Brain Mechanisms and Drug Action

A SYMPOSIUM: FOURTH ANNUAL SCIENTIFIC MEETING OF THE HOUSTON NEUROLOGICAL SOCIETY TEXAS MEDICAL CENTER, HOUSTON, TEXAS

The subject was selected because of the growing interest in the mechanism of action of many new drugs which act selectively on the nervous system.

Features: Present day thinking on the subject.

This symposium should be of interest to neurologists, psychiatrists and others concerned with understanding the mechanisms by which the tranquillizing drugs act on the nervous system.

CHARLES C THOMAS • PUBLISHER
Springfield, Illinois

Compiled and Edited by

WILLIAM S. FIELDS
Professor of Neurology
Baylor University
College of Medicine

Contributors

JOSEPH V. BRADY
ROGER GUILLEMIN
HAROLD E. HIMWICH
HEBBEL E. HOFF
EVA KING KILLAM
KEITH F. KILLAM
ROBERT B. LIVINGSTON
AMEDEO S. MARRAZZI
DAVID McK. RIOCH
FRANCO RINALDI

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A Symposium
Fourth Annual Scientific Meeting of the
Houston Neurological Society
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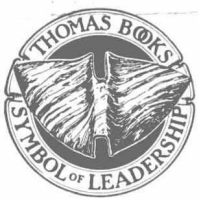

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CONTRIBUTORS

Dr. Joseph V. Brady: *Chief, Department of Experimental Psychology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C.*

Dr. Roger Guillemin: *Assistant Professor of Physiology, Baylor University College of Medicine, Houston, Texas; Scholar of the John & Mary R. Markle Foundation.*

Dr. Harold E. Himwich: *Director, Research Division, Galesburg State Research Hospital, Galesburg, Illinois.*

Dr. Hebbel E. Hoff: *Chairman: Professor of Physiology, Baylor University College of Medicine, Houston, Texas.*

Dr. Eva King Killam: *Assistant Research Pharmacologist, University of California Medical Center, Los Angeles, California.*

Dr. Keith F. Killam: *Department of Physiological Chemistry, University of California Medical Center, Los Angeles, California.*

Dr. Robert B. Livingston: *Associate Professor of Physiology and Anatomy, University of California Medical Center, Los Angeles, California.*

Dr. Amedeo S. Marrazzi: *Director, Veterans Administration Research Laboratories in Neuropsychiatry, Veterans Administration Hospital, Pittsburgh, Pennsylvania.*

Dr. David McK. Rioch: *Director, Division of Neuropsychiatry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C.*

Dr. Franco Rinaldi: *Research Division, Galesburg State Research Hospital, Galesburg, Illinois.*

A Symposium — March 16, 1956

FOREWORD

THE Houston Neurological Society, founded in 1951, has succeeded in maintaining the interest of workers in the clinical and basic science fields. Since 1952, an annual meeting has included both clinical presentations and a symposium on some basic subject of neurologic interest. It has been our good fortune to obtain outstanding contributors to these symposia. The subject, *Brain Mechanisms and Drug Action* was selected because of the growing interest in the mechanisms of action of many new drugs which act selectively on the nervous system. We were fortunate in having as chairman Dr. Hebbel E. Hoff, who skillfully guided the discussion and fused the varied contributions of the speakers.

The Society wishes to thank the following for making the symposium possible:

Ayerst Laboratories
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Wyeth Laboratories

The well integrated symposium and the carefully planned meeting did not just happen. We are indebted to Dr. William S. Fields and Dr. Charles A. Carton for effort and time expended in preparation of the program and in editing these proceedings. Our thanks are given to Dr. Claude Pollard, Jr., for his uncomplaining fulfillment of the never-ending duties of Secretary.

F. KEITH BRADFORD, M.D.
President, Houston Neurological Society

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BRAIN MECHANISMS AND DRUG ACTION

NEUROPHYSIOLOGY OF THE RETICULAR FORMATION

ROBERT B. LIVINGSTON, M.D.

University of California at Los Angeles

SEVENTY-FIVE years ago with the introduction of technics for fixing, slicing, and staining thin sections of the central nervous system, much of the basic research was carried out by clinicians, for at that time there was the buoyant hope that the unfolding details of neuroanatomy would lay bare the mechanisms underlying all brain functions. Clinicians looking forward to an early revelation of these marvels wanted to be on hand to pull back the curtain.

