Brain Stem Reticular Formation and Activation of the EEG

G. Moruzzi, M.D.
H. W. Magoun, M.D.

Transitions from sleep to wakefulness, or from the less extreme states of relaxation and drowsiness to alertness and attention, are all characterized by an apparent breaking up of the synchronization of discharge of elements of the cerebral cortex, an alteration marked in the EEG by the replacement of high-voltage slow waves with low-voltage fast activity. The magnitude of the electrical change parallels the degree of transition, and that most commonly observed in clinical electroencephalography is a minimal one, consisting of an alpha-wave blockade during attention to visual stimulation. Such activation of the EEG may be produced by any type of afferent stimulus that arouses the subject to alertness, or it may be centrally generated, but the basic processes underlying it, like those involved in waking from sleep, have remained obscure.

Recent experimental findings which may contribute to this subject have stemmed from the observation that EEG changes seemingly identical with those in the physiological arousal reactions can be produced by direct stimulation of the reticular formation of the brain stem. The following account describes such features of the response and its excitable substrate as have been determined, provides an analysis of changes in cortical and thalamic activity associated with it, and explores the relations of this reticular activating system to the arousal reaction to natural stimuli. Alterations produced by acute lesions in this system are presented in a succeeding paper. The effects of chronic lesions within it are under investigation.

METHODS

The experiments were performed in cats under chloralosane anesthesia (35–50 mg/K, intraperitoneally) or in the "encéphale isolé" of Bremer, prepared under ether, with exposure margins infiltrated with procaine. Ephedrine was administered intravenously immediately after transection of the cord at C 1. At least an hour elapsed after ether was discontinued before work was begun.

Concentric bipolar electrodes, oriented with the Horsley-Clarke technique, were used for stimulation of, or pickup from, the brain stem. Condenser discharges from a Goodwin stimulator were employed routinely. Lesions were made surgically or electrolytically, and their positions, together with those of electrode placements, were verified histologically.

Potentials were recorded with a Grass model III amplifier and inkwriter. Some cortical records were taken directly from the pial surface, but usually as much of the brain case as possible was left intact, and most cortical pickups were between two screw electrodes, 5–10 mm apart, inserted through burr holes in the calvarium until their tips rested on the dura overlying functional areas. With bipolar leads and by grounding the scalp, stimulus artifacts were negligible. Other technical details are given in the legends.

RESULTS

The response to reticular stimulation consisted of cessation of synchronized discharge in the EEG and its replacement with low-voltage fast activity. The intensity of the alteration varied with the degree of background synchrony present. Conspicuous effects were thus observed against the high-voltage slow waves of chloralosane anesthesia (Figure 1C, 1D), while a fully activated EEG was not further affected (Figure 2A).

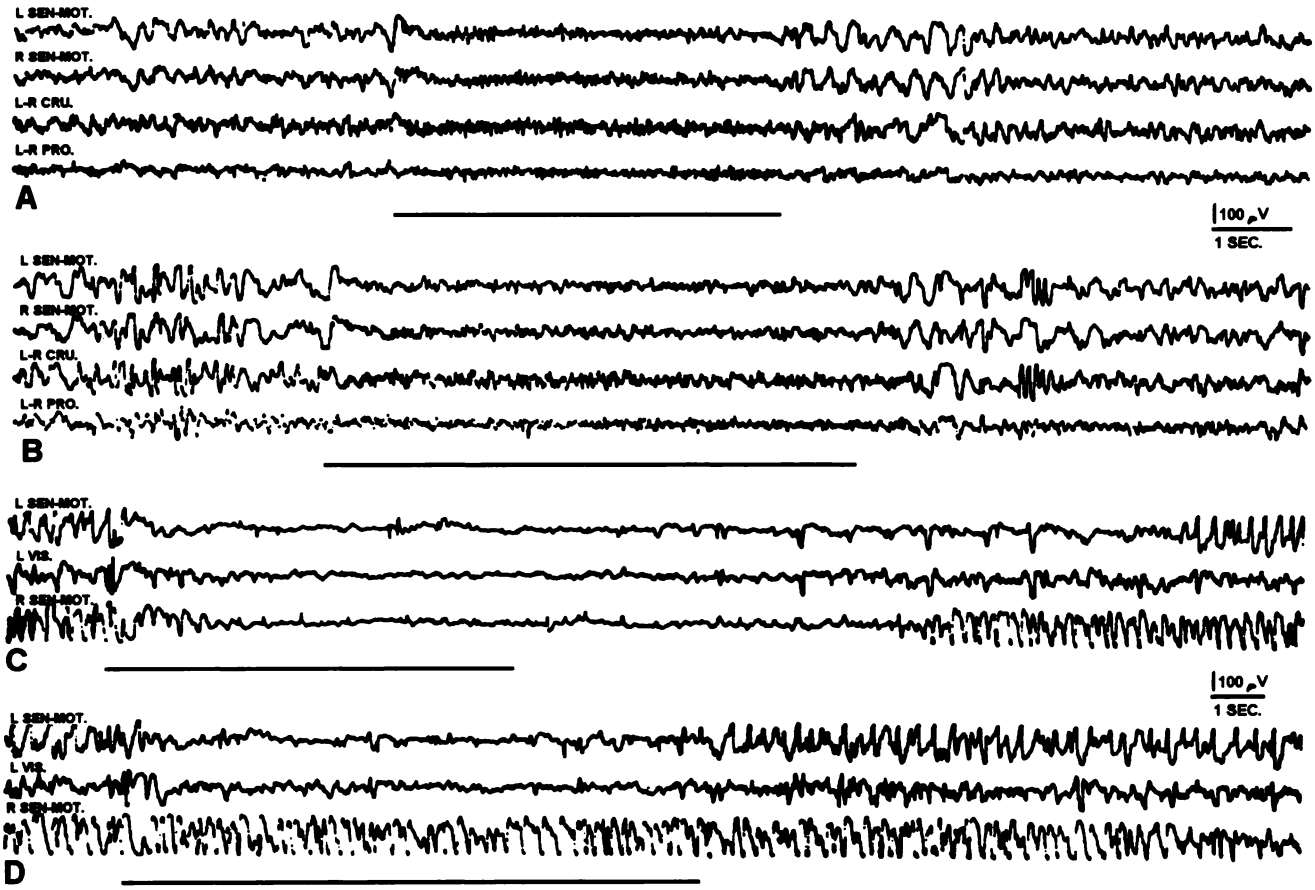
Responses were seen to best advantage when the unanesthetized brain exhibited some relaxation (Figure 2B, 2C) or when light chloralosane anesthesia had induced synchronization without greatly impairing neural excitability (Figure 1A, 1B) . With deeper chloralosane, slow waves were blocked, but low-voltage fast activity was not elicited (Figure 1C, 1D).

The response was a generalized one, being observed in the sensori-motor cortex (Figure 1), where it was often most pronounced, and in the visual (Figure 1C) and auditory (Figure 2B, 2C) cortical areas as well. With minimal reticular stimulation, alterations were best obtained in the ipsilateral hemisphere and were sometimes limited to it (Figure 1D).

The response was readily obtained with low intensities of reticular stimulation, voltages of 1-3 being usually employed. Brief shocks, with a falling phase of 1 msec., were used routinely and were as effective as longer lasting ones. Stimulus frequencies of 50/sec were the lowest

"Brain Stem Reticular Formation and Activation of the EEG," by G. Moruzzi and H. W. Magoun, is reprinted from *Electroencephalography and Clinical Neurophysiology*, Vol. 1, 1949, pp. 455–473, copyright © 1949. Reprinted by permission of Elsevier Science Ireland Ltd.

FIGURE 1. **Effect of stimulation of the brain stem reticular formation upon electro-cortical activity of chloralosane preparations.**
A, B. "Encéphale isolé" with 7 mg chloralosane/K. Replacement of high voltage slow waves, present in A and more pronounced in B, with low voltage fast activity during left bulbo-reticular stimulation (1.5 V, 300/sec).
C. Intact cat with 50 mg chloralosane/K. Left bulbo-reticular stimulation (3 V, 300/sec) blocks chloralosane waves bilaterally, but more rapidly and for a longer time in the ipsilateral cortex. Note that low voltage fast activity does not appear.
D. Like C, but frequency of reticular stimulation reduced to 100/sec. Effect limited to ipsilateral cortex and doesn't outlast stimulus.
In all records, the origin of activity in different channels is given at the left: L. SEN. MOT. signifies left sensory-motor cortex; L.-R. CRU., left to right cruciate gyrus; L.-R. PRO., left to right gyrus proreus; L. VIS., left visual area; L. AUD., left auditory area; L. THAL., left thalamus. The period of bulbar stimulation is marked by a heavy line beneath the record. Calibration and time are stated.



at which definite alterations could be elicited and the response was considerably improved by increasing frequencies up to 300/sec, which were regularly utilized. Thus the EEG response to reticular excitation was best obtained with low voltage, high frequency stimulation.

These responses were not secondary to any peripheral effects of brain stem stimulation. By direct test they were independent of changes in respiration, blood pressure, and heart rate. They occurred in the isolated brain after full atropinization and curarization. As will be seen, they were unquestionably mediated by neural connections between the reticular formation and the cerebral hemisphere.

The distribution of the excitable area is projected upon a reconstruction of the midsagittal plane in Figure 3, and includes the central core of the brain stem, extending from the bulbar reticular formation forward through the pontile and mesencephalic tegmentum into the caudal diencephalon. At the bulbar level, excitable points were distributed in the ventromedial reticular formation and the area of their distribution coincided with that from which suppression of motor activity (Magoun and Rhines, 1946) could be elicited (Figure 4A). Exploration of the overlying cerebellum has revealed excitable points in its fastigial nuclei, the responses possibly being mediated by connections of the roof nuclei with the brain stem reticu-

FIGURE 2. **Effect of reticular stimulation on electro-cortical activity of the unanesthetized "encéphale isolé"**
A–C. Left bulbo-reticular stimulation (3 V, 300/sec) is without effect upon the fully activated cortex (A), but evokes characteristic low voltage fast activity when spontaneous synchrony is present (B and C).

