Effects of Thiopental on Human Cerebral Evoked Responses

H. Arto Abrahamian, M.D., Truett Allison, Ph.D., William R. Goff, Ph.D., Burton S. Rosner, Ph.D.

MODERN neurophysiology recognizes two different classes of sensory systems in the brain, the "lemniscal" and "extralemniscal" pathways. The rapidly conducting lemniscal group carries impulses from peripheral sensitive surfaces such as skin or retina and projects them systematically onto restricted cerebral cortical areas. Lemniscal pathways synapse in thalamic nuclei which Rose and Woolsey [1] term "extrinsic," since these structures receive the bulk of their afferents from outside the thalamus. The medial and lateral geniculate bodies, for example, are extrinsic. The right-hand side of figure 1 diagrammatically represents a lemniscal system. "Extralemniscal" systems, in contrast, have rather different properties. These systems conduct more slowly and anatomically do not possess a highly topical organization. The left-hand half of figure 1 shows that extralemniscal pathways arise collaterally from lemniscal systems and synapse in a variety of subcortical structures including thalamic nuclei which Rose and Woolsey term "intrinsic." These nuclei, such as centrum medianum, receive their afferents primarily from other thalamic structures. Several workers [2, 3, 4] have shown that one extralemniscal paths runs via centrum medianum and caudate nucleus to frontal and parietal cortical zones. French *et al.*[5] had demonstrated earlier that another extralemniscal pathway involves synapses in the reticular system of the brain stem and projects diffusely to the entire cerebral cortical mantle. The precise route of this projection is still uncertain.[6] Both sets of extralemniscal paths appear in figure 1. Extralemniscal systems seem particularly sensitive to barbiturates. Pentobarbital abolishes electrical responses evoked in the ascending reticular system by external stimuli [7] and cerebral cortical responses mediated by projections through the centrum medianum.[8, 9] This drug, however, does not reduce but frequently potentiates activity evoked in lemniscal systems.[7]

All of the studies cited above were conducted on animals. Until recently, similar investigations of neural mechanisms of anesthesia in man have been difficult. Study of evoked responses in intact man requires use of scalp leads. With conventional electrophysiological recording equipment, much of the evoked activity obtained at the scalp is very small or totally undetectable in the "noise" presented by spontaneous activity of the brain. Investigation of these responses in man therefore requires a technique for enhancing small signals at the expense of interfering noise. Automatic averaging methods [10, 11] meet this need. This paper describes differential effects of thiopental on averaged cerebral somatosensory evoked responses in man. Some of our findings already have appeared elsewhere.[12, 13]

Methods

Automatic Averaging. Figure 2 shows how averaging brings into clear display a small recurrent signal hidden in unwanted noise. In column A, trace 1 shows a rectangular pulse locked in time to the start of the oscilloscope sweep at t_o. A2 and A3 represent four different samples of the pulse hidden in random noise. The amplitude of the pulse is smaller than in A1, so that this signal is barely discernible in the noise. Imagine a column of

Accepted for publication April 1, 1963. Dr. Abrahamian is in the Anesthesiology Section, Yale University School of Medicine and Anesthesiology Service, West Haven Veterans Administration Hospital; Dr. Allison, Department of Psychology, Yale University, New Haven; Dr. Goff, Department of Psychiatry, Yale University School of Medicine; and Dr. Rosner, Department of Psychiatry, Yale University School of Medicine and Psychology Service, West Haven Veterans Administration Hospital, Connecticut.

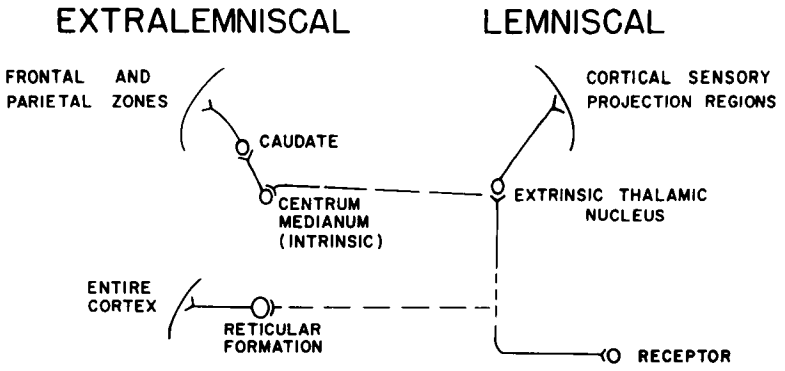

FIG. 1. Diagrammatic representation of lemniscal and extralemniscal pathways. Former give rise collaterally to latter. Extralemniscal paths may involve more synapses than are shown.

