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Sedative & Hypnotic Drugs

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A Neural Basis for the Anesthetic State

Horace W. Magoun, Ph.D.

Since the chief aims for which the drugs under discussion are employed, the relief of discomfort and suffering, appear to result as a feature of a generalized reduction of wakefulness, I should like first to present current findings in the neurophysiology of the waking state, before discussing some early beginnings in its neural pharmacology.

Experimental approaches to this subject rest heavily upon records of the electrical activity of the brain and in fact stem from the observation, with the development of electroencephalography, that the electrical activity of the brain is markedly different in wakefulness and in sleep. I think it would help if we could look at records as we go along, and those in Figure 1 are discontinuous strips of amplified electrical activity from various parts of the cerebral hemisphere, in this instance of a cat. These data which have been obtained from rabbits, cats and monkeys, are in general similar in all of them and, we think, are applicable to man.

These strips start out with the animal awake (Fig. 1, A). In B, it drowses, and in C and D goes unmistakably to sleep, to reawaken ultimately in E. In wakefulness, at the top and bottom, the record is composed of generalized low voltage fast discharge and, in EEG terms, is called desynchronized, with the implication that the neural units are firing out of phase with one another in the regions from which the record is taken.

During drowsiness and sleep, in contrast, the record exhibits generalized large slow waves and spindle bursts and is described as being synchronous. Whether these waves are truly envelopes of the in-phase discharge of component units or rest upon dendritic, post-synaptic or other potential changes unrelated to neuronal discharge is, at present, under debate. The waves themselves, however, do occur as stated.

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Horace W. Magoun, Ph.D.

Chairman, Department of Anatomy,
School of Medicine, University of California at Los Angeles

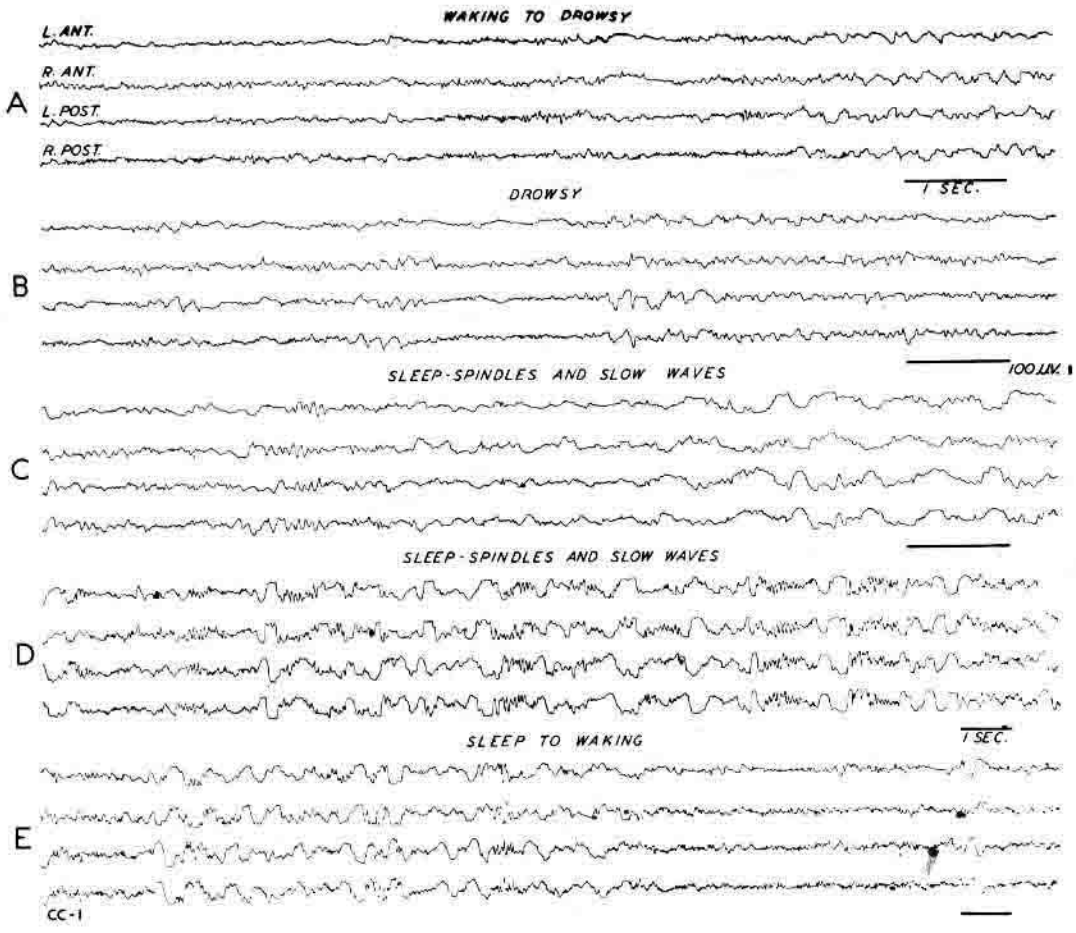

FIG. 1

This contrasting pattern of the electrical activity of the brain in sleep and wakefulness is displayed more strikingly when a sleeping animal is awakened suddenly, as by hand clap, when behavioral arousal is seen to be associated with abrupt desynchronization of the EEG (Fig. 2). Such a record illustrates, too, the capacity of afferent stimulation to induce the waking state, and with this we are all familiar. Shown as well is the characteristic tendency for wakefulness to persist for a long period which outlasts the stimulus that has initiated it.

