of a control cell fixed 149 minutes after fertilization, a time when the population was entering the fourth division. The cell shown in the figure had evidently been sectioned in a plane including four nuclei, each of which was labeled, as evidenced by the accumulation of silver grains.

The multiple cleavages in the cells from which the D_2O had been removed are shown in vivo in Fig. 5, and an autoradiogram of the same material in section is shown in Fig. 6. *The nuclei are now labeled.* The sections shown in the figure include two nuclei each, and all four of these exposed the emulsion strongly. Thus, the release of the block to cell division releases as well the block to the synthesis of DNA. It is not yet possible to conclude that this rather remarkable "switching-on" of DNA synthesis is matched by an equally abrupt "switching-off" upon deuteration, since we do not know whether or not synthesis had begun when the eggs were immersed in D_2O. Because the pronuclei had not yet fused, it is possible that DNA replication had in fact not begun, which would make the mechanism of action of D_2O in the present case an inhibition of the *onset* of synthesis, rather than the blockade of a process already in full career. These qualifications are mitigated, however, by the interesting finding of Bucher and Mazia (*7*) that H^3-thymidine is incorporated into the DNA of *Strongylocentrotus purpuratus* eggs whether the pronuclei have fused or not.

Failure of the H^3-thymidine to penetrate the deuterated cells, rather than any chemical isotope effect, might explain these results. Such an absolute permeability differential for normal and deuterated sea urchin eggs is rather unlikely, but the possibility does require experimental study (*10*).

PAUL R. GROSS
CLIFFORD V. HARDING
Department of Biology, New York University, and *Departments of Physiology* and *Ophthalmology, Columbia University College of Physicians* and *Surgeons, New York*, and *Marine Biological Laboratory, Woods Hole, Massachusetts*

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Bulbar Control of Cortical Arousal

Abstract. In the cat, the cortical arousal induced by reticular or nociceptive stimulation is more intense and more long-lasting after elimination of the caudal and medial part of the medulla than in preparations with intact brain. This difference is explained by the intervention of a phasic-ascending inhibitory bulbar control secondarily triggered by the mesencephalic activating system.

We have recently published experimental data which led to the conclusion that a brief stimulation of the mesencephalic reticular facilitating system is able to set secondarily into action a phasic-descending bulbar inhibitory control. This control was evidenced by the decreased amplitude of a sympathetic response, the galvanic skin response recorded on the cat's foot pad (*1*). During these experiments, we noticed that the depression of the sympathetic response was accompanied by decreased intensity of the cortical response to the same mesencephalic stimulation. Because of the simultaneity of both these descending and ascending effects which follow reticular stimulation, we assumed that the decrease of the cortical response might also be the consequence of a bulbar control mechanism. The present investigation was designed to test this hypothesis of bulbar control of cortical arousal.

The experiments were performed on acute spinal cats (cord section at T_2 level), which had been operated under ether. A few hours after the surgical procedure, the preparations were paralyzed with Flaxedil, artificially ventilated and slightly nembutalized (3 to 7 mg/kg). This narcosis, by depressing the normally predominant reticular activating influence, facilitates the "unmasking" of coexisting inhibitory processes. The spontaneous electrical cortical activity of such preparations shows sleep patterns (see Fig. 1); a cortical arousal, however, may easily be evoked by the stimulation of the mesencephalic reticular activating system or by the stimulation of an afferent nerve of the anterior limb (median, cubital, or superficial radial nerve). Because of the spinal section, these stimuli do not affect the cardiovascular sympathetic tone.

The electroencephalographic responses to reticular or afferent stimulation have been compared in preparations (i) with the intact brain and (ii) after elimination of the effects of the bulbar inhibitory formation (*2*) by either a prebulbar (retropontine) tran-

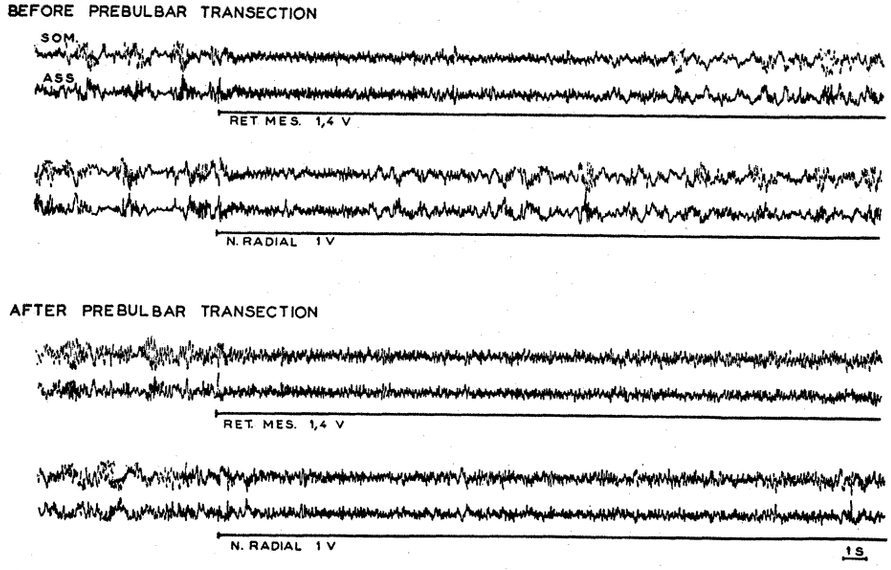

Fig. 1. Cat; spinal cord section at T_2; Nembutal, 7 mg/kg. Effect of a medial prebulbar section of the brain stem on the duration of the cortical arousal induced by long-lasting reticular (mesencephalic) and afferent (superficial radial nerve) stimulation. Before the section (upper traces) the arousal is short and soon followed by the return of the initial sleep pattern. After the section (lower traces), the arousal remains sustained as long as the stimuli are applied.

section or by novocainization of the caudal medulla.

