# CHEMICAL MANIPULATION OF THE OCCIPITAL

5

EEG POWER SPECTRUM

•

# SOME ATTEMPTS TO MANIPULATE THE HUMAN ALPHA FREQUENCY AND THE APPLICATION OF A FOURIER ANALYSIS TO THE EEG FREQUENCY SPECTRUM

ΒY

JOHN SANTA-BARBARA, B.A.

### A Thesis

Submitted to the Faculty of Graduate Studies in Partial Fulfilment of the Requirements

for the Degree

Master of Arts

McMaster University October 1967 MASTER OF ARTS (1967)

McMASTER UNIVERSITY

(PSYCHOLOGY)

#### Hamilton, Ontario

1 hr

TITLE: Some Attempts to Manipulate the Human Alpha Frequency and the Application of a Fourier Analysis to the EEG Frequency Spectrum.

AUTHOR: John Santa-Barbara, B.A. (Boston College)

SUPERVISOR: Professor A.B. Kristofferson

NUMBER OF PAGES: viii, 141

SCOPE AND CONTENT:

The present study has two objectives. The first is to apply a reliable and valid technique of eeg frequency analysis to the measurement of the human alpha rhythm. The second objective is to find a chemical agent which will alter an individual's dominant occipital frequency 2 Hz from its resting frequency. The techniques used are: dextrose ingestion, fasting, oxygen inhalation, hyperventilation, carbon dioxide inhalation, diamox, alcohol, librium and dexedrine. The treatments which did produce a 2 Hz shift in dominant frequency also produced new peaks in other parts of the frequency spectrum. Evidence is presented which suggests that the alpha rhythm can be made to fluctuate over a very narrow frequency range ( approx. 1 Hz ).

### ACKNOWLEDGMENTS

I would like to acknowledge the guidance of Dr. A.B. Kristofferson in this project. His influence on my scientific standards has been as powerful as it has been subtle. Dr. G.K. Smith provided much honest criticism which has saved the author considerable embarrassment. Dr. R.W. Einhorn, M.D. is to be thanked for his practical advice concerning the administration of the drugs and gases used. He generously provided the prescriptions needed and supervised the medical aspects of this project. The computor program for the power spectral density function was written by Ron Harper. His generous assistance is appreciated. Finally, I would like to thank my wife, Holly, for putting constraints on my exotic grammar, and for typing the manuscript.

### TABLE OF CONTENTS

| GENERAL INTRODUCTION<br>THEORETICAL INTRODUCTION<br>SUMMARY 3<br>STATEMENT OF PURPOSE 3<br>METHODOLOGY 3<br>EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND | aç |
|--|----|
| THEORETICAL INTRODUCTION SUMMARY STATEMENT OF PURPOSE METHODOLOGY EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND   | 1  |
| SUMMARY3STATEMENT OF PURPOSE3METHODOLOGY3EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND  | 3  |
| STATEMENT OF PURPOSE 3<br>METHODOLOGY 3<br>EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND  | i4 |
| METHODOLOGY 3<br>EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND  | 5  |
| EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND   | 7  |
|  |    |
| A VISUAL METHOD OF EEG FREQUENCY   |    |
| ANALYSIS 4   | 3  |
| EXPERIMENT 2. ALCOHOL 5  | ;1 |
| EXPERIMENT 3. CARBON DIOXIDE METABOLISM 6  | 3  |
| EXPERIMENT 4. GLUCOSE  | 6  |
| EXPERIMENT 5. CHLORDIAZEPOXIDE(LIBRIUM) 9  | 7  |
| EXPERIMENT 6. DEXTRO-AMPHETAMINE SULFATE(DEXEDRINE) 10   | 15 |
| SUMMARY OF RESULTS 11  | 2  |
| DISCUSSION 11  | 7  |
| CONCLUSION 12  | 8  |
| REFERENCES 12  | 9  |

### LIST OF FIGURES

.

.

| FIGURE | 1.  | AUTOCOVARIANCE AND POWER SPECTRAL FUNCTIONS   |     |
|--------|-----|---|-----|
|        |     | IN THE NORMAL AND DRUG (DEXEDRINE) CONDITIONS | 48  |
| FIGURE | 2.  | POWER SPECTRA OBTAINED WHILE HYPERVENTILATING |     |
|        |     | AT HIGH BLOOD ALCOHOL LEVELS                  | 59  |
| FIGURE | 3.  | BETWEEN-DAY VARIABILITY OF POWER SPECTRA FOR  |     |
|        |     | ONE SUBJECT                                   | 61  |
| FIGURE | 4.  | POWER SPECTRA DURING HYPERVENTILATION         | 73  |
| FIGURE | 5.  | POWER SPECTRA DURING HYPERVENTILATION         | 74  |
| FIGURE | 6.  | POWER SPECTRA DURING HYPERVENTILATION         | 76  |
| FIGURE | 7.  | POWER SPECTRA DURING HYPERVENTILATION AFTER   |     |
|        |     | DIAMOX INGESTION                              | 79  |
| FIGURE | 8.  | POWER SPECTRA DURING HYPERVENTILATION AFTER   |     |
|        |     | DIAMOX INGESTION                              | 80  |
| FIGURE | 9.  | POWER SPECTRA DURING HYPERVENTILATION AFTER   |     |
|        |     | DIAMOX INGESTION                              | 81  |
| FIGURE | 10. | POWER SPECTRA OBTAINED WHILE HYPERVENTILATING |     |
|        |     | AFTER FASTING OVERNIGHT                       | 93  |
| FIGURE | 11. | POWER SPECTRA OBTAINED AFTER DEXTROSE         |     |
|        |     | INGESTION AND OXYGEN INHALATION               | 96  |
| FIGURE | 12. | POWER SPECTRA AFTER INGESTING VARIOUS DOSES   |     |
|        |     | OF LIBRIUM                                    | 100 |
| FIGURE | 13. | POWER SPECTRA DURING HYPERVENTILATION AFTER   |     |
|        |     | INGESTING LIBRIUM                             | 102 |

v

| FIGURE | 14. | POWER  | SPECTRA  | DURING | HYPERVE | INTILATION  | AFTER             |     |
|--------|-----|--------|----------|--------|---------|-------------|-------------------|-----|
|        |     | INGEST | ING LIBP | NUIN   |         |             |                   | 103 |
| FIGURE | 15. | POWER  | SPECTRA  | DURING | OXYGEN  | INHALATION  | AFTER             |     |
|        |     | INGEST | ING DEXE | IDRINE |         |             |                   | 109 |
| FIGURE | 16. | POWER  | SPECTRA  | AFTER  | NGESTIN | NG DEXEDRIN | ार<br>अ<br>ब्रह्म | 110 |

## LIST OF TABLES

•

|       |     |  | Page        |
|-------|-----|--|-------------|
| TABLE | 1.  | COMPARISON OF THE POWER SPECTRAL AND A   |             |
|       |     | VISUAL METHOD OF EEG FREQUENCY ANALYSIS  | 45          |
| TABLE | 2.  | POWER SPECTRAL ESTIMATES(Hz) OF BETWEEN- |             |
|       |     | DAY VARIABILITY                          | 47          |
| TABLE | 3.  | DOMINANT OCCIPITAL FREQUENCY(Hz) DURING  |             |
|       |     | HYPERVENTILATION                         | 58          |
| TABLE | 4.  | DOMINANT OCCIPITAL FREQUENCY(Hz) DURING  | ,           |
|       |     | HYPERVENTILATION                         | . 72        |
| TABLE | 5.  | DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER   |             |
|       |     | DIAMOX AND DURING HYPERVENTILATION       | 77          |
| TABLE | 6.  | DOMINANT OCCIPITAL FREQUENCY(Hz) DURING  |             |
|       |     | CARBON DIOXIDE INHALATION                | 84          |
| TABLE | 7.  | DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER   |             |
|       |     | FASTING AND DURING HYPERVENTILATION      | 88          |
| TABLE | 8.  | DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER   |             |
|       |     | DEXTROSE INGESTION AND DURING OXYGEN     |             |
|       |     | INHALATION                               | 95          |
| TABLE | 9.  | DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER   |             |
|       |     | VARIOUS DOSES OF LIBRIUM                 | 99          |
| TABLE | 10. | DOMINANT OCCIPITAL FREQUENCY(Hz)AFTER    |             |
|       |     | VARIOUS DOSES OF DEXEDRINE AND DURING    |             |
|       |     | OXYGEN INHALATION                        | 10 <b>7</b> |

| TABLE | 11. | SUMMARY  | OF  | POWER   | SPECT | RAL  | CHANC | GE S | FOR | EACH |   |        |  |
|-------|-----|----------|-----|---------|-------|------|-------|------|-----|------|---|--------|--|
|       |     | EXPERIME | INT | AL TREA | TMENT | ſ    |       |      |     |      | 1 | 13-114 |  |
| TABLE | 12. | SUMMARY  | OF  | CHANGE  | S IN  | DOMI | NANT  | PE   | AK  |      |   | 115    |  |

### GENERAL INTRODUCTION

Modern neurophysiology regards the electrical activity of the brain as a most important indicator of cerebral functioning. Even the technique of recording the brain's electrical activity through the intact skull and scalp, as in the electroencephalogram or eeg, has proven to be a valuable clinical and experimental tool. Yet the phenomenon which led to the discovery of the human eeg, the alpha rhythm, remains an elusive, eclectic's panacea. Hans Berger (1929), the discoverer of the human eeg, believed that the alpha rhythm was the physiological substratum of the "waxing and waning of attention," a concept borrowed from James (1890). This hypothesis and others, concerning the relationship of the alpha rhythm to attentional processes, have been reviewed in a number of papers (Ellingson,1956; Harter,1967; Lindsley,1952; McReynolds,1953; Obrist,1965; Walter,1950,1953; and White,1963).

Although the basic concept appears relatively simple and straightforward, proof that the alpha rhythm is related to attentiveness has been beset with technical and theoretical difficulties. The technical difficulties are at least twofold. On the one hand, characteristics of the alpha rhythm such as frequency, have usually been determined by descriptive, nonquantitative techniques of questionable reliability and validity. On the other hand, the methodologies used for measuring rapid changes in attention are often not the best which present technology offers. The latter difficulty arises, in part, from theoretical ambiguity concerning exactly what type of process is to be measured. Is attention continuous or discrete ? Does attention involve a scanning device or a gating mechanism ? In short, the ambiguity concerns exactly what is meant by "attention," or what aspect of "attention" is to be measured. A clear position must be taken before precise behavioral or neurophysiological measurement can be made.

Another characteristic of research on the relationship of the alpha rhythm and "attention" is a tendency to compare averaged, group data, and to use correlational rather than experimental designs. <u>Intra</u>subject designs, in which one of the relevant variables ( alpha frequency ) is manipulated, and concomitant variations are measured in the other variable ( some well defined aspect of attention), would be a very strong test of the basic hypothesis. Such a study would require:

1). a precise theoretical statement concerning the aspects of attention to be measured;

2). a precise and reliable technique for measuring these aspects of attention;

 a reliable and accurate method of measuring intraindividual differences in alpha frequency;

and 4). a reliable technique for manipulating the alpha frequency.

The first two requirements appear to be satisfied in the work of Kristofferson(1965,1966,1967). The requirements concerning the measurement and manipulation of the alpha frequency are the objectives of the present study.

#### THEORETICAL INTRODUCTION

Historical Background.

The historical background of the present research contains two, somewhat independent issues. There is the notion of "attention" as a discrete, central process, as discussed by psychologists from James (1890) to the present. These is also the notion of a "cortical excitability cycle," associated with the alpha rhythm, as described by Bishop (1933), and other neurophysiologists (Bartley,1940; Bartley and Bishop,1939). Both terms, "attention" and "cortical excitability cycle," have each been used in different ways by different investigators. Furthermore, another set of investigators has dealt with phenomena which may be relevant to the meaning of these terms, as they are to be developed here. Yet these investigators have not used the terms "attention" or "cortical excitability cycle " (e.g., Boynton, 1961; Stroud, 1949). Even more confusion has been introduced into the issue by a number of studies concerned with the relationship between the alpha rhythm and some aspects of attention which have not been related to the aspect of periodicity as described here ( e.g., Williams, et.al., 1962).

Several reviews (Bertelson,1966;Ellingson,1956; Harter, 1967; Lindsley,1952;McReynolds,1953; Obrist,1965;Walter,1950, 1953; White,1963) have discussed one or more of these issues, and no attempt will be made to produce a comprehensive review of them here.

Rather, it is the purpose of this introduction to clearly describe and compare: 1) some behavioral aspects of attention which follow from the view that attention is periodic and discrete; and 2) a particular type of cortical excitability cycle, which is thought to be related to the periodic nature of attention.

A Discrete Model of Attention.

The notion that attention is basically a discrete, rather than a continuous process, is an old one. James (1890), Wundt (1893), and Freud (1911), for example, each suggested that discrete, psychological intervals were the basic units of attention. Arguments supporting this view are both theoretical and empirical, as well as behavioral and physiological. These arguments have recently been reviewed by Bertelson (1966) and Harter (1967).

To describe attention as discrete hardly begins to eliminate theoretical ambiguity. Several theories which incorporate this notion are different from each other in other important ways. Ellingson's (1956) review gives examples of a). different kinds of scanning models (Pitts and McCulloch, 1947;Stroud,1949; Walter,1950,1953; and Wiener,1948) which are based on an analogy with the television scanning principle; b). a "neuronic shutter" model (Meister,1951), based on the shutter principle of a movie camera; and c). a sensory timing model (Bartley and Bishop,1939). More recently, Harter (1967) has described two types of hypotheses which have been used to explain the discrete nature of temporal perception. One type

of hypothesis assumes a "gating or timing device," the other assumes a "cortical scanning mechanism." Harter (1967) describes several different models of central intermittency for each of these hypotheses. The notion of attention to be discussed here has properties contained in several of these theories.

Kristofferson (1965,1966,1967) has developed a theory of the microstructure of attention which focuses on the temporal aspects of human information processing. Attention is regarded as a centrally controlled, single channel process. The single attention channel has the function of gating sensory channels at a maximum rate of one channel per quantum, or discrete unit of duration. The quantum is a characteristic of the attention channel, not the sensory channels. It is considered to be of constant duration, at least under environmental condition which vary within the normal range.

The manner in which the sensory channels are scanned has several important features. It is part of the discrete nature of attention that once it is locked onto a particular sensory channel, it must remain on that channel for the entire duration of a quantum. It may remain on the same channel for an integral number of quanta. However, if the central attention channel receives a message from another sensory channel, and a decision is made to switch to that channel, the switch can occur only at the end of a quantum. This viewpoint specifically assumes that the attention channel may be influenced by a sensory channel

other than the one it is gating at the moment.

Kristofferson's model of attention includes discrete intervals which serve to order events in time. The model contains a central processor which operates on a constant periodicity, and which may be influenced by elements ( sensory channels ) other than the one to which it is locked at any specific time. It also contains a delay when switching from one element to another, if the signal to switch is initiated at any point during a period of the central processor.

The evidence being accumulated (Schmidt and Kristofferson, 1963; Kristofferson, 1965, 1966, 1967) not only gives strong qualitative support to the theory, but also provides a precise measure of the duration of the quantum for an individual subject. The fact that three qualitatively different methods of measuring the duration of the quantum have been developed, lends even further support to the theory.

One method involves the distribution of reaction times (Kristofferson,1965,1966). A three-stage quantal model is presented to explain the characteristic, three equal segments of a reaction time distribution. The quantity Q is a measure of the periodicity of the central processor. A second method attempts to measure the time required to switch from one sensory channel to another, by measuring the effect upon discrimination reaction time of uncertainty regarding the channel over which the next signal will arrive. This method yields the coefficient K (Kristofferson,1965,1966).

б

The most precise technique developed to date involves the discrimination of successive stimuli from simultaneous stimuli (Kristofferson,1965; Schmidt and Kristofferson,1963). The precision is such that the duration of an individual's quantum may be measured a second time to within a 5 millisecond accuracy of the first measurement. The procedure leads to a value of the quantum called M, which is correlated with K and Q across individuals and is equal to them in magnitude.

The experimental procedures used to obtain values of M take into account the time required for a signal to reach the postulated cortical display areas. In fact, the model which is used contains the difference in afferent latency, or conduction time, between the visual and auditory channels as a parameter. This issue of afferent latency has frequently been ignored by investigators, and consequently has detracted from their measurement of a purely central periodicity.

Aside from the quantitative estimates of the relevant parameters, the technique for measuring M has other methodological advantages. The parameters are estimated for individual subjects, not groups of subjects. Each subject is highly practiced, and only the stabilized data enter into the final computation of M. Furthermore, the stimuli are fully specified for the subject. The latter two points are important if optimal performance is required from the subject. The kinds of tasks needed to measure the periodicity of the central processor are unusual in the demands they make upon the subject.

This seemingly obvious point has also been ignored by many investigators.

More recently, Kristofferson(1966,1967) has shown a very close relationship between M and the alpha half-cycle, for 21 subjects. The alpha half-cycle is the interval between zero-crossings of the subject's alpha rhythm.

Kristofferson's model of attention has a precise theoretical framework and accurate and reliable techniques for measuring certain temporal aspects of a mechanism which may control attention. Furthermore, the model appears compatible with the notion of a cortical excitability cycle to be outlined in the next section.

Two comments should be made concerning the general approach. The first concerns the level of analysis. The model is concerned with what has been called the "microstructure" of attention(Kristofferson,1965). The discrete psychological interval, or quantum, is considered to be the basic temporal dimension of central activity involved in processing sensory information. The second comment is implied in the first. The unit of analysis is a temporal unit. The basic properties of the quantum are temporal, and the functions of the quantum are manifested in the time flow of certain events.

The Cortical Excitability Cycle.

The notion of a cortical excitability cycle was first used by Bishop (1933) to describe spontaneous fluctuations in cortical sensitivity, associated with the alpha rhythm, to sensory stimuli. The term has since been used by a variety of investigators (Chang, 1950, 1951; Cigánek, 1964; Gastaut, 1953; and Schwartz and Shagass, 1964) to describe certain characteristics of evoked cortical responses which are not directly related to Bishop's original usage.

The notion of a cortical excitability cycle to be discussed here has properties to be found in Bishop's use of the term, and in similar usages. Bishop described the term as follows.

> "There is a spontaneously rhythmic variation in excitability...the time in this cycle at which the stimulus falls determines whether or not a response shall take place in the cortex...if the first of the two stimuli falls in a refractory part of the cycle, it does not alter the cycle in phase, and a second stimulus, falling necessarily later in this cycle must be effective if the first is ineffective, because by this time these particular elements will have become excitable again." (Bishop, 1933, p. 216).

Bishop (1933) based this notion on the following observations. If a rabbit's optic nerve is electrically stimulated with repetitive submaximal stimuli, the magnitude of the cortical responses is variable unless the stimuli are timed at a certain critical frequency. The critical frequency which produced maximal cortical responses of constant amplitude

was equal to the spontaneous frequency of the rabbit's cortex. Bishop (1933) and Bartley (1940) present evidence that the amplitude of the cortical response can be made to vary, or be inhibited, by altering the relationship between the frequency of the repetitive stimulation and the frequency of the spontaneous cortical activity.

Ellingson (1956) calls the cortical excitability cycle a "sensory timing mechanism" and describes its properties in the following manner:

> "The proposed mechanism is relatively simple. The probability that incoming impulses will cause a neuron to fire will vary with the phase of the excitability (alpha) cycle. Impulses arriving at synapses when the trans-synaptic neuron is in the phase of increased excitability will be more likely to fire the trans-synaptic neuron...And when the excitability cycles of a group of neurons are synchronized, then the flow of impulses through that group will be timed by the frequency and phase of the cycle." (p. 9).

These notions of a cortical excitability cycle signify that the alpha rhythm describes the state of cortical receptivity. Cortical sensitivity to sensory stimuli is seen as changing spontaneously, and in a periodic manner. Implied in the descriptions of these notions is a variety of functions which have been attributed to the alpha rhythm by other investigators.

Walsh (1952) made the suggestion that the alpha rhythm may be at least partly responsible for the fluctuations in detection thresholds. If a stimulus, whose intensity is just adequate to initiate a cortical response when the excitability cycle is in its most sensitive phase, is introduced into an insensitive phase of the cycle, no response should occur, although the stimulus intensity has remained constant.

If a supraliminal stimulus is introduced into an insensitive or "off" phase of the excitability cycle, and its sensory signal persists until the sensitive or "on" phase recurs, there will be a delay in the cortical response to the stimulus. This line of reasoning has led several investigators to use reaction time measures as an indicator of cortical sensitivity (Birren, 1965; Callaway, 1961; Obrist, 1965; Surwillo, 1961; and Walsh, 1952). If the on-off cycle is very rapid, the mean reaction times should be lower than if the on-off cycle is very slow. It is argued that in the latter case, the delays which are introduced when the sensory signal interacts with the "off" phase will be longer than when the cycle is rapid.

This on-off periodicity attributed to the sensory cortex is similar to the gating or switching mechanism found in digital computing devices. With such an internal periodicity, the input-output and internal processing activities of the computer may be simplified. Walter (1950, 1953) has argued that the brain must have an internal periodicity in order to organize its activity. It is argued that such an internally generated time base is necessary to provide information concerning the sequential aspects of sensory and central messages. In short, Walter has proposed that the brain has the properties of a discrete state machine (Turing, 1956). The same viewpoint has been advanced from a purely neurophysiological

consideration of the properties of cortical neurons (Robertson, 1966).

There are two important properties in such a notion of brain function which should be distinguished - the notions of discreteness and periodicity. The brain may function with the aid of a discrete time base, but it is not necessary to make this assumption. Analogue devices exist which can deal with continuous or discrete signals. The primary property attributed to the excitability cycle is its periodicity. Furthermore, the periodicity is designated to be equivalent to the alpha frequency. The description of the periodicity as containing an on-off sequence is unnecessary. At best, these terms describe a functional relationship between the phase of excitability and some measure of that excitability. At worst, these terms are confused with the term periodicity.

As it will be used here, the notion of a cortical excitability cycle has the following properties. The fluctuations in excitability are considered to be <u>spontaneous</u> and <u>central</u> in origin. The excitability cycle describes the <u>periodicity</u> of cortical receptivity to sensory stimuli. Its primary psychological function is to <u>order events in time</u>, and it is associated with the <u>alpha rhythm</u>.

It is necessary to explicate the points of similarities and differences between the notions of a cortical excitability cycle and Kristofferson's model of attention. First, the similarities: The most important properties both notions have in common is a periodicity which sets limits on the time

flow of events in the central nervous system. Neither the quantum nor the cortical excitability cycle is regarded as controlling attention in the sense of deciding which sensory channel is to be gated. An attention mechanism, unspecified in both notions, exerts this type of control. The quantum and the excitability cycle control some aspects of the temporal organization of this attention mechanism, restricting <u>when</u> the attention mechanism may switch channels, and <u>how long</u> it must remain on that channel after switching.

