
   a. If such differences exist, are they related to the predisposing causes of alcoholism or primarily the effects of drinking?
   b. Does the extent of such changes have any diagnostic or prognostic utility in assessing either the severity or the clinical course of the illness, or the nature and extent of underlying brain damage caused by alcohol?

The Electroencephalogram During Acute Alcoholic Psychosis

1. Are there distinctive EEG signs characteristic of the acute withdrawal syndrome?
   a. Do these signs change progressively during the course of the illness and subsequent recovery?
2. Are there distinctive EEG signs differentially associated with the specific symptom patterns seen during alcoholic psychosis: hallucinosis, convulsive seizures, delirium, etc.?
3. Do changes in the EEG rhythm occur only during the course of the illness, or are there long-lasting changes indicating functional pathology and possible permanent CNS damage?

Specific methodological questions raised by the studies reviewed will be discussed in the main body of the text. However, since some methodological problems occur so frequently, they will be considered at this point.

Definition of the Chronic Alcoholic and Selection of Study Samples

Since most studies of alcoholism are carried out in a hospital, setting the diagnosis of "chronic alcoholism" is implicitly defined by two criteria: (1) a history of drinking, and (2) the occurrence of alcohol-related symptoms severe enough to require hospitalization. Because of this bias in sampling, if studies of patients report a higher incidence of EEG abnormalities, this should not be interpreted to mean either that the chronic use of alcohol generally produces

cerebral dysfunctioning, or that a completely random sample of alcoholics would show a higher incidence of abnormalities. Hospital-based samples include only patients in whom drinking produced severe symptomatology and also necessarily excludes those persons in whom heavy drinking did not produce psychiatric symptoms. These two groups, although similar in their consumption of alcohol, are undoubtedly quite different in other characteristics, possibly including their response to alcohol and their EEG records. An alternative hypothesis which requires testing is that individuals with preexisting abnormalities are also more likely to develop psychiatric symptoms as a result of drinking and consequently be more likely to be hospitalized.

Hospital-based samples are biased in other ways which affect the interpretation placed on the reported frequency of abnormalities found in these groups. Upper middle-class and upper-class patients more frequently enter private hospitals than state hospitals, and if they do enter the latter, are perhaps more often admitted to a general medical rather than a detoxification ward. Patients admitted with alcohol-related physical symptoms (cirrhosis, alcohol-aggravated ulceritis, etc.) rather than psychiatric symptoms are also less likely to be included in studies of chronic alcoholism. Such implicit selection of patients making up the group defined as "chronic alcoholics" necessarily qualifies the interpretation placed on the frequency of EEG abnormalities reported in the literature.

A related problem which helps to account for some of the discrepancies between studies is the wide individual differences in patients who are diagnosed as "chronic alcoholics" (cf. Kaim *et al.*, 1968). The only characteristic which they appear to have in common is hospitalization because of alcohol-related symptoms, while they may differ markedly in the pattern or type of drinking, amount of alcohol consumption, duration of drinking, history of alcohol-related disturbances, and nature of presenting symptoms. And contrary to some psychoanalytic writers, there are little objective data supporting the hypothesis that alcoholics share a common personality pattern (Shagass and Jones, 1957). Some researchers (e.g., Arentsen and Sindrup, 1963; Predescu *et al.*, 1967) have attempted to deal with this problem by breaking their sample down into various psychiatric groups (normal, psychopathic, neurotic, psychotic, etc.). While this procedure is useful for obtaining clinical information about subgroups of alcoholics, it is of doubtful value in assessing the effects of chronic alcoholism *per se* on CNS functioning. Since psychopathic personalities (Knott, 1965; Simon, O'Leary and Ryan, 1946) and neurotics (Wilson and Short, 1965) also show a higher incidence of EEG abnormalities, the role of alcoholism in these groups is difficult to assess.

Generally, the more homogeneous the sample, the greater the reliability of the data, and the more interpretable the findings. Perhaps one way out of the dilemma which has not yet been tried systematically would involve the classification of patients into relatively homogeneous subgroups either in terms of their

past medical history or in terms of their current symptomatology. Jellinek's (1946) interview schedule on the phases of the drinking history records the time of the first appearance of the behavioral symptoms defining chronic alcoholism: morning drinking, sleeping difficulties, uncontrollable tremors, first appearance of amnesia or blackouts, hallucinations, delirium, etc. Since these symptoms tend to occur in a natural sequence and generally appear within a fixed number of years of heavy drinking, the questionnaire provides a natural index of the progression and severity of the disease prior to hospitalization. If chronic drinking does result in permanent impairment of CNS functioning, the incidence of EEG abnormalities should show a progressive increase related to the severity of the score on the Jellinek scale.

Differences in the kinds of patients included in the alcoholic samples studied at different hospitals probably account for much of the discrepancy in the reported frequency of EEG abnormalities in alcoholics and for the controversy as to whether this incidence is significantly greater than in normal subjects. Contributing to the problem of comparability of studies is the tendency of individual researchers to use different criteria in subject selection. In the papers to be reviewed, subjects range from nonhospitalized individuals with a history of heavy drinking to patients hospitalized with delirium tremens. Criteria for inclusion in different studies varied from selection on the basis of the occurrence of specific symptoms (e.g., blackouts) in the medical case history, to the presence of specific characteristics in the EEG record (e.g., occurrence of a predominant alpha pattern).

Nature of the Control Group

The logic of the control group requires that it be identical to the experimental group in all characteristics except the variable being investigated. However, in most studies of group differences, the variable defining membership in a clinical group is also associated with a number of other extraneous characteristics which differ from a true random sample (Feldman and Hass, 1970). Where possible, the experimental and control groups are matched on extraneous variables which might be expected to affect the dependent variable being studied.

If matching is not adequately done, the interpretation of group differences becomes quite ambiguous. As an example, alcoholics as a group have a history of more frequent accidents involving head injuries with consequent brain trauma than the normal population. Since such trauma may also affect cerebral activity, the possible finding of a higher incidence of pathological EEG's in alcoholics, while characteristic of alcoholics as a clinical group, could not be interpreted as evidence that alcohol *per se* results in functional brain impairment. Similarly, although Korsakov's psychosis and Wernicke's disease are commonly associated with a history of heavy drinking, the neurological deterioration found in these

disorders is attributed to thiamine deficiency and not to alcohol (Victor and Adams, 1953). In Laennec's cirrhosis, the EEG abnormalities are a result of the toxic effect of high blood ammonia levels leading to hepatic coma (Green, 1965). Although these states are typically the result of prolonged heavy drinking, the EEG abnormalities characterizing them cannot be interpreted as evidence of a direct effect of alcohol on CNS functioning.

Sometimes even the most obvious contaminating variables are not controlled by matching. In one study alcoholic patients were classified on the basis of the presence or absence of EEG abnormalities, but age was not controlled. Patients showing EEG abnormalities in general were slightly older than the other group. Since age had the same effect on the dependent variable being investigated (alpha blocking) as the independent variable (EEG), it is difficult to determine how much of the reported difference is actually related to the EEG differences.

Longitudinal *vs.* Cross-Sectional Studies

Since alcoholics only become available for evaluation when they are hospitalized, almost all of the studies reported in the literature are limited to data collected at a single point of time during the life history of the alcoholic. While such cross-sectional studies are useful in establishing that two variables are correlated, the meaning of the association and the direction of the causal relation are frequently difficult to interpret. Two examples from the literature on alcoholism illustrate the difficulty involved. Several investigators (cf. Greenblatt *et al.*, 1944) have reported that the frequency of EEG abnormalities increases in older alcoholics. The usual interpretation is that age is related to the length of drinking and that cerebral dysfunctioning is more frequent since the patient has been exposed to the toxic effects of alcohol for a longer time. However, an alternative interpretation is possible. Several studies on the treatment of outpatient alcoholics indicate that those patients most likely to become abstinent are those showing least pathology on both social and psychological measures of adjustment (Kissin and Platz, 1968). Possibly older alcoholics show greater pathology than younger patients primarily because the more "healthy" alcoholics have become abstinent and consequently dropped out of the sample at each successive age grouping. How much of the increased pathology in the older group is related to age *vs.* selective dropout of the healthier alcoholics can only be adequately determined by a longitudinal study with repeated measurements of the same subjects over time.

A second illustration relates to the interpretation of EEG differences between heavy drinkers and nondrinkers. Although it is questionable whether alcoholics as a group show an increased incidence of EEG abnormalities, there are consistent findings across several studies indicating differences in alpha

activity compared to normal controls (Davis *et al.*, 1941; Funkhouser, 1953; Little and McAvoy, 1952). However, since the findings are based on a single testing of patients with a long history of drinking, the temporal or causal relation between the impoverished alpha and alcoholism is unclear. Two rival interpretations may be suggested: (1) the impoverished alpha pattern precedes heavy drinking and may be related to possible neurological and psychological states which predispose the individual to alcoholism; or (2) the poor alpha is a neurological consequence of prolonged drinking. Again, it is clear that a longitudinal study involving repeated measurements is necessary in order to choose between the rival hypotheses.

Time of Testing and Concurrent Medication

Since most of the generalizations about the electroencephalogram in alcoholism are made on the basis of tests run on patients hospitalized for acute withdrawal effects, it is important to know the clinical state of the patient, the time of testing in relation to the cessation of drinking, and whether the patient was under medication at the time of testing. This information is frequently not reported or the variable adequately controlled.

On the basis of extensive observation of the withdrawal pattern, Victor and Adams (1953) have concluded that the appearance of symptoms falls into three distinct stages: (1) tremulousness and transient hallucinosis; (2) seizures; and (3) motor and autonomic hyperactivity and confusional states, which follow a somewhat different time course. The incidence of tremulousness and hallucinosis peaks during the first 24 hr following cessation of drinking. Seizures peak slightly later, while the incidence of delirium and confusional states is greatest between 72 and 96 hr postdrinking. Not all patients show the same symptoms, and the time of appearance and duration of symptoms varies widely. Approximately 90% of the patients are symptom-free by the fifth day, although in some cases symptoms may persist for as long as 2 weeks.

That the time course of the separate components of the withdrawal syndrome is related to CNS excitability is shown in a subsequent study by Victor and Brausch (1967). Patients during withdrawal were tested at 4- to 8-hr intervals by exposure to fast frequency photic stimulation (4–24 Hz). The incidence of abnormal photic responses (photomyoclonus, photoconvulsions, or paroxysmal discharges on the EEG) showed a close temporal relationship to the time course of spontaneous seizures. Photosensitivity tended to be greatest shortly after the occurrence of a seizure, and lasted from several hours to as long as 4 days. Patients not showing overt seizures showed a similar time course of photosensitivity. Of 84 patients, only one showed an abnormal photic response during the first 12 hr immediately following cessation of drinking, and by 72 hr the frequency had dropped to near zero. Peak frequency occurred between 31 and

48 hr. Lloyd-Smith and Gloor (1961) also report that CNS hyperexcitability characteristic of the withdrawal state is associated with heightened sensitivity to photic flicker which may produce epileptiform disturbances in the EEG.

The Victor and Brausch data indicate that the time of testing should be known in order to evaluate the frequency of abnormalities obtained in alcoholics compared to the observed rate in normals. The frequency of paroxysmal spiking in the photically activated EEG is time related, with the period of photosensitivity transient and generally limited to the five days immediately following alcohol withdrawal. Testing during this period would give a falsely high estimate of EEG abnormalities in alcoholics if the results were generalized to nonhospitalized alcoholics or alcoholics between drinking bouts.

A related problem in drawing conclusions about chronic alcoholics as a group from data based on hospitalized patients is that the latter are frequently under medication at the time of testing. In one study 90% of the patients were tested within 2 weeks of admission (exact time neither specified nor analyzed in relation to incidence of abnormalities) and 60% "were known to be on" some type of medication, generally a phenothiazine or barbiturate. Another study reports approximately 50% of its patients having received Antabuse sometime within the week preceding testing. While the effects of such drugs on the EEG are not precisely known, a recent study by Ulett *et al.* (1965) should make one extremely cautious in making generalizations about the EEG of alcoholics on the basis of patients who have recently received drug treatment. Ulett *et al.* studied the effects of eight ataractic drugs, each administered for a period of 3 weeks, on the electroencephalogram of 21 psychiatric patients. Changes in the EEG occurred with all drugs, with the drugs distinguishable on the basis of the effects produced. Although the drugs were distinguishable and there were marked individual differences in response, the usual pattern seen under tranquilization was a slowing in frequency and an increase in dysrhythmias. Some phenothiazines (notably chlorpromazine) induced paroxysmal discharges in some nonepileptic patients, especially at higher dose levels. Especially noteworthy in connection with alcoholism studies were two findings: (1) a majority of the drugs produced a worsening of the dysrhythmia in patients who showed evidence of dysrhythmia prior to medication, and (2) typically, the effects of the drugs were still evident in the EEG as long as 5 or 6 weeks after medication had been discontinued. In one case (chlorpromazine) effects were still present after 10 weeks.

