THE EFFECTS OF DRUGS UPON THE ELECTRICAL ACTIVITY OF THE BRAIN*

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I. INTRODUCTION

It is now twenty years since Hans Berger (20) presented to the world a revolutionary new method for the investigation of the function of the brain in health and disease, namely, *electroencephalography*. His contribution was threefold. To the clinician he gave a diagnostic instrument with sharp differential and localizing value, without which the notable advances of the last two decades in the pharmacological and surgical treatment of central nervous disorders would have been sorely handicapped. To the neurophysiologist he gave a research tool of great precision and relative simplicity for the unraveling of the central nervous pathways by the monitoring of their electrical signs. Lastly, to all those who strive to understand the mode of operation of the organ of thought, he gave a new point of departure. The brain could no longer be considered a passive switchboard through which impulses coursed on their way to and from the periphery; it was now revealed as a dynamic participant in the affairs of the body, possessing an inherent spontaneous and rhythmic activity which could modify the soma and be modified in turn by the soma.

Berger did not neglect to investigate the effects of drugs upon the electrical activity of the brain (21). He looked for electroencephalographic signs of the central nervous actions of barbital, morphine, cocaine, amyl nitrite, scopolamine, chloroform and other substances then in common clinical use. Thus he opened a field of research which has many potentialities not only for the determination of the mechanism of action of centrally acting drugs, but also for the analysis of the nature of the electroencephalogram itself, for the reason that substances with known specific action are among the most precise tools available for investigations in the biological sciences.

Unfortunately, the rapidly increasing volume of literature in the field of electroencephalography contains relatively few systematic studies of the effects of drugs on the electrical activity of the brain, although there are many empirical reports on the alterations produced by particular chemical agents. Among previous reviews relevant to this subject should be mentioned those of Hayslip (176), Gibbs and Gibbs (135), Finesinger and Brazier (108), Gibbs (130, 131, 132), Lennox and Lennox (217), and Walter and Walter (331).

The present review will consider primarily the effects of drugs upon the normal human EEG. This will necessarily exclude from discussion most of the large

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body of clinical reports containing casual observations of drug alterations of the EEG in convulsive disorders, cerebral trauma, etc. Experimental studies in animals will be included to the extent that they contribute to an understanding of drug actions or of the neurophysiological basis of the recorded electrical activity of the brain. Only the more relevant work dealing with topical application of drugs to the brain will be evaluated. Finally, priority will be given to a few selected agents which are either of heuristic value or commonly used in the treatment of disease. In atonement for this cavalier treatment of a large section of the electroencephalographic literature, the reviewers hope to emerge with a few examples of the usefulness and limitations of the EEG as an aid to the understanding of the mechanism of action of drugs upon the central nervous system, and also of drugs as analytical tools for investigating the nature of the EEG.

II. ON THE GENESIS OF THE ELECTROENCEPHALOGRAM

Any rational discussion of the mechanism of action of drugs upon the EEG presupposes some knowledge of the nature of the electrical discharges recorded from the brain. Unfortunately this body of information is still in the most primeval state, and consequently the most divergent extremes of interpretation persist in the literature (cf. 331). Thus the EEG is viewed by some investigators as the synchronized summation of large numbers of action potential spikes (2); by others, as slow fluctuations in the somatic membrane potential of cortical neurones (43, 127). Some view the rhythmic activity as an inherent property of the individual neurones (142), while others emphasize the importance of cyclic reverberations in closed neuronal chains (26). Some regard the grossly recorded EEG as a mixture of sinusoidal oscillations (62); others, as a composite of discrete non-sinusoidal pulses (2). Functionally, the dominant resting cortical rhythms have been viewed as merely fortuitous synchronizations of groups of cortical neurones (2); as a mechanism of alternating excitation and inhibition, which tends to regulate the overall excitability of the cortex (42); as a spatial scanning device for the comparison of new and stored information (245, 276); or as an escapement system limiting cortical output to fixed time intervals (71, 72). If the reviewers seem somewhat partisan in their attitude toward these various controversies, it is only to maintain a reasonable working hypothesis against which the observed actions of drugs may be projected.

First, with regard to the wave composition of the EEG, although much of the clinical literature implies a mixture of sinusoidal oscillations (cf. 135) and attempts have been made to synthesize even the abnormal paroxysmal discharges from a summation of pure frequency components (62), this conception may be somewhat misleading. By analogy, the gross electromyogram of a muscle which contains many discharging motor units may give the appearance of a mixture of pure frequencies, but finer analysis reveals the existence of discrete and characteristic action potential spikes. Unfortunately, the recording of spontaneous single unit discharges in the brain is technically most difficult. Renshaw *et al.* (279) have recorded such unit action potentials from the olfactory cortex, Moruzzi *et al.* (259) from Purkinje cells of the cerebellum, and Adrian and

Moruzzi (3) indirectly from pyramidal cells of the motor cortex. In general these studies show discrete spikes rather than an underlying sinusoidal rhythm.

Even with gross recording of the electrical activity of the brain, one cannot but be impressed with the amount of fine detail submerged in the overt sinusoidal rhythm. For example, the so-called "Dial" potentials (60, 88), recorded from rostral areas of animals under light barbiturate anesthesia and resembling "sleep spindles" (75) in man, are complex in form even when recorded with scalp electrodes; when led off from pial electrodes, they may be observed as discrete repetitive diphasic or polyphasic responses, in which the several components may be independently modified by drug action (317).

A useful method for analysis of the EEG is the evocation of synchronized discharges from brain by stimulation of sensory nerves and organs or of central tracts. The best such studies in anesthetized experimental animals reveal early spike components which may be attributed to arriving tract impulses, monosynaptic transmission, and the activation of subsequent banks of synapses (69, 264). They may also be seen in the electrocorticogram of unanesthetized animals (244, 346). Even the firing of a single bank of cells gives a complex response because of the different time characteristics of dendrites, somata and axones (239, 264). The initial sequence of spike-like events may be followed by one or more waves having in general the time course and spatial distribution of the characteristic "spontaneous" waves arising in the same locus at rest. They appear to originate from the entire thickness of the cortex (3, 264). In appearance they approximate the spontaneous EEG at all levels of central responsiveness from deep anesthesia to the subconvulsive state, but the evoked records preserve a discreteness and reproducibility which is not as evident in the spontaneous activity, probably because of the greater dispersion of the latter (315).

From the above considerations it is evident that the "spontaneous" electroencephalogram of a brain receiving impulses from sensory or other sources must in part represent the summation of many unit discharges, varying in their time course from spikes of the order of a millisecond to slow waves of 100 milliseconds or more. If these were completely random in occurrence, no observable rhythms would be grossly recorded in the EEG. If they were completely synchronized in homogeneous brain areas, much of the fine detail seen in the evoked discharges could be observed with a suitably rapid recording system. The true state of affairs would appear to lie intermediate between the extreme states of dispersion and synchrony. In this intermediate state it is evident that partial dispersion will attentuate the fast more than the slow components in the gross EEG record.

Secondly, as to the possibility of an inherent rhythmicity of cerebral cells, the respiratory "center" was at one time exploited as an analog of inherently spontaneous cerebral rhythms (135). More recently, the work of Pitts, Magoun and Ranson (275) has revealed the role of bulbar and peripheral inhibitory feedback circuits in the maintenance of the respiratory cycle, and concurrently the role of reverberating circuits in maintaining cortical rhythms has been emphasized. To complete the cycle, current evidence now indicates the possibility that with a

suitable chemical drive the isolated inspiratory center may act as a relaxation oscillator (195). In peripheral nerve, spontaneous rhythms having a slower time course than action potential spikes are well known (8, 47, 238). The cerebral cortex deprived of all afferent connections (40) or so treated by drugs as to render synaptic transmission presumably impossible (230) may continue to show rhythmic activity. Thus it is not impossible that non-propagated fluctuations in neuronal membrane potential may contribute to the EEG. This in no way diminishes the significance of reverberating circuits such as those which have been postulated for cortico-thalamic (26) and cortico-hypothalamic (263) interaction. Since oscillations in membrane potential tend to be associated with cyclic changes in excitability of neurones, giving rise to propagated spikes when the fluctuations are sufficiently great (47), and since the local oscillations themselves can be intensified and synchronized by arriving propagated impulses (238), it is conceivable that both the local periodicity and the total time delay of a reverberating pathway may enter into the determination of the frequency of a recorded rhythm in an active and transmitting brain.

Finally, as to the functional significance of the EEG, certain generalizations must be borne in mind, particularly in evaluating drug action. Although the dominant alpha rhythm is commonly considered an indicator of the resting wakeful state, it is obvious that many subjects at rest and almost all with eyes open show only a highly desynchronized and irregular low-voltage fast activity, which is also typical of most unanesthetized animals in the waking state. Furthermore, it is common clinical experience that consciousness and other attributes of the functionally normal brain may persist in patients with bizarre diffuse dysrhythmias, either of pathological origin or pharmacologically induced. However, there are extreme EEG states in which higher function is grossly impaired, such as the hypersynchronized hyperdischarge of the tonic-clonic and the petit mal seizure, the hypersynchrony of moderate barbiturate anesthesia, or the complete inactivity characterizing very deep anesthesia or post-seizure depression. Thus the ability of the brain to receive, store and transmit information is not incompatible with a wide range of EEG patterns, except at the extremes of gross diffuse hypersynchronization, hyperactivity or complete inactivity.

III. SOME HYPOTHETICAL MECHANISMS OF ACTION OF DRUGS UPON THE EEG

Having disposed of these preliminary non-pharmacological considerations of the complex origin of the EEG, one can now appropriately inquire into the known mechanisms by which drugs may alter the properties of the grossly recorded electrical activity of the brain. The effects of drugs upon the properties of neurones will be the subject of a subsequent review (318), and only brief mention of some of the possible alterations will be attempted here.

Among the passive properties of nerve cells, which can be measured without the elicitation of a test response, should be included the membrane resistance, capacity, inductance and voltage. The capacity and inductance are not known to be easily modified by drug action; in the presence of a suitably low damping membrane resistance, they may determine the frequency of cyclic oscillations in

the membrane potential (47). Together with the membrane and longitudinal resistances they enter into the determination of the spatial and temporal characteristics of excitation and response (238). Membrane resistance is known to be reduced by potassium ion (193), and perhaps may be increased in central neurones by the barbiturates (93). Membrane voltage must be maintained above a critical level to provide a resting, excitable cell. Since the voltage is dependent upon metabolic work, it is subject to alteration by a wide variety of metabolic agents as well as by respiratory gas tensions and the electrolyte pattern of the extracellular fluid; its separable components, which enter into the excitation and response characteristics of nerve cells, may be independently modified by drug action (238).

Among the active properties of neurones are those concerned with excitation: the threshold, or critical potential to which membrane potential must be reduced in order to initiate a propagated discharge; the temporal and spatial requirements for excitation; and the rate and extent of accommodation, or the change in threshold with applied stress. Relatively little is known about drug effects on these properties, with the exception of threshold, which by gross methods is generally but not always found to be elevated by depressants and reduced by excitants. Changes in cerebral cortical threshold are not necessarily reflected in EEG alterations; for example, in experimental animals the threshold may be considerably raised by benzimidazole with no change in EEG (154), and wide spontaneous fluctuations in cortical threshold may be seen without corresponding EEG manifestations, all of which would seem to indicate that the stability and frequency of cortical rhythms are insured by regulating mechanisms which correct for threshold alterations within wide limits.

A second set of neuronal properties are those relevant to the response; these include the form, duration and amplitude of the action potentials and the velocity with which they are propagated, as well as the tendency toward spontaneous discharges and the occurrence of high frequency trains of spikes instead of isolated unit discharges. Again little is known of these aspects of responsiveness in cerebral neurones, except insofar as high frequency discharges appear to be associated with convulsive responses, may be elicited by various convulsant drugs, and are reflected in the gross EEG as high voltage spikes (3, 258).

Finally, there are those phenomena associated with recovery following antecedent stimulation; these include the absolute and relative refractory periods and the supernormal and subnormal phases of recovery of excitability, as well as oscillatory phenomena in the recovery cycle. It might be expected that in an active region of brain any prolongation of the recovery cycle would have profound effects on the EEG, particularly in the direction of slowing spontaneous rhythms; indeed, this seems to be the case at least with the barbiturates (198, 243). Also there must be included the long periods of facilitation seen after excessive stimulation of peripheral nerve, which may be abolished by anticonvulsant drugs and which have been assumed to play a role centrally in the development and spread of seizures (317).

In addition to those properties which characterize neurones in isolation, there

are those qualitatively new properties which result from the organization of central neurones into complex nerve nets and which give to brain functional potentialities far beyond those of the individual neurones of which it is composed. From the standpoint of the EEG, these networks provide for synchronization and rhythmicity of activity, but their physiological significance is hardly revealed by a study of the EEG. They may multiply tremendously the impulses derived from a few afferent fibers or from spontaneously firing cells, or they may channel or terminate such activity by inhibition, thereby subserving the more elementary reflex functions of brain. By suitable arrangements of re-entrant circuits they may form a self-regulating system of variable output, capable of receiving, storing and transmitting patterns of information (245). Two reflections of the organized activity of these networks are probably commonly observed in the EEG. One concerns local field effects originating in the interaction of adjacent neurones and resulting in inhibition or excitation, depending upon the polarity of the potential gradient and the rate and extent of accommodation of the responding neurones. This type of activity may be involved in the slowly spreading electrical waves which propagate through the cortical feltwork with velocity far less than that for ordinary conduction (1, 212, 255). The other concerns reverberating circuits between cortex and subcortical centers such as thalamus (26) and hypothalamus (263), which presumably contribute heavily to the stability of at least some cortical rhythms as judged by the profound disorganization of the EEG after injury to the subcortical centers. Certain theoretical properties of these circuits deserve attention. Their characteristic period may be far greater than the total conduction time around the circuit, since part of the cycle may be consumed in the building up of facilitatory activity in local internuncial pools within each center, or in the progressive inhibition of activity within these pools. Therefore drug effects upon the frequency of the observed EEG cycle might arise from any combination of actions upon the various parameters of excitation, response and recovery. That the effects of drugs upon the frequency of EEG rhythms are usually seen as sharp, qualitative transitions in period, rather as a progressive modification over a wide range, would seem to indicate the establishment of new resonant circuits when sufficient quantitative alteration in the old circuit has made resonance inefficient or impossible.

To what extent may changes in the EEG be attributed to alterations in those properties of neurones and networks already described? Of the measurable aspects of the EEG, changes in frequency are commonly reported in connection with drug action. These may reflect bona fide changes in the underlying cycles of reverberating circuits or local oscillatory behavior, as previously discussed for drugs changing the recovery phase, or they may be the spurious result of changes in degree of synchronization, with apparent fast activity resulting from the fragmentation of established rhythms on the one hand, or slow activity from the grouping of cycle fragments on the other. The voltage of the recorded discharges is likewise dependent upon the degree of synchronization, and therefore does not indicate the actual amount of neuronal activity except within the

wide limits of convulsive bursts on the one hand or deepest anesthesia on the other. The degree of synchronization also contributes to the sharpness and complexity of wave-form, to the regularity of dominant rhythms and their stability toward sensory stimulation, etc. As to what might determine the degree of synchronization, it can only be said that there are two extreme situations resulting in synchrony. One would be any depressant effect making reverberation impossible in any but the longest available circuits. The other would be any excitant effect, such as a decrease in threshold, leading to the easy interlocking of existent circuits. The EEG alone does not offer any simple choice between these alternatives.

Another category of drug action upon the EEG includes the modification or abolition of abnormal activity, in particular the paroxysmal dysrhythmias associated with convulsive disorders. The possible mechanisms of anticonvulsant action have been reviewed elsewhere (316, 321) and will be discussed later under anticonvulsants.

If one were to attempt to compile a list of those substances whose actions upon the EEG are well described in the literature and whose mechanism of action upon neurones has also been well defined, the list would be short indeed. Furthermore, the correlation between drug effects upon properties of neurones and upon EEG manifestations would not be very impressive. For example, ether acts as a depolarizing agent upon nerve (238, 347) whereas CO_2 increases membrane potential (238); yet an increase in frequency of cortical waves is the EEG manifestation usually described for both ether (136) and CO_2 (126, 142, 215, 244). Some drugs which increase neuronal thresholds without depolarizing, such as the local anesthetics and DFP (17, 25, 323), may produce convulsive manifestations in the EEG (56, 57, 148); other non-depolarizing threshold-raisers such as benzimidazole (147, 317) may have relatively little effect upon the EEG even when cortical thresholds are demonstrably raised. Inconsistencies such as these illustrate the difficulties encountered in transferring our knowledge of basic neuropharmacology to an interpretation of the EEG.

In turning now to the main body of this review, namely, the description of the effects of specific substances upon the EEG, the reader should be forewarned that only in a few cases will it be possible to define a mechanism of action with any degree of satisfaction to either the pharmacologist or the neurophysiologist.

IV. PHARMACOLOGICAL AGENTS ACTING UPON THE EEG

A. Substances used primarily for their central nervous effects

1. Predominantly depressant drugs. a. Barbiturates: Because of the widespread use of barbiturates for sedation, anesthesia, and in the therapy of convulsive disorders, the EEG effects of this drug group have been studied more widely than others. Earlier reports emphasized the similarity between records obtained under barbiturate sedation and those of natural sleep (21, 136, 224). More recently there has been increasing emphasis on the initial appearance of fast activity preceding the loss of consciousness (33, 34, 64).

The intravenous administration of phenobarbital in human subjects has been

reported to produce either an increase in amplitude of cortical activity (224), or an initial decrease in amplitude followed by an increase as the effect progresses or when larger doses are used (141); these changes are followed in turn by a gradual slowing of the record and the appearance of normal sleep patterns. M. Lennox (216) studied the effects of relatively small doses of phenobarbital, pentobarbital, amytal and seconal in normal human subjects. Pentobarbital and seconal, in particular, produced fast activity ranging between 20 and 30 per second and most pronounced in the frontal and parietal leads. However, some subjects showed no change and some presented slow rather than fast activity. Similar variability was noted in a group of psychiatric patients receiving barbiturate medication. The observed EEG changes were not attributable to drowsiness, were more characteristic of the patient than of the drug used, and were also influenced by the dosage and the time interval before recording.

Analyses of the cortical frequency spectrum have been made by Gibbs and Maltby (141) and by Brazier (33) in an attempt to make a more quantitative evaluation of the EEG effects of barbiturates and other agents than that provided by the original EEG tracing. Gibbs and Maltby found pentothal the most effective of various barbiturates in producing slow changes, and correlated this with the greater depressant potency of the drug. Brazier routinely found the appearance of fast activity as the first manifestation of intravenously administered pentothal, and noted that during this stage there was some degree of mental clouding or euphoria. The first appearance of slow activity coincided dramatically with loss of consciousness, and fast activity disappeared at the same time. Brazier found that activity in the alpha frequency range persisted even during unconsciousness, but that it no longer could be blocked by sensory stimulation. In speculating upon the transition from the initial fast to the final slow type of record, Brazier invokes several possible alternative explanations: an initial state of acceleration by the appearance of acid metabolites, followed by the overwhelming effect of the slowing of the principal chemical reactions as a result of the accumulation of metabolites; an early depression of cortical function followed by a sharp transition to subcortical dominance; an early shift from an excitatory to an inhibitory function of the small Golgi cells (49), further transformed by the deprivation of incoming sensory impulses to the cortex. From a comparison of the effects of pentothal with those of anoxia and hypoglycemia, which produce only a progressive slowing of the EEG, Brazier concludes that the data "are consistent with a postulate that the alpha rhythm results from repetitive action of cells in neurone chains, that the rate can be modified within certain limits by metabolic changes in cortical cells, that it can be disrupted by any agent which inactivates a link in the chain, and that it is thrown out of synchrony by the arrival of action potentials originating as sensory impulses."