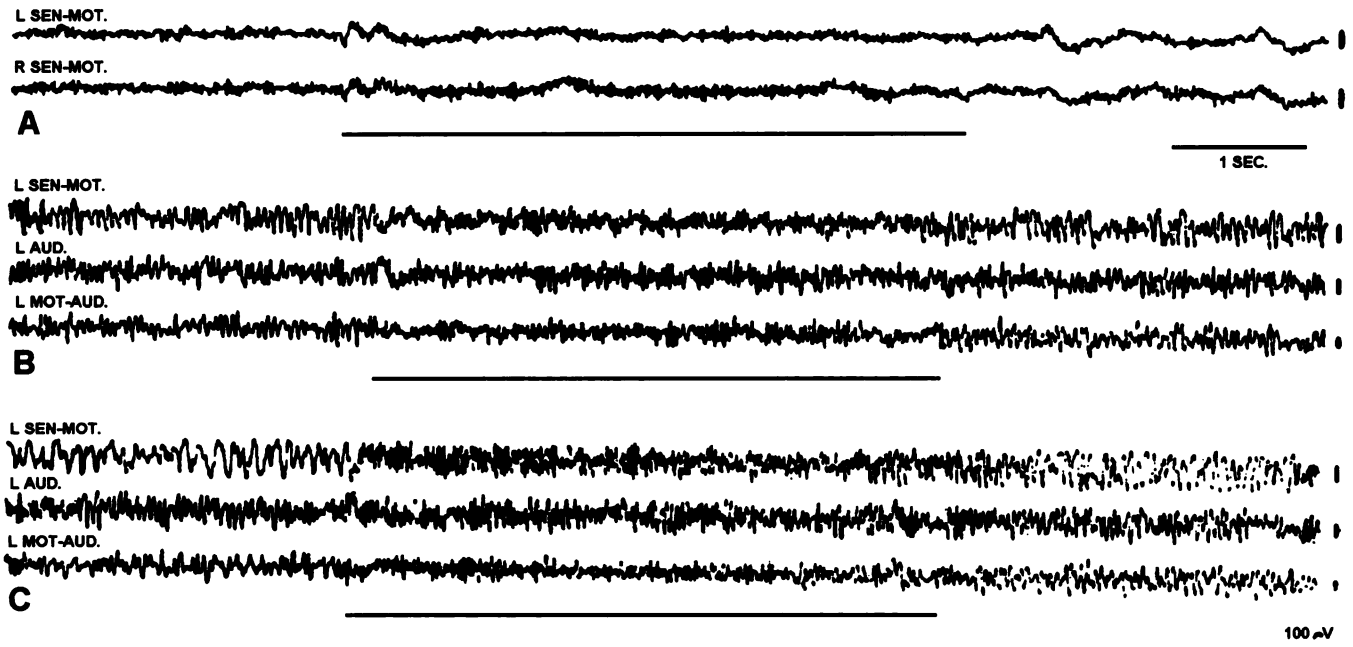
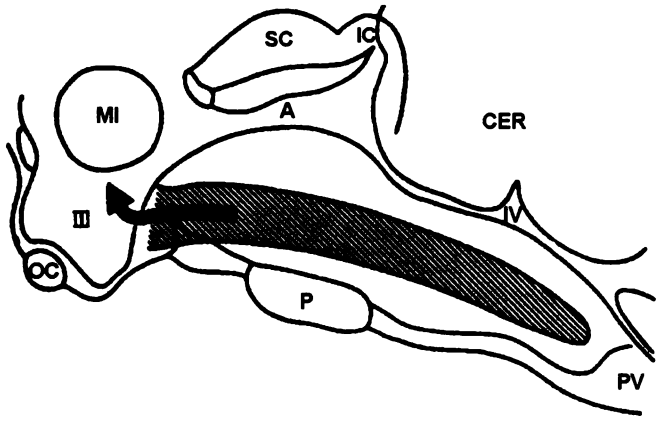


FIGURE 3. **Reconstruction of midsagittal plane of cat's brain stem upon which is projected, with cross-lining, the distribution of the ascending reticular activating system. Abbreviations are as follows: A, aqueduct; CER, cerebellum; IC, interior colliculus; MI, massa intermedia; OC, optic chiasma; P, pons; PY, pyramidal crossing; SC, superior colliculus; III, third ventricle; IV, fourth ventricle.**



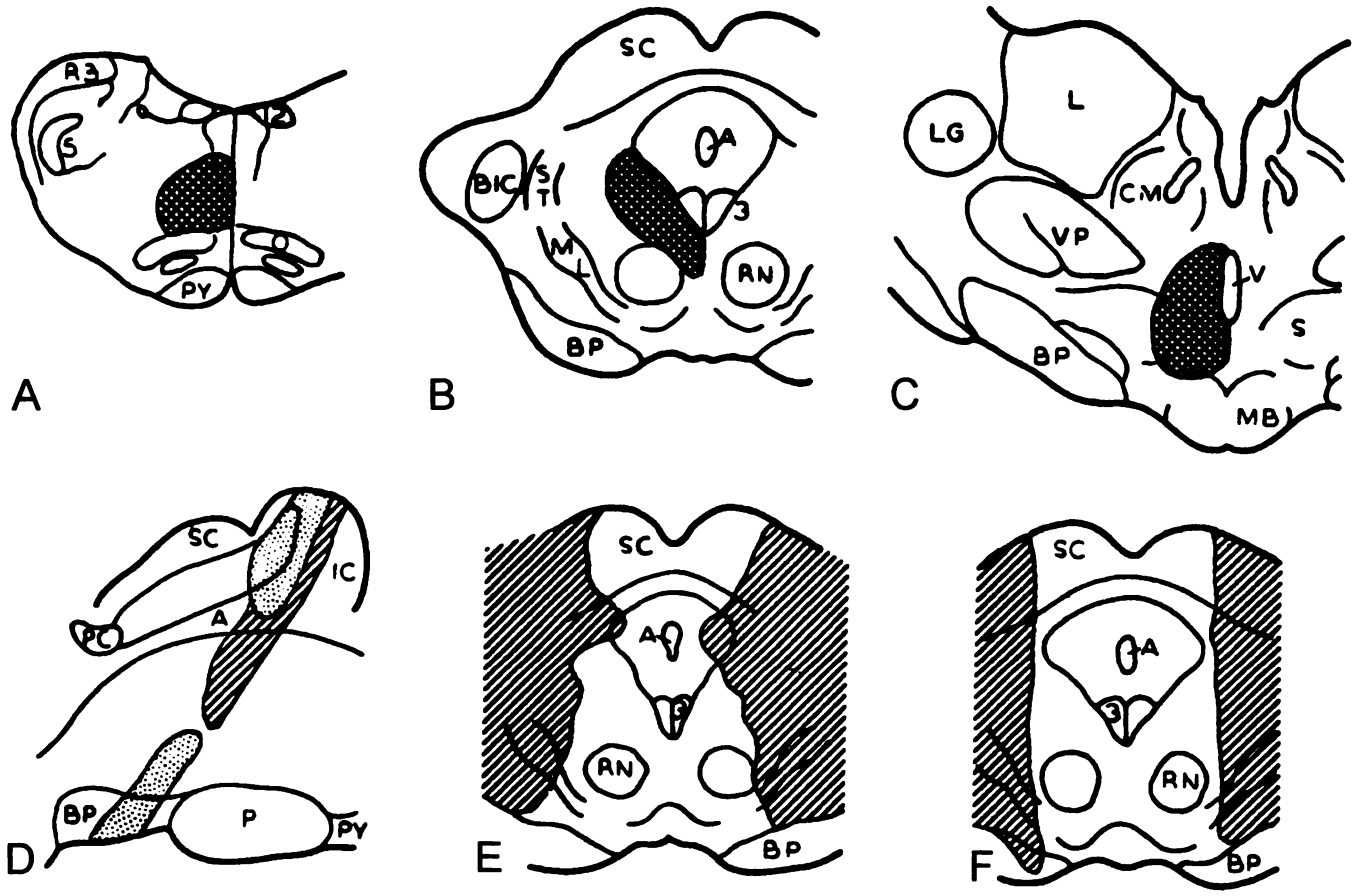
lar formation (Snider, Magoun and McCulloch, 1949). In the midbrain, responses were obtained from the tegmentum bordering the central grey and extending in a paramedian position beneath it (Figure 4B). In the caudal diencephalon, effective points were located near the midline in the dorsal hypothalamus and subthalamus (Figure 4C). From this region, the excitable system is evidently distributed to the overlying thalamus, through which its effects are exerted upon the cortex, and some data bearing on its thalamic mediation will be given later.

The distribution of this ascending system within the midbrain was studied further by observing the effect of lesions here upon the EEG response to bulbo-reticular stimulation. Such responses were unimpaired following sections of the cerebral peduncles or tectum, but were blocked by injury to the mesencephalic tegmentum (Figure 4D). Typical cortical responses to bulbo-reticular stimulation were still obtained after bilateral destruction of all laterally placed mesencephalic structures, including the medial and lateral lemnisci and the spinothalamic tracts (Figure 4E, 4F), leaving intact only the paramedian region from which responses were obtained on direct stimulation (Figure 4B).

A series of ascending reticular relays is presumed to constitute the structural substrate of this brain stem activating system. That responses are not attributable to the antidromic excitation of corticifugal paths, nor to the dromic stimulation of known afferent paths bordering the reticular area, is indicated by a variety of data.

As regards the pyramidal tract, movements referable

FIGURE 4. A–C. Transverse sections through bulbar (A), mesencephalic (B), and caudal diencephalic (C) levels, with cross-lining indicating the area from which reticular responses were elicited with lowest voltage and without complications from exciting other ascending or descending neural connections.
D. Reconstruction of midsagittal plane of the midbrain upon which is projected, with stipple, the position of tectal and peduncular lesions which failed to block the EEG response to bulbo-reticular stimulation. Cross-lining marks the position of a tegmental lesion which abolished this response to bulbar stimulation.
E, F. Transverse sections through the midbrain of two cats, showing the extent of lesions which interrupted the medial and lateral lemnisci and spinothalamic tracts, but which failed to impair the EEG response to bulbo-reticular stimulation.
Abbreviations are as follows: A, aqueduct; BIC, brachium of inferior colliculus; BP, basis pedunculi; CM, centre médian; IC, inferior colliculus; L, lateral thalamic nucleus; LG, lateral geniculate body; MB, mammillary body; ML, medial lemniscus; O, inferior olive; P, pons; PY, pyramid; RB, restiform body; S, subthalamus; SC, superior colliculus; ST, spino-thalamic tract; VP, posterior part of ventral thalamic nucleus; 3, oculomotor nucleus; 5, spinal fifth tract and nucleus; 12, hypoglossal nucleus.



to its excitation never accompanied EEG responses to reticular stimulation, and the latter were still obtained from the bulbar level after section of the fibers of this tract in the basis pedunculi (Figure 4D). Furthermore, single shock stimuli to effective reticular sites did not evoke antidromic potentials in the sensori-motor cortex (Figure 5C, 5E) (Figure 10A), nor did direct stimulation of the bulbar pyramid reproduce the EEG response to reticular stimulation.