A similar problem arises in investigating whether the EEG shows systematic changes characteristic of the different stages of the withdrawal syndrome. If a treatment drug like paraldehyde is prescribed, its chemical similarity to alcohol may produce some degree of cross tolerance which would attenuate the full-scale development of withdrawal symptoms.

The methodological problems discussed are common to many of the studies in the area and provide the framework for evaluating the reliability and validity of the findings reported in the specific studies reviewed. The review will be divided into four sections and be limited to human studies:

I. The Electroencephalogram in Chronic Alcoholics
II. The Effects of Short-Term Alcohol Administration on the Electroencephalogram
III. The Effects of Long-Term Alcohol Administration on the Electroencephalogram
IV. The Effects of Alcohol on the Average Evoked Response and Recovery Function

THE ELECTROENCEPHALOGRAM IN CHRONIC ALCOHOLICS

The electroencephalogram provides an index of the ongoing electrophysiological activity of the brain and a basis for assessing the functional and structural changes resulting from brain injuries and various toxic conditions such as acute alcoholic intoxication. In interpreting the EEG in alcoholism studies, several questions must be kept in mind in determining whether the reported findings are characteristic of chronic alcoholics as a group, or whether they are temporary manifestations which reflect either current signs or sequelae of the acute illness for which the patient was hospitalized. Since the acute phase of withdrawal typically lasts from 3 to 7 days, aberrations in the EEG's taken during this period may characterize only the course of the illness. In addition, the report by Ulett *et al.* (1965) that changes in the EEG induced by 3 weeks' administration of chlorpromazine can still be detected in the recordings up to 10 weeks after cessation of the drug should increase one's caution in generalizing about the EEG pattern based on alcoholics undergoing medical treatment. Although several experimental studies involving sustained alcoholization over a period of weeks have been reported, there is little comparable data on how long EEG changes may persist after the termination of drinking. Mello and Mendelson (1968) emphasize that most patients admitted with withdrawal signs usually have a number of intercurrent illnesses (primarily nutritional deficiencies) which may also contribute to derangements in mental states. Finally, if the patient is tested while still being treated with psychoactive drugs, or even for a period of several weeks after discontinuance of the drug, this may have an undeterminable effect on the EEG, making it impossible to separate changes attributable to alcoholism from those due to other causes. The research literature will be reviewed with these considerations in mind in evaluating the reported findings. In each section one or two studies will be examined in detail in order

to focus on the methodological problems common to many studies in the area, and then the findings of the remaining studies will be briefly summarized.

One of the best and most extensive electroencephalographic investigations of chronic alcoholics is a Danish study by Arentsen and Sindrup (1963) based on a mixed sample of 317 hospitalized and outpatient alcoholics. Approximately one-third of the patients had not received any medication for at least 8 days prior to testing; the remaining two-thirds were under a daily regimen of disulfiram. Although not explicitly stated, the manner in which patients were selected suggests that a very large percent had not been drinking heavily for at least a week preceding testing, nor were they acutely ill when the EEG was administered. The incidence of serious medical complications due to alcoholism (delirium tremens, convulsions, etc.) was apparently low, and the patients probably less seriously disturbed than those usually included in American studies.

Twenty-one percent showed either borderline or slightly abnormal EEG's; 11% had moderate to severe abnormalities. Approximately half the abnormalities were exclusively or mainly in the temporal region. Two-thirds of the abnormal records were characterized by diffuse theta activity (4–7 cycles/sec). In comparison, the base rate for EEG abnormalities in "normals" is usually reported to run between 10 to 15%.

The incidence of abnormalities was further studied in more homogeneous subgroups of patients classified by either drinking pattern or psychiatric diagnosis. The simple alcoholic (excessive social drinking) showed a 13% rate of abnormality, which falls within the range reported for normals. Symptomatic alcoholism (dipsomania without loss of control of drinking) and addictive alcoholism (loss of control) had abnormality rates of 39% and 30% respectively. In the "complicated" group (history of delirium tremens, seizures, etc.) six of eight patients showed abnormalities.

The psychiatric classification was also related to the incidence of abnormalities, with the lowest rate in the "normal" group (18%); intermediate in the neurotics (25%) and highest in the psychopaths (42%). Several other writers have reported similar findings, with the percent of patients showing EEG irregularities generally increasing with the severity of the concurrent psychiatric illness (Predescu *et al.*, 1967; Greenblatt *et al.*, 1944). The rate reported for specific diagnostic categories, however, varies widely, presumably because certain psychiatric classifications are difficult to make reliably and because different investigators use somewhat different criteria for rating pathological signs in the electroencephalogram. The findings, although valid from a clinical point of view in describing the electroencephalographic picture of different subgroups of alcoholics, are difficult to interpret. Many of the functional mental disorders are also associated with an increased frequency of EEG abnormalities (Wilson, 1965). Data indicating whether the alcoholic who is also psychotic or

psychopathic differs in degree, kind, or frequency of EEG abnormalities from the nonalcoholic psychotic or psychopath are not reported. Consequently, one cannot assess to what degree chronic drinking has contributed to the observed pathology in cerebral functioning.

The occurrence of abnormality was not related to age which, the authors state, distinguishes alcoholism from other psychiatric disorders where there is a tendency toward decreasing abnormalities with increasing age. However, Greenblatt (1944) in a study investigating the relation between EEG abnormalities and age reports a trend toward increasing abnormalities in older psychiatric patients, including neurotics and psychopaths. The relation between age and EEG findings in alcoholics is difficult to interpret with cross-section sampling since the patients hospitalized in their twenties may differ on a number of extraneous variables from patients hospitalized in their fifties. As a single example, the age of Negroes at the time of first hospitalization for alcoholism is several years younger than whites, and the mortality rate higher at any given age level. If this factor alone were operating, it would produce a consistent decrease in the percent of Negroes in each successively older age sample. Only a relatively small percent of patients hospitalized in their twenties for detoxification are hospitalized again for the same reason in their fifties. Since the nature of the patient sample is changing in a number of unknown ways, which may be reflected in the EEG findings, the effect of age *per se* can only be evaluated on the basis of longitudinal studies using repeated tests on the same individuals.

A weakness in the authors' interpretation of their data is illustrative of one of the pitfalls frequent in studies in this area. The authors point out that in the normal group the incidence of abnormalities in "simple alcoholism" is 1 in 23, while in "addictive alcoholism" it is 13 out of 62. They suggest that "addiction" to alcohol causes brain damage which is reflected in the increased percent of EEG irregularities. An analysis of their data ($X^2 = 2.27$, $p < 0.20$) indicates that this difference is not statistically significant; that is, a difference this large could be due to sampling error rather than to the independent variable (type of drinking) being investigated. (Many studies in this area lack adequate statistical analyses, with the result that much time is spent discussing data which are not statistically significant.) Second, the groups based on drinking pattern probably vary systematically on a number of other variables, and since they are based on different "kinds" of people, the possibility exists that the EEG differences antedated and were possibly a causative factor in the development of the drinking pattern rather than a consequence of it. The failure to find an effect related to age, which should be highly correlated with length of drinking, also weakens the argument somewhat. In contrast to these findings, Greenblatt *et al.* (1944) in a study of 157 hospitalized chronic alcoholics reported increased EEG pathology with age, which was especially marked in the over-50 group. The two studies are strikingly discrepant in their under-30 group where Greenblatt *et al.* report

a 5% incidence of abnormalities (higher than his "normal" control group) while Arentsen and Sindrup report a 39% incidence (the highest of all their age groups). Greenblatt *et al.* also report that while age is related to EEG abnormalities, duration of chronic drinking in nonpsychotic alcoholics is not associated with increased abnormality. Since one would normally expect age and duration of drinking to correlate highly, this finding would also suggest that the nature of the patient sample has changed systematically over the age groups studied. The use of correlational procedures to measure the degree of association between such variables as age or length of drinking and measure of pathology would help in partialling out the contribution each makes in producing EEG irregularities. Until this is done within a well-designed longitudinal study, it will be difficult to specify the precise role that duration of drinking (with age statistically controlled by partial correlation procedures) or age may play in producing EEG pathology. Similarly, alcoholics subdivided into various psychiatric groupings should be compared to the appropriate group of psychiatric patients rather than to a normal group in order to control for the effect of an extraneous variable (mental illness) on the dependent variable.

The findings of similar studies on the incidence of EEG pathology in chronic alcoholics may be briefly summarized. Dyken *et al.* (1961) report that approximately 10% of their sample of 553 patients admitted to an alcoholic care unit showed minimal to marked abnormalities in the electroencephalogram. However, in 70% of the cases where the abnormality was marked, causes other than alcoholism (severe head trauma, syphilitic damage to the central nervous system, evidence of epilepsy preceding alcoholism, etc.) were also present. Since the incidence of EEG abnormalities in their patient group is comparable to the usual base rate found in normative samples, the authors conservatively conclude that if long-term drinking impairs CNS functioning, this impairment may not necessarily be reflected in the EEG record.

As reported earlier, Greenblatt *et al.* (1944) found only a 5% incidence of EEG abnormalities in their subgroup of alcoholics without psychoses. Arentsen and Sindrup's (1963) "simple" alcoholic group showed a 13% abnormality rate. Funkhouser *et al.* (1953) report that in a group of 81 "uncomplicated" alcoholics (patients who had never shown convulsions or psychotic manifestations) 21% showed either abnormally fast or slow wave activity. Little and McAvoy (1952) report that 80% of their alcoholic group had normal records as compared to 84% of their normal control group. The alcoholics included showed no evidence of mental deterioration or CNS disease, and were not intoxicated or in delirium tremens when tested.

In summary, several studies report that the percent of EEG abnormalities found in chronic alcoholics without complications ranges from approximately 5 to 20%, which is roughly comparable to the 10–15% incidence usually accepted as a normal base rate. As suggested earlier, considerable fluctuation in the

incidence of reported abnormalities is to be expected across studies for a number of reasons: differences in the makeup and selection of the patient sample, differences in the length of time between the patient's last intoxication and the electroencephalographic examination, frequent lack of control of concurrent medication, and the less than perfect reliability and the use of somewhat different criteria in the ratings of EEG abnormalities. Interestingly, European investigators tend to report considerably higher percentages of abnormal recordings for alcoholics (Delay *et al.*, 1957; Lafon *et al.*, 1956). Partly this is due to the use of somewhat less severe criteria for judging abnormalities, as suggested by Arentsen and Sindrup, or possibly to differences in the type of liquor, especially wines, consumed. In an American sample Dyken *et al.* (1961) consider the excessive use of wine to be a sign of the increasing severity of the drinking problem. Murphree, Schultz, and Jusko (1970) have also reported that the congener content of liquor affects the EEG, so possibly differences resulting from the long-term use of different beverages might also reasonably be expected. The effects of absinthe in producing brain damage, which resulted in its prohibition, is perhaps an obvious example.

The American studies generally support the conclusion by Naitoh and Docter (1968) and Green (1965) that chronic alcoholism without complications is not associated with pathological changes in the EEG rhythm in the form of persistent arrhythmias and dysrhythmia or abnormal spikings and paroxysmal high voltage slow waves. This conclusion can only be tentative on the basis of the available research and should be supported by additional studies. A longitudinal study of changes in the same subjects over time is needed so that the incidence of EEG abnormalities may be plotted as a function of duration of drinking. These data would provide a more definitive answer to the question of whether progressive changes occur during long-term excessive drinking. Studies reporting significantly higher rates of abnormality in different subgroups of alcoholics also require replication with appropriate control groups in order to assess the relative contribution of alcoholism *vs.* psychiatric disorders in EEG abnormalities.

As reported earlier, Arentsen and Sindrup (1963) found impairment in cerebral functioning to increase with severity of the drinking problem ("type of drinking pattern") and with the severity of concurrently present psychiatric symptoms. The classification of drinking pattern is somewhat confusing since it is apparently based on two different variables: degree of control over drinking and the past occurrence of alcohol-related psychiatric disorders. Because of this confusion, and the selective nature of patients included in both classification systems, it is difficult to tell whether the increased EEG pathology is necessarily related to excessive alcoholism or may be primarily accounted for by pre-existing patient characteristics. Greenblatt *et al.* (1944) report that a ranking of clinical groups of alcoholics in terms of the incidence of EEG abnormalities

roughly corresponds to the severity of the clinical picture, chronicity of symptoms, and "probably the severity and extent" of brain damage. Especially high rates of abnormality are associated with "alcoholic deterioration" and Korsakov's psychosis.