Our own interest in this subject began with the chance observation that direct electrical stimulation of a central portion of the brain was able to reproduce the desynchronization of the EEG, observed in awakening from sleep. In Figure 3 are records from the monkey, with the period of brain stimulation marked by solid lines. EEG arousal is seen best against a background of previous synchronization, and such brain stimulation produces little additional effect when the record is

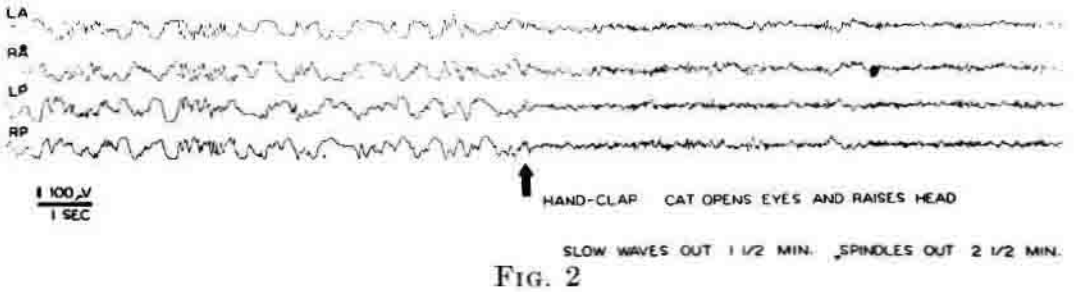

FIG. 2

already of a waking type (Fig. 3, upper left). The change is generalized through the hemisphere, as the multi-channel records indicate, and one can observe again the long-lasting nature of this arousal or desynchronization, once it has been induced.

The brain areas exhibiting this excitability are subcortical in distribution, and their position is indicated by shading in outlined figures of the monkey's brain stem shown in Figure 4. Included in the excitable region are the medially placed reticular formation and tegmentum of the lower brain stem, the sub- and hypothalamus, and the diffusely projecting nuclei of the thalamus (Fig. 4, A). From these studies the excitable area appears to be composed of a collection of reticular relays ascending to the diencephalon for widespread distribution to the overlying cerebral hemisphere. To give this region a name, it has been called the ascending reticular activating system.