ten different samples of signal plus noise such as those in A2 and A3 with each sample starting at the line representing t_o. Choose any particular time t_i after t_o and algebraically add up the instantaneous voltages at t_i over the ten samples. Repetition of this process for every time point t_i after t_o yields the result in A4. Since the pulse signal is in phase with itself across the individual samples but the noise is not, the signal summates more rapidly than the noise. Thus, algebraic summation, which is equivalent to averaging, brings the hidden pulse out of the noise. Trace A5 shows that doubling the number of individual samples from 10 to 20 improves resolution even further.

Column B of figure 2 illustrates detection of small cerebral evoked responses in man by averaging. B1 shows three individual samples of evoked activity from a scalp lead over the right post-Rolandic hand area. The stimuli occurred at the start of each sweep and were brief electric shocks delivered percutaneously to the left median nerve. B2 displays twenty photographically superimposed sweeps like those in B1. Some evoked activity is just detectable. B3, B4, and B5 show respectively the results of averaging 10, 20, and 40 evoked potentials. Once again, averaging provides a clear picture of a small, obscure signal. The averaged records in this and all succeeding figures were obtained with a special-purpose computer described previously.[14] The computer has two independent data channels and summates evoked responses as soon as they come from the subject.

Subjects and Procedure. Subjects for this study were 10 surgical patients at the West Haven VA Hospital. The patients were scheduled for various elective procedures requiring general anesthesia. Each subject was less than 50 years old, in good general health, and free of any history of neurologic or psychiatric illness. Stimuli were 100 μsec. constant current rectangular pulses applied to disc electrodes over the left median nerve at the wrist. Intensity of stimulation was sufficiently high to evoke a thumb twitch. The short duration of each stimulus, however, prevented pain. EEG needle electrodes in the scalp picked up the evoked responses; an indifferent electrode was taped to the bridge of the nose. In order to estimate the scalp location overlying the contralateral (right) post-Rolandic hand representation, a coronal interaural circle was drawn and a recording electrode inserted in the scalp at a point 7 cm. lateral to the midline on this circle. Other measurements[15] have shown that this method locates the desired site within 1 cm. without the need for proportional adjustment of the 7 cm. distance to compensate for different conformations of the head. Data were always recorded on one channel of the computer from this post-Rolandic site or from a locus 4 cm. posterior to it. These points give the largest short-latency activity evoked by stimulation of left median nerve.[15] The point which yielded the larger response was chosen; the other data channel of the computer usually recorded from the vertex. An Offner Type R Dynograph simultaneously picked up and displayed the EEG from the same scalp electrodes used to study the evoked responses. The computer and associated equipment were installed in a room in the operating suite. During all ses-