Lafon *et al.* (1956) found minimal to severe disturbances in the EEG pattern of 80% of nonselected chronic alcoholics admitted for detoxification or seen during periods of severe agitation. Although some of the cases had severe psychiatric and neurological symptoms, the high rate of abnormality may be attributed primarily to the use of somewhat lenient criteria for judging EEG disturbances and to the testing of patients during the clinical course of the withdrawal syndrome. The most frequent findings were instability or disappearance of the alpha rhythm and the occurrence of low voltage, fast activity, both common characteristics of agitated states. Somewhat more compelling are the pneumoencephalographic findings of some degree of cerebral atrophy in 78% of the cases, the atrophy generally being diffuse in nature and frequently "latent" in its clinical expression. (The base rate using the same criteria on patients in the same age range is not known.) In 58% of the cases there is good correspondence between the electroencephalographic and pneumoencephalographic findings. In long-term alcoholics severe cortical atrophy was associated with marked perturbations of the EEG, while mild EEG disturbances were associated with relatively discrete cerebral atrophy. Although the correspondence is apparently striking in specific cases, the authors do not evaluate whether the overall correspondence between the PEG and EEG was significantly different from chance in terms of the criteria used for evaluating deviations from normal functioning. On a chance basis, if the two measures were not related, one would expect to find a 66% agreement between the presence or absence of irregularities in the EEG pattern and evidence of cerebral atrophy ($\overline{78.80 + 22.20}$). Whether the actual correspondence is significantly greater than this is not clear from the data.

Predescu *et al.* (1967) also found increasing EEG disturbances paralleling the severity of concomitant psychological disorders. Approximately 22% of their sample showed moderate to severe anomalies, mostly diffuse theta and delta waves and medium voltage spiking in the frontal and temporal regions.

In a series of papers, Bennett and his associates (1956, 1960a, 1960b, 1967) have argued that EEG abnormalities indicate the existence of "alcoholic brain disease" which in the chronic stage (organic dementia, or Korsakov's and Wernicke's disease) is usually characterized by nonreversible brain damage. [However, Victor and Adams (1953) have pointed out that some of the symptoms of Wernicke's disease are partially reversible by thiamine administration.] Eighty percent of 48 patients in the chronic stage showed EEG abnormalities. Of 11 patients given psychological testing, all showed evidence of organic brain damage, and seven of eight patients evaluated by the PEG showed signs of

cortical atrophy. In general, the more severe the "alcoholic brain disease," the less reversible the pathology shown in the EEG records. In repeat examinations 87% of the "acute stage" showed decreased abnormality, 54% of the "intermediate stage," but only 25% of the chronic showed improvement, while 16% actually showed increased abnormality. (The interval between testings is not given, but apparently ranged from several days to over a year. It is not possible to tell from the data whether the interval between tests was approximately the same for the three groups, or to what extent the length of time between testings was related to the probability of improvement.)

Although severe abnormalities in the EEG do not occur with greater frequency than in normal groups except in the case of advanced, deteriorated alcoholics, there is considerable evidence that the percent alpha time and characteristics of the alpha rhythm differ significantly between alcoholics and normals. Davis *et al.* (1941) were among the first to point out this difference. In a group of hospitalized chronic alcoholics they observed that only two of 15 patients showed a strong alpha pattern, the most common pattern found in relaxed normal subjects, while 13 of their patients showed mixed frequency records. The period of time elapsing between the EEG examination and cessation of drinking was not reported so that one cannot judge whether the poor alpha pattern is characteristic of the chronic alcoholic (either as a result of prolonged drinking or as an antecedent characteristic of CNS functioning which may be a predisposing factor in alcohol addiction), or whether the impoverished alpha is a transient characteristic of the withdrawal syndrome. Patients newly admitted for detoxification are typically in a state of heightened anxiety or agitation which is frequently associated with a poor or unstable alpha pattern and the presence of diffuse, low voltage, fast activity beta waves (Henry, 1965; Wilson and Short, 1965; Lafon *et al.*, 1956; Predescu *et al.*, 1967). Bennett *et al.* (1956) note that the heightened percentage of fast activity decreases gradually during treatment and that clinical improvement seems to coincide with the restoration of normal alpha activity. Varga and Nagy (1960) noted similar changes in newly admitted patients tested the first day after withdrawal and again at 2 weeks. Using a visual histogram method, they found a relative shift of the frequency band toward the slower frequencies and less dispersion across frequencies. Usually a dominant alpha frequency appeared at 2 weeks or grew stronger if previously present. However, the period required for normalization of the EEG pattern may extend over a period of several days to as long as several weeks in some cases. Kennard *et al.* (1945) also noted that during symptomatic recovery from delirium tremens there was a parallel decrease in the amount of fast activity and either an initial appearance or increase in slower alpha activity. Corresponding increases in amplitude and regularity in the EEG rhythm occurred during the same period. Patients who showed the most fast activity and lowest amplitude at the onset of delirium generally showed the slowest recovery rate.

In this connection the observation by Engel and Rosenbaum (1945) that a moderate dosage of ethanol (1 g/kg of body weight) resulted in some abnormally fast records becoming more "normal" during intoxication is of interest. It is now generally accepted that withdrawal symptoms are usually precipitated either by abrupt cessation of drinking or by a relative drop in blood alcohol levels (Mello and Mendelson, 1968). To some extent the abstinence syndrome may be temporarily prevented or ameliorated by the readministration of alcohol. Varga and Nagy (1960), for instance, view the faster and more labile frequencies seen during this period as a manifestation of a functional disturbance in cerebral homeostasis "which seems to be temporarily normalized by acute alcohol consumption." The literature on the acute effects of small doses of alcohol suggests that the CNS counterpart of the abeyance of the withdrawal syndrome (e.g., the use of a "morning after" drink to quiet the "shakes") may be a partial "normalization" of the EEG rhythm.

From a somewhat different perspective, the question of whether the addictive drinker derives some immediate short-term physiological "benefits" from alcohol intake has been investigated in a series of studies by Kissin, Schenker, and their co-workers (1959a, 1959b, 1960). Their data indicate that chronic alcoholics show a high frequency of abnormal values on a number of tests of endocrine and autonomic nervous system functions (measures of adrenocortical responses, regulation of arterial blood pressure, etc.) and that these abnormalities may be primarily constitutional in nature rather than the effects of alcoholism since they were also found in a group of alcoholics who had been abstinent for a period of at least 2 years. The most interesting observation of these studies was the finding that the ingestion of small amounts of alcohol tended to normalize these disturbances in physiological functioning. On the basis of these data, the authors suggest that the underlying functional abnormalities provide a continual source of discomfort which motivates the alcoholic to drink in order to relieve or "normalize" the physiological dysfunctioning producing the discomfort.

Naitoh and Docter (1968) have made a similar argument regarding the possible relationship between quantitative characteristics of the EEG which differentiate chronic alcoholics from nonalcoholics and the motivation to drink. In summarizing the literature they conclude that global ratings of EEG pathology are a poor method of differentiating chronic alcoholics since gross disturbances in the recordings such as spikings and paroxysmal high-voltage diffuse slow waves occur only infrequently, and probably not significantly more often than in normal groups. However, they point out that chronic alcoholics as a group tend to show poor alpha activity. In their study they report that low dosages of alcohol (0.5 mg/kg) in alcoholic subjects had primarily a stimulant-euphoriant effect, with the subjects reporting that they felt more alert, pepped up, and sociable. (Ekman *et al.*, 1963 and 1964, report similar effects in nonalcoholics,

with a majority of their normal subjects rating themselves more "elated," "happy," and "talkative" and less "tired" after drinking. Peak effects occurred between 30 and 40 min after ingestion, with subjective variables showing greater change than performance variables.) Paralleling the affective changes, the EEG measure of brain activity showed an increase in the amount of alpha activity and a slight slowing of approximately 1 cycle/sec in its frequency. On the basis of these data, Naitoh and Docter suggest the intriguing hypothesis that the alcoholic drinks in order to achieve the psychological state (calm-alert, mildly stimulated) which is associated with an increase and slowing of alpha activity. While carefully disclaiming that persons with alpha-poor records are necessarily inclined to chronic alcoholism, or that they drink specifically to achieve a "good alpha," the suggestion of an underlying CNS state which may be related to the motivation to drink does open up a potentially valuable direction for future research.

Before the testable consequences of the hypothesis can be evaluated, several questions should be explored. The first concerns how close the association is between affective states and specific EEG characteristics such as cycle frequency or percent time of alpha. The subjective reaction to a fixed dosage of alcohol may vary considerably, both in different people and at different times. Are the different effects of alcohol related in any systematic way either to the kind of prealcohol EEG activity, or to the kind and amount of change following alcohol? Engel and Rosenbaum (1945) report that a close correlation exists between the EEG and level of consciousness but not with the "more personal aspects of behavior" during alcoholization. The amount of slowing rather than the attainment of a specific frequency seemed to be the critical variable, with the development of intoxication being accompanied by progressive slowing of the brain waves. Gross intoxication usually was associated with an average change of 2 to 3 cycles/sec.

A second question which requires more extensive investigation concerns how accurately the addictive drinker can titrate or regulate his intake to maintain a consistent subjective state over time. Mello and Mendelson (1968) have reviewed the evidence indicating that alcohol acts as a stimulant only at low doses. At higher doses it exerts an increasingly depressant effect at both the neurophysiological and behavioral level. Casual observation at bars or parties suggests that many drinkers are not too successful in maintaining the "alert-pepped up" state which they supposedly drink to achieve. In addition, the subjective effects of drinking also apparently change during the course of sustained drinking. Nathan (1970) observed that alcoholics who were allowed *ad lib* alcohol in an operant conditioning situation initially showed a reduction in rated anxiety and depression during the first 24–48 hr of drinking. However, after the second or third day anxiety and depression invariably increased, with the increased level being maintained during the remaining course of drinking.

Nevertheless, the Naitoh–Docter hypothesis does suggest several interesting studies:

1. Are individuals with poor alpha activity more likely to become alcoholics?
2. In alcoholics whose drinking pattern is markedly aperiodic, is the occurrence of a drinking bout related to a temporary impoverishment of alpha activity, possibly induced by environmental stress or intercurrent constitutional factors?
3. In long-term *ad lib* alcoholization studies, is the tendency to drink at a given time related to the amount of preceding alpha activity?
4. Are there drugs which produce similar alterations in EEG activity as alcohol and, if so, would the chronic administration of such drugs reduce alcohol intake?

Studies such as these might help delineate the possible relationship between measures of CNS activity and alcohol addiction. Several studies do support the observation of alpha impoverishment in alcoholics as a group, although the interpretation of this relationship is not yet clear. Little and McAvoy (1952) compared the EEG during the resting state and after hyperventilation in 34 alcoholics and 55 controls. The alcoholics had been abstinent from 1 to 21 days and showed no clinical evidence of CNS disease, mental deterioration, or delirium tremens. There was little difference between the two groups in the percentage showing some alpha activity (80% of the controls and 70% of the alcoholics) or in the average amplitude of the alpha rhythm. However, when a 100-sec epoch of the record showing the greatest amount of alpha activity was evaluated, the groups were clearly different. The percent time alpha for the normal controls was 72% compared to only 46% in the alcoholics. A "blind" rating of alpha modulation (degree of differentiation of the alpha activity in the ongoing record) showed "good" modulation in 86% of the controls but in only 50% of the alcoholics.

Many of the alcoholics were tense and restless at the time of examination and showed the suppressed alpha activity during the resting EEG which is also typically seen during anxiety states. For instance, Wilson and Short (1965) report a mean alpha index of 0.55 in a group of chronic alcoholics and a mean alpha of 0.51 in patients diagnosed as "anxiety reaction." The authors argue that their group differences could not be attributed to the effects of anxiety *per se* since few of the alcoholics showed the rapid increase in alpha activity usually seen in anxiety states during hyperventilation. Little and McAvoy also propose a possible CNS state (low alpha activity) which may underlie addictive drinking, although their psychological interpretation of this association is quite different from that of Naitoh and Docter. Poor alpha is assumed to be a possible predisposing factor in the development of anxiety which leads to drinking for its anxiety-relieving effects. Thus, poor alpha activity may reflect a cerebral condition which is a cause rather than a result of alcoholism, although the

authors recognize the desirability of testing this hypothesis with a longitudinal study.

Funderburk (1949) divided chronic alcoholics into two groups depending upon whether alcoholism was felt to be the primary difficulty or only secondary. Patients with "secondary" alcoholic symptoms usually showed an alpha type tracing, while the other group showed little alpha activity. Seventy-three percent of the alcoholics showed a fast type record without alpha. This is markedly different from the 23% reported by Little and McAvoy, although the comparability of the patient samples, time of testing, concurrent medication, etc., cannot be evaluated from the written reports. [Medication commonly given to relieve withdrawal symptoms may also affect the prevalence of alpha activity in the EEG record. Fink (1965) for example, found that both acute and chronic administration of imipramine reduced alpha abundance, while chlorpromazine increased alpha in subjects with low predrug alpha index but decreased alpha when the predrug level was high. Ulett *et al.* (1965) found similar effects with a number of phenothiazines, although there were marked individual differences in drug response.]