A cortico-bulbo-reticular path from area 4-S is distributed to the excitable reticular area of the lower brain stem (Figure 4A) (McCulloch, Graf and Magoun, 1946), but it is similarly impossible to attribute the EEG responses to its antidromic stimulation. This path accompanies the pyramidal tract in the basis pedunculi (McCulloch, Graf and Magoun, 1946) section of which, as noted, left reticular responses unimpaired. The absence of antidromic potentials in the sensori-motor cortex, on single shock stimuli to the bulbar reticular formation (Figure 5C; 10A), might be explained by the small size of the suppressor areas in the cat (Garol, 1942), but a more likely possibility is that the unmyelinated terminals of this extrapyramidal path were never excited with the low intensities of reticular stimulation employed in the present experiments. Reticular responses elicited from brain stem levels cephalad to the bulb are, moreover, impossible to explain on

the basis of antidromic stimulation of this extrapyramidal pathway.

It is equivalently impossible to ascribe reticular responses to the dromic activation of known afferent pathways ascending to the cortex through the brain stem. The medial lemniscus is adjacent to the excitable reticular area through much of its course, and high frequency stimulation of the lemniscal system, like that of the sciatic nerve (Gellhorn, 1947), exerts a desynchronizing influence upon the EEG (Figure 5B). This influence is not as pronounced as that of the reticular formation and higher voltages of stimulation are required to induce it than those which yield primary and secondary cortical sensory responses.

Three lines of evidence clearly show, however, that the desynchronizing influence of the reticular formation cannot be attributed to activation of the lemniscal system, either through physical spread of stimulating current, or by antidromic excitation of possible lemniscal collaterals to the brain stem reticular formation. First, single shock stimuli to excitable reticular points at bulbar (Figure 5C) or midbrain (Figure 5E) levels never evoked potentials in the sensori-motor cortex, as was invariably the case when such shocks were applied to the lemniscal system (Figure 5A), and this simple control was routinely applied throughout the work. Second, the distribution of the excitable reticular area was distinct from that of the course of the medial lemniscus through the brain stem (Figure 4A–4C). Third and finally, EEG responses to bulbar stimulation were unaffected by mesencephalic lesions which bilaterally interrupted the medial and lateral lemnisci and the spino-thalamic tracts (Figure 4E, 4F).

Elimination of these possibilities and the distribution of excitable points through the brain stem both indicate that this response is mediated by a paramedian system of ascending reticular connections. Single shock stimuli to effective bulbar sites do not evoke potentials at effective midbrain or diencephalic sites, however, suggesting that a number of relays are present and that the synapses involved are iterative in nature.

Having now described the desynchronization of the EEG induced by brain stem stimulation and presented evidence that this alteration results from exciting a system of reticular relays ascending to the diencephalon, attention may next be directed to the effect of reticular stimulation upon types of evoked activity in the cortex.

Effect upon evoked sensory potentials. In the chloralosane cat, a single afferent volley, initiated either by natural stimuli or by shocks to the sciatic nerve or posterior column, evokes primary and secondary[1] cortical potentials and sensory "after-discharge" succeeding them. The secondary response and after-discharge occur generally in the cortex and are readily observed in the EEG. During stimulation of the brain stem reticular formation, such secondary responses continued to be evoked by afferent volleys, usually without alteration (Figure 6A), but sometimes with reduction of amplitude and simplification of potential form, particularly in cortical areas outside the sensori-motor region (Figure 8B). Following conclusion of reticular stimulation, transient enhancement of the secondary response was occasionally observed (Figure 6B).

The succeeding high-voltage slow waves, called sensory after-discharge, were invariably abolished during reticular stimulation (Figure 6A–6C). In full anesthesia, the cortical record then became flat between secondary responses (Figure 6A, 6B), while, if anesthesia was light, low-voltage fast activity was present in these intervals (Figure 6C). The abolition of sensory after-discharge might thus be simply another manifestation of the desynchronization of the EEG induced by brain stem stimulation.

Such sensory after-discharge was not impaired, however, during cortical desynchronization induced by high frequency stimulation of the sciatic nerve (Figure 8D).

Effect upon evoked pyramidal discharge. In the chloralosane cat, afferent volleys arriving at the cortex there evoke pyramidal discharges which are responsible for the jerky movements characteristic of this anesthesia (Adrian and Moruzzi, 1939). Although afferent volleys continued to reach the cortex during stimulation of the brain stem reticular formation, such pyramidal discharge, recorded from the basis pedunculi, was reduced or abolished (Figure 7A) and contraction of leg muscles, induced by it, disappeared (Figure 7B; 8F). This disappearance of movement was not attributable to spinal inhibition, for reflexly induced contraction of the same muscles was not affected by such midbrain stimulation (Figure 8G). The movements induced by this pyramidal discharge were not reduced during desynchronization of cortical electrical activity by high-frequency sciatic stimulation (Figure 8E), and the facilitation observed might have been due to spinal alterations. Whether the more pronounced cortical desynchronization resulting from reticular stimulation (Figure 5B, 5D, 5F) opposed

[1]These "secondary potentials" resemble those of Forbes and Morison (1939) recorded, in deep barbiturate anesthesia, in and also outside of the somatic receiving area and disappearing when the frequency of afferent stimuli rose above 5/sec. Since under chloralosane anesthesia they are associated with pyramidal discharge, they correspond to the "efferent waves" of Adrian (1941).

FIGURE 5. Comparison of the effects of stimulating the right posterior column (A, B) and the left reticular activating system at bulbar (C, D) and midbrain (E, F) levels, under full chloralosane anesthesia. Stimulus frequency is 1/sec in left records (A, C, E) and 300/sec in right records (B, D, F); intensity is 3 V throughout.
Single shock stimuli to the posterior column evoke sensory potentials in the cortex (A), not elicited by similar reticular stimulation (C, E). High frequency stimulation of the posterior column causes some desynchronization of the EEG (B), but more pronounced effects are induced by reticular stimulation (D, F).

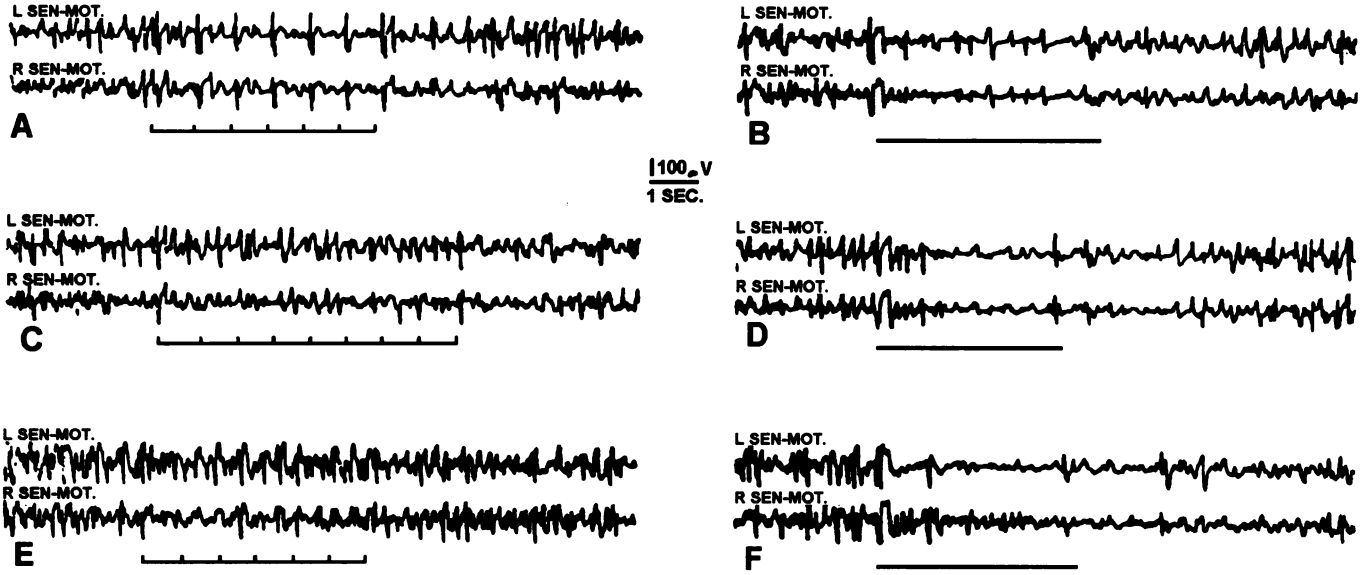


FIGURE 6. Effect of reticular stimulation upon cortical sensory responses.
A. Tapping skin of ankle.
B. Make and break shocks to the sciatic nerve, under full chloralosane anesthesia as in A.
C. Single shocks to the upper end of the posterior column, in "encéphale isolé" with 7 mg chloralosane/K.
In each instance the evoked sensory spike is unaffected, while consequent after-discharge is abolished.
Note low voltage fast activity during reticular stimulation in C, with minimal anesthesia, and its absence in A and B, with full anesthesia.