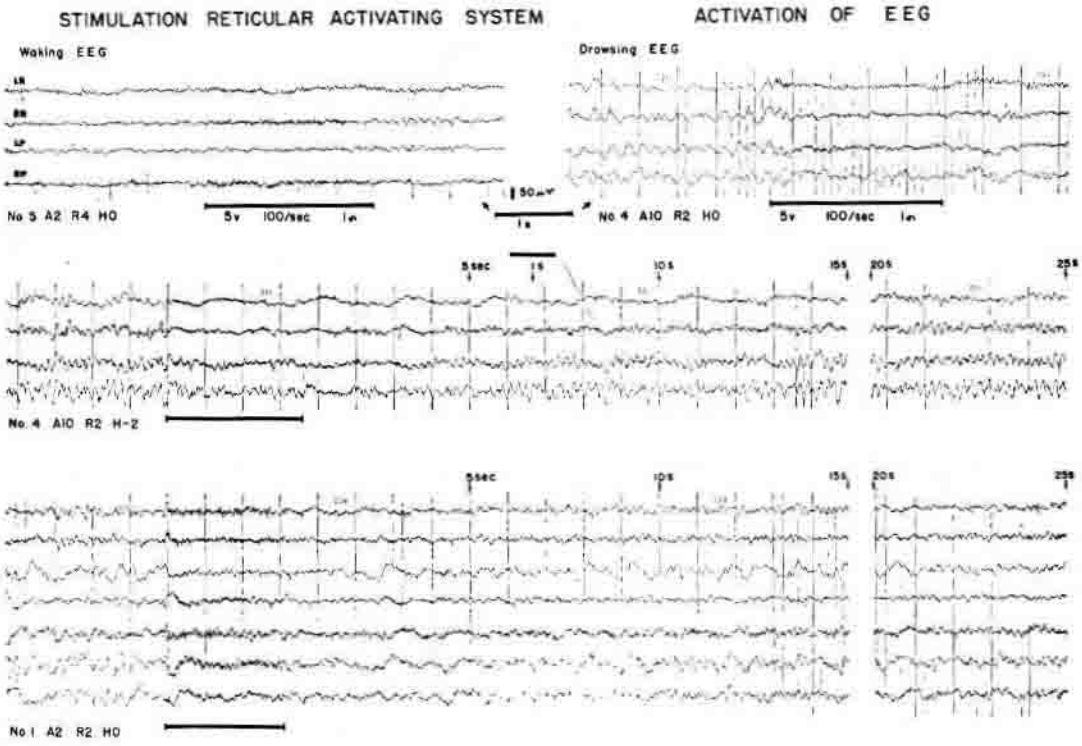

FIG. 3

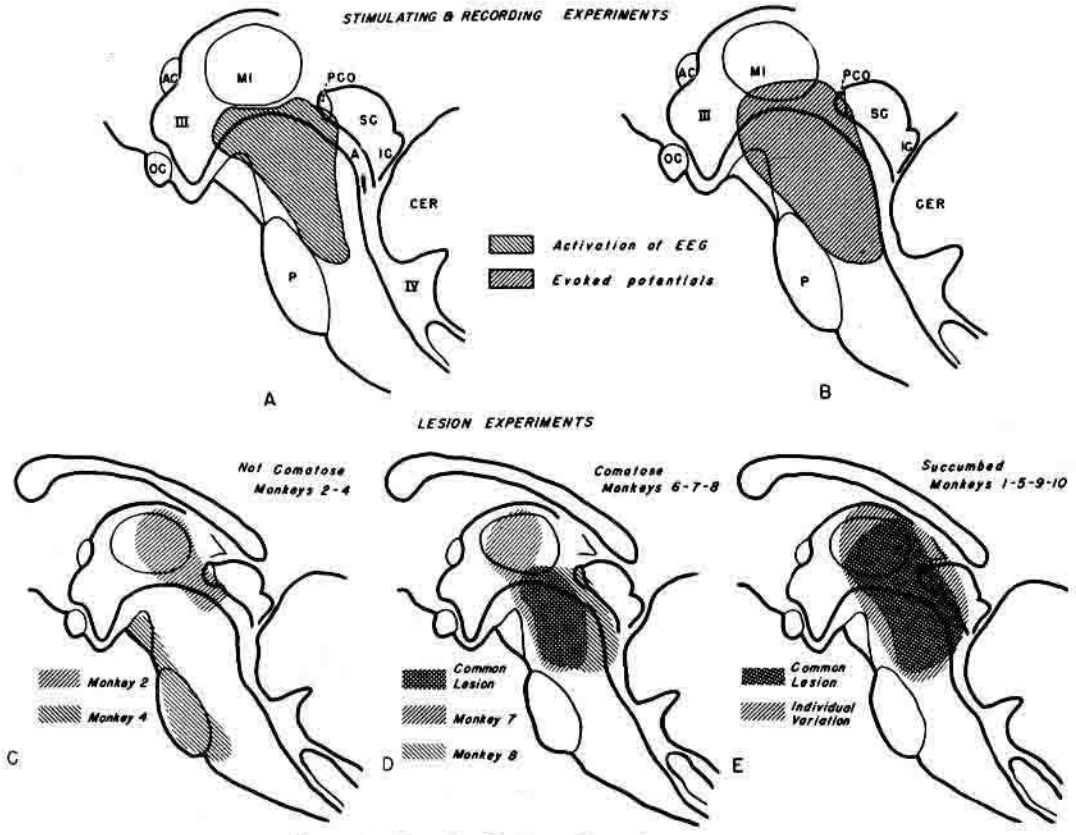

FIG. 4. Reticular activating system

If this subcortical activating system serves usefully in awakening the brain, afferent pathways should make connections with it; and in experiments like that illustrated in Figure 5 it has been probed for discharge evoked by stimulating the sciatic nerve, taking similar records for control from the direct, through or classical pathway to the receiving area of the cortex. When central anesthesia is avoided, major discharge can be recorded from this central arousing mechanism, indicated in black in Figure 5, upon stimulating somatic, visceral, auditory, visual or olfactory receptors (see also Fig. 4, B).

As illustrated in oscilloscopic records (Fig. 5, right), a greater latency to discharge, a slower rise to peak, and a gradual fall-off of activity are all features of the central reticular-evoked potentials (thick beam, bottom tracing) that contrast with those recorded from the direct or classical somatic pathway passing to the receiving cortex (thin beam). These differences in evoked activity in the two are attributable, we think, to the multi-neuronal nature of the ascending reticular path as contrasted with pauci-neuronal conduction in the direct path.

Its multi-synaptic organization may similarly explain the prolonged recovery time of this reticular activating system, which prevents its

following rapidly repeated stimuli with full discharge. This characteristic is illustrated in Figure 6, B by the decline of amplitude of succeeding responses with stimuli delivered as slowly as five per second; and in this respect, too, this medial or ascending system differs from the classical lemniscal pathway (compare A and B with C and D, Fig.6).

Advantage of this feature, namely, its long recovery time after activity, has been taken to test the response of the reticular system to one modality of stimulation shortly after it has been fired by another. In records E and F of Figure 6, one sees the response from the medial brain stem to a series of click stimuli. Immediately before the second click, discharge is evoked by a shock to the sciatic nerve. One can see that, following this discharge, the click stimulus is unable to induce a response, demonstrating interaction or occlusion between auditory and somatic modalities of excitation. The findings suggest that as the