Within twenty-five years, however, there had been a gradual reckoning. Already by that time there had developed a fairly complete division of labor. The anatomist was working with special stains such as the Golgi for detailed anatomy. Physiologists were analyzing spinal reflexes such as the scratch reflex. Psychologists were coming to grips with the problems of testing intelligence, and of developing and understanding learning mechanisms. Neurologists and psychiatrists were becoming more and more restricted to the problem of coping with "organic" and "functional" problems as presented by their patients. It was difficult during this period to bear in mind that each of these specialists was studying the same organ. The literature of this era, fifty years ago, is characterized by a general despair that there ever could be a meaningful resolution of the divergent concepts which were being studied from such widely separated points of experimental departure.

When we now employ the advantages of hindsight and look backwards upon those times, the periods of our intellectual great-grandfathers and grandfathers, I think it is reasonable to assert that our great-grandfathers were too buoyantly hopeful and that

our grandfathers were overcome by unwarranted despair. Excessive hope seventy-five years ago was born of innocence: excessive despair fifty years ago was born of technical limitations. Our grandfathers could not imagine that we would be able to amplify the electrical activity of neurons—to "hear" them firing over a loudspeaker and "see" them on an oscilloscope screen—and by these means to gain some insight into neuronal activity taking place in widespread cellular aggregates throughout the brain. They couldn't have imagined that this could be accomplished with freely moving animals behaving in experimentally controlled situations.

Without feeling particularly bold one can venture the notion in 1956 that we have inherited some of our grandfathers' attitude of despair and that we are inclined to cling to it perhaps more than is desirable. Not only is the time now ripe for making a number of closures between formerly isolated disciplines, but I think it is realistic now to exhibit a larger confidence than is generally expressed, in progress which can be made during the next few years. If only the technics already available are to be exploited this confidence will be justified. Moreover, new technics being introduced by scientists in various laboratories throughout the world suggest that these will take us a very long way toward making indistinguishable the boundaries between psychology and neurophysiology, between psychiatry and the neurological disciplines.

This *Symposium on Brain Mechanisms and Drug Action* promises to illuminate progress especially in those areas where our intellectual grandfathers despaired the most. It is my privilege to present some neurophysiological information relating to the reticular formation, especially that coming out of Magoun's laboratories at the University of California at Los Angeles and the Veterans Administration Hospital at Long Beach, California. First, let me say that the reticular formation is not as some have suggested a tangled mish-mosh of tiny neurons imbedded in the central core of the neuraxis. Instead, as Cajal [1] noted at the turn of the century, reticular cells resemble motor cells having long and divergent dendrites and axons which may continue in the central gray or white reticular substance sometimes to a considerable dis-

tance across and up and down the length of the brainstem. These great shaggy neurons seem in some respects to stitch the CNS together. Into this system come collaterals of the long sensory paths—which are so numerous that they constitute "the principal element of the interstitial plexus" in the brainstem reticular formation. Sensory collaterals course in every direction, divide and subdivide and form nests around cell bodies and dendrites of the reticular neurons and of the motor neurons belonging to the cranial nerve nuclei. In addition there are motor collaterals from both the pyramidal tract and from the extra-pyramidal pathways which enter the brainstem from its cephalic end. Collaterals of the corticopontile and pyramidal tracts turn off along the entire length of the brainstem and develop intimate synaptic relations with many of the same reticular cells which are apparently under the influence of the sensory collaterals.

Cajal concluded that cells in the reticular formation not only have multiple influences borne upon them but even adjacent cells do not all have the same connections. He recognized some of the implications of multiple influences coming to reticular cells from the spinal ascending tracts, the acoustic ganglia, the tectum, the cerebellum, the basal ganglia and the cerebral cortex. Some reticular cells he noted receive terminal arborizations of sensory axons of the third order. "This addition of the fourth order neuron is more complicated than it appears, the effect being more than additive, for it demands an organization so inextricable that one hesitates to consider it; furthermore, the sensory tracts of the second and third order and their connections with the motor nuclei appear to suffice *a priori* for all the exigencies of reflexes and combinations of movements."