The differences between the two notions arise from the fact that the cortical excitability cycle does not account for all of the functions performed by the quantum model. Kristofferson's model asserts that the attention channel has access to several sensory channels. Although the alpha rhythm is recordable over large areas of the cortex (parietal and temporal, as well as occipital lobes) (Perez-Borja, et. al., 1962; and Walter, 1960), it is impossible to attribute this property to it. Not enough is known about the mechanisms which generate the alpha rhythm. Similarly, it is not possible to attribute the single channel property which is assigned to the attention channel in the quantum model, to the cortical excitability In view of these restrictions, it is also impossible cvcle. to know whether the excitability cycle can be influenced by sensory channels other than the one it is gating at any particular moment. A final important difference between the two notions is that the quantum is described as a discrete interval. This issue is left open in the notion of a cortical excitability

cycle, at least for the present.

It might be pointed out that the notion of an excitability cycle, cast in one form or another, is a notion widely held by physiologists and psychologists alike. The need for such a concept is hardly disputed. Attributing the role of an excitability cycle to the alpha rhythm, however, is somewhat more controversial. The evidence, pro and con, is presented below.

It should be noted that no causal role is attributed to the alpha rhythm in this notion of a cortical excitability cycle. The alpha rhythm is thought to be associated with certain temporal aspects of information processing. These rhythms are considered to be a manifestation of more basic neurophysiological mechanisms. The exact mechanisms responsible for the generation of alpha rhythms are not well understood. The alpha rhythm may serve as a tool to understand these mechanisms, but it should not be confused with the mechanisms themselves.

It should also be noted that the physiological evidence for a cortical excitability cycle is not conclusive. The notion has been developed here as a precise working hypothesis concerning the relationship between the alpha rhythm and certain temporal aspects of human information processing. The evidence that has been accumulated is largely behavioral and correlational.

### The Alpha Rhythm and Attention

This section will not review all those studies which have investigated a relationship between the alpha rhythm and some aspect of attention. Only those studies which have been concerned with the aspects of attention and a cortical excitability cycle as previously described, will be discussed.

In a relaxed, waking state, the human eeg often shows a predominance of 8-12 Hz waves of approximately 50  $\mu$ V, called the alpha rhythm. For the full range of frequency and amplitude variations in the normal adult, see Walter (1959), and Cobb (1963).

Four sets of relationships have been investigated in this type of research. The <u>phase</u> of the alpha cycle has been correlated with 1) visual detection thresholds and 2) reaction times. The alpha <u>frequency</u> has been correlated with 3) reaction times, and 4) central switching times. All of the studies to be cited used a visual method of determining the eeg frequency.

Walsh (1952) attempted to measure both reaction time and visual threshold as a function of alpha phase. He reports a lack of correlation between alpha phase and visual thresholds, and a positive correlation between alpha phase and reaction times. However, the results of both experiments are questionable, in that no account was taken of the time required for the signal from the receptor organ to reach the relevant cortical projection area. Walsh merely estimated the phase of the alpha rhythm "at the moment of stimulation." Such a technique has dubious reliability, considering the variability in latency of visual evoked responses across and even within individual subjects (Kooi and Bagchi, 1964; and Werre and Smith, 1964).

Lansing (1957) attempted to account for the effects of afferent latency by taking Monnier's (1952) estimate of 35 ms. However, individual differences in both alpha frequency and the latency of visual evoked responses (Kooi and Bagchi, 1964; and Werre and Smith, 1964) make this procedure questionable for accurately determining the phase of the alpha cycle which is stimulated. Lansing reported that there are points on the alpha cycle which are associated with reliably long or short reaction times.

Another series of experiments was performed by Callaway (1960, 1961, 1962, and 1965). Callaway also neglected the issue of afferent latency. He did use a particular phase of the alpha cycle, plus some variable delay, to electronically trigger a stimulus into a particular phase of the next alpha cycle (assuming the variability of individual alpha cycles and afferent latency to be small enough to be ignored). Such a procedure may allow for consistent results, but it does not permit a description of the "true excitability period," defining the exact phase of the alpha cycle associated with the longest or shortest duration times. In Callaway's experiments, the maximum absolute difference in reaction time obtained from different phases of the alpha rhythm was only 6 msec.

The most recently reported study is that of Dustman and Beck (1965). This study is the first and only one to measure

afferent latency directly. The authors did so by measuring the visual evoked response (VER) elicited by the same light source that signaled reaction time. They found that the latencies of certain waves of the VER were positively correlated with reaction time. They chose the earliest wave which showed a highly positive correlation as an estimate of afferent latency. They then chose six points on the alpha cycle and attempted to deliver stimuli to each of these points. After correcting their data for afferent latency, the correlation of reaction time with points on the alpha cycle indicated a point of maximal excitability near the positive peak of the cycle. The point approaching the peak on the positive slope gave the shortest reaction time. The point equidistant from the peak, but on the negative slope, gave a slower reaction This suggests that cortical excitability is influenced time. by the direction of potential change.

Although the study of Dustman and Beck (1965) seems to be the best to date using this design, there are two important criticisms to be made. The authors give no indication that their subjects reached an asymtote in reaction time. Secondly, grouped data were used to determine the points on the alpha cycle of maximal and minimal excitability, and the absolute time difference between these points. If the data for individual subjects are considered separately, the results are more consonant with other experimental findings. For example, Dustman and Beck (1965) report the absolute difference

between points on the alpha cycle of maximal and minimal excitability to be about 34 ms. As calculated from their data by the present author, however, the differences for individual subjects vary from 17\_83 msec, and have a mean value of approximately 50 msec, which is identical to the value of M obtained by Kristofferson (1965, 1966).

The above studies seem to indicate that reliable differences in reaction time may be obtained from different phases of the alpha cycle. Other issues, such as the exact location of the points of maximal and minimal excitability, and the magnitude of the interval between these points, have not received sufficient experimental clarification.

Those investigators who have correlated reaction times with alpha frequency, have usually done so by using groups of subjects who have different alpha frequencies. The dominant eeg frequency is known to vary with age (Gibbs and Knott, 1949; Knott and Gibbs, 1936; Lindsley, 1936; Obrist, 1954, 1963, 1965; and Pond, 1963). In general, young children and aged adults have lower dominant frequencies than individuals in the middle age bracket (approx. 15-60 years). Similarly, simple reaction time varies in the same non-monotonic fashion with age changes. It is higher in young children (Bellis, 1932-33; Goodenough, 1935), and aged adults (Obrist, 1963, 1965; Surwillo, 1961, 1963, 1964).

Obrist (1963) has shown that in aged adults, little or no correlation between dominant frequencies and reaction time is obtained if the measures are recorded at different times.

Simultaneous recordings, however, do indicate a positive correlation. Similarly, Surwillo (1961, 1963) has shown that "age" changes in reaction time are best accounted for in terms of changes in the dominant frequencies, rather than age alone. Some healthy elderly subjects do not show a shift to lower frequencies until very late in life.

Experimental studies which have attempted to alter the dominant eeg frequency, have also shown a strict relationship between the eeg frequency and reaction time. Williams, et. al. (1962) induced a slowing of the eeg frequency by depriving their subjects of sleep for 64 hours. Cortical waves as slow as 4 - 6 Hz may be induced in this way. These authors reported that reaction time could be predicted (correlation significant at the .01 level) by the eeg frequency just prior to the presentation of a signal. The slower the eeg frequency, the greater the reaction time.

Other authors (Birren, 1965; Griesel, 1966; and Rahn, et. al., 1946) have used the technique of hyperventilation to induce a slowing of the eeg frequency. These authors report that an increase in reaction time is associated with a slowing of the dominant eeg frequency. Okuma, et. al., (1966), who conducted a psychophysiological study on the depth of sleep, also report an association between slowing of the eeg and increased reaction time. Similar evidence is available from studies of sensory deprivation. Zubeck (1963, 1964) has shown that the eeg indicates a shift to lower frequencies after

prolonged periods of sensory deprivation. Others (Vernon, et. al., 1961) have shown a general decrement in psychomotor functions after sensory deprivation.

Morrell (1966) used a prolonged vigilance task in her study of eeg frequency and reaction time. Three categories of spontaneous activity were used: alpha (8 - 12 Hz activity), mixed (low voltage activity of random frequencies), and slow (delta and theta activity). Reaction times were fastest when alpha activity was present, and slowest during "slow" activity. There was also a high percentage (29%) of response failures during this "slow" activity.

It should be noted that the experimental studies of Birren (1965), Griesel (1966), Morrell (1966), Okuma, et. al., (1966), Rahn, et. al., (1946), and Williams, et. al., (1962), all produced slow wave frequencies outside of the alpha bandwidth. Theta (4 - 8 Hz) and delta (0.5 - 4 Hz) activity was obtained by their experimental procedures. Such slow wave activity is attributed to subcortical structures not thought to be responsible for the generation of the alpha rhythm (Lindsley, 1960; and Oswald, 1962).

The "Bartley" or "brightness enhancement" effect also suggested the importance of the alpha rhythm to some investigators (Bartley, 1939; Boynton, 1961; and Walter, 1950). If the perceived brightness of a flashing light is measured as a function of flash frequency, it is reported that subjective brightness is greatest when the light flashes at the rate of the alpha rhythm, and the light's "on" period coincides with the positive alpha peaks. Synesthesia is also

reported by some subjects, and epileptic discharges may be induced by such "driving" if the subject is prone to this type of seizure. Although findings of this sort are open to many interpretations, they do demonstrate the significance of the alpha rhythm for basic and intermodal cerebral functions.

The only studies in which a measure of the alpha frequency has been correlated with central switching time have been performed by Kristofferson (1965,1966,1967). Kristofferson uses a measure of the alpha half-cycle because the values obtained for the central switching time, M , are closer to the values obtained from this measure than to the usual frequency measure. Although a visual technique has been used to determine the alpha half-cycle, a recent comparison ( cf. Result\_section, Experiment 1 ) of this method with a power spectral estimate of the alpha frequency ( converted into half-cycle values ) shows the two methods to be highly reliable. Kristofferson is also the only investigator to provide quantitative data for individual subjects. For the 21 subjects used to date, there is a very close relationship between the alpha half-cycle and M. The rank-order coefficient is 0.74.

Critics of such attempts to relate the alpha rhythm to attention often use indirect arguments and point to inconsistencies in the results of various experiments. Detailed criticisms of methodology or theory are the exception. The general criticisms go somewhat as follows. During sleep deprivation or sensory deprivation, the human eeg may indicate patterns ordinarily found in natural sleep although

the subjects remain awake. Patients with brain stem lesions may remain unconscious, but are capable of showing an alpha pattern. Patients in a profound coma have an exceptionally flat eeg, which is capable of showing an arousal pattern of low frequency waves without any evident change in their level of consciousness. Drugs (Bradley and Elkes, 1957) may also produce slow wave activity normally found in the sleeping cat, although the animal is still awake. Selected lesions (Feldman and Waller, 1962) also show a dissociation of electrocortical activity and behavioral arousal.

Such criticisms are not very forceful arguments against designating the alpha rhythm as an excitability cycle. They do,however, point to the dissociation of scalp electrocortical arousal and behavioral arousal, and the danger of associating all eeg patterns with levels of consciousness in any strict, infallible manner. Furthermore, the conditions cited which show this dissociation are abnormal. The few studies directly concerned with the frequency of the eeg and any precise measure of change in attention (Kristofferson,1967; Morrell, 1966; Obrist,1965; Surwillo,1963) show that the relationship between alpha frequency and attention is a direct one.

Another type of criticism points out that some individuals do not show any slow waves in the alpha band, yet are obviously capable of attentive acts; and function normally. It is true that researchers in this area have tended to select subjects with a dominant alpha rhythm. This is largely for the sake of expediency. In answer to this

it might first be noted that nothing is known about the actual attentive abilities of individuals who show no alpha rhythm. The kinds of attentive acts that the excitability cycle is capable of influencing to any noticeable degree, are very demanding ones, not ordinarily encountered.

More to the point is the argument that a distinction must be made between alpha rhythm and alpha activity, as Bartley(1940) and Walter(1950) have suggested. The alpha rhythm is what ordinarily appears in the eeg record. Alpha activity is"the activity which, if not masked by other activity of opposite sign, would appear in the record as the familiar undulations"(Bartley, 1940, p. 635). Such a suggestion is not the tour de force it might first appear The eeg recorded at the surface of the intact skull to be. is not an exact replica of activity at the cortical surface (DeLucchi, et.al., 1962; Perez-Borja, et.al., 1962). Furthermore, more sophisticated methods of measuring eeg frequencies, such as the frequency spectrum analysis of Grass and Gibbs (1938), suggest that certain frequencies may be masked in the paper writeout by an increase in energy at other frequencies (Gibbs, et.al.,1940).

A third type of criticism cites the well known "alpha blocking " reaction as an indication that the alpha rhythm is not present when the person is most attentive. When a stimulus is presented to a subject, or he is instructed to perform some mental task, it is generally held that the alpha rhythm is "blocked" by low voltage fast waves (beta waves). Attention seems to require beta waves to operate efficiently, the argument goes. Actually, this blocking reaction is not the universal response indicated by many authors. The effects of a stimulus or mental activity upon the scalp eeg is simply not that clear cut. Several authors have reported an increase in the amount of alpha rhythm present after a stimulus is presented or mental activity has begun (Darrow,1947; Kreitman and Shaw,1965; Morrell,1966; and Williams,1940). These authors indicate a facilitation of the alpha rhythm in expectation of a signal, when trains of stimuli are used, or when a "Ready" signal is given. Similar findings have been reported in cats by Yoshi,et.al.(1957), who showed a dominant eeg frequency in the occipital cortex and reticular formation identical to the frequency of the stimulating light source, during the intertrial interval.

There are several studies concerned with the relative effects of alpha present or absent, and spontaneous or evoked blocking, on reaction time (Dustman and Beck,1966; Fedio,et.al.,1961; Lansing,et.al.,1959; Morrell,1966; and Stamm,1952). Their results are not in agreement with each other and no conclusion can be drawn from them concerning whether reaction time is faster under blocking conditions or the presence of alpha waves. It should also be noted that alpha blocking, when it does occur, becomes habituated (Wells, 1963) after repeated stimulus presentation. Reaction time, on the other hand, decreases with practice. The complexity of

this problem is further emphasized by the finding (Bechtereva and Zontov,1962) that the effect of a stimulus in producing synchronized or desynchronized activity depends upon which phase of the alpha cycle is stimulated. Several of the studies cited in connection with this issue report some facilitation of the alpha rhythm upon stimulation. The tendency has been to neglect such findings. Those investigators more directly concerned with the facilitating effects of a stimulus upon the alpha rhythm also report a wide range of individual differences. The Bechtereva and Zontov (1962) data may be a way of explaining these discrepancies.

Another way of answering the criticism that beta, and not alpha waves, are most important to attentive acts, is to cite the distinction between alpha rhythm and alpha activity already mentioned. If blocking does result from stimulus presentations, and if it elicits shorter reaction times, spectrum analysis of the eeg record may indicate that an alpha rhythm component is still present and is slightly accelerated under the blocking conditions.

The attempts to correlate alpha frequency and changes in attention seem to be fairly reliable and capable of sustaining the criticisms against them.

Electrogenesis of Spontaneous Cortical Rhythms

The reason for the present interest in the electrogenesis of spontaneous cortical rhythms is to determine whether what is known about the basic functions of such rhythms is compatible with the notion of an excitability cycle. Bremer (1958) and Pupura (1959) have presented reviews on the theories of the origin of cortical rhythms.

At least two general issues can be distinguished concerning the origin of cortical rhythms. One issue involves the mechanism responsible for the synchronous activity itself, and the other involves the nature of the "frequency generators" which regulate the characteristic periodicities of the synchronous activity.

A great number of cellular units are involved in producing the rhythmic waves which are recordable from the surface of the cortex or scalp. Two types of explanation have been proposed to account for this synchrony. Both types involve the notion that one cell can influence other cells, and that it does so in such a way that the excitability cycle of the other cells become synchronized with its bursts and refractory periods. The two types of explanation differ in that one uses the concept of field effects, or ephaptic transmission, whereas the other explanation involves synaptic transmission between systems of interconnected neurons.

Indirect evidence that field effects are important in synchronous activity is available from the work of Gerard and

Libet (1940). They showed that the spread of large electrical potentials induced by application of caffeine was not blocked by a cut through the brain. Spreading depression, however, can be blocked by placing insulating mica strips in such cuts (Sloan and Jasper, 1950). Somewhat more direct evidence is available from the microelectrode studies of Mountcastle, et. al., (1957). These investigators demonstrated that the diameter of the current which develops about an active cortical cell is at least 100µ and probably greater. Using the quantitative data of Sholl (1953, 1955), these authors estimate that a field of 100µ diameters would transect a few hundred perikarya of neighboring cells.

The second type of mechanism offered to explain the synchronous nature of brain waves involves synaptic transmission between the many interconnections of cells in the CNS. Burns (1950, 1951) has used the technique of isolating cortical slabs to provide a demonstration of this mechanism. Stimulating such a slab with a weak, brief, stimulus, similar to natural physiological stimuli, produces a burst response with a number of properties which suggests that synaptic, rather than ephaptic, transmission is involved. The firing of a small number of cells leads to the firing of many more cells, in several directions. These other cells, not under sensory control, are thought to act together by depressing the activity of neurons whose fluctuations of excitability are out of phase, and faci litating the activity of those units that are in phase.

Another possible explanation which has been offered,
is that the synchronization is caused by metabolic processes (cf. the review by Dawson, et. al., 1963). Cortical electrical activity is highly dependent upon an adequate blood supply for normal functioning. Special regulatory mechanisms exist to ensure the necessary cortical circulation, often at the expense of some peripheral system. The mechanisms, still unknown, by which the blood transfers vital substances to cortical structures, act with great rapidity (Kuffler and Nicholls, 1965). Localized increases in blood flow are associated with the local functioning of certain brain regions (Serota and Gerard, 1938). Cortical areas subjected to electrical stimulation also show increased blood flow (Jasper and Erikson, 1941). Hoagland (1936a, 1936b) has reported that changes in the human eeg frequency can be obtained by raising the subject's basal temperature.

The second major issue involved in the electrogenesis of spontaneous waves centers on the nature of the mechanisms producing the particular frequency patterns found in the normal human eeg. Three conceptually distinct mechanisms have been offered to account for frequency characteristics of the eeg. Some authors (Dawson, et. al., 1963; Hoagland, 1936a, 1936b) have suggested that the rate of metabolism of cortical neurons controls cortical frequency. Others (Burns, 1950, 1951; Pinsky, 1966; and Sherrington, 1947), have presented evidence that certain physical properties of cortical organization are responsible. Still others (cf. Bremer, 1958; Dempsey and Morison, 1942; Jasper, 1949; and Hanbery and Jasper, 1953)

have suggested that subcortical nuclei serve as cortical pacemakers.

The metabolic viewpoint assumes that the frequency of the recorded brain potentials is a manifestation of the rate of some underlying chemical process. Oxygen and glucose produce some typical effects. Anoxia is reported to produce a shift in the eeg energy distribution from the 8-12 Hz alpha band to slower delta and theta waves (Gibbs, et. al., 1940). Similar effects are reported by inducing hypoglycaemia: and an intravenous injection of glucose rapidly brings the activity back to its original pattern (Gibbs, et. al., 1940; Engel, et. al., 1944). Hoagland (1936a, 1936b, and 1938) found a simple linear-relation between the logarithm of the dominant eeg frequency and the absolute temperature in patients undergoing diathermy treatment. The results conformed to the Arrhenius equation, and the calculated values of the critical thermal increment were found to be 8, 11, and 16 Calories, common values for steps in the intermediate carbohydrate metabolism studied in vitro.

Those investigators interested in the physical or organizational properties of cortical neurons have suggested several different types of mechanisms to account for cortical frequency. Variations in excitability are characteristic of all nervous tissue. One way of looking at these changes in excitability is in terms of the differential rates of repolarization of different parts of the neurons. The uniform layer of apical dendrites toward the surface of the cortex is

thought to repolarize after an initial firing, at a faster rate than the cell bodies. Current would then flow from the dendrite to the cell bodies. Once this current reached a critical threshold level, the cell would fire again and the process would be repeated.

Evidence for this sort of mechanism is available from the work of Burns (1950, 1951). Repeated stimulation of an isolated cortical slab will produce a series of afterbursts. These afterbursts are usually an all-or-none phenomenon, and are independent of stimulus parameters. Any procedure which blocks a single burst is effective in blocking the entire train, suggesting that each burst is responsible for setting up the next discharge. Such results would be expected from a mechanism based on differential repolarization.

Sherrington's (1947) demonstration that electrical activity may persist for a considerable length of time after the stimulus has terminated, suggests the existence of self-reexciting chains of interneurons. The period of reverberation would be determined by the number of elements and the excitability characteristics of the units in the chain.

Pinsky (1966) has constructed a physical model of what he believes to be one type of cortical neuron. His emphasis is on the geometric characteristics of the dendritic branches. If the soma of Pinsky's model is stimulated randomly in time, an "alpha rhythm" is recordable from the surface of the dendritic branch. The implication is that the indigenous cable characteristics of some cortical dendrites are responsible for

the frequency of the eeg.

The third mechanism of frequency control involves the relationship between cortical and subcortical structures. Dempsey and Morison's (1942) demonstration of a thalamocortical "recruiting response" led to much research and speculation. They showed that repetitive stimulation of the medial thalamic nuclei initiates wide-spread activity in the cortex after the third to fifth shock is delivered. The cortical frequency was found to equilibrate withing the alpha band. If the frequency of thalamic stimulation is greater or less than the alpha frequency, the recruiting response is either a submultiple or multiple of the stimulating frequency, thereby maintaining average 10 Hz slow waves in the cortex. At stimulating frequencies above 25-30 Hz, this relationship breaks down and the recruiting response is suppressed. With strong stimuli, this response is widespread (Starzl and Whitlock, 1952), but is found to be well localized if just adequate stimulus intensities are used (Jasper, 1949; and Hanbery and Jasper, 1953). The dominant role of the diffuse or nonspecific thalamic recruiting response has been demonstrated by several investigators (Jasper, 1949; Hanbery and Jasper, 1953; and Ralston, et. al., 1956).

Although once popular, the viewpoint that thalamic pacemakers drive the cortical rhythms must be qualified. At a very low frequency of stimulation, the cortical rhythms remain unaffected (Dempsey and Morison, 1942). Verzeano, et. al., (1953) have demonstrated that the "recruiting" responses in the cortex occur simultaneously with the thalamic recruiting responses. And Clare and Bishop (1956) demonstrated that direct stimulation of the cortex results in a recruiting response which has the same characteristics as the thalamic recruiting response. These results led Bremer to conclude that the mechanism of frequency control could be thought of as the "periodic resetting of an autorhythmical activity having a tendency to run down and die away" (1958, p. 370).

