Thiopental: Effects on Subcortical Mechanisms in Temporal Lobe Epilepsy

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This report describes some observations on the action of the barbiturates, and of thiopental in particular, on the interactions among the great systems of the brain in man—the thalamocortical systems, the limbic system with its inter-relations between hippocampus and hippocampal gyrus, and the amygdala. The studies reported all concern the electrical activity of these structures in man.

These electrophysiological studies on deep structures in the brain have been made, with one exception, on patients with temporal lobe epilepsy, for such material is not available from the brain of normal man. Moreover, it is only in special cases, as detailed later, that this procedure is employed and as a consequence we have a rather meager series on which to report: 20 up to the present, and not every one of these has had all the studies that are discussed here. This warning emphasizes the danger of making generalizations from the brain of the epileptic to the brain of normal man, and stresses the ever-present hazard in clinical work of generalizing to a disease state, from the findings on a small series of patients. Each patient with temporal lobe epilepsy has his own particular brain disturbance: in the intimate characteristics of this he is unique, and all one can do is search for any components of this disturbance that he may share with others whose disordered behavior has elements in common.

In this discussion of a neurophysiologist's approach to the mechanisms of anesthesia, remarks will be restricted almost entirely to the action of the barbiturates, for it is with these agents that this work has mostly been concerned. The pioneer work on the action of barbiturates on brain stem mechanisms is too well known to be repeated in detail here, and therefore only the briefest review of this classic material will be given. The outstanding contribution that fundamentally changed all previously held concepts of the physiology of consciousness was the observation of Moruzzi and Magoun 21 that high frequency repetitive excitation of the reticular formation in the central core of the brain stem induced EEG arousal. The later expansion of this discovery emphasized its implications for the states of vigilance and of impaired consciousness.11

For those interested in anesthesia these findings suggested that loss of consciousness was likely to be caused more by blockade of the afferent system in the central core than by deafferentation of the lateral classical sensory paths, and early experiments in the cat and in the monkey clearly indicated the role of this afferent system in the reversible blockade produced by anesthesia.12, 15, 18 These studies showed that single volleys entering the brain by sensory nerves reached the cortex through two major systems: first, via the fast conducting specific pathways, and then via the ascending reticular system in the more slowly conducting central core. The anatomical studies of several workers (for example, references 5, 20, 22) make it clear that the classical ascending spinthalamic fibers send collaterals into the reticular core and therefore provide a morphological basis for these electrophysiological and behavioral indications of interaction. Transmission in this midline route was early shown to be extremely vulnerable to barbiturate nar-
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Nevertheless the parallelism between natural sleep and induced barbiturate anesthesia is not very close, either behaviorally or electroencephalographically, and the neurophysiologist needs to search for differentiating mechanisms.

The electrographic differences between stages of sleep and stages of thiopental anesthesia can be seen by comparing figures 1 and 2. The EEG of natural sleep has several stages in man: a slowing of the alpha rhythm in drowsiness, a stage of high voltage slow waves usually seen at the beginning of a night's sleep, and a low voltage stage of faster frequencies which supplants it. The stages of thiopental anesthesia are quite different: first there is the development of high voltage fast frequencies which, on loss of consciousness, give way to slow waves and finally, when a surgical level of anesthesia is reached, to alternating periods of electrical silence and bursts of irregular activity. This is the stage that electroencephalographers call 'burst-suppression.'

The closest electrographic sign, then, that sleep and barbiturate anesthesia have in common is a stage of slow wave activity. The question naturally arises: what brain mechanisms, other than the reticulo-cortical relations, are disturbed in sleep, and are these also disturbed in thiopental anesthesia?

Methods

In our laboratory, we have begun to make an inroad on this question as it relates to man. We have few cases so far, so this must be taken as a preliminary report rather than as a finished study. Thanks to a collaborative research program at the Brain Research Institute, where I am greatly indebted to my neurosurgical and neurological colleagues, I have had the opportunity to record from electrodes implanted and left in place for several weeks in deep structures of the brain in patients with temporal lobe epilepsy, and in one case in a patient with intractable psychosis. This work cannot, of course, give information about deep structures of the normal brain but is the nearest approach one can make.