Funkhouser *et al.* (1953) recorded the EEG in patients grouped according to predominant symptomatology. Approximately 53% of the "uncomplicated" alcoholics and patients with hallucinosis had an alpha pattern rated "poor." This is not appreciably different from the 45% incidence of "mixed" and "rare" alpha reported in a normal sample by Davis and Davis, cited by Funkhouser *et al.*, which they consider comparable to their "poor" rating. This suggests that finer measures of alpha activity such as those used by Little and McAvoy may be necessary to detect possible impairment in alcoholics. Patients tested shortly after delirium tremens or convulsions showed a somewhat higher incidence of poor alpha, 58 and 68% respectively. Over half of the patients showed increased beta activity, probably reflecting the agitation and restlessness typical of the withdrawal syndrome. A final study by Kessler (1949) also reports fast, low amplitude activity in all regions, and the absence of a stable alpha rhythm. The time of testing is not recorded, but her patient sample appears to be more severely organically impaired than those tested in the other studies reviewed.

An interesting variant in the investigation of the alpha pattern is a study by Delamonica *et al.* (1966) on the alpha blocking response in chronic alcoholics. Citing studies indicating that brain-damaged patients show decreased alpha blocking to photic stimulation, the authors felt that the procedure might also provide a possible measure of the degree of impairment of cerebral functioning and/or the amount of brain damage in alcoholic patients. Forty-two hospitalized alcoholics who showed no abnormal neurological signs and had been drug-free for at least 1 week were divided into two groups, one showing normal EEG's and the second showing minimal to severe abnormalities. A Grass stroboscopic unit was triggered to present a 1.5-sec train of flashes during periods of prominent

alpha activity for a total of 50 trials. The alcoholics with normal baseline EEG's averaged 37 trials on which blocking occurred as compared to an average of 29 for the patients showing EEG abnormalities. The authors suggest that the reduction in alpha blocking in the second group is due to "probable brain damage," although they later note that there was no relationship between the frequency of alpha blocking and the severity of the EEG abnormality.

Although the authors suggest a response measure which may be quite useful in assessing the CNS effects of chronic alcoholism, their study is difficult to evaluate. The statistical significance of the difference is not reported nor is the possible contaminating factor of age considered. Obrist and Busse (1965) note that with increased age there is both a tendency for less desynchronization of the alpha rhythm to visual stimulation and a faster habituation curve, with the older person adapting sooner and more completely with repeated stimulation. In the study by Delamonica *et al.*, reanalysis of the data from their abnormal EEG group gives a rank order correlation of -0.35 between age and number of alpha blocking responses; i.e., the older patients showed fewer trials on which alpha blocking occurred. Although the mean ages of the groups are not given, the data reported suggest that the group with EEG abnormalities is somewhat older. Since age and brain damage are both related to alpha blocking, the control of the extraneous effect due to age, either by matching subjects or by partialling the effect out statistically, would attenuate the reported differences to some degree. The addition of a nonalcoholic control group in order to evaluate the alpha blocking response in the alcoholic group not showing EEG abnormalities would also strengthen the study. In light of the number of studies reviewed which indicate differences in the alpha activity of alcoholics as a group, this would appear to be a profitable line of investigation to follow. A related study investigating the frequency of alpha blocking and its rate of habituation as a function of blood alcohol level would also be of some interest because of the possible biphasic stimulant-depressant action of alcohol at different dosage levels (cf. Mello and Mendelson, 1968).

EXPERIMENTAL STUDIES OF CNS ACTIVITY DURING ACUTE ADMINISTRATION OF ALCOHOL

In contrast to clinical studies of the EEG in alcoholics where there is still considerable controversy, the experimental studies investigating the effects of alcohol on the EEG are generally quite consistent. Most studies report an increase in percent time alpha and alpha abundance, greater synchronization of the EEG pattern with less dispersion and greater stability of component waveforms, and a slowing in the dominant alpha frequency. Loosely paralleling these changes in CNS activity are corresponding changes in the level of consciousness

and affective state of the subject varying as a function of dosage and change in blood alcohol level over time.

In one of the earliest investigations Davis *et al.* (1941) studied the effects of ethanol administered 2 ml/kg body weight to six normal subjects over a 1-hr period. A spectral analysis of the distribution of energy by wave frequency showed a moderate shift indicating less energy at the faster frequencies, primarily between 10 and 13 cycles, and relatively more energy at the slower frequencies, particularly between 6–8 cycles. Although the peak alpha frequency (about 10 cycles) showed little change, the increase at the slower frequencies would indicate a slower mean alpha frequency. EEG changes appeared soon after alcohol ingestion when the blood alcohol level was less than 0.35 mg%. During the first hour the amount of displacement roughly paralleled the increase in blood alcohol level. However, the peak change in the EEG was not reached until after the BAL began to decline, and was maintained over a longer time period. At 5 hr the BAL had dropped from its maximum of 120 mg% to approximately 80, while the EEG displacement was still near its maximum value even though the subjects were judged fairly sober.

The authors conclude that the EEG changes were "surprisingly slight" given the marked changes in mood and behavior of the subjects. During periods of lethargy brief episodes of 2 or 3 sec of slow activity (4–8 Hz) frequently occurred interspersed between the usual alpha pattern. These changes were not like those seen during light sleep but rather resembled the pattern seen when breathing a low oxygen mixture. Engel *et al.* (1945) have drawn a similar analogy between the EEG pattern seen during alcoholic intoxication and anoxia. Pre-alcoholization irregularities in the EEG were either maintained or somewhat accentuated during the period of intoxication.

In two studies Engel and Rosenbaum (1945) and Engel *et al.* (1945) reported a close correspondence between clinical ratings of the degree of intoxication, the extent of disturbances in consciousness and level of awareness, and the amount of slowing of the brain waves. Gross intoxication was associated with a decrease in the mean frequency of 2 to 3 cycles/sec. The amount of slowing in the EEG was not related to the mean frequency before alcoholization, although the range of initial values was relatively small and mostly within normal limits. In subjects showing fast normal or even abnormally fast patterns before drinking, the EEG became more "normal" during intoxication. [Varga and Nagy (1960) observed a similar "normalization" in fast, low voltage records taken during withdrawal when alcohol was administered to the patients.] After intoxication the EEG gradually returned to the predrinking pattern. The authors argue that changes in the level of consciousness during progressive intoxication are related to the amount of slowing in the alpha rhythm, regardless of the initial pattern, and not to the absolute frequency obtained. Subjects showed similar degrees of intoxication and impaired consciousness when the

change in the mean frequency of the EEG was equivalent even though the spectral frequency distribution of the record was quite dissimilar, both immediately before drinking and throughout the period of intoxication. However, this correlation apparently breaks down during recovery, since patients become sober before the EEG has returned to the prealcohol pattern. This finding is consistent with the Davis study in which a considerable drop in blood alcohol level occurred while the EEG still showed peak changes.

The authors also note that with similar EEG patterns during the development of and the subsequent recovery from intoxication, both subjective and objective measures of the subject's state were consistently better during recovery. Victor and Adams (1953) have pointed out a similar phenomenon with patients showing greater evidence of intoxication at a given blood alcohol level during the ascending than during the descending BAL curve.

Two findings reported by Engel *et al.* are discrepant from results discussed earlier. The subjects in the Engel and Rosenbaum study showed periods of pronounced somnolence during which the EEG resembled the pattern seen during normal sleep. While the subjects in the study by Davis *et al.* occasionally fell into "stuporous naps" characterized by very low-voltage, flat periods seen at certain stages of sleep, for the most part the alpha rhythm remained prominent instead of dropping out as in sleep. This difference is possibly related to differences in the alcoholization procedures in the two studies. Although the dosages were roughly comparable, the subjects in the Engel–Rosenbaum study were administered alcohol after an overnight fast and required to drink it more quickly than in the Davis study. This difference in administration and time of day of testing may account for the appearance of typical sleep EEG's in one study but not the other.

Second, Engel and his associates (1944, 1945a, 1945b, 1959) emphasize the relationship between the amount of slowing in wave frequency and both the degree of intoxication and change in level of consciousness, but also point out that the EEG changes were not correlated with "the more personal aspects of behavior," such as the affective changes and mood occurring during intoxication which differed considerably between subjects. This would appear contradictory to the assertion by Naitoh and Docter (1968) that the alcoholic drinks specifically in order to achieve a state of feeling more alert, perked up, and sociable which the authors state accompanies the increase in alpha abundance and slowing of alpha frequency produced by drinking.

A possible limitation of the Naitoh–Docter hypothesis lies in the extreme variability in the subjective response to alcohol by different people, and by the same individual at different times. Partly because of these differences, the association between the specific affective state postulated by Naitoh and Docter and the reported alcohol-induced changes in the alpha rhythm is somewhat tentative. A reanalysis of the EEG data presented in Fig. 4 (in Engel *et al.*, 1945)

in conjunction with the authors' discussion of the subjective changes during intoxication in the article by Engel *et al.* (1945) suggests a possible line of inquiry which might strengthen the Naitoh–Docter hypothesis. Although the *N* is too small to warrant drawing any conclusions, the graph indicates that all four subjects showed an almost identical slowing of slightly less than 1 cycle/sec in their alpha frequency during the earliest signs of intoxication (approximately 45 min after drinking). However, the two subjects who showed a euphoriant, "happy drunk" response had initial mean frequencies between 10.6 and 10.8 cycles/sec, while the other two subjects who showed only slight behavioral changes had initial levels of 8.8 and 9.2.

The question of whether predrinking characteristics of the EEG pattern partially determine the degree and kind of affective and behavioral changes produced by alcohol, or even whether initial brain state determines whether small amounts of alcohol have primarily a stimulating or depressant effect, would appear to be a fruitful area of investigation. An observation by Doenicke, Kugler, and Laub (1967) that preadministration irregularities in the EEG are sometimes associated with atypical or marked reactions to anesthesia provides some reason for believing that similar factors may account for some of the individual differences in response to alcohol.

Since the recordings of alcoholics typically show poor or impoverished alpha activity, different indices of the alpha rhythm—mean frequency, percent time alpha, alpha abundance, degree of alpha modulation—are logical starting places for investigation. Positive findings would not only help explain individual differences in reaction to alcohol, but would also be useful in predicting which individuals are most likely to become addicted to drinking; or within individuals, at what times they are most likely to drink. The finding of a relation between a specific subjective state and a specific characteristic of the brain rhythm which modulates either the craving for, or the response to alcohol would stimulate the search for drugs capable of inducing the appropriate changes in the brain state controlling addictive drinking.

The slowing in the frequency of the alpha rhythm after drinking has been confirmed in a number of studies using a wide variety of patient and nonpatient samples, including alcoholics during the withdrawal period, hospitalized alcoholics tested after remission of symptoms, alcoholic groups based on the severity of past alcohol-related symptoms, schizophrenics, nonhospitalized chronic drinkers, and normal nonalcoholic control groups (Davis *et al.*, 1941; Docter *et al.*, 1966; Engel and Rosenbaum, 1945; Engel *et al.*, 1945; Holmberg and Martens, 1955; Kotani, 1965; Naitoh and Docter, 1968; Newman, 1959; Varga and Nagy, 1960). Although there were some differences between the groups both in the kind and extent of the EEG changes observed, as well as in the time course, all studies reviewed reported the characteristic slowing in the alpha rhythm. The extent of alpha slowing tended to parallel the BAL curve,

especially during the ascending portion of the curve, reaching its maximum at approximately the same time or shortly after the peak blood alcohol level, and declining somewhat more slowly than the alcohol curve (Davis *et al.*, 1941; Holmberg and Martens, 1955; Newman, 1959). These findings are somewhat impressionistic since no one has yet reported any statistical measure (perhaps some form of cross-correlational analysis) of the degree of correspondence between the two curves representing the BAL and changes in the EEG. Ideally, a more complete picture of the changes during alcoholization could be obtained by collecting time course data simultaneously on four major variables: blood alcohol concentration, measures of brain activity (EEG), measures of subjective states, and behavioral measures for a given dose and regimen of alcohol. A statistical analysis of the degree of correspondence between any two curves would answer the question of whether the timing and amount of change during intoxication was parallel for these variables, and also indicate whether some measures showed a continuous change under alcoholization, while others followed a discrete all-or-none pattern. Since the correlation between curves can be run separately for each individual, atypical values, or correlations markedly different from those based on group values, may point to some factor causally related to either the motivation to drink or to the effects of alcohol. For example, Greenblatt *et al.* (1944) discuss a clinical syndrome which they refer to as "pathologic intoxication" in which small amounts of alcohol produce disproportionate "clouding of consciousness" and "violent, aggressive overactivity." Three of the five patients showed abnormal EEG's after recovery from intoxication but whether small amounts of alcohol also produced atypical blood alcohol curves and concurrent EEG changes consistent with the subjective and behavioral changes in these patients was not determined.