Reviewers (Bremer, 1958; Pupuræ, 1959) usually conclude that the mechanisms which control cortical frequencies are complex. By this, they mean that several of the above-mentioned mechanisms are likely to be acting simultaneously, and interacting to various degrees. The relative importance of each of the proposed mechanisms is still to be determined. Furthermore, recent studies (cf. Ady, 1966; and Smith and Langsam, 1967) have emphasized the relationship of previously unconsidered aspects of single cell activity, to the cortical eeg.

Before going on to a consideration of the human alpha rhythm as an indicator of attention, it is necessary to compare the characteristics of the eeg recorded through the skull and scalp, with those of direct, cortical recordings. De-Lucchi, et. al., (1962) have described the scalp as an eeg averager. If several interconnected electrodes are placed close together on the cortical surface, the degree of synchrony with the scalp recording obtained at the appropriate site is very high. Synchrony here refers to the similarities in amplitude and phase relations between the two records. The greater the number of interconnected cortical electrodes, the

greater the degree of synchrony with the rhythms recorded through the scalp. The authors conclude that the scalp acts as an averager of electrical activity which is common to, and synchronous over, relatively large cortical areas.

Reports are available of eeg recordings directly from the cortex of psychiatric and neurological patients. Perez-Borja, et. al., (1962) suggest there are two distinct, yet functionally related systems, based on direct recordings from such patients. The alpha rhythm was found throughout the entire depth of the occipital lobe, as well as in the parietal and temporal lobes. They report slight differences in the frequencies of the alpha rhythm recorded from different leads in both the ipsi- and contra-lateral occipital lobes. However, occasional widespread phase synchrony was also observed. The amplitude of the alpha rhythm was maximal at the cortical surface, suggesting the importance of the apical dendrites. Occasionally, prominent alpha rhythms appeared in the direct leads, when only poorly organized alpha was present in the scalp recording.

In response to single light flashes, evoked responses were confined to small medially located foci surrounding the calcarine fissure. Alpha and fast rhythms were recorded in the resting state, from areas which exhibited responses to single flashes of light.

The second functional system is comprised of rhythms which are mostly restricted to small areas of the occipital lobes. These areas respond to light flashes, and patterned visual stimulation.

#### SUMMARY

 A discrete model of attention was presented. This model views attention as a temporally discrete, single channeled, central process.

2.) A particular notion of a cortical excitability cycle associated with the alpha rhythm was developed.

3.) The similarities and differences between the model of attention and the cortical excitability cycle were described. The differences arise from the fact that the model of attention is a stronger concept than the cortical excitability cycle, and not from any apparent incompatibilities. The most important property both notions have in common is a periodicity which sets limits on the time flow of events in the central nervous system.

4.) Experimental evidence was presented which describes a relationship between alpha frequency and some temporal aspects of attention. The nature of these studies has been correlational rather than experimental.

5.) Several theories concerning the electrogenesis of spontaneous cortical waves have been presented. In view of these theories, all that can be said is that the alpha rhythm does not seem incapable of performing the functions attributed to it by the notion of a cortical excitability cycle.

### STATEMENT OF PURPOSE

The primary purpose of the present study is to develop a technique which will permit an experimental investigation of the hypothesis that the alpha rhythm is related to the periodic nature of attention. The present study seeks to accomplish this by finding agents capable of manipulating the frequency of an individual's alpha rhythm. The selection of a particular chemical agent was influenced by a desire to avoid making the subject drowsy or disorganized, or activating any cerebral mechanisms not ordinarily involved in the production of alpha rhythms.

A 2 Hz shift, in both directions from the dominant resting frequency, is the goal. The long-term research plan calls for measuring an individual's time quantum, M (Kristofferson, 1965, 1966), before and after his alpha frequency has been temporarily altered. A 2 Hz shift in dominant frequency is equivalent to an 8 - 12 ms. interval. Since the reliability of measures of M are approximately 5 ms, the experimental procedure should produce changes which cannot be attributed to measurement errors.

A secondary purpose of the present study is to apply a relatively new technique of measuring eeg frequency spectrums to human subjects. There are many reports in the literature concerning chemical agents which alter eeg frequency. Most of these reports used a visual analysis of the eeg. Some of the same chemical agents will be used in the present study, and it

will be interesting to compare the results obtained with both methods of eeg analysis. The technique to be used here first performs an autocorrelation of the eeg data. The resulting autocovariance function then undergoes a Fourier analysis. The result is called a power spectral density function.

#### METHODOLOGY

### Apparatus.

All of the following experiments were conducted with the subjects in a darkened, sound-attenuated, electrically shielded chamber. Grass silver chloride electrodes were placed on the right occipital lobe, approximately  $l_2^1$  cm to the right, and 1 cm above the inion. A disc electrode held under the tongue served to ground the subjects. The eeg was recorded between the vertex and occiput.

The resistance of the electrodes was less than 5 K ohms in all cases. A Grass Model V polygraph was used. From the polygraph, the eeg signal was fed into an Ampex SP-300, 4channel tape recorder, and stored on magnetic tape for later processing. A paper writeout was also obtained from the polygraph, and the signal as it appeared from the tape recorder output was monitored on an oscilloscope. The polygraph filter controls were set as follows: 60 cycle filter, IN;  $\frac{1}{2}$  amplitude low frequency filter at 0.6 Hz; and  $\frac{1}{2}$  amplitude high frequency filter at 38 Hz.

All eeg recordings were obtained with the subjects in a sitting position. In those experiments requiring an anesthesiology machine, the equipment was kept outside the chamber. The gas was fed to the subject via corrugated rubber tubing through a hole in the chamber wall.

### Data Analysis.

All data analysis was performed on the IBM 7040 computer

at the McMaster University Computer Center. Data analysis consisted of three main parts: the analog to digital conversion; the autocovariance functions; and the Fourier analysis. The magnetic tape containing the eeg signal was fed into the analog to digital converter (ADC), to reduce the continuous eeg signal to a binary form compatible with the IBM 7040 computer. Such a process involves defining the moment at which the voltage is to be "observed" by the ADC (sampling), and conversion of the observed voltage to a number (quantization). The sampling rate used was 100 samples per second, which is sufficient to prevent aliasing the frequency range of interest (Blackman and Tukey, 1958, sect. 12 and 22). Detrending was also performed to eliminate any biasing of low frequency responses. The ADC was performed by the method of successive approximations.

The autocovariance function yields information which extracts the regular activity in an eeg record, at the expense of the irregular. If any regular periodicities occur in the eeg record, they will also be contained in the autocovariance. The autocovariance is obtained by multiplying the eeg record by a displaced version of itself. The displacement begins at zero lag, at which point the record is maximally correlated with itself. The displacements occur in an orderly, discrete fashion, the interval of the lag being determined by the particular needs of the user. The lag used in the present computations was .Ol seconds.

If a pure sine wave is the data of an autocorrelation, the autocorrelogram will be a sinusoid with the frequency of

the sine wave. The autocorrelogram is the normalized version of the autocovariance function. Each time the sinusoidal signal is displaced a number of lags equivalent to one full cycle, the autocorrelogram will show a peak. A half cycle displacement will create a trough in the autocorrelogram, for the original and displaced signals will be 180° out of phase. The autocorrelogram of a pure sine wave will show peaks of the same amplitude out to an infinite lag, even though fewer samples are being used in the computation of later lags.

If the signal is a sine wave plus some irregular activity (noise), the autocorrelogram will be a sinusoidal trace with the same frequency. But the amplitude of the successive peaks will decrease in amplitude, since the sine waves will tend to be distorted by the irregular activity and thus appear slightly out of phase.

If a signal contains more than one sine-like process, the autocorrelogram will contain a corresponding number of periodicities. Determining the exact periodicities contained in a complex autocorrelogram is not possible on the basis of the autocorrelogram alone (Blackman and Tukey, 1958, p. x). A further transformation of the data is required to extract this information.

Autocovariance functions are used as the raw data of the power spectral density functions. Through the Fourier analysis, the periodicity information in the autocovariance is translated into frequency information. For each periodicity, there is, of course, a corresponding frequency. For each periodicity contained in the autocovariance, there occurs in the power spectral density function a peak at the corresponding frequency. For a pure sinusoidal signal, there occurs a peak in the power spectrum at the corresponding frequency. For two or more sinusoidal traces contained in the same record, the power spectrum will contain peaks at each of the corresponding frequencies. There are two, and only two, ways in which power may be attributed to a particular low frequency which is not present in the original signal. The use of detrending and the selection of the sampling rate have eliminated these possibilities.

The Fourier analysis makes use of cosine functions to establish a set of mathematical filters, or weights. The autocovariance is multiplied by these weighted values, and the amount of "power" in each of the filters is plotted in arbitrary units in the power spectrum. The "power" coordinate of the autocovariance is described in terms of volts squared per second, the standard (P =  $V^2/R$ ) electrical usage. The "power" coordinate of the power spectral density function is volts squared per cycle per second. Power values were computed for every .5 Hz from 0 - 50 Hz. This .5 Hz resolution is determined by the number of data points, the amount of time between data points, and the maximum number of lags used in the computation of the autocorrelogram. Since resolution and stability of a spectral curve are directly related, statistically, these same parameters are responsible for the stability of the power spectral estimate. The stability of a power spectral

estimate may be measured by analogy with the number of degrees of freedom associated with a multiple of a chi-square variate (Blackman and Tukey, 1958, p. 24). Measured by this criterion, the present technique is adequate. However, since certain assumptions concerning the nature of the signal most certainly cannot be met in practice, the safest measure of lack of stability in power spectral estimates are the observed changes from trial to trial (Blackman and Tukey, 1958, p. 21). By this criterion also, the present technique is adequate (cf. Result section, Experiment 1).

There are several advantages in obtaining a power spectral density function, over visual methods of determining eeg frequency. Visual analysis is invariably tedious and consequently samples are usually small. In contrast, each of the power spectra obtained in the present study, were computed on all the activity in a 45-60 sec epoch. The stability of repeated power spectra is a function of sample length (Hord, et. al., 1965). A long sample length also avoids nonstationarity if there are slow waves of the order of 1-0.1 Hz in the record.

In a method of visual analysis, there is always a problem of selecting certain waves to measure or not to measure. When the process is automated, all data are treated in an identical fashion, with no room for personal selection once the necessary parameters have been established. This criticism may not apply to all visual methods of analysis, but the possibility certainly exists for many.

Furthermore, visual analyses may give information regarding the dominant frequency and little else. The power spectra give information about the relative power contained over a wide frequency range. Power spectra may also show more than one peak frequency which are usually missed in visual analyses. The resolution of each peak may be honed down to .10 Hz before stability becomes a problem (Hord, et. al., 1965).

### A Note on Data Presentation

In most instances the power spectra presented in the following Result section extend from 4-13Hz, although the spectra obtained extended from 0 to 50 Hz. Most of the changes which occurred in the spectra were within this range. For those rare cases when changes occurred outside this range, the spectra are extended.

In the text and tables, a single dominant frequency is often used to describe each of the spectra. This dominant peak is the frequency with the largest power value for that spectrum. If two adjacent frequencies have power values within 10% of each other, the dominant peak is described as being midway between them.

For the sake of economy, the figures often do not contain all the spectra obtained from a subject under a particular experimental treatment. Instead, the spectra which show the maximal amount of change, compared to the resting spectra, are presented.

## EXPERIMENT 1. COMPARISON OF THE POWER SPECTRAL AND A VISUAL METHOD OF EEG ANALYSIS

### INTRODUCTION

The power spectral technique used here has been used in a number of other studies. Its validity has been established by passing several different sine waves through appropriate amplifers, and then performing the autocorrelation and Fourier analysis on these artificial signals (Hord, et.al., 1965). It was decided to test the validity of the present power spectral program by performing a totally different type of analysis on the same biological signals. If both methods of analysis gave the same results, the validity of both would be established. Furthermore, such a comparison might provide a sense of security concerning the adequacy of the equipment used in the power spectral data acquisition and computation procedures.

The visual technique for determining the alpha half-cycle as developed by Kristofferson(1966,1967), yields reliable measures of both inter-and intraindividual differences. The reliability of measurements obtained for two eeg recording sessions spaced one week apart, was 0.79. Within each session the reliability of measurement was at least 0.89. These reliability coefficients were obtained under conditions of maximum variability; only 40 samples ( individual alpha cycles ) for each of the twenty subjects were used in the computation of the average frequency. If one compares the peak alpha half-cycle obtained by this method, before

and after an experimental session, the rank-order correlation is 0.86 (Kristofferson, 1967).

### METHOD

<u>Subjects</u>. A total of 14 normal subjects, both male and female, were used. Their ages varied from 19 to 33 years. <u>Apparatus</u>. The eeg recording and computation facilities for the power spectral program are described on page 37. The polygraph paper writeout provided the raw data for the visual analysis.

<u>Procedure</u>. At least two records were obtained for each subject in a resting state. For many subjects, repeated measures were made on different days. The power spectral and visual analyses were performed on the same epoch of eeg record. The two analyses were performed independently by different individuals.

The mean frequency for each subject was computed by averaging the mean frequencies of the alpha half-cycle obtained for each recording session. The visual technique utilized 20 samples for each recording. The power spectral technique utilized all the activity in a 45-60 second epoch of eeg record. A rank-order correlation was computed for the mean alpha halfcycle values obtained for each subject by both techniques.

### RESULTS

The mean alpha half-cycle values obtained by both the visual and power spectral techniques for each subject, are presented in Table 1. For all subjects the two techniques yield remarkably similar values. For only one subject, HVD, are

## TABLE 1

COMPARISON OF THE POWER SPECTRAL AND A VISUAL

## METHOD OF EEG ANALYSIS (ALPHA

HALF-CYCLE IN MSEC)

| Subjects | Visual Analysis | Power Spectral<br>Analysis |  |  |  |  |
|----------|-----------------|----------------------------|--|--|--|--|
| R.M.     | 55.6            | 55.6                       |  |  |  |  |
| • W.A.   | 52.6            | 52.5                       |  |  |  |  |
| M.A.     | 51.1            | 52.1                       |  |  |  |  |
| D.S.     | 49.4            | 50.9                       |  |  |  |  |
| P.M.     | 50.5            | 50.0                       |  |  |  |  |
| B.B.     | 50.3            | 48.6                       |  |  |  |  |
| K.U.     | 49.6            | 48.8                       |  |  |  |  |
| D.V.     | 48.3            | 48.2                       |  |  |  |  |
| R.Z.     | 47.8            | 46.0                       |  |  |  |  |
| H.V.D.   | 47.4            | 50.1                       |  |  |  |  |
| M.N.     | 47.3            | 46.0                       |  |  |  |  |
| R.H.     | 44.8            | 45.0                       |  |  |  |  |
| H.B.     | 45.2            | 44.0                       |  |  |  |  |
| T.M.     | 43.8            | 43.8                       |  |  |  |  |
| X        | 48.8            | 487                        |  |  |  |  |

the values different by more than 2 msec. Only two eeg epochs were used in the calculation of his mean alpha half-cycle. Within this frequency range, a 2.5 msec interval is equivalent to a .5 Hz frequency shift. The rank-order correlation for these values is 0.88. For the group the mean alpha half-cycle computed by the visual method was 48.8 msec. For the power spectral analysis, it was 48.7 msec. The visual method yielded individual alpha half-cycle values ranging from 55.6 to 43.8 msec. The range of the power spectral values is identical (cf. Table 1).

Table 2 contains information concerning power spectral estimates of the between-day variability for the nine subjects who participated in the present series of experiments. The range, modal value, and the proportion of eeg epochs which did not yield the modal value,  $P(\overline{MV})$ , are presented. The average range value is .5 Hz. The two subjects (NW and TG ) who showed the largest range values, each gave only one power spectral estimate at the limit of their range. Their values of  $P(\overline{MV})$  were not high.

Little information is available concerning within-day variability of the dominant occipital frequency. Indirectly the between-day variability, and the few occasions on which more than one Pre-resting record was obtained, suggest it is also less than .5Hz.

Figure 1 contains the autocorrelation and power spectral estimates for subject RH in two different conditions. These figures indicate several features of the power spectral program. In the Pre-resting condition, there is a very dominant, narrowband peak in the spectra. The drug-peak is defined as being at 11.25

### TABLE 2

POWER SPECTRAL ESTIMATES OF BETWEEN-

### DAY VARIABILITY

| Subject           | Range<br>(Hz) | Mode<br>(Hz) P(MV |     | N  |  |
|-------------------|---------------|-------------------|-----|----|--|
| R.M.              | .25           | 9.0               | .20 | 10 |  |
| N.W.              | 1.0           | 9.5 .38           |     | 8  |  |
| B.B.              | .50           | 10.0              | .50 | 10 |  |
| P.M.              | .50           | 10.0              | .40 | 10 |  |
| M <sup>c</sup> N. | .00           | 11.0 .00          |     | 4  |  |
| H.V.D.            | .50           | 10.5              | .50 | 4  |  |
| T.G.              | .75           | 9.75              | .25 | 4  |  |
| R.Z.              | .50           | 11.0              | .36 | 11 |  |
| R.H.              | .50           | 11.0              | .36 | 11 |  |
| x                 | .50           |                   | .33 |    |  |

Proportion of power spectral estimates other than the modal value.



FIG.1. Autocovariance and power spectral functions from subject RH in the normal and drug(Dexedrine) conditions. The terms EC and EO refer to eyes closed, and eyes opened, respectively, in this and all subsequent figures.

Hz, since the 11.0 Hz and 11.5 Hz power spectral estimates are within 10 % of each other. The autocorrelation from which these values were obtained is extremely regular and shows only a slight decrease in power at the maximum lag. In contrast, the autocorrelation for the drug condition contains several periodicities which cannot easily be converted into frequency values by eye. The power spectrum for this condition shows several distinct peaks at frequencies which are roughly harmonic values.

### DISCUSSION

The results of the comparison between the visual and power spectral techniques lend strong support to the validity and reliability of both techniques. Both techniques are capable of detecting small (.5 Hz) frequency changes between repeated measures on the same subject, or between subjects. Larger changes between subjects are also detected reliably by both techniques. The reliability of both techniques eliminates the possibility that these changes are due to measurement error. The finding that spontaneous frequency shifts of .5 Hz occur in the records of all subjects, presents a problem for establishing control values for detecting væry small changes in frequency. This problem will be discussed in detail in a subsequent section.

The proportion of eeg epoch<sub>s</sub>in which a power spectral estimate was obtained, other than the modal value, or  $P(\overline{MV})$ , is an indication of the between-day stability of the dominant peak. The lower the value of  $P(\overline{MV})$  the less likely it is that the dominant peak will change from day to day. The present data indicate that the dominant peak is likely to differ from

its modal value, on the average for the group, in one third of the epochs measured.

The figures presented give an indication of the range of information provided by the power spectral program.

Since the primary interest in the present study concerns the relative power at different frequencies, the total power changes in the spectrum as a whole have not been considered.

### EXPERIMENT 2. ALCOHOL

### INTRODUCTION

Engel and Rosenbaum(1945), Engel,et.al.,(1945), Hedenström and Schmidt(1951), Holmberg and Martens(1955), Loomis,et.al.,(1936), Müller and Rutenfranz (1960), and Newman(1959), each reports a slowing of the cortical frequency across all leads used ( frontal,precentral, parietal, and occipital ) after administering alcohol to their subjects. Their subjects included both normals and alcoholics who varied widely in age (20-59 years ). The dosages used by these investigators also varied from 0.3 to 2.0 cc/kg of body weight.

The one point of methodology these investigators had in common was their use of some visual method of determining the eeg frequency. Some investigators used a particular method of determining the eeg frequency developed by Engel,et.al.,(1944) (Engel,et.al.,1945; Engel and Rosenbaum,1945; Holmberg and Martens 1955). The others simply report a "slowing " and give no indication of what criteria they used to determine this change.

Two studies used automatic electronic analysis to determine alcohol-induced eeg changes (Davis,et.al.,1940; and Lolli,et.al.,1964). Davis,et.al.(1940) used the Grass and Gibbs (1938) method of spectrum analysis, but only on two of their six subjects who ingested alcohol. Lolli,et.al.(1964) used some form of "electronic computer analysis," but they do

not specify the details.

The results of Davis, et.al.(1940) indicate a decrease in energy on the fast side of the frequency spectrum (above 10-12 Hz ), and an increase on the slow side (below 10 Hz ). They gave their subjects 2 cc/kg of body weight of 100 % absolute alcohol. The increased amount of energy on the slow side is attributed to episodes of 4-8 Hz waves. These episodes on the slow side occurred prior to the maximum blood alcohol levels (120-140 mg. per 100 cc ), and were seen even at low, declining values.

Lolli,et.al.(1964) report only an "increased alpha rhythm." They neglect to mention if they are referring to amplitude, frequency, % time, or some other measure. The concentration of alcohol they gave to their subjects was less than 0.15 cc/kg body weight.

The results of the above studies may be abstracted and summarized in the following way:

1). Absolute alcohol, in sufficient doses, produces a slowing of the occipital eeg frequency in normal subjects.

2). The development and final degree of slowing is related, but not directly correlated, to the rise and subsequent decline of blood alcohol level. The eeg changes can occur prior to peak blood alcohol levels, and they may persist during the declining phase of intoxication.

3). The eeg changes can occur at blood alcohol levels which are lower than those levels required to produce an alcoholic stupor ( i.e., loss of consciousness ).

### MECHANISMS OF ACTION

It is not known how alcohol mediates its effects on the eeg. Several observations do lend suggestions, however. Although alcohol is at first absorbed into the blood stream very rapidly, the absorption rate declines sharply in a matter of minutes. Moreover, the rate of oxidation of absorbed alcohol is very slow and is only moderately increased by an increased concentration of alcohol in the blood. Because of the large cerebral blood supply, the alcoholic concentration of the brain quickly approaches that of the blood (Kalant, 1962; Mardones, 1963; and Ritchie, 1965).

Most of the absorbed alcohol (over 90 per cent) is oxidized and destroyed in the body (Ritchie, 1965). In spite of the prolonged oxidation, doses of alcohol sufficient to produce moderate intoxication have no effect on either the cerebral blood flow, or oxygen consumption of the brain (Kety and Schmidt, 1948).

The primary metabolic effect of alcohol on the neuron involves a blockage of the metabolism of glucose via pyruvate. This blockage is thought to be the origin of a reversible depolarization, which in low concentrations increases cellular excitability, and in high concentrations decreases or even abolishes excitability (Mardones, 1963).

Alcohol is known to affect several properties of central neurons. Ethanol acts as a depolarizing agent (Gallego, 1948). The membrane potential decreases as a function of alcoholic concentration. This depolarization blocks the conduction of

impulses; but the conductivity can be recovered after reestablishing the membrane potential, by the application of an external anodic current. In the presence of low ethanol concentrations, the neuron repolarizes spontaneously (Mardones, 1963).