All the patients in this series were intensively studied by Dr. Richard Walter and selected by him as cases whose epileptic seizures were resistive to medication. They were patients in whom EEG recordings from the scalp failed (in spite of several activating techniques) to yield sufficient evidence for lateralization of abnormality for the neurosurgeon to reach a decision on the operative procedure to follow. Our neurosurgeon, Dr. Paul Crandall, inserts the recording electrodes according to the stereotactic coordinates of the Talairach atlas, the final placements being checked by X-ray with contrast medium and later, in the case of the hemisphere from which the temporal lobe is excised, by histological examination.

Fig. 1. Typical EEG recordings from normal man in different stages of vigilance and natural sleep. (Brazier, M. A. B.: The Electrical Activity of the Nervous System. London, Pitman; New York, Macmillan, 1960.)
The majority of deep placements have been in the hippocampus, hippocampal gyrus and amygdala, though in a few subjects in whom a diencephalic component was suggested by the seizure pattern, electrodes have also been implanted in the anterior nucleus of the thalamus and in the centre median. In the one non-epileptic psychiatric case, electrodes were also placed in the dorsal medial nucleus. Electrodes have not been inserted into the human brain stem and we still have to rely, in this respect, on parallel experiments in lower animals with all the hazards of species differences that such analogies introduce. These placements in our patients have provided the rare opportunity to explore the electrophysiological relationships between the hippocampus and its gyrus, which are known to have two-way connections in lower animals \(^1\) and \(^{11}\); the relations between amygdala and hippocampus \(^2\); and between certain association nuclei of the thalamus and the cortex.

In the pilot work which is reported briefly here, interest has been focussed on the degree of correlation or coherence between the ongoing EEG activity of these various pairs of structures (hippocampus and its gyrus, amygdala and hippocampus, some of the association nuclei of the thalamus and their projection cortices): (1) in the waking state; (2) in natural sleep; and (3) in thiopental anaesthesia, for it seemed possible that here might lie some of the connections that are interrupted when consciousness is lost.

In order to achieve a more quantitative estimate of the relationship of the ongoing activity between one site and another than can be obtained by mere visual inspection of ink-written EEG traces, a form of computer analysis has been employed which gives, not only the frequency spectrum of the activity at each of the many locations of the electrodes, but also the correlation, or degree of coherence between any 2 sites at each frequency present in the EEG.\(^{*}\) For the purpose of making the data available to computer analysis, recordings are always made on 14 channel magnetic tape at the same time as the ink record is being taken.

Results

Relationships between Hippocampus and Ipsilateral Hippocampal Gyrus in the Waking State and in Natural Sleep. This kind of analysis has revealed a strong coherence between the EEG activities of these structures when the subject is awake. In other words, when bursts in the theta or alpha ranges appear in the hippocampal leads they also appear with the same component frequencies in the hippocampal gyrus (to a degree greater than chance). If fast activity is also present in the hippocampus, one finds it in the hippocampal gyrus. Figure 3 shows the results from 2 patients when awake, and demonstrates the strong ipsilateral coherence and complete lack

\(^{*}\) For a description of this form of analysis see reference 28. (This is a program available in the Health Sciences Computing Facility at U.C.L.A.)
of interhemispheric coherence of these structures. Thus, when this analysis is made in the waking state, the on-going activity of the hippocampus is found to be strongly correlated, usually at several frequencies, with that in the ipsilateral, though not in the contralateral gyrus. Perhaps rather surprisingly the EEG of each hippocampus was found to be completely independent of the other, a result, incidently, in contrast to the findings in lower animals, and one for which we have further evidence. Whether or not this is a species difference or evidence for a very refined homotopic projection in the human brain is not possible to determine by electrophysiological means.

The existence of a strong hippocampal commissure in man (serving the functions of both the dorsal and ventral commissures in lower animals) suggests that the above result may indicate a very exact homotopic crossing, one so exact as to escape detection by gross electrodes, stereotactically placed.

