

Prenarcotic Doses of Barbiturates as an Aid in Localizing Diseased Brain Tissue

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THE STUDIES REPORTED HERE, carried out in collaboration with Dr. Richard Walter and Dr. Martin Lebowitz, concern some uses of sodium thiopental (Pentothal) other than those commonly employed in anesthesiology, and in particular the use of this drug to detect and localize abnormalities of neuronal function in the brains of patients with seizures.

The reaction of the normal human brain's electrical activity to barbiturates has been known well for years. This was first established¹ in terms of the EEG as recorded from the scalp, where light pre-narcotic dosages were shown to produce fast frequencies of approximately 20-28 cycles per second, that is, waves considerably faster than the familiar alpha band which centers around 10 cps, and in striking contrast to the very slow waves that develop in the anesthetic stage.

Thiopental, as a diagnostic aid in epilepsy, was first used by Fuster, Gibbs and Gibbs² as an activator—i.e., in the attempt to produce spiking. In following up this work, Heuyer, Rémond and Delarue³ noted that the slow-wave stage was reached in the EEG's of epileptic patients at lower dosages than in those of non-epileptic control subjects. When recorded simultaneously from several locations on the scalp of man, the fast activity of the pre-narcotic stage is found to develop first in

the frontal regions, progressing gradually more posteriorly. The recovery process proceeds in the opposite direction, the frontal regions being the last to relinquish the effect. Although at first glance this might appear to indicate a reaction of cells in the superficial layers of the brain, later work with deeply implanted electrodes demonstrated that regions of the brain in which the cell bodies of the neurons lie generate the same fast activity as previously had been seen in scalp recordings.⁴ These studies made it clear that this effect is at the level of the cell bodies and is a reaction of all normal neurons.

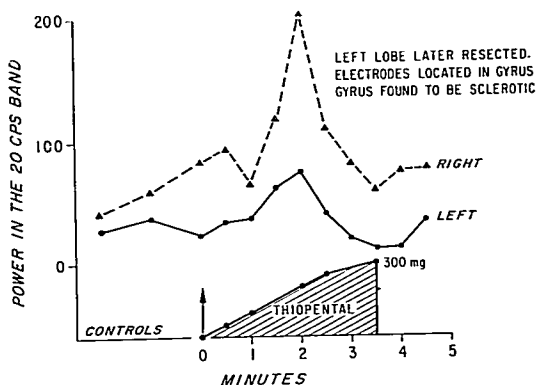
The stage at which this fast activity appears in the EEG is not, in any sense, that of anesthesia, but it is almost certainly one at which the neurons are called upon to react with the agent.

Brain tumors, on the other hand, in general contain no electrically-active nerve cells, and might reasonably be expected to fail to react to barbiturates in this way. The first investigators to test this hypothesis and prove its correctness were Alema and Sinisi⁵ in Bologna who published their findings in 1950. In contrast to Rémond and his colleagues, Alema and Sinisi specifically advocated the use of the stage of EEG fast activity to detect hemispheric asymmetries, and demonstrated their ability to lateralize, and in some cases to localize, tumors in patients with neoplasms using as their hypothesis that the metabolic condition of tumor tissue must differ profoundly from that of normal neurons. This early work has since been plentifully confirmed by others, e.g., Pampiglione⁶ in the case of lesions which he described as "very large, involving a lobe or more."

Received from the Brain Research Institute, School of Medicine, University of California, Los Angeles, California. Accepted for publication February 27, 1969. The work of this investigator is supported by #5-K6-NB 18,608 from the National Institutes of Health, Grant #NB 04773 from the USPHS, and Contract NR 233 (69) from the U. S. Office of Naval Research.

Paper presented at the annual meeting of the American Society of Anesthesiologists, October, 1968.

FIG. 1. Computer-quantified measurements of the amount of EEG activity in the 20-cps band developing as the result of injection of thiopental. In this patient the fast activity began to be replaced by slow waves when the dosage passed 200 mg. Left side later resected.