Regardless of the mechanism assumed, it is apparent from the foregoing studies that doses of barbiturates which are insufficient to produce sleep may produce changes in the EEG which are usually but not always in the direction of fast activity. M. Lennox (216) points out the importance of these findings in avoiding misinterpretation of the EEG of patients who are receiving barbiturate medication.

The technical difficulties encountered in attempting to obtain artifact-free recordings from infants and children have caused some electroencephalographers to use barbiturates in doses sufficient to produce sleep. Barnes *et al.* (10, 11) describe 15 per second fast activity and 2 to 4 per second slow waves as typical normal EEG findings in year-old infants under light pentothal anesthesia. The reviewers (319) studied the effects of various barbiturates in a group of normal infants and children in comparison with a series of cases of convulsive disorders. In general, the sleep records were like those of normal non-sedated individuals in sleep and were dominated by slow activity of high voltage of various frequencies up to the alpha range, and variable amounts of fast activity as well. Wide variations in frequency, amplitude and regularity of the slow activity were noted. Precentral spindles of the 14 per second type were sometimes bilaterally synchronous and sometimes not, and could be evoked by sensory stimulation when they were absent from the spontaneous record at a deeper stage of sleep. There were no notable differences between the barbiturates used. The variations in EEG pattern of barbiturate-induced sleep were sufficiently wide so that the reviewers feel that such sleep records should not be considered abnormal unless they exhibit one or more of the following signs: gross asymmetry of slow activity; unilateral or bilateral absence of spindles; clearly localizable focal paroxysmal discharges; well-defined spikes, sharp waves, spike and wave patterns, or other forms normally absent from either the sleeping or waking record. Abnormal discharges should be distinguished from the high voltage K-complexes normally seen during sensory stimulation or spontaneous movement. Pentothal sleep has been found useful in the localization of convulsive dysrhythmias (116).

The EEG effects of barbiturates have also received sporadic interest in connection with their effects upon slow abnormalities frequently noted in children with behavior disorders. Cutts and Jasper (70) noted that the most striking effect of phenobarbital in such children was an increase in the amplitude of the beta activity (24–32/second), which was most marked in central and frontal bipolar recording. The effect of phenobarbital on the slower activity was to increase the amplitude and amount of 6 per second activity while decreasing that of the slower random 2 to 4 per second waves. These changes bore no correlation with the alterations in behavior in this group of children, who usually showed exacerbation of symptoms during barbiturate therapy. The addition of amphetamine to the phenobarbital medication failed to alter the EEG in these cases, although it produced clinical improvement. Lindsley and Henry (231) also found no correlation between the exacerbation of behavior disorders in children treated with phenobarbital and the alterations produced in the EEG. They report an increased amplitude of alpha rhythm in frontal leads, increased stability of precentral alpha, decreased precentral 5–8 per second slow activity with a concomitant increase occipitally and frontally.

In patients habituated to barbiturates, convulsions are sometimes noted in the several days following the withdrawal of the drug, even when the patient has no previous history of convulsive disorder. One report of such a case (51) showed hyperventilation-induced slow activity in frontal leads during the post-

withdrawal interseizure period. These were no longer evocable when more gradual withdrawal was carried out.

In summary, the clinical literature on the EEG effects of barbiturate medication shows a general but not invariable appearance of fast activity or increase of beta activity after small doses which produce minimal psychic effects, whereas larger doses sufficient to produce sleep alter the record in the direction of dominant slow rhythms with the appearance of spindles and other features of the EEG in natural sleep.

For the effects of still higher concentrations of barbiturates on the EEG, one must turn to observations on laboratory animals. Although most of the literature concerning the effects of barbiturates on the electrical activity of the brains of animals deals with pentobarbital as the test agent and the cat as the test animal, the results in general have been confirmed for other barbiturates and other species, and differ only in a few respects from the more limited range of observations in man.

Clark and Ward (60) have described somewhat more fully than earlier investigators the effects of pentobarbital on the EEG of the cat. The waking record in their animals was characterized at rest by low amplitude somewhat irregular activity in the 10–15 per second range. When the animal was alerted by sensory stimulation, an "activation pattern" of irregular low voltage fast activity in the 20–40 per second range was seen, as previously reported by Rheinberger and Jasper (280). With the onset of normal sleep, regular and high amplitude activity of 5–7 per second appeared occipitally, spindle-like formations of 14–16 per second appeared independently and asynchronously in the frontal poles, and finally random slow activity prevailed in all leads. These were essentially the changes seen with the development of light pentobarbital anesthesia. However, in contrast to normal sleep, the typical activation pattern was less easily induced, and consisted of the superposition of fast activity upon the slow rhythms, together with a lessening of the amplitude of the slow activity. At surgical levels of anesthesia the EEG was no longer alterable by painful stimulation. With still deeper anesthesia, quiescent periods appeared in the record, from which emerged bursts of slow monophasic spindles or isolated sharp waves. At still deeper levels the record became completely flat, but even after prolonged inactivity of this type the normal EEG returned when the anesthetic wore off.

Numerous experiments have been devoted to the search for a mechanism of barbiturate action upon the EEG. Bremer (37) found that various barbiturates administered to cats caused a type of cortical activity similar to that of natural sleep. Since the activity in moderate barbiturate anesthesia was similar to that seen also after transection of the brain stem, was not modifiable by sensory stimulation, and showed rhythmic activity of higher voltage than in the waking state, he concluded that barbiturates produced essentially a functional deafferentation of the cortex, permitting it to discharge in a synchronized autonomous manner. He recognized that the barbiturates must have some direct action upon the cortex itself, since there was a decreased sensitivity to the effects of locally applied strychnine.

In further analysis of barbiturate action, Bremer (39) studied responses of the auditory cortex of the cat. Normally these consist of a primary response and an afterdischarge to abrupt stimulation (handclap), and the appearance of higher frequencies at increased amplitude during continuous stimulation (whistle). Barbiturate narcosis, like natural sleep, was characterized by retention of the primary response and loss of the afterdischarge following handclap, and loss of the response to whistle. The results might be interpreted as indicating that barbiturate sedation left the cortex accessible to sensory stimuli, but abolished reverberating discharges and modifiability of cortical activity by continuous stimulation.

Drohocki and Drohocka (90) made simultaneous records from cortex and various subcortical centers in several species of animals under pentobarbital or amytal anesthesia. They were impressed by the qualitative change from low voltage fast activity of the waking state to high voltage slow waves having many new properties unlike those of normal activity. Since these qualitative changes occurred simultaneously in cortex and thalamus, they concluded that there was no specific locus of action of the barbiturates.

Heinbecker and Bartley (178) attempted to define the mechanism of action of pentobarbital by studies at various levels of the nervous system. They found that responses in the sensorimotor cortex of the rabbit evoked by stimulation of the saphenous nerve were depressed even in light pentobarbital anesthesia before notable changes occurred in the spontaneous cortical activity. The late components of the evoked response attributable to stimulation of C fibers of the saphenous nerve were the first to be depressed; this suggests an electrical counterpart of the early obtundation of pain under light anesthesia which leaves other sensory modalities intact. The period of facilitation normally seen after local stimulation of the cortex was delayed and reduced in extent. In the spinal cord of the turtle, reflex motor discharges elicited by stimulation of sensory trunks were regularly diminished in amplitude and duration, with only occasional evidence of a transient initial excitatory effect. Temporal summation and later facilitation were reduced in the excised superior cervical ganglion of the turtle. The small unmyelinated fibers of the vagus in the turtle were the first to be blocked by pentobarbital, while the large myelinated fibers were the most resistant. Spontaneous discharges from the ganglion cells of the limulus heart were slowed by pentobarbital. A variety of effects were noted after the application of pentobarbital to frog sciatic nerve, including reduction in amplitude of spike and negative afterpotential, increased threshold, prolongation of absolute and relative refractory period, slowing of conduction velocity, and a slight decrease in extent of accommodation. Since the concentrations used were inordinately high in all but the cortical observations, there might be some question concerning the relevance of these findings to the action of the barbiturate upon the brain. However, the peripheral nerve data are compatible with the effects observed upon the cortex in that no excitatory effects were seen, thresholds were increased, recovery time delayed, facilitation reduced, and spontaneous rhythms slowed.

A number of investigators have attempted to define the centers and anatomical pathways involved in the elaboration of the several types of electrical activity recorded from the cortex during the course of barbiturate action. The simplest of these types would appear to be the highly localized, brief, monophasic, surface-positive response to sensory stimulation which represents the invasion of the cortex by afferent impulses. This response has been widely used in mapping the representation of body surface and special sense organs upon the cortex. Marshall, Woolsey, and Bard (244), in the course of their topographical studies, noted that pentobarbital did not affect any of the characteristics of this primary response except for its recovery time, which was greatly prolonged. Since the primary response can be observed at any level of anesthesia and in the unanesthetized animal, it undoubtedly contributes to the recorded "spontaneous" activity as long as any sensory impulses are being propagated along the ascending tracts. However, under deep pentobarbital anesthesia a mechanism has been described by Marshall and his collaborators which operates to limit the amount of sensory activity reaching the cortex. Marshall *et al.* (243, 244) observed the effects of pentobarbital on responses evoked by discrete tactile stimulation of the hair of a forefoot of the cat. At the level of the cortex, there was a prolongation of the recovery time (cf. 198) and little other change in the character of the highly localized primary response, a reduction in complexity of various secondary reactions, and the loss of long-lasting facilitation effects. Marshall (243) found that the absolute unresponsive time was prolonged at the thalamic level, rostral to the ventrolateral nucleus pars externa, but not caudally, so that the normally arriving continuous barrage of lemniscus impulses tended to produce only grouped discharges after transmission through the thalamus.

In addition to the primary responses, sensory stimulation may set off several types of more generalized and drug-sensitive secondary discharges (243, 244). One of these has been described in more detail by Forbes and Morison (113) who studied the responses evoked in the cortex of the cat by sciatic nerve stimulation under conditions of relatively deep pentobarbital or dial anesthesia, when spontaneous activity was absent or consisted only of occasional slow bursts. The evoked responses were characterized by brief and relatively local primary responses which continued undiminished with fairly rapid repetitive stimulation, and by more prolonged and generalized secondary discharges resembling the spontaneous bursts, which were characterized by easy fatiguability during rapid stimulation and a refractory period of a second or more. Thus it would appear that the relatively quiescent cortex under deep barbiturate anesthesia is not only still accessible to sensory impulses, but that these may set off generalized secondary discharges of slow wave type; such discharges may also arise spontaneously in the absence of apparent stimulation.

A further analysis of these secondary discharges has been made by Swank *et al.* (310, 311, 312) who investigated the effects of amytal on cortical activity of the dog. In the normal resting state these animals typically showed dominant 25 per second activity, mixed with 12 per second activity which was more prominent posteriorly, and 50 per second activity anteriorly, the latter predominating

in states of enhanced excitement. During the induction stage of amytal narcosis, the faster activity disappeared first, while spindle activity occurred. In deeper narcosis there was a progressive slowing of dominant frequency, with least change in the motor area. In deep surgical anesthesia the record was characterized by alternating slow bursts and periods of inactivity, these periods of suppression occurring first in the occipital cortex. The suppression phenomenon could be partly reversed by administration of oxygen. The synchronized bursts of activity occurring at this level of anesthesia were shown to originate independently in either hemisphere or in the lateral nuclei of either thalamus, and to be rapidly propagated through both hemispheres in a few milliseconds. Propagation between the hemispheres occurred by way of the corpus callosum, and within the hemispheres by way of the internal capsule and lateral portion of the thalamus. The medial nuclei and massa intermedia of the thalamus were not involved, although these may play an important role in cortical synchronization in lighter anesthesia (200). At this deep level of anesthesia fast activity was still recorded independently in the pons and reticular formation of the midbrain. Cortical thresholds for evoked discharges were considerably raised at this stage and were particularly high at the end of each isolated burst, recovering slowly over a period of several seconds. Evoked afterdischarge could not be elicited even under light anesthesia.

Swank *et al.* attempted to explain their findings on the basis that barbiturates first depress the function of the smaller neurones, leaving only activity which can originate and propagate in the largest cells, on the basis of the finding of Heinbecker and Bartley (178) that barbiturates first depressed small fibers in peripheral nerve and cord tracts. However, their results illustrate directly two other important actions of barbiturates, namely, increase in threshold and prolongation of recovery time.

These observations suggest the existence even in deep barbiturate anesthesia of a potential reverberating circuit involving cortex and lateral thalamic nuclei and capable of synchronizing a large mass of brain tissue. That the circuit fires only sporadically in deep anesthesia is easily explained by the slow recovery time. In lighter narcosis this limiting factor disappears, and high voltage slow activity now dominates the EEG.

As an alternative mechanism, the reviewers would like to suggest that the sporadically firing mechanism seen in deep narcosis becomes more highly fractionated as the recovery time is shortened toward normal; this results in the appearance of more asynchronous and superficially faster activity. In studies of evoked cortical responses in the rabbit (315), the reviewers have followed the progress of the slow secondary component at all stages from deep barbiturate anesthesia to metrazol convulsions. Even in the resting untreated animal the slow component fires only once, and only with subconvulsive doses of metrazol does it develop the rhythmic character expected of a reverberating circuit. Therefore, it seems plausible to postulate that the action of barbiturates in slowing the grossly recorded EEG is neither the prolongation of the transit time around a fixed circuit, nor the slowing of an intrinsic frequency of a sinusoidal

oscillator, but the obligatory condensation of normally fractionated and asynchronous neurone populations by virtue of the delay in their recovery times.

As to the origin of the spindle type of activity appearing in the EEG of the sensorimotor cortex under barbiturate sedation, Morison *et al.* (255, 256) have shown that it continues to occur in the thalamus, unilaterally or bilaterally, after bilateral removal of the cerebral cortex, which indicates that reverberating circuits through the cortex are not essential. Obrador (263) has shown that the discharges are abolished by lesions limited to the hypothalamus and basal regions of the brain, and by lesions of the thalamus and thalamocortical pathways, but not by section of the brain stem (cf. 37). Hoagland *et al.* (189) have shown that the hypothalamus is more resistant than the cortex to the slowing effects of pentobarbital. From these observations it would appear that the sensorimotor cortex passively received the spindle bursts from a more rugged system of thalamic and hypothalamic nuclei. This system may constitute a true reverberating circuit, since trains of cortical spindle activity rather than isolated spikes are elicited by single shocks delivered to the cortex in light barbiturate anesthesia or even in the waking state (315). Why they should be relatively limited to the sensorimotor cortex and why they should be characteristic of only a limited range of sleep or anesthesia are unanswered questions.

An even more difficult problem concerns the origin of the generalized fast activity in light barbiturate anesthesia, particularly in man. It may represent intrinsic cortical activity, since Bishop (26) and Chatfield and Dempsey (53) have found that frequencies faster than the alpha range persist after section of the thalamic radiations. Activity even in the alpha range need not depend on subcortical reverberations, but may result from periodic summation in the cortex subjected to a constant subcortical bombardment of subliminal impulses, according to the studies of Dempsey and Morison (85, 86). Kristiansen and Courtois (210) have recently shown that even isolated portions of cerebral cortex continue to show 8–12/second discharges. That at least the upper layers of cortex may behave relatively independently is indicated in studies of their electrical activity and excitability by Adrian (1) and Rosenblueth and Cannon (285). However, it should be noted that thermocoagulation of the outer three layers does not abolish cortical activity in the alpha range of frequencies, according to Dusser de Barenne and McCulloch (91). Pending a more precise localization of alpha and faster activity, it is not impossible that the fast waves of light barbiturate anesthesia are of cortical origin and represent some degree of autorhythmicity.

A quite different mechanism for the initially observed changes in light barbiturate anesthesia might be the progressive synchronization of afferent discharges by a slowing of the recovery time of the thalamus, as shown by Marshall (243), coupled with similar slowing in the cortex. This effect would tend to cause the appearance of recordable fast discharges from a previously completely asynchronous and therefore unrecorded background of arriving sensory impulses. Whatever the anatomical localization of the faster activity may be, it cannot represent a fundamental change in cortical function, since it may occur in the

presence of little or no impairment of consciousness, as previously noted. The transformation of this state into the qualitatively different electrical and psychic activity of sleep constitutes one of the most dramatic and challenging problems in neurophysiology.

In the entire foregoing description, there seems to be nothing incompatible with the view that the essential mechanisms of barbiturate action are increased recovery time and increased threshold for cerebral neurones in general, with a somewhat greater sensitivity of cortex than of diencephalic centers. In this light the various qualitative changes in the EEG should be looked upon not as the sudden appearance of an additional type of drug action, but as an expression of the functional organization of the brain itself, which can operate within several semistable states of self-regulation, the state being determined in part by the prevailing time and voltage parameters of excitability, in part by the inflow of afferent impulses, and in part by some as yet unknown perversities that characterize a machine evolved for learning and dreaming.

b. General anesthetics: Despite the wide use of general anesthetics, EEG studies have been relatively few. In one of the first demonstrations of electrical activity in the brain of animals, Fleischl von Marxow (110) reported in 1890 that the electrical activity of the cerebral cortex could be modified by chloroform. In the first equivalent observations on the human EEG, Berger (21) observed that the alpha waves in man were greatly increased in amplitude during the excitement phase of chloroform anesthesia, but that alpha activity was abolished in surgical anesthesia with chloroform.

The effects of ethyl ether have been studied in slightly more detail. Gibbs, Gibbs and Lennox (136) noted in 1937 that during the early stages of ether anesthesia there was first an increase in voltage in frequencies around 20 per second, with a diminution in voltage in frequencies around 10 per second. As consciousness was lost these high voltage fast waves disappeared, giving way to high voltage slow waves at the rate of about 5 per second. The latter gradually were reduced to a frequency of 1 per second, with some persistent 10 to 20 per second activity superimposed, as surgical anesthesia was reached.

In contrast to ether, induction with nitrous oxide does not appear to produce a pattern of fast activity. Derbyshire *et al.* (87) observed that the number of alpha waves per unit time was decreased with mixtures up to 70 per cent nitrous oxide, first in the motor areas and subsequently in the occipital region. Mixtures of 70 to 90 per cent nitrous oxide produced slowing of the pattern to 4–8 per second in most subjects, particularly evident in the motor area. With pure nitrous oxide two possible patterns appeared: A frequency of 2.5 per second with an amplitude of 250 microvolts occurred if the induction was rapid, but if the patient had a slower induction followed by pure nitrous oxide, an irregular delta pattern of about 40 microvolts was evoked. Both patterns appeared simultaneously with beginning cyanosis of the nail bed. Wide individual variations of the EEG pattern were encountered for each particular mixture of nitrous oxide and oxygen. In contrast, mixtures of nitrogen and oxygen produced no change in normal subjects when the oxygen content was above 10 per cent; however,

normal subjects exposed for a short time to very low oxygen tensions showed an increase in voltage and the appearance of slow 4–8 per second rhythms in the EEG. Although the effects of nitrous oxide somewhat resemble those of anoxia, they are not simply the result of the relative anoxia frequently encountered during the use of this anesthetic agent.