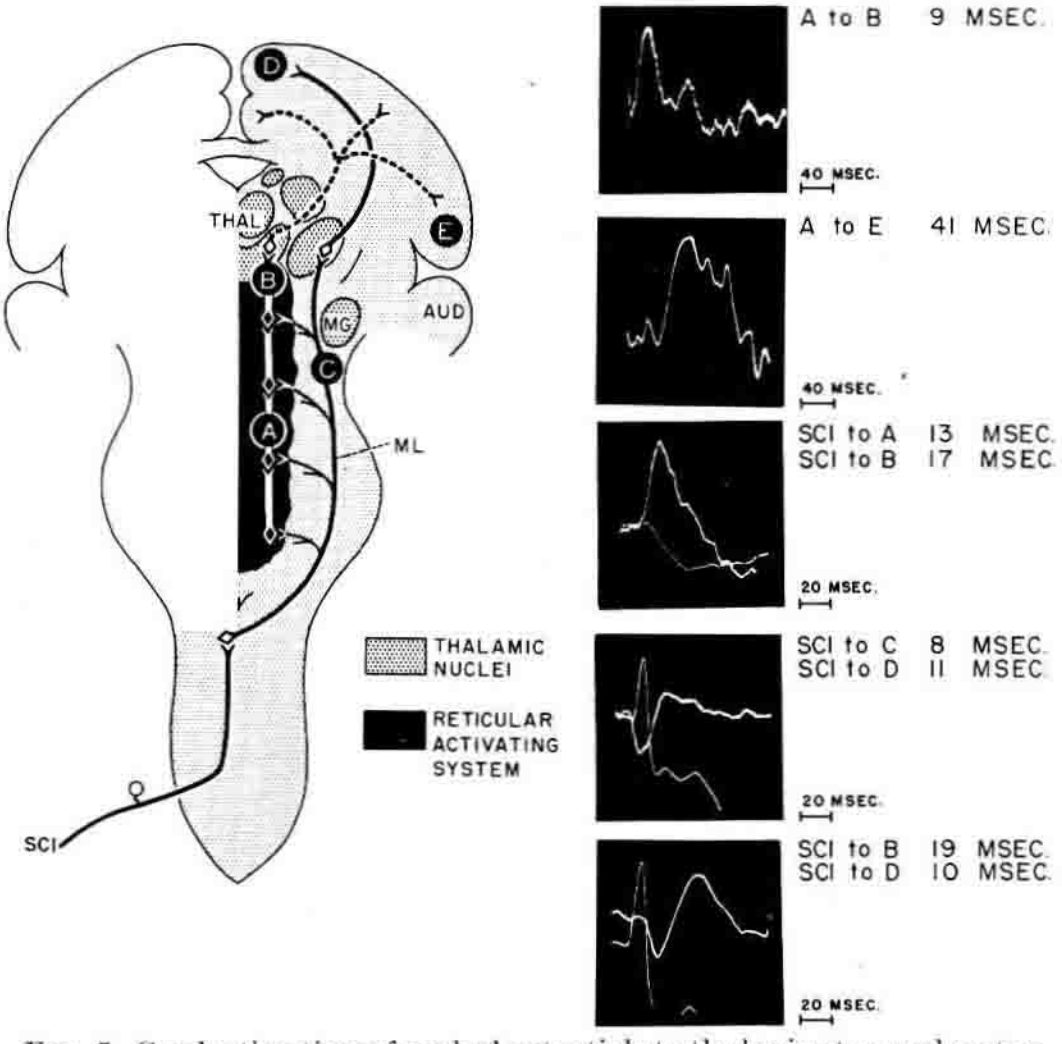

FIG. 5. Conduction time of evoked potentials to the brain stem and cortex

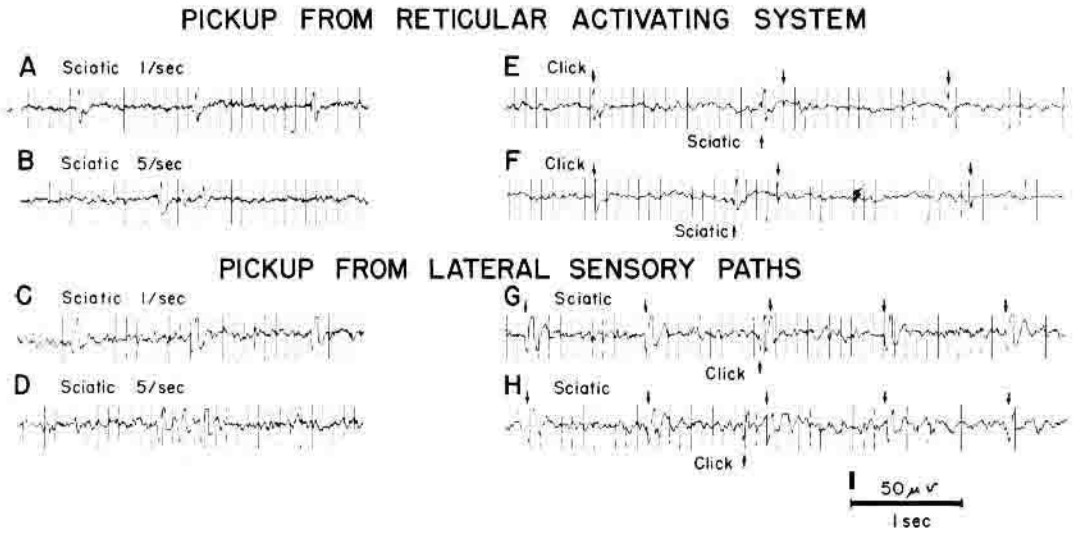

FIG. 6

direct afferent paths ascend through the brain stem toward the cortex, collaterals turn from them into a common system of ascending reticular relays, within which the modality of the initiating signal can no longer be discriminated.

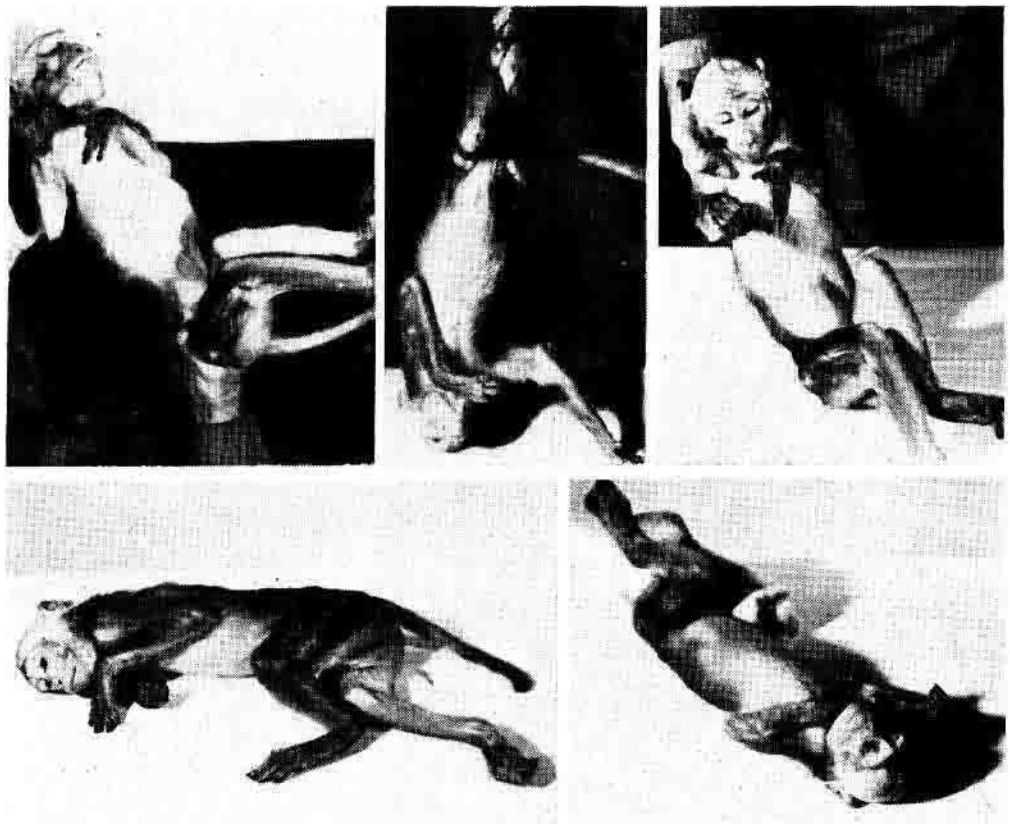

FIG. 7

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The essential role of this medial brain stem system in the induction and maintenance of wakefulness is tested by the consequences of its experimental destruction. Shown in Figure 7 are monkeys with lesions in the central cephalic brain stem (Fig. 4, D) which appear as though asleep or deeply anesthetized for as long as they can be nursed to survival. They display no signs of awareness, either of their internal or external environment. The EEG tracings from such injured animals (Fig. 8) exhibit chronic synchrony, like that of a stupor or coma tracing in man; and although the direct afferent paths to the cortex were not