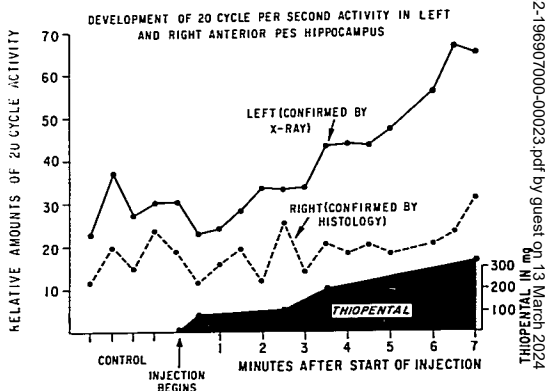
The work described here concerns patients with temporal-lobe epilepsy, a condition in which gross lesions are extremely rare. However, since the days of these earlier workers, a great deal of information which suggests that anomalies at the membrane of neurons are involved in the abnormal electrical discharges of the epileptic brain has accumulated.^{7, 8, 9}

Intracellular recordings from cortical cells have shown a close relationship between slow membrane changes of the soma and the epi-

leptiform activity recorded at the surface. It seemed possible, therefore, that abnormal functioning of the nerve cell membrane might also manifest itself as a failure to react in a normal way to the impact of barbiturate drugs and thus prove useful in localization not only of non-neuronal tumor tissue, but also of malfunctioning neuronal aggregates.

Direct evidence for the action of barbiturates on the nerve cell membrane cannot, of course, come from studies in man, but the ex-

FIG. 2. Lateralization in a second patient. Right side later resected.



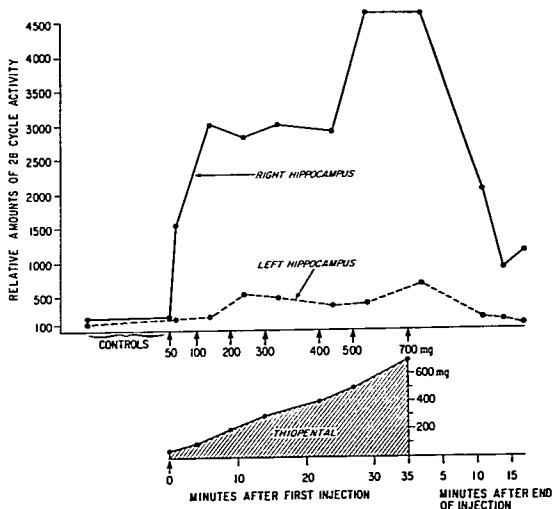


Fig. 3. Lateralization in a third patient, whose EEG reacted maximally in the 28-cps band when thiopental was injected. Increments were given slowly over a 35-minute period; in this way the fast-activity stage in the EEG was maintained. Note the immediate onset and decline of this activity.

quisite analyses made from intracellular recordings in invertebrates by Chalazonitis¹⁰ and in vertebrates by Somjen¹¹ made it clear that the site of action is at the membrane of the postsynaptic cell. Changes in membrane conductance are also found with many volatile anesthetics, such as ether, halothane and chloroform, but for a simply-administered diagnostic test, quick-acting thiopental is the chosen agent.

One of the collaborative research programs^{*} at this Brain Research Institute concerns a series of patients with temporal-lobe epilepsy whose seizures are resistant to control by medication and who are therefore candidates for unilateral temporal lobe resection as a therapeutic measure. Adequate lateralizing signs are needed to guide the surgeon in his choice of hemisphere. Frequently these patients show no hemispheric asymmetry in scalp EEG's, for the trouble lies deeper and can be reached only by electrodes inserted deep within the brain in such structures as the hippocampus and the amygdala.† In cases such as these, with the hope that it might pinpoint

the epileptogenic zones, we have been exploring the use of light doses of thiopental in search for neuronal tissue that does not react in the normal way by developing fast activity. The effect, of course, can be expected only if electrodes are indeed within recording distance of a malfunctioning zone of neurons.

The procedure is to administer the thiopental extremely slowly in a series of small increments whose timing is decided by the changes occurring in the EEG. The sign looked for is the development of fast waves in the 20-to-28-cps frequency range, though this can be narrowed down to activity in a narrower frequency band in most patients. This can be seen by eye, but for purposes of quantification the amount of this activity has been assessed by computer, and it is this computer measurement that is plotted in the accompanying

^{*} This program is supported by Grant #NS-02808 to the Brain Research Institute.