The effects of cyclopropane on brain potentials in man were studied by Rubin and Freeman (291, 292). Initially, after a mixture of cyclopropane (350 cc) and oxygen (250 cc per minute) was breathed for one to two minutes, there was noted a decrease in frequency to 7–8 per second with an increase in amplitude of 100 per cent or more. At this stage the patient was in light anesthesia, with disappearance of the corneal reflexes. The next stage was marked by an increase in amplitude, with the appearance of regular 3 per second waves at the onset of surgical anesthesia. Electrocortical changes during recovery did not follow those observed during induction. If the subject was not kept in deep anesthesia more than 3 to 5 minutes, the early stages of recovery were extremely rapid. When the patient was allowed to breathe warm air, low voltage waves of mixed frequency appeared immediately. However, if the period of surgical anesthesia had been appreciably longer than 5 minutes, upon substitution of warm air for the cyclopropane-oxygen mixture there was further slowing of frequency to less than 3 per second; this was attributed by the authors to reflex vasodilatation and consequent flooding of the brain with increased amounts of cyclopropane. The next stage of recovery was characterized by an increase in frequency to a predominate pattern of 18 per second with a decrease in amplitude; in some instances this stage was preceeed by a regular 7–8 per second rhythm. The final stage was marked by a decrease in frequencies to 12–14 per second, with eventual restoration of the normal waking pattern. The amplitude and regularity of slow potential changes during anesthesia were greatest in the frontal lobe, and were less regular and of lower amplitude posteriorly. The 12–14 per second activity during recovery was most marked in the motor and pre-motor areas, where the waking potential pattern was first established after discontinuance of cyclopropane. It is certainly not clear to what extent the changes during recovery represent direct effects of the anesthetic as opposed to those of post-anesthetic sleep. More detailed analysis of the induction period is desirable.

Laboratory observations with regard to the influence of general anesthetics on cortical potentials have been rather more extensive than clinical reports. Beecher and McDonough (13, 14) studied in detail the effects of 17 anesthetics on cortical action potentials from the sensory areas in cats. Two levels of anesthesia were arbitrarily chosen: the lightest anesthesia which could be maintained without producing generalized muscular response on sciatic stimulation, and the level at which the flexion reflex just disappeared. They were able to classify the anesthetics into two distinct groups. The first consisted of those which were volatile (exception for urethane) and of low molecular weight; these produced a dominant frequency under light anesthesia of more than 26 per second. The second consisted of nonvolatile anesthetics, including tribromoethanol (avertin), evipal, paraldehyde, barbital, chloralosane and pentobarbital; these produced

high voltage 1–10 per second waves on which faster activity of low voltage were superimposed. The high voltage slow waves appeared in bursts at 3 to 5 second intervals, each lasting 1 to 2 seconds. Anesthesia with the non-volatile agents more nearly resembled natural sleep than did that induced by the volatile agents. Central sciatic stimulation failed to alter cortical discharges under light or deep anesthesia with any of the non-volatile anesthetics; but under light anesthesia with the volatile group, such stimulation greatly increased the voltage of the cortical waves.

Beecher (13) reported similar studies on a series of alcohols, all of which behaved like the volatile anesthetics with respect to their effect on electrical cortical activity. The pattern during light anesthesia was characterized by rapid small amplitude waves, and an increase in voltage was elicited by sciatic stimulation. The average frequency of the waves was inversely related to the anesthetic potency which in turn was directly related to the molecular weight, except that the secondary and tertiary alcohols were more potent than the primary alcohols.

The effects of ether on the EEG of the dog have been analyzed by Swank and Watson (312). They found that the fastest activity (50 per second) in the normal EEG was at first increased in amplitude by ether, beginning in the parietal area and then in the premotor area, while it was decreased in the motor area. In deep anesthesia, low amplitude slow waves began to replace the fast activity concomitant with the disappearance of the corneal reflex. Bursts of spindle activity to that seen during light barbiturate anesthesia occurred during recovery phase; but since these were also observed in the hemispheres of decerebrate animals which had fully recovered from ether anesthesia (37) and are a characteristic of the normal sleep record, the spindles should probably be attributed to post-anesthetic sleep rather than to the effect of ether itself. During the induction and recovery stages of ether anesthesia, cortical thresholds for the elicitation of afterdischarge (*i.e.*, seizure activity) were lower than normal, particularly in the motor cortex; but at surgical levels of anesthesia, afterdischarge could not be obtained.

Forbes *et al.* (112) observed mixed fast and slow activity in light ether anesthesia in the EEG of the cat, reverting to slow activity as the anesthetic was deepened, in contrast to the spindle and high voltage slow sequence of pentobarbital or tribromoethanol. They were impressed by the parallellism between potentials evoked by sciatic stimulation and the spontaneous cortical activity at various levels of depression by these three drugs, and concluded that the anesthetics acted not merely by blocking afferent impulses but by directly modifying the action of the cortex.

An interesting contrast between ether and barbiturates has been reported by Marshall, Woolsey and Bard (244) who noted that ether did not alter the threshold, latency or size of the primary response evoked in the somesthetic area of the cortex of the cat by tactile stimulation of the body surface. Even with deep ether anesthesia the recovery time was shorter than with pentobarbital, and with moderately light ether it was relatively normal.

Possibly related to this difference between ether and barbiturates are some

observations of Bremer (39), who found that ether anesthesia depressed equally the primary and secondary responses of the auditory cortex of the cat to abrupt auditory stimulus, without altering the fast activity which normally appeared in response to a continuous whistle. In contrast, the barbiturates abolished the whistle and secondary responses in doses which did not impair the primary response. With regard to the primary response, it should be noted that Marshall, Woolsey and Bard (244) did not find any reduction of amplitude under ether anesthesia, but found the action potential harder to identify and localize because of the background fast activity. The differential effects of ether and barbiturates on the whistle response would seem to indicate that ether does not impair the ability of the cortex to respond to stimulation of high frequency to the same extent as do the barbiturates.

Still another difference between ether and barbiturates has been reported by Forbes and Morison (113). They observed that ether added to preexisting deep barbiturate anesthesia, up to the point of respiratory failure, abolished the secondary cortical responses to peripheral nerve stimulation without altering the primary response. Deepening the barbiturate narcosis alone did not abolish the secondary responses. These investigators had previously shown that the secondary discharges were not characteristic of deep other anesthesia. The implications of their studies are two-fold: first, that afferent impulses may still reach the cortex at levels of ether or barbiturate anesthesia sufficient to abolish any spontaneous activity of the cortex; secondly, that while the barbiturates may leave the cortex in a quiescent state from which secondary discharges may still be elicited, ether has a more profound effect on the ability of the cortex to respond at all.

In an attempt to differentiate the mechanisms of action of ether and barbiturates on a more simple reflex system, Beecher *et al.* (15) compared the effects of evipal and ether on flexion reflexes mediated through the spinal cord of the cat. Ether did not prevent the development of sustained and cumulative responses to rapid reflex stimulation, in contrast to evipal which permitted only discrete responses to individual stimuli. Likewise they found that afterdischarge following the cessation of stimulation was more seriously impaired under barbiturate anesthesia than under ether, and concluded that "long-circuiting" of sensory impulses along internuncial chains was less curtailed by ether. This explanation is of course more descriptive than definitive, since the possible actions leading to failure of internuncial reverberation are not taken into account. One of these actions, prolongation of recovery time, has been a universal finding with barbiturates but not with ether.

The systematic investigations of Heinbecker and Bartley (178) on the mechanism of action of pentobarbital have already been discussed. Parallel observations on the effects of ether showed many similarities at all levels of the nervous system, but a few differences are worthy of mention. Ether increased while pentobarbital slightly decreased the extent of accommodation in frog sciatic nerve. The rhythmic discharge of impulses from neurones of the Limulus heart ganglion was typically accelerated by ether and slowed by pentobarbital. Reflex dis-

charges initiated from the spinal cord of the turtle were initially increased in frequency and duration by ether, whereas pentobarbital usually had a progressive depressant effect without initial excitation. Ether increased whereas pentobarbital decreased the frequency of impulses in the phrenic nerve associated with respiration. Ether increased the frequency of cortical spontaneous activity in the rabbit, in contrast to the sleep pattern seen after pentobarbital, and deeper ether anesthesia reduced the amplitude of the EEG progressively, the effect occurring earlier in cortex than in thalamus. The secondary period of facilitation following a cortical response to saphenous nerve stimulation occurred earlier than normal with ether and was delayed by pentobarbital, although both drugs reduced the magnitude of the facilitation effect. This latter phenomenon would seem to bear a more direct relation to the increase in cortical frequencies than to some of the other effects studied by Heinbecker and Bartley. At any rate it is of interest to note that increased frequency of electrical rhythms and some evidence of an initial excitatory effect of ether have been seen in other tissues than brain.

As to the basic mechanism of action of ether, Lorente de Nó (238) found that conduction block produced by ether in frog sciatic nerve was attributable to depolarization, but that the excitability of the blocked fibers could be restored if the membrane potential was artificially increased toward normal by an applied anodal current. In the earliest stage of ether action there was a tendency toward increased excitability associated with an increase in membrane potential before the ultimate depolarizing effect set in. That the excitability may eventually be progressively diminished by increasing the ether concentration is suggested by the work of Wright (347) who found that the exposure of mammalian peripheral nerves to ether vapor resulted in a progressive depolarization, loss of action potential amplitude, and increase in threshold. The last named effect was unlike that of anoxia, which was found to have little effect on threshold until critical depolarization causing conduction failure was achieved, at which point the threshold rose precipitously. Ether in high concentrations blocked conduction with relatively little change in membrane potential. The effects of ether seemed to be independent of the presence or absence of oxygen.

If ether acts primarily as a depolarizing agent, it might also be expected to increase membrane permeability if the mechanism of action were similar to that of potassium (193). However, Spiegel and Spiegel-Adolf (302) have concluded from conductivity measurements that the permeability of brain cells is decreased by ether and chloroform as well as by the barbiturate Dial. Whether such measurements truly reflect changes in cell permeability might be questioned, since decreased neural activity itself, secondary to the anesthesia, might reduce the average permeability of brain cells by reducing the number of impulses per unit time and therefore the number of occasions in which the membrane resistance is transitorily reduced. It is hoped that in the future a large body of valid observations on the effects of drugs on resting membrane resistance will be forthcoming, since the concept of change in permeability has all too frequently been invoked without rigorous experimental support.

From the foregoing observations, it can be seen that among the general anesthetics only ether has been analyzed sufficiently to permit some tentative conclusions concerning mechanism of action. The ultimate action of ether upon neurones is depolarization, but it is doubtful whether a depth of anesthesia sufficient to produce conduction failure by depolarization throughout the nervous system is ever reached. It is not unlikely that a moderate degree of depolarization is critical for synaptic transmission in the cortex and occurs at lighter levels of anesthesia. At any rate it may be stated with assurance that prolongation of recovery time is not an important factor in ether anesthesia.

The following picture of the effect of ether anesthesia on the EEG may now be synthesized. Under light anesthesia, the frequency of spontaneous activity may be increased, concomitant with a shortening of the facilitation interval and in accord with the action of ether on other nervous aggregates. In spite of this effect and overriding a moderate increase in excitability there may be a progressive failure of synaptic transmission within the cortex as the most sensitive synaptic regions partially depolarize. Slow activity of low amplitude and probable subcortical origin may appear, but not the high voltage discharges characteristic of barbiturate anesthesia; the subcortical reverberations represented by spindles do not occur. Eventually the cortex and related structures may become unresponsive in deepest ether anesthesia, but at this stage the afferent systems are still able to project to the cortex. By more refined analysis, particularly of the extent of the depolarization effect, it should be possible to verify or reject this tentative conception and to evaluate the role of threshold changes induced by ether.

c. Analgesics: The EEG effects of analgesics have generally been described as slowing of frequency or the appearance of sleep-like records. Thus, according to Gibbs *et al.* (136, 141), the intravenous administration of a single dose of morphine in normal subjects produces changes similar to those observed during normal sleep or following the administration of phenobarbital or pentothal. Patients receiving morphine were found by Peterson *et al.* (269) to have more slow wave EEG abnormalities than untreated patients in response to the same degree of anoxia at high altitudes.

The most extensive studies on the effects of morphine in addicted patients have been conducted by Andrews (6). His results show interesting differences in response to morphine, apparently dependent on the prior status of addiction. For example, he studied a group of patients with previously well-established physical dependence on morphine. In this group, following the withdrawal of all opiates and the appearance of the characteristic withdrawal syndrome, the administration of sufficient morphine to prevent physiological signs of abstinence gave an abnormally high percent time alpha. Results were somewhat different in a group of post-addicts who had received no narcotics for at least one year. In no case was there any significant change in the brain potential rhythms following injection of a single dose of 20 mgm. of morphine sulphate, sufficient to produce mild stimulation. However, there was a tendency for the occipital alpha blocking time to increase following injection, an incidence considered to be on the borderline

of statistical significance. Other subjects with no previous history of addiction were given single doses of 12 to 15 mgm., sufficient to produce marked symptoms consisting of nausea, vomiting, lassitude and general depression without preliminary excitement. Two cases showed no EEG changes, and the third exhibited a typical sleep pattern three to four hours after injection, although the patient was definitely not asleep during recording. During this period the alpha rhythm could be brought back temporarily by repeated light or sound stimuli.

Andrews (7) also observed the effect of meperidine in five patients who were previously addicted to opiates but had received no drug for at least six months. An initial dose of 100 mgm. daily was given, and each subject then chose his own frequency and dose within imposed limits of 1½ hours and 300 mgm. The EEG was recorded each week throughout the study period and every fifteen days after withdrawal until the record returned to the pre-experimental norm. Early in the study, the EEG showed slow waves which became progressively slower and of greater amplitude. After withdrawal, the slow waves persisted for about 48 hours, after which there was a progressive return to the original type of record. When slow wave activity occurred in response to morphine, it was relatively slower but also more transient than that seen after meperidine.

The effects of methadone have been studied by Isbell *et al.* (197). Single doses of less than 30 mgm. failed to produce significant changes in the EEG of normal subjects. However, one subject showed a marked slowing of frequencies following 30 mgm. of methadone. No definite correlation could be made between the EEG changes and the sedation produced by the drug, but the degree of sedation was difficult to measure. Similar EEG changes were seen in all patients receiving repeated smaller doses.

In contrast to these observations in man, Leimdorfer (214) has noted a tendency toward fast activity and spiking in the EEG of cats given either morphine or meperidine subcutaneously. It should be recalled that in the cat the effects of morphine are predominantly excitatory, with frequent occurrence of frank seizures.

Because of species differences in response to analgesics, it is difficult to relate the results of animal experimentation to the changes noted in the EEG of man. Wikler (338, 339, 340, 341) has made a careful study of the action of morphine at all levels of the central nervous system. He found that morphine in relatively small doses enhanced two-neurone reflexes while depressing multineuronal responses in the spinal cord of the cat. In contrast, pentobarbital and ether depressed both types of response. Eserine enhanced both types of discharge following a small dose of morphine, but had no effect on the multineuronal reflexes when given alone. This finding is of some interest in view of a possible cholinergic action of morphine. Observations of the mixed signs of excitation and depression produced by morphine at various levels of the cerebrospinal axis led Wikler to conclude that this alkaloid produced selective depression of interneurones accompanied by release phenomena, and to suggest that species differences may pertain to differences in neural organization. Until further evidence is forthcoming, it would seem wise to withhold judgment on the mechanism of action of

morphine and other analgesics on the EEG, and the possible relationship of those effects to analgesia.

d. Alcohol: Reports on the effects of ethyl alcohol upon the EEG have usually described a slowing of activity. Thus Loomis, Harvey and Hobart (237) noted an increase in amplitude of brain potentials and slowing of the rhythm during alcoholic stupor. Engel *et al.* (99), in a study of normal subjects and chronic alcoholics during acute intoxication, observed progressive slowing of the brain waves accompanying the development of intoxication. The degree of slowing produced a more reliable index of intoxication than the development of any particular frequencies. The mean frequency of the EEG was decreased by two to three cycles per second in association with intoxication. Patients who had abnormally fast records showed more normal discharges during intoxication. With recovery the EEGs returned to the pre-intoxication status. Very close correlation was demonstrated between the EEG and the level of consciousness, but no correlation was evident with various aspects of behavior. Greenblatt *et al.* (161) reported an incidence of 24 per cent abnormal EEGs among 157 patients with chronic alcoholism, alcoholic psychoses and alcoholic convulsions. An increasing incidence of dysrhythmias was found when the various chronic alcoholic disorders were roughly classified according to the severity of the clinical picture, the chronicity of symptoms, and the assumed severity and extent of damage to the brain. Seventeen per cent of those with "rum fits" or seizures associated with alcoholism had abnormal records, a lower incidence than for the group as a whole.

Somewhat related observations were made by Kaufman *et al.* (204) who administered 40 to 150 cc of 10 per cent alcohol intravenously over a period of 2 to 3 minutes to 16 patients. All individuals examined showed clinical evidence of alcoholic intoxication. In four instances the alcohol level reached 100 to 150 mgm. per cent. No alterations in the EEG patterns were observed in four non-epileptics. The epileptic group showed increasing prominence of the alpha rhythm, and previously abnormal activity decreased. That the rate of development of alcoholic intoxication is a factor in the relative preponderance of EEG over clinical signs is suggested by a comparison of these results with those of Davis *et al.* (83) who studied the effects of alcohol on the EEG and on psychometric performance in six normal male subjects. Using a Grass analyzer for quantitation of the frequency components of the EEG, they found that low concentrations of alcohol reduced activity particularly in the range of 10 to 13 cycles per second. With higher concentrations, episodes of slow waves of 4–8 per second appeared in the frequency spectrum. There was a definite impairment of the subjects' performance in psychometric tests at the higher blood concentrations of alcohol (125 to 140 mgm.%), but the EEG continued to show abnormalities for some time after recovery of intellectual functions.

In regard to possible mechanisms of action of alcohol, Wright (347) found that exposure of mammalian peripheral nerves to alcohol vapor resulted in a concomitant reduction in membrane potential and action potential amplitude, associated with a progressive rise in threshold. The last-named effect was in

contrast to that of anoxia, in which condition the threshold was found to remain relatively constant until a critical value of depolarization was reached and conduction failure supervened, at which point the threshold rose precipitously.

Thus, although alcohol produces a progressive slowing of the EEG not unlike that of anoxia, it should not be concluded that the mechanisms are identical. Further research upon the brain itself would be required to determine the relative importance of the threshold-raising and depolarizing effects of ethyl alcohol, and it is not impossible that still other changes as yet uninvestigated may play a role in the progressive slowing of cortical frequencies.

e. Anticonvulsants: It has now become established with fair certainty that drugs used in the treatment of convulsive disorders need not have a depressant action upon the central nervous system (321), and therefore it is not surprising that there are no universal EEG findings during anticonvulsant medication equivalent to those seen, for example, with adequate doses of the various sedatives.