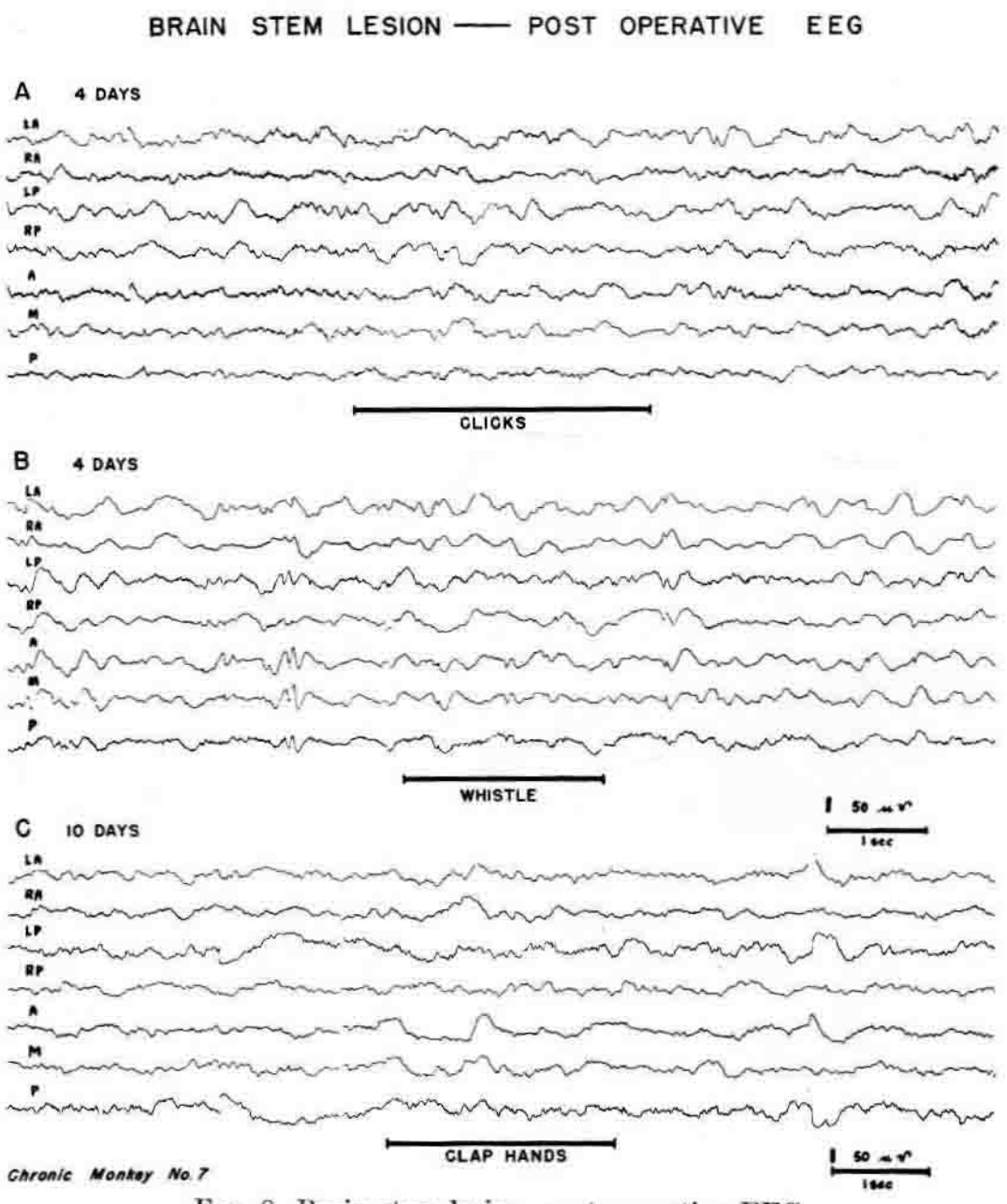

FIG. 8. Brain stem lesion, post-operative EEG

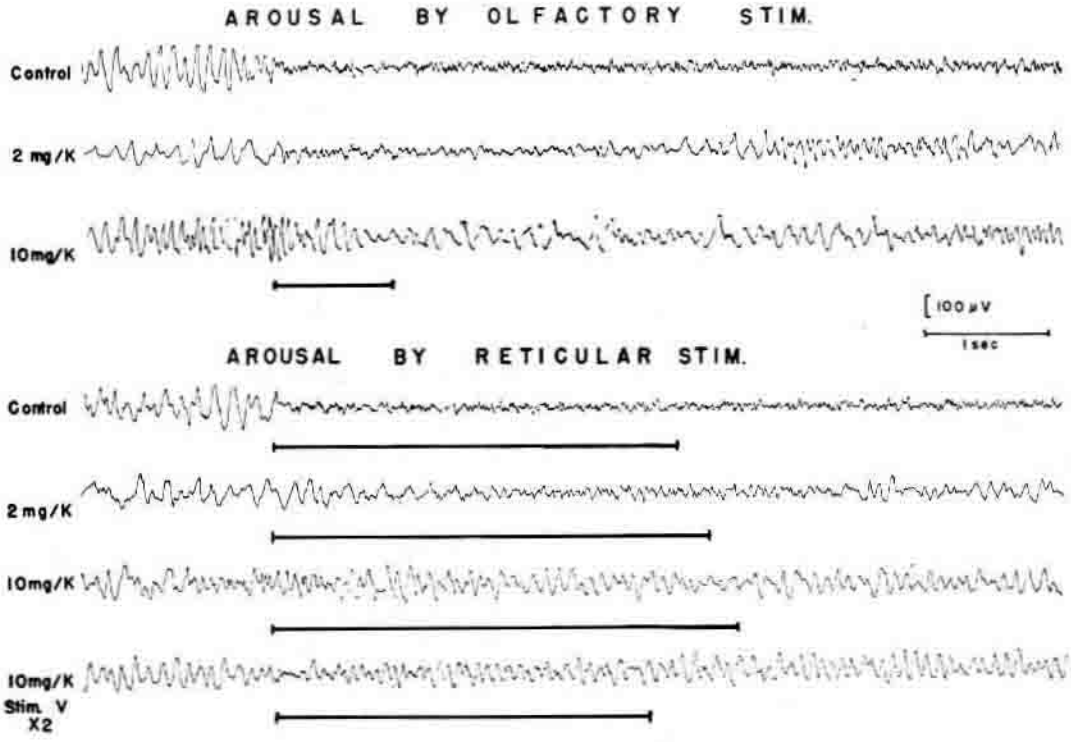

FIG. 9. Effect of Nembutal on EEG arousal

interrupted by the lesions in these cases, intense afferent stimulation is unable to desynchronize the EEG or provoke behavioral arousal for as long as the animals can be maintained.

The findings in such experiments led us to wonder whether loss of wakefulness in anesthesia might depend upon a reversible pharmacological block of this subcortical arousing system, and I should like to tell you in the remaining few minutes what we have so far learned of the effect of drugs upon its activity.

Illustrated in Figure 9 above is the arousal or desynchronization of the EEG induced by afferent stimulation delivered in this instance to the olfactory system. Compared with the record of this response is the EEG arousal induced (below) by direct electrical stimulation of this medial brain stem system. In each case we see the alterations in the tracings that are induced by administering nembutal. The dose at each stage is indicated on the left margin. One can observe that with the induction of sedation the arousal response begins to be impaired with minimal quantities of the agent and, with doses far below those necessary for surgical anesthesia, it can no longer be evoked. The result is the same whether natural afferent stimulation is employed or whether the reticular activating system in the brain stem is stimulated. Here, then, in our opinion, is the EEG record of induction of anesthesia, the

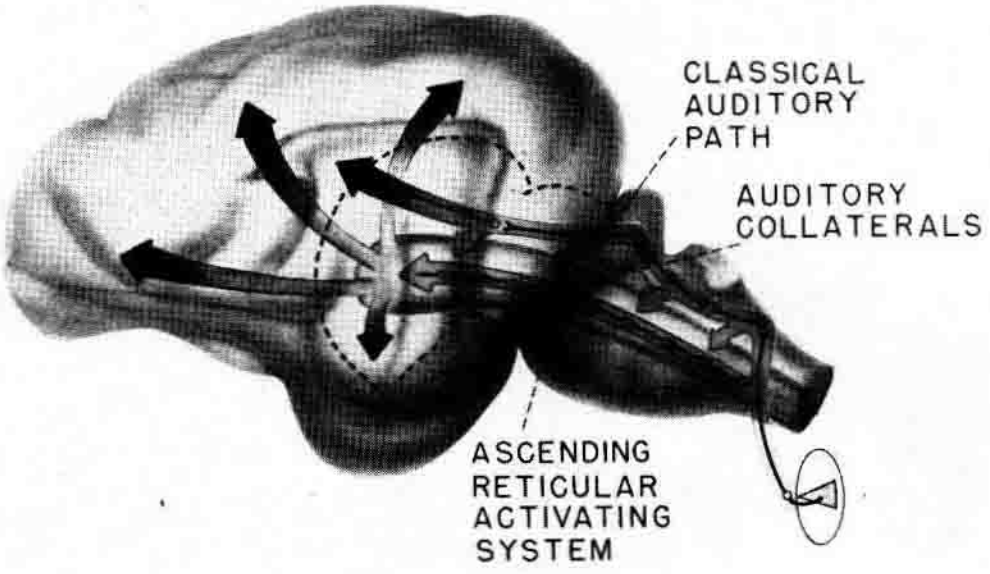

FIG. 10

prevention of arousal by afferent or direct brain stimulation because of the drug that has been employed.

Now, to get into a little more detail, the relations of the classical ascending auditory pathway to the receiving area of the cortex and to this medial brain stem arousal mechanism is indicated in Figure 10. In the unanesthetized brain of the feline *encephale isole*, which is the brain transected from the spinal cord at the first cervical level, it is possible to record the discharge evoked by click stimulation, both in the auditory receiving cortex and from the central cephalic brain stem, and to observe the consequences of administering anesthetic agents or other procedures.

In each of the groups of records seen in Figure 11, the upper channel records from the auditory cortex, and the lower from the medial brain stem; and in each the response to a click is tested before, during and after the procedure indicated. As with somatic or other stimulation, the initial phase, at least, of the primary cortical response to auditory excitation is not reduced by nembutal or by ether anesthesia. As before, with the arousal response induced by repetitive stimuli, the discharge evoked in the medial portion of the brain stem by single clicks is considerably impaired or abolished. In the records below, you see the consequences of interfering with the oxidative metabolism of the brain in a manner leading also to impairment of consciousness. When the utilization of oxygen is prevented by cyanide, or when the supply of sugar is reduced by insulin, there is not in the initial stages in our