† The author is grateful to the neurosurgeon, Dr. Paul Crandall, for the opportunity to record from patients in whom he has made these implantations.

ing illustrations.† The effect is fleeting, and within two minutes of stopping the infusion the curve returns to normal. However, as is well known, if thiopental is given in larger amounts, the EEG changes even further, the fast activity ceases and slow waves supervene. We have found no lateralizing function of this slow-wave stage—only the stage of fast activity has served this function.

This can be clearly seen in figure 1, from a patient whose maximum fast activity occurred

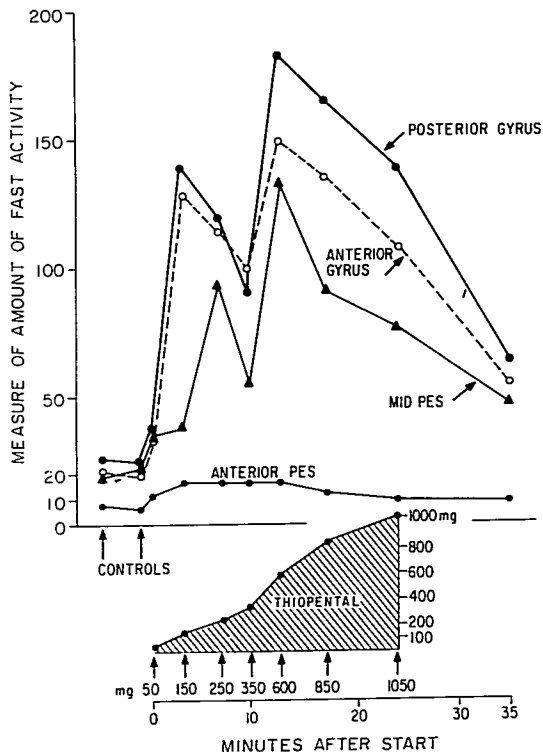
when the thiopental dosage had reached 200 mg, two minutes after the first injection had been given. Increasing the amount to 300 mg replaced the fast activity by slow waves, and the lateralizing signs were lost.

Figure 1 shows recordings from electrodes in the patient's left and right hippocampal gyri. The placement of electrodes was checked by x-ray and found correct in both cases. Later, a left temporal topectomy was performed and histologic examination revealed mesial temporal sclerosis but no neoplasm.

An example from another patient is given in figure 2. These data are from a 21-year-old

† Program X92 of the Health Sciences Computing Center, UCLA, which is supported by USPHS FR 3.

FIG. 4. Localization within the right hippocampus of a fourth patient, which on later resection showed marked atrophy of the pes hippocampi. Note normal reaction of the more posterior zone of the hippocampus and of both sites in the ipsilateral hippocampal gyrus. Increments were given slowly over a period of 24 minutes, but dosages from 600 mg upwards increasingly cut down the amount of fast activity.



man who had had seizures since infancy, uncontrollable by medication, who later had a right temporal topectomy performed by Dr. Crandall. A confirmation of electrode placements on the right was therefore available by both x-ray and histologic examination, and on the left by x-ray alone.

We have found considerable differences between patients as regards the "absolute" dosage at which fast activity is replaced by slow waves, though this has not been found to affect the lateralizing potential of this technique. In addition, the exact frequency band of maximum reactivity may differ from patient to patient. In figures 1 and 2, the frequency band examined centered on 20 cps. In figure 3, from another patient, 28-cps activity was chosen for graphing, and the contrast between left and right anterior pes hippocampi is striking.

In the course of our studies of the hippocampus of man, it has become clear that there is electrophysiologic dissociation between the various zones even in the absence of epileptogenic activity. Such dissociations had been shown in the structurally-very-different hippocampi of lower animals such as the rat¹² and the cat.¹³ In man the ongoing electrical activity of the hippocampus in the waking state has been found to be usually quite independent in different parts, for example, the wave-trains recorded from pairs of electrodes only 7 mm apart have been found to be unrelated in timing and spectral content.¹⁴