Two distinct types of EEG change should be taken into account in any discussion of the anticonvulsants. The first is the alteration in the cortical electrical activity of normal subjects, or in normal interseizure records of patients of abnormal EEG manifestations. These two categories seem to involve mechanisms sufficiently different to merit separate consideration.

Bromide, the oldest of the effective antiepileptic agents, might be expected to produce EEG alterations when the concentration in body fluids is sufficient to produce psychic disturbances. Since the therapeutic margin of safety is relatively narrow in the treatment of epilepsy with bromide, and because of the wide and unregulated use of this anion, the central manifestations of bromide intoxication are frequently encountered. In a series of cases observed by Greenblatt *et al.* (162), 18 per cent of patients showed some EEG abnormalities with serum bromide concentrations of 100 mgm. per cent; 88 per cent, with levels of 200 mgm. per cent or above. Concentrations above 200 mgm. per cent were usually associated with diffuse slow activity, a typical finding being irregular high voltage 2–5 per second waves. Patients in this range were confused and inarticulate. At 180 mgm. per cent, fast activity was seen to be mixed with the slow component, while at 160 mgm. per cent the frequency was predominantly in the 12–25 per second range, similar to that reported by others for a moderate degree of barbiturate intoxication. The appearance of fast activity during the decline of the serum bromide level was associated with a progressive improvement in mental clarity. Below 100 mgm. per cent, only occasional abnormalities were seen. Considerable individual variation was noted in the relationship between serum bromide level, degree of EEG abnormality and psychic impairment in this group of patients. However, the general correspondence between bromide concentration and incidence of EEG abnormalities confirms the previous studies of Rubin and Cohen (288), and the extreme changes observed in chronic intoxication are similar to those reported by Lennox *et al.* (224) for intravenous administration of sodium bromide.

The *barbiturates* have already been discussed in detail, but it might be in order

to reiterate that fast activity and to a lesser extent slow or mixed patterns are frequently seen with phenobarbital and other barbiturate therapy used in convulsive disorders. M. Lennox (216) has pointed out the importance of recognizing these effects in the evaluation of EEG recordings in epileptic patients, since the dysrhythmia may otherwise be mistakenly considered a sign of the disorder rather than of the treatment.

The literature seems to be remarkably free of descriptions of EEG changes produced by *diphenylhydantoin* except upon preexisting dysrhythmias, which probably attests to the well-known lack of sedative effect and fair margin of safety of this substance. However, the same cannot be said of the related hydantoin, *mesantoin* (3-methyl-5,5-phenyl ethyl hydantoin), which exhibits sedative side-effects in sufficient dosage. Little (234) has observed consistent changes in the EEG of patients undergoing treatment with mesantoin, in contrast to the lack of EEG effect of therapeutic doses of diphenylhydantoin. The changes were observed particularly with mesantoin doses of 0.4 gm./day or greater, and in order of decreasing incidence included increase in fast activity, decrease in alpha rhythm, and decrease in slow activity. Only 12 per cent of their patients failed to show a demonstrable EEG effect of mesantoin. The changes were closely correlated with dosage and duration of administration of the drug, but not with other factors in the patient's history.

Although the oxazolidine-2,4-diones, *trimethadione* and *paradione* (3,5-dimethyl-5-ethyl oxazolidine-2,4-dione), have not been reported clinically to produce consistent and significant EEG changes other than upon preexisting abnormalities, animal experiments indicate that doses of trimethadione sufficient to produce sedation cause typical sleep records, with bursts of spindles against a background of slow activity (155). In this respect trimethadione resembles the barbiturates. The authors (78) and Perlstein (267) have noted a tendency in patients toward fast activity similar to that seen with barbiturates.

In spite of its chemical relationship to the hydantoins, *phenurone* (phenacetylurea) produces sedative effects similar to those of the barbiturates (134). It will be interesting to note whether further EEG experience places this new anticonvulsant among those producing initial fast activity.

Whether to classify *glutamic acid* as an anticonvulsant is a controversial point, even though Price *et al.* (277) have reported some clinical benefit in petit mal. Wager (324) failed to find that the frequency of clinical seizures in a group of 6 adult epileptics was materially influenced by nine grams of glutamic acid per day for 30 days, but reported that "electroencephalographically it was not unusual to observe an increase in recorded definition of photic drive responses and an equally noticeable removal or reduction in the recorded post-ictal psychomotor period." The nature of these changes is not immediately evident. Even the largest quantities of glutamic acid which could be safely administered to laboratory animals have been found ineffective in changing either normal or metrazol-modified EEG; neither did they produce any demonstrable anticonvulsant effect (157).

From this incomplete survey of the clinically effective anticonvulsant drugs

the chief conclusion to be drawn is that abnormalities may be produced by those agents having central side-actions such as sedation, and that these changes should be considered in the evaluation of records of patients receiving anticonvulsant therapy.

The second category of action of anticonvulsants, namely, their ability to improve the abnormal EEG, seems to vary with regard both to the character of the convulsive disorder and to the type of treatment. Although the EEG often shows dramatic improvement associated with clinical remission, it is also frequently found that the clinical picture improves while the EEG remains relatively abnormal (194, 220, 242, 283). These discrepancies have usually been reported in cases of grand mal or psychomotor seizures under treatment with barbiturates or hydantoins. If any general rule can be deduced from the plethora of clinical observations, it would be that frank seizures may be aborted by therapy in spite of persisting excessive discharge in the interseizure EEG. This would seem to indicate that some anticonvulsants may act to a considerable extent upon normal brain cells to protect them against invasion by seizure activity from hyperactive foci. Such a phenomenon has been noted by the reviewers (321), who observed a number of cases in which a previously diffusely abnormal EEG improved considerably under anticonvulsant therapy, but left a focus of paroxysmal discharge more sharply defined than before. Diphenylhydantoin in particular produced this effect. The most likely explanation would be that in some cases the anticonvulsant so alters the properties of normal neurones that they can no longer be secondarily involved in discharges from the epileptogenic lesion, even though the injured cells of the lesion itself continue to fire excessively.

There are also occasional reports of a salutary effect of anticonvulsant therapy upon dysrhythmias other than those associated with frank convulsive disorders. Thus, diphenylhydantoin was found by Lindsley and Henry (231) to reduce frontal slow activity without producing other EEG changes in children with behavior disorders. There was some improvement in personality but it was not well correlated with the EEG changes.

In contrast to the variable actions of hydantoins and barbiturates upon the abnormal EEG, the oxazolidine-2,4-diones have been generally reported to produce a specific depression of the spike and some dysrhythmia characteristic of the petit mal triad (pyknoepilepsy, akinetic seizures, myoclonus), and there is a good correlation between EEG improvement and clinical remission. This is well illustrated by the observations of Lennox (222). He studied 100 cases of epilepsy, 59 of which had petit mal and were treated with trimethadione or paradione. Of 22 patients in the petit mal group who were rendered seizure-free, the EEGs of 72 per cent contained no spike and wave discharges, whereas none of 13 cases without clinical improvement had an improved EEG. Forty-nine patients with grand mal or psychomotor epilepsy were treated with phenobarbital, diphenylhydantoin or mesantoin. Of 16 who were rendered seizure-free, the EEGs became normal in only 31 per cent and were unimproved in 21 per cent. Of 18 patients who reported fewer attacks, 11 per cent had normal tracings. Seventy-three per

cent of those with petit mal showed agreement between clinical and EEG results, compared with 57 per cent for other types of seizures. In two thirds of the cases, when seizures were absent, improved or unimproved, the EEGs were normal, improved or unimproved, respectively. Although more specific effects of individual drugs were not noted in this study, the tabulation indicates a general tendency for seizures and EEG to follow a parallel course.

The clinical and electroencephalographic specificity of action of trimethadione in petit mal has been confirmed by a number of investigators (79, 155, 221, 265, 266, 268, 299). To a lesser extent trimethadione has been found to suppress other types of dysrhythmia. Perlstein (266) has presented evidence to show that elimination of seizure discharges not only of petit mal but also of psychomotor types and of focal fast activity may result from trimethadione therapy. Belnap *et al.* (16) treated seven consecutive patients who had frequent grand mal seizures and spontaneous slow-wave dysrhythmia with a combination of trimethadione and diphenylhydantoin. The initial dysrhythmia was focal in two cases, bilaterally symmetrical frontal in three and diffuse in two. Prompt and complete clinical remission was obtained in six patients (with 1 to 9 months follow-up). Of the six patients, the EEG returned to normal in four and was improved in two.

That trimethadione may exacerbate EEG dysrhythmias in certain cases has also been noted (155); the effect is particularly striking in some patients during the first day of therapy of petit mal, and is associated with an increased seizure frequency. However, trimethadione has not been found to produce activation of latent dysrhythmias, according to Kaufmann *et al.* (204) who administered 50 to 500 mgm. of trimethadione intravenously in 18 patients with post-traumatic epilepsy in an attempt to localize a focus of abnormal activity. They found no noticeable effect on the EEG in any instance.

In addition to the ability of anticonvulsants to abolish convulsive discharges completely or to restrict their spatial spread over the hemispheres, certain other manifestations of protective action may be seen. For example, Lennox *et al.* (224) noted, in occasional petit mal cases which responded to sodium bromide or phenobarbital, that the spike and wave episodes were sometimes reduced in frequency of occurrence, shortened in duration and distorted in pattern. With trimethadione, the reviewers have observed two interesting types of intermediate modification of the spike and wave EEG. In some patients the recurrent 3 per second pattern may be replaced by isolated single wave and spike complexes. In others, the rhythmicity may be retained but the spike component disappears, leaving episodes of regular slow waves. Finally, all investigators seem to be in agreement that in the usual case of petit mal the paroxysmal dysrhythmia is much harder to elicit by hyperventilation when the patient is under trimethadione therapy (221).

The interpretation of the favorable action of anticonvulsants upon the abnormal EEG would require a better understanding of the nature of the convulsive discharges themselves. The records of Adrian and Moruzzi (3) from single fibers of the pyramidal tract of the cat strongly suggest that convulsive discharges from the motor cortex are characterized by trains of impulses at very

high frequency, and that these may be elicited by excessive or repeated stimulation or by the application of convulsant drugs. The reviewers (316) have studied a similar phenomenon in peripheral nerve and found that pre-treatment with relatively low concentrations of the common anticonvulsant drugs protect against this effect. Part of this action was found to involve the prevention of abnormal lowering of threshold by excessive stimulation or treatment with excitant agents. In the case of diphenylhydantoin, the action was exhibited at concentrations far lower than those necessary to modify other measurable properties of nerve. If peripheral nerve data are transferrable to cerebral cortex, it is easy to see that action upon abnormal EEG discharges may occur without necessary modification of the background interseizure record or of normal function may be achieved. The question has been considered in a previous review (321).

In summary, there are two general types of action of anticonvulsants upon the EEG. On the one hand, there are effects upon the normal EEG which may be characteristic of the side-actions of the drug and are more specific for the drug than for the anticonvulsant action. On the other hand, there are the effects upon the abnormal EEG associated with convulsive disorders; these are manifested either as complete suppression of the paroxysmal dysrhythmia, or its modification by shortening the paroxysm, slowing of the frequency and disintegration of the rhythm of discharge, change in the abnormal wave form, or decrease in the evocability of the EEG signs by such activation procedures as hyperventilation. Although there are probably several mechanisms by which these ends may be achieved—mechanisms which determine the clinical specificity of the anticonvulsants—the general *modus operandi* of these drugs may be the stabilization of neuronal threshold against excessive stimulation or exciting agents in such a way as to prevent excessive facilitation and discharge of impulses at high frequency.

f. Miscellaneous depressants: Other than the specific drug groups already considered, there are a number of agents, such as paraldehyde and chloral hydrate, which could also be loosely classified as central depressants. To the extent that they have sedative action, they appear to produce EEG effects like those of normal sleep (21, 136, 224), and in this respect resemble the barbiturates.

One group of central depressants which has attracted recent interest includes those which have a selective action against certain nonconvulsive motor manifestations of hyperactivity such as chorea, athetosis, tremor, etc. Among the more effective of these so-called "anti-Parkinsonism" agents is *myanesin*, which has been reported particularly effective in relieving involuntary movements of the type seen in paralysis agitans (18, 19, 295). Stephen and Chandy (305) recorded the EEG tracings during the intravenous administration of 30 mgm./kg., a dose which abolished involuntary movements in paralysis agitans and stopped intractable pain of thalamic origin for short periods of time. There was no significant alteration in EEG activity except an increased alpha rhythm in certain cases with increased nervous tension, an observation suggesting general relaxation. No slow waves indicative of possible cortical depression appeared, but in one case "abnormal waves" were recorded from the base of the brain; they disap-

peared with remission of clinical signs and symptoms. Gammon and Churchill (118) found no alteration of normal EEG patterns with doses of myanesin which abolished the tremors of Parkinsonism or suppressed choreoathetotic movements. However, in six cases of petit mal without generalized seizures, the spike and wave discharges were abolished. Convulsive states with focal cortical abnormalities and two cases of "petit mal variant" associated with generalized seizures, supposedly the result of brain damage, were unaffected by myanesin.

Experimental animal studies (317) indicate that quantities of myanesin sufficient to produce generalized muscle relaxation, particularly of the hindlimb and abdominal musculature, may cause the appearance of sleep activity in the EEG, but the extent of loss of muscular tone is considerably greater than that seen with an amount of a rapidly acting barbiturate causing an equivalent EEG change. That the EEG changes may be irrelevant to the basic action of centrally effective muscular relaxants is illustrated by benzimidazole, which can produce an extreme loss of tone with no observable change in the EEG (147). Observations on peripheral nerve and on brains of animals indicate that these agents act by raising threshold rather than by altering the membrane potential, put the precise mechanism of their apparent specificity as muscle relaxants is still to be elucidated (317).

2. Predominantly excitant drugs. The drugs which exhibit a predominantly excitatory effect upon the central nervous system vary widely in the degree and kind of excitation they produce. Some agents, such as metrazol and picrotoxin, may produce full convulsive seizures and corresponding EEG signs of paroxysmal hyperdischarge, whereas others, such as amphetamine, produce a relatively mild analeptic effect which is best observed against a background of central depression produced by other drugs. Thus it is not surprising that there is no uniform EEG manifestation of the action of central stimulants.

a. Strychnine: Strychnine is among the most ancient of the central stimulants and has received experimental attention and wide clinical usage far out of proportion to its therapeutic value. Its most striking central action in man and animals is the production of hyperexcitability of the spinal cord so that stimulation which would ordinarily produce only localized responses, or even inhibition of reflexes, is capable of evoking massive and diffuse tonic spasms of the body musculature (148). However, its excitant effects are not restricted to the cord but are also seen at higher levels.

The EEG manifestations of strychnine poisoning have not been adequately investigated in man (136), but considerable information has been derived from work with experimental animals. Bremer (38) reported that topical application of strychnine to the cortex of the cat at first produced an amplification of the preexisting spontaneous rhythm, but eventually this background activity became weaker and high voltage, highly synchronized spikes appeared, initially in isolation and then in trains. As with other types of convulsive discharge, these were followed by a period of functional depression lasting many minutes. Adrian and Moruzzi (3) found that the strychnine spikes recorded from the motor cortex of the cat after topical application of the drug were associated with bursts of

impulses in individual pyramidal fibers at frequencies greater than 1000 per second. After systemic administration of strychnine to cats and rabbits, Heinbecker and Bartley (177) recorded an initial increase in frequency and amplitude of cortical activity, followed by the appearance of high voltage synchronized discharges. The threshold for responses evoked from the cortex by sciatic stimulation was somewhat reduced by strychnine, and the late components of the evoked potential were dramatically increased in size. In addition, the period of facilitation following a single response was considerably prolonged. These cortical effects could be abolished by calcium gluconate.

The early literature on the mechanism of action of strychnine has been reviewed by Dusser de Barenne (90a), whose own work seems to demonstrate a selective excitant action of strychnine upon cell bodies. This action has been widely exploited by Dusser de Barenne and his colleagues (cf. 246) in neuronographic mapping of the interrelation between various cortical areas and subcortical structures, since after topical application of the drug the excessive firing manifested by strychninized cell somata is propagated to other parts of the brain by the terminations of the activated neurones.

Systematic investigation of the actions of strychnine on various levels of the nervous system has been made by Heinbecker and Bartley (177). They noted two significant effects of relatively low concentrations upon peripheral nerve, namely, a lowering of threshold and a decrease in the degree of accommodation. In isolated autonomic ganglia they observed an increase in excitability and a great prolongation of the period of enhanced excitability following an inadequate preganglionic volley. Reflex discharges obtained from the spinal cord were characterized by a great prolongation of the period of firing following a single afferent shock. The effect was greatest when both dorsal and ventral quadrants were strychninized; it was still apparent when the ventral surface only was treated, but was absent when the drug was applied only to the dorsal horn. These results on the cord were essentially similar to the findings of Dusser de Barenne (90a), who had also shown a hypersensitivity of the body segments innervated by the dorsal surface of a strychninized portion of cord, but an absence of tetanic reflex contractions unless the ventral surface was also treated. Heinbecker and Bartley demonstrated an increase in the frequency, amplitude and duration of discharges from the pacemaker neurones of the limulus heart treated with strychnine.

Since strychnine acts upon many types of neurones both to cause a moderate increase in excitability and to prolong the duration and increase the frequency of trains of impulses from the excited cells, possibly by reducing accommodation, it does not seem necessary to postulate additional mechanisms for the appearance of strychnine spikes in the EEG. Each strychnine spike may be considered to be a synchronized composite of high frequency discharges from individual neurones with periods of recovery intervening between the summated bursts. It would be interesting to know to what extent the high degree of synchronization shown in each burst is predicated on a loss of cortical inhibition, particularly since the failure of inhibition is known to be so pronounced at the spinal level.

Also, the role of loss of accommodation in this phenomenon would be worth further study.

b. Metrazol: Metrazol differs from strychnine in having its most pronounced effects upon the higher centers of the brain rather than upon the cord, and in producing complete tonic-clonic convulsions rather than brief tonic spasms. Its chief valid uses in the past have been in the shock therapy of psychoses and as a cerebral and respiratory stimulant to combat the effects of central depressant drugs. Of greater interest to electroencephalographers is the recent use of metrazol as an "activating" agent for latent dysrhythmias. Kaufman *et al.* (204, 205) have reviewed various methods now used clinically to elicit abnormalities in the EEG, particularly in patients with suspected convulsive disorders. Metrazol has been used more than other convulsant drugs for the purpose of provoking paroxysmal discharges in susceptible individuals, and at least some epileptic patients have abnormally low thresholds for metrazol activation. Ziskind and Bercel (348, 349) have been foremost in using the minimal threshold quantity of metrazol as a diagnostic procedure to elicit EEG abnormalities. The typical minimal activation pattern was found to consist of high voltage 4–5 per second oscillations occurring in bursts. Unfortunately these bursts tend to be generalized even in the presence of well-defined foci, and the technic is of no unusual advantage in localization.