Although the cortex shows a higher tissue-to-blood ratio after alcohol ingestion (Meyer, 1959), electrophysiological studies indicate that alcohol exerts its primary depressant action upon the more primitive brain stem reticular formation (Caspers, 1958; Horsey and Akert, 1953; and Ritchie, 1965). The cortex does not seem to be the part of the brain most sensitive to alcohol. Caspers (1958) studied the effects of alcohol in the conscious, unanesthetized cat with microelectrodes. He found that alcohol depressed the reticular formation and that this depression led to synchronous cortical activity. He also found that the depression of the reticular formation is related to the blood alcohol level. The extent of the inhibition was dependent on both the blood alcohol level and its rate of ascent. Only when this level was high enough to produce coma did the activity of the cortex decline to a subnormal level.

Horsey and Akert (1953) investigated the effects of a wide range of blood alcohol levels on the spontaneous and evoked electrical activity of both cortical and subcortical structures. They found a simultaneous slowing in both cortical and thalamic leads (intralaminar and medial and ventral nuclei). The slowing which occurred in the striatal lead (cuneate nucleus) appeared to be independent of cortical activity.

The reticular formation is a series of polysynaptic

connections (Brodal, 1957), and alcohol is known to have a greater effect on polysynaptic pathways than on monosynaptic ones (Kalant, 1962). High doses of alcohol produce a decrease in the cholinesterase (ChE) concentration at rats' synapses (Barnes, 1948; and Kinard and Hay, 1960). One would expect a decrease in ChE activity to lead to an accumulation of acetylcholine (ACh) and subsequent hyperexcitability. Eventually the synaptic activity would become depressed. This biphasic action of cellular excitability is in fact observed with alcohol (Mardones, 1963). Similarly, the observation that at the peak of intoxication, the gamma-aminobutyric acid (GABA) concentration increases (Häkkinen and Kulonen, 1959), may be related to the greater effect of alcohol on polysynaptic pathways. GABA is thought to be an inhibitory substance which tends to depress the transmission of nerve impulses across the synapses.

The proposed mechanisms by which alcohol is thought to influence the eeg may be summarized as follows:

1.) Alcohol is known to interfere with some neurochemical transmitters at synaptic junctions.

2.) Alcohol does alter several properties of central neurons (depolarizes membranes, decreases excitability to direct stimulation, and blocks the conduction of impulses).

3.) The primary depressant effect of alcohol does not seem to be upon the cortex, but upon the lower brain stem reticular formation.

### METHOD

Subjects. Five healthy male students were used. They ranged

in age from 21 to 33 years, and all were moderate drinkers. Apparatus. Pure absolute ethyl alcohol ( $C_2H_5OH$ ) was used.

Blood alcohol levels were determined by the Breathalyzer, Model 900 (Stephenson Corp., Red Bank, N.J.). This device operates by first trapping a sample of alcoholic alveolar air. This sample is passed through a potassium dichromate-sulfuric acid solution of known quantity, where the alcoholic content of the sample is oxidized. The amount of potassium dichromate solution required to complete this oxidation causes a photocell to displace a pointer a specific distance on a meter. This diplacement may then be read off directly in per cent blood alcohol.

The apparatus used to record and calculate the eeg frequency was the same as described in an earlier section. <u>Procedure</u>. Resting eegs were obtained, prior to ingestion of alcohol. All of the doses of alcohol were mixed with fruit juice, and were completely ingested in 5 to 15 minutes.

All subjects received a single dose of approximately O.5 cc/kg of body weight of absolute alcohol, which is roughly equivalent to the alcoholic content of 2-3 ounces of commercial (80 proof) whiskey. A similar dose was repeated on another day for all subjects. Four of the five subjects also received a single dose of approximately 1.0 cc/kg of body weight at a later date. Two subjects were asked to hyperventilate while their blood alcohol levels were still high.

Blood alcohol levels and eegs were obtained approximately every 20 minutes after ingestion was complete, until the blood

alcohol levels showed a decline. Blood alcohol levels were obtained immediately before and after each eeg recording.

Subjects were not allowed to smoke, eat, drink or sleep during the experiment. All subjects had fasted at least four hours. Subjects were also asked to rinse out their mouths with water before providing a breath sample for the Breathalyzer.

Subjective reports concerning the subjects' state of intoxication were elicited, if not offered voluntarily.

### RESULTS

A total of 92 power spectra were computed in this experiment. Table 3 contains information regarding the various doses of alcohol each subject received, the blood alcohol levels recorded after each dose, and the dominant occipital frequency recorded at those blood alcohol levels. The column designated Blood Alcohol Level, .00, contains the dominant resting occipital frequency of each subject prior to ingestion of alcohol. It will be noted that in this experiment, for any particular subject, there is a high level of stability in the occipital frequency, at least when measured over several consecutive days.

Figure 2 shows the power spectral estimates for subject PM, taken prior to ingesting the alcohol. Not only is the peak frequency stable over days, but the amplitude and variability of the peaks are also remarkably similar from day to day. Power spectral estimates of other subjects' resting occipital frequencies are very similar to those shown in Figure 2. The only

### TABLE 3

# DOMINANT OCCIPITAL FREQUENCY(Hz) OBTAINED AT

### VARIOUS BLOOD ALCOHOL LEVELS

| SUBJECTS      |          | %   | BLO | OD A       | LCO                | HOL       | LE | EVEL |       |     |     |     |
|---------------|----------|-----|-----|------------|--------------------|-----------|----|------|-------|-----|-----|-----|
| DOSE          | .00      | .02 | .03 | .04        | .05                | .0e       | .0 | 7.0  | 8     | .09 | .10 | .11 |
| B. B.         |          |     |     |            |                    |           |    |      |       |     |     |     |
| 38.5cc        | 10.25    | 9.5 |     | 9.5-10     | 0                  | 10.0      |    |      |       |     |     |     |
| 48.0cc        | 10.00    |     |     | 9.5        | 9.5                |           |    |      |       |     |     |     |
| N.W. 36.0cc   | 9.75     |     |     | 9.5        | 10                 | ).0       |    | 10.0 |       |     |     |     |
| 48.0cc        | 8.5-10.0 |     |     |            |                    | 9.        | 5  | 9.5  |       | 9.5 |     |     |
| 70.0 cc       | 9.50     |     |     |            |                    |           |    |      | 9.0   | 9.0 | 9.0 | 9.0 |
| P. M. 37.5 cc | 10.0     |     |     | 9.5        | -9.75              |           |    |      |       |     |     |     |
| 45.0cc        | 10.0     |     |     |            | 9.5                | 9.        | 5  |      |       |     |     |     |
| 73.0cc        | 10.0     |     |     |            |                    |           | 9. | 59.  | 5 9.0 | )   |     |     |
| R.Z. 39.5 cc  | 10.5     |     |     | 10.5       | 10.5<br>).5        |           |    |      |       |     |     |     |
| 39.0 cc       | 10.5     |     | 10  | ).5 10.5   | 10.5               |           |    |      |       |     |     |     |
| 64.0cc        | 10.5     |     |     |            |                    | 10.5      |    |      | 10.2  | 5   |     |     |
| R.H. 43.5 cc  | 11.25    |     |     | 10.5       | ).5 <sup>11.</sup> | 0<br>11.0 |    |      |       |     |     | ۰.  |
| 47.5 cc       | 11.25    |     |     | 11.0<br>1( | 0.5-11.0           | 10.5<br>) |    |      |       |     |     |     |
| 78.0 cc       | 11.00    |     |     | 10         | .5                 | 10.5      | .5 |      |       |     |     |     |
|               |          |     |     |            | ÷.,                |           |    |      |       |     |     |     |

Note.- In this and all subsequent Tables, the value of the dominant peak is presented alone if there is only one peak in the spectrum. If a peak is unusually broad, its limits are defined thus, e.g., 9.5-10.0.





FIG. 2. Power spectra from subject PM showing between-day variability, effects of raised blood alcohol level, and hyperventilation. BAL refers to blood alcohol level, HV refers to hyperventilation and PHV refers to post hyperventilation, in this and all subsequent figures. exceptions are the power spectral estimates for subject NW. These are shown in Figure 3. Such day to day variations in peak frequencies, and such variability as occurred on 5/16, are both very unusual. In fact, subject NW is the only one who displayed such variability. The subject did not report any unusual sensations when such changes were noted. This subject reported that he had unusual sleep patterns, often remaining awake 40-50 hours at a time. He appeared alert, and functioned normally.

Table 3 indicates a very loose relationship between dose of alcohol and blood alcohol level. But in general, the higher the dose, the higher the blood alcohol level. The relationship between blood alcohol level and eeg frequency appears to be even less strict. Although fluctuations in the dominant occipital peak do occur, the same occipital frequencies may be maintained over a wide range of blood alcohol levels (e.g., Table 3, subjects PM and RH).

Concerning the magnitude of eeg fluctuation, the dominant peak after alcohol ingestion was .5 Hz slower than the peak recorded in the pre-alcohol state, for four of the five subjects (cf. Table 3). These .5 Hz fluctuations in frequency occurred at varying doses and blood alcohol levels. There is only one case (subject PM, 73 cc absolute alcohol, BAL = .085; Table 3), in which the occipital frequency slowed by a full cycle per second. One subject (RZ) showed only a slight difference between the spectra obtained at his highest blood alcohol level (BAL = .085), and his pre-alcohol state. All of the fluctuations





in dominant peak (except for subject NW) were decreases.

Figure 2 contains the power spectral estimates for subject PM at various intervals after ingesting the alcohol, for three different days and doses. These figures are presented as beingrepresentative of the other subjects' power spectra. They are representative in terms of both stability across varying experimental conditions, and amplitude. They are not representative of the dominant peak values, which vary from subject to subject.

Subject PM was asked to hyperventilate for three minutes after having ingested 73cc of absolute alcohol. His blood alcohol level was .080 before he started to hyperventilate. The power spectra of his occipital frequency while hyperventilating are presented in Fig. 2. Within the first minute of hyperventilation the dominant peak slowed by 1.5 Hz compared to the alcohol induced changes prior to the start of hyperventilation, and a full 2 Hz compared to the normal resting peak. There was also an increase in power in the 4 Hz range. He reported feeling "exhilarated" while hyperventilating. Subject RH also hyperventilated while his blood alcohol level was high (.065). A flattening of the peak occurred, with a broad peak appearing from 9.5 - 10.5 Hz. He reported feeling very disorganized and apprehensive about becoming ill.

Observation showed that both motor coordination and verbal fluency were affected, and both subjects reported feeling "drunk" in several instances. But at no time during the testing were any of the subjects stuporous.

### EXPERIMENT 3. CARBON DIOXIDE METABOLISM

#### INTRODUCTION

There is a vast literature on the effects of carbon dioxide on the electrical activity of the brain (cf. reviews by Dawson and Greville, 1963; Roman and Davis, 1952; and Woodbury and Karler, 1960). Hyperventilation produces a decrease in the blood carbon dioxide tension (Wollman and Dripps, 1965). This decrease in carbon dioxide tension leads to a slowing of the occipital eeg frequency (Brazier, et. al., 1944; Davis and Wallace, 1942; Engel, et. al., 1944; and Gibbs, et. al., 1940).

Each of the above investigators made some attempt to objectify and quantify the reported eeg changes. Gibbs, et. al., (1940) used a Fourier analysis of the eeg to extract the various frequency components. Davis and Wallace (1942) used three broadly tuned filters at 2.8, 5 and 7 cycles per second, while the others (Brazier, et. al., 1944; and Engel, et. al., 1944) used specific visual techniques for determining the number of waves occurring at each of several frequencies.

Increasing the blood carbon dioxide tension may be accomplished either by inhalation of a carbon dioxide gas mixture or by the ingestion of the carbonic anhydrase inhibitor diamox (acetazolamide) (Wollman and Dripps, 1965; Woodbury and Esplin, 1957; and Woodbury and Karler, 1960). The qualitative effects of increasing the blood carbon dioxide tension on the eeg depend on the percentage of carbon dioxide inhaled.
At very low concentrations of carbon dioxide (5-10%) there is a reported increase in the frequency of cortical potential changes. At higher concentrations (30%) the eeg shows an activation pattern, with intermittent bursts of slow, high voltage activity (Morrice, 1956). At even higher levels (50%), the amplitude of the eeg is greatly depressed (Woodbury and Karler, 1960).

The study of Gibbs, et. al., (1940) is unique in two respects. They obtained estimates of cerebral carbon dioxide tension from samples of blood taken from the internal jugular vein, which is normally in equilibrium with the brain fluids. They also determined changes in eeg frequency by use of an automatic Fourier analysis developed by Grass and Gibbs (1938). For each of the four normal subjects used, they report an increase in the frequency of the resting eeg as the % of carbon dioxide in the internal jugular rises.

There are no reports in the literature regarding the effects of diamox on the eeg. However, this drug has several properties which suggest it might be a useful agent for manipulating the eeg frequency. These properties will be discussed in the next section.

#### MECHANISMS OF ACTION

The various effects of carbon dioxide on cortical electrical activity seem to be mediated by several different mechanisms. Carbon dioxide is produced in the mitochondria as a byproduct of cellular metabolism (Woodbury and Karler, 1960). Normally, this metabolic carbon dioxide is transported by the blood to the lungs, where it is exhaled at the same rate at which it is produced (Wollman and Dripps, 1965). Hyperventilation creates a condition in which the amount of carbon dioxide exhaled is greater than that produced. However, if carbon dioxide is inhaled, the arterial carbon dioxide tension rises and the rate of diffusion from the cell to the extracellular fluid decreases (Wollman and Dripps, 1965). Thus, the initial increase in cortical frequencies caused by mixtures of air and low carbon dioxide concentrations, is due to the direct action of carbon dioxide on the cortical cells (Woodbury and Esplin, 1957; and Woodbury, et. al., 1958). In either case, the internal environment of the cell is altered.

The activation of the eeg at intermediate concentrations of carbon dioxide is caused by the chemical stimulation of centers in the hypothalamus, brain stem reticular formation and medulla. These sites can be locally excited or aroused via carotid and aortic chemoreceptors that are sensitive to changes in blood carbon dioxide (Wollman and Dripps, 1965). This stimulation leads to the release of epinephrine and adrenal-cortico hormones of the cortisol type (Gelhorn and Heymans, 1948; Woodbury, et. al., 1958; and Woodbury and Karler , 1960). The results of sympathetic nervous system activity are in general opposite to the local cortical effects of carbon dioxide. The net effect of carbon dioxide is therefore determined by the balance between local and sympathetic activities.

The anesthetic phase of carbon dioxide inhalation at

high concentrations is attributed to marked cortical and subcortical depression (Gelhorn, 1953; Woodbury, et. al., 1958; and Woodbury and Karler , 1960). At high levels of carbon dioxide the pH falls, producing respiratory acidosis, thereby radically changing the cellular environment (Wollman and Dripps, 1965). Woodbury and Karler (1960) hold that the depression of subcortical centers is due to inhibition of the reticular activating system in a manner similar to the blockage produced by the barbiturates and other anesthetic agents.

Conditions which are capable of changing the carbon dioxide tension in the brain are capable of affecting brain function. Carbonic anhydrase is important in regulating the carbon dioxide tension, by the dissociation or formation of carbonic acid (Mudge, 1965). One of the most potent carbonic anhydrase inhibitors is diamox (acetazolamide). The sole pharmacological action of diamox is the inhibition of carbonic anhydrase wherever it is found (Mudge, 1965).

Carbonic anhydrase is found in the mitochondria (Woodbury and Karler, 1960), and throughout the nervous system of several species, increasing rostrally in a pattern peculiar to the species (Merlis, 1954). More carbonic anhydrase is found per unit volume of tissue in the cerebrum than in the cord of man, and more in the subcortical white matter than in the cortex. Fibers which make extrinsic corticocortical connections are found in the areas with high carbonic anhydrase contents (Merlis, 1954).

The effects of diamox parallel those of carbon dioxide

(Woodbury and Karler, 1960). Both agents have the same spectrum of activity on experimental seizures; both agents produce the same effects on brain electrolyte concentrations; and both affect brain amino acid concentrations in a similar manner. Furthermore, changes in brain excitability induced by various concentrations of carbon dioxide are enhanced by diamox (Gray, et. al., 1957; Koch and Woodbury, 1958; and Merlis, 1954). These authors conclude that diamox exerts its effect on brain electrical activity by inhibiting carbonic anhydrase, thereby decreasing the rate of elimination of carbon dioxide from the cells.

67

Diamox has a direct effect on the carbonic acid concentrations of nerve cells. When diamox inhibits carbonic anhydrase, there is a decrease in the rate at which intracellular carbonic acid is dehydrated. Since carbonic acid is much less diffusable than carbon dioxide, and since it is presumed that the carbon dioxide produced metabolically is in the form of carbonic acid, the result of carbonic anhydrase inhibition is an increase in the steady state concentration of carbonic acid in the brain nerve cells. This increase reduces the permeability of the brain cell membrane to sodium (Na). Inasmuch as the Na-pump is unchanged, the result is a lower steady state concentration of Na in the brain cells, and a higher gradient of Na across the cell membrane. The decrease in cell membrane permeability increases the threshold of neurons, and to some extent, decreases the amplitude of the propagated impulse (Woodbury and Esplin, 1957).

Due to the similarity of diamox and carbon dioxide at the many levels of activity described above, one might expect diamox to produce eeg effects similar to those produced by carbon dioxide. The ease of administering diamox tablets has distinct advantages over the more cumbersome techniques involved in carbon dioxide inhalation.

In summary, the main points concerning carbon dioxide metabolism and the eeg are the following.

1.) Decreasing arterial carbon dioxide tension by hyperventilation leads to a slowing of the occipital eeg frequency below the normal resting level.

2.) Increasing the arterial carbon dioxide tension by inhaling low concentrations of the gas, leads to an increase in the cortical frequency.

3.) These conclusions have been reached through the use of several specific, visual methods of eeg analysis, as well as automatic electronic, and mathematical analyses.

4.) Carbon dioxide has a depressant action on the cerebral cortex, which is interrupted at intermediate concentrations of the gas by chemical arousal of sympathetic centers in the subcortex.

5.) The effects of carbon dioxide on the cerebrum are mediated by altering the cellular environment toward a state of decreased sensitivity.

6.) The effects of diamox (acetazolamide) in many cases, parallel those of carbon dioxide, and diamox may therefore have an effect on the eeg similar to that of carbon dioxide.

#### METHODOLOGY

<u>Subjects</u>. A total of nine normal males, ages 19-33 years, were used. All nine subjects were asked to hyperventilate. Six of the nine subjects received various doses of diamox. Five of these six subjects inhaled various concentrations of carbon dioxide.

Apparatus. The eeg and tape recording apparatus were the same as described on page 37.

The carbon dioxide was delivered to the subject through an anesthesiology machine (Midget-Kinet-O-Meter, Heidbrink, Co., Minneapolis, Minnesota). The carbon dioxide was mixed with either compressed air or 100% pure oxygen. The apparatus allows a direct reading of the relative amounts of each gas, in liters or cc. per minute. The gas mixture was delivered through a non-rebreathing system. The face mask contained two one-way valves and was designed so that room air could not enter into it.

Procedure. The diamox was administered in 250mg. tablets. Experiment 3A. Hyperventilation.

All subjects hyperventilated in a sitting position, in a darkened, sound-attenuated room. The experimenter demonstrated the technique of hyperventilating to each subject, emphasizing the importance of exhaling as completely as possible on each breath. No attempt was made to standardize either the rate or depth of hyperventilation. The subject was asked to demonstrate how he hyperventilated before the actual recording

began. His technique was corrected if necessary.

The subject was instructed to begin hyperventilating when he received a prearranged signal, and to continue at as constant a rate as possible, until given the signal to stop. The usual length of a hyperventilation session was  $4\frac{1}{2}$  minutes. EEG recordings were taken before, during and after hyperventilation.

Experiment 38. Diamox.

Diamox was administered in either 250 mg or 500 mg doses. Several replications were made at a later date. Two subjects received three 250 mg doses, spread out over several hours. EEGs were recorded 30-60 minutes after the last dose. Each of the subjects who received diamox was also asked to hyperventilate while under the influence of the drug. Experiment 3C. Carbon dioxide.

Five subjects were given carbon dioxide in amounts varying from 3-40%. The subject was first seated and fitted with the face mask to ensure a tight fit. EEG recordings were begun. Then carbon dioxide was slowly added to the air mixture which the subject had been receiving via the face mask. The experimenter adjusted the flow of gas so that the total amount delivered was approximately 10-12 liters per minute. All subjects found this amount to be comfortable. The duration of the carbon dioxide inhalation varied from 10-50 minutes. Four subjects inhaled varying amounts of carbon dioxide while under the influence of diamox.

In all of the above experiments, subjective reports concerning effects of the various treatments were elicited if not

offered spontaneously.

#### RESULTS

Experiment 3A. Hyperventilation.

A total of 241 power spectra were calculated while subjects were hyperventilating, in conjunction with a variety of other treatments. Only those cases in which subjects hyperventilated without any drug at all, are included in this section. These cases include 51 power spectral estimates. Hyperventilation without Drug

Table 4 contains the power spectra of all 9 subjects who hyperventilated. The effects of hyperventilation were not the same for all subjects. At least four of the nine subjects showed a decrease in the dominant frequency (HVD, BB, TG, and NW). Two of these four subjects (BB and TG) produced activity in the theta range. Figure 4 contains the power spectra for subjects BB and HVD.

Two unusual cases are those of subjects RZ and RH, both of whom evidenced an increase (.75 - 1 Hz) in occipital frequency upon hyperventilation. In the case of subject RZ, a new peak also appeared in the theta band. For subject RH, an increase in the band width around the dominant peak occurred. The power spectra for these subjects are presented in Figure 5.

For two subjects (RM and PM) the dominant peak remained the same during hyperventilation. For subject PM, a new peak appeared from 4-7 Hz and the variability of the dominant peak increased. For subject RM, no recordable change occurred, nor did the subject report any unusual sensations upon hyperventilation.

### TABLE 4

### DOMINANT OCCIPITAL FREQUENCY(Hz)

### DURING HYPERVENTILATION

| SUBJECTS          | MINUTES OF HYPERVENTILATION |          |               |             |                       |               |               |           |                |   |
|-------------------|-----------------------------|----------|---------------|-------------|-----------------------|---------------|---------------|-----------|----------------|---|
|                   | PRE<br>RESTI                | E-<br>NG | 1             | 2           |                       | 3             | 4             | Ę         | 5<br>I         | 6 |
| P.M.              | 10.5                        | t        | 10.75         |             | 10.5                  | 1             | 10.5          | •         | ↓ 10.5         |   |
| H.V.D.            | 10.75                       | t        | 10.25         |             | 9.                    | 75            | 9.5 ↓         |           | 10.75          |   |
| R.M.              | 9.0                         | 1        | 9.0           |             | 9.0                   |               | 9.0 +         |           | 9.0            |   |
| B.B.              | 10.5                        | ٨        | 10.25<br>9.25 |             | 7.25<br>10.25<br>5.75 |               | 10.75         |           |                |   |
| T.G.              | 9.75                        | ↑        | 1             | 10.0<br>7.0 | )                     | 4 - 6<br>10.0 | \$<br>}       | 4 -<br>10 | -6<br>).0      | 1 |
| R.Z.              | 11.0                        | t        | 11.75<br>4-7  | 1           | 11.5<br>4-5           | 1             | 11.5<br>4-6 ↓ |           | 11.0           |   |
| R.H.              | 11.0                        | ¥        | 11.75         | 1           | 11.0<br>1.5-12.5      |               | 11-12 ↓       |           | 12.0<br>11-125 | 5 |
| N.W.              | 10.0<br>8.5-9.5             | 1        | 8.25<br>10    | S           | 8.0<br>).5-10.5       | ļ.            | 9.0<br>10.25  |           |                | 1 |
| M <sup>C</sup> N. | 11.0                        | t        | 11.0          |             | 10.75                 |               | 10.75 ↓       |           | 11.0           |   |

Note.-If one or more non-dominant peaks are present in the spectrum, their values are presented directly below the value of the dominant peak. The arrows  $\uparrow$ ,  $\downarrow$  define the beginning and end, respectively, of the experimental treatment. These conventions are maintained in this and all subsequent Tables.