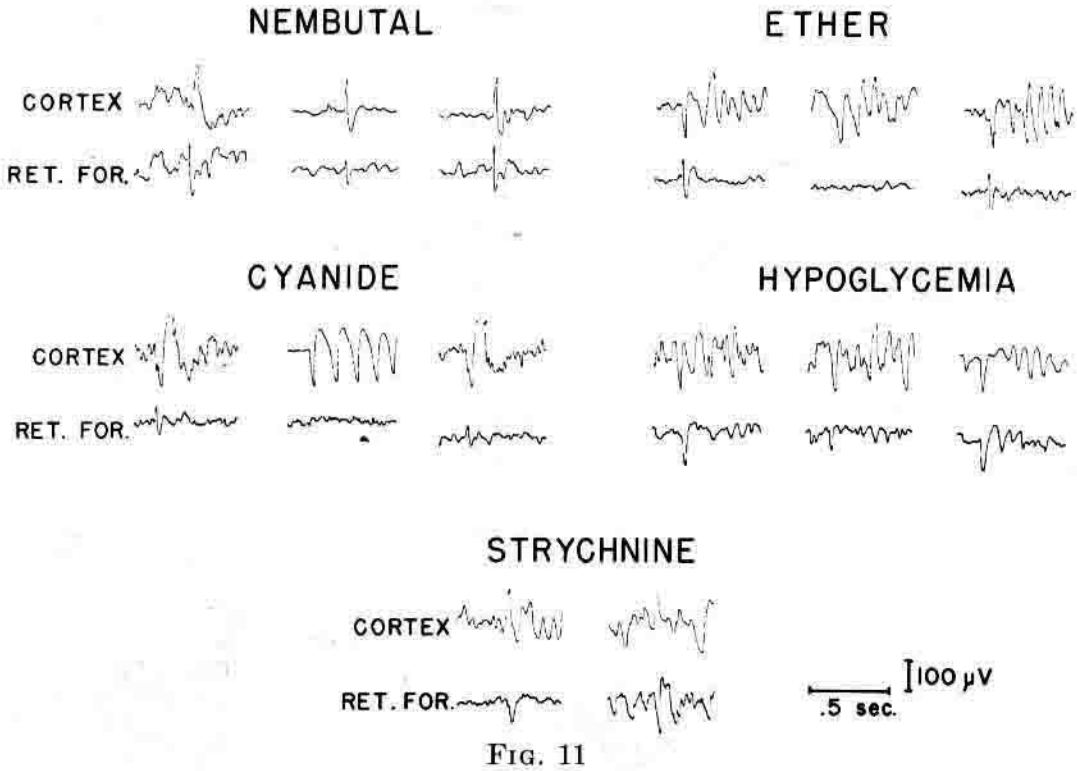
NEMBUTAL
ETHER
CORTEX
RET. FOR.
CYANIDE
HYPOGLYCEMIA
CORTEX
RET. FOR.
STRYCHNINE
CORTEX
RET. FOR.
100 μv
.5 sec.

FIG. 11

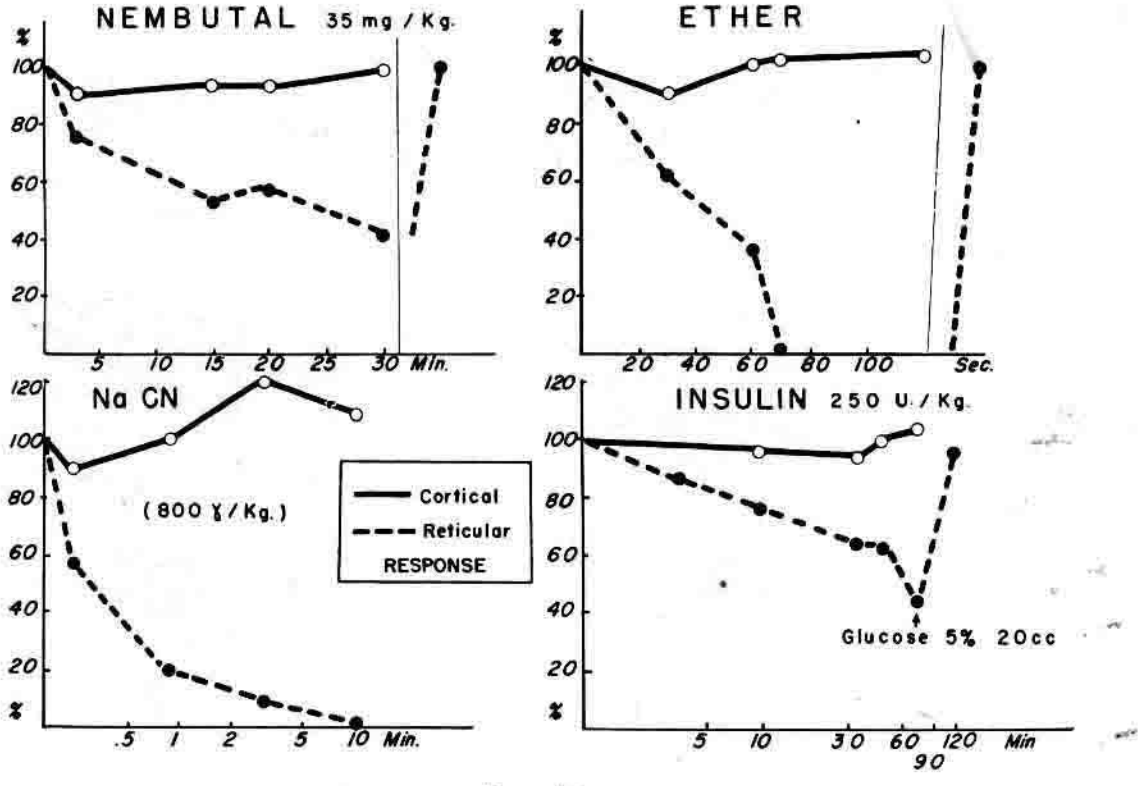
NEMBUTAL 35 mg / Kg.
%
100
80
60
40
20
5 10 15 20 25 30 Min.
ETHER
20 40 60 80 100 Sec.
Na CN
(800 γ / Kg.)
120
100
80
60
40
20
.5 1 2 5 10 Min.
Cortical
Reticular
RESPONSE
INSULIN 250 U. / Kg.
Glucose 5% 20cc
5 10 30 60 90 120 Min

FIG. 12

findings a reduction in the primary response of the auditory cortex to clicks. By contrast, the click-evoked discharge in the central brain stem is greatly reduced or is abolished.

This data of which you have just seen records is graphed in Figure 12, with the solid line indicating the per cent amplitude of the click-evoked response in the auditory cortex at varying intervals of time, and the dashed line that in the central cephalic brain stem (control, 100 per cent. The effects of the agents are indicated. One sees in general that this ascending reticular response is impaired or wiped out at times, and with doses at which the evoked response in the receiving area of the cortex either is not reduced or sometimes is actually augmented.