In preparations with the intact brain, short stimulation (0.2 to 0.5 second) of the mesencephalic reticular formation induces a brief and intense burst of cortical activation, but an identical stimulus applied a few seconds later results in a second cortical response which is less intense and much shorter than the first one. In the same preparations, however, after a prebulbar brainstem transection, the two cortical bursts of activation produced by two consecutive reticular stimuli are of the same intensity and duration.

These observations prove that in the intact preparation the depression of the second cortical response is not due to a reticular "fatigue," but to an active inhibitory mechanism lying below the transection and set in action by stimulation of the midbrain reticular formation.

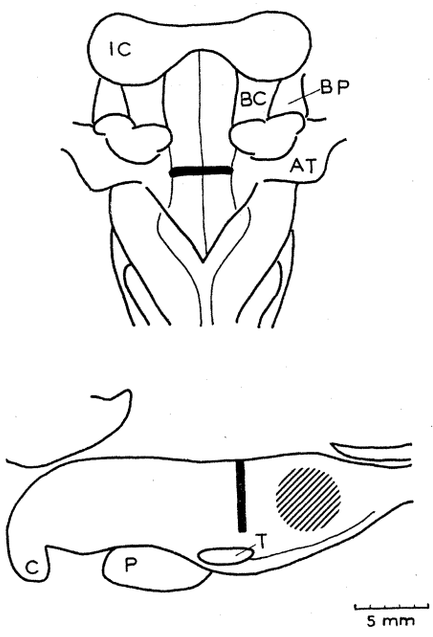

Fig. 2. Semischematic drawings of the lower brain stem of the cat, showing the location of a medial bulbar transection and of a local injection of novocaine, both of which suppress the bulbar control of cortical arousal. In the upper diagram the level and width of the section are shown on the floor of the fourth ventricle. In the lower diagram, the level and depth of the same section are shown in a midsagittal section. In the same diagram, the hatched circle shows the approximate extent of the novocainized area in another preparation. *AT*, Acoustic tubercule; *BC*, brachium conjunctivum; *BP*, brachium pontis; *C*, corpus mamillare; *IC*, inferior colliculus; *P*, pons; *T*, trapezoid body.

In the preparations with the intact brain, a sudden and long-lasting stimulation of either the mesencephalic reticular formation or a somesthetic nerve provokes at its onset a cortical arousal. Progressively however, in spite of the maintenance of the stimulus, the frequency of the cortical waves decreases and spindle bursts and slow waves appear on the electroencephalogram (Fig. 1, two upper traces). When low stimulation voltages (0.5 to 1 v) are used, the arousal is short and the cortical deactivation is usually completed in less than 20 to 40 seconds. After a medial prebulbar transection sparing the lemniscal pathways, or after a local injection of novocaine in the ventro-caudal part of the medulla (see Fig. 2), the arousal induced by the same stimuli persists unchanged throughout the duration of the stimulation (Fig. 1, two lower traces). In many cases a typical activation pattern was still present after 3 or 4 minutes of reticular or afferent stimulation. These results indicate that an ascending bulbar mechanism is able to antagonize the cortical arousing effect of a sustained reticular excitation, but that this mechanism reacts with some inertia and is only progressively brought into action.

The inhibitory mechanism may be more easily activated if repetitive stimuli are used, the voltage of which is linearly increased in 1 or 2 minutes from zero to the voltage normally sufficient to provoke a typical arousal. In such a case, it frequently occurs that the cortical activity remains synchronized during the whole duration of the stimulation, even when a voltage is reached that is sufficient to induce an intense arousal when applied suddenly. It may be shown that the difficulty of evoking a cortical activation in this case is not due to the mode of stimulation but to an active inhibitory discharge. After a medial prebulbar transection of the brain stem, or after the novocainization of the caudal medulla, progressively increasing reticular or afferent stimuli regularly induce a progressively increasing cortical activation.

Although most of this experimentation was performed on lightly nembutalized preparations, observations identical to those described above were also made by stimulating the reticular mesencephalic formation in a few "encephale isolé" unanesthetized cats, whose cortical activity was spontaneously of the drowsy type. Thus the bulbar inhibitory mechanism exerts its control under physiological conditions.

These experiments suggest the following considerations:

The foregoing results show that structures localized in the medial and caudal part of the medulla are able to decrease or suppress the arousing influence of the excitation of the reticular activating system. It seems highly probable that these structures are the same which are at the origin of the tonic synchronizing influence recently described by Moruzzi and his colleagues (*3*).

The present investigation proves, on the other hand, that the bulbar-ascending deactivating control is phasically brought into action each time the reticular activating system is activated. Our previous experiments (*1*) have demonstrated that this is also the case for the descending bulbar inhibitory discharges, even when the supramesencephalic structures are eliminated. Taken together, these data suggest that it is the reticular activating system itself which triggers the reticular bulbar antagonistic mechanism. Depending upon whether the stimuli are abrupt or gradual, this interreticular regulating mechanism may either shorten or completely suppress the cortical activation (*4*).

MARTHE BONVALLET
VINCENT BLOCH
Laboratoire de Neurophysiologie, Hôpital Henri-Rousselle, and *Laboratoire de Psychophysiologie, Sorbonne, Paris*

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