Because of the current interest in activation procedures, it is worthwhile to mention some of the more detailed observations made by the above investigators. A study of 25 epileptics with a preliminary normal EEG (348) showed that the average minimal dose of metrazol for evoking EEG changes was 2.3 cc of a 10 per cent solution; for non-epileptics, 3.4 cc. However, there was considerable overlapping of the two groups. Records obtained from epileptics before and after the administration of 1 or 2 doses of 0.1 gram of phenobarbital and 0.1 gram of diphenylhydantoin showed a definite rise in threshold. In patients with spontaneous larval "spike and wave" attacks, the paroxysmal record was very sensitive to the intravenous injection of either sodium phenobarbital or trimethadione, which obliterated or greatly diminished the abnormal discharges. Hyperventilation and sub-convulsive doses of metrazol readily reproduced these larval attacks and restored the same pattern which was present in the preliminary record. Kaufman *et al.* (204, 205), in a study of metrazol activation in post-traumatic epilepsy, administered 2 cc. of a 10 per cent solution intravenously as rapidly as possible during EEG recording, and produced localized alterations in the cortical rhythms in 60 per cent of 97 patients. Focal changes included slow waves and single or multiple spikes, giving the appearance of a localized EEG seizure. Ten per cent of patients showed generalized alterations consisting of single or multiple slow waves or spikes appearing simultaneously from several areas of the head. A small percentage of the patients examined experienced sensory aura or motor prodromata. The seizure induced by metrazol had the characteristics of the patient's ordinary attacks. In approximately one-half the attack remained confined to one portion of the body as a focal convulsion. Patients on anticonvulsant therapy showed a lower incidence of activation, and none of them had

clinical convulsions with the dosage used. Intramuscular administration was found to be less effective than intravenous administration in producing clinical seizures and in localizing an epileptogenic focus.

The use of metrazol in convulsive therapy has also led to sporadic studies of the associated EEG changes (84, 306). These are usually reported to be similar to the patterns occurring during spontaneous convulsions. Post-seizure EEGs taken for several months following a series of metrazol convulsions have shown residual disturbances in as many as 50 per cent of patients, associated with evidences of impaired cerebral function lasting sometimes as long as six months (207, 227). The reported EEG abnormalities include slow activity ranging down to 3 per second, bicuspid and dicrotic waves, spike and wave formations and greatly increased amplitude. Presumably these persistent changes are the result of the cumulative effects of a series of seizures however produced, and have no special significance for the action of metrazol.

The EEG changes produced by metrazol in experimental animals have received considerable attention and have found a practical application in investigations of the protective action of anticonvulsants (155, 315, 317, 320, 322, 348, 349). In rabbits, approximately one half of a convulsive dose of metrazol produces a dysrhythmia characterized by bursts of smooth 5 per second waves of high voltage, usually with a small spike component which gives the record the superficial appearance of a petit mal spike and wave burst. The spike is more prominent in rats and monkeys and is the dominant feature of the discharge in cats. In rabbits the metrazol threshold for this type of discharge is lowest for the auditory cortex, next for the visual cortex, and higher still for the rostral sensorimotor cortex. When the bursts occur intermittently, they are usually associated with quiescence of the animal, and are easily abolished during spontaneous movements or sensory stimulation. Larger doses of metrazol lead to the development of a continuous dysrhythmia of this type, but until the discharge has become continuous in the rostral cortex there are no overt convulsive manifestations and no gross evidences of excitation except for hyperpnea. The onset of a seizure is usually heralded by the appearance of groups of high voltage spikes particularly in the motor cortex, associated with clonic movements, and this is then followed typically by the development of a full clinical and EEG tonic-clonic seizure.

Such an EEG pattern provides an interesting preparation for the study of anticonvulsant drug action (320). Trimethadione has been found highly effective and specific in raising the metrazol threshold for these discharges, but all the barbiturates which have been studied are also active. Benzimidazole, in spite of its ability to raise electrical threshold in the brain, is relatively ineffective against the metrazol discharges. The reviewers have found diphenylhydantoin, glutamic acid, and respiratory and metabolic acidosis all relatively ineffective against metrazol. Amphetamine increases the sensitivity of the brain to metrazol, although it is not in itself capable of producing this type of dysrhythmia.

The reviewers have studied cortical responses to electrical stimulation in an analysis of the action of metrazol (315, 320, 322). The characteristic EEG discharge may be evoked by electrical stimulation of the brain even when the dos-

age of metrazol is too small to alter the spontaneous record. During continuous intravenous injection of metrazol the single slow wave component of the normal evoked discharge can be seen to grow progressively in amplitude and then to become repetitive. These changes are associated with a progressive lowering of threshold for the evocation of EEG discharges, nonconvulsive movements and seizures. At a point just short of the occurrence of seizures, the electroshock threshold may be reduced to about half, and single shocks, which ordinarily do not produce seizures no matter how high the voltage, now may precipitate a convulsion. The development of the preconvulsive state is also associated with evidences of loss of local sign for stimulation of motor points and wide irradiation of sensory discharges. For example, auditory click stimulation which ordinarily gives small local responses confined to the primary auditory areas, now produces diffuse subconvulsive EEG bursts and may even precipitate seizures.

Thus the characteristic features of metrazol action as deduced from EEG observations include the development of repetitiveness, increased amplitude of discharges, a moderate lowering of threshold, and widespread irradiation. In contrast there seems to be little effect on the time relations of the recovery cycle of the cortex.

These same features are also seen to some extent when metrazol is used in animals already depressed by trimethadione or barbiturates. For example, metrazol increases the voltage, frequency, duration and rate of recovery of cortical responses evoked by sciatic or cortical stimulation in cats and rabbits under deep barbiturate anesthesia. In light anesthesia metrazol increases the frequency and also the voltage of the "spindle" bursts, amplifying particularly the surface-negative component of these discharges, an indication of increased synaptic transfer within the cortical layers. The antagonism of metrazol is more specific for trimethadione than for the barbiturates, so that the various EEG stages of anesthesia and sleep produced by trimethadione can be progressively overcome with increasing doses of metrazol.

The authors (317) have been unable to find any action of metrazol on peripheral nerve corresponding to its excitant effect upon the cerebrospinal axis. With unphysiologically high concentrations (30 mMol/l or more) an increase in threshold and other depressant effects may be observed. In this respect metrazol differs from strychnine, and the difference may have relevance to the more selective action of metrazol on higher centers. If further definition of the mechanism of action of metrazol is to be found, it might therefore be sought most profitably at the level of the cerebral cortex itself.

c. Picrotoxin: Picrotoxin is a convulsant which does not differ significantly from metrazol in its effects upon the nervous system except insofar as its onset of action and rate of destruction are somewhat slower. Its clinical use has been largely restricted to the treatment of barbiturate poisoning (148), and its EEG effects have not attracted the same wide interest as those of metrazol. Sporadic observations on laboratory animals (311, 317) indicate that it produces the same EEG changes as does metrazol.

d. Camphor: Camphor, which resembles metrazol and pictrotoxin in produc-

ing seizures by a higher central action, is not clinically used for its convulsant or analeptic properties, and its EEG effects have therefore been of little interest. Lennox, Gibbs and Gibbs (224) observed that after the intravenous injection of small amounts of camphor, the brain potentials increased in amplitude, becoming progressively larger and more frequent until a convulsion occurred. In one patient in their series, a short but typical petit mal seizure developed. In another patient with a history of seizures, psychomotor attacks as well as generalized seizures were produced. These observations might suggest camphor for use in EEG activation procedures, but it is unlikely that this drug possesses any advantages over metrazol.

e. Amphetamine: Among the central stimulants, amphetamine has received increasing attention because of its popular use in allaying drowsiness and in dulling the appetite of the obese. Its reported effects on the EEG of normal patients have included an increase in percentage time alpha, according to Rubin *et al.* (293), and a shift toward higher frequencies in the EEG spectrum as studied by Gibbs and Malty (141). Although Cutts and Jasper (70) failed to find any definite effect of amphetamine in the EEG of behavior problem children who showed clinical improvement during treatment, Lindsley and Henry (231) in a similar group reported some reduction in slow frontal abnormalities, and an increase in frequency and decrease in amplitude of the normal alpha rhythm. A more specific effect of amphetamine on EEG abnormalities has been observed in petit mal cases by Golla *et al.* (146) and Livingston *et al.* (235), who found that the characteristic 3 per second spike and wave pattern was often abolished by treatment. The latter investigators did not find a close correlation between EEG improvement and clinical remission in their series, and noted that amphetamine was less effective when the EEG dysrhythmia deviated from the classical petit mal type. These effects of amphetamine should probably not be attributed to a specific action of the drug in changing cortical parameters, since petit mal discharges are notoriously easily suppressed by procedures which increase alertness and activity.

The reviewers (317) have noted no outstanding changes in the EEG or thresholds of experimental animals treated with amphetamine. Interestingly enough, the petit mal-like dysrhythmia produced by subconvulsive doses of metrazol was found to be exacerbated rather than improved by amphetamine. M. Lennox and Ruch (217a) have observed that post-seizure abnormalities of the 2–3 per second type which usually appear in monkeys during recovery from electroshock convulsions may be abolished by pretreatment with amphetamine. The drug also produced a more rapid recovery from post-seizure depression.

The mechanism of action of amphetamine is far from understood; it is probably unrelated to its sympathomimetic action (148). The work of Maling and Acheson (241a) would indicate, at least to the reviewers, that amphetamine can compensate to a considerable degree for the effects of various central nervous lesions, possibly by replacing through increased internuncial function the loss of facilitation from the centers destroyed. That the mechanism is considerably different from that of the convulsant drugs may be inferred from the failure of

amphetamine to produce seizures or subconvulsive dysrhythmias in laboratory animals, and its ability to combat drowsiness without interfering with the anti-epileptic action of such agents as phenobarbital in the treatment of convulsive disorders.

f. Xanthines: The xanthines, although widely used as central stimulants, have not been favored with extensive observations of their EEG effects. Gibbs and Maltby (141) reported that caffeine causes a shift in the human EEG frequency spectrum toward faster activity. This shift included both an increase in frequency of the alpha rhythm and increased voltage in the 14–30 per second range. Swank and Foley (311) noted that caffeine and aminophylline differed from metrazol and picrotoxin in having no effect upon the EEG in doses which were definitely analeptic against the respiratory depression induced by barbiturates.

g. Cocaine and procaine: Although useful primarily as local anesthetics, procaine and cocaine have important central nervous actions which are attracting increasing attention—procaine because of its use as an analgesic by intravenous administration, and cocaine because of the public health problem created by its chronic use particularly among the hunger-ridden Indian miners of the Andes. Both may produce extreme excitation and convulsions on systemic administration. The EEG correlates of their central action have not been extensively studied. Berger (21) observed an increase in the amplitude of the alpha waves without change in frequency following the administration of cocaine to 10 subjects. Rubin *et al.* (293) administered 50 mgm. of cocaine subcutaneously to each of 11 subjects and found a decrease in the percentage of alpha activity, without significant change in the alpha frequency or in the amount of slow activity. The reviewers (317) have recorded the effects of intravenous procaine on the EEG of the rabbit and observed changes essentially similar to those obtained with metrazol, including the early appearance of high voltage 5 per second spike and wave bursts. Procaine differs from metrazol in increasing rather than decreasing the threshold for evoked cortical responses, but both cause repetition and increased voltage of the evoked responses as well as widespread irradiation. As to the basic mechanism of action of the local anesthetics, it is well known from the classical investigations of Gasser and Erlanger (118a) that conduction is first blocked in the small and unmyelinated fiber groups, and it might be expected that the small neurones of the brain would be the earliest to fail after systemic administration. How this mechanism could operate to permit irradiation and seizures remains to be determined. The important factor in conduction block by the local anesthetics has been shown to be increase in threshold rather than depolarization (17, 25, 238, 323). This raises the possibility that a threshold-increasing drug may cause seizures by selective depression of inhibitory systems. Further investigations on the apparent paradoxical action of procaine might do much to clarify the mechanism of origin of subconvulsive EEG dysrhythmias produced by this and other convulsant drugs.

h. Mescaline: Mescaline, a pharmacologically active substance derived from cactus, is capable of producing bizarre psychic effects and hallucinations (148);

it is also occasionally used in the laboratory as a convulsant (123). Rubin *et al.* (293) have examined its EEG effects in man. The oral administration of 300 mgm. of mescaline in divided doses to a group of seven schizophrenics produced extreme states of anxiety, correlated with a 25 to 30 per cent increase in the frequency of the alpha rhythm. Chweitzer (59) reported that, in a normal individual during mescaline intoxication, there was a reduction in the amplitude of the alpha waves, with prolonged intervals of inactivity associated with the hallucinations. These observations are of little help in interpreting the peculiar psychic effects of mescaline, and the literature has been more concerned with the exotic features of mescaline intoxication than with its mechanism of action.

i. DDT: Occasional cases of poisoning in animals and man by the insecticide DDT (Dichloro-diphenyl-trichloro-ethane), and the unusual character of the seizures induced in animals, prompted Crescitelli and Gilman (66) to study the alteration in the electrical activity of the cerebellum and cerebral cortex resulting from the intravenous administration of DDT emulsions in cats and monkeys. In animals which had been treated previously with small doses of sodium pentobarbital to suppress the convulsive activity of DDT, the cerebellar rhythm progressively increased in magnitude over the course of one to two hours, to a level five times that recorded during the control period. The pattern remained essentially unchanged, except for a slight increase in frequency. Cortical activity increased somewhat in magnitude and frequency, but the chief effect, especially in cats, was the conversion of previously irregular 8–12 per second pattern into an almost continuous and regular rhythm at the same frequency or slightly higher. With further action of DDT, episodic convulsive activity was recorded from both the cerebellar and cerebral cortex, preceded by fast waves. These fast discharges were completely synchronized in the motor cortex and cerebellum; in monkeys they were surface positive at the motor cortex and either surface negative or diphasic, with an initial negative deflection, at the cerebellum. The fast activity increased in magnitude and frequency until eventually periodic electrical seizures appeared in both the cerebellum and cerebral cortex, similar to the electrical pattern observed in major seizures in man or that following the administration of convulsive drugs or electrical stimulation of the cortex in animals.

A detailed analysis of the preconvulsive fast waves in monkeys revealed that they were most prominent in leads from areas 4 and 6. With leads placed progressively away from the motor cortex, the fast waves became less prominent. From the cerebellum, these discharges were recorded most prominently from the pyramic vermis and portions of the lobulus simplex. In most instances, the lobulus ansiformis was silent or relatively inconspicuous. The ansiform lobe and the vermis of the cerebellum, like the cerebrum, participated in the periodic "tonic-clonic" electrical manifestations of DDT.

The authors concluded that on the basis of polarity, the cerebellar-cortical synchronization could only be explained as the result of efferent impulses from cerebellum to cortex. However, they were unable to explain the EEG findings on the basis of known connections between the cortex and various parts of the cerebellum, and have suggested the possibility that both the cerebellum and motor

cortex were being simultaneously activated by impulses from a mass of neurones linked to both areas. It would be interesting indeed if agents could be found which have a selective convulsant action on particular subcortical centers, but the physiological mechanism would still require as careful analysis as that of the more diffusely acting convulsants.

B. Substances used primarily for other than central nervous system effects

1. Autonomic agents. During the past decade, considerable attention has been given to the role of acetylcholine in central synaptic transmission, and the search for a universal chemical mediator has generated many investigations of the effects of cholinergic and other autonomic drugs on the EEG. Indeed, the ability of any cholinergic drug or blocking agent to change the EEG is all too frequently seized upon as verification of an essential central role of acetylcholine, even when the most unphysiologically high concentrations are used. Despite these excesses, there is no doubt that acetylcholine and many agents which modify its actions or alter its rate of destruction may have profound effects on central nervous function, with corresponding repercussions in the EEG. The problem of the significance of acetylcholine in cerebral function has been recently reviewed by Feldberg (106) and Whitteridge (337), among others.

a. Acetylcholine: There has been no dearth of empirical observations on the effects of acetylcholine on the EEG, particularly of animals. Sjoestrand (300) found that acetylcholine topically applied to the cortex increased the amplitude of strychnine and eserine spikes and caused increased frequency and grouping of waves. Stronger concentrations or repeated applications inhibited the spikes. Bonnet and Bremer (28) and Bremer (41) injected small doses into the carotid artery of midbrain-transected cats and found increased amplitude and frequency of the dominant waking rhythm, and increased after-discharge following auditory stimuli. Larger doses had a depressant effect. Moruzzi (257) confirmed these observations in the rabbit, and also noted a decrease in electrical threshold. Miller *et al.* (254) found a desynchronizing effect of topically applied acetylcholine on the EEG of the cat, and a strychnine-like effect on the previously eserinized cortex. Chatfield and Dempsey (53) saw no effect with acetylcholine alone; but after prostigmine, which itself caused bursts, acetylcholine produced increased spiking and low voltage fast activity. The latter remained even after isolation of the cortex from the thalamus. Williams (344) found that acetylcholine and carbaminoylcholine produced petit mal-like activity in susceptible patients. Intracisternal injection of acetylcholine in cats and man produces generalized convulsions (45, 107, 114), as does intravenous injection of large doses (61, 174, 287). That these seizures are not necessarily due to direct action on central nervous system is suggested by the recent report of Ajmone-Marson and Fuortes (5) who studied the convulsions elicited in dogs by intravenous acetylcholine. The seizures were associated with flattening of the EEG rather than with convulsive discharges, and the changes were similar to those of asphyxiation, such as might be expected from the cardiac arrest produced by acetylcholine intravenously. The investigators give the same explanation for the hyperactivity of the spinal cord

seen under these conditions, and conclude that the observed convulsive movements are clearly not of cortical origin. However, this objection need not apply to focal or intracisternal injection of acetylcholine and other choline esters, and the work of Brenner and Merritt (45) and Forster (114) suggests that EEG and motor manifestations of these drugs may be elicited directly from the cortex.

In any consideration of the suspected functional role of a chemical substance, the relationship between the amount normally present and the amount required for the functional change should be in reasonable agreement. Such a comparison has been made by Bornstein (30), who found that acetylcholine perfused over the cortex of dogs and cats produced high amplitude sharp waves in low concentrations (1 μgm. per cent), whereas flattening of the EEG occurred with higher concentrations (2 μgm. per cent or more). Both of these EEG effects were also seen after experimental trauma to the head; the trauma was shown to result in the appearance of "free" acetylcholine in the cerebrospinal fluid in concentrations up to 9 μgm. per cent. The EEG and behavioral effects of both trauma and intracisternal acetylcholine could be abolished by the subcutaneous administration of atropine sulfate, 0.5 to 1.0 mgm/kg. Bornstein suggests that "free acetylcholine" may be one of the physiological factors underlying the acute paralytic and excitatory phenomena of cerebral concussion and more severe craniocerebral injuries.

b. Pilocarpine: In contrast to acetylcholine, pilocarpine in systemically effective concentrations was without EEG action in the patients examined by Williams (344) and in the cats studied by Miller *et al.* (254).

c. Anticholinesterases: If acetylcholine is present in the central nervous system in sufficient quantities to exert some physiological action, regardless of the essential role of this action, then those agents which retard the hydrolysis of acetylcholine by cholinesterase might be expected to produce functional central changes and associated EEG signs similar to those elicited by exogenous acetylcholine. In general, this appears to be the case, and the few reported differences in the action of the various anticholinesterases may tentatively be ascribed either to side-effects unrelated to cholinesterase inhibition or to differences in enzyme specificity or ability to penetrate cells. The most complete observations to date have been made with the reversible anticholinesterases eserine (physostigmine and neostigmine and the irreversible inhibitor di-isopropyl fluorophosphate (DFP).