Returning now to oscilloscopic records (Fig. 13), when the sensory cortical and ascending reticular responses evoked by sciatic shocks are recorded simultaneously, the contrasting features of the classical

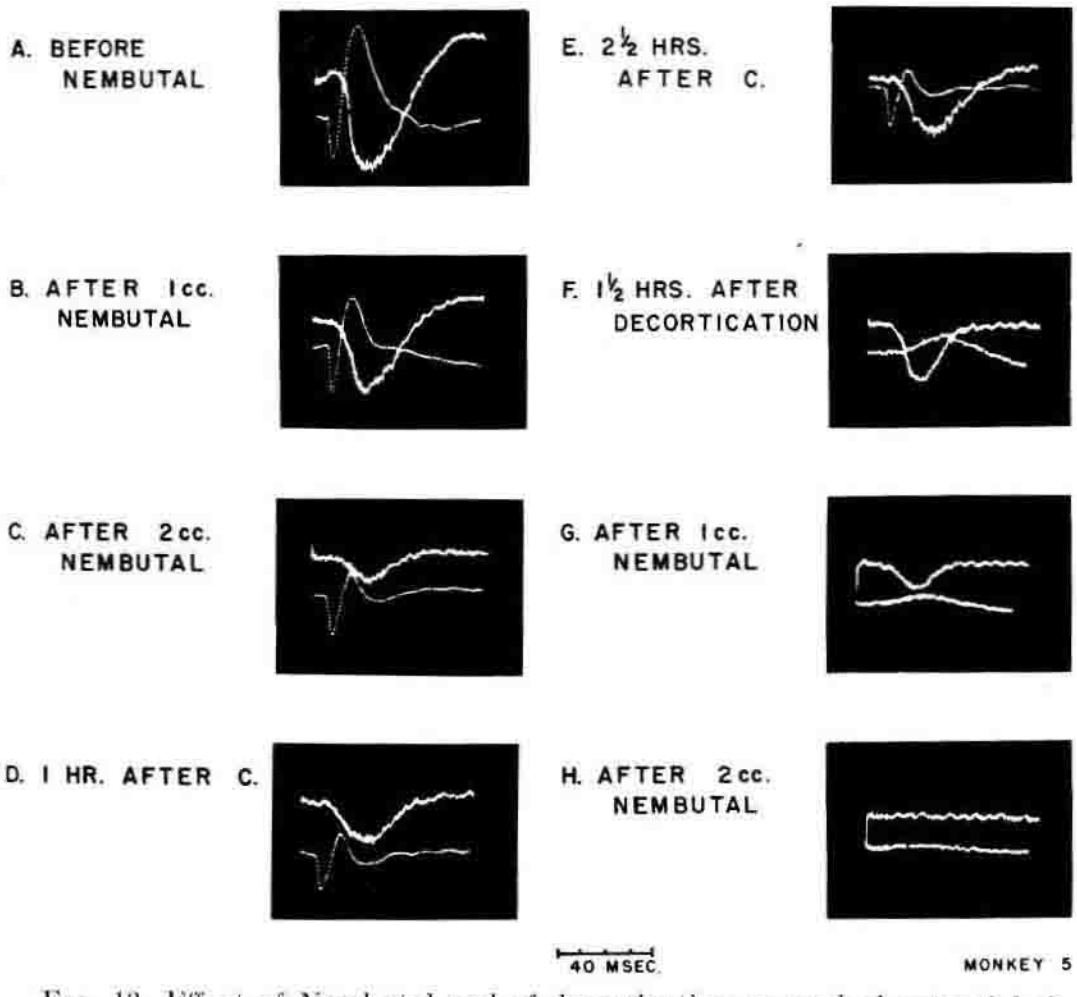

FIG. 13. Effect of Nembutal and of decortication on evoked potentials in the brain stem and cortex.

afferent response (thin beam) and the response in the medial brain stem (thick beam) are evident. We have been over these before (Fig. 5), and I shall not elaborate upon them further. Upon induction of nembutal anesthesia the arrival of afferent volleys in the receiving area of the cortex continues undiminished, while the medial brain stem discharge evoked by sciatic stimulation is very considerably reduced, and recovers again as anesthesia wears off (Fig. 13, A–E).

Coincident with this reduction of evoked activity in the subcortical activating system is a diminution of late events in the cortical response, observed in the thin beam tracings (Fig. 13, A–E); but the block of ascending brain stem activity by anesthesia can occur independently of events in the cortex, since medial brain stem responses evoked after decortication are similarly abolished upon induction of nembutal anesthesia (Fig. 13, F–H).

In a comparable sequence, shown in Figure 14, D–F, the initial phase of the classical cortical response to a sciatic shock (thin beam) actually becomes augmented upon induction of nembutal anesthesia while, in marked contrast, the multi-phasic activity simultaneously recorded from the medial brain stem is practically wiped out (see also Fig. 14, G, H). This block of evoked brain stem activity by anesthesia can similarly be demonstrated after ablation of the cerebellum (Fig. 14, I–K), and so seems definitely to be a primary one within the brain stem. In the sequence in Figure 14, A–C, identical results follow administration of a volatile anesthetic, ether. The initial phase of the cortical response to sciatic stimulation is augmented as ether is given, while that in the medial brain stem is abolished.

This represents about as far as I can go in terms of work that has been completed. There is another very exciting chapter opening in this program through the efforts of Drs. Livingston, Jr. and French, who have been exploring the contributions that areas of the cerebral cortex make to this subcortical arousing system. I hope that you will all have occasion in the future to hear them present these findings to you.

A view of the monkey's brain (Fig. 15), which shows this ascending arousing system and collaterals from afferent paths into it, will serve to enable me to summarize this data, for you have seen records indicating that direct electrical stimulation of this subcortical activating system reproduces EEG and behavioral arousal. You will observe that all afferent modalities turn into this ascending system, and you have seen that arousal by afferent stimulation can be shown to be mediated

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