In lower animals (rat, rabbit and cat) Andersen has found homotopic crossing restricted to the ventral hippocampal commissure. Hippocampal areas CA 1 and CA 3 were found to have point-to-point connections with the opposite side, those from CA 1 connecting with apical dendrites, those from CA 3 with basal dendrites. Stimulation of CA 1 could, however, evoke a response in CA 3. The anatomical studies of Blackstad support these electrophysiological findings, though the work of Cragg and Hamlyn in the rabbit suggests a rather different view; they suggest that evoked responses in CA 1 are not directly relayed from the opposite hemisphere but have a synaptic relay in CA 4 which is revealed by the development of recruitment. This would implicate CA 4 as the main receiver of transhemispheric hippocampal impulses in the rabbit. The more recent anatomical studies of Raisman are also relevant to this question in lower animals but how confident one can be in making the analogy in man is conjectural. The exact position of the electrodes in these patients can only be known in the temporal lobe that is removed; for the other hemisphere, matching by X-ray with these subsequently confirmed locations is the only guide.

In contrast to the findings in the awake state, when the subject falls asleep, although slow frequencies are present, they appear independently of each other in these two locations. Apparently the ipsilateral interaction

† The terminology used here is that of Lorente de Nô and illustrations of the exact anatomical regions to which these terms refer are found in his classic work, J. Psychol. Neurol. 46: 113–171, 1934.

![Diagram of EEG coherence](https://example.com/diagram.png)
present in the waking state is lost when sleep ensues. In the patient whose record is shown in figure 4, there was strong coherence between the hippocampus and its gyrus, in the theta and alpha bands (i.e., frequencies lower than 13 cycles per second). All of this coherence was lost when he fell into natural sleep.

Relationships between Amygdala and Hippocampus in the Waking State and in Natural Sleep. Turning now to the interactions between amygdala and hippocampus, there is electrophysiological evidence from the work of Green,25 Cloor13,14 and others, as well as from the anatomical studies of Cajal,24 of LeGrois Clark19 and of Nauta22 in lower animals, that these structures have some interconnection, even if indirect. Stimulation of the amygdala in both man7 and cat14 produces recruitment of the response, suggestive of a polysynaptic route.

As figure 5 demonstrates, a strong coherence was found between EEG activity in amygdala and hippocampus in man, in the waking state. This figure charts 6 samples of the EEG of one patient when awake, and 4 samples taken when he fell into natural sleep. The loss of

Fig. 4. Coherence between hippocampus and ipsilateral hippocampal gyrus. Two examples from a patient when awake, and two examples when in natural sleep. His EEG activity when awake was almost entirely in frequencies lower than 12 cps. Note loss of coherence in natural sleep even in the delta band. Level of significant coherence for the number of degrees of freedom in the length of sample analyzed indicated by the horizontal line.

Fig. 5. Coherence between amygdala and ipsilateral hippocampus. Six examples when awake (upper curves) and 4 examples when in natural sleep (lower curves).

Fig. 6. Coherence between dorsal medial nucleus and its projection center. Examples from a psychotic patient. Strong coherence in theta and alpha bands when awake, lost in natural sleep.
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Fig. 7. Coherence between anterior thalamic nucleus and ipsilateral cortex. Same patient as in figure 8. Coherence of activity in theta and alpha bands is lost in natural sleep.

Relations between Nonspecific Thalamic Nuclei and Cortex in the Waking State and in Natural Sleep. Figure 6 provides data from four different samples derived from recordings from electrodes in the dorsal medial nucleus and its projection cortex in the frontal lobe, as recorded from electrodes in the outer table of the skull. In each sample there is considerable coherence in both the slow delta band and in the alpha in the waking state; this is lost in sleep.

Figure 7 is a recording from another nonspecific thalamic nucleus, the anterior thalamic nucleus, and shows the coherence when awake between its on-going electrical activity and that of the cortex as derived from skull electrodes near the vertex. The subsequent loss of coherence at the onset of natural sleep is again very striking.

Thus we have seen three of the major intercerebral connections break down when natural sleep ensues: that between the hippocampus and its gyrus, that between the amygdala and the hippocampus and that between certain thalamic nuclei and the cerebral cortex.