FIG. 4. Power spectra from subjects BB and HVD before, during and after hyperventilation.



FIG. 5. Power spectra from subjects RZ and RH before, during and after hyperventilation.

The subject's technique for hyperventilating was checked and found satisfactory. Figure 6 contains the power spectra for subject PM.

Table 4 also shows that not all of the power spectra returned to their prehyperventilation state 30-90 seconds after hyperventilation ended. The post-hyperventilation power spectra for five subjects are the same as their prehyperventilation power spectra. Two subjects (TG and NW) show a continued decrease in occipital frequency. The remaining two subjects (BB and RH) show an increase in frequency over their prehyperventilation condition.

Experiment 38. Hyperventilation with Diamox.

A total of 96 power spectra were computed in this experiment. Six subjects were asked to hyperventilate, 30-60 minutes after receiving various doses of diamox. Two of these subjects had also fasted overnight. Table 5 contains the power spectra obtained at various intervals after hyperventilation had begun.

By comparing the first column of power spectral estimates of Table 5 with the corresponding column of Table 4, it may be seen that the power spectra obtained from subjects under the influence of diamox, did not change the resting eeg by more than .25-.50 Hz. This .25-.50 Hz change occurred in both directions, and appears to be within the normal range of variability.

In three out of six cases (subjects PM, RM, and BB), the effects of hyperventilation were more pronounced with diamox, than without. However, the kinds of changes which occurred



FIG. 6. Power spectra from subject PM before, during and after hyperventilation.

# TABLE 5

# DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER DIAMOX AND DURING HYPERVENTILATION

| SUB.               | JECTS           | TS MINUTES OF HYPERVENTILATION |   |                    |                    |                          |                        |  |  |  |  |
|--------------------|-----------------|--------------------------------|---|--------------------|--------------------|--------------------------|------------------------|--|--|--|--|
|                    | DIAMOX<br>(mg.) | PRE-<br>RESTING                | 0 | 1                  | 2 3                | 4 5                      | 56                     |  |  |  |  |
|                    | 250             | 10.5                           | 1 | 10.5<br>8.5-9.5    | 9.5<br>5.5;3.75;75 | 8-9 +                    | 10.25<br>6-7           |  |  |  |  |
| P.M.               | 250             | 10.75                          | † | 9.25<br>20;5.5     | 8.5<br>6.25        | 8.25 <del>\</del><br>5.5 | 9.75<br>6-8            |  |  |  |  |
|                    | 500             | 10.5                           | Ť | 10.5<br>6.0;8.0    | 10.5<br>5-7.5      | 10,5 ↓<br>5-6            | 10.E                   |  |  |  |  |
|                    | 750             | 10.0                           | 1 | 10.25              | 10.0<br>6-8        | 10.0 ↓<br>8,75           | 10.25                  |  |  |  |  |
|                    | 250             | 11.0                           | 1 | 11.0<br>4.75       | 11.0               | 11.25 ¥<br>10.0          | 11.0                   |  |  |  |  |
| H.V.D.             | 500             | 10.5                           | 1 | 10.25              | 10.25<br>9-9.5     | 100 ↓<br>8.5-9.5         | 10.5                   |  |  |  |  |
|                    | 750             | 10.5                           | ↑ | 10.5               | 10.5<br>3-4.5      | 10.5 +                   | 10.75                  |  |  |  |  |
|                    | 250             | 9.0                            | 1 | 9.0                | 9.0                | 8.75 ↓<br>7.0            | 9.25                   |  |  |  |  |
| R.M.               | 250             | 9.0                            | t | 9.0                | 875<br>5-6;70      | 8.75 ↓<br>7.0;5.5        | 9.0                    |  |  |  |  |
|                    | 500             | 9.25                           | † | 9.0                | 8.75               | 8.5 ↓                    | 8.75                   |  |  |  |  |
| 14                 | 250<br>hrs.Fast | 9.0                            | 1 | 8.75<br>2–3        | 8.5<br>3.0         | 8.75 ↓<br>4.5            | 9.25                   |  |  |  |  |
|                    | 750             | 9.0                            | 1 | 9.0                | 9.0                | 9.0 🕴                    | 9.0                    |  |  |  |  |
| B.B.               | 250             | 10.25                          | 1 | 10.5<br>8.5-9;13.0 | 50,75<br>10.25     | 1000 ↓<br>5.5;7.5        | 10.5<br>4.5;5-6,8-9    |  |  |  |  |
|                    | 500             | 10.25                          | 1 | 10.5<br>7.0;85-9.5 | 7.0                | 5-7 ↓<br>10,0            | 10 <u>0</u><br>8-9,5-6 |  |  |  |  |
| R.H. <sub>13</sub> | 250<br>hrs.Fast | 10.75                          | † | 11.25              | 10.5<br>10-11      | 10.25                    | 12.0<br>10.5-11.5      |  |  |  |  |
| T.G.               | 250             | 9.75                           | 1 | 975                | 9.75<br>6.5-7.5    | 10.0 ¥                   | 5.5-70<br>100          |  |  |  |  |

differed greatly between subjects. RM showed a fluctuation in peak frequency and a new, slow peak upon hyperventilation with diamox. Without the drug, no change occurred. BB showed greater slowing of the occipital frequency upon hyperventilation with diamox at the 500 mg dose level. At the 250 mg dose level, the degree of occipital slowing was similar to the drugfree state, but occurred later.

An entirely different type of change occurred for PM upon hyperventilation with diamox. PM's power spectra show a 2 Hz change in dominant frequency (no change occurred in the drug-free case), as well as a greater degree of slowing in the theta band. Figure 7 contains the power spectra for subjects RM and PM.

Of particular interest are the diamox-hyperventilation power spectra of subjects HVD, BB, and TG. The effects of hyperventilation with diamox for each of these subjects, were to stabilize the dominant occipital frequency at some dose levels. This result is particularly interesting in that, from the entire group of subjects, both BB and TG showed the most pronounced effects of hyperventilation in the drug-free state (cf. Table 4). Changes did occur when these subjects hyperventilated under the influence of diamox. Increases in theta activity are seen, but the dominant resting frequency retains considerable power. The fluctuations in dominant peak that do occur are of smaller magnitude than in the drug-free state. Figure 8 contains power spectra for BB. Figure 9 contains the power







FIG. 8. Power spectra from subject BB after he ingested diamox and was hyperventilating.



FIG. 9. Power spectra from subject TG after he ingested diamox and was hyperventilating.

spectra for TG.

Table 5 allows for a comparison of three different doses of diamox. Of the four subjects who received both 250 and 500 mg doses, subjects BB and HVD showed a more pronounced hyperventilation reaction to the larger dose, in comparison to both their drug-free and low dose states. These are the same subjects whose power spectra were stabilized at the lower doses. One of these subjects (HVD) also received 750 mg of diamox over a 24 hr. period. This large dose served to stabilize the dominant frequency even more than the 500 mg dose, although a new peak appeared at 3-4.5 Hz.

For the other two subjects (PM and RM), the 500 mg diamox-hyperventilation led to a greater change as compared to the drug-free case. Compared to the 250 mg diamox-hyperventilation, however, the larger dose led to a stabilization of the hyperventilating eeg, in both cases. At the 750 mg dose level, both PM and RM showed less theta activity upon hyperventilation. In this case, their cortical responses to hyperventilation were similar to their drug-free states, with the exception that PM produced a new peak in the theta range at the 750 mg dose level.

Two subjects ingested 250 mg of diamox after having fasted overnight. Both subjects showed greater changes upon hyperventilation in this condition, as compared to their drugfree states. For RM, the effects of fasting plus diamox were even greater than for diamox alone, in that a 3-4 Hz peak appears in the power spectra, as well as a slow shift of the

dominant frequency. For RH the slowing of the dominant peak with diamox plus fasting, was exactly the opposite to the increase in dominant frequency which occurred in the drugfree state upon hyperventilation.

Of the sixteen cases of hyperventilation with diamox recorded in Table 5, six post-hyperventilation power spectra show that cortical activity did not return to the prehyperventilation condition 30-90 seconds after hyperventilation ended. Experiment 3C. Carbon Dioxide and Diamox.

A total of 124 power spectra were computed in this experiment. Table 6 contains a summary of the experimental conditions and results.

Table 6 indicates that changes in power spectra occurred for all subjects in at least one of the experimental conditions. These changes, however, did not occur each time the subject inhaled carbon dioxide. Nor did they occur each time the subject inhaled carbon dioxide after ingesting diamox.

Upon inhalation of carbon dioxide, two subjects (PM and HVD) showed a slight increase in theta activity. HVD produced this increase in slow wave activity when inhaling 10% carbon dioxide, but only after 5 min. of inhalation. At 20% carbon dioxide, the bandwidth of HVD's dominant peak was broadened. At 10% carbon dioxide, PM's power spectra showed a slight increase in theta activity. But this result could not be replicated on two other occasions.

When carbon dioxide was inhaled after PM had ingested

| TABLE | 6 |
|-------|---|
|-------|---|

DOMINANT OCCIPITAL FREQUENCY(Hz) DURING CARBON DIOXIDE INHALATION

| SUBJ   | ECTS            |            |                 | MINUTES OF CARBON DIOXIDE INHALATION  |
|--------|-----------------|------------|-----------------|---|
| C      | )IAMOX<br>(ma.) | °/₀<br>CO₂ | PRE-<br>RESTING | 0 10 20 30 40 50  |
|        |                 | 10         | 10.0            | ♦ 9.75 9.75 10.0 10.0 10.0 10.0 9.75 10.25 ↓ 10.25<br>7.5-8.5                   |
|        | 250             | 13         | 10.5            | 1025 100 105 105 105 1025 1025 10 10 ↓ 10<br>5.5 2-4 50 5.5 5.5 4;5.5 6         |
| P.M.   | <u></u>         | 13         | 10.25           | 9.5 10.5 10.5 10.5 10.5 10.5 10.25 10.25 10.0 10.0 10.25 ↓                      |
|        |                 | 5-15       | 10.3            | 10.4 10.42 10.55 10.4 10.6 ↓ 10.5<br>5% 10% 15%                                 |
|        |                 | 10         | 10.0            | +9.5 10.0 10.0 10.0 10.0 10.0 10.0↓<br>12.5;6.5                                 |
| п.v.D. |                 | 20         | 10.0            | 10.75 10.75 10.25 10.5 10.25 10.0 10.0 10.0 10.0 10.0 10.0 10.0 10.             |
| DM     | 250             | 5          | 9.25            | 9.25 9.25 9.0 9.0 9.25 9.0 9.25 9.0 9.0   |
| R.M.   | 250             | 10         | 9.25            | 19.0 9.0 9.0 9.0 ↓9.5<br>,3.25 3.75 3-4   |
| B.B.   | 250             | 8          | 10.5<br>2.25    | 18.25 7.0 10.7511.0 10.75 11.0 10.75 10.75↓11.0<br>10.75 8-10 9.25 875 7.75 8-9 |
| TC     | 250             | 10         | 9.0             | 49.25 925 100 4-6 9.5 4-6 9.5↓ 9.25<br>4.5-5.5 4-6 9.75 4-6 9.5 4-5             |
| 1.0.   | 250             | 3-40       | 9.75<br>6.0     | <b>1</b> 5-6.5 5-7 5-7 2.0 2.5 2 2.5 ↓ 3.0<br>7.75 9.5 10.25 100 9.75 10.0 10.0 |

 $^{\rm a}40\%$  CO  $_2$  for first 30 seconds; 20% CO  $_2$  from 0:30 -1:30 minutes; 5% CO  $_2$  from 1:30 -2:30 minutes; and 3% CO  $_2$  from 2:30 -30 minutes.

diamox, theta activity appeared, disappeared, and reappeared at various intervals. The dominant peak, however, was maintained at its resting frequency. Similar increases in theta activity, along with a stable dominant peak, also occurred for RM, BB and TG when they inhaled carbon dioxide after ingesting diamox. For BB and TG, changes in the frequency of the dominant peak occurred in the early minutes of carbon dioxide inhalation, but the dominant peak either returned to its resting frequency (BB), or retained some power (TG) as carbon dioxide inhalation continued. Subject TG showed the most pronounced reaction to the diamox-carbon dioxide combination. The slow waves indicated in his power spectra were both the slowest that were obtained in any of the present series, and persisted for the duration of the inhalation period. The subject reported feeling disorganized during these sessions.

#### EXPERIMENT 4. GLUCOSE

#### INTRODUCTION

Numerous investigators (Brazier, et. al., 1944; Cruetzfeldt and Meisch, 1963; Davis, 1941, 1943; Engel, et. al., 1944; Gibbs, et. al., 1940; Himwich, et. al., 1939; Hoagland, et. al., 1937; and Ziegler and Presthus, 1957) report a direct relationship between blood sugar levels and eeg frequencies. When the blood sugar level falls, the cortical frequency first shows a slight decrease. As the blood sugar level drops even more, and the subject approaches a coma-like state, very slow delta waves predominate (Himwich, et. al., 1939; Hoagland, et. al., 1937). However, the cortical frequency will not increase beyond a certain maximum, even after a considerable increase in the blood sugar level (Brazier, et. al., 1944).

These results have been obtained with normal subjects (Brazier, et. al., 1944; Davis, 1941, 1943; Engel, et. al., 1944; Gibbs, et. al., 1940), schizophrenics (Himwich, et. al., 1939, 1941; and Hoagland, et. al., 1937), and neurological patients (Ziegler and Presthus, 1957). Both overnight fasting and insulin have been used to produce the eeg slowing. Slowing of the alpha rhythm is reported at blood levels between 55 and 85 mgms% (Davis, 1943), although the slow delta waves do not appear until the blood sugar drops to approximately 30 mgms% (Gibbs, et. al., 1940). Administering glucose is reported to

increase the occipital frequency (Engel, et. al., 1944; Gibbs, et. al., 1940). Blood sugar levels as high as 300 - 400 mgms% can be obtained by administering oral or IV glucose.

Most of these investigators used a visual analysis of the eeg in determining their results. Engel, et. al., (1944) are a notable exception in that they attempt to objectify their method of visual analysis. Gibbs, et. al., (1940) offer the only objective, automatic technique using a Fourier analysis.

Just as blood sugar levels are said to be directly correlated with cortical frequencies, so too are oxygen concentrations (cf. Dawson and Greville, 1963). Increasing the oxygen concentration inhaled is reported to produce an increase in the cortical frequency as determined by both visual (Engel, et. al., 1944) and mathematical analyses (Gibbs, et. al., 1940).

#### MECHANISMS OF ACTION

In the central nervous system, the relationship between functional and metabolic activity is not as close as in other organs, or as in the peripheral nervous system. But in general, an increase or decrease in activity is related to an increase or decrease in glycolysis. The net energy made available to the brain must ultimately be derived from the oxidation of glucose (McIlwain, 1966; Sokoloff, 1960). Several of the other sugars may maintain normal functioning, but only after conversion to glucose (McIlwain, 1966).

Animal experiments indicate that cortical and subcortical structures are affected differently by hypoglycemia (Himwich, 1951).

At deep levels of hypoglycemia, the electrical activity of the cortex disappears before that of the subcortical structures. After the injection of glucose, the cortical activity takes longer to return to its original pattern.

A singular study was performed by Creutzfeldt and Meisch (1963). They recorded both single unit and eeg activity from an <u>encephalé isolé</u> cat, during various stages of insulin induced hypoglycemia. They found a concomitant variation between the eeg and unit discharges. As the eeg showed slower waves, the single units displayed a decrease in spontaneous activity, but an increased synchrony. Some units, however, displayed a slight increase in their rate of discharge during the early stages of hypoglycemia.

In summary, the following points may be noted:

 A degree of hypoglycemia may be induced in normal subjects by fasting, of sufficient depth to elicit a slowing of the occipital eeg frequency.

2). Hyperglycemia induced by oral or IV glucose ingestion, leads to an increase in the occipital frequency.

3). The primary effect of hypoglycemia on the central nervous system appears to be a metabolic action on cortical cells. At the deepest levels of hypoglycemia, the activity of subcortical structures is also depressed.

4). Although there appears to be a direct metabolic effect of hypoglycemia on the cortical cells, there is no information available concerning the exact mechanism which might mediate this effect upon the eeg ( i.e., regarding rate of repolarization, level of membrane potential, etc.).

#### METHOD

<u>Subjects.</u> Seven healthy males, ages 20 -33 years, were used. <u>Apparatus.</u> The eeg recording and computation facilities are described on page 37. Sugar was administered in the form of dextrose anhydrose ( d-glucose), mixed with water and flavored with lemon.

Oxygen was delivered via a face mask through an anesthesiology machine ( Miget Kinet-O-Meter, Heidbrink,Co., Minneapolis, Minnesota ). A non-rebreathing system was used. The apparatus allows a direct reading of the amount of gas delivered in liters per minute. The face mask contained two one-way valves and was designed so that room air could not enter into it.

### Procedure.

Experiemnt 4A. Fasting.

All seven subjects were asked to fast overnight and were tested in the morning. The durations of the fasts varied from 10-14 hours. Nothing but water was allowed during the fast. Several subjects repeated the procedure but never on consecutive days.

Four of the seven subjects fasted overnight after having received a large dose of dextrose ( cf. section 4D ) the previous afternoon or evening.

Experiment 48. Fasting plus Hyperventilation.

Six subjects were asked to hyperventilate while in the fasting state. The hyperventilation procedure was the

same as described in section 3C.

Experiment 4C. Fasting plus Diamox.

Two subjects ingested 250mg of diamox ( cf. section 3 ) at the end of their fasting periods, and were tested 30-60 minutes later.

Experiment 4D. Dextrose Ingestion.

Four subjects were given a large dose of dextrose ( 150 gm of dextrose in 400 cc of water, with lemon ). Such large doses of dextrose induce an initial hyperglycemia, which may trigger an insulin reaction, and finally result in a moderate hypoglycemia (Kleiner, 1948). Subjects were tested at various intervals up to three hours after dextrose ingestion, and the following morning after an overnight fast. Experiment 4E. Dextrose plus Oxygen.

The subjects who received the doses of dextrose were also given 100 % pure oxygen (10-12 liters per minute), at various intervals after ingesting the dextrose. The anesthesiology machine was used to deliver the oxygen.

In all of the above experiments, subjective reports were elicited if not freely offered.

#### RESULTS

Experiment 4A. Easting.

A total of 59 power spectra were computed in parts A and B of this experiment. Table 7 contains both the "normal" and fasting dominant frequency for each of the seven subjects. Of the eleven fasting cases, there were only four cases in which the fasting peaks appeared different than the subjects'

# TABLE 7

# DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER FASTING

## AND HYPERVENTILATION

| SUBJECTS          | MINUTES OF HYPERVENTILATION |                                    |   |                   |                           |                     |      |                     |  |  |
|-------------------|-----------------------------|------------------------------------|---|-------------------|---------------------------|---------------------|------|---------------------|--|--|
|                   | PRE-<br>RESTING             | FASTING<br>10.5-14hrs.             | 0 | 1                 | 2                         | 3 4                 |      | 56                  |  |  |
| P.M.              | 10.0-10.5                   | 10.0                               | 1 | 10.2              | 58.<br>6                  | .75↓<br>.0          | 10.2 | 5                   |  |  |
| R.M.              | 9.0                         | 8.5<br>4-5<br>9.0 <sup>&amp;</sup> | Ť | 8.5<br>4-5<br>8.5 | 8.5<br>4-6<br>8.5<br>4.75 | 4-6<br>8.0<br>8.5   | Ļ    | 8.5<br>4.25<br>8.5  |  |  |
| B.B.              | 10.0                        | 10.0<br>10.0<br>10.0               | 1 | 100<br>80<br>4.0  | 4-7                       | 4-6.5↓<br>8.5       |      | 975<br>475          |  |  |
| R.H.              | 11.0                        | 11.0 <sup>a</sup>                  | 1 | 11.0              | 10.25<br>4-6.5            | 10.25<br>5.75       | ţ    | 11.5                |  |  |
| R.Z.              | 11.0                        | 10.5 a<br>7.75<br>5-6<br>10.0      | Ť | 10.5              | 10.5                      | 11.0<br>4-5<br>6.25 | ¥    | 11.0<br>6.0<br>8.75 |  |  |
| M <sup>C</sup> N. | 11.0                        | 10.25 a<br>5.0                     | 1 | 10.5<br>8,25      | 10.25<br>8.25             | 10.0<br>6.0<br>8.0  | Ŷ    | 10.5<br>8.25        |  |  |
| N.W.              | 9.5                         | 9.5                                |   |                   |                           |                     |      |                     |  |  |

a These subjects fasted overnight after receiving a large dose of dextrose the previous evening. resting peaks. In three of these four cases, new peaks appeared in the theta range ( subjects RM,RZ, AND McN ). Subject RM showed a fluctuation in his dominant peak on one day, but not another.

Four of the seven subjects fasted overnight after having received 150 gm of d-glucose the previous evening. Only two subjects ( RZ and McN ) produced power spectra with a dominant peak different from their resting peaks. They also showed an increase in theta activity. Both RM and RH failed to show a change under these conditions. All of the fluctuations in dominant peak which did occur were decreases. Experiment 48. Fasting plus Hyperventilation.

Six of the subjects who participated in the fasting experiment were asked to hyperventilate while still in the fasting state. In all cases, the effects of hyperventilation were equal to, or greater than, hyperventilation in the nonfasting state ( compare the corresponding power spectral estimates of Tables 4 and 7). Fasting-hyperventilation elicited a more pronounced response than the non-fasting hyperventilation, even if the subjects' resting dominant peaks after fasting did not change ( PM,RM,BB, and RH ). The kinds of changes which did occur were similar for fasting and non-fasting hyperventilation. In both cases, increases in theta activity occurred, which may be accompanied by a slowing in occipital frequency ( e.g., subject PM, HV 2:30-3:30 min.). Figure 10 presents the power spectra for subjects PM and RM.



FIG. 10. Power spectra from subjects PM and RM while they were hyperventilating, after fasting overnight.

Experiment 4C. Fasting Plus Diamox.

The results of this experiment are presented in section 38.