GENERAL BRAINSTEM FUNCTIONS

Although they were not the first to search through the brainstem reticular formation, Magoun,[2] Magoun and Rhines[3] about twelve years ago, and others following in their wake[4, 6] began to make some generalizations which helped greatly to disentangle brainstem physiology. It was discovered that the reticular formation performs some functions which seemed to be widespread in their pattern of effects. This was difficult at first to accept

because it was in direct opposition to widely held notions that the nervous system would prove to have more and more refined localization of function and detailed point-to-point relationships. Out of a large number of studies there came to be recognized two general divisions of the nervous system: that relating to the classical sensory and motor pathways, which appeared to be relatively discrete and to support notions of the localization of function to a remarkable degree, and the great matrix of the nervous system including the brainstem reticular formation which appeared to have diffuse or generalized functions. This latter system at the level of the bulb could induce widespread inhibition of cranial and spinal motor mechanisms. More anteriorly it had a generalized facilitatory influence on motor outflow. This facilitatory portion of the reticular formation provided an ascending system of projections which tended to activate in a generalized way the entire cortical mantle.[4, 6-8] Thus the reticular formation turned out to be capable of modifying the central excitatory state, both upwards and downwards; to be able, so to speak, to burn the nervous system candle at both ends.

CORTICAL INFLUENCES ON AROUSAL

More recently the cortex has been found to project from certain discrete areas down into the reticular formation.[9] The places of origin of this corticifugal projection are the frontal eye fields, the sensory motor cortex, the para-occipital cortex, the first temporal gyrus, the orbital surface of the frontal lobe, the cingulate gyrus, the tip of the temporal lobe, and the medio-basal portions of the temporal lobe. Each of these cortical fields appears to project down into the reticular formation to very much the same brainstem territories that receive collaterals from all of the afferent systems of the body. Indeed, the descending cortical influences are seen to interact in the reticular formation with impulses generated along sensory pathways.[5, 5a, 9, 11] We find that sensory projections, e.g., from the sciatic or the trigeminal nerves will interact in the reticular formation with each other and with each of the projections descending from any one of the cortical areas projecting into the reticular formation. There is no question, then, that the reticular formation constitutes a kind of Grand Central Sta-

tion for the interaction of impulses generated in remote parts of the nervous system.

Not only is there interaction between descending projections from the cortex with sensory input, but each of the cortical fields interacts with each other.[9] Moreover, each individual cortical field appears to have a rather special pattern of influence within the brainstem reticular formation.[10] For example, some of these fields will augment intrinsic activity of the brainstem while others will diminish it. Most of the cortical areas projecting into the brainstem give rise to a complex sequence of alternating excitement and depression. These influences last from several tenths of a second to several seconds. We are therefore provided with the comforting notion that the cortex is not simply the victim of whatever the reticular activating system might demand of it, but the cortex itself possesses corticifugal regulating mechanisms which in turn can influence the level of activity within the reticular formation. What has been determined as yet relative to the nature and possible functional role of these descending projections?

Investigators in Magoun's laboratories have shown that electrical activation of these certain cortical fields, in monkeys immobilized with curare but otherwise free of centrally acting anesthesia, will induce EEG arousal.[12] Therefore, at least some of the corticifugal projections may play a part in activating the rest of the brain by way of the reticular activating system. Another group has disclosed that naturally sleeping monkeys with electrodes implanted in these cortical fields are awakened and behaviorly aroused when stimulation is applied.[13] It is further noteworthy that stimulation of other cortical sites which do not have projections to the reticular formation will not elicit such EEG changes or behavioral arousal even though rather high intensities of current are applied. Thus, a monkey will sleep right through the application of high intensity stimulation to negative cortical points whereas he will be instantly awakened from sleep and aroused for a long time by a brief activation of one of the positive cortical fields even with only low intensity stimulation. If moderate strengths of stimuli are used, the monkey is not only aroused but he is agitated, shows signs of "fear" and attempts to escape

from the cage. Such an animal will sleep right through far stronger stimulation of cortical points which lack the appropriate brainstem connections. We can conclude, therefore, that not only does the cortex have downward projections upon the brainstem, but that these projections may play some role in relation to arousal and in the maintenance of a centrally aroused state.