Relations Found During Thiopental Anesthesia

Moving then to an exploration of these relationships during artificially induced impairment of consciousness in contrast with its natural occurrence in sleep, we have used thiopental anesthesia.

Relationships between Hippocampus and Ipsilateral Hippocampal Gyrus. Figure 8 illustrates the strong coherence in one of our patients between the on-going EEG activity of the hippocampus and the ipsilateral hippocampal gyrus before any drug was given (fine continuous line marked C). The three other curves are the results found at three dosage levels of thiopental: 100 mg. (dashed line); 200 mg. (heavy unbroken line); and 320 mg. (dash-dotted line). Each curve is the average of 3 samples. There is a striking persistence of coherence even at the 320 mgm. dosage at which the patient lost contact with his environment.

Relationships between Amygdala and Ipsilateral Hippocampal Gyrus. Figure 9 illustrates, in the upper half, in one of our patients, the strong coherence, in almost all frequencies of the EEG, between amygdala and

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† I am indebted to Dr. Richard Walter, and to Dr. John Dillon's Division of Anesthesiology for collaboration in this research.
the ipsilateral hippocampus that has already been described. Three samples from his record are plotted. This as we have seen, is one of the relationships disrupted in natural sleep.

In the lower half are three curves, one for the EEG when 100 mg. of thiopental had been given (the solid line), one at 200 mg. (fine line) and one at 320 mg. (broken line). Unlike natural sleep, no amount of thiopental destroyed the close relationship between the EEG activity in these two sites.

*Relationships between a Nonspecific Thalamic Nucleus and Cortex.* In figure 10 is shown the lack of effect on the correlation of EEG activity in the center median nucleus and that recorded from a centro-temporal lead from the skull. Above one sees the average of 10 control samples from a patient, and below are the results at 3 levels of thiopental dosage in the same patient: 100, 200 and 225 mg. At the last of the levels this patient lost contact with her environment.

What is noticeable here is that not only is there no loss of coherence but an increase; although significant in some frequency bands, the coherence in the control runs was never very strong; this increase on administration of thiopental seems to be, at least in this patient, independent of the level of dosage. We do not know whether or not this finding can be generalized to apply all patients, for we do not have a large number of patients with electrodes in this particular thalamic nucleus.

![Fig. 9. Lack of effect of thiopental at 3 dosage levels on coherence between amygdala and ipsilateral hippocampus.](image)

**FIG. 10.** Effect of thiopental at 3 dosage levels on the coherence between a non-specific thalamic nucleus (center median) and scalp. The upper curve is average of 10 control samples and shows only a weak coherence in any frequency band. At all 3 levels of thiopental dosage used, the coherence of the slow delta activity was greatly enhanced.

**Summary and Conclusions**

These few opportunities for studying the effect of loss of consciousness on intracerebral connections in man, as witnessed by EEG rhythms in common, have indicated a marked difference between consciousness impaired by natural sleep and consciousness impaired by thiopental anesthesia. Although both states are marked by slow delta activity at the scalp, these studies of concurrent deep structures indicate a lack of common mechanisms, at least in terms of interaction.

There is obvious danger in generalizing from the brain of the epileptic to the brain of normal man, even greater perhaps than the ever present hazard in clinical work of generalizing from a small series of highly selected cases.
Therefore whether these findings can be extrapolated, from the particular few cases we have had the opportunity to study, is a question whose answer lies in the future and is a challenge for future research.

References


DISCUSSION

Dr. Fink: In these patients have you had the opportunity to observe whether any change in correlation at the various sites occurs during natural sleep?

Dr. Brazier: Only one nonepileptic patient was analyzed during a night’s sleep, and lack of correlation was present in all phases of sleep. In normal man, the low voltage phase of sleep lasts for a much longer period during the night, than the high voltage phase. Our epileptic patients have been tested during sleep in the laboratory, but they too show lack of correlation in both phases.

Dr. Fink: Are there any animals in which the same kind of correlation changes occur?

Dr. Brazier: I have recently implanted electrodes in cats to examine this. But I am cautious about drawing analogies between species, when there are such tremendous differences between the EEG in cat and man.

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