Experiment 4D. Dextrose.

A total of 77 power spectra were computed in sections D and E of this experiment. Table 8 contains the power spectral estimates obtained after various intervals following the ingestion of dextrose. Of the twelve cases of dextrose ingestion, only three showed a fluctuation in dominant frequency. In three cases, theta activity appeared in the post-dextrose resting eeg.

Experiment 4E. Dextrose Plus Oxygen.

Table 8 contains power spectral estimates obtained after subjects ingested dextrose and inhaled oxygen. Upon inhalation of 100% oxygen, at least some power spectra for each subject show a fluctuation in dominant frequency. Inhalation of oxygen is often accompanied by a slight increase in theta activity, regardless of whether or not there are fluctuations in dominant frequency. All of the fluctuations in dominant frequency were increases. Figure 11 contains the power spectra for subjects RH and RM.

### TABLE 8

# DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER DEXTROSE

# INGESTION AND DURING OXYGEN

INHALATION

| SUBJE             | CTS           |                 |                  | M | NUTE         | SOF          | OXYC       | GEN I            | NHAL          | ATION                                 |              |      |        |
|-------------------|---------------|-----------------|------------------|---|--------------|--------------|------------|------------------|---------------|---------------------------------------|--------------|------|--------|
|                   | TIME<br>(hrs) | PRE-<br>RESŢING | POST<br>DEXTROSE | 0 | 1 2          | 2 3          | 4 5        | 5 6              | 78            | 9 10                                  | 11 12        | 13   | 14     |
|                   |               | 11.0            |                  |   |              |              |            |                  |               |                                       |              |      |        |
| R.H.              | 1             |                 | 11.5<br>4-5      | † |              | 11.5 11.5    | 5          | 115<br>4-5       | 115<br>4-6    | 4-5                                   |              |      |        |
|                   | 2             |                 | 11.5             | 1 | 11.5         | 11.5         | 5          | 11.5             | 11.5 J<br>4-6 | 4-6                                   |              |      |        |
|                   |               | 11.0            |                  |   | · · · ·      |              |            |                  |               |                                       |              |      |        |
|                   | 1             |                 | 11,0             | 1 |              | 11.25<br>4-5 | 4-         | 11.25<br>5:6.0   | 11.25<br>4-5  | 11.5 ↓<br>4-5:7                       | 11.75<br>4-6 |      |        |
|                   | 2             |                 | 11.0             | 1 |              | 11.25        | 11.0       | 11(<br>          | 0↓ 1<br>74    | 15<br> -7                             |              |      | •      |
|                   |               | 9.0             |                  |   |              |              |            |                  |               |                                       |              |      |        |
| R.M.              | 11/2          |                 | 9.0              | 1 | 9.0<br>5.0   | 9.5          | 9.0        | 9 <u>(</u><br>4- | 0 <b>∔ S</b>  | 9.5                                   |              |      |        |
|                   | 3             |                 | 9.0              | 1 | 9.0          | 9.5          | 9.5<br>6-8 | ↓ 9.0            | )             |                                       |              |      |        |
|                   | _             | 9.0             |                  |   |              |              |            |                  | -             | · · · · · · · · · · · · · · · · · · · |              |      |        |
|                   | 1/2           |                 | 9.0              | 1 | 9.0<br>4.25  |              |            | 9.0<br>6.0       |               | 9.54<br>6-8                           | S            | 9.5  |        |
|                   | 31/2          |                 | 9.5              | 1 | 9.0<br>4-5   |              |            | 95<br>42         | 5             | 9.01                                  | ç            | 0.25 |        |
|                   |               | 11.0            |                  |   |              |              |            |                  |               |                                       |              |      |        |
| R.Z.              | 1             |                 | 11.0<br>5.75;75  | Ŧ | 11.0<br>4-6  | 11.5<br>55   | 5          | ↓11.0            |               |                                       |              |      |        |
|                   | 11/2          |                 |                  | 1 | 11.5<br>5.75 | 11.0<br>5.5  | )          | 110<br>5.5       | 11.0<br>5.75  | ↓ 11.0<br>5-6                         |              |      |        |
|                   | 3             |                 | 11.0<br>525,775  | 1 | 11.0<br>5.0  | 11.0<br>4-6  | }          | 11.0             | 11.0<br>4-6   | 11.0↓<br>4-6;80                       | 11.5<br>.4-5 |      |        |
|                   |               | 10.5            |                  |   |              |              |            |                  |               |                                       |              |      |        |
| M <sup>C</sup> N. | 1             |                 | 10,5             | 1 | 11.0         |              | 11.0       |                  |               | 11.0 ↓                                | 11.0         | 11.0 | 2<br>D |
|                   | 2             |                 | 10.5             | † | 1075         |              | 11.0       |                  | •             | 1054                                  | 11.0         |      |        |



FIG. 11. Power spectra from subjects RH and RM after they ingested dextrose(150gm in 400cc of water), and while they inhaled 100% pure oxygen.

### EXPERIMENT 5. CHLORDIAZEPOXIDE (LIBRIUM)

### INTRODUCTION

There are few studies which have investigated the effects of librium on the frequency of the eeg. Those that have been made report a slowing of the alpha rhythm (Carter, 1962; Jarvik, 1965; Keskiner and Lloyd-Smith, 1963; and Sternbach, et. al., 1964). None of the above investigators used normal subjects, nor did they use any method other than an unspecified visual analysis of the eeg.

Since librium has definite anticonvulsant properties (Randall, 1961; Sternbach, et. al., 1964), is said to produce an eeg typical of a drowsy state (Brazier, 1964), does not have the hypnotic effect of barbiturates (Randall, 1961; Jarvik, 1965; and Sternbach, et. al., 1964), and produces a slowing of the alpha rhythm in a variety of neurological patients, it was decided to test its effects on the frequency characteristics of the normal eeg.

Librium is a relatively new drug, and very little has been published concerning its effects upon the brain (Jarvik, 1965). It has been shown, however, that the limbic system (septum, amygdala and hippocampus) is more sensitive to the drug than is the reticular activating system. Both systems are depressed by librium (Schallek and Kuehn, 1960).

#### METHOD

Subjects. Six healthy males, ages 19-33 years, were used. Apparatus. The eeg recording and computation equipment have been described on page 37. Librium was obtained in 5 and 10 mg. tablets.

Procedure. Each subject was given at least two different doses of librium, the exact amount depending upon the subject's body weight and his reaction to the first dose. One subject received the same 25 mg. dose on three consecutive days, in order to test the cumulative effects of the drug. Other doses ranged from 20-50 mg., taken orally in single doses (cf. Table 9). The subjects were not told what kind of drug they were receiving.

EEGs were obtained at intervals varying from 20 minutes to  $9\frac{1}{2}$  hours after ingesting the drug. Four of the six subjects were asked to hyperventilate while under the influence of the drug.

Subjective reports were elicited if not freely offered.

#### RESULTS

A total of 135 power spectra were computed in this experiment.

Table 9 indicates the dominant occipital peak for each subject, under conditions of maximal change induced by various doses of librium. Four of the six subjects showed fluctuations in their dominant peak under librium. For three of these subjects (RZ, BB, and NW) the fluctuations were .5 Hz decreases. The fourth subject's (PM) dominant peak fluctuated toward the fast side of the spectrum by .5 Hz.

Figure 12 presents some of the power spectra of subjects

# TABLE 9

DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER VARIOUS DOSES OF CHLORDIAZEPOXIDE

| SUBJECTS |                      | LIBRIUM (mg.)   |                      |      |         |     |           |              |  |  |  |
|----------|----------------------|-----------------|----------------------|------|---------|-----|-----------|--------------|--|--|--|
|          | PRE-<br>RESTIN       | G <sup>20</sup> | 25                   | 30   | 35      | 40  | 45        | 50           |  |  |  |
| D 7      | 11.0                 | 10.5            |                      |      |         |     |           |              |  |  |  |
| Π.Ζ.     | 11.0                 |                 |                      |      | 10.5    |     |           |              |  |  |  |
| R.H.     | 11.0<br>11.0<br>11.0 |                 | 11.0<br>11.0<br>11.0 |      |         |     |           |              |  |  |  |
|          | 11.0                 |                 | · <u> </u>           | .0.  |         |     | 11.0-11.5 | 5            |  |  |  |
| 514      | 10.0                 |                 |                      | 10.2 | 25-10.5 | 5   |           |              |  |  |  |
| P.M.     | 10.0                 |                 |                      |      |         |     | 10.5      |              |  |  |  |
| 514      | 90                   |                 |                      |      | 9.0     |     |           |              |  |  |  |
| R.M.     | 9.0                  |                 |                      |      |         | 9.0 |           |              |  |  |  |
|          | 10.0                 | <u></u>         |                      |      | 10.0    | ,   |           |              |  |  |  |
| B.B.     | 10.0                 |                 |                      |      |         |     |           | 9.5          |  |  |  |
|          | 9.5                  |                 |                      | 8    | 8.5-9.5 |     |           |              |  |  |  |
| N.W.     | 95                   |                 |                      |      |         | •   |           | 9 <u>.</u> 0 |  |  |  |


FIG. 12. Power spectra from subjects RH and RZ after they ingested various doses of Librium.

RH and RZ, obtained at various intervals after ingesting librium. The power spectra from RZ show changes in dominant frequency, whereas the spectra from RH show changes elsewhere in the spectrum.

Figure 13 contains power spectra of RH's occipital frequency while the subject was hyperventilating under the influence of librium. Also in Figure 13 are the power spectra of PM's occipital frequency during hyperventilation after ingesting librium. The power spectra of both these subjects (RH and PM) evidenced considerable change upon hyperventilation, yet each changed in a different manner. For subject PM, the dominant peak shifted to the slow side by a full cycle per second, and a new smaller peak appeared in the theta range (4-8 Hz). For subject RH, the dominant peak appeared in the theta range, where previously no peak existed (Figure 13). Even after hyperventilation had stopped, there remained considerable power in the theta band (Figure 13). The only unusual sensation reported by RH while hyperventilating, was a feeling of "pins and needles" in his fingers and toes. The power spectrum for subject PM also shows effects after hyperventilation had ceased (Figure 13).

In contrast, the power spectra for subjects RM and RZ (Figure 14) show only slight changes upon hyperventilation. For subject RM, the librium-hyperventilation power spectra show a more pronounced effect than when the subject hyperventilated without the drug (compare Figs. 8 and 14). For subject RZ, the power spectra for both conditions are extremely similar



FIG. 13. Power spectra from subject RH while he was hyperventilating after ingesting Librium.



FIG. 14. Power spectra from subjects RM and RZ after ingesting Librium and hyperventilating.

( compare Figs. 7 and 14 ). Both subjects show an oscillation around their dominant resting frequency when hyperventilating under the influence of librium. But no new peaks appear in the theta band or elsewhere, as with subjects PM and RH.

## EXPERIMENT 6. DEXTRO-AMPHETAMINE SULFATE ( DEXEDRINE )

#### INTRODUCTION

The few studies concerned with the effects of amphetamines on the eeg report either an increase in alpha frequency(Gibbs and Maltby,1943; Lindsley and Henry,1942), or no appreciable effect (Gastaut,et.al.,1960; Gibbs,et.al., 1937). Little work has been done on the effects of amphetamines on the normal human eeg. Most of the above studies used psychiatric or neurological patients. Only Gibbs and Maltby(1943) used a power spectrum technique to determine eeg frequency changes. They administered benzedrine to two normal subjects.

It is known that amphetamines affect the reticular formation by lowering the threshold for arousal by electrical stimulation of this region (Bradley and Key,1958; Rothballer, 1957). However, little is known about the direct action of the drug on cortical cells (Innes and Nicherson,1965).

#### METHOD

Subjects. Six healthy male subjects, ages 19 - 33 years, were used.

Apparatus. The eeg recording and computation facilities are described on page 37. Dexedrine was obtained in 5,10 and 25 mg tablets.

Pure oxygen was delivered via a face mask, through an anesthesiology machine (Miget Kinet-O-Meter,Heidbrink,Co., Minneapolis, Minnesota). A non-rebreathing system was used.

The face mask contained two one-way valves which were designed so that room air could not enter into it.

<u>Procedure</u>. Table 10 contains a summary of the experimental conditions. Three subjects were given three different doses of dexedrine ( 5, 10, and 25 mg.) on separate occasions. These same three subjects also received 100 % oxygen (10-12 liters per minute) for various durations, after ingesting the dexedrine. Another subject received two doses of dexedrine (10 and 25 mg.) on two separate occasions, and room air. And two other subjects received only a single dose of dexedrine, one of whom also received oxygen. Subjects were not told what kind of drug they were receiving. EEGs were recorded at various intervals from 30 minutes to 3 3/4 hours after receiving the drug.

#### RESULTS

A total of 55 power spectra were obtained in this experiment. Table 10 presents the maximal changes in occipital frequency induced by various doses of dexedrine and oxygen. With dexedrine alone, five of the six subjects showed fluctuations in occipital frequency, at one or more dose levels. In two cases (subject RH, 5 mg; and subject NW,25 mg.) the fluctuations were toward the slow side of the spectrum.

Three of the four subjects who also received oxygen showed a further .25-.5 Hz increase in frequency. However, the full .5 Hz increase with oxygen occurred only when the dexedrine alone produced no fluctuations. If the dexedrine had already produced a fluctuation toward the fast side, the

# TABLE 10

# DOMINANT OCCIPITAL FREQUENCY(Hz) AFTER VARIOUS

DOSES OF DEXTRO-AMPHETAMINE SULFATE AND

# DURING OXYGEN INHALATION

| SUBJECTS |                  | DEXEDRINE (mg.)      |                       |                      |  |  |  |
|----------|------------------|----------------------|-----------------------|----------------------|--|--|--|
| STATE    |                  | PRE- 5mg.<br>RESTING | PRE- 10mg.<br>RESTING | PRE- 25mg<br>RESTING |  |  |  |
| RM       | Drug<br>alone    | 9.0 9 <u>.</u> 0     |                       |                      |  |  |  |
|          | +0 <sub>2</sub>  | 90                   |                       |                      |  |  |  |
| RH       | Drug<br>alone    | 11.0 11.0            | 11.0 11.25            | 11.0 11.5            |  |  |  |
|          | + 0 <sub>2</sub> | 11.5                 | 11.5                  |                      |  |  |  |
| R7       | Drug<br>alone    | 11.0 10.5            | 10.25<br>10.5-11.0    | 10.75 11.0           |  |  |  |
|          | +0 <sub>2</sub>  | 11.0                 |                       |                      |  |  |  |
| PM       | Drug<br>alone    | 10.0 10.25           | 10.0 9.5+10.75        | 10.0 10.0            |  |  |  |
|          | +0 <sub>2</sub>  | 10.5                 | 11.0                  |                      |  |  |  |
| N.W.     | Drug<br>alone    |                      | 9.0 9.5               | 9.5 8.5-10.5         |  |  |  |
| B.B.     | Drug<br>alone    |                      | 10.0 10.25            |                      |  |  |  |

effects of oxygen were mitigated. Oxygen did not produce fluctuations in frequency in all cases ( e.g., subject RM).

Figure 15 contains power spectra for subject RH after ingesting dexedrine and inhaling oxygen. Figure 15 contains estimates of the power spectra out to 24 Hz. In Figure 15 the dominant peak remains at 11Hz, but new peaks appear at 16.5 Hz and 22.5 Hz. After receiving oxygen for 5-6 minutes, the subject's dominant peak fluctuated toward the fast side by .5 Hz, and the peak at 22.5 Hz remained. These instances are unusual in that changes were found in frequencies outside the alpha and theta bands. The output in this freqeuncy range was not altered by the filters of the polygraph.

Figure 15 contains the power spectra for subject RH at two dose levels, one of which was accompanied by oxygen inhalation. The effect of oxygen was similar to that of a larger dose of dexedrine.

Figure 16 contains the power spectra for NW at two dose levels and two post-drug intervals. With 10 mg.of dexedrine the occipital frequency fluctuated toward the fast side. With 25 mg.of dexedrine, two separate peaks appeared within the alpha band 30 minutes after ingesting the drug. One of the peaks was below, the other above, the resting peak value. At 1 3/4 hours after ingesting the drug, the dominant frequency was .5 Hz below the resting peak value, but the fast side of the peak (10-11 Hz) showed an increase in power. The double peak in Figure 16 for subject NW is unusual, but has



FIG. 15. Power spectra from subject RH after ingesting dextroamphetamine sulfate and inhaling 100% pure oxygen.



FIG. 16. Power spectra from subject NW after ingesting various doses of dextro-amphetamine sulfate.

appeared in the same subject's power spectra under other conditions. Subject PM also produced a power spectrum with a dual peak, 90 minutes after ingesting 10 mg.of dexedrine. It was the only occasion on which a double peak appeared in this subject's eeg.

#### SUMMARY OF RESULTS

The power spectral and visual techniques of eeg analysis have proven to be reliable and valid methods of determining the dominant eeg frequency. Variability in dominant peaks was detected across and within subjects. The between-day variability is less than .5 Hz for the group as a whole. The within-day variability also appears to be of the order of .5 Hz. Because these sources of variability were obviously small compared to the changes sought, the study was not designed to measure their distribution.

Eight out of the nine subjects showed a full 1 Hz change in dominant frequency under at least one of the experimental treatments (cf. Table 11). Only one subject (PM) showed 1 Hz changes in both directions. When these 1 Hz changes occurred, theta activity often appeared. All of the 1 Hz shifts were in the expected directions, with the exception of subject RZ's 1 Hz increase in frequency upon hyperventilation.

Carbon dioxide inhalation and hyperventilation procedures produced the largest changes in the cortical frequency spectrum. Considerable theta and delta activity appeared most often, occasionally accompanied by a change in dominant occipital frequency.

The changes in dominant occipital frequency alone, without changes occurring elsewhere in the spectrum, are summarized for each treatment in Table 12. Dexedrine and dextrose plus

TABLE 11

# SUMMARY OF POWER SPECTRAL CHANGES FOR EACH EXPERIMENTAL TREATMENT

| Subject           | Fasting      | Dextrose  | Dextrose<br>plus<br>Oxygen | Carbon<br>Dioxide     | Diamox    | Alcohol  |
|-------------------|--------------|-----------|----------------------------|-----------------------|-----------|--|
| R.M.              | 1∕₂ c <      | ¹/₂ c     | ¹½c ⟩<br>theta<br>delta    | No Change<br>delta    | No Change |  |
| N.W.              | No Change    |           |                            |                       |           | <sup>1</sup> / <sub>2</sub> c ><br><sup>1</sup> / <sub>4</sub> c > + < |
| B.B.              | No Change    |           |                            | 3c≮<br>theta          | No Change | ¹⁄₂ c <  |
| P.M.              | 1/₂c <       |           |                            | No Change<br>> theta  | 1/2 ⊂ <   | <sup>1</sup> ⁄₂-1.0c <   |
| M <sup>C</sup> N. | ¹⁄₂ c <      | No Change | 1/2c>                      | No Change<br>theta    |           |  |
| H.V.D.            |              |           |                            | ¹⁄₂c ><br>theta       | No Change |  |
| T.G.              |              |           |                            | 1c><br>theta<br>delta | No Change |  |
| R.Z.              | 1/₂ - 1.0c < | No Change | theta                      |                       |           | No Change  |
| R.H.              | No Change    | 1/2C >    | ½c><br>theta               |                       | No Change | 1/2 c <  |

| SUBJECT           | Librium   | Dexedrine             | Dexedrine<br>plus<br>Oxygen | Hyper-<br>Ventilation | H.V. plus<br>Fasting | H <u>.V.</u> plus<br>Diamox | H.V. plus<br>Alcohol | H.V. plus<br>Librium |
|-------------------|-----------|-----------------------|-----------------------------|-----------------------|----------------------|-----------------------------|----------------------|----------------------|
| R.M.              | No Change | No Change             | No Change                   | No Change             | 1cく<br>theta         | ½c<<br>theta<br>delta       |                      | ½c <<br>theta        |
| N.W.              | 1⁄₂c <    | <sup>1</sup> ⁄₂-1.0c< |                             | 1c<                   |                      |                             |                      |                      |
| B.B.              | ¹⁄₂ c <   | No Change             |                             | 3¼ c <<br>theta       | 3cく<br>theta         | 2¾c <<br>theta              |                      |                      |
| P.M.              | ½c >      | ¼-½c>                 | _ 1c >                      | No Change<br>theta    | 1½ c <<br>theta      | 2½c <<br>theta<br>delta     | 2c≮<br>theta         | 1c <<br>theta        |
| M <sup>C</sup> N. |           |                       |                             | No Change             | 1c <<br>theta        |                             |                      |                      |
| H.V.D.            |           |                       |                             | 1¼ c <                |                      | ½c <<br>theta<br>delta      |                      |                      |
| T.G.              |           |                       |                             | theta                 |                      | ¼c ><br>theta               |                      |                      |
| R.Z.              | 1/2 c <   | ¼-¾c><br>½c<          | No Change                   | ½c ><br>theta         | ½c <<br>theta        |                             |                      | ½c><br>theta         |
| R.H.              | No Change | 1/2 c >               | 1/2 c >                     | 1c>                   | ³⁄₄c <<br>theta      | 1/2 c <                     | No Change            | theta                |

SUMMARY OF CHANGES IN DOMINANT PEAK

|          | Condition             | Slower    | No Change | Faster | Total<br>Subjects |
|----------|-----------------------|-----------|-----------|--------|-------------------|
| Increase | Dextrose              | 0         | 2         | . 2    | 4                 |
|          | Dextrose<br>+ Oxygen  | 0         | 1         | 3      | 4                 |
|          | Dexedrine             | 0         | 2         | 4      | 6                 |
|          | Dexedrine<br>+ Oxygen | 0         | 2         | · 2    | 4                 |
|          | Carbon<br>Dioxide     | 1         | 3         | 2      | 6                 |
|          | Total<br>Cases        | 1         | 10        | 13     | 24                |
|          | Fasting               | 4         | 3         | 0      | 7                 |
|          | Diamox                | 1         | 5         | 0      | 6                 |
|          | Hyper-<br>Ventilation | 4         | 3         | 2      | 9                 |
|          | Alcohol               | Alcohol 4 |           | 0      | 5                 |
|          | Librium               | 3         | 2         | 1      | 6                 |
|          | Total<br>Cases        | 16        | 14        | 3      | 33                |

lucre

EXPECTED

oxygen, were most successful in producing increases in alpha frequency. Alcohol was most effective in producing a decrease in alpha frequency. Changes in dominant alpha frequency greater than 1 Hz, unaccompanied by an increase in theta or delta activity, did not occur.

Individual differences were noted in:

1.) the values of the dominant resting peak;

the amount of variability in the resting dominant peak;

3.) the kinds of changes which occurred upon the administration of any particular treatment;

and 4.) subjective reports concerning the effects of the experimental treatments.