(1). Di-isopropyl fluorophosphate: Extensive studies on the effects of di-isopropyl fluorophosphate (DFP) in man have been carried out by Grob and his associates (169, 170, 171, 175). The daily intramuscular injection of 1 to 2 mgm. of DFP in 23 subjects (19 normals, 4 with myasthenia gravis) resulted in increased electrical activity in 17, manifested by greater variation in amplitude, increased frequency, more beta activity, more irregularities in rhythm, and the intermittent appearance of abnormal high voltage 3–6 per second waves similar to those frequently seen in patient with convulsive disorders. These alterations were usually most marked in the frontal regions and were increased by hyperventilation. The most striking changes were observed in those subjects who showed greatest lability of pattern in their control records. The EEG signs ap-

peared after 2 to 7 days of DFP administration, usually following the onset of central nervous symptoms. After cessation of DFP administration, symptoms disappeared in 1 to 4 days, whereas EEG changes persisted in diminishing degree for eight to 42 days.

The EEG effects of DFP could be abolished temporarily by intravenous administration of atropine, or delayed considerably by chronic atropine therapy. In contrast, intravenous injection of neostigmine, curare or *d*-tubocurarine resulted in no change in the central nervous symptoms or EEG signs of DFP poisoning, although the doses of curare and *d*-tubocurarine were sufficient to cause weakness of the facial and ocular muscles, and the amount of neostigmine was adequate to produce gastrointestinal effects.

The onset of central nervous symptoms and the appearance of EEG changes after DFP could usually be correlated with a depression of red blood cell cholinesterase activity to 70% and 60% respectively of the original activity, when DFP was administered over a relatively short period (up to 3 days). However, when DFP was administered over a longer period of time or when administration was stopped, correlation between central nervous effects and erythrocyte cholinesterase activity no longer existed. The onset and severity of symptoms and EEG changes bore no relationship to the cholinesterase activity of the plasma.

The mode of action of DFP was considered by Grob and associates to be the irreversible inhibition of the central nervous system by DFP cholinesterase. The persistence of the EEG changes for as long as three to four weeks after the last dose of the drug probably reflects the slow regeneration of brain cholinesterase. The lack of correlation of DFP effects with erythrocyte cholinesterase activity after the first few days presumably is due to the different rates of regeneration of the cholinesterases in the central nervous system and in the red blood cells. Because neostigmine could not be given in amounts sufficient to duplicate or potentiate the central effects of DFP without causing gastrointestinal distress, the authors conclude that the greater lipid solubility of DFP favors its selective action upon the central nervous system. However, the possibility of a difference in enzymatic structure or in rate of regeneration at the two sites should not be automatically excluded.

The EEG effects of DFP have been further analyzed in experimental animals. In the cat and monkey Wescoe *et al.* (335) observed an increase in frequency and a decrease in amplitude of cortical discharges within one minute after intravenous injection of DFP. These effects could be abolished or prevented by the intravenous administration of atropine or scopolamine. Intracarotid injection of DFP in the curarized rabbit was found by Himwich and his colleagues (115, 172) to result in a slight decrease in fundamental frequency accompanied by a decrease in voltage, followed by the appearance of high amplitude discharges. These occurred first on the side of injection and then became generalized and persistent, resembling the pattern of status grand mal. Small doses of atropine administered after the high amplitude discharges had become established restored the pattern to normal; larger doses of atropine injected prior to the administration of DFP prevented the high amplitude waves, and a further increase in dosage eliminated

all abnormal responses. The electrical changes induced by DFP were associated with a severe depression of anticholinesterase activity of the cerebral hemispheres, the cerebellum and the brain stem, but in no instance was the cholinesterase activity completely eliminated.

(2). Eserine and neostigmine: The reversible anticholinesterases also have been shown to cause EEG changes resembling those seen with acetylcholine. Sjoestrand (300) reported a potentiation of strychnine spikes by eserine in the EEG of experimental animals. Miller *et al.* (253, 254) observed a reduction of voltage and a dissociation of previously synchronized cortical waves in the EEG of the rabbit and cat after topical application of eserine, and Chatfield and Dempsey (53) observed a similar initial depression of voltage with neostigmine. Darrow *et al.* (73) found that eserine prevented hyperventilation-induced slow waves in cats whose parasympathetic innervation to pial vessels had been cut.

In patients with petit mal, Williams and Russell (345) have demonstrated an interesting difference between eserine and neostigmine, the former decreasing and the latter increasing the incidence of spike and wave discharges. To explain this paradox they have invoked Schweitzer's (296) schema in which eserine (as a fat-soluble tertiary ammonium base) excites by penetrating the neurone soma, whereas neostigmine (as a water-soluble quaternary base) inhibits at the synapse. This explanation is somewhat compromised by the many and apparently inconsistent similarities and differences in the action of the two drugs as reported by various other investigators (106).

d. Atropine: Of the various drugs which can inhibit the action of acetylcholine upon effector cells, atropine is the only one which is consistently reported effective in studies on central neurones. Feldberg (106) has reviewed a large body of evidence for a blocking action of atropine against the effects of cholinergic and anticholinesterasic agents at all levels of the central nervous system. That the blocking action of atropine is often exhibited in concentrations which alone have little or no effect on normal central functions suggests no vital role of endogenous acetylcholine in the ordinary activities of the brain. However, reports of direct actions of atropine upon the EEG have not been lacking. Grob *et al.* (169) found that the intravenous administration of 1.2 mgm. of atropine to 39 normal subjects resulted in an immediate decrease in frequency and voltage, with decreased beta and increased alpha rhythm, a decrease in the irregularities of the rhythm and a decrease in the appearance of abnormal slow waves during hyperventilation in over one third of the subjects. The same dose of atropine in 16 subjects with a history of grand mal and with an EEG pattern "characteristic of this disease" resulted in some reduction of abnormal discharges and of amplitude in one half of the subjects. These changes, which occurred immediately following intravenous injection, were in the same direction as those occurring both in control subjects and in those who had received DFP, but were less marked than in the latter group and were dramatic in only one case.

Increased EEG activity following DFP was inhibited by atropine in all 17 subjects studied by Grob *et al.* (169). Intravenous injection of 1.2 mgm. of atropine resulted in an immediate decrease in potential and frequency, with decreased beta

and increased alpha rhythm, a decrease in the irregularities of the rhythm, and decrease in the incidence of abnormal waves at rest and during hyperventilation. Daily administration of atropine concomitant with daily administration of DFP delayed the onset of both central nervous symptoms and EEG changes, the former for a few days and the latter for as long as three to four weeks, at which time the erythrocyte cholinesterase activity had been reduced to 33% of the original activity. Some of the subjects who had received atropine and DFP daily for several weeks had pronounced central nervous symptoms despite the absence of EEG changes. Withdrawal of atropine was followed within several days by the appearance of EEG abnormalities.

Williams (343, 344) found that spontaneous and hyperventilation-induced spike and wave paroxysms were sometimes blocked by atropine in patients with petit mal, and that atropine prevented the exacerbation of these attacks by acetylcholine and other cholinergic agents. On the other hand Darrow *et al.* (74) observed an increase in hyperventilation-induced slow waves and in various resting abnormalities in patients who were given sufficient atropine to cause cardiac acceleration, although the EEG was sometimes improved when the systemic actions of atropine were incomplete.

Not all investigators have been able to demonstrate an atropine blockade of the EEG effects of cholinergic agents. In the studies of Forster (114), atropine failed to prevent the initial depression and ultimate paroxysmal EEG effects of intracisternally or topically applied acetylcholine in the cat. Brenner and Merritt (45) also were unable to prevent cholinergically-induced convulsive EEG discharges with atropine. On the other hand, Chatfield and Dempsey (53) abolished acetylcholine-induced spikes in the EEG of the cat by giving atropine intravenously. Miller *et al.* (254) also found that spikes occurring after local application of eserine and acetylcholine were suppressed by intravenous injected or locally applied atropine. Atropine itself produced unusual EEG abnormalities when applied locally. Darrow *et al.* (73) observed that after a sufficient dose of atropine, hyperventilation caused the appearance of high voltage slow waves in cats. They also found that atropine restored the hyperventilation dysrhythmia when it had been blocked by eserine. Finally, Bornstein (30) observed that atropine prevented the EEG effects of both concussion and exogenous acetylcholine in cats.

c. Curariform agents: If central synaptic transmission were dependent upon the same chemical mechanism as that in autonomic ganglia and the neuromyal junction, curare would be expected to have significant central blocking actions. However, a definitive experiment demonstrating the lack of cerebral effects of curare in man was conducted by Smith and his colleagues (301). These observers administered a total of 500 units of *d*-tubocurarine intravenously to a healthy trained adult during a period of 33 minutes, an amount at least $2\frac{1}{2}$ times that required to produce complete respiratory paralysis, and adequate for complete skeletal muscular paralysis. No impairment of consciousness, memory or sensorium was observed; likewise, no evidence was obtained of central stimulant, depressant or analgesic properties of curare. The amplitude, frequency and per-

centage time alpha of the EEG remained unchanged, and blocking of the alpha rhythm by pattern vision remained normal. A total of 3.5 mgm. of neostigmine, given intravenously to facilitate recovery, also failed to alter the EEG.

Some animal observations have suggested central actions of curare. McIntyre (247, 248, 249) reported that *d*-tubocurarine modifies the electrical activity of the brain of dogs lightly anesthetized with various barbiturates. He noted an initial transient increase in activity simultaneously in the occipital, parietal and frontal regions, with as much as a three-fold increase in voltage. The frequency was irregular, sometimes exhibiting spikes followed by low voltage 100/sec. activity. Immediately thereafter, electrocortical activity was depressed, even with doses insufficient to prevent diaphragmatic respiration. With larger doses the electrical activity of the frontal areas was decreased very rapidly and the initial transient stimulation was very brief. Depression of the frontal areas occurred before peripheral paralysis. Since adequate details of experimental technic were not presented, it is not clear whether the barbiturates were in part responsible for the results, or whether some degree of hypoxia occurred.

When the complicating factor of respiratory depression and secondary anoxia is avoided by adequate artificial ventilation, most investigators find no effect of curare on the EEG (102, 103, 143, 144, 317). Everett (102) observed no demonstrable effect on the EEG of cats, rats and rabbits, given curare in doses 5 to 50 times greater than necessary to produce respiratory paralysis. Furthermore, a convulsive dose of metrazol after curarization produced a typical seizure discharge although all motor manifestations were absent and the electromyograph showed no spikes. Also, no change in electroshock threshold is produced by curare. On the other hand, Everett (103) found that curare given intracisternally could produce violent convulsions in rabbits. The effect was similar to that of penicillin, which causes convulsions following local application to the brain but not following intravenous administration. There have been no systematic studies of the possible protective action of curare against central effects of cholinergic drugs equivalent to the investigations conducted with atropine. However, the incidental use of curariform agents to immobilize animals for EEG records apparently does not militate against the characteristic effects of acetylcholine or cholinergic agents (73).

One group of investigators (105, 273) has consistently found blocking effects of curariform drugs on the EEG of the frog, in doses equal to or more than necessary to cause a reversible neuromuscular paralysis. Curare, *d*-tubocurarine chloride and dihydro-beta-erythroidine hydrochloride all caused a depression of cortical activity which could not be restored by neostigmine, strychnine or picrotoxin. Quinine ethochloride, nicotine and thiamine likewise flattened the EEG after an initial acceleration of frequency, and neostigmine was of no avail in reviving the silent hemispheres. A more analytical reinvestigation of these findings would be of interest.

f. Epinephrine: The attention given to the action of epinephrine upon the EEG has been disproportionately small in comparison with that lavished upon the more popular neurohumor acetylcholine, despite the fact that the latter substance

has not been conclusively demonstrated to produce central changes other than through a vascular action. Among sporadic studies with the adrenergic mediator are those of Grinker and Serota (168) who recorded increased fast and random slow activity with disappearance of the alpha rhythm in the hypothalamus as well as the cortex of patients receiving intravenous epinephrine. Schizophrenic patients were found less responsive than controls to the psychic and EEG effects of epinephrine. The newer sympathetic blocking agents, especially dibenamine, have been shown to produce interesting central effects, but these may in some cases be nonspecific and obtainable with the autonomically inactive degradation products (262).

g. Histamine and antihistaminics: Because of the possible role of vascular lesions in the etiology of convulsive and other central nervous disorders with EEG manifestations, and the presumed role of histamine in various inflammatory reactions, the effects of antihistaminics on the EEG are worthy of consideration. Churchill and Gammon (58) have observed that diphenhydramine can reduce the frequency of attacks in patients with petit mal, with a corresponding reduction in the incidence of spike and wave discharges in the EEG, whereas tripelennamine has the opposite effect. In this connection it should be noted that diphenhydramine has been generally reported to have more sedative and other central nervous actions than tripelennamine for equivalent antihistaminic effects. Swinyard (313) has observed that both drugs have some anticonvulsant effect on rats in doses which otherwise produce no gross neurological effects, and that both produce signs of excitation in the central nervous system when given in larger doses. However, tripelennamine may cause the appearance of recurrent spontaneous seizures following an initial electroshock seizure, whereas this effect has not been seen with diphenhydramine. This differentiation between the two antihistaminics may have some relevance to the clinical observations of Churchill and Gammon. Histamine itself even in doses causing severe symptoms was without effect on the EEG of petit mal patients studied by Williams (343), in contrast to the sensitivity of these patients to acetylcholine and anticholinesterases.

In concluding this discussion on the EEG effects of autonomic drugs, the reviewers feel impelled to point out a remarkable contrast between the almost purely empirical data collated for these agents and the more analytical investigations which have been devoted to other drugs such as the barbiturates, for which plausible mechanisms of action could not so readily be assumed *a priori*. The result is that we have as yet no useful body of measurements on parameters of excitation and response against which to equate the observed EEG effects of these agents. Neither is there any body of knowledge which can be transposed from the periphery to the central nervous system to provide a working hypothesis for the interpretation of cortical electrical activity. Peripheral nerve cannot be used in this case to build a working model of the central nerve net, since the autonomic drugs, for example acetylcholine, are for the most part inactive on peripheral nerve (238). When they are effective in high concentrations, their actions may be attributable to side-effects which bear no relation to their *in vivo* specificity, as in the case of nerve conduction block by DFP (50, 52, 67, 281, 323). Even in the

case of neuroeffector junctions and autonomic ganglia, the attention of investigators has been occupied with the fact of chemical mediation rather than the intimate mechanism of activation or inhibition of the effector or post-synaptic cell. Since the central effects of autonomic agents cannot be inferred automatically from our present knowledge of peripheral fibers and synapses, it devolves upon the neuropharmacologist to approach the problem of the central action of a particular autonomic drug with as much variety of procedure, precaution and imagination as if the substance were new and unfamiliar.

In summary, the literature in general suggests that acetylcholine administered by various routes to man and animals may have excitant effects ranging from increasing frequency of EEG rhythms and facilitation of cortical excitation to seizure discharges in the EEG and frank motor convulsions. Depressant effects are occasionally reported, particularly with higher concentrations. These effects are potentiated by the prior administration of the common anticholinesterases, which by themselves may produce central responses not unlike those to acetylcholine, although certain discrepancies in their actions cast some doubt upon an identical and sole anticholinesterasic mechanism of action. Finally, the excitant or depressant effects of the cholinergic substances and anticholinesterases are usually found to be abolished by atropine in doses which alone may not significantly influence the normal EEG or produce neurological manifestations. Other anticholinergic drugs such as curare do not appear to have significant central effects comparable to atropine. These considerations should cast some suspicion on the concept that acetylcholine is the chemical mediator at central synapses rather than merely an auxiliary agent which acts indirectly, perhaps through its effect upon the vascular supply of the brain. Of other possible chemical mediators, neither histamine nor epinephrine has received enough attention to justify any conclusion regarding their role, if any, in central synaptic transmission.

2. Metabolic agents. To what extent does the EEG reflect changes in cerebral metabolism? Throughout much of the literature on the electrical activity of the brain, there runs a strong thread of conviction that the frequency and amplitude of the recorded brain potentials are manifestations of the rates and magnitudes of underlying chemical processes, and that those drugs which modify the EEG do so by alteration of metabolic events (135). In a very general sense this is undoubtedly true, but the temptation is sometimes strong to oversimplify, for example, by considering cortical frequencies to be functions only of oxidative metabolic rates. That the situation must be more complicated is suggested by a brief consideration of the relation between function and metabolism in peripheral neurones as shown particularly by the work of Lorente de Nó (238). Oxygen is necessary for the maintenance of a membrane potential, which must be held above a critical value if excitation and propagation of impulses is to occur. However, the membrane potential may be experimentally restored by anodal polarization after nerves have been made non-conductive by anoxia or by metabolic blocking agents, and the nerve is then excitable and able to propagate impulses. Excitability is lost in the absence of sodium (and no other) ion even if membrane potential is maintained. No exogenous substance other than oxygen is required

for maintenance of membrane potential, since endogenous stores of metabolites may be drawn upon. Depolarization by anoxia or by inhibition of oxidative metabolism is not associated with changes in threshold until the critical point of conduction block is reached. Other aspects of function, such as the recovery process, are more sensitive to metabolic interference than those immediately concerned with impulse propagation. Carbon dioxide at physiological tensions maintains a greater membrane potential, a higher threshold and a great stability of the membrane against spontaneous firing or the effects of various excitant substances. Changes in environmental temperature produce complex effects which indicate that different temperature coefficients of underlying processes are concerned in several aspects of nerve function. Many substances act upon nerve in a manner not obviously related to oxidative metabolism.

The above are some of the metabolic factors which apply to relatively rugged large myelinated fibers. The situation is certainly more complicated for the more sensitive neurones of the central nervous system, with their higher metabolic rate and their requirement for exogenous metabolites. Therefore a simple and universal relationship between cerebral cortical function as represented by frequencies of EEG rhythms and the rates of underlying chemical processes should not be expected, and by the same token metabolic effects should not be assumed *a priori* for drugs which alter cortical rhythms.

Alteration in body temperature may be taken as one of the simple nonpharmacological methods for altering the rates of chemical processes in the brain. Hoagland (184, 185, 186, 187) found a simple linear relation between the logarithm of the frequency of the dominant EEG rhythm 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 intermediate carbohydrate metabolism studied *in vitro*. The lower temperature coefficients were characteristic of normal subjects and the higher of advanced cases of general paresis. The results seemed to indicate that the alpha rhythm was a simple indication of metabolic rate determined by a limiting chemical pacemaker reaction, and to reveal changes in the limiting reaction in disease. However, Greenblatt and Rose (164) found complex changes in the EEG of patients with neurosyphilis treated with fever induced by typhoid vaccine or malaria. In the majority of these records alterations consisted of an increase in the irregularity of the pattern with increased amplitude and number of slow waves. A few fever records presented both rapid and slow activity, but with the slow activity dominating the pattern. Decline in fever resulted in the gradual resumption of the original characteristics. The authors found more marked changes in the EEG with a more rapid rise in temperature and with the higher final elevations of fever. In addition, the more severe the clinical picture of the disease the more marked were the changes elicited by fever therapy. Thus the manner of altering body temperature as well as the status of the patient enters into the EEG findings, and there seems to be no doubt but that the EEG can be grossly and qualitatively altered at the extreme tolerated limits of the temperature scale.