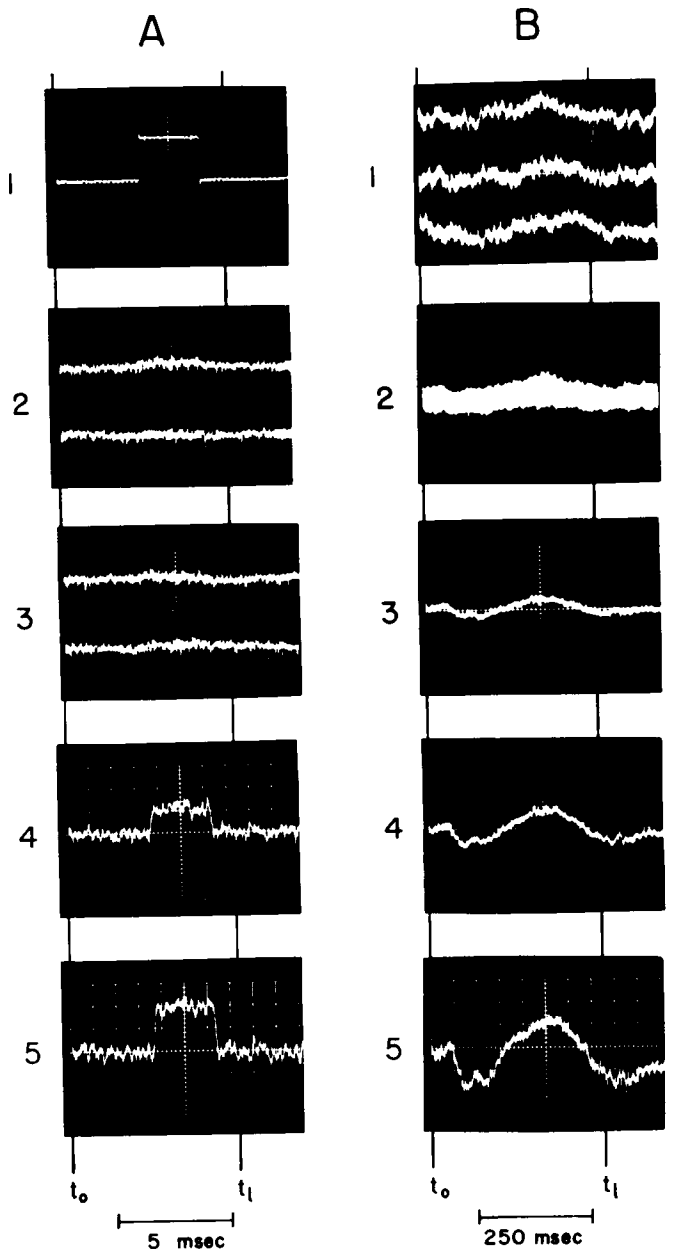

FIG. 2. A. Operation of automatic averaging to extract a pulse signal from random noise. A1: Pulse. A2, A3: Four samples of pulse (amplitude reduced from that in A1) in random noise. A4, A5: Effects of summating respectively ten and twenty samples like those in A2 and A3. Vertical graticule calibration for column A: 0.5 v/major division. B. Extraction of evoked potential following median nerve stimulation in man. B1: Three samples of cerebral evoked activity following stimuli at t_o. B2: Photographic superimposition of twenty traces like those in B1. Vertical calibration for B1 and B2: 25 μv/major division. B3: Average of ten responses. Vertical calibration: 25 μv/major division. B4: Average of twenty responses. Vertical calibration: 12.5 μv/major division. B5: average of forty responses. Vertical calibration: 6.25 μv/major division.

sions, the subject lay supine on an operating table.

One day prior to operation, normal control records were obtained from the subject. On the day of operation, each patient received 100–150 mg. secobarbital and 0.4–0.6 mg. atropine intramuscularly as premedication. Two patients received 70 and 100 mg. meperidine in addition. Further control records were taken no earlier than 45 minutes after premedication. Thiopental then was administered intravenously in successive doses of 10 to 100 mg. each. A single average response was taken after each dose of thiopental; each patient gave four to nine such records. Since stimuli occurred once every 4 sec. and since

each record represented an average of 40 responses, 3 minutes usually elapsed between successive doses. Administration of thiopental ceased when the patient manifested the vital signs characteristic of the clinically desired depth of "anesthesia." No patient received more than 650 mg. of thiopental. EEG records showed that no patient ever went beyond light "pattern 3" as defined by Kiersey *et al.*[16] At this level, there are occasional burst suppressions of one or two seconds duration.

Results

Waveform of Evoked Response. Human cerebral evoked responses to stimulation of median nerve consist of a series of deflections which may last at least 300 msec. Although there is considerable individual variation in the waveform of the response, practically all subjects show certain regularly identifiable components. All components are present in responses recorded over contralateral post-Rolandic regions. Figure 3 shows normal control records from a subject used in this study. The two upper traces in the left-hand column were taken at a sweep duration of 100 msec. The lower pair shows a sweep duration of 500 msec. Within each pair, the top and bottom records respectively are averaged responses at electrodes over the vertex and a contralateral post-Rolandic locus. The right side of figure 3 contains tracings of the post-Rolandic records in the other column. The *x*'s connected by the arrows in these tracings show that the 10 msec. sweep represents the first one-fifth of the 500 msec. sweep. The numbers below various deflections in the tracings indicate consistently identifiable components.