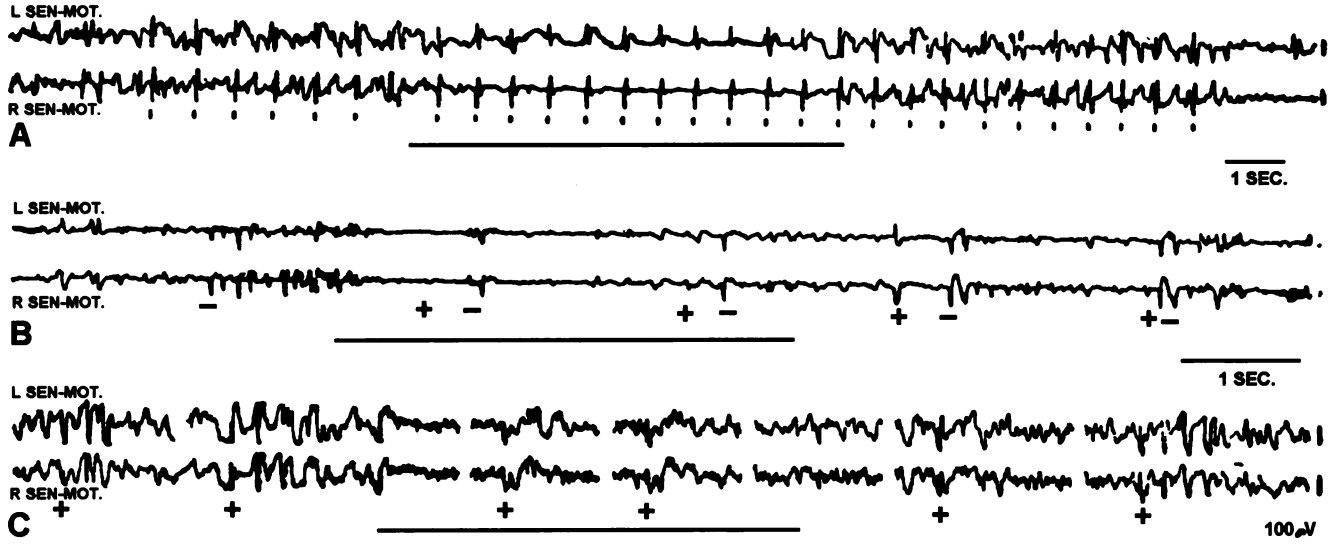
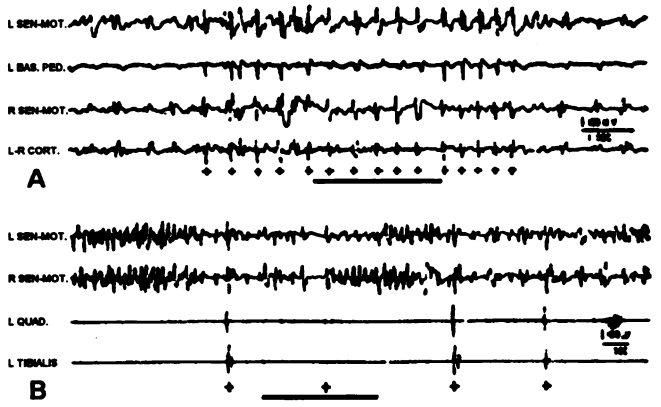


FIGURE 7. **Effect of reticular stimulation on pyramidal discharges and chloralosane jerks.**
A. Break shocks to sciatic nerve cause sensory cortical responses and corresponding pyramidal discharge, recorded from the basis pedunculi (channel 2). The latter and sensory after-discharge are almost abolished by bulbo-reticular stimulation (3 V, 300/sec), which leaves cortical sensory spikes unaffected.
B. Break shocks to sciatic nerve cause chloralosane jerks, recorded in myograms of the quadriceps and tibialis (channels 3 and 4). Movement was abolished during stimulation of the midbrain tegmentum (3 V, 300/sec), although cortical sensory potentials were still elicited. Such midbrain stimulation had no effect on spinal reflexes.



simultaneous discharge of a sufficient number of interneurons connecting the sensory with the motor cortex to prevent threshold activation of the cells of origin of the pyramidal tract, or whether these cells were somehow rendered incapable of being excited by afferent cortical volleys, during brain stem stimulation, remains unsettled.

Effect upon cortical strychnine spikes. The recurring spikes produced by local strychninization of the sensorimotor cortex were not prevented by exciting the brain stem reticular formation, nor was conduction of this discharge to the opposite cortex interfered with (Figure 9B). Synchronized convulsive waves in a cortical fit, induced by supramaximal stimulation of the motor cortex, were similarly unaffected by bulbo-reticular stimulation.

Effect upon recruiting response. The cortical response to low frequency stimulation of the diffuse thalamic projection system consists of a series of high-voltage slow waves, one for each shock, which recruit to a maximum during the initial period of stimulation (Figures 10–13) (Morison and Dempsey, 1942; Dempsey and Morison, 1942; Jasper and Droogleever-Fortuyn, 1946; Jasper, 1949). These waves may be confined to the ipsilateral hemisphere, but are usually present, though smaller, contralaterally as well. Depending upon the site of thalamic stimulation, they may be distributed anteriorly, posteriorly, or generally in the cortex.

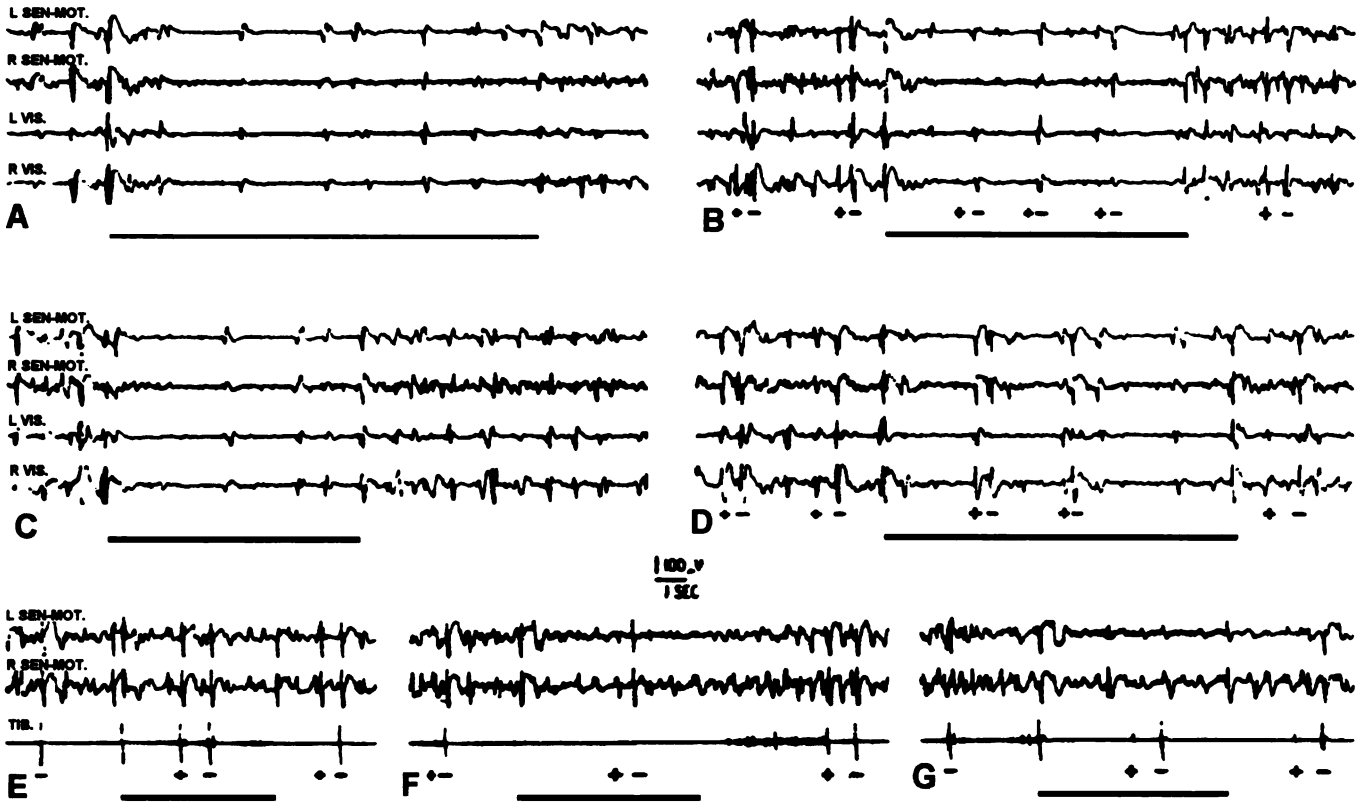
In the unanesthetized "encéphale isolé," such a recruiting response, in both sensori-motor cortices and the ipsilateral auditory area (Figure 10D), was either abolished or greatly reduced in all regions during intercurrent bulbo-reticular stimulation and recruited again upon its cessation (Figure 10E, 10F). Exciting the rostral end of the reticular system in the subthalamus had a similar effect (Figure 11E). Another instance is shown in Figure 9A, in which case strychnine was then applied locally to the cortex. The recruiting response was transiently abolished following strychnine spikes interspersed in its course, suggesting that identical cortical neurons were involved in these two activities (Figure 9C). Subsequent repetition of reticular stimulation again opposed the recruiting response without, as noted above, altering the spikes induced by strychnine (Figure 9D). It should be noted that low frequency stimulation of the ascending reticular system, even in the subthalamus, did not itself induce a recruiting response (Figures 10B; 11D).

Of the different types of evoked cortical activity upon which the effect of reticular stimulation was tested, certain ones, then, secondary sensory responses and strychnine spikes, exhibited little or no alteration, while others, sensory after-discharge and recruiting responses, were abolished. Of the two types of transcortical conduction observed, that from the sensory to the motor cortex, underlying the pyramidal discharge to afferent volleys under chloralosane anesthesia, was blocked, while the other, from a strychninized area of the cortex to the opposite cortex, was unaffected. It is not at present possible to decide whether any common factors underlie these similarities and differences.

Thalamic mediation of response. The generalized distribution of the alteration in the EEG induced by reticular stimulation has implications for the manner of its mediation by the thalamus. It seems likely that the reticular formation could exert its influence upon all parts of the cortex either by acting generally upon the thalamus or by influencing its diffuse projection system alone. At present, each possibility appears relevant, for there is indication both that the diffuse projection system is involved and that the reticular influence may not operate exclusively through it.