With this introductory note of caution, some of the EEG findings associated with gross metabolic changes, alterations in respiratory gas tensions and blood sugar, and the effects of metabolic blocking agents will now be considered.

a. Thyroid: A correlation between the alpha frequency and the basal metabolic rate was found by Lindsley and Rubenstein (232); the administration of thyroxin to one subject over a period of three days increased the metabolic rate from 53.7 to 59.0 Calories per hour and increased the frequency of the alpha waves from 10.5–11.4 per second. Examination of the alpha rhythm in patients with various thyroid disorders has likewise revealed a direct relationship between basal metabolism and the rate of cortical discharge. Bertrand *et al.* (23, 24) found a correlation between the alpha frequency and the basal metabolic rate in individuals with hypothyroidism, and Ross and Schwab (286), in 80 determinations of the dominant EEG frequency in a group of patients with thyroid disorders, found good correlation to exist within the whole group, which suggested a simple relation between the alpha rate and the metabolic state of the individual. Other authors (135, 181) have confirmed these observations in both hypo- and hyperthyroidism. Hoagland *et al.* (187, 289) found that increase in the metabolic rate was associated with a rise in alpha frequency following the administration of large doses of thyroxin intravenously for a period of 4 weeks.

b. Dinitrophenol: Dinitrophenol, a specific metabolic stimulant, has likewise been observed by Hoagland *et al.* (182, 191) to cause an increase in the alpha frequency, the progressive and continuous acceleration tending to confirm the view that the frequencies are a measure of cortical respiration under these conditions.

c. Anoxia: The effect of oxygen lack on the human EEG has usually been reported as a slowing of frequency, and has often been taken to indicate a direct relation between oxygen uptake and dominant EEG frequency. The literature has been reviewed by Brazier (31, 33). Her own investigations (33) indicate that with increasing depths of anoxia there is a progressive slowing of the alpha rhythm, suggestive of deceleration of the synchronized beat of a uniform neurone population, as long as consciousness is retained. With the onset of unconsciousness there is an abrupt appearance of slow activity, suggesting the disorganization or depression of cortical rhythms in such a way as to release slow rhythms originating from subcortical structures. These findings agree in a general way with those of previous investigators, although a number of variations on this theme have been reported. Berger (22) was impressed more by the irregularity of the alpha rhythm than by any change in frequency prior to the onset of slow activity during anoxia, and Lindsley and Rubenstein (232) also failed to find any consistent change in frequency or amplitude of alpha rhythm during moderate anoxia.

Davis *et al.* (82) observed the following more detailed sequence in subjects breathing 8 to 11 per cent oxygen mixtures: at first there was a slight increase in average voltage, with the appearance of alpha waves in those records which had originally shown none; then the alpha voltage decreased, the alpha trains were reduced in duration and the intervals between them became longer; 7 to 8 per

second activity began at the vertex while 10 per second alpha continued at the occiput; with the development of slight cyanosis and the first subjective changes, irregular slow waves appeared at the vertex and almost immediately thereafter at the occiput, alternating with a 10 per second rhythm; finally, after 10 to 15 minutes of hypoxia, slow waves dominated the record, and consciousness was definitely lost in some subjects. An abrupt transition from slow waves to alpha rhythm occurred promptly on restoration to room air. Thus the records of Davis *et al.* are more indicative of qualitative transitions than of progressive continuous slowing of frequency. Gibbs *et al.* (133, 140, 142), who observed that alpha rhythm was maintained at relatively normal frequency up to the point of unconsciousness during anoxia provided that the pCO_2 of the internal jugular blood was maintained at normal levels, have pointed to the role of cerebral acapnia during hypoxic overventilation as a factor in the slowing of cerebral rhythms.

Among those who have emphasized a progressive slowing of frequency during anoxia are Hoagland (187) and Engel *et al.* (97, 100), using manual methods of frequency analysis, and Brazier *et al.* (32, 33, 109), using the Walter method of frequency analysis (330). It is interesting to note that the shifts in frequency reported by this latter group are not very great and are increased by a fall in pCO_2. The alternative method of frequency analysis devised by Grass and Gibbs (160) shows a maintenance of frequency of the dominant alpha peak with some reduction in height of this component, associated with an increase in the energy distributed through lower frequency bands.

Thus the controversy concerning the effects of anoxia on the human EEG is based to a considerable extent on the method of interpretation of frequencies and will probably not be resolved until single unit discharges can be analyzed experimentally. Meanwhile the conclusion may be drawn that there is an average slowing of frequency based in part on a small change in frequency of particular components and in part on the entry of new slower components in the composite record. The variations in results reported by different investigators may depend in part on the method of frequency analysis, the area from which recording was taken, and the degree of hypocapnia associated with hypoxic overventilation, which is notoriously variable in man.

More severe degrees of anoxia than are feasible in man have been studied in experimental animals. Bremer and Thomas (44) observed a period of sleep-like activity in the EEG of the midbrain-transected cat preceding complete suppression of the EEG by asphyxiation. Sugar and Gerard (309) recorded the electrical activity of the cortex and various subcortical structures of the cat during and following a period of ischemia of the brain. In the motor cortex they observed an early increase in frequency and amplitude of the dominant activity of the EEG, associated with such motor signs as hyperpnea and convulsive movements. The fast activity was replaced by 1–3 per second slow activity before complete suppression of the EEG. On restoration of the blood supply, slow waves reappeared first, followed by bursts of unusual spindle activity of 6–9 per second and high amplitude, preceding the return of normal fast activity. A similar sequence was seen qualitatively in various subcortical regions, the functionally lower and less

complex centers requiring a longer period of ischemia. Throughout the brain fast activity was more susceptible than slow waves to ischemia, except for the initial transient increase in fast waves noted early in the records. Increased synchronization of various brain areas was noted during moderate ischemia.

Gellhorn and Heymans (123) compared the effects of anoxia and asphyxia on the EEG of dogs and cats. Simple anoxia produced by ventilation with low oxygen gas mixtures failed to produce the initial increase in fast activity noted with asphyxiation. Convulsive spikes evoked by strychnine were more vulnerable to suppression by anoxia or asphyxia than was the prevailing background activity. Since carbon dioxide alone produced increased frequency and amplitude of both normal and convulsive potentials, it is evident that the initial acceleration of activity during asphyxia should not be attributed to oxygen lack (309). A "rebound" phase of increased excitability and electrical activity was seen during the recovery period. Gellhorn (120) has also presented evidence that under conditions of asphyxia and anoxia the hypothalamus and thalamus may act as pacemakers of cortical activity.

Although Sugar and Gerard (309) had found that slow activity was more resistant than fast potentials to asphyxia, this relation does not appear to hold for recovery after prolonged asphyxia. Van Harreveld (173) found that after 15 minutes or less of asphyxiation, bursts of 7–12 per second activity similar to those found in sleep were the characteristic feature of the EEG of the cat. They were considered to be of cortical origin because of their asynchrony in various EEG leads, but the possibility of a mosaic subcortical origin should also have been considered. After more than 15 minutes of asphyxial suppression of the EEG, the typical activity on recovery consisted of smooth sinusoidal spindles of 12–16 per second frequency, synchronous throughout the cortex and presumably of subcortical origin.

As an illustration that neurones at all levels of the nervous system do not behave identically, attention should be called to the research of Brooks and Eccles (48) on the effects of asphyxia and anoxia on monosynaptic transmission in the spinal cord of the cat. Their results are the inverse of those of Gellhorn on the cerebral cortex. They found that anoxia produced a phase of hyperexcitability associated with progressive depolarization until the critical point for synaptic failure was reached. A period of depression followed the readmission of oxygen. Asphyxia was similar in effect except for a transient initial depression, and carbon dioxide had a purely depressant action. The direct effects of anoxia on peripheral nerve, as observed by Wright (347) and Lorente de Nó (238), do not seem to include marked changes in threshold until the degree of depolarization becomes critical.

d. Hyperoxia: Detailed reviews of the effects of excessive oxygen on the nervous system have been published by Stadie *et al.* (303) and Bean (12). In laboratory animals, convulsive activity is a characteristic feature of the effect of oxygen pressures considerably in excess of one atmosphere. EEG observations on the effects of compression are largely limited to the work of Cohn and Gersh (63) who studied the effects of oxygen poisoning in cats confined in pressure tanks.

With oxygen at atmospheric pressure, the records were essentially unchanged from those observed in room air. After one minute under a pressure of 8 atmospheres, high voltage slow discharges appeared, superimposed on the 20 per second activity observed under control conditions. The convulsive phase began with an increase in the number of high voltage slow waves, then high voltage 15–18 per second discharges appeared, and finally after 6 minutes a typical seizure pattern occurred and was repeated for several minutes. The seizures could be prevented by pretreatment with anticonvulsant drugs (270). The investigators considered the ultimate cause of seizures during oxygen poisoning to be damage to the metabolic system of nerve cells, perhaps to enzymes having SH groups, and to a consequent reduction in threshold. Since oxygen poisoning is apparently associated with increases in blood and brain glucose, pO_2, pCO_2, and acidity, all of which militate against the appearance of slow waves in the EEG, the early appearance of slow activity was attributed to some basic intracellular change rather than to the gross secondary alterations in the internal environment. The specificity of oxygen excess for particular enzyme systems is still to be worked out in relation to the observed neurological syndrome of oxygen poisoning.

e. Carbon dioxide: It has long been recognized that changes in CO_2 tension have important effects upon central nervous function, and those alterations produced by hyperventilation have been of particular interest to the electroencephalographer because of the ease with which paroxysmal dysrhythmias can be precipitated by overbreathing in some types of convulsive disorder. The subject has been reviewed by Brazier (31) and will be dealt only a glancing blow in the present discussion.

Foerster (111) is usually given credit for the demonstration that epileptic attacks can sometimes be elicited by hyperventilation, and before the advent of electroencephalography this diagnostic method had already been used critically by Lennox (219) in petit mal. In one of his classical studies, Berger (22) elicited high voltage slow wave discharges preceding a major seizure in one patient with a previous history of attacks. It has gradually been established that seizures of the petit mal triad rather than convulsive disorders in general are sensitive to small charges in CO_2 tension (139, 218, 219, 221, 224); however, other types of attack or EEG abnormalities may occasionally be induced by prolonged hyperventilation (46, 282), and occasional atypical forms of petit mal are resistant to hyperventilation or CO_2 excess in spite of the presence of a typical 3 per second spike and wave dysrhythmia (317).

The effects of overventilation on the normal EEG are usually reported as slowing of frequency, with the appearance of high voltage 3–6 per second slow wave discharges particularly in the frontal leads in some patients. In the experience of the reviewers, these paroxysms are found in about 10 per cent of healthy male medical students. They are more easily elicited in infants and children, decline in incidence with advancing age (139, 229), are easier to invoke at low blood sugar levels (36, 81, 180, 294, 307), and are subject to modification by anoxia and other metabolic variables (76, 77, 94, 97, 122). The dependence of hyperventilation-induced changes in the EEG upon cerebral blood flow has been established by

Gibbs *et al.* (129, 140, 225) who recorded the EEG responses during overbreathing or CO_2 inhalation while making simultaneous determinations of CO_2 content, pH, CO_2 tension and oxygen saturation of arterial and venous blood. The dilatation or constriction of cerebral arterioles which follows an increase or decrease of CO_2 in arterial blood normally serves to protect the brain against an undue shift of CO_2 tension. The slow waves that appear in the EEG with hyperventilation are concluded by these investigators to be caused by a drop in CO_2, not by anoxia secondary to cerebral vasoconstriction as had been previously postulated (76, 77, 129). The ease with which slow waves can be evoked by hyperventilation is a rough index of the relative incompetence of the cerebral vasoconstrictor response to a low CO_2 tension.

The effects of inhalation of CO_2 on the human EEG are usually described as an increase in frequency of cortical potentials (126, 142, 215, 224). The experimental literature does not show good agreement as to the EEG and other central nervous effects of changes in CO_2 tension. An excitatory effect of CO_2 has been described, evidenced by an increase in frequency both of background activity and of convulsive potentials (123). However, some investigators have reported a protective effect of carbon dioxide inhalation against metrazol (125) and strychnine (209) seizures, whereas others (179, 201) have found that convulsive metrazol discharges are singularly unresponsive to hyperventilation, CO_2 inhalation, and intravenous injection of acid or alkaline solutions. As for the normal EEG of animals, it has been reported that metabolic or respiratory alkalosis increases spontaneous cortical activity and decreases the threshold for afterdischarge while acidosis has the opposite effects (92). But others have found that severe acid-base changes are required to produce EEG abnormalities (240) or changes in seizure threshold (179).

To the extent that conclusions can be drawn from these observations, it seems clear that alterations in the EEG or in excitability are relatively difficult to evoke by acid-base changes, are more related to pCO_2 than to corresponding pH changes effected by other procedures, and are in the direction of increased EEG frequency and amplitude and decreased electrical threshold when the pCO_2 is reduced. These changes are what might be expected from the behavior of peripheral neurones, which show increased excitability to low CO_2 (213), dependent upon the pCO_2 itself rather than the induced pH change (238). Although increased pCO_2 in the absence of pH changes tends to raise threshold and prevent spontaneous firing in nerve (238), there are associated changes, such as increased amplitude of action potentials and after-potentials with associated changes in the post-firing recovery of excitability, which might complicate the behavior of a neural network. The sensitivity of various central neurones to acid-base changes varies widely (208). As an example of the extreme contrast to be found in the central nervous system, CO_2 has a purely depressant action on spinal motorneurones (48), but it increases discharges from the inspiratory center of the medulla (304).

If one important lesson can be drawn from the literature on the effects of CO_2 on the EEG, it is that the petit mal 3 per second spike and wave discharges are

far more sensitive to pCO_2 than is any other type of cortical electrical activity. While for a long time there was a tendency to ascribe petit mal to diffuse changes in cerebral function, there has been a recent revival of the Jacksonian principle that different seizure types arise from the different anatomical foci, and this concept has led to a clinical and experimental search for a subcortical origin of petit mal discharges (200). If such centers can be identified with certainty, it would be most interesting to determine whether they show unusual sensitivity to changes in pCO_2, and whether this is an attribute of the neurones as such or a result of peculiarities of their vascular supply.

f. Ketogenic diet: Although numerous clinical reports of the antiepileptic effects of the ketogenic diet have been published, few data concerning its effect on the EEG have appeared. Logan and Baldes (236) reported that there was a good correlation between clinical and EEG improvement in a series of 10 patients with convulsive disorders treated by ketogenic diet. Hoffman (196) has obtained records from 20 epileptic children with spike-wave dysrhythmias before and during their preliminary fast and at intervals thereafter while they were receiving a ketogenic diet. During the third, fourth and fifth days of fasting and at the time when hypoglycemia, ketosis and acidosis were most pronounced, EEG frequencies became slower, with a high voltage 3 per second rhythm predominating. As this phase gave way to compensated ketosis, frequency and amplitude returned toward normal, and a more prolonged period of hyperventilation was required to bring out the characteristic spike and wave picture than in the control period. When the diet successfully controlled seizures over a long period, the paroxysmal dysrhythmia disappeared from the resting record and could not be restored by hyperventilation.

The reviewers (317) have looked unsuccessfully for changes in the properties of peripheral nerve after immersion in high concentrations of several substances which have been considered by various authors as the effective therapeutic agents resulting from a ketogenic diet, including glycerol, beta-hydroxy butyric acid, acetone and acetoacetic acid.

g. Blood sugar: Interest in the EEG effects of insulin and blood sugar changes has been heightened by the wide use of insulin hypoglycemia in the shock treatment of the major psychoses. Numerous investigators (9, 35, 80, 81, 100, 145, 188, 190, 192, 215) have observed progressive slowing of the dominant frequencies associated with lowering of the blood sugar level, followed by the abrupt appearance of very slow waves as the patient lapsed into coma.

A direct relationship has been found by Himwich, Hoagland, and their colleagues between the frequency of the alpha waves and the cerebral oxygen consumption; both decline during hypoglycemia and increase after the administration of carbohydrate. Conversely, the delta index, a measure of the percentage time and amplitude of irregular high voltage slow waves, displays an inverse relationship to the blood sugar concentration and the oxygen utilization of the brain. These relationships are thought to indicate that the slowing of the EEG depends upon a progressive decrease in cerebral metabolism when the concentration of the principal substrate is reduced (182, 183, 188).

In contrast to the effects of hypoglycemia, Brazier *et al.* (35) have found that above 130 mgm. per cent further elevation of the blood sugar fails to alter the EEG of the normal adult. Abnormal records may be more sensitive to hyperglycemia, since Lennox and the Gibbs (137, 138, 224) have demonstrated that elevation of the blood sugar concentration tends to prevent the 3 per second spike and wave discharges of petit mal. This finding is of some practical importance in the establishment of relatively basal conditions for EEG recording. Failure to take into account the postprandial biphasic variation in blood sugar may be a source of uncontrolled variability in the incidence of EEG abnormalities and may give a false impression of the effectiveness of drug or other therapy.

The tendency for a low blood sugar level to increase the sensitivity to hyperventilation has been reported by several investigators (36, 180, 294, 307) Gibbs, Gibbs and Lennox (137, 138) have pointed out that abnormal discharges which were affected by variations in the blood sugar level (particularly the 3 per second spike and wave of petit mal) also generally responded to variation in the CO_2 and vice versa.

A summation of the central effects of oxygen lack and hypoglycemia has been demonstrated clinically and experimentally by Gellhorn *et al.* (119, 124). For example, in rats and cats whose blood sugar level had been reduced by insulin to the point where slow activity dominated the EEG, the administration of pure oxygen could restore the normal activity, whereas inhalation of 7 to 8% oxygen mixtures, which normally had no EEG effect, could abolish the electrical activity of the cortex entirely. Sugar and Gerard (309) observed that insulin hyperglycemia hastened the EEG failure produced by cerebral ischemia in the brain of the cat.

Maddock *et al.* (241) have studied the effects of hypoglycemia produced by hepatectomy and evisceration of various laboratory animals, and found the EEG changes essentially similar to those produced by insulin. Utilizing this method to determine whether other substances could substitute for glucose in brain metabolism, they found that the EEG effects could be reversed by the intravenous administration of glucose, mannose and maltose, but not by fructose, galactose, hexose diphosphate (with or without adenylic acid), glyceric aldehyde, succinate, fumarate, pyruvate, glutamate, or mixtures of glyceric aldehyde and glutamate or of glutamate and pyruvate.