In the records from the post-Rolandic lead, the earliest visible activity is a triphasic, positive-negative-positive sequence which begins about 17 msec. after stimulation. The negative spike peaks at about 19 msec. and the

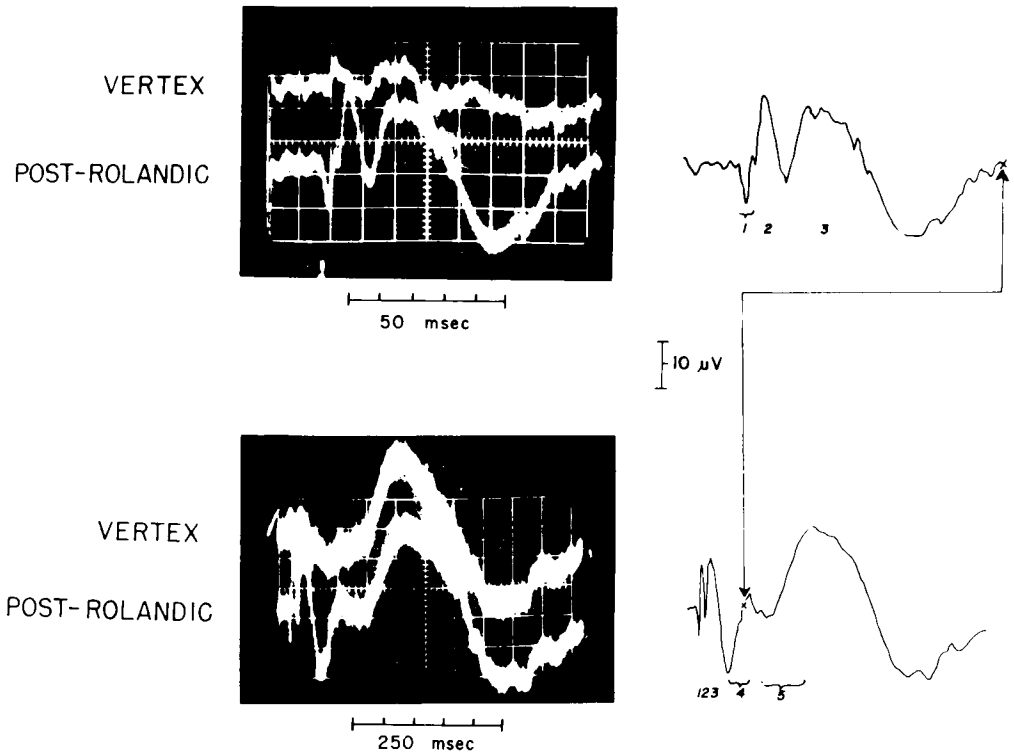

FIG. 3. Normal control records for subject L. G. Numbers under tracings indicate regularly identifiable components of post-Rolandic response. *x*'s joined by arrows show identical time points on fast (upper) and slow (lower) traces.