Evidence for the mediation of the reticular effect by the diffuse thalamic projection system is presented in Figure 12. The low-frequency stimulation of a portion of this system, on one side of the midline, induced recruiting responses not only in both cortices but in a corresponding region of the opposite thalamus as well (Figure 12A). This evoked intra-thalamic activity was then abolished during intercurrent bulbo-reticular stimulation and returned

FIGURE 8. **Comparison of effect of reticular and sensory stimulation upon spontaneous and evoked electro-cortical activity.**
A, C. Abolition of chloralosane waves during (A) bulbo-reticular stimulation (2 V, 300/sec) and (C) sciatic nerve stimulation (3 V, 300/sec).
B, D. Sensory cortical potentials evoked by make and break shocks to sciatic nerve are reduced by bulbo-reticular stimulation at 2 V, 300/sec (B), but not by stimulation of the contralateral sciatic nerve at 3 V, 300/sec (D).
E, F. Chloralosane jerks evoked by break shocks to the sciatic nerve, and recorded in myograms of the tibialis anticus, were augmented (E) by contralateral sciatic nerve stimulation (3 V, 300/sec) and abolished (F) by stimulation of the midbrain tegmentum (3 V, 300/sec). Such midbrain stimulation did not influence tibialis contraction in the ipsilateral flexor reflex (G).

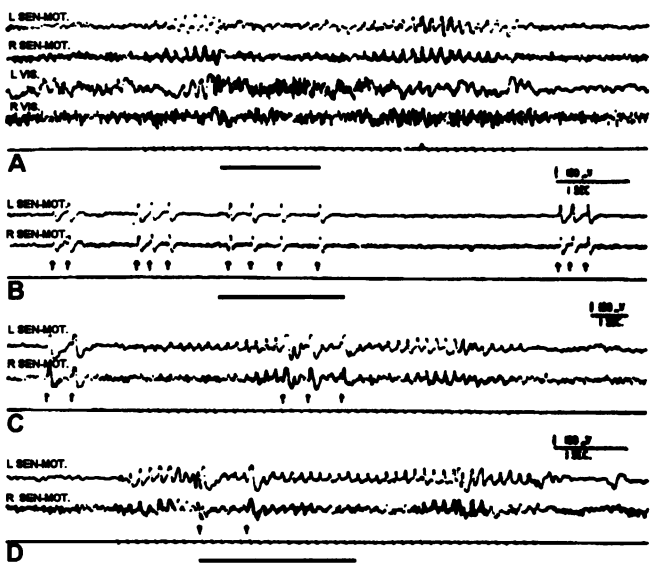


again upon its cessation (Figure 12B, 12C), thus demonstrating a reticular influence upon the diffuse projection system at the thalamic level. It is uncertain whether the corresponding cortical changes were secondary to those in the thalamus in these instances, however, for though cortical recruiting responses were greatly reduced, small cortical waves were still present during reticular stimulation at a time when all synchronized activity was absent from the record of this thalamic sample (Figure 12B, 12D: compare left cortical and thalamic channels).

This same preparation was next lightly anesthetized with chloralosane, with the development of characteristic high-voltage slow waves both in the cortex and subcortically, within and between components of the diffuse thalamic projection system. Bulbo-reticular stimulation then desynchronized this activity as effectively in the electrothalamogram as in the EEG (Figure 12D, 12E).

Further indication that the reticular influence may be mediated by the diffuse thalamic projection system is provided by comparing its effect upon the EEG with that of direct, intra-thalamic stimulation of this system. Recruiting responses were obtained by successively stimulating portions of the diffuse system in the left (Figure 11A) and right (Figure 11B) sides of the thalamus. The recruiting response to left thalamic stimulation was then repeated and intercurrent stimulation of the same right thalamic site at 300/sec abolished it as effectively (Figure 11C) as did subsequent stimulation of the rostral end of the reticular system in the subthalamus (Figure 11E). As regards the diffuse thalamic projection system, then, reticular stimulation has the same effect upon the electrogram of its thalamic components that it does upon the EEG, and this influence upon the EEG can be reproduced by the direct high-frequency stimulation of this system within the thalamus.

FIGURE 9. **Effect of reticular stimulation upon recruiting response and cortical strychnine spikes.**
A. Recruiting response to left thalamic stimulation (5 V, 7.5/sec) in "encéphale isolé," abolished by left bulbo-reticular stimulation (2 V, 300/sec)
B. Strychnine spikes in both sensory-motor areas, induced by local application of strychnine to left motor cortex, were not decreased by left bulbo-reticular stimulation (2 V, 300/sec).
C. Decrease of recruiting response (evoked as in A), following interspersed strychnine spikes.
D. Recruiting response (evoked as in A) markedly decreased by left bulbo-reticular stimulation (2 V, 300/sec) which did not affect strychnine spikes.



Similar desynchronization, both of spontaneous activity and of the recruiting response, has been observed, however, to result from high frequency stimulation of the discretely projecting, posterior part of the ventral thalamic nucleus, and the effect was generalized in the cortex. It remains for further study to determine whether such responses were mediated by direct cortical projections or, as seems more likely, through other subcortical systems.

After ipsilateral destruction of the intralaminar thalamic region, bulbo-reticular stimulation still desynchronized the EEG bilaterally and as markedly as in initial controls. After extending the lesion until the massa intermedia and intralaminar regions of the thalamus were destroyed bilaterally, bulbar stimulation still seemed to have some effect upon the EEG, but cortical activity was then so reduced that it was difficult to draw conclusions concerning the significance of the results. These findings only serve to introduce the problem of thalamic mediation of the lower brain stem influence upon the EEG, and much added study will be necessary to clarify this subject.

The reticular effect and arousal reactions. In the acute study of arousal reactions, anesthesia cannot be employed, for its major action is to block them, nor is the unanesthetized "encéphale isolé" suitable, for its EEG is typically activated and only rarely exhibits spontaneous synchrony. In the latter preparation, however, recruiting responses sometimes provide a background of cortical activity upon which the arousal effect of natural stimuli can be tested. Figure 13 shows a series of such instances, in which the high-voltage slow waves of the recruiting response were abolished and replaced by low-voltage fast activity, during loud whistling (A), rubbing the nose (B), and blowing air on the head (C) and eyes (D). Indistinguishable from these changes to natural stimuli, except for somewhat faster low-voltage activity, were those produced by electrical stimulation of the posterior column (E) and bulbar reticular formation (F).

Such abolition of recruiting responses by natural or bulbar stimulation was observed only when the frequency and intensity of thalamic stimulation yielding the recruiting response was just above threshold, and in some cases reticular stimulation could still abolish the recruiting response at a time when natural stimuli were ineffective. Because of these and other difficulties in securing stable testing conditions, attempted repetition of arousing natural stimuli after differential interruption of ascending sensory and reticular paths in the anterior brain stem was abandoned in favor of chronic preparations.

DISCUSSION

The evidence given above points to the presence in the brain stem of a system of ascending reticular relays whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity. This effect is exerted generally upon the cortex and is mediated, in part, at least, by the diffuse thalamic projection system. Portions of this activating system, chiefly its representation in the basal diencephalon, have previously been identified.

In the pioneer studies of Morison and his associates, in which the foundation for so much current work upon the EEG was laid, hypothalamic, subthalamic and medial thalamic excitation was found, in 1943, to suppress intermittent Dial bursts without affecting other types of cortical activity, such as responses to sensory stimulation (Morison, Finley and Lothrop, 1943; Dempsey and Morison, 1943). The effect was considered to be inhibitory in nature and was attributed to the excitation of afferent

FIGURE 10. Effect of reticular stimulation upon recruiting response. Left bulbo-reticular stimulation at 3 V in "encéphale isolé."
A. Single shocks to bulb do not evoke cortical potentials.
B. Bulbar stimulation at 7.5/sec does not evoke recruiting response.
C. Bulbar stimulation at 300/sec activate EEG.
D. Recruiting response evoked by left thalamic stimulation (5 V, 7.5/sec).
E. Recruiting response to left thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec).
F. Recruiting response to right thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec).