Therefore, it is perhaps not surprising that in patients with temporal-lobe epilepsy the EEG may be able to detect circumscribed zones of malfunction within the hippocampus. In the context of using thiopental to highlight localization, figure 4 is an illustration. The graph shows the development of fast activity in the 20-cps band as recorded by bipolar electrodes in four different electrode sites in the right temporal lobe. The locations, confirmed by x-ray, were the anterior and mid zones of the pes hippocampi and the anterior and posterior zones of the ipsilateral hippocampal gyrus. With the exception of the anterior pes hippocampi, the almost immediate increase in fast activity on injection of 50 mg to 150 mg thiopental is the normal reaction, falling off during the lull of four minutes before a booster

dose of a further 100 mg was given. This stage of fast activity of the EEG is very fleeting and soon declines, but can be reinstated by a further small dose. When the dosages reached the higher range of 600, 800 and 1,050 mg, the patient passed the preanesthetic stage and the fast activity began to be replaced by the familiar slow waves associated with loss of contact with the environment. Noticeable, however, is the failure of the activity of the anterior pes hippocampi to react to the drug. In this patient severe atrophy of this region subsequently was found at surgical operation.

To refer briefly to the basic laboratory work on this problem, the early explorations of the effects of anesthetic agents on the nerve axon revealed that, in the concentrations used in clinical work, it was extremely unlikely that this was where a block in conduction took place during general anesthesia. Nerve fibers are very resistant to interference with transmission of nerve impulses along them, except by dosages used in laboratory work that have no parallel in clinical use. Attention then turned to the much-more-vulnerable link in the chain of transmission, namely the synapse. There have been several fine laboratory studies of the passage of the nerve impulse across the synapse and its invasion of the membrane of the postsynaptic cell. There have also been several detailed studies of how anesthetic agents impede and delay this action on the postsynaptic membrane, as already mentioned.^{10, 11}

The mass effect of the behavior of neurons such as one sees in the EEG, is just as vulnerable as that of the units of which it is composed, and the development of the fast activity described here (which, incidentally, is also found in light stages of ether anesthesia) may be taken as a sign of membrane disturbance. We have made use of this characteristic to seek lateralizing signs in our patients with neurons whose malfunctions reveal themselves as the epileptic discharge.

In conclusion, in the search for the basic mechanisms by which different agents affect cellular membranes, changes in their electrical activity may be regarded as a promising clue, even in the difficult circumstances of examinations of human beings.

The author is greatly indebted to her colleagues in the Division of Anesthesiology and in the Division of Neurology in the School of Medicine for collaboration in this research.

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Obstetrics and Pediatrics

PARACERVICAL BLOCK Paracervical block was performed in 15 mothers in labor and maternal and fetal mepivacaine concentrations were determined. Blood was obtained from the maternal vein, fetal scalp during labor, and umbilical vessels at birth. Fetal blood also was analyzed for acid-base parameters. Mepivacaine levels averaged 8.5 $\mu\text{g/ml}$ in the mothers and 7.4 $\mu\text{g/ml}$ in the fetuses. Fetal blood levels were consistently lower than maternal levels. All but one infant had Apgar scores of 8 or 9. Fetal bradycardia was encountered in three cases; two episodes were transient and associated with Apgar scores of 8, and in the third, bradycardia persisted until delivery and was associated with a score of 4. The only significant pH variation was in the infant with persistent bradycardia. The highest mepivacaine concentrations were found in the three cases with fetal bradycardia. It is probable that a normal fetus can tolerate clinically-induced levels of mepivacaine, but that infants depressed by acidosis may be compromised. Fetal bradycardia as a result of drug toxicity should be distinguished from that due to fetal asphyxia. Paracervical block is contraindicated when placental insufficiency is anticipated. (*Cordon, H. R.: Fetal Bradycardia After Paracervical Block, New Eng. J. Med.* 279: 910 (Oct.) 1968.)

ABSTRACTER'S COMMENT: Drs. Sol Shnider and associates, in the correspondence section of the same journal, report significantly higher fetal mepivacaine levels in infants that had bradycardia than those that did not. Furthermore, mepivacaine levels in the infants with bradycardia exceeded maternal levels, indicating the drug found its way directly from paracervical tissue to the intervillous space. Objective data such as these will help decide the usefulness of paracervical block with mepivacaine.