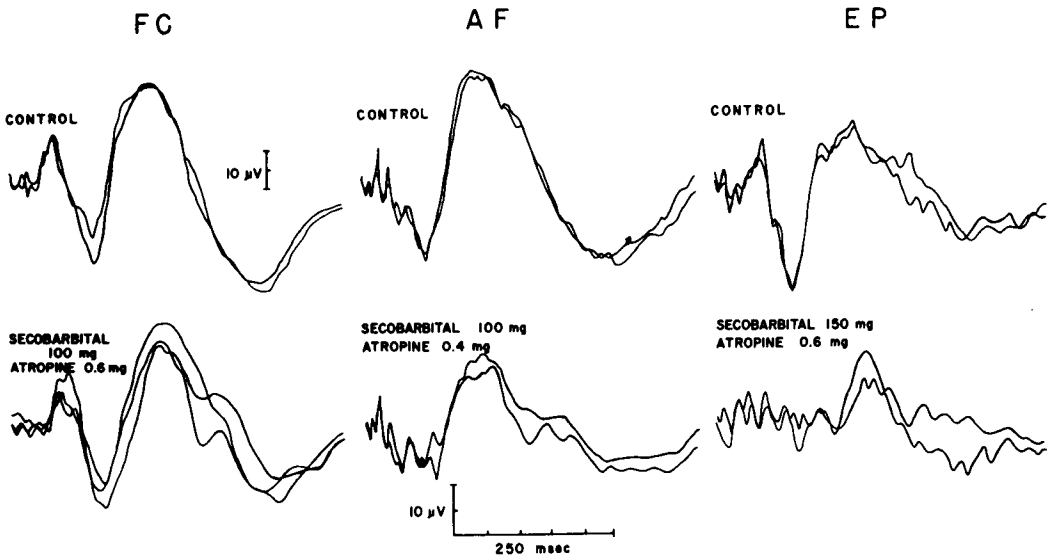

FIG. 4. Effects of premedication (secobarbital and atropine) on late components (*4* and *5*) of response at vertex.

second positive spike at about 22–24 msec. We designate this entire sequence as component *1*. This component may be small or undetectable with a sample of 40 responses in some subjects. In those who show it, the second positive spike often coalesces with the rising edge of another component labelled *2*. This latter deflection is a positive wave reaching maximum at about 30 msec. The next event, component 3, is a slow positivity which peaks at about 50 msec. These three components essentially are absent at the vertex. After 3 comes a negative wave and a positive deflection of variable amplitude. We desig-

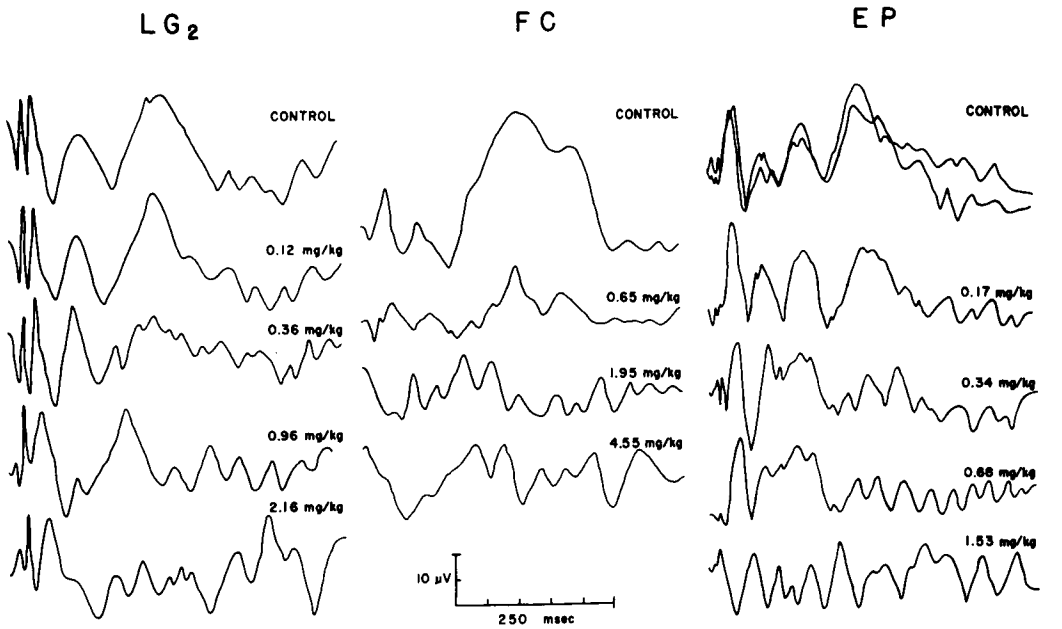

FIG. 5. Effects of progressive doses of thiopental on post-Rolandic late components *4* and *5*.

nate this negative-positive sequence as component *4*. Finally, there is a large diphasic, negative-positive complex which we call component *5*. These last two components appear at both the vertex and at the post-Rolandic locus. We emphasize that our designations do not imply that each component necessarily represents a unitary physiological process. For the moment, these labels are merely convenient descriptive devices.