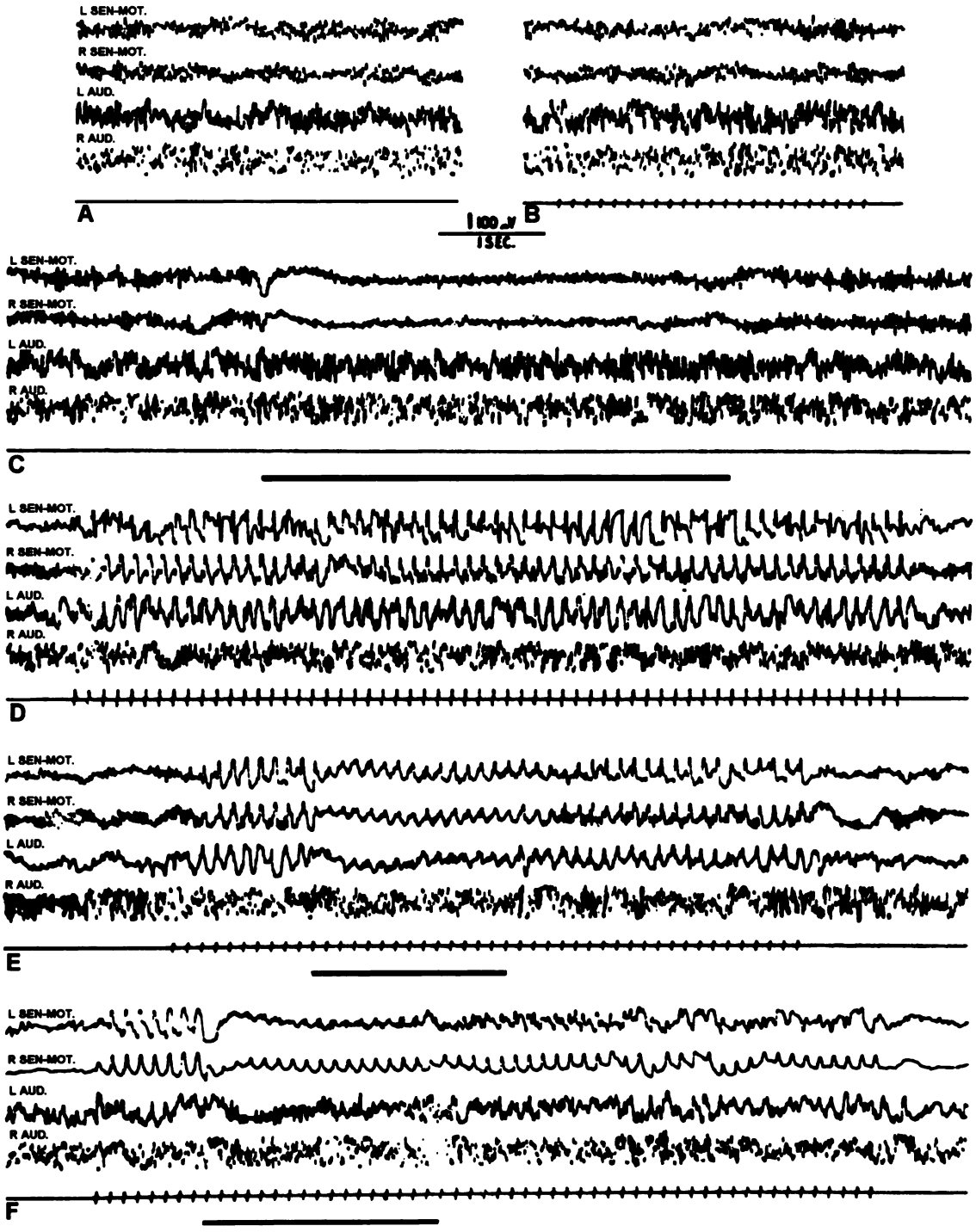


FIGURE 11. Reproduction of reticular response by high frequency stimulation of diffuse thalamic projection system.
A, B. Recruiting responses induced by left (A) and right (B) thalamic stimulation (5 V, 7.5/sec) in "encéphale isolé."
C. Recruiting response to left thalamic stimulation reduced or abolished by stimulating the same right thalamic site as in B, but with 5 V, 300/sec.
D. Right electrode lowered into subthalamus, the stimulation of which with 5 V, 7.5/sec fails to induce a recruiting response.
E. Subthalamic stimulation, with 5 V, 300/sec, reduces or abolishes the recruiting response to left thalamic stimulation.

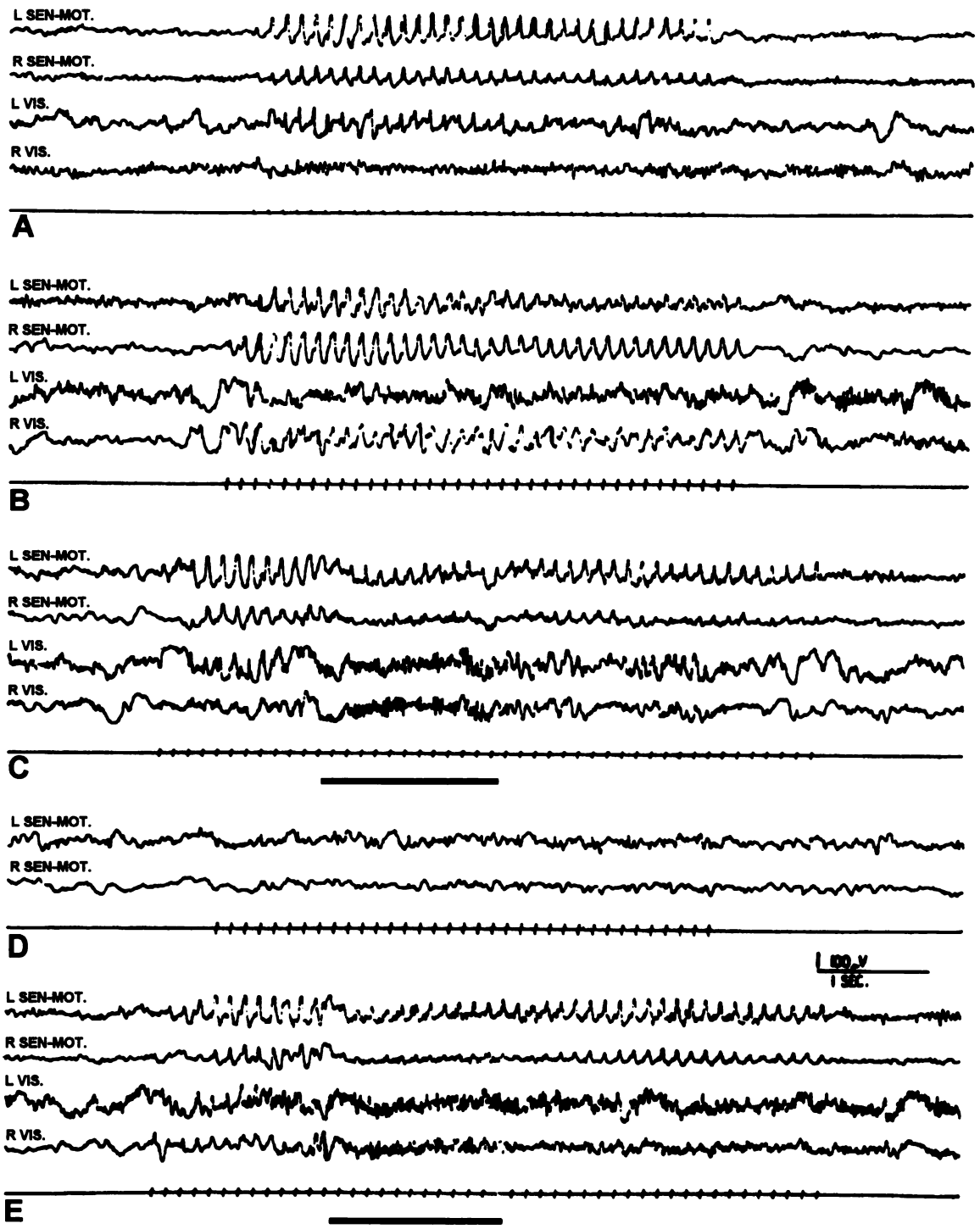


FIGURE 12. Effect of reticular stimulation upon electrothalamogram of diffuse projection system. A–C. Unanesthetized "encéphale isolé."
A. Recruiting response to right thalamic stimulation (8 V, 7.5/sec) is recorded both from cortex and from and between thalamic sites yielding recruiting responses or response on stimulation.
B, C. Recruiting response in cortex and left thalamus, evoked by right thalamic stimulation as in A, is reduced or abolished during left bulbo-reticular stimulation (3 V, 300/sec).
D, E. Same preparation with 7 mg chloralosane/K. Chloralosane waves recorded from cortex and from left thalamic site (channel 3), which itself yielded a recruiting stimulation, are abolished in all areas and replaced by low voltage fast activity during left bulbo-reticular stimulation (2 V, 300/sec).

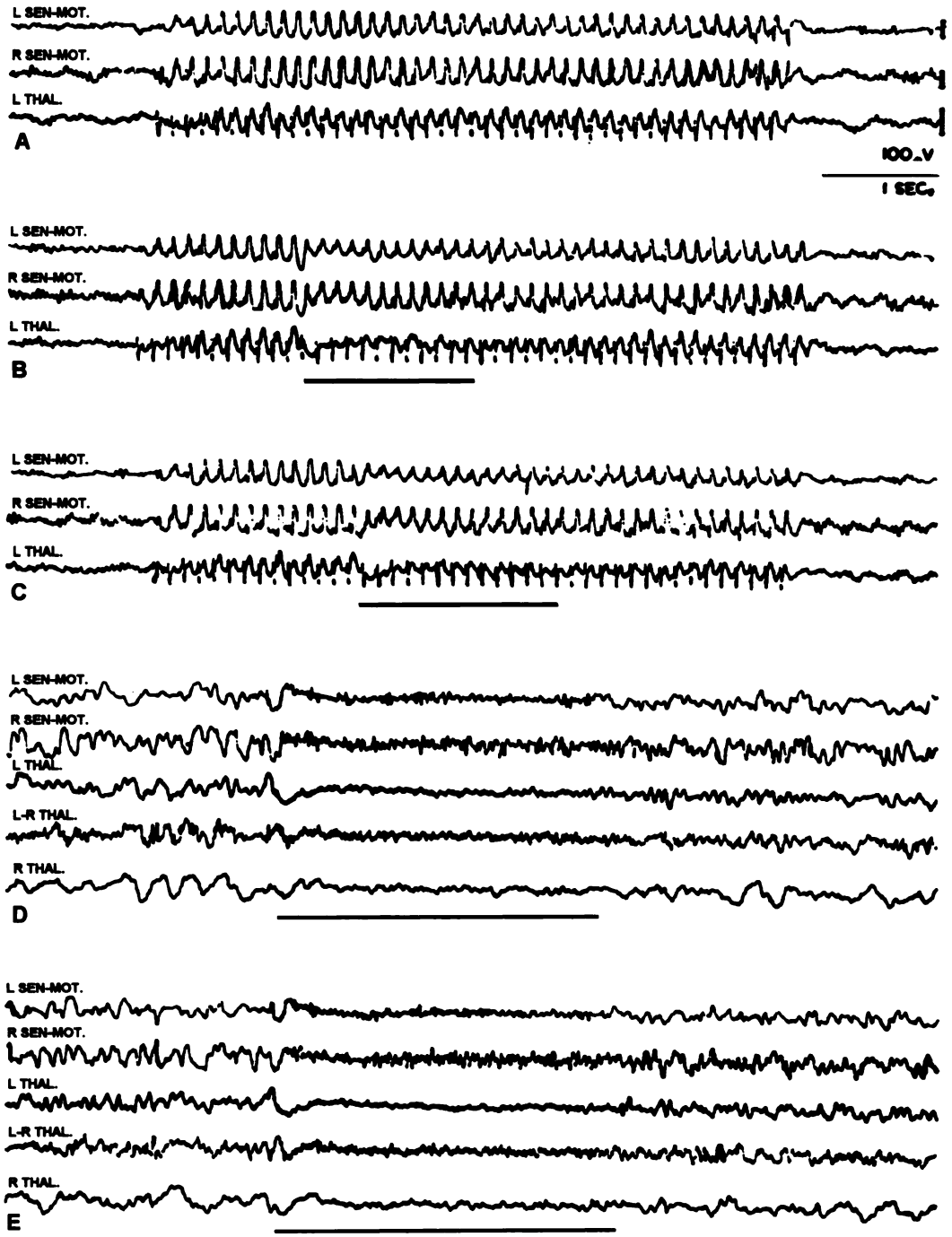
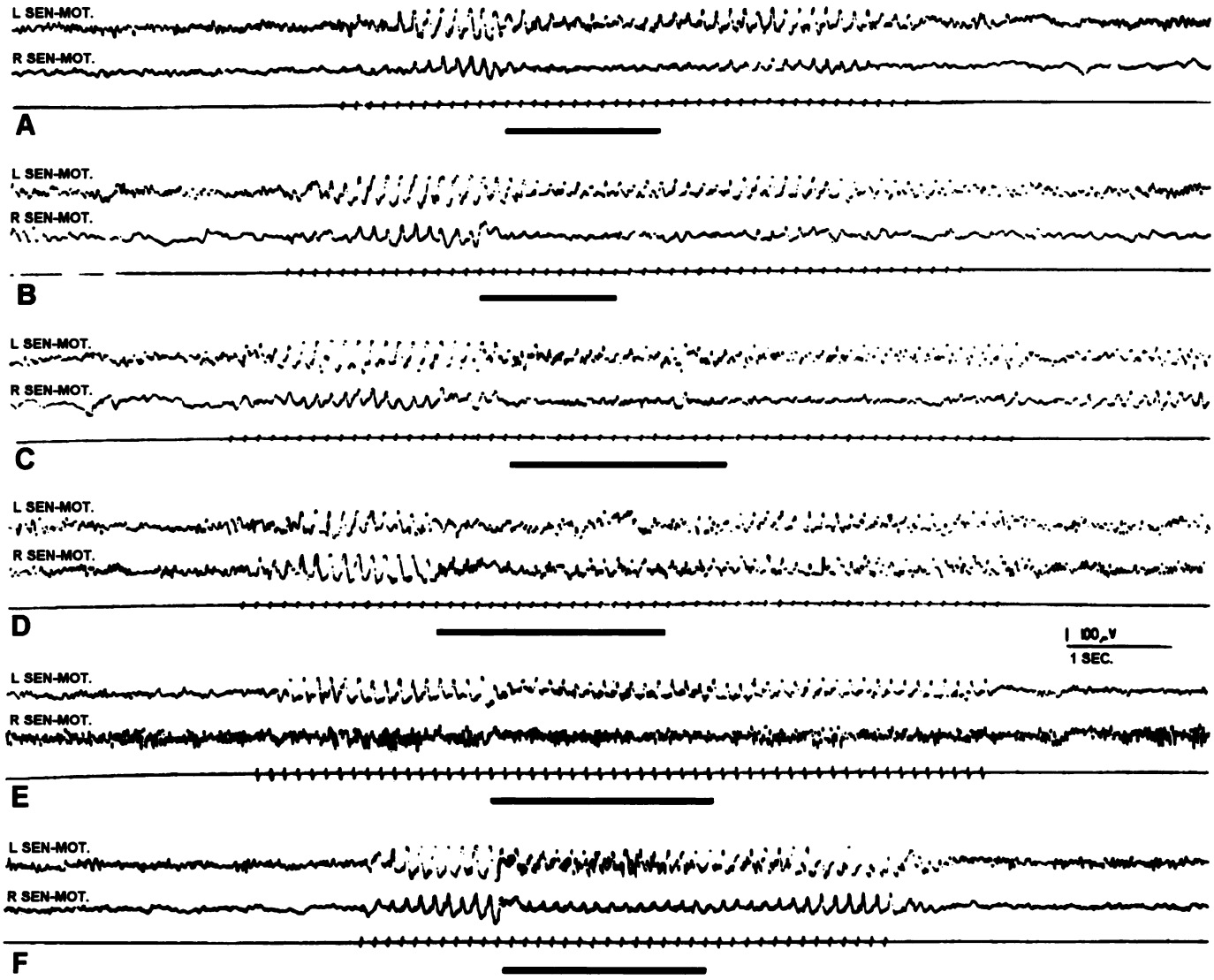