#### DISCUSSION

The power spectral technique has proven its usefulness in detecting a variety of changes in the eeg, as well as its validity. The technique allows a direct test of certain assumptions concerning some characteristics of the eeg. For instance, the resting power spectra are essentially flat on both sides of the dominant peak, indicating that the frequency components present which are not in the alpha range, are essentially random. The technique's precision, reliability, and the range of information which it provides, as well as its relative ease of calculation, make it possible to deal with several questions which other techniques of eeg measurement could not easily handle.

The present set of data indicates that the alpha rhythm is fairly stable and resistant to change. None of the techniques used were able to manipulate the alpha frequency 2 Hz from its resting frequency, without also increasing the amount of theta activity. The presence of theta activity is likely to be attributed to the activation of subcortical structures, rather than the occipital lobe itself. The fact that 1 Hz shifts in frequency occur only when theta is present, raises the possibility that the mechanisms responsible for the theta activity may influence the alpha generators, rather than the chemical agents directly. Could it be that the desired goal

of a 2 Hz shift in dominant frequency is unattainable? Phrased in more general terms, to what extent are the mechanisms responsible for the alpha frequency capable of shifting these rhythms over a wide frequency range? Can the mechanisms responsible generate any frequency up to a cutoff point? Can the mechanisms responsible generate a frequency only within a narrow band? Can they generate harmonics and subharmonics of this dominant frequency?

The answers to these questions would help to understand the nature of the mechanisms themselves. Pinsky's (1966) model of a cortical neuron and its dendritic branches may account for some of the frequency characteristics of the eeg. If the model cannot account for the answers to the above questions, then it must be asked how the model can be changed to incorporate these characteristics. Such a strategy would be an aid to further understanding the mechanisms responsible for the characteristic frequency components of the eeg. Such questions as those posed above then become tools for testing and improving the model. This is true, of course, for any model which may account for some of the frequency characteristics of the eeg. At worst, this strategy may point out the ways in which a particular model is inadequate.

On the basis of the present data, some very tentative answers may be suggested to some of the questions raised above. In actuality, these "answers" will be an abstracted summary and discussion of the qualitative frequency changes encountered in

the present study.

The first issue concerns the normal range of variability, or spontaneous fluctuations. There are several kinds of variability, noted in the early eeg literature (Jasper, 1936), but unattended since. There is a within-day and a between-day variability. In the present study, the between-day variability was .5 Hz (cf. Table 2). Information regarding within-day variability is not available from the present study. Indirectly, the few occasions on which more than one Pre-resting record was obtained, and the magnitude of the between-day variability, give some suggestion of the within-day variability. This scant information suggests it is also of the order of .5 Hz.

Since both the within-day and between-day variability appeared to be very small relative to changes sought, the present studies were not designed to measure their distribution. If one were interested in small frequency changes in studies of this type, adequate control data would require drug-free eeg measures over a time period similar to that over which the drug effects would be measured. Controls would have to be determined for each subject and the measurements would have to be repeated on different days, to determine if the withinsession variability is similar across days. Increasing the resolution of the power spectra to detect smaller changes in dominant frequency would also help to distinguish spontaneous from induced changes.

In spite of this lack of adequate control data to make

reliable statements about small changes in dominant frequency, there are several trends in the oresent data which make it difficult to support the position that all of the .5 Hz fluctuations encountered were unrelated to the experimental treatments. For instance, the alcohol spectra show .5 Hz fluctuations for four out of five subjects. All four subjects showed these changes in the expected direction, a decrease in frequency. The fasting spectra also reveal a trend toward the slow side of the spectra for four of the seven subjects. The subjects who did not show this .5 Hz decrease, showed no change at all. Similarly, the oxygen plus dextrose spectra show .5 Hz fluctuations, all toward the fast side, for three of the four subjects. Again, this change was in the expected direction, and no fluctuations in the opposite direction were recorded. The results for dexedrine are a bit more complex in that one subject (RZ) showed fluctuation in both directions. However, this subject's increase in frequency (the expected direction) was larger than the decrease which occurred. Including this subject, four of the six subjects showed increases in dominant frequency under dexedrine. The other two subjects showed no changes. Similar trends may be noted for dextrose, and dexedrine plus oxygen. No changes were noted for diamox.

Although the directions of these trends, and the proportion of the subjects who displayed them (cf. Table 12), suggest that the chemical agents actually did have some influence on the eeg frequency, it must be kept in mind that these changes

were small and appear to be within the range of normal variability. Without adequate control data, no conclusions can be reached as to whether these fluctuations are spontaneous or induced. The term spontaneous is used here to describe fluctuations within the normal range of variability. At best, the lack of control data may tend to exaggerate the trends noted.

The second issue concerns those changes which were greater than any spontaneous fluctuations recorded. Changes of 1 Hz in dominant frequency may be induced in some individuals, by some agents, without other changes occurring elsewhere in the spectrum (0-50 Hz) (cf. Table 11). If a change in dominant frequency greater than 1 Hz is induced, it is invariably accompanied by changes elsewhere in the spectrum. These changes are increases in delta and theta activity.

The finding that changes in dominant frequency greater than 1 Hz did not occur, unless theta and/or delta activity also appeared, does not mean that such frequency changes cannot occur alone. A negative generalization of this sort cannot be conclusive. Furthermore, the only treatments which produced changes in dominant frequency greater than 1 Hz were involved with carbon dioxide metabolism. This relationship between dominant frequency and theta activity might hold for carbon dioxide metabolism, but not for other agents. Usually, the theta activity did not occur at a subharmonic of the dominant frequency (cf. Figs. 9-11). Higher frequency responses also occurred at harmonics of the dominant frequency (cf. Fig. 13),

but not always (cf. Fig. 15). Individual differences occurred concerning the presence or absence of harmonics.

The finding that theta and delta activity may be recorded from the occipital lobe raises the question of the source of these rhythms. It is unlikely that the same cells which generate the alpha rhythm, are also responsible for the theta and delta activity recorded. The amplitude of these slower rhythms is usually reported to be greatest in parietal and temporal leads. They are generated by deep subcortical structures, and capable of spreading electrotonically over relatively large areas (Adey, et. al., 1960; Gelhorn, 1953; and Morrice, 1956). Furthermore, in the present studies, theta activity appeared accompanied by no change in the position of the peak in the alpha range. In any event, the present practice of recording with a single occipital lead is not sufficient to determine the source of the theta and delta rhythms recorded there.

A final, general comment concerning the alpha rhythm is in order. The alpha rhythm, and indeed all eeg activity, have been written off by some investigators as an epiphenomenon. At best, they argue, it is nothing more than a resonator, generating the same frequency no matter what input is delivered into the system. The present data do lend support to this idea. The alpha rhythm has proven to be remarkably stable and resistant to the chemical agents administered to the subjects.

The present interest in the alpha rhythm centers on

some of its temporal properties. These temporal properties are considered to reflect some temporal characteristics of the mechanisms responsible for generating the alpha rhythm. Going one step further, the question is asked whether these temporal characteristics of the alpha generators are related to the temporal periodicity of Kristofferson's (1965) model of attention.

It should be noted that the alpha mechanisms may indeed function as a resonator, without becoming incompatible with Kristofferson's notion of the quantum. The quantum is not a physical entity; it is an interval. Resonators generate such intervals, and may impose time limits on the flow of signals. Ignorance about the exact mechanisms responsible for the alpha rhythm leave the rhythm itself as the only index of the mechanism's performance. The notion of a cortical excitability cycle does not claim that the alpha rhythm itself performs certain functions, but that it may be an index of these functions, albeit, an imperfect one.

An obvious question arises concerning the discrepancy between the present results, and those of other investigators who report eeg frequency changes using the same chemical agents. The agents used in the present study may each be placed in one of three categories. Dextrose, oxygen, alcohol, carbon dioxide, and fasting, have each been reported to produce a 2 Hz shift in the occipital frequency of normal subjects.' Librium and dexedrine have been reported to produce 1 Hz shifts in dominant occipital frequency, but there is little information on these agents for

normal subjects. The effects of diamox upon the frequency of the normal eeg have not been reported, to the knowledge of the present reviewer. The agents used in the present study which fall into the first two categories, were administered in higher doses than those used by other investigators, with two exceptions, as noted below.

There were a number of procedural differences between prior studies with these agents, and the present investigation. The most common, and perhaps the most important difference, is the type of eeg frequency analysis used. Of all the prior studies with any of these agents, only those of Davis, et. al., (1940), Gibbs, et. al., (1940), and Gibbs and Maltby (1943), used a Fourier analysis of the eeg to extract the frequency components. The present results are most similar to the findings of these studies. All other investigators used a variety of visual analyses.

Davis, et. al., (1940) administered 2 cc/kg of body weight of absolute alcohol to their subjects. Although this dose is higher than that used in the present study, the blood alcohol levels attained were nearly similar for the subjects in both studies. Many of Davis' subjects became ill from the treatment. None of the subjects in the present study became ill. These authors report a 2 Hz decrease in occipital frequency, and considerable theta activity. Power spectra were computed for only two of their subjects.

Gibbs, et. al., (1940) studied the effects of carbon

dioxide, blood sugar, and oxygen tension on the normal eeg. For carbon dioxide inhalation, they show a 2 Hz increase in occipital frequency for one subject, and a 1 Hz increase for another. Both subjects showed an increase in the power of the slower, theta and delta rhythms. Only two subjects were used in this experiment. The authors do not mention how they raised the blood sugar level. The subject showed a 1 Hz increase in dominant peak, and a considerable increase in theta activity. Their oxygen experiment was performed with a rabbit, and shows a 1 Hz increase in occipital frequency after an increase in oxygen pressure.

Gibbs and Maltby (1943) administered a large IV dose of benzedrine to two normal subjects and reported a 1 Hz increase in occipital frequency, along with increases in theta activity. Benzedrine is a slightly different amphetamine than the dexedrine used in the present study. Dexedrine is considered the more potent agent as a central nervous system stimulant. The different results of these agents on the normal eeg may be due to their slightly different chemical structures, or the different routes of administration (benzedrine, IV; dexedrine, oral).

The other studies which report 2 Hz shifts in occipital frequency, for dextrose (Engel, et. al., 1944; Davis, 1943), fasting (Engel, et. al., 1944), and alcohol (Engel and Rosenbaum, 1945), all used visual techniques to determine the eeg frequency distribution. First of all, it must be noted that

they did not attempt to measure the same characteristics of the eeg that are measured in the power spectral analysis used here. The visual analyses often produced frequency histograms, giving a count of the number of 5 Hz, 6 Hz, etc., waves present in a certain epoch of eeg record. Their frequency categories were a full 1 Hz wide. The power spectral technique computes the amount of power in the frequency spectrum from 0 - 50 Hz, with a .5 Hz resolution. If the reliability of these visual techniques is also questioned (none of the studies presented adequate proof of reliability or validity of their techniques), it is quite obvious that they are measuring very different eeg characteristics than the technique used in the present study. This difference in technique of eeg measurement may account for the discrepancy of results between the present study and others which used the same chemical agents.

The librium and diamox literature concerning eeg effects in normal subjects is scant. Librium is reported to produce a slowing of the alpha rhythm (Carter, 1962; Tobin, et. al., 1960) in hospital patients. If there is an effect on the normal eeg, the present study suggests that it is small. Although diamox mimics the action of carbon dioxide on a number of physiological levels, it does not seem to have an effect on the occiptial eeg frequency. This finding may be due to the fact that the cerebral arterial carbon dioxide tension is not increased after diamox is administered (Ehrenreich, et. al., 1961).

It might be argued that the agents which did not produce

any large effects (dexedrine, librium and diamox) were simply not administered in large enough doses. In answer to this, it can only be noted that all of the doses used were well above the usual clinical doses. Furthermore, subjective reports, as well as casual observation, indicated that each of these agents did have an effect on some level of behavior.

The present studies have not provided a technique for testing the relationship between attention and the alpha rhythm, as desired. They have indicated that 1 Hz changes in dominant. frequency do occur in both directions from the mean resting frequency, without changes elsewhere in the spectrum. This finding presents some possibilities for further study. It may be possible to use one agent to induce a 1 Hz decrease in frequency, and another agent to induce a 1 Hz increase. This would give the desired 2 Hz difference in dominant frequency required to perform the planned experimental manipulations. Such a study would require information concerning the distribution of normal within-session variability. It would also involve manipulating other parameters of the agents, such as dose level, multiple dose, etc., to determine the conditions of maximal change.

#### CONCLUSION

The power spectral technique proved to be a reliable and valid method of eeg analysis. The technique is able to detect a variety of qualitatively different types of eeg changes, and to provide quantitatively precise measures of these changes. This study has thus succeeded in the first of two goals - to provide a reliable and valid measure of eeg frequency analysis.

The second goal of the study was not reached. The experimental techniques used were not able to produce 2 Hz fluctuations of the dominant alpha frequency, without also activating cerebral mechanisms ordinarily not involved in the generation of the alpha rhythm. The finding that the alpha rhythm can be made to oscillate only within a very narrow frequency band (approx. 1 Hz), without new peaks appearing in the spectrum, lends support to the notion that the alpha rhythm is a stable resonator frequency.

The discrepancies between the present results with the various chemical agents used, and the findings of other investigators using the same agents, are attributed to the difference in methods of eeg frequency analysis. Studies which did not use a Fourier analysis similar to the one used in the present case, report larger frequency changes than were found in the present study.

#### REFERENCES

- Adey, W.R. Neurophysiological correlates of information transaction and storage in brain tissue. In Stellar, E. and Sprague, J.M. (Eds), <u>Progress in Physiological</u> <u>Psychology</u>. Vol.1., New York: Academic Press.1966, <u>Pp. 3-44</u>.
- Barnes, T.C., Beutner, R., and Beutner, K.R. The effect of alcohol on the acetylcholine metabolism of the brain. Anat. Record, 1948, 101, 739.
- Bartley, H.S. Some factors in brightness discrimination. Psychol. Rev., 1939, 46, 337-358.
- Bartley,H.S. The relation between cortical responses to visual stimuli and changes in alpha rhythm. <u>J.</u> exp. Psychol., 1940,27, 624-639.
- Bartley, H.S. and Bishop, G.H., The cortical response to stimulation of the optic nerve in the rabbit. <u>Amer. J. Physiol.</u>, 1933, 103, 159-172.
- Bechetereva, N.P. and Zontov, V.V. The relation between certain forms of potentials and the variation in brain excitability. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1962, 14, 320-330.
- Bellis, C.J. Reaction time and chronological age. <u>Proc.</u> Soc. exp. Biol. Med., 1932,30, 801-803.
- Berger, H. Uber das elektroenkephalogram des menschen. Arch. Psychiat. Nervenkrankh., 1929,87, 527-590.
- Bertelson, P. Central intermittancy twenty years later. Quart. J. Exp. Psychol., 1966,18,153-162.
- Birren, J.E. Age changes in speed of behavior; its central nature and physiological correlates. In Welford, A.T.(Ed), <u>Behavior</u>, <u>Aging</u>, <u>and the Nervous</u> <u>System</u>. Springfield, Ill: Thomas, 1965, Pp. 191-216.
- Bishop,G.H. Cyclic changes in excitability of the optic pathway of the rabbit. <u>Amer. J. Physiol.</u>, 1933, 103, 213-224.
- Blackman, R.B. and Tukey, J.W. The Measurement of Power Spectra. New York: Dover Publication, S507, 1958.
- Boynton,R.M. Temporal factors in vision. In Rosenblith, W.A. (Ed). <u>Sensory Communication</u>. New York: Wiley,1961,Pp.739-756.

Bradley, P.B. and Elkes, J. The effects of some drugs on the electrical activity of the brain. Brain, 1957, 80,77.

- Bradley, P.B. and Key, B.J. The effect of drugs on arousal responses produced by electrical stimulation of the reticular formation of the brain. <u>Electroenceph</u>. clin. Neurophysiol., 1958,10, 97-110.
- Brazier, M.A.B. The effect of drugs on the electroencephalogram of man. Clin. Pharm. Ther., 1964,5,102-116.
- Brazier, M.A.B., Finesinger, J.E., and Schwab, R.S. Characteristics of the normal eeg. II. the effects of varying blood sugar levels on the occipital cortical potentials in adults during quiet breathing. <u>J</u>. <u>Clin</u>. Invest., 1944,23,313-317.
- Brazier, M.A.B., Finesinger, J.E., and Schwab, R.S. Characteristics of the normal eeg.III. the effects of varying blood sugar levels on the occipital cortical potentials in adults during hyperventilation. <u>J.</u> <u>Clin. Invest.</u>, 1944,23,319-323.
- Bremer,F. Cerebral and cerebellar potentials. <u>Physiol</u>. <u>Rev.</u>, 1958,<u>38</u>,357-388.
- Brodal, A. The <u>Reticular</u> Formation of the Brain Stem. Edinburg, England: Oliver and Boyd, 1957.
- Burns, D.B. Some properties of the cat's cerebral cortex. <u>J. Physiol.</u>, 1950,<u>111</u>,50-60.
- Burns,D.B. Some properties of the isolated cerebral cortex in the unanesthetized cat. <u>J. Physiol.</u>, 1951,<u>112</u>, 156-175.
- Callaway,E. Day-today variability in relationship between electroencephalographic alpha phase and reaction time to visual stimuli. <u>Ann. N.Y. Acad. Sci.</u>, 1961,92,1183-1186.
- Callaway, E. Factors influencing the relationship between alpha activity and visual reaction time. <u>Electroenceph</u>. <u>clin. Neurophysiol</u>., 1962,14, 674-682.
- Callaway,E. Reaction speed, the eeg alpha cycle, and the autonomic cardiovascular cycle. In Welford, A.T. (Ed), <u>Behavior</u>, <u>Aoing</u>, <u>and the Nervous System</u>. Springfield,Ill: Thomas, 1965,Pp.217-234.
- Callaway, E., and Yeager, C. Relationship between reaction time and electroencephalographic alpha phase. <u>Science</u>, 1960,132,1765-1766.

- Carter, C.H. Librium in spastic disorders, Clinical evaluation. Arch. Pediat., 1962,79,22.
- Caspers,H. Die beeinflussung der corticalen krampherregbarkeit durch das aufsteigende reticularsystem des hirnstammes. II. Narkosewirkungen. <u>Z.ges.exp.Med</u>., 1958, 129,582-600.
- Chang,H.T. The repetitive discharges of corticothalamic reverberation circuit. <u>J. Neurophysiol</u>., 1950, <u>13</u>, 235-258.
- Chang,H.T. Changes in excitability of cerebral cortex following single electric shock applied to cortical surfaces. J. Neurophysiol., 1951,14,95-112.
- Ciganek,L. Excitability cycle of the visual cortex in man. Ann. N.Y. Acad. Sc., 1964,112(Art.1), 241-253.
- Clare, M.H. and Bishop, G.H. Potential wave mechanisms in cat cortex. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1956,<u>8</u>,582-602.
- Cobb,W.A. The normal adult eeg. In Hill,J.D.N.,and Parr, G.(Eds), <u>Electroencephalography</u>, 2nd Ed., London: Macdonald and Co., 1963,Pp.232-249.
- Creutzfeldt, O.D., Meisch, J.J. Changes of cortical neuronal activity and eeg during hypoglycemia. <u>Electroenceph</u>. <u>clin, Neurophysiol</u>., Suppl.#24,1963,158-171.
- Creutzfeldt,O.D.,Watanabe,S., and Lux,H.D. Relations between eeg phenomena and potentials of single cells II. spontaneous and convulsoid activity. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1966,<u>20</u>, 19-37.
- Darrow,C.W., Wilson,J.P., Veith,R.N. and Maller,J.M. Acceleration and momentum in cerebral function reflected in eeg phase relations. In Wortis,J. (Ed), <u>Recent Advances in Biological Psychiatry</u>, London: Grune and Stratton,1960,Pp.51-59.
- Davis, P.A. Effects on the eeg of alterations of blood sugar levels. <u>Amer. J. Physiol.</u>, 1941,<u>133</u>, 259-260.
- Davis, P.A. Effects of the eeg of changing blood sugar levels. <u>Arch. Neurol. Psychiat.</u>, 1943,49, 186-194.
- Davis, P.A., Gibbs, F.A., Davis, H., Jetter, W.W., and Trowbridge, L. The effects of alcohol upon the eeg(brainwaves). Quart. J. Stud. Alc., 1940-41, 1,626-637.

- Davis,H. and Wallace,H.McL. Factors affecting changes produced in electroencephalogem by standarized hyperventilation. <u>Arch. Neurol. Psychiat.</u>, 1942,47,606-625.
- Dawson, M.E. and Greville, G.D. Biochemistry. In Hill, J.D.N. and Parr, G., (Eds), <u>Electroencephalography</u>, 2nd.Ed., London: Macdonald and Co., 1963, 147-192.
- Dustman, R.E., Boswell, R.S. and Porter, P.B. Beta brain waves as an index of alertness. <u>Science</u>, 1962,137,533-534.
- DeLucchi, M.R., Garoutte, B. and Aird, R.B. The scalp as an eeg averager. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1962,14,191-196.
- Dempsey,E.W. and Morison,R.S. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. <u>Amer. J. Physiol.</u>, 1942,135, 293-300.
- Ehrenreich, D.L., Burns, R.A., Alman, R.W. and Razekas, J.F. Influence of acetazolomide on cerebral blood flow. Arch. Neurol., 1961, 5, 227-232.
- Ellingson,R.J. Brain waves and problems of psychology. <u>Psychol. Bull.</u>, 1956,<u>53</u>, 1-34.
- Engel,G.L., Romano,J., Ferris,E.B.,Webb,J.P. and Stevens,C.D. A simple method of determining frequency spectrums in the eeg. <u>Arch. Neurol. Psychiat.</u>, 1944,51,134-146.
- Engel,G.L. and Rosenbaum,M. Delirium:III. Electroencephalographic changes associated with acute alcohol intoxication. <u>Arch. Neurol. Psychiat.</u>, 1945,53 44-50.
- Engel, G.L., Webb, J.P., Ferris, E.B. Quantitative electroencephalographic studies of anoxia in humans: comparison with acute alcoholic intoxication and hypoglycemia. J. Clin. Invest., 1945,24,691.
- Fedio, P., Mirsky, A.F., Smith, W.J. and Parry, D. Reaction time and eeg activation in normal and schizophrenic subjects. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1961, <u>13</u>,923-926.
- Feldman, S.M. and Waller, H.J. Dissociation of electrocortical activation and behavioral arousal. <u>Nature</u>, 1962, <u>196</u>, 1320-1322.
- Freud, S. A note upon the mystic writting pad.(1911). In <u>Collected</u> Papers, London: Hogarth Press, 1956.

Fromm, G.H. and Bond', H.W. Slow changes in the electrocorticogram and the activity of cortical neurons. <u>Electroenceph. clin. Neurophysiol.</u>, 1964,<u>17</u>,520-523.