CENTRAL INFLUENCES ON SENSORY CONDUCTION

In 1950, Magoun suggested that the brainstem reticular formation might be able to influence conduction along sensory as well as motor paths.[14] Hagbarth and Kerr[15] and subsequently Hernández-Peón and Hagbarth[20] and Kerr and Hagbarth[16] and others[17, 22] demonstrated that such an influence does indeed exist. It appears to act tonically to cause a moderate but steady inhibition of the relay of afferent impulses along the classical sensory pathways. This tonic influence is interrupted by anesthesia, hence conduction along the classical sensory systems is enhanced during anesthesia. This explains why it is often easier to pick up sensory evoked potentials in anesthetized than in unanesthetized animals. In addition to showing this tonic brainstem influence, Hagbarth and Kerr demonstrated that either direct stimulation of the reticular formation or its indirect activation by way of cerebellicifugal or corticifugal systems projecting into the reticular formation would further depress impulses being conducted along sensory pathways. Thus sensory impulses, destined for higher integrative centers, can be "nipped in the bud" on their way through the first, second or third synaptic relays within the central nervous system by the brainstem reticular formation and areas of cortex and cerebellum projecting there. This extends in scope the effects already demonstrated by Eldred, Granit and Merton,[18] that may be imposed by the reticular formation upon sensory organs outside the nervous system. A control system exercising its effects in the periphery has now been shown to have a continuing control over sensory impulses, from their points of origin to their destinies deep within the brain. Sensory pathways so long considered by psychologists and philosophers to be relatively inviolate until they reached the cerebral cortex have been found to be subject to control by events taking place in parts of the central brainstem.

One might easily be persuaded that these astonishing facts have little or nothing to do with behavior. But Hernández-Peón, Scherrer and Jouvet [19] and others [21] continued pursuing the problem by making use of implanted electrodes and unanesthetized animals. By such means it has been shown that the sensory paths are remarkably plastic in relation to the animal's past history and current experiences. Thus at the first sensory relays [21] and at the cortical levels [23] sensory habituation or adaptation to reiterated stimulation occurs. Moreover, when the animal shifts the focus of its attention the amplitude of impulses along the sensory paths is correspondingly affected. That these dynamic alterations along the sensory pathways are related to activity in the brainstem reticular formation is made clear by the effects of anesthesia and of brainstem lesions. Neither the effects of habituation or focus of attention nor of conditioning appears to survive after brainstem lesions although interference by anesthesia is only transient.

It is unnecessary in so brief a discussion of these fields to list all that is being omitted for want of time. However, two areas of current neurophysiological investigation need to be linked closely to the complex of functions we have been describing. One of these relates to the limbic or "visceral forebrain" mechanisms as presently being elucidated by Mac Lean [24] and the second relates to the central mechanisms governing drive, as currently being studied by Olds.[25] Research in these two areas combines effectively with the present studies to add two further dimensions—relating to emotional mechanisms and motivation.

CONCLUSIONS

The reticular activating system in the cephalic end of the brainstem appears to be intimately joined functionally with the cortical areas projecting into the brainstem. There is what might be termed a cortical activating system. Moreover, the cortex is seen to exercise a complex control over intrinsic conduction in the brainstem. The brainstem in turn not only influences cortical activation and the downstream regulation of motor mechanisms, but it also controls the central relay of sensory impulses. It appears that the brainstem reticular formation not only participates in determining the level of consciousness in its arousal capa-

cities, but also the content of consciousness in its capacities for sensory control.

We have come, therefore, to an appreciation of the central nervous system as including a diffusely projecting system in the reticular formation and cortex which provides some of the neural mechanisms heretofore relegated to "psychic mystery." This news would relieve some of the pessimism of our grandfathers and perhaps justify the optimism of our great-grandfathers. Rather than suppose we are due now for a swing of the pendulum toward the side of discouragement and retrenchment, I am inclined to view this as only the beginning of a kind of renaissance in neurological sciences. The time is ripe for the synthesis of knowledge from clinical and basic science fields such as Doctor Fields has proposed for this meeting.

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DISCUSSION

Dr. Hebbel E. Hoff: I wonder, Dr. Livingston, if you would just say a word about the possibility of topography within this system? We have been brought up on point relations in the more direct projecting systems, and here we seem to be discussing things that seem to be omnipotent, you might say. Now you did point out that not all neurons in this system react the same to sensory stimulation and the like. Is there anything by way of topography or functional localization that could account for this?

Dr. William T. Lhamon, Houston, Texas: I would like to know