FIGURE 13. **Abolition of recruiting responses by sensory and reticular stimulation. Recruiting responses, evoked by left thalamic stimulation (5 V, 300/sec) in an "encéphale isolé," identically reduced or abolished by loud whistling (A), blowing air on head (B), rubbing nose (C), blowing air on eyes (D), stimulating the right posterior column at 2 V, 300/sec (E), and stimulating the left bulbar reticular formation at 2 V, 300/sec (F).**



pathways simply passing through this region.

Two years later, Murphy and Gellhorn (1945) found this suppression of Dial bursts, on hypothalamic stimulation, to be accompanied by dispersal of strychnine spikes and by prolonged increase in the frequency and amplitude of low-voltage, background, electro-cortical activity. They pointed out that these latter alterations were excitatory or facilitatory in nature, and attributed the disappearance of bursts to an associated lessened degree of synchrony of firing of cortical neurons, rather than to inhibition. Connections from the hypothalamus to the dorso medial and intralaminar thalamic region, and thence to cortex, were suggested to provide the channels by way of which these effects were produced and, though the study was undertaken principally to elucidate hypothalamic facilitation of the motor cortex, the generalized distribution of the EEG changes was emphasized.

More recently still, Jasper and his associates (1948) observed a generalized acceleration of spontaneous elec-

trocortical activity, simulating an arousal or waking reaction, from stimulation of the periaqueductal portion of the midbrain, the posterior hypothalamus, and the massa intermedia of the thalamus; and Ward (1949) obtained a prolonged generalized increase in both voltage and frequency of the EEG following stimulation of the bulbar reticular formation.

While interpretation of these findings has been varied, their basic similarity can leave little doubt that each of these investigators has dealt with manifestations of the same system as that described above. The present work thus confirms, extends, and interrelates these earlier contributions and, from the mass of observations brought to bear upon it, the existence of this brain stem activating system now seems firmly established.

In discussing the general significance of these findings for electroencephalography, attention should certainly be focussed upon the arousal reaction. The breaking up of synchronous cortical discharge by afferent stimulation, first observed by Berger (1930) as alpha blockade on opening the lids, and since found to be a common response to any type of afferent stimulation, is currently attributed to the desynchronizing action of afferent volleys arriving directly at the receiving areas of the cerebral cortex (Adrian and Matthews, 1931; Adrian, 1947; Bremer, 1938, 1944; Walter and Walter, 1949). A number of relevant observations are difficult to explain on this basis, however.

More than a decade ago, Ectors (1936) and Rheinberger and Jasper (1932) observed that serially repeated stimulation soon failed to induce activation, though afferent volleys presumably continued to reach the cortex, and it was noted that, in order to be effective in this regard, such stimuli must arouse the subject to alertness or attention. In addition, when an activation pattern was so induced, it was by no means confined to the receiving area of the afferent system stimulated (see also Bremer, 1943), nor did it appear first in this area and radiate from it. Whether somatic, auditory or, to a lesser extent, visual stimulation was employed, when an arousal reaction was evoked, it appeared simultaneously in all parts of the cortex and often continued for considerable periods in it after afferent stimulation had ceased.

More recently, Monnier's (1949) analysis of the sequence of EEG events induced by visual stimulation in man has shown that alpha blockade is not initiated for a considerable period after the electrocortical changes evoked by the afferent volley are completed, and its prolonged latency might more easily be explained by invoking a subsidiary mechanism than by accounting for it through direct cortical action. Furthermore, the generalized arousal reaction to vestibular stimulation has been shown by Gerebtzoff (1940) to be still elicitable after ablation of the cortical receiving area for this afferent system.

In the present experiments, typical EEG arousal reactions have been reproduced by stimulating the brain stem reticular formation, without exciting classical sensory paths. Crucial evidence that the reticular formation is involved in the arousal reaction to natural stimuli may not yet be obtained but, in addition to being suggested by the data at hand, such a possibility might offer an explanation for the failure of afferent stimuli to evoke arousal from somnolence, lethargy or coma, resulting from injury to the upper brain stem, which left the major sensory paths to the cortex intact (Ingram, Barris and Ranson, 1936; Ranson, 1939; Magoun, 1948). A conception of the arousal reaction in which collaterals from sensory paths first activated the brain stem reticular formation and exerted their influence upon cortical electrical activity indirectly through it seems a logical postulate from all these observations, and was, in fact, proposed as long ago as 1940 by Gerebtzoff to account for his observations to which reference was made above.

The proposed participation of the brain stem activating system in the arousal reaction, if established, might represent an aspect of its function concerned with alerting the cortex to abrupt and more or less pronounced alterations in the external environment. It may next be proposed that the presence of a steady background of less intense activity within this cephalically directed brain stem system, contributed to either by liminal inflows from peripheral receptors or preserved intrinsically, may be an important factor contributing to the maintenance of the waking state, and that absence of such activity in it may predispose to sleep.

Bremer's fundamental discovery (1935, 1938) that the EEG of the unanesthetized cerebrum, isolated from the rest of the nervous system by mesencephalic transection, resembled that of an intact brain in natural sleep or under barbiturate anesthesia, led him to the conclusion that sleep is the result of deafferentation of the cerebral cortex. Afferent impulses from olfactory and visual receptors are still accessible to such a "cerveau isolé," and more recent work has indicated that sleep changes in the EEG are best produced by basal diencephalic injury (Lindsley, Bowden and Magoun, 1949). But putting these qualifications aside, it should be pointed out that at the time Bremer's discovery was made, classical sensory paths were the only known connections ascending through the midbrain, to the interruption of which the ensuing sleep changes in the "cerveau isolé" could be attributed. The present identification of a second, parallel system of ascending reticular relays, whose direct stimulation induces EEG changes characteristic of wakefulness, now raises a possible alternative inter-

pretation of Bremer's observations, for the obvious question arises: is the production of sleep in the cerebrum, following mesencephalic transection, to be attributed to deafferentation in the strict sense, or to the elimination of the waking influence of the ascending reticular activating system? Two lines of evidence favor this latter possibility.

As regards barbiturate sleep, Forbes et al. (1949) have recently pointed out that the ready conduction of afferent impulses to the cortex under deep barbiturate anesthesia is inconsistent with the view that the sleep-inducing properties of these drugs depend upon functional deafferentation.[2] Conversely, it has been found in the present study that under barbiturate anesthesia, bulbo-reticular stimulation is much less effective in activating the EEG than in a chloralosane or unanesthetized preparation. The fact that hypothalamic stimulation is effective under such anesthesia (Morison, Finley and Lothrop, 1943: Murphy and Gellhorn, 1945: Jasper, Hunter and Knighton, 1948) suggests that the blocking of reticular relays within the brain stem may be involved in the production of sleep by barbiturates.

As regards sleep induced by rostral brain stem injury, prolonged somnolence has followed chronic lesions in the basal diencephalon and anterior midbrain which did not involve afferent pathways to the cortex, but which were placed medial and ventral to them in the region of distribution of the ascending reticular activating system (Ingram, Barris and Ranson, 1936; Ranson, 1939), and similar results have followed injury to this region from tumors (Fulton and Bailey, 1929) or encephalitis (von Economo, 1918; Richter and Traut, 1940) in man.