Effects of Premedication. Premedication (secobarbital and atropine) had no visible effects on components *1* through *3*. Components *4* and *5*, however, proved susceptible to these drugs; particularly high sensitivity characterizes *5*. In seven subjects, these two late events increased in latency, decreased in amplitude, or did both. The other three patients showed no obvious effects following premedication. One of these patients had such small late components in his control records that any effect of premedication would have been hard to establish. Figure 4 illustrates the various actions of premedication on components *4* and *5* of evoked responses at the vertex.

Effects of Thiopental. Following premedication, the addition of very small doses of thiopental completely abolished component *5*. Figure 5 shows this effect for post-Rolandic responses. In most patients, as little as 300 μg./kg. of thiopental severely suppressed or even abolished component *5*. This extreme sensitivity of *5* to thiopental may reflect effects of premedication. The figure also shows that further doses of thiopental then blockaded component *4*. The rhythmic waves in traces taken during this stage of "anesthesia" represent summated 16 to 30 c.p.s. activity in the EEG. At certain stages of induction, a large late diphasic wave reminiscent of *5* tempo-

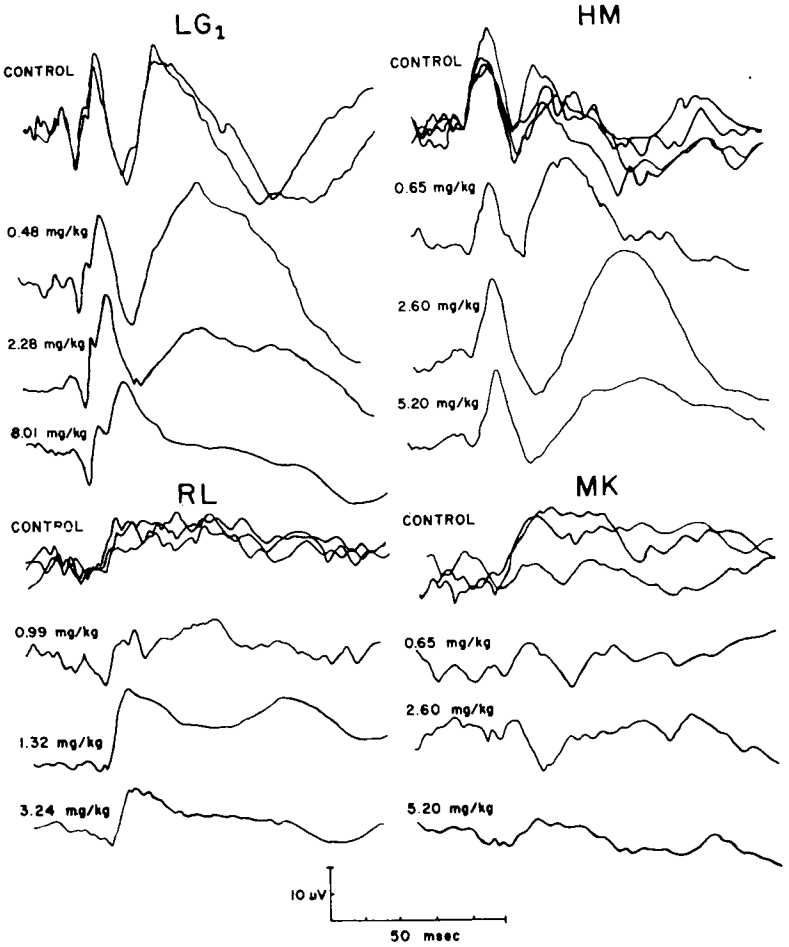

FIG. 6. Effects of progressive doses of thiopental on first three components of post-Rolandic evoked response. Adapted from Allison *et al.*[12]

rarily reappeared in the averaged records of a few subjects. We do not wish to assert that these somewhat similar deflections are physiologically identical.