Under some conditions, and for certain types of patients, the usual correlations may be markedly distorted. The extent of the correspondence between the BAL and changes in the EEG is apparently higher during the ascending portion of the BAL curve than during the descending phase (Davis *et al.*, 1941). The correlation between the two curves may also differ between alcoholics and nonalcoholics since Holmberg and Martens (1955) data indicate that the BAL peaked at approximately the same time (about 1 hr past ingestion) for their alcoholic and normal control groups, but the maximum slowing in mean EEG frequencies lagged behind the peak concentration by only 6 min in the alcoholic group but by an average of 45 min in the nonalcoholics.

A number of variables affect the relationship between the amount of alcohol ingested and the appearance of behavioral changes. The phenomenon of tolerance indicates that more alcohol is required to produce either subjective changes or behavioral impairment in the chronic drinker than in the nondrinker. In the Holmberg and Martens study the alcoholic group showed less ataxia and almost none of the nausea and vomiting seen in the control group's reaction to a

standard dose of alcohol, even though their blood alcohol level was moderately higher throughout the 4½-hr test period (mean peak values of 177 and 150 mg per 100 ml respectively). (The mean age of the alcoholic sample is 16 years greater than that of the control group, so that age differences are a possible contributing factor.) Both the rate of intake and changes in the usual amount of alcohol ingestion may affect the relation between dosage, BAL, and psychological effects. Subjective and behavioral changes are more marked at comparable levels during a rapidly rising BAL than in one increasing slowly, even though the peak BAL is the same under the two conditions. In the classic study by Isbell *et al.* (1955) on the effects of experimental chronic alcoholization, it was found that small increases in dosage over the usual daily maintenance intake resulted in marked increases in blood alcohol level and signs of gross intoxication. However, if the raised dosage was maintained, the blood alcohol level and degree of intoxication declined rapidly over a period of days, indicating a fairly rapid habituation to a repeated level of alcohol intake. Victor and Adams (1953) have discussed some of the factors which lower the correlation between amount of alcohol ingested and subjective and behavioral signs of intoxication. Whether these same factors would attenuate the relation between alcohol intake and alpha slowing has yet to be investigated. It would be of considerable interest to know whether the EEG paralleled the psychological states, or if, instead, it remained consistent to the alcohol dosage.

In summarizing their work on experimentally induced slowing in the EEG during hypoxia, hypoglycemia, and alcohol intoxication, Engel and Romano (1959) draw three major conclusions. The first is that drugs or physiological states which produce a slowing in the EEG also reduce the "level of consciousness and the efficiency of cognitive processes." The psychological changes "correlating most precisely" with the slowing of EEG frequency have to do with functions such as awareness, attention, memory, and comprehension. Although the cognitive changes were similar, changes in behavior and emotional expression varied considerably between subjects. Second, the degree of impairment in cognitive functioning is related to the amount of slowing rather than to the absolute frequency of the EEG during the intoxicated state. However, in hypoxia at least, EEG changes can be detected before any cognitive deficit occurs. (Whether the same is true following alcohol ingestion, or if changes in cognitive functioning sometimes precede, or occur without changes in the EEG frequency, apparently has not been investigated.) Third, the degree of slowing is not related to either the initial frequency of the EEG or to the postintoxication frequency. Consequently, an initially fast record may be slowed sufficiently under the drug condition so that the EEG appears more "normal" according to the accepted criteria, yet the "normal" EEG may be accompanied by "an appreciable degree of cerebral insufficiency and reduction in the level of awareness."

While these general conclusions are probably valid for major changes in the EEG such as might occur during gross intoxication, some qualifications should be made regarding their applicability to the effects of low to moderate dosages of alcohol, and to their usefulness in attempting to predict or account for individual response differences under similar conditions. In regard to the psychological effects of alcohol, the review by Carpenter (1962) supports the conclusion that moderate to heavy drinking generally impairs cognitive functioning and motor performance. However, individual differences in response to a fixed dosage of alcohol are large, and obviously both the occurrence and the extent of impairment are dose and task related. Under some conditions, lower dosages may improve performance. Korman *et al.* (1960) report that alcoholics did better in solving simple arithmetic problems after drinking than without alcohol. Docter *et al.* (1966) found that 0.5 mg/kg of ethanol administered to alcoholics improved performance on a 50-min signal detection task, primarily because there was less deterioration in performance over time under the alcohol condition than during the control run. This result is consistent with the authors' argument that low dosages of alcohol act as a stimulant, even though the blood alcohol level of 30 mg% at the start of testing was within the range where Davis *et al.* reported EEG slowing. However, the apparent failure to find an alcohol-control difference in normal subjects (Naitoh and Docter, 1968) suggests several testable alternative interpretations—perhaps that alcohol has a "normalizing" effect on alcoholics as discussed earlier, or that the alcoholic has learned to habitually compensate for the effects of drinking on his behavior. In any case, it is likely that alcohol produces a different subjective state in the alcoholic than the normal, and that their responses on the alcohol-sensitive items of the Addiction Research Center Inventory for evaluating subjective drug effects would differ significantly from normals (Hill *et al.*, 1963).

The finding by Docter *et al.* (1966) that alcohol, at a dose level reported to produce slowing in the alpha rhythm in other studies, had an apparent stimulant effect and improved performance on a cognitive task suggests that Engel's assumption of impairment of cognition concomitant with EEG slowing probably only holds true with relatively large changes in EEG frequency. The assumed correlation between BAL, amount of slowing, and degree of cognitive impairment is open to the same criticism. Newman (1959) in a small sample study (seven normals, two alcoholics) concluded that the EEG slowing was roughly proportional to the blood alcohol level, and that subjects with a history of greater use of alcohol showed a high tolerance both clinically, as measured by the ability to balance on one foot, and electroencephalographically. This is inconsistent with the Holmberg–Martens data which showed a partial dissociation between the EEG changes and clinical measures of intoxication in the alcoholic group as compared to the normal controls. Although the degree of slowing in the alpha rhythm was roughly comparable for the two groups (mean value

of −1.4 *vs.* −1.5 Hz respectively), the alcoholics showed less ataxia and markedly less evidence of intoxication. A reanalysis of their data presented in Table 1 also indicates that slowing in the EEG record was not related to either the concentration of blood alcohol or the degree of ataxia across subjects administered a standard dose of aquavit equivalent to 1.25 g/kg of ethanol. Rank order correlations indicating the degree of association between the peak values of the three variables are shown in Table 1. (The range and mean values are reproduced from Holmberg and Martens, 1955, p. 414.)

Two findings are apparent from the table. First, there were marked individual differences in response, especially in the control group, on all three variables. Second, none of the correlations between the variables is statistically significant. (Possibly with a larger N the relation between BAL and ataxia would be significant.) The alcohol intake was sufficient to produce intoxication and nausea, marked cognitive and behavioral changes (drowsiness, ataxia), peak blood alcohol levels ranging up to 200 mg/100 ml, and slowing of the EEG by as much as 3 cycles/sec. Yet, across subjects the maximum BAL was not related to the amount of slowing in the EEG, nor was the slowing in the EEG related to the degree of ataxia.

A third observation from the Holmberg–Martens data indicates that the time course for the three variables differs, so that the peak change in ataxia, for instance, occurs over an hour before the peak EEG change in the control group.

TABLE 1. Correlations Between Blood Alcohol Concentration, Slowing in EEG Frequency and Degree of Ataxia[a]

Alcoholic Group (N = 10)

	EEG	*BAL*	*Ataxia*
EEG (1.40, 0.70–1.76)	—	0.04	0.10
BAL (177, 156–196)		—	0.19
Ataxia (3.6, 2.0–5.5)			—

Control Group (N = 10)

	EEG	*BAL*	*Ataxia*
EEG (1.52, 0.81–3.03)	—	0.02	0.01
BAL (150, 108–187)		—	0.38
Ataxia (5.5, 2.5–8.0)			—

[a] Rank order correlations based on data presented by Holmberg and Martens (1955). The EEG measure is maximum slowing in cycles per second; BAL is in milligrams per 100 ml, and ataxia is based on ratings of several behavioral tests. Range and mean values are given in parentheses. None of the correlations is significantly different from chance.

Since the relation between the time curves apparently differs between subjects, and is markedly different between the alcohol and control group, it is possible that the correlation between variables would have been somewhat higher if they had been based on values at the same time period. However, this analysis suggests that in a group study using a fixed dosage, knowing the blood alcohol concentration for a given individual would not make it possible to predict the degree of slowing in his alpha rhythm, nor would knowing the change in alpha frequency allow prediction of the severity of ataxia. The reason that prediction of change in the EEG cannot be made from the blood alcohol concentration, or why the extent of EEG slowing does not predict ataxia can be illustrated by examining the response of individual subjects. Normal control subjects 9 and 10 had almost identical blood alcohol levels (187 *vs.* 183) yet differed markedly in the extent to which they showed alpha slowing (1.38 *vs.* 3.03 Hz) or exhibited signs of ataxia (3.0 *vs.* 8.0). Similarly, subjects 1 and 2 showed identical EEG slowing (1.53 *vs.* 1.52 Hz), but very different maximum blood alcohol levels (179 *vs.* 108) and degree of ataxia (8.0 *vs.* 4.5). Although it has not been investigated, the failure to find a correlation between EEG changes and either BAL or ataxia shown in Table 1 also makes it appear unlikely that variability in an individual's response at different times to identical amounts of alcohol would be highly correlated with the degree of alpha slowing. The correlation between EEG changes and accompanying changes in level of awareness apparently holds true only when the differences between doses are large and extend over a wide range of values.

Engel's third generalization, that the degree of slowing in the alpha rhythm is independent of the initial mean frequency, should be evaluated by a correlation coefficient to determine if they are related. The law of initial values, which holds true for a large number of physiological variables, states that the magnitude of the response change in an ongoing physiological response to a stimulus is dependent upon the initial level of activity; e.g., the amount of change in skin conductance to stimulation varies as a function of the prestimulus conductance level. On this basis one would expect the amount of slowing in the mean EEG frequency under alcoholization to be related to the predrug mean frequency. There is considerable evidence that drug effects on the EEG, most notably on the percent time of activity within a given frequency band, are dependent upon the predrug level, and are an important source of individual differences in the EEG response to drugs (cf. Murphree *et al.*, 1970). As previously discussed, some of the phenothiazines may either increase or decrease percent alpha time, depending upon its rate before drug administration (Fink, 1965; Ulett *et al.*, 1965). The virtual disappearance of the low voltage fast activity beta waves after drinking, with the concomitant appearance of an alpha pattern, has also been commented upon (Engel and Rosenbaum, 1945; Murphree *et al.*, 1970; Varga and Nagy, 1960). At the low end of the spectrum, Murphree *et al.* (1970) have

pointed out that the relaxed subject with a slow alpha pattern is more apt to be made drowsy by alcohol than the tense-alert subject, and consequently shows an opposite effect: a decrease in alpha activity. This point is further shown in the Holmberg–Martens study. Although the degree of slowing in the mean frequency was almost identical for the alcohol and control groups (1.40 *vs.* 1.52 Hz), the alcoholics had a prealcoholization mean frequency 0.5 cycles lower than the controls (9.5 *vs.* 10.0). As a consequence, the alcoholics showed a much greater amount of activity within the 4–6 Hz range after alcoholization than did the controls, although neither group showed an appreciable amount of theta activity before drinking. In evaluating drug effects, the predrug EEG, especially when such measures as percent time of a given frequency or wave amplitude are used, is an important determinant of the postdrug pattern. Failure to take into account the effect of different initial patterns may account for some of the discrepancies between different studies of alcohol effects using these measures. Whether there is an initial level effect in the amount of alpha slowing under alcohol has yet to be adequately evaluated. In the Holmberg–Martens study shifts in the mean alpha frequency varied widely in the control group, from 0.81 to 3.03 cycles/sec. Since the amount of slowing was not related to the blood alcohol concentration, it would be worth investigating whether such large individual variations in response may be partially accounted for in terms of the prealcohol level.