Though somnolence was incontestable, EEG studies were not undertaken in the animals or patients to which reference is made, but more recently Ingram, Knott and Wheatley (1949) have studied alterations in the EEG following chronic, experimental hypothalamic lesions, and the results of acute basal diencephalic and lower brain stem destruction are reported in the succeeding paper (Lindsley, Bowden and Magoun, 1949). In the latter investigation, sleep changes in the EEG, identical with those of barbiturate anesthesia, resulted from basal diencephalic and anterior midbrain lesions which spared sensory pathways to the cortex, but interrupted the rostral distribution of the ascending reticular activating system. Conversely, extensive deafferentation of the cortex, by section of ascending pathways in the lateral portion of each side of the midbrain, together with bilateral interruption of the optic and olfactory tracts, failed to induce such alterations.

The conception of sleep as a functional deafferentation of the cerebrum is not opposed by this evidence if the term "deafferentation" is broadened to include interruption of the ascending influence of the brain stem reticular activating system, the contribution of which to wakefulness now seems more important than that conducted to the cortex over classical sensory paths.

SUMMARY

1. Stimulation of the reticular formation of the brain stem evokes changes in the EEG, consisting of abolition of synchronized discharge and introduction of low-voltage fast activity in its place, which are not mediated by any of the known ascending or descending paths that traverse the brain stem. The alteration is a generalized one but is most pronounced in the ipsilateral hemisphere and, sometimes, in its anterior part.
2. This response can be elicited by stimulating the medial bulbar reticular formation, pontile and midbrain tegmentum, and dorsal hypothalamus and subthalamus. The bulbar effect is due to ascending impulses relayed through these more cephalic structures. The excitable substrate possesses a low threshold and responds best to high frequencies of stimulation.
3. Some background synchrony of electrocortical activity is requisite for manifestation of the response. In the "encéphale isolé," reticular stimulation has no additional effect upon the fully activated EEG. With synchrony, in spontaneous drowsiness or light chloralosane anesthesia, the effect of reticular stimulation is strikingly like Berger's alpha-wave blockade, or any arousal reaction. In full chloralosane anesthesia, high-voltage slow waves are blocked but no increase in lower amplitude, fast activity occurs. With barbiturate anesthesia, the reticular response is difficult to elicit or is abolished.
4. In the chloralosane preparation, the secondary cortical response evoked by a sensory volley is generally unaffected by reticular stimulation. Consequent sensory after-discharge is abolished, however, as is pyramidal tract discharge and jerky movements referable to it. Outside the sensory receiving area, sec-

[2]This argument would appear to apply only to the conduction of a single afferent volley. W. H. Marshall (J Neurophysiol 1941; 25–43) has observed impairment of conduction of repeated afferent volleys to the cortex under Nembutal anesthesia, due to great prolongation of thalamic recovery time.

ondary responses themselves may be reduced or prevented.

5. The convulsive spikes produced by local strychnine and those of a fit following supramaximal cortical excitation are not decreased by stimulating the reticular formation.
6. The cortical recruiting response induced by low frequency stimulation of the diffuse thalamic projection system is reduced or abolished by reticular stimulation.
7. There is some indication that the cortical effect of reticular stimulation may be mediated by this diffuse thalamic projection system, for synchronized activity within it is similarly prevented by reticular excitation, and direct high frequency stimulation of this system, within the thalamus, reproduces the reticular response. It is possible, however, that other mechanisms may be involved in its mediation.
8. The reticular response and the arousal reaction to natural stimuli have been compared in the "encéphale isolé," in which EEG synchrony was present during spontaneous relaxation or was produced by recruiting mechanisms, and the two appear identical.
9. The possibility that the cortical arousal reaction to natural stimuli is mediated by collaterals of afferent pathways to the brain stem reticular formation, and thence through the ascending reticular activating system, rather than by intra-cortical spread following the arrival of afferent impulses at the sensory receiving areas of the cortex, is under investigation.
10. The possibility is considered that a background of maintained activity within this ascending brain stem activating system may account for wakefulness, while reduction of its activity either naturally, by barbiturates, or by experimental injury and disease, may respectively precipitate normal sleep, contribute to anesthesia, or produce pathological somnolence.

CONCLUSIONS

Experiments on cats have identified a cephalically directed brain stem system, the stimulation of which desynchronizes and activates the EEG, replacing high-voltage slow waves with low-voltage fast activity. This system is distributed through the central core of the brain stem and appears to comprise a series of reticular relays ascending to the basal diencephalon. Its effects are exerted generally upon the cortex and are mediated, in part, at least, by the diffuse thalamic projection system.

Possible implication of this system in the arousal reaction to afferent stimulation and in the maintenance of wakefulness is discussed.

References

Adrian ED: Afferent discharges to the cerebral cortex from peripheral sense organs. J Physiol 1941; 100:159–191

Adrian ED: The physical background of perception. Oxford, The Clarendon Press, 1947, 95 pp

Adrian ED, Matthews BHC: The interpretation of potential waves in the cortex. J Physiol 1934; 81:440–471

Adrian ED, Matthews BHC: The Berger rhythm: potential changes from the occipital lobes in man. Brain 1934; 57:355–385

Adrian ED, Moruzzi G: Impulses in the pyramidal tract. J Physiol 1939; 97:153–199

Berger H: Uber das Elektrenkephalogramm des Menschen, II. J Physiol Neurol 1930; 40:160–179

Bremer F: Cerveau isolé et physiologie du sommeil. C R Soc Biol Paris 1935; 118:1235–1242

Bremer P: L'activité cérébrale et le problème physiologique du sommeil. Boll Soc It Biol Sp 1938; 13:271–290

Bremer F: L'activité électrique de l'écorce cérébrale. Paris, Hermann, 1938

Bremer F: Etude oscillographique des réponses sensorielles de l'aire acoustique corticale chez le chat. Arch Int Physiol 1943; 53:53–103

Bremer F: Aspect theorique de l'électro-encéphalographie. Arch Néerl Physiol 1944–1947; 28:481–482

Dempsey E W, Morison RS: The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. Am J Physiol 1942; 135:293–300

Dempsey EW, Morison RS: The electrical activity of a thalamocortical relay system. Am J Physiol 1943; 138:283–298

Economo C von: Die Encephalitis lethargica. Vienna, Deuticke, 1918

Ectors L: Etude de l'activité électrique du cortex cérébral chez le lapin non narcotisé ni curarisé. Arch Int Physiol 1936; 43:267–298

Forbes A, Battista AF, Chatfield PO, Garcia IP: Refractory phase in cerebral mechanisms. Electroencephalogr Clin Neurophysiol 1949; 1:141–193

Forbes A, Morison BR: Cortical responses to sensory stimulation under deep barbiturate narcosis. J Neurophysiol 1939; 2:112–128

Fulton JF, Bailey P: Tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. J Nerv Ment Dis 1929; 69:1–25, 145–164, 261–272

Garol HW: The functional organization of the sensory cortex of the cat. J Neuropathol Exp Neurol 1942; 1:320–329

Gellhorn E: Effect of afferent impulses on cortical suppressor areas. J Neurophysiol 1947; 10:125–132

Gerebtzoff MA: Recherches sur la projection corticale du labyrinthe, I: Des effets de la stimulation labyrinthique sur l'activité électrique de l'écorce cérébrale. Arch Int Physiol 1940; 50:59–99

Hunter J, Jasper H: Reactions of unanesthetized animals to thalamic stimulation. Trans Am Neurol Assoc 1948; 73:171–172

Ingram WR, Barris RW, Ranson SW: Catalepsy: an experimental study. Arch Neurol Psychiatry (Chicago) 1936; 35:1175–1197

Ingram WR, Knott JR, Wheatley MD: Electroencephalograms of cats with hypothalamic lesions, III. Meeting, American Electroencephalographic Society, 1949

Jasper HH, Droogleever-Fortuyn J: Experimental studies on the functional anatomy of petit mal epilepsy. Res Publ Ass Nerv Ment Dis 1947; 26:272–298

Jasper H, Hunter J, Knighton R: Experimental studies of thalamocortical systems. Trans Am Neurol Assoc 1948; 73:210–212

Lindsley DB, Bowden J, Magoun HW: Effect upon the EEG of acute injury to the brain stem activating system. Electroencephalogr Clin Neurophysiol 1949; 1:475–486

Magoun HW: Coma following midbrain lesions in the monkey. Anat Rec 1948; 100:120

Magoun HW, Rhines R: An inhibitory mechanism in the bulbar reticular formation. J Neurophysiol 1946; 9:165–171

McCulloch WS, Graf C, Magoun HW: A cortico-bulbo-reticular pathway from area 4-S. J Neurophysiol 1946; 9:127–132

Monnier M: Retinal time, retino-cortical time and motor reaction time in man, III. Meeting, American Electroencephalographic Society, 1949

Morison RS, Dempsey EW: A study of thalamocortical relations. Am J Physiol 1942; 135:281–292

Morison RS, Finley KH, Lothrop GN: Influence of basal forebrain areas on the electrocorticogram. Am J Physiol 1943; 139:410–416

Murphy JP, Gellhorn E: The influence of hypothalamic stimulation on cortically induced movements and on action potentials of the cortex. J Neurophysiol 1945; 8:339–364

Ranson SW: Somnolence caused by hypothalamic lesions in the monkey. Arch Neurol Psychiatry (Chicago) 1939; 41:1–23

Rheinberger MB, Jasper HH: Electrical activity of the cerebral cortex in the unanesthetized cat. Am J Physiol 1937; 119:186–196

Richter RB, Traut EF: Chronic encephalitis: pathological report of a case with protracted somnolence. Arch Neurol Psychiatry (Chicago) 1940; 44:848–866

Snider RS, Magoun HW, McCulloch WS: A suppressor cerebello-bulbo-reticular pathway from anterior lobe and paramedian lobules. Fed Proc 1947; 6:207

Walter WG, Walter VJ: The electrical activity of the brain. Annu Rev Physiol 1949; 11:199–230

Ward AA: The relationship between the bulbar-reticular suppressor region and the EEG. Electroencephalogr Clin Neurophysiol 1949; 1:120