### Gallego, A. On the effect of ethyl alcohol upon the frog nerve. J. <u>Cellular Comp. Physiol.</u>, 1948,31,97.

- Gastaut,H.J.P. Electroencephalographic records as an aid to the study of the action of the reticular system of the brain-stem on the electrical activity of the cerebral cortex in relation to states of consciousness. In Laurentian Symposium, Ste.Marguerite. Symposium presented at University of California,LA.,1953.
- Gastaut, H., Plas, R., and Bert, J. Effects of intravenous administration of amphetamine in man. <u>Electroenceph</u>. <u>clin. Neurophysiol.</u>, 1960,12,942.
- Gelhorn,E. On the physiological action of carbon dioxide on the cortex and hypothalamus. <u>Electroenceph.clin</u>. <u>Neurophysiol</u>., 1953,5,401-413.
- Gelhorn,E. and Heymans,K. Differential action of anoxia, asphyxia and carbon dioxide on normal and convulsive potentials. J. Neurophysiol., 1948,11,261-273.
- Gerard, R.W. and Libet, B. The control of normal and "convulsive" brain potentials. <u>Amer. J. Psychiat.</u>, 1940,96, 1125-1153.
- Gibbis, F.A., Gibbs, E.L. and Lennox, W.G. Effect on electroencephalogram of certain drugs which influence nervous activity. <u>Arch. Int. Med.</u>, 1937,60,154-166.
- Gibbs, F.A. and Knott, J.R. Growth of the electrical activity of the cortex. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1949,<u>1</u>,223-229.
- Gibbs,F.A. and Maltby,G.L. Effect on the electrical activity of the cortex of certain depressant and stimulant drugs - barbiturates, morphine, caffeine, benzedrine and adrenaline. J. Pharm. & Exp Ther., 1943,78,1-10.
- Gibbs,F.A., Willdams,D. and Gibbs,E.L. Modification of the cortical frequency spectrum by changes in carbon dioxide, blood sugar and oxygen. <u>J. Neurophysiol</u>., 1940,3,49-58.
- Goodenough, F.L. The development of the reacting process from early childhood to maturity. <u>J. exp. Psychol.</u>, 1935, 18, 431-450.
- Grass, A.M. and Gibbs, F.A. A fourier transform of the electroencephalogram. J. <u>Neurophysiol.</u>, 1938, 1,521-526.
- Gray, W.D., Maren, T.H., Sisson, G.M. and Smith, F.H. Carbonic anhydrase inhibition. VII. Carbonic anhydrase inhibition and anticonvulsant effect. <u>J. Pharm</u>. <u>& Exp. Ther</u>., 1957, <u>121</u>, 160-170.

Griesel, R.D. Awareness during abnormal eeg activity accompanying hýperventilation. <u>Psychologia</u> <u>Africana</u>, 1966, <u>11</u>, 64-73.

- Hakkinen,H.M.,Kulonen,E. Increase in the gamma-aminobutyric acid content of rat brain after ingestion of ethanol. <u>Nature</u>, 1959,<u>184</u>,726-727.
- Hanbery, J. and Jasper, H. Independence of diffuse thalamocortical projection system shown by specific necular destruction. <u>J. Neurophysiol</u>, 1953, 16, 252-271.
- Harter, M.R. Excitability cycles and cortical scanning; a review of two hypotheses of central intermittency in perception. <u>Psychol. Bull.</u>, 1967,<u>68</u>,47-58.
- v.Hedenstrom,I, and Schmidt,O. Elektroencephalographische untersuchungen nach alkoholgabe. <u>Dtsch. Z. ges.</u> <u>gerichtl. Med.</u>, 1951,40,234-251.
- Himwich, H.E., Bowman, K.M., D<sub>a</sub>ly, C., Fazekas, J.F., Wortis, J., and Goldfarb, W. Cerebral blood flow and brain metabolism during insulin hypoglycemia. <u>Amer. J.</u> <u>Physiol., 1941, 123, 640-647.</u>
- Himwich, H.E. Brain Metabolism and Cerebral Disorders. Baltimore: Williams and Wilkins, 1951.
- Himwich, H.E., Hadidian, Z., Fazekas, J.F. and Hoagland, H. Cerebral metabolism and electrical activity during insulin hypoglycemia in man. <u>Amer. J. Physiol.</u>, 1939, <u>125</u>, 578-585.
- Hoagland, H. Pacemakers of human brain waves in normal and in general paretics. <u>Amer. J. Physiol.</u>, 1936a,<u>116</u>, 604-615.
- Hoagland, H. Temperature characteristics of the "Berger Rhythm" in man. <u>Science</u>, 1936b, <u>83</u>, 84-85.
- Hoagland,H.,Rubin,M.A. and Cameron,D.E. The eeg of schizophrenics during hypoglycemia and recovery. Amer. J. Physiol., 1937,120,559-570.
- Holmberg,G. and Martens,S. Electroencephalographic changes in man correlated with blood alcohol concentrations and some other conditions following standarized ingestion of alcohol. <u>Quart</u>. J. <u>Stud</u>. <u>Alc</u>., 1955, <u>16</u>,411-424.
- Hord, D.J., Johnson, L.C., Lubin, A. and Austin, M.Y. Resolution and stability in the autospectra of eeg. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>, 1965, <u>19</u>, 305-308.
- Horsey, W.J. and Akert, K. The influence of ethyl alcohol on the spontaneous electrical activity of the cerebral cortex and subcortical structures of the cat. Quart.

- Innes,I.R.,Nickerson,M. Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them(sympathomimetic drugs) In Goodman,L.S. and Gilman,A. (Eds), The Pharmacological Basis of Therapeutics. New York: Macmillan Co., 1965,3rd Ed., Pp.477-520.
- James, W. The Principles of Psychology, Vol.I. New York: Holt, Pp.605-642, 1890.
- Jarvik, M.E. Drugs used in the treatment of psychiatric disorders, In Goodman, G.S. and Gilamn, A. (Eds), 3rd Edition, <u>Pharmacological Basis</u> of <u>Therapeutics</u>, New York: Macmillian, 1965, 159-214.
- Jasper,H. Cortical excitability states and variability in human brain rhythms. <u>Science</u>,1936,<u>83</u>,259-260.
- Jasper, H. Diffuse projection systems: the integrative action of the thalamic reticular system. <u>Electroenceph</u>. <u>clin. Neurophysiol.</u>, 1949,1,405-420.
- Jasper,H. Unspecific thalamocortical relations. In Fields,J. (Ed), <u>Handbook of Physiology</u>. Vol.II. Washington,D.C.: American Physiological Society. 1960,Pp.1307-1327.
- Jasper,H. and v.Buren,J. Interrelationship between cortex and subcortical structures: clinical electroencephalographic studies. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1953,Suppl.#4,Pp. 168-188.
- Kalant,H. Some recent physiological and biochemical investigations on alcohol and alcoholism. <u>Quart</u>. J. <u>Stud</u>. <u>Alc</u>., 1962,23,52-93.
- Keskiner,A. and Lloyd-Smith,D.L. Effects of intravenous chlordiazepoxide on the electroencephalogram with some clinical observations. J. Ner. Ment. Dis., 1962,<u>134</u>,218-227.
- Kety,S.S. and Schmidt,C.F. The nitrous oxide method for the quantitative determination of cerebral blood flow in man; theory, procedure and normal values. J. Clin. Invest., 1948,27, 476-483.
- Kinard, F.W. and Hay, M.G. Effect of ethanol administration on brain and liver enzyme activity. <u>Amer.J. Physiol.</u>, 1960,<u>198</u>,189-196.
- Kleiner, I.S. <u>Human Biochemistry</u>, St. Louis: C.V. Mosby, Co., 1948, Pp. 359-387.
- Knott, J.R. and Gibbs, F.A. A fourier analysis of the eeg from one to eighteen years. <u>Psychol</u>. <u>Bull.</u>, 1939, 36, 512-513.
- Koch,A. and Woodbury,D.M. Effects of carbonic anhydrase inhibition on brain excitability. J. Pharm. Exp. Ther.,1958,122,335-342.
- Kooi,K.A. and Bagchi,B.K. Visual evoked responses in man: normative data. <u>Ann. N.Y. Acad. Sci.</u>, 1964,<u>112</u>, (Art. 1),254-269.
- Kreitman, N. and Shaw, J.C. Experimental enhancement of alpha activity. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1965, <u>18</u>,147-155.
- Kristofferson,A.B. Attention in time discrimination and reaction time. 1965. NASA Contract Report, NASA/ CR - 194.
- Kristofferson, A.B. A time constant involved in attention and neural information processing, 1965. NASA Contract Report. NAS - 2486.
- Kristofferson, A.B. A quantal interpretation of sensory channel uncertainty and reaction time and the psychological time quantum and the discrimination of sucession. 1966, NASA Contract Report. NAS2-2486.
- Kristofferson, A.B. Attention and psychophysical time. Acta Psychologica, 1967,27,93-100.
- Kristofferson,A.B. Sucessiveness discrimination as a twostate, quantal process. McMaster University, Psychology Department. Technical Report.No.7. July 14,1967.
- Kuffler,S.W. and Nicholls,J.g. How do materials exchange between blood and nerve cells in the brain. Perspect. biol. med., 1965,9,69-76.
- Lansing, R.W. Relation of brain and tremor rhythms to visual reaction time. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1957,9,497-504.
- Lansing, A.W., Schwartz, E. and Lindsley, D.B. Reaction time and electroencephalographic activation under alerted and nonalerted conditions. J. <u>Exp.</u> <u>Psychol</u>., 1959, <u>58</u>,1-7.
- Li,C. and Jasper,H. Microelectrode studies of electrical activity of cerebral cortex in the cat. J. <u>Physiol.</u>, 1953,<u>121</u>,117-140.
- Lindsley, D.B. Brain potentials in children and adults. Science, 1936, 84, 354.
- Lindsley, D.B. Psychological phenomena and the electroencephalogram. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1952, <u>4</u>,443-456.

- Lindsley,D.B. Attention, consciousness, sleep and wakefulness. In Fields,M.J. (Ed), <u>Handbook of Physiology</u>, Sect.I., Vol.III, Washington,D.C.: Amer. Physiol. Soc., 1960, Pp. 1553-1594.
- Lindsley, D.B. and Henry, C.E. The effect of drugs on behavior and the electroencephalogram of children with behavior disorders. <u>Psychosom. Med.</u>, 1942, 4, 140-149.
- Lolli,G., Nencini,R. and Misits,R. Effects of two alcoholic beverages on the eeg and electromyographic tracings of healthy men. Quart. J. Stud. Alc., 1964,25,451-458.
- Loomis, A., Harvey, E.N. and Hobart, G. Electrical potentials of the human brain. J. Exp. Psychol., 1936,19,239-249.
- Mardones, J. The alcohols , In Root, W.S. and Hofman, F.G. (Eds), <u>Physiological Pharmacology</u>, New York: Academic Press, 1963, Pp.100-183.
- McIlwain,H. <u>Biochemistry and the Central Nervous System</u>, London: 3rd. Ed., J & A Churchil,Ltd.,1966.
- Meister,R.K. A hypothesis concerning the function of the occipital alpha rhythm in vision with special reference to the perception of movement. Unpublished doctoral dissertation, University of Chicago,1951.
- Merlis, S. Diamox: a carbonic anhydrase inhibitor. Its use in epilepsy. Neurol., 1954,4,863-868.
- Meyer,K.H. Experimentelle untersuchungen uber das verhaltnis des blutalkohols zum alkoholgeholt des gehirn. Doctoral dissertation, University of Bonn.1957. Abstract in <u>Quart</u>. J. <u>Stud</u>. <u>Alc</u>., 1959,20,785.
- McR<sub>e</sub>ynolds, P. Thinking conceptualized in terms of interacting moments. <u>Psychol. Rev.</u>, 1953,<u>60</u>,319-330.
- Monnier, M. Retinal, cortical and motor responses to photic stimulation in man. J. <u>Neurophysiol</u>., 1952,<u>15</u>, 469-486.
- Morrell,L.K. EEG frequency and reaction time a sequential analysis. <u>Neuropsychologica</u>, 1966,<u>4</u>,41-48.
- Mountcastle, V.B., Davis, P.W. and Berman, A.L. Response properties of neurons of cats' somatic sensory cortex to peripheral stimuli. <u>J.</u>, <u>Neurophysiol</u>., 1957, 20, 374-407.
- Morrice,J.K.W. Slow wave production in the eeg, with reference to hyperpnoea, carbon dioxide and automomic balance. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1956,<u>8</u>,49-72.

- Mudge,G.H. Diuretic and other agents employed in the mobilization of edema fluid, In Goodman,L.S. and Gilman, J. (Eds), 3rd Ed. <u>Pharmacological Basis of</u> <u>Therapeutics</u>. New Yord: Macmillan, 1965,Pp.838-842.
- Muller,E. and Rutenfranz,J. Das EEG als test der cerebralen funktionsstrorung nach alkohol. <u>Dtsch. Z. ges.</u> <u>gerrichtl. Med.</u>, 1960,50, 54-61.
- Newman, H.W. The effects of alcohol on the eeg . <u>Stanf.</u> <u>Med. Bull.</u>, 1959,17,55-60.
- Obrist, W.D. The electroencephalogram of normal aged adults. Electroenceph. clin. Neurophysiol., 1954,6,235-244.
- Obrist,W.D. The electroencephalogram of healthy aged males. In Birren,J.E., et.al.,(Eds), <u>Human Aging</u>. Bethesda, M.D.: U.S. Dept. of Health, NIMH. 1963,Pp.79-93.
- Obrist,W.D. Electroencephalographic approach to age changes in reaction speed. In Welford,A.T. and Birren,J.E. (Eds), <u>Behavior</u>, <u>Aging</u> and <u>the Nervous System</u>, Springfield, Ill.: Thomas. 1965,Pp. 259-271.
- Okuma, T. Nakamura, K., Hayashi, A. and Fujimori, M. Psychophysiological study of the depth of sleep in normal human subjects. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1966, <u>21</u>, 140-147.
- Oswald, I. <u>Sleeping and Waking</u>. New York: Elsevier Pub. Co., 1962.
- Perez-Borja,C., Chatrian,G.E. Tyce,F.A. and Rivers,M.H. EEG patterns of the occipital lobe in man. a topographic study based on use of implanted electrodes. Electroenceph. clin. Neurophysiol., 1962,14,171-182.
- Pinsky, C. ( personal communication), 1966.
- Pitts,W. and McCulloch,W.S. How we know universals: the perception of auditory and visual forms. Bull. Math. Biophys., 1947,9,127-147.
- Pond,D.A. The development of normal rhythms. In Hill,J.D.N. and Parr,G. (Eds), <u>Electroencephalography</u>, 2nd.Ed., London: Macdonald and Co., 1963,Pp.193 -205.
- Pupura, D.P. Nature of electrocortical potentials and synaptic organization in cerebral and cerebellar cortex. Int. Rev. Neurobiol., 1959,1,47-163.
- Rahn,H.,Otis,A.B.,Hodge,M., Epstein,M.A. Hunter,S.W. and Fenn, W.O. The effects of hypocapnia on performance. <u>J</u>. <u>Aviat</u>. <u>Med</u>., 1946,<u>17</u>,164-172.

- Ralston, B. and Ajmore Marsan, C. Thalamic control of certain normal and abnormal cortical rhythms. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1956, <u>8</u>, 559-582.
- Randall,L.O. Pharmacology of chlordiazepoxide(Librium). Dis. nerv. Syst., 1961,22,7-15.
- Ritchie, J.M. The aliphatic alcohols, In Goodman, L.S. and Gilman, A. <u>The Pharmacological Basis of Therapeutics</u>. New York: <u>Macmillian Co.</u>, 3rd Ed., 1965, Pp.143-153.
- Robertson, A. Cortical neurons. Science Journal, 1966, 2, 32-37.
- Rothballer,A.B. The effect of phenylephrine, methamphetamine, cocaine, and serotonin upon the adrenaline-sensitive component of the reticular activating system. <u>Electroenceph. clin. Neurophysiol.</u>, 1957,9,409-417.
- Schallek,W. and Kuehn,A. Effects of psychotrophic drugs on the limbic system of the cat. <u>Proc. Soc. Exp. Biol.</u> <u>Med.</u>, 1960, <u>105</u>, 115-117.
- Schmidt,M.W. and Kristofferson,A.B. Discrimination of successiveness: a test of a modal of attention. Science, 1963,139, 3550,112-113.
- Schwartz, M. and Shagass, C. Recovery functions of human somatosensory and visual evoked responses. <u>Ann.</u> <u>N.Y. Acad. Sc.</u>, 1964,<u>112</u>,(Art. 1 ), 510-525.
- Serota,H. and Gerard,R.W. Localized thermal changes in the cat's brain. J. <u>Neurophysiol</u>., 1938,1,115-124.
- Sherrington, C.S. Man and His Nature. London: Cambridge. 1947.
- Sholl,D.A. Dendritic organization in the neurons of the visual and motor cortices of the cat. <u>J. Anat. Lond.</u>, 1953, <u>87</u>,387-406.
- Sholl,D.A. The organization of the visual cortex in the cat. J. Anat. Lond., 1955,89,33-46.
- Sloan,N. and Jasper,H. The identity of spreading depression and suppression. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1950,<u>2</u>,59-78.
- Smith, G.K. and Langsam, H. (personal communication) 1967.
- Sokoloff,L. Metabolism of the central nervous system in vivo. In Fields,M.J.(Ed), <u>Handbook of Physiology</u>, Vol.III. Washington,D.C. : Amer. Physiol. Soc.,1960,Pp.1848-1964.
- Stamm, J.S. On the relationship between reaction time to lights and latency of blocking of the alpha rhythm. <u>Electroenceph</u>. <u>clin. Neurophysiol.</u>, 1952,4,61-68.

Starzl, T.E. and Whitlock, D.G. Diffuse thalamic projection system in the monkey. <u>J.</u> Neurophysiol., 1952,15,449-468.

- Sternbach,L.H.,Randall,L.O. and Gustafon,S.R. 1,4-Benzodiazeoines (chlordiazepoxide and related compounds). In Gordon,R. (Ed.), <u>Psychopharmacological Agents</u>,Vol.I. New York: Academic Press. 1964. Pp.137-224.
- Stroud, J.M. Psychological moment in perception. In Forester, H.V.(Ed), <u>Conference on Cybernetics</u>. New York: Josiah Macy, Jr., Foundation, 1949. Pp. 27-63.
- Surwillo, W.W. Frequency of the alpha rhythm: reaction time and age. <u>Nature</u>, 1961,<u>191</u>,823-824.
- Surwillo,W.W. The relation of simple response time to brain wave frequency and the effects of age. <u>Electroenceph</u>. <u>clin. Neurophysiol.</u>, 1963,15,105-114.
- Turing,A.M. Can a machine think ? In Newman,J.R. (Ed), <u>The</u> <u>World of Mathematics</u>,Vol. 4. New York: Simon and Schuster,Inc.,1956.Pp.2099-2123.
- Toman, J.E.P. and Davis, J.P. The effects of drugs on the electrical activity of the brain. <u>Pharmacol. Rev.</u>, 1949, <u>1</u>, 425-492.
- Vernon,J., McGill,T.E.,Gulich,W.L. and Candland,D.K. The effects of human isolation upon some perceptual and motor skills. In Solomom,P. (Ed), <u>Sensory Deprivation</u>. Cambridge: Harvard Univ. Press, 1961. Pp.41-57.
- Verzeano, M., Lindsley, D.B. and Magoun, H.W. Nature of the recruiting response. J. <u>Neurophysiol</u>., 1953,<u>16</u>, 183-196.
- Walsh,E.G. Visual reaction time and the alpha rhythm, an investigation of a scanning hypothesis. <u>J. Physiol</u>., 1952,<u>118</u>,500-508.
- Walter,W.G. The twenty-fourth Maudsley lecture: the function of electrical rhythms in the brain. <u>J. Ment. Sc.</u>, 1950,<u>96</u>,1-31.

Walter, W.G. The Living Brain. New York: Norton, 1953.

- Walter,W.G. Intrinsic rhythms of the brain. In Magoun,H.W. (Ed),<u>Handbook of Physiology</u>,Vol.I. Washington,D.C.: Amer. Physiol. Soc.,1959. Pp.279-298.
- Wells,C.E. Alpha wave responsiveness to light in man. In Glaser,G.H. (Ed), <u>EEG and Behavior</u>. New York: Basic Books. 1963.Pp.27-59.

- Werre, P.F. and Smith, C.J. Variability of reaction evoked by flashes in man. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1964,<u>17</u>,644-652.
- White, C.T. Temporal numerosity and the psychological united duration. <u>Psychol. Monogr.</u>, 1963,<u>77</u>, Whole No. 575.
- Wiener, N. Cybernetics. New York: Wiley.1948. Pp.165-166.
- Williams, A.C. Facilitation of alpha rhythm of the eeg. J. <u>Exp</u>. <u>Psychol</u>., 1940, <u>26</u>, 413-422.
- Williams,H.L., Granada, A.M., Jones, R.C. Lubin, A.L. and Armington, J.C. EEG frequency and finger pulse volume as predictors of reaction time during sleep loss. <u>Electroenceph</u>. clin. <u>Neurophysiol</u>., 1962,14,64-70.
- Wollman, H. and Dripps, R.D. The therapeutic gases. In Goodman, L.S. and Gilman, A. (Eds), <u>Pharmacological</u> <u>Basis of Therapeutics</u>. 3rd. Ed., New York: Macmillian Co., 1965, Pp. 906-910.
- Woodbury,D.M. and Esplin,D.W. Neuropharmacology and neurochemistry of anticonvulsant drugs. In Braceland,F.S. (Ed), <u>The Effect of Pharmacological</u> <u>Agents on the Nervous System</u>, Vol.37. 1957,Pp.24-56.
- Woodbury, D.M. and Kraler, R. The role of carbon dioxide on the nervous system. <u>Anesthesiology</u>, 1960,<u>21</u>,686-703.
- Woodbury, D.M., Rollins, L.T., Gardner, M.D., Hirschi, W.L. Hogan, J.R., Rallison, M.L., Tenner, G.S. and Brodi, D.A. Effects of carbon dioxide on brain excItability and electrolytes. <u>Amer. J. Physiol.</u>, 1958, <u>192</u>(1), 79-90.
- Wundt,K.(1893) quoted by Sutton,S. and Zubin,J. Effects of sequence on reaction time in schizophrenia. In Welford, A.T.(Ed), <u>Behavior,Aging and the Nervous</u> <u>System</u>. Springfield,Ill: Thomas,1965,P.563.
- Yoshii, N., Pruvot, P. and Gastaut, H. Electrographic activity of mesencephalic reticular formation during conditioning in the cat. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1957,9,595-608.
- Ziegler, G.K. and Presthus, J. Normal eeg at deep levels of hypoglycemia. <u>Electroenceph</u>. <u>clin</u>. <u>Neurophysiol</u>., 1957,9,523-526.
- Zubeck, J.P. Behavioral and eeg changes after 14 days of perceptual isolation. <u>Psychonom. Sci.</u>, 1964,<u>1</u>,57-58.
- Zubeck, J.P. and Welch, G. Electroencephalographic changes after prolonged sensory and perceptual deprivation. <u>Science</u>, 1963,<u>139</u>,1209-1210.