Although the slowing of the alpha rhythm after drinking has been consistently reported in a number of studies, Docter *et al.* (1966), in a well-designed study, have shown that alcohol affects different measures of alpha activity in somewhat different ways. Healthy nonhospitalized male alcoholics were given five administrations of vodka equivalent to 0.3 ml/kg of alcohol at 15-min intervals. Breath sample estimates of mean blood alcohol levels increased linearly from 0.026% to 0.104% at the last administration. Alpha abundance (total alpha activity reflecting both the amplitude and the number of waves occurring during a time sample) increased markedly after the first drink, but then showed a tendency to decrease slightly after the fourth drink and with higher blood alcohol levels. However, the number of seconds of alpha activity tended to increase regularly with the increasing blood alcohol level over successive drinks. The authors point out that the different course of these two measures of alpha activity suggests that the early change in alpha abundance reflects initial amplitude changes which are not maintained over the successive periods of alcoholization. If the amplitude of the alpha waves does show a curvilinear relation to blood alcohol or varies over time, this might partially account for the conflicting reports in the literature on alcohol effects on amplitude measures. Holmberg and Martens, using a single administration of alcohol given orally, reported a 50 to 100% increase in the amplitude of the EEG. However, it is not clear whether the amplitude of individual alpha waves

increased, or whether the change is due to an increase in alpha abundance. The authors note that as the amplitude increased, the number of countable waves in the EEG also rose. The latter effect is consistent with the increase in the amount of alpha activity reported by Docter *et al.* (1966),and Kotani (1965), using a drip infusion procedure extending over 2 hr, reported slower alpha but with lower amplitudes. Murphree *et al.* (1970) also report a reduction in alpha amplitude.

Regarding specific frequencies, the major findings were substantial reductions in 10 and 11 Hz activity and a concomitant increase in 8 and 9 Hz. An increase in slow wave activity below the alpha range which had been reported in other studies was not seen, probably because of the low blood alcohol levels. The time course of individual frequencies, whether measured in terms of abundance (Docter *et al.*, 1966) or number of waves per interval (Holmberg and Martens, 1955), shows distinctive changes with increasing blood alcohol. Although the rate at which blood alcohol level increases may modify the curves, generally the faster frequency waves, 9–11 Hz, show an initial increase and then begin declining as the BAL increases. With increasing time after alcohol ingestion, progressively slower wave frequencies successively appear and gradually increase in frequency of occurrence. With sufficiently high alcohol levels, bursts of slow wave activity within the theta range (4–7 Hz) may appear, interspersed between the dominant alpha pattern, usually during periods of pronounced drowsiness or alcoholic stupor (Davis *et al.*, 1941; Newman, 1959).

Several investigators have studied the effects of alcohol on the EEG in special subgroups of alcoholics classified on the basis of the presence or absence of specific symptom patterns in the medical history. Kotani (1965) used four patient groups: two groups with endogenous psychoses, "typical schizophrenia" ($N = 15$) and "atypical psychoses" ($N = 20$), and two groups of chronic alcoholics, those with a history of clouding of consciousness and/or hallucinations ("complex form," $N = 9$) and a group who had not shown these symptoms ("simple form," $N = 7$). The resting EEG's of the alcoholics and psychotics were similar on a 3-point rating scale of normality, although both the "complex form" alcoholics and "atypical psychotics" showed a higher frequency of abnormal recordings characterized by either high voltage slow waves or dysrhythmia.

One hundred grams of ethanol in solution were administered by drip infusion, with EEG's taken at regular intervals. The first detectable change to appear was a slowing in the alpha rhythm, followed at a slightly higher dosage by a reduction in amplitude. There was little difference in the EEG response between the alcoholics as a group and the psychotics. However, in both the "complex form" alcoholics and the "atypical psychotics," changes appeared earlier and were generally greater until the final stages of alcoholization. The greater rate in the development of EEG changes in the atypical groups is

assumed to reflect a faster rise time in blood alcohol level relative to a given dosage, which is a distinguishing characteristic between normal and pathological drunkenness. In general, a fast increase in BAL produces more severe psychological and somatic changes than a slow increase (see Victor and Adams, 1953). Appearance of theta waves was infrequent in any of the groups.

In regard to psychological changes, initial euphoria followed by sleepiness was more frequently seen in the simple than in the complex alcoholics. The latter, however, showed more subjective changes sometimes associated with abnormal or pathological drunkenness, such as moodiness and restless excitement. A tolerance effect, similar to that reported in other studies, was also found, with the psychotic group showing more frequent and severe somatic symptoms such as nausea, vomiting, and changes in the pulse rate than the alcoholic group. Although the greater frequency of abnormalities in the prealcoholization records of the "atypical" groups (24% *vs.* 0%) would suggest that the initial brain state is related both to the greater magnitude of the EEG changes under alcohol and to the development of symptoms of pathological drunkenness (dysphoria, agitation), this relationship was not directly tested. Such a finding, however, would be consistent with the observation by Doenicke *et al.* (1967) that atypical and stronger reactions to anesthesia are frequently associated with mild abnormalities in the predrug EEG.

In two studies, Marinacci (1955, 1963) investigated the alcohol-activated EEG in 402 patients in whom alcohol produced abnormal states of consciousness: confusional episodes, trance-like states, fugues, or convulsions. Prealcohol EEG's showed normal records in 80% of the cases, borderline abnormalities in 16%, and 4% with moderate generalized slowing. These frequencies are within the limits usually found in normal control groups. After drinking (variable dosage and type of liquor) no diagnostic abnormalities were found in 86% of the cases, but 14% showed anterior temporal lobe spikes, generally about $\frac{1}{2}$ hr after the first drink. About a third of these patients showed "definite automatic (psychomotor) episodes" associated with the EEG abnormalities, and another third showed moderate to severe mental confusion. The author concludes that in a select few cases alcohol may lower the convulsive threshold sufficiently to trigger temporal lobe seizures with associated psychomotor epileptic attacks even in the absence of known organic brain pathology. However, many of these patients showed some irregularities in the prealcohol EEG, suggesting a possible predisposition to paroxysmal dysrhythmias. Victor (1968) also reports that alcohol may precipitate seizure discharges in patients with idiopathic epilepsy (with unknown organic basis and with the first appearance of seizures antedating the onset of drinking by several years) and also in patients with definite cerebral trauma. In some of the latter patients, seizures occurred only in connection with drinking, but usually followed the cessation of drinking by several hours. In some, but not all cases, the seizures were associated with focal EEG abnormalities.

Thompson (1963) studied the alcohol-activated EEG in three cases of pathological intoxication; that is, patients who showed either abnormal mental or behavioral responses to relatively small amounts of alcohol, followed by partial or total amnesia. Three types of abnormalities were found: (1) localized spiking, usually in the temporal or frontal lobes, (2) bursts of high voltage slow wave activity, from 2 to 6 Hz, in the same areas, and (3) mixtures of spike and slow wave activity in localized bursts. The author argues that pathological intoxication is usually indicative of lesions in the frontal or temporal lobes, or the connecting subcortical pathways, although one of the cases reported showed a normal prealcohol electroencephalogram.

Two groups of investigators have looked for distinctive EEG characteristics related to the kind of liquor ingested. Murphree *et al.* (1967) studied the effects of equal amounts of alcohol administered to normal moderate drinkers in three forms: vodka (low congener content), bourbon, and "superbourbon" (artificially increased congener content). All three beverages produced similar effects: a reduction in alpha amplitude and an increase in slow wave activity consistent with behavioral drowsiness. The added congeners in the superbourbon tended to increase both the degree and the duration of the EEG changes, and to heighten the depressant effect of the alcohol, although the blood alcohol concentrations as measured by the Breathalyzer were not significantly different for the three beverages (see also Murphree *et al.*, 1970).

Lolli *et al.* (1964) studied the effects of low dosages of alcohol (equivalent to 0.40 g/kg of ethanol) administered in the form of either a dry red wine or a dry martini (gin and dry vermouth) to 10 normal males in each group. Within subject comparisons of EEG activity before and after alcohol were made under four conditions: resting with eyes closed, during a reaction time task, arithmetic tests, and photic flicker. Mean blood alcohol values ranged between 0.03 and 0.04% during the alcohol runs. The index of EEG activity used was a combined measure reflecting both the number of occurrences of a wave of a given frequency and their amplitudes.

At these blood alcohol levels most of the tests were not statistically significant. However, it was apparent that wine produced a much greater effect than the martini in enhancing alpha activity (21% of the comparisons showing a significant increase *vs.* 11%), theta activity (11% *vs.* 2%), and delta activity (14% *vs.* 3%). Little significant change under either beverage was seen in beta activity, although slightly more decreases were observed than increases. Equally noteworthy was the variability in the EEG changes. Although only about 2–3% of the tests showed a statistically significant decrease in alpha activity, non-significant decreases ($0.05 < p < 0.25$) occurred in a fairly large percent of the cases, especially in the martini group. Under the latter condition, alpha activity decreased in 30% of the tests; theta in 15%; and delta in 29%. To a lesser extent decreases in the four rhythms also occurred under the wine condition, although

the majority of the changes indicated a slowing of the mean EEG frequency. Presumably these contradictory changes are partly due to the low dose of alcohol administered, since larger doses generally produce a more uniform response across subjects and a more consistent shift to slower frequencies. To some extent differences between subjects in the initial EEG pattern may also contribute to the discrepancy. A subject whose initial prealcohol alpha was in the high range, or who showed considerable beta activity, would show an increase in alpha abundance under alcohol-induced slowing; while the subject whose initial mean alpha frequency was in the low range, 8–9 Hz, might show a decrease in alpha abundance because the same amount of slowing would increase the amount of theta activity.

The "magnification" of the alpha rhythm from the pre- to postalcohol condition was greatest on those tests where the external stimulus was highly salient (reaction time, flicker). Since the initial effect of photic stimulation is usually to disrupt the alpha rhythm and initiate a low-voltage, fast activity arousal pattern, the authors argue that the increased alpha abundance suggests a decreased receptivity to external stimuli under alcohol. This interpretation is similar to that offered by Engel to the effect that alcohol reduces the level of awareness, although Engel might also predict an equal impairment in cognitive functioning as reflected in the arithmetic tests. The suggestion of a decrease in stimulus receptivity is supported by a number of studies reporting a reduction in sensory evoked potentials under alcohol to repetitive stimulation, which has been interpreted as indicating an inhibitory or depressant effect of alcohol on the cerebral cortex.

THE EFFECTS OF LONG-TERM ADMINISTRATION ON THE ELECTROENCEPHALOGRAM

Beginning with the classic studies by Isbell *et al.* (1955) and Wikler *et al.* (1956), several studies have investigated EEG changes recorded at regular intervals during experimental chronic alcoholization and the subsequent withdrawal period. Wikler *et al.* (1956) present data on three subjects who were maintained on a variable dosage of 95% ethyl alcohol, averaging between 458 and 489 ml daily. Alcohol was administered regularly throughout the day over a 48–55 day period, followed by abrupt withdrawal. Blood alcohol levels were variable, partly because of the development of tolerance effects during periods of constant daily dosages, but remained over 200 mg% for long periods. Prior to alcoholization, EEG records were within normal limits and subjects showed no signs of CNS pathology.

The initial change in the EEG was one of diffuse slowing which persisted in a milder degree throughout the alcoholization period and which was much

like that seen after the ingestion of a single large dose of alcohol. In general, there was a marked increase in the percentage of slow wave activity (4–6 Hz), increase in the occipital alpha percentage and slowing of the mean alpha frequency. (The relation between changes in percent alpha time and the degree of slowing after alcoholization may be either positive or negative, depending upon the amount of slowing—primarily a function of the amount of alcohol ingested—and the initial mean frequency. Diffuse slowing may produce either an increase or decrease in percent alpha time in different subjects.) When the same dosage was maintained over several days, tolerance effects become apparent in the declining BAL, the rapid disappearance of signs of behavioral intoxication, and a partial return of the EEG pattern to that characteristic of the prealcoholization period. A small increase in the alcohol dosage (e.g., a 1-ml change from 19 to 20 ml hourly) reinstated the cycle, producing large increases in the BAL and concomitant behavioral and electroencephalographic changes. The authors note, however, that the correlation between behavioral intoxication and the EEG pattern was sometimes inconsistent since on occasion the subject might appear to be more intoxicated when the degree of slowing in the EEG frequency was slight or, conversely, greater slowing in the EEG pattern would occur with little behavioral indication of intoxication. Even with high daily alcohol intake, lower blood alcohol levels and lesser degrees of intoxication were seen in association with a "normal" EEG pattern. In this connection, the observation by Mello and Mendelson (1968) that the textbook descriptions of the behavioral effects of high blood alcohol levels are probably not accurate for the chronic drinker is of some relevance. In their studies they found no significant decrement in performance on vigilance and reaction time tasks despite blood alcohol levels approaching 200 mg/100 ml, and relatively little disruption of verbal, motor, or social behavior during periods of sustained blood alcohol levels ranging between 150 and 300 mg/100 ml.

After abrupt withdrawal of alcohol, the subjects showed similar EEG changes. At approximately 12 hr, when the BAL had declined from over 200 mg% to between 30 and 40 mg%, the EEG resembled the prealcohol pattern. At 15 to 20 hr, when the blood alcohol level was zero, subjects exhibited marked anxiety and tremulousness and EEG activity characterized by moderate to high voltage, rhythmic slow waves (4–6 Hz) and a consequent marked drop in alpha percent. Random spikes and paroxysmal bursts of slow wave, high voltage activity and transient, mild dysrhythmias appeared at the same time and lasted throughout the second day. Some subjects later showed one or more of the classical signs of the withdrawal syndrome: hallucinosis, autonomic irregularities, convulsive seizures and full-blown delirium tremens. No specific EEG patterns were associated with the specific mental states occurring during the later stages of withdrawal. At 3 months there was no evidence of residual impairment or abnormalities in the EEG record.