Figure 6 shows the effects of thiopental on components *1* through *3*. Five subjects, including L. G. and H. M., had particularly prominent early components in their post-Rolandic control records. As they received thiopental, component *3* grew later and finally disappeared; concomitantly, a negativity appeared after *2*. The drug had relatively little effect on components *1* or *2;* if anything, *2* became somewhat larger. In some subjects, *1* and *2* also slightly increased in latency. Control records for subjects R. L. and M. K. did not contain clear indications of the first two components. The effects of thiopental in these and three other subjects with small early components were somewhat complicated but entirely consistent with the results just described. For example, M. K. showed a wave in his control responses which had the latency and waveform of *3*. Thiopental abolished this deflection. In subject R. L., the first three components were hard to discriminate. The heavier doses of thiopental potentiated early activity whose latency and waveform characterize components *1* and *2*.

Finally, two subjects who underwent successive operations were each studied twice. The data for each subject on the second occasion entirely replicated his first series of observations.

Discussion

Study of the distribution across the scalp of human somatosensory evoked responses indicates that components *1* and *2* represent activity in lemniscal pathways. Both components are concentrated in the posterior quadrant of the scalp contralateral to the site of stimulation.[15] The rest of the evoked response has a broader distribution. Component *3* appears in frontal and parietal regions of contralateral scalp in all subjects and also at ipsilateral sites in some.[13, 15] Components *4* and *5* are bilaterally distributed. These observations suggest that the last three components of the evoked response reflect extralemniscal activity, which generally is bilateral. Furthermore, the first two components have much shorter recovery cycles than do *4* and *5*.[17] Lemniscal systems characteristically show faster recovery times than do extralemniscal ones.[18, 19] (Measurement of recovery cycles involves observing the effect of a response to a conditioning stimulus upon the response to a subsequent test stimulus occurring at systematically varied inter-stimulus intervals.)

The data presented in this paper are further evidence that components *1* and *2* signal lemniscal activity while *3*, *4*, and *5* represent extralemniscal events. Thiopental abolishes the latter but does not blockade the former. Similar effects occur in animals.[8, 9] In *Cebus* monkeys, this drug potentiates a deflection which seems homologous to *2* in man and makes a wave apparently homologous to *3* grow progressively smaller and later.[20] In brief, our data indicate that in man as in animals thiopental acts at least partly by blocking extralemniscal sensory systems while leaving open lemniscal paths. Thus, thiopental apparently does not prevent initial rapid transmission of sensory information all the way up to the cortex. Instead, it seems to interfere with subsequent neural processes which may modulate, organize, and interpret such input.

Our observations also indicate that various subdivisions of the extralemniscal paths are differentially sensitive to thiopental. Premedication and remarkably small doses of thiopental may completely suppress component *5*. More drug is necessary to abolish *4* and still more is needed before *3* finally vanishes. Thiopental apparently does not make a synchronous, massive attack on the entire extralemniscal system but rather produces an orderly series of selective blockades in different parts of that system.

French, Verzeano, and Magoun found that ether and pentobarbital exert similar neurophysiological actions in animals. Both agents disrupted extralemniscal transmission but did not block lemniscal activity. Our observations on man, together with their results, suggest that extralemniscal blockade may form the basis for loss of consciousness and amnesia characteristic of the action of all general anesthesias. Correlation of all these data with production of analgesia poses a difficult problem. There is a general belief that barbiturates at the usual clinical doses are not analgesics, although ether clearly seems to be so. The precise relationships of drug-induced

changes in evoked potentials to clinical manifestations of various stages of anesthesia remains a problem for further research.

Summary

Averaged evoked cerebral somatosensory responses were obtained from ten surgical patients before and during induction of thiopental "anesthesia." Premedication (seconal and atropine) produced some interference with late portions of the response. Thiopental quickly abolished these parts of the response and then slowed and reduced a still earlier deflection. All of these components of the response seem of extralemniscal origin. In contrast, the initial deflections of the response which apparently signal lemniscal activity remained essentially unaffected. Thus, some neural mechanisms of thiobarbiturate anesthesia in man seem quite like those previously found in animals: blockade of extralemniscal pathways without suppression of activity in the lemniscal sensory systems.

This work was supported in part by grants M-1530 and M-5286 from the National Institute of Mental Health, United States Public Health Service. Dr. W. W. Lindenmuth, Chief of Surgery, and Miss R. Kruk, Supervisor, Operating Room, and their staffs provided facilities for this study. Mr. Gerald Wasserman aided in collection of the data.