In addition to the acute effects of low blood sugar, the persistent EEG sequelae of repeated bouts of hypoglycemia have also been investigated. Knott and Gottlieb (206) concluded that the outstanding effect of a course of insulin shock treatments on EEGs taken one to 12 days after completion of a series of treatments was an increase in the alpha index, most prominent in the frontal areas. Some patients showed an increase of activity below 6 per second. Greenblatt *et al.* (163) found an incidence of more than 50 per cent abnormal EEGs during long-term observations of the effects of hypoglycemia on a group of diabetics who had suffered repeated insulin reactions.

To summarize, the effects of insulin hypoglycemia on the EEG include some degree of slowing of the dominant frequency and a sharp transition to slower

activity with the onset of coma; these charges are potentiated by anoxia and by low CO_2 tension. They are presumably related to a limitation of cerebral metabolism by restriction of the principal substrate, but the actual neural mechanism of slowing has not been experimentally defined.

h. Cyanide: The use of cyanide in the determination of circulation time in man has presented an opportunity for the study of the EEG effects of this ion. After intravenous injection, the arrival of cyanide in the arterial circulation is signalled by a brief hyperpnea, probably of carotid body origin, and EEG signs can be detected shortly thereafter. Rubin and Freeman (290) usually observed an increase in the amplitude, regularity and amount of alpha activity following the intravenous administration of 0.7 cc of two per cent sodium cyanide solution. In a few instances, the increase of alpha activity was followed by a decrease. In addition, higher frequencies became more predominant and slow, irregular rhythms tended to disappear, while the frequency remained unaltered. An initial slight decrease of alpha activity was observed in a few cases; in some instances, it remained unchanged. In two cases however, bursts of high voltage regular slow activity were seen. This is more in line with the experience of Lipton and Gibbs (233), who also recorded an initial increase in activity in the alpha range following rapid intravenous injection of unspecified small doses, but in addition saw high voltage 2–3 per second waves at the peak of drug action. With still higher doses, very slow activity at $\frac{1}{2}$–1 per second appeared, with a decrease in amplitude which sometimes proceeded to complete flattening of the record. When cyanide was given rapidly in sufficiently high dosage, sudden flattening occurred without preceding slowing.

In cats given a sufficiently large dose of cyanide, an interesting form of decerebrate rigidity occurs, often irreversibly. Ward and Wheatley (33) have investigated this phenomenon and found that it is based on swelling of the diencephalon secondary to circulatory changes and severe brain edema produced by the substance.

Since the cyanide ion is primarily an inhibitor of oxidative metabolism, it might be expected that the effects in all systems would be identical with those of anoxia. The accentuation of alpha rhythm described above in human patients indicates that the effects are not identical. Although the difference might be ascribed to the extra-cerebral (*e.g.*, carotid body) effects, Lorente de Nó (238) in his studies on peripheral nerve has observed an interesting action of cyanide in increasing the negative after potential. This and alterations in other properties of neurones indicate that cyanide, unlike anoxia, produces a relative increase in the labile fraction of the membrane potential even while typical anoxic depolarization is progressing. In other respects the ion acts simply as if it were an inhibitor of oxygen uptake.

i. Fluoroacetate: The rodenticide fluoroacetate offers a minor public health problem in that it is an occasional source of epileptiform seizures after accidental ingestion by man. The physiology, pharmacology and biochemistry of this substance have recently been reviewed in the most definitive fashion by Chenoweth (54), who has also made extensive EEG studies (56, 57). Fluoroacetate blocks

a number of metabolic reactions involving the acetate ion, but the ultimate manifestations of this common action vary widely from species to species, depending apparently on quantitative differences in various tissues in the effects of the disruption of intermediate carbohydrate metabolism (54, 55). In man, fluoroacetate poisoning may be manifested by epileptiform seizures, but death may result from cardiac failure as a result of ventricular fibrillation. Some species, such as dogs and rats, show predominantly central nervous effects, including convulsions and respiratory failure. Other species, such as the rabbit, show primary cardiac failure. Man and rhesus monkey are intermediate in response.

Chenoweth and St. John (56, 57) recorded the EEG of curarized dogs following the intravenous administration of fluoroacetate. The first changes observed were increases in frequency and amplitude of temporoparietal and occipital activity while frontal and cerebellar potentials remained unaffected. Two types of seizure patterns were observed in the EEG: a high frequency high voltage discharge of the kind commonly seen during major convulsions in human or animals, and a spike and wave type of discharge sometimes resembling superficially that of the paroxysmal dysrhythmia of petit mal in man. Chenoweth *et al.* have stressed this resemblance to clinical petit mal, but their records seem to indicate that the spike-wave discharges may be of many forms and may occur over a wide frequency range. Convulsive discharges in the EEG and convulsive motor manifestations could be prevented by treatment with barbiturates, anticonvulsants and carbon dioxide excess.

Ward (332) has recorded simultaneously the electrical activity of the cortex and subcortical structures following intravenous administration of fluoroacetate in cats. After a latent period of several hours characterized only by depression, seizure discharges began in the cortex, thalamus and hypothalamus, associated with motor manifestations. Hypothalamic slow activity occurred independently of that of the cortex, which showed waves or spike and wave formations of 3 to 8 per second, while the thalamic records were characterized by spikes of high frequency and low amplitude. The three centers were unsynchronized except that the thalamic spikes were modulated in synchrony with the cortical waves.

Among interesting findings related to fluoroacetate seizures, Chenoweth (54) points out that animals such as rabbits which do not convulse after intravenous administration of fluoroacetate in any dosage may be made to do so by intracranial injection. Fluoroacetate seizures are preceded by a progressive decrease in the threshold for electroshock convulsions. They are potentiated by neostigmine, which suggests but does not prove a role of acetylcholine in their production. The substance is not specific for higher centers, since local application to the cord or systemic administration after spinal transection may produce cord seizures following a period of accentuation of all spinal reflexes. Peripheral nerve treated with methyl fluoroacetate does not exhibit increased excitability; conduction is ultimately blocked following an increase in threshold.

The metabolic correlates of these actions have also been reviewed by Chenoweth (54). Gerard and his students (50a, 128) have shown that in frog brain the amplitude of the electrical activity and the oxygen consumption both may be re-

duced to about 50 per cent of normal by saturating doses of methyl fluoroacetate. However, the lack of enzymatic specificity is seen in the depression of activity of other enzymes such as cholinesterase. Of various carbohydrate intermediates, fumarate is most effective in preventing the effects of fluoroacetate. In frog nerve the resting oxygen uptake is depressed while the active rise during propagation of impulses is unaffected (30a, 89).

Chenoweth (54) emphasizes the parallelism in resistance of various species and tissues to fluoroacetate, anoxia and cyanide, based presumably on the importance of oxidative as against glycolytic metabolism in the maintenance of their function. The specific metabolic blocking action of fluoroacetate is apparently based on its close structural similarity to acetate ion, preventing both complete oxidation of acetate and its entry into the Krebs cycle. Thus, *in vitro* studies have shown that acetate accumulates from a pyruvate substrate with a fall in oxygen uptake, and the formation of succinate is blocked. Acetoacetate may still be formed from acetate but not vice versa,—apparently a mass action effect. Various foreign amines may be acetylated in the presence of the excess acetate, but acetylcholine formation is not altered.

In summary, the structural blocking action of fluoroacetate may result in convulsive manifestations and associated EEG changes, apparently in part through an increase in excitability which is seen throughout the central nervous system but not in peripheral nerve, although oxygen uptake of both brain and nerve is depressed. Obviously these effects are quite different from those of simple anoxia. Skillful use of such pharmacological tools as fluoroacetate brings promise of the early unraveling of many problems in the relation of specific enzyme systems to nervous function. It should of course be kept in mind that nonspecific side effects of blocking agents are the rule rather than the exception, and the specificity requires proof in each new experimental situation.

3. Miscellaneous agents and procedures. There are many casual reports in the literature concerning the EEG effects of substances which have not been further investigated in regard to their mechanism of action, either because of their apparent lack of theoretical or practical interest or because of the peculiar tenacity with which neuropharmacological research clings to comfortable channels until social urgency and new financial sources of aid to research cause the stream to overflow. Conversely, many substances for which other effects upon the central nervous system or upon peripheral nerve have been well described have failed to appear in the schedule of the busy electroencephalographer, sometimes even when their clinical usage is quite general. The resulting lack of tangency between empirical EEG effects and other neurological actions has been the subject of previous complaint in this review, and has discouraged the reviewers from any attempt to be complete and systematic until the field has matured considerably. Therefore, the remainder of this discussion will be devoted to a consideration of a few agents which have sufficient clinical or theoretical interest to merit further research on the mechanism of their action upon the EEG.

a. Water: The effects of hydration on the EEG have received attention only recently, although pitressin antidiuresis and forced water ingestion have been

used for many years to precipitate seizures for diagnostic purposes (250), and dehydration has long been known to have some therapeutic value in convulsive disorders (104). Wikler (342) recorded the EEG of 14 male patients who had no history or clinical evidence of epilepsy. After injection of pitressin and an intake of water sufficient to raise the body weight an average of three kg., half of the cases showed paroxysmal slow activity. This change was poorly correlated with the degree of hydration. No seizures were produced in this control series. The alpha frequency showed a tendency to slowing, but in only three instances was the degree of change greater than that expected from day to day variation. There was no significant change in the percentage time alpha activity. Cohn, Kolb and Mulder (65) attempted to validate the pitressin-water test in a group of 23 men, some of whom showed clinical and EEG evidence of a convulsive disorder, while the control series had no manifestations that supported the diagnosis of epilepsy. Of the 23 men, 20 showed a progressive increase in slow activity in the EEG regardless of previous history; of five patients who developed convulsive seizures, two manifested no preconvulsive changes during the procedure. Blier and Redlich (27) obtained somewhat more positive results with the pitressin water test in three groups of patients with initially normal EEG records. After hydration, three of the 11 patients with a definite history of convulsive seizures revealed paroxysmal EEG changes, including fast activity, petit mal bursts, and "psychomotor" sharp waves; six showed minor alterations, as did one of 11 patients with a questionable diagnosis and one out of 10 controls. Kaufmann *et al.* (204) attempted hydration as an activation technic in a group of post-traumatic epileptics and a group of control post-traumatic encephalopathies without seizures. No patient showed EEG changes, although one epileptic had a generalized seizure two hours after the test. Summarizing these clinical observations, it can be said that the EEG changes observed during hydration are not highly specific for convulsive disorders.

Water intoxication in rats has been found by Gellhorn and Ballin (121) to produce slow waves of 1–3 per second frequency and high amplitude, appearing singly or in groups. When the water dosage was lethal, these waves gradually declined in amplitude until the animals died in deep coma as cortical activity disappeared. Following the onset of slow waves, convulsive discharges also were seen in some animals either as single or multiple spikes or in combination with slow waves, occurring either as larval discharges or associated with convulsions. In animals treated with desoxycorticosterone, the EEG changes consisted largely of slow waves only, without convulsive discharges.

Pick and Miller (272) found that loss of diffusible electrolyte in frogs, accomplished by keeping them in distilled water for one to four weeks, caused a marked decrease in frequency and amplitude of brain potentials.

Both animal and clinical investigations therefore seem to indicate that water intoxication can cause the appearance of slow waves if the hydration is severe enough, and that more vigorous dilution of the body fluids sometimes but not invariably may elicit convulsive discharges.

There have been no systematic studies of the effects of hydration at all levels

of the nervous system, but it is known that cortical threshold for electrically or chemically induced seizures are dramatically lowered by hydration (314).

b. Antibiotics: The occasional occurrence of seizures following the therapeutic intraventricular use of penicillin has led to a number of studies of the EEG effect of this and other antibiotics, chiefly by Walker and his colleagues (29, 202, 203, 204, 308, 326, 328, 329), who have also reviewed the literature in the field (327, 328). Seizures and EEG changes are not seen when even large doses are given intravenously or intrathecally, but may appear when the antibiotics have direct access to the brain by intracisternal, intraventricular or subdural administration. Subconvulsive EEG changes in man following intraventricular penicillin include slowing of the alpha rhythm, increased amplitudes and the appearance of fast spike activity. Preconvulsive single and multiple spikes have been described in cats and monkeys after local application of penicillin to the cortex (29, 326), and a similar picture is reported for streptomycin in various species (308). Fortunately, there seems to be a wide margin of safety between antibiotic concentration and convulsive threshold for both penicillin and streptomycin, so that their use in cerebral infections is not dangerous if the final concentration in the cerebrospinal fluid is properly controlled; however, the margin is less for streptothricin, actinomycin and clavacin (203, 328).

As to the mechanism of convulsive action of the antibiotics, little can be deduced from the literature. The reviewers (317) have noted that streptomycin is unlike the typical convulsants in that it produces only evidence of depression when administered intracisternally or intrathecally in frogs. High concentrations appear to block conduction in frog peripheral nerve by a process of depolarization.

c. Sulfonamides: The sulfonamides are also capable of producing convulsive manifestations upon local application to the cerebral cortex. Epileptic seizures have been observed following topical application of sulfathiazole to the brain of man (334) and of experimental animals (274). Jasper *et al.* (199) have studied the effects of microcrystalline sulfonamides upon the EEG of the monkey. With sulfathiazole this vigorous treatment of the cortex resulted in the appearance of a variety of persistent dysrhythmias, with preconvulsive spikes or sharp waves and focal seizure activity as frequent findings. Sulfapyridine produced only depression of activity and sulfanilamide and sulfadiazine were without effect. Aside from osmotic and other factors which may facilitate seizures when sulfonamides are applied topically, sulfathiazole may have convulsant effects when given systemically (199). The mechanism has not been studied.

d. Antimalarials: Because the EEG effect of antimalarials in routine clinical practice may be complicated by fever and cerebral involvement, the observations of Engel *et al.* (96) on normal control subjects receiving quinacrine are of some interest. These authors report a progressive and sustained increase in average frequency of cortical rhythms, associated with signs of restlessness and tension. The supposed anticholinesterasic activity of quinacrine is invoked by Engel *et al.* to explain the clinical and EEG findings. In contrast, Pick and Hunter (271) conclude that quinacrine has a depressant effect on cortical activity of cats

and frogs. Gallouin and Lemaire (117) have noted a reduction in amplitude of alpha rhythm in patients receiving single doses of quinine. Perhaps more systematic examination of the antimalarials will be inspired by the growing realization that these and other chemotherapeutic agents may have highly specific effects upon particular enzyme systems.

e. Steroid hormones: Passing mention will be made of progesterone and desoxycorticosterone acetate (DOCA) only because these steroids have frequently been reported to have central depressant effects in large doses (cf. 297). Engel and Romano (95) found that DOCA could partially restore the abnormally slow EEG in patients in Addisonian crisis. Clinical anticonvulsant effects have been claimed for chronic DOCA administration (251), and adrenal cortical extracts have been reported to improve both clinical and EEG signs of post-concussion syndrome (4) and to protect the exposed brains of animals from edema and associated slowing and reduction in amplitude of the EEG, presumably by a stabilizing action upon blood vessels (165, 166). Total adrenal cortical extract is said to increase the frequency of the dominant EEG rhythm in man, in contrast to a slowing effect of DOCA (167). The central effects of the adrenal cortical steroid hormones could perhaps be better evaluated if a greater effort were made to differentiate experimentally their concomitant actions upon water and electrolyte balance.

Progesterone (with diethyl stilbestrol) in doses sufficient to induce menstruation in menopausal women is said to be without effect upon the EEG (68).

f. Agenized flour products: Recent investigations on "canine hysteria", a convulsive disorder in dogs maintained upon a white flour diet, have roused considerable apprehension regarding the possibility of related central nervous dysfunctions in man. The syndrome was identified with the wheat gluten fraction by Wagner and Elvehjem (325), and was shown by Mellanby (252) to result from the "agene" process utilizing nitrogen chloride as a bleaching agent. The active principle was finally localized by Silver *et al.* (298) to agenization products of cysteine and cystine. The EEG correlates of the syndrome in dogs were studied by Erickson *et al.* (101, 260, 261), who recorded preconvulsive 2–3 per second waves of high voltage and typical tonic-clonic seizure discharges during the attacks. Silver (298) observed convulsive dysrhythmias in cats and dogs, and occasional slow abnormalities in monkeys, which ordinarily develop asynergy, tremor and weakness rather than seizures; these investigators established the ominous fact that the disorder once initiated was relatively irreversible. Newell *et al.* (261) failed to find EEG or clinical changes in patients given a diet rich in agenized products for periods of several weeks, but the invulnerability of man to this civilized dietary refinement has not yet been proved beyond a doubt.

V. CONCLUSION

From the foregoing review it should by now be obvious that the actions of drugs upon the EEG are at best poorly understood, even though the literature is replete with empirical observations of chemically induced alterations in the electrical activity of the brain. Only a limited number of drugs,—chiefly strychnine,

ether, the barbiturates, and some of the antiepileptics effective in grand mal,—have been examined with sufficient thoroughness to permit a tentative interpretation of their observed effects on the EEG in the light of their ability to bring about particular changes in the neurones of the brain.

Our prevailing ignorance of the mechanisms of action of most drugs upon the EEG should therefore serve as a warning against any easy classification of drug effects as depressant, excitant, etc., on the basis of their modification of the EEG. For example, to interpret an increase in frequency of cortical waves as evidence of an excitant pharmacological effect is to ignore the many other mechanisms by which even depressant substances such as the barbiturates may cause an apparent increase in EEG frequencies at some particular dose level or stage of action. Here as in other fields the passive acceptance of oversimplified generalizations can lead to the disorientation of further investigation and delay progress both in research and in therapy.

Another source of error in the interpretation of the EEG is the assumption that any observed alterations are the result of the direct action of the drug upon the cortex itself, when in the particular case the effects may be secondary to more fundamental actions elsewhere in the body. Thus curariform drugs were thought to have profound direct EEG manifestations at one time until the role of anoxia secondary to neuromuscular paralysis was taken into account.

Finally it should be remarked that the action of drugs on the normal EEG must be sharply distinguished from those manifested in the presence of preexisting abnormalities, particularly discharges of convulsive type. Since convulsive discharges seem to arise in a way qualitatively different from the normal components of the EEG and may be altered or obliterated by a number of different mechanisms, erroneous conclusions may easily be drawn in attempting to translate evidence from one category to the other.

With respect to future work, it becomes clear that many refined and thorough neurophysiological investigations will be needed to close the gap between our present empirical information and our theoretical insight into mechanisms of drug action upon the EEG. Such analysis will undoubtedly necessitate the development of new methods for measuring the excitable and response characteristics of cerebral neurones, preferably of single cells. Meanwhile the empirical clinical literature would benefit from more careful description of the character of drug-induced changes in the EEG as well as the circumstances under which they were elicited, in preference to the mere classification of EEG changes. Similarly it is important to record other observed or known effects of the drugs used, in order to be able to recognize secondary effects upon the EEG when they occur.

In conclusion, the EEG taken alone may often give frivolous or misleading information concerning the nature of drug action, but when supplemented with information obtained by other methods it can add materially to our knowledge of the pharmacological actions of those drugs which have demonstrable central nervous effects. Conversely, a more systematic pursuit of the EEG correlates of drugs with well-known specific effects upon properties of neurones or upon

enzyme systems would in turn probably lead to a better understanding of the nature of the recorded electrical activity of the brain.

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