These data on the effects of experimental chronic alcoholization appear remarkably consistent with the data reported by Victor (1968) on naturally occurring withdrawal symptoms. Photomyoclonus, usually accompanied by paroxysmal discharges in the EEG to a high intensity flickering light, generally did not appear until some 15 hr after cessation of drinking, and reached its peak frequency from 31 to 48 hr after withdrawal. Abnormal responses to photic stimulation are infrequent after the fifth day, suggesting that the period of CNS hyperexcitability is quite brief, and roughly parallels the time course of the clinical withdrawal syndrome.

Isbell *et al.* and Wikler *et al.*, on the basis of experimental chronic intoxication, and Victor, on the basis of clinical observations of the withdrawal syndrome, agree on three major conclusions:

1. Patients with normal EEG patterns and no evidence of CNS pathology may go into convulsions after prolonged drinking.
2. The seizures and abnormal paroxysmal EEG activity usually occur after withdrawal from alcohol rather than during drinking. However, a sharp drop in blood alcohol from a higher level maintained over several days may also precipitate withdrawal symptoms. In the Victor sample 50% of the patients developing seizures did so within 13–24 hr after the last drink. This roughly corresponds to the time at which EEG spiking and paroxysmal slow wave activity appeared in Wikler's subjects.
3. The EEG abnormalities appearing during withdrawal are short lasting and do not result in any detectable residual impairment. EEG's recorded shortly after seizures or between drinking bouts generally fall within normal limits.

Isbell *et al.* also note that the severity of symptoms in their experimental subjects correlated roughly with the amount of alcohol consumed and the duration of the drinking period. Mello and Mendelson (1968), however, feel that in clinical cases the severity and duration of symptoms "do not appear to be directly related" to either the amount of alcohol consumed or the duration of the drinking bout, and that nutritional deficiencies, concurrent illnesses, and environmental factors play an important role in the development of symptoms after withdrawal.

Weiss *et al.* (1964) studied the effects of 24 days of chronic alcoholization on 10 subjects who had previously experienced withdrawal symptomatology, but with a negative history of convulsive seizures. A fixed incremental dosage schedule was followed, with the subjects receiving between 20 and 30 oz of 86 proof whiskey by the fourteenth day and between 30 and 40 oz on the twenty-fourth day.

The dominant alpha frequency recorded from a monopolar occipital lead slowed significantly from the fourteenth to the twenty-fourth day of alcoholization (10 Hz to 8 Hz) and increased significantly (to 10.5 Hz) by the second day

of withdrawal. Hyperventilation produced little effect, but a flickering stimulus produced significantly less photic driving from the fourteenth to twenty-fourth day with a return to normal by the second day of withdrawal. Unlike Wikler *et al.*, no indication of seizure patterns was observed.

The slowing of the alpha rhythm during the period of heaviest alcoholization parallels the findings of Wikler *et al.* The authors suggest that the failure to find EEG seizure activity may be related to the shorter alcoholization period used: 24 days *vs.* 48–55 days in the study by Wikler *et al.* Other differences in the alcohol regimen may also be involved. The BAL's appeared to be generally lower, averaging 100 mg/100 ml during most of the first 2 weeks, and the 4-hr intake *vs.* the hourly intake in the Wikler study may have resulted in a higher and more constant BAL in the latter study.

The finding of significantly reduced photic driving is interpreted to indicate alcohol-induced suppression of the cortical response to photic stimulation. Some support for this interpretation is provided by studies showing a reduction in amplitude of the scalp-recorded sensory-evoked potentials after alcohol. Lolli *et al.* (1964), using a similar flicker procedure, have also interpreted their finding of a relatively greater increase in alpha activity during this task after a single administration of alcohol as indicating a decreased receptivity to external stimulation since flicker usually disrupts alpha activity.

Docter and Bernal (1964) studied pre- to postdrinking changes in the EEG recorded during a sustained period of alcoholization lasting 2 weeks. Two paid male alcoholics received vodka twice a day in an amount equivalent to a daily intake of 1.8 ml/kg of ethanol. Daily Breathalyzer readings ranged from 0.01 to 0.04% during the morning predrink period, and averaged 0.15% and 0.19% for the two subjects 40 min after alcoholization.

The most striking effect was a marked pre- to postdrink increase in seconds of alpha activity recorded from bipolar occipital leads. The amount of change in alpha activity did not appear to vary systematically during the 14-day course of alcoholization. Changes during the course of alcoholization in the daily pre-drink EEG were not reported. Changes in the EEG, in frequency of rapid eye movements, and social behavior were discussed as possible indicators of an "excitatory effect of alcohol."

Newman (1959) investigated the effects of sustained heavy drinking in two chronic alcoholics. A male patient received a daily dose averaging 480 ml of alcohol over a 4-day period. When blood alcohol was maximal, 150 mg%, the EEG's showed a marked increase in slow wave activity in the theta range not seen before alcoholization. Records taken at 1, 2, and 3 days after withdrawal were similar to the predrinking records.

A female who received an average daily dose of 216 ml of alcohol over 5 days showed considerably less slowing in spite of generally higher blood alcohol levels. However, at 48 hr after withdrawal, short bursts of high-voltage

3-4 Hz waves appeared, which were not present before or during the alcoholization period. The patient's history contained several episodes of grand mal type seizures associated with cessation of drinking in the past. Consistent with the discussion by Wikler *et al.*, the paroxysmal slow activity is interpreted as reflecting a hyperexcitable brain state attributable to the withdrawal of alcohol.

In summary, these studies show that a high blood alcohol level sustained over a period of several days to several weeks produces some of the same EEG changes seen after a single large dose of alcohol: a general slowing in the frequency of the predominant wave seen in the EEG and usually an increase in the percent time of alpha activity. Depending upon the alcohol dosage and schedule, tolerance effects may be noted in the EEG records taken during the course of the alcoholization, and paroxysmal slow wave activity typically seen during convulsive seizures may appear from 12 to 48 hr after abrupt termination of drinking.

THE EFFECTS OF ALCOHOL ON BRAIN EVOKED RESPONSES

Technique

The relation between the electrical responses in the human brain and mental processes of integration and association is perhaps the most challenging of all the problems facing psychophysiologists today. Until quite recently, the prospect of unifying physiological and psychological concepts by EEG techniques seemed to be receding because of the baffling complexity of the electrical rhythms, and this difficulty has still not been overcome. The most intriguing, and at the same time most elusive, of the properties of these rhythms is that although often remarkably constant in their variations with respect to time, they fluctuate also, in a much less regular manner, within the three-dimensional space of the brain. The continuous analysis and display of such phenomena presents serious difficulties, and no method has yet given entirely satisfactory results.

However difficult they may be to unravel, the time and space relations of the intrinsic brain rhythms cannot be ignored, if only because so intricate and orderly an arrangement seems unlikely to have survived the struggle for existence with no functional identification. The awkward fact that these rhythms are highly individual—even to the extent of total absence in some people—must be accepted as a fascinating part of the enigma, where personality and disposition are essential features in the architecture of human physiology.

The introduction of more versatile and sophisticated methods for extracting information about transient components of the EEG inevitably diverted interest from the background activity because, by definition, the methods of transient

analysis tend to efface or at least diminish those rhythmic features which are most prominent in the conventional EEG record. This unfortunate technical incompatibility has somewhat discouraged correlative studies, but interaction between the multitude of intrinsic rhythms and the response evoked by sensory stimuli seems an indispensable part of the cerebral information flow system. These influences are complex and often reciprocal: intrinsic rhythms of excitability variation can modify the amplitude and latency of evoked potentials, and the arrival of signals in an afferent channel can modulate the amplitude, phase, and frequency of intrinsic rhythms.

By an evoked potential is meant the detectable electrical change of any part of the brain in response to deliberate stimulation of a peripheral sense organ, a sensory nerve, a point on the sensory pathway, or any related structure of the sensory system. This stimulation can be photic in nature, such as a flash of light; auditory, such as a distinct click or tone; electric, such as a pulse of voltage or current; olfactory, such as a distinct odor; or of any other nature that can be sensed by the nervous system. The stimulus must be controlled as to its rate of occurrence, duration, and amplitude, since each factor may affect the shape of the response.

Each of the above-mentioned stimuli has one basic characteristic in common: the occurrence of the stimulus can be controlled from some external source, such as a pulse generator and, hence, a time reference point for each response is established.

If one looks at the time-varying neuroelectric potential waveforms (EEG) immediately after each stimulus (reference point), we will actually see the total random fluctuations, part of which are caused by the stimulus. The other portions of the fluctuations in the total (noise) are not related to the stimulus and, therefore, are not repetitive or at least not locked in time to the reference point.

The basic assumption made in the method of detecting signals in noise concerns the properties of the noise. The noise component of the signal under consideration must be composed of or approximated by stationary Gaussian random processes with zero averages. By stationary we mean that the random process is independent of time and therefore is unaffected by translations of the origin of time. Although it is not strictly imperative that the probability distribution of the noise be Gaussian, we would not know as much statistically about our results if it were not. Another property sometimes mentioned in relation to noise is that of ergodicity. Since we do not operate on a time function of infinite extent but rather with an ensemble of finite pieces of such functions, it is required that averages across the ensemble be equivalent to averages over time along a stationary function of infinite length. Such a property is termed ergodic. The absence of the above properties can be circumvented to a certain extent in some cases when using the average response method.

To obtain an increase in the signal-to-noise ratio of some functions, one must increase the period of time over which the measurement is made. Since we are dealing with integrative processes, our increase in the signal-to-noise ratio will be approximately proportional to the square root of the time over which the measurement is made.

The theory behind the average response technique is a relatively simple concept. Upon the occurrence of the first timing pulse (stimulus), the analogue function is sampled at regular intervals, the samples being stored in the memory of the computer. The rate of sampling and the number of samples made for each response is determined prior to the start of computation and often depends upon the highest frequency component present in the response and the length of time of the response respectively. Upon the occurrence of the second timing pulse, the signal is again sampled and each sample is added to the value stored during the sample number at the previous response. This cycle is repeated until the desired number of responses have been summated. This method achieves a number of results. Those components of the time function which are random and therefore not phase-locked to the time reference (i.e., the noise) will add algebraically and if enough responses are summed, will tend to cancel or average out to zero. The components of the time function locked in phase to the stimulus are additive themselves with each successive summation. The improvement in the signal-to-noise ratio can be shown to be proportional to the square root of the number of responses summed.

The study of evoked potentials in different brain structures is a powerful tool for obtaining increased insight into the functioning and communication of the brain. Evoked potentials spread and travel from one part of the brain to another. By means of simultaneous averaging processes with separate electrodes, the way in which the evoked potential travels can be mapped. This spread and transformation of evoked potentials in brain space constitutes an important measure which can also, under some circumstances, be related to psychological, physiological, and pharmacological variables. Many drugs have been shown to affect the manner of occurrence of evoked potentials in different brain areas.

Drug Effects

In recent years a few investigators have studied the evoked potentials of alcoholics and the effects of alcohol on evoked potentials in man.

Bergamasco and Gandiglio (1965) investigated the somatosensory evoked potentials in chronic alcoholics. Ten chronic alcoholics without signs of peripheral neuropathy were used as subjects. In each subject the ulnar nerve was stimulated at the wrist and at the epitrochleo-oleocranic groove, and the lateral popliteal nerve at the capitulum fibulae and the neck of the foot. The evoked potentials were obtained by means of electrode needles attached to the scalp in

a position corresponding to the somatosensory area of the leg and hand. In the same subjects, the motor and sensory conduction velocity of the lateral popliteal nerve was measured.

The latencies of various components of the somatosensory evoked potentials were clearly longer than those obtained in normal subjects. The authors state that the increase in latencies and duration might be an indication of the time dispersion at the cortical level of a signal coming from peripheral stations. In these same subjects Bergamini *et al.* (1965) studied nerve conduction velocity and found a slowing of the afferent volley. The authors concluded that a sensory fiber lesion and damage of root and posterior medullary columns are two pathological conditions which alter somatosensory potentials evoked by electrical nerve stimulation. A lesion of the afferent peripheral fiber reduces its excitability and elicits a temporal dispersion of the afferent volley. This causes a decrease in the peripheral afferent conduction velocity, which expresses itself in the cortex by an increase in evoked potential latencies. At the same time the evoked response will have a longer duration accompanying the temporal dispersion of the impulses arising from the periphery. In nerve lesions the somatosensory evoked potential is characterized by an increase of the different peak latencies and particularly by an increase of wave duration.