References

1. Rose, J. E., and Woolsey, C. N.: Organization of the mammalian thalamus and its relationships to the cerebral cortex, Electroenceph. clin. Neurophysiol. 1: 391, 1949.
2. Buser, P., Borenstein, P., and Bruner, J.: Etude des systemes "associatifs" visuels et auditifs chez le chat anesthesie au chloralose, Electroenceph. clin. Neurophysiol. 11: 305, 1959.
3. Albe-Fessard, D. M., and Rougeul, A.: Activites d'origine somesthesique evoquees sur le cortex non-specifique du chat anesthesie au chloralose: role du centre median du thalamus, Electroenceph. clin. Neurophysiol. 10: 131, 1958.
4. Albe-Fessard, D., Rocha-Miranda, C., and Oswaldo-Cruz, D.: Activites evoquees dans le noyau caude du chat en reponse a des types divers d'afferences, Electroenceph. clin. Neurophysiol. 12: 405, 1960.
5. French, J. D., Verzeano, M., and Magoun, H. W.: An extralemniscal sensory system in the brain, Arch. Neurol. Psychiat. 69: 505, 1953.
6. French, J. D.: The reticular formation, *In:* Handbook of Physiology, vol. 2. Edited by J. W. Field, V. Hall, and H. W. Magoun, Washington, D. C., The American Physiological Society, 1960.
7. French, J. D., Verzeano, M., and Magoun, H. W.: A neural basis of the anesthetic state, Arch. Neurol. Psychiat. 69: 519, 1953.
8. Buser, P., and Borenstein, P.: Responses somesthesiques, visuelles et auditives recueillies au niveau du cortex "associatif" suprasylvien chez le chat curarise non anesthesie, Electroenceph. clin. Neurophysiol. 11: 285, 1959.
9. Amassian, V. E.: Studies on organization of a somesthetic association area, including a single unit analysis, J. Neurophysiol. 17: 39, 1954.
10. Dawson, G. E.: A summation technique for the detection of small evoked potentials, Electroenceph. clin. Neurophysiol. 6: 65, 1954.
11. Commmunication Biophysics Group and Siebert, W. H.: Processing neuroelectric data, Technical Report No. 351, Research Laboratory of Electronics, Massachusetts Institute of Technology. Cambridge, Technology Press, 1959.
12. Allison, T., Goff, W. R., Abrahamian, H. A., and Rosner, B. S.: The effects of barbiturate anesthesia upon human somatosensory evoked responses, Electroenceph. clin. Neurophysiol., In press.
13. Rosner, B. S., Goff, W. R., and Allison, T.: Cerebral electrical responses to external stimuli, *In:* EEG and Behavior. Edited by G. H. Glaser, New York, Basic Books, 1963.
14. Rosner, B. S., Allison, T., Swanson, E., and Goff, W. R.: A new instrument for the summation of evoked responses from the nervous system, Electroenceph. clin. Neurophysiol. 12: 745, 1960.
15. Goff, W. R., Rosner, B. S., and Allison, T.: Distribution of cerebral somatosensory evoked responses in normal man, Electroenceph. clin. Neurophysiol. 14: 697, 1962.
16. Kiersey, D. B., Bickford, R. G., and Faulconer, A., Jr.: Electroencephalographic patterns produced by thiopental sodium during surgical operations: description and classification, Brit. J. Anesth. 23: 141, 1951.
17. Allison, T.: Recovery functions of somatosensory evoked responses in man, Electroenceph. clin. Neurophysiol. 14: 331, 1962.
18. Forbes, A., and Morrison, B. R.: Cortical response to sensory stimulation under deep barbiturate narcosis, J. Neurophysiol. 2: 112, 1939.
19. Towe, A. L.: Evoked potentials and phenomena of the somatosensory cortex, Confin. Neurol. (Basel) 16: 333, 1956.
20. Rosner, B. S., Goff, W. R., and Allison, T.: Properties of cerebral somatic evoked responses in unanesthetized *Cebus* monkeys, Electroenceph. clin. Neurophysiol., In press.