In a recent study Spilker and Callaway (1969) reported that the average evoked response to sine wave light is apparently related to "augmenting/reducing" since augmentors (as defined on a kinesthetic test) have visual evoked responses that increase in amplitude as the depth of modulation is increased. In contrast, "reducers" show a leveling off or an actual decrease in visual evoked responses at high depths of modulation. In an attempt to test the effects of arousal, these investigators studied the effects of various drugs on the amplitude of the visual evoked response. They found that sodium pentobarbital and ethyl alcohol both significantly decreased the slope of the visual evoked response amplitude at the four highest depths of modulation.

The effects of alcohol on the auditory evoked response have been studied in our laboratory and reported by Gross *et al.* (1966). We found that the amplitudes of the auditory evoked response are significantly reduced after alcohol ingestion, with maximal effects observed at 15–30 min after ingestion.

Salamy *et al.* (1969) have reported that the late components of the somatosensory evoked response are also quite sensitive to the depressant effects of alcohol. They found the amplitude of this late component to be inversely related to the alcohol level in the blood. In keeping with these results, Lewis *et al.* (1970) reported that after ingestion of 3 oz of alcohol, the amplitude of a number of late waves of both visual and somatosensory-evoked responses recorded from central areas was significantly decreased.

In conclusion, it may be said that alcohol significantly reduces the late component of the visual, auditory, and somatosensory evoked responses in man.

Recently, Stohr and Goldring (1969) reported that the late components of the somatosensory-evoked response originate in the primary cortical area and Vaughan and Ritter (1970) concluded that the late vertex response to sound originates in the primary auditory cortex of the brain. Consequently, it appears quite likely that the cortex is the primary site of action for alcohol. In a preceding chapter, Himwich and Callison (Chapter 3) reached a similar conclusion based on the effects of alcohol on evoked potentials of various parts of the central nervous system of the cat.

THE EFFECTS OF ALCOHOL ON THE RECOVERY FUNCTION OF EVOKED POTENTIALS

The concept of a cortical excitability cycle rests principally on amplitude measures of cortical potentials evoked by a sensory stimulus or by direct cortical stimulation, although other criteria could be used (rate of neuron firing, thresholds of single neural units, convulsive threshold). Typically, it has been based on the observed phenomena that when a stimulus is presented to the nervous system, the amplitude of its resulting evoked potential varies as a function of the temporal relationship between the stimulus and the spontaneous potentials or previously evoked potentials in the brain.

Recovery time studies using paired stimuli are good indicators of temporal periodicities. The cycle activity of evoked potentials in anesthetized cats elicited by direct cortical stimulation (Chang, 1951) and by afferent stimulation (Chang, 1950) reflected changes in excitability in terms of the amplitude of a second evoked potential elicited by a second stimulus. Such recovery cycles have also been found when nonanesthetized animals were used (Evarts *et al.*, 1960; Palestini *et al.*, 1965).

Changes in cortical excitability cycles have also been studied with various drugs. Schwartz *et al.* (1962) reported that the recovery cycle of somatosensory-evoked responses was more sensitive to pentobarbital sodium than was the amplitude of single evoked responses. Gartside *et al.* (1966) studied the effects of lithium carbonate on the somatosensory recovery function of nondepressed volunteers. They were able to produce a decrease in the recovery function comparable to that found in depressive patients. Shagass and Schwartz (1962) found that imipramine and tranylcypromine were able to bring the recovery function of patients with psychotic depression back to a normal level.

Evarts *et al.* (1961) studied the effects of alcohol on the recovery cycle in cats and reported an increase in excitability. Consequently, we undertook a study (Begleiter *et al.*, in preparation) of the effects of alcohol on the somatosensory recovery function in humans.

The experiment was performed on 16 healthy adult male volunteers. Somatosensory responses were evoked by stimulating the median nerve of the right wrist through electrodes placed on the skin 3 cm apart. The stimulus was a pulse of 1 msec duration at an intensity 3 mA above the subject's thumb twitch.

Recording electrodes were placed in the parasagittal plane 7 cm left of the midline. The posterior lead was 2 cm behind a line from vertex to external auditory meatus and the other was 6 cm anterior to it. The EEG was amplified and fed into a computer using a 512 msec analysis time.

Twelve interstimulus intervals were used for recovery cycle determinations. These were as follows: 2.5, 5, 10, 15, 20, 35, 50, 65, 80, 95, 110 and 130 msec. These intervals were randomized across subjects. Stimulus repetition frequency was variable from 1 to 3 sec. Each stimulus sequence involved alternating presentation of two paired and two unpaired stimuli. Fifty pairs and fifty single stimuli were summated.

Recovery curves were derived only from the initial, or primary, response. The amplitude taken was the deflection from the maximum negative trough to the positive peak.

Since a recovery function determination may last over 2 hr, it became important for us to maintain a fairly constant blood alcohol level during that period of time. In order to accomplish this, we conducted a pilot study using eight subjects. Multiple dose administration with doses spaced to maintain a constant blood alcohol level was followed in accordance with the method developed by Goldberg (1960, 1961).

In the recovery function experiment the subjects received alcohol (80-proof bourbon) on one morning and an equal amount of water on the other morning. These two conditions were counterbalanced for all 16 subjects. Before the electrodes were placed on the scalp, each subject was asked to drink an amount of alcohol in the ratio of 1.5 g of alcohol per kilogram of body weight. The subject was given a period of 5 min to finish his drink. Approximately 60 min after the intake of alcohol, the first blood alcohol level was determined. The second dosage of alcohol given was calculated on the first blood alcohol level. Two hours after alcohol intake another blood alcohol level was obtained which determined the amount to be given in the third dose.

The usual way of illustrating recovery functions has been to plot the ratio of the second to the first response, i.e., the R_2/R_1 ratio. If we display the data in this fashion (Fig. 1) the difference between the alcohol curve and water curve is statistically significant. This would support the findings of Evarts *et al.* (1961) who found greater excitability with alcohol.

Recently Shagass (1968) reported that R_1 and R_2 are significantly correlated, and that the regression of R_2 and R_1 does not pass through the origin. In order to correct R_2, the correlation between R_1 and R_2 was determined for each interstimulus interval, with calculation of the "within-groups" regression

equation. The regression equation was then used to adjust the R_2 value for its covariance with R_1. The adjusted R_2 values (Fig. 2) were then compared to determine the significance of treatment differences. The difference between the adjusted R_2 alcohol curve and that for the water curve was not statistically significant.

In recent years, a number of investigators (Isbell *et al.*, 1955; Mendelson *et al.*, 1964) have postulated that alcohol withdrawal represents a process of physiological addiction or physical dependence and that this process is similar to addiction induced by other pharmacological agents. We have postulated that the mechanisms of physical dependence become operative much before total withdrawal from alcohol. It is felt that after a relatively short period of drinking, the cessation of alcohol intake might be accompanied by incipient withdrawal symptoms.

In their studies of critical flicker fusion, Weiss *et al.* (1964) advanced the hypothesis that the effect of alcohol on the nervous system is to suppress both excitatory and inhibitory components, the latter more than the former. This differential suppression becomes greater as the duration and extent of alcohol intake increase. After alcohol withdrawal, the excitatory components recover

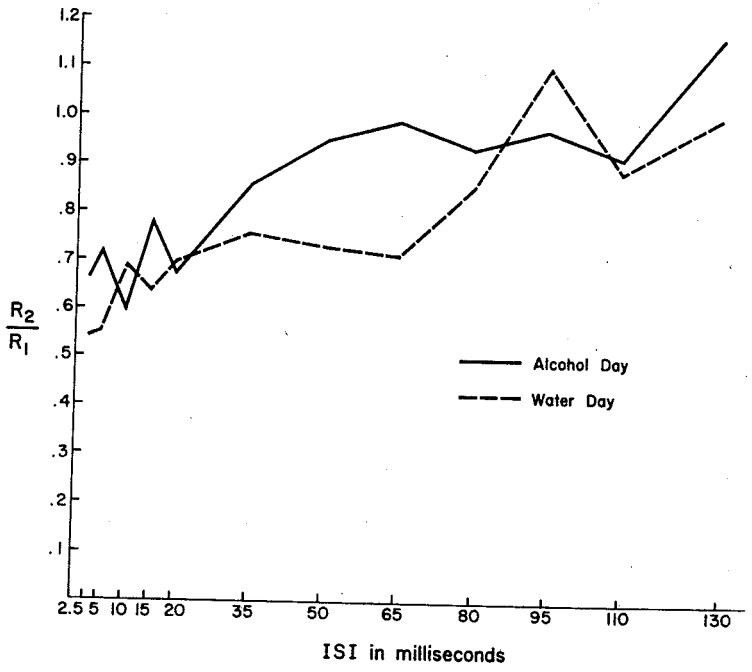

FIGURE 1

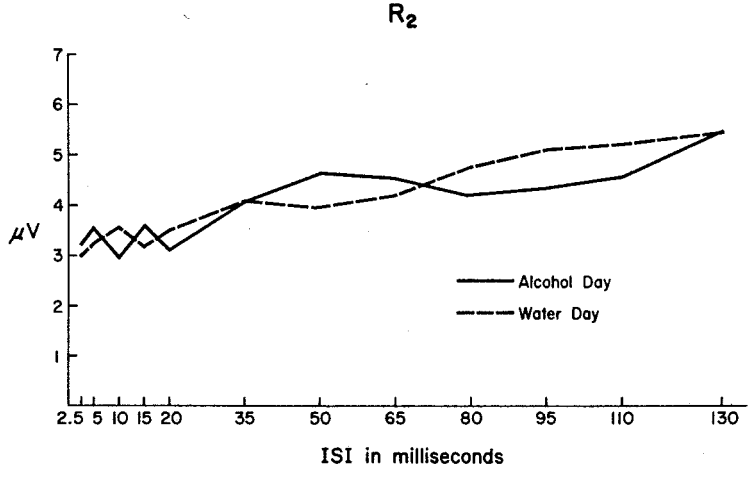

FIGURE 2

more rapidly than the inhibitory components; this inhibition is manifested as a seeming hyperexcitability.

In an attempt to test this hypothesis, we have recently undertaken to study the excitability cycle of the somatosensory recovery function in man, during alcoholization and withdrawal. The four subjects used were all alcoholics who had been sober in the hospital for a period of 6 to 8 weeks. A recovery function determination was always made in the morning during the 2 days of baseline, 4 days of alcoholization, and the 4 days subsequent to alcoholization. The subjects were asked to drink 30 oz of 90-proof whiskey during the 4 days of alcoholization. The alcohol intake was divided in four equal doses and always took place in the afternoon between 1 p.m. and 11 p.m.

Each subject was also tested for a comparable period of days without alcohol. Two subjects received the drug condition first and then the no-drug condition. The other two subjects received the no-drug condition first and then the alcohol condition. The recovery function was always taken at 9 a.m. in the morning after the subject had received his last drink at 11 p.m. the preceding day.

We postulated that after each of the 4 days of alcoholization, the cessation of drinking at night might be accompanied by incipient withdrawal the next morning.

The preliminary results indicate a progressive increase of excitability starting with the alcoholization period and reaching asymptote with the first day of total alcohol withdrawal. During the subsequent days of testing the recovery function decreased, approaching the level obtained during baseline determinations.

The recovery function determinations obtained during the control period for the four subjects showed no significant change over time.

The results we have obtained with the recovery function of somatosensory-evoked potentials during alcoholization and withdrawal appear to be in general agreement with the findings of Isbell *et al.* (1955), Wikler *et al.* (1956), Weiss *et al.* (1964), and Victor (1968).

SUMMARY

It is obvious that many alcoholics with a long history of heavy drinking develop certain brain aberrations. However, electroencephalographers have not enjoyed much success in detecting EEG abnormalities in chronic alcoholics. It appears quite reasonable to suspect that our present methods of EEG recording and analysis are rather insensitive to the damaging effects of chronic alcohol intake.

Acute intoxication produced by increasing concentrations of alcohol in the blood produces impairment of psychological functions such as perception, discrimination, association, and voluntary response. These functions are often attributed to neural activity at the cortical levels of the central nervous system. The study of direct effects of alcohol upon brain processes is rather limited by the close reciprocal influences exerted between cortical and subcortical systems. Consequently, an effect of alcohol upon changes in electrical activity of the cortex may result from either a direct action on cortical neurons or an indirect one exerted via a change in modulatory influences of subcortical neurons.

It is quite possible that instead of a progression of alcohol effects from the cortex downward, there may be a progression of effects at all levels concurrently, with the preponderance of effects being subcortical.

At this point it is clear that alcohol exerts direct and indirect actions at many levels of the nervous system. The possible sites of primary action of alcohol in the brain should be greatly clarified by further single neuron studies